Sustainable Strategies for Carbon-Sulfur Bond Formation Reactions in Organic Synthesis

By

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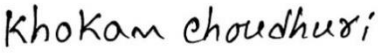

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3. # **Choudhuri, K**.; Pramanik, M.; Mandal, A.; Mal, P. *Asian J. Org. Chem.* **2018**, *7*, 1849.

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Dedicated

To

My Parents

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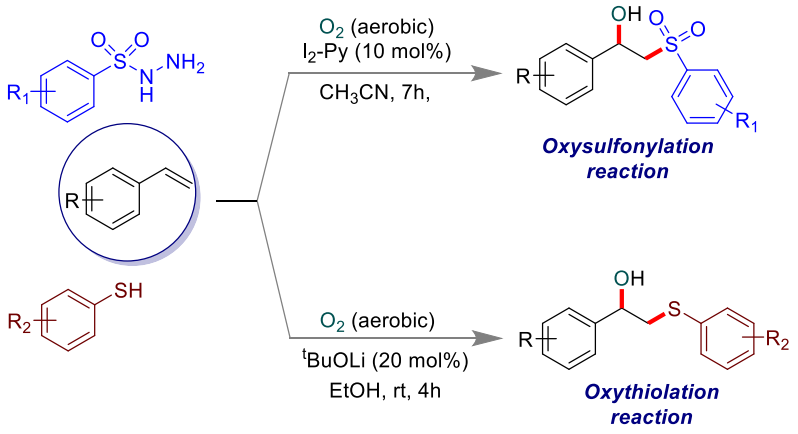

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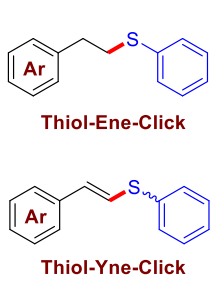

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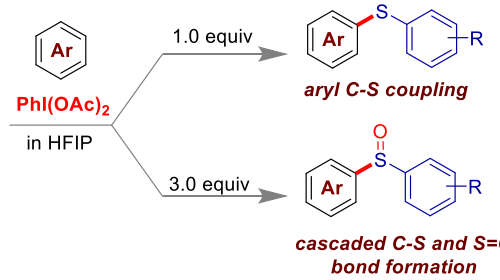

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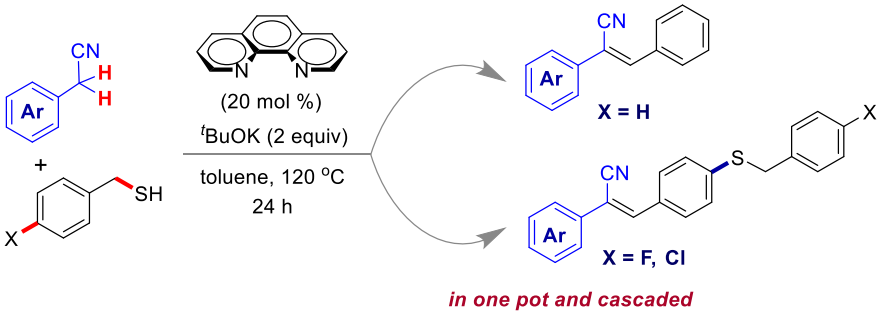
Organo-Catalytic C-S bond activation



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SUMMARY

Organosulfur compounds are widely founds in agrochemicals, pharmaceuticals, pesticides, medical chemistry as well as in material science. Therefore, the research area on carbon – sulfur bond formation reaction is becoming an attractive research field in organic chemistry. Oxidative cross coupling *via* transition metal catalysis is one of the convenient ways to construct the C-S bonds. However, these methods have several shortcomings high catalyst loading and post reaction contamination of hazardous heavy metals makes the reaction systems unpopular in pharmaceutical industries. So, metal-free sustainable approaches have gained significant popularities and the use of environment-friendly reagents makes this protocol more ecological.

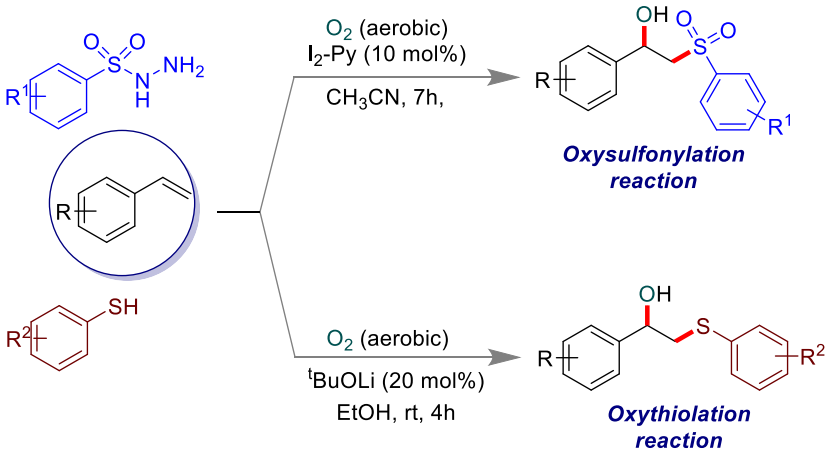


Figure 2. Aerial dioxygen activation leads to C-S bond formation reaction.

Herein, we have demonstrated an expedient aerial dioxygen activation method towards the synthesis of *β*-hydroxysulfones and *β*-hydroxysulphide from commercially available chemical feedstock. Iodine-pyridine (10 mol% of each) catalyzed oxysulfonylation of olefins lead to delivered *β*-hydroxysulfones derivative using sulfonyl hydrazine as sulfur precursor at ambient condition. The other way, *β*-hydroxysulphide was obtained from styrene and thiophenol using catalytic amount of base ^{t}BuOLi at room temperature. Radical trapping and ^{18}O labelling experiments helps to established the mechanistic pathway.

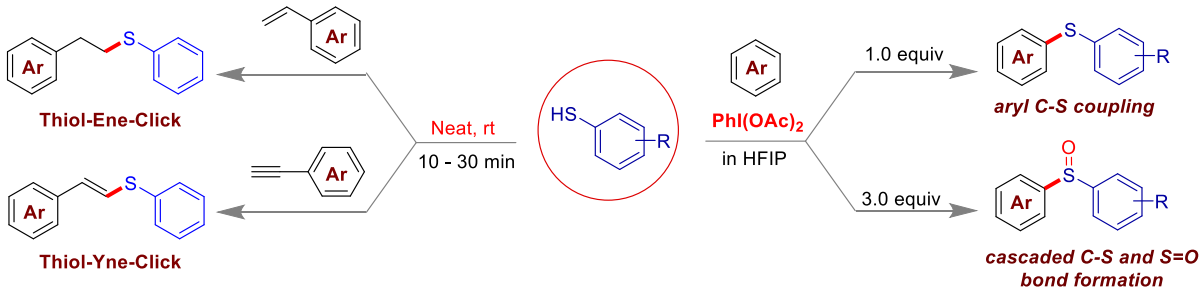


Figure 2. Thiophenol driven C-S coupling reaction.

We have shown weak interaction control click reaction. The S-H...π and π...π stacking interaction controls the regioselectivity of Thiol-Ene-Click (TEC) an Thiol-Yne-Click (TYC) reaction to achieve 100% selective anti-Markovnikov product from styren and thiophenol *via* umpolung addition under solvent and additive free neat condition.

Metal free dehydrogenative aryl C-S coupling reaction between electron-rich arene and thiophenol *via* umpolung approach have also been discussed. *In-situ* electrophilic sulfenium ions were generated from thiophenol using $PhI(OAc)_2$ (PIDA) and subsequently used for aromatic electrophilic substitution (EArS) to synthesize diaryl sulfides. Covalent self-sorting or competitive experiments further confirmed the involvement of sulfenium ion in the EArS.

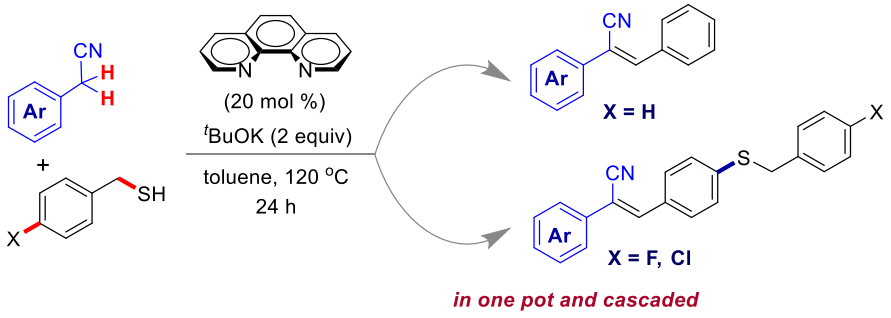


Figure 3. Organo-catalytic cascaded C-C and C-S bond formation reaction

E-Selective alkenylation of nitrile *via* C-S bond cleavage under metal free condition was established in our lab. The reactions were done using *in situ* generated organo-catalyst in combination of catalytic amount of 1,10-phenanthroline with potassium *tert*-butoxide (^{t}BuOK).

CHAPTER 1

An Introduction to Organo-Sulphur Reagents and Carbon-Sulphur Bond Formation Reaction

1.1 ABSTRACT

This chapter is mainly focuses on a brief introduction of organo-sulfur reagents and their application in the development of C-S bond formation reaction. The Chapter is divided in three parts: (1) Importance of sulfur in our daily life. (2) Brief introduction about the Organo-Sulfur reagent and their reactivity towards Carbon-Sulfur bond formations reactions. (3) C-S bond formations reaction and their application in medicinal and pharmaceutical field. Finally the Chapter is concluded with a brief discussion about the aim of present thesis for C-S bond formation reaction.

1.2 INTRODUCTION

Sulfur is the tenth most abundant element by mass and fifth supreme element on earth.[1] It is existed on earth as sulfide or sulfate mineral and also found in pure native form. Mostly elemental sulfur[2] can be found in the areas on earth including hot springs, hydrothermal vents, salt domes, volcanic emissions, etc. In ancient times India, China, Greece and Egypt used sulfur as a combustion source in the religious ceremonials. It is also called as brimstone,[3] which means burning stone. In 1777, an alchemist Antoine Lavoisier has been recognized sulfur is an element, however, not a compound by the principle of combustibility. Later, French chemist Joseph Gay-Lussac and Louis Thenard established its elemental property. Sulfur is an element with symbol S and atomic number 16. Sulfur belongs to p-block, group 16, third row element with electronic configuration [Ne]d^{10} S^2 P^4. Therefore preferred oxidation state of sulfur is -2. It exist in zero (0) oxidation state in elemental sulfur

and +2 oxidation state in covalent organosulfur compound like thiophenols. However, because of electropositive nature, larger size and amphoteric behavior, sulfur can also form stable poly co-ordinated multivalent compounds with relatively weak bonds to electronegative groups or elements such as oxygen[4], nitrogen[5], pseudo halide[6] or itself sulfur.[7]

1.3 Sulfur in daily life

Sulfur is one of the most essential elements for living organism[8]. Next to calcium and phosphorus, it is the most abundance mineral in our body. It accumulates into the body in the form of organo sulfur compounds like proteins,[9] amino acids,[10] etc. Sulfur is one of the main responsible elements for producing insulin, keratin, arthritis and collagen into the body.[11] National Academics Food and Nutrition Board have ensured that healthy human bodies need 0.2-1.5 g of sulfur in each day. Nature provides some enriched sources of organosulfur compounds[12] in the form of fruits and vegetables which we take in our daily life to maintain the sulfur level.

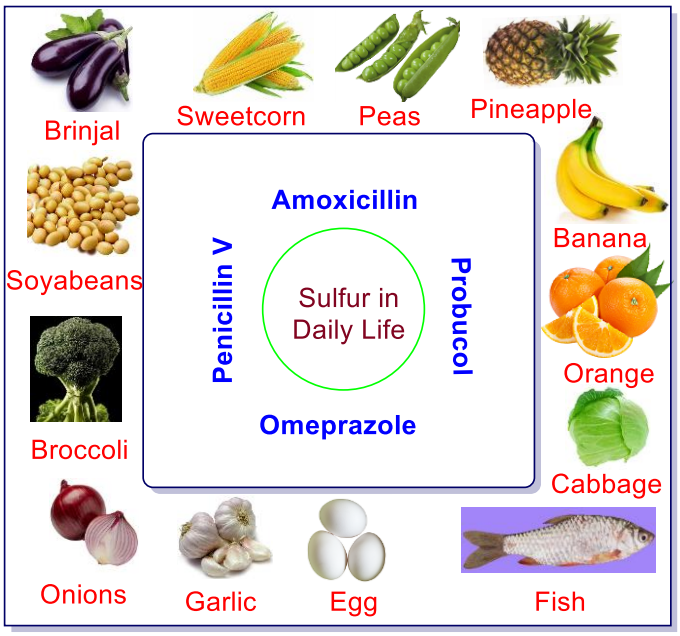


Figure 1.1 Natural source of organosulfur compound

Out of 20 amino acids only cysteine and methionine are sulfur containing which are found in proteins.[10] Methionine could not be synthesized by our body, so it is supplied through diet. Another sulfur containing amino acid is Cysteine which could be synthesized by our body but the process requires a demure supply of sulfur. The organosulfur compound such as amino acid (methionine and cysteine), peptide (glutathione), protein with cross linking agent and biotin plays an important role for the living organism.[13] In addition, organosulfur compounds[8,14-17] are ubiquitous in many natural products and was widely used in agrochemicals, pharmaceuticals, pesticides, medical chemistry as well as in material science. It was also found in many synthetic drugs.[11]

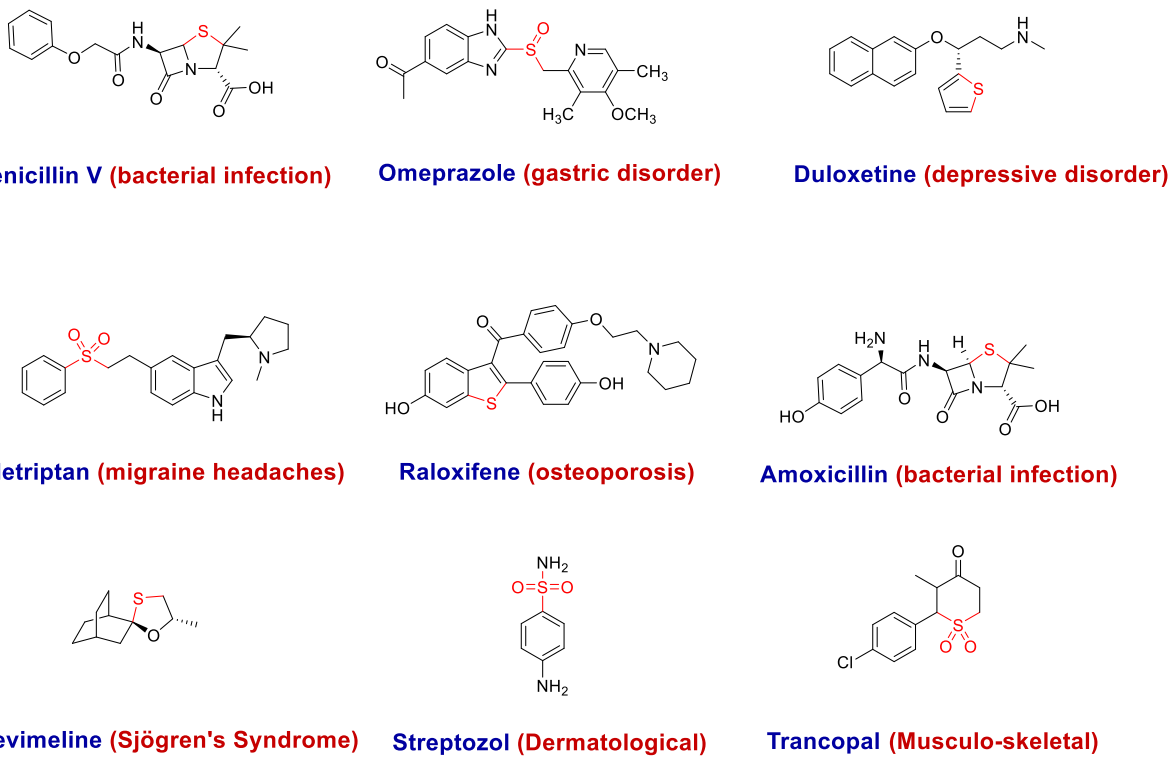


Figure 1.2 Biological active organosulfur compound used as drugs candidate.

1.3 Organo-Sulfur reagent

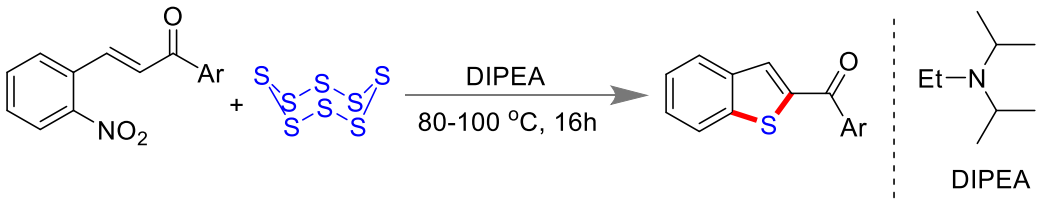
Sulfur surrogate are mainly classified into two category 1) organo-sulfur reagent like thiophenol, sulfonyl chloride etc. 2) inorganic salt of sulfur like $PhSO_2Na$, K_2S etc. Among

them we have chosen organo-sulfur reagent to make the C-S bond in a single step process under mild condition due to its versatile nature[18]. In synthetic organic chemistry, the scope and application of organosulfur compound have tremendously increases due to sulfur-containing group serve as important auxiliary in reaction sequences. Structurally diverse, many types of organosulfur compounds (sulfides, disulfides, thioether, sulfoxide, sulfone, thiosulfinates, sulfinamides, sulfoximides, sulfonediimines, *S*-nitroso thiol, sulfur halides, thiocarbonyl compounds, thio carboxylic acid, thioamide, thio yilides, sulfurance etc.) have been documented in literature with simple or complex molecular structure. We have arbitrarily chosen some simple organo-sulfur surrogates which are commonly available in the market or easy to prepare, for making the complex organic molecule in an easier way with step economically method using sustainable reagent condition.

1.3.1 Elemental Sulfur

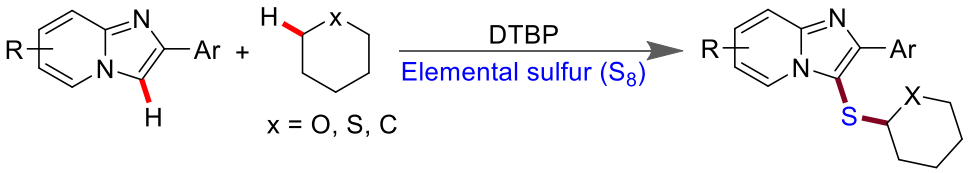
Elemental sulfur[2] is odorless pale yellow solid, which is soluble in CS_2. It is easily available and inexpensive, generally used for the making of C-S bond. The elemental sulfur is genrally found in natural sources like crude petroleum, minerals, etc. and appears in several allotropic forms *viz.* rhombic, octahedral, monoclinic, prismatic, α or β-sulfur. Several, literature reports reveal that elemental sulfur (S_8) has been extensively used in numerous organic transformations.[5]

Retailleau and coworkers have synthesized 2-benzoylbenzothiophenes derivative from 2-nitrochalcones by using elemental sulfur and diisopropyl ethylamine (DIPEA) as activator under heating at 80 ^{o}C (Scheme 1.1).[19]



Scheme 1.1 Retailleau's approach for substituted benzothiophenes formation.

Tang group reported an intermolecular oxidative dual C-H thiolation of imidazopyridines derivatives using elemental sulfur by heating at 120 °C (Scheme 1.2).[20] In this reaction, DTBP (*di-tert-butyl peroxide*) was used as radical initiator to activate the C(Sp^3)-H bond of inert alkanes or ethers which would react with elemental sulfur to provide the thiyl radical intermediate. At the final step thiyl radical reacted with the heterocyclic moiety to afford the products with single bridge headed sulfur atom.



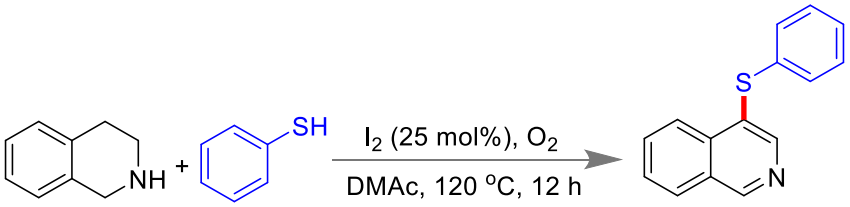
Scheme 1.2 Tang's approach for dual C-H thiolation.

1.3.2 Thiophenol

Thiophenol is foul smelling colorless liquid, acidic in nature with Pk_a value 6.62. The oxidation state of sulfur in thiophenol is +2. It can possess nucleophilic as well as electrophilic character[4,21,22] due to the presence of two sets of lone pair of electron and vacant 3d orbital. Thiophenol could be easily prepared by the reduction of sulfonyl chloride with metallic zinc in acidic medium.

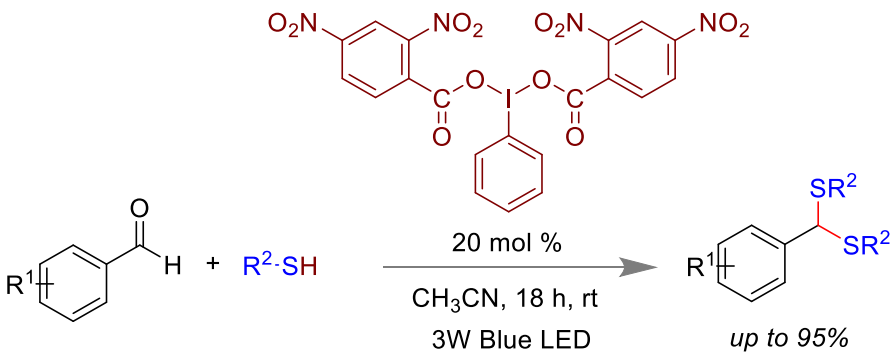
Lei and coworkers have established iodine catalyzed oxidative *β*-selective C(Sp^3)-H thiolation of *N*-heterocyclic amine (Scheme 1.3).[23] Mechanistically they have shown that first

oxidative N-S bond formation followed by rearrangement provided the *β*-functionalization of *N*-hetrocycle amine.



Scheme 1.3 Lei's approach for oxidative *β*-selective C-H bond thiolation.

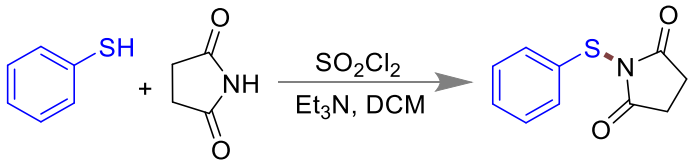
Mal and his group have reported λ^3-Iodanes catalysed chemoselective dithioacetalization of aldehyde using 3W Blue LED at ambient condition (Scheme 1.4).[24]



Scheme 1.4 Mal's approach for chemoselective dithioacetalization of aldehyde.

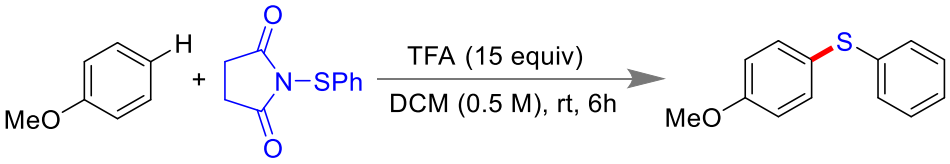
1.3.3 *N*-phenylthio-succinimide

N-Phenylthio-succinimide is a colorless solid. It is used as sulfur precursor for the cleavage of N-S bond *via* single electron transfer (SET) in acidic condition. It is prepared by the reaction of thiophenol and succinimide in presence of sulfuryl chloride and triethyl amine in anhydrous DCM at 0 °C (Scheme 1.5).



Scheme 1.5 Preparation of *N*-phenylthio-succinimide.

Cossy and coworkers developed TFA (Trifluoro acetic acid) promoted regioselective C(Sp^2)-H sulfenylation of electron rich arene by using *N*-(arylthio)-succinimides as sulfur surrogate at room temperature (Scheme 1.6).[5]

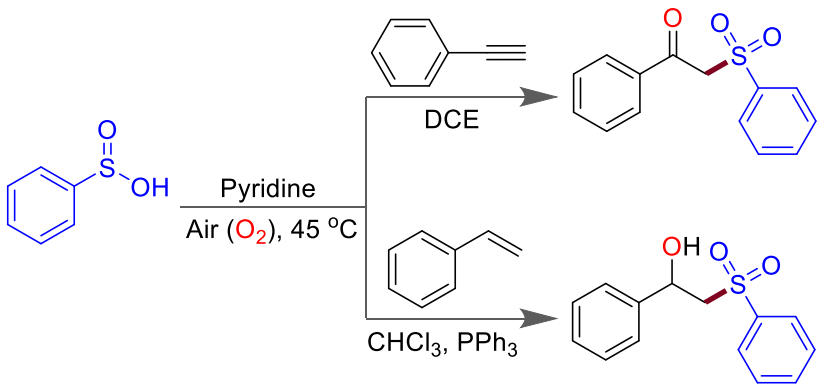


Scheme 1.6 Cossy's regioselective C-H sulfenylation.

1.3.4 Benzenesulfonic acid

Benzenesulfonic acid is colourless waxy solid, highly soluble in water or ethanol. The oxidation state of sulfur in benzenesulfonic acid is +6. It is commonly used as household detergent. The benzenesulfonic acid could be easily prepared by the treatment of benzene with conc. H_2SO_4. In synthetic organic chemistry, benzenesulfonic acid is either as a catalyst[25] for various organic transformations or as a reagent[26] in C-S bond formation reaction.

Either *β*-hydroxysulfones or *β*-keto sulfones shown to be synthesized within a reaction system by choosing the appropriate reaction condition. Lei and coworkers demonstrated either of the *β*-hydroxysulfones or *β*-keto sulfones could be synthesized *via* aerial dioxygen activation mechanism using benzenesulfonic acid and styrene or phenyl acetylene, respectively (Scheme 1.7).[26,27] Pyridine plays a dual role in this transformation acting as a base to generate the sulfonyl radical from benzenesulfonic acid and also successfully prevents the atom transfer radical addition (ATRA) process to removes the possibility of by-products (vinyl sulfone) formation.



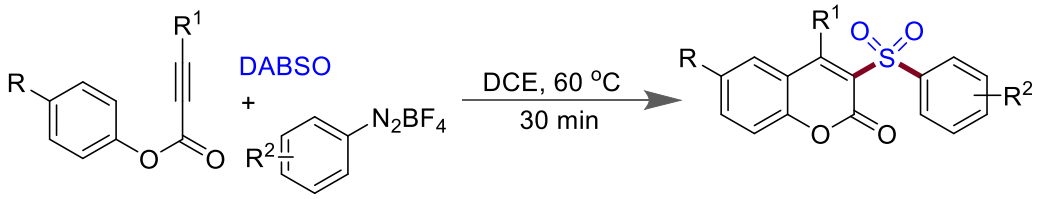
Scheme 1.7 Lei's aerial dioxygen activation report

Herein, pyridine played a dual role in this transformation by acting as a base to generate a sulfonyl radical from benzenesulfonic acid and also successfully prevents the atom transfer radical addition (ATRA) process to rule out any by-products (vinyl sulfone) formation.

1.3.5 1,4-Diazabicyclo[2,2,2]octane bis(sulfur dioxide) adduct (DABSO)

DABSO is colorless crystalline bench stable solid, soluble mostly in organic solvent. The oxidation state of sulfur in DABSO is +4. Generally it is used as alternative source of gaseous SO_2 in synthesis. DABSO was prepared by the combination of DABCO and gaseous SO_2 to form a charge transfer white crystalline solid.

Wu and his group established a three-component tandem process for the synthesis of 3-sulfonated coumarins derivative by the combination of aryldiazonium salt and DABSO with aryl propiolates in DCE solvent at 60 °C (Scheme 1.8).[28] Kinetics and experimental studies reveal that the reaction proceeded through the *in situ* generation of sulfonyl radical by the treatment of aryldiazonium tetrafluoroborates and DABSO *via* charge-transfer complex formation.

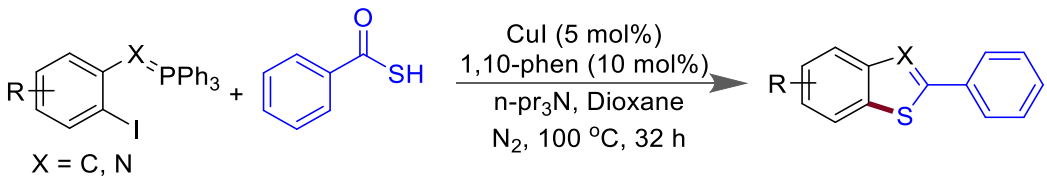


Scheme 1.8 Wu's report for 3-sulfonated coumarins synthesis.

1.3.6 Thiobenzoic acid

Thiobenzoic acid is a yellow liquid with two tautomeric forms thione (RC(S)OH) and thiol (RC(O)SH). It is also called as carbothioic *O*-acid" and "carbothioic *S*-acid" respectively. The oxidation state of sulfur in thiobenzoic acid is +4. The pK_a value of thiobenzoic acid is 2.48 which is ~100 times stronger than analogous carboxylic acid. It is prepared by two steps, first benzoyl chloride are treated with potassium pulfide to form potassium thiobenzoate and followed by hydrolysis with 6N HCl to achieve thiobenzoic acid.

Yu and coworkersdeveloped a Cu catalyzed Ullmann type C-S coupling and Wittig reaction (Scheme 1.9).[29] In presence of catalytic amount of CuI and 1,10-phen, thiobenzoic acid reacted smoothly with (2-iodobenzyl)triphenylphosphonium salt to afford benzothiophenes or benzothiazoles derivative.

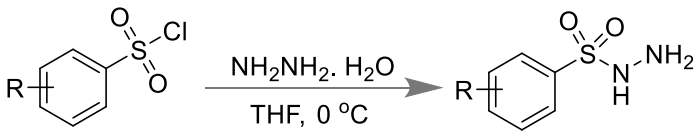


Scheme 1.9 Yu's approach for Cu catalyzed Ullmann type C-S coupling and Wittig reaction.

1.3.6 Sulfonyl Hydrazine

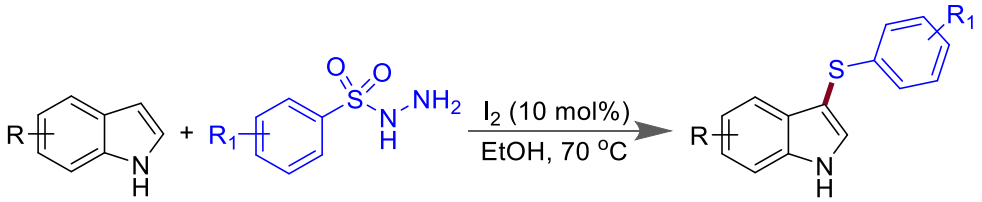
Sulfonyl Hydrazine is a colorless crystalline solid and basic in nature with pKa of 17.1. The oxidation state of sulfur in sulfonyl hydrazine is +6. Sulfonyl hydrazines are readily accessible, have been utilized as thiyl source[30] for sulfonylating reactions[31] by the breaking of

S-N bond. It can be easily prepared by the combination with sulfonyl chloride and hydrazine hydrate solution in THF at 0 °C (Scheme 1.10).



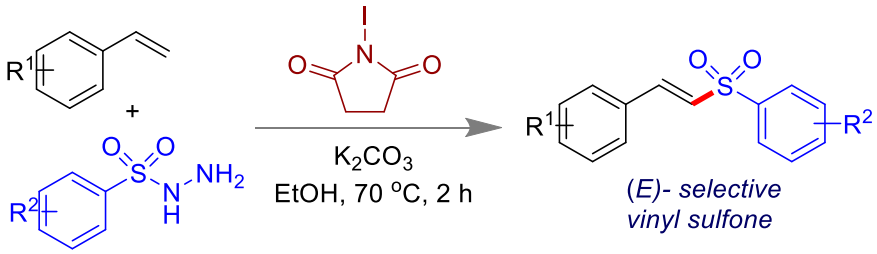
Scheme 1.10 Preparation of sulfonyl hydrazine.

Tian and coworkers developed molecular iodine catalyzed regioselective sulfenylation of indoles using sulfonyl hydrazine as sulfur precursor (Scheme 1.11).32 In presence of catalytic amount of iodine, sulfonyl hydrazine decomposed to form sulfenium ion intermediate which was trapped by indole at the 3 position via electrophilic aromatic substitution reaction to synthesize structurally diverse indole thioether derivatives.



Scheme 1.11 Tian's approach for regioselective sulfenylation of indoles.

Mal and coworkers established highly regio- and stereoselective C(sp2)-H sulfonylation of styrenes using sulfonyl hydrazine as a sulfur surrogate. In this reaction, NIS plays a dual role. At the initial stage, it was used to generate sulfonyl radical from sulfonyl hydrazides through the cleavage of S-N bond and in the final step it provides the iodine source to form *β*-iodosulfone intermediate which would decomposed to formed vinyl sulfone in presence of K2CO3 (Scheme 1.12).[21]

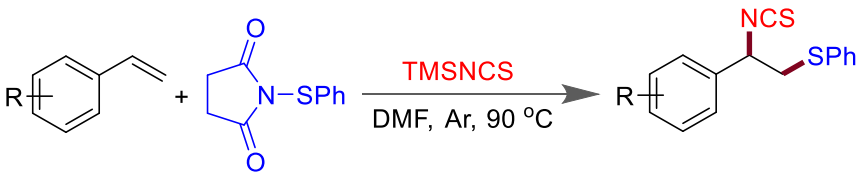


Scheme 1.12 Mal's approach for stereoselective C(sp2)-H sulfonylation of styrenes.

1.3.7 (Trimethylsilyl)isothiocyanate (TMSNCS)

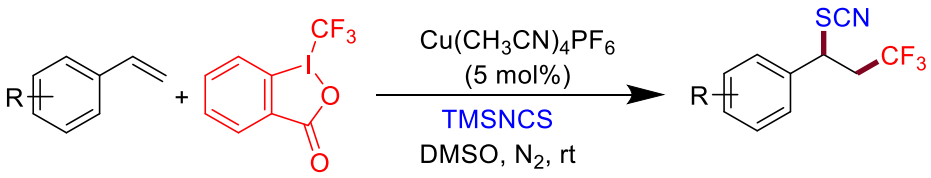
(Trimethylsilyl)isothiocyanate (TMSNCS) is pale yellow liquid with unpleasant pungent smell and decomposes on reaction with water. TMSNCS is used as a versatile reagent in organic synthesis. The -NCS being an ambidentate chelating ligand, generally used for the introduction of thiocyanate[33] or isothiocyanate[34] groups in synthesis. Also, it can be utilized to make nitrogen-containing heterocycles by co-coordinating with both the chelating center (N, S). It can be prepared by the treatment of trimethylchlorosilane (TMSCl) with excess of silver isothio cyanate in inert solvents at 80 °C.

Fu and coworkers developed isothiocyanatoalkylthiation of olefins using *N*-phenylthio-succinimide and trimethylsilyl isothiocyanate in DMF under inert condition heating at 90 °C (Scheme 1.13).[34] The transformation starts with the formation classical sulfenium ion intermediate by the treatment of *N*-phenylthio-succinimide with styrene, which was trapped by TMSNCS through the hard nucleophilic center (-NCS) to afford isothiocyanatoalkylthiation product.



Scheme 1.13 Fu's approach for isothiocyanatoalkylthiation of styrene.

Liu group have established an efficient copper catalyzed intermolecular trifluoromethylthiocyanation of alkenes using Togni reagent as -CF_3 source and TMSNCS as –SCN source (Scheme 1.14).[33] In presence of Cu(I) salt, Togni reagent might have activated to generate CF_3 radical for trapping of styrene moiety to form a stable benzylic radical intermediate. Finally, a nucleophilic attack by thiocyanates radical through the more nucleophilic soft center (-SCN) afforded trifluoromethylthiocyanation product.



Scheme 1.14 Liu's approach for Cu catalyzed trifluoromethylthiocyanation of alkenes

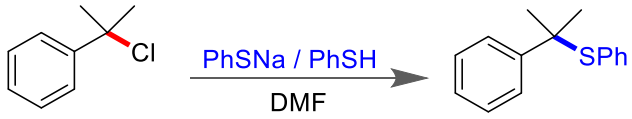
1.4 Carbon-Sulfur bond formation reaction

Among the discussed sulfur surrogate, mainly we are focusing on thiophenol and sulfonyl hydrazine to make this report. Construction of C-S bond has always received enormous attention because of its widespread application in natural products, pharmaceutical, agrochemical, material sciences and most importantly in many drug molecules. We have classified the Carbon-Sulfur bond formation reaction according to their mechanistic rationalization, 1) Carbon-Sulfur bond formation reaction using sulfur as radical center 2) Carbon-Sulfur bond formation reaction using sulfur as electrophilic center 3) Carbon-Sulfur bond formation reaction using sulfur as nucleophilic center 4) solvent promoted Carbon-Sulfur bond formation reaction.

1.4.1 C-S bond formation reaction using sulfur as radical center

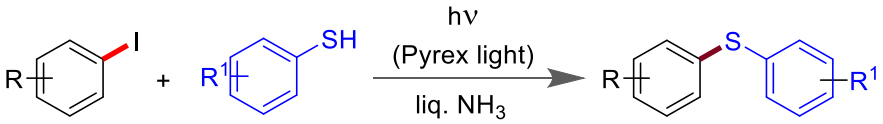
In the history of C–S bond formation reactions, the pioneering work reported by Donald H. Snow[35] and coworkers in 1967. They demonstrated a facile substitution reaction using

sodium thiophenoxide / thiophenol at the tertiary carbon atom of *p*-nitrocumyl chloride in DMF at 0 ^{o}C, to obtain 95% yield of the product within 2 h of reaction time (Scheme 1.15). They proposed that, this reaction proceeded through a radical anion intermediate formation.



Scheme 1.15 Substitution reaction at the tertiary carbon atom

Then Creary[36,37] and coworkers have applied photolytic conditions using Pyrex-filtered light source (350 nm) to make the C-S bond from aryl iodides and thiophenol in liquid ammonia (Scheme 1.16). They proposed that in presence of light source, thiolate anion would act as a single electron transfer (SET) agent and produced aryl and thiyl radical from aryl iodide and thiophenol, respectively. Then the coupling of the two radical afforded the diphenyl sulfide adduct.



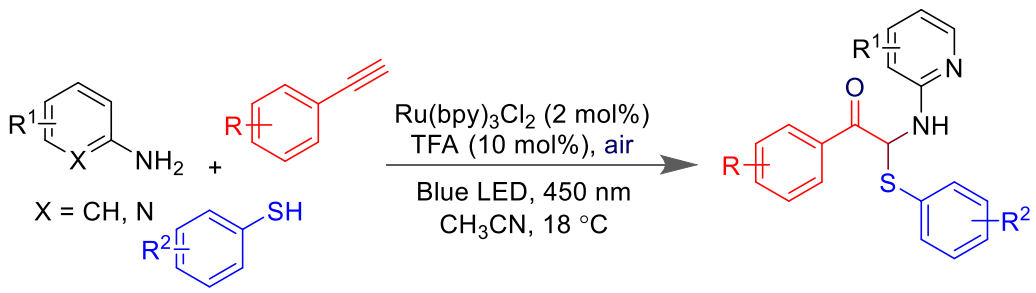
Scheme 1.16 Pyrex-light promoted C-S coupling

Later, they have demonstrated when dihalobenzenes were employed under the same reaction condition, a dithiosubstituted product formation was observed. Moreover, kinetics and experimental investigation reveals that the reaction may proceed *via* formation of radical anion intermediate and monosubstituted product is not the intermediate for the production of dithiophenylsubstituted benzene formation.

1.4.1.1 Photo-redox catalyzed C-S bond formation reaction

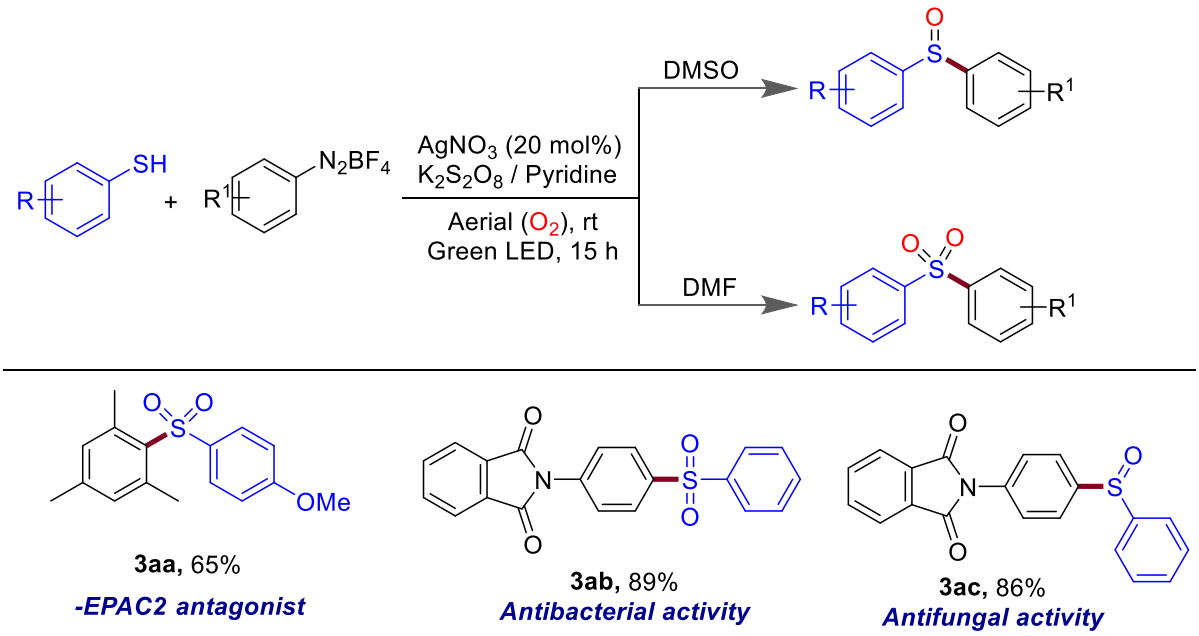
Recently, visible light induced photoredox catalysts mediated synthetic transformation reactions have received significant attention. These reactions also include the making of various C-S bonds. Mostly, the photoredox catalysts used in organic synthesis are based on two categories, 1) Metal complexes of Ru and Ir etc. 2) Organic dye like Eosin-Y, Rose-Bengal, etc.

Shah and coworkers established geminal difunctionalization of alkynes for the synthesis of α, α-aminothioketones under visible light (Scheme 1.17).[38] In the presence of $Ru(bpy)_3Cl_2$ photocatalyst, the concomitant introduction of two different nucleophiles led to the formation of *α*-C−N and C−S bonds in a cascaded manner. Experimental investigations revealed that the activate photocatalyst generated thiyl and peroxide radical in a single cycle from the thiophenol and aerial oxygen, respectively. Then these two radicals plays the key role to form geminal di-functionalized products *i.e.*, α,α-aminothioketones.



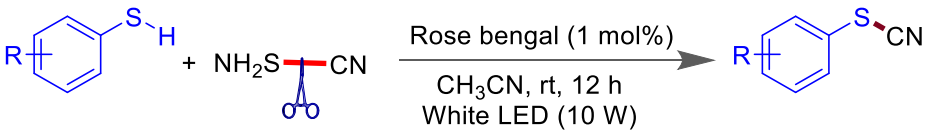
Scheme 1.17 Shah's approach for geminal difunctionalization of alkyne

Lee group also reported visible light induced one pot synthesis of diaryl sulfoxide and diaryl sulfone from thiophenol and aryl diazonium salt through switching of solvents (Scheme 1.18).[39] The singlet oxygen quenching[40] property of sulfoxide group of DMSO offered diaryl sulfoxide as one of the products, whereas use of DMF produced diaryl sulfoxide exclusively.



Scheme 1.18 Lee's approach for selective synthesis of diaryl sulfide and diaryl sulfoxide

Rose bengal catalyzed S-H cyanation of thiophenol have been developed by Fan and coworkers by using photolytic condition from thiophenol and inorganic ammonium thiocyanate salt (Scheme 1.19).[41] It was anticipated that C-S bond cleavage in ammonium thiocyanate followed by reconstruction with thiyl radical provided the phenyl thiocyanats as products.

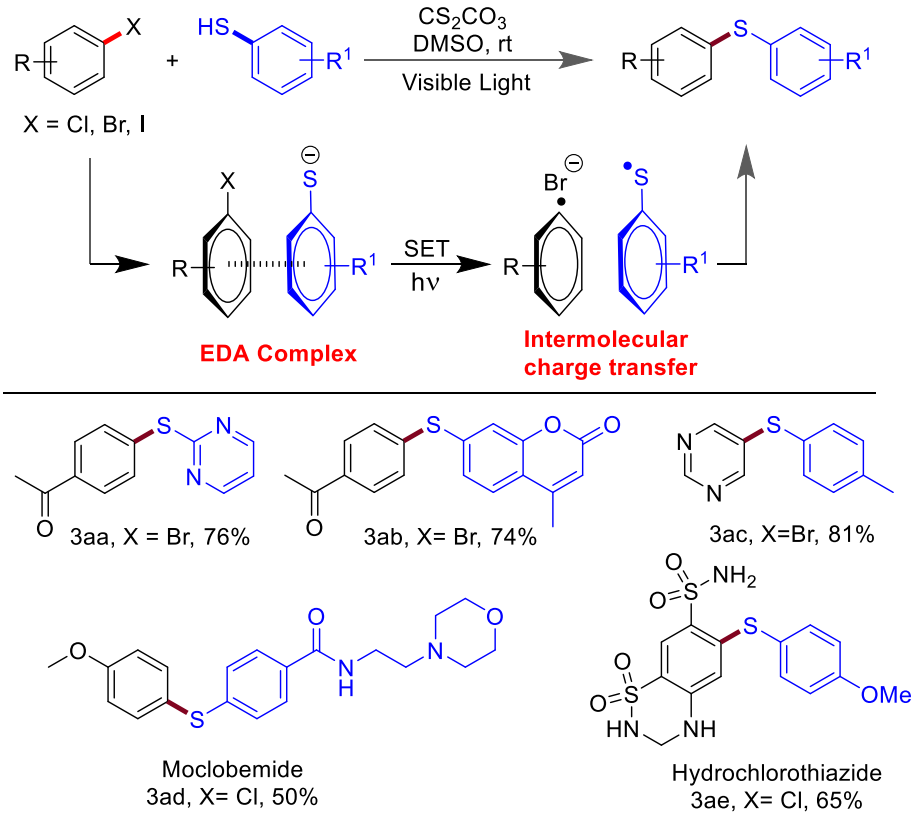


Scheme 1.19 Fan's approach for thiocyanation of thiophenol

1.4.1.2 Base mediated C-S bond formation reaction *via* radical pathway

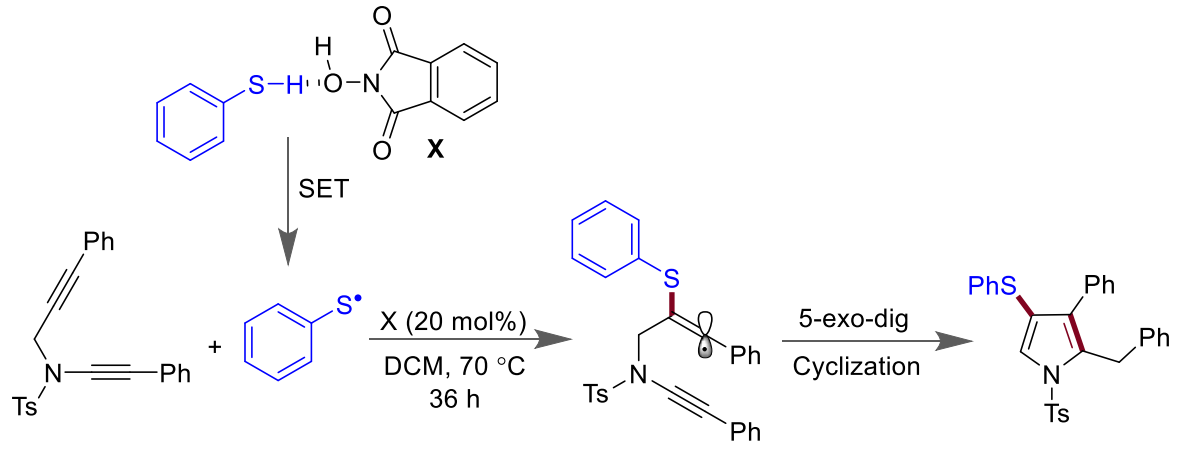
Under visible light irradiation, an intermolecular cross coupling reaction of thiophenols and aryl halides is reported by Miyake group in which CS_2CO_3 acted as a base to initiate the reaction (Scheme 1.20).[42] Theoretical (TD-DFT calculation) and experimental studies suggested that an electron donor acceptor (EDA) complex between electron deficient aryl

halide and electron rich thiophenol through the π-π stacking was the intermediate. This EDA complex further led to the formation of intermolecular charge transfer complex. The rection proceeded well in the highly polar solvent DMSO and under visible light.



Scheme 1.20 Miyake's approach for intermolecular C-S coupling

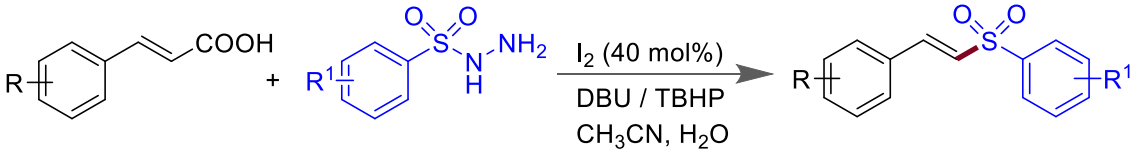
Recently Sahoo's group showed the synthesis of substituted pyrroles from yne-ynamide and thiophenol through 5-exo-dig cyclization (Scheme 1.21).[43] This protocol revealed that simple alkynes were found to be more reactive than that of ynamides. *N*-Hydroxythalimide possibly formed an associative hydrogen bonding and followed by oxidation thiyl radical was generated. After that, thiyl radical reacted with the alkyne and followed by 5-exo-dig attack to ynamide led to substituted pyrrole derivatives.



Scheme 1.21 Sahoo's approach for the synthesis of *N*-protected *4*-thioaryl-pyrrole.

1.4.1.3 Iodine mediated C-S bond formation reaction *via* radical pathway

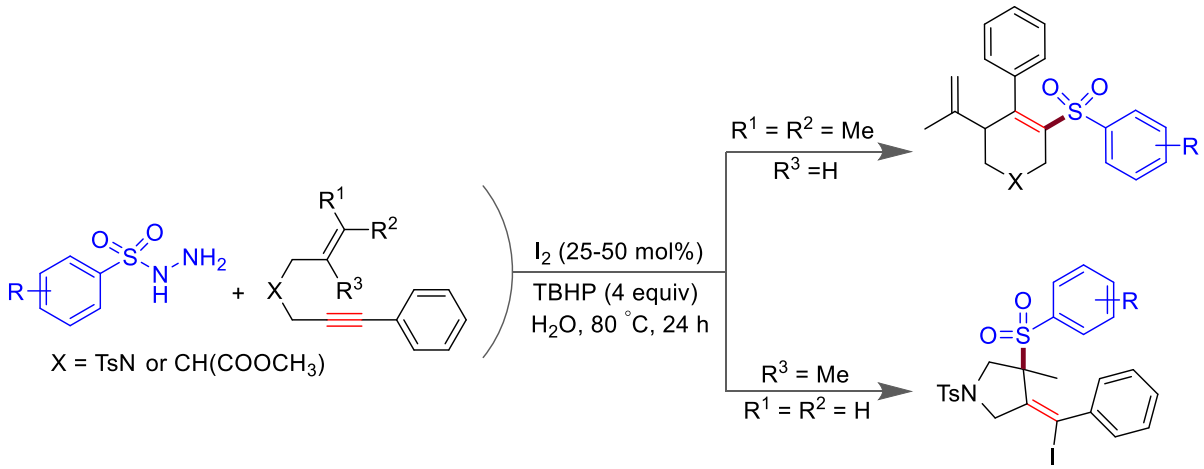
Singh and coworkers described a decarboxylative cross coupling reaction between aryl sulfonylhydrazine and cinnamic acid for stereo- and regioselective synthesis of (*E*)-vinyl sulfone by using the catalytic amount of iodine and TBHP as oxidant in a solvent mixture CH_3CN:H_2O (3:1) (Scheme 1.22).[31]



Scheme 1.22 Sing's approach for *E*-selective synthesis of vinyl sulfone.

Liang and coworkers developed iodine mediated regioselective cyclization reaction of 1,6-enynes with sulfonyl hydrazine to obtain either five or six member sulfonylated product from the same reaction system (as shown in Scheme 1.22), using TBHP in water at 80 ^{o}C (Scheme 1.23).[44] The regioselectivity of the product formation was controlled by steric effect of R_1 and R_2. When R_1 and R_2 were methyl groups, then the generated sulfonyl radical could attack at the sterically less crowed alkyne moiety to form the six membered sulfonylated product. However, when it was a hydrogen atom then sulfonyl radical was trapped by the more

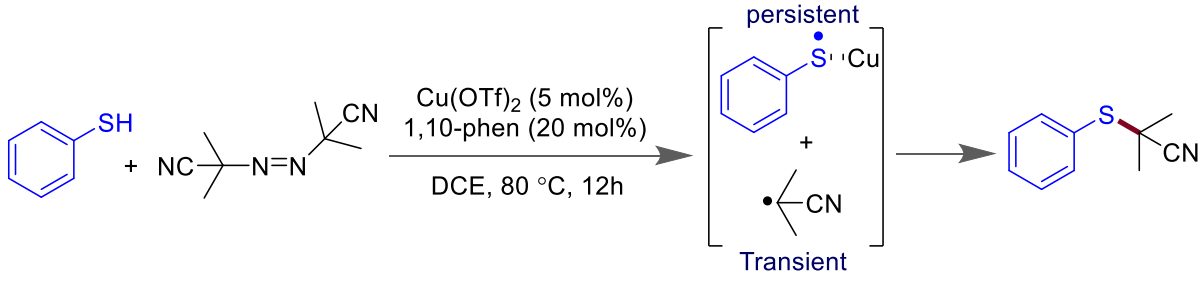
activated alkene moiety and led to the formation of a five membered sulfonylated products.



Scheme 1.23 Liang's approach for regioselective cyclization reaction.

1.4.1.4 Metal catalyzed C-S bond formation reaction *via* radical pathway

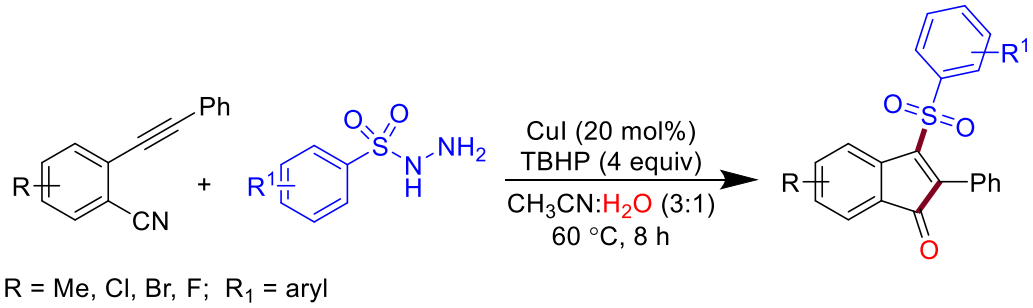
Lei group reported a copper-catalyzed cross-coupling reaction between thiyl radical and isobutyronitrile radical to access α-alkylthionitriles derivative from thiophenol and azobisisobutyronitrile (AIBN) in DCE at 80 ^{o}C (Scheme 1.24).[45] Mechanistically they have proposed that the copper catalyst stabilized thiyl radical by transforming into a persistent form which was the key step for the selective radical-radical cross-coupling reaction.



Scheme 1.24 Lei's approach for copper-catalyzed radical-radical coupling reaction.

Zhao and coworkers reported copper-catalyzed intermolecular cascaded radical cyclization strategy for the synthesis of 3-sulfonated indenones from 2-alkynylbenzonitriles and sulfonyl hydrazides by using TBHP as a sole oxidant in CH_3CN: H_2O (3:1) at 60 ^{o}C (Scheme 1.25).[46]

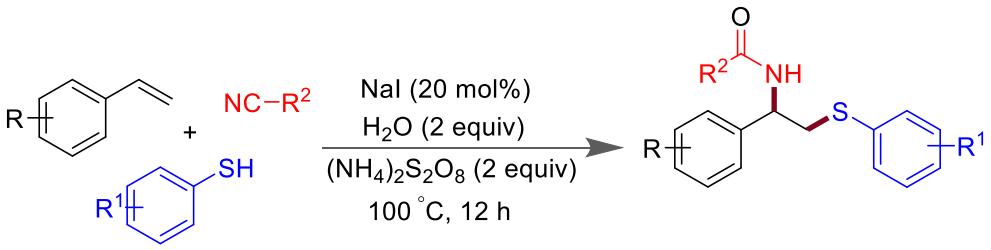
Isotope labeling experiments helped to prove that H_2O was used as an oxygen source for the introduction of –CO group in the 3-sulfonated indenones. In addition, they reported that 3-sulfonyl indenones exhibited aggregation-induced emission (AIE) properties which could further be used for cell imaging studies with excellent biocompatibility.



Scheme 1.25 Zhao's approach for synthesis of 3-sulfonated indenones dreivative.

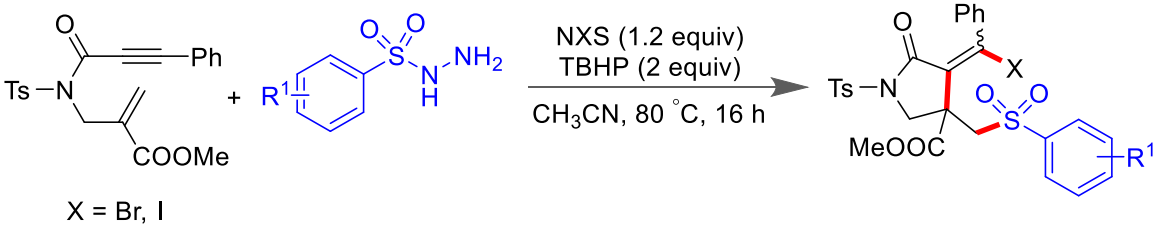
1.4.1.5 Peroxide mediated C-S bond formation reaction *via* radical pathway

An efficient sodium iodide catalyzed peroxide mediated acetamidosulphenylation reactions of alkenes have been reported by Mao group to direct access acetamidosulfides derivative by using nitrile as nucleophilic coupling partner in H_2O at high 100 ^oC (Scheme 1.26)[47].



Scheme 1.26 Mao's approach for acetamidosulphenylation reactions of alkenes.

Xuan and coworkers developed arylsulfonyl radical triggered cascaded cyclization of 1,6-enynes to have direct access to the biologically important γ-lactams having alkenyl carbon-halogen bonds by using TBHP as sole oxidant in acetonitrile at 80 ^oC (Scheme 1.27).[48]

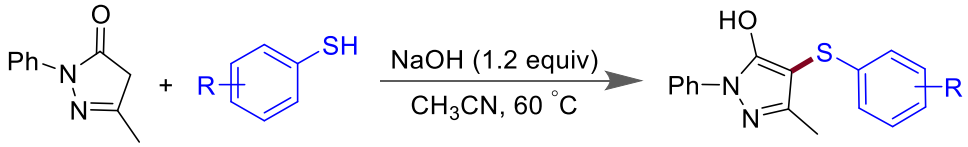


Scheme 1.27 Mao's approach for γ-lactams synthesis.

1.4.2 C-S bond formation reaction using sulfur as electrophilic center

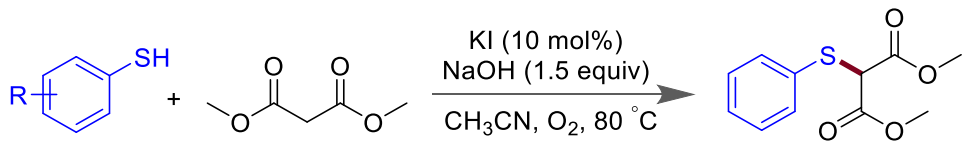
1.4.2.1 Base mediated C-S bond formation reaction *via* cationic pathway

Wang group have developed a protocol for the synthesis of sulfenylated pyrazoles derivative using thiophenol as sulfur precursor and under metal free condition in acetonitrile at 60 ^{o}C (Scheme 1.28).[49] In presence of NaOH, the reaction was started with the formation of 1,2-diphenyldisulfane intermediate.



Scheme 1.28 Wang's approach for sulfenylation of pyrazolones.

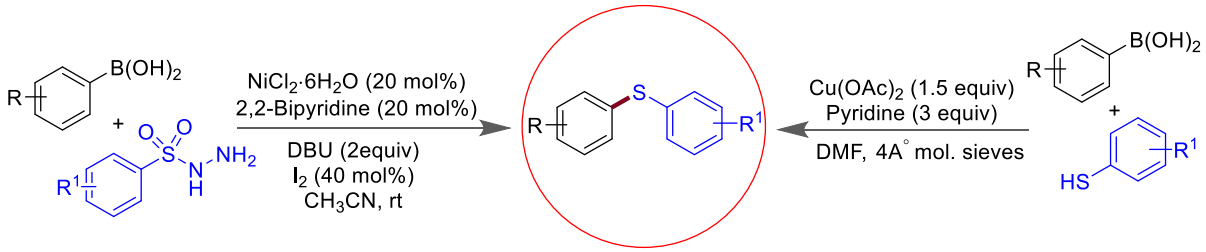
Zhang and wang with coworkers reported an efficient synthesis of symmetrical/unsymmetrical *α*-sulfenylated diketones by the reaction of thiophenol and dimethyl malonate in presence of potassium iodide (KI) as catalyst and NaOH in CH_3CN under aerobic condition, and at 80 ^{o}C (Scheme 1.29).[50]



Scheme 1.29 Zhan's approach for synthesis of *α*-thio-*β*-dicarbonyl compounds.

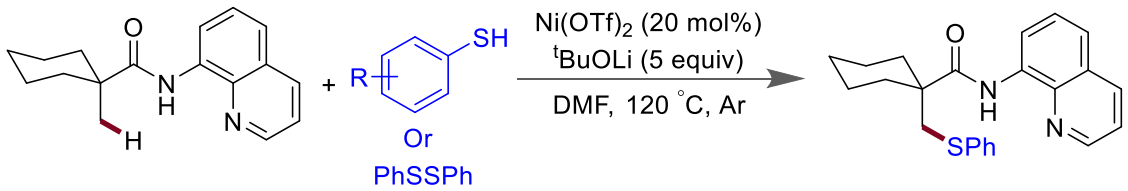
1.4.2.1 Metal mediated C-S bond formation reaction *via* cationic pathway

Guy and coworkers established an efficient protocol for the synthesis of diaryl sulfide from phenyl boronic acid and thiophenol by using stoichiometric amount of copper and pyridine in DMF under refluxing condition and inert atmosphere (Scheme 1.30).[51] They used 4Å molecular sieves to absorb the produced water during the course of the reaction.



Scheme 1.30 Synthesis of diaryl sulfide molecule.

Recently, Singh group reported catalytic version of a reaction for the formation of diaryl sulfides from phenyl boronic acid using sulfonyl hydrazine as sulfur precursor, 2,2-bipyridine and catalytic amount of Nickel chloride in acetonitrile at room temperature (Scheme 1.30).[52] The co-oxidant iodine and DBU were used to prepare *in situ* sulfenium ion intermediate from sulfonyl hydrazine during the transformation.

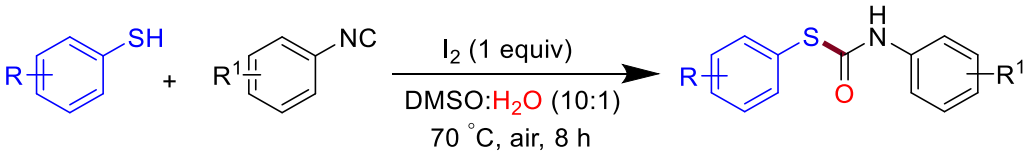


Scheme 1.31 Shi's approach for Ni-catalyzed C(Sp3)-H sulfenylation.

Recently, Shi group has reported an efficient Ni-catalyzed, directed group assisted C(Sp3)-H sulfenylation of amide derivatives by using thiophenol or 1,2-diphenyldisulfane as the sulfur precursors under refluxing condition in DMF (Scheme 1.31).[53]

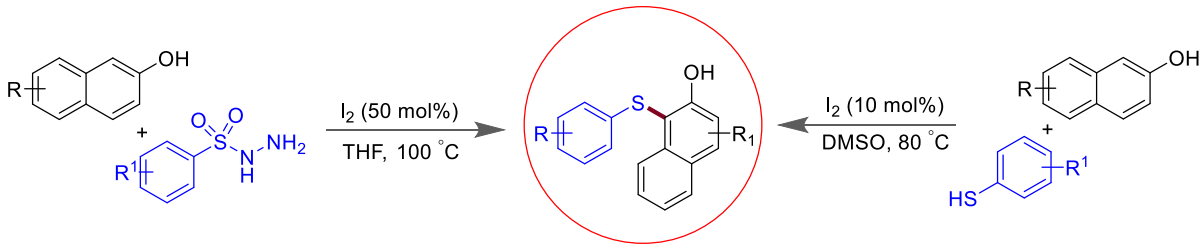
1.4.2.2 Iodine mediated C-S bond formation reaction *via* cationic pathway

He and coworkers developed a simple efficient method for the formation of thiocarbamates from thiophenol, isocyanides and water by using stoichiometric amount iodine in DMSO by heating at 70 ^{o}C and under open atmosphere (Scheme 1.32).[54] From isotope labeling experiment they proposed that water was the oxygen source for the formation of thiocarbamates.



Scheme 1.32 He's approach for synthesis of thiocarbamates.

Iodine mediated C(Sp^2)-H bond functionalization of naphthols is developed by Huang and coworkers, for the synthesis of thioether by using sulfonyl hydrazine as sulfur precursor in THF at 100 ^{o}C (Scheme 1.33).[30] This reaction was started with the *in situ* generation of thiyl cationic intermediate from sulfonyl hydrazine *via* cleavage of S-O and S-N bond, and followed by nucleophilic attack of naphthols to obtain the products.



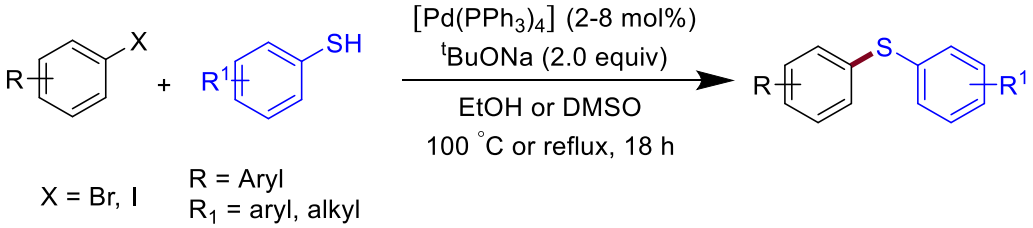
Scheme 1.33 Iodine catalyzed thioether synthesis.

Later, Peddinti group have expanded the scope, for the synthesis of thioether by using thiophenol as sulfur precursor *via* umpolung strategy form readily available thiophenol derivative and electron rich scaffold (Scheme 1.33)[55].

1.4.3 C-S bond formations reaction using sulfur as nucleophilic center

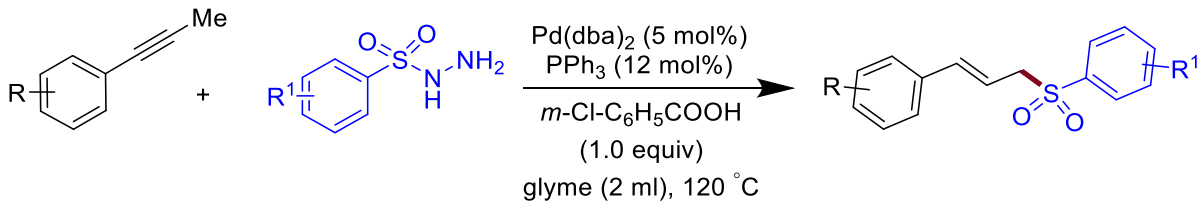
1.4.3.1 Metal catalyzed C-S bond formation reaction *via* anionic pathway

Migita and coworkers have pioneered for the metal catalyzed C-S bond formation reaction. For the first time in 1978, they have reported $Pd(PPh_3)$ catalyzed intermolecular oxidative cross coupling reaction between aryl halide and thiophenol in DMSO at 100 ^oC under inert condition to access the thioethers (Scheme 1.34).[56] Afterwards, this research field of metal catalyzed C-S bond formation reaction have been progressed significantly.[57]



Scheme 1.34 Migita approach for Pd catalyzed C-S bond formation reaction.

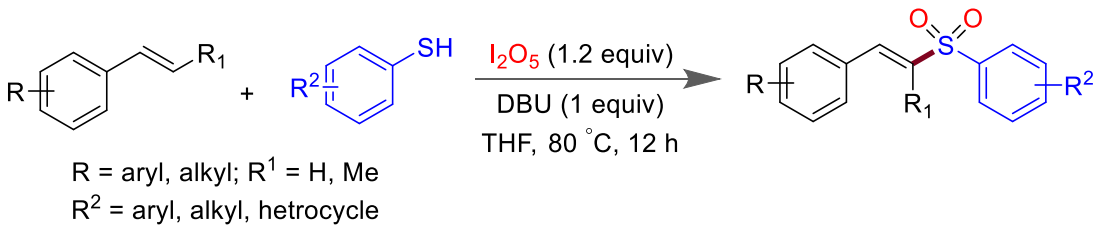
Jin group have established $Pd(dba)_2$ catalyzed regioselective synthesis of allyl arylsulfone derivative by the reaction between internal alkyne and sulfonyl hydrazine in glyme as solvent at 120 ^oC under inert condition (Scheme 1.35).[58] The transformation started with the formation of phenylallene intermediates from internal alkynes, and sulfonyl hydrazine provided the nucleophile source as sulfonyl anion through the cleavage of N-S bond.



Scheme 1.35 Jin's approach for regioselective synthesis of allyl arylsulfone.

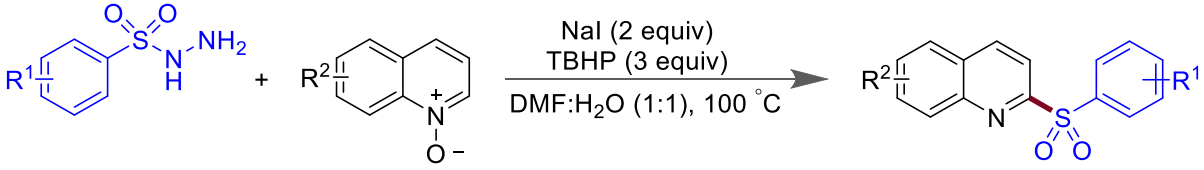
1.4.3.2 Iodine mediated C-S bond formation reaction *via* anionic pathway

Wang and coworkers developed hypervalent iodine (I_2O_5) reagent mediated oxidative cross coupling reaction towards the synthesis of (*E*)-selective vinyl sulfone derivatives from unactivated alkene and thiophenol in THF at 80 ^oC (Scheme 1.36).[59] The reaction started with the formation of benzenesulfonothioate as intermediate by oxidizing of thiophenol in presence of I_2O_5. In the final step the base DBU helped to obtain the product from *β*-iodo sulfone derivative.



Scheme 1.36 Wang's approach for regioselective synthesis of vinylsulfone.

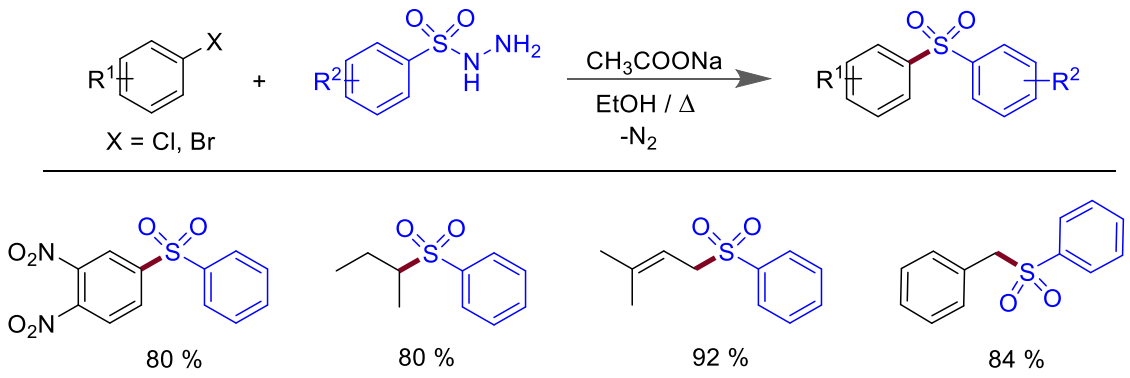
An efficient protocol for the synthesis of C_2-sulfonylation of hetroaromatic *N*-oxide has been established by He group. Upon treatment of sulfonyl hydrazine with pyridine/quinoline *N*-oxide, in presence of sodium iodide and TBHP in a mixture of solvent DMF:H_2O (1:1) at higher temperature, synthesis of C_2-sulfonylation of hetroaromatic *N*-oxide were achived (Scheme 1.37).[60] By combining NaI and TBHP, hypoiodites were generated within the reaction system, which promoted the reaction by coordinating with *N*-oxide to form a six membered ionic intermediate and followed by nucleophilic attack of sulfenium anion the products formation took place.



Scheme 1.37 He's approach for C2 sulfonylation of hetrocycle.

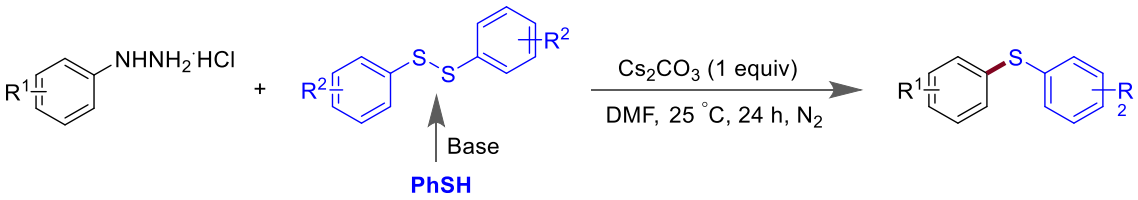
1.4.3.3 Base promoted C-S bond formation reaction *via* anionic pathway

In 1989, first Ballini's group have shown that sulfonyl hydrazine could be used as a nucleophile source towards the synthesis of sulfones through the displacement reaction by using suitable aryl halide in the presence of sodium acetate in ethanol under reflux condition (Scheme 1.38).[61]



Scheme 1.38 Ballini's approach for the synthesis of sulfone.

Taniguchi and cowrokers reported base mediated inter molecular cross coupling reaction towards the formation of unsymmetrical sulfides from aryl hydrazine and 1,2-diphenyldisulfane in DMF at room temperature under inert condition (Scheme 1.39).[62]

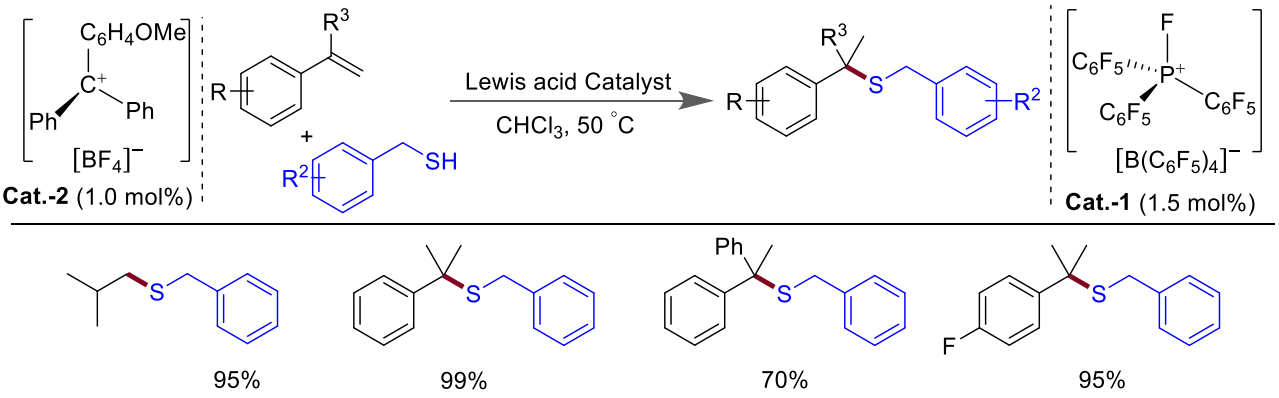


Scheme 1.39 Taniguchi's report for the synthesis of unsymmetrical sulfide.

1.4.3.4 Lewis acid promoted C-S bond formation reaction *via* anionic pathway

Stephan and coworkers reported Lewis acid catalyzed Markovnikov selective hydrothiolation reaction using unactivated olefins and thiophenol in $CHCl_3$ at room temperature (Scheme 1.40). As catalyst electrophilic phosphonium cations[63] were used, which coordinated with the

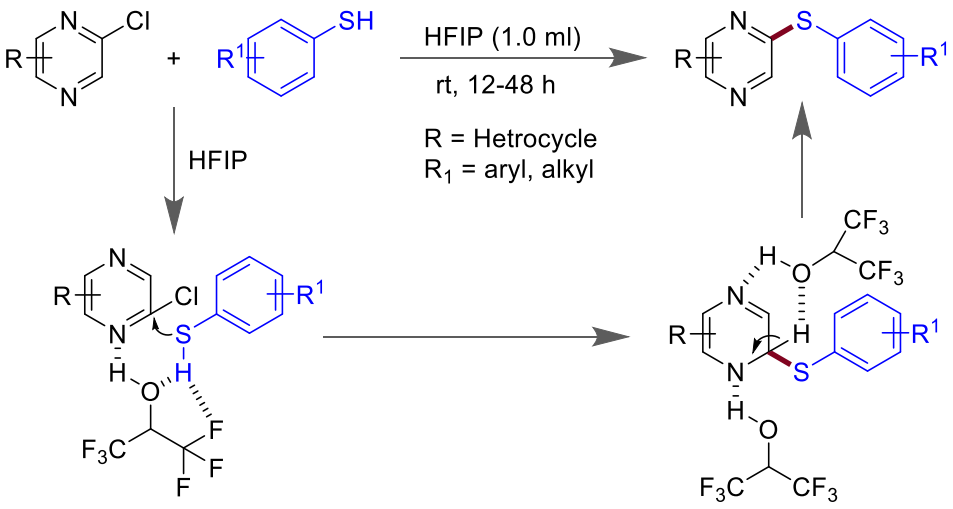
terminal position of the olefins to promote the reaction by the formation of stable carbocationic intermediate at the α-position of olefins, followed by nucleophilic attack of thiophenol afforded the Markovnikov selective product. Later they have expanded the scope of hydrothiolation reaction using air stable trityl-cation salt $[(MeOC_6H_4)CPh_2][BF_4]$.[64]



Scheme 1.40 Stephan's report for Markovnikov selective hydrothiolation reaction.

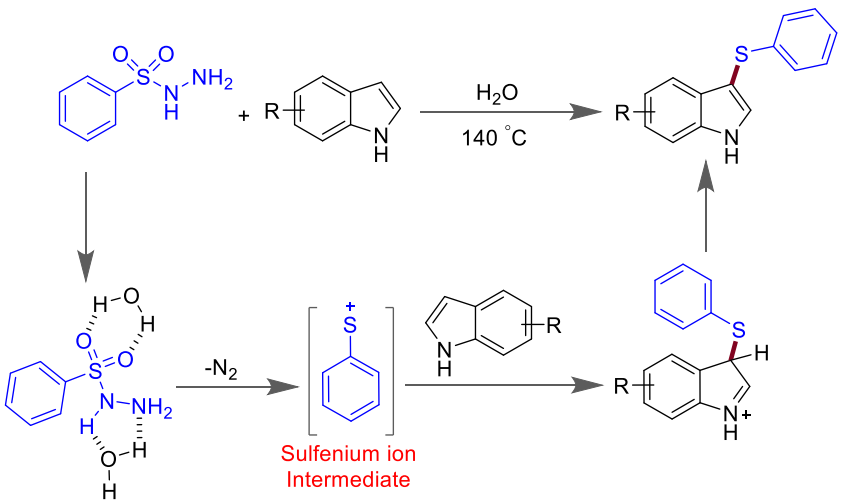
1.4.4 Solvent promoted C-S bond formation reaction

Recently, Kapdi and coworkers introduced an efficient and sustainable method for synthesis of hteroaromatic thioether using HFIP solvent as a reaction controller (Scheme 1.41).[65] They have reported that aromatic nucleophilic substitution of chloroheteroarene led to the formation of new C-S bond by the cleavage of C-Cl bond. HFIP showed versatility in many chemical transformations because of it's strong hydrogen bond donor capability, acidic nature and very good ability to ionize substrates. Utilizing hydrogen bonding property, HFIP coordinated with nitrogen center of nitrogenius chloro-arene through N…H-O hydrogen bonding[66] and weakened the C-Cl bond. Consequently, it also promoted nucleophilic attack of thiol through halogen bonding within fluorines of HFIP and proton of thiophenol. Notably, the developed methodology was unsuccessful for non-nitrogenous system.



Scheme 1.41 Kapdi's approach for solvent promoted C-S bond formation reaction.

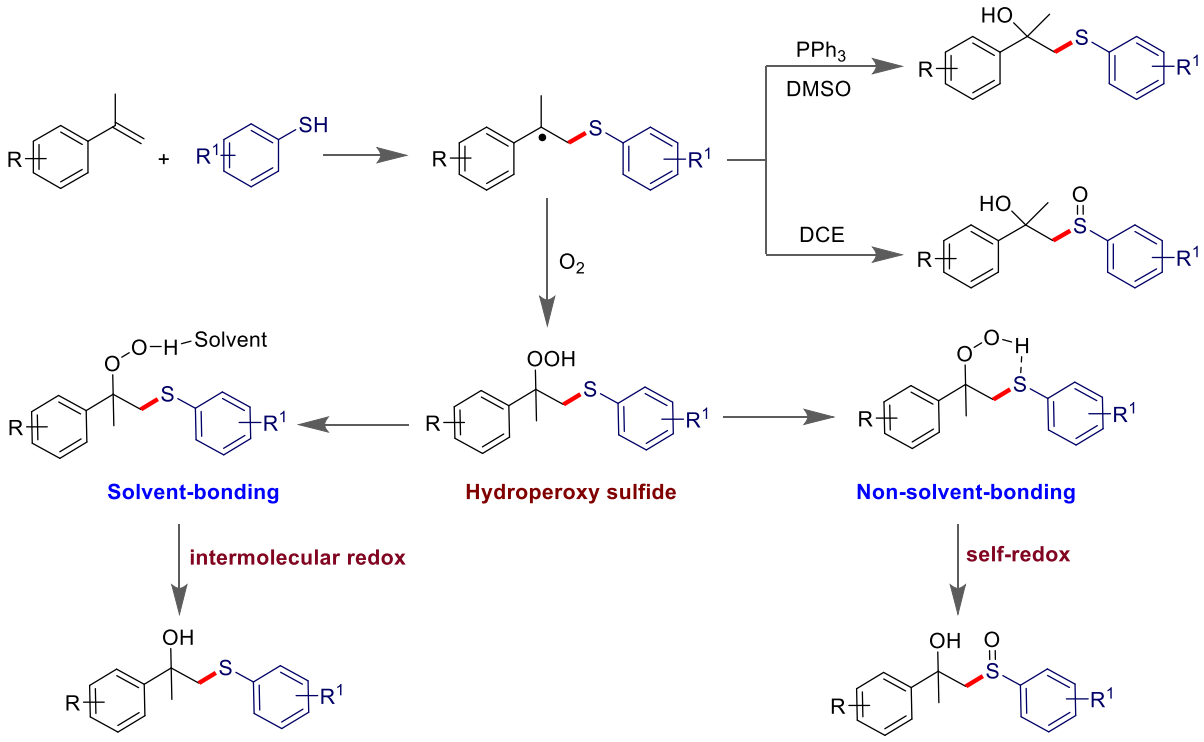
C-3 Sulfenylation of indole has been reported by Wang group in water medium (Scheme 1.42).[67]. It was anticipated that water molecule formed a stable intermediate with sulfonyl hydrazides through noncovalent interactions. As a result, sulfenium intermediate was generated which was further attacked by C-3 position of indole to offer sulfenylated indoles. Various substituted indoles were prepared with good to excellent yields.



Scheme 1.42 Wang's approach for thiolation of indoles.

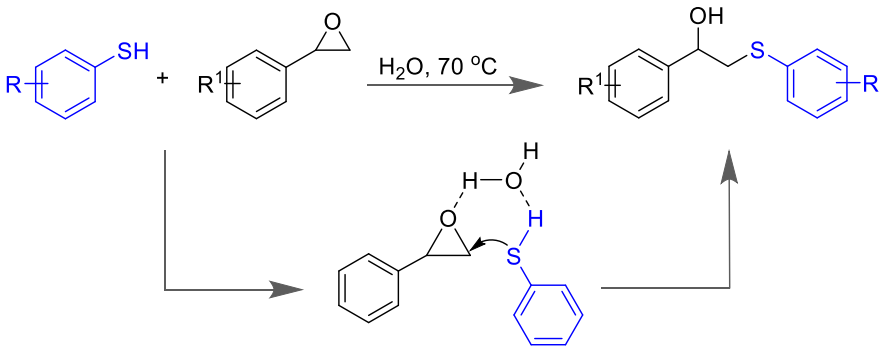
In 2016, Lei and coworkers described a radical mediated synthesis of *β*-hydroxy sulfides and sulfoxide from alkene and thiophenol through solvent binding (Scheme 1.43).[68] Due to the

strong H-bond accepter property of DMSO resulted in *β*-hydroxy sulphides formation with the assistant of solvent-solute interaction. On the other hand the weakly hydrogen bond accepter solvents such as $CHCl_3$, DCE preferred to give *β*-hydroxy sulfoxide formation due to absence of solute-solvent interaction.



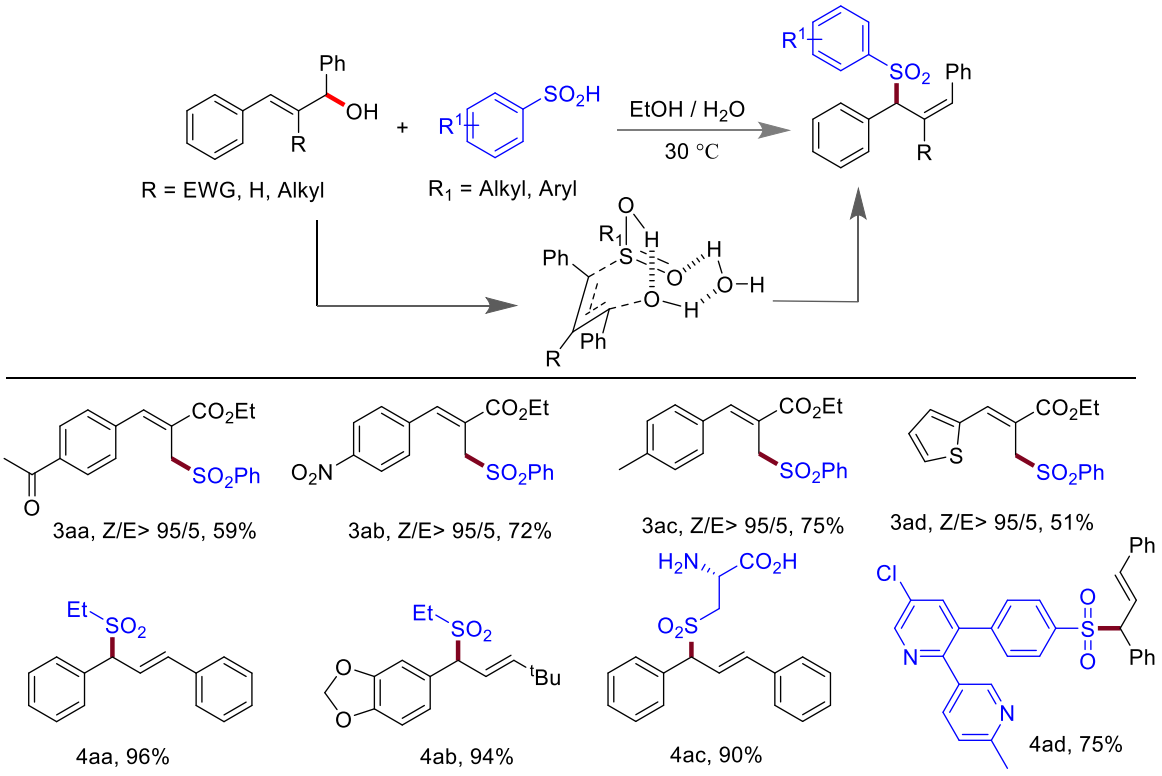
Scheme 1.43 Lei approach solvent-enabled syntheses of sulfoxides and sulfides.

Later, regioselective thiolation of epoxide in water medium is reported by Misra and coworkers (Scheme 1.44).[69] It was recognized that thiol and epoxide associated closely through a strong H-bond between both epoxide oxygen and thiophenyl hydrogen by the water molecule which enhanced the nucleophilic attacking ability of thiol to afford *β*-hydroxyl sulfides. However, aliphatic thiophenol did not respond this reaction system.



Scheme 1.44 Misra's approach for regioselective ring opening of epoxides with thiols.

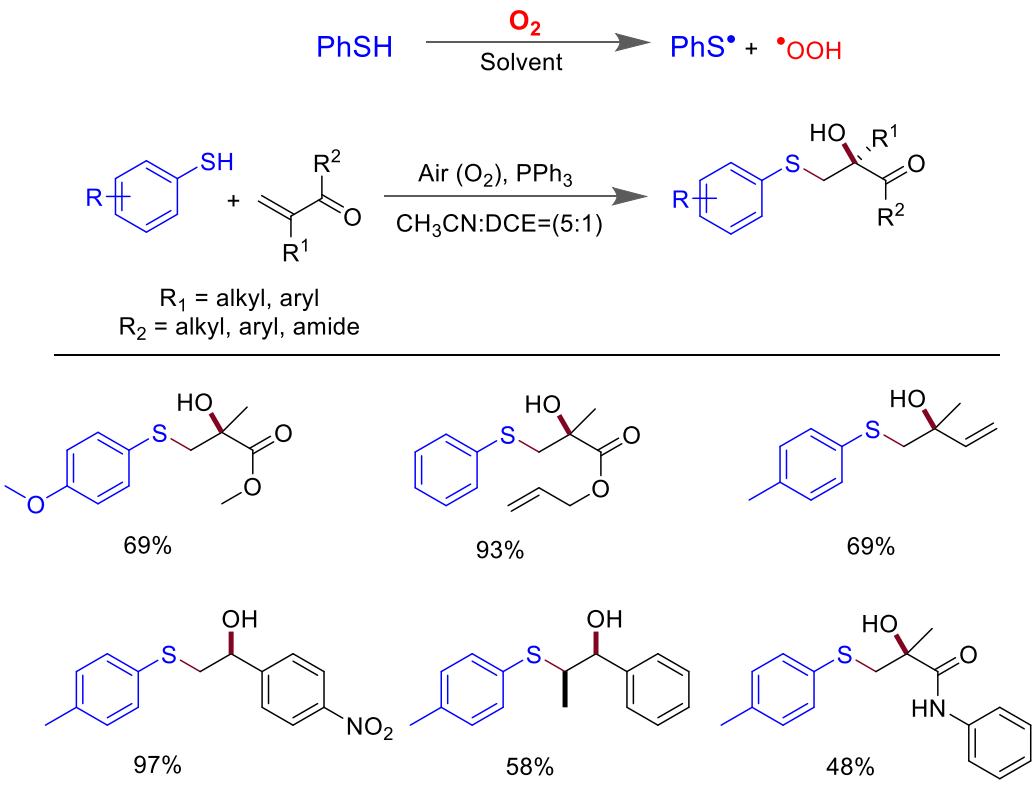
Recently Loh's group established water promoted allylic sulfonylation reaction with high regioselectivity (Scheme 1.45).[70] It was proposed that multiple hydrogen bonding interaction *via* six membered cyclic transition state within hydroxyl group of allylic alcohol, sulfinic acid and water stabilized the system.



Scheme 1.45 Loh's approach water promoted C-S bond formation reaction.

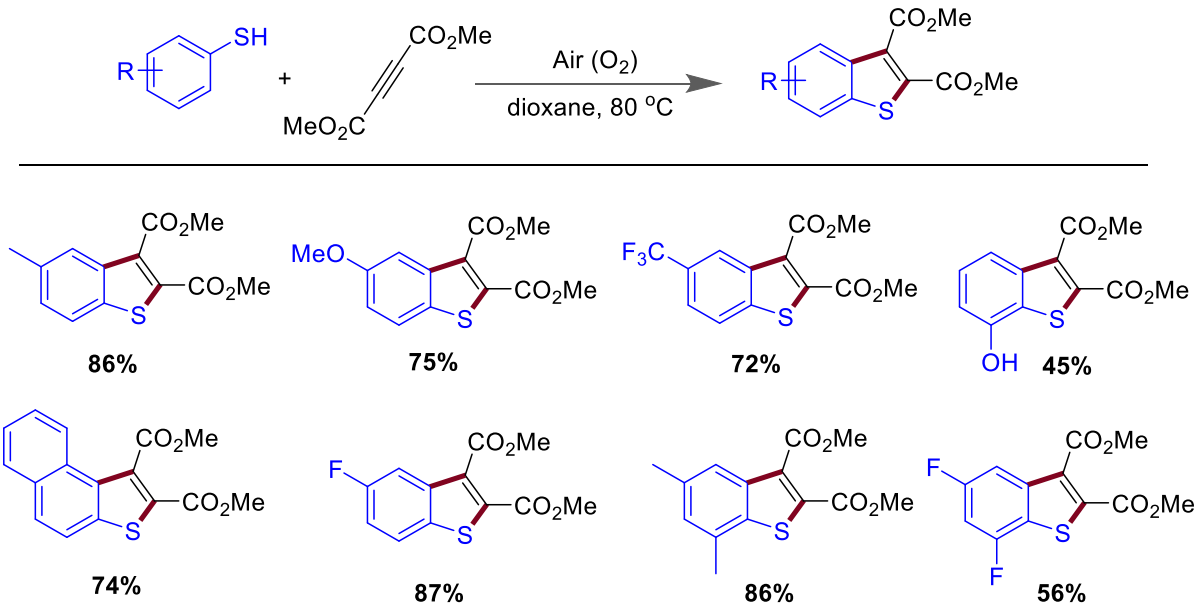
Thus, co-operative weak interaction not only helped to increase the nucleophilicity of sulfinic acid but also activated the C-O bond to eliminate hydroxyl group as water. This unique protocol showed excellent tolerance with carbonyl group, electron donating, electron withdrawing, hetero substituted allylic alcohols, aliphatic sulfinic acids, etc. Cysteine sulfinic acid also afforded the products with 90% yield (dr =76/24). A drug named as Etoricoxib (MK-0663), was synthesized under acidic condition with 75% yield.

Huo's group developed a synthetic method for hydroxysulfenylation of alkenes by auto-oxidation of thiol under aerobic condition (Scheme 1.46).[71] It is well known that acetonitrile solvent[72] can dissolve (8.0 - 8.1) mM oxygen at 25 ºC which is significantly higher than other commonly used solvents. Thus, due to good oxygen dissolving ability, combination of MeCN-DCE enhanced the reaction rate. After following as usual route for generation of benzylic radical intermediate, oxygen was trapped at benzylic position at the prefinal step. Finally, PPh_3 was used to reduce the dimeric form of oxygen.



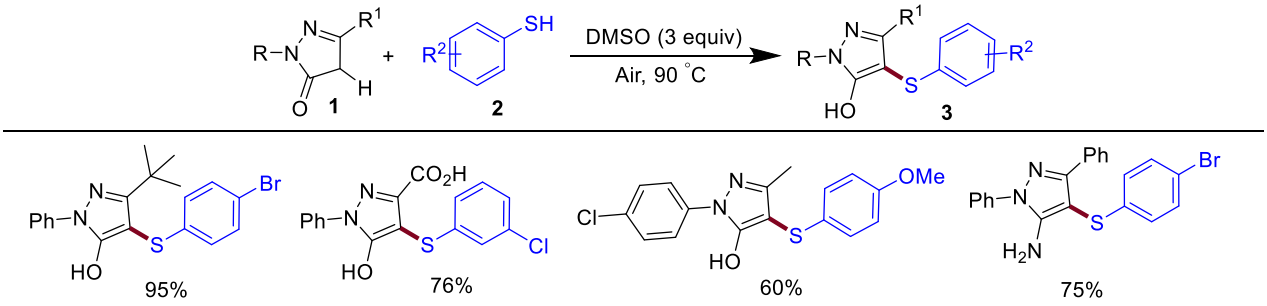
Scheme 1.46 Huo's approach for hydroxysulfenylation of alkenes.

Later, they introduced similar type of solvent mediated generation of thiyl radical in annulations of electron deficient alkyne and thiophenol (Scheme 1.47).[73] Reaction of benzene thiol and alkyne led to benzothiophenes derivatives with good to excellent yield. It has also been observed that reaction was limited for Michel type acceptor of conjugated alkynes.



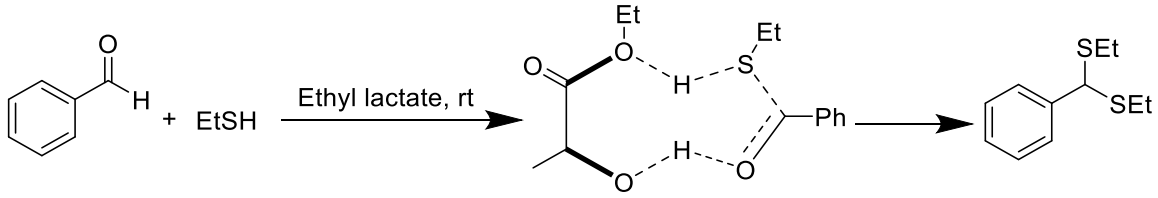
Scheme 1.47 Huo's approach for air promoted annulation of thiophenols.

Regioselective Sulfenylation of pyrazoles was reported by Wang group in 2017. In this protocol, DMSO favored enolization of the carbonyl carbon in pyrazole and thus activated C-4 position of pyrazoles (Scheme 1.48).[74] On the other hand aerial dioxygen helped to produce thiyl radical from thiophenol by auto oxidation. The nuclophilic attack by thiyl radical to C-4 position of pyrazoles helped to selective thiolysis in pyrazoles. All aromatic thiol except aliphatic partner produced good to excellent yields (60-95%). Acid and amine substituted pyrazole also was tolerated to give sulfenylated product.



Scheme 1.48 Wang's approach for regioselective synthesis of sulfenylated pyrazoles.

Liu and coworkers reported dithioacetalization reaction in ethyl lactate without using any additive or catalyst (Scheme 1.49).[75] In this work, ethyl lactate played a vital role to promote the reaction. It also activated aldehyde as well as thiophenol through hydrogen bond. Hydroxy group being slightly acidic, it underwent hydrogen bonding interaction with carbonyl oxygen of aldehyde and on the other hand ethoxy oxygen formed H-bond with thiol. Thus, these two hydrogen bonding interactions like O-H...O and O…H-S hydrogen bonding helped to move the reaction to forward direction.



Scheme 1.49 Liu's approach for ethyl lactate mediated thioacetalization of aldehydes.

1.5 OBJECTIVE

In summary we have discussed briefly about the historical background of organo-sulfur reagents and their applications towards organic synthesis. The objective of the present thesis was to develop simple and efficient methods for the construction of C-S bonds using suitable reagent that can have pharmaceutical and medicinal applications. The present thesis is also focusing on aerial dioxygen activation methodology using two different types important

sulfur surrogates such as thiophenol (phenyl mercaptans) and sulfonyl hydrazine. Futhermore, C-S and C-O bond formation reactions are explored by using these organo-sulfur surrogates.

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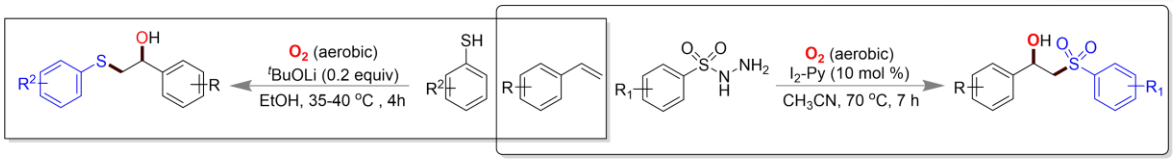
CHAPTER 2

Aerial Dioxygen activation toward the synthesis of *β*-hydroxysulfones and *β*-hydroxysulfides

2.1 ABSTRACT



Herein we have described an expedient aerial dioxygen activation method for oxysulfonylation and oxythiolation reaction towards the synthesis of *β*-hydroxysulfones and *β*-hydroxysulfides from unactivated olefins. The aerial dioxygen was activated towards the introduction of -OH group at benzylic position and near quantitative synthesis of *β*-hydroxysulfones and *β*-hydroxysulfides was achieved from unactivated olefins using sulfonyl hydrazides or thiophenol as reagent combination either by using pyridine-iodine (10 mol % each) or ^{t}BuOLi as catalyst. A details mechanistic pathway was established by radical trapping and $^{18}O_2$ labeling experiments.

2.2 INTRODUCTION

Activation of dioxygen is a popular research topic in the area of bioinorganic chemistry, [1,2] synthetic chemistry,[3,4] enzymology[5-7] and others.[8] Addition to use of terminal oxidant, dioxygen is also considered as an ideal oxygen source for the functionalization of organic molecules to develop green and sustainable protocols in organic synthesis. Dioxygen activation is mainly known by using transition metals like Pd,[9,10] Ni,[11] Fe,[12] Cu,[13-15] etc.[16] Transition metal and peroxides mediated radical reactions generally leads to undesired products and thus limited to be used in pharmaceuticals and materials industries.[17-19]

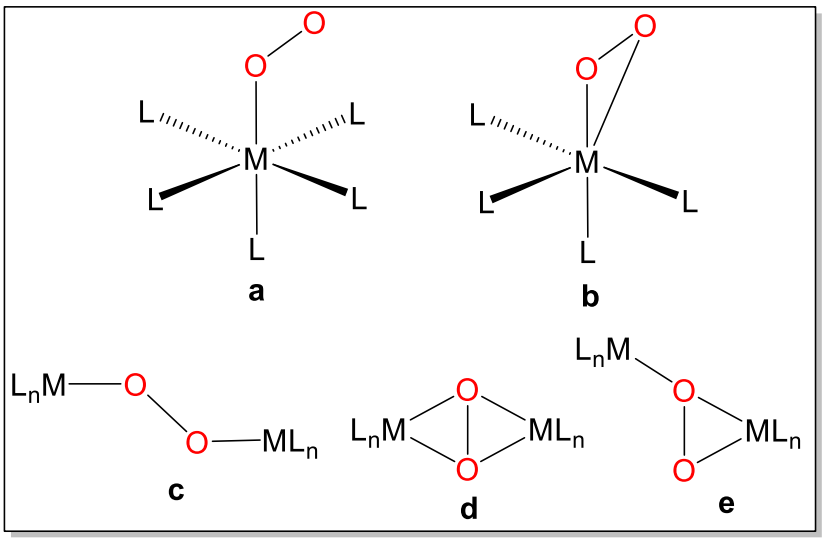


Figure 2.1. Transition metal mediated dioxygen activation mode.

Anaerobic oxidation and oxygenation of biological C-H bond hydroxylation process has been successfully done by enzymes such as tyrosinase, monooxygenation and dopamine β-monooxygenase. Encouraged by these biological transformations[20] our mind attracted to mimic the aerial dioxygen activation process for the difunctionalization of olefins under metal-free conditions. It is undoubtedly the encouraging route to widen the potential practicality in the pharmaceutical industry and the green synthesis of fine chemicals. Best of our knowledge very few literatures[6,21,22] have been reported of dioxygen activation under metal free conditions. To broaden this area tremendous effort is necessary. We present herein our initial finding on molecular-iodine triggered dioxygen activation, which demonstrates an expedient method towards the synthesis of *β*-hydroxysulfones from unactivated olefins under transition-metal-free conditions. Further effort on aerial dioxygen activation strategy made us an efficient method for ^{t}BuOLi catalysed oxythiolation of olefins towards the regioselective synthesis of *β*-hydroxysulfones from non-prefunctionalized olefins and thiophenol.

CHAPTER 2: Part A

Iodine Triggered Aerobic Oxysulfonylation of Styrenes

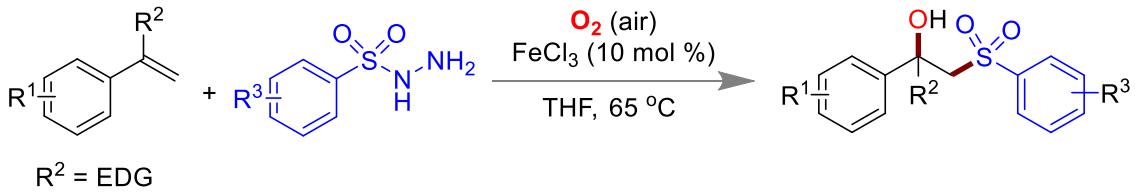
2A.1 ABSTRACT

Iodine triggered dioxygen activation in oxysulfonylation reaction of unactivated olefins using sulfonyl hydrazides and iodine catalyst is reported here. In one pot, near quantitative synthesis of β-hydroxysulfones were achieved at 70 ºC, within 7 h, in acetonitrile and under aerobic condition. A plausible mechanism is established by radical trapping and ^{18}O labelling experiments for the operationally simple, efficient and economically viable transformation. The direct activation of aerial oxygen under metal free and mild condition is anticipated for the oxysulfonylation of olefins.

2A.2 INTRODUCTION

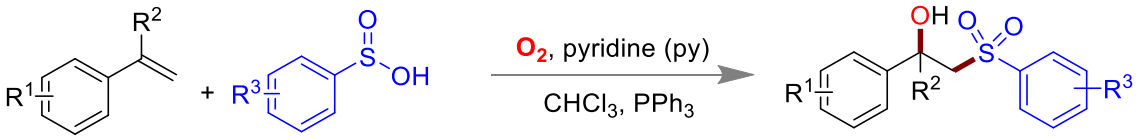
Sulfonyl group is one of the important precursors in natural and non-natural products.[23-25] In particular, *β*-hydroxysulfones are present as a basic scaffold in numerous biologically active molecules, and provide useful building blocks in organic synthesis.[17,26] *β*-Hydroxysulfones are prepared *via* chemical or bioreduction of *β*-keto-sulfones, nucleophilic ring opening of epoxides with sulfinate, or *via* hydroxylation of *α,β*-unsaturated sulfones.[27-32] Despite of the efficiency and flexibility of these transformations, these methods adopt significant limitations, such as multistep step synthetic procedure for synthesis of starting materials, production of unwanted by-products, quite complicated or harsh reaction conditions which lead the environmentally unfavourable synthetic protocols.[33] In this regard, development of efficient, direct and environmentally benign synthetic methods are highly desirable.[34-36]

Towards synthesis of organosulfur compounds oxidative cross-coupling reactions between different nucleophiles in the presence of appropriate oxidant have gained popularity.[17,37,38] In the view of importance of olefin difunctionalization, the oxysulfonylation of olefins has arisen as an ideal approach for the synthesis of β-hydroxy sulfones.



Scheme 2A.1. Taniguchi's approach for Fe catalyzed oxysulfonylation of styrene.

Taniguchi and co-worker developed iron catalyzed oxysulfonylation of styrene by using sulfonyl hydrazine *via* S-N bond cleavage under oxygen atmosphere in THF at 65 °C (Scheme 2A.1).[12] But this methodology was limited only for electron rich vinylic scaffold, having an electron donating group (EDG) at α-position of the styrene moiety to stabilize the *in-situ* generated benzylic radical intermediate.



Scheme 2A.2. Lei's approach for Fe catalyzed oxysulfonylation of styrene.

Recently Lei and co-workers have reported pyridine mediated aerobic oxysulfonylation of alkenes using sulfinic acids as the sulfonyl source in $CHCl_3$ (Scheme 2A.2).[29] Mechanistic investigations suggest that *β*-hydroperoxysulfone intermediate formation was the key point to afford the product formation. But the main limitation of this methodology is that moisture sensitive sulfinic acid and stoichiometric amount of reductant triphenylphosphine.

Conversely, Sulfonyl hydrazides are readily accessible, have been utilized usually as aryl source through the cleavage of C–S bonds.

2A.3 RESULT AND DISCUSSION

In continuation of our research interest in iodine reagent mediated reactions,[39-44] herein we report a metal-free approach *via* iodine triggered[45,46] and an expedient dioxygen activation method for an oxysulfonylation reaction[45] towards synthesis of *β*-hydroxysulfones from styrenes (Figure 2A.1a).[47] The aerial oxygen was activated for the introduction of -OH group at benzylic position and near quantitative synthesis of *β*-hydroxysulfones was achieved from styrenes and sulfonyl hydrazides using pyridine as additive (10 mol %) and iodine (10 mol %) as catalyst.[48,49]

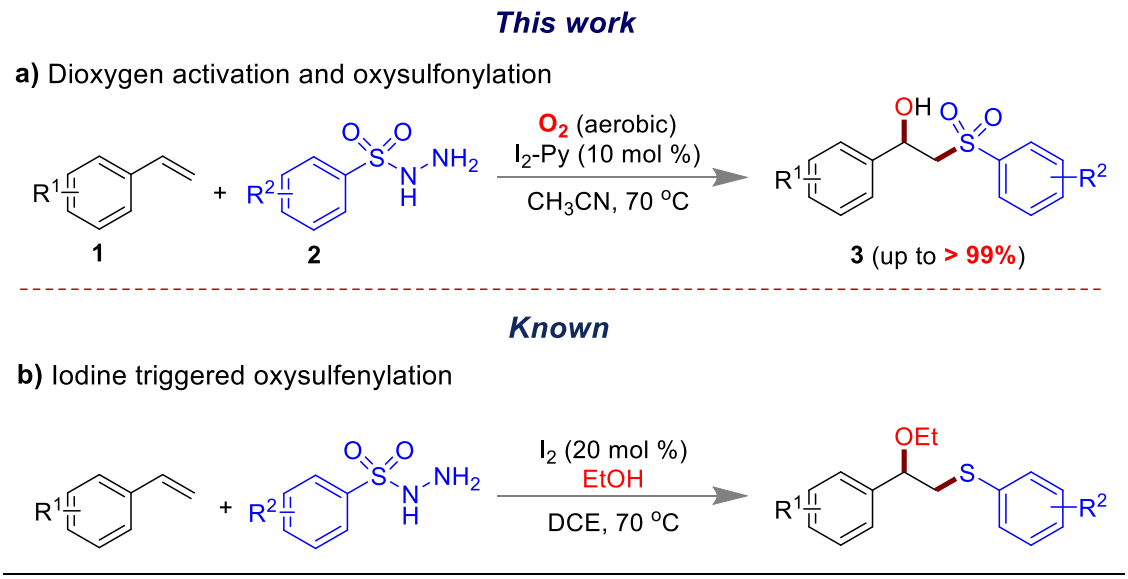
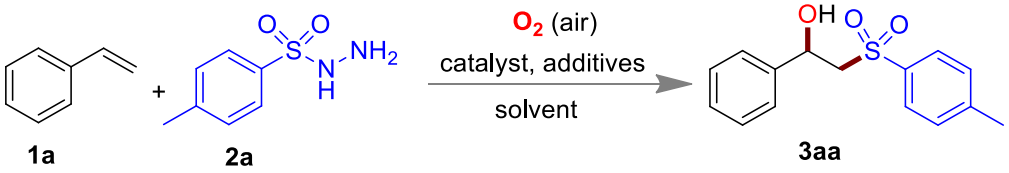


Figure 2A.1. *β*-Hydroxysulfone synthesis by dioxygen activation. a) Our approach based on iodine as catalyst. b) Yang *et al.*, described the oxysulfonylation using iodine catalyst.[50].

Sulfonyl hydrazides are well known aryl source through the cleavage of C–S bonds[36,45,50-52] but limited for direct sulfonylation.[12,53] Eco-friendly molecular iodine triggered reactions are

popular but inadequate examples are known towards functionalization of aromatic olefinis.[45,46,54] The iodine catalyzed example of oxysulfonylation from sulfonyl hydrazide and olefins is depicted in Figure 2A.1.[50]

Table 2A.1. Optimization Method for oxysulfonylation reaction[a]



Entry	Catalyst (equiv)	Additive (equiv)	Solvent	3aa (%)[b]
1	I_2 (0.2)	---	MeCN	65[c]
2	I_2 (0.1)	Pyridine (0.1)	EtOH	85
3	I_2 (0.1)	Pyridine (0.1)	DCE	82
4	I_2 (0.1)	Pyridine (0.1)	DMSO	38
5	I_2 (0.1)	Pyridine (0.1)	MeCN-H_2O	96
6	I_2 (0.1)	Pyridine (0.1)	MeCN	99
7	I_2 (0.05)	Pyridine (0.05)	MeCN	40
8	--	Pyridine (0.1)	MeCN	--[d]
9	I_2 (0.1)	Pyridine (0.05)	MeCN	83
10	I_2 (0.1)	2,6-Lutidine	MeCN	30
11	I_2 (0.1)	2,4,6-Collidine	MeCN	49
12	I_2 (0.1)	Pyrrole (0.1)	MeCN	10
13	I_2 (0.1)	Et_3N (0.1)	MeCN	19
14	I_2 (0.1)	DMAP (0.1)	MeCN	39
15	I_2 (0.1)	K_2CO_3 (1)	MeCN	--[d]
16	I_2 (0.1)	$KHPO_4$ (1)	MeCN	--[d]
17	TBAI	Pyridine (0.1)	MeCN	--[d]
18	TBAB	Pyridine (0.1)	MeCN	--[d]
19	I_2 (0.1)	Pyridine (0.1)	MeCN	59[e]
20	I_2 (0.1)	Pyridine (0.1)	MeCN	63[f]

[a]Condition: **1a** (0.26 mmol), **2a** (0.39 mmol), solvent (1.5 mL), 70 °C, 7 h. [b]After column chromatography. [c]24 h. [d]Inconclusive. [e]25 °C, 24 h. [f]50 °C.

The reaction condition was optimized (Table 2A.1) with the substrates, styrene (1a) and 4-methylbenzenesulfonyl hydrazide (2a). *β*-Hydroxysulfone 3aa was obtained in excellent yield (> 99%) using iodine catalyst (10 mol %) and pyridine-additive (10 mol %) in acetonitrile at 70 ºC under aerobic condition (Table 2A.1, entry 6). No additional source of oxygen was supplied for this reaction and sulfonyl radicals were possibly generated from sulfonyl hydrazides. Besides, when the reaction was performed under N_2 atmosphere no desired product was detected which indicated that the source of hydroxyl group is possibly from aerial oxygen. A wide range of solvents were screened and it was found that acetonitrile worked best for this reaction (Table 2A.1, entries 2-6). The solvent acetonitrile is known to dissolve ~8.1 mM oxygen at 25 ºC which is significantly higher than commonly used solvents.[55] The best results were obtained at 70 ºC and at lower temperature the yield of the product 3aa was sufficiently lowered (Table 2A.1, entries 19-20). Compared to pyridine, other bases like 2,6-lutidine, 2,4,6-collidine, pyrrole, Et_3N, DMAP, K_2CO_3, $KHPO_4$ were found to be less efficient (Table 2A.1, entries 10-16). Similarly, I_2 was the superior as catalyst (Table 2A.1, entries 17-18) compared to TBAI, TBAB, etc. Interestingly, when pyridine was solely used as a catalyst no product formation was detected (Table 2A.1, entry 8). Based on our preliminary findings, the substrate scope for oxysulfonylation between various olefins and sulfonyl hydrazides was explored (Figure 2A.2). Using 10 mol % of iodine as catalyst under aerobic condition, a range of unactivated olefins reacted with sulfonyl hydrazides to afford a variety of *β*-hydroxysulfones in good to excellent yields (> 99%). This method was compatible with aromatic ring having electron-donating and electron-withdrawing groups. Similarly, -Cl and -Br substituents on styrene have also worked well. Bulky substrates, 2-methylstyrene and 2-chlorostyrene efficiently reacted with sulfonyl hydrazides and yielded 3ga (72%) and 3ib (61%), respectively. Notably, *α*-methylstyrene has also afforded sterically congested *β*-hydroxysulfone in very good yield (3da, 3dc).

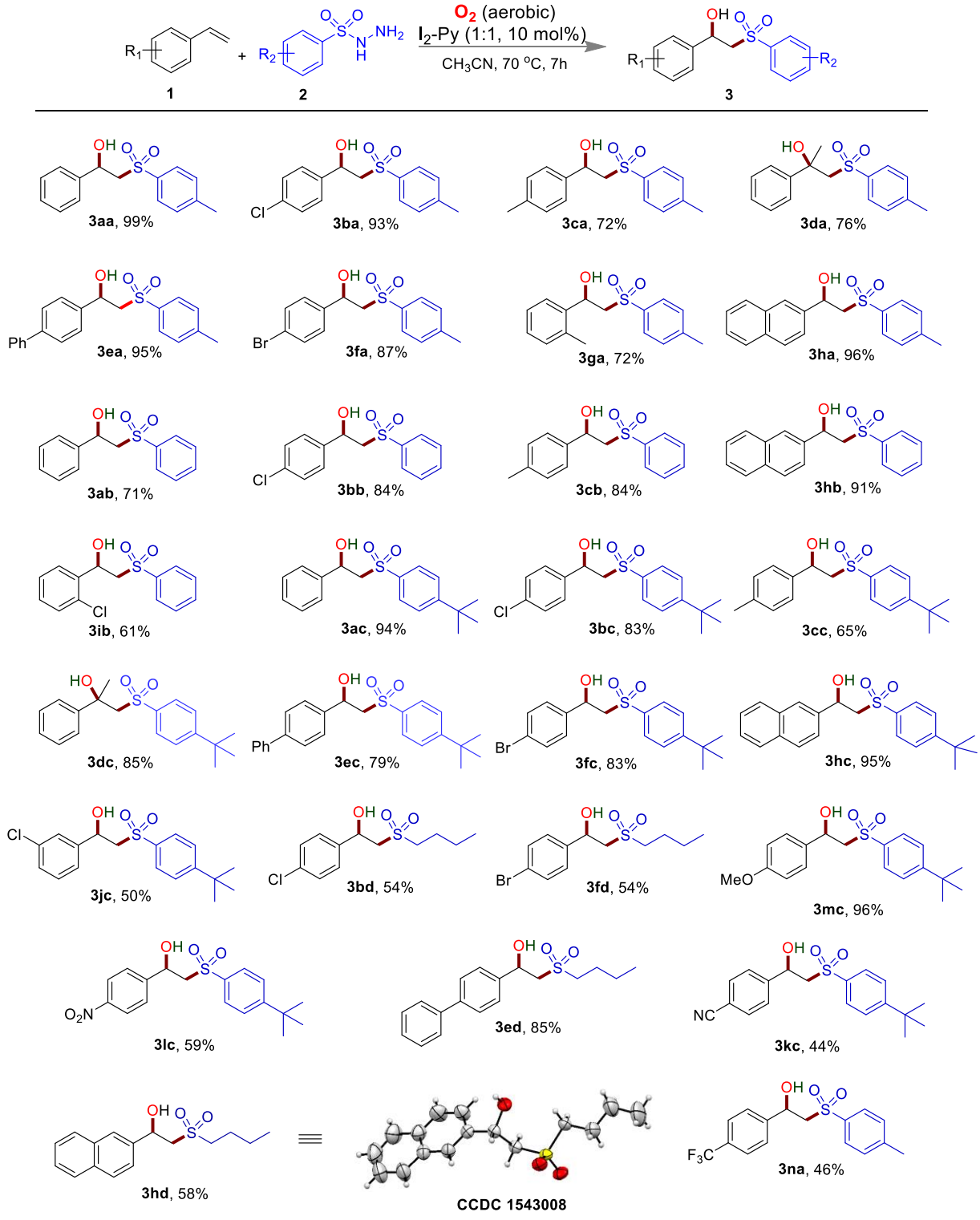


Figure 2A.2. Scope of Oxysulfonylation of Olefins.

The reaction was found to be efficient with both aromatic as well as aliphatic sulfonyl hydrazides. Relatively poor yields were obtained for the styrenes with electron withdrawing

groups (3kc, 3lc and 3na). However, methoxy substituted styrene (1m) led to the corresponding *β*-hydroxysulfone (3mc) in excellent yield (96%). In gram scale (9.58 mmol) the product 3aa was obtained in 84 % yield (2.22 g).

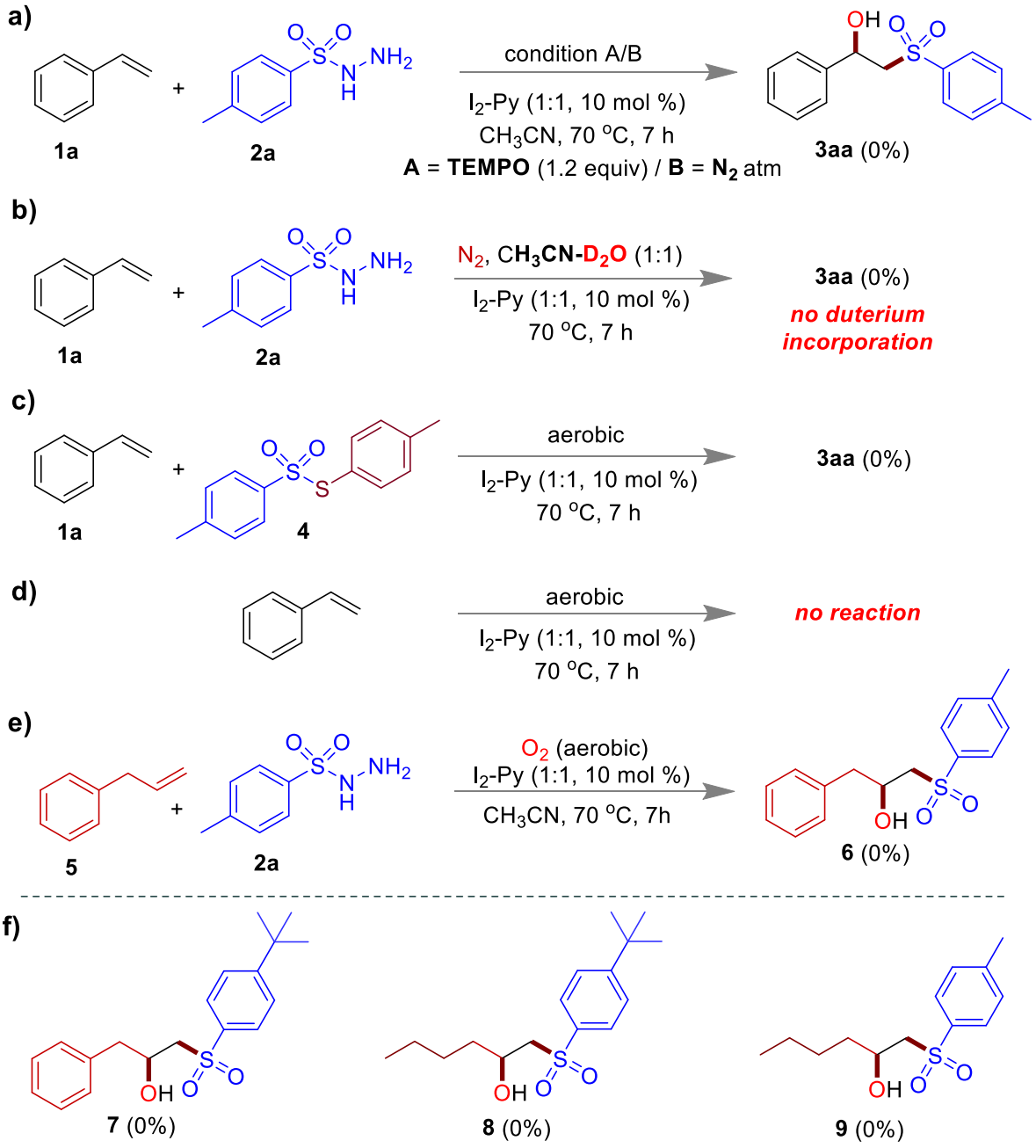


Figure 2A.3. Control Experiments.

Control experiments were performed to understand the mechanism of the iodine catalyzed[49,56,57] oxysulfonylation reaction (Figures 2A.3 and 2A.4). Under aerobic condition,

at 1 atm near quantitative 3aa was obtained from styrene 1a and tosyl hydrazide 2a. In an oxidative environment, formation of sulfonyl radical from sulfonyl hydrazides *via* diazene intermediate was known.[58] Involvement of radical pathway was confirmed by TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) radical trapping experiment (Figure 2A.3a). Under optimized condition, also in dry acetonitrile and in absence of olefins, sulfonyl hydrazides led to sulfonothioic acid in low yield (14%). As shown in Figure 2A.3c, when 1a was treated with sulfonothioic acid derivative 4, no 3aa could be obtained which ruled out the possibility for the formation of sulfonyl radical *via* sulfonothioic acid. Furthermore, there was no deuterium incorporation and a failure of the reaction under nitrogen atmosphere (Figure 2A.3b) also supported the hypothesis of aerial dioxygen activation. The reaction was completely failed in presence of any aliphatic olefins like allyl benzenes and 1-hexenes (Figures 2A.3e,f). Moreover, under standard condition and in absence of sulfonyl hydrazide no reaction was observed with styrene (Figure 2A.3d).

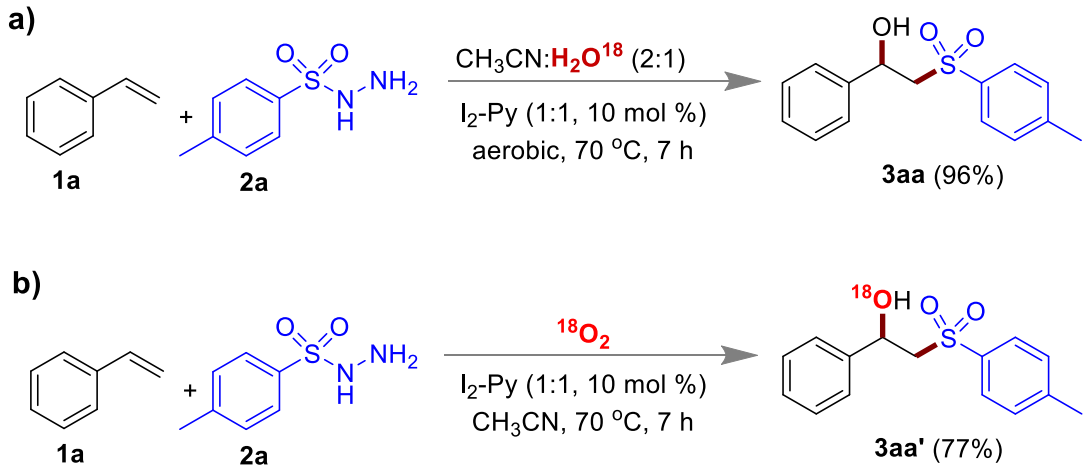


Figure 2A.4. ^{18}O Isotope Labelling Experiments.

Shown in Figure 2A.4, ^{18}O labelling experiments[29] also helped to understand the origin of the hydroxyl oxygen of *β*-hydroxysulfone. When **1a** and **2a** were treated in the presence of aerobic condition in MeCN:H_2O^{18} (2:1), the reaction failed to produce any ^{18}O incorporated

β-hydroxysulfone, instead ^{16}O incorporated 3aa was isolated in 96% yield. Nevertheless, in presence of $^{18}O_2$, reaction of 1a and 2a afforded 77% of ^{18}O incorporated 3aa. So, the role of aerial oxygen was confirmed for the oxysulfonylation reaction.

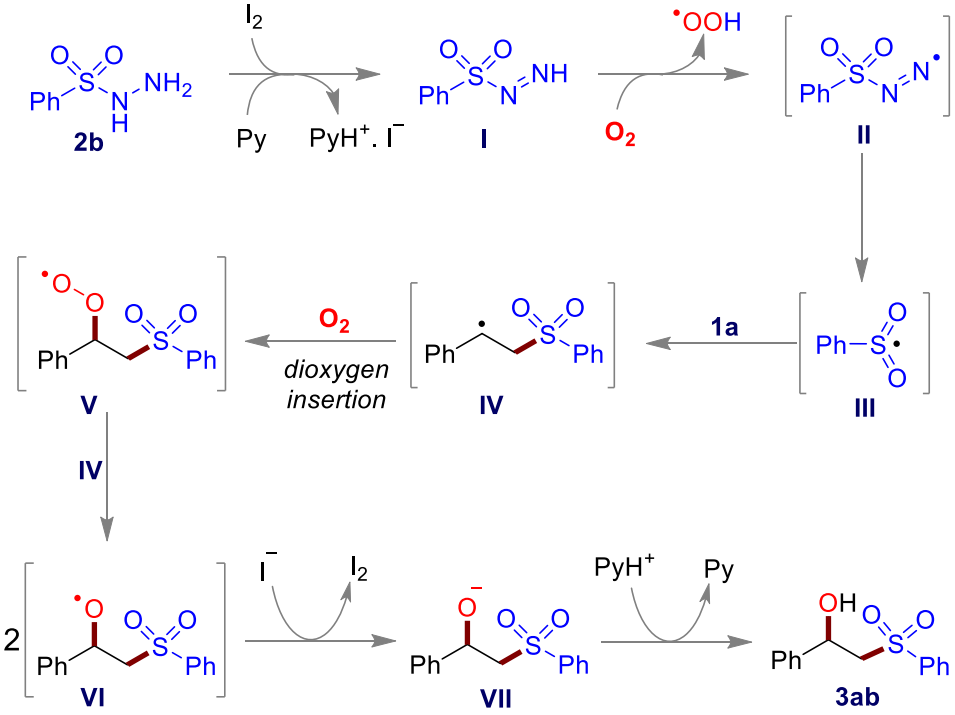
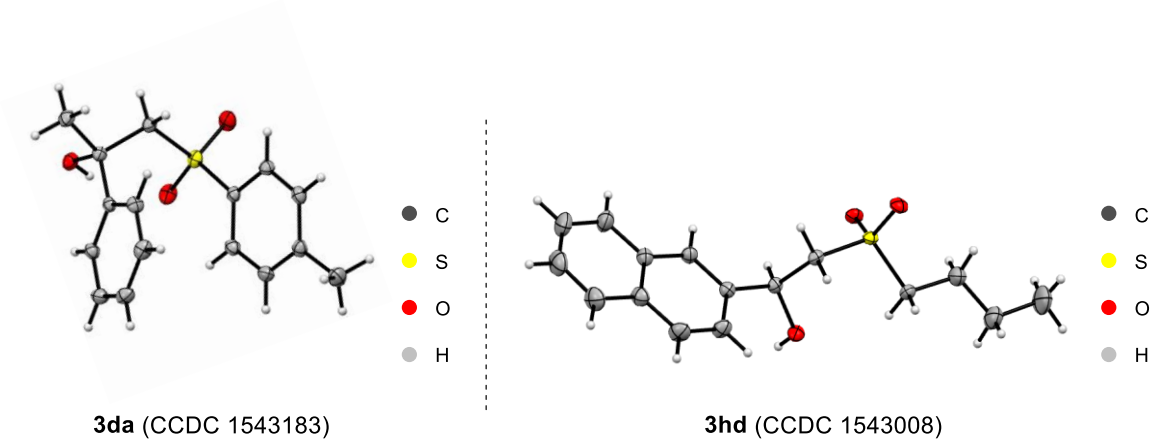


Figure 2A.5. Plausible Mechanism.

A plausible mechanism for oxysulfonylation of olefins (Figure 2A.5) *via* radical pathway was rationalized[59] from control experiments. Sulfonyl hydrazides reacted with iodine to give diazene **I**, which could further be oxidized to sulfonyl radical **III** by triplet dioxygen. Following, sulfonyl radical (**III**) might react with the olefins 1a to produce stable benzylic radical **IV**. The stability of radical **IV** was important and essential requirement for the reaction. It has been found that allyl benzene which generally produce less stable radical could not led to the formation of any oxysulfonylated product (Figure 2A.3d). Further, the benzylic radical **IV** possibly trapped the dioxygen dissolved in acetonitrile to produce alkylhydroperoxy radical intermediate **V**.[60,61] And then, the intermediate **V** led to **VI** by homolytic cleavage of peroxy linkage by influence of **IV**.[60] The intermediate **VI** afforded

anionic intermediate **VII** by single-electron transfer (SET) from iodide and concomitant proton transfer (PT) from PyH^+ and further produced desired *β*-hydroxysulfone 3ab. In this reaction amphoteric pyridine[3,62] could play another important role by stopping the formation of sulfonothioic acid from sulfonyl hydrazide. This is because pyridine might have accepted the proton from hydroiodic acid (HI) and generated iodide anion which stopped to generate -SPh radical from diazene (**I**). It was also confirmed that sulfonothioic acid derivative 4 with styrene did not result in 3aa. In parallel, formation of 65% of 3aa (entry 1, Table 1) in absence of pyridine indicated that the generated sulfonyl radical might have rapidly reacted with olefins and led to the stable benzyl radical for follow up reactions. The stability of the benzyl radical was important because no product could be detected with aliphatic olefins (Figure 2A.3f). These aliphatic olefins expected to create unstable radicals after reaction with sulfonyl radicals. Also, no reaction in absence of sulfonyl hydrazide (Figure 2A.3d) indicated for the involvement of the sulfonyl radical during the reaction.



3da (CCDC 1543183) **3hd** (CCDC 1543008)

Figure 2A.6 X-ray crystal structure of compound **3da** and **3hd**

2A.4 CONCLUSION

In conclusion, we have developed an operationally simple and efficient method of aerial dioxygen activation for oxysulfonylation reaction towards synthesis of regioselective *β*-

hydroxysulfones from non-prefunctionalized olefins and sulfonyl hydrazides. Using a simple and readily available metal-free reagents like 10 mol % iodine as catalyst and as pyridine additive (10 mol %), successful construction of new C–O and C–S bond in one-pot were achieved *via* an intermolecular reaction. We anticipate that this oxysulfonylation approach *via* organic pathway and direct aerial dioxygen activation might offer an access to several organosulfur compounds in the synthesis of functionalized materials, complex molecules and pharmaceuticals.

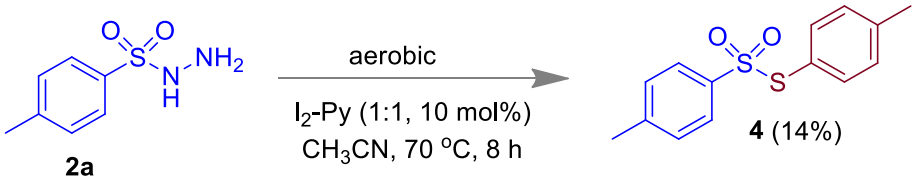
2A.4 EXPERIMENTAL SECTION

Instrumentation and Chemicals: Styrene was purchased from commercial source used without further purification. Tosyl hydrazines were prepared according to the standard procedure.[63] All the reactions were done under open atmosphere. Column chromatographic purification of the compounds was done using silica gel (mess 230-400) and hexane/ethyl acetate as eluent. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz and/or 700 MHz instruments at 25 °C. The chemical shift (δ, ppm) values were reported with respect to residual chloroform (7.26 for ^{1}H and 77.16 ppm for ^{13}C). High resolution mass spectroscopy (HR-ESIMS) was recorded on ESI-TOF (Time-of-flight) mass spectroscopy. Infrared spectra were recorded in wave number (cm^{-1}). Melting points of the compound were determined using digital melting point apparatus and uncorrected.

Preparation of arylsulfonyl hydrazides.[63] In a round bottom flask (250 mL) charged with *p*-tolylsulfonyl chloride (26.2 mmol) in THF (15 mL). Then hydrazine mono hydrates (3.37 mL as 80% in water, 55 mmol) were added drop wise to the solution. Following, the reaction mixture were stirred at 0 ºC for 30 min. After that the mixture was concentrated under vacuum and diluted with ethyl acetate. The solution was washed with water and dried over anhyd sodium sulphate. Solvents were removed under reduced pressure and followed by

recrystallization from ethanol to obtain pure sulfonyl hydrazide.

General procedure for the preparation of Sulfone. Styrene (60 mg, 0.52 mmol), p-toluenesulfonyl hydrazide (146 mg, 0.78 mmol) and pyridine (4.5 µL, 0.052 mmol) were placed in an oven-dried seal tube. Then acetonitrile (3.0 mL) and iodine (13.2 mg, 0.052 mmol) were added. Then the mixture was allowed to stir for 7 h at 70 ºC. After that the mixture was concentrated under vacuum and diluted with ethyl acetate. The solution was washed with water and dried over anhyd sodium sulphate. Resulting mixtures were purified through column chromatography using silica gel and n-hexane, ethyl acetate (9:1) solvent mixture as an eluent to afford the product.

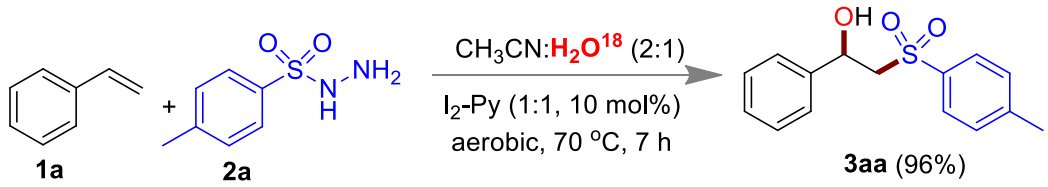


Scheme 2A.3. Preparation of sulfothionic acid

Preparation of sulfothionic acid. *p*-Toluenesulfonyl hydrazide (100 mg, 0.54 mmol) was allowed to stir at standard condition for 8 h. Then the mixture was concentrated under vacuum and purified through silica gel column chromatography to afford the 14% of **4** (Scheme 2A.3).

Gram scale synthesis. Styrene (1.1 mL, 9.58 mmol), *p*-toluenesulfonyl hydrazide (2.68 g, 14.37 mmol) and pyridine (0.077 mL, 0.96 mmol) were placed in two necked round bottom flask (500 mL). Then acetonitrile (80 mL) and iodine (0.243 mg, 0.96 mmol) were added. Then the mixture was allowed to stir for 7 h at 70 ºC. After that the mixture was concentrated under vacuum and diluted with ethyl acetate. The solution was washed with water and dried over anhyd sodium sulphate. Resulting mixtures were purified through column

chromatography using silica gel and *n*-hexane, ethyl acetate (9:1) solvent mixture as an eluent to afford **3aa** in 84% (2.22 g).



Scheme 2A.4. Isotope labelling experiments (H_2O^{18})

H_2O^{18} and $^{16}O_2$ labelling experiments. An oven dried schlenk tube was charged with dry CH_3CN (3.0 mL), styrene (60 mg, 0.522 mmol), *p*-toluenesulfonyl hydrazide (146 mg, 0.784 mmol), iodine (13.2 mg, 0.052 mmol), pyridine (4.5 μL, 0.052 mmol). Then 0.5 mL of H_2O^{18} was added to the reaction mixture and stirred at 70 °C for 7 h. After that the mixture was concentrated under vacuum and diluted with ethyl acetate. The solution was washed with water and dried over anhyd sodium sulphate. Silica gel column chromatographic purification of the crude product afforded 96% of **3aa** (Scheme 2A.4).

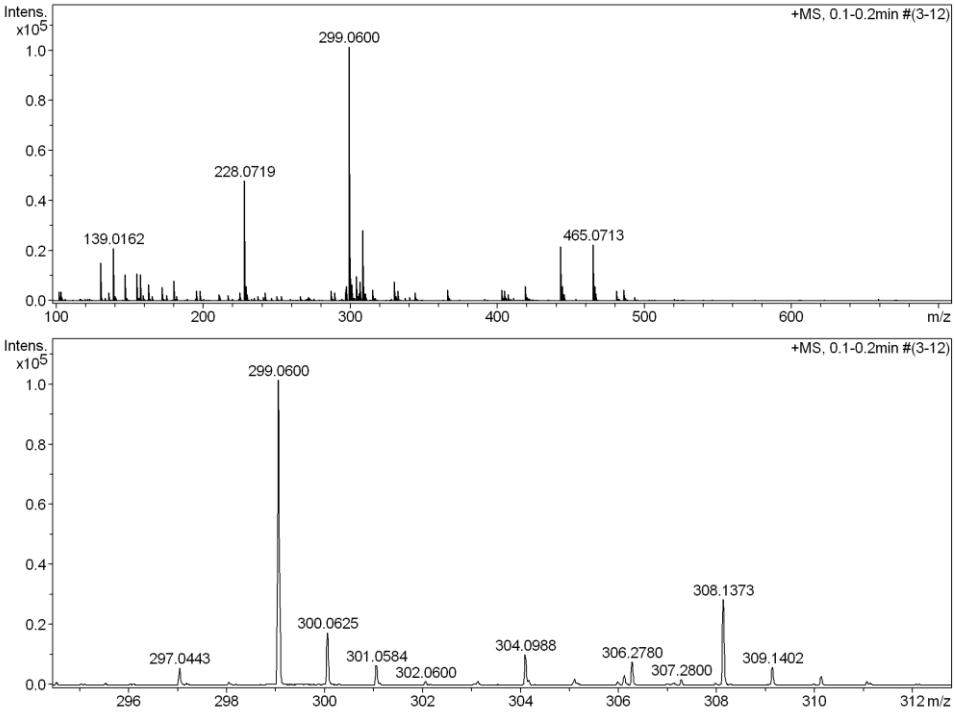
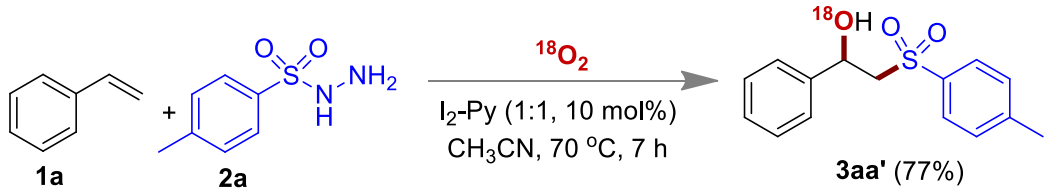


Figure. 2A.7. The ESI-TOF MS spectra of **3aa** in $(M + Na)^+$ mode.



Scheme 2A.5. Isotope labelling experiments ($^{18}O_2$)

O^{18} Labelling experiments. An oven dried schlenk tube was charged with dry dry CH_3CN (3.0 mL), styrene (60 mg, 0.52 mmol), *p*-toluenesulfonyl hydrazide (146 mg, 0.78 mmol), iodine (13.2 mg, 0.052 mmol), pyridine (4.5 µL, 0.052 mmol) in a glove box. After taking out the schlenk tube from glove box $^{18}O_2$ gas purged and stirred at 70 ºC for 7 h. After that the mixture was concentrated under vacuum and diluted with ethyl acetate. The solution was washed with water and dried over anhyd sodium sulphate. Silica gel column chromatographic purification of the crude product afforded 77% of **3aa′**.

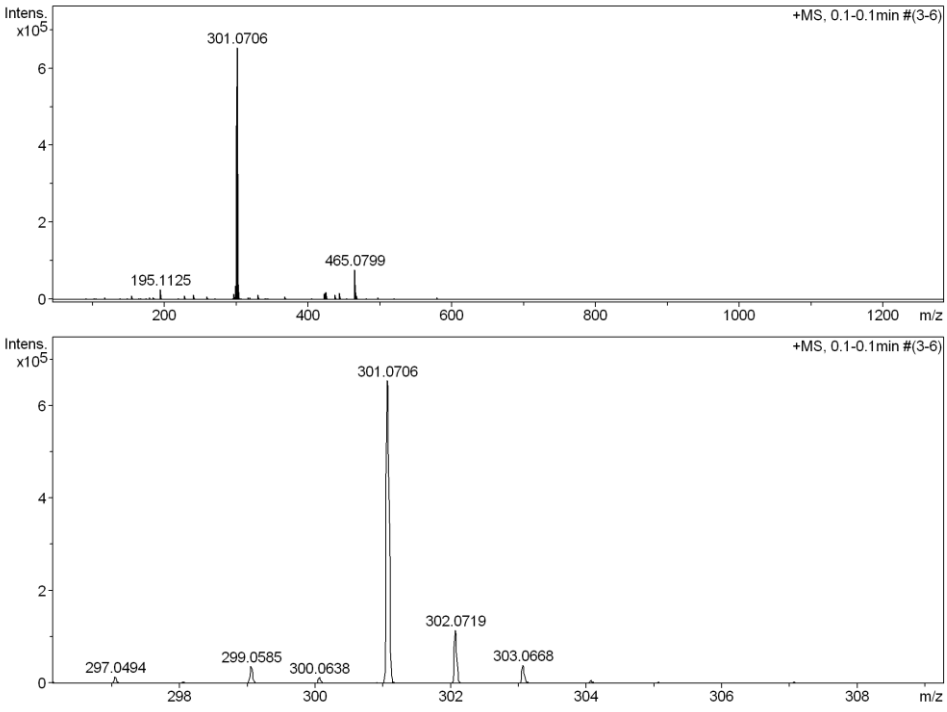


Figure 2A.8. The ESI-TOF Mass spectra of **3aa′** in $(M + Na)^+$ mode.

Compound Characterization Data:

4-Methylbenzenesulfonohydrazide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.74 (br s, 1H), 3.38 (br s, 2H), 2.45 (s, 3H).

4-Methylbenzenesulfonohydrazide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.74 (br s, 1H), 3.38 (br s, 2H), 2.45 (s, 3H).

4-(tert-butyl)benzenesulfonohydrazide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.82 (m, 2H), 7.57 – 7.54 (m, 2H), 5.99 (br s, 1H), 3.63 (br s, 2H), 1.34 (s, 9H).

Benzenesulfonohydrazide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 2H), 5.76 (br s, 1H), 3.62 (br s, 2H).

Butane-1-sulfonohydrazide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (br s, 1H), 3.71 (br s, 2H), 3.12 – 3.08 (m, 2H), 1.82 – 1.74 (m, 2H), 1.46 (dd, *J* = 14.8, 7.6 Hz, 2H), 0.94 (t, *J* = 7.2 Hz, 3H).

***S*-*p*-Tolyl-4-methylbenzenesulfonothioate.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.19 (m, 4H), 7.14 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 142.2, 140.6, 136.6, 130.3, 129.5, 127.8, 124.8, 21.8, 21.62.

1-Phenyl-2-tosylethanol (3aa).[64] R_f = 0.28 (20% ethyl acetate in hexane); off white solid; yield 99% (142 mg); mp 72-74 ºC (lit.[65] 130 - 131 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.34-7.23 (m, 5H), 5.24 (d, *J* = 10.0 Hz, 1H), 3.78 (br s, 1H), 3.47 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.31 (dd, *J* = 14.4, 2 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 140.8, 136.2, 130.1, 128.8, 128.3, 128.1, 125.7, 68.5, 64.0, 21.7; IR (KBr) ῡ 3484, 3063, 2924, 1640, 1598, 1494, 1453, 1401, 1300, 1288, 1137, 1087, 994, 816; HRMS (ESI-TOF) calcd for $C_{15}H_{16}O_3S$ $(M + Na)^+$ 299.0712, found 299.0713.

1-(4-Chlorophenyl)-2-tosylethanol (3ba).[64] R_f = 0.30 (20% ethyl acetate in hexane); White solid; yield 93% (144 mg); mp 94-96 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz,

2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.31-7.21 (m, 4H), 5.23 (d, *J* = 10.0 Hz, 1H), 3.82 (d, *J* = 1.6 Hz, 1H), 3.44 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.28 (dd, *J* = 14.4, 2.0 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 139.3, 136.1, 134.2, 130.3, 129.0, 128.1, 127.2, 68.0, 64.0, 21.8; IR (KBr) ῡ 3419, 3055, 2987, 2305, 2125, 1641, 1549, 1493, 1264, 1145, 1088, 896; HRMS (ESI-TOF) calcd for $C_{15}H_{15}ClO_3S$ $(M + Na)^+$ 333.0323, found 333.0332.

1-(p-Tolyl)-2-tosylethanol (3ca).[29] R_f = 0.28 (20% ethyl acetate in hexane); Colourless oil; yield 70% (77 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.21 (d, *J* = 10.0 Hz, 1H), 3.65 (d, *J* = 2.0 Hz, 1H), 3.47 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.30 (dd, *J* = 14.4, 2.0 Hz, 1H), 2.47 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 138.2, 137.9, 136.3, 130.2, 129.5, 128.1, 125.7, 68.5, 64.1, 21.8, 21.2; IR (KBr) ῡ 3422, 2963, 2877, 2090, 1640, 1422, 1265, 896; HRMS (ESI-TOF) calcd for $C_{16}H_{18}O_3S$ $(M + Na)^+$ 313.0869, found 313.0883.

2-Phenyl-1-tosylpropan-2-ol (3da).[64] R_f = 0.40 (20% ethyl acetate in hexane); White solid; yield 76% (102 mg); mp 100-102 ºC (lit.[12] 84-85 ºC) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.36-7.26 (m, 2H), 7.26-7.08 (m, 5H), 4.63 (br s, 1H), 3.70 (d, *J* = 14.4 Hz, 1H), 3.59 (d, *J* = 14.4 Hz, 1H), 2.38 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 144.6, 137.5, 129.8, 128.4, 127.7, 127.3, 124.8, 73.3, 66.8, 30.9, 21.7; IR (KBr) ῡ 3500, 3062, 2984, 2930, 2101, 1632, 1598, 1494, 1447, 1381, 1268, 1184, 1122, 1083, 1048, 1028, 945, 850; HRMS (ESI-TOF) calcd for $C_{16}H_{18}O_3S$ $(M + Na)^+$ 313.0869, found 313.0889.

1-([1,1'-Biphenyl]-4-yl)-2-tosylethanol (3ea). R_f = 0.26 (20% ethyl acetate in hexane); White solid; yield 95% (111 mg); mp 105-106 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.60-760 (m, 4H), 7.48-7.30 (m, 7H), 5.31 (d, *J* = 10.0 Hz, 1H), 3.78 (d, *J* = 1.6 Hz, 1H), 3.52(dd, *J* = 14.4, 10.0 Hz, 1H), 3.37 (d, *J* = 14.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 141.4, 140.6, 139.8, 136.3, 130.2, 128.9, 128.2, 127.62, 127.60,

127.2, 126.3, 68.4, 64.1, 21.8; IR (KBr) ῡ 3475, 3031, 2995, 2155, 1639, 1598, 1487, 1402, 1288, 1137, 1087, 844; HRMS (ESI-TOF) calcd for $C_{21}H_{20}O_3S$ $(M + Na)^+$ 375.1025, found 375.1022.

1-(4-Bromophenyl)-2-tosylethanol (3fa).[29] R_f = 0.35 (20% ethyl acetate in hexane); White solid; yield 87% (141 mg); mp 109-110 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.22 (d, *J* = 10.0 Hz, 1H), 3.82 (d, *J* = 1.6 Hz, 1H), 3.42 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.28 (dd, *J* = 14.4, 2.0 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 139.8, 136.1, 132.0, 130.3, 128.1, 127.5, 122.3, 68.0, 63.9, 21.8; IR (KBr) ῦ 3484, 3063, 2982, 2924, 2305, 2104, 1916, 1641, 1596, 1487, 1400, 1300, 1288, 1196, 1137, 1102, 1087, 1070, 1010, 913, 863; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrO_3S$ $(M + Na)^+$ 376.9817, found 376.9827.

1-(o-Tolyl)-2-tosylethanol (3ga).[64] R_f = 0.27 (20% ethyl acetate in hexane); White solid; yield 72% (97 mg); mp 125-126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.24-7.12 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 5.44 (d, *J* = 10.0 Hz, 1H), 3.67 (d, *J* = 1.6 Hz, 1H), 3.40 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.24 (d, *J* = 14.4 Hz, 1H), 2.47 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 138.8, 136.2, 133.8, 130.7, 130.3, 128.21, 128.18, 126.7, 125.4, 65.2, 63.1, 21.8, 18.7; IR (KBr) ῡ 3420, 3105, 2975, 2115, 1643, 1554, 1264, 1140, 896; HRMS (ESI-TOF) calcd for $C_{16}H_{18}O_3S$ $(M + Na)^+$ 313.0869, found 313.0844.

1-(Naphthalen-2-yl)-2-tosylethanol (3ha).[28] R_f = 0.27 (20% ethyl acetate in hexane); off white solid; yield 96% (142 mg); mp 102-103 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.79-7.72 (m, 4H), 7.46 (dd, *J* = 6.0, 3.2 Hz, 2H), 7.36-7.28 (m,3H), 5.41 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.96 (br s, 1H), 3.57 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.41 (dd, *J* = 14.4, 2.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 138.1, 136.2, 133.2, 133.1, 130.1, 128.7, 128.0 (x 2), 127.7, 126.4, 126.3, 124.8, 123.4, 68.7, 63.9, 21.7; IR (KBr) ῡ

3420, 2965, 2876, 2376, 2307, 2114, 1641, 1550, 1511, 1264, 1136, 1087, 896, 860; HRMS (ESI-TOF) calcd for $C_{19}H_{18}O_3S$ $(M + Na)^+$ 349.0869, found 349.0871.

1-Phenyl-2-(phenylsulfonyl)ethanol (3ab).[66] R_f = 0.38 (20% ethyl acetate in hexane); White solid; yield 71% (97 mg); mp 91-93 ºC (lit.[67] 92-94 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.73-7.65 (m, 1H), 7.64-7.54 (m, 2H), 7.36-7.27 (m, 5H), 5.28 (d, *J* = 10.0 Hz, 1H), 3.68 (br s, 1H), 3.51 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.34 (dd, *J* = 14.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 139.3, 134.2, 129.6, 128.9, 128.5, 128.1, 125.8, 68.6, 64.1; IR (KBr) ῡ 3483, 2927, 2089, 1641, 1494, 1479, 1394, 1303, 1199, 1138, 1085, 1025, 996; HRMS (ESI-TOF) calcd for $C_{14}H_{14}O_3S$ $(M + Na)^+$ 285.0556, found 285.0572.

1-(4-Chlorophenyl)-2-(phenylsulfonyl)ethanol (3bb).[30] R_f = 0.32 (20% ethyl acetate in hexane); White solid; yield 84% (124 mg); mp 104-105 ºC (lit.[68] 61 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.77-7.65 (m, 1H), 7.65-7.55 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.27 (d, *J* = 10.0 Hz, 1H), 3.75 (br s, 1H), 3.46 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.31 (dd, *J* = 14.0, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 139.1, 134.4, 134.3, 129.7, 129.1, 128.1, 127.2, 68.0, 63.9; IR (KBr) ῡ 3443, 3055, 2987, 2305, 1641, 1492, 1447, 1421, 1306, 1265, 1146, 1086, 896; HRMS (ESI-TOF) calcd for $C_{14}H_{13}ClO_3S$ $(M + Na)^+$ 319.0166, found 319.0180.

2-(Phenylsulfonyl)-1-(p-tolyl)ethanol (3cb).[30] R_f = 0.33 (20% ethyl acetate/hexane); white solid; yield 84% (105 mg); mp 82-83 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-7.85 (m, 2H), 7.75-7.65 (m, 1H), 7.64-7.53 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.24 (d, *J* = 10.0 Hz, 1H), 3.59 (d, *J* = 1.6 Hz, 1H), 3.50 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.33 (dd, *J* = 14.4, 2.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 138.3, 137.8, 134.2, 129.6, 129.5, 128.1, 125.7, 68.4, 64.1, 21.2; IR (KBr) ῡ 3483, 3062, 2923, 1994, 1907, 1641, 1585, 1548, 1514, 1478, 1447, 1304, 1199, 1138, 1086, 1022, 998, 913, 864; HRMS (ESI-TOF) calcd for $C_{15}H_{16}O_3S$ $(M + Na)^+$ 299.0712, found 299.0694.

1-(Naphthalen-2-yl)-2-(phenylsulfonyl)ethanol (3hb). R_f = 0.34 (20% ethyl acetate in hexane); White solid; yield 91% (110 mg); mp 94-96 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.92 (m, 2H), 7.82-7.76 (m, 4H), 7.71-7.64 (m, 1H), 7.61-7.54 (m, 2H), 7.50-7.44 (m, 2H), 7.36 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 3.81 (br s, 1H), 3.59 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.43 (dd, *J* = 14.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.0 (x2C), 134.3, 133.31, 133.29, 129.6, 128.8, 128.1, 127.8, 126.6, 126.5, 124.9, 123.4, 68.7, 64.0; IR (KBr) ῡ 3455, 3089, 2096, 1632, 1509, 1476, 1446, 1387, 1367, 1266, 1136, 1085,737; HRMS (ESI-TOF) calcd for $C_{18}H_{16}O_3S$ $(M + Na)^+$ 335.0712, found 335.0691.

1-(2-Chlorophenyl)-2-(phenylsulfonyl)ethanol (3ib).[30] R_f = 0.34 (20% ethyl acetate in hexane); Colourless liquid; yield 61% (84 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.96 (m, 2H), 7.73-7.57 (m, 4H), 7.33-7.27 (m, 1H), 7.25-7.17 (m, 2H), 5.44 (d, *J* = 10.0 Hz, 1H), 3.99 (br s, 1H), 3.52 (dd, *J* = 14.4, 1.2 Hz, 1H), 3.30 (dd, *J* = 14.4, 10.0 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.6, 137.9, 134.3, 131.0, 129.6, 129.5, 129.4, 128.3, 127.5, 127.3, 65.6, 61.9; IR (KBr) ῡ 3421, 3056, 2998, 2305, 2114, 1641, 1447, 1421, 1265, 1143, 909, 896; HRMS (ESI-TOF) calcd for $C_{14}H_{13}ClO_3S$ $(M + Na)^+$ 319.0166, found 319.0174.

2-((4-^{t}Butylphenyl)sulfonyl)-1-phenylethanol (3ac). R_f = 0.32 (20% ethyl acetate in hexane); white solid; yield 94% (120 mg); mp 113-115 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.30-7.19 (m, 5H), 5.25 (d, *J* = 10.0 Hz, 1H), 3.77 (d, *J* = 1.6 Hz, 1H), 3.46 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.30 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 140.8, 136.2, 128.8, 128.4, 127.9, 126.6, 125.8, 68.5, 64.0, 35.4, 31.1; IR (KBr) ῡ 3444, 2965, 2865, 2100, 1641, 1550, 1492, 1451, 1396, 1288, 1197, 1140, 1084, 844; HRMS (ESI-TOF) calcd for $C_{18}H_{22}O_3S$ $(M + Na)^+$ 341.1182, found 341.1172.

2-((4-^{t}Butylphenyl)sulfonyl)-1-(4-chlorophenyl)ethanol (3bc). R_f = 0.30 (20% ethyl acetate in hexane); White solid; yield 83% (146 mg); mp 120-122 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.84 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.30-7.21 (m, 4H), 5.27 (d, *J* = 10.0 Hz, 1H), 3.84 (d, *J* = 1.6 Hz, 1H), 3.45 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.31 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.5, 139.3, 136.1, 134.2, 129.0, 127.9, 127.2, 126.7, 67.9, 63.9, 35.5, 31.2; IR (KBr) ῡ 3422, 3057, 2968, 2377, 2306, 2115, 1785, 1640, 1550, 1493, 1399, 1307, 1263, 1198, 1107, 1085, 1014, 995, 896, 864; HRMS (ESI-TOF) calcd for $C_{18}H_{21}O_3SCl$ $(M + Na)^+$ 375.0792, found 375.0782.

2-((4-^{t}Butylphenyl)sulfonyl)-1-(p-tolyl)ethanol (3cc). R_f = 0.34 (20% ethyl acetate in hexane); White solid; yield 65% (98 mg); mp 97-99 ºC; 1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.24 (d, *J* = 10.0 Hz, 1H), 3.70 (d, *J* = 1.6 Hz, 1H), 3.49 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.33 (dd, *J* = 14.4, 2.0 Hz, 1H), 2.31 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 138.2, 137.9, 136.2, 129.5, 127.9, 126.6, 125.7, 68.4, 64.0, 35.4, 31.1, 21.2; IR (KBr) ῡ 3474, 3060, 2967, 2871, 2307, 2099, 1923,1640, 1514, 1476, 1399, 1306, 1267, 1199, 1107, 1085, 1057, 1014, 864, 840; HRMS (ESI-TOF) calcd for $C_{19}H_{24}O_3S$ $(M + Na)^+$ 355.1338, found 355.1325.

1-((4-^{t}Butylphenyl)sulfonyl)-2-phenylpropan-2-ol (3dc). R_f = 0.40 (20% ethyl acetate in hexane); White solid; yield 85% (130 mg); mp 92-93 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.27-7.23 (m, 2H), 7.18-7.08 (m, 3H), 4.69 (br s, 1H), 3.73 (d, *J* = 14.4 Hz, 1H), 3.60 (d, *J* = 14.4 Hz, 1H), 1.68 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 144.4, 137.2, 128.3, 127.5, 127.3, 126.2, 124.8, 73.2, 66.6, 35.3, 31.2 (x2C); IR (KBr) ῡ 3450, 2965, 2076, 1640, 1493, 1397, 1307, 1251, 1158, 1082, 850; HRMS (ESI-TOF) calcd for $C_{19}H_{24}O_3S$ $(M + Na)^+$ 355.1338, found 355.1343.

1-([1,1'-Biphenyl]-4-yl)-2-((4-(tert-butyl)phenyl)sulfonyl)ethanol (3ec). R_f = 0.35 (20% ethyl acetate in hexane); White solid; yield 79% (103 mg); mp 115-116 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.57-7.52 (m, 4H), 7.47-

7.29 (m, 5H), 5.35 (d, *J* = 10.0 Hz, 1H), 3.81 (d, *J* = 1.6 Hz, 1H), 3.53 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.39 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 141.4, 140.6, 139.8, 136.2, 128.9, 128.0, 127.62, 127.59, 127.2, 126.7, 126.3, 68.3, 64.0 35.5, 31.2; IR (KBr) ῡ 3443, 2928, 2850, 2358, 2096, 1642, 1275, 1261, 764; HRMS (ESI-TOF) calcd for $C_{24}H_{26}O_3S$ $(M + Na)^+$ 417.1495, found 417.1467.

1-(4-Bromophenyl)-2-((4-(tert-butyl)phenyl)sulfonyl)ethanol (3fc). R_f = 0.33 (20% ethyl acetate in hexane); White solid; yield 83% (150 mg); mp 134-136 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.76 (m, 2H), 7.62-7.54 (m, 2H), 7.47-7.38 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.26 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.84 (br s, 1H), 3.44 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.31 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 139.8, 136.0, 131.9, 127.9, 127.6, 126.7 122.3, 68.0, 63.8, 35.5, 31.2; IR (KBr) ῡ 3508, 3055, 2969, 2305, 2099, 1643, 1594, 1421, 1398, 1306, 1291, 1198, 1107, 1085, 1011, 895; HRMS (ESI-TOF) calcd for $C_{18}H_{21}BrO_3S$ $(M + Na)^+$ 419.0287, found 419.0269.

2-((4-^{t}Butylphenyl)sulfonyl)-1-(naphthalen-2-yl)ethanol (3hc). R_f = 0.34 (20% ethyl acetate in hexane); White solid; yield 95% (136 mg); mp 132-134 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.83-7.74 (m, 4H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.52-7.43 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 5.47 (d, *J* = 10.0 Hz, 1H), 3.89 (br s, 1H), 3.58 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.44 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 138.1, 136.2, 133.3, 133.2, 128.8, 128.1, 128.0, 127.8, 126.6, 126.5, 126.4, 125.0, 123.4, 68.7, 63.9, 35.4, 31.1; IR (KBr) ῡ 3507, 3085, 2970, 2340, 2098, 1642, 1510, 1476, 1399, 1365, 1291, 1265, 1152, 1085, 896, 860; HRMS (ESI-TOF) calcd for $C_{22}H_{24}O_3S$ $(M + Na)^+$ 391.1338, found 391.1357.

2-((4-^{t}Butylphenyl)sulfonyl)-1-(3-chlorophenyl)ethanol (3jc). R_f = 0.38 (20% ethyl acetate in hexane); White solid; yield 50% (83 mg); mp 77-79 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2H), 7.64-7.56 (m, 2H), 7.32 (s, 1H), 7.25-7.15 (m, 3H), 5.27 (dd, *J* = 10.0, 2.0

Hz, 1H), 3.85 (br s, 1H), 3.45 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.32 (dd, *J* = 14.0, 2.0 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 142.8, 136.0, 134.8, 130.2, 128.6, 128.0, 126.7, 126.1, 124.0, 68.0, 63.9, 35.5, 31.2; IR (KBr) ῡ 3421, 2956, 2356, 2090, 1640, 1275, 1260, 1055; HRMS (ESI-TOF) calcd for $C_{18}H_{21}ClO_3S$ $(M + Na)^+$ 375.0792, found 375.0776.

4-(2-((4-^{t}Butylphenyl)sulfonyl)-1-hydroxyethyl)benzonitrile (3kc): R_f = 0.25 (20% ethyl acetate in hexane); White solid; yield 44% (69 mg); mp 120-124 ºC; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.57 - 7.63 (m, 4H), 7.45 (d, *J* = 8.0 Hz, 2H), 5.37 (d, *J* = 10.0 Hz, 1H), 4.03 (s, 1H), 3.43 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.32 (d, *J* = 14.4 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.7, 145.9, 135.8, 132.6, 127.9, 126.8, 126.6, 118.5, 112.2, 67.9, 63.6, 35.5, 31.1; IR (KBr) ῡ 3484, 3059, 2966, 2871, 2304, 2229, 2098, 1636, 1463, 1397, 1291, 1266, 1198, 1143, 1107; HRMS (ESI-TOF) calcd for $C_{19}H_{21}NO_3S$ $(M + Na)^+$ 366.1146, found 366.1134.

2-((4-^{t}Butylphenyl)sulfonyl)-1-(4-nitrophenyl)ethanol (3lc): R_f = 0.22 (20% ethyl acetate in hexane); White solid; yield 59% (100 mg); mp 130-132 ºC; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 5.43 (d, *J* = 10.0 Hz, 1H), 4.08 (brs, 1H), 3.45 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.34 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.8, 147.82, 147.81, 135.8, 128.0, 126.8, 126.7, 124.1, 67.8, 63.6, 35.5, 31.1; IR (KBr) ῡ 3487, 2964, 2870, 1594, 1521, 1346, 1305, 1198, 1144, 1107, 1084; HRMS (ESI-TOF) calcd for $C_{18}H_{21}NO_5S$ $(M + Na)^+$ 386.1007, found 386.1033.

2-((4-^{t}Butylphenyl)sulfonyl)-1-(4-methoxyphenyl)ethanol (3mc): R_f = 0.32 (20% ethyl acetate in hexane); white solid ; yield 96% (125 mg); mp 115-119 ºC; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.23 (d, *J* = 10.0 Hz, 1H), 3.77 (s, 3H), 3.69 (d, *J* = 1.2 Hz, 1H), 3.49 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.31 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (175 MHz,

$CDCl_3$) δ 159.7, 158.3, 136.3, 133.0, 128.0, 127.2, 126.6, 114.2, 68.2, 64.0, 55.4, 35.5, 31.2. IR (KBr) ῡ 3466, 2966, 2084, 1632, 1514, 1397, 1304, 1249, 1141, 1032; HRMS (ESI-TOF) calcd for $(M + Na)^+$ 371.1290, found 371.1288.

2-(Butylsulfonyl)-1-(4-chlorophenyl)ethanol (3bd). R_f = 0.32 (20% ethyl acetate in hexane); White solid; yield 54% (74 mg); mp 97-99 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 4H), 5.39-5.34 (m, 1H), 3.36 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.22 (d, *J* = 2.0 Hz, 1H), 3.18-3.05 (m, 3H), 1.90-1.80 (m, 2H), 1.53-1.43 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 134.5, 129.3, 127.2, 68.4, 60.4, 54.7, 24.0, 21.9, 13.7; IR (KBr) ῡ 3422, 3055, 2987, 2685, 2410, 2305, 2124, 1640, 1551, 1421, 1265, 1127, 895; HRMS (ESI-TOF) calcd for $C_{12}H_{17}ClO_3S$ $(M + Na)^+$ 299.0479, found 299.0501.

1-([1,1'-biphenyl]-4-yl)-2-(butylsulfonyl)ethanol (3ed). R_f = 0.30 (20% ethyl acetate in hexane); White solid; yield 85% (90 mg); mp 115-118 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.54 (m, 4H), 7.53-7.40 (m, 4H), 7.39-7.33 (m, 1H), 5.44 (d, *J* = 10.0 Hz, 1H), 3.45 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.23-3.05 (m, 4H), 1.93-1.82 (m, 2H), 1.52-1.46 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.5, 140.2, 129.0, 127.8, 127.7, 127.2, 126.3, 68.9, 60.5, 54.7, 24.0, 21.9, 13.7; IR (KBr) ῡ 3422, 3056, 2988, 2306, 2115, 1641, 1534, 1421, 1265, 895; HRMS (ESI-TOF) calcd for $C_{18}H_{22}O_3S$ $(M + Na)^+$ 341.1182, found 341.1162.

1-(4-Bromophenyl)-2-(butylsulfonyl)ethanol (3fd). R_f = 0.31 (20% ethyl acetate in hexane); White solid; yield 42% (62 mg); mp 94-95 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.45 (m, 2H), 7.28-7.25 (m, 2H), 5.33 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.35 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.30 (d, *J* = 2.8 Hz, 1H), 3.16-3.04 (m, 3H), 1.90-1.77 (m, 2H), 1.55-1.40 (m, 2H), 0.96 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 132.2, 127.5, 122.6, 68.4, 60.4, 54.7, 24.0, 21.8, 13.7; IR (KBr) ῡ 3442, 2965, 2875, 2115, 1639, 1527, 1489, 1398, 1124, 1069, 1010; HRMS (ESI-TOF) calcd for $C_{12}H_{17}BrO_3S$ $(M + Na)^+$ 342.9974, found 342.9987.

2-(Butylsulfonyl)-1-(naphthalen-2-yl)ethanol (3hd). R_f = 0.33 (20% ethyl acetate in hexane); White solid; yield 58% (66 mg); mp 112-114 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.80 (m, 4H), 7.55-7.44 (m, 3H), 5.56 (d, *J* = 10.0 Hz, 1H), 3.49 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.37-3.08 (m, 4H), 1.92-1.82 (m, 2H), 1.53-1.43 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 133.37, 133.36, 129.1, 128.2, 127.9, 126.8, 126.6, 124.9, 123.3, 69.2, 60.5, 54.7, 24.0, 21.8, 13.7; IR (KBr) ῡ 3422, 2104, 1640, 1264, 1128, 803; HRMS (ESI-TOF) calcd for $C_{16}H_{20}O_3S$ $(M + Na)^+$ 315.1025, found 315.1014.

2-Tosyl-1-(4-(trifluoromethyl)phenyl)ethanol (3na): R_f = 0.30 (20% ethyl acetate in hexane); White solid; yield 46% (55 mg); mp 98-100 ^oC; ^1H NMR (700 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.34 (d, *J* = 10.0 Hz, 1H), 3.91 (s, 1H), 3.44 (dd, *J* = 14.4, 10.0 Hz, 1H), 3.32 (d, *J* = 14.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 145.7, 144.6, 136.0, 130.4, 128.1, 126.20, 125.84 (q, *J* = 3.7 Hz), 124.8, 123.3, 68.1, 63.9, 21.8; IR (KBr) ῡ 3400, 3034, 2986, 2928, 2306, 2106, 1926, 1633, 1494, 1412, 1324, 1162, 1133, 1066, 1016; HRMS (ESI-TOF) calcd for $C_{16}H_{15}F_3O_3S$ $(M + Na)^+$ 367.0579, found 367.0586.

^{1}H and ^{13}NMR Spectra of Selected Compounds

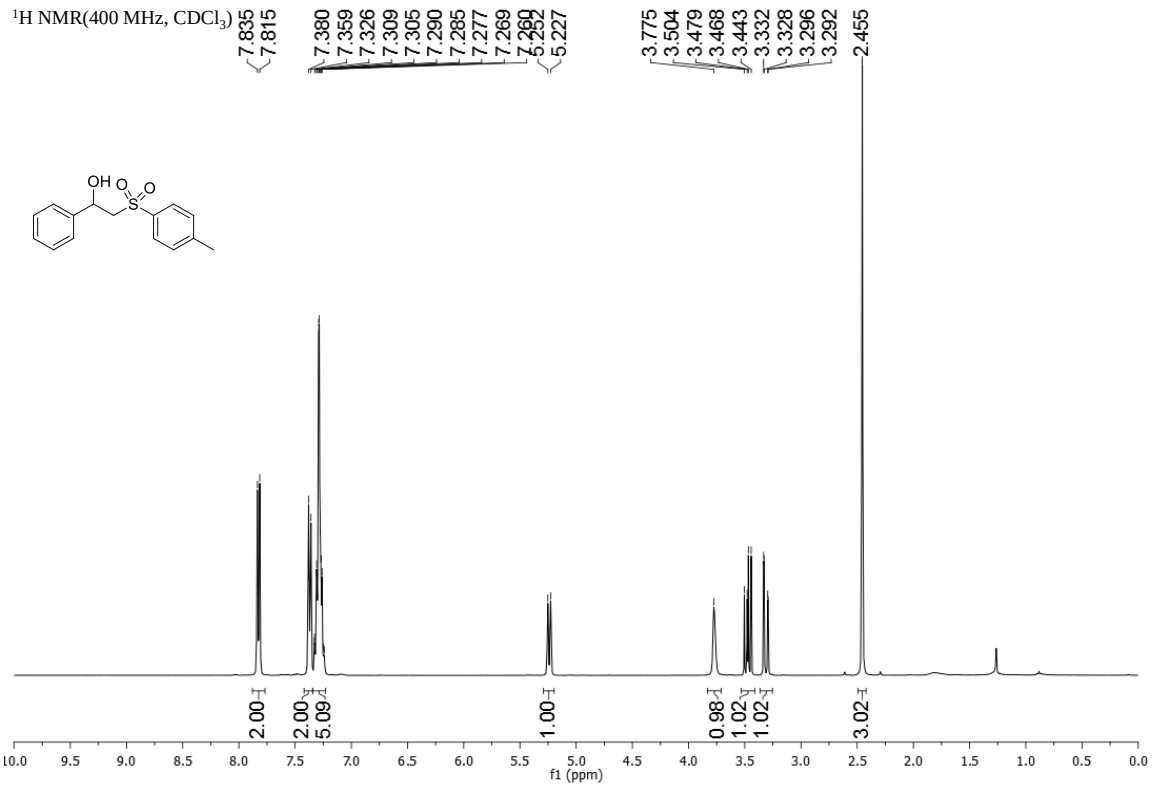


Figure 2A.9. ^{1}H NMR spectrum of 1-Phenyl-2-tosylethanol **(3aa)**

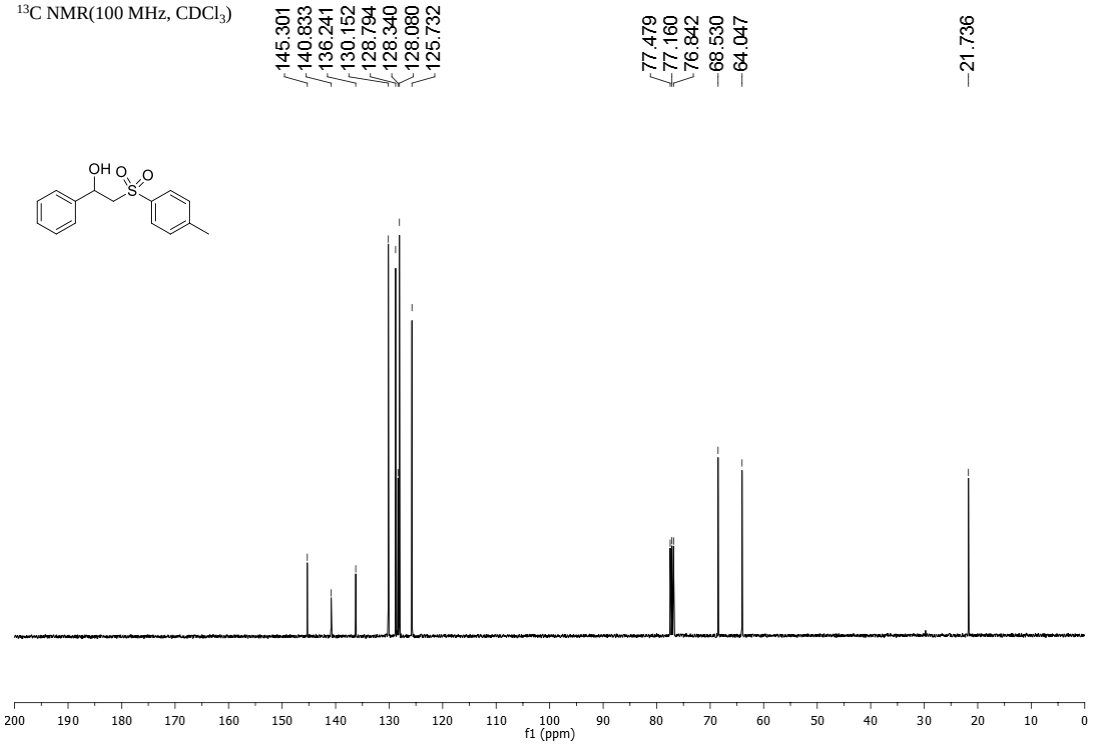
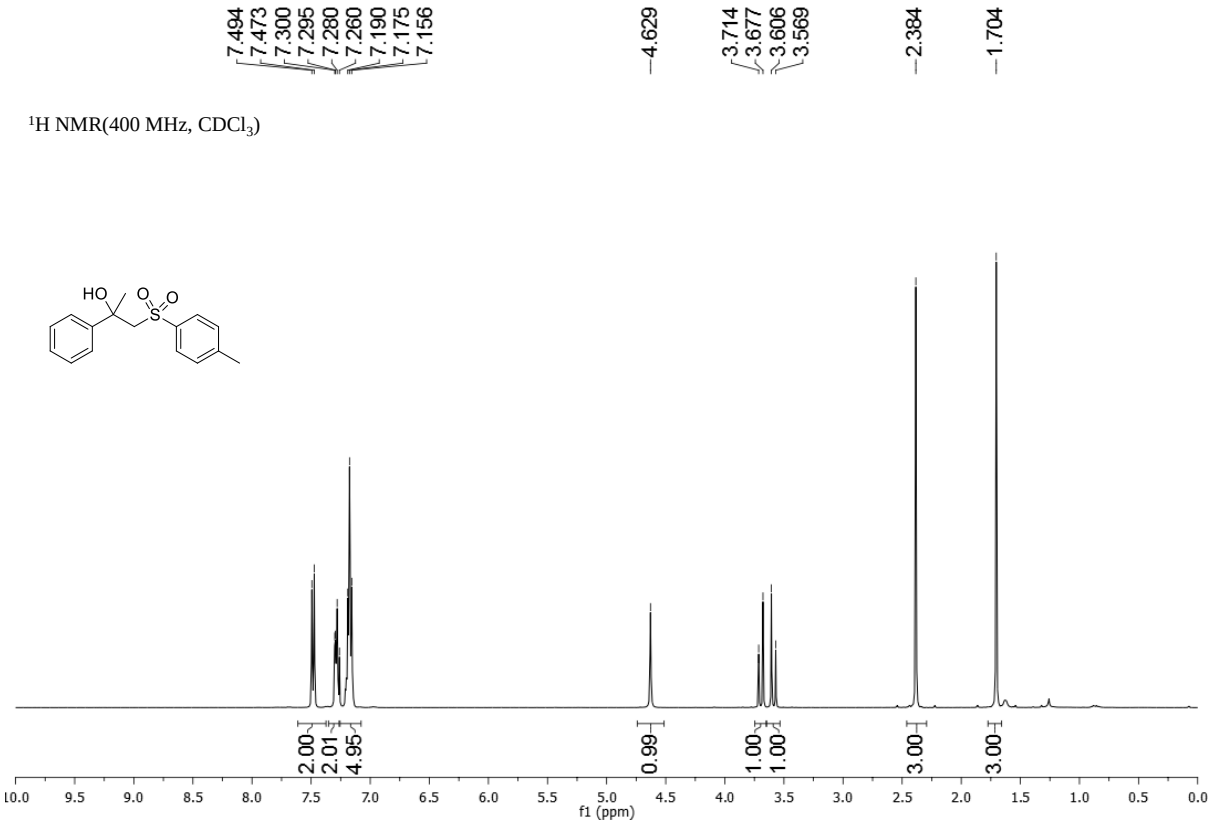
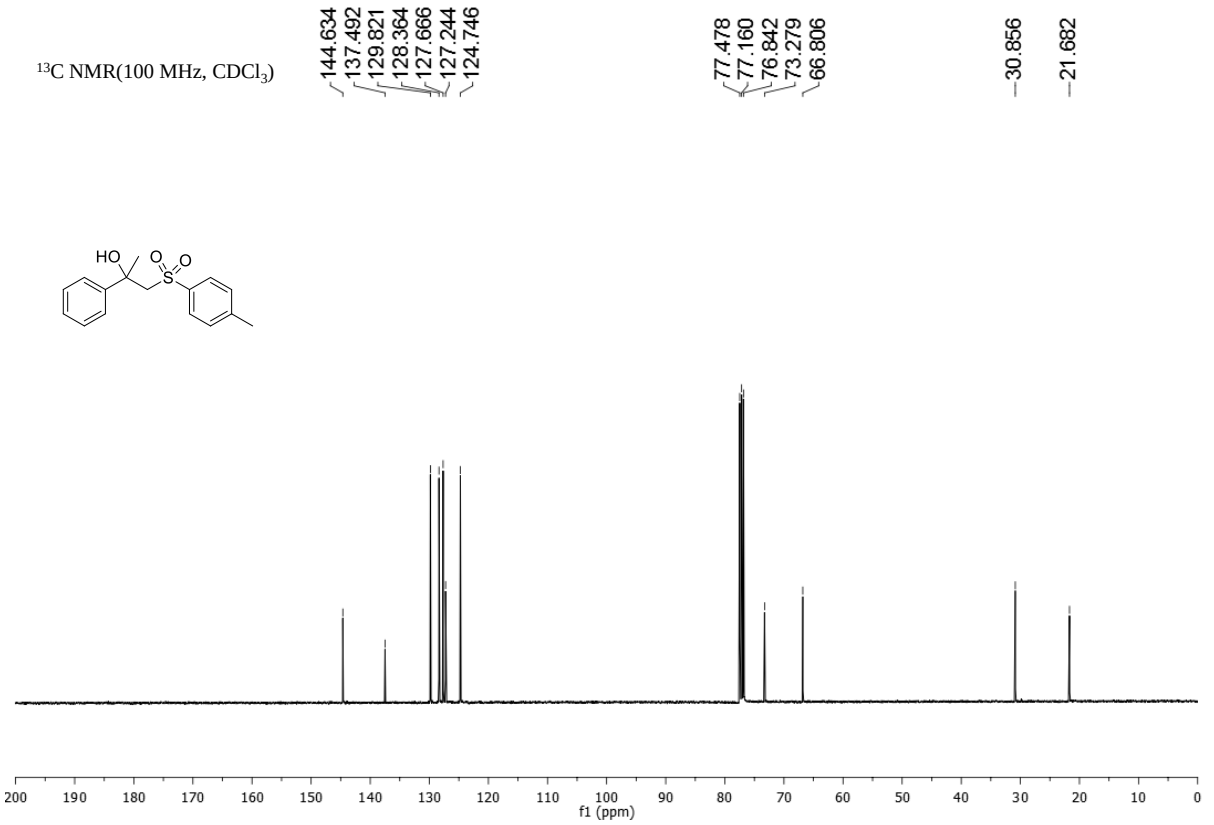


Figure 2A.10. ^{13}C NMR spectrum of 1-Phenyl-2-tosylethanol **(3aa)**



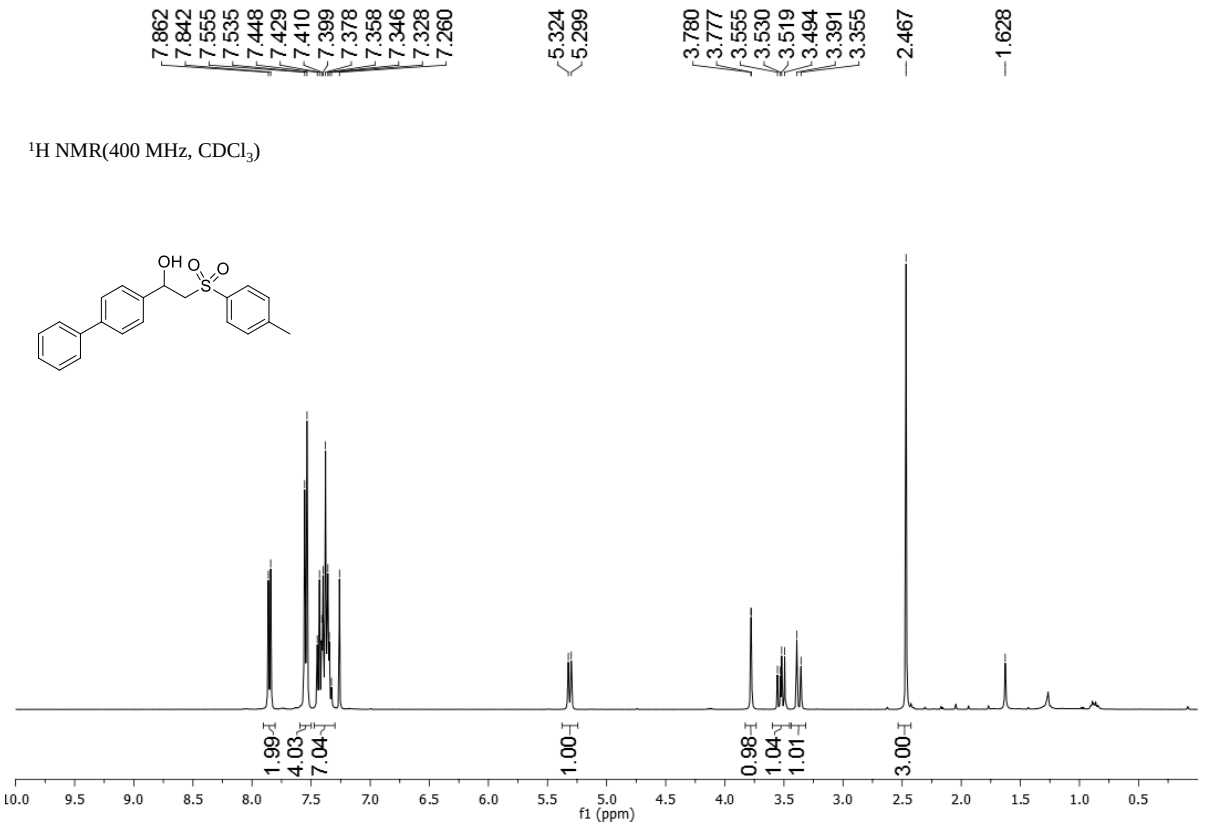
^{1}H NMR(400 MHz, $CDCl_3$)

Figure 2A.11. ^{1}H NMR spectrum of 2-phenyl-1-tosylpropan-2-ol **(3da)**



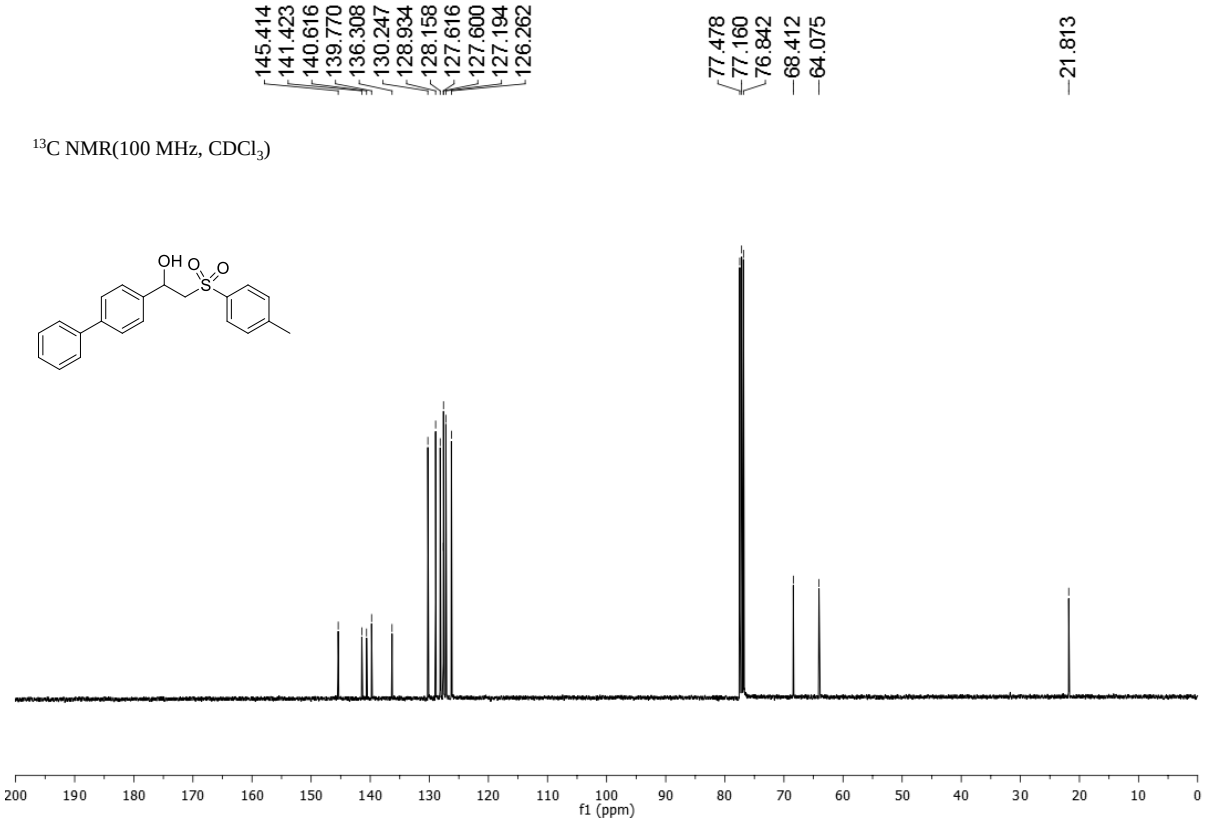
^{13}C NMR(100 MHz, $CDCl_3$)

Figure 2A.12. ^{13}C NMR spectrum of 2-phenyl-1-tosylpropan-2-ol **(3da)**



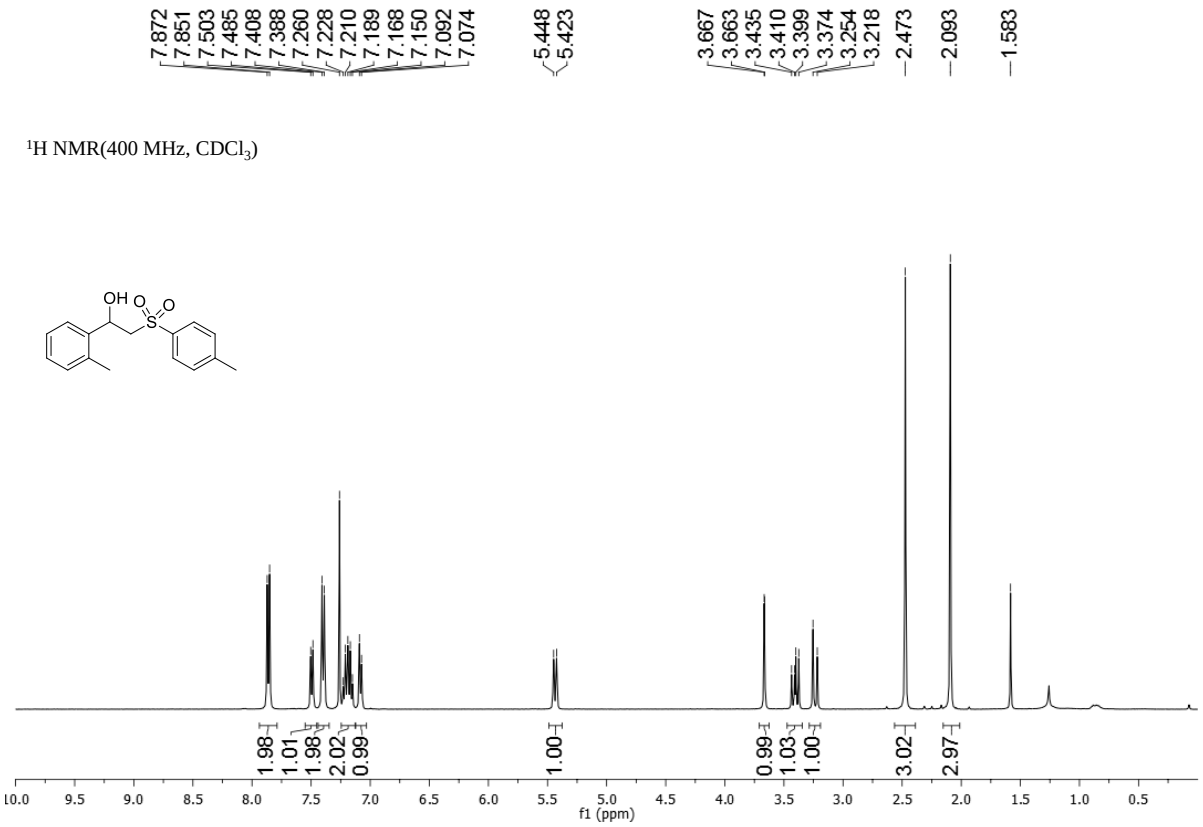
^{1}H NMR(400 MHz, $CDCl_3$)

Figure 2A.13. ^{1}H NMR spectrum of 1-([1,1'-biphenyl]-4-yl)-2-tosylethanol **(3ea)**



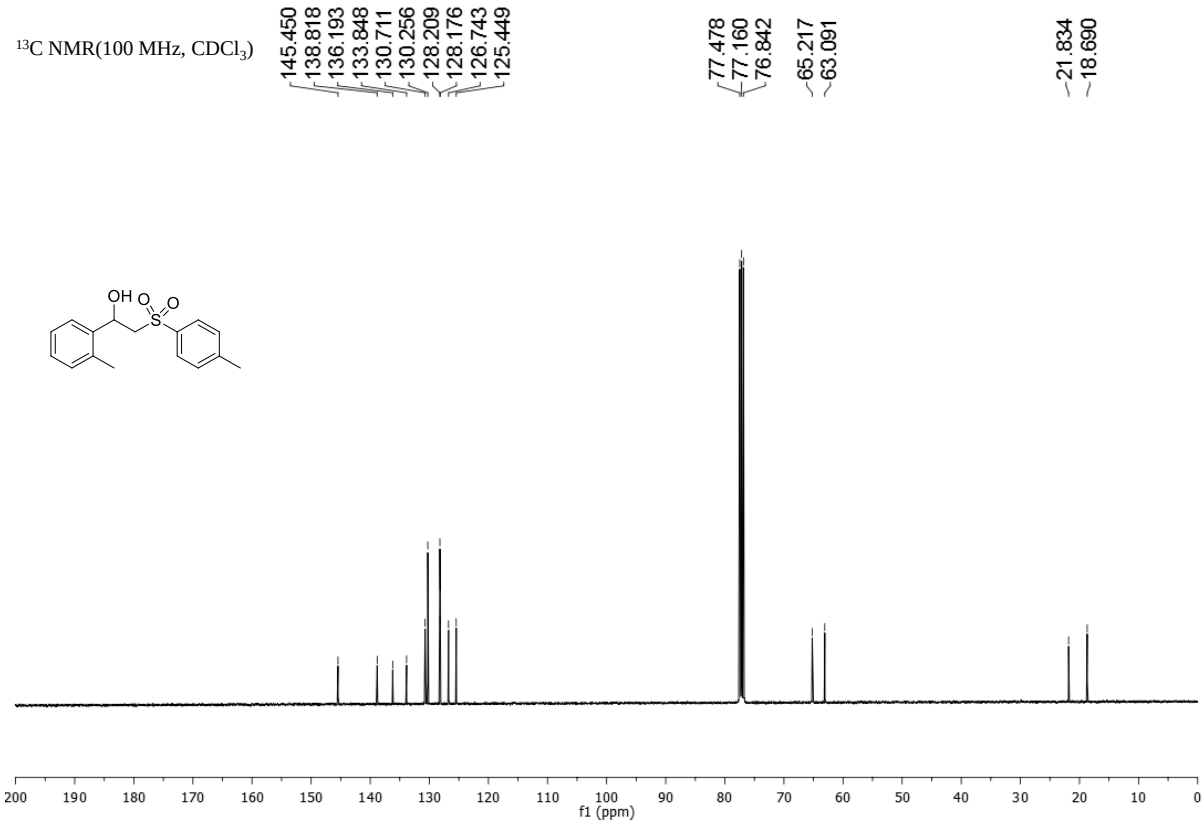
^{13}C NMR(100 MHz, $CDCl_3$)

Figure 2A.14. ^{13}C NMR spectrum of 1-([1,1'-biphenyl]-4-yl)-2-tosylethanol **(3ea)**



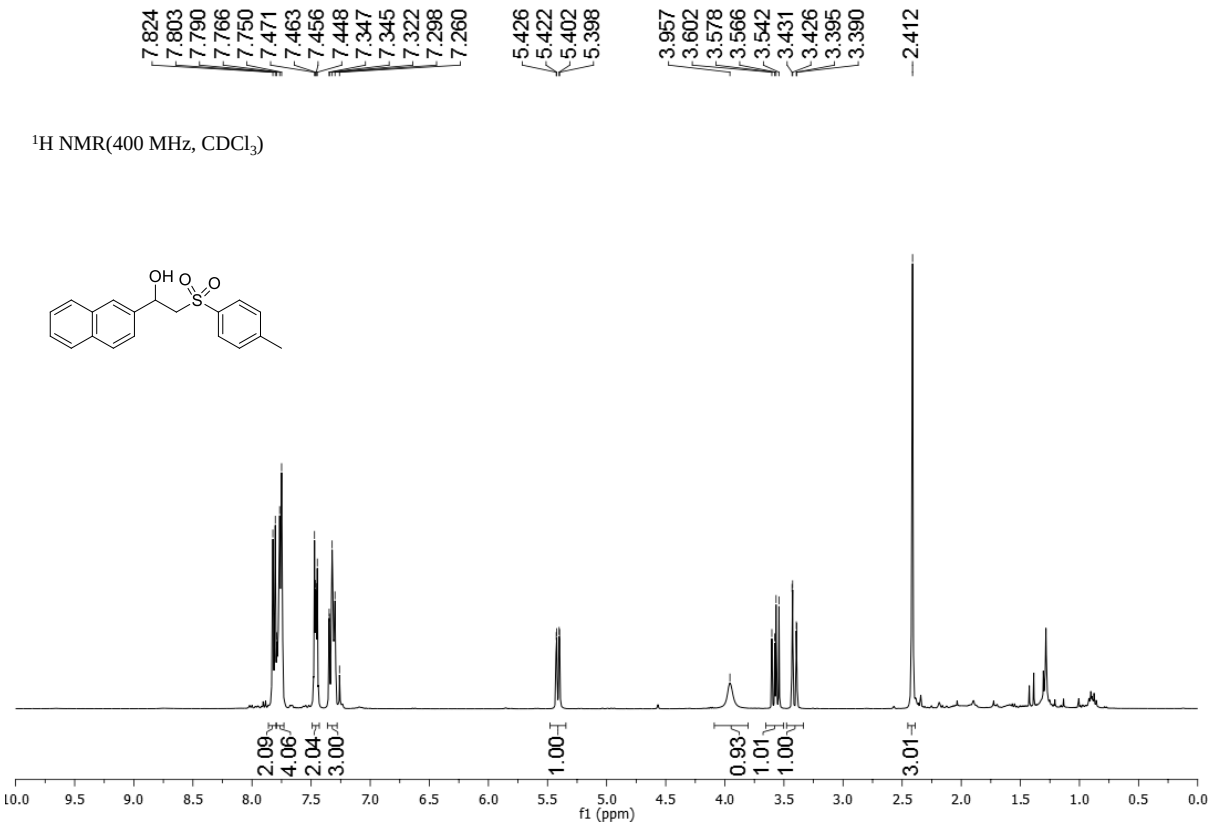
^{1}H NMR(400 MHz, $CDCl_3$)

Figure 2A.15. ^{1}H NMR spectrum of 1-(o-tolyl)-2-tosylethanol **(3ga)**



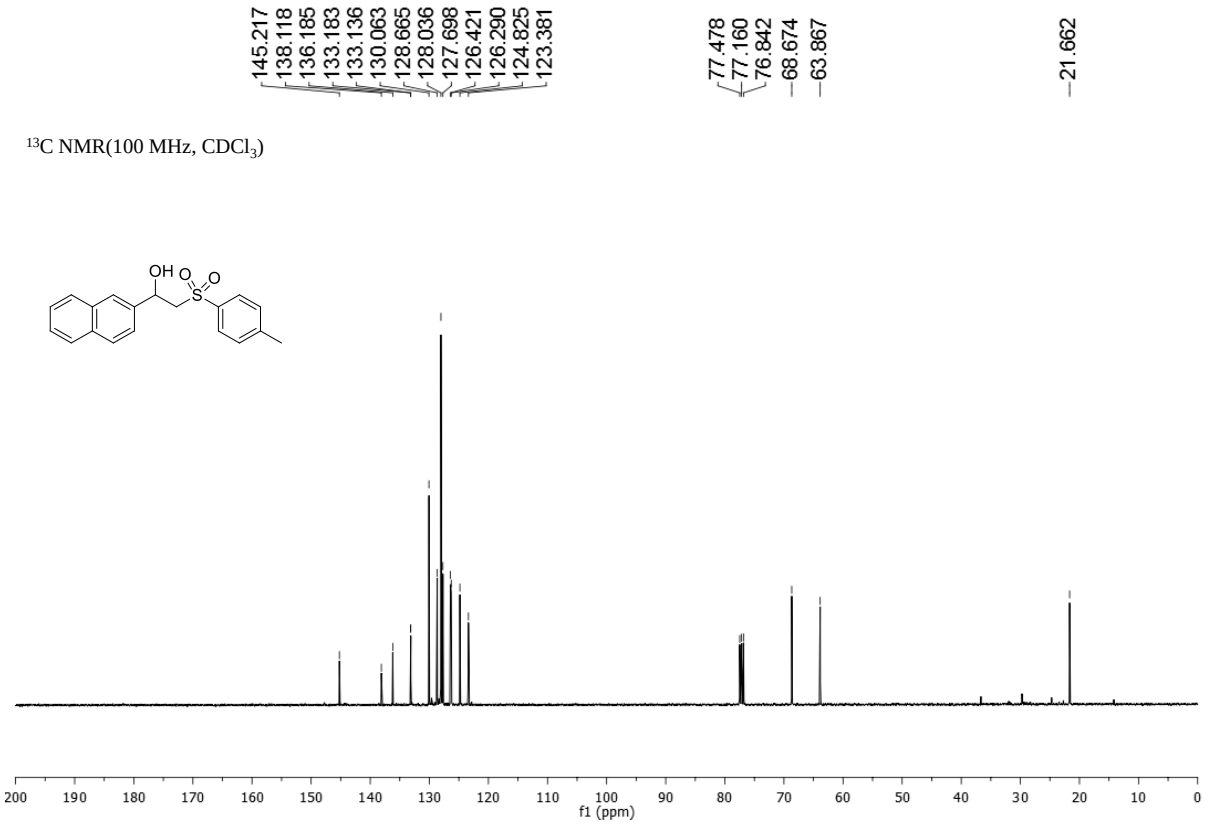
^{13}C NMR(100 MHz, $CDCl_3$)

Figure 2A.16. ^{13}C NMR spectrum of 1-(o-tolyl)-2-tosylethanol **(3ga)**



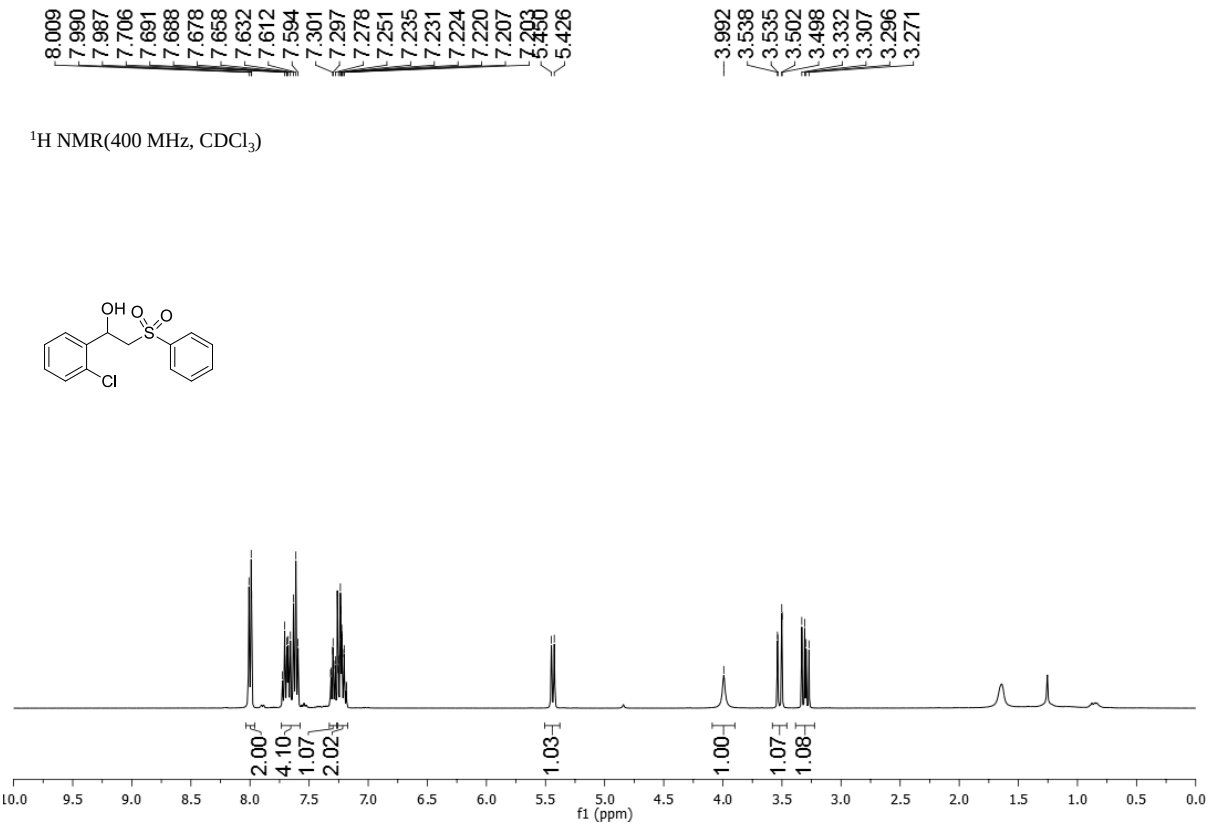
^{1}H NMR(400 MHz, $CDCl_3$)

Figure 2A.17. ^{1}H NMR spectrum of 1-(naphthalen-2-yl)-2-tosylethanol **(3ha)**



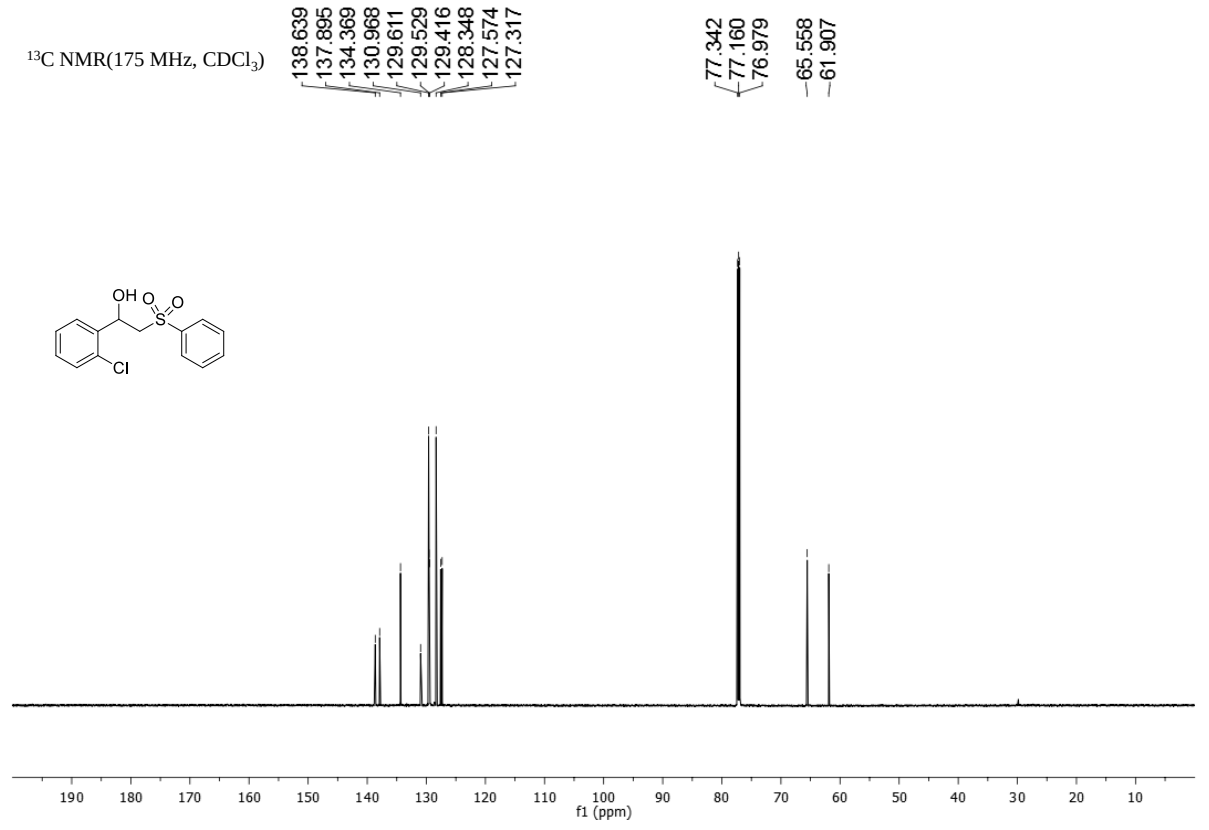
^{13}C NMR(100 MHz, $CDCl_3$)

Figure 2A.18. ^{13}C NMR spectrum of 1-(naphthalen-2-yl)-2-tosylethanol **(3ha)**



^{1}H NMR(400 MHz, $CDCl_3$)

Figure 2A.19. ^{1}H NMR spectrum of 1-(2-chlorophenyl)-2-(phenylsulfonyl)ethanol **(3ib)**



^{13}C NMR(175 MHz, $CDCl_3$)

Figure 2A.20. ^{13}C NMR spectrum of 1-(2-chlorophenyl)-2-(phenylsulfonyl)ethanol **(3ib)**

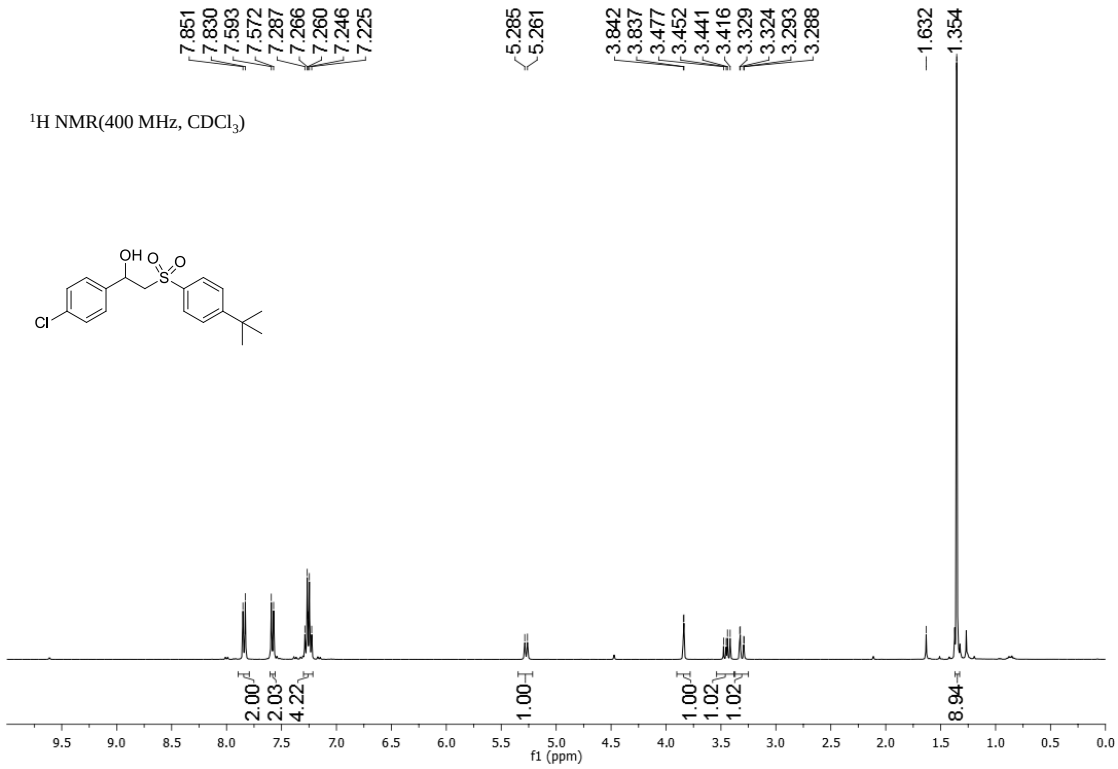


Figure 2A.21. ^{1}H NMR spectrum of 2-((4-(tert-butyl)phenyl)sulfonyl)-1-(4-chlorophenyl)ethanol **(3bc)**

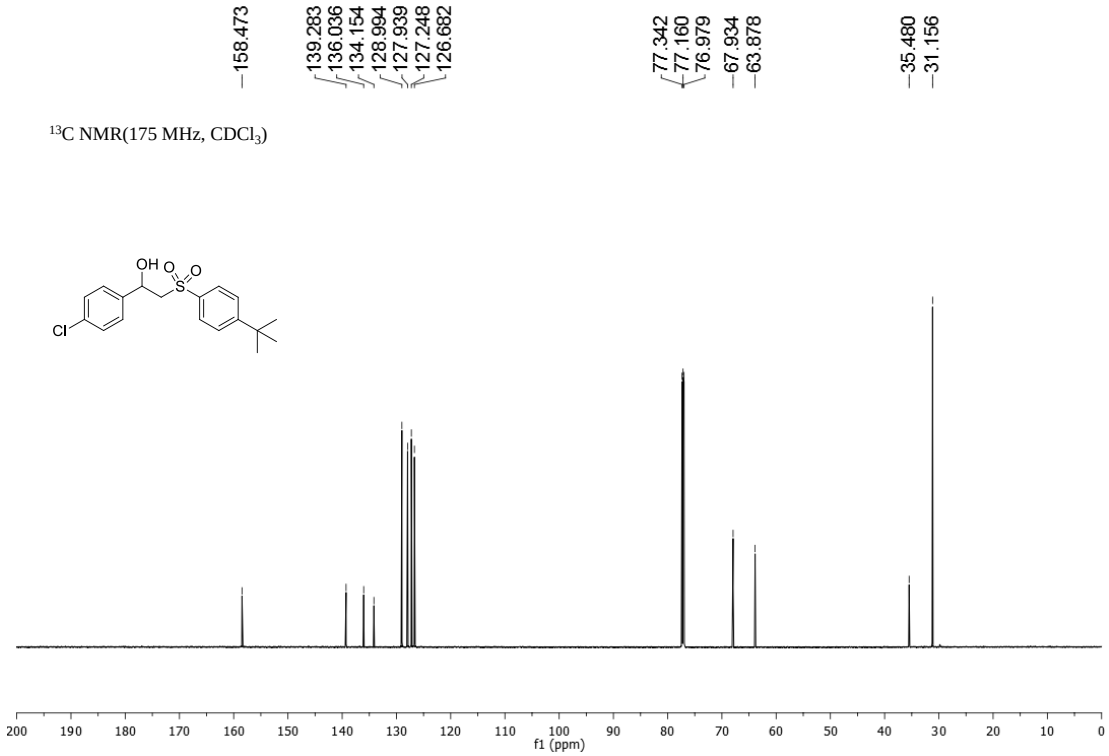


Figure 2A.22. ^{13}C NMR spectrum of 2-((4-(tert-butyl)phenyl)sulfonyl)-1-(4-chlorophenyl)ethanol **(3bc)**

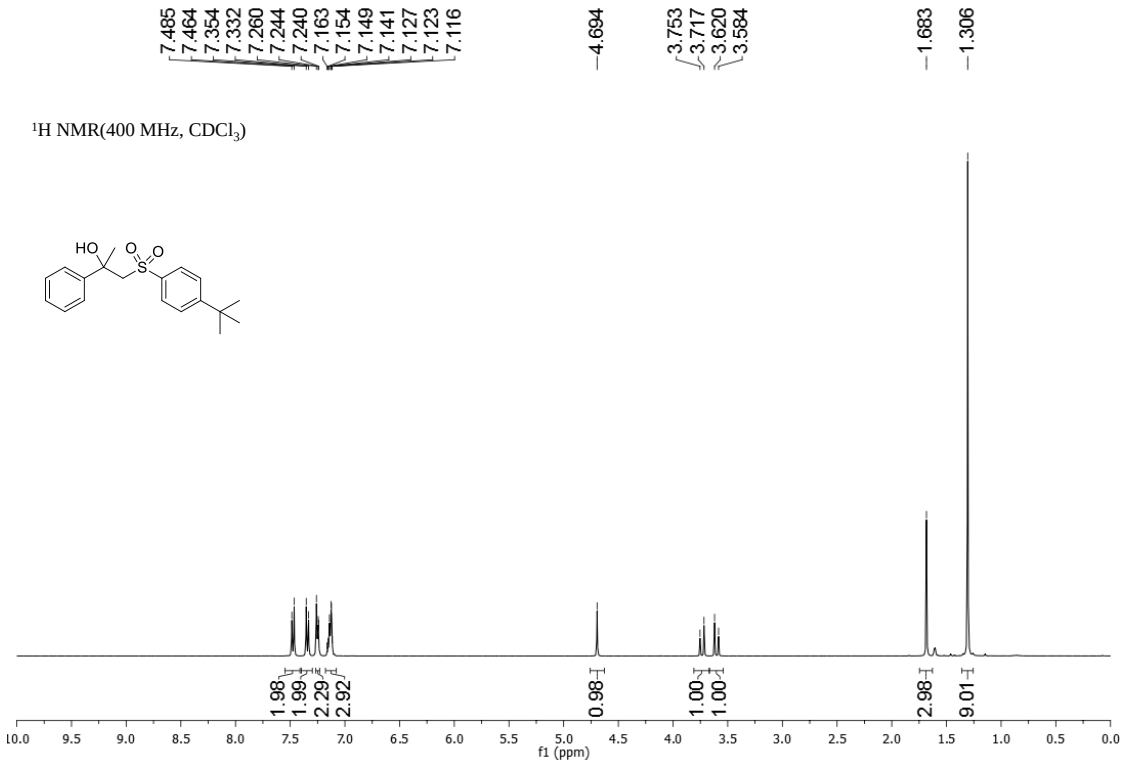


Figure 2A.23. ^{1}H NMR spectrum of 1-((4-(tert-butyl)phenyl)sulfonyl)-2-phenylpropan-2-ol **(3dc)**

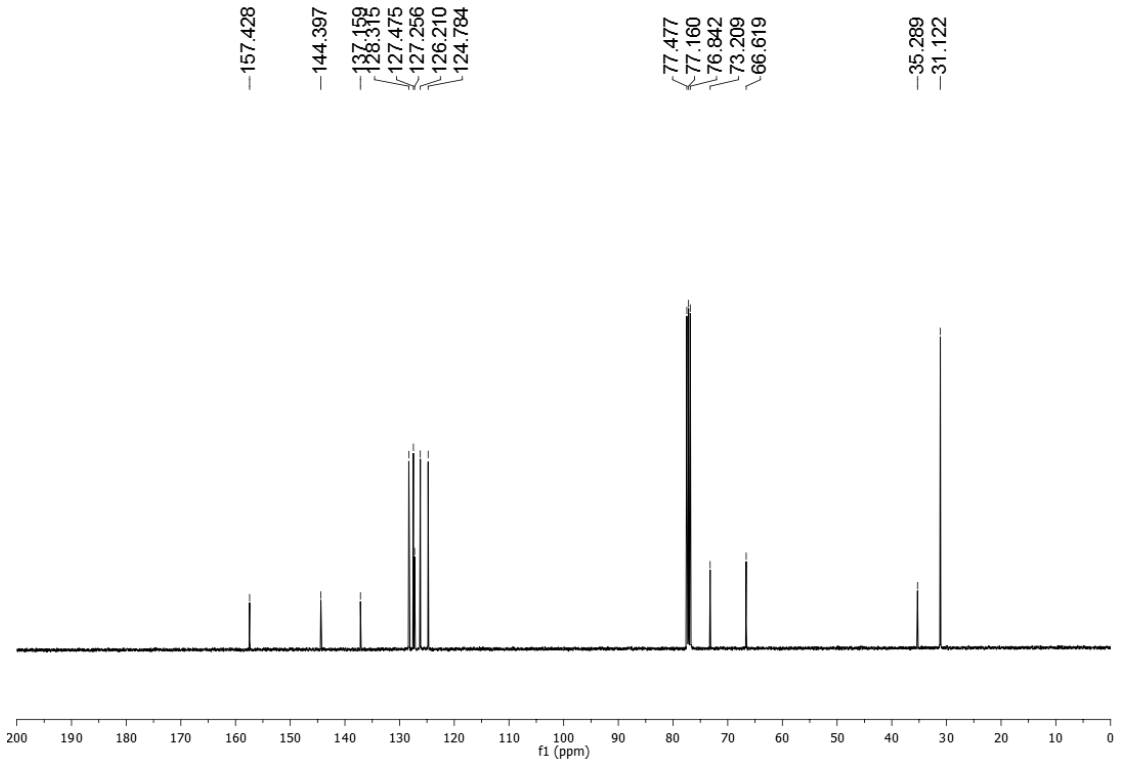


Figure 2A.24. ^{13}C NMR spectrum of 1-((4-(tert-butyl)phenyl)sulfonyl)-2-phenylpropan-2-ol **(3dc)**

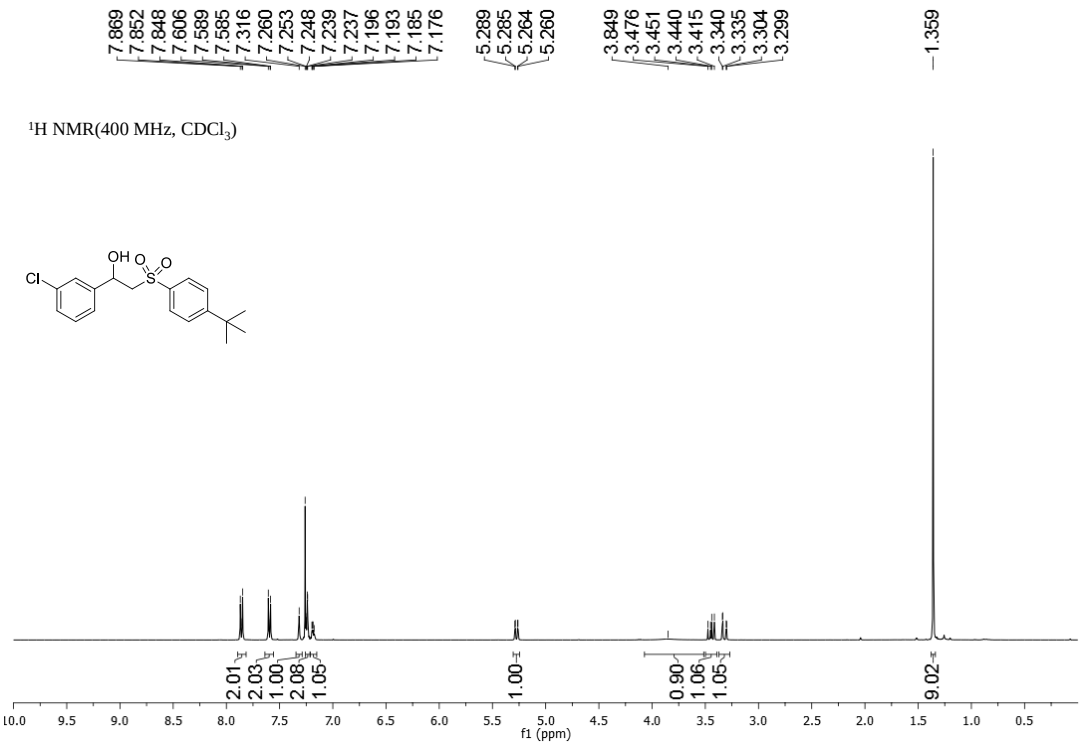


Figure 2A.25. ^{1}H NMR spectrum of 2-((4-(tert-butyl)phenyl)sulfonyl)-1-(3-chlorophenyl)ethanol **(3jc)**

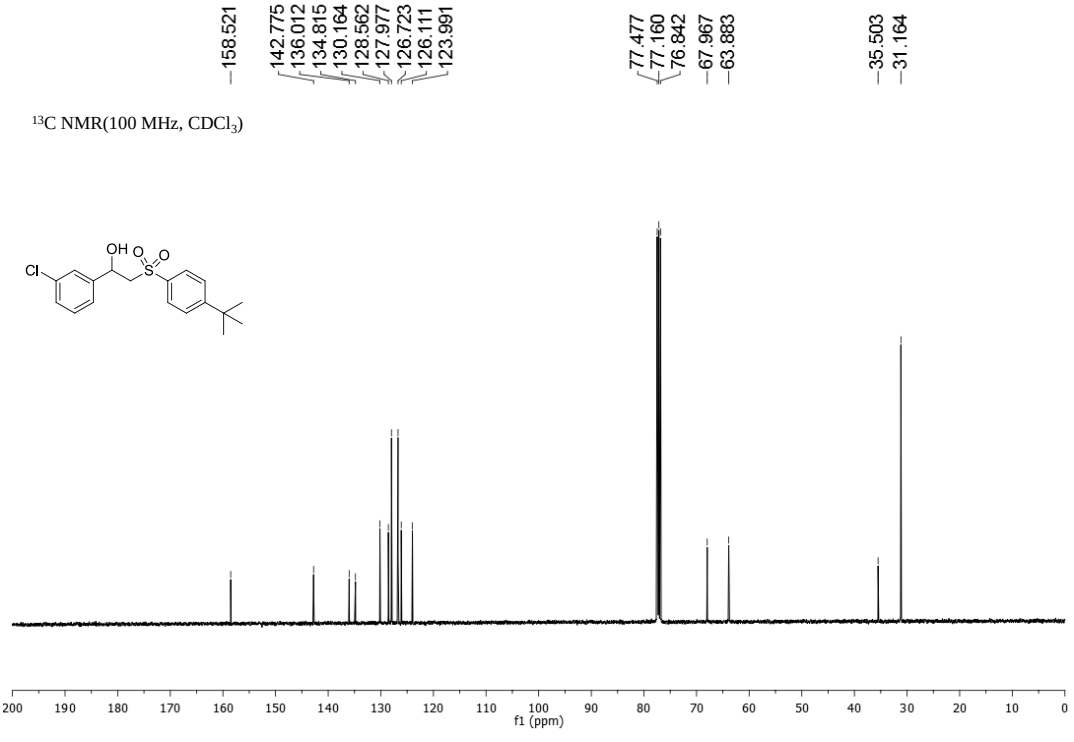


Figure 2A.26. ^{13}C NMR spectrum of 2-((4-(tert-butyl)phenyl)sulfonyl)-1-(3-chlorophenyl)ethanol **(3jc)**

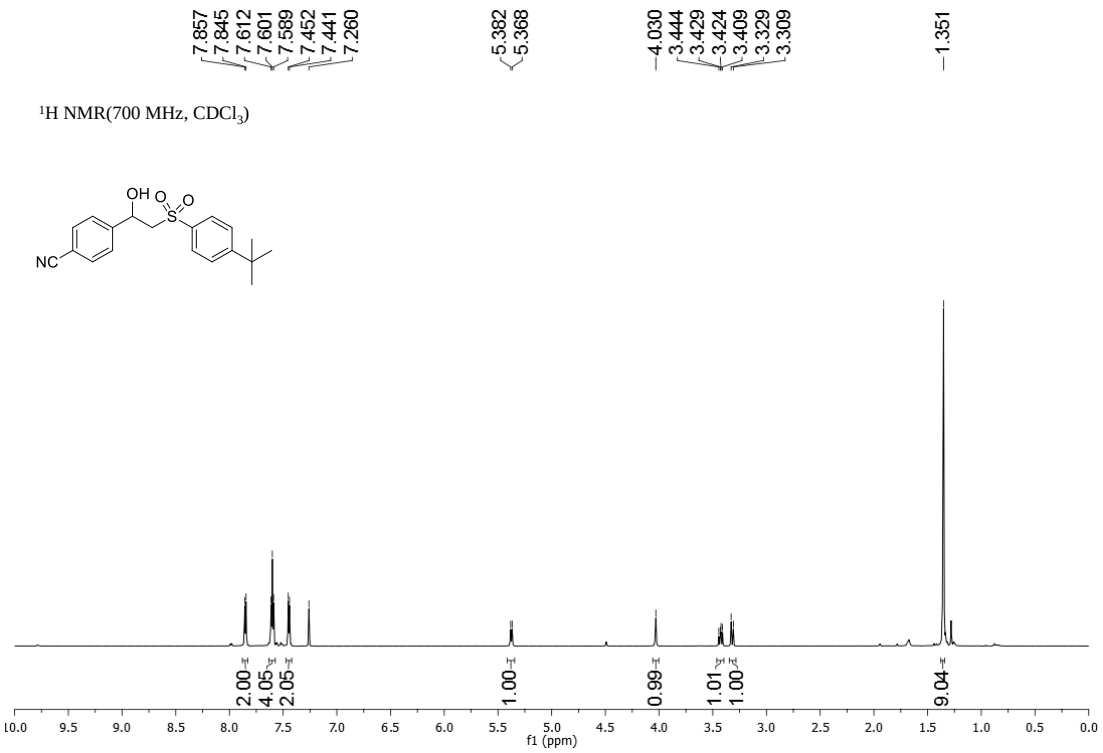


Figure 2A.27. ^{1}H NMR spectrum of 4-(2-((4-(tert-butyl)phenyl)sulfonyl)-1-hydroxyethyl)benzonitrile **(3kc)**

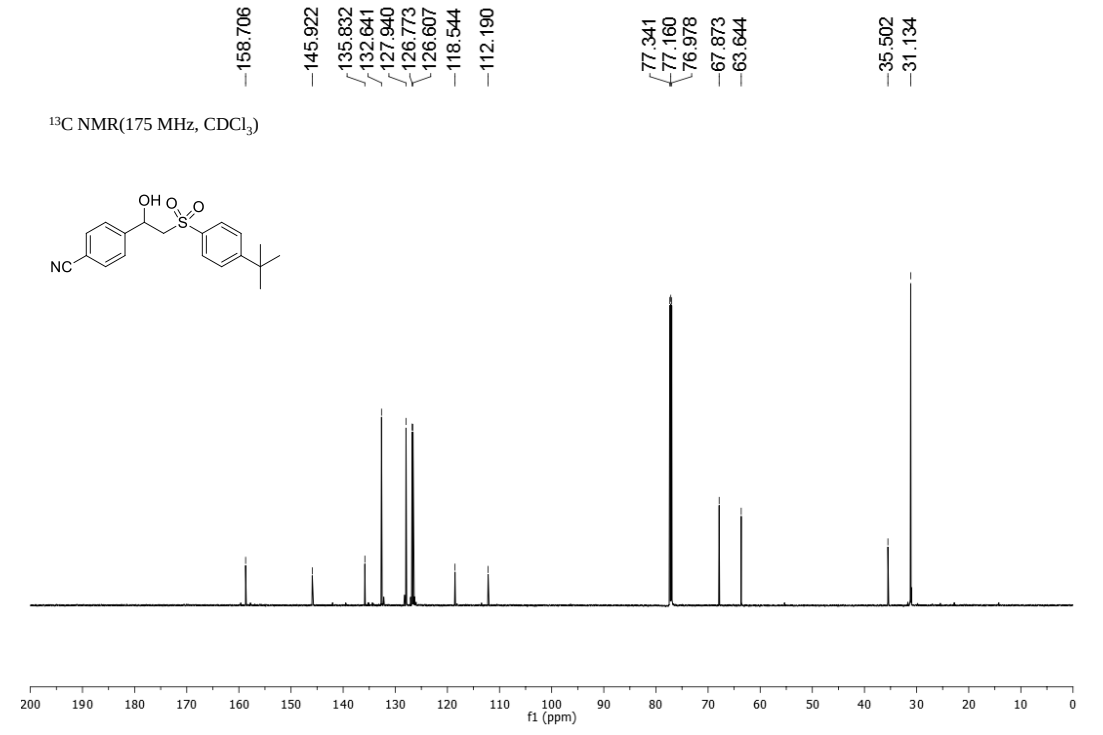


Figure 2A.28. ^{13}C NMR spectrum of 4-(2-((4-(tert-butyl)phenyl)sulfonyl)-1-hydroxyethyl)benzonitrile **(3kc)**

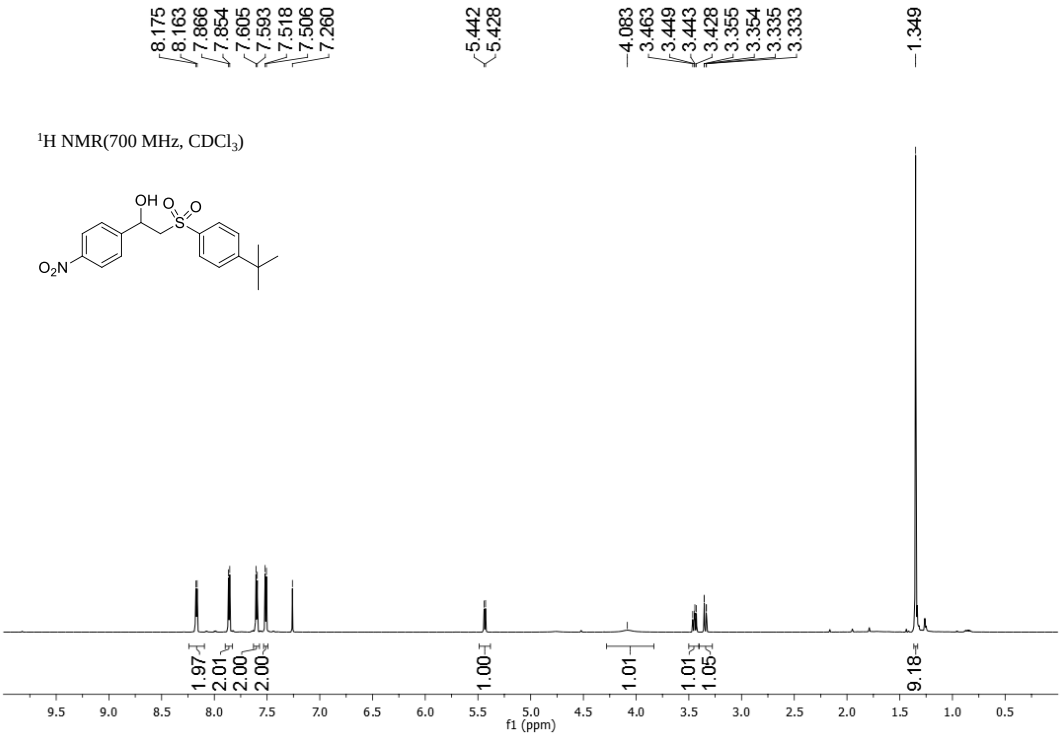


Figure 2A.29. ^{1}H NMR spectrum of 2-((4-(tert-butyl)phenyl)sulfonyl)-1-(4-nitrophenyl)ethanol **(3lc)**

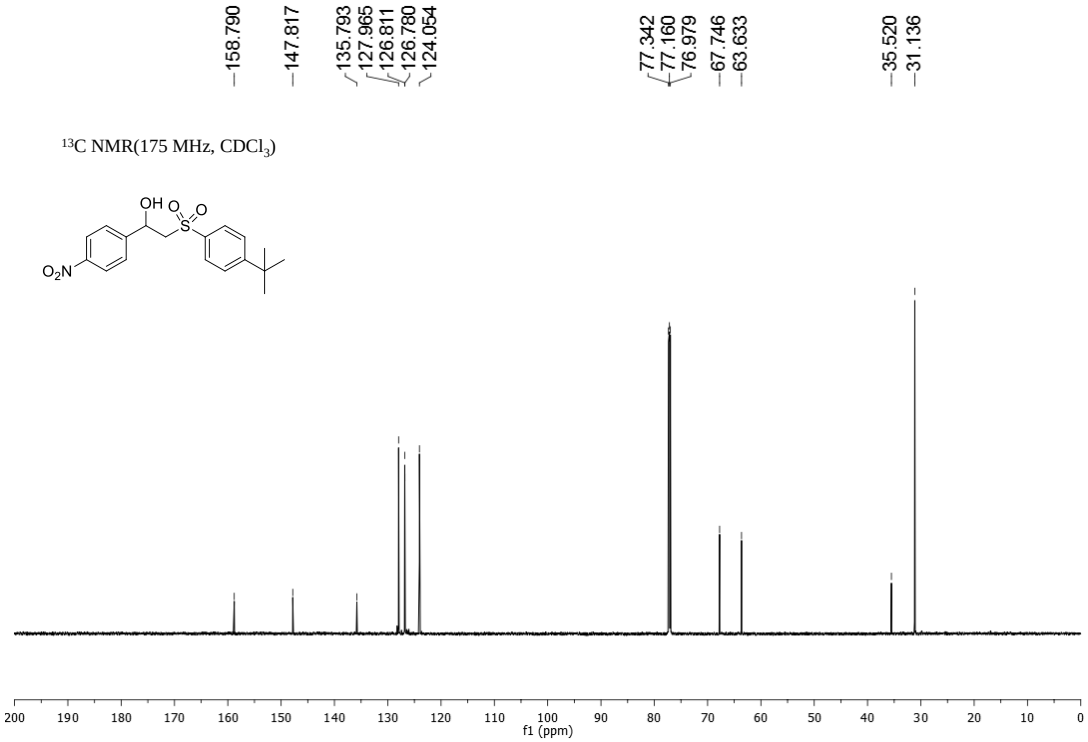


Figure 2A.30. ^{13}C NMR spectrum of 2-((4-(tert-butyl)phenyl)sulfonyl)-1-(4-nitrophenyl)ethanol **(3lc)**

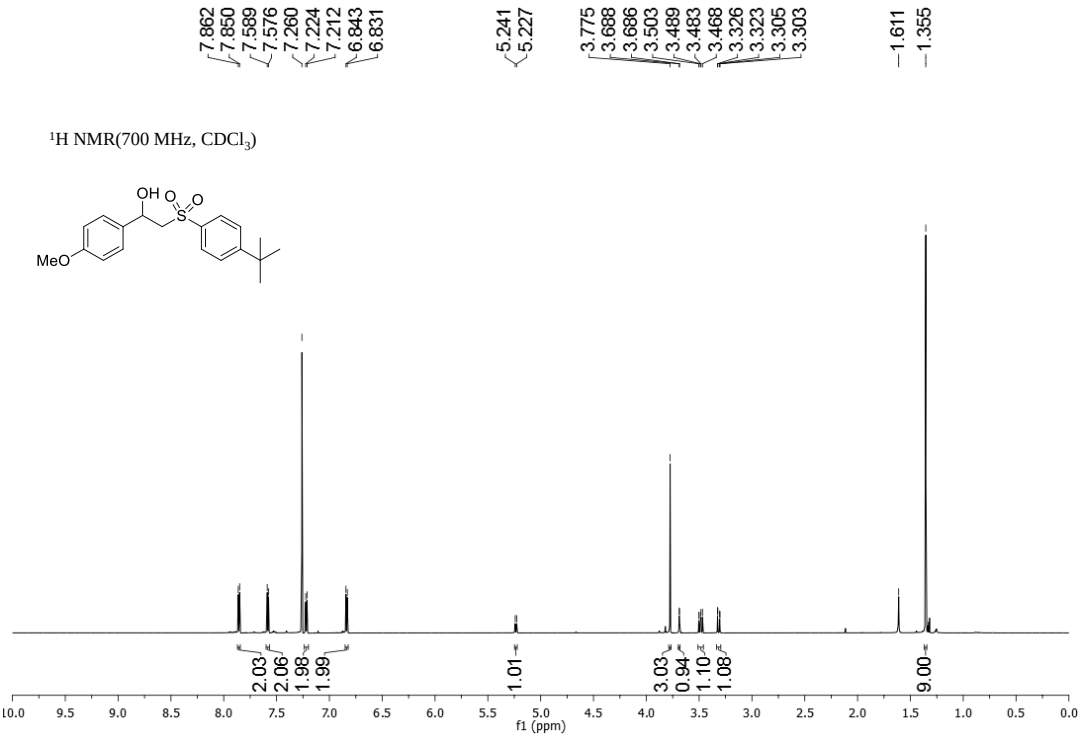


Figure 2A.31. ^{1}H NMR spectrum of 2-((4-(tert-butyl)phenyl)sulfonyl)-1-(4-methoxyphenyl)ethanol **(3mc)**

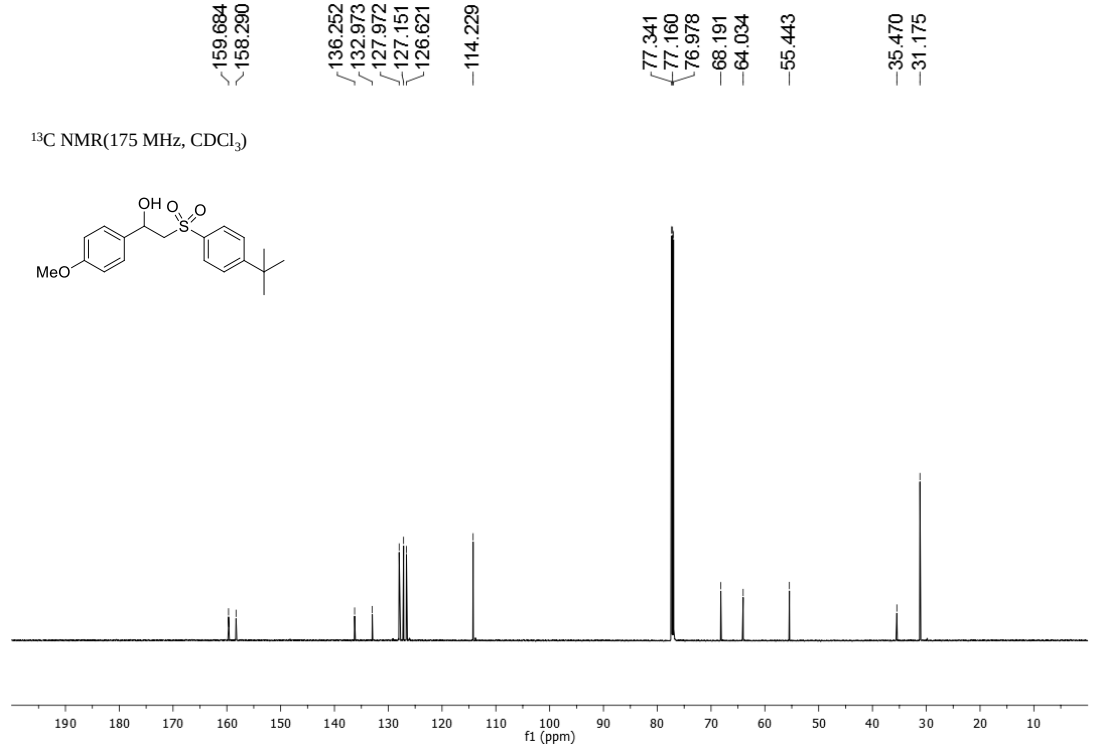


Figure 2A.32. ^{13}C NMR spectrum of 2-((4-(tert-butyl)phenyl)sulfonyl)-1-(4-methoxyphenyl)ethanol **(3mc)**

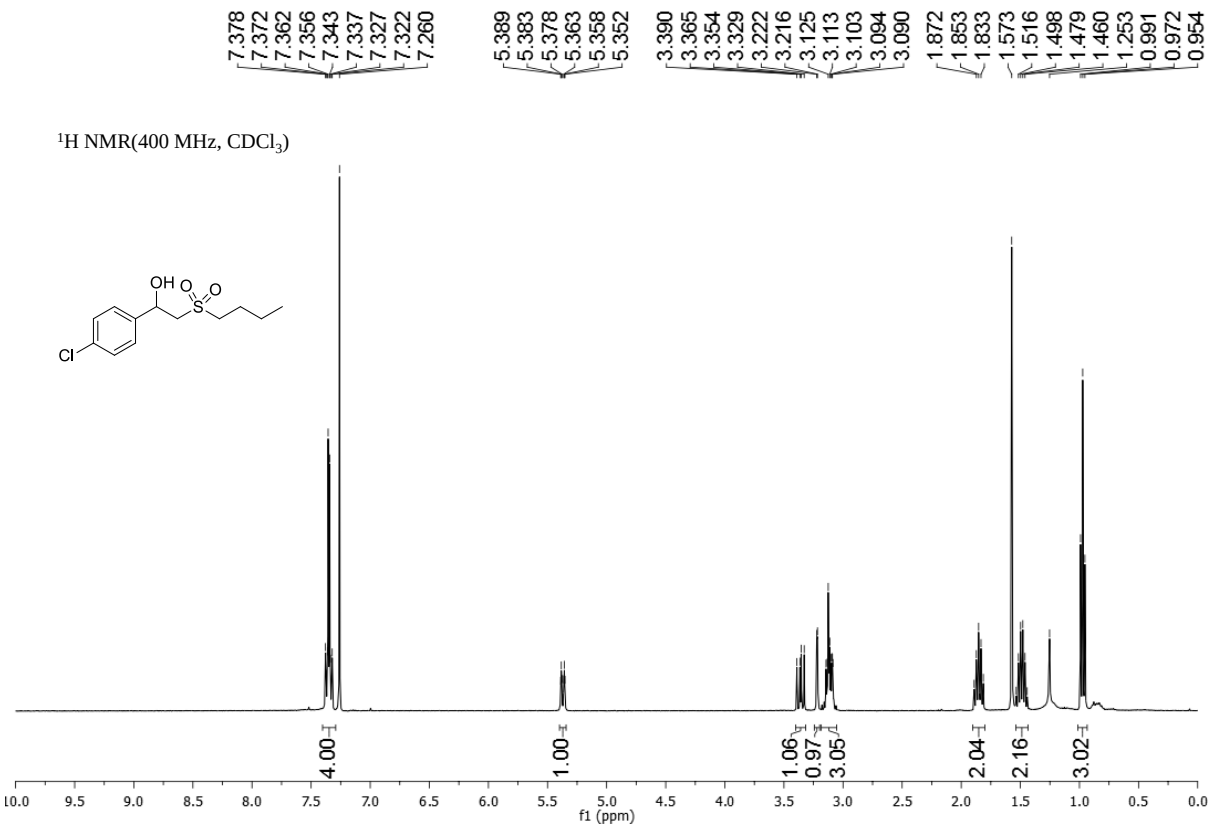


Figure 2A.33. ^{1}H NMR spectrum of 2-(butylsulfonyl)-1-(4-chlorophenyl)ethanol **(3bd)**

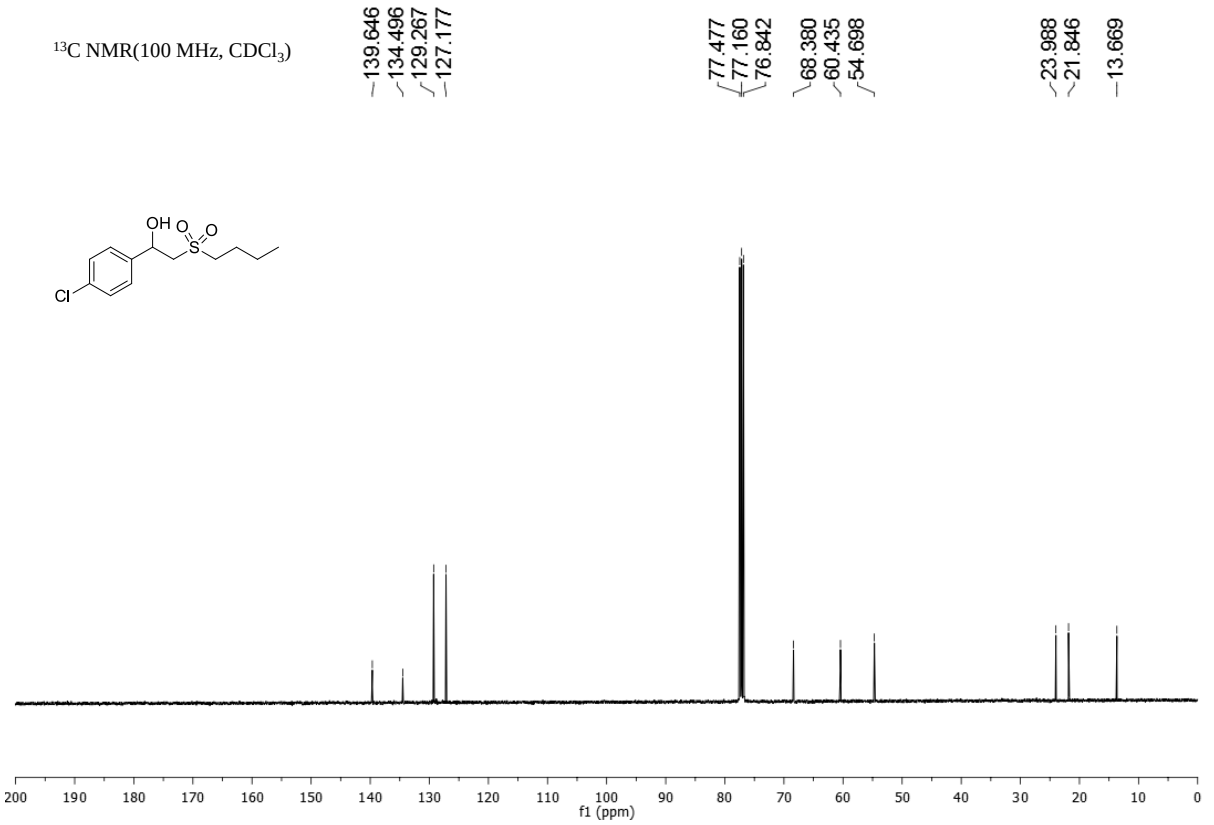
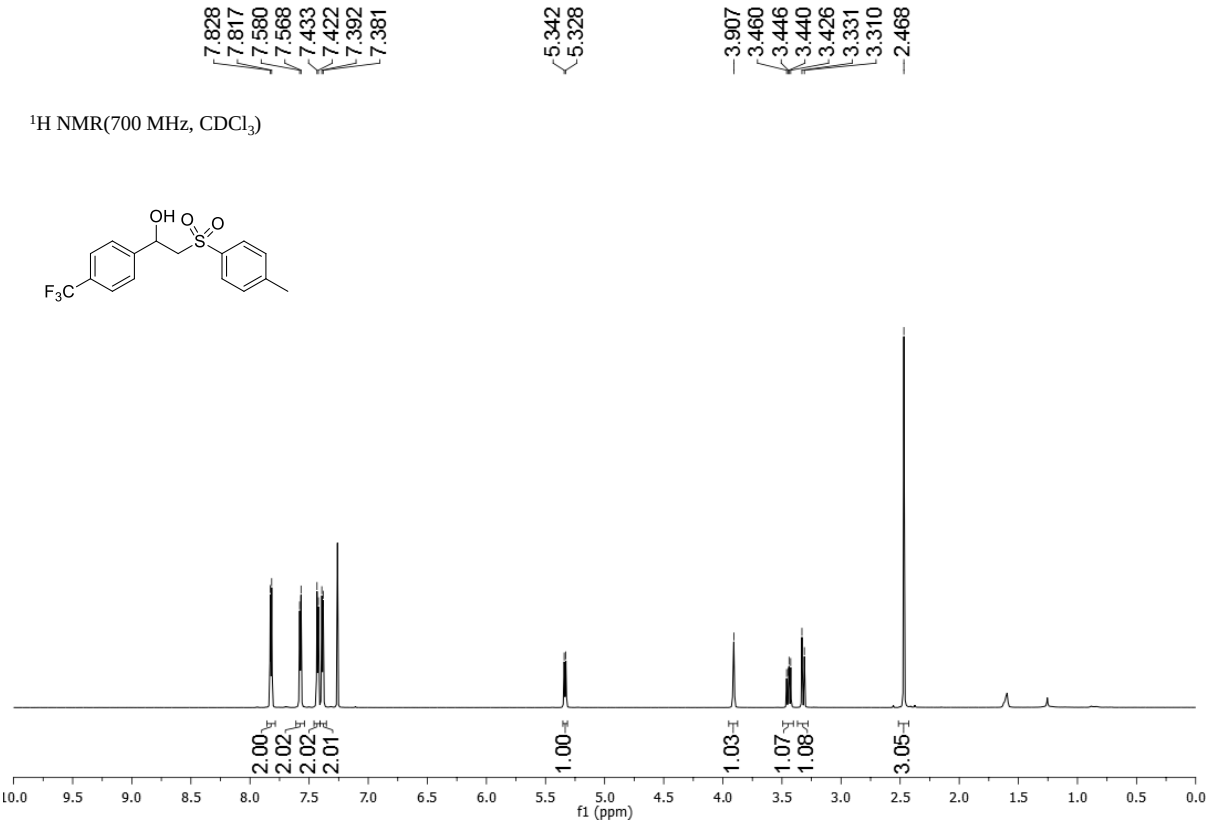
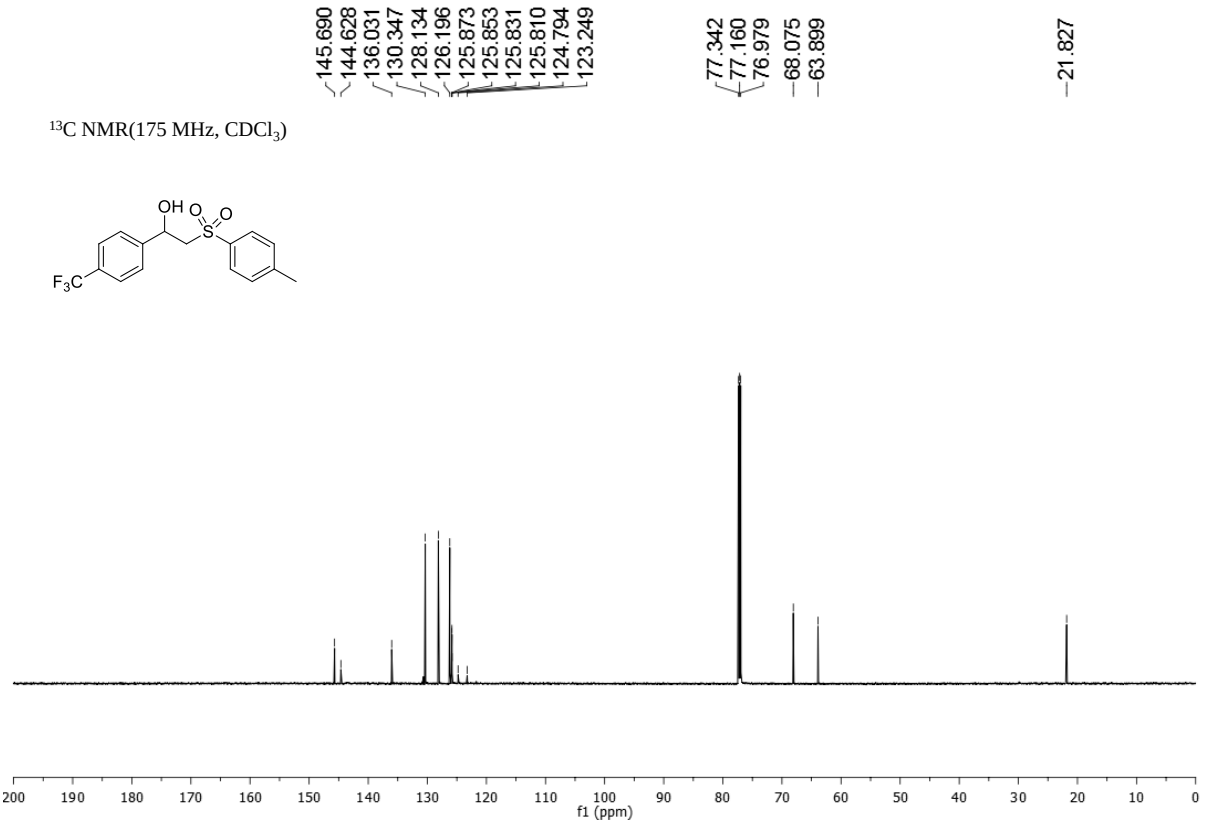


Figure 2A.34. ^{13}C NMR spectrum of 2-(butylsulfonyl)-1-(4-chlorophenyl)ethanol **(3bd)**



^{1}H NMR(700 MHz, $CDCl_3$)

Figure 2A.35. ^{1}H NMR spectrum of 2-tosyl-1-(4-(trifluoromethyl)phenyl)ethanol **(3na)**



^{13}C NMR(175 MHz, $CDCl_3$)

Figure 2A.36. ^{13}C NMR spectrum of 2-tosyl-1-(4-(trifluoromethyl)phenyl)ethanol **(3na)**

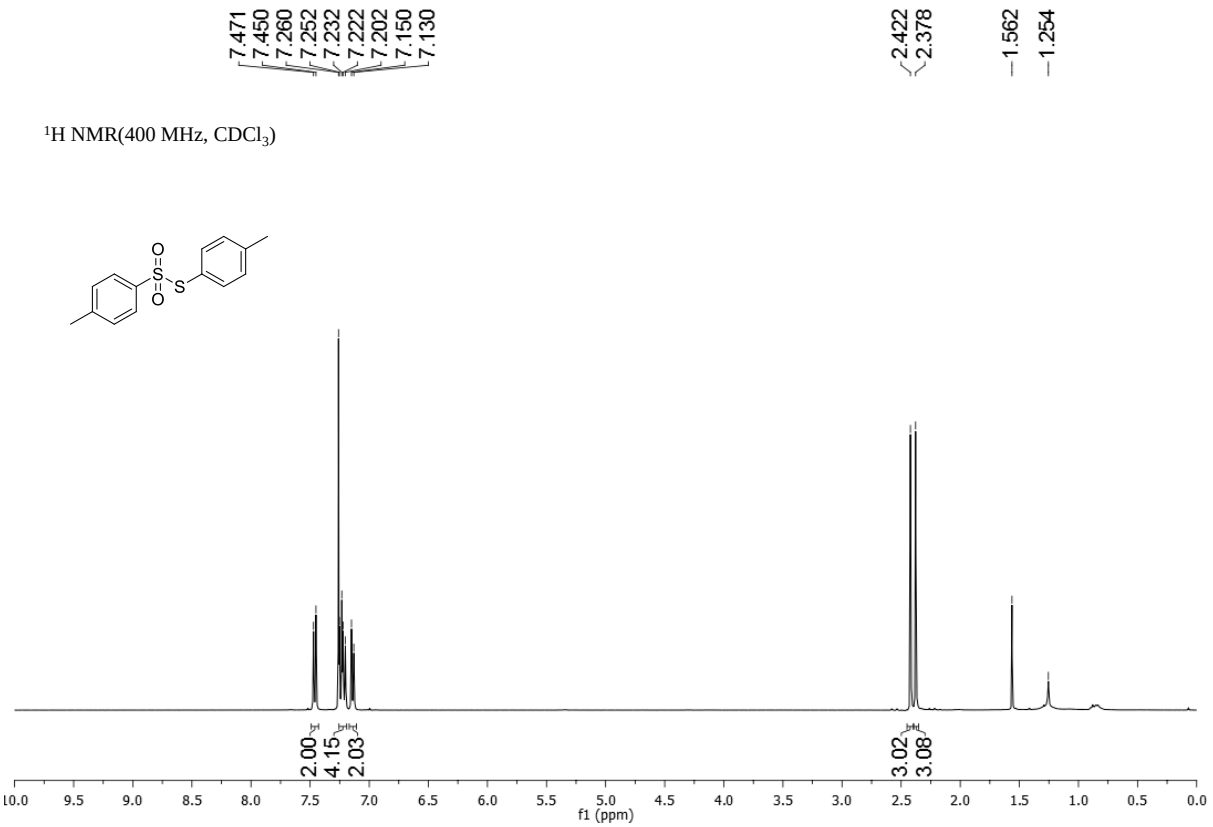


Figure 2A.37. ^{1}H NMR spectrum of S-p-tolyl 4-methylbenzenesulfinothioate

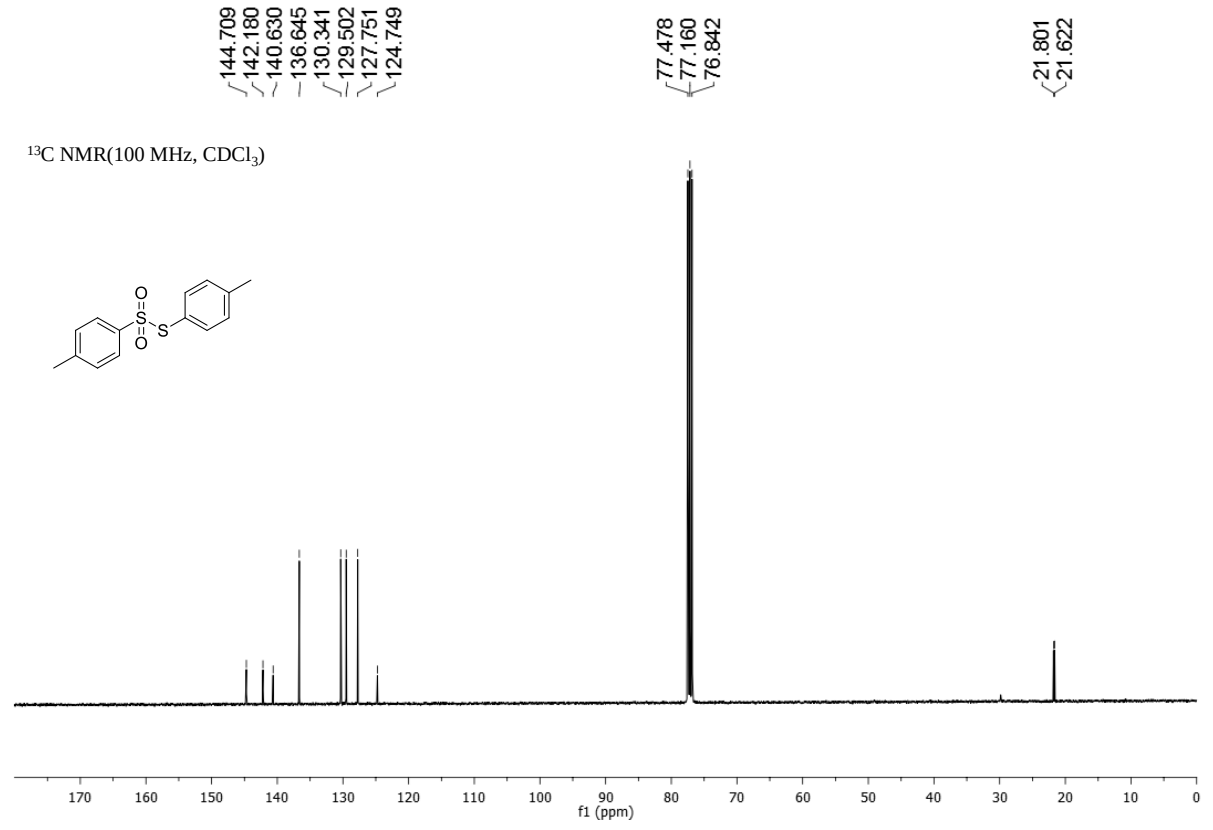


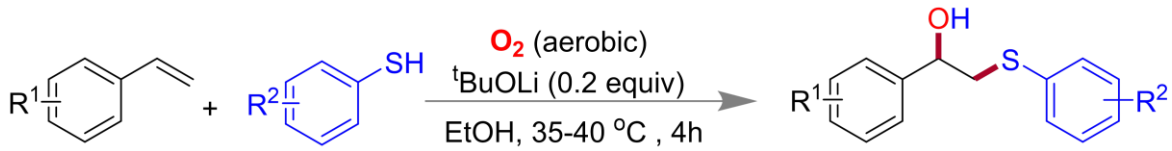
Figure 2A.38. ^{13}C NMR spectrum of S-p-tolyl 4-methylbenzenesulfinothioate

CHAPTER 2B

^{t}BuOLi Promoted Aerial Dioxygen Activation: A Convenient Method to Access the β-hydroxysulfides

2B.1 ABSTRACT

2



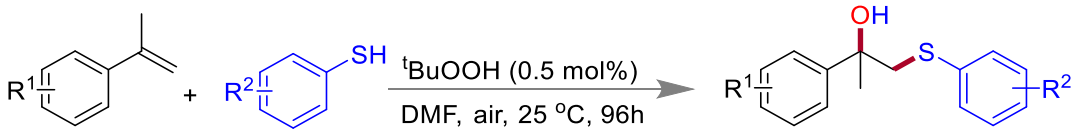
Herein, we have disclosed a methodology for the preparation of *β*-hydroxysulfides derivative from styrene and thiophenol by activating aerial dioxygen using catalytic amount of base. The reactions were performed in open air at the ambient temperature and found to be eco-friendly with the environment. Different functional group attached with the styrene or thiophenol moiety are well tolerated the reaction condition, which gave us a library of *β*-hydroxysulfides derivative. Radical trapping and ^{18}O labelling experiments helps to established the mechanistic pathway.

2B.2 INTRODUCTION

Owing to readily availability and versatility, olefins draw a significant attention in synthetic community in broad array of chemical transformations[69]. 1,2-Difunctionalization of olefins is one of the most powerful strategy[70,71] for the introduction of functional groups into desire compounds. Mostly transition metal catalysts have been elegantly exploited for the introduction of two new vicinal functional groups concurrently. Despite of the flexibility and efficiency of the transformation, these method lead to the difficult purification of the desire products from large amount of toxic by-products and residual catalysts. These disadvantages have led to the emergence of metal-free sustainable approach.

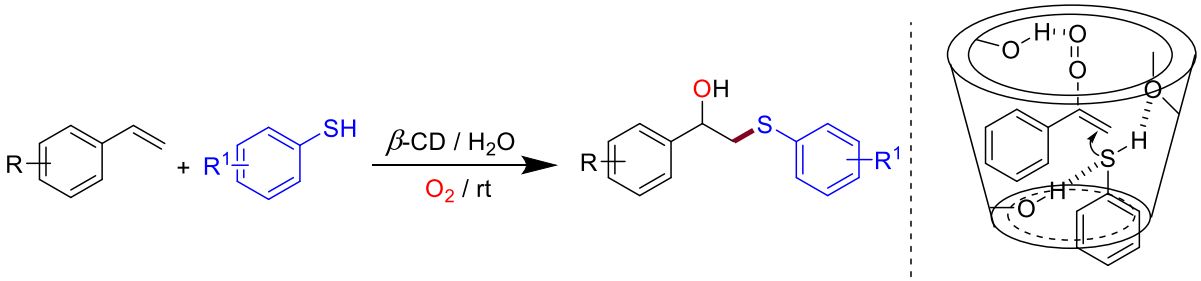
In recent year, base promoted radical reaction[72,73] has been increasingly explored to supplant the toxic heavy metals. Introduction of aerial dioxygen as an oxidant in organic synthesis has drawn substantial interest of chemist for the development of green and sustainable protocols. Not only as terminal oxidant, dioxygen is used an ideal oxygen source for the functionalization of organic molecules. Dioxygen activation methodology was explored by using transition metal catalysis[9-12,15,74], photoredox catalysis[75-77] and grown a challenging topic under metal free condition.

β-Hydroxysulfides are an important class of compound due to its versatile nature. It was extensively used in medicinal[78-80] and pharmaceutical[81-84] science and also served as useful building block in organic synthesis[85-87]. *β*-Hydroxysulfides was found as a convenient intermediates for the synthesis of many natural products[88], biologically active heterocycles[89], pharmaceuticals active compound[84]. Subsequently, numerous synthetic methods have been documented in the literature involving epoxide ring opening with thiophenol and co-oxidation reaction of thiophenol and alkene.



Scheme 2B.1. Zou's approach for TBHP catalyzed hydroxysulfurization of styrenes.

Zou and co-worker have reported oxidative hydroxysulfurization of styrenes using catalytic amount of TBHP as radical initiator in DMF at room temperature (Scheme 2B.1). They have proposed that the reaction may proceed *via* formation of hydroperoxide radical intermediate.



Scheme 2B.2. Rao's approach for Cyclodextrin catalyzed hydroxysulfurization of styrenes.

β- Hydroxysulfides were also reported by Rao's group using supramolecular catalysis (Scheme 2B.2). They showed that Cyclodextrin catalyzed reaction of styrene and thiophenol under aerobic condition. Here cyclodextrin, being an excellent host formed a host-guest complex through its hydrophobic cavities. It stabilized thiophenol and aerobic molecular oxygen through intermolecular hydrogen bonding. Consequently, hydrophobic styrene was stabilized through complexation with host molecule. Following, favourable nucleophilic attack was occurred by thiol to maintain proper regioselectivity. Finally oxygen insertion from the cavity led to formation of *β*- Hydroxysulfides product.

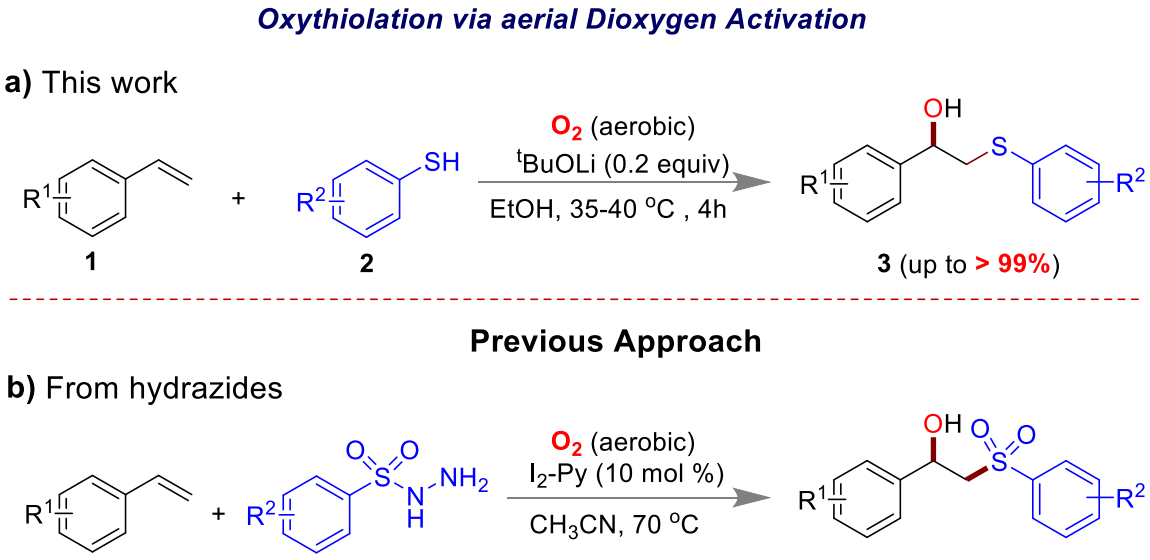


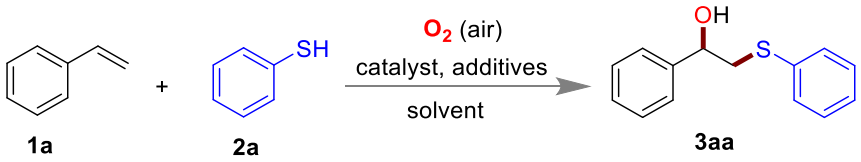
Figure 2B.1. *β*-Hydroxysulfide synthesis by dioxygen activation.

With our continuing interest in radical chemistry, we disclosed herein ^{t}BuOLi catalysed an efficient aerial dioxygen activation method for oxythiolation reaction towards the synthesis of β-hydroxy sulfide from unactivated olefins under transition metal free condition (Figure 2B.1a). Our previous approach was iodine catalyzed oxysulfonylation of olefins from sulfonyl hydrazide via dioxygen activation has been depicted in Figure 2B.1b. The aerial oxygen was activated for the introduction of -OH group at benzylic position and near quantitative synthesis of *β*-hydroxysulfides was achieved from styrenes and thiophenol using ^{t}BuOLi (20 mol%) as catalyst.

2B.3 RESULT AND DISCUSSION

We started our study with styrene (1a) and thiophenol (2a) as model substrates to test the reaction. Delightedly, 1a and 2a smoothly reacted to afford the desired *β*-hydroxysulfide (3aa) in 92% yield in the presence of 20 mol% of ^{t}BuONa after 4h in benzene at room temperature under aerobic condition (Table 2B, Entry 1).

Table 2B.1. Optimization Condition of oxythiolation reaction[a]



1a 2a 3aa

Entry	Additive (equiv)	Solvent[b]	3aa (%)
1	^{t}BuONa (0.2)	C_6H_6,	92
2	^{t}BuOK (0.2)	C_6H_6	90
3	^{t}BuOLi (0.2)	C_6H_6	96
4	NaOH (0.2)	EtOH	44
5	K_2CO_3 (1.0)	EtOH	55
6	--	EtOH	22

7	^{t}BuOLi (0.2)	DCE	25
8	^{t}BuOLi (0.2)	DMSO	38
9	^{t}BuOLi (0.2)	H_2O	10
10	^{t}BuOLi (0.2)	EtOH	98

[a]**Condition**: 1.0 equiv of **1a** and 4.0 equiv of **2a** were used and the reactions were done at 35-40 ºC; [b]Under aerobic condition, if not specified.

To get the optimized reaction condition several screenings have been done. Surprisingly when excess amount of thiophenol was used in presence of 20 mol% of lithium tert-butoxide in ethanol the yield of 3aa was drastically increased to 99% (Table 2B.1, Entry 10). Furthermore several other bases, such as ^{t}BuONa, ^{t}BuOK, NaOH, K_2CO_3 (entry 1-5) have been used but no promising the yields were obtained than ^{t}BuOLi. Further screening of a range of common solvents revealed that the choice of ethanol was the best for this reaction (Table 2B.1, Entry 7- 9). In absence of ^{t}BuOLi, the reaction provided 22% yield of the product, led to understand the necessity of ^{t}BuOLi in this transformation (Table 2B.1, Entry 6). Besides, when the reaction was performed under N_2 atmosphere, no desired product was detected which confirmed the importance of the presence of molecular oxygen.

With the preliminary findings, next we investigate the scope of the reaction between various olefins and thiophenol and the results are presented in Figure 2B.2. In the presence of 20 mol% of $^{t-}$BuOLi, under aerobic condition a range of unactivated olefins smoothly reacted with thiophenol to afford structurally diverse *β*-hydroxysulfides in good to excellent yield. We explored our method to series of olefins bearing electron-donating groups (R = –OMe, napthyl, –Ph, –Me) and electron-withdrawing groups (R = –NO2, –CN, $–CF_3$) to prepare an array of *β*-hydroxysulfide. Delightfully, Cl and Br substituents on phenyl ring were also well tolerated which enable to further functionalization. Bulky substrates, 2-methylstyrene and

satirically congested 2,4,6-trimethyl styrene were also efficiently reacted with thiophenol giving the respective products in 96% and 76% yield. It is noteworthy that α-methylstyrene was also worked well to afford sterically congested teriary β-hydroxysulfides (3ea) in very good yield. Further we tested our method on various thiophenol. The reaction was also found to be successful with different thiophenols. Aliphatic alkenes were failed to produce any dioxygen activated products.

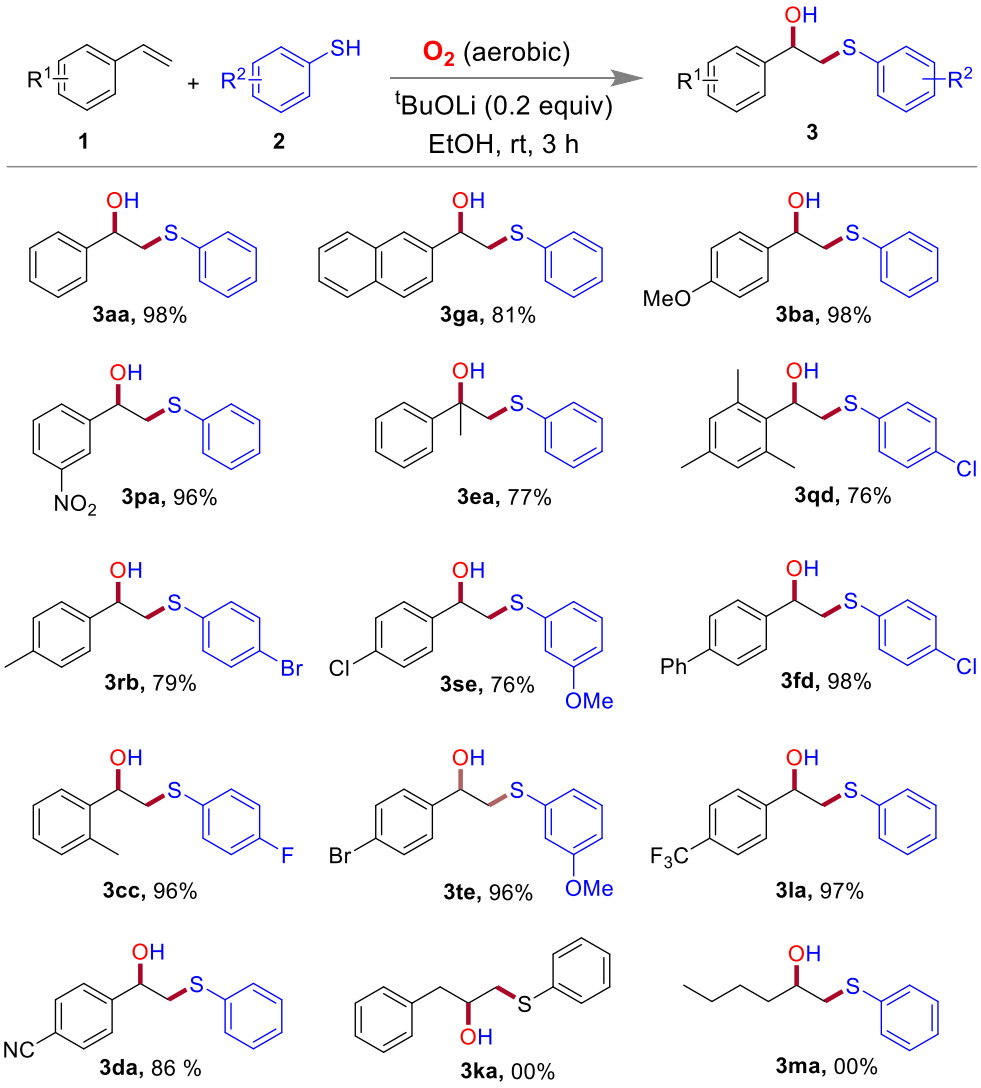


Figure 2B.2. Substrate scope for oxythiolation reaction.

Control experiments (Figure 2B.3) helped to establish the mechanism of the reaction. The dioxygen activated product 3aa was obtained in near quantitative yield from styrene 1a and

thiol 2a in the solvent ethanol with 0.2 equiv of ^{t}BuOLi. However, when the same reaction was performed with 1,2-diphenyldisulfide instead of 2a, no product could be obtained (Figure 2B.3.a). This clearly indicated that presence of thiol was necessary for the reaction. TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) radical trapping experiment (Figure 2B.3.b) further confirmed that reaction proceeded *via* radical pathway.

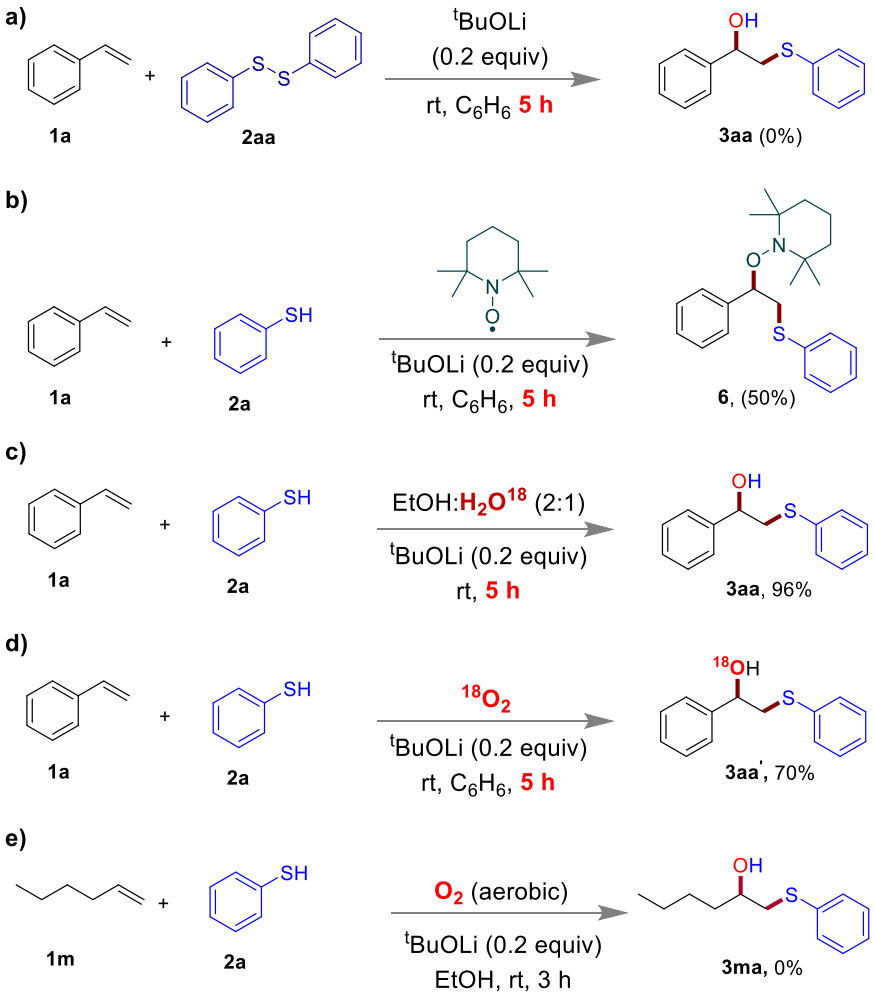


Figure 2B.3. Control experiment.

The hypothesis of radical dioxygen activation was further proved from the ^{18}O labelling experiments[29] shown in Figure 2B.3.c,d. Under optimized condition, when the reaction of 1a and 2a was performed in solvent EtOH:H_2O^{18} (2:1), the reaction failed to produce any ^{18}O incorporated *β*-hydroxysulfide, instead ^{16}O incorporated 3aa was isolated in 96% yield. However, under $^{18}O_2$ atmosphere, reaction of 1a and 2a afforded 70% of ^{18}O incorporated

3aa. Unsuccessful result was obtained when aliphatic alkenes were employed for the reaction (Figure 2B.3.e). This observation further confirmd the key role of the formation benzylic radical intermediate in the dioxygen activation reaction

A plausible mechanism of the aerial dioxygen activation (Figure 2B.4) was proposed based on literature precedence and controlled experiments (Figure 2B.3). The TEMPO (Figure 2B.3.a) radical experiments supported for the formation of a stable benzylic radical intermediate (IV, Figure 2B.4). Towards benzylic radical intermediate IV, two possible pathways (path a or b) could be anticipated. In absence of base ^{t}BuOLi, 1a and 2a led to formation of significant quantity (ca. 22%) of *β*-hydroxysulfides 3aa and supported the path b. In presence of base ^{t}BuOLi indicated for the **path a** to be followed. The benzylic radical intermediate IV reacted with aerial oxygen led to the final product 3 *via* the oxygenated intermediates V and VI.

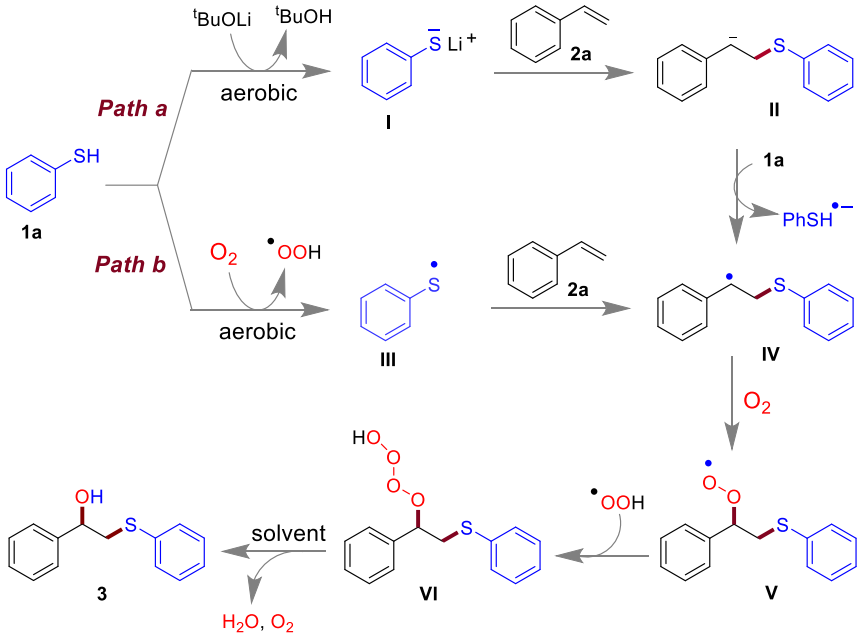


Figure 2B.4. Plausible mechanism of the aerial dioxygen activation.

2B.4 CONCLUSIONS

In conclusion, we have developed an operationally simple and efficient greener method for regioselective intermolecular oxythiolation method to construct new C–O and C–S bond in One pot for the synthesis of *β*-hydroxysulfide using dioxygen as the sole oxidant. Diverse array of olefins smoothly tolerated the reaction condition to afford secondary and tertiary β-hydroxysulfide in good to excellent yield. Use of ^{t}BuOLi and oxygen hastened the importance of this simple protocol in pharmaceutical industry by avoiding the tedious metal leaching process. Developed method revealed iodine triggered dioxygen activation under mild reaction conditions. Radical trapping and ^{18}O labelling experiments established the plausible reaction pathway for this transformation.

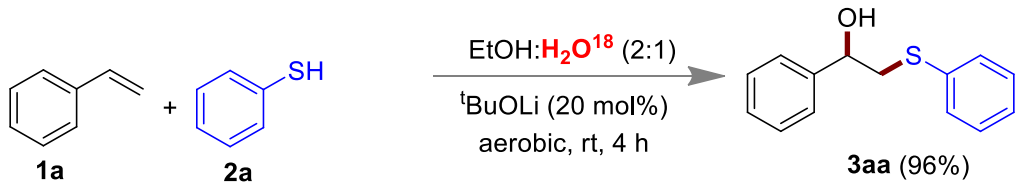
2B.5 EXPERIMENTAL SECTION

General information. All the chemicals were purchased from the commercially available sources and used without further purification. The reactions were done mainly under open atmosphere. Column chromatographic purification of the compounds were performed using (230-400) mess silica gel and hexane/ethyl acetate as an eluent. ^{1}H and ^{13}C spectra of the compounds were recorded on Bruker 400 and 700 MHz instrument at 25 ^{o}C. The chemical shift value (δ, ppm) were reported with respect to the residual chloroform (7.26 for ^{1}H and 77.16 ppm for ^{13}C). High resolution mass spectroscopy (HR-ESIMS) was recorded on ESI-TOF (Time-of-flight) mass spectroscopy.

General procedure for the preparation of *β*-hydroxysulfides (3). An oven dried round bottom flux was charged with thiophenol (0.213 μL, 2.09 mmol) and ^{t}BuOLi (8.5 mg, 0.104 mmol) in ethanol solvent. Then styrene (60 μL, 0.522 mmol) was added and the resulting mixture was stirred for 4 h at room temperature (35-40 ^{o}C) in open atmosphere. After that the mixture was concentrated under vacuum. The mixture was diluted with dichloromethane and

washed with water and dried over anhydride sodium sulphate. The resulting mixture was purified by silica gel column chromatography hexane/ethyl acetate mixture an eluent.

H_2O^{18} and $^{16}O_2$ labelling experiments.



Scheme 2B.3. Isotope labelling experiments (H_2O^{18})

In an oven dried Schlenk tube charged with dry ethanol, thiophenol (0.213 µL, 2.09 mmol), lithium tert-butoxide (8.5 mg, 0.104 mmol) and styrene (60 µL, 0.522 mmol). Then 0.5 mL of H_2O^{18} was added to the mixture and stirred for 4 h at room temperature in open atmosphere. Then the resulting mixture was concentrated under vacuum and diluted with dichloromethane, washed with water and dried over anhydride sodium sulphate. After that the mixture was purified with silica gel column chromatography to afford the product 3aa in 94% yield.

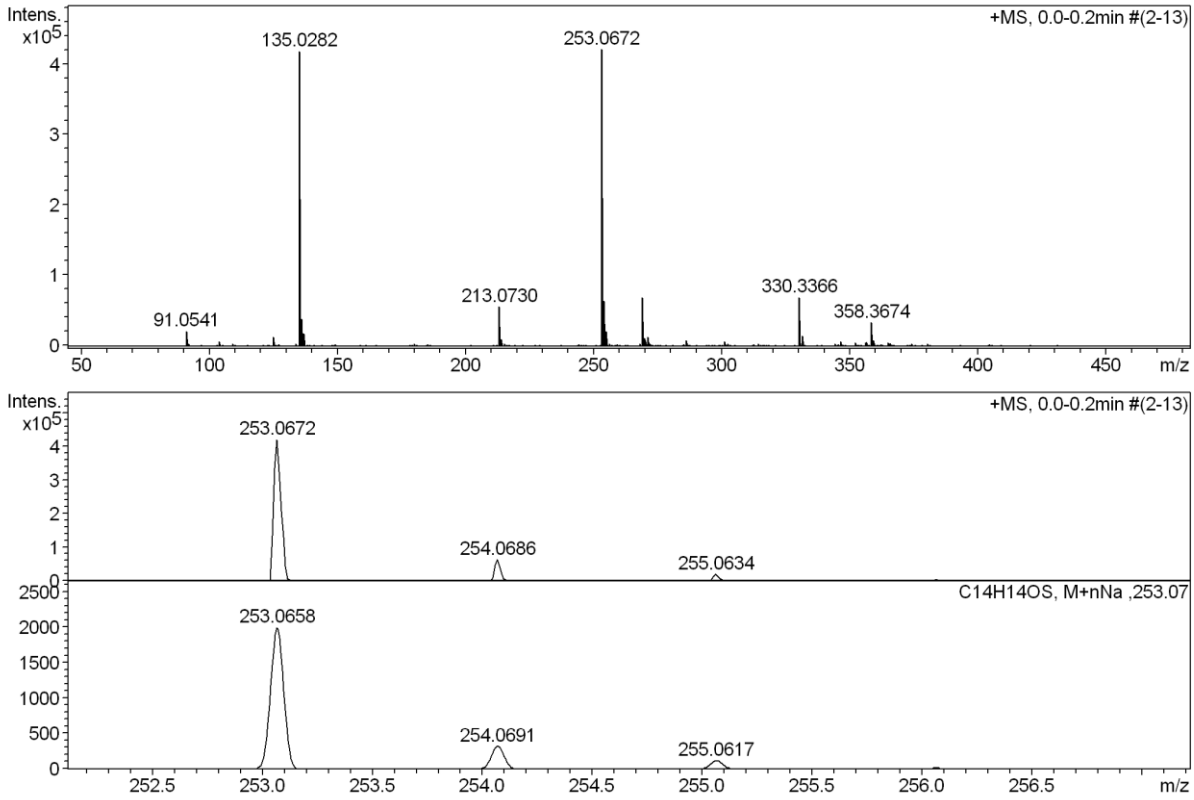
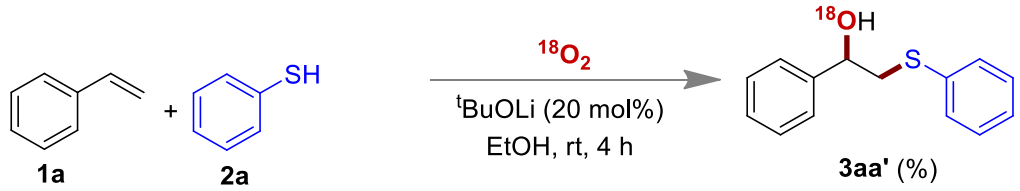


Figure 2B.5 The ESI-TOF Mass spectra of **3aa** in $(M + Na)^+$ mode.

O^{18} Labelling experiments.



Scheme 2B.4. Isotope labelling experiments (O^{18})

An oven dried Schlenk tube was charged with dry ethanol, thiophenol (0.213 µL, 2.09 mmol), ^{t}BuOLi (8.5 mg, 0.104 mmol) and styrene (60 µL, 0.522 mmol) in an argon atmosphere. Then the schlenk tube was purged with labelling O^{18} isotope. The mixture was stirred for 4h at room temperature. Then the resulting mixture was concentrated with vacuum and diluted with dichloromethane, washed with water and dried over sodium sulphate. Column chromatography purification using silica gel affords the product 3aa' 70% yield.

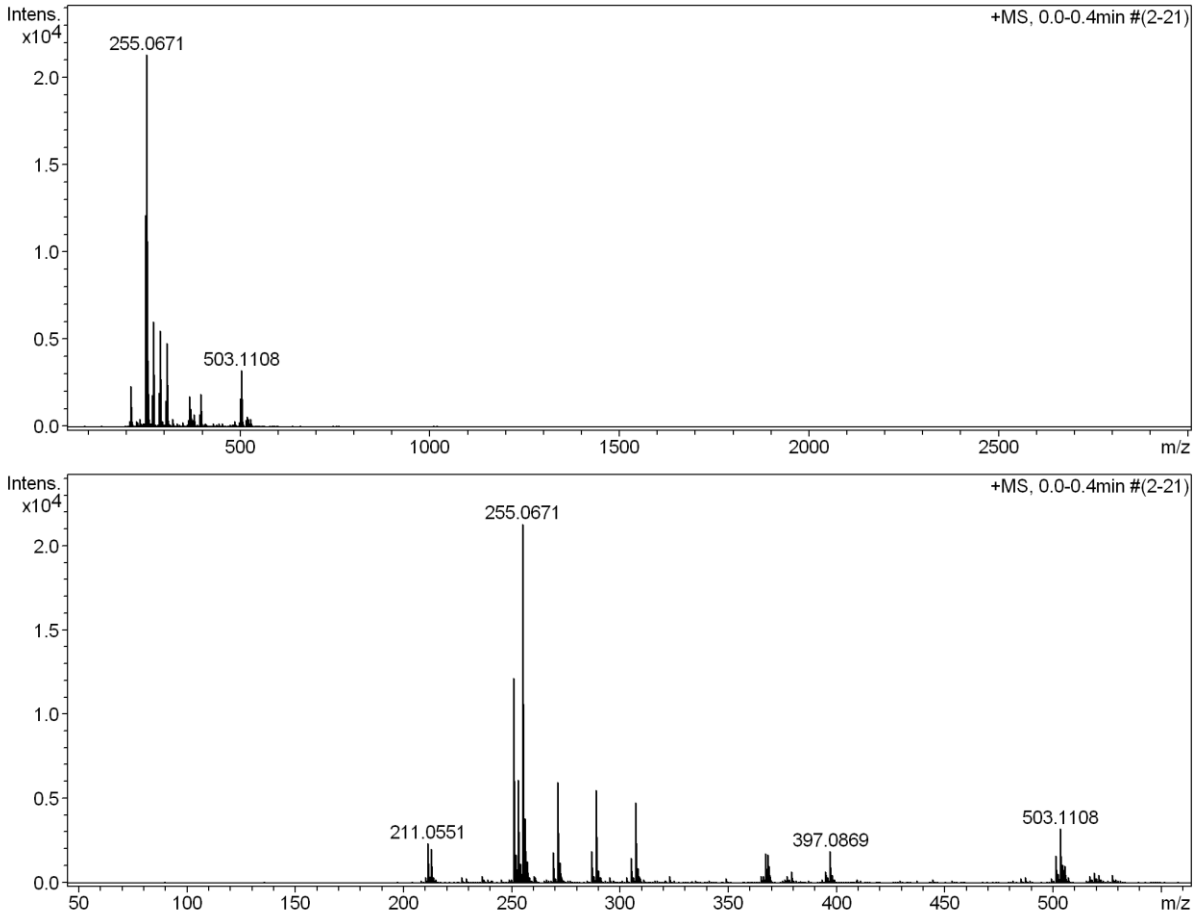


Figure 2B.6 The ESI-TOF Mass spectra of **3aa′** in $(M + Na)^+$ mode.

CHARACTERIZATION DATA:

1-Phenyl-2-(phenylthio)ethanol (3aa):[59] R_f = 0.2 (5% ethyl acetate in hexane); colorless liquid; yield 98% (119 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.31 – 7.27 (m, 4H), 7.25 – 7.18 (m, 3H), 7.18 – 7.14 (m, 1H), 4.65 (dd, *J* = 6.8, 2.0 Hz, 1H), 3.25 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.03 (dd, *J* = 13.6, 9.4 Hz, 1H), 2.86 (d, -OH, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 135.0, 130.3, 129.2, 128.7, 128.1, 126.9, 126.0, 71.8, 44.1; HRMS (ESI-TOF) calcd for $C_{14}H_{14}SO$ $(M + Na)^+$ 253.0658, found 253.0686.

1-(Naphthalen-2-yl)-2-(phenylthio)ethanol (3ga):[90] R_f = 0.2 (5% ethyl acetate in hexane); colorless liquid; yield 81% (89 mg);^{1}H NMR (700 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 4H), 7.53 – 7.45 (m, 5H), 7.38 – 7.32 (m, 2H), 7.29 – 7.27 (m, 1H), 4.91 (d, *J* = 9.0 Hz, 1H), 3.43 (dd, *J* = 14.0, 3.5 Hz, 1H), 3.19 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.99 (s, -OH, 1H); ^{13}C NMR (175 MHz,

$CDCl_3$) δ 139.6, 134.9, 133.4, 133.3, 130.5, 129.3, 128.6, 128.1, 127.9, 127.0, 126.4, 126.2, 124.9, 123.9, 71.9, 44.2; HRMS (ESI-TOF) calcd for $C_{18}H_{16}OS$ $(M + Na)^+$ 303.0814, found 303.0797.

1-(4-Methoxyphenyl)-2-(phenylthio)ethanol (3ba):[91] R_f = 0.2 (10% ethyl acetate in hexane); colorless liquid; yield 98% (115 mg);^{1}H NMR (700 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.27 (m, 2H), 7.27 – 7.23 (m, 1H), 6.93 – 6.86 (m, 2H), 4.70 (dd, *J* = 9.8, 4.2 Hz, 1H), 3.82 (s, 3H), 3.31 (dd, *J* = 14.0, 3.5 Hz, 1H), 3.12 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.82 (s, -OH, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.5, 135.1, 134.4, 130.3, 129.3, 127.3, 126.9, 114.1, 71.5, 55.4, 44.0.

1-(3-Nitrophenyl)-2-(phenylthio)ethanol (3pa): R_f = 0.4 (20% ethyl acetate in hexane); light yellow colour liquid; yield 96% (116 mg);^{1}H NMR (700 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.16 – 8.09 (m, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.28 – 7.26 (m, 1H), 4.88 – 4.70 (m, 1H), 3.34 (dd, *J* = 14.0, 3.6 Hz, 1H), 3.11 (s, -OH, 1H), 3.07 (dd, *J* = 14.0, 8.4 Hz, 1H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 148.5, 144.3, 134.0, 132.1, 131.0, 129.6, 129.5, 127.5, 123.0, 121.2, 70.7, 44.4; IR (KBr) $\bar{\upsilon}$ 3437 (br), 3037, 2920, 1582, 1530, 1479,; HRMS (ESI-TOF) calcd for $C_{14}H_{13}NO_3S$ $(M + Na)^+$ 298.0508, found 298.0506.

2-Phenyl-1-(phenylthio)propan-2-ol (3ea):[91] R_f = 0.3 (5% ethyl acetate in hexane); colorless liquid; yield 77% (86 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.54 – 7.42 (m, 2H), 7.41 – 7.30 (m, 4H), 7.29 – 7.24 (m, 3H), 7.21 – 7.17 (m, 1H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.38 (d, *J* = 14.0 Hz, 1H), 2.92 (brs, -OH, 1H), 1.65 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 146.3, 136.6, 130.1, 129.1, 128.4, 127.2, 126.6, 124.9, 74.1, 49.7, 29.5.

2-((4-Chlorophenyl)thio)-1-mesitylethanol (3qd): R_f = 0.25 (5% ethyl acetate in hexane); colorless liquid; yield 76% (86 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.31 – 7.27 (m, 2H), 6.82 (s, 2H), 5.13 (dd, *J* = 9.8, 4.2 Hz, 1H), 3.40 (dd, *J* = 14.0, 9.8 Hz, 1H),

3.20 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.59 (brs, -OH, 1H), 2.32 (s, 6H), 2.26 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 137.4, 136.4, 134.1, 133.78, 133.0, 131.9, 130.4, 129.3, 69.4, 40.7, 20.9, 20.8; IR (KBr) ῡ 3418 (br), 2921, 1609, 1506, 1475; HRMS (ESI-TOF) calcd for $C_{17}H_{19}ClOS$ $(M + Na)^+$ 329.0737, found 329.0728.

2-((4-Bromophenyl)thio)-1-(*p*-tolyl)ethanol (3rb):[92] R_f = 0.2 (5% ethyl acetate in hexane); colorless liquid; yield 79% (116 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.29 – 7.26 (m, 2H), 7.26 – 7.22 (m, 2H), 7.20 – 7.15 (m, 2H), 4.84 – 4.64 (m, 1H), 3.27 (dd, *J* = 14.0, 3.6 Hz, 1H), 3.13 (dd, *J* = 14.0, 9.8 Hz, 1H), 2.71 (brs, -OH, 1H), 2.36 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 139.2, 138.0, 134.6, 132.2, 131.6, 129.4, 125.9, 120.7, 71.9, 43.9, 21.3.

1-(4-Chlorophenyl)-2-((3-methoxyphenyl)thio)ethanol (3se): R_f = 0.15 (5% ethyl acetate in hexane); colorless liquid; yield 79% (111 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.94 (s, 1H), 6.82 – 6.74 (m, 1H), 4.71 (dd, *J* = 9.8, 4.2 Hz, 1H), 3.80 (s, 3H), 3.28 (dd, *J* = 14.0, 3.6 Hz, 1H), 3.05 (dd, *J* = 14.0, 9.8 Hz, 1H), 2.95 (brs, -OH, 1H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.1, 140.7, 136.0, 133.8, 130.2, 128.8, 127.4, 122.4, 115.8, 112.6, 71.2, 55.4, 43.9; IR (KBr) ῡ 3427 (br), 3001, 2934, 1589, 1479; HRMS (ESI-TOF) calcd for $C_{15}H_{15}ClO_2S$ $(M + Na)^+$ 317.0373, found 317.0356.

1-([1,1'-Biphenyl]-4-yl)-2-((4-chlorophenyl)thio)ethanol (3fd): R_f = 0.2 (5% ethyl acetate in hexane); colorless liquid; yield 98% (112 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 4H), 7.47 – 7.43 (m, 2H), 7.43 – 7.40 (m, 2H), 7.39 – 7.31(m, 3H), 7.31 – 7.27 (m, 2H), 4.81 – 4.75 (m, 1H), 3.33 (dd, *J* = 14.0, 3.6 Hz, 1H), 3.19 – 3.14 (m, 1H), 2.79 (brs, -OH, 1H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 141.2, 141.1, 140.8, 133.7, 133.0, 131.7, 129.4, 128.9, 127.6, 127.5, 127.2, 126.4, 71.8, 44.2; IR (KBr) ῡ 3404 (br), 3054, 2920, 1622, 1485, 1475; HRMS (ESI-TOF) calcd for $C_{20}H_{17}ClOS$ $(M + Na)^+$ 363.0581 found 363.0577.

2-((4-Fluorophenyl)thio)-1-(o-tolyl)ethanol (3cc): R_f = 0.2 (5% ethyl acetate in hexane); colorless liquid; yield 96% (117 mg);^{1}H NMR (700 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.06 – 6.98 (m, 2H), 4.89 (d, *J* = 9.8 Hz, 1H), 3.20 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.98 (dd, *J* = 14.0, 9.8 Hz, 1H), 2.87 (brs, 1H), 2.14 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 162.4 (d, J_{CF1} = 247.6 Hz), 140.1, 134.5, 133.7 (d, J_{CF3} = 8.2 Hz), 130.6, 129.9 (d, J_{CF4} = 3.4 Hz), 127.8, 126.6, 125.4, 116.3 (d, J_{CF2} = 21.8 Hz), 68.3, 44.3, 18.9; IR (KBr) ῡ 3408 (br), 3065, 2923, 1589, 1487; HRMS (ESI-TOF) calcd for $C_{15}H_{15}FOS$ $(M + Na)^+$ 285.0720, found 285.0701.

1-(4-Bromophenyl)-2-((3-methoxyphenyl)thio)ethanol (3te): R_f = 0.15 (5% ethyl acetate in hexane); colorless liquid; yield 96% (148 mg);^{1}H NMR (700 MHz, $CDCl_3$) δ 7.46 (d, *J* = 9.1 Hz, 2H), 7.25 – 7.19 (m, 3H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.93 (s, 1H), 6.80 – 6.76 (m, 1H), 4.69 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.80 (s, 3H), 3.27 (dd, *J* = 14.0, 3.5 Hz, 1H), 3.04 (dd, *J* = 14.0, 9.8 Hz, 1H), 2.99 (s, 1H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.0, 141.2, 136.0, 131.7, 130.1, 127.7, 122.3, 121.9, 115.8, 112.6, 71.2, 55.4, 43.8; IR (KBr) ῡ 3429 (br), 3061, 3001, 2957, 1589, 1574, 1479; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrO_2S$ $(M + Na)^+$ 360.9868, found 360.9868

2-(Phenylthio)-1-(4-(trifluoromethyl)phenyl)ethanol (3la): R_f = 0.2 (5% ethyl acetate in hexane); colorless liquid; yield 97% (118 mg);^{1}H NMR (700 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.36 – 7.29 (m, 2H), 7.28 – 7.25 (m, 1H), 4.81 – 4.72 (m, 1H), 3.32 (dd, *J* = 14.0, 3.5 Hz, 1H), 3.05 – 3.05 (m, 1H), 3.04 (s, 1H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 146.2, 134.4, 130.7, 130.2 (q, $^2J_{FC}$ = 32 Hz), 129.4, 127.3, 126.3, 124.2 (q, $^1J_{FC}$ = 270 Hz), 125.6 (q, $^3J_{FC}$ = 3.7 Hz), 71.1, 44.3; IR (KBr) ῡ 3408 (br), 3059, 2920, 1619, 1583, 1480; HRMS (ESI-TOF) calcd for $C_{15}H_{13}F_3OS$ $(M + Na)^+$ 321.0531 found 321.0544.

4-(1-Hydroxy-2-(phenylthio)ethyl)benzonitrile (3da):[91] R_f = 0.1 (5% ethyl acetate in hexane); colorless liquid; yield 86% (119 mg);^{1}H NMR (700 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.28 – 7.25 (m, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 3.30 (dd, *J* = 14.0, 3.5 Hz, 1H), 3.16 (s, 1H), 3.04 (dd, *J* = 14.0, 9.8 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 147.5, 134.2, 132.4, 130.8, 129.4, 127.4, 126.7, 118.8, 111.7, 71.0, 44.2; HRMS (ESI-TOF) calcd for $C_{15}H_{13}NOS$ $(M + Na)^+$ 278.610, found 278.0617.

2,2,6,6-Tetramethyl-1-(1-phenyl-2-(phenylthio)ethoxy)piperidine (6): R_f = 0.2 (In hexane); colorless liquid; yield 50% (160 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 4H), 7.28 – 7.24 (m, 3H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.13 (t, *J* = 7.0 Hz, 1H), 4.82 (dd, *J* = 9.1, 3.5 Hz, 1H), 3.76 (dd, *J* = 12.6, 4.2 Hz, 1H), 3.23 (dd, *J* = 12.6, 9.8 Hz, 1H), 1.50 – 1.44 (m, 2H), 1.40 – 1.34 (m, 2H), 1.32 – 1.23 (m, 5H), 1.17 (s, 3H), 1.01 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 136.9, 130.9, 129.6, 128.8, 128.0, 127.8, 126.0, 85.4, 60.1, 40.6, 39.6, 34.4, 20.5, 17.3; IR (KBr) ῡ 3058, 2929, 1583, 1454; HRMS (ESI-TOF) calcd for $C_{23}H_{31}NOS$ $(M + nH)^+$ 370.2199 found 370.2196.

2.3 Notes and Reference

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^{1}H and ^{13}NMR Spectra of Selected Compounds

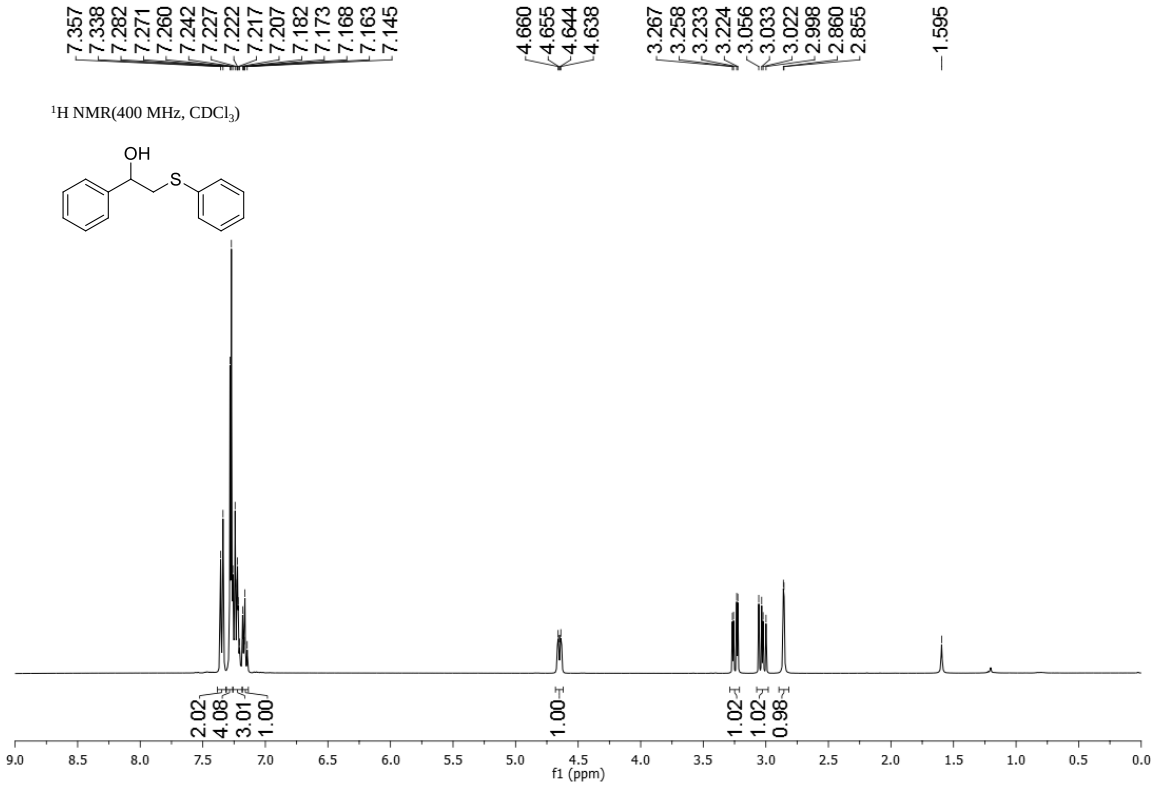


Figure 2B.7 ^{1}H NMR spectrum of 1-phenyl-2-(phenylthio)ethanol **(3aa)**

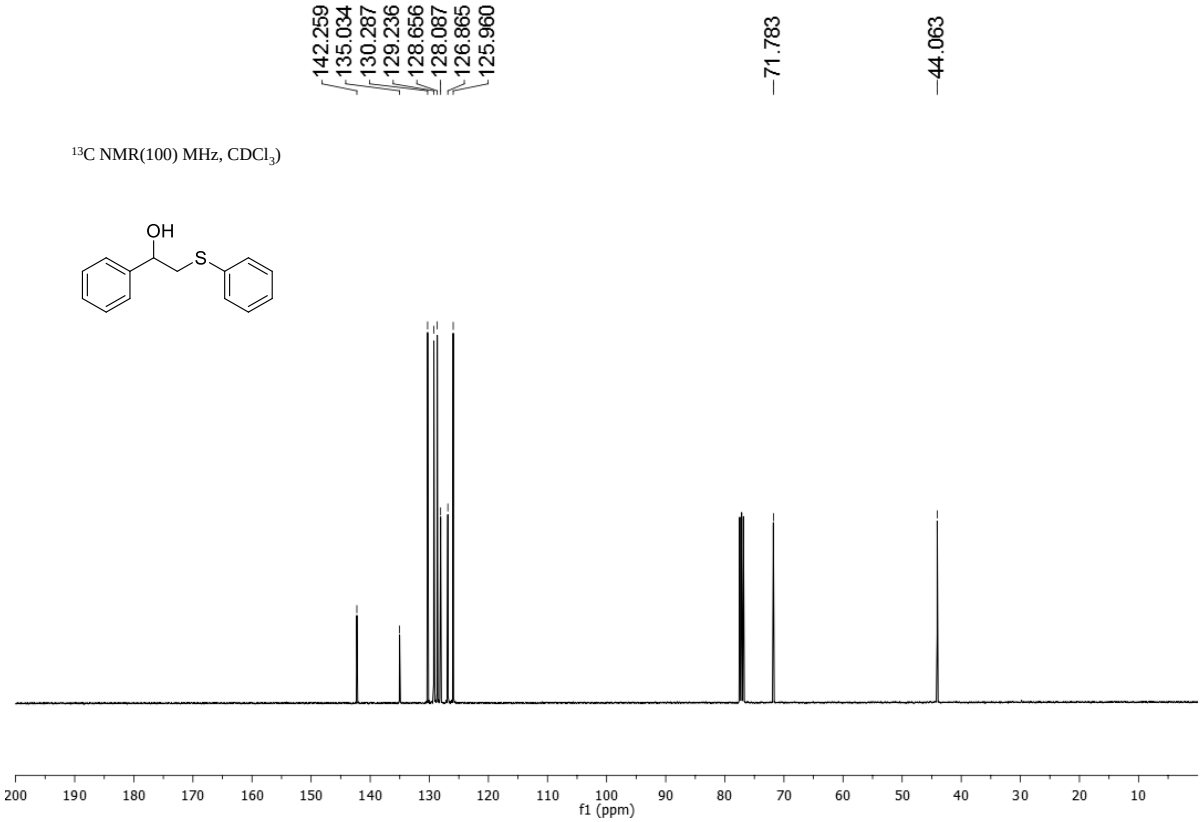


Figure 2B.8 ^{13}C NMR spectrum of 1-phenyl-2-(phenylthio)ethanol **(3aa)**

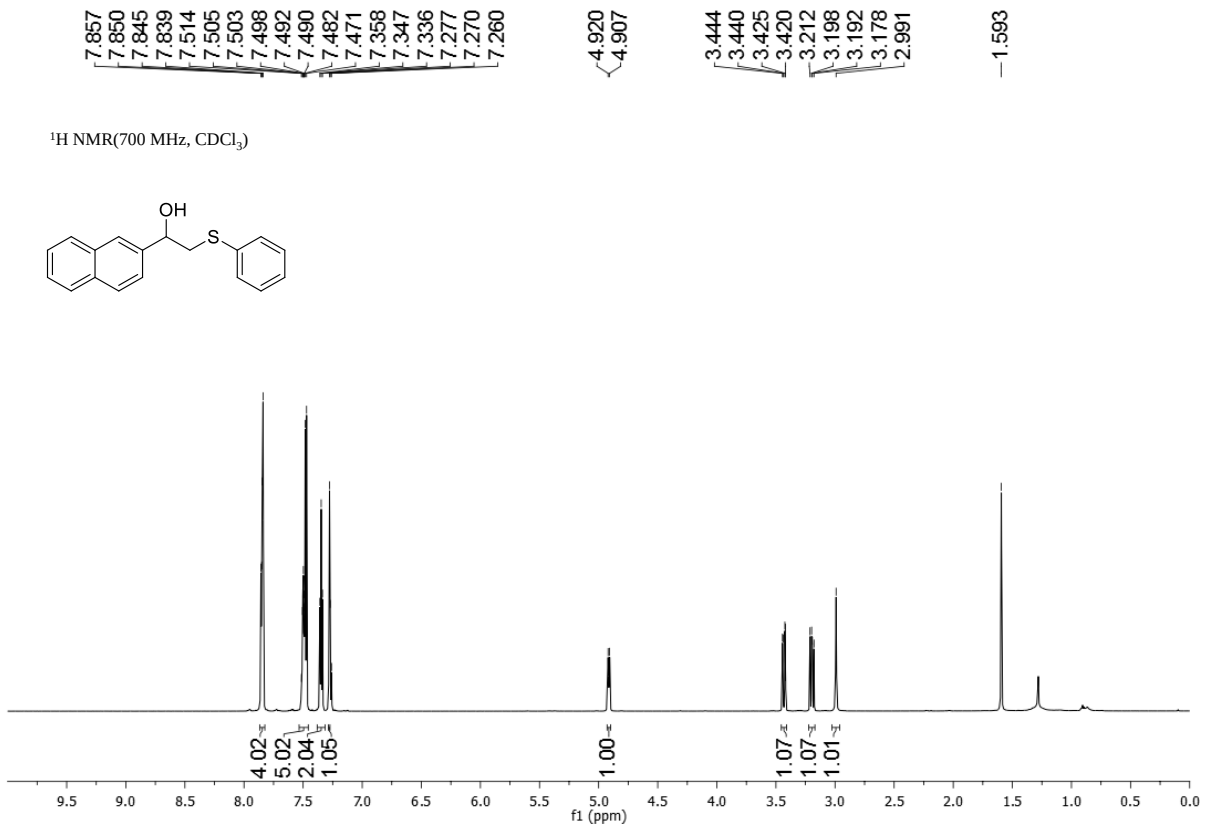


Figure 2B.9 ^{1}H NMR spectrum of 1-(naphthalen-2-yl)-2-(phenylthio)ethanol **(3ga)**

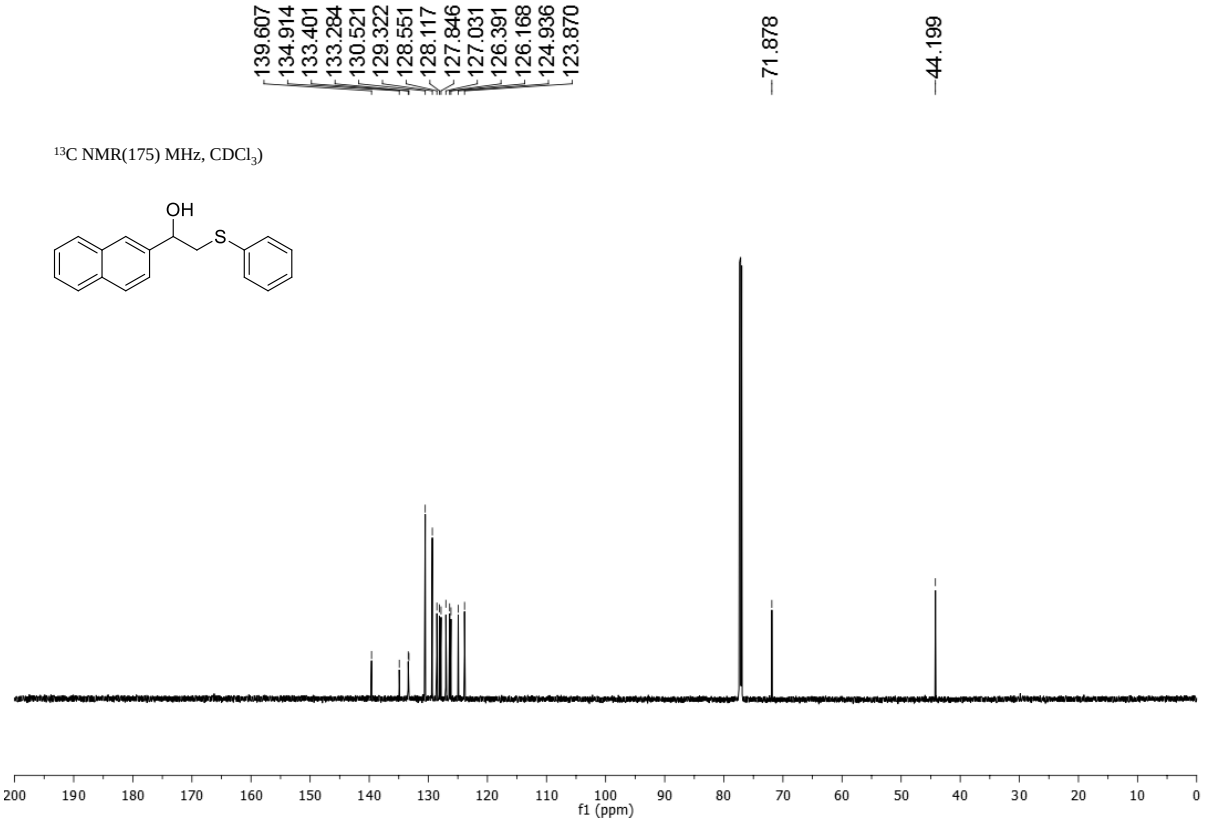


Figure 2B.10 ^{13}C NMR spectrum of 1-(naphthalen-2-yl)-2-(phenylthio)ethanol **(3ga)**

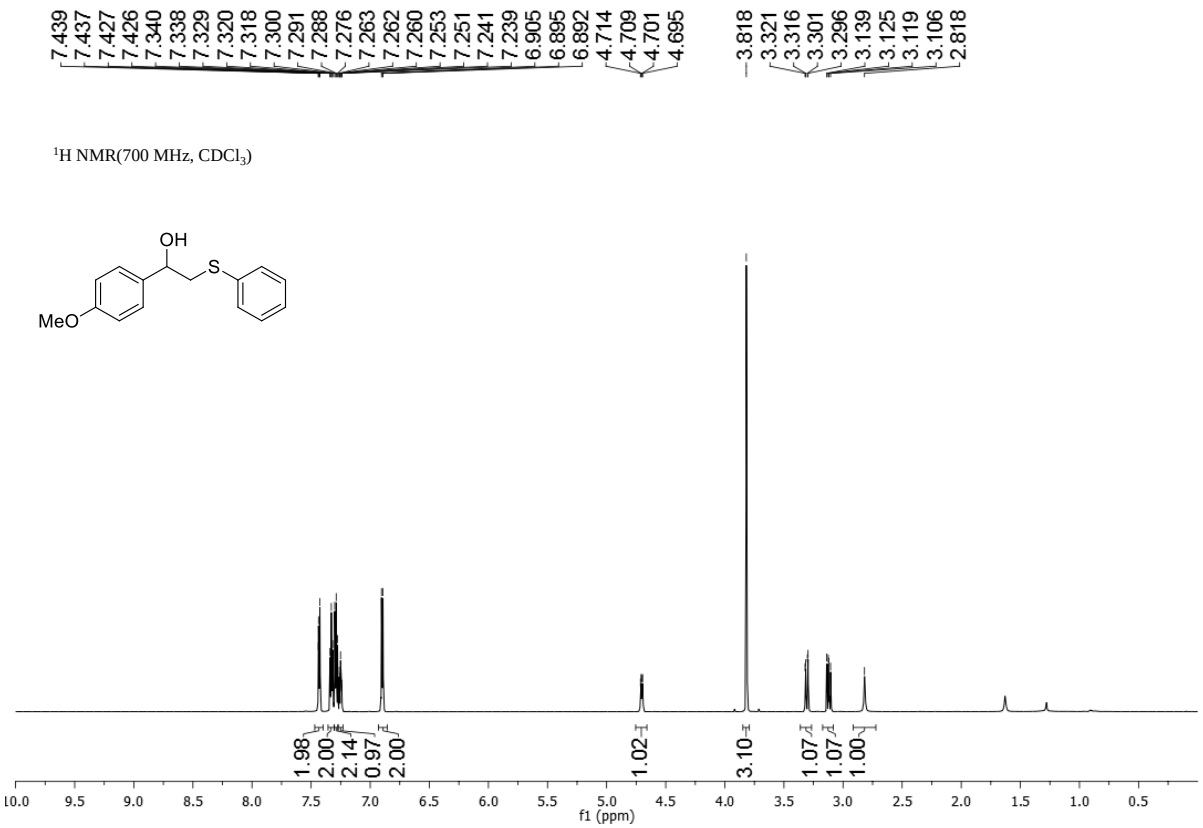


Figure 2B.11 ^{1}H NMR spectrum of 1-(4-methoxyphenyl)-2-(phenylthio)ethanol **(3ba)**

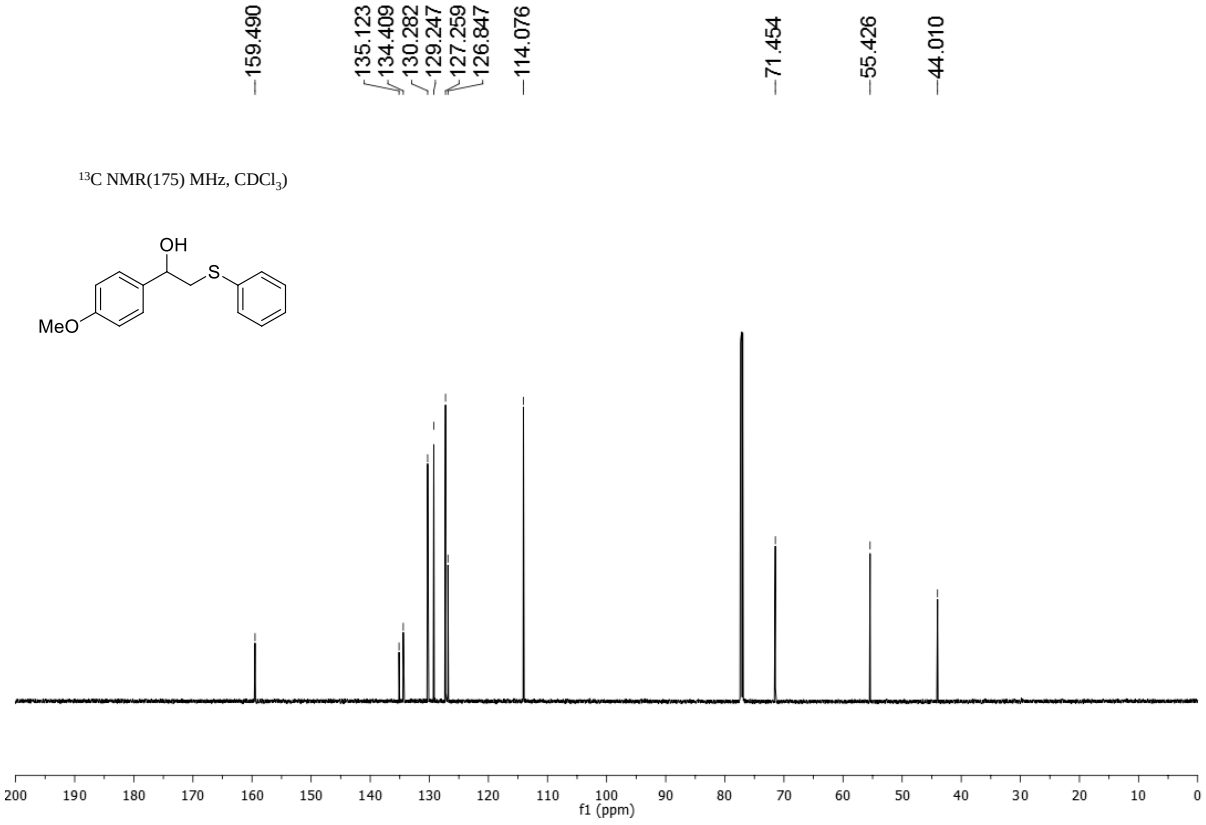


Figure 2B.12 ^{13}C NMR spectrum of 1-(4-methoxyphenyl)-2-(phenylthio)ethanol **(3ba)**

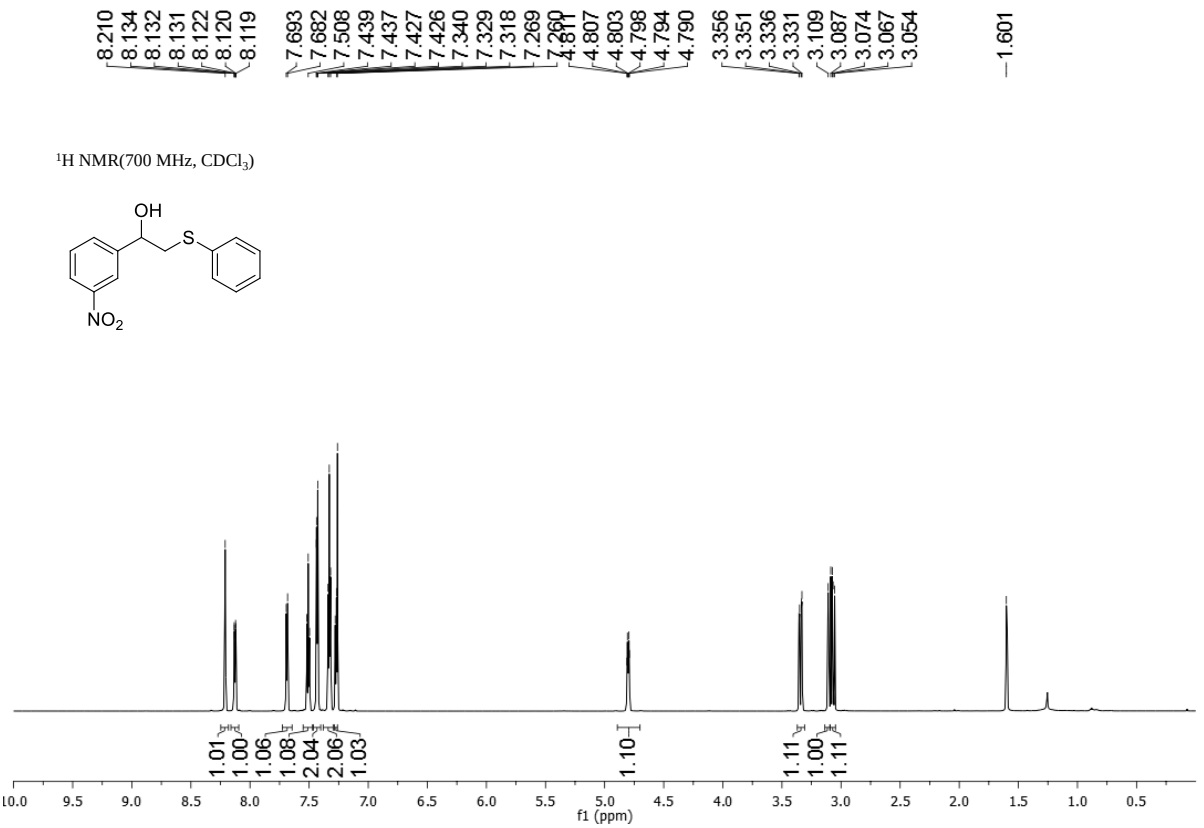


Figure 2B.13 ^{1}H NMR spectrum of 1-(3-nitrophenyl)-2-(phenylthio)ethanol **(3pa)**

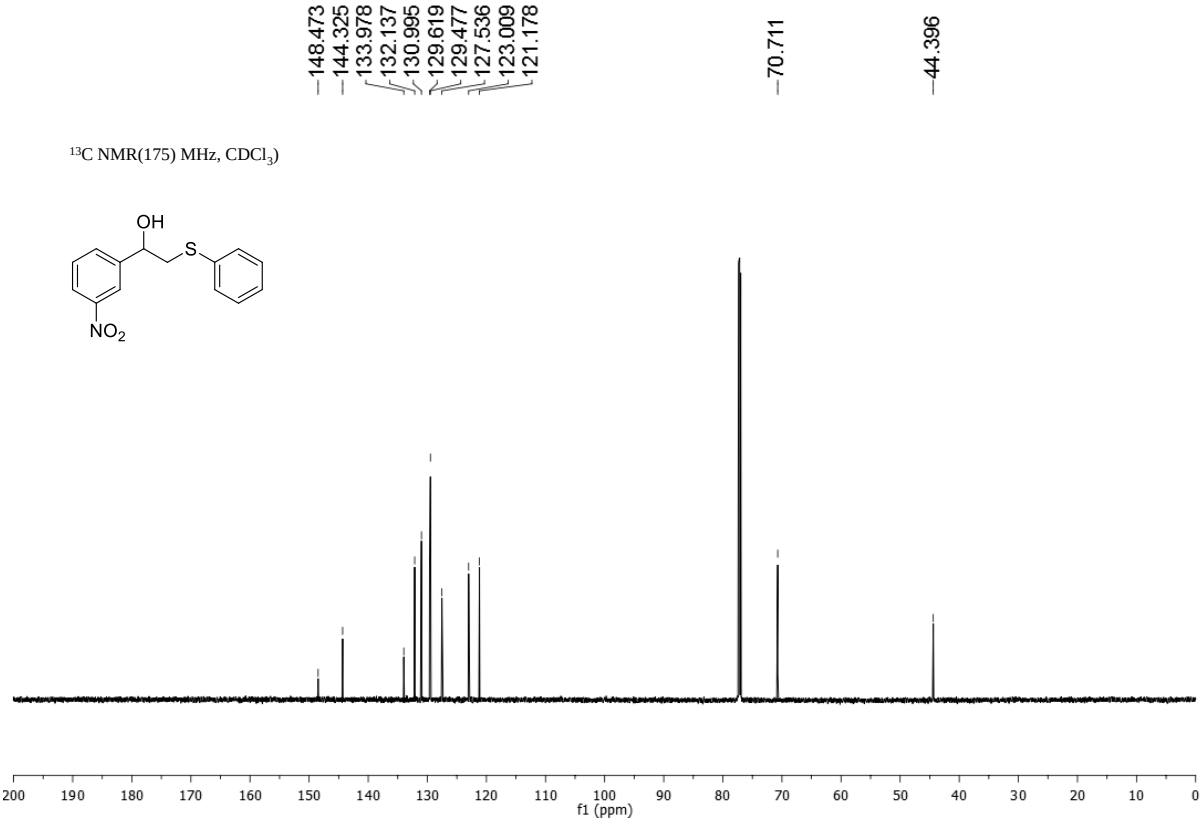
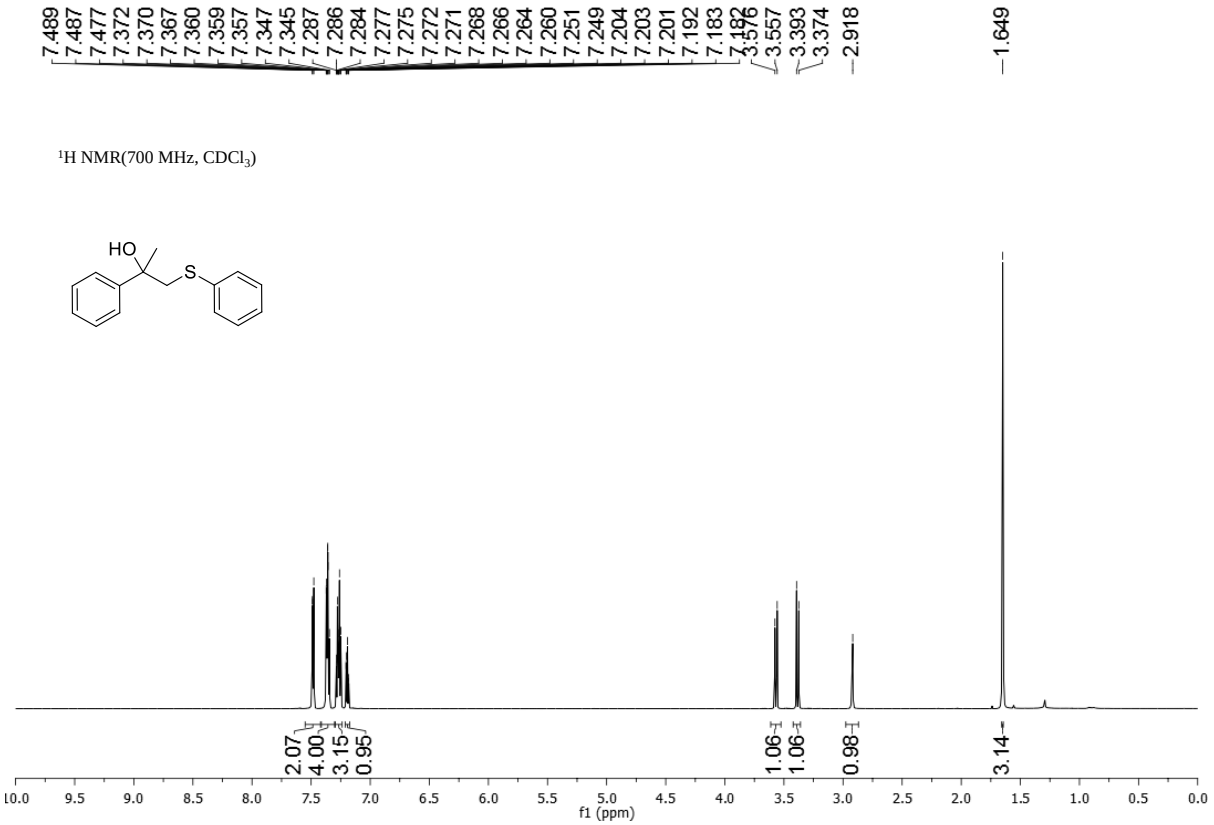
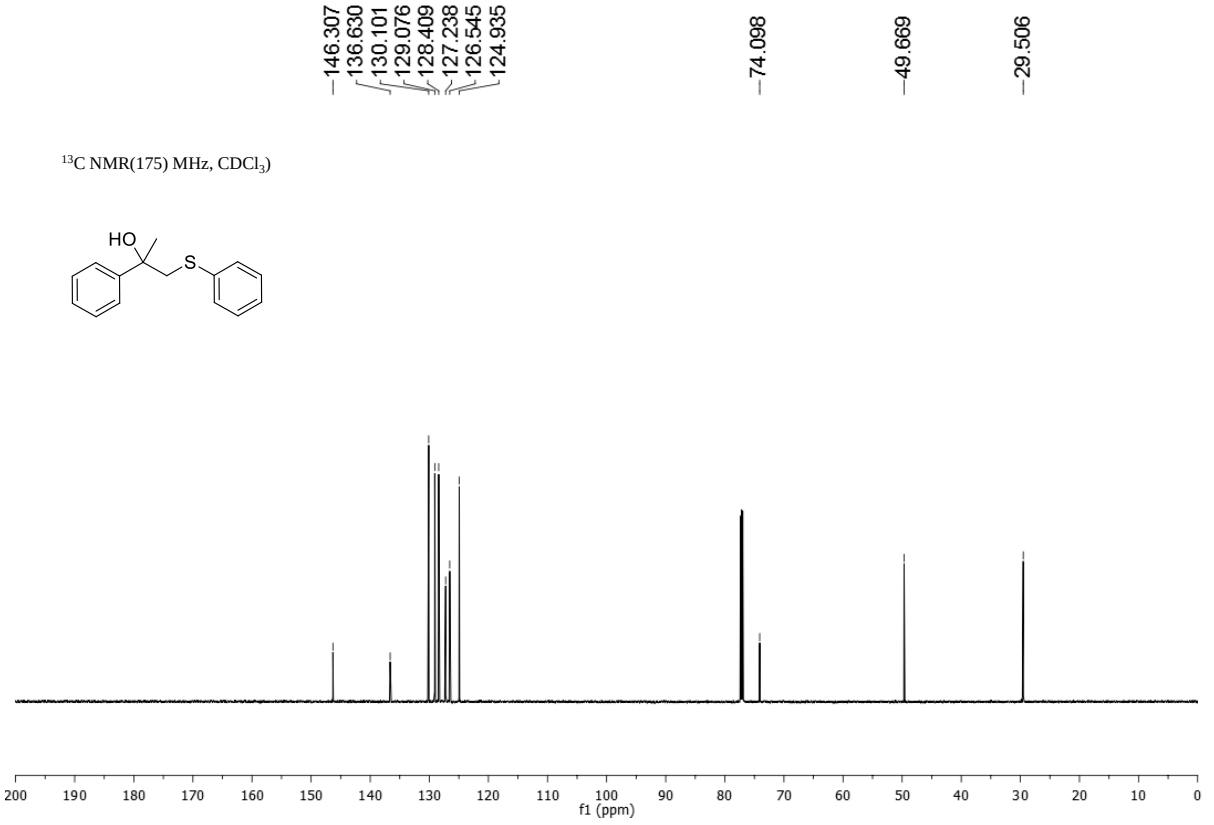


Figure 2B.14 ^{13}C NMR spectrum of 1-(3-nitrophenyl)-2-(phenylthio)ethanol **(3pa)**



^{1}H NMR(700 MHz, $CDCl_3$)

Figure 2B.15 ^{1}H NMR spectrum of 2-phenyl-1-(phenylthio)propan-2-ol **(3ea)**



^{13}C NMR(175) MHz, $CDCl_3$)

Figure 2B.16 ^{13}C NMR spectrum of 2-phenyl-1-(phenylthio)propan-2-ol **(3ea)**

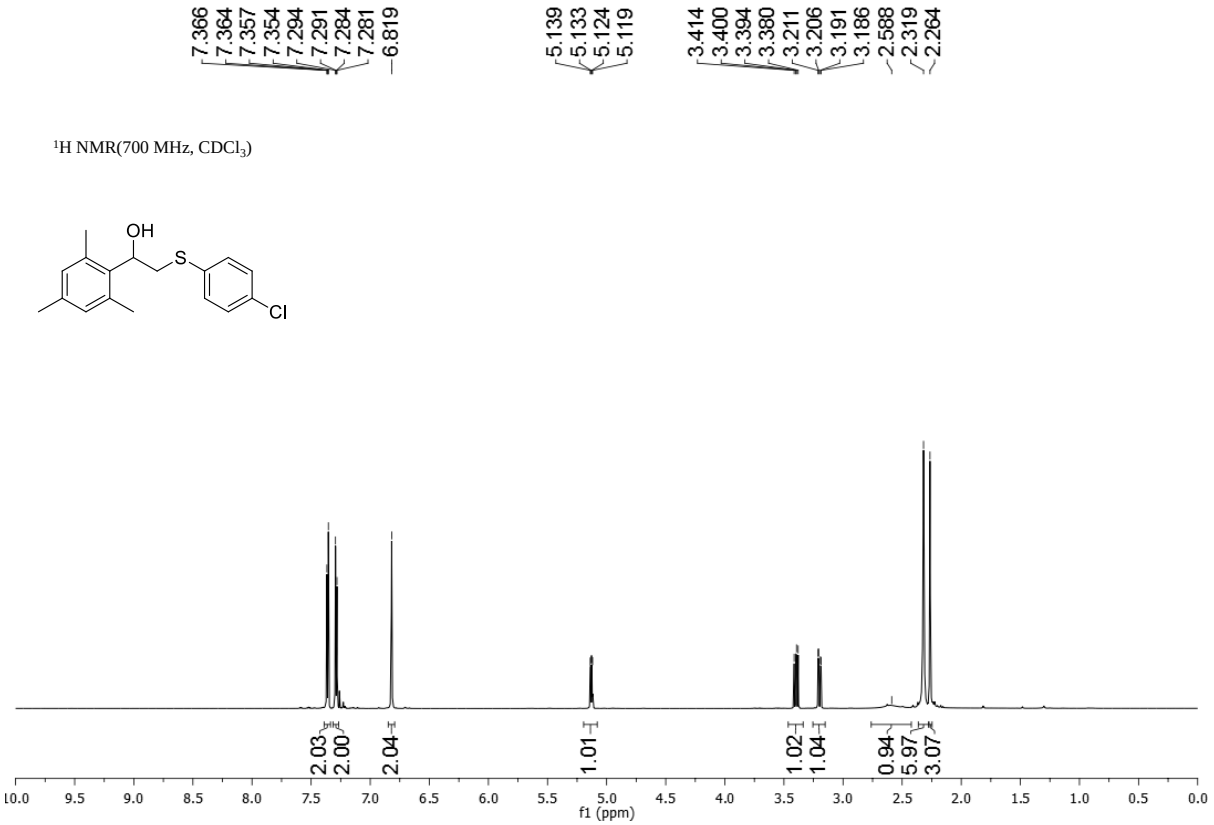


Figure 2B.17 ^{1}H NMR spectrum of 2-((4-chlorophenyl)thio)-1-mesitylethanol **(3qd)**

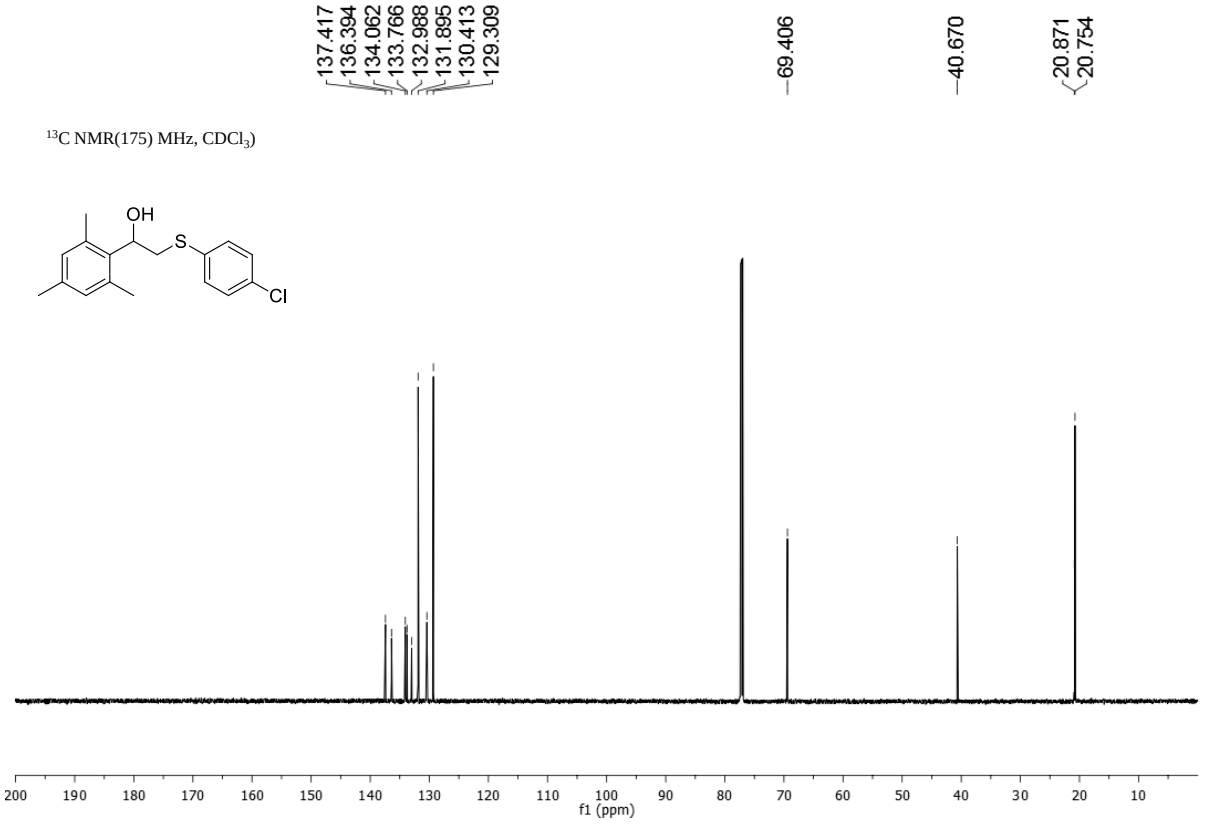


Figure 2B.18 ^{13}C NMR spectrum of 2-((4-chlorophenyl)thio)-1-mesitylethanol **(3qd)**

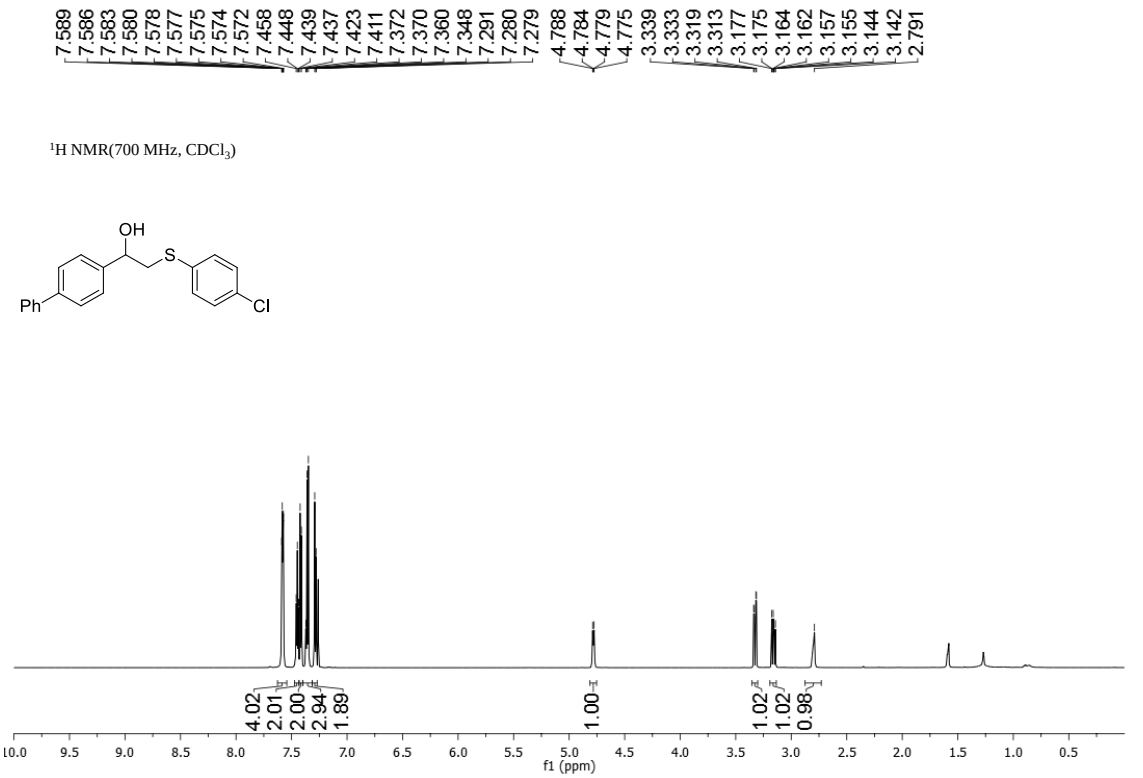


Figure 2B.19 ^{1}H NMR spectrum of 1-([1,1'-biphenyl]-4-yl)-2-((4-chlorophenyl)thio)ethanol **(3fd)**

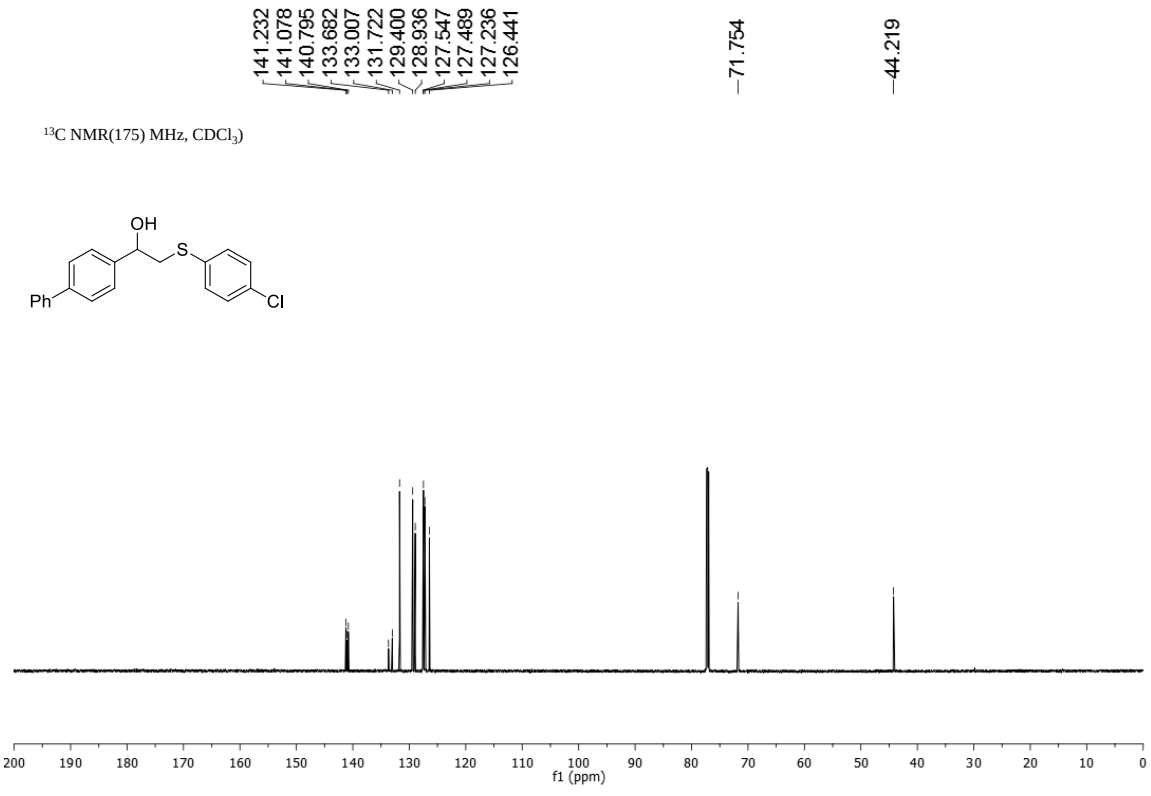
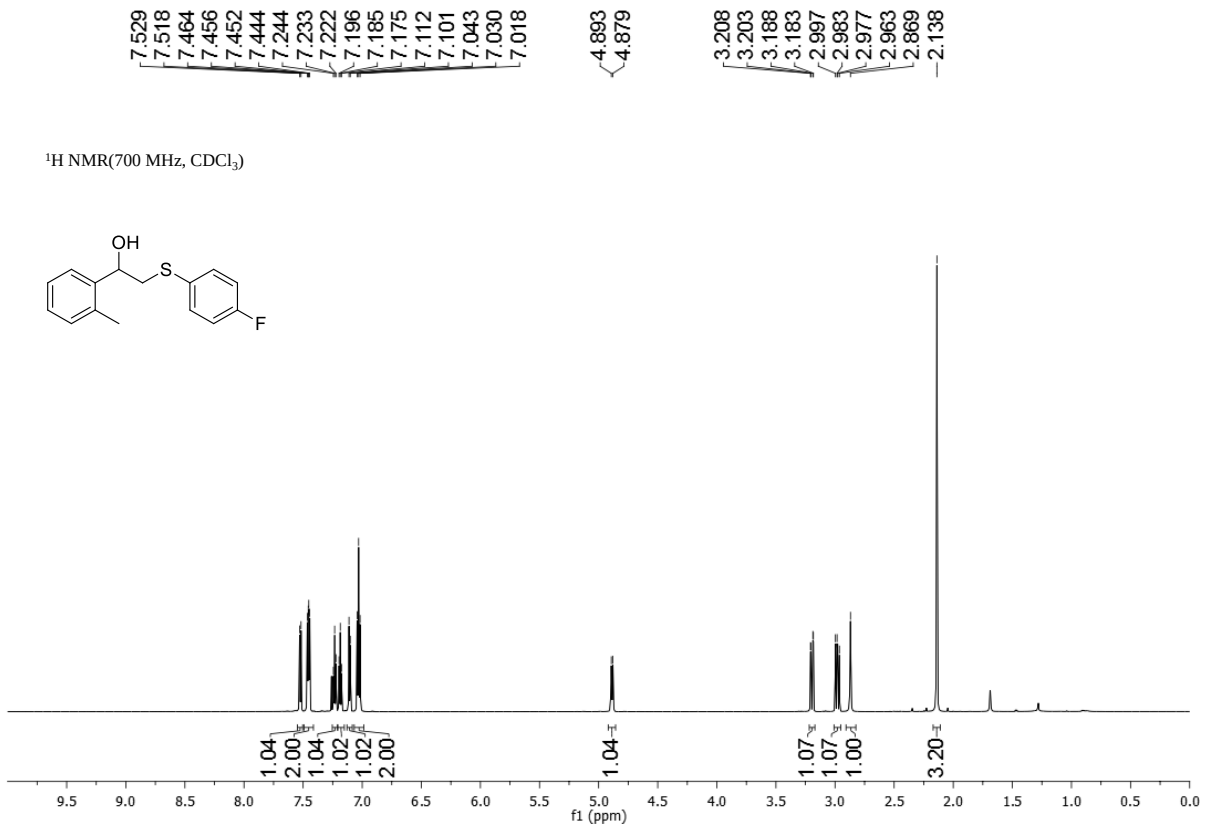
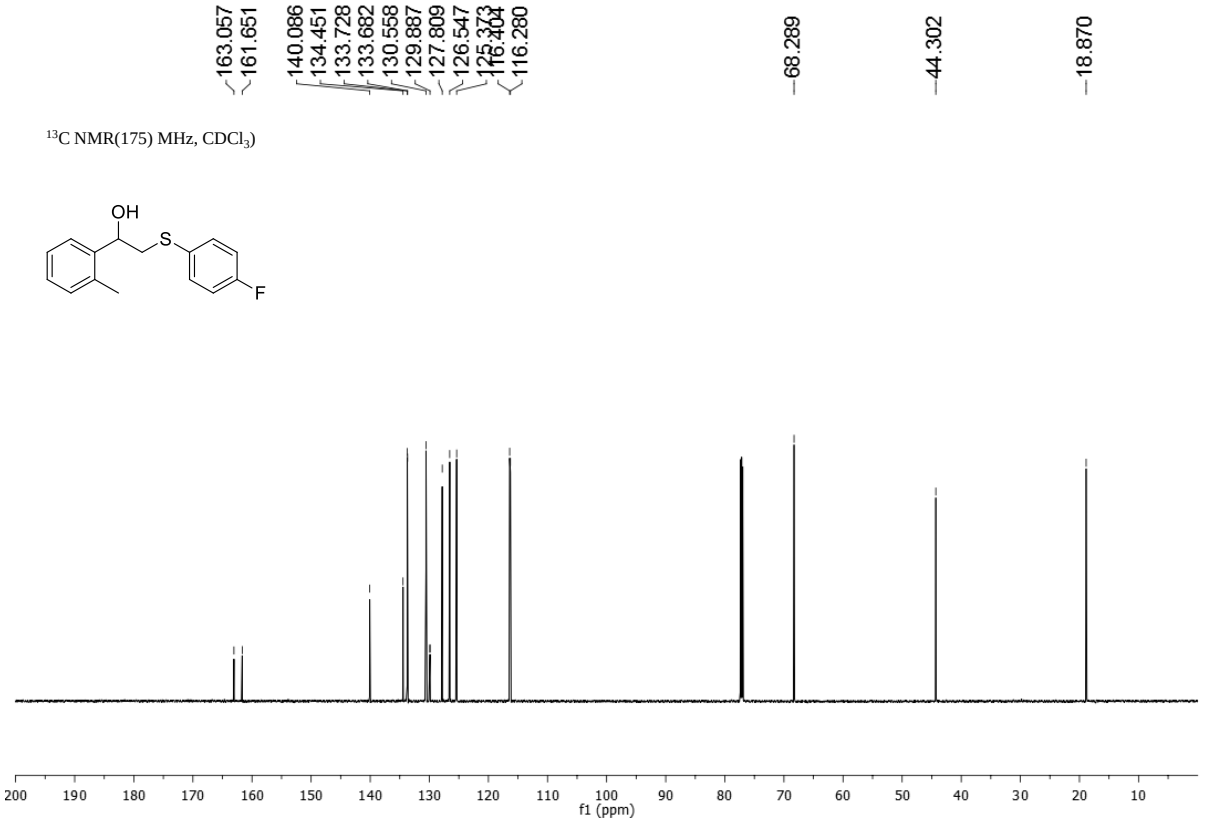


Figure 2B.20 ^{13}C NMR spectrum of 1-([1,1'-biphenyl]-4-yl)-2-((4-chlorophenyl)thio)ethanol **(3fd)**



^{1}H NMR(700 MHz, $CDCl_3$)

Figure 2B.21 ^{1}H NMR spectrum of 2-((4-fluorophenyl)thio)-1-(o-tolyl)ethanol **(3cc)**



^{13}C NMR(175) MHz, $CDCl_3$)

Figure 2B.22 ^{13}C NMR spectrum of 2-((4-fluorophenyl)thio)-1-(o-tolyl)ethanol **(3cc)**

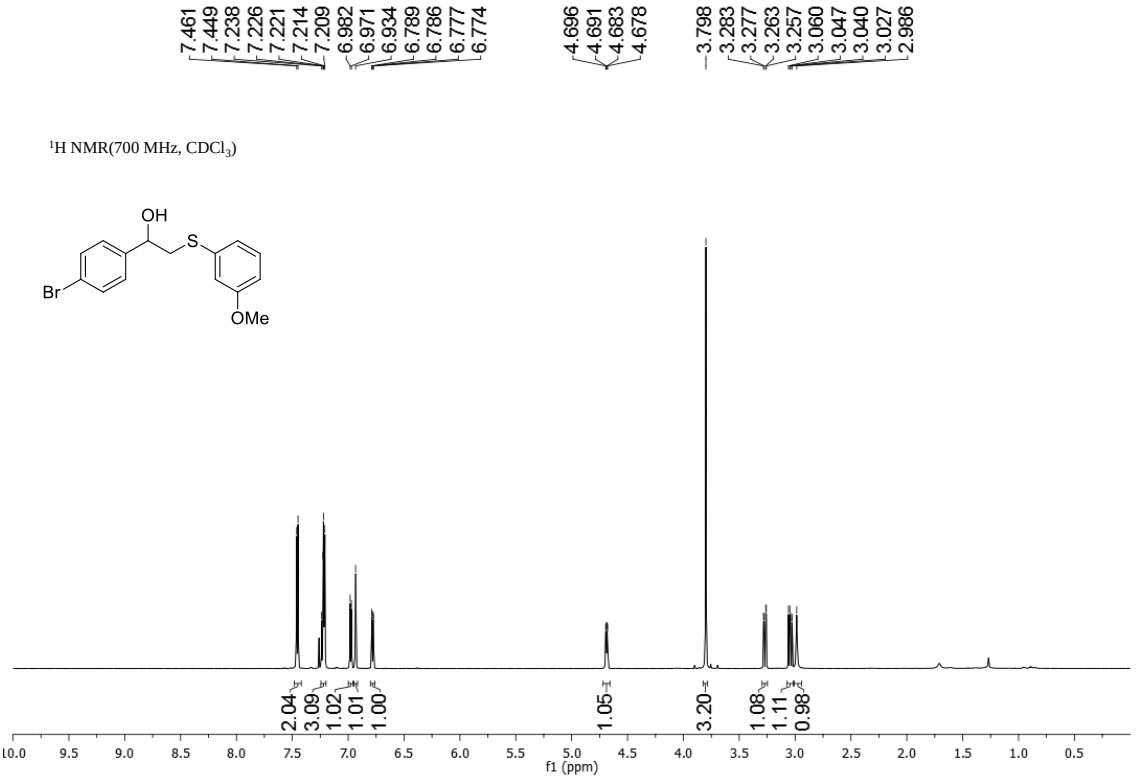


Figure 2B.23 ^{1}H NMR spectrum of 1-(4-bromophenyl)-2-((3-methoxyphenyl)thio)ethanol **(3te)**

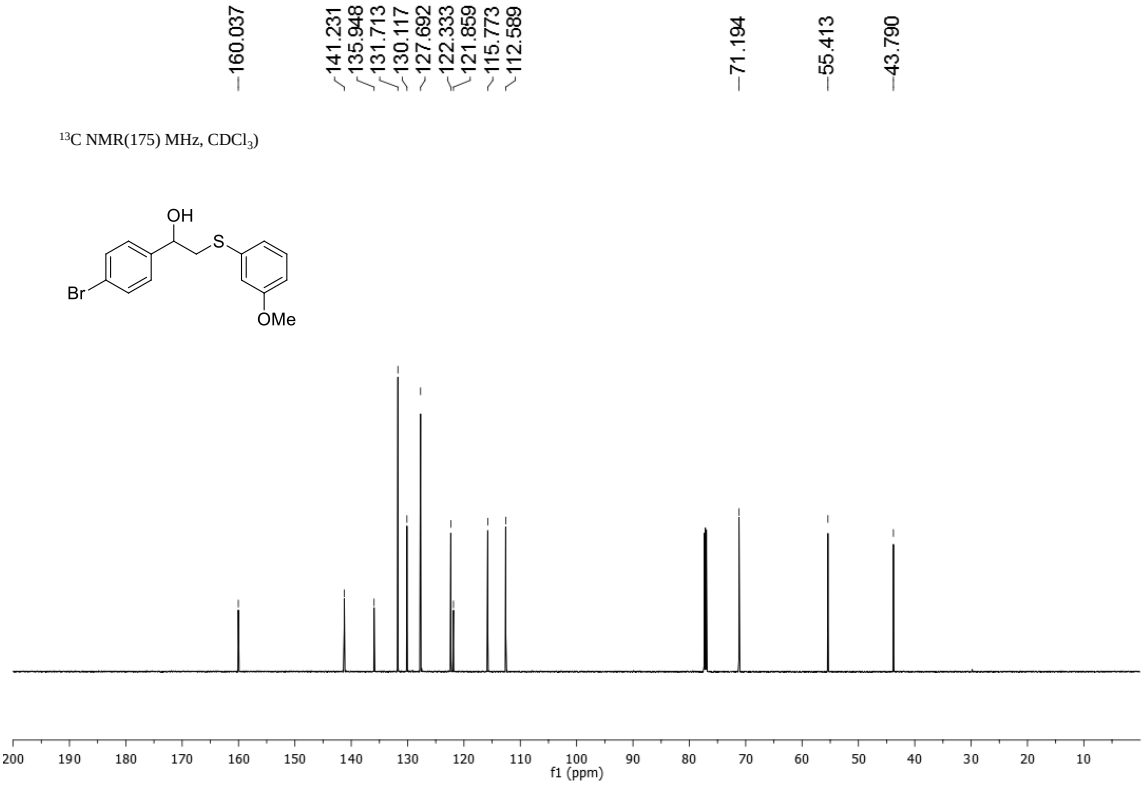


Figure 2B.24 ^{13}C NMR spectrum of 1-(4-bromophenyl)-2-((3-methoxyphenyl)thio)ethanol **(3te)**

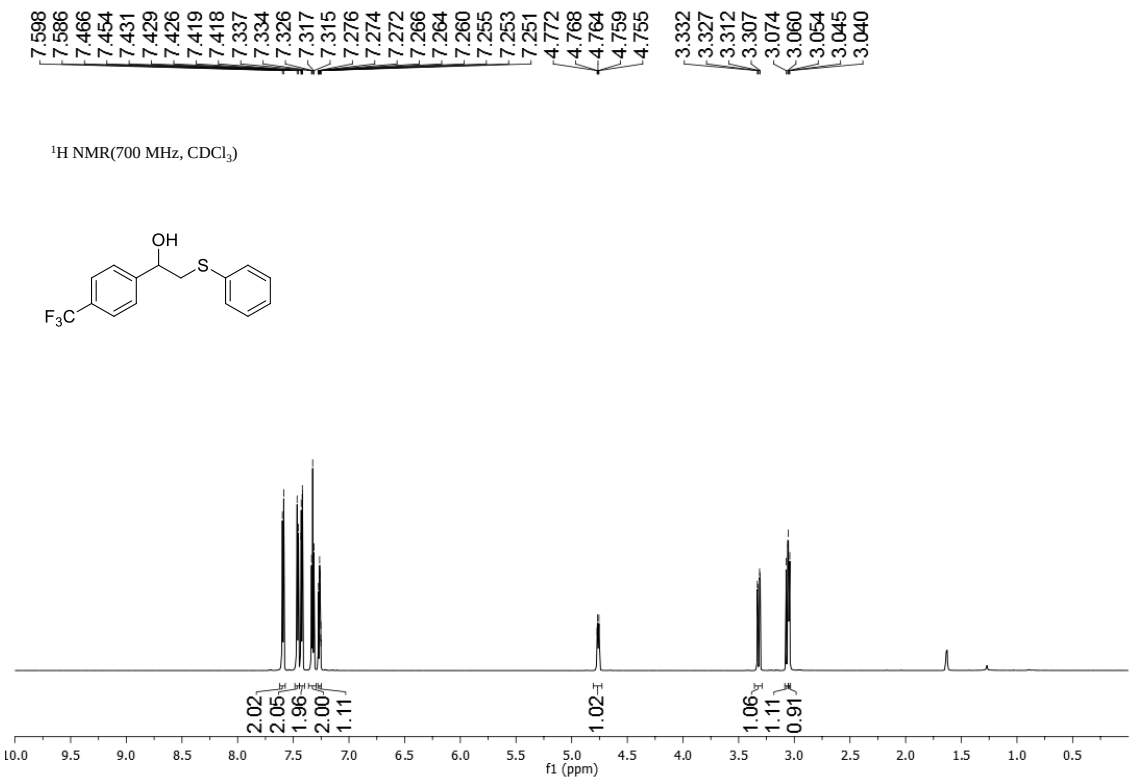


Figure 2B.25 ^{1}H NMR spectrum of 2-(phenylthio)-1-(4-(trifluoromethyl)phenyl)ethanol **(3la)**

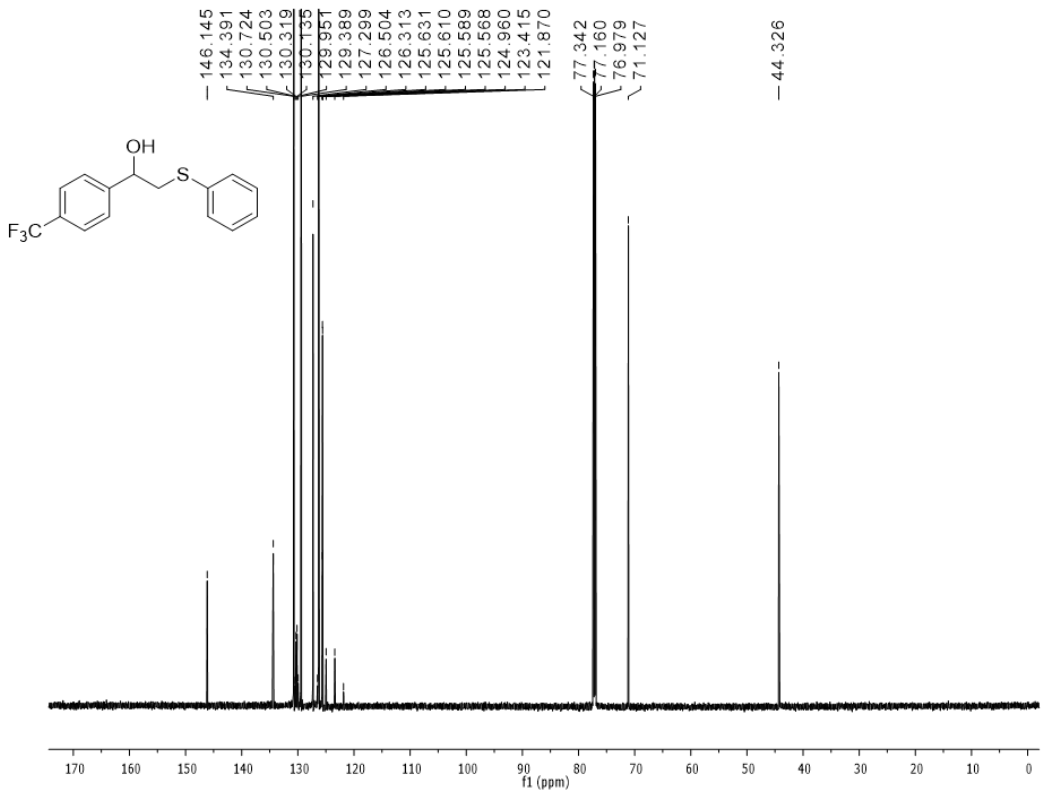
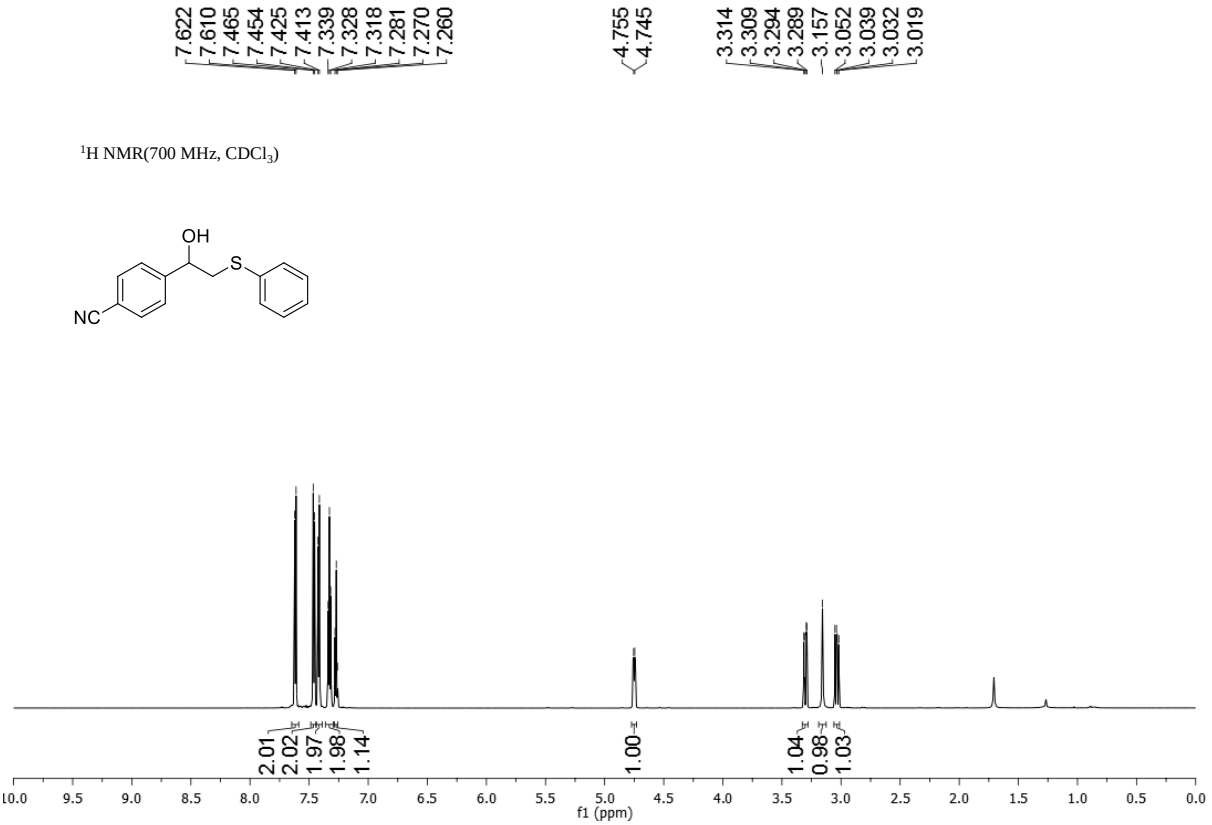
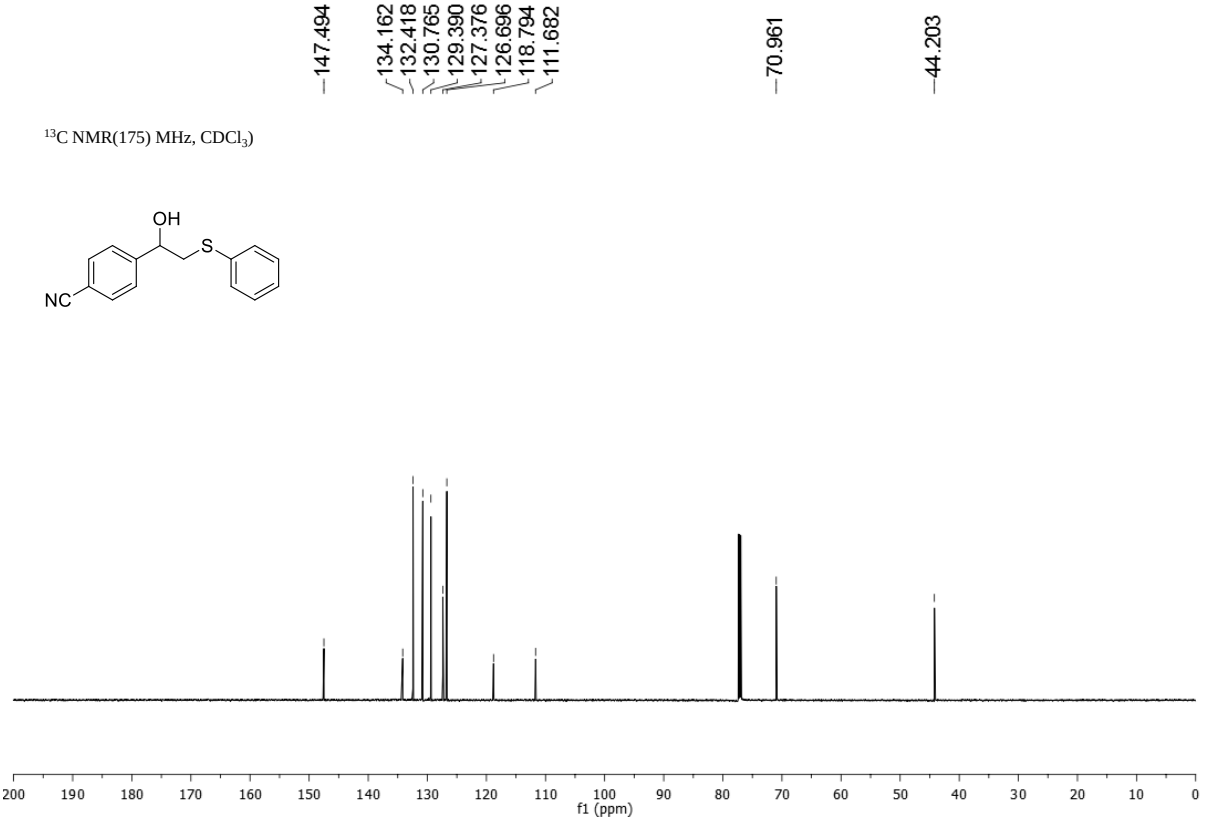


Figure 2B.26 ^{13}C NMR spectrum of 2-(phenylthio)-1-(4-(trifluoromethyl)phenyl)ethanol **(3la)**



^{1}H NMR(700 MHz, $CDCl_3$)

Figure 2B.27 ^{1}H NMR spectrum of 4-(1-hydroxy-2-(phenylthio)ethyl)benzonitrile **(3da)**



^{13}C NMR(175) MHz, $CDCl_3$)

Figure 2B.28 ^{13}C NMR spectrum of 4-(1-hydroxy-2-(phenylthio)ethyl)benzonitrile **(3da)**

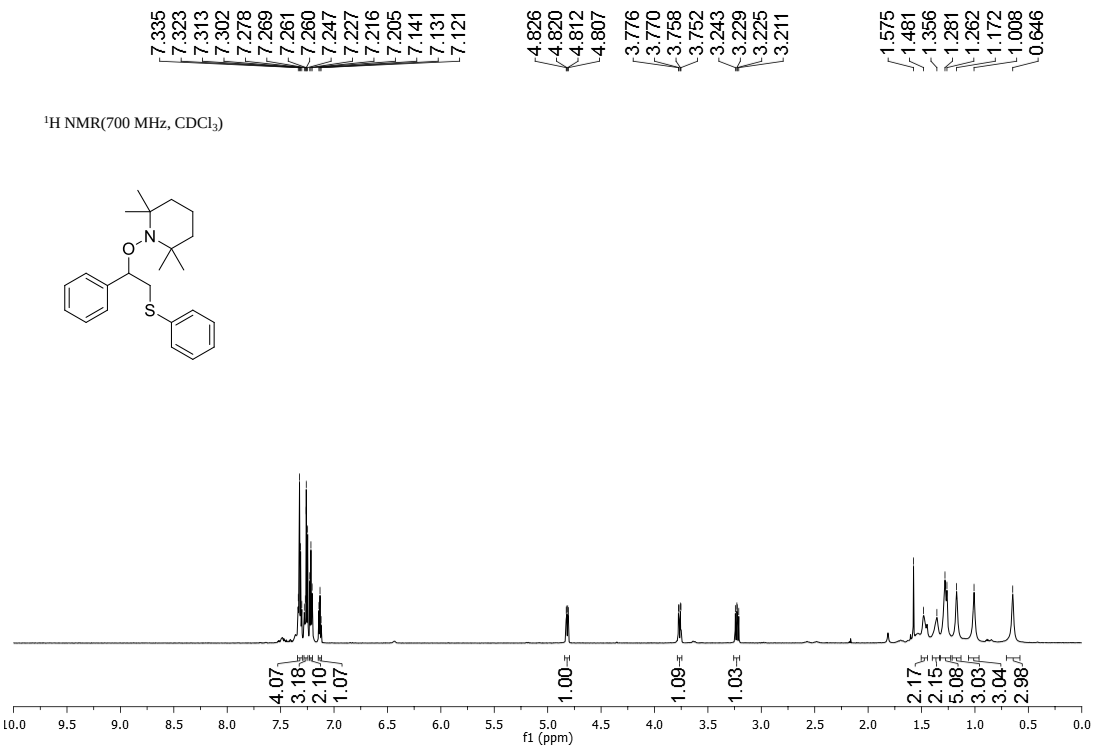


Figure 2B.29 ^{13}C NMR spectrum of 2,2,6,6-tetramethyl-1-(1-phenyl-2-(phenylthio)ethoxy)piperidine

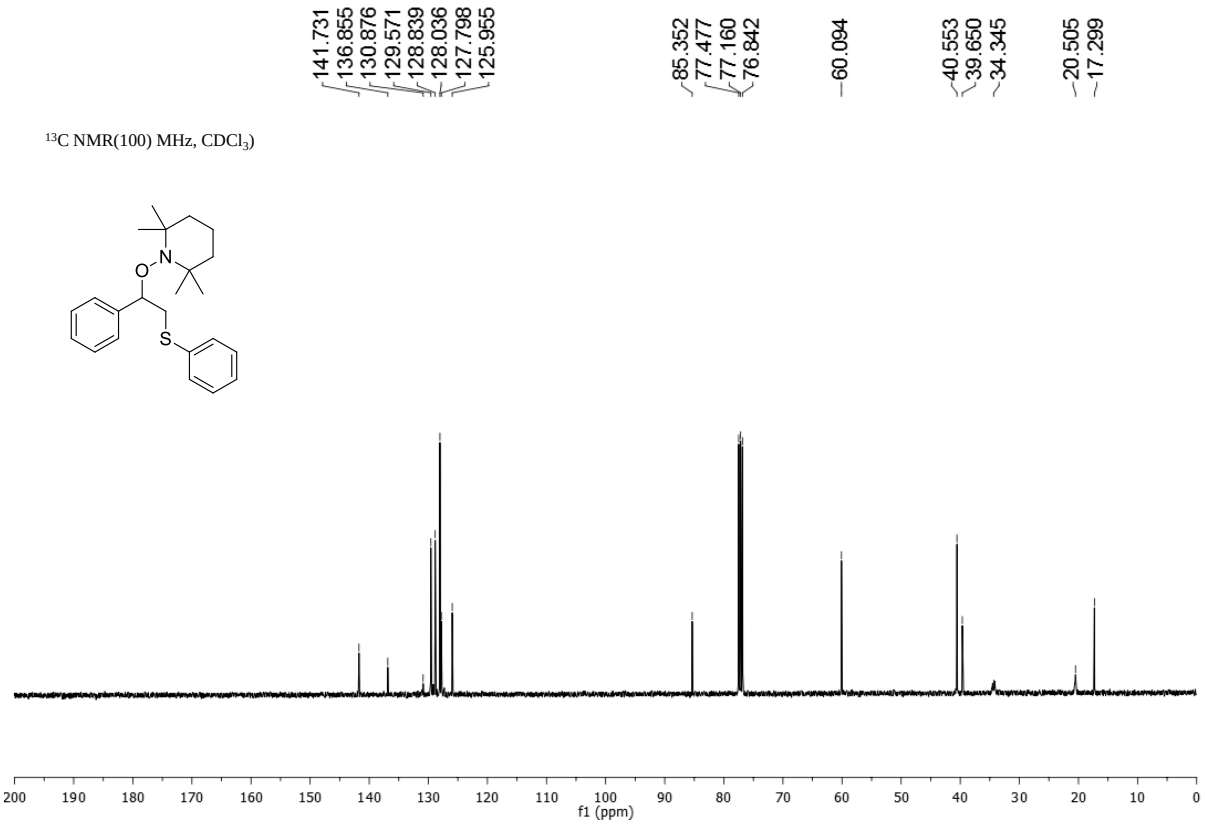
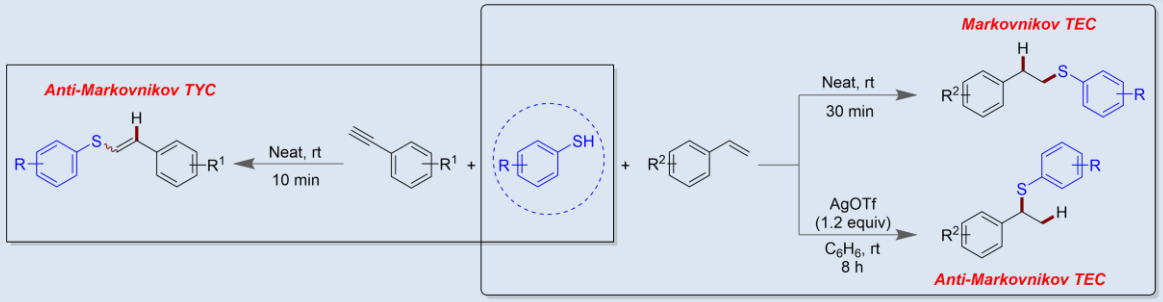


Figure 2B.30 ^{13}C NMR spectrum of 2,2,6,6-tetramethyl-1-(1-phenyl-2-(phenylthio)ethoxy)piperidine.

CHAPTER 3

S - H•••π Driven Click Reaction

3.1 ABSTRACT



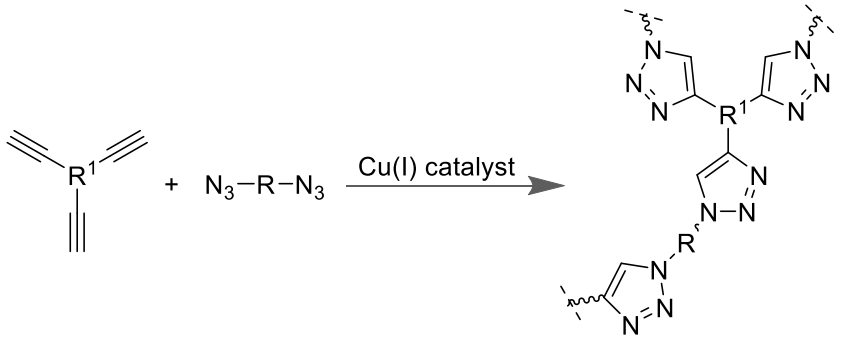
Herein we have successfully demonstrated the use of weak interactions to control click reaction between thiophenol and styrene or phenyl acetylene towards the synthesis of ethyl sulfane and vinyl sulfide derivatives under solvent free, neat condition at room temperature. The S-H...π and π...π stacking interaction helped to achieve 100% selective anti-Markovnikov product *via* umpolung addition which was further proved from theoretical and experimental investigations. A self-sorting experiment helped to establish the preference of TYC reaction over the TEC reaction.

3.2 INTRODUCTION

With growing public concern on renewable energy[1] and global warming, it is essential to minimize the usage of chemicals in routine synthesis both in industrial and academic research and possible recycle the waste materials to obtain better result in a greener fashion. To minimizing the chemical / energy wastage, solvent free synthesis under neat condition have become a popular research topics[2] in green chemistry.

Click chemistry was 1st discovered by Huisgen in 1950s; however the term "click" chemistry was coined by Sharpless, it and defined a highly efficient synthetic route which can

be tolerable by various type functional group under mild condition[3,4]. Henceforth, the click chemistry has encountered a synthetic renaissance in polymer chemistry[5]. Later it was extended across the multidisciplinary system. Huisgen[6] have established copper catalysed coupling reaction between terminal alkyne with terminal azide to afford exclusively 1,2,3-triazole unit.



Scheme 3.1. Huisgen's approach for the synthesis of 1,2,3-triazole unit.

Click reaction is an atom and step economical process and proceeds without elimination of any small molecule with high conversion rate in solvent free condition at relatively lower temperature. A major benefit of click chemistry is that it is highly reactant specific and tolerates any type of functional group. In this regards, herewith we have disclosed an efficient protocol based on weak interaction control Thiol-ene or Thiol-yne click reaction towards the synthesis of Phenethyl phenyl sulfane and vinyl sulphide under neat condition.

Controlling chemical reactions by the use of weak or non-covalent interactions in organic synthesis has become a popular subject of interest.[7,8] Therefore, understanding and implementing approaches towards making the complex chemical reactions in a simpler way, the research area systems chemistry of small molecules is developed.[9,10] Commonly, by applying systems chemistry principles[11] synthesis of many high-purity complex architectures from mixtures of reactants in fewer reaction steps are established, but general approaches on small molecules synthesis are less explored.[12] Among the non-covalent interactions[13] or soft forces[14] being used to control chemical reactions,[15] relatively less explored S–H···π

interaction is one of the newest additions to the family.[16,17] The synthetic applications using S–H···π interaction are mainly unexplored except our recent contribution on thiol-ene click reaction *vs.* aerial dioxygen activation within a system.[18]

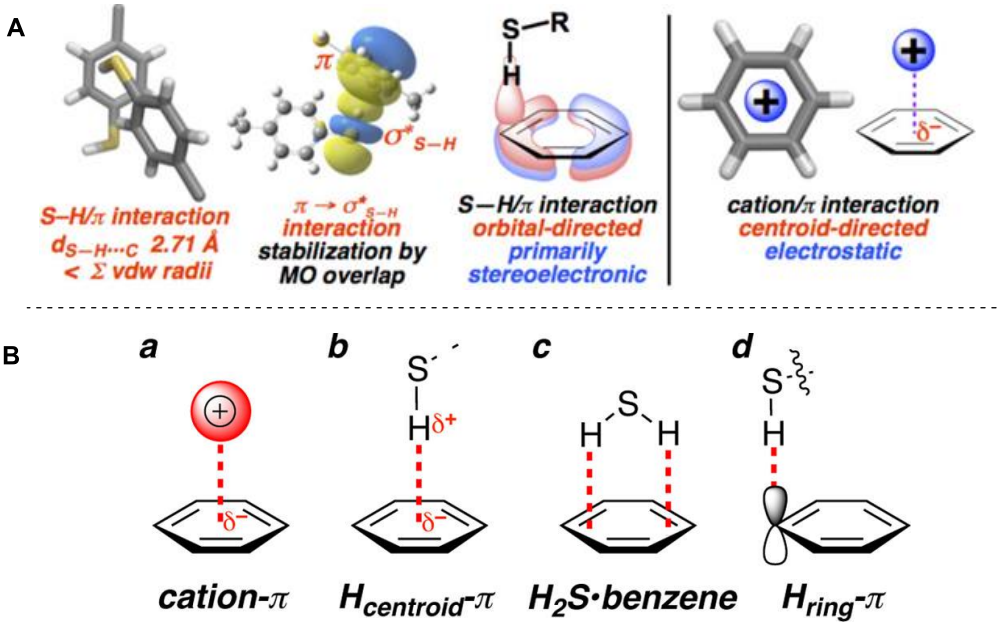


Figure 3.1. Different types of cation···π and S–H···π interaction. A) S–H···π interaction stabilized by MO overlap. a) Cation···π interaction. b) Typical S–H···π interaction, where H located to the centroid of the aromatic ring c) S–H···π with the H_2S molecule. d) S–H···π interaction with the *p*-orbital of the aromatic ring. (Permission has been taken from *J. Am. Chem. Soc.* **2017**, *139*, 1842)

S–H···π interaction is a one type of H-bonding and its energy is very much comparable with the H-bonding energy likes of water system (4-120 kj/mole). In spite of low electronegativity of sulfur,[19] N-H…S type of hydrogen bond is one of the strongest H-bond among commonly observed hydrogen bonds.[20] There are very few reports on hydrogen bond where sulfur atom behaves as either hydrogen bond donor (S-H) or acceptor (S).[21]Herein we have reported S–H···π interaction, exclusively control regioselectivity and reactivity of Thiol Ene Click (TEC) and Thiol Yne Click (TYC) reactions of internal alkene and alkynes.

CHAPTER 3: Part A

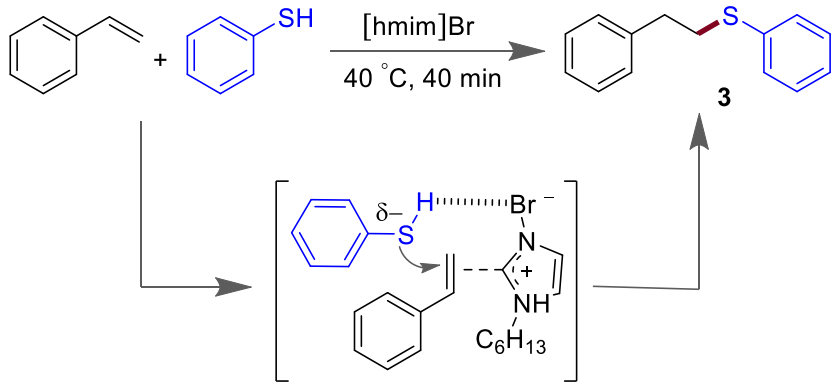
S - H•••π Driven Thiol-Ene Click (TEC) Reaction

3A.1 ABSTRACT

Markovnikov or anti-Markovnikov selective thiol-ene click (TEC) reactions are the powerful tool for C-S bond forming reactions by employing styrenes and thiophenols. Herein we demonstrate a systems chemistry approach by choosing appropriate reaction systems using solvents with additives or solvent free neat condition, any one of these two reactions could be obtained exclusively in excellent yields. In the TEC reaction switching of anti-Markovnikov to Markovnikov selective products could be achieved by controlling cooperative weak interactions like π-π stacking and S-H…π and cation-π interaction.

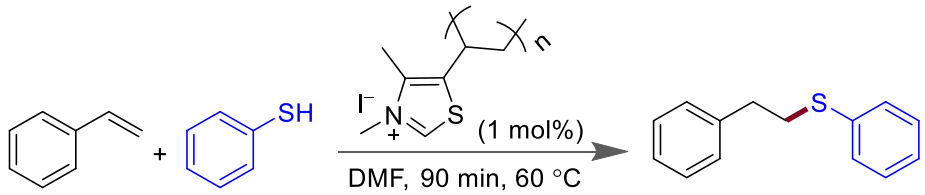
3A.2 INTRODUCTION

Construction of C-S bond has always achieved enormous attention because of its widespread application in natural products, pharmaceutical, agrochemical, material sciences[22-24] and most importantly in many drug molecules[25-31]. The thiol–ene "click" (TEC) reaction of conjugated alkenes and thiols represent a powerful tool for the construction of carbon-sulfur bonds. Nevertheless, formations of two regioisomers are observed from the Markovnikov or anti-Markovnikov selective TEC reactions. Recently, many approaches like ionic liquid mediated,[32] gold-catalyzed,[33] visible light photoredox catalyzed,[34] photo-initiated organocatalysis,[35] etc. are being well explored for the TEC reaction. Among them, metal free routes have high applicability in pharmaceuticals and synthetic laboratories.[36]



Scheme 3A.1. Sinha's approach for hydrothiolation reaction under ionic liquid medium.

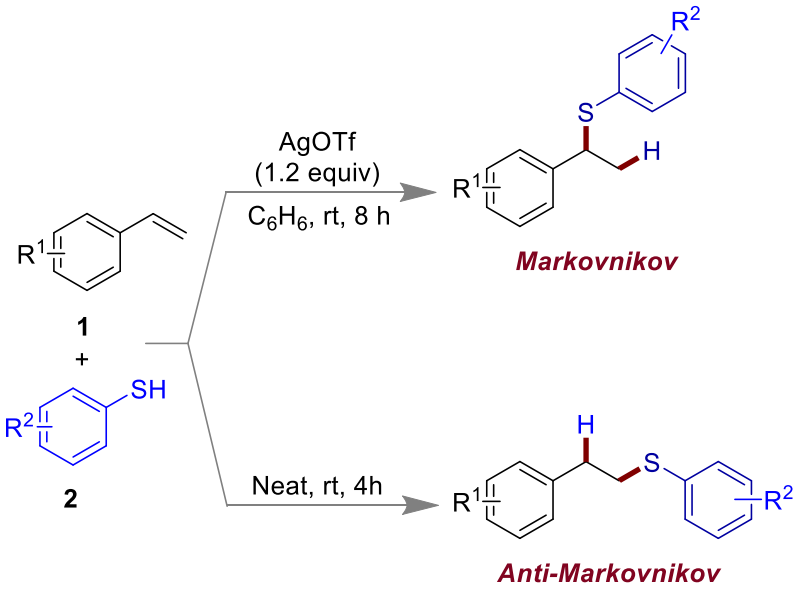
In 2015, A.K.Sinha established ionic liquid driven anti-Markovnikov selective thiol-ene-click reaction under ionic liquid [hmim]Br medium (Scheme 3A.1) [32]. The amphoteric nature of [hmim]Br activated both thiophenol as well as olefin. Counter anion (Br^-) of ionic liquid formed halogen bonding with the proton of thiophenol and thus increased the nuclophilic character of thiophenol. On the other hand, C-2 hydrogen of $[hmim]^+$ activated olefin through C-H…π interaction. As a result, nucleophilic attack of thiophenol to styrene afforded to anti Markovnikov selective vinyl sulfide product with excellent yield.



Scheme 3A.2. Chung's approach for poly(vinylthiazolium) catalysed hydrothiolation reaction

Later Chung and co-worker have extended the methodology using catalytic amount of poly(vinylthiazolium) salt (Scheme 3A.2). They have proposed that the reaction might go through the formation of thiyl radical intermediate which was stabilized by hydrogen bonding with poly(vinylthiazolium) salt in the medium. The role of the catalyst was confirmed by theoretical (DFT) calculation. Thus, it is important to understand the role of weak or non-covalent interactions towards controlling of chemical reactions. The systems chemistry approach of small molecules has become a popular subject of research by understanding and

implementing methods to simplify the complex chemical reactions.[9,10] Generally, systems chemistry principles provides primary insights into the self-sorting principles of molecular networks which may assist us to design new systems possessing improved functions.[11] The systems chemistry approach is a promising method for the synthesis of high- purity complex molecules from mixtures of reactants in fewer reaction steps but the studies on small molecules in organic synthesis are relatively less explored.[12] Weak interactions play a pivotal role in the formation and stabilization of reactive intermediates.[37] Cooperative[38] multiple weak interactions[13] like hydrophobic effect,[39] halogen bonding,[40] anion-π,[41] etc. are being well explored in the chemical systems. Therefore many difficult reactions can be performed easily by the intervention of appropriate weak interactions.



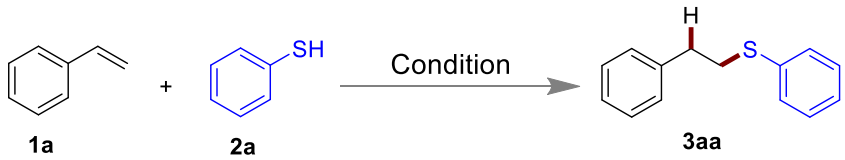
Scheme 3A.3. Our approach for S-H...π controlled hydrothiolation reaction.

Herein we have demonstrated S–H···π driven hydrothiolation reaction with exclusive switching of Markovnikov selective[42] and anti-Markovnikov selective products.[43] Under open atmosphere and at ambient temperature any product could be obtained exclusively from the reactions of styrenes and thiophenols (Scheme 3A.3.). The products from TEC (thioethers) reaction are found in natural products,[44,45] drug intermediate in organic synthesis,[46] etc.

3A.3 RESULT AND DISCUSSION

The reaction between styrene (1a) and thiophenol (2a) led to anti-Markovnikov selective hydrothiolation product at room temperature (Table 3A.1). Under neat condition and at 35-40 ºC within 30 min, 3aa was isolated as a single product in near quantitative yield (ca. 98%, entry 1) with exclusive anti-Markovnikov selectivity. However we have screened the reaction condition with different solvent but the yield was not promising (Table 3A.1, entry 2-6). The reaction at inert condition also delivered excellent yield (Table 3A.1, entry 7). Decreasing the amount of thiophenol led to the less yields (Table 3A.1, entry 8).

Table 3A.1. Optimization condition for TEC reaction[*a*]



1a 2a 3aa

Entry	solvent[b]	3aa (%)[a]
1	Neat	98
2	EtOH	47
3	DCE	79
4	C_6H_6	84
5	DMSO	61
6	H_2O	78
7	Neat	92[b]
8	Neat	86

[a]Condition, 1.0 equiv of **1a** and 2.0 equiv of **2a** were used, at 35-40 ºC; [b]under argon atmosphere; [c] For1.5 equiv 2a was used at 35-40 ºC.

We have further explored the substrate scope of the anti-Markovnikov selective TEC reaction. It was anticipated that the current approach under neat and any additive free condition for the 100% anti-Markovnikov selective thioether synthesis is simple, convenient and worked at ambient laboratory condition. A range of styrenes were efficiently reacted with

thiophenol to obtain a series of thioethers compounds in very good to excellent yields (Figure 3A.1).

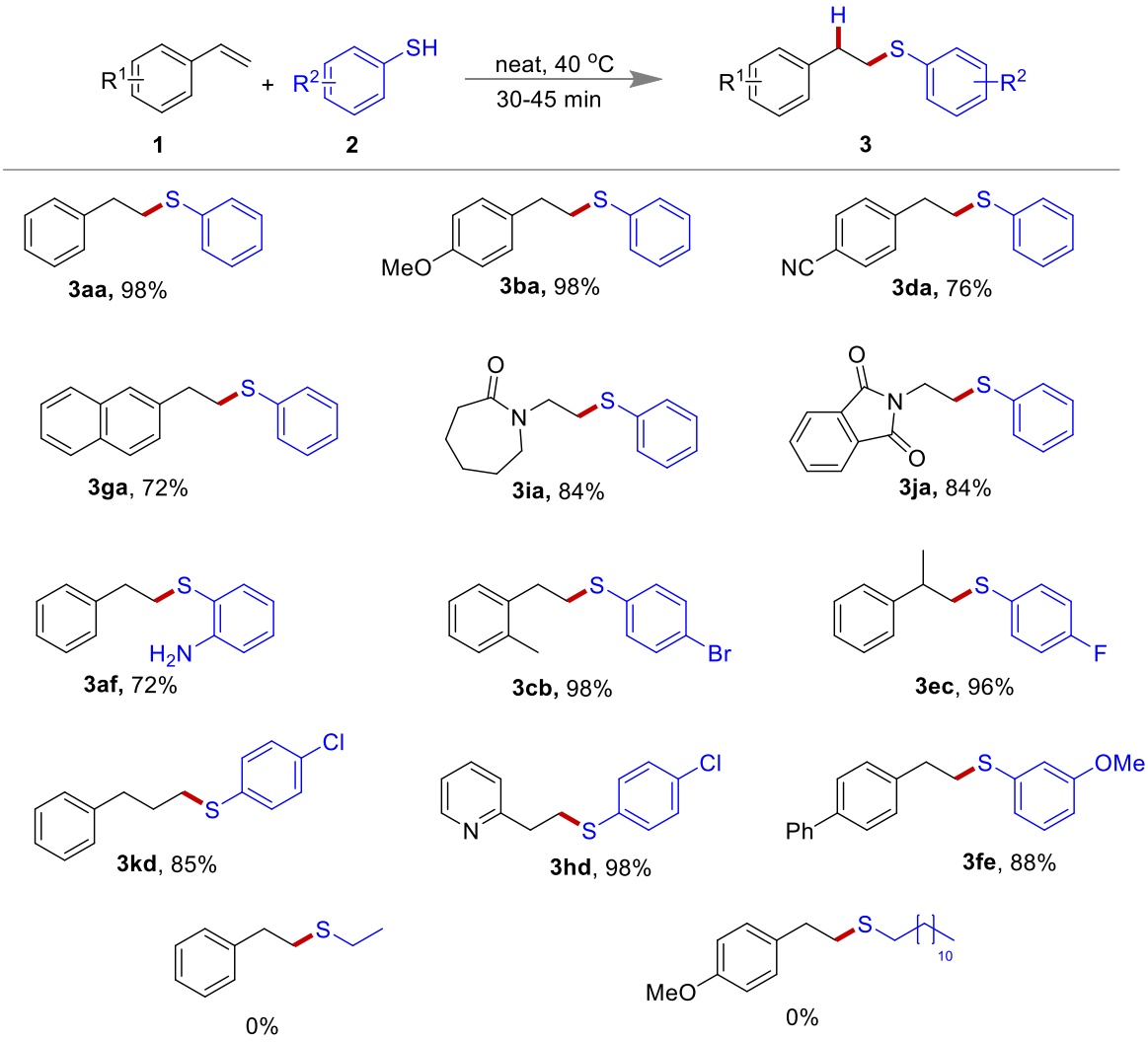


Figure 3A.1. Scope of anti-Markovnikov selective hydrothiolation reaction.

We have tested our methodology with a series of styrene bearing electron donating groups (-Me, -Ph, -OMe, -Napthyl) as well as electron withdrawing group (-CN) to prepare an array of ethyl sulfane derivative. Delightfully, *N*-vinylcaprolactam and *N*-Vinylphthalimide were also efficiently reacted with thiophenol giving the respected product (3ia, 3ja). Due to the very mildness of the system, any kind of functional group could be tolerated the reaction system. It is noteworthy that α-methylstyrene was also worked well to afford sterically congested ethyl sulfane derivative (3ec) in excellent yield. Furthet effort has been done with hetrocyclic

ring containing olefins and offered the respected anti-Markovnikov selective product in excellent yield (3hd). Equally both electron donating (-OMe, -NH_2) and withdrawing group (-F, -Cl) containing thiophenol were afforded good to excellent yield. Amusingly, Cl and Br substituents on thiophenol ring were also well tolerated which enabled to further functionalization. Aliphatic styrene also worked well to provide excellent yield (3kd). It is noted that aliphatic thiophenol are not responding the reaction system due to S–H···π interaction was unsusceptible to create enough electrophilicity on sulphur atom of aliphatic mercaptain.

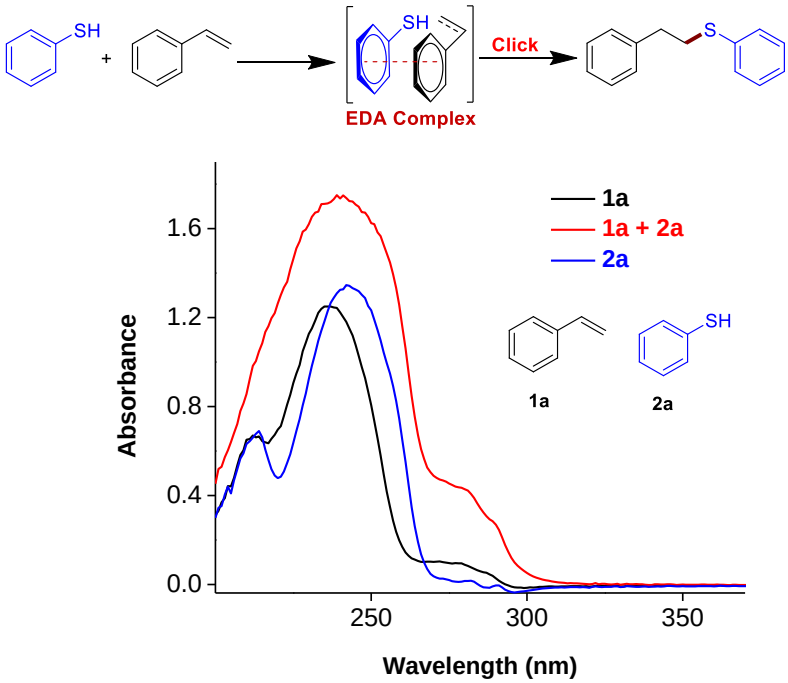


Figure 2A.2. UV-Vis absorption spectra at 2.2 × 10-4 M concentration in ethanol.

Next, we investigated the mechanistic pathway for the anti-Markovnikov Thiol-ene click reaction (TEC) shown in Figure 3A.3 in which we observed that Markovnikov selective product (5aa) formation was occured exclusively in presence of AgOTf and anti-Markovnikov selectivity product was obtained under neat condition with no additive. From the UV-Vis absorption spectra shown in Figure 3A.2, a clear charge transfer band (270-300 nm) appeared possibly due to the formation electron donor-acceptor[47] or charge transfer (CT)

complex. When the reactants 1a and 2a were in close proximity, the click reaction was anticipated for the formation of a single regioisomer 3aa. The exclusive anti-Markovnikov selectivity under neat condition might be due to the primarily S-H…π interaction[16] and followed by CT complex formation. It is anticipated that driving force for the formation of the CT complex is S-H…π interaction involving the π-cloud of C=C and consequential parallel displaced weak π-π stacking. The possibility of aggregation between 1a and 2a increased under neat condition and the formation of CT complex was favorable. Therefore due to the formation of CT complex umpolung reactivity was observed and it led to exclusive anti-Markovnikov selectivity. In this reaction, the absence of any Markovnikov selective product[48] indicated that the reaction did not proced either through radical pathway by single electron transfer[42] or *via* concerted [2+2] cycloaddition as shown in Figure 3A.3a. Interestingly, when the reaction of **1a** and **2a** were carried out in presence of Lewis acid AgOTf in benzene (Figure 3A.3b), Markovnikov selective product (**5aa**) was observed exclusively in 84% yield. Possibly, the thiophilic promoter AgOTf[49,50] inhibited S-H…π interaction *via* coordination of sulfur lone pair and the cation-π interaction[51] of styrene-Ag^+ induced the normal polarity click reaction (Figure 3A.3b) for the Markovnikov selective product (5aa) formation. Also, during the Ag^+ coordination π-π stacking could not be operative between the aromatic rings. Kinetic experiments with large excess (up to 20 equiv) of thiols (2a) and 1a (1 equiv) under neat condition did not affect any rate of formation of 3aa at 40 ºC. Thus proved, 1:1 adduct of 1a-2a was crucial for the anti-Markovnikov TEC. To confirm the mechanistic pathway of anti-Markovnikov selective TEC reaction, theoretical study (Td-DFT) was also performed. Natural Bond Orbital (NBO) calculation on optimized structure at M06-2X/6-31++G(d,p) level ensure us π(C=Colefin)→σ*(S-H) charge transfer is 1.01 kcal/mol and the structure is further stabilized*via* parallel displacement π-π stacking interaction between 1a and 2a with the stacking distance of 3.64 Å.

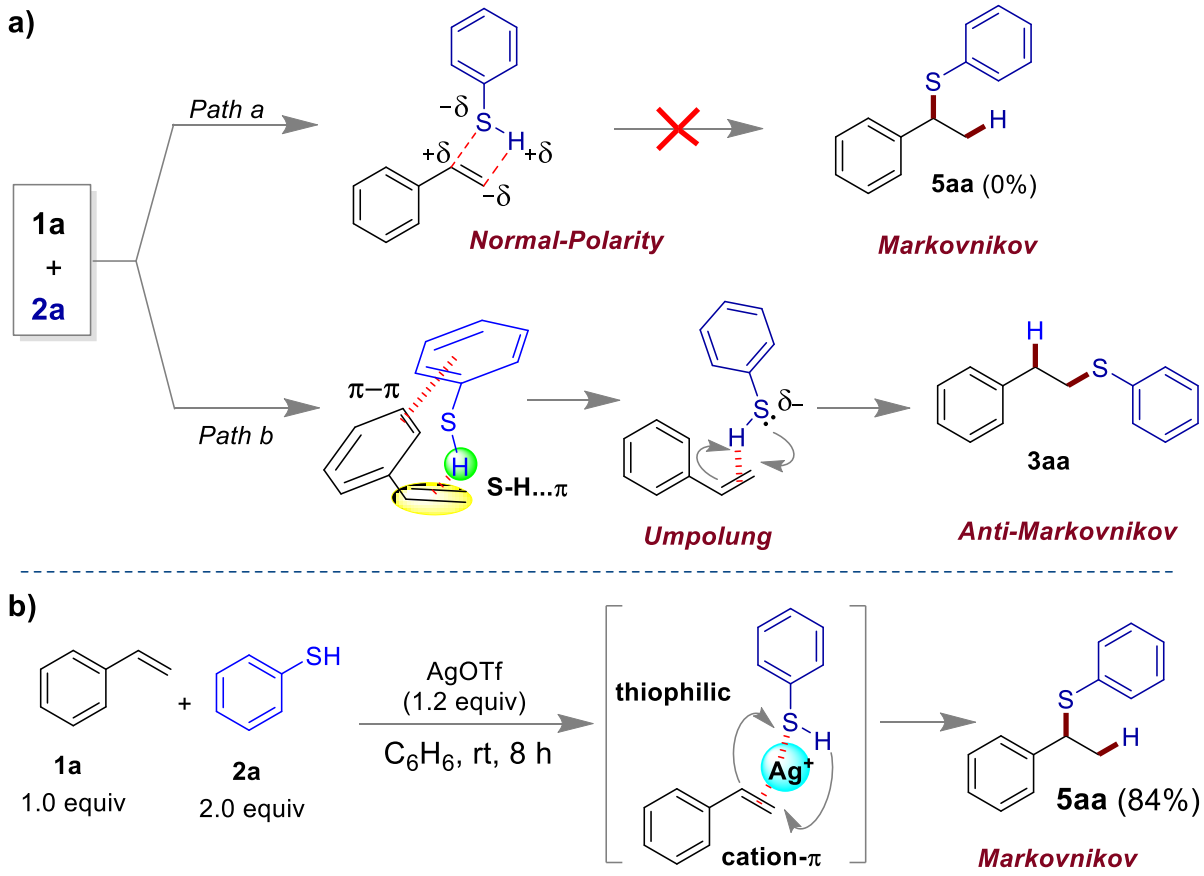


Figure 2A.3. Mechanism for TEC reaction. a) S-H…π and π-π stacking influence for anti-Markovnikov TEC *via* umpolung. b) The thiophilic promotion and cation-π interaction by AgOTf led to normal-addition Markovnikov selective product.

TD-DFT study at rCAM-B3LYP/6-31+G(d,p)/CPCM-EtOH level confirms the transition at λmax =289 nm has simultaneous contribution of local and charge transfer excitations from π-orbitals of thiol to styrene. (For details about DFT calculation, please follow the article "*Chem. Commun.* **2018**, *54*, 3759").

3A.4 CONCLUSION

In conclusion, we have developed an operationally simple and efficient greener method for weak interaction controlled regioselective anti-Markovnikov hydrothiolation reaction under neat condition. The described method for the anti-Markovnikov TEC reaction is the simplest approach till known so far and validated the concept of system chemistry for small molecule.

We have confirmed that these reactions can offer easy access to several organosulfur compounds. Also, we have mechanistically shown weak interaction (S-H…π and π-π stacking) played the pivotal roles to obtain anti-Markovnikov selective products. However, thiophilic promoter silver (I) inhibited S-H…π interaction and Markovnikov selective TEC reaction was observed exclusively. The ability to switch the reactivity of a reaction system towards desired products within a system can have significant applications in synthesis and supramolecular chemistry.

3A.5 EXPERIMENTAL SECTION

General information. All the chemicals were purchased from the commercially available sources and used without further purification. The reactions were done mainly under open atmosphere. Column chromatographic purification of the compounds was performed using (230-400) mess silica gel and hexane/ethyl acetate as an eluent. ^{1}H and ^{13}C spectra of the compounds were recorded on Bruker 400 and 700 MHz instrument at 25 ^{o}C. The chemical shift value (δ, ppm) were reported with respect to the residual chloroform (7.26 for ^{1}H and 77.16 ppm for ^{13}C). High resolution mass spectroscopy (HR-ESIMS) was recorded on ESI-TOF (Time-of-flight) mass spectroscopy.

General procedure for the preparation of thioethers (3). Styrene (60 μL, 0.522 mmol) and thiophenol (80 μL, 0.784 mmol) were placed in an oven dried round bottom flask. Then the mixture was allowed to stir for 30 min at room temperature (35-40 ^{o}C). The resulting mixture was purified by silica gel column chromatography using hexane as eluent.

NMR characterization Data.

Phenethyl(phenyl)sulfane (3aa):[32] R_f = 0.75 (in hexane); colorless liquid; yield 98% (119 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2H), 7.34 – 7.26 (m, 4H), 7.25 – 7.15 (m, 4H), 3.21 – 3.15 (m, 2H), 2.97 – 2.91 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 140.3, 136.5, 129.3, 129.1, 128.6 (×2), 126.6, 126.1, 35.7, 35.2.

(4-Methoxyphenethyl)(phenyl)sulfane (3ba):[32] R_f = 0.75 (5% ethyl acetate in hexane); colorless liquid; yield 98% (105 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.31 – 7.27 (m, 2H), 7.21 – 7.16 (m, 1H), 7.14 – 7.09 (m, 2H), 6.86 – 6.82 (m, 2H), 3.79 (s, 3H), 3.17 – 3.10 (m, 2H), 2.91 – 2.83 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.4, 136.6, 132.5, 129.6, 129.3, 129.1, 126.1, 114.1, 55.4, 35.5, 34.9.

4-(2-(Phenylthio)ethyl)benzonitrile (3da): Rf = 0.2 (5% ethyl acetate in hexane); colorless liquid; yield 76% (100 mg); 1H NMR (700 MHz, $CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.32 – 7.27 (m, 4H), 7.23 – 7.20 (m, 1H), 3.17 (t, J = 7.7 Hz, 2H), 2.98 (t, J = 7.7 Hz, 2H); 13C NMR (175 MHz, $CDCl_3$) δ 145.7, 135.7, 132.4, 129.9, 129.6, 129.2, 126.6, 119.0, 110.5, 35.7, 34.8; IR (KBr) ῡ 3056, 2923, 2227, 1920, 1606, 1582, 1480; HRMS (ESI-TOF) calcd for C15H13NS (M + H)+ 240.0841, found 240.0836.

(2-(Naphthalen-2-yl)ethyl)(phenyl)sulfane (3ga):[32] R_f = 0.75 (5% ethyl acetate in hexane); colorless liquid; yield 72% (75 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 3H), 7.64 (s, 1H), 7.49 – 7.41 (m, 2H), 7.41 – 7.36 (m, 2H), 7.35 – 7.27 (m, 3H), 7.23 – 7.17 (m, 1H), 3.30 – 3.23 (m, 2H), 3.14 – 3.06 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 137.8, 136.5, 133.7, 132.4, 129.5, 129.1, 128.3, 127.8, 127.7, 127.2, 127.0, 126.2, 126.2, 125.6, 36.0, 35.2.

1-(2-(Phenylthio)ethyl)azepan-2-one (3ia):[52] R_f = 0.2 (20% ethyl acetate in hexane); colorless liquid; yield 84% (90 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.0 Hz, 1H), 3.62 – 3.55 (m, 2H), 3.37 – 3.32 (m, 2H),

3.10 (t, *J* = 7.0 Hz, 2H), 2.54 – 2.48 (m, 2H), 1.74 – 1.62 (m, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 176.1, 135.9, 129.1, 128.8, 126.1, 51.1, 49.1, 37.3, 31.3, 30.0, 28.9, 23.4.

2-(2-(Phenylthio)ethyl)isoindoline-1,3-dione (3ja):[53] R_f = 0.25 (5% ethyl acetate in hexane); colorless liquid; yield 84% (82 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.70 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.25 – 7.23 (m, 2H), 7.15 – 7.11 (m, 1H), 3.95 – 3.92 (m, 2H), 3.27 – 3.20 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.2, 135.0, 134.1, 132.1, 129.9, 129.2, 126.6, 123.4, 37.7, 31.8. HRMS (ESI-TOF) calcd for $C_{16}H_{13}NO_2S$ $(M + H)^+$ 284.0740, found 284.0747.

2-(Phenethylthio)aniline (3af):[54] R_f = (10% hexane/ethyl acetate); colorless liquid; yield 72% (87 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 1H), 7.31 – 7.27 (m, 2H), 7.23 – 7.19 (m, 1H), 7.18 – 7.15 (m, 2H), 7.15 – 7.11 (m, 1H), 6.78 – 6.68 (m, 2H), 4.08 (br, 2H), 3.03 – 2.99 (m, 2H), 2.89 – 2.83 (m, 2H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 148.0, 140.4, 135.9, 129.8, 128.7, 128.5, 126.4, 118.9, 118.1, 115.3, 36.2, 36.1; HRMS (ESI-TOF) calcd for $C_{14}H_{15}NS$ $(M + H)^+$ 230.0998, found 230.0856.

(4-Bromophenyl)(2-methylphenethyl)sulfane (3cb): R_f = 0.7 (in hexane); colorless liquid; yield 98% (140 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.48 – 7.34 (m, 2H), 7.27 – 7.21 (m, 2H), 7.19 – 7.09 (m, 4H), 3.14 – 3.07 (m, 2H), 2.96 – 2.88 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.2, 136.1, 135.8, 132.1, 130.9, 130.5, 129.2, 126.9, 126.3, 119.9, 34.1, 33.1, 19.4; IR (KBr) ῡ 3061, 2923, 1603, 1566, 1470; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrS$ $(M + O + Na^+)$ 344.9919, found 344.9921.

(4-Fluorophenyl)(2-phenylpropyl)sulfane (3ec): R_f = 0.6 (hexane); colorless liquid; yield 96% (108 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 4H), 7.28 – 7.15 (m, 3H), 7.12 – 6.92 (m, 2H), 3.25 – 3.18 (m, 1H), 3.11 – 3.03 (m, 1H), 3.00 – 2.93 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.8 (d, $^1J_{CF}$ = 246.2 Hz), 145.5, 132.3 (d, $^3J_{CF}$ = 8.0 Hz), 131.7 (d, $^4J_{CF}$ = 3.2 Hz), 128.7, 127.1, 126.7, 116.1 (d, $^4J_{CF}$ = 21.9 Hz), 43.6, 39.7, 21.1, IR

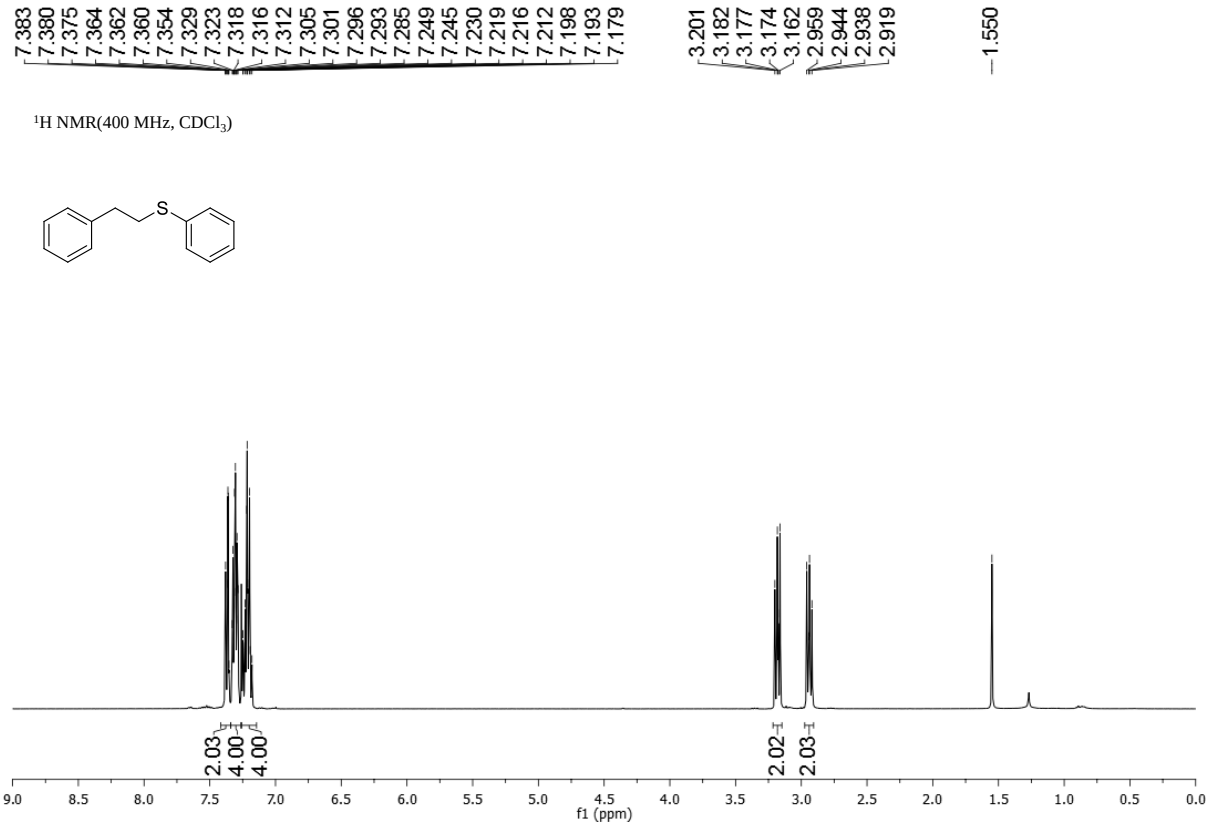
(KBr) ῡ 3060, 2962, 1601, 1589, 1505; HRMS (ESI-TOF) calcd for $C_{15}H_{15}FS$ (M + O + Na^+) 385.0720, found 385.0722.

(4-Chlorophenyl)(3-phenylpropyl)sulfane (3kd):[55] R_f = 0.8 (hexane); colorless liquid; yield 85% (100 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 5H), 7.18 – 7.15 (m, 2H), 2.89 (t, *J* = 7.7 Hz, 2H), 2.75 (t, *J* = 7.7 Hz, 2H), 1.99 – 1.91 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 141.2, 135.2, 131.9, 130.6, 129.1, 128.6, 128.6, 126.2, 34.7, 33.2, 30.6.

2-(2-((4-Chlorophenyl)thio)ethyl)pyridine (3hd): R_f = 0.2 (5% ethyl acetate in hexane); colorless liquid; yield 98% (138 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.58 – 8.52 (m, 1H), 7.65 – 7.58 (m, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.25 (d, *J* = 9.0 Hz, 2H), 7.18 – 7.12 (m, 2H), 3.34 (t, *J* = 7.7 Hz, 2H), 3.10 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.5, 149.5, 136.4, 134.9, 132.0, 130.7, 129.1, 123.3, 121.7, 37.7, 33.4; IR (KBr) ῡ 3060, 2926, 1592, 1568, 1474; HRMS (ESI-TOF) calcd for $C_{13}H_{12}NClS$ $(M + H)^+$ 250.0452, found 250.0438.

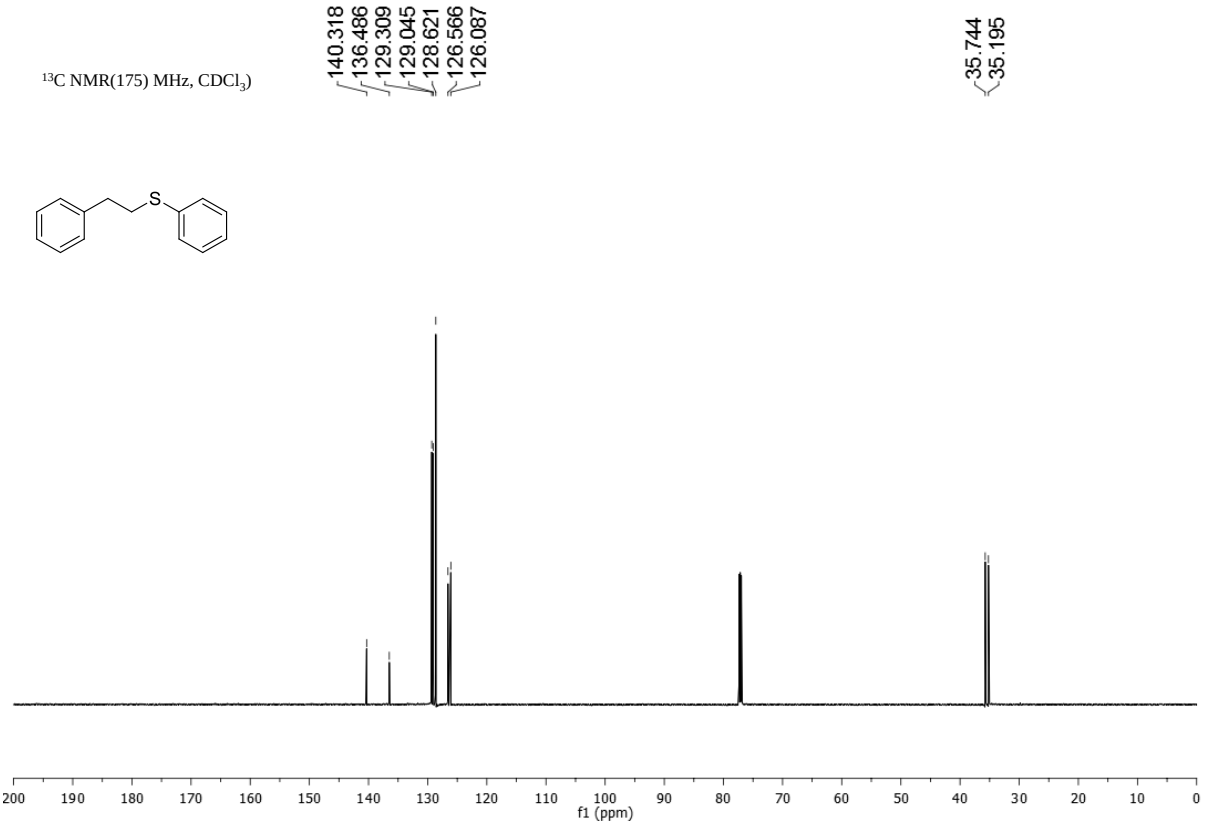
(2-([1,1'-Biphenyl]-4-yl)ethyl)(3-methoxyphenyl)sulfane (3fe): R_f = 0.2 (hexane); colorless liquid; yield 88% (94 mg); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.7 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.30 – 7.27(m, 2H), 7.24 – 7.21 (m, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.92 (s, 1H), 6.78 – 6.72 (m, 1H), 3.81 (s, 3H), 3.26 – 3.19 (m, 2H), 3.04 – 2.96 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.0, 141.0, 139.6, 139.4, 137.8, 129.9, 129.1, 128.9, 127.4, 127.3, 127.2, 121.3, 114.6, 111.8, 55.4, 35.4, 35.0; IR (KBr) ῡ 3054, 2933, 1589, 1573, 1480; HRMS (ESI-TOF) calcd for $C_{21}H_{20}OS$ $(M + Na)^+$ 343.1127 found 343.1226.

^{1}H and ^{13}NMR Spectra of Selected Compounds



^{1}H NMR(400 MHz, $CDCl_3$)

Figure 3A.4. ^{1}H NMR spectrum of phenethyl(phenyl)sulfane **(3aa)**



^{13}C NMR(175) MHz, $CDCl_3$)

Figure 3A.5. ^{13}C NMR spectrum of phenethyl(phenyl)sulfane **(3aa)**

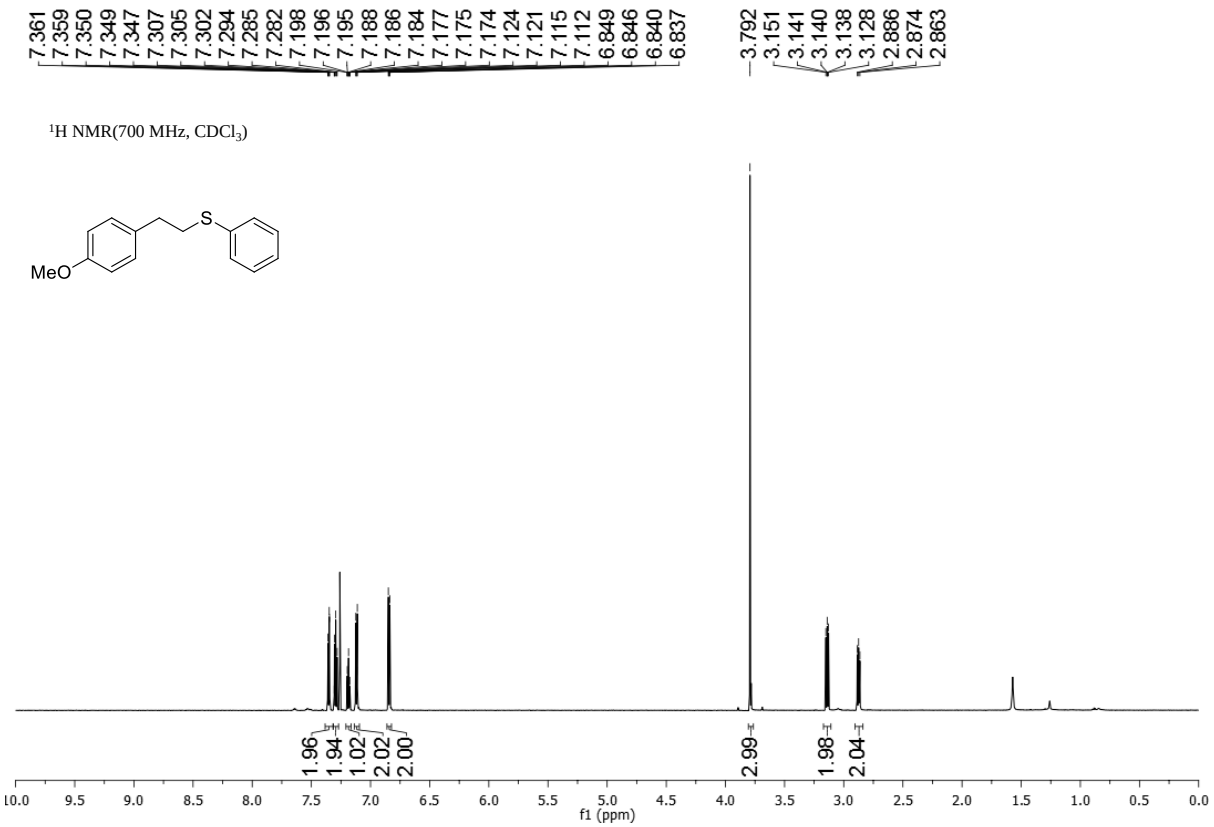


Figure 3A.6. ^{1}H NMR spectrum of (4-methoxyphenethyl)(phenyl)sulfane **(3ba)**

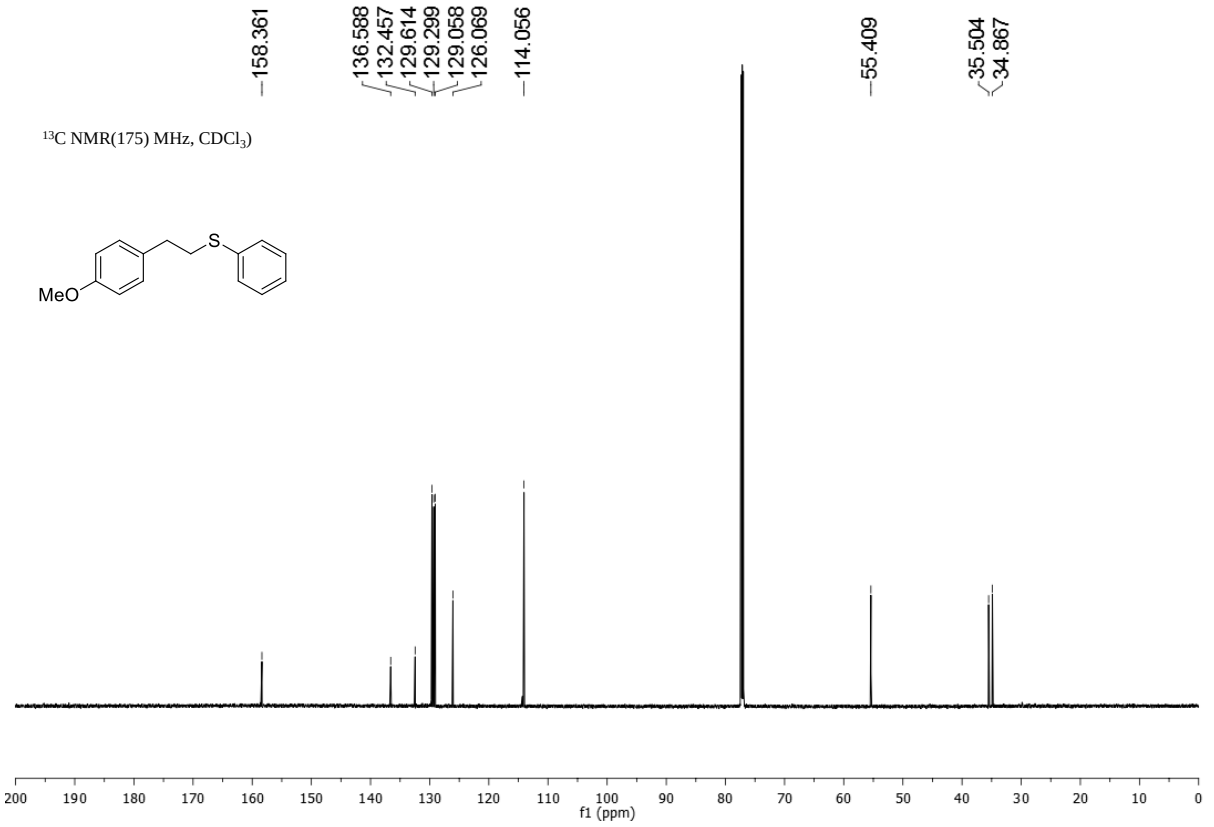


Figure 3A.7. ^{13}C NMR spectrum of (4-methoxyphenethyl)(phenyl)sulfane **(3ba)**

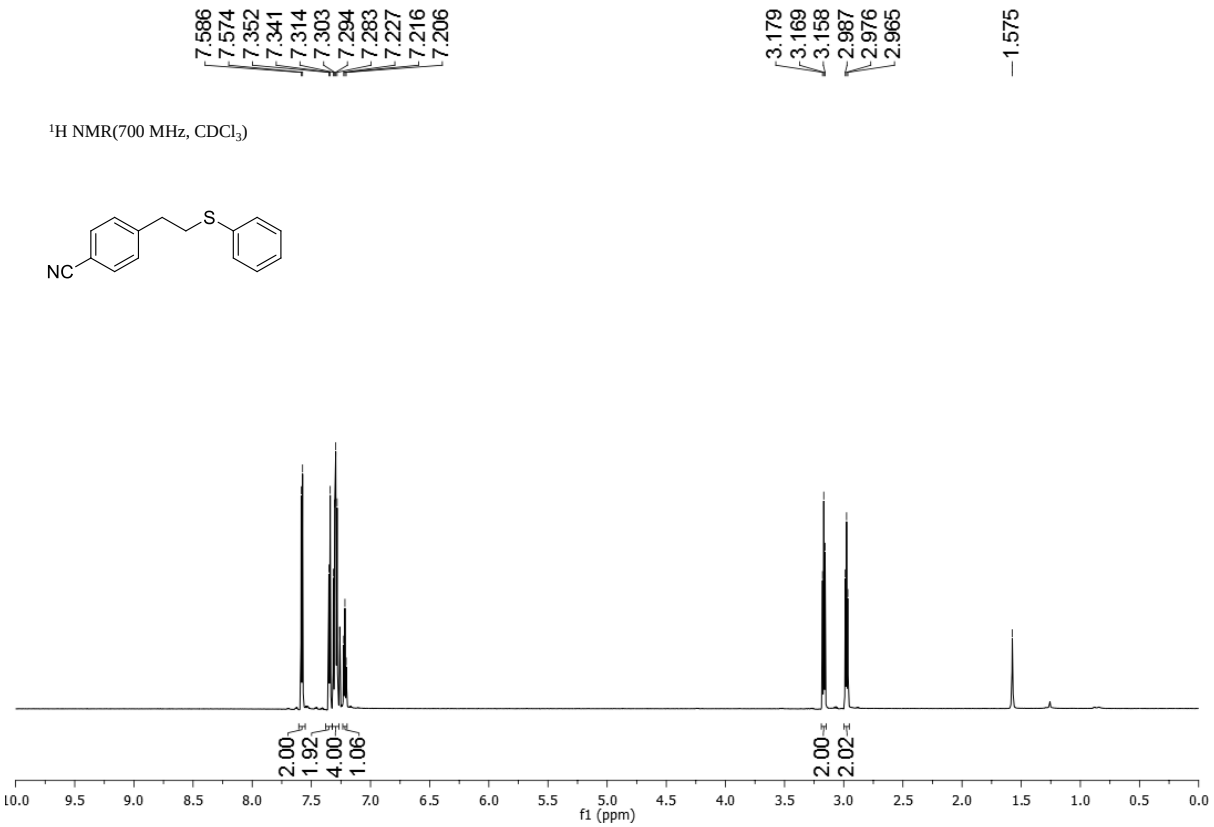


Figure 3A.8. ^{1}H NMR spectrum of 4-(2-(phenylthio)ethyl)benzonitrile **(3da)**

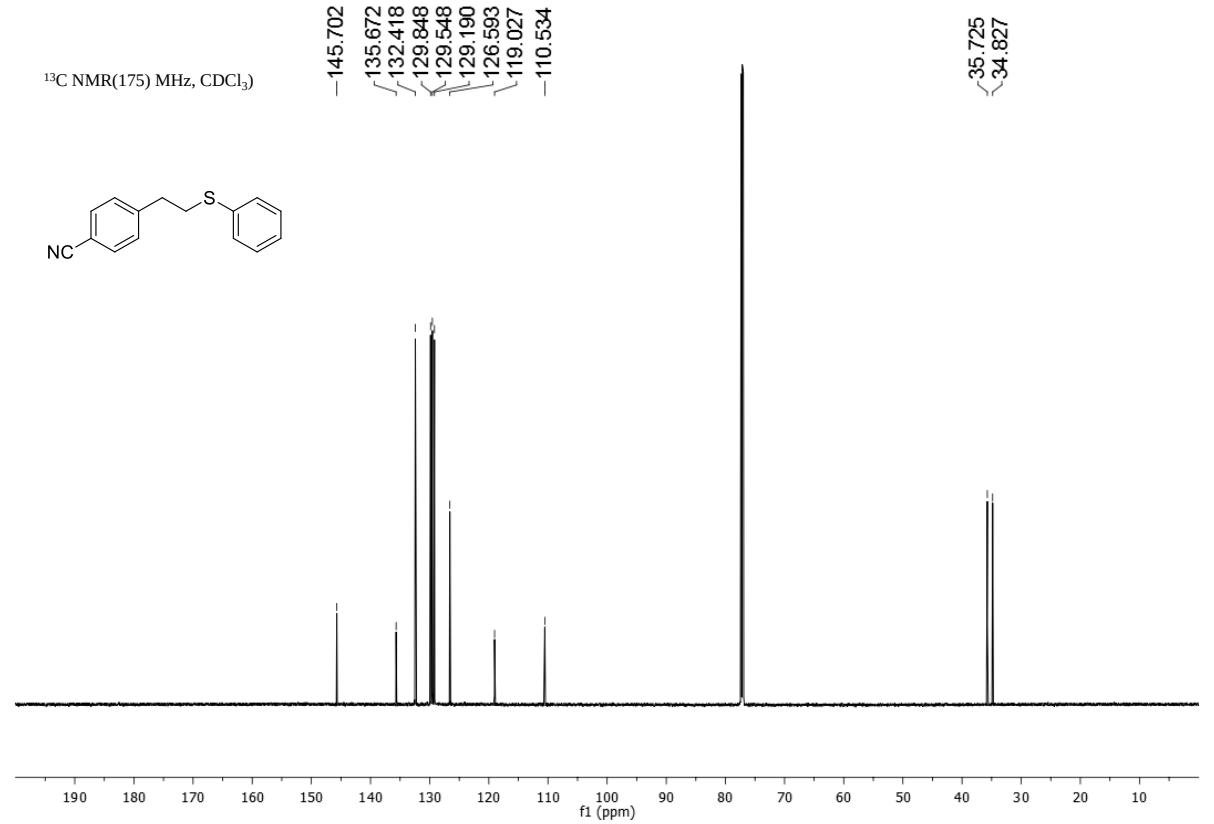


Figure 3A.9. ^{13}C NMR spectrum of 4-(2-(phenylthio)ethyl)benzonitrile **(3da)**

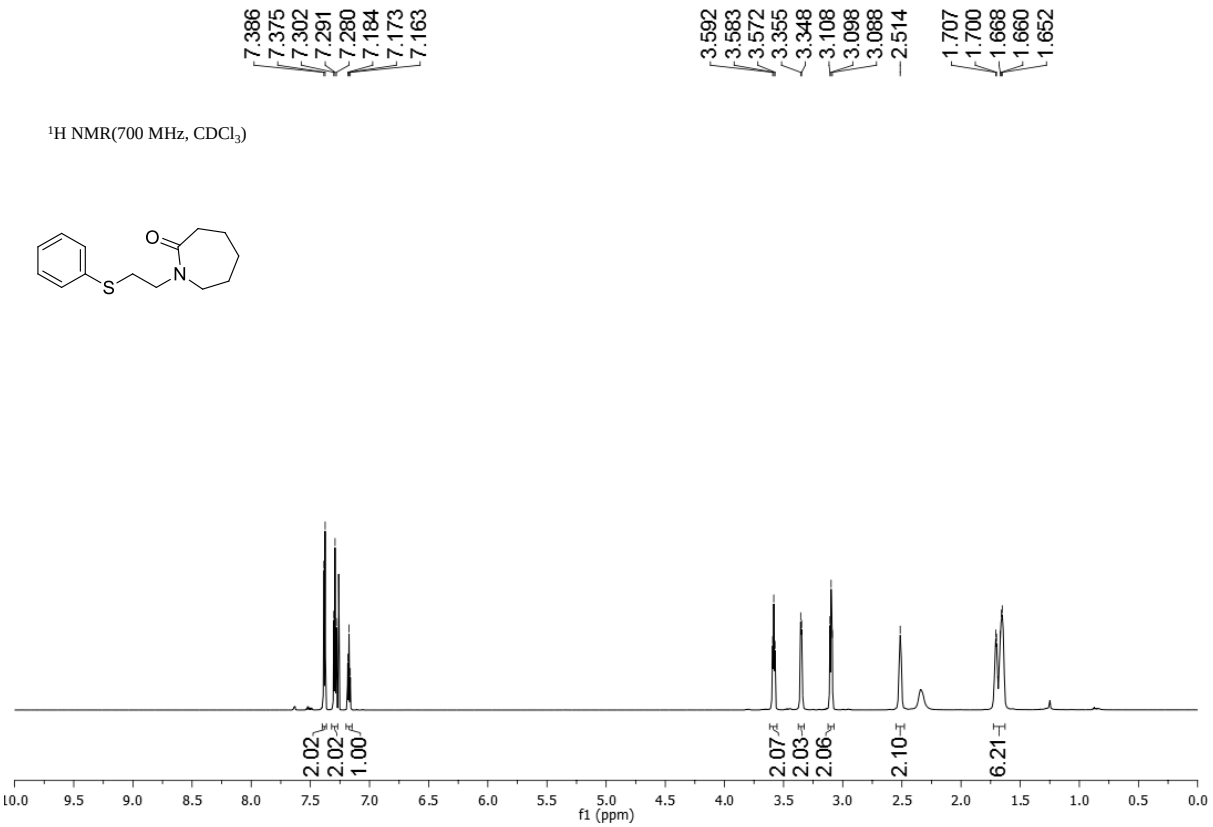


Figure 3A.10. ^{1}H NMR spectrum of 1-(2-(phenylthio)ethyl)azepan-2-one **(3ia)**

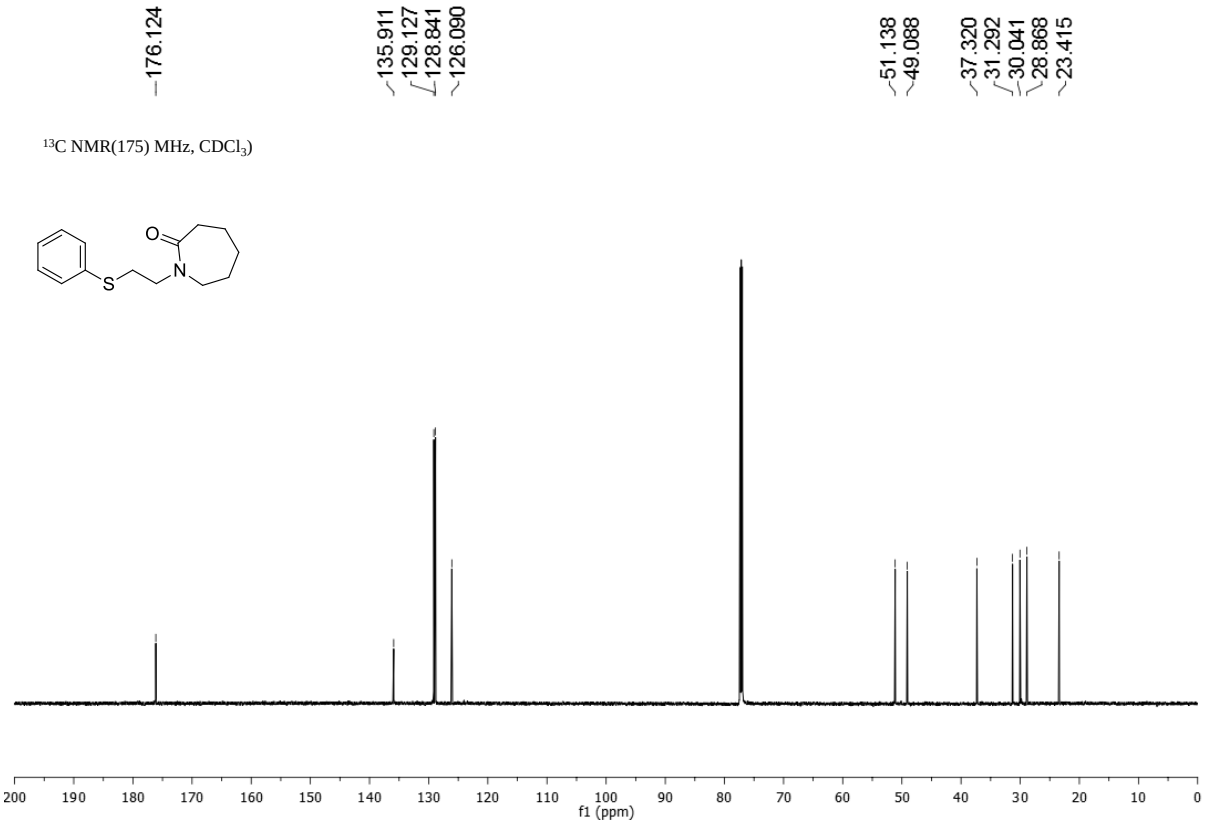


Figure 3A.11. ^{13}C NMR spectrum of 1-(2-(phenylthio)ethyl)azepan-2-one **(3ia)**

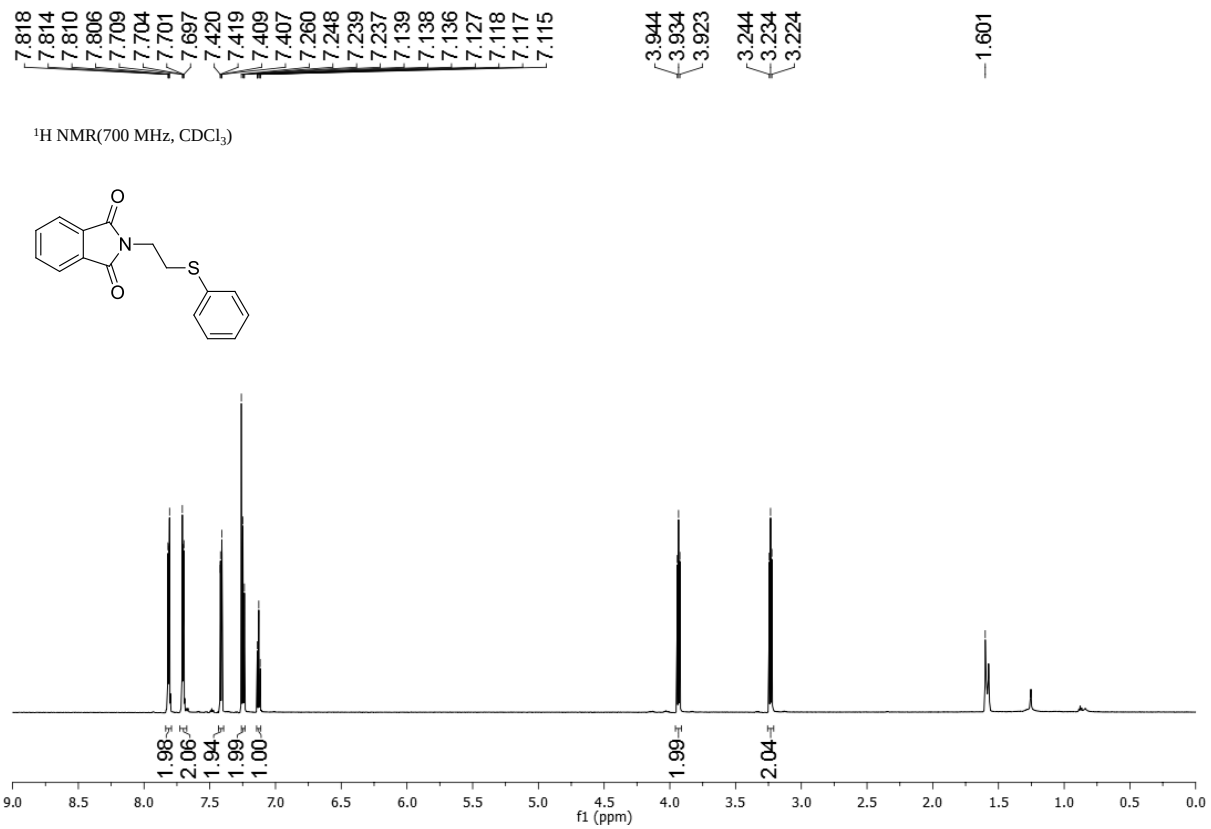


Figure 3A.12. ^{1}H NMR spectrum of 2-(2-(phenylthio)ethyl)isoindoline-1,3-dione **(3ja)**

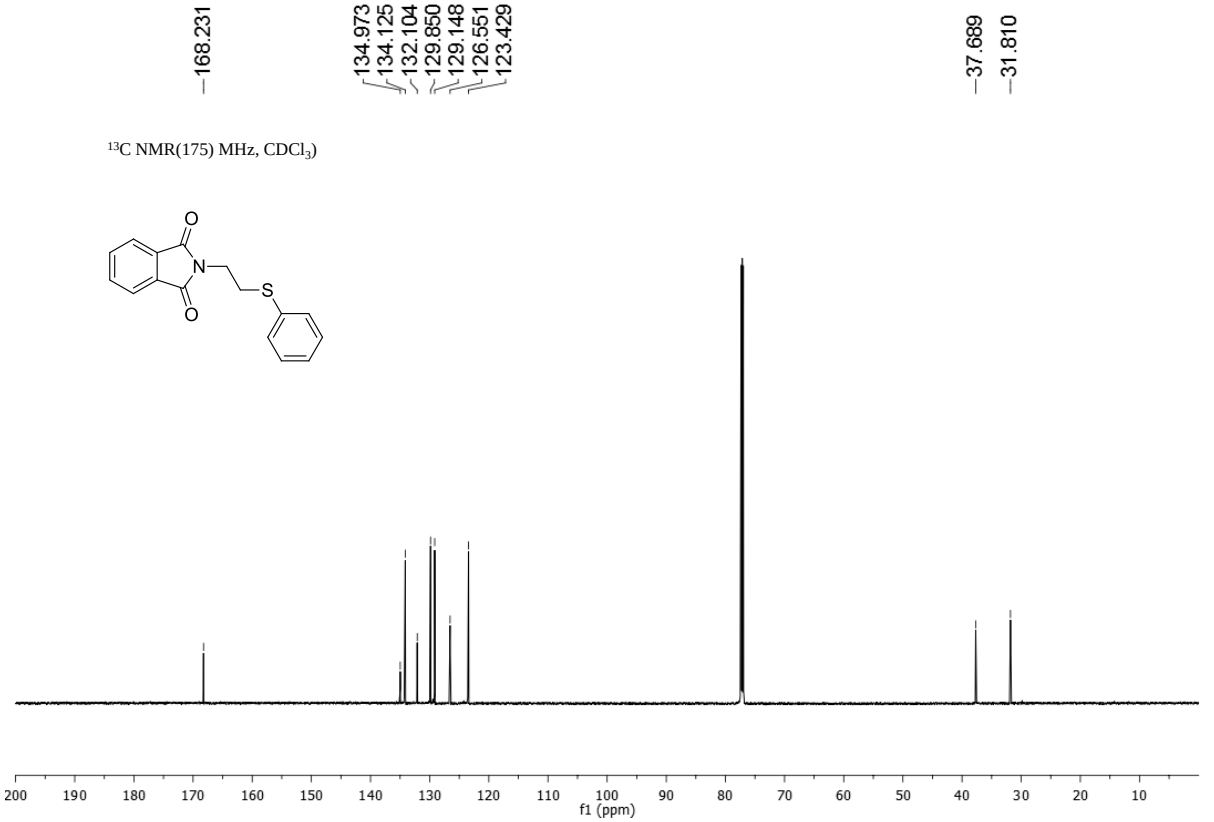
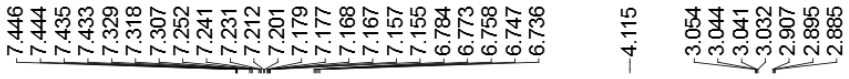
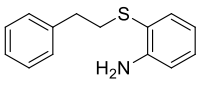


Figure 3A.13. ^{13}C NMR spectrum of 2-(2-(phenylthio)ethyl)isoindoline-1,3-dione **(3ja)**



^{1}H NMR(700 MHz, $CDCl_3$)



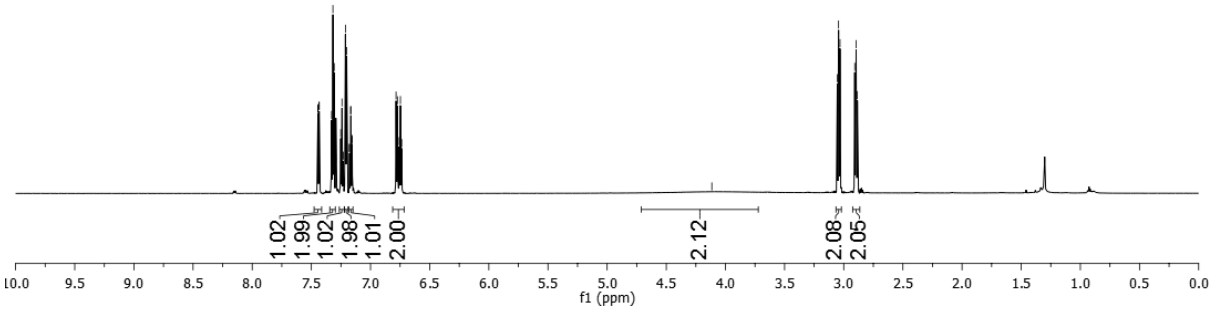
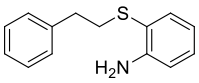


Figure 3A.14. ^{1}H NMR spectrum of 2-(phenethylthio)aniline **(3af)**

^{13}C NMR(175) MHz, $CDCl_3$)



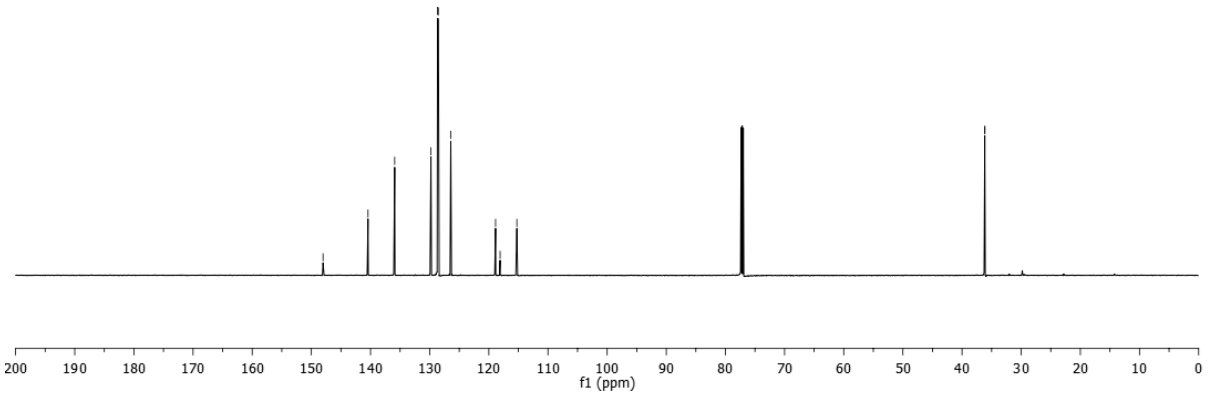


Figure 3A.15. ^{13}C NMR spectrum of 2-(phenethylthio)aniline **(3af)**

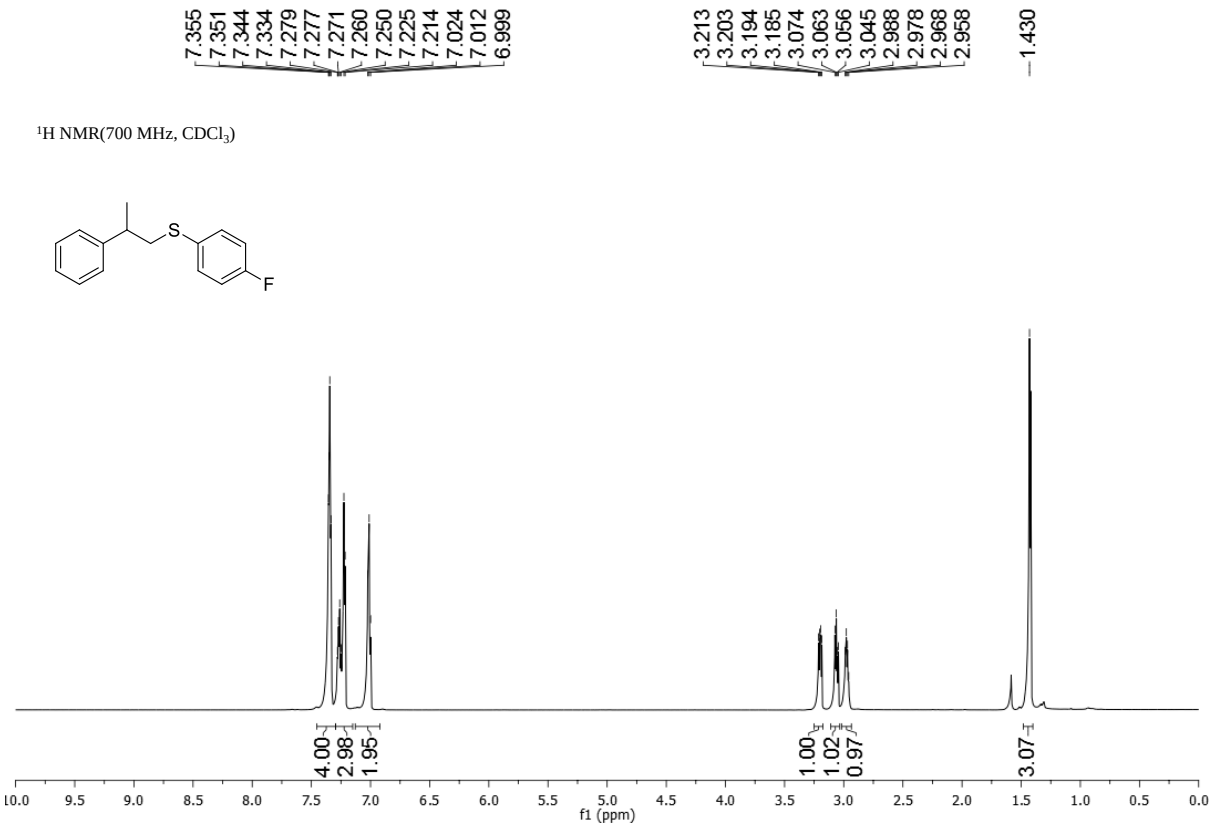


Figure 3A.16. ^{1}H NMR spectrum of (4-fluorophenyl)(2-phenylpropyl)sulfane **(3ec)**

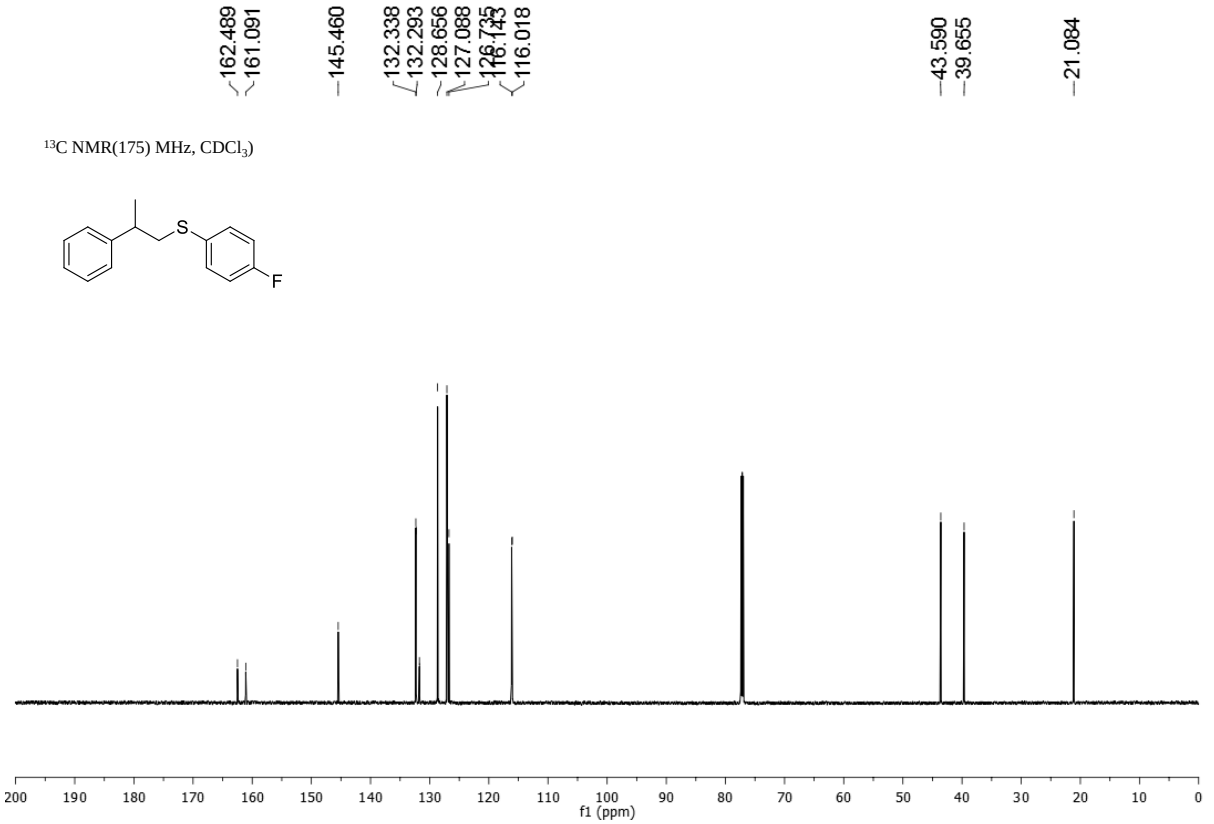
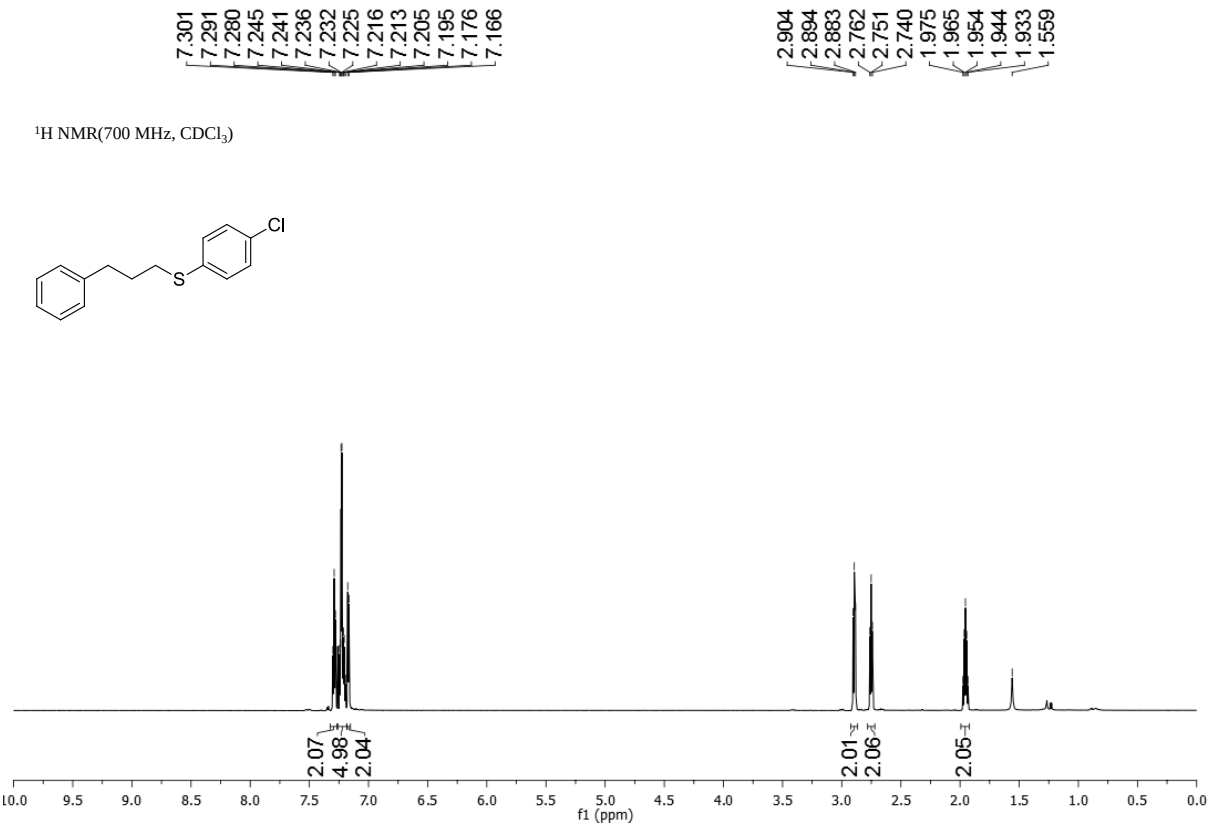
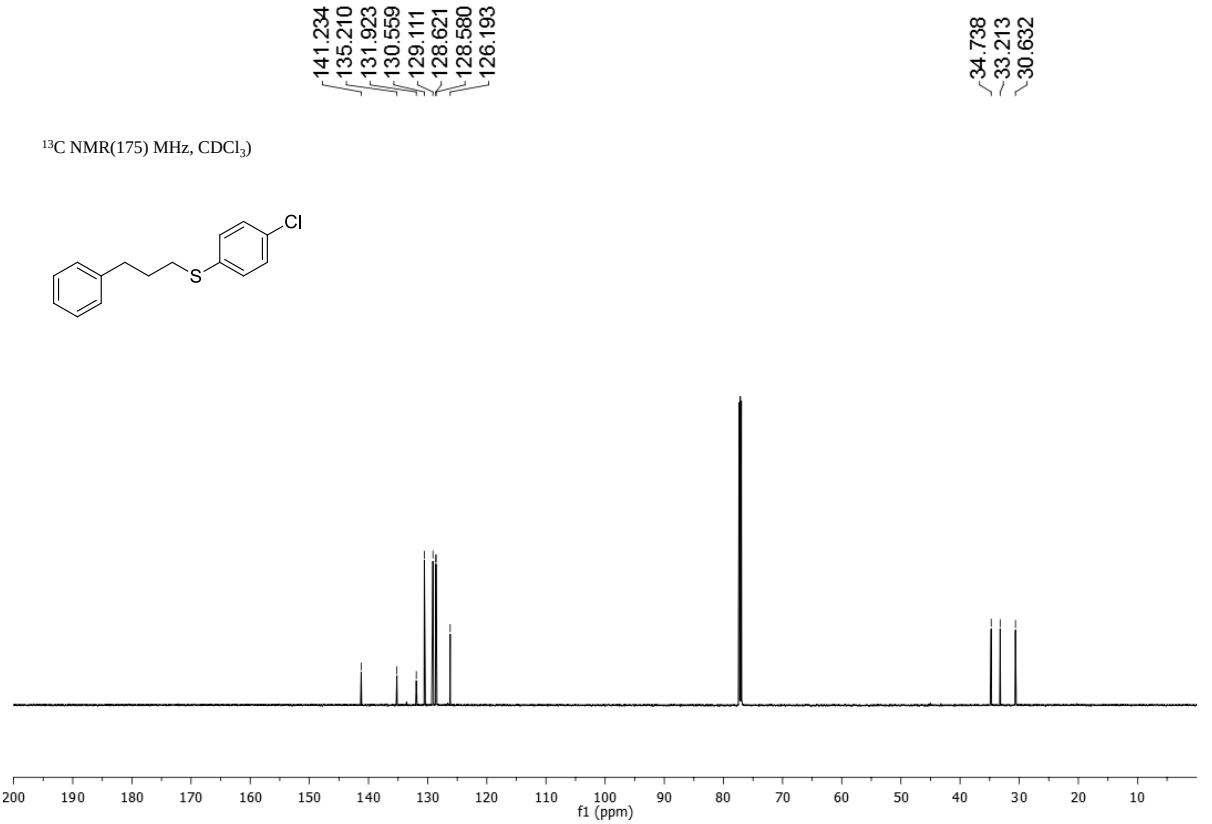


Figure 3A.17. ^{13}C NMR spectrum of (4-fluorophenyl)(2-phenylpropyl)sulfane **(3ec)**



^{1}H NMR(700 MHz, $CDCl_3$)

Figure 3A.18. ^{1}H NMR spectrum of (4-chlorophenyl)(3-phenylpropyl)sulfane **(3kd)**



^{13}C NMR(175) MHz, $CDCl_3$)

Figure 3A.19. ^{13}C NMR spectrum of (4-chlorophenyl)(3-phenylpropyl)sulfane **(3kd)**

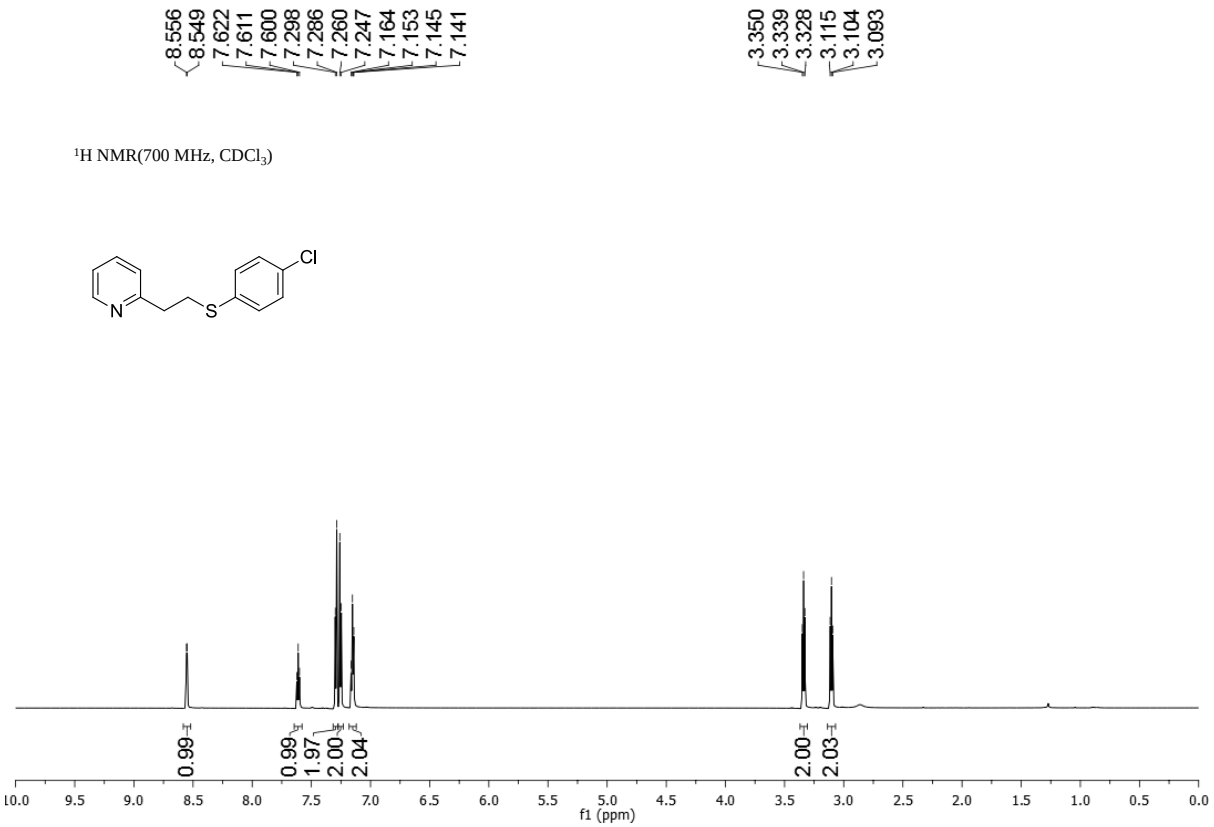


Figure 3A.20. ^{1}H NMR spectrum of 2-(2-((4-chlorophenyl)thio)ethyl)pyridine **(3hd)**

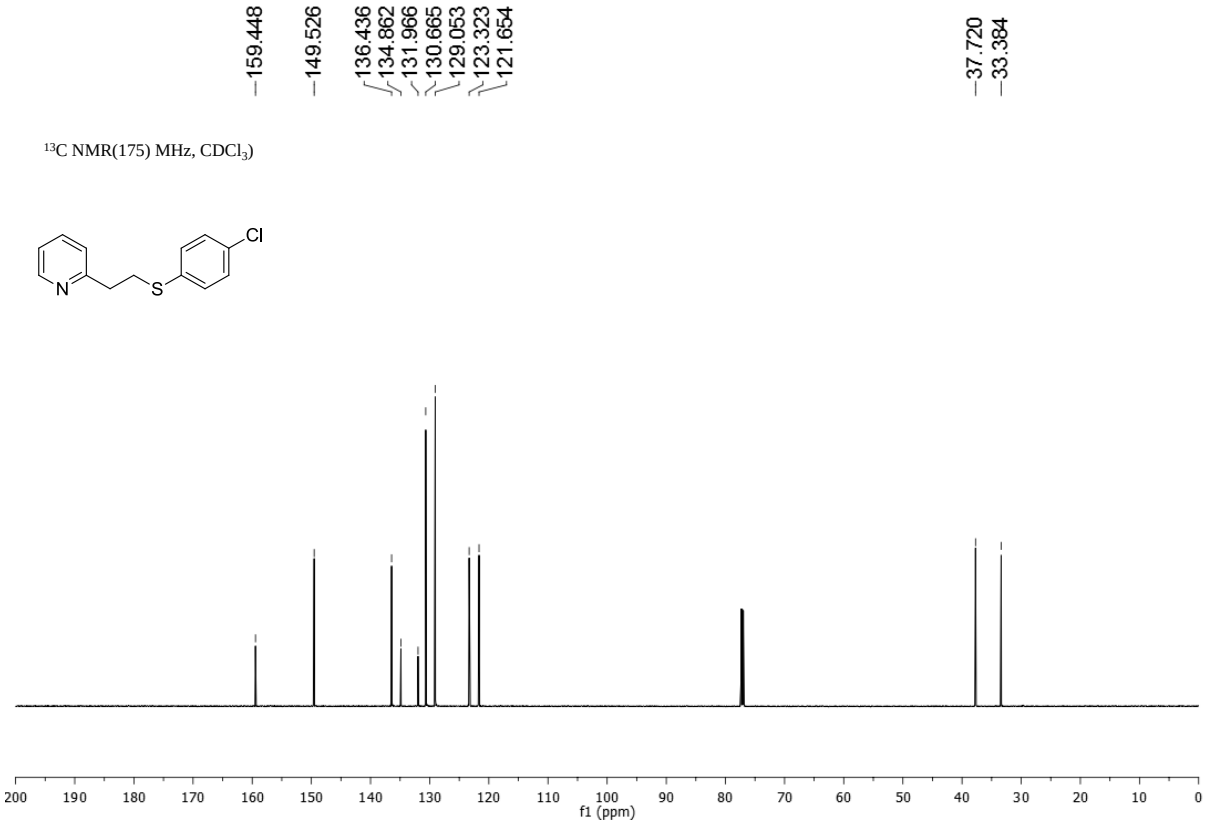


Figure 3A.21. ^{13}C NMR spectrum of 2-(2-((4-chlorophenyl)thio)ethyl)pyridine **(3hd)**

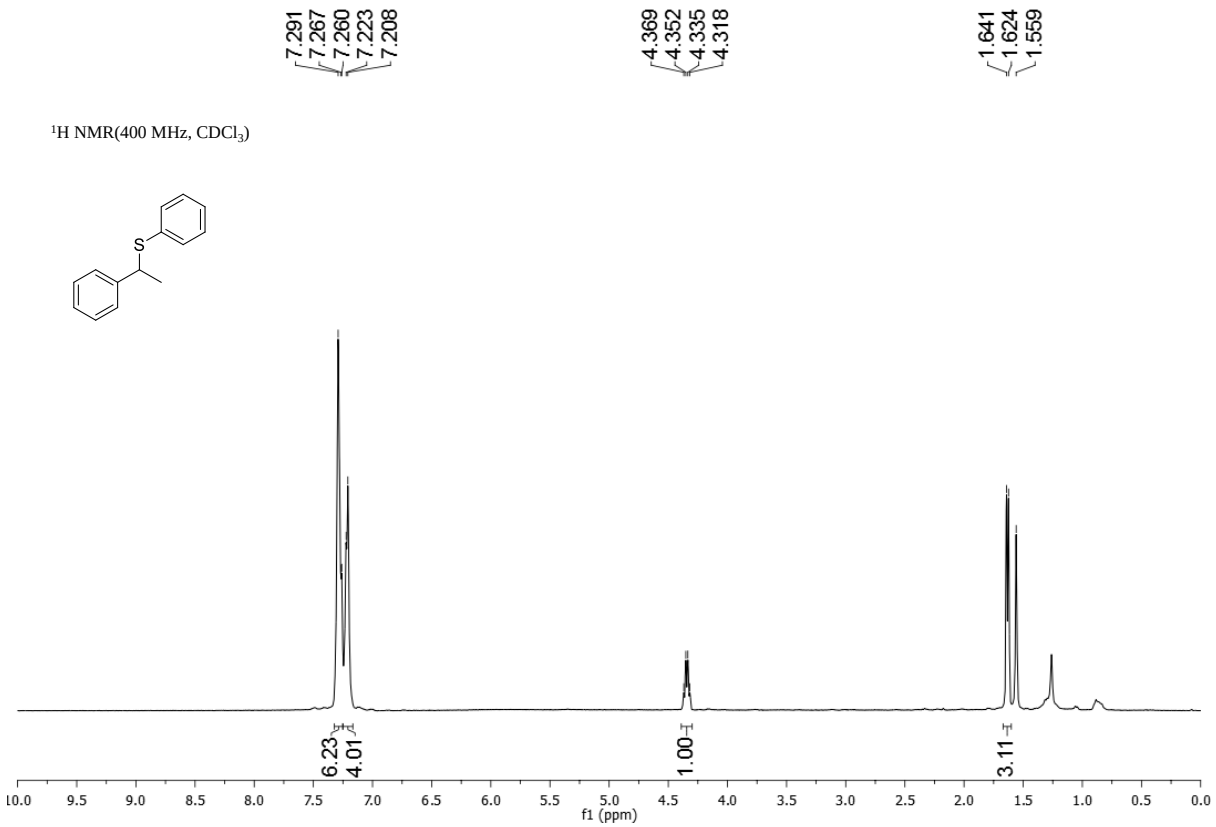


Figure 3A.22. ^{1}H NMR spectrum of phenyl(1-phenylethyl)sulfane

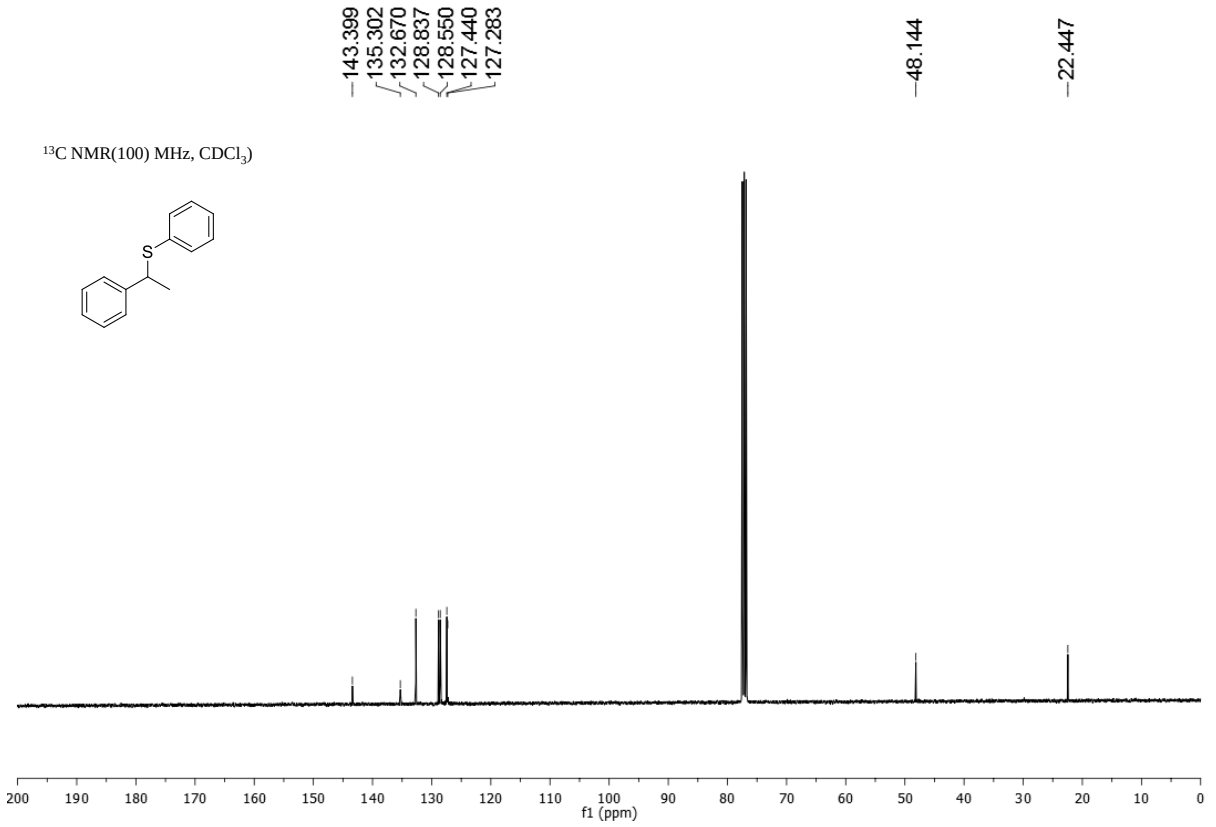
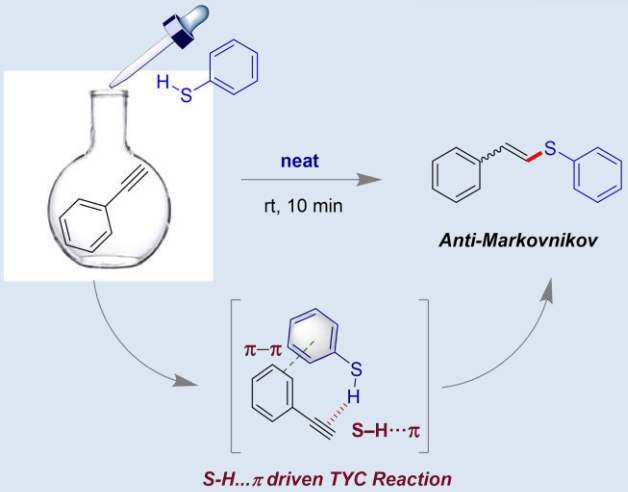


Figure 3A.23. ^{13}C NMR spectrum of phenyl(1-phenylethyl)sulfane

CHAPTER 3: Part B

S - H•••π Driven Thiol-Yne Click (TEC) Reaction

3B.1 ABSTRACT



S-H...π driven TYC Reaction

Herein we have demonstrated anti-Markovnikov selective Thiol-Yne-Click (TYC) reactions that could be achieved by exploiting cooperatively S-H…π and π-π stacking interaction under additive and solvent free condition. The hydrothiolation reaction of phenyl acetylene and thiophenol led to anti-Markovnikov selective TYC product within 10 min, under the neat condition and at room temperature. A self-sorting experiment helped to establish the preference of TYC reaction over the TEC.

3B.2 INTRODUCTION

"Thiol-Yne Click" (TYC) reaction or alkyne hydrothiolation is well-known for making organo-sulfur compounds in many research areas of chemistry like supramolecular,[56] medicinal,[57] materials,[58] polymer,[59] etc. The TYC reaction was first reported in 1949,[60] though, it has experienced a renaissance over the last decade.[61-63] Vinyl sulfides as two regioisomeric products are generally obtained from the respective Markovnikov and anti-Markovnikov selective TYC reactions.[64] Towards synthesis of vinyl sulfides *via* TYC

reaction, many approaches, for example, catalyst free *via* radical path,[26,65-67] organoactinide-mediated,[68] using photo-redox catalyst,[69] visible light photo-catalyst,[70,71] UV-light initiated,[72] transition metal catalyzed,[73,74] ionic-liquid mediated,[62] using *N*-heterocyclic carbene (NHC),[75-77] etc. are well documented in literature. Mechanistically it has been proposed that the reactions could be controlled either by the initiation through radical pathway[78-80] or ionic[81] pathway.

However, in most of the methodologies have some shortcomings such as use of hazardous toxic chemical, expansive metal catalyst, inaccessible substrate scope, poor yield, and formation of unwanted side product. Therefore synthesis of vinyl sulfone in a greener way under mild condition is highly desirable. Towards our research focus on the use of weak interactions in organic synthesis,[82-86] herein, we disclose the unprecedented and simplest approach of anti-Markovnikov selective TYC reaction. This protocol allows the simple addition of thiophenols to an alkyne (Figure 3B.1a), towards generating vinyl sulfides under neat condition under open atmosphere, at room temperature and thus expected to be the greenest. It is anticipated that the reaction control *via* weak interaction can be used to switch the reactivity towards either anti-Markovnikov or Markovnikov selective product formation (Figure 3B.1b). The anti-Markovnikov selectivity is possibly due to the control by S–H···π interaction or ethynyl-H hydrogen bonding among the alkynes and thiophenol *via* umpolung. However, the dipole-dipole interaction would have led to the vinyl sulfides with Markovnikov selectivity by following normal polarity addition.[74,87]

3B.3 RESULT AND DISCUSSION

The reaction system established for the hydrothiolation was shown in Figure 3B.1a. Under neat condition at room temperature (~ 25 ºC), within 10 min, the anti-Markovnikov selective TYC product 3aa was isolated in near quantitative yield (> 98%) from the reactions of

phenylacetylene (1a) and thiophenol (2a). Possibly, the reaction proceeded *via* the control of cooperative weak interactions like S–H···π hydrogen bonding between ethynyl group and S-H, and π-π stacking of the aromatic groups (Figure 3B.1c). Otherwise normal polarity preference between 1a and 2a would have produced the Markovnikov selective product (Figure 3B.1b).

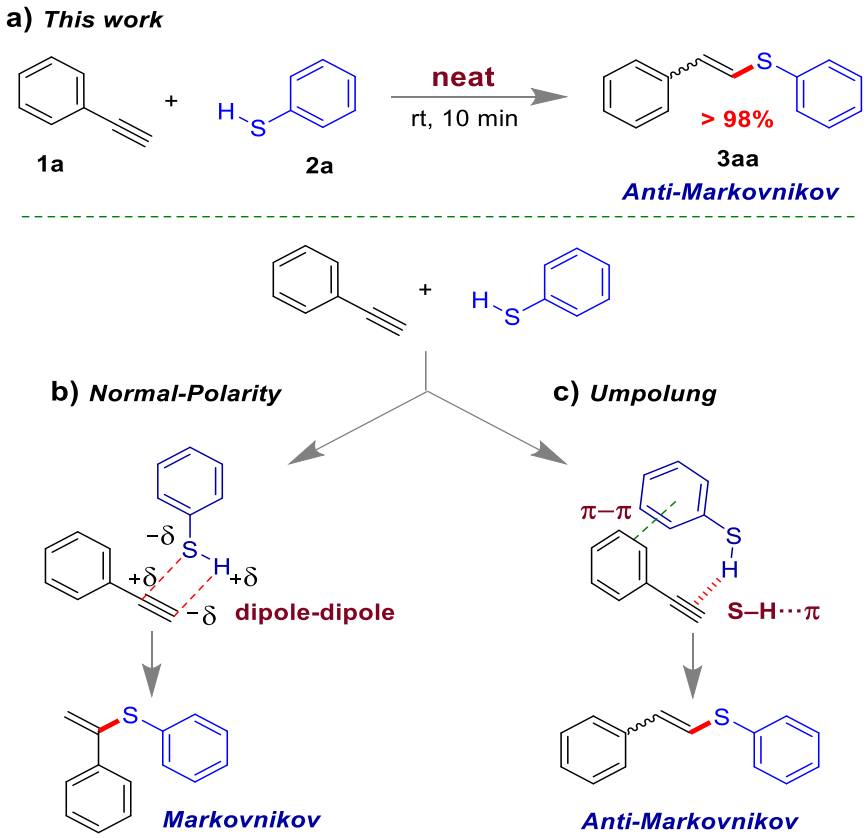


Figure 3B.1. a) Our approach for anti-Markovnikov TYC reaction b) Normal polarity lead to Markovnikov and c) Umpolung polarity lead to anti-Markovnikov selective TYC product.

The proposed mechanism of the reaction (Figure 3B.1c) was supported by theoretical investigations (Td-DFT calculation). The geometry of weak S–H···π hydrogen bonded dimer was optimized at rM06-2X/6-31+G(d,p) level of theory. TD-DFT calculation on optimized dimer at CAM-B3LYP/6-31+G(d,p)/CPCM-EtOH level shows the transition at λ_{max} =275 nm (calculated λ_{max} =293 nm) has sole contribution of charge transfer from HOMO located on thiol to LUMO located on alkyne. Natural bond orbital (NBO) analyses optimized dimer

shows that the second order perturbation energy $E^{(2)}$ in TYC system for $\pi(C{=}C_{alkyne}){\rightarrow}\sigma^*(S\text{-}H)$ charge transfer is 1.45 kcal/ mol which is higher than the reported styrene-thiol system.[18] As the lower π-π stacking distance (3.425 Å) was observed compared to that in styrene-thiol system, 3.640 Å.[18] The optimized dimeric structure was further stabilized by weak π-π stacking as confirmed by perturbation energy values, $\pi_{1a}{\rightarrow}\pi^*_{2a}$, 0.21 kcal/mol, $\pi_{2a}{\rightarrow}\pi^*_{1a}$, 0.44 kcal/mol and 0.35 kcal/mol. (For details about DFT calculation please follow the article *Asian J. Org. Chem.* **2018**, *7*, 1849).

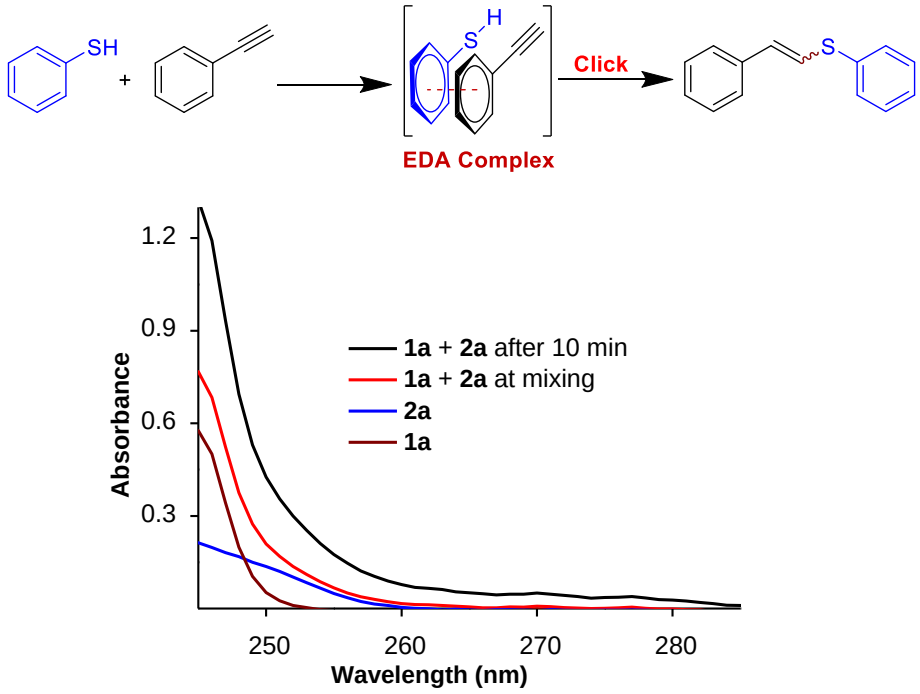


Figure 3B.2. UV-Vis absorption spectra at 2.2 × 10-4 M concentration in ethanol.

We have also performed some experimental investigation for the confirmation of anticipation on S–H···π interaction over the anti-Markovnikov TYC system (Figure 3B.3). When 4-mercaptophenol (2k) reacted with phenyl acetylene (1a), only –SH group had reacted and the corresponding vinyl sulfide derivative was isolated in 96% yield with mainly Z-selectivity (~99%, Figure 3B.3a).

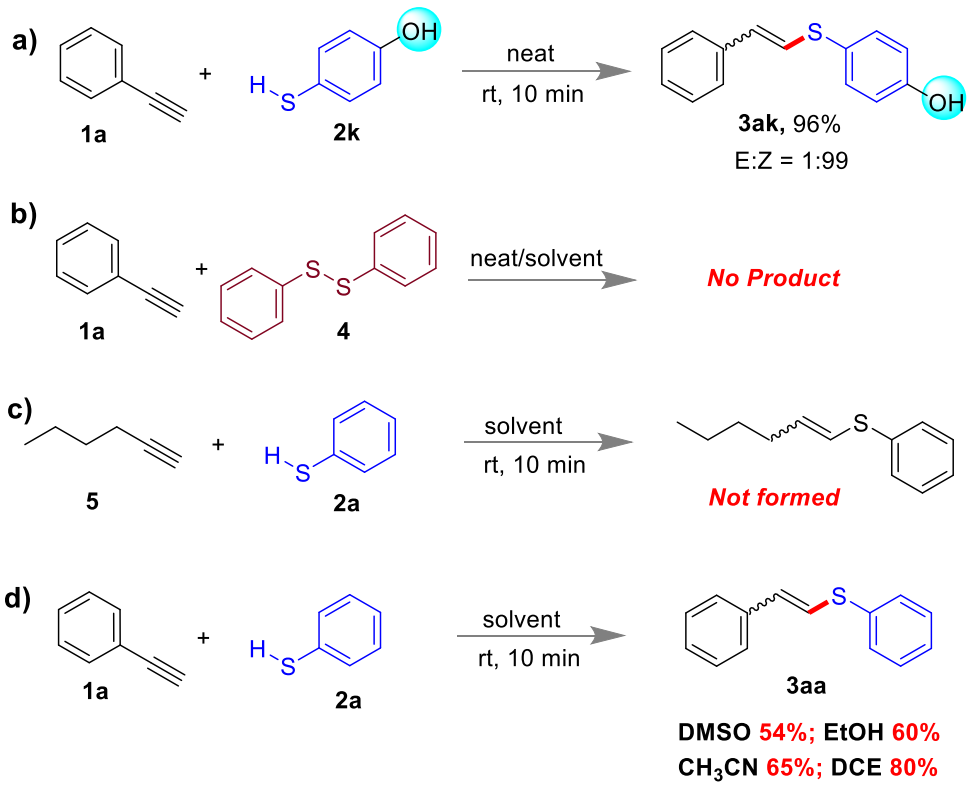


Figure 3B.3. Control experiments. a) a) –SH *vs.* -OH preference towards alkyne. b) Unsuccessful reaction from phenyl acetylene and disulfides. c) No response from aliphatic alkyne on the system. d) Yields of vinyl sulfide in different solvents.

Interestingly, diphenyldisulfide (4) did not produce any product formation upon reaction with 1a might be due to the absence of any S–H···π interaction (Figure 3B.3b). We have predicted that weak π-π stacking interaction between 1a and 2a could also be one of the important requirements towards the anti-Markovnikov selective TYC reaction. Therefore, no product could be detected with 1-hexyne (5) and thiophenol (2a) (Figure 3B.3c). Furthermore, it was also expected that the solvent polarity could influence the weak interactions like S–H···π or π-π stacking. Hence significantly lower yield was observed while solvent polarity was going towards higher (Figure 3B.3d). Notably, higher yield (80%) was obtained in less polar solvent such as dichloroethane and fewer yields (54%) in more polar solvent dimethyl sulfoxide (DMSO).

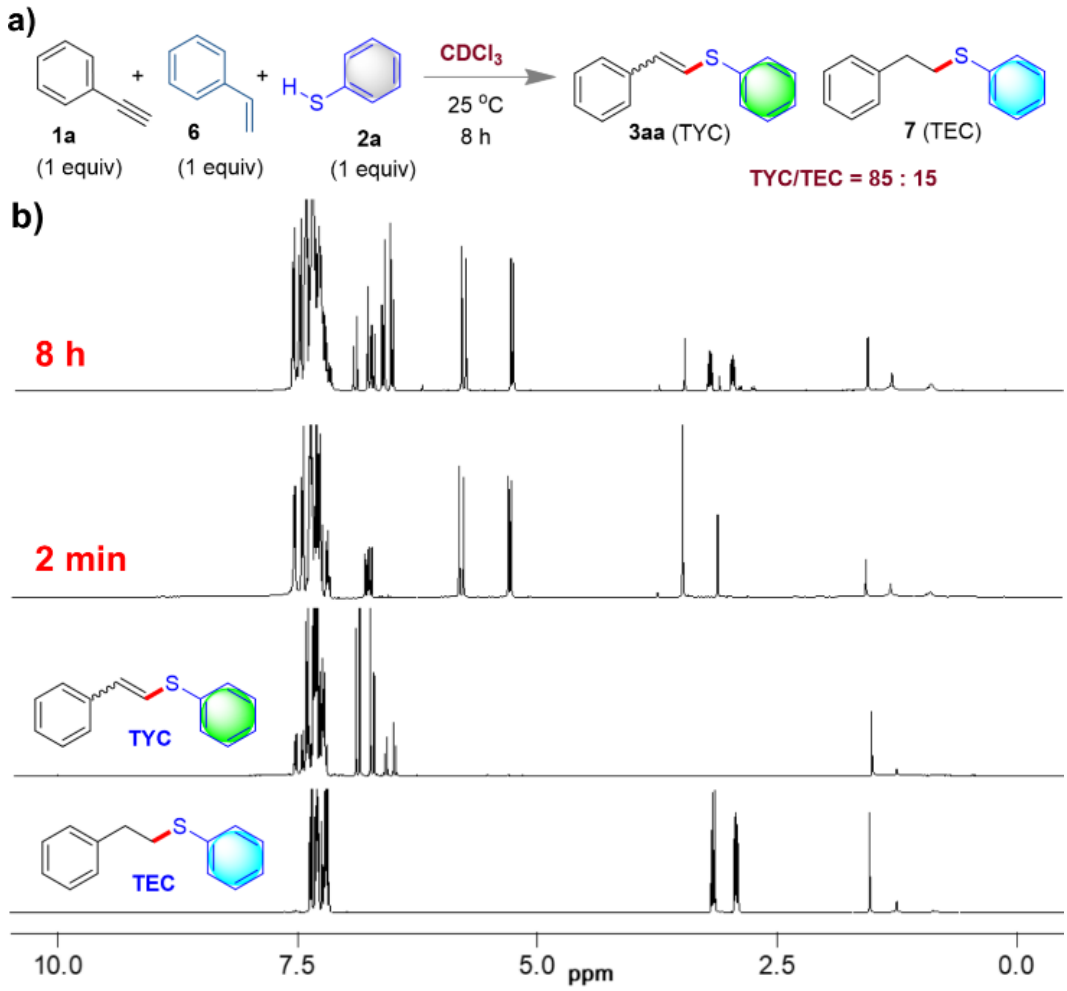


Figure 3B.4.Competitive experiment between TYC and TEC system.

The proposal of S–H···π interaction is given from the literature precedence. [16-18] Secondly, no disulphide was detected. This observation ruled out the possibility of radical pathway. Also, self-sorting experiments shown in Figure 3B.4 clearly supported that S–H···π interaction was more favourable for alkyne (TYC) than alkene (TEC). The understanding of self-sorting[11] could be demonstrated by exemplifying the stronger S–H···π preference of ethynyl (triple bond)-H ($E^{(2)}$, 1.45 kcal/mol) over the vinyl (double bond)-H hydrogen bond ($E^{(2)}$, 1.01 kcal/mol). As shown in Figure 3B.4a, in addition to the formation of TYC product 3aa from 1a and 2a, styrene 6 could react with 2a to produce thiol-ene-click (TEC) product **7**.[32] The relative ratio of 3aa : **7** was found to be 85 : 15 in $CDCl_3$ after 8 h of reaction time (NMR analysis, Figure 3B.4b). Notably, both the TYC and TEC reactions are found to be highly

exothermic in nature and therefore self-sorting could not be controlled under neat or solvent free condition.

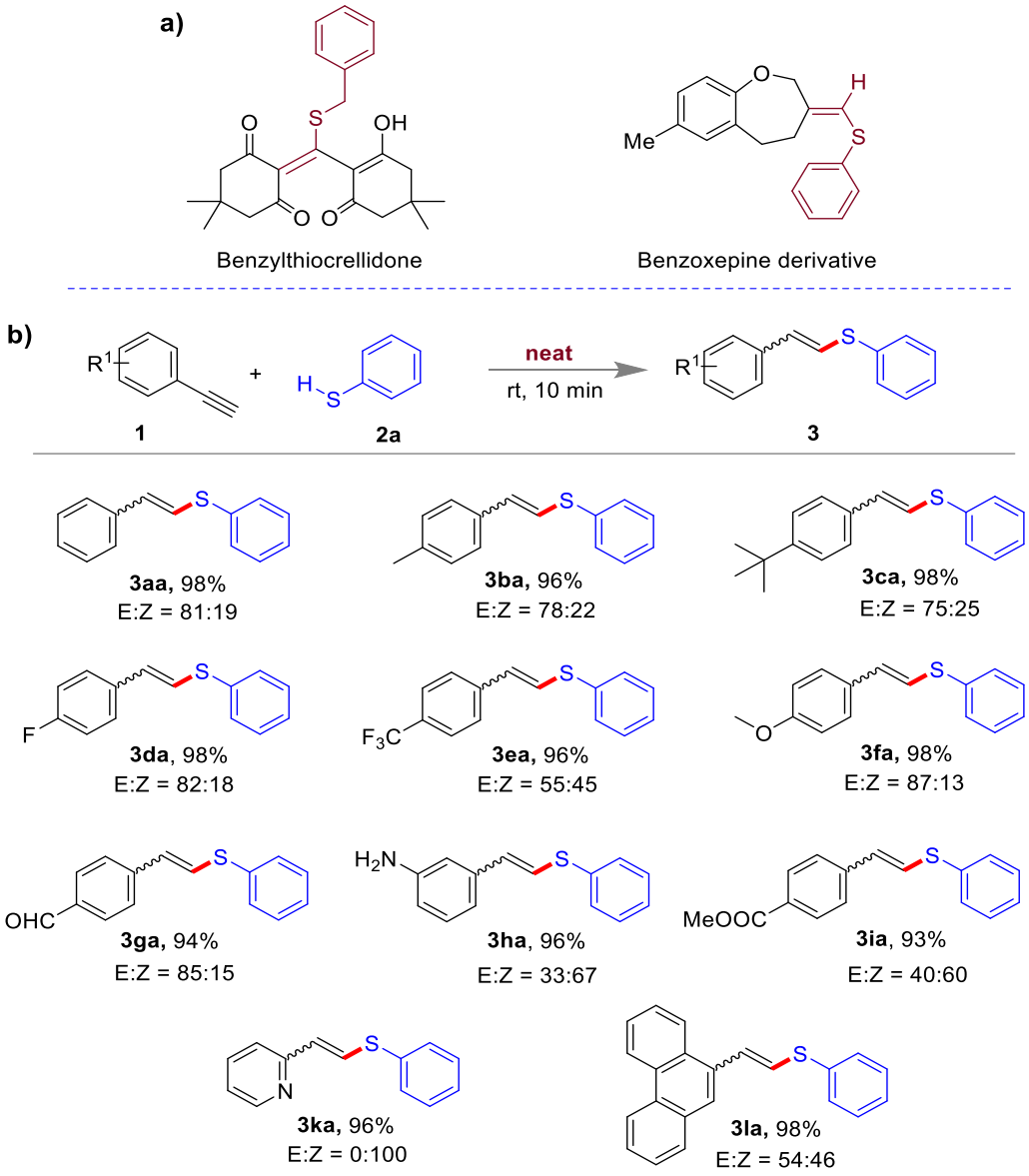


Figure 3B.5. a) Examples of sulfur-containing bioactive compounds. b) Substrates scope of TYC reaction using different kinds of alkyne and thiophenol.

Organo-sulfur compounds are also prevalent in natural products and medicinal chemistry. In Figure 3B.5a, two of the important vinyl sulfide containing molecules is shown which are found in natural products. For example, benzylthiocrellidone[88] is dimedone-based vinyl sulfide obtained from the sponge Crella spinulata. Similarly, benzoxepin derivatives are one

of the important building blocks in many natural products.[89] The substrate scope of the TYC reaction with anti-Markovnikov selectivity is shown in Figure 3B.5b. From the reactions of various alkynes with thiophenols (2a), the products vinyl sulfides were isolated excellent yield. Irrespective of the electron donating or withdrawing substituents at the aromatic ring of the alkyne system, the yields were not varied significantly. We have also further tested that the methodology was working very well in presence of functional groups like –CHO (3ga), –NH_2 (3ha), –COOMe (3ja), etc.

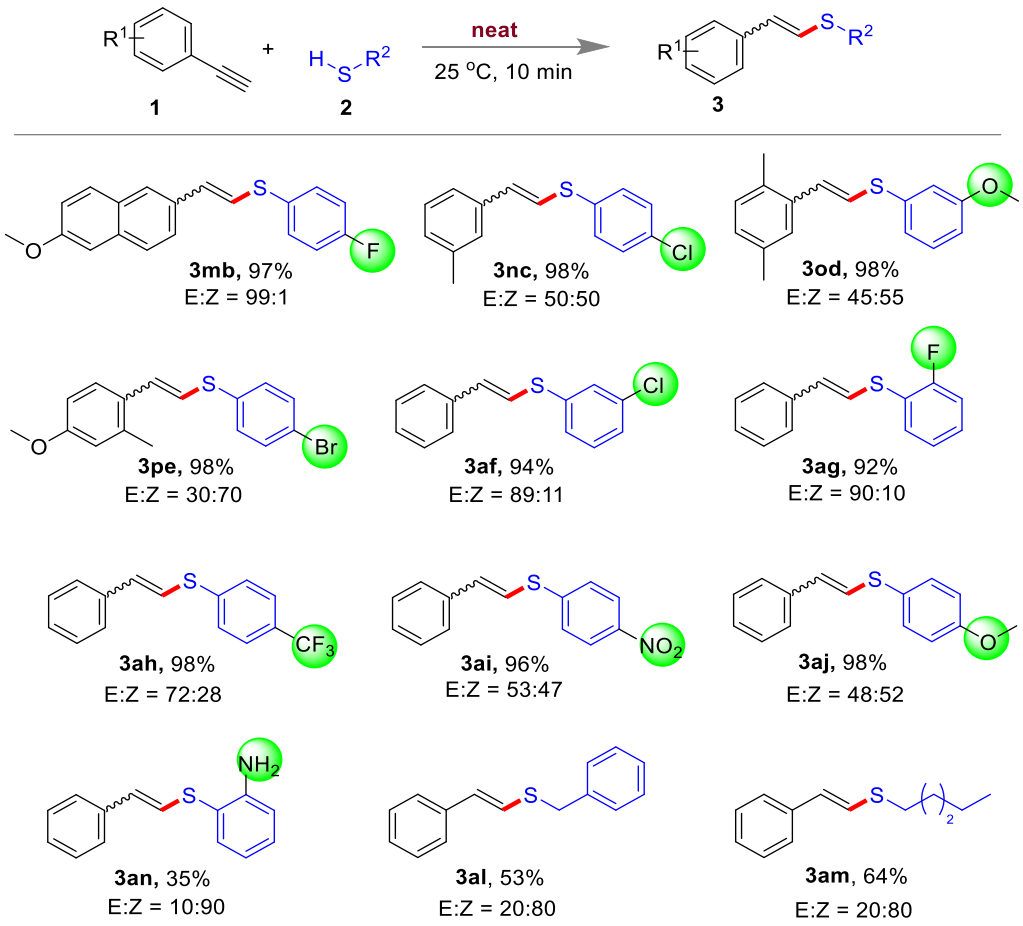


Figure 3B.6.Substrate scope of TYC reaction using different kinds of thiophenol and alkyne.

Moreover, the substrates scope from the reactions of alkynes and substituted-thiophenols and aliphatic thiols shown in Figure 3B.6. Excellent yields of the products were obtained with the thiophenols having substituents like –Br (3pe), –Cl (3nc, 3af), –F (3mb, 3ag), –CF_3 (3ah), –

NO_2 (3ai), –OMe (3od, 3aj), etc. However, relatively poor yields were obtained from the reactions of phenyl acetylene and aliphatic thiols (3al, 3am). Possibly, due to the lack of π-π stacking interaction the reaction could not led to the expected ant-Markovnikov TYC. Similarly, unsuccessful reaction from 1-hexyne and thiophenol (2a) were also observed (Figure 3B.3c).

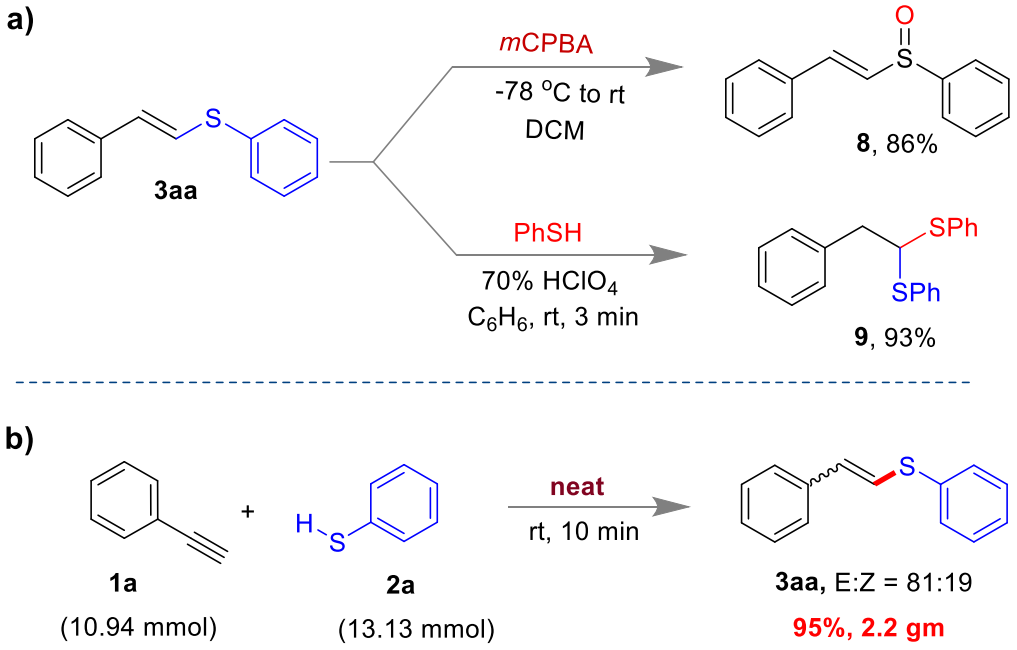


Figure 3B.7. Synthetic applications. a) Further functionalization of vinyl sulfides. b) Gram scale synthesis.

To explore the potential applicability of vinyl sulfides in organic synthesis, different reaction schemes are shown in Figure 3B.7. For example, 3aa was oxidized to 8 with 86% yield using *meta*-chloroperbenzoic acid (*m*CPBA).[90] Similarly the (2-phenylethane-1,1-diyl)bis(phenylsulfane) 9 was synthesized in 93% yield from 3aa using perchloric acid and thiophenol (2a).[91,92] The gram scale synthesis of 3aa (isolated, 2.2 g) was performed under neat condition and the product was isolated in 95% yield (Figure 3B.7b)

3B.4 CONCLUSIONS

In conclusion, we have successfully demonstrated that in a reaction system, by using cooperative weak interactions like S–H···π and π-π stacking, exclusive anti-Markovnikov TYC reaction could be obtained without using any catalyst, in shorter reaction time (ca. 10 min) and under neat condition by mixing the reactants at room temperature. Natural bond orbital (NBO) analyses and various experimental evidences also supported that the reaction could be controlled by one of the newly identified weak and non-covalent interactions like S–H···π. From synthetic aspects, many organo-sulfur compounds were isolated effortlessly by performing the reactions at ambient condition from easily accessible starting reagents. We believe that the systems chemistry approach developed from the study will have significant impact to the research area of organic synthesis and supramolecular catalysis. Finally, it is anticipated that this example can also be considered as the proof-of-concept of "The best catalyst is no catalyst".[93]

3A.5 EXPERIMENTAL SECTION

General Information: All the chemicals were purchased from the commercial suppliers and used without further purification. All the reactions were done under open atmosphere in neat condition. Chromatographic purification of the compounds was done using silica gel (Mesh 230-400) and ethyl acetate/hexane as an eluent. ^{1}H and ^{13}C spectra of the compounds were recorded on 400 and 700 MHz spectrometer at 25 ^{o}C. The chemical shift value (δ, ppm) were reported with respect to the residual chloroform (7.26 for ^{1}H and 77.16 ppm for ^{13}C). Infrared (IR) spectra were recorded in wave number (cm^{-1}). Digital melting point apparatus were used to record the melting point of the compound. The HRMS of the compounds was recorded on ESI-TOF (Time-of-flight) mass spectroscopy.

General Procedure for the Preparation of Vinyl Sulfane. Phenyl acetylene (60 μL, 0.547 mmol) and thiophenol (67 μL, 0.656 mmol) were mixted in an oven dried round bottom flask and stirred for (10-15) minutes under open atmosphere at room temperature. Then the silica gel column chromatography was done using hexane as an eluent, to afford the pure product.

Phenyl(styryl)sulfane (3aa):[94] E:Z ratio 81:19, R_f = 0.6 (hexane); colourless liquid; yield 99% (115 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.18 (m, 10H), 6.89 (d, *J* = 15.4 Hz, 1H, major), 6.73 (d, *J* = 15.4 Hz, 1H, major), 6.59 (d, *J* = 10.8 Hz, 1H, minor), 6.50 (d, *J* = 10.8 Hz, 1H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 136.6, 136.3, 135.3, 131.9, 130.2, 129.9, 129.3, 129.2, 128.9, 128.8, 128.4, 127.7, 127.6, 127.4, 127.3, 127.2, 127.1, 126.1, 123.5; HRMS (ESI-TOF) calcd for $C_{14}H_{12}S$ $(M + H)^+$ 211.0576, found 211.0563.

(4-Methylstyryl)(phenyl)sulfane (3ba):[94] E:Z ratio 78:22, R_f = 0.85 (hexane); White solid; yield 96% (110 mg); mp 42-44 ºC (lit.[95] 39-41 ºC) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.12 (m, 9H), 6.85 (d, *J* = 15.4 Hz, 1H), 6.76 (d, *J* = 15.4 Hz, 1H), 6.60 (d, *J* = 10.8 Hz, 1H), 6.46 (d, *J* = 10.8 Hz, 1H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 137.2, 135.8, 133.9, 133.8, 132.6, 130.1, 129.7, 129.5, 129.3, 129.2, 129.2, 129.2, 128.9, 127.5, 127.2, 126.9, 126.1, 124.9, 121.9, 21.4, 21.4.

(4-(Tert-butyl)styryl)(phenyl)sulfane (3ca):[94] E:Z ratio 75:25, R_f = 0.75 (hexane); colourless liquid; yield 98% (87 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.19 (m, 9H), 6.89 (d, *J* = 15.4 Hz, 1H), 6.81 (d, *J* = 15.4 Hz, 1H), 6.63 (d, *J* = 10.8 Hz, 1H), 6.49 (d, *J* = 10.8 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 150.4, 136.6, 135.9, 133.9, 133.9, 132.6, 130.1, 129.7, 129.3, 129.2, 128.7, 127.5, 127.2, 126.9, 126.0, 125.8, 125.4, 125.1, 122.3, 34.8, 34.8, 31.4, 31.4.

(4-Fluorostyryl)(phenyl)sulfane (3da):[96] E:Z ratio 82:18, R_f = 0.85 (hexane); colourless liquid; yield 98% (114 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.40 (m, 2H), 7.40 – 7.25 (m, 5H), 7.12 – 6.98 (m, 2H), 6.81 (d, *J* = 15.4 Hz, 1H, major), 6.70 (d, *J* = 15.4 Hz, 1H,

major), 6.57 (d, *J* = 10.6 Hz, 1H, minor), 6.49 (d, *J* = 10.6 Hz, 1H, minor); ^{13}C NMR (175 MHz, $CDCl_3$) δ 162.8 (d, *J* = 107.6 Hz), 161.4 (d, *J* = 108.0 Hz), 136.1, 135.2, 133.1, 133.0, 132.9 (d, *J* = 3.3 Hz), 132.8, 130.7, 130.6 (d, *J* = 8.0 Hz), 130.2, 130.0, 129.3, 129.3, 127.7, 127.6, 127.4, 127.16, 126.3, 125.7 (d, *J* = 2.0 Hz), 123.3 (d, *J* = 2.4 Hz), 115.8 (d, *J* = 21.8 Hz), 115.4 (d, *J* = 21.5 Hz).

Phenyl(4-(trifluoromethyl)styryl)sulfane (3ea):[97] E:Z ratio 55:45, R_f = 0.7 (Hexane); White solid; yield 97% (95 mg); mp 60-64 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.28 (m, 9H), 7.03 (d, *J* = 15.4 Hz, 1H, major), 6.65 (m, 1H), 6.59 (d, *J* = 10.8 Hz, 1H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1 (d, *J* = 8.2 Hz), 135.7, 134.1, 130.9, 130.5, 129.6, 129.5, 129.4, 129.3, 129.2, 129.0, 128.9, 128.5, 127.8, 127.8, 127.7, 127.3, 126.1, 125.8 (q, *J* = 3.9 Hz), 125.7, 125.5, 125.4 (q, *J* = 3.9 Hz), 123.0

(4-Methoxystyryl)(phenyl)sulfane (3fa):[80] E:Z ratio 87:13, R_f = 0.6 (5% Ethyl acetate/hexane); White solid; yield 98% (110 mg); mp 42-44 ºC (lit[80]. 39-42); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55 – 7.22 (m, 7H), 6.98 – 6.86 (m, 2H), 6.79 (d, *J* = 15.4 Hz, 1H, major), 6.75 (d, *J* = 15.4 Hz, 1H, major), 6.59 (d, *J* = 10.6 Hz, 1H, minor), 6.40 (d, *J* = 10.6 Hz, 1H, minor), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 158.8, 136.6, 136.1, 132.9, 130.3, 130.0, 129.5, 129.5, 129.4, 129.3, 129.2, 127.5, 127.4, 127.1, 126.7, 123.4, 120.2, 114.3, 113.9, 55.5, 55.4.

4-(2-(Phenylthio)vinyl)benzaldehyde (3ga): E:Z ratio 85:15, R_f = 0.8 (5% ethyl acetate/hexane); Yellow oil; yield 94% (104 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s 1H), 7.92 – 7.30 (m, 9H), 7.11 (d, *J* = 15.4 Hz, 1H, major), 6.72 (d, *J* = 10.6 Hz, 1H, minor), 6.62 (d, *J* = 15.4 Hz, 1H, major), 6.57 (d, *J* = 10.6 Hz, 1H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 191.6, 142.6, 142.6, 135.5, 135.1, 134.7, 133.7, 131.2, 130.9, 130.6, 130.4, 130.2, 129.9, 129.5, 129.4, 129.2, 128.0, 127.9, 127.9, 126.3, 125.4; IR (KBr) ῡ 3190, 2950, 2402,

1693, 1591, 1280, 788, 690; HRMS (ESI-TOF) calcd for $C_{15}H_{12}OS$ $(M + H)^+$ 241.0682, found 241.0670.

3-(2-(Phenylthio)vinyl)aniline (3ha): E:Z ratio 33:67, R_f = 0.5 (20% ethyl acetate/hexane); Light yellow solid; yield 96% (108 mg); mp 45-50 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.06 (m, 6H), 7.00 – 6.89 (m, 1H), 6.85 (d, *J* = 15.4 Hz, 1H, minor), 6.80 – 6.56 (m, 2H), 6.53 (d, *J* = 10.8 Hz, 1H, major), 6.47 (d, *J* = 10.8 Hz, 1H, major), 3.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 146.4, 137.6, 137.5, 136.4, 132.3, 130.1, 129.7, 129.6, 129.3, 129.2, 129.18, 127.5, 127.2, 126.9, 125.8, 123.1, 119.5, 116.8, 115.8, 115.2, 114.7, 114.3, 112.5; IR (KBr) ῡ 3363, 3050, 2402, 1600, 1477, 1275, 742, 686; HRMS (ESI-TOF) calcd for $C_{14}H_{13}NS$ $(M + H)^+$ 228.0841, found 228.0843.

Methyl 4-(2-(phenylthio)vinyl)benzoate (3ia): E:Z ratio 40:60, R_f = 0.4 (5% ethyl acetate/hexane); White solid; yield 93% (94 mg); mp 104-106 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.95 (m, 2H), 7.63 – 7.27 (m, 7H), 7.05 (d, *J* = 15.4 Hz, 1H, minor), 6.68 – 6.61 (m, 1H), 6.58 (d, *J* = 10.8 Hz, 1H, major), 3.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.01, 166.9, 141.1, 135.8, 134.2, 130.9, 130.5, 130.2, 129.8, 129.7 (x2), 129.5, 129.4, 128.9, 128.8, 128.7, 128.4, 127.9, 127.7 (x2), 125.8, 125.8, 52.3, 52.2; IR (KBr) ῡ 2850, 2393, 2057, 1633, 1283, 752, 676; HRMS (ESI-TOF) calcd for $C_{16}H_{14}O_2S$ $(M + H)^+$ 271.0787, found 271.0757.

(Z)-2-(2-(Phenylthio)vinyl)pyridine (3ka):[75] E:Z ratio 0:100, R_f = 0.7 (10% ethyl acetate/hexane); Light yellow solid; yield 46% (57 mg); mp 93-96 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.6 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.35 – 7.27 (m, 2H), 7.16 – 7.11 (m, 1H), 6.87 (d, *J* = 10.4 Hz, 1H), 6.60 (d, *J* = 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 148.7, 138.3, 136.3, 134.0, 130.9, 129.3, 127.6, 123.7, 123.0, 120.9.

(2-(Phenanthren-9-yl)vinyl)(phenyl)sulfane (3la): E:Z ratio 54:46, R_f = 0.5 (5% Ethyl acetate/hexane); White solid; yield 98% (91 mg); mp 81-83 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 – 8.59 (m, 2H), 8.21 – 7.82 (m, 3H), 7.75 – 7.21 (m, 10H), 7.08 (d, *J* = 15.4 Hz, 1H, major), 6.86 (d, *J* = 10.6 Hz, 1H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 135.3 (x 2), 133.2 (x 2), 131.8, 131.7, 131.5, 130.8, 130.72, 130.7, 130.6, 130.5, 130.3, 130.3, 130.2, 130.0, 129.9, 129.4, 129.3, 129.2, 128.9, 128.8, 128.74, 127.72, 127.2, 127.1, 126.9, 126.9, 126.8, 126.7 (x 2), 126.6, 125.6, 125.0, 124.7, 124.7, 123.2, 122.6, 122.6; IR (KBr) ῡ 2810, 2404, 2070, 1638, 1479, 722, 689; HRMS (ESI-TOF) calcd for $C_{22}H_{16}S$ $(M + H)^+$ 313.1045, found 313.1049.

(4-Fluorophenyl)(2-(6-methoxynaphthalen-2-yl)vinyl)sulfane (3mb): E:Z ratio 99:1, R_f = 0.6 (5% ethyl acetate/hexane); White solid; yield 97% (97 mg); mp 120-124 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 2H), 7.62 (s, 1H), 7.53 – 7.41 (m, 3H), 7.16 – 7.03 (m, 4H), 6.88 (d, *J* = 15.4 Hz, 1H, major), 6.79 (d, *J* = 15.4 Hz, 1H major), 6.69 (d, *J* = 10.6 Hz, 1H, minor), 6.43 (d, *J* = 10.6 Hz, 1H, minor), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 161.2, 158.0, 134.2, 132.7, 132.6, 131.9, 131.9, 130.25 (d, *J* = 3.3 Hz), 129.6, 129.1, 127.3, 125.8, 123.92, 122.9, 119.3, 116.6, 116.4, 106.0, 55.4; IR (KBr) ῡ 2840, 2385, 1605, 1625, 1503, 1482, 628; HRMS (ESI-TOF) calcd for $C_{19}H_{15}FOS$ $(M)^+$ 310.0822, found 310.0826.

(4-Chlorophenyl)(3-methylstyryl)sulfane (3nc): E:Z ratio 50:50, R_f = 0.8 (Hexane); White solid; yield 98% (118 mg); mp 48-50 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.05 (m, 8H), 6.81 (d, *J* = 15.4 Hz, 1H), 6.73 (d, *J* = 15.4 Hz, 1H), 6.61 (d, *J* = 10.8 Hz, 1H), 6.40 (d, *J* = 10.8 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.1, 136.4, 136.3, 135.0, 134.1, 133.4, 133.2, 133.1, 131.4, 131.0, 129.6, 129.4 (x2), 128.82, 128.8, 128.4, 128.33, 128.32, 126.9, 126.0, 125.0, 123.4, 122.2, 21.7, 21.5; IR (KBr) ῡ 3052, 2923, 2684, 2304,

2054, 1894, 1633, 1475, 628; HRMS (ESI-TOF) calcd for $C_{15}H_{13}ClS$ $(M)^+$ 260.0421, found 260.0423.

(2,5-Dimethylstyryl)(3-methoxyphenyl)sulfane (3od): E:Z ratio 45:55, R_f = 0.25 (Hexane); colourless liquid; yield 98% (111 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.24 (m, 2H), 7.14 – 6.98 (m, 4H), 6.86 – 6.78 (m, 1H), 6.74 (d, *J* = 10.4 Hz, 1H, major), 6.58 (d, *J* = 10.4 Hz, 1H, major), 3.83 (s, 3H), 2.35 (s, 6H, two CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 160.0, 137.7, 137.1, 135.6, 135.3, 135.1, 133.1, 132.3, 130.7, 130.5, 130.12, 130.1, 130.0, 129.1, 128.6, 128.3, 126.8, 126.1, 125.8, 123.5, 122.0, 121.6, 115.1, 114.7, 112.8, 112.6, 55.5, 55.4, 21.2, 21.1, 19.5, 19.4; IR (KBr) ῡ 3008, 2865, 2308, 2075, 1588, 1463, 721, 684; HRMS (ESI-TOF) calcd for $C_{17}H_{18}OS$ $(M + H)^+$ 271.1151, found 271.1159.

4-Bromophenyl)(4-methoxy-2-methylstyryl)sulfane (3pe): E:Z ratio 30:70, R_f = 0.8 (Hexane); White solid; yield 98% (118 mg); mp 60-62 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.34 (m, 3H), 7.30 – 7.22 (m, 2H), 7.01 (d, *J* = 15.4 Hz, 1H, minor), 6.85 – 6.72 (m, 2H), 6.71 (d, *J* = 10.4 Hz, 1H, major), 6.59 (d, *J* = 15.4 Hz, 1H, minor), 6.39 (d, *J* = 10.4 Hz, 1H, major), 3.81 (s, 3H), 2.33 (d, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 159.1, 138.0, 137.1, 135.8, 135.7, 132.3, 132.2, 131.1, 130.4, 129.8, 128.2, 127.8, 127.4, 126.8, 123.6, 120.8, 120.4, 120.1, 116.1, 115.8, 111.9, 110.6, 55.4, 55.3, 20.3, 20.2; IR (KBr) ῡ 2836, 2510, 2390, 2076, 1900, 1637, 1495, 690; HRMS (ESI-TOF) calcd for $C_{16}H_{15}BrOS$ $(M + H)^+$ 335.0100, found 335.0111.

(3-Chlorostyryl)(phenyl)sulfane (3af): E:Z ratio 89:11, R_f = (Hexane); white solid; yield 94% (126 mg); mp 48-52 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.25 (m, 9H), 6.90 – 6.85 (m, 2H, major), 6.71 (d, *J* = 10.6 Hz, 1H, minor), 6.50 (d, *J* = 10.6 Hz, 1H, minor); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.3, 137.9, 136.3, 136.2, 135.1, 135.0, 134.0, 130.2, 130.2, 129.4, 128.94, 128.9, 128.8, 128.8, 128.5, 128.1, 127.8, 127.5, 127.3, 127.2, 126.9, 126.3, 124.3,

121.6, IR (KBr) ῡ 3023, 2393, 1574, 1461, 734, 676; HRMS (ESI-TOF) calcd for $C_{14}H_{11}ClS$ $(M)^+$ 246.0265, found 246.0266.

(2-Fluorophenyl)(styryl)sulfane (3ag):[94] E:Z ratio 90:10, R_f = 0.8 (Hexane); colourless liquid; yield 92% (116 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.23 (m, 7H), 7.21 – 7.07 (m, 2H), 6.82 (d, *J* = 15.4 Hz, 1H, major), 6.76 (d, *J* = 15.4 Hz, 1H, major), 6.66 (d, *J* = 10.8 Hz, 1H, minor), 6.41 (d, *J* = 10.8 Hz, 1H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 159.7, 136.4, 136.3, 132.8, 132.52 (d, *J* = 1.1 Hz), 132.18 (d, *J* = 1.5 Hz), 129.5, 129.4, 129.2, 129.1, 128.9, 128.8, 128.5, 128.3, 127.9, 127.4, 126.2, 124.9 (d, *J* = 3.7 Hz), 124.58 (d, *J* = 1.7 Hz), 122.3, 122.2, 121.69 (d, *J* = 1.5 Hz), 116.2, 116.1, 115.9, 115.9

Styryl(4-(trifluoromethyl)phenyl)sulfane (3ah): E:Z ratio 72:28, R_f = 0.8 (Hexane); White solid; yield 97% (149 mg); mp 78-80 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.50 (m, 3H), 7.49 – 7.24 (m, 6H), 6.93 (d, *J* = 15.4 Hz, 1H, major), 6.86 (d, *J* = 15.4 Hz, 1H, major), 6.75 (d, *J* = 10.6 Hz, 1H, minor), 6.50 (d, *J* = 10.6 Hz, 1H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4 (d, *J* = 1.0 Hz), 136.1, 136.1, 135.5, 129.9, 129.1, 129.0, 128.9, 128.5, 128.4, 128.3, 127.8, 126.5, 126.1 (dq, *J* = 7.5, 3.8 Hz), 125.5, 123.1, 122.8, 120.5; IR (KBr) ῡ 2835, 2392, 2055, 1633, 1401, 743, 684; HRMS (ESI-TOF) calcd for $C_{15}H_{11}F_3S$ $(M)^+$ 280.0528, found 280.0528.

(4-Nitrophenyl)(styryl)sulfane (3ai):[92] E:Z ratio 53:47 , R_f = 0.5 (5% ethyl acetate/hexane); Yellow solid; yield 96% (136 mg); mp 82-85 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.11 (m, 2H), 7.59 – 7.28 (m, 7H), 7.03 (d, *J* = 15.4 Hz, 1H, major), 6.89 (m, 1H, major), 6.85 (m, 1H, minor), 6.52 (d, *J* = 10.4 Hz, 1H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 146.2, 145.9, 145.8, 138.1, 135.7, 135.6, 132.2, 129.1, 129.0, 128.9, 128.6, 128.1, 128.0, 127.1, 126.7, 124.3, 124.2, 120.7, 118.3.

(4-Methoxyphenyl)(styryl)sulfane (3aj):[98] E:Z ratio 48:52, R_f = 0.2 (Hexane); White solid ; yield 98% (130 mg); mp 62-64 ºC (lit.[98] 58-60); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.22

(m, 7H), 6.94 – 6.87 (m, 2H), 6.84 (d, *J* = 15.4 Hz, 1H, minor), 6.56 – 6.48 (m, 1H), 6.42 (d, *J* = 10.8 Hz, 1H, major), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 136.8, 133.6, 133.1, 132.8, 129.1, 128.8, 128.7, 128.5, 128.4, 127.3, 127.1, 126.9, 125.9, 125.9, 125.8, 124.6, 115.0, 114.9, 114.7, 55.5, 55.48.

Benzyl(styryl)sulfane (3al):[96] E:Z ratio 20:80, R_f = 0.4 (Hexane); colourless liquid; yield 53% (65mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.22 (m, 9H), 6.74 (d, *J* = 15.4 Hz, 1H, minor), 6.56 (d, *J* = 15.4 Hz, 1H, minor), 6.45 (d, *J* = 10.8 Hz, 1H, major), 6.28 (d, *J* = 10.8 Hz, 1H, major), 4.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.0, 129.5, 129.1, 128.9, 128.8, 128.7, 128.7, 128.6, 128.3, 128.2, 128.1, 127.6, 127.5, 127.4, 127.1, 126.8, 126.1, 126.0, 125.7, 124.5, 39.6, 37.5.

Dodecyl(styryl)sulfane (3am):[62] E:Z ratio 20:80, R_f = 0.8 (Hexane); colourless liquid; yield 60% (100 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.27 (m, 4H), 7.20 (m, 1H), 6.73 (d, *J* = 15.4 Hz, 1H, minor), 6.51 – 6.40 (m, 1H), 6.26 (d, *J* = 10.6 Hz, 1H, major), 2.84 – 2.73 (m, 2H), 1.74 – 1.63 (m, 2H), 1.47 – 1.33 (m, 3H), 1.32 – 1.26 (m, 15H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 137.2, 128.74 (x 2), 128.3, 127.8, 126.9, 126.8, 126.7, 125.6, 125.5, 125.4, 36.1, 34.2, 32.8, 32.7, 32.0, 30.4, 29.8 (x 2), 29.7 (x 2), 29.7 (x 2), 29.6 (x 2), 29.6, 29.5, 29.3, 29.2, 28.9 (x 2), 28.7, 28.5, 22.8, 14.2.

2-(Styrylthio)aniline (3an):[62] E:Z ratio 10:90, R_f = (Hexane); yellow colour solid; yield 35% (44 mg); mp 57-61 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.51 (m, 2H), 7.50 – 7.30 (m, 3H), 7.31 – 7.25 (m, 1H), 7.23 – 7.16 (m, 1H), 6.81 – 6.72 (m, 2H), 6.69 (d, *J* = 15.4 Hz, 1H, minor), 6.54 (d, *J* = 10.8 Hz, 1H, major), 6.37 (d, *J* = 15.4 Hz, 1H, minor), 6.20 (d, *J* = 10.8 Hz, 1H, major), 4.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 136.7, 136.1, 135.4, 130.6, 128.9, 128.7, 128.5, 128.1, 127.8, 127.2, 127.1, 126.8, 125.9, 124.0, 118.9, 118.8, 117.9, 115.5.

4-(Styrylthio)phenol (3ak): E:Z ratio 0:100, R_f = (Hexane); white solid; yield 96% (130 mg); mp 88-90 ºC (lit. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.45 (m, 2H), 7.44 – 7.34 (m, 4H), 7.32 – 7.25 (m, 1H), 6.86 – 6.80 (m, 2H), 6.50 (d, *J* = 10.8 Hz, 1H), 6.40 (d, *J* = 10.8 Hz, 1H), 4.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 136.7, 133.8, 133.3, 128.8, 128.4, 128.3, 127.1, 126.0, 116.4; IR (KBr) ῡ 3417, 2925, 2810, 2351, 1622, 1599, 1494, 696; HRMS (ESI-TOF) calcd for $C_{14}H_{12}OS$ $(M + H)^+$ 229.0682, found 240.0680.

(2-Phenylethane-1,1-diyl)bis(phenylsulfane) (9):[91] R_f = 0.3 (Hexane); colourless liquid; yield 94% (86 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.38 (m, 4H), 7.37 – 7.27 (m, 9H), 7.26 – 7.22 (m, 2H), 4.63 (t, *J* = 7.0 Hz, 1H), 3.19 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 134.4, 132.8, 129.5, 128.9, 128.4, 127.8, 126.9, 59.7, 42.3.

(2-(Phenylsulfinyl)vinyl)benzene (8):[90] R_f = 0.35 (20% ethylacetate/Hexane); colourless liquid; yield 86% (70 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 2H), 7.55 – 7.48 (m, 3H), 7.48 – 7.41 (m, 2H), 7.41 – 7.32 (m, 4H), 6.83 (d, *J* = 15.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 136.6, 133.8, 133.1, 131.3, 130.0, 129.6, 129.0, 127.9, 124.8.

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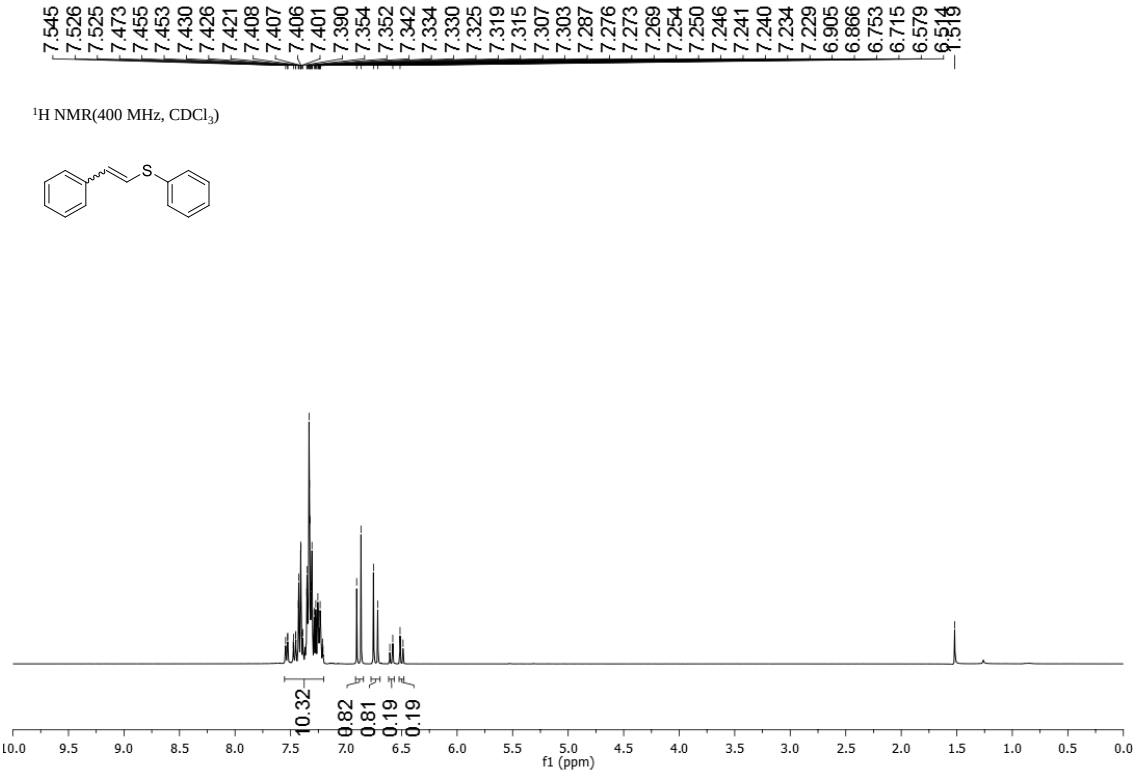
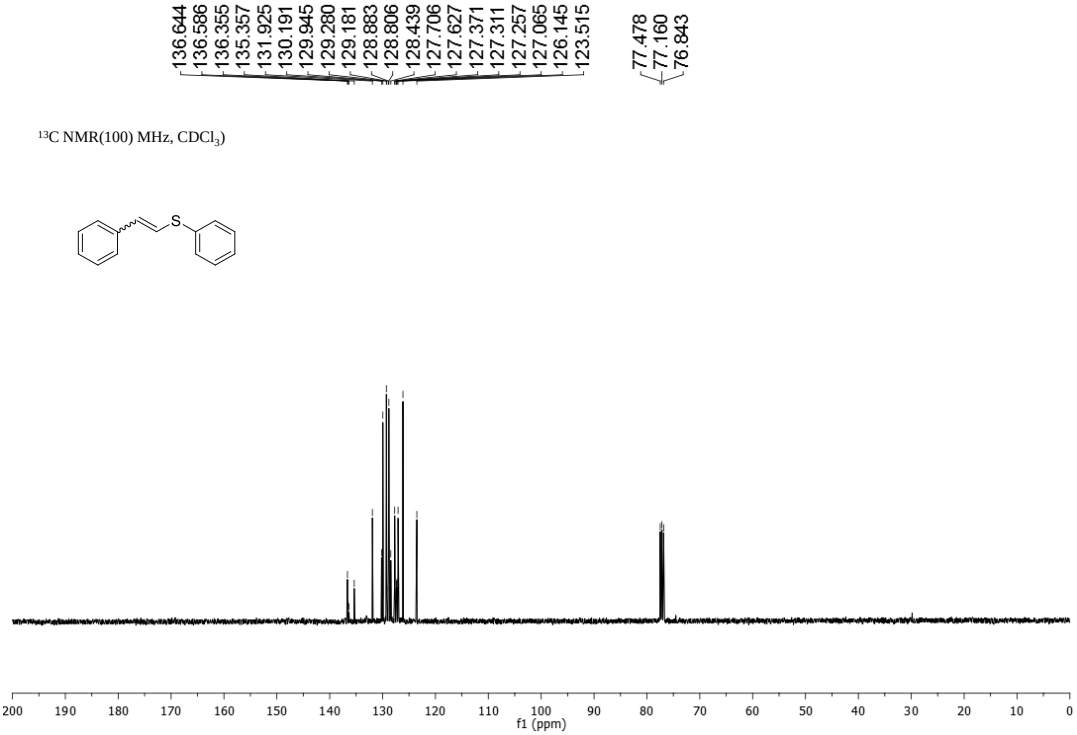
^{1}H and ^{13}NMR Spectra of Selected Compounds



^{1}H NMR(400 MHz, $CDCl_3$)

Figure 3B.7. ^{1}H NMR spectrum of phenyl(styryl)sulfane (**3aa**).



^{13}C NMR(100) MHz, $CDCl_3$)

Figure 3B.8. ^{13}C NMR spectrum of phenyl(styryl)sulfane (**3aa**).

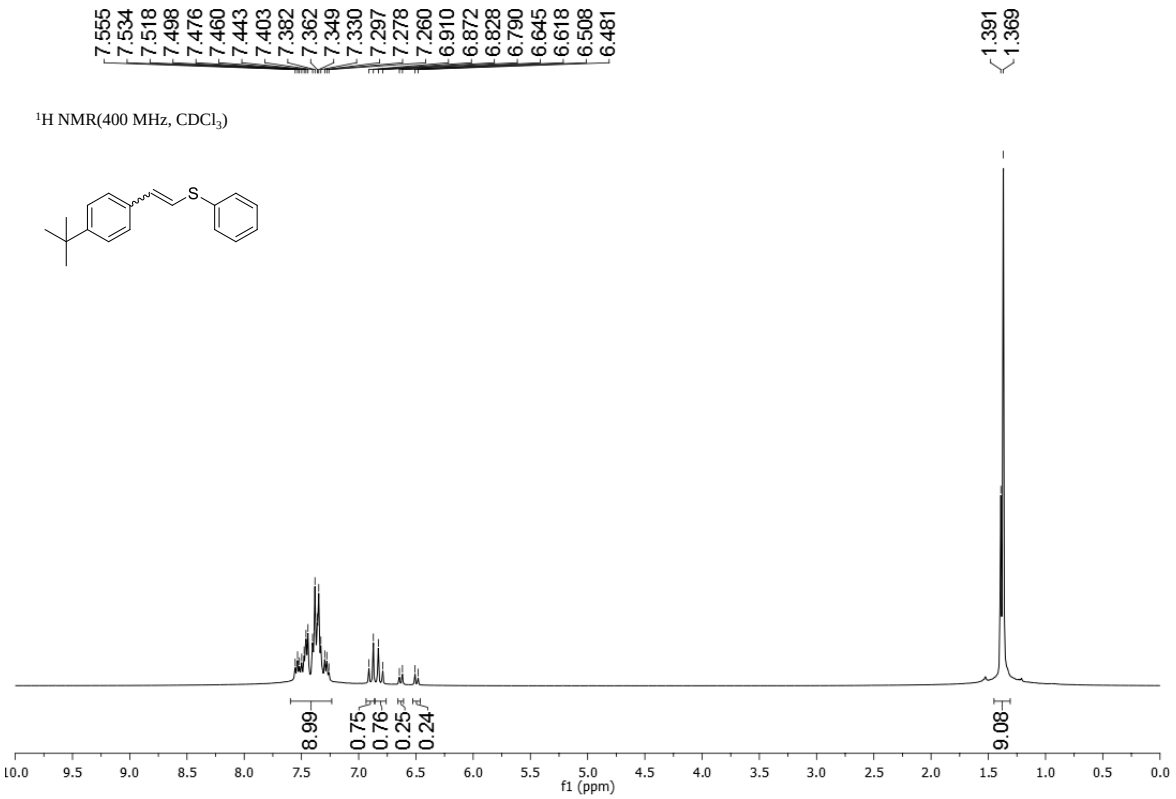


Figure 3B.9. ^{1}H NMR spectrum of (4-(tert-butyl)styryl)(phenyl)sulfane (**3ca**).

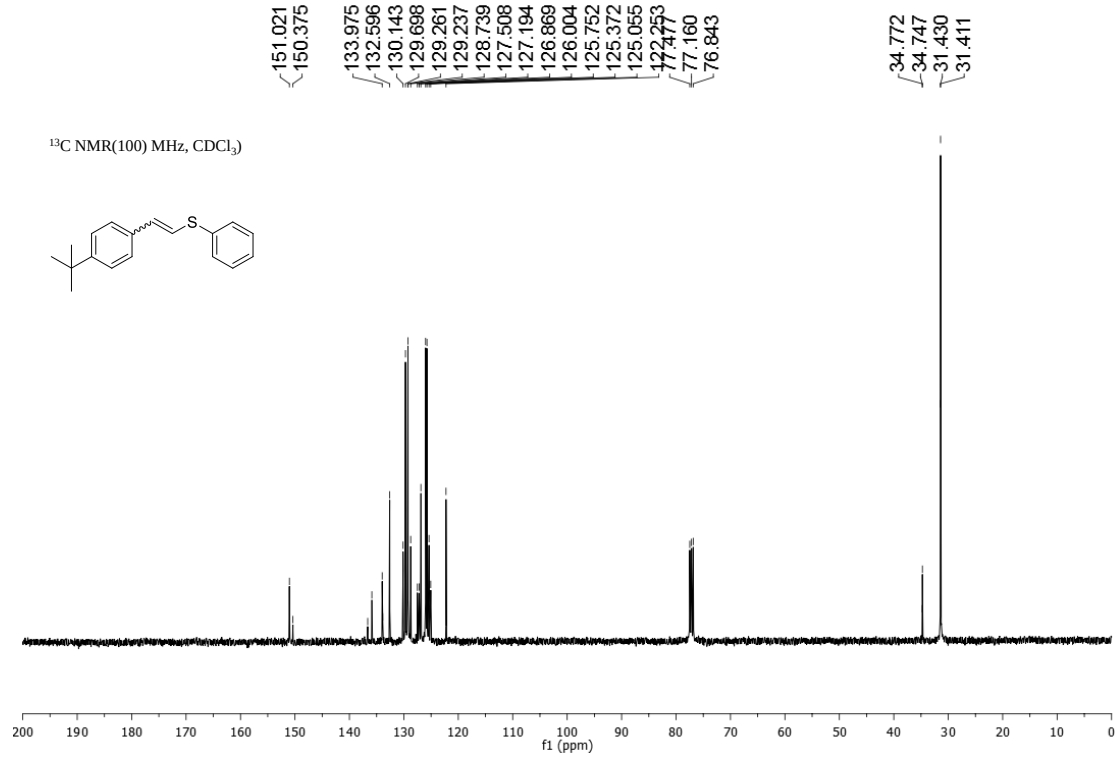


Figure 3B.10. ^{13}C NMR spectrum of (4-(tert-butyl)styryl)(phenyl)sulfane (**3ca**).

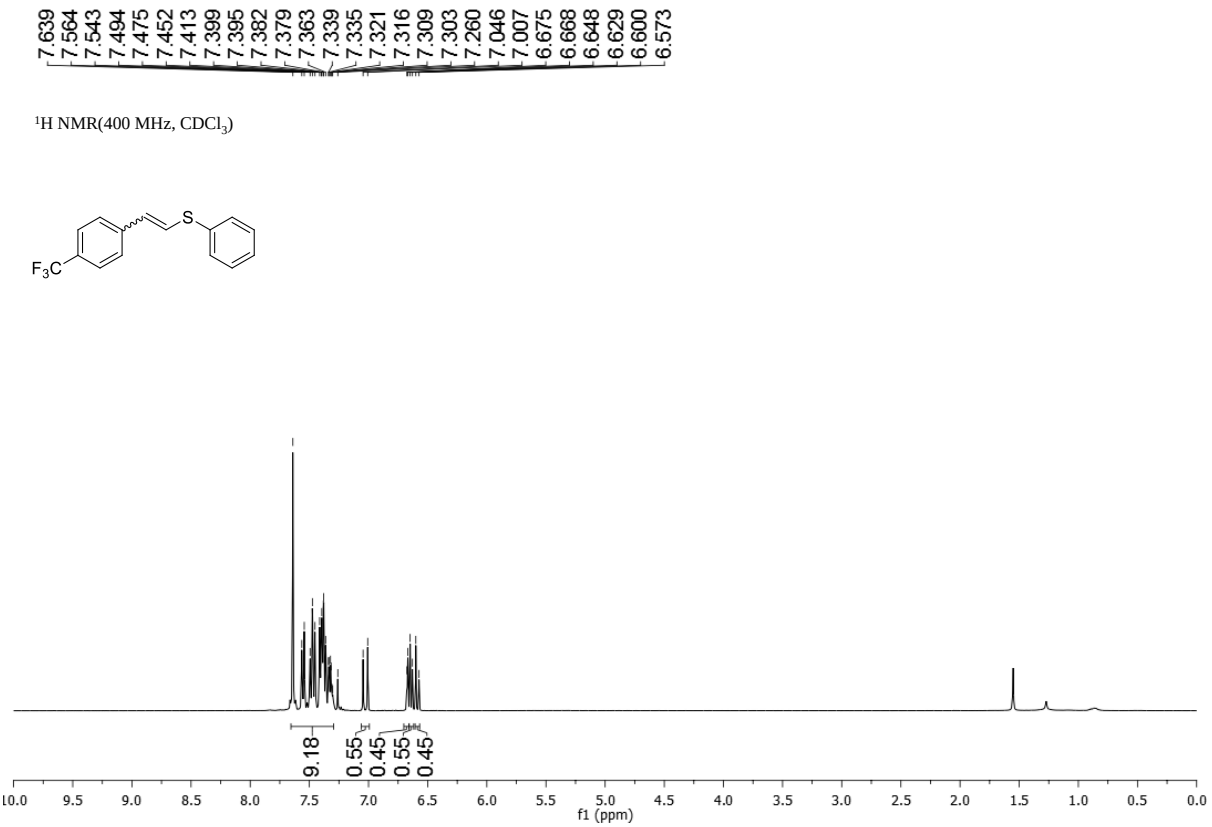


Figure 3B.11. ^{1}H NMR spectrum of phenyl(4-(trifluoromethyl)styryl)sulfane (**3ea**).

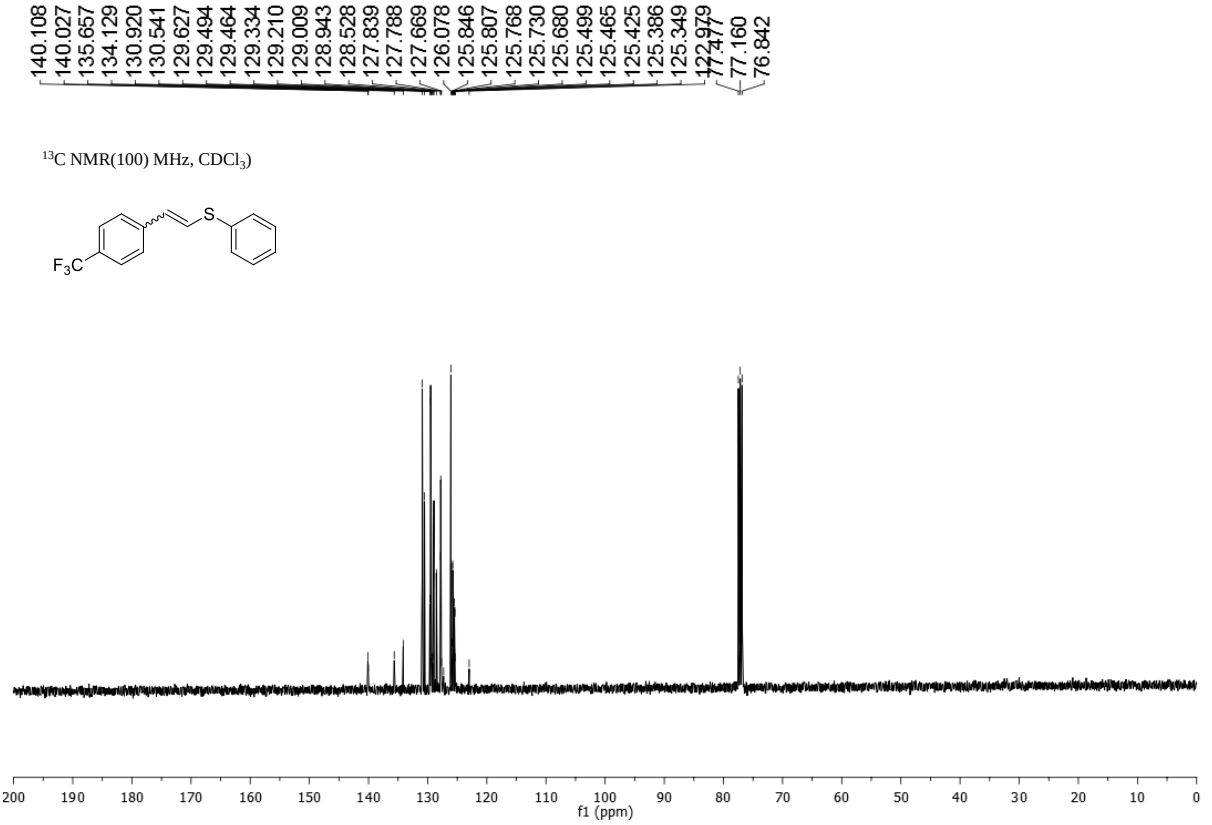


Figure 3B.12. ^{13}C NMR spectrum of phenyl(4-(trifluoromethyl)styryl)sulfane (**3ea**).

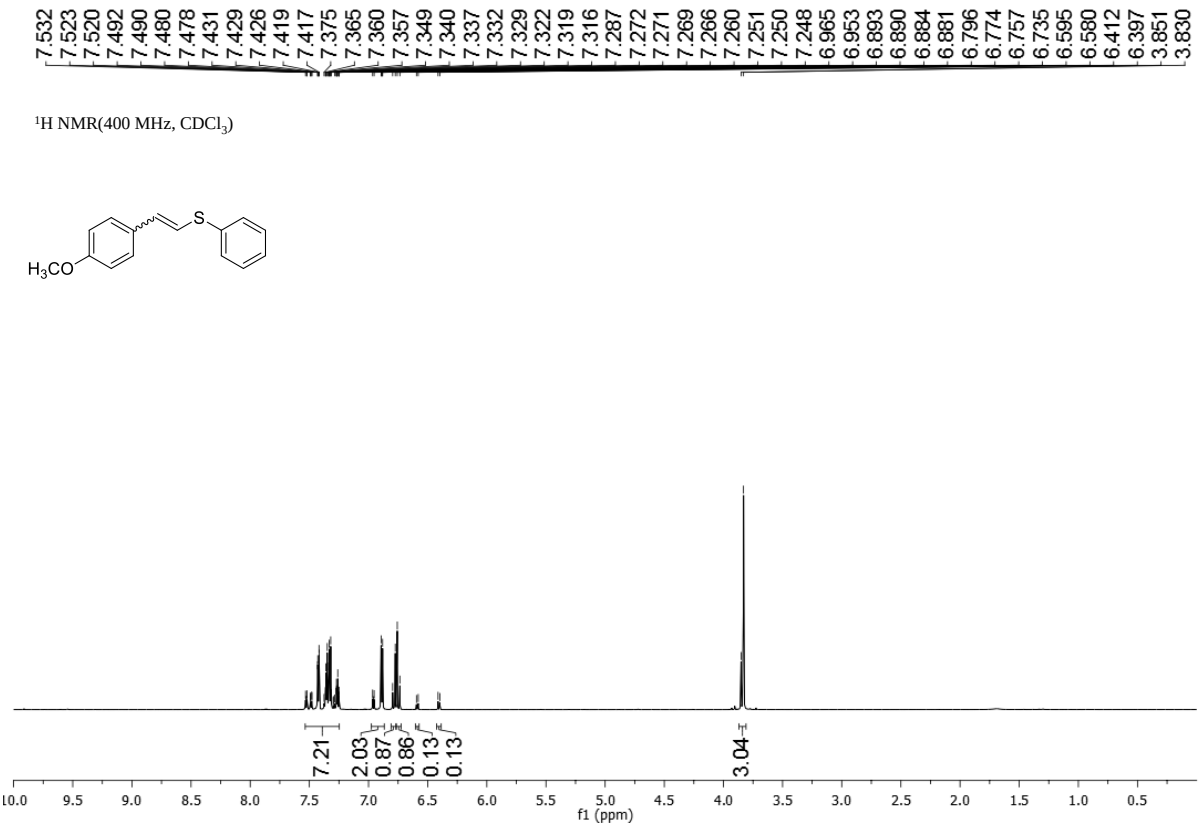


Figure 3B.13. ^{1}H NMR spectrum of (4-methoxystyryl)(phenyl)sulfane(**3fa**).

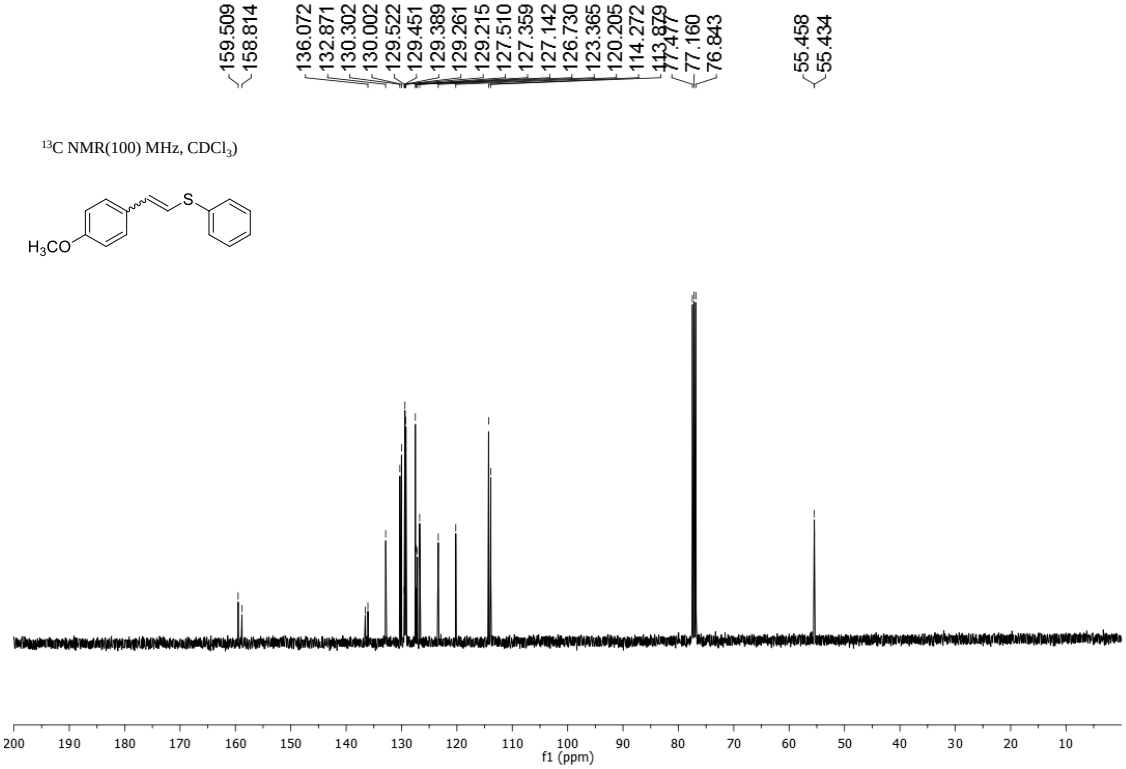


Figure 3B.14. ^{13}C NMR spectrum of (4-methoxystyryl)(phenyl)sulfane(**3fa**).

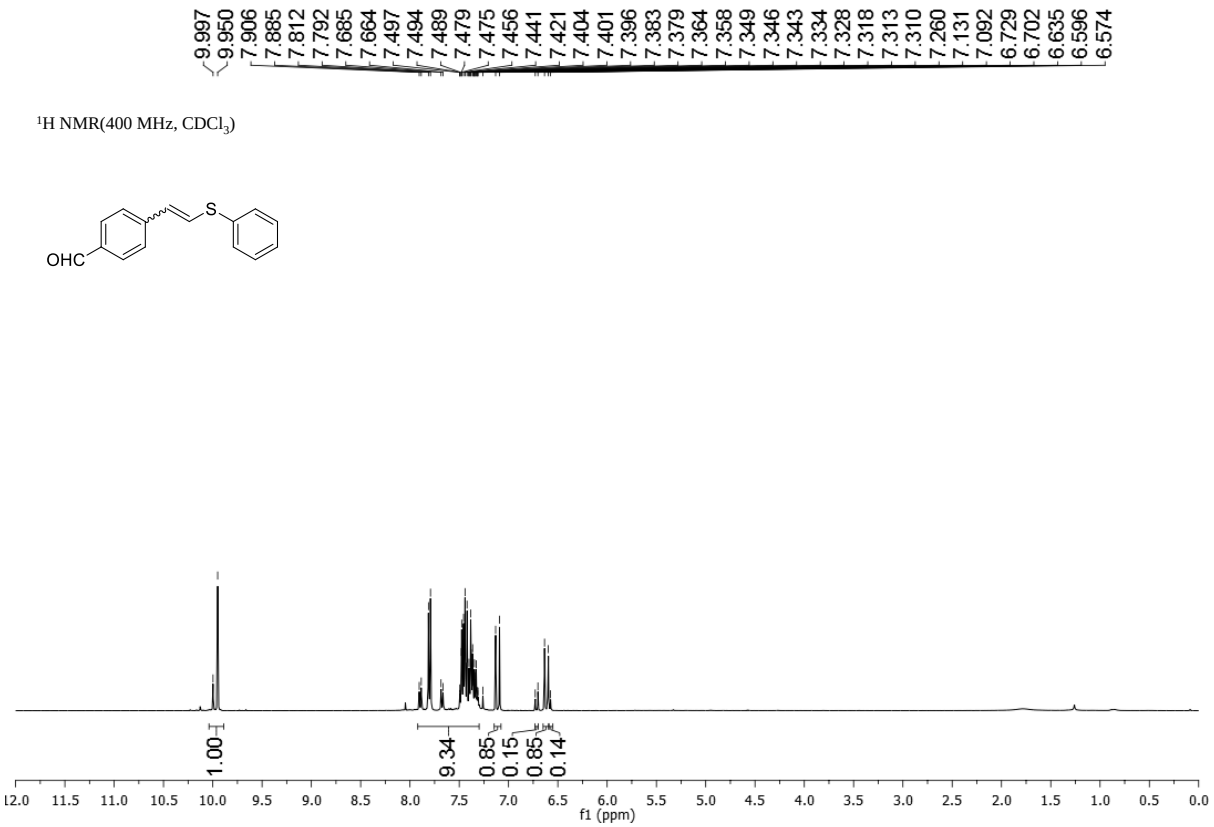


Figure 3B.15. ^{1}H NMR spectrum of 4-(2-(phenylthio)vinyl)benzaldehyde (**3ga**).

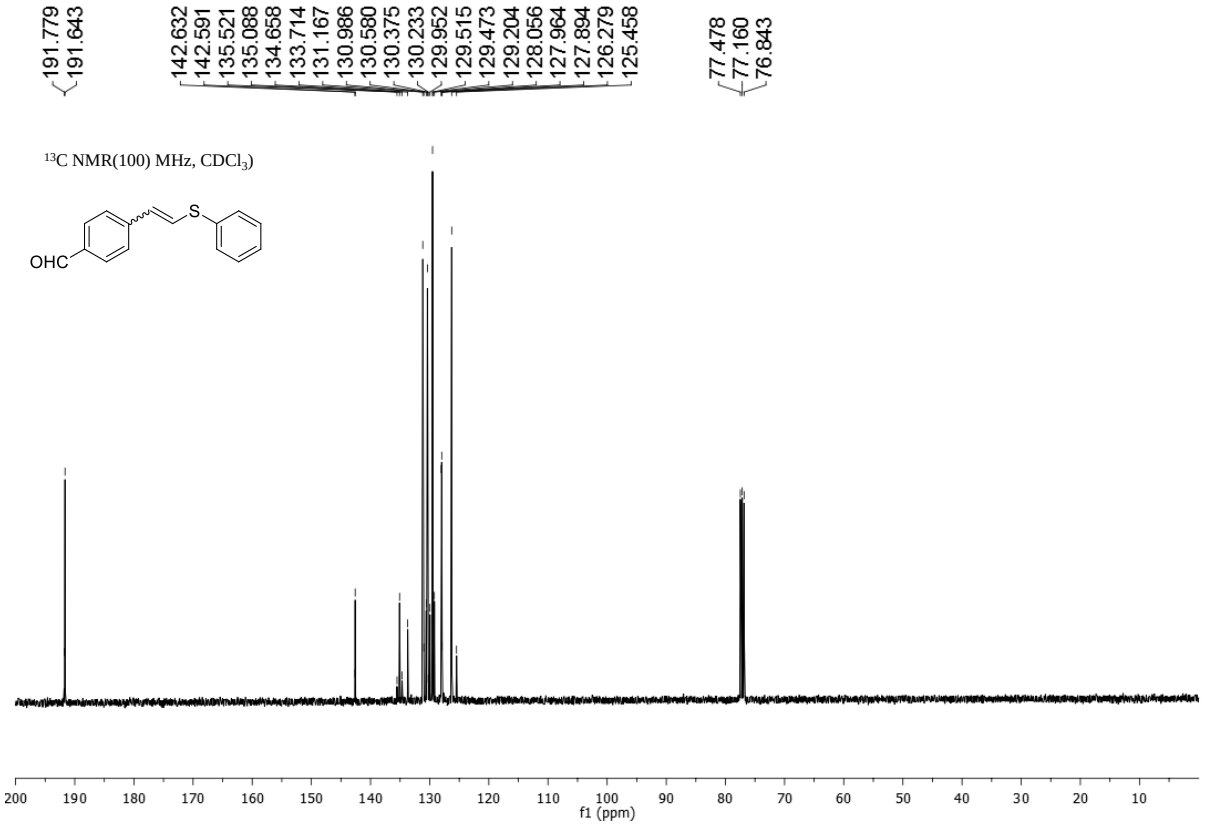


Figure 3B.16. ^{13}C NMR spectrum of 4-(2-(phenylthio)vinyl)benzaldehyde (**3ga**).

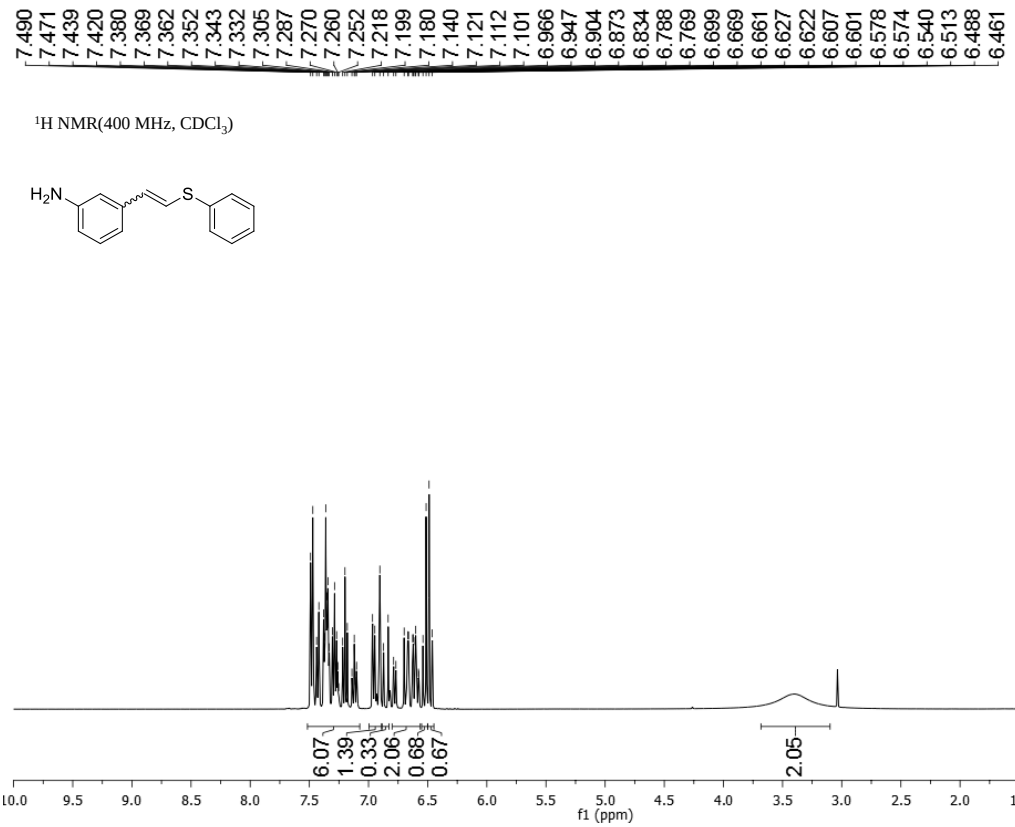


Figure 3B.17. ^{1}H NMR spectrum of 3-(2-(phenylthio)vinyl)aniline(**3ha**).

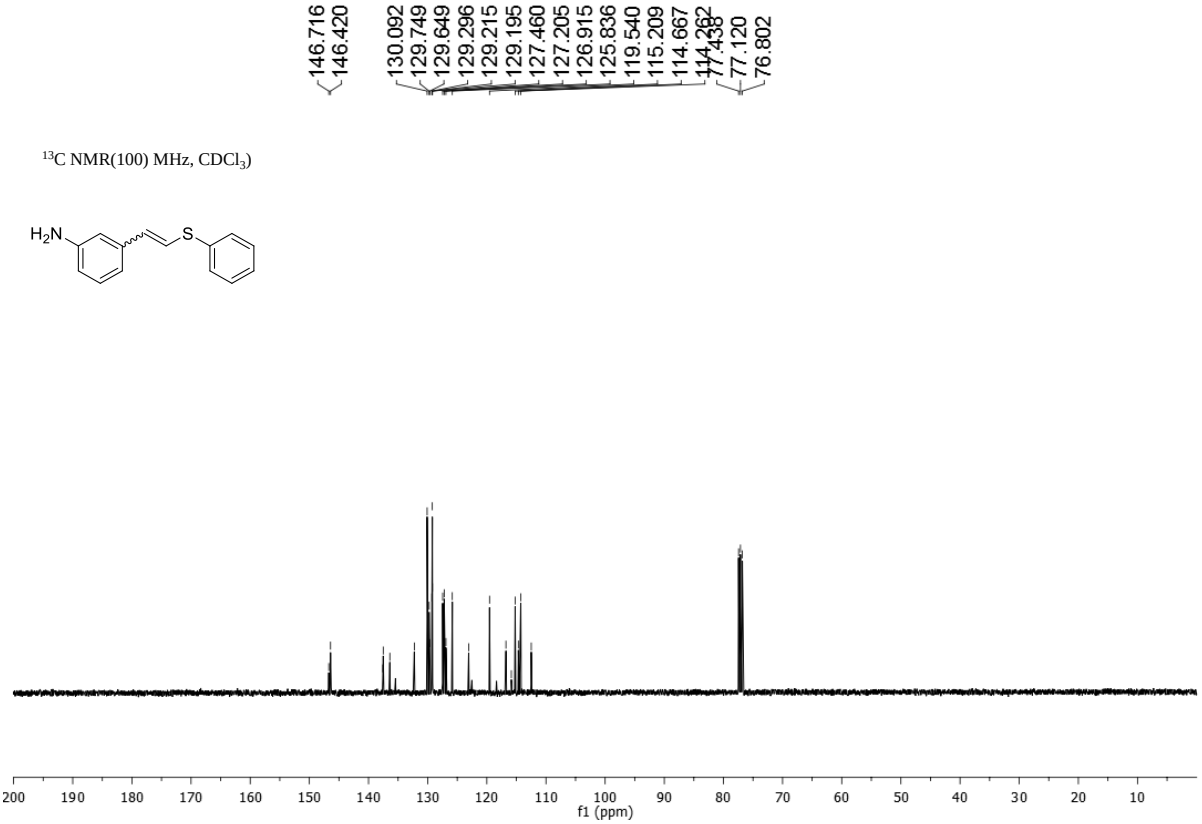


Figure 3B.18. ^{13}C NMR spectrum of 3-(2-(phenylthio)vinyl)aniline(**3ha**).

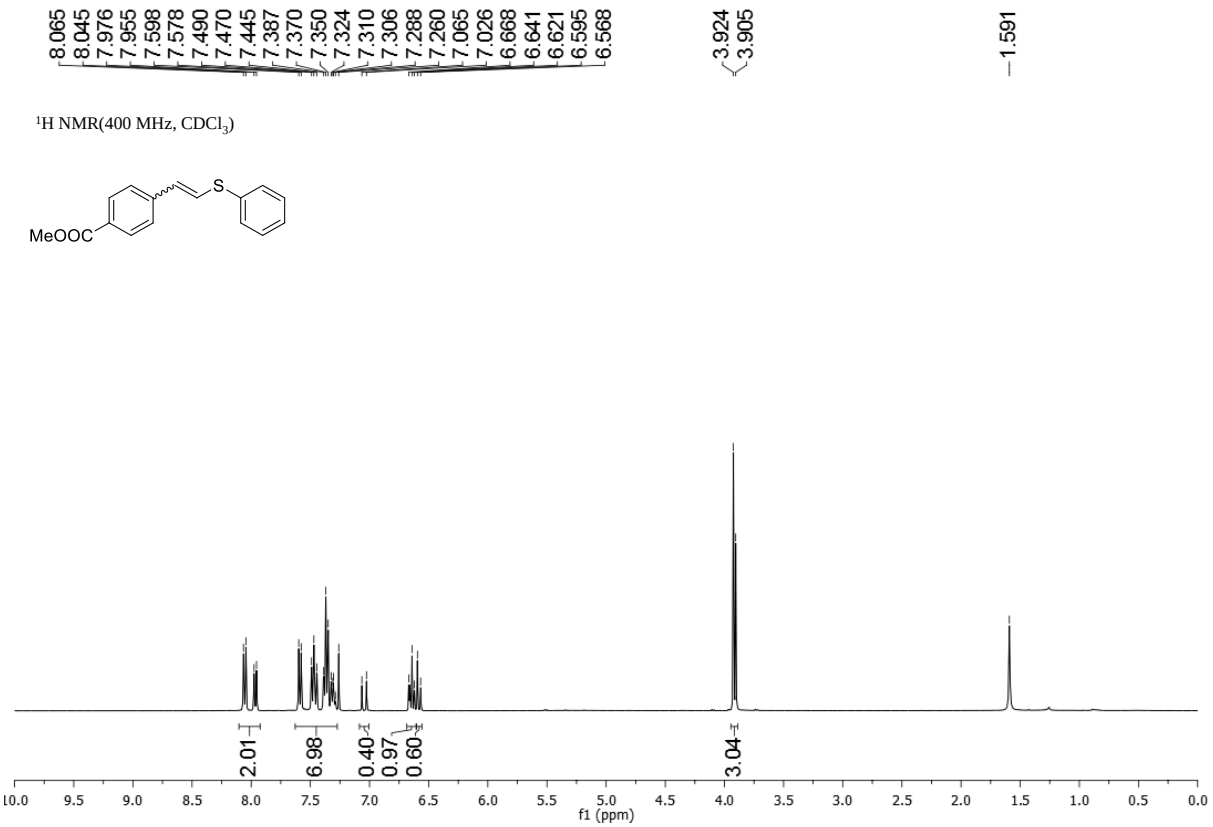


Figure 3B.19. ^{1}H NMR spectrum of Methyl 4-(2-(phenylthio)vinyl)benzoate (**3ia**).

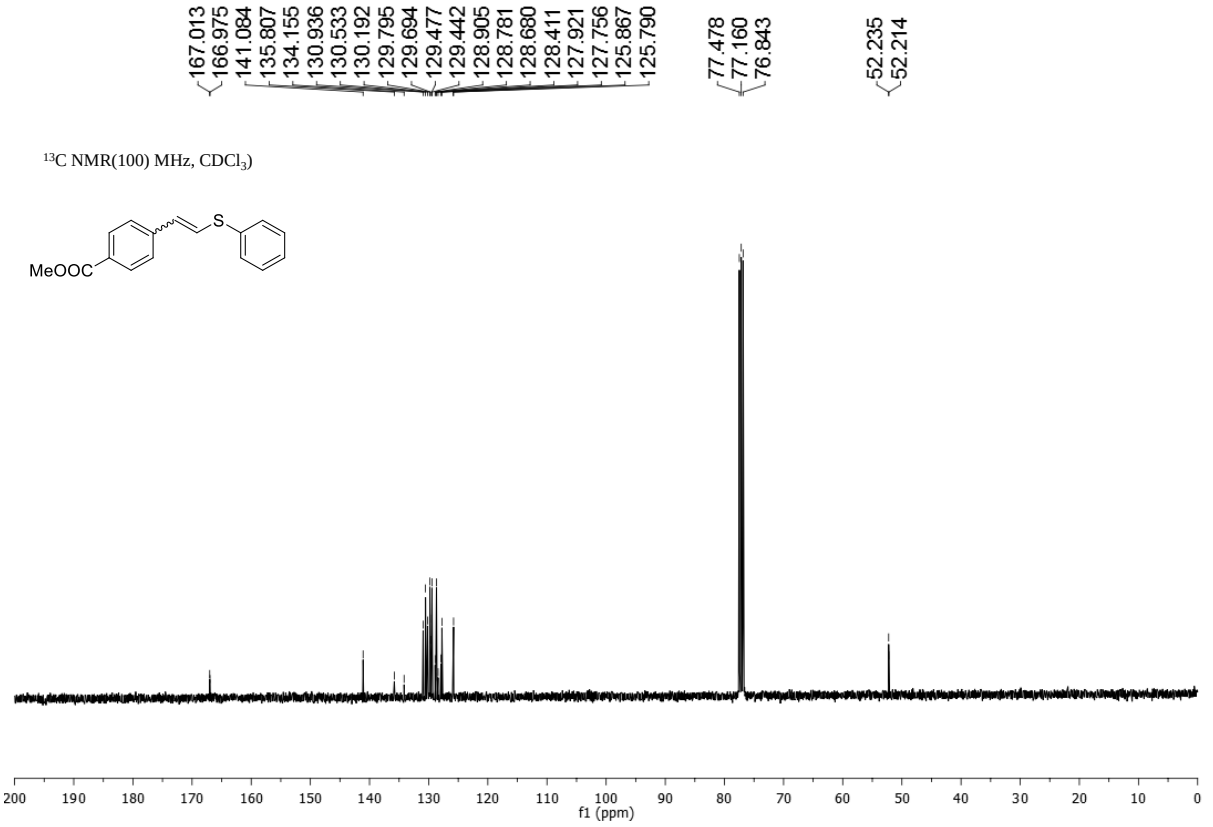
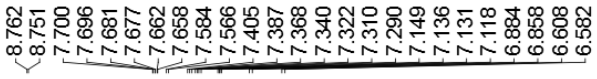
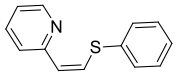


Figure 3B.20. ^{13}C NMR spectrum of Methyl 4-(2-(phenylthio)vinyl)benzoate (**3ia**).



^{1}H NMR(400 MHz, $CDCl_3$)



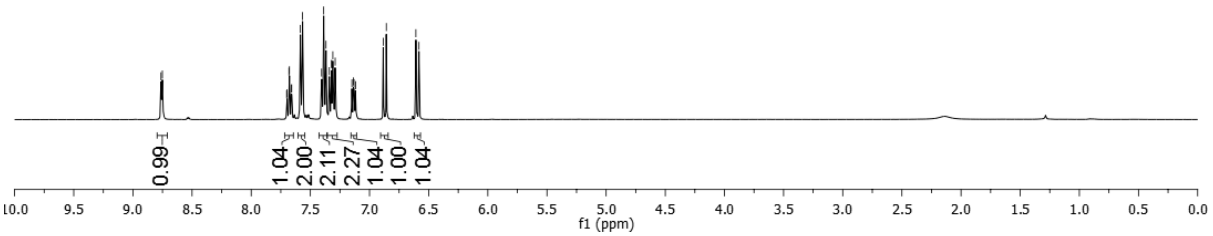
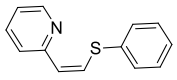


Figure 3B.21. ^{1}H NMR spectrum of (Z)-2-(2-(phenylthio)vinyl)pyridine (**3ka**).

^{13}C NMR(100) MHz, $CDCl_3$)



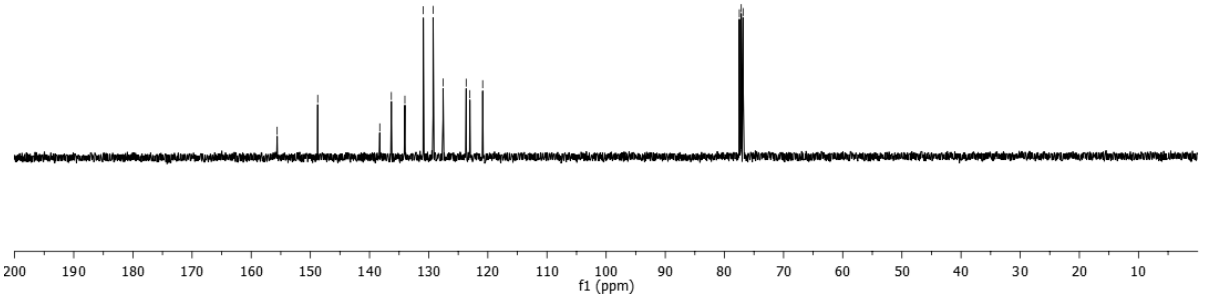


Figure 3B.22. ^{13}C NMR spectrum of (Z)-2-(2-(phenylthio)vinyl)pyridine (**3ka**).

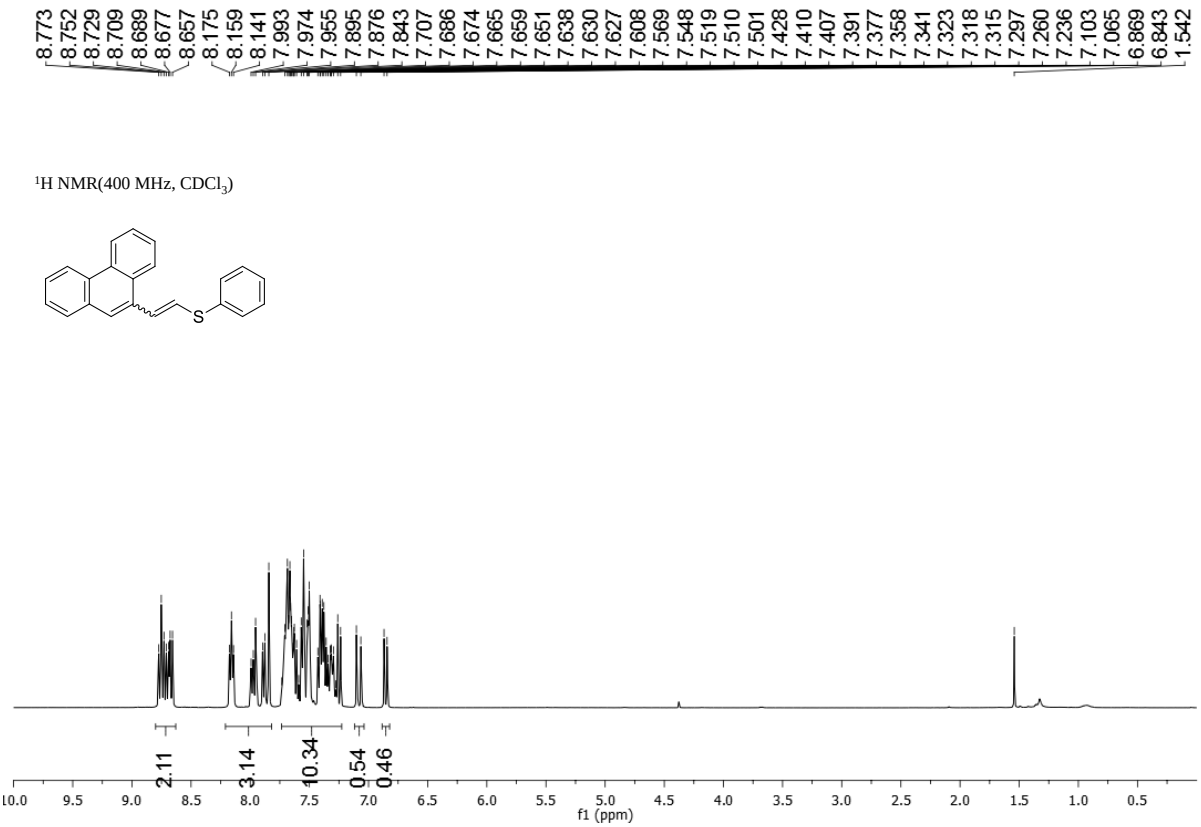


Figure 3B.23. ^{1}H NMR spectrum of (2-(phenanthren-9-yl)vinyl)(phenyl)sulfane (**3la**).

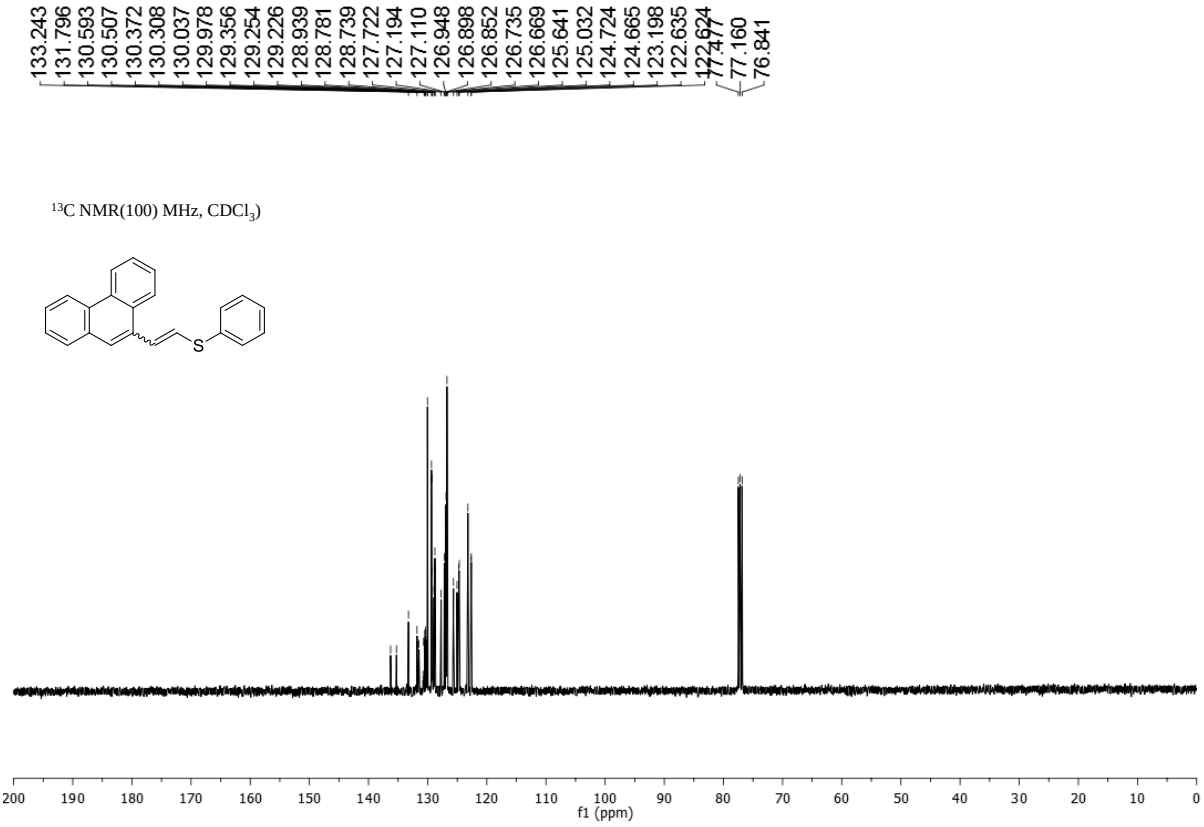


Figure 3B.24. ^{13}C NMR spectrum of (2-(phenanthren-9-yl)vinyl)(phenyl)sulfane (**3la**).

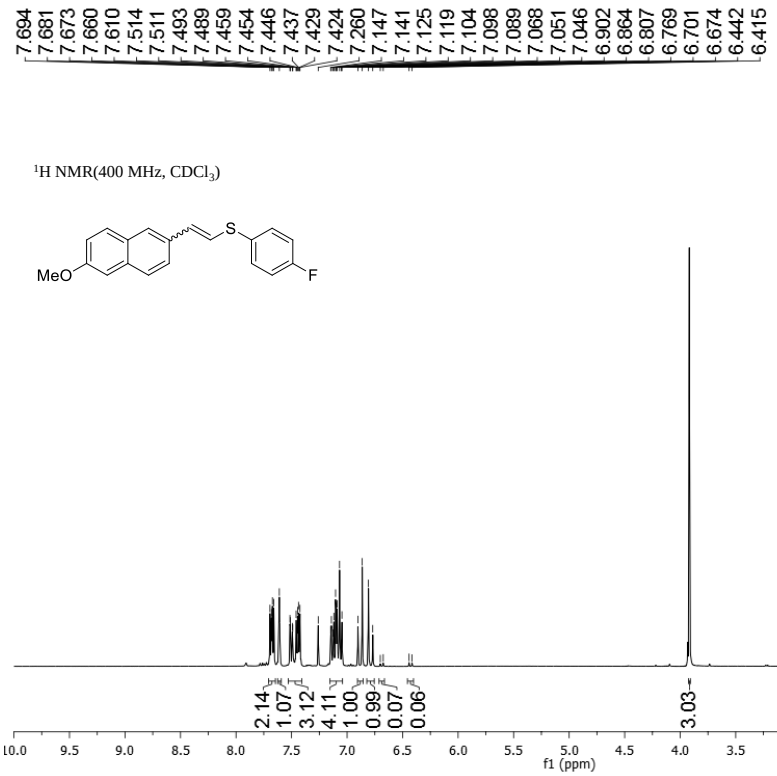


Figure 3B.25. ^{1}H NMR spectrum of (4-fluorophenyl)(2-(6-methoxynaphthalen-2-yl)vinyl)sulfane (**3mb**).

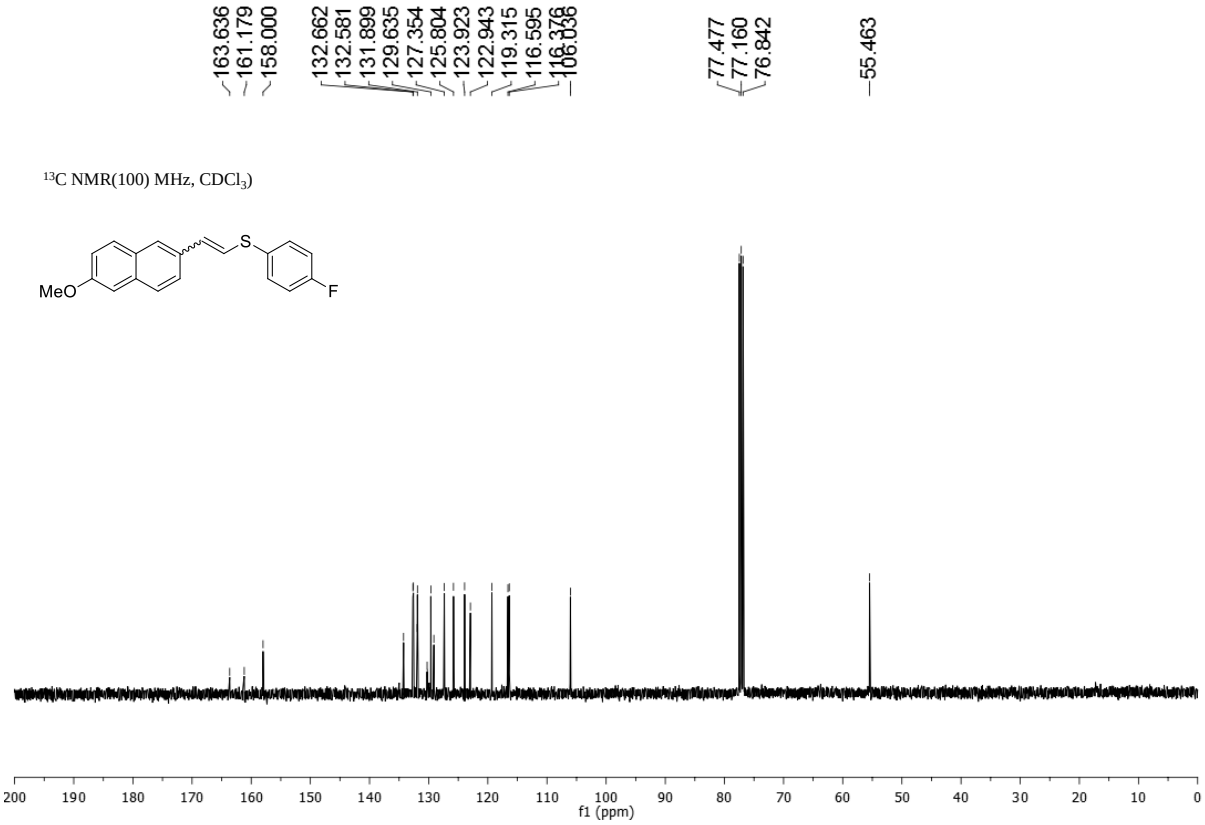


Figure 3B.26. ^{13}C NMR spectrum of (4-fluorophenyl)(2-(6-methoxynaphthalen-2-yl)vinyl)sulfane (**3mb**).

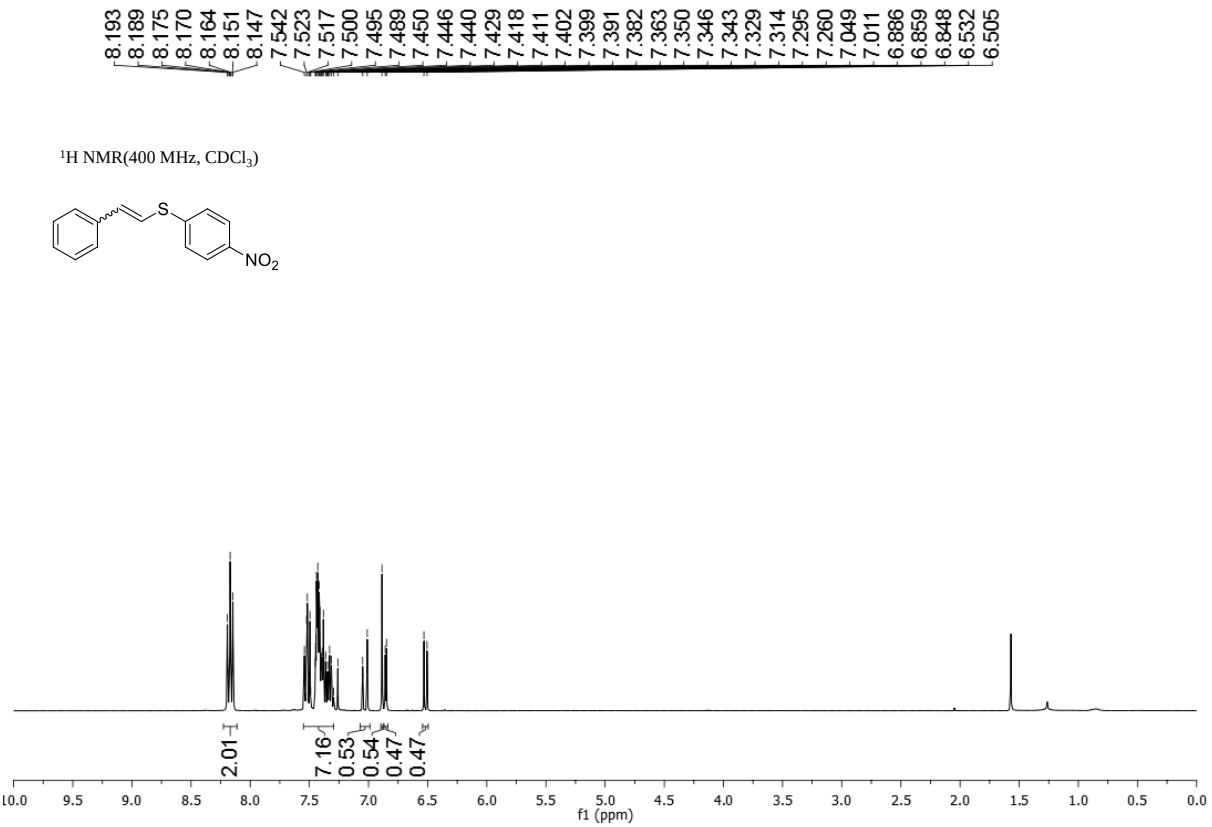


Figure 3B.27. ^{1}H NMR spectrum of (4-nitrophenyl)(styryl)sulfane (**3ai**).

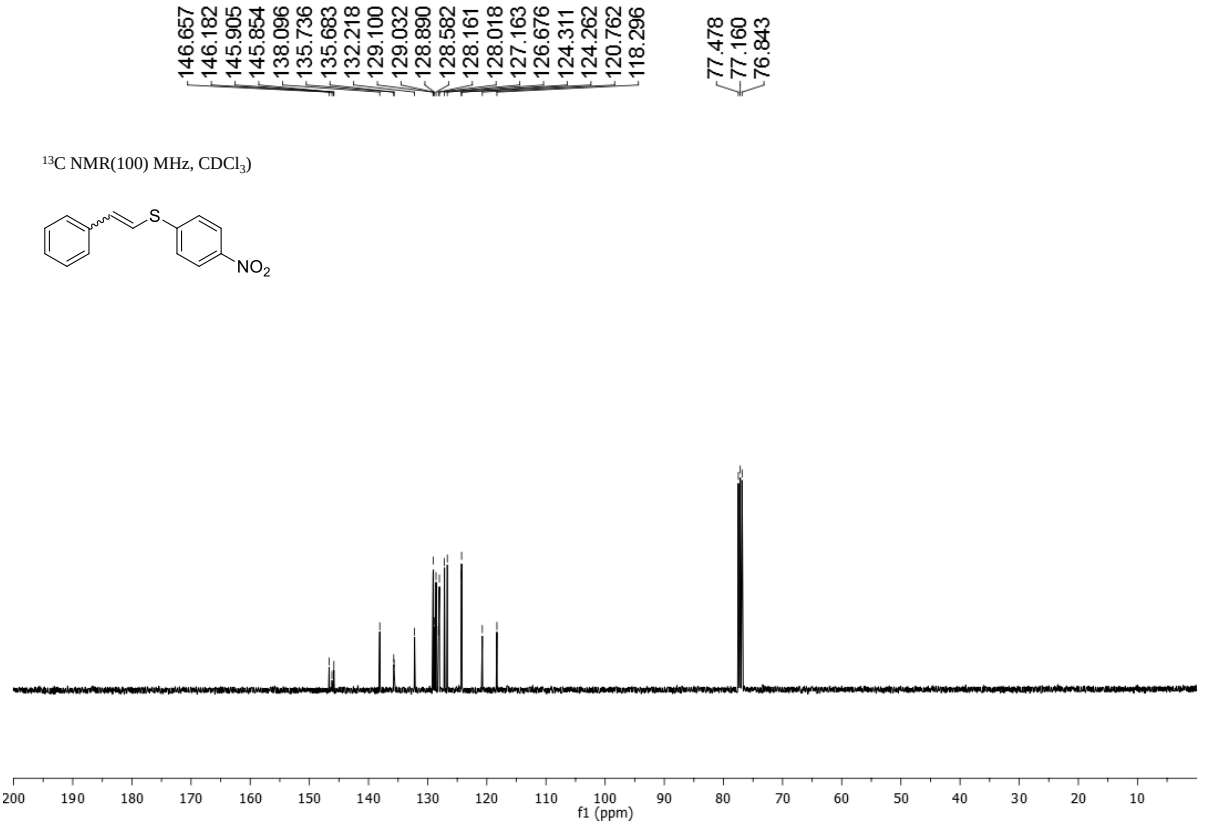


Figure 3B.28. ^{13}C NMR spectrum of (4-nitrophenyl)(styryl)sulfane (**3ai**).

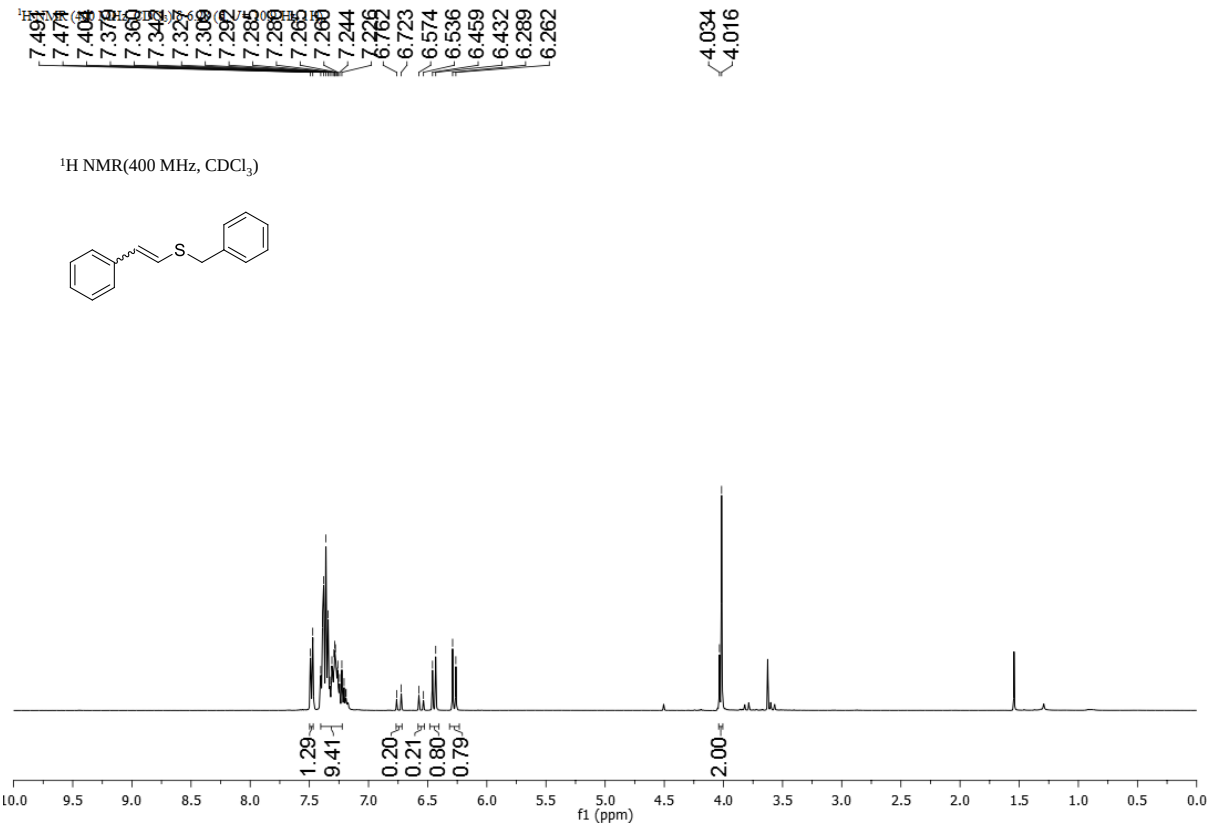


Figure 3B.29. ^{1}H NMR spectrum of Benzyl(styryl)sulfane (**3al**).

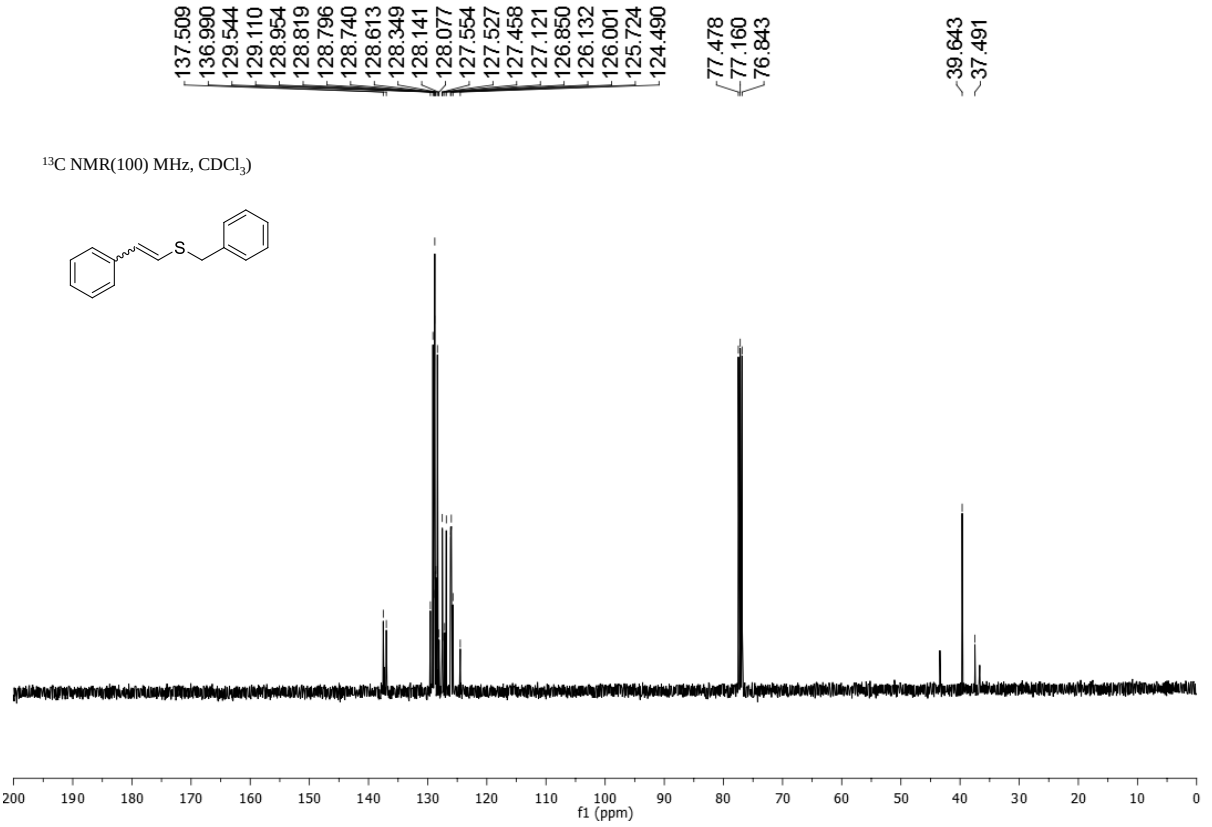


Figure 3B.30. ^{13}C NMR spectrum of Benzyl(styryl)sulfane (**3al**).

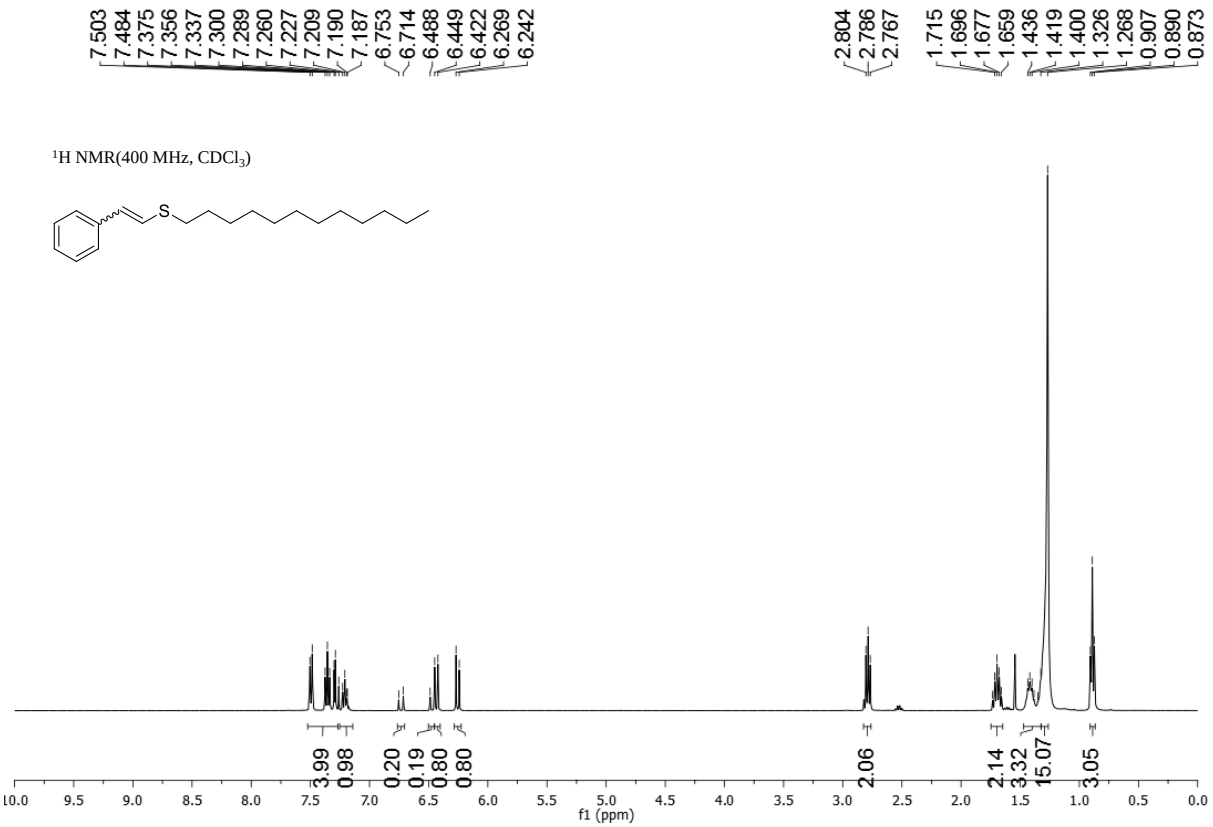


Figure 3B.31. ^{1}H NMR spectrum of dodecyl(styryl)sulfane (**3am**).

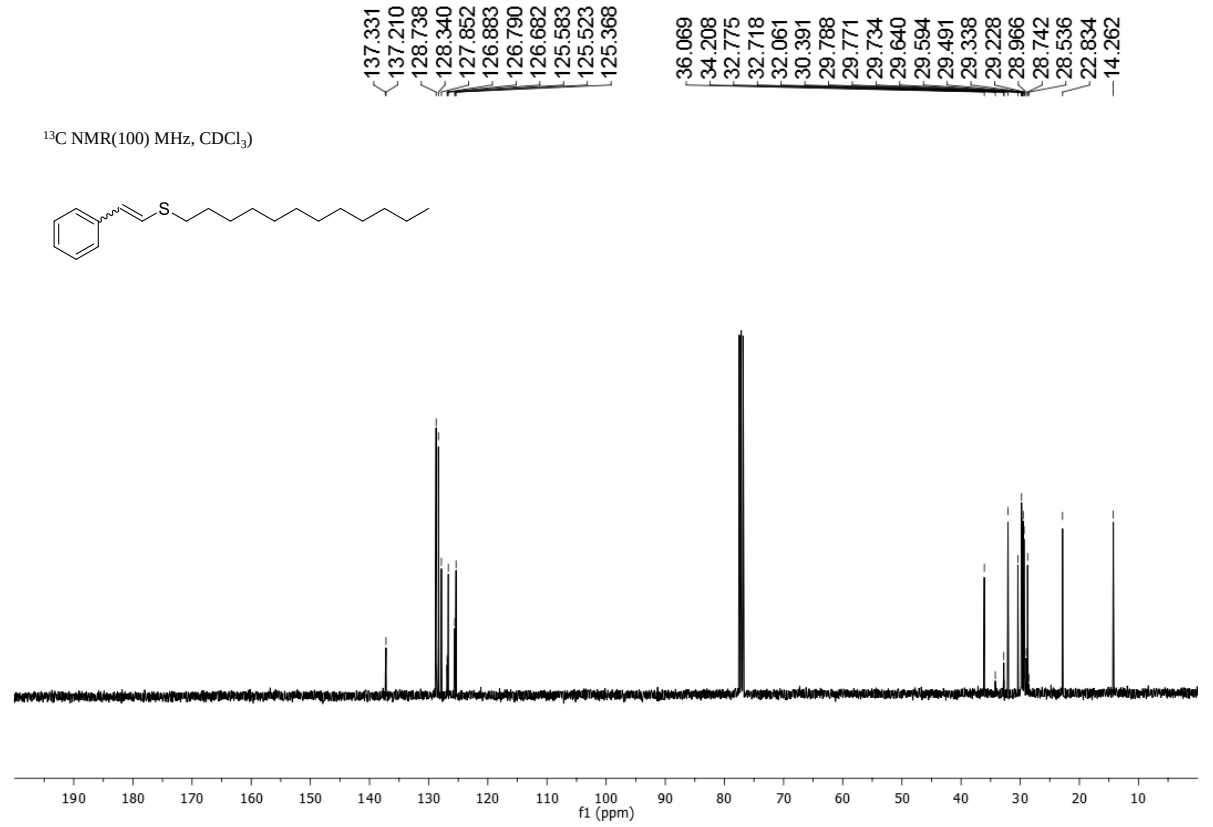


Figure 3B.32. ^{13}C NMR spectrum of dodecyl(styryl)sulfane (**3am**).

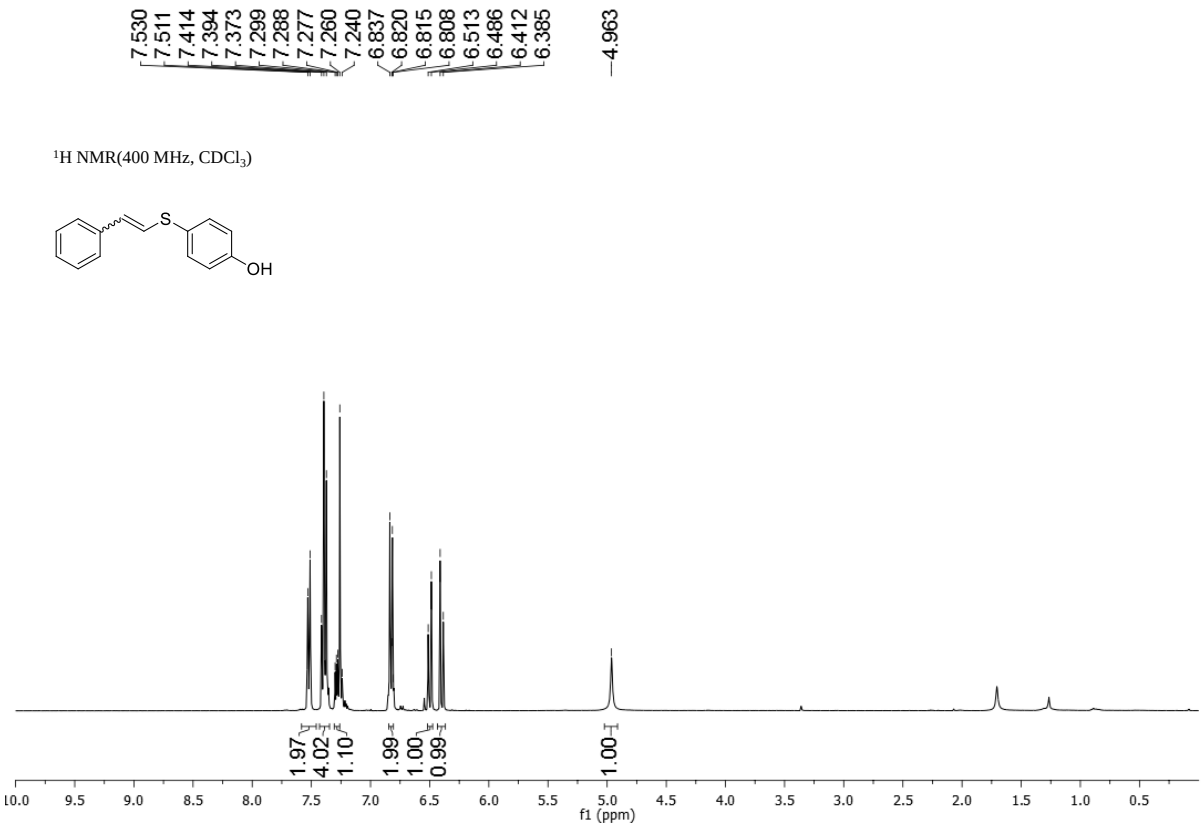


Figure 3B.33. ^{1}H NMR spectrum of 4-(styrylthio)phenol (**3ak**).

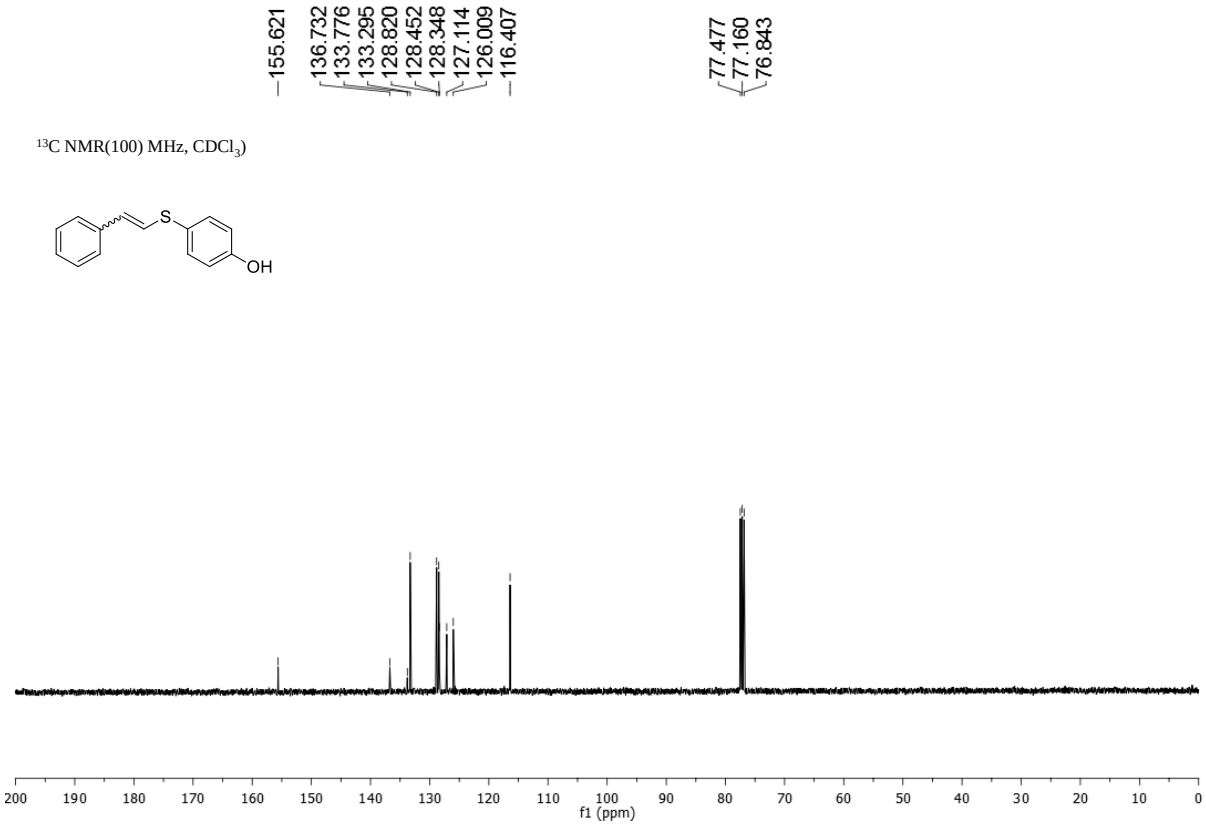
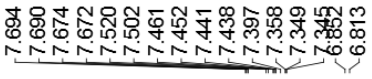
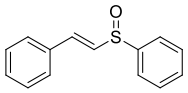


Figure 3B.34. ^{13}C NMR spectrum of 4-(styrylthio)phenol (**3ak**).



^{1}H NMR(400 MHz, $CDCl_3$)



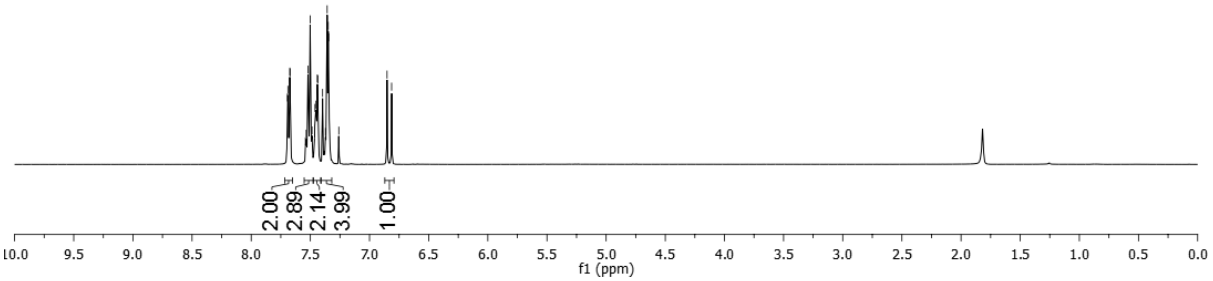
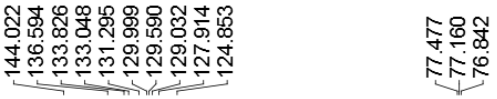
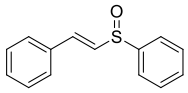


Figure 3B.35. ^{1}H NMR spectrum of (2-(phenylsulfinyl)vinyl)benzene (**8**)



^{13}C NMR(100) MHz, $CDCl_3$)



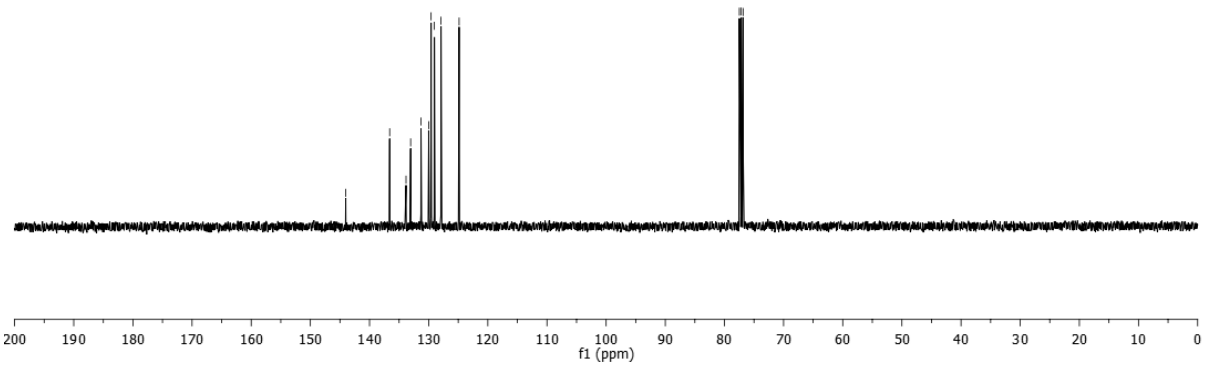


Figure 3B.36. ^{13}C NMR spectrum of (2-(phenylsulfinyl)vinyl)benzene (**8**)

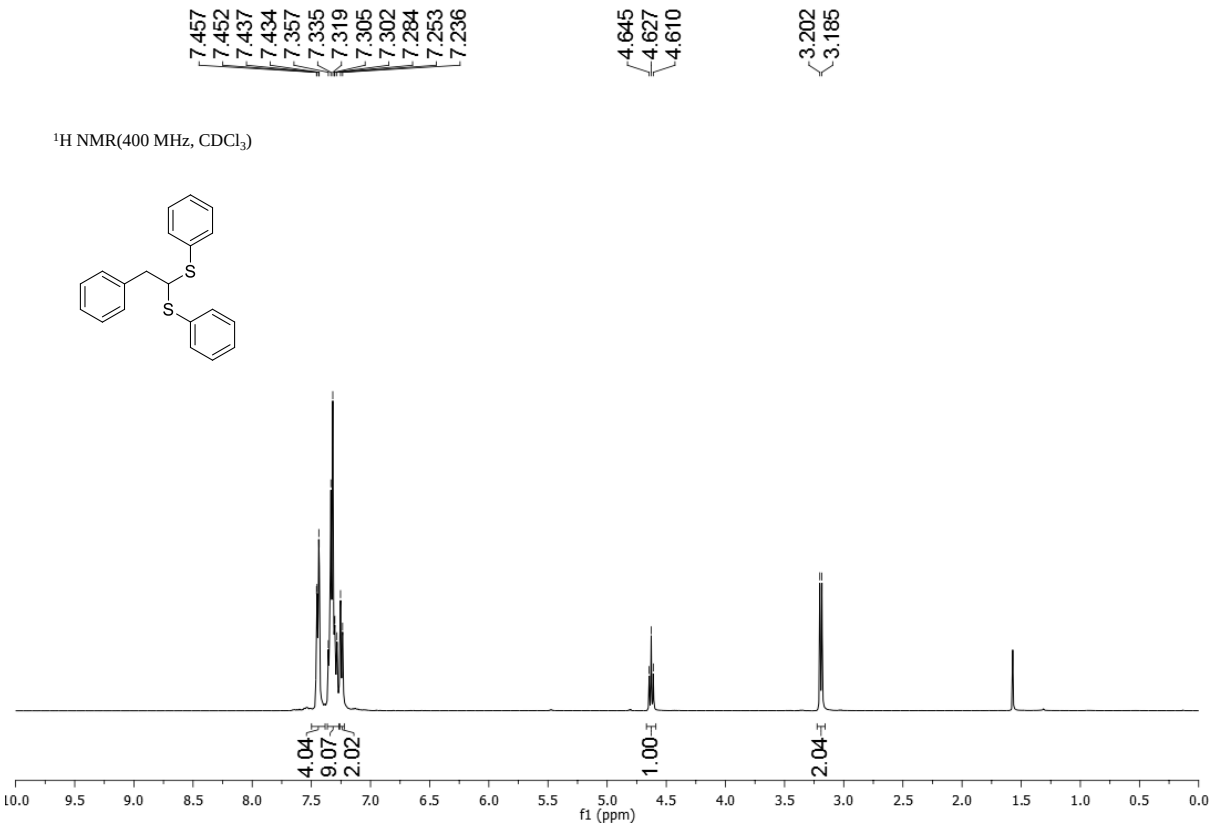


Figure 3B.37. ^{1}H NMR spectrum of (2-phenylethane-1,1-diyl)bis(phenylsulfane) (**9**).

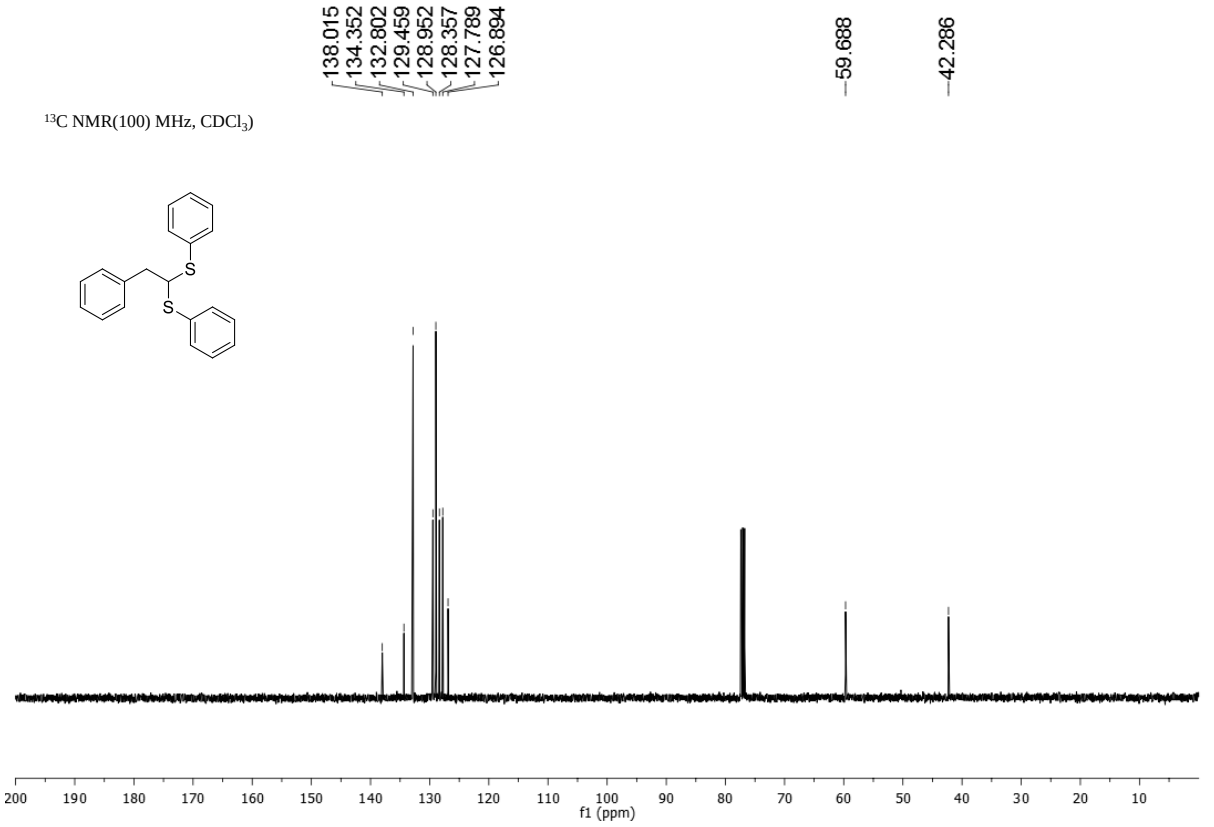
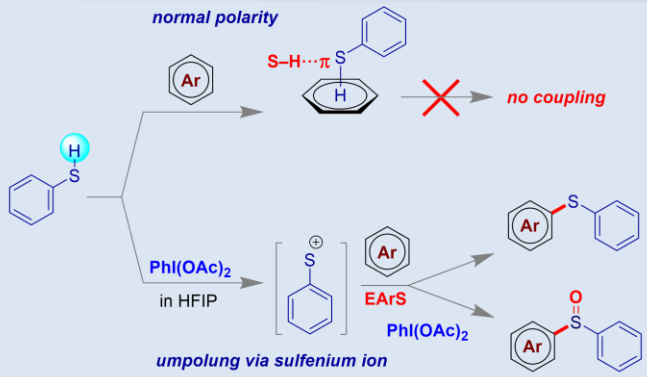


Figure 3B.38. ^{13}C NMR spectrum of (2-phenylethane-1,1-diyl)bis(phenylsulfane) (**9**).

CHAPTER 4

Iodine(III) Enabled Dehydrogenative Aryl C-S Coupling by *in situ* Generated Sulfenium Ion

4.1 ABSTRACT



Due to the normal polarity preferences, arenes form stable complexes with thiols through S–H···π interaction[1,2] and direct dehydrogenative aryl C-S coupling is usually restricted. We reported here an umpolung based one pot and direct C-S coupling approach under metal free and mild condition. Electrophile sulfenium ions were generated in situ from thiols using PhI(OAc)2 (PIDA) and subsequently used for aromatic electrophilic substitution (ArSE) to synthesize diaryl sulfides. Also by the use of appropriate amount of PIDA, cascaded synthesis of C-S and S=O bonds led to aryl sulfinyl arenes in one pot. Covalent self-sorting experiments further proved the involvement of sulfenium ion in the ArSE.

4.2 INTRODUCTION

The C-S bond formation reactions have received significant interest to the researchers because organosulfur compounds are found in many important natural products, biological and pharmaceutical compounds.[3] Nexium, provigil, nelfinavir,[4] AZD4407[5] etc. are some notable sulfur containing drug molecules. Several sulfides and aryl sulfoxides are also known

to be used as HIV-1 integrase inhibitor, antidepressant, anticancer, antifungal, antibacterial, antimicrobial, anti-tumor activities, etc.[6] The drug esomeprazole (Nexium), having a sulfoxide moiety was found to be one of the best-selling drugs in 2009.[7] Thioether and sulfoxide are also important class of heterocyclic motifs holding a broad range of biological and pharmaceutical activities (Figure 4.1).[8-11] Therefore many researchers devoted their attention towards selective and highly efficient method for the construction of thioether and diarylsulfoxide scaffold. Various methods for the synthesis of sulfide, and sulfoxide have been explored, with having some limitation.

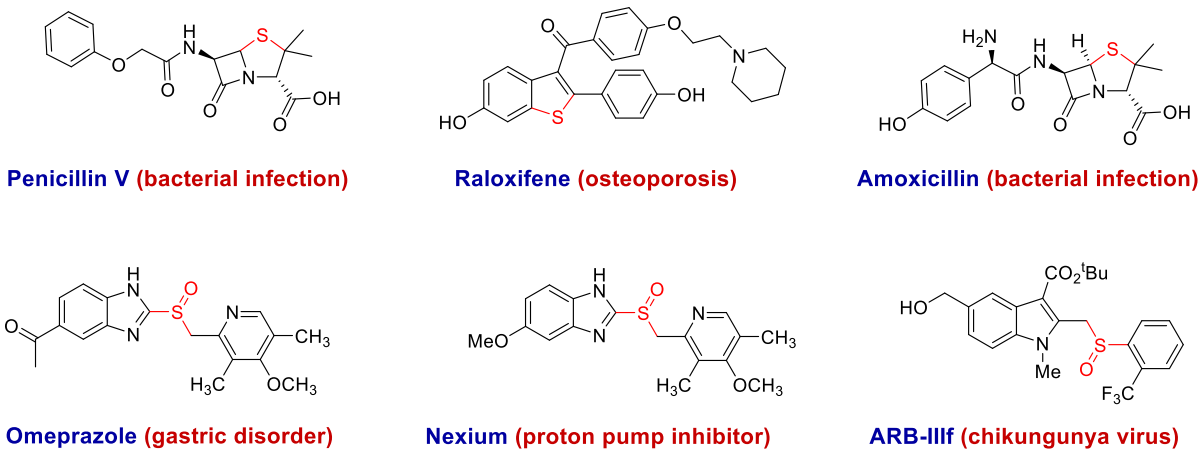
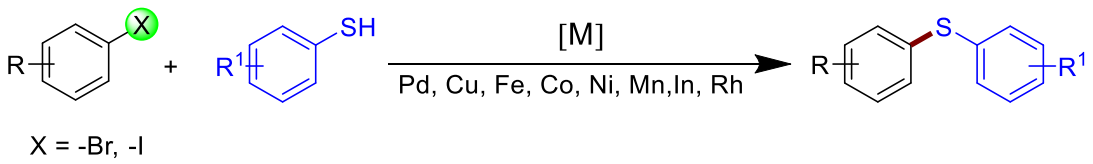


Figure 4.1. Thioether and sulfoxide containing drug molecule.

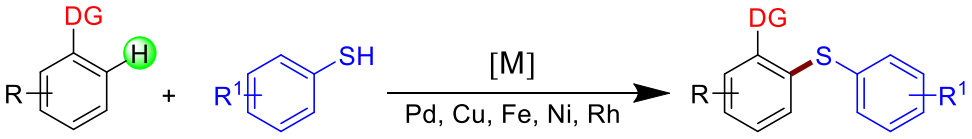
Conventionally, transition metals catalyzed[12-19] cross coupling reaction of aryl halides with thiophenols are mostly followed with pre-functionalized substrate scope (Scheme 4.1).



Scheme 4.1. Metal catalyzed C-S coupling on pre-functionalized substrate.

However, these transformations have many shortcomings for example: (I) requirement of prefunctionalized substrates *i.e.*, preparation of aryl halides or metal reagents prior to the bond formation and making the overall transformation multistep in nature (II) use of stoichiometric amounts of metal based oxidizing agent under harsh reaction condition.

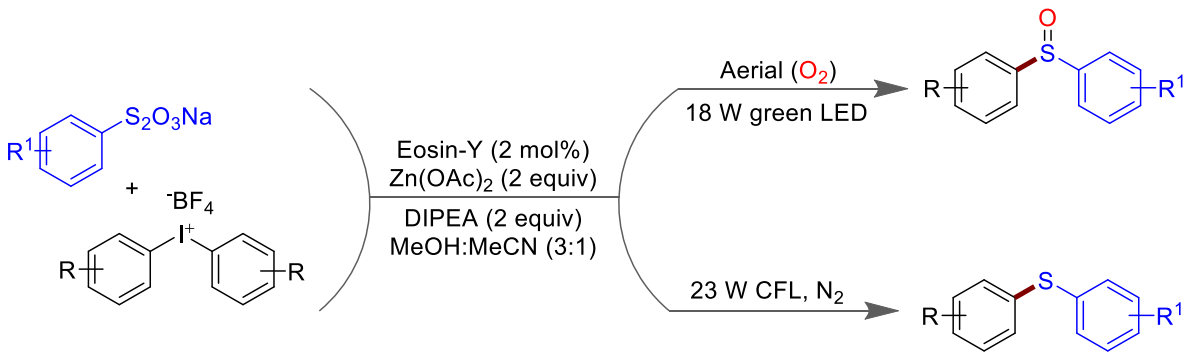
Therefore, direct couplings of diverse functional groups are particularly attractive because they do not necessary pre-activation of coupling partners, and atom and step economical. Recently, C-H activation of directing group strategy[20-25] has emerged as a powerful technique for direct incorporation of various functional groups in a selective manner (Scheme 4.2).



X = -Br, -I

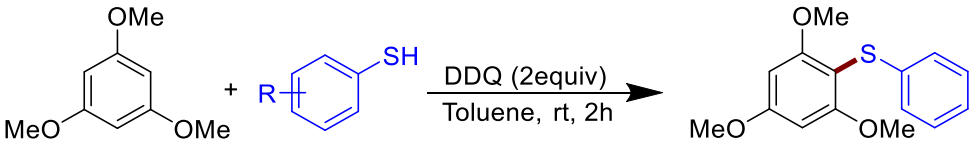
Scheme 4.2. Directing group assisted C-S coupling reaction.

However in this method high catalyst loading and hazardous chemical contamination of heavy metals into the final products made the fatal problem in bioactive and pharmaceutical drug synthesis. Recently, aryl sulfenylation and sulfoxidation under photocatalytic condition have also been developed but the method contained drawback such as use of thiosulfate salts as prefunctionalized substrate (Scheme 4.3).[9,10,26]



Scheme 4.3. Jiang's report of Eosin-Y catalysed C-S bond formation reaction.

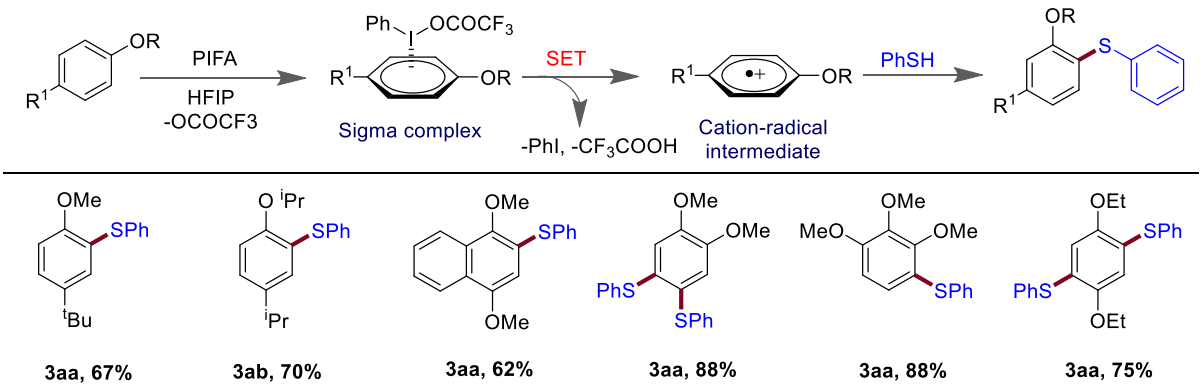
Among the metal free methods, dehydrogenative coupling reactions *via* non-requirement of prefunctionalized substrates are mostly desirable. To the best of our knowledge, very few literature reports are available for diaryl sulphide synthesis *via* metal free cross dehydrogenative approach.[5,27] Recently, Lei's group have demonstrated an oxidant (DDQ) control selective radical-radical intermolecular cross coupling reaction for the synthesis of asymmetric diaryl sulfides from electron rich arenes and thiophenol in toluene at room temperature (Scheme 4.4).[28] Theoretical (DFT calculation) and experimental calculations reveal that the reactions followed radical pathway *via* SET mechanism with the formation of thiyl radical and 1,3,5-trimethoxyphenyl radical cation intermediate from thiophenol and 1,3,5-t rimethoxybenzene respectively. The kinetics data claimed that the SET process between DDQ and thiophenol with an energy barrier 11.2 kcal/mol is the rate determining step of the reaction and the C-H cleavage in the final step facile the process for the radical-radical cross coupling reaction with an exothermic energy barrier 16.3 kcal/mol.



Scheme 4.4. Lei's report of DDQ control radical-radical cross coupling reaction.

Metal-free hypervalent iodine(III) reagents are highly popular in organic synthesis owing to their easy accessibility, environmentally benign nature. Also, depending on the substituents on iodine center, hypervalent iodine(III) reagents show a wide range of discrepancies in reactivity towards oxidative transformations. For example, Kita and co-workers reported a dehydrogenative C-S coupling reaction using strong oxidant PIFA. The reaction was based on single electron transfer (SET) pathway from electron rich *para*-substituted phenol ether compounds to highly electron deficient iodine(III) centre of PIFA followed by nucleophilic

substitution by thiol (Scheme 4.5). However, the key drawback associated with Kita's report, it is only applicable with electron rich phenolic ether compounds for C-S coupling reaction.



Scheme 4.5 Kita's approach for dehydrogenative C-S coupling reaction

To overcome the problems associated with the Kita's report, we have developed a metal-free dehydrogenative aryl C-S coupling reaction *via* umpolung approach, from the respective arenes and thiophenols under metal free, mild condition (Figure 4.2a). These transformations involved generation of *in-situ* electrophilic sulfenium ions intermediate from thiophenol by the treatment with iodine (III) reagent PhI(OAc)2 (PIDA). The sulfenium ion intermediate stabilized in polar aprotic solvent HFIP through H-bonding used for aromatic electrophilic substitution (EArS) to synthesize diaryl sulfides. Also by using of appropriate amount of PIDA, cascaded synthesis of C-S and S=O bonds led to the formation of aryl sulfinyl arenes in one pot (Figure 4.2b).

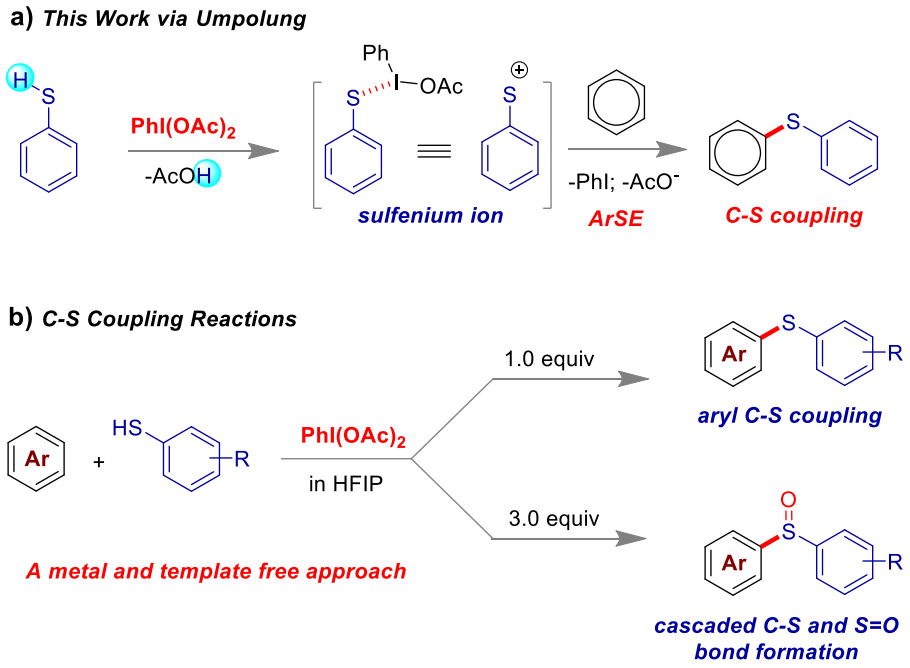
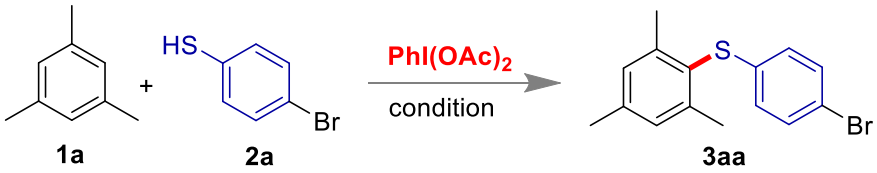


Figure 4.2. Aryl C-S coupling reactions under mild condition. a) Our hypothesis towards dehydrogenative aryl C-S coupling reaction *via* sulfenium ion. b) Selective synthesis of either diaryl sulfides or aryl sulfinyl arenes by using appropriate amount of oxidant.

4.3 RESULTS AND DISCUSSION

Towards optimization of the reaction condition, initially we started with mesitylene (1a) 4-bromo-thiophenol (2a) as model substrates (Table 4.1). When the mixture of 1a and 2a were treated with 1.0 equiv of PIDA in various solvents at ambient condition the desired product (4-bromophenyl)(mesityl)sulfane (3aa) was isolated (Table 4.1). Among the solvents examined, HFIP was found to be the most efficient (entry 2-6); use of 1:1 HFIP-DCM (dichloromethane) was most accessable for this transformation. Use of oxidants other than PIDA like $PhI(OPiv)_2$ (entry 8), $PhI(OCOCF_3)_2$ (entry 9) and molecular iodine (entry 7) were also not encouraging the yields.

Table 4.1. Screening condition for C-S coupling reaction.



1a 2a 3aa

Entry	Oxidant (1.0equiv)	Solvent	Yield (%)[a]
1	PIDA	HFIP/DCM (1:1)	85
2	PIDA	HFIP	99 (96)[b]
3	PIDA	DCM	9
4	PIDA	EtOH	15
5	PIDA	CH_3CN	31
6	PIDA	H_2O	38
7	I_2	HFIP	00
8	I_2	DMSO	00
9	$PhI(OPiv)_2$	HFIP	90
10	PIFA	HFIP	62
11	PIFA	TFE	48

[a]NMR Yields; [b]Isolated yields

Under optimized condition a range of thiols and arenes were reacted to explore the scope of the coupling reactions (Figure 4.3). A series of thiophenols bearing electron-withdrawing groups like halogen (3aa, 3ac-d, 3ai-j, 3ba, 3ca), nitro (3ag), trifluoromethyl (3ah) as well as electron-donating substituents such as alkyl (3ae, 3de), alkoxy (3af, 3hf) were fair-yielding to produce C-S coupled products. Aliphatic thiols also efficiently reacted with mesitylene to produce 3ak and 3al with quite good yield (*vide infra*). Similarly, formation of diarylsulfides from alkoxy (3ba, 3ca, 3da, 3eb, 3lb, 3ib, 3de) as well as alkyl (3fb, 3gb, 3hf) substituted arenes were also found to be compatible to this methodology.

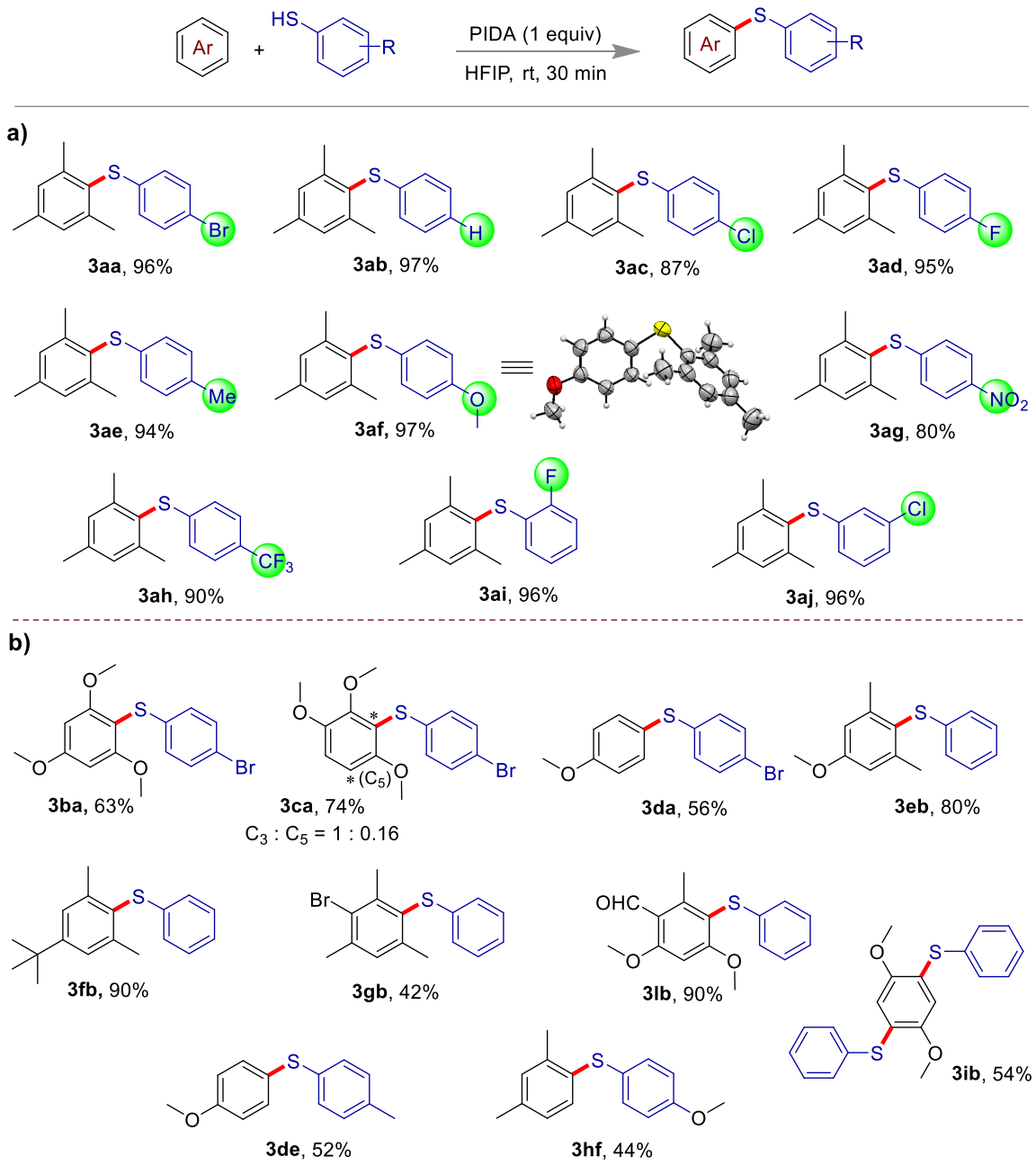


Figure 4.3. Substrate scope for the dehydrogenative C-S coupling reaction. a) C-S coupled products from mesitylene with various thiols. b) Different kinds of arenes were also reacted.

In case of 1,2,4-trimethoxy benzene, formation of two different regioisomers (3ca) were noticed with the ratio of 1 : 0.16. However, only single regioisomer was formed when either 3,5-dimethyl anisole (3eb) or 1,3-dimethyl-5-*tert*-butylbenzene (3fb) was used as arene source for the coupling reaction. Relatively lower yield of products was witnessed by using

m-xylene (3hf), 2-bromo-mesitylene (3gb), and anisole (3de). It is also noticed that –CHO group containing electron rich arene also worked well to afford the desired product 3lb with 90% yield. More interestingly, two consecutive C-S bond could have been possible during the reaction between thiophenol and 1,4-dimethoxybenzene to produce 3ib.

Control experiments shown in Figure 4.4 helped us to understand the reaction proceeded *via* the sulfenium ion (*vide supra*, Figure 4.2). At the standard condition, addition of radical scavenger TEMPO (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) could not inhibit the product formation and 3aa was isolated with 44% yield (Figure 4.4a). This result confirmed that the reaction did not follow the radical pathway. We anticipated that the formation of the intermediate sulfenium ion was essential for the aryl C-S bond formation reaction. When the thiol 2a was treated with PIDA, disulfides 5aa was obtained as the only product (Figure 4.4b). Possibly, the sulfenium ion could react with available nucleophile thiols for the S-S bond formation. In addition, one of the disulfides (5bb) was oxidized to the sulfenium ion[29] using the PIDA and in presence of mesitylene, product 3aa could be isolated in 80% yield (Figure 4.4c). We anticipated that the ArSE reaction proceeded *via* the generation of sulfenium ion. Moreover, the isolation of aryl C-S coupled products with alkyl thiols in fair yields (Figure 4.4d) also supported for the formation sulfenium ion. The research area of supramolecular catalysis or small molecules systems chemistry approach[30,31] are not well-defined, however they deal with the methods of performing chemical reactions using non-covalent interactions in organic synthesis.[32-36]

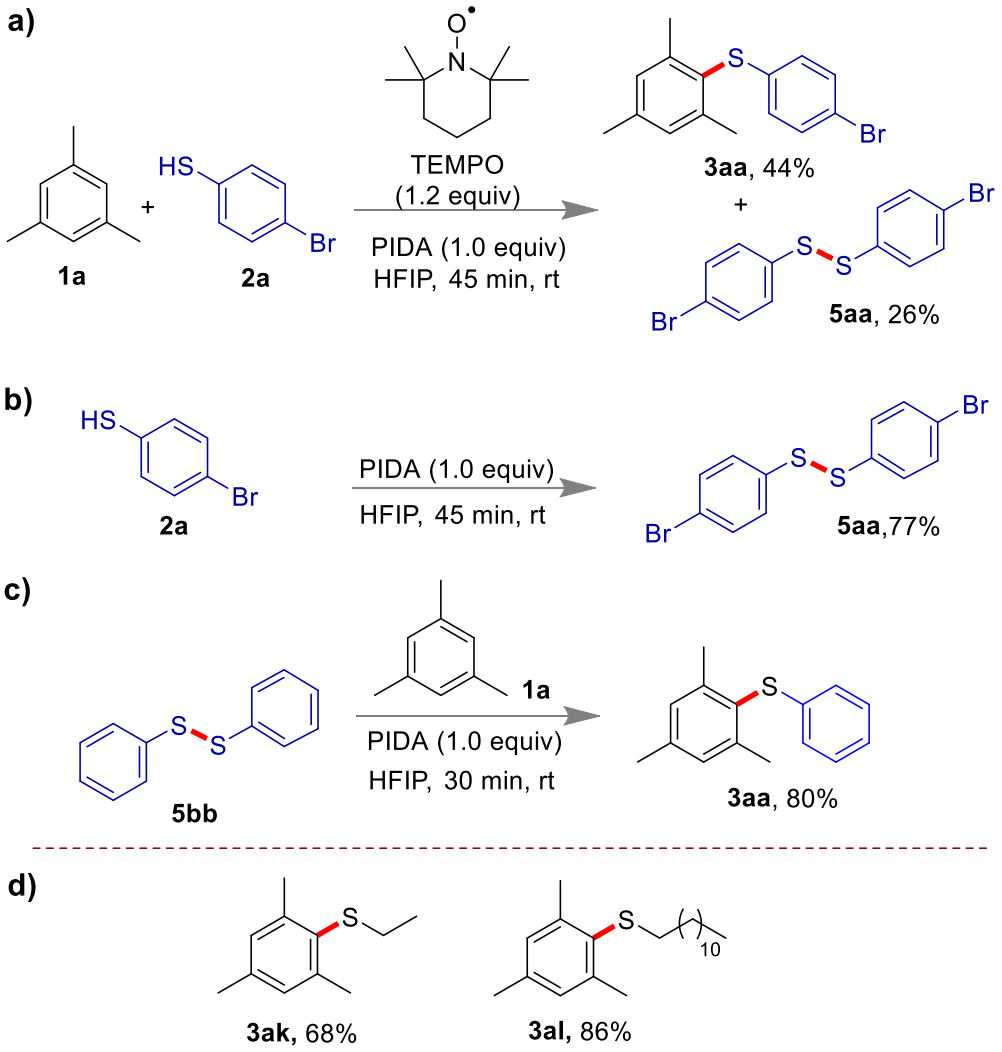


Figure 4.4. Control experiments. a) Radical scavenger experiment established non-radial pathway. b) Disulfide formation was observed in absence of nucleophile. c) Sulfenium ion was generated from disulfide for the ArSE. d) Aliphatic thiophenols are also successful to generate *in-situ* sulfenium ions.

Moreover, limited examples are known for the use of systems chemistry towards synthesis of small molecules.[37,38] Therefore, the self-sorting[37,39] experiments shown in Figure 4.5 were performed to prove that the sulfenium ion was one of the intermediate in the reaction. Once the sulfenium ion was generated *in situ* the nucleophilicity of the arenes was found to be controlling factor for the product selection process within the system *via* a covalent self-

sorting.[40] Herein, mesitylene as a better nucleophile than anisole afforded greater selectivity towards the product formation (Figure 4.5a). Similarly, when 1.1 equiv of PIDA and thiophenol (1.0 equiv) were reacted with 1:1 mixture of mesitylene and *m*-xylene **3ae** (only mesitylene reacted) was obtained exclusively (Figure 4.5b). Likewise, 3,5-dimethyl anisole being a better nucleophile led to the selective formation of the **3ee** (Figure 4.5c) and no mesitylene adduct could be isolated.

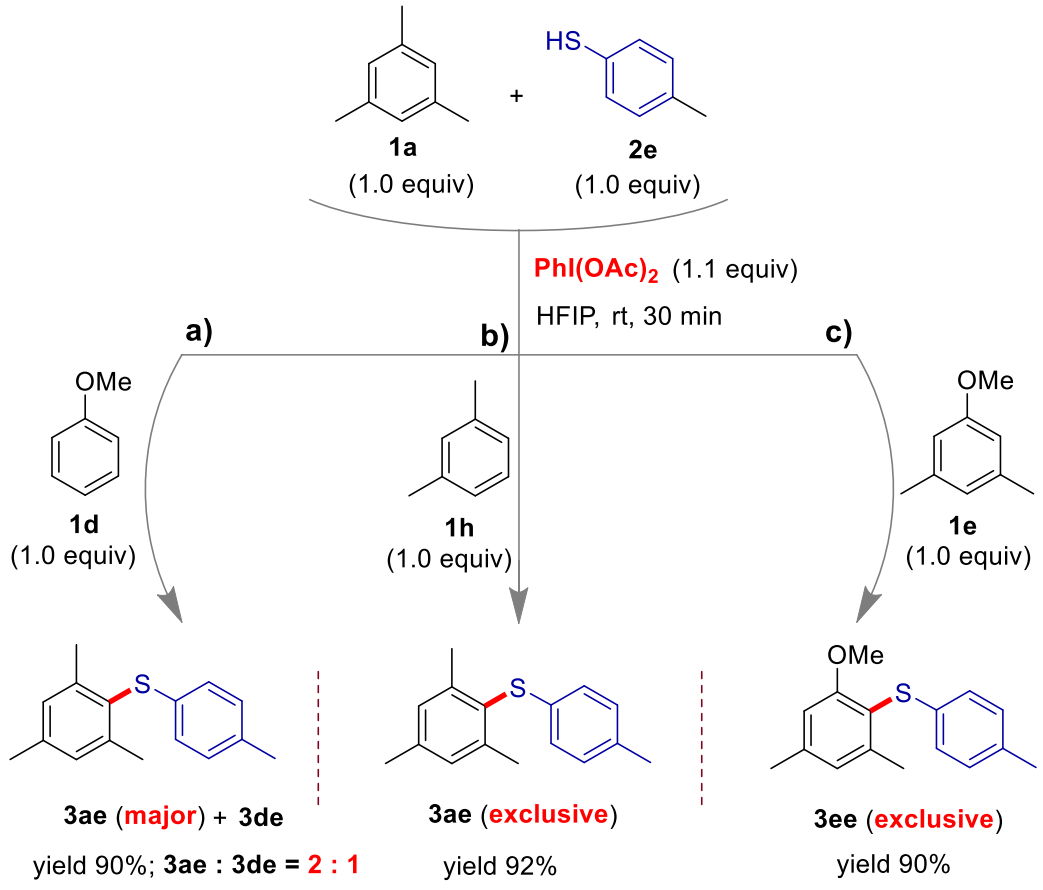


Figure 4.5. ArSE in the covalent self-sorting *via* sulfenium ion.

Thus rationalize it was that the product selectivity was observed due to the relative nucleophilicity of arenes for the ArSE reaction *via* sulfenium ion intermediate. Mesitylene was better nucleophile than anisole and *m*-xylene, but inferior than 3,5-dimethylanisole.

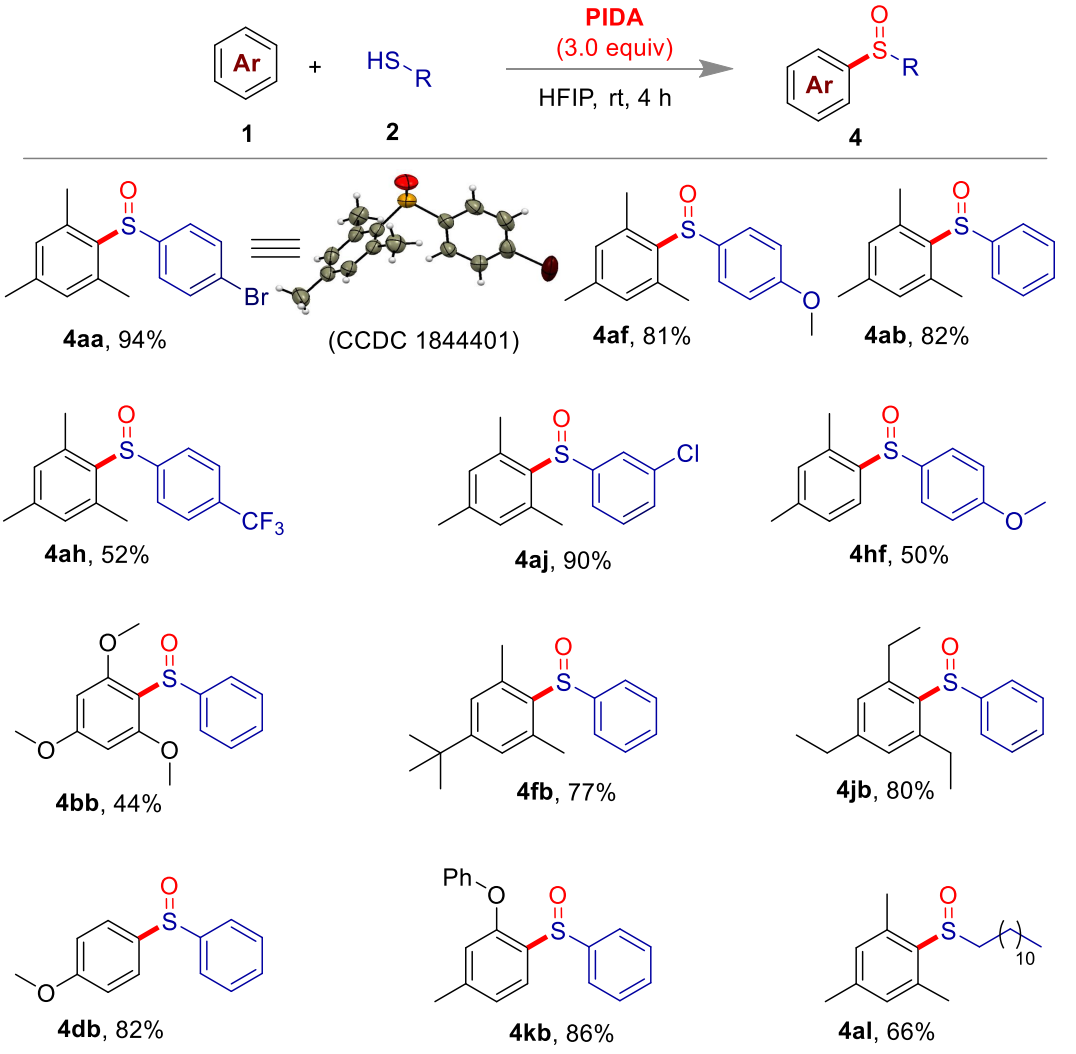
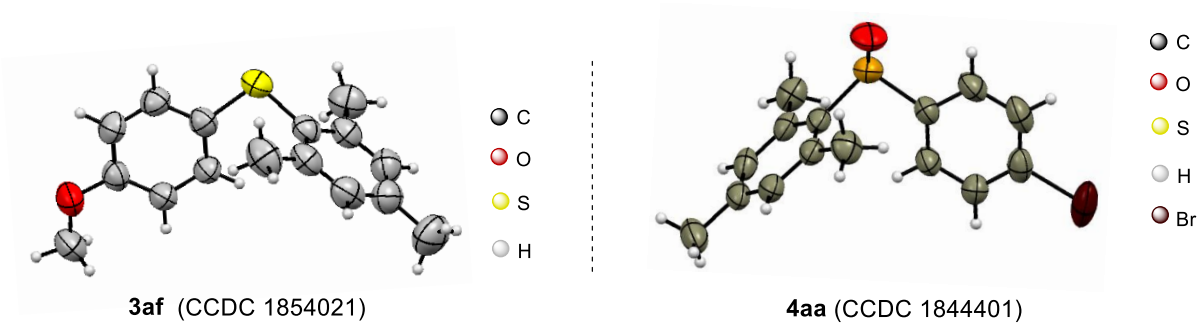


Figure 4.6. Scope of the reaction for different kinds of aryl sulfinyl arenes synthesis.

The C-S coupling methodology was further extended to the cascaded C-S and S=O bond formation reaction starting from the arenes and thiols towards synthesis of aryl sulfinyl arenes or diaryl sulfoxides (Figure 4.6).[41,42] The synthetic procedures of sulfoxides[6] are difficult and known *via* multistep methodology.[43,44] However, we reported herein the synthesis of various aryl sulfinyl arenes in a single step and mild condition (Figure 4.6). A wide range of aromatic thiols were treated with various arenes in presence of 3.0 equiv of PIDA in HFIP solvent at room temperature condition to afford the aryl sulfinyl arenes in good to excellent yields. Electron withdrawing groups such as halogens (4aa, 4aj), trifluoromethyl (4ah), electron donating methoxy (4af, 4hf) or unsubstituted thiophenols (4ab,

4bb, 4fb, 4jb, 4db, 4kb) underwent smooth conversion towards the generation of sulfoxides with moderate to excellent yields. Additionally, using aliphatic thiol also we could isolate the desired product 4al with good yield (66%). Also, a wide range of electron donating arenes such as mesitylene, *m*-xylene, 1,3,5-trimethoxybenzene, 1,3,5-triethylbenzene, 3,5-dimethyl-tert-butyl-benzene, anisole, 3-phenoxytoluene were tested for the coupling reaction. Exclusive regioselectivity was observed in products **4hf**, **4fb**, **4db**, **4kb**.



3af (CCDC 1854021) **4aa** (CCDC 1844401)

Figure 4.7 X-ray crystal structure of compound **3af** and **4aa**.

4.4 CONCLUSION

In summary, a unique protocol for the dehydrogenative aryl C-S coupling was shown under mild condition. The umpolung approach, ArSE reaction towards making the aryl C-S bond could be performed by in situ generation of sulfenium ions from thiols and PIDA. Self-sorting experiments also supported for the involvement of sulfenium ion intermediate. The same coupling protocol was further extended for the one step synthesis of aryl sulfinyl arenes directly from arenes and thiols by controlled use of the PIDA. We anticipated that this unprecesented work might find suitale applications in organic synthesis and physical organic chemistry.

4.5 EXPERIMENTAL SECTION

Instrumentation and Chemicals: All the chemicals were purchase from commercial source and used as received. All the reactions were carried out in an open atmosphere condition.

Column chromatographic purification was performed using silica gel (Mesh 230-400) and ethyl acetate/hexane as eluent unless otherwise specified. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} aluminium plate and visualized with UV lamp (254 nm). ^{1}H and ^{13}C NMR spectra of the compounds were recorded on either 400 or 700 MHz spectrometer at 25 ^{o}C. The chemical shift value in ppm (δ) was reported with respect to the residual chloroform (7.26 for ^{1}H and 77.16 ppm for ^{13}C). Infrared (IR) spectra were recorded in wave number (cm^{-1}). Digital melting point apparatus were used to record the melting point of the compound. High resolution mass spectroscopy (HRMS) was recorded on ESI-TOF (Time-of-flight) mass spectroscopy.

Representative procedure for the preparation of (4-Bromophenyl)(mesityl)sulfane (3aa). To the stirring solution of 4-bromo thiophenol (**2a**, 60 mg, 0.317 mmol) and mesitylene (**1a**, 88 μL, 0.635 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), PIDA (Diacetoxy phenyliodide) (102 mg, 0.317 mmol) was added slowly at room temperature then the resulting solution were stirred for 30 min under open atmosphere. After the completion of reaction resulting solution was evaporated to dryness. The crude residue was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to obtain **3a** (94 mg off white solid, 0.306 mmol, yield 96%).

Representative procedure for the preparation of 2-((4-Bromophenyl)sulfinyl)-1,3,5-trimethylbenzene (4aa). In a 10 mL round bottom flask, charged with 4-bromo thiophenol (**2a**, 60 mg, 0.317 mmol) and mesitylene (**1a**, 111 μL, 0.793 mmol) in HFIP, then PIDA (307 mg, 0.952 mmol) was added and the resulting solution were stirred for 4 hour at room temperature under open atmosphere. After completion, the solvent was evaporated to dryness under reduced pressure and the crude reaction mixture was purified with silica gel column chromatography using ethyl acetate, hexane mixture as an eluent to get **4aa** (96 mg, 0.297 mmol, yield 94%).

General procedure for the self-sorting experiment. In a round bottom flask charged with 4-methyl benzenethiol (**2e**, 60 mg, 0.483 mmol) in HFIP corresponding two arene molecules (1.0 equiv each) were added to the solution. After that PIDA (Diacetoxy phenyliodide) (172 mg, 0.531 mmol) were added slowly at room temperature and the resulting solution were stirred for 45 min under open atmosphere. Then the mixture was concentrated under reduced pressure and dried over high vacuum to record the NMR spectrum.

Compound Characterization Data:

(4-Bromophenyl)(mesityl)sulfane (3aa):[5] R_f = 0.85 (Hexane); off white solid; yield 96% (94 mg); mp 96 - 100 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 7.03 (s, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 2.38 (s, 6H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 139.8, 137.9, 131.9, 129.6, 127.1, 126.5, 118.0, 21.8, 21.3.

Mesityl(phenyl)sulfane (3ab):[5] R_f = 0.9 (Hexane); Colourless liquid; yield 97% (120 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 7.4 Hz, 1H), 7.02 (s, 2H), 6.93 (d, *J* = 7.6 Hz, 2H), 2.39 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 139.4, 138.5, 129.5, 129.0, 127.1, 125.6, 124.6, 21.8, 21.3; HRMS (ESI-TOF) calcd for $C_{15}H_{16}S$ $(M)^+$ 228.0967, found 228.0956.

(4-Chlorophenyl)(mesityl)sulfane (3ac):[45] R_f = 0.85 (Hexane); white solid; yield 87% (95 mg); mp 78 – 80 ºC (lit.[12] 74 – 75 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.6 Hz, 2H), 7.02 (s, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 2.38 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 139.7, 137.2, 130.4, 129.6, 129.1, 126.8, 126.7, 21.8, 21.3.

(4-Fluorophenyl)(mesityl)sulfane (3ad): R_f = 0.85 (Hexane); Colourless liquid; yield 95% (110 mg); ^{1}H NMR (400 MHz, DMSO) δ 7.14 – 7.08 (m, 2H), 7.07 (s, 2H), 6.95 – 6.87 (m, 2H), 2.31 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.8 (d, $^1J_{CF}$ = 243.6 Hz), 143.7, 139.5, 133.5 (d, $^4J_{CF}$ = 3.1 Hz), 129.6, 127.5, 127.4 (d, $^3J_{CF}$ = 7.7 Hz), 116.1 (d, $^2J_{CF}$ =

21.9 Hz), 21.8, 21.3; IR (KBr) $\bar{\upsilon}$ = 2921, 2037, 1875, 1602, 1488, 1227, 629, 558; HRMS (ESI-TOF) calcd for $C_{15}H_{15}FS$ $(M)^+$ 246.0873, found 246.0873.

Mesityl(p-tolyl)sulfane (3ae):[5] R_f = 0.9 (Hexane); White solid; yield 94% (110 mg); mp 90 – 94 ºC (lit.[12] 88 – 90 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.96 (m, 4H), 6.85 (d, *J* = 8.2 Hz, 2H), 2.40 (s, 6H), 2.33 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 139.2, 134.9, 134.3, 129.8, 129.4, 127.6, 125.8, 21.9, 21.3, 21.0.

Mesityl(4-methoxyphenyl)sulfane (3af):[5] R_f = 0.8 (5% ethyl acetate in hexane); White solid; yield 97% (122 mg); mp 75 – 77 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 3H), 2.40 (s, 6H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 143.5, 139.0, 129.4, 129.1, 128.5, 127.8, 114.8, 55.4, 21.9, 21.2.

Mesityl(4-nitrophenyl)sulfane (3ag):[5] R_f = 0.6 (5% ethyl acetate in hexane); light yellow solid; yield 80% (85 mg); mp 86 – 88 ºC (lit.[12] 83 – 85 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.8 Hz, 2H), 7.06 (s, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 2.36 (s, 6H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.8, 144.9, 143.8, 140.7, 129.9, 124.9, 124.8, 124.2, 21.6, 21.3 cm^{-1}.

Mesityl(4-(trifluoromethyl)phenyl)sulfane (3ah): Rf = 0.75 (Hexane); White solid; yield 90% (119 mg); mp 72 – 74 ºC; 1H NMR (400 MHz, CDCl3) δ 7.41 (d, J = 7.8 Hz, 2H), 7.05 (s, 2H), 6.98 (d, J = 7.8 Hz, 2H), 2.38 (s, 6H), 2.35 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 143.9, 140.1, 129.7, 126.8, 126.5, 125.82 (q, 1JCF = 3.7 Hz), 125.6, 125.1, 123.1, 21.7, 21.3; IR (KBr) $\bar{\upsilon}$ = 2973, 1909, 1604, 1401, 1323, 1173, 827, 589; HRMS (ESI-TOF) calcd for C16H15F3S (M)+ 296.0841, found 296.0829.

(2-Fluorophenyl)(mesityl)sulfane (3ai): Rf = 0.8 (Hexane); Colourless liquid; yield 96% (132 mg); 1H NMR (400 MHz, DMSO) δ 7.25 – 7.15 (m, 2H), 7.12 (s, 2H), 7.03 (t, J = 7.6 Hz, 1H), 2.30 (s, 6H), 2.29 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 159.4 (d, 1JCF = 243.5

Hz), 144.1, 139.7, 129.6, 126.7 (d, 4JCF = 2.6 Hz), 125.9 (d, 3JCF = 7.4 Hz), 125.7 (d, 2JCF = 16.9 Hz), 125.2, 124.6 (d, 3JCF = 3.4 Hz), 115.3 (d, 2JCF = 21.1 Hz), 21.7, 21.3; IR (KBr) ῡ 2950, 2724, 1998, 1601, 1469, 1217, 849, 748 cm-1; HRMS (ESI-TOF) calcd for C15H15FS (M + H)+ 247.0951, found 247.0951.

(3-Chlorophenyl)(mesityl)sulfane (3aj): R_f = 0.85 (Hexane); Colourless liquid; yield 96% (130 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, *J* = 7.8 Hz, 1H), 7.05 – 7.00 (m, 3H), 6.87 (s, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 2.38 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 140.9, 139.9, 135.0, 130.0, 129.7, 126.1, 125.1, 124.8, 123.6, 21.8, 21.3; IR (KBr) ῡ = 2843, 2077, 1639, 1575, 1459, 1256, 850, 773 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}ClS$ $(M)^+$ 262.0578, found 262.0572.

Ethyl(mesityl)sulfane (3ak):[5] R_f = 0.9 (Hexane); Colourless liquid; yield 68% (104 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 2H), 2.69 (q, *J* = 7.4 Hz, 2H), 2.55 (s, 6H), 2.30 (s, 3H), 1.22 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 138.0, 130.1, 129.0, 29.5, 22.1, 21.1, 15.0.

Dodecyl(mesityl)sulfane (3al): R_f = 0.9 (Hexane); Colourless liquid; yield 86% (81 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 2.62 (t, *J* = 7.4 Hz, 2H), 2.52 (s, 6H), 2.27 (s, 3H), 1.62 – 1.47 (m, 2H), 1.44 – 1.30 (m, 4H), 1.29 – 1.25 (s, 14H), 0.90 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 137.9, 130.8, 129.0, 35.7, 32.1, 30.0, 29.8 (x2), 29.7, 29.6, 29.5, 29.4, 29.1, 22.8, 22.1, 21.1, 14.3, IR (KBr) ῡ = 2924, 2853, 2729, 2058, 1631, 1462,1374, 1295, 848, 721 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{36}S$ $(M + H)^+$ 321.2610, found 321.2599.

(4-Bromophenyl)(2,4,6-trimethoxyphenyl)sulfane (3ba):[5] R_f = 0.3 (5% ethyl acetate /hexane); White solid; yield 63% (71 mg); mp 130 – 132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.21 (s, 2H), 3.87 (s, 3H), 3.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 162.6, 138.3, 131.5, 127.4, 117.9, 98.3, 91.4, 56.4, 55.6.

(4-Bromophenyl)(2,3,6-trimethoxyphenyl)sulfane (3ca): R_f = 0.3 (5% ethyl acetate /hexane); off white solid; yield 74% (84 mg); mp 76 - 78 ºC; ^{1}H NMR (400 MHz, DMSO) δ 7.43 (d, *J* = 8.6 Hz, 2H), 7.01 (s, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.83 (s, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 151.2, 143.5, 137.5, 131.8, 128.7, 119.2, 118.9, 109.6, 98.0, 56.9, 56.6, 56.2; IR (KBr) $\bar{\upsilon}$ = 2933, 2840, 2531, 2030, 1632, 1581, 1470, 1208, 812, 737 cm^{-1}; HRMS (ESI-TO F) calcd for $C_{15}H_{15}BrO_3S$ $(M)^+$ 353.9920, found 353.9924.

(4-Bromophenyl)(4-methoxyphenyl)sulfane (3da):[46] R_f = 0.4 (Hexane); White solid; yield 56% (52 mg); mp 72 – 74 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 138.3, 135.8, 132.0, 129.6, 123.7, 119.5, 115.3, 55.5.

(4-Methoxy-2,6-dimethylphenyl)(phenyl)sulfane (3eb):[47] R_f = 0.8 (5% ethyl acetate /hexane); White solid; yield 80% (115 mg); mp 77 – 79 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.98 – 6.90 (m, 2H), 6.79 (s, 2H), 3.84 (s, 3H), 2.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 145.7, 138.9, 128.9, 125.3, 124.5, 121.5, 114.0, 55.3, 22.2.

(4-(Tert-butyl)-2,6-dimethylphenyl)(phenyl)sulfane (3fb):[48] R_f = 0.8 (Hexane); White solid; yield 90% (132 mg); mp 67 – 71 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 2H), 2.43 (s, 6H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 143.5, 138.6, 129.0, 127.2, 125.8, 125.7, 124.6, 34.6, 31.4, 22.2.

(3-Bromo-2,4,6-trimethylphenyl)(phenyl)sulfane (3gb):[48] R_f = 0.85 (Hexane); White solid; yield 42% (77 mg); mp 52 – 54 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.6 Hz, 2H), 7.11 (s, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 2H), 2.64 (s, 3H), 2.44 (s, 3H), 2.37

(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.7, 139.9, 137.9, 130.5, 129.4, 129.1, 126.0, 125.8, 125.0, 24.4, 23.2, 21.9.

4,6-dimethoxy-2-methyl-3-(phenylthio)benzaldehyde (3lb): R_f = 0.1 (10% ethyl acetate /hexane); White solid; yield 90% (154 mg); mp 145 - 150 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.44 (s, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 166.1, 165.7, 149.8, 137.9, 128.9, 125.9, 124.9, 118.3, 113.1, 92.9, 56.5, 56.0, 18.7; IR (KBr) ῡ = 2981, 2072, 1653, 1574, 1467, 1317, 1213, 815, 743 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{16}O_3S$ $(M + H)^+$ 289.0893, found 289.0917.

(2,5-Dimethoxy-1,4-phenylene)bis(phenylsulfane) (3ib):[49] R_f = 0.5 (5% ethyl acetate /hexane); White solid; yield 74% (77 mg); mp 148 - 150 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 1H), 7.35 – 7.33 (m, 4H), 7.33 – 7.31 (m, 2H), 7.31 – 7.27 (m, 2H), 7.26 – 7.24 (m, 1H), 6.65 (s, 2H), 3.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 134.4, 131.5, 129.4, 127.4, 123.9, 114.7, 56.6.

(4-Methoxyphenyl)(p-tolyl)sulfane (3de):[50] R_f = 0.85 (Hexane); White solid; yield 52% (76 mg); mp 48 – 50 ºC (lit.[51] 46 – 48 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 136.2, 134.4 (x2), 129.9, 129.5, 125.8, 115.0, 55.5, 21.1.

(2,4-Dimethylphenyl)(4-methoxyphenyl)sulfane (3hf):[52] R_f = 0.8 (5% Ethyl acetate in hexane); Colourless liquid; yield 44% (53 mg); mp ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 7.07 – 6.98 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.3, 136.9, 133.3, 132.7, 131.4, 131.0, 127.4, 126.0, 115.0, 55.5, 21.1, 20.5.

2-((4-Bromophenyl)sulfinyl)-1,3,5-trimethylbenzene (4aa): R_f = 0.2 (5% ethyl acetate /hexane); White solid; yield 94% (96 mg); mp 120 – 122 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.87 (s, 2H), 2.41 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 142.6, 140.0, 136.3, 132.1, 131.0, 126.4, 124.1, 21.3, 19.5; IR (KBr) ῡ = 2855, 2069, 1635, 1463, 1382, 1239,811, 722 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrOS$ $(M + H)^+$ 323.0100, found 323.0102.

1,3,5-Trimethyl-2-(phenylsulfinyl)benzene (4ab): R_f = 0.25 (5% Ethyl acetate in hexane); Colourless liquid; yield 82% (118 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 5H), 6.85 (s, 2H), 2.40 (s, 6H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 142.2, 139.9, 136.6, 130.8, 129.5, 128.8, 124.5, 21.2, 19.4; IR (KBr) ῡ = 3055, 2923, 2403, 1600, 1442, 1294, 748, 694; HRMS (ESI-TOF) calcd for $C_{15}H_{16}OS$ $(M + H)^+$ 245.0995, found 245.0997.

2-((4-Methoxyphenyl)sulfinyl)-1,3,5-trimethylbenzene (4af): R_f = 0.15 (5% Ethyl acetate in hexane); off white solid; yield 81% (109 mg); mp 95 – 97 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.86 (s, 2H), 3.82 (s, 3H), 2.42 (s, 6H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 142.1, 140.0, 136.7, 135.5, 130.9, 126.3, 114.5, 55.6, 21.3, 19.4; IR (KBr) ῡ = 2959, 2837, 2550, 2046, 1594, 1492, 1250, 1172, 828, 794 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{18}O_2S$ $(M + H)^+$ 275.1100, found 275.1120.

1,3,5-trimethyl-2-((4-(trifluoromethyl)phenyl)sulfinyl)benzene (4ah): R_f = 0.15 (5% Ethyl acetate in hexane); White solid; yield 52% (72 mg); mp 108 - 110 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 6.89 (s, 2H), 2.41 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 142.9, 140.1, 136.2, 131.9, 131.6, 131.1, 125.9 (q, *J* = 3.7 Hz), 125.2, 21.3, 19.5; IR (KBr) ῡ = 2894, 2070, 1635, 1398, 1321, 1127, 826, 695 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{15}F_3OS$ $(M + H)^+$ 313.0868, found 313.0892.

2-((3-Chlorophenyl)sulfinyl)-1,3,5-trimethylbenzene (4aj): R_f = 0.2 (5% Ethyl acetate in hexane); White solid; yield 90% (130 mg); mp 112 – 114 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.43 (s, 1H), 7.38 – 7.33 (m, 2H), 7.31 – 7.25 (m, 1H), 6.89 (s, 2H), 2.42 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 142.7, 140.1, 136.1, 135.3, 131.1, 130.2, 129.9, 124.8, 122.9, 21.3, 19.5; IR (KBr) ῡ 2922, 2851, 2728, 1600, 1573, 1457, 1294, 1076, 784, 680 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}ClOS$ $(M + H)^+$ 279.0605, found 279.0602.

1-((4-Methoxyphenyl)sulfinyl)-2,4-dimethylbenzene (4hf): R_f = 0.2 (20% Ethyl acetate in hexane); Colourless liquid; yield 50% (60 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 6.97 (s, 1H), 6.95 – 6.90 (m, 2H), 3.80 (s, 3H), 2.34 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 141.2, 139.8, 136.0, 135.4, 131.8, 128.3, 127.8, 124.6, 114.8, 55.6, 21.4, 18.5; IR (KBr) ῡ = 2837, 2046, 1636, 1591, 1490, 1253, 827, 615 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{16}O_2S$ $(M + H)^+$ 261.0944, found 261.0964.

1,3,5-Trimethoxy-2-(phenylsulfinyl)benzene (4bb): R_f = 0.2 (50% ethyl acetate/hexane); White solid; yield 44% (76 mg); mp 114 – 116 ºC; ^{1}H NMR (400 MHz, DMSO) δ 7.50 – 7.35 (m, 5H), 6.26 (s, 2H), 3.81 (s, 3H), 3.66 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ 164.82, 160.8, 145.6, 129.1, 128.4, 123.8, 112.2, 91.7, 56.1, 55.7; IR (KBr) ῡ = 3007, 2842, 2074, 1592, 1413, 1229, 750, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{16}O_4S$ $(M + H)^+$ 293.0842, found 293.0812.

5-(tert-butyl)-1,3-dimethyl-2-(phenylsulfinyl)benzene (4fb): R_f = 0.3 (5% ethyl acetate /hexane); White solid; yield 77% (130 mg); mp 119 – 121 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.34 (m, 5H), 7.04 (s, 2H), 2.45 (s, 6H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 144.4, 139.7, 136.6, 129.5, 128.9, 127.3, 124.7, 34.7, 31.1, 19.8; IR (KBr) ῡ = 2962, 2868, 2072, 1633, 1592, 1442, 1362, 1227, 749, 695 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{22}OS$ $(M + H)^+$ 287.1464, found 287.1471.

1,3,5-Triethyl-2-(phenylsulfinyl)benzene (4jb): R_f = 0.15 (5% ethyl acetate /hexane); Colourless liquid; yield 80% (135 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 5H),

6.96 (s, 2H), 2.97 – 2.74 (m, 4H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 146.7, 145.8, 136.3, 129.4, 128.9, 128.1, 124.8, 28.8, 25.6, 16.1, 15.2; IR (KBr) ῡ = 2966, 2932, 2872, 2724, 1596, 1442, 1374, 1173, 744, 695 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{22}OS$ $(M + H)^+$ 287.1464, found 287.1467.

1-methoxy-4-(phenylsulfinyl)benzene (4db):[53] R_f = 0.2 (20% ethyl acetate /hexane); Colourless liquid; yield 82% (110 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 7.78 (m, 4H), 7.67 – 7.37 (m, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 145.8, 136.7, 130.7, 129.2, 127.2, 124.5, 114.8, 55.4.

1-Methyl-3-phenoxy-2-(phenylsulfinyl)benzene (4kb): R_f = 0.15 (5% Ethyl acetate in hexane); Colourless liquid; yield 86% (156 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.6 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.50 – 7.41 (m, 3H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 2H), 6.94 (dd, *J* = 8.68; 2.2 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 155.8, 144.9, 138.5, 136.8, 131.0, 130.1, 129.4, 127.4, 125.6, 124.4, 120.1, 120.0, 116.5, 18.8; IR (KBr) ῡ = 2966, 2880, 1585, 1472, 1232, 744, 695 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{19}H_{16}O_2S$ $(M + H)^+$ 309.0944, found 309.0956.

2-(Dodecylsulfinyl)-1,3,5-trimethylbenzene (4al):[54] R_f = 0.25 (5% ethyl acetate /hexane); Colourless liquid; yield 66% (56 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 2H), 3.29 – 3.19 (m, 1H), 2.85 – 2.76 (m, 1H), 2.53 (s, 6H), 2.28 (s, 3H), 1.85 – 1.71 (m, 1H), 1.70 – 1.61 (m, 2H), 1.51 – 1.38 (m, 2H), 1.35 – 1.26 (m, 5H), 1.25 – 1.23 (s, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 138.5, 135.2, 131.0, 52.6, 32.0, 29.7, 29.7 (x2), 29.5, 29.4, 29.3, 28.9, 23.9, 22.8, 21.2, 19.4, 14.3.

4.6 Notes and Reference

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^{1}H and ^{13}C NMR spectra of selected compound

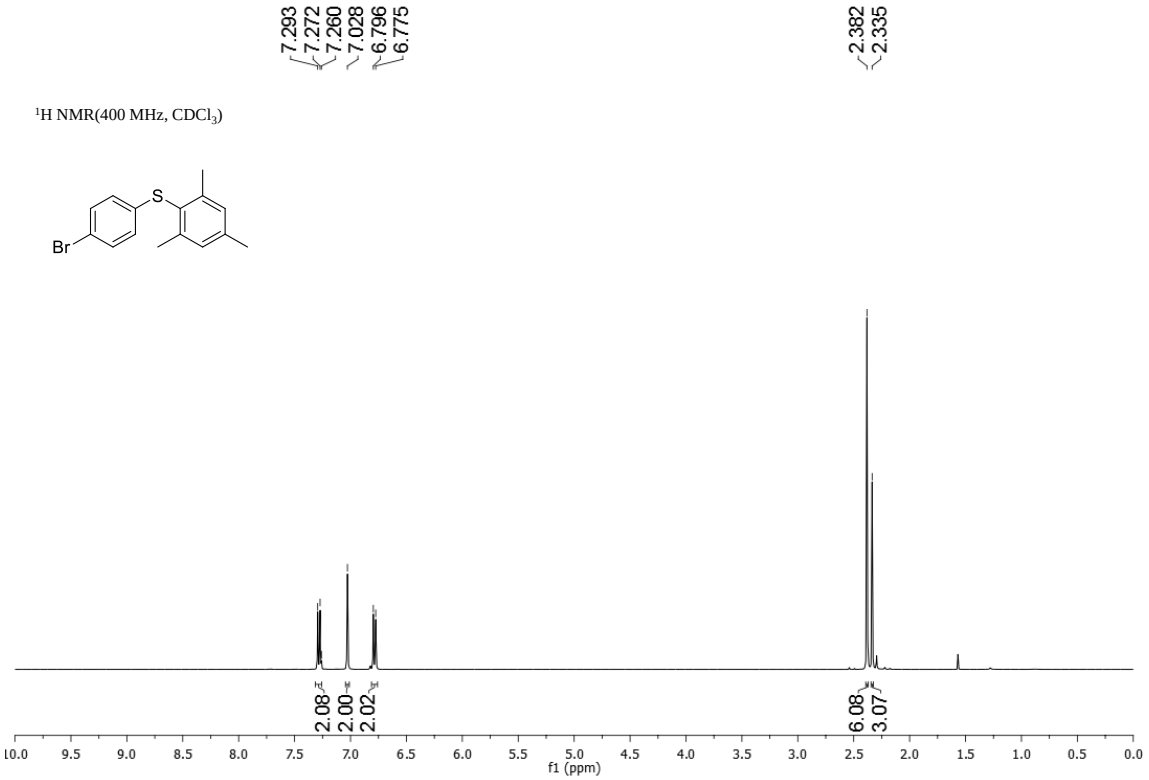


Figure 4.8. ^{1}H NMR spectrum of (4-bromophenyl)(mesityl)sulfane (**3aa**).

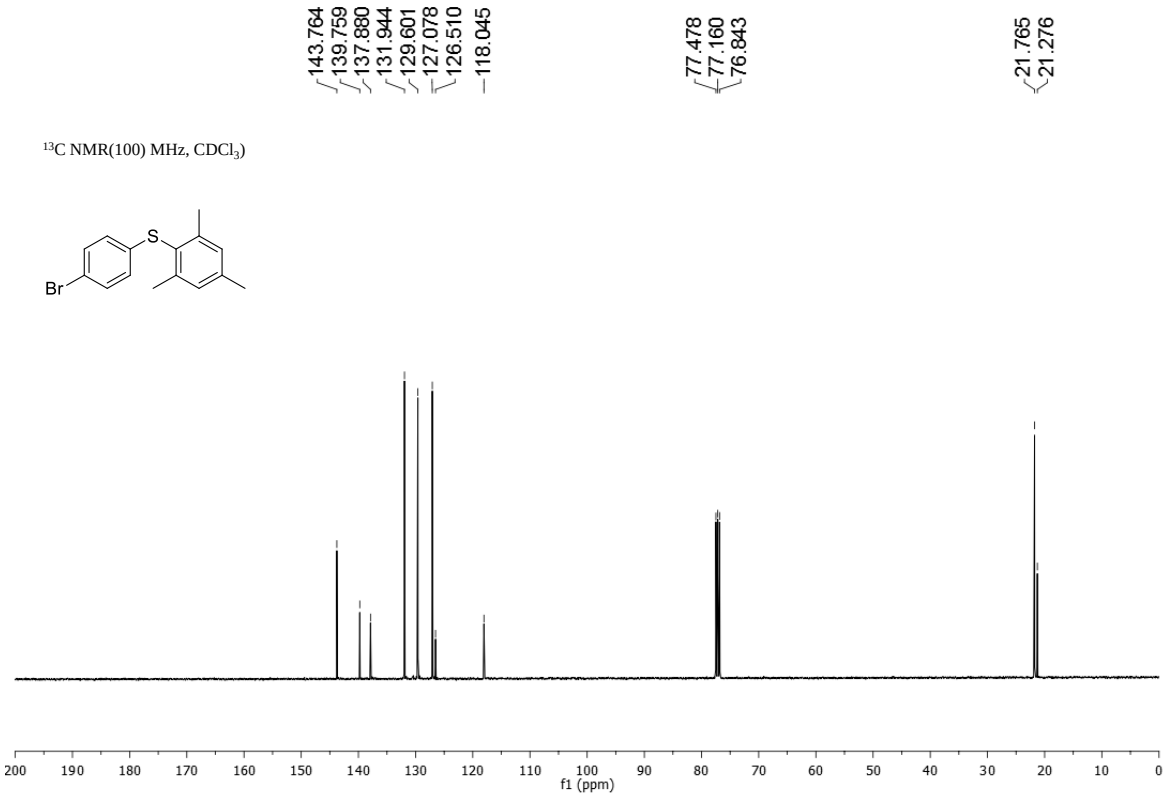


Figure 4.9. ^{13}C NMR spectrum of (4-bromophenyl)(mesityl)sulfane (**3aa**).

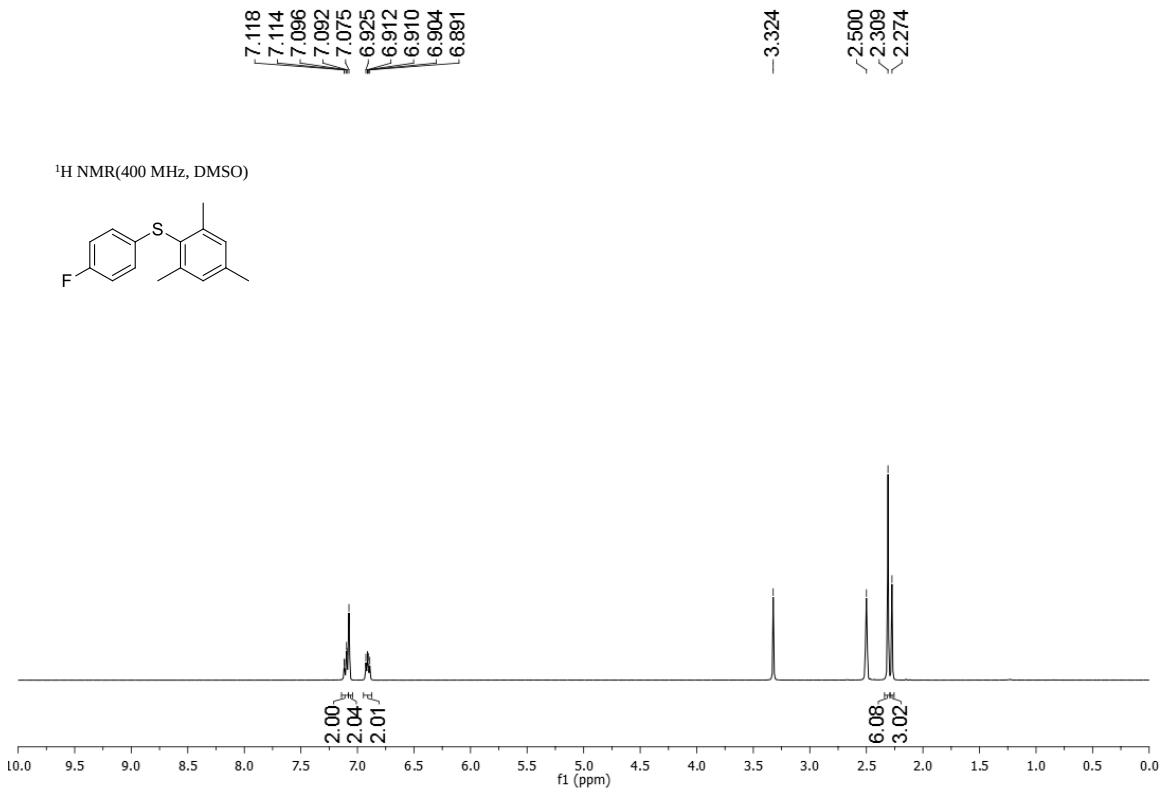


Figure 4.10. ^{1}H NMR spectrum (4-fluorophenyl)(mesityl)sulfane (**3ad**).

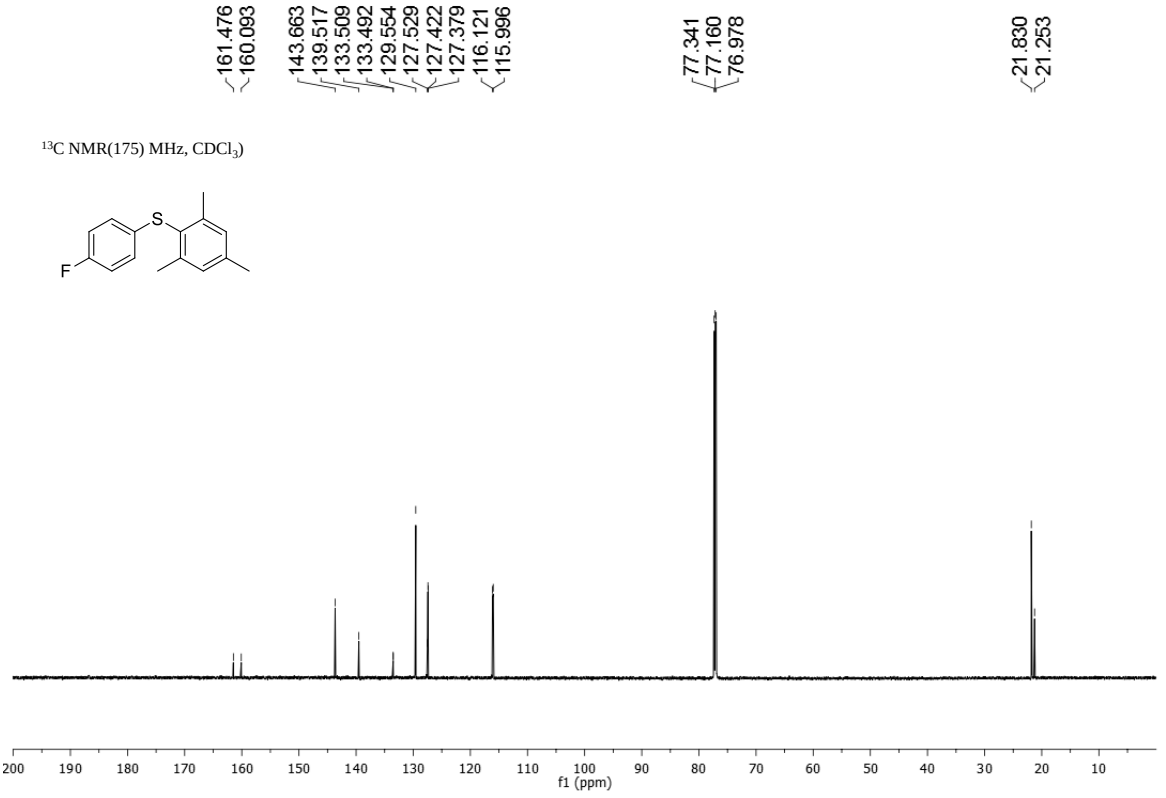


Figure 4.11. ^{13}C NMR spectrum of (4-fluorophenyl)(mesityl)sulfane (**3ad**).

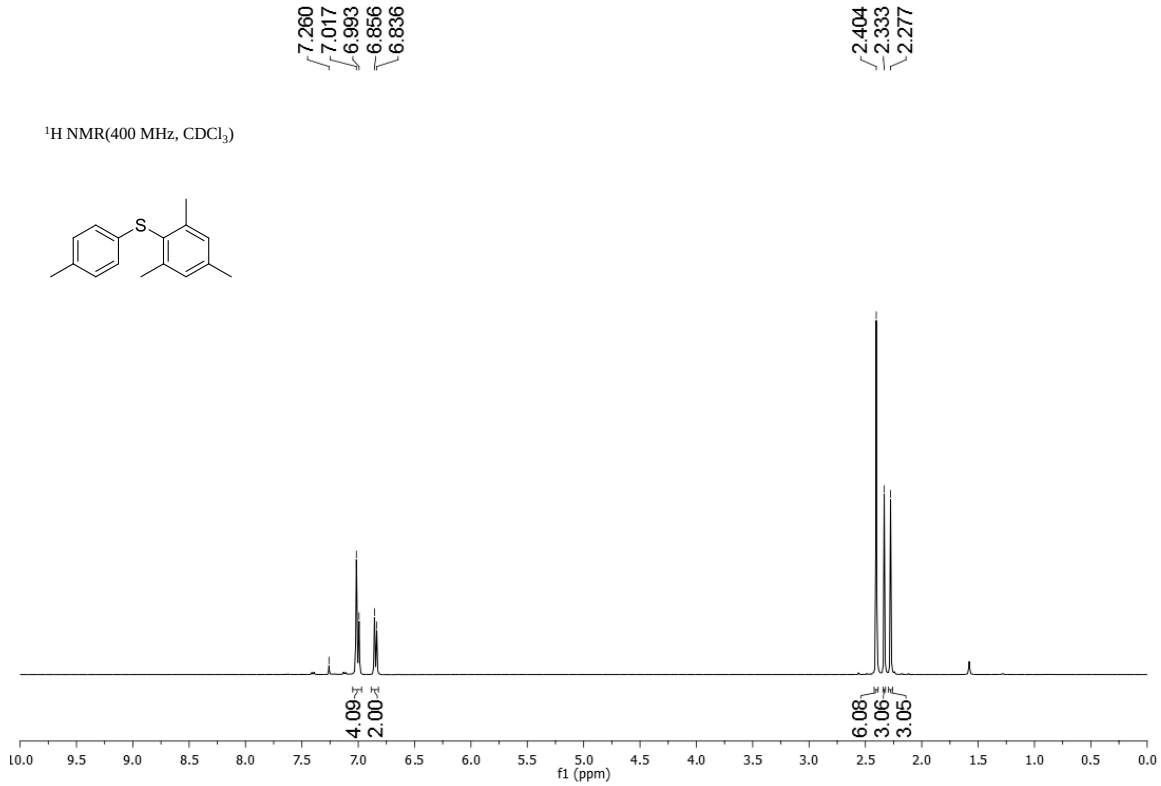


Figure 4.12. ^{1}H NMR spectrum mesityl(p-tolyl)sulfane (**3ae**).

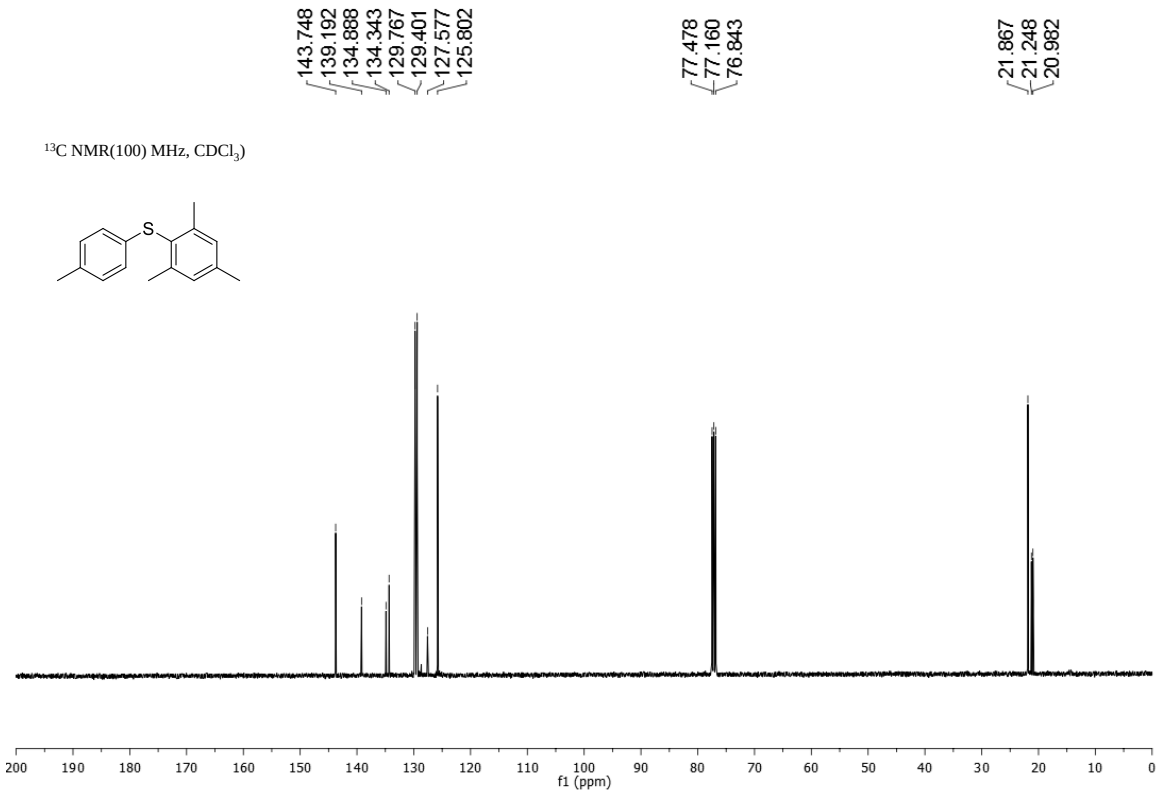


Figure 4.13. ^{13}C NMR spectrum of mesityl(p-tolyl)sulfane (**3ae**).

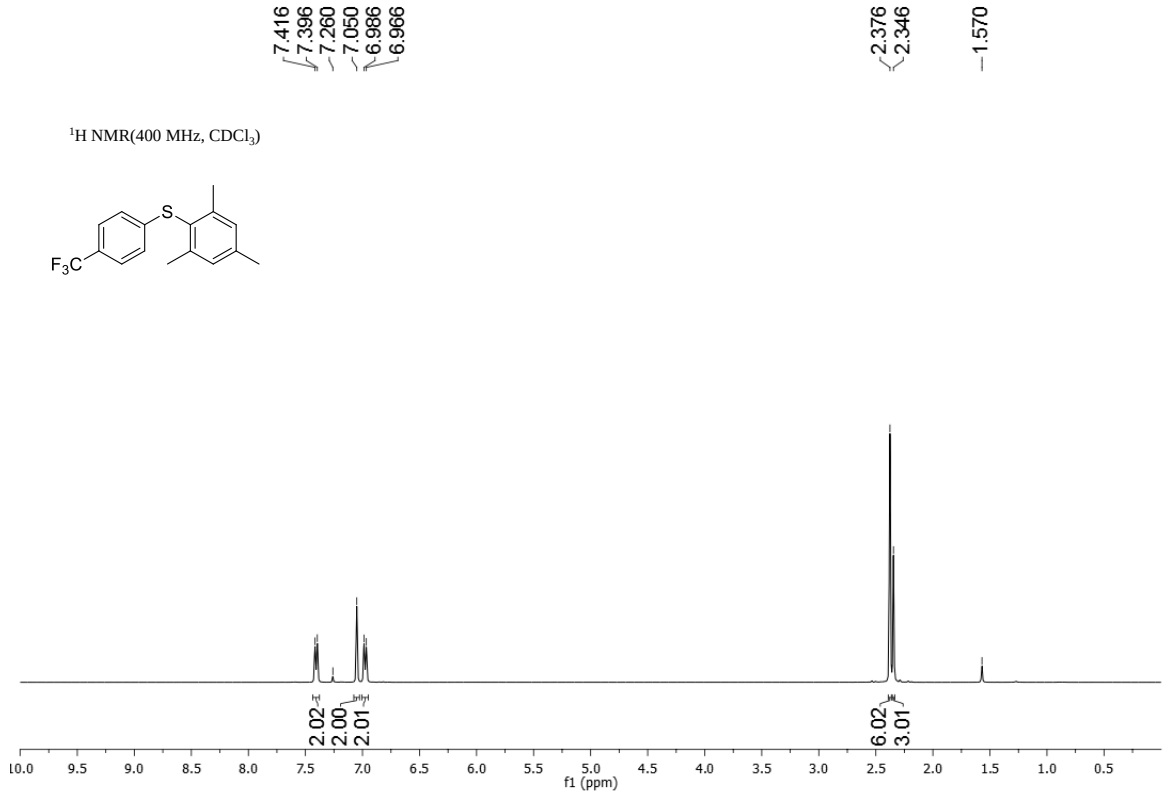


Figure 4.14. ^{1}H NMR spectrum mesityl(4-(trifluoromethyl)phenyl)sulfane (**3ah**).

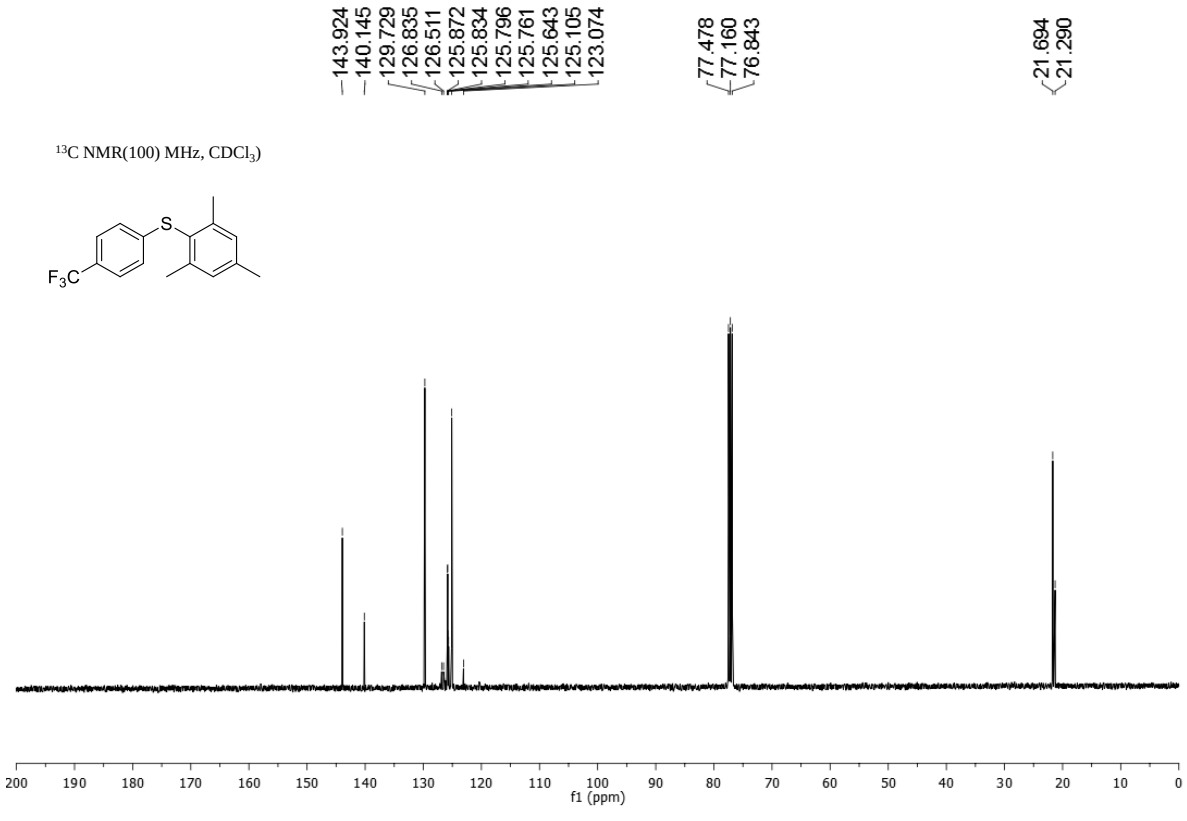


Figure 4.15. ^{13}C NMR spectrum of mesityl(4-(trifluoromethyl)phenyl)sulfane (**3ah**).

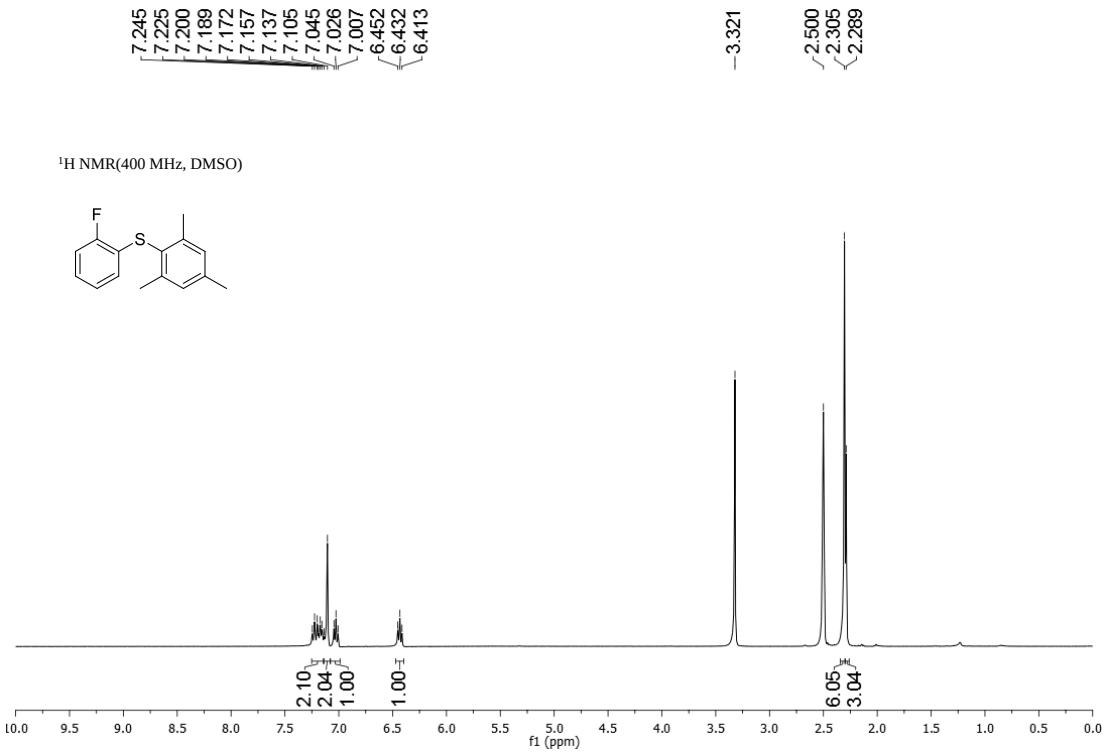


Figure 4.16. ^{1}H NMR spectrum of (2-fluorophenyl)(mesityl)sulfane (**3ai**).

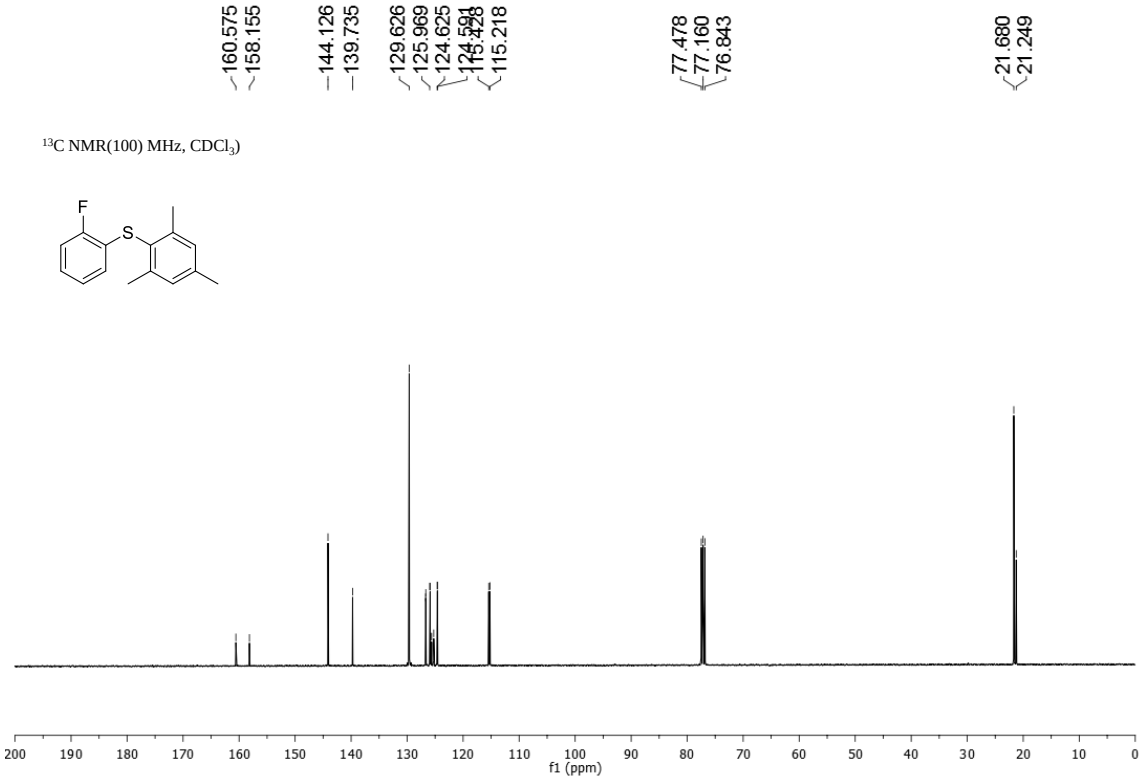


Figure 4.17. 13C NMR spectrum of (2-fluorophenyl)(mesityl)sulfane (**3ai**).

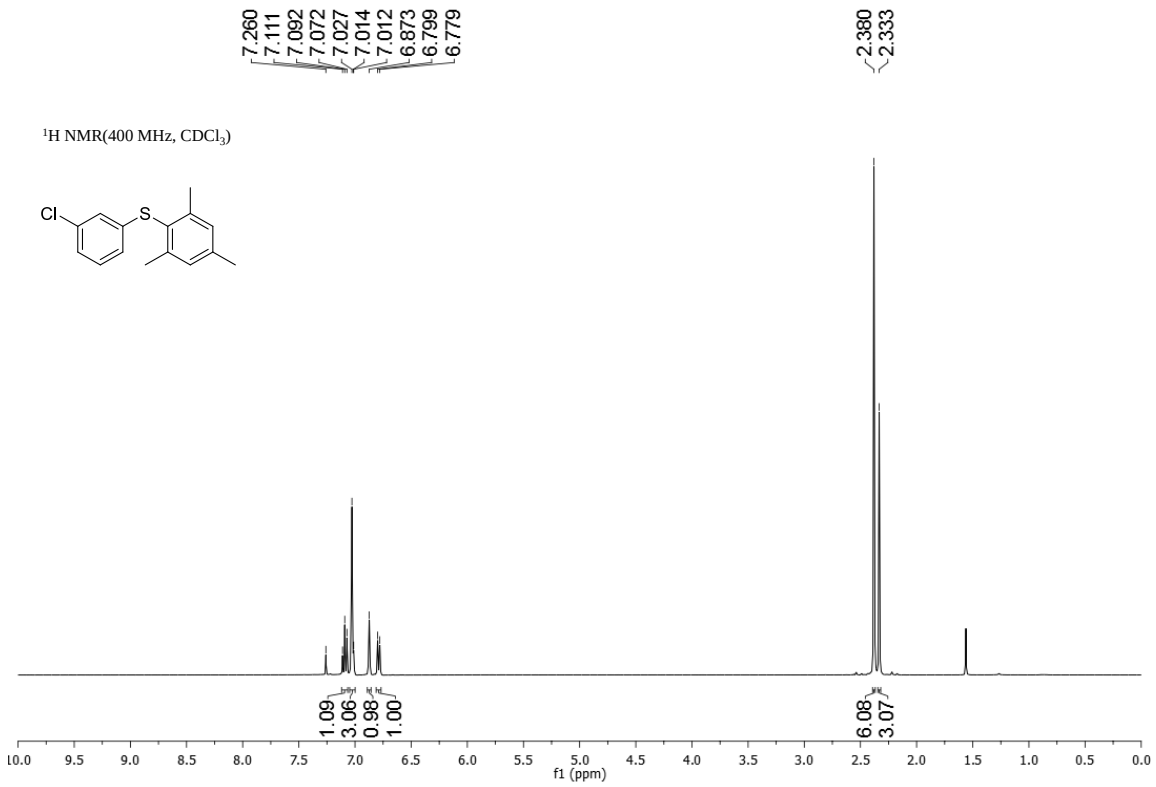


Figure 4.18 ^{1}H NMR spectrum of (3-chlorophenyl)(mesityl)sulfane (**3aj**).

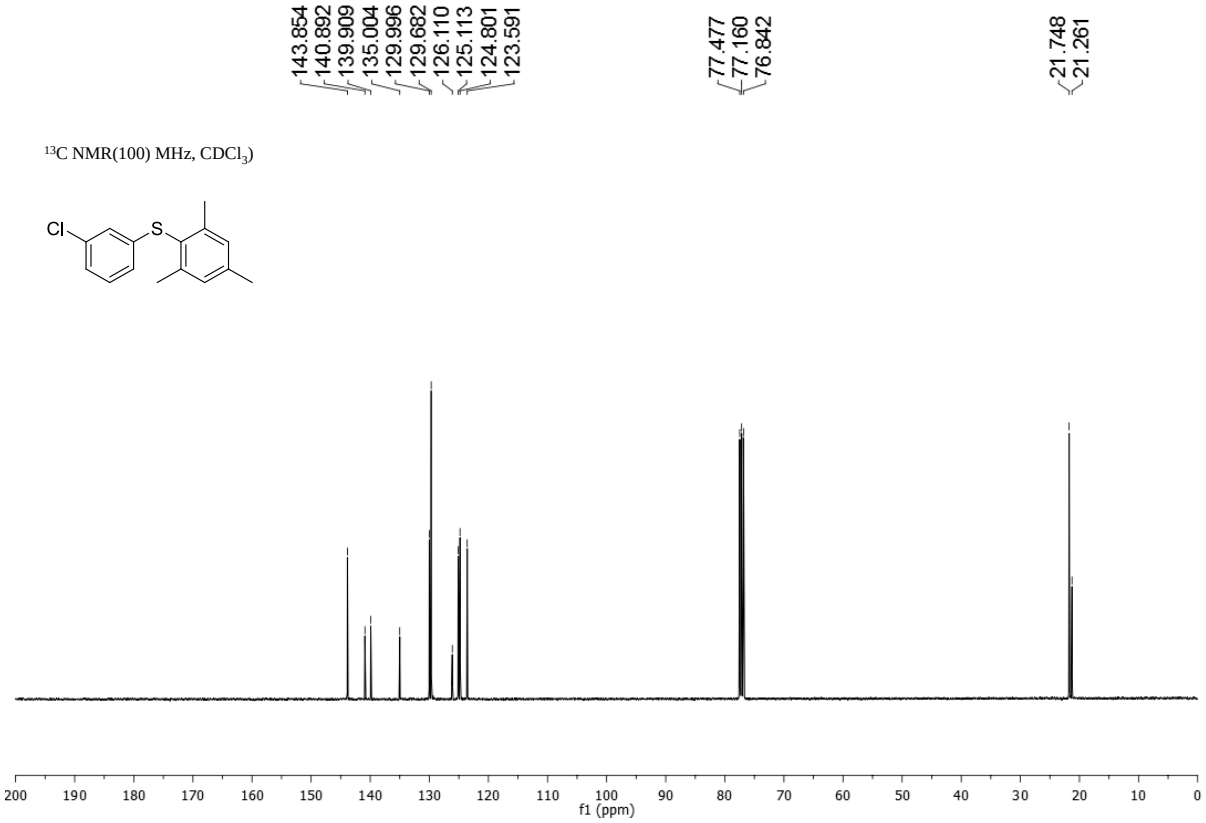


Figure 4.19. ^{13}C NMR spectrum of (3-chlorophenyl)(mesityl)sulfane (**3aj**).

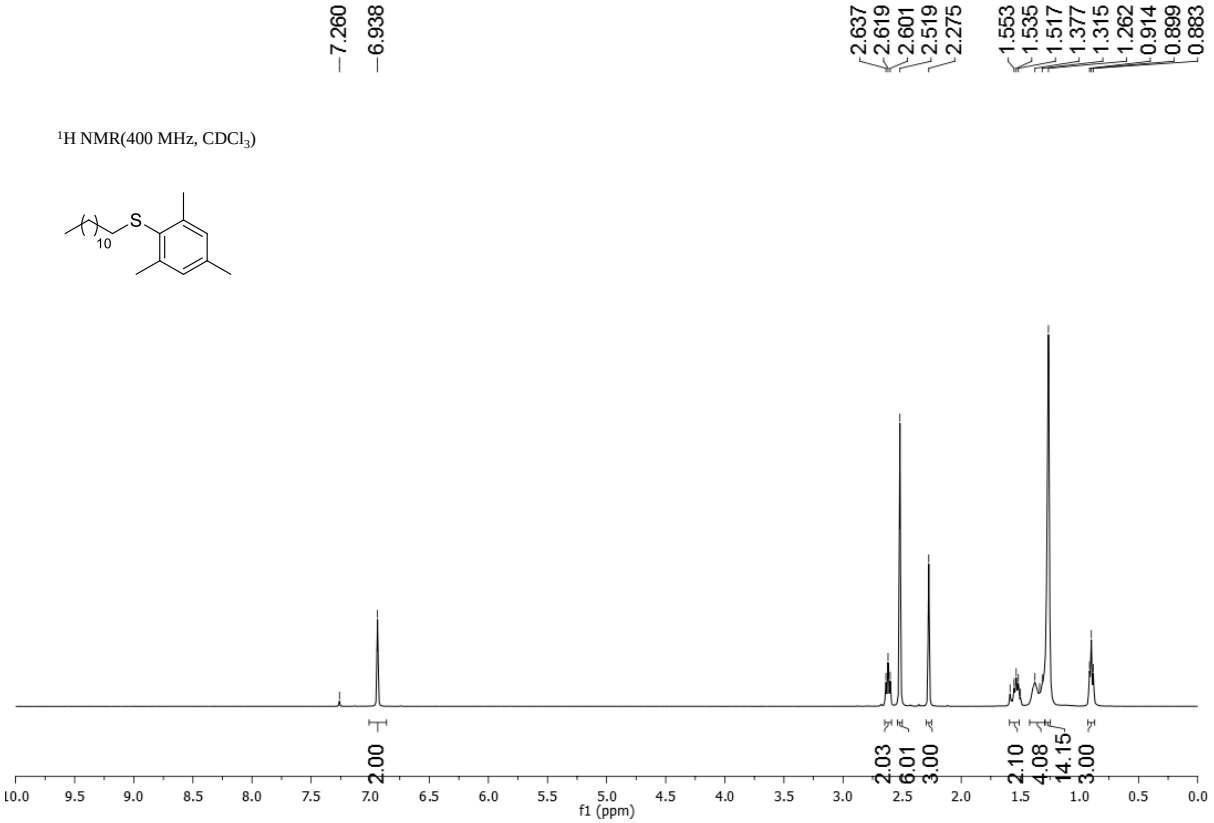


Figure 4.20. ^{1}H NMR spectrum dodecyl(mesityl)sulfane (**3al**).

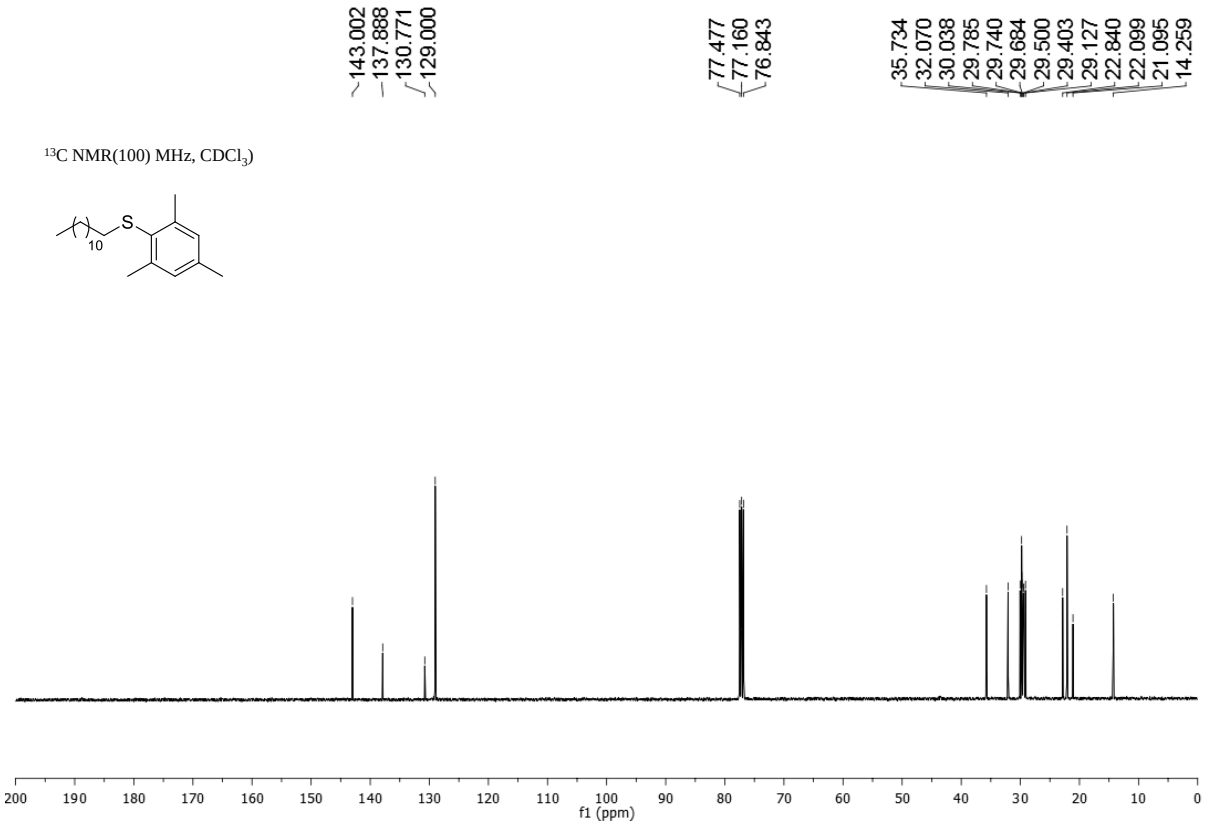


Figure 4.21. ^{13}C NMR spectrum of dodecyl(mesityl)sulfane (**3al**).

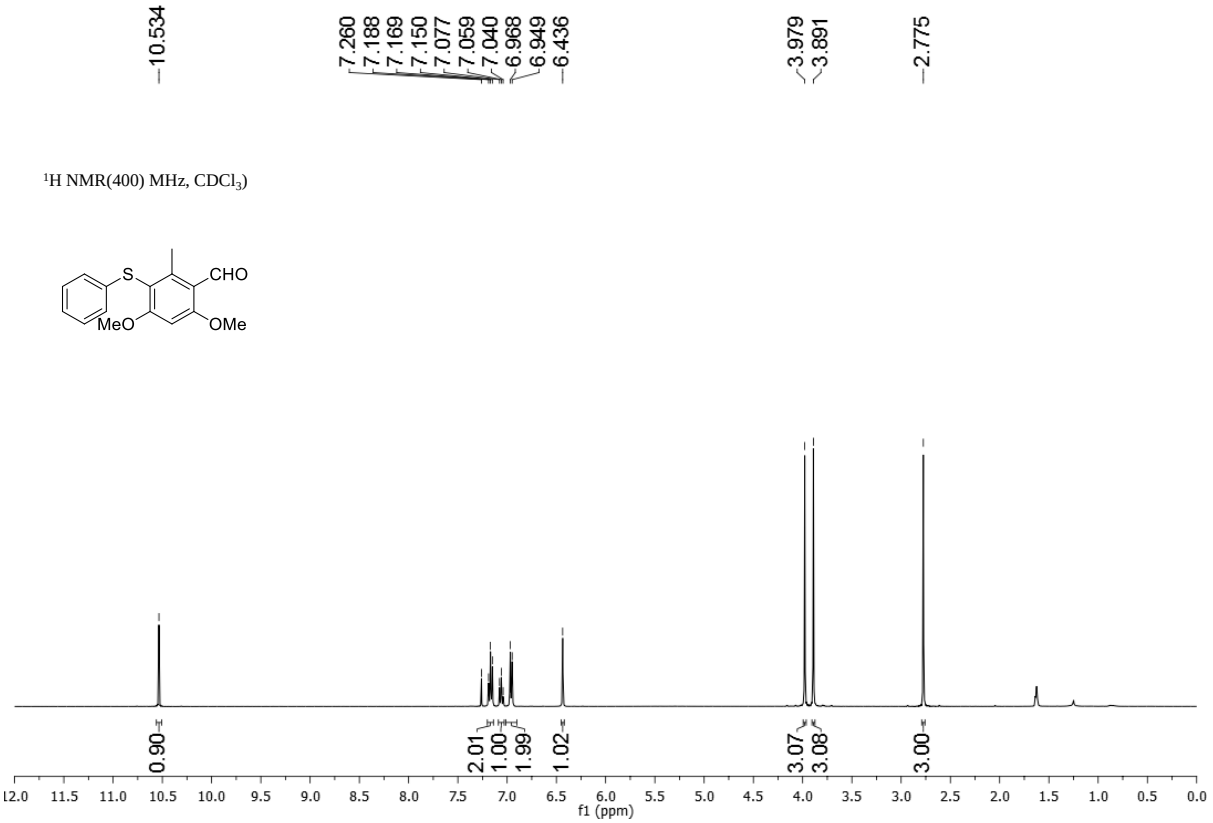


Figure 4.22. ^{1}H NMR spectrum 4,6-dimethoxy-2-methyl-3-(phenylthio)benzaldehyde (**3lb**).

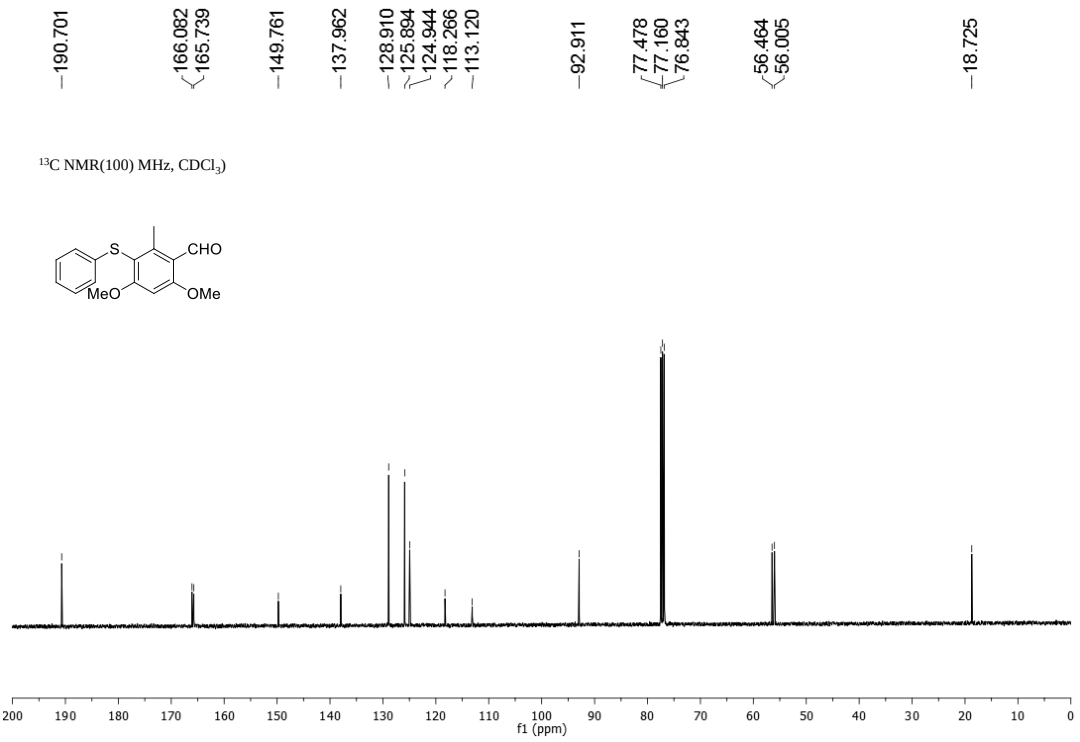


Figure 4.23. ^{13}C NMR spectrum of 4,6-dimethoxy-2-methyl-3-(phenylthio)benzaldehyde (**3lb**).

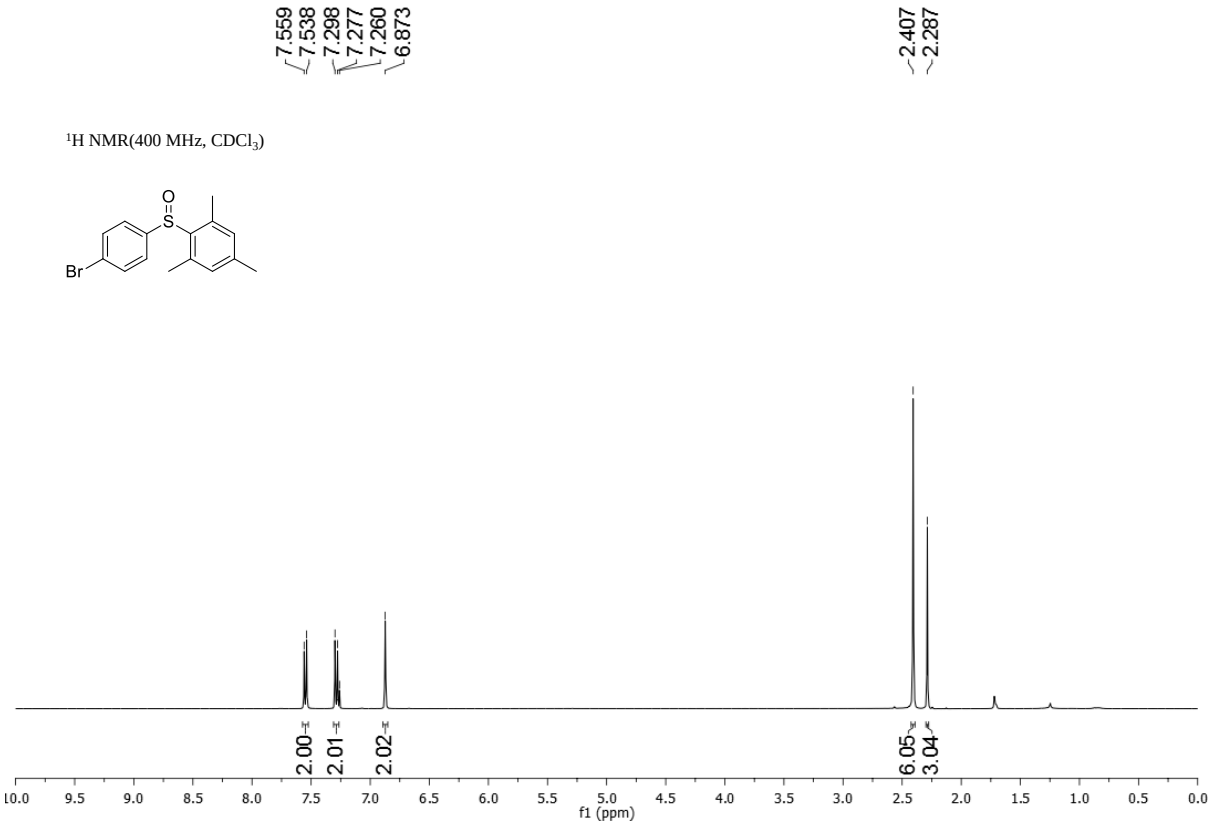


Figure 4.24.1H NMR spectrum 2-((4-bromophenyl)sulfinyl)-1,3,5-trimethylbenzene (**4aa**).

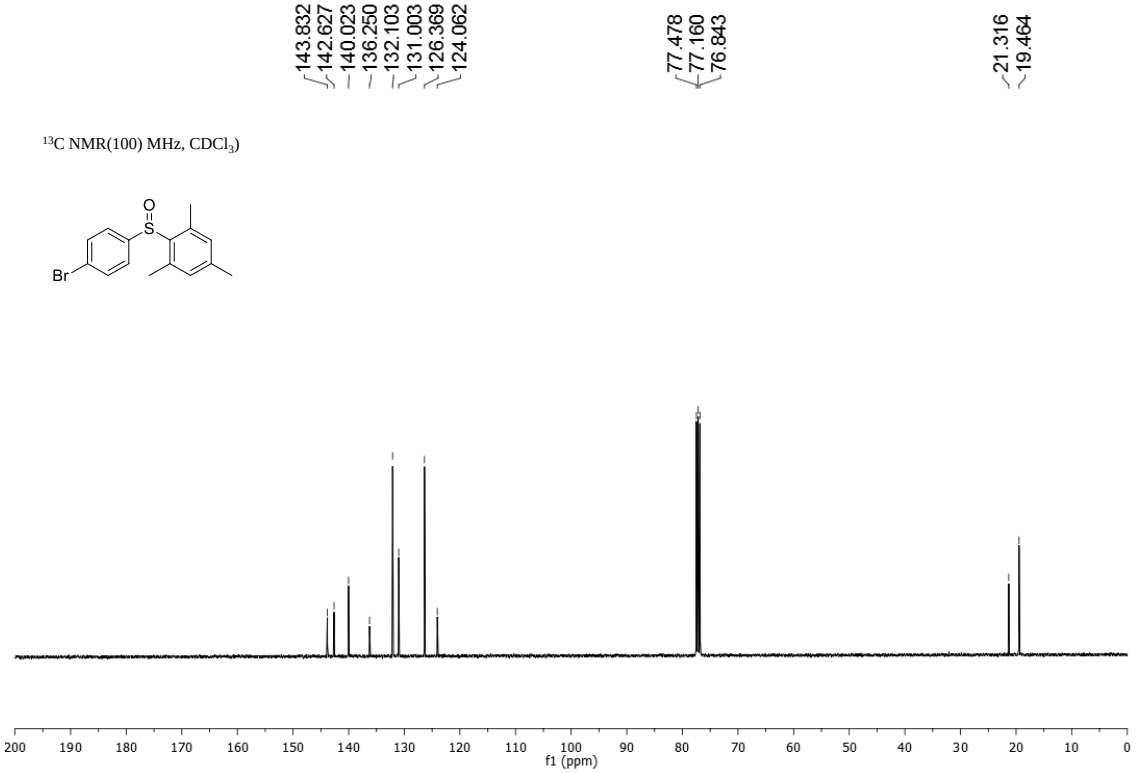


Figure 4.25.^{13}C NMR spectrum of 2-((4-bromophenyl)sulfinyl)-1,3,5-trimethylbenzene (**4aa**).

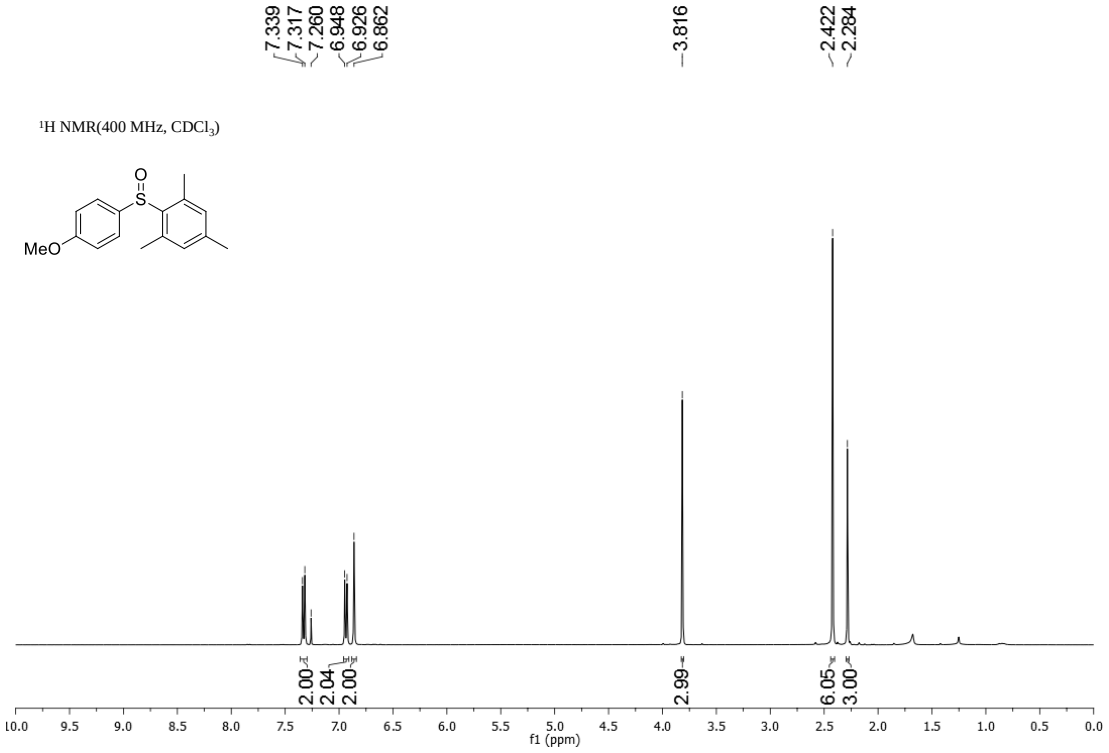


Figure 4.26. ^{1}H NMR spectrum of 2-((4-methoxyphenyl)sulfinyl)-1,3,5-trimethylbenzene (**4af**).

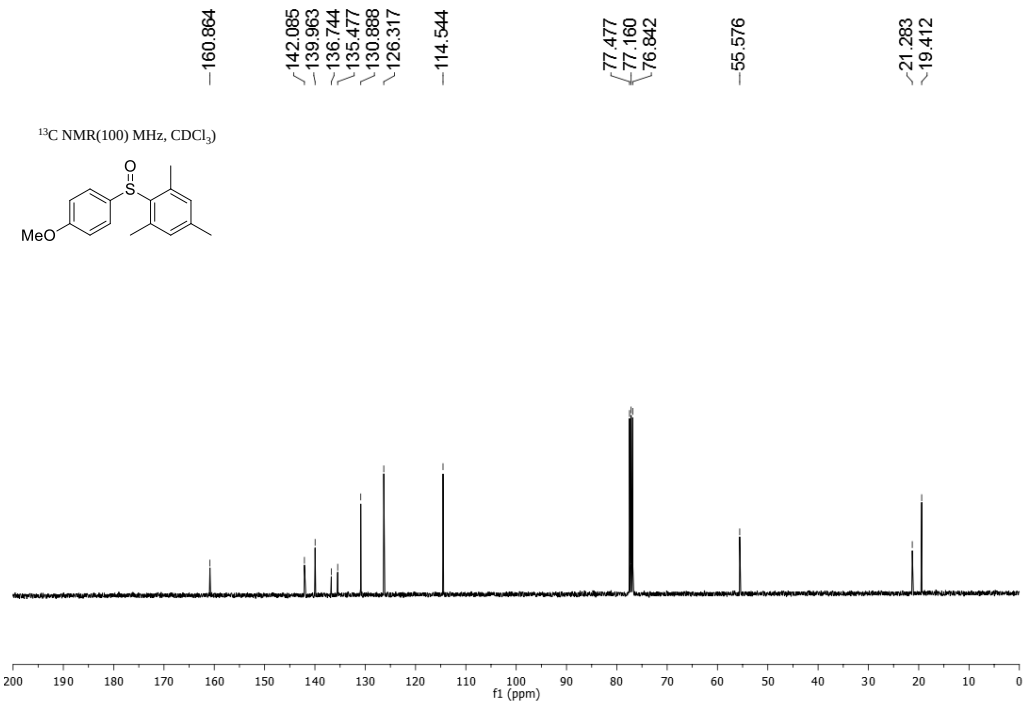


Figure 4.27. ^{13}C NMR spectrum of 2-((4-methoxyphenyl)sulfinyl)-1,3,5-trimethylbenzene (**4af**).

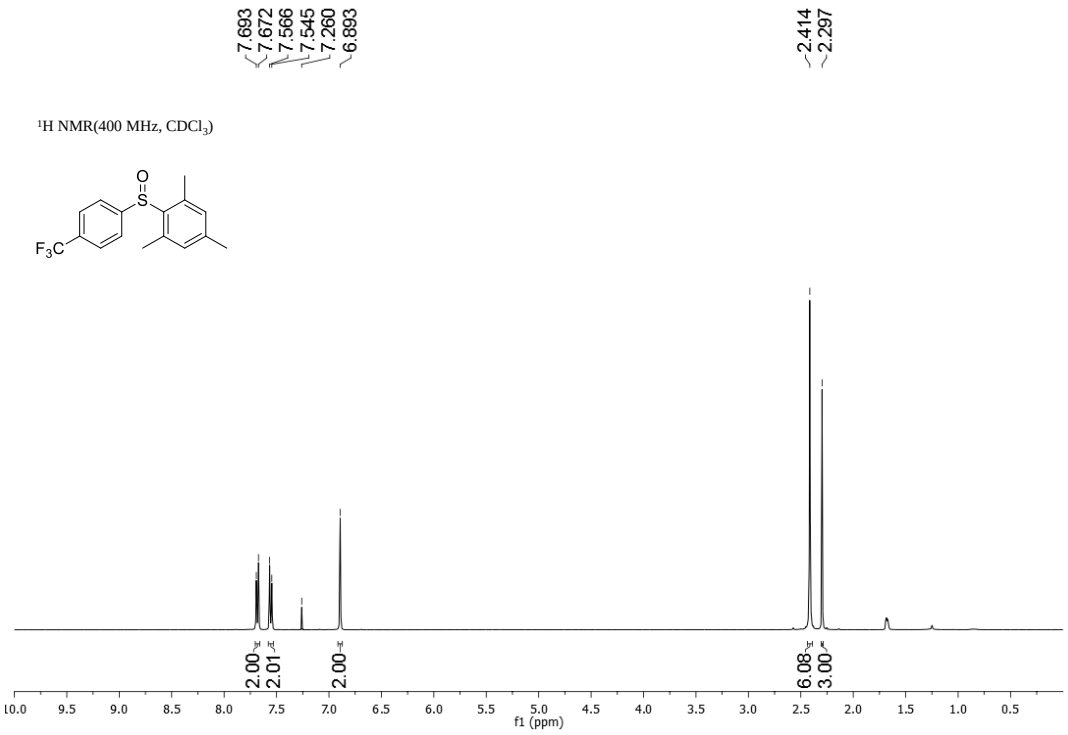


Figure 4.28. ^{1}H NMR spectrum 1,3,5-trimethyl-2-((4-(trifluoromethyl)phenyl)sulfinyl)benzene (**4ah**).

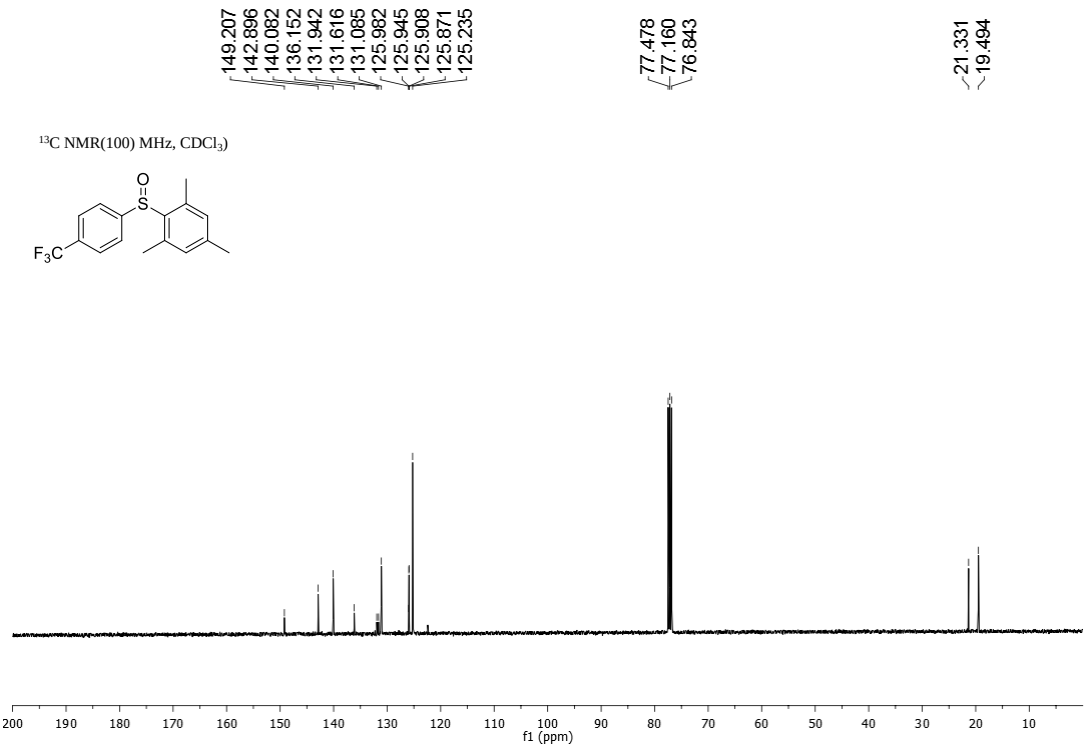


Figure 4.29. ^{13}C NMR spectrum of 1,3,5-trimethyl-2-((4-(trifluoromethyl)phenyl)sulfinyl)benzene (**4ah**).

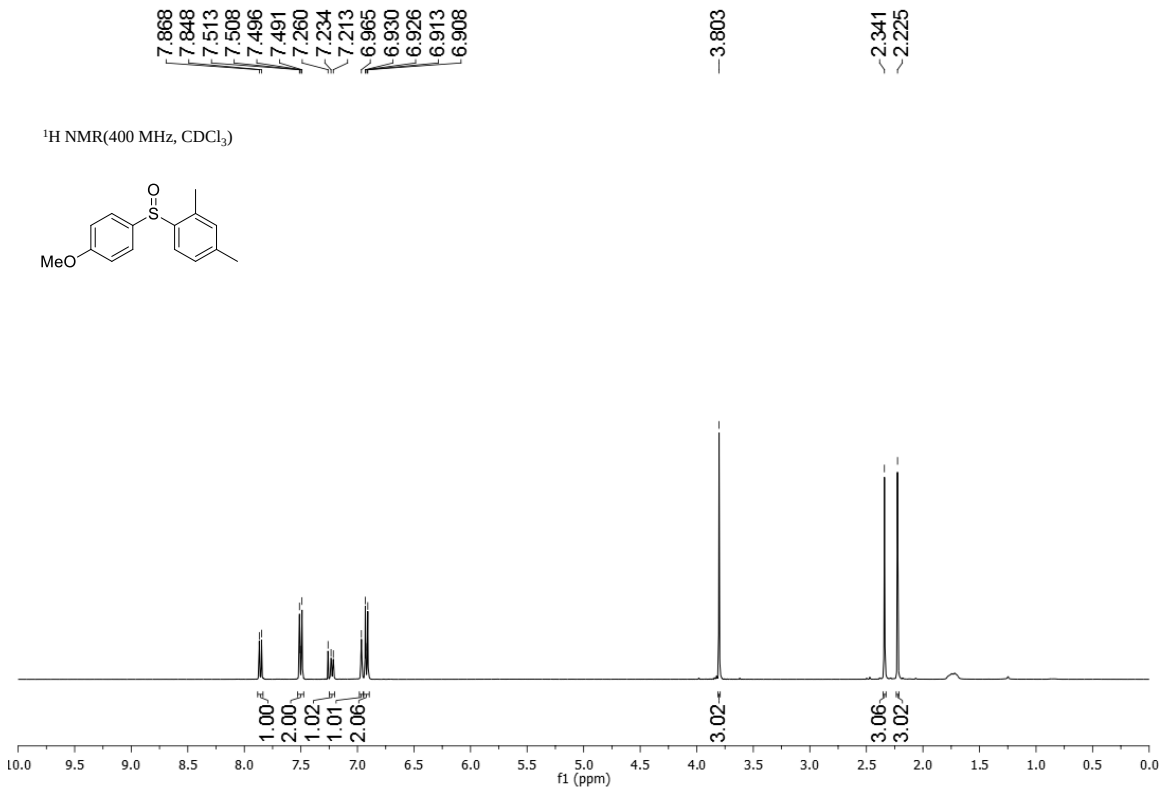


Figure 4.30. ^{1}H NMR spectrum 1-((4-methoxyphenyl)sulfinyl)-2,4-dimethylbenzene (**4hf**).

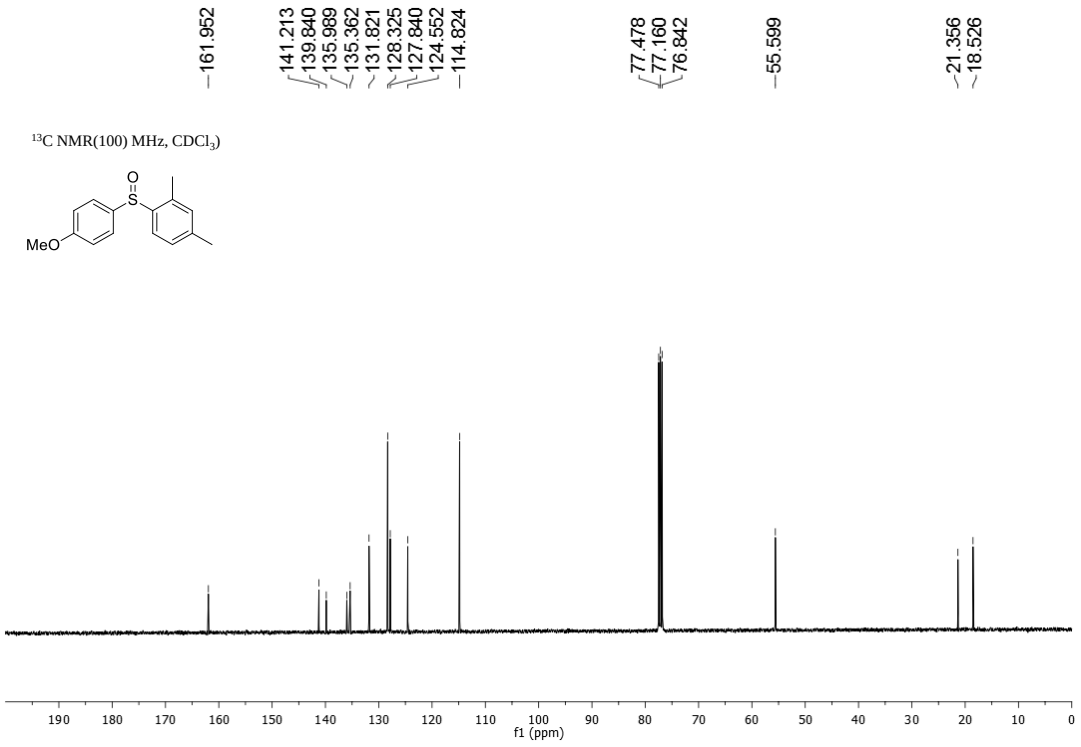


Figure 4.31. ^{13}C NMR spectrum of 1-((4-methoxyphenyl)sulfinyl)-2,4-dimethylbenzene (**4hf**).

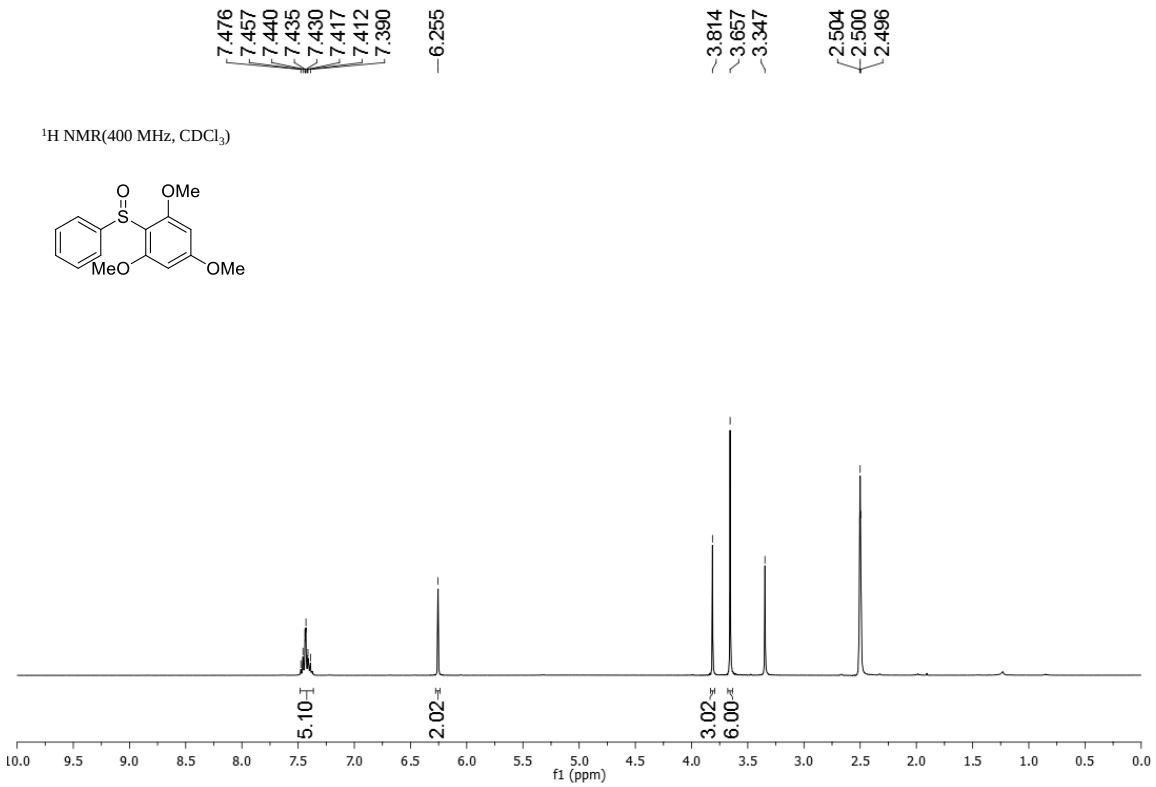


Figure 4.32. ^{1}H NMR spectrum 1,3,5-trimethoxy-2-(phenylsulfinyl)benzene (**4bb**).

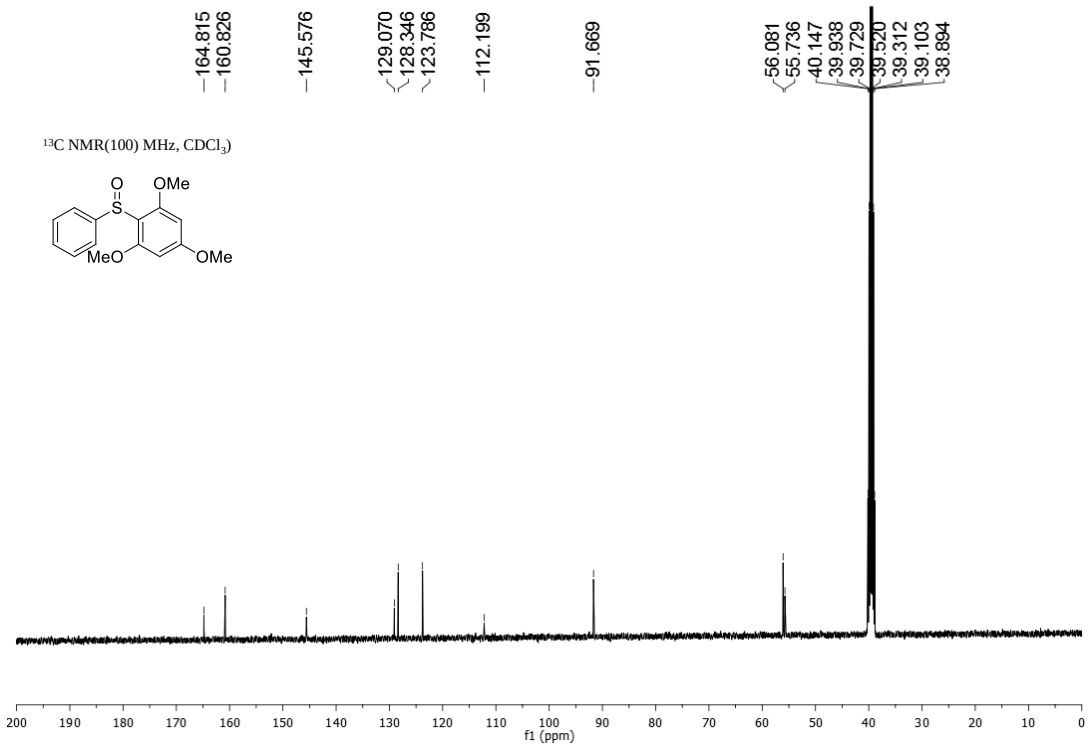


Figure 4.33. ^{13}C NMR spectrum of 1,3,5-trimethoxy-2-(phenylsulfinyl)benzene (**4bb**).

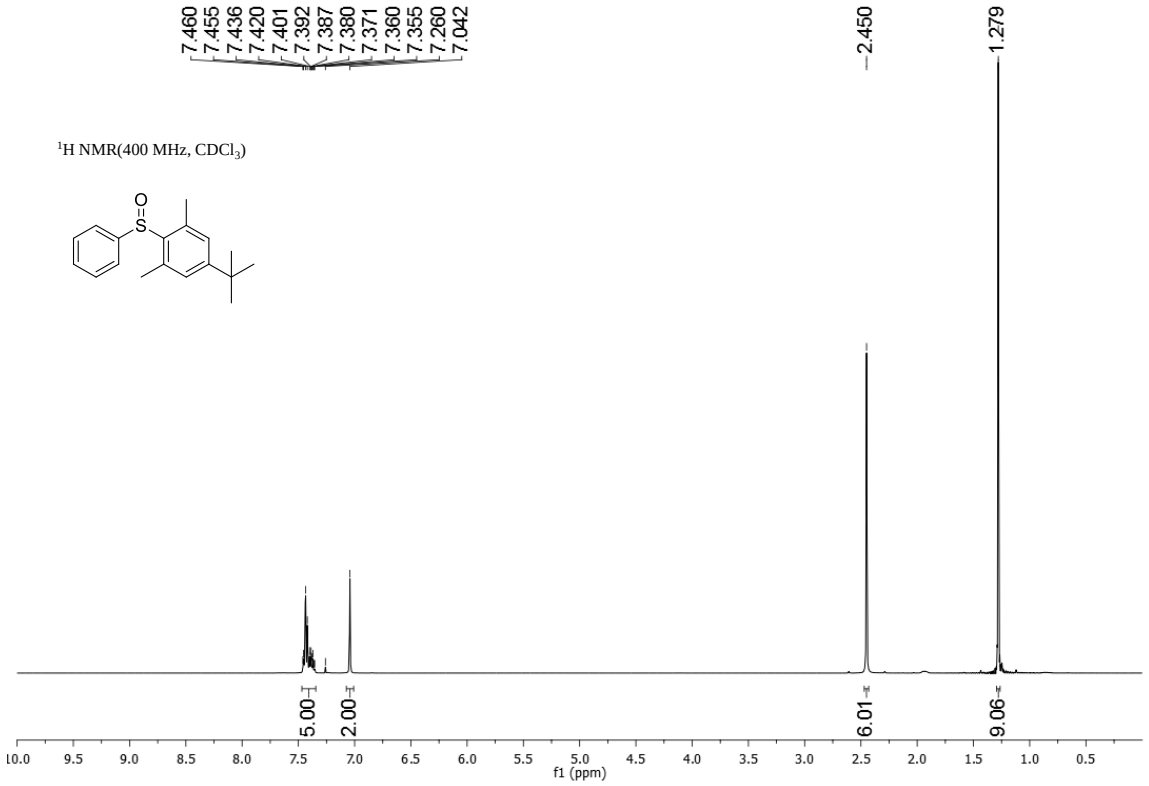


Figure 4.34. ^{1}H NMR spectrum 5-(tert-butyl)-1,3-dimethyl-2-(phenylsulfinyl)benzene (**4fb**).

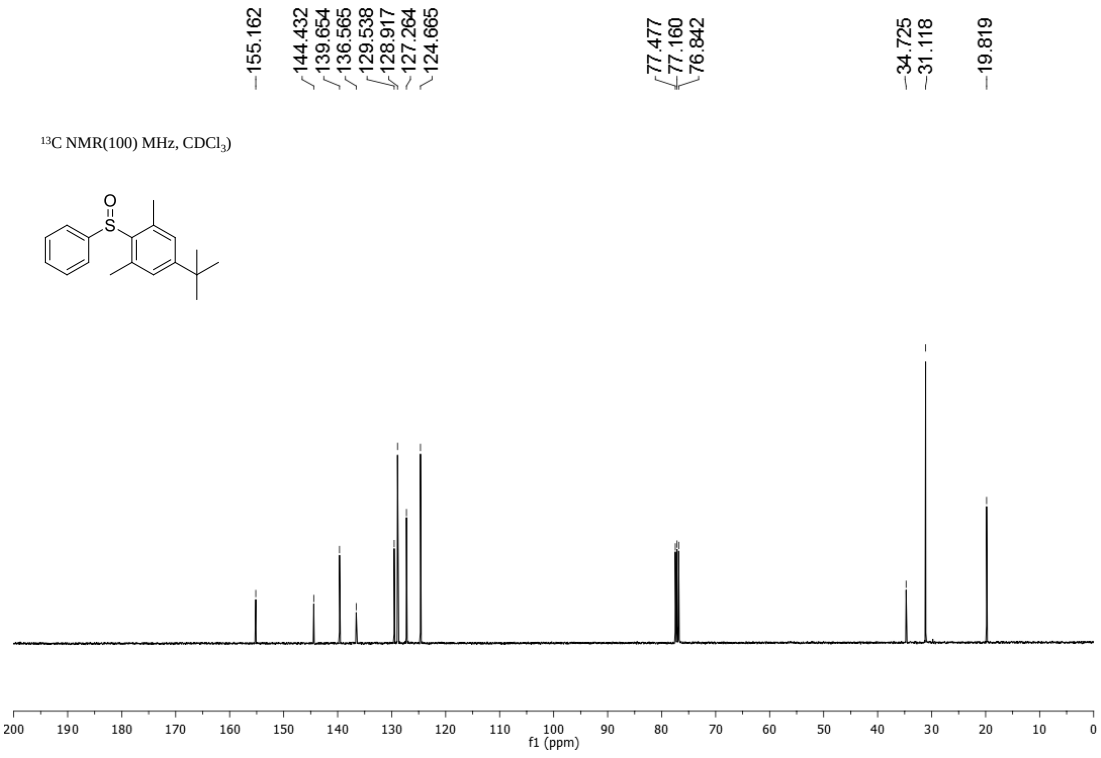


Figure 4.35. ^{13}C NMR spectrum of 5-(tert-butyl)-1,3-dimethyl-2-(phenylsulfinyl)benzene (**4fb**).

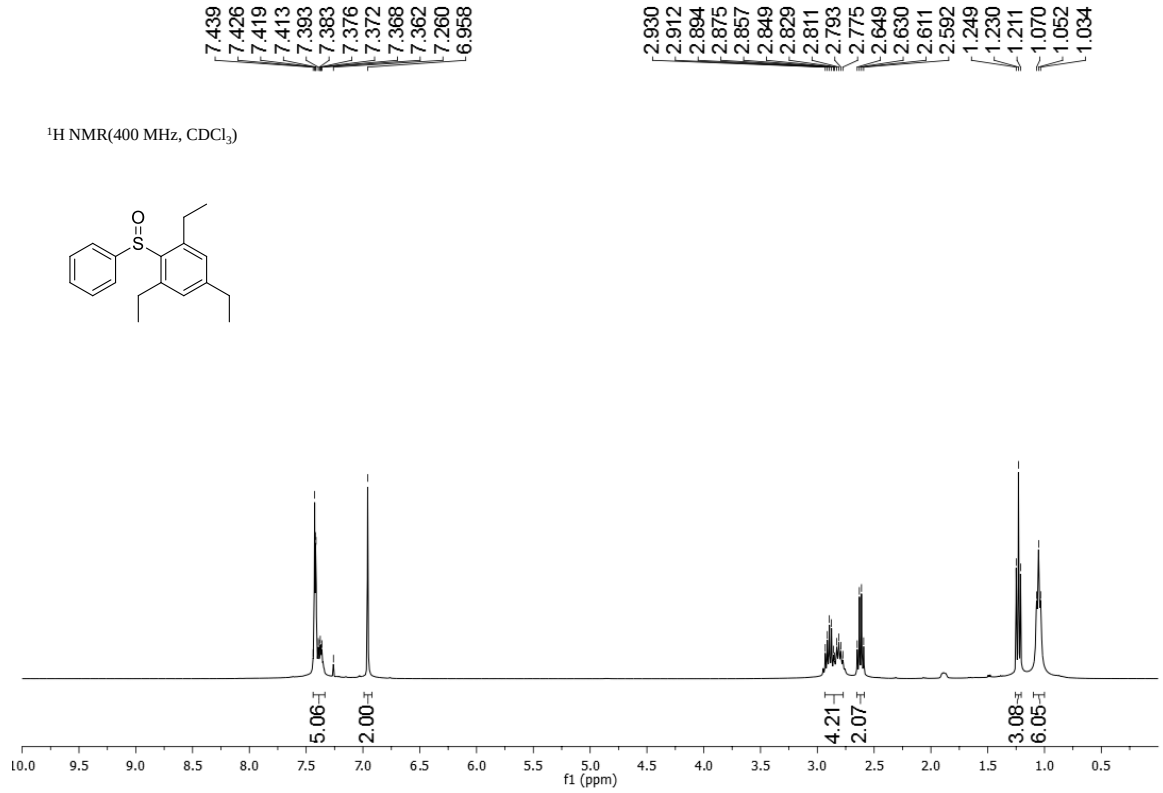


Figure 4.36. ^{1}H NMR spectrum 1,3,5-triethyl-2-(phenylsulfinyl)benzene (**4jb**).

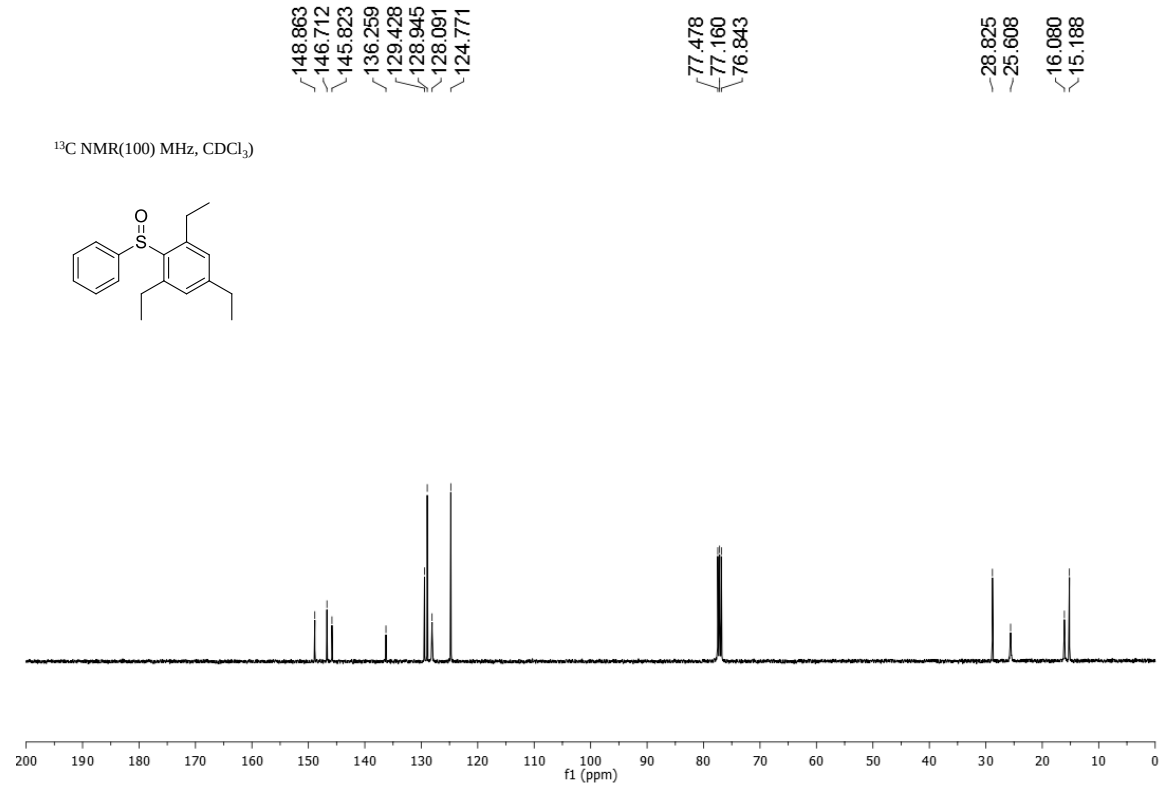
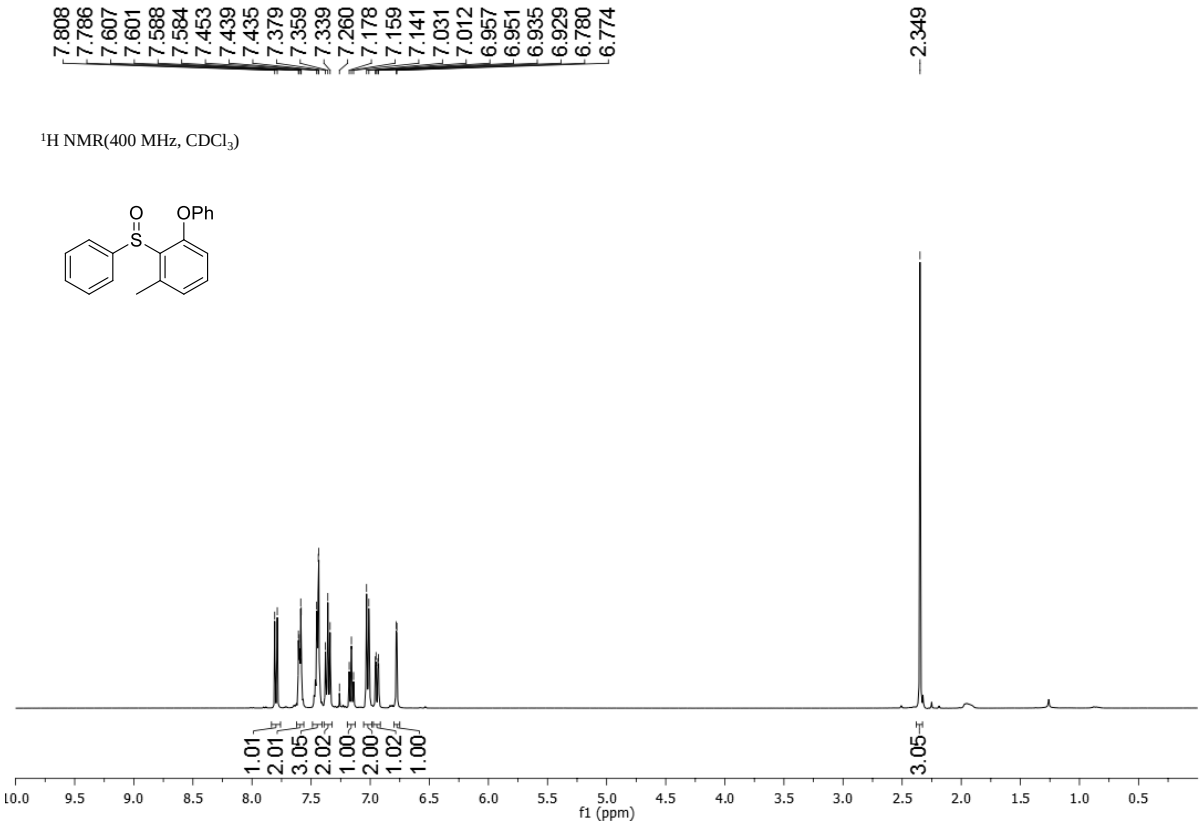
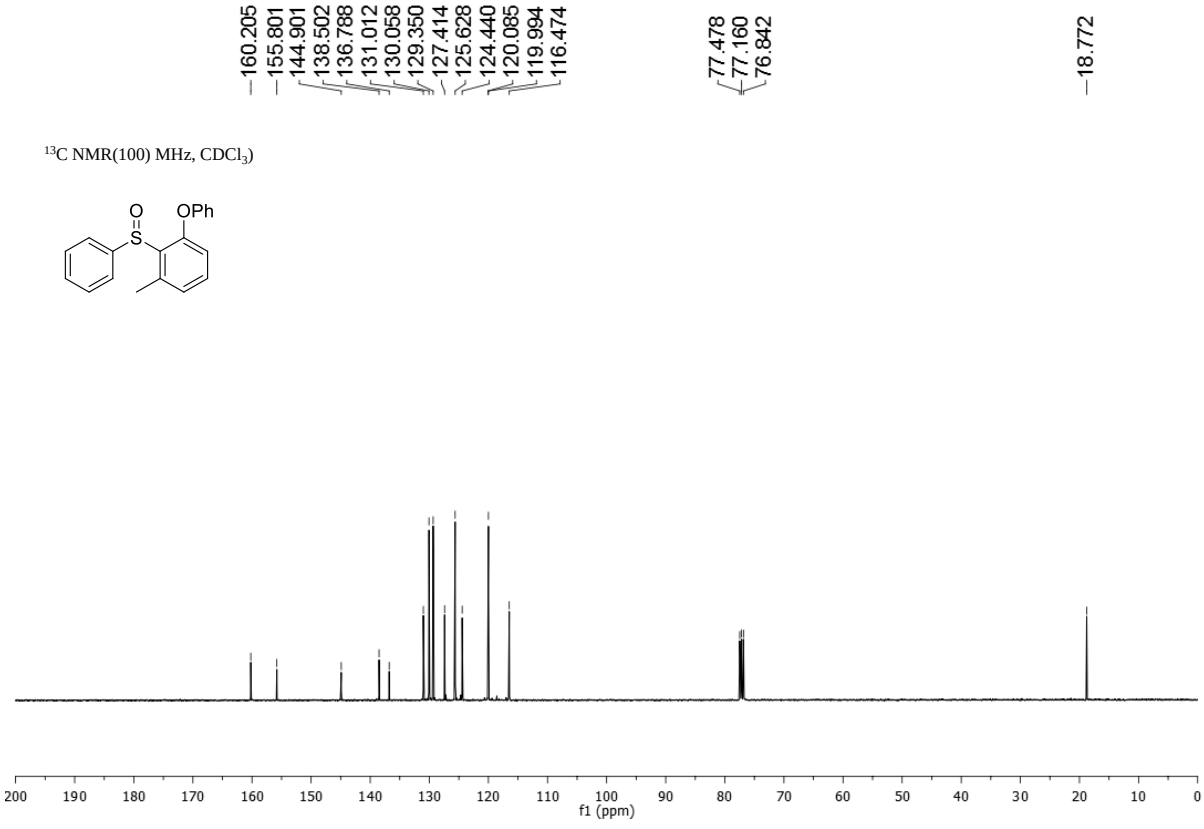


Figure 4.37. ^{13}C NMR spectrum of 1,3,5-triethyl-2-(phenylsulfinyl)benzene (**4jb**).



^{1}H NMR(400 MHz, $CDCl_3$)

Figure 4.38. ^{1}H NMR spectrum of 1-methyl-3-phenoxy-2-(phenylsulfinyl)benzene (**4kb**).



^{13}C NMR(100) MHz, $CDCl_3$)

Figure 4.39. ^{13}C NMR spectrum of 1-methyl-3-phenoxy-2-(phenylsulfinyl)benzene (**4kb**).

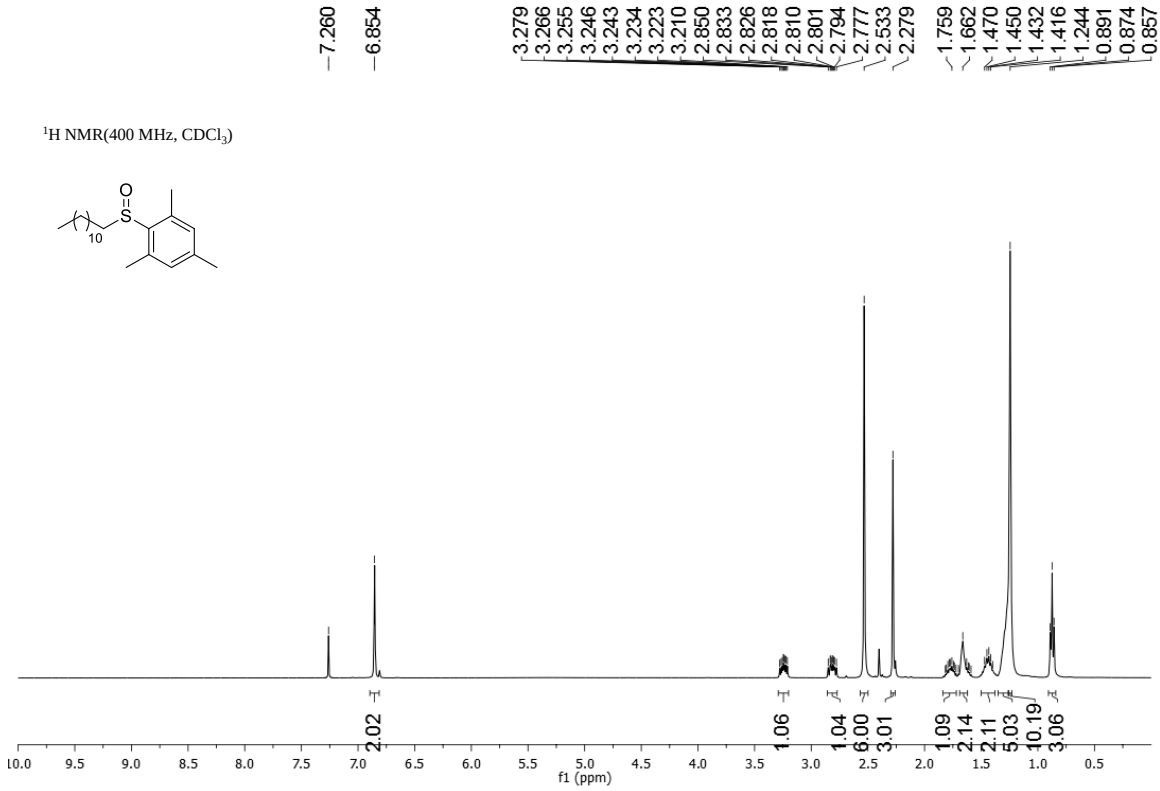


Figure 4.40. ^{1}H NMR spectrum 2-(dodecylsulfinyl)-1,3,5-trimethylbenzene (**4al**).

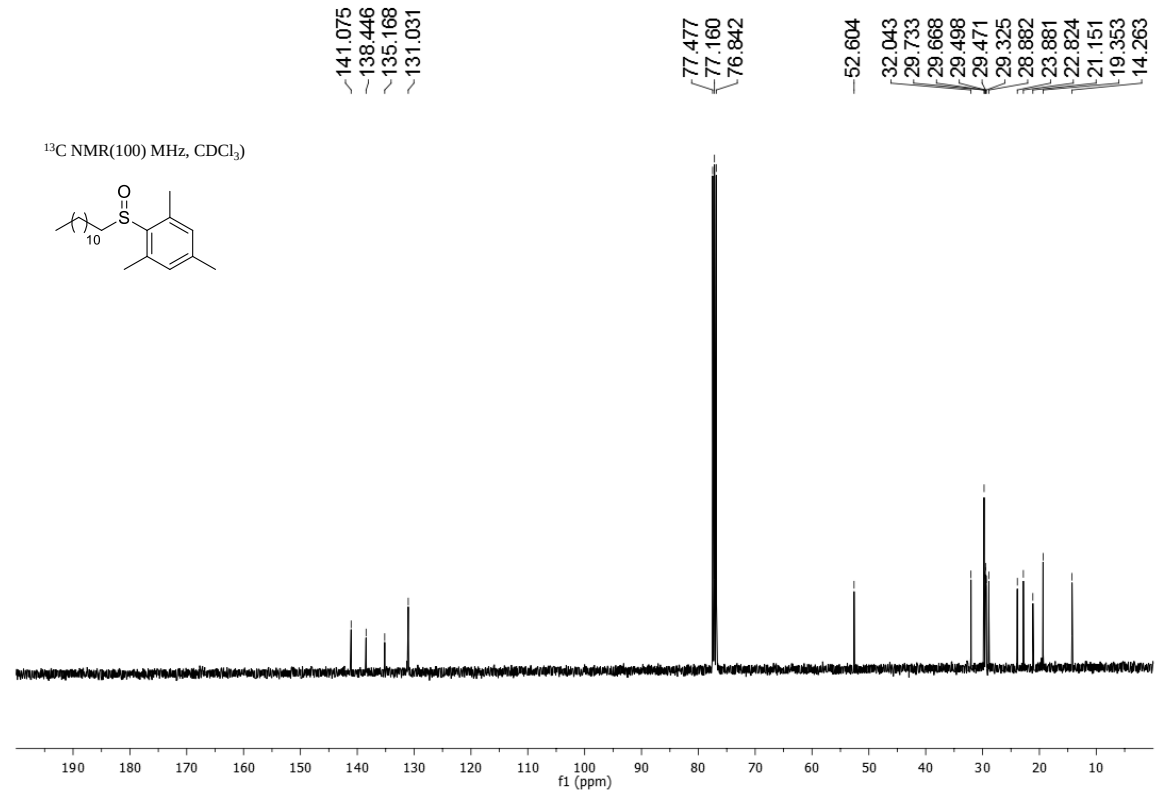


Figure 4.41. ^{13}C NMR spectrum of 2-(dodecylsulfinyl)-1,3,5-trimethylbenzene (**4al**).

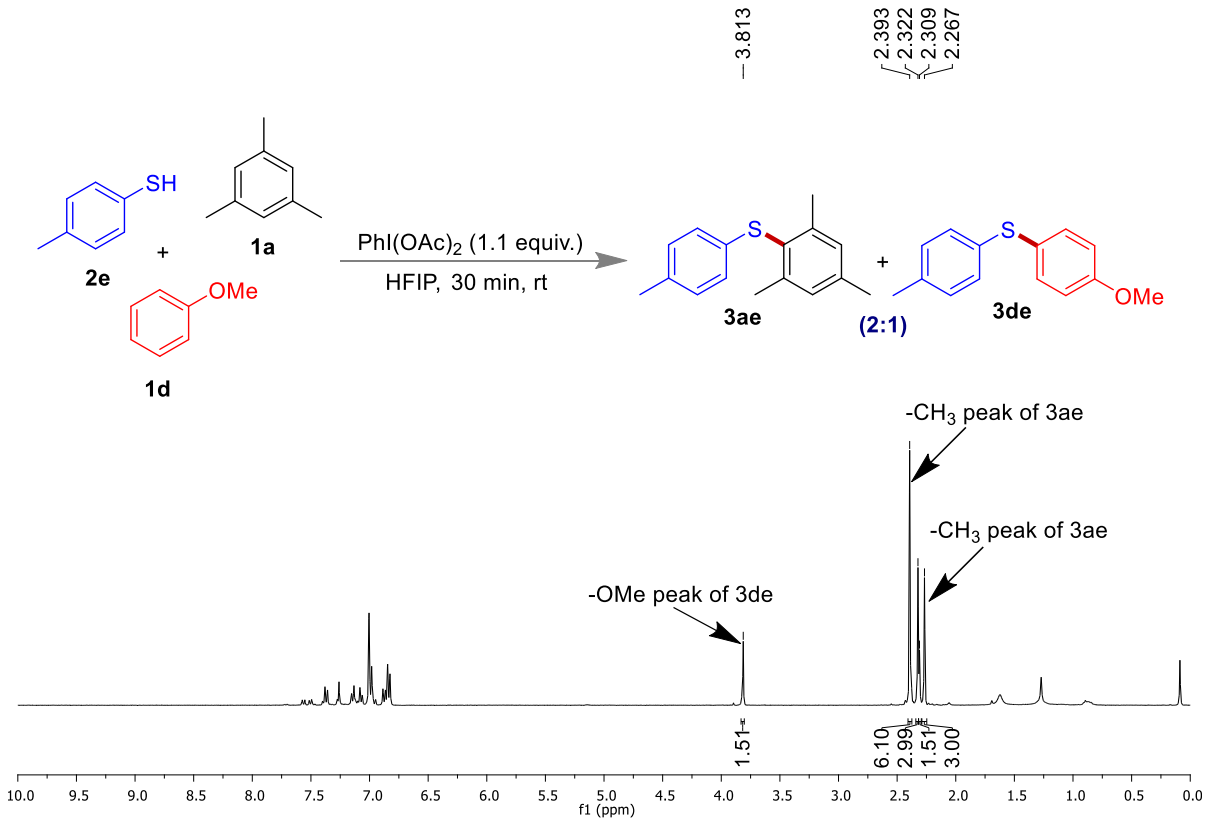


Figure 4.42. ^{1}H NMR spectrum of self-sorting experiment between **2e**, **1e** and **1d.**

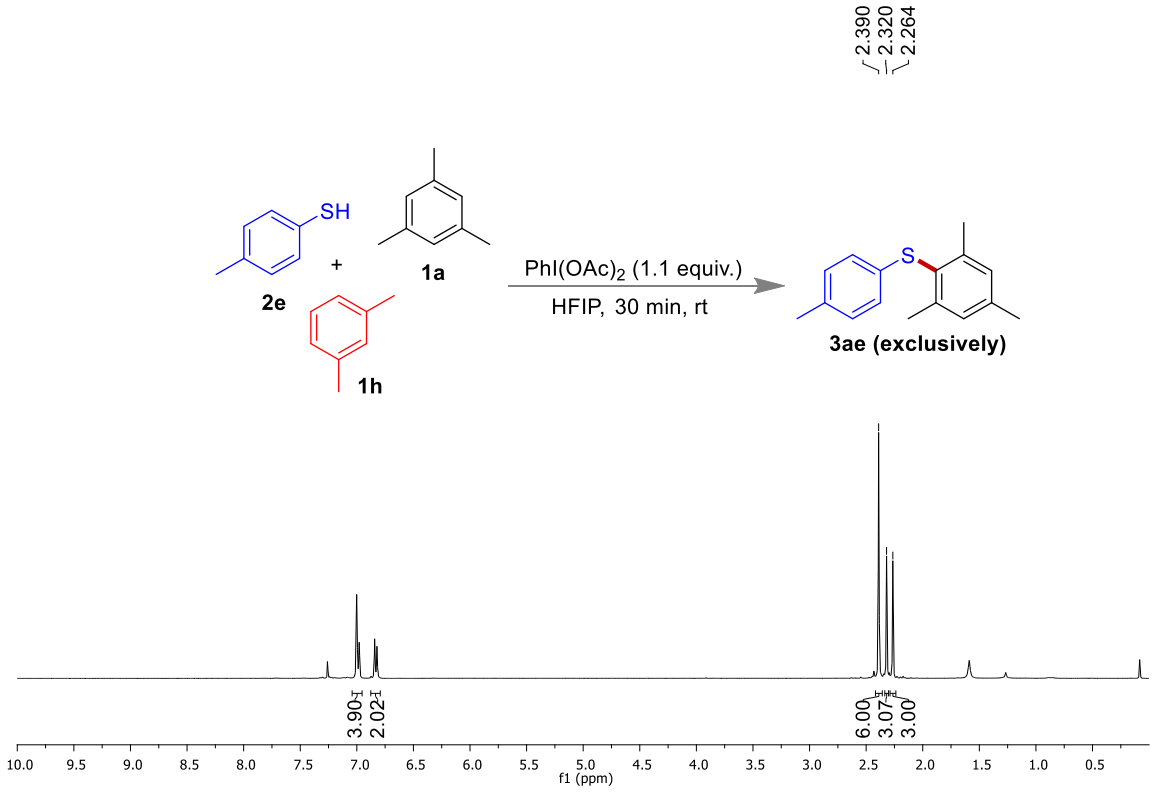


Figure 4.43. ^{1}H NMR spectrum of self-sorting experiment between **1e, 2a** and **1h.**

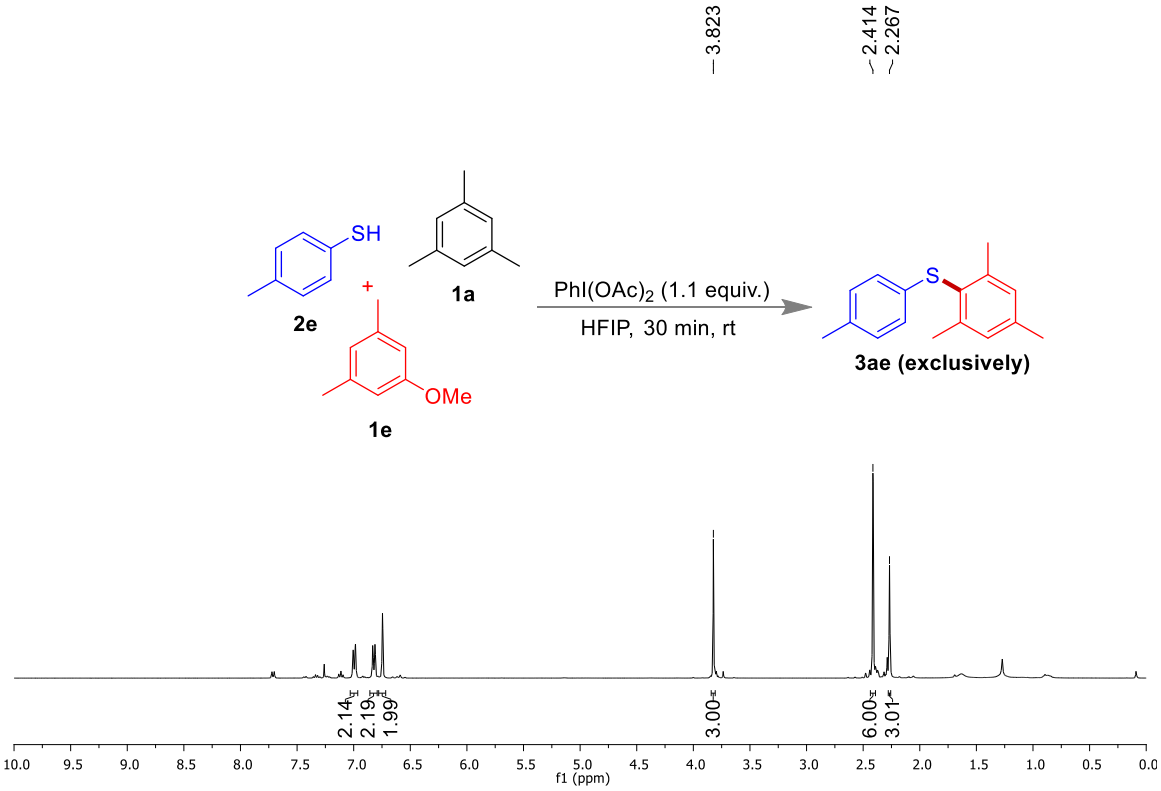


Figure 4.44. ^{1}H NMR spectrum of self-sorting experiment between **1e**, **2a** and **2e.**

CHAPTER 5

Organo-Catalytic Alkenylation of Nitrile *via* C-S Bond Cleavage

5.1 ABSTRACT

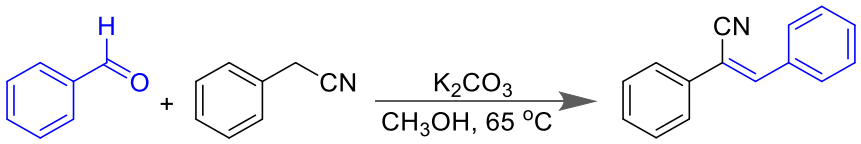
Herein we have demonstrated an *E*-Selective alkenylation of nitrile *via* organo-catalytic pathway towards the synthesis of 1, 2 diphenylacrylonitrile derivatives through the cleavage of C-S bond in unbiased mercaptan. Cascaded activation of three different bonds like C(sp3)-H, benzylic C-S and aryl-halide could be achieved *via* organocatalysis in one pot. The catalyst was generated *in situ* using 1, 10-phenanthroline and tBuOK. The reaction sequence is as follows: The benzyl mercaptan was converted to benzyl carbocation *via* C(sp3)-H and benzylic C-S activation, followed by exclusive stereoselective Knoevenagel condensation reaction of benzyl carbocation with benzyl cyanide. The final step is the C-X (X = Cl, F) functionalization of the Knoevenagel products.

5.2 INTRODUCTION

α,β-unsaturated diphenylacrylonitrile is the central core of the drug molecule,[1-3] as they possess anti-cancer,[4] anti-microbial,[5] antioxidative,[6] antitumor,[7] spasmolytic,[8] and cytotoxic activity[9,10] and also serves as valuable intermediate for the synthesis of herbicides,[11] dyes,[12] pharmaceutical[3] and natural product.[13] Few examples of nitrile containing marketed drugs are Entacapone (for Parkinson's disease), Saxagliptin (dipeptidyl peptidase-4 inhibitor), Milrinone (phosphodiesterase 3 inhibitor), CC-5079, Verapamil, Luliconazole etc. They are also used as organic lighting-emitting diodes[14] (OLEDs) and provide key building block for the synthetic transformation.[15]

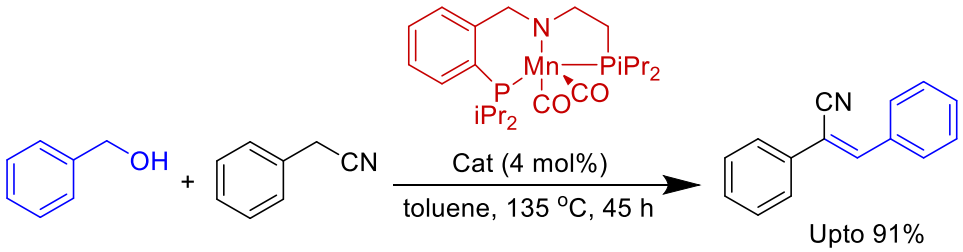
Traditionally diphenylacrylonitrile was synthesized by Knoevenagel condensation[16,17] involving aldehyde and phenyl acetonitrile. But it has several shortcomings such as, self-

coupling of the nitrile group, Cannizzaro reaction, aldol condensation of the carbonyl group bearing enolizable α-H atoms. Therefore synthesis of α,β-unsaturated diphenylacrylonitrile in an unrestricted way is a challenging topic of research in organic chemistry.



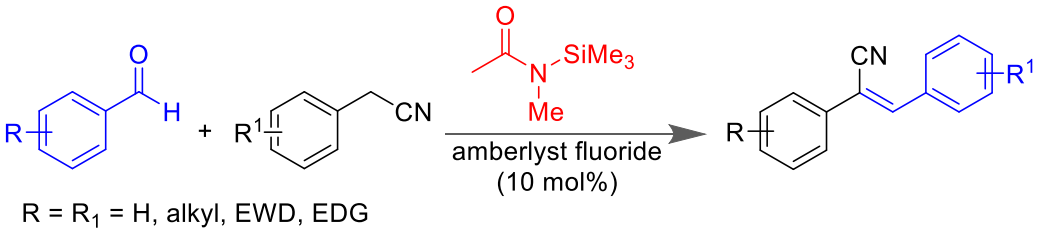
Scheme 5.1. Knoevenagel condensation reaction.

However, some other methods have also been documented in the literature for the synthesis of substituted 1, 2 diphenylacrylonitrile derivatives. Herein some selected reports have been discussed. Milstein *et. al*. developed an intermolecular dehydrogenative α-olefination of nitriles using Manganese pincer complex as catalyst from benzyl cyanide and benzyl alcohol (Scheme 5.2).[18] Both electron donating and withdrawing group containing benzyl cyanide were well tolerated the reaction condition. Mechanistically they have proved that the manganese pincer complex *in-situ* oxidized the benzyl alcohol to benzaldehyde to follow-up the product formation.



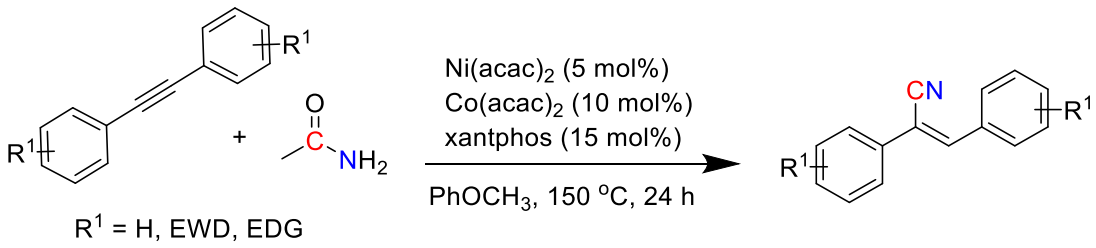
Scheme 5.2. Milstein's pincer complex catalyzed α-olefination of nitriles.

Vaccaro and co-workers have reported Amb-F Catalysed alkenylation of nitrile form aldehyde and substituted acetonitrile derivative using silazene under solvent free condition at 60 °C (Scheme 5.3).[19]



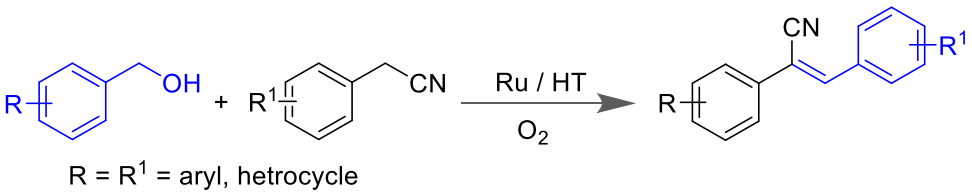
Scheme 5.3. Vaccaro's Amb-F catalyzed synthesis of alkenyl nitriles.

Chang and co-worker established Ni-catalysed hydrocyanation of alkyne using $Co(acac)_2$ as co-catalyst and xanthphos as ligand in anisole at high temperature (Scheme 5.4).[20] In presence of Ni catalyst and heating at 150 ^oC, formamide were acted as an active source of –CN ion in hydrocyanation reaction.



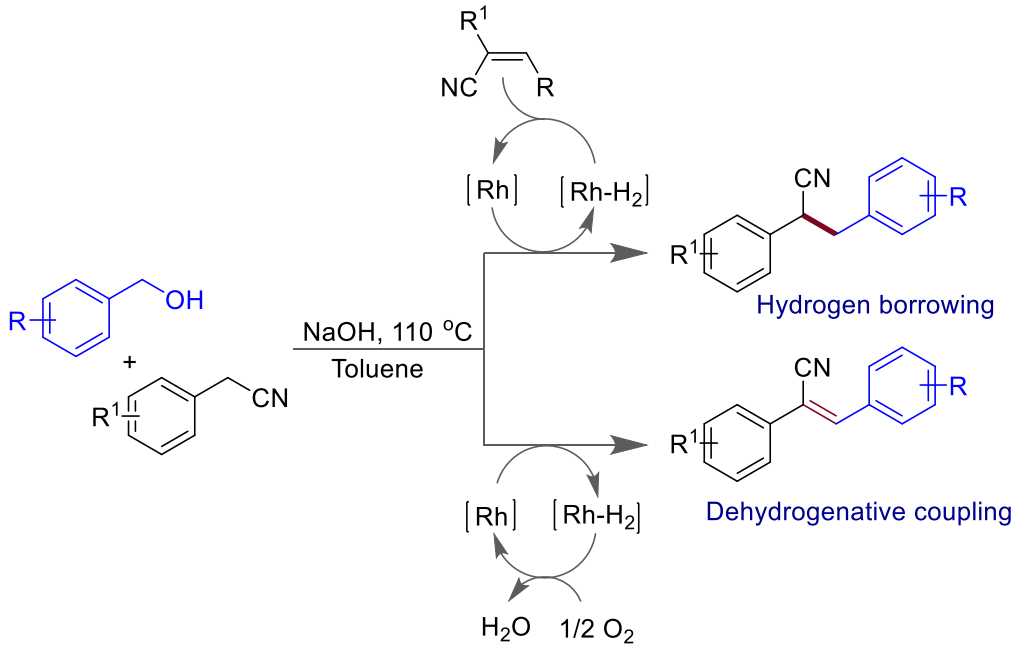
Scheme 5.4. Chang's Ni catalyzed hydrocyanation of alkyne.

Kaneda and his group described ruthenium-grafted hydrotalcite (Ru/HT) acting as efficient catalyst for the synthesis of α,β-unsaturated nitriles from benzyl alcohol and benzyl nitrile under oxygen atmosphere (Scheme 5.5).[21]



Scheme 5.5. Kaneda's Ru/HT catalyzed diphenylacrylonitrile synthesis.

Wang and co-workers established a protocol for chemo selective alkylation and olefination of nitriles with alcohols in a control manner (Scheme 5.6).[22] A binuclear rhodium complex catalysed the alkylation process *via* hydrogen-borrowing pathway under argon atmosphere and olefination reaction under oxygen atmosphere. Mechanistic studies revealed that alkylation reaction involved conjugate reduction process and olefination reaction involved oxidation of the rhodium hydride complex with molecular oxygen.



Scheme 5.6. Wang's chemoselective process.

However, the discussed methodologies have some shortcomings like toxicity issue, use of expensive metal catalyst, poor yield, inaccessible substrate scope and formation of unwanted side product. Therefore synthesis of α,β-unsaturated acrylonitrile in a milder condition is highly desirable. Herein we have reported a unique route of Knoevenagel condensation reaction towards the synthesis of 1,2 diphenylacrylonitrile from benzyl cyanide and benzyl mercaptan by activating three different types of bond-like C(sp3)-H, benzylic C-S and aryl-halide through *in-situ* generated organocatalytic pathway. Among the C(sp3)-H, benzylic C-S and aryl-halide bonds, C-S bond activation is most crucial for biological system because,

breaking of C-S bond can introduce a new class of chemistry by the replication of DNA.[23] Sulfur center in mercaptan behaves like highly nucleophile as well as electrophile depending upon the reaction environment. In addition, mercaptans are prone to get oxidize to form disulfide. Moreover benzyl marcaptan are readily accessible to utilize as thiyl source for the formation of C–S bonds.[24] Therefore, the C-S bond cleavage of unbiased mercaptans and thus utilization of mercaptans as benzyl synthon is extremely challenging and remained unexplored in domino synthesis. Few examples on the formation of C-C,[25] C-Si,[26] C-O,[27] C-B[28] bond are documented in literature *via* breaking of respective pre-functionalized C-S bonds. Mainly, UV light[27] or metal catalysts like Rh[29] and Pd[28] are used to activate the C-S bond on pre-functionalized mercaptans. Recently Masson group has reported a metal catalyzed C-S bond functionalization of benzylic thioether to obtain triarylalkanes *via* cationic pathway.[25] However, these metal catalyzed methods have produced unwanted side products due to the strong affinity of metals with the thiolate anion.[30] Herein, the approach towards metal free base mediated alkenylation of nitrile via C-S bond functionalization of benzyl mercaptan can have potential application in the pharmaceutical industry or in the green synthesis of fine chemicals. To the best of our knowledge, no report is available in the literature for the synthesis of stereoselective α,β-unsaturated diphenylacrylonitrile derivatives from mercaptan as benzyl synthon source via C-S bond cleavage. In addition, cascaded C-S and C-X (X= Cl, F) bond functionalization led to thiolated-diphenylacrylonitrile derivatives. These compounds are mostly used as radiation curing photosensitive initiator. The C-F bond is relatively less reactive nature and therefore difficult to functionalize due to high bond energy. So, development of cascaded C-S and C-X (X = F, Cl) bond functionalization might be helpful in organic synthesis.

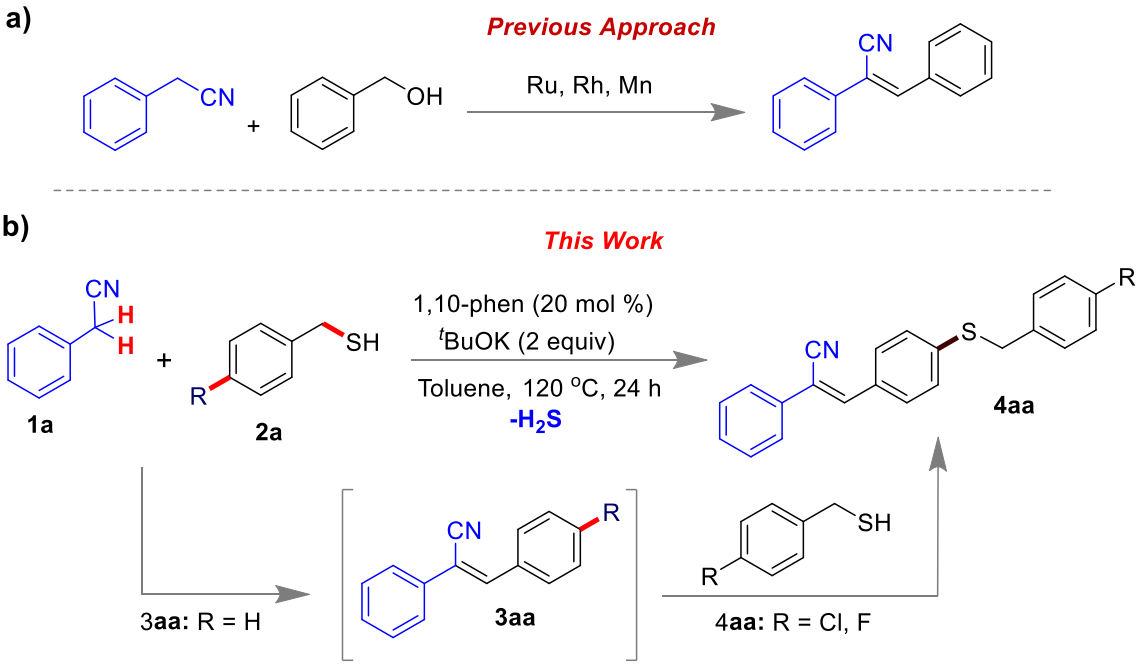


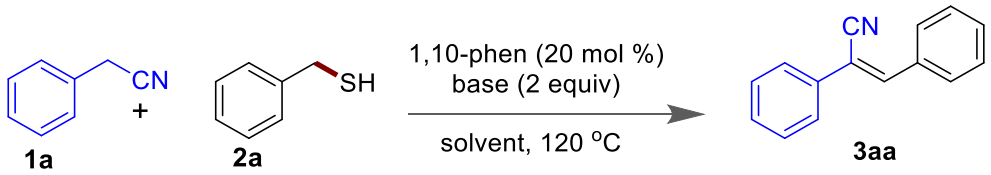
Figure 5.1. a) Known approach for α-olefination of nitriles using benzyl alcohol b) Our approach for alkenylation of nitrile through the breaking and reforming of C-S bond from benzyl mercaptan.

5.3 RESULT AND DISCUSSIONS

Before aryl-halide bond activations reactions, we have optimized the reaction sequence for the synthesis of diphenylacrylonitrile from benzyl cyanide (1a) and benzyl mercaptan (2a) using tBuOK and 1,10-phenanthroline (1,10-phen) (Table 1). The reactions were performed at 120 ºC and under open atmosphere. The compounds 1a and 2a smoothly reacted to afford the diphenylacrylonitrile (3aa) in 90% yield in presence of ^{t}BuOK and 1,10-phen within 24 h in benzene (entry 1). Varying the ratio of ^{t}BuOK and 1,10-phen led to inferior results (entries 2-3). Use of bases other than ^{t}BuOK was also not giving encouraging results (entries 4-6). This can be attributed to strong σ-donating and π-accepting ability of 1,10-phen,[31] to bind potassium(I) ion as the optimum. Solvents other than toluene were also ineffective to have better yield of 3aa (entries 7-12). Notablely, yield was reduced to 62 % when 1.5 equiv of

benzyl mercaptan was used (entry 13). Upon lowering temperature than 120 ºC did not have any better impact (entry 14).

Table 5.1. Optimization condition for alkenylation reaction.



Entry	Base (equiv)	1,10-phen (mol %)	Solvent	Yield (%)[a]
1	^{t}BuOK (2.0)	1,10-phen (0.2)	benzene	90
2	^{t}BuOK (1.0)	1,10-phen (0.2)	benzene	75
3	^{t}BuOK (2.0)	1,10-phen (0.1)	benzene	40
4	^{t}BuOLi (2.0)	1,10-phen (0.2)	benzene	12
5	^{t}BuONa (2.0)	1,10-phen (0.2)	benzene	38
6	KOH (2.0)	1,10-phen (0.2)	benzene	0
7	^{t}BuOK (2.0)	1,10-phen (0.2)	DMF	17
8	^{t}BuOK (2.0)	1,10-phen (0.2)	DCE	15
9	^{t}BuOK (2.0)	1,10-phen (0.2)	EtOH	50
10	^{t}BuOK (2.0)	1,10-phen (0.2)	toluene	96
11	^{t}BuOK (2.0)	1,10-phen (0.2)	DMSO	--
12	^{t}BuOK (2.0)	1,10-phen (0.2)	xylene	91
13	^{t}BuOK (2.0)	1,10-phen (0.2)	toluene	62[b]
14	^{t}BuOK (2.0)	1,10-phen (0.2)	toluene	67[c]
15	^{t}BuOK (2.0)	--	toluene	28
16	--	1,10-phen (0.2)	toluene	0
17	^{t}BuOK (2.0)	1,10-phen (0.2)	toluene	0[d]
18	^{t}BuOK (2.0)	1,10-phen (0.2)	toluene	82[e]

Reaction Condition: 1a (0.517 mmol), 2a (1.034 mmol), 1,10-Phenanthroline (0.103 mmol), tBuOK (1.034 mmol) in toluene for 24 h. aIsolated yield; b1.5 equiv 2a was used; c100 ºC, 24 h, dN2 atmosphere, eAfter 18 h.

Very poor yield 3aa (28%) was observed in absence of 1,10-phen (entry 15). However, no product could be detected in absence of ^{t}BuOK (entry 16) and in inert atmosphere (entry 17). However 82% yield of 3aa was observed when reaction time was reduced to 18 h (entry 18). Finally, the most suitable condition was found to be using ^{t}BuOK (2 equiv) and 1,10-phen (0.2 equiv) in toluene (entry 10).

Using the optimized reaction condition, substrate scope for the synthesis of α,β-diphenylacrylonitrile derivatives are shown in Figure 2. Reactions involving both electron donating (-Me, -OMe, -napthyl) and halide groups (-Cl, -F, -Br) at phenyl acetonitriles led to excellent yields (80-96%) of the products 3aa-3ha. Similarly, 3db, 3cc, 3fc, 3dc and 3dd were isolated in 82%, 84%, 71%, 95% and 93% yields, respectively. However, no product formation was observed with nitrile derivatives with electron withdrawing -NO2 or -CN substituted phenyl groups (3ic, 3jc). Possibly, after proton abstraction, phenyl acetonitrile led to benzylic anion intermediate which was not nucleophilic enough for condensation reaction due to –R effect of the -NO2 or –CN groups. Furthermore, the versatility of the reaction was explored using heterocyclic coupling partners (both aryl mercaptan and nitrile substrates). 2-Furfurylthiol reacted with substituted phenyl acetonitrile to produce 3hf, 3df and 3kf in 82%, 94% and 81% yields, respectively. Similarly, 2-thenylmercaptan led to 3dg and 3kg in 76% and 74% yields, respectively. 2-Thiopheneacetonitrile also reacted with benzyl cyanide and yielded **3ka** in 85% yield. Likewise, we have extended our methodology towards *in situ* cascaded C-S and C-X (X = Cl, F) bond functionalization reaction *via* ipso substitution having halo substituted benzyl mercaptans. Under the standard condition benzyl mercaptan containing halogen group (X = -F, -Cl) at para position, selectively activated to form (Z)-3-(4-((4-fluorobenzyl)thio)phenyl)-2-phenylacrylonitrile *via* cascaded C-X bond activation (Figure 5.3). Fluorine substitute benzyl mercaptan lead to the products **4bh**, **4dh**, **4jh**, in good yields (73%, 67% and 50% respectively) *via* C-F bond activation.[32] In addition, chloro substituted benzyl mercaptan provided **4ae** and **4ge**, in 65% and 74% yield, respectively. Mixture of product **3be** and **4be** was obtained in (3:4) ratio when *p*-tolylacetonitrile was taken as one of the coupling partner. Anomalously, 2-chloro-4-fluoro phenylacetonitrile selectively delivered the para selective C-F bond activated product in 36% yield.

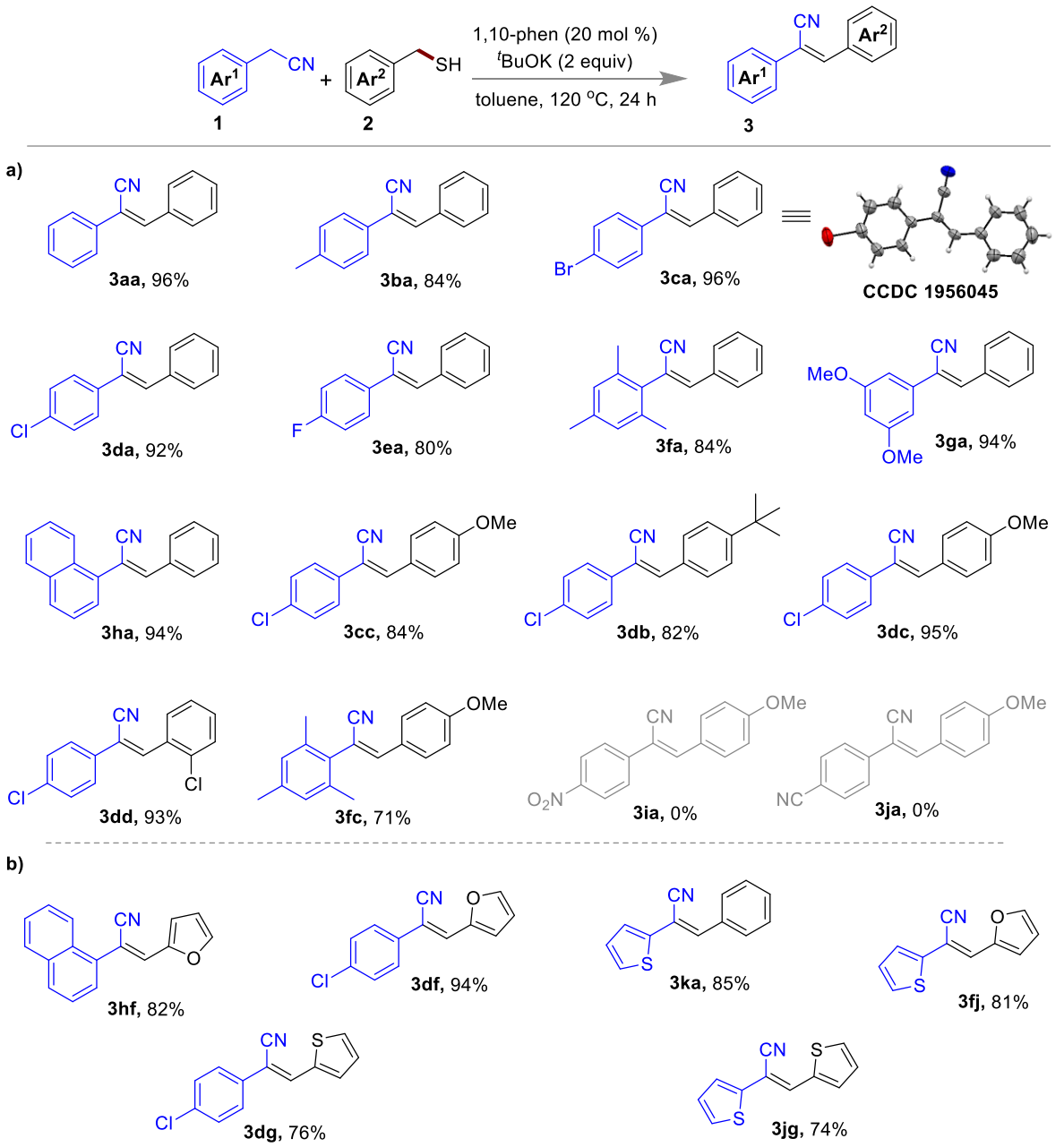


Figure 5.2. Substrate scope for the substituted 1,2-diphenylacrylonitrile synthesis. a) C-C coupling reaction using different kinds of benzyl cyanide and mercaptans. b) C-C bond formation using heterocyclic coupling partner.

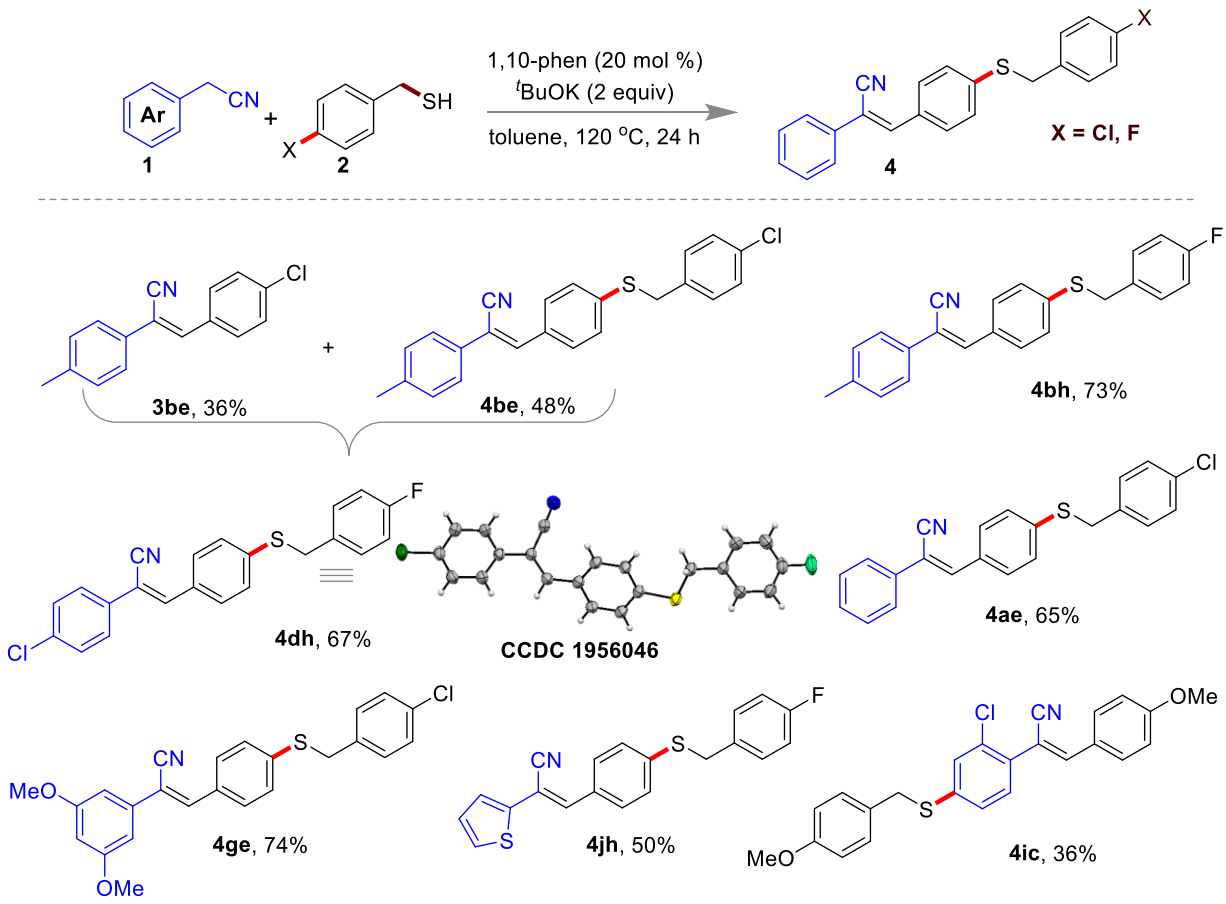


Figure 5.3. Scope of the reaction for cascaded C-S and C-X (X = -F, -Cl) bond activation.

Control experiments shown in Figure 5.4, helped to establish the mechanism of the reaction. Radical pathway was initially anticipated, because 1,10-phenanthroline and ^{t}BuOK are known to produce ^{t}BuO$^{\cdot}$ *via* single electron transfer pathway.[33] However, stoichiometric amount of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or BHT led to provide 76% or 86% yield of the products 3aa**,** respectively (Figure 5.4a). This fact supported for an ionic pathway. In presence of base, the benzyl mercaptan generally produce 1,2-dibenzyldisulfane. As expected, 85% yield of 3aa was isolated, when 1,2-dibenzyldisulfane was employed under optimized condition (Figure 5.4b) and proved to be an intermediate. A kinetic isotopic effect was also measured and found to be K_H/K_D= 2.23.

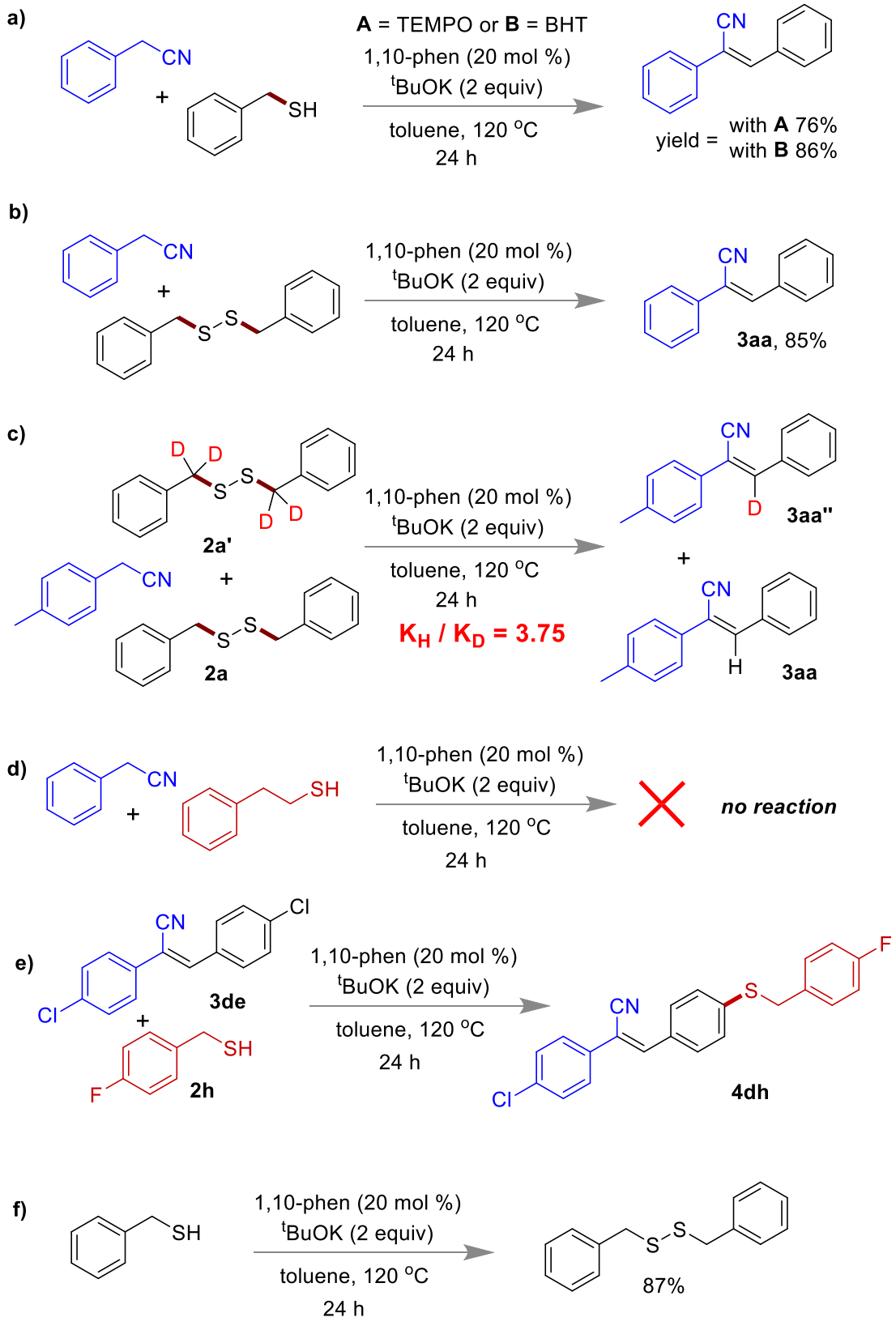


Figure 5.4. Control experiments.

This indicates that the benzylic C(sp3)–H bond was actively participating to form a stable benzyl carbanionic intermediate during the reaction (Figure 5.4c). Contrastingly, 2-phenylethane-1-thiol and phenyl acetonitrile under standard condition did not furnish any products (Figure 5.4d). This result indicated that stability of benzylic carbanion is an important factor for the reactions to proceed. In addition, reaction of **3de** with **2h** led to the formation of **4dh** in 68 % yield (Figure 5.4e). This fact confirms that the α,β-diphenylacrylonitrile might be the intermediate for the formation of *ipso* substituted product **4dh** *via* cascaded C-S and C-X bond functionalization reaction. Also, in absence of phenyl acetonitile, 87% yield of 1,2 dibenzyldisulfane was isolated (Figure 5.4f).

A plausible mechanism for the cascaded benzylic C-S and aryl-halide bond functionalization has been proposed in Figure 5.5. Literature report[34,35] suggested that K^+ ion from inorganic salt ^{t}BuOK and 1,10-phen might have a reliable interaction with toluene *via* π-π stacking[36] and ion-π interaction[37] to form a stable complex **5** in which the counter anion of ^{t}BuOK could be available for acidic H-abstraction (Figure 5.5a). Following, complex **5** under the treatment with **2a** in presence of aerial dioxygen led to intermediate **2aa**. Further, with the help of complex **5**, disulfides expected to get converted to a stable benzyl carbanion intermediate **2aa'** (Figure 5.5c). Under standard condition, benzyl carbanion intermediate **2aa'** is expected to produce thiobenzaldehyde **6** and the intermediate **7** (Figure 5.5c). Following, carbanion intermediate **1a'** generated from phenyl acetonitrile **1a** (Figure 5.5b) was coupled with thiobenzaldehyde **6** to provide intermediate **8**. Finally, release of H_2S (turned the led-acetate paper into black, Figure 5.7b) from **8** could lead to formation of **3aa** through E2 elimination. On the other hand compound **9** having F/Cl atom underwent *ipso* substitution by benzyl thiolate to produce compound **4ah**. ^{1}H NMR studies also supported for the formation of complex **5** (Figure 5.6) from 1,10-phen and ^{t}BuOK in toluene-d_8 (Figure

5.6b). A new peak at 5.1 ppm suggested a strong H-bonding between C(sp^3)-H of toluene and oxygen atom of ^{t}BuOK.

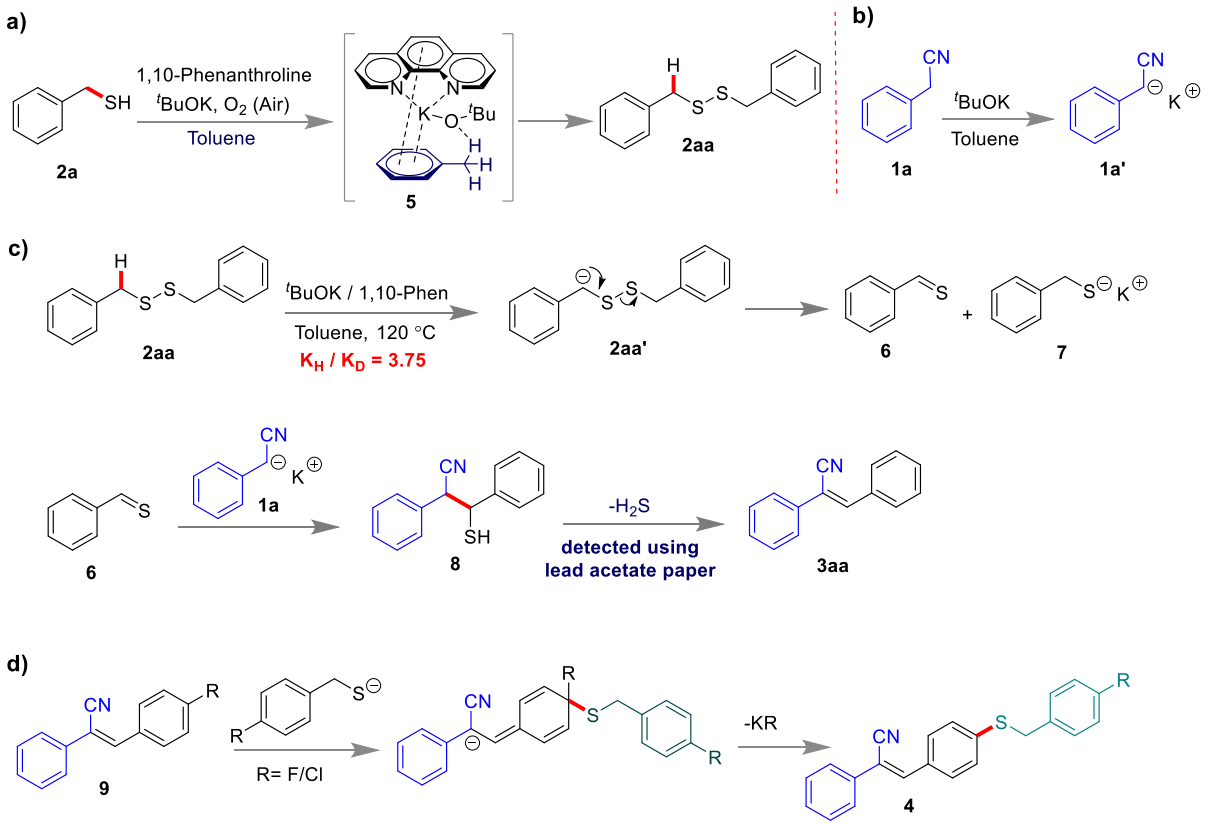


Figure 5.5. Plausible mechanism of the reaction. a) Activation of base by 1,10-phen. b) Generation of benzyl carbocation intermediate from disulfane. c) C-C bond formation reaction. d) *Ipso*-substitution and C-S coupling reaction.

The cascaded C-S and C-X (X = Cl, F) bond functionalization reactions were truly controlled by electronic effect. For aromatic nucleophilic substitution reactions, stability of the sigma complexes is crucial. When Fluorine substituted benzyl mercaptan were used, the anionic intermediates were stabilized through the resonance conjugation with the –CN group. But such type resonance conjugation with –CN (electron withdrawing) group is absent for 2-(4-fluorophenyl) acetonitrile **1e** and getting unreactive towards aromatic nucleophilic substitution reactions.

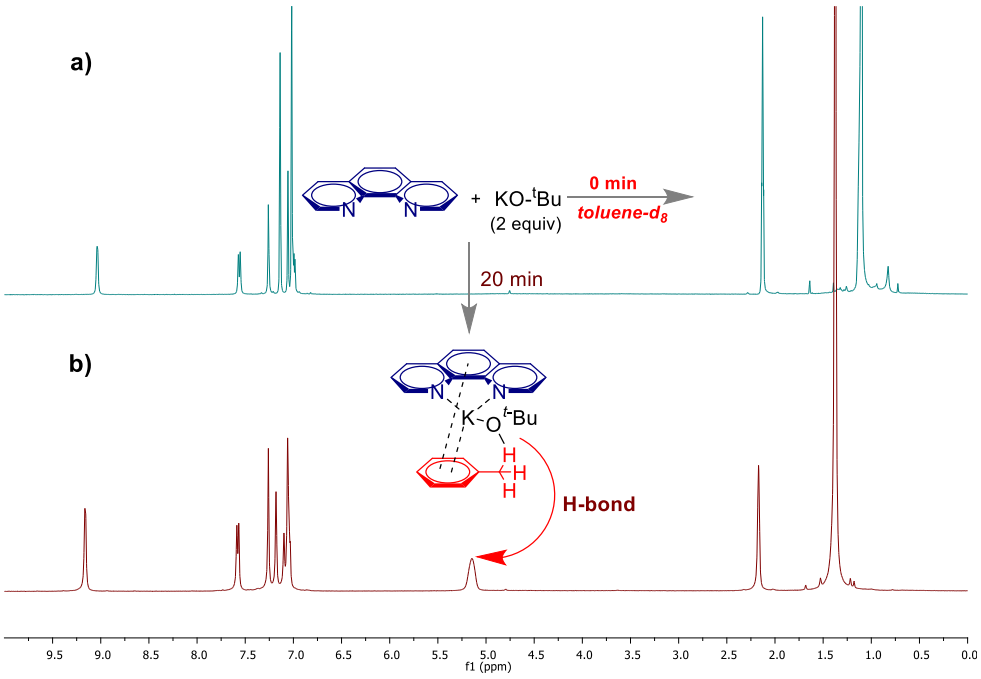


Figure 5.6. Possible interaction between the phenanthroline, ^{t}BuOK and the solvent molecule. a) ^{1}H-NMR spectra of 1,10-phenanthroline and ^{t}BuOK in toluene-d_8 after 0 min. b) ^{1}H-NMR spectra of 1,10-Phenanthroline and ^{t}BuOK after 15 min heating at 120 °C.

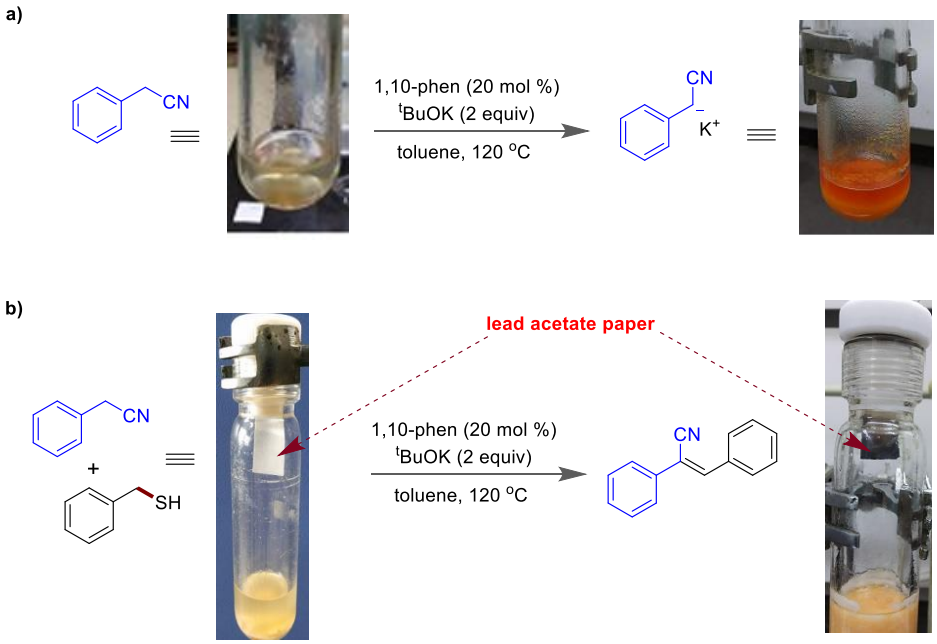
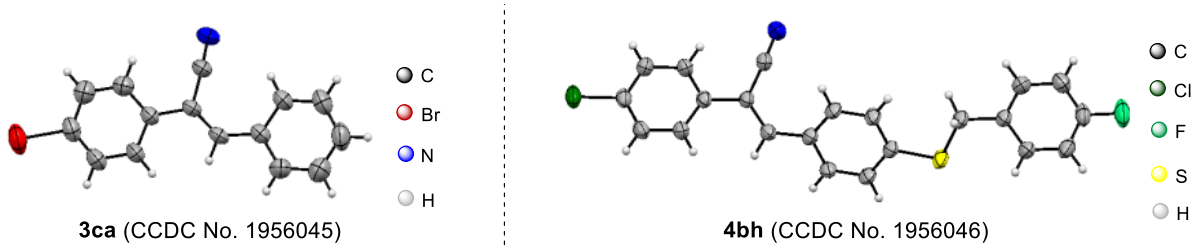


Figure 5.7. a) Color changes during the formation of benzyl carbanion. b) $Pb(OAc)_2$ experiment confirms the releasing of H_2S gas during the reaction.



3ca (CCDC No. 1956045) **4bh** (CCDC No. 1956046)

Figure 5.8 X-ray crystal structure of compound 3ca and 4bh.

5.4 CONCLUSIONS

In conclusion, we have developed a new synthetic route for the knoevenagel condensation reaction *via* domino C(sp3)-H, Benzylic C-S and Aryl-Halide bond functionalization in one-pot. *In-situ* generated organo-catalysis from the combination of ^{t}BuOK and 1,2-phenthroline led to formation of highly stereoselective diphenylacrylonitriles in good to excellent yields. Following, derivatization of knoevenagel products has also been achieved in the same reaction pot by activation of C-X bond. Thus this current method overcomes the limitation of knoevenagel condensation reaction by introducing a new C-S bond in diphenylacrylonitriles. Simultaneously C-S bond cleavage and formation in one pot have gained a new area in synthetic organic chemistry. We foresee that current methodology will be highly appealing in organic synthesis, pharmaceutical chemistry and drug discovery.

5.5 EXPERIMENTAL SECTION

General Information: All the chemicals were purchase from the commercially available source and used as received. All the reactions were carried out at 120 ^{o}C in open atmosphere. Column chromatography purification was performed using silica gel (Mesh 230-400) and ethyl acetate/hexane as an eluent unless otherwise specified. TLC was performed on Merck

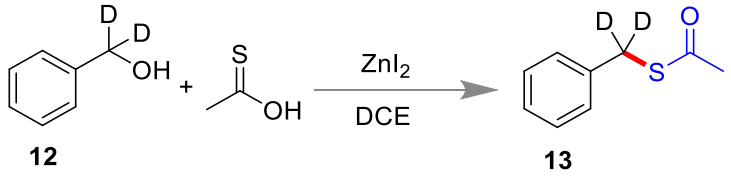
silica gel 60 F_{254} aluminium plate and visualized with UV lamp. ^{1}H and ^{13}C NMR spectra of the compounds were recorded on 400 and 700 MHz spectrometer at 25 ^{o}C. The chemical shift value (δ, ppm) were reported with respect to the residual chloroform (7.26 for ^{1}H and 77.16 ppm for ^{13}C) and DMSO-d_6 (2.50 for ^{1}H and 39.520 ppm for ^{13}C). Infrared (IR) spectra were recorded in wave number (cm^{-1}). Digital melting point apparatus were used to record the melting point of the compound. High resolution mass spectroscopy (HR-ESIMS) was recorded on ESI-TOF (Time-of-flight) mass spectroscopy.

General procedure for the preparation of diphenylacrylonitrile

To a stirred solution of 1,10-Phenanthroline (19 mg, 0.103 mmol) and ^{t}BuOK (116 mg, 1.034 mmol) in toluene, benzyl cyanide (60 μL, 0.517 mmol) and benzyl mercaptan (121 μL, 1.034 mmol) were added. Then the resulting mixture was allowed to stir at 120 ^{o}C for 24 h under open atmosphere. After that the solution was concentrated under vacuum, diluted with CH_2Cl_2 and washed with brine solution. Then the organic layer was dried over anhydrous sodium sulphate and purified through silica gel column chromatography using *n*-hexane and ethyl acetate solvent mixture as an eluent to afford the product.

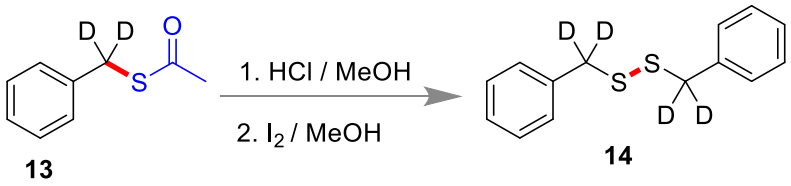
Kinetics Experiment. To a stirred solution of 1,10-phenanthroline (0.021 mg, 0.114 mmol) and ^{t}BuOK (0.129 mg, 1.150 mmol) in toluene, benzyl cyanide (0.076 mg, 0.574 mmol), 1,2-dibenzyldisulfane (0.070 mg, 0.287 mmol) and 1,2-bis(phenylmethyl-d2)disulfane (0.071 mg, 0.287 mmol) were added. Then the resulting mixture was allowed to stir at 120 ^{o}C for 24 h under open atmosphere. After that the solution was concentrated under vacuum, diluted with CH_2Cl_2 and washed with brine solution. Then the organic layer was dried over anhydrous sodium sulfate and purified through silica gel column chromatography using *n*-hexane and ethyl acetate solvent mixture as an eluent to afford the mixture of (3aa and 3aa') product. After that, K_H / K_D ratio was calculated from NMR analysis and found to be K_H / K_D 2.23.

Preparation of 1,2-bis(phenylmethyl-d2)disulfane: We have prepared 1,2-bis(phenylmethyl-d2)disulfane using the standard procedure[38] by the two step sequence described in details.



Scheme 5.7. Preparation of 1,1-[D2]Phenylmethanethiol acetate.

Thioacetic acid (12.03 mmol) and ZnI_2 (2.405 mmol) were added to a solution of phenylmethan-d2-ol (4.81 mmol) in dichloroethane. Then the solution was refluxed for 1 h to complete the reaction. After that the resulting solution was diluted with CH_2Cl_2 and washed with water, purified over silica-gel column chromatography to afford **13** as yellow color oil. ^{1}H NMR (400 MHz, CDCl3) δ 7.62 – 6.93 (m, 5H), 2.35 (s, 3H).



Scheme 5.8. Di-(1,1-[D2]Phenylmethyl) disulfide.

To a room temperature solution of 13 in methanol, 0.25 mL conc. HCl was added and the resulting solution was refluxed for 14 h. After that, the solution was cooled to room temperature. Following, 5% solution of I_2 in methanol was added and stirred for 30 min. After completion of the reaction, saturated $Na_2S_2O_3$ was added to remove the excess amount of I_2 and the organic layer was separated. Then the crude mixture was purified over silica gel column chromatography using *n*-hexane and ethyl acetate solvent mixture to afford the product 14. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 8H), 7.25 – 7.24 (m, 1H), 7.24 – 7.22 (m, 1H).

Compound Characterization Data:

(Z)-2,3-Diphenylacrylonitrile (3aa). Rf = 0.6 (5% ethyl acetate in hexane); White solid; yield 96% (102 mg); mp 80 - 82 ºC (lit.[39] 86-87 ºC); 1H NMR (700 MHz, DMSO-d6) δ 8.05 (s, 1H), 7.94 (d, J = 7.6 Hz, 2H), 7.77 (d, J = 7.6 Hz, 2H), 7.57 – 7.49 (m, 5H), 7.46 (t, J = 7.2 Hz, 1H); 13C NMR (175 MHz, DMSO) δ 143.1, 133.8, 133.79, 130.7, 129.4, 129.3, 129.2, 129.0, 125.9, 118.0, 110.4.

(Z)-3-Phenyl-2-(p-tolyl)acrylonitrile (3ba). R_f = 0.62 (5% ethyl acetate in hexane); White solid; yield 84% (84 mg); mp 62 - 64 ºC (lit.[40] 73-74 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.0 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.50 (s, 1H), 7.49 – 7.40 (m, 3H), 7.25 (d, *J* = 8.2 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.6, 134.0, 131.8, 130.5, 129.9, 129.3, 129.1, 126.0, 118.2, 111.8, 21.4.

(Z)-2-(4-Bromophenyl)-3-phenylacrylonitrile (3ca). R_f = 0.6 (5% ethyl acetate in hexane); White solid; yield 96% (84 mg); mp 105-107 ºC (lit.[41] 135-137 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.60 – 7.52 (m, 5H), 7.51 – 7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 133.6, 133.6, 132.4, 131.0, 129.5, 129.2, 127.6, 123.6, 117.8, 110.8.

Z)-2-(4-Chlorophenyl)-3-phenylacrylonitrile (3da). R_f = 0.5 (5% ethyl acetate in hexane); White solid; yield 92% (110 mg); mp 117-119 ºC (lit.[42] 121-122 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.85 (m, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.52 (s, 1H), 7.50 – 7.44 (m, 3H), 7.42 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 135.4, 133.6, 133.1, 130.9, 129.5, 129.4, 129.2, 127.4, 117.8, 110.7.

(Z)-2-(4-Fluorophenyl)-3-phenylacrylonitrile (3ea). R_f = 0.48 (5% ethyl acetate in hexane); White solid; yield 80% (89 mg); mp 85-87 ºC (lit.[43] 88-89 ºC);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.66 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.52 – 7.42 (m, 4H), 7.15 (t, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, $^1J_{CF}$ = 248 Hz), 142.3 (d, $^4J_{CF}$ = 1.8 Hz), 133.7, 130.84, 130.78, 129.3 (d, $^2J_{CF}$ = 21.2 Hz), 128.0 (d, $^3J_{CF}$ = 8.3 Hz), 118.0, 116.4, 116.2, 110.8

(Z)-2-Mesityl-3-phenylacrylonitrile (3fa). R_f = 0.4 (5% ethyl acetate in hexane); Colourless liquid; yield 84% (78 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.32 – 7.25 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 2H), 6.94 (s, 2H), 2.33 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 145.6, 139.1, 136.2, 134.2, 130.4, 129.5, 129.3, 128.9, 119.7, 112.2, 21.3, 19.8; IR (KBr) ῡ = 3017, 2921, 2205, 1610, 1448, 1217 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{17}N$ $(M+H)^+$ 248.1434, found 248.1415.

(Z)-2-(3,5-dimethoxyphenyl)-3-phenylacrylonitrile (3ga).[44] R_f = 0.2 (5% ethyl acetate in hexane); Off white solid; yield 94% (84 mg); mp 68-70. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 6.8 Hz, 2H), 7.53 (s, 1H), 7.51 – 7.41 (m, 3H), 6.81 (d, *J* = 2.2 Hz, 2H), 6.50 (t, *J* = 2.2 Hz, 1H), 3.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 142.7, 136.5, 133.6, 130.6, 129.4, 129.0, 118.0, 111.6, 104.3, 101.3, 55.6; HRMS (ESI-TOF) calcd for $C_{17}H_{15}NO_2$ $(M+H)^+$ 266.1176, found 266.1185.

(Z)-2-(Naphthalen-1-yl)-3-phenylacrylonitrile (3ha).[18] R_f = 0.2 (5% ethyl acetate in hexane); Colourless liquid; yield 94% (86 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.63 – 7.56 (m, 3H), 7.55 – 7.50 (m, 4H), 7.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 134.0, 133.8, 133.7, 130.9, 130.9, 130.0, 129.4, 129.2, 128.9, 127.4, 127.2, 126.6, 125.5, 124.7, 118.7, 110.0.

(Z)-3-(4-(tert-Butyl)phenyl)-2-(4-chlorophenyl)acrylonitrile (3db). Rf = 0.65 (5% ethyl acetate in hexane); Light yellow solid; yield 82% (95 mg); mp 182-184 ºC; 1H NMR (400 MHz, CDCl3) δ 7.84 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.52 – 7.46 (m, 3H), 7.41 (d, J = 8.6 Hz, 2H), 1.35 (s, 9H); 13C NMR (100 MHz, CDCl3) δ 154.7, 142.6, 135.2, 133.3, 130.9, 129.4 (x2), 127.3, 126.2, 118.1, 109.6, 35.2, 31.3; IR (KBr) ῡ = 2976, 2958, 2359, 2339, 2220, 1402 cm-1; HRMS (ESI-TOF) calcd for C19H18NCl (M +Na)+ 318.1020, found 318.1005.

(Z)-2-(4-Bromophenyl)-3-(4-methoxyphenyl)acrylonitrile (3cc). Rf = 0.35 (5% ethyl acetate in hexane); Light yellow solid; yield 84% (81 mg); mp 128-130 ºC; 1H NMR (700 MHz, CDCl3) δ 7.88 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.45 (s, 1H), 6.98 (d, J = 8.6 Hz, 2H), 3.88 (s, 3H); 13C NMR (175 MHz, CDCl3) δ 161.8, 142.4, 134.0, 132.3, 131.5, 127.4, 126.4, 123.0, 118.3, 114.6, 107.7, 55.6; IR (KBr) ῡ = 2923, 2852, 2359, 2214, 1511, 1273; HRMS (ESI-TOF) calcd for C16H12NOBr (M +Na)+ 335.9994, found 335.9995.

(Z)-3-(4-Chlorophenyl)-2-(*p*-tolyl)acrylonitrile (3be). R_f = 0.4 (5% ethyl acetate in hexane); Off white solid; yield 36% (40 mg); mp 118-120 ºC (lit.[2] 119-120 ºC); ^{1}H NMR (700 MHz, DMSO) δ 8.01 (s, 1H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (175 MHz, DMSO) δ 140.4, 139.3, 134.9, 132.7, 130.8, 130.7, 129.8, 129.1, 125.7, 117.7, 110.9, 20.8.

(Z)-3-(2-Chlorophenyl)-2-(4-chlorophenyl)acrylonitrile (3dd). R_f = 0.5 (5% ethyl acetate in hexane); White solid; yield 93% (110 mg); mp 110-112 ºC (lit.[45] 109-110 ºC); ^{1}H NMR (700 MHz, DMSO) δ 8.13 (s, 1H), 7.96 (dd, *J* = 7.0, 1.8 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.67 – 7.63 (m, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.57 – 7.51 (m, 2H); ^{13}C NMR (175 MHz, DMSO) δ 140.2, 134.5, 133.4, 132.3, 131.9, 131.8, 129.8, 129.8, 129.4, 127.9, 127.6, 116.7, 113.8.

(Z)-2-Mesityl-3-(4-methoxyphenyl)acrylonitrile (3fc). Rf = 0.15 (5% ethyl acetate in hexane); Colourless liquid; yield 71% (74 mg); 1H NMR (400 MHz, CDCl3) δ 7.32 (s, 1H), 6.94 (s, 2H), 6.93 – 6.88 (m, 2H), 6.71 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 2.33 (s, 3H), 2.20 (s, 6H); 13C NMR (100 MHz, CDCl3) δ 161.1, 144.9, 138.8, 136.3, 131.2, 129.2, 128.9, 127.0, 120.0, 114.2, 109.1, 55.3, 21.2, 19.7; IR (KBr) ῡ = 2961, 2811, 2248, 1931, 1661, 1154 cm-1; HRMS (ESI-TOF) calcd for C19H19NO (M +H)+ 278.1539, found 278.1548.

(Z)-2-(4-Chlorophenyl)-3-(4-methoxyphenyl)acrylonitrile (3dc). R_f = 0.2 (5% ethyl acetate in hexane); Off white solid; yield 95% (100 mg); mp 118-120 ºC (lit.[42] 128-129 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.44 (s, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 142.2, 134.7, 133.4, 131.3, 129.2, 127.0, 126.3, 118.2, 114.5, 107.5, 55.5.

(Z)-3-(Furan-2-yl)-2-(naphthalen-1-yl)acrylonitrile (3hf): R_f = 0.4 (5% ethyl acetate in hexane); Yellow color liquid; yield 82% (72 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 1.2 Hz, 1H), 7.62 – 7.46 (m, 4H), 7.24 (d, *J* = 3.6 Hz, 1H), 7.21 (s, 1H), 6.62 (dd, *J* = 3.4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 145.1, 134.1, 134.0, 132.9, 130.9, 130.0, 128.9, 127.4, 127.2, 126.6, 125.5, 124.7, 118.7, 115.5, 112.9, 106.3; IR (KBr) $\bar{\upsilon}$ = 3141, 3058, 2924, 2207, 1614, 1471, 1248 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{11}NO$ $(M+Na)^+$ 268.0733, found 268.0732.

(Z)-2-(4-Chlorophenyl)-3-(furan-2-yl)acrylonitrile (3df). R_f = 0.25 (5% ethyl acetate in hexane); Brown solid; yield 94% (85 mg); mp 74-76 ºC (lit.[42] 80-88 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.36 (s, 1H), 7.21 (d, *J* = 3.6 Hz, 1H), 6.59 (dd, *J* = 3.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 145.2, 135.1, 132.2, 129.3, 128.2, 126.8, 117.5, 115.7, 112.9, 106.4

(E)-3-Phenyl-2-(thiophen-2-yl)acrylonitrile (3ja). R_f = 0.4 (5% ethyl acetate in hexane); Yellow solid; yield 85% (100 mg); mp 78-80 ºC (lit.[46] 76-77 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 6.4 Hz, 2H), 7.49 – 7.42 (m, 3H), 7.40 – 7.37 (m, 2H), 7.31 (d, *J* = 5.2 Hz, 1H), 7.08 (dd, *J* = 5.2, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 139.3, 133.5, 130.7, 129.3, 129.1, 128.3, 127.4, 126.4, 117.0, 106.3.

(E)-3-(Furan-2-yl)-2-(thiophen-2-yl)acrylonitrile (3fj): Rf = 0.4 (5% ethyl acetate in hexane); Yellow solid; yield 81% (92 mg); mp 84-86 ºC; 1H NMR (400 MHz, CDCl3) δ 7.59 (d, J = 1.2 Hz, 1H), 7.35 (d, J = 3.6 Hz, 1H), 7.29 (d, J = 5.2 Hz, 1H), 7.19 (s, 1H), 7.10 (d, J

= 3.6 Hz, 1H), 7.06 (dd, J = 5.2, 3.6 Hz, 1H), 6.57 (dd, J = 3.6, 1.6 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 149.8, 145.1, 138.8, 128.4, 127.2, 126.2, 125.9, 116.8, 115.3, 113.0, 102.6; IR (KBr) ῡ = 3115, 2923, 2853, 2216, 1609, 1468, 1225, 745; HRMS (ESI-TOF) calcd for C11H17NOS (M +H)+ 202.0321, found 202.0332.

(Z)-2-(4-Chlorophenyl)-3-(thiophen-2-yl)acrylonitrile (3dg). R_f = 0.4 (5% ethyl acetate in hexane); Yellow solid; yield 76% (80 mg); mp 115-117 ºC (lit.[42] 135-136 ºC); ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.95 (d, *J* = 4.8 Hz, 1H), 7.78 (d, *J* = 3.4 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.28 (dd, *J* = 4.9, 3.8 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 137.4, 136.3, 135.0, 133.5, 132.3, 132.0, 129.2, 128.1, 127.2, 117.8, 104.9.

(E)-2,3-Di(thiophen-2-yl)acrylonitrile (3jg). R_f = 0.35 (5% ethyl acetate in hexane); Yellow solid; yield 74% (90 mg); mp 130-132 ºC (lit.[46] 130-131 ºC); ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.90 (d, *J* = 5.0 Hz, 1H), 7.75 (d, *J* = 3.5 Hz, 1H), 7.66 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.39 (dd, *J* = 3.5, 0.8 Hz, 1H), 7.25 (dd, *J* = 5.0, 3.8 Hz, 1H), 7.16 (dd, *J* = 5.0, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 137.6, 132.1, 132.1, 130.0, 128.2, 127.9, 127.0, 125.9, 117.0, 103.2; IR (KBr) ῡ = 3097, 3081, 2185, 1545, 1430, 750, 713; HRMS (ESI-TOF) calcd for $C_{11}H_7NS_2$ $(M+Na)^+$ 239.9912, found 239.9916

(Z)-3-(4-((4-Chlorobenzyl)thio)phenyl)-2-(*p*-tolyl)acrylonitrile. R_f = 0.3 (5% ethyl acetate in hexane); White solid; yield 48% (80 mg); mp 114-116 ºC; ^{1}H NMR (700 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.36 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 141.0, 139.6, 138.9, 136.3, 131.8, 131.1, 130.9, 130.7, 129.7, 129.5, 128.4, 127.3, 125.6, 118.1, 109.2, 34.7, 20.7; IR (KBr) ῡ = 3026, 2923, 2853, 2212, 1588, 1512, 1491, 746 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{18}NSCl$ $(M+Na)^+$ 398.0741, found 398.0731.

(Z)-3-(4-((4-Fluorobenzyl)thio)phenyl)-2-(p-tolyl)acrylonitrile. R_f = 0.3 (5% ethyl acetate in hexane); Off white solid; yield 73% (115 mg); mp 120-122 ºC; ^{1}H NMR (700 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.49 – 7.42 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.8 Hz, 2H), 4.35 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 161.3 (d, $^1J_{CF}$ = 243.3 Hz), 141.0, 139.9, 138.9, 133.3 (d, $^4J_{CF}$ = 2.9 Hz), 131.1, 130.8, 130.8, 129.7, 129.5, 127.3, 125.5, 118.1, 115.2 (d, $^2J_{CF}$ = 21.3 Hz), 109.1, 34.7, 20.7; IR (KBr) $\bar{\upsilon}$ = 2923, 2853, 2211, 1600, 1510, 754; HRMS (ESI-TOF) calcd for $C_{23}H_{18}NSF$ $(M+Na)^+$ 382.1036, found 382.1034.

(Z)-3-(4-((4-Chlorobenzyl)thio)phenyl)-2-(3,5-dimethoxyphenyl)acrylonitrile. R_f = 0.15 (5% ethyl acetate in hexane); Light yellow solid; yield 74% (106 mg); mp 98-104 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.41 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 3H), 7.24 (s, 1H), 6.76 (d, *J* = 2.2 Hz, 2H), 6.46 (t, *J* = 2.1 Hz, 1H), 4.13 (s, 2H), 3.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 141.8, 140.3, 136.6, 135.3, 133.4, 131.3, 130.2, 129.9, 129.0, 128.5, 118.2, 111.1, 104.4, 101.4, 55.7, 37.3; IR (KBr) $\bar{\upsilon}$ = 2925, 2852, 2211, 1598, 1491, 1206, 737 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{20}NO_2SCl$ $(M+Na)^+$ 444.0795, found 444.0770.

(Z)-2-(4-Chlorophenyl)-3-(4-((4-fluorobenzyl)thio)phenyl)acrylonitrile. R_f = 0.3 (5% ethyl acetate in hexane); Light yellow solid; yield 67% (100 mg); mp 160-162 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.39 (m, 3H), 7.37 – 7.27 (m, 4H), 7.00 (t, *J* = 8.6 Hz, 2H), 4.18 (s, 2H); 13C NMR (100 MHz, CDCl3) δ 162.2 (d, $^1J_{CF}$ = 246.2 Hz), 141.6, 140.7, 135.2, 133.0, 132.2 (d, $^4J_{CF}$ = 3.2 Hz), 130.9, 130.4 (d, $^3J_{CF}$ = 8.1 Hz), 129.7, 129.3, 128.3, 127.2, 117.8, 115.6 (d, $^2J_{CF}$ = 21.6 Hz), 109.7, 37.0; ^{19}F NMR (376 MHz, CDCl3) δ -114.8; IR (KBr) $\bar{\upsilon}$ = 3049, 2922, 2853, 2210, 1697, 1592, 755; HRMS (ESI-TOF) calcd for $C_{22}H_{15}NSClF$ $(M+Na)^+$ 402.0490, found 402.0484.

(Z)-3-(4-((4-Chlorobenzyl)thio)phenyl)-2-phenylacrylonitrile. R_f = 0.3 (5% ethyl acetate in hexane); Yellow solid; yield 65% (120 mg); mp 109-111 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 7.4 Hz, 2H), 7.48 – 7.38 (m, 4H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.26 (m, 4H), 4.16 (s, 2H); ^{13}C NMR (175 MHz, DMSO-d_6) δ 142.2, 139.9, 136.3, 133.9, 131.8, 130.8, 130.7, 129.6, 129.2, 129.2, 128.5, 127.3, 125.7, 118.1, 109.2, 34.7; IR (KBr) ῡ = 2954, 2923, 2853, 2185, 1605, 1409, 697; HRMS (ESI-TOF) calcd for $C_{22}H_{16}NSCl$ $(M)^+$ 361.0686, found 361.0717.

(E)-3-(4-((4-Fluorobenzyl)thio)phenyl)-2-(thiophen-2-yl)acrylonitrile. R_f = 0.2 (5% ethyl acetate in hexane); Yellow solid; yield 50% (98 mg); mp 90-92 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 3.5 Hz, 1H), 7.35 – 7.26 (m, 6H), 7.10 – 7.04 (m, 1H), 7.00 (t, *J* = 8.6 Hz, 2H), 4.17 (s, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 162.3 (d, $^1J_{CF}$ = 246.2 Hz), 142.8, 140.4, 139.4, 138.9, 132.4 (d, $^4J_{CF}$ = 3.2 Hz), 131.0 (s), 130.5 (d, $^3J_{CF}$ = 8.1 Hz), 129.6, 128.5, 128.3, 127.3, 126.3, 117.1, 115.7 (d, $^2J_{CF}$ = 21.6 Hz), 105.6, 37.2; IR (KBr) ῡ = 2923, 2853, 2216, 1583, 1507, 1275, 848, 751 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{14}NS_2F$ $(M+H)^+$ 352.0624, found 352.0612.

(Z)-2-(2-Chloro-4-((4-methoxybenzyl)thio)phenyl)-3-(4-methoxyphenyl)acrylonitrile. R_f = 0.2 (5% ethyl acetate in hexane); Light yellow solid; yield 36% (54 mg); mp 108-110 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 1.6 Hz, 1H), 7.27 – 7.19 (m, 3H), 7.17 – 7.09 (m, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.09 (s, 2H), 3.83 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 159.1, 147.6, 140.0, 133.3, 132.0, 131.3, 130.8, 130.0, 129.6, 128.2, 127.2, 126.0, 117.9, 114.4, 114.1, 105.4, 55.5, 55.3, 37.6; IR (KBr) ῡ = 2954, 2925, 2853, 2125, 1608, 1250, 1177, 738 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{20}NO_2SCl$ $(M+Na)^+$ 444.0795, found 444.0798.

5.6 Notes and Reference

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^{1}H and ^{13}NMR Spectra of Selected Compounds

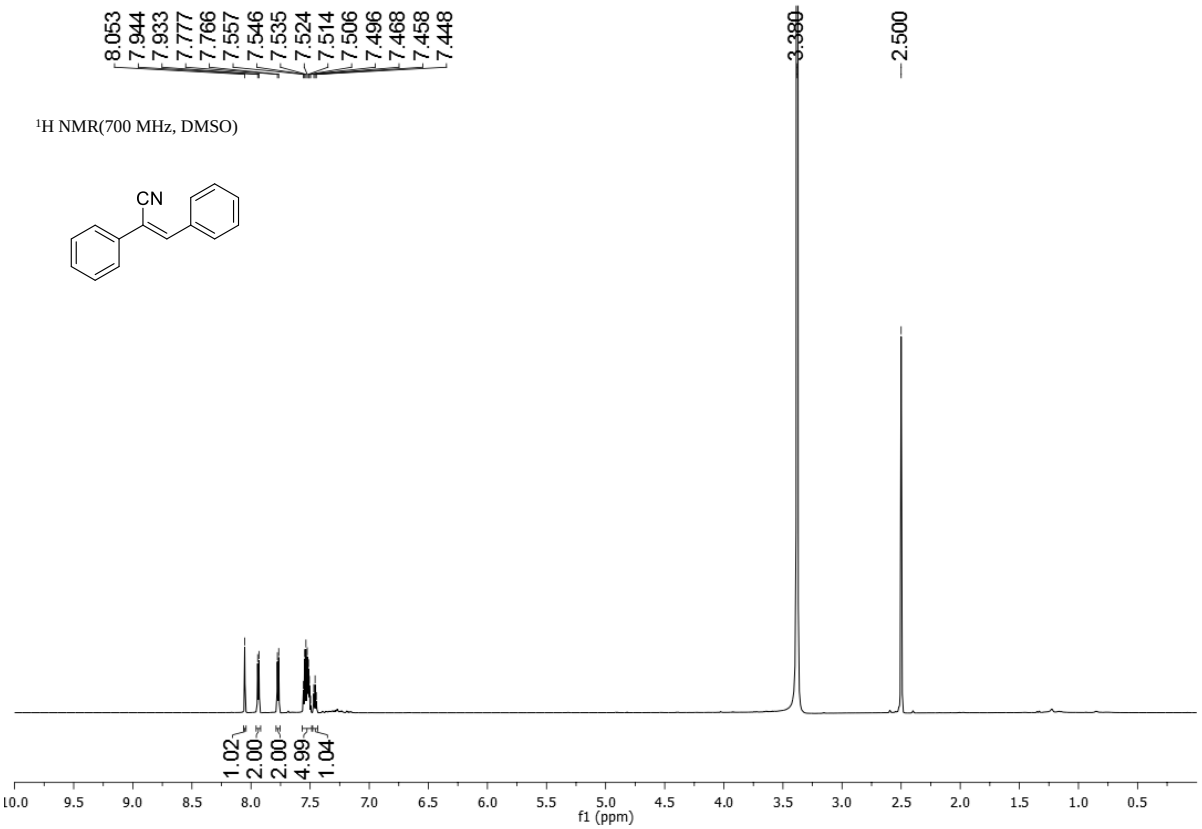


Figure 5.9. ^{1}H NMR spectrum of (Z)-2,3-diphenylacrylonitrile (**3aa**).

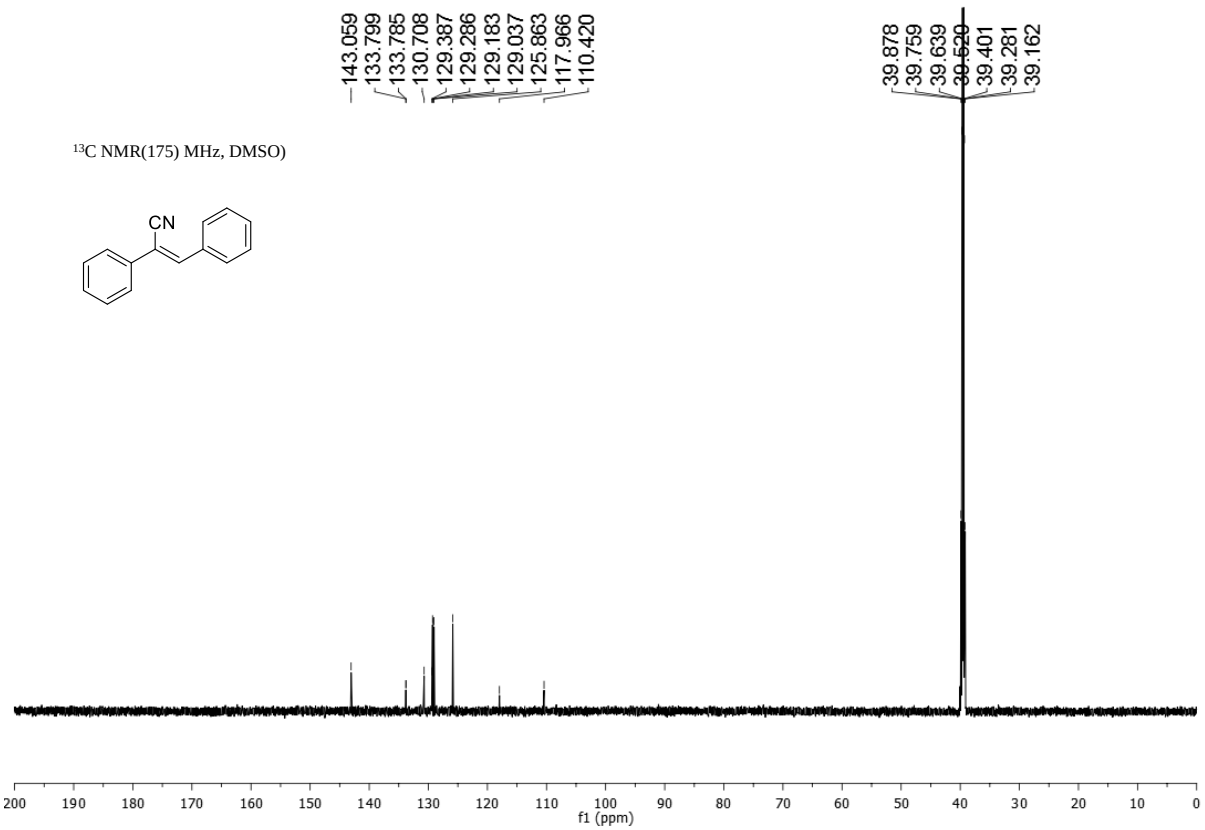


Figure 5.10. ^{13}C NMR spectrum of (Z)-2,3-diphenylacrylonitrile (**3aa**).

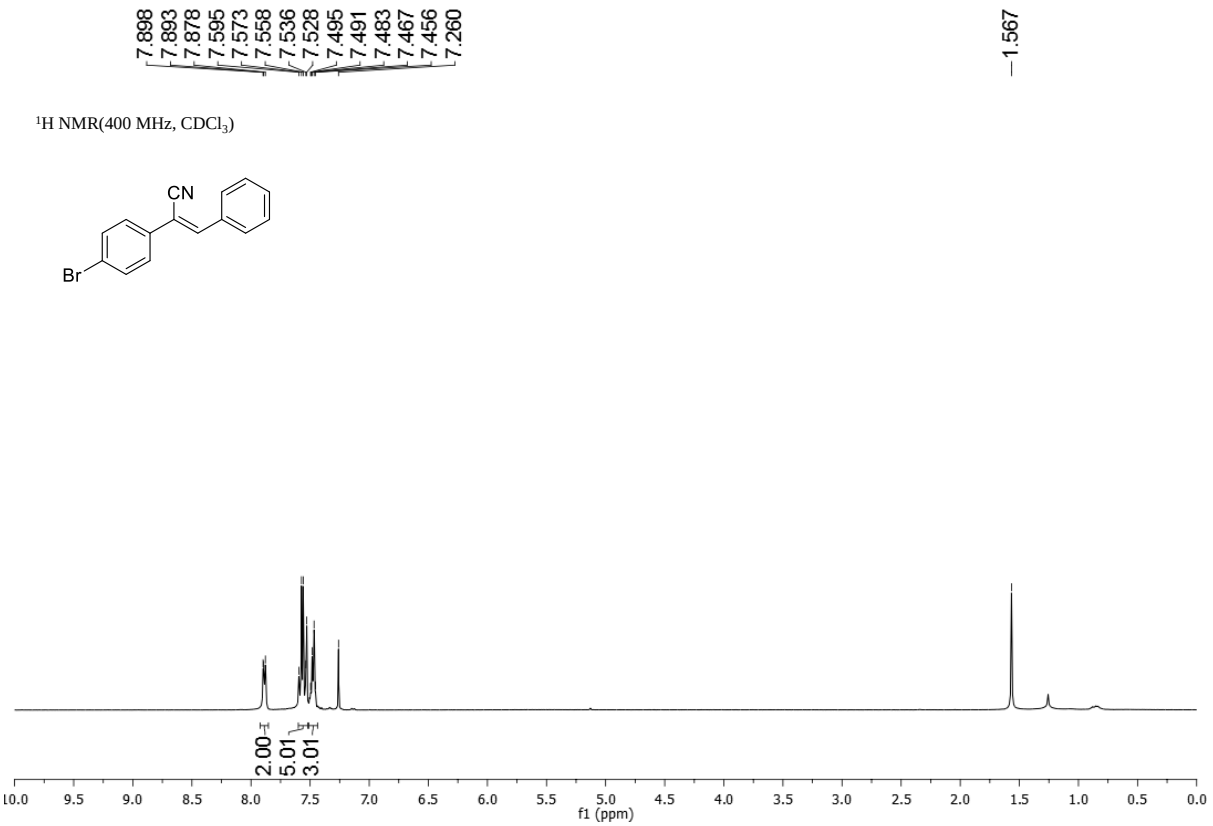


Figure 5.11 ^{1}H NMR spectrum of (Z)-2-(4-bromophenyl)-3-phenylacrylonitrile (**3ca**).

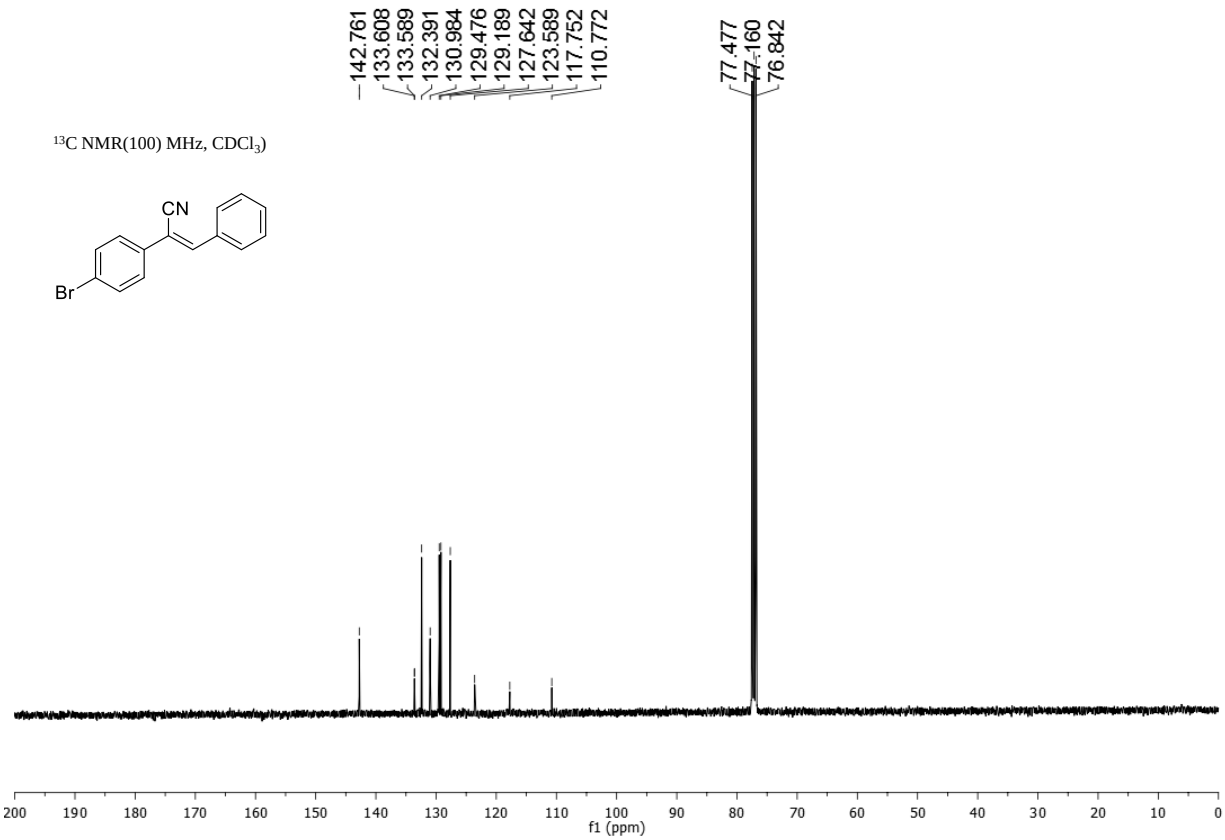


Figure 5.12. ^{13}C NMR spectrum of (Z)-2-(4-bromophenyl)-3-phenylacrylonitrile (**3ca**).

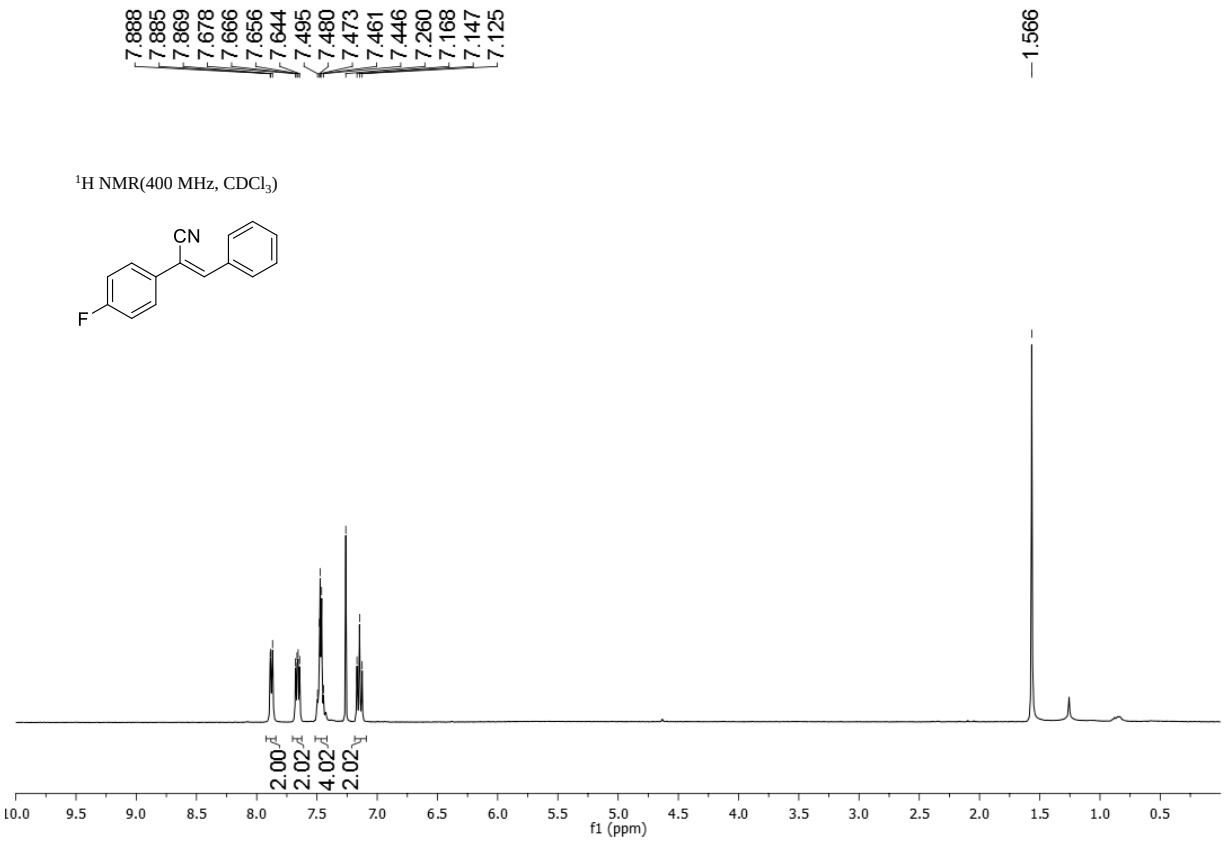


Figure 5.13. ^{1}H NMR spectrum of (Z)-2-(4-fluorophenyl)-3-phenylacrylonitrile (**3ea**).

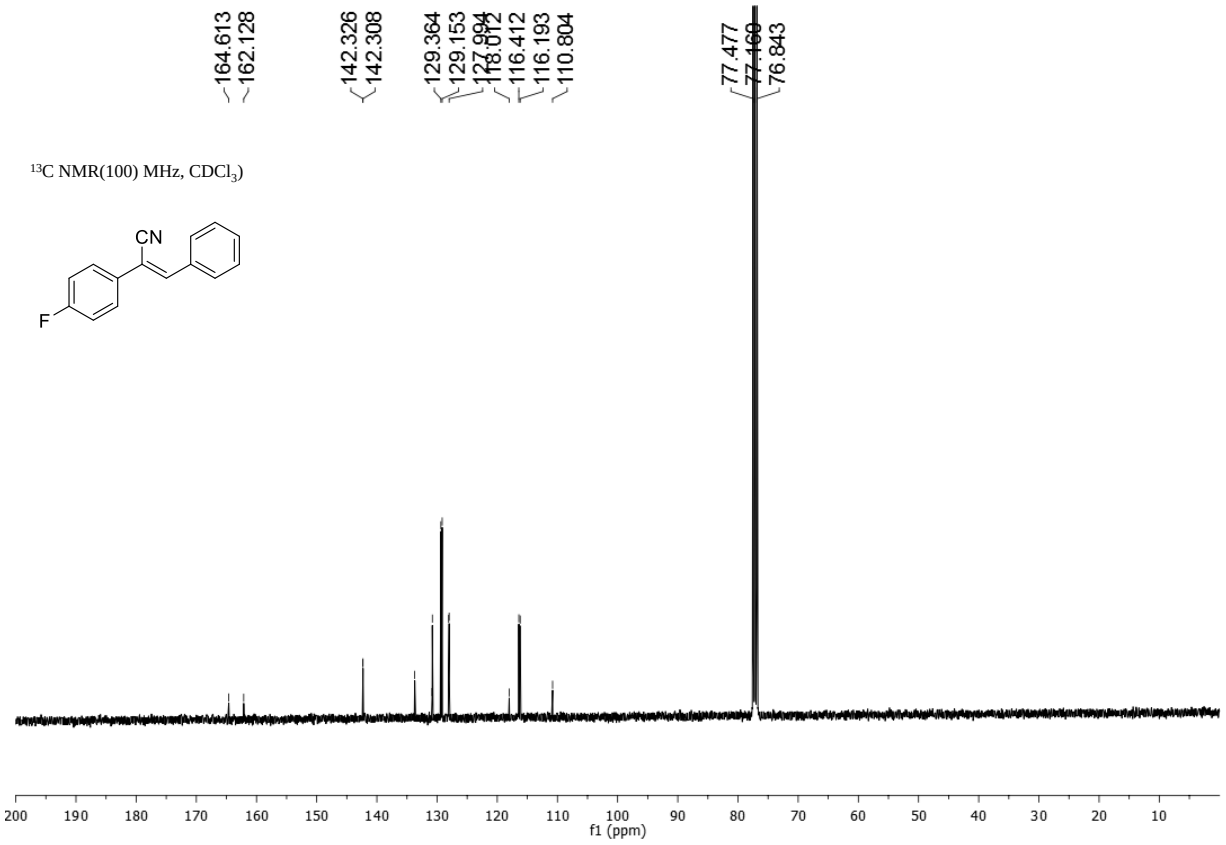


Figure 5.14. ^{13}C NMR spectrum of (Z)-2-(4-fluorophenyl)-3-phenylacrylonitrile (**3ea**).

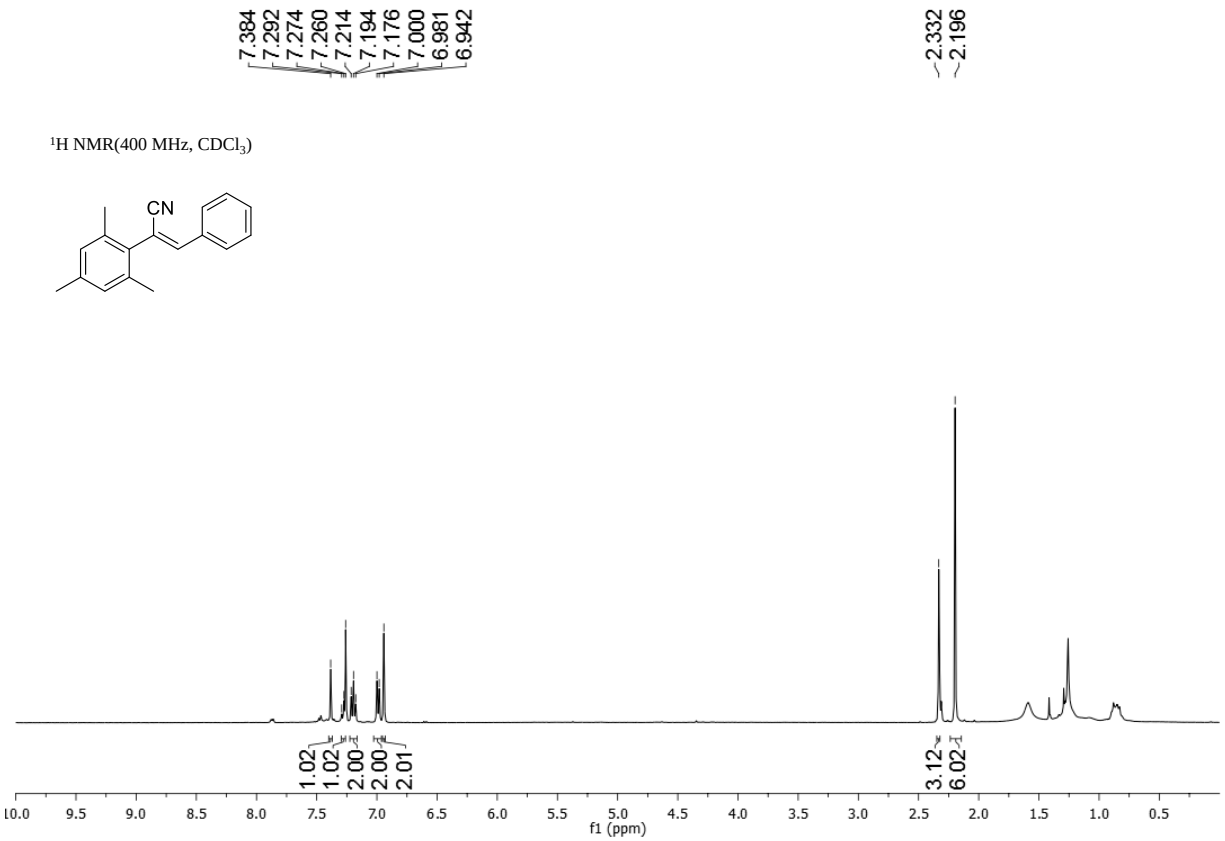


Figure 5.15. ^{1}H NMR spectrum of (Z)-2-mesityl-3-phenylacrylonitrile (**3fa**).

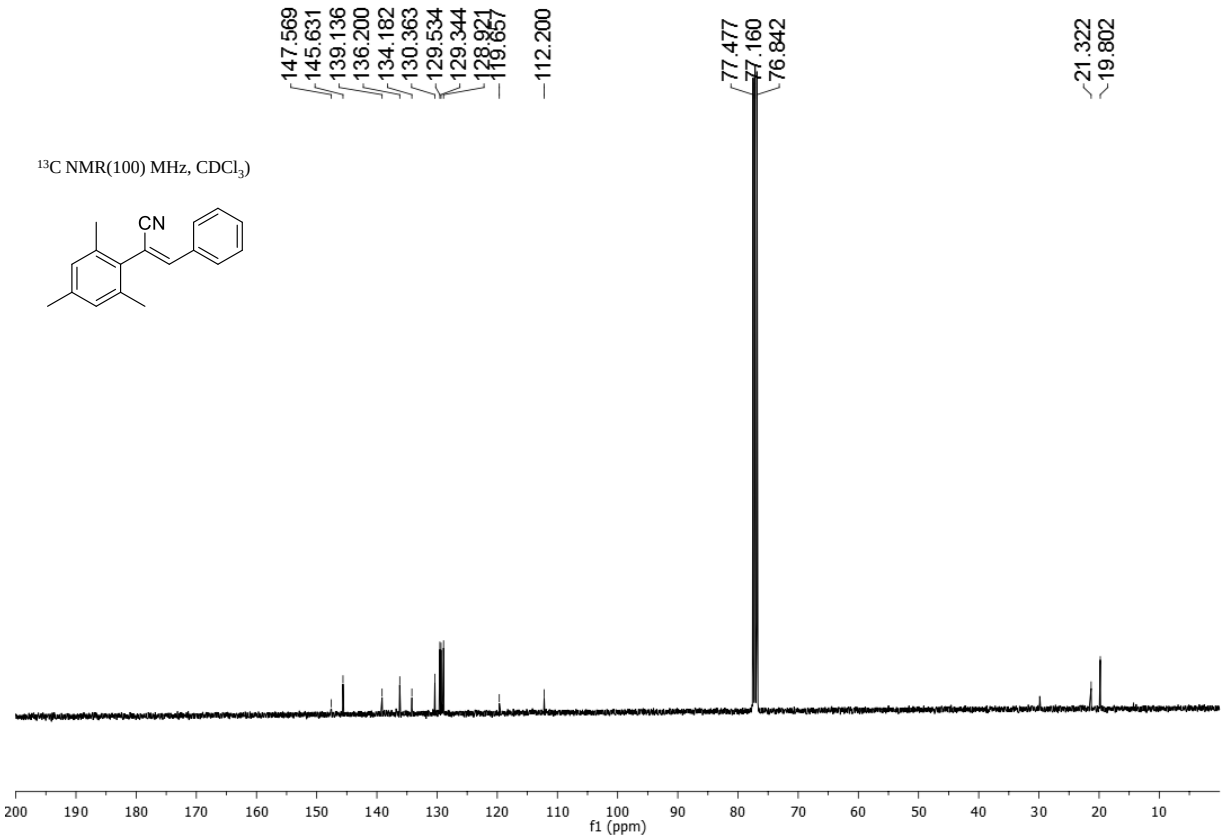


Figure 5.16. ^{13}C NMR spectrum of (Z)-2-mesityl-3-phenylacrylonitrile (**3fa**).

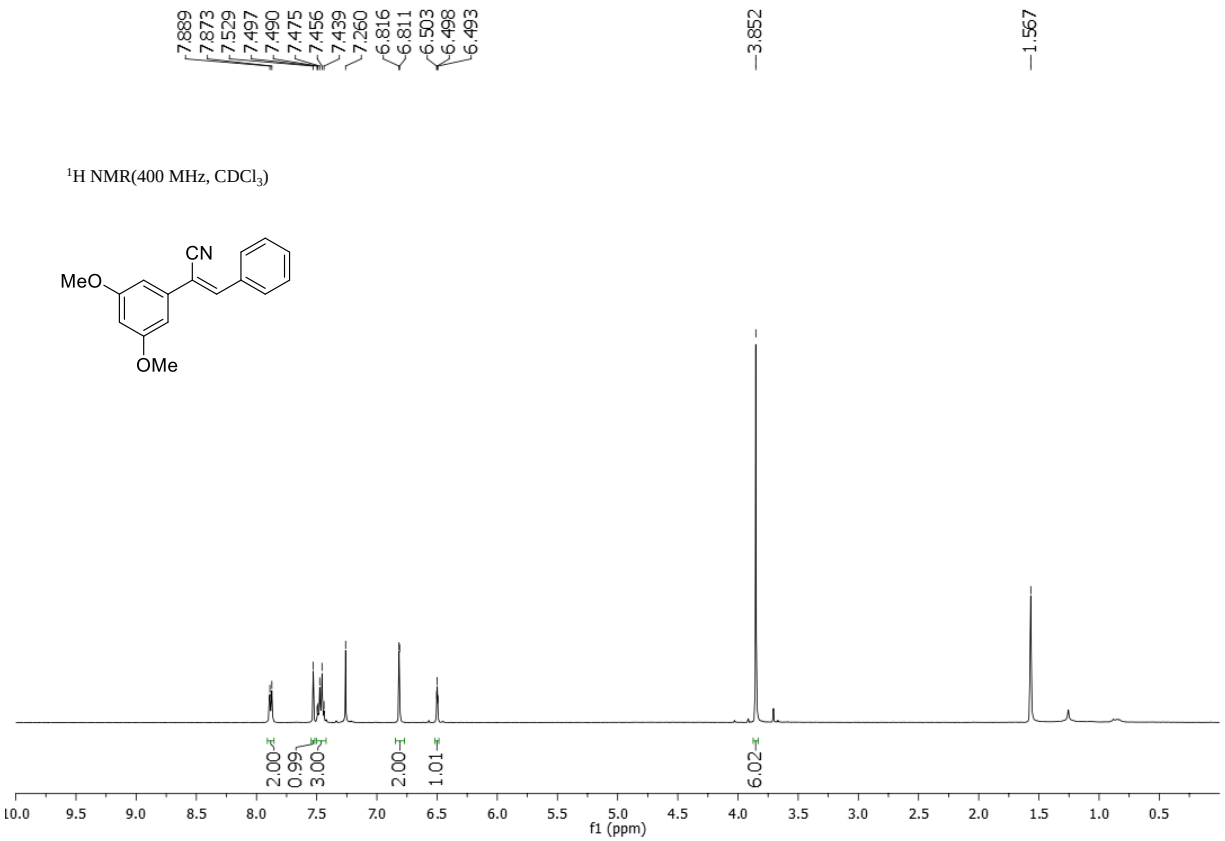


Figure 5.17. ^{1}H NMR spectrum of (Z)-2-(3,5-dimethoxyphenyl)-3-phenylacrylonitrile (**3ga**)

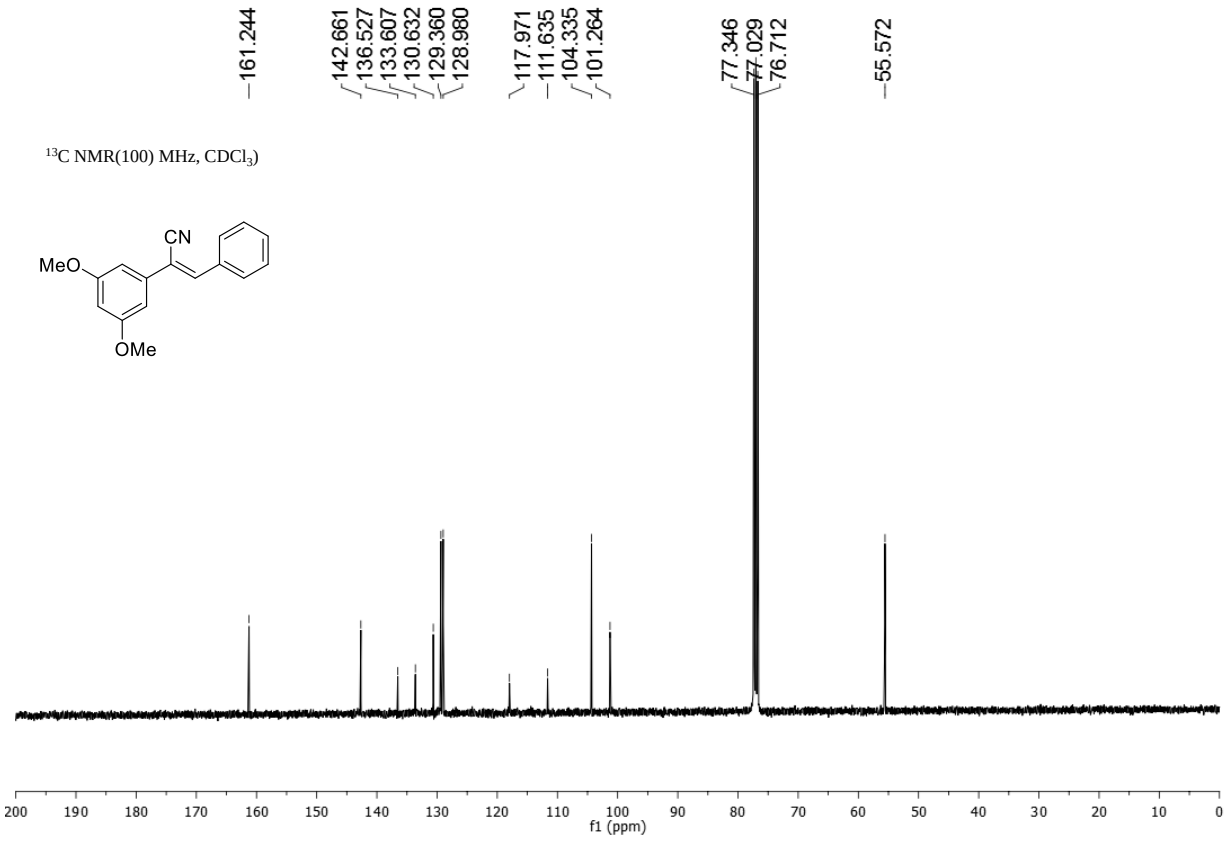
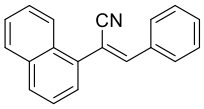


Figure 5.18 ^{13}C NMR spectrum of (Z)-2-(3,5-dimethoxyphenyl)-3-phenylacrylonitrile (**3ga**)

^{1}H NMR(400 MHz, $CDCl_3$)



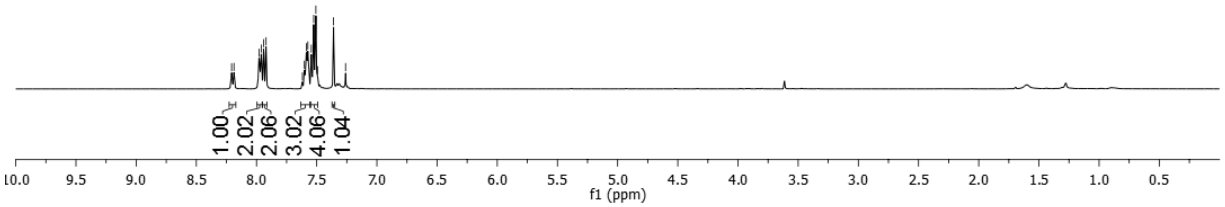
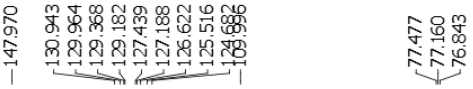
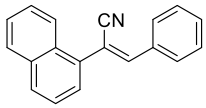


Figure 5.19. ^{1}H NMR spectrum of (Z)-2-(naphthalen-1-yl)-3-phenylacrylonitrile (**3ha**).



^{13}C NMR(100) MHz, $CDCl_3$)



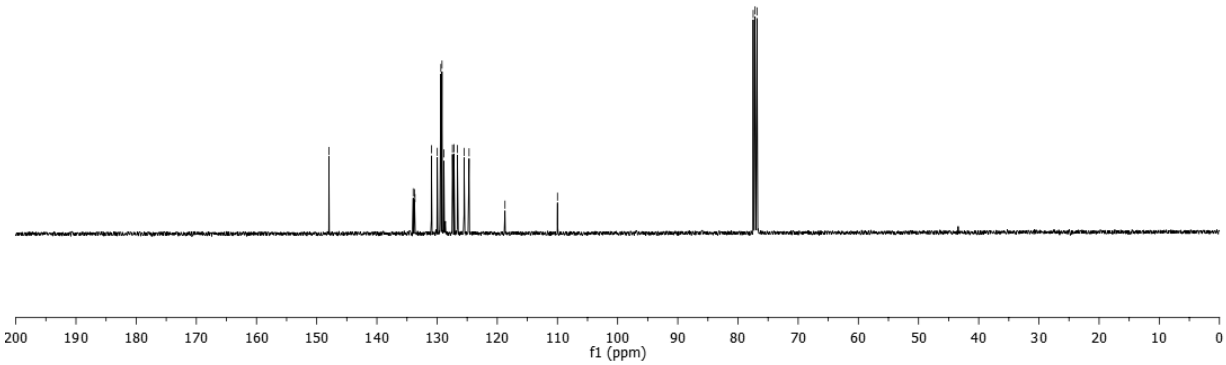


Figure 5.20. ^{13}C NMR spectrum of (Z)-2-(naphthalen-1-yl)-3-phenylacrylonitrile (**3ha**).

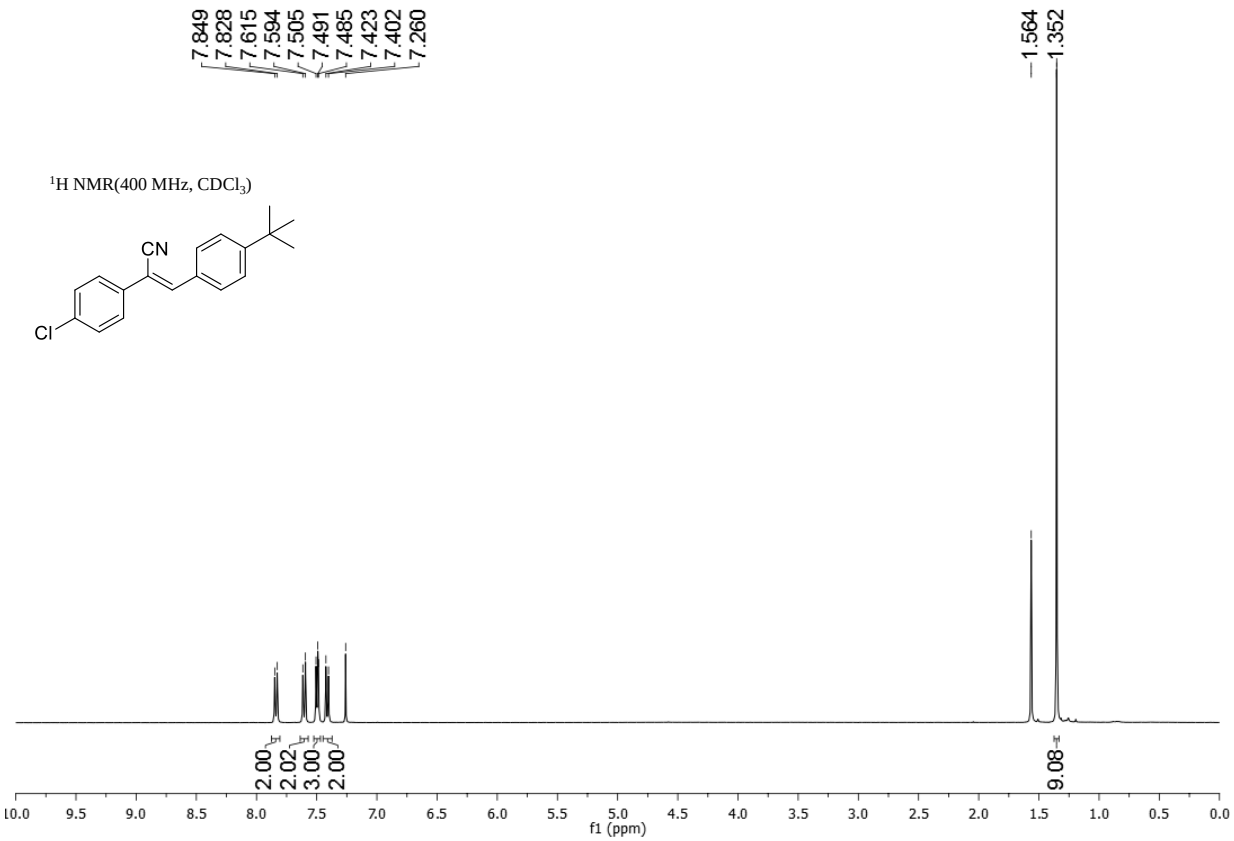


Figure 5.21. ^{1}H NMR spectrum of (Z)-3-(4-(tert-butyl)phenyl)-2-(4-chlorophenyl)acrylonitrile (**3db**).

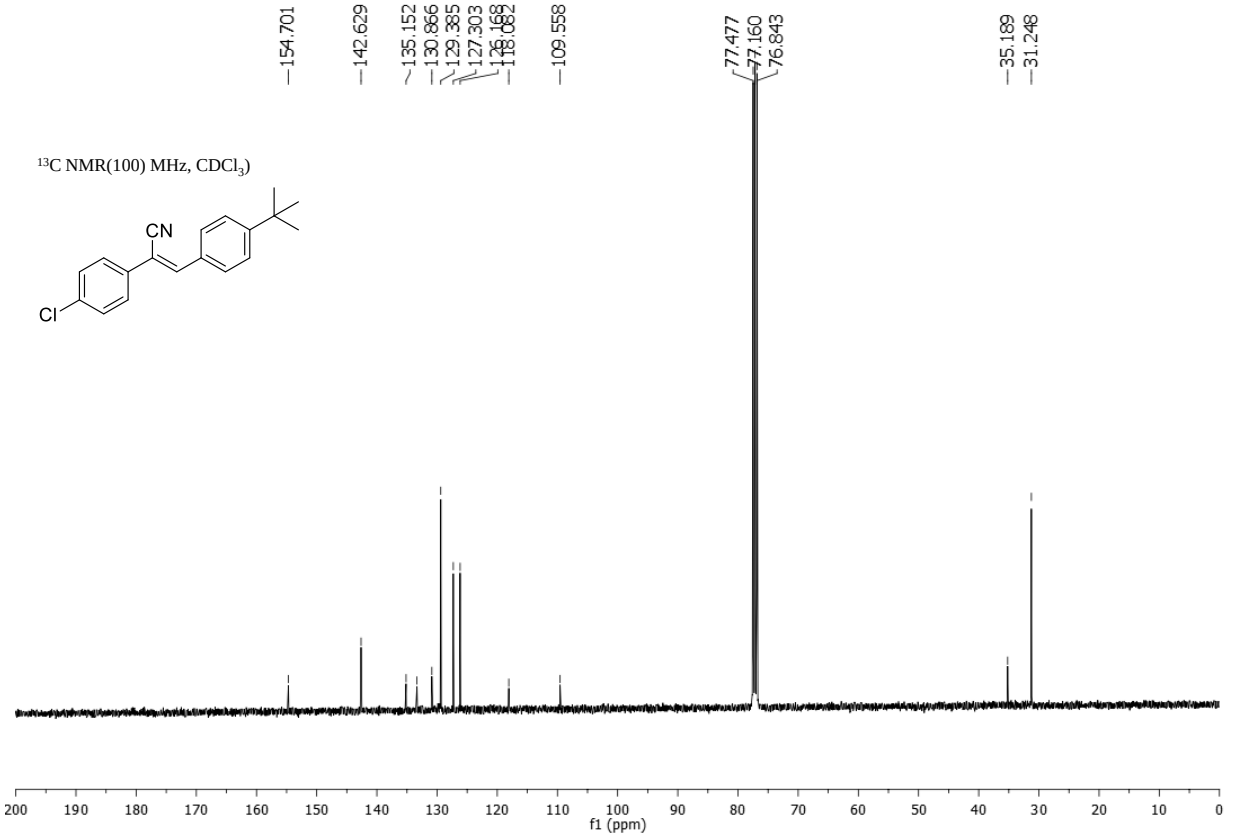


Figure 5.22 ^{13}C NMR spectrum of (Z)-3-(4-(tert-butyl)phenyl)-2-(4-chlorophenyl)acrylonitrile (**3db**).

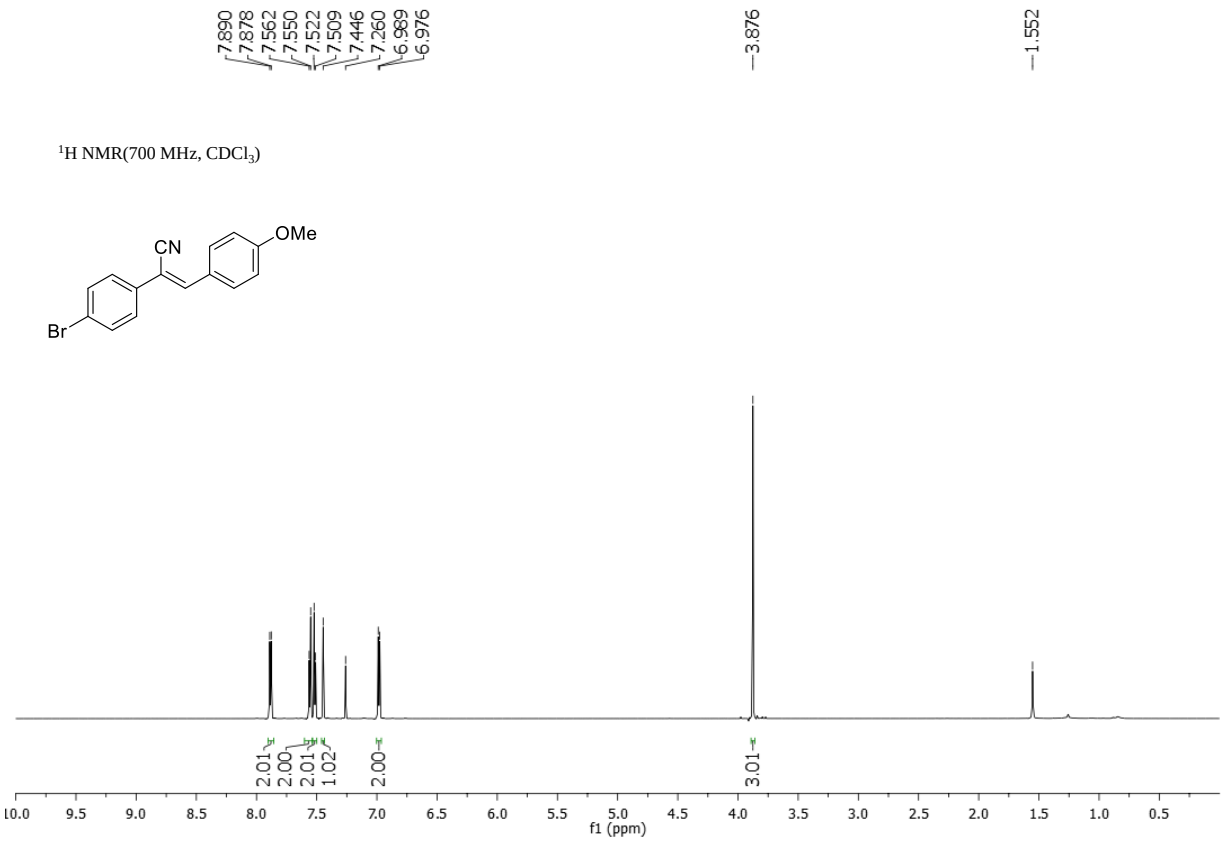


Figure 5.23. ^{1}H NMR spectrum of (Z)-2-(4-bromophenyl)-3-(4-methoxyphenyl)acrylonitrile (**3cc**).

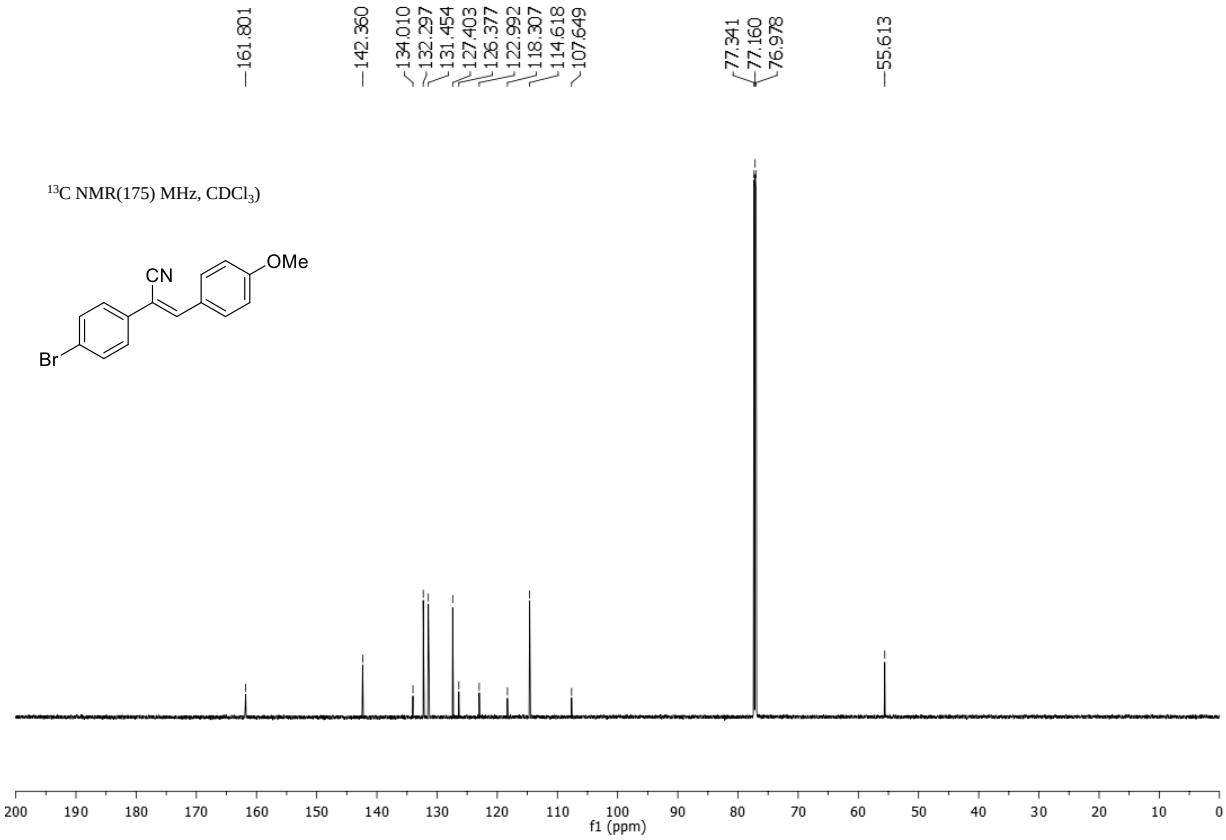


Figure 5.24. ^{13}C NMR spectrum of (Z)-2-(4-bromophenyl)-3-(4-methoxyphenyl)acrylonitrile (**3cc**).

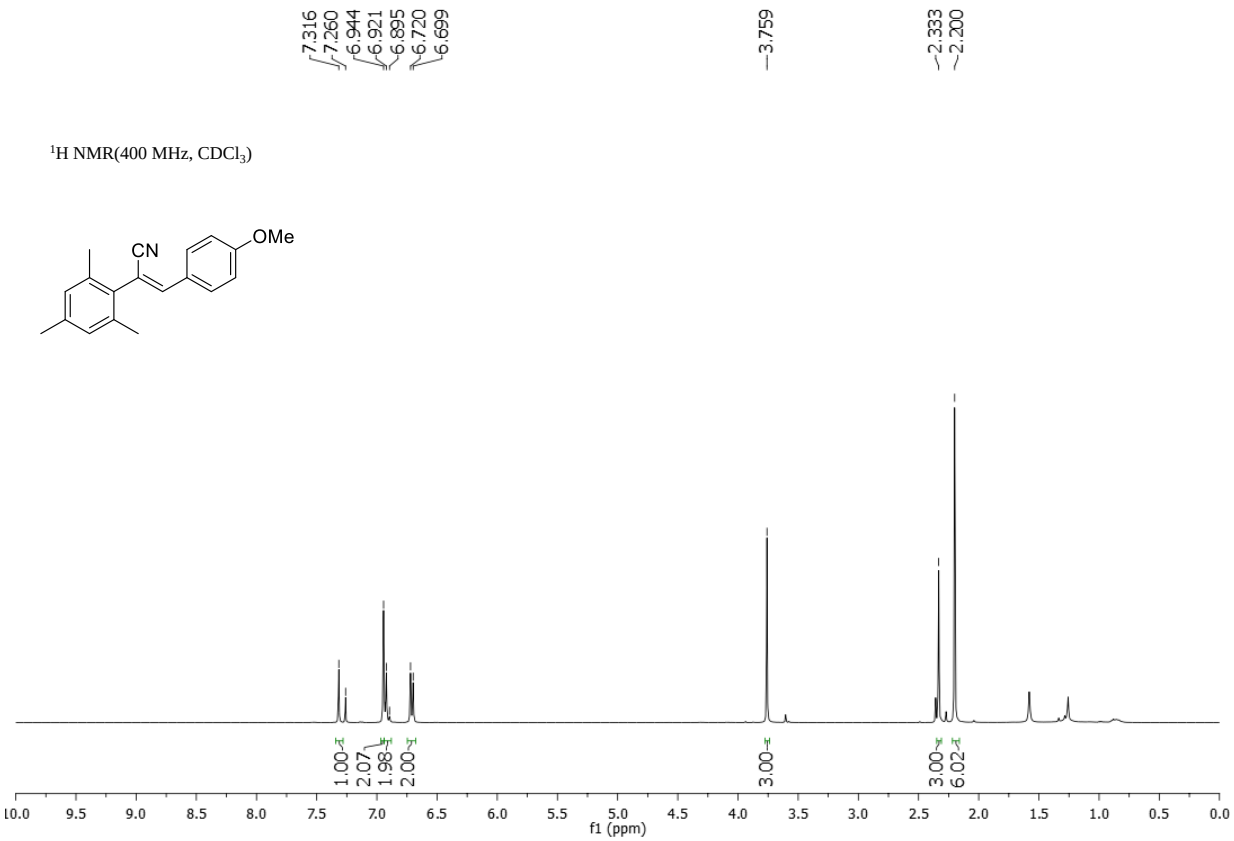


Figure 5.25. ^{1}H NMR spectrum of (Z)-2-mesityl-3-(4-methoxyphenyl)acrylonitrile (**3fc**).

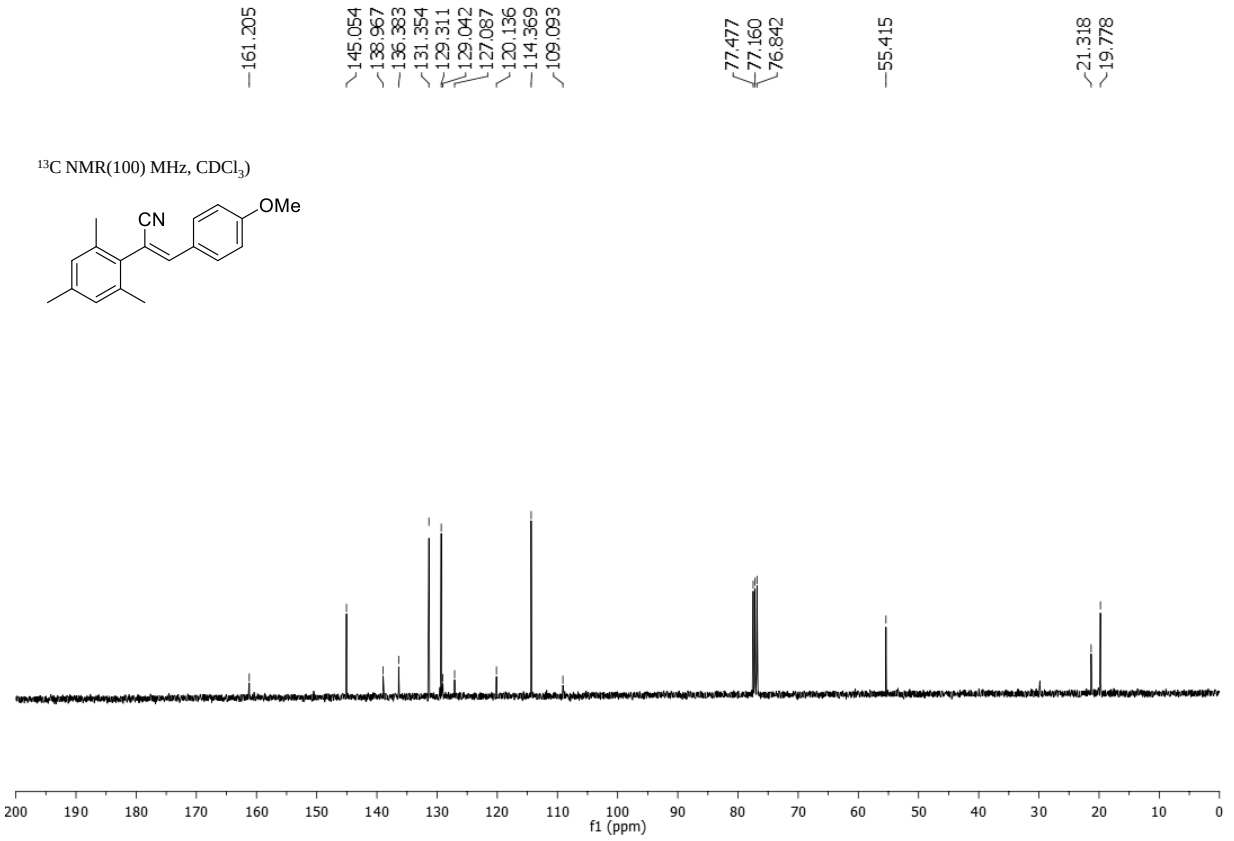


Figure 5.26. ^{13}C NMR spectrum of (Z)-2-mesityl-3-(4-methoxyphenyl)acrylonitrile (**3fc**).

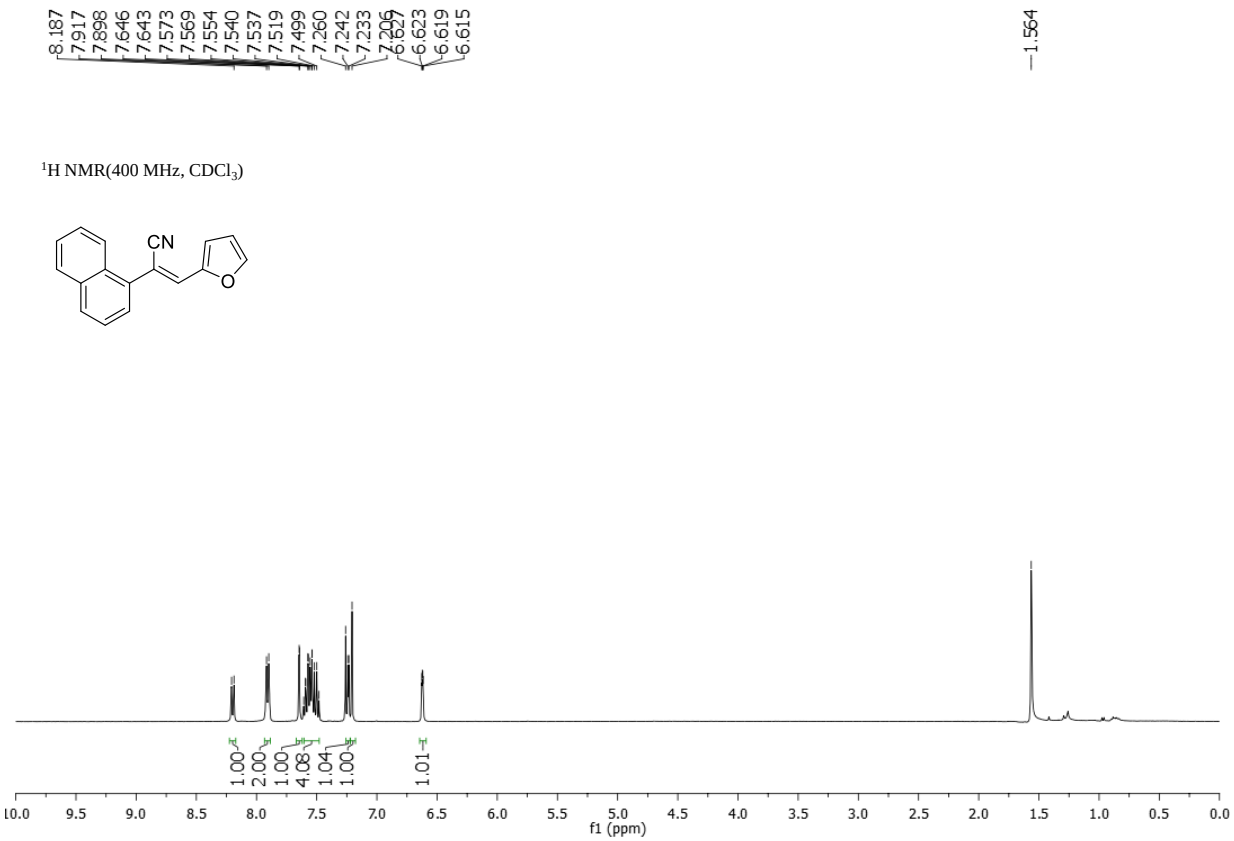


Figure 5.27. ^{1}H NMR spectrum of (Z)-3-(furan-2-yl)-2-(naphthalen-1-yl)acrylonitrile (**3hf**).

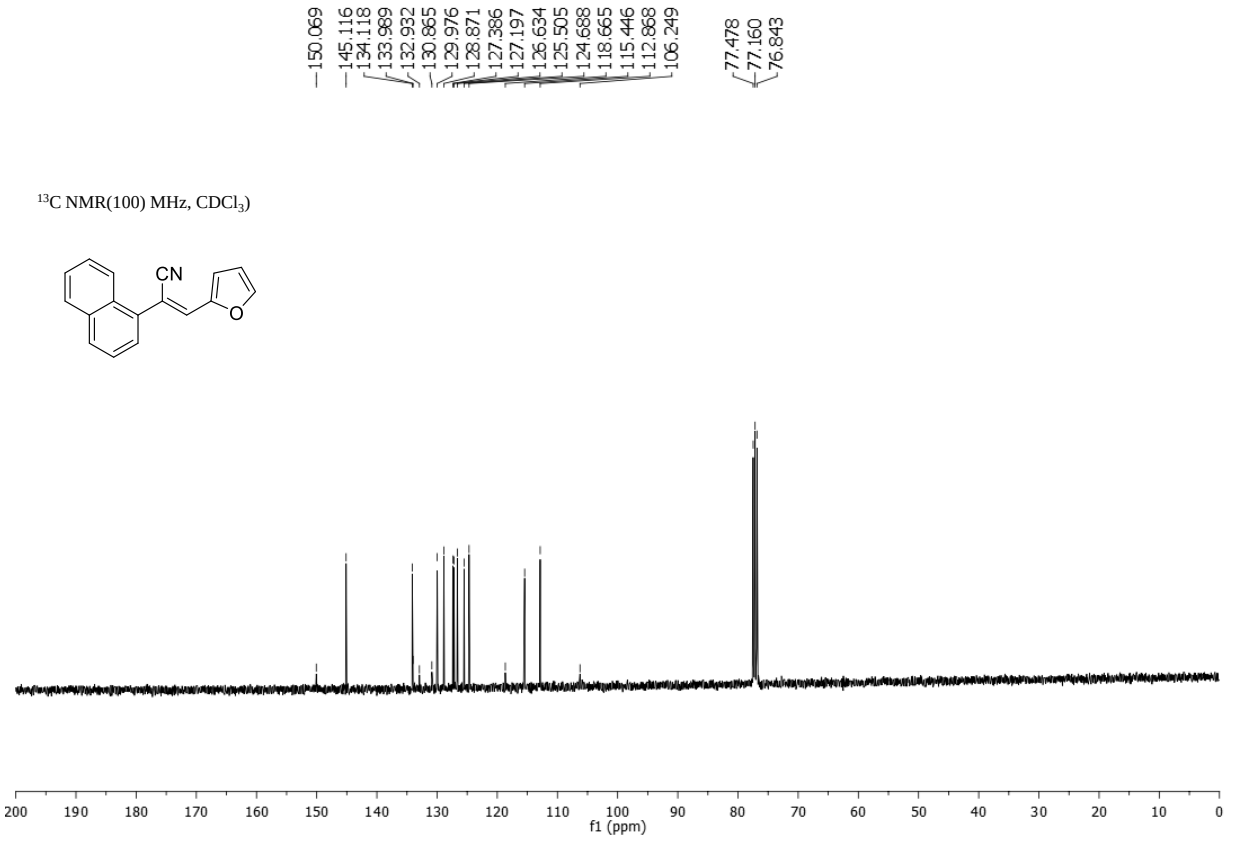


Figure 5.28. ^{13}C NMR spectrum of (Z)-3-(furan-2-yl)-2-(naphthalen-1-yl)acrylonitrile (**3hf**).

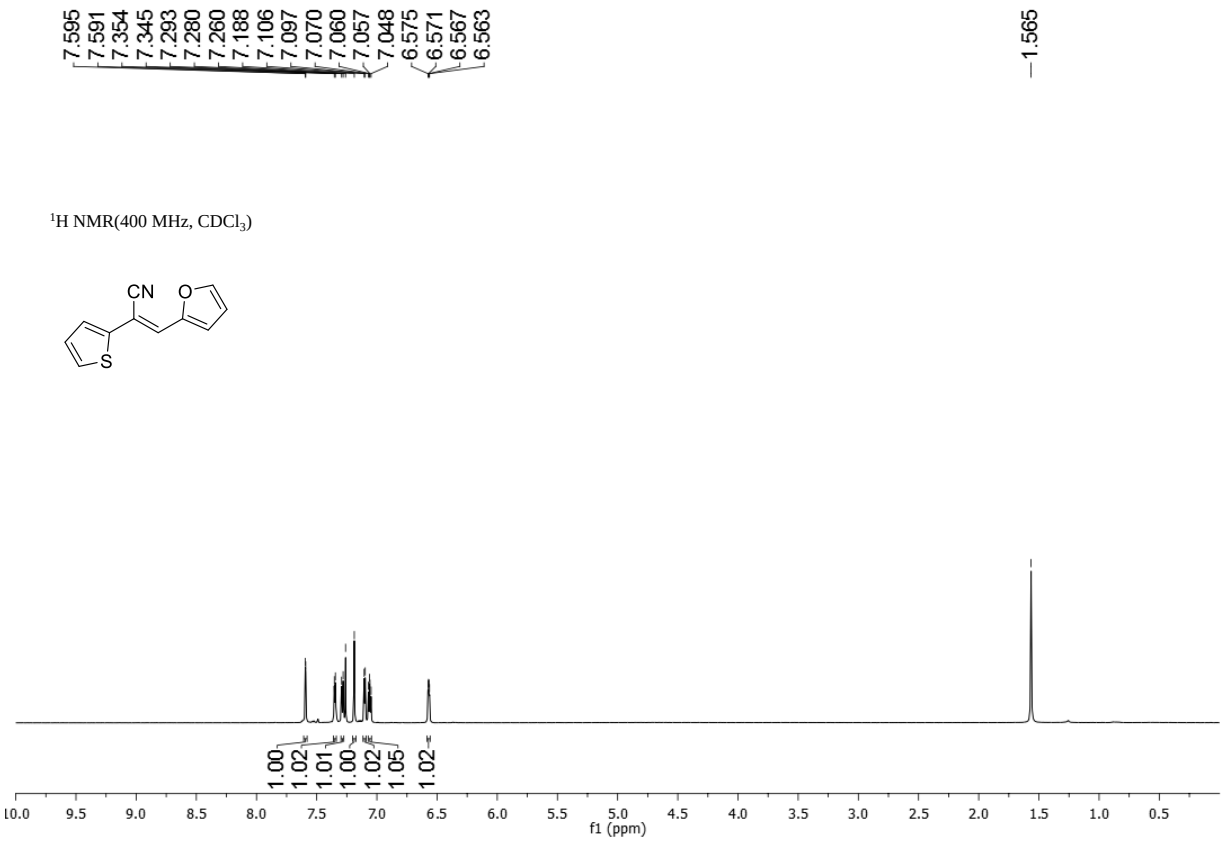


Figure 5.29. ^{1}H NMR spectrum of (E)-3-(furan-2-yl)-2-(thiophen-2-yl)acrylonitrile (**3fj**).

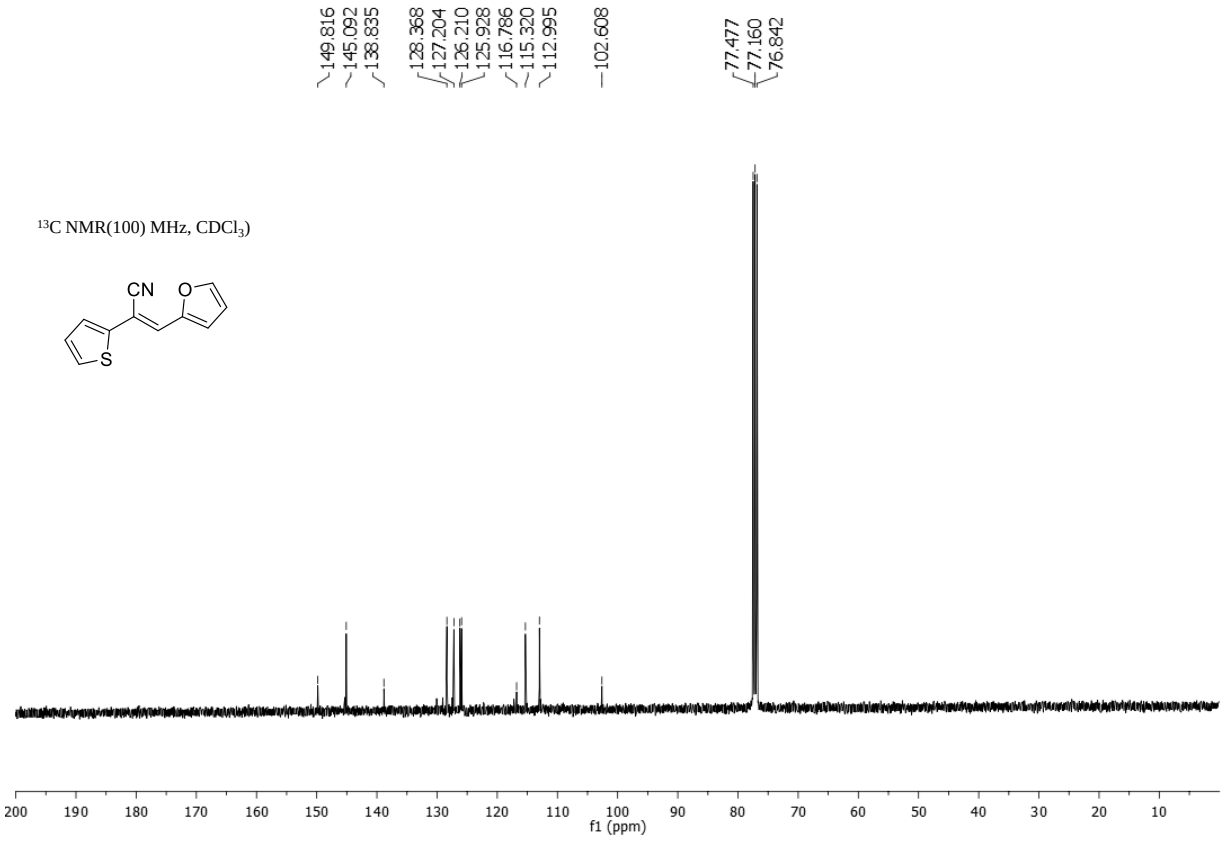


Figure 5.30. ^{13}C NMR spectrum of (E)-3-(furan-2-yl)-2-(thiophen-2-yl)acrylonitrile (**3fj**).

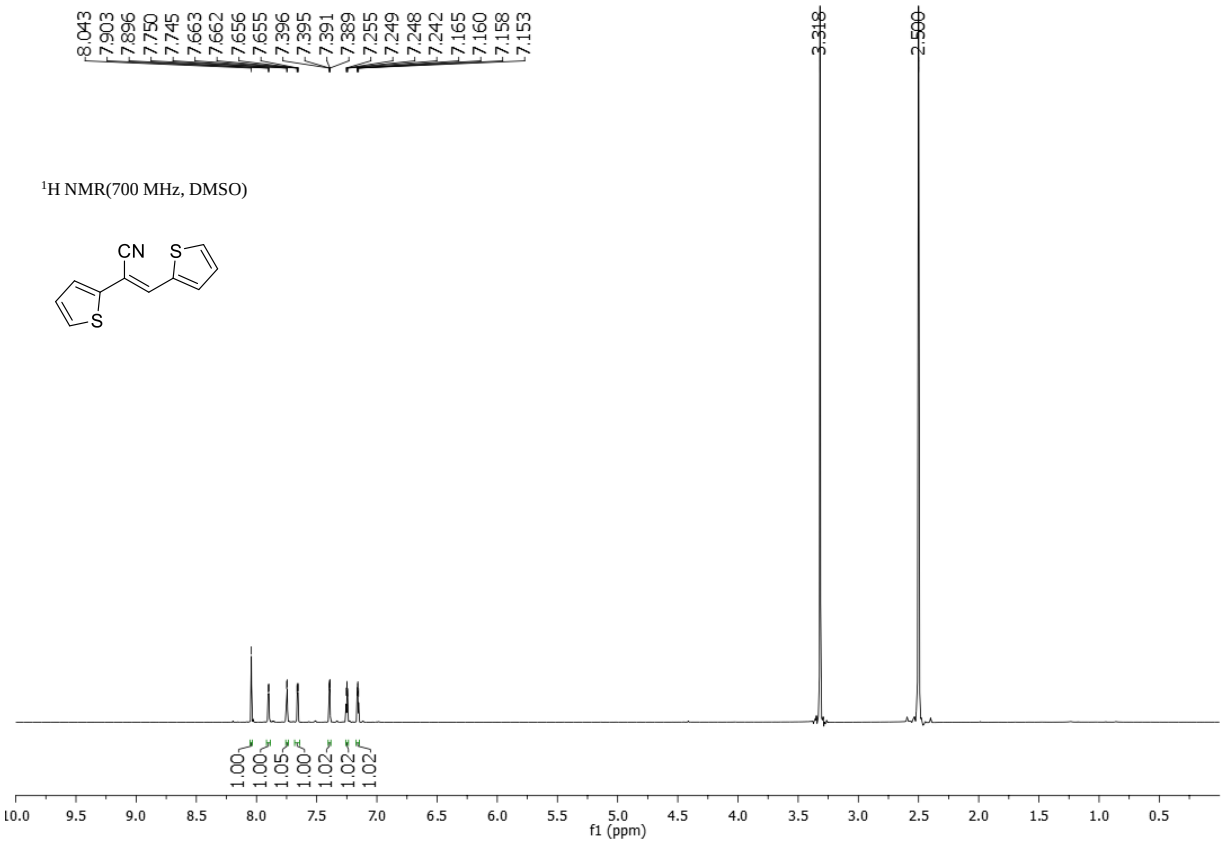


Figure 5.31. ^{1}H NMR spectrum of (E)-2,3-di(thiophen-2-yl)acrylonitrile (**3jg**).

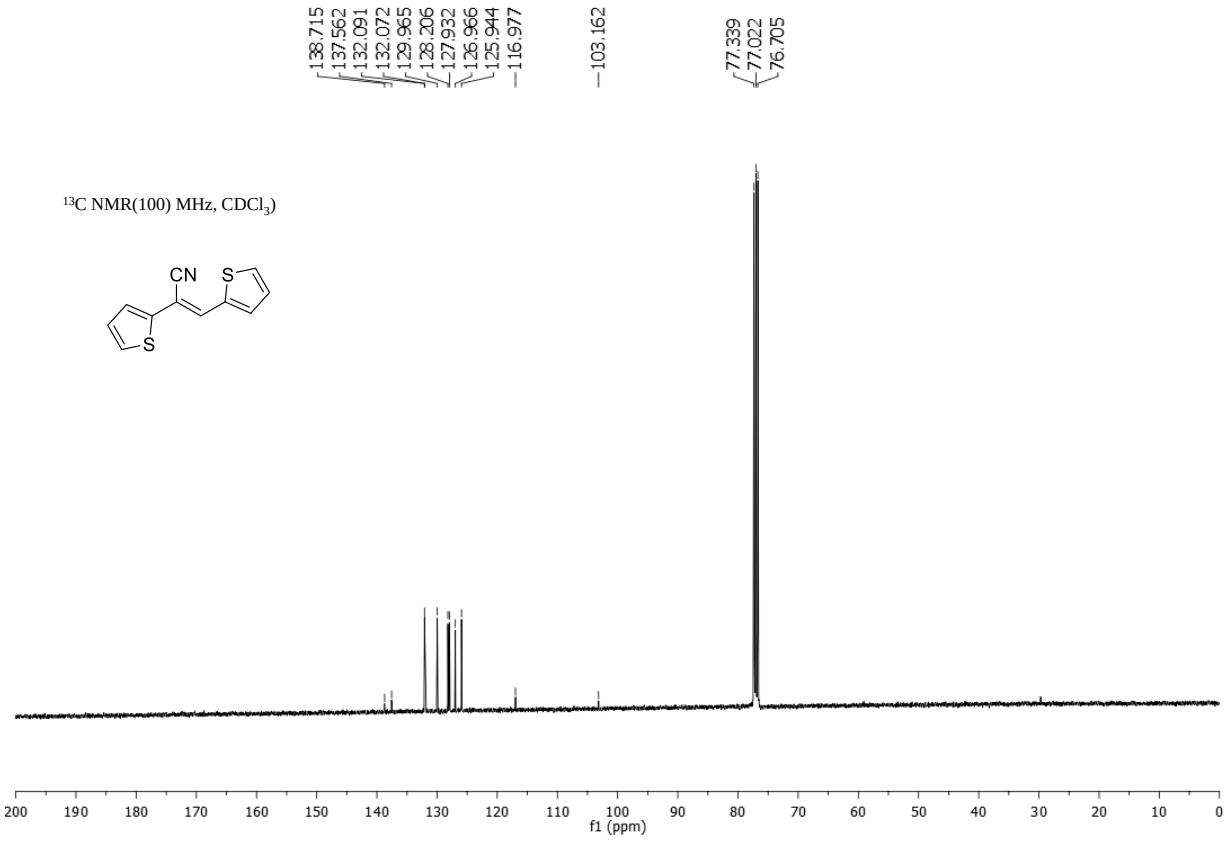


Figure 5.32. ^{13}C NMR spectrum of (E)-2,3-di(thiophen-2-yl)acrylonitrile (**3jg**).

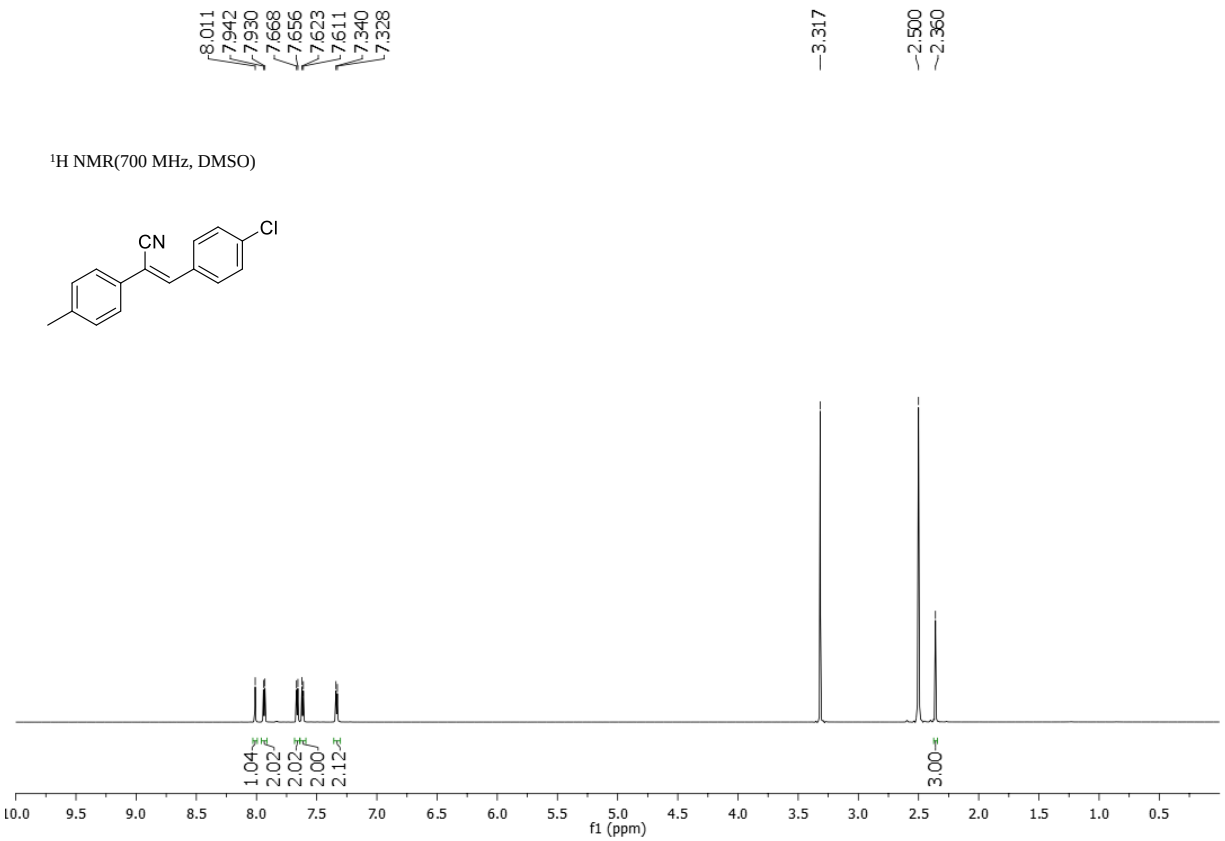


Figure 5.33. ^{1}H NMR spectrum of (Z)-3-(4-chlorophenyl)-2-(p-tolyl)acrylonitrile (**3be**).

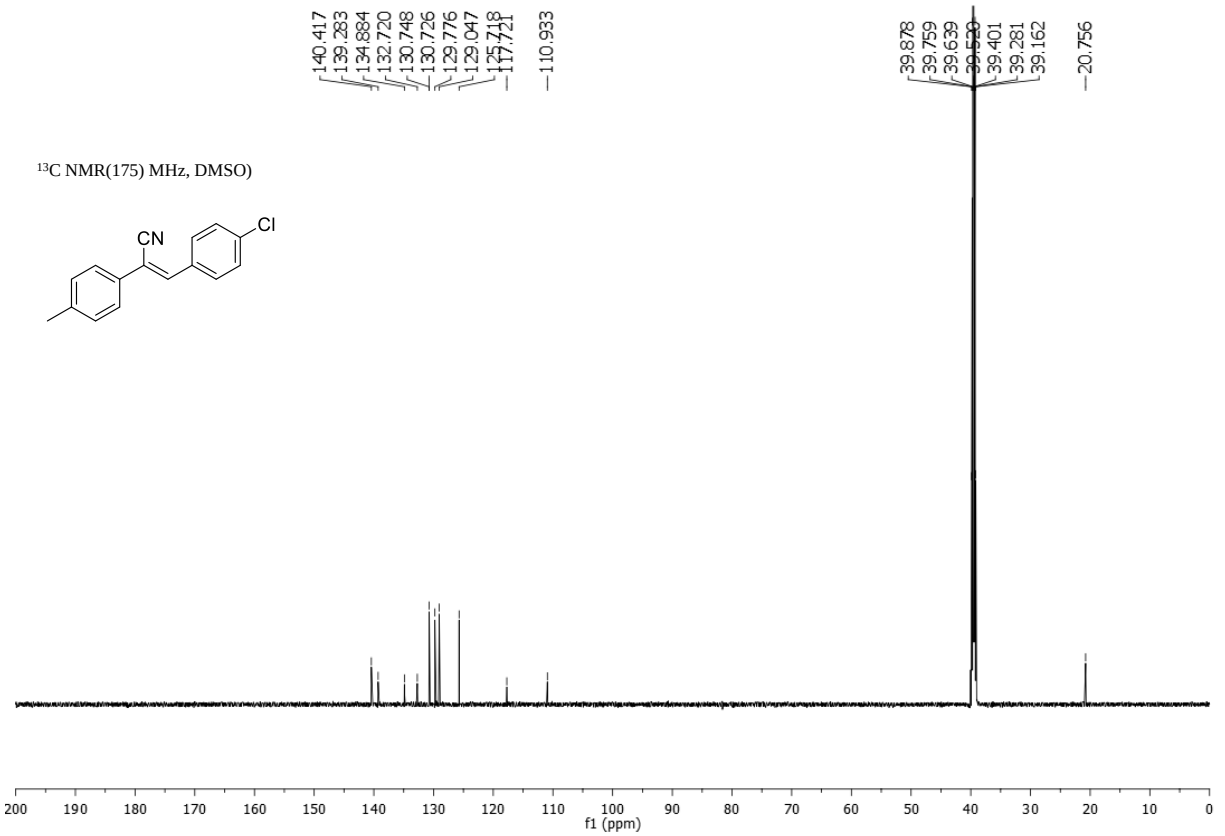


Figure 5.34. ^{13}C NMR spectrum of (Z)-3-(4-chlorophenyl)-2-(p-tolyl)acrylonitrile (**3be**).

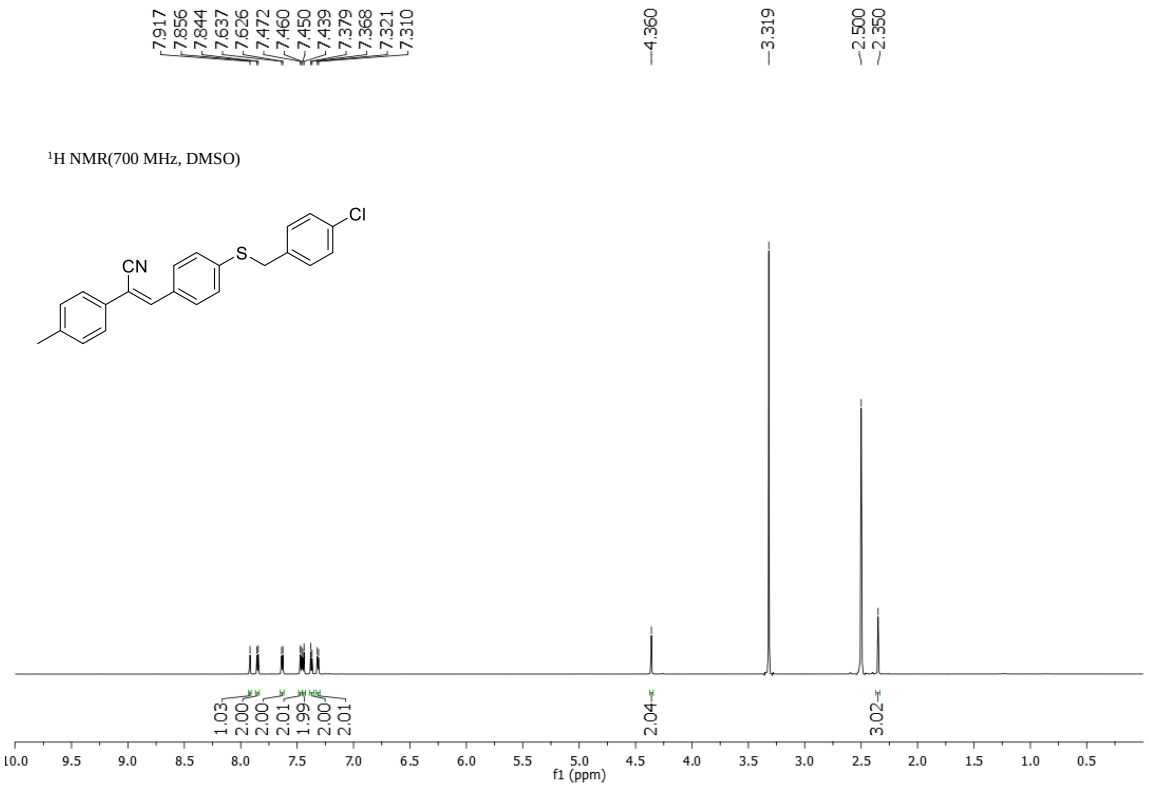


Figure 5.35. ^{1}H NMR spectrum of (Z)-3-(4-((4-chlorobenzyl)thio)phenyl)-2-(p-tolyl)acrylonitrile (**4be**).

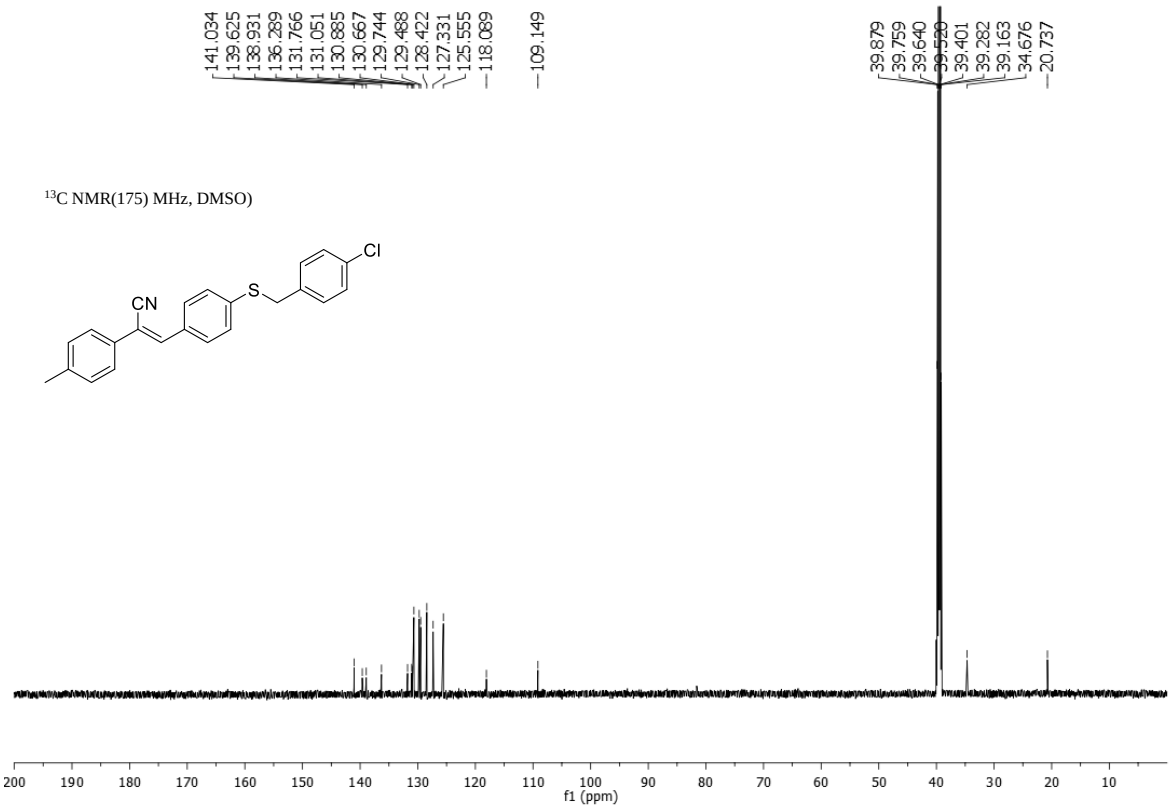


Figure 5.36. ^{13}C NMR spectrum of (Z)-3-(4-((4-chlorobenzyl)thio)phenyl)-2-(p-tolyl)acrylonitrile **(4be).**

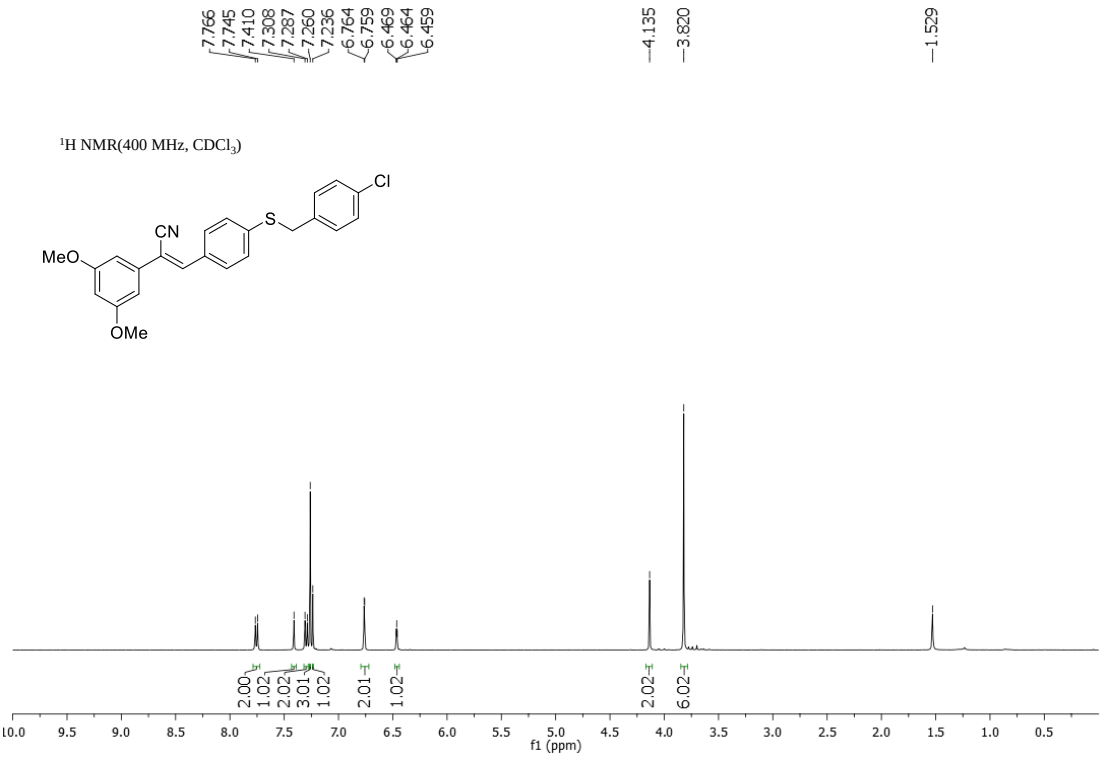


Figure 5.37. ^{1}H NMR spectrum of (Z)-3-(4-((4-chlorobenzyl)thio)phenyl)-2-(3,5-dimethoxyphenyl)acrylonitrile (**4ge**).

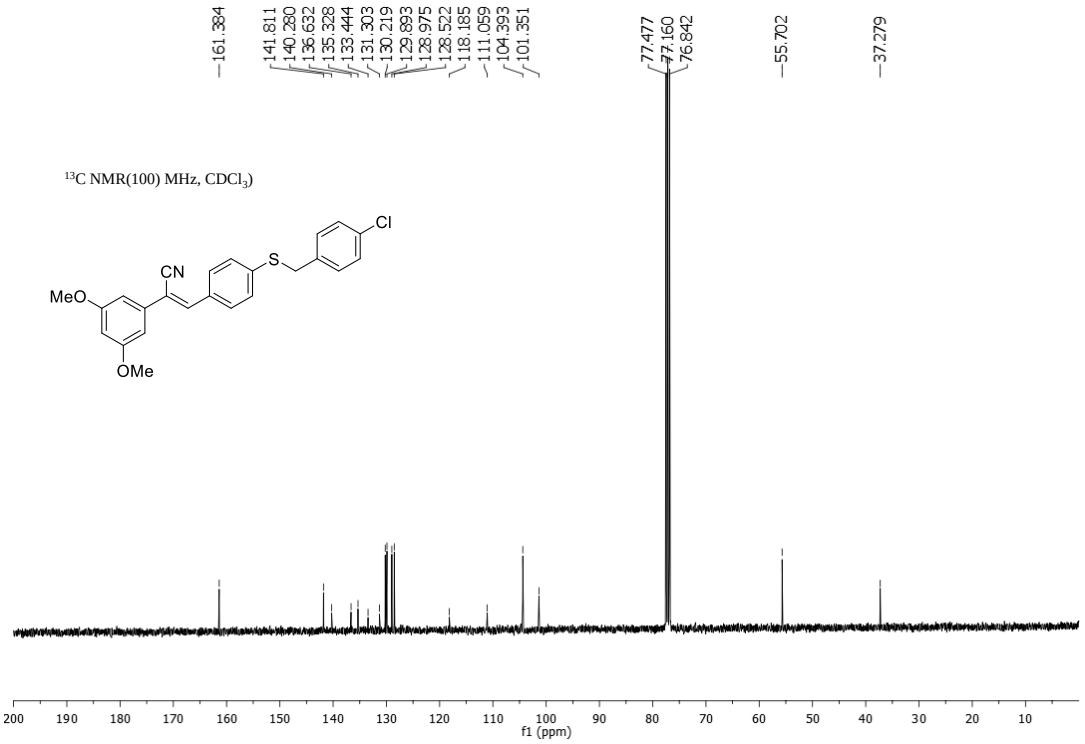


Figure 5.38. ^{13}C NMR spectrum of (Z)-3-(4-((4-chlorobenzyl)thio)phenyl)-2-(3,5 dimethoxyphenyl)acrylonitrile (**4ge**)

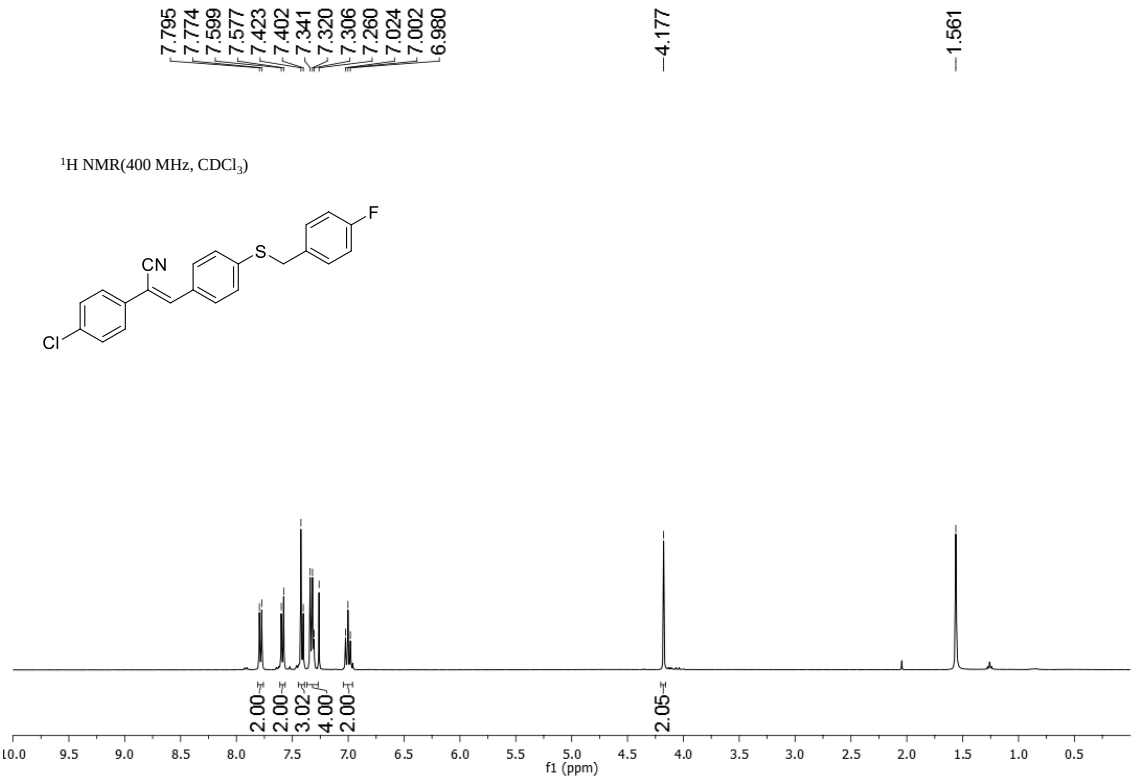


Figure 5.39 ^{1}H NMR spectrum of (Z)-2-(4-chlorophenyl)-3-(4-((4-fluorobenzyl)thio)phenyl)acrylonitrile (**4dh**).

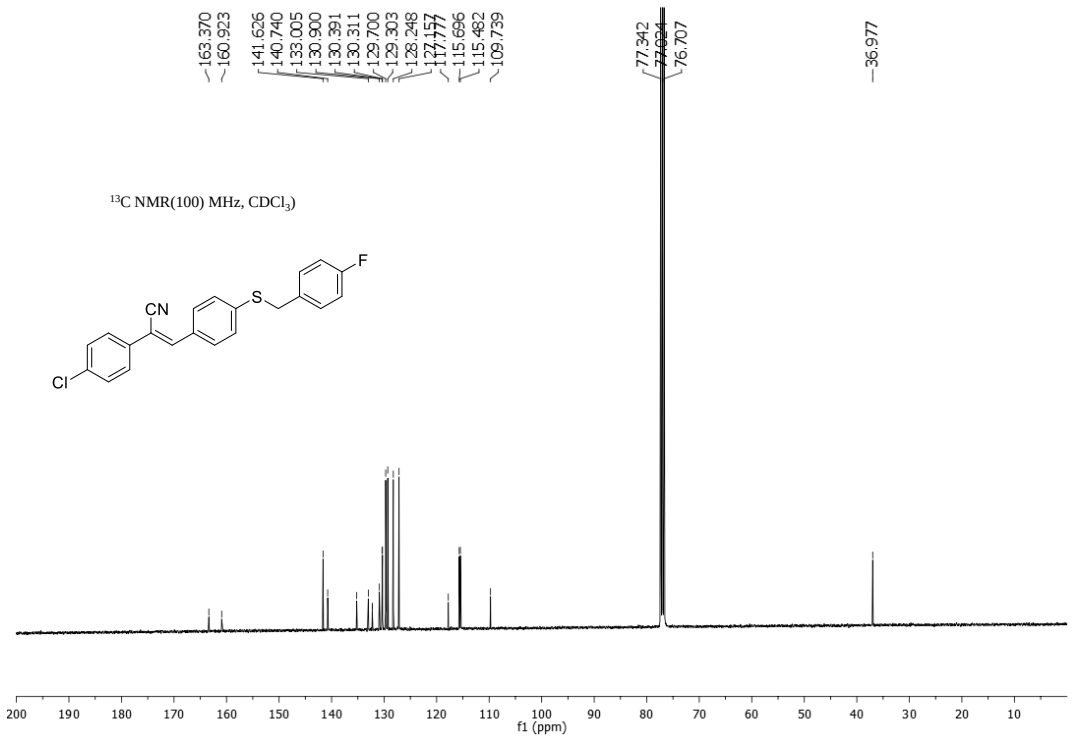


Figure 5.40. ^{13}C NMR spectrum of (Z)-2-(4-chlorophenyl)-3-(4-((4-fluorobenzyl)thio)phenyl)acrylonitrile (**4dh**).

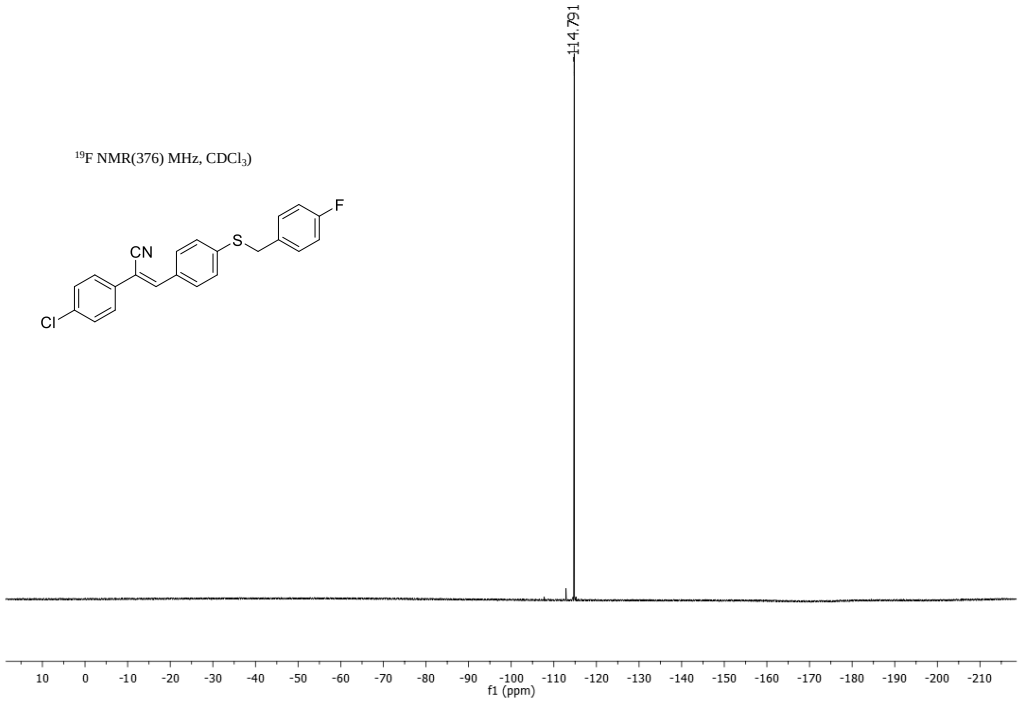


Figure 5.41. ^{19}F NMR spectrum of (Z)-2-(4-chlorophenyl)-3-(4-((4-fluorobenzyl)thio)phenyl)acrylonitrile (**4dh**).

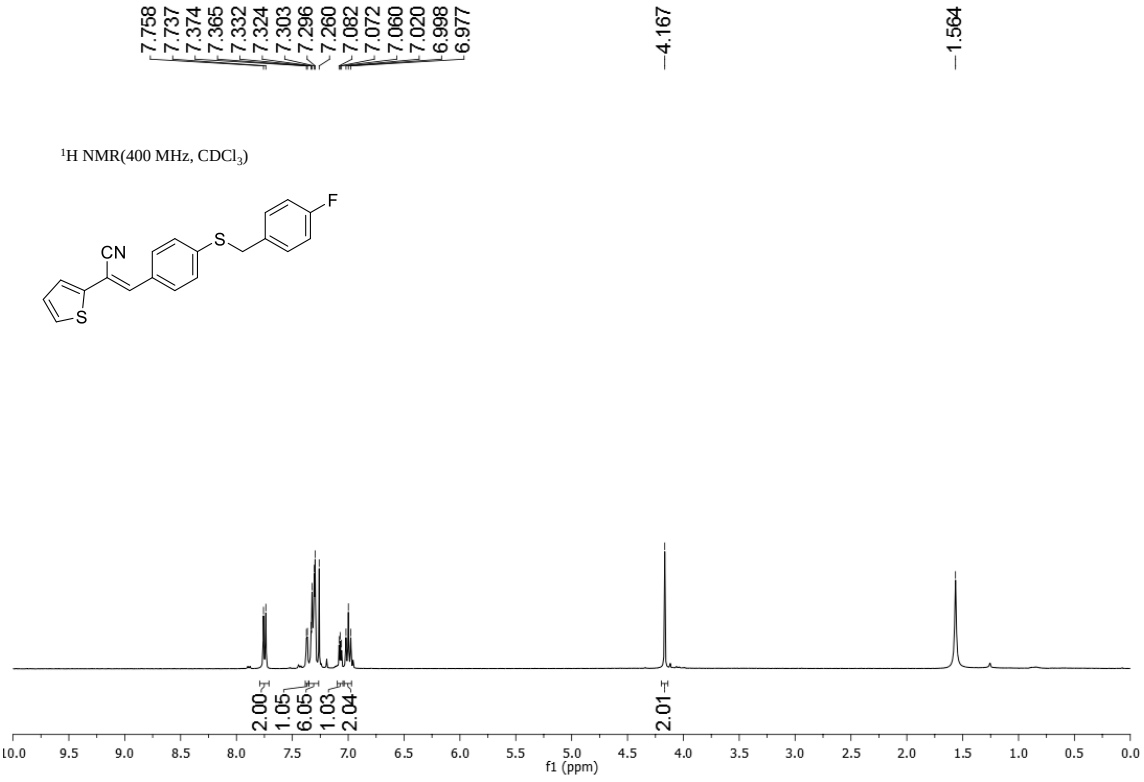


Figure 5.42. ^{1}H NMR spectrum of (E)-3-(4-((4-fluorobenzyl)thio)phenyl)-2-(thiophen-2-yl)acrylonitrile (**4jh**).

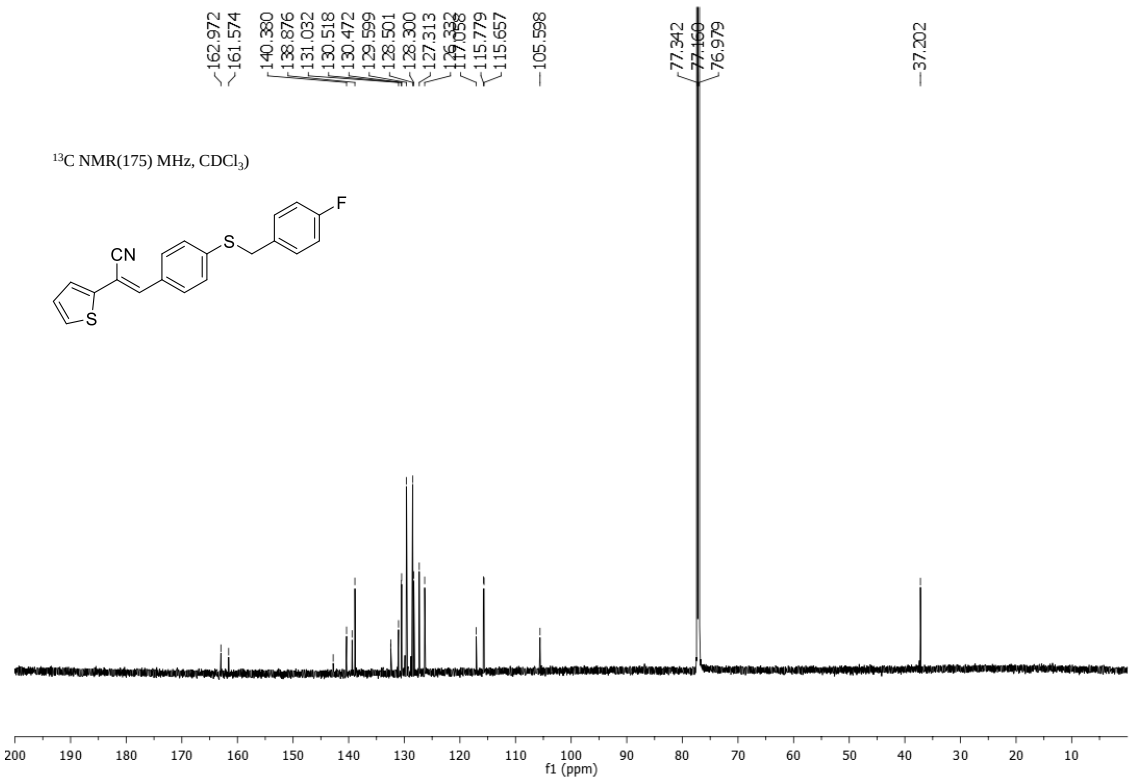


Figure 5.43. ^{13}C NMR spectrum of (E)-3-(4-((4-fluorobenzyl)thio)phenyl)-2-(thiophen-2-yl)acrylonitrile (**4jh**).

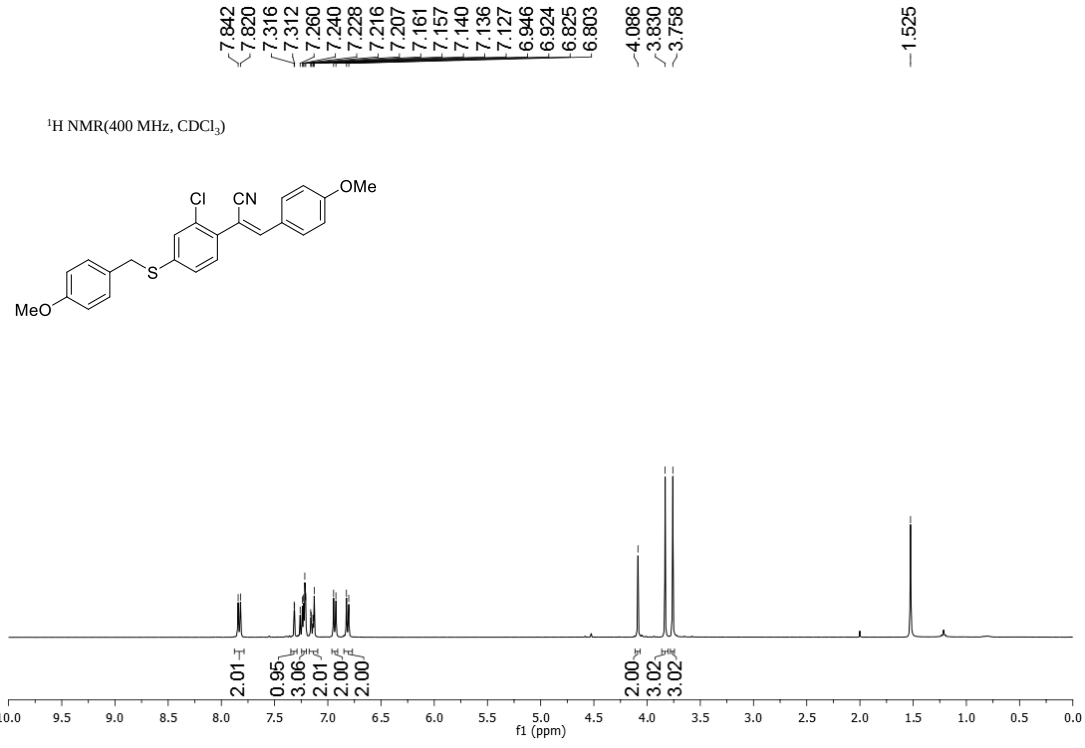


Figure 5.44 ^{1}H NMR spectrum of (Z)-2-(2-chloro-4-((4-methoxybenzyl)thio)phenyl)-3-(4-methoxyphenyl)acrylonitrile (**4ic**).

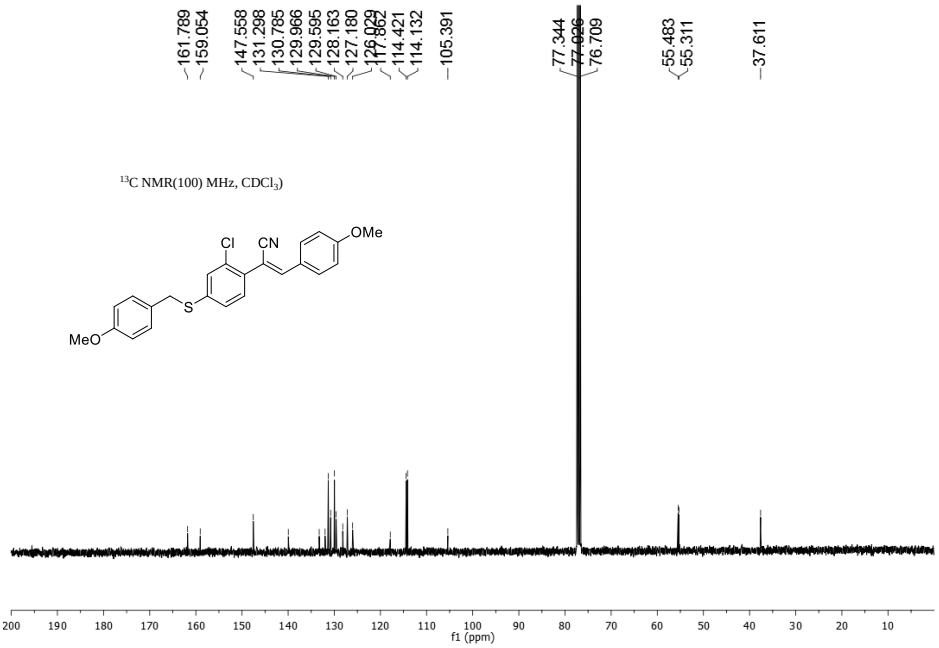


Figure 5.45 ^{13}C NMR spectrum of (Z)-2-(2-chloro-4-((4-methoxybenzyl)thio)phenyl)-3-(4-methoxyphenyl)acrylonitrile (**4ic**).

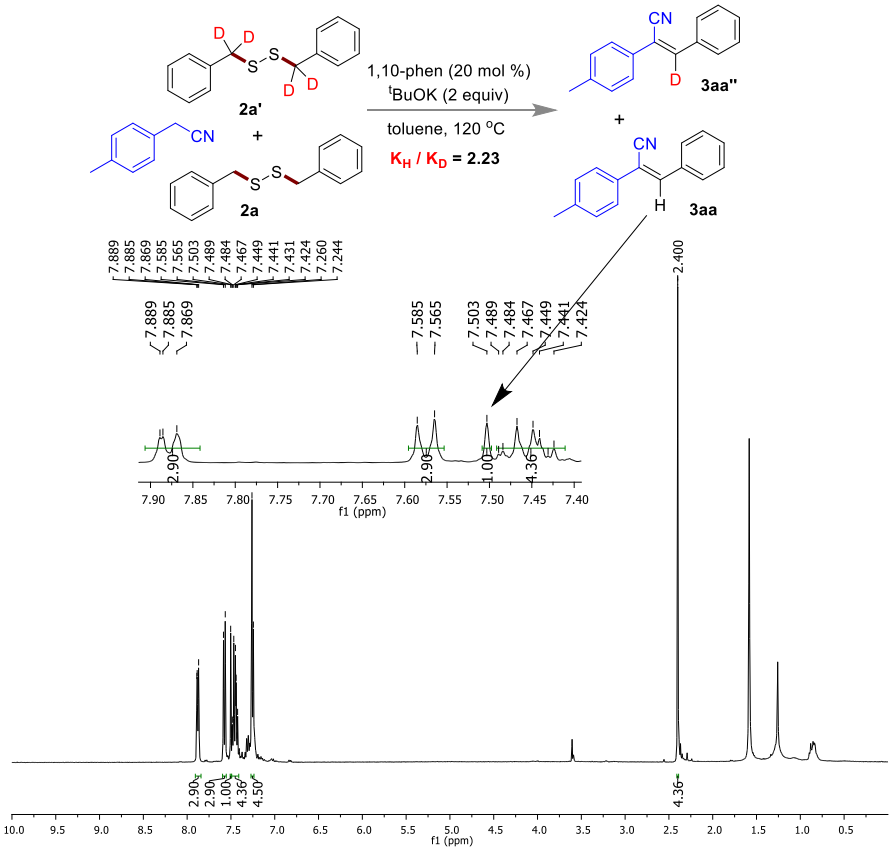


Figure 5.46 ^{1}H NMR spectrum of **3aa** and **3aa''** to determine the K_H /K_D value.

Homi Bhabha National Institute

Report of Ph.D. Viva-Voce

Board of Studies in Chemical Sciences

A. General Details:

1. **Name of the Constituent Institution: National Institute of Science Education and Research (NISER), Bhubaneswar.**

2. **Name of the Student: Khokan Choudhuri**
3. **Enrolment Number: CHEM11201504003**
4. **Date of Enrolment in HBNI: 29.12.2014**
5. **Date of Submission of Thesis: 23.12.2019**
6. **Title of the Thesis: Sustainable Strategies for Carbon-Sulfur Bond Formation Reactions in Organic Synthesis**

7. **Number of Doctoral Committee Meetings held with respective dates:**

Review Period	Date	Review Period	Date
1. 2015-2016	20.01.2016	2. 2016-2017	17.01.2017
3. 2017-2018	11.01.2018	4. 2018-2019	21.01.2019
5. 2019-2020	21.10.2019	6.	

8. **Name and Affiliation of the Thesis Examiner 1: Dr. Rajarshi Samanta, Associate Professor, Department of Chemistry, Indian Institute of Technology-KGP, Kharagpur-721302**

   Recommendations of the Examiner 1 (Thesis Evaluation) (i) accepted, (ii) accepted after revisions, or (iii) rejected: (i) accepted, the thesis in is present form is commended for the award of PhD. degree.

9. **Name and Affiliation of the Thesis Examiner 2: Prof. Subhas Chandra Pan, Department of Chemistry, IIT Guwahati**

   Recommendations of the Examiner 2 (Thesis Evaluation) (i) accepted, (ii) accepted after revisions, or (iii) rejected: (i) accepted, the thesis in is present form is commended for the award of PhD. degree.

B. Record of the Viva-Voce Examination

1. **Date of Viva Voce Examination: 04.06.2020**

2. **Name and affiliation of External Examiner: Dr. Rajarshi Samanta, Associate Professor, Department of Chemistry, Indian Institute of Technology-KGP**

3. **Whether there were other experts / faculty/students present ? Please enclose a soft copy of attendance sheet indicating participation in person/over video as per proforma given below at (5)**

4. **Recommendations for the award of the Ph.D. degree: Recommended / Not Recommended**

   (If Recommended, give summary of main findings and overall quality of thesis)
   (If Not Recommended, give reasons for not recommending and guidelines to be communicated by Convener of the Doctoral committee to the student for further work)

Mr. Khokan Choudhuri, delivered the research work in front of the committee and general audience. The candidate satisfactorily answered all the questions raised by the committee members and general audience. Based on overall performance, the committee unanimously recommended for doctoral degree.

5. **Attendance at Viva Voce (Doctoral Committee, External Examiner, others):**

Sr No	Composition	Name	Attended in person or through video; if in person, signature
1.	**Chairman**	**Prof. A. Srinivasan**	4.6.2020
2.	**Convener** (Guide)	**Dr. Prasenjit Mal**	4.6.2020
3.	**Co-Guide/External Guide** (if any)	--	
4.	**External Examiner**	**Dr. Rajarshi Samanta**	
5.	**Member**	**Dr. C. S. Purohit**	04.06.20
6.	**Member**	**Dr. Subhadip Ghosh**	4.6.2020
7.	**The Technology Adviser**, if any	--	
Others: list in separate sheet			
8	**Member**	**Dr. Joydeep Bhattacharjee**	04/06/2020

04.06.2020

(Convener, Viva Voce Board)

Thesis Highlight

Name of the Student: Khokan Choudhuri

Name of the CI/OCC: National Institute of Science Education and Research

Enrolment No.: CHEM11201504003

Thesis Title: Sustainable Strategies for Carbon-Sulfur Bond Formation Reactions in Organic Synthesis

Discipline: Chemical Sciences **Sub-Area of Discipline:** Organic Chemistry

Date of viva voce: 04.06.2020

Sulfur is one of the most essential elements for living organism. It is stored into the body as a form of organosulfur compound. Therefore, synthesis of C-S bond using sustainable reagent condition is a popular topic of research. In this current thesis, iodine triggered oxysulfonylation of olefins have been achieve *via* aerial dioxygen activation strategy. Markovnikov selective or *anti*-Markovnikov selective Thiol-Ene click (TEC) and Thiol-Yne click (TYC) reactions were also developed by exploiting newly identified S–H···π non-covalent interaction under neat condition *via* umpolung addition. Also, by using appropriate amount of PIDA, cascaded C-S and S-O bond formation reactions led to form aryl sulfinyl arenes and sulfoxide arenes adduct. A unique synthetic route of Knoevenagel condensation reaction has been established for the synthesis of *α,β*-Unsaturated diphenylacrylonitrile derivative from benzyl cyanide and benzyl mercaptan *via* C-S bond cleavage under basic condition. Also, *in situ* C-X (X = Cl, F) bond functionalization were accomplished for the respective halo substituted diphenylacrylonitriles in a cascaded manner.

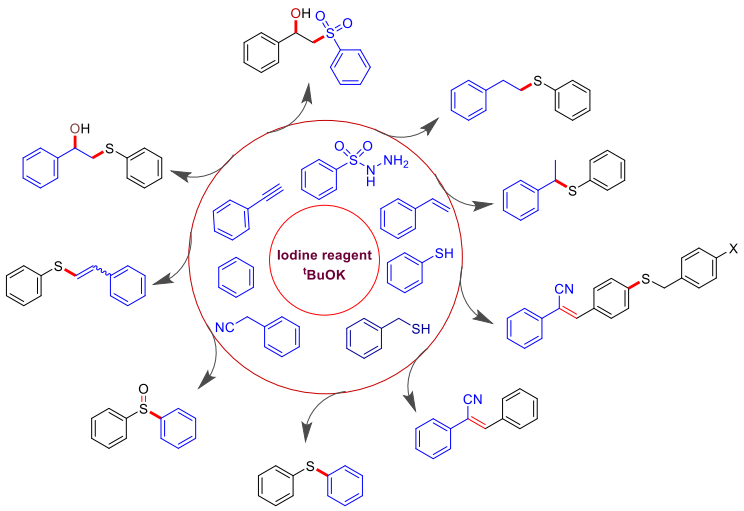


Figure 1. *Sustainable reagent promoted C-S bond formation reaction.*