Water Promoted Sulfa-Michael Addition Reaction using Hydrazones as Sulfonyl Transfer Reagent

A

Thesis Submitted

In the partial fulfillment of requirement of degree

Masters of Science

In

Chemistry

Submitted By

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UNDER THE SUPERVISION OF

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PATIALA-147001

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CERTIFICATE

This is to certify that the thesis entitled **"Water Promoted Sulfa-Michael Addition Reaction using Hydrazones as Sulfonyl Transfer Reagent"** submitted by **Ms. Shagun** in the partial fulfillment of the requirement for the degree of **Masters of science in Chemistry** from **Thapar Institute of Engineering and Technology, Patiala** is a bonafide piece of work carried out under the guidance and supervision of **Dr. Vikas Tyagi,** Assistant Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala and no part of project has been submitted for award of any other degree in this or any other university.

Shagun.

(SHAGUN)

This is to certify above statement made by student concerned is correct and true to the best of my knowledge.

Dr. Vikas Tyagi
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SELF DECLARATION

The work embodied in the project entitled **"Water Promoted Sulfa-Michael Addition Reaction using Hydrazones as Sulfonyl Transfer Reagent"** has been done by me in the partial fulfillment of the requirement for the Award of degree of **Masters of science in Chemistry,** submitted in the **School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala** is an authentic record of my own carried under the guidance and supervision of **Dr. Vikas Tyagi**, Assistant Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala. All the ideas and references has been duly acknowledged.

Shagun

(SHAGUN)
Date – 15 July 2019

This is to certify above statement made by student concerned is correct and true to the best of my knowledge.

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ACKNOWLEDGMENT

The success and final outcome of this project would never have been accomplished without the blessings of God and support of my parents and it required a lot of guidance and assistance from many people who motivated, encouraged and helped me in the project work and I am extremely privileged to have got this all along the completion of my project.

I respect and thank **Dr Amjad Ali**, *Professor and Head, School of Chemistry and Biochemistry for providing me an opportunity to do the project work and* **Dr. Vikas Tyagi,** *Assistant Professor, School of Chemistry and Biochemistry, Thapar Institute, Patiala for introducing this topic to me and directing me to work in a field that has huge applications and scope for further research and learning, for giving all support and guidance which made me complete the project duly and for your optimistic approach which kept me motivated throughout the course of this project.*

*I owe my deep gratitude to the PhD scholars Mr***. Sunil Dutt** *and* **Mr. Ashok Kumar**, *for their generous guidance, help and useful suggestions and Project Assistant* **Mr. Imran Khan** *for providing all the necessary requirements for carrying out this work. A sincere thanks to my labmates* **Ms. Hashmita** *and* **Ms. Priya** *for their supporting behavior.*

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Words are not enough to express my feelings about my immense gratitude that I owe to my dear parents and for their endless love, care and blessings. Last but not the least I would also like to express my immense gratitude to all the people who directly or indirectly contributed during the tenure of my project work.

Place: Patiala Shagun

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ABSTRACT

A catalyst free, facile and green route has been identified for the synthesis of α-keto sulfones through highly efficient water promoted sulfa-Michael addition. Sulfonyl hydrazones have been exploited as magnificent sulfonyl anion surrogate in presence of water with enones and with other α, β unsaturated alkenes for the synthesis of functionalized sulfones. To test the feasibility of the reaction a number of substituent has been screened and to our delight we got good to excellent yield with all substitutions. Further, to check the scalability of the transformation a reaction was set-up with one gm scale of starting materials and the higher yield of product proves that this transformation might be useful at industrial scale.

1.1 Introduction

Sulfone compounds exhibit a miscellaneous range of behavior in pharmaceuticals[1–4], agrochemicals[5–7], pesticides[8], advanced organic materials[8], and in synthetic organic chemistry[9,10], Trost mentioned organosulfones as "chemical chameleons" for synthetic building block as they act as electrophiles in lewis acidic medium and as nucleophiles in basic medium whereas Fuchs *et al*. described them as "pluripotent".[11,12] The amalgamation of all these applications of sulfones make them unique and valuable structural motif as well as synthetic precursor for various organic compounds which draws the considerable attention towards the synthesis of sulfones.

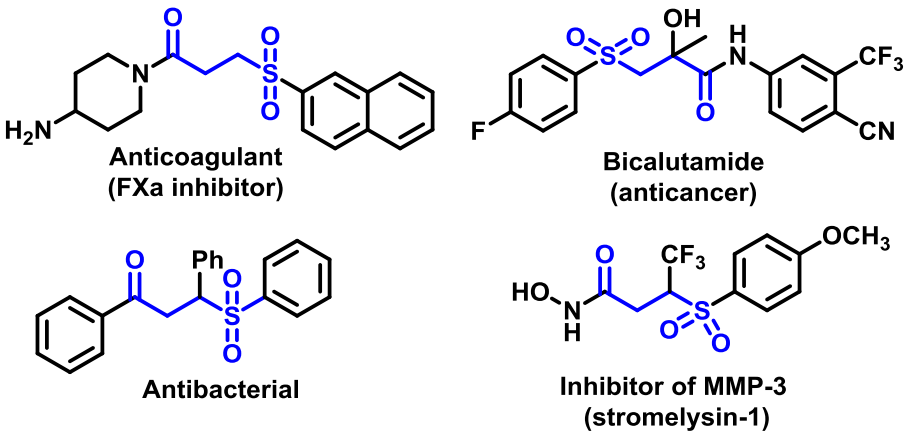


Figure 1. Representative structures of biologically important sulfones

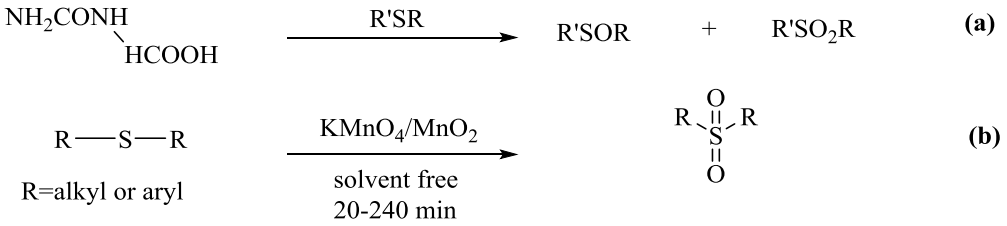
Among these sulfones, the γ-keto sulfones are substantial class of compounds possessing a wide range of pharmaceutical properties (**Figure 1**), including anticoagulant, antitumor, antibacterial and antifungal activities.[13–16] The crucial step in the synthesis of γ-keto sulfones is the formation of C-S bond and the potential method for this is sulfa-Michael addition reaction.[17] The universal presence of sulfur containing compounds enhances the different approaches for this reaction like stimulating the reaction by using transition metals or organocatalysts in a catalytic fashion. [18,19]

On the other hand, water is a green and environment benign solvent due to its easy availability, cost effectivity, waste prevention and environment safe properties. Moreover water acting both as a proton donor and acceptor, is the most promising solvent for creating organic compounds. For the advancement of green and sustainable chemistry, water has replaced many organic solvents and there are many examples of Michael addition reactions in water.[20–22] Further, organic reactions promoted in water medium with highly water insoluble precursors are termed as on-water reactions.[23] The liquefaction of reactants in presence of a liquid organic oily phase to generate an organic oily layer is important for the interaction with bulk water layer at the interface.[24] In addition, water when heated above its boiling point under pressure behaves as superheated water due to which hydrogen bonds break rapidly and properties of water become more like an organic solvent.

1.2 Literature Review

Traditionally, γ-keto sulfones were prepared from α,β-enones by Michael type addition with thiols followed by oxidation.[25–28] Further, there are a number of ways for the synthesis of γ-keto sulfones and in recent years, many efficient approaches have been reported.

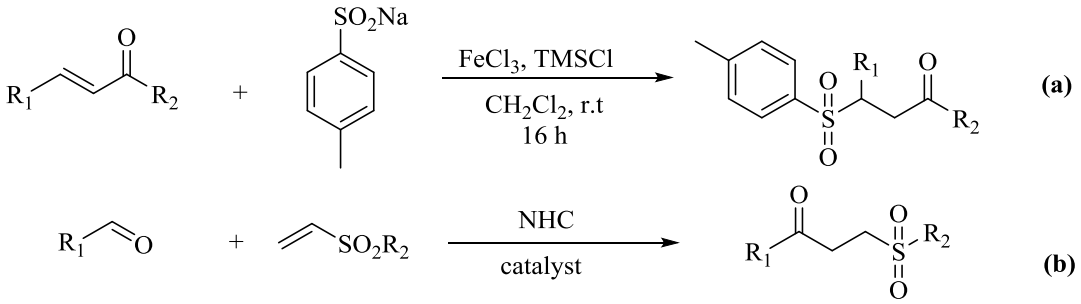
Varma and Naicker proposed a solvent-free oxidative method by using urea-hydrogen peroxide adduct for the conversion of sulfides to sulfoxides and sulfones (**Scheme 1(a)**)[29] whereas Jana and his coworkers successfully used the phase-vanishing technology to carry out the oxidation of sulfides to sulfones with m-CPBA.[30] Shaabani *et al.* effectively used potassium permanganate on a solid support of manganese dioxide to achieve the solvent free oxidation of sulfoxides to sulfones.[31](**Scheme 1(b)**)



Scheme 1. Traditional methods for sulfone synthesis

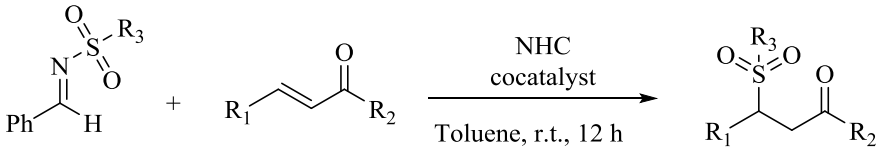
By passing time, alternative approaches have been put forward by using different catalytic methods to form the γ-keto sulfone derivatives. In 2008, Sreedhar and coworkers employed

$FeCl_3$ as catalyst with TMSCl as additive and found a new protocol using sodium p-toluenesulfinate for conjugate addition to enones[32](**Scheme 2(a)**). In 2012, Bhunia *et al.* efficiently synthesized γ-keto sulfones in good yields by using N-heterocyclic carbene catalyst for intermolecular Stetter reaction of aldehydes with α,β unsaturated sulfones[33](**Scheme 2(b)**).



Scheme 2. Catalytic methods for sulfone synthesis

Yang *et al.* worked in a new direction with sulfonylimines and reported the first enantioselective catalytic sulfonation of enones. They used two organic catalysts, a chiral thiourea/amine cocatalyst and an N-heterocyclic carbene(NHC) catalyst. NHC catalyze the generation of sulfinic anion as a nucleophile. Non-covalent interactions and anion recognization by the chiral cocatalyst drives the sulfinic anion to enones in an enantioselective manner[34](**Scheme 3**).



Scheme 3. Catalytic sulfonation of enones using sulfonylimines.

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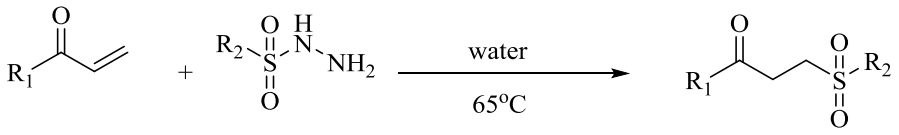
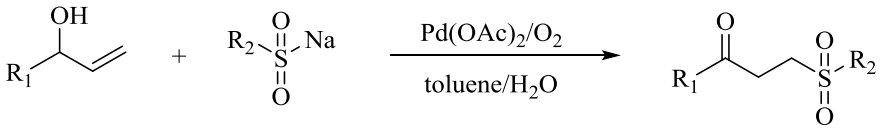
Green and sustainable chemistry is the modern approach for the researchers in the direction to promote the catalysis-free synthesis of γ-keto sulfones. Yang and his coworkers meticulously adopted this approach by developing a green pathway of sulfonylation of activated ketones with sulfonyl hydrazides to synthesize sulfones via a sulfinyl anion generation mechanism[35] (**Scheme 4**).



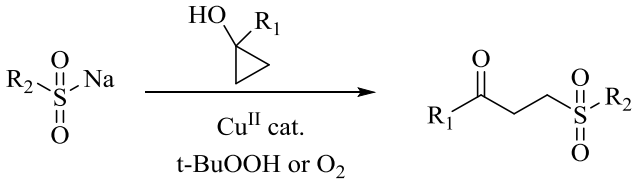
Scheme 4. Green approach for sulfone synthesis

However, many of the methods described above require multiple steps and harsh conditions along with the formation of undesirable side products. In 2016, Vellakkaran *et al.* reported a sustainable route to synthesize γ-keto sulfones by using one-pot Pd^{II}-catalysed oxidation of allylic alcohols which are precursor of enones pursued by sulfa-Michael addition of organosulfinates promoted by water to resulted enones. Oxygen is used as terminal oxidant to achieve the oxidation of Pd^{0} species into Pd^{II} species[36](**Scheme 5**).



Scheme 5. One-pot palladium(II) catalysed synthesis of γ -keto sulfones

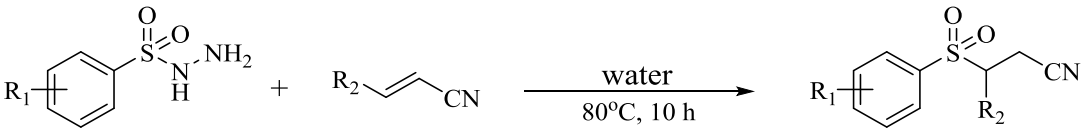
Recently, scientists came up with an idea of using more synthetically useful precursors for synthesis of γ-keto sulfones. Konik and his coworkers reported a protocol that used tertiary cyclopropanols which undergo ring opening via oxidative sulfonylation with sulfinate salts using Cu^{II} catalyst to afford γ -keto sulfones in good yields. The mechanism of the process was proposed to be one-pot oxidative-Michael addition[37](**Scheme6**).



Scheme 6. Synthesis of γ -keto sulfones from cyclopropanols and sulfinate salts

Reminiscent of the concepts of green chemistry, Gao *et al.* developed a catalyst free methodology to synthesize 3-sulfone nitrile compounds in water[38](**Scheme 7**). Sulfone and nitrile compounds play an important role in constructing many biomolecules and thus this methodology is crucial to understand. The reaction proceeds via a proton transfer mechanism

catalyzed by water forming sulfur-centered anion intermediate which undergoes the Michael addition generating 3-sulfone nitriles.

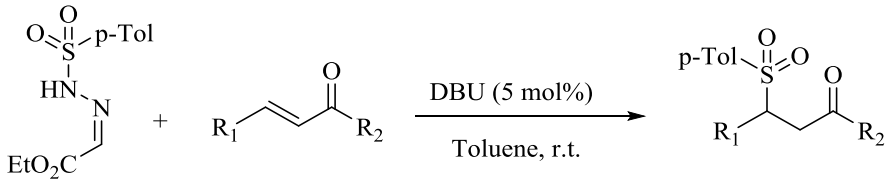


Scheme 7. Methodology for the synthesis of 3-sulfone nitriles.

1.3 Sulfonyl Hdrazones as Precursors

Tosyl hydrazones have been used in synthetic organic chemistry from decades as useful synthetic intermediates and precursors. The recent discoveries in the field of catalyst promoted cross-coupling reactions using tosyl hydrazones as a precursor for a number of intermediates have grabbed lot of attention. In this context, many of the reported methodologies have shown that the acidic proton of the hydrazone dissociate in presence of a base resulting in the formation of sulfinate anion and a diazo compound which is then used for the generation of carbene species as intermediate in many reaction[(39)]. However in 2013, researchers illustrated that these tosyl hydrazones can possibly be used for generating S-based nucleophiles which can be used in forming γ-keto sulfones.

Fernández and his coworkers reported the potential of ethyl glyoxylate N-tosylhydrazones to be used as a source to generate sulfonyl anions which can undergo conjugate addition reaction with α,β-unsaturated aldehydes and ketones in presence of catalytic amount of Bronsted base[(40)](**Scheme 8**). They used different enones along with cyclic enones as Michael acceptors leading to the direct synthesis of sulfonyl compounds in high chemical yields which proves this strategy a useful addition in the previously developed methods and useful to use hydrazones as sulfur-centered pro nucleophiles.

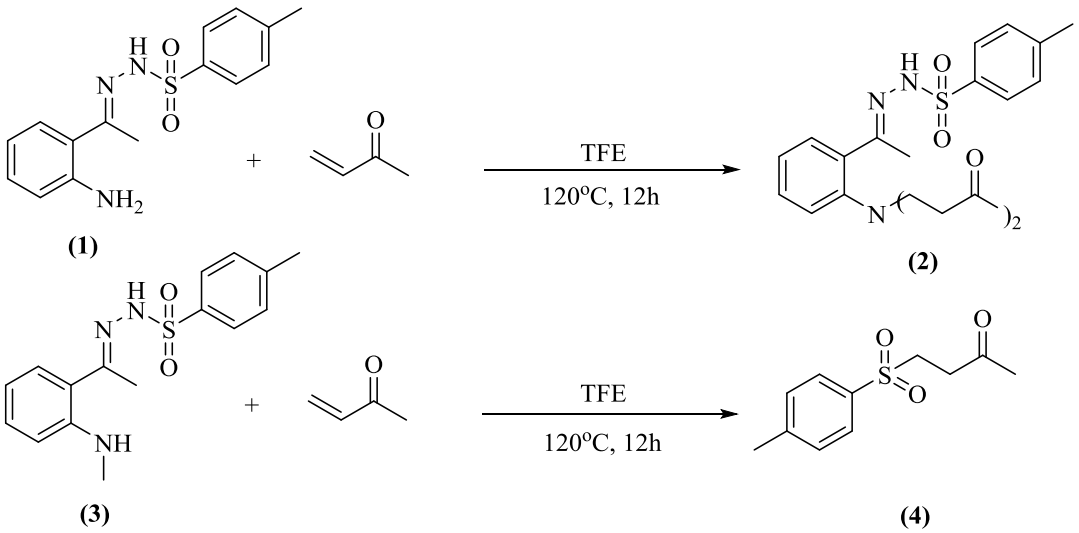


Scheme 8. Ethyl glyoxylate N-tosylhydrazone as precursor for the synthesis of γ-keto sulfones

1.4 Gap in Studies

The major drawback in the methodology lies within the use of tosylhydzrazones as precursor. Hydrazone structures with an electron withdrawing group i.e, N-ethyl glyoxylate group at the azomethine carbon were found operative for carrying out sulfa-Michael addition reaction. However the tosylhydrazones obtained from acetaldehyde or benzaldehyde were found inactive so their work restricted only with the use of hydrazones with electron withdrawing substituents. While using cyclic enones as Michael acceptors, they performed the *in situ* reduction of carbonyl group generating γ-hydroxy sulfones to avoid the retro Michael reaction. The reaction was efficient only with the use of enones and no Michael addition reaction was done on other α,β unsaturated alkenes. Moreover, the approach is not green and environmental friendly as the reaction proceeds via using base as a catalyst and organic solvents which provoke more waste.

1.5 Hypothesis



(1) (2) (3) (4)

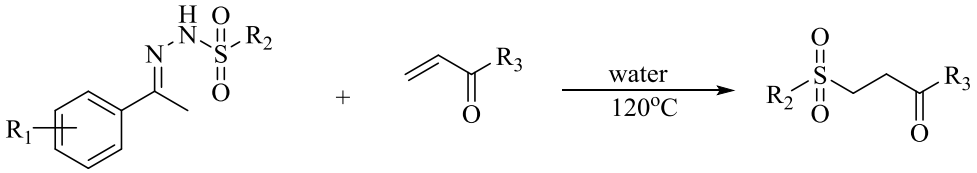
Scheme.9 Formation of 4-tosylbutan-2-one

Initial effort was to carry out aza-Michael addition using 2-amino-N-tosyl hydrazone **(1)** and methyl vinyl ketone catalysed by trifloroethanol (TFE) as a solvent[41] in order to obtain monoadduct product. However upon characterization of the product by NMR, diadduct product formation **(2)** was obtained. This instigated the methylation of 2-amoniacetophenone **(3)** before the hydrazone formation and the same process was carried forward. This time the NMR spectra

predicted the formation of γ-keto sulfone i.e, 4-tosylbutan-2-one **(4)** which directed us to work in this direction. **(Scheme.9)**

1.6 This Work

This work enlightens a very effective way for the catalyst and organic solvent free synthesis of $\gamma-$ keto sulfones through sulfa-Michael addition of N-substituted hydrazones to enones in water. (**Scheme 10**).

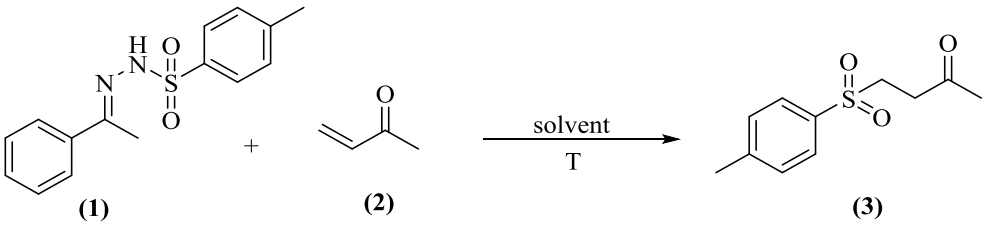


Scheme 10. Catalyst free sulfa-Michael addition using hydrazones as precursors

An oily layer is formed between liquid ketones and water insoluble hydrazones in bulk phase water and the ability of water to participate as a source of both proton donor and acceptor forms a sulfinate anion which undergoes sulfa-Michael addition reaction. The use of hydrazones having electron withdrawing and electron donating R_1 and R_2 groups instead of having only electron withdrawing groups as reported in previous work make them an exquisite sulfonyl transfer surrogate. The reaction procceds even with cyclic enones and acetonitriles exhibiting the versatility of this work. This is a very green and sustainable approach which uses no harsh reagents or catalysts and no organic solvents, only promoted by water as a green solvent.

2.1 Optimization on Model Substrate

In order to optimize the reaction conditions, N-tosyl hydrazone **(1)** and methyl vinyl ketone **(2)** were taken as model substrate and the optimizations were done by screening different solvents, temperature and molar ratios.



Scheme 11. Template reaction for optimizing the reaction conditions.[a]

[a] Reaction conditions: (**1**) (0.70 mmol) and **(2)** in 2 mL of solvent at specified temperature.

2.11 Effect of Solvent

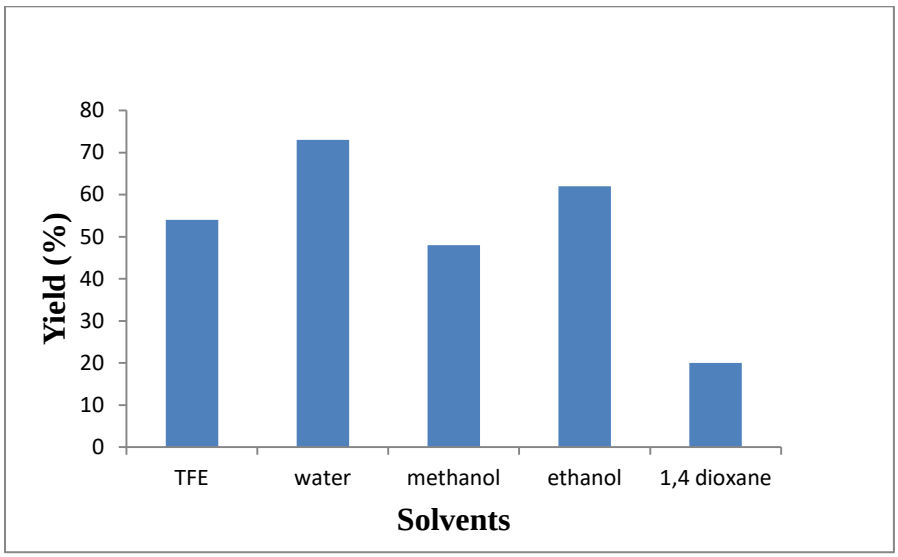


Fig 2. The outcome of different solvents on the yield of **(3)**

Initially, the reaction was performed in trifluoroethane (TFE) resulted 54% yield which encouraged use to use other solvents for example water, ethanol, methanol and 1,4-dioxane. The reaction was best promoted by water as shown in **Fig 2.** This was then chosen as solvent for further optimizations. The results showed that it is the formation of oily layer emulsion of N-tosyl hydrazone with vinyl ketones which promotes the reaction in water.

2.12 Effect of Temperature

The temperature of reaction plays an important role in reaction promoted by water owing to its effects on the properties of N-tosyl hydrazones as shown in **Fig 3.** At lower temperature range, the reaction does not proceed well whereas higher yield is obtained in 100-120 ºC range of temperature. The optimization of the process show that high temperature drives the bond breaking of tosyl hydrazones forming diazo intermediates which facilitates the attack of sulfinate anions to enones. Moreover hydrogen bonds of water start breaking more rapidly at high temperature and hence promoting the yield of the reaction.

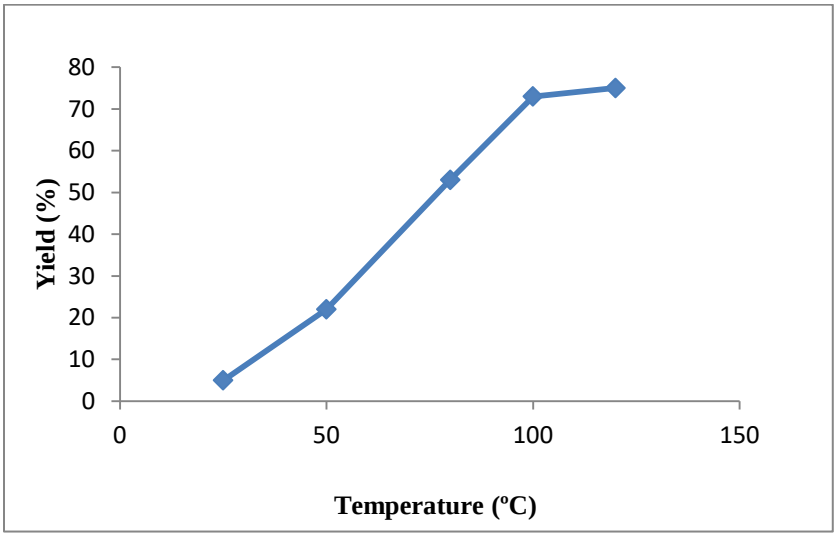


Fig 3. The effect of temperature on the yield of 4-tosylbutan-2-one

2.13 Effect of Molar Ratio

Encouraged by the above results, the influence of different molar ratios of **(2)** on reaction with **(1)** in water at 100 ºC was investigated and the results have been shown in **Fig 4.** When the

molar ration of **(1)** to **(2)** was varied from 1:0.5 to 1:1, the yield was improved from 20% to 58% whereas no obvious change in yield was observed as molar ratio was continually increased from 1:2 to 1:5. The maximum conversion obtained when the ratio of (1) to (2) was 1:3, so this was chosen for further work in this project.

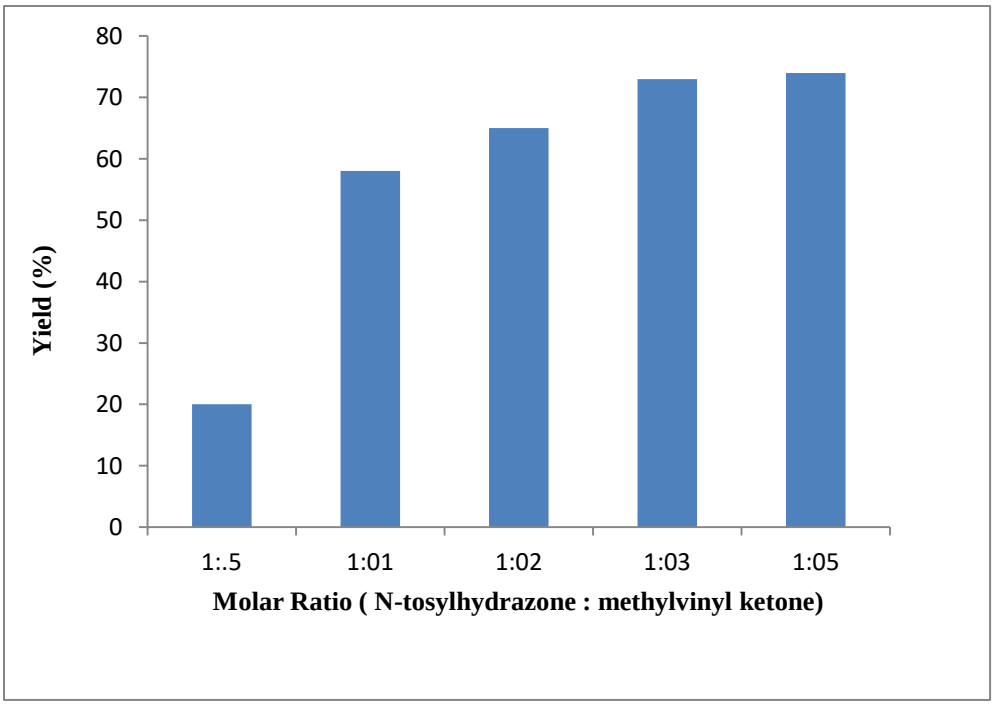
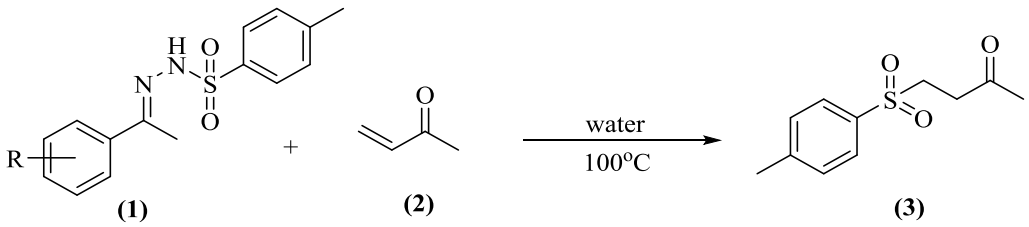


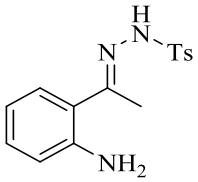
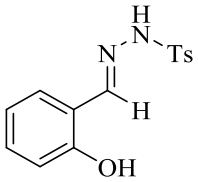
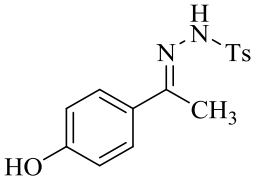
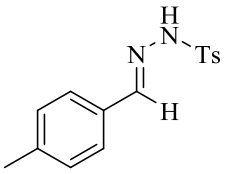
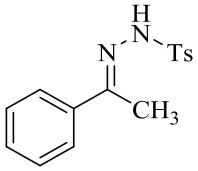
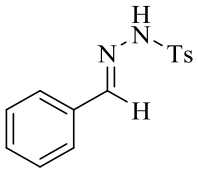
Fig 4. The influence of molar ratio of N-tosylhydrazone to methyl vinyl ketone

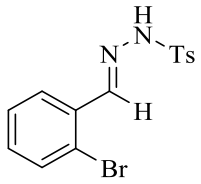
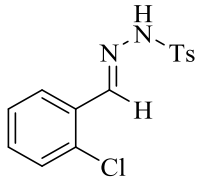
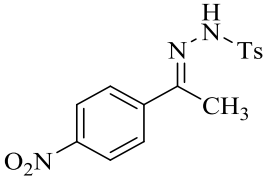
2.2 Effect of substituent's on N-tosylhydrazone

Further to screen the electronic effects of the substituents on the feasibility of this reaction, while keeping N-tosyl group fixed, different substituents on hydrazones were explored as shown in **Table 1** and to our surprise there was no appreciable change in the yield of the product on moving from one electron donating to other (entry 1-4). However, a slight decrease in the yield was observed in case of electron withdrawing substituents (entry 7-8) excluding p-nitro substituent (entry 9) which gave only 20% yield which can be possibly expected due to their negligible solubility in water. Also the results showed that we obtained maximum yield (73%) when we used N-tosyl hydrazone which was synthesized by acetophenone (Entry 5). Delighted by this result, we used N-tosyl hydrazone as a precursor for further investigation in this project.

Table 1. Effect of different groups on hydrazone.[a]



Entry	Hydrazone (1)	Yield (%)[b]
1		58
2		62
3		65
4		59
5		**73**
6		53

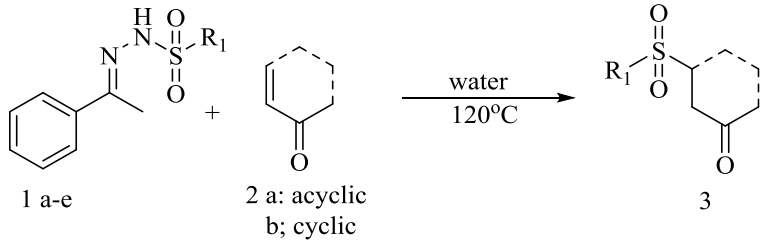
7		50
8		48
9		20

[a]Conditions: sulfonyl hydrazone derivates (1mmol) with enones (3mmol) in 2mL water at 120ºC. [b]Yield of isolated product after column chromatography on silica gel

2.3 Substrate Scope of the Reaction

After establishing an optimized protocol for the methodology, more efforts were directed to extend its scope by using different sulfonyl hydrazone derivatives on enones as well as other α, β unsaturated alkenes. As shown in **Table 1.** vinyl ketone effectively participates with aryl groups where an electron withdrawing substituent at phenyl ring showed the maximum yield of 73% although, with no substituent the yield was decreased to 60%. In addition, the electron withdrawing p-nitro substituent made a great difference to the yield by reducing it to 22%. We hypothesized that this decrement in the yield might be due to insolubility of nitro containing hydrazones which make them unable to form the oily layer with vinyl ketone, so the reaction was done with 50% DMSO in water which elevated the yield upto 91%. Further, to check the effect of DMSO, the model substrate reaction was also done with 50% DMSO in water by which the yield was enhanced from 73% to 95% which explained the fact that DMSO increase only the solubility of the substrate and do not have any other effect. Moreover, aliphatic hydrazones also exhibited good yields from 73-75% with vinyl ketone. Next the feasilibility of reaction was tested with cyclic ketone however the yield was lower with respect to vinyl ketones which might be due to steric hindrance.

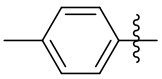
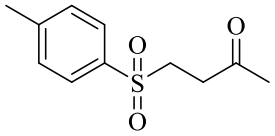
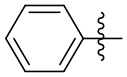
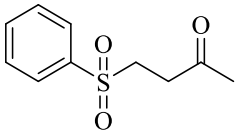
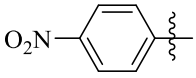
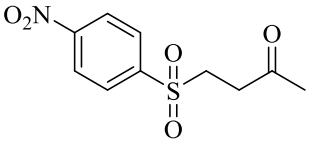
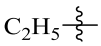
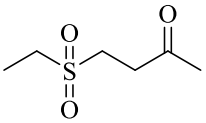
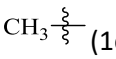
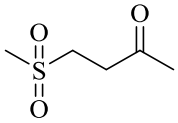
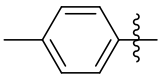
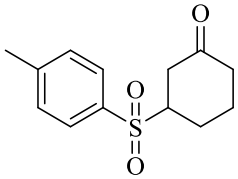
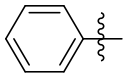
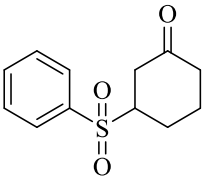
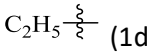
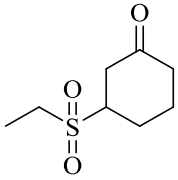
Table 2. Substrate Scope of the Reaction: Enones as Michael Acceptors[a]



1 a-e

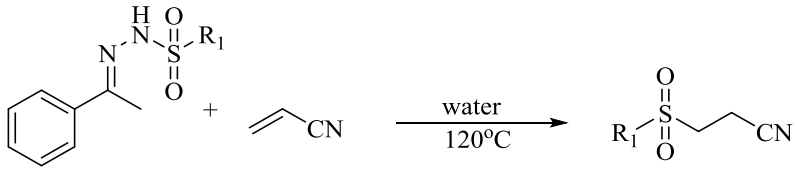
2 a: acyclic
b; cyclic

3

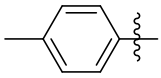
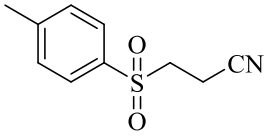
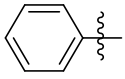
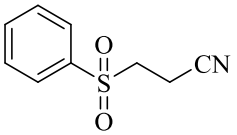
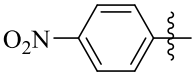
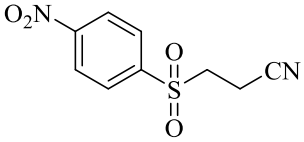
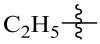
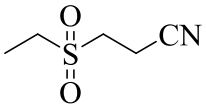
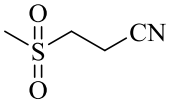
Entry	1 (R^1)	2	3	Yield (%)[b]
1	 (1a)	2a	 (3aa)	73 (95)[a]
2	 (1b)	2a	 (3ba)	60
3	 (1c)	2a	 (3ca)	22 (91)[c]
4	 (1d)	2a	 (3da)	73
5	 (1e)	2a	 (3ea)	75
6	 (1a)	2b	 (3ab)	53
7	 (1b)	2b	 (3bb)	45
8	 (1d)	2b	 (3db)	76

[a]Conditions: sulfonyl hydrazone derivates (1mmol) with enones (3mmol) in 2mL water at 120°C. [b]Yield of isolated product after column chromatography on silica gel [c] 50% DMSO in water used as solvent.

Table 3. Substrate Scope of the Reaction: Acetonitrile as Michael Acceptor[a]



1 a-e 2 c 3

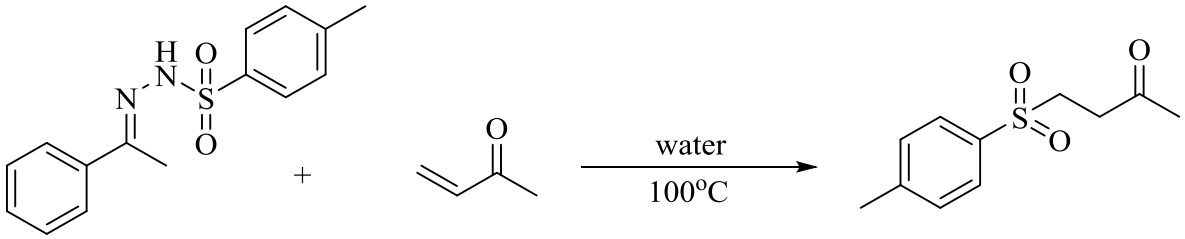
Entry	1 (R^1)	2	3	Yield (%)[b]
1	 (1a)	2c	 (3ac)	79
2	 (1b)	2c	 (3bc)	49
3	 (1c)	2c	 (3cc)	25(92)[c]
4	 (1d)	2c	 (3dc)	82
5	 (1e)	2c	 (3ec)	71

[a]Conditions: sulfonyl hydrazone derivates (1mmol) with acrylonitrile (3mmol) in 2mL water at 120ºC. [b]Yield of isolated product after column chromatography on silica gel [c] 50% DMSO in water used as solvent.

To show the breadth of methodology with other α, β unsaturated alkenes, the reaction was tried in acrylonitrile. As shown in **Table 2.** in case of aryl groups the yield was maximum i.e, 79% with electron donating group, it decreased to 49% without any substituent and least effective with electron withdrawing group whereas yield was enhanced from 25% to 92% with 50% DMSO in water. Also, the reaction was found most efficient with alkyl substituents generating the aliphatic γ-sulfone nitriles in good yields (71-82%)

2.6 Scale-up Reaction and Green Parameters

The scale-up of reactions is a very important challenge to extend the applications from laboratory to commercial pilot scale, to prove the scalability of our methodology, we implemented the reaction with 1g scale using previously optimized reaction conditions and to our delight we got 73% (0.575, 2.54 mmol) isolated yield. **Scheme 12.**



1g, 3.5mmol 0.8mL, 10.4mmol 0.575g, 2.54mmol

Scheme 12. Scale up reaction

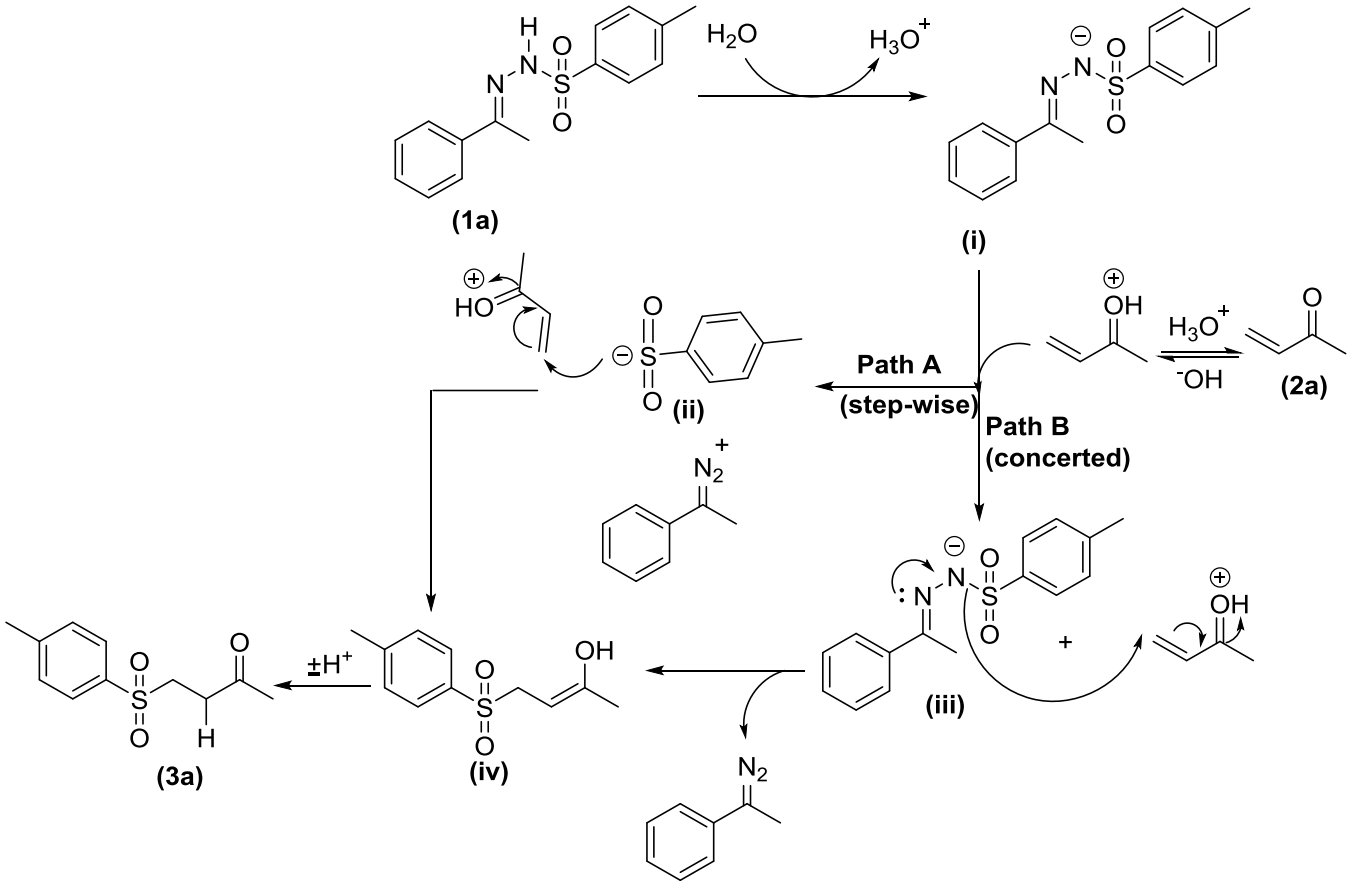
Further to quantify the greenness of the process and environmental impact various green chemistry parameters were observed as shown in **Table 4.**

Table 4. Green Parameters

E-factor (without solvent)	2.0
E-factor (with solvent)	143.18
Process Mass Intensity (PMI) (without solvent)	3.0
Process Mass Intensity (PMI) (with solvent)	144.18
Atom Economy	45.28 %
Reaction Mass Efficiency	33.27 %
Percentage Yield	73.25 %
Selectivity	76 %

2.5 Proposed Mechanism

Further, a tentative mechanism was proposed based on our observation and information's revealed in the literature. The plausible role of water is to dissociate *N*-tosylhydrazone (1a) via abstracting a proton from nitrogen to form the species (i) as shown in Scheme 3. Next, there is two possible pathways, path A consisting complete dissociation of sulfonyl anion and diazo compound followed by the conjugated addition of sulfonyl anion (ii) with methyl vinyl ketone and subsequent tautomerization to attained the final product (3a). While pathways B, comprising the concerted dissociation of species (i) and conjugated addition with methyl vinyl ketone (2a) to give intermediate (iv) which furnished the product (3a) through tautomerization.



Scheme 13. Plausible mechanism of water assisted sulfa-Michael addition using *N*-tosylhydrazone as sulfonyl anion source

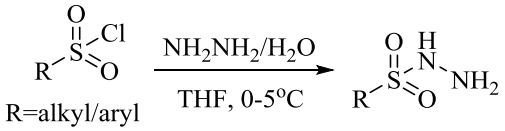
CHAPTER – 3: EXPERIMENTAL SECTION

3.1. General Information

Unless mentioned, all economically accessible reagents and analytical grade solvents were used without purification. The progress of reaction was inspected by thin layer chromatography (TLC) on silica gel coated glass plates. For column chromatography, 100-120 mesh silica gel was used to purify the products. A Bruker spectrometer: 400 and 100 MHz was used to record ^{1}HNMR and ^{13}CNMR respectively at ambient temperature with TMS as internal reference and $CDCl_3$ and DMSO as deuterated solvents. Chemical shift (δ) values are reported in parts per million (ppm) and coupling constant (J) values in Hertz (Hz). Multiplicities of the peak are indicated as s:singlet, d:doublet, t:triplet, q:quartet, m:multiplet.

3.2 i) General procedure for the synthesis of sulfonohydrazides

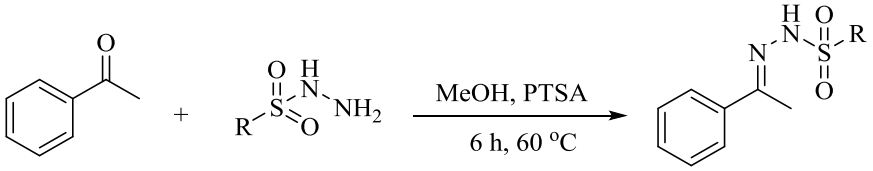
In a round bottom flask having stir bar added sulfonyl chloride (1 equiv.) in 5 mL of THF, and stirred vigorously at low temperature (~10 ^{o}C) then hydrazine hydrate (2.5 equiv.) was added dropwise and mixture was stirred for 15 minutes. The reaction was monitored by TLC and after completion of the reaction, mixture was diluted in water (5 mL) and extracted by ethyl acetate (2x10 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure affording the sulfonyl hydrazides in 50-80% yields and used in next step without any further purification.



ii) General procedure for the synthesis of sulfonyl hydrazones

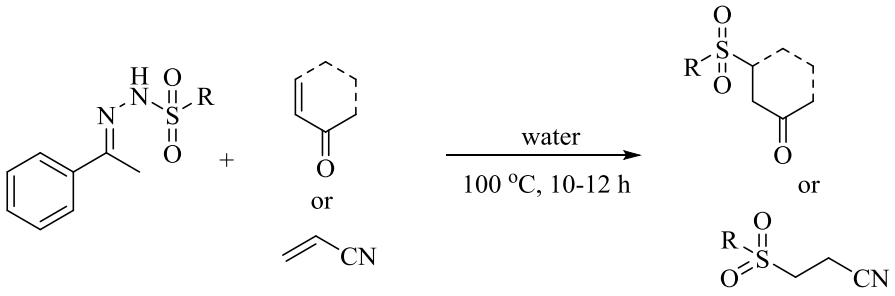
To a solution of sulfonyl hydrazides (1.5 equiv.) in methanol (5-10 mL) added acetophenone (1 equiv.) and p-toluenesulfonic acid (catalytic amount) and stirred the reaction mixture for ~8 h at 60 ^{o}C. After completion of reaction as monitored by TLC, the reaction mixture was cooled at

room temperature and obtained crude product as white colored precipitate. The product was filtered and washed the precipitates with methanol and obtained the pure product in 90% yield.



iii) General procedure for the synthesis of γ-keto sulfones and γ-sulfone nitrile.

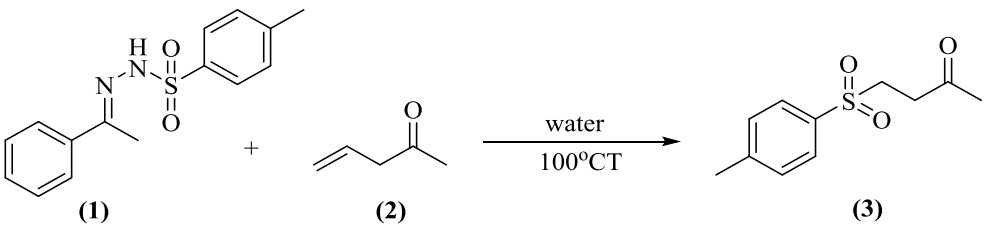
In a sealed tube with teflon cap having a stirrer bar added hydrazone (1 equiv.) and enones or acrylonitrile (3 equiv.) in water (2 mL) as a solvent. The resultant mixture was stirred at 100 ^{o}C for 10-12 h and the reaction was monitored by TLC using ethyl acetate in hexane as mobile phase. After completion of the reaction, mixture was diluted in water (5 mL) and extracted by ethyl acetate (2x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The desired γ-keto sulfones and γ-nitrile sulfones were obtained by column chromatography on silica gel using ethyl acetate in hexane as eluent in 40-90 % yields.



iv) Gram scale synthesis of γ-keto sulfones (4-tosylbutane-2-one).

In a sealed tube with teflon cap having a stirrer bar added N-tosylhydrazone (1g, 3.5 mmol) and methyl vinyl ketone (0.8mL, 10.4mmol) in water (4 mL) as a solvent. The resultant reaction mixture was stirred at 100 ^{o}C for 10-12 h and the reaction was monitored by TLC using ethyl acetate in hexane as mobile phase. After completion of the reaction, mixture was diluted in water (15 mL) and extracted by ethyl acetate (3x30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The desired 4-tosylbutan-2-one (0.575g, 2.54mmol) was obtained by column chromatography on silica gel using ethyl acetate in hexane as eluent in 73% yield.

Green chemistry metrics calculations for the scale up reaction:



(1) **(2)** **(3)**

E-factor (without solvent) = [1 g (N-tosyl hydrazone 1) + 0.728 g (methylvinyl ketone 2) -0.575 g (4-tosylbutan-2-one 2)]/ 0.575 g

E-factor (with solvent) = [1 g (N-tosyl hydrazone 1) + 0.728 g (methylvinyl ketone 2) + 81.18 g (solvent) - 0.575 g (4-tosylbutan-2-one 2)]/ 0.575 g

E-factor = 2.0 (without solvent)

E-factor = 143.18 (with solvent)

Process mass intensity (PMI) = 2 + 1 (without solvent)

143.18 + 1 (with solvent)

PMI = 3.0 (without solvent)

PMI = 144.18 (with solvent)

Atom economy (AE) = 226.29g/mol (4-tosylbutan-2-one 2) / [288.365g/mol (N-tosyl hydrazone 1) + 210.273g/mol (methylvinyl ketone 2)] × 100

AE = 45.38%

Reaction mass efficiency (RME) = 0.575g (4-tosylbutan-2-one 2) / [1g (N-tosyl hydrazone 1) + .728 (methylvinyl ketone 2)] × 100

RME = 33.27%

Percentage Yield = 0.785g (4-tosylbutan-2-one 2) / .575g (4-tosylbutan-2-one 2) × 100

Percentage Yield = 73.25%

Selectivity = 76 %

3.3. Characterization of compounds:

4-tosylbutan-2-one (3aa) :

Liquid, Yellow, Yield = 73%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 3.37 (t, *J* = 7.2 Hz, 2H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.46 (s, 3H), 2.18 (s, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 203.9, 145.1, 136.2, 130.2, 128.1, 50.8, 36.1, 30.0, 21.9 ppm.

4-(phenylsulfonyl)butan-2-one (3ba) :

Liquid, Yellow, Yield = 73%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.2 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 2H), 3.39 (t, *J* = 7.2 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.17 (s, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 203.8, 139.1, 134.1, 129.5, 128.1, 50.7, 36.0, 30.0 ppm.

4-((4-nitrophenyl)sulfonyl)butan-2-one (3ca) :

Solid, White, Yield = 99%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 8.4 Hz, 2H), 3.46 (t, *J* = 7.2 Hz, 2H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.21 (s, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 203.3, 151.2, 144.9, 129.7, 124.8, 50.7, 35.6, 30.0 ppm.

4-(ethylsulfonyl)butan-2-one (3da) :

Liquid, Colorless, Yield = 73%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27 (t, *J* = 7.2 Hz, 2H), 3.05-2.99 (m, 4H), 2.25 (s, 3H), 1.44 (t, *J* = 7.6 Hz, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 204.4, 48.3, 46.0, 35.1, 30.0, 6.8 ppm.

4-(methylsulfonyl)butan-2-one (3ea) :

Solid, White crystals, Yield = 75%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (t, *J* = 7.2 Hz, 2H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.94 (s, 3H), 2.25 (s, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 204.2, 49.1, 41.8, 35.7, 30.0 ppm.

3-tosylcyclohexan-1-one (3ab) :

Liquid, Yellow, Yield = 53%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 3.30-3.23 (m, 1H), 2.59-2.51 (m, 2H), 2.46 (s, 3H), 2.43-2.21 (m, 4H), 1.96-1.87 (m, 1H), 1.68-1.62 (m, 1H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 206.7, 145.5, 133.7, 130.2, 129.1, 62.5, 40.7, 40.6, 23.9, 23.6, 21.8 ppm.

3-(phenylsulfonyl)cyclohexan-1-one (3bb) :

Liquid, Yellow, Yield = 45%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.87 (m, 2H), 7.72-7.68 (m, 1H), 7.62-7.50 (m, 2H), 3.35-3.24 (m, 1H), 2.61-2.53 (m, 2H), 2.44-2.18 (m, 4H), 1.99-1.88 (m, 1H), 1.70-1.59 (m, 1H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 206.6, 136.8, 134.3, 129.6, 129.1, 62.5, 40.6, 40.5, 23.8, 24.0 ppm.

3-(ethylsulfonyl)cyclohexan-1-one (3db) :

Liquid, Yellow, Yield = 76%, ^{1}H NMR (400 MHz, $CDCl_3$): 3.34-3.26 (m, 1H), 3.03 (q, *J* = 7.6 Hz, 2H), 2.77-2.65 (m, 2H), 2.49-2.25 (m, 4H), 2.08-1.96 (m, 1H), 1.79-1.67 (m, 1H), 1.43 (t, *J* = 7.6 Hz, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 206.5, 58.8, 44.9, 40.6, 40.0, 23.7, 23.2, 6.3 ppm.

3-tosylpropanenitrile (3ac) :

Solid, White, Yield = 79%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 3.38 (t, *J* = 8 Hz, 2H), 2.82 (t, *J* = 8 Hz, 2H), 2.48 (s, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 146.2, 134.7, 130.6, 128.5, 116.2, 51.4, 21.9, 12.2 ppm.

3-(phenylsulfonyl)propanenitrile (3bc) :

Solid, White, Yield = 49%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.93 (m, 2H), 7.76-7.72 (m, 1H), 7.66-7.62 (m, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 137.7, 134.9, 130.0, 128.4, 116.1, 51.3, 12.2 ppm.

3-((4-nitrophenyl)sulfonyl)propanenitrile (3cc) :

Solid, White, Yield = 93%, ^{1}H NMR (400 MHz, DMSO): δ 8.50 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.8 Hz, 2H), 3.92 (t, *J* = 7.2 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H) ppm, ^{13}C NMR (100 MHz, DMSO): 150.8, 143.3, 129.9, 124.7, 117.5, 49.3, 11.3 ppm.

3-(ethylsulfonyl)propanenitrile (3dc) :

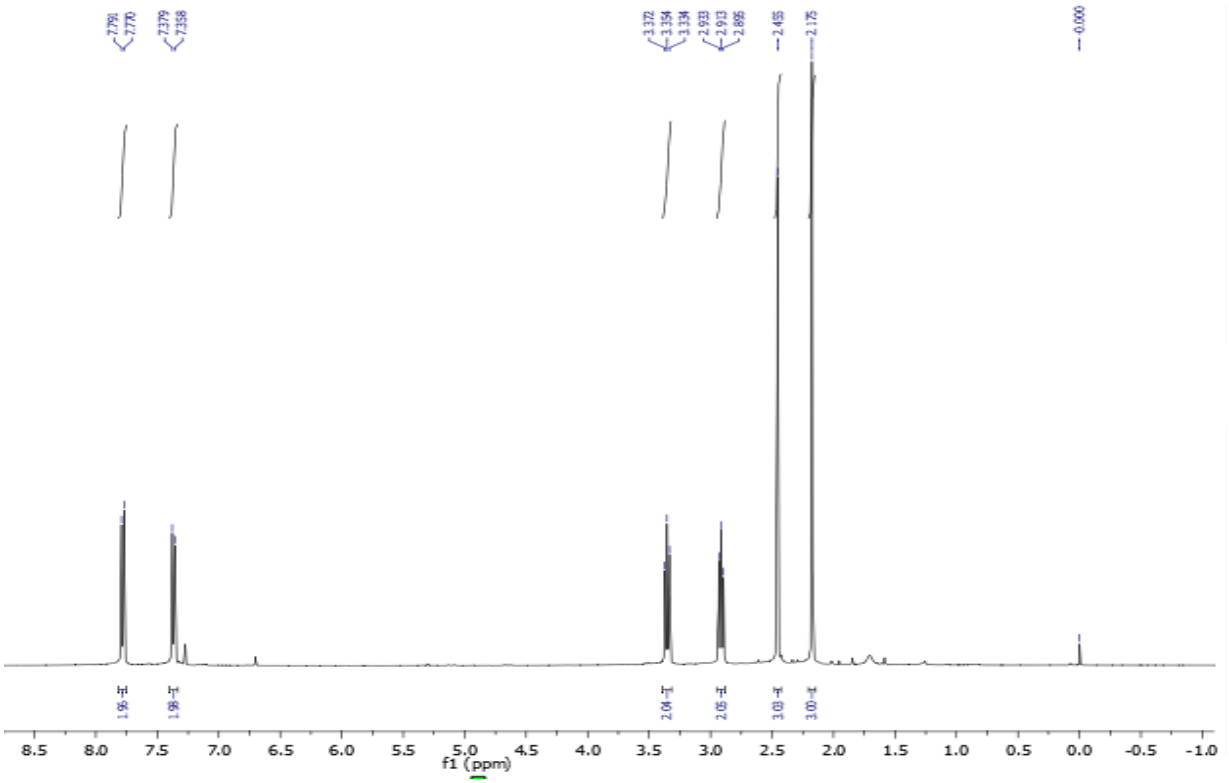
Liquid, Yellow, Yield = 82%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.31 (t, *J* = 7.2 Hz, 2H), 3.16 (q, *J* = 7.6 Hz, 2H), 2.95 (t, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.6 Hz, 3H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 116.8, 48.2, 47, 11.3, 6.6 ppm.

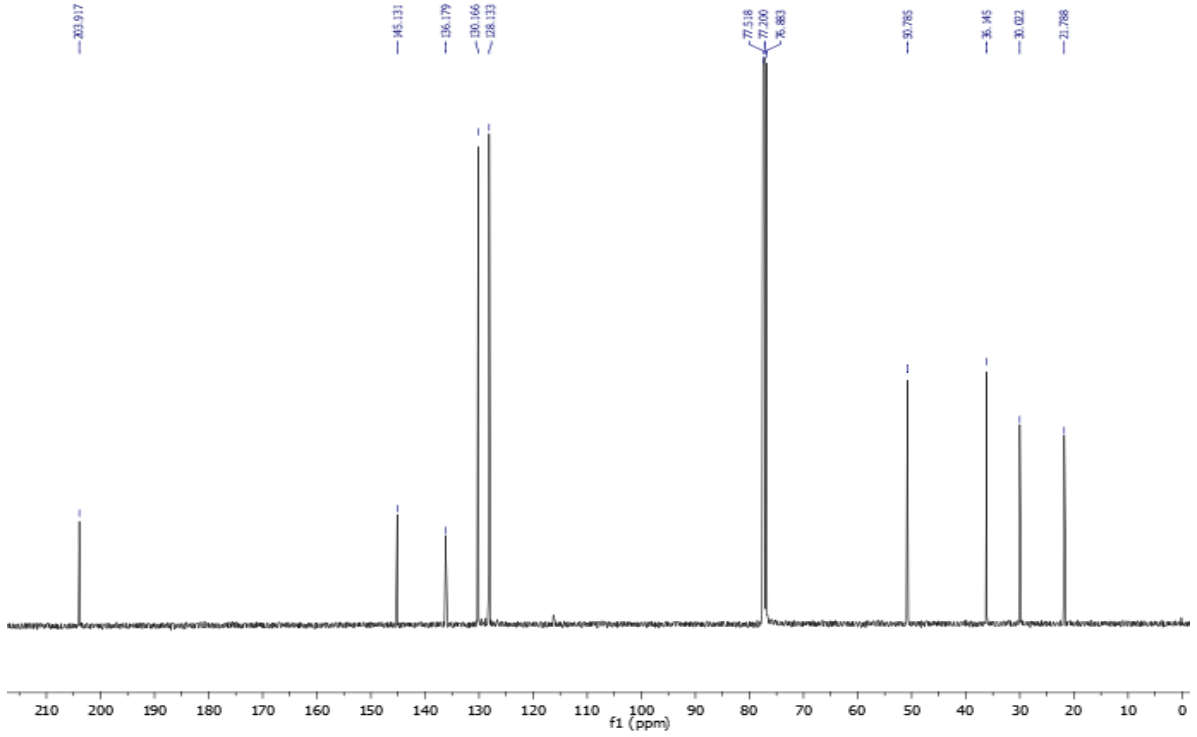
3-(methylsulfonyl)propanenitrile (3ec) :

Solid, White crystals, Yield = 71%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (t, *J* = 7.2 Hz, 2H), 3.06 (s, 3H), 2.96 (t, *J* = 7.2 Hz, 2H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$): 116.6, 79.9, 41.7, 11.9 ppm.

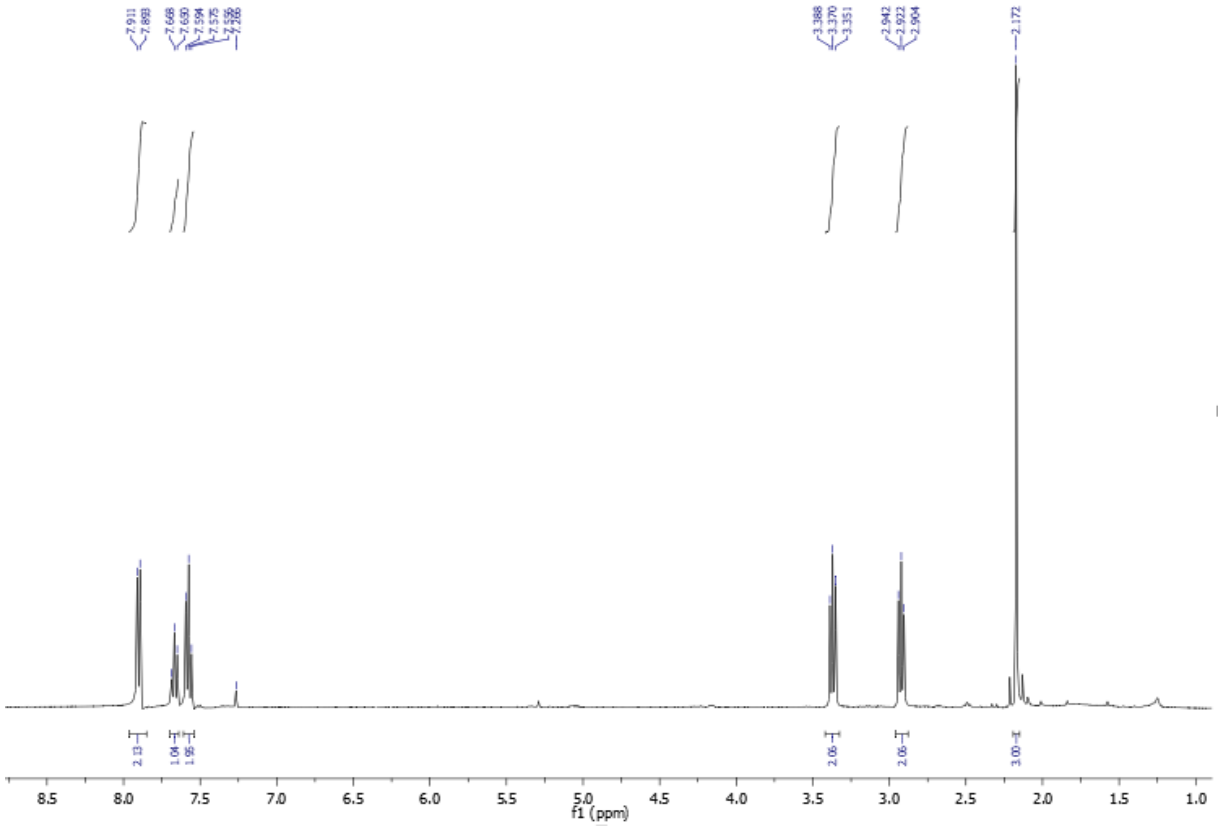
3.4 ^{1}H NMR and ^{13}C NMR Spectra

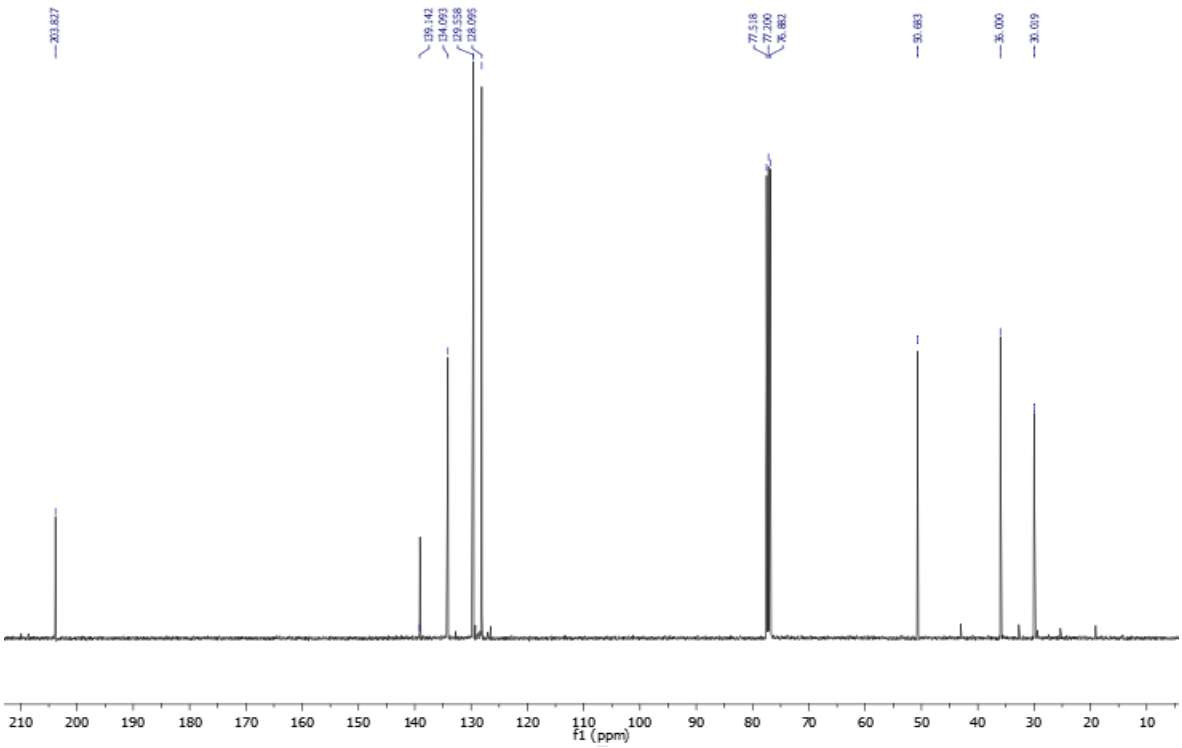
1H NMR and 13C NMR Spectra of 3aa



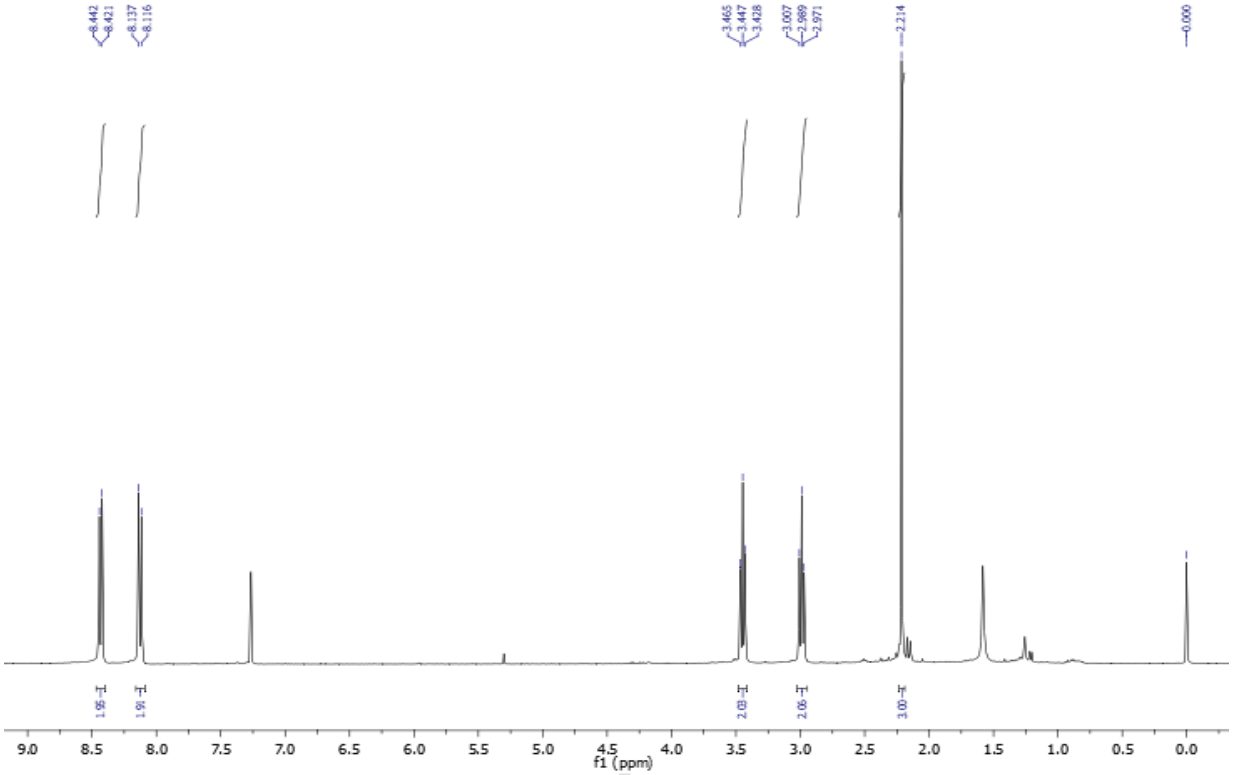


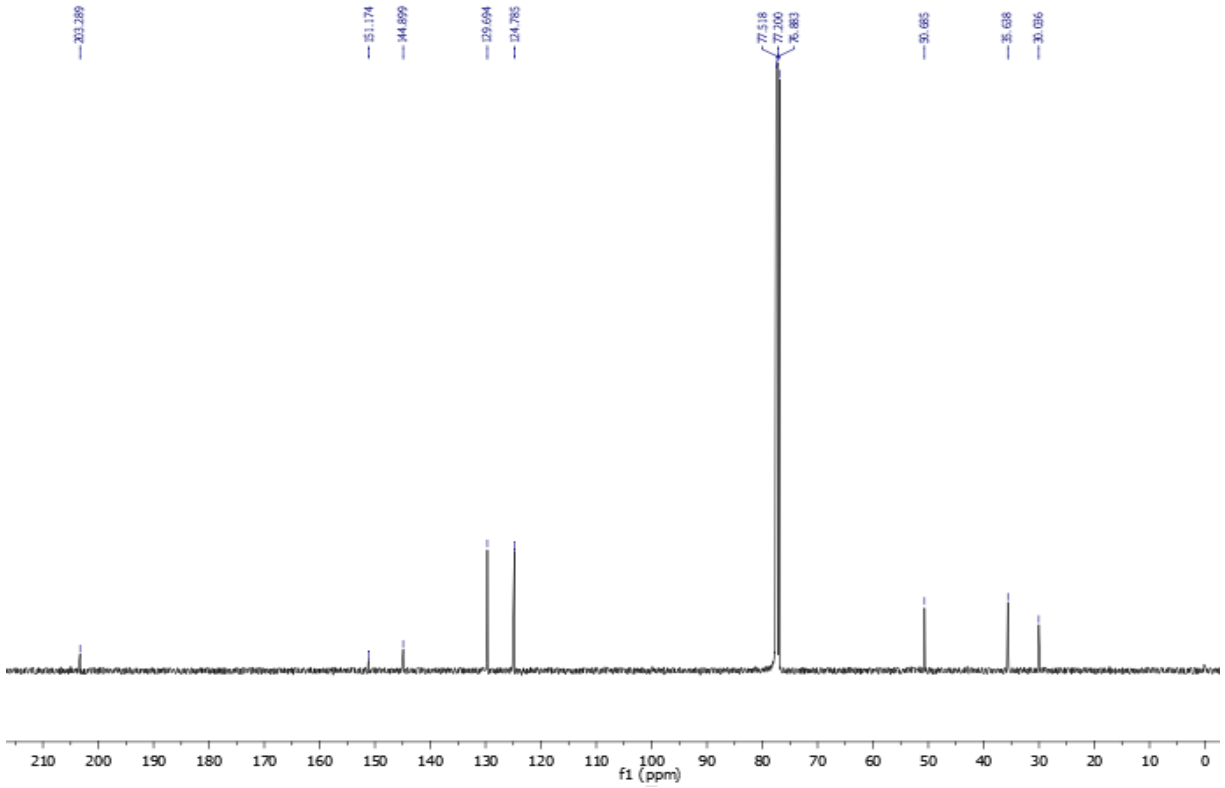
1H NMR and 13C NMR Spectra of 3ba



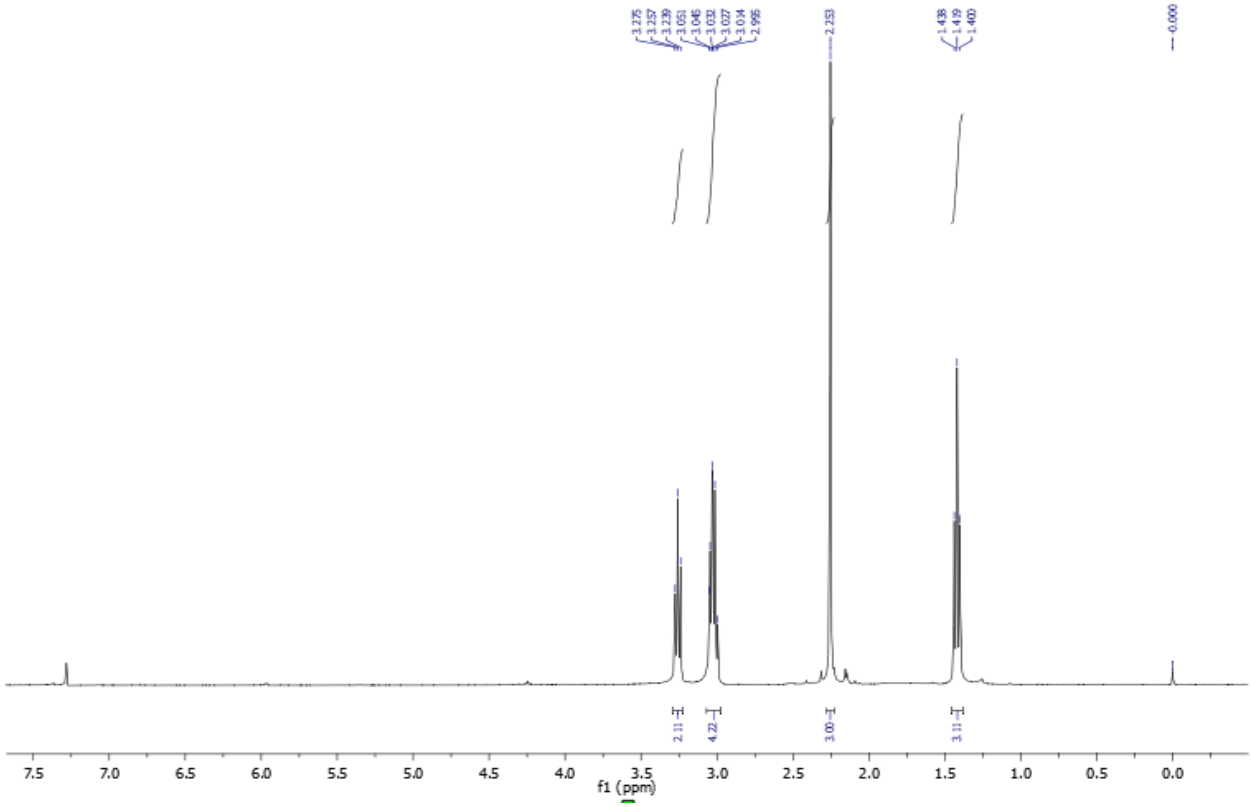


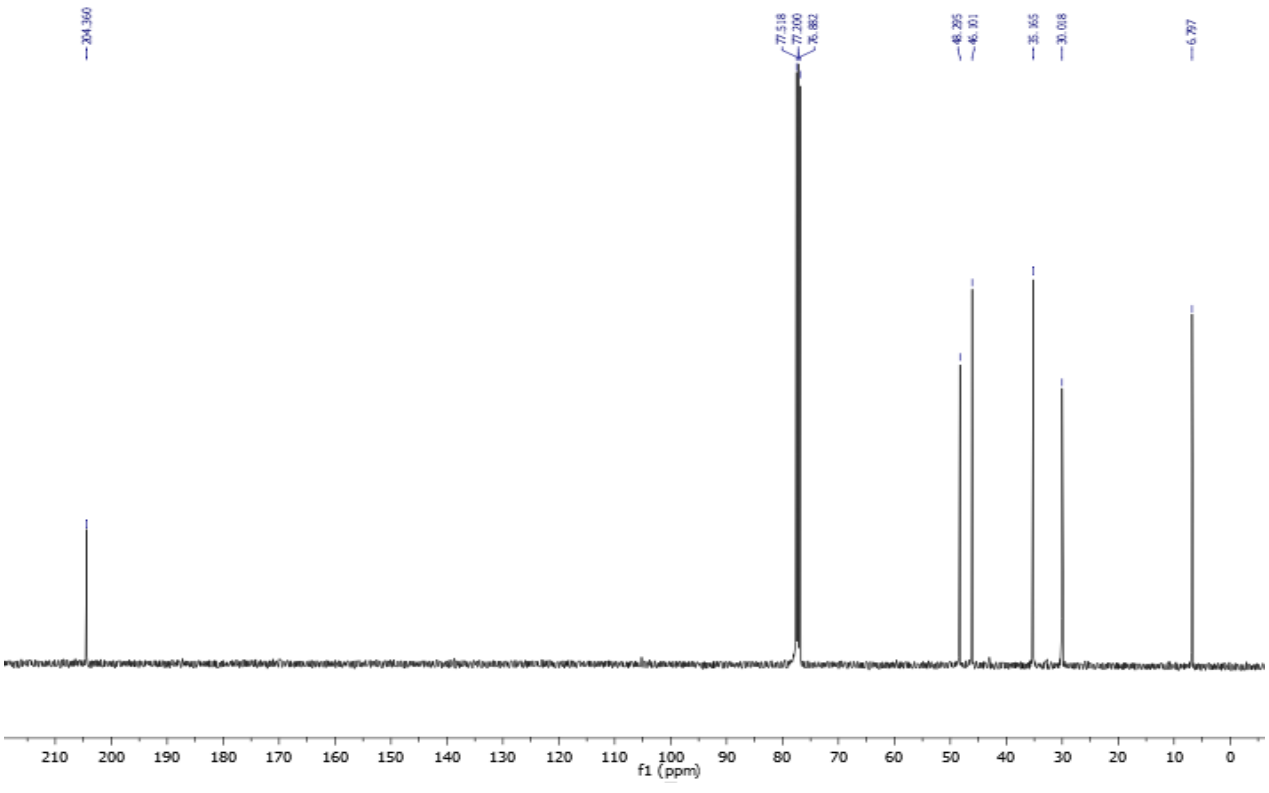
1H NMR and 13C NMR Spectra of 3ca



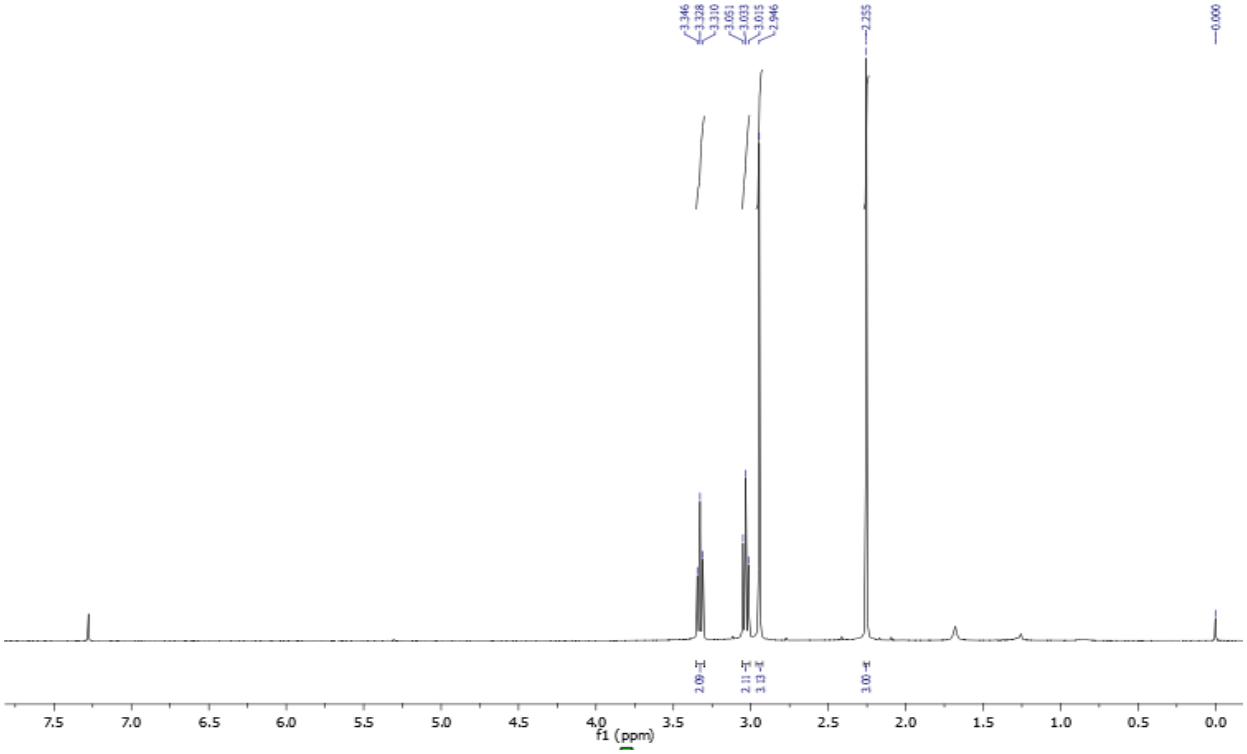


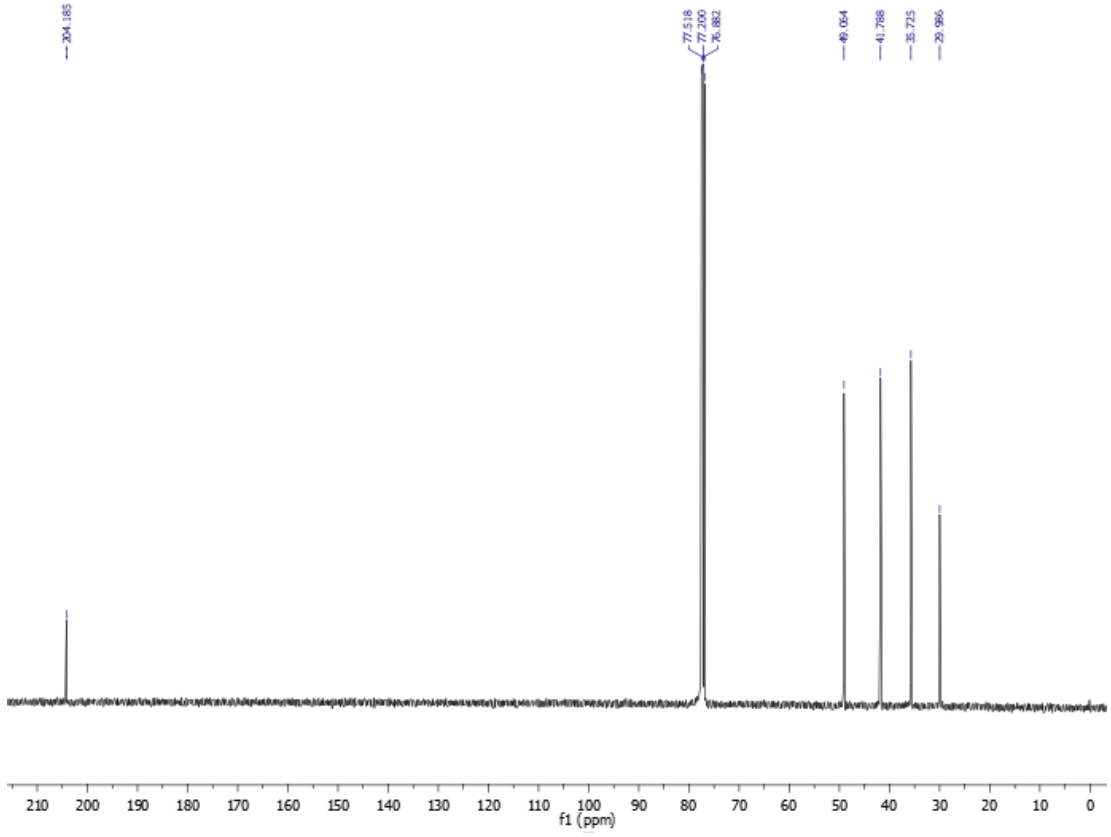
1H NMR and 13C NMR Spectra of 3da



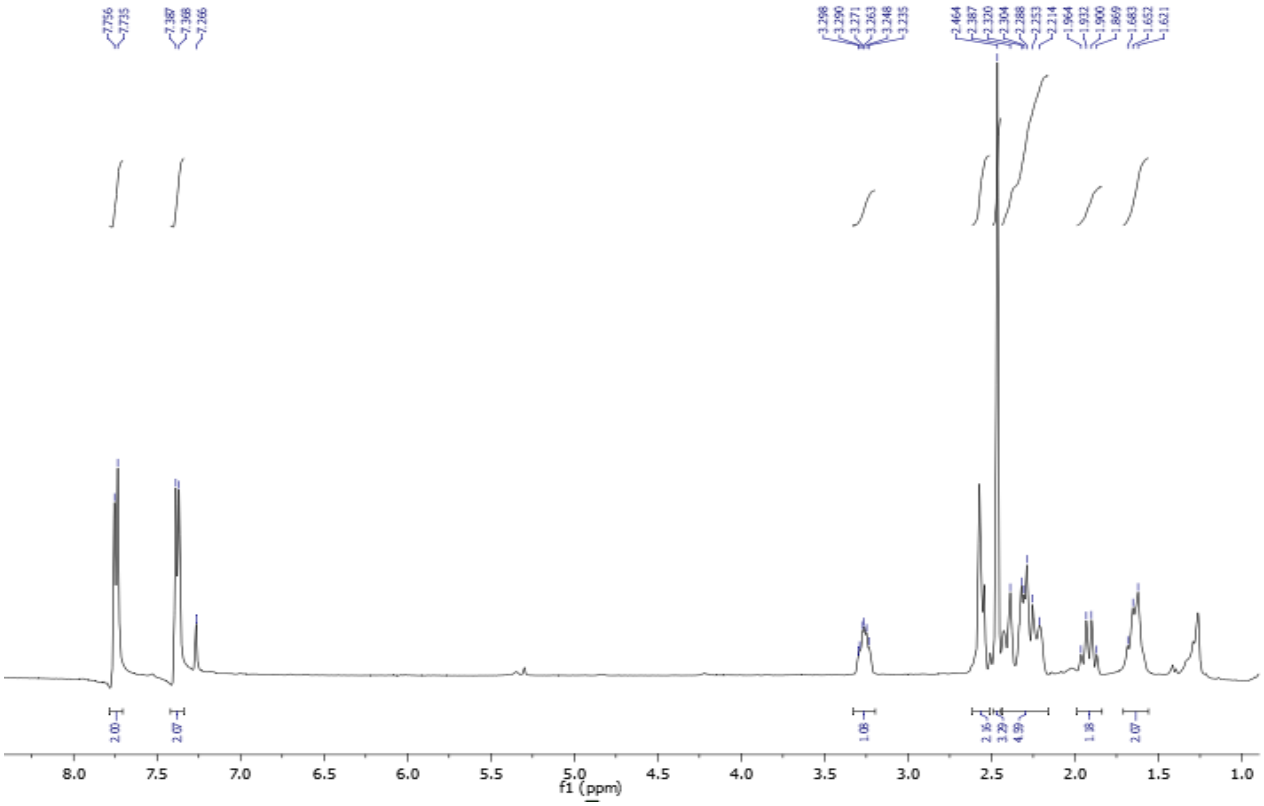


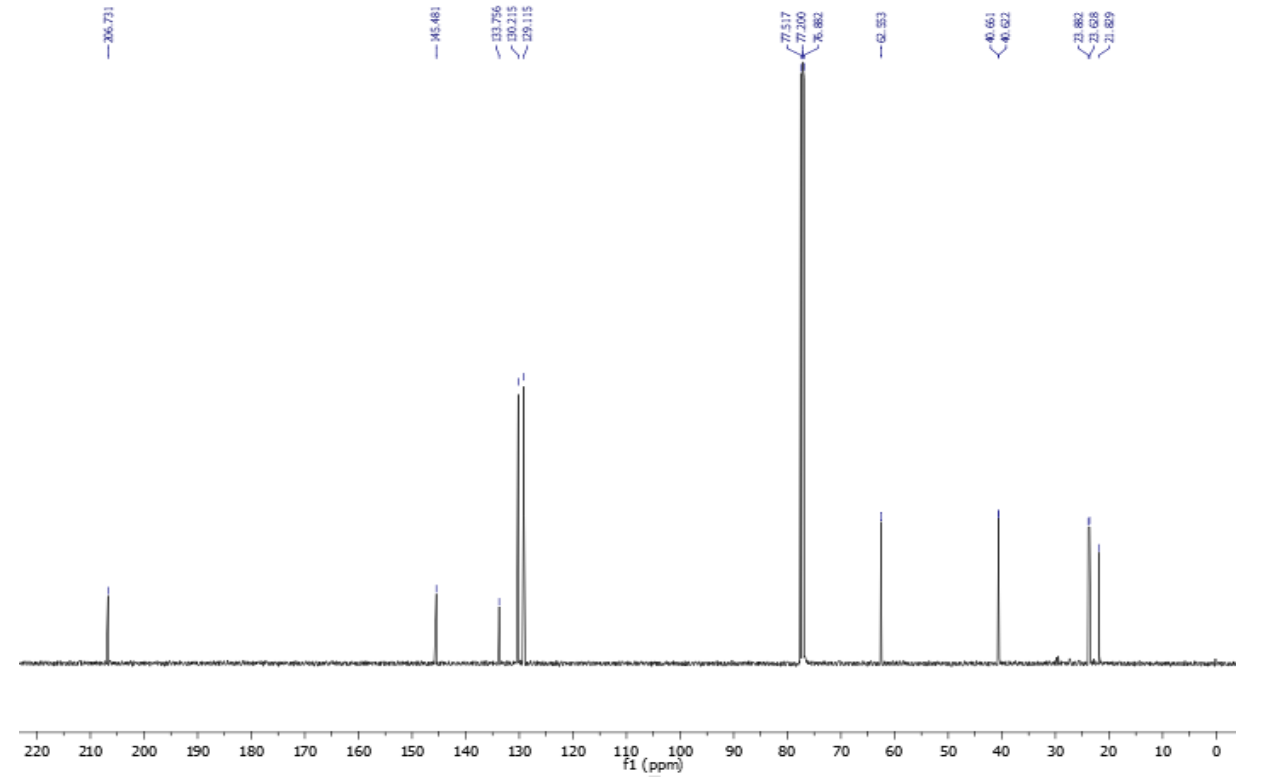
1H NMR and 13C NMR Spectra of 3ea



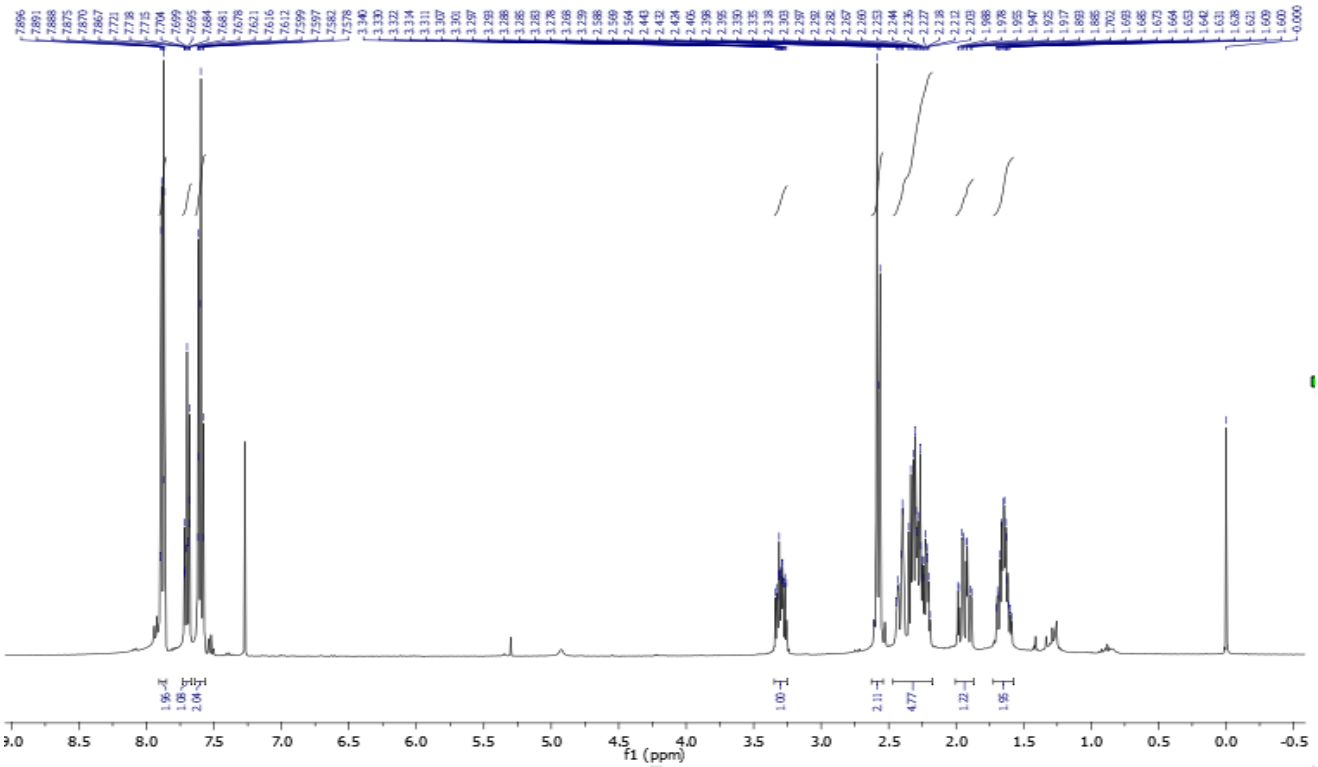


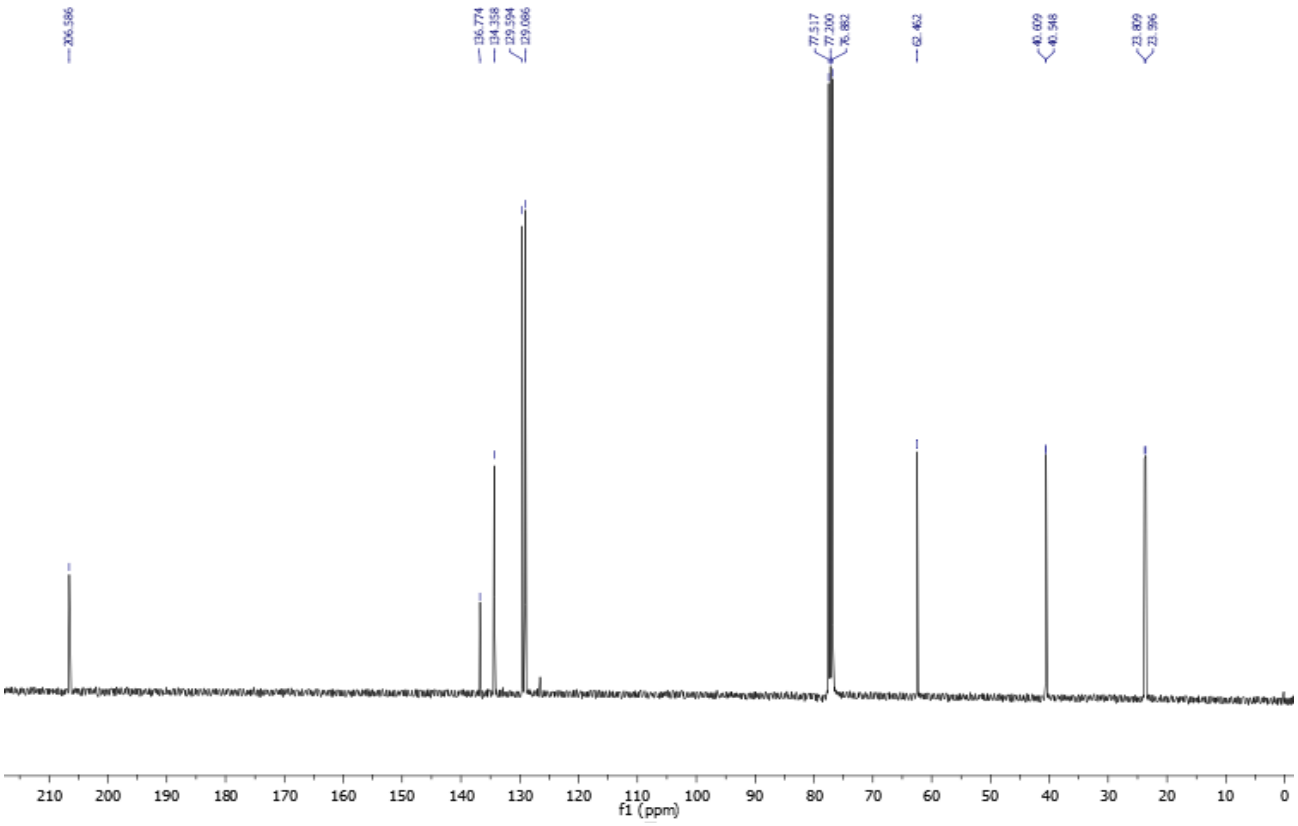
1H NMR and 13C NMR Spectra of 3ab



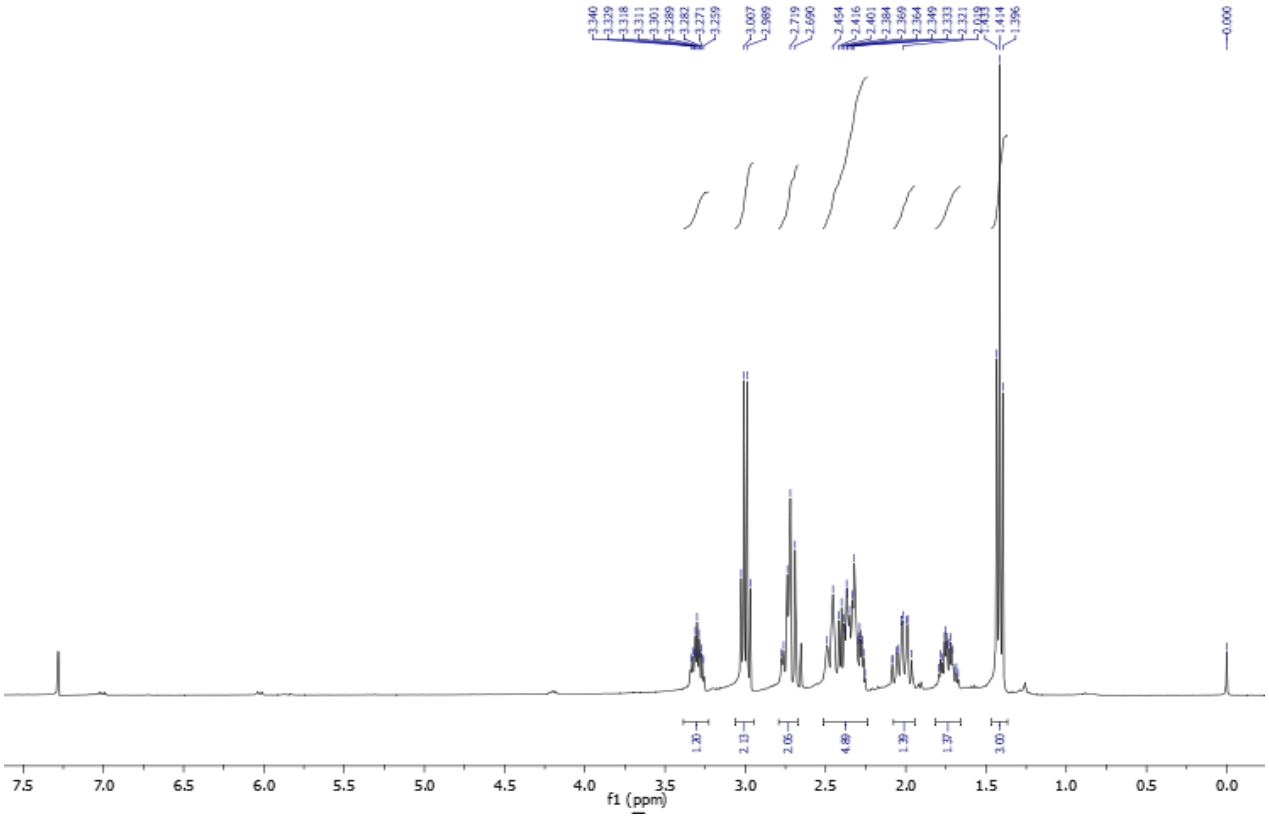


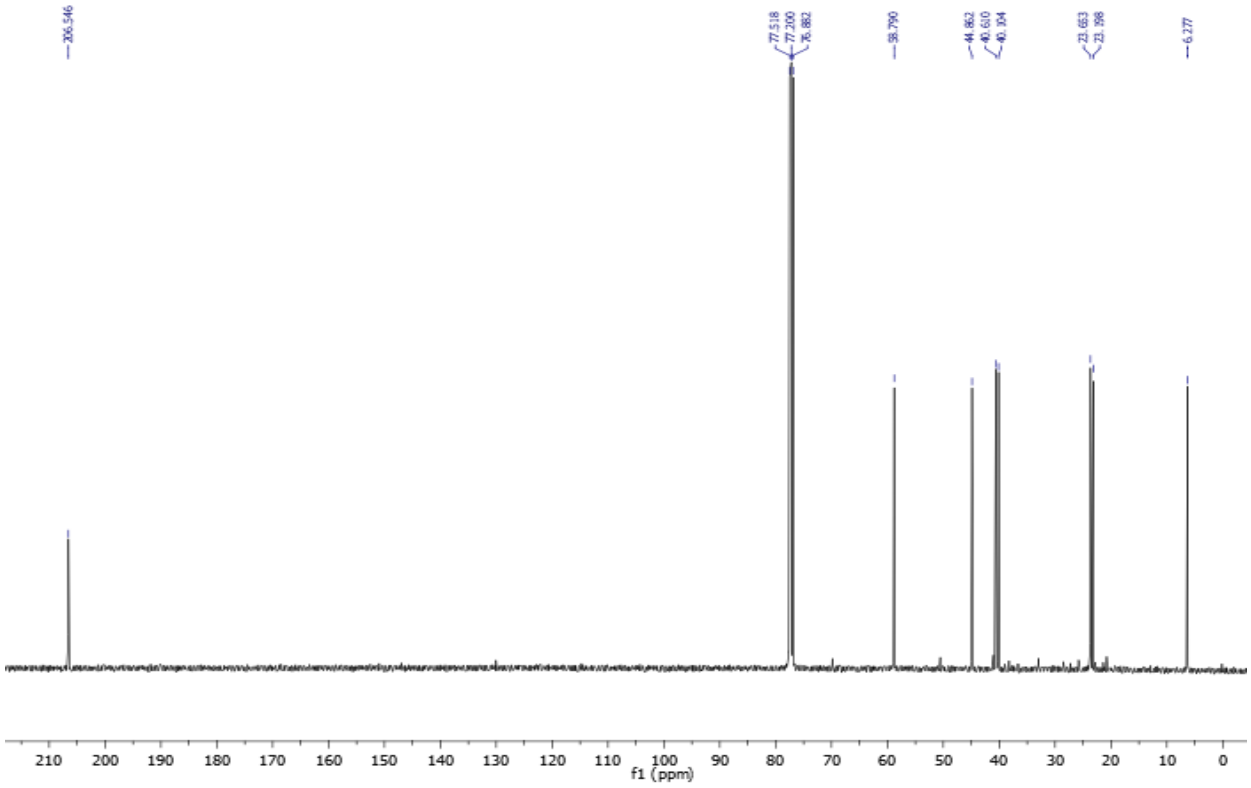
1H NMR and 13C NMR Spectra of 3bb



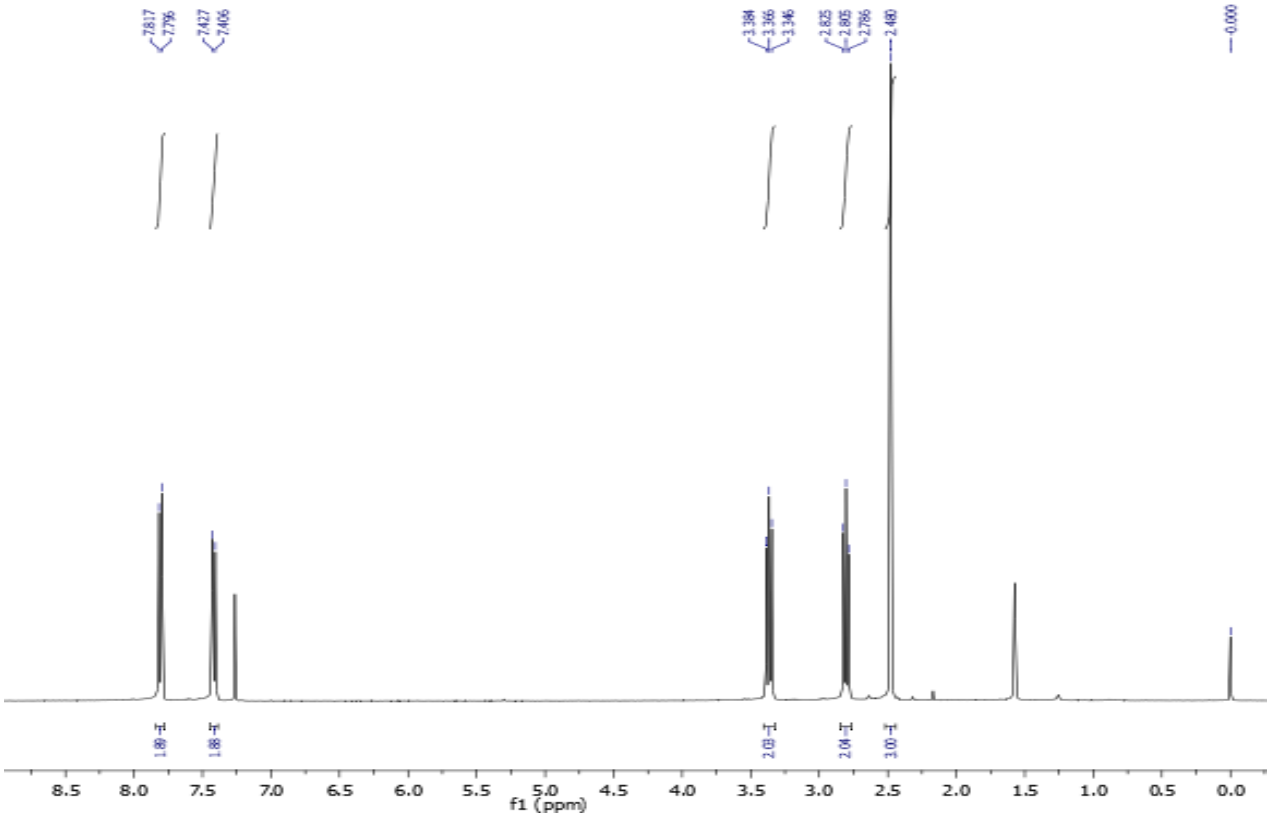


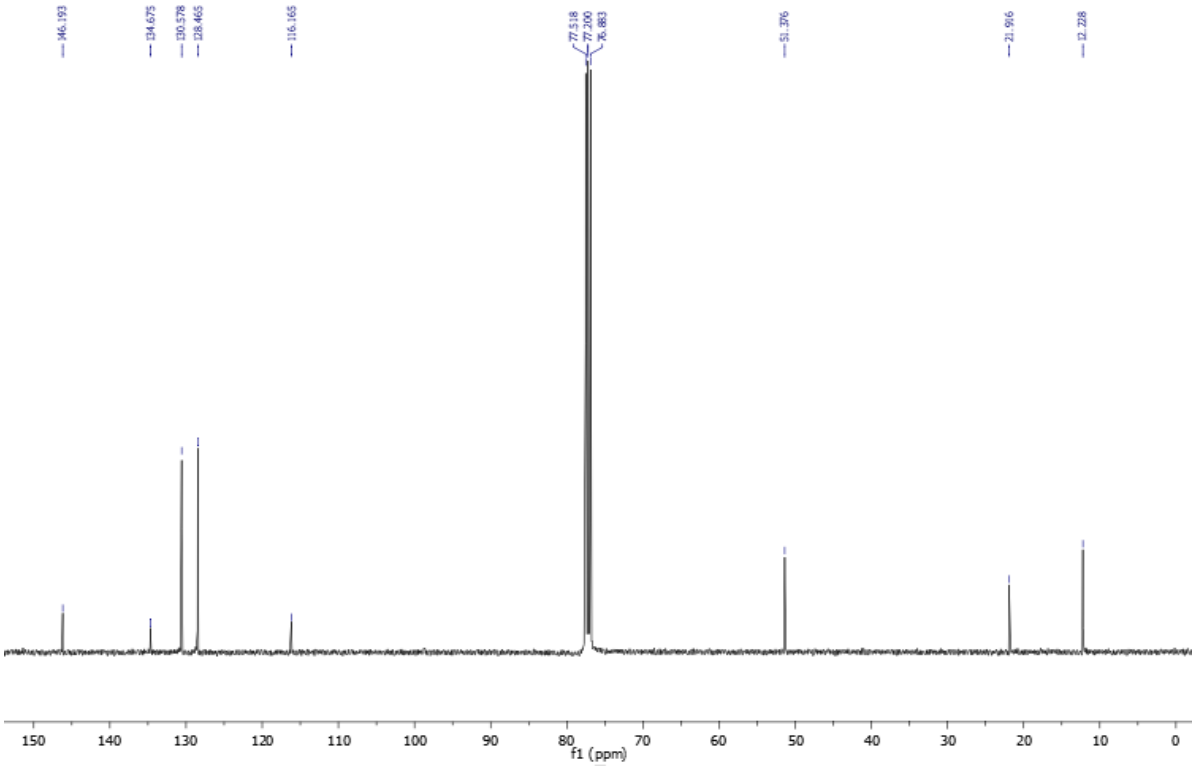
1H NMR and 13C NMR Spectra of 3db



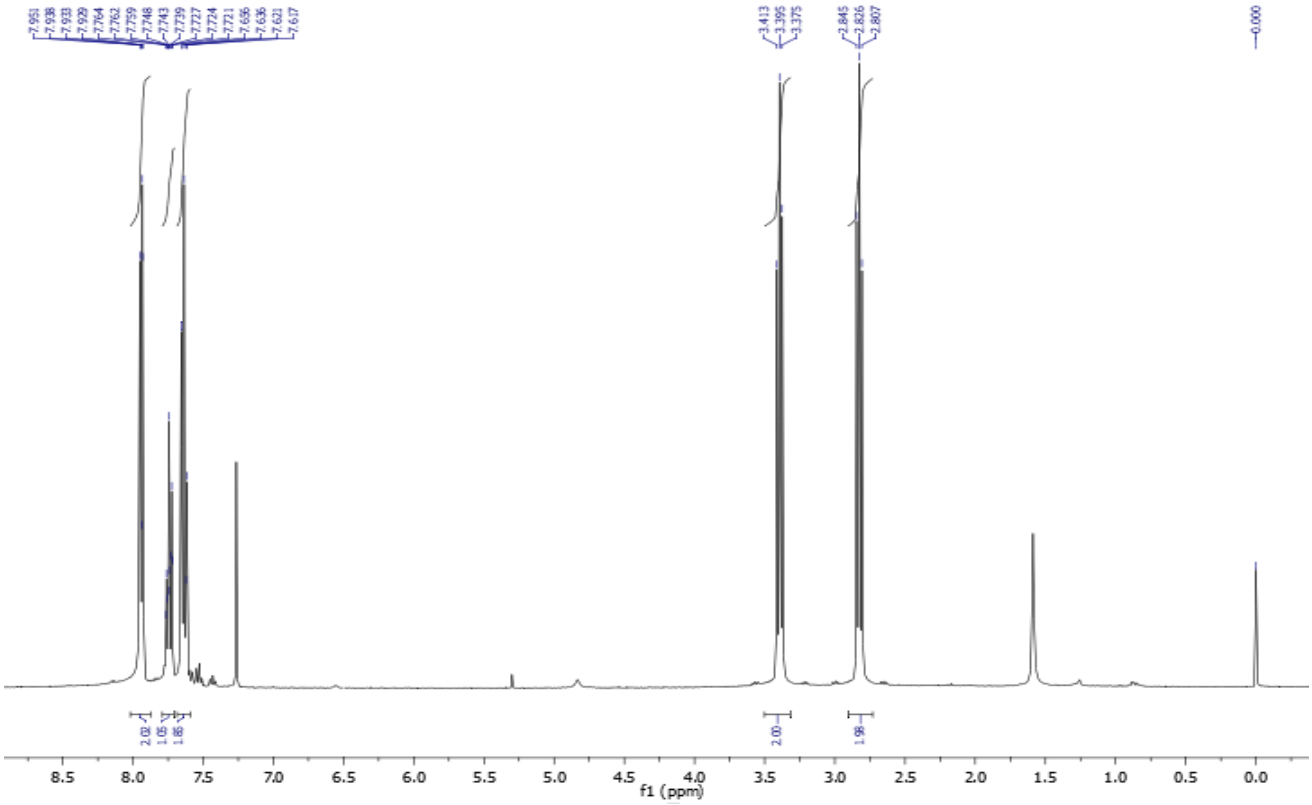


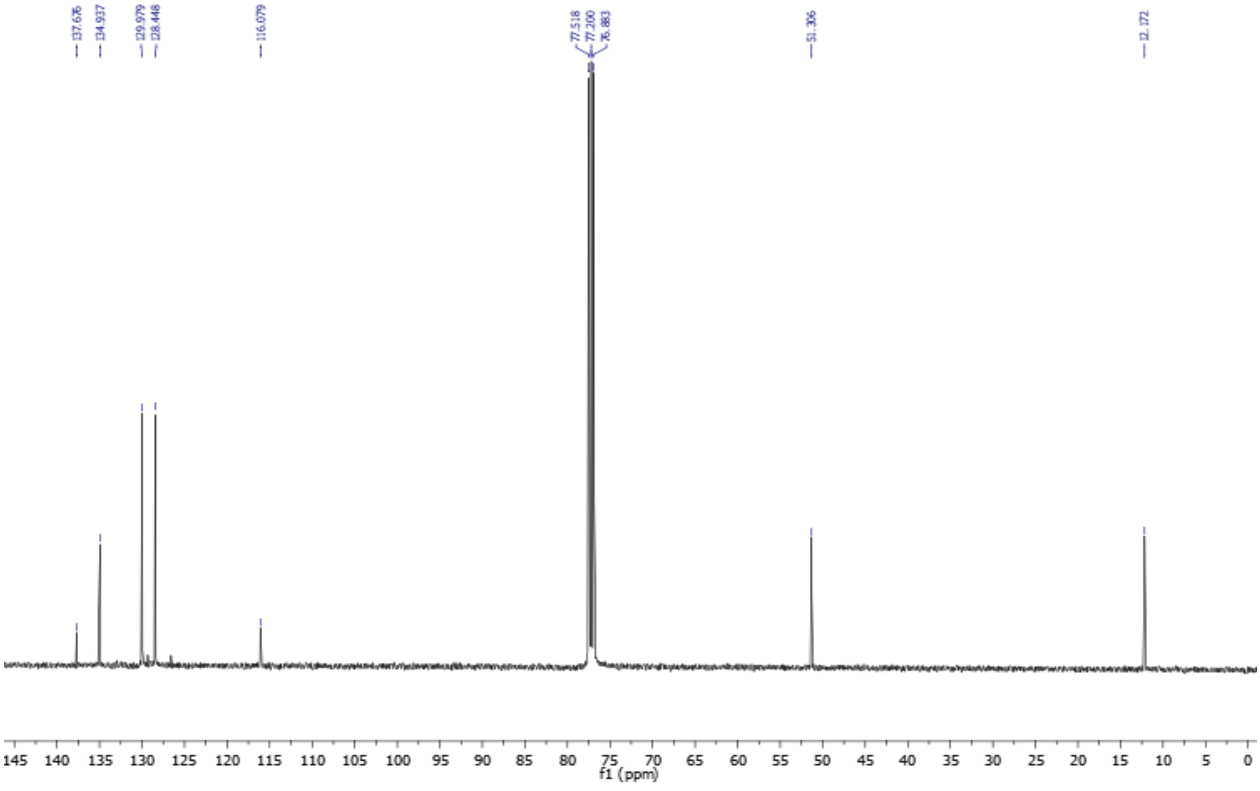
1H NMR and 13C NMR Spectra of 3ac



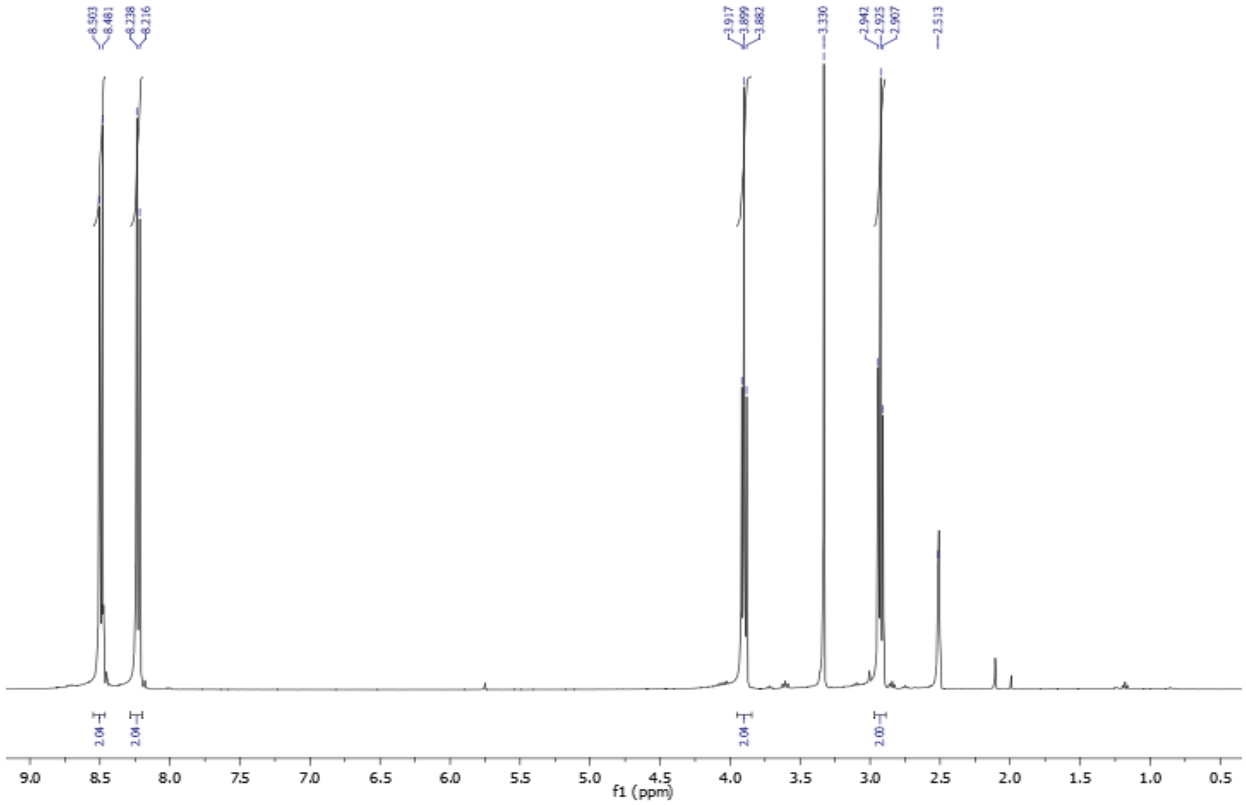


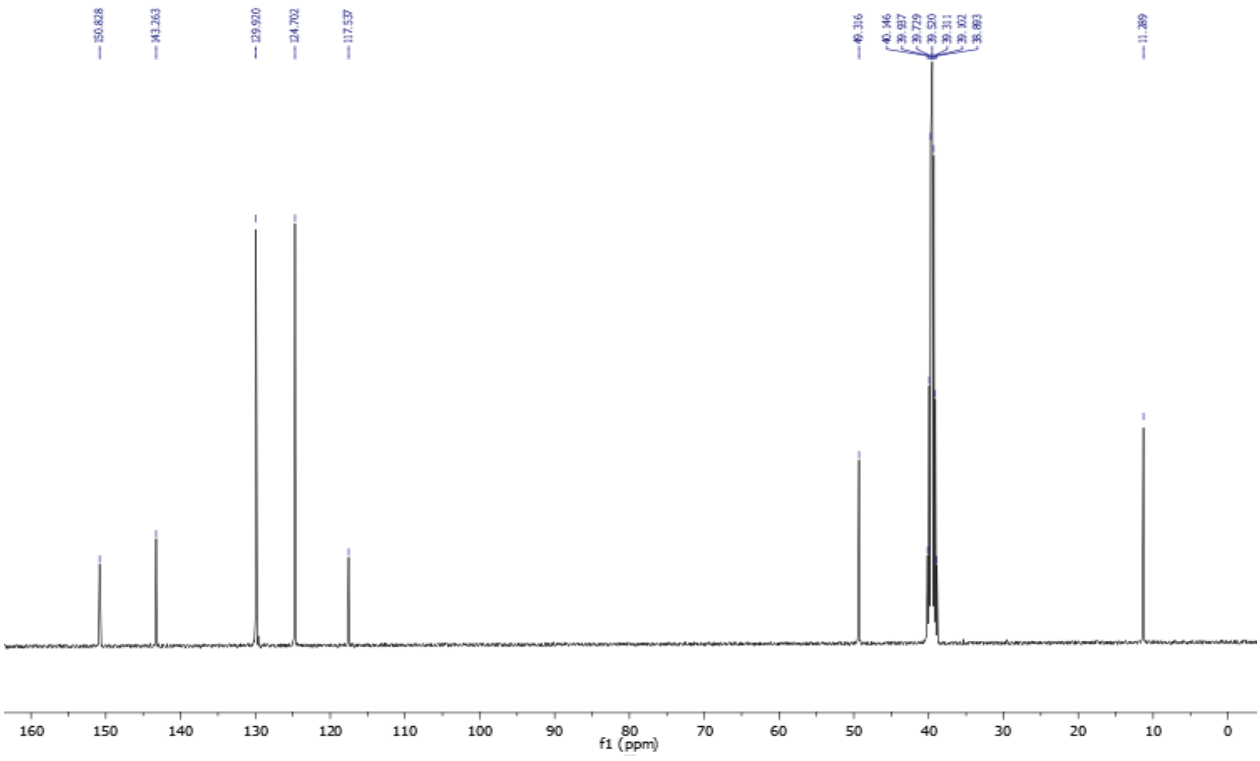
1H NMR and 13C NMR Spectra of 3bc



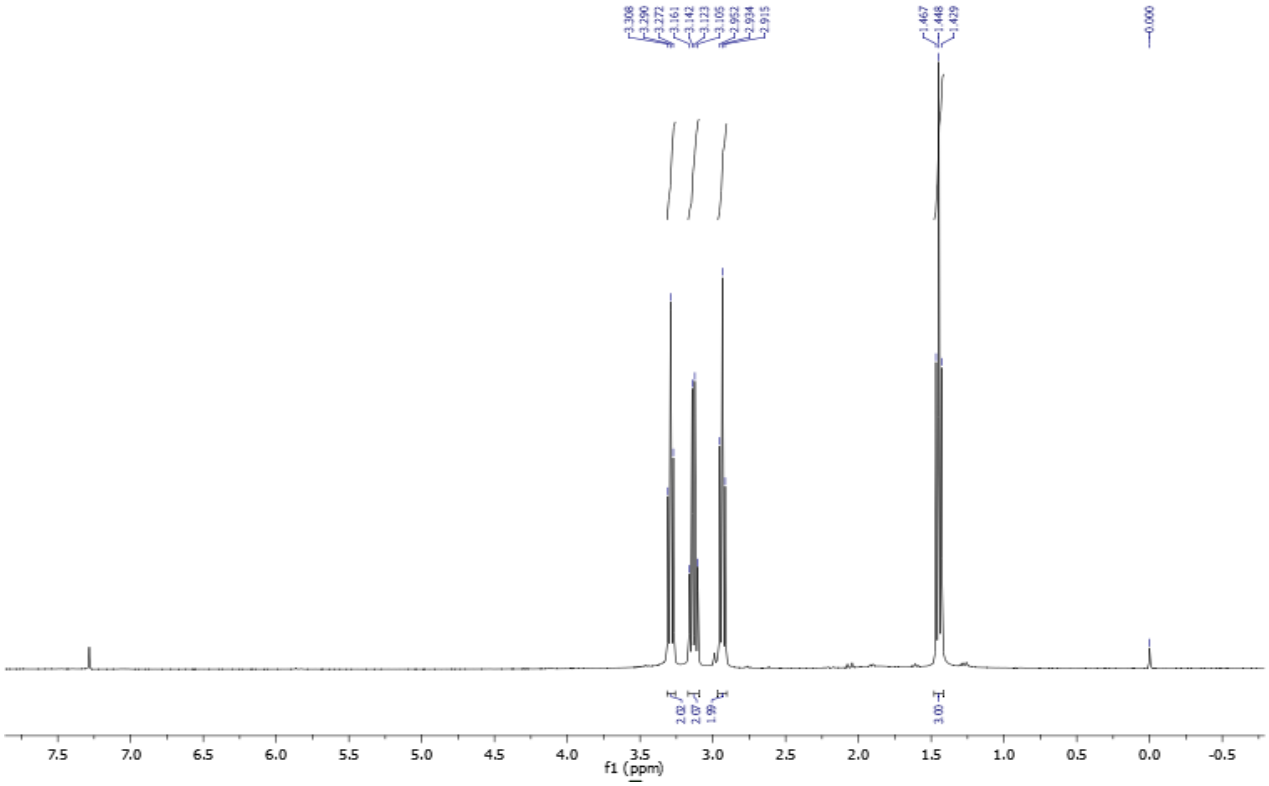


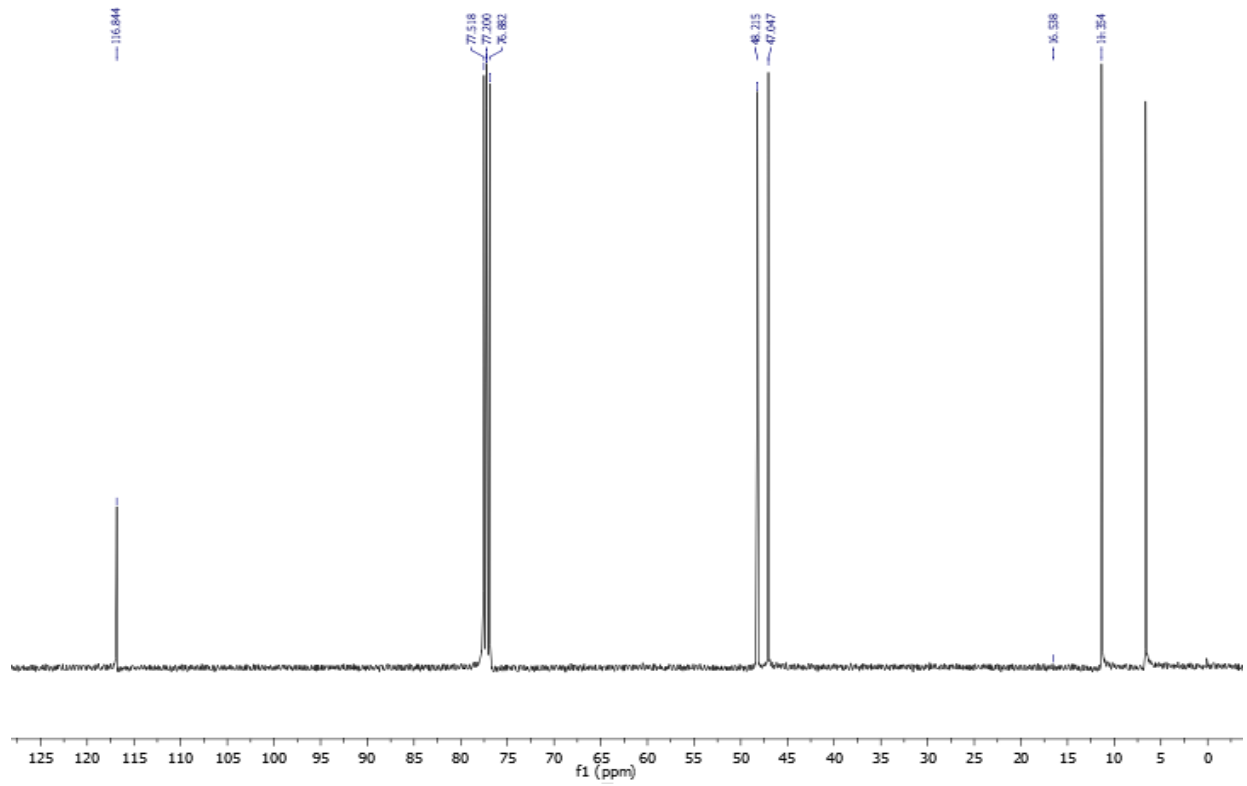
1H NMR and 13C NMR Spectra of cc



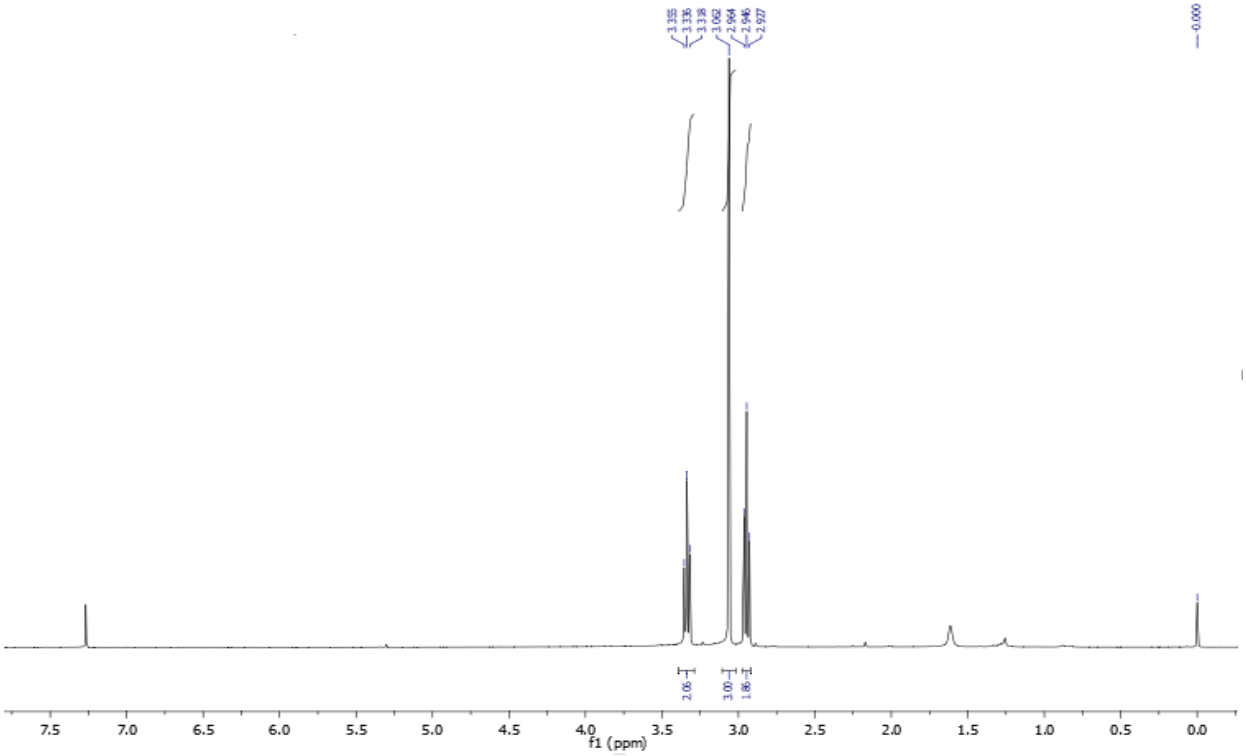


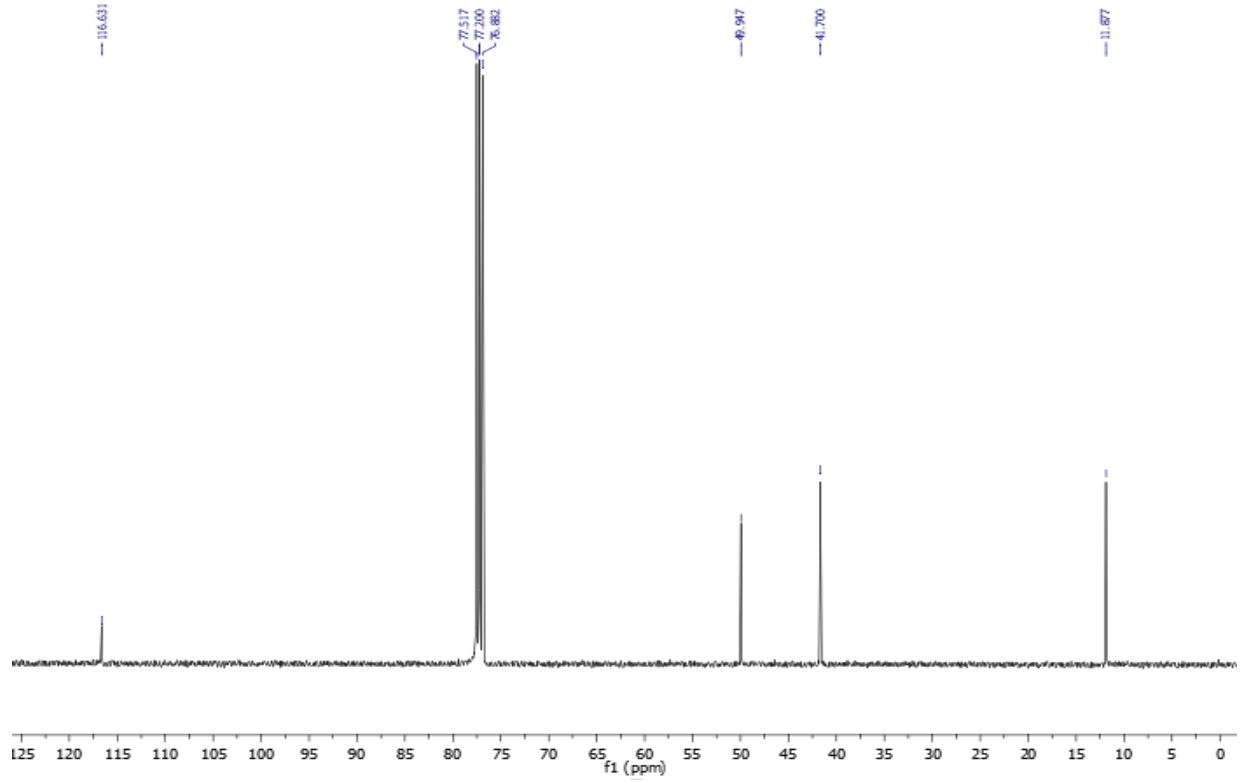
1H NMR and 13C NMR Spectra of 3dc





1H NMR and 13C NMR Spectra of 3ec





CHAPTER – 4: CONCLUSION

We have established that sulfonyl hydrazones can be adopted as sulfur-centered pro-nucleophiles for carrying out sulfa-Michael addition reaction with enones and other α,β unsaturated alkenes promoted by water providing a direct synthesis of γ-keto sulfones. The reaction processed via environmentally benign conditions without use of any organic solvents or catalyst. The method shows a wide scope with large number of substrate. Due to overall simplicity of the process, research is being carried out to find its mechanistic details and its further applications in organic synthesis.

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