SYNTHESIS OF USEFUL ORGANIC MOLECULES INVOLVING *N*-THIOIMIDES AND DITHIOCARBAMATES

THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (SCIENCE)

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MANAS MONDAL

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ORGANIC CHEMISTRY SECTION

DEPARTMENT OF CHEMISTRY

JADAVPUR UNIVERSITY

KOLKATA-700032

INDIA

Dedicated
To
My Family

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কলকাতা – ৭০০ ০৩২, ভারত

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TO WHOM IT MAY CONCERN

This is to certify that the thesis entitled "**SYNTHESIS OF USEFUL ORGANIC MOLECULES INVOLVING *N*-THIOIMIDES AND DITHIOCARBAMATES",** submitted by **Mr. Manas Mondal** who got his name registered on 21/08/2019 for the award of Ph.D. (Science) degree, Jadavpur University, is absolutely based upon his own research work under my supervision and that neither this thesis nor any part of it has been submitted for either any degree or diploma or other academic award anywhere else before.

Amit Saha
Signature of the Supervisor
with official seal

Place: Jadavpur
Date: 13.11.2024

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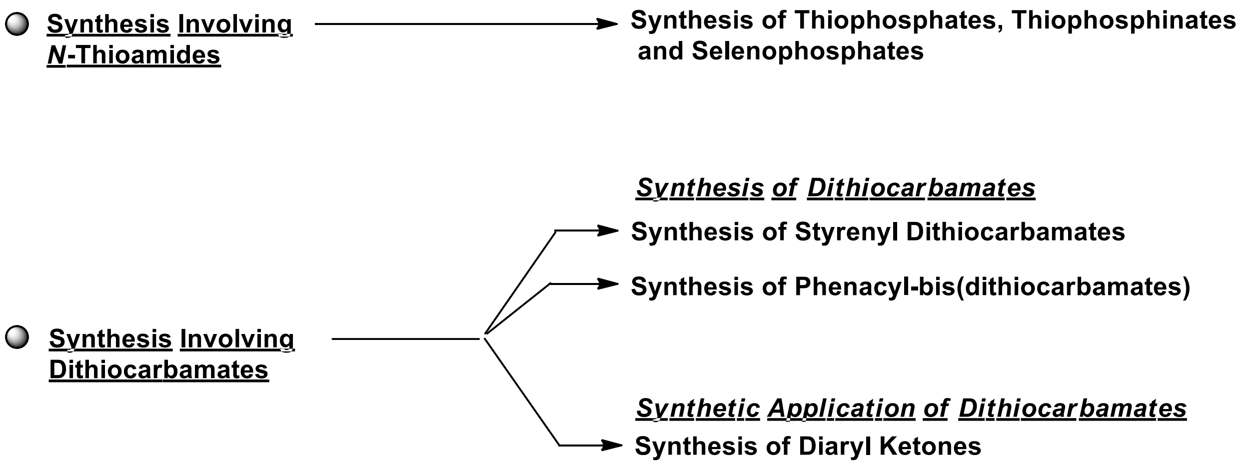
Preface

Investigation embodied in this desertion entitled "**SYNTHESIS OF USEFUL ORGANIC MOLECULES INVOLVING *N*-THIOIMIDES AND DITHIOCARBAMATES",** was initiated in May 2018 under the supervision of Dr. Amit Saha, Assistant Professor, Organic Chemistry Section, Department of Chemistry, Jadavpur University, Kolkata 700032.

The prime focus of this research work is to explore the synthetic utility of *N*-thioimides and dithiocarbamates for developing various synthetic procedure to synthesize useful organic molecules using benign reaction conditions.



This thesis has been categorized into three chapters. Chapter-1 consists of two sections, Section-1 includes a short review on synthetic application of *N*-chalcogenoimides and Section-2 describes the formation of P-S/Se bond in neat condition using *N*-chalcogenoimides as the source of electrophilic sulfur/selenium. In Chapter-II synthesis of dithiocarbamate compounds have been discussed and the chapter is divided into three sections. Section-1 demonstrates a short review on the topic of various type of dithicarbamate compounds that have already been synthesized using transition metal catalyzed condition as well as under metal free condition. Synthesis of styrenyl dithiocarbamates from styrene without using any metal catalyst have been discussed in Section-2. Section-3 describes the metal free dithiocarbamylation of phenylacetylene. Chapter-III consists of two sections which describe synthetic application of dithiocarbamate compounds. Sections-1 includes a short review of synthetic application of dithiocarbamate compounds where dithiocarbamate compounds are used as substrate. Section-2 describes the unique role of dithiocarbamate ester as the carbonyl alternative in Pd-catalyzed carbonylative homocoupling reaction of arylboronic acids.

MANAS MONDAL

Acknowledgement

I would like to extend my deepest gratitude and respect to Dr. Amit Saha, Assistant Professor, Organic Chemistry Section, Department of Chemistry, Jadavpur University, Jadavpur, Kolkata 700032, for introducing me to the fascinating field of “Synthetic Organic Chemistry”. Whose unwavering support and mentorship have been invaluable throughout my research journey. From our very first meeting, he provided insightful feedback that not only refined my research question but also inspired me to think critically about my work. His expertise in “Synthetic Organic Chemistry” has significantly enriched my understanding, and his encouragement during challenging moments was crucial in keeping me motivated. Being embowered always by his graceful behavior, I feel proud that I have enjoyed the full freedom while carrying out my research work with him.

I am grateful to Professor Rina Ghosh (Department of Chemistry, JU) and Dr. Mijanur Rahaman Molla (Department of Chemistry, Calcutta University) for their advice in different occasions.

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I proffer my heartiest appreciation to Mr. Subhashis Mandal for his tremendous help during my research period. I also express my thanks to Mr. Raju Biswas (Microanalyst, Dept. of Chemistry), Mr. Sumanta Jana, for their help in getting NMR spectra and HRMS spectra, Dr. Adwitiya Pal for recording GC-MS data and also Mr. Susanta Dinda for recording XRD data.

I am really proud to have some lab-mates like Dr. Soumya Dutta, Mr. Debabrata Patra, Mr. Sourav Mondal, Mr. SK. Shamim, Dr. Anirban Bera, Dr. Debasish Roy, Dr. Avrajit Manna, Dr. Ipsita Chakraborty, Mr. Pintu Das, Dr. Krishnamohan Das, Mr. Sayan, Dr. Arunavo Misra, Dr. Sudipta Mondal for their wholehearted co-operation during my research work.

I would like to express my deepest gratitude to my teacher, Mr. Prasanta Sardar. Their passion for teaching and dedication to their students have profoundly inspired me. He not only imparted knowledge but also instilled in me a love for learning that has shaped my academic journey. I am truly grateful for his unwavering support and guidance, which have been instrumental in helping me achieve my goals.

I would like to extend my heartfelt thanks to my friends, Dr. Avijit Sardar, Mr. Susovan Ghosh, Mr. Soumya Adak, Mr. Debabrata Patra and Mr. Dipanjay Ghosh. Your support, encouragement, and companionship have made this journey so much more enjoyable. Your ability to listen and provide insightful advice during challenging times has meant the world to me. I am grateful for our countless conversations and shared experiences, which have inspired me to keep pushing forward.

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I would like to express my heartfelt gratitude to my parents, Mr. Ajit Mondal and Mrs. Krishna Mondal. Their unwavering support, love, and encouragement have been the foundation of my success. They taught me the value of hard work and perseverance, inspiring me to pursue my dreams with determination. I am deeply thankful for their sacrifices and belief in my potential, which have motivated me throughout this journey. I would like to extend my heartfelt thanks to my elder brother, Mr. Tapas Mondal. His constant support, encouragement, and ability to make me laugh during stressful times have been invaluable. I am truly grateful for his presence in my life and he has provided the motivation throughout this journey.

I would like to express my sincere gratitude to my uncle, Mr. Ashim Kumar Banerjee and aunt, Mrs. Kakoli Banerjee. Their support and encouragement have been a source of strength for me throughout my journey. They have always been there to offer guidance and share their wisdom, helping me navigate challenges with confidence. I am truly thankful for their belief in me and the love they have shown.

At the moment of submitting my thesis, I express my deep respect and love to all of my family members and relatives for their blessing as well as inspiration for my Ph.D. work.

Finally, I must sincerely acknowledge NFSC for awarding me fellowship, which has enabled me to carry out my research work successfully.

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Chapter-I

Section-I

Synthetic Applications of N-Chalcogenoimides

1.1/a. Introduction

Organosulfur compounds have great importance in the field of organic synthesis, medicinal chemistry, and materials science. [1-5] Organic compounds containing different sulfur functional groups are used in the treatment of cancer, [6-8] inflammation, [9-11] human immunodeficiency virus, [12, 13] Alzheimer's and Parkinson's diseases etc. [14, 15] They are also used as pesticides, [16] insecticides, [17] enzyme modifiers [18] and therapeutic agent such as HIV-1, ACHE inhibitors. [19] Thiosulphonates show a wide range of biological activities. [20] As a result numerous effective techniques have been created for the synthesis of thiosulphonates. [21] Biologically important natural products such as the Lissoclinotoxin and Lissoclibadin family of natural products[22] contain diaryl sulfides (arylalkyl sulfides) moieties. Dibenzothiophene derivatives, a fused form of dithiothylsulfides, are widely utilized subunits found in many organic semiconductors[23] in material science. In organic syntheses, thiophosphate and selenophosphate serve as useful reaction intermediates.

Techniques of effective thiolation have created a lot of attention in the synthetic organic chemistry because of wide application of organosulphur compounds in biological, pharmacological, and material sciences. [24] Nucleophilic thiols react with different electrophiles mostly through addition and substitution techniques[25] to produce the thiolated compounds. But due to their offensive smell, high toxicity, and catalyst poisoning effect, certain eco-friendly substitutes of thiols have been discovered for preparing thiolated compounds. [26] However, due to the larger van der Waals radius and polarizability of the sulphur atom, [27] thiols can be easily converted to sulphur radicals or sulphur electrophiles as complementary strategies. These compounds can then react with radical acceptors (like alkenes and alkynes) or nucleophiles to access a variety of functional sulfurides. Industrial dichlorodiethyl sulphide, or mustard gas, was created as early as the 19th century by the umpolung of thiols for the creation of sulphur electrophiles. The first example of an electrophilic sulphur reagent[28] was created in 1870 by Professor Rathke when he developed trichloromethylthio chloride. It took several decades for the development of further electrophilic sulphur reagents to satisfy the various needs of materials and pharmaceutical chemistry. Electrophilic sulphur reagents are typically produced through the oxidation of thiols or disulfides, [29] followed by the replacement of the counter anion with various masks to stabilise the sulphur cations. A large number of researchers have noted that these scaffolds have promising potency in synthetic applications of sulfur-based compounds. Thiols, [30-32] disulfides, [33-36] sulfenyl halides, [37-39] sulfonamides, 40 sulfenate esters, [41,42] thiosulphonate and methyl(bismethylthio)sulfonium salts [43, 44] are frequently used as sulfenylating agent, which play significant role in the sulfenylation of organic molecules. In recent years, *N*-sulfenylimides {*N*-(alkylthio)succinimides and *N*-(arylthio)phthalimides} and *N*-selenoimides have widely been used in the field of organic synthesis as new substitute of sulfenylating agent. Compared to poisonous, unstable and odorous thiols, these molecules are more stable, easily available and harmless. Preparation of these compounds is very easy and proceed in one step. [45] Some sulfur containing pharmaceutically active molecule are shown in Figure 1.1.

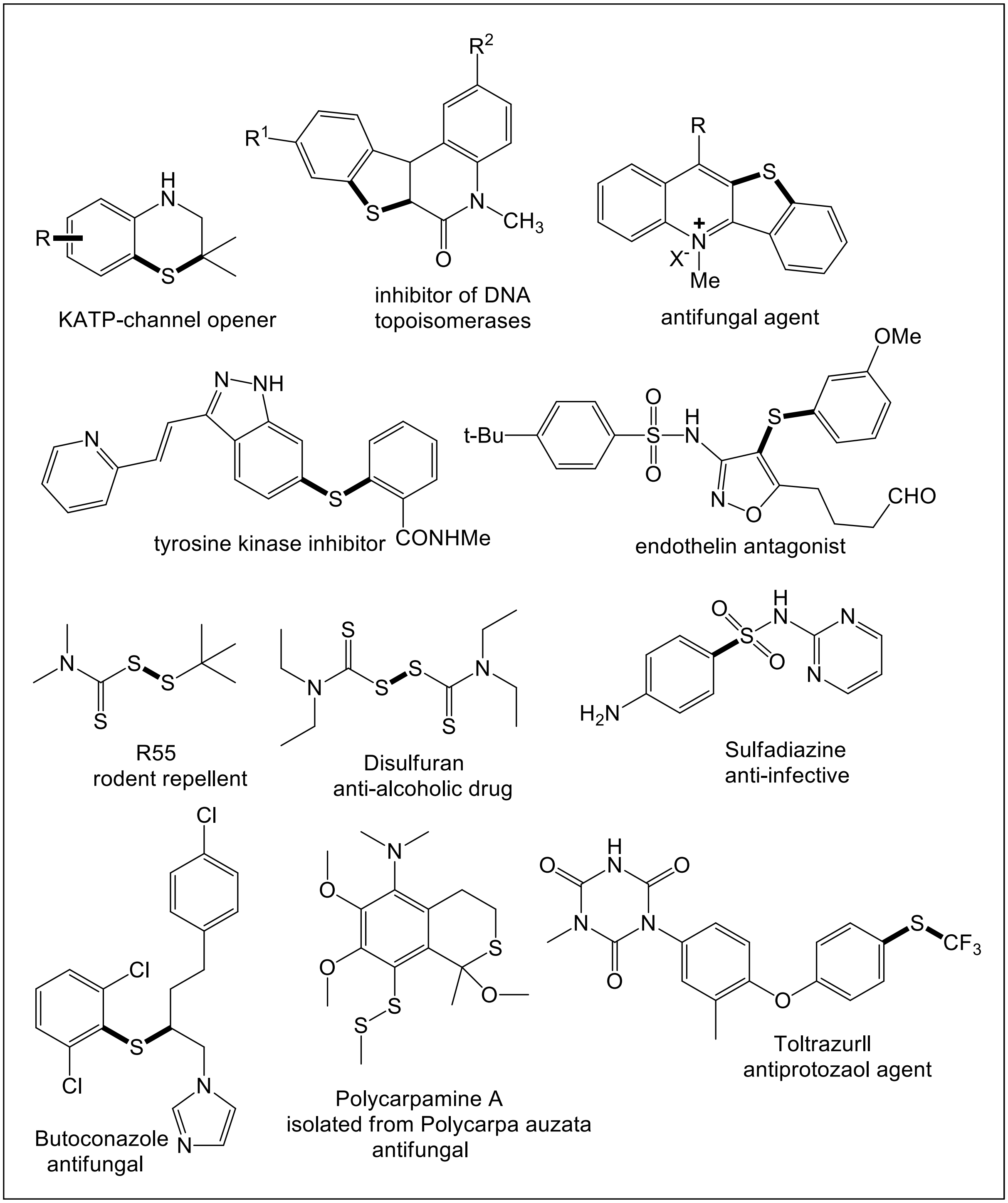


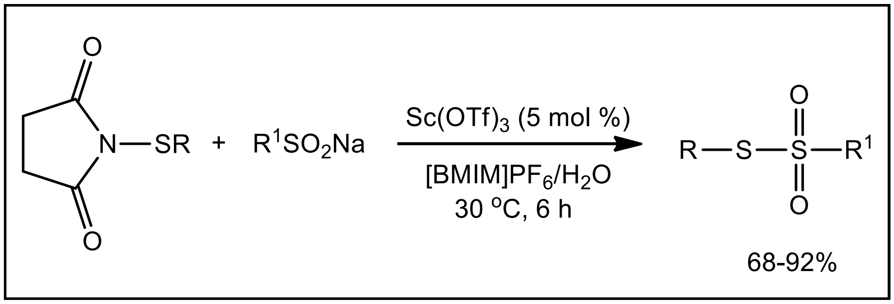
Figure: 1.1

1.1/b. Review

Strategies for (*C–S, N-S, P-S*) bonds production in the realm of organosulfur chemistry heavily depend on sulfenylating chemicals. When it comes to the synthesis of several organic compounds, *N*-sulfenylsuccinimide/phthalimide derivatives have demonstrated a high degree of electrophilic reactivity among other organosulfur precursors. Therefore, the synthetic application of *N*-sulfenylsuccinimide/phthalimide has gained considerable attention. This short review is mainly focused on various synthetic application of *N*-sulfenylsuccinimide/phthalimide.

(I) $Sc(OTf)_3$-catalyzed sulfenylation of sodium sulfinates with *N*-(organothio)succinimides in ionic liquid-water:

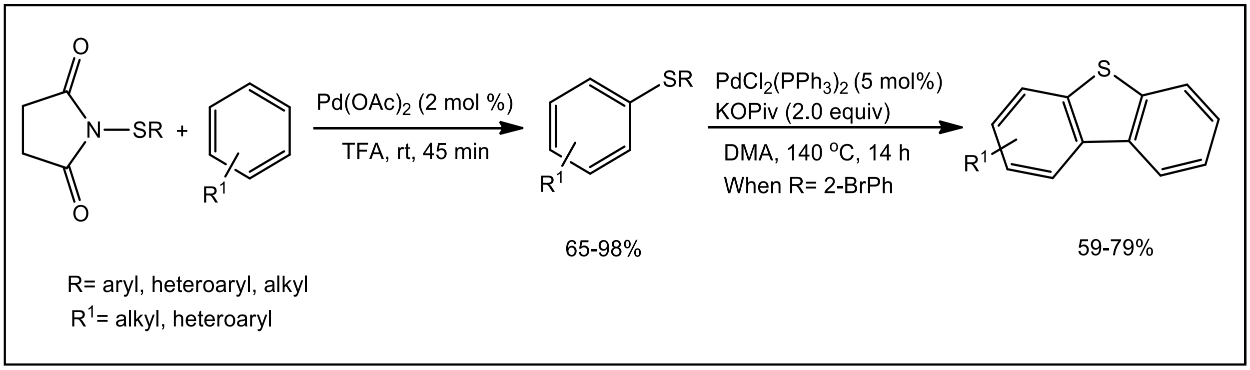
Utillising *N*-(Organothio)succinimides and ionic liquid as a cosolvent system, Gaigai Liang and his group[46] have created the $Sc(OTf)_3$-catalyzed sulfenylation of sodium sulfinates. Five runs of the catalytic system ($Sc(OTf)_3$/[BMIM]PF_6) were performed without discernible decrease in catalytic activity. In this catalytic system, the fluoro, chloro and bromo moieties found in arylsulfinates were all tolerated and offered a unique pathway to the corresponding products in moderate to good yields (Scheme 1.01).



Scheme 1.01

(II) Synthesis of Arylalkyl sulfides from unactivated arenes by using Pd-catalyst:

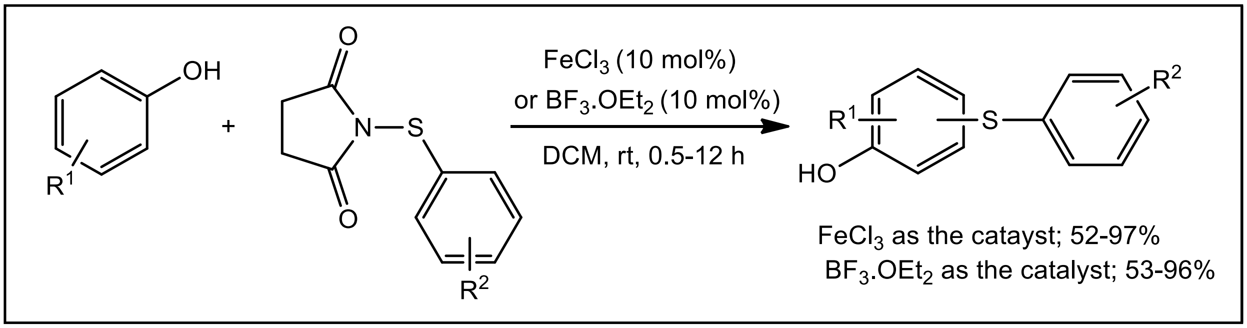
Perumal Saravanan and Pazhamalai Anbarasan[47] have revealed tha aryl(alkyl)thiolation of unactivated arenes C-H bond, which is directly catalyzed by palladium. Under mild circumstances, a variety of unsymmetrical diaryl or dialkyl sulfides can be synthesized from readily available arenes with acceptable yield (Scheme 1.02) and selectivity using the easily accessible succinimide based electrophilic reagent. Reaction conditions were also fine-tuned for the intramolecular arylation of diaryl sulphide C-H bonds by palladium catalyst. In this protocol, dibenzothiophene a crucial framework in material science was synthesized.



Scheme 1.02

(III) Environmentally friendly method for synthesis of diaryl sulfides through the C–H functionalization strategy:

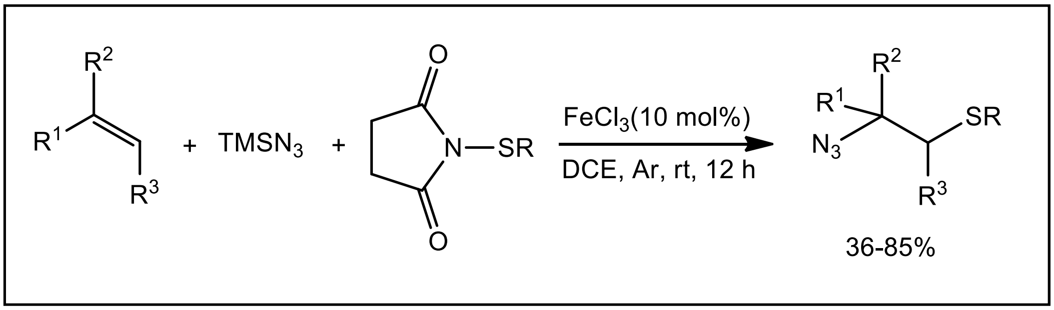
Hua Tian and his group[48] have developed a simple and efficient arylthiation of substituted phenols. The procedure employed affordable and ecologically friendly $FeCl_3$ or $BF_3.OEt_2$ as the catalyst and easily accessible 1-(substituted phenylthio)pyrrolidine-2,5-diones as the arylthiation reagents. Moreover, no ligands, chemicals, or air extrusion were needed. The reactions were effectively carried out at room temperature with a high degree of functional group tolerance.



Scheme 1.03

(IV) Iron catalyzed difunctionalizations of Alkene:

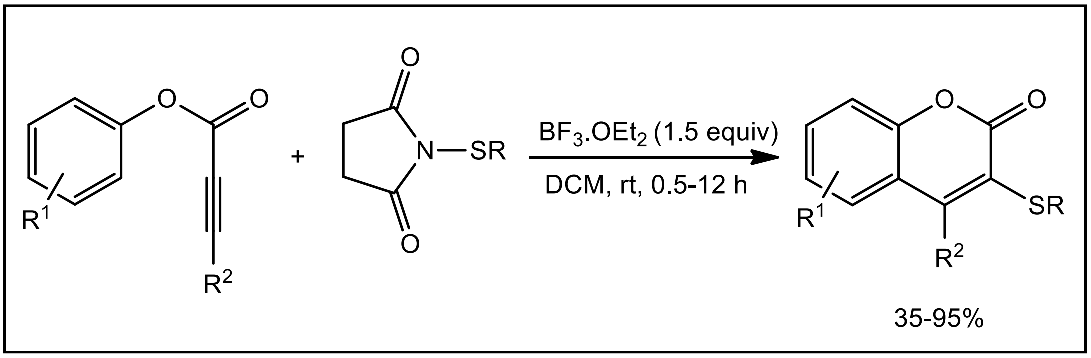
With widely available starting material 1-(alkylthio)pyrrolidine-2,5-diones and $TMSN_3$, Jipan Yu and his group[49] have developed a straightforward and easy method for azidoalkylthiation of alkene using iron catalysis. A variety of compounds having azide and sulphide units are produced in good yields by the gentle technique, with some functional group tolerance. Without the need for ligand and additive, iron chloride, which is affordable and environmentally safe, is utilised as a catalyst.



Scheme 1.04

(V) A simple and efficient metal-free sulfenylation/cyclization of aryl alkynoates:

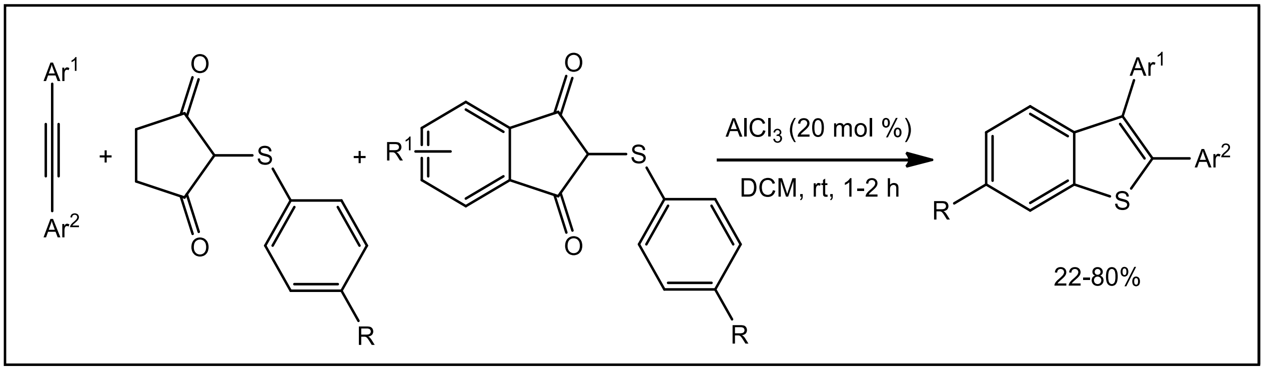
Wen-Chao Gao have created an easy method for producing 3-sulfenylated coumarins by cylizing aryl alkynoates electrophilically. *N*-sulfanylsuccinimides were used as electrophiles to cause the cyclization in the presence of $BF_3.Et_2O$ and introduce the sulfenyl group at the C3 position of coumarins. Under mild and metal-free conditions, a series of 3-sulfenylated coumarins were effectively synthesized (Scheme 1.05)[50] in a single step from the corresponding aryl alkynoates. This technique proved to be particularly helpful for the synthesis of coumarins containing sulphur due to its broad substrate scope, excellent reaction efficiency, and successful selective oxidation under environmentally acceptable conditions.



Scheme 1.05

(VI) $AlCl_3$-catalyzed intramolecular oxidative annulation of *N*-(arylthio)phthalimide derivatives with alkynes:

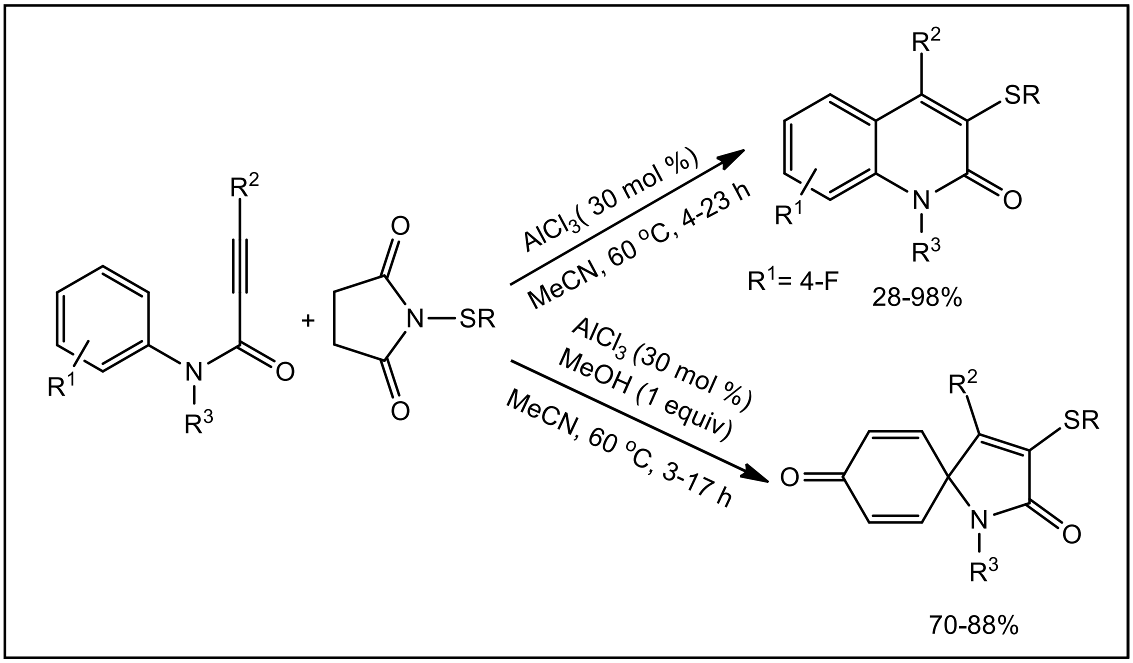
E. Ramesh and his group[51] have successfully shown how to obtain the difficult pi-conjugated 6-substituted 2,3-diarylbenzothophenes via a modified direct annulation technique of *N*-(arylthio)phthalimide derivatives with unactivated alkynes. In the presence of inexpensive $AlCl_3$, the reaction progressed effectively and was successfully carried out at ambient temperature. The procedure is reasonable since the reaction is scalable and permits the separation of the phthalimide moiety. To produce *β*-chloroalkenyl sulphides, the same process was performed with dialkylalkynes.



Scheme 1.06

(VII) Synthesis of both 3-sulfenyl quinolin-2-ones and azaspiro[4,5]trienones by using *N*-sulfanylsuccinimide as general sulfur source:

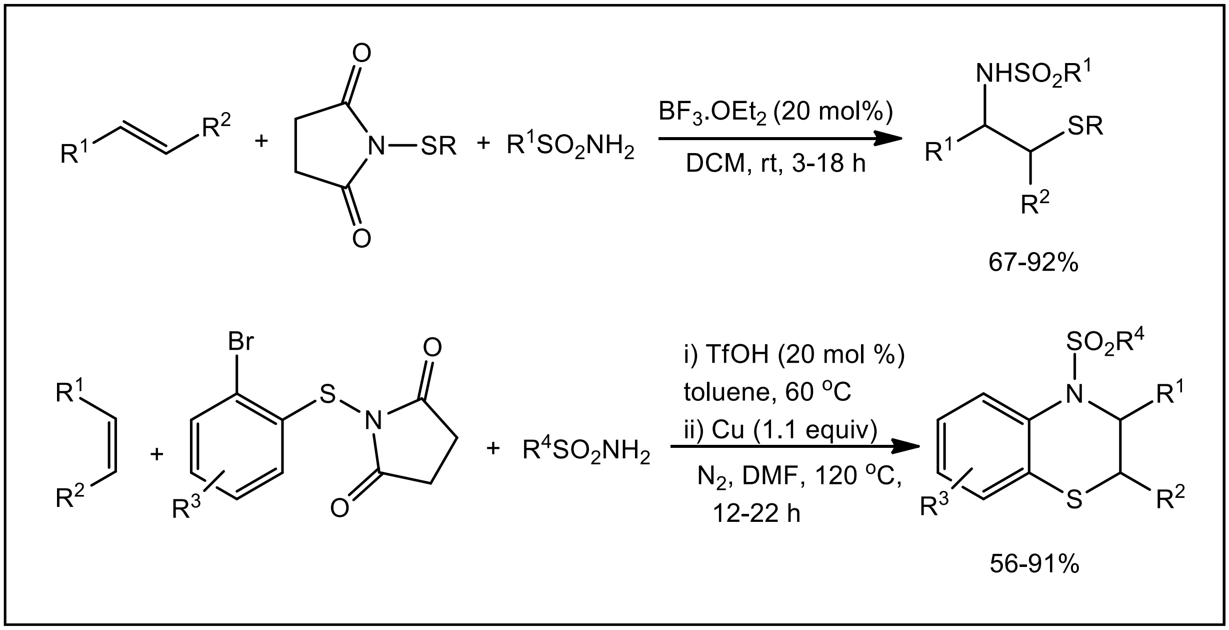
N-sulfenylsuccinimides, as a general sulphur reagent, produce switchable ortho/ipso-cyclization of *N*-arylpropynamides; the results are described. Only parafluoro *N*-arylpropynamides experience ipsocyclization in the presence of MeOH, yielding 3-sulfenyl azaspiro[4,5]triones. Benzothieno-[3,2-b]quinoline and [2,3-C]quinoline are two types of bioactive heterocycles that can be effectively and directly synthesized (Scheme 1.07)[52] from their corresponding sulfenylated derivatives.



Scheme 1.07

(VIII) An acid catalyzed intermolecular sulfenoamination reaction of alkene:

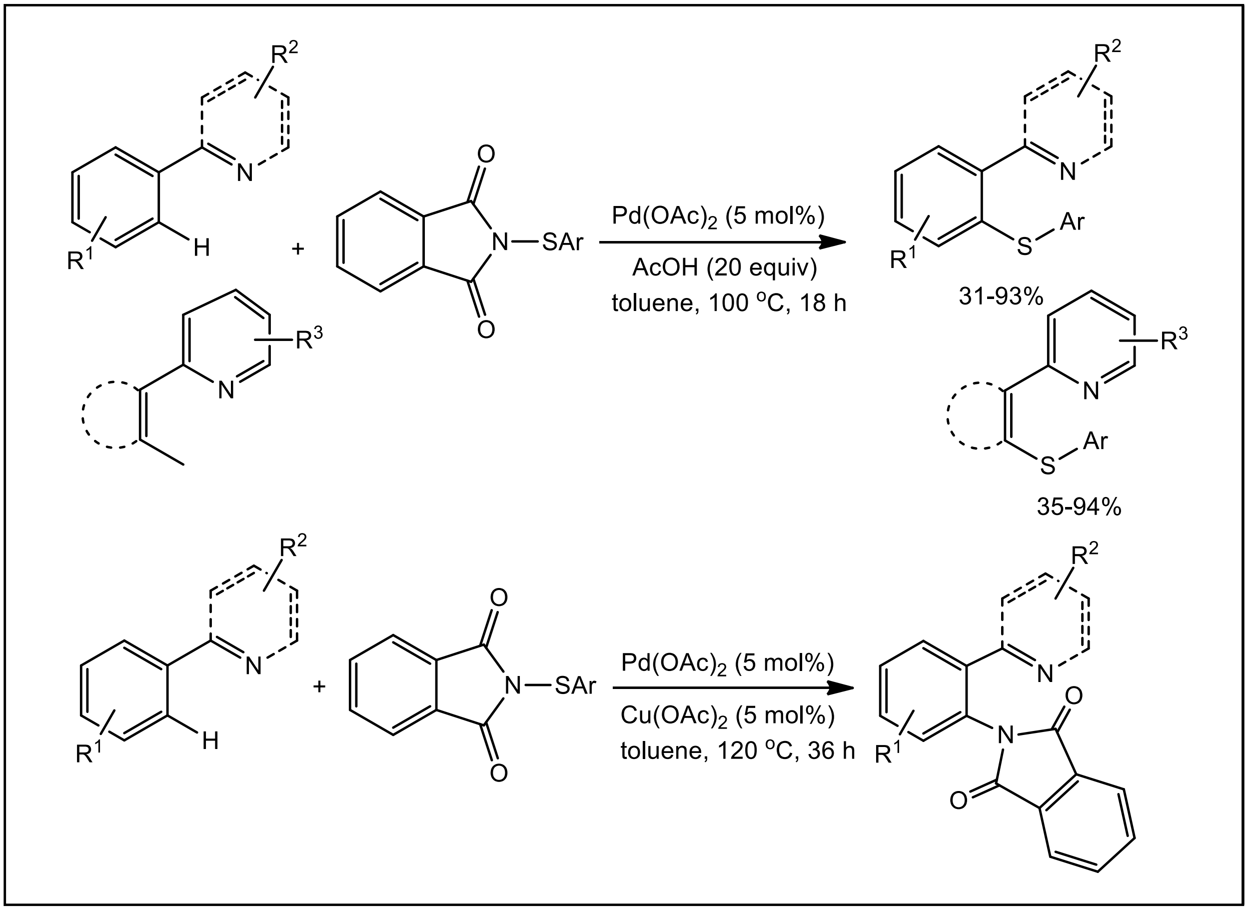
N-sulfanylsuccinimides serve as the sulphur supply and sulfonamides as the nitrogen source in an acid-catalyzed intermolecular sulfenoamination reaction of alkene. High regio and diastreoselectivity *β*-sulfonylamino sulphides can be synthesised in an easy and universal manner according to the approach. In a one-pot process, the proposed approach was combined with intramolecular C-N coupling to produce a range of dihydrobenzothiazine derivatives. The current approach is beneficial due to its mild reaction conditions, easy access to starting materials, good selectivity and efficiency of the reaction, wide range of substrates, and practical desulfonation of the products (Scheme 1.08). [53]



Scheme 1.08

(IX) An efficient and chemodivergent palladium-catalyzed thiolation (C-S) and imidation (C-N):

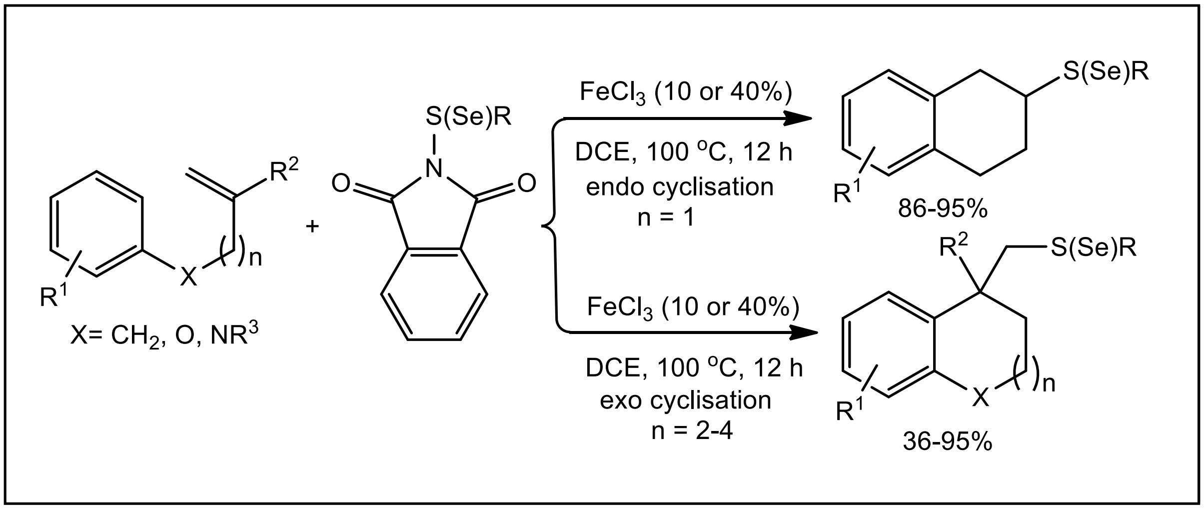
Using *N*-(arylthio)imides in conjunction with either bronsted acid or lewis acid, respectively, effective and chemodivergent thiolation (C-S*)* and imidation (C-N) of directing group assisted C-H bonds have been achieved. The presented techniques have several noteworthy advantages, such as high functional group tolerance, wide substrate scope, outstanding variety, and single-use N-S reagent usage. This protocol [54] was also effectively applied to C-H bond amidation.



Scheme 1.09

(X) FeCl$_3$ catalyzed regiodivergent carbosulfenylation of unactivated alkene:

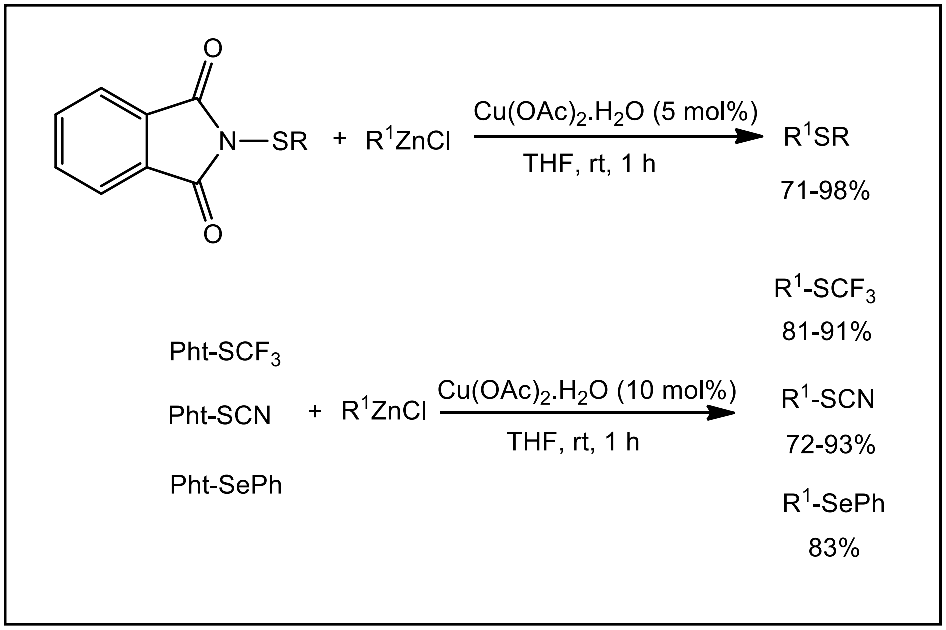
It has been designed to carbosulfenylate unactivated alkenes using electrophilic *N*-sulfenophthalimides in a regiodivergent manner catalysed by FeCl$_3$. This procedure offers a simple and effective way to access a variety of medium-sized rings, particularly strained 7- and 8-membered carborings that include an attached sulphur atom. The number of atoms in the chain connecting the arene and the alkene determines the endo/exo selectivity in the reaction. This protocol's (Scheme 1.10)[55] broad substrate breadth, high yields, and gram-scale synthesis demonstrated its practicality and usefulness. It is possible to use this methodology to carboselynate isolated alkenes.



Scheme 1.10

(XI) Cu-catalyzed thiolation of organozinc halide:

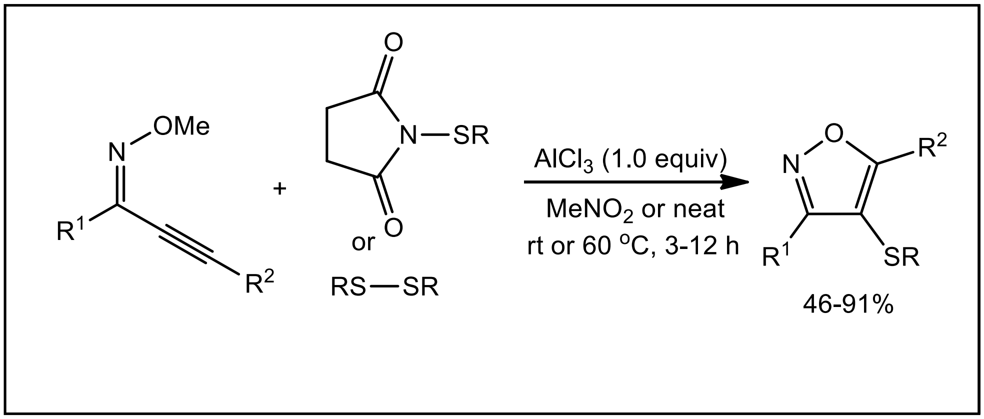
In the presence of $Cu(OAc)_2.H_2O$, *N*-thiophthalimides were used to thiolate heteroaryl, benzylic, and alkyl zinc halides at 25 °C for one hour to produce the corresponding polyfunctionalized thioether in good yields (Scheme 1.11). [56] This technique works with a wide range of reactive functional groups, such as nitro and aldehyde groups. The introduction of the SCF_3, SCN, and SePh groups was also done.



Scheme 1.11

(XII) AlCl$_3$ mediated electrophilic cyclization and sulfenylation of 2-alkyn-1-one-*O*-methyloximes:

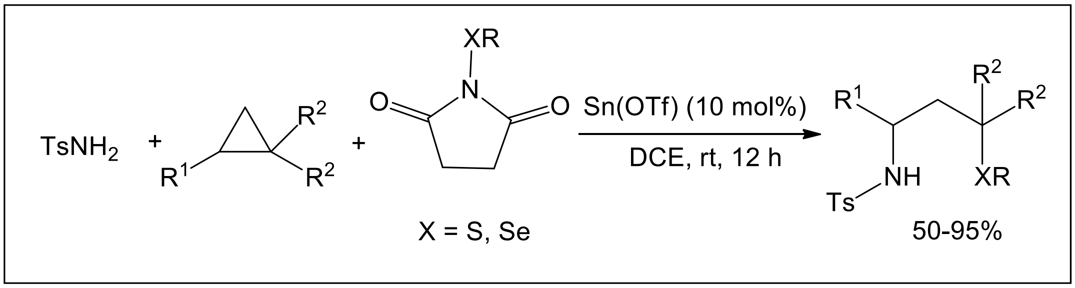
Using AlCl$_3$ as a medium for electrophilic cyclization and sulfenylation of 2-alkyn-1-one *O*-methyloximes, an effective synthesis process for 4-sulfenylisoxazoles has been established (Scheme 1.12). [57] Remarkably, 4-arylsufanyl isoxazoles are constructed using *N*-arylsulfanyl succinimides as electrophiles, while 4-alkylsufanyl isoxazoles are accessible using dialkyl disulfides as electrophiles.



Scheme 1.12

(XIII) 1,3-aminothiolation of 2-substituted cyclopropane:

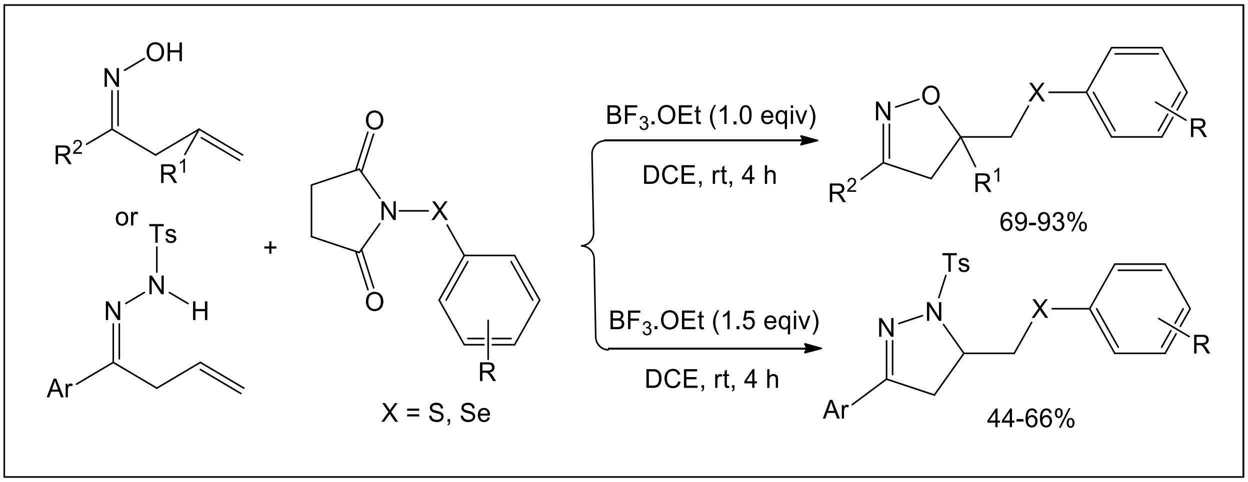
In this protocol, 1,3-aminothiolation and 1,3-aminoselenation were performed by ring opening of D-A cyclopropanes. In the presence of Sn(OTf)$_2$, tosyl amides as nucleophiles, the cyclopropane as a masked zwitterion and chalcogenosuccinimides as electrophilic components were used to produce to 1,3-aminothiolated and 1,3-aminoselenated product (Scheme 1.13). [58]



Scheme 1.13

(XIV) Cyclisation of *β,Υ*-unsaturated oximes and hydrazones with *N*-(arylthio/arylseleno)succinimides:

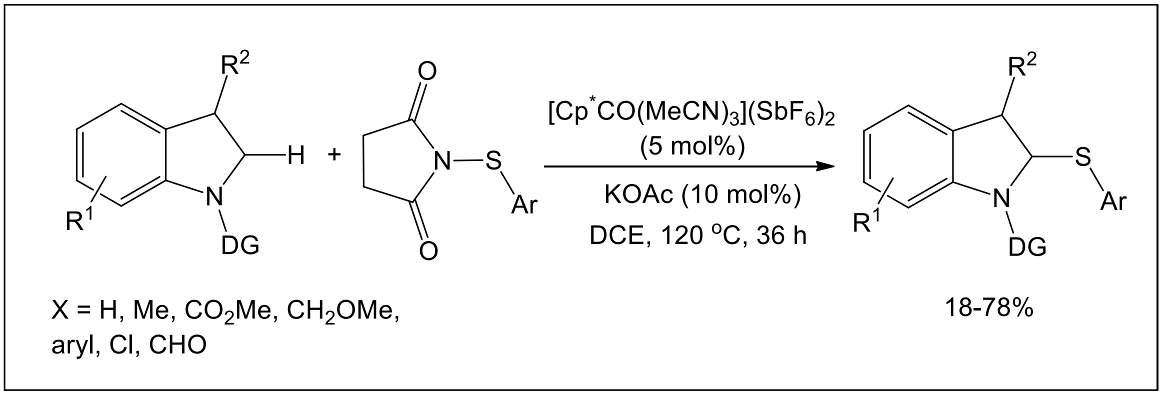
For the one-step synthesis of *N*-heterocycles, a highly effective BF$_3$.OEt$_2$-mediated cyclization of *β,Υ*-unsaturated oximes and tosylhydrazones with *N*-(arylthio/arylseleno)succinimides has been developed. At room temperature, this metal-free cyclization offers good to outstanding yields of isoxazoles and dihydropyrazoles (Scheme 1.14). [59]



Scheme 1.14

(XV) Cp*Co(III)-catalyzed C$_2$-thiolation and C2,C3- dithiolation of indole derivatives:

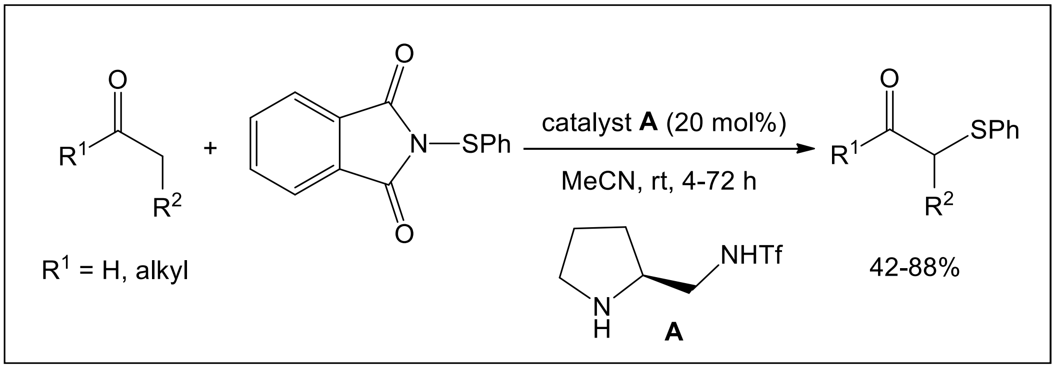
Using *N*-(aryl/alkylthio)succinimide as a thiolating reagent, a general and effective Cp*CoIII-catalyzed C2-thiolation and C2,C3-dithiolation of indole derivatives has been accomplished. Different type of thiolated compounds can be produced in good yields by using only catalytic amounts of additive without help of any external oxidant and tolerating different functional groups (Scheme 1.15). [60]



Scheme 1.15

(XVI) direct sulfenylation of aldehydes and ketones:

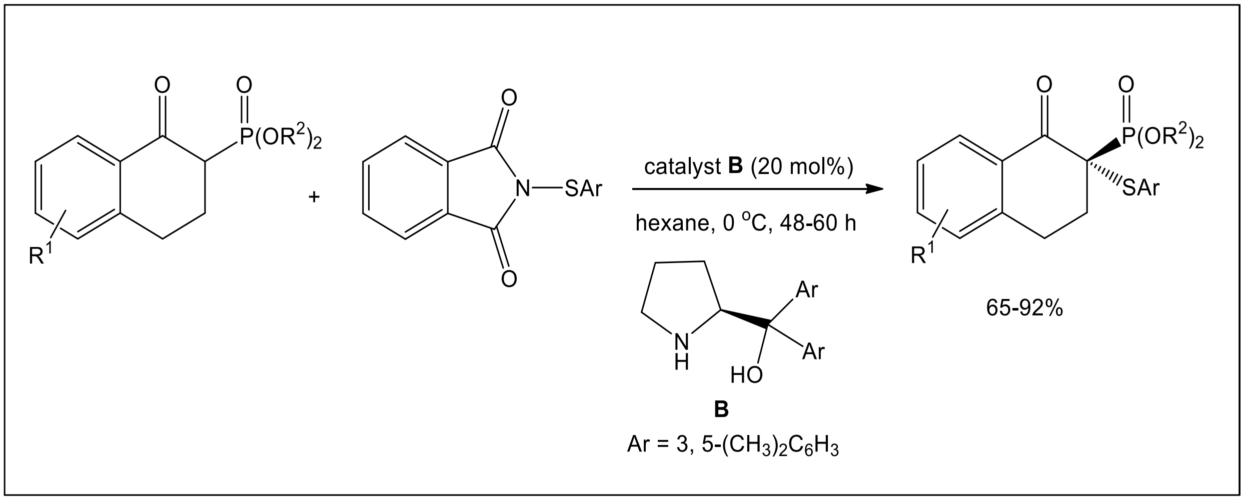
A novel pyrrolidine trifluoromethanesulfonamide organocatalyst has been discovered that catalyses the direct sulfenylation of aldehydes and ketones. This procedure is a mild and effective way to prepare α-phenylthio-ketones and –aldehydes (Scheme 1.16). [61]



Scheme 1.16

(XVII) Enantioselective sulfenylation of *β*-keto phosphonates catalyzed by *α,α*-diaryl-*L*-prolinols:

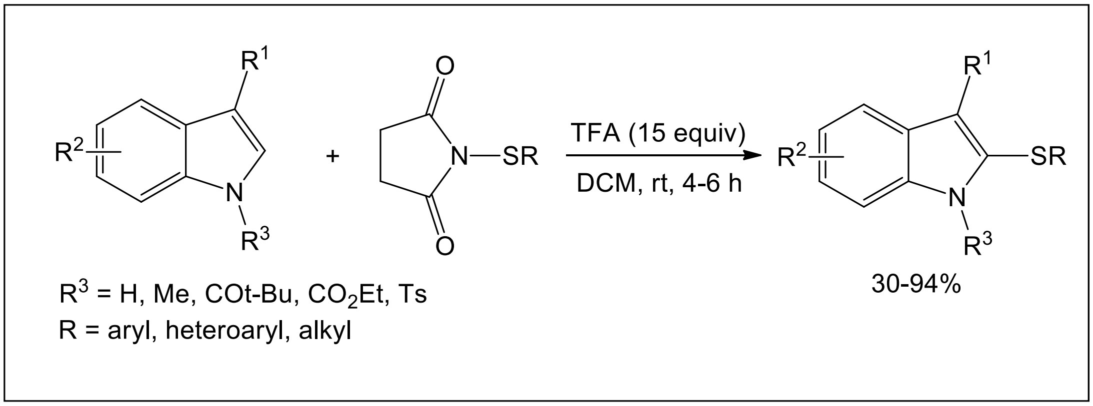
α,α-diaryl-*L*-prolinols have been found to be a highly effective and enantioselective sulfurylating agent for *β*-keto phosphonates. Under mild reaction conditions, the optically active a-sulfenylated *β*-keto phosphonates could be produced in good yields (up to 92%) and with outstanding enantioselectivities (up to 92% ee) (Scheme 1.17). [62]



Scheme 1.17

(XVIII) C–H sulfenylation at the C2 position of non-protected indoles:

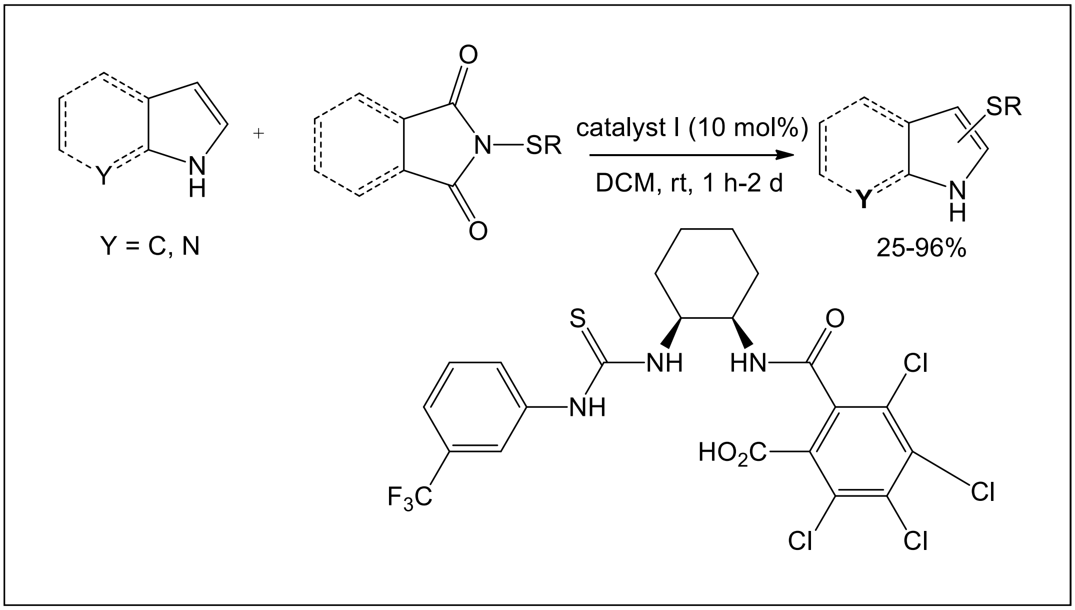
A straightforward, effective, and useful metal-free *C–H* sulfenylation procedure has been created for non-protected indole's C2 position. 2 -Thioindoles were produced at room temperature in the presence of TFA in moderate to high yields utilising stable and easily accessible *N*-(thio)succinimides (Scheme 1.18). [63]



Scheme 1.18

(XIX) sulfenylation of nitrogen containing heterocycles:

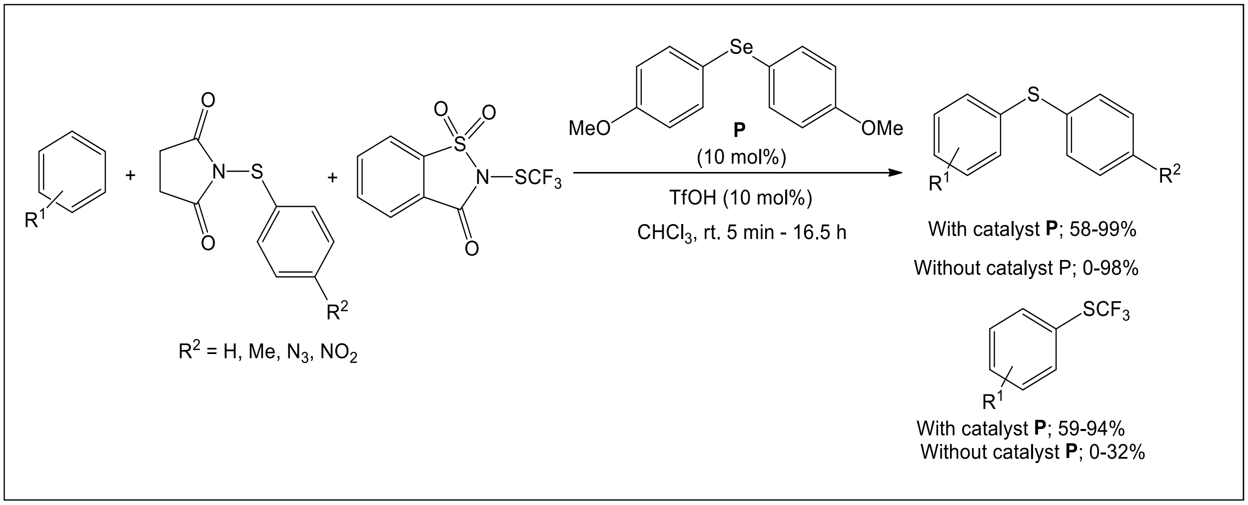
Christopher J. Nalbandian and his group[64] have created a mild catalytic system that can sulfenylate electron-rich heterocycles, such as peptides and tiny compounds that are important to biology. These mild conditions made it possible to include a variety of functionality into more complex heterocycles.



Scheme 1.19

(XX) Acid catalyzed aromatic sulfenylation:

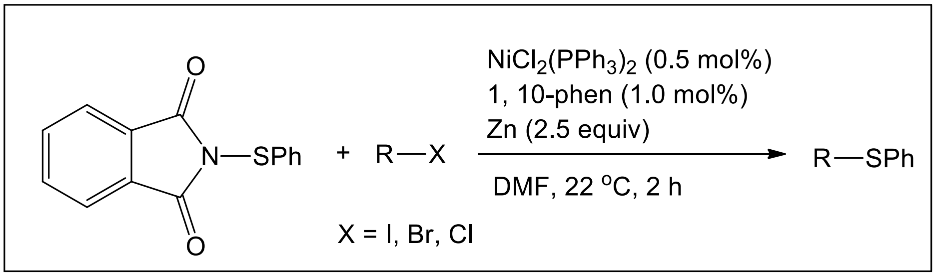
Christopher J. Nalbandian and his group[65] showed that the addition of sulfenyl groups rich in electrons happened in the lack of a Lewis base. kinetic analyses suggest that an autocatalytic process is involved. This approach demonstrated adaptability to a wide range of arenes and heterocycles and shown efficacy when used to the late-stage functionalization of small molecules with biological activity.



Scheme 1.20

(XXI) Nickel-catalyzed cross-electrophile coupling of organic halides with "thiol-free" synthesized *N*-thiophthalimide:

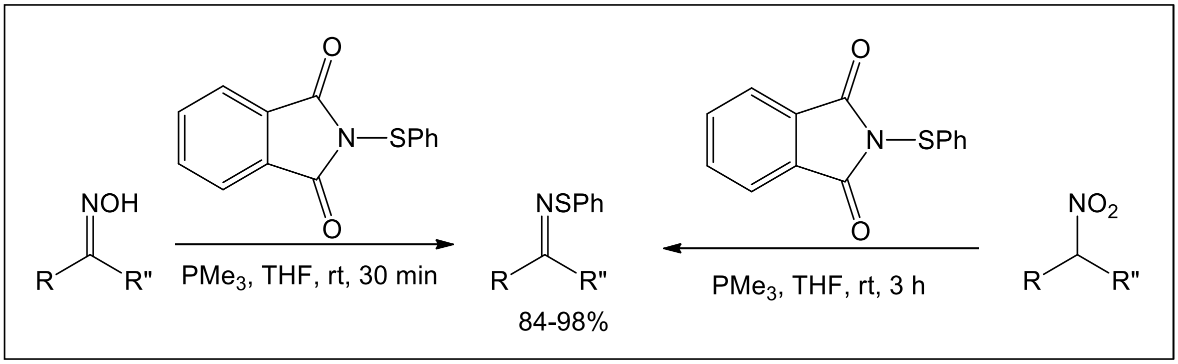
Yong Liu and his group[66] were reported that *N*-thiophthalimides, which are a potent electrophilic sulphur reagent and bench-stable and easily accessible, catalysed the reductive thiolation of organic halides with nickel. This non basic process is further demonstrated by the late-stage modification of biologically complex drug molecules, the downstream synthesis of related important compounds, and the sustainable use of the original starting materials. It can proceed well under extremely mild reactions supported by as little as 5.0 mol% loading of nickel catalyst. The remarkable reactivity of sulphur transfer reagents of the "N-S" type in the reductive production of C-S bonds was investigated in this protocol. Therefore, their approach offered a useful, simple, and modular framework for assembling a range of asymmetrical sulphides with high to exceptional yields.



Scheme 1.21

(XXII) Preparation of *N*-Phenylsulfenyl Ketimines:

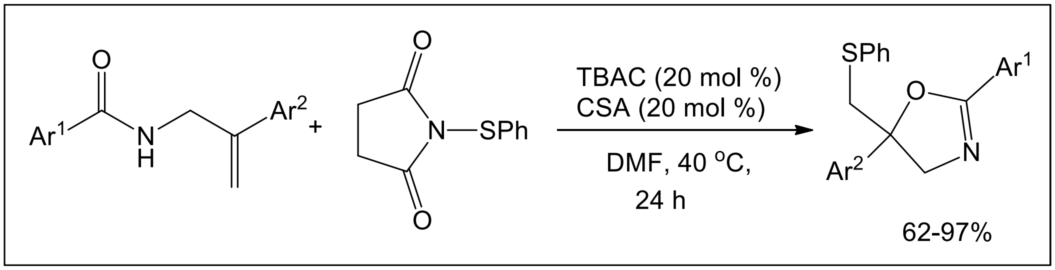
The very mild process developed to convert ketoximes and secondary nitro derivatives to *N*-arenesulfenyl ketotimines constitutes a new and efficient route to all these series of compounds because *N*-sulfenyl imines can be readily transformed to their *N*-sulfinyl imines, *N*-sulfonyl imines, and *N*-sulfonyl oxaziridines (Scheme 1.22). [67]



Scheme 1.22

(XXIII) Synthesis of oxazolines using electrophilic cyclization of allylic amide:

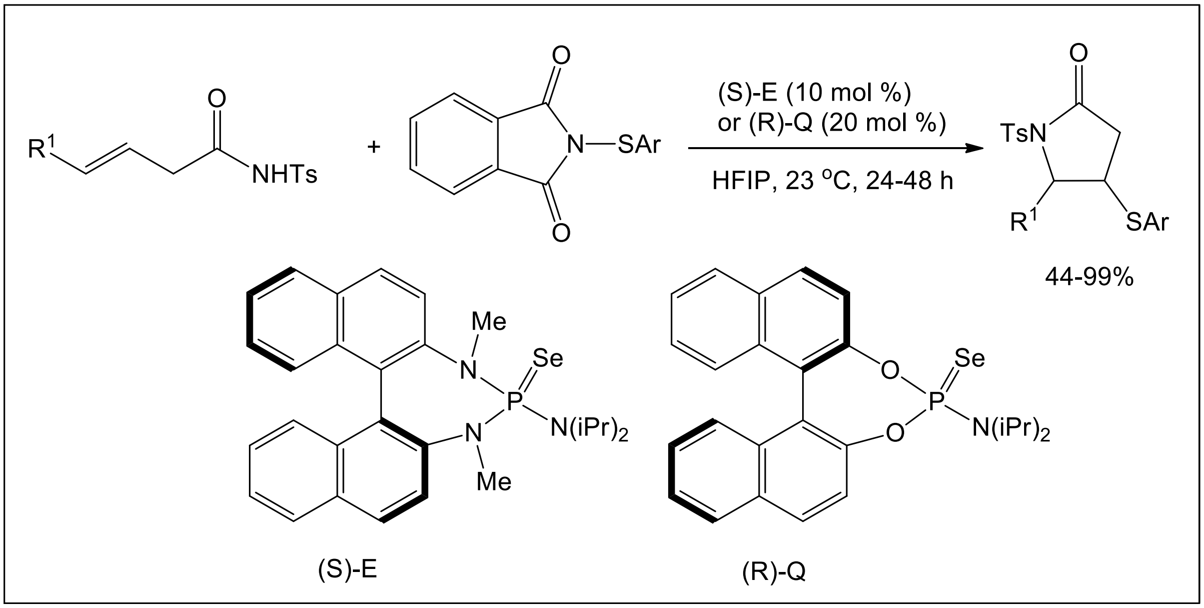
An effective and straightforward process for synthesising oxazolines is the electrophilic cyclization of allylic amide. Tetrabutylammonium chloride and Bronsted acid are combined, and the reaction proceeds under low heating conditions. With this technique, 5-[(arylsulfenyl)methyl]oxazoline derivatives could be synthesised in a gentle environment and showed good tolerance to a range of functional groups (Scheme 1.23). [68]



Scheme 1.23

(XXIV) Enantioselective Synthesis of *γ*-Lactams by Lewis Base Catalyzed Sulfenoamidation of Alkenes:

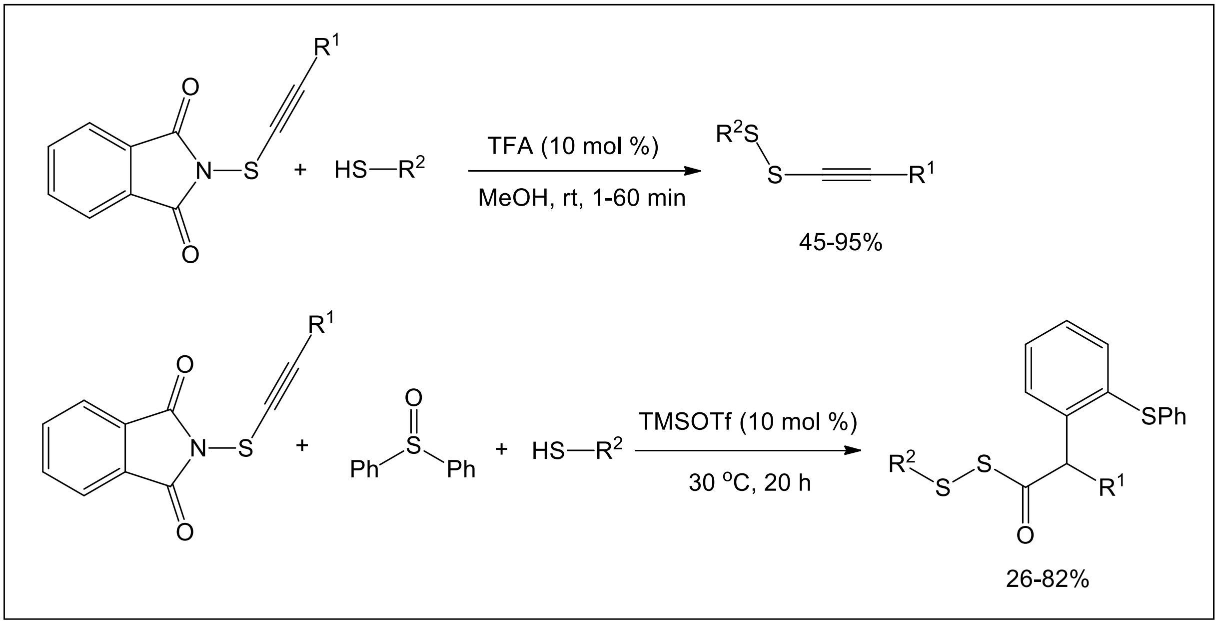
The *β,γ*-unsaturated sulfonyl carboxamides have been described to undergo an enantioselective Lewis base catalysed sulfenolactamization. Under mild circumstances, the reaction produces an enantiomerically enriched thiiranium ion, which is then captured with nitrogen in a diastereospecific manner to yield highly functionalized *γ*-lactams. A wider range of less nucleophilic alkenes as substrates have been made possible by the creation of a novel Lewis base catalyst (Scheme 1.24). [69]



Scheme 1.24

(XXV) Synthesis of alkynyl disulfides and acyl disulfides directly from thiols:

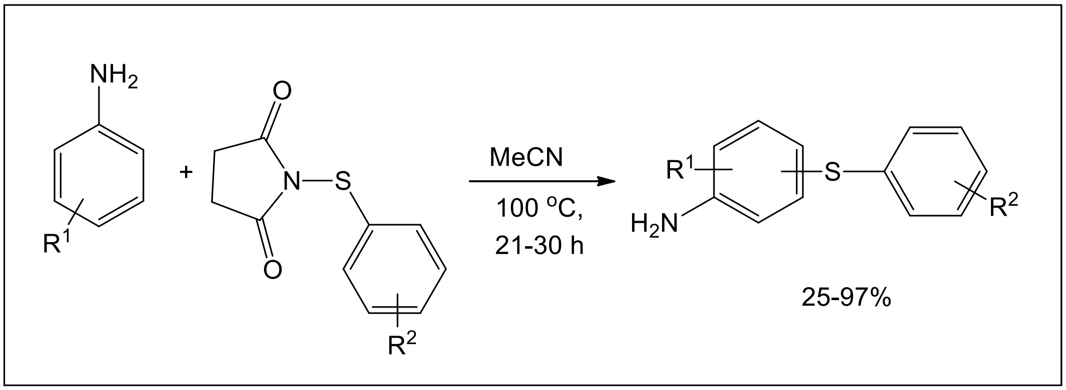
Yao-Nan Xue and his group[70] have created a brand-new technique that uses acid catalysis to create functionalized disulfides with alkynyl or acyl groups straight from easily accessible thiols. With *N*-alkynylthiophthalimides catalysed by TFA, alkynylthiolation of thiols was effectively and chemoselectively achieved. Moreover, acyl disulfides were produced by one-pot alkynylthiolation and hydrative oxyarylation under TMSOTf catalysis.



Scheme 1.25

(XXVI) Arylthiolation of Arylamine Derivatives:

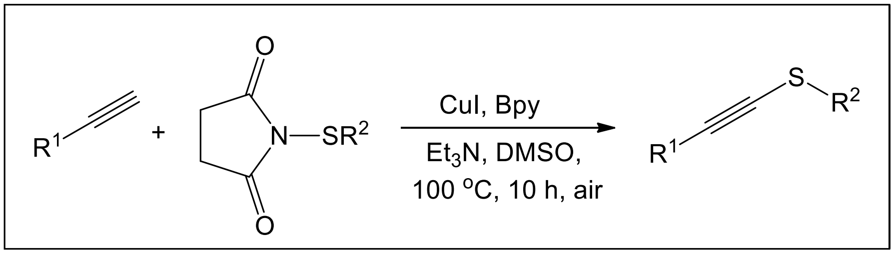
A straightforward and effective technique for arylthiolating arylamines has been created. The procedure avoids contamination from the transition metal catalysts in the target products by using (arylthio)pyrrolidine-2,5-diones as the arylthiolating reagents, acetonitrile as the solvent, and no catalyst or additive needed (Scheme 1.26). [71]



Scheme 1.26

(XXVII) Thiolation of Terminal Alkynes:

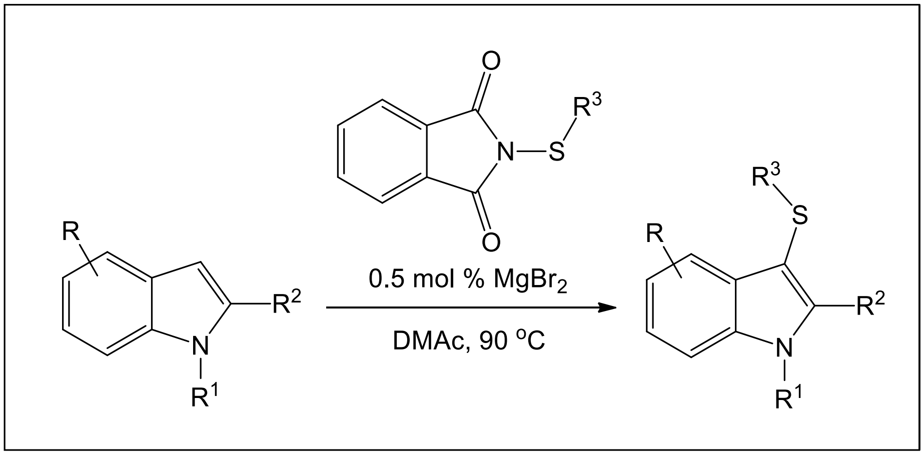
A productive method for thiolating terminal alkynes with *N*-thiosuccinimides was created, utilising copper as the catalyst. The reaction demonstrated an expanded substrate scope and produced various alkynyl sulfides in moderate to good yields. Further transformations and gram-scale synthesis validated the synthetic utility of this approach. Alkynylthiolation most likely included a Cu(I)/Cu(III) catalytic cycle, according to preliminary mechanistic investigations (Scheme 1.27). [72]



Scheme 1.27

(XXVIII) Sulfenylation reaction of indole to produce 3-thioindoles:

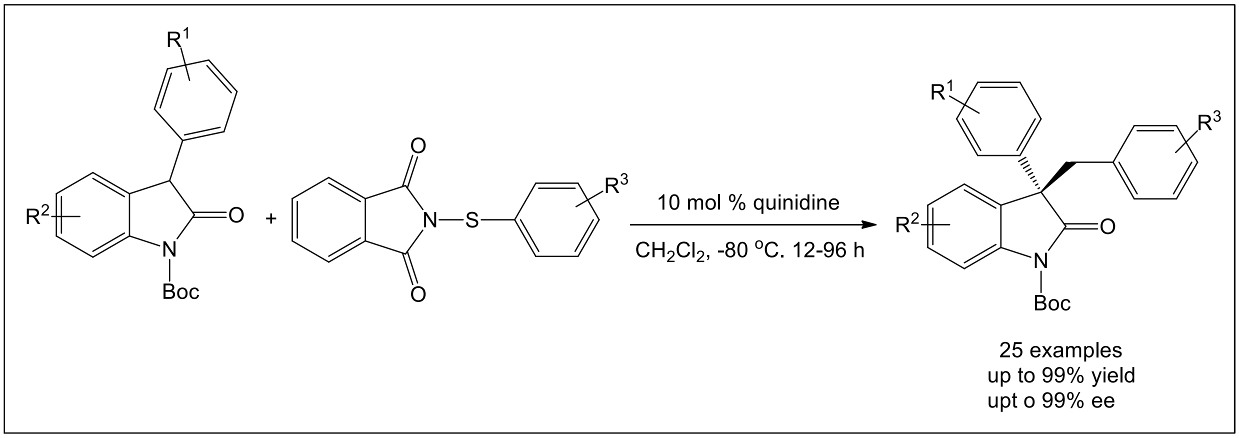
Matthew Tudge his group[73] reported on how different indoles react with *N*-thioalkyl- and *N*-thioarylphthalimides to form 3-thioindoles. Catalytic quantities of halide-containing salts are play important role in this reaction. Sulfenylated indoles are produced in good to outstanding yield from bench-stable, easily accessible starting materials by this extremely efficient process.



Scheme 1.28

(XXIX) Enantioselective sulfenylation of 3-substituted oxindoles:

Xin Li and his group[74] have described the reaction of sulfenylation of 3-substituted oxindoles using electrophilic sulphur reactants with Cinchona alkaloid type catalysts. Surprisingly, a variety of 3-aryl or 3-alkyl substituted oxindoles and substituted *N*-(arylthio)phthalimides underwent the reaction smoothly in the presence of a very simple and easy-to-make natural product called quinidine. This resulted in excellent yields (up to 99%) and enantioselectivities of chiral sulfur-containing oxindole compounds with a quaternary stereocenter (up to 99% ee).



Scheme 1.29

1.1/c. Conclusion

In response to the demand of synthesizing medicines, agrochemicals, and organic compounds containing sulfur, numerous thiolation techniques and thiolating reagents have been developed to introduce various sulfur functional groups into the organic molecules. Sulphur electrophiles are a valuable tool for the production of C-S bonds because of their odourless nature, stability, reactivity, and availability. Organic chemists still face difficulties when it comes to direct sulfenylation using more cost-effective, eco-friendly, and green sulfenylating chemicals, despite the fact that considerable efforts have been made to generate enantioselective C-S bonds. This need can be satisfied by new alternative sulfenylating reagents such as *N*-(sulfenyl)succinimides and phthalimides. Asymmetric sulfenylation reactions were catalyzed by chiral organocatalysts. Usually *N*-(sulfenyl)succinimides/phthalimides act as active electrophilic sulfur source in absence of metal catalyst, base, or additive. Therefore, *N*-(sulfenyl)succinimides/phthalimides have extensively been used in field of organic syntheses.

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Section-II

Formation of P-S/Se Bond in Neat Condition Using N-Chalcogenoimide as the Source of Electrophilic Sulfur/Selenium

1.2/a. Introduction

Thiophosphates are having widespread applications as pesticides, [1] insecticides, [2], enzyme modifiers[3] and therapeutic agents such as HIV-1, AChE inhibitors. [4] Thiophosphate and selenophosphate compounds also offer valuable reaction intermediates in organic syntheses. [5] Various methodologies have been developed to prepare this important class of compounds. However, in most of the cases the syntheses of thiophosphates[6,7,8b–e] and selenophosphates[8] were carried out using different organic solvents as the reaction media. Some 'Phosphorus' containing pharmaceutical active molecule are shown in Figure 1.2.

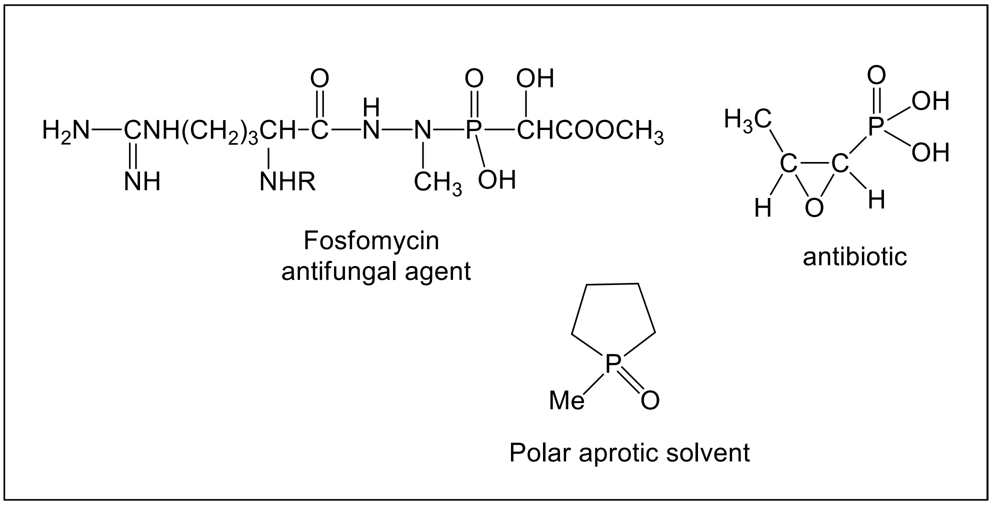
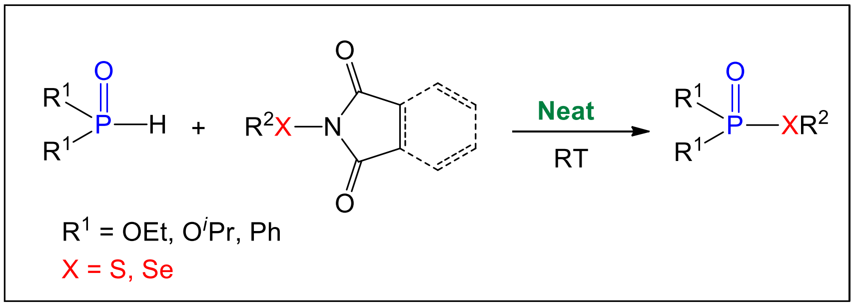


Figure: 1.2

To minimize the chemical hazards of a synthetic procedure, it is essential to reduce the usage of toxic organic solvents. Thus, it is now desirable to cultivate benign solvent free reaction conditions for synthesis of thiophosphate compounds. A microwave assisted solvent free reaction was reported by Kaboudin *et. al.* for the synthesis of thiophosphates using elemental sulfur and alkyl halides/tosylates[7d] in presence of tri- ethylamine and acidic alumina. Iodine catalyzed, aqueous H_2O_2 mediated thioarylation of various H-phosphonates were carried out by Wu and coworkers[7b] under solvent free condition using diaryl disulfide and excess of H-phosphonates. Zhan *et. al.* [6c] recently reported a neat reaction protocol to produce thiophosphates by the reaction of organic disulfides with silyl phosphites, however, a more generalized and benign protocol is needed to be developed for the synthesis of various phosphorothioate and phosphoroselenoate compounds. In our current study, we have accomplished the synthesis of phosphorothioate/selenoate com- pounds in neat reaction medium at room temperature under open aerial atmosphere. Earlier Saha and coworkers have used *N*-thioimides and *N*-selenoimide to prepare mixed disuldfide[9a] and diorganyl selenide[9b] compounds respectively. Here, we have employed *N*-thioimides and *N*-selenoimide for chalcogenylation of phosphites under neat reaction condition. Thiophosphate, thiophosphinate and selenophosphate compounds were prepared efficiently in an environmentally benign room temperature condition without using any metal, catalyst, base and solvent (scheme 1.30).



Scheme 1.30

1.2/b. Results and Discussion

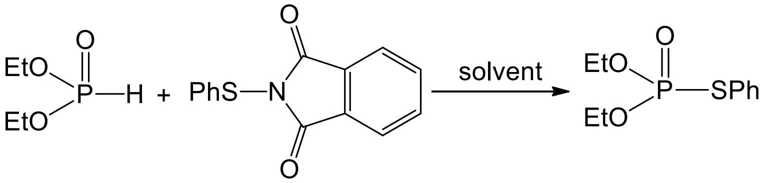
The reaction is easy to handle and proceeds under mild condition. A mixture of dialkyl phosphite and *N*-thioimide was stirred at room temperature in neat condition under aerial atmosphere until completion of the reaction (monitored by TLC).

In our first attempt, the thiophenylation of diethyl phosphite was tried using *N*-thiophenyl phthalimide in DMF solvent at 80 °C (entry 1, Table 1.1). However, the reaction was not very clean and desired product was formed along with some unidentified side products. The reaction in DMF solvent produced the thiophosphate product in improved yield (63%) at room temperature (RT) (entry 2, Table 1.1). The reaction did not proceed at all in water medium (entry 9, Table 1.1). Surprisingly, when the reaction was carried out in neat condition the desired thiophosphate was obtained in good yield (86%) within 40 min of time period at room temperature (entry 7, Table 1.1). Increasing the reaction time period beyond 40 min did not improve the yield of the product.

The optimized reaction condition was then explored to prepare a series of phosphorothioate/thiophosphinate compounds using *N*-thioimides (2) as the source of sulfur. Various *S*-aryl thiophosphates (3a - 3c, 3g, 3j, 3n, 3o) and *S*-aryl thiophosphinate (3k) were prepared using *N*-(phenylthio)phthalimide (entries 1 and 10, Table 1.2), *N*-(p-methoxyphenylthio)phthalimide (entries 2, 7 and 11, Table 1.2), *N*-(p-chlorophenylthio)phthalimide (entry 3, Table 1.2), *N*-(p-fluorophenylthio)phthalimide (entry 14, Table 1.2) and *N*-(p-t-butylphenylthio)phthalimide (entry 15, Table 1.2) in good yields under the neat reaction condition. Thioalkylations were also carried out under the similar reaction condition using *N*-(ethythio)succinimide (entry 4, Table 1.2), *N*-(octylthio)succinimide (entries 5, 8 and 12, Table 1.2) and *N*-(benzylmercapto)succinimide (entries 6, 9 and 13, Table 2) to produce desired *S*-alkyl thiophosphates (3d - 3f, 3h, 3i) and S-alkyl thiophosphinates (3l, 3m). Diethyl phosphite, diisopropyl phosphite and diphenylphosphine oxide were successfully employed in the synthesis of phosphorothioate/thiophosphinate compounds.

We also tried the synthesis of selenophosphate compounds under the similar reaction condition. Phenylselenylations of diethyl phosphite and diisopropyl phosphite were carried out efficiently using *N*-(phenylseleno)phthalimide under the solvent free condition (Scheme 1.31).

Table 1.1: Optimization of the reaction condition:

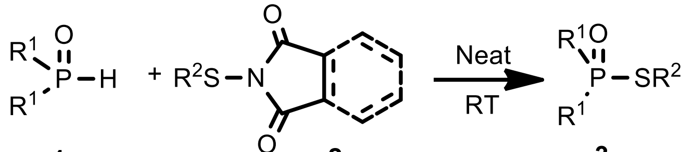


entry	solvent	temp. (°C)	time	yield (%)
1	DMF	80	4 h	48
2	DMF	RT	4 h	63
3	THF	RT	4 h	57
4	DMSO	RT	4 h	69
5	MeCN	RT	4 h	60
6	Toluene	RT	4 h	45
7	neat	RT	40 min	86
8	neat	RT	30 min	72
9	H_2O	RT	4 h	-

Reaction condition: A mixture of N-(phenylthio)phthalimide (1 mmol) and diethyl phosphite (1 mmol) in 4 mL of solvent was stirred in aerial atmosphere for certain time period. Yields reported are the isolated yields.

*N-(*phenylseleno)phthalimide plays the role of electrophilic selenium donor in presence of phosphorous nucleophiles like dialkyl phosphites at room temperature under the neat reaction condition in aerial atmosphere.

Table 1.2: Synthesis of various thiophosphate and thiophosphinate compounds



1 2 3

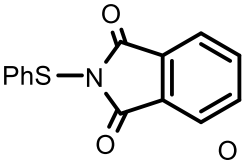
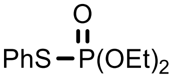
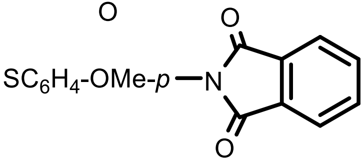
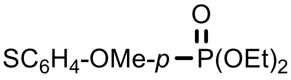
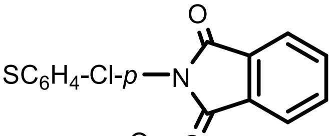
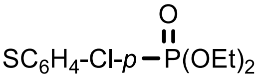
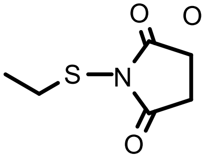
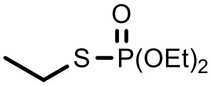
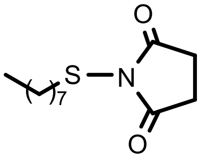
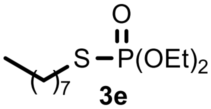
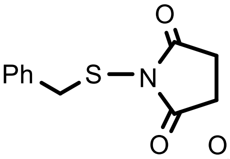
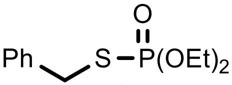
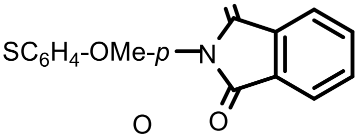
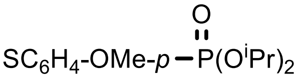
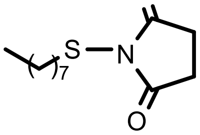
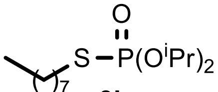
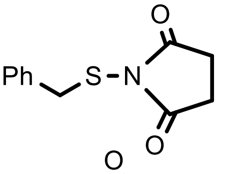
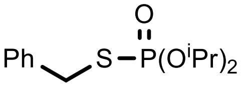
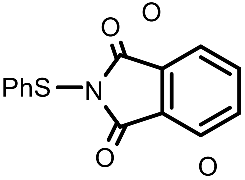
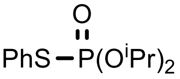
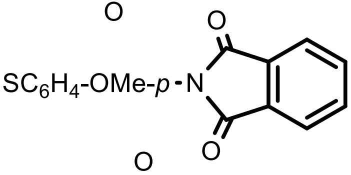
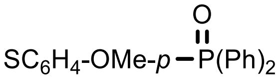
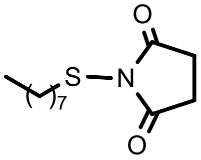
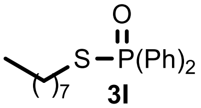
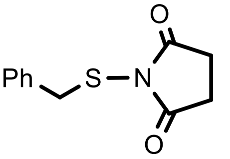
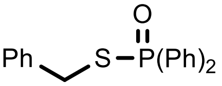
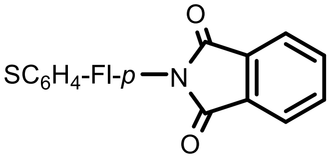
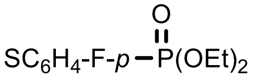
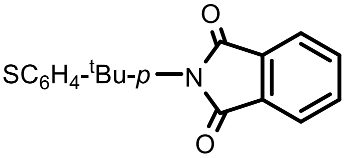
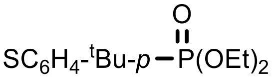
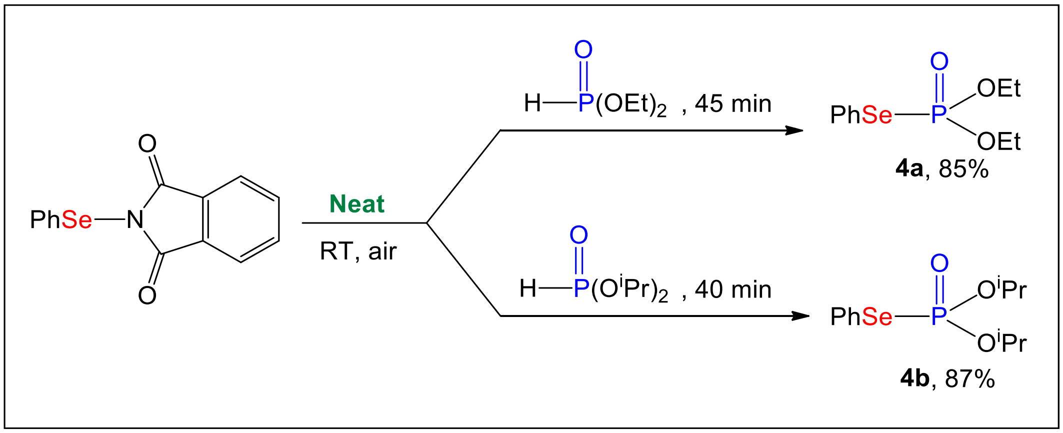
entry	R^1	*N*-thioimide	time (min)	product	yield (%)
1	OEt		40	 $PhS-\overset{O}{\overset{\|}{P}}(OEt)_2$ **3a**	86
2	OEt		90	 $SC_6H_4\text{-OMe-}p-\overset{O}{\overset{\|}{P}}(OEt)_2$ **3b**	87
3	OEt		90	 $SC_6H_4\text{-Cl-}p-\overset{O}{\overset{\|}{P}}(OEt)_2$ **3c**	84
4	OEt		60	 **3d**	89
5	OEt		60	 **3e**	90
6	OEt		60	 **3f**	91
7	O^iPr		90	 $SC_6H_4\text{-OMe-}p-\overset{O}{\overset{\|}{P}}(O^iPr)_2$ **3g**	85
8	O^iPr		60	 **3h**	91

Table 1.2: Continued.

entry	R^1	*N*-thioimide	time (min)	product	yield (%)
9	O^iPr		60	 **3i**	89
10	O^iPr		40	 $PhS-P(O)(O^iPr)_2$ **3j**	86
11	Ph		90	 $SC_6H_4\text{-}OMe\text{-}p-P(O)(Ph)_2$ **3k**	83
12	Ph		60	 **3l**	88
13	Ph		60	 **3m**	90
14	OEt		90	 $SC_6H_4\text{-}F\text{-}p-P(O)(OEt)_2$ **3n**	90
15	OEt		90	 $SC_6H_4\text{-}{}^tBu\text{-}p-P(O)(OEt)_2$ **3o**	89

*Reaction condition: A mixture of N-thioimide (**2**) (1 mmol) and $R^1{}_2P(O)H$ (**1**) (1 mmol) was stirred at room temperature in aerial atmosphere for certain time period. Yields reported are the isolated yields.*



Scheme 1.31: Phenylselenylation of dialkyl phosphite

1.2/c. Conclusion

In conclusion, this is a convenient and general method to prepare structurally variable thiophosphate/thiophosphinate compounds. The neat reaction protocol also works satisfactorily for synthesis of selenophosphates. All the reactions were performed at room temperature under solvent free condition without using any catalyst, base or additive. The reactions do not require any sophisticated inert reaction set up. Thus, the described method offers an environmentally friendly route to prepare phosphorothioate/thiophosphinate and phosphoroselenoate compounds.

1.2/d. Experimental Section

General Information:

All commercial reagents were used without additional purification. TLC was checked on silica gel plates (Merck silica gel, f_{24}). Silica gel 60-120 mesh has been used in all column chromatography. ^{1}H spectra were recorded using Brucker Spectrometer at 300, 400, 500 MHz frequency and ^{13}C spectra were recorded at 75, 100, 125 MHz frequency in $CDCl_3$ solvent medium and TMS is used as internal standard. Chemical shifts were reported in ppm referenced to 0.00 ppm for TMS. All coupling constants (J values) were reported in Hz. HRMS were measured in methanol solvent on a Waters Micromass Q-tofMicromass spectrometer.

General Experimental Procedure for the Synthesis of *N*-thioimides

Synthesis of *N*-(arylthio)phthalimides:

Phthalimide (5.87 mmol, 1 equiv) and aryl thiol (6.16 mmol, 1.05 equiv) were added in a mixture of acetonitrile (2.6 mL) and pyridine (4.5 mL). The reaction mixture was allowed to stir at 80 ^{o}C for 5 min. Then the reaction mixture was cooled to 0 ^{o}C. Bromine (6.46 mmol, 1.1 equiv) in acetonitrile (3 mL) was added drop wise to the reaction mixture at 0 ^{o}C and was stirred for 1 hour at that temperature. After completion of the reaction, 12 mL of H_2O was added dropwise into the reaction mixture. Then it was filtered, dried under suction and recrystallized from methanol.

Synthesis of *N*-(alkylthio)succinamide:

Thiol (5.07 mmol, 1 equiv) was added drop wise to a solution of *N*-chlorosuccinimide(5.33 mmol, 1.05 equiv) in DCM (25 mL) at 0 ^{o}C and stirred for 20 min. The color of the solution changed to greenish yellow and became cloudy. A solution of triethylamine (5.58 mmol, 1.10 equiv) in DCM (3.5 mL) was added drop wise to the reaction mixture and it was stirred for 2.5 hour. Upon completion of the reaction (monitored by TLC), the reaction mixture was washed with saturated aqueous NaCl solution for 4 times. The organic layer was dried over anhydrous $NaSO_4$ and evaporated to give the crude product as colorless oil. The crude product was purified by column chromatography.

General Experimental Procedure for the Synthesis of Thiophosphates/Thiophosphinates (3a-3o):

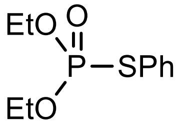
N-thioimide (**2**) (1 mmol, 1 equiv) and -P(O)H (**1**) compound (1 mmol, 1 equiv) were mixed together and allowed to stir at room temperature for a certain time period (as mentioned in Table 2). After completion of the reaction (checked by TLC), the resulting reaction mixture was diluted with EtOAc (15 mL) and washed with cold 15% aq. NaOH (4 x 15 mL) solution followed by washing with water (2 x 15 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was purified by column chromatography using ethyl acetate / hexane (5:95 to 15:85) solvent mixture.

General Experimental Procedure for the Synthesis of Selenophosphates (4a and 4b):

N-(phenylseleno)phthalimide (1 mmol, 1 equiv) and dialkylphosphite (1 mmol, 1 equiv) were mixed together and allowed to stir at room temperature for a certain time period (as mentioned in Scheme 1.31). After completion of the reaction (checked by TLC), the resulting reaction mixture was diluted with EtOAc (15 mL) and washed with cold 15% aq. NaOH (4 x 15 mL) solution followed by washing with water (2 x 15 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was purified by column chromatography using ethyl acetate / hexane (10:95 to 15:85) solvent mixture.

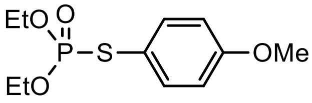
Characterization data of synthesized Compounds

O,O-diethyl S-phenyl phosphorothioate (**3a**, Table 1.2)



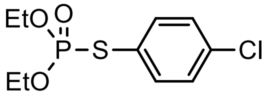
Light yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.56 – 7.54 (m, 2H), 7.33 – 7.32 (m, 3H), 4.23 – 4.11 (m, 4H), 1.28 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$, ppm) δ: 134.55 (d, J=5.1 Hz), 129.33 (d, J=1.7 Hz), 129.0 (d, J=2.3 Hz), 126.53 (d, J=7.3 Hz), 64.10 (d, J=6.3 Hz), 15.97 (d, J=7.1 Hz).

O,O-diethyl S-(4-methoxyphenyl) phosphorothioate (**3b**, Table 1.2)



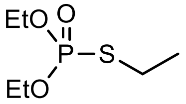
Light yellow oil, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.43 (d, J= 7.8 Hz, 2H), 6.83 (d, J=8.4 Hz, 2H), 4.19 –4.08 (m, 4H), 3.75 (s, 3H), 1.29 – 1.21 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$, ppm) δ: 160.53, 136.34 (d, J = 4.6 Hz), 116.54 (d, J = 7.4 Hz), 114.99, 64.0 (d, J = 6.3 Hz), 55.34, 16.02 (d, J = 7.1 Hz).

*S-(*4-chlorophenyl) O,O-diethyl phosphorothioate (**3c**, Table 1.2)



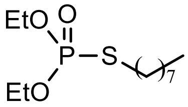
Colorless oil, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.49 (d, J = 8 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.24 – 4.13 (m, 4H), 1.31 (t, J = 1.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ: 135.89 (d, J = 5 Hz), 135.64 (d, J = 4 Hz), 129.67 (d, J = 2 Hz), 125.28 (d, J = 7 Hz), 64.41 (d, J = 6 Hz), 16.14 (d, J = 7 Hz).

O,O,S-triethylphosphorothioate (**3d**, Table 1.2)



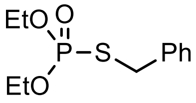
Colorless oil, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 4.20 – 4.05 (m, 4H), 2.86 – 2.77 (m, 2H), 1.35 – 1.30 (m, 9H); ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ: 63.48 (d, J=6Hz), 25.43(d, J=4Hz), 16.42(d, J = 6 Hz), 16.11 (d, J = 7 Hz), HRMS (ESI$^+$) Calcd m/z $C_6H_{15}O_3PS$ (M + Na)$^+$: 221.049, found : 221.081.

O,O-diethyl *S*-octylphosphorothioate (**3e**, Table 1.2)



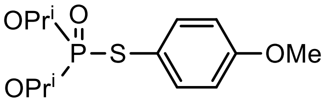
Colorless oil, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 4.20 – 4.09 (m, 4H), 2.84 – 2.77 (m, 2H), 1.68 – 1.62 (m, 2H), 1.36 – 1.25 (m, 16H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C (100 MHz, CDCl$_3$, ppm) δ: 63.47 (d, J = 6 Hz), 31.81, 31.00 (d, J = 4 Hz), 30.85 (d, J = 6 Hz), 29.17, 29.04, 28.62, 22.67, 16.13 (d, J = 7 Hz), 14.12.

S-benzyl *O,O*-diethyl phosphorothioate (**3f**, Table 1.2)



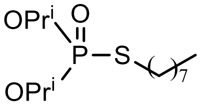
Colorless oil, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.31 – 7.19 (m, 5H), 4.09 – 3.93 (m, 6H), 1.22 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$, ppm) δ: 137.58 (d, J = 5.3 Hz), 128.96, 128.71, 127.68, 63.59 (d, J = 5.3 Hz), 35.03 (d, J = 3.8 Hz), 16.01 (d, J = 7.5 Hz).

S-4-methoxyphenyl *O,O*-diisopropylphosphorothioate (**3g,** Table 1.2)



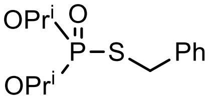
Yellow oil, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.49 (d, J = 8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.77 – 4.69 (m, 2H), 3.78 (s, 3H), 1.30 (d, J = 6 Hz, 6H), 1.25 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ: 160.50, 136.26 (d, J = 5 Hz), 117.57, 114.95, 73.24(d, J = 6 Hz), 55.43, 23.94(d, J = 3 Hz), 23.66(d, J = 5 Hz), HRMS (ESI$^+$) Calcd m/z $C_{13}H_{21}O_4PS$ (M + Na)$^+$: 327.0796, found : 327.0620.

S-octyl *O,O*-diisopropylphosphorothioate (**3h**, Table 1.2)



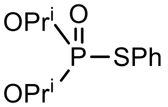
Colorless oil, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 4.75 – 4.67 (m, 2H), 2.84 – 2.77 (m, 2H), 1.70 – 1.62 (m, 2H), 1.35 – 1.25 (m, 22H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ: 72.51 (d, J = 6 Hz), 31.86, 31.05 (d, J = 4 Hz), 30.69 (d, J = 7 Hz), 29.08, 28.97, 28.60, 23.86 (d, J = 4 Hz), 23.61 (d, J = 6 Hz), 22.59, 14.15.

S-benzyl *O,O*-diisopropylphosphorothioate (**3i**, Table 1.2)



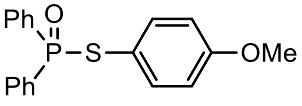
Colorless oil, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.33 – 7.19 (m, 5H), 4.69 – 4.61 (m, 2H), 4.02 (d, J = 12 Hz, 2H), 1.29 (d, J = 6 Hz, 6H), 1.24 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ: 137.52, 129.0, 128.70, 127.61, 72,74 (d, J = 6 Hz), 35.25, 23.88 (d, J = 4 Hz), 23.59 (d, J = 5 Hz).

S-phenyl *O,O*-diisopropylphosphorothioate (**3j,** Table 1.2)



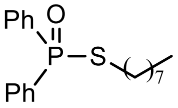
Colorless oil, ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ: 7.58 – 7.56 (m, 2H), 7.31 – 7.30 (m, 3H), 4.78 – 4.71 (m, 2H), 1.30 (d, J = 6.5 Hz, 6H), 1.23 (d, J = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$, ppm) δ: 1134.32 (d, J = 5.3 Hz), 129.24 (d, J = 2.3 Hz), 128.74 (d, J = 2.3 Hz), 123.45, 73.45 (d, J = 6.8 Hz), 23.90 (d, J = 3.8 Hz), 23.55(d, J = 5.3 Hz).

S-4-methoxyphenyl diphenylphosphinothioate (**3k**, Table 1.2)



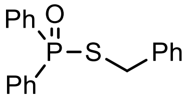
White solid, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.84 – 7.79 (m, 4H), 7.50 – 7.46 (m, 2H), 7.44 – 7.39 (m, 4H), 7.32 – 7.29 (m, 2H), 6.70 (d, J = 8.8 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ: 160.54 (d, J = 2 Hz), 137.13 (d, J = 4 Hz), 133.26, 132.3 (d, J = 4 Hz), 131.7 (d, J = 10 Hz), 128.58 (d, J = 14 Hz), 116.09 (d, J = 5 Hz), 114.87 (d, J = 4 Hz), 55.35.

S-octyldiphenylphosphinothioate (**3l,** Table 1.2)



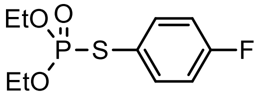
Colorless oil, ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.89 – 7.84 (m, 4H), 7.54 – 7.44 (m, 6H), 2.81 – 2.75 (m, 2H), 1.64 – 1.56 (m, 2H), 1.31 – 1.19 (m, 10H), 0.85 (t, J = 7.24 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, ppm) δ: 133.5 (d, J = 106.5 Hz), 132.20 (d, J = 2.5 Hz), 131.43(d, J = 10.4 Hz), 128.61(d, J = 12.3 Hz), 31.69, 30.52 (d, J = 4.9 Hz), 29.29, 29.00, 28.85, 28.54, 22.57, 14.06.

S-benzyl diphenylphosphinothioate (**3m,** Table 1.2)



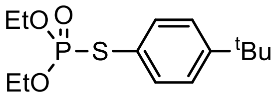
Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.87 – 7.82 (m, 4H), 7.47 – 7.38 (m, 6H), 7.17 – 7.15 (m, 5H), 4.00 (d, J = 9.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 136.80, 132.94(d, J = 106.5 Hz), 132.4 (d, J = 3 Hz), 131.53 (d, J = 10.6 Hz), 129.04, 128.79, 128.62, 127.47, 32.25.

O,*O*-Diethyl *S*-(4-fluorophenyl) phosphorothioate (**3n**, Table 1.2)



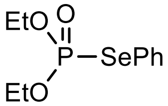
Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.53 – 7.47 (m, 2H), 7.02 – 6.96 (m, 2H), 4.20 – 4.06 (m, 4H), 1.26 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 163.38 (dd, J = 248.8 Hz, 3.2 Hz), 136.76 (dd, J = 8.5 Hz, 5 Hz), 121.69 (dd, J = 7.2 Hz, 3.2 Hz), 116.60 (dd, J = 22 Hz, 2.2 Hz), 64.27 (d, J = 6.2 Hz), 16.05 (d, J = 6.9 Hz).

S-(4-(*tert*-Butyl)phenyl) *O*,*O*-diethyl phosphorothioate (**3o**, Table 1.2)



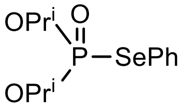
Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.45 (dd, J = 8.7 Hz, 2.1 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.24 – 4.09 (m, 4H), 1.30 – 1.25 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 152.41 (d, J = 3.1Hz), 134.38 (d, J = 5.1 Hz), 126.49 (d, J = 2.3 Hz), 122.78 (d, J = 7.2 Hz), 64.07 (d, J = 6.1 Hz), 34.69, 31.20, 16.00 (d, J = 7.1 Hz).

O,O-diethyl Se-phenyl phosphoroselenoate (**4a**)



Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.62 (d, J = 7.2 Hz, 2H), 7.34 – 7.27 (m, 3H), 4.19 – 4.13 (m, 4H), 1.28 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 135.55 (d, J = 4.4 Hz), 129.49, 128.78 (d, J = 2.0 Hz), 123.79 (d, J = 8.1 Hz), 63.87 (d, J = 5.6 Hz), 15.91 (d, J = 7.1 Hz).

Se-phenyl *O,O*-diisopropylphosphoroselenoate **(4b)**

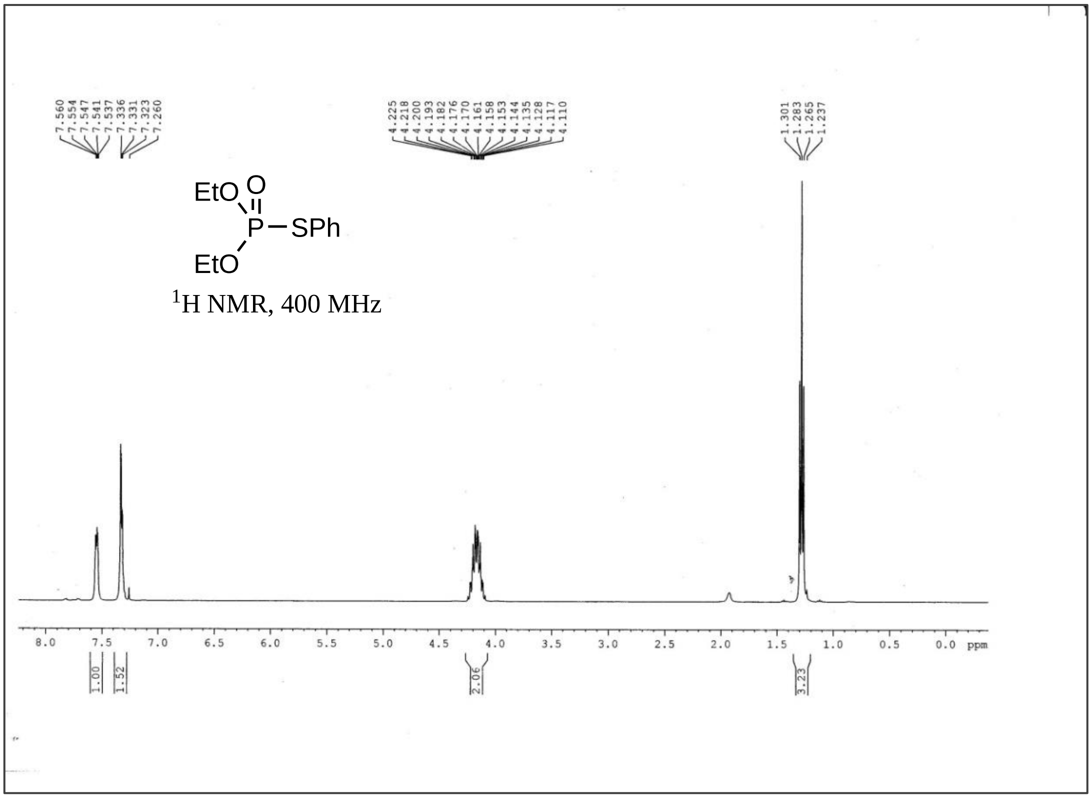


Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.65 – 7.62 (m, 2H), 7.31 – 7.24 (m, 3H), 4.78 – 4.70 (m, 2H), 1.30 (d, J = 6 Hz, 6H), 1.22 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 135.27 (d, J = 5 Hz), 129.42 (d, J = 2 Hz), 128.56 (d, J = 2 Hz), 124.64 (d, J = 8 Hz), 73.25 (d, J = 6 Hz), 23.94 (d, J = 4 Hz), 23.54 (d, J = 6 Hz).

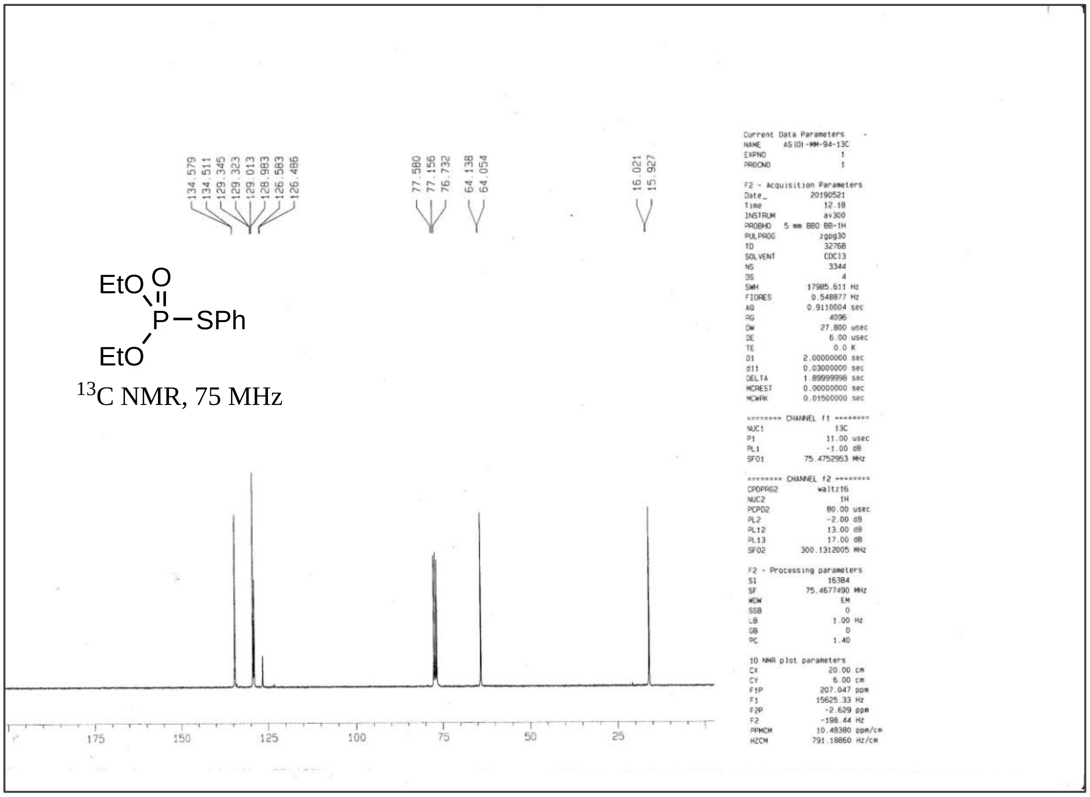
2/e.

^{1}H and ^{13}C NMR spectra of all synthesized products described in section -II

O,O-diethyl *S*-phenyl phosphorothioate (**3a**, $CDCl_3$)



^{1}H NMR, 400 MHz



^{13}C NMR, 75 MHz

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PROCNO                  1

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TD                 32768
SOLVENT            CDCl3
NS                  3344
DS                     4
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FIDRES          0.548877 Hz
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RG                  4096
DW                27.800 usec
DE                  6.00 usec
TE                   0.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 11.00 usec
PL1                -1.00 dB
SFO1          75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                -2.00 dB
PL12               13.00 dB
PL13               17.00 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
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WDW                   EM
SSB                    0
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GB                     0
PC                  1.40

1D NMR plot parameters
CX                 20.00 cm
CY                  6.00 cm
F1P              207.047 ppm
F1              15625.33 Hz
F2P               -2.629 ppm
F2               -198.44 Hz
PPMCM           10.48380 ppm/cm
HZCM           791.18860 Hz/cm
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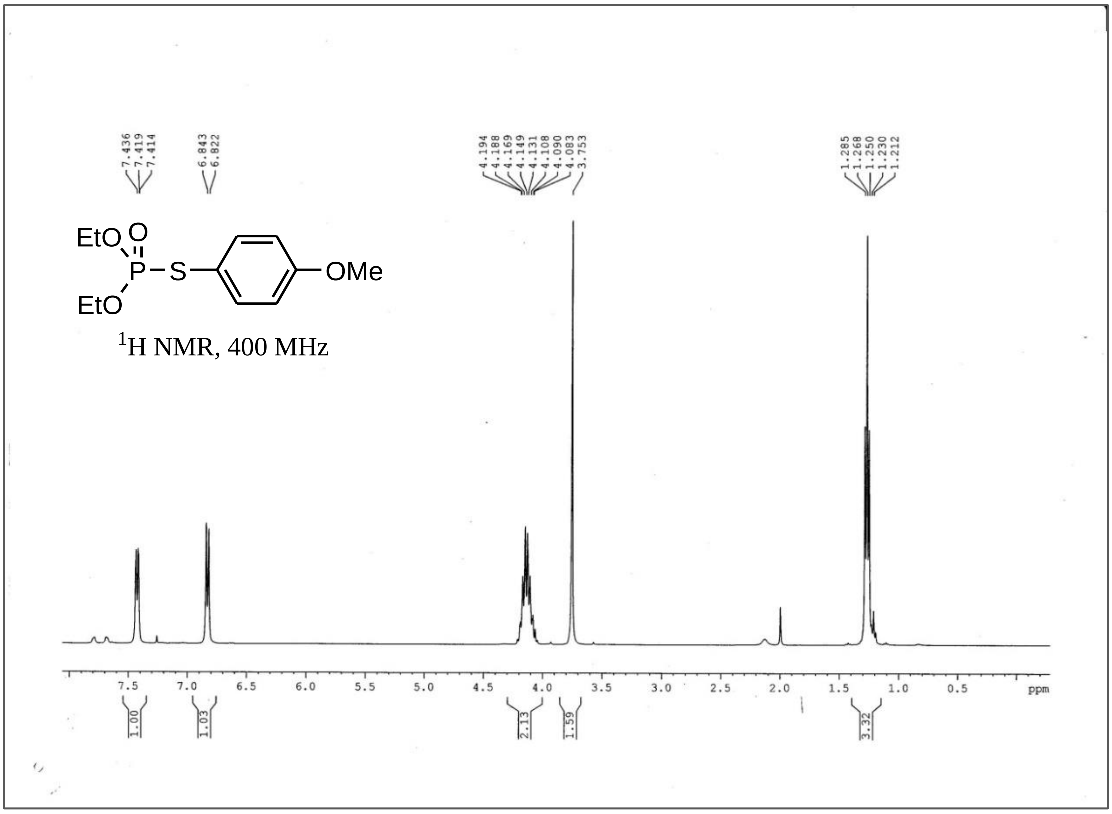
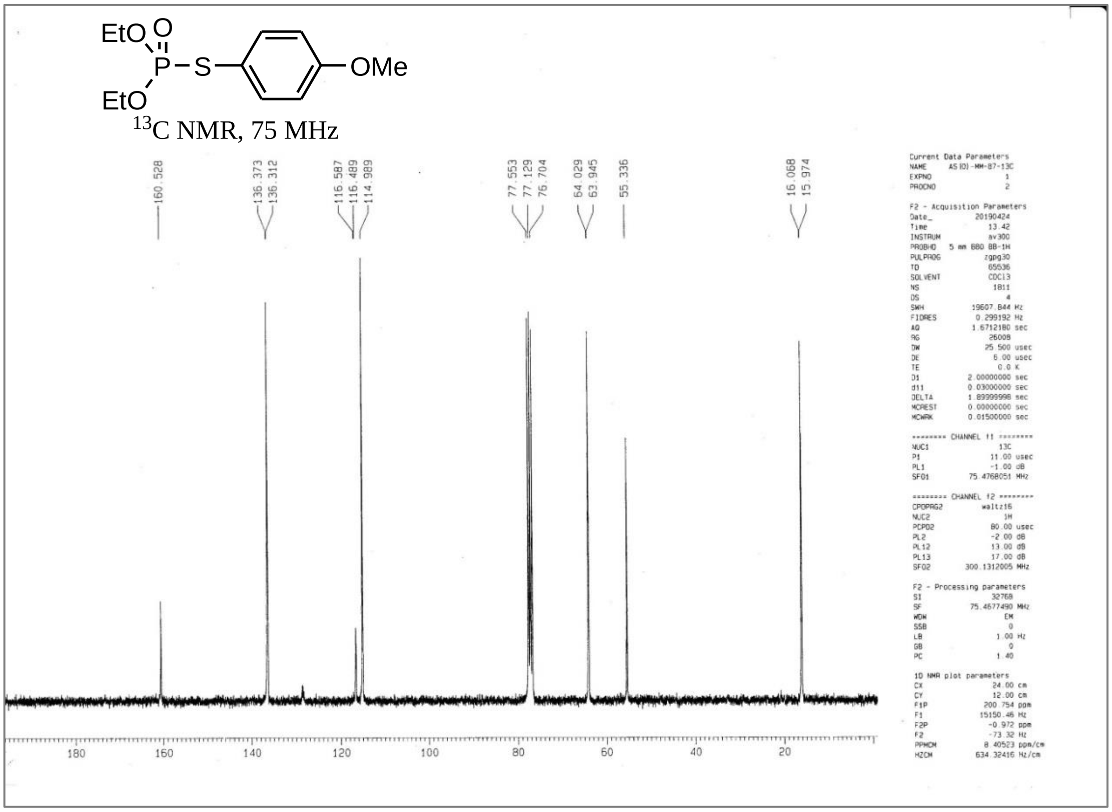
O,O-diethyl *S*-(4-methoxyphenyl) phosphorothioate (**3b**, $CDCl_3$)





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FIDRES          0.299192 Hz
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DW                25.500 usec
DE                  6.00 usec
TE                   0.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

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PL1                -1.00 dB
SFO1          75.4768051 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                -2.00 dB
PL12               13.00 dB
PL13               17.00 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
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SF            75.4677490 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                 24.00 cm
CY                 12.00 cm
F1P              200.754 ppm
F1              15150.46 Hz
F2P               -0.972 ppm
F2                -73.32 Hz
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HZCM           634.32416 Hz/cm
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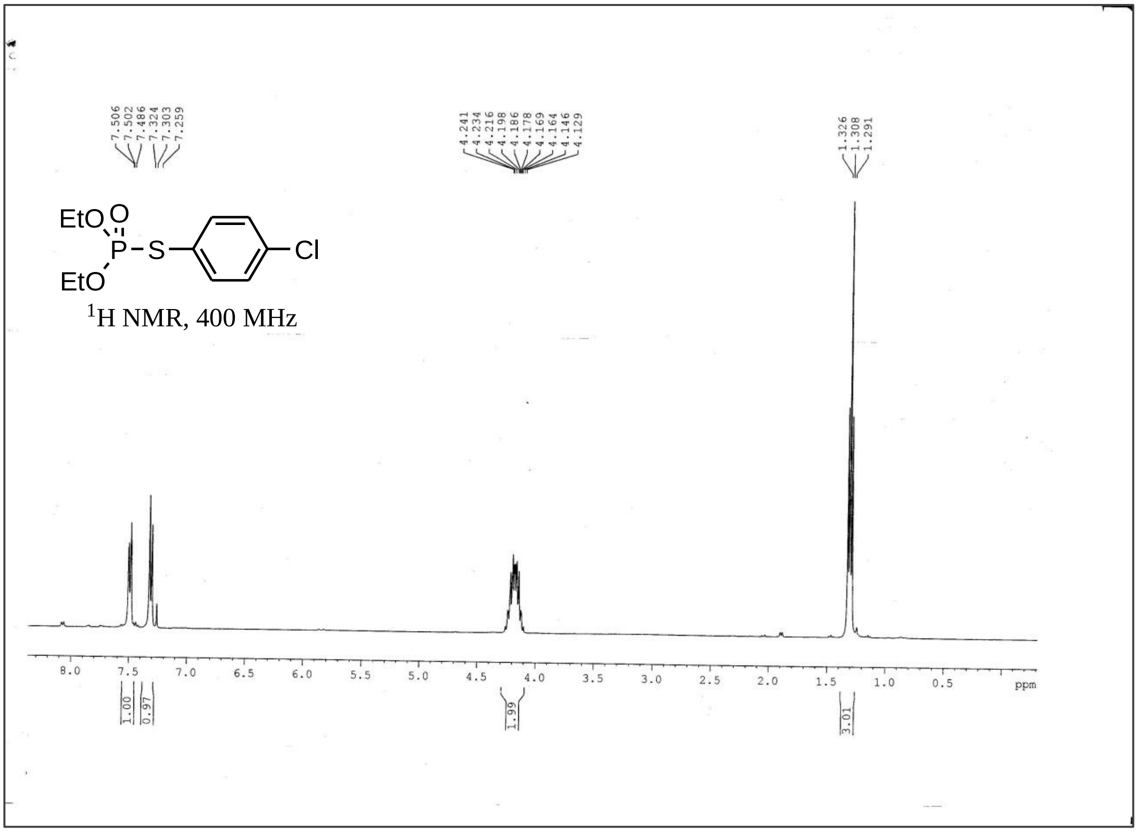
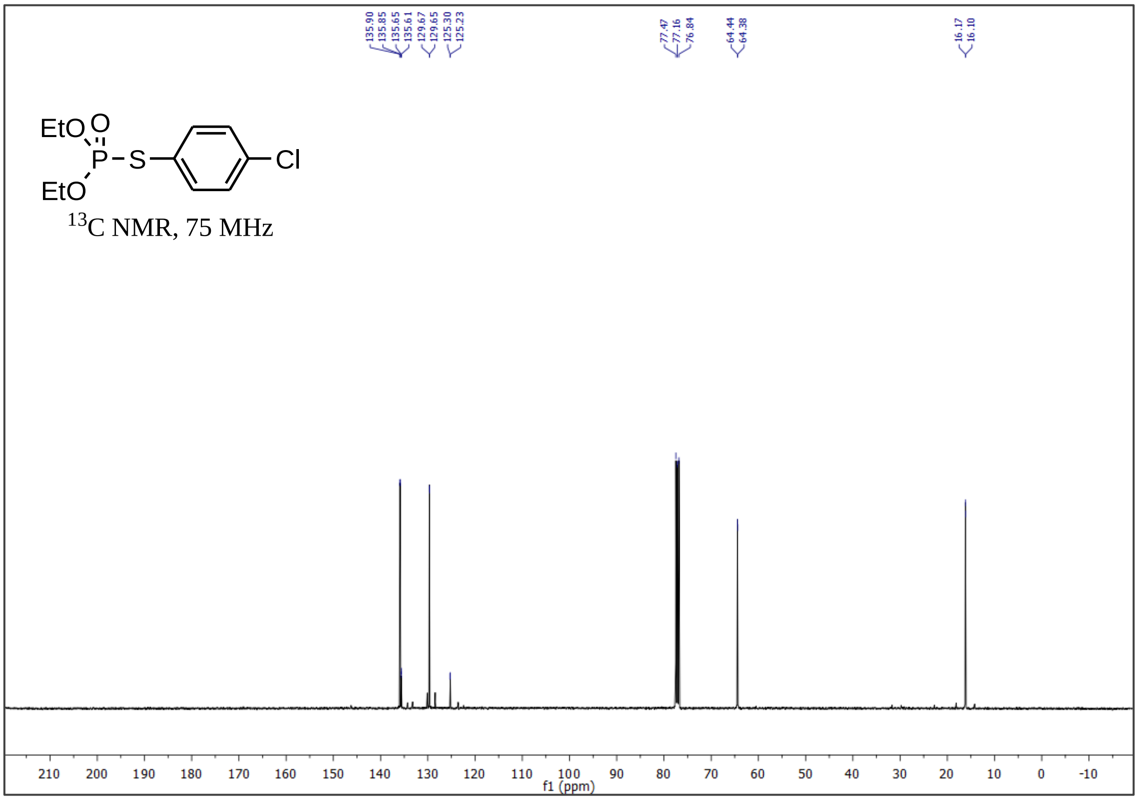
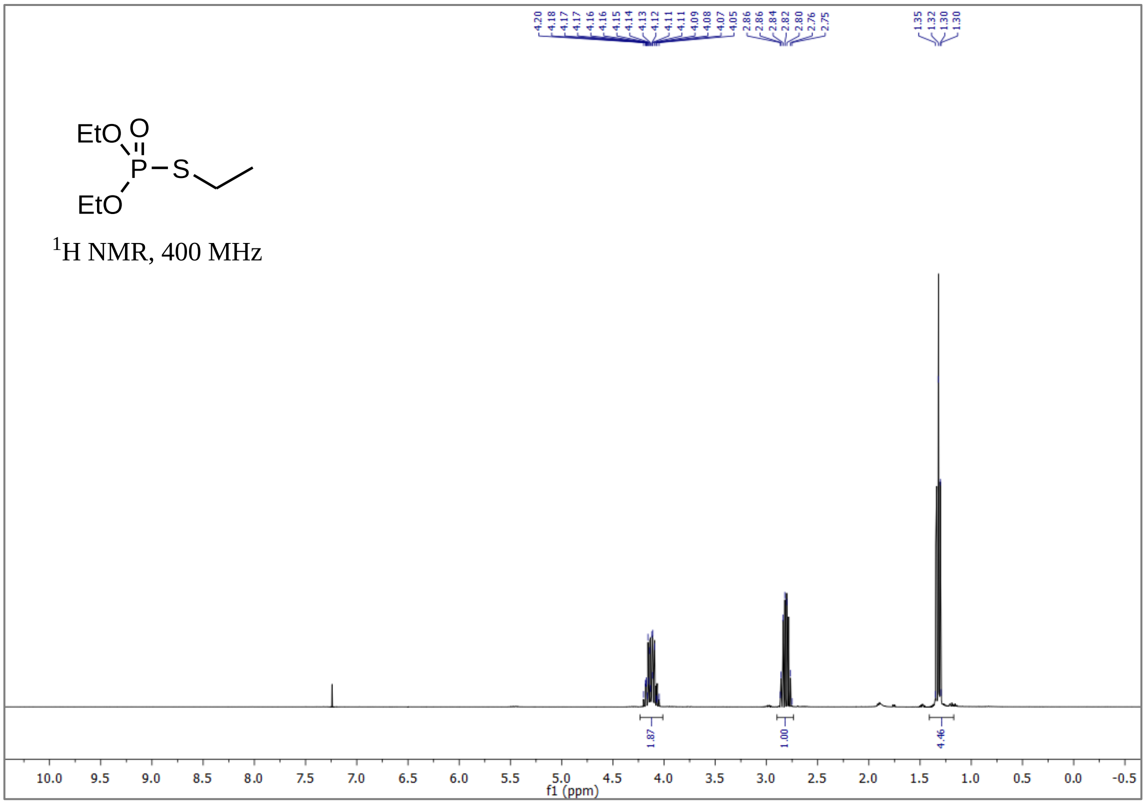
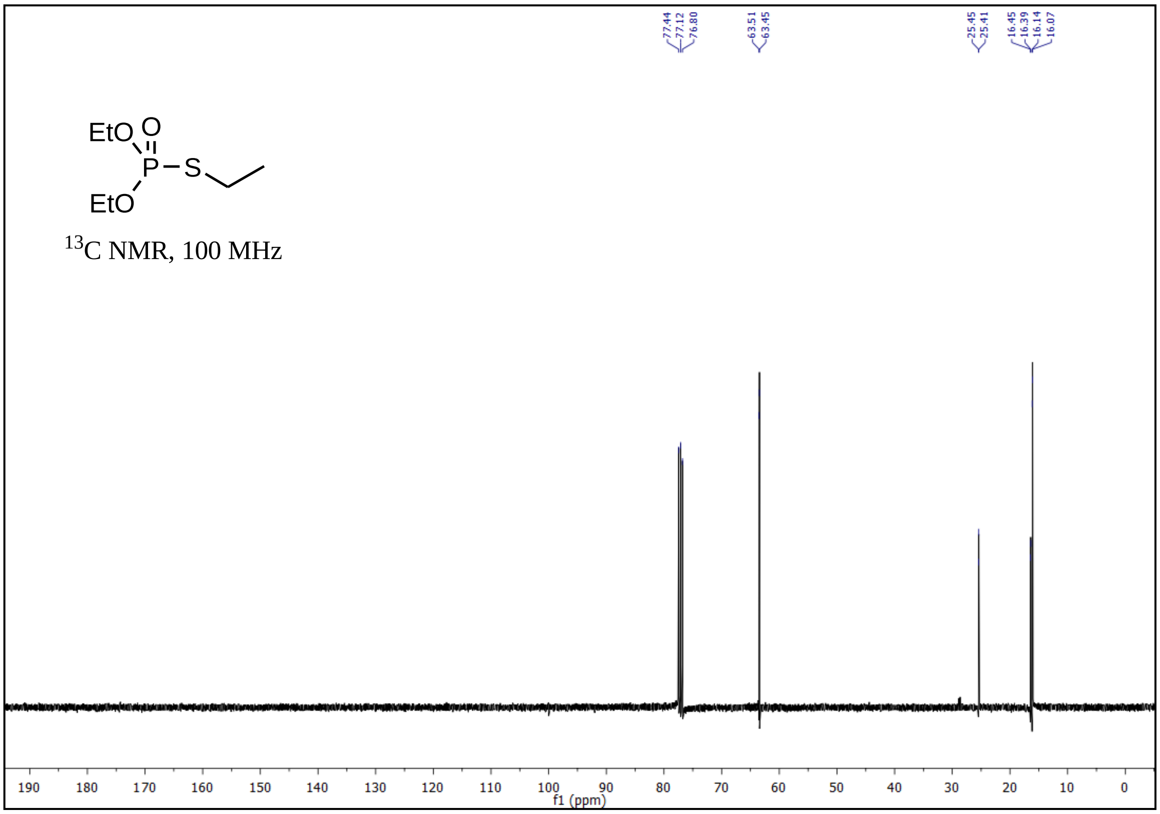
S-(4-chlorophenyl) *O,O*-diethyl phosphorothioate (**3c**, CDCl$_3$)



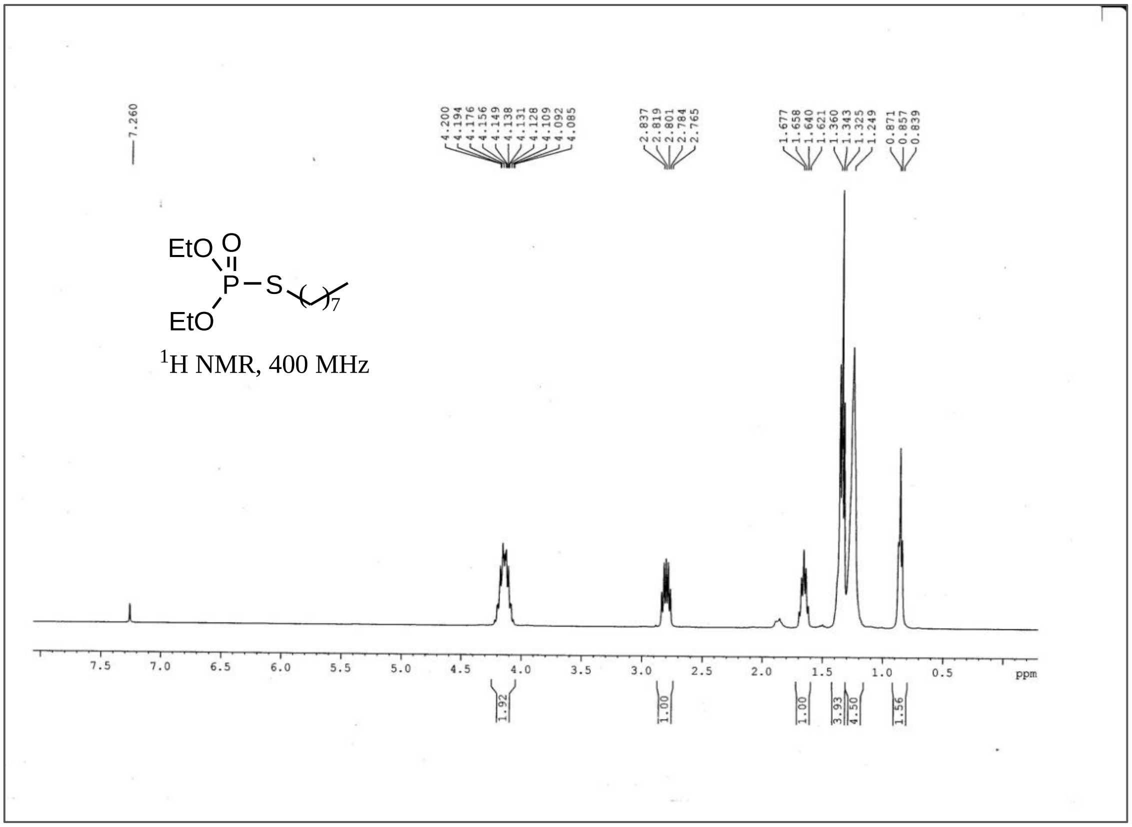


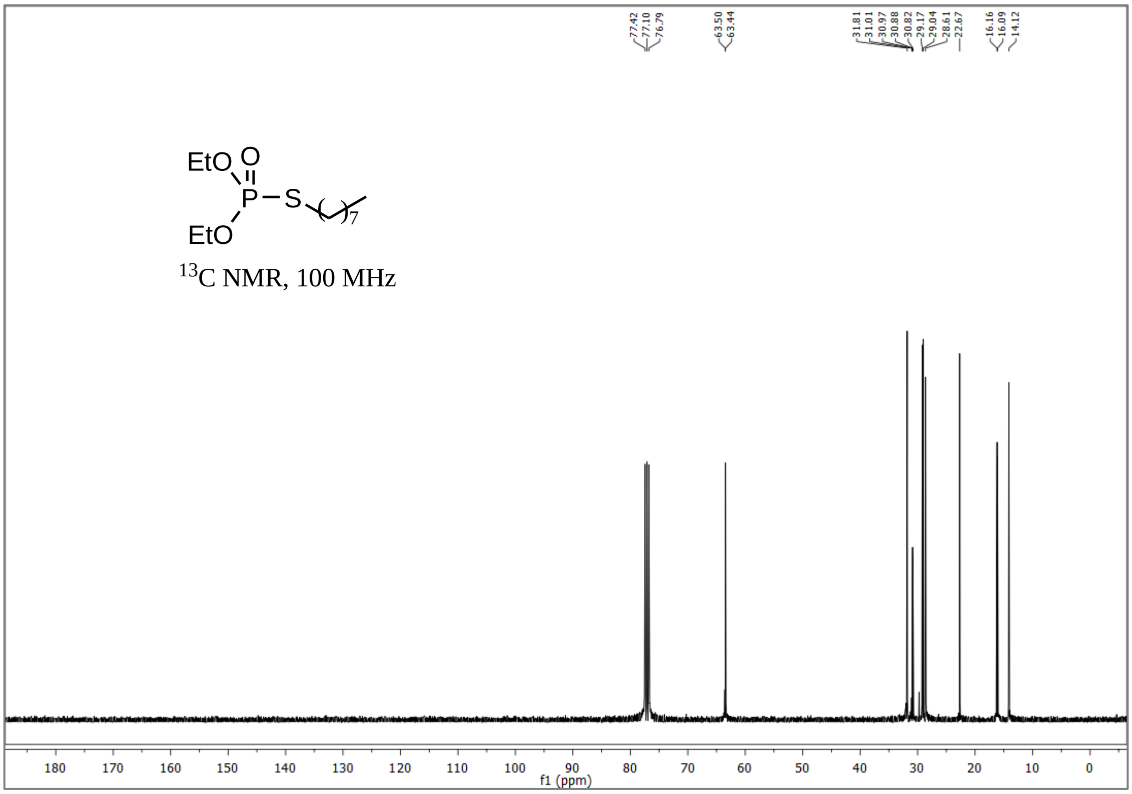
O,O,S-triethylphosphorothioate (**3d,** $CDCl_3$)



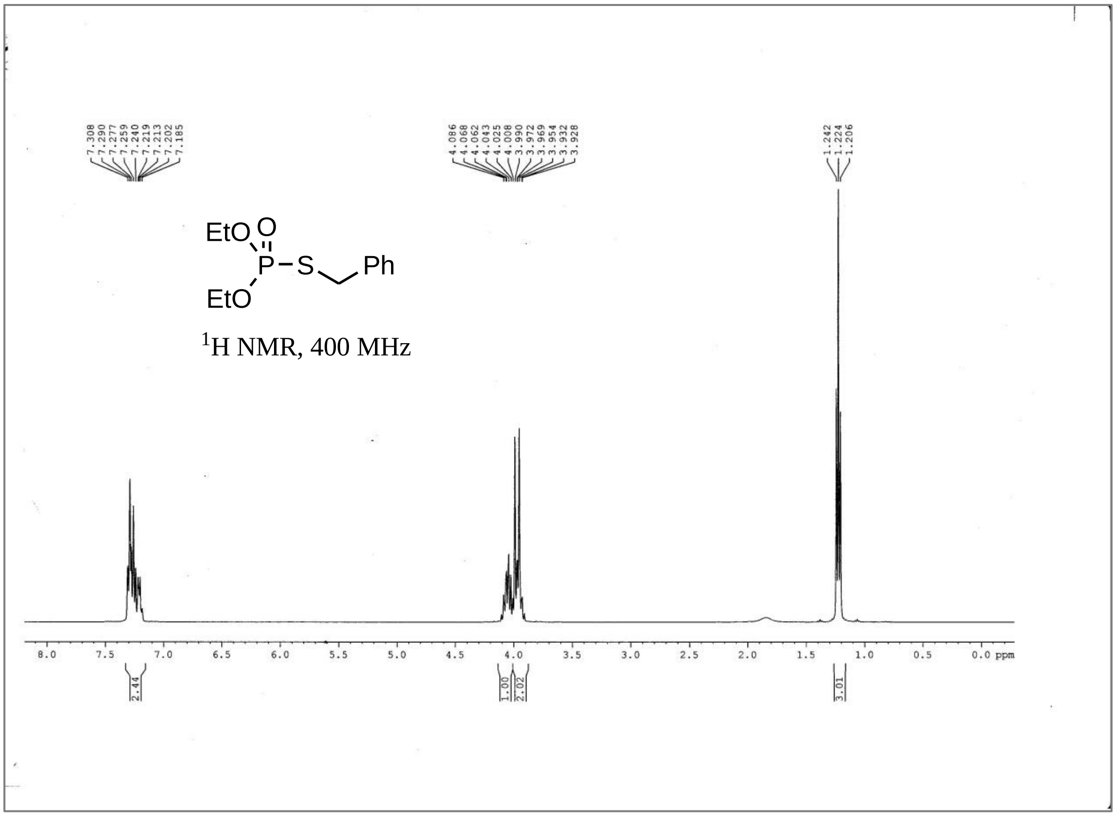


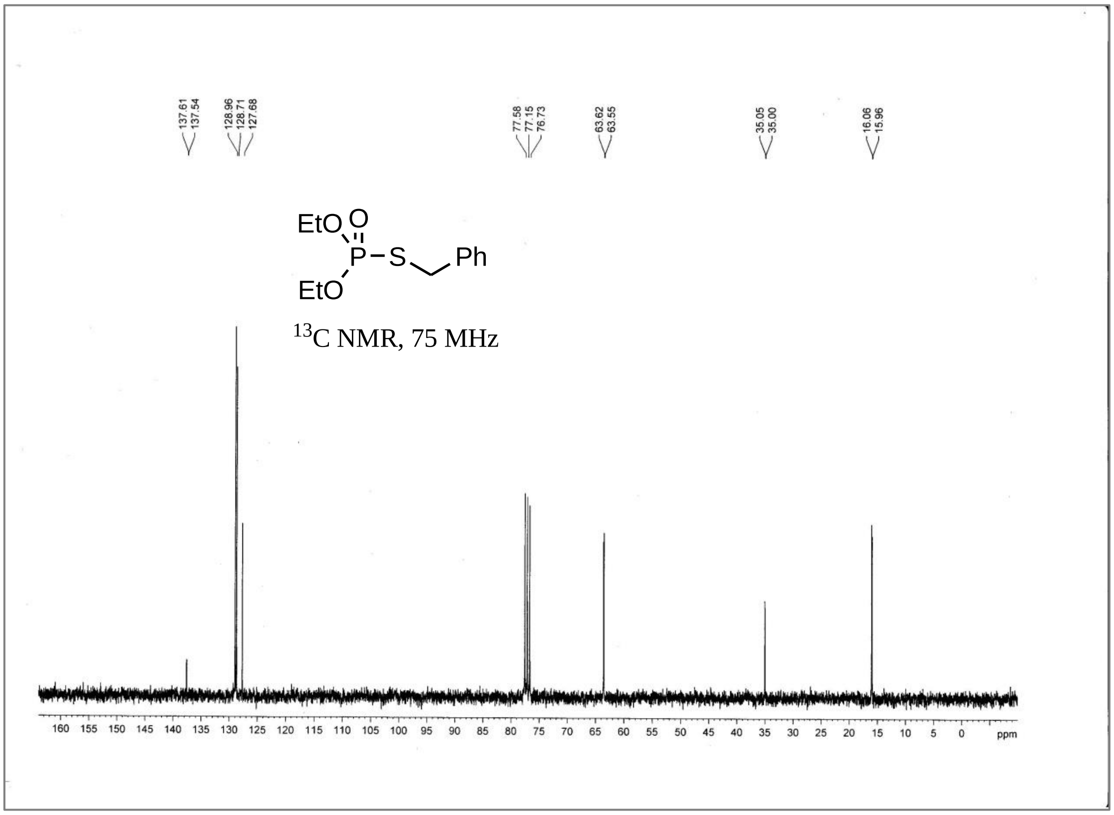
O,O-diethyl *S*-octylphosphorothioate (**3e**, $CDCl_3$)



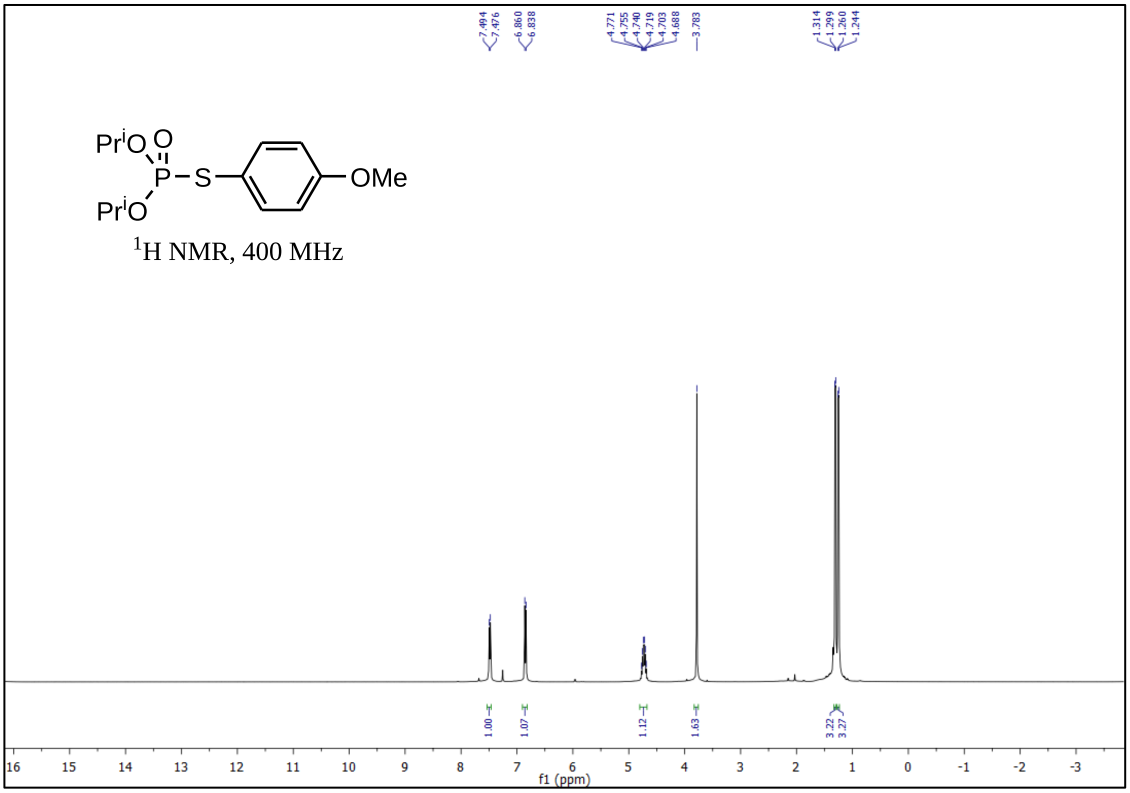


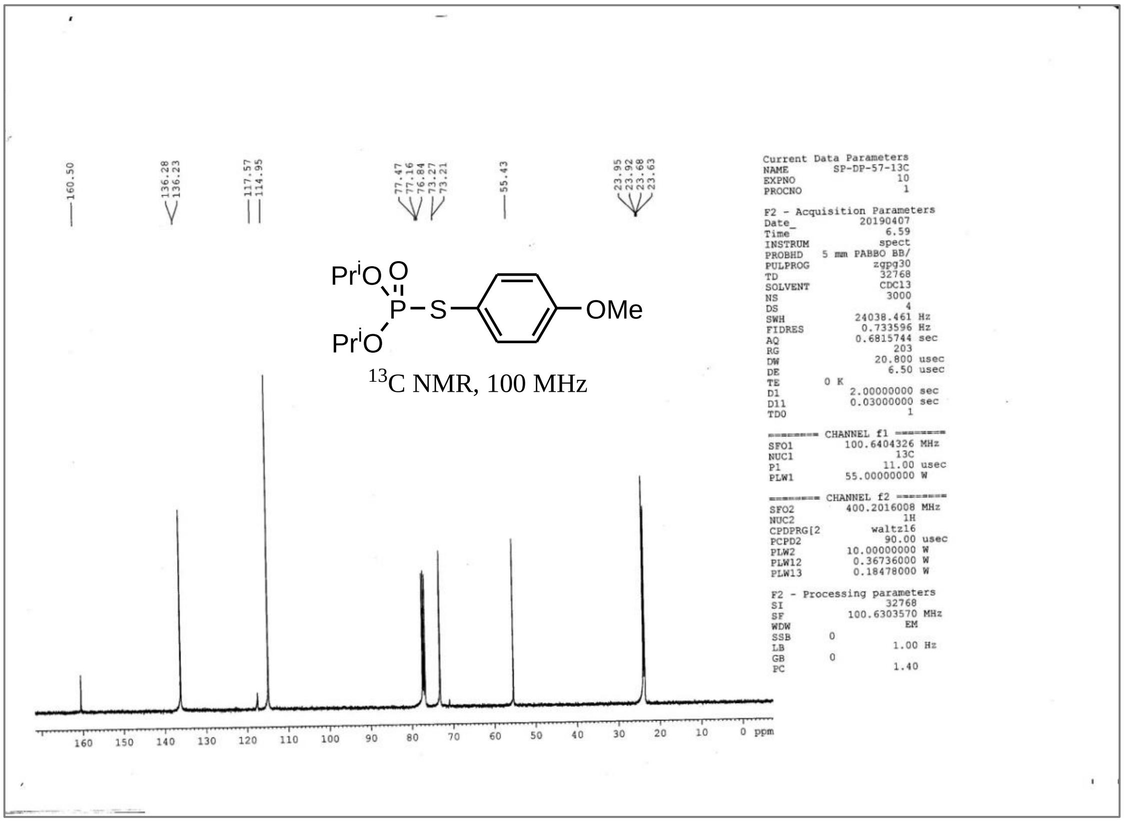
S-benzyl *O,O*-diethyl phosphorothioate (**3f**, $CDCl_3$)





S-4-methoxyphenyl *O,O*-diisopropylphosphorothioate (**3g**, $CDCl_3$)





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DE                   6.50 usec
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D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
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NUC1                  13C
P1                  11.00 usec
PLW1          55.00000000 W

======== CHANNEL f2 ========
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NUC2                   1H
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PCPD2               90.00 usec
PLW2          10.00000000 W
PLW12          0.36736000 W
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F2 - Processing parameters
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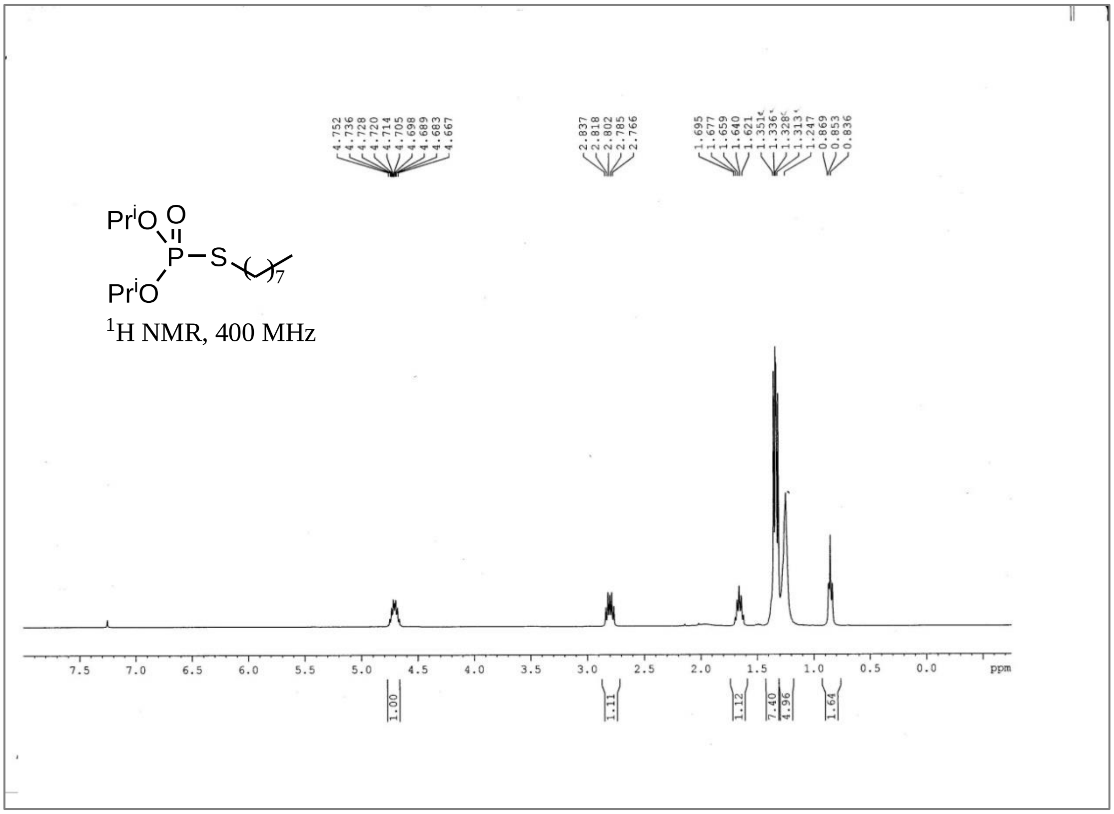
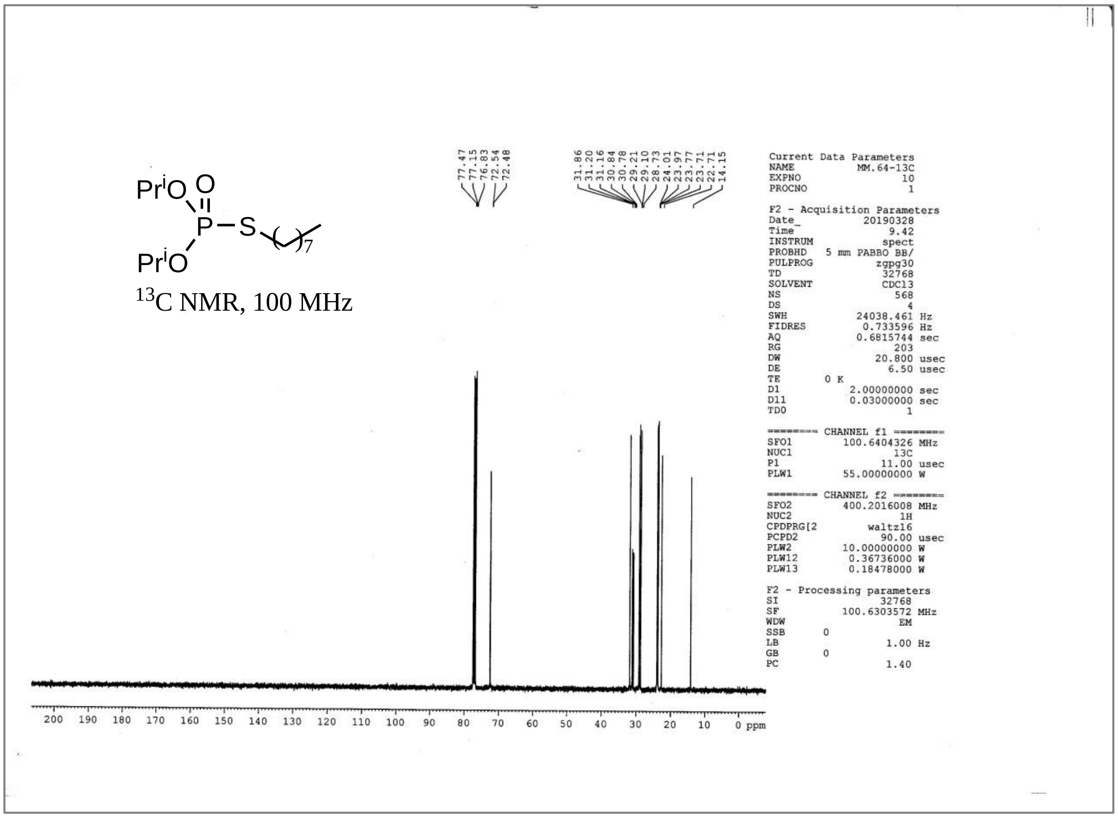
S-octyl *O,O*-diisopropylphosphorothioate (**3h**, $CDCl_3$)





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PROCNO                  1

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D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

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PLW1         55.00000000 W

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NUC2                  1H
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PCPD2              90.00 usec
PLW2         10.00000000 W
PLW12         0.36736000 W
PLW13         0.18478000 W

F2 - Processing parameters
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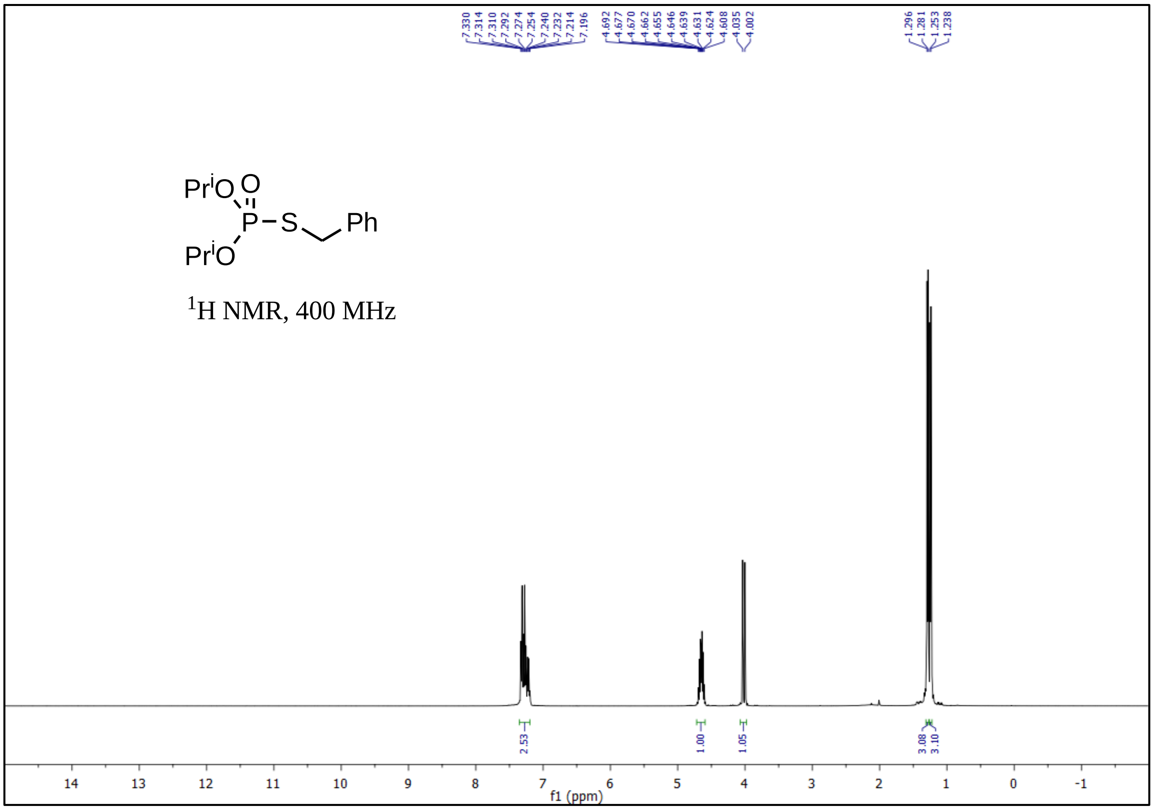

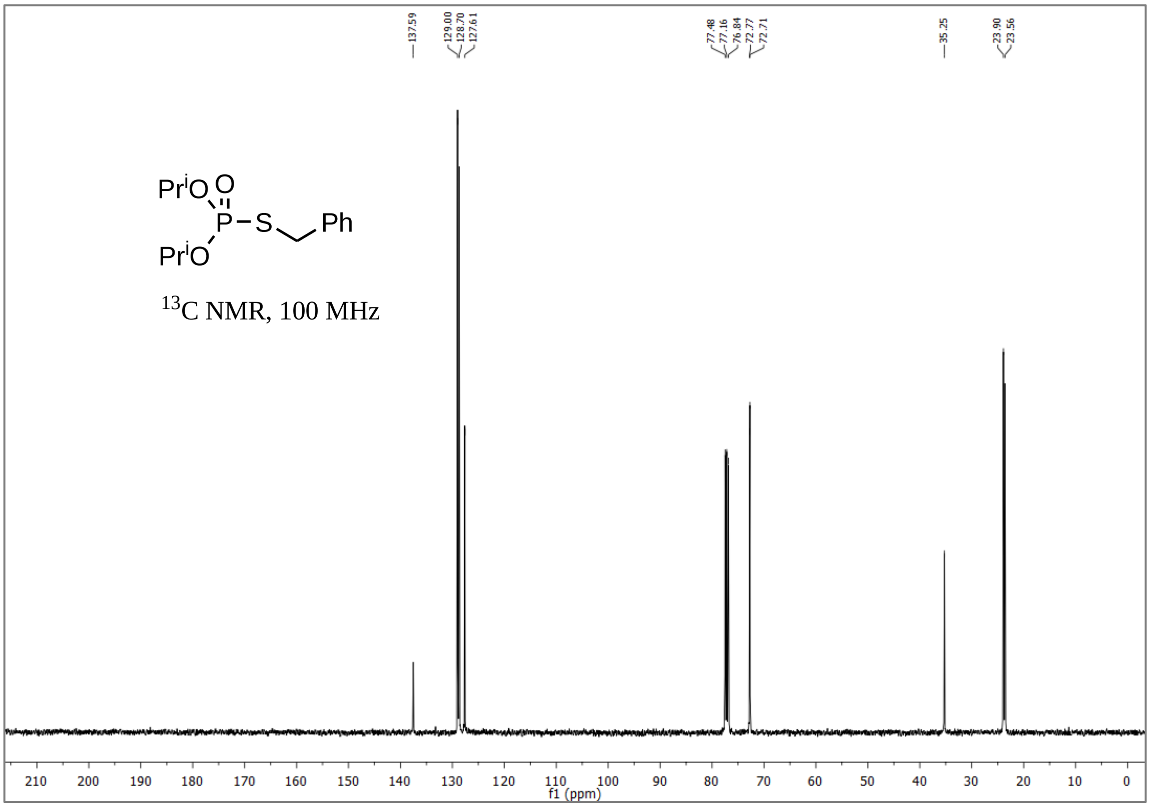

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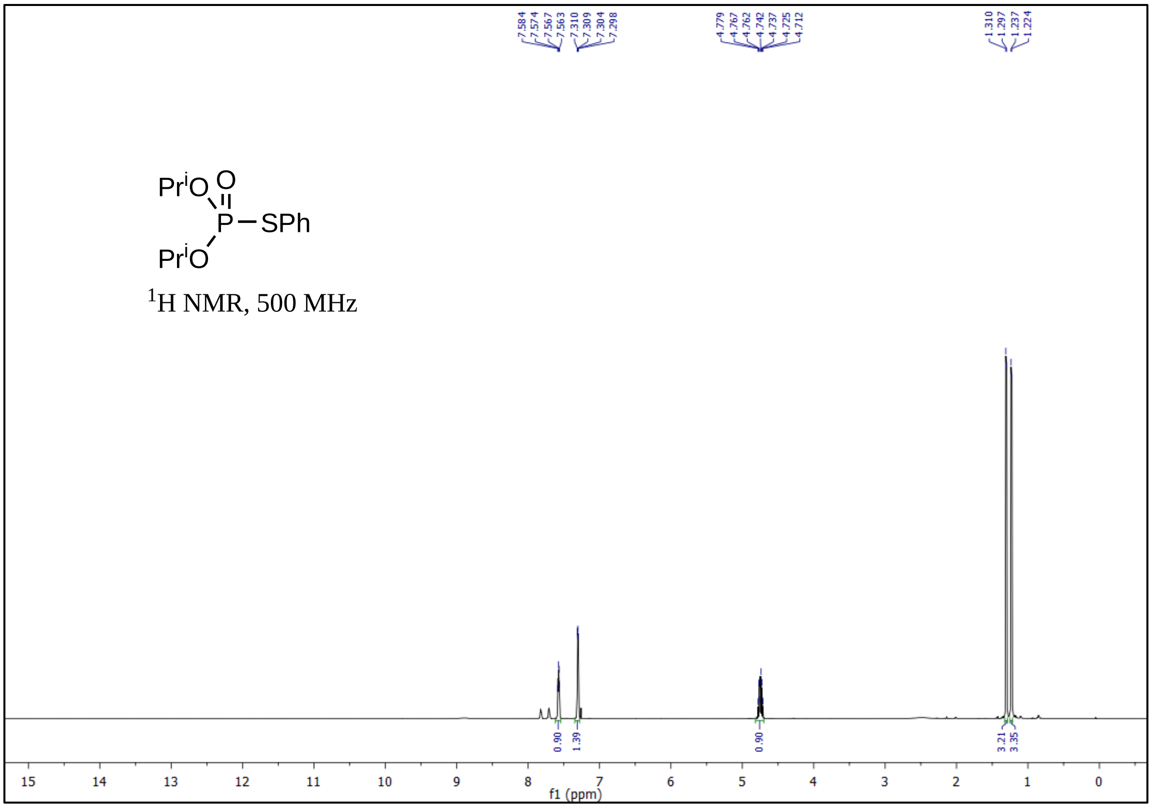

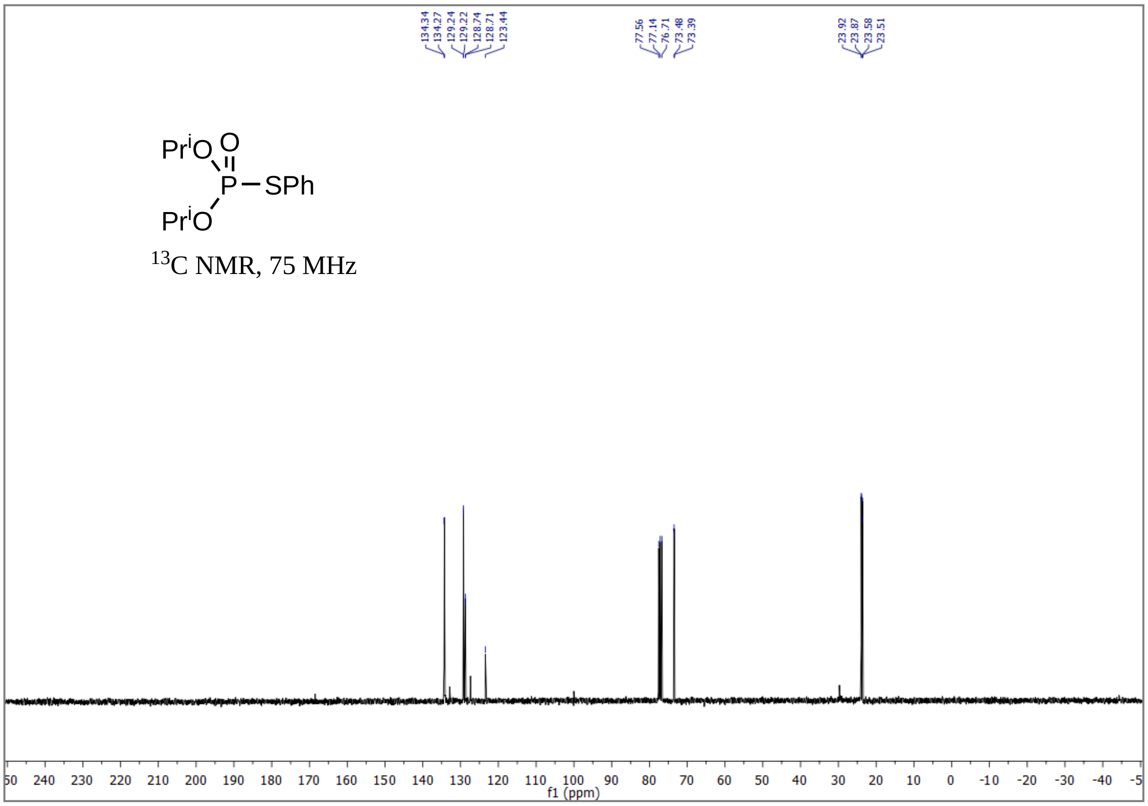

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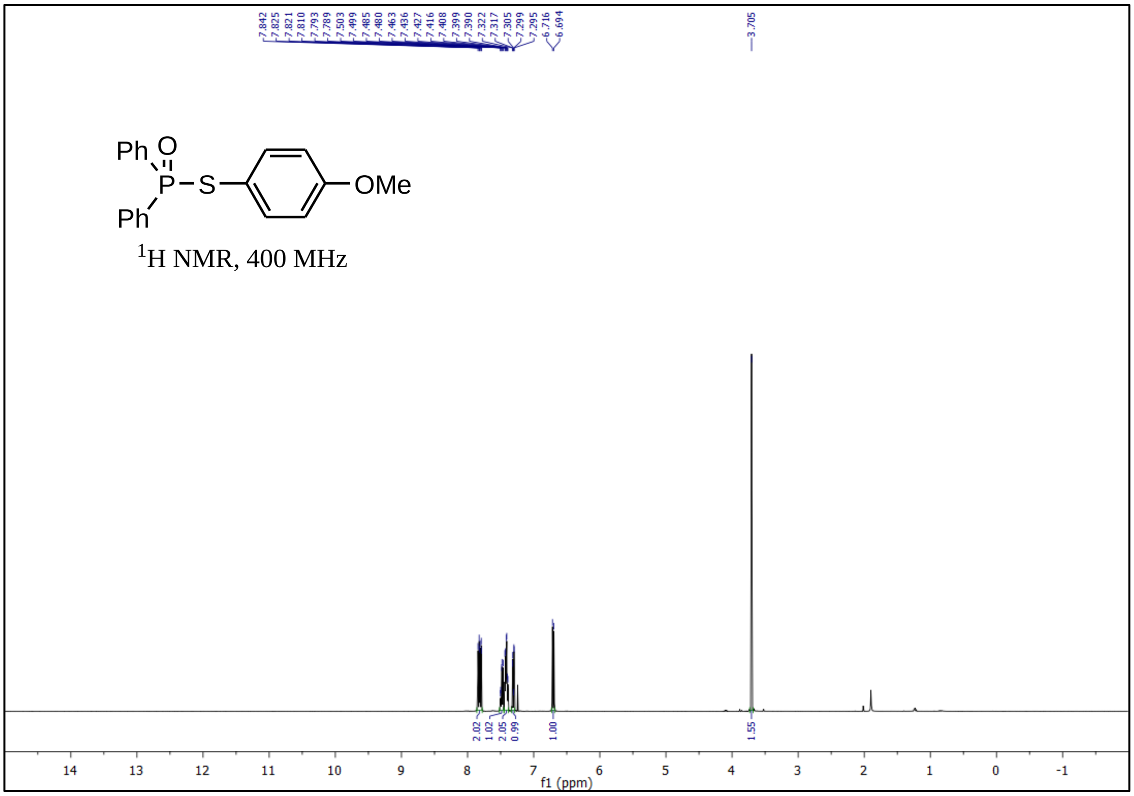

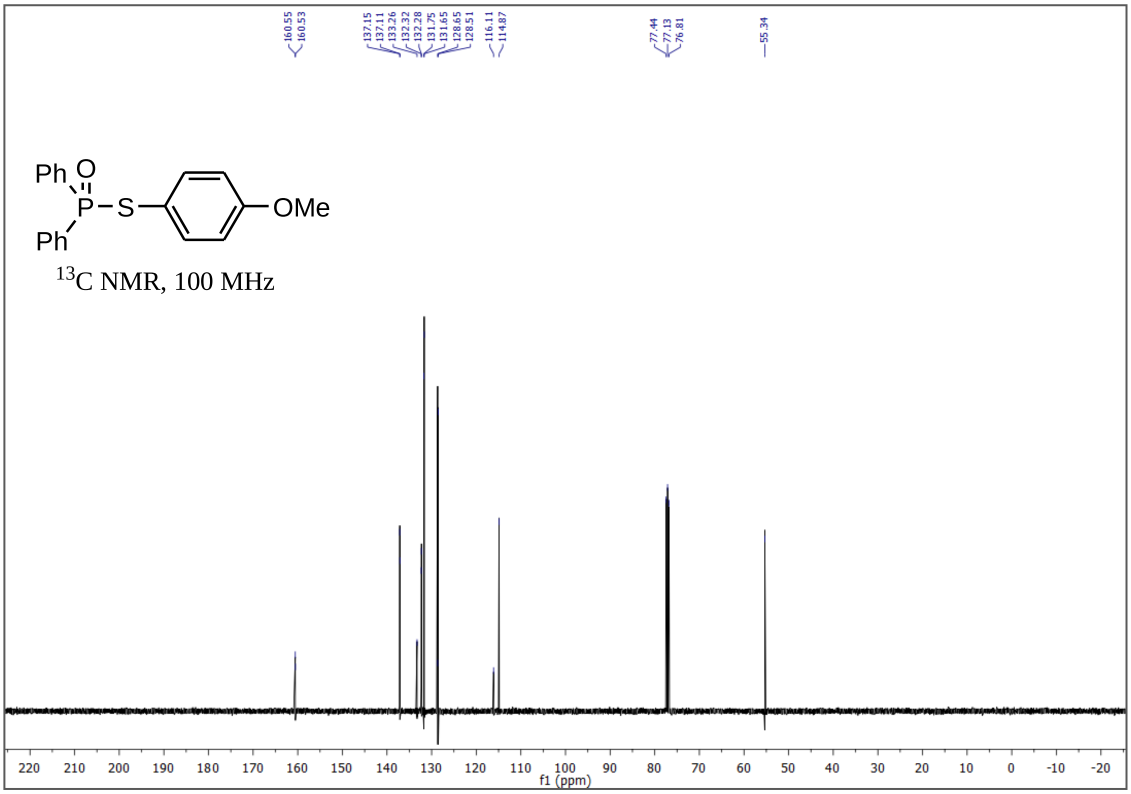

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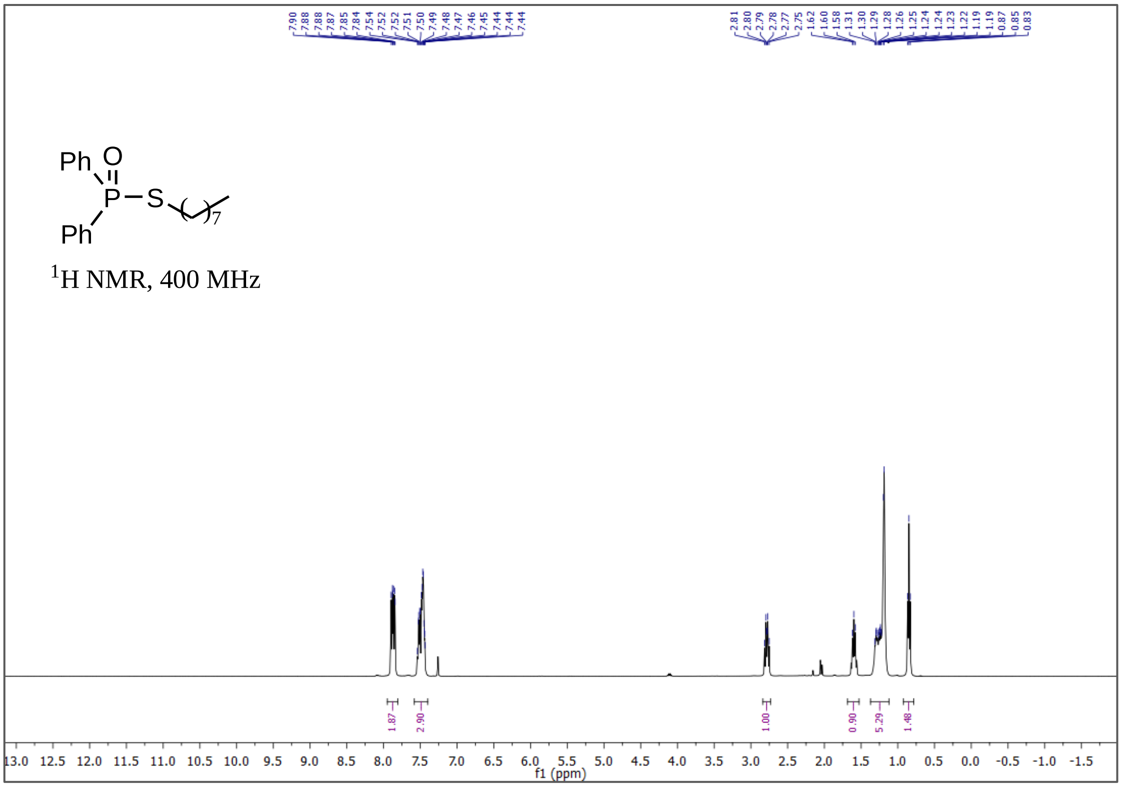

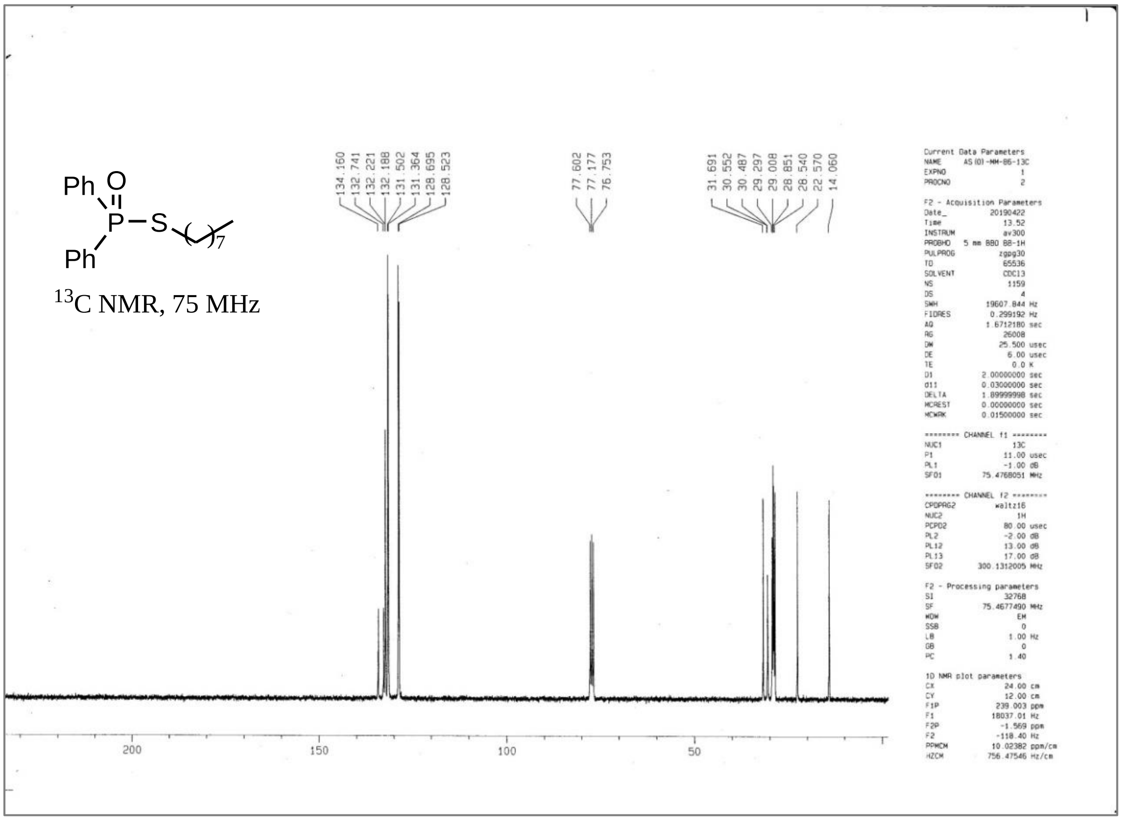

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PCPD2               80.00 usec
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F2 - Processing parameters
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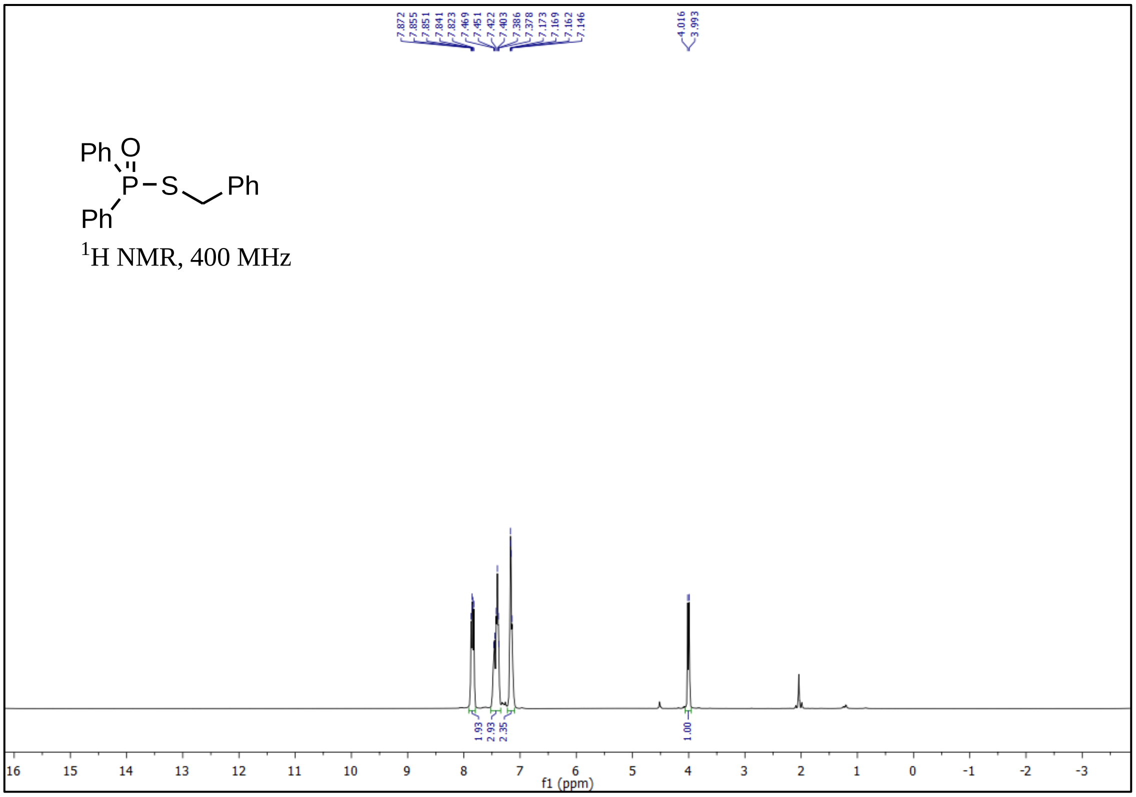
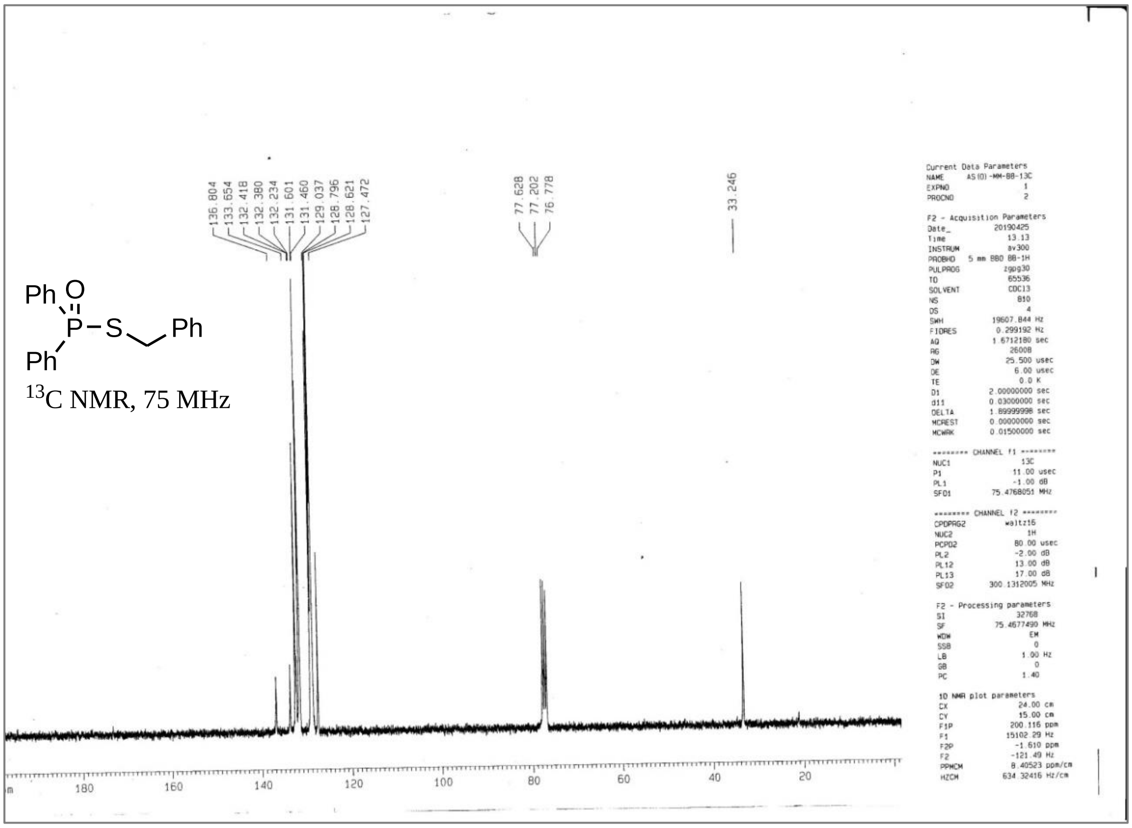
S-benzyl diphenylphosphinothioate (**3m**, $CDCl_3$)





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DW               25.500 usec
DE                 6.00 usec
TE                  0.0 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                  11.00 usec
PL1                 -1.00 dB
SFO1          75.4768051 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
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PL12                13.00 dB
PL13                17.00 dB
SFO2         300.1312005 MHz

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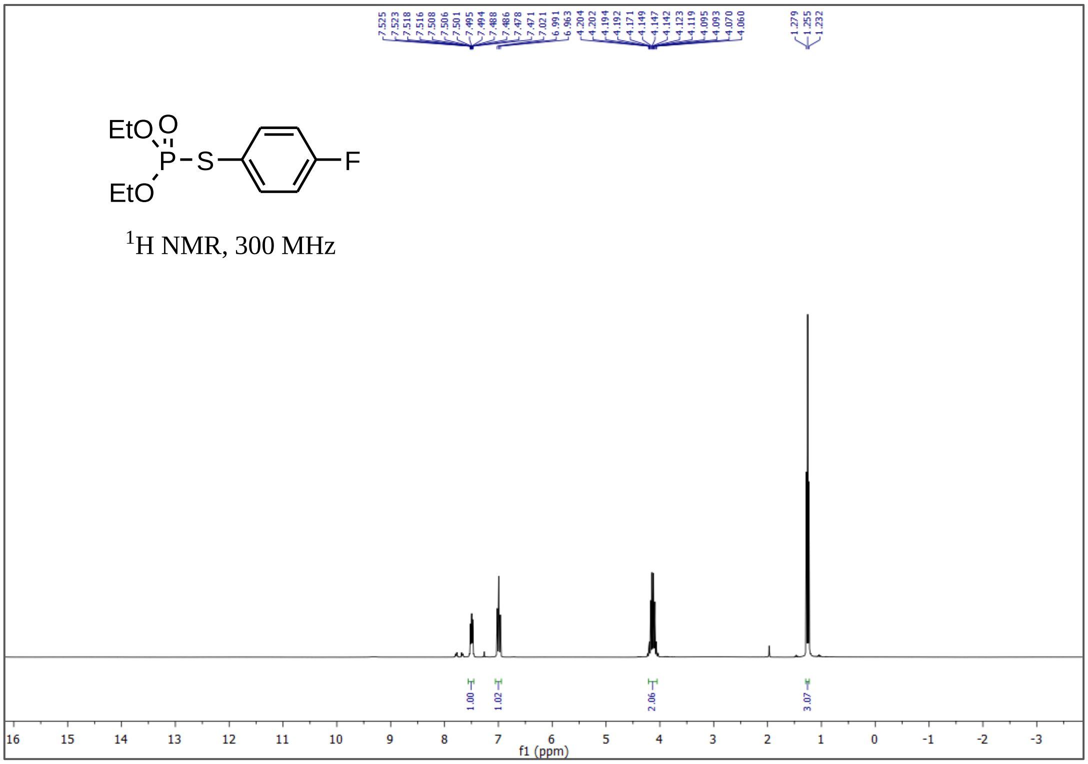
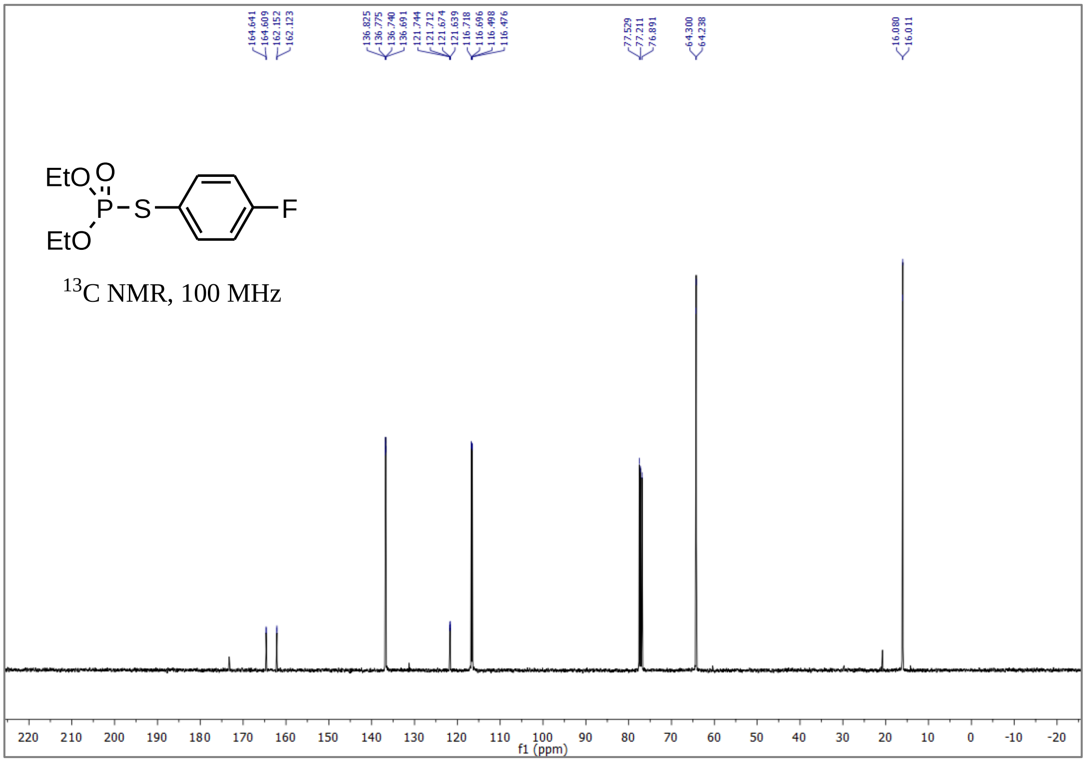
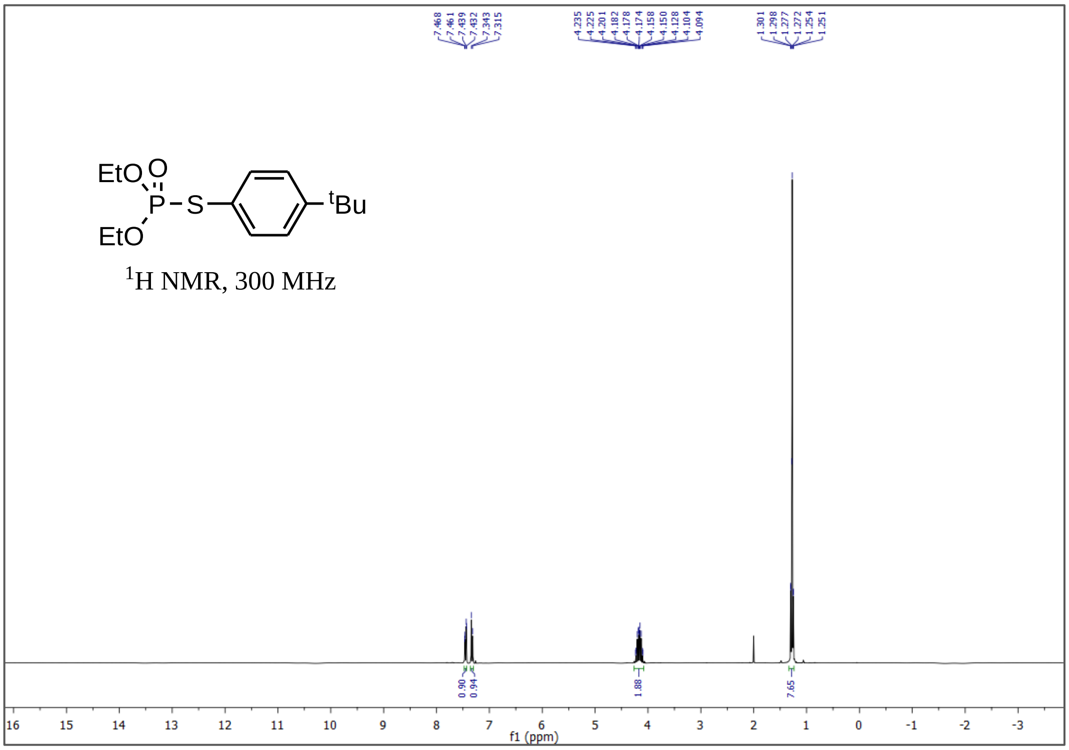
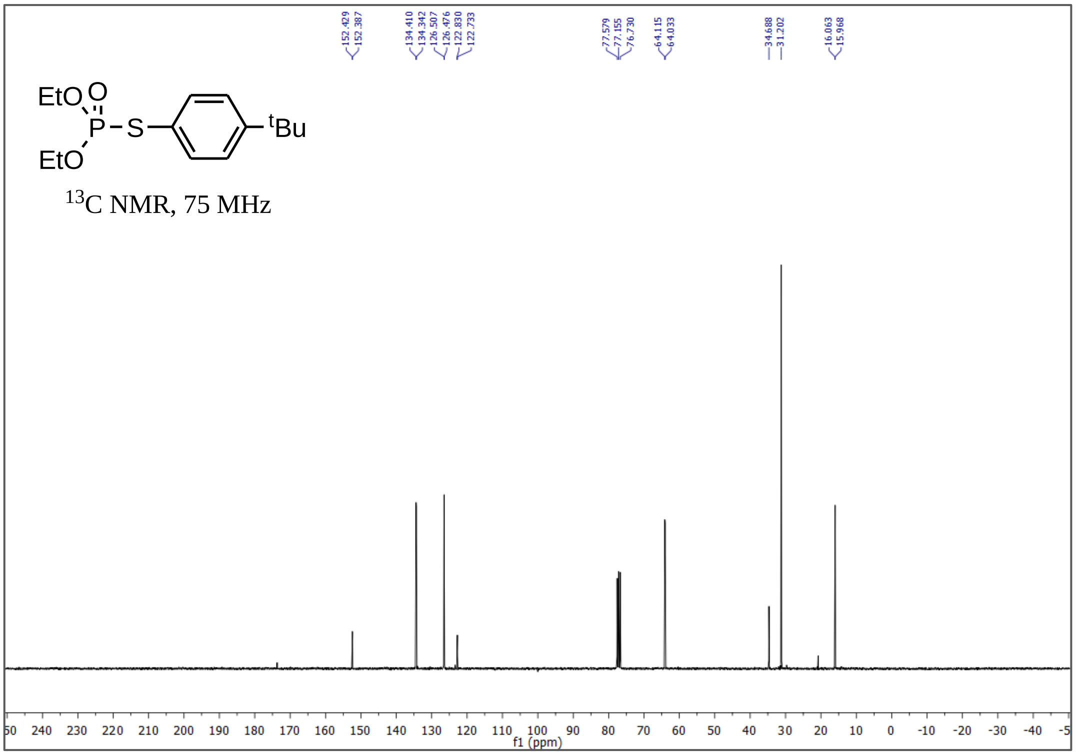
O,O-Diethyl *S*-(4-fluorophenyl) phosphorothioate (**3n,** $CDCl_3$)



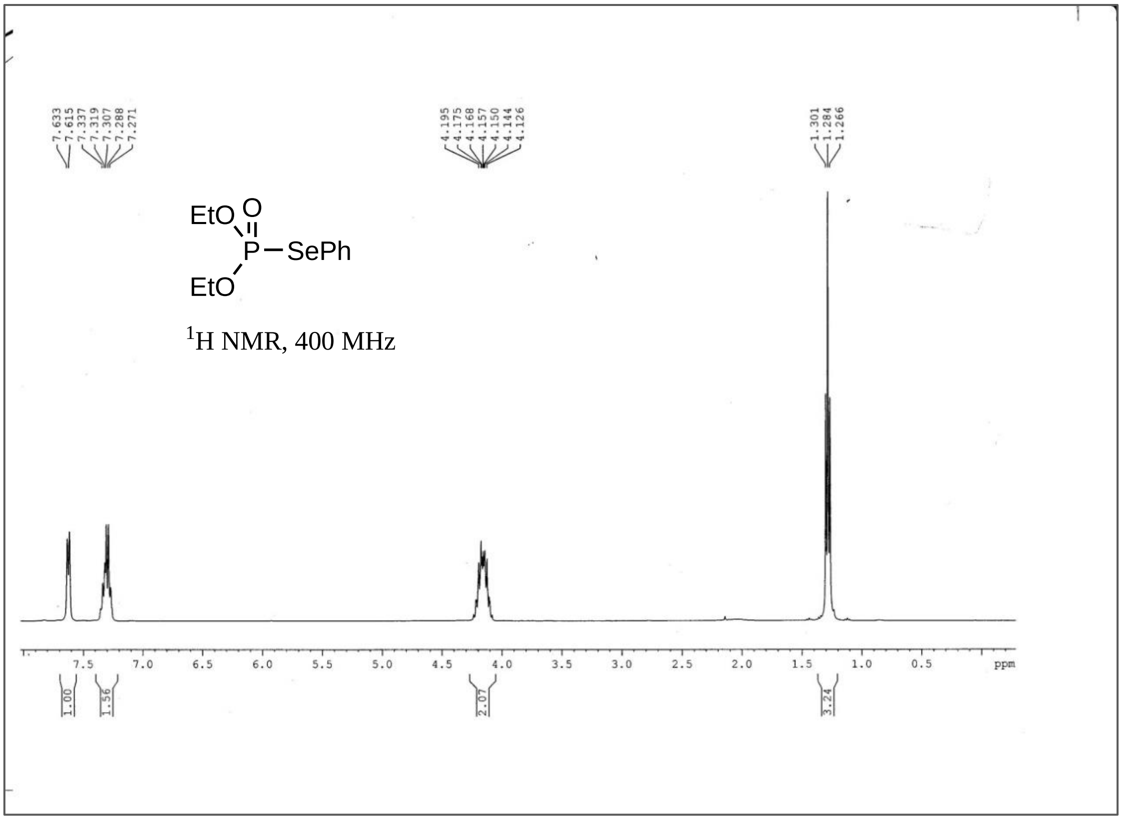


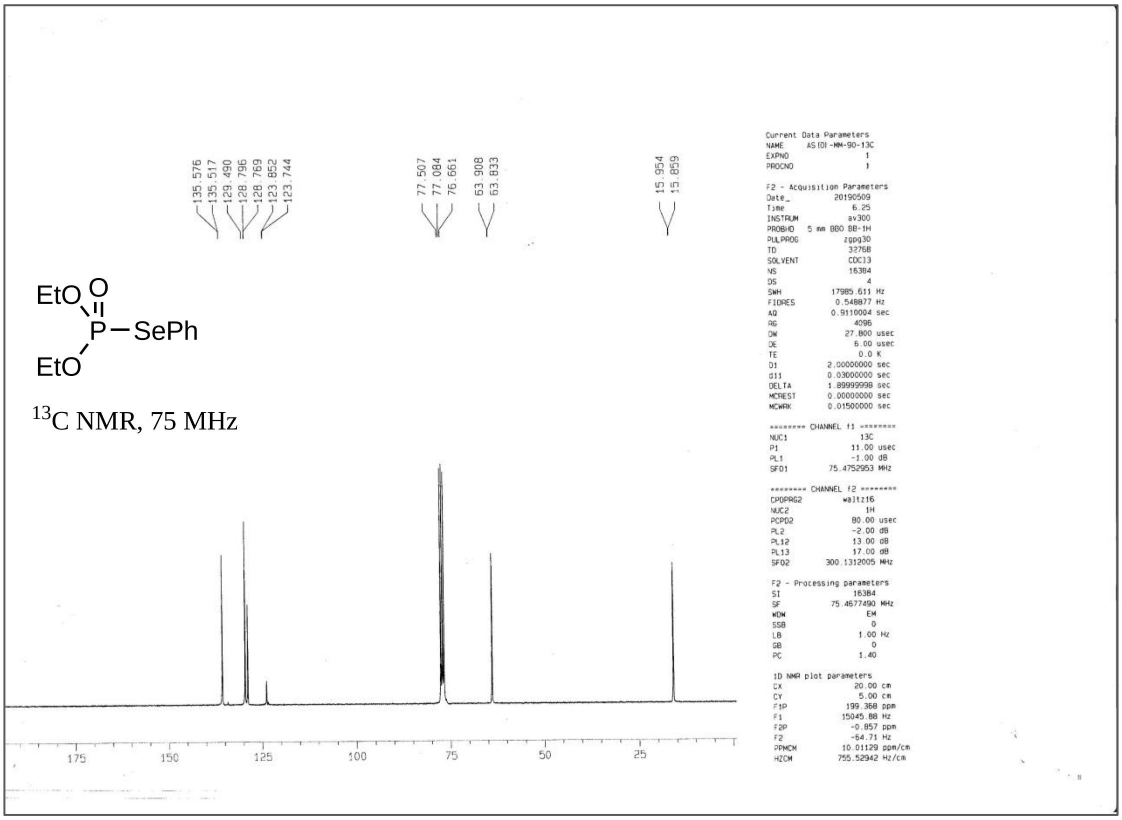
S-(4-(*tert*-Butyl)phenyl) *O*,*O*-diethyl phosphorothioate (**3o**, $CDCl_3$)





O,O-diethyl *Se*-phenyl phosphoroselenoate (**4a**, $CDCl_3$)





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======== CHANNEL f1 ========
NUC1                    13C
P1                    11.00 usec
PL1                   -1.00 dB
SFO1             75.4752953 MHz

======== CHANNEL f2 ========
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NUC2                     1H
PCPD2                 80.00 usec
PL2                   -2.00 dB
PL12                  13.00 dB
PL13                  17.00 dB
SFO2            300.1312005 MHz

F2 - Processing parameters
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SF               75.4677490 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40

1D NMR plot parameters
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CY                     5.00 cm
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F2P                  -0.857 ppm
F2                   -64.71 Hz
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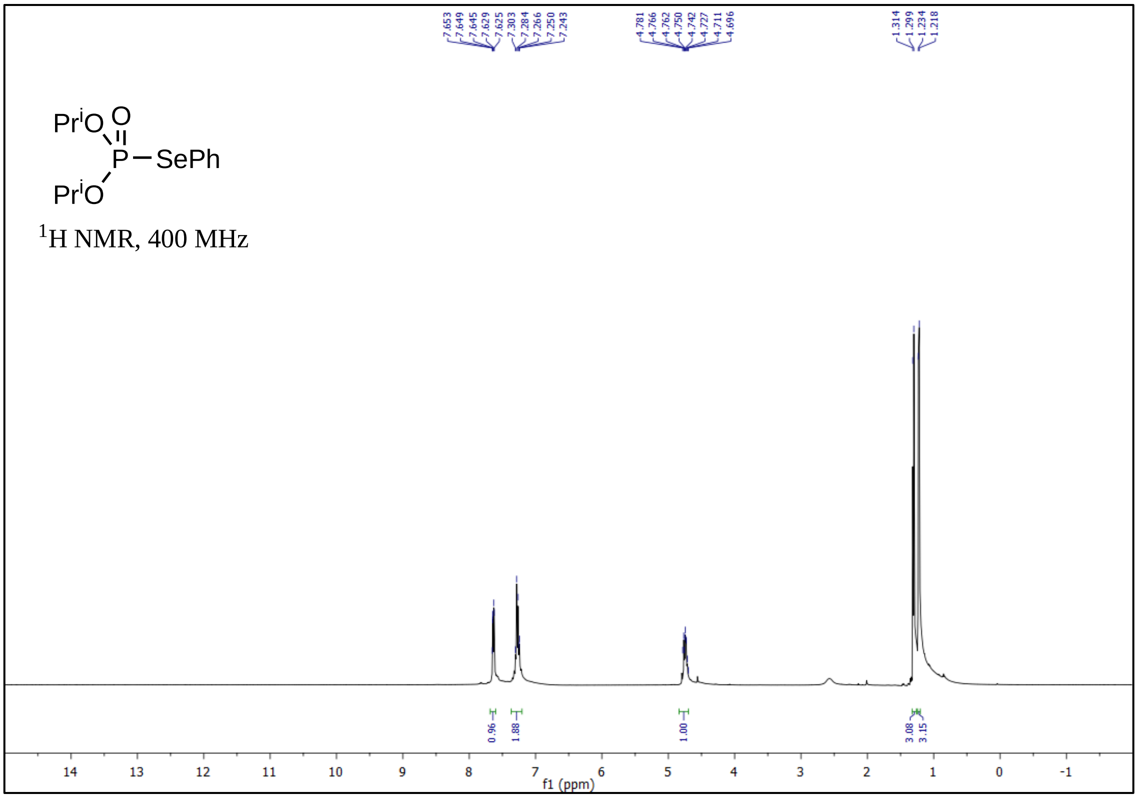
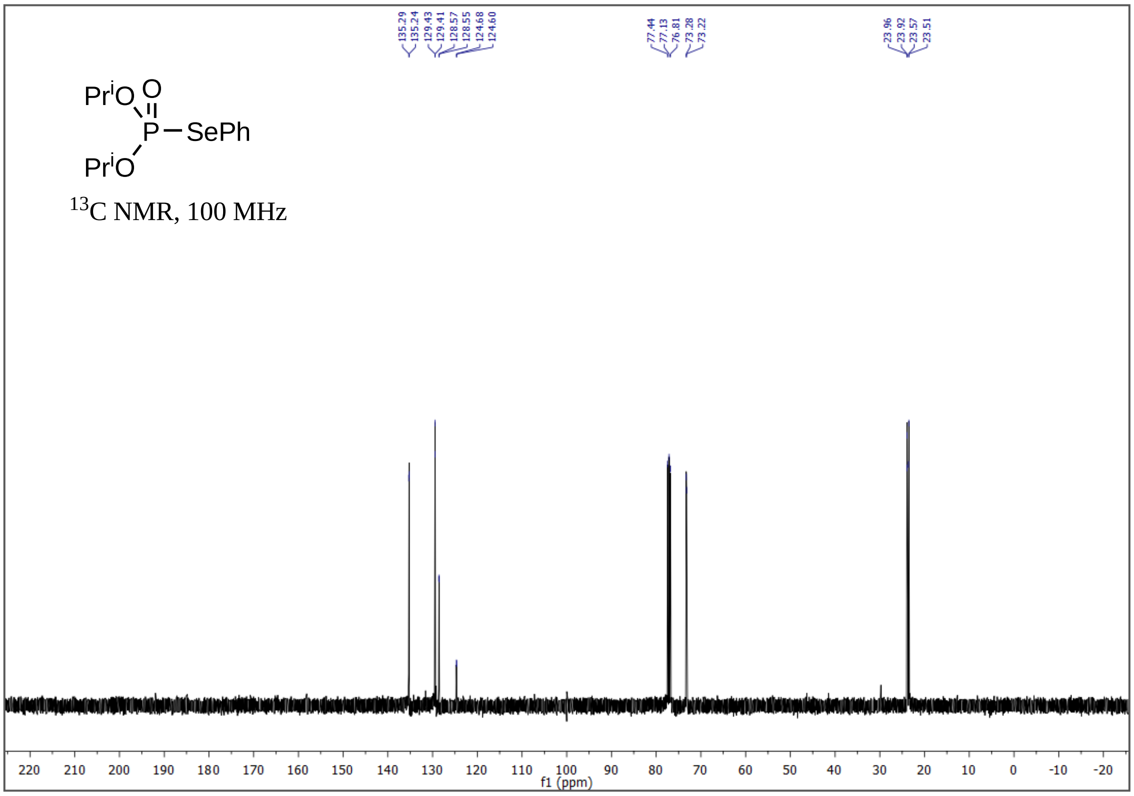
Se-phenyl *O,O*-diisopropylphosphoroselenoate (**4b**, $CDCl_3$)





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Sci. Technol., **2017**, 7, 2356; (r) R. D. Crocker, M. A. Hussein, J. Ho, T. V. Nguyen*, Chem. Eur. J.* **2017**, 23, 6259; (s) T. Liu, X. Cui, Z. Yu, C. Li, *Phosphorus, Sulfur, and Silicon and the Related Elements* **2012**, 187, 606; (t) S. Kovacs, B. Bayarmagnai, A. Aillerie, L. J. Gooßen, *Adv. Synth. Catal.,* **2018**, 360, 1913.

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Chapter-II

Section-I

Synthesis of Dithiocarbamate Compounds

2.1/a. Introduction

The importance of dithiocarbamates (DTCs) have increased during the last few decades in a variety of chemical fields from material to medicinal. Dithiocarbamate scaffold-containing compounds have received particular attention due to their exceptional pharmacological properties, including antifungal, [1] antioxidative, [2] antiparasitic, [3] antiviral, [4] antibacterial, [5] antituberculosis, [6] antibiofilm, [7] fungisidal, [8] insectisidal, [9] pesticidal, [10] herbicidal, [11] algicidal, [12] antileprocy, [13] antitubercular, [14] antimicrobial, [3] antiprotozoal, [15] anthelmintic, [16] antihistaminic, [17] antifouling, anticancer, [18] antialzheimer, [19] growth depressant activities[20] and also act as cell apoptosis, monoacylglycerollipase and indoleamine 2,3-dioxygenase inhibitors[21] properties. These days, a number of DTCs are being studied in clinical trials for a range of conditions, such as HIV, chronic alcoholism, arteriosclerosis, and fungi and bacteria-related diseases. [4, 22] They also act as potential auxiliaries in oncological chemotherapy. [23] Additionally, a recent publication suggests that the addition of a dithiocarbamate molecules enhance the biological activities[24] of such synthetic, semisynthetic, and natural compounds. dithiocarbamates exhibit a great propensity to complex formation with a wide variety of metal as monodentate and bidentate ligands or podants, where they are considered as four electron donor. [25] It has various application like photochemistry, [26] RAFT polymerization, [27] synthesis of NO, [28] catalysis in the vulcanization of rubber, [29] determination of heavy metal and waste water treatment. [30] In addition, they serve as a valuable synthetic precursor for the production of thioureas, isothiocyanates trifluoromethylamines, alkoxyamines, various heterocyclic compounds, [31] linkers in solid phase organic synthesis, [32] protecting group in peptide chemistry, [33] and in the molecular electronic devices. [34] They have also been found in materials and separation sciences. [35] Molecules containing thiocarbamide or thiourea scaffolds are also utilized in commercial purposes like in dyes, photographic films, textile, plastics and polymer industries. Recently, a new class of thiourea derivatives have also been identified which act as potent inhibitors of β-glucuronidase, free radicals such as 2,2-diphenyl-1-picrylhydrazyl and 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), α-amylase, α-glucosidase, acetylcholinesterase (AChE), buturyl-cholinesterase (BuChE), glucose-6-phosphate (G6Pase), urease, histone deacetylase and phenoloxidase enzyme. [36] Many synthetic procedures have been published for the synthesis of various dithiocarbamate derivatives due to its vast applicability. Herein, a brief review is presented that synthesis of various useful organic molecule by using dithiocarbamate as synthetic precursor. Some dithiocarbamate moiety containing important molecules are shown in Figure 2.1.01.

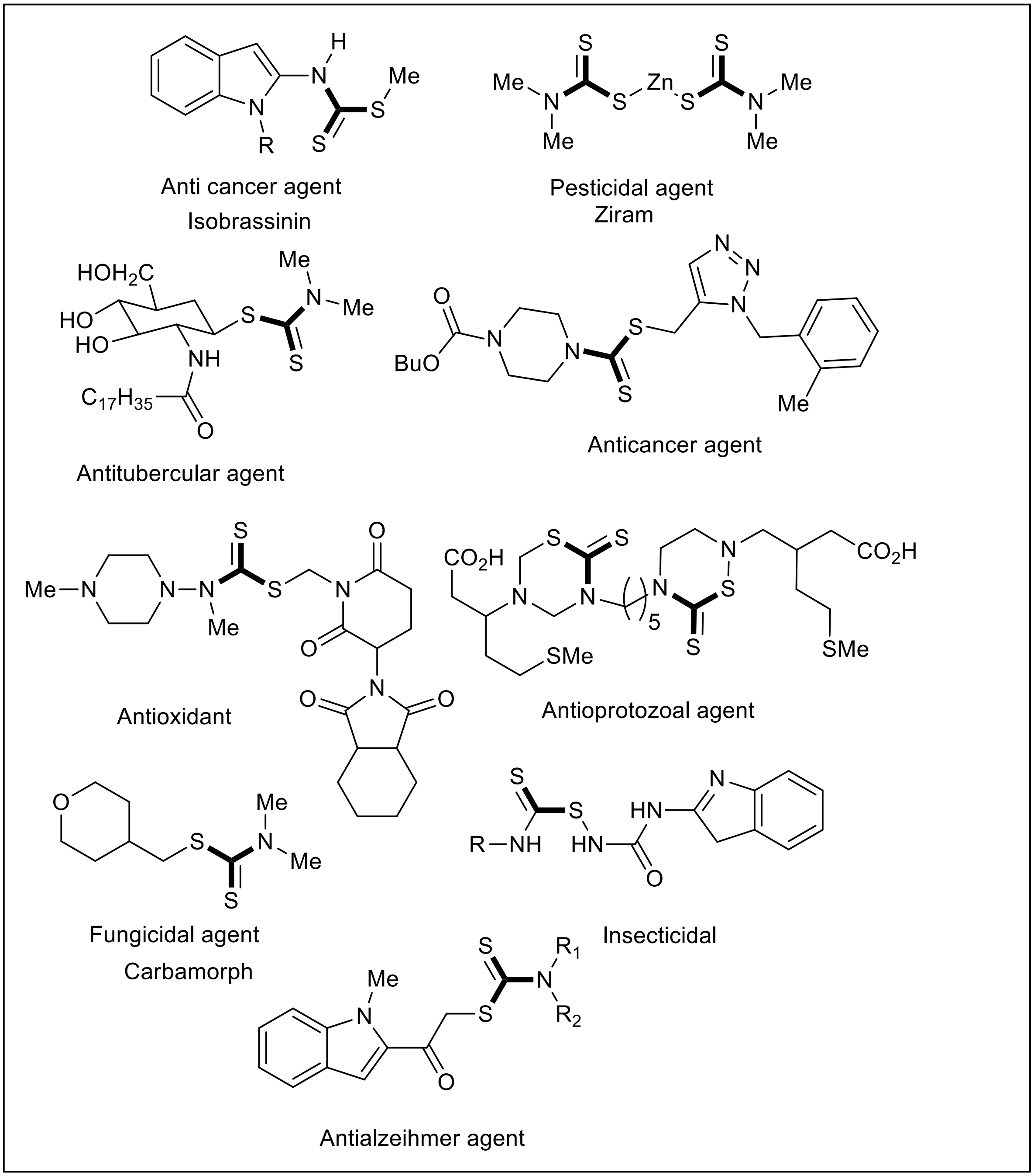

Anti cancer agent
Isobrassinin
Pesticidal agent
Ziram
Antitubercular agent
Anticancer agent
Antioxidant
Antioprotozoal agent
Fungicidal agent
Carbamorph
Insecticidal
Antialzeihmer agent

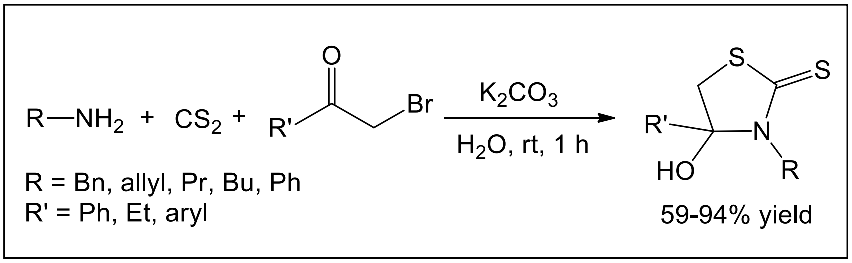
Figure 2.1.01

2.1/b. Review

Due to immense importance of dithiocarbamate molecules, organic chemists have showed great attention in their synthesis and application. As a result of that, a large number of synthetic strategies were developed to synthesize dithiocarbamate compounds. Along with the growth of dithiocarbamate chemistry, their derivatives have also emerged as useful synthetic precursor. In this short review, various synthetic protocols of dithiocarbamate derivatives have been discussed.

(I) Synthesis of polysubstituted thiazolidine-2-thione derivatives:

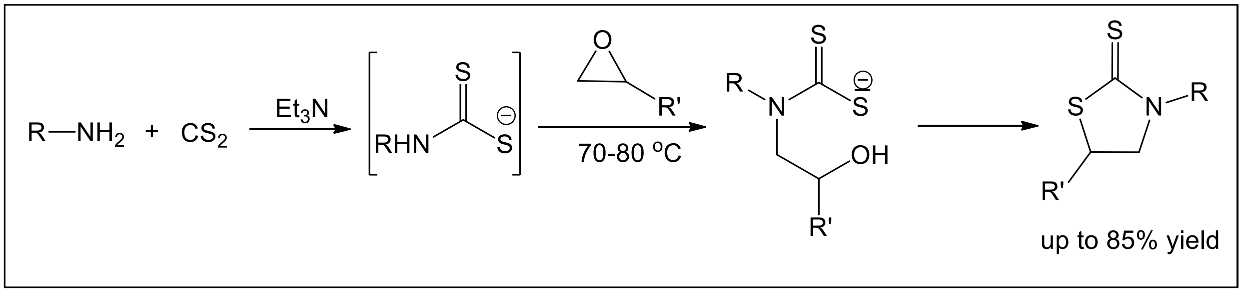
Sun and his co-workers[37] have been described the synthesis of polysubstituted thiazolidine-2-thione derivatives using a three-component process involving primary amine, carbon disulphide, and α-bromoketone in an aqueous medium (Scheme 2.1.01). This synthetic procedure offered good to exceptional yields of the intended products under mild to moderate reaction conditions, a broad range of substrates scope, strong functional group tolerance, a straightforward reaction, and environmental friendliness.



Scheme 2.1.01

(II) Synthesis of 1,3-thiazoline-2-thiones:

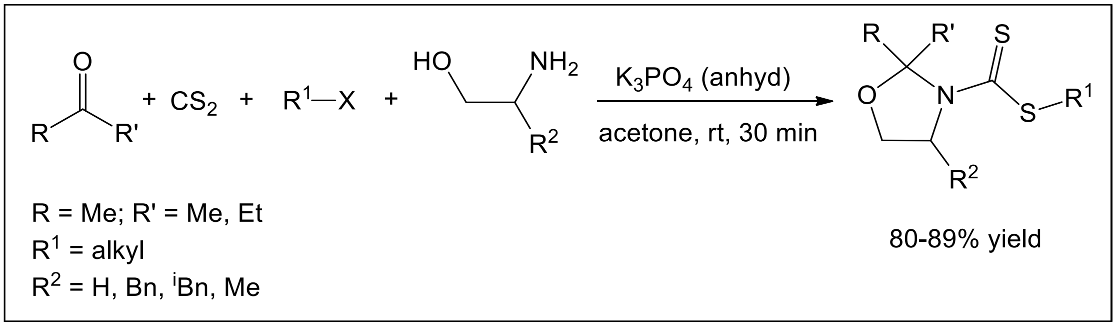
Based on the reaction of dithiocarbamate anion with oxirane at 70–80 °C, Kulakov and his group[38] have developed another synthetic procedure towards 1,3-thiazoline-2-thiones. Dithiocarbamate anions' nitrogen served as a nucleophile to open the oxirane ring in this instance (Scheme 2.1.02).



Scheme 2.1.02

(III) Synthesis of 3-alkyldithiocarbonyloxazolidines:

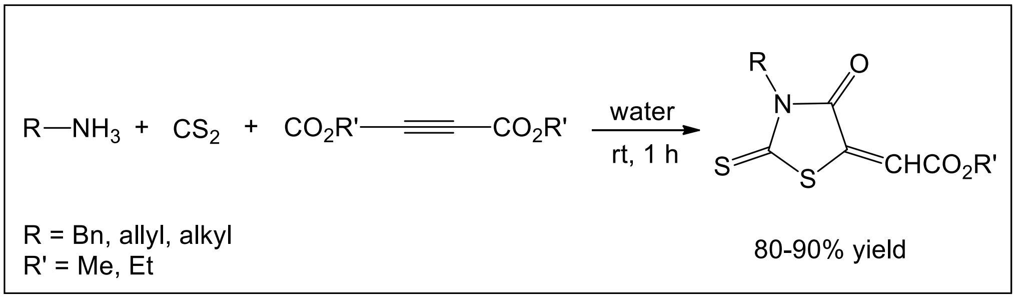
Li and his group[39] synthesised 3-alkyldithiocarbonyloxazolidines by a four-component reaction at room temperature from aminothiols, ketone, carbon disulphides, and alkyl halides as starting materials and utilising potassium phosphate and dry acetone as a solvent. In addition to being a base, potassium phosphate also played as a phase transition catalyst and dehydrator.



Scheme 2.1.03

(IV) Synthesis of rhodamine derivatives:

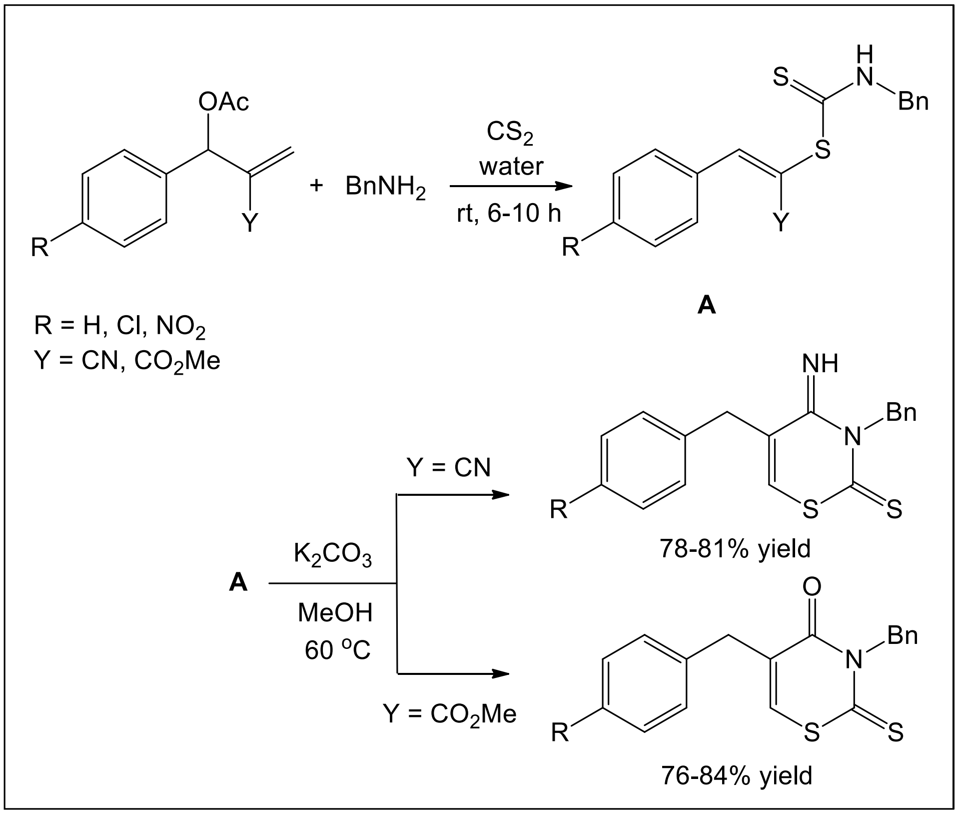
Alizadeh et al[40] reported a three-component coupling of primary amines, carbon disulphide, and dialkylacetylenedicarboxylate in aqueous medium at ambient temperature for one hour to synthesis of rhodamine derivatives. A hypothesised mechanistic pathway states that the corresponding intended product was formed when the in situ produced dithiocarbamate salt reacted with acetylenic esters, followed by cyclisation and the concomitant loss of alcohols.



Scheme 2.1.04

(V) Base catalyzed intramolecular cyclisation of *N*-benzylallyldithiocarbamates:

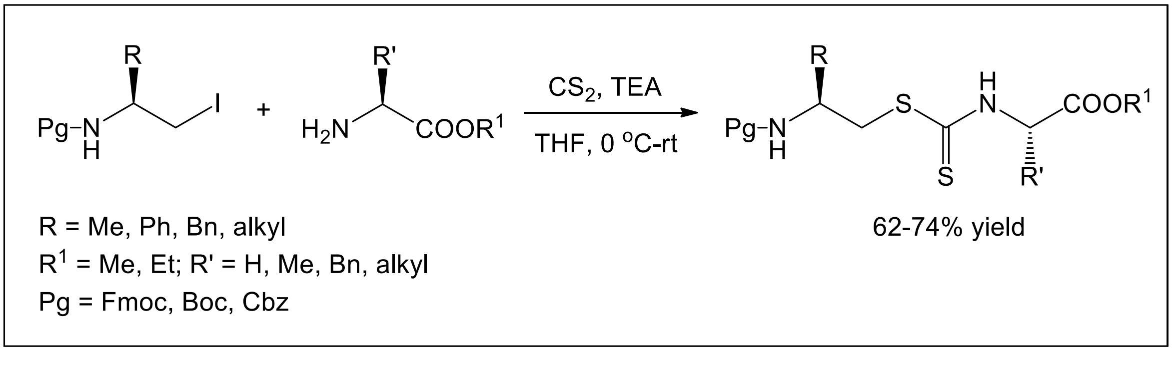
The preparation of functionalised 1,3-thiazines was also achieved by base catalyzed intramolecular cyclisation of in situ produced *N*-benzylallyldithiocarbamates, which were created by nucleophilically displacing Baylis-Hillman acetates by dithiocarbamte anions in a water medium (Scheme 2.1.05). The cyclisation processes produced good to high yields of the desired heterocyclic products at 60 °C in a methanolic solvent for 3-4 hour. [41]



Scheme 2.1.05

(VI) Synthesis of dithiocarbamte-lined peptidomimetics:

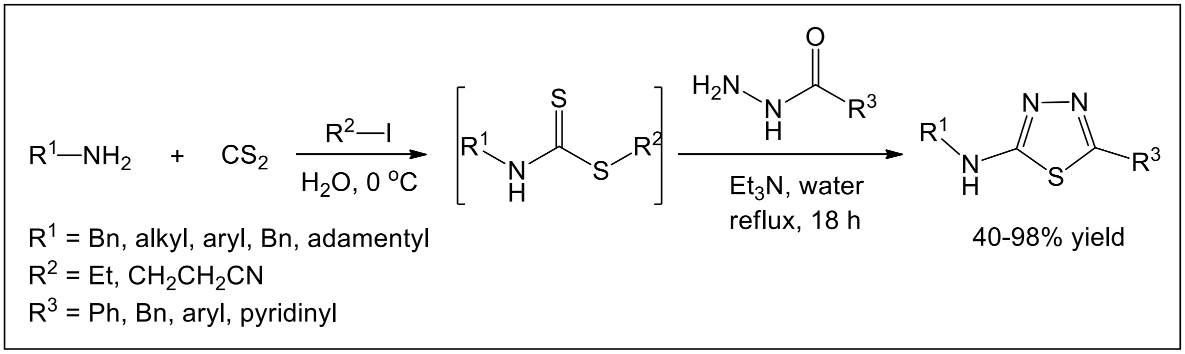
Sureshbabu and his team[42] synthesized dithiocarbamte-lined peptidomimetics by the reaction of in situ generated dithiocarbamic acid with *N*-protected amino alkyl iodide using trimethylamine as base in THF solvent. This synthetic protocol offered good to moderate yield of the products, mild reaction condition.



Scheme 2.1.06

(VII) Synthesis of 2-amino-1,3,4-thiadiazoles:

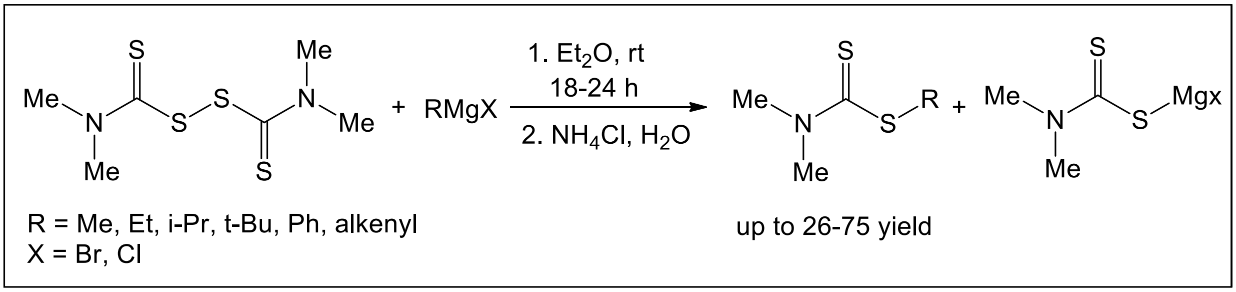
Saidi and his group[43] synthesized 2-amino-1,3,4-thiadiazoles in good to excellent yields by the reaction of acid hydrazides and freshly prepared S-alkyl dithiocarbamates which were obtained from a reaction mixture of amine, carbon disulfide and alkyl iodide (Scheme 2.1.07). All reactions were carried out in aqueous medium using triethylamine under refluxing condition.



Scheme 2.1.07

(VIII) Preparation of alkyl-*N,N*-dimethyldithiocarbamates:

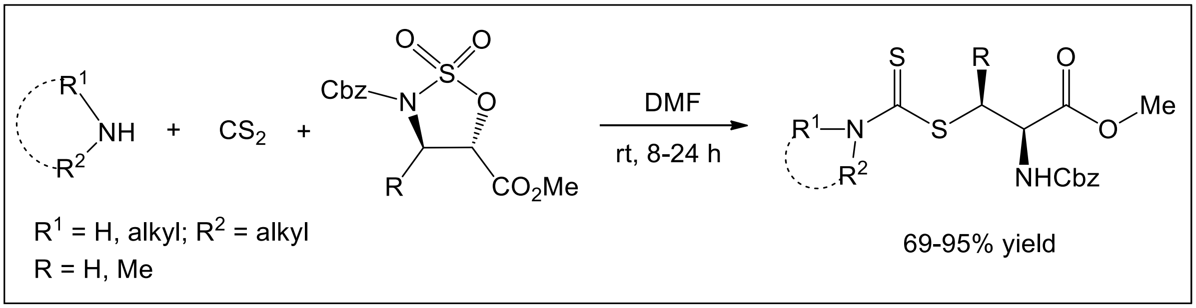
J. R. Grunwell[44] first successfully prepared alkyl-*N,N*-dimethyldithiocarbamates by the reaction of tetramethylthiuram disulfide [$(Me_2NCS_2)_2$] and Grignard reagent such as (primary, secondary tertiary), aryl, alkenyl magnesium halide (Scheme 2.1.08). Along with the formation of desired product, magnesium dithiocarbamate salt was formed as by product. This reaction was performed in water medium at room temperature for 18-24 h affording 26-75% yield of the desired product.



Scheme 2.1.08

(IX) Synthesis of Unnatural α-amino acid derivatives:

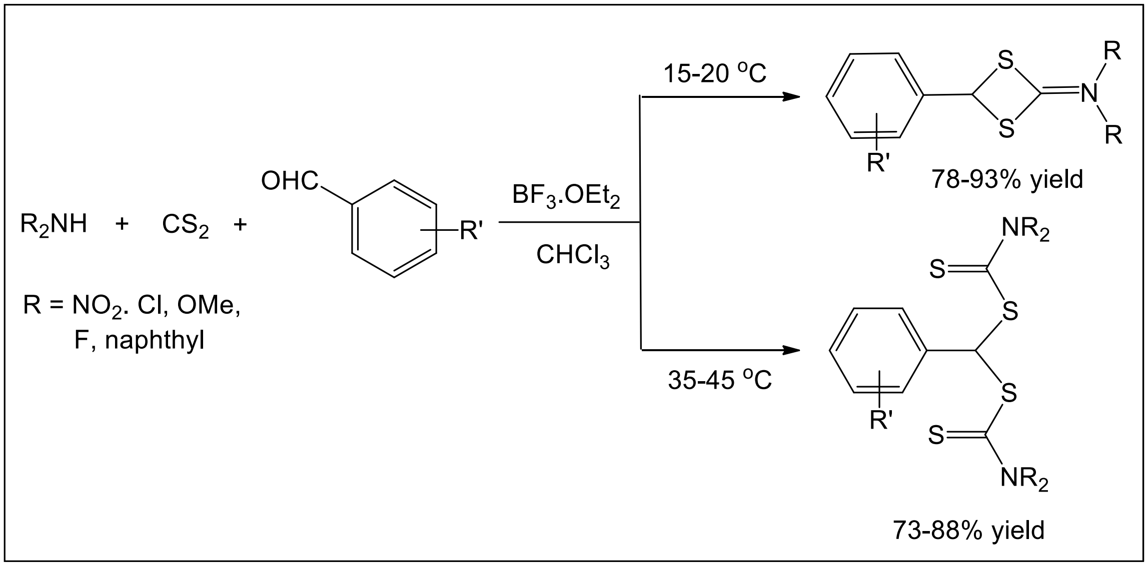
Verma and his group[45] developed a highly region-selective one-pot procedure to prepare the Dithiocarbamate side chain containing Unnatural α-amino acid derivatives by the reaction of a series of sulfamidates and freshly prepared dithiocarbamate salts. All reactions were carried out in DMF solvent at room temperature for 12 h.



Scheme 2.1.09

(X) $BF_3.OEt_2$ catalyzed dithiocarbamylation:

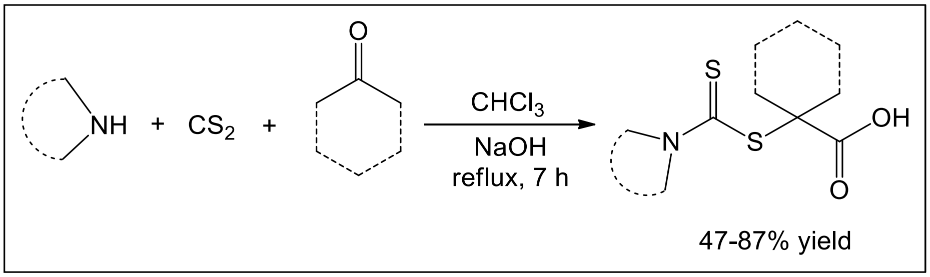
According to Helimehjani and his team, [46] two distinct products were formed when aryl aldehyde compounds and dithiocarbamic acid salts reacted in the presence of the catalytic quantity $BF_3.OEt_2$ in chloroform. At 15-20 °C Substituted 2-iminium-1,3-dithietane compounds were obtained exclusively whereas gem-bis(dithiocarbamates) were obtained at 35-45 °C. Various type of aromatic aldehyde performed efficiently to produce desired product (Scheme 2.1.10).



Scheme 2.1.10

(XI) Synthesis of α-dithiocarbamate pendant carboxylic acid derivatives:

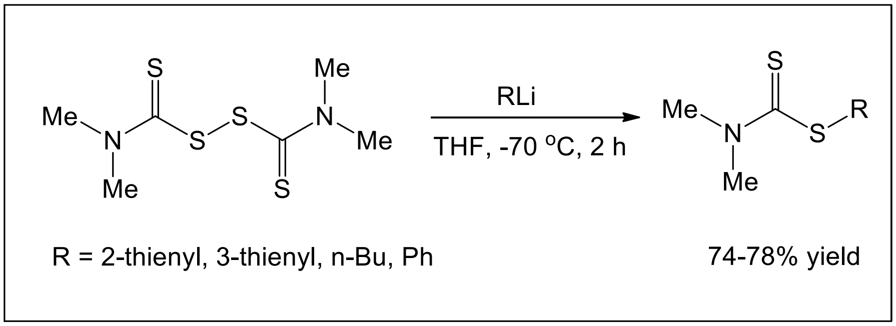
Dithiocarbamte anions were introduced by Saidi and his group[47] as a useful nucleophile in the Bargellini process. Acetone, cyclohexanone and various dithiocarbamate salts used as starting material under refluxing condition for 7 h to produce α-dithiocarbamate pendant carboxylic acid derivatives in 47-87% yield (Scheme 2.1.11).



Scheme 2.1.11

(XII) Synthesis of both aromatic and aliphatic thioamides:

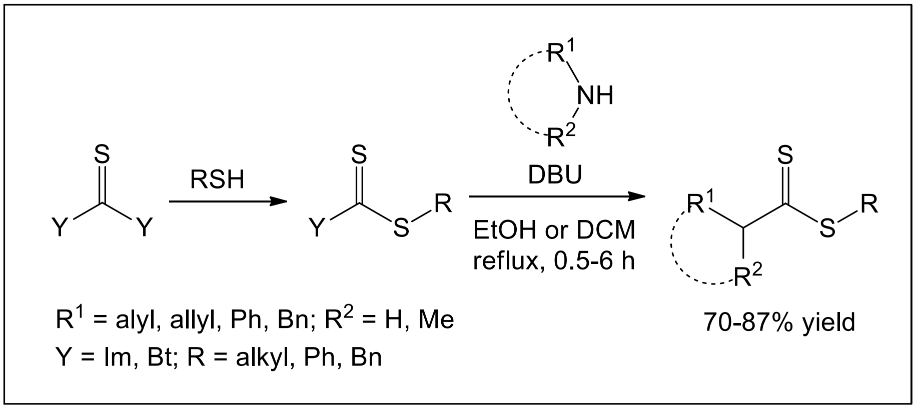
Later, Gronowitz and his co-workers[48] developed a convenient method for the synthesis of both aromatic and aliphatic thioamides in good yields from the reaction of organolithium derivatives and thiuram monosulfides. But, the reaction of organolithium derivatives with tetramethylthiuram disulfide gave only dithiocarbamate and not a mixture of these and thioamides.



Scheme 2.1.12

(XIII) Synthesis of symmetrical and unsymmetrical mono-, di-, and tri-substituted thioureas, as well as methyl dithiocarbamates:

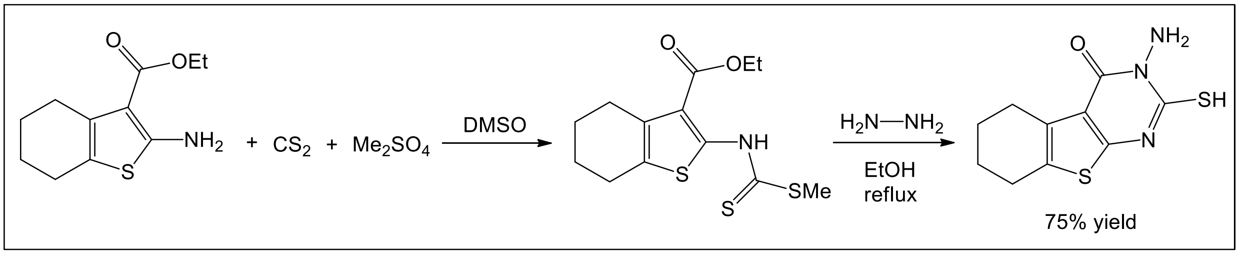
The synthetic potential of 1-(methyldithiocarbonyl)imidazole and its quaternary salt as methyldithiocarbonyl and thiocarbonyl transfer reagents has been successfully demonstrated by Mohanta et al (Scheme 3.4). [49] A synthesis of symmetrical and unsymmetrical mono-, di-, and tri-substituted thioureas, as well as methyl dithiocarbamates, has been produced with a high yield. A variety of thioureas with a wide range of structural variations can be synthesised using this process, which is convenient and less dangerous.



Scheme 2.1.13

(XIV) Synthesis of 3-amino-2-mercapto-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidine-4-one:

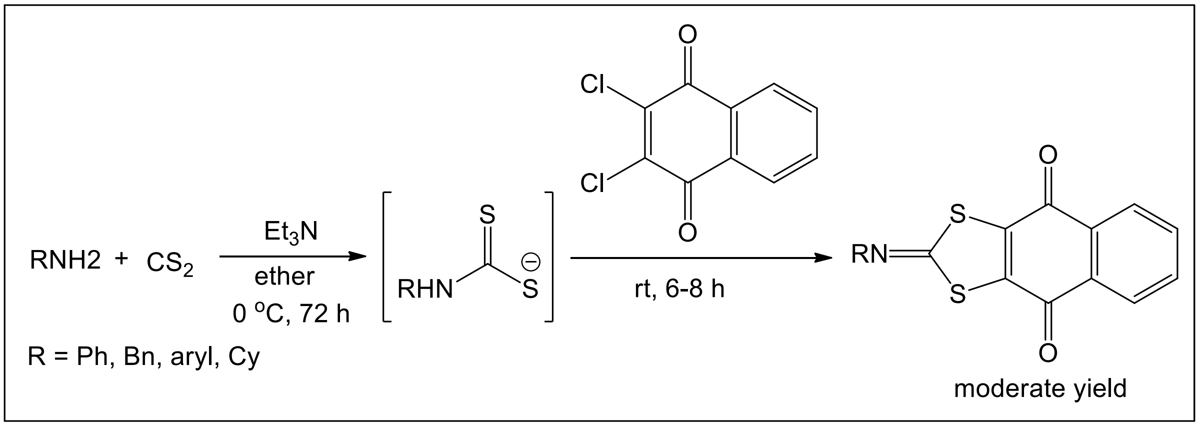
Alagarsamy et al[50] synthesized 3-amino-2-mercapto-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidine-4-one from the reaction of carbon disulfide with a stirred solution of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene, dimethyl sulphate and sodium hydroxide in DMSO solvent followed by the reaction with hydrazine hydrate under refluxing condition.



Scheme 2.1.14

(XV) Synthesis of 2-iminonaphtho[2,3-d][1,3]dithiole-4,9-diones:

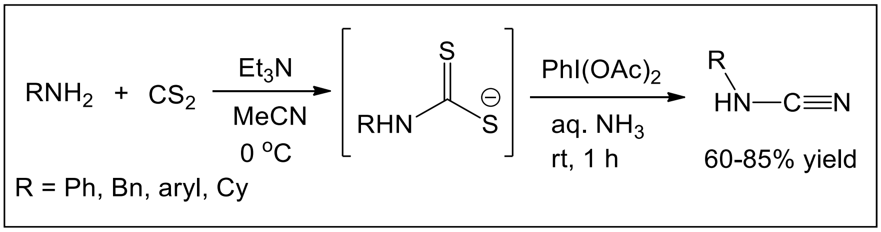
Aly et al[51] prepared 2-iminonaphtho[2,3-d][1,3]dithiole-4,9-diones by the reaction of carbamodithioates and 2,3-dichloro-1,4-naphthoquinone in ether solvent at room temperature for 6-8 h.



Scheme 2.1.15

(XVI) Preparation of organic cyanamide:

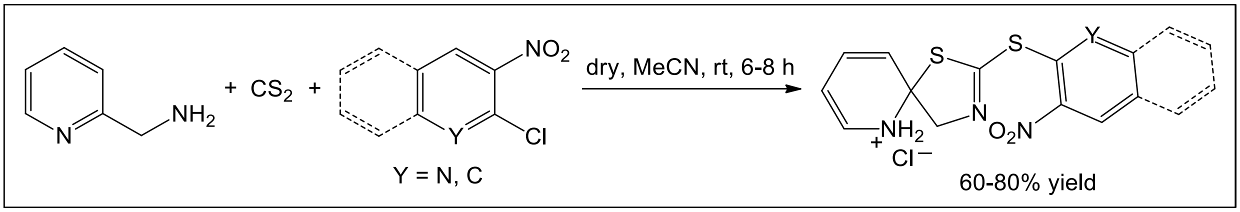
Patel and his team[52] prepared organic cyanamide from the reaction between (diacetoxyiodo)benzene and in situ generated dithiocarbamic acid salts in aqueous ammonia solution. These reactions were proceeded through the formation of two intermediate like alkyl or aryl isothiocyanates and alkyl or aryl thiourea. This protocol offered good yield of the desired product, mild reaction conditions, shorter reaction time (Scheme 2.1.16).



Scheme 2.1.16

(XVII) Preparation of 3,6-diazaspiro[4.5]deca-2,7,9-trienium chloride derivatives:

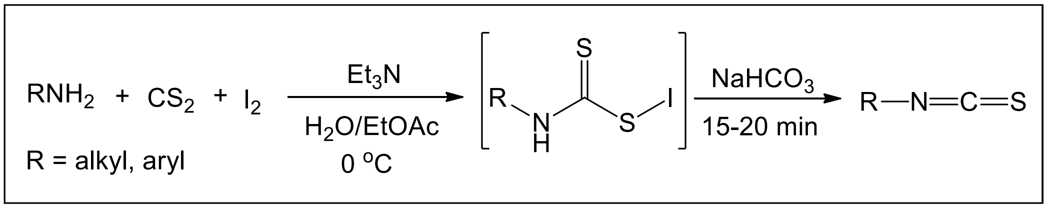
Karimi et al[53] established a novel synthetic route to prepare 3,6-diazaspiro[4.5]deca-2,7,9-trienium chloride derivatives by the reaction of 2-(aminomethyl)pyridine with carbon disulfide and electron deficient derivatives of chloropyridine or chlorobenzene in dry acetonitrile solvent at room temperature for 6-8 h (Scheme 2.1.17).



Scheme 2.1.17

(XVIII) Preparation of isothiocyanate derivatives *via* iodine mediated desulfurization:

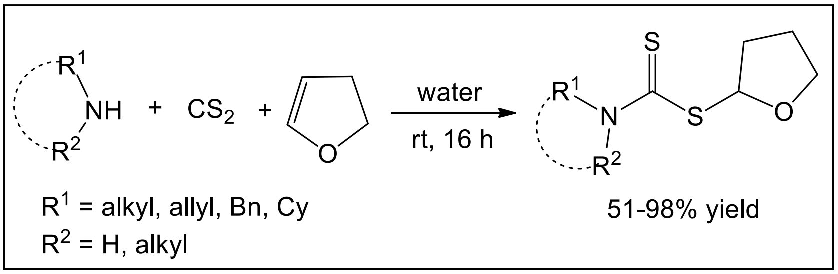
Patel and his co-workers developed a simple protocol to prepare isothiocyanate derivatives *via* iodine mediated desulfurization of in situ generated dithiocarbamic scid salts in presence of sodium bicarbonate and water-ethyl acetate mixture (Scheme 2.1.18). [54]



Scheme 2.1.18

(XIX) Dithiocarbamylation of alkyl vinyl ethers:

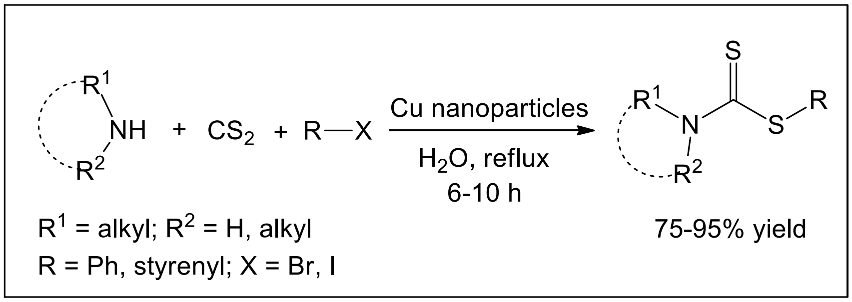
Azim and his group synthesized dithiocarbamate derivatives by the reaction of primary or secondary amine and carbon disulfide with alkyl vinyl ethers in water as solvent. This protocol provided excellent yield of the desired product with regiospecificity. This is catalyst and base free technique (Scheme 2.1.19). [55]



Scheme 2.1.19

(XX) Reaction of aryl iodide or styrenyl bromide with copper nanoparticles catalyst:

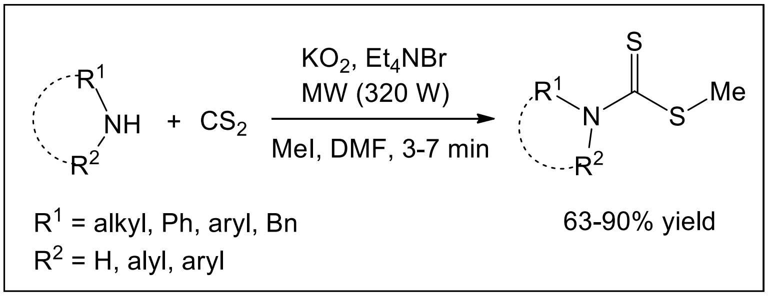
B. C. Ranu and his team[56] developed copper nanoparticles catalyzed one-pot reaction of amine, carbon disulfide and aryl iodide or styrenyl bromide to prepare aryl or vinyl dithiocarbamates in aqueous medium under refluxing condition for 6-10 h with excellent yield.



Scheme 2.1.20

(XXI) Microwave-tetraethylammonium superoxide mediated alkylation:

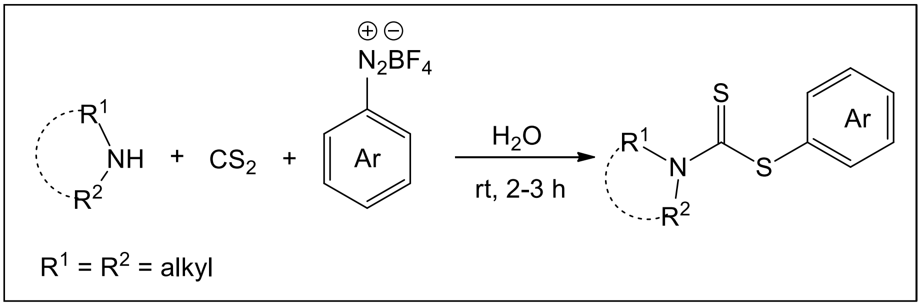
Singh and his group synthesized s-alkylated derivatives by microwave-tetraethylammonium superoxide mediated alkylation of in situ generated dithiovarbamate salts with methyl iodide in DMF solvent for 3-7 min with excellent yield (Scheme 2.1.21). [57]



Scheme 2.1.21

(XXII) Reaction of aryl diazonium chloride with sodium salt of dithiocarbamate:

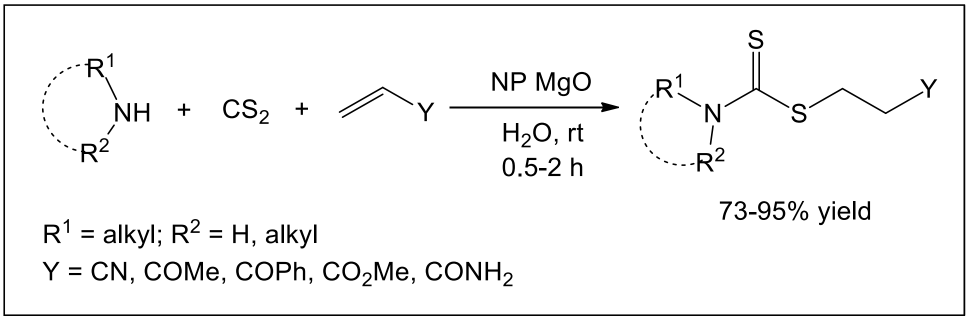
According to Clifford and his co-workers, [58] Aryl dithiocarbamates first synthesized by the reaction of aryl diazonium chloride with sodium salt of dithiocarbamate in water medium. This protocol offered large substrate scope, excellent yield of the reaction and one step strategy (Scheme 2.1.22).



Scheme 2.1.22

(XXIII) Synthesis of organic dithiocarbamate compounds using basic nanocrystalline MgO catalyst:

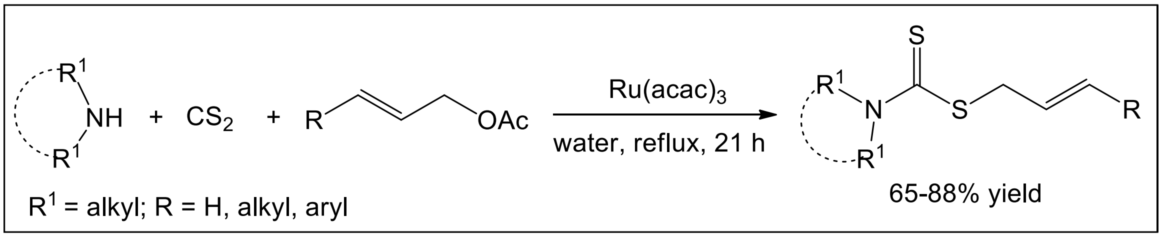
Banerjee et al developed environment friendly route to prepare organic dithiocarbamate compounds from the reaction of amines, carbon disulfides and electron deficient alkenes (in a 1:1.2:3) in presence of basic nanocrystalline MgO catalyst and water as solvent at room temperature (Scheme 2.1.23). [59]



Scheme 2.1.23

(XXIV) Ru-catalyzed dithiocarbamylation:

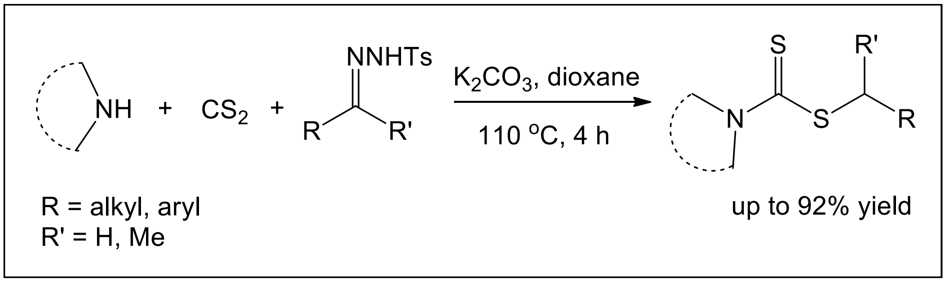
Ranu and his group synthesized S-allyl or cinnamyl dithiocarbamates from the reaction of allyl or cinnamyl acetate, secondary amine and carbon disulfide in presence of ruthenium catalyst and water as solvent under refluxing condition for 21 h. Here, non-activated allyl or cinamyl acetates underwent the reaction easily to produce corresponding dithiocarbamate with high yields (Scheme 2.1.25). [60]



Scheme 2.1.24

(XXV) Synthesis of *S*-alkyldithiocarbamates:

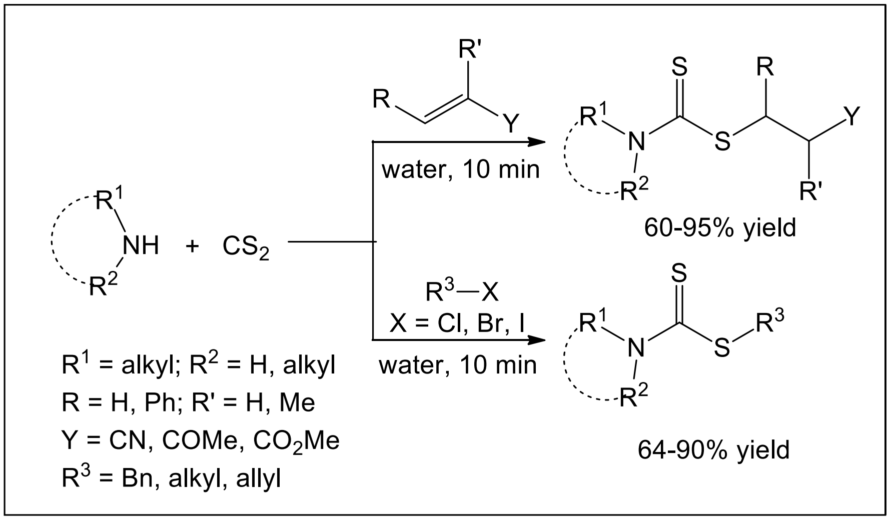
Another synthetic protocol was reported by Wei and his team where amines, carbon disulfide and in situ generated *N*-tosylhydrazone reacted towards in presence of K_2CO_3 in dioxane medium at 110 °C for 4 h to produce corresponding *S*-alkyldithiocarbamates in good yields (Scheme 2.1.25). [61]



Scheme 2.1.25

(XXVI) Reaction of unsaturated carbonyl compounds or alkyl halides:

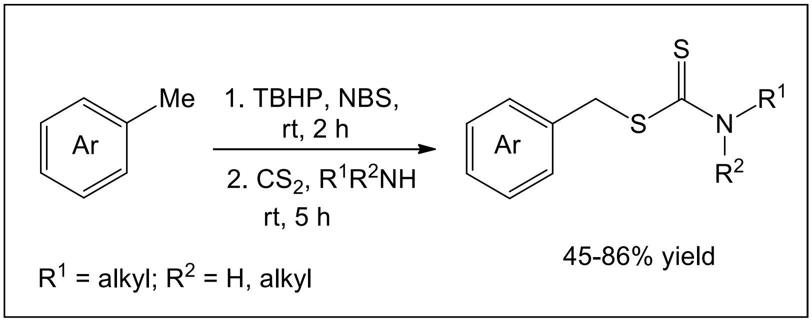
Nayeri et al synthesized dithiocarbamate derivatives by ultrasound assisted various multicomponent reaction using amines (primary and secondary), carbon disulfide and unsaturated carbonyl compounds or alkyl halides in water (Scheme2.1.26). [62]



Scheme 2.1.26

(XXVII) Synthesis of *S*-alkyl dithiocarbamates *via* radical pathway:

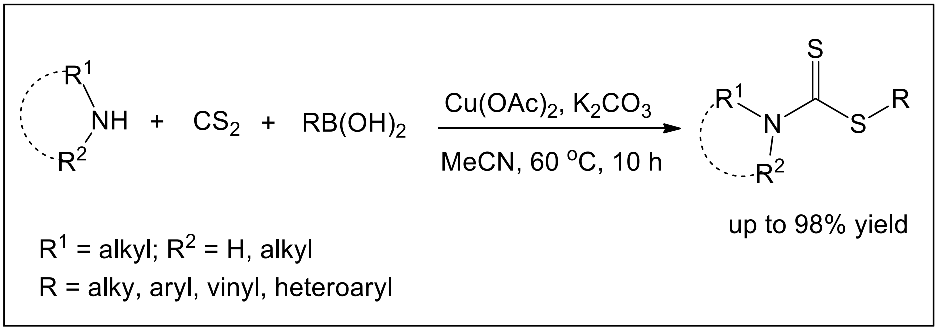
Singh et al synthesized a series of *S*-alkyl dithiocarbamates from readily available starting material methylarenes under catalyst free and solvent free condition at room temperature for 7 h. Combination of TBHP-NBS reagent was used to produce desired product *via* radical pathway (Scheme 2.1.27). [63]



Scheme 2.1.27

(XXVIII) Synthesis of functionalized dithiocarbamate derivatives from boronic acid:

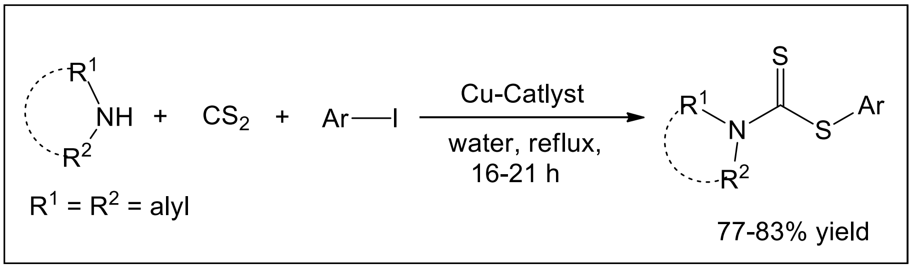
Qi and his team synthesized a wide range of functionalized dithiocarbamate derivatives in good yield by the reaction of primary or secondary amine, carbon disulfide and alkyl boronic acid in presence of copper acetate and potassium carbonate in acetonitrile solvent at 60 ^{o}C for 10 h under open air atmosphere (Scheme 2.1.28). [64]



Scheme 2.1.28

(XXIX) Preparation of *S*-aryl dithiocarbamate using copper nanocatalyst:

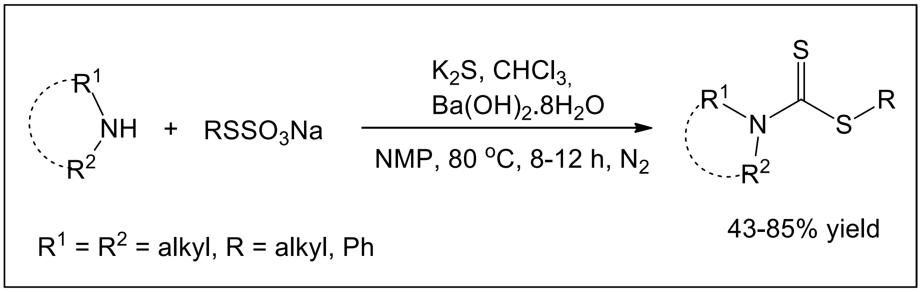
Sharghi and his group[65] developed a one-pot three components reaction using amine, carbon disulfide aryl iodide and copper nanocatalyst to produce *S*-aryl dithiocarbamate in water solvent under refluxing condition for 16 to 21 h. Copper nanocatalyst was characterized by various technique like SEM, TEM AFM, ICP from which the particle size was found between 60-110 nm.



Scheme 2.1.29

(XXX) Synthesis of dithiocarbamate derivatives from *S*-alkyl or *S*-phenyl thiosulfate salts:

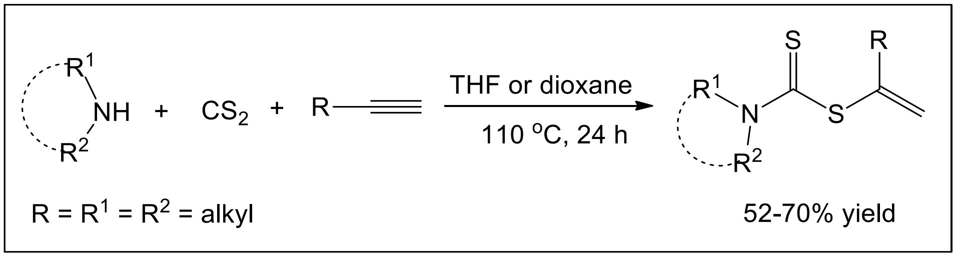
Jiang and his co-workers[66] synthesized S-alkyl or *S*-phenyl dithiocarbamate from the reaction of *S*-alkyl or *S*-phenyl thiosulfate salts and secondary amine in presence of potassium sulfide, chloroform, barium hydroxide and NMP solvent at 80 °C for 8-12 h under nitrogen atmosphere. Thioamide also was formed along with the desired product.



Scheme 2.1.30

(XXXI) Regio- and stereocontrolled catalyst free reaction:

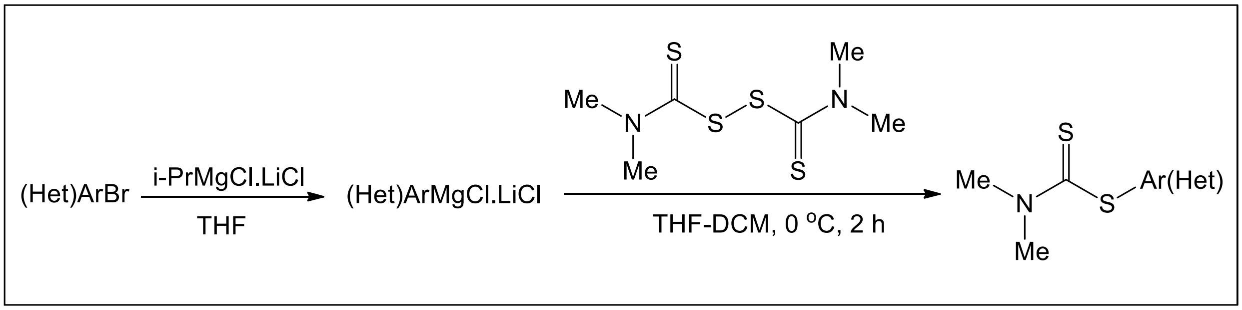
Halimehjani et al[67] established a straightforward route to prepare vinyl dithiocarbamate derivatives from the reaction of unactivated alkynes with in situ generated dithiocarbamic acid (Scheme 2.1.31).



Scheme 2.1.31

(XXXII) Synthesis of Dithiocarbamate:

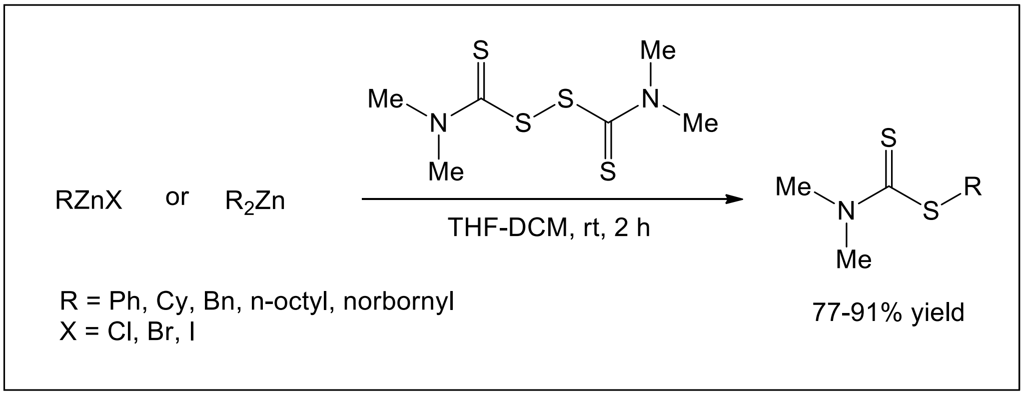
Knochel et al[68] have demonstrated a variety of aryl and heteroaryl magnesium reagents react with TMTD in the presence of LiCl to produce the corresponding dithiocarbamates in high yields. Different functional groups are compatible with this reaction because of the mild circumstances. A thiol, a thiol salt, or a thioether can be easily formed from the dithiocarbamate function. They developed facile, cheap and general method for the preparation of the variety of sulfur-containing compounds starting from easily accessible Grignard reagents.



Scheme 2.1.32

(XXXIII) Synthesis of Dithiocarbamate:

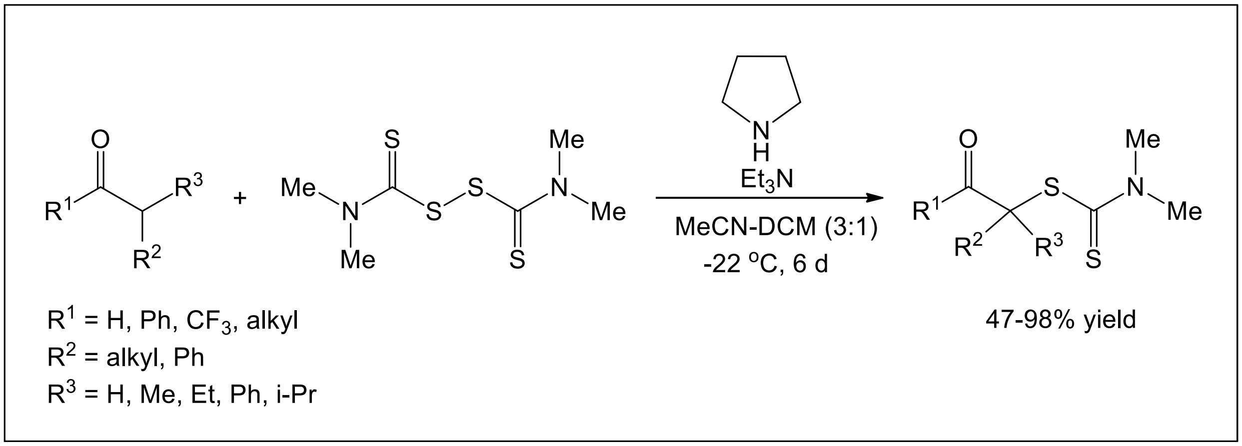
Knochel and his co-workers[69] have shown that various classes of organozinc compounds react with TMTD affording the corresponding dithiocarbamates. The finest outcomes and consistently very good yields were obtained with the usage of diorganozinc derivatives. This reaction works with configuration retention and can be further extended to easily accessible functionalised alkyl zinc reagents.



Scheme 2.1.33

(XXXIV) α-dithiocarbamoylation of aldehydes and ketones:

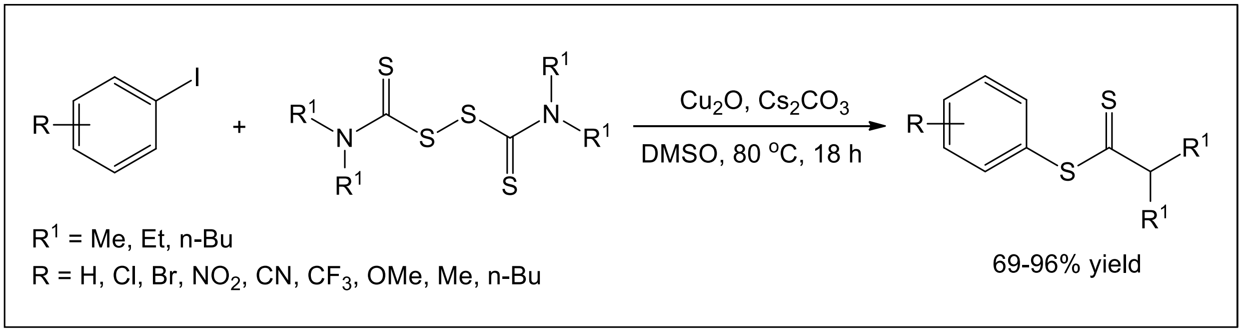
Enders et al[70] have developed a direct pyrrolidine-catalyzed α-dithiocarbamoylation of aldehydes and ketones by using the extremely affordable, readily accessible tetramethylthiuram disulphide (thiram) as an electrophilic sulfenylation reagent. In addition to acyclic and cyclic ketones, aldehydes can also be sulfenylated in this manner, yielding good to exceptional quaternary stereocenters.



Scheme 2.1.34

(XXXV) Synthesis of *S*-Aryldithiocarbamates:

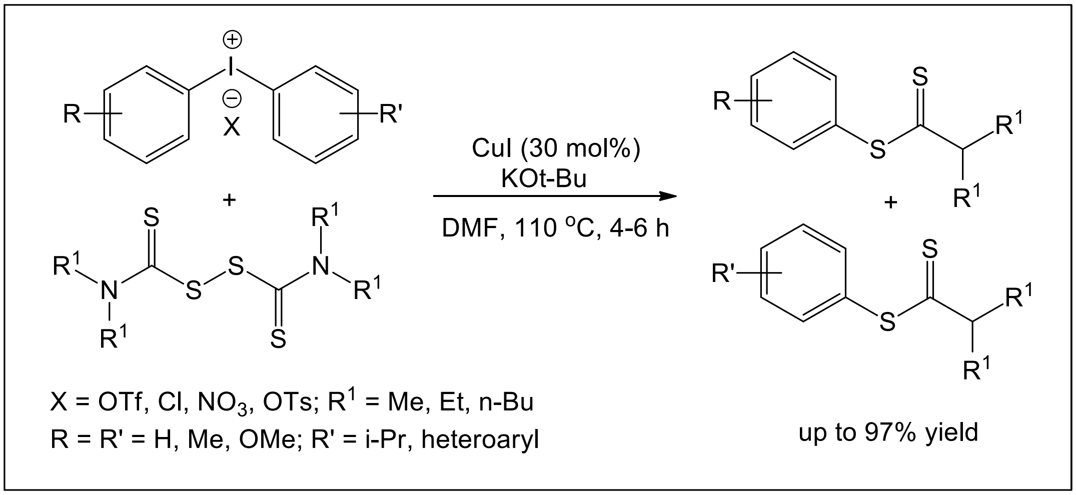
Later, Dong et al[71] have developed convenient and useful synthetic approach to produce aryl dithiocarbamates in 69-96% yields using aryl iodides and inexpensive, environmentally benign thiuram disulfide reagents in presence of copper-catalyst. There is no need for an extra ligand because the catalytic system is based on easily accessible reagents (Cu_2O and Cs_2CO_3). A scaled up reaction (30 mmol) also performed in this protocol.



Scheme 2.1.35

(XXXVI) Synthesis of *S*-Aryldithiocarbamates:

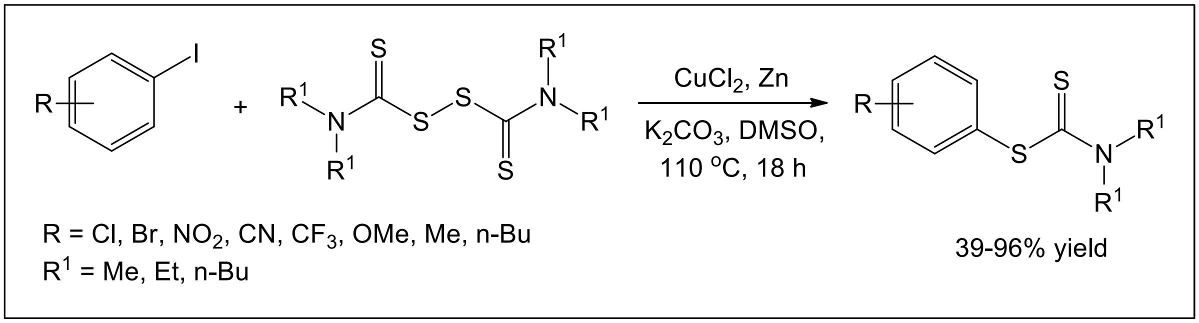
Dong and his team herein reported an efficient and convenient procedure for the synthesis of *S*-aryl dithiocarbamates from diaryliodonium salts and tetraalkylthiuram disulfides. Two different types of *S*-aryl dithiocarbamates were produced in good yields in presence of CuI/KOtBu (Scheme 2.1.36). [72] The reaction offers a wide range of substrate compatibility, high atom economy, and efficiency. With this technique, several potentially physiologically active chemicals could be prepared quickly and via an alternate mechanism.



Scheme 2.1.36

(XXXVII) Copper catalyzed Dithiocarbamylation:

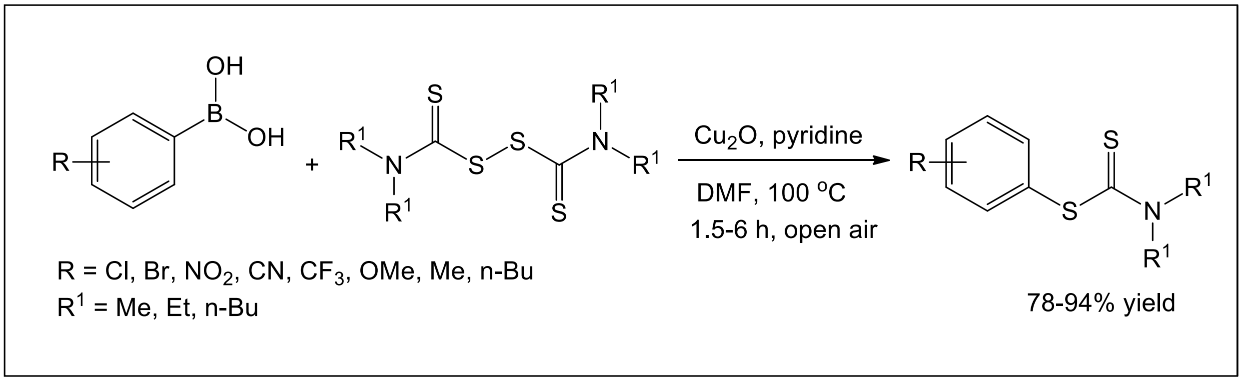
A highly effective C–S cross-coupling reaction between aryl iodides and tetraalkylthiuram disulphides generated using copper(II) as the catalyst. Tetraalkylthiuram disulphides and aryl iodides interacted in DMSO with only 1 mol% of $CuCl_2$ acting as catalyst, zinc powder acting as reductant, and K_2CO_3 acting as base. The reaction produced the corresponding aryl dithiocarbamates in good to exceptional yields. The method has a broad substrate scope and uses cheap and readily available starting materials (Scheme 2.1.37). [73a]



Scheme 2.1.37

(XXXVIII) Synthesis of S-Arylthiocarbamates:

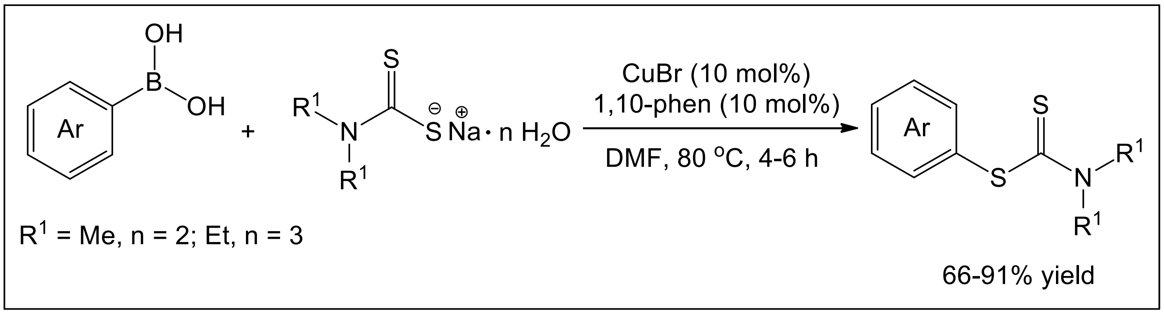
The same group[73b] further developed a convenient and useful protocol for the synthesis of diverse *S*-aryl dithiocarbamates. Copper-catalyzed C–S coupling proceeds smoothly from the mixture of arylboronic acid and tetraalkylthiuram disulfide to give the desired *S*-aryl dithiocarbamates in good to excellent yields. This methodology has the potential to be a useful synthetic method for the synthesis of physiologically or pharmaceutically active molecules due to its broad substrate scope, fast reaction time, ease of use, inexpensive substrates, and nice yields.



Scheme 2.1.38

(XXXIX) S-arylation of sodium dialkyldithiocarbamates:

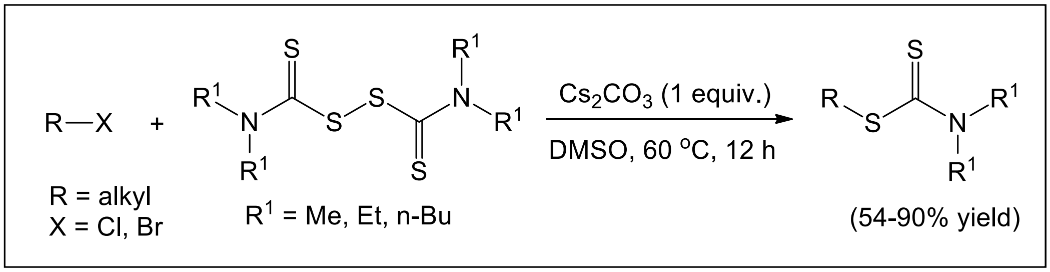
A convenient and efficient protocol have been developed for *S*-arylation of sodium dialkyldithiocarbamates. Sodium dialkyldithiocarbamates combined with aryl boronic acids in presence of copper(I) bromide to produce C-S coupling products with very good to exceptional yields. This approach has significant synthetic relevance for the facile synthesis of some potentially physiologically active compounds because to its readily available starting ingredients, ease of performance, fast reaction time, broad substrate scope, and good yields (Scheme 2.1.39).[74]



Scheme 2.1.39

(XXXX) Synthesis of *S*-alkyl dithiocarbamates:

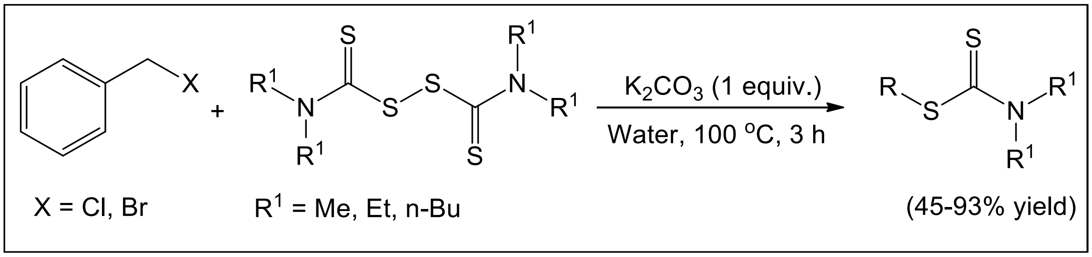
Synthesis of *S*-alkyl dithiocarbamates has been done by an efficient and environmentally benign protocol. Good to exceptional yields of the desired products produced by reacting tetraalkylthiuram disulphides with alkyl halides. Such simple and efficient method was able to produce some potential biologically active molecules. The reaction has advantages of transition metal-free, easy performance, versatility, nice yield and environmental friendliness (Scheme 2.1.40). [75]



Scheme 2.1.40

(XXXXI) Synthesis of benzyl dithiocarbamates:

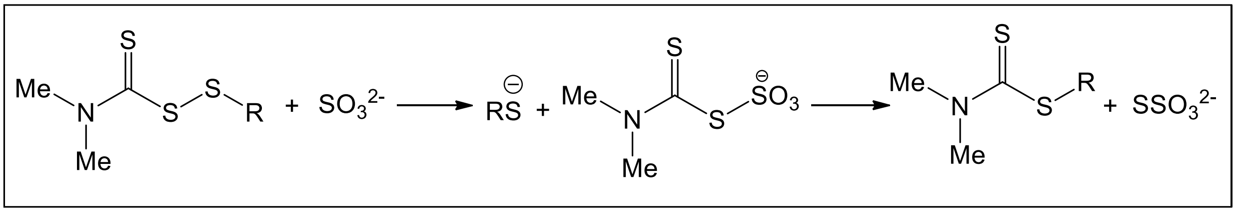
A straightforward, incredibly effective, and ecologically safe process for producing benzyl dithiocarbamates was revealed by Dong and his team. [76] By treating benzyl halides with tetraalkylthiuram disulphides in water, a series of 34 benzyl dithiocarbamates were produced in good to outstanding yields without the inclusion of metal catalyst. The procedure has the potential to be useful for the synthesis of a few biologically active chemicals since it makes it simple to produce C(SP^3)–S bonds and has other benefits including easy performance, environmental friendliness, good to exceptional yields, and strong functional tolerance.



Scheme 2.1.41

(XXXXII) Synthesis of dithiocarbamate:

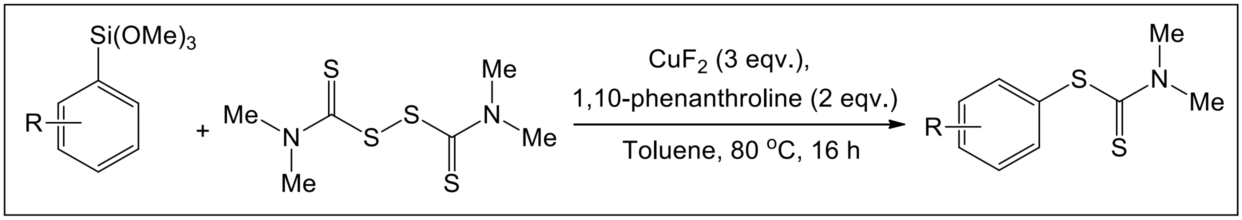
Due to the weak nucleophilic nature of dimethyldithiocarbamate ion in neutral media, sulphite ion must be removed from the reaction mixture in order to facilitate the forward direction of equilibrium and prevent sulphite ion from reacting with disulphide. Barium chloride was added for this purpose, and it deposit as barium sulphite throughout the reaction. Such type of side reaction with sulphite ion was anticipated from the observed reactions of certain mixed disulphides resulting in desulphuration of the required product (Scheme 2.1.42). [77]



Scheme 2.1.42

(XXXXIII) Preparation of valuable *S*-aryl dithiocarbamates:

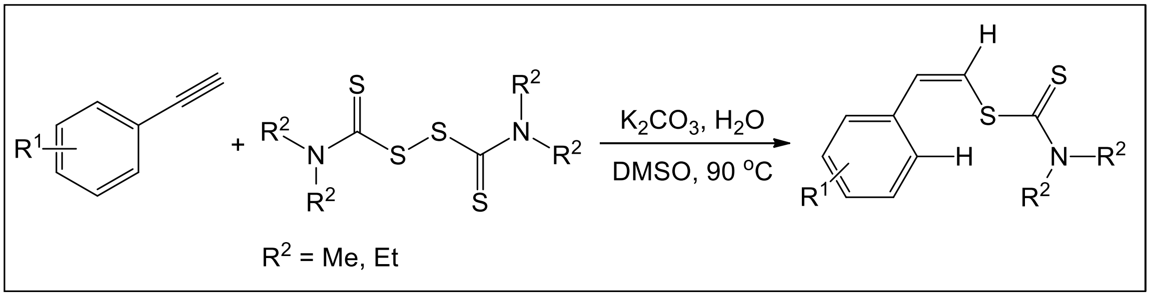
Wu and his team[78] have developed an interesting methodology to prepare valuable *S*-aryl dithiocarbamates on in moderate to good yields by copper-promoted cross-coupling of arylsilanes and thiuram reagents (TATD or TMTM). This protocol offers friendly reaction conditions, broadens the substrate scope, functional group compatibility, and emphasizes the synthetic application in complex molecules and also a new example for the application of Hiyama cross-coupling in biological interesting molecules construction.



Scheme 2.1.43

(XXXVXI) Synthesis of (Z)-vinyl sulphides:

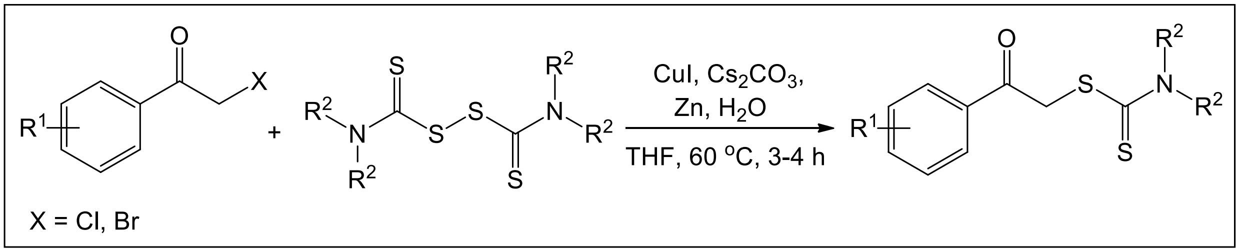
Dong and his team[79] developed a benign protocol of a stereoselective and environmentally friendly thiolation of terminal alkynes. Good yields (up to 88%) of (*Z*)-vinyl sulphides could be obtained by reacting thiuram disulphide reagents (tetramethylthiuram disulphide and tetraethylthiuram disulphide) with alkynes in dimethyl sulfoxide (DMSO)/H_2O. This protocol offers broad substrate scope, good stereoselectivity, high atom economy, good yields. Water and DMSO were found to function as hydrogen sources by mechanistic investigations, which amplified the exceptional reactivity of this particular reaction involving two H-atom donors.



Scheme 2.1.44

(XXXXV) Synthesis of β-keto dithiocarbamates:

Dong and his team[80] have been developed a highly efficient and convenient method for the water-involved synthesis of β-keto dithiocarbamates. Using substituted α-haloacetophenones and thiuram disulphide reagents as starting materials, the desired products were produced in good to outstanding yields in the presence of negligible water. Good to outstanding yields, good functional tolerance, low conditions, and high atom economy make this technique valuable for the synthesis of various biologically and medicinally active chemicals.



Scheme 2.1.45

2.1/c. Conclusion

In conclusion, the synthesis of dithiocarbamate compounds is a significant area of study in organic chemistry, because of their applications in agriculture, medicine, and material science. The typical synthetic route involve the reaction of carbon disulfide with primary amines/secondary amines/ammonia, leading to the formation of dithiocarbamate anions. *In situ* generated dithiocarbamate anions or dithiocarbamate salts are usually allowed to react with various electrophiles in presence of different tranisition metal catalysts or under metal free conditions. Thiuram disulfides, the dimeric form of dithiocarbamates, also have been used to prepare various dithiocarbamate molecules. Ongoing research continues to explore the optimization of their synthetic methods, the development of novel dithiocarbamate derivatives, and their potential applications in various fields, highlighting their importance in both academic and industrial contexts.

2.1/d. References

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Section-II

Synthesis of Styrenyl Dithiocarbamates from Styrene without Using any Metal Catalyst

2.2/a. Introduction

Functionalization of styrene has become an important area of research because of the potential uses of various styrene derivatives in organic synthesis, [1] polymer chemistry[2] and material sciences. [3] Styrene has been functionalized many ways among which *β*-functionalization[4] is a popular technique to prepare useful *β*-substituted styrene molecules. Dithiocarbamate is a valuable sulfur containing functionality due to the extensive applications of the dithiocarbamate compounds mainly in biological and medicinal chemistry (Fig. 2.2.01).

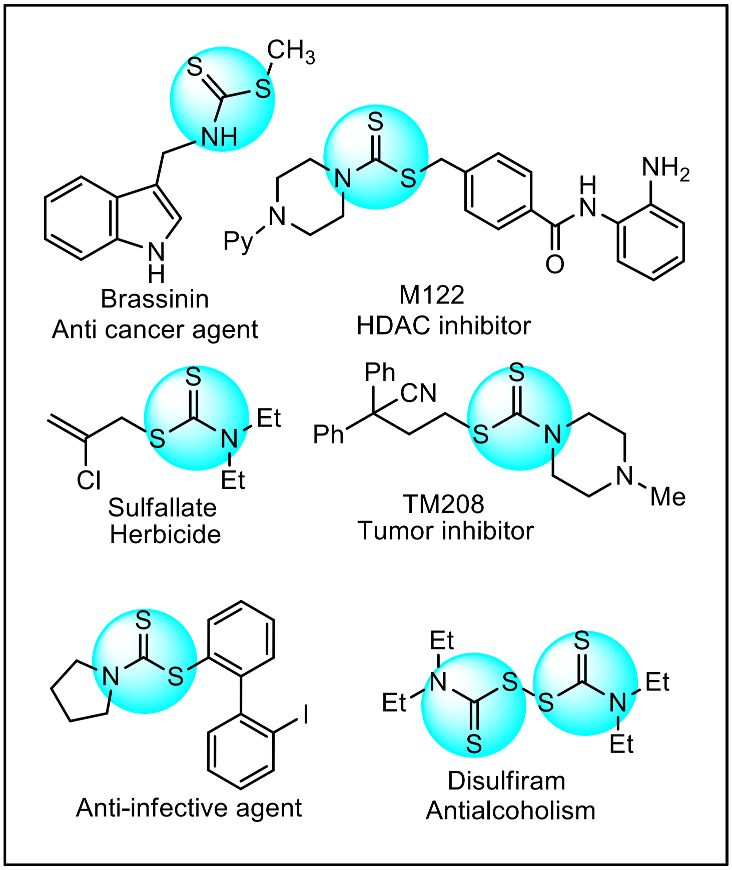
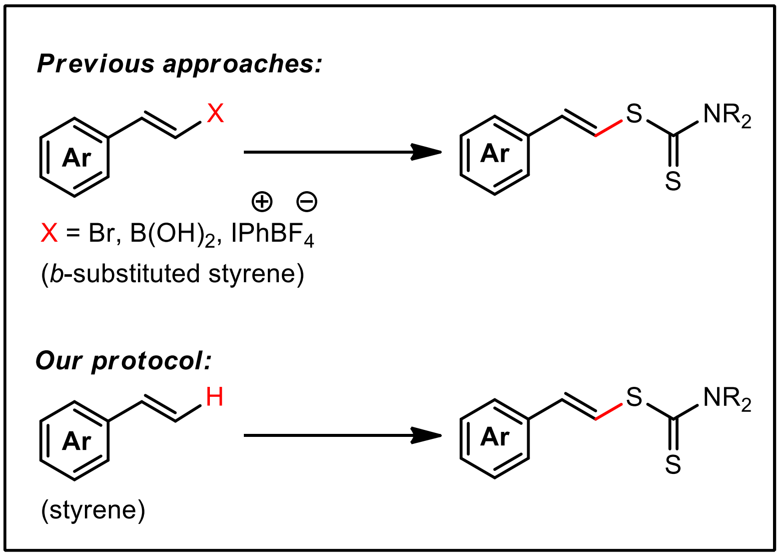


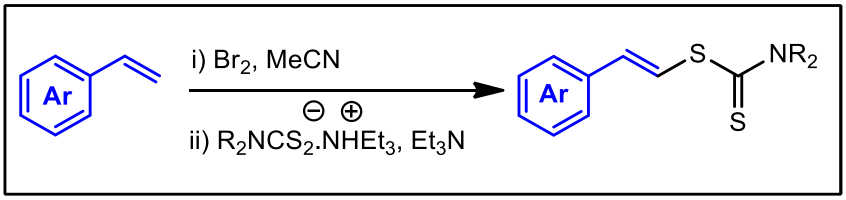
Fig. 2.2.01 Biologically active dithiocarbamate compounds.

Dithiocarbamate compounds have potential applications in biomedical science, [5] agricultural chemistry, [6] material chemistry, [7] organometallic chemistry, [8] polymer science[9] and organic synthesis. [10] As a part of our continued research interest to explore the dithiocarbamate chemistry in organic synthesis, [11] here we have developed a metal-free strategy for dithiocarbamylation of styrene molecules to synthesize various styrenyl dithiocarbamate compounds. The classical route to synthesize styrenyl dithiocarbamate compounds involves the Wittig reaction of the dithiocarbamate-phosphonium ylide with benzaldehyde. [12] The modern techniques use various *β*-substituted styrenes to synthesize the styrenyl dithiocarbamates[13] (Scheme 2.2.01).



Scheme 2.2.01 *β*-substituted styrenes and styrenes as the starting materials for the synthesis of styrenyl dithiocarbamates.

Cu-catalyzed cross-coupling reactions of styryl bromides[13a, 13b] or styrylboronic acids[13c] are the popular methods to prepare *S*-styryl dithiocarbamates. However, one-pot transformation of styrene to the styrenyl dithiocarbamate is more desirable due to easy availability of the substrates. Recently some attempts have been taken to functionalize the styrene molecules with dithiocarbamate groups. [14] In this report, we have demonstrated a one-pot two-step conversion of styrene to the styrenyl dithiocarbamate *via* stereoselective dithiocarbamylation reaction. Styrene has been functionalized using the freshly prepared dithiocarbamate anion in presence of molecular bromine mediator (Scheme 2.2.02). Styrene undergoes bromine addition followed by domino nucleophilic substitution by dithiocarbamate anion and HBr elimination under the present reaction condition. This method can be considered as an alternate of *β*-C-H activation of styrene.



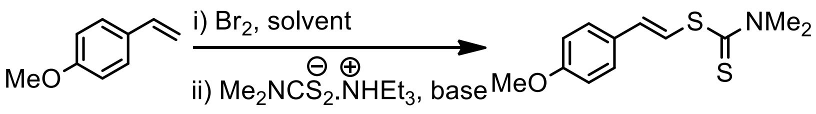
Scheme 2.2.02 Dithiocarbamylation of styrene.

2.2/b. Results and Discussion

The experimental procedure is simple and easy to perform. Styrene was brominated by Br_2 in acetonitrile followed by addition of freshly prepared dithiocarbamate anion and stirring the reaction mixture in presence of triethylamine at 65 °C. The reaction was monitored by the TLC. Upon completion of the reaction the product was obtained by purifying the crude reaction mixture through column chromatography.

In order to optimize the reaction condition, 4-methoxystyrene was chosen as the substrate and it was allowed to react with the dithiocarbamate anion ($Me_2NCS_2^{\ominus}$) which was prepared freshly by the reaction of dimethylamine and CS_2. The reaction between 4-methoxystyrene and $Me_2NCS_2^{\ominus}$ was checked under various reaction conditions employing different bases and solvents (Table 2.2.01).

Table 2.2.01 Standardization of the reaction condition.

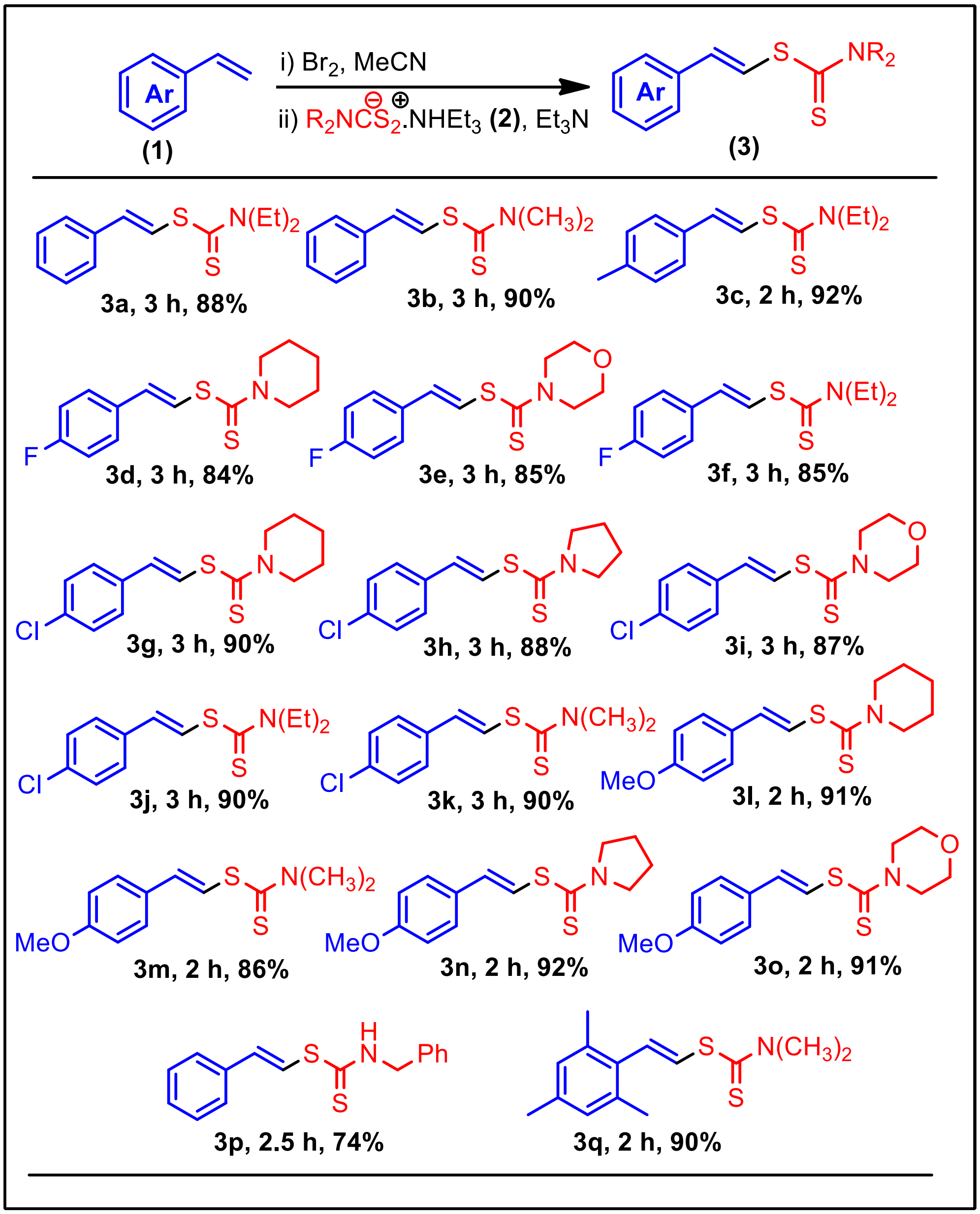


Entry	Solvent	Base	Temp (°C)	Time (h)	Yield (%)
1	MeCN	K_2CO_3	65	3	40
2	DMF	K_2CO_3	120	3	trace
3	THF	K_2CO_3	65	3	13
4	H_2O	K_2CO_3	80	3	-
5	Toluene	K_2CO_3	70	3	-
6	MeCN	Na_2CO_3	65	3	35
7	MeCN	Et_3N	65	3	88
8	MeCN	Et_3N	80	3	57
9	MeCN	Et_3N	50	3	70
10	MeCN	Et_3N	65	5	76
11	MeCN	Et_3N	65	2	62

Reagents and conditions: (i) 4-methoxystyrene (1 mmol), Br_2 (1 mmol), solvent (3 ml), r.t., 30 min, (ii) brominated styrene was stirred in presence of dithiocarbamate anion (1 mmol) and base (2 mmol) at a certain temperature for the required time period. Yields reported are the isolated yields.

In our first attempt, the reaction was performed in acetonitrile medium in presence of K_2CO_3 at 65 °C. However, the desired styrenyl dithiocarbamate was obtained only in 40% of yield in 3 h of time period (entry 1, Table 2.2.01). Other reaction media such as DMF, H_2O, toluene, THF were not found suitable for the reaction (entries 2 - 5, Table 2.2.01).

Table 2.2.02 Synthesis of *trans*-styrenyl dithiocarbamates from styrenes.



3a, 3 h, 88% **3b, 3 h, 90%** **3c, 2 h, 92%**

3d, 3 h, 84% **3e, 3 h, 85%** **3f, 3 h, 85%**

3g, 3 h, 90% **3h, 3 h, 88%** **3i, 3 h, 87%**

3j, 3 h, 90% **3k, 3 h, 90%** **3l, 2 h, 91%**

3m, 2 h, 86% **3n, 2 h, 92%** **3o, 2 h, 91%**

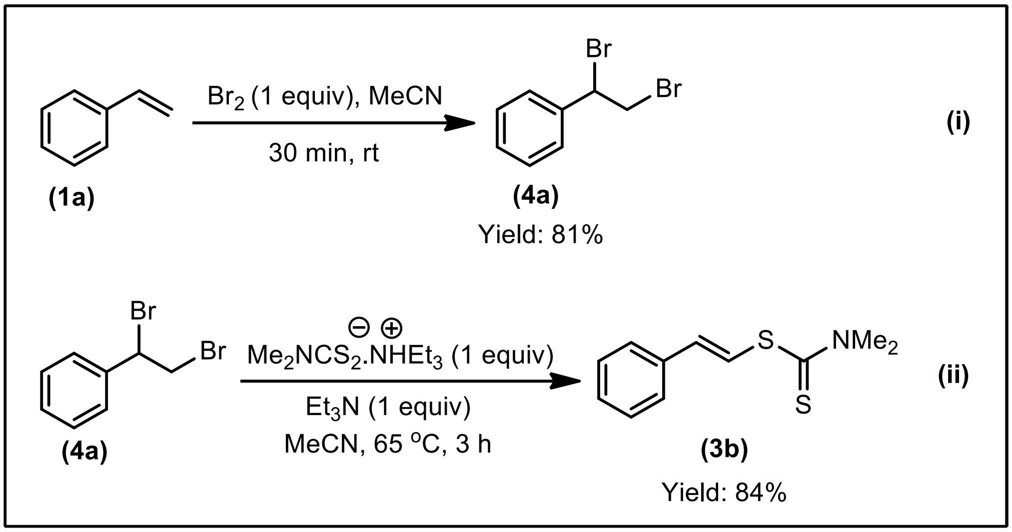
3p, 2.5 h, 74% **3q, 2 h, 90%**

Reagents and conditions: *(i) styrene (1 mmol), Br_2 (1 mmol), acetonitrile (3 ml), r.t., 30 min, (ii) brominated styrene was stirred in presence of dithiocarbamate anion (1 mmol) and Et_3N (2 mmol) at 65 °C for a certain time period. Yields reported are the isolated yields.*

Instead of desired product some unidentified side products were obtained. Use of Na_2CO_3 also did not improve the yield of the reaction (entry 6, Table 2.2.01). However, the reaction was found to proceed satisfactorily in presence of triethyamine as base (yield: 88% in 3 h) (entry 7, Table 2.2.01). At an elevated temperature (80 °C), the reaction shows adverse effect on the yield of the desired product (entry 8, Table 2.2.01). The yield of the reaction was also not improved under the prolonged reaction time period (entry 10, Table 2.2.01). The reaction remains incomplete in 2 h of time period (entry 11, Table 2.2.01).

The optimized protocol was then explored to establish a wide substrate scope. Acyclic secondary amines (dimethylamine, diethylamine) responded to the reaction efficiently and the desired products (**3a** - **3c**, **3f**, **3j**, **3k**, **3q** Table 2.2.02) were obtained satisfactorily. Cyclic secondary amines such as piperidine, pyrrolidine and morpholine also produced the desired styrenyl dithiocarbamates (**3d**, **3e**, **3g** - **3i**, **3l**, **3n**, **3o**, Table 2.2.02) in good yields. Benzylamine underwent *β*-dithiocarbamylation of styrene to produce the desired styrenyl dithiocarbamate, **3p** in 74% of yield. Styrenes containing different substituents like Me, OMe, F, Cl in the aromatic ring, participated in the *β*-functionalization reaction smoothly. Styrene containing *ortho*-substituents, such as 2,4,6-trimethylstyrene underwent smooth reaction with the dimethylamine-dithiocarbamate anion to produce the desired styrenyl dithiocarbamate product **3q** in good yield. In all cases the reactions were highly stereoselective producing the *trans*-styreneyl dithiocarabamates exclusively. However, 3-nitrostyrene and 4-nitrostyrene did not respond to the reactions. The reaction mixtures contained some unidentified side products along with some amount of dimer of the dithiocarbamate anion.

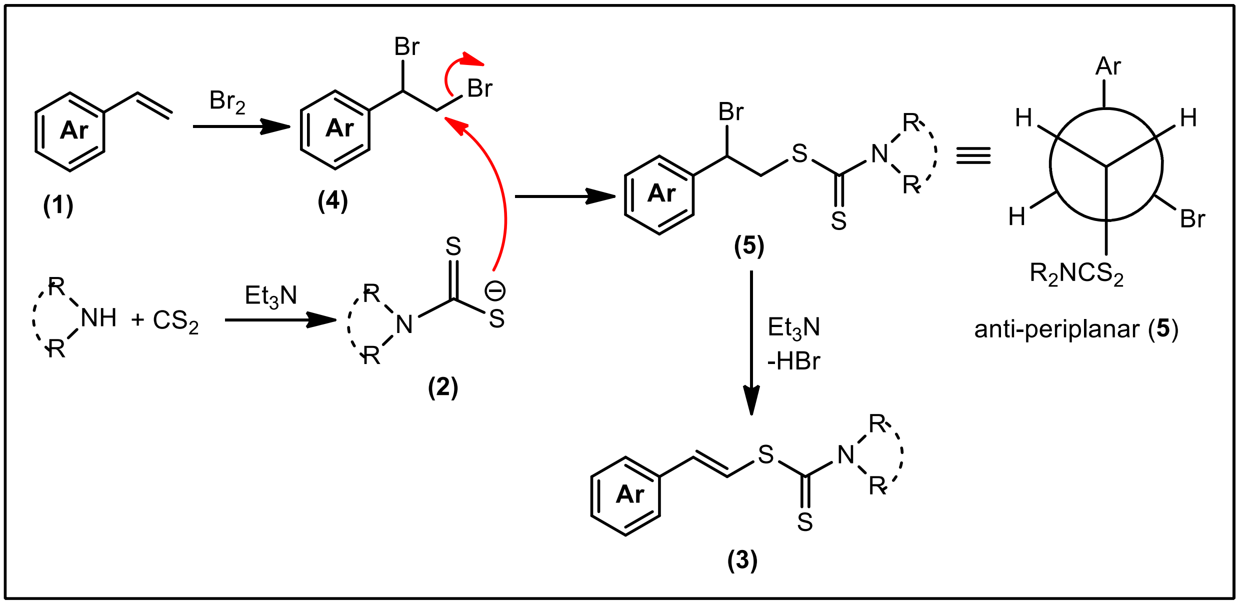
To understand the mechanism, some control experiments were performed. The reaction of styrene (**1a**) with molecular bromine was quenched after 30 min of stirring (Scheme 2.2.03 - i) under the similar reaction condition as Table 2.2.02.



Scheme 2.2.03 Control experiments to identify the intermediate of the reaction.

The intermediate generated in this control experiment was isolated and characterized (^{1}H and ^{13}C NMR included in Supporting Information) to be the styrene dibromide (**4a**). Styrene dibromide was also found to react with $Me_2NCS_2^{\ominus}$ in presence of triethylamine under the identical reaction condition and produced the desired styrenyl dithiocarbamate (**3b**) in good yield (Scheme 2.2.03 - ii). Thus, it is confirmed that the reaction proceeds *via* styrene dibromide intermediate.

We propose formation of styrene dibromide (**4**) by the addition of bromine to styrene. The nucleophilic attack of dithiocarbamate anion (**1**), generated by the reaction of amine and carbon disulfide, occurs selectively at the less hindered primary alkyl bromide centre of styrene dibromide (**4**) (Scheme 2.2.04). The nucleophilic substitution results to the formation of intermediate **5** which undergoes HBr elimination in presence of triethylamine to produce the desired styrenyl dithiocarbamate (**3**).



Scheme 2.2.04 Probable mechanism.

To prove the intermediacy of **5**, the reaction of 4-methoxystyrene with molecular bromine and piperidine-dithiocarbamate anion (generated by the reaction of piperidine and CS_2) was carried out under the identical reaction condition as mentioned in Table 2.2.02 only for 10 min of time period at 65 °C. The incomplete reaction was quenched after 10 min and we were able to isolate the intermediate **5** by chromatographic purification of the crude reaction mixture. The structure of intermediate **5** was characterized by ^{1}H and ^{13}C NMR spectroscopy (^{1}H and ^{13}C NMR included in Supporting Information). The elimination occurs from the more stable conformer of **5** with the aryl and dithiocarbamate groups anti-periplanar to each other and it leads to the formation of *trans*-styrenyl dithiocarbamate.

2.2/c. Conclusion

In conclusion, we have developed an efficient metal free one-pot two-step protocol to functionalize the styrene at *β*-position. Styrene has been converted to *trans*-styrenyl dithiocrbamate *via* dibromo-intermediate. This *β*-dithiocarbamylation offers an easy access of structurally diverse dithiocarbamate-substituted styrenes. The use of expensive catalyst has been avoided. Operational simplicity, easy availability of the starting materials, good yields and high stereoselectivity of the reactions render the protocol synthetically important and economically attractive.

2.2/d. Experimental Section

General Information:

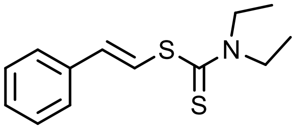
All chemicals were used without further purification. All the reactions were checked by using TLC on silica gel plates (Merck silica gel, f_{24}). All synthesized products were purified by column chromatography on 100-200 mesh silica gel. The ^{1}H spectra of synthesized products were recorded in $CDCl_3$ on Brucker Spectrometer at 300, 400 MHz. The ^{19}F spectra of synthesized fluorinated products were recorded in $CDCl_3$ on Brucker Spectrometer, 300 MHz. The ^{13}C spectra of synthesized products were recorded in $CDCl_3$ on Brucker Spectrometer at 75, 100 MHz. Chemical shifts were reported in ppm referenced to 0.00 ppm for TMS. The coupling constant (*J*) values are shown in hertz, and splitting patterns of the proton are described as *s* (singlet), *d* (doublet), *t* (triplet), and *m* (multiplet). HRMS were measured in methanol solvent on a Waters Micromass Q-tofMicromass spectrometer.

General experimental procedure:

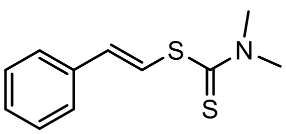
Preparation of dithiocarbamate anion: CS_2 (0.1 mL, 1.5 mmol) was added drop wise to asolution of secondary amine (1 mmol) and Et_3N (0.28 mL, 2 mmol) in acetonitrile (1 ml) at 5 ^oC. The resulting solution was stirred at room temperature for 5 min.

Synthesis of styrenyldithiocarbamate: Br_2 (0.05 mL, 1 mmol) in MeCN (1 mL) was added drop wise to the styrene (1 mmol) solution in MeCN (2 mL) at 5 ^oC. After complete addition, the reaction mixture was allowed to stir for 30 min at room temperature. Then the solution of freshly prepared dithiocarbamateanion (1 mmol) containing Et_3N (0.28 mL, 2 mmol) was added slowly into the brominated reaction mixture. The reaction mixture was allowed to stir at 65 $^oC$for a certain reaction time period. After completion of reaction (checked by TLC), the solvent was evaporated under reduced pressure. The crude product was extracted with ethyl acetate and purified by column chromatography to obtain the desired product.

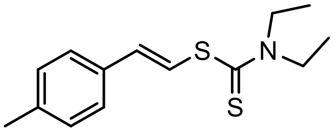
Characterization Data of Synthesized Compounds



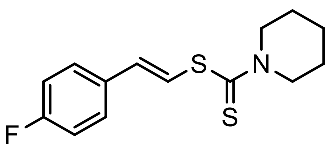
Styryldiethylcarbamodithioate (**3a**): White solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.26-1.34(m, 6H), 3.74-3.77(m, 2H), 4.04-4.06(m, 2H), 6.75(d, J=15.9 Hz, 1H), 7.28-7.51(m, 6 Hz), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 11.69, 12.74, 47.11, 49.42, 122.92, 126.68(2C), 128.13, 128.74(2C), 132.28, 136.43, 193.31, HRMS (ESI) m/z calcd for $C_{13}H_{17}NS_2$ $[M + H]^+$, 252.0802, found 252.0194.



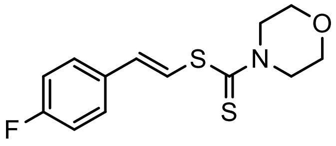
Styryldimethylcarbamodithioate (**3b**).^{1}White solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.43(s, 3H), 3.60(s, 3H), 6.79(d, J=15.9 Hz, 1H), 7.28-7.39(m, 3H), 7.43-7.52(m, 3H) , ^{13}C NMR (75 MHz, CDCl$_3$) δ: 41.61, 45.09, 123.06, 126.63(2C), 128.15, 128.69(2C), 132.37, 136.25, 194.84.



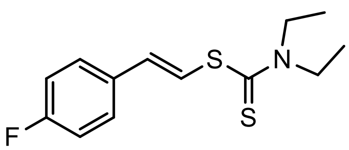
Diethyl-1-carbodithioic acid(4-methyl-phenyl-vinyl ester) (**3c**): Light yellow solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.30-1.39(m, 6H), 2.37(s, 3H), 3.72-3.79(m, 2H), 4.04-4.11(m, 2H), 6.75(d, J=15.9 Hz, 1H), 7.17(d, J=8.1 Hz, 1H), 7.37-7.44(m, 3H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 11.62, 12.66, 21.30, 47.02, 49.31, 121.50, 126.55(2C), 129.38(2C), 132.49, 133.63, 138.05, 193.53, . HRMS (ESI) m/z calcd for $C_{14}H_{19}NS_2$ $[M + H]^+$, 265.1039, found 265.8385.



Piperidine-1-carbodithioic acid(4-fluoro-phenyl-vinyl ester) (**3d**): Yellow solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.73(s, 6H), 3.88(broad, 2H), 4.29(broad, 2H), 6.70(d, J=15.9 Hz, 1H), 7.00-7.06(m, 2H), 7.36-7.45(m, 3H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.33, 25.59, 26.22, 51.85, 52.76, 115.77(d, $J_{C\text{-}F}$ = 21.75 Hz, 2C), 122.48(d, $J_{C\text{-}F}$ = 2.25 Hz), 128.33(d, $J_{C\text{-}F}$ = 8.25 Hz, 2C), 131.44, 132.70(d, $J_{C\text{-}F}$ = 3.75 Hz),162.71(d, $J_{C\text{-}F}$ = 246.75 Hz), 193.27, ^{19}F NMR(300 MHz, CDCl$_3$) δ: -113.40 HRMS (ESI) m/z calcd for $C_{14}H_{16}NFS_2$ $[M + H]^+$, 282.0788, found 282.0788.

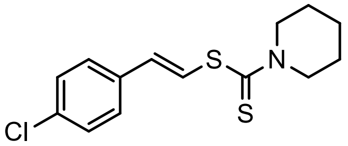


Morpholine-1-carbodithioic acid(4-fluoro-phenyl-vinyl ester) (**3e**): Yellow solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.75-3.81 (m, 4H), 4.06-4.24 (m, 4H), 6.73 (d, J=15.9 Hz, 1H), 7.00-7.06 (m, 2H), 7.34 (d, J=15.9 Hz, 1H), 7.40-7.45 (m, 2H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 50.96 (d, $J_{C\text{-}F}$ = 13.5 Hz,2C), 66.29 (2C), 26.22, 115.74 (d, $J_{C\text{-}F}$ = 21.75 Hz, 2C), 121.34 (d, $J_{C\text{-}F}$ = 2.25 Hz), 128.31 (d, $J_{C\text{-}F}$ = 8.25 Hz, 2C), 132.30, 132.36 (d, $J_{C\text{-}F}$ = 3 Hz),162.73 (d, $J_{C\text{-}F}$ = 246.75 Hz), 195.16, ^{19}F NMR (300 MHz, CDCl$_3$) δ: -112.97, HRMS (ESI) m/z calcd for $C_{13}H_{14}NFOS_2$ $[M + H]^+$, 284.0581, found 284.0100.

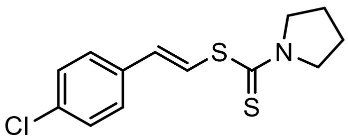


Diethyl-1-carbodithioic acid(4-fluoro phenyl-vinyl ester) (**3f**): Yellow oil, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.26-1.37 (m, 6H), 3.72-3.79 (m, 2H), 4.01-4.08 (m, 2H), 6.71 (d, J=15. 9, 1H), 7.00-7.06 (m, 2H), 7.36-7.45 (m,3H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 11.70, 12.76, 47.14, 49.44, 122.95, 126.69 (2C), 128.22, 128.77 (2C), 132.27, 136.44, 193.28, ^{19}F NMR (300 MHz, CDCl$_3$) δ: -113.44, HRMS (ESI) m/z calcd for $C_{13}H_{16}NFS_2$ $[M + H]^+$, 270.0788, found 270.0788.

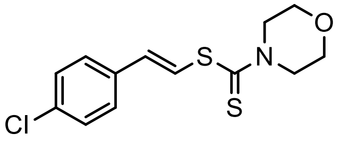
Piperidine-1-carbodithioic acid(4-chloro-phenyl-vinyl ester) (**3g**).[1] Yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.73 (s, 6H), 3.88 (broad, 2H), 4.30 (broad, 2H), 6.69 (d, J=15.9 Hz, 1H), 7.30 (d, J=8.4 Hz, 2H), 7.38 (d, J=8.7 Hz, 2H), 7.50 (d, J=15.9 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.23, 25.46, 26.05, 51.80, 52.71, 123.69, 127.76 (2C), 128.87 (2C), 130.83, 133.73, 134.87, 192.84.



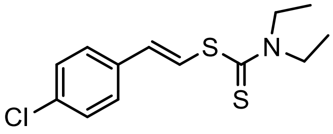
Pyrolidine-1-carbodithioic acid(4-chloro-phenyl-vinyl ester) (**3h**).[1] Yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.96-2.16 (m, 4H), 3.68 (t, J=6.9 Hz, 2H), 3.96 (t, J=6.9 Hz, 2H), 6.70 (d, J=16.2 Hz, 1H), 7.28-7.39 (m, 4H),7.58 (d, J=16.2 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.36, 26.19, 50.85, 54.96, 123.78, 127.79 (2C), 128.93 (2C), 130.25, 133.76, 134.88, 189.84.



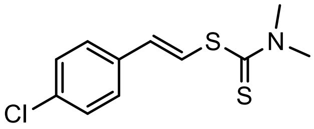
Morpholine-1-carbodithioic acid(4-chloro-phenyl-vinyl ester) (**3i**): Yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.77-3.80 (m, 4H), 4.10 (broad, 4H), 6.71 (d, J=16.2 Hz, 1H), 7.29-7.40 (m, 4H), 7.44 (d, J=15.9 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 50.85 (2C), 66.18 (2C), 122.59, 127.81 (2C), 128.92 (2C), 131.79, 133.99, 134.60, 194.79, HRMS (ESI) m/z calcd for $C_{13}H_{14}NClOS_2$ $[M + H]^+$, 300.0285 found 300.0286.



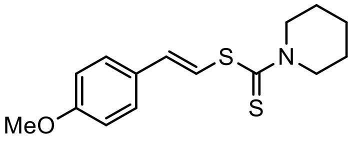
Diethyl-1-carbodithioic acid(4-chloro-phenyl-vinyl ester) (**3j**): Yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27-1.35 (m, 2H), 3.71-3.77 (m,2H), 4.01-4.06 (m, 2H), 6.69 (d, J=16 Hz, 1H), 7.28-7.31 (m, 2H), 7.36-7.38 (m, 2H), 7.49 (d, J=16 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.46, 12.74, 47.15, 49.44, 123.95, 127.82 (2C), 128.93 (2C), 130.59, 133.76, 134.95, 192.83, HRMS (ESI) m/z calcd for $C_{13}H_{16}NClS_2$ $[M + H]^+$, 285.0413, found 286.0493.



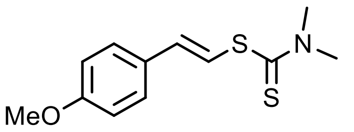
Dimethyl-1-carbodithioic acid(4-chloro-phenyl-vinyl ester) (**3k**).[2] Light yellow solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.43(s, 3H), 3.60(s, 3H), 6.73(d, J=15.9 Hz, 1H), 7.33(d, J=8.4 Hz, 2H), 7.41(d, J=8.1 Hz, 2H), 7.50(d, J=16.2 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 41.61, 45.13, 124.03, 127.77, 128.88, 130.74, 133.80, 134.77, 194.42.



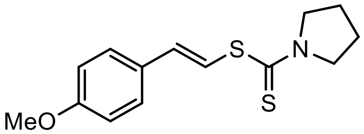
Piperidine-1-carbodithioic acid(4-methoxy-phenyl-vinyl ester) (**3l**).[1] White solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.74(s, 6H), 3.84(s, 3H), 3.90(broad, 2H), 4.31(broad, 2H), 6.72(d, J=16.5 Hz, 1H), 6.89(d, J=7.2 Hz, 2H), 7.27(d, J=12.9 Hz, 1H), 7.43(d, J=6.6 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.31, 25.52, 26.01, 51.72, 52.50, 55.42, 114.09(2C), 119.77, 127.97(2C), 129.37, 132.88, 159.73, 193.90.



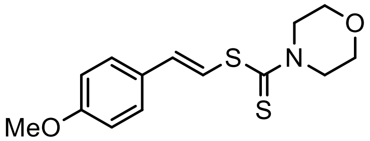
Dimethyl-1-carbodithioic acid(4-methoxy-phenyl-vinyl ester) (**3m**).[1] Yellow solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.38 (s, 3H), 3.55 (s, 3H), 3.81 (s, 3H), 6.70 (d, J=15.9 Hz, 1H), 7.28-7.39 (m, 4H), 7.58 (d, J=16.2 Hz, 1H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 41.60, 45.05, 55.35, 114.12 (2C), 120.06, 127.97 (2C), 129.13, 132.65, 159.71, 195.38.



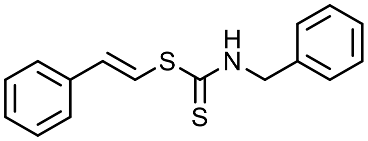
Pyrolidine-1-carbodithioic acid(4-methoxy-phenyl-vinyl ester) (**3n**): Yellow solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.98-2.07 (m, 2H), 2.09-2.18 (m, 2H), 3.70 (t, J=6.6 Hz, 2H), 3.84 (s, 3H), 3.98 (t, J=6.9 Hz, 2H), 6.73 (d, J=15.9 Hz, 1H), 6.93 (d, J=8.7 Hz, 2H), 7.33-7.43 (m, 3H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.32, 26.15, 50.72, 54.77, 55.34, 114.10 (2C), 119.70, 127.93 (2C), 129.19, 132.19, 159.66, 190.81, HRMS (ESI) m/z calcd for $C_{14}H_{17}NOS_2$ $[M + H]^+$, 279.0752, found 279.0913.



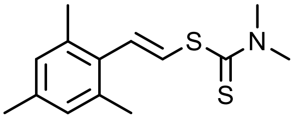
Morpholine-1-carbodithioic acid(4-methoxy-phenyl-vinyl ester) (**3o**): White solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.79-3.82 (m, 4H), 3.84 (s, 3H), 4.0-4.50 (m, 4H), 6.74 (d, J=15.9 Hz, 1H), 6.90 (d, J=8.7 Hz, 1H), 7.22 (d, J=15.6 Hz, 1H), 7.42 (d, J=8.7 Hz, 2H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 50.79, 51.06, 55.35, 66.28 (2C), 114.15 (2C), 118.65, 128.06(2C), 129.01, 133.76, 159.85, 195.89, HRMS (ESI) m/z calcd for $C_{14}H_{17}NO_2S_2$ $[M + H]^+$, 296.0701, found 296.0780.



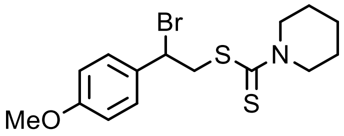
Styrylbenzylcarbamodithioate (**3p**): yellow solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.43 (s, 2H), 6.51 (s, 1H), 6.94-6.95 (m, 2H), 7.11 (d, J=7.2 Hz, 2H), 7.21-7.23 (m, 3H), 7.42-7.44 (m, 5H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 50.87, 108.95, 127.06 (2C), 127.57, 128.49 (2C), 128.68 (2C), 129.49 (2C), 129.89, 130.61, 135.33, 144.85, 189.08, HRMS (ESI) m/z calcd for $C_{16}H_{15}NS_2$ $[M + H]^+$, 286.0646, found 286.0726.



Dimethyl-1-carbodithioic acid(2,4,6-trimethyl-phenyl-vinyl ester) (**3q**): White solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.29 (s, 3H), 2.38 (s, 3H), 3.41 (s, 3H), 3.57 (s, 3H), 6.82 (d, J=16.2 Hz, 1H), 6.90 (s, 2H), 6.97 (d, J=16.5 Hz, 1H),), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.03, 21.29 (2C), 41.68, 45.01, 126.49, 128.84 (2C), 131.30, 132.58, 136.20 (2C), 136.93, 195.37, HRMS (ESI) m/z calcd for $C_{16}H_{15}NS_2$ $[M + H]^+$, 266.0959, found 266.1044.



2-bromo-2-(4-methoxyphenyl)ethyl piperidine-1-carbodithioate (**5**) Yellow liquid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.67 (s, 6H), 1.75 (s, 1H), 1.78 (s, 1H), 3.79 (s, 3H), 3.81 (broad, 2H), 4.26 (broad, 2H), 5.20-5.27 (m, 1H), 6.83-6.87 (m, 2H), 7.33-7.38 (m, 2H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.90, 24.25, 25.34, 26.16, 50.42, 51.16, 52.42, 55.21, 113.81 (2C), 128.87 (2C), 134.09, 158.67, 194.74

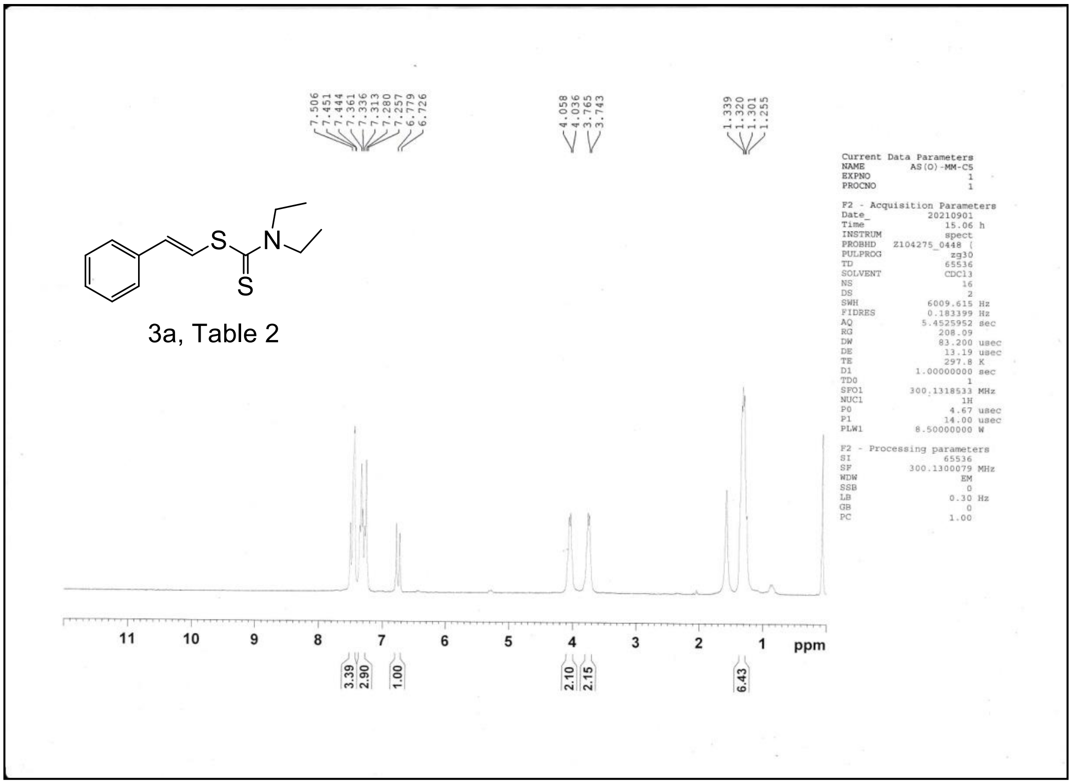


All the styrenyldithiocarbamate products (3a-3p) were characterized by ^{1}H and ^{13}C NMR spectroscopy. HRMS was recorded for the all unknown compounds.

2.2/e.

^{1}H and ^{13}C NMR spectra of all synthesized products described in section -II

^{1}H NMR (300 MHz, CDCl3) spectrum of **3a**



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PROCNO                  1

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PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              6009.615 Hz
FIDRES           0.183399 Hz
AQ              5.4525952 sec
RG                 208.09
DW                 83.200 usec
DE                  13.19 usec
TE                  297.8 K
D1             1.00000000 sec
TD0                     1
SFO1          300.1318533 MHz
NUC1                   1H
P0                   4.67 usec
P1                  14.00 usec
PLW1           8.50000000 W

F2 - Processing parameters
SI                  65536
SF            300.1300079 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
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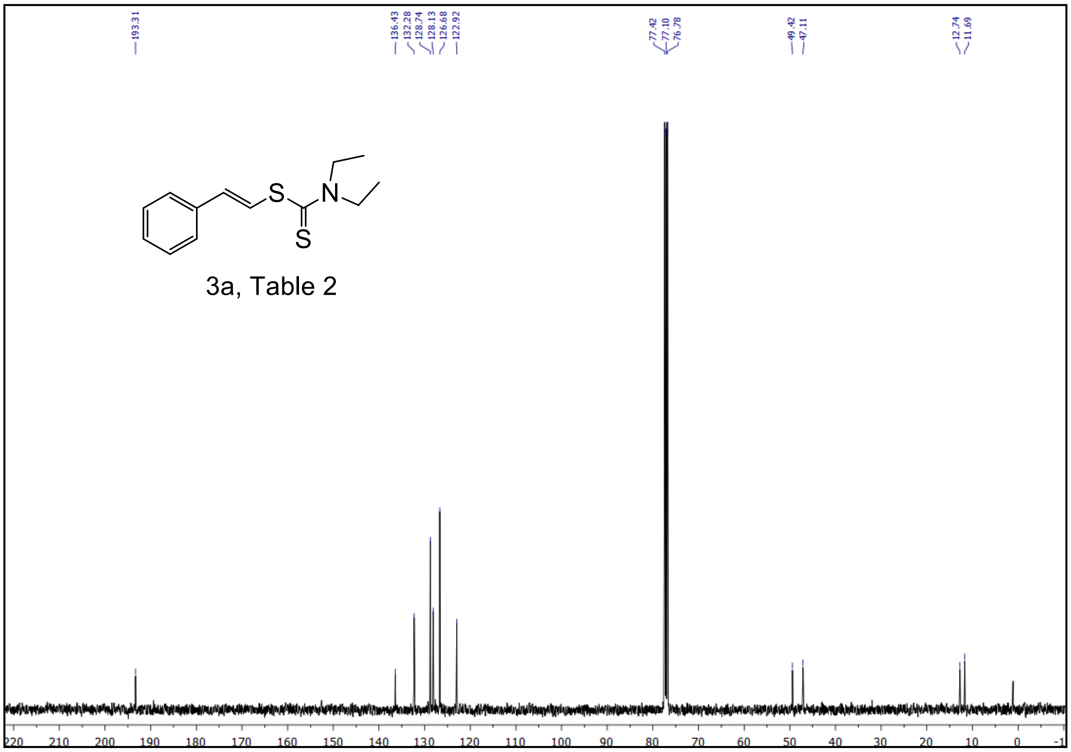
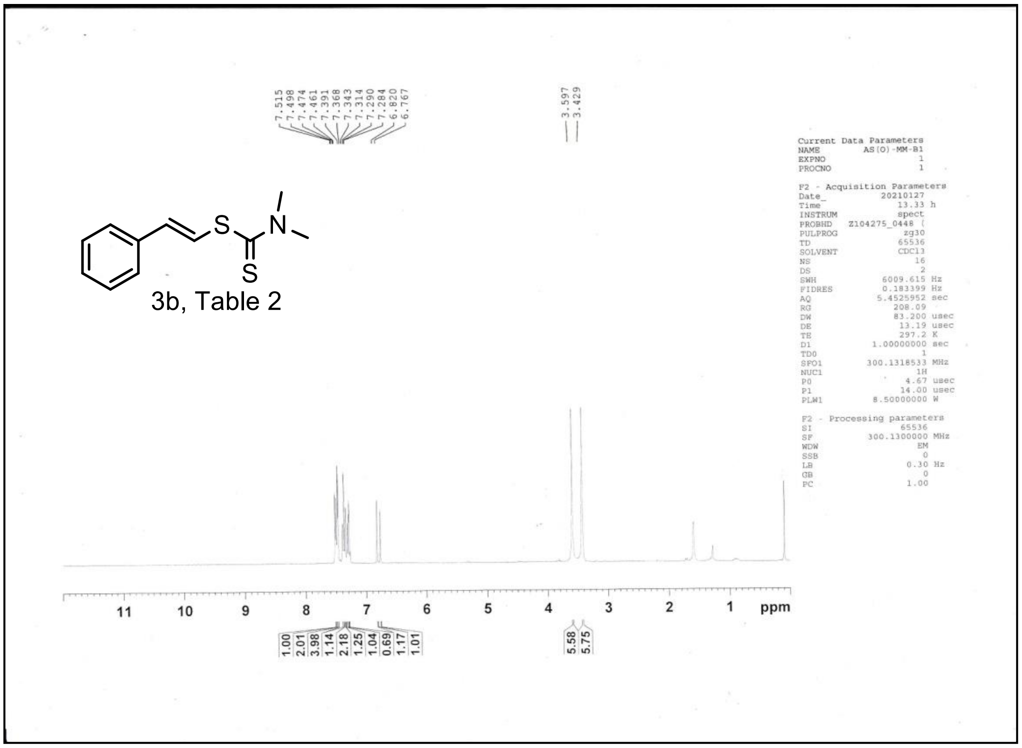


2.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3b**



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Current Data Parameters
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EXPNO                   1
PROCNO                  1

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PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              6009.615 Hz
FIDRES           0.183399 Hz
AQ              5.4525952 sec
RG                 208.09
DW                 83.200 usec
DE                  13.19 usec
TE                  297.2 K
D1             1.00000000 sec
TD0                     1
SFO1          300.1318533 MHz
NUC1                   1H
P0                   4.67 usec
P1                  14.00 usec
PLW1           8.50000000 W

F2 - Processing parameters
SI                  65536
SF            300.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
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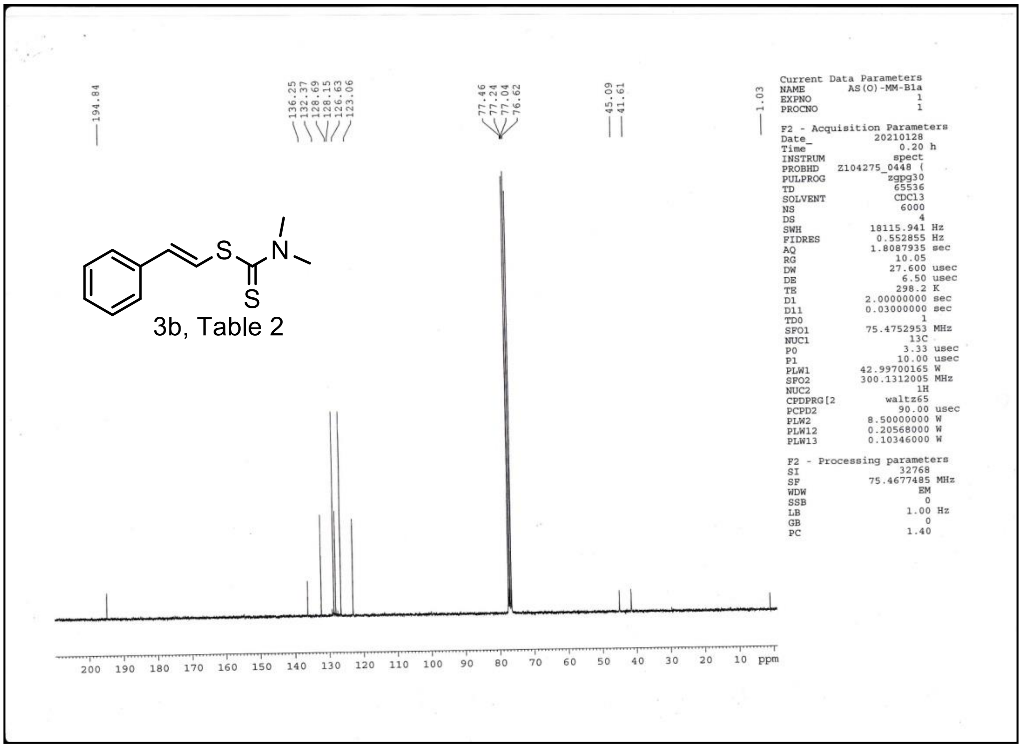

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Current Data Parameters
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EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
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PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    6000
DS                       4
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FIDRES            0.552855 Hz
AQ               1.8087935 sec
RG                   10.05
DW                  27.600 usec
DE                    6.50 usec
TE                   298.2 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1
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NUC1                   13C
P0                    3.33 usec
P1                   10.00 usec
PLW1           42.99700165 W
SFO2           300.1312005 MHz
NUC2                    1H
CPDPRG[2           waltz65
PCPD2                90.00 usec
PLW2            8.50000000 W
PLW12           0.20568000 W
PLW13           0.10346000 W

F2 - Processing parameters
SI                   32768
SF              75.4677485 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
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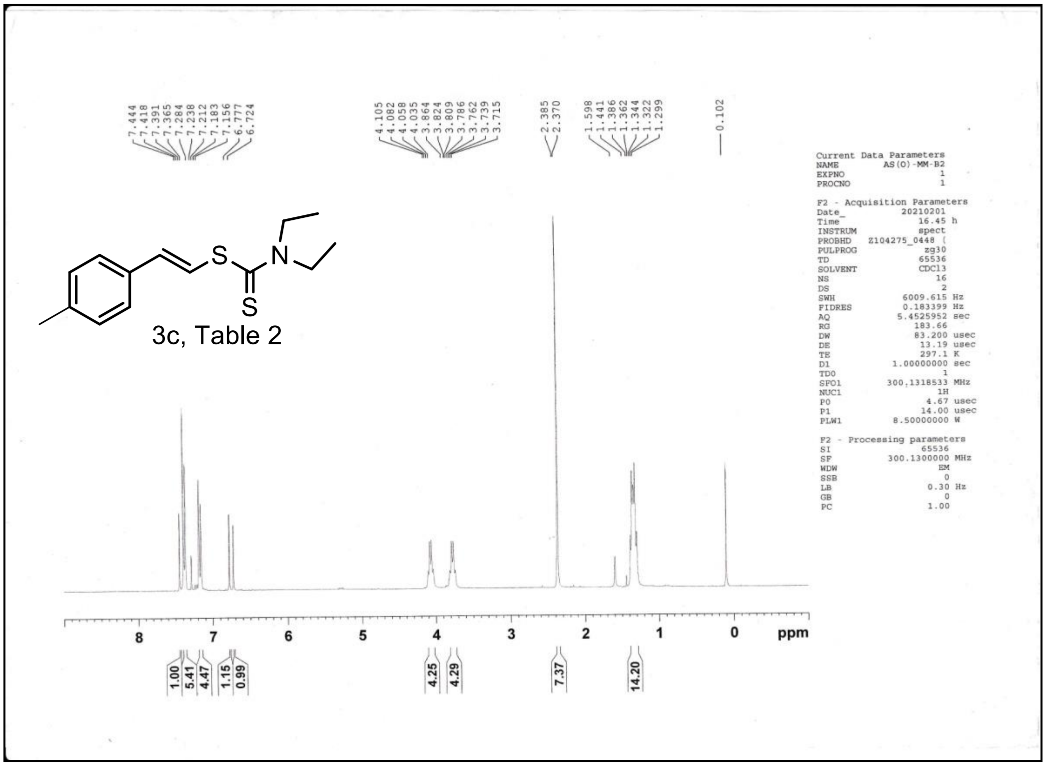
3.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3c**



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Current Data Parameters
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EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
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Time                  16.45 h
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PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                6009.615 Hz
FIDRES             0.183399 Hz
AQ                5.4525952 sec
RG                   183.66
DW                   83.200 usec
DE                    13.19 usec
TE                    297.1 K
D1               1.00000000 sec
TD0                       1
SFO1            300,1318533 MHz
NUC1                     1H
P0                     4.67 usec
P1                    14.00 usec
PLW1             8.50000000 W

F2 - Processing parameters
SI                    65536
SF              300.1300000 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
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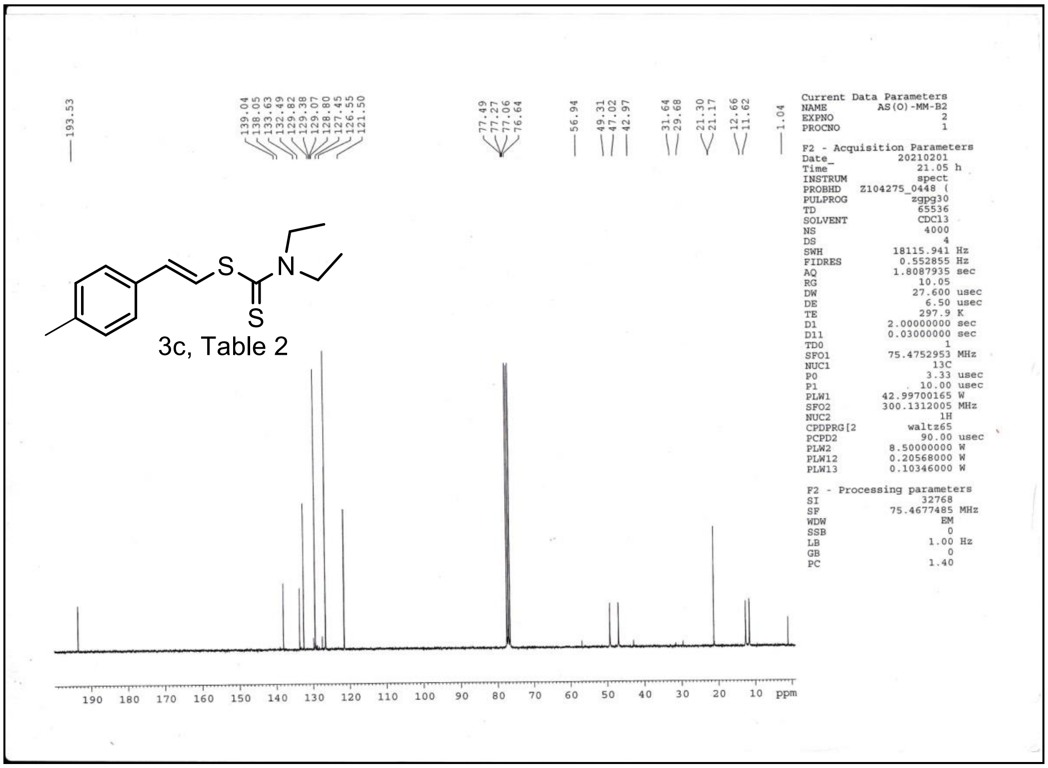

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Current Data Parameters
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EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
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TD                    65536
SOLVENT               CDCl3
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DS                        4
SWH               18115.941 Hz
FIDRES             0.552855 Hz
AQ                1.8087935 sec
RG                    10.05
DW                   27.600 usec
DE                     6.50 usec
TE                    297.9 K
D1               2.00000000 sec
D11              0.03000000 sec
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NUC1                    13C
P0                     3.33 usec
P1                    10.00 usec
PLW1            42.99700165 W
SFO2            300.1312005 MHz
NUC2                     1H
CPDPRG[2            waltz65
PCPD2                 90.00 usec
PLW2             8.50000000 W
PLW12            0.20568000 W
PLW13            0.10346000 W

F2 - Processing parameters
SI                    32768
SF               75.4677485 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
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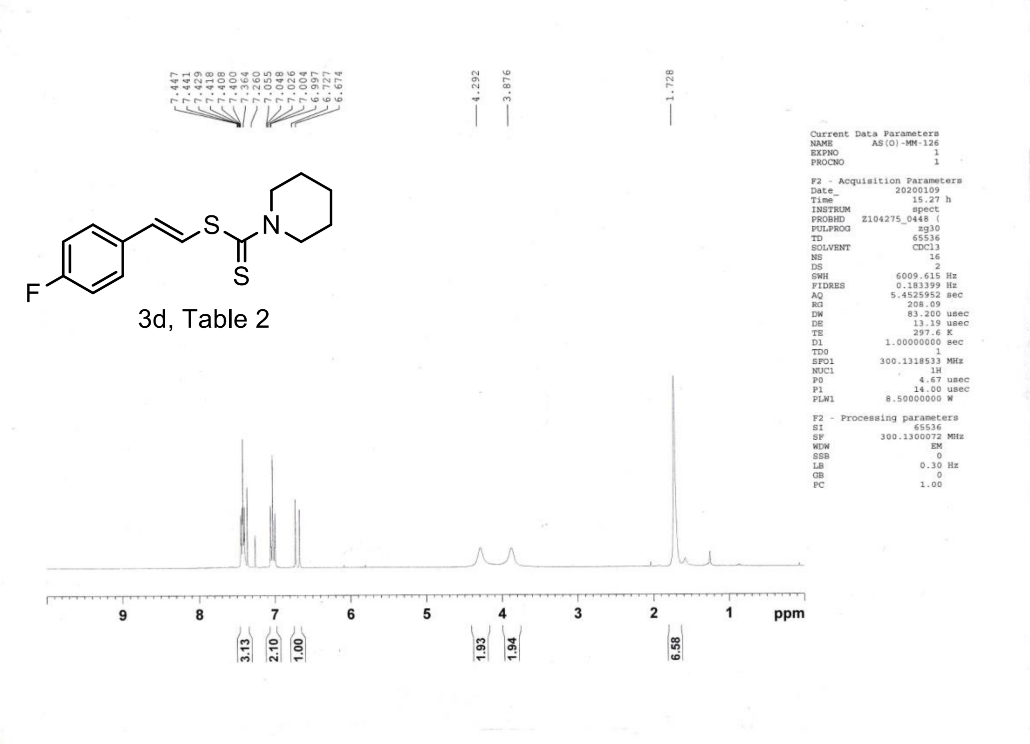
4.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, CDCl$_3$) spectrum of **3d**



```
Current Data Parameters
NAME          AS(O)-MM-126
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20200109
Time                 15.27 h
INSTRUM              spect
PROBHD    Z104275_0448 (
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               6009.615 Hz
FIDRES            0.183399 Hz
AQ               5.4525952 sec
RG                  208.09
DW                  83.200 usec
DE                   13.19 usec
TE                   297.6 K
D1              1.00000000 sec
TD0                      1
SFO1           300.1318533 MHz
NUC1                    1H
P0                    4.67 usec
P1                   14.00 usec
PLW1            8.50000000 W

F2 - Processing parameters
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SF             300.1300072 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
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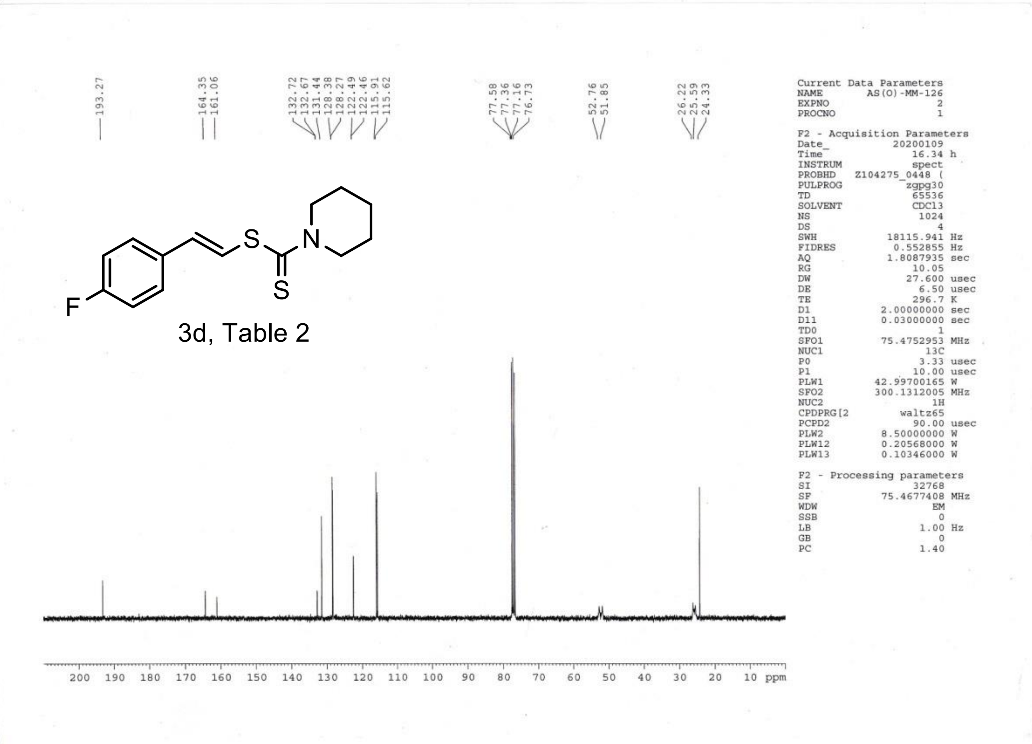

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Current Data Parameters
NAME          AS(O)-MM-126
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
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TD                   65536
SOLVENT              CDCl3
NS                    1024
DS                       4
SWH              18115.941 Hz
FIDRES            0.552855 Hz
AQ               1.8087935 sec
RG                   10.05
DW                  27.600 usec
DE                    6.50 usec
TE                   296.7 K
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NUC1                   13C
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P1                   10.00 usec
PLW1           42.99700165 W
SFO2           300.1312005 MHz
NUC2                    1H
CPDPRG[2           waltz65
PCPD2                90.00 usec
PLW2            8.50000000 W
PLW12           0.20568000 W
PLW13           0.10346000 W

F2 - Processing parameters
SI                   32768
SF              75.4677408 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
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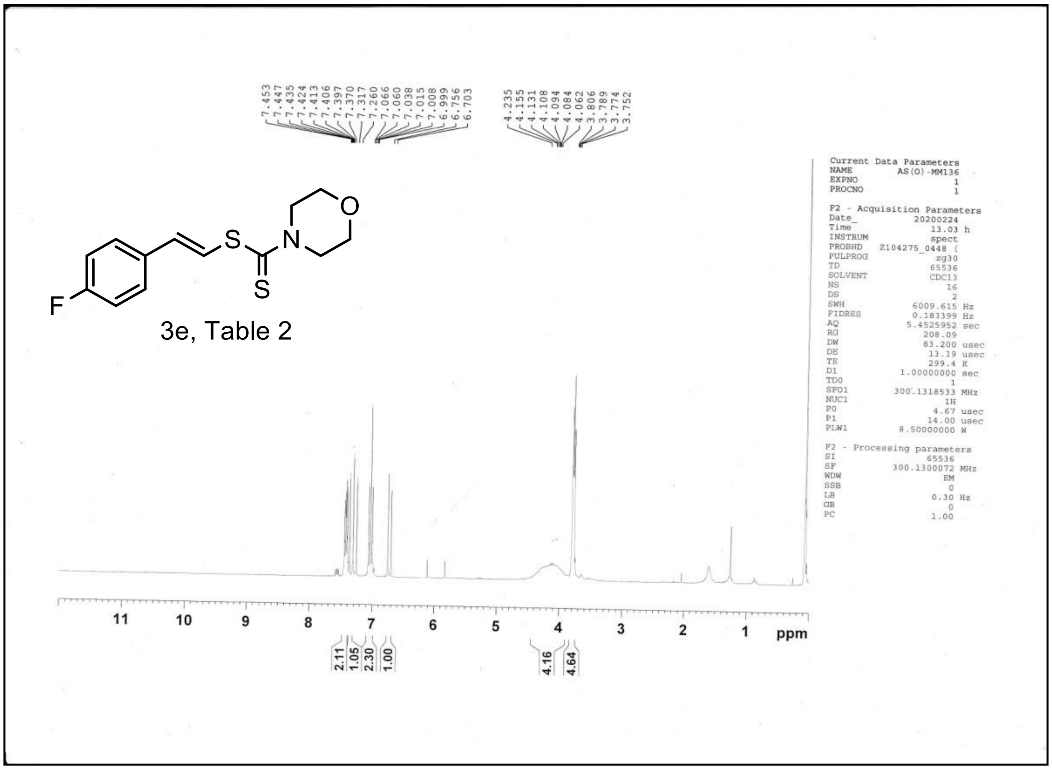
5.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, CDCl$_3$) spectrum of **3e**



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Current Data Parameters
NAME            AS(O)-MM136
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
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INSTRUM               spect
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PULPROG                zg30
TD                    65536
SOLVENT               CDC13
NS                       16
DS                        2
SWH              6009.615 Hz
FIDRES           0.183399 Hz
AQ              5.4525952 sec
RG                   208.09
DW                 83.200 usec
DE                  13.19 usec
TE                  299.4 K
D1             1.00000000 sec
TD0                       1
SFO1          300.1318533 MHz
NUC1                     1H
P0                   4.67 usec
P1                  14.00 usec
PLW1           8.50000000 W

F2 - Processing parameters
SI                    65536
SF            300.1300072 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
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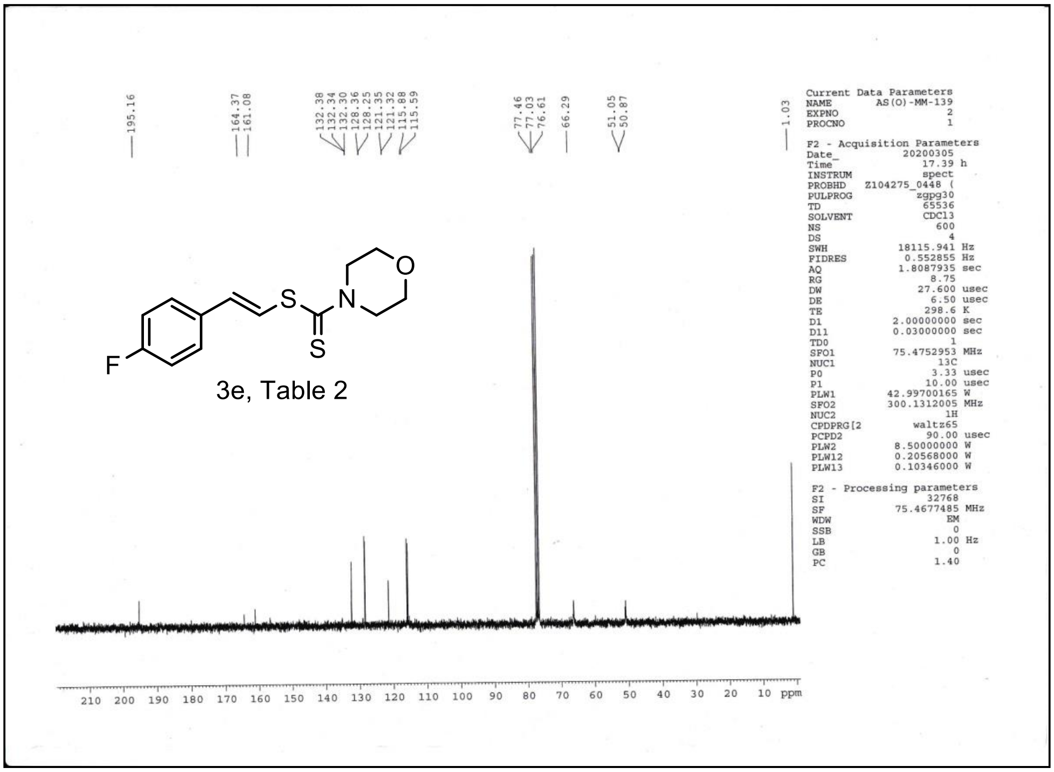

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Current Data Parameters
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PROCNO                   1

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TD                   65536
SOLVENT              CDC13
NS                     600
DS                       4
SWH             18115.941 Hz
FIDRES           0.552855 Hz
AQ              1.8087935 sec
RG                   8.75
DW                 27.600 usec
DE                   6.50 usec
TE                  298.6 K
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D11            0.03000000 sec
TD0                      1
SFO1           75.4752953 MHz
NUC1                   13C
P0                   3.33 usec
P1                  10.00 usec
PLW1          42.99700165 W
SFO2          300.1312005 MHz
NUC2                    1H
CPDPRG[2           waltz65
PCPD2               90.00 usec
PLW2           8.50000000 W
PLW12          0.20568000 W
PLW13          0.10346000 W

F2 - Processing parameters
SI                   32768
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WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
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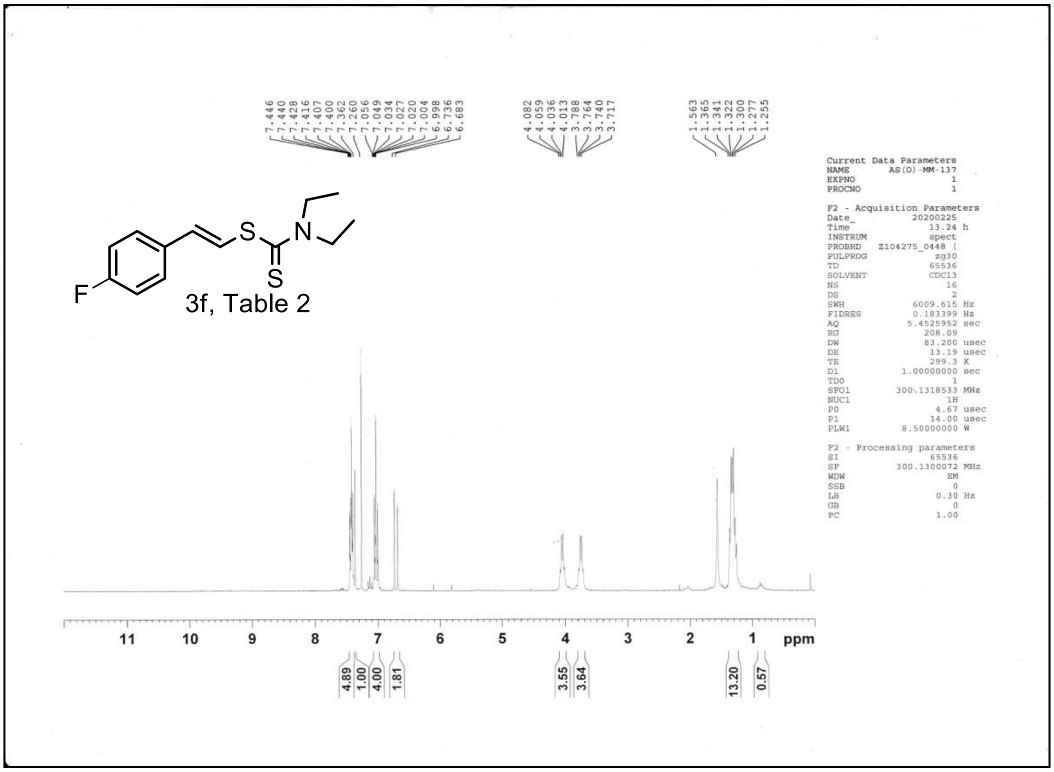
6.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3f**



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Current Data Parameters
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EXPNO                   1
PROCNO                  1

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PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              6009.615 Hz
FIDRES           0.183399 Hz
AQ              5.4525952 sec
RG                 208.09
DW                 83.200 usec
DE                  13.19 usec
TE                  299.3 K
D1             1.00000000 sec
TD0                     1
SFO1          300.1318533 MHz
NUC1                   1H
P0                   4.67 usec
P1                  14.00 usec
PLW1           8.50000000 W

F2 - Processing parameters
SI                  65536
SF            300.1300072 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```
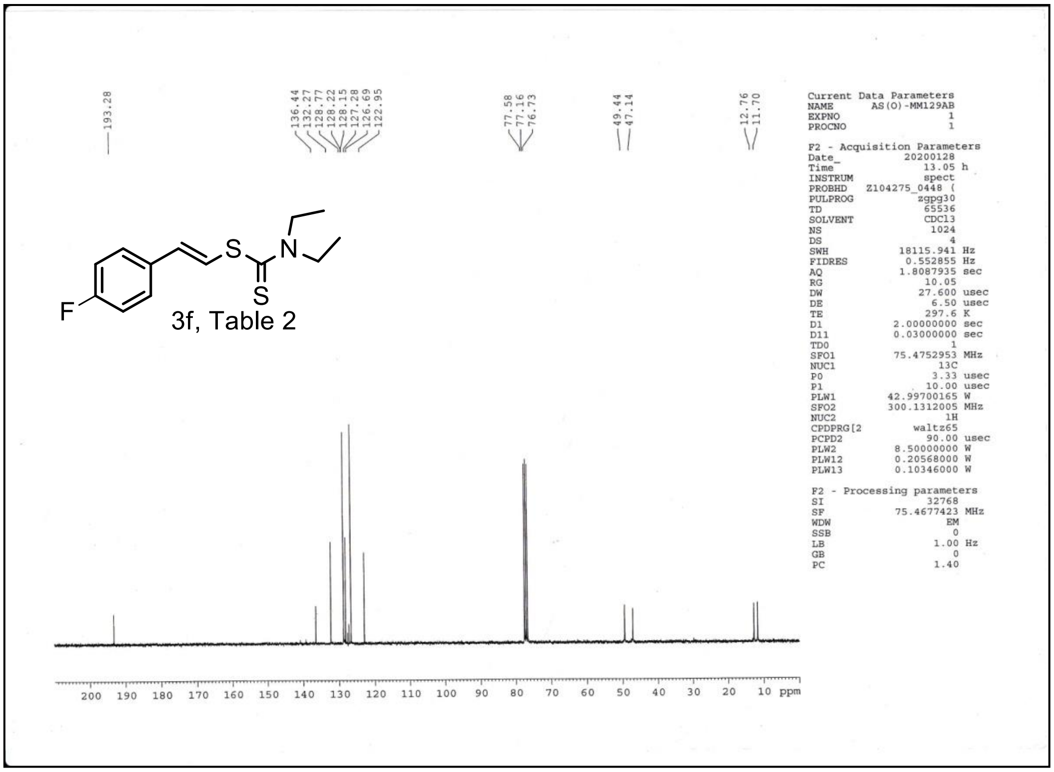
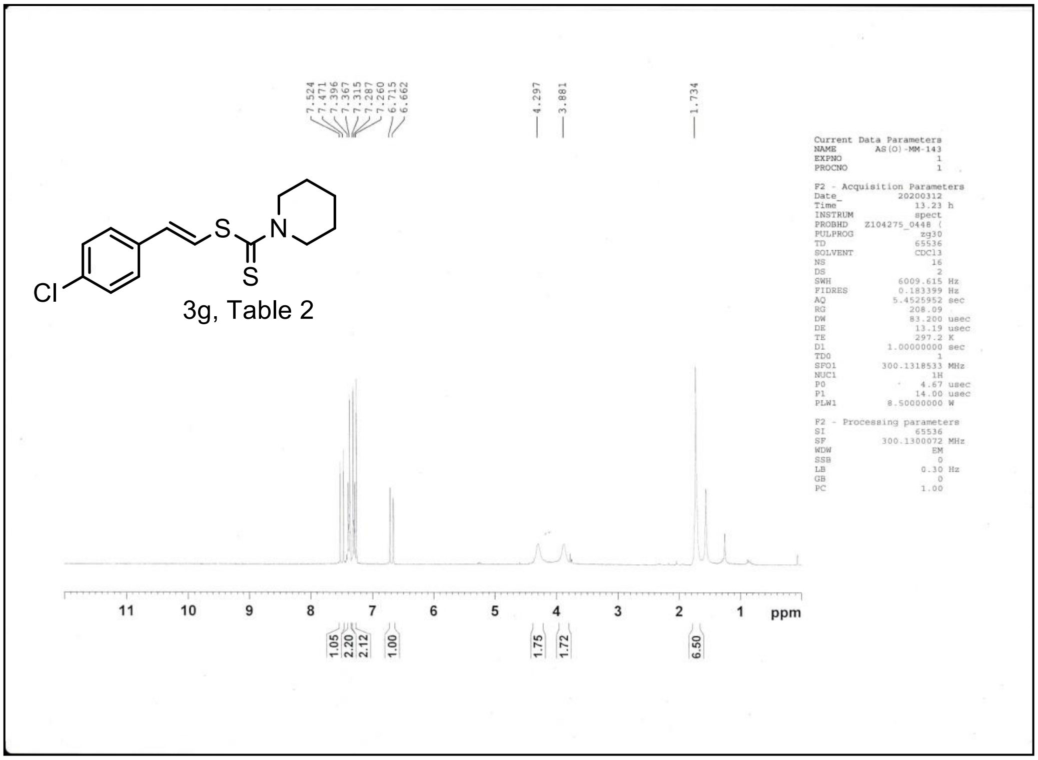
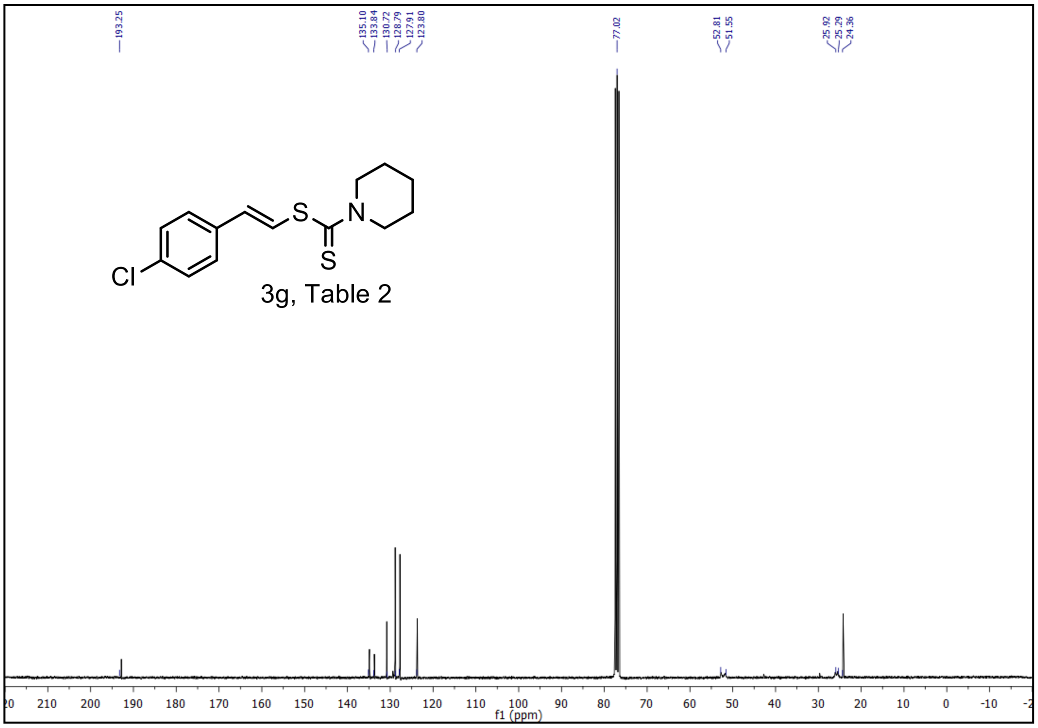



```
Current Data Parameters
NAME         AS(O)-MM129AB
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20200128
Time                13.05 h
INSTRUM             spect
PROBHD   Z104275_0448 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      4
SWH             18115.941 Hz
FIDRES           0.552855 Hz
AQ              1.8087935 sec
RG                  10.05
DW                 27.600 usec
DE                   6.50 usec
TE                  297.6 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1           75.4752953 MHz
NUC1                  13C
P0                   3.33 usec
P1                  10.00 usec
PLW1          42.99700165 W
SFO2          300.1312005 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2           8.50000000 W
PLW12          0.20568000 W
PLW13          0.10346000 W

F2 - Processing parameters
SI                  32768
SF             75.4677423 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

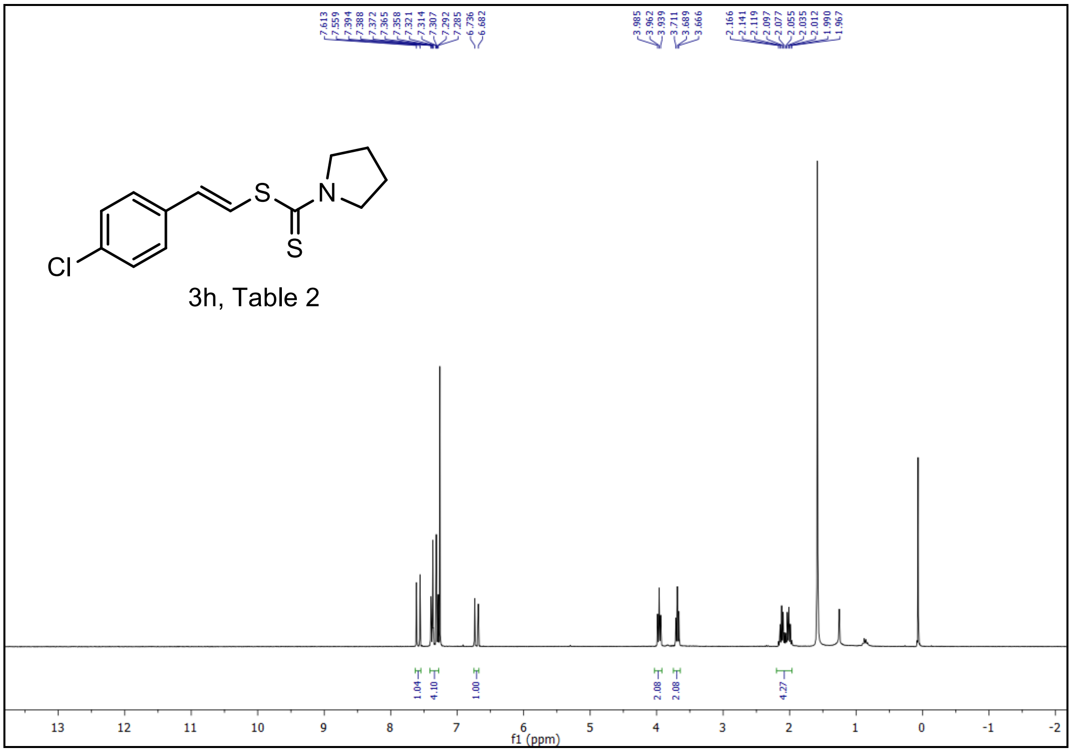
7.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3g**

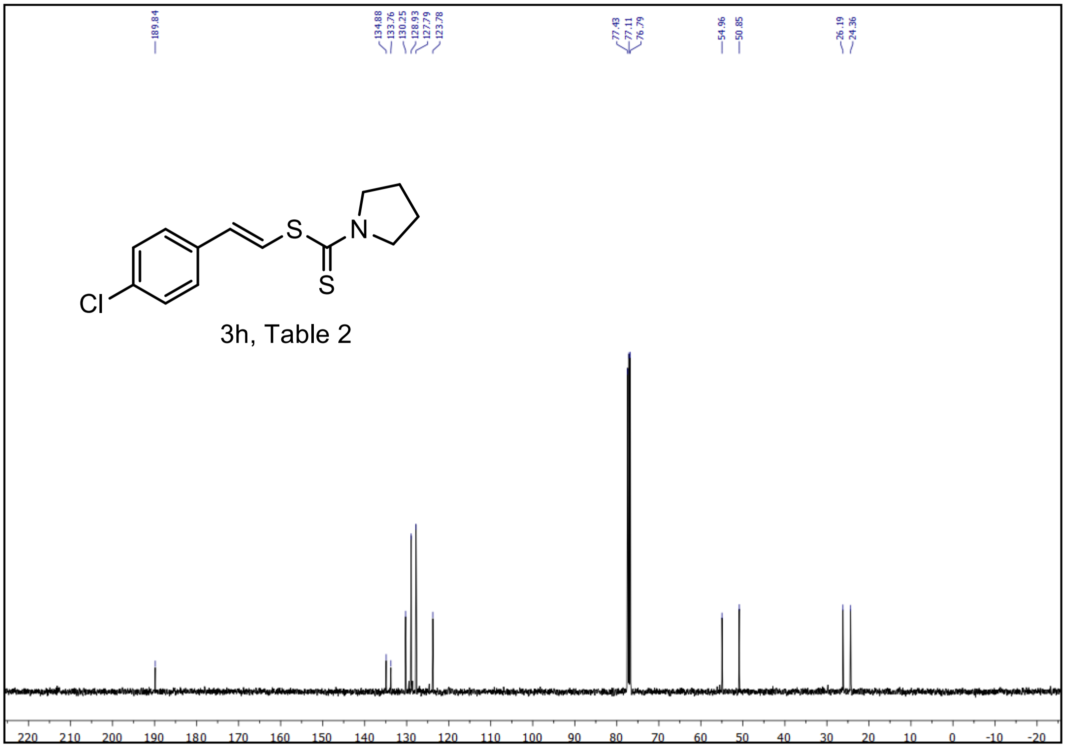


```
Current Data Parameters
NAME        AS(O)-MM-143
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20200312
Time               13.23 h
INSTRUM            spect
PROBHD   Z104275_0448 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             6009.615 Hz
FIDRES          0.183399 Hz
AQ             5.4525952 sec
RG                208.09
DW                83.200 usec
DE                 13.19 usec
TE                 297.2 K
D1            1.00000000 sec
TD0                    1
SFO1         300.1318533 MHz
NUC1                  1H
P0                  4.67 usec
P1                 14.00 usec
PLW1          8.50000000 W

F2 - Processing parameters
SI                 65536
SF           300.1300072 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

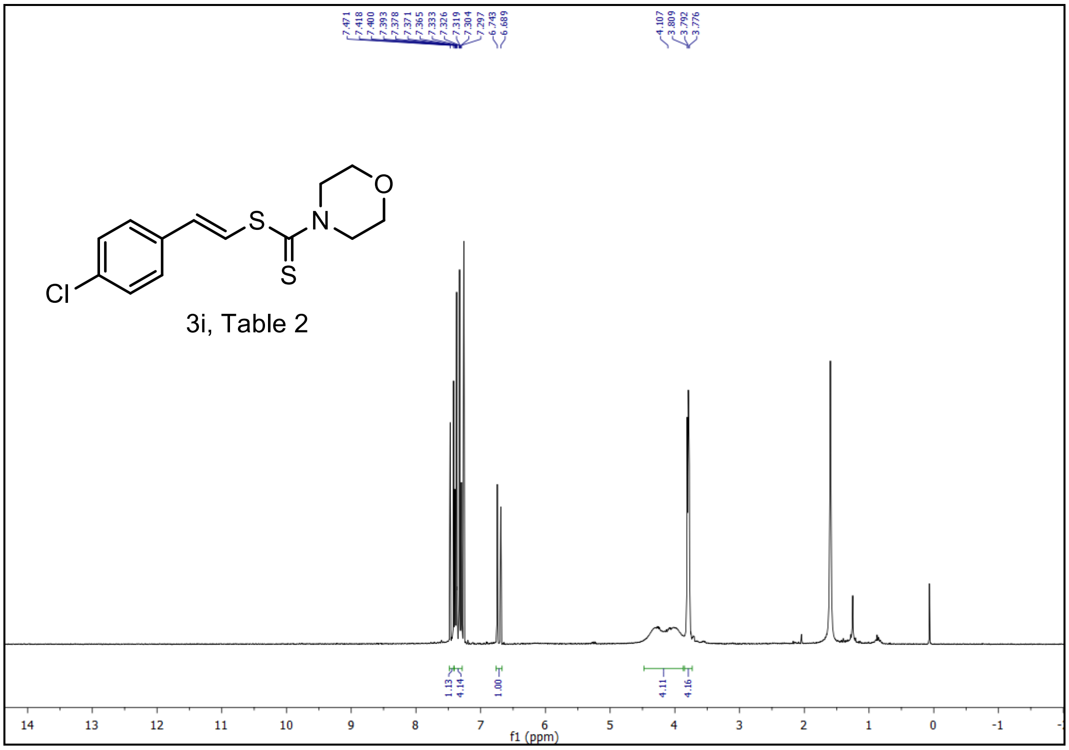


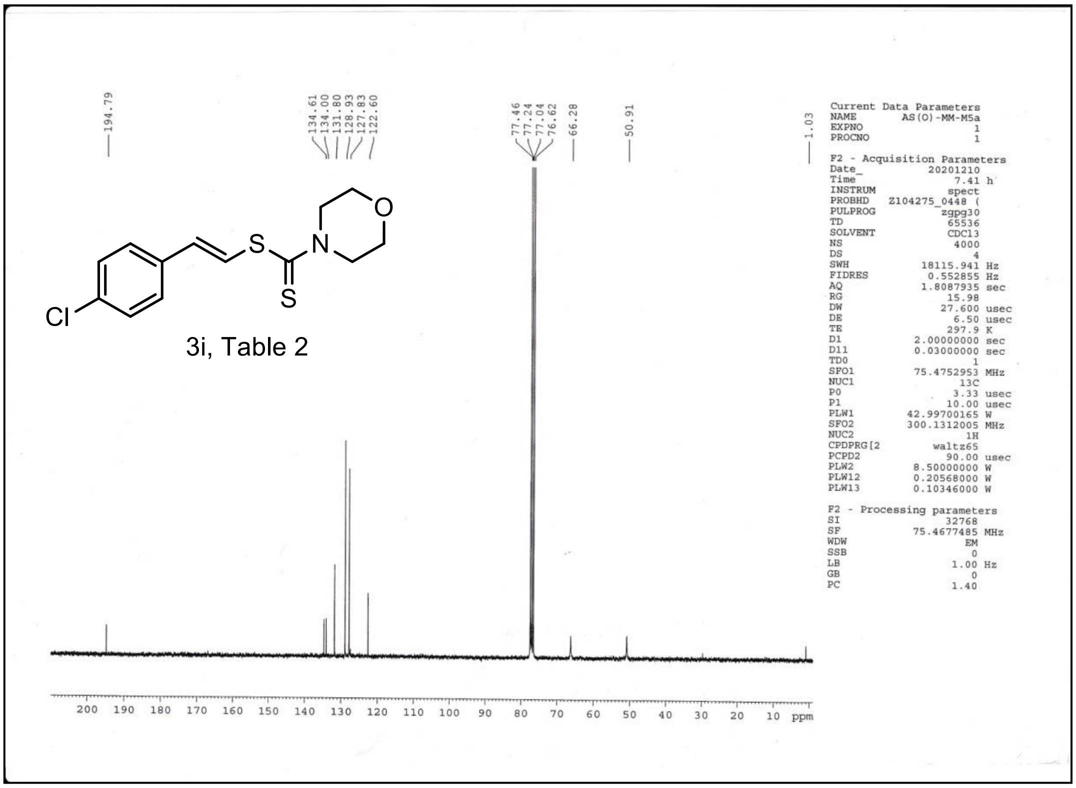
8.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3h**





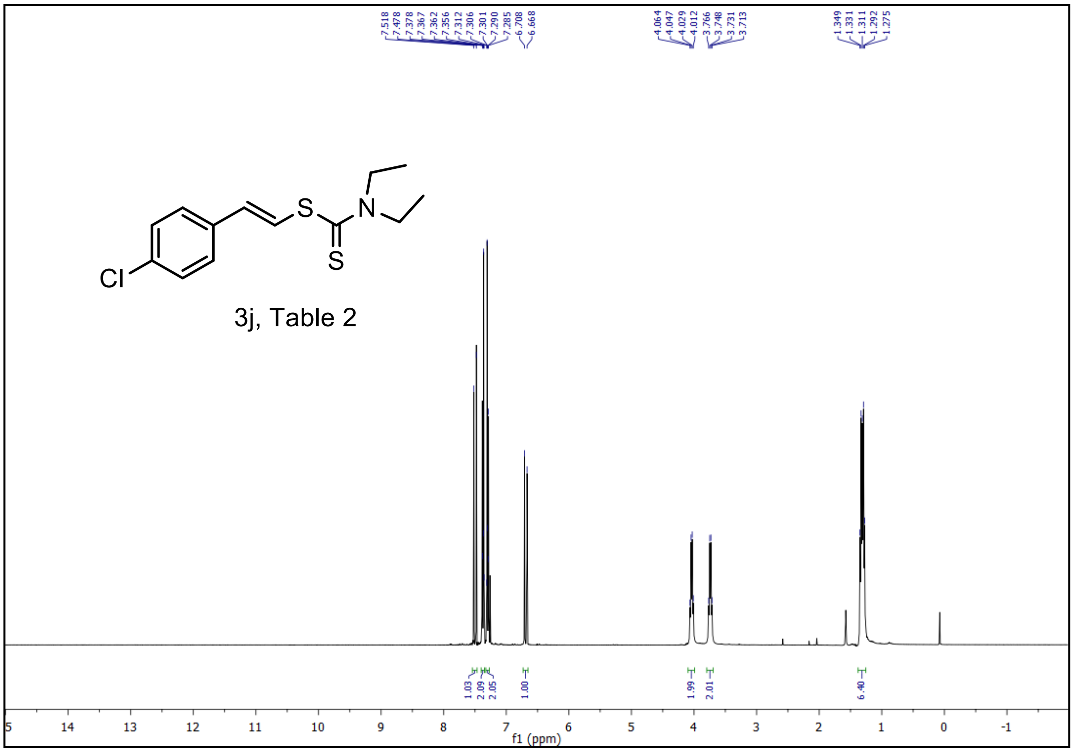
9.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3i**

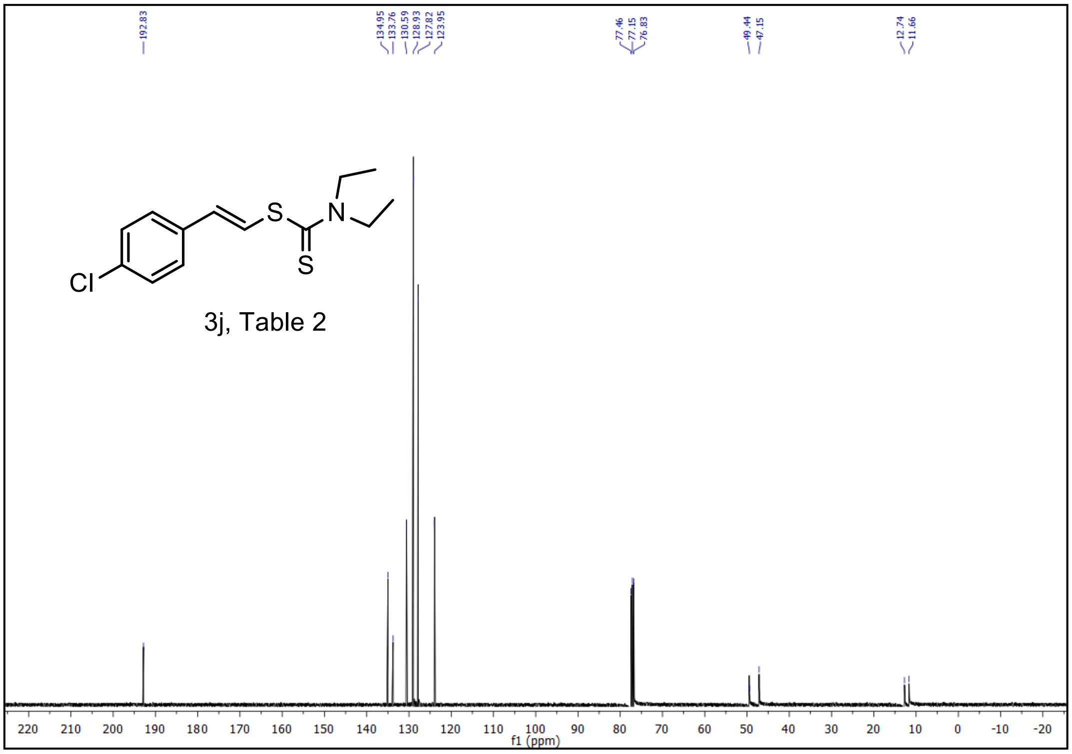




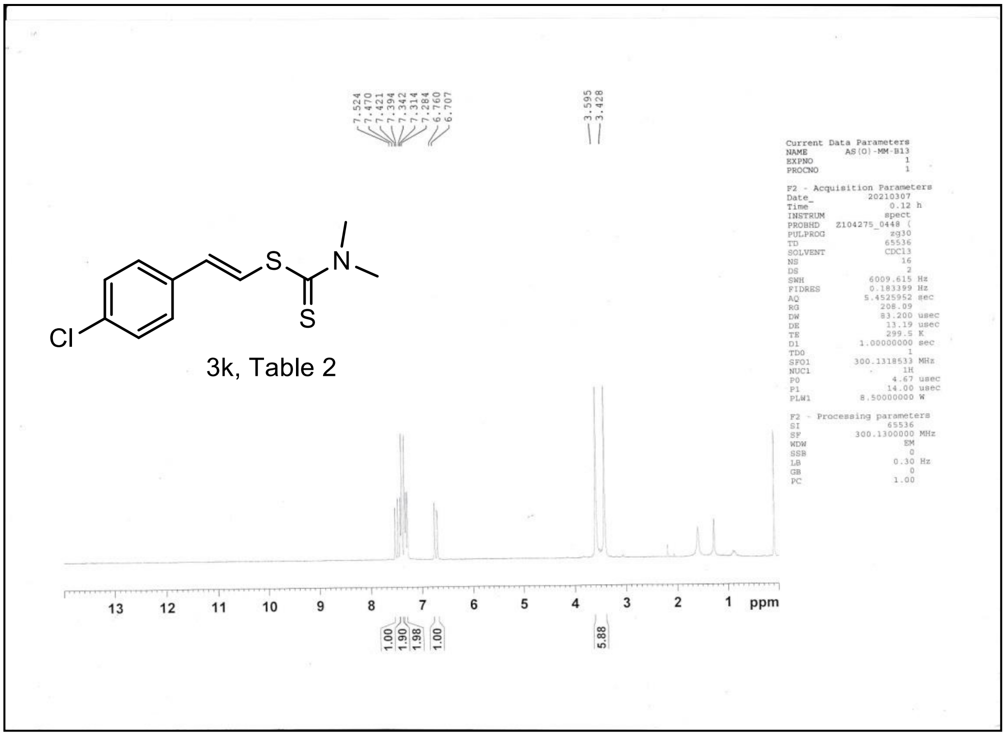
```
Current Data Parameters
NAME          AS(O)-MM-M5a
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20201210
Time                  7.41 h
INSTRUM              spect
PROBHD    Z104275_0448 (
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    4000
DS                       4
SWH              18115.941 Hz
FIDRES            0.552855 Hz
AQ               1.8087935 sec
RG                   15.98
DW                  27.600 usec
DE                    6.50 usec
TE                   297.9 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1
SFO1            75.4752953 MHz
NUC1                   13C
P0                    3.33 usec
P1                   10.00 usec
PLW1           42.99700165 W
SFO2           300.1312005 MHz
NUC2                    1H
CPDPRG[2          waltz65
PCPD2                90.00 usec
PLW2            8.50000000 W
PLW12           0.20568000 W
PLW13           0.10346000 W

F2 - Processing parameters
SI                   32768
SF              75.4677485 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

10.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3j**



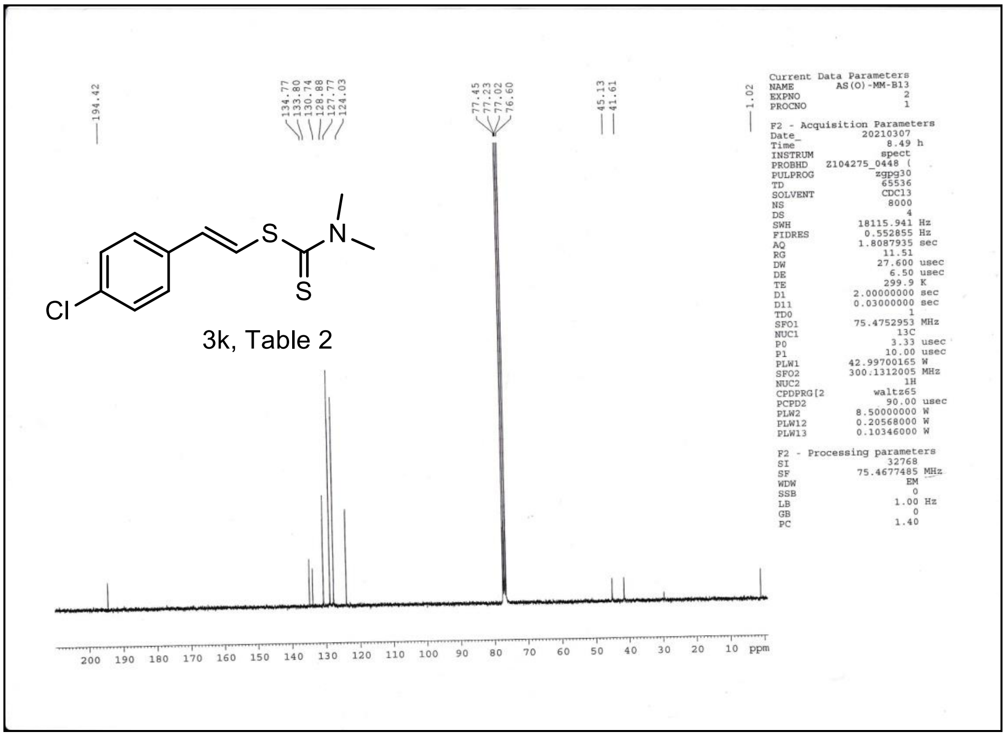


11.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3k**



3k, Table 2

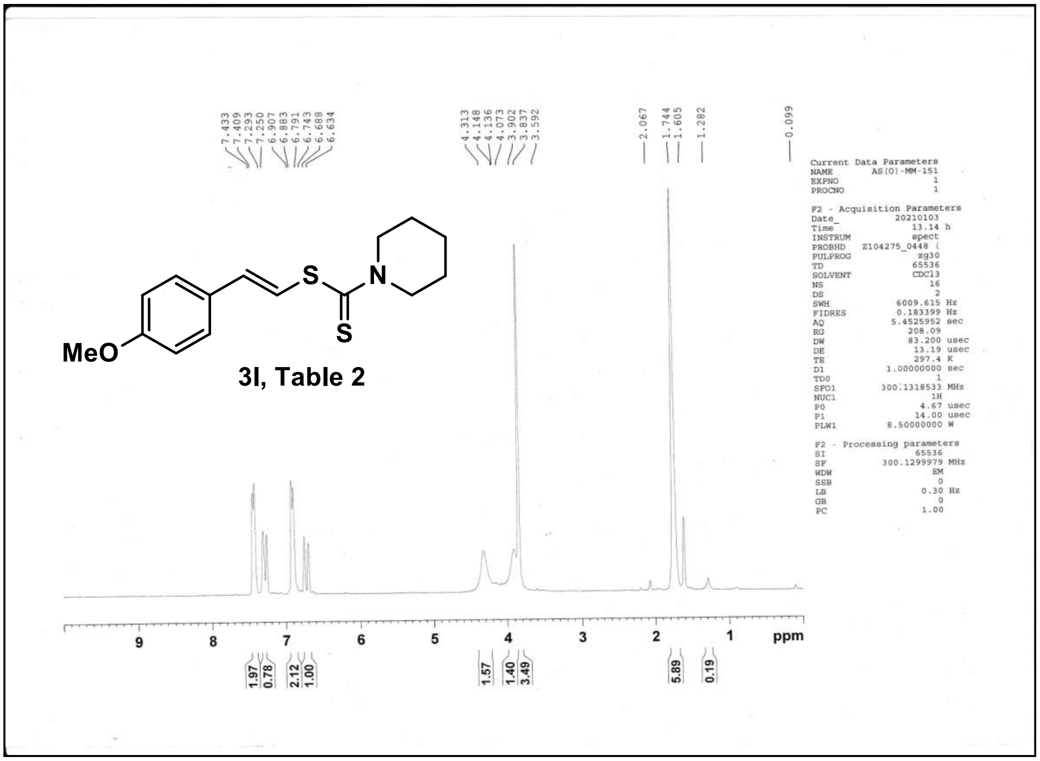
```
Current Data Parameters
NAME          AS(O)-MM-B13
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20210307
Time                  0.12 h
INSTRUM              spect
PROBHD    Z104275_0448 (
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               6009.615 Hz
FIDRES            0.183399 Hz
AQ               5.4525952 sec
RG                  208.09
DW                  83.200 usec
DE                   13.19 usec
TE                   299.5 K
D1              1.00000000 sec
TD0                      1
SFO1           300.1318533 MHz
NUC1                    1H
P0                    4.67 usec
P1                   14.00 usec
PLW1            8.50000000 W

F2 - Processing parameters
SI                   65536
SF             300.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



3k, Table 2

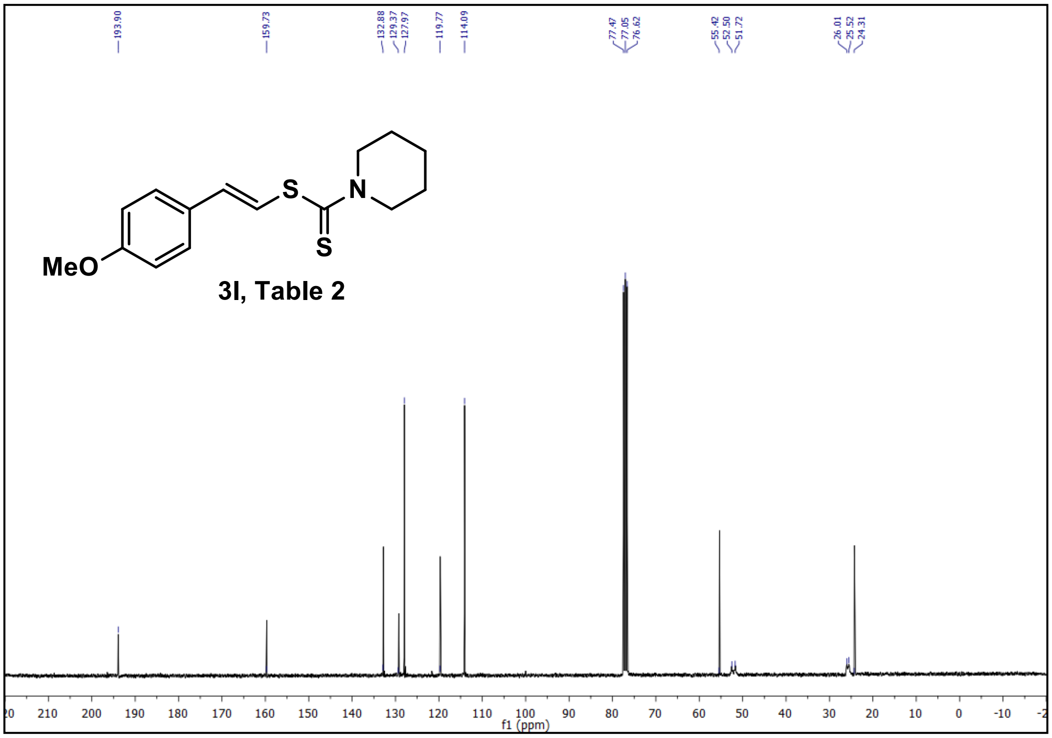
```
Current Data Parameters
NAME          AS(O)-MM-B13
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20210307
Time                  8.49 h
INSTRUM              spect
PROBHD    Z104275_0448 (
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    8000
DS                       4
SWH              18115.941 Hz
FIDRES            0.552855 Hz
AQ               1.8087935 sec
RG                   11.51
DW                  27.600 usec
DE                    6.50 usec
TE                   299.9 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1
SFO1            75.4752953 MHz
NUC1                   13C
P0                    3.33 usec
P1                   10.00 usec
PLW1           42.99700165 W
SFO2           300:1312005 MHz
NUC2                    1H
CPDPRG[2           waltz65
PCPD2                90.00 usec
PLW2            8.50000000 W
PLW12           0.20568000 W
PLW13           0.10346000 W

F2 - Processing parameters
SI                   32768
SF              75.4677485 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

12.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, CDCl$_3$) spectrum of **3l**



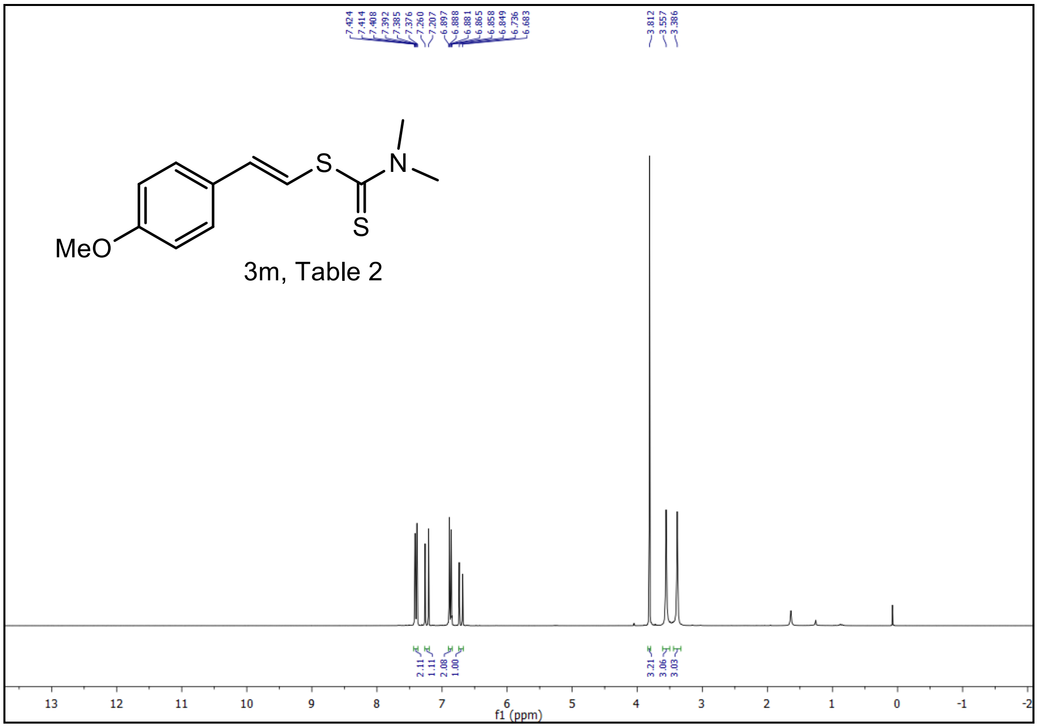
3l, Table 2

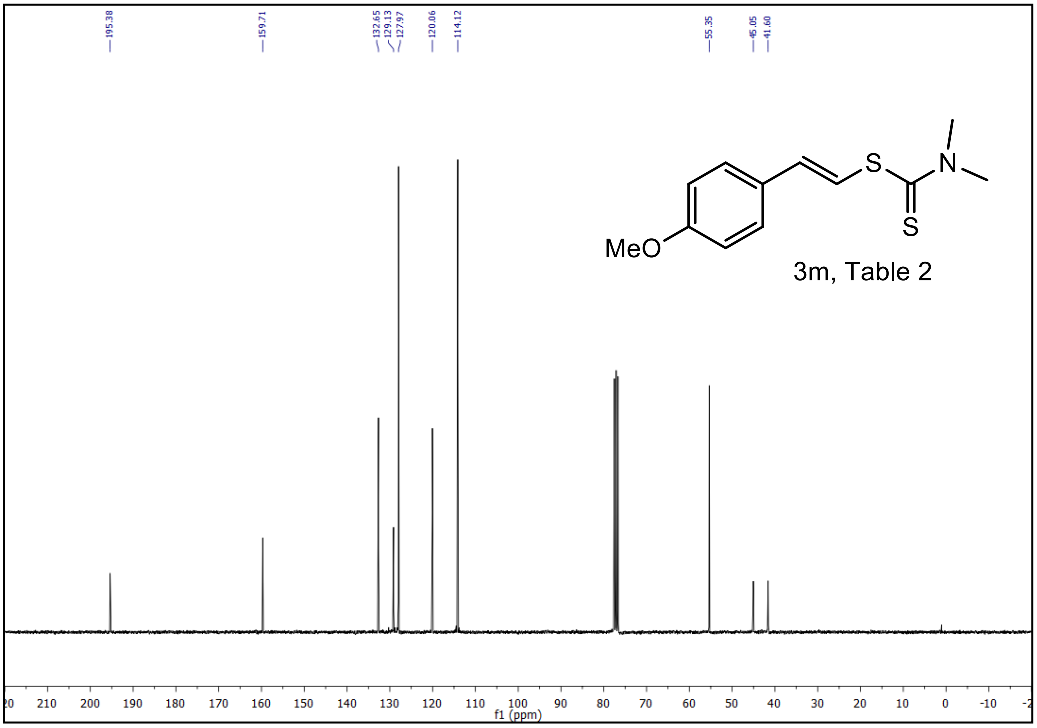
```
Current Data Parameters
NAME        AS(O)-MM-151
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20210103
Time               13.14 h
INSTRUM            spect
PROBHD   Z104275_0448 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             6009.615 Hz
FIDRES          0.183399 Hz
AQ             5.4525952 sec
RG                208.09
DW                83.200 usec
DE                 13.19 usec
TE                 297.4 K
D1            1.00000000 sec
TD0                    1
SFO1         300.1318533 MHz
NUC1                  1H
P0                  4.67 usec
P1                 14.00 usec
PLW1          8.50000000 W

F2 - Processing parameters
SI                 65536
SF           300.1299979 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



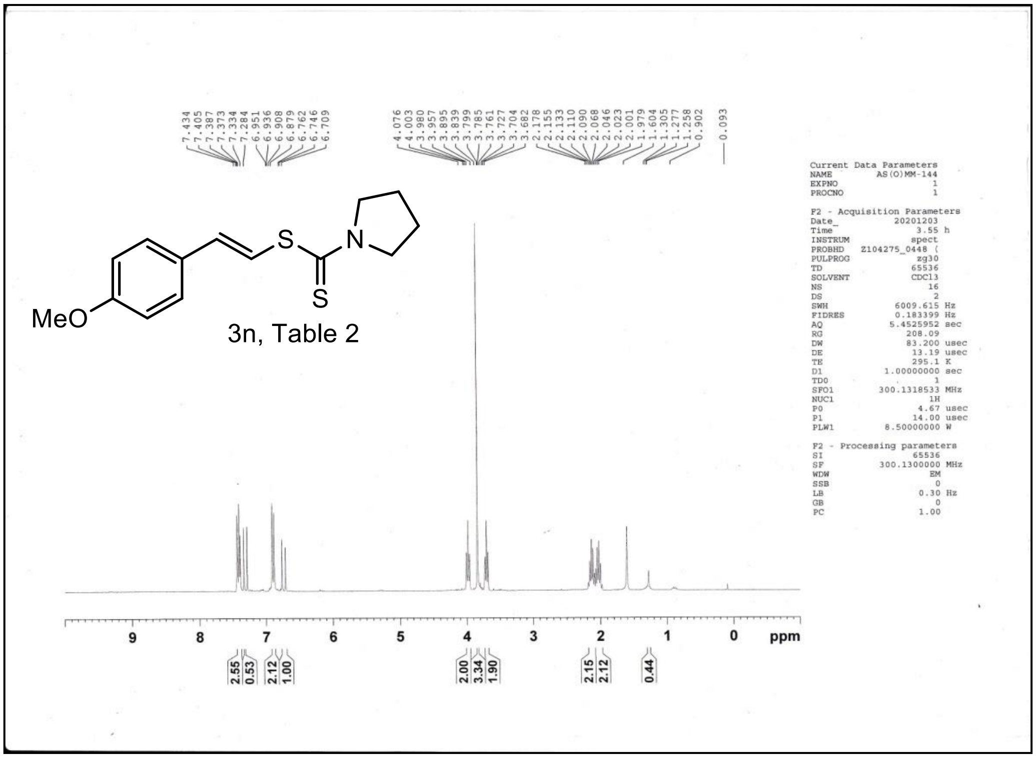
3l, Table 2

13.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3m**

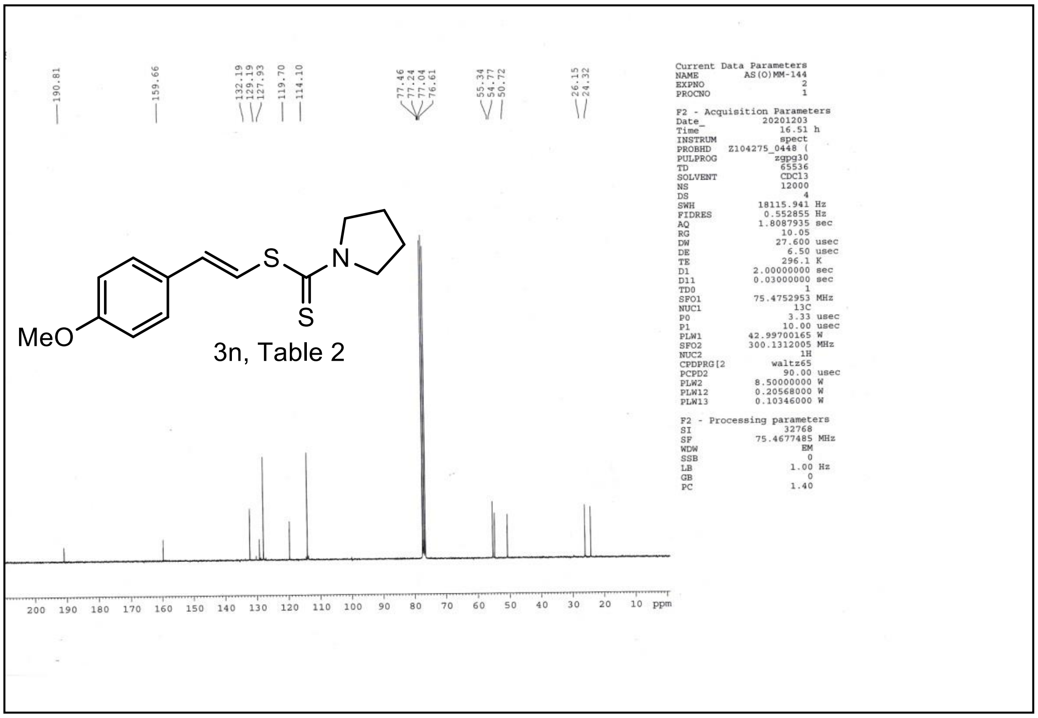




14.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3n**

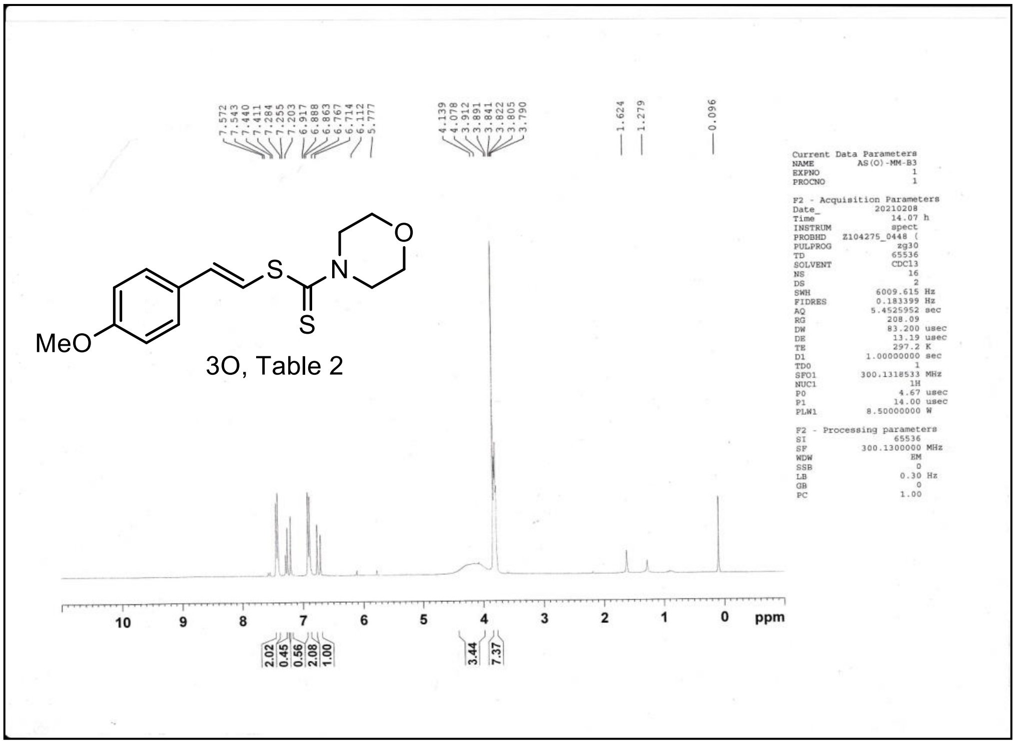


```
Current Data Parameters
NAME          AS(O)MM-144
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20201203
Time                 3.55 h
INSTRUM             spect
PROBHD   Z104275_0448 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              6009.615 Hz
FIDRES           0.183399 Hz
AQ              5.4525952 sec
RG                 208.09
DW                 83.200 usec
DE                  13.19 usec
TE                  295.1 K
D1             1.00000000 sec
TD0                     1
SFO1          300.1318533 MHz
NUC1                   1H
P0                   4.67 usec
P1                  14.00 usec
PLW1           8.50000000 W

F2 - Processing parameters
SI                  65536
SF            300.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

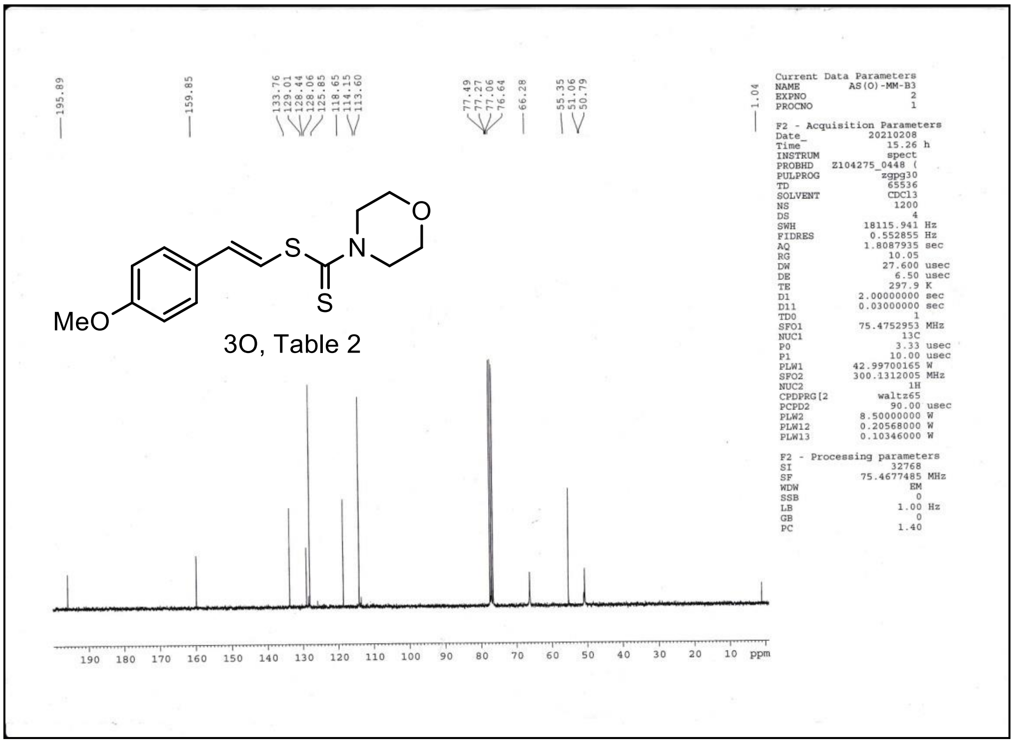


```
Current Data Parameters
NAME          AS(O)MM-144
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20201203
Time                16.51 h
INSTRUM             spect
PROBHD   Z104275_0448 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                  12000
DS                      4
SWH             18115.941 Hz
FIDRES           0.552855 Hz
AQ              1.8087935 sec
RG                  10.05
DW                 27.600 usec
DE                   6.50 usec
TE                  296.1 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1           75.4752953 MHz
NUC1                  13C
P0                   3.33 usec
P1                  10.00 usec
PLW1          42.99700165 W
SFO2          300.1312005 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2           8.50000000 W
PLW12          0.20568000 W
PLW13          0.10346000 W

F2 - Processing parameters
SI                  32768
SF             75.4677485 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

15.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, CDCl$_3$) spectrum of **3o**

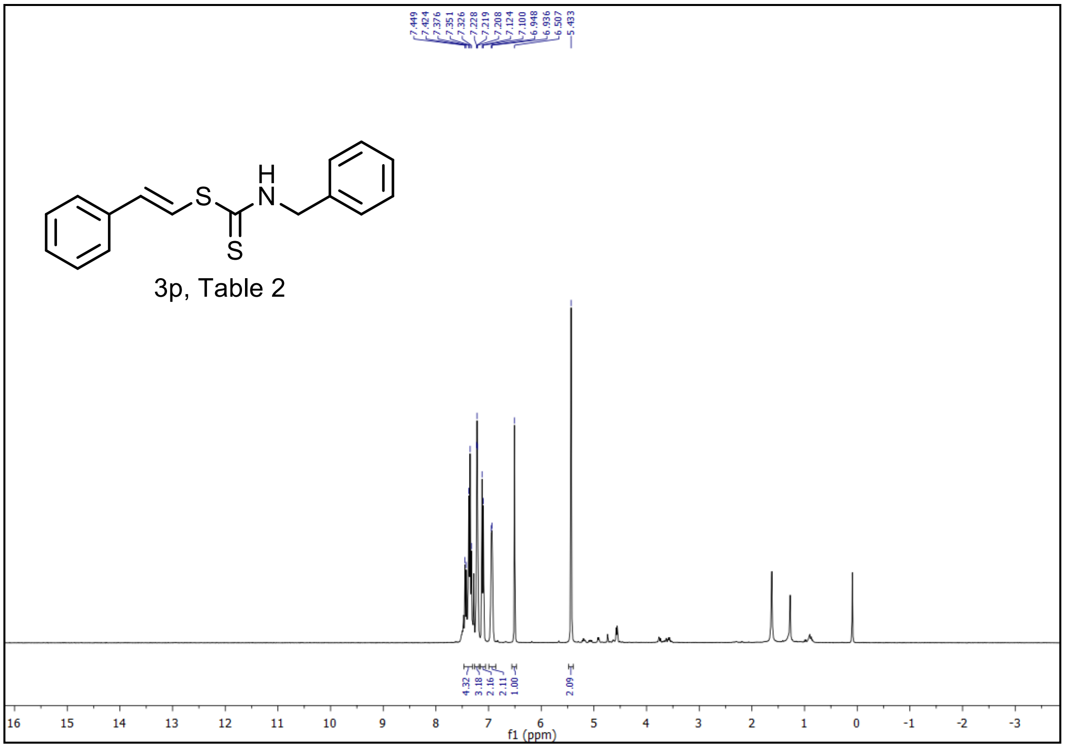


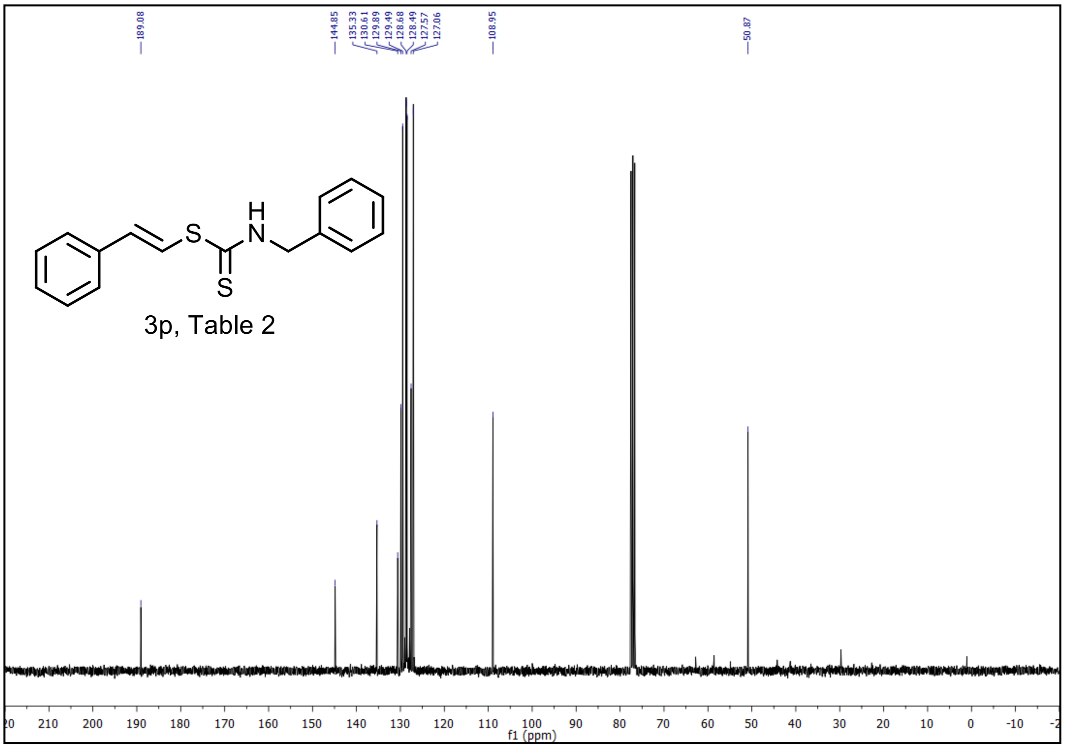
```
Current Data Parameters
NAME          AS(O)-MM-B3
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20210208
Time                14.07 h
INSTRUM             spect
PROBHD   Z104275_0448 (
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              6009.615 Hz
FIDRES           0.183399 Hz
AQ              5.4525952 sec
RG                 208.09
DW                 83.200 usec
DE                  13.19 usec
TE                  297.2 K
D1             1.00000000 sec
TD0                     1
SFO1          300.1318533 MHz
NUC1                   1H
P0                   4.67 usec
P1                  14.00 usec
PLW1           8.50000000 W

F2 - Processing parameters
SI                  65536
SF            300.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



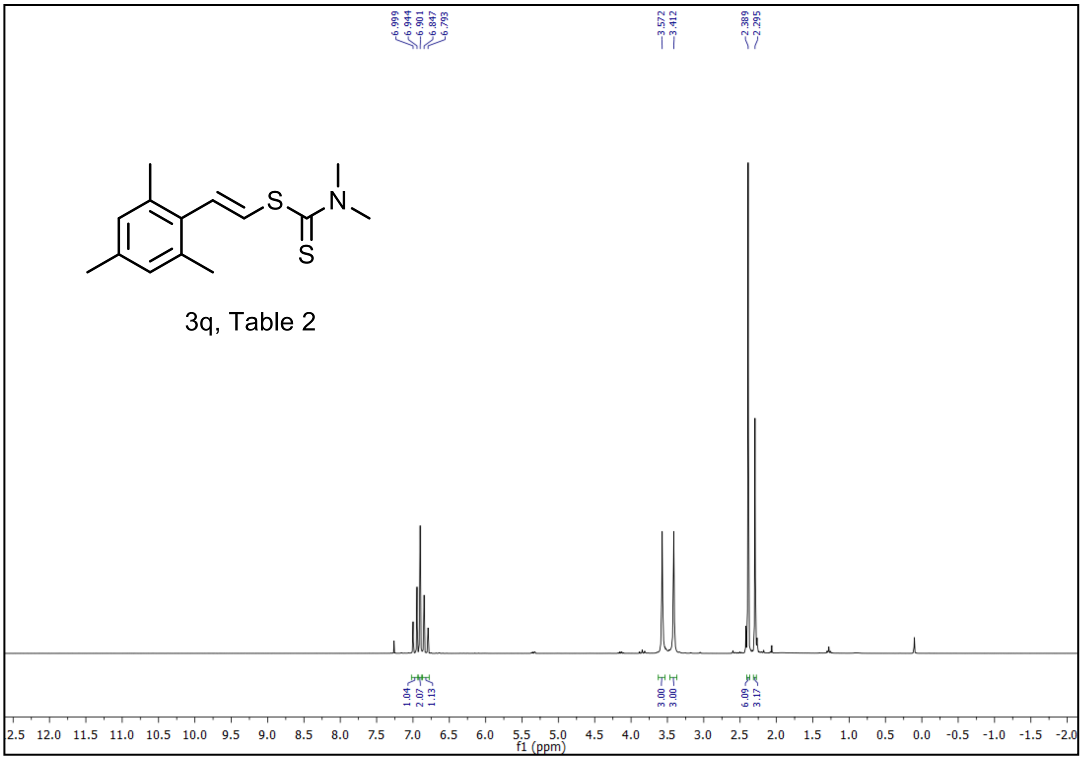
```
Current Data Parameters
NAME          AS(O)-MM-B3
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20210208
Time                15.26 h
INSTRUM             spect
PROBHD   Z104275_0448 (
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   1200
DS                      4
SWH             18115.941 Hz
FIDRES           0.552855 Hz
AQ              1.8087935 sec
RG                  10.05
DW                 27.600 usec
DE                   6.50 usec
TE                  297.9 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                     1
SFO1           75.4752953 MHz
NUC1                  13C
P0                   3.33 usec
P1                  10.00 usec
PLW1          42.99700165 W
SFO2          300.1312005 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2           8.50000000 W
PLW12          0.20568000 W
PLW13          0.10346000 W

F2 - Processing parameters
SI                  32768
SF             75.4677485 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

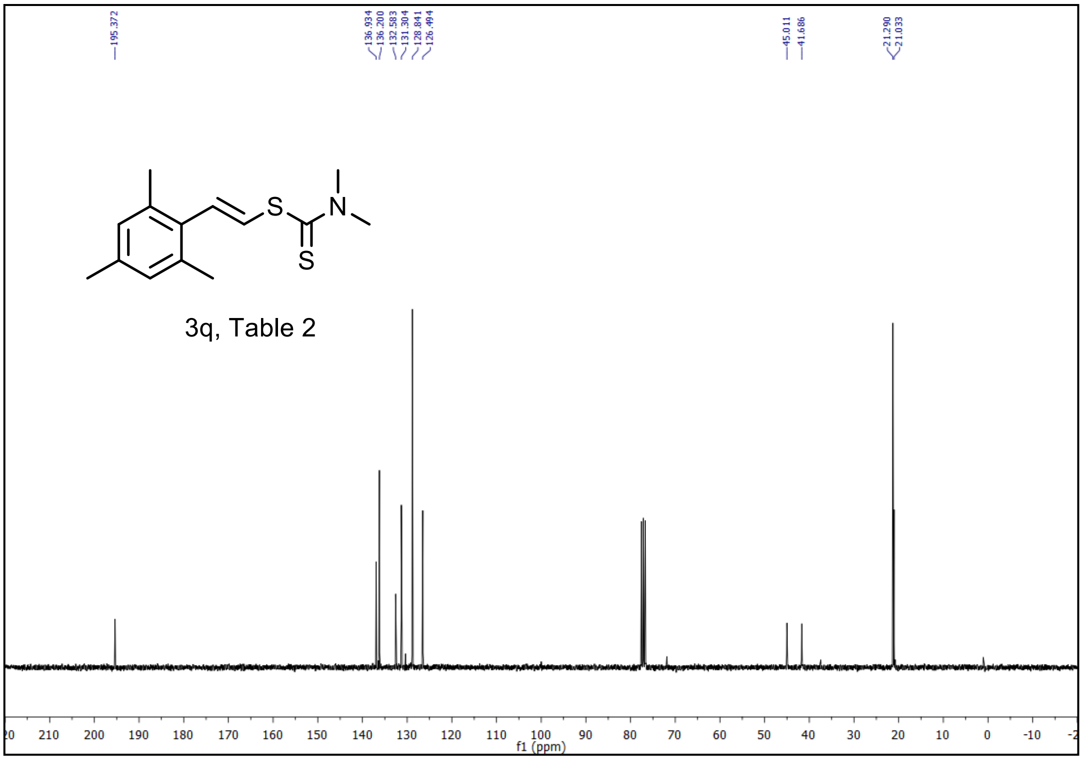
16.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **3p**



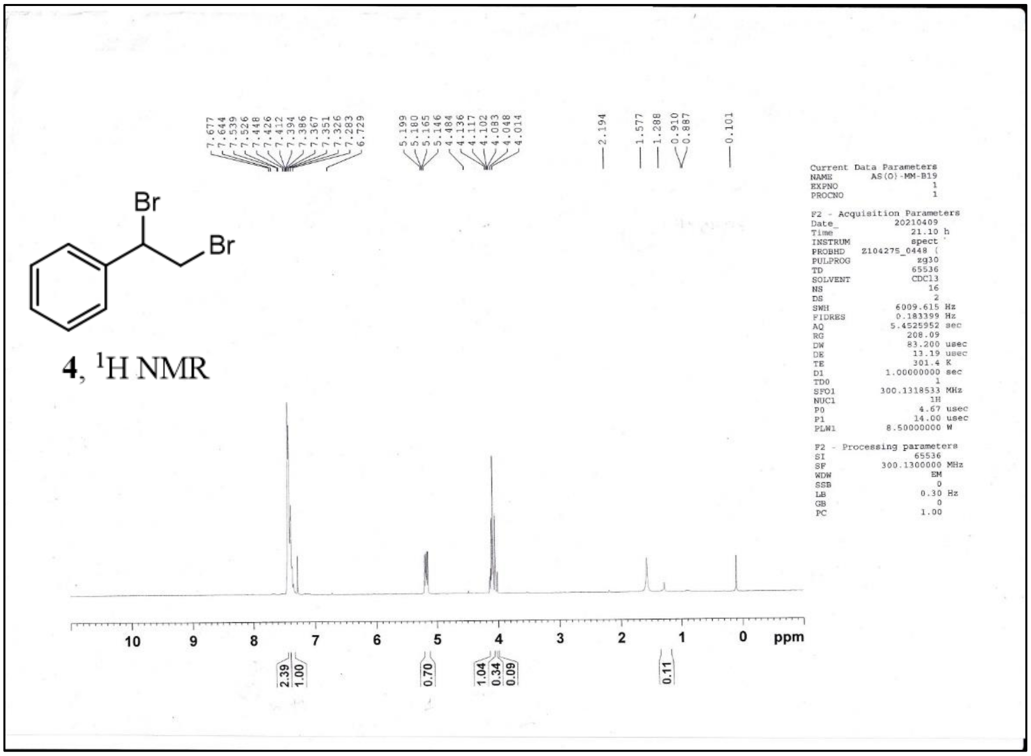


17.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of 3q

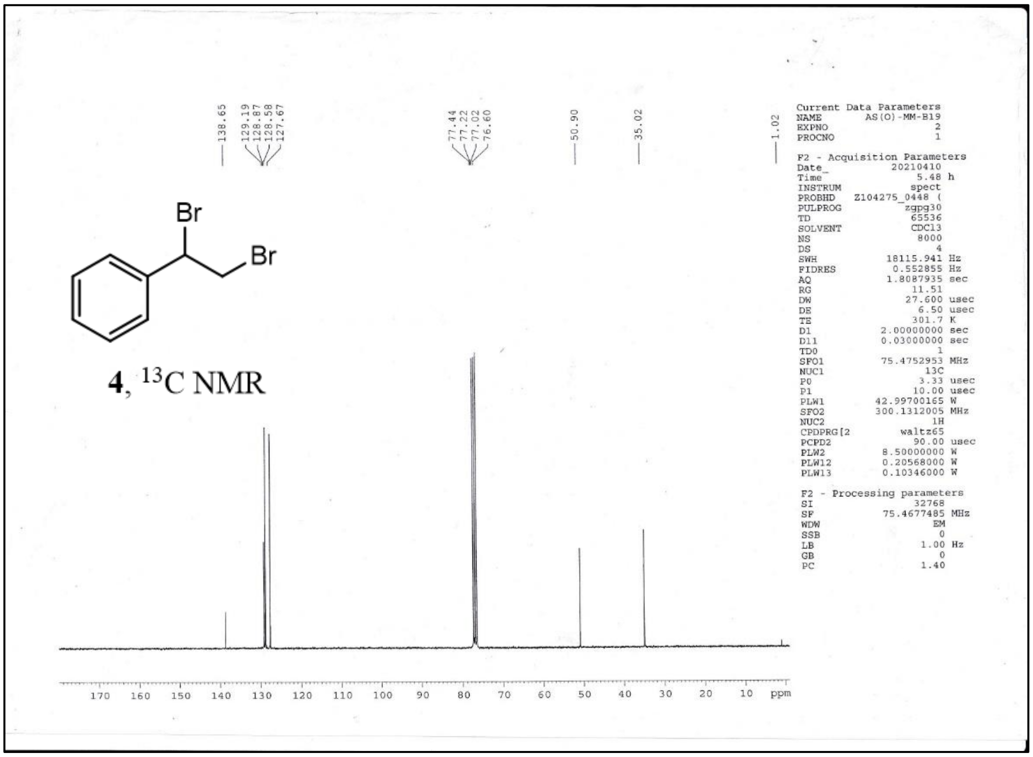




18.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound **4**

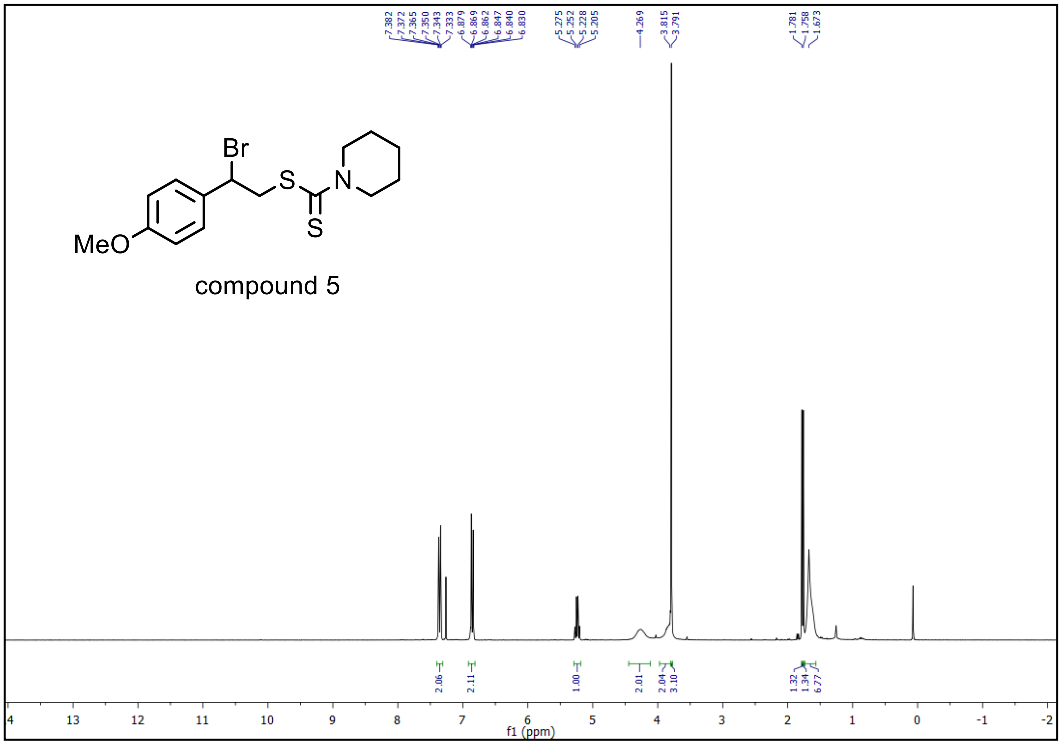


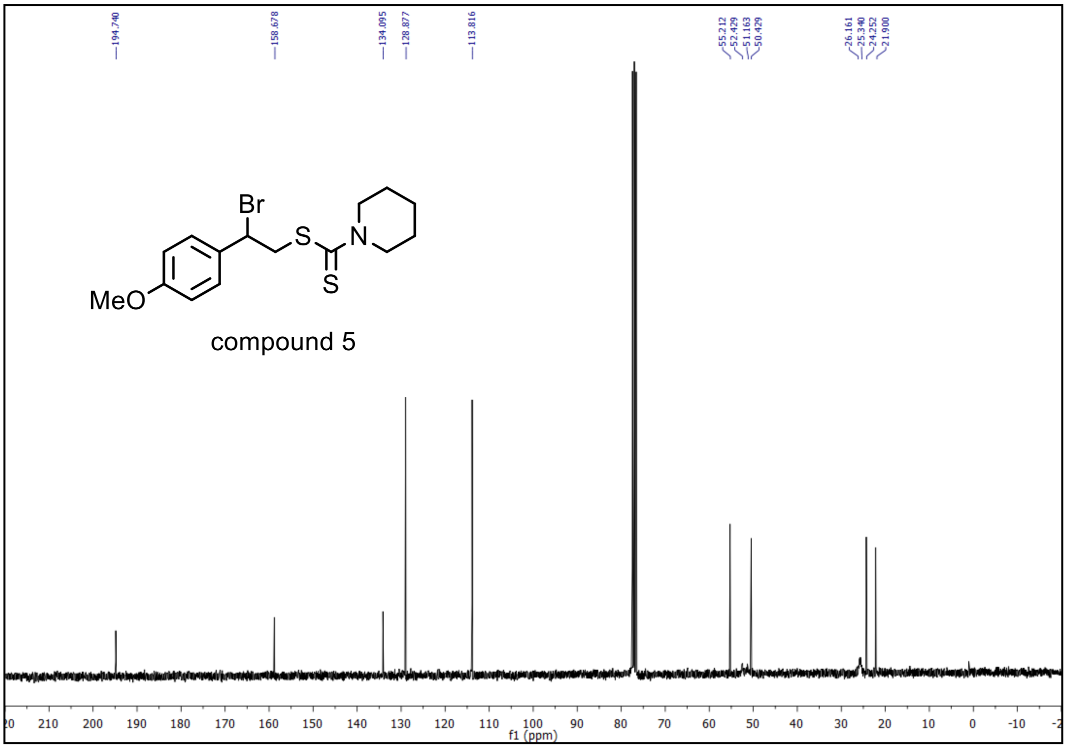
```
Current Data Parameters
NAME          AS(O)-MM-B19
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20210409
Time                 21.10 h
INSTRUM              spect
PROBHD     Z104275_0448 (
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               6009.615 Hz
FIDRES            0.183399 Hz
AQ               5.4525952 sec
RG                  208.09
DW                  83.200 usec
DE                   13.19 usec
TE                   301.4 K
D1              1.00000000 sec
TD0                      1
SFO1           300.1318533 MHz
NUC1                    1H
P0                    4.67 usec
P1                   14.00 usec
PLW1            8.50000000 W

F2 - Processing parameters
SI                   65536
SF             300.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



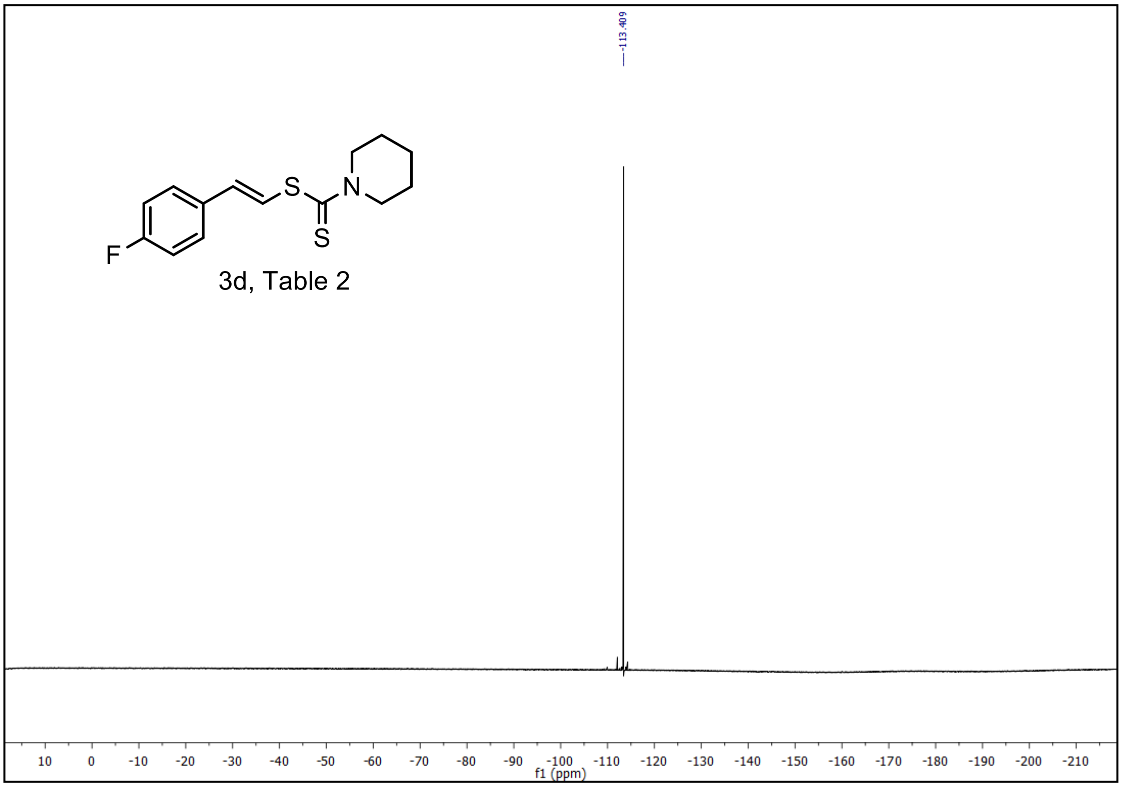
```
Current Data Parameters
NAME          AS(O)-MM-B19
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20210410
Time                  5.48 h
INSTRUM              spect
PROBHD     Z104275_0448 (
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    8000
DS                       4
SWH              18115.941 Hz
FIDRES            0.552855 Hz
AQ               1.8087935 sec
RG                   11.51
DW                  27.600 usec
DE                    6.50 usec
TE                   301.7 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1
SFO1            75.4752953 MHz
NUC1                   13C
P0                    3.33 usec
P1                   10.00 usec
PLW1           42.99700165 W
SFO2           300.1312005 MHz
NUC2                    1H
CPDPRG[2           waltz65
PCPD2                90.00 usec
PLW2            8.50000000 W
PLW12           0.20568000 W
PLW13           0.10346000 W

F2 - Processing parameters
SI                   32768
SF              75.4677485 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

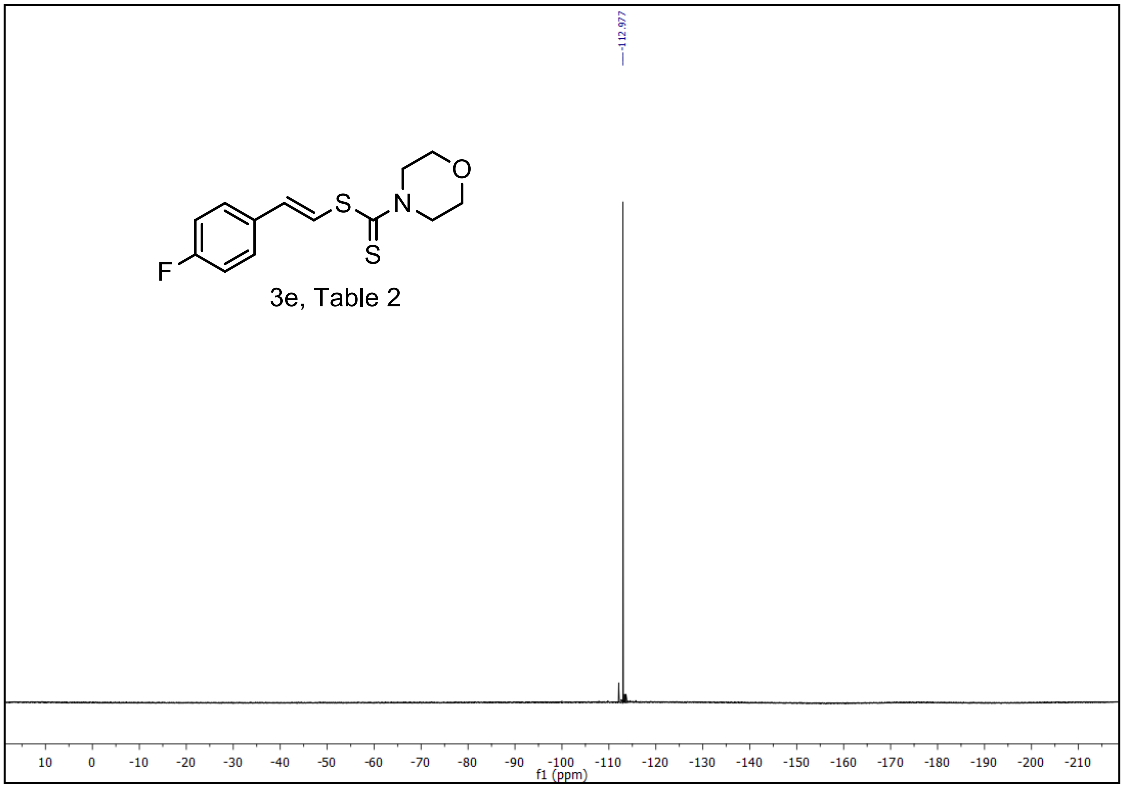
19.^{1}H NMR (300 MHz, CDCl3) and ^{13}C NMR (75 MHz, CDCl$_3$) spectrum of compound **5**



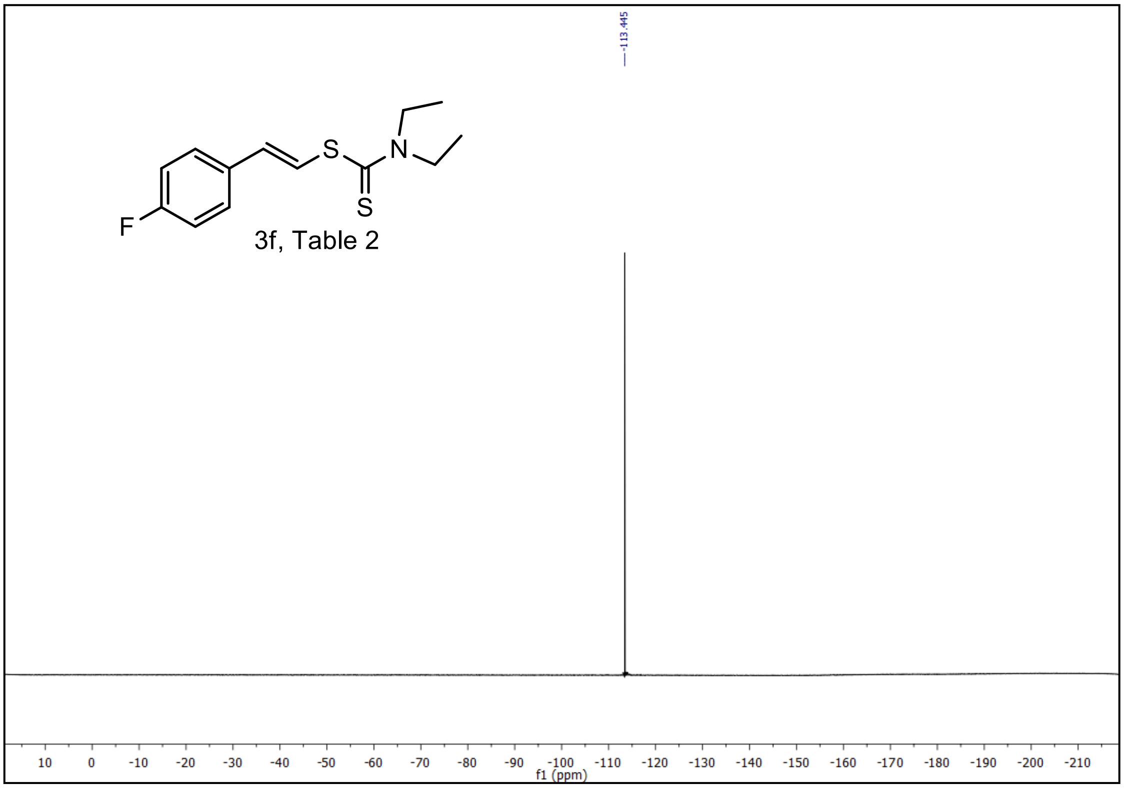


E. ^{19}F NMR spectra of fluorinated products


3d, Table 2

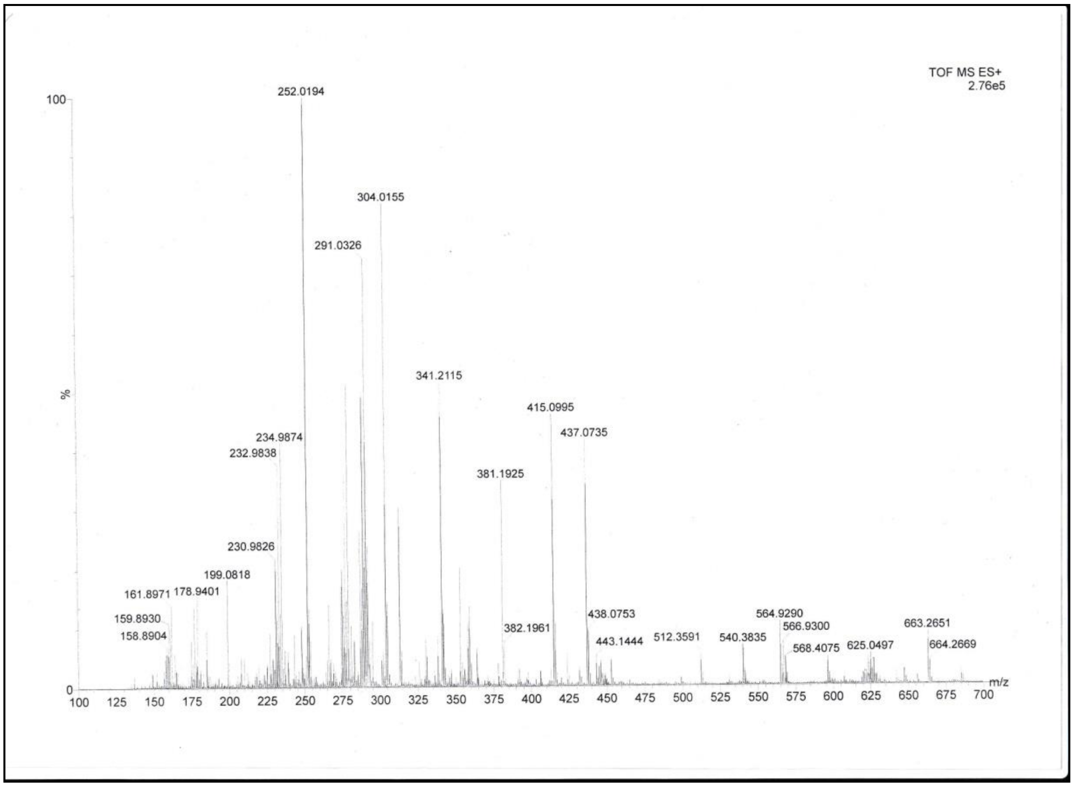


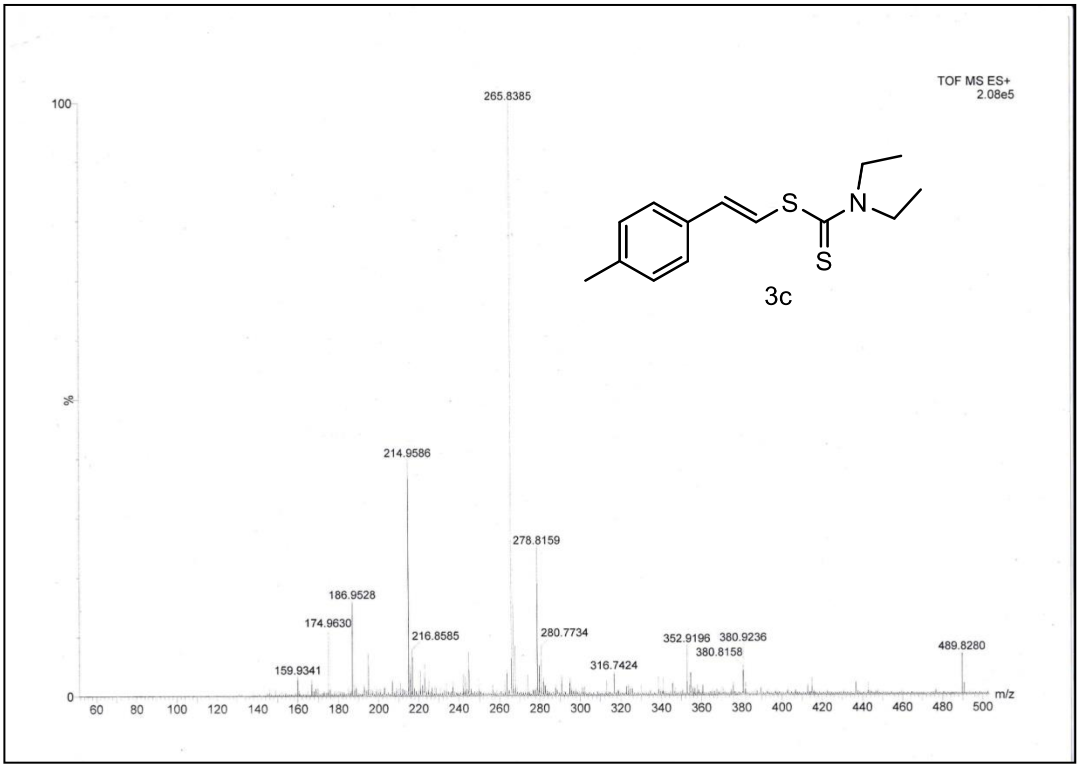
3e, Table 2

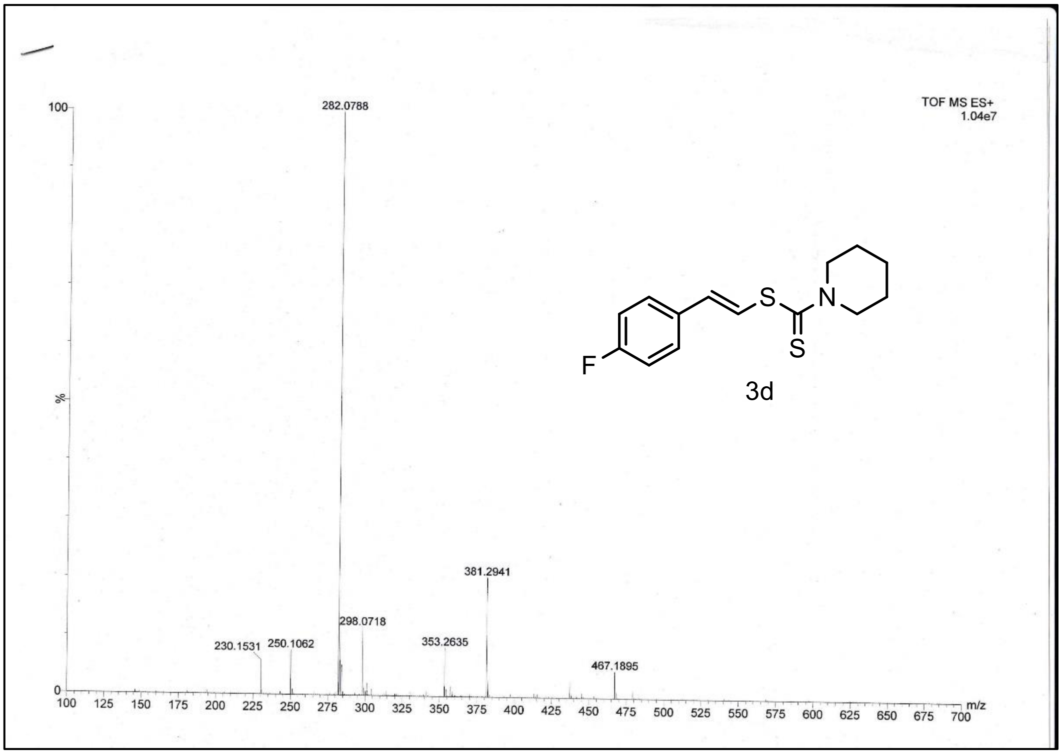


3f, Table 2

Mass spectra of products (**3a, 3c, 3d,3e, 3f, 3i, 3j, 3n, 3o, 3p,3q**)



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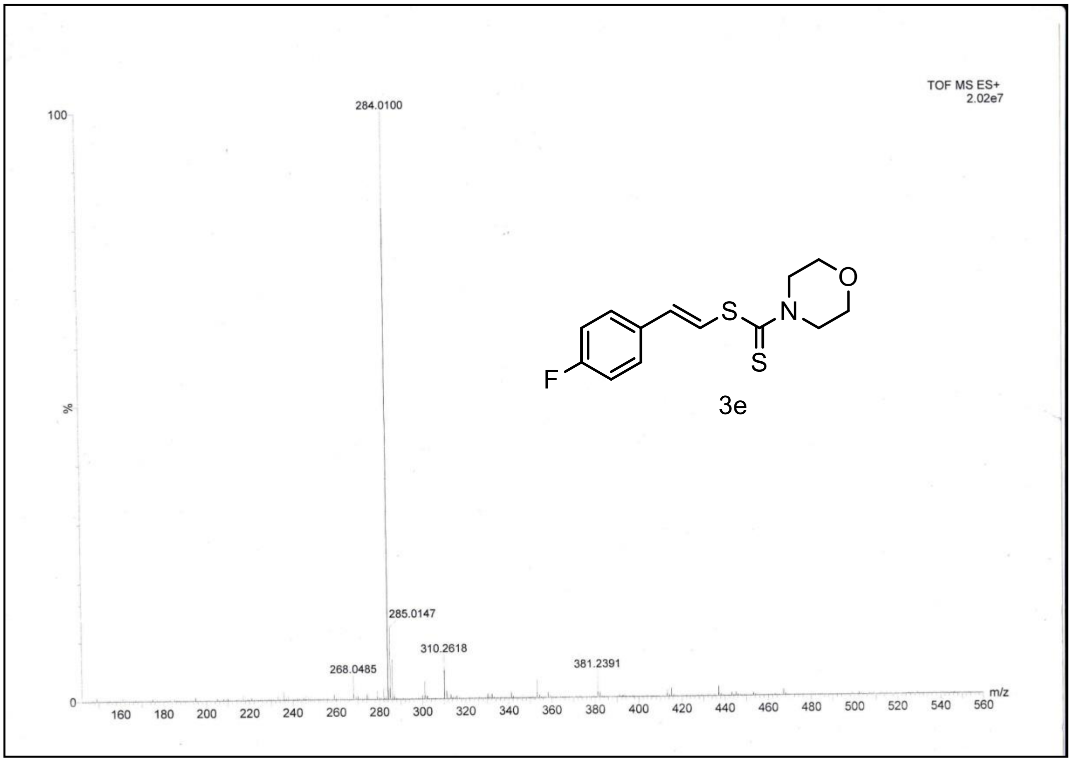
3d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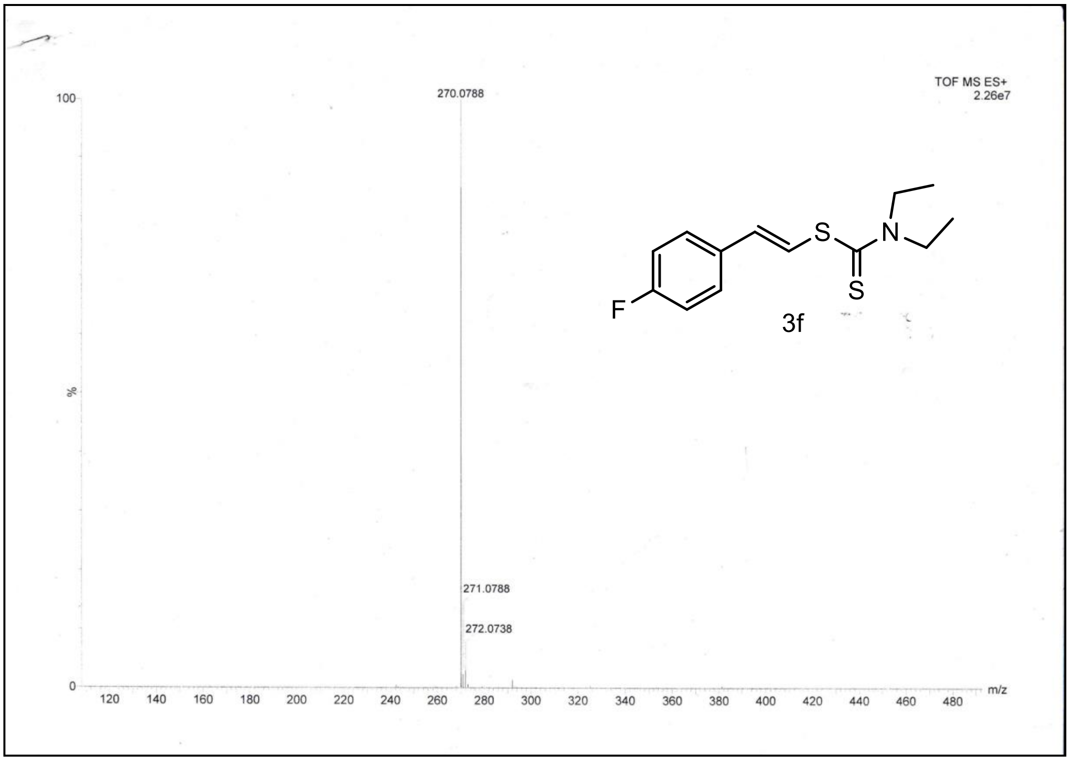
3e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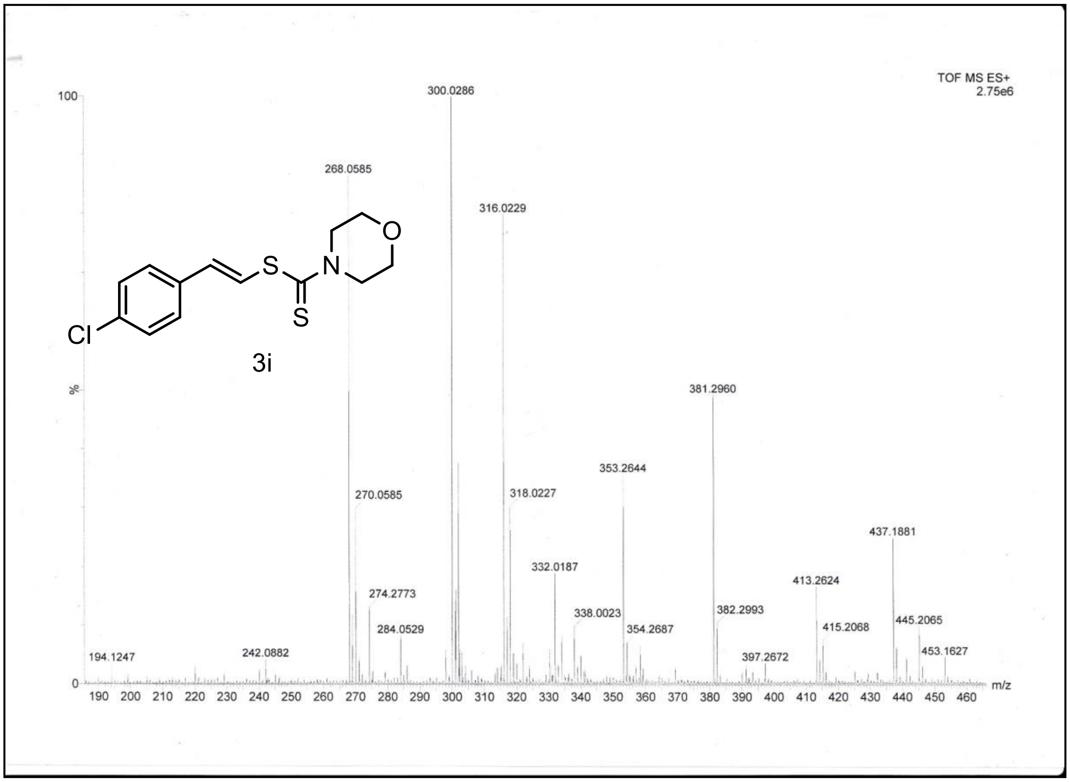
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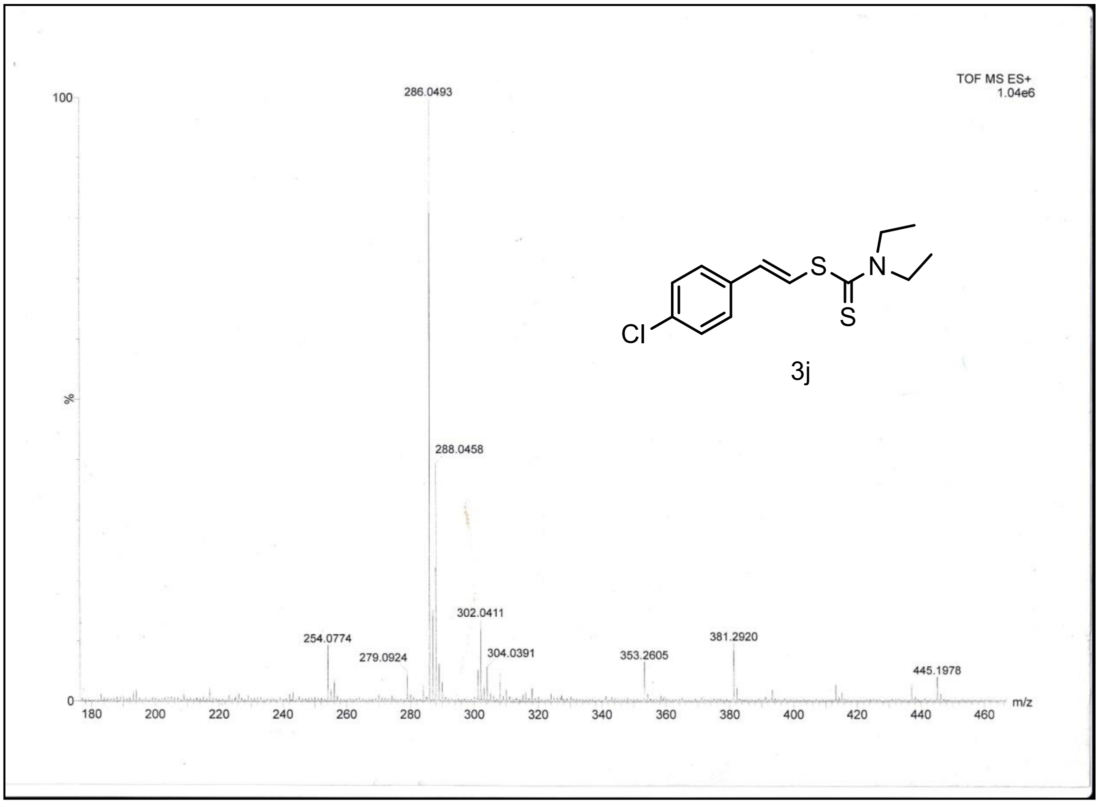
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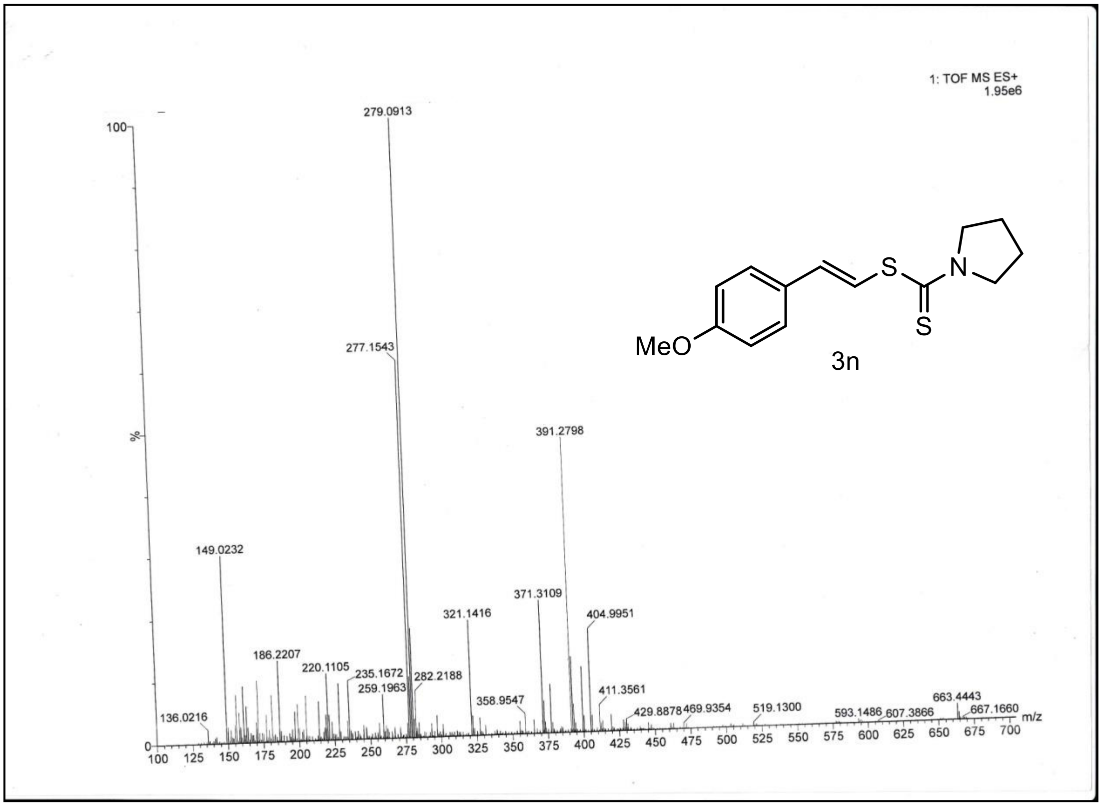
3j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m/z
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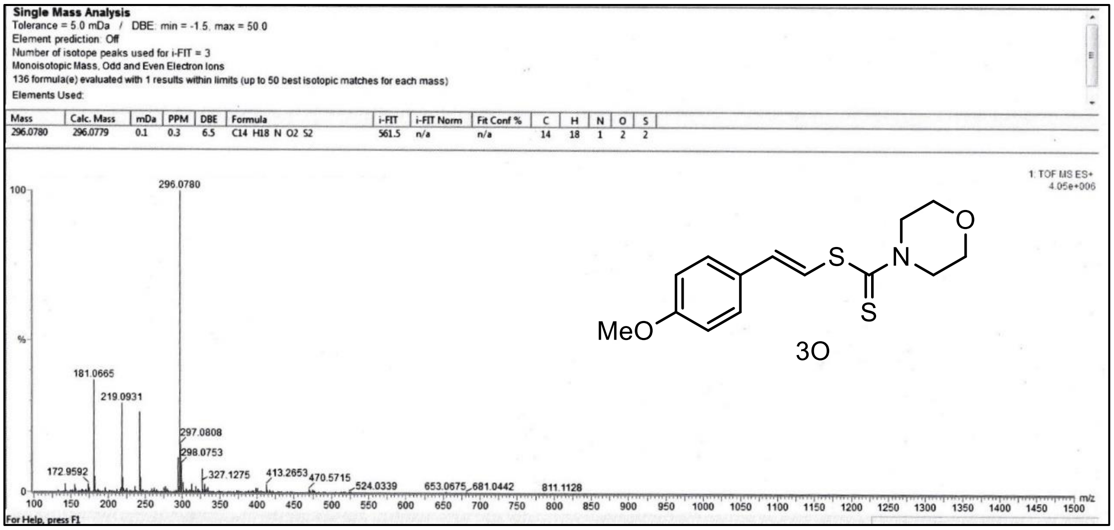
N
S

3n



Single Mass Analysis
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Monoisotopic Mass, Odd and Even Electron Ions
136 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	O	S
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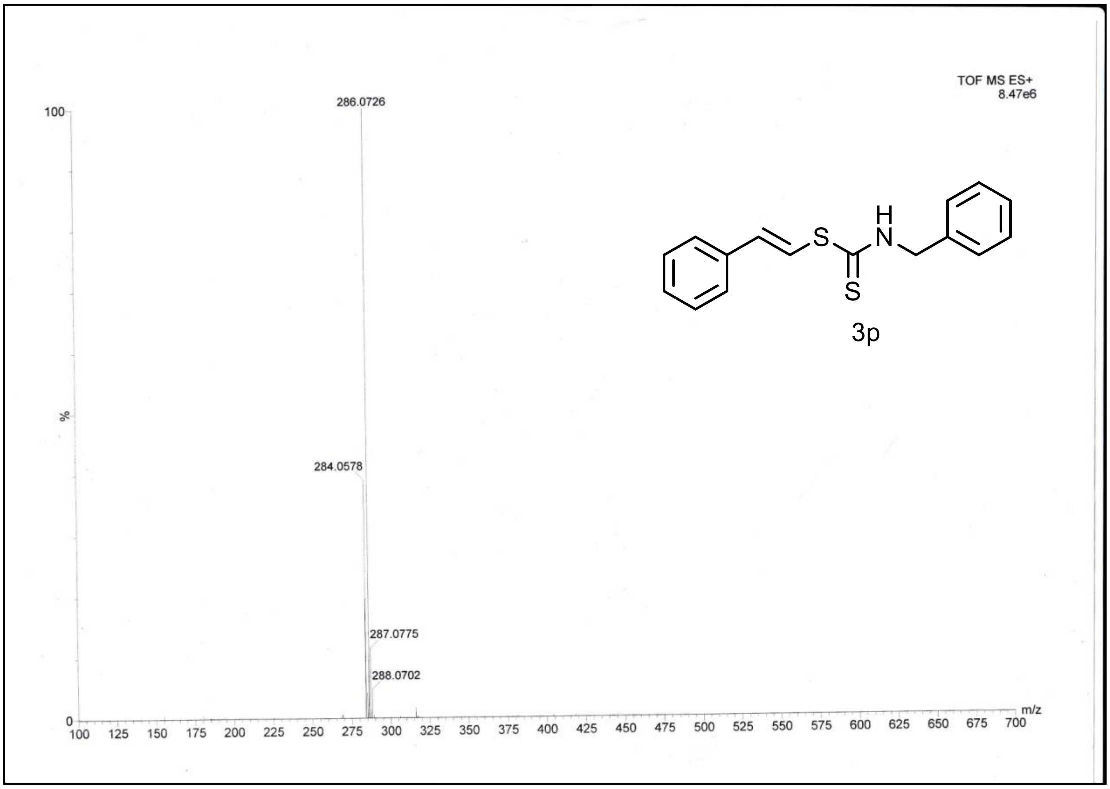
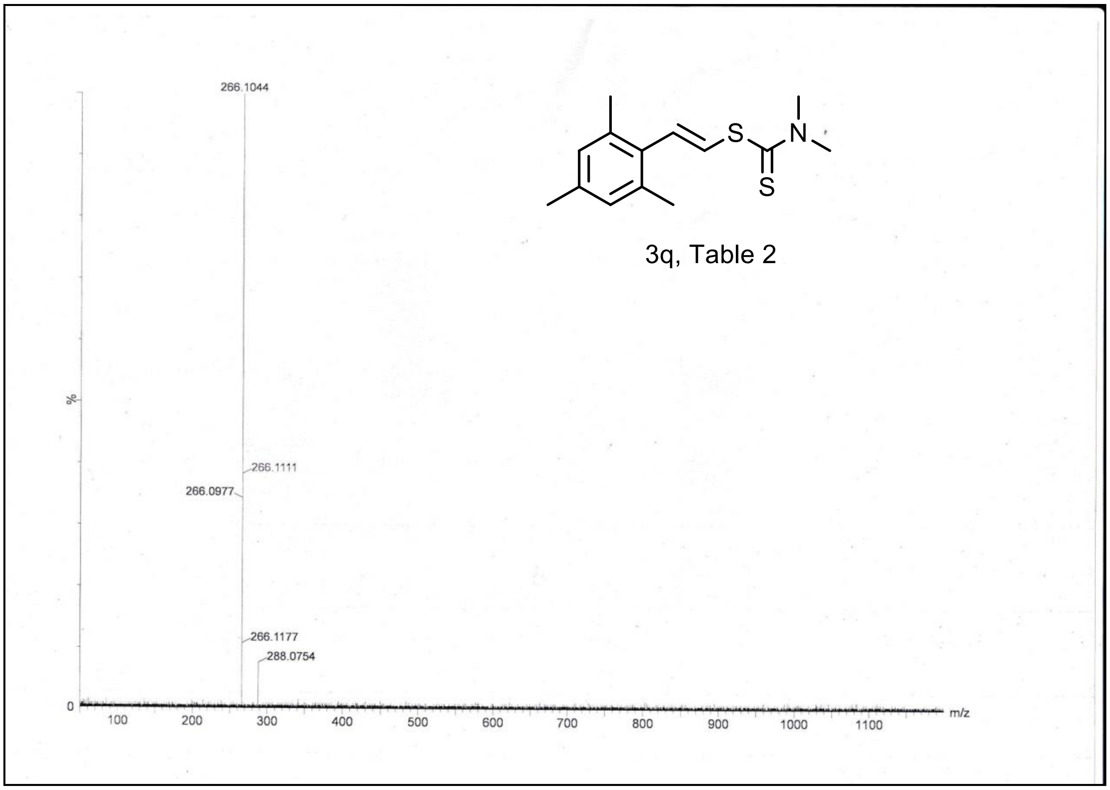
3O



3p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700
800
900
1000
1100
m/z

3q, Table 2

2.2/f. References

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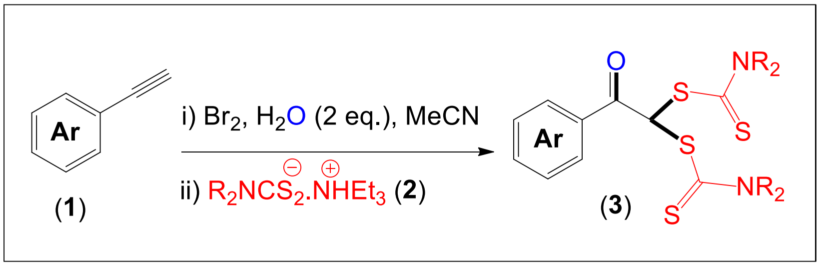
Section-III

Metal free Dithiocarbamylation Reaction of Phenylacetylene

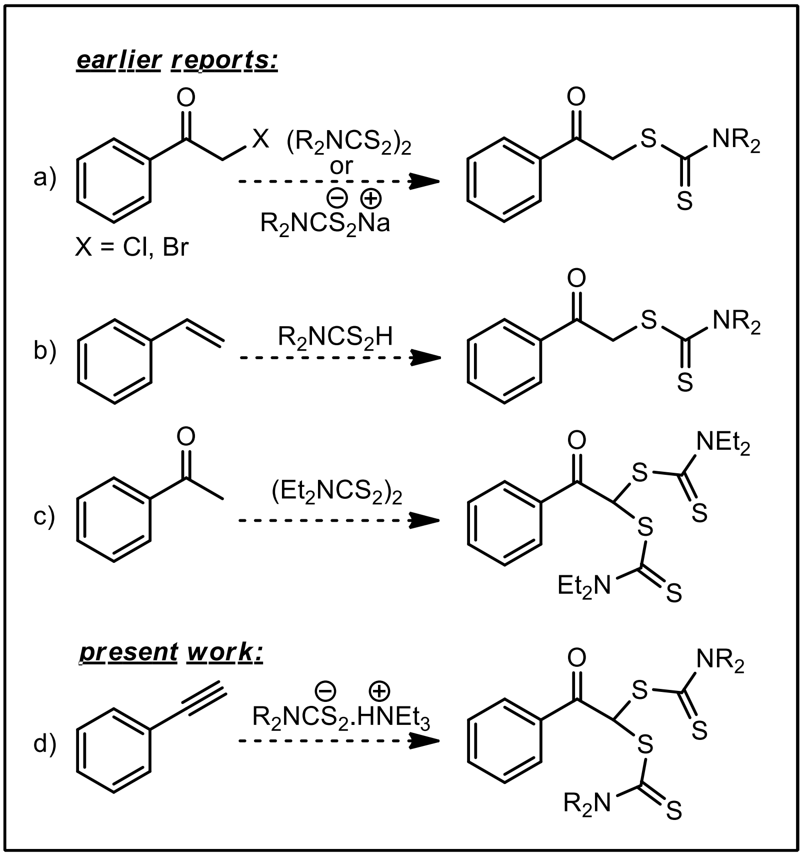
2.3/a. Introduction

Dithiocarbamate molecules have received ongoing interest due to their significant applications in medical sciences.[1] Many organic dithiocarbamates show potential biological activity as antioxidants, enzyme inhibitors, fungicides, antitrypanosomatid drugs and anticancer, anti-inflammatory, antimicrobial, anti-HIV agents. Dithiocarbamates have also been used extensively in agriculture, [2] polymer science[3] and material science. [4] In the past few decades, they have become popular as valuable synthetic intermediates. [5] Trifunctionalization of alkynes is an attractive synthetic tool to the synthetic organic chemists due to easy access of the complex molecular frameworks[6] from easily available starting materials. Considering wide application of dithiocarbamates, we envisioned to functionalize the phenylacetylene systems with dithiocarbamate moieties. In our previous report we demonstrated the *β*-dithiocarbamylation of styrenes. [7] As a continuation of our research work involving the dithiocarbamate chemistry, [8] here we are introducing a novel strategy to obtain phenacyl-bis(dithiocarbamates) by molecular bromine mediated trifunctionaliztion of phenylacetylenes (Scheme 2.3.01).



Scheme 2.3.01 Synthesis of phenacyl-bis(dithiocarbamate) by trifunctionalization of phenylacetylene.

Phenacyl dithiocarbamates have earlier been synthesized from phenacylhalides using thiuramdisulfide[9] or *in situ* generated dithiocarbamate salts[10] (Scheme 2.3.02a) and from styrene using *in situ* generated dithiocarbamic acid[11] (Scheme 2.3.02b). Synthesis of phenacyl-bis(dithiocarbamate) has been reported very recently by the reaction of acetophenone and tetraethylthiuram disulfide (Scheme 2.3.02c). [12] However, the reaction was limited to the synthesis of only one *gem*-bis(dithiocarbamate) compound with diethylamino ($-NEt_2$) moiety using excess of dithiocarbamate source. Here, we have developed a generalized protocol for the synthesis of a wide variety of phenacyl-bis(dithiocarbamates) by dithiocarbamylation of phenylacetylene following a one-pot two-step strategy (Scheme 2.3.02d). Phenylacetylene undergoes oxidative-bromination followed by dithiocarbamylation using freshly prepared dithiocarbamate salt to produce the gem-bis(dithiocarbamate) product (Scheme 2.3.01).



Scheme 2.3.02: Synthesis of phenacyl dithiocarbamates and phenacyl-bis(dithiocarbamates).

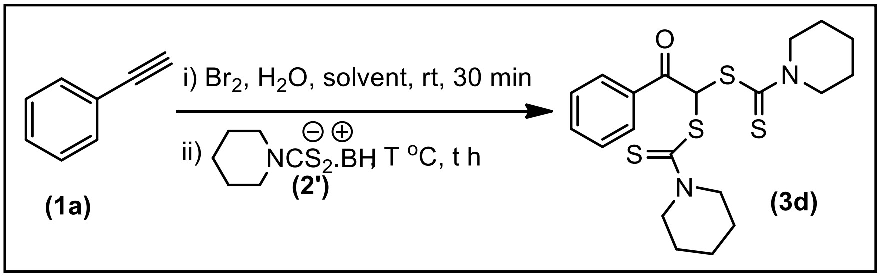
2.3/b. Results and Discussion

The reaction is very easy to perform. Phenylacetylene was brominated using molecular bromine in presence of two equivalent of water in acetonitrile solution. The brominated reaction mixture was then stirred with freshly prepared dithiocarbamate salt at 65 ^{o}C for a certain time period. After completion of the reaction (checked by TLC), the crude product was obtained by usual work-up and was purified by column chromatography.

In order to standardize the reaction condition, phenylacetylene (1a) and piperidine-dithiocarbamate salt (2’) was considered as the model starting materials. At first the reaction was conducted in DMF-H_2O (1:1) medium with the piperidine-dithiocarbamate salt of K_2CO_3 base. However, the desired product was formed only with 35% of yield (entry 1, Table 2.2.01) after 4 h of reaction at 65 ^oC. Other reaction media, such as THF-H_2O (1:1) and toluene-H_2O (1:1) did not improve the yield of the reaction (entries 2 and 3, Table 2.3.01). However, in MeCN-H_2O (1:1) solvent mixture the reaction produced 45% yield of the desired bis-dithiocarbamate product, 3d (entry 4, Table 2.3.01). Changing the base with Na_2CO_3 did not improve the reaction outcome (entry 5, Table 2.3.01). Even the water medium was not at all suitable for the reaction (entry 6, Table 2.3.01) providing the desired product only in trace amount. However, the yield of the reaction improved a bit upon decreasing the amount of water in acetonitrile medium. In presence of 20 equivalent of water the reaction provided 51% yield of the desired *gem*-bis(dithiocarbamate) product (3d) in acetonitrile medium (entry 8, Table 2.3.01). Surprisingly, the reaction proceeded much better in presence of triethylamine as base (entry 9, Table 2.3.01). Further decrease of the amount of water was found to have a positive effect on the reaction outcome producing the product in improved yields (entries 10, 11, Table 2.3.01). The use of two equivalent of water in the acetonitrile medium was optimized to be the standard condition to provide the desired phenacyl bis-dithiocarbamate in 90% yield within 2.5 h of time period at 65 ^oC (entry 11, Table 2.3.01). Prolonged reaction time period did not have any effect on the reaction yield (entry 14, Table 2.3.01). However, elevation of the reaction temperature (80 ^oC) had an adverse effect producing the dimer of the dithiocarbamate as the side product and hence decreasing the yield of the desired product (entry 12, Table 2.3.01).

The optimized reaction condition was then followed to prepare a series of structurally variable phenacyl-bis(dithiocarbamates) (Table2.3.02). Dithiocarbamate salts (**2**) based on cyclic secondary amines (piperidine, pyrrolidine, morpholine) and acyclic secondary amines (dimethylamine, diethylamine) participated to the reaction efficiently to produce the desired *gem*-bis(dithiocarbamates) in good yields. Aromatic amine, such as *N*-methylaniline has also been used in the reaction to produce the corresponding *gem*-bis(dithiocarbamate) (**3e**, **3p**, Table 2.3.02) smoothly. Phenylacetylenes containing aromatic substituents like -OMe, -Br, -F, -Me, -CN responded to the reactions with equal efficiency. Interestingly, dithiocarbamate anion did not participated to the nucleophilic aromatic substitution[13] at C(sp^2)-Br and C(sp^2)-F moieties of the products (**3j** - **3o**) containing aromatic –Br and –F substituents which may allow post structural modifications. The structure of the phenacyl-bis(dithiocarbamate), **3d** was confirmed by single crystal XRD analysis (Fig. 2.3.01).

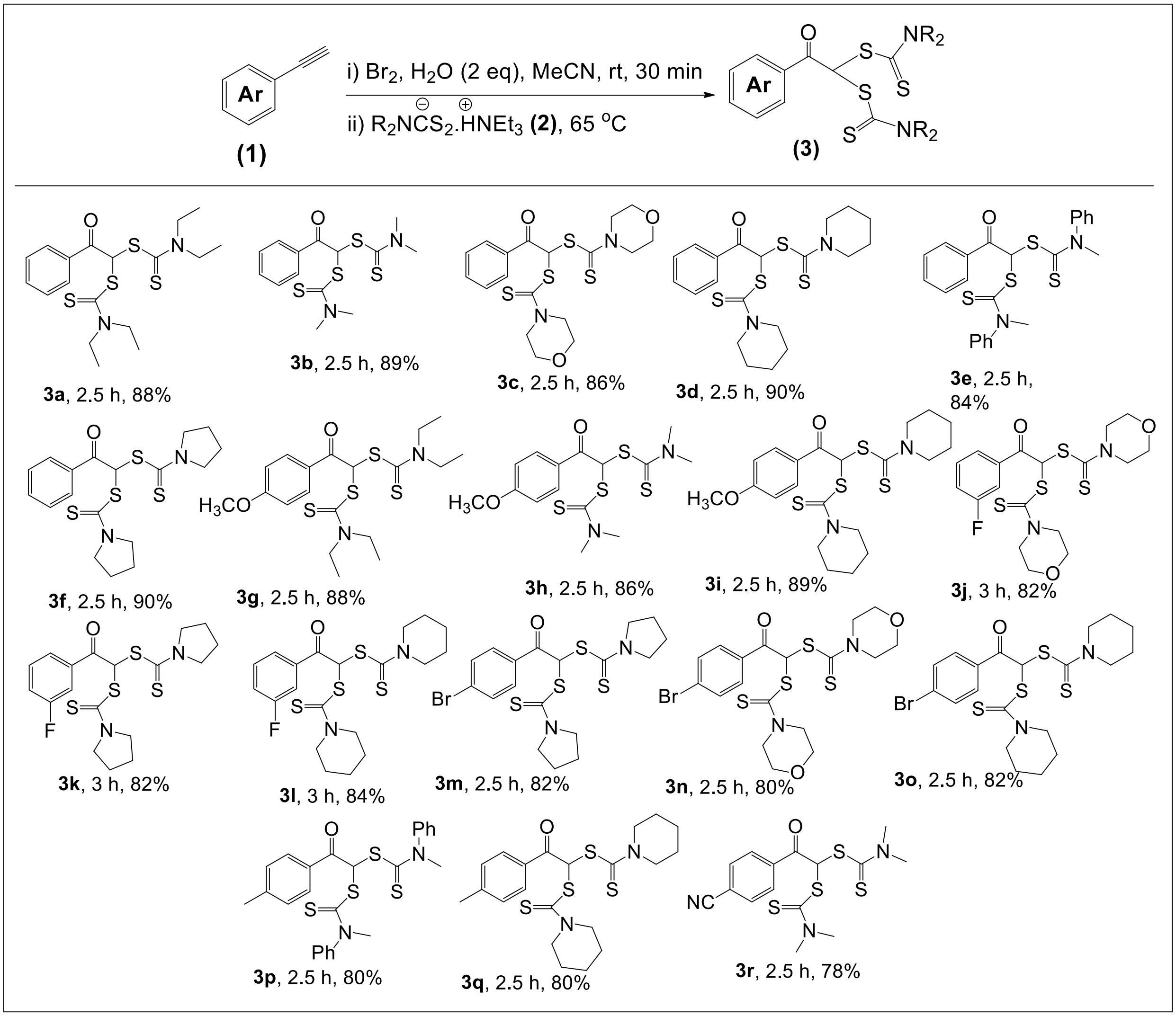
Table 2.3.01 Optimization of the reaction condition



Entry	Solvent (amount of H_2O)	Base (B)	T (°C)	t (h)	Yield (%)
1	DMF-H_2O (1:1)	K_2CO_3	65	4	35
2	THF-H_2O (1:1)	K_2CO_3	65	4	trace
3	Toluene-H_2O (1:1)	K_2CO_3	65	4	18
4	MeCN-H_2O (1:1)	K_2CO_3	65	4	45
5	MeCN-H_2O (1:1)	Na_2CO_3	65	4	40
6	H_2O	K_2CO_3	80	4	trace
7	MeCN (without H_2O)	K_2CO_3	65	4	-
8	MeCN (20 eq H_2O)	K_2CO_3	65	2.5	51
9	MeCN (20 eq H_2O)	Et_3N	65	2.5	63
10	MeCN (10 eq H_2O)	Et_3N	65	2.5	72
11	MeCN (2 eq H_2O)	Et_3N	65	2.5	90
12	MeCN (2 eq H_2O)	Et_3N	80	2.5	57
13	MeCN (2 eq H_2O)	Et_3N	50	2.5	70
14	MeCN (2 eq H_2O)	Et_3N	65	5	90
15	MeCN (2 eq H_2O)	Et_3N	65	2	62

Reaction condition: (i) Br_2 (1 mmol) in 1 ml of solvent was added to the solution of phenylacetylene (1 mmol) in 2 ml of solvent containing certain amount of H_2O and the reaction mixture was stirred at room temperature for 30 minutes (ii) brominated phenylacetylene was stirred in presence of freshly prepared piperidine-dithiocarbamate salt (2 mmol) at a certain temperature for the required time period. Dithiocarbamate salts were freshly prepared by the reaction of piperidine and CS_2 in 2 ml of solvent in the presence of a suitable base (B). Yields reported are the isolated yields.

Table 2.3.02 Synthesis of phenacyl-bis(dithiocarbamates).



3a, 2.5 h, 88%
3b, 2.5 h, 89%
3c, 2.5 h, 86%
3d, 2.5 h, 90%
3e, 2.5 h, 84%
3f, 2.5 h, 90%
3g, 2.5 h, 88%
3h, 2.5 h, 86%
3i, 2.5 h, 89%
3j, 3 h, 82%
3k, 3 h, 82%
3l, 3 h, 84%
3m, 2.5 h, 82%
3n, 2.5 h, 80%
3o, 2.5 h, 82%
3p, 2.5 h, 80%
3q, 2.5 h, 80%
3r, 2.5 h, 78%

Reaction condition: *(i) Br_2 (1 mmol) in acetonitrile (1 ml) was added to the solution of phenylacetylene (1 mmol) in acetonitrile (2 ml) containing 2 mmol of H_2O and the reaction mixture was stirred at room temperature for 30 minutes (ii) brominated phenylacetylene was stirred in presence of freshly prepared dithiocarbamate salt (2 mmol) at 65 °C for the required time period. Dithiocarbamate salts were freshly prepared by the reaction of amine (R_2NH, 2 mmol) and CS_2 (3 mmol) in presence of triethylamine (2 mmol in acetonitrile (2 ml) solution. Yields reported are the isolated yields.*

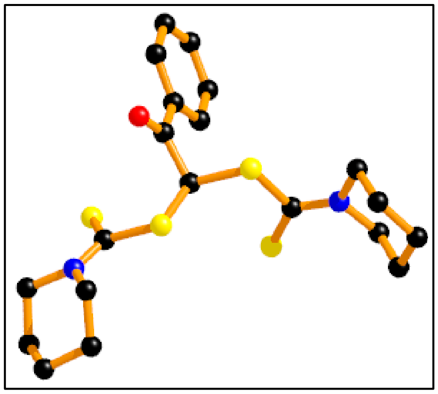
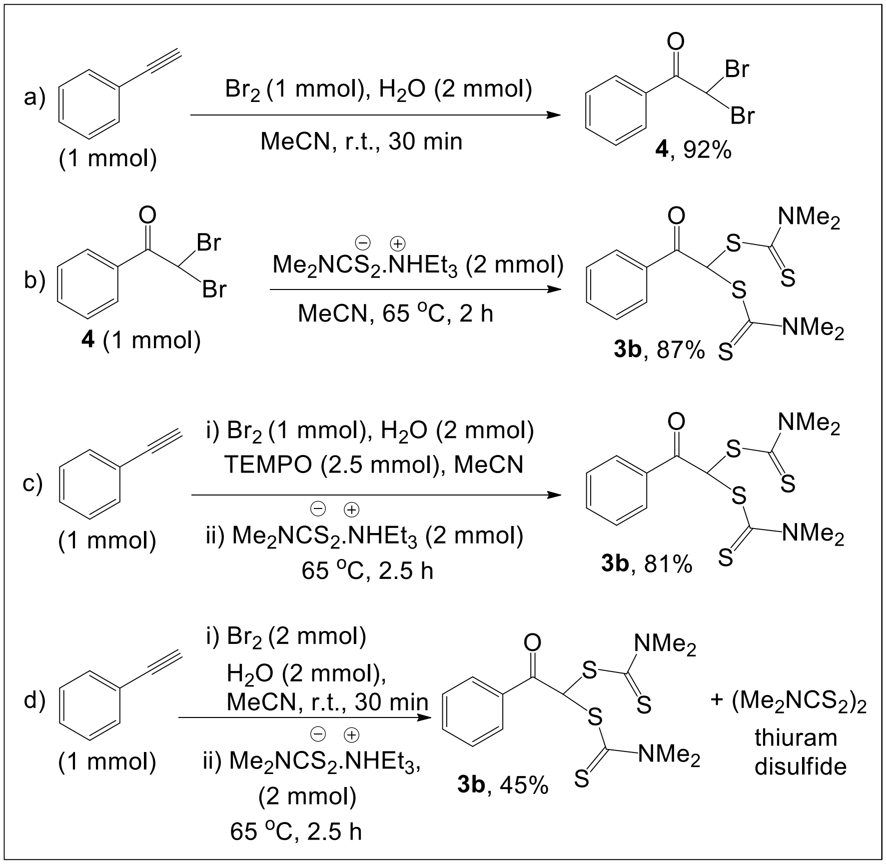


Fig. 2.3.01 Molecular view of phenacyl-bis(dithiocarbamate), **3d** (CCDC deposition no. 2246557)

To understand the mechanism, we carried out some control experiments (Scheme 2.3.03). We treated phenylacetylene with one equivalent of molecular bromine and 2 equivalent of H_2O in acetonitrile medium followed by stirring at room temperature for 30 min. The intermediate compound formed was isolated and characterized (^1H and ^{13}C NMR included in Supporting Information) to be the phenacyl dibromide (**4**) (Scheme 2.3.03a).



Scheme 2.3.03: Control experiments.

Phenacyl dibromide (**4**) produces the desired bis-dithiocarbamate product (**3b**) in good yield by the reaction with dimethylamine-dithiocarbamate salt (Scheme 2.3.03b). Thus, compound-**4** is assumed to be the probable intermediate for this dithiocarbamylation reaction. To check the possibility of radical reaction pathway, we conducted the bis-dithiocarbamylation reaction of phenylacetylene in presence of 2.5 equivalent of TEMPO (a well-known radical quencher) under the identical reaction condition (Scheme 2.3.03c). However, the desired bis-dithiocarbamate product **3b** was obtained in significant amount (81% of yield). Thus, radical pathway was ruled out for the current protocol. The bis-dithiocarbamylation reaction was found to be highly dependent on the nature of solvent (entries 1 - 4, 6, 7, Table 2.3.01). The reaction provided good result only in acetonitrile medium in presence of 2 equivalent of water. However, upon increasing the amount of water in the reaction medium the yield of the desired compound decreases significantly. The reaction doesn't go at all in absence of water (entry 7, Table 2.3.01). Thus, presence of both acetonitrile and water was crucial for the reaction. The effect of water on the reaction outcome may be understood from the plot of reaction yield vs. amount of water used in the reaction (Fig. 2.3.02). The decrease of yield of the reaction upon increasing the amount of water may be due to the low solubility of the starting material and intermediate. In presence of 2 mmol of molecular bromine, the reaction provides much poor yield of the desired bis-dithiocarbamate product (3b) along with the formation of the dimer of dithiocarbamate, $(Me_2NCS_2)_2$ by the action of excess bromine left in the reaction medium (Scheme 2.3.03d).

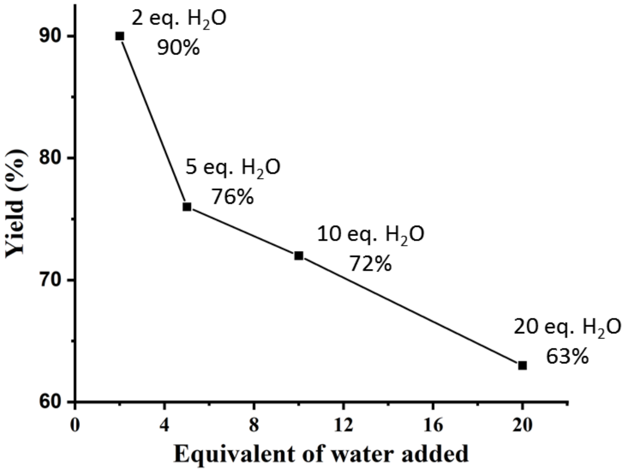
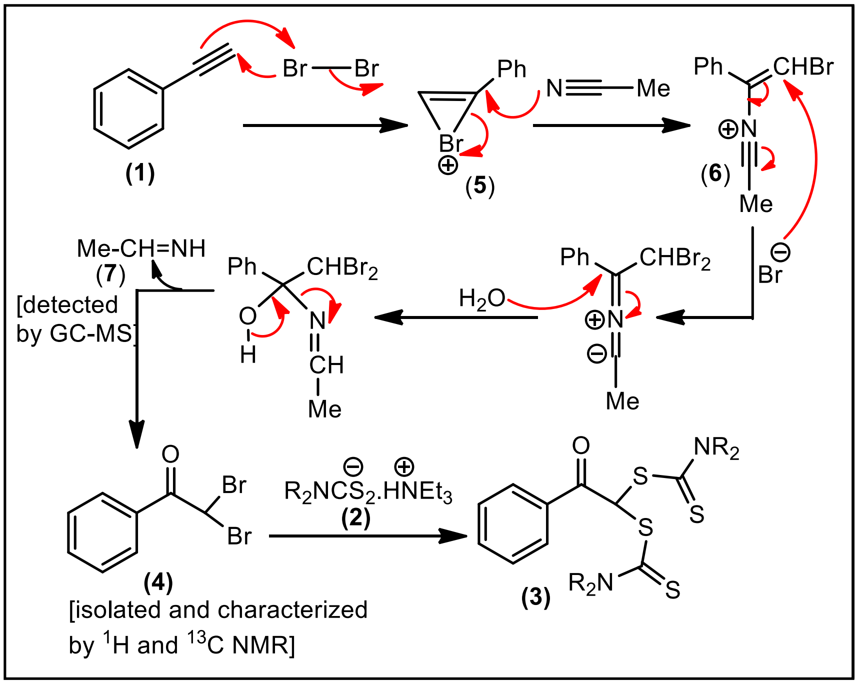


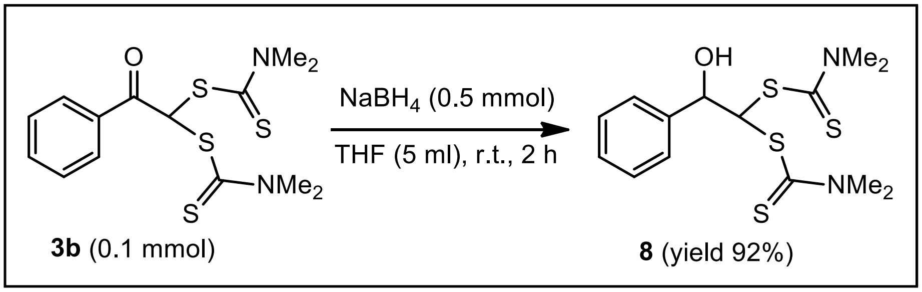
Fig. 2.3.02 Plot of reaction yield *vs.* amount of water used.

Based on above observations, we propose a mechanism which proceeds through the formation of phenacyl dibromide intermediate (**4**) mediated by acetonitrile in presence of molecular bromine and water (Scheme 2.3.04). Phenylacetylene reacts with molecular bromine to produce the bridged bromonium ion (**5**) which undergoes ring opening by the nucleophilic attack of acetonitrile to produce the cationic species (**6**). Similar reaction of acetonitrile with the bridged halonium ion is also reported earlier.[14] Successive attack of bromide (Br^-) to the cationic intermediate (**6**) followed by nucleophilic attack of water produces the phenacyl dibromide intermediate (**4**) along with the formation of imine, CH_3-CH=NH (**7**) which was detected by GC-MS analysis of the crude reaction mixture mentioned in Scheme 3a.



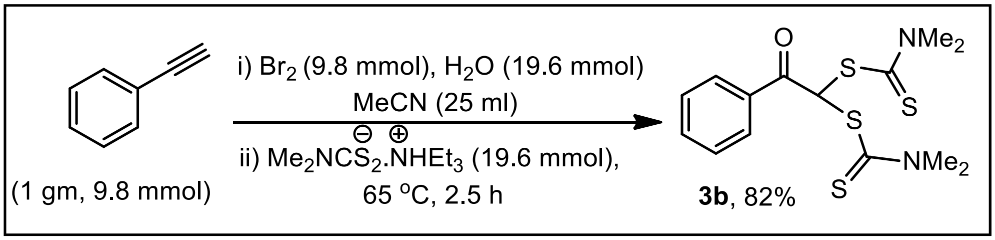
Scheme 2.3.04 Proposed mechanism.

In the GC-MS analysis, we observed the presence of significant amount of acetaldehyde (CH_3-CHO) which has been formed by the hydrolysis of imine-**7** (GC-MS spectra are included in the Supporting Information). In order to study the synthetic potential of bis-dithiocarbamate product, the phenacyl-bis(dithiocarbamate) compound, **3b** was reduced by $NaBH_4$ in THF medium to produce the corresponding 2°-alcohol (**8**) by the reduction of the carbonyl group keeping the bis-dithiocarbamate moiety intact (Scheme 2.3.05).



Scheme 2.3.05 Reduction of the carbonyl group in compound-**3b**.

Bis-dithiocarbamylation reaction was also carried out in gram scale with phenylacetylene and dimethylamine-dithiocarbamate salt (Scheme 2.3.06). The reaction provided good yield of the desired product even in gram scale synthesis.



Scheme 2.3.06 Scale-up of bis-dithiocarbamylation reaction.

2.3/c. Conclusion

In conclusion, we have demonstrated a general and convenient method to prepare a series of phenacyl-bis(dithiocarbamates) from easily available starting materials. Phenylacetylene systems undergo efficient metal free dithiocarbamylation with freshly prepared dithiocarbamate salts. The one-pot strategy avoids the isolation and purification steps of the reaction intermediate and reduces organic solvent usage, time and labour. Operational simplicity, easily available starting materials and good yields of products render the protocol valuable in the field of organic synthesis.

2.3/d. Experimental Section

General Information:

All chemicals were purchased and used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (Merck silica gel, f_{24}). In column-chromatographic purification process, silica gel 60-120 mesh has been used. The ^{1}H spectra of synthesized products were recorded in $CDCl_3$ on Brucker Spectrometer at 300, 400 MHz. The ^{19}F spectra of synthesized fluorinated productswere recorded in $CDCl_3$ on Brucker Spectrometer, 300 MHz. The ^{13}C spectra of synthesized products were recorded in $CDCl_3$ on Brucker Spectrometer at 75, 100 MHz. In all NMR experiments, $CDCl_3$ were used as solvent and TMS as internal standard. Chemical shifts were reported in ppm referenced to 0.00 ppm for TMS. HRMS were measured in methanol solvent on a Waters Micromass Q-tof Micromassspectrometer.

General experimental procedure:

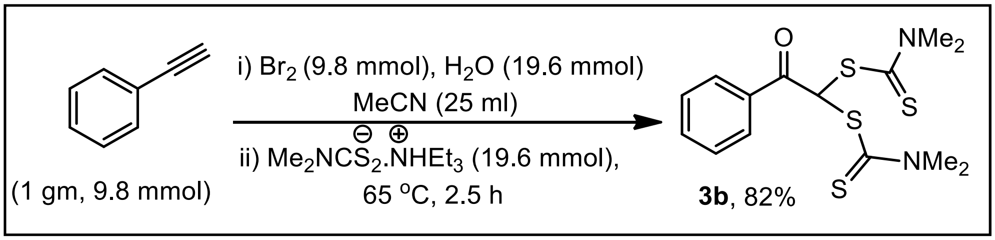
Preparation of dithiocarbamates salts:

CS_2 (0.2 mL, 3 mmol) was added dropwise to a solution of secondary amine (2 mmol) and Et_3N (0.28 mL, 2 mmol) in acetonitrile (2 mL) at 5 °C. The resulting solution was stirred at room temperature for 5 min.

Preparation of *gem*-bis(dithiocarbamates):

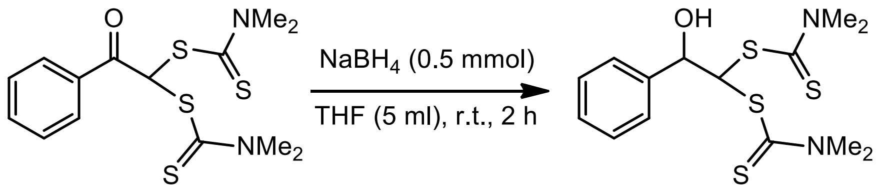
Br_2 (0.05 mL, 1 mmol) in MeCN (1 mL) was added dropwise to the solution of aromatic acetylene (1 mmol) in MeCN (2 mL) containing 0.04 mL of water at 5 °C. After complete addition, the reaction mixture was allowed to stir for 30 min at room temperature. Then the freshly prepared dithiocarbamate salt (2 mmol) was added to the reaction mixture and was stirred at 65 °C for a certain reaction time period. After completion of the reaction (checked by TLC), the solvent was evaporated under reduced pressure. The crude product was extracted with ethyl acetate and purified by column chromatography to obtain the desired product.

Gram-scale Experiment (9.8 mmol scale)



Br_2 (0.49 mL, 9.8 mmol) in MeCN (5 mL) was added dropwise to the solution of phenylacetylene (1.08 ml, 9.8mmol) in MeCN (10 mL) containing 0.4 mL of water at 5 °C. After complete addition, the reaction mixture was allowed to stir for 30 min at room temperature. Then the freshly prepared dithiocarbamate salt ($Me_2NCS_2.NHEt_3$, 19.6 mmol) was added to the reaction mixture and was stirred at 65 °C for 2h. After completion of the reaction (checked by TLC), the solvent was evaporated under reduced pressure. The crude product was extracted with ethyl acetate and purified by column chromatography to obtain the desired product.

Post functionalization

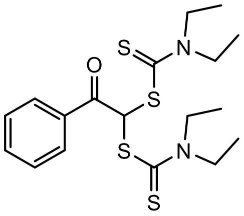


3b (0.1 mmol) **8** (yield 92%)

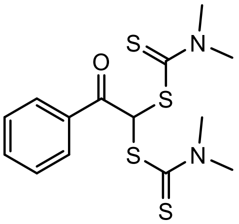
To a solution of compound 3b (35.8 mg, 0.1 mmol) in THF (5 ml) at 0 °C, was added THF solution of $NaBH_4$ (19 mg, 0.5 mmol) for a period of 30 min duration. Then the reaction mixture was stirred at room temperature for 2 h. It was quenched with saturated NH_4Cl aqueous solution and the aqueous phase was extracted three times with ethyl acetate. The combined organic phase was dried over sodium sulphate. Then, the crude compound was purified by column chromatography to obtain the desired product.

Characterization Data of Synthesized Compounds:

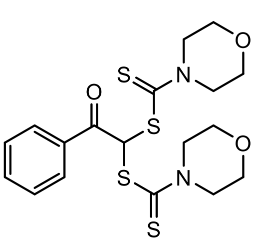
1. 2-oxo-2-phenylethane-1,1-diylbis(diethylcarbamodithioate) (3a)[1]: White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25-1.32 (m, 12H), 3.66-3.74 (m, 4H), 3.90-4.02 (m, 4H), 7.43-7.49 (m, 2H), 7.52-7.57 (m, 1H), 7.78 (s, 1H), 8.16-8.20 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.52, 11.74, 46.25, 48.96, 60.92, 127.50 (2C), 128.24 (2C), 132.08, 134.37, 189.98, 190.76 (2C).



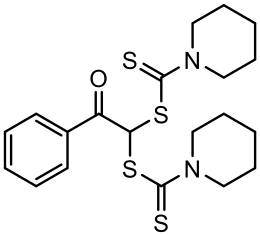
2. 2-oxo-2-phenylethane-1,1-diylbis(dimethylcarbamodithioate) **(3b)**: Yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.35 (s, 6H), 3.50 (s, 6H), 7.43-7.49 (m, 2H), 7.53-7.59 (m, 1H) 7.73 (s, 1H), 8.14-8.17 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.72, 45.77, 62.90, 128.63(2C), 129.22 (2C), 133.34, 135.14, 190.51, 193.04, HRMS (ESI) m/z calcd for $C_{14}H_{18}N_2OS_4$ $[M + H]^+$, 358.0302, found 359.0526.



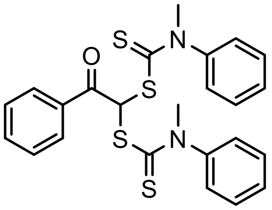
3. 2-oxo-2-phenylethane-1,1-diylbis(morpholine-4-carbamodithioate) (3c): White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75(s, 8H), 3.88 (broad, 4H), 4.25 (broad, 4H), 7.45-7.51 (m, 2H), 7.59-7.61(m, 1H), 7.89 (s, 1H), 8.14-8.17 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 50.80, 51.71, 61.55, 66.13(2C), 128.73(2C), 129.23(2C), 133.55, 134.91, 190.45, 193.16(2C). HRMS (ESI) m/z calcd for $C_{18}H_{22}N_2O_3S_4$ $[M + H]^+$, 442.0513, found 443.0593.



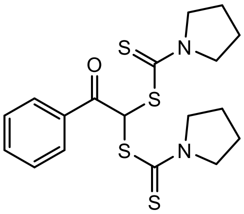
4. 2-oxo-2-phenylethane-1,1-diylbis(piperidine-1-carbamodithioate) (3d): Light yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.69 (s, 12H), 3.84 (broad, 4H), 4.19-4.23 (broad, 4H), 7.45-7.49 (m, 2H), 7.54-7.59 (m, 1H), 7.88 (s, 1H), 8.18-8.20 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.05, 25.32, 26.07, 51.89, 53.38, 61.85, 128.58 (2C), 129.27 (2C), 133.22, 135.24, 190.97, 191.57 (2C), HRMS (ESI) m/z calcd for $C_{20}H_{26}N_2OS_4$ $[M + H]^+$, 438.0928, found 439.0497.



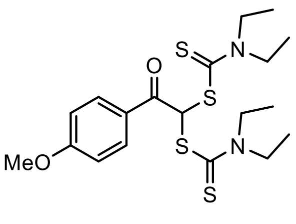
5. 2-oxo-2-phenylethane-1,1-diylbis(methyl(phenyl)carbamodithioate) (3e): Light yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.71 (s, 6H), 7.20-7.22 (m, 4H), 7.37-7.48 (m, 8H), 7.54-7.60 (m, 2H), 8.11-8.13 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 46.53, 63.27, 126.91, 128.54, 129.14, 129.28, 129.87, 133.16, 135.35, 143.96, 190.96, 195.36(2C), HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2OS_4$ $[M + H]^+$, 482.061, found 483.108.



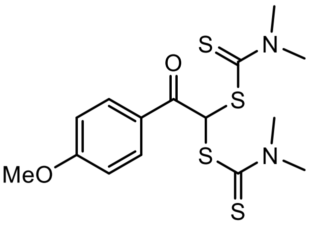
6. 2-oxo-2-phenylethane-1,1-diylbis(pyrrolidine-1-carbamodithioate) (3f): White solid, ^{1}HNMR (300 MHz, $CDCl_3$) δ: 1.95-2.10(m, 8H), 3.64(t, J=6.9 Hz, 4H), 3.87(t, J=6.9 Hz ,4H), 7.43-7.58(m, 3H), 7.83(s, 1H), 8.17-8.20(m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.30, 26.12, 50.73, 51.43, 60.87, 128.60(2C), 129.30(2C), 133.30, 135.12, 186.60, 190.97(2C), HRMS (ESI) m/z calcd for $C_{18}H_{22}N_2OS_4$ $[M + H]^+$, 410.0615, found 411.0692.



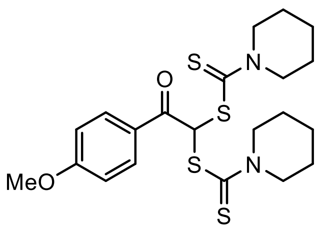
7. 2-(4-methoxyphenyl)-2-oxoethane-1,1-diyl bis(diethylcarbamodithioate) (3g): Light yellow solid, ^{1}HNMR (300 MHz, $CDCl_3$) δ: 1.22-1.31(m, 12H), 3.67-3.74(m, 4H), 3.86(s, 3H), 3.92-4.01(m, 4H), 6.94(d, J= 8.7 Hz, 2H), 7.74(s, 1H), 8.18(d, J= 9 Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ:10.51, 11.72, 46.17, 54.44, 60.67, 112.79(2C), 127.19, 130.63(2C), 162.64, 188.70, 190.81(2C), HRMS (ESI) m/z calcd for $C_{19}H_{28}N_2O_2S_4$ $[M + Na]^+$, 467.0931, found 467.0988.



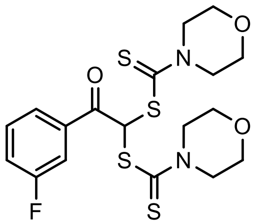
8. 2-(4-methoxyphenyl)-2-oxoethane-1,1-diyl bis(dimethylcarbamodithioate) (3h): Light yellow solid, ^{1}H NMR (300MHz, CDCl$_3$) δ: 3.35 (s, 6H), 3.50 (s, 3H), 3.86 (s, 3H), 6.94 (d, J= 9 Hz, 2H), 7.69 (s, 1H), 8.16 (d, J= 9 Hz, 2H), ^{13}C NMR (75MHz, CDCl$_3$) δ: 41.67, 45.71, 55.49, 62.73, 113.89 (2C), 128.08, 131.62 (2C), 189.42, 193.22 (2C), HRMS (ESI) m/z calcd for $C_{15}H_{20}N_2O_2S_4$ $[M]^+$, 388.04, found 388.21.



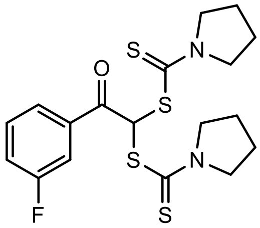
9. 2-(4-methoxyphenyl)-2-oxoethane-1,1-diyl bis(piperidine-1-carbamodithioate) (3i): White solid, ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.67(s, 12H), 3.82(broad, 4H), 3.86(s, 3H), 4.19(broad, 4H), 6.94(d, J= 9.2 Hz, 2H), 7.81(s, 1H), 8.18(d, J= 8.8 Hz, 2H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.08, 25.31, 26.05, 51.81, 53.81, 55.51, 61.73, 113.85(2C), 128.16, 131.67(2C), 163.70, 189.64, 191.76(2C), HRMS (ESI) m/z calcd for $C_{21}H_{28}N_2O_2S_4$ $[M + Na]^+$, 491.0931, found 491.0933.



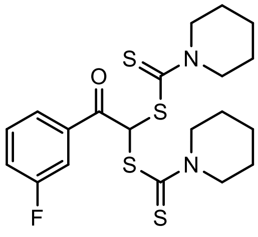
10. 2-(3-fluorophenyl)-2-oxoethane-1,1-diyl bis(morpholine-4-carbamodithioate) (3j): White solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.75 (s, 8H), 3.88 (broad, 4H), 4.25 (broad, 4H), 7.24-7.31 (m, 1H), 7.42-7.49 (m, 1H), 7.80-7.84 (m, 2H), 7.95-7.97 (m, 2H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 50.94, 51.76, 61.46, 66.17 (2C), 115.92 (J=22.8 Hz), 120.52 (J=21.37 Hz), 124.93 (J=3.07 Hz), 130.36 (J=7.42 Hz), 137.05 (J=6.6 Hz), 162.78 (J=246 Hz), 189.41 (J=2.17 Hz), 192.93 (2C), HRMS (ESI) m/z calcd for $C_{18}H_{21}FN_2O_3S_4$ $[M + H]^+$, 460.0419, found 461.0156.



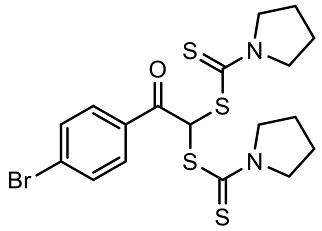
11. 2-(3-fluorophenyl)-2-oxoethane-1,1-diyl bis(pyrrolidine-1-carbamodithioate) (3k): Light yellow solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.95-2.15 (m, 8H), 3.67 (t, J=6.9 Hz, 4H), 3.91 (t, J=6.9 Hz, 4H), 7.28-7.31 (m, 1H), 7.44-7.51 (m, 1H), 7.81 (s, 1H), 7.87-7.90 (m, 1H), 8.03-8.05 (m, 1H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.30, 26.23, 50.78, 55.50, 60.80, 115.93 (J=23.25 Hz), 120.27 (J=21 Hz), 125.03 (J=3 Hz), 130.25 (J=7.5 Hz), 137.27 (J=6.75 Hz), 162.75 (J=246 Hz), 188.33 (2C), 189.91 (J=2.25 Hz), HRMS (ESI) m/z calcd for $C_{18}H_{21}FN_2OS_4$ $[M + H]^+$, 428.0521, found 429.0115.



12. 2-(3-fluorophenyl)-2-oxoethane-1,1-diyl bis(piperidine-1-carbamodithioate) (3l): Light yellow solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.72(s,12H), 3.86(broad,4H), 4.23 (broad,4H), 7.28-7.31 (m,1H), 7.44-7.51 (m,2H), 7.86-7.91 (m,2H), 8.02-8.05 (m,1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.04, 25.32, 26.07, 51.93, 53.46, 61.78, 115.93 (J=22.5 Hz),120.16 (J=21 Hz) , 125.01 (J=3 Hz), 130.20 (J=8.25 Hz), 137.41 (J=6.75 Hz), 162.76 (J=246 Hz), 189.91 (J=2.25 Hz), 191.35 (2C), HRMS (ESI) m/z calcd for $C_{20}H_{25}FN_2OS_4$ $[M + H]^+$, 456.0834, found 457.0468.

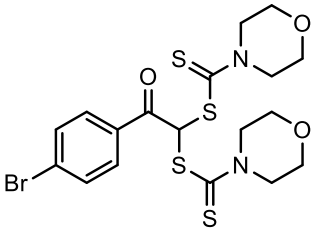


13. 2-(4-bromophenyl)-2-oxoethane-1,1-diyl bis(pyrrolidine-1-carbamodithioate) (3m): White



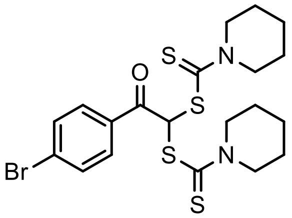
solid, ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.93-2.00 (m, 4H), 2.04-2.11 (m, 4H), 3.64 (t, J=6.8 Hz, 4H), 3.88 (t, J=7.2 Hz, 4H), 7.59-7.62 (m, 2H), 7.79 (s, 1H), 8.05-8.08 (m, 2H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.30, 26.22, 50.77, 55.51, 60.67, 128.46, 130.82 (2C), 131.92 (2C), 133.96, 188.40, 190.19 (2C), HRMS (ESI) m/z calcd for $C_{18}H_{21}BrN_2OS_4$ [M + H]$^+$, 489.5361, found 490.9411.

14. 2-(4-bromophenyl)-2-oxoethane-1,1-diyl bis(morpholine-4-carbamodithioate) (3n): White



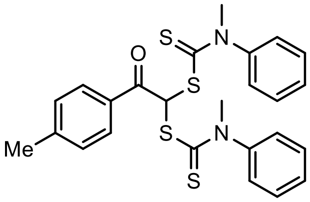
solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.74(s, 8H), 3.88(broad, 4H), 4.24(broad, 4H), 7.61(d, J=8.4 Hz, 2H), 7.85(s, 1H), 8.02(d, J=8.7 Hz, 2H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 50.85, 51.74, 61.30, 66.17(2C), 128.75,130.73(2C), 132.05(2C), 133.73, 189.66, 192.94(2C). HRMS (ESI) m/z calcd for $C_{18}H_{21}BrN_2O_3S_4$ [M + H]$^+$, 519.9618, found 520.9148.

15. 2-(4-bromophenyl)-2-oxoethane-1,1-diyl bis(piperidine-1-carbamodithioate) (3o): Light



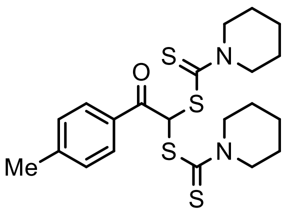
yellow solid, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.50 (s, 12H), 3.76 (broad, 4H), 4.13 (broad, 4H), 7.52-7.55 (m, 2H), 7.76 (s, 1H), 7.98-8.00 (m, 2H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.02, 25.30, 26.04, 51.90, 53.45, 61.67, 128.32, 130.81 (2C), 131.88 (2C), 134.14, 190.13, 191.44(2C), HRMS(ESI) m/z calcd for $C_{20}H_{25}BrN_2OS_4$ [M + H]$^+$, 516.0033, found 517.0233.

16. 2-oxo-2-(p-tolyl)ethane-1,1-diyl bis(methyl(phenyl)carbamodithioate) (3p): White



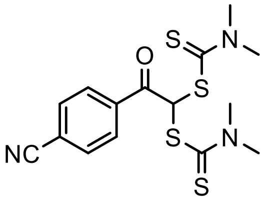
solid, ^{1}HNMR (400 MHz, CDCl$_3$) δ: 2.41 (s, 3H), 3.70 (s, 6H), 7.20-7.27 (m, 6H), 7.37-7.41 (m, 6H), 7.56 (s, 1H), 8.01-8.03 (m. 2H), ^{13}C NMR (100 MHz, CDCl$_3$) δ: 21.79, 46.48, 63.24, 126.93, 129.28, 129.85, 132.81, 144.03, 190.61, 195.45 (2C).), HRMS (ESI) m/z calcd for $C_{25}H_{24}N_2OS_4$ [M + H]$^+$, 496.077, found 497.0989.

17. 2-oxo-2-(p-tolyl)ethane-1,1-diyl bis(piperidine-1-carbamodithioate) **(3q):** White solid, ^{1}H

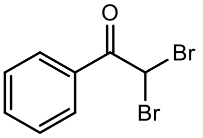


NMR (300 MHz, CDCl$_3$) δ : 1.69 (s, 12H), 2.41 (s, 3H), 3.83 (broad, 4H), 4.20 (broad, 4H), 7.28 (broad, 1H),7.84 (s, 1H) , 8.09 (d, J=8.1 Hz, 2H), ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.78, 24.07, 25.32, 26.04, 51.84, 53.31, 61.82, 129.33 (2C), 129.44 (2C), 132.68, 144.09, 190.63, 191.74 (2C), HRMS (ESI) m/z calcd for $C_{21}H_{28}N_2OS_4$ [M + H]$^+$, 452.108, found 453.629.

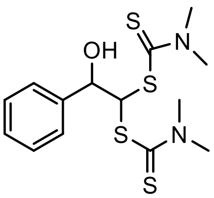
18. 2-(4-cyanophenyl)-2-oxoethane-1,1-diylbis(dimethylcarbamodithioate) **(3r):** White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.36 (s, 6H), 3.51 (s, 6H), 7.75-7.77 (m, 3H), 8.23-8.26 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.78, 44.92, 61.62, 115.19, 117.14, 128.79 (2C), 131.44 (2C), 137.50, 188.51, 191.52, HRMS (ESI) m/z calcd for $C_{15}H_{17}N_3NaOS_4$ $[M + Na]^+$, 406.0152, found 406.0144.



19. 2,2-dibromo-1-phenylethan-1-one (4): Yellow liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.71 (s, 1H), 7.49-7.54 (m, 2H), 7.62-7.67 (m, 1H), 8.07- 8.10 (m, 2H), ^{13}C NMR (75MHz, $CDCl_3$) δ: 39.69, 128.96 (2C), 129.73 (2C), 130.87, 134.47, 185.99



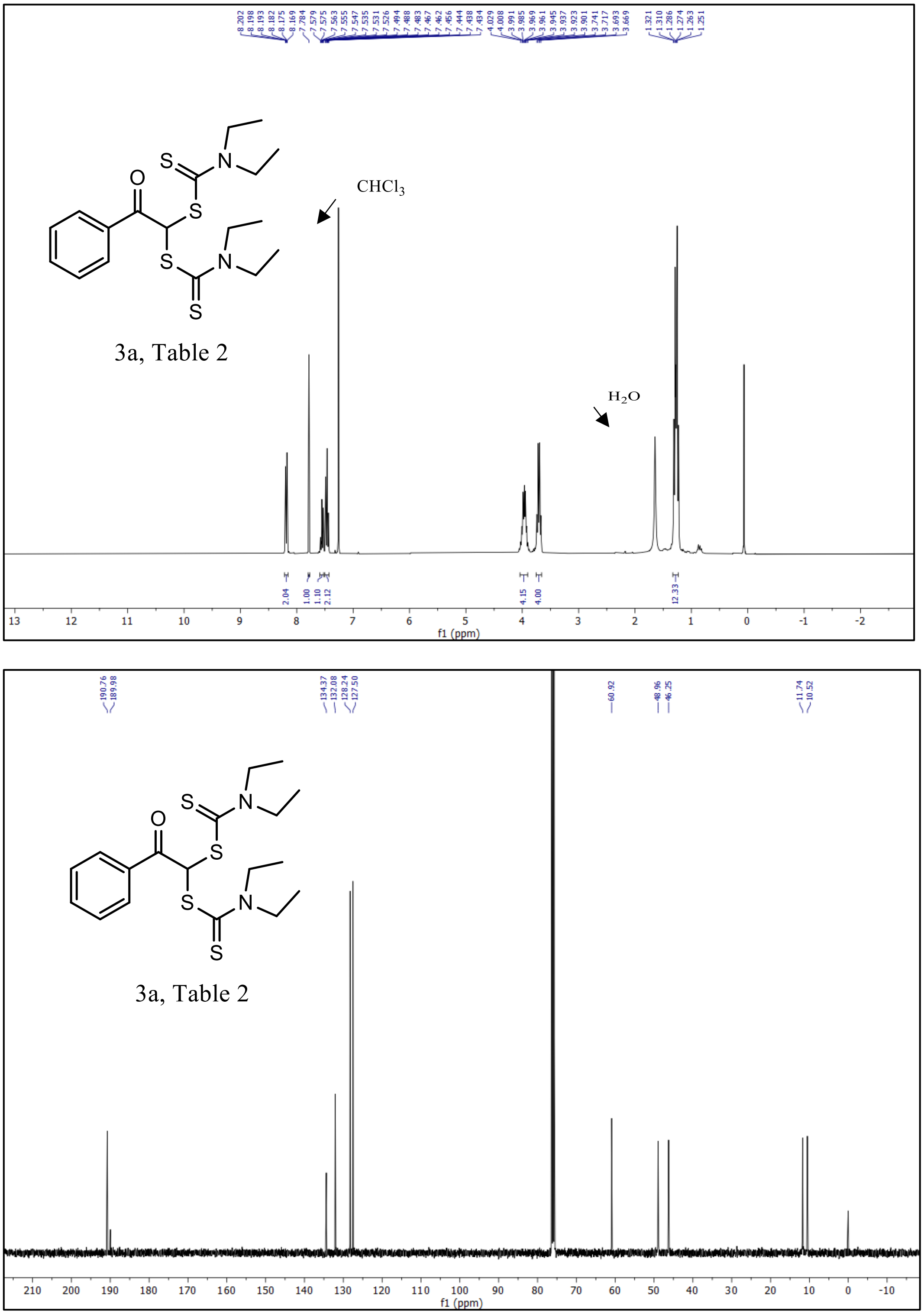
20. 2-hydroxy-2-phenylethane-1,1-diyl bis(dimethylcarbamodithioate) (8): White solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.33-3.37 (m, 6H), 3.50-3.55 (m, 7H), 5.66-5.67 (broad, 1H), 6.64 (m, 1H), 7.28-7.39 (m, 3H), 7.66-7.68 (m, 2H), ^{13}C NMR (75MHz, $CDCl_3$) δ: 41.64, 41.73, 45.16, 45.72, 69.24, 75.15, 126.77 (2C), 127.84, 128.06 (2C), 140.42, 194.19, 195.20.



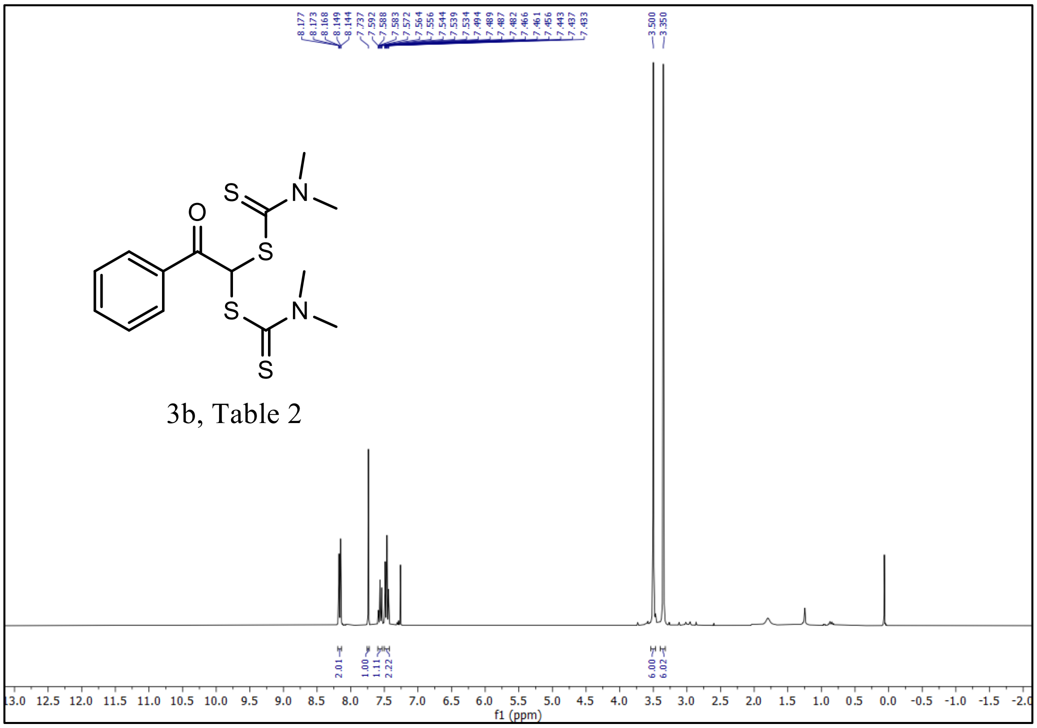
2.3/e.

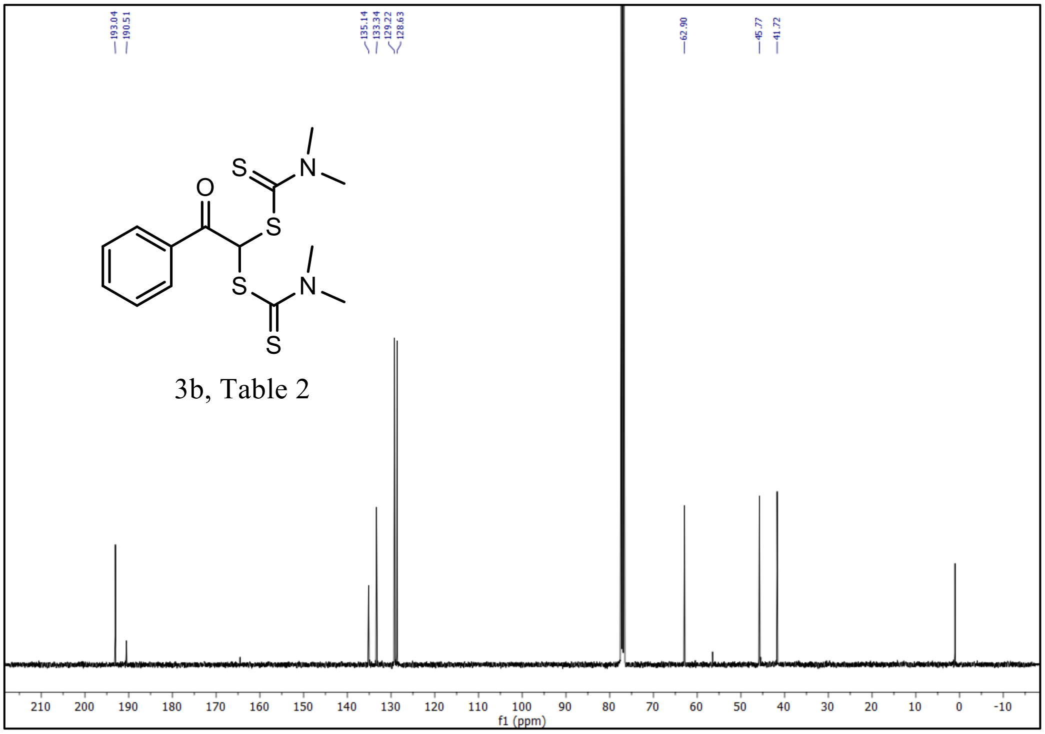
^{1}H and ^{13}C NMR spectra of all synthesized products described in section -III

1. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra of **3a**

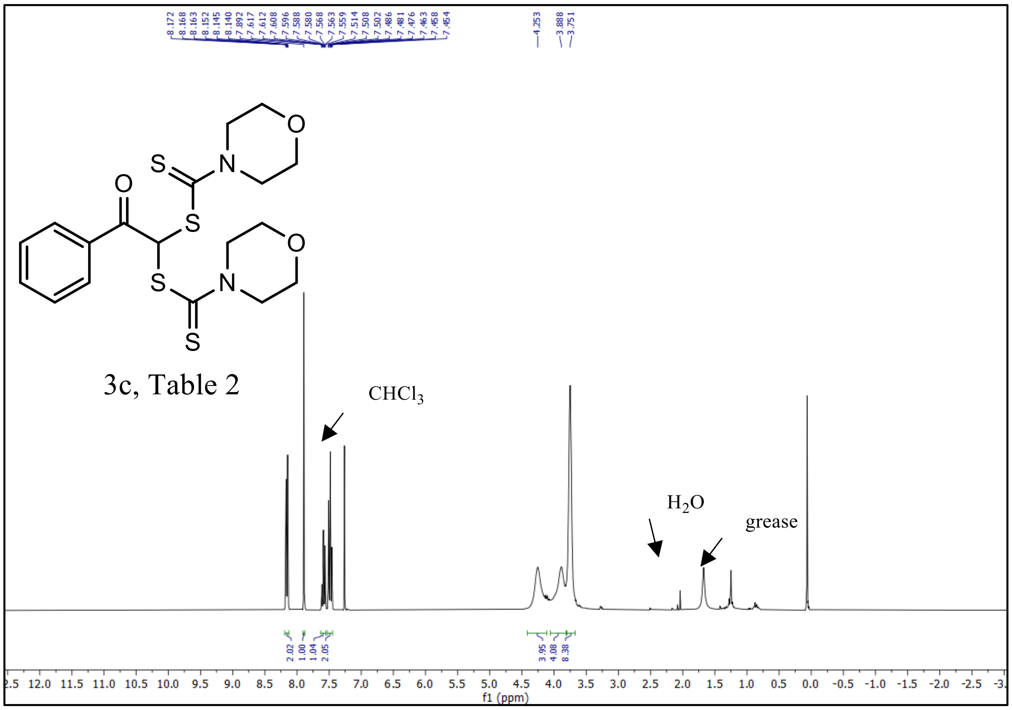


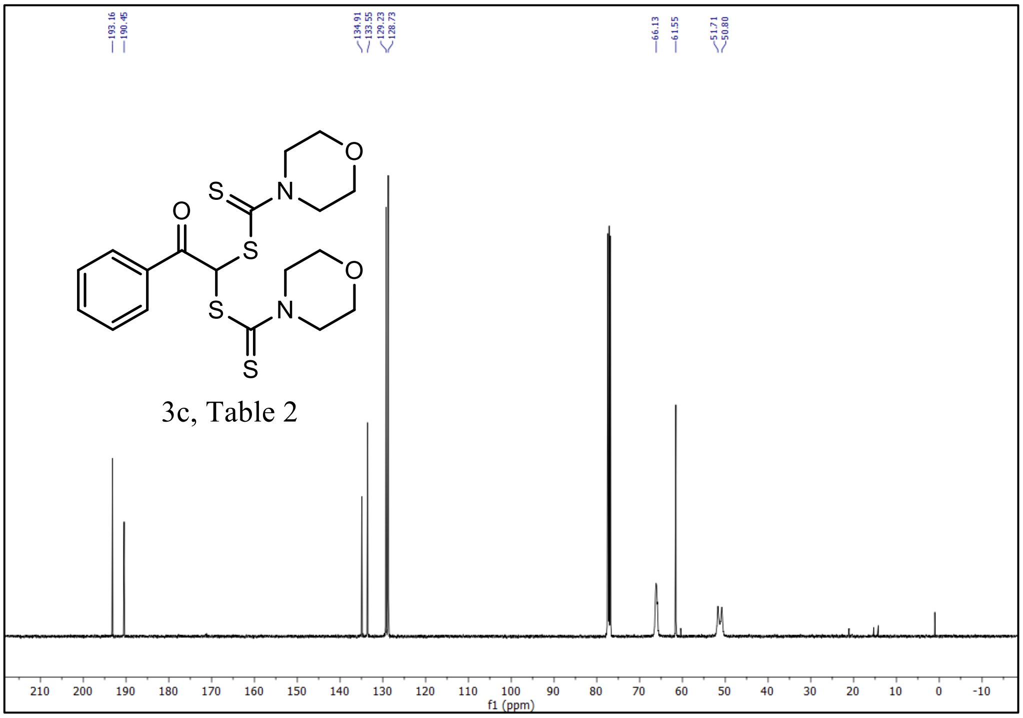
2. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra of **3b**



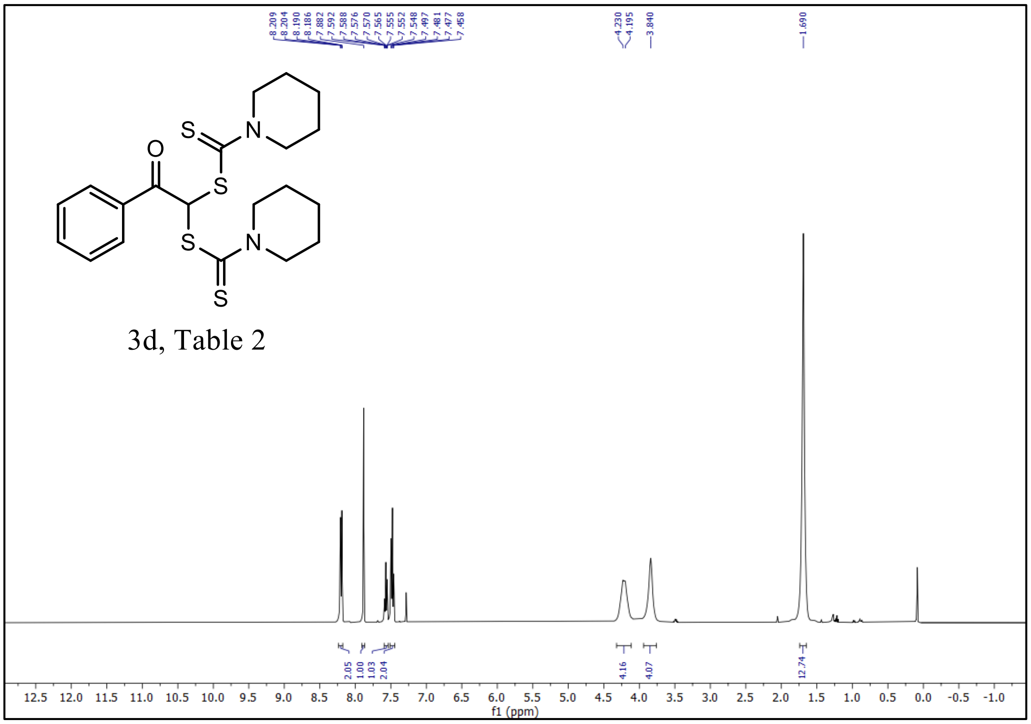


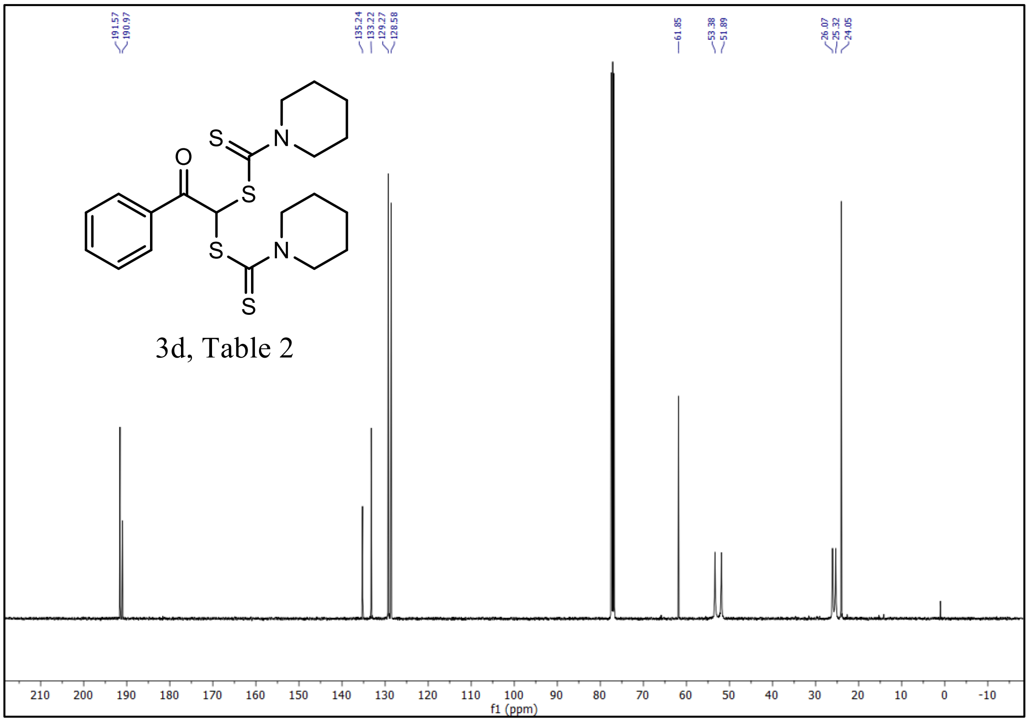
3. ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra of **3c**



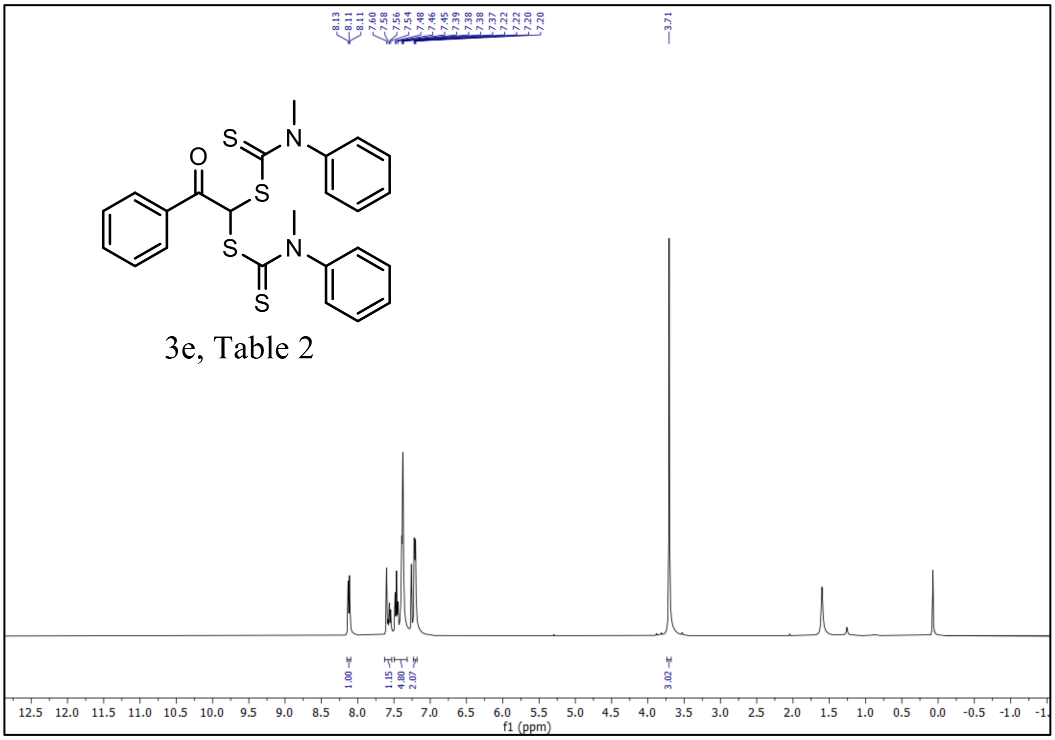


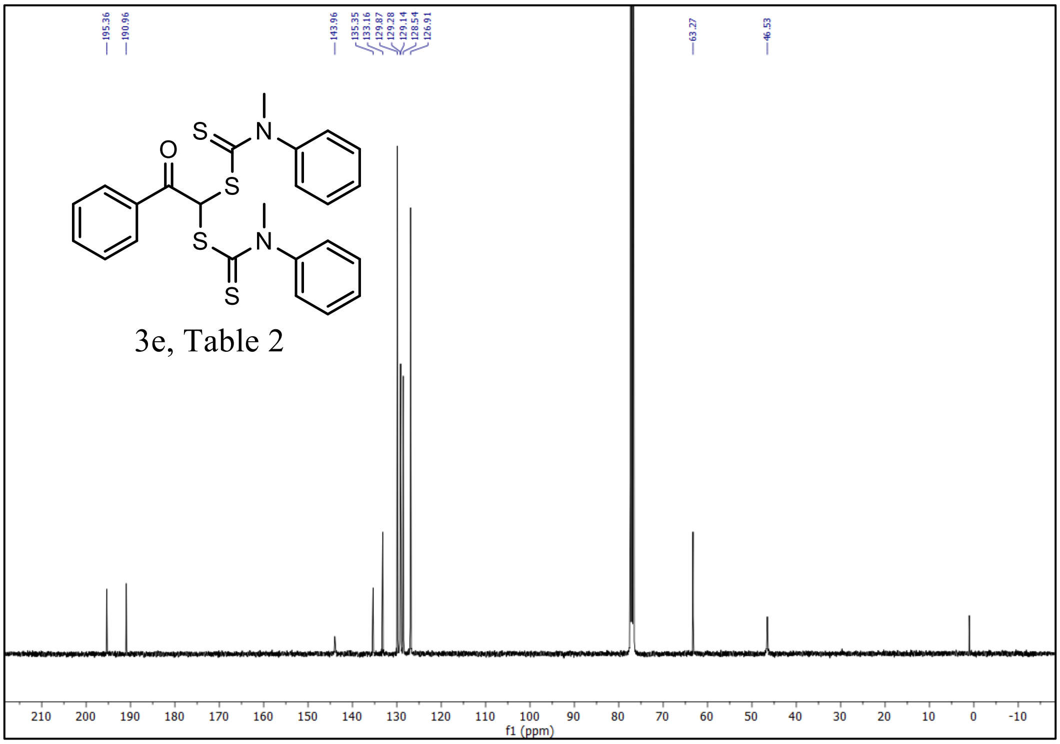
4. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra of **3d**



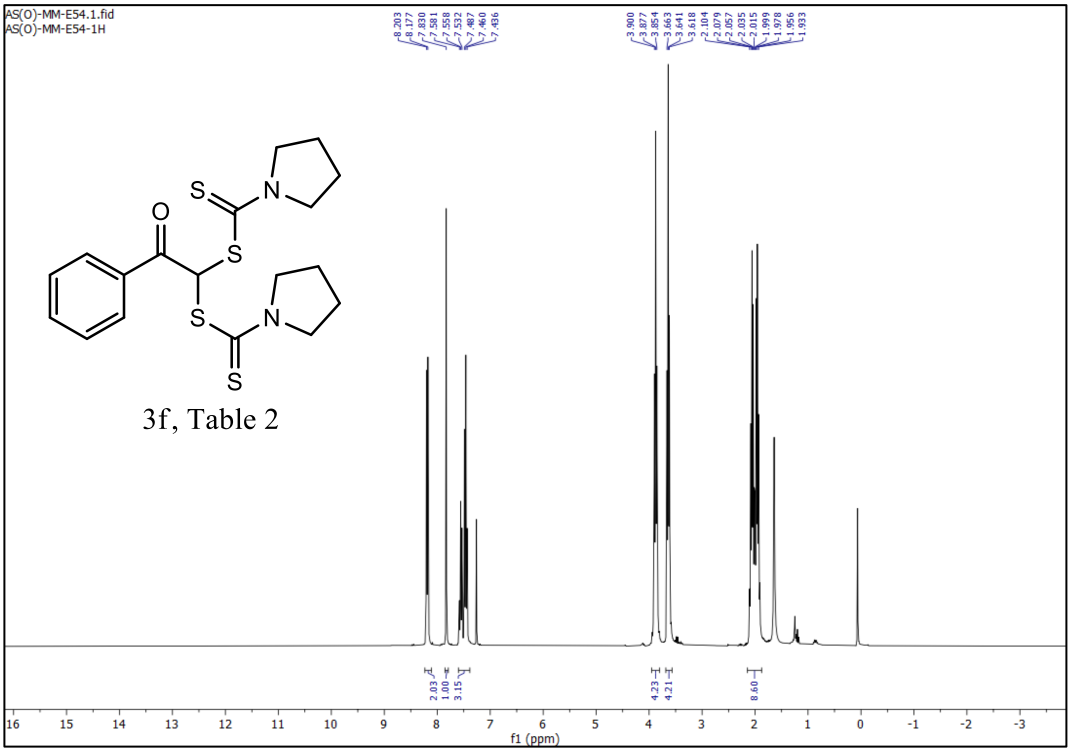


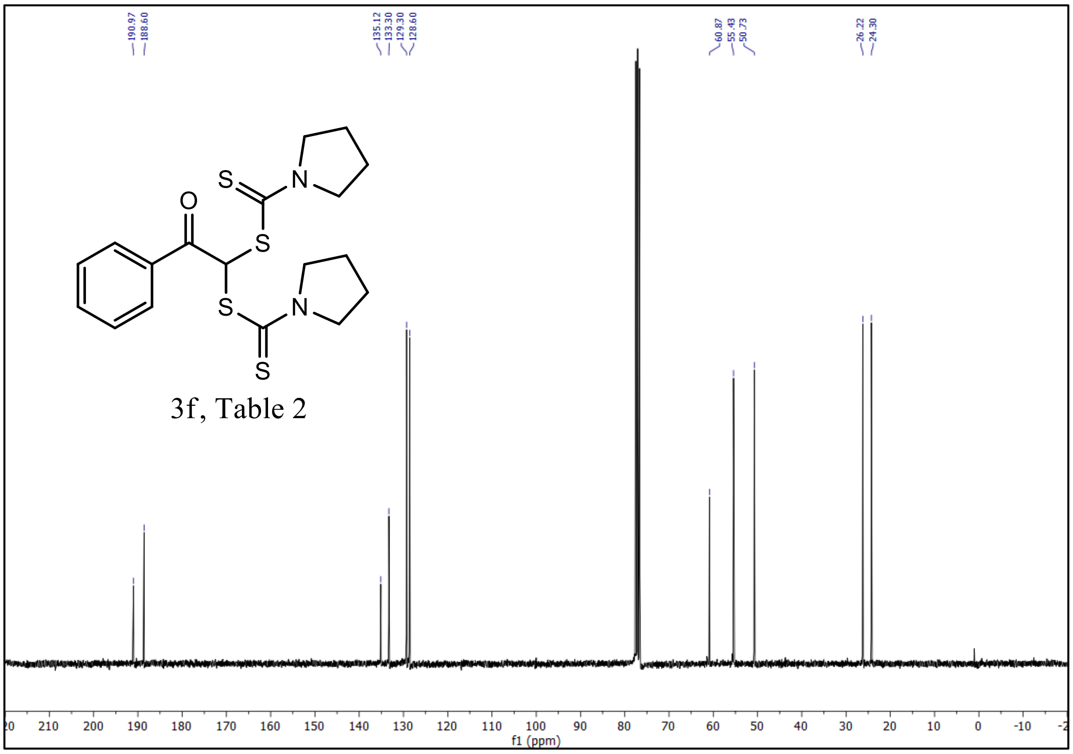
5. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra of **3e**



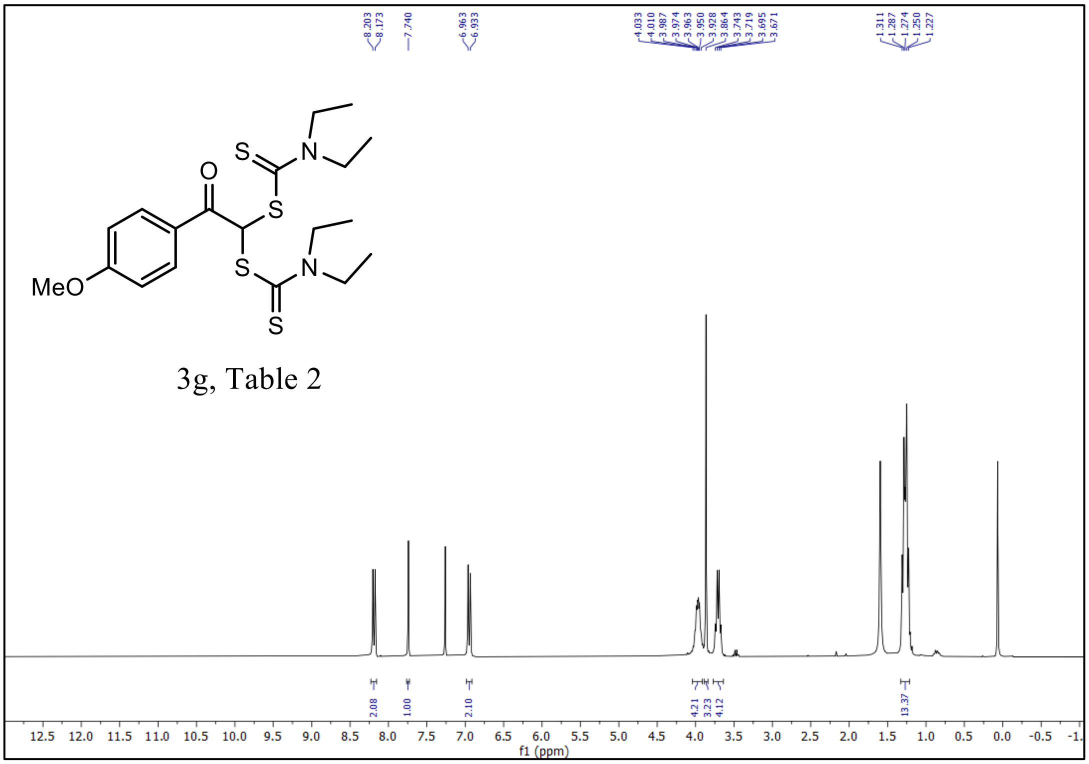


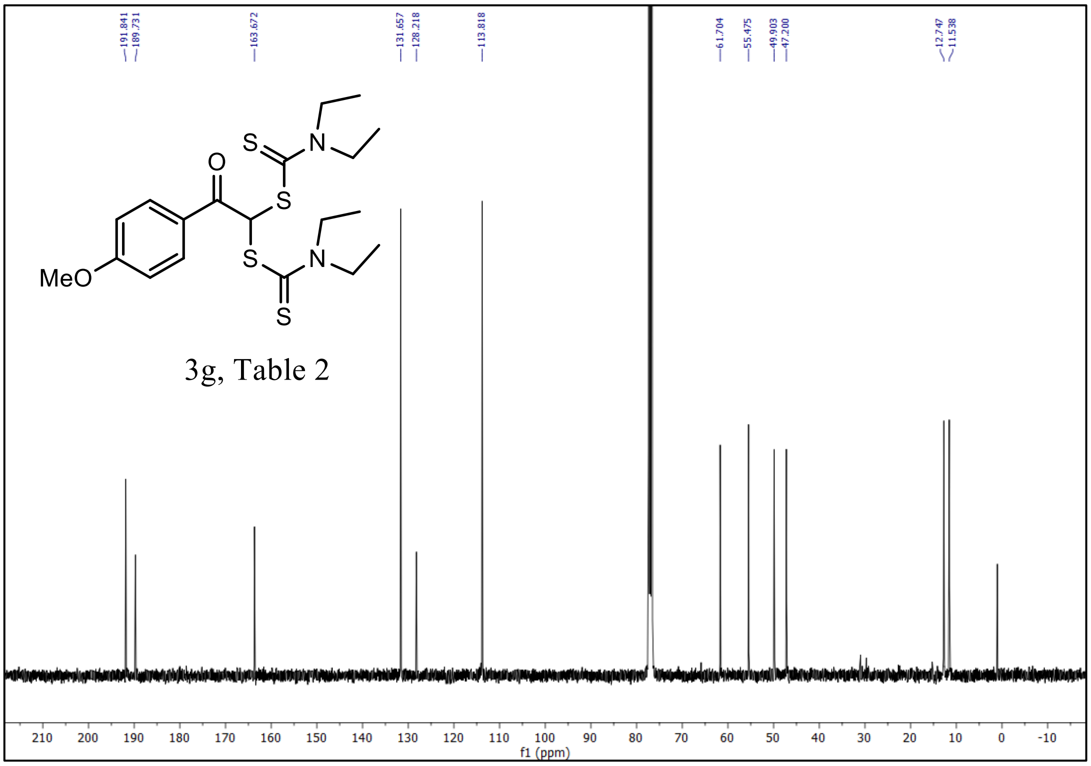
6. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra of **3f**



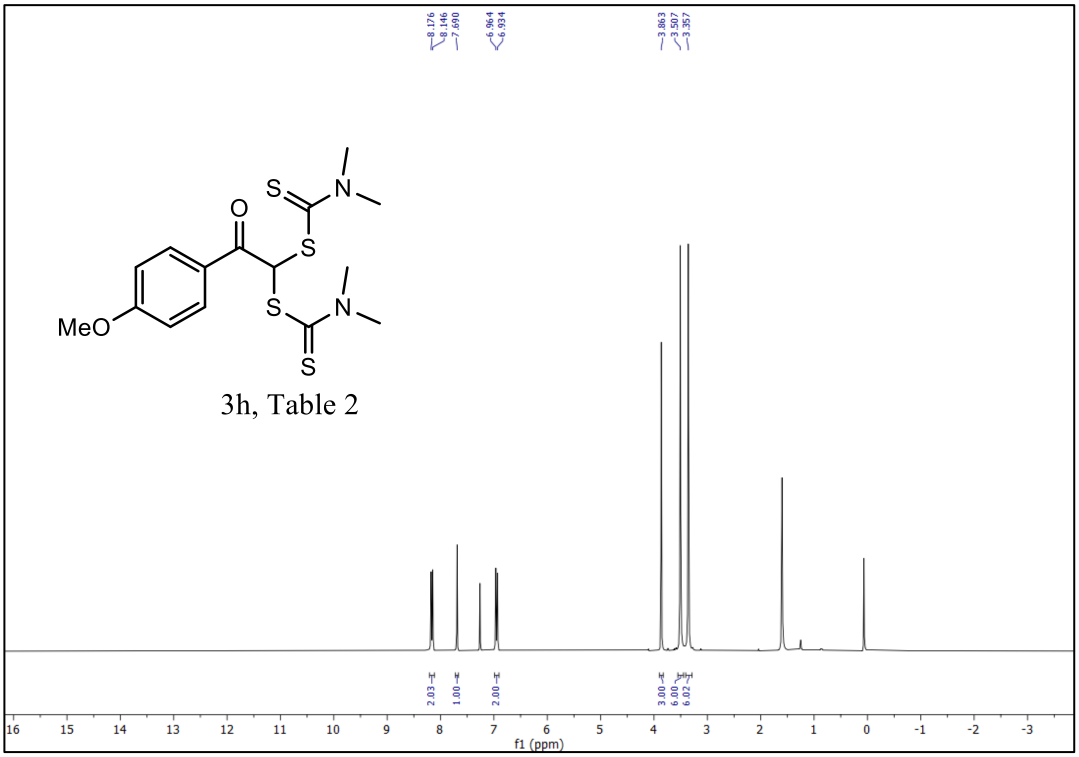


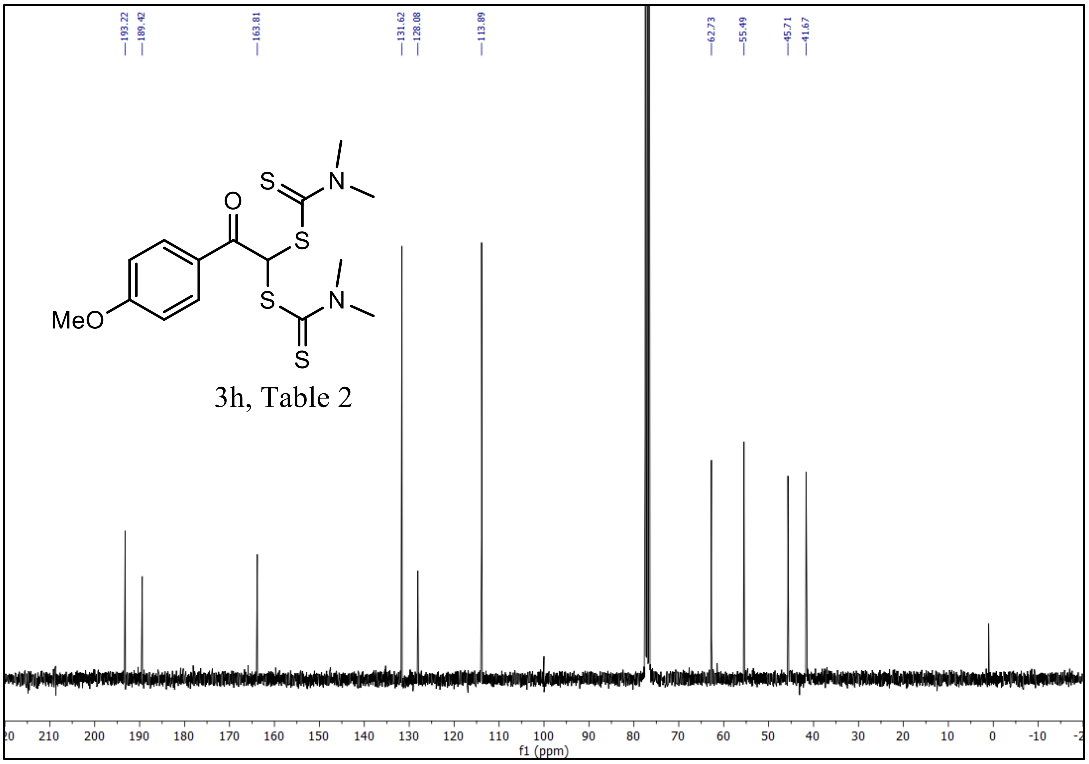
7. ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra of **3g**


3g, Table 2

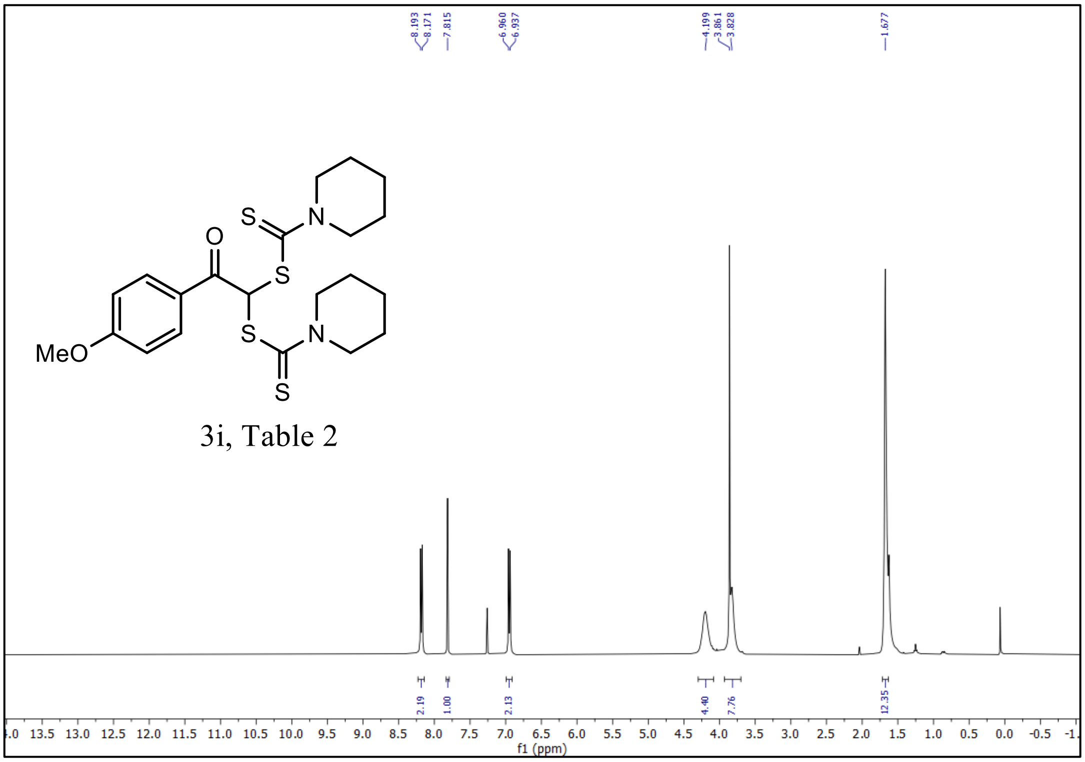

3g, Table 2

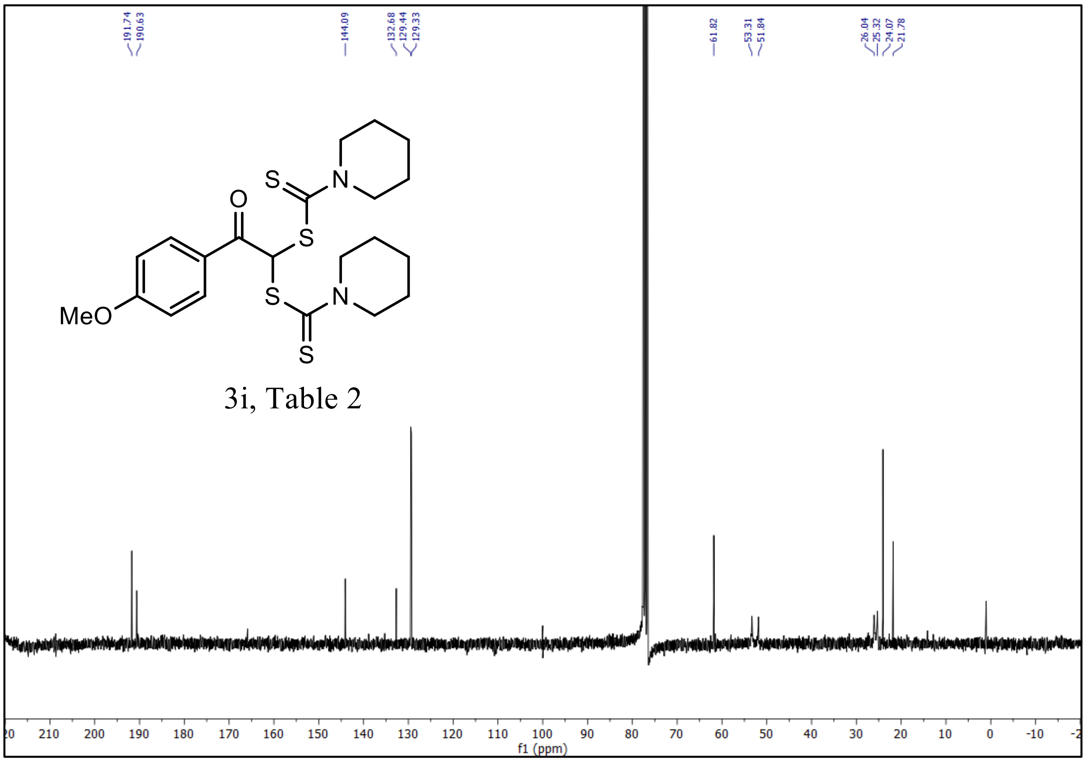
8. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra of **3h**



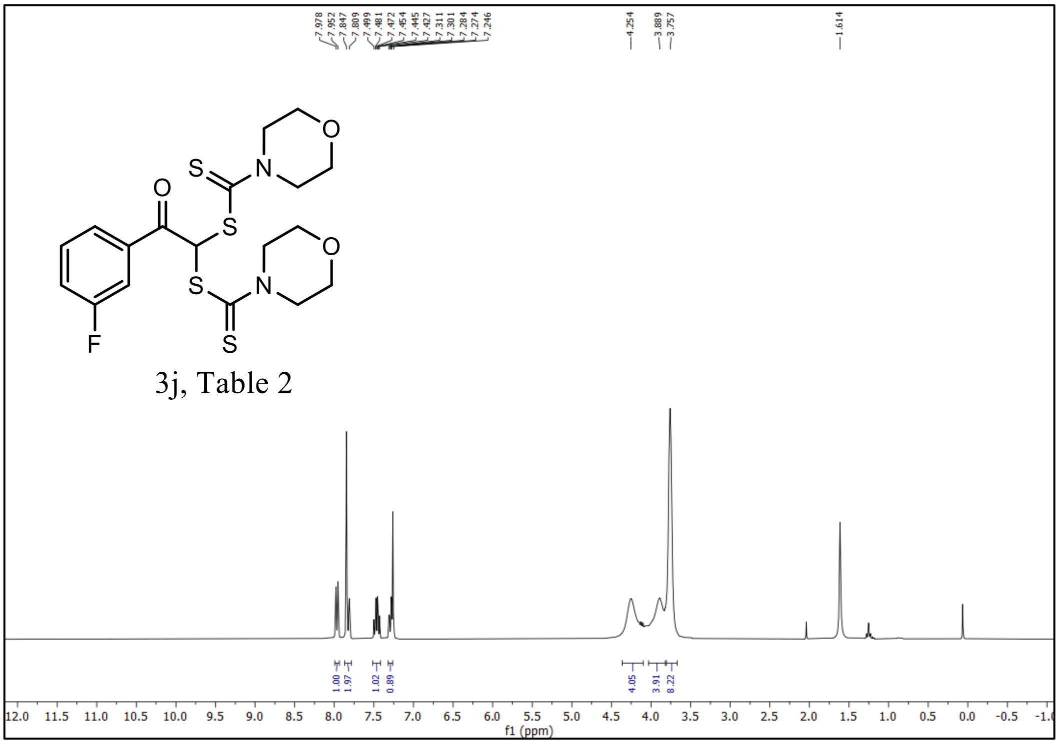


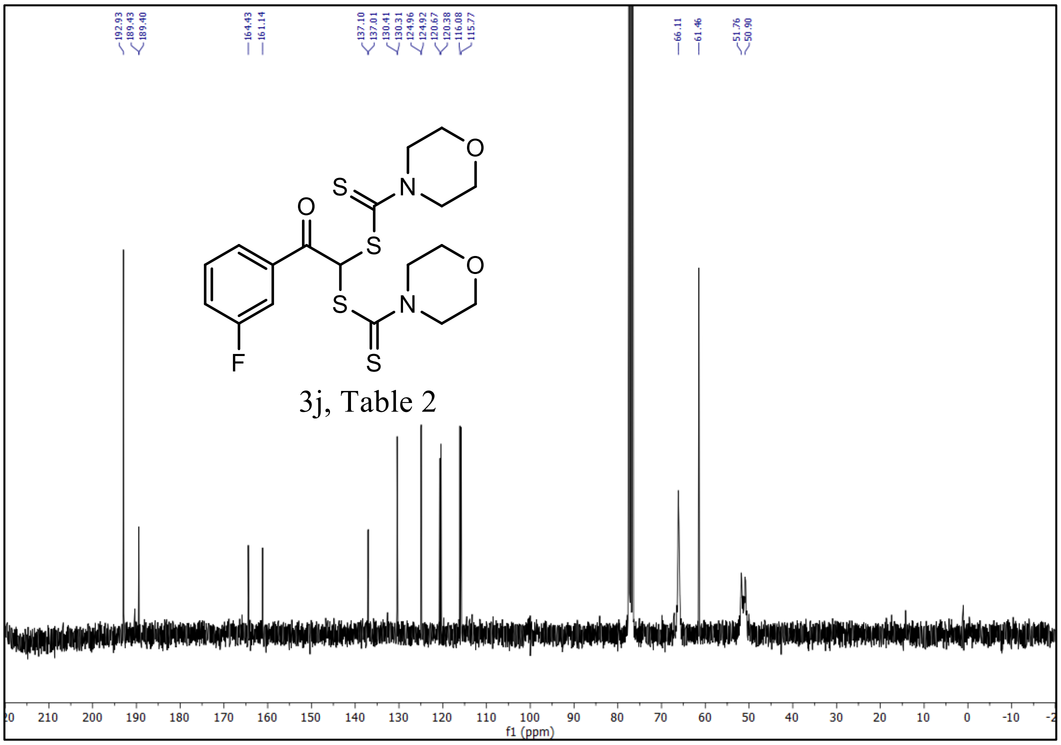
9. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra of **3i**



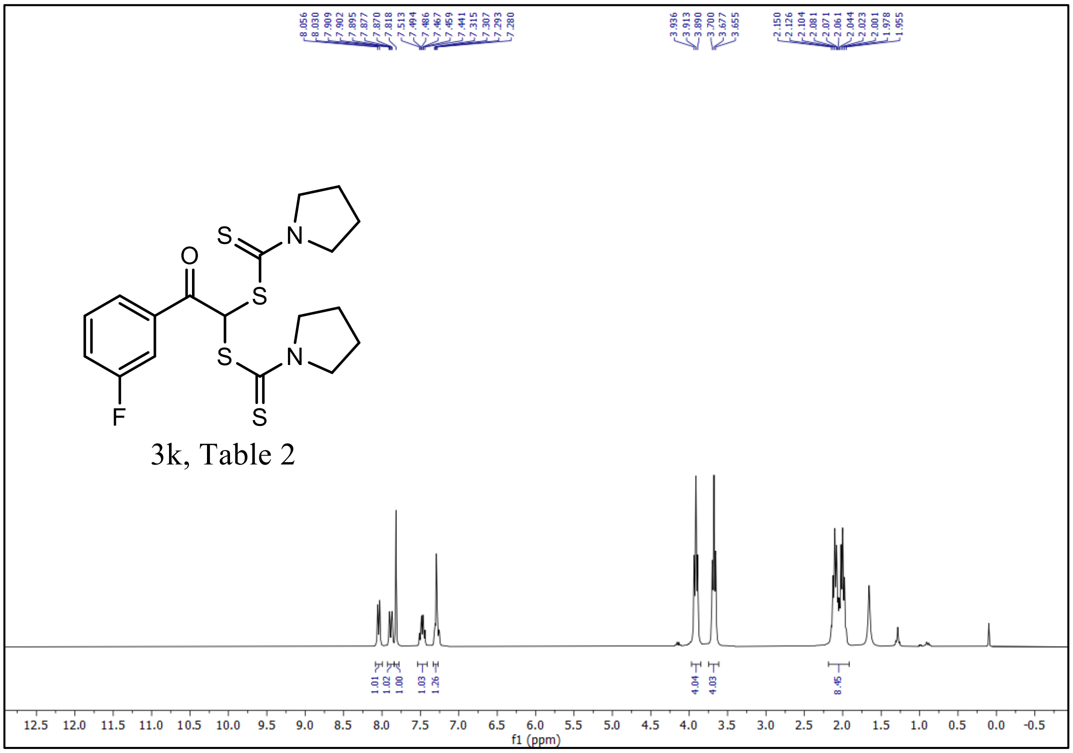


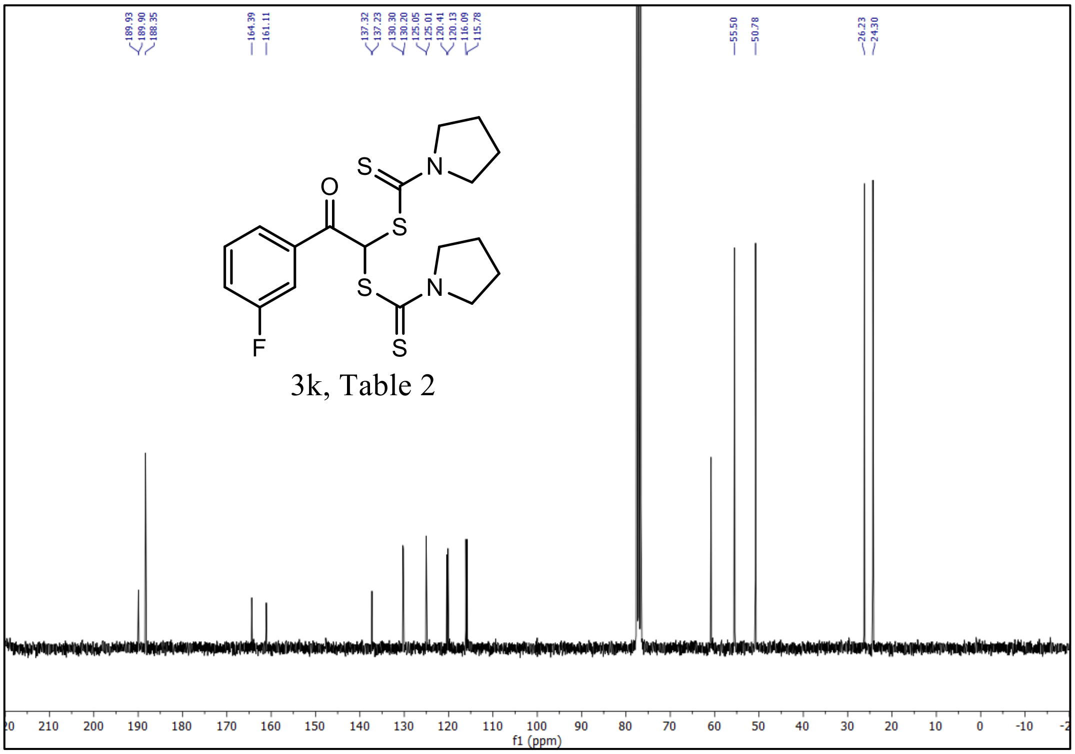
10. ^{1}H NMR (300 MHz, CDCl$_3$) and ^{13}C NMR (75 MHz, CDCl$_3$) spectra of **3j**



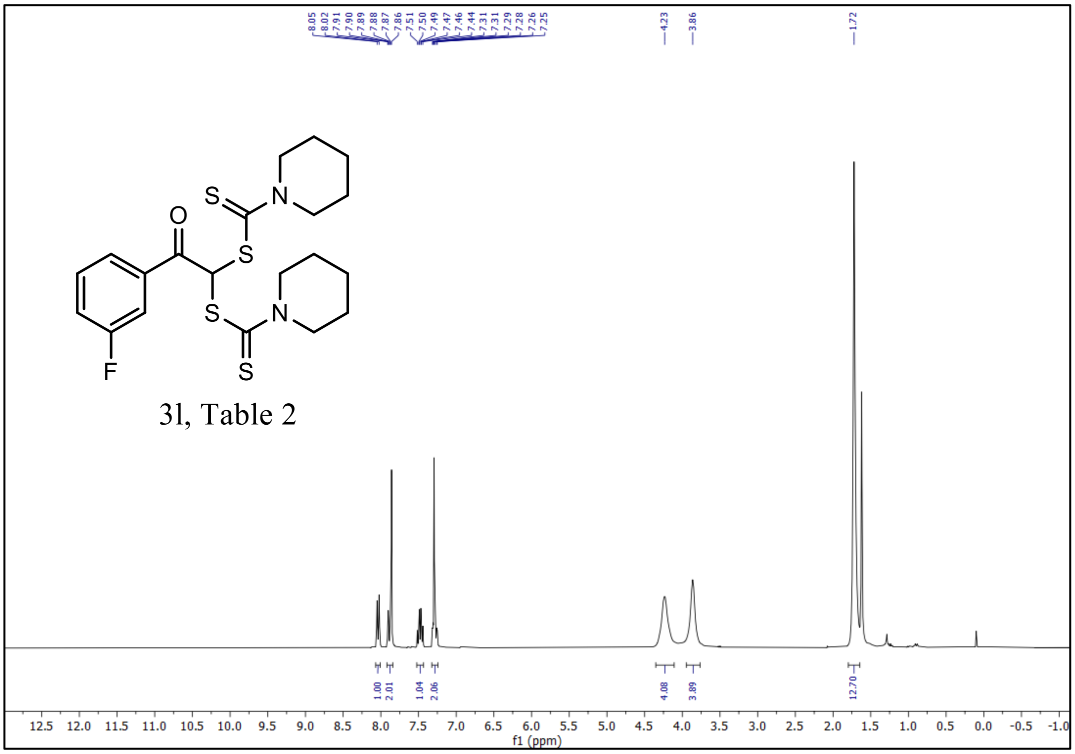


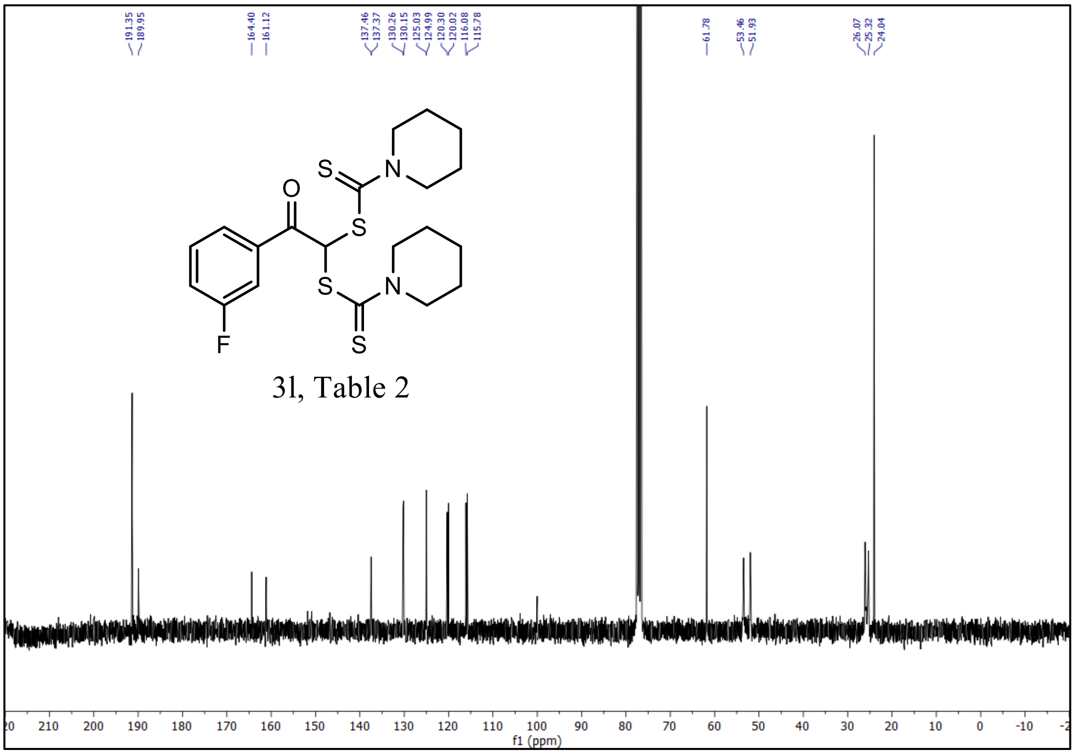
11. ^{1}H NMR (300 MHz, CDCl$_3$) and ^{13}C NMR (75 MHz, CDCl$_3$) spectra of **3k**



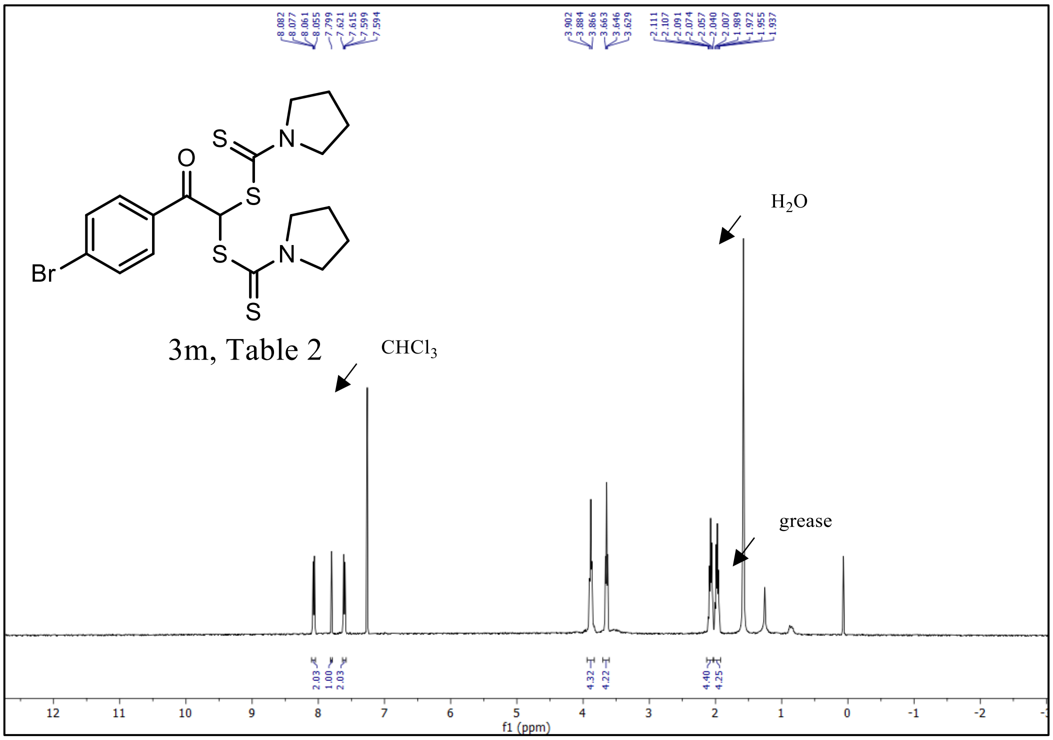


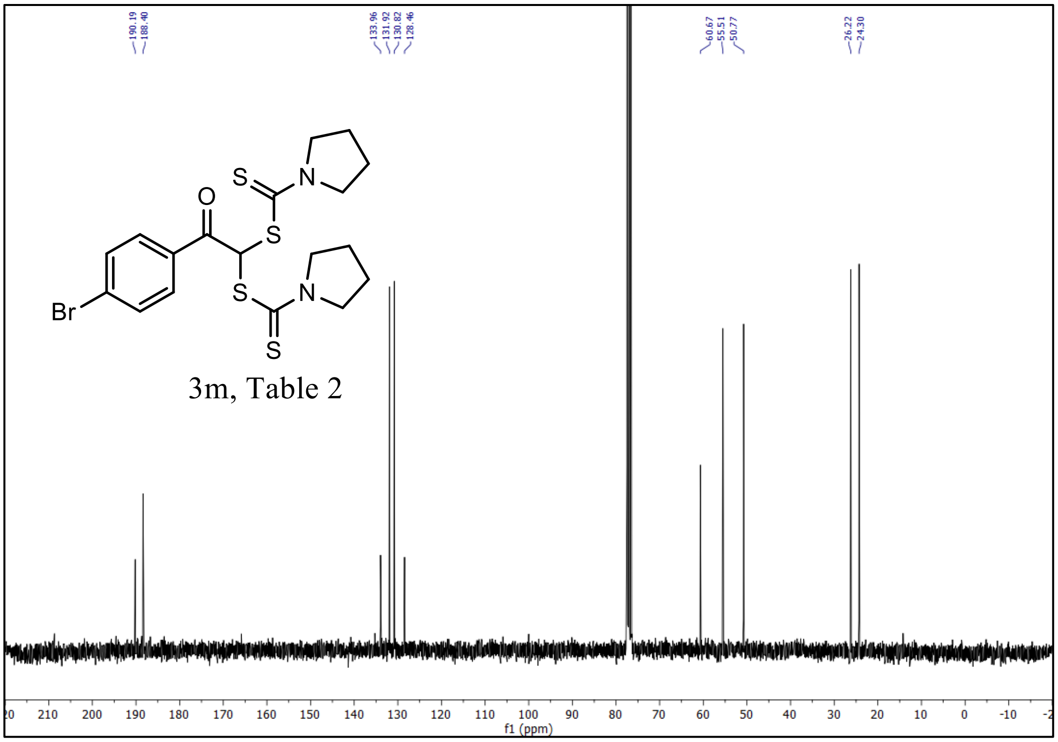
12. ^{1}H NMR (300 MHz, CDCl$_3$) and ^{13}C NMR (75 MHz, CDCl$_3$) spectra of **3l**



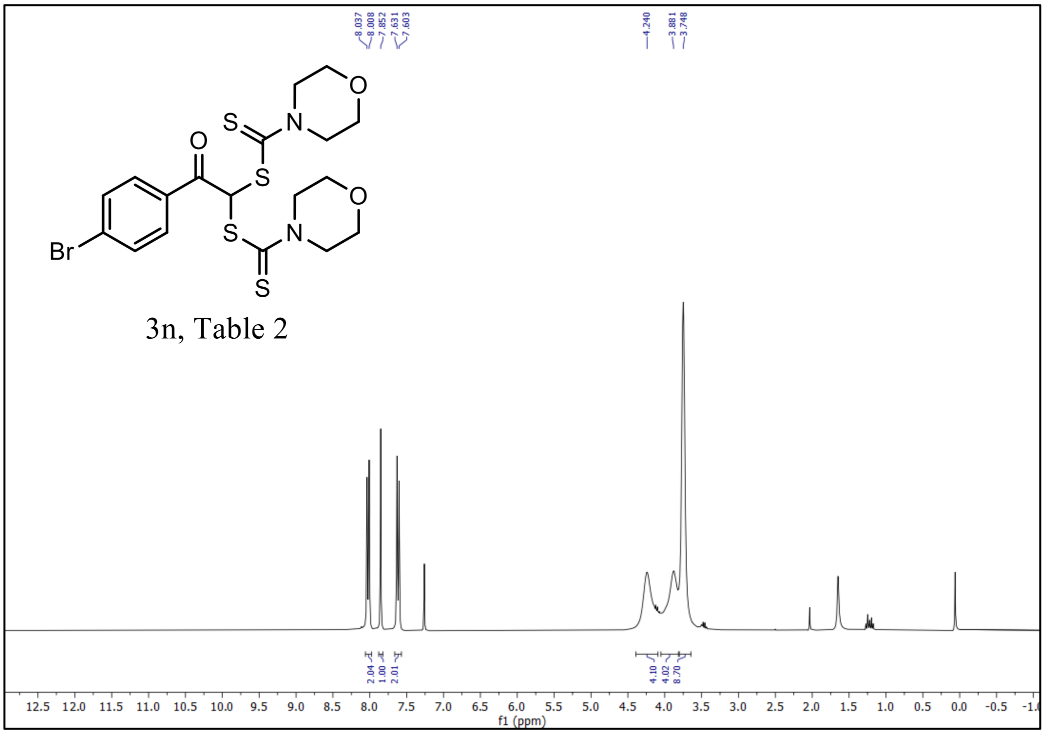


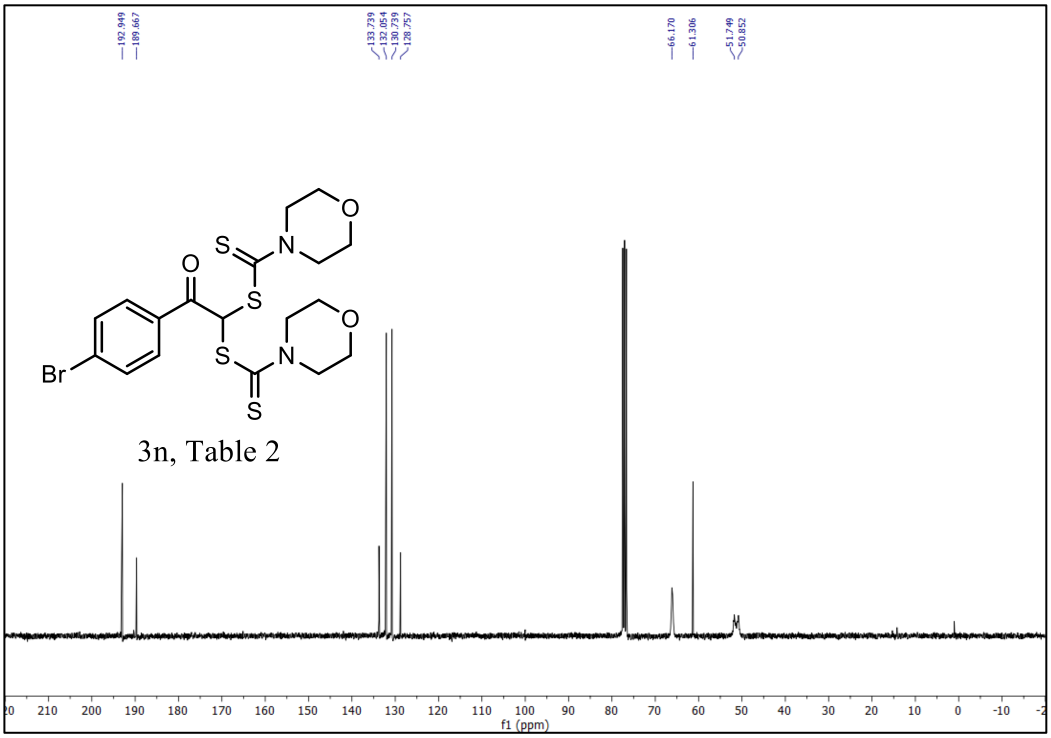
13. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra of **3m**



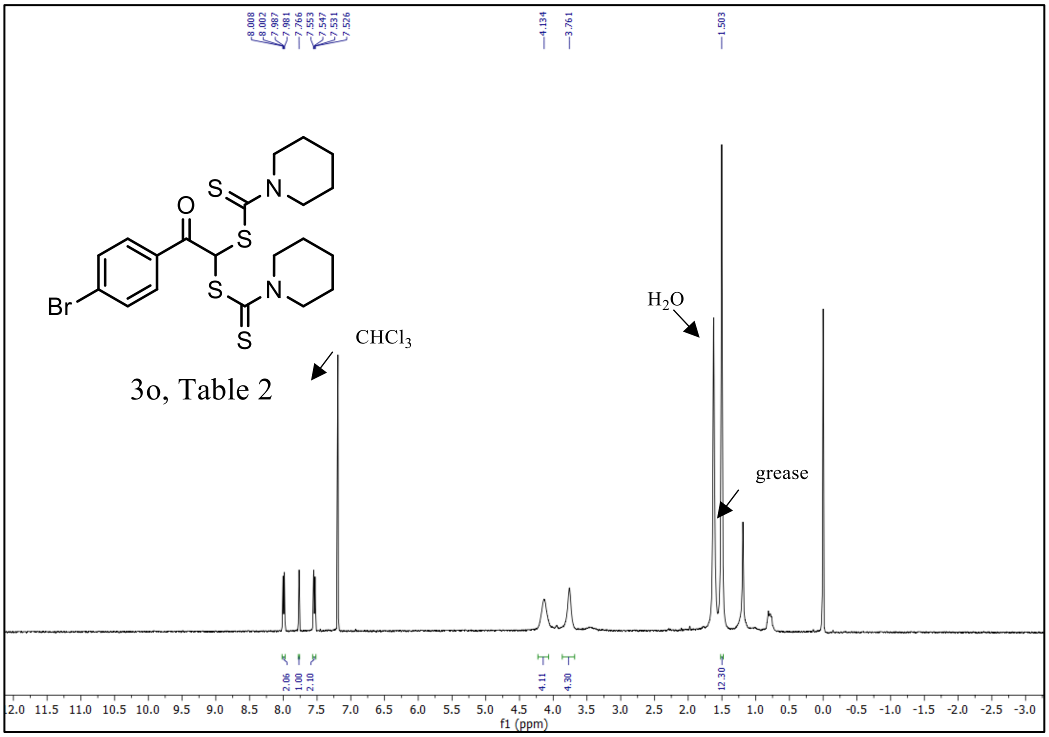


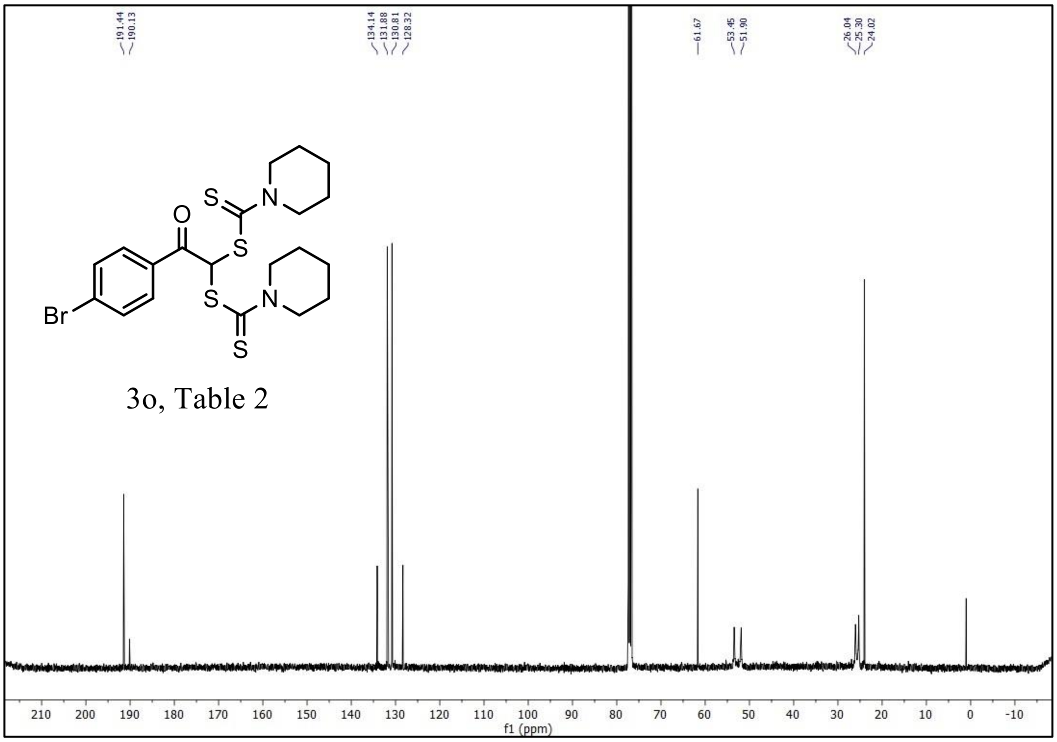
14. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra of **3n**



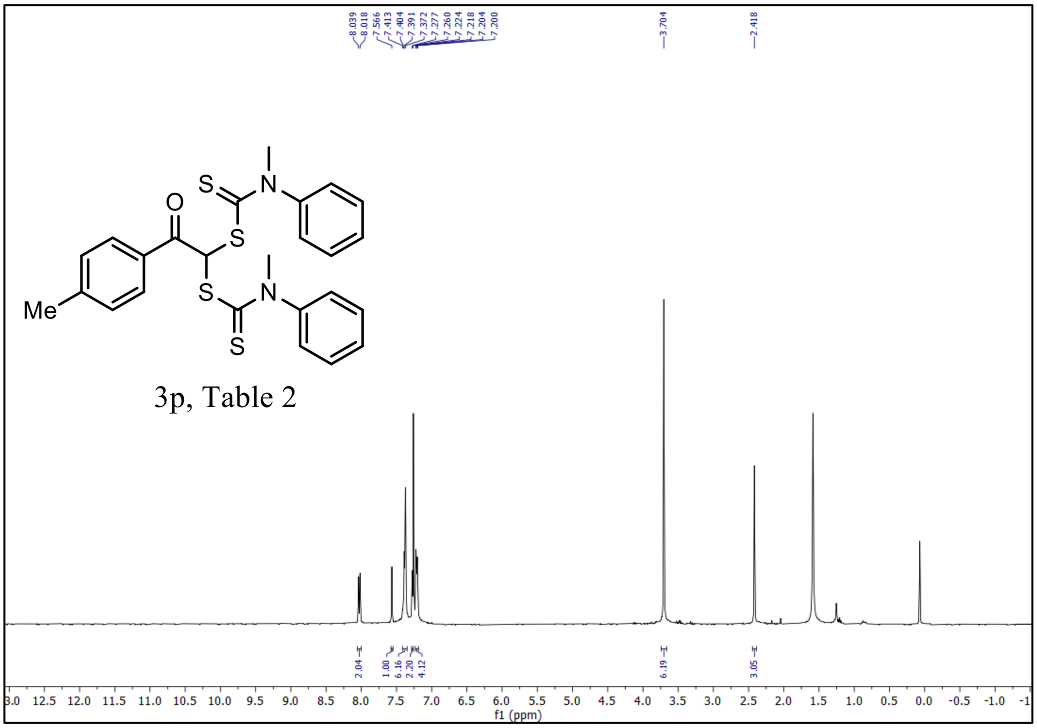


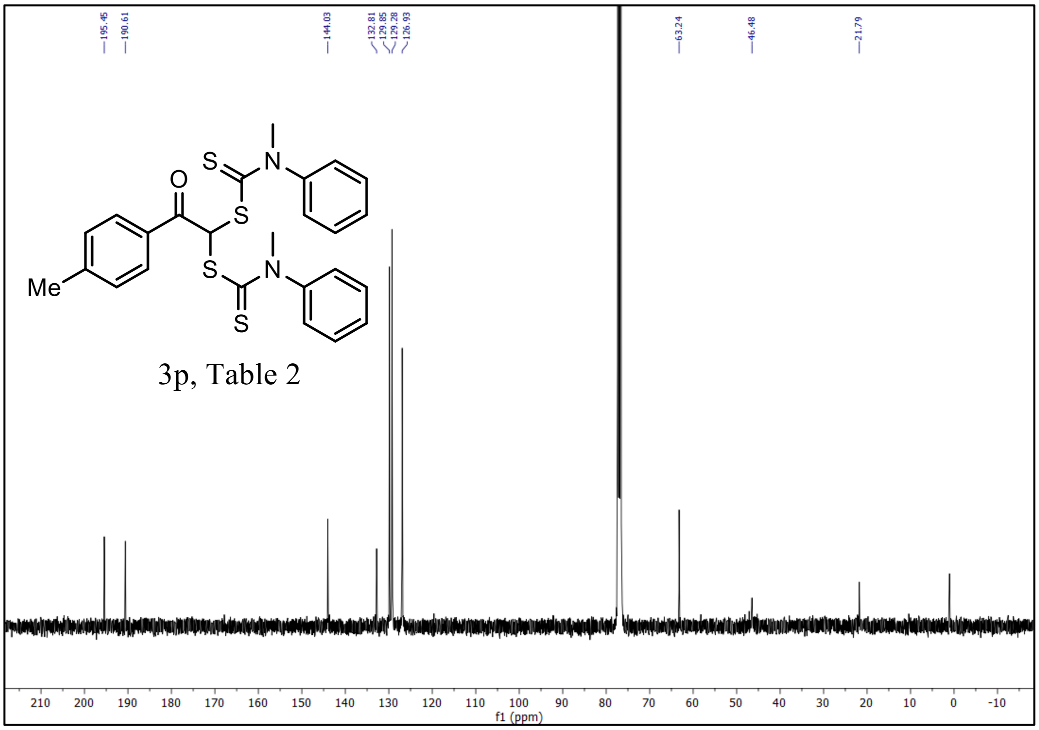
15. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra of **3o**



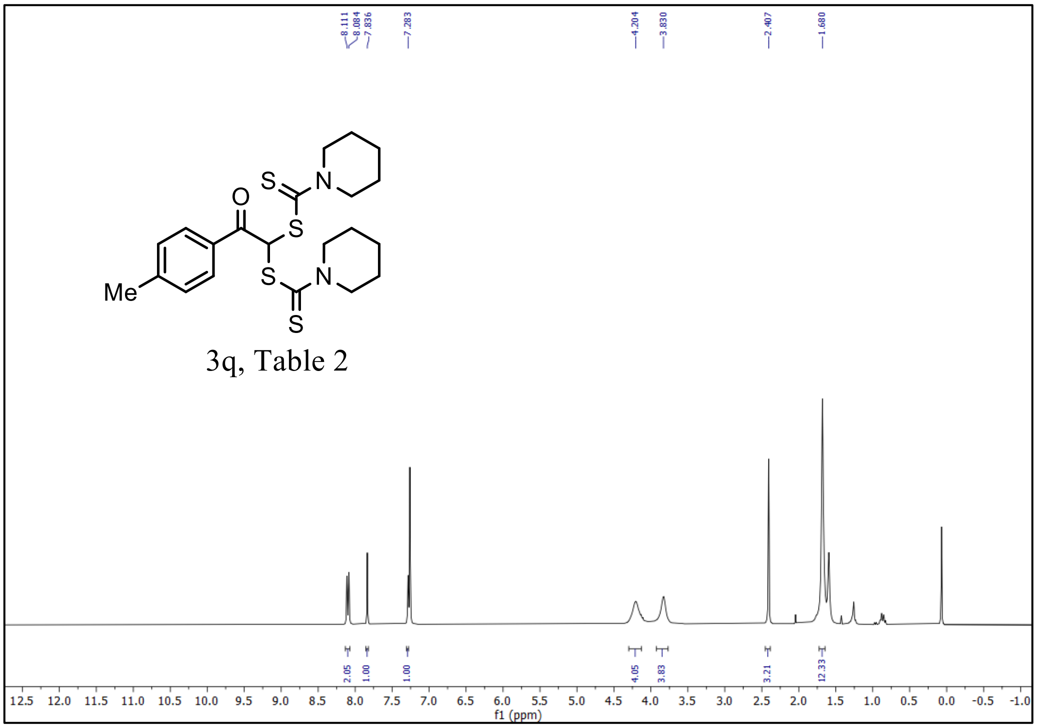


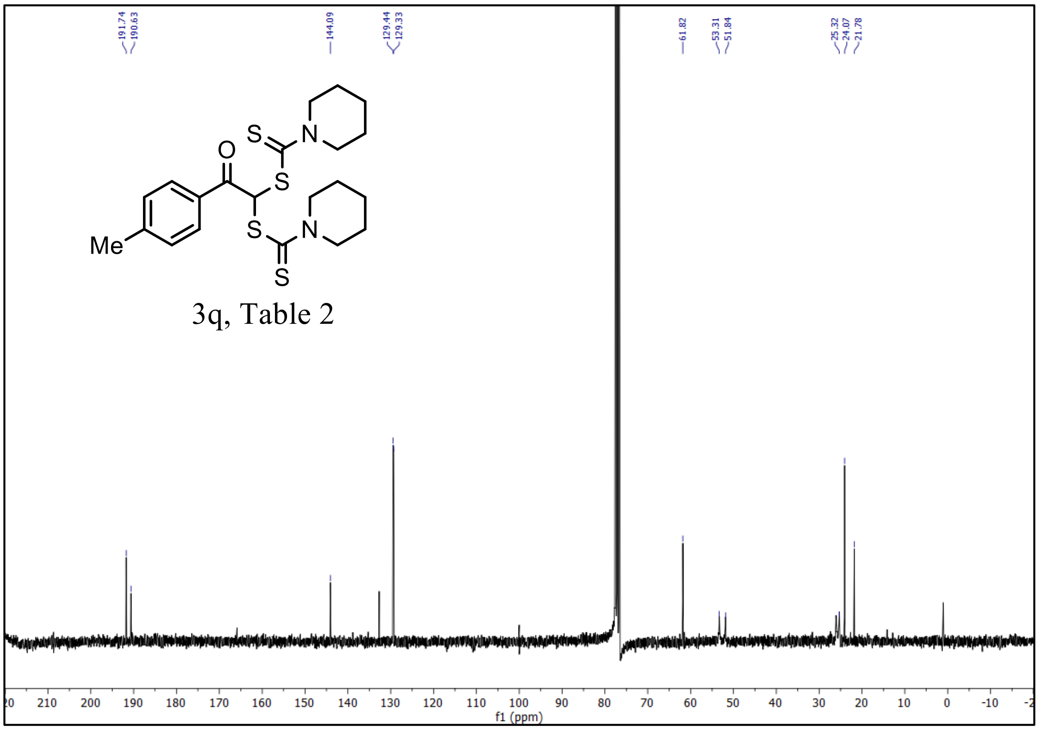
16. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, CDCl$_3$) spectra of **3p**



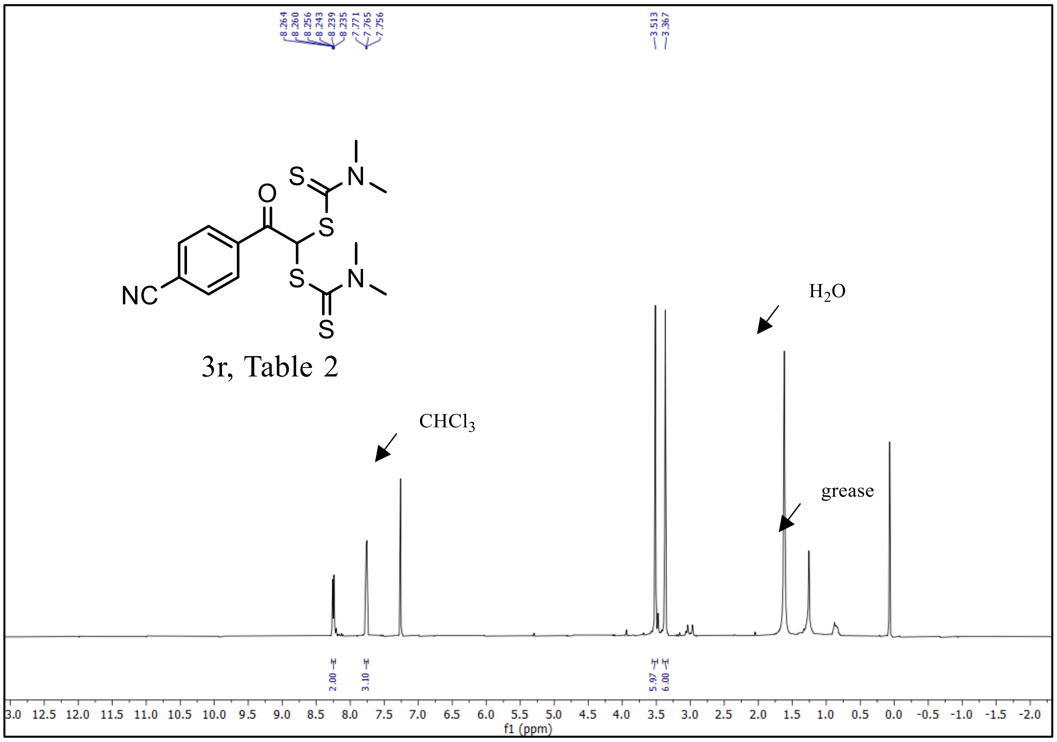


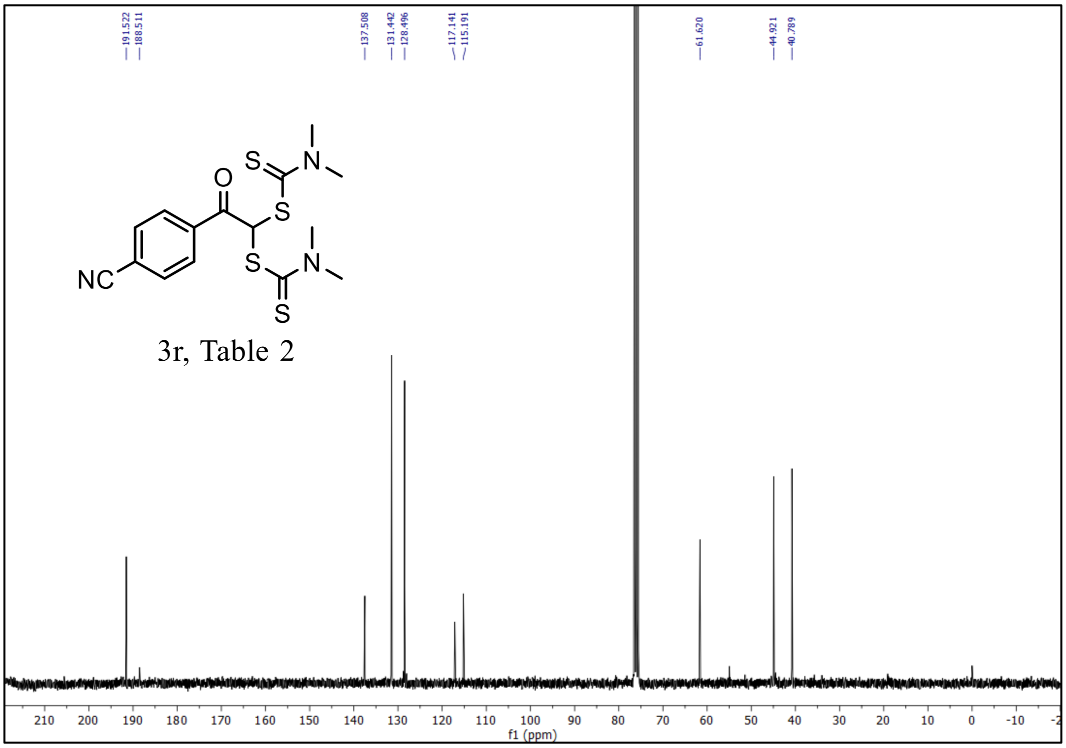
17. ^{1}H NMR (300 MHz, CDCl$_3$) and ^{13}C NMR (75 MHz, CDCl$_3$) spectra of **3q**



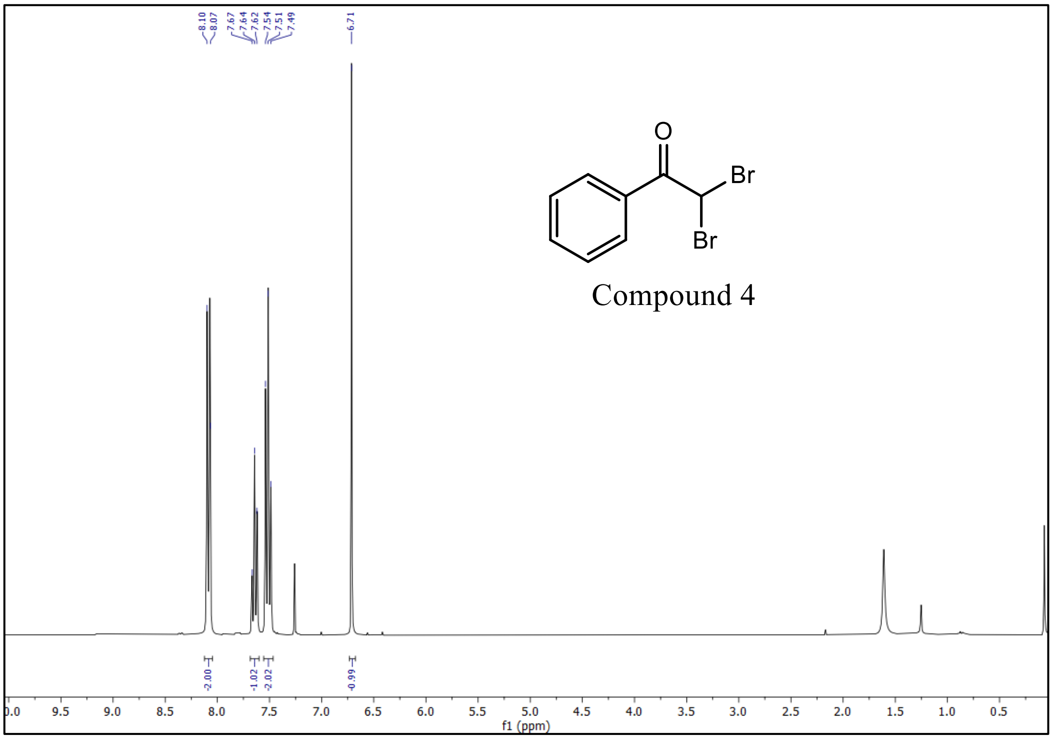


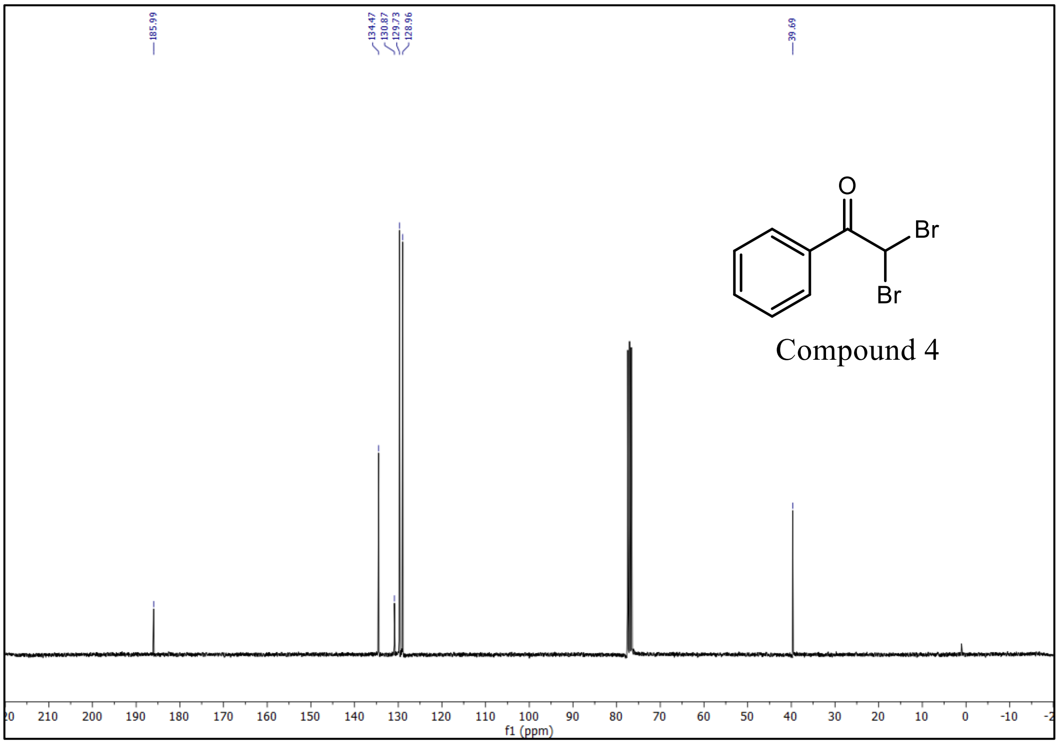
18. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra of **3r**



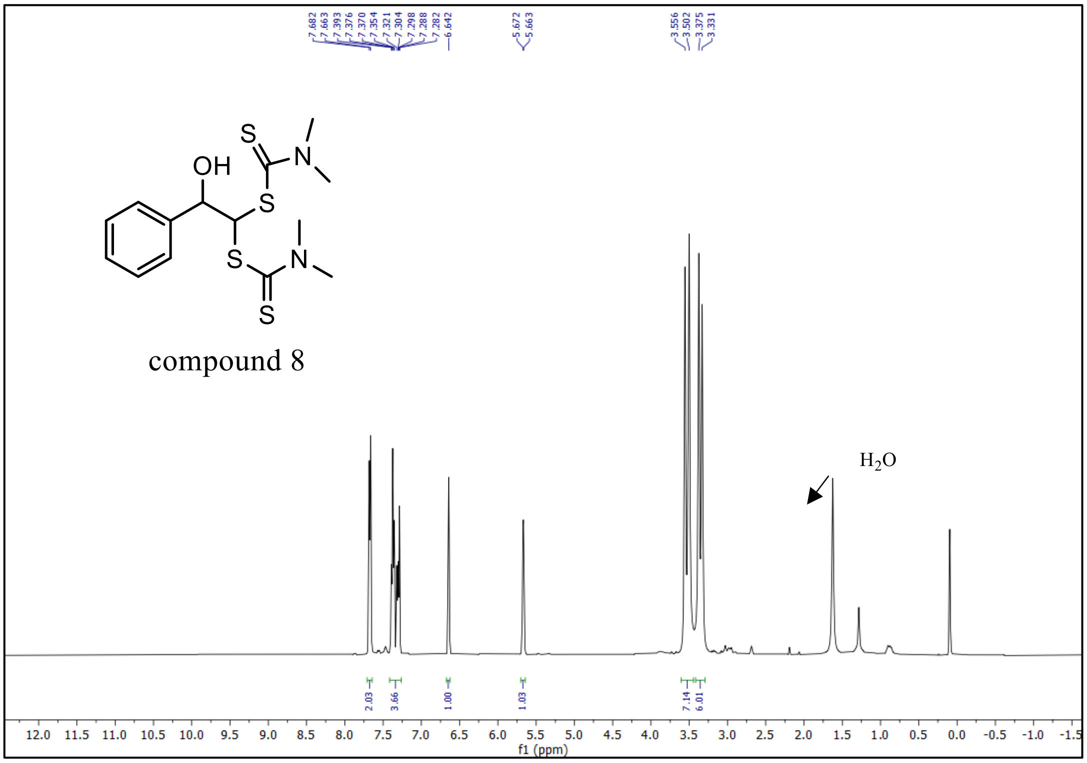


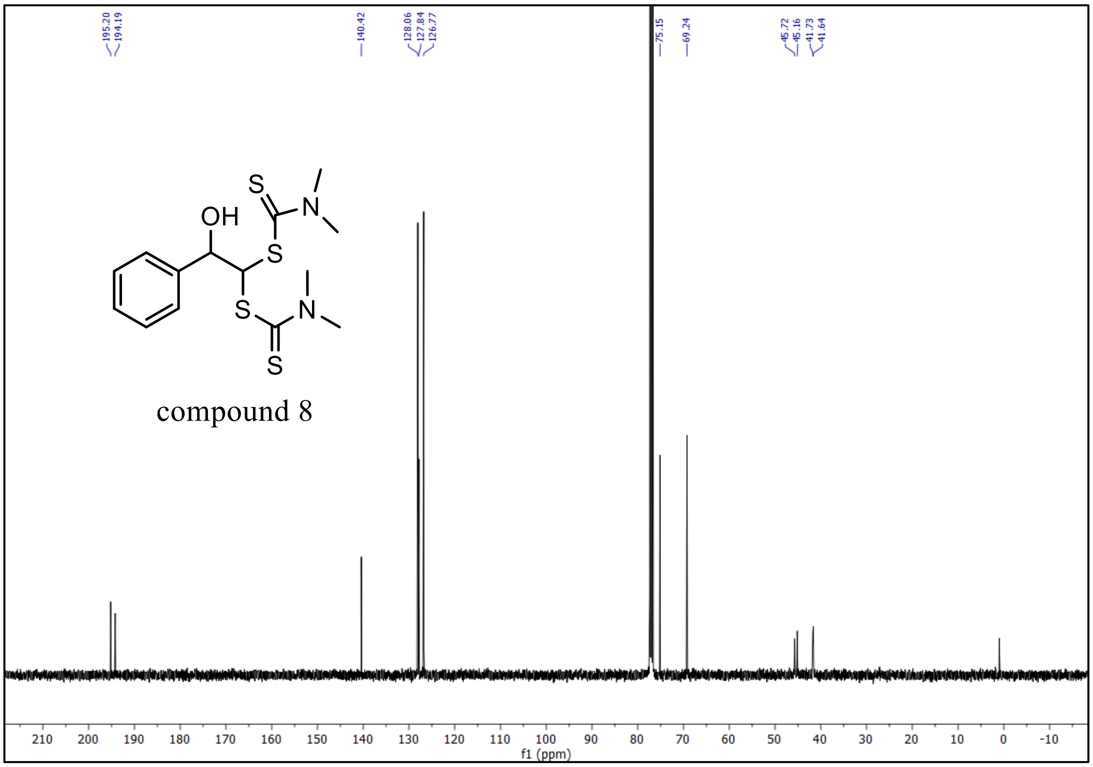
19. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) spectra of **compound 4**



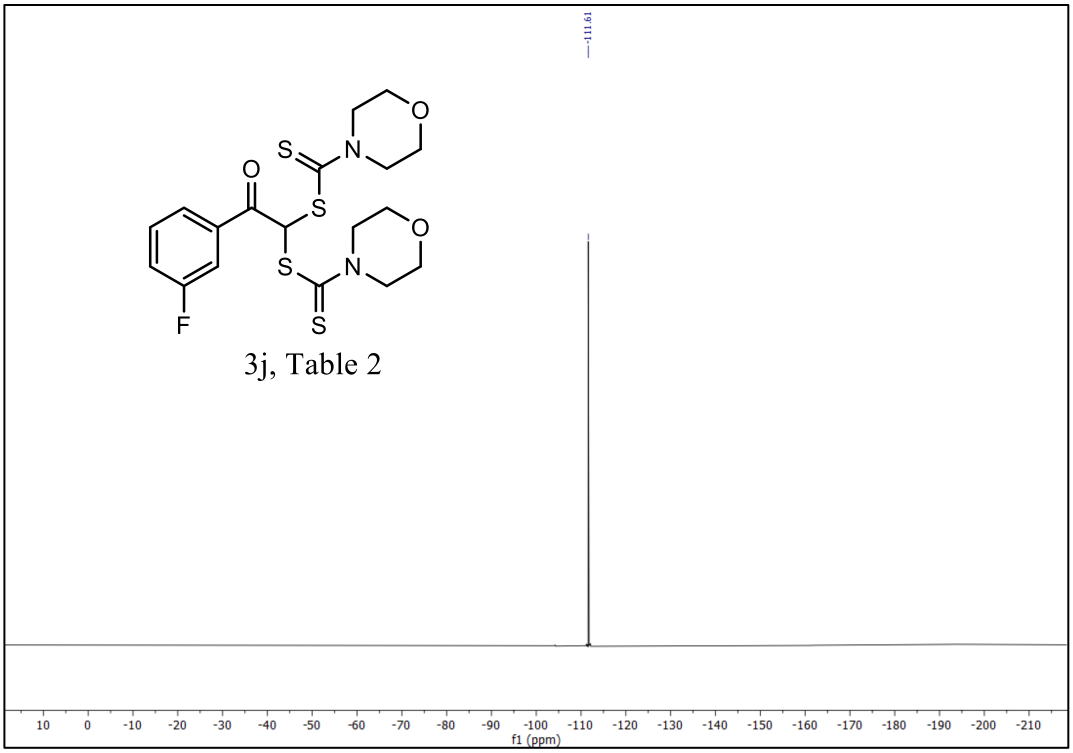


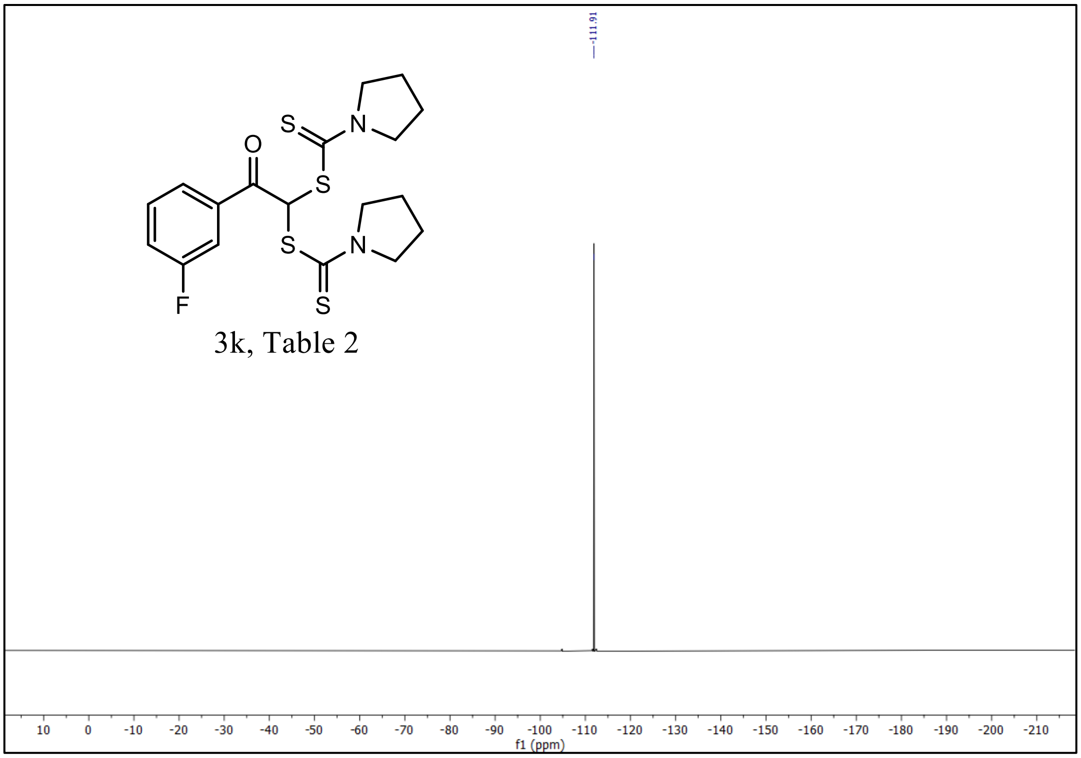
20. ^{1}H NMR (300 MHz, CDCl$_3$) and ^{13}C NMR (75 MHz, CDCl$_3$) spectra of **compound 8**



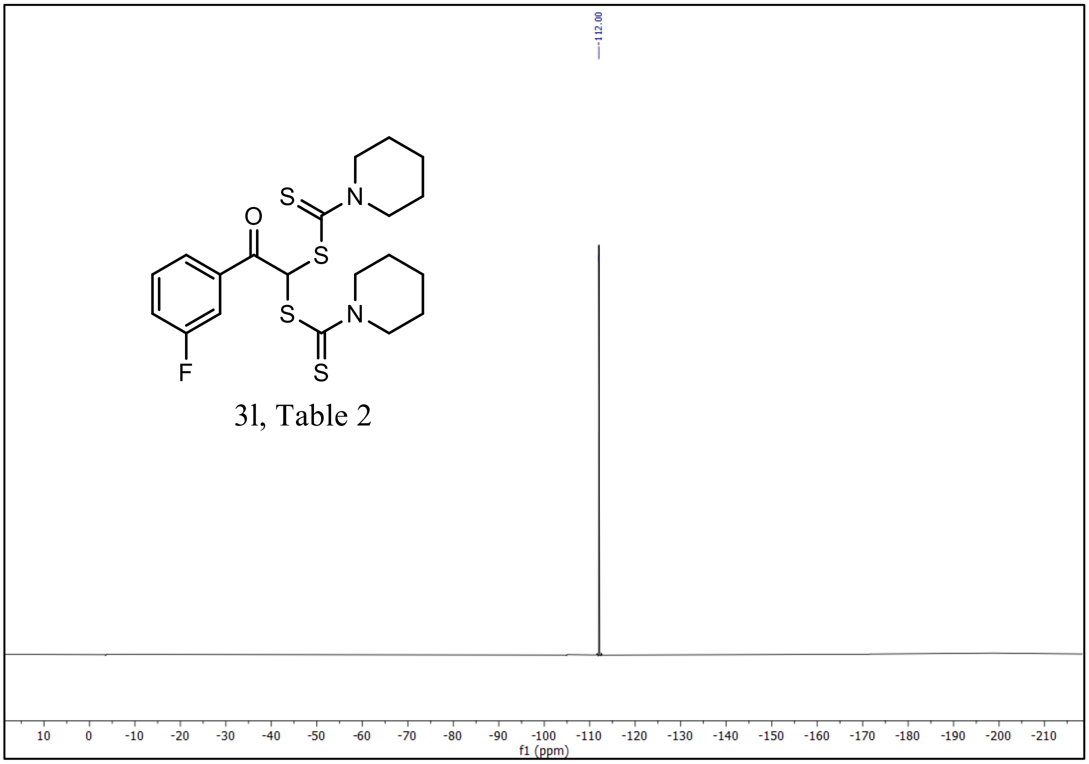


G. ^{19}F NMR spectra of fluorinated products (3j, 3k, 3l):


3j, Table 2

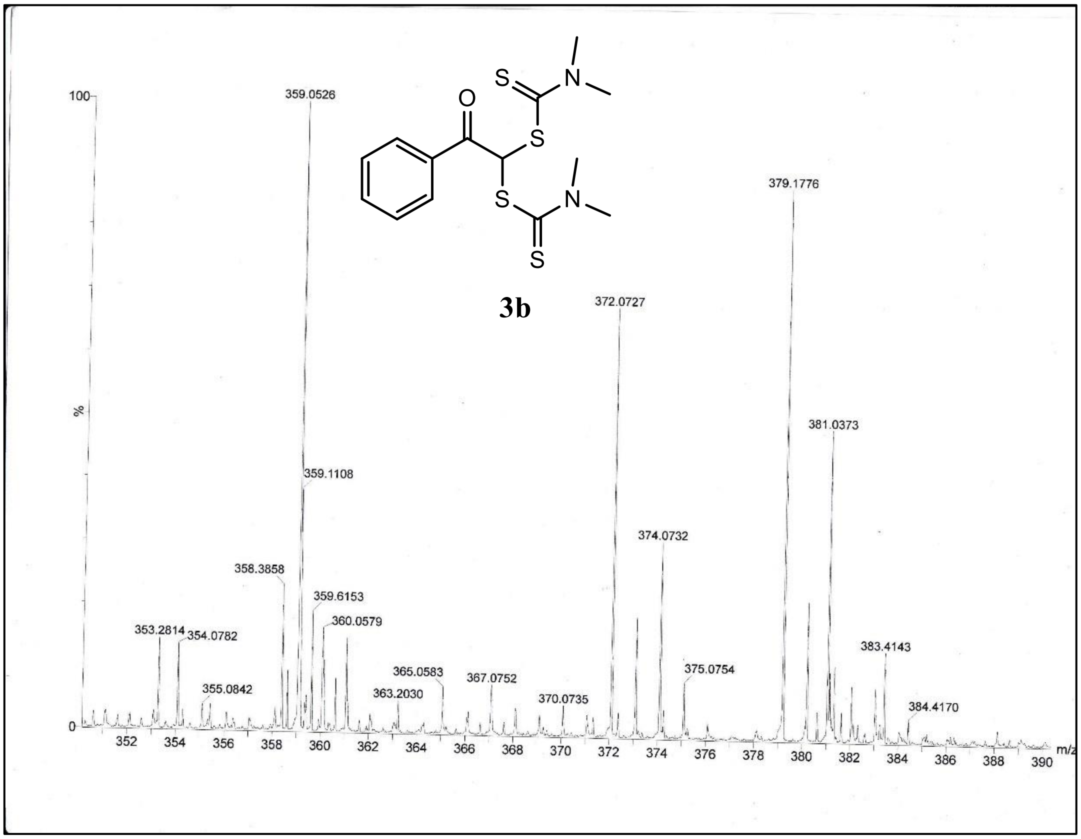


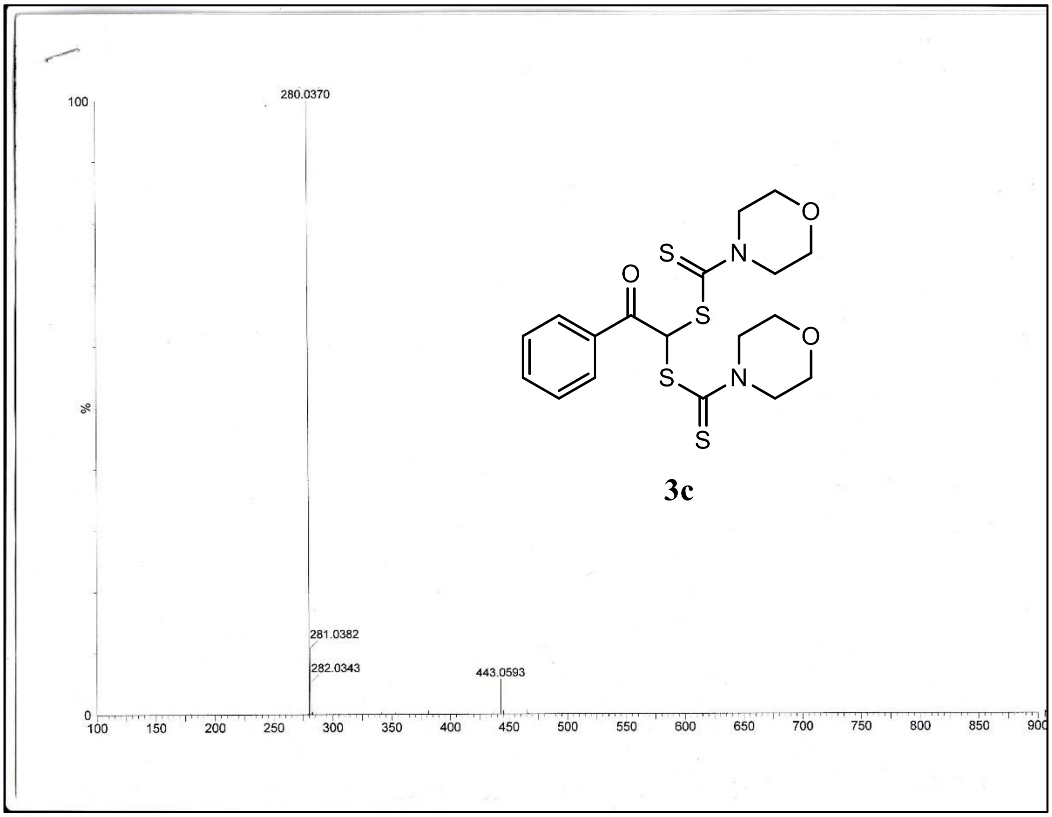
3k, Table 2



3l, Table 2

HRMS spectra of few selected products (3b, 3c, 3d, 3e, 3f, 3h, 3k, 3l, 3n, 3p, 3r):

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282.0343
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S
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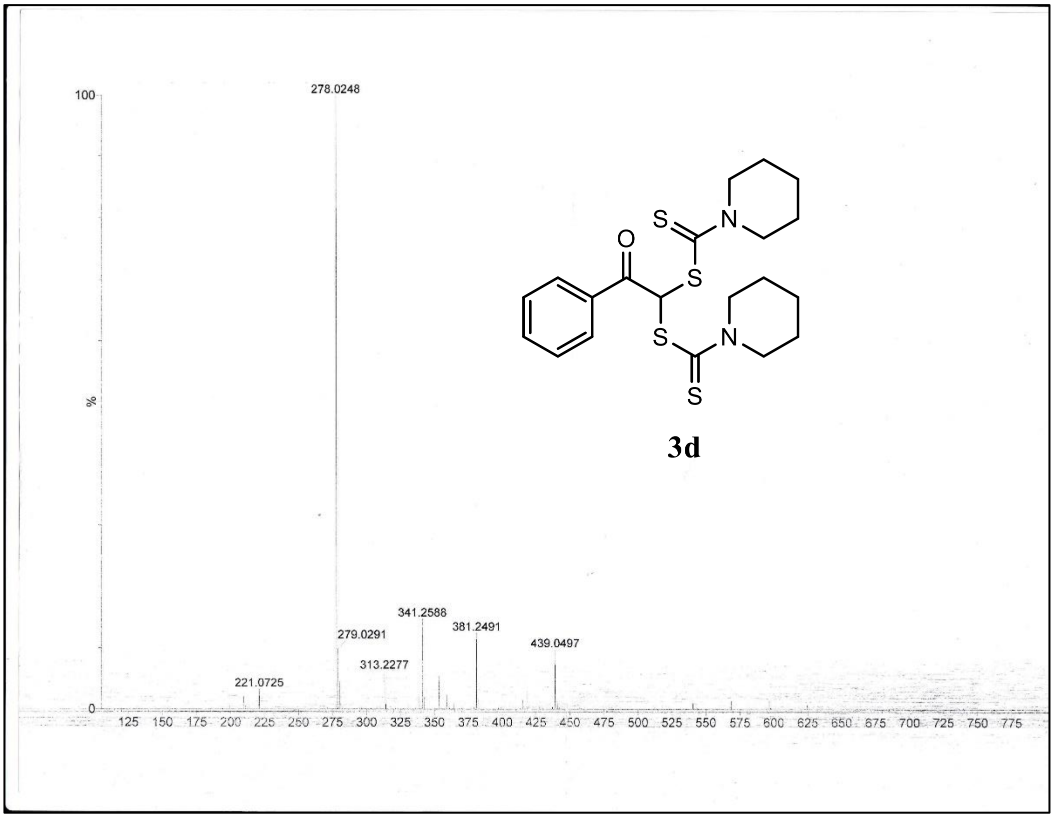
S
N
O
S
S

3c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%
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313.2277
341.2588
381.2491
439.0497
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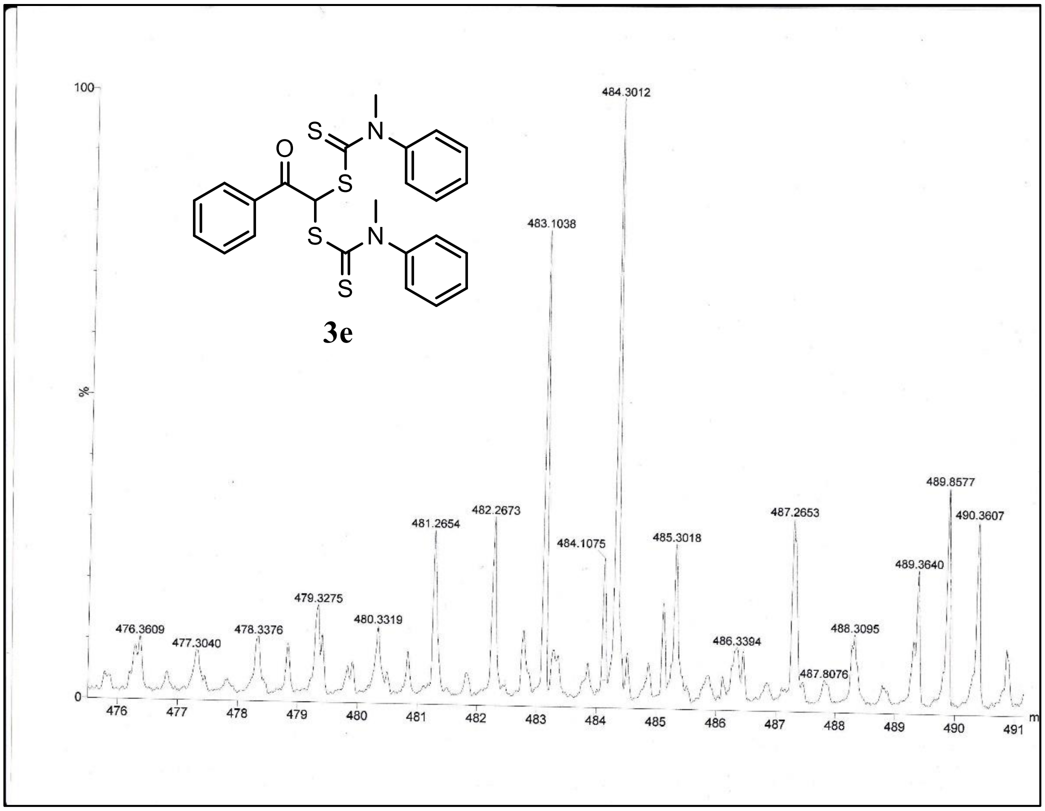
O
S
N
S
S
N
S

3d



3e

100
%
0
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489.3640
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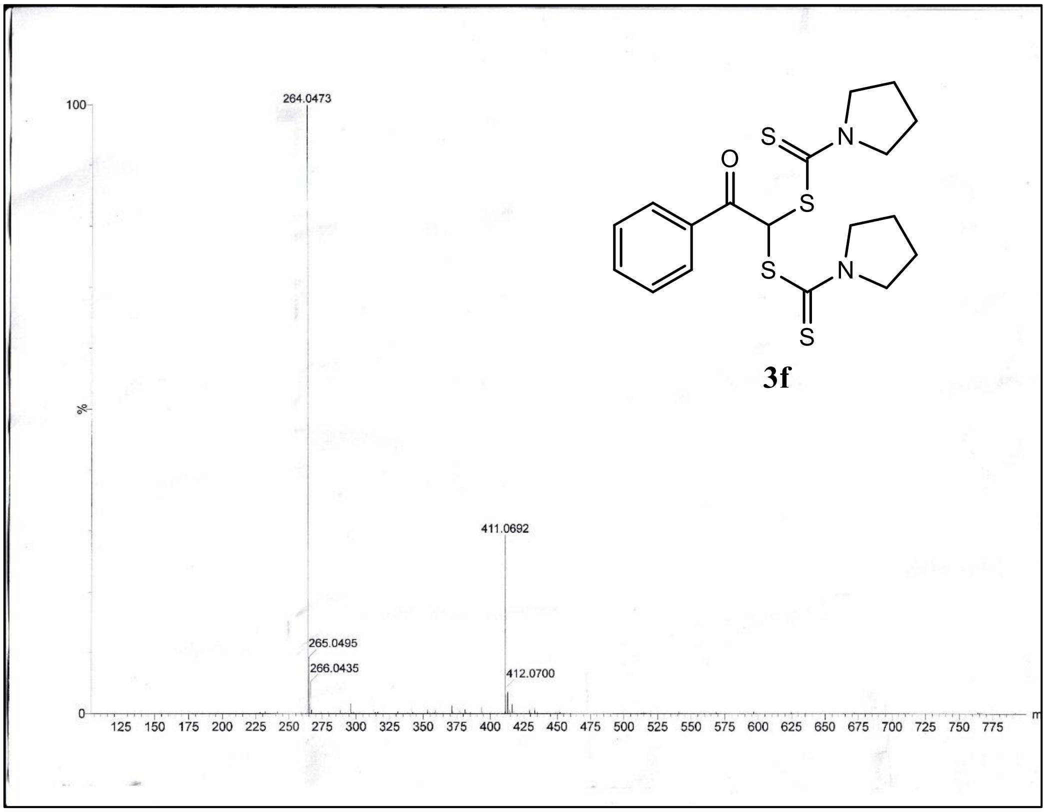

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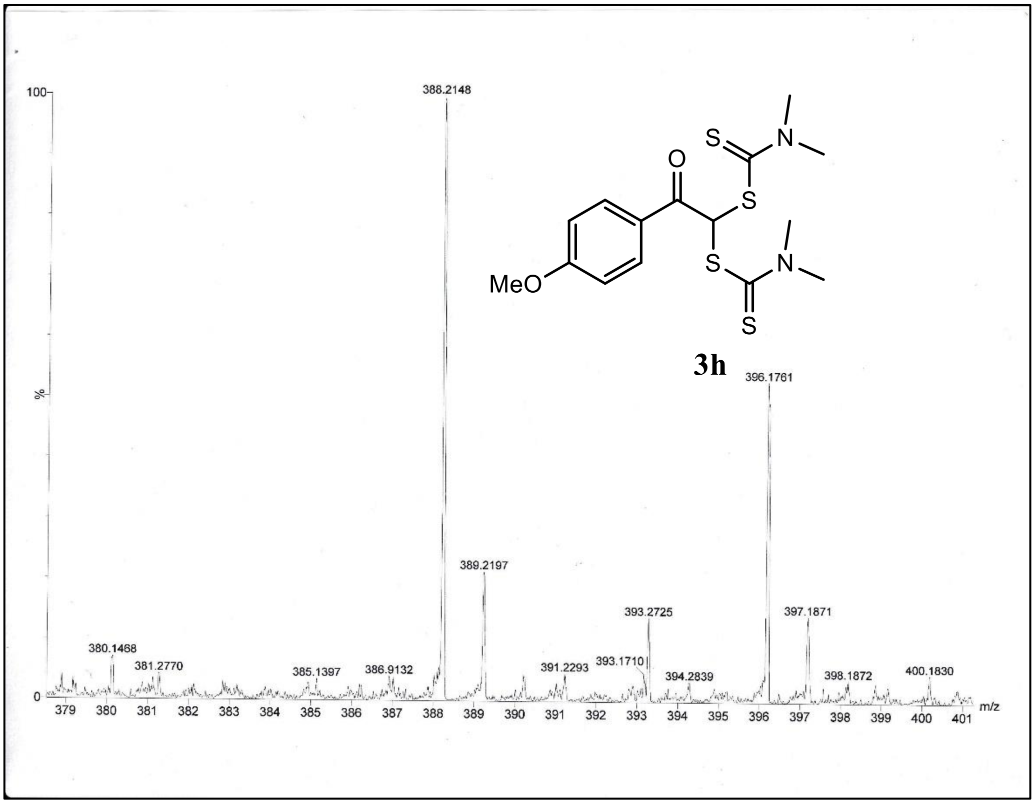
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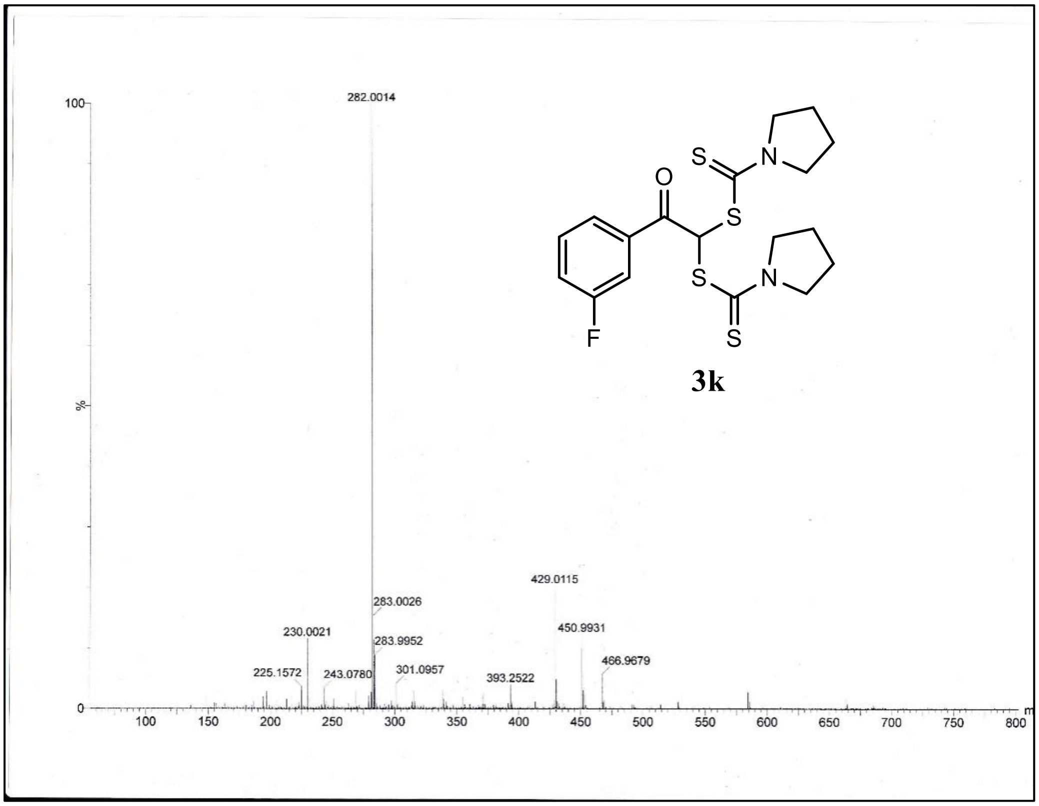
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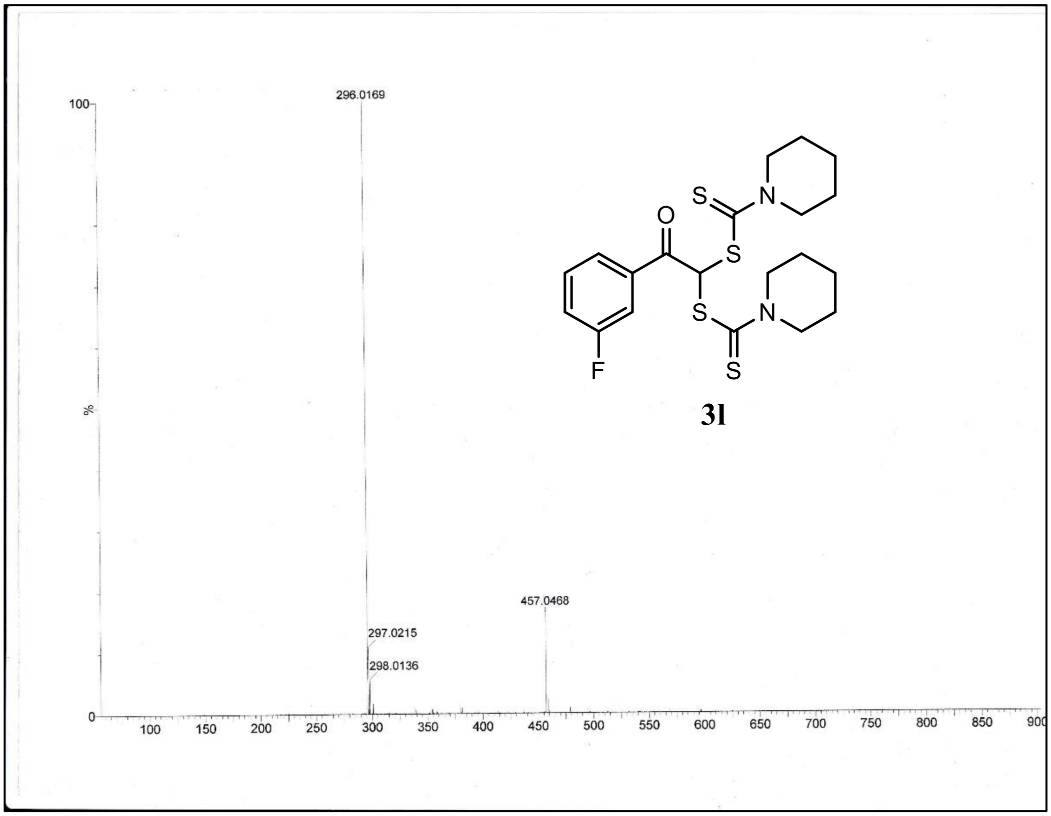
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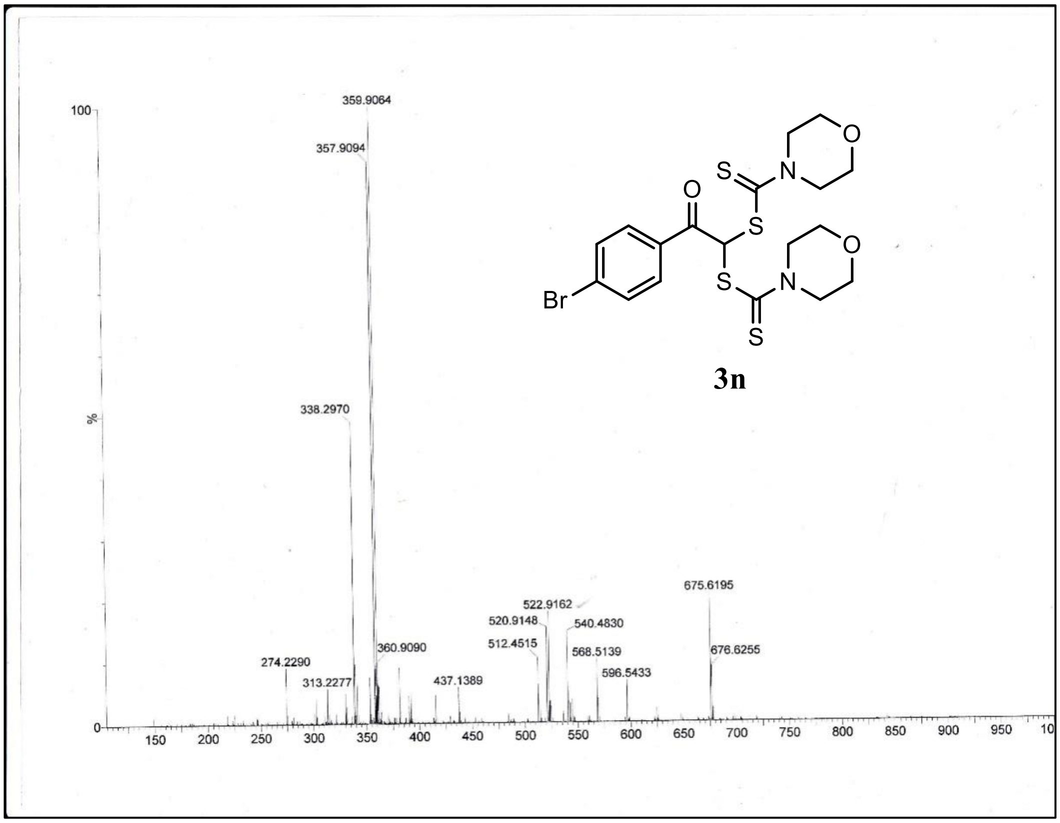
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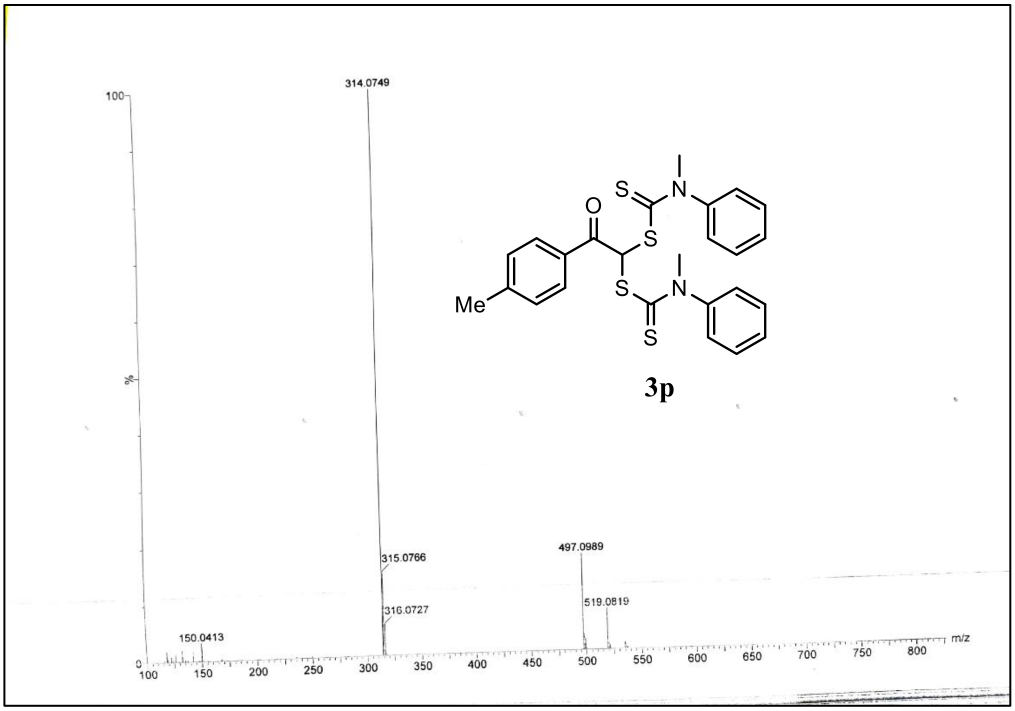
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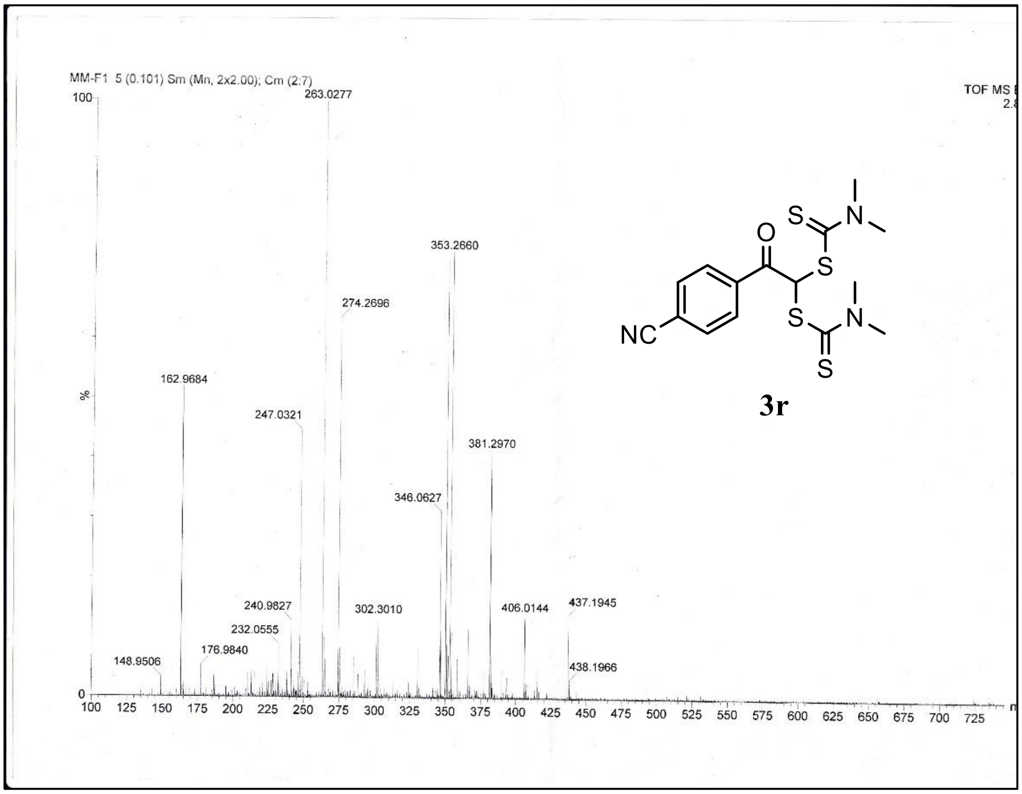
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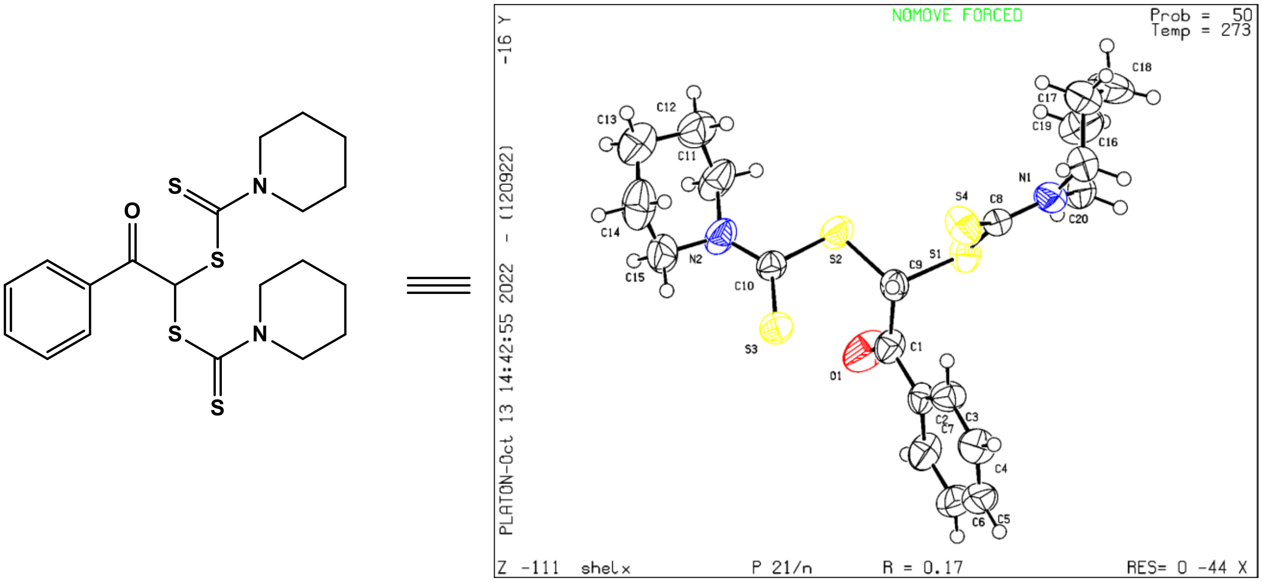
I. X-ray Crystallography Data:

Fig. 1. ORTEP diagram of the crystal structure of **3d** at 50% probability level



Details of the crystal structure investigation can be obtained from the Cambridge crystallographic data centre, 12 Union Road, Cambridge, CB2 1EZ, UK (3d: CCDC deposition no 2246557)

Crystallographic data and structural refinement parameters for 3d

Bondprecision: C-C=0.0154A Wavelength=0.71073

Cell: a=16.9533(15) b=7.7548(6) c=17.8906(15)

alpha=90 beta=110.685(2) gamma=90

Temperature: 273K

	Calculated	Reported
Volume	2200.5(3)	2200.4(3)
Spacegroup	P21/n	P21/n
Hallgroup	-P2yn	-P2yn
Moietyformula	C20H26N2OS4	?
Sumformula	C20H26N2OS4	C20H26N2OS4
Mr	438.67	438.67
Dx,gcm-3	1.324	1.324
Z	4	4
Mu(mm-1)	0.445	0.445
F000	928.0	928.0
F000’	930.23	
h,k,lmax	22,10,23	22,10,23
Nref	5062	4977
Tmin, Tmax		
Tmin		

Correctionmethod=Notgiven

Datacompleteness=0.983 Theta(max)=27.532

R(reflections)=0.1652(3887) WR2 (reflections) = 0.2800 (4977)

S=1.562 Npar=248

Gas chromatograms:

GC-MS data were collected from PerkinElmer Clarus SQ 8 C Mass spectrometer. Column specification (COL-Elite-5mS-30).

Experimental procedure of the preparation of GC-MS sample:

Br_2 (0.05 mL, 1 mmol) in MeCN (1 mL) was added drop-wise to the solution of phenylacetylene (0.1 ml, 1 mmol) in MeCN (2 mL) containing 0.04 mL of water at 5 ^{o}C. After complete addition, the reaction mixture was allowed to stir for 15 min at room temperature. Then, two drop of reaction mixture was taken in a vial and diluted with 2 ml acetonitrile solvent. This dilute reaction mixture was used for GC-MS analysis.

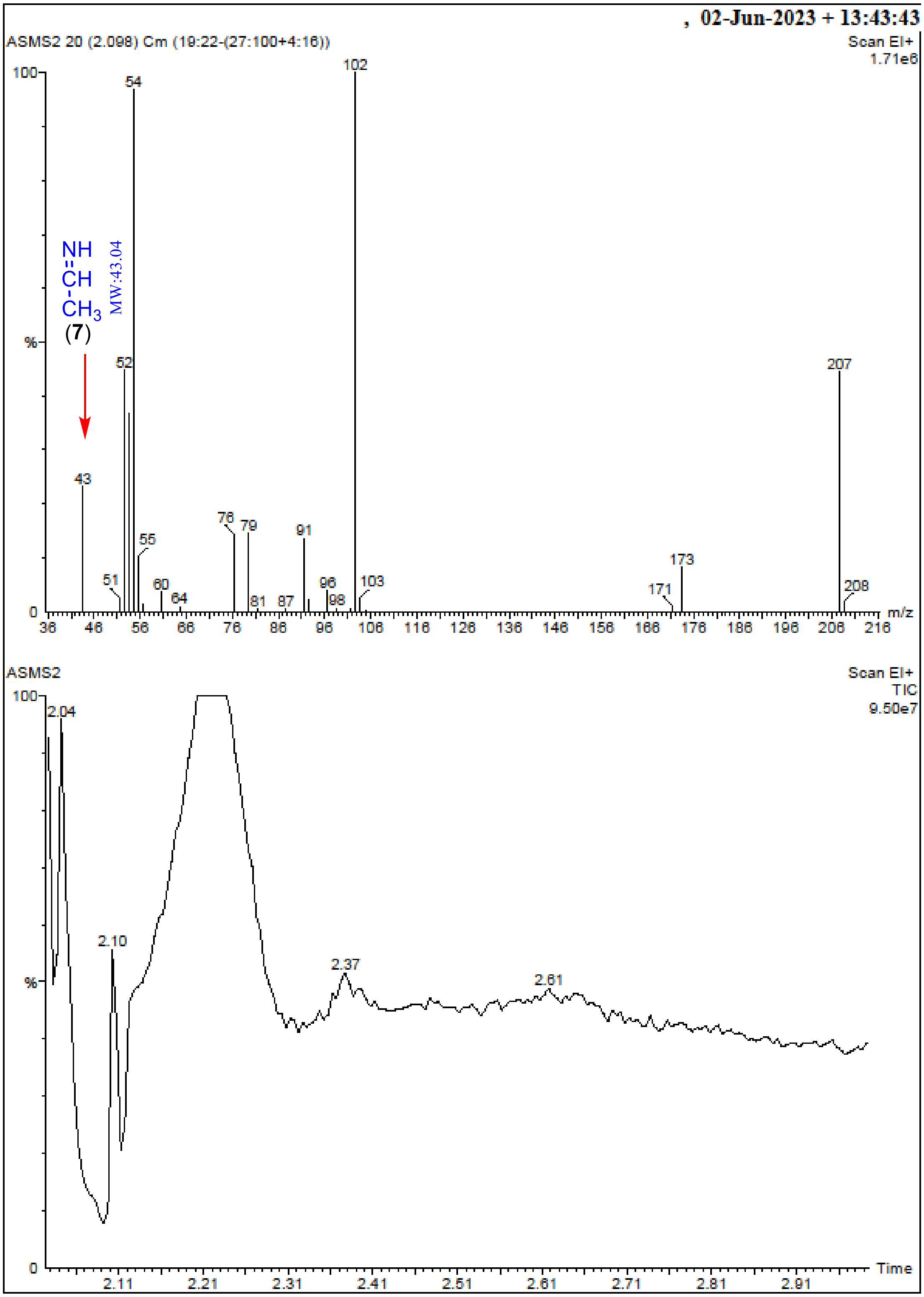


Fig. 2. GC spectrum of the reaction mixture described in Scheme **3a.**

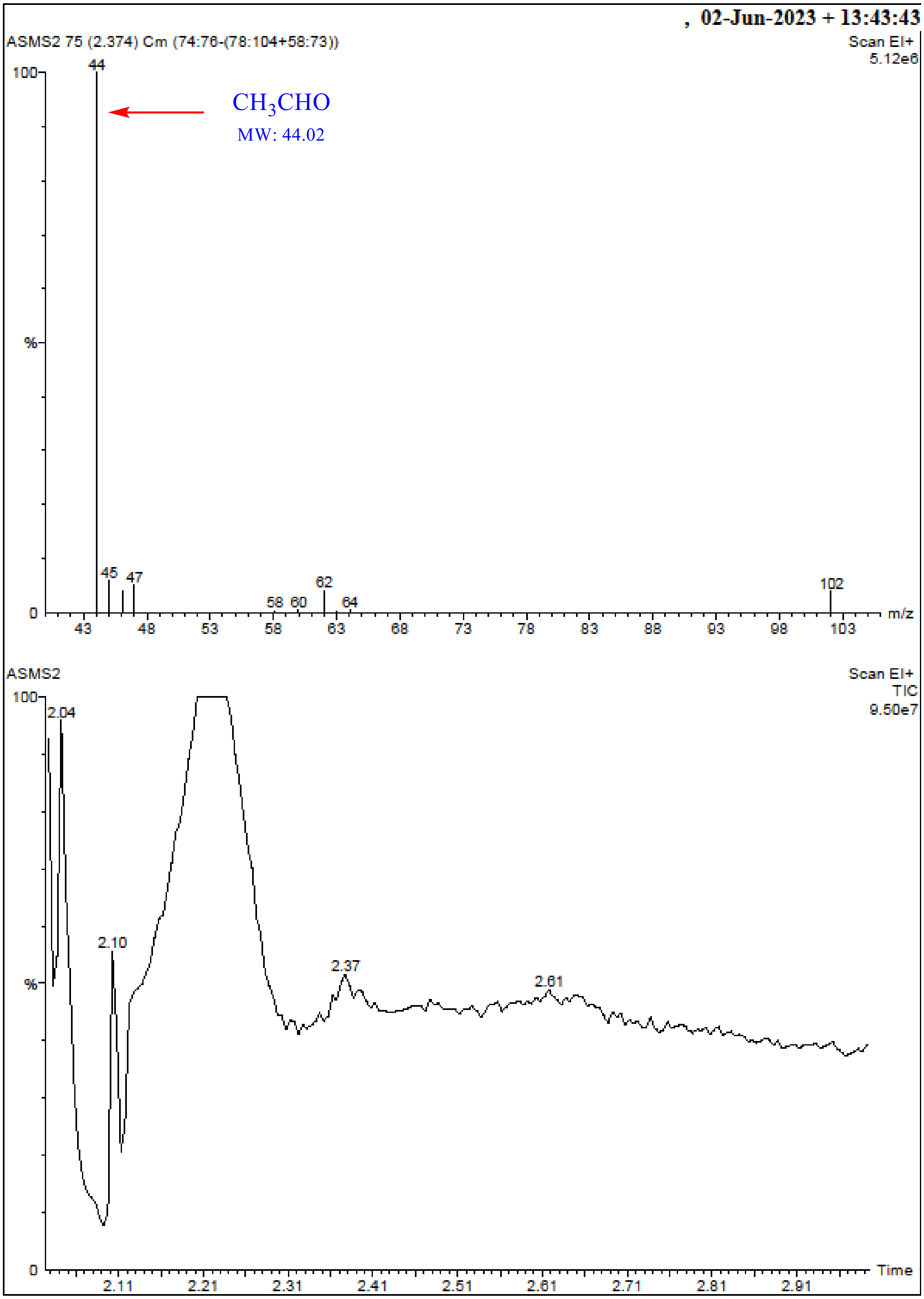


Fig. 3. GC spectrum of the reaction mixture described in Scheme 3a.

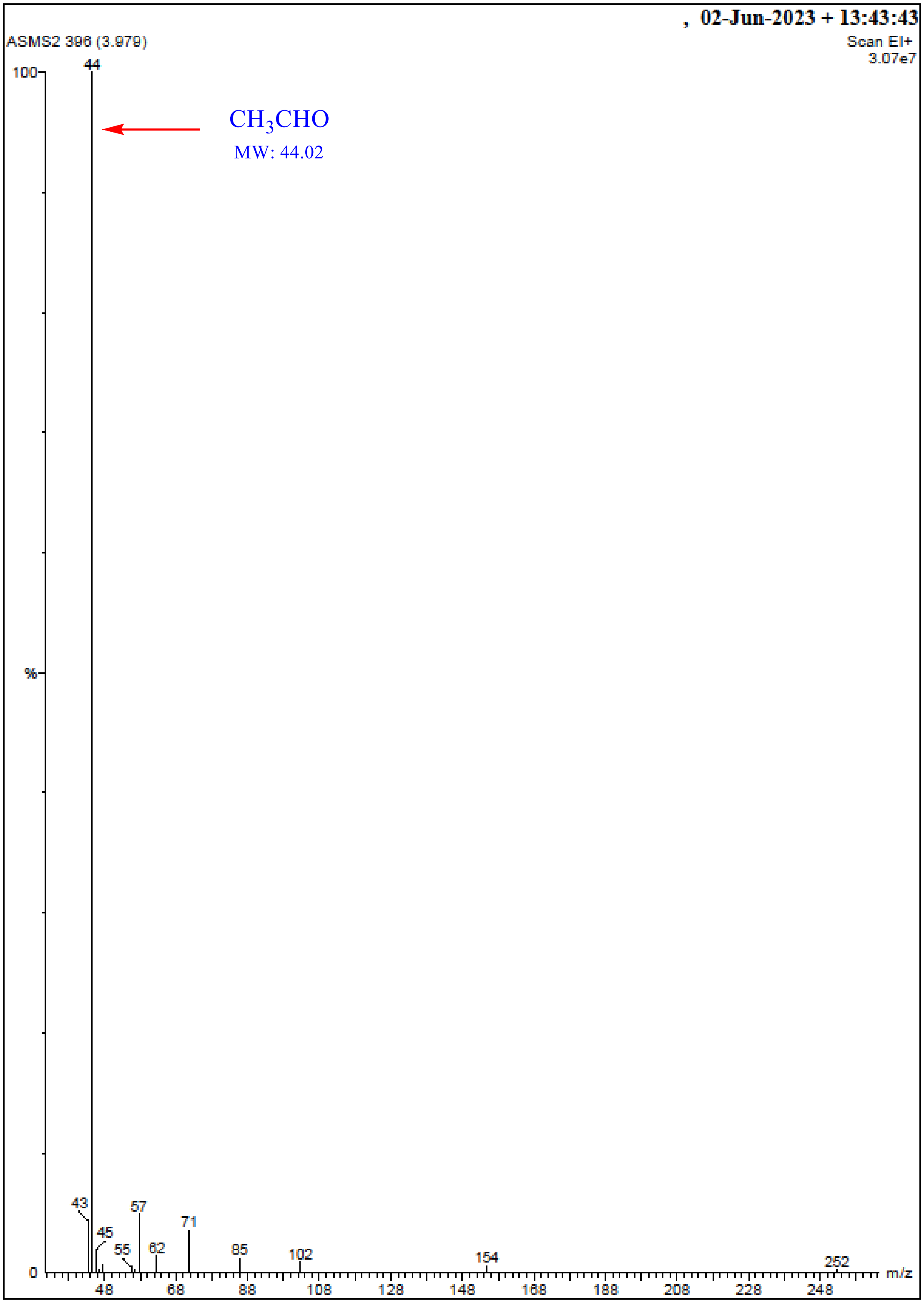


Fig. 4. GC spectrum of the reaction mixture described in Scheme **3a.**

2.3/f. References

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Chapter-III

Section-I

Synthetic application of Dithiocarbamate Compounds

3.1/a. Introduction

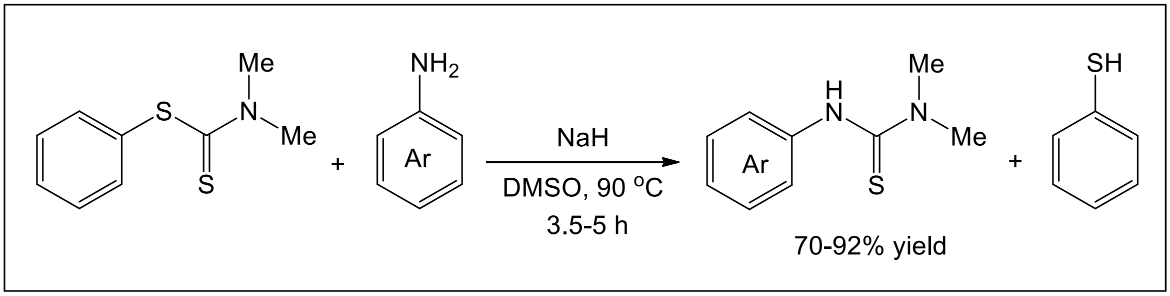
Dithiocarbamates represent a class of chemicals that have immense importance in several biomedical applications. Dithiocarbamate compounds[1] have already been linked to a number of pharmacological actions, including antiparasitic, antiviral, anticancer, antifungal, antimicrobial, antihistaminic, and antibacterial properties. The chemistry of transition-metal sulphide complexes[2] reflects its enormous importance as a ligand. They can suppress enzymatic activity and have a significant impact on biological systems due to their strong affinity for binding metals. Coordinating with heavy metals increases the biological activity of dithiocarbamates. Transition metals with a wide range of oxidation states can be stabilised by dithiocarbamate ligands. They also serve as effective ligands in the fields of nanomaterial chemistry[3] and surface science. Moreover, dithiocarbamates are crucial intermediates in a number of chemical transformation processes. Their application in the production of ionic liquids has also been found recently. [4] Catalytic application of dithiocarbamate has attracted lots of research attention. It has significant role for the synthesis of catalyst during organic synthesis as well as catalysts in polymerization. Magnetic dithiocarbamate has been coated on gold to functionalise core/shell nanostructures, which are then used as catalysts in the A^3 coupling reaction to synthesis propargyl amines. [5] Dithiocarbamate molecules have been useful in the synthesis of metal chalcogenides and organic intermediates. Lactam containing dithiocarbamates formed from light-catalyzed reaction of dithiocarbamates in cyclohexane or chlorobenzene solvent. Due to highly poisonous nature of cyanogen halide, researchers have faced significant difficulties in the synthesis of cyanamide, which is important intermediate for the production of medicinal molecules. Now, the synthesis is done in a "greener" manner by employing dithiocarbamate. Thiourea is another intermediate that was synthesized by using dithiocarbamate, this protocol eliminated the requirement for hazardous chemicals like hydrogen sulphide and thiophosgene. [6] Through a three-step process involving iodocyclization, dehydrohalogenation, and nucleophilic substitution processes, thiazolidine-2-thiones have also been synthesised from dithiocarbamate. [7] Utilising dithiocarbamate molecule as the starting material various amides have been synthesized as well.[8] Another important compound 1,3,4-thiadiazoles have also been synthesized by the reaction of acid hydrazides with *S*-alkyl dithiocarbamates. [9] Diaryl sulfide have been synthesized from *S*-alkyl dithiocarbamates without using any thiol compound.

3.1/b. Review

Primarily, chemists have focused on the synthesis of dithiocarbamate derivatives due to their ubiquitous applications and as a result of that, a large number of synthetic methodologies leading to dithiocarbamate scaffolds have been developed but later, their prime interest has been shifted to explore the synthetic applications of dithiocarbamates which ultimately results the accomplishment of several organic transformations to produce useful organic molecules. Over the past 20 years, there has been a noticeable advancement in the chemistry of many dithiocarbamate-related reactions. This short review demonstrates various synthetic applications of dithiocarbamate compounds. Some relevant examples of reactions have been depicted here.

(I) Synthesis of 1,1-dimethyl-3-arylthioureas:

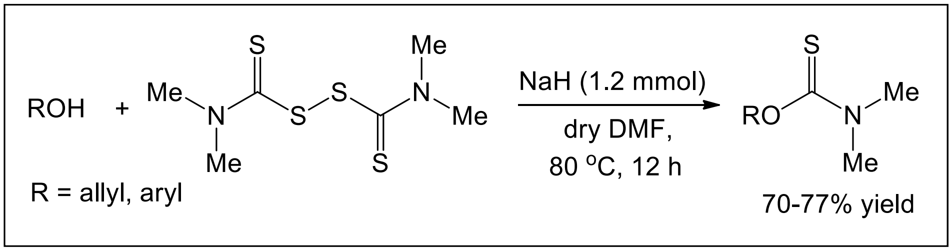
Dong et al[10] synthesized 1,1-dimethyl-3-arylthioureas in moderate to good yields from the reaction of *S*-aryl-*N,N*-dimethylthiocarbamate and arylamines in presence of sodium hydride and DMSO at 90 °C (Scheme 3.1.01). All type of aromatic amine including sterically hindered also produced desired product along with by product thiophenol.



Scheme 3.1.01

(II) Synthesis of *O*-aryl (alkyl) *N,N*-dimethylthiocarbamates:

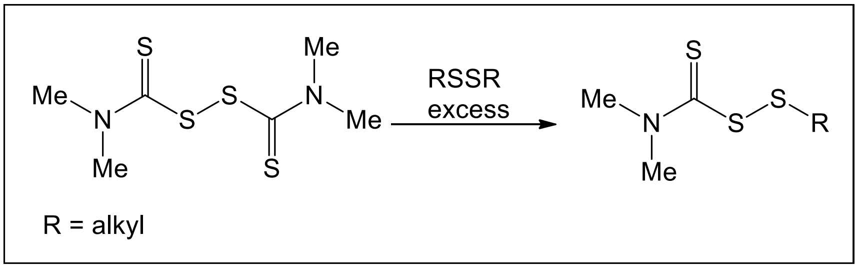
By reacting economical, stable, and environmentally benign tetramethylthiuram disulphide (TMTD) in the presence of NaH, a series of *O*-aryl (alkyl) *N,N*-dimethylthiocarbamates were synthesised in good yields (70–77%) (Scheme 3.1.02). [11] Additionally, the procedure might be used with aliphatic alcohols as well. The method offers a simple and environmentally friendly way to prepare several significant precursors of chemicals that may be physiologically reactive, without using the hazardous and caustic *N,N*-dialkylthiocarbamoyl chloride.



Scheme 3.1.02

(III) Synthesis of alkyl dimethylthiocarbamoyldisulphides:

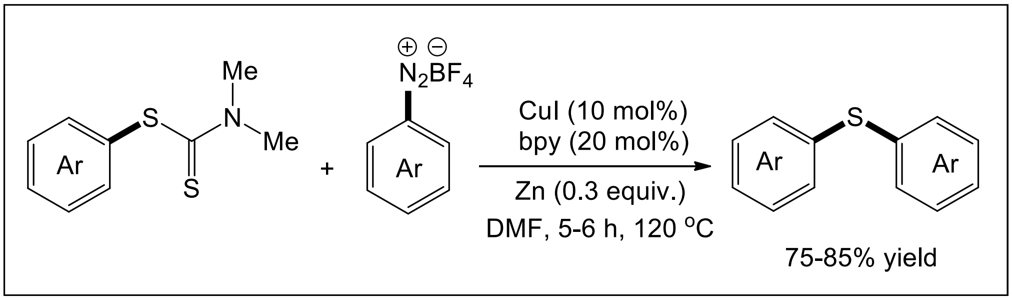
Klemain have synthesized alkyl dimethylthiocarbamoyldisulphides by a disproportionation reaction of tetramethylthiuram disulphide with a large excess of dialkyl disulphide (Scheme 3.1.03). [12]



Scheme 3.1.03

(IV) Preparation of unsymmetric diaryl sulfides:

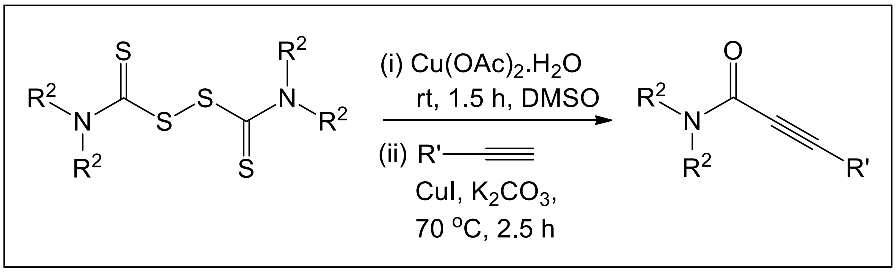
Dutta *et. al.*[13] have been developed a general and convenient CuI-catalyzed one-pot synthetic route to prepare diaryl sulfides from aryldithiocarbamates and aryldiazonium salts. Synthesis of unsymmetric diaryl sulfides can be achieved very easily by using such protocol. Protocol offers a simple one-pot operation, broad substrate scope and good isolated yields of products.



Scheme 3.1.04

(V) Carbon monoxide-free aminocarbonylation of terminal alkynes:

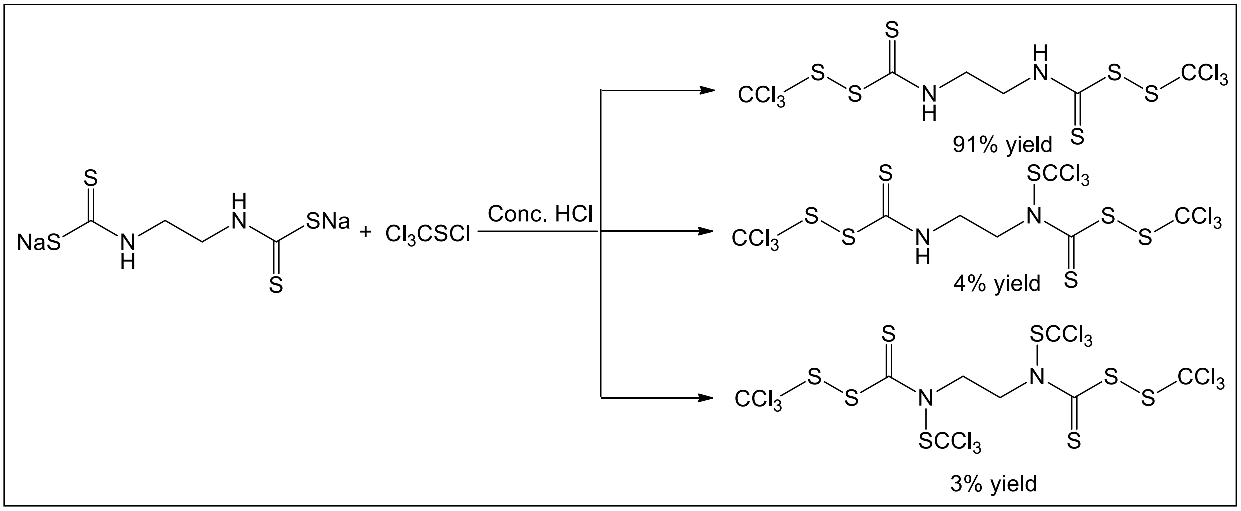
Saha and his team[14] have demonstrated a convenient protocol for carbon monoxide-free aminocarbonylation of terminal alkynes. In this amidation technique, the carbamoyl moiety is provided by thiuram disulphide, an air-stable crystalline solid organic molecule. With the use of a catalyst, inexpensive Cu-based reagent, and readily accessible starting materials, a variety of alkynyl amides have been produced. Using XRD analysis, the mixed disulphide reaction intermediate has been identified and isolated. The aminocarbonylation of terminal alkynes by thiuram disulphide has never been reported before.



Scheme 3.1.05

(VI) Synthesis of bis(trichloromethyl)ethylenebistrithiopercarbamate:

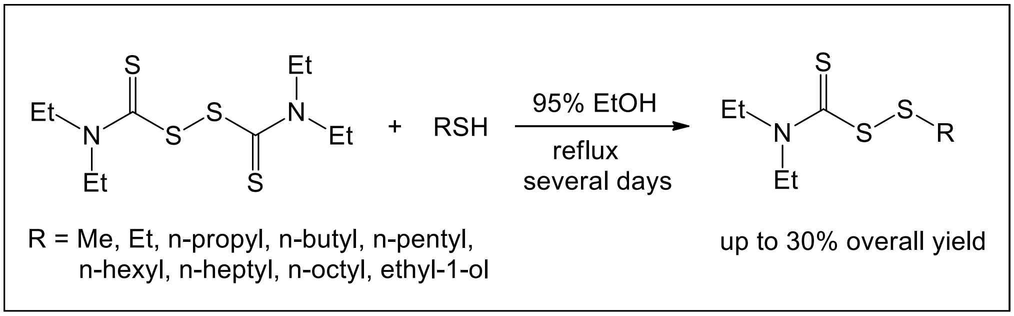
H. L. Klopping developed a convenient protocol to prepare a complex mixture of solid materials by the reaction of disodiumethylenebisdithiocarbamate and trichloromethanesulfenyl chloride in presence of concentrated hydrochloric acid using water as a solvent. During such reaction bis(trichloromethyl)ethylenebistrithiopercarbamate was formed in major amount (91%) along with the formation of other by-product (Scheme 3.1.06). [15]



Scheme 3.1.06

(VII) Synthesis of alkyl thiocarbamoyl disulphide derivatives:

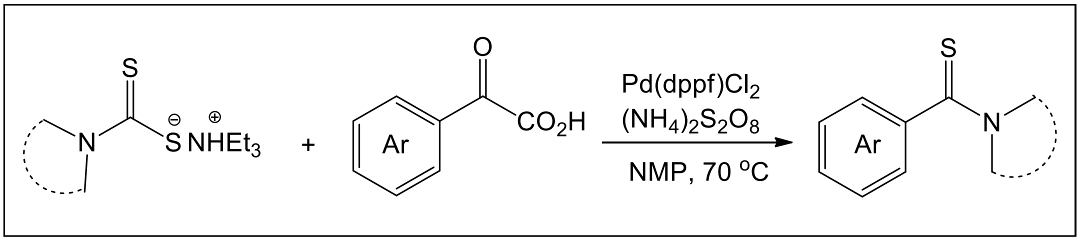
Pietruszko and his team synthesized a series of alkyl thiocarbamoyl disulphide derivatives by the reaction of tetraethyldisulfuram and alkyl thiol in ethanol as solvent under refluxing condition for several days. Overall yields of the products were quite less (up to 20-30%).



Scheme 3.1.07

(VIII) Synthesis of thioamide from Arylglyoxylic acids:

Arylglyoxylic acids have been employed in a novel decarboxylative–decarbonylative thioamidation reaction with dithiocarbamate intermediates prepared in situ by the prompt reaction of amines and carbon disulfide. A series of thioamide compounds were synthesized using different arylglyoxylic acids, various secondary amines, a primary amine, aniline, and an amino acid derivative (Scheme 2.1.33). [16]



Scheme 3.1.08

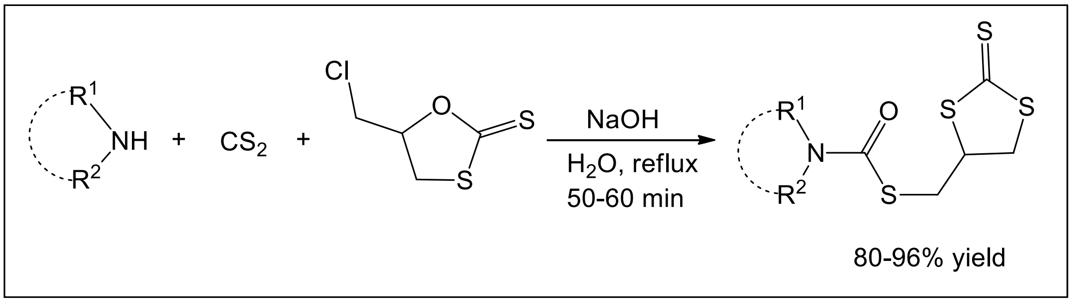
(IX) Synthesis of thioamide from different substrate:

Dithiocarbamate salts have been explored in a novel C–C thioamidation of styrene in the presence of ammonium persulfate and molecular oxygen. A series of thioamide compounds with different structural variations have been prepared in good yields (Scheme 2.34). [17] Various cyclic/acyclic secondary amine, aromatic amine, benzylamine and amino acid based thioamides have been prepared following the protocol. The protocol has further been applied to decarbonylative thioamidation of benzaldehyde and toluene and decarboxylative thioamidation of benzoic acid. The reaction mechanism has been proposed by isolation of the reaction intermediate and GC-MS analysis of the reaction mixture. The post-synthetic potential of the synthesized thioamide has been checked through a C–C cross-coupling reaction *via* C–N bond cleavage.

Scheme 3.1.09

(X) Synthesis of *S*-(2-thioxo-1-dithiolan-4-yl)methyldialkylcarbamodithioates:

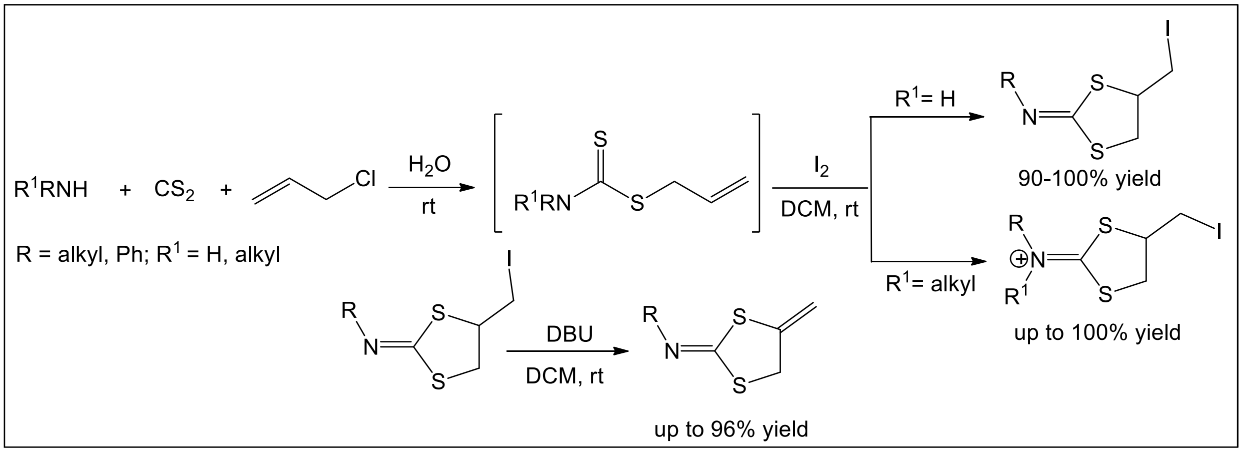
Sharma et al[18] introduced a novel synthetic protocol to preparation of *S*-(2-thioxo-1,-dithiolan-4-yl)methyldialkylcarbamodithioates by the reaction of 5-(chloromethyl)-1,3-oxathiolane-2-thione and in situ generated dithiocarbamate salt. All reactions were carried out in aqueous solvent medium. And yield of the reaction was very good.



Scheme 3.1.10

(XI) Iodocyclization of *S*-allyl dithiocarbamates derivatives:

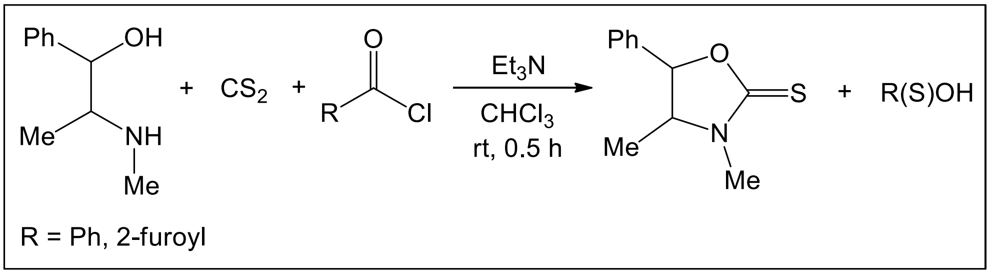
After undergoing an iodocyclization reaction in dichloromethane solvent at room temperature, *S*-allyl dithiocarbamates, which were produced in situ by the reaction of different primary or secondary amines, carbon disulphide, and allyl chloride, produced the desired 4-alkyl-2-imino-1,3-dithiolanes and 4-alkyl-2-iminium-1,3-dithiolanes. 2-imino-4-methylidene-1,3-dithiolanes derivatives were obtained by dehydrohalogenation of 2-imino-1,3-dithiolanes in presence of DBU (Scheme 2.1.12). [19]



Scheme 3.1.11

(XII) Heterocyclization of benzoyl chloride or 2-furoyl chloride:

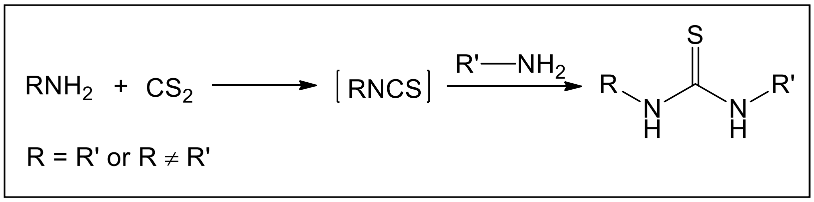
Nurkenov and his co-workers developed a synthetic protocol to prepare 3,4-dimethyl-5-phenyl-1,3-oxazolidine-2-thione by heterocyclization of benzoyl chloride or 2-furoyl chloride with in situ generated dithiocarbamate salts (Scheme 3.1.12). [20]



Scheme 3.1.12

(XIII) Preparation of substituted thiourea derivatives:

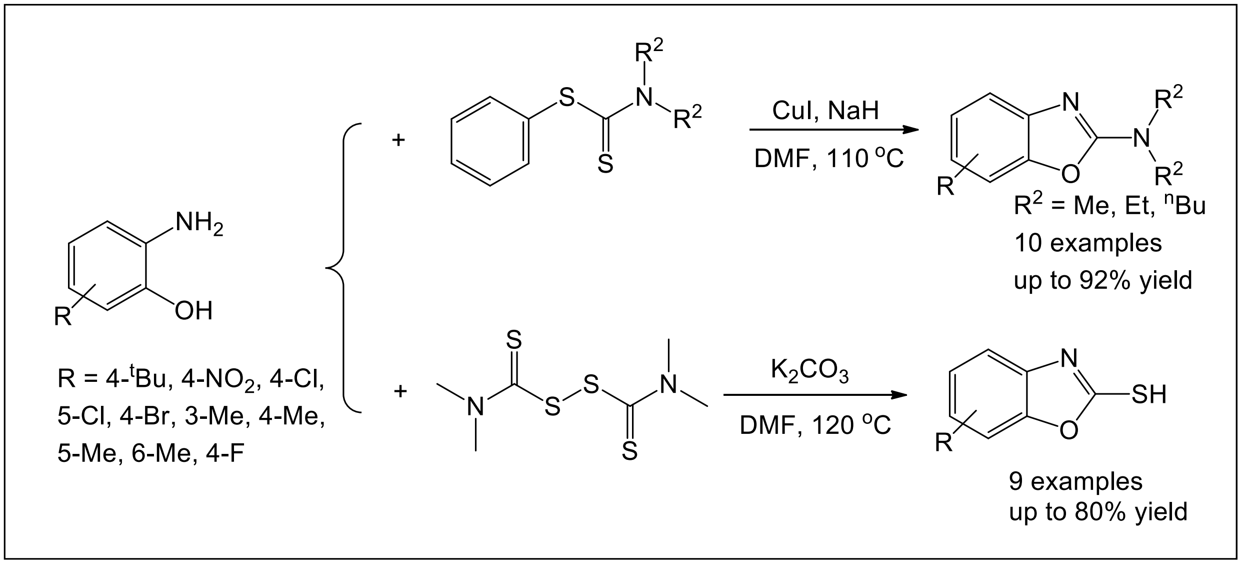
Di/tri/tetra substituted thiourea derivatives were synthesized by the reaction of primary or secondary amine (aliphatic or aromatic) and carbon disulfide under various condition.



Scheme 3.1.13

(XIV) Synthesis of 2-aminobenzoxazoles and 2-mercaptobenzoxazoles:

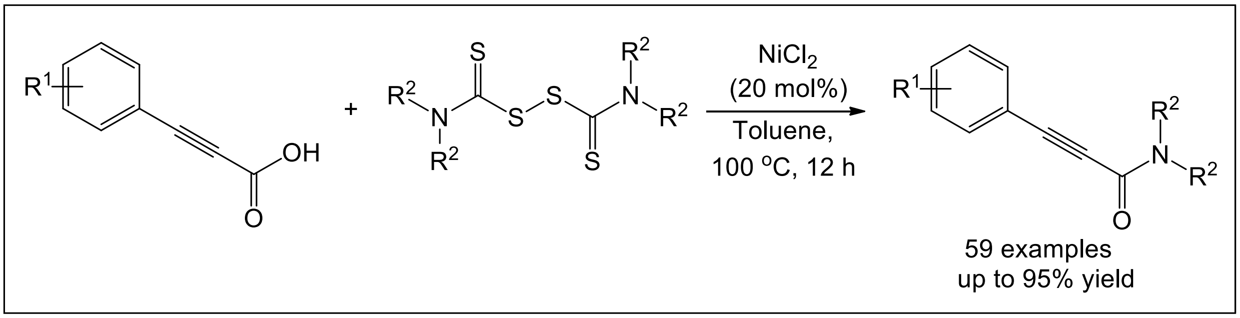
Dithiocarbamates and tetramethylthiuram disulphide (TMTD) were used to treat aminophenols in order to preferentially synthesise 2-aminobenzoxazoles and 2-mercaptobenzoxazoles, respectively. When NaH/CuI was promoted, o-aminophenols reacted with dithiocarbamates to produce 2-aminobenzoxazoles with a good yield (70–92%) in a one-pot method. When *o*-aminophenols were treated with tetramethylthiuram disulphide (TMTD), 2-mercaptobenzoxazoles were synthesised (yield: 55–80%) in the presence of K_2CO_3. This methodology[21] is feasible and appealing for the synthesis of various possible pharmaceutically active compounds due to its features, which include good to outstanding yield, facile performance, and broad substrate scope.



Scheme 3.1.14

(XV) Nickel-catalyzed amidation of aryl alkynyl acids using tetraalkylthiuram disulphides as the amine source:

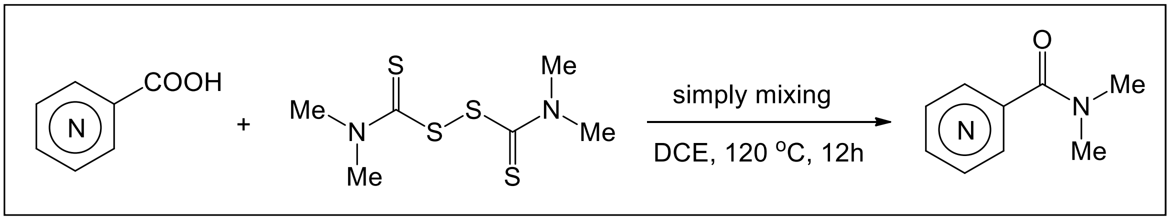
A series of aryl alkynyl amides were produced in good to exceptional yields under mild circumstances by nickel-catalyzed amidation of aryl alkynyl acids using tetraalkylthiuram disulphides as the amine source. This broad methodology provides[22] synthetic utility in organic synthesis by offering an alternate pathway for the synthesis of important aryl alkynyl amides in an operationally straightforward manner. This transformation's mechanism was investigated by DFT calculations and control experiments.



Scheme 3.1.15

(XVI) Amidation reaction of quinoline-3-carboxylic acids:

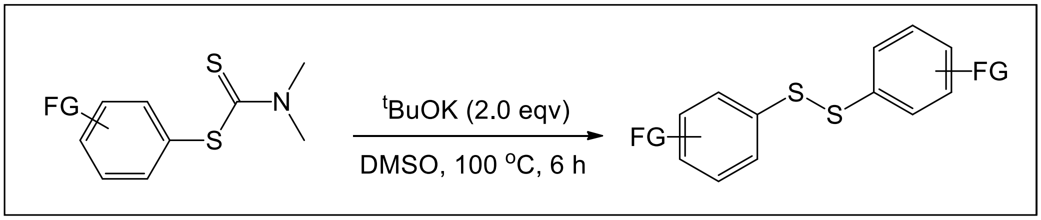
The amidation reaction of quinoline-3-carboxylic acids with tetraalkylthiuram disulphides has been developed into a highly efficient and straightforward process for the synthesis of quinoline-3-carboxamides and their equivalents. The reaction provides a broad scope of substrates with good yields (Scheme 3.1.16)[23] and proceeds well under straightforward reaction conditions.



Scheme 3.1.16

(XVII) Synthesis of symmetric diaryl disulphides from phenyl dimethylcarbamodithioates:

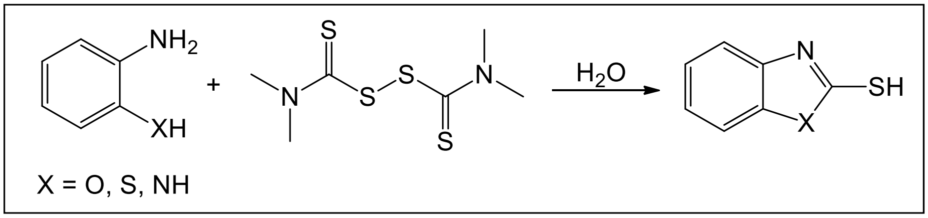
A novel synthesis procedure was synthesized to yield a range of symmetric diaryl disulphides from odourless, readily accessible phenyl dimethylcarbamodithioates. The target compounds were obtained easily through straightforward hydrolysis, yielding a succession of symmetric diaryl disulphides, by using phenyl dimethylcarbamodithioates as an organosulfur source. This protocol[24] offers a high yield, odourless and readily available organosulfur feedstock, and easy operation.



Scheme 3.1.17

(XVIII) Synthesis of benzothiazole-2-thiols, benzoxazole-2-thiols, and benzimidazoline-2-thiones:

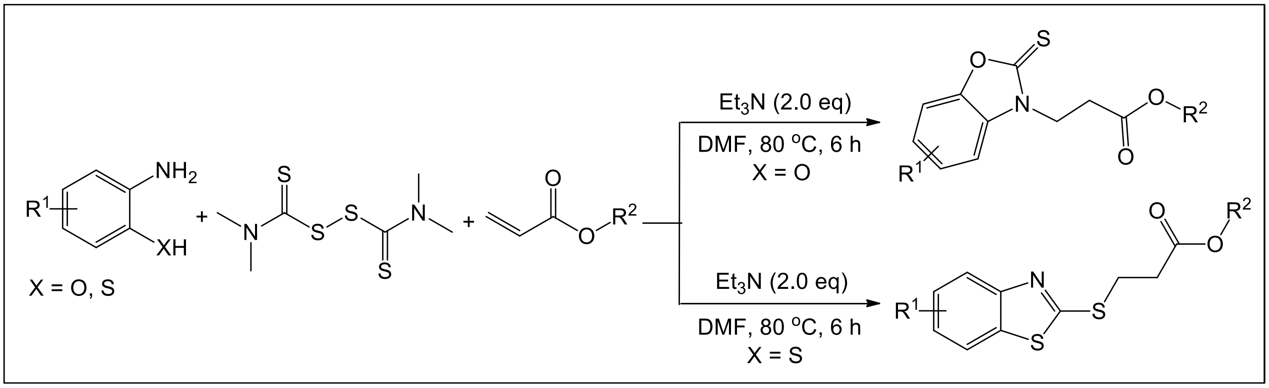
The cyclisation of 2-aminothiophenols, 2-aminophenols, and 1,2-phenylenediamines with tetramethylthiuram disulphide (TMTD) in water was reported as an effective and feasible approach for the one-step synthesis of benzothiazole-2-thiols, benzoxazole-2-thiols, and benzimidazoline-2-thiones. This approach has a wide range of substrate compatibility, is metal/ligand free, produces great yields, and requires little reaction time. The technique[25] makes it easy and convenient to prepare a few chemicals that may have biological activity.



Scheme 3.1.18

(XIX) Synthesis of benzoxazole/benzothiazole-substituted esters:

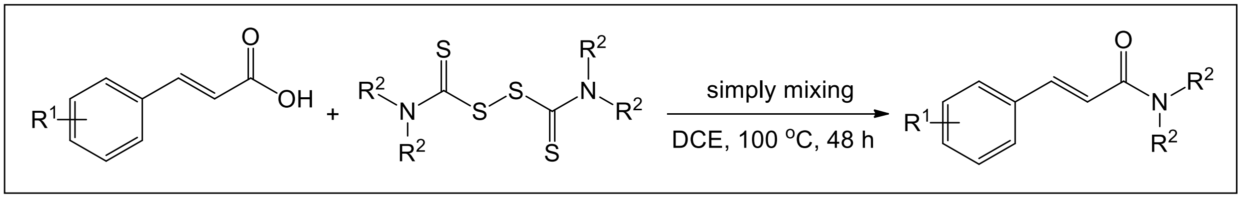
A one-pot method for the efficient and practical synthesis of benzoxazole/benzothiazole-substituted esters is described. In this study, C-N and C-S bonds are selectively constructed using basic addition. Thus, C-N and C-S bonds can be selectively generated by means of the Michael addition process, using substituted 2-aminophenols/2-aminobenzenethiols, TMTD (tetramethylthiuram disulphide), and *α,β*-unsaturated esters as starting substrates. With its great atomic economy, strong functional tolerance, gentle conditions, good selectivity, and good to exceptional yields, this approach[26] has the potential to be useful for the synthesis of various physiologically and pharmaceutically active molecules.



Scheme 3.1.19

(XX) Synthesis of cinnamides:

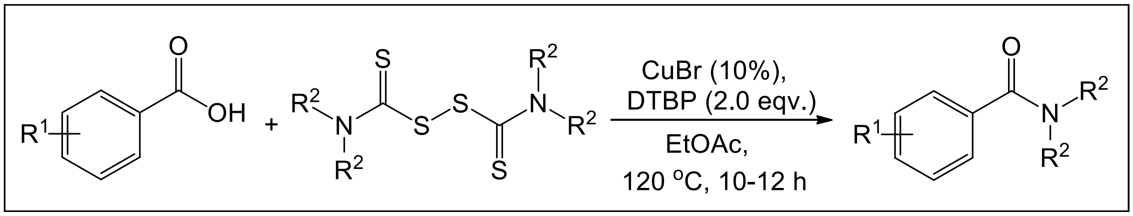
A simple and effective protocol to synthesise cinnamides without using any metals or additives has been developed by Miao Lai and his team. [27] With this approach, several cinnamic acids effectively coupled with tetraalkylthiuram disulphides by simply combining them in 1,2-dichloroethane at 100 °C. Its broad substrate scope and easily accessible starting materials demonstrate the protocol's practical synthetic usefulness in organic synthesis. It also offers a direct path to cinnamides (Scheme 3.1.20).



Scheme 3.1.20

(XXI) Synthesis of *N*-substituted benzamides:

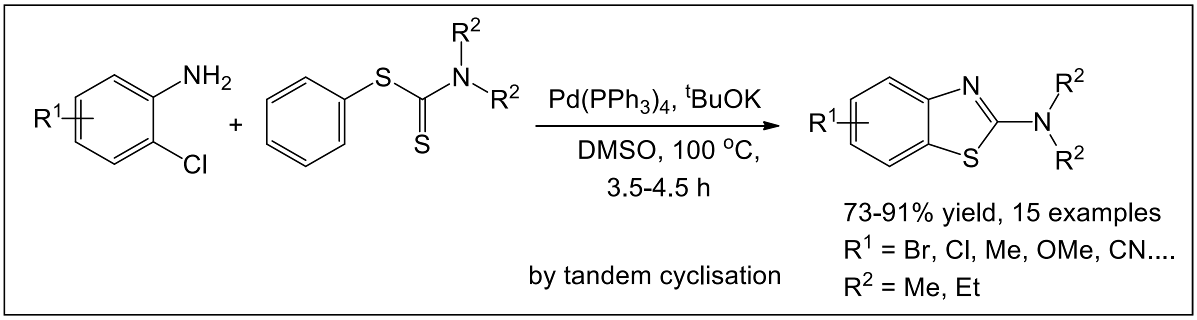
A facile method for the copper-catalyzed synthesis of *N*-substituted benzamides was developed by Meng-Tiang Jeng and his team. [28] Tetraalkylthiuram disulphides, which are readily accessible and reasonably priced, were used as amine sources to facilitate the preparation of several *N*-substituted benzamides by amiminating benzoic acid in the presence of CuBr and di-tert-butyl peroxide. This technique produced a good to outstanding yield of a series of *N*-substituted benzamides. Its usefulness in organic synthesis is demonstrated by its good to outstanding yield and wide range of substrates.



Scheme 3.1.21

(XXII) Synthesis of a series of 2-aminobenzothiazoles:

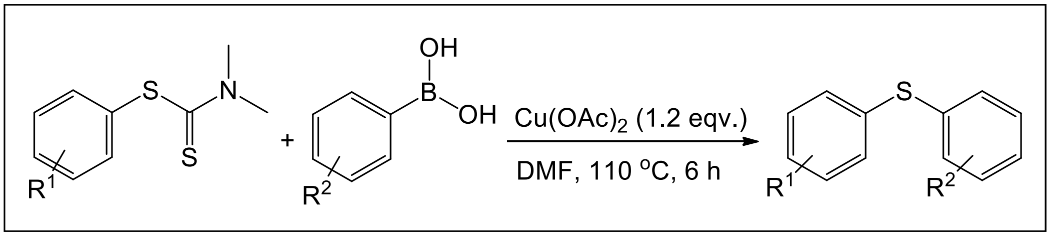
Using 2-chloroanilines and dithiocarbamates in a tandem manner with $Pd(PPh_3)_4$ and t-BuOK, a range of 2-aminobenzothiazoles were produced. The reaction proceeded at a good rate with outstanding yields thanks to the simple and effective technique (Scheme 3.1.22). [29]



Scheme 3.1.22

(XXIII) Synthesis of substituted biaryl sulphides:

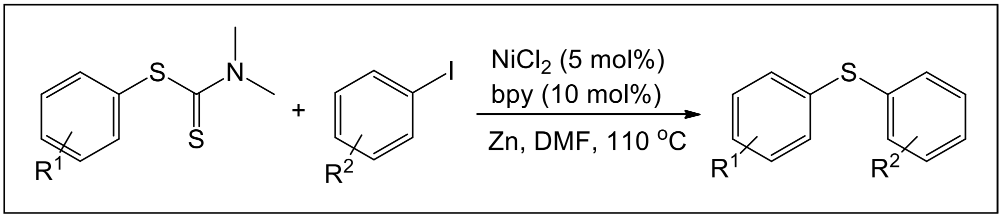
Yu Cheng and his team demonstrated to be good sulfuration reagents in the Chan–Lam coupling to prepare biaryl sulfides. With this technique, they synthesized desired substituted biaryl sulphides by exploring dithiocarbamate substrates with a wide range of functional groups, including electron-rich and electron-deficient ones. [30]



Scheme 3.1.23

(XXIV) Synthesis of diaryl sulfides from iodobenzene:

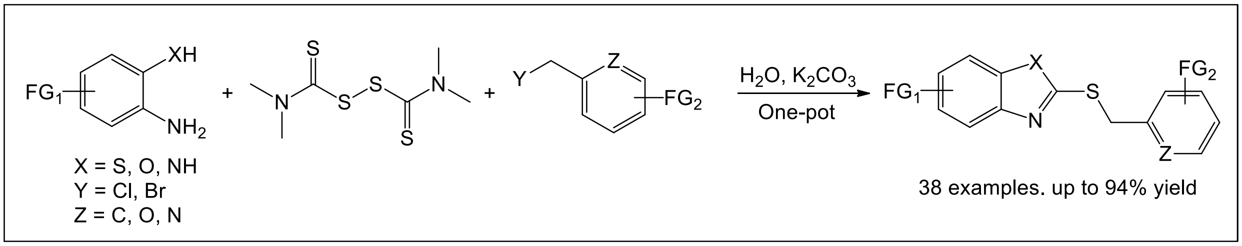
In this protocol, Xing Liu and his team smoothly synthesized diaryl sulfides with good to excellent yields (66–93 %) by using phenyldithiocarbamates, iodobenzenes and $NiCl_2$ catalyst. This protocol offers a broad substrate scope, good to excellent yield and easy to carry out. [31]



Scheme 3.1.24

(XXV) Synthesis of 2-benzyl/2-allyl-substituted thiobenzoazoles:

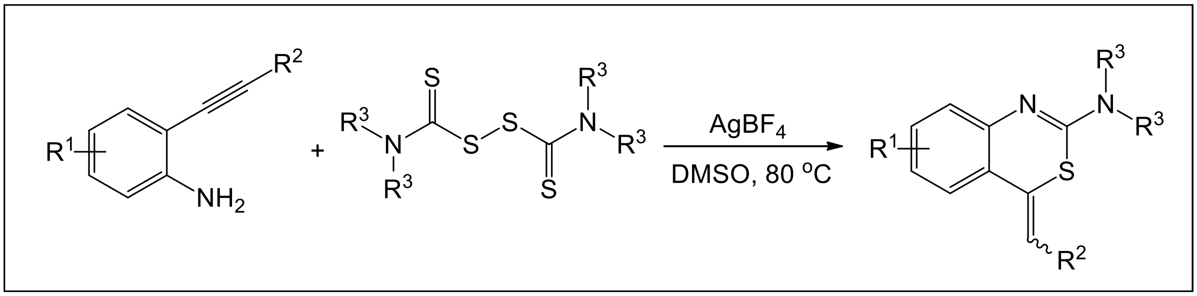
Shi-Bo Zhang and his team were developed a transition metal-free protocol for the one-pot synthesis of 2-benzyl/2-allyl-substituted thiobenzoazoles in water. The cyclization of 2-aminothiophenols, 2-aminophenols, and 1,2-phenylenediamines with tetramethylthiuram disulfide (TMTD) produced mercapto benzoheterocycles and the subsequent C–S coupling with benzyl or allyl halides generated the desired products in good to excellent yields. [32]



Scheme 3.1.25

(XXVI) Ammonolysis–cyclization of various 2-alkynylbenzenamines with tetraalkylthiuram disulfides:

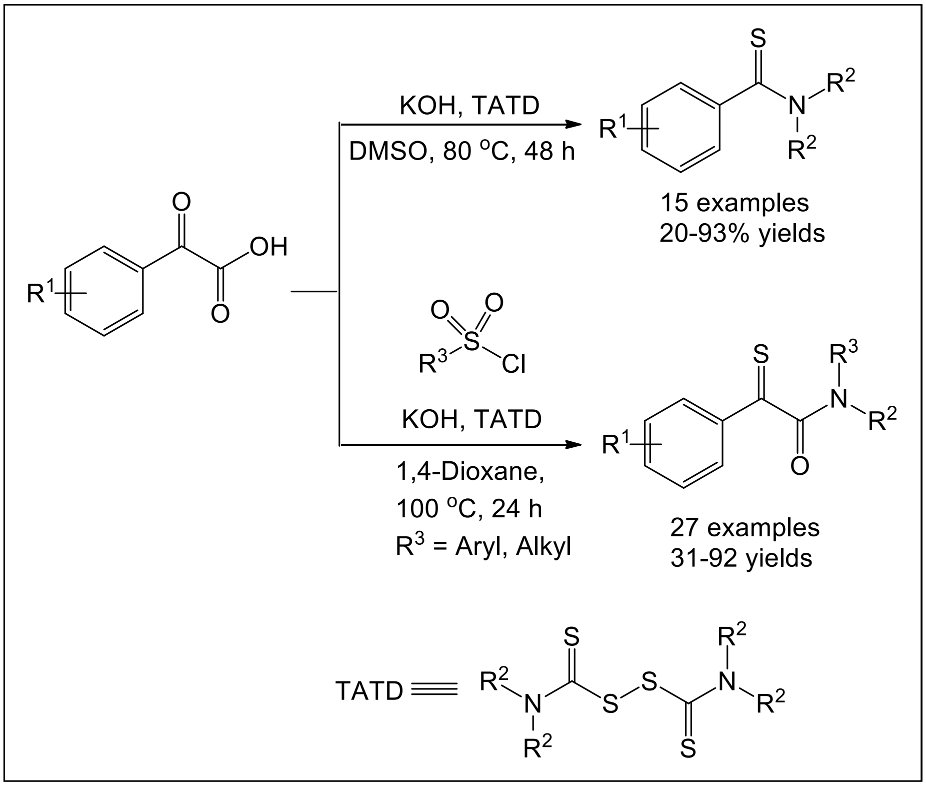
Ri-Yuan Tang and his team developed a protocol to produce 4-methylene-4H-benzo[d][1,3]thiazin-2-amines in moderate to good yields by the ammonolysis–cyclization tandem reactions of various 2-alkynylbenzenamines with tetraalkylthiuram disulfides in the presence of $AgBF_4$ catalyst. [33]



Scheme 3.1.26

(XXVII) Decarboxylative functionalization of *α*-oxocarboxylic acids with tetraalkylthiuram disulfides:

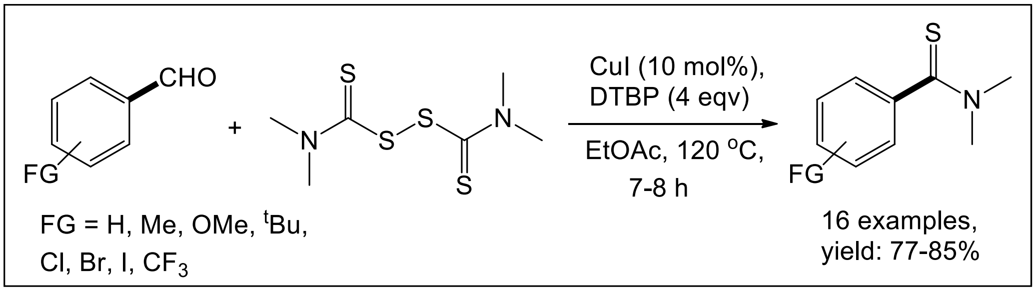
Miao Lai and his team[34] have been established a general protocol to prepare aryl thioamides and aromatic *α*-ketoamides from the reaction decarboxylative functionalization of *α*-oxocarboxylic acids with tetraalkylthiuram disulfides.



Scheme 3.1.27

(XXVIII) Synthesis of aryl thioamides:

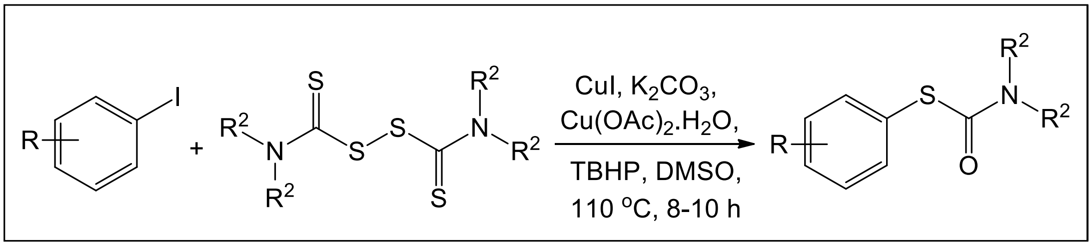
Meng-Tian Zeng and his team[35] have developed a novel and convenient method for the synthesis of aryl thioamides from aryl aldehydes and tetramethylthiuram disulfide (TMTD) without the use of sulfurating reagent.



Scheme 3.1.28

(XXIX) Cu(I)-catalyzed C-S cross-coupling with aryl iodides:

Saha and his team synthesized Thiuram disulfide undergoes Cu(I)-catalyzed C-S cross-coupling with aryl iodides via $Cu(OAc)_2.H_2O$-assisted desulfurization to produce the *S*-thiocarbamate ester compounds efficiently. Under an open air atmosphere, a series of cyclic and acyclic secondary amine-based thiuram disulphides are produced desired product by the smooth reaction of aryl iodides with varying substituents. The present methodology has substantial synthetic values because to its easy to use reagents and starting materials, as well as its air and moisture-tolerant reaction conditions and simple experimental setup.



Scheme 3.1.29

3.1/c. Conclusion

In conclusion, the synthetic application of dithiocarbamate molecules represents a fascinating and versatile area of chemistry with significant implications across various fields. Dithiocarbamates, characterized by their unique sulfur-nitrogen bonding and ability to form chelates with metals, have proven to be valuable in numerous applications. Dithiocarbamates are widely used as ligands in coordination chemistry due to their strong binding affinity for a range of metal ions. This property allows for the creation of metal complexes with diverse structures and functionalities, which can be utilized in catalysis, materials science, and medicinal chemistry. These molecules often serve as catalysts or catalyst precursors in organic synthesis. Their ability to stabilize metal centers and facilitate various reactions, such as oxidation and polymerization, highlights their importance in both industrial and academic research. In material science, dithiocarbamates contribute to the development of novel materials, including polymers and nanoparticles. Their coordination properties are harnessed to design materials with specific electronic, optical, or mechanical properties. Dithiocarbamate derivatives exhibit potential therapeutic properties, including antimicrobial, antiviral, and anticancer activities. Their ability to interact with biological systems and modulate biochemical pathways makes them candidates for drug development and medical applications. These compounds also have applications in environmental chemistry, particularly in the removal and recovery of heavy metals from polluted environments. Their chelating properties aid in the extraction and remediation of toxic metal ions. Different valuable organic compounds have been prepared from dithiocarbamate synthetic intermediates. It appears that dithiocarbamate synthetic precursors can be used to generate many heterocyclic rings having therapeutic importance under mild reaction conditions. Various type of compounds like arylthioamides, diarylsulfides, *N*-substituted benzamide, arylalkynyl amide have already been synthesized from dithiocarbamate compounds. In our current protocol, we have synthesized various diaryl ketones by using dithicarbamate compounds.

Overall, the synthetic application of dithiocarbamate molecules is a dynamic and evolving field, with ongoing research expanding their utility and uncovering new possibilities. Numerous synthetic methods have been developed to date because dithiocarbamate molecules offer potential pharmacological and synthetic applications. The continued exploration of their chemical behavior promises to drive innovations across multiple scientific and industrial domains.

3.1/d. References

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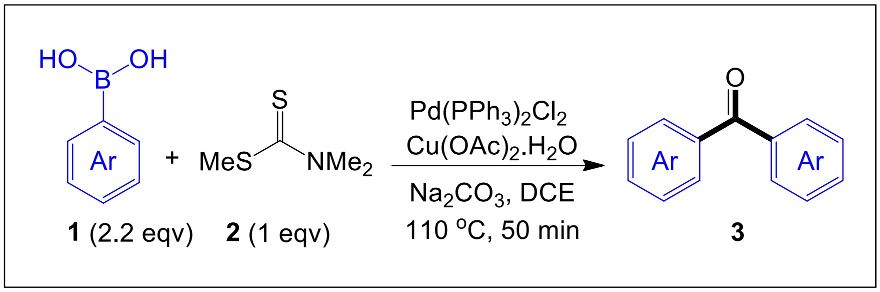
Section-II

Carbonylative homocoupling of arylboronic acids using dithiocarbamate ester as the carbonyl alternative

3.2/a. Introduction

Dithiocarbamate compounds are extremely important due to their broad applications in the area of biomedical sciences. [1] They also have potential uses in polymer science, [2] material science, [3] coordination chemistry[4] and agricultural science. [5] In last two decades dithiocarbamates have gained increasing popularity as valuable synthetic intermediates[6] and catalyst. [7] Our group is dedicatedly working on dithiocarbamate chemistry exploring the synthetic applicability of dithiocarbamates for the synthesis of useful organic molecules, such as thiourea, [6a] thioamide, [6b,c] mixed disulfide, [6d] biarylsulfides, [6e] alkynyl amide, [6f] *O*-thiocarbamate. [6g] In this report we are demonstrating a unique synthetic application of dithiocarbamate which serves as carbonyl surrogate in Pd-catalyzed carbonylative coupling of organoboronic acids (Scheme 3.2.01).



Scheme 3.2.01. Dithiocarbamate Mediated Carbonylative Homocoupling of Arylboronic Acid

Transition metal catalyzed carbonylative coupling reaction is an interesting tool of organic synthesis and provides wide range of synthetic building blocks. [8] Direct carbonylative coupling is a step-economic way to incorporate CO moiety into the organic framework. Importance of biaryl ketones as natural product, [9] photosensitizers, [10] bioactive molecules[11] and advanced materials[12] instigated us to develop a straight forward way to prepare biaryl ketones from easily available starting materials such as organoboronic acids avoiding the use of toxic CO gas. Herein, dithiocarbamate ester (Me_2NCS_2Me) has been used as CO alternative in carbonylative homocoupling of organoboronic acid. The commonly used CO surrogates includes metal-carbonyl complexes, [13] *N*-formyl saccharine, [14] DMF, [15] chloroform, [16] formic acid/formate salt, [17] isocyanides[18a] etc. [18] Dithiocarbamate ester, Me_2NCS_2Me is stable white solid compound, easy to prepare, store and handle and highly effective as carbonyl equivalent under the present Pd-catalyzed reaction condition. Previously reported protocols of oxidative carbonylative homocoupling of arylboronic acids mediated by CO gas, [8a-c] DMF[15b] or *N*-formyl saccharine[14a] (Scheme 3.2.02) suffer from drawbacks such as toxicity of CO gas, long reaction time, expensive ligand, use of specially designed Pd-catalyst. Here some important molecules are shown in Figure 3.2.01.

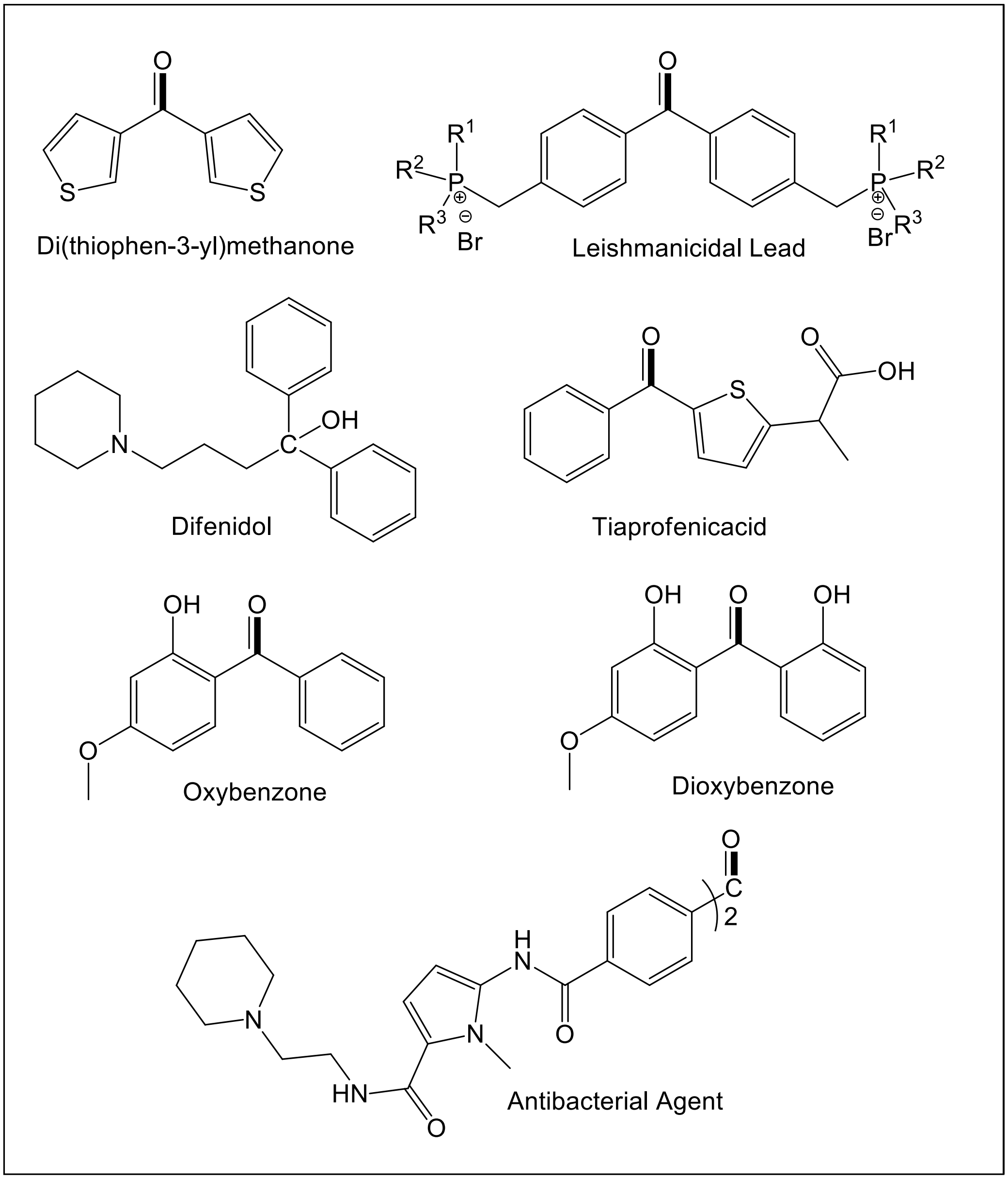
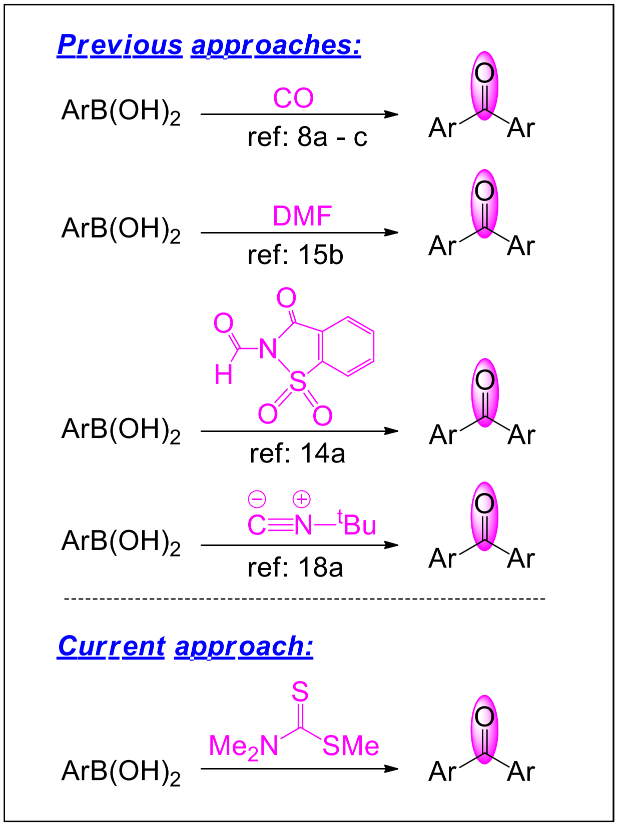


Figure 3.2.01

We are introducing here dithiocarbamate compound, Me_2NCS_2Me as the carbonyl alternative in carbonylative homocoupling of arylboronic acids in presence of $Cu(OAc)_2.H_2O$, Na_2CO_3 and $Pd(PPh_3)_2Cl_2$ catalyst in DCE solvent medium at 110 ^oC within 50 min of reaction time period to produce the diaryl ketones efficiently. The reaction involves two $C(sp^2)$-$C(sp^2)$ bond formations *via* Cu(II)-assisted desulfurization in presence of Pd(II) catalyst. To the best of our knowledge this is the first report of using dithiocarbamate as carbonyl alternative in oxidative homocoupling of organoboronic acids.



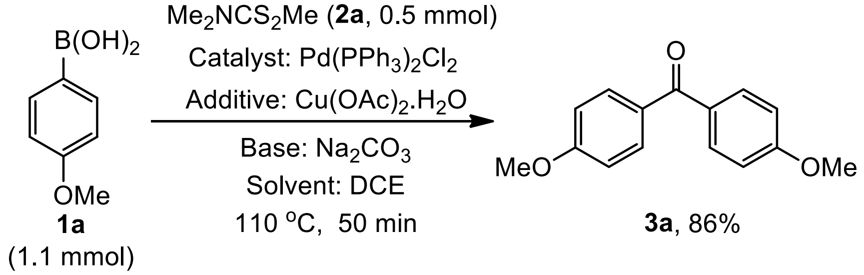
Scheme 3.2.02. Various Approaches of Carbonylative Homocoupling of Arylboronic Acids

3.2/b. Results and Discussion

The reaction is very easy to perform. A mixture of arylboronic acid and dithiocarbamate ester (Me_2NCS_2Me) in DCE solvent was heated at 110 °C in a sealed tube in presence of Pd-catalyst, $Cu(OAc)_2.H_2O$ and Na_2CO_3 for 50 min of time period. The crude product obtained by usual work-up was purified by column chromatography.

The reaction condition was optimized with the help of a series of reactions under variable reaction parameters. The optimization study was conducted with 4-methoxyphenylboronic acid as the model substrate (Table 3.2.01). $Pd(PPh_3)_2Cl_2$ was found to catalyze the reaction effectively in comparison to other common Pd-based catalysts, such as $Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_4$ (See the Supporting Information for the complete optimization table). Among various additives, bases and solvents, the combination of $Cu(OAc)_2.H_2O$ along with Na_2CO_3 and DCE solvent provided the best result at 110 °C within 50 min of reaction time period (Table 3.2.01). The reaction does not proceed at all either in absence of Pd-catalyst or Cu-additive (Table 3.2.01).

Table 3.2.01. Optimization of Reaction Condition



1a
(1.1 mmol)

3a, 86%

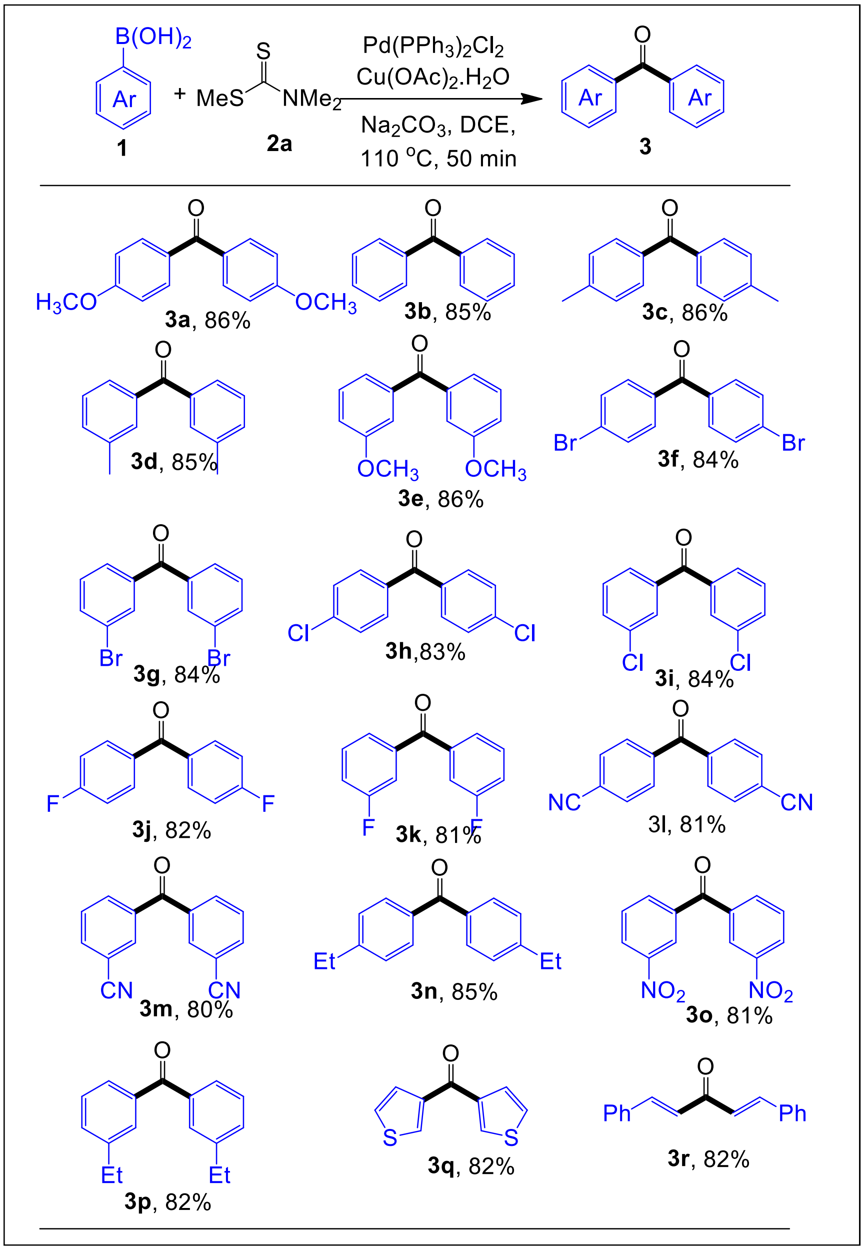
Deviation from the standard condition	Yield (%)
60 °C	38
Catalyst: $PdCl_2$ or $Pd(PPh_3)_4$, 60 °C	trace
Catalyst: $Pd(OAc)_2$, 60 °C	-
Additive: $CuSO_4.5H_2O$ or CuO, 60 °C	-
Base: K_2CO_3 or Cs_2CO_3 or Et_3N, 60 °C	32 - 40
Solvent: H_2O or ACN or THF, 60 °C	trace - 25
Solvent: 1,4-Dioxane	75
without Pd-Catalyst	-
without Cu-Additive	-

Reaction conditions: ***1a*** *(1.1 mmol),* ***2a*** *(0.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.03 mmol), $Cu(OAc)_2.H_2O$ (1 mmol) and Na_2CO_3 (1 mmol) in 3 mL DCE at 110 °C for 50 min. Yields reported are the isolated yields.*

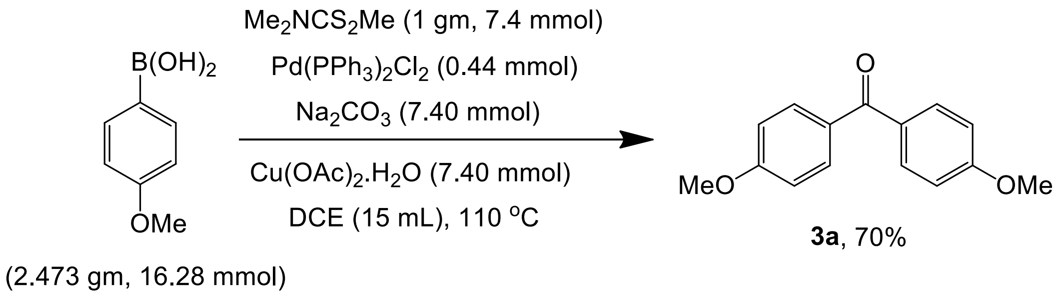
The optimized reaction condition was explored to establish the substrate scope with a broad range of arylboronic acids (Table 3.2.02). The reaction proceeds well with the arylboronic acids containing electron donating substituents, such as Me, OMe and Et to provide the desired diaryl ketones efficiently (**3a**, **3c**-**3e**, **3n**, **3p**). Diaryl ketones with electron withdrawing substituents (F, CN, NO_2) were also prepared in good yields following the present protocol (**3j**-**3m**, **3o**). The reaction shows high selectivity in case of -Cl and -Br substituted substrates. Desired diaryl ketones (**3f**-**3i**) were produced smoothly under the present reaction condition without formation of any biaryl side products by the Suzuki cross-coupling reactions between the halogen substituted diaryl ketone and arylboronic acid. 3-Thiopheneboric acid produces the desired heterobiaryl ketone (**3q**) which is useful in preparing electric materials. [8a] *Trans*-styrenyl boronic acid also has been used to prepare stereospecifically the corresponding *trans*-dibenzylideneacetone product

(**3r**). The dithiocarbamate ester, Me_2NCS_2Me (**2a**) responded well to the gram scale synthesis of diaryl ketone, **3a** by the homocoupling of 4-methoxyphenylboronic acid, **1a** (Scheme 3.2.03).

Table 3.2.02. Synthesis of Symmetrical Diaryl Ketones



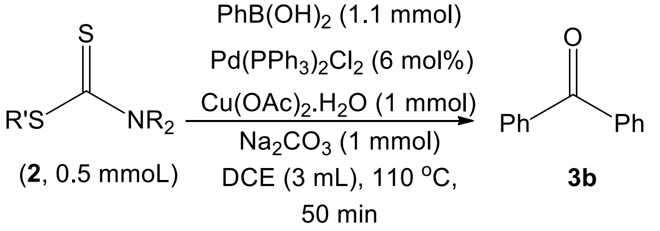
Reaction conditions: **1** (1.1 mmol), **2a** (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.03 mmol), $Cu(OAc)_2.H_2O$ (1 mmol) and Na_2CO_3 (1 mmol) in DCE (3 mL) at 110 °C for 50 min. Yields reported are the isolated yields. In all cases trace amount of biphenyl compound has been formed by the homocoupling of arylboronic acid (**1**).

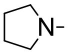
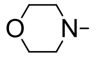
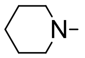
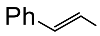
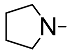
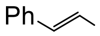
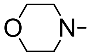
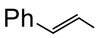
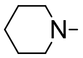
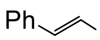
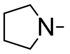
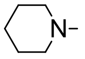
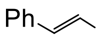
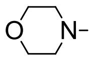


Scheme 3.2.03. Gram-scale Synthesis of Diaryl Ketone, 3a

Dithiocarbamate compounds with different structural variations (such as S-methyl, S-phenyl, S-styrenyl, dimethylamino, diethylamino, piperidinyl, pyrrolidinyl, morpholinyl) show similar reactivity towards carbonylative homocoupling of phenylboronic acid to produce the desired product, benzophenone (**3b**) in 78-86% yield (Table 3.2.03).

Table 3.2.03. Structural Variation of Dithiocarbamate Esters in the Homocoupling of Phenylboronic Acid

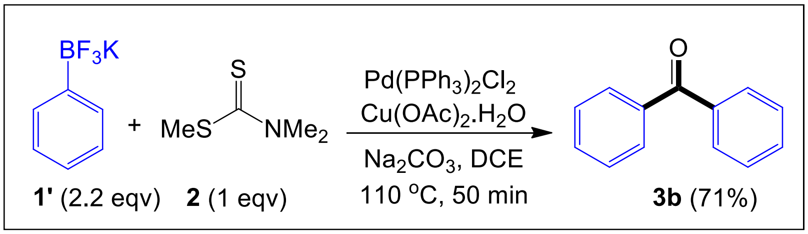


Entry	R'-	R_2N-	Yield of **3b** (%)	Entry	R'-	R_2N-	Yield of **3b** (%)
1	Me	Me_2N-	85	9	Ph		80
2	Me	Et_2N-	82	10	Ph		82
3	Me		81	11		Me_2N-	82
4	Me		81	12		Et_2N-	78
5	Me		82	13			78
6	Ph	Me_2N-	84	14			79
7	Ph	Et_2N-	81				
8	Ph		80	15			80

*Reaction conditions: **1a** (1.1 mmol), **2** (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.03 mmol), $Cu(OAc)_2.H_2O$ (1 mmol) and Na_2CO_3 (1 mmol) in DCE (3 mL) at 110 °C for 50 min. Yields reported are the isolated yields.*

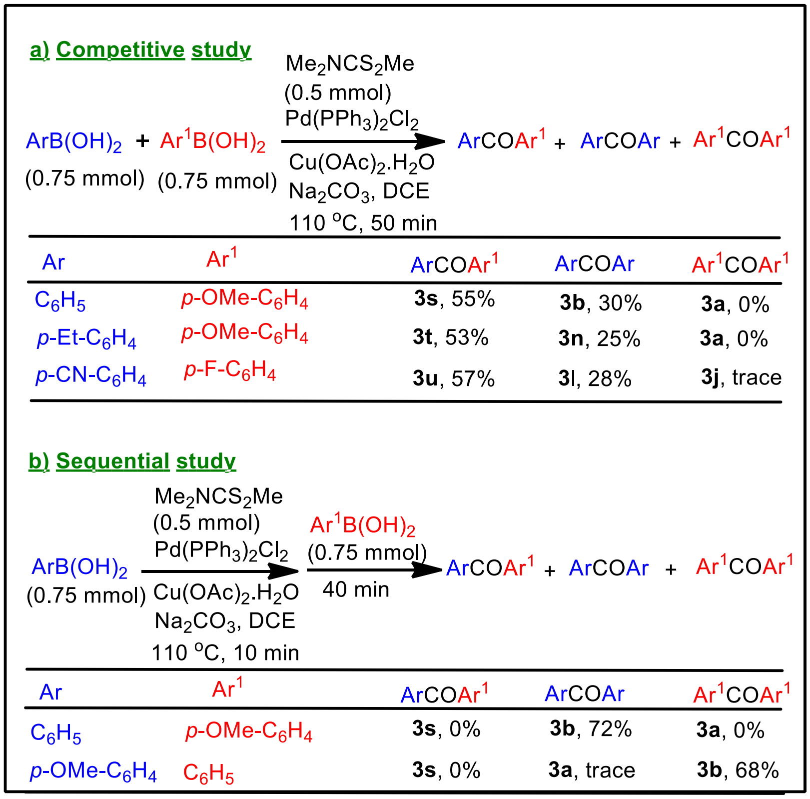
A one-pot reaction using *in situ* generated Me_2NCS_2Me was also performed with phenylboronic acid in presence of $Pd(PPh_3)_2Cl_2$, $Cu(OAc)_2.H_2O$ in DCE solvent. The one-pot reaction produced the desired diaryl ketone with 52% yield.

The carbonylative coupling reaction has been tried with other organoboron reagents, such as $PhBF_3K$ and PhBpin. $PhBF_3K$ was found to produce the desired diaryl ketone (**3b**) in good yield (Scheme 3.2.04). However, PhBpin did not respond to the reaction at all.



Scheme 3.2.04. Carbonylative Coupling Reaction Using $PhBF_3K$

In order to prepare the unsymmetrical diaryl ketone, we have performed the carbonylative coupling reactions using two different arylboronic acids (Scheme 3.2.05). In the competitive study (Scheme 3.2.05a), both the arylboronic acids have been added at the same time.



a) Competitive study

$$ArB(OH)_2 + Ar^1B(OH)_2 \xrightarrow[\substack{Cu(OAc)_2.H_2O\\ Na_2CO_3,\ DCE\\ 110\ ^oC,\ 50\ min}]{\substack{Me_2NCS_2Me\\ (0.5\ mmol)\\ Pd(PPh_3)_2Cl_2}} ArCOAr^1 + ArCOAr + Ar^1COAr^1$$

(0.75 mmol) (0.75 mmol)

Ar	Ar^1	$ArCOAr^1$	ArCOAr	Ar^1COAr^1
C_6H_5	*p*-OMe-C_6H_4	**3s**, 55%	**3b**, 30%	**3a**, 0%
p-Et-C_6H_4	*p*-OMe-C_6H_4	**3t**, 53%	**3n**, 25%	**3a**, 0%
p-CN-C_6H_4	*p*-F-C_6H_4	**3u**, 57%	**3l**, 28%	**3j**, trace

b) Sequential study

$$ArB(OH)_2 \xrightarrow[\substack{Cu(OAc)_2.H_2O\\ Na_2CO_3,\ DCE\\ 110\ ^oC,\ 10\ min}]{\substack{Me_2NCS_2Me\\ (0.5\ mmol)\\ Pd(PPh_3)_2Cl_2}} \xrightarrow[40\ min]{\substack{Ar^1B(OH)_2\\ (0.75\ mmol)}} ArCOAr^1 + ArCOAr + Ar^1COAr^1$$

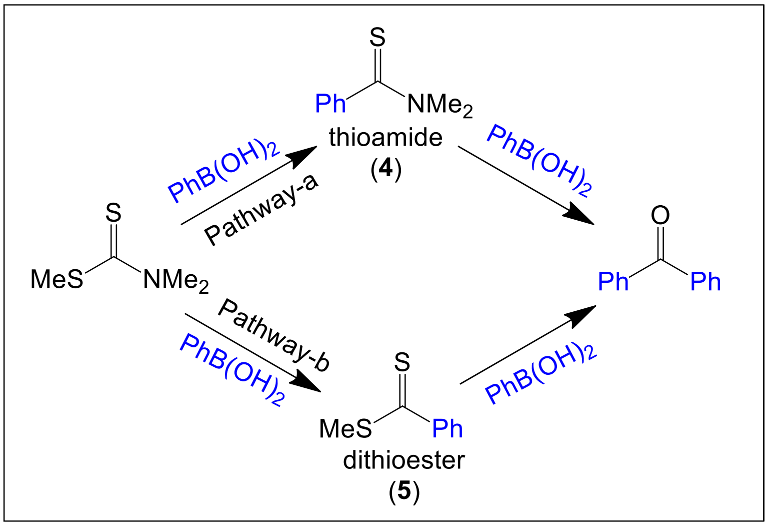
(0.75 mmol)

Ar	Ar^1	$ArCOAr^1$	ArCOAr	Ar^1COAr^1
C_6H_5	*p*-OMe-C_6H_4	**3s**, 0%	**3b**, 72%	**3a**, 0%
p-OMe-C_6H_4	C_6H_5	**3s**, 0%	**3a**, trace	**3b**, 68%

Scheme 3.2.05. Synthesis of Unsymmetrical Diaryl Ketones

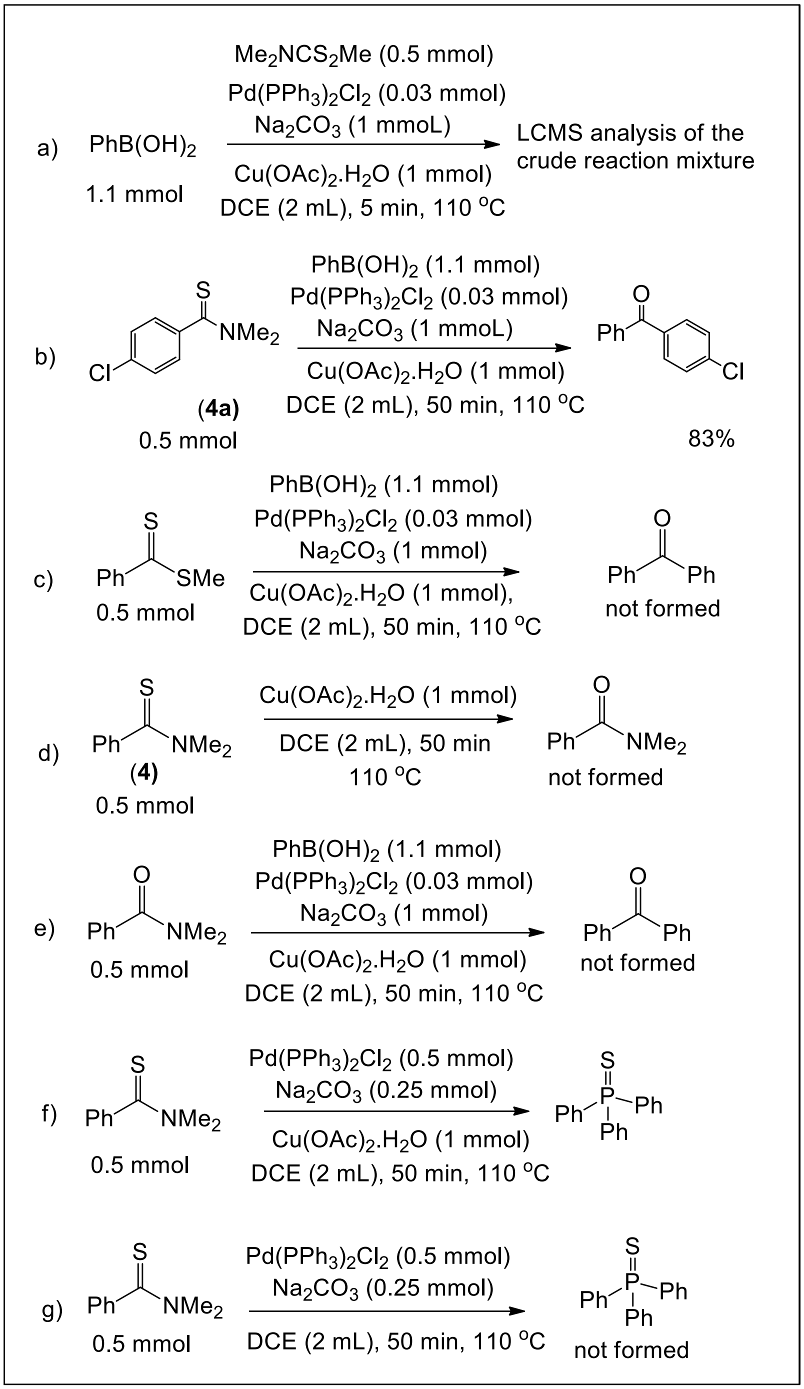
We found the formation of unsymmtrical ketones (**3s, 3t**, **3u**) predominantly along with the symmetrical ketone generated from the less electron rich arylboronic acid. It appears that the less electron rich arylboronic acid is more reactive in this carbonylative coupling reaction. Next we performed the sequential study to prepare the unsymmtrical ketone (Scheme 3.2.05b). The second arylboronic acid has been added after 10 min of the addition of the first arylboronic acid. Unfortunately, we did not find the formation of unsymmetrical ketone in these cases (Scheme 3.2.05b). Reversing the sequence of addition of boronic acids also did not improved the result. The less electron rich arylboronic acid was found to produce the corresponding symmetrical ketone only.

Dithiocarbamate ester may follow either pathway-a (through C-S bond cleavage) or pathway-b (through C-N bond cleavage) as shown in Scheme 6. Pathway-a and pathway-b involve the thioamide (**4**) and the dithioester (**5**) intermediates respectively.



Scheme 3.2.06. Two Probable Pathways of the Reaction

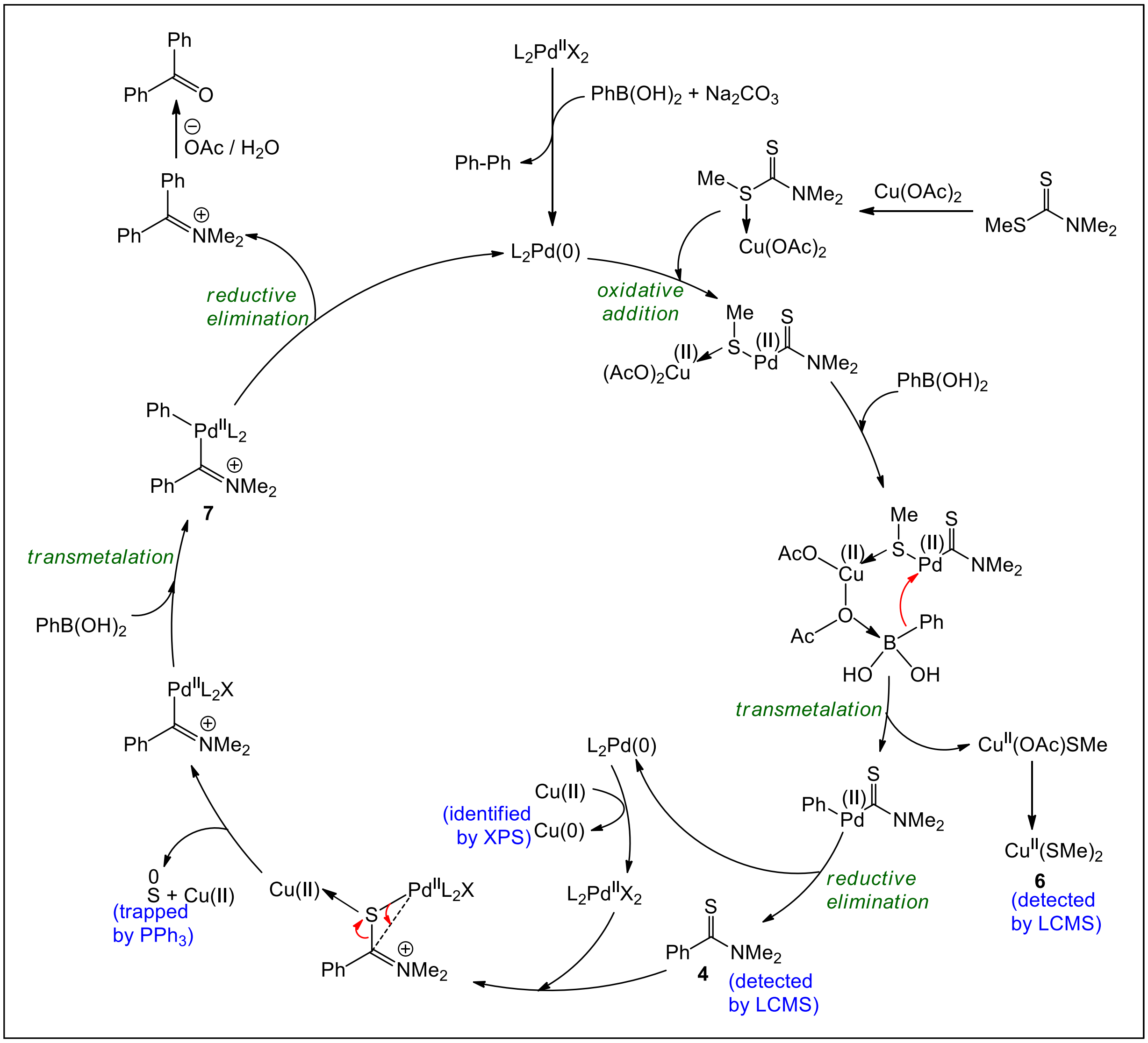
To understand the reaction mechanism, a series of control experiments have been performed (Scheme 3.2.07). The crude reaction mixture, obtained from the reaction of $PhB(OH)_2$ and Me_2NCS_2Me under the standard condition was analyzed by LCMS after an intermediate time period of reaction (5 min) (Scheme 3.2.07a). LCMS analysis reveals the presence of thioamide intermediate ($PhCSNMe_2$, **4**) and $Cu(SMe)_2$ (**6**) in the crude reaction mixture. Thus thioamide (**4**) may be a probable intermediate formed by Pd-catalyzed Cu(II)-mediated Liebeskind–Srogl type cross-coupling reaction.[19] To study the actual pathway of reaction we performed two separate reactions as shown in Scheme 3.2.07b and 3.2.07c. The compound 4-chlorophenylthioamide, **4a** produced the desired diarylbenzophenone compound, *p*-Cl-$C_6H_4COC_6H_5$ with good yield (83%) (Scheme 3.2.07b). Whereas, dithioester ($PhCS_2Me$) did not produce the desired ketone, Ph_2CO at all under the identical condition (Scheme 3.2.07c). Thus, we believe the reaction proceeds through thioamide intermediate (pathway a, Scheme 3.2.06) *via* prior C-S bond cleavage. To check the desulfurization mechanism, the thioamide, $PhCSNMe_2$ (**4**) was heated with 2 equiv. of $Cu(OAc)_2.H_2O$ at 110 ^{o}C for 50 min of time period (Scheme 7d). However, no amide compound ($PhCONMe_2$) was found to produce by desulfurization. Upon prolong heating (4 h) at 110 ^{o}C, some amount of thioamide was found to be converted to the corresponding amide ($PhCONMe_2$) in 43% yield.



Scheme 3.2.07. Control Experiments

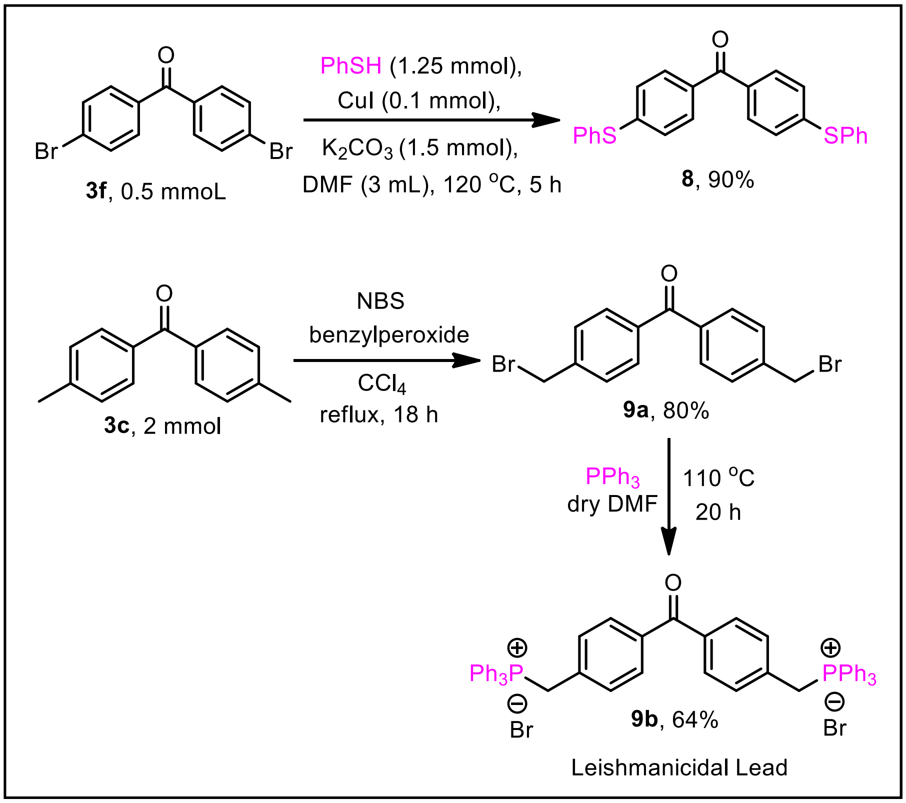
However, the amide, $PhCONMe_2$ does not produce the desired diaryl ketone, Ph_2CO in the presence of Pd(II)-catalyst and Cu(II)-additive under the standard reaction condition (Scheme 3.2.07e). Thus, the probability of $PhCONMe_2$ as a reaction intermediate was ruled out. It has been found that thioamide, $PhCSNMe_2$ (**4**) produces triphenylphosphine sulphide (Ph_3PS) in significant amount in presence of 1 equiv. of $Pd(PPh_3)_2Cl_2$ and 2 equiv. of $Cu(OAc)_2.H_2O$ at 110 °C within 50 min of time period (Scheme 3.2.07f). However, no Ph_3PS has been generated in absence of $Cu(OAc)_2.H_2O$ (Scheme 3.2.07g). Triphenylphosphine sulphide is well known to be generated by the reaction triphenylphosphine with elemental sulfur. [20] Thus, we believe thioamide produces the desired product diaryl ketone *via* generation of elemental sulfur in presence of Pd-catalyst and $Cu(OAc)_2.H_2O$ additive.

Based on the control experiments we propose the probable reaction pathway as depicted in Scheme 3.2.08. We found the formation of small amount of biphenyl compound by the homocoupling of the arylboronic acid along with the formation of desired ketone product. We believe the generation of Pd(0)-active catalytic species by the reduction of Pd(II) in presence of $PhB(OH)_2$ and carbonate base. [21]



Scheme 3.2.08. Probable Mechanistic Pathway

Dithiocarbamate ester (Me_2NCS_2Me) undergoes $Cu(OAc)_2$ mediated[19c] Liebeskind–Srogl type cross-coupling reaction with phenylboronic acid in presence of Pd(0) active catalytic species to produce the dimethylaminothiomide intermediate (**4**, $PhCSNMe_2$) (Scheme 3.2.08). The oxygen of OAc group coordinates with boron center of arylboronic acid and makes the transmetalation easier. The coordination of OAc with the boron center is more preferred in case of electron deficient aryboronic acid. Thus, we found higher reactivity of electron deficient arylboronic acids in our competitive study (Scheme 3.2.05a), similar to the observation found by Hu *et. al.* [22] Along with the transmetaltion, -SMe group is removed as $Cu^{II}(OAc)SMe$ which is further converted to $Cu^{II}(SMe)_2$ in the next reaction cycle. $Cu^{II}(SMe)_2$ is identified by LCMS experiment (spectra included in the Supporting Information). The thioamide intermediate (**4**) is generated by the reductive elimination along with the generation of Pd(0) which is oxidized to Pd(II) by the Cu(II)-additive. Cu(II) is reduced to Cu(0) which is identified by the XPS analysis of the Cu-residue obtained after completion of the reaction. XPS data and the spectra is included in the Supporting Information. In presence of thiophilic additive ($Cu(OAc)_2.H_2O$), Pd(II)-catalyst produces Pd-aminocarbene complex (**7**) *via* Cu(II)-assisted desulfurization to generate the elemental sulfur (trapped by Ph_3P as $Ph_3P{=}S$) following a similar mechanism as proposed by Song *et. al.*[8i] Reductive elimination from complex-**7** regenerates the Pd(0) and the iminium cationic species ($Ph_2C{=}N^+Me_2$) which undergoes imine-hydrolysis by acetate anion or H_2O (present in the Cu-additive) to produce the desired benzophenone product.



Scheme 3.2.09. Post-synthetic Modification: Synthesis of Diarylsulfide (**8**) and Leishmanicidal Lead Compound (**9b**)

The reaction shows high selectivity where C(aryl)-Br and C(aryl)-Cl groups remain intact under the present reaction condition and it allows post-functional modification of the C(aryl)-halide bonds of the diaryl ketone products. We have performed the C-S cross-coupling reaction with the diaryl ketone, **3f** and thiophenol to produce the thiolated compound **8** (Scheme 3.2.09). The diaryl ketone (**3c**) also has been used to synthesize a known Leishmanicidal lead compound[11i] (**9b)** *via* the brominated compound-**9a** (Scheme 3.2.09).

3.2/c. Conclusion

In conclusion, we have developed an efficient protocol for carbonylative homocoupling of arylboronic acid avoiding the use of gaseous CO. The dithiocarbamate ester, Me_2NCS_2Me is a stable solid compound and easily prepared from cheap starting materials. To the best of our knowledge this is the first report of using dithiocarbamate compound as CO alternative. The reaction shows good functional group tolerance and respond equally with a series of structurally variable dithiocarbamate esters. Cheap and easily available starting materials, general applicability and operational simplicity make the protocol synthetically attractive.

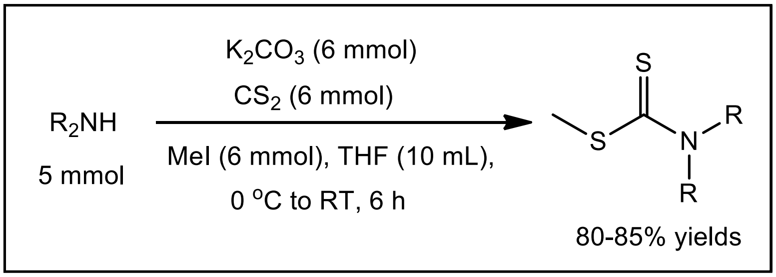
3.2/d. Experimental Section

General Information:

All chemicals were obtained from commercial supplies and used without further purification. Dithiocarbamate ester (compound 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2l, 2m, 2n, 2o) were known and synthesized following the published literature. All the reactions were checked by TLC on silica gel plates (Merck silica gel, f_{24}). Column chromatography was done on 100-200 mesh silica gel for purification of the products. The ^{1}H spectra were recorded in $CDCl_3$ on Brucker Spectrometer at 300, 400 MHz. The ^{13}C spectra were recorded in $CDCl_3$ on Brucker Spectrometer at 75, 100 MHz. Chemical shifts were reported in ppm. The coupling constant (*J*) values are shown in hertz, and splitting patterns of the proton are described as *s* (singlet), *d* (doublet), *t* (triplet), and *m* (multiplet). HRMS were measured in methanol solvent on a Waters Micromass Q-tof Micromassspectrometer. LCMS was recorded using COLUMN-X-Bridge-C18 (4.6 x 50 mm, 5 µm).

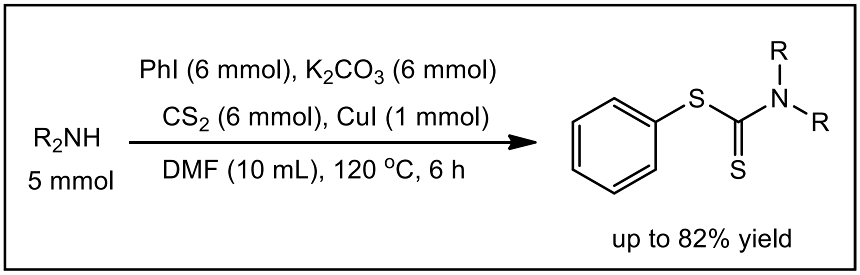
Synthesis of Dithiocarbamate ester:

Synthesis of methyl dialkylcarbamodithioate:



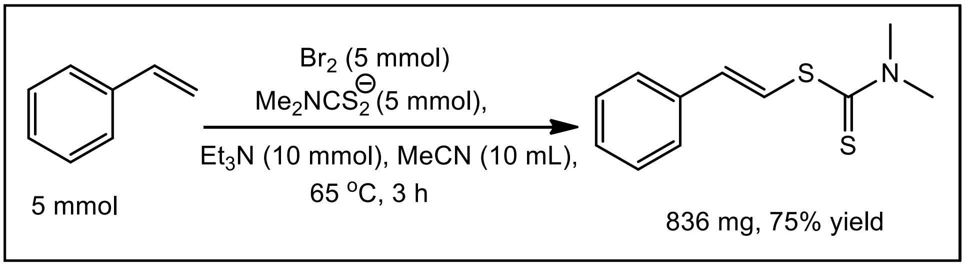
CS_2 (0.4 mL, 6 mmol) was added drop wise to a mixture of secondary amine (5 mmol) and K_2CO_3 (828 mg, 6 mmol) in THF (10 mL) at 0 °C. After completion of addition, the reaction mixture was stirred for 20 min. Then MeI (0.37 mL, 6 mmol) was added slowly into the reaction mixture. The reaction mixture was allowed to stir at room temp for 6 h. After completion of reaction (checked by TLC), the solvent was evaporated under reduced pressure. The crude product was extracted with ethyl acetate and purified by column chromatography to obtain the desired product**s** up to 85% yield.

Synthesis of phenyl dialkylcarbamodithioate:



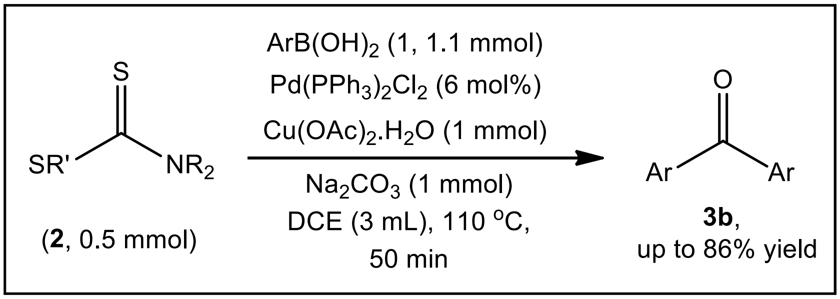
CS_2 (0.4 mL, 6 mmol) was added drop wise to a mixture of secondary amine (5 mmol) and K_2CO_3 (828 mg, 6 mmol) in DMF (10 mL) at 0 °C. After completion of addition, the reaction mixture was stirred for 20 min. Then PhI (0.66 mL, 6 mmol) and CuI (1 mmol) was added slowly into the reaction mixture and allowed to stir in an oil bath at 120 °C for 6 h. After completion of reaction (checked by TLC), cold water was added to the mixture. Then extracted with ethyl acetate and purified by column chromatography to obtain the desired product**s** up to 82% yield.

Synthesis of styryl dialkylcarbamodithioate:



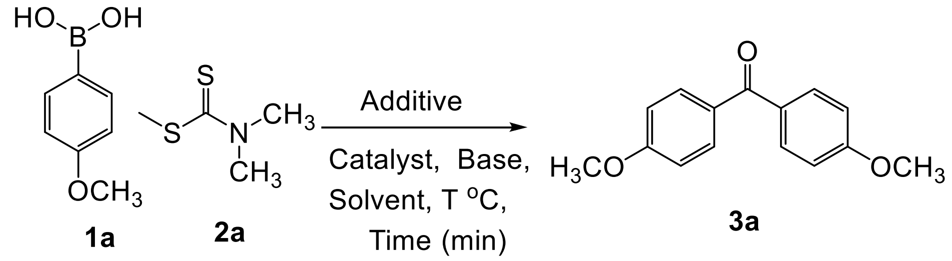
Br_2 (0.25 mL, 5 mmol) in MeCN (4 mL) was added drop wise to the styrene (5 mmol) solution in MeCN (6 mL) at 5 °C. After complete addition, the reaction mixture was allowed to stir for 30 min at room temperature. Then the solution of freshly prepared dithiocarbamateanion (5 mmol) containing Et_3N (1.4 mL, 10 mmol) was added slowly into the brominated reaction mixture. The reaction mixture was allowed to stir in an oil bath at 65 °C for a certain reaction time period. After completion of reaction (checked by TLC), the solvent was evaporated under reduced pressure. The crude product was extracted with ethyl acetate and purified by column chromatography to obtain the desired product (836 mg, 75% yield).

Synthesis of Diarylketone (3a-3r):



An oven-dried sealed tube (15 mL) equipped with a stir bar was charged with dithiocarbamate ester (**2**) (0.5 mmol, 1.0 equiv.), $Pd(PPh_3)_2Cl_2$ (0.03 mmol, 6 mol%), $Cu(OAc)_2.H_2O$ (1 mmol, 2 equiv.), Na_2CO_3 (1 mmol, 2 equiv.), arylboronic acid (1) (1.1 mmol, 2.2 equiv.) and 3 mL DCE solvent. Then, reaction mixture was stirred and heated in an oil barth at 110 ^{o}C for 50 min. After completion of the reaction (checked by TLC), the resulting mixture was cooled to room temperature and evaporated under reduced pressure. The crude product was extracted with ethyl acetate and purified by column chromatography to obtain the desired products up to 86% yield.

Optimization of the reaction condition:

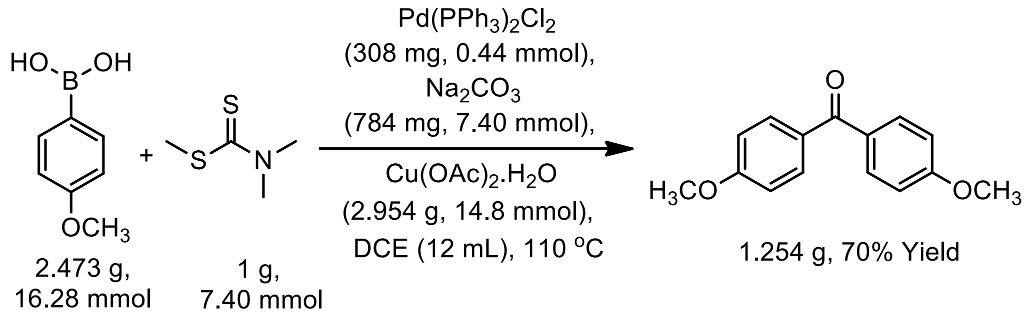


Sl. no.	Cu(II) additive (equiv)	Pd catalyst (equiv)	base	solvent	T (°C)	Time (min)	Yield (%)
1	$CuSO_4.5H_2O$ (1)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	60	60	-
2	CuO (1)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	60	60	-
3	$Cu(OAc)_2.H_2O$ (1)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	60	60	30
4	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	60	60	38
5	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	25	60	-
6	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_4$ (0.06)	Na_2CO_3	DCE	60	60	Trace
7	$Cu(OAc)_2.H_2O$ (2)	$Pd(OAc)_2$ (0.06)	Na_2CO_3	DCE	60	60	-
8	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	K_2CO_3	DCE	60	60	35
9	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Cs_2CO_3	DCE	60	60	40
10	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Et_3N	DCE	60	60	32
11	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	H_2O	60	60	Trace
12	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	ACN	60	60	-
12	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	THF	60	60	25
14	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	80	60	68
15	**$Cu(OAc)_2.H_2O$ (2)**	**$Pd(PPh_3)_2Cl_2$ (0.06)**	**Na_2CO_3**	**DCE**	**110**	50	**86**
16	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	1,4-Dioxane	110	50	75
17	$Cu(OAc)_2.H_2O$ (2)	$PdCl_2$(0.06)	Na_2CO_3	DCE	110	50	55
18	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.02)	Na_2CO_3	DCE	110	50	35
19	$Cu(OAc)_2.H_2O$ (2)	-	Na_2CO_3	DCE	110	50	-
20	-	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	110	50	-
21	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	-	DCE	110	50	35

22	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	110	50	86
23	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	110	30	55
24	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	110	45	65
25	$Cu(OAc)_2.H_2O$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	110	60	86
26	$Cu(OAc)_2$ (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	110	60	51
27[a]	Ag_2O (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	110	60	17
28	TBHP (2)	$Pd(PPh_3)_2Cl_2$ (0.06)	Na_2CO_3	DCE	110	60	-

Reaction conditions: Reaction were carried out using ***1a*** *(1.1 mmol) and* ***2a*** *(0.5 mmol) with catalyst, base and additive in 3 mL solvent at a certain temperature for the required time period. Yields reported are the isolated yields.* [a]*Thioamide intermediate compound has been isolated along with the desired diarylketone.*

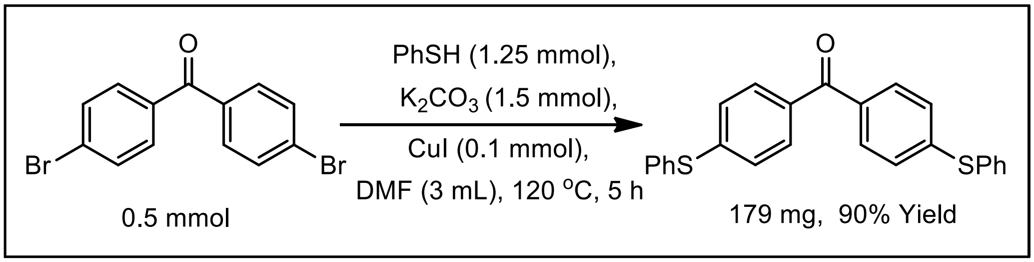
Gram-scale Experiment (7.40 mmol scale):



An oven-dried sealed tube (30 mL) equipped with a stir bar was charged with methyl dimethylcarbamodithioate (1 g, 7.40 mmol), $Pd(PPh_3)_2Cl_2$ (0.44 mmol), $Cu(OAc)_2.H_2O$ (14.8 mmol), Na_2CO_3 (7.40 mmol), 4-methoxyphenylboronic acid (2.473 g, 16.28 mmol) and 12 mL DCE solvent. Then, the reaction mixture was stirred and heated in an oil bath at 110 °C for 50 min. After completion of the reaction (checked by TLC), the resulting mixture was cooled to room temperature and evaporated under reduced pressure. The crude product was extracted with ethyl acetate and purified by column chromatography to obtain the desired product (1.254 g, 70% yield).

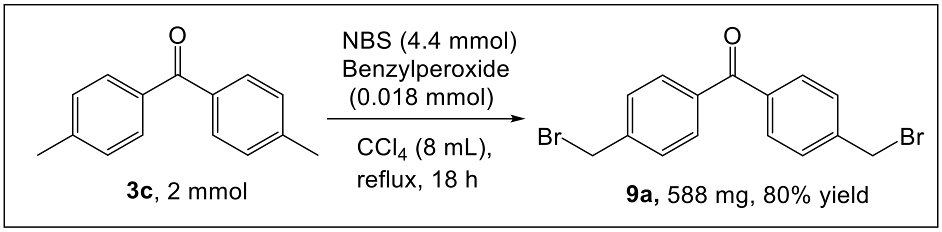
Experimental Procedure of Post-functionalization:

Synthesis of bis(4-(phenylthio)phenyl)methanone:

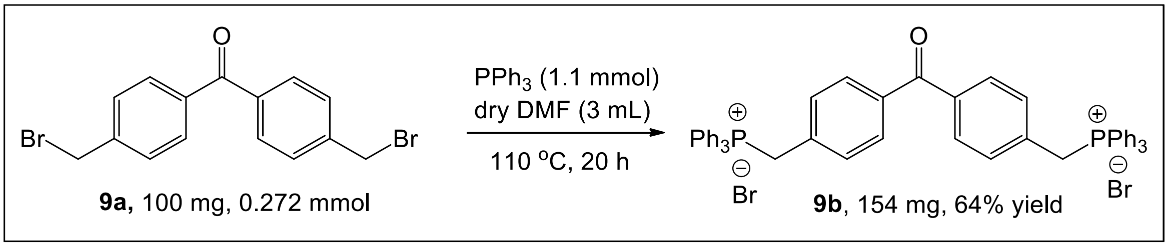


A 10 mL round bottom flask was charged with bis(4-bromophenyl)methanone (170 mg, 0.5 mmol), K_2CO_3 (207 mg, 1.5 mmol), CuI (19 mg, 0.1 mmol), thiophenol (0.13 mL, 1.25 mmol) and DMF (3 mL). The resulting solution was stirred in an oil bath at 120 °C for 5 h. After completion of the reaction (checked by TLC), the resulting mixture was cooled to room temperature and cold water was added to this solution. The crude product was extracted with ethyl acetate and purified by column chromatography to obtain the desired product (179 mg, 90% yield).

Synthesis of 4,4'-Bis((triphenylphosphonio)methyl)benzophenone Dibromide:



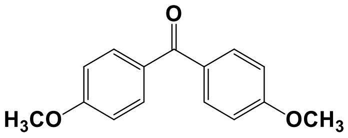
NBS (783.11 mg, 4.4 mmol) and benzylperoxide (4 mg, 0.018 mmol) were added to the solution of di-*p*-tolylmethanone (**3c**, 420 mg, 2 mmol) in 8 mL CCl_4. The reaction mixture was allowed to stir and heat in an oil bath at refluxing condition. After completion of the reaction (checked by TLC), the resulting mixture was cooled to room temperature and the crude product was extracted with DCM and purified by column chromatography (98:2 hexane/ethyl acetate) to obtain the desired product **9a** (588 mg, 80% yield).



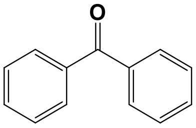
An oven-dried sealed tube (15 mL) equipped with a stir bar was charged with bis(4-(bromomethyl)phenyl)methanone (**9a**, 100 mg, 0.272 mmol), triphenylphosphine (288 mg, 1.1 mmol) and 3 mL dry DMF solvent. The tube was flushed with argon and then, reaction mixture was stirred and heated in an oil bath at 110 °C for 20 h. After completion of the reaction (checked by TLC), the resulting mixture was cooled to room temperature and toluene (10 mL) was added to the reaction mixture. Resulting reaction mixture was stored in the refrigerator overnight. The precipitate formed was triturated with spatula, washed with diethyl ether and dried under vacuum. The desired product was obtained as pale yellow solid (154 mg, 64%).

Characterization Data of Synthesized Compounds:

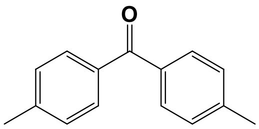
bis(4-methoxyphenyl)methanone (**3a**): [23] Light yellow solid (104 mg, 86% yield), Petroleum ether/ethyl acetate (97:3, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.78 (d, J= 8.8 Hz, 4H), 6.95 (d, J=8.8 Hz, 4H), 3.90 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 194.4, 162.8, 132.2, 130.7, 113.4, 55.4.



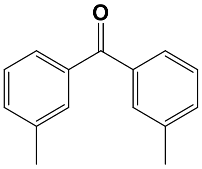
benzophenone (**3b**): [23] White solid (77 mg, 85% yield), Petroleum ether/ethyl acetate (199:1, v/v) as the eluent. ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.79-7.82 (m, 4H), 7.55-7.61 (m, 2H), 7.44-7.50 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ (ppm): 196.8, 137.6, 132.4, 130.0, 128.3.



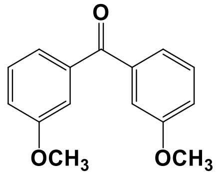
di-p-tolylmethanone (**3c**): [23] Yellow solid (90 mg, 86% yield), Petroleum ether/ethyl acetate (199:1, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.62 (d, J=8 Hz, 4H), 7.19 (d, J=8 Hz, 4H), 2.36 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 195.2, 141.9, 134.2, 129.1, 127.8, 20.6,



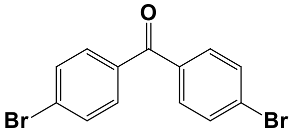
di-m-tolylmethanone (**3d**): [23] Yellow liquid (89 mg, 85% yield), Petroleum ether/ethyl acetate (199:1, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.62 (broad, 2H), 7.55-7.58 (m, 2H), 7.33-7.41(m, 4H), 2.42 (s, 6H), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 196.2, 137.1, 136.7, 132.0, 129.4, 127.0, 126.3, 20.3.



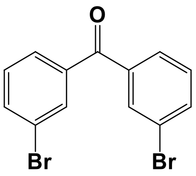
bis(3-methoxyphenyl)methanone (**3e**): [23] Yellow liquid (104 mg, 86% yield), Petroleum ether/ethyl acetate (198:2, v/v) as the eluent. ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.33-7.39 (m, 6H), 7.11-7.14 (m, 2H), 3.85 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 195.3, 158.5, 137.9, 128.1, 117.8, 113.3, 54.4.



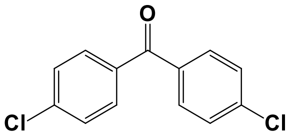
bis(4-bromophenyl)methanone (**3f**): [23] Yellow solid (142 mg, 84% yield), Petroleum ether/ethyl acetate (99:1, v/v) as the eluent. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64 (s, 8H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 193.5, 134.9, 130.7, 130.4, 126.8.



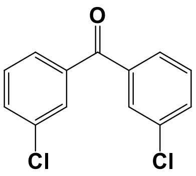
bis(3-bromophenyl)methanone (**3g**): [24] Yellow liqid 142 mg, (84% yield), Petroleum ether/ethyl acetate (99:1, v/v) as the eluent. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.92-7.93 (m, 2H), 7.72-7.75 (m, 2H), 7.67-7.68 (m, 2H), 7.36-7.40 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 193.6, 138.8, 135.7, 132.7, 130.0, 128.5, 122.8.



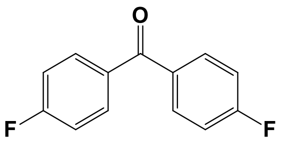
bis(4-chlorophenyl)methanone (**3h**): [23] Light yellow solid (104 mg, 83% yield), Petroleum ether/ethyl acetate (99:1, v/v) as the eluent. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71-7.73 (m, 4H), 7.45-7.48 (m, 4H), $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 194.2, 139.1, 135.5, 131.3, 128.7.



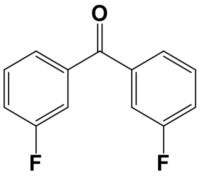
bis(3-chlorophenyl)methanone (**3i**): [23] Yellow solid (105 mg, 84% yield), Petroleum ether/ethyl acetate (99:1, v/v) as the eluent. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.76-7.77 (m, 2H), 7.57-7.66 (m, 2H), 7.41- 7.47 (m, 4H), $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm): 192.8, 137.5, 133.7, 131.7, 128.8, 128.7, 127.0.



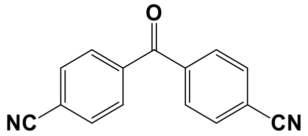
bis(4-flulorophenyl)methanone (**3j**): [23] Yellow solid (89 mg, 82% yield), Petroleum ether/ethyl acetate (99:1, v/v) as the eluent. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.13-7.19 (m, 4H), 7.78-7.83 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 192.7, 164.3 (d, J=252.7 Hz), 132.7 (d, J=3 Hz), 131.47 (d, J=9 Hz), 114.5 (d, J=21.7 Hz).



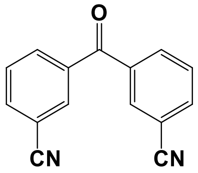
bis(3-flulorophenyl)methanone (**3k**): [23] Pale yellow solid (88 mg, 81% yield), Petroleum ether/ethyl acetate (99:1, v/v) as the eluent. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.585-7.57 (m, 2H), 7.45-7.51 (m, 4H), 7.28-7.33 (m, 2H), $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 192.8, 161.5 (d, J=246.9 Hz), 138.0 (d, J=6.3 Hz), 129.1 (d, J=7.6 Hz), 124.7 (d, J=3 Hz), 118.7 (d, J=21.3 Hz), 115.6 (d, J=22.4 Hz).



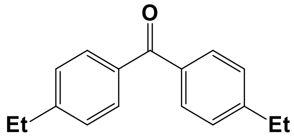
4, 4'-carbonyldibenzonitrile (**3l**): [23] Light yellow solid (93 mg, 81% yield), Petroleum ether/ethyl acetate (97:3, v/v) as the eluent. ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.81-7.89 (m, 8H), ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ (ppm): 193.4, 139.7, 132.5, 132.5, 130.2, 117.7, 116.5.



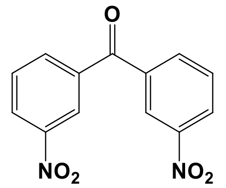
3, 3'-carbonyldibenzonitrile (**3m**): Yellow solid (92 mg, 80% yield), Petroleum ether/ethyl acetate (97:3, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.91-8.06 (m, 6H), 7.68 (t, J=8 Hz, 2H), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 191.2, 136.3, 135.0, 132.6, 132.3, 128.7, 112.4. HRMS (EI, m/z,): calcd for $C_{16}H_{13}N_2O_2$: 265.0977; found: 265.0467 [M+MeOH+H].



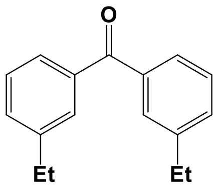
bis(4-ethylphenyl)methanone (**3n**): [23] Yellow liquid (101 mg, 85% yield), Petroleum ether/ethyl acetate (199:1, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.73 (d, J=8.4 Hz, 4H), 7.29 (d, J=8.4 Hz, 4H), 2.70-2.76 (m, 4H), 1.28 (t, J=7.6 Hz, 6H), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 195.2, 148.0, 134.4, 129.2, 126.7, 27.9, 14.2.



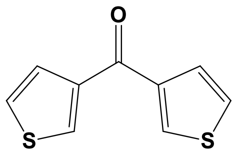
bis(3-nitrophenyl)methanone (**3o**): [25] Yellow solid (110 mg, 81% yield), Petroleum ether/ethyl acetate (97:3, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 8.62 (s, 2H), 8.50-8.52 (m, 2H), 8.14 (d,J=7.6 Hz, 2H), 7.77 (t, J=7.6 Hz, 2H), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 191.5, 148.3, 137.7, 135.2, 130.1, 127.5, 124.6,



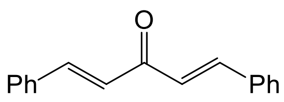
bis(3-ethylphenyl)methanone (**3p**): Yellow liquid (97 mg, 82% yield), Petroleum ether/ethyl acetate (199:1, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.57-7.66 (m, 4H), 7.35-7.44 (m, 4H), 2.68-2.76 (m, 4H), 1.27 (t, J=10 Hz, 6H), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 196.2, 143.4, 136.8, 130.9, 128.3, 127.0, 126.6, 27.3, 14.5. HRMS (EI, m/z,): calcd for $C_{17}H_{19}O$: 239.1436; found: 239.1401 [M+H].



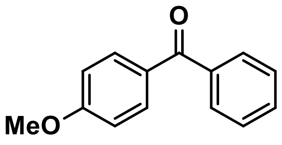
di(thiophen-3-yl)methanone (**3q**): [26] White solid (79 mg, 82% yield), Petroleum ether/ethyl acetate (99:1, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 8.03-8.04 (m, 2H), 7.62-7.63 (m, 2H), 7.40-7.42 (m, 2H), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 182.2, 141.0, 131.6, 127.2, 125.3.



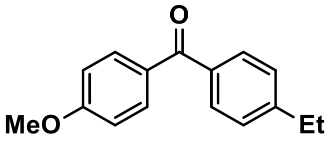
(1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (**3r**): [27] white solid (95 mg, 82% yield), Petroleum ether/ethyl acetate (99:1, v/v) as the eluent. ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.7 (d, J = 15.9 Hz, 2H), 7.63-7.66 (m, 4H), 7.43-7.45 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ (ppm): 188.7, 143.3, 134.8, 130.5, 128.9, 128.4, 125.4.



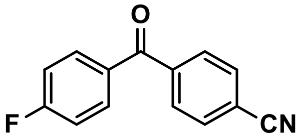
(4-methoxyphenyl)(phenyl)methanone (**3s**): [28] white solid (58 mg, 55% yield), Petroleum ether/ethyl acetate (98:2, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.81-7.84 (m, 2H), 7.74-7.76 (m, 2H), 7.54-7.58 (m, 1H), 7.44-7.49 (m, 2H), 6.94-6.98 (m, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 195.6, 163.2, 138.3, 132.5, 131.9, 130.1, 129.7, 128.2, 55.5.



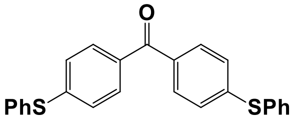
(4-ethylphenyl)(4-methoxyphenyl)methanone (**3t**): [29] white solid (63 mg, 53% yield), Petroleum ether/ethyl acetate (98:2, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.72-7.76 (m, 2H), 7.60-7.63 (m, 2H), 7.20-7.22(m, 2H), 6.87-6.89 (m, 2H), 3.80 (s, 3H), 2.62-2.68 (m, 2H), 1.20 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 194.3, 162.0, 147.7, 134.7, 131.4, 129.4, 129.0, 126.6, 54.4, 27.9, 14.2.



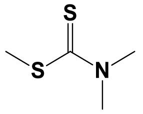
4-(4-fluorobenzoyl)benzonitrile (**3u**): [30] white solid (64 mg, 57% yield), Petroleum ether/ethyl acetate (97:3, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.71-7.78 (m, 6H), 7.08-7.15 (m, 2H), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 193.5, 165.8 (J = 254 Hz), 141.1, 132.7 (J = 10 Hz), 132.6 (J = 3 Hz), 132.2, 130.0, 117.9, 115.9 (J = 22 Hz), 115.7.



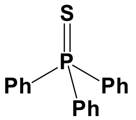
bis(4-(phenylthio)phenyl)methanone **7**: [31] White solid (179 mg, 90% yield), Petroleum ether/ethyl acetate (99:1, v/v) as the eluent. ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.54-7.58 (m, 4H), 7.38-7.43 (m, 4H), 7.27-7.33 (m, 6H), 7.11-7.16 (m, 4H), ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ (ppm): 194.8, 144.1, 134.8, 133.8, 132.2, 130.6, 129.7, 128.7, 127.4.



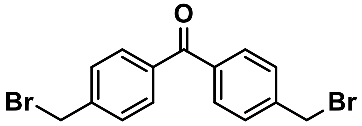
methyl dimethylcarbamodithioate 2a: White solid (60 mg, 90% yield). Petroleum ether/ethyl acetate (100:1, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 3.55 (s, 3H). 3.37 (s, 3H), 2.63 (s, 3H), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 197.4, 44.3, 40.3, 19.4.



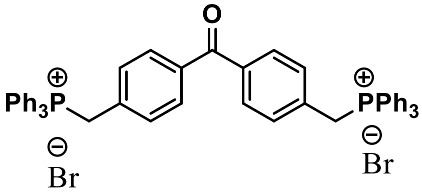
triphenylphosphine sulfide: [32] Yellow solid (110 mg, 75% yield), Petroleum ether/ethyl acetate (100:0, v/v) as the eluent. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.71-7.77 (m, 6H), 7.44-7.55 (m, 9H), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ (ppm): 132.9 (J=84.7 Hz), 132.2 (J=10.6 Hz), 131.5 (J=3 Hz), 128.5 (J=12.4 Hz).



Bis(4-(bromomethyl)phenyl)methanone (**9a**): [33] Yellow solid (588 mg, 80% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.77 (d, J = 8.4 Hz, 4H), 7.50 (d, J = 8.4 Hz, 4H), 4.53 (s, 4H).



4,4’-Bis((triphenylphosphonio)methyl)benzophenone Dibromide (**9b**): [34] Yellow solid (154 mg, 64% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.90-7.94 (m, 6H), 7.71-7.79 (m, 24H), 7.51 (d, J = 7.6 Hz, 4H), 7.15 (d, J = 6.4 Hz, 4H), 5.36 (d, J = 16.4 Hz, 4H).

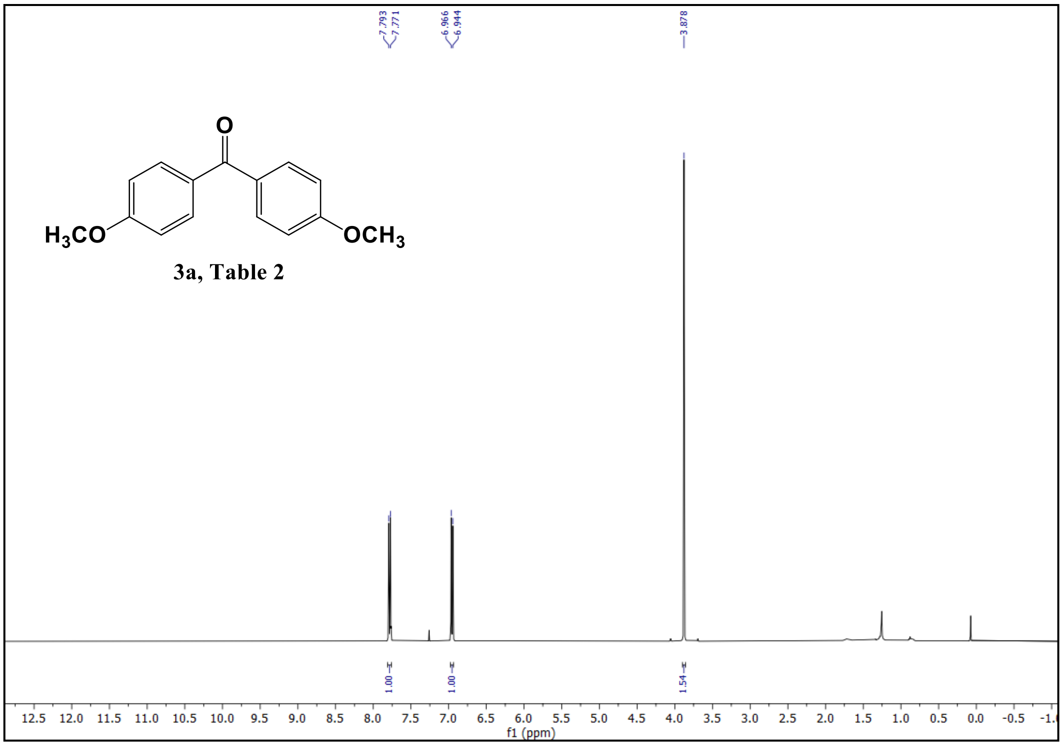


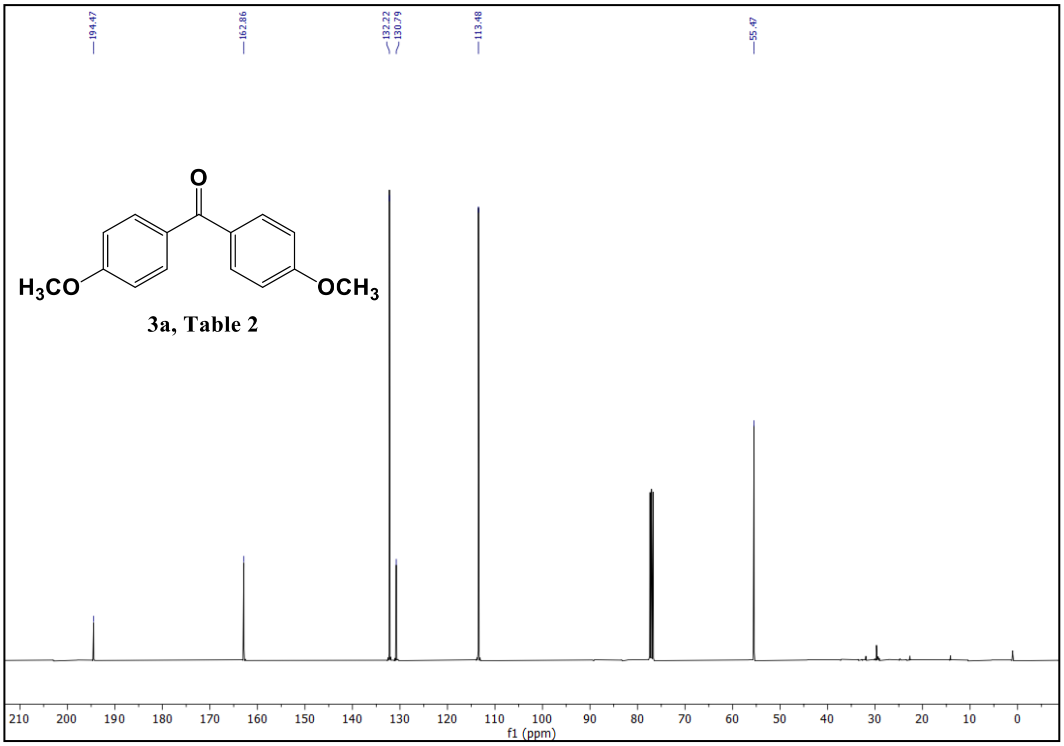
3.2/e.

^{1}H and ^{13}C NMR spectra of all synthesized products described in section -II

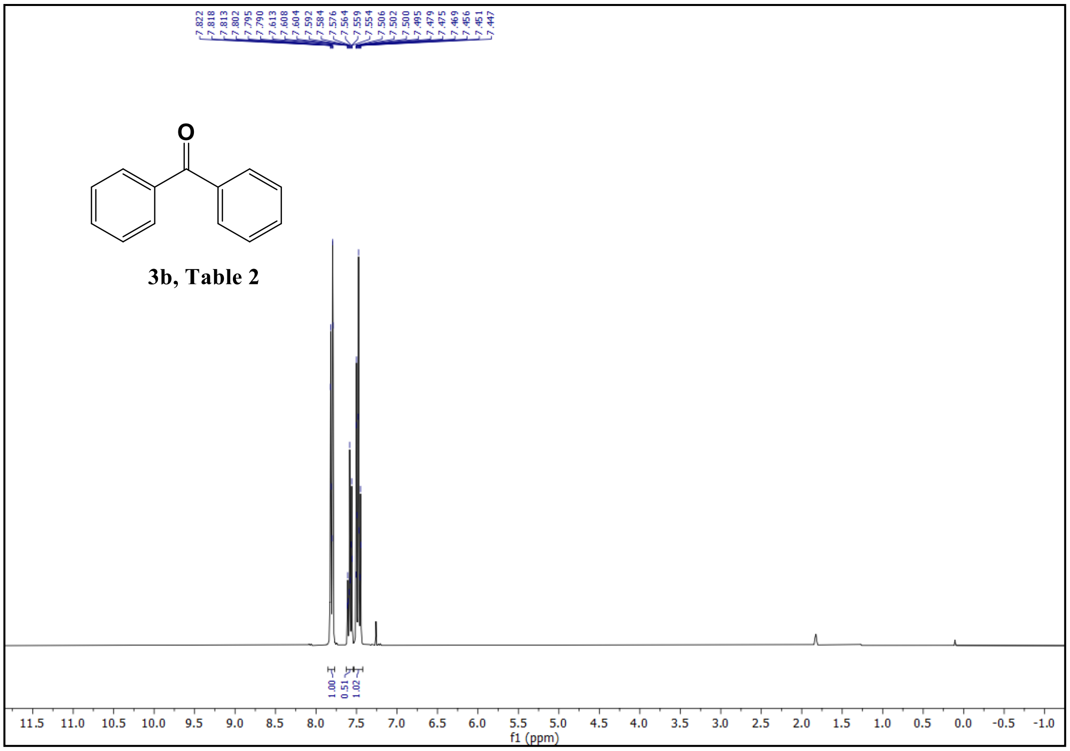
^{1}H, ^{13}C and ^{19}F NMR spectra of products:

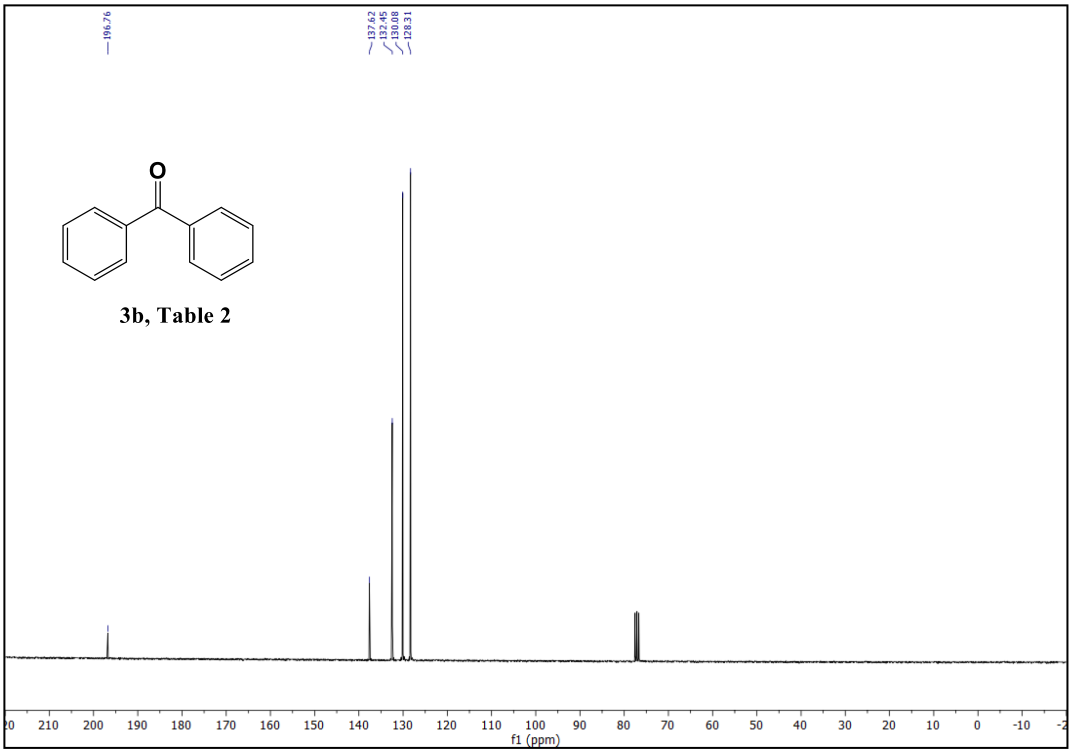
1. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum **3a**



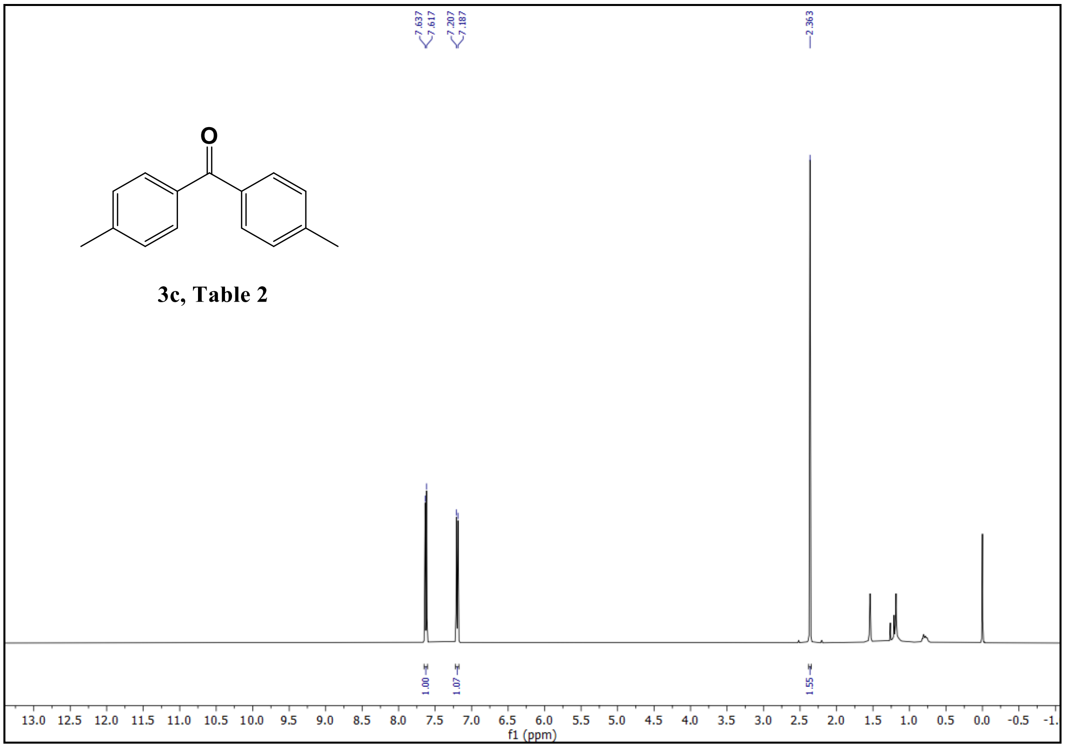


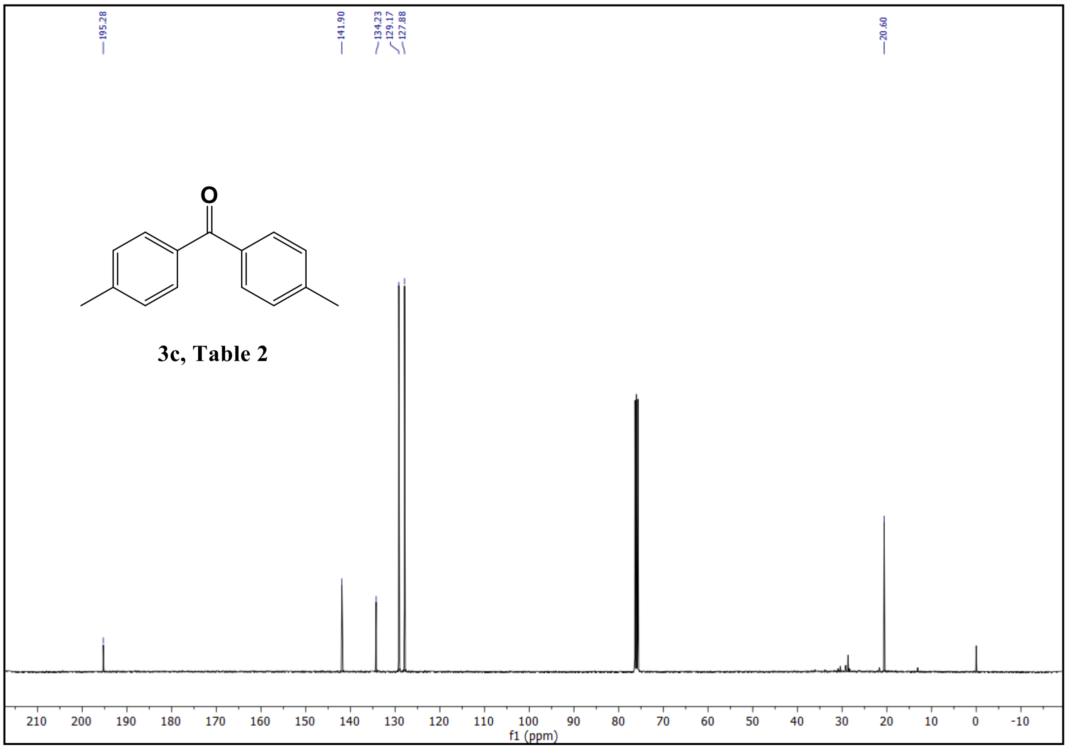
2.^{1}H NMR (300 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) spectrum of **3b**



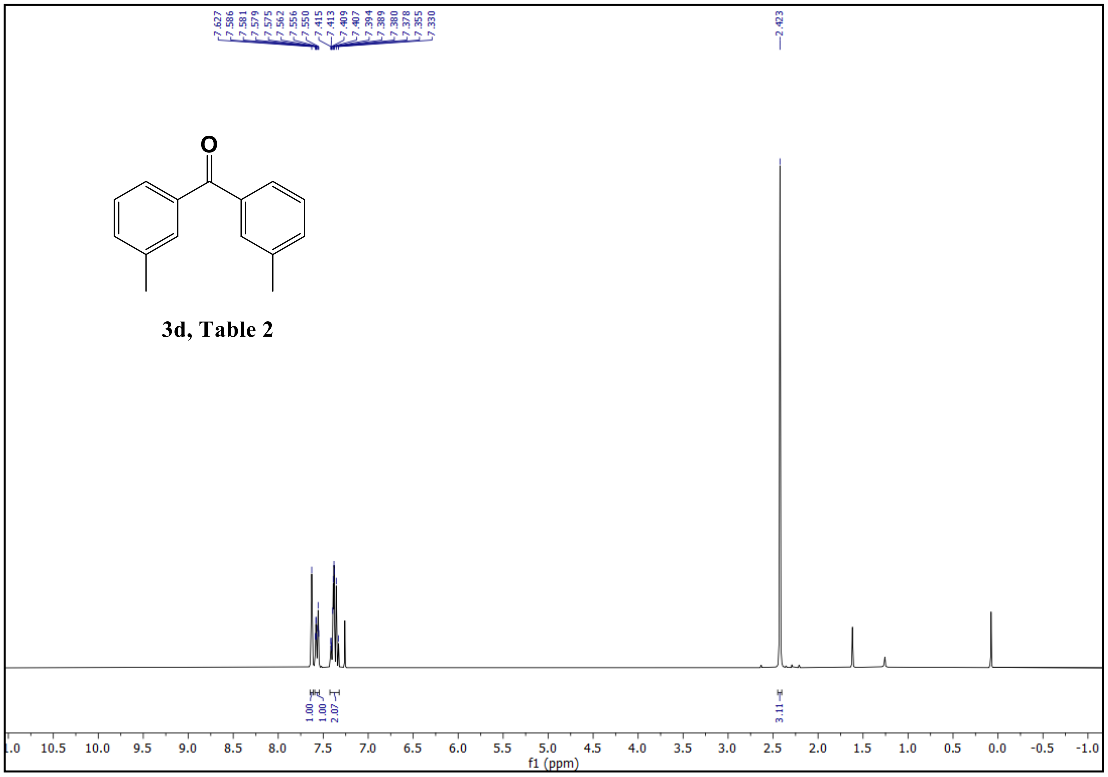


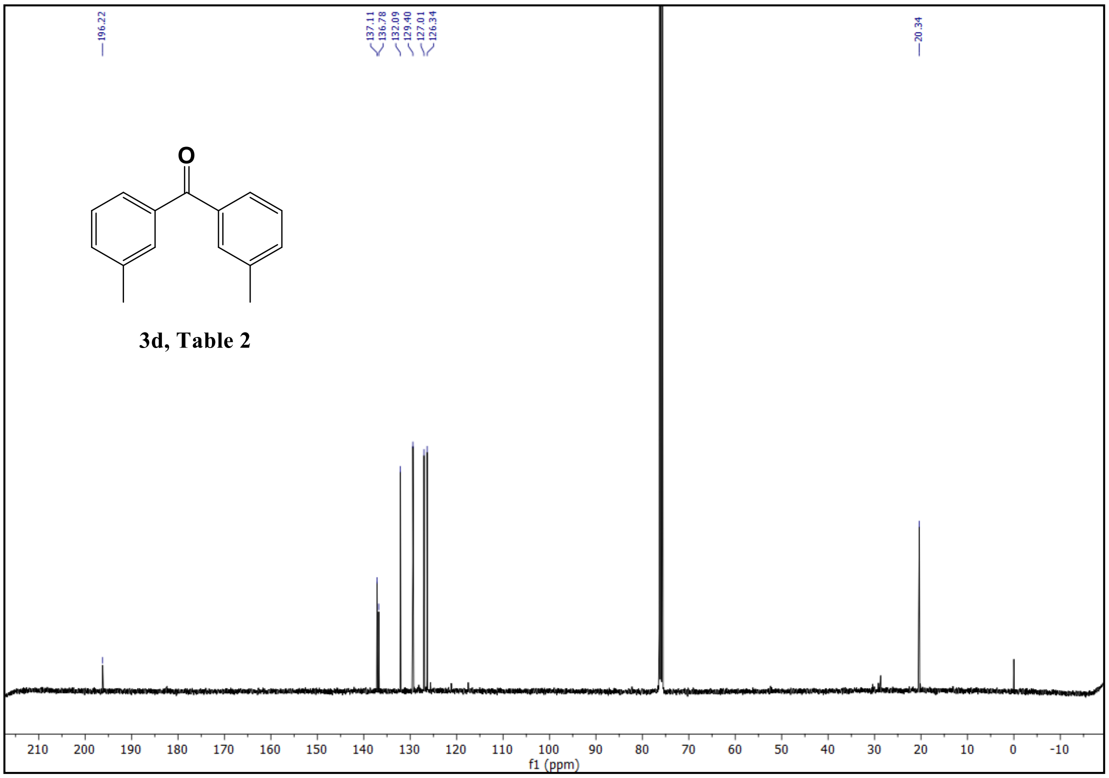
3. ^{1}H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **3c**



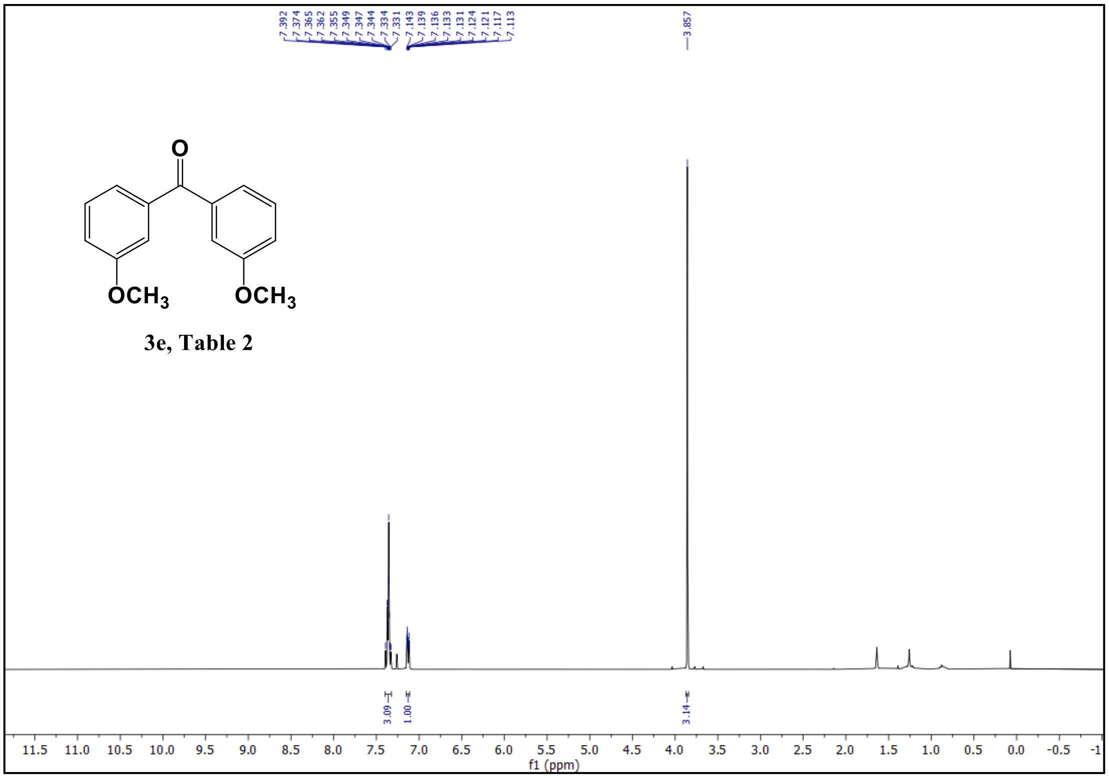


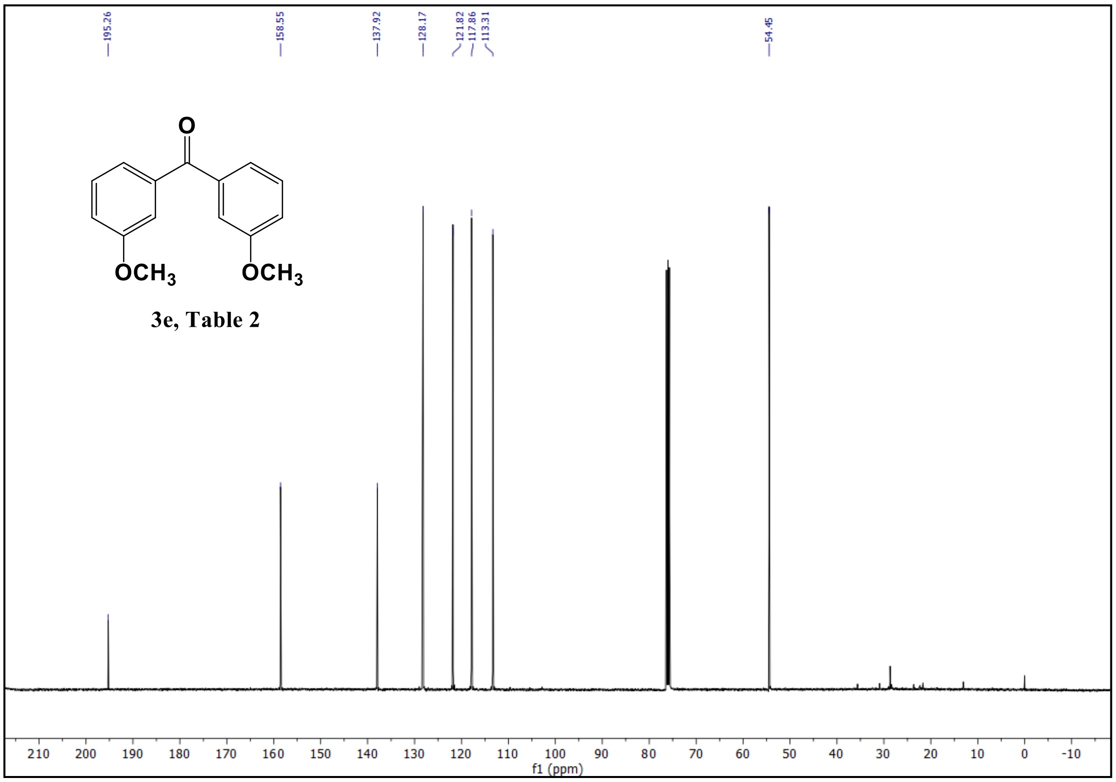
4. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **3d**



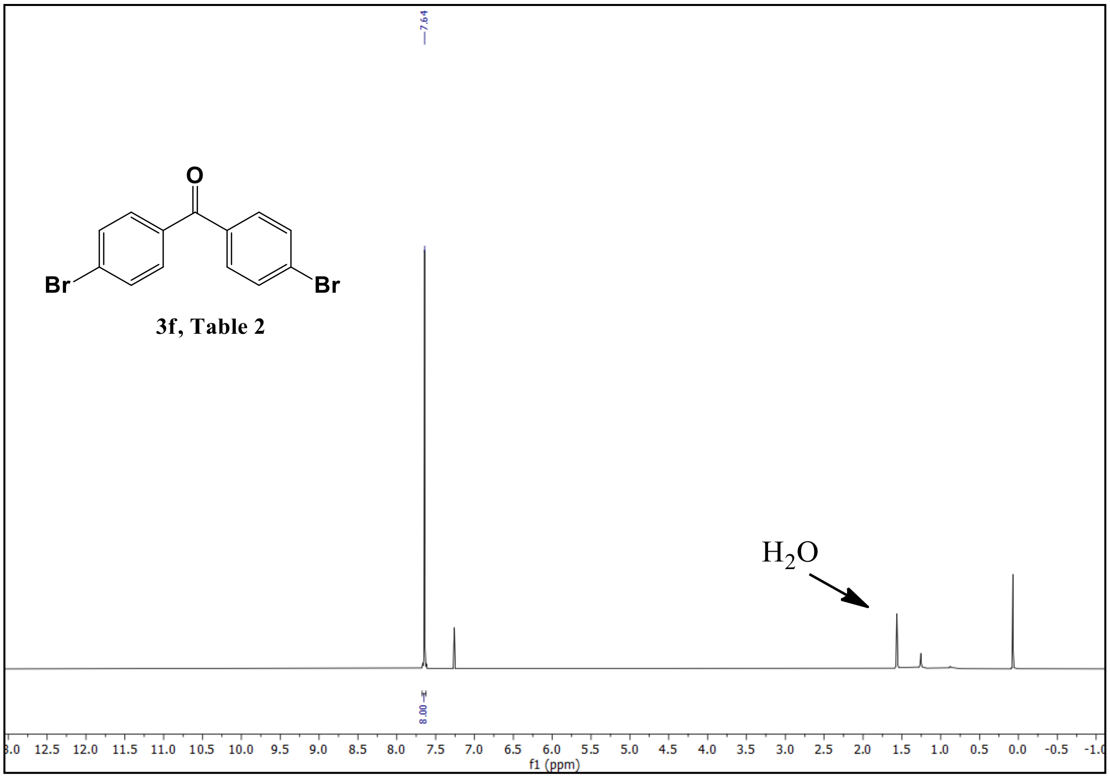


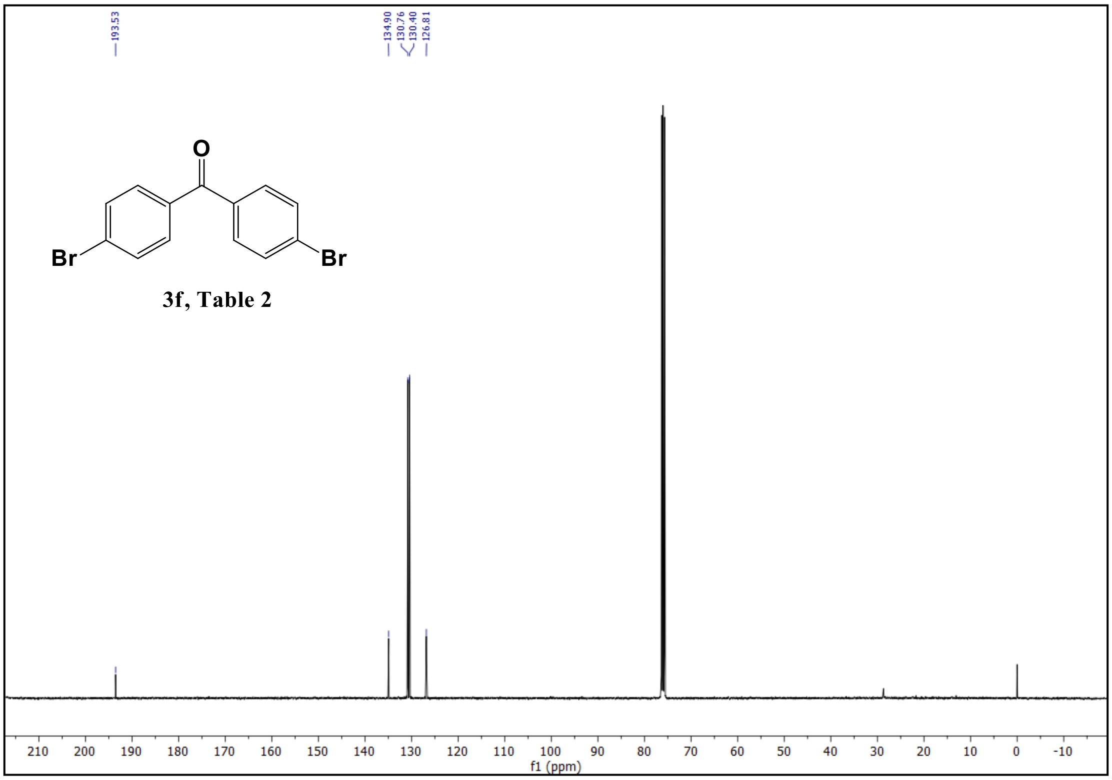
5. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **3e**



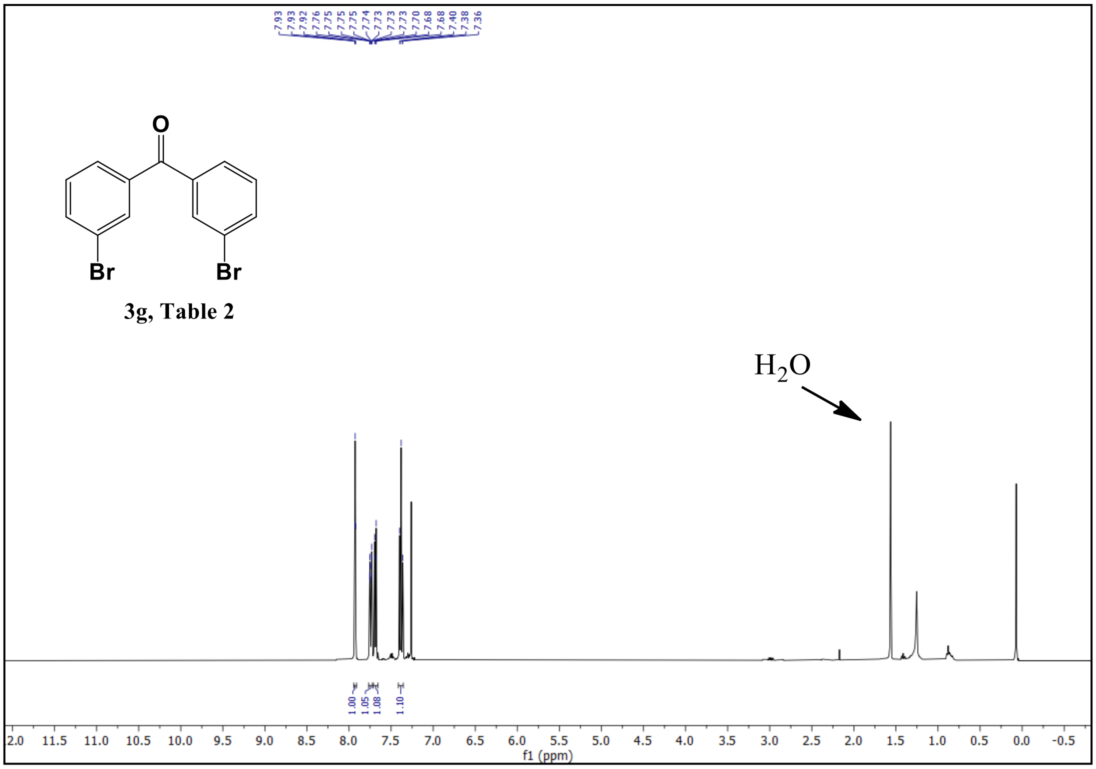


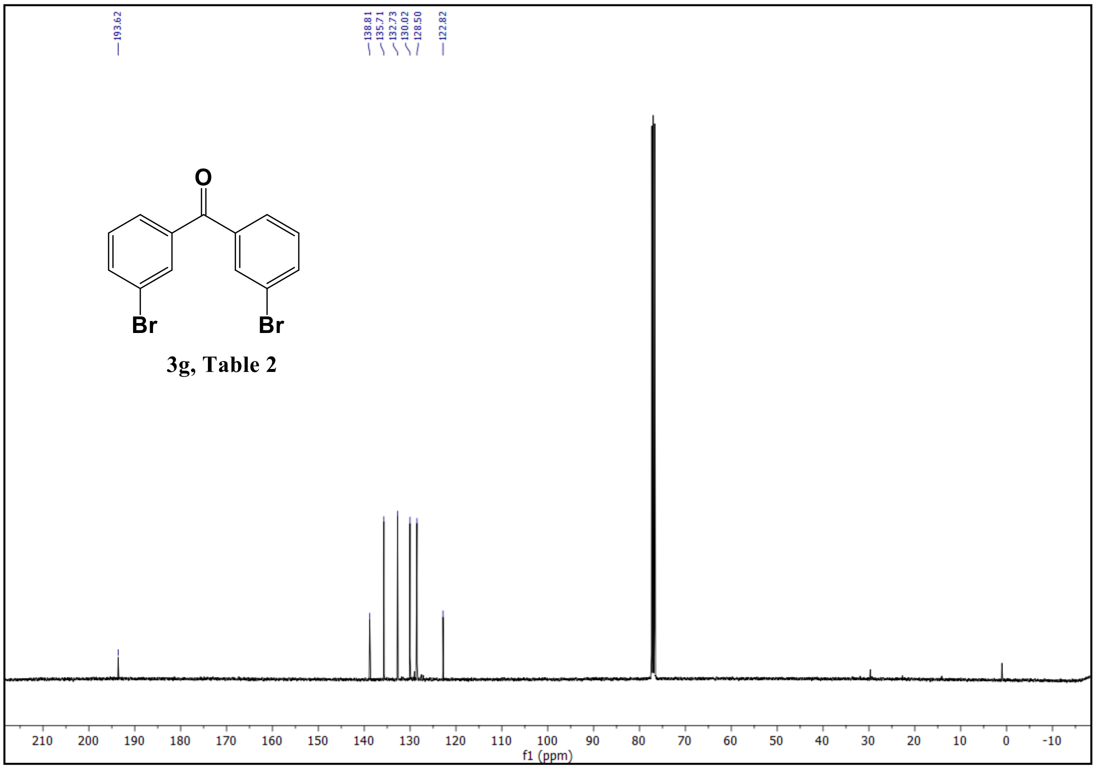
6. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **3f**



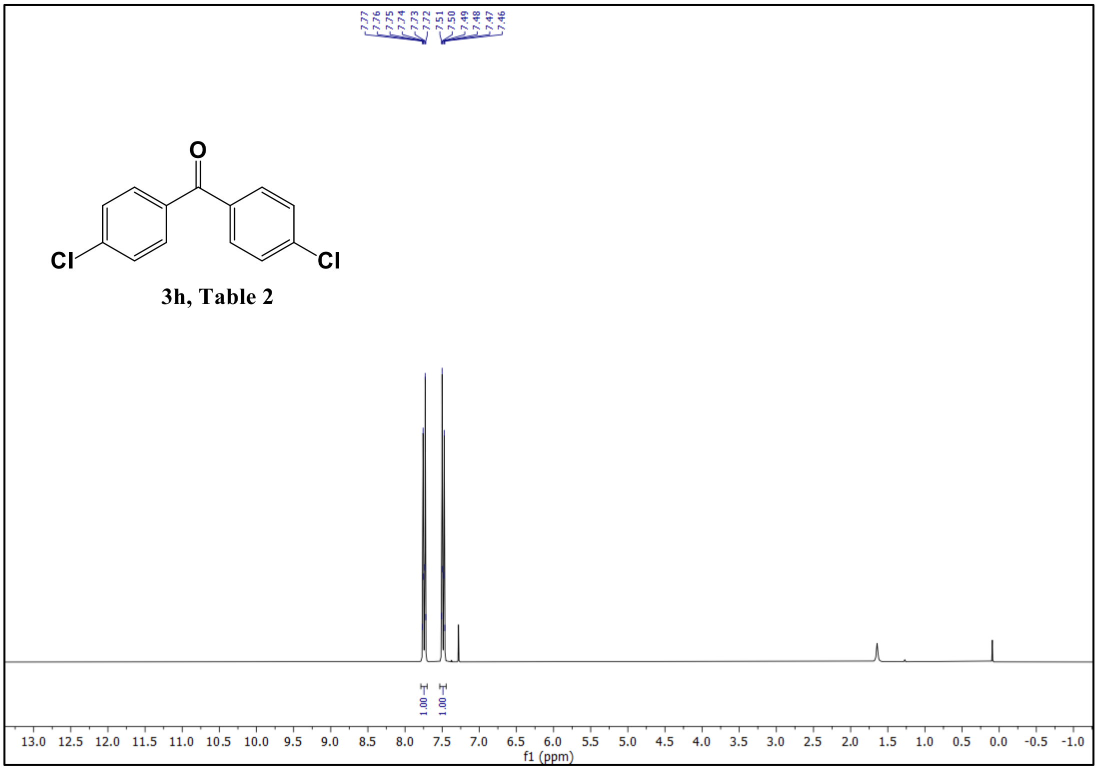


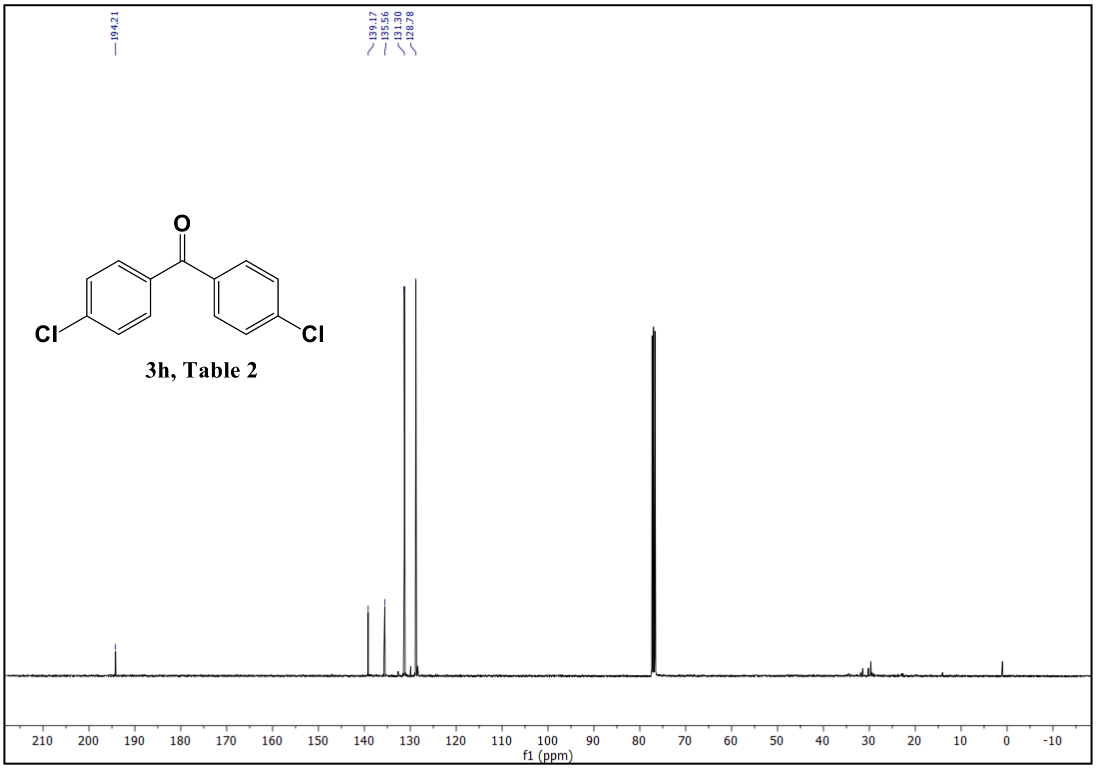
7. ^{1}H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **3g**



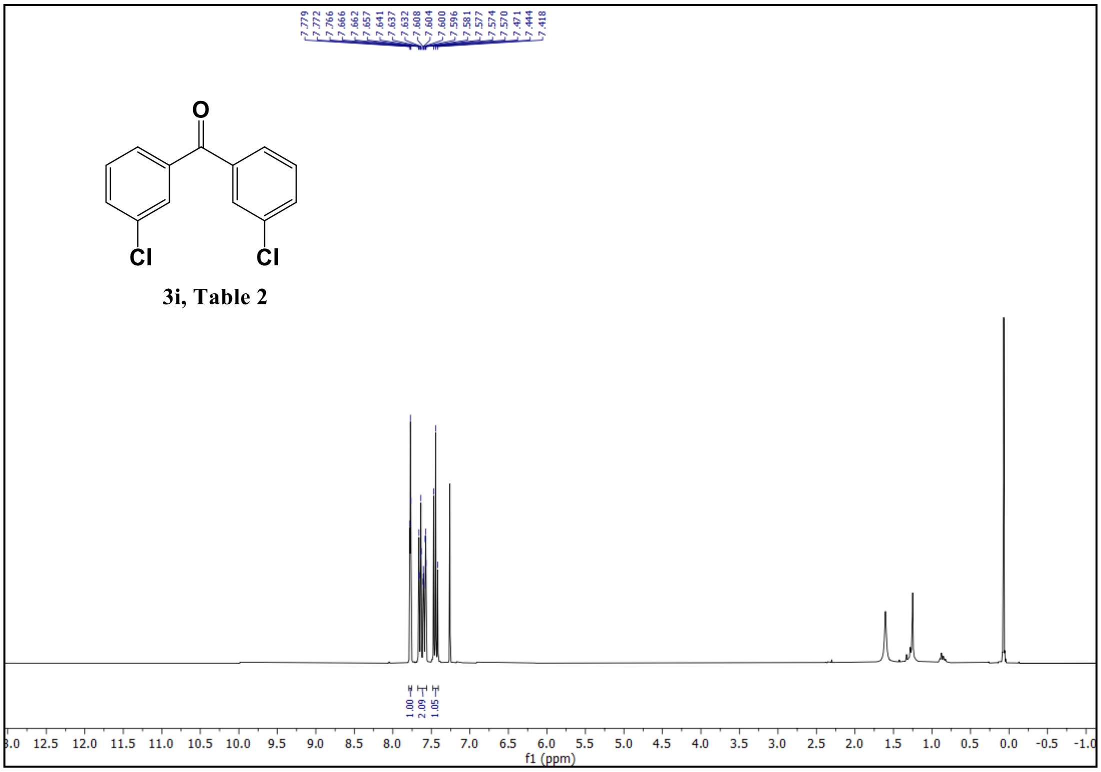


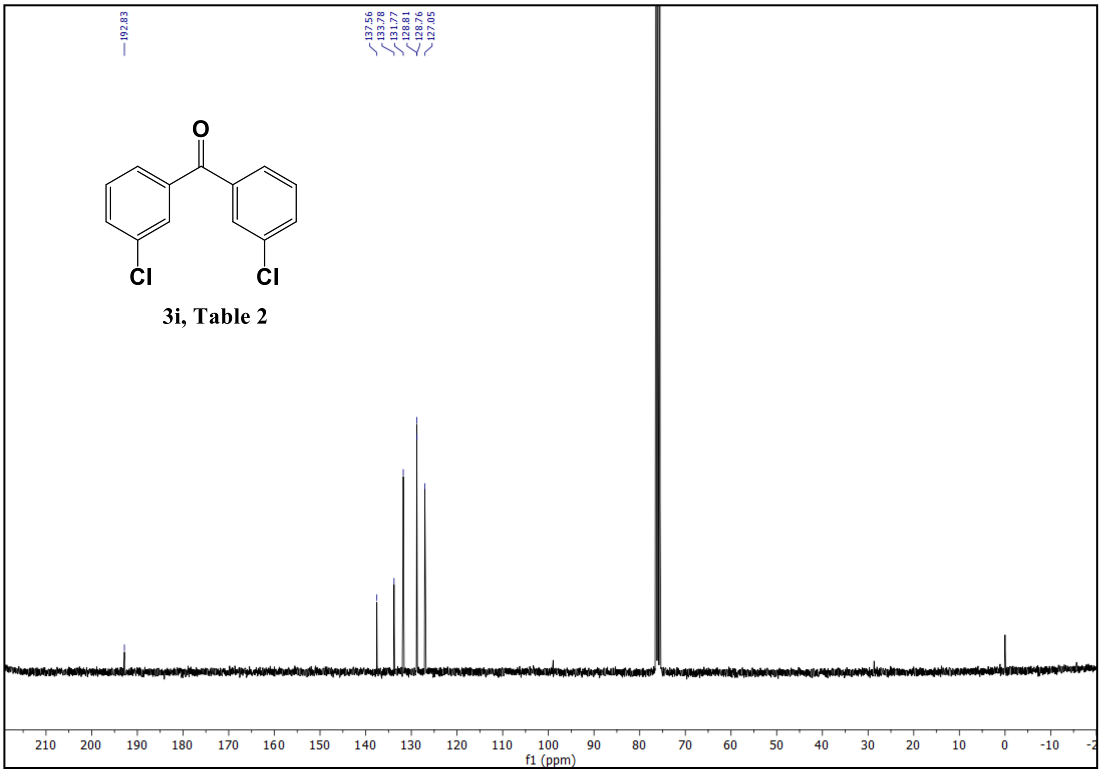
8. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **3h**



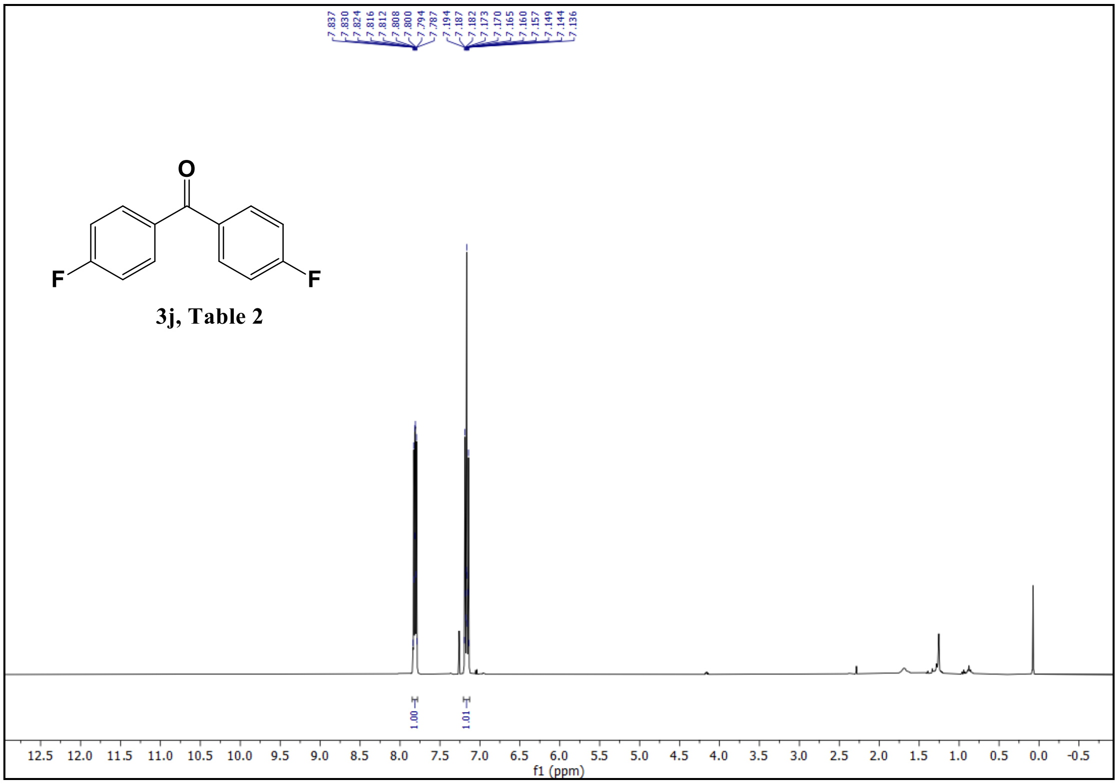


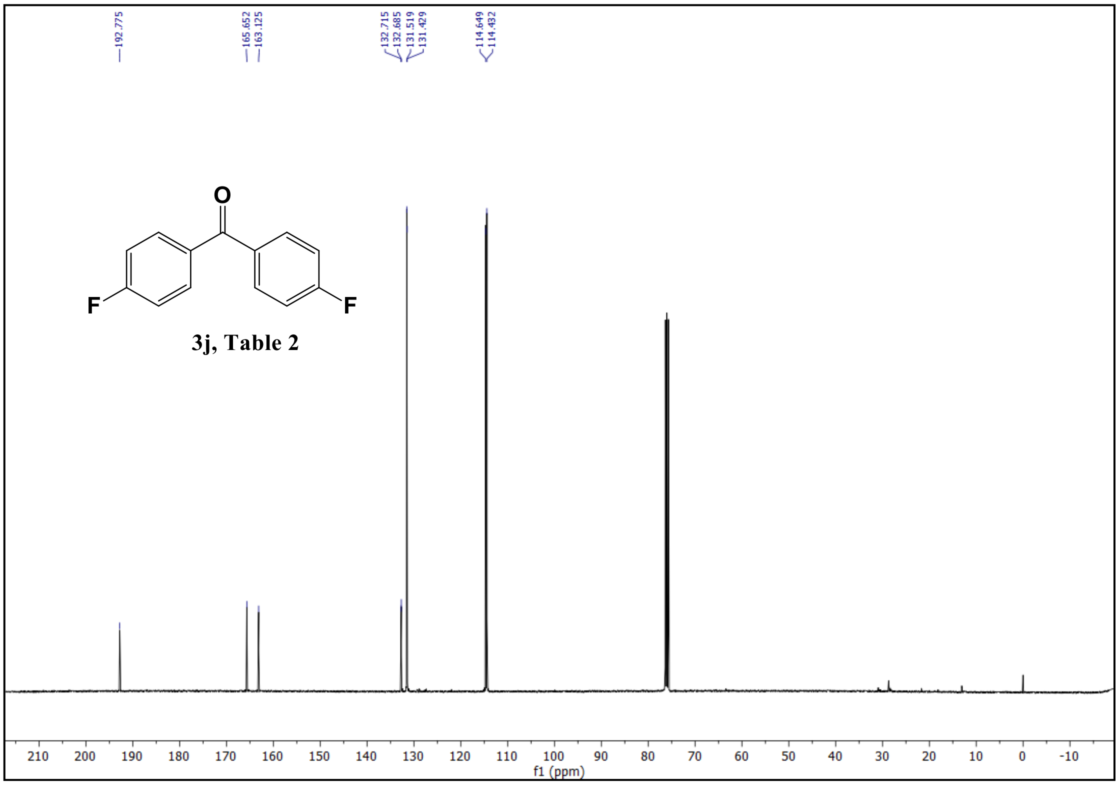
9.^{1}H NMR (300 MHz, CDCl$_3$) and ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) spectrum of **3i**

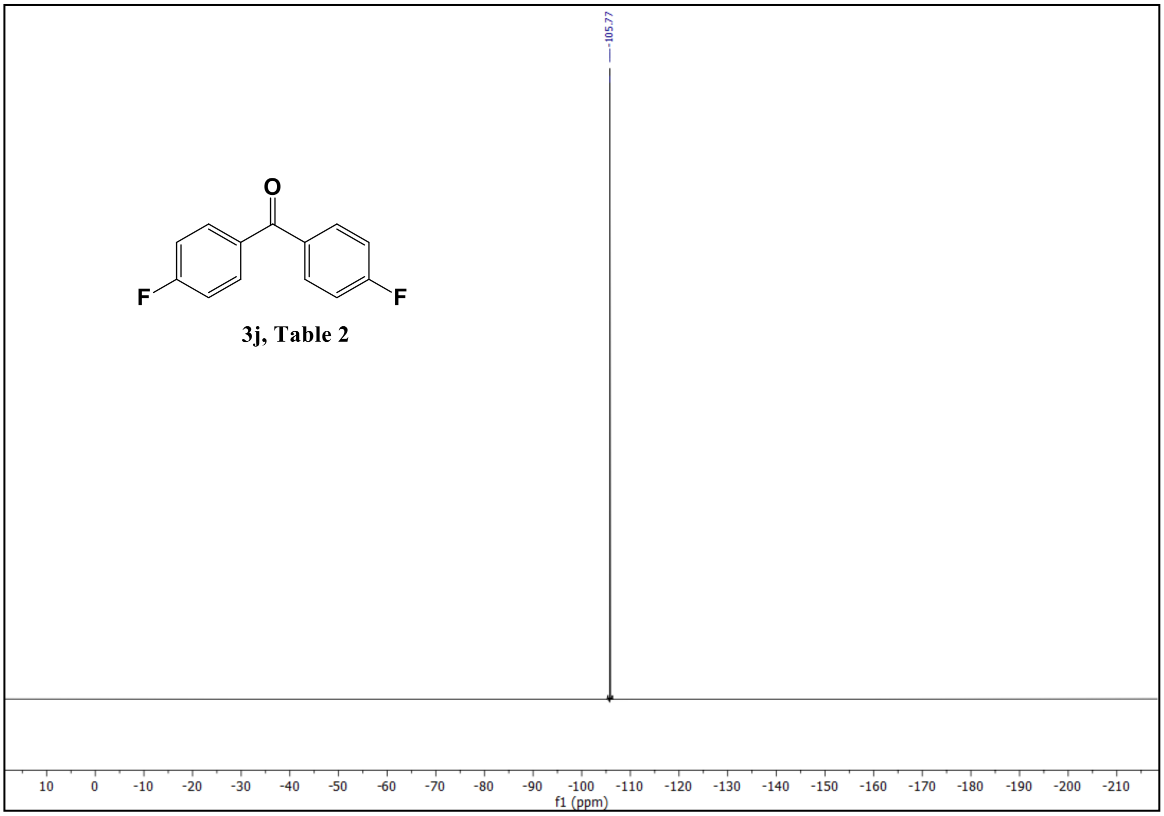




10. ^{1}H NMR (400 MHz, CDCl$_3$), ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum and ^{19}F spectrum of **3j**



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F
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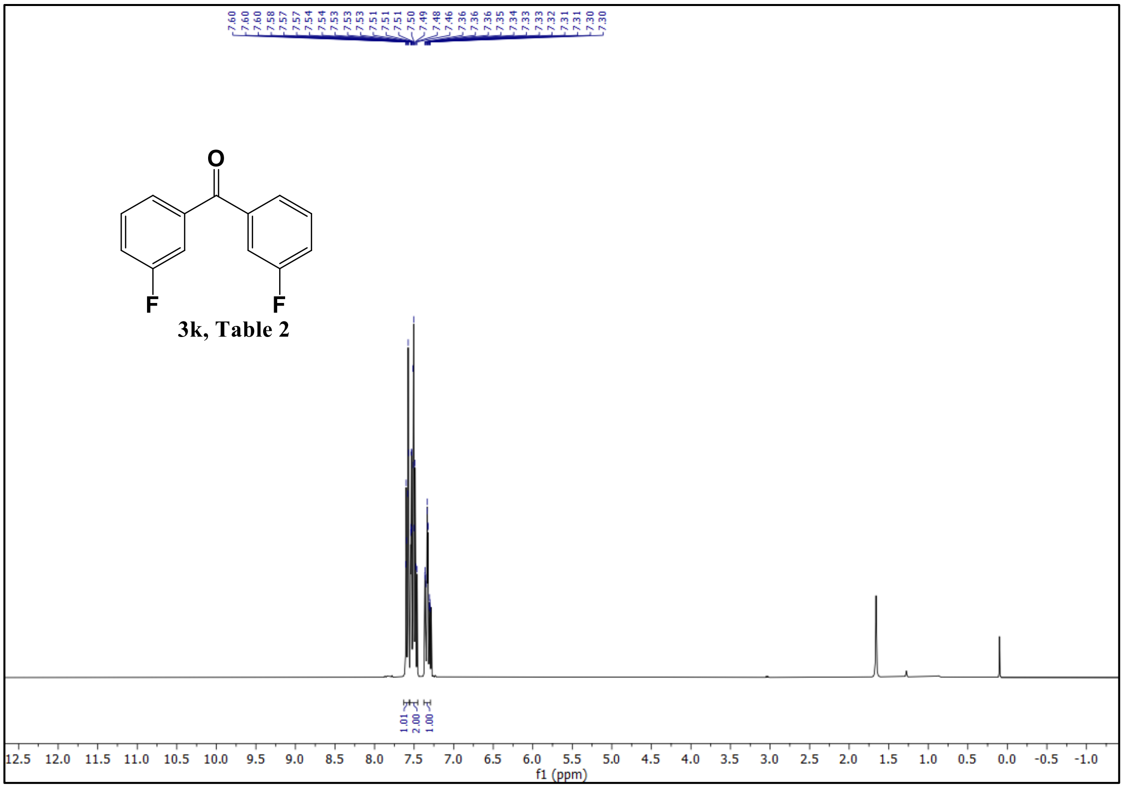
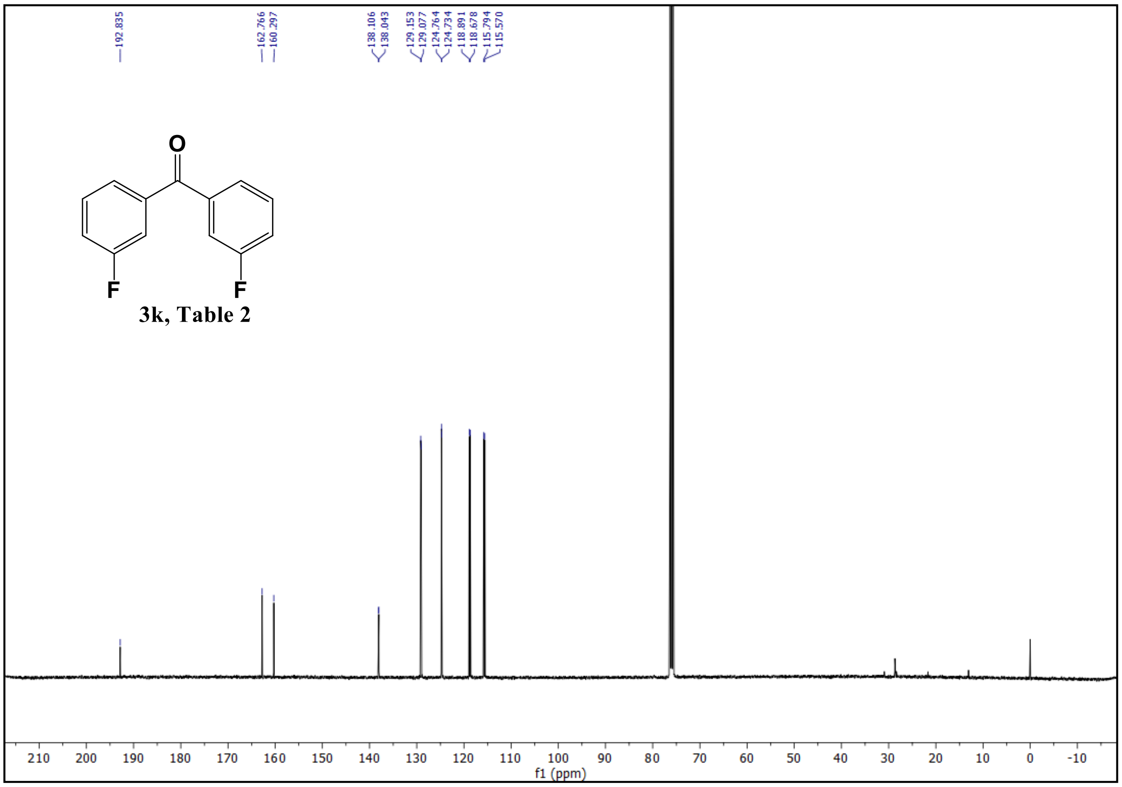
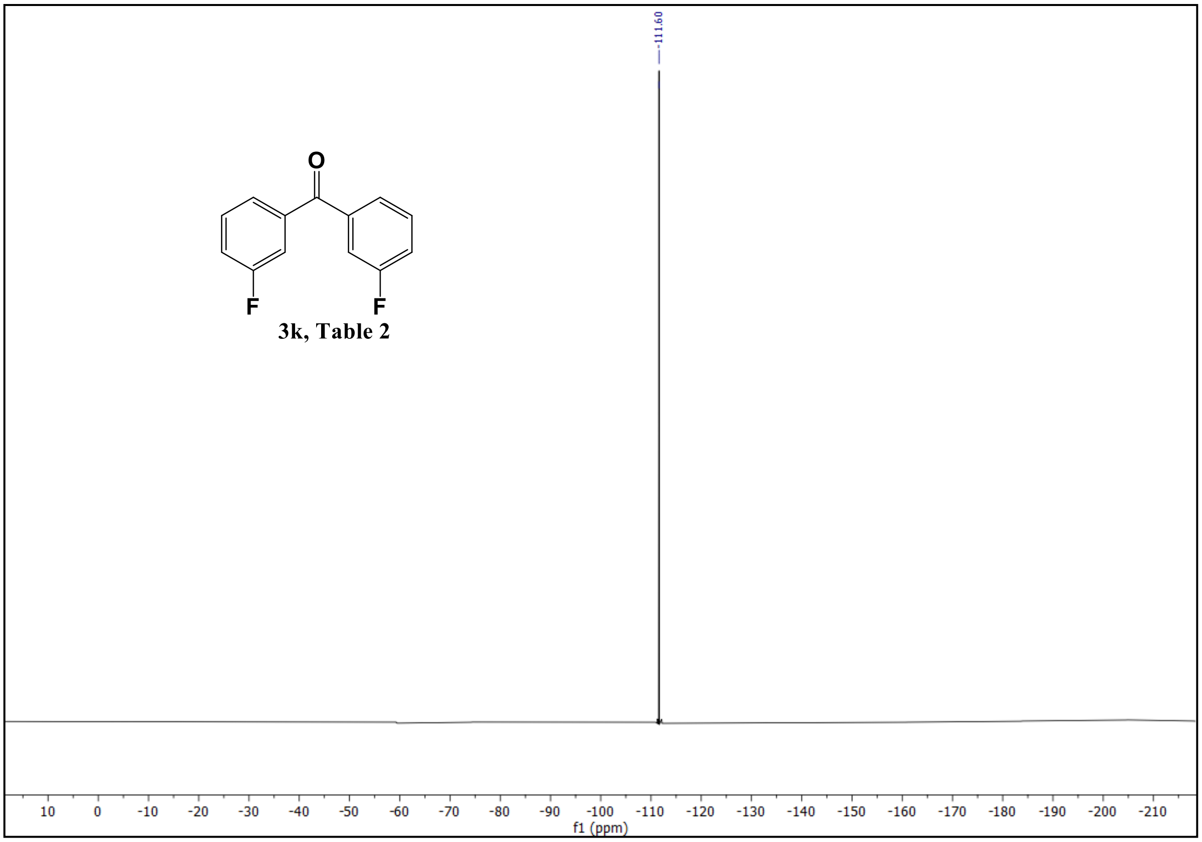
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

3j, Table 2

11. ^{1}H NMR (400 MHz, $CDCl_3$), $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum and ^{19}F spectrum of **3k**







3k, Table 2

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-50
-60
-70
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-110
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-160
-170
-180
-190
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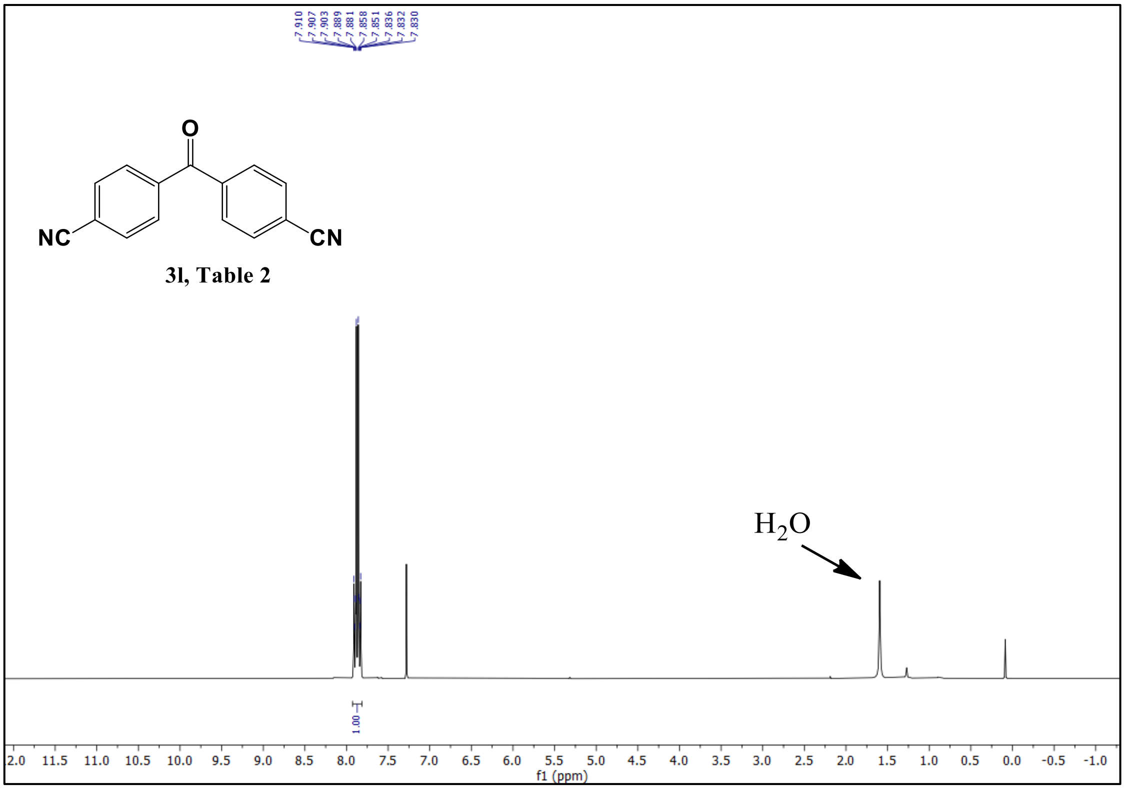
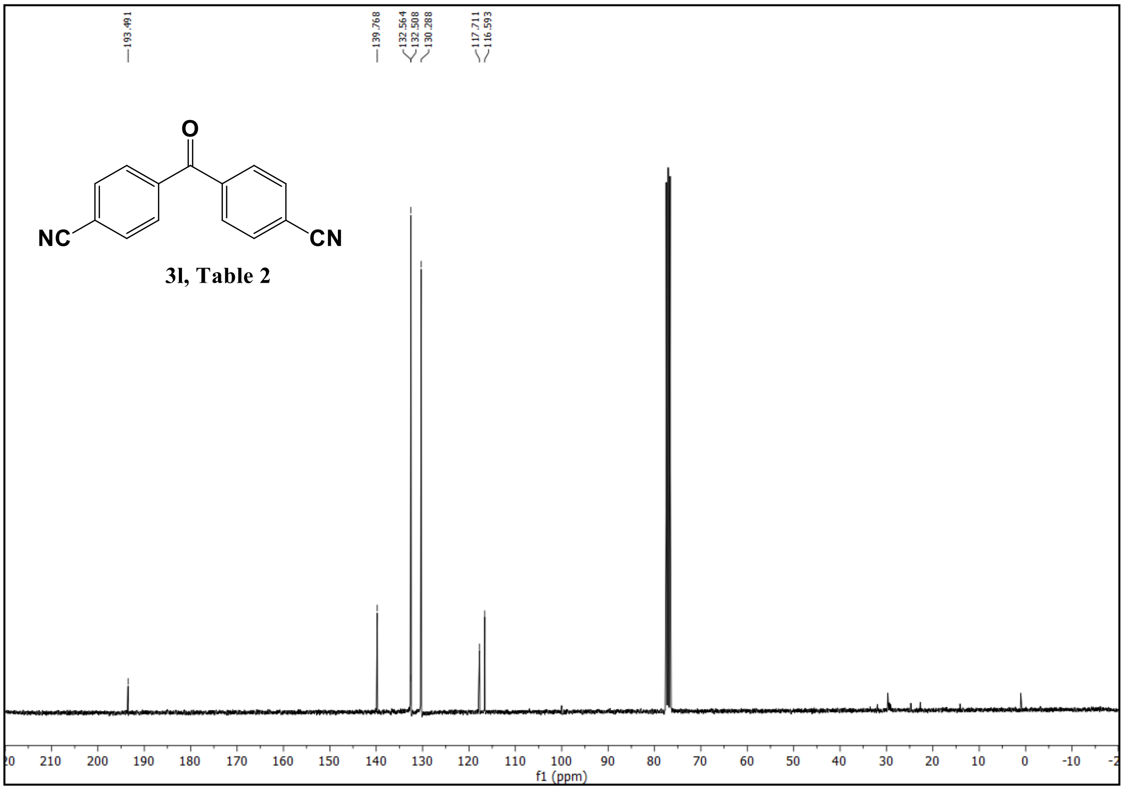
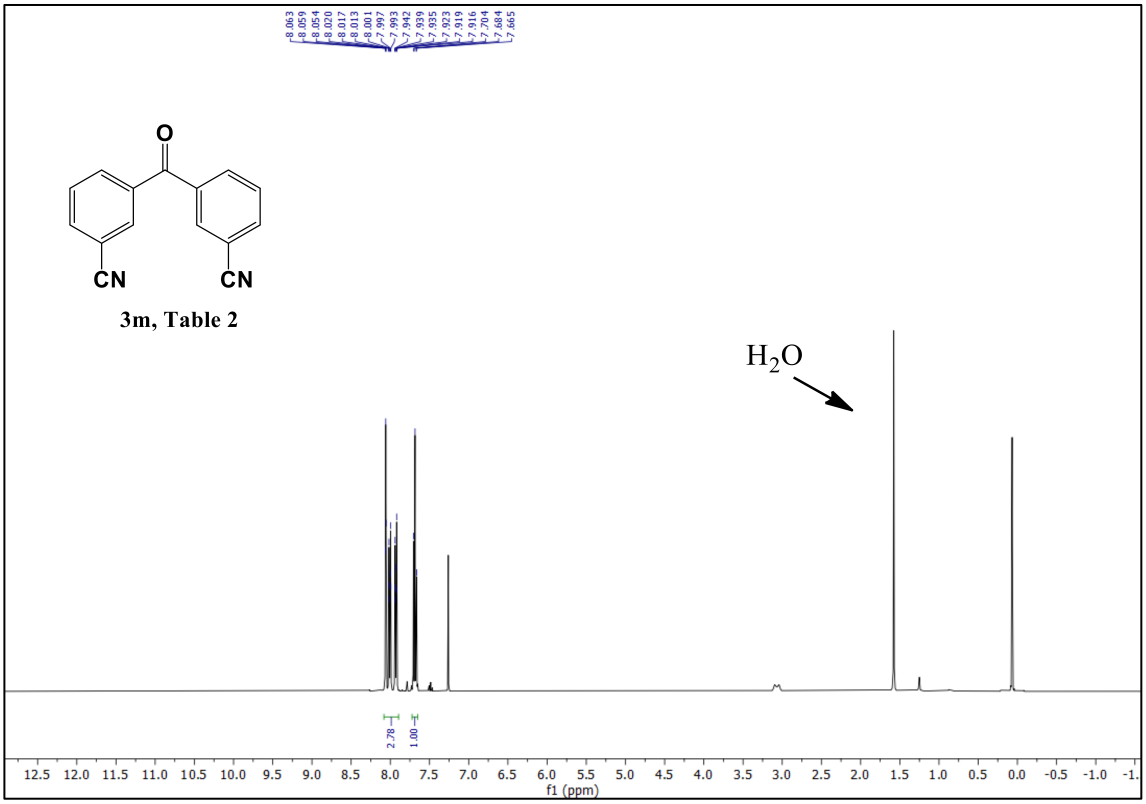
f1 (ppm)

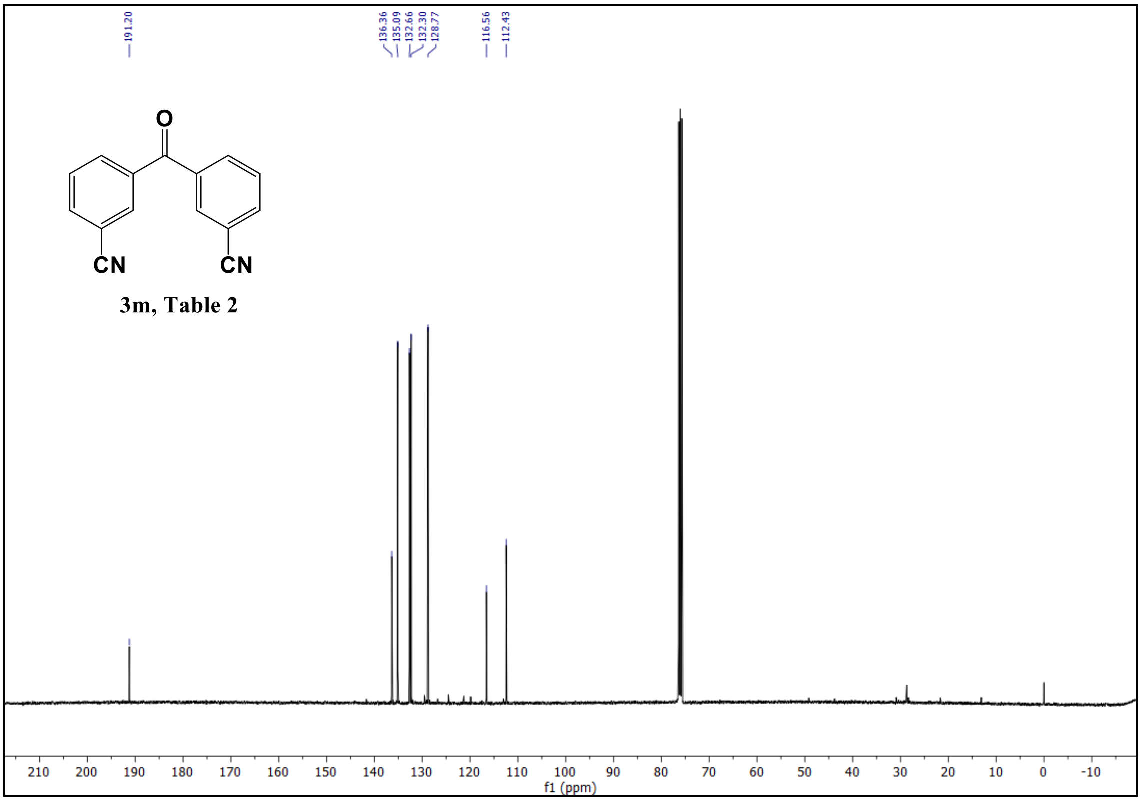
12. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) spectrum of **3l**



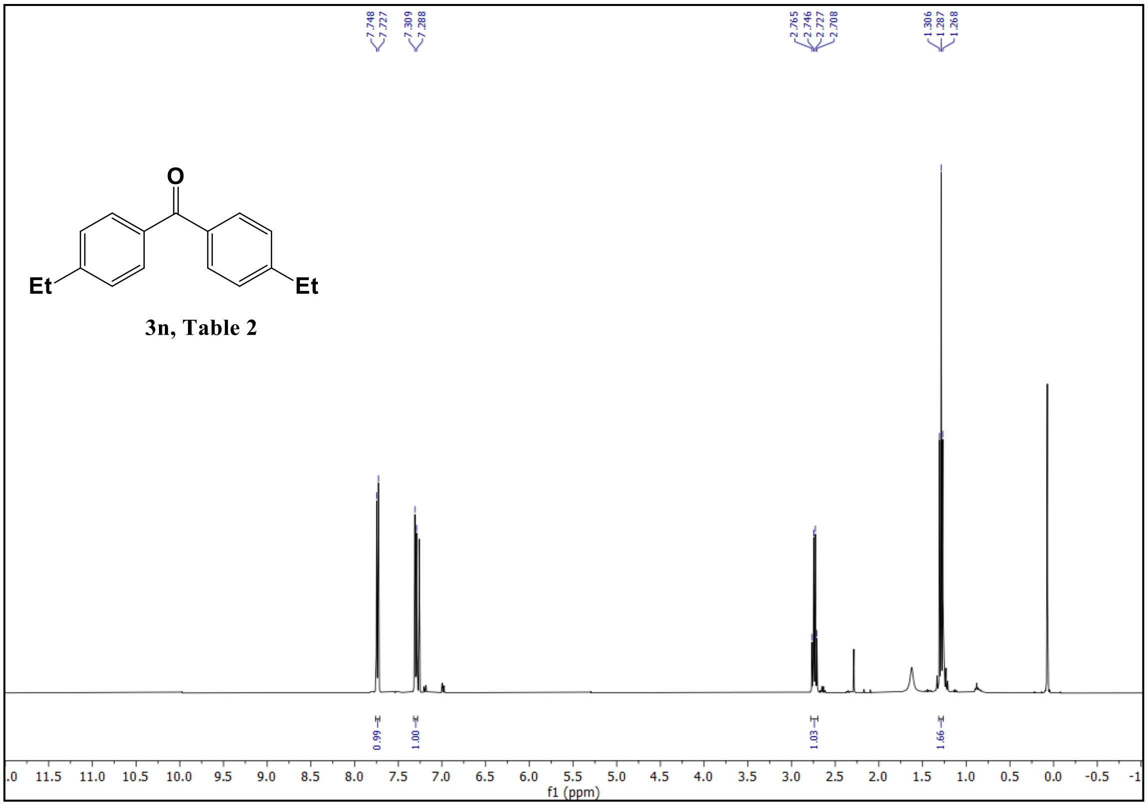


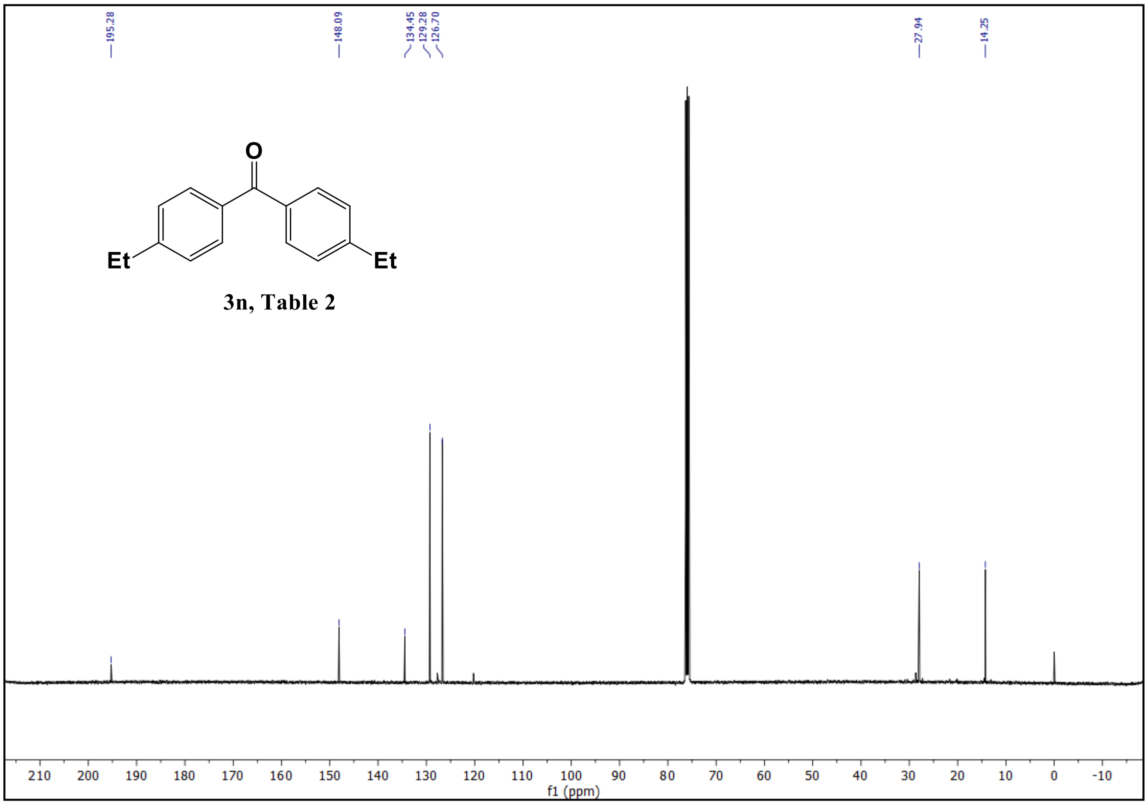
13. ^1H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **3m**



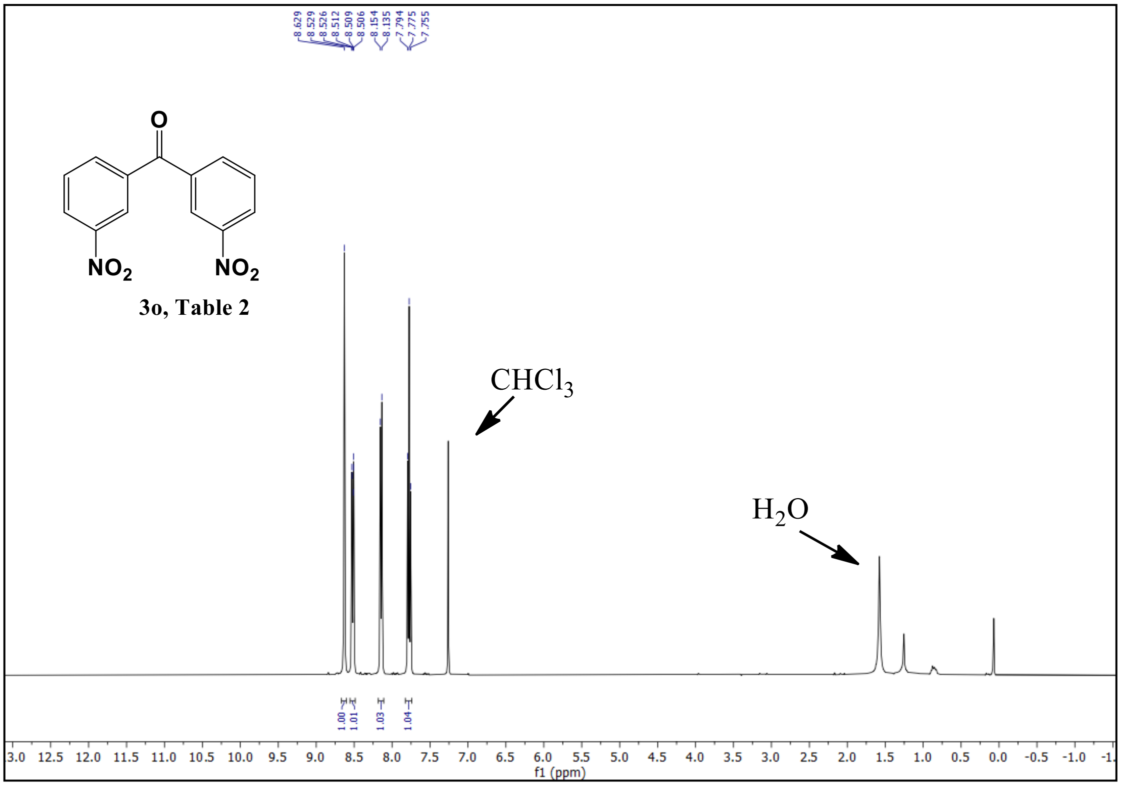


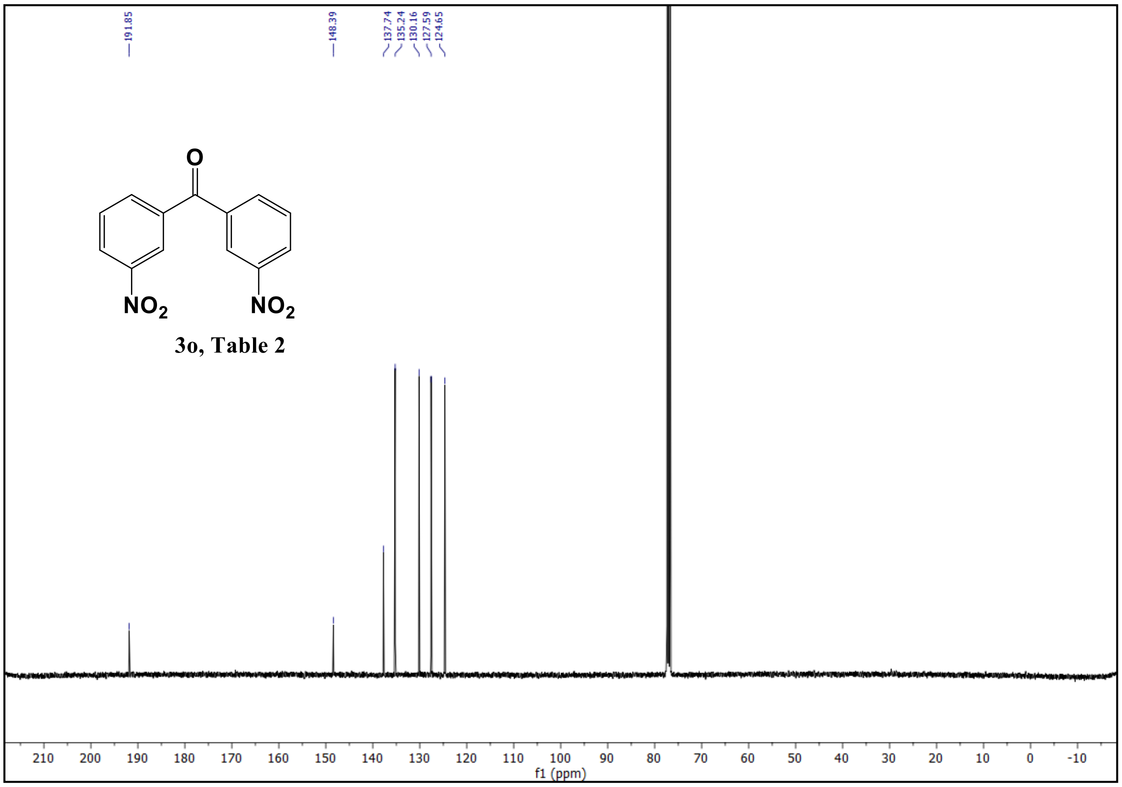
14. ^{1}H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **3n**



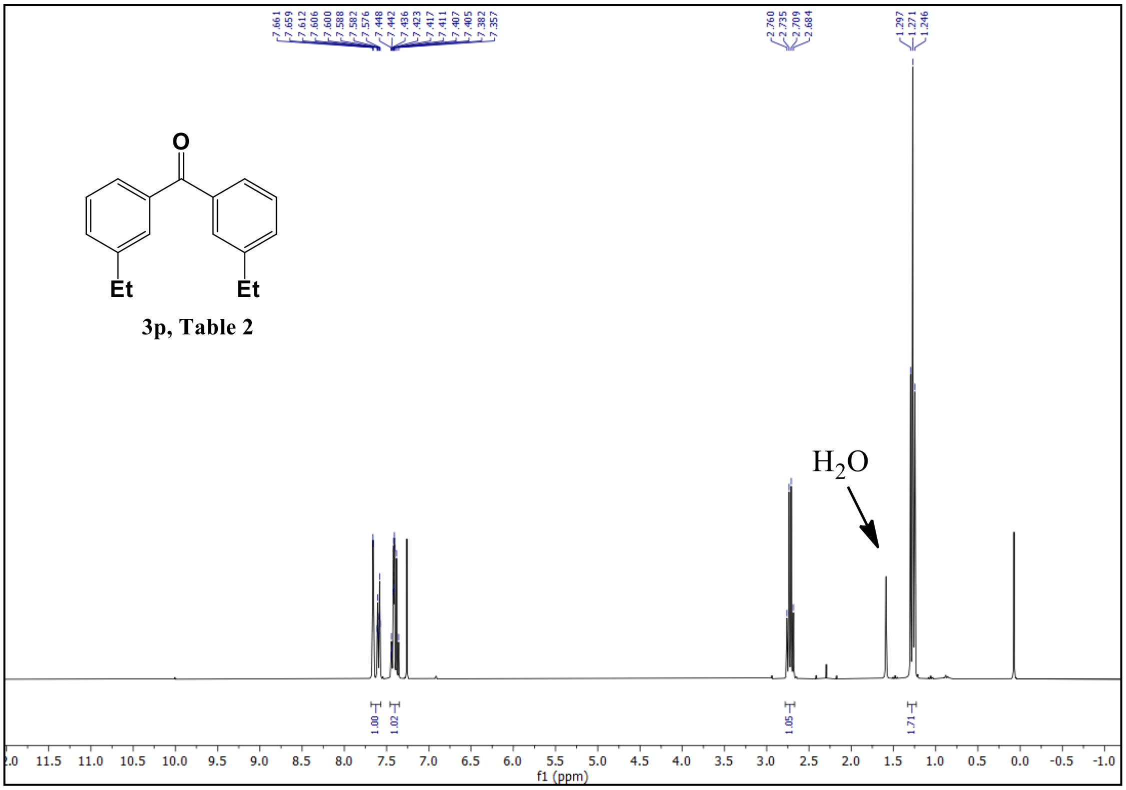


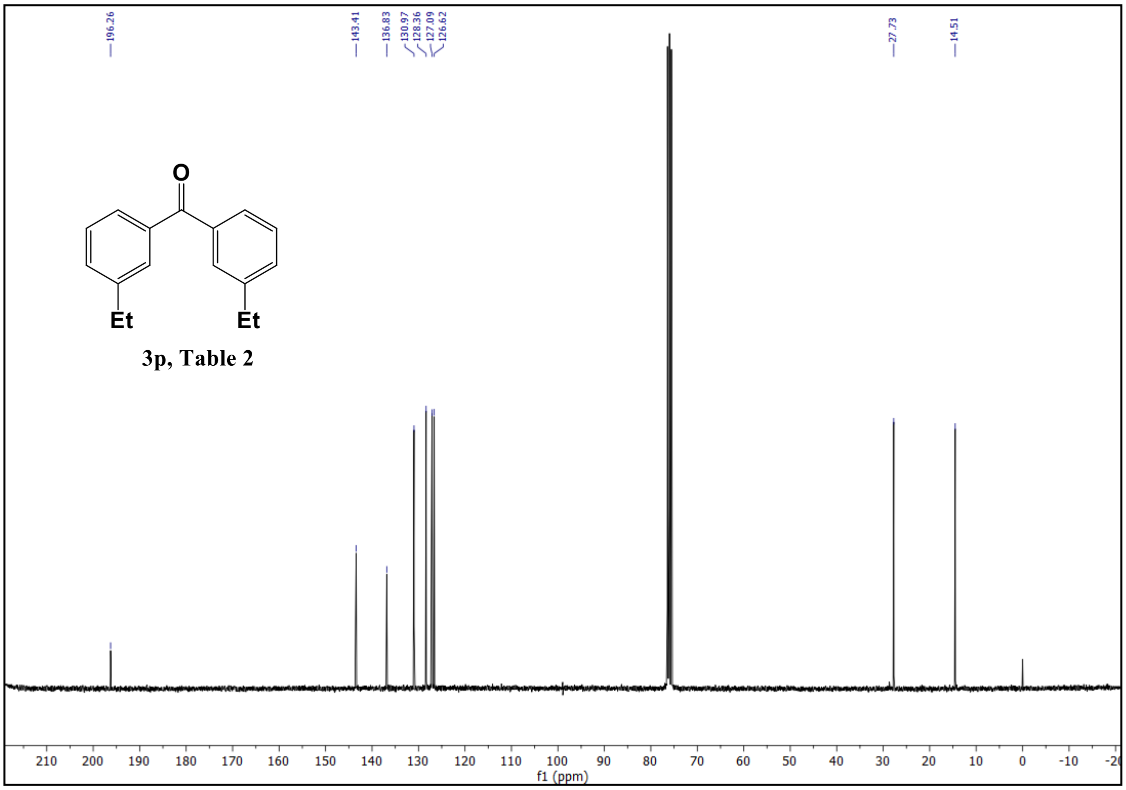
15. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **3o**



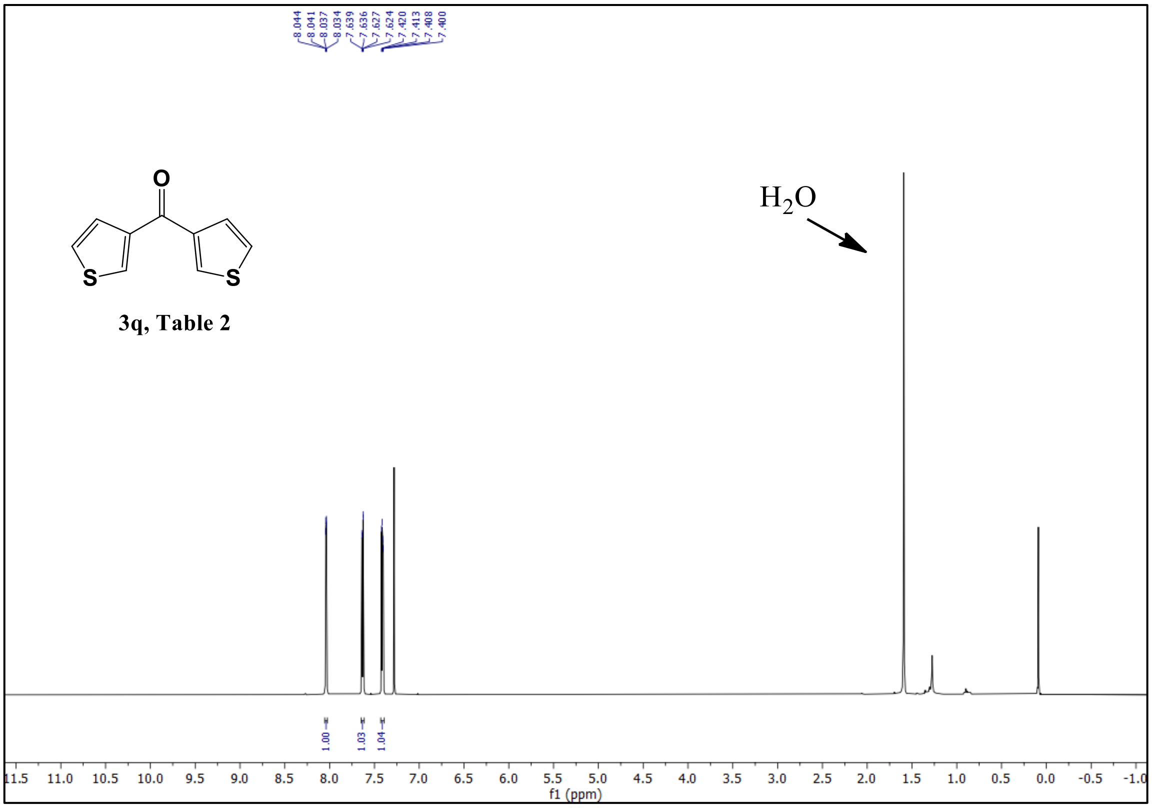


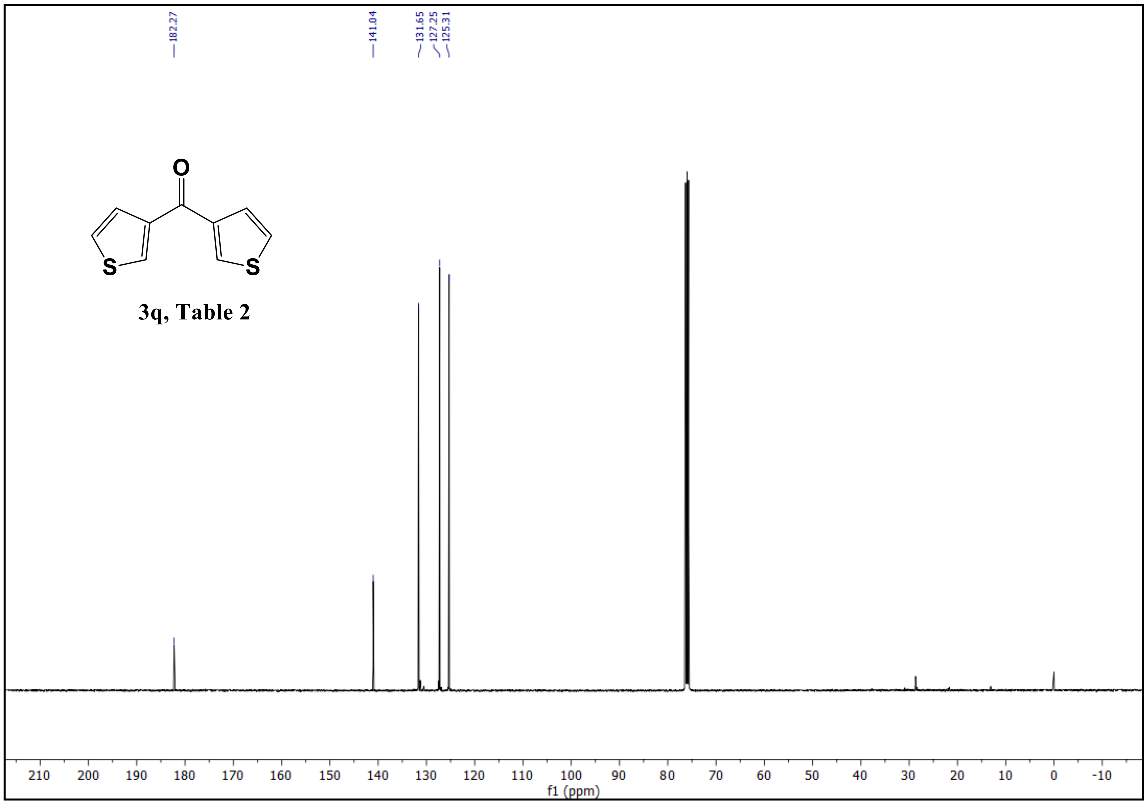
16. ^1H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **3P**



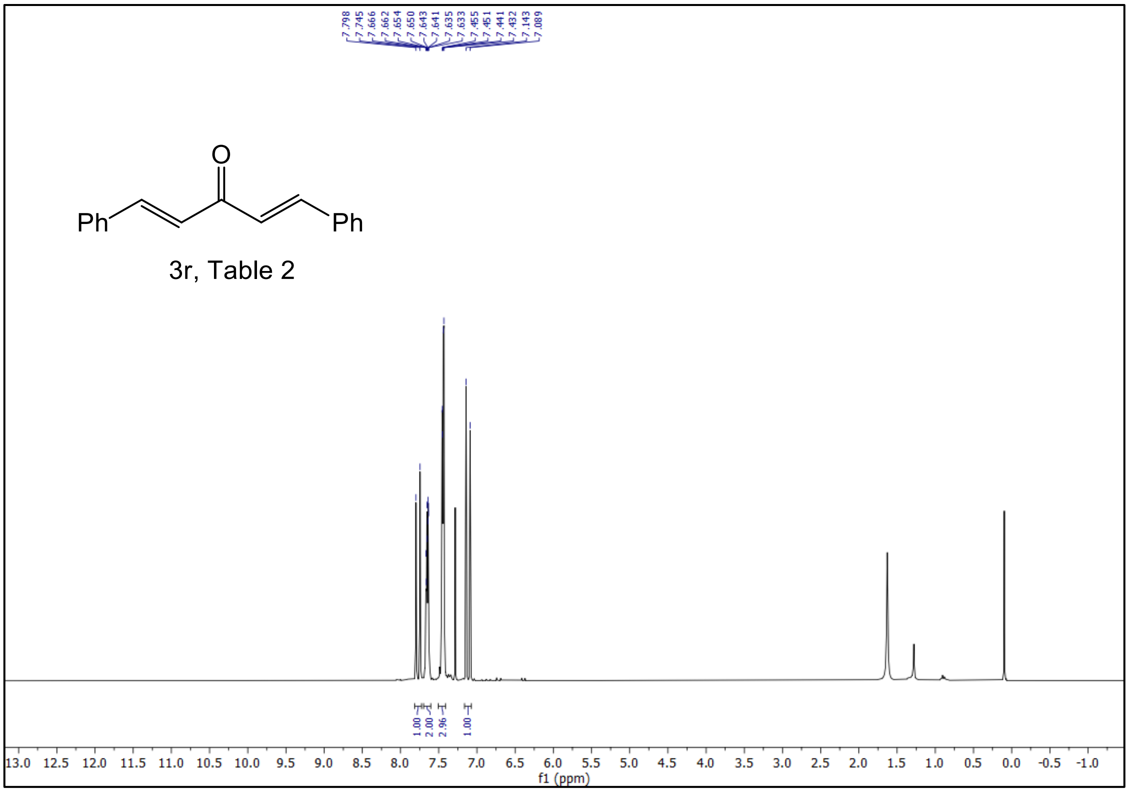


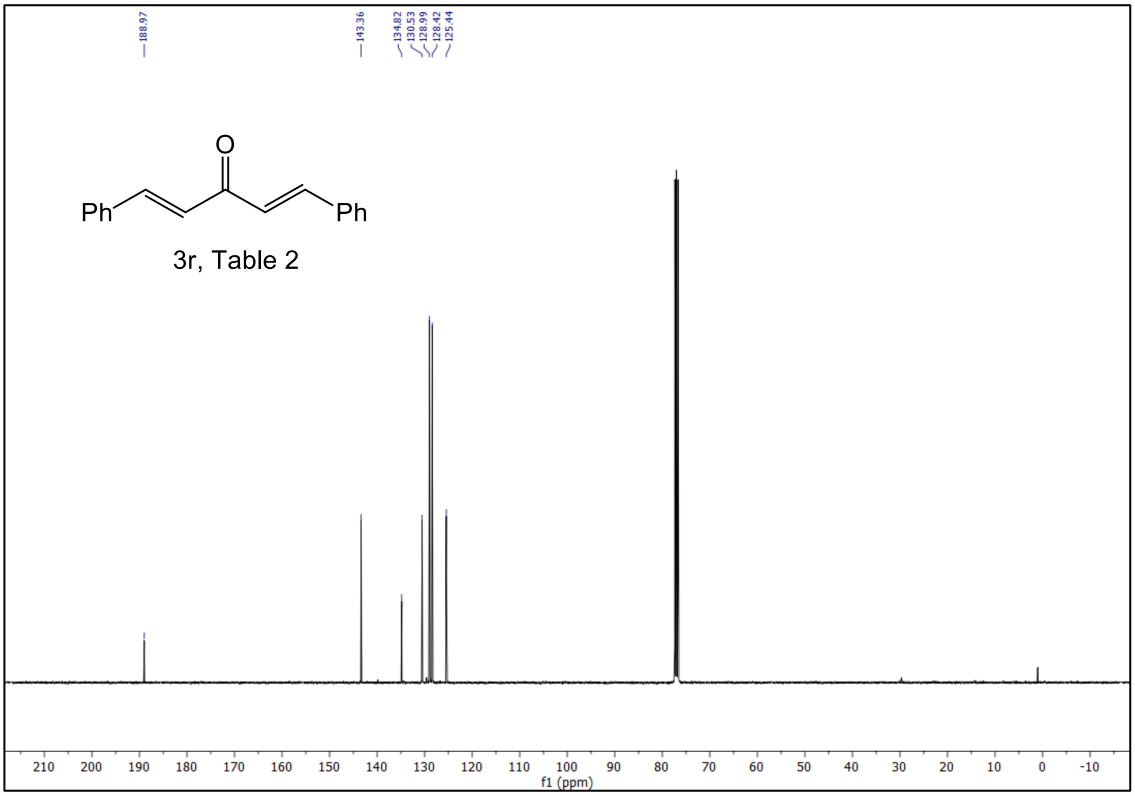
17.^{1}H NMR (400 MHz, CDCl3) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **3q**



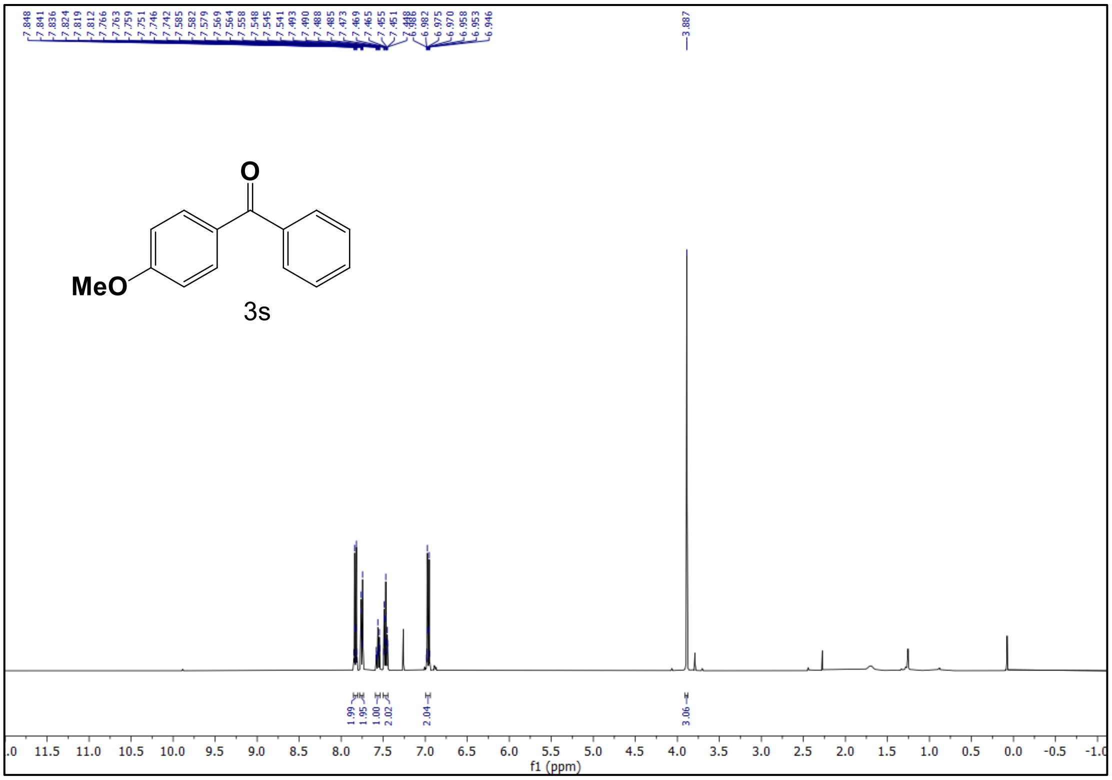


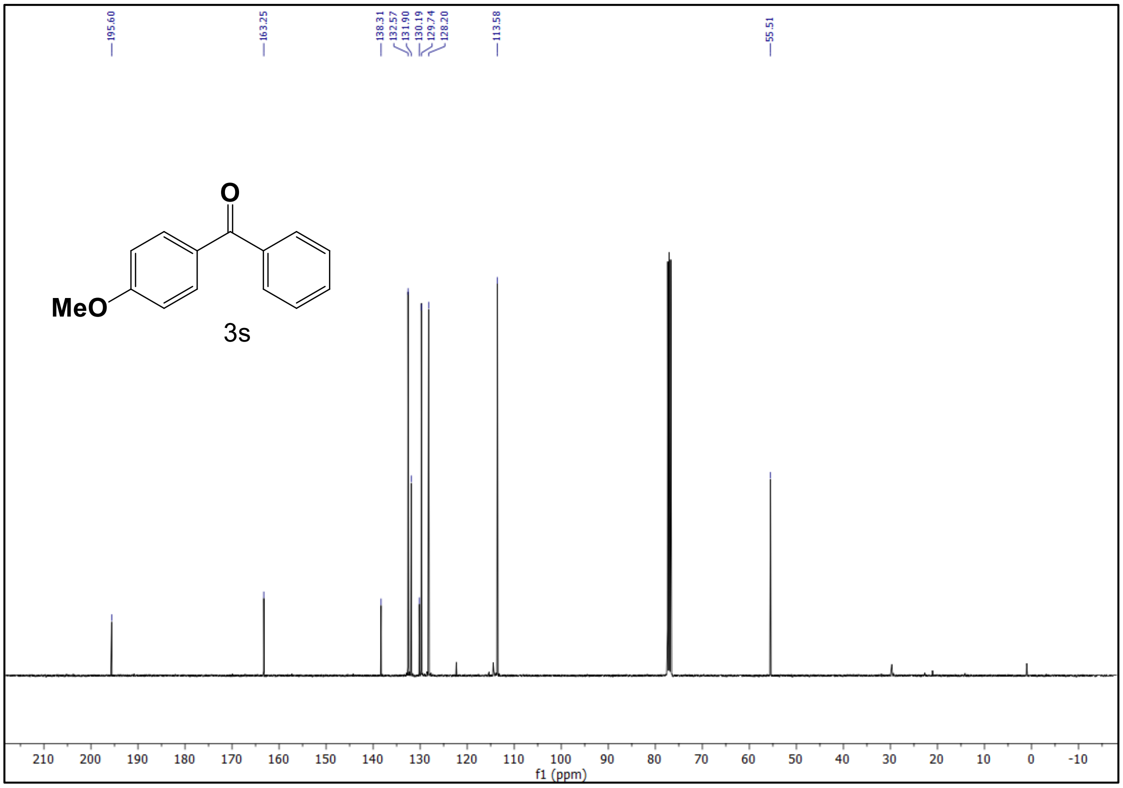
18.^{1}H NMR (400 MHz, CDCl3) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **3r**



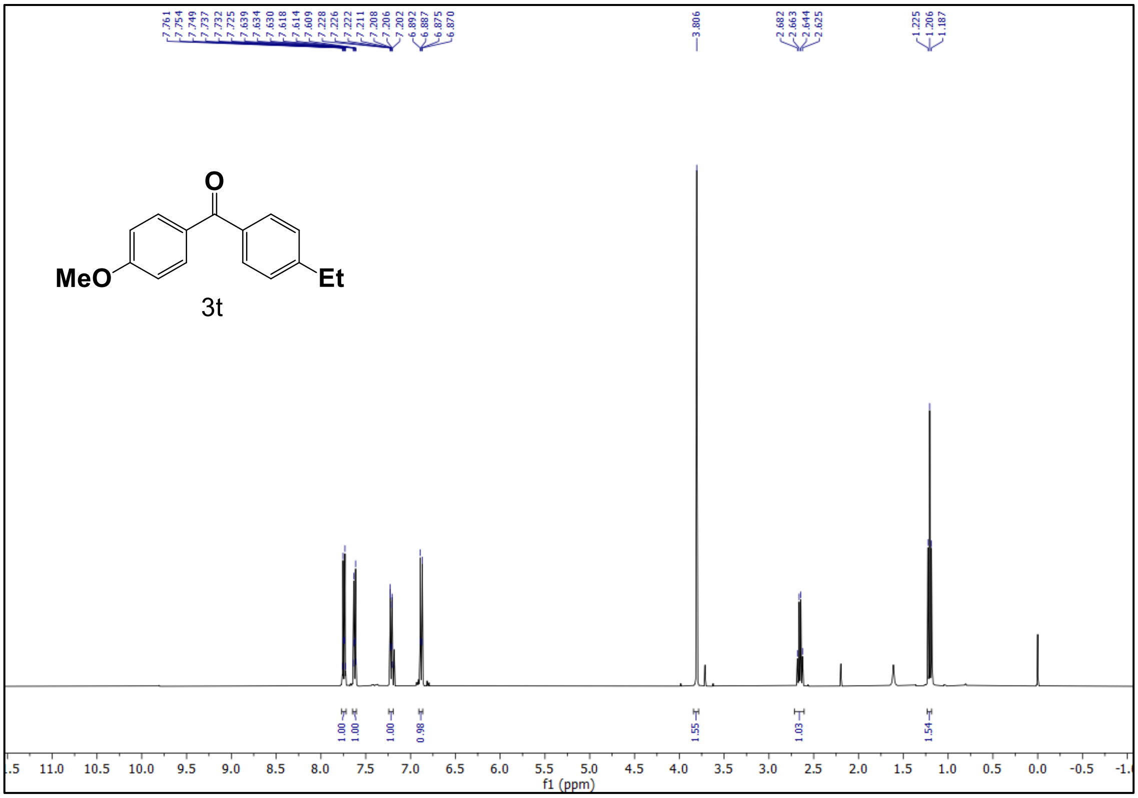


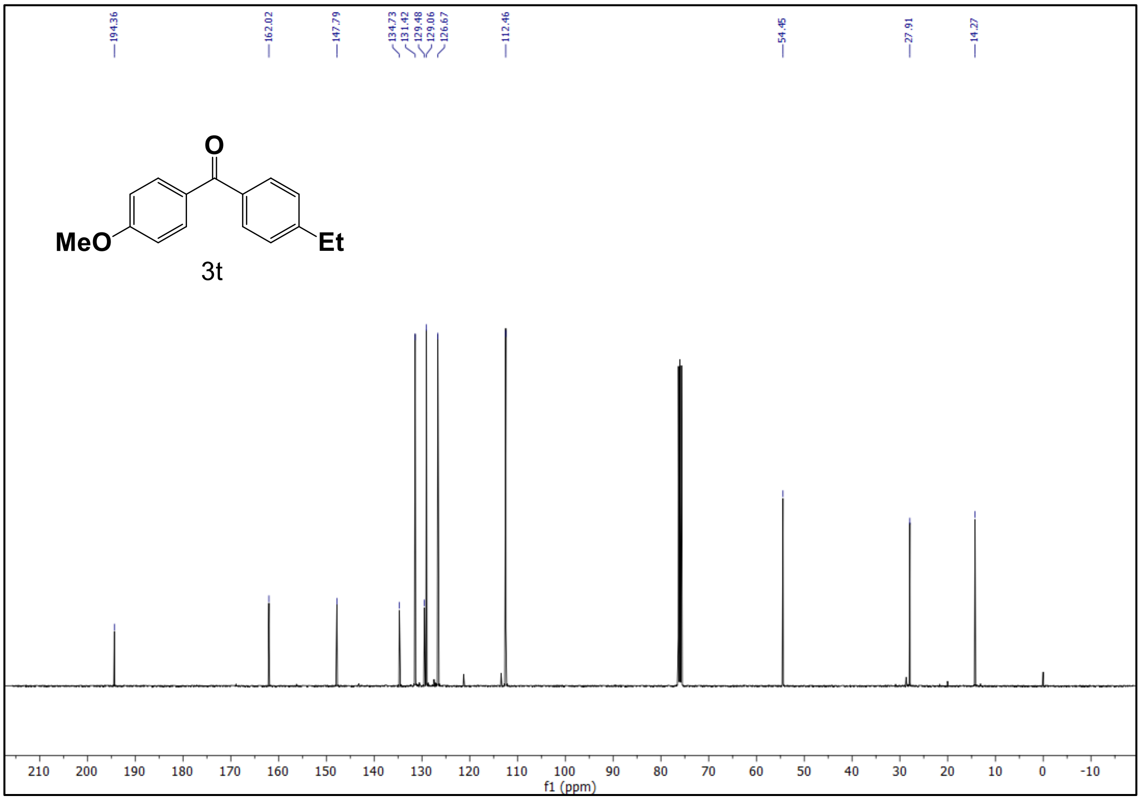
19.^{1}H NMR (400 MHz, CDCl3) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **3s**



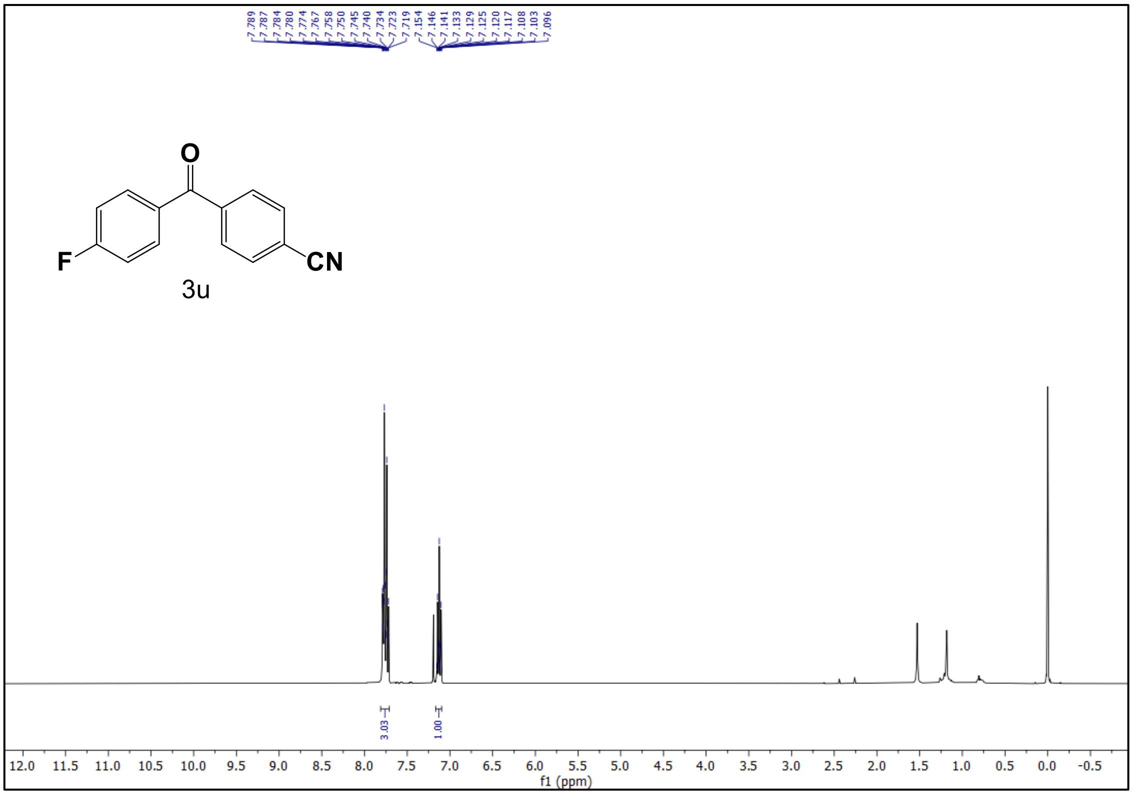


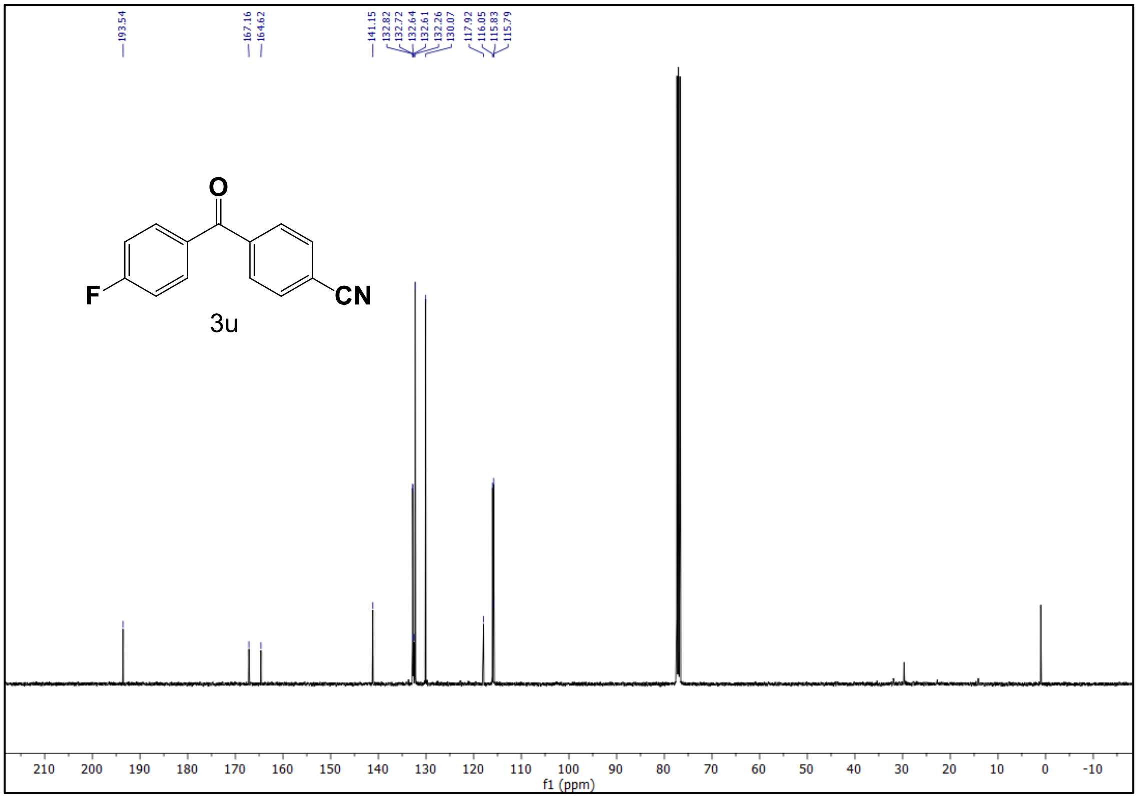
20.¹H NMR (400 MHz, CDCl3) and $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **3t**



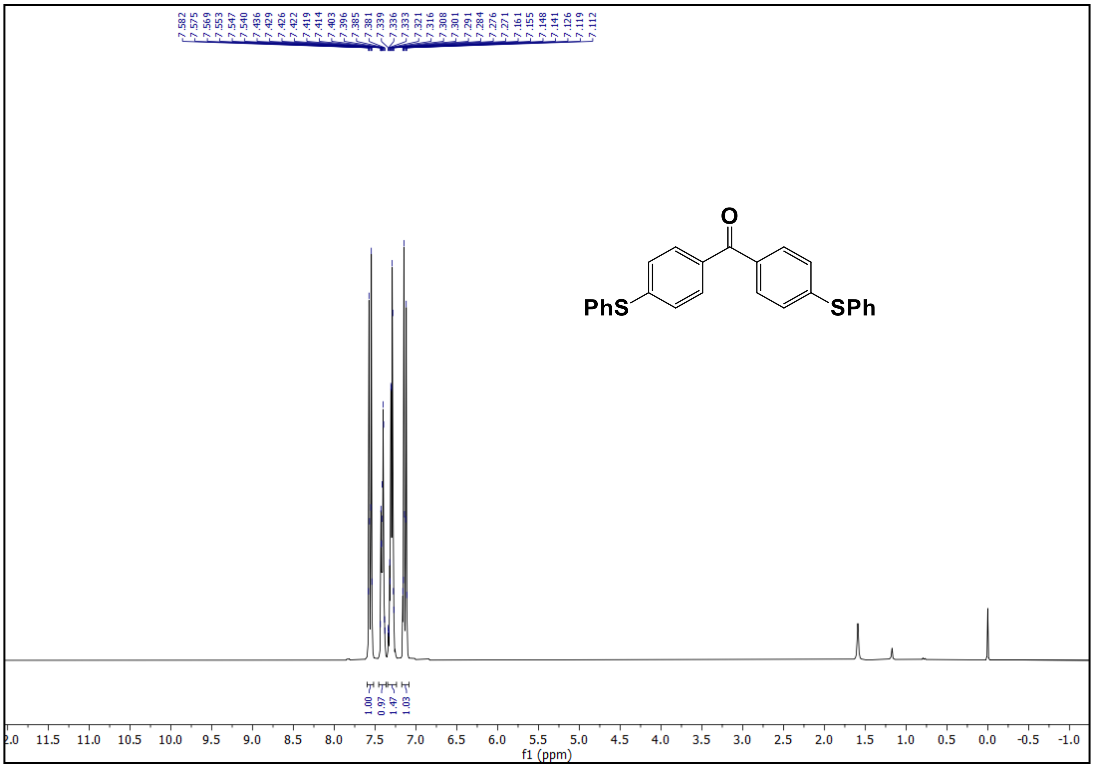


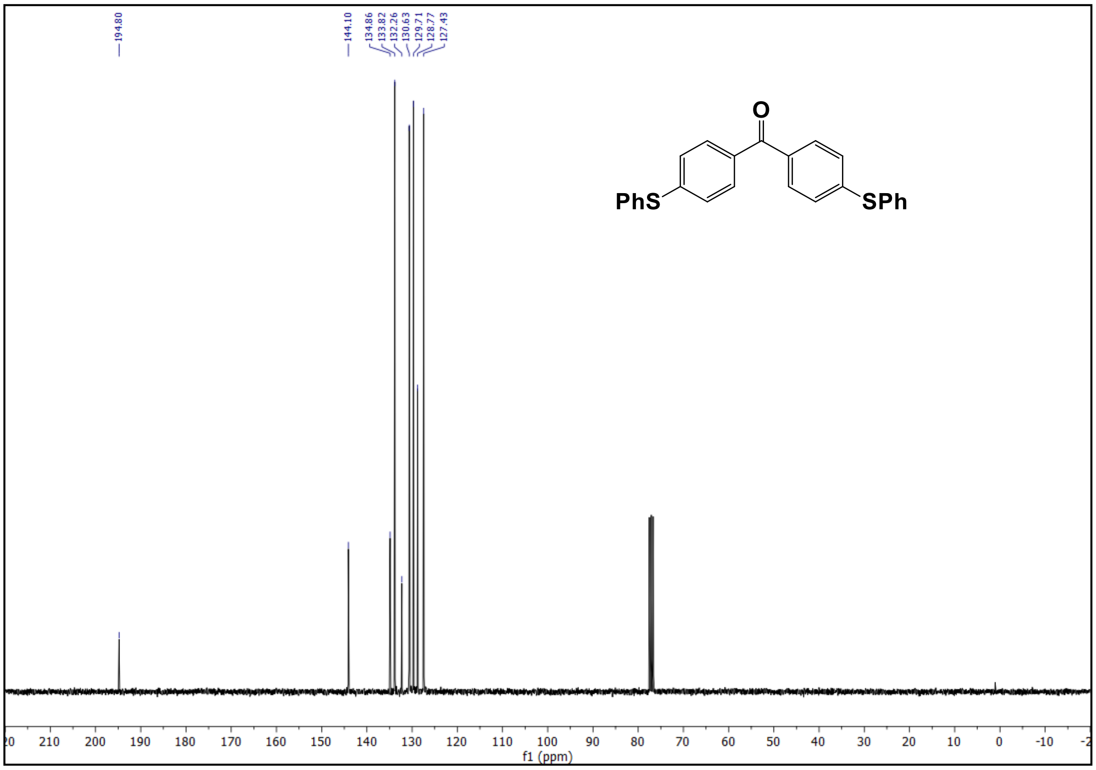
21.^{1}H NMR (400 MHz, CDCl3) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **3u**



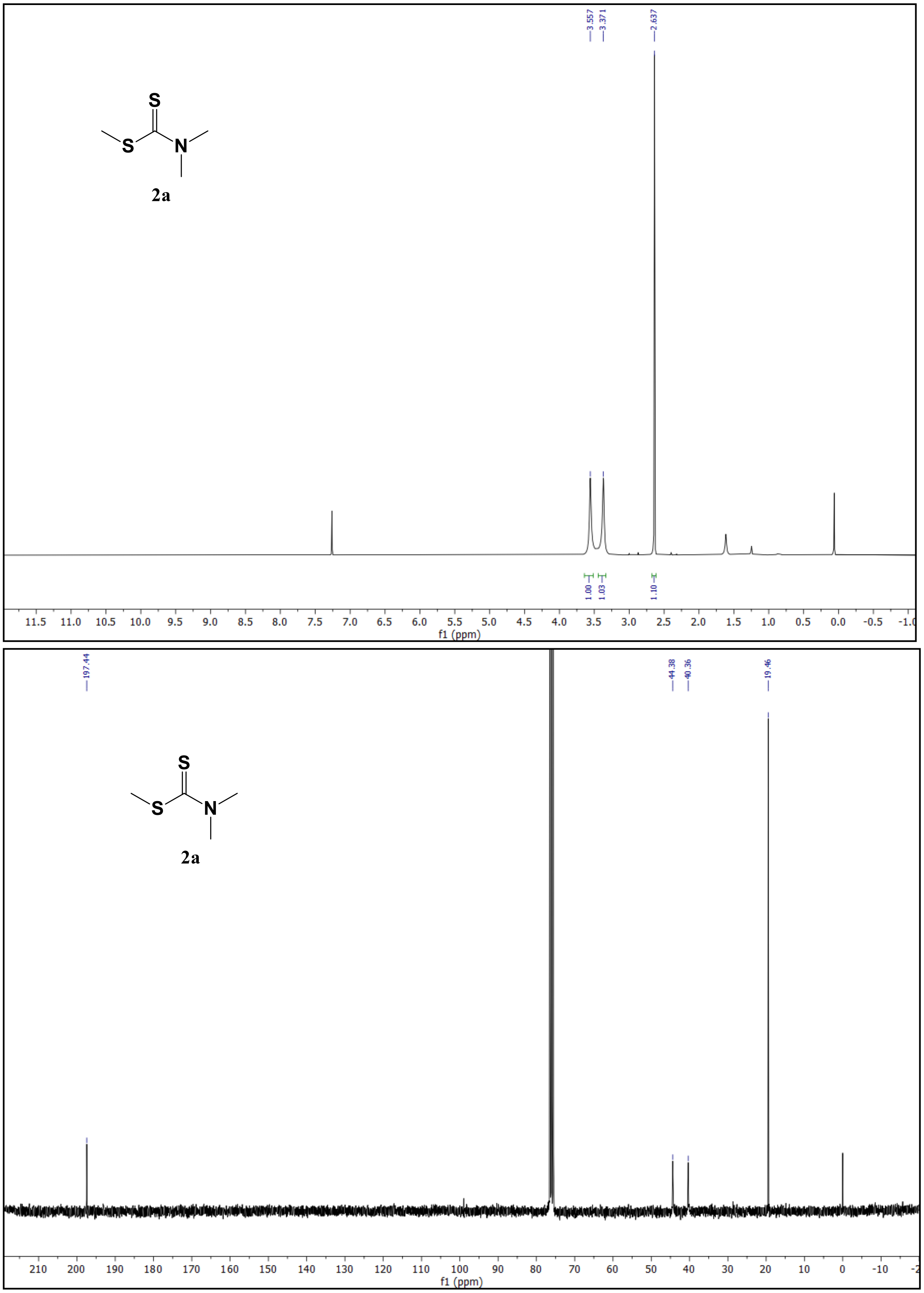


22.^{1}H NMR (300 MHz, CDCl3) and ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) spectrum of compound **7**

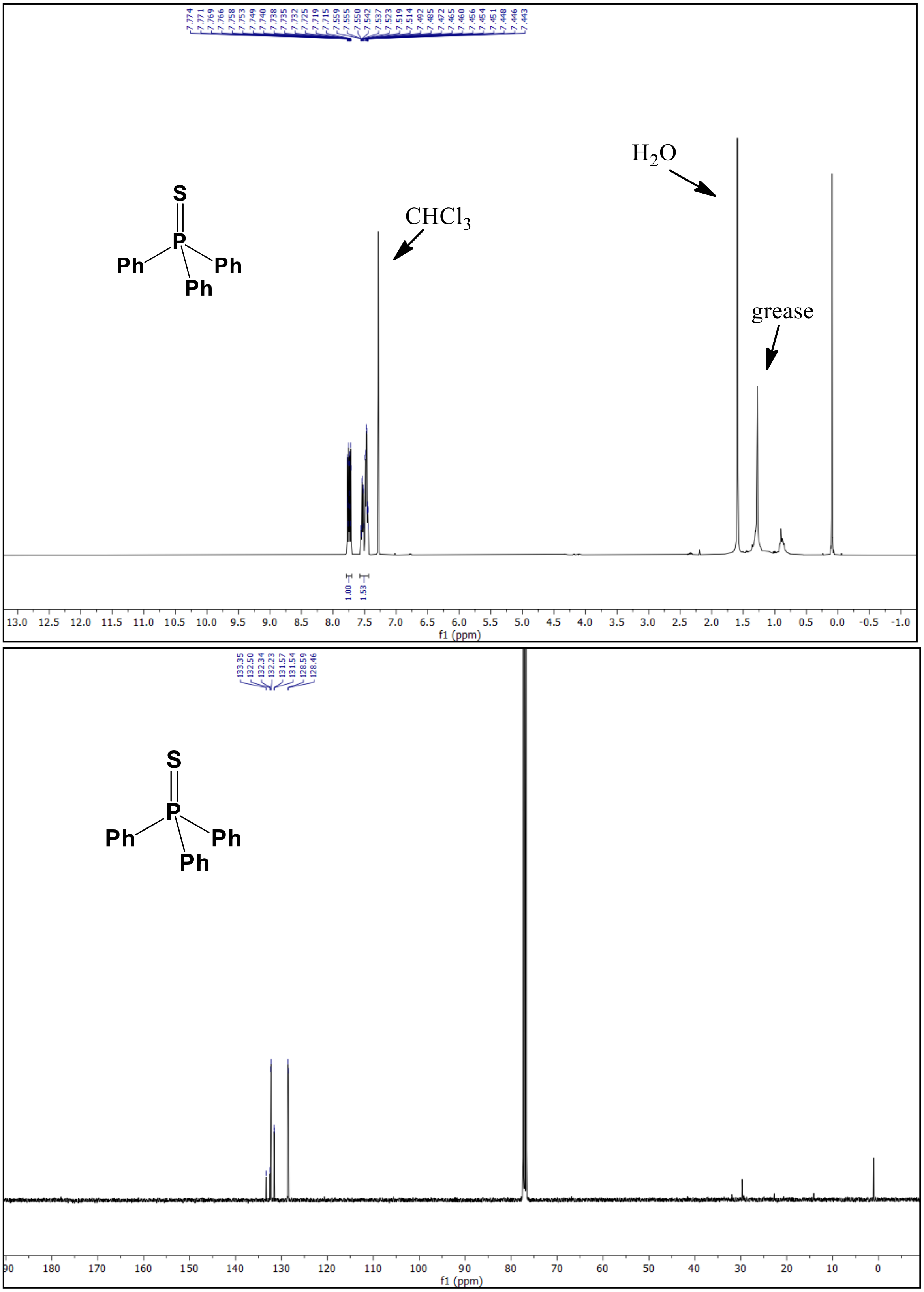




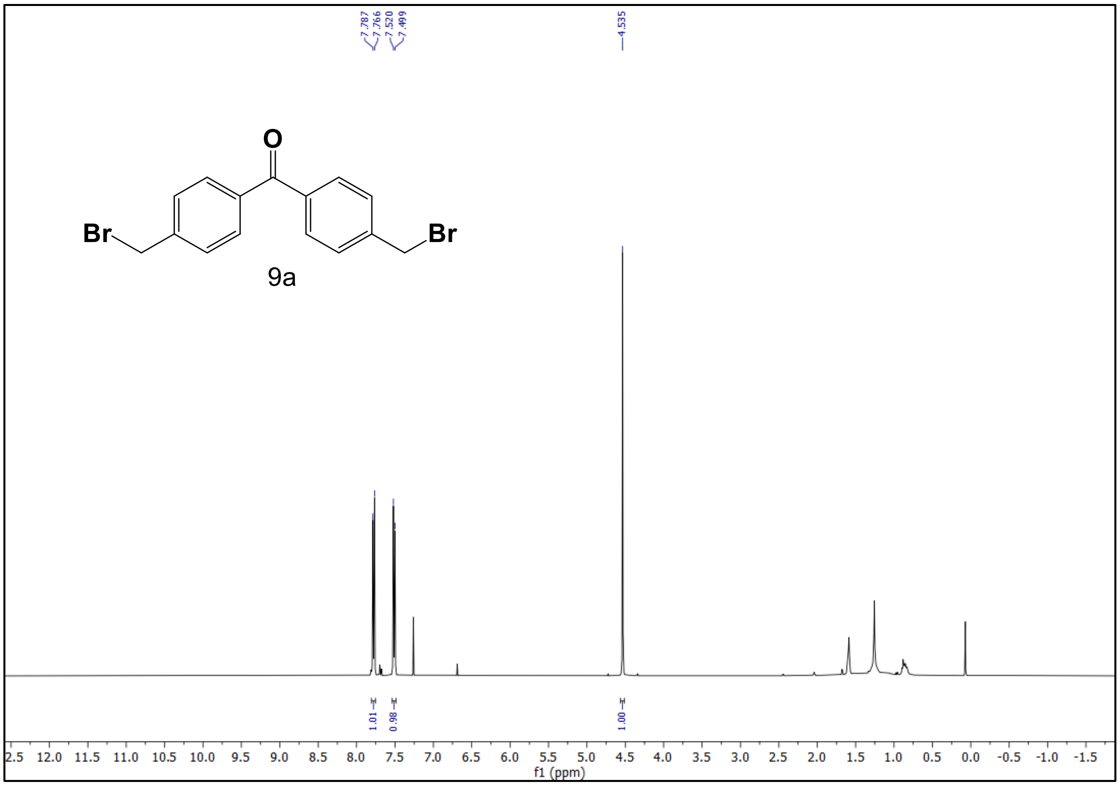
23. ^{1}H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **2a**



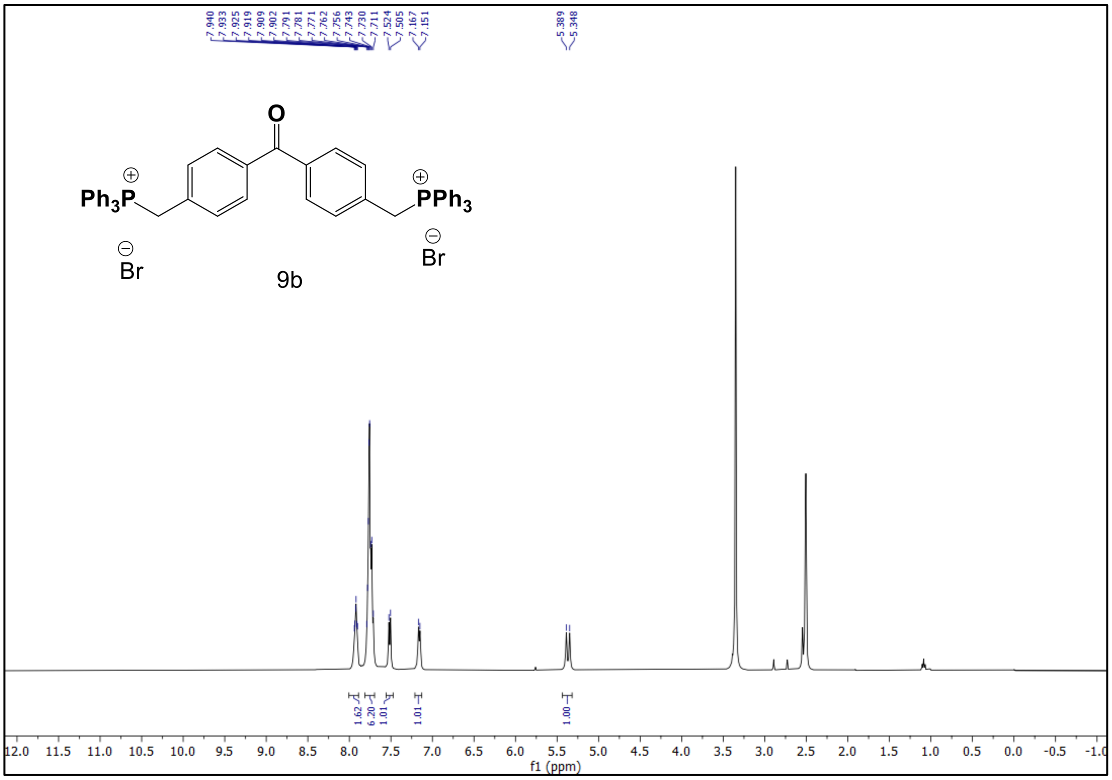
24. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) spectrum of **(PPh$_3$)$_3$PS**



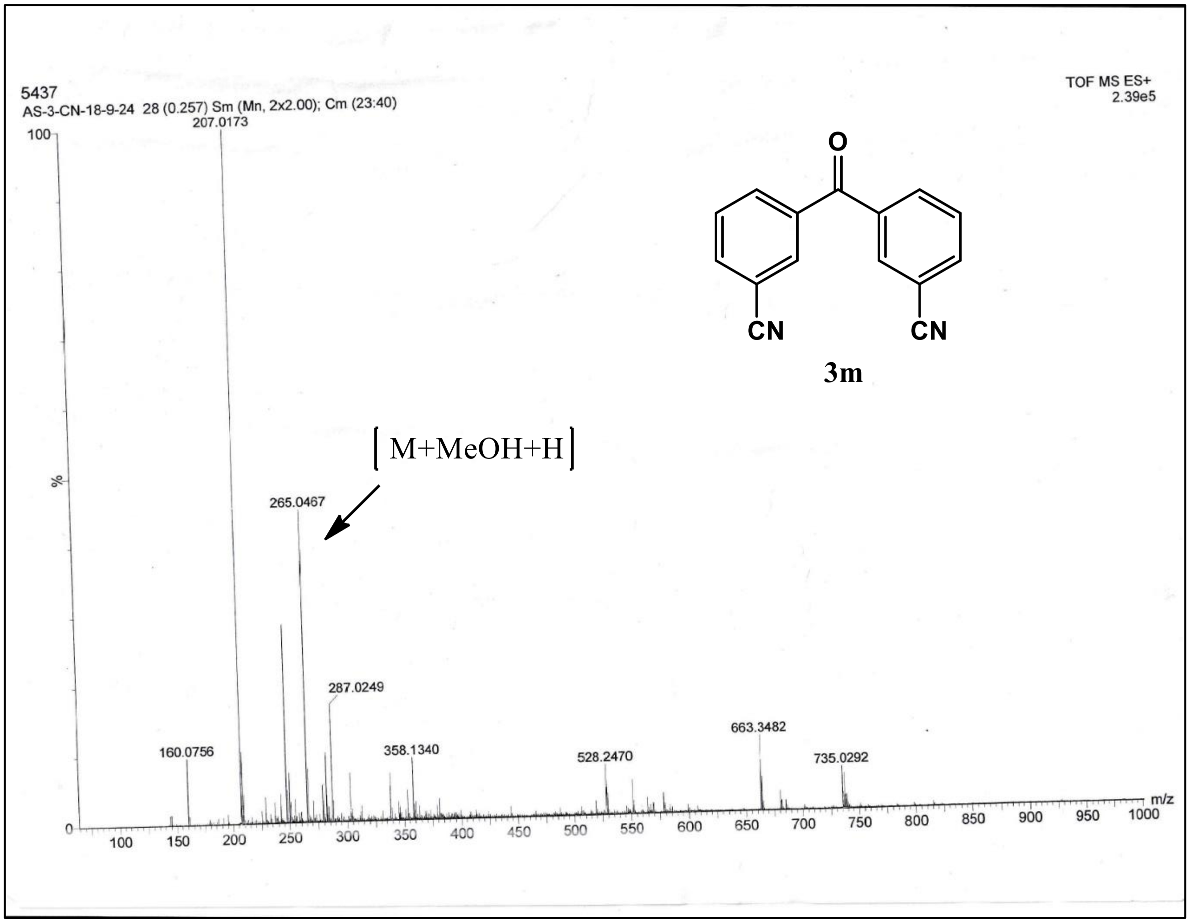
25. ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **9a**

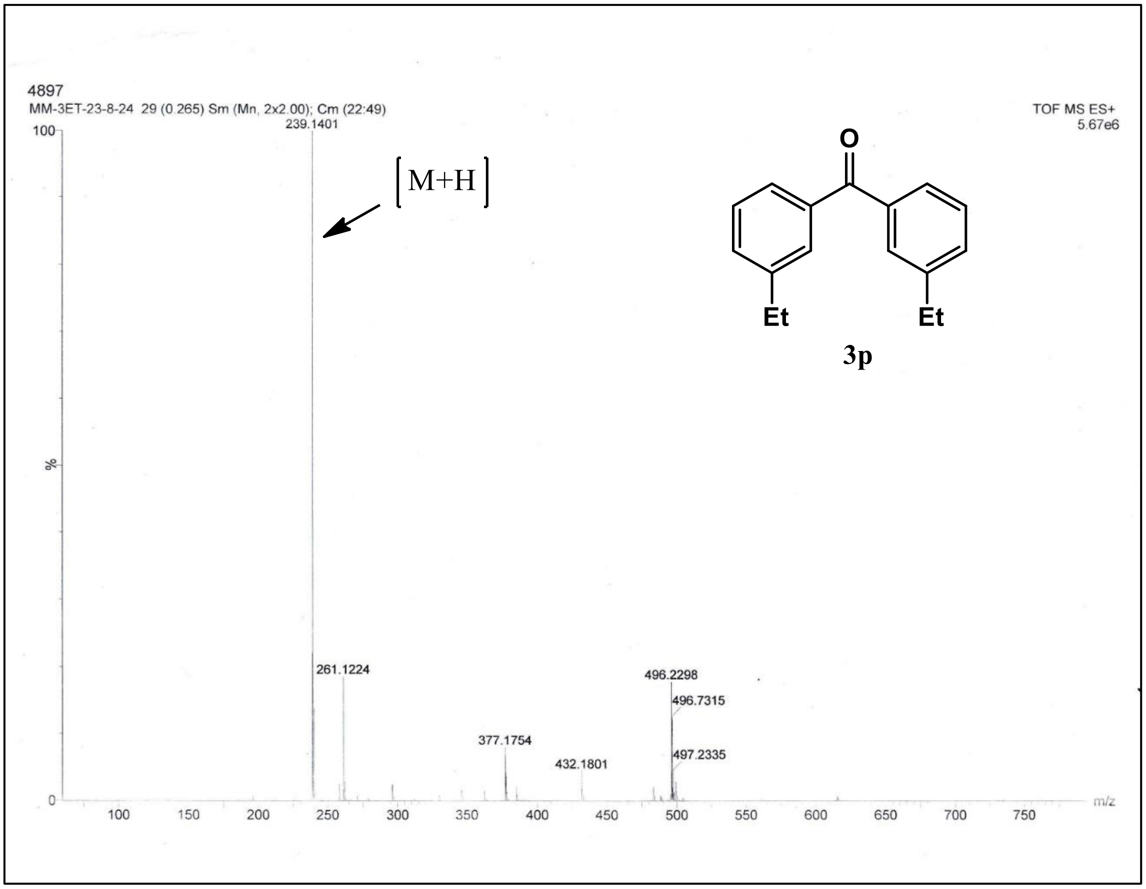


26. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9b**



I.Mass spectrum of compound **3m** and **3p**




4897
MM-3ET-23-8-24 29 (0.265) Sm (Mn, 2x2.00); Cm (22:49)
TOF MS ES+
5.67e6
100
%
0
239.1401
[M+H]
261.1224
377.1754
432.1801
496.2298
496.7315
497.2335
100
150
200
250
300
350
400
450
500
550
600
650
700
750
m/z
O
Et
Et
3p

XPS DATA: Evidence of Cu^0 and Cu^{2+} metal state:

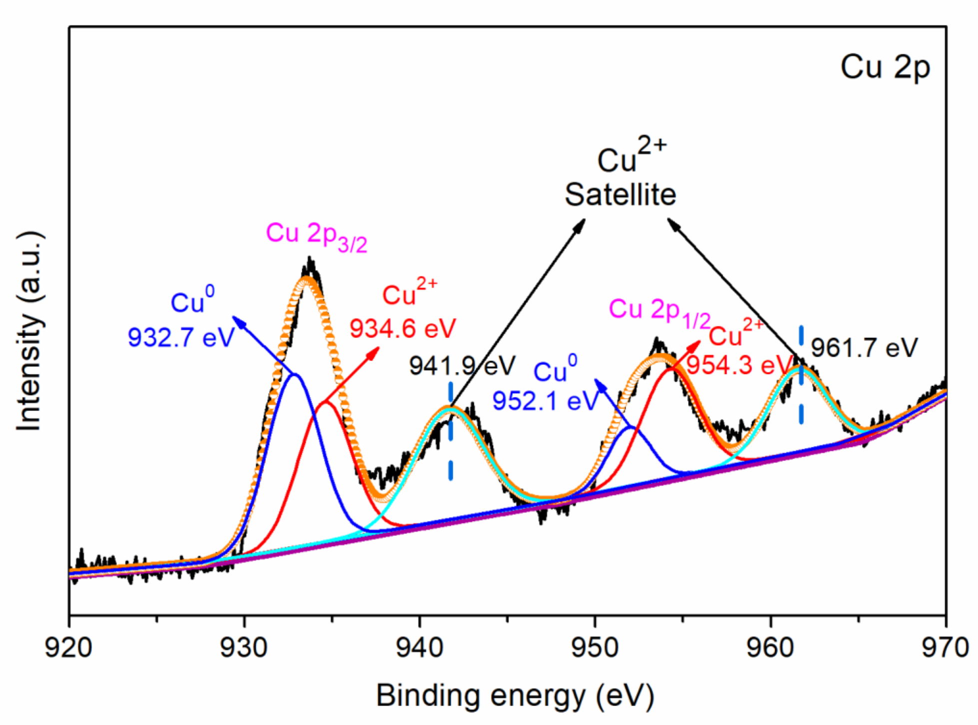
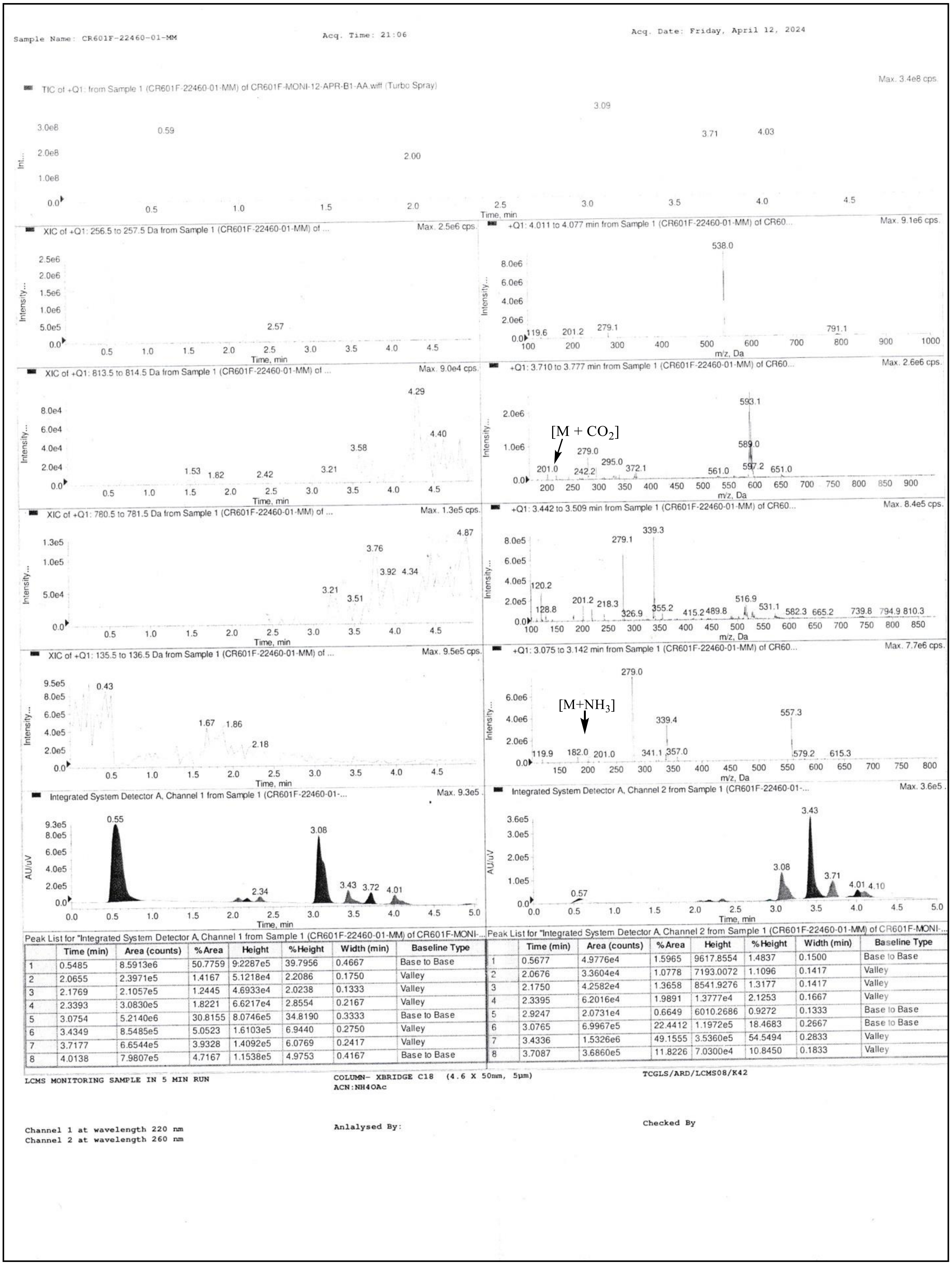


Figure 1: Cu 2p XPS spectra of Cu-residue obtained after completion of reaction

Binding energy:

	$2P_{3/2}$ (eV)	$2P_{1/2}$ (eV)
Cu (0)	932.70	952.10
Cu (II)	934.60	954.30

LCMS data for compound 4 and 6:



Sample Name: CR601F-22460-01-MM Acq. Time: 21:06 Acq. Date: Friday, April 12, 2024

Peak List for "Integrated System Detector A, Channel 1 from Sample 1 (CR601F-22460-01-MM) of CR601F-MONI-...

	Time (min)	Area (counts)	%Area	Height	%Height	Width (min)	Baseline Type
1	0.5485	8.5913e6	50.7759	9.2287e5	39.7956	0.4667	Base to Base
2	2.0655	2.3971e5	1.4167	5.1218e4	2.2086	0.1750	Valley
3	2.1769	2.1057e5	1.2445	4.6933e4	2.0238	0.1333	Valley
4	2.3393	3.0830e5	1.8221	6.6217e4	2.8554	0.2167	Valley
5	3.0754	5.2140e6	30.8155	8.0746e5	34.8190	0.3333	Base to Base
6	3.4349	8.5485e5	5.0523	1.6103e5	6.9440	0.2750	Valley
7	3.7177	6.6544e5	3.9328	1.4092e5	6.0769	0.2417	Valley
8	4.0138	7.9807e5	4.7167	1.1538e5	4.9753	0.4167	Base to Base

Peak List for "Integrated System Detector A, Channel 2 from Sample 1 (CR601F-22460-01-MM) of CR601F-MONI-...

	Time (min)	Area (counts)	%Area	Height	%Height	Width (min)	Baseline Type
1	0.5677	4.9776e4	1.5965	9617.8554	1.4837	0.1500	Base to Base
2	2.0676	3.3604e4	1.0778	7193.0072	1.1096	0.1417	Valley
3	2.1750	4.2582e4	1.3658	8541.9276	1.3177	0.1417	Valley
4	2.3395	6.2016e4	1.9891	1.3777e4	2.1253	0.1667	Valley
5	2.9247	2.0731e4	0.6649	6010.2686	0.9272	0.1333	Base to Base
6	3.0765	6.9967e5	22.4412	1.1972e5	18.4683	0.2667	Base to Base
7	3.4336	1.5326e6	49.1555	3.5360e5	54.5494	0.2833	Valley
8	3.7087	3.6860e5	11.8226	7.0300e4	10.8450	0.1833	Valley

LCMS MONITORING SAMPLE IN 5 MIN RUN

COLUMN- XBRIDGE C18 (4.6 X 50mm, 5µm)
ACN:NH4OAc

TCGLS/ARD/LCMS08/K42

Channel 1 at wavelength 220 nm
Channel 2 at wavelength 260 nm

Anlalysed By:

Checked By

3.2/e. References

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Benign synthesis of thiophosphates, thiophosphinates and selenophosphates in neat condition using *N*-chalcogenoimides as the source of electrophilic sulfur/selenium

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ABSTRACT

A neat reaction protocol has been developed for synthesis of thiophosphate, thiophosphinate and selenophosphate compounds. *N*-chalcogenoimides have been used for chalcogenylation of P(O)H moieties of various H-phosphonates under solvent, catalyst and base free condition at room temperature in aerial atmosphere. Both *S*-aryl and *S*-alkyl phosphorothioate compounds were prepared by this method in good yields. Selenophosphates were also synthesized using *N*-(phenylseleno)phthalimide under solvent free condition.

Introduction

Thiophosphates are having widespread applications as pesticides [1], insecticides [2], enzyme modifiers [3] and therapeutic agents such as HIV-1, AChE inhibitors [4]. Thiophosphate and selenophosphate compounds also offer valuable reaction intermediates in organic syntheses [5]. Various methodologies have been developed to prepare this important class of compounds. However, in most of the cases the syntheses of thiophosphates [6,7,8b–e] and selenophosphates [8] were carried out using different organic solvents as the reaction media. To minimize the chemical hazards of a synthetic procedure, it is essential to reduce the usage of toxic organic solvents. Thus, it is now desirable to cultivate benign solvent free reaction conditions for synthesis of thiophosphate compounds. A microwave assisted solvent free reaction was reported by Kaboudin *et. al.* for the synthesis of thiophosphates using elemental sulfur and alkyl halides/tosylates [7d] in presence of triethylamine and acidic alumina. Iodine catalyzed, aqueous H_2O_2 mediated thioarylation of various H-phosphonates were carried out by Wu and coworkers [7b] under solvent free condition using diaryl disulfide and excess of H-phosphonates. Zhan *et. al.* [6c] recently reported a neat reaction protocol to produce thiophosphates by the reaction of organic disulfides with silyl phosphites. However, a more generalized and benign protocol is needed to be developed for the synthesis of various phosphorothioate and phosphoroselenoate compounds. In our current study, we have accomplished the synthesis of phosphorothioate/selenoate compounds in neat reaction medium at room temperature under open aerial atmosphere. Earlier we have used *N*-thioimides and *N*-selenoimide to prepare mixed disuldfide [9a] and diorganyl selenide [9b] compounds respectively. Here, we have employed *N*-thioimides and *N*-selenoimide for chalcogenylation of phosphites under neat reaction condition. Thiophosphate, thiophosphinate and selenophosphate compounds were prepared efficiently in an environmentally benign room temperature condition without using any metal, catalyst, base, and solvent (scheme 1).

Results and discussion

The reaction is easy to handle and proceeds under mild condition. A mixture of dialkyl phosphite and *N*-thioimide was stirred at room temperature in neat condition under aerial atmosphere until completion of the reaction (monitored by TLC).

In our first attempt, the thiophenylation of diethyl phosphite was tried using *N*-thiophenyl phthalimide in DMF solvent at 80 °C (entry 1, Table 1). However, the reaction was not very clean and desired product was formed along with some unidentified side products. The reaction in DMF solvent produced the thiophosphate product in improved yield (63%) at room temperature (RT) (entry 2, Table 1). The reactions in other solvents like THF, DMSO, MeCN and

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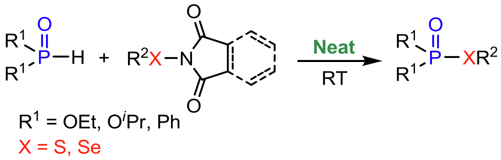
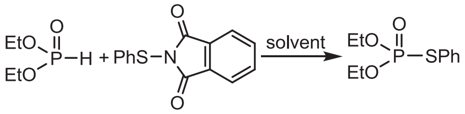


Scheme 1. Synthesis of chalcogenophosphates under neat reaction condition.

Table 1
Optimization of the reaction condition.



entry	solvent	temp. (°C)	time	yield (%)
1	DMF	80	4 h	48
2	DMF	RT	4 h	63
3	THE	RT	4 h	57
4	DMSO	RT	4 h	69
5	MeCN	RT	4 h	60
6	Toluene	RT	4 h	45
7	neat	RT	40 min	86
8	neat	RT	30 min	72
9	H_2O	RT	4 h	

Reaction condition: A mixture of *N*-(phenylthio)phthalimide (1 mmol) and diethyl phosphite (1 mmol) in 4 ml of solvent was stirred in aerial atmosphere for certain time period. Yields reported are the isolated yields.

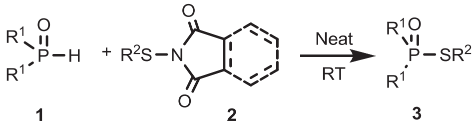
toluene (entries 3–6, Table 1) also did not produce the product in satisfactory yield.

The reaction did not proceed at all in water medium (entry 9, Table 1). Surprisingly, when the reaction was carried out in neat condition the desired thiophosphate was obtained in good yield (86%) within 40 min of time period at room temperature (entry 7, Table 1). Increasing the reaction time period beyond 40 min did not improve the yield of the product.

The optimized reaction condition was then explored to prepare a series of phosphorothioate/thiophosphinate compounds using *N*-thioimides (**2**) as the source of sulfur. Various *S*-aryl thiophosphates (**3a**–**3c**, **3g**, **3j**, **3n, 3o)** and *S*-aryl thiophosphinate (**3k**) were prepared using *N*-(phenylthio)phthalimide (entries 1 and 10, Table 2), *N*-(*p*-methoxyphenylthio)phthalimide (entries 2, 7 and 11, Table 2), *N*-(*p*-chlorophenylthio)phthalimide (entry 3, Table 2), *N*-(*p*-fluorophenylthio)phthalimide (entry 14, Table 2) and *N*-(*p*-*t*-butylphenylthio)phthalimide (entry 15, Table 2) in good yields under the neat reaction condition. Thioalkylations were also carried out under the similar reaction condition using *N*-(ethythio)-succinimide (entry 4, Table 2), *N*-(octylthio)succinimide (entries 5, 8 and 12, Table 2) and *N*-(benzylmercapto)succinimide (entries 6, 9 and 13, Table 2) to produce desired *S*-alkyl thiophosphates (**3d**–**3f**, **3h**, **3i)** and *S*-alkyl thiophosphinates (**3l**, **3m**). Diethyl phosphite, diisopropyl phosphite and diphenylphosphine oxide were successfully employed in the synthesis of phosphorothioate/thiophosphinate compounds.

We also tried the synthesis of selenophosphate compounds under the similar reaction condition. Phenylselenylations of diethyl phosphite and diisopropyl phosphite were carried out efficiently using *N*-(phenylseleno)phthalimide under the solvent free condition (Scheme 2). *N*-(phenylseleno)phthalimide plays the role of electrophilic selenium donor in presence of phosphorous nucleophiles like dialkyl phosphites at room temperature under the neat reaction condition in aerial atmosphere.

Table 2
Synthesis of various thiophosphate and thiophosphinate compounds.



1 **2** **3**

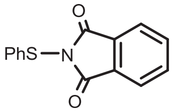
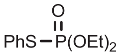
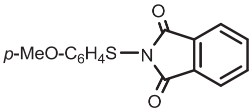
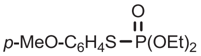
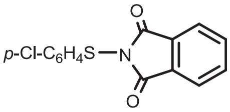
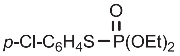
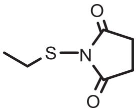
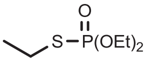
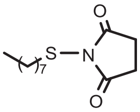
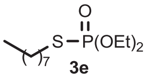
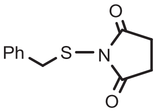
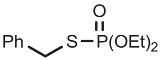
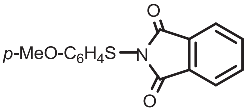
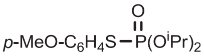
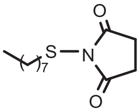
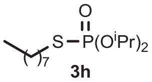
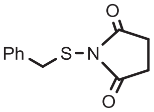
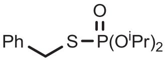
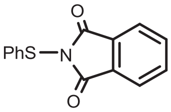
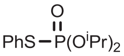
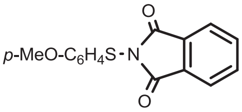
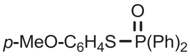
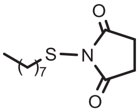
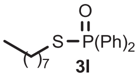
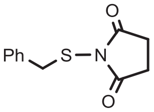
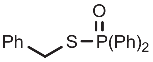
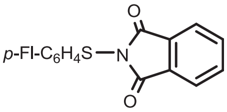
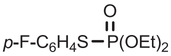
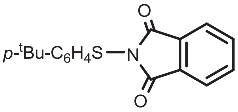
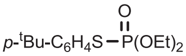
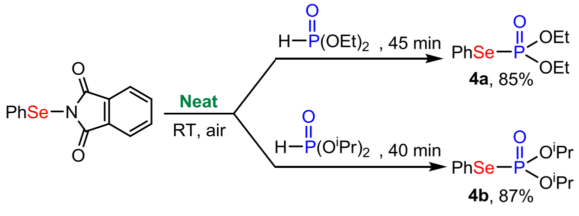
Entry	R^1	*N*-thioimide	Time (min)	product	Yield (%)
1	OEt		40	 $PhS-\overset{O}{\overset{\|}{P}}(OEt)_2$ **3a**	86
2	OEt		90	 $p\text{-}MeO\text{-}C_6H_4S-\overset{O}{\overset{\|}{P}}(OEt)_2$ **3b**	87
3	OEt		90	 $p\text{-}Cl\text{-}C_6H_4S-\overset{O}{\overset{\|}{P}}(OEt)_2$ **3c**	84

Table 2 (*continued*)

Entry	R^1	*N*-thioimide	Time (min)	product	Yield (%)
4	OEt		60	 **3d**	89
5	OEt		60	 **3e**	90
6	OEt		60	 **3f**	91
7	O^{i}Pr		90	 $p\text{-MeO-}C_6H_4S-\overset{O}{\overset{\Vert}{P}}(O^iPr)_2$ **3g**	85
8	O^{i}Pr		60	 **3h**	91
9	O^{i}Pr		60	 **3i**	89
10	O^{i}Pr		40	 $PhS-\overset{O}{\overset{\Vert}{P}}(O^iPr)_2$ **3j**	86
11	Ph		90	 $p\text{-MeO-}C_6H_4S-\overset{O}{\overset{\Vert}{P}}(Ph)_2$ **3k**	83
12	Ph		60	 **3l**	88
13	Ph		60	 **3m**	90
14	OEt		90	 $p\text{-F-}C_6H_4S-\overset{O}{\overset{\Vert}{P}}(OEt)_2$ **3n**	90
15	OEt		90	 $p\text{-}^tBu\text{-}C_6H_4S-\overset{O}{\overset{\Vert}{P}}(OEt)_2$ **3o**	89

Reaction condition: A mixture of *N*-thioimide (**2**) (1 mmol) and $R^1_2P(O)H$ (**1**) (1 mmol) was stirred at room temperature in aerial atmosphere for certain time period. Yields reported are the isolated yields.



Scheme 2. Phenylselenylation of dialkyl phosphites.

Conclusions

In conclusion, this is a convenient and general method to prepare structurally variable thiophosphate/thiophosphinate compounds. The neat reaction protocol also works satisfactorily for synthesis of selenophosphates. All the reactions were performed at room temperature under solvent free condition without using any catalyst, base or additive. The reactions do not require any sophisticated inert reaction set up. Thus, the described method offers an environmentally friendly route to prepare phosphorothioate/thiophosphinate and phosphoroselenoate compounds.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.150965.

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One-pot two-step dithiocarbamylation of styrenes: metal-free stereoselective synthesis of styrenyl dithiocarbamates†

Manas Mondal and Amit Saha *

Styrenes have been functionalized to produce styrenyl dithiocarbamates by a one-pot two-step procedure without using any metal catalysts. Styrene was transformed into a bromo-derivative, which undergoes a domino nucleophilic substitution followed by elimination in the presence of a dithiocarbamate anion and triethylamine to produce *trans*-styrenyl dithiocarbamates exclusively. The reaction shows a wide substrate scope and good yields of products.

Functionalization of styrenes has become an important area of research because of the potential uses of various styrene derivatives in organic synthesis,[1] polymer chemistry[2] and materials sciences.[3] Styrenes have been functionalized in many ways, among which β-functionalization[4] is a popular technique to prepare useful β-substituted styrene molecules.

Dithiocarbamate is a valuable sulfur containing functionality due to the extensive applications of the dithiocarbamate compounds mainly in biological and medicinal chemistry (Fig. 1). Dithiocarbamate compounds have potential applications in biomedical science,[5] agricultural chemistry,[6] materials chemistry,[7] organometallic chemistry,[8] polymer science[9] and organic synthesis.[10] As a part of our continued research interest to explore dithiocarbamate chemistry in organic synthesis,[11] here we have developed a metal-free strategy for dithiocarbamylation of styrene molecules to synthesize various styrenyl dithiocarbamate compounds. The classical route to synthesize styrenyl dithiocarbamate compounds involves the Wittig reaction of the dithiocarbamate-phosphonium ylide with benzaldehyde.[12] The modern techniques use various β-substituted styrenes to synthesize the styrenyl dithiocarbamates[13] (Scheme 1). Cu-Catalyzed cross-coupling reactions of styryl bromides[13a,b] or styrylboronic acids[13c] are popular methods to prepare *S*-styryl dithiocarbamates. However, a one-pot transformation of styrenes into styrenyl dithiocarbamates is more desirable due to easy availability of the substrates. Recently some attempts have been made to functionalize the styrene molecules with dithiocarbamate groups.[14] In this report, we have demonstrated a one-pot two-step conversion of styrenes into styrenyl dithiocarbamates *via* a stereoselective dithiocarbamylation reaction. Styrenes have been functionalized using a freshly prepared dithiocarbamate anion in the presence of a molecular bromine mediator (Scheme 2). Styrenes undergo a bromine addition, followed by a domino nucleophilic substitution by a dithiocarbamate anion and HBr elimination under the present reaction conditions. This method can be considered as an alternative to the β-C–H activation of styrenes.

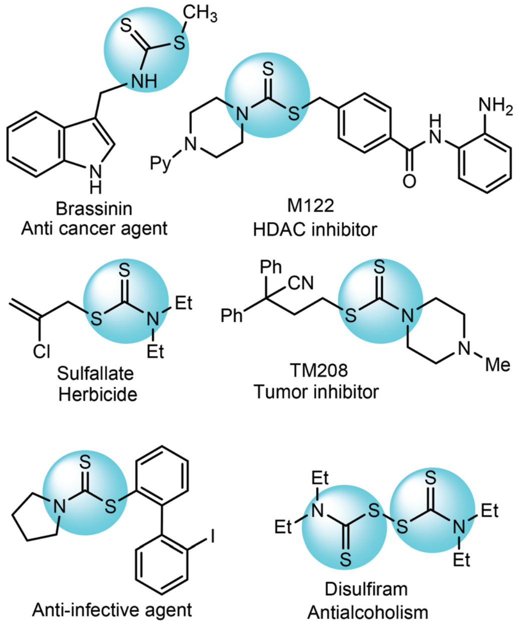

Fig. 1 Biologically active dithiocarbamate compounds.

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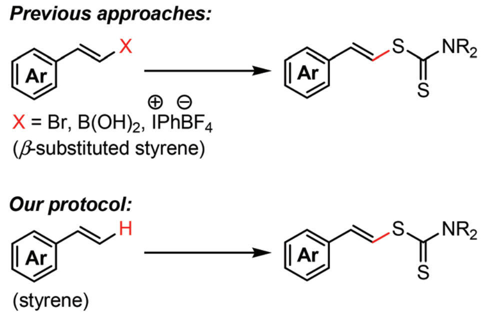
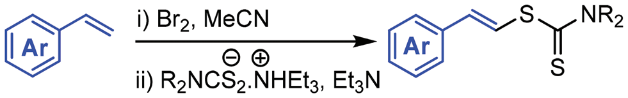
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and ^{1}H, ^{13}C, ^{19}F NMR and HRMS spectra. See DOI: https://doi.org/10.1039/d2ob00315e



Scheme 1 β-Substituted styrenes and styrenes as the starting materials for the synthesis of styrenyl dithiocarbamates.



Scheme 2 Dithiocarbamylation of styrenes.

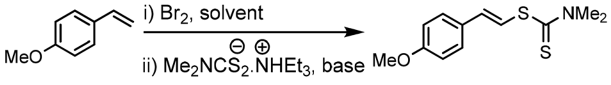
The experimental procedure is simple and easy to perform. Styrenes were brominated by Br_2 in acetonitrile, followed by addition of a freshly prepared dithiocarbamate anion, and the reaction mixture was stirred in the presence of triethylamine at 65 °C. The reaction was monitored by TLC. Upon completion of the reaction, the product was obtained by purifying the crude reaction mixture through column chromatography.

In order to optimize the reaction conditions, 4-methoxystyrene was chosen as the substrate and it was allowed to react with the dithiocarbamate anion ($Me_2NCS_2^{\ominus}$) which was prepared freshly by the reaction of dimethylamine and CS_2. The reaction between 4-methoxystyrene and $Me_2NCS_2^{\ominus}$ was checked under various reaction conditions employing different bases and solvents (Table 1). In our first attempt, the reaction was performed in acetonitrile medium in the presence of K_2CO_3 at 65 °C. However, the desired styrenyl dithiocarbamate was obtained only in 40% of yield under a time period of 3 h (entry 1, Table 1). Other reaction media such as DMF, H_2O, toluene and THF were not found suitable for the reaction (entries 2–5, Table 1). Instead of the desired product, some unidentified side products were obtained. Use of Na_2CO_3 also did not improve the yield of the reaction (entry 6, Table 1). However, the reaction was found to proceed satisfactorily in the presence of triethylamine as the base (yield: 88% in 3 h) (entry 7, Table 1). At an elevated temperature (80 °C), the reaction shows an adverse effect on the yield of the desired product (entry 8, Table 1). The yield of the reaction was also not improved under the prolonged reaction time period (entry 10, Table 1). The reaction remains incomplete under a time period of 2 h (entry 11, Table 1).

The optimized protocol was then explored to establish a wide substrate scope. Acyclic secondary amines (dimethylamine and diethylamine) responded to the reaction efficiently and the desired products (**3a–3c**, **3f**, **3j**, **3k** and **3q**, Table 2) were obtained satisfactorily. Cyclic secondary amines such as piperidine, pyrrolidine and morpholine also produced the desired styrenyl dithiocarbamates (**3d**, **3e**, **3g–3i**, **3l**, **3n** and **3o**, Table 2) in good yields.

Benzylamine underwent β-dithiocarbamylation of styrenes to produce the desired styrenyl dithiocarbamate **3p** in 74%

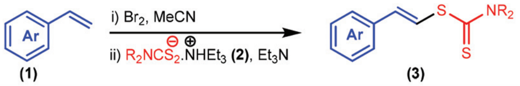
Table 1 Standardization of the reaction conditions

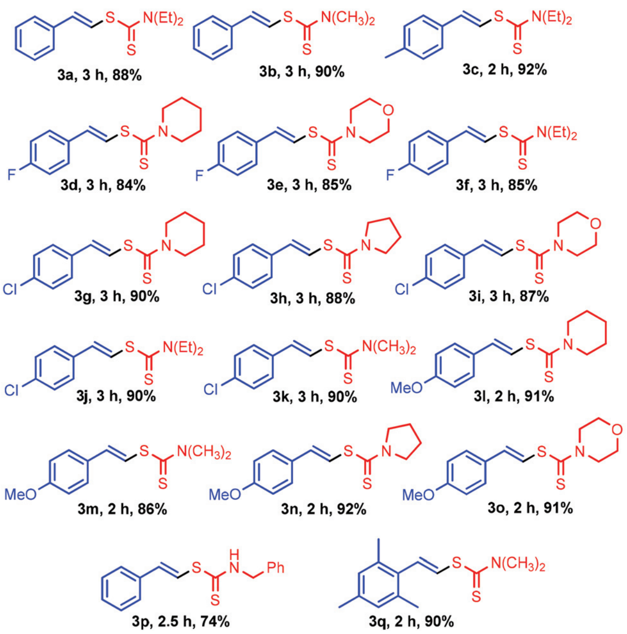


Entry	Solvent	Base	Temp. (°C)	Time (h)	Yield (%)
1	MeCN	K_2CO_3	65	3	40
2	DMF	K_2CO_3	120	3	Trace
3	THF	K_2CO_3	65	3	13
4	H_2O	K_2CO_3	80	3	—
5	Toluene	K_2CO_3	70	3	—
6	MeCN	Na_2CO_3	65	3	35
7	MeCN	Et_3N	65	3	88
8	MeCN	Et_3N	80	3	57
9	MeCN	Et_3N	50	3	70
10	MeCN	Et_3N	65	5	76
11	MeCN	Et_3N	65	2	62

Reagents and conditions: (i) 4-methoxystyrene (1 mmol), Br_2 (1 mmol), solvent (3 ml), r.t., 30 min. (ii) Brominated styrene was stirred in the presence of a dithiocarbamate anion (1 mmol) and base (2 mmol) at a certain temperature for the required time period. Yields reported are the isolated yields.

Table 2 Synthesis of *trans*-styrenyl dithiocarbamates from styrenes





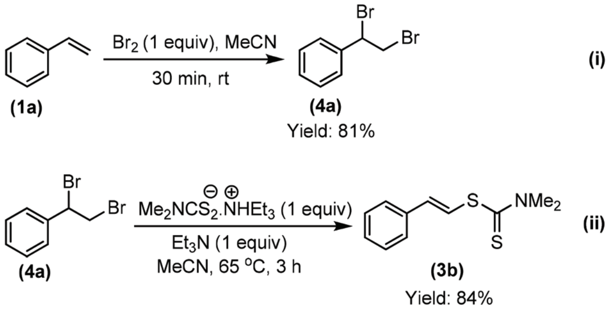
3a, 3 h, 88%
3b, 3 h, 90%
3c, 2 h, 92%
3d, 3 h, 84%
3e, 3 h, 85%
3f, 3 h, 85%
3g, 3 h, 90%
3h, 3 h, 88%
3i, 3 h, 87%
3j, 3 h, 90%
3k, 3 h, 90%
3l, 2 h, 91%
3m, 2 h, 86%
3n, 2 h, 92%
3o, 2 h, 91%
3p, 2.5 h, 74%
3q, 2 h, 90%

Reagents and conditions: (i) styrene (1 mmol), Br_2 (1 mmol), acetonitrile (3 ml), r.t., 30 min. (ii) Brominated styrene was stirred in the presence of a dithiocarbamate anion (1 mmol) and Et_3N (2 mmol) at 65 °C for a certain time period. Yields reported are the isolated yields.

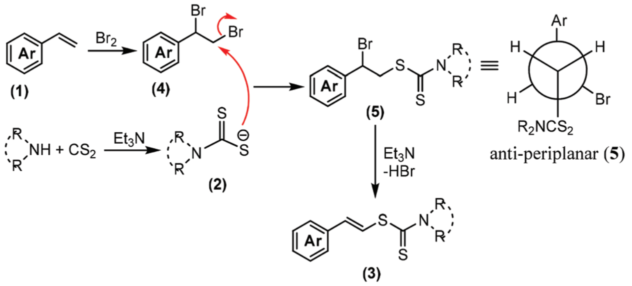
yield. Styrenes containing different substituents such as Me, OMe, F and Cl in the aromatic ring, participated in the β-functionalization reaction smoothly. Styrenes containing *ortho*-substituents, such as 2,4,6-trimethylstyrene, underwent a smooth reaction with a dimethylamine-dithiocarbamate anion to produce the desired styrenyl dithiocarbamate product **3q** in good yield. In all cases, the reactions were highly stereoselective, producing *trans*-styrenyl dithiocarabamates exclusively. However, 3-nitrostyrene and 4-nitrostyrene did not respond to the reactions. The reaction mixtures contained some unidentified side products along with some amount of dimer of the dithiocarbamate anion.

To understand the mechanism, some control experiments were performed. The reaction of styrene (**1a**) with molecular bromine was quenched after 30 min of stirring (Scheme 3 – i) under similar reaction condition as shown in Table 2. The intermediate generated in this control experiment was isolated and characterized (^{1}H and ^{13}C NMR included in the ESI†) to be the styrene dibromide (**4a**). Styrene dibromide was also found to react with $Me_2NCS_2^{\ominus}$ in the presence of triethylamine under identical reaction condition and produced the desired styrenyl dithiocarbamate (**3b**) in good yield (Scheme 3 – ii). Thus, it is confirmed that the reaction proceeds *via* a styrene dibromide intermediate.

We propose the formation of styrene dibromide (**4**) by the addition of bromine to styrene. The nucleophilic attack of the dithiocarbamate anion (**1**), generated by the reaction of amine and carbon disulfide, occurs selectively at the less hindered primary alkyl bromide centre of the styrene dibromide (**4**) (Scheme 4). The nucleophilic substitution results in the formation of intermediate **5**, which undergoes HBr elimination in the presence of triethylamine to produce the desired styrenyl dithiocarbamate (**3**). To prove the intermediacy of **5**, the reaction of 4-methoxystyrene with molecular bromine and a piperidine-dithiocarbamate anion (generated by the reaction of piperidine and CS_2) was carried out under identical reaction condition (as shown in Table 2) only for a time period of 10 min at 65 °C. The incomplete reaction was quenched after 10 min and we were able to isolate intermediate **5** by chromatographic purification of the crude reaction mixture. The structure of intermediate **5** was characterized by ^{1}H and ^{13}C NMR spectroscopy (^{1}H and ^{13}C NMR included in the ESI†). The elimination occurs from the more stable conformer of **5** with the aryl and dithiocarbamate groups anti-periplanar to each other and it leads to the formation of *trans*-styrenyl dithiocarbamates.



Scheme 3 Control experiments to identify the intermediate of the reaction.



Scheme 4 Probable mechanism.

In conclusion, we have developed an efficient metal-free one-pot two-step protocol to functionalize styrenes at the β-position. Styrenes have been converted into *trans*-styrenyl dithiocarbamates *via* a dibromo intermediate. This β-dithiocarbamylation offers an easy access to structurally diverse dithiocarbamate-substituted styrenes. The use of expensive catalysts has been avoided. Operational simplicity, easy availability of the starting materials, good yields and high stereoselectivity of the reactions render this protocol synthetically important and economically attractive.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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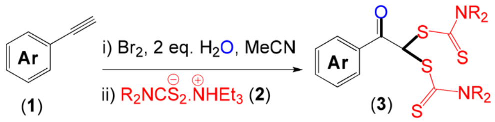
Metal-free trifunctionalization of phenylacetylenes: an efficient one-pot two-step synthesis of *gem*-bis(dithiocarbamates)†

Manas Mondal,[a] Debajyoti Saha *[b] and Amit Saha *[a]

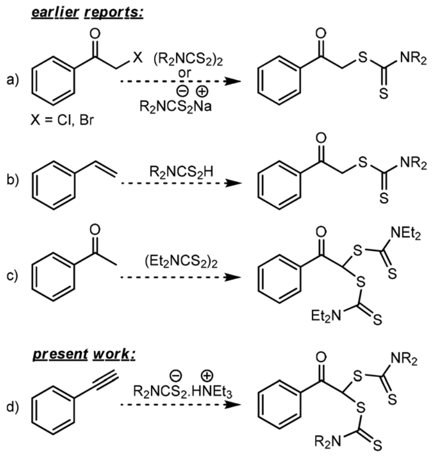
The synthesis of phenacyl-bis(dithiocarbamates) has been reported by metal-free trifunctionalization of phenylacetylene systems by following a one-pot two-step strategy. Phenyl acetylene undergoes molecular bromine-mediated oxidative bromination followed by nucleophilic substitution with the freshly prepared dithiocarbamate salt which is prepared by the prompt reaction of amine and CS_2 in the presence of triethylamine base. A series of *gem*-bis (dithiocarbamates) are prepared using various secondary amines and phenylacetylene systems containing different substituents.

Dithiocarbamate molecules have received ongoing interest due to their significant applications in medical sciences.[1] Many organic dithiocarbamates show potential biological activities as antioxidants, enzyme inhibitors, fungicides, anti-trypanosomatid drugs and anticancer, anti-inflammatory, antimicrobial, and anti-HIV agents. Dithiocarbamates have also been used extensively in agriculture,[2] polymer science[3] and materials science.[4] In the past few decades, they have become popular as valuable synthetic intermediates.[5] Trifunctionalization of alkynes is an attractive synthetic tool for synthetic organic chemists due to easy access of complex molecular frameworks[6] from easily available starting materials. Considering the wide application of dithiocarbamates, we envisioned functionalizing phenylacetylene systems with dithiocarbamate moieties. In our previous report, we demonstrated the β-dithiocarbamylation of styrenes.[7] As a continuation of our research work involving the dithiocarbamate chemistry,[8] here we are introducing a novel strategy to obtain phenacyl-bis (dithiocarbamates) by molecular bromine-mediated trifunctionalization of phenylacetylenes (Scheme 1).

Phenacyl dithiocarbamates have been synthesized earlier from phenacylhalides using thiuramdisulfide[9] or *in situ* generated dithiocarbamate salts[10] (Scheme 2a) and from styrene using *in situ* generated dithiocarbamic acid[11] (Scheme 2b). The synthesis of phenacyl-bis(dithiocarbamate) has been reported very recently by the reaction of acetophenone and tetraethylthiuram disulfide (Scheme 2c).[12] However, the reaction was limited to the synthesis of only one *gem*-bis(dithiocarbamate) compound with a diethylamino ($-NEt_2$) moiety using an excess of the dithiocarbamate source. Here, we have developed a generalized protocol for the synthesis of a wide variety of phena-



Scheme 1 Synthesis of phenacyl-bis(dithiocarbamate) by trifunctionalization of phenylacetylene.



Scheme 2 Synthesis of phenacyl dithiocarbamates and phenacyl-bis (dithiocarbamates).

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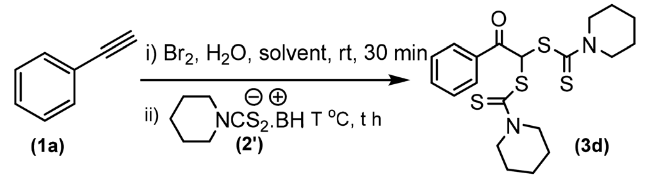
† Electronic supplementary information (ESI) available: Experimental procedure, characterization data and ^1H, ^{13}C, ^{19}F NMR and HRMS spectra. CCDC 2246557. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ob00712j

cyl-bis(dithiocarbamates) by dithiocarbamylation of phenylacetylene by following a one-pot two-step strategy (Scheme 2d). Phenylacetylene undergoes oxidative bromination followed by dithiocarbamylation using the freshly prepared dithiocarbamate salt to produce the *gem*-bis(dithiocarbamate) product (Scheme 1).

The reaction is very easy to perform. Phenylacetylene was brominated using molecular bromine in the presence of two equivalents of water in acetonitrile solution. The brominated reaction mixture was then stirred with the freshly prepared dithiocarbamate salt at 65 °C for a certain time period. After completion of the reaction (checked by TLC), the crude product was obtained by the usual work-up and was purified by column chromatography.

In order to standardize the reaction conditions, phenylacetylene (**1a**) and piperidine-dithiocarbamate salt (**2′**) were considered as the model starting materials. At first, the reaction was conducted in DMF–H_2O (1 : 1) medium with the piperidine-dithiocarbamate salt of the K_2CO_3 base. However, the desired product was formed only with 35% yield (entry 1, Table 1) after 4 h of reaction at 65 °C. Other reaction media, such as THF–H_2O (1 : 1) and toluene–H_2O (1 : 1), did not improve the yield of the reaction (entries 2 and 3, Table 1). However, in MeCN–H_2O (1 : 1) solvent mixture, the reaction produced 45% yield of the desired bis-dithiocarbamate product, **3d** (entry 4, Table 1). Replacing the base with Na_2CO_3 did not improve the reaction outcome (entry 5, Table 1). Even the water medium was not at all suitable for the reaction (entry 6, Table 1), providing the desired product only in a trace amount. However, the yield of the reaction improved a bit upon decreasing the amount of water in the acetonitrile medium. In the presence of 20 equivalents of water, the reaction provided 51% yield of the desired *gem*-bis(dithiocarbamate) product (**3d**) in the acetonitrile medium (entry 8, Table 1). Surprisingly, the reaction proceeded much better in the presence of triethylamine as the base (entry 9, Table 1). A further decrease of the amount of water was found to have a positive effect on the reaction outcome producing the product in improved yields (entries 10 and 11, Table 1). The use of two equivalents of water in the acetonitrile medium was found to be the standard condition to provide the desired phenacyl bis-dithiocarbamate in 90% yield within 2.5 h of time at 65 °C (entry 11, Table 1). The prolonged reaction time did not have any effect on the reaction yield (entry 14, Table 1). However, elevation of the reaction temperature (80 °C) had an adverse effect, producing the dimer of the dithiocarbamate as the side product and hence decreasing the yield of the desired product (entry 12, Table 1).

Table 1 Optimization of the reaction conditions



Entry	Solvent (amount of H_2O)	Base (B)	T (°C)	t (h)	Yield (%)
1	DMF–H_2O (1 : 1)	K_2CO_3	65	4	35
2	THF–H_2O (1 : 1)	K_2CO_3	65	4	Trace
3	Toluene–H_2O (1 : 1)	K_2CO_3	65	4	18
4	MeCN–H_2O (1 : 1)	K_2CO_3	65	4	45
5	MeCN–H_2O (1 : 1)	Na_2CO_3	65	4	40
6	H_2O	K_2CO_3	80	4	Trace
7	MeCN (without H_2O)	K_2CO_3	65	4	—
8	MeCN (20 eq. H_2O)	K_2CO_3	65	2.5	51
9	MeCN (20 eq. H_2O)	Et_3N	65	2.5	63
10	MeCN (10 eq. H_2O)	Et_3N	65	2.5	72
11	MeCN (2 eq. H_2O)	Et_3N	65	2.5	90
12	MeCN (2 eq. H_2O)	Et_3N	80	2.5	57
13	MeCN (2 eq. H_2O)	Et_3N	50	2.5	70
14	MeCN (2 eq. H_2O)	Et_3N	65	5	90
15	MeCN (2 eq. H_2O)	Et_3N	65	2	62

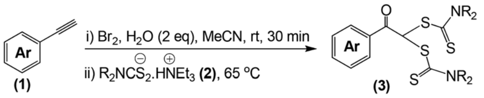
Reaction conditions: (i) Br_2 (1 mmol) in 1 ml of solvent was added to the solution of phenylacetylene (1 mmol) in 2 ml of solvent containing a certain amount of H_2O and the reaction mixture was stirred at room temperature for 30 minutes. (ii) Brominated phenylacetylene was stirred in the presence of the freshly prepared piperidine-dithiocarbamate salt (2 mmol) at a certain temperature for the required time. Dithiocarbamate salts were freshly prepared by the reaction of piperidine and CS_2 in 2 ml of solvent in the presence of a suitable base (B). Yields reported are the isolated yields.

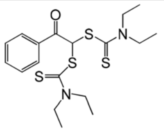
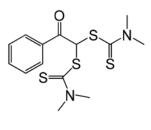
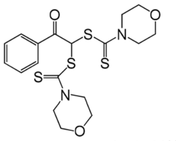
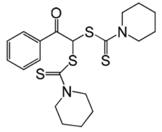
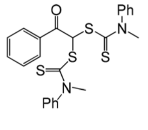
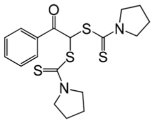
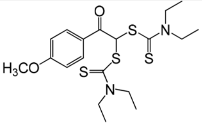
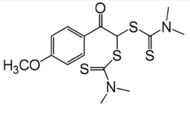
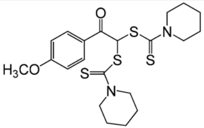
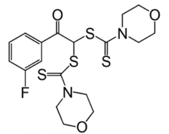
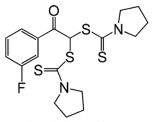
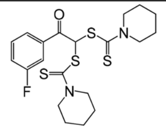
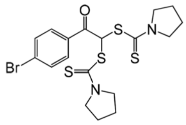
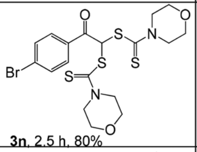
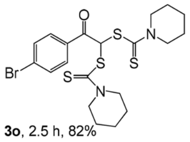
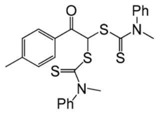
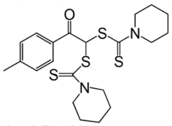
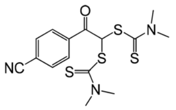
The optimized reaction conditions were then followed to prepare a series of structurally variable phenacyl-bis(dithiocarbamates) (Table 2). Dithiocarbamate salts (**2**) based on cyclic secondary amines (piperidine, pyrrolidine, and morpholine) and acyclic secondary amines (dimethylamine and diethylamine) participated in the reaction efficiently to produce the desired *gem*-bis(dithiocarbamates) in good yields. An aromatic amine, namely *N*-methylaniline, was also used in the reaction to produce the corresponding *gem*-bis(dithiocarbamate) (**3e** and **3p**, Table 2) smoothly. Phenylacetylenes containing aromatic substituents like –OMe, –Br, –F, –Me, and –CN responded to the reactions with equal efficiency. Interestingly, the dithiocarbamate anion did not participate in the nucleophilic aromatic substitution[13] at the C(sp^2)–Br and C(sp^2)–F moieties of the products (**3j**–**3o**) containing aromatic –Br and –F substituents which may allow post-structural modifications. The structure of phenacyl-bis(dithiocarbamate) **3d** was confirmed by single crystal XRD analysis (Fig. 1).

To understand the mechanism, we carried out some control experiments (Scheme 3). We treated phenylacetylene with one equivalent of molecular bromine and 2 equivalents of H_2O in the acetonitrile medium, followed by stirring at room temperature for 30 min. The intermediate compound formed was isolated and characterized (^1H and ^{13}C NMR included in the ESI†) to be phenacyl dibromide (**4**) (Scheme 3a).

Phenacyl dibromide (**4**) produces the desired bis-dithiocarbamate product (**3b**) in a good yield by the reaction with the dimethylamine-dithiocarbamate salt (Scheme 3b). Thus, compound **4** is assumed to be the probable intermediate for this dithiocarbamylation reaction. To check the possibility of the radical reaction pathway, we conducted the bis-dithiocarbamylation reaction of phenylacetylene in the presence of 2.5 equivalents of TEMPO (a well-known radical quencher) under

Table 2 Synthesis of phenacyl-bis(dithiocarbamates)



 **3a**, 2.5 h, 88%	 **3b**, 2.5 h, 89%	 **3c**, 2.5 h, 86%
 **3d**, 2.5 h, 90%	 **3e**, 2.5 h, 84%	 **3f**, 2.5 h, 90%
 **3g**, 2.5 h, 88%	 **3h**, 2.5 h, 86%	 **3i**, 2.5 h, 89%
 **3j**, 3 h, 82%	 **3k**, 3 h, 82%	 **3l**, 3 h, 84%
 **3m**, 2.5 h, 82%	 **3n**, 2.5 h, 80%	 **3o**, 2.5 h, 82%
 **3p**, 2.5 h, 80%	 **3q**, 2.5 h, 80%	 **3r**, 2.5 h, 78%

Reaction conditions: (i) Br_2 (1 mmol) in acetonitrile (1 ml) was added to the solution of phenylacetylene (1 mmol) in acetonitrile (2 ml) containing 2 mmol of H_2O and the reaction mixture was stirred at room temperature for 30 minutes. (ii) Brominated phenylacetylene was stirred in the presence of the freshly prepared dithiocarbamate salt (2 mmol) at 65 °C for the required time. Dithiocarbamate salts were freshly prepared by the reaction of amine (R_2NH, 2 mmol) and CS_2 (3 mmol) in the presence of triethylamine (2 mmol) in acetonitrile (2 ml) solution. Yields reported are the isolated yields.

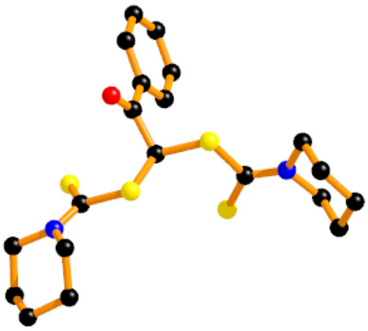
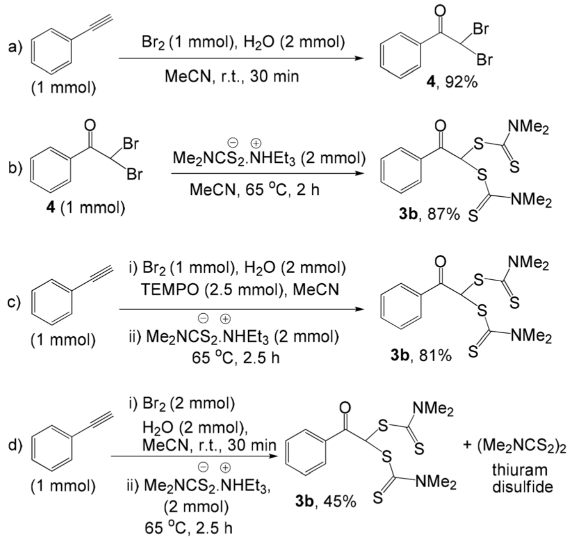


Fig. 1 Molecular view of phenacyl-bis(dithiocarbamate) **3d** (CCDC deposition no. 2246557†).



Scheme 3 Control experiments.

identical reaction conditions (Scheme 3c). However, the desired bis-dithiocarbamate product **3b** was obtained in a significant amount (81% yield). Thus, the radical pathway was ruled out for the current protocol. The bis-dithiocarbamylation reaction was found to be highly dependent on the nature of the solvent (entries 1–4, 6 and 7, Table 1). The reaction provided good results only in the acetonitrile medium in the presence of 2 equivalents of water. However, upon increasing the amount of water in the reaction medium, the yield of the desired compound decreased significantly. The reaction did not proceed at all in the absence of water (entry 7, Table 1). Thus, the presence of both acetonitrile and water was crucial for the reaction. The effect of water on the reaction outcome can be understood from the plot of the reaction yield *vs.* the amount of water used in the reaction (Fig. 2). The decrease of the yield of the reaction upon increasing the amount of water may be due to the low solubility of the starting material and intermediate. In the presence of 2 mmol of molecular bromine, the reaction provided a much poor yield of the desired bis-dithiocarbamate product (**3b**) along with the for-

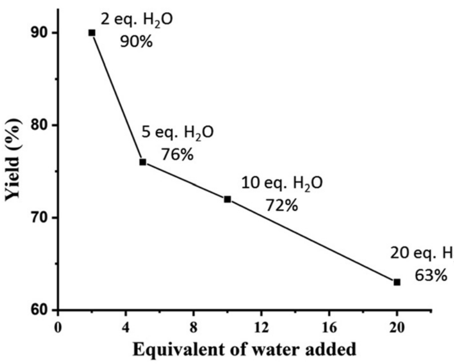


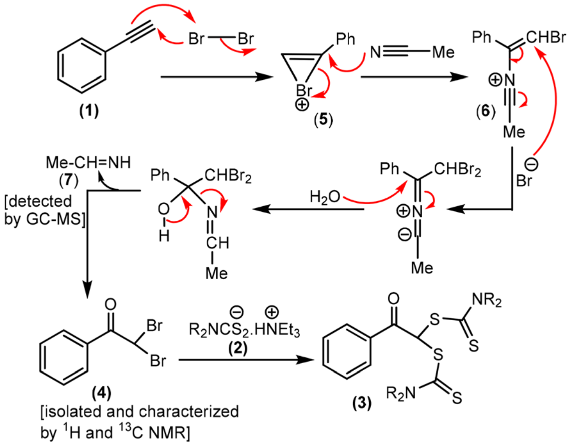
Fig. 2 Plot of the reaction yield *vs.* the amount of water used.

mation of the dimer of dithiocarbamate, $(Me_2NCS_2)_2$ by the action of excess bromine left in the reaction medium (Scheme 3d).

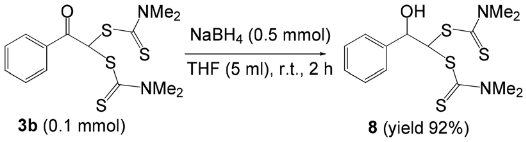
Based on the above observations, we propose a mechanism that proceeds through the formation of the phenacyl dibromide intermediate (**4**) mediated by acetonitrile in the presence of molecular bromine and water (Scheme 4). Phenylacetylene reacts with molecular bromine to produce the bridged bromonium ion (**5**), which undergoes ring opening by the nucleophilic attack of acetonitrile to produce the cationic species (**6**). A similar reaction of acetonitrile with the bridged halonium ion has also been reported earlier.[14] A successive attack of bromide (Br^-) on the cationic intermediate (**6**) followed by a nucleophilic attack of water produces the phenacyl dibromide intermediate (**4**) along with the formation of imine, CH_3–CH═NH (**7**), which was detected by GC-MS analysis of the crude reaction mixture as mentioned in Scheme 3a. In the GC-MS analysis, we observed the presence of a significant amount of acetaldehyde (CH_3–CHO), which was formed by the hydrolysis of imine **7** (GC-MS spectra are included in the ESI†).

In order to study the synthetic potential of the bis-dithiocarbamate product, the phenacyl-bis(dithiocarbamate) compound, **3b**, was reduced by $NaBH_4$ in THF medium to produce the corresponding 2° alcohol (**8**) by the reduction of the carbonyl group keeping the bis-dithiocarbamate moiety intact (Scheme 5).

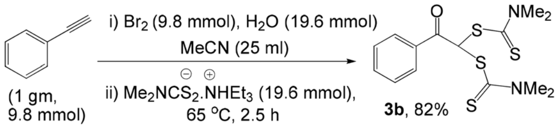
The bis-dithiocarbamylation reaction was also carried out on a gram scale with phenylacetylene and dimethylamine-dithiocarbamate salt (Scheme 6). The reaction provided a good yield of the desired product even in gram-scale synthesis.



Scheme 4 Proposed mechanism.



Scheme 5 Reduction of the carbonyl group in compound **3b**.



Scheme 6 Scale-up of the bis-dithiocarbamylation reaction.

In conclusion, we have demonstrated a general and convenient method to prepare a series of phenacyl-bis(dithiocarbamates) from easily available starting materials. Phenylacetylene systems undergo efficient metal-free dithiocarbamylation with freshly prepared dithiocarbamate salts. This one-pot strategy avoids the isolation and purification steps of the reaction intermediate and reduces organic solvent usage, time and labour. Operational simplicity, easily available starting materials and good yields of the products make this protocol valuable in the field of organic synthesis.

Conflicts of interest

There are no conflicts to declare.

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