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Cyclic Sulfones from Double Conjugate Addition of Rongalite

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Abstract

We report a cyclic sulfone synthesis method from the addition of sodium hydroxymethanesulfinate to doubly electrophilic dienone substrates. The novel synthesis of the cyclic sulfone thus avoided the using the toxic and odorous sulfides, and also oxidizing reagents. We prepared both the symmetrical and unsymmetrical substrates, and then used the substrate for the synthesis of cyclic sulfone.

MONTCLAIR STATE UNIVERSITY
CYCLIC SULFONES FROM DOUBLE CONJUGATE ADDITION OF
RONGALITE

by

Hao Zong

A Master's Thesis Submitted to the Faculty of

Montclair State University

In Partial Fulfillment of the Requirements

For the Degree of

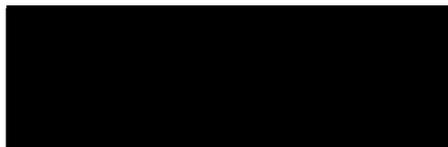
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Thesis Committee:

Department of Chemistry & Biochemistry



Dr. Magnus Bebbington

Thesis Sponsor



Dr. David Rotella

Committee Member



Dr. David Konas

Committee Member

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OF RONGALITE

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Introduction

Background information

Sulfones are organosulfur compounds that have been used in different fields as pharmaceuticals and polymeric components. (Whitham, 1995). A sulfone (Figure 1.) results from the attachment of two carbon atoms and the sulfonyl group where a sulfur atom is connected with the two carbons via a single bond and connects to two oxygen atoms via a double bond.

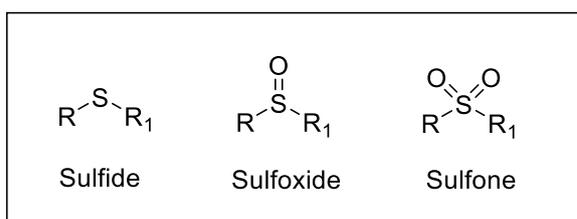
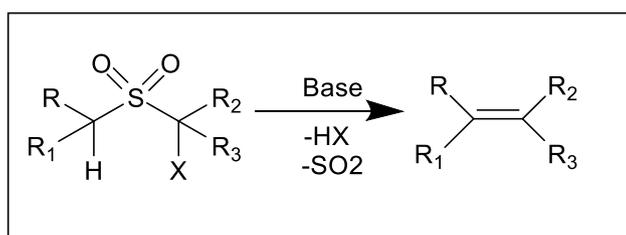


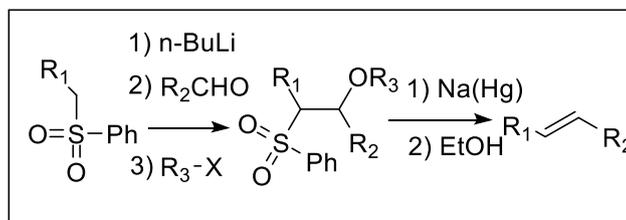
Figure 1. Oxidation levels of organic sulfur compounds

Sulfones are S, S-dioxides of sulfides and denoted by structural formula $R-S(O)_2-R_1$ (R and R_1 are organic groups). (Patai, Rappoport, & Stirling, 1988) The sulfone group can act as a temporary modulator in chemical reactions hence applied in

many transformations. They act as activators and electron withdrawers in Michael acceptors and as good leaving groups via generation sulfinate anion. Common reactions of sulfones encountered in synthetic organic chemistry include the Ramberg–Bäcklund reaction (Scheme 1) of α -halo sulfones (Hartman & Hartman, 1982) and the Julia–Lythgoe olefination (Scheme 2) (Pospíšil, Pospíšil, & Markó, 2005).

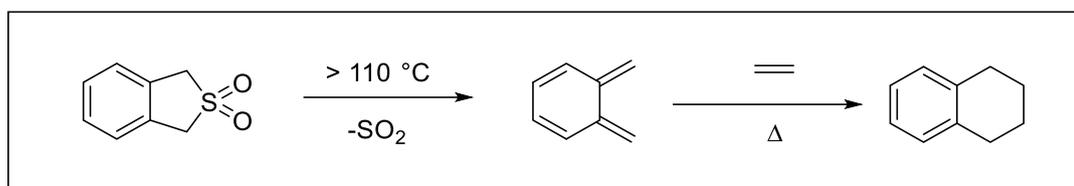


Scheme 1. the Ramberg–Bäcklund reaction



Scheme 2. Julia–Lythgoe olefination

Many types of sulfone compounds have been studied because of their various strong medicinal activities like as biological, antimalarial, antimicrobial, anti-inflammatory, anticancer, anti-HIV, and anti-inflammatory and in other sectors (Ruhee, Roberts, Ma, & Suzuki, 2020). Various cyclic sulfone compounds exist and may differ based on the ring number. As a major organosulfur, sulfones are significant intermediates of organic synthesis. (Stirling, 1975) Therefore, the development of methods in organic chemistry for sulfone and their derivatives synthesis has attracted a lot of attention. Moreover, they can be used for the transformation of a molecule with the presence of a sulfonyl functional group. Several substituted cyclic sulfones are conjugated dienes sources aided by SO₂ extraction and applied in synthesis as masked dienes in Diels-Alder reactions. (Scheme 3) Although different methods for the synthesis of cyclic sulfones are exists, there is a need to establish the best effective and efficient approach for the synthesis of various ring sizes cyclic sulfones for effective in a different application (Alam et al., 2018).



Scheme 3. Cyclic sulfones to dienes

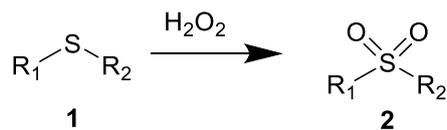
Methods for sulfone synthesis

Traditional methods for the sulfone synthesis

There are four main traditional approaches applied in the synthesis of sulfones i.e., oxidizing corresponding sulfoxides or sulfides, alkylation of sulfinic salts, sulfonyl radical additions, and Friedel–Crafts-type arenes sulfonylation. With time these reactions have been improved thus yielding better substrate scope, tolerance and efficiency of functional group, and innovative reagents. (Liu et al., 2016; Patai et al., 1988)

1.1 Oxidation of Sulfides

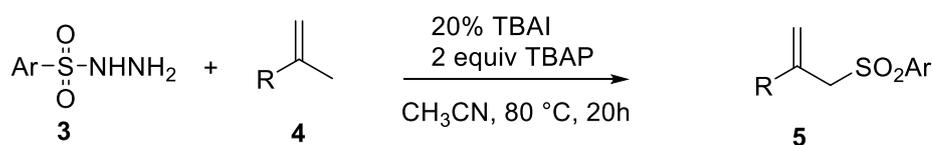
Oxidation is the most preferred method to synthesize sulfones in particular the oxidation of sulfides. Generally, excessive oxidants, high temperatures, and/or prolonged reactions are needed to fully convert sulfides **1** or sulfoxides to sulfone **2**. Among the oxidants used for these transformations, the main ones are peracids or hydrogen peroxide combined with acetic acid. (Scheme 4) (Pritzius & Breit, 2015)



Scheme 4. Oxidation of Sulfides

1.2 Sulfonyl radical additions

Sulfonyl radicals are added to alkenes and alkynes to synthesize sulfones. This involves the use of radical initiators in an atom-transfer radical addition (ATRA) process. Various improvements and modifications of this atom-transfer radical addition (ATRA) process have been developed. Sulfonyl radicals are generated via sulfonyl selenides, sulfinic acids, Dimethyl sulfoxide (DMSO), sulfonyl halides, sulfonyl hydrazides **3**, sulfonyl azides, or sodium sulfinates (scheme 5). (Fang, Luo, & Xu, 2016; Hart, 2001; Zhang, Ding, Pu, Qian, & Xiao, 2020) Addition of sulfonyl halides to alkynes **4** afforded halogenated vinyl sulfones **5**. Nakamura and co-workers (Zeng, Ilies, & Nakamura, 2012) described an iron-catalyzed Regio- and stereoselective addition of sulfonyl chlorides to terminal alkynes. A bromo-sulfonylation of terminal alkynes resulted and generated a triethylborane-initiated sulfonyl radical. (Gilmore, Gold, Clark, & Alabugin, 2013)

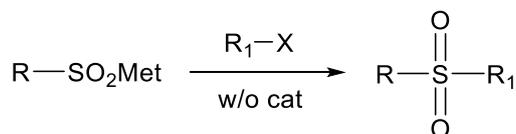


Scheme 5. Sulfonyl Radical additions

TBAI: Tetra-n-butylammonium iodide
TBAP: Tetrabutylammonium perchlorate

1.3 Alkylation of sulfinate salts

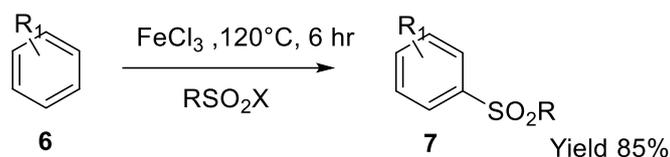
The sulfinate salts are known to react with many alkylating reagents to give the sulfones. (Kobayashi, 1966) The synthesis of the sulfinate salts is the key problem for this type of reaction. Sulfinate salts (RSO_2Met) have received wide attention among organic chemists in recent years due to their stability and versatile reactivity. (Scheme 6) As a more convenient and easy-to-handle substitute of traditional sulfonylating reagents, such as sulfonyl chlorides, sulfinate salts can be used to introduce the $-\text{SO}_2-$ moiety into a variety of different sulfonyl-group-containing molecules, such as sulfones, sulfonamides or sulfonylfluorides. (Liang, 2020)



Scheme 6. Alkylation of sulfinate salts

1.4 Friedel–Crafts-type arenes sulfonylation

The Friedel–Crafts sulfonylation of arenes to the corresponding sulfones using a catalytic amount of reusable solid acid and arene- or alkane sulfonyl chlorides, sulfonic anhydrides, and sulfonic acids as sulfonylating agents under mild and catalytic conditions. (Choudary, 2020) This method provides an efficient way to synthesis the arenes sulfone compounds. (Scheme 7)



Scheme 7. Friedel-Crafts sulfonylation of arenes

Sulfone synthesis via Rongalite

Compared to the traditional sulfone synthesis method, the Rongalite reagent (Fig.2) provide an easier way for the synthesis of the sulfone compound. Due to the difficulties in the preparation of this important compound, sulfone have prompted progressive interest among synthetic chemists globally. In their pursuit to synthesize sulfones, a sulfoxylate dianion (SO_2^{2-}) source which provides a simple process for preparing sulfone, Rongalite has been identified. (Schank, 1988) The IUPAC name of Rongalite is sodium hydroxymethanesulfinate dihydrate (chemical formula $\text{Na}^+\text{HOCH}_2\text{SO}_2^- \cdot 2\text{H}_2\text{O}$), which is a registered BASF trademark. It is water-soluble and mostly sold as a dihydrate (\$23/500grams). (Ali, 2020)

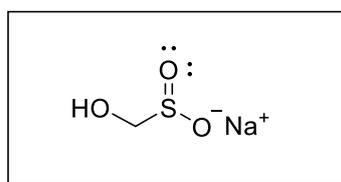


Figure 2. The structure of Rongalite

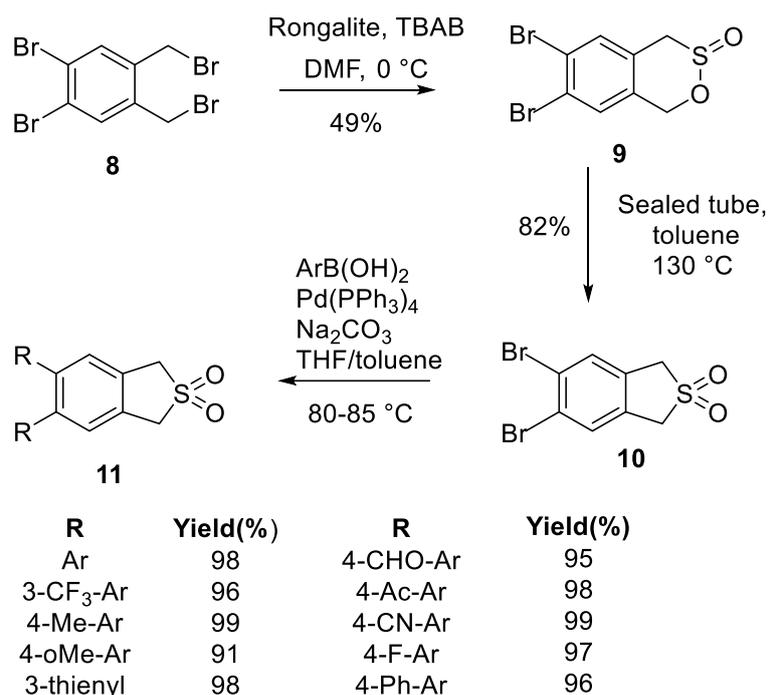
Rongalite has several applications. As an excellent decoloring agent, in the print and dye industry, it is a major bleaching agent and is used as a decolorant of some organic compounds as well as sugar juice, caramel, etc. As a reducing agent, Rongalite has an integral part in various redox-initiator systems for emulsion polymerization. Interestingly, it exhibits excellent bactericidal and fungicidal activities. (Sambasivarao Kotha & Priti Khedkar, 2012) In organic synthesis, Rongalite installs SO_2 functionality to organic molecules. (Wang, Xiang, Cheng, Wu,

& Wu, 2016). Remarkably, this valuable and low toxic reagent can find its application in challenging organic transformations like the synthesis of unnatural-amino acids, Spiro-cycles, functionalized benzo-crown ethers, polycycles. It is a very practical and economically viable reagent for the production of sulfones under mild conditions.(Sambasivarao Kotha, Khedkar, & Dommaraju, 2019)

Rongalite serves as an SO_2^{2-} equivalent and so far, it is hardly used in organic synthesis. It is useful reagent for reductive dehalogenation, reduction of carbonyl compounds and nitro-aromatics. It has been used towards the synthesis of a variety of compounds such as fluoro-organics, selenides, sulfides, thioesters, and selenoethers. Rongalite is proven to be very practical, economical reagent for the construction of sulfones and sulfoxides under mild conditions which has broad synthetic utility. (Kotha, 2019)

2.1 One-pot synthesis of sulfones via Rongalite

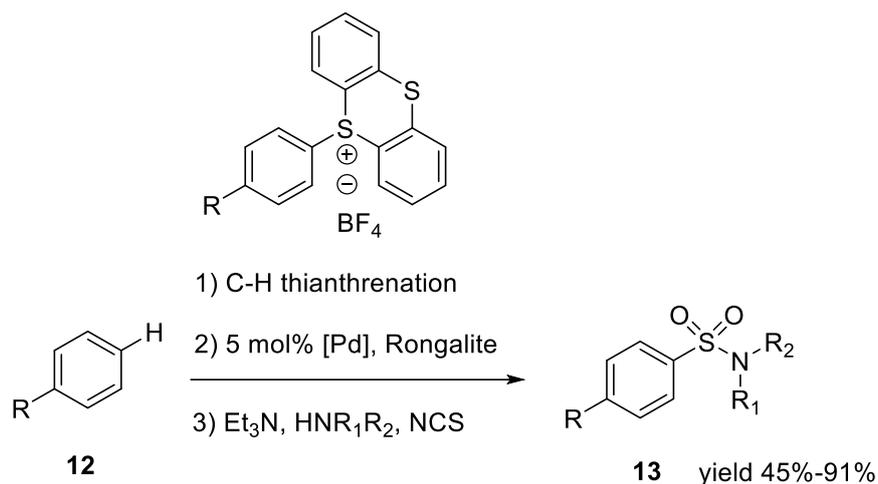
Oxidation is a preferred method to synthesize sulfones especially the oxidation of sulfides.(Pritzius & Breit, 2015) requires an oxidant, heating, and long-term reaction. However, these conditions are atom inefficient and are expensive and a one-pot procedure like the use of Rongalite is preferred.(Sambasivarao Kotha et al., 2019) Highly functionalized benzosulfones were prepared by using Rongalite. Here, Rongalite was used to prepare the sulfone precursor, sulfone **9** from dibromide in a solution of tetrabutylammonium bromide (TBAB) (phase-transfer catalyst (PTC)) and DMF. Subsequently, thermal rearrangement of sulfone derivative resulted in the corresponding sulfone **10**. Afterward, Suzuki–Miyaura cross-coupling reactions of dibromo-sulfone and boronic acids in the presence of Pd (0) catalyst produced cross-coupling products **11** (Scheme 8).(S. Kotha & Ghosh, 2006) The extra functional groups in the cross-coupling products can be manipulated for important product synthesis. This route is an attractive choice since boronic acid is readily available in the market.(Chung, Lin, Liu, & Chen, 1995)



Scheme 8. one-pot synthesis of sulfone via Rongalite

2.2 Aromatic Sulfonylation via Rongalite

As a common method for the synthesis of sulfones, aromatic sulfonylation employs sulfonyl chlorides in a Friedel–Crafts type reaction. The (hetero)arene substituents produce activation/deactivation and directing effects in electrophilic aromatic substitutions. (Ruff, 1964). Sulfones mainly present as side-products of the sulfonation of arenes with sulfuric acid salts. (Rueggerberg, Sauls, & Norwood, 1955) Aromatic bisulfones have been obtained by using Rongalite as the source of SO₂ to the benzyl halides. A report by Alvarez outlined the site-selective two-step C–H sulfination sequence via aryl sulfonium salts to access arylsulfonamides **13**. (Scheme 9) Combined with site-selective aromatic thianthreneation, an operationally simple one-pot palladium-catalyzed protocol introduces the sulfonyl group using sodium hydroxymethylsulfinate (Rongalite) as a source of SO₂²⁻. (E. M. Alvarez et al. 2020)



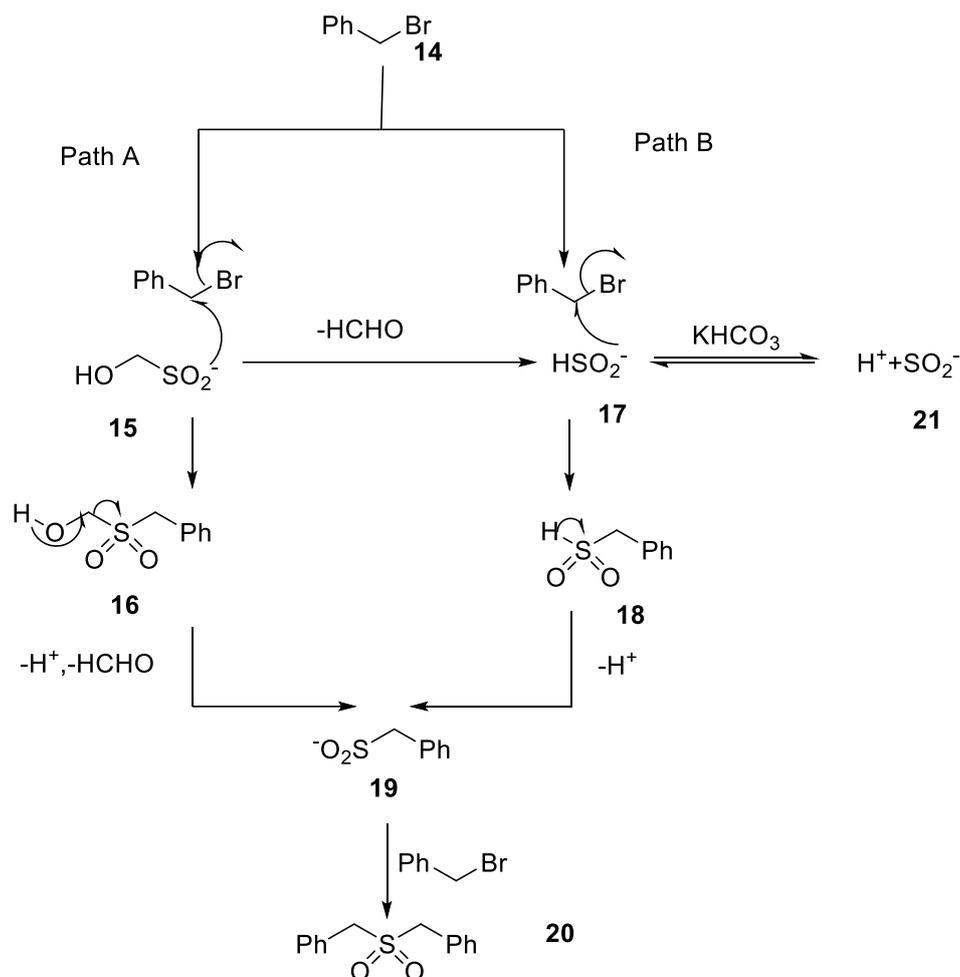
Scheme 9. Aromatic Sulfonylation via Rongalite

2.3 Alkylation/Arylation of Rongalite

The sulfonic acids salts form integral precursors for synthesizing sulfones. Sulfonates like Rongalite act as potent nucleophiles and react with various electrophiles at the sulfur atom producing sulfones. Typical electrophiles consist of alkyl halides, epoxides, Michael acceptors, and aryl halides that are activated for nucleophilic aromatic substitution. These reactions have a high yield, simple, and suited in many alkylating agents. (Liu et al., 2016) Therefore, using Rongalite is the main approach for synthesizing sulfones as exhibited by the following approaches.

2.3.1 Nucleophilic displacement of halides by Rongalite

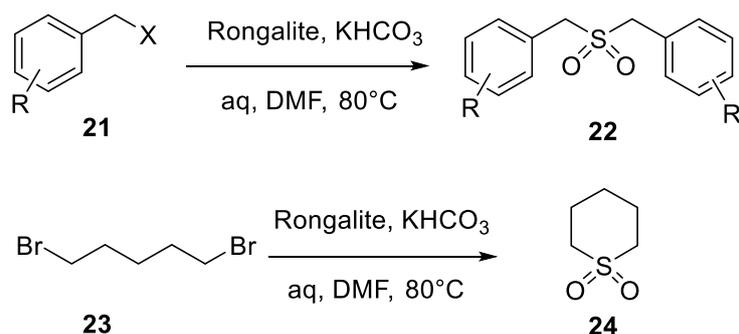
As shown in scheme 10, there are two feasible mechanisms for the formation of sulfone. First, bromide in benzyl bromide **14** undergoes nucleophilic displacement by hydroxymethanesulfinate anion **15**. Thereafter, a formaldehyde molecule is lost in the presence of a base to generate a nucleophile, important for the second step. Sulfone is formed via initial nucleophilic displacement from sulfinate anion from Rongalite. These routes operate concurrently to generate sulfones **20**. A study by Dittmer's lab group (Jarvis, Hoey, Finocchio, & Dittmer, 1988) have proved that adding potassium bicarbonate to this reaction mixture forms SO_2^{2-} dianion by deprotonating HSO_2^- , a superior electron donor compared to HSO_2^- . Benzyl halides that have electrophilic moieties easily accept an electron of the SO_2^{2-} **21** dianion, consequently undergoing substitution through radical anions. (Shavnaya, Coffey, Hesp, Ross, & Tsai, 2016)



Scheme 10. Mechanism of nucleophilic displacement of halides by Rongalite

2.3.2 Sulfones via the treatment of primary halides with Rongalite

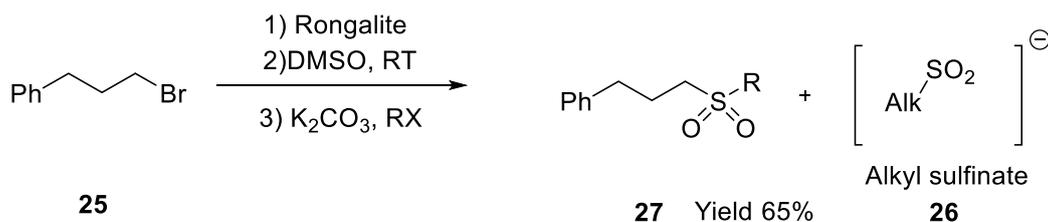
Symmetrical sulfones **22** were prepared by Dittmer's group by treating primary halides **21** with Rongalite. (Sambasivarao Kotha, Deodhar, & Khedkar, 2014) When heated at 80 °C with Rongalite in DMF and potassium bicarbonate, benzyl bromides yield 45-88% dibenzyl sulfone. Under the same conditions, allyl bromide reacted with Rongalite to yield 20% diallyl sulfone (Sambasivarao Kotha & Meshram, 2014). Moreover, a 43% yield of cyclic sulfone **24** was attained via the treatment of 1,5-dibromopentane **23** with Rongalite. (Scheme 11). (Sambasivarao Kotha & Priti Khedkar, 2012)



Scheme 11. Sulfones via the primary halides with Rongalite

2.3.3 Aliphatic unsymmetrical sulfones via Rongalite

In the case of reaction of alkyl halides Rongalite, an interception ensues after initial alkylation. Under the condition developed by Shavnya, unsymmetrical sulfones synthesized, this is a significant advance, only symmetrical sulfones were available previously. This reaction is followed by cleavage of the intermediate hydroxymethyl sulfone to yield sulfonamides, unsymmetrical sulfone, and sulfonamides. Mono-alkylation of Rongalite with an alkyl halide **25** in DMSO via PTC resulted in intermediate alkyl sulfonate. Further alkylation resulted in the formation of unsymmetrical sulfone **27**. Alkyl sulfinate **26** can be quenched by amines to furnish corresponding sulfonamides. Moreover, sulfinates were fluorinated into respective sulfonyl fluorides after reacting with N-fluorobenzenesulfonimide (Shavnya et al., 2016). (Scheme 12)(Sambasivarao Kotha & Priti Khedkar, 2012)

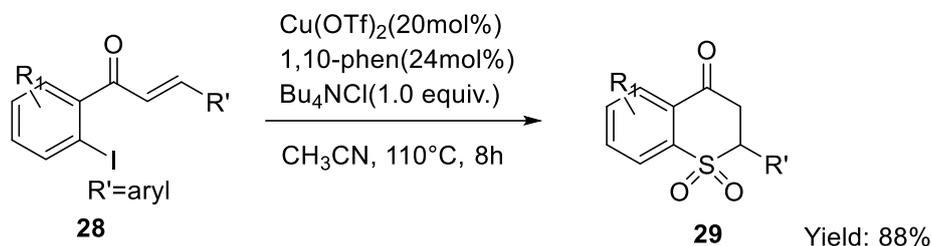


Scheme 12. Aliphatic unsymmetrical sulfones via Rongalite

3. Copper catalyzed sulfone synthesis via Rongalite

A novel process to incorporate SO_2^{2-} into 2-iodochalcones **28** for the construction of 1-thiaflavanonesulfones **29** using Rongalite as a sulfone source was established. This sulfonylation proceeded to achieve in situ incorporation of sulfone cores through the

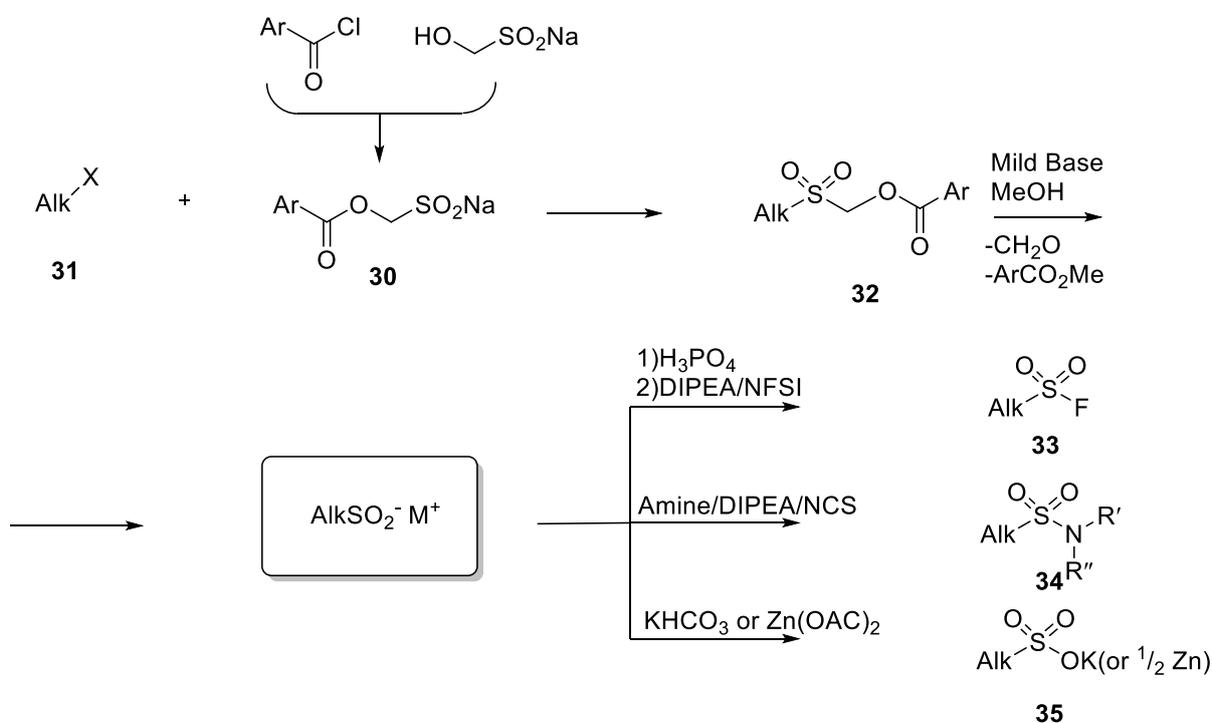
consecutive formation of two C–S bonds. (Chen et al., 2020) They used Rongalite as a low-cost readily available sulfur dioxide anion equivalents compared with other alternatives.



Scheme 13. Copper catalyzed sulfone synthesis via Rongalite

4. Sulfonylation with a derivative of Rongalite

The Shavnya group developed a versatile, stable, and low-cost sulfonylating reagent(**30**) via Rongalite. This reagent also developed a methodology for the expedient preparation of aliphatic sulfinates, sulfones, sulfonamides **34**, and sulfonyl fluorides **33** starting from primary and secondary alkyl halides and tosylates. (Scheme 14)(Shavnya et al., 2018) The hydroxyl group in the Rongalite protect the sulfinate by reacting with some electrophiles. The new sulfonylation reagent provides a good equivalent of the SO_2^{2-} anion.



Scheme 14. Sulfonylation with a derivative of Rongalite

Perspective

The previous part gives an overview of various important synthetic processes for sulfones, which emphasize the role of Rongalite in synthetic chemistry. As an inexpensive, available, and easy to handle reagent it can efficiently mediate sulfone synthesis. The reactions supported by Rongalite especially the alkyl/arylation have been immensely applied in the synthesis of sulfones and provide an alternative for other methods implicated with shortcomings like the oxidation of sulfides or sulfoxides. Tactical use of Rongalite in the synthesis of sulfones and cyclic sulfones is a substitute for longer routes to these compounds. Accordingly, we want to explore more application of the Rongalite reagent.

Our hypothesis is that Rongalite can undergo double conjugate addition in reaction with dienones in order to give cyclic sulfones. (Figure 3). We want to use this low odor, environmentally friendly reagent to broaden the cyclic sulfone synthesis methodology.

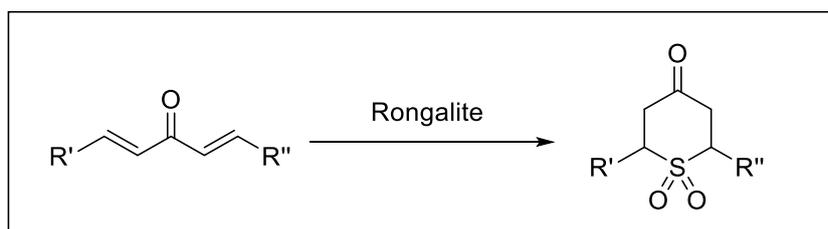
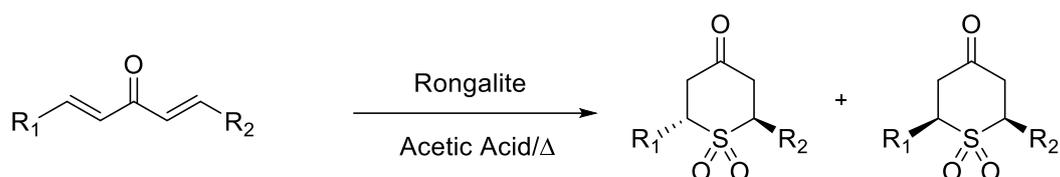


Figure 3. Conjugate addition of Rongalite to dienones

In this thesis, we report the progress toward the synthesis of several different cyclic sulfones and some symmetrical and unsymmetrical dibenzalacetone substrates. Our synthetic plan is using cheap and readily available starting materials to prepare the diene substrate using aldol reactions. Then using Rongalite reagent in the double conjugate addition.

Results and Discussion

The synthesis of the cyclic sulfone via the double conjugate addition of Rongalite followed the synthetic route from the cyclic sulfone from Mannich Base and hydroxymethanesulfinate (Gesellschaft & Deutscher Apotheke, 1977). We took this route as our base and then take a deeper study on this reaction.



1a. R₁=R₂=Ph

1b. R₁=R₂=4-Methylphenyl

1c. R₁=R₂=2-Thienyl

1d. R₁=R₂=3-(trifluoromethyl)phenyl

1e. R₁=Ph R₂=2,6-dimethylphenyl

2a. R₁=R₂=Ph

2b. R₁=R₂=4-Methylphenyl

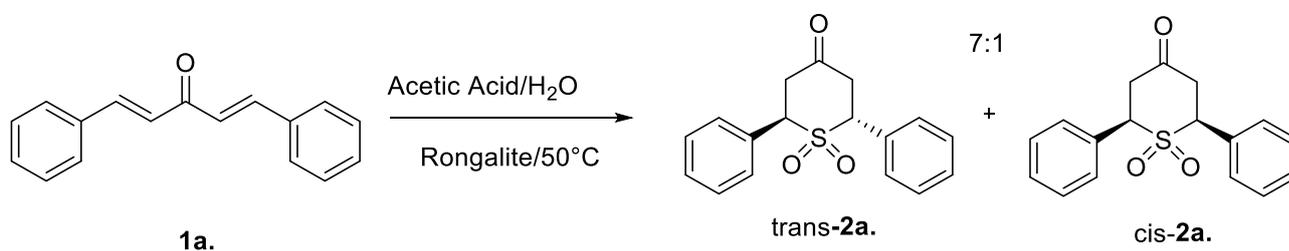
2c. R₁=R₂=2-Thienyl

2d. R₁=R₂=3-(trifluoromethyl)phenyl

2e. R₁=Ph R₂=2,6-dimethylphenyl

Scheme 15. The scope of substrates and products

Initially, dibenzalacetone **1a** was selected as a model substrate for optimization of the reaction conditions. We examined different solvent previously used for Rongalite reaction, then we found that the acetic acid had a better catalytic result compared to other conditions. Thanks for the work of Jazmin Prana, we got some good reaction condition for the dibenzalacetone **1a**. Our study began with the dibenzalacetone **1a** at 50°C using DMSO, but only 28% yield was obtained (Table 1, Entry 3). When using the acetic acid, 81% yield was obtained. (Table 1, Entry 1)

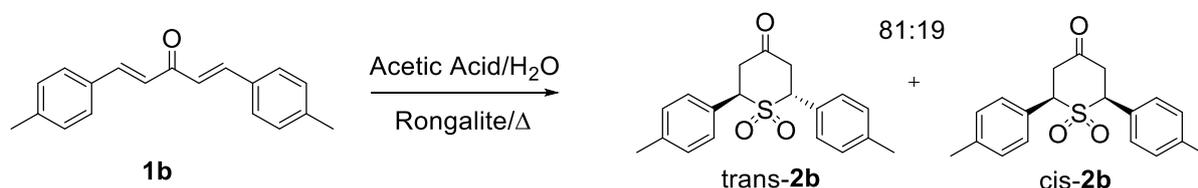


Entry	Time	Conditions	Rongalite e.q.	%Yield
1	24 hr	Acetic Acid	1.5	81
2	18 hr	Acetic Acid	1.5	75
3	18 hr	DMSO	1.5	28
4	1 hr	DMSO, K ₂ CO ₃	1.5	9
5	2 hr	DMSO, Acetic Acid	1.5	28
6	2 hr	EtOH	1.5	23
7	24 hr	Acetic Acid	1.1	64
8	3 hr	EtOAc, TBAB	1.5	8
9	3 hr	EtOH, Acetic Acid	1.5	42

Table 1. The Optimization and results with dibenzalacetone **1a** (Jazmine Prana)

Considering the acetic acid system has been successfully applied in the preparation of the 2,6-diphenyltetrahydro-4H-thiopyran-4-one 1,1-dioxide **2a**, we tried to broaden the scope of our reaction with the other substituents.

We initiate the experiment for the compound **1b** with the same reaction condition as the dibenzalacetone **1a**. The results turned out the yield was 47% (Table 2, Entry 1), that is far away from the best yield we got in table 1. Compared to the dibenzalacetone **1a**, compound **1b** had a lower reactivity. The methyl group on the benzene ring is an electron donating group, which increased the electron density of the ketone group. In order to increase the reactivity of the reaction, we tried two ways: increase the reaction temperature or increase the concentration of the reagent. Firstly, we tried to increase the reaction temperature from 50°C to 80°C and kept the Rongalite equivalents the same. The yield increased to 58% (Table 2, Entry 2). Then we tried to increase the Rongalite equivalent from 1.5 to 2.5 and increase the temperature from 50°C to 80°C as well. The yield was 73% (Table 2, Entry 3), which is better than increasing temperature only. Lastly, we tried to increase the equivalents of the Rongalite only, then an improved 77% yield was acquired. (Table 2, Entry 4)



Entry	Time	Temperature	Rongalite e.q.	%Yield
1	24 hr	50°C	1.5	47
2	3 hr	80°C	1.5	58
3	3 hr	80°C	2.5	73
4	24 hr	50°C	2.5	77

Table 2. Optimization and results for the substrate **1b**.

Then, we tested several symmetrical and unsymmetrical substituents for the double conjugate addition of the Rongalite. The reaction could be carried out with a series of substituents benzene rings, affording the corresponding products in moderate to good yields. Interestingly, the reactivity of the substrate differs with the electronic properties of the substituents: when the phenyl ring contains the electron withdrawing group such as

trifluoromethyl **1d**, the reaction proceeds smoothly at 50°C and 1.5 Rongalite equivalents. However, when the phenyl bears electron-donating substituents, such as methyl group **1b**, lower conversion to the desired product was observed. (**Table 2, Entry 1**). Fortunately, with the substrate **1b**, when we increased the Rongalite equivalents from 1.5 to 2.5, a better yield was achieved. We also studied the unsymmetrical substrate **1e**, and the effect of the steric hindrance effects (**2e, 3**) on the reaction, the reactivity dropped, but both substrates worked for the cyclic sulfone synthesis.

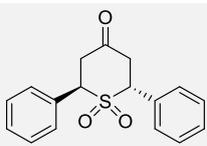
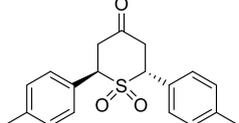
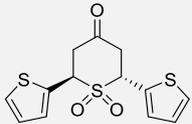
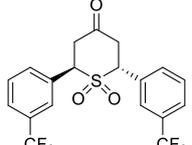
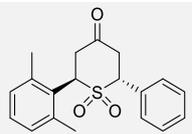
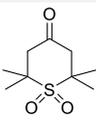
Entry	Temperature	Products	Rongalite e.q.	De(trans)	Yield%
1	50°C		1.5	85:15	86%
		2a			
2	50°C		2.5	81:19	77%
		2b			
3	50°C		1.5	72:28	38%
		2c			
4	50°C		1.5	63:36	54%
		2d			
5	50°C		2.5	69:31	55%
		2e			
6	50°C		2.5	-	43%
		3			

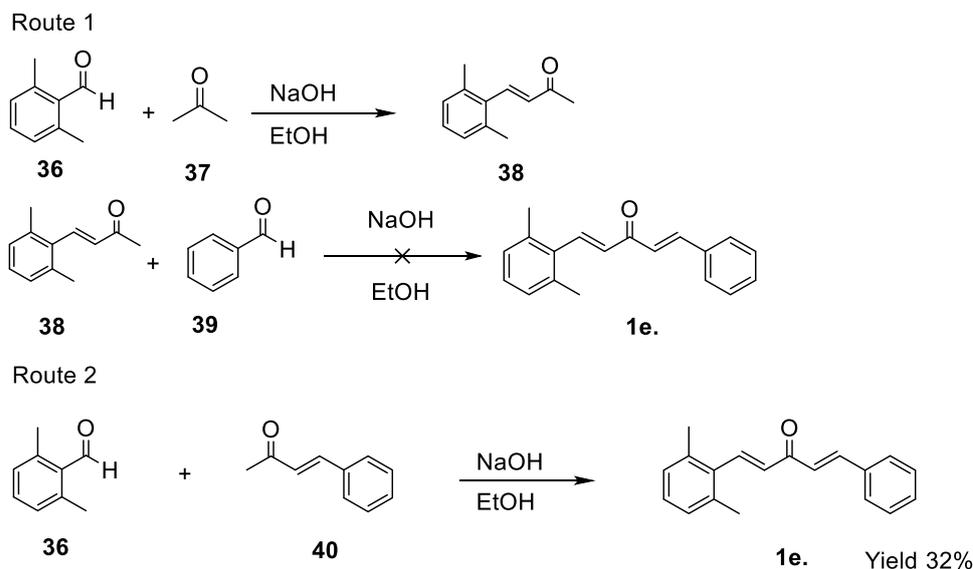
Table 3. Scope of the synthesis of cyclic sulfone

Aromatic Sterics Effects

For the substrate from the **1a** to **1d**, we followed the procedure of the double aldol reaction from a US patent.(Vander Jagt, 2006).

For the synthesis of the substrate **1e**, we tried two different synthesis routes (scheme **16**). The route 1 was a two steps reaction. For the first step, we used the 2,6-Dimethoxybenzaldehyde **36** and acetone **37** to run an aldol reaction. The reaction took half hour and the yellow product **38** precipitated. Vacuum filtrated to get the product **38** and then mixed with benzaldehyde **39** to run another aldol reaction. For the second aldol reaction, we kept it ran for 24 hrs. and the ^1H NMR showed no reaction happened. We used the same reaction condition as the first step, and we found that the product **38** didn't dissolve well in the ethanol. This could be a reason that led to the failure of the second aldol reaction. This may result the decrease of the acidity of the α -H of the ketone, we may need to change the base to make the second aldol reaction to go well.

Then, we tried the route 2, substituting acetone **37** with the commercial compound 4-phenyl-3-buten-2-one **40**, and the one step aldol reaction worked. We tracked the reaction by TLC every 30 minutes. And the reaction went off after 2 hrs. There was some yellow precipitate after 2 hrs. reaction, when the reaction kept on, the precipitate disappeared. When the reaction kept on after 2 hrs., some of the products decomposed. We used the flash chromatography to pure the extracted products. The yield was 32%.



Scheme 16. The synthesis route of substrate **1e**

In order to check the aromatic steric effect on the cyclization, we synthesized substrate **1e** and **1f**. (Figure 4) For the substrate **1e**, the double addition worked with a 55% yield. While for the substrate **1f**, the reaction did not work. During the cyclization reaction (scheme 17),

one of the phenyl groups must be in the axial position for the major product. The large hindered 2,6-dimethyl phenyl substituents would make the axial position less stable, which led the substrate **1f** could not go through the reaction with Rongalite. For the substrate **1e**, one of the phenyl groups could be stabilized at the axial position, then the cyclization process could go smoothly.

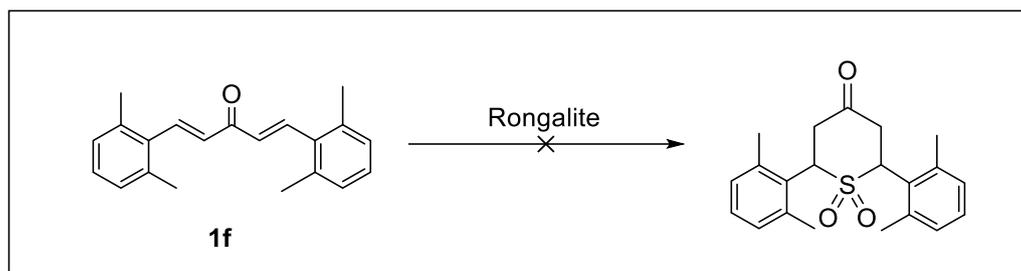
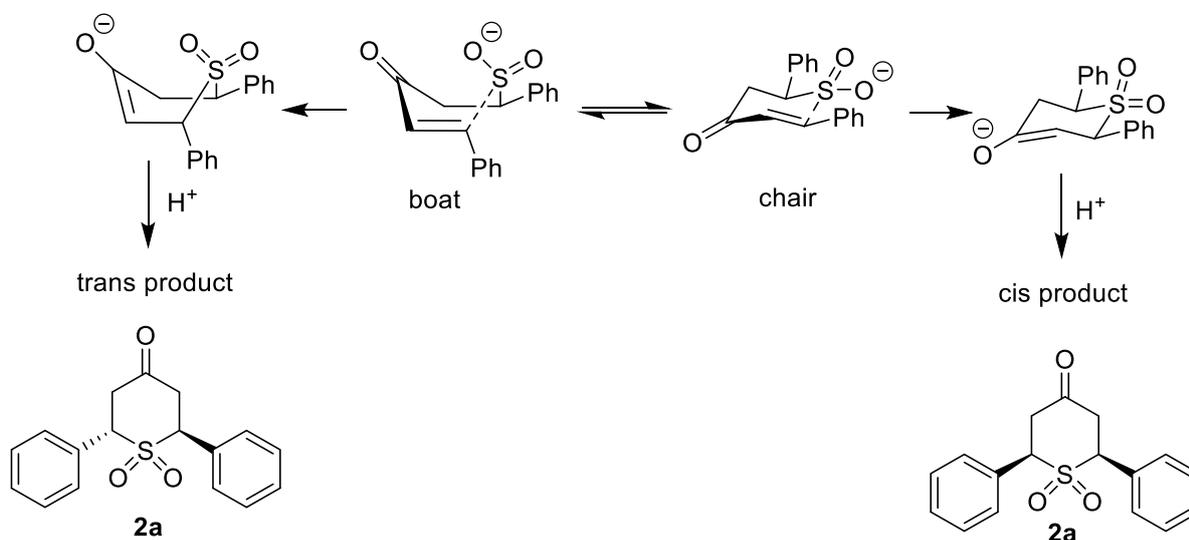


Figure 4. aromatic steric hindered effect
(Antonia Muro)

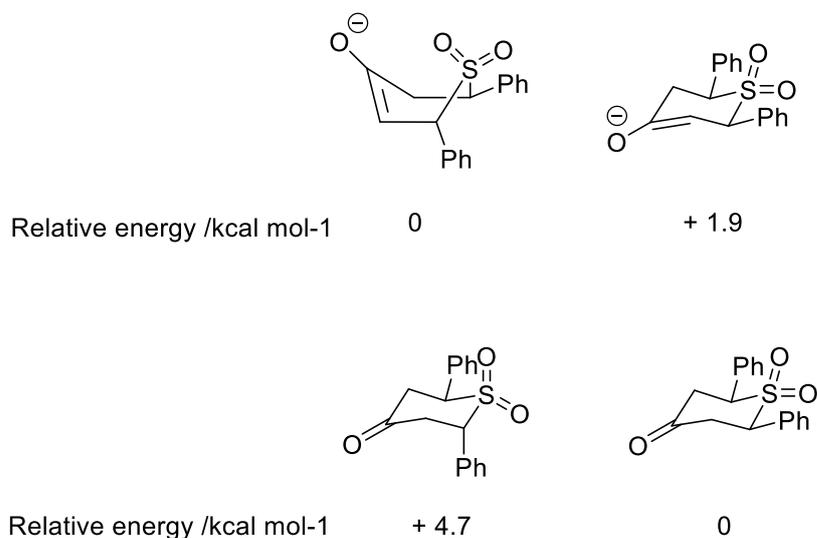
Rationalization of Stereochemistry



Scheme 17. The boat and chair conformation during the cyclization process

Evidence suggests that the trans product arises from a boat-like transition state. (Scheme 17) The longer C-S bond in the boat conformation transition state may increase the stability. (Baxter & Whiting, 1968) . The double conjugate addition allows two chiral centers to be created in our final cyclic sulfone product. These two chiral centers make the final product

have two isomers, which allow us to assess the effect of the stereochemistry of the same reaction.



Scheme 18. DFT: PBE0 functional, def2-TZVP basis set
(H. Eshuis, Scott Piotrowsky)

According to the computational analysis (Scheme 18) of the *cis* and *trans* isomer of the dibenzalacetone **1a**, the relative energy showed the *cis* product had a relative lower energy than the *trans* product, which means the *trans* product may isomerize to the *cis* product in some conditions. And during my experiment of **2b** synthesis, some part of the major product was found isomerized from the chair to the boat conformation when the temperature kept at 80 °C degree overnight. For the enolate form, the *trans*-boat is more stable than the *cis*-chair conformation. The *trans* vs *cis* ratio was 81:19 at 50 °C 24hrs reaction, when we increased the temperature to 80 °C and heated for 3hrs. the *trans* vs *cis* ratio remained at 78:22. After the reaction was kept at 80 °C for 24 hrs., the *trans* vs *cis* ration change to 69:31. The isomerization may happen due to the higher reaction temperature. Then we used the pure *trans* **2a** product to test the isomerization in pure acetic acid. After heating at 80 °C for 24 hrs., the ¹H NMR showed no isomerization happened. This result conflicted with the result in the synthesis of **2b**, but we need more data to draw the conclusion. A deeper and more thoroughly investigation is needed to be done for a plausible explanation.

Future work and Conclusions

For the future work, we can have some more different substrate to take a deeper look on the reaction, and the different electronic effect from the substituents may have a better illustration once more substrates are engaged in this reaction. The pH of the reaction system could induce a lower yield of the reaction. Thus, the yield difference under buffered aqueous system could be another aspect that is worthy of investigation. For the isomerization of the diastereomers, the major product was able to isomerize to the minor product when the temperature remained high. We need to heat the pure major product at 80°C with Rongalite to see if that produce the isomerization. Also, the appearance of the isomerization could be a good starting point to investigate the desired diastereomers synthesis for the double conjugate addition.

In summary, we have developed a new cyclic sulfone synthesis method with the Rongalite reagents under moderate conditions. This sulfonylation process was achieved by the sulfone core incorporation with two C-S bond formation. The Rongalite as a low-odor, environmentally friendly sulfur dioxide anion equivalents, was successfully applied as a nucleophile in the double conjugate addition reaction for the cyclic sulfone synthesis. Furthermore, we expanded the scope of the substrate to unsymmetrical and sterically hindered examples, which prove the versatility of this cyclic sulfone synthesis reaction. We believe that this work may open up new possibilities for the sulfone synthesis and application of Rongalite.

Experimental

All chemicals were purchased from the Fisher Scientific, all commercial starting materials were used without further purification.

The ^1H NMR and ^{13}C NMR spectra was recorded using 400 MHz and 300 MHz Bruker NMR Spectrometer with solvent peaks as reference. The IR spectra were recorded by Perkin Elmer. The mass spectrum was recorded by Shimadzu HPLC. The Flash Chromatography was performed using silica gel (60-100 mesh) columns. Thin Layer Chromatography (TLC) was used to trace the reactions. The visualization was performed using UV light, or by dipping in KMnO_4 followed by heating.

General procedure for the preparation of Dienones from 1a-d

The reaction mixture of **1a-d** (5 mmol), acetone (2.5 mmol, 0.145 g), NaOH (5 mmol) in the solvent of EtOH-H₂O (5 ml + 2.5 ml) was stirred at room temperature until completed, check with TLC. The crystalline solid was collected by filtration and dried.

(1E, 4E)-1,5-di-(p-toly)penta-1,4-dien-3-one (1b).

A mixture of p-tolu aldehyde (41.6 mmol, 5.00 g), acetone (20.8 mmol, 1.209 g), NaOH (41.6 mmol), 30 ml EtOH, 15 ml deionized water was stirred at Room temperature for 1 hr. The resulting precipitate was filtered and recrystallized from Hexane / Ethyl Acetate system. The yield was 85%. The weight was 4.63 g.

(1E, 4E)-1,5-bis-(2-Thienyl) penta-1,4-dien-3-one (1c)

A mixture of 2-thiophenecarboxaldehyde (44.6 mmol, 5.00 g), acetone (22.3 mmol, 1.30 g), NaOH (41.6 mmol), 13 ml EtOH, 6.5 ml deionized water was stirred at Room temperature for 0.5 hr. The resulting yellow precipitate was filtered and dried. The reaction yield was 97%. The weight was 5.32 g.

(1E, 4E)-1,5-bis(3-(trifluoromethyl)phenyl)penta-1,4-dien-3-one (1d)

A mixture of 3-(trifluoromethyl)benzaldehyde (13.2 mmol, 2.30 g), acetone (6.7 mmol, 0.390 g), NaOH (13.2 mmol), 18 ml EtOH, 12 ml deionized water was stirred at Room temperature for 15 minutes. The yellow crystal was filtered and dried. After the flash chromatography, we got the pure product. The yield was 40%. The weight was 0.98 g.

(1E,4E)-1-(2,6-dimethylphenyl)-5-phenylpenta-1,4-dien-3-one (1e)

A mixture of 2,6-dimethylbenzaldehyde (6 mmol, 0.805 g), 4-phenyl-3-buten-2-one (6 mmol, 0.877 g), NaOH (18 mmol), 60 ml EtOH, 10 ml deionized water was stirred at Room temperature for 2 hrs. The reaction was monitored by TLC. The mixture was extracted by 100 ml Ethyl Acetate and 100 ml Deionized water. Dried with the Magnesium sulfate. Solvent removed at reduced pressure. The yellow crystalline solid was then purified by flash chromatography (15/85, ethyl acetate/ Hexane). The yield was 32%. The weight was 0.50 g.

2,6-Diphenyltetrahydro-4H-thiopyran-4-one 1,1-dioxide. (2a)

The substrate **1a** dibenzalacetone (0.5 g, 2.13 mmol) was dissolved in 10 ml Acetic acid, and then the 1.5 ml Sodium hydroxymethanesulfinate dihydrate (0.493 g, 3.23 mmol) water solution was added. The well mixed solution was heated to 50 °C and stirred for 24 hrs. 20 ml Deionized water was added to wash the mixture. Then the mixture was extracted by 50 ml Ethyl Acetate 3 times. The organic phase was then neutralized with the saturated NaHCO₃ solution. The combined organic phase was dried by the magnesium sulfate. Solvent removed at reduced pressure. The yellow solid product was purified and separated by flash chromatography (20/80, ethyl acetate/ Hexane). The yield was 81%. The weight was 1.10 g. Major product was 0.96 g, the minor product was 0.14 g.

2,6-Di-p-tolyltetrahydro-4H-thiopyran-4-one 1,1-dioxide. (2b)

The substrate **1b** (E, E)-1,5-di-p-tolypenta-1,4-dien-3-one (0.25 g, 0.95 mmol) was dissolved in 5 ml Acetic acid, and then the 1 ml Sodium hydroxymethanesulfinate dihydrate (0.367 g, 2.40 mmol) water solution was added. The well mixed solution was heated to 50 °C and stirred for 24 hrs. 20 ml Deionized water was added to wash the mixture. Then the mixture was extracted by 50 ml Ethyl Acetate 3 times. The organic phase was then neutralized with the saturated NaHCO₃ solution. The combined organic phase was dried by the magnesium sulfate. Solvent removed at reduced pressure. The yellow solid product was purified and separated by flash chromatography (20/80, ethyl acetate/ Hexane). The yield was 77%. The weight was 0.24 g. Major product was 0.19 g, minor product was 0.05 g.

2,6-Di(thiophen-2-yl)tetrahydro-4H-thiopyran-4-one 1,1-dioxide. (2c)

The substrate **1c** (E, E)-1,5-di-(2-Thienyl) penta-1,4-dien-3-one (0.52 g, 2.11 mmol) was dissolved in 10 ml Acetic acid, and then the 1.5 ml Sodium hydroxymethanesulfinate dihydrate (0.49 g, 3.15 mmol) water solution was added. The well mixed solution was heated

to 50 °C and stirred for 24 hrs. 20 ml Deionized water was added to wash the mixture. Then the mixture was extracted by 50 ml Ethyl Acetate 3 times. The organic phase was then neutralized with the saturated NaHCO₃ solution. The combined organic phase was dried by the magnesium sulfate. Solvent removed at reduced pressure. The yellow solid product was purified and separated by flash chromatography(20/80, ethyl acetate/ Hexane). The yield was 38%. The weight was 0.25g. Major product was 0.18 g, minor product was 0.07 g.

2,6-Bis(3-(trifluoromethyl)phenyl)tetrahydro-4H-thiopyran-4-one 1,1-dioxide. (2d)

The substrate **1d** (E, E)-1,5-di-(3-(trifluoromethyl)phenyl) penta-1,4-dien-3-one (0.300 g, 0.810 mmol) was dissolved in 5 ml Acetic acid, and then the 1 ml Sodium hydroxymethanesulfinate dihydrate(0.187 g, 1.22 mmol) water solution was added. The well mixed solution was heated to 50 °C and stirred for 24 hrs. 20 ml Deionized water was added to wash the mixture. Then the mixture was extracted by 50 ml Ethyl Acetate 3 times. The organic phase was then neutralized with the saturated NaHCO₃ solution. The combined organic phase was dried by the magnesium sulfate. Solvent removed at reduced pressure. The yellow solid product was purified and separated by flash chromatography(20/80, ethyl acetate/ Hexane). The yield was 54%, the weight was 0.19 g. Major product was 0.12 g, minor product was 0.07 g.

2-(2,6-Dimethylphenyl)-6-phenyltetrahydro-4H-thiopyran-4-one 1,1-dioxide. (2e)

The substrate (**1e**)(1E,4E)-1-(2,6-dimethylphenyl)-5-phenylpenta-1,4-dien-3-one (0.51 g, 1.95 mmol) was dissolved in 10 ml Acetic acid, and then the 1.5 ml Sodium hydroxymethanesulfinate dihydrate(0.75 g, 4.88 mmol) water solution was added. The well mixed solution was heated to 50 °C and stirred for 24 hrs. 20 ml Deionized water was added to wash the mixture. Then the mixture was extracted by 50 ml Ethyl Acetate 3 times. The organic phase was then neutralized with the saturated NaHCO₃ solution. The combined organic phase was dried by the magnesium sulfate. Solvent removed at reduced pressure. The yellow solid product was purified and separated by flash chromatography(20/80, ethyl acetate/ Hexane). The yield was 55%, and the weight was 0.35 g. Major product was 0.24 g, minor product was 0.11 g.

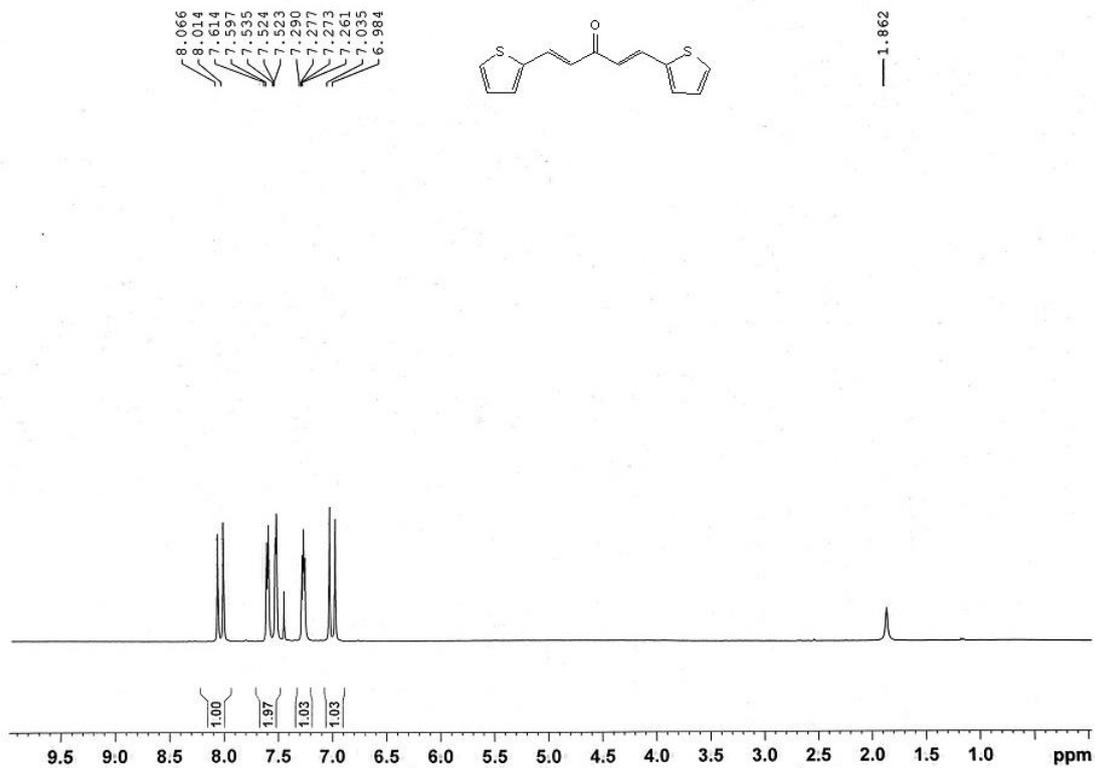
2,2,6,6-Tetramethyltetrahydro-4H-thiopyran-4-one 1,1-dioxide.(3)

The substrate 2,6-Dimethyl-2,5-heptadien-4-one(0.82 g, 5.93 mmol) was dissolved in 30 ml Acetic acid, and then the 4.5 ml Sodium hydroxymethanesulfinate dihydrate(2.29 g, 14.83

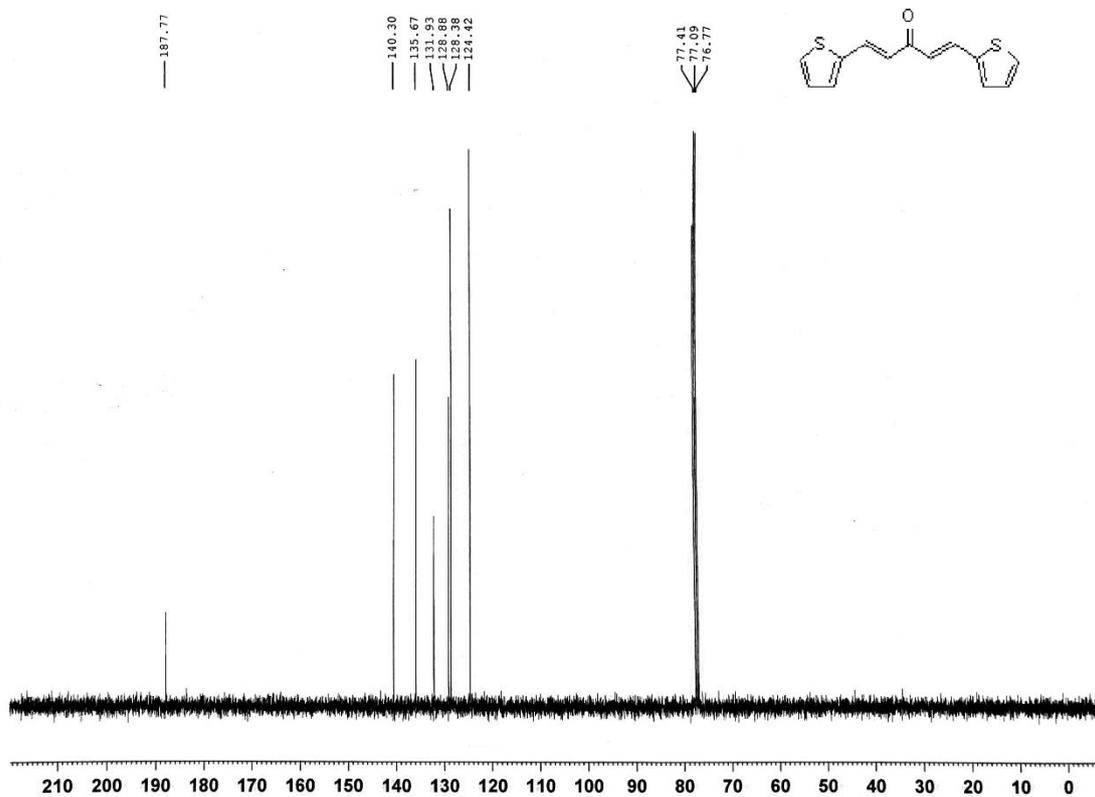
mmol) water solution was added. The well mixed solution was heated to 80 °C and stirred for 24 hrs. 20 ml Deionized water was added to wash the mixture. Then the mixture was extracted by 50 ml Ethyl Acetate 3 times. The organic phase was then neutralized with the saturated NaHCO₃ solution. The combined organic phase was dried by the magnesium sulfate. Solvent removed at reduced pressure. The white solid product was purified and separated by flash chromatography(20/80, ethyl acetate/ Hexane). The yield was 43%, and the weight was 0.52 g.

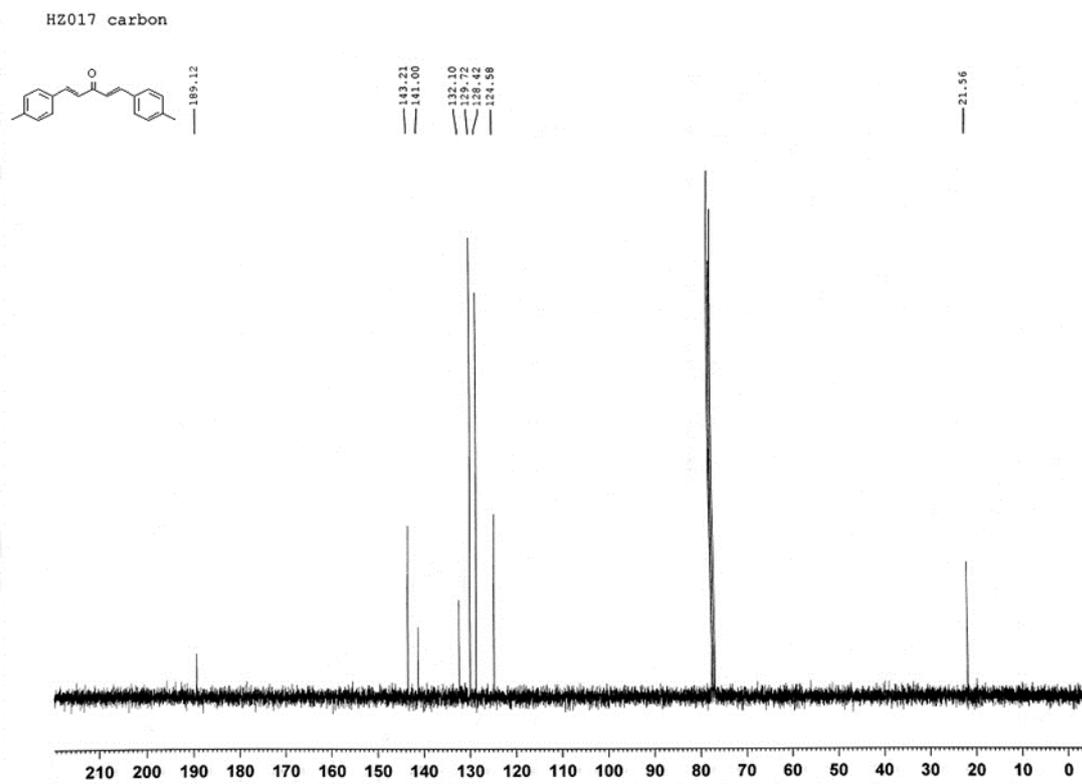
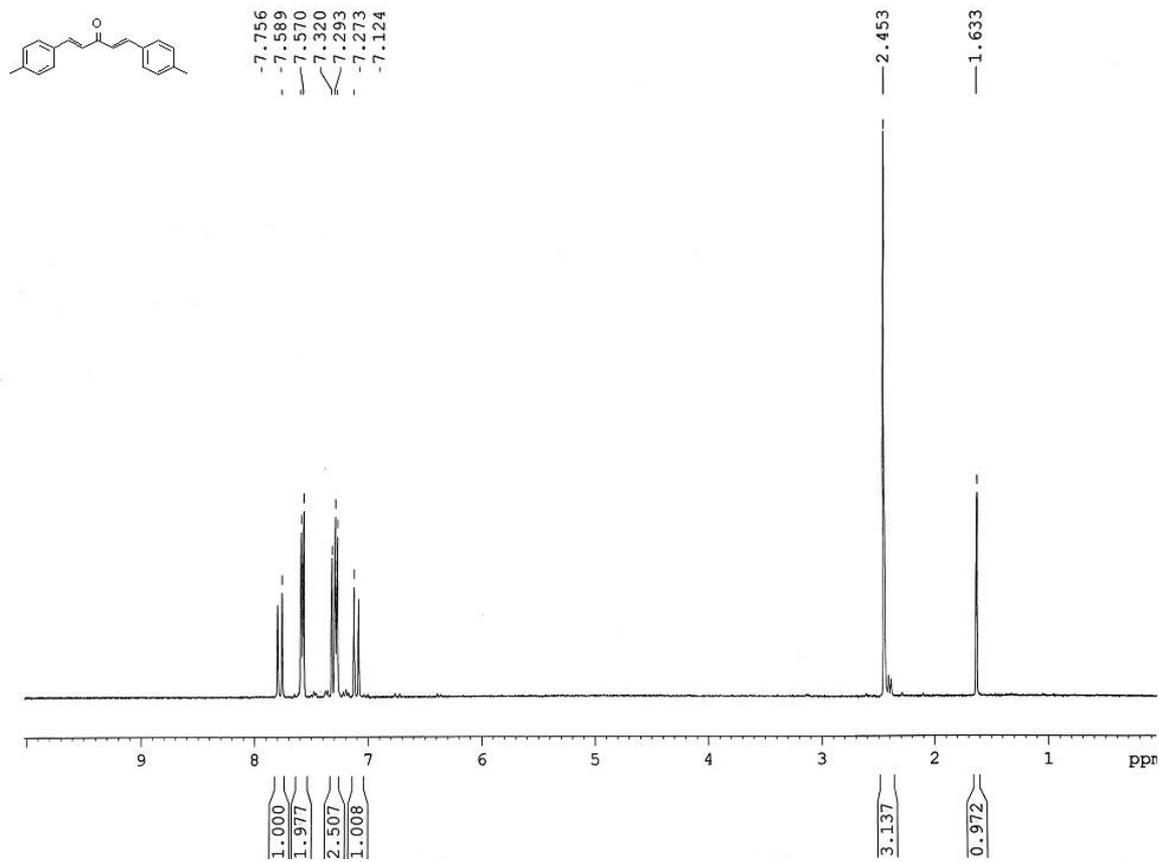
The ^1H NMR and ^{13}C NMR spectra

HZ001 substrate check

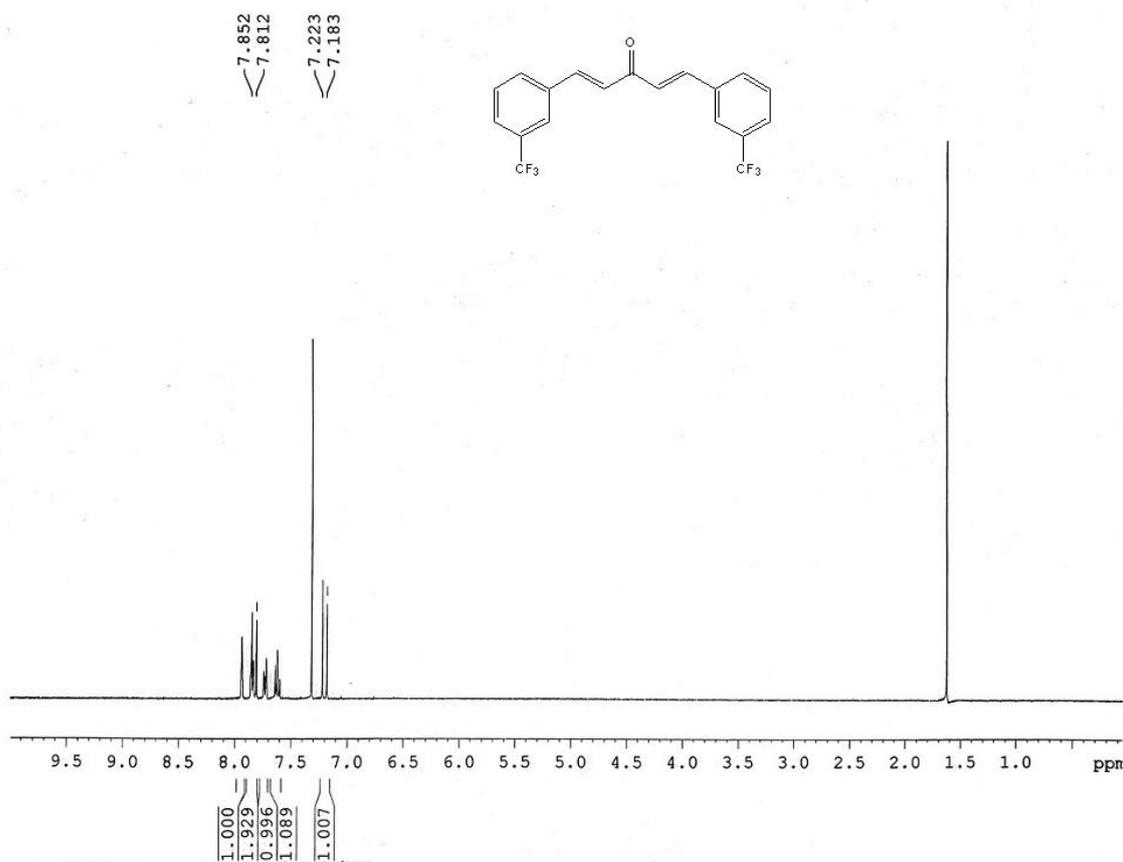


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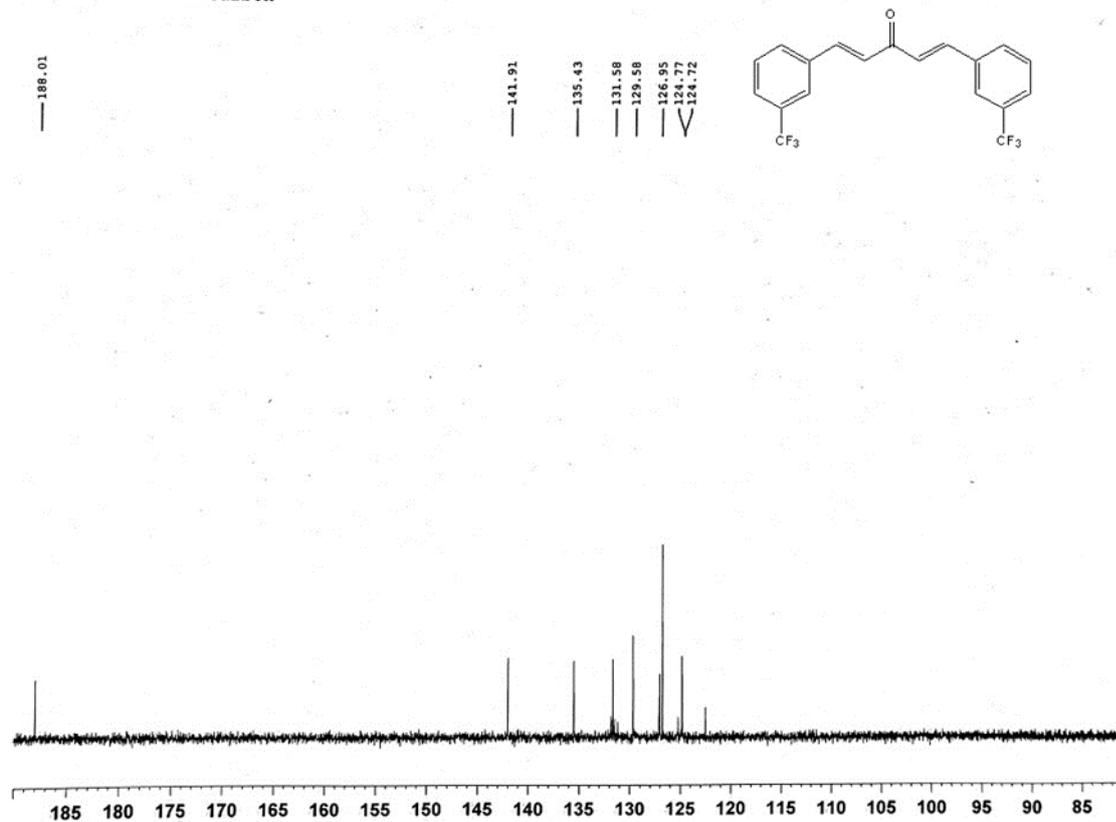


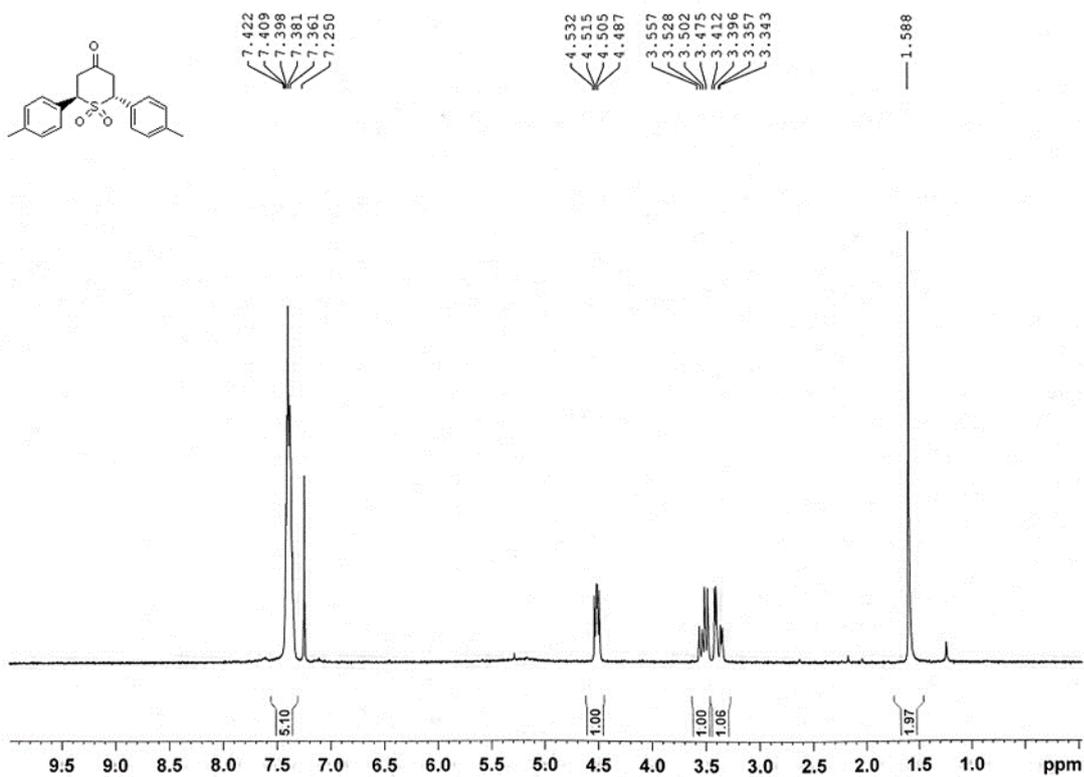


CF3 column HZ012

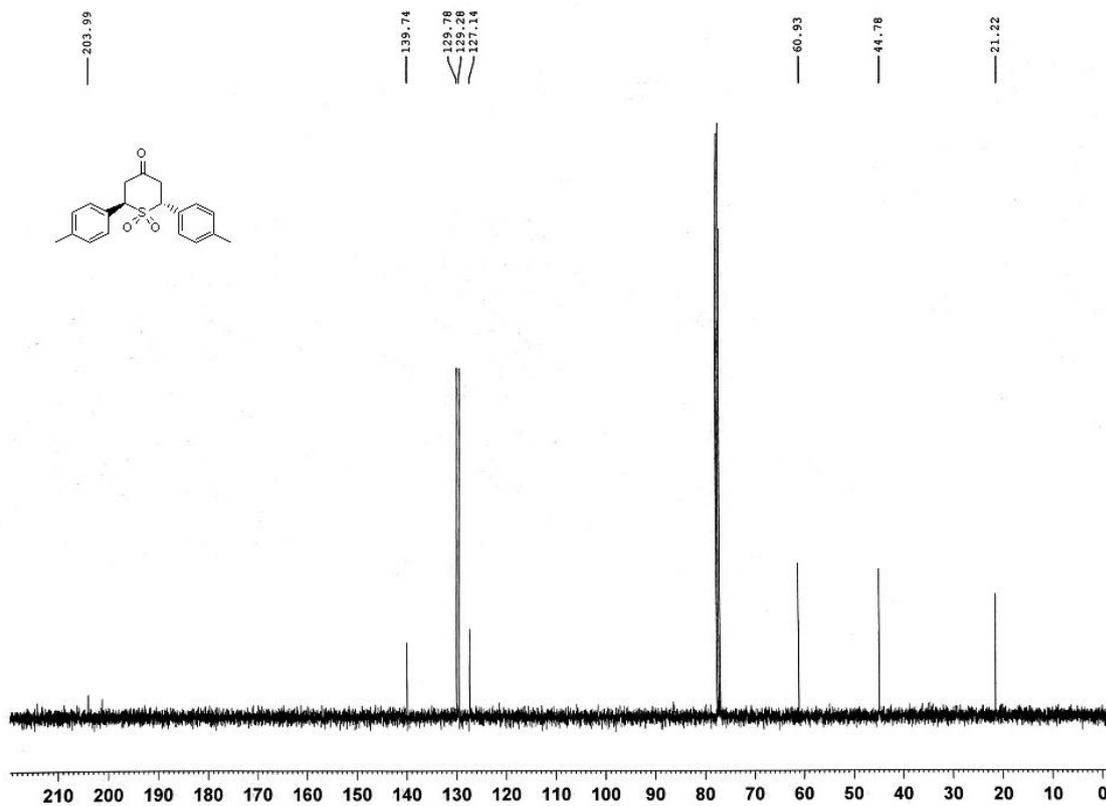


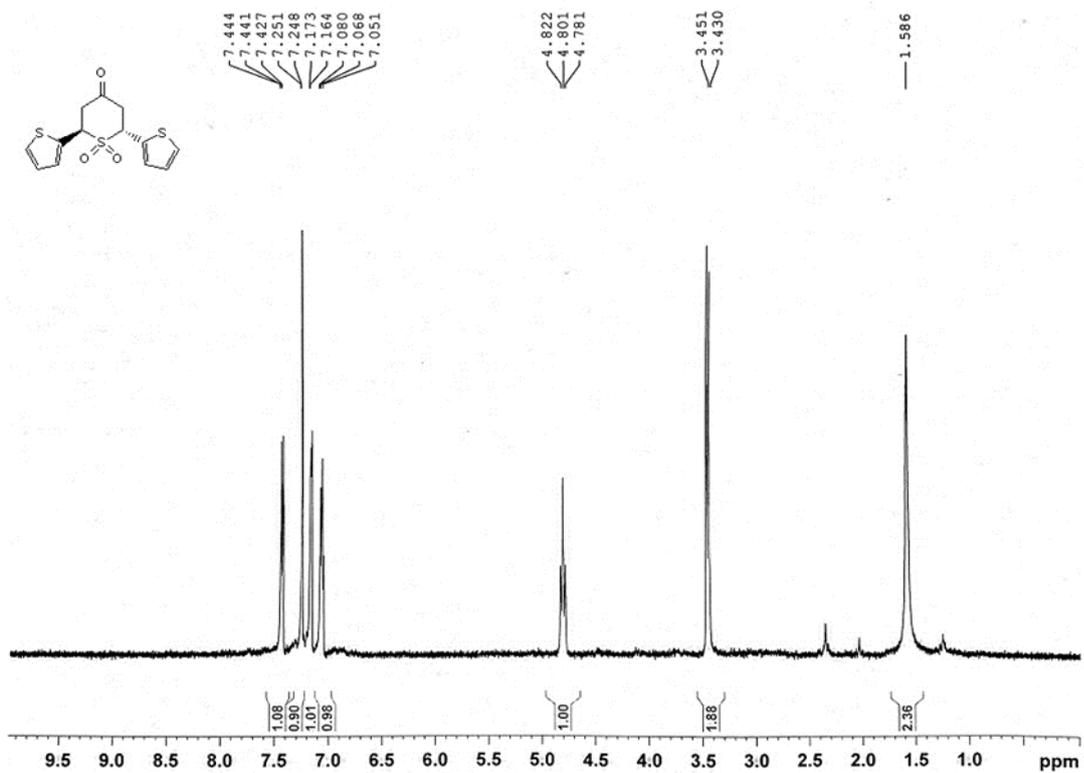
CF3 column HZ012 carbon



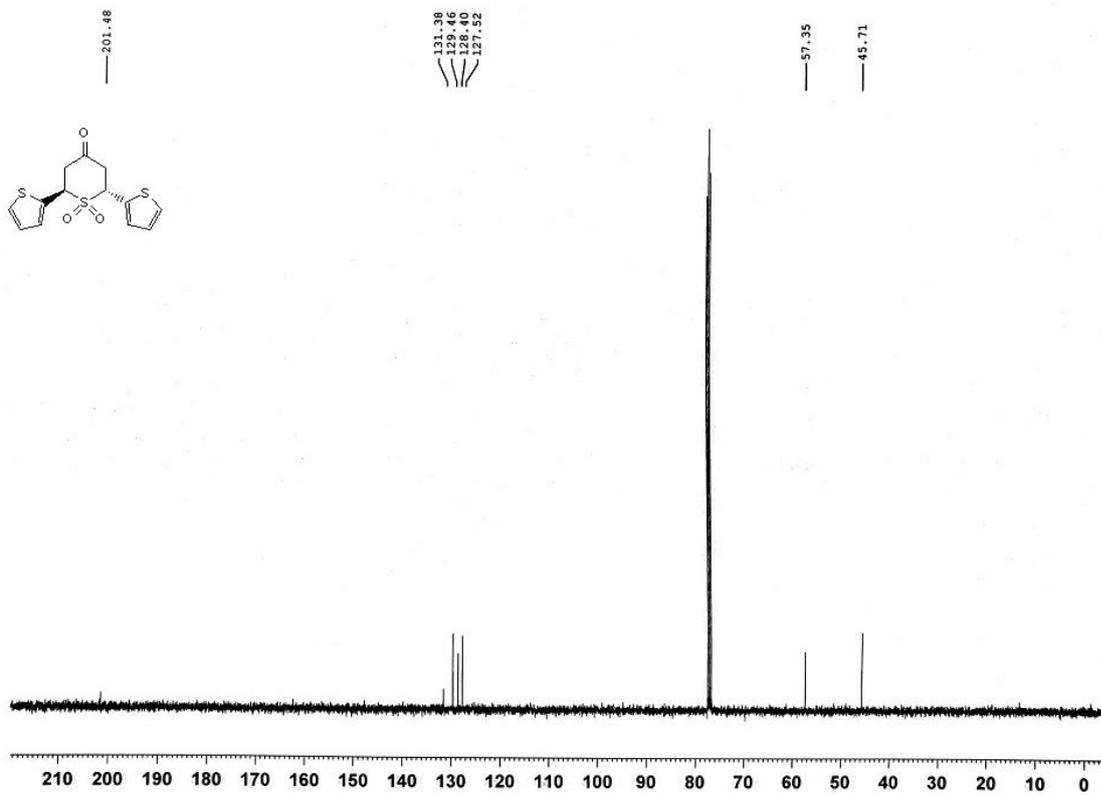


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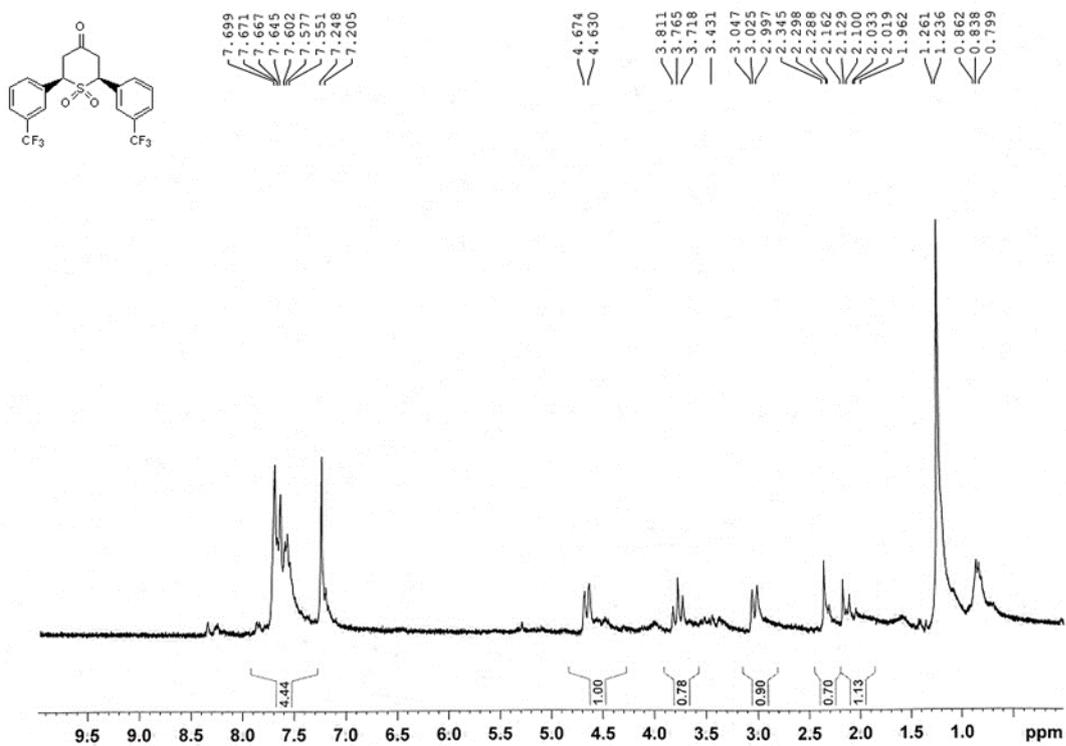
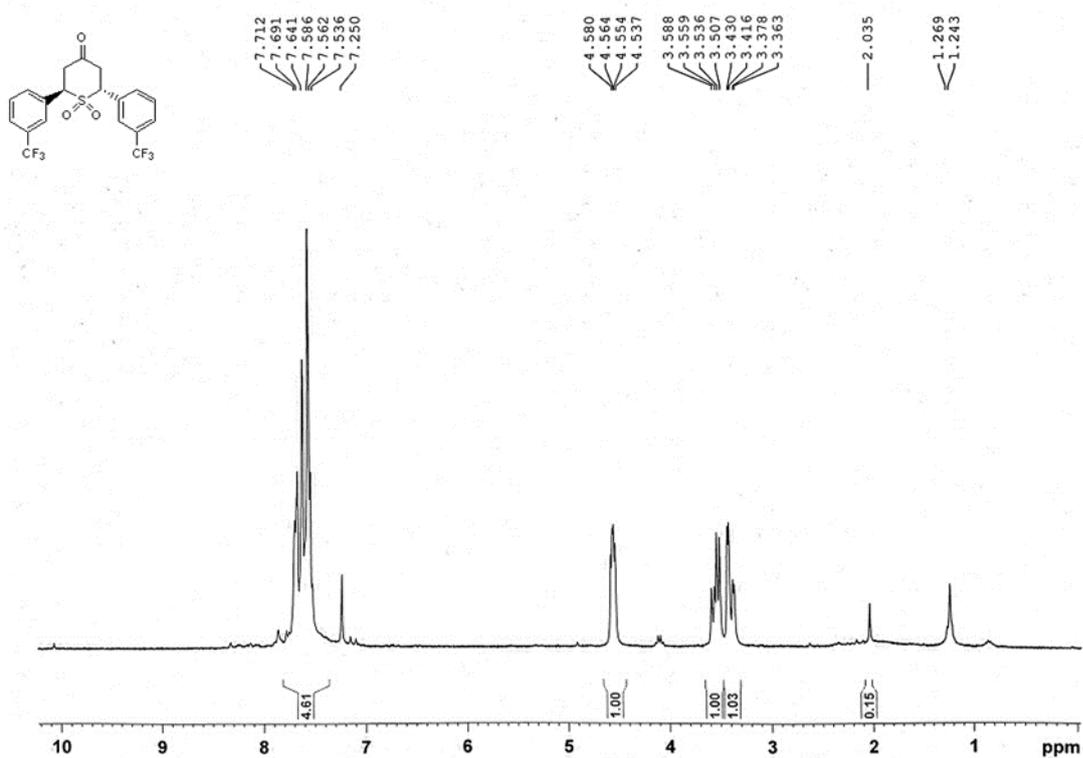


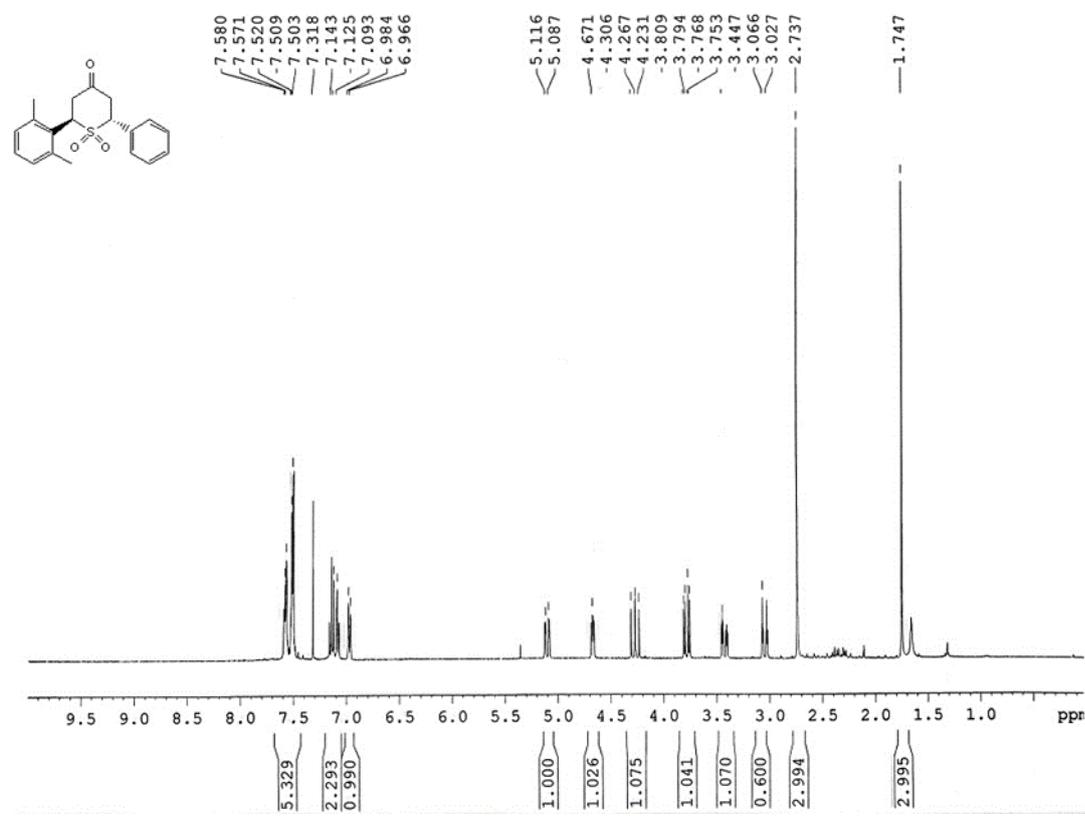
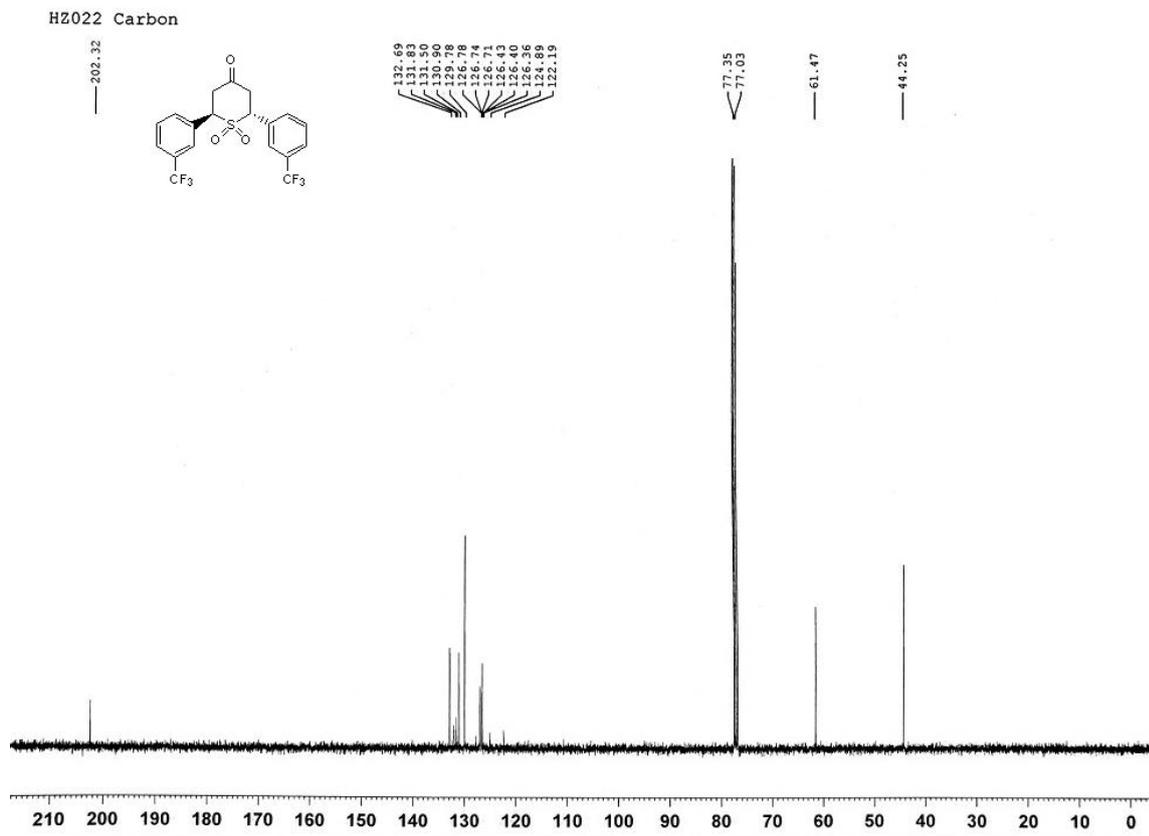


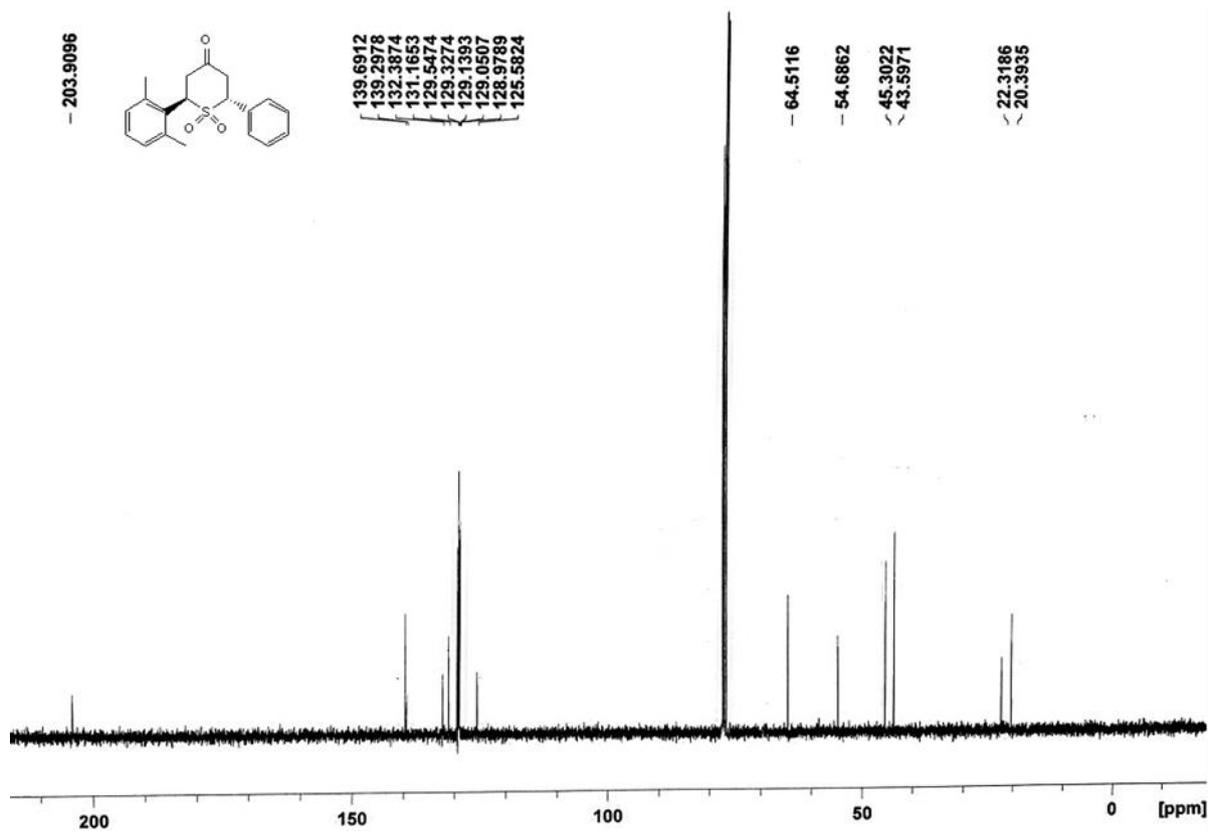
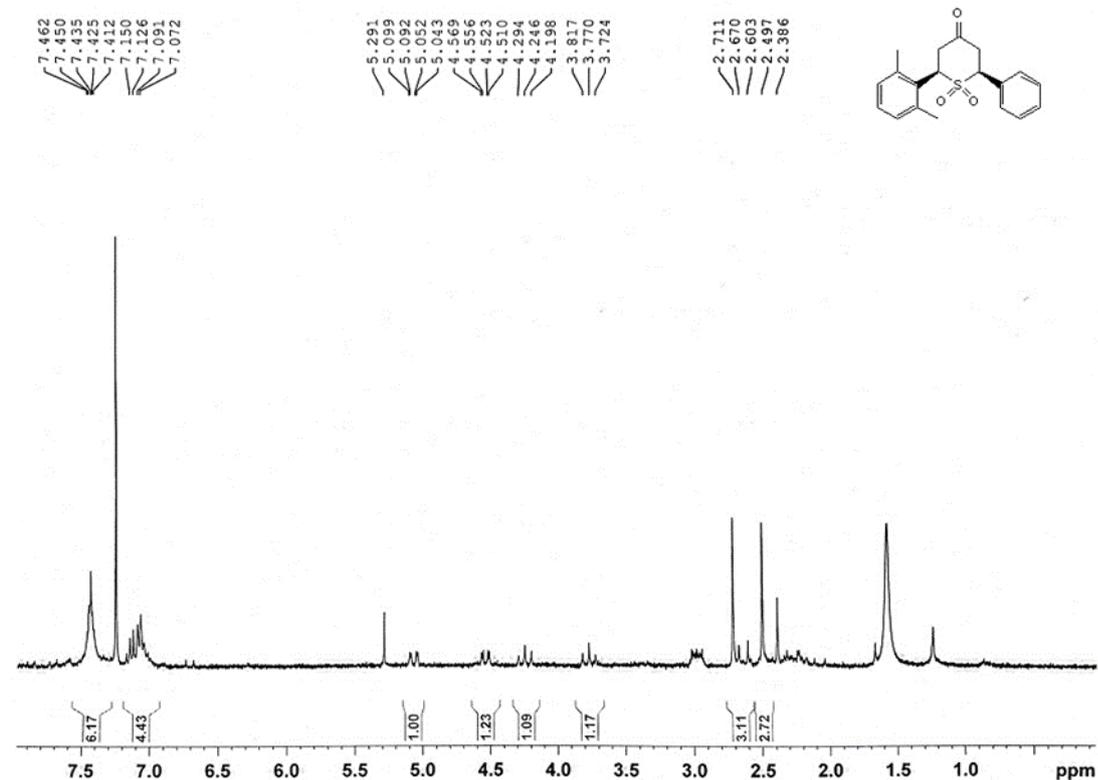
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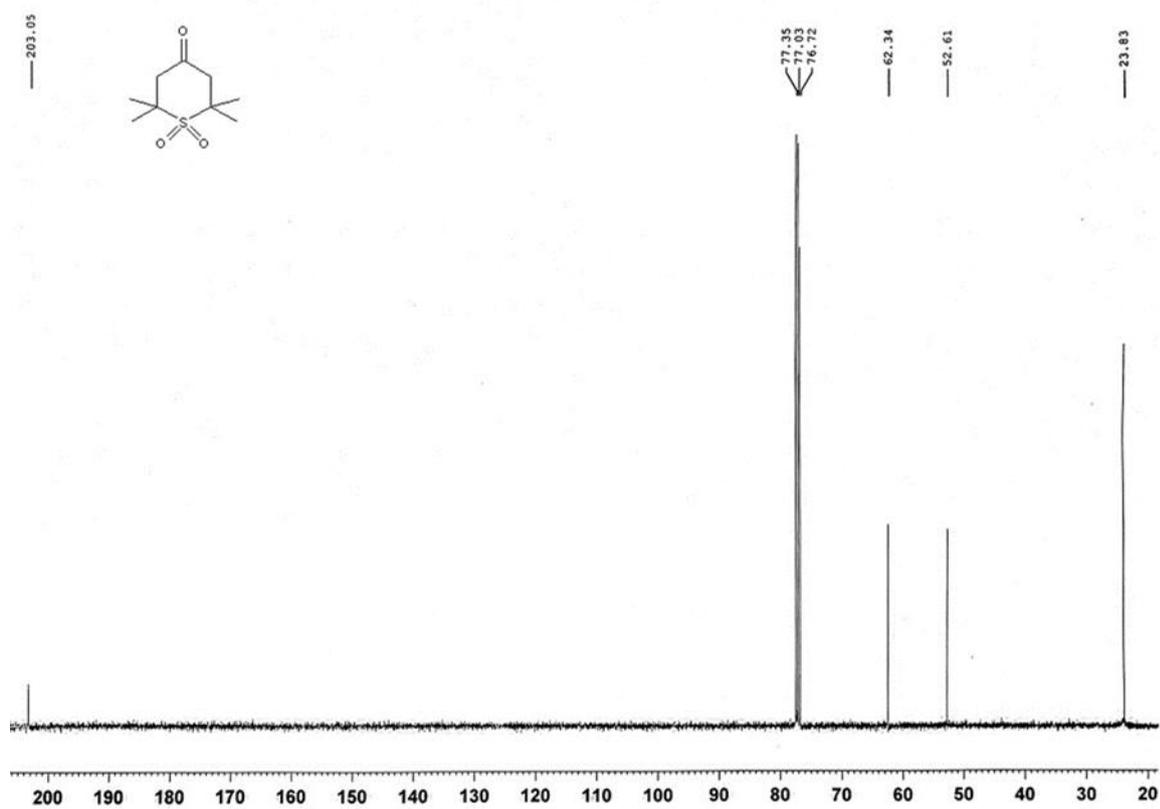
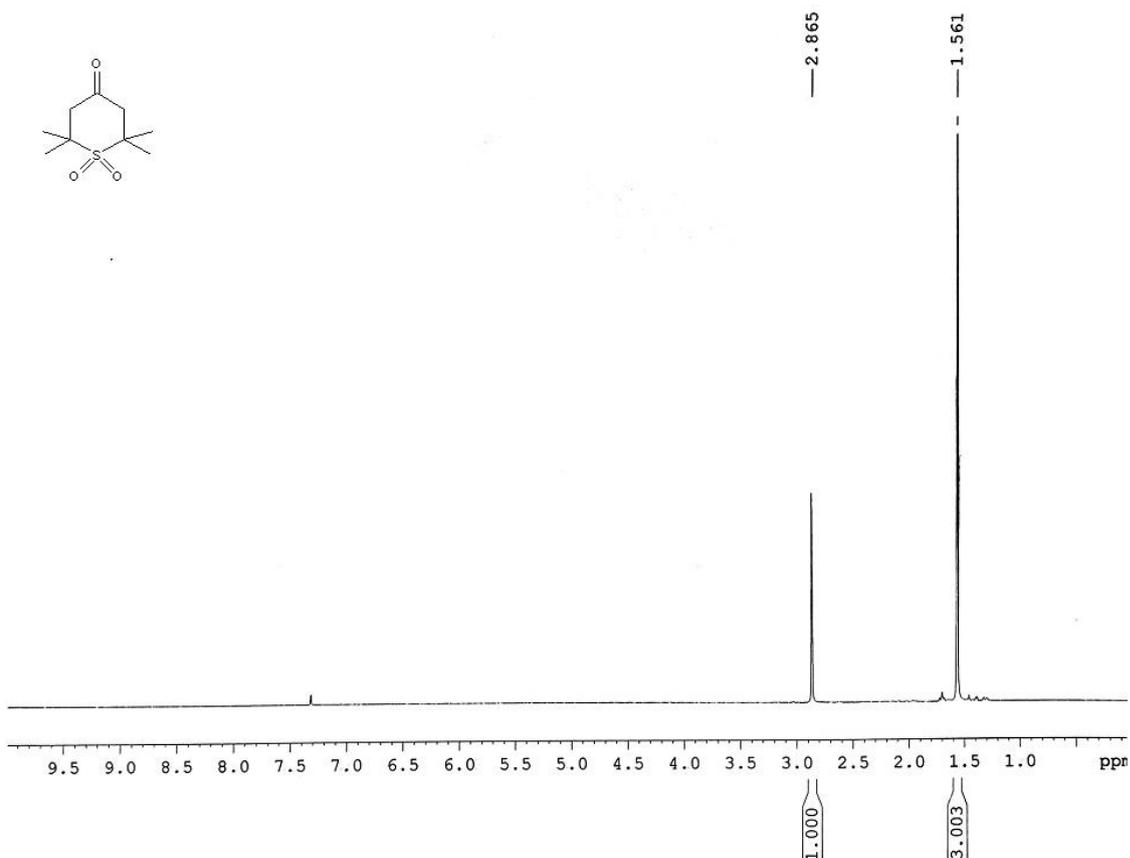


H2022 column major









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