UNIVERSIDADE FEDERAL DE PELOTAS

CENTRO DE CIÊNCIAS QUÍMICAS, FARMACÊUTICAS E DE ALIMENTOS

PROGRAMA DE PÓS-GRADUAÇÃO EM QUÍMICA

Ultrasound-accelerated synthesis of thioesters through the Ag(I)-catalyzed decarboxylative coupling between α-keto acids and diorganyl disulfides, under mild reaction conditions

DISSERTAÇÃO DE MESTRADO

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Pelotas, RS, Brasil

Agosto de 2018

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Dissertação apresentada ao Programa de Pós-Graduação em Química da Universidade Federal de Pelotas como requisito parcial para a obtenção do título de Mestra em Química.

Orientador: Prof. Dr. Eder João Lenardão

Co-orientador: Prof Dr. André Ricardo Fajardo

Pelotas, 28 de Agosto de 2018

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Data da Defesa: 28 de Agosto de 2018.

Banca Examinadora:

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Prof. Dr. Eder João Lenardão - Orientador - UFPel

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Prof. Dr. Claudio Santi – UNIPg (Itália)

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Prof. Dr. Marcio Santos da Silva- UFPel

RESUMO

Titulo: Síntese de tioésteres acelerada por ultrassom através do acoplamento descarboxilativo catalisada por Ag(I) entre α-cetoácidos e dissulfetos de diorganoíla, sob condições brandas de reação

Autor: Laura Abenante

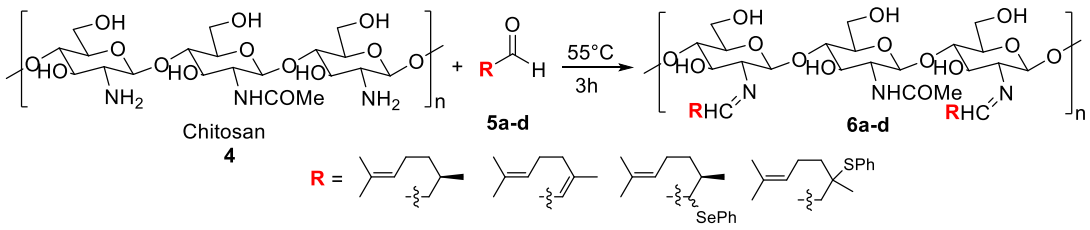
Orientador: Prof. Dr. Eder João Lenardão

Co-orientador: Prof. Dr. André Ricardo Fajardo

No presente trabalho foi desenvolvido um novo método alternativo para a obtenção de tioésteres, utilizando materiais de partida acessíveis e ecológicos, como α-ceto ácidos, e ultrassom como fonte de energia alternativa. Os compostos **3a**-**3j** foram obtidos com rendimentos entre bons e moderados, através da reação entre ácidos glioxílicos como agentes de transferência de acila e dissulfetos de diorganoíla, na presença de $AgNO_3$ como catalisador, $K_2S_2O_8$ como oxidante e uma mistura de DMSO/H_2O como solvente, em 20 minutos sob sonicação.

R = H, *p*-Me, *p*-OMe
R^1 = Ph, *p*-MePh, *p*-OMePh, *p*-FPh, *p*-ClPh, *o*-ClPh, Pr

Adicionalmente, foi realizada a modificação química da quitosana **4** para formar diferentes materiais poliméricos **6a-6d** com o objetivo de aumentar suas propriedades antifúngica e antibacteriana. A presença de grupos amina no seu esqueleto permitiu a formação de bases de Schiff após a reação com aldeídos. Os aldeídos usados foram citronelal **5a**, citral **5b**, α-fenilselenocitronelal **5c** e 3-feniltiocitronelal **5d**.



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ABSTRACT

Title: Ultrasound-accelerated synthesis of thioesters through the Ag(I)-catalyzed decarboxylative coupling between α-keto acids and diorganyl disulfides, under mild reaction conditions

Author: Laura Abenante

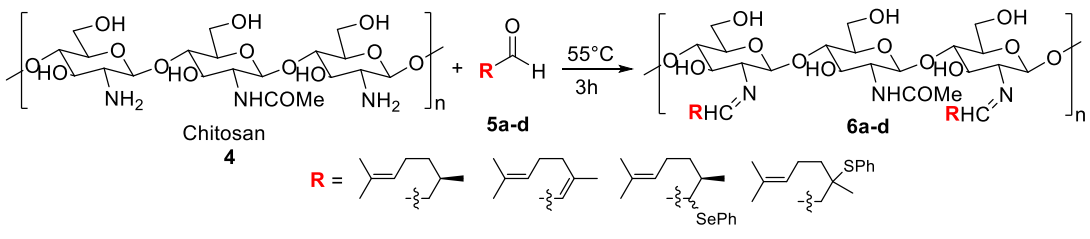
Academic Advisor: Prof. Dr. Eder João Lenardão

Academic Co-advisor: Prof. Dr. André Ricardo Fajardo

Here is reported a new, green method to obtain thioesters, using available and ecofriendly starting materials, as α-keto acids and an alternative energy source, the ultrasound. The title compounds **3a**-**3i** were prepared in moderate to good yields, through the reaction between glyoxylic acids as acyl transfer agents and diorganyl disulfides, in the presence of $AgNO_3$ as catalyst, $K_2S_2O_8$ as an oxidant and a mixture of DMSO/H_2O as the solvent, in 20 minutes under sonication.

R = H, *p*-Me, *p*-OMe
R^1 = Ph, *p*-MePh, *p*-OMePh, *p*-FPh, *p*-ClPh, *o*-ClPh, Pr

In addition, it was performed the chemical modification of chitosan (Cs) **4** with the aim of preparing new biopolymers **6a**-**6d** with improved antifungal and antibacterial properties. The presence of the amine groups in its backbone allows the formation of Schiff bases by reacting them with aldehydes. In this work the aldehyds used were citronellal **5a**, citral **5b**, α-phenylseleno-citronellal **5c** and 3-phenylthio-citronellal **5d**.



UNIVERSIDADE FEDERAL DE PELOTAS
PROGRAMA DE PÓS-GRADUAÇÃO EM QUÍMICA
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Al mio papà,

Ovunque Tu sia io so amare fino a lì.

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Thanks to my mum and my sister: near or far we are an invincible team.

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List of Abbreviations

A-Dipp	4-methyl-3-(2,6-diisopropylphenyl)thiazolium tetrafluoroborate
A-Mes	4-methyl-3-(2,4,6-trimethylphenyl)thiazolium tetrafluoroborate
CETP	Cholesteryl ester transfer protein
Cs	Chitosan
DCE	Dichloroethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DTBP	Di-*tert*-butyl peroxide
EA	Ethyl acetate
EDS	Energy Dispersive X-ray
ESR	Experiments of electron spin resonance
FTIR	Fourier Transform Infrared Spectroscopy
HDL	High density lipoprotein
NMR	Nuclear Magnetic Resonance
PGA	Phenyl glyoxylic acid
PVA	Polyvinyl alcohol
r.t.	Room temperature
SEM	Scanning Electron Microscope
SET	Single Electron Transfer
TBP	*tert*-butyl peroxide
TEAB	Tetraethylammonium tetrahydroborate
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TLC	Thin layer chromatography
TMS	Tetramethylsilane
US	Ultrasound

1.Introduction and aim of the work

1- Introduction and aim of the work

Organochalcogen compounds are organic molecules which contain chalcogen atoms on their structure. The term “chalcogen” is used to describe the atoms present in the sixteenth group of the periodic table: oxygen, sulphur, selenium, tellurium and polonium.[1,2]

Over the years up to date various organochalcogen compounds have been synthesized by several research groups, due to the many properties of this type of compounds in chemical, pharmacological and pharmaceutical fields. In fact, the compounds containing chalcogens have been presenting anticarcinogenic, antinoceptive, anti-inflammatory and antioxidant activities.[3] Furthermore, they are important for the organic synthesis as intermediates, catalysts or ligands.[4]

Among them, the thioesters compounds, generated by the reaction of a thiol and a carboxylic acid (Figure 1), have been playing an important role in the biosynthesis of many natural antibiotics, for example Bacitracin, Penicillin and Enterobactin (Figure 2, compounds **7**, **8**, **9**).[5]

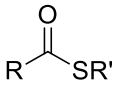


Figure 1. General structure of thioester.

This class of compounds can also allow native chemical ligations, which is a technique used to create long peptide and protein chains of moderate size, otherwise the construction of polypeptide and the synthesis of the large protein’s backbone is

[1] Jensen, W. B. *J. Chem. Educ.* **1997**, *74*, 1063.
[2] Fischer, W. *J. Chem. Educ.* **2001**, *78*, 1333.
[3] a) Schulz, J.; Renfrewb, A. K.; Císařová, I.; Dyson, P. J.; Štěpnička, P. *Appl. Organometal. Chem.* **2010**, *24*, 392. b) Savegnago, L.; Pinto, L. G.; Jesse, C. R.; Alves, D.; Rocha, J. B. T.; Nogueira, C. W.; Zeni, G. *Eur. J. Pharmacol.*, **2007**, *555*, 129. c) Nogueria, C. W.; Quinhones, E. B.; Jung, E. A. C.; Zeni, G.; Rocha, J. B. T. *Inflamm. Res.* **2003**, *52*, 56. d) Rossato, J. I.; Ketzer, L. A.; Centurião, F. B.; Silva, S. J. N.; Lüdtke, D. S.; Zeni, G.; Braga, A. L.; Rubin, M. A.; Rocha, J. B. T. *Neurochem. Res.* **2002**, 27, 297.
[4] a) Braga, L. A.; Lüdtke, D. S.; Sehnem, J. A.; Alberto, E. E. *Tetrahedron*. **2005**, *61*, 11664. b) Alberto, E. E.; do Nascimento, V.; Braga, A. L. *J. Braz. Chem. Soc.* **2010**, *21*, 2032. c) Dabdoud, M. J.; Silveira, C. C.; Lenardão, E. J.; Guerrero, Jr. P. G.; Viana, L. H.; Kawasoko, C. Y.; Baroni, A. C. M. *Tetrahedron Lett.* **2009**, *50*, 5569.
[5] a) Keating, T. A.; Walhs, C. T. *Curr. Opin. Chem. Biol.* **1999**, *3*, 598. b) Kholsa, C.; Tang, Y.; Chen, A. Y.; Schnarr, N. A.; Cane, D. E. *Annu. Rev. Biochem.* **2007**,*76*, 195.

impossible to make.[6] In this reaction, an unprotected C-terminal peptide thioester reacts with an N-terminal cysteine residue of a second unprotected peptide to form a native amide bond.

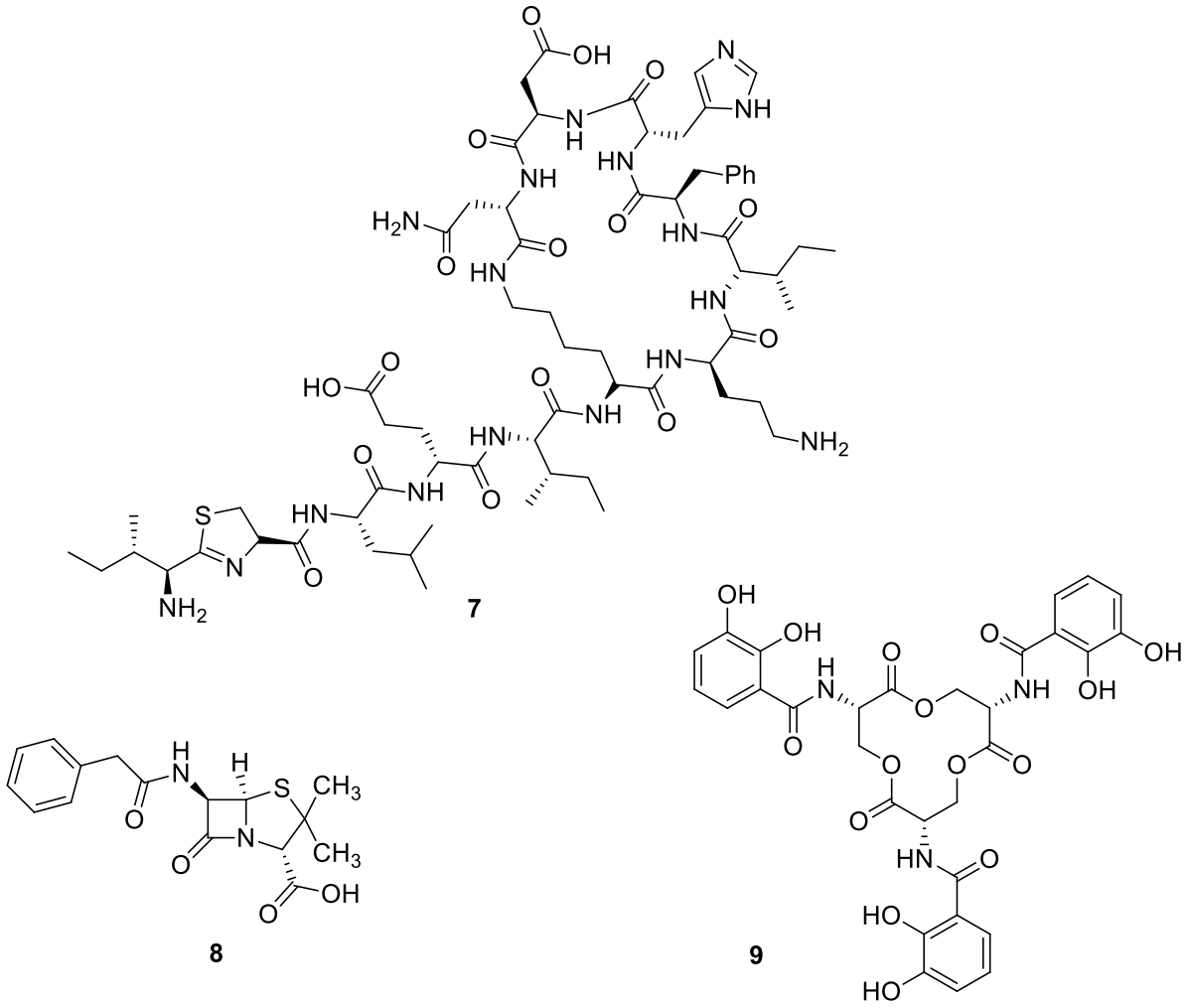


Figure 2. Bacitracin **7**, Penicillin **8**, Enterobactin **9**.

In addition, thioesters are part of molecules with pharmaceutical activity, few of them are shown in Figure 3. For example, compound **10** is a potent inhibitor of IMP-1, a metallo- lactamase, responsible for the resistance of microorganisms to antibiotics.[7] The thioester **11** presents a good antitumor action, inhibiting telomerase.[8]

[6] Mende, F.; Seitz, O. *Angew. Chem. Int. Ed.* **2011**, *50*, 1232.
[7] Greenlee, M. L.; Laub, J. B.; Balkovec, J. M.; Hammond, M. L.; Hammond, G. G.; Pompliano, D. L.; Epstein-Tonev, J. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2549.
[8] Jew, S.; Park, B.; Lim, D.; Kim, M. G.; Chung, I. K.; Kim, J. H.; Hong, C. I.; Kim, J. K.; Park, H. J.; Lee, J. H.; Park, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 609.

Instead, compound **12** presents anti-HIV activity and low toxicity,[9] while Dalcetrapid (**13**) is a cholesteryl ester transfer protein (CETP) modulator, and after the hydrolisis of the thioester group, the actual pharmacologically active thiol is formed, raising the blood levels of HDL, high density lipoprotein.[10] The Ceftiofur (**14**) is an antibiotic of the cephalosporin type (third generation), licensed for use in veterinary medicine.[11]

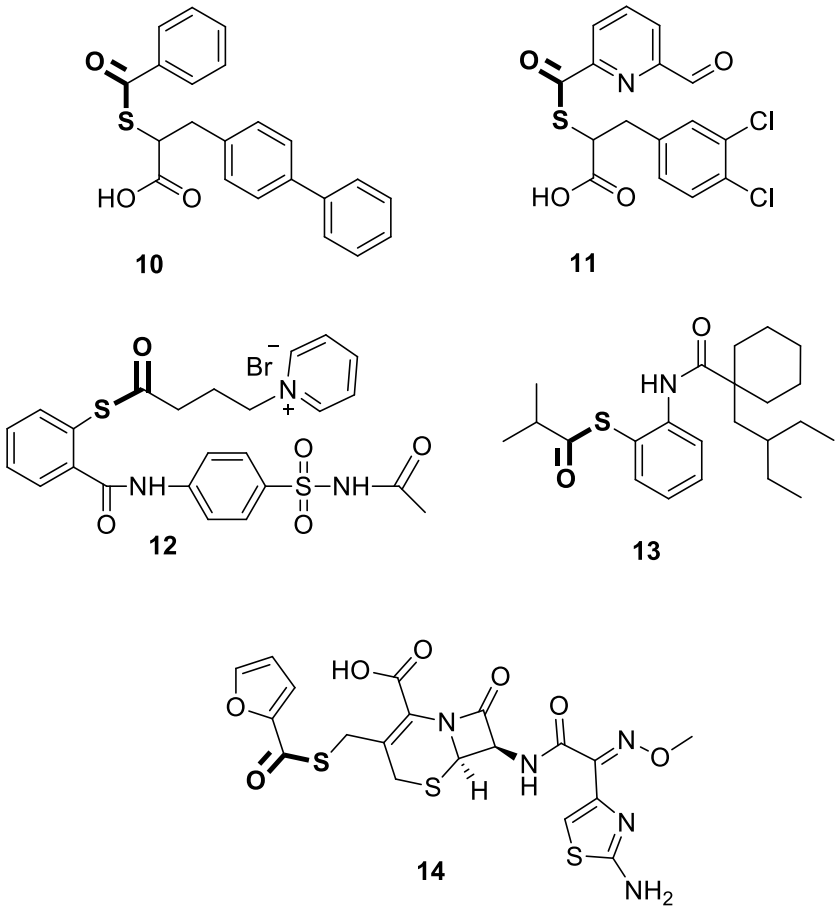
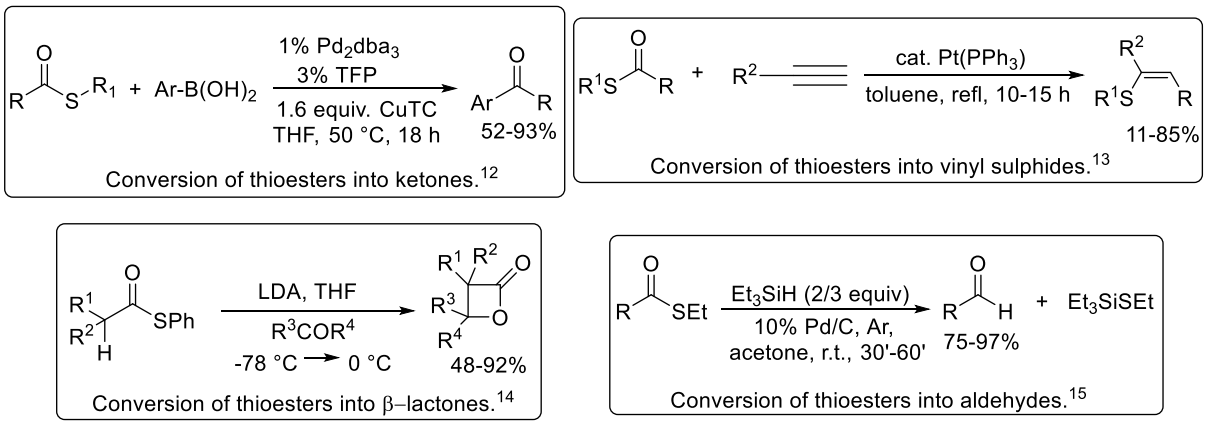


Figure 3. Biologically active thioesters.

The thioesters are versatile reagents in organic synthesis, being precursor of ketones,[12] vinyl sulphides,[13] β-lactones,[14] and aldehydes (Scheme 1).[15]

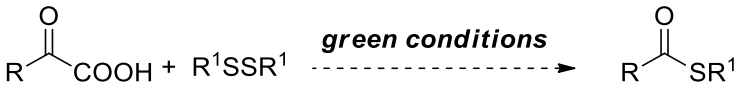
[9] Turpin, J. A.; Song, Y.; Inman, J. K.; Huang, M.; Wallqvist, A.; Maynard, A.; Covell, D. G.; Rice, W. G.; Appella, E. *J. Med. Chem.* **1999**, *42*, 67.
[10] Phelan, M.; Anzures-Cabrera, J.; Carlile, D. J.; Rowell, L.; Kuhlmann, O.; Arold, G.; Robson, R.; Bentley, D. *Clin. Pharmacokinet.* **2013**, *52*, 255.
[11] Yancey, R. J. Jr.; Kinney, M. L.; Roberts, B. J.; Goodenough, K. R.; Hamel, J. C.; Ford, C. W. *Am. J. Vet. Res.* **1987**, *48*, 1050.
[12] Liebeskind, L.S.; Srogl, J. *J. Am. Chem. Soc.*, **2000**, 122, 11260.
[13] Sugoh, K.; Kuniyasu, H.; Sugae, T.; Ohtaka, A.; Takai, Y.; Tanaka, A.; Machino, C.; Kambe, N.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 5108.
[14] Danheiser, R.L.; Nowick, J.S. *J. Org. Chem.* **1991**, *56*, 1176.



Scheme 1. Conversion of thioesters.[12,13,14,15]

Several protocols, from many research groups, are reported in the literature to obtain thioesters, highlighting their relevance in organic synthesis and medicinal chemistry.[16]

In this panorama of the literature, my target work was to improve the synthesis of thioesters, by finding a greener methodology. The idea was to start from easily to handle and ecofriendly reagents, such as the α-ketoacids and disulfides (Scheme 2).



Scheme 2. Our proposal for the synthesis of thioesters.

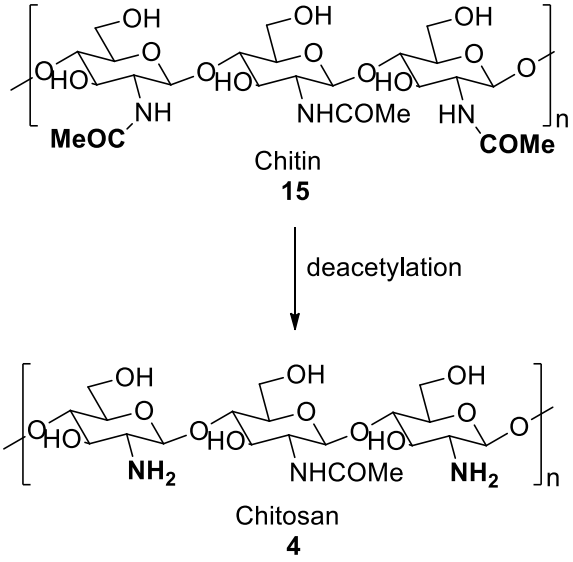
On the other hand, chitosan (Cs), a well-known chitin derivative, has been extensively used to formulate different kinds of materials due to its interesting properties, such as biodegradability, biocompatibility, nontoxicity, antimicrobial activity, among others. The chitin can be found among the shells of crustaceans such as crabs, shrimps and lobsters.(Scheme 3).[17]

---

[15] Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

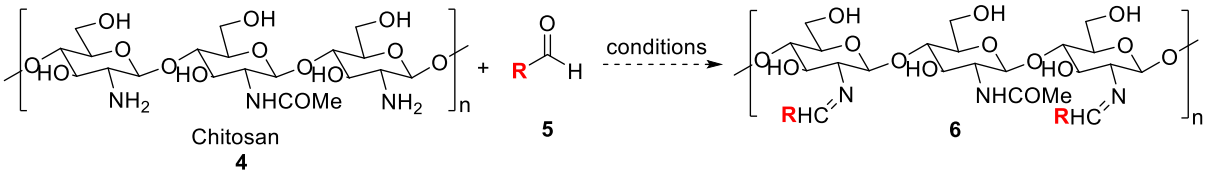
[16] a) Kazemi, M.; Shiri, L *J. Sulfur. Chem.* **2015**, DOI: 10.1080/17415993.2015.1075023. b) Fujiwara, S.-I-; Kambe, N. *Thio-, Seleno-, and Telluro-Carboxylic Acid Esters*, Berlino, © Springer-Verlag Berlin Heidelberg, 2015.

[17] Alves, N.M.; Mano, J.F. *Int. J. Biol. Macromol.* **2008**, *43*, 401.



Scheme 3. Chitosan's formation from chitin.

Cs is a linear polysaccharide composed by repeated β-(1-4) linked units of either 2-amino-2-deoxy-β-D-glucopyranose (glucosamine) or 2-acetamido-2-deoxy-β-D-glucopyranose (glucosacetamide), depending on the degree of *N*-acetylation (DA) units. It exhibits two types of reactive groups bound to the main backbone: free amine groups on deacetylated units and hydroxyl groups on acetylated or deacetylated units. The free amine groups allow preparing Schiff bases by reacting such groups with aldehydes and ketones (linear or aromatics).[18] Herein, we investigated the synthesis of Schiff bases **6** by reacting Cs **4** with citronellal, citral, and their derivatives containing selenium and sulfur, in order to obtain Cs-derivatives with enhanced biological properties (Scheme 4).



R = natural and semi-synthetic aldehydes

Scheme 4. New chitosan derivatives.

[18] a) Jin, X.; Wang, J.; Bai, J. *Carbohydr. Res.* **2009**, *344*, 825. b) Yue, L.; Jingru, L.; Chen, W.; Liu, X.; Jiang, Q.; Xia, W. *Carbohydr. Polym.* **2017**, *176*, 356.

2. Literature review

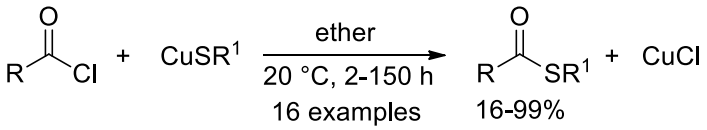
2- Literature review

In this chapter it will be discussed the literature's panorama regarding the methods existing to obtain thioesters, will be discussed the importance of the α-keto acids and their reactivity, the use of ultrasound in organic synthesis and some aspects on the modification of chitosan polymer.

2.1- Synthesis of thioesters

Probably, the most common way to prepare the thioesters is through the nucleophilic addition/elimination of thiols to acyl chlorides. In the following lines we will present some representative approaches to prepare this class of compounds.

In 1980, Reiβig and co-workers[19] reported a synthesis starting from acyl chlorides and copper mercaptides, which reacted in ether at 20 °C for 2 hours to 150 hours, forming the thioesters in yields from 16% to 99%, and copper chloride as byproduct (Scheme 5).

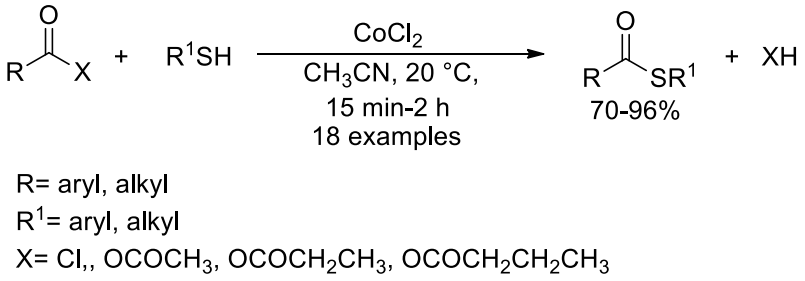


R= aryl, alkyl
R^1= aryl, alkyl

Scheme 5. Synthesis of thioesters reported by Reiβig.[19]

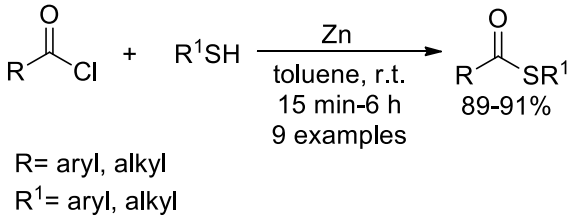
In 1986, Ahmad and co-workers[20] developed a reaction between acyl compounds and a thiols, using cobalt chloride in acetonitrile. The authors have prepared 18 different thioesters in 70% to 96% yields after 15 minutes to 2 hours at 20 °C. Despite good yields, this method suffers of some drawbacks, like the use of acyl chloride as starting material and the formation of HCl as a side product (Scheme 6).

[19] Reiβig, H. U.; Scherer, B. *Tetrahedron Lett.* **1980**, *21*, 4259.
[20] Ahmad, S.; Iqbal, J. *Tetrahedron Lett.* **1986**, *27*, 3791.



Scheme 6. Synthesis of thioesters reported by Ahmad.[20]

In 1998, Meshram and co-workers[21] published the synthesis of thioesters from the reaction of acyl chlorides with thiols in the presence of zinc and using toluene as the solvent. A total of nine thioesters were prepared in 89% to 91% yields after 15 minutes to 6 hours of reaction at room temperature (Scheme 7).

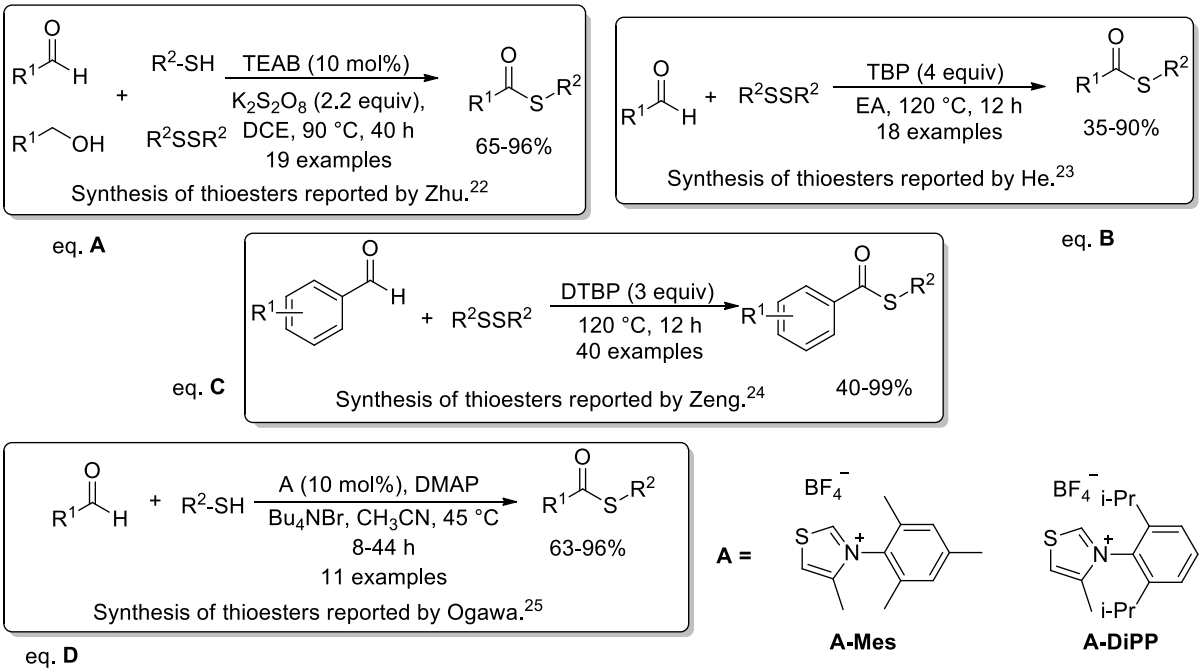


Scheme 7. Synthesis reported by Meshram.[21]

More recently, aldehydes have been shown to be an alternative and useful acyl source for the synthesis of thioesters. In 2013, Zhu and co-workers[22] developed a protocol to obtain thioesters in high yields (65-96%) through a tetraethylammonium bromide-catalyzed oxidative coupling of aldehydes or alcohols with thiophenols or disulfides under a metal-free condition, at 90 °C and for 40 hours (Scheme 8, eq. **A**). In 2014, He and his group[23] developed a direct oxidative coupling reaction, through a metal-free condition, between aldehydes and disulfides in ethyl acetate, in the presence of *tert*-butyl peroxide, affording the thioesters in moderate to good yields (30-90%), at 120 °C for 12 hours (Scheme 8, eq. **B**). In the same year, Zeng and co-workers[24] reported a thiolation of aldehydes with disulfides promoted by di-*tert*-butyl peroxide under metal- and solvent-free conditions. The authors have prepared a total

[21] Meshram, H. M.; Reddy, G. S.; Bindu, K. H.; Yadav, J. S. *Synlett*. **1998**, *8*, 877.
[22] Zhu,, X.; Shi, Y.; Mao, H.; Cheng, Y.; Zhu, C. *Adv. Synth. Catal.* **2013**, *355*, 3558.
[23] He, C.; Qian, X.; Sun, P. *Org. Biomol. Chem.* **2014**,*12*, 6072.
[24] Zeng, J.-W.; Liu, Y.-C.; Hsieh, P.-A.; Huang, Y.-Y.; Yi, C.-L.; Badsara, S. S.; Lee, C.-F. *Green Chem.* **2014**, *16*, 2644.

of 40 thioesters in moderate to excellent yields (40-99%), after reaction at 120 °C for 12 hours (Scheme 8, eq. **C**). Later, in 2014, Ogawa and Boydston[25] developed a method for the direct conversion of aldehydes to thioesters via integration of organocatalysis and electrosynthesis, using 4-methyl-3-(2,4,6-trimethylphenyl)-thiazolium tetrafluoroborate (A-Mes) or 4-methyl-3-(2,6-diisopropylphenyl)thiazolium tetrafluoroborate (A-DiPP) as pre-catalysts, compounds which are transformed in catalyst during the reaction. In this protocol, the oxidation of thiolate anions was facilitated, leading to the desired products in good to excellent yields (63-96%), after 8-44 h at 45 °C. It was used a graphite anode, Pt cathode and constant cell potential of +0.1 V (*vs* Ag/$AgNO_3$) (Scheme 8, eq. **D**).

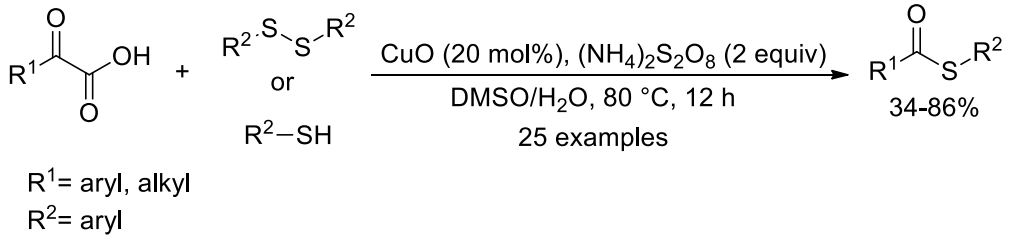


Scheme 8. Synthesis of thioesters using aldehyds.

However, the aldehydes are difficult to handle due to their relative instability under moisture, because they can be easily hydrolyzed or oxidized to the respective carboxylic acid.

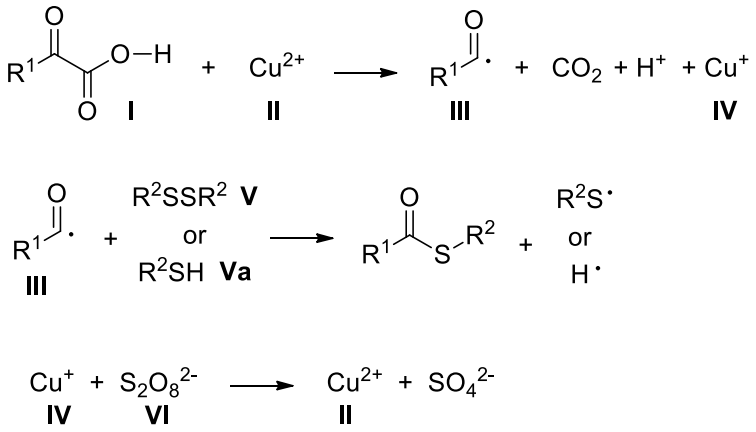
[25] Ogawa, K. A.; Boydston, A. J. *Org. Lett.* **2014***, 16*, 1928.

Trying to avoid this problem, in 2015 Rong and co-workers[26] reported a new method to obtain thioesters in moderate to good yields (34-86%) through a copper-catalyzed decarboxylative coupling between α-oxocarboxylic acids and diphenyl disulfides or thiophenols, leading to the C(sp^2)-S bond formation in 12 hours at 80 °C (Scheme 9).



Scheme 9. Synthesis of thioesters reported by Rong.[26]

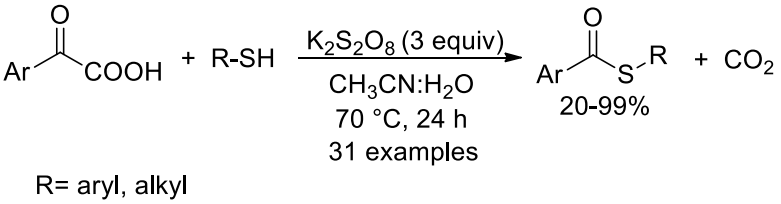
The proposed mechanism involved firstly the formation of the aryl radical **III** from the benzoylformic acid **I** in the presence of copper(II) catalyst **II**. This radical **III** then reacted with disulfide **V** or thiophenol **Va** to give the thioester. The copper(I) ion **IV** was next oxidized to copper(II) **II** by ammonium persulfate **VI** and commenced a new cycle (Scheme 10).



Scheme 10. Proposed mechanism of Rong's reaction.

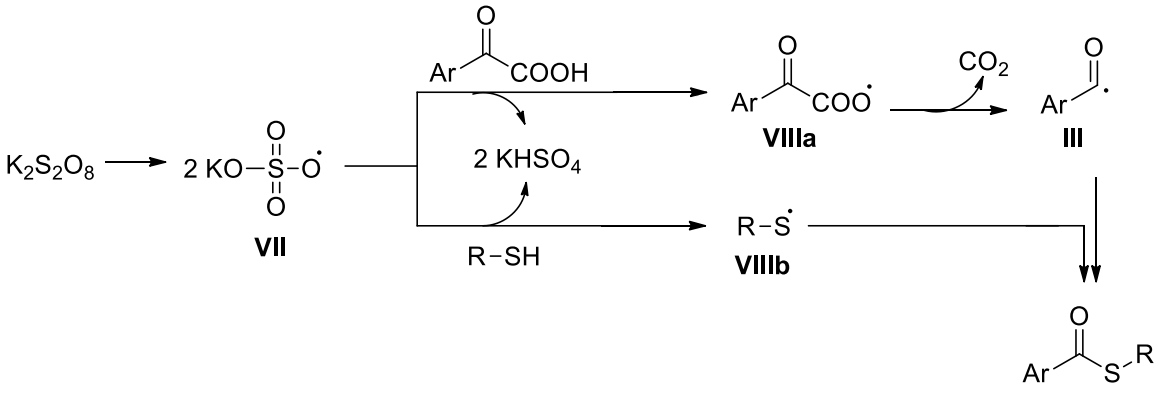
[26] Rong, G.; Mao, J.; Liu, D.; Yan, H.; Zheng, Y.; Chen, J. *RSC Adv.* **2015**, *5*, 26461.

In the same year, Yan[27] and his group developed a similar strategy to obtain thioesters. A catalyst-free reaction v*ia* the direct radical oxidative decarboxylation of α-keto acids with thiols. The desired products were obtained in very good to excellent yields (82-99%) after 24 hours at 70 °C (Scheme 11).



Scheme 11. Synthesis of thioesters developed by Yan.[26]

In the proposed mechanism, $K_2S_2O_8$ was initially heated to generate the active radical anion $SO_4^{-\cdot}$ **VII**. Then the anionic radical abstracts the hydrogen from the acidic bond of carboxylic acid and thiophenol, leading to a α-keto carboxyl radical **VIIIa** and a sulfur radical **VIIIb**. Consequently, the decarboxylation of the α-keto carboxyl radical affords to the corresponding acyl radical **III** that, finally, couples with sulfur radical **VIIIb**, forming the thioester (Scheme 12).



Scheme 12. Plausible mechanism of the Yan's reaction.

These two methods make the use of α-keto acids as acylating agents, superior respect other sources, because they involve the release CO_2 as the only waste, giving to these protocols a green and atom-economic feature. Despite the

[27] Yan, K., Yang, D., Wei, W., Zhao, J., Shuai, Y., Tian, L., Wang, H. *Org. Biomol. Chem.* **2015**, *13*, 7323.

apparent advances in using these two methods, certain obstacles remain, particularly with regard to the long reaction time under thermal heating and the use of bad smelling thiols as sulfur source.

2.2- α-keto acids

The keto acids **16**, **17** and **18**, respectively α-, β- and γ-keto acids, are organic compounds containing a carboxylic acid group and a ketone group (Figure 4, compounds **16**, **17**, **18**).

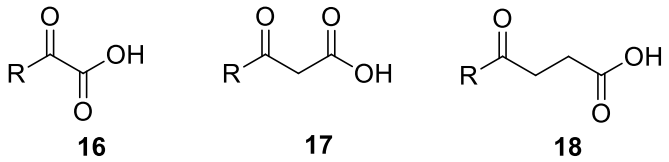


Figure 4. General structure of α-, β- and γ-keto acids.

The α-keto acids are especially important in biology, thus, pyruvic acid **19** is a metabolite involved in a number of enzyme-catalyzed intracellular phenomena. It plays a crucial role as precursor of cell supplying energy processes in living organism, such as, animals, plants and bacteria (Figure 5, compound **19**).

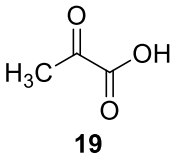


Figure 5. Structure of pyruvic acid.

The α-keto acids are in continuing interest as intermediates in chemical synthesis due to the important role which they have been playing in nature. In 1835, Berzelius[28] prepared for the first a α-keto acid, the pyruvic acid **19**. Several protocols, from many research groups are reported on the literature to obtain these compounds,

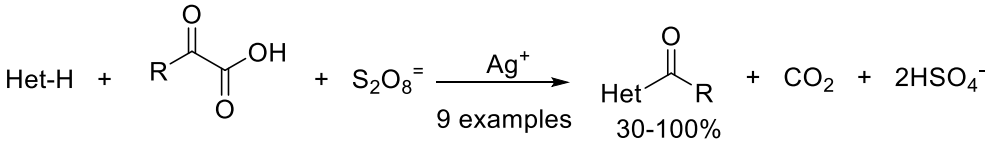
[28] Berzelius, J. J. *Ann. Phys.* **1835**, *36*, 1.

highlighting their relevance and opening a new way to investigate their chemical properties and applications.[29]

2.2.1- Reactivity of α-keto acids

The α-keto acids are easy to handle and ecofriendly reagents, widely used in organic synthesis as acylating agents.

Among several applications of α-keto acids and its derivatives, in 1991 Fontana and co-workers[30] described a homolytic acylation of protonated pyridines and pyrazines, promoted by $Ag(I)S_2O_8^{2-}$ with α-keto acids, using them as an acyl source, *via* the formation of an acyl radical intermediate (Scheme 13).



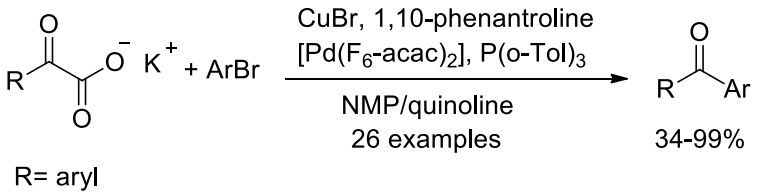
Het = quinoline, quinazoline, 4-cyanopyridine, 4-acetylpyridine, pyrazine
R = Me, Et, Pr, Ph

Scheme 13. Synthesis of Fontana.[30]

After this study, several methodologies describing the α-keto acids as acylating agents appeared on the literature, through the formation of new Csp^2-acyl and Csp-acyl bonds in different compounds.

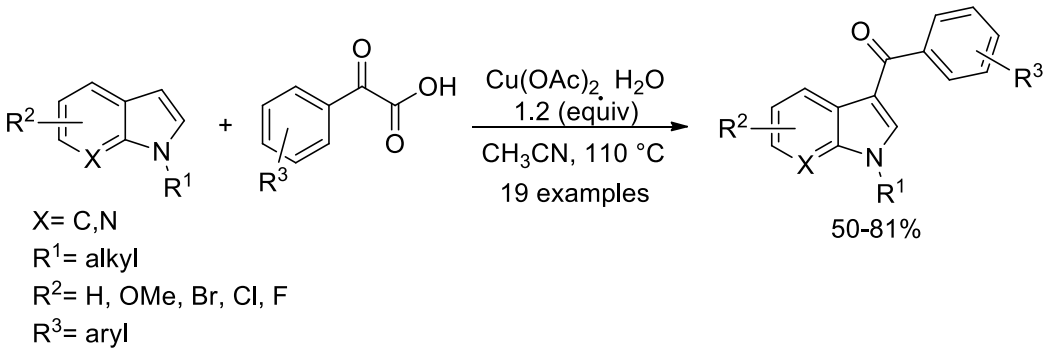
An interesting reaction of α-keto acids is in the synthesis of aryl ketones, starting from benzene-derivatives.[31] An example is the protocol of Gooβen and co-workers,[31a] developed in 2008, which reports a coupling reaction between aryl bromides and α-oxocarboxylates, catalyzed by a bicatalytic system of Cu/Pd, forming in this way ketones and CO_2 as the only waste product (Scheme 14).

[29] Cooper, A. J. L.; Ginos, J. Z.; Meister, A. *Chem. Rev.* **1983**, *83*, 321.
[30] Fontana, F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866.
[31] a) Gooβen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 3043. b) Li, M.; Wang, C.; He, H. *Org. Lett.* **2011**, *13*, 2062. c) Cheng, K.; Zhao, B.; Qi, C. *RSC Adv.* **2014**, *4*, 48698.



Scheme 14. Synthesis reported by Gooβen.[31a]

In addition, the α-keto acids were used in heteroaromatic systems.[32] For example, Yu and co-workers[32a] reported in 2013 a synthesis where the α-oxocarboxylic acids were involved in a copper-promoted decarboxylative acylation of *N*-substituted indoles (Scheme 15).

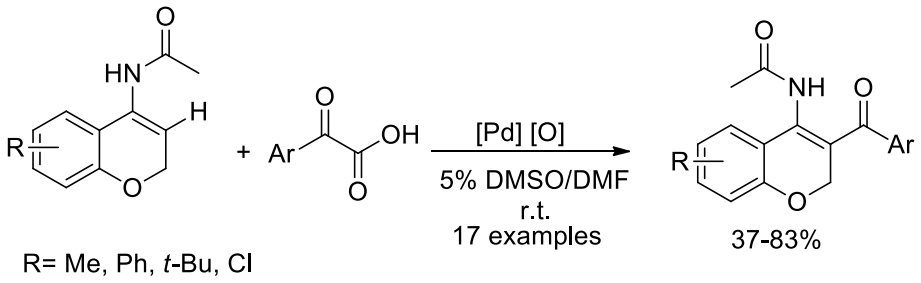


Scheme 15. Synthesis reported by Yu.[32a]

The α-keto acids were used also in alkenes[33] system, and an example of this is the work of Wang and co-workers,[33a] developed in 2012. They have described a palladium-catalyzed decarboxylative acylation of cyclic enamides with α-oxocarboxylic acids (Scheme 16).

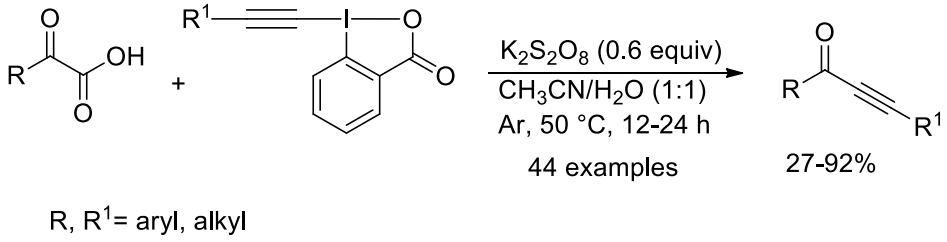
[32] a) Yu, L.; Li, P.; Wang, L. *Chem. Commun.* **2013**, *49*, 2368. b) Gu, L.; Jin, C.; Liu, J.; Zhang, H.; Yuan, M.; Li, G. *Green Chem.* **2016**, *18*, 1201. c) Yang, K.; Zhang, C.; Wang, P.; Zhang, Y.; Ge, H. *Chem. Eur. J.* **2014**, *20*, 7241. d) Yang, K.; Chen, X.; Wang, Y.; Li, W.; Kadi, A. A.; Fun, H.-K.; Sun, H.; Zhang, Y.; Li, G.; Lu, H. *J. Org. Chem.* **2015**, *80*, 11065.

[33] a) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2012**, *14*, 4358. b) Zhang, N.; Yang, D.; Wie, W.; Yuan, L.; Nie, F.; Tian, L.; Wang, H. *J. Org. Chem.* **2015**, *80*, 3258. c) Wang, H.; Guo, L.-N.; Duan, X.-H. *Chem. Commun.* **2014**, *50*, 7382. d) Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Yao, F. *Org. Lett.* **2015**, *17*, 4830.



Scheme 16. Synthesis reported by Wang.[33a]

Moreover, the α-keto acids were used in the acylation of alkynes compounds,[34] such as in the synthesis reported in 2015 by Wang and co-workers,[34c] *via* decarboxylative alkynylation of α-keto acids under metal-free conditions (Scheme 17).

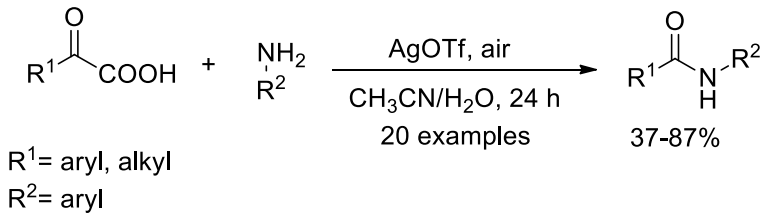


Scheme 17. Synthesis reported by Wang.[34c]

Furthermore, the α-keto acids were used in the acylation of heteroatoms, such as the *N*-acylation to obtain amides.[35] An example is the work of Xu and co-workers,[35b] published in 2016, which describes a silver- promoted decarboxylative amidation of α-keto acids with amines (Scheme 18).

[34] a) Huang, H.; Zhang, G.; Chen, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 7872. b) Tan, H.; Li, H.; Ji, W.; Wang, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 8374. c) Wang, P.-F.; Feng, Y.-S.; Cheng, Z.-F.; Wu, Q.-M.; Wang, G.-Y.; Liu, L.-L.; Dai, J.-J.; Xu, J.; Xu, H.-J. *J. Org. Chem.* **2015**, *80*, 9314. d) Wang, H.; Guo, L.-N.; Wang, S.; Duan, X.-H. *Org. Lett.* **2015**, *17*, 3054.

[35] a) Liu, J.; Liu, Q.; Yi, H.; Qin, C.; Bai, R.; Qi, X.; Lan, Y.; Lei, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 502. b) Xu, X.-L.; Xu, W.-T.; Wu, J.-W.; He, J.-B.; Xu, H.-J. *Org. Biomol. Chem.* **2016**, *14*, 9970. c) Xu, W.-T.; Huang, B.; Dai, J.-J.; Xu, J.; Xu, H.-J. *Org. Lett.* **2016**, *18*, 3114. d) Pimpasri, C.; Sumunnee, L.; Yotphan, S. *Org. Biomol. Chem.* **2017**, *15*, 4320.



Scheme 18. Synthesis reported by Xu.[35b]

2.3- Ultrasound in organic synthesis

Ultrasound was discovered through the study of the piezoelectric effect, by Marrie Currie in 1980.[36] Ultrasonic-promoted reactions have reached a prominent position in the promotion of green chemistry in organic synthesis and drug discovery.[37] It is possible with this methodology to reach excellent yields and selectivity under mild conditions and in short reaction times.[38] For these reasons, the organic synthetic chemists turned their interest to this non-classical energy source.[39] Its use is linked to the cavitation phenomenon, which is a physical phenomenon based on the process of create, increase and implode microbubbles of vapor and gases in a liquid through rarefaction and compression cycles, thus promoting activation effects in chemical reactions.[40] Experiments of electron spin resonance (ESR) and spin-trapping have shown the formation of radicals of H and OH when water is subjected to sonication. This is probably the reason why a radical mechanism could be involved in ultrasonic-promoted reactions in aqueous solution.[41]

Over the last years, this alternative energy source was used in the synthesis of organochalcogen compounds, such as in the work of Vieira and co-workers, from

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[36] Lorimer, J. P.; Mason, T. *J. Chem. Soc. Rev.* **1987**, *16*, 239.

[37] Lenardão, E. J.; Freitag, R. A.; Dabdoub, J. M.; Batista, A. C. F.; Silveira, C. C. *Quim. Nova.* **2003**, *26*, 123.

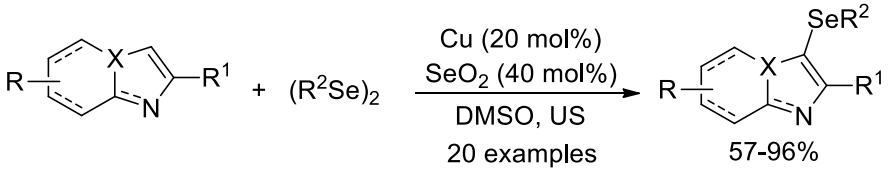
[38] Thompson, L. H.; Doraiswamy, L. K. *Ind. Eng. Chem. Res.* **1999**, *38*, 1215.

[39] a) Mendes, S. R.; Thurow, S.; Penteado, F.; da Silva, M. S.; Gariani, R. A.; Perin, G.; Lenardão, E. J. *Green Chem.* **2015**, *17*, 4334. b) Vieira, B. M.; Thurow, S.; Brito, J. S.; Perin, G.; Alves, D.; Jacob, R. G.; Santi, C.; Lenardão, E. J. *Ultrason. Sonochem.* **2015**, *27*, 192. c) Vieira, B. M.; Thurow, S.; da Costa, M.; Casaril, A. M.; Domingues, M.; Schumacher, R. F.; Perin, G.; Alves, D.; Savegnago, L.; Lenardão, E. J. *Asian J. Org. Chem.* **2017**, *6*, 1635.

[40] Nowak, F. M. Sonochemistry: Theory, Reactions, Syntheses and Applications, Nova science publishers Inc., New York, 2010.

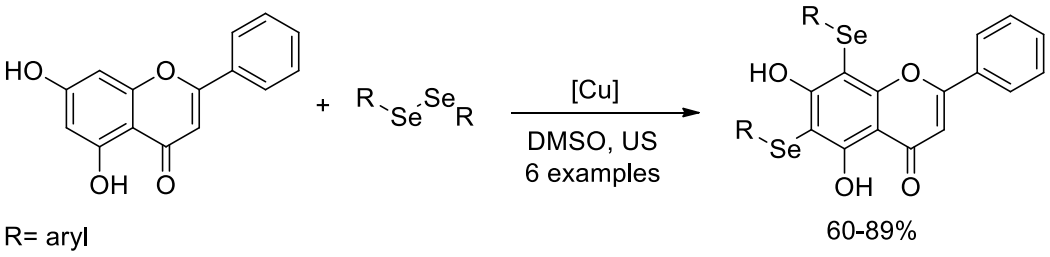
[41] Riesz, P.; Kondo, T. *Free Rad. Biol. Med.* **1992**, *13*, 247

2017.[38c] In this work, US irradiation was used in the synthesis of 3-selanyl-1*H*-indole and 3-selanylimidazol[1,2-*a*]pyridine derivatives (Scheme 19).



Scheme 19. Synthesis of Vieria.[38c]

Another recent example was developed in 2017, by Fonseca and co-workers,[42] who developed an ultrasound-promoted, copper-catalyzed synthesis of bisarylselanyl chrysin derivatives with boosted antioxidant and anticancer activities (Scheme 20).



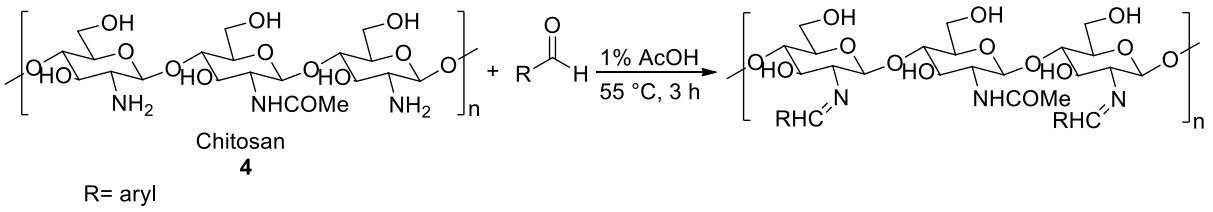
Scheme 20. Synthesis reported by Fonseca.[40]

2.4- Chitosan's polymers

The use of compounds extracted from nature is not a novelty considering the development of functional materials for a wide range of applications. Chitosan (**4**), as we have already mentioned, has been largely used to prepare several of materials derivatives due to its biological and mechanical properties.[17]

[42] Fonseca, S.F.; Padilha, N.B.; Thurow, S.; Roehrs, J.A.; Savegnago, L.; De Souza, M.N.; Fronza, M.G.; Collares, T.; Buss, J.; Seixas, F.K.; Alves, D.; Lenardão, E.J. *Ultrason. Sonochem.* **2017**, *39*, 827.

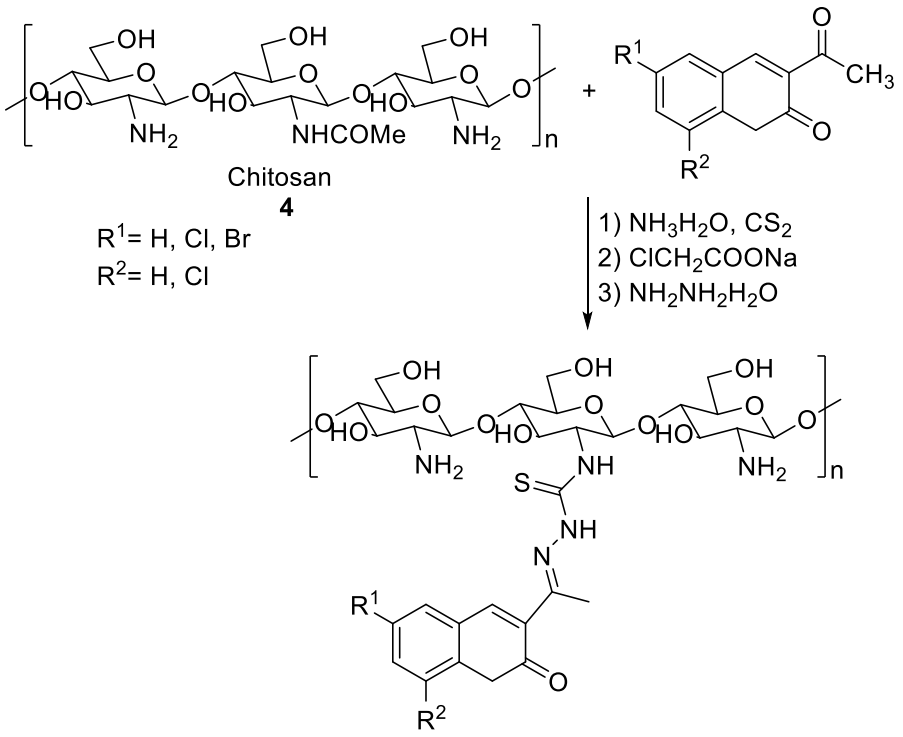
For example, Soliman and co-workers[43] have prepared, in 2013, a series of four chitosan's derivatives with aromatic aldehydes, benzaldehyde, *p*-chlorobenzaldehyde, *p*-N,N-dimethylaminobenzaldehyde and *p*-methoxybenzaldehyde, presenting antibacterial. The reaction was conducted at 55 °C for three hours in acetic acid aqueous solution (1%) and the products obtained were characterized by FTIR, ^{1}H NMR analysis and SEM analysis (Scheme 21).



Scheme 21. Synthesis reported by Soliman.[41]

In 2018, Yang and co-workers[44] published a synthesis of coumarin-functionalized chitosan derivatives with antifungal activity, via a condensation of thiosemicarbazide chitosan. The derivatives were synthesized in one pot by mixing chitosan with carbon disulfide, sodium chloroacetate and hydrazine hydrate (Scheme 22). After the preparation the new polymers were characterized by FTIR and ^{1}H NMR analysis.

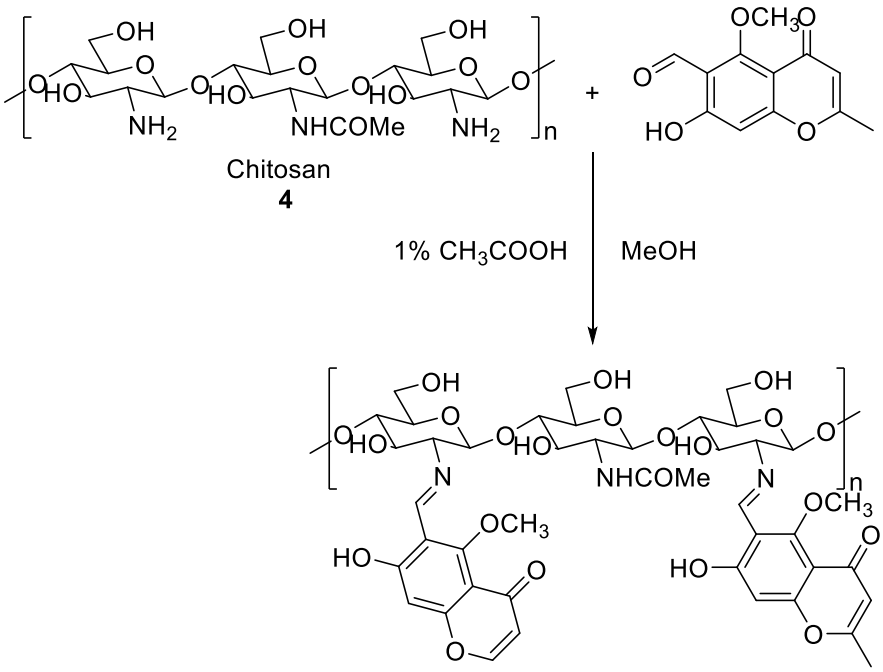
[43] Soliman, E.A.; El-Kousy, S.M.; Adb-Elbary, H.M.; Abou-Zeid, A.R. *Am. J. Pharmacol. Toxicol.* **2013**, *8*, 17.
[44] Yang, G.; Jin, Q.; Xu, C.; Fan, S.; Wang, C.; Xie, P. *Int. J.Biol. Macr.* **2018**, *106*, 179.



Scheme 22. Synthesis reported by Yan.[42]

In the same year, Demetgül and co-workers[45] reported a synthesis of chitosan-chromone derivatives in mild acidic conditions how it shown in the Scheme 23. Completed the reaction the derivatives were characterized by ^{1}H NMR, SEM and FTIR analysis.

[45] Demetgül, C.; Beyazit, N. *Carbohydr. Polym.* **2018**, *181*, 812.



Scheme 23. Synthesis reported by Demetgül.[43]

It is noteworthy that citronellal **20** and citral **21** present biological activity.[46] Citronellal is used as repellent and antifungal agent, while citral presents flavoring and antibacterial properties, besides is a component of pheromones (Figure 6, compounds **20** and **21**).

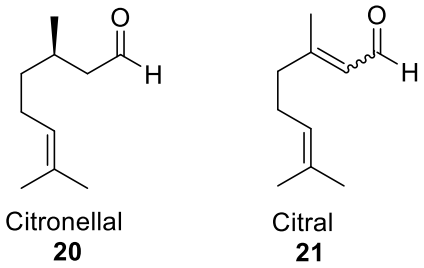


Figure 6. Structure of citronellal **20** and citral **21**.

[46] Prabuseenivasan, S.; Jayakumar, M.; Ignacimuthu, S. *BMC Complement. Altern. Med.* **2006**, *6*, 1.

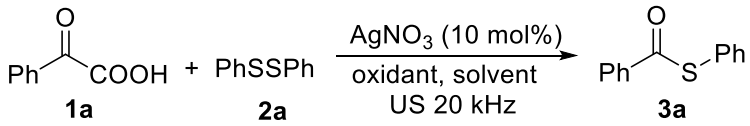
3. Results and Discussion

3- Results and Discussion

In this chapter it will be discussed the results obtained in this work, from the optimization stage to the scope of the reaction, besides the presentation of a probably mechanism of the reaction involved in the synthesis of the thioesters.

Firstly, for the reaction optimization, phenyl glyoxylic acid (PGA) **1a**, diphenyl disulfide **2a** and $AgNO_3$ as catalyst were employed aiming to obtain *S*-phenyl benzothioate **3a**. The results are displayed in Table 1.

Table 1. Reaction optimization to obtain **3a**[a].



Entry	Oxidant (2 equiv)	Solvent (1.0 mL)	Time (min)	Conv. (%)[b]
1	$K_2S_2O_8$	DMSO:H_2O (1:1)	60	58
2	$K_2S_2O_8$	DMSO:H_2O (1:1)	30	75
3	**$K_2S_2O_8$**	**DMSO:H_2O (1:1)**	**20**	**75**
4	$K_2S_2O_8$	DMSO:H_2O (1:1)	15	69
5	$K_2S_2O_8$	DMSO:H_2O (1:1)	10	60
6	$K_2S_2O_8$	DMSO	20	63
7	$K_2S_2O_8$	Acetone:H_2O (1:1)	20	37
8	$K_2S_2O_8$	CH_3CN:H_2O (1:1)	20	59
9	$K_2S_2O_8$	AcOEt:H_2O (1:1)	20	16
10	$K_2S_2O_8$	PEG 400:H_2O (1:1)	20	20
11	$(NH_4)_2S_2O_8$	DMSO:H_2O (1:1)	20	45
12	$Na_2S_2O_8$	DMSO:H_2O (1:1)	20	44
13	$(^tBuO)_2$	DMSO:H_2O (1:1)	20	NR
14	^{t}BuOOH	DMSO:H_2O (1:1)	20	NR
15	CAN	DMSO:H_2O (1:1)	20	NR
16	none	DMSO:H_2O (1:1)	20	7
17[c]	$K_2S_2O_8$	DMSO:H_2O (1:1)	20	56
18[d]	$K_2S_2O_8$	DMSO:H_2O (1:1)	20	74
19[e]	$K_2S_2O_8$	DMSO:H_2O (1:1)	20	14
20[f]	$K_2S_2O_8$	DMSO:H_2O (1:1)	24 h	78

[a]Reaction conditions: in a round-bottomed flask were added **1a** (0.6 mmol), **2a** (0.25 mmol), $AgNO_3$ (10 mol%), oxidant (2.0 equiv) and the solvent mixture (1.0 mL).The mixture was submitted to ultrasonic irradiation (20 kHz, 60% sonic amplitude) for the time indicated. [b] Determined by GC, based on the amount of diphenyl disulfide **2a**.[c] Used 5 mol% of AgNO3. [d] Used 15 mol% of $AgNO_3$. [e] Without $AgNO_3$. [f] Reaction performed at room temperature, without sonication.

Based on the literature[26,27] regarding the *in situ* generation of acyl radical species from α-keto acids **1**, we investigated firstly the use of potassium persulfate (2.0 equiv) as oxidizing agent, using as solvent a mixture of DMSO:H_2O (1:1). The reaction mixture was sonicated (60% of amplitude) for different times: 60, 30, 20, 15 and 10 minutes, following the consumption of the diphenyl disulfide **2a** by GC (Table 1, entries 1-5). After 60 minutes, the product **3a** was obtained in 58% yield, instead after 30 minutes the yield increased to 75% (Table 1, entries 1 and 2). After 20 minutes, the yield remained the same obtained after 30 minutes, while when the time was reduced to 15 and 10 minutes, the yields were 69% and 60% respectively (Table 1, entries 3-5). So, the best results were obtained after 30 and 20 minutes (Table 1, entries 3 and 2), leading to the desired product **3a** in 75% yield.

After these preliminary investigations, we tried to change the solvent mixture, using different solvents. In the entry 6, when pure DMSO alone was used, the yield decreased to 63%, meaning the positive effect of water to the reaction (Table 1, entry 6). The use of water allowed the formation of the free radicals H· and HO· induced by US, and also it could help the solubilization of the inorganic species, which is responsible of the key step of the reaction. Other solvent tested was the mixture of acetone:H_2O (1:1), leading to the product in 37% yield (Table 1, entry 7). The mixture of CH_3CN:H_2O (1:1) generated 59% of the expected product, while the mixture of AcOEt:H_2O (1:1) gave 16% yield of **3a** (Table 1, entries 8 and 9). Finally, it was tested the mixture of PEG 400:H_2O (1:1), which afforded **3a** in 20% yield (Table 1, entry 10). All the other solvents tested showed worse results than those obtained with DMSO/H_2O.

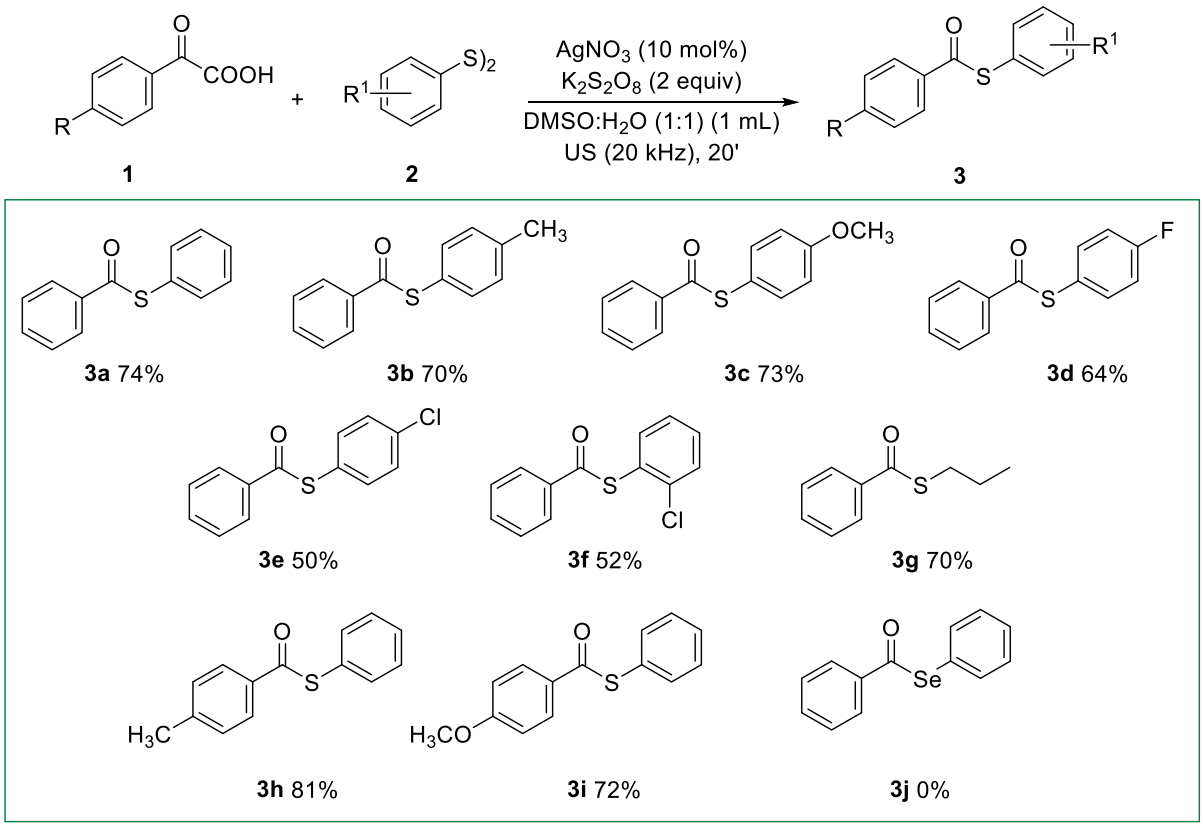
Regarding the study on the best oxidant agent, we have tested different ones, such as $(NH_4)_2S_2O_8$, $Na_2S_2O_8$, (^{t}BuO)$_2$ and ^{t}BuOOH. When $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$ were used, the yield of **3a** decreased to 45% and 44%, respectively (Table 1, entries 11 and 12). However, when (^{t}BuO)$_2$, ^{t}BuOOH and cerium ammonium nitrate (CAN) were used, the product was not observed (Table 1, entries 13-15). In summary, none of the other tested oxidants shown better results than $K_2S_2O_8$. Instead, in absence of the oxidant the yield decreased to 7% (Table, entry 16).

Then, we studied the effect of the catalyst amount in the reaction. Different amounts of $AgNO_3$ were tested, and it was observed that if, on one hand the decrease of the amount to 5 mol% affected negatively the reaction, giving the product **3a** in only 56% yield, on the other hand the increase of the amount to 15 mol% did not alter the reaction yield (Table 1, entries 17 and 18). In the line 19 we can observe that without the catalyst the product was obtained but with only 14% of yield.

Lastly, it was performed an experiment without the use of US and the result shown in Table 1, entry 20, demonstrates that were necessary 24 hours to obtain the product **3a** in 78% yield under stirring.

With the best reaction conditions in hand: 10 mol% of catalyst $AgNO_3$, 2 equiv of the oxidant $K_2S_2O_8$, in a solvent mixture of DMSO/H_2O (1:1) under US (60% of amplitude) in 20 minutes (Table 1, entry 3), a series of thioesters **3** were prepared (Table 2).

Table 2. Scope of the reaction.[a]



[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.25 mmol), $AgNO_3$ (10 mol%), $K_2S_2O_8$ (2 equiv) and the solvent mixture DMSO:H_2O (1:1; 1.0 mL), under ultrasonic irradiation (20 kHz, 60% of sonic amplitude) for 20 min. Yields were determined after purification by column chromatography.

Firstly, PGA **1a** was employed with different disulfides **2**, containing electron-donor or electron-withdrawing groups. The disulfides **2b** and **2c** bearing electron-donor groups (R^1= 4-CH_3 and R^1= 4-OCH_3 respectively), reacting with PGA **1a**, leaded to thioesters **3b** and **3c** in 70% and 73% yields, respectively. On the other hand, the disulfides **2d**, **2e** and **2f**, bearing electron-withdrawing groups (R^1= 4-F, R^1= 4-Cl and R^1= 2-Cl, respectively), reacting with PGA **1a**, leaded to thioesters **3d**, **3e** and **3f** in 64%, 50% and 52% yields, respectively. Using the dialkyl disulfide **2g** (R^1= propyl), the thioester **3g** was obtained in 70% yield. This good outcome represents an improvement from the previous method.[35]

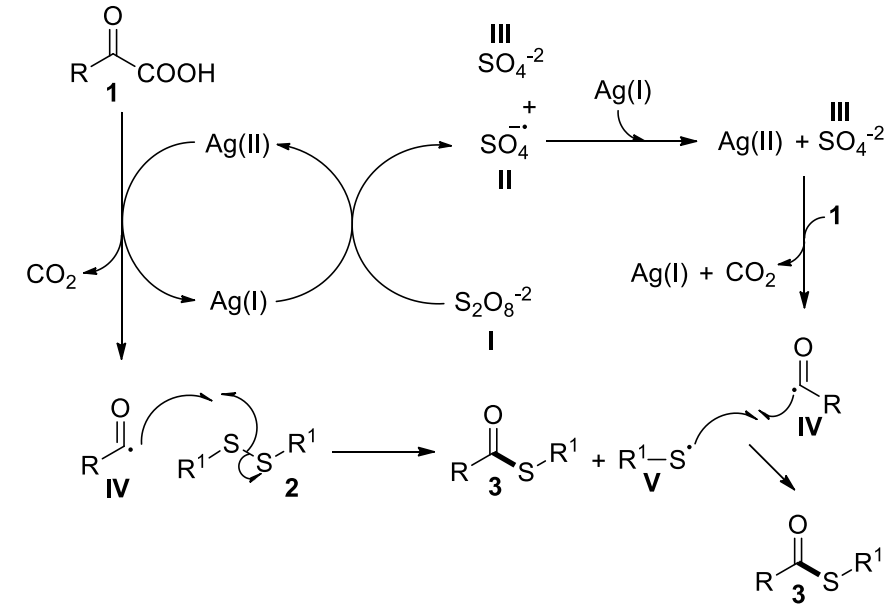
Then, we studied the reaction of diphenyl disulfide **2a** with different arylglyoxylic acids **1** (Table 2). The arylglyoxylic acids bearing electron-donor groups in the aromatic ring **1h** and **1i** (R= 4-CH_3 and R= 4-OCH_3, respectively) formed the respective thioesters **3h** and **3i** in 81% and 72% yields.

Finally, diphenyl diselenide **2j** was used instead of diphenyl disulfide **2a**, but the corresponding selenoester **3j** was not obtained, and after the sonication period, the starting diphenyl diselenide and benzoic acid, formed by the reaction between PGA **1a** and water, could be isolated. The probably reason to the failure of this reaction is the oxidation of the diphenyl diselenide to seleninic acid, inhibiting the oxidation of the Ag(I) and additionally the diphenyl diselenide can react with the $AgNO_3$ to form the complex $[(PhSe)_2Ag]NO_3$, suppressing in this way the formation of the key acyl radical **IV**.

Taking together, these results demonstrated a good tolerance of this new protocol regarding different disulfides and α-keto acids.

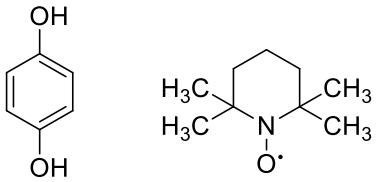
Based on the literature[35] and in our own experiments, a plausible mechanism for this reaction was proposed (Scheme 24). Initially, Ag(I) catalyst underwent an single electron transfer (SET) oxidation to Ag(II) species, promoted by persulfate ion **I**, which is reduced to sulfate anion **III** and to sulfate anion radical **II**. Then, the α-keto acid **1**, in the presence of Ag(II), is decarboxylated, releasing CO_2, and forming the reactive acyl radical **IV**, with the regeneration of the Ag(I) catalyst. At this point, the disulfide **2** underwent a homolytic cleavage of the S-S σ-bond, promoted by the acyl

radical **IV** and, in this way, the thioester **3** is obtained, with the concomitant formation of the sulfur radical specie **V**. Furthermore, the initially formed sulfate anion radical was responsible to oxidize another Ag(I) specie, leading to the formation of Ag(II), which promotes an oxidative decarboxylation of a molecule of α-keto acid **1**, generating more acyl radical **IV**. Finally, the acyl radical **IV** reacts with the sulfur radical **V**, allowing the formation of the desired product **3**.



Scheme 24. Proposed reaction mechanism for the synthesis of thioesters **3**.

The proof of the involvement of radical species in the reaction was found with two control experiments, using two radical scavengers: hydroquinone **22** and TEMPO[36] **23** (Figure 7, **22** and **23**). It was observed that when these two species **22** or **23** were used, the thioester product **3** was not formed, meaning that one or more radical pathways are involved.



22 **23**

Figure 7. Structures of hydroquinone **22** and TEMPO **23**.

3.1- Presentation and discussion of the spectral data

In this section, it will be discussed the nuclear magnetic resonance (NMR) spectra of hydrogen and carbon-13 of the thioester **3c**, *S*-(4-methoxyphenyl) benzothioate.

In the Figure 8 is represented the ^{1}H NMR spectrum of the compound **3c** and it is possible to see its characteristic peaks. In 3.85 ppm there is a singlet belonged to the hydrogens of the methoxy group (CH_3O). In 7.00 ppm there is a multiplet, due to the two aromatic hydrogens H-2 and H-3, in the *ortho* position to the methoxy group. In 7.43 ppm there is a doublet (J = 8.8 Hz) belonged to H-4 and H-5, in *meta* position to the methoxy group. In 7.48 ppm there is a triplet (J = 7.7 Hz) belonged to the two aromatic hydrogens H-8 and H-9, in *meta* position to the carbonyl group. In the region of 7.58 ppm to 7.63 ppm, there is a multiplet belonged to the aromatic hydrogen H-10, in *para* position to the carbonyl group. Finally, in the region of 8.02 ppm to 8.04 ppm there is the multiplet belonged to the two aromatic hydrogens H-5 and H-6, in *ortho* position to the carbonyl group.

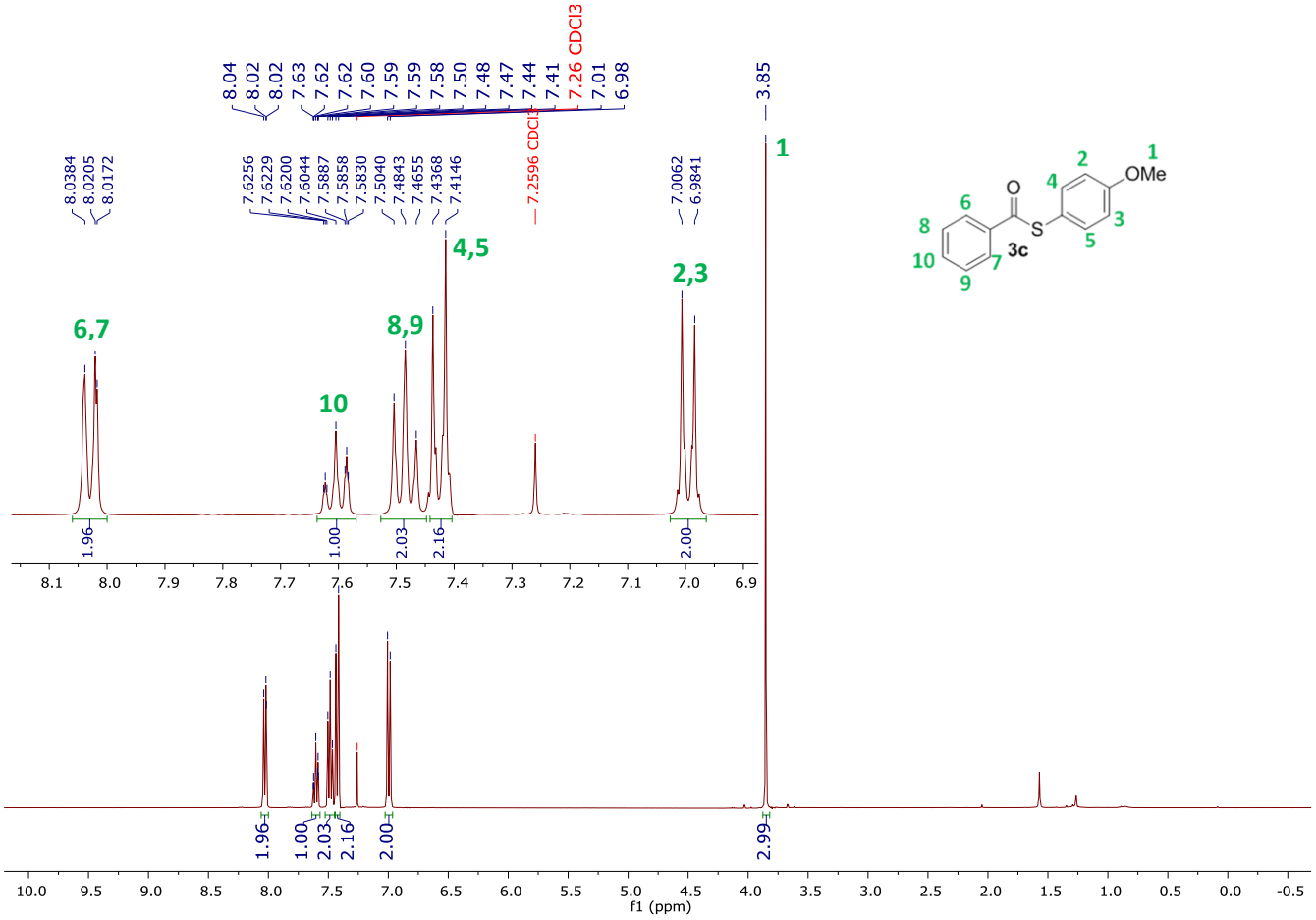


Figure 8. ^{1}H (400 MHz, $CDCl_3$) NMR spectrum of **3c**.

In the Figure 9 is presented the ^{13}C NMR spectrum of the compound **3c** and it is possible to see its characteristic peaks. In 55.35 ppm there is a signal belonged to C-1, of the methoxy group. In 114.95 ppm there is a signal belonged to the aromatic carbons C-3 and C-4, in the *ortho* position to the methoxy group. In 117.86 there is a signal belonged to C-7, the aromatic carbon in the *para* position at the methoxy group. In 127.43 ppm there is a signal belonged to the aromatic carbons C-12 and C-13, at the *meta* position to the carbonyl group. In 128.69 ppm there is a signal belonged to the aromatic carbons C-5 and C-6, in the *meta* position to the methoxy group. In 133.53 ppm there is a signal belonged to the aromatic carbon C-14, in the *para* position to the carbonyl group. In 136.61 ppm appears the signal of C-10 and C-11, the aromatic carbons in *ortho* position to the carbonyl group. In 136.64 is the signal due to C-9, the carbon directly bonded to the carbonyl group. In 160.77 ppm there is a signal belonged to C-2,

the carbon directly bonded to the methoxy group. Finally, in 191.02 ppm there is a signal belonged to the carbonyl carbon, C-8.

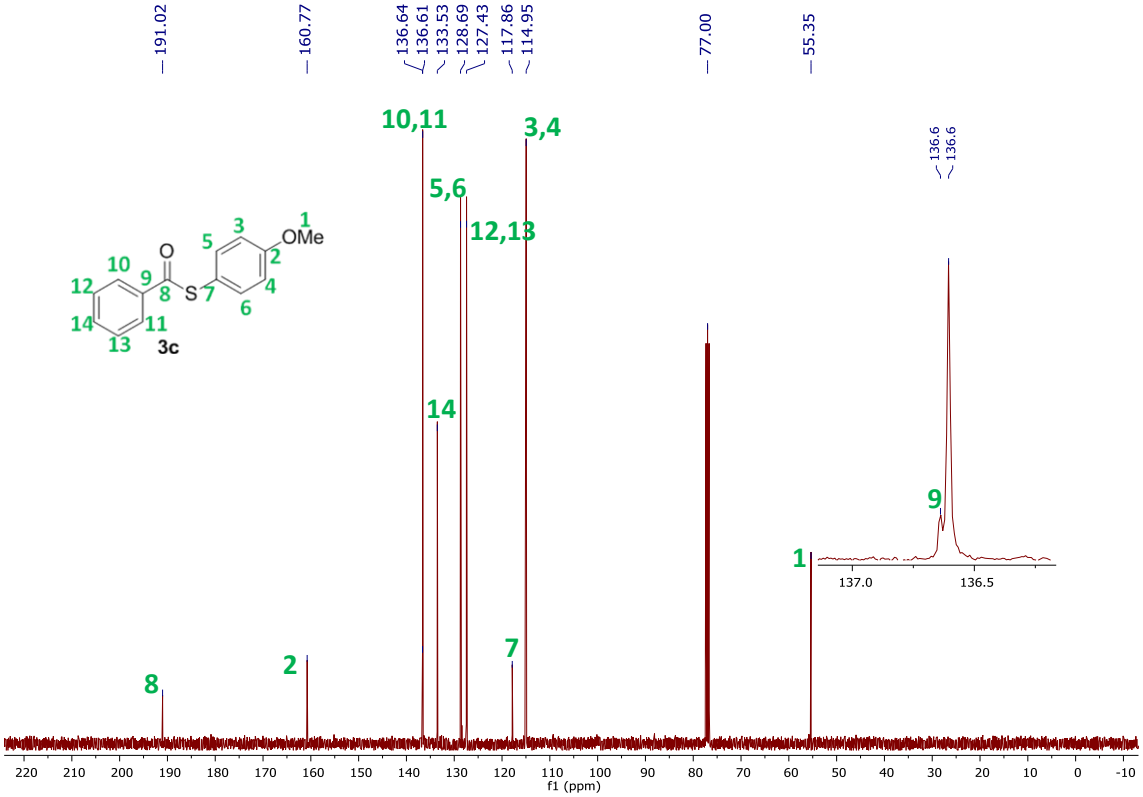
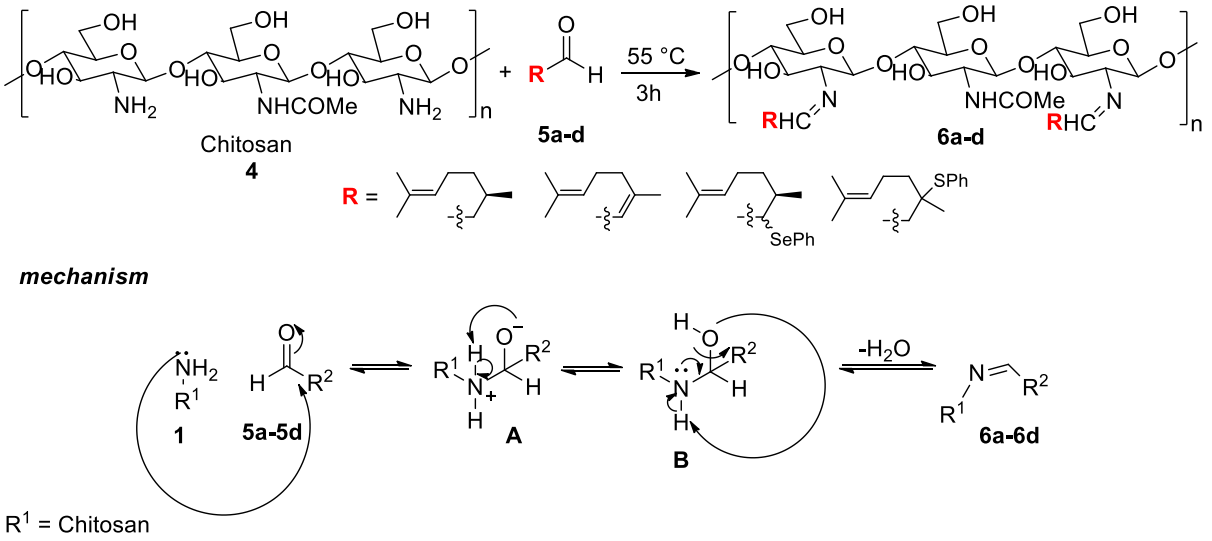


Figure 9. ^{13}C (100 MHz, $CDCl_3$) NMR spectrum of **3c**.

3.2- New chitosan's compounds

New chitosan derivatives were synthesized through the reaction between Cs and different aldehydes, through the reaction shown in the Scheme 25. The citronellal **5a** and the citrl **5b** were commercially, instead the phenylselenium citronelal[47] **5c** and the phenylthio citral[48] were synthesized according to the literature.

[47] Victoria, F. N.; Radatz, C. S.; Sachini, M.; Jacob, R. G.; Perin, G.; da Silva, W. P.; Lenardão, E. J. *Tetrahedron Lett.* **2009**, *50*, 6763.
[48] Lenardão, E. J.; Trecha, D. O.; da C. Ferreira, P.; Jacob, R. G.; Perin, G. *J. Braz. Chem. Soc.* **2009**, *20*, 93.



Scheme 25. Synthesis of new chitosan's derivatives.

Based on the literature,[41] the reactions were performed in aqueous acetic acid solution, and after 3 hours at 55 °C, the Schiff bases **6a**-**6d** were formed (Figure 9).

These new compounds were characterized by FTIR and NMR analysis and used to made biofilm with polyvinyl alcohol (PVA) to test their healing, antifungal and antibacterial properties.

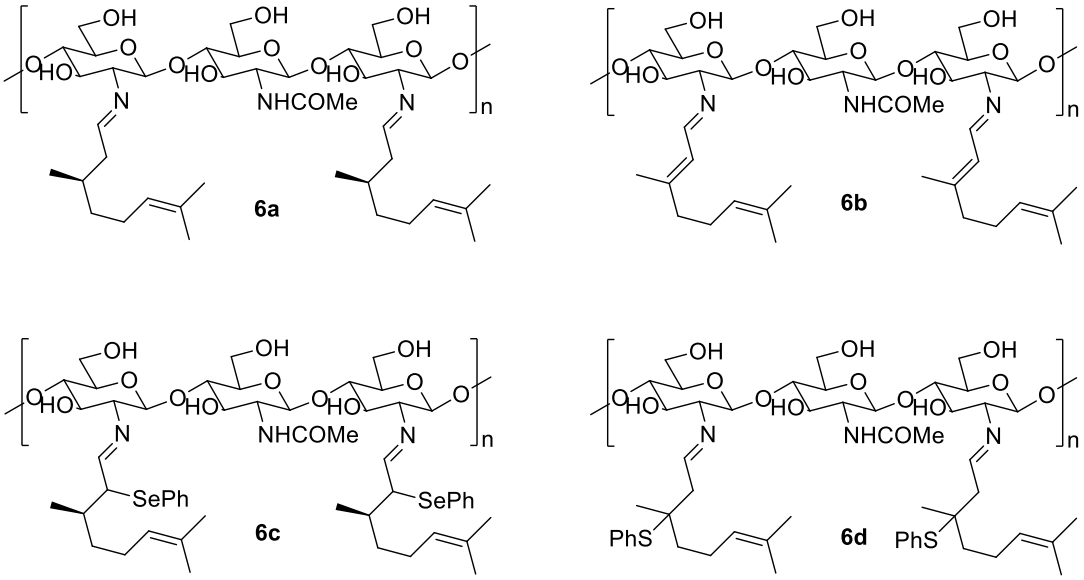


Figure 10. New Chitosan modified polymers.

In the Figure 11 is reported the FTIR spectrum of chitosan and its derivatives. It is possible to see the modification of Cs with the reduction of the band assigned to the N-H stretching about at 3000-3100 cm^{-1}, the reduction or desappearance of the amine band about at 1650 cm^{-1}, the appearance of the bands assigned to C-H vibration, derived from the alkyl and methyl groups and C-H aromatic about at 2800-2900 cm^{-1} and finally the appearance of the bands referred to C=N bond about at 2600 cm^{-1}.

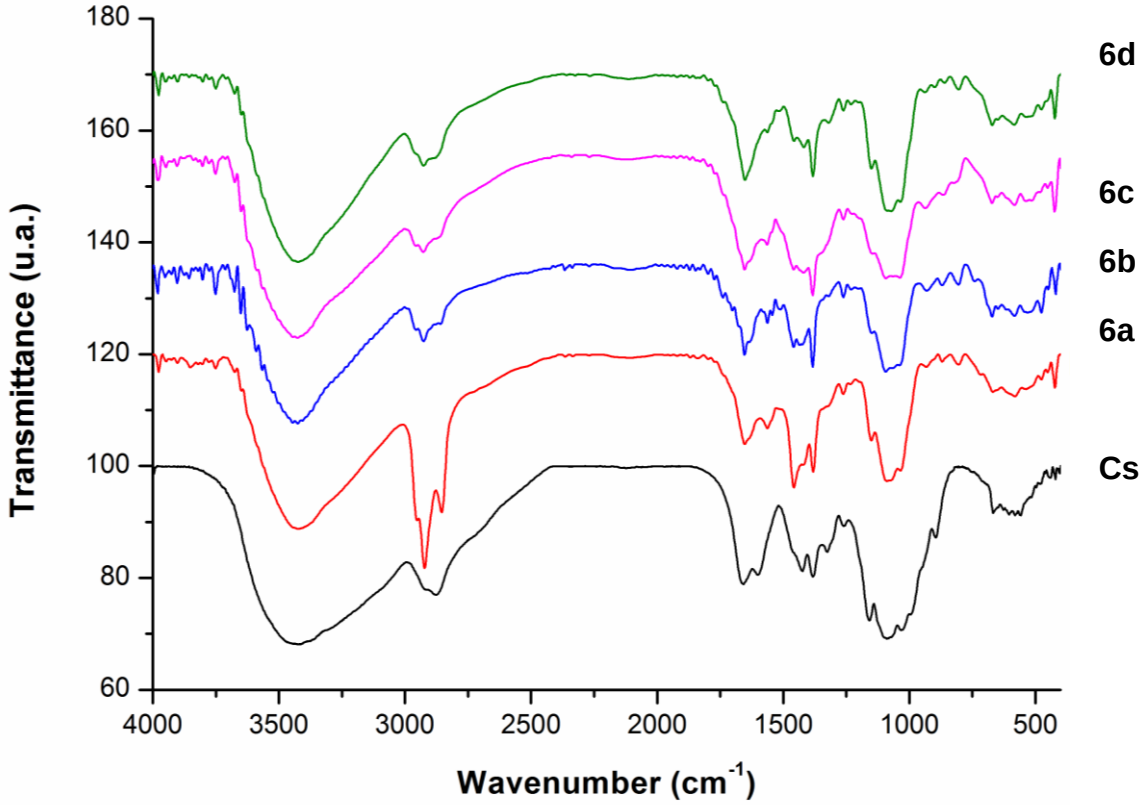


Figure 11. FTIR of chitosan and chitosan polymers.

In Figures 12-16 are shown the ^{1}H NMR spectrum of the Cs and the polymers **6a**-**6d**. Overall, the recorded NMR spectra presented the characteristic resonance peaks of Cs with some modifications. In the spectra of Cs we can observed in the region of 2.05 to 2.07 ppm the signal of the H of the acetyl groups. In 3.17 there is the signal of the H of the carbon close to the imminic carbon. In 3.90-3.92 there is the

signal of the H of the carbon between the two oxygen. In the spectras of Cs-citronellal **6a**, Cs-citral **6b**, Cs-phenylselenocitronellal **6c** and Cs-phenylthiocitronellal **6d** exhibit new peaks: between 4.5 and 5.0 ppm, referring to the C=C double bonds and peaks at 1.0-1.5 ppm due to the methyl groups of citral and citronellal. For the Cs-derivatives with aromatic moieties, the spectra have new peaks in the region of 7-8 ppm also. Moreover, peak attributed to the C=N bound were observed in all Cs-derivatives in 9-10 ppm, confirming the Cs-derivatization.

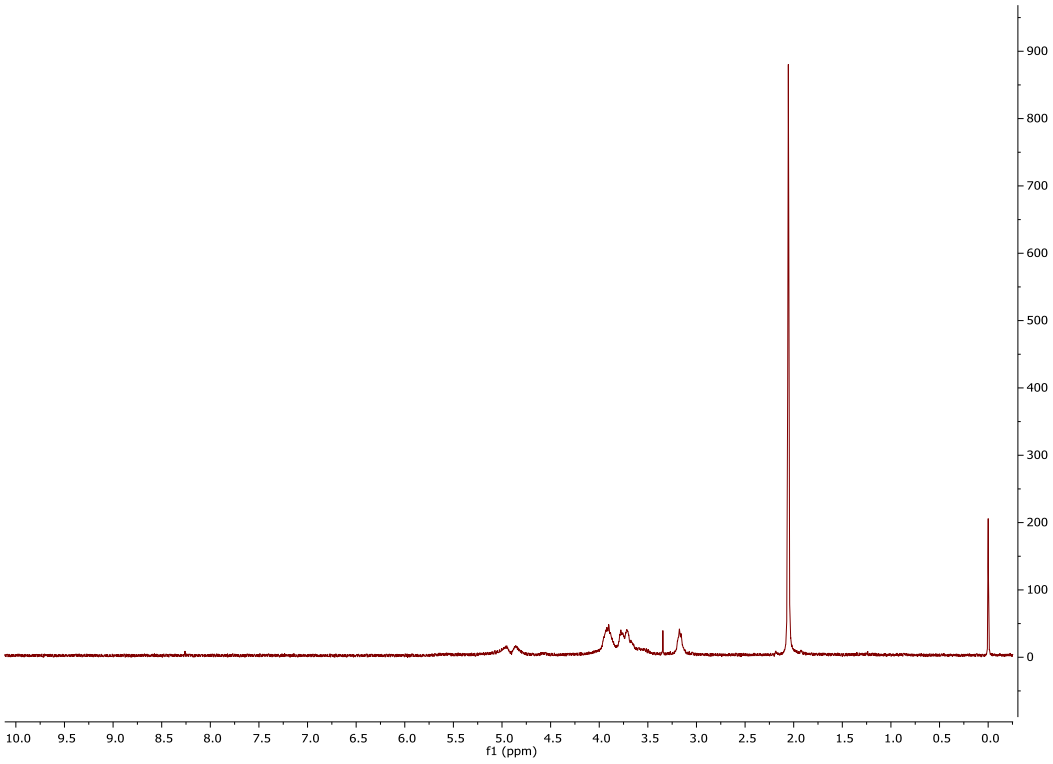


Figure 12. ^{1}H (400 MHz 10-20 wt% CD_3COOD/D_2O) NMR of Chitosan **4**.

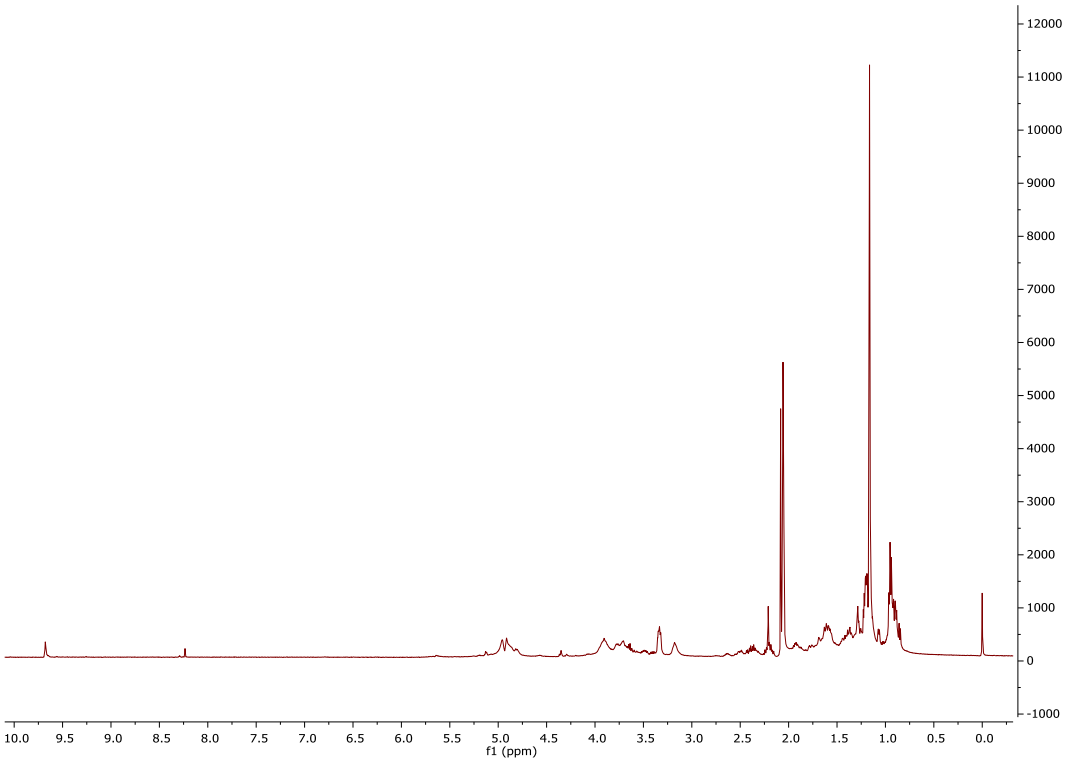


Figure 13. ^{1}H (400 MHz 10-20 wt% CD_3COOD/D_2O) NMR of chitosan derivate **6a**.

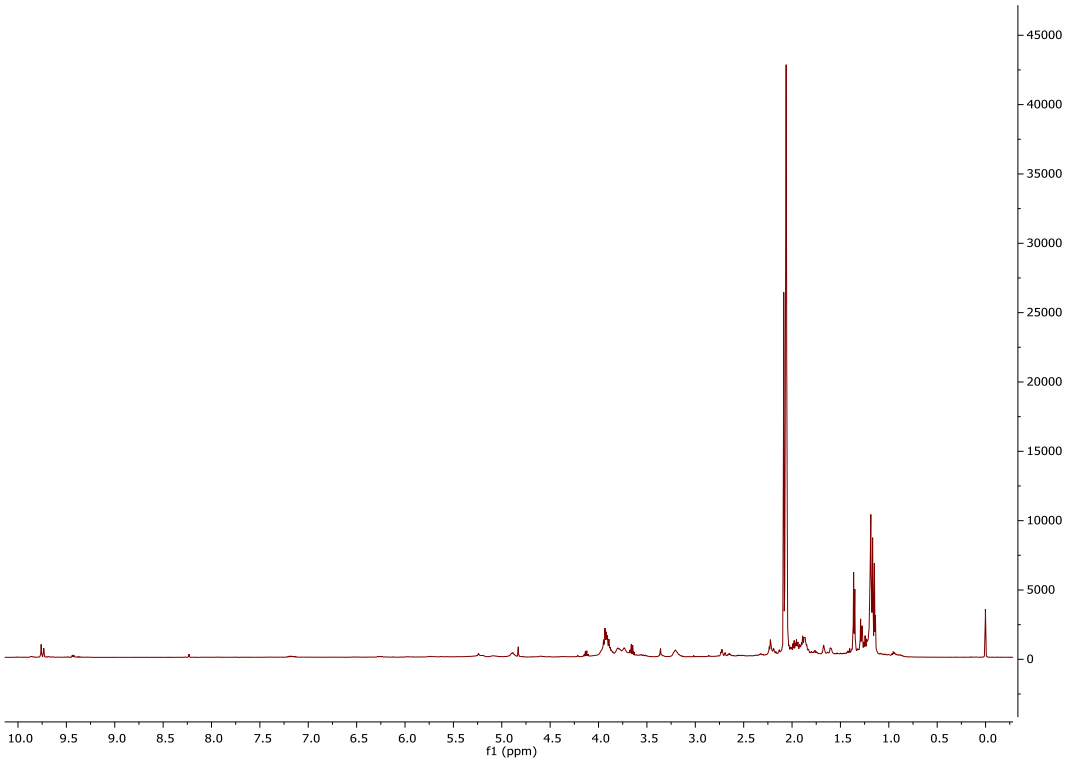


Figure 14. ^{1}H (400 MHz 10-20 wt% CD_3COOD/D_2O) NMR of chitosan derivate **6b**.

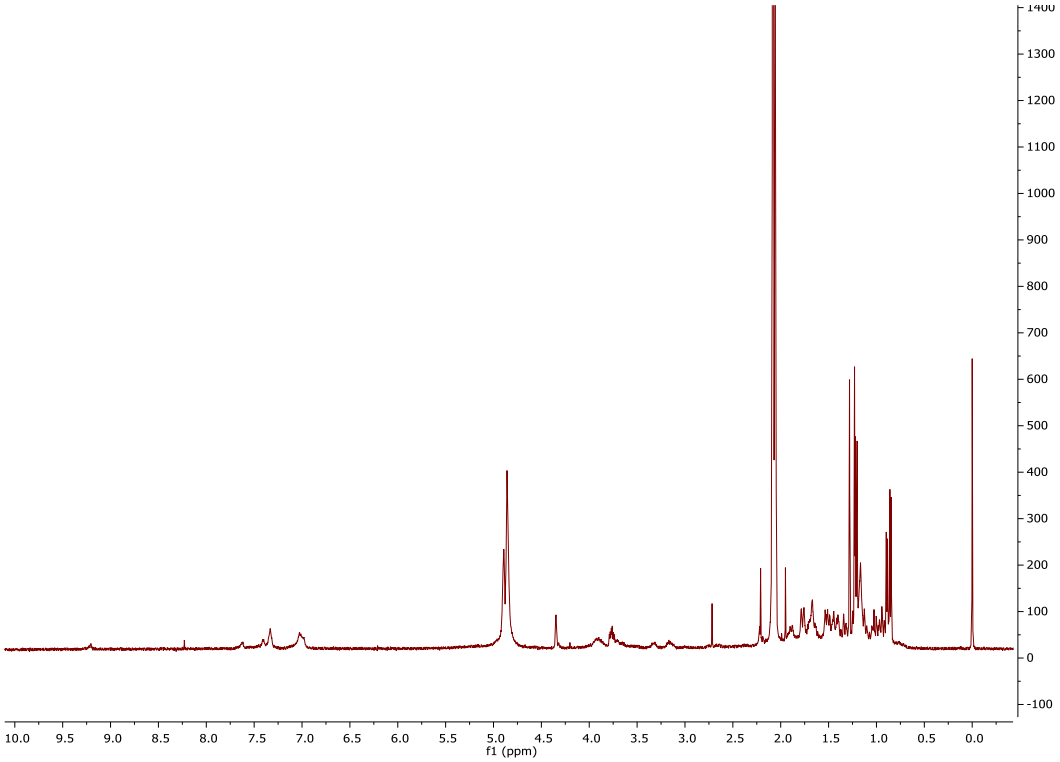


Figure 15. ^{1}H (400 MHz, 10-20 wt% CD_3COOD/D_2O) NMR of chitosan derivate **6c**.

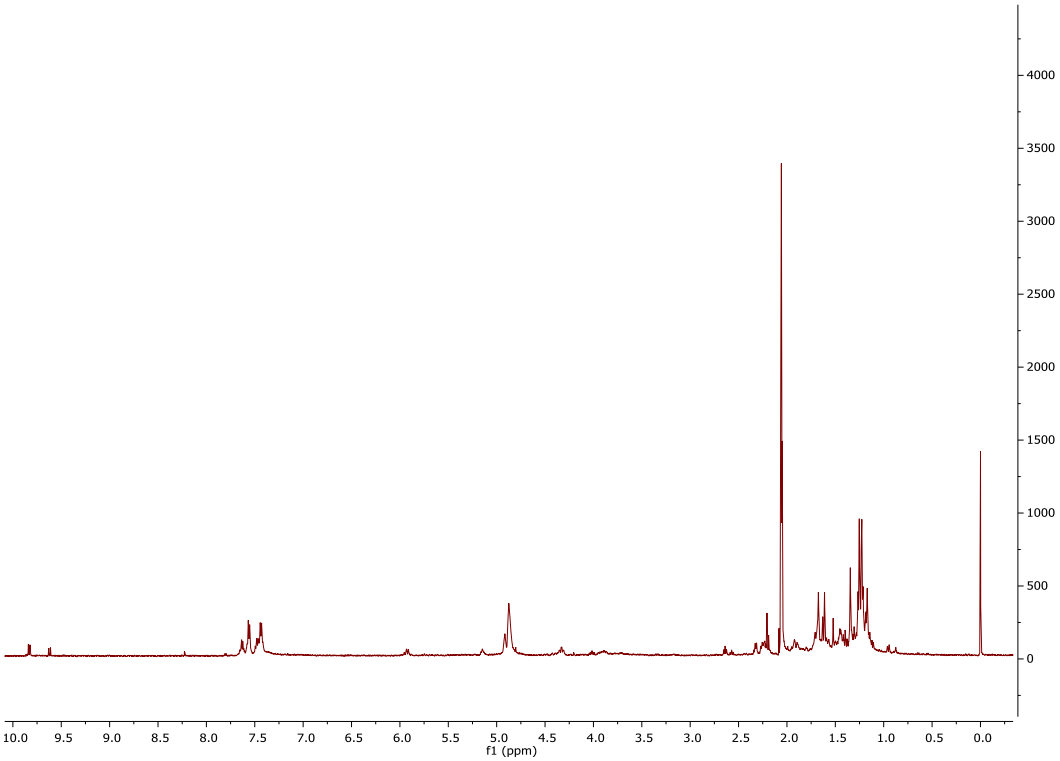


Figure 16. ^{1}H (400 MHz, 10-20 wt% CD_3COOD/D_2O) NMR of chitosan derivate **6d**.

4. Conclusions

4- Conclusions

In this work it was discussed a new ultrasound-promoted selective method for the synthesis of the important class of compounds, the thioesters. As starting materials were used readily available glyoxylic acids as acyl transfer agents, in the presence of silver carbonate as an efficient catalyst and $K_2S_2O_8$ as an oxidant, diorganyl disulfides and mixture of DMSO/H_2O as the solvent. This method represents also the first example of the application of ultrasound to promote this type of reaction, that involved the S-S bond cleavage and the formation of new S-Csp^2 bond. Furthemore it takes advantage of the US-induced radical generation in aqueous system and was faster than similar reactions under conventional heating, ocurring in 20 minutes instead of 12-24 hours. The desired products were achieved in moderate to very good yields.

Besides, we have prepared Cs-based Schiff bases derived from citronellal, citral, α-phenylselenocitronellal and 3-phenylthiocitronellal. The Cs-derivatives were characterized by NMR and FTIR, which confirmed the modification with efficiency. Moreover, films based on these Cs-derivatives were prepared and additional experiments are in course in order to investigate the applicability of these films as biomaterials for wound healing.

5. Experimental

5- Experimental part

5.1- Materials and general methods

Pre-coated TLC sheets ALUGRAM®Xtra SIL G/UV_{254} using UV light and acidic ethanolic vanillin solution (5% in 10% aq. H_2SO_4) were used to follow the reaction progress. Aldrich technical grade silica gel (pore size 60 Å, 230-400 mesh) was used for flash chromatography. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on a Bruker Avance III HDNMR 400 spectrometer. The spectra were recorded in $CDCl_3$ solutions. The chemical shifts are reported in ppm, referenced to tetramethysilane (TMS) as internal reference. Hydrogen coupling patterns are described as singlet (s), doublet (d), triplet (t) and multiplet (m). Coupling constants (*J*) are reported in Hertz. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on a Bruker Avance III HDNMR 400 spectrometer. The chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. For the chitosan and derivatives all spectra were acquired using a deuterated aqueous solution of acetic acid (10-20 wt% CD_3COOD/D_2O) as solvents and tetramethylsilane (TMS) was used as internal standard. The ultrasound-promoted reactions were performed using a Cole Parmer-ultrasonic processor Model CPX 130, with a maxim power of 130 W, operating at amplitude of 60% and a frequency of 20 kHz. The temperature of the reaction under US was monitored using a Incoterm digital infrared thermometer Model Infraterm (Brazil). Melting point (mp) values were measured in a Marte PFD III instrument with a 0.1 ºC precision.

5.2- Synthesis of thioesters 3

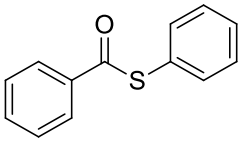
In a round-bottomed flask were added α-keto acid **1** (0.6 mmol), diorganyl disulfide **2** (0.25 mmol), $AgNO_3$ (10 mol%), $K_2S_2O_8$ (2 equiv) and the solvent mixture DMSO:H_2O (1:1) (1.0 mL), which was submitted to ultrasonic irradiation (20 kHz, 60% of sonic amplitude) using an ultrasonic probe, for 20 min. After that, the reaction mixture was received in water (20 mL), extracted with ethyl acetate (3 x 10 mL), dried over $MgSO_4$ and concentrated under vacuum. Then, the residue was purified by

column chromatography on silica gel utilizing a mixture of hexanes/ethyl acetate as the eluent.

5.3- Synthesis of compounds 6a-6d

In a becker at 55 °C, under stirring, chitosan **4** (0.100 g; 85% deacetylated) was dissolved in 60 mL of acidic aqueous solution (1.5% v/v of AcOH). After the solubilization, the aldehydes **5a-5d** (2 mmol) were added. After 3 h, the resulting Cs-derivatives **6a-6d** were dried (using a rotary evaporator), recovering the precipitate, which was exhaustively washed with ethanol (5 x 2.0 mL) to remove the non-reacted materials. Finally, the Cs-derivatives were dried under reduced pressure at 70 °C for 4 hours.

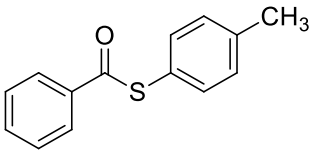
5.4- Physical and spectral data



***S-Phenyl benzothioate** (**3a**)*

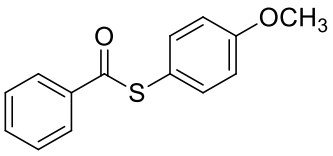
White solid; mp: 53-55 ºC (Lit[49] 56 ºC). Yield: 0.079 g (74%).^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.04 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.54–7.46 (m, 7H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 190.16, 136.56, 135.08, 133.65, 129.52, 129.24, 128.73, 127.45, 127.26.

[49] Villalobos, J.M.; Srogl, J.; Liebeskind, L.S. *J. Am. Chem. Soc.* **2007**, *129*, 15734.



S-(p-Tolyl) benzothioate (3b)

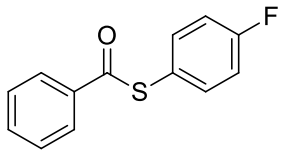
White solid; mp: 73-74 ºC (Lit.[50] 72-74 ºC). Yield: 0.078 g (70%).^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.03 (d, *J* = 7.3 Hz, 2H), 7.63-7.59 (m, 1H), 7.51-7.47 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 190.57, 139.79, 136.70, 135.00, 133.54, 130.09, 128.69, 127.45, 123.74, 21.36.



S-(4-Methoxyphenyl) benzothioate (3c)

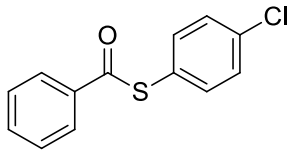
White solid; mp: 92-93 ºC (Lit.[51] 90-91 ºC). Yield: 0.089 g (73%).^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.04–8.02 (m, 2H), 7.63–7.58 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.00 (m, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$,100 MHz) δ (ppm) 191.02, 160.77, 136.64, 136.61, 133.53, 128.69, 127.43, 117.86, 114.95, 55.35.

[50] Ajiki, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2005**, *7*, 4193.
[51] Barbero, M.; Degani, I.; Dughera, S.; Fochi, R. *Synthesis* **2003**, 1225.



S-(4-Fluorophenyl) benzothioate (3d)

White solid; mp: 45-47 ºC (Lit.[52] 47-49 ºC). Yield: 0.074 g (64%).^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.02 (d, *J* = 7.3 Hz, 2H), 7.64–7.60 (m,1H), 7.52–7.47 (m, 4H), 7.16 (m, 2H). ^{13}C NMR ($CDCl_3$,100 MHz) δ (ppm) 190.09, 163.62 (d, *J* = 250.2 Hz), 137.13 (d, *J* = 8.7 Hz), 136.38, 133.78, 128.78, 127.47, 122.60 (d, *J* = 3.4 Hz), 116.52 (d, *J* = 22.1 Hz).



S-(4-Chlorophenyl) benzothioate (3e)

White solid; mp: 71-73 ºC (Lit.[53] 71-72 ºC). Yield: 0.062 g (50%).^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.03–8.01 (m, 2H), 7.64–7.60 (m, 1H), 7.52–7.48 (m, 2H), 7.47–7.42 (m, 4H). ^{13}C NMR ($CDCl_3$,100 MHz) δ (ppm) 189.56, 136.33, 136.27, 135.95, 133.82, 129.47, 128.78, 127.48, 125.83.

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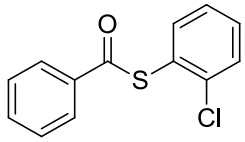
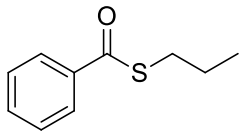


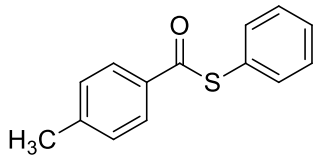
S-(2-Chlorophenyl) benzothioate (3f)

White solid; mp: 70-73 ºC (Lit.[26]:72-74 ºC). Yield: 0.064 g (52%).^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.07–8.04 (m, 2H), 7.64–7.61 (m, 2H), 7.58–7.56 (m, 1H), 7.52–7.49 (m, 2H), 7.44–7.39 (m, 1H), 7.37–7.33 (m, 1H). ^{13}C NMR ($CDCl_3$,100 MHz) δ (ppm) 188.27, 139.12, 137.59, 136.33, 133.81, 131.22, 130.29, 128.78, 127.60, 127.31, 126.95.



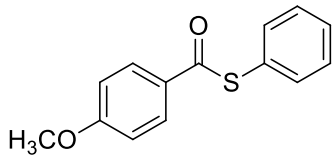
S-Propylbenzothioate (3g)[26]

Colorlessoil. Yield: 0.063 g (70%).^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.97 (d, *J* = 7.6 Hz, 2H), 7.54–7.51 (m, 1H), 7.43–7.39 (m, 2H), 3.04 (t, *J* = 7.3 Hz, 2H), 1.69 (sex, *J* = 7.3 Hz, 2H), 1.02 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$,100 MHz) δ (ppm) 191.82, 137.12, 133.03, 128.39, 127.02, 30.76, 22.87, 13.31.



S-Phenyl 4-methylbenzothioate (3h)

White solid; mp: 77-79 ºC (Lit.[26] 78-80 ºC). Yield: 0.092 g (81%).^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.94 (d, *J* = 8.0 Hz, 2H), 7.54–7.52 (m, 2H), 7.48–7.44 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$,100 MHz) δ (ppm) 189.66, 144.54, 135.09, 134.07, 129.37, 129.16, 127.53, 21.68.



S-Phenyl 4-methoxybenzothioate (3i)

White solid; mp: 90-93 ºC (Lit.[26] 92-94 ºC). Yield: 0.087 g (72%).^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.03 (d, *J* = 8.9 Hz, 2H), 7.55–7.53 (m, 2H), 7.48–7.45 (m, 3H), 6.97 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$,100 MHz) δ (ppm) 188.44, 163.90, 135.09, 129.61, 129.27, 129.07, 127.57, 113.83, 55.43.

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7. Selected spectra

Selected spectra

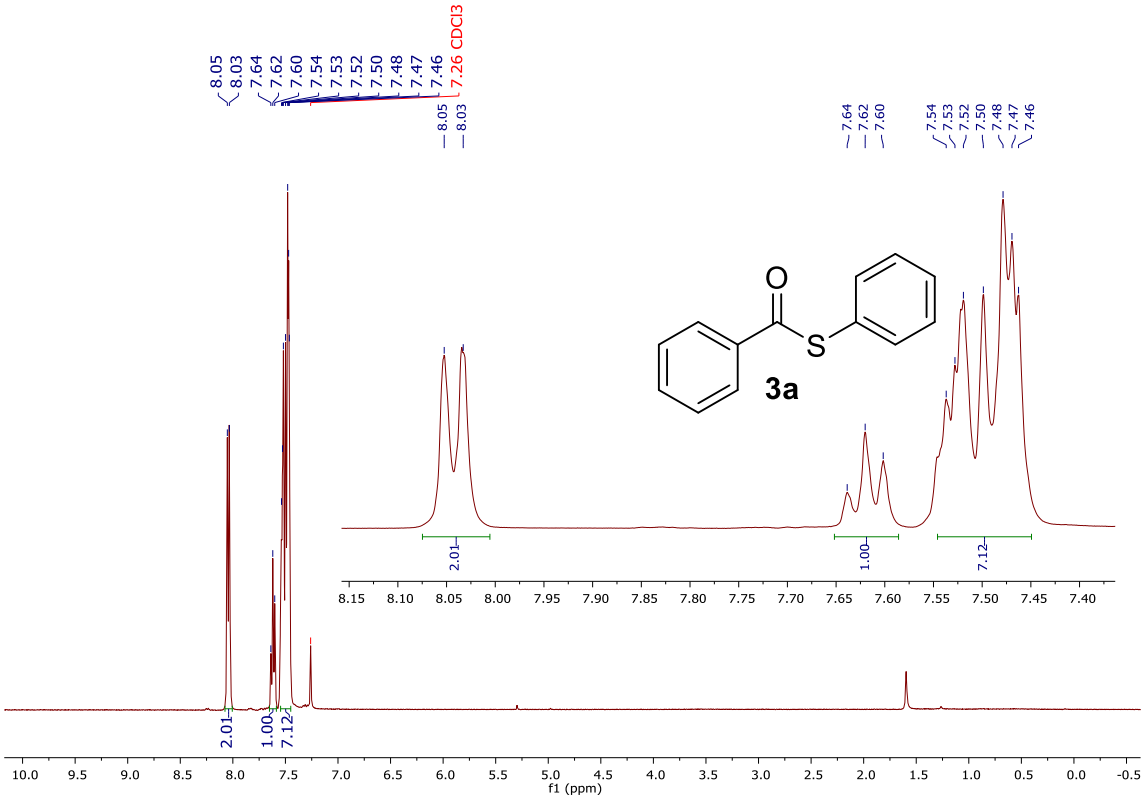

Figure 17. ^{1}H NMR spectrum of compound **3a** (400 MHz, $CDCl_3$).

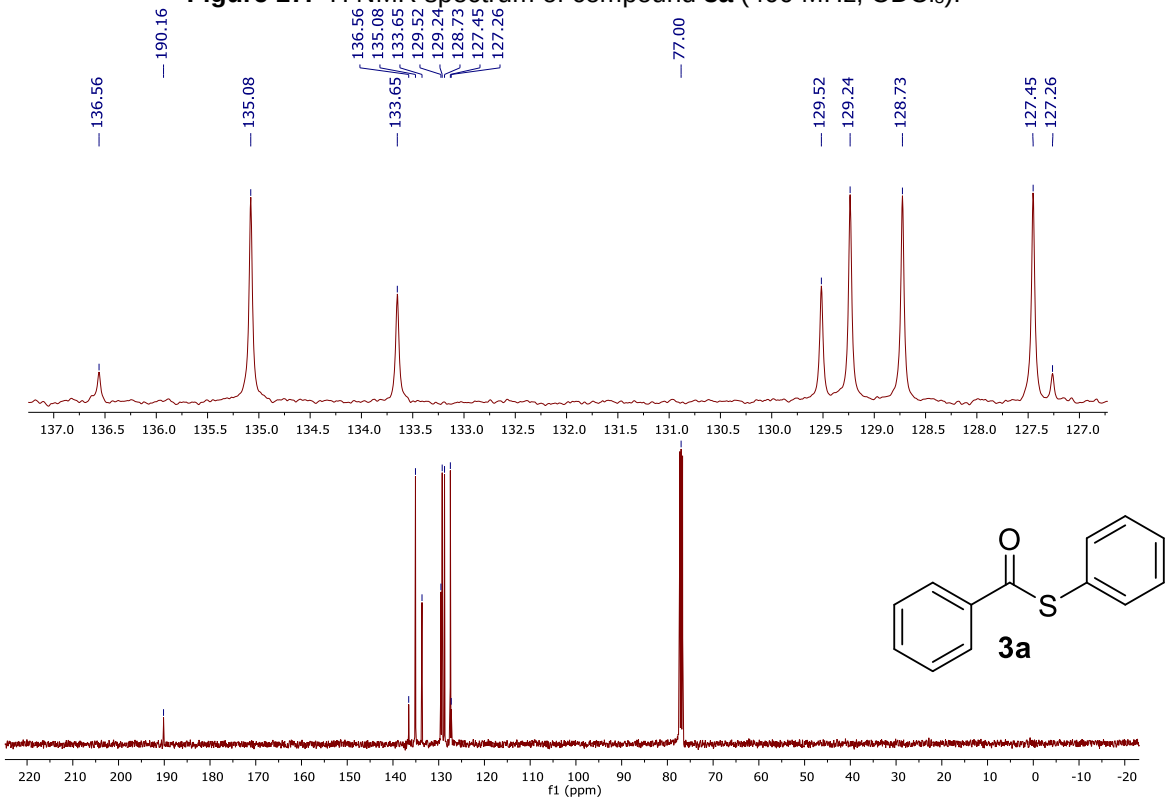

Figure 18. ^{13}C NMR spectrum of compound **3a** (100 MHz, $CDCl_3$).

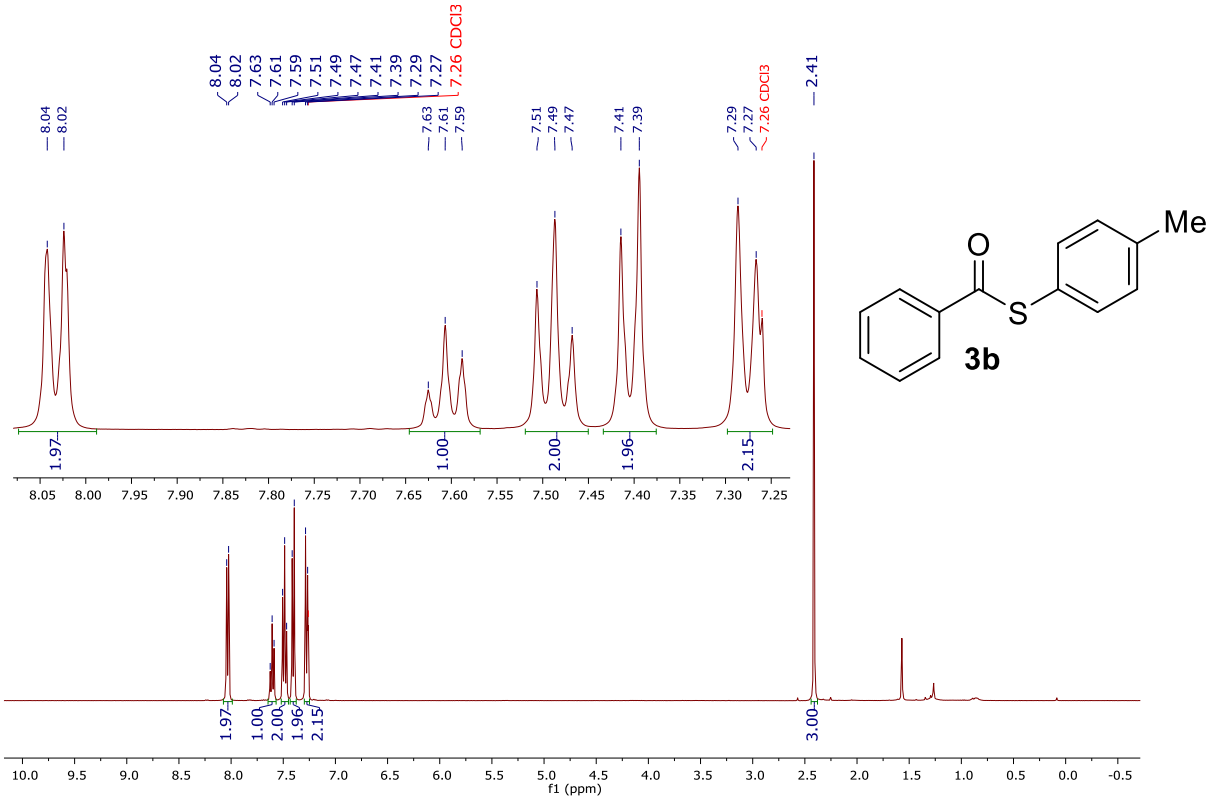

Figure 19. ^{1}H NMR spectrum of compound **3b** (400 MHz, $CDCl_3$).

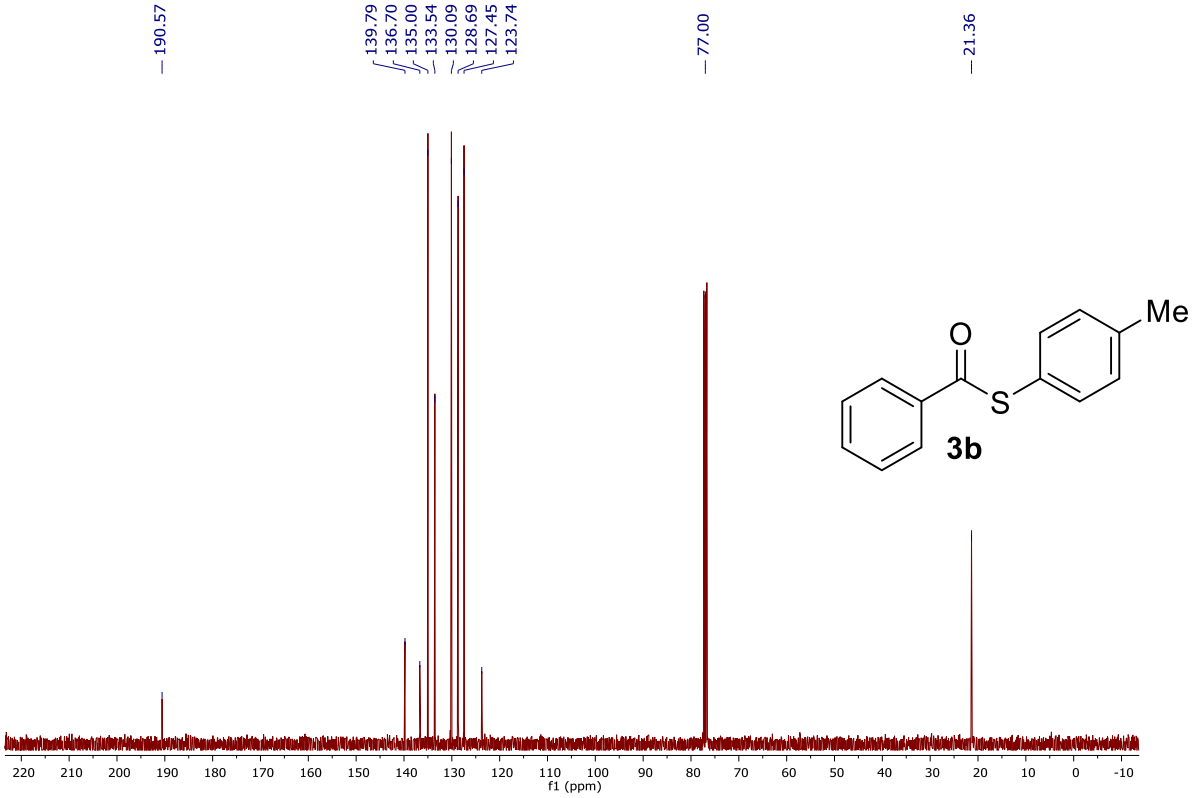

Figure 20. ^{13}C NMR spectrum of compound **3b** (100 MHz, $CDCl_3$).

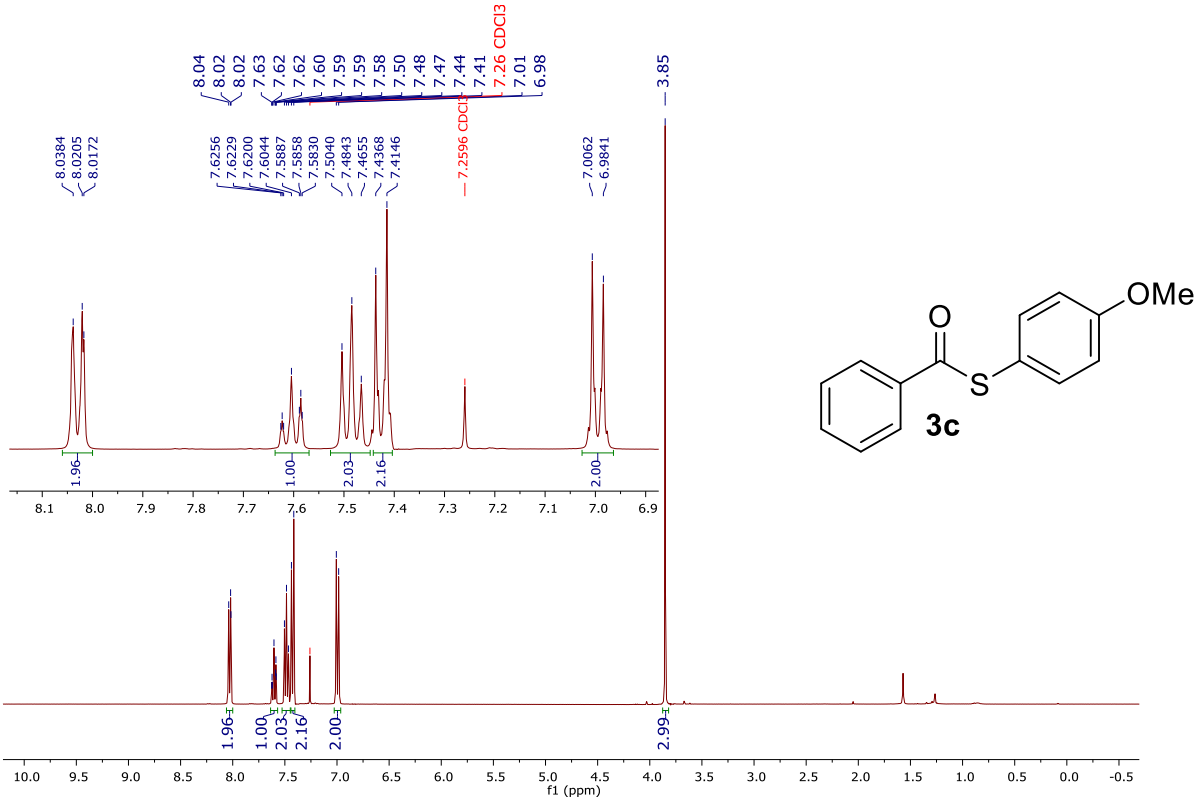

Figure 21. ^{1}H NMR spectrum of compound **3c** (400 MHz, $CDCl_3$).

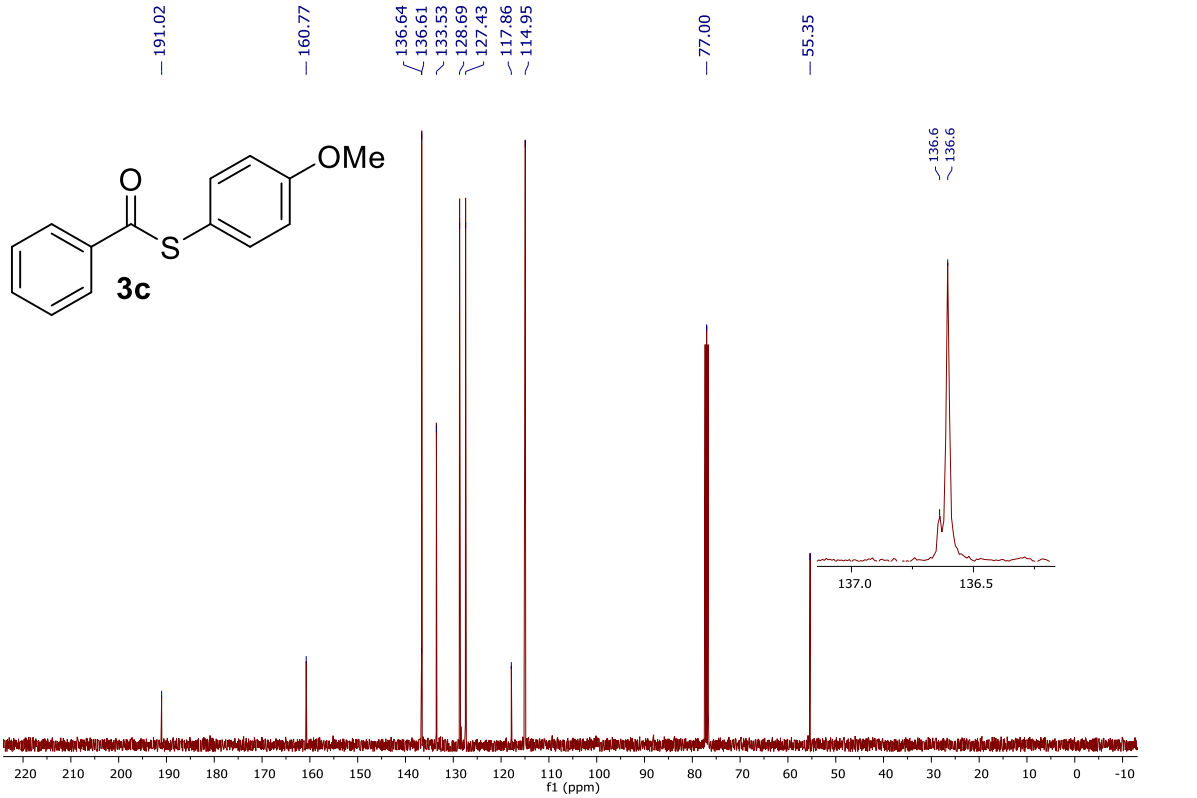

Figure 22. ^{13}C NMR spectrum of compound **3c** (100 MHz, $CDCl_3$).

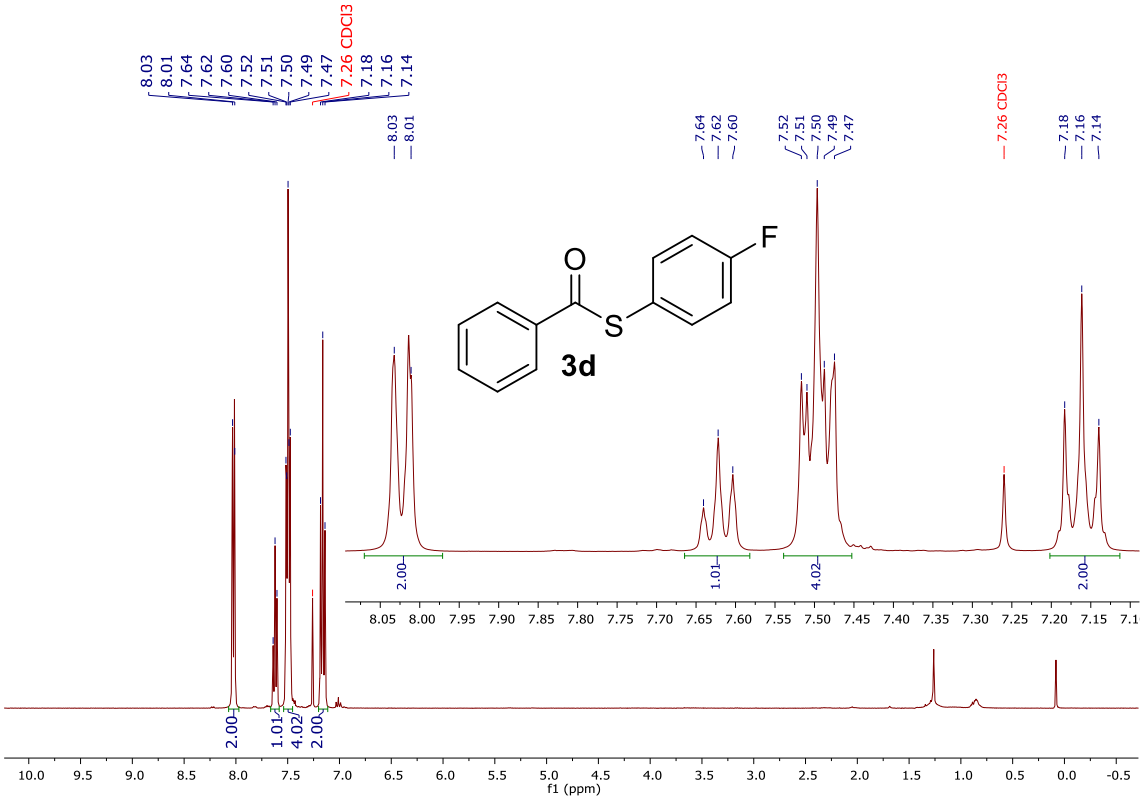

Figure 23. ^{1}H NMR spectrum of compound **3d** (400 MHz, $CDCl_3$).

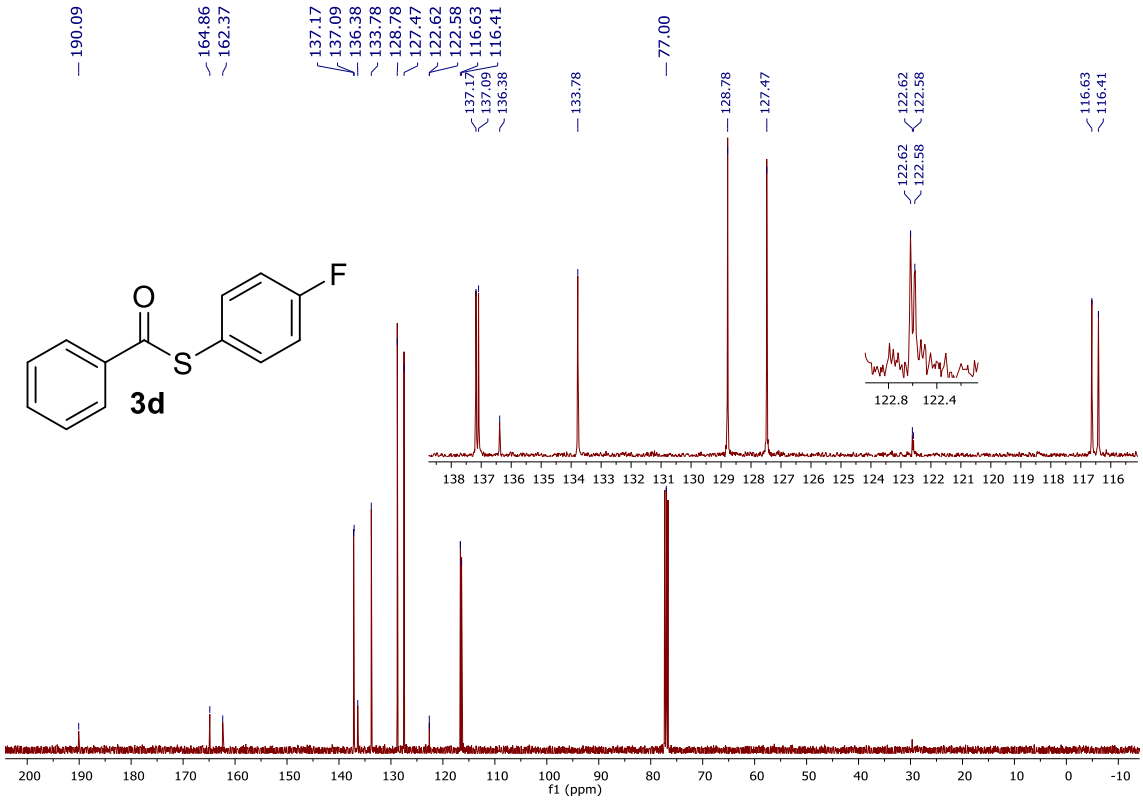

Figure 24. ^{13}C NMR spectrum of compound **3d** (100 MHz, $CDCl_3$).

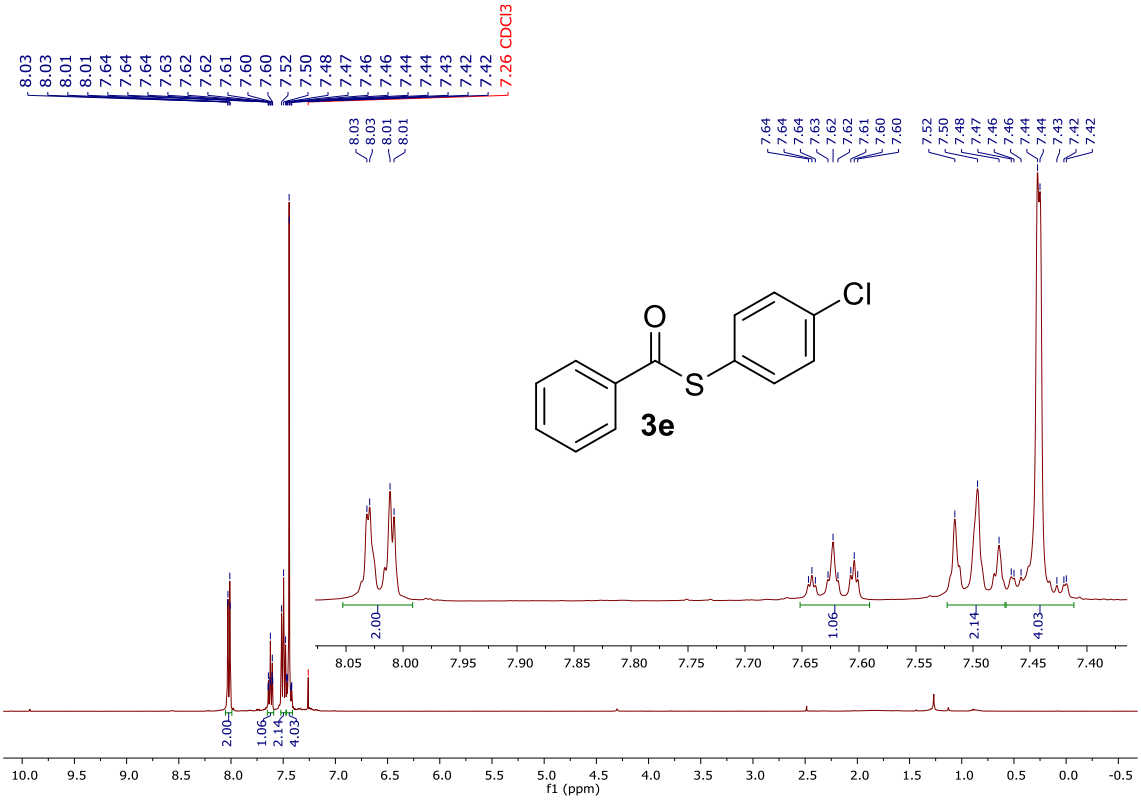

Figure 25. ^{1}H NMR spectrum of compound **3e** (400 MHz, $CDCl_3$).

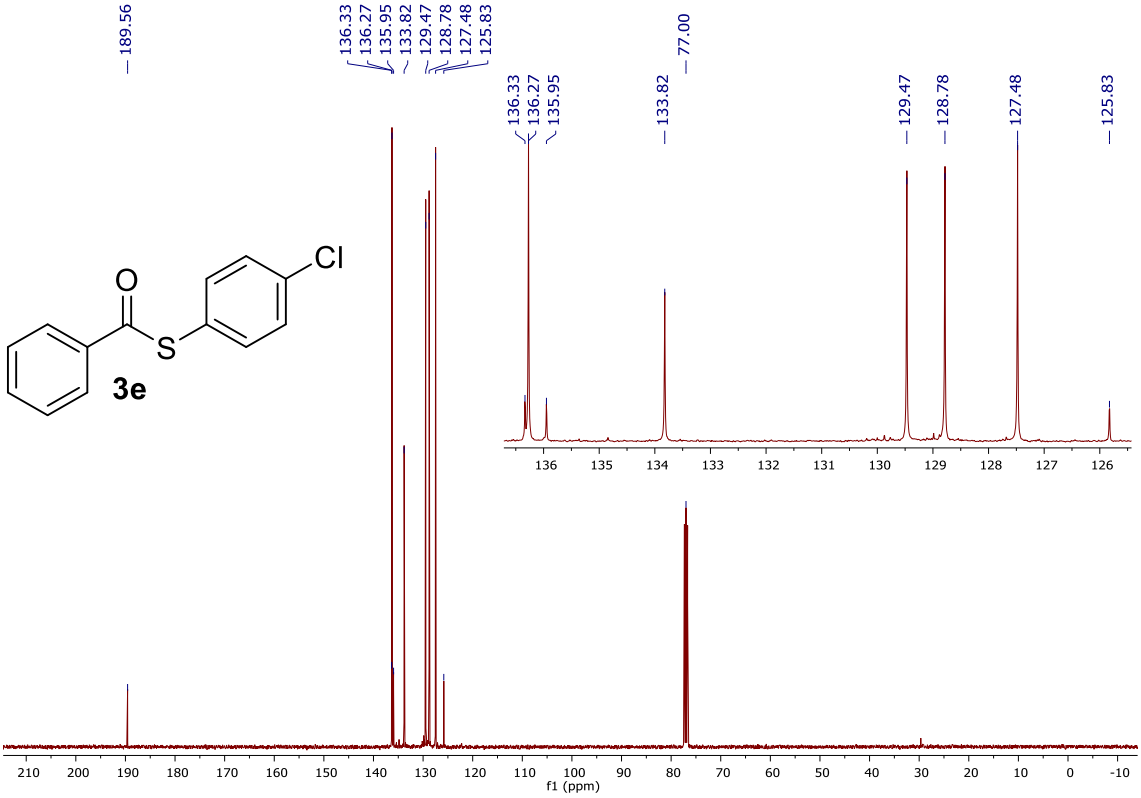

Figure 26. ^{13}C NMR spectrum of compound **3e** (100 MHz, $CDCl_3$).

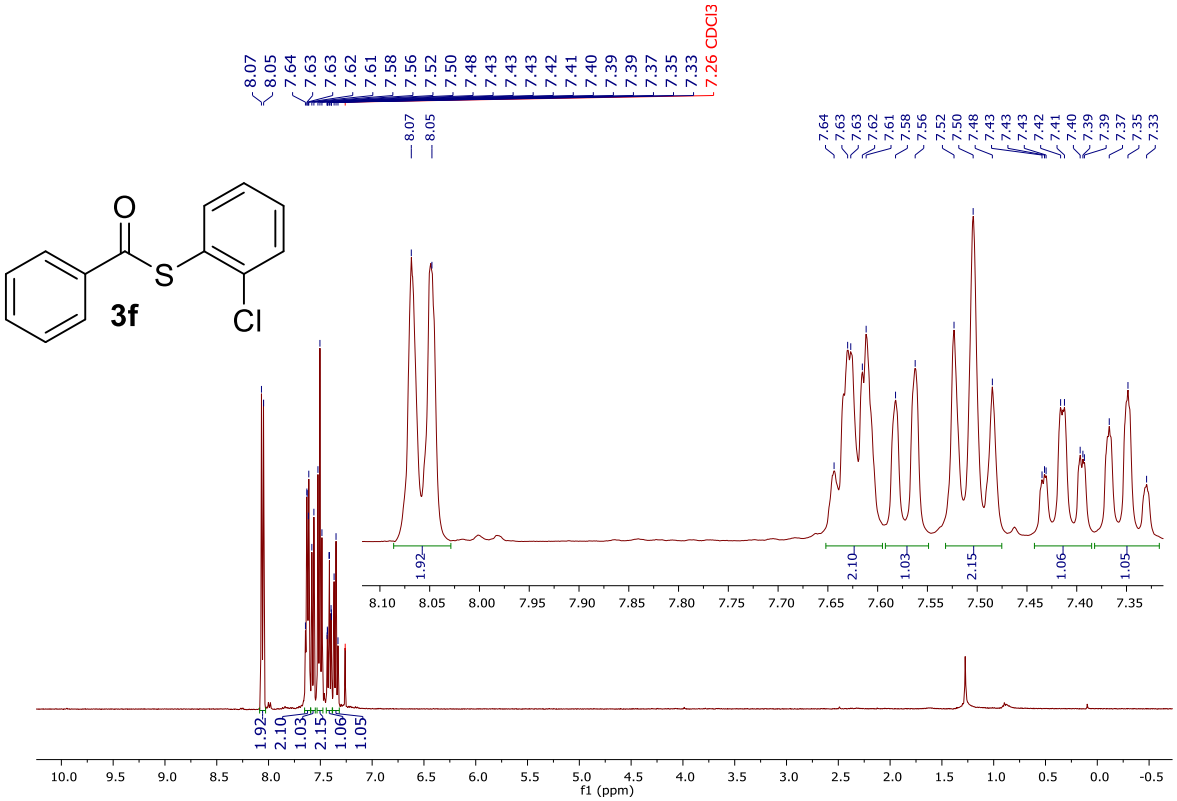

Figure 27. ^{1}H NMR spectrum of compound **3f** (400 MHz, $CDCl_3$).

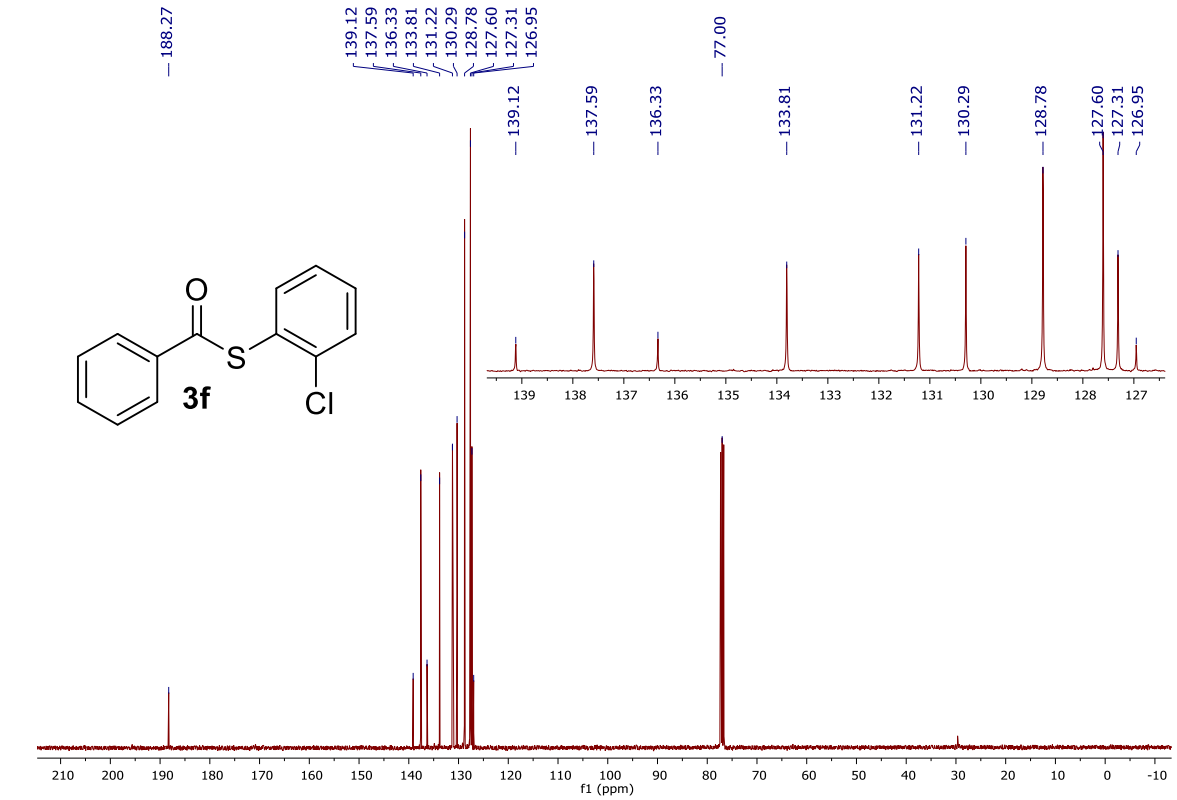

Figure 28. ^{13}C NMR spectrum of compound **3f** (100 MHz, $CDCl_3$).

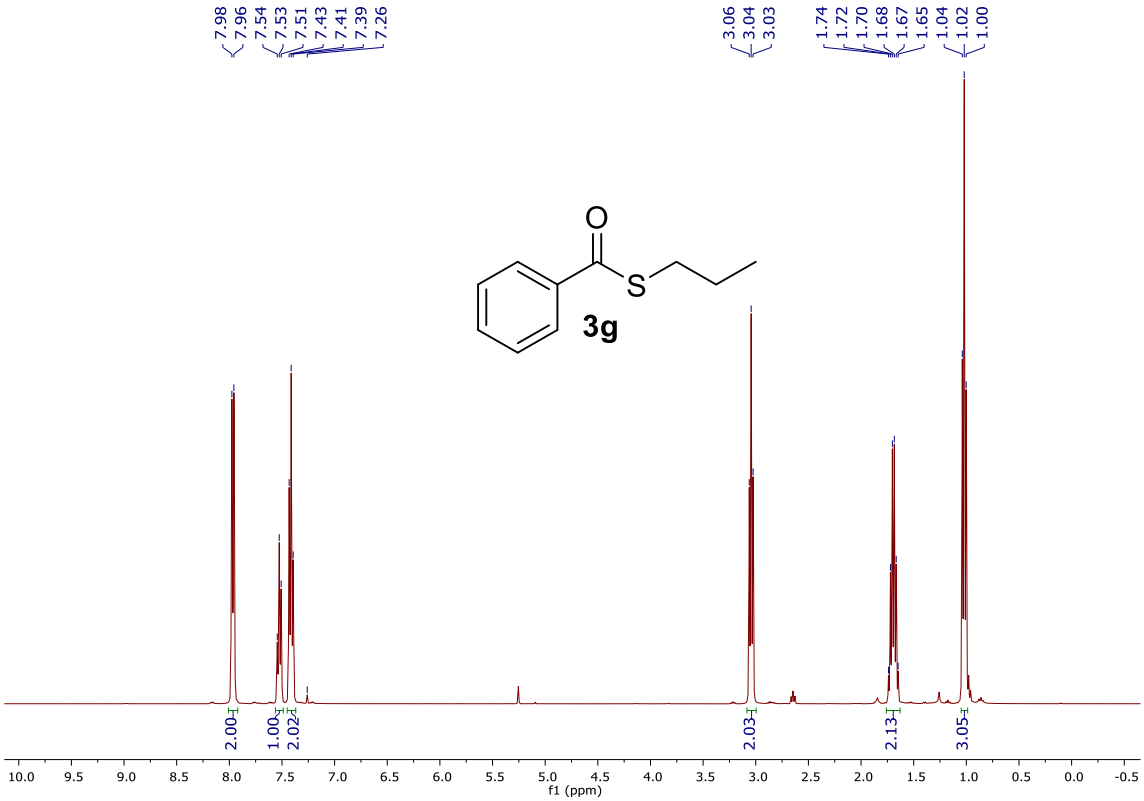

Figure 29. ^{1}H NMR spectrum of compound **3g** (400 MHz, $CDCl_3$).

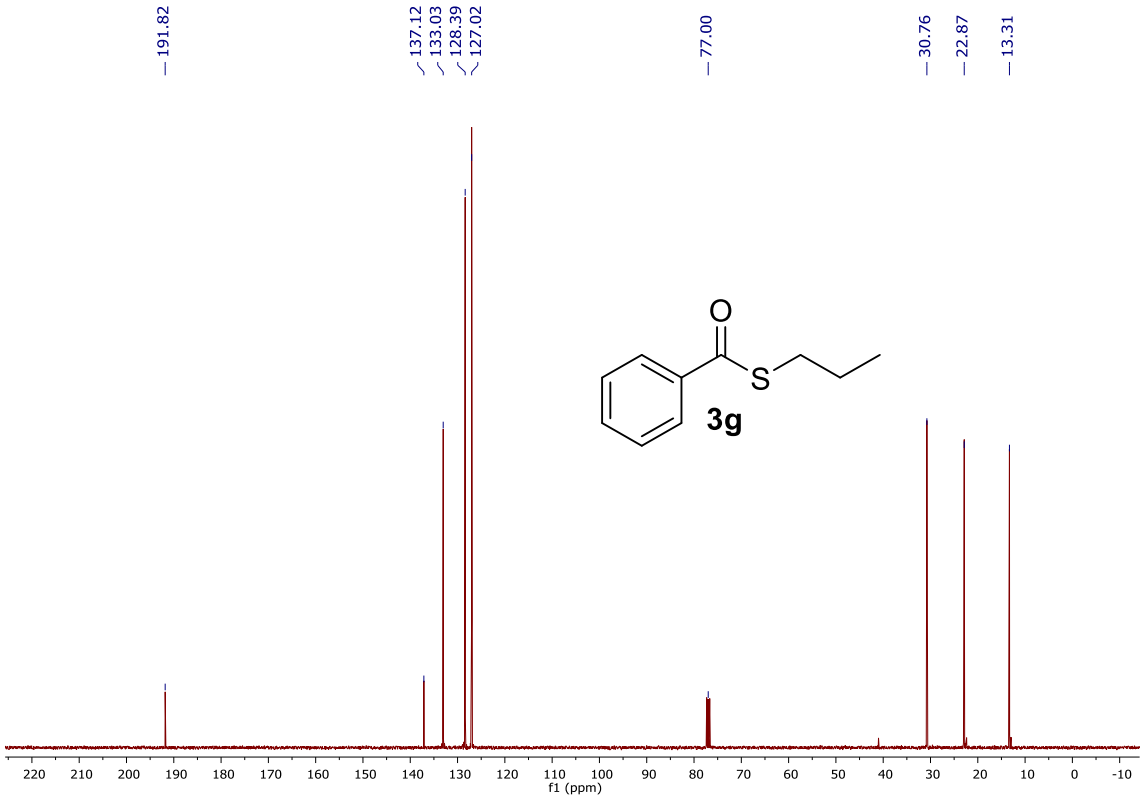

Figure 30. ^{13}C NMR spectrum of compound **3g** (100 MHz, $CDCl_3$).

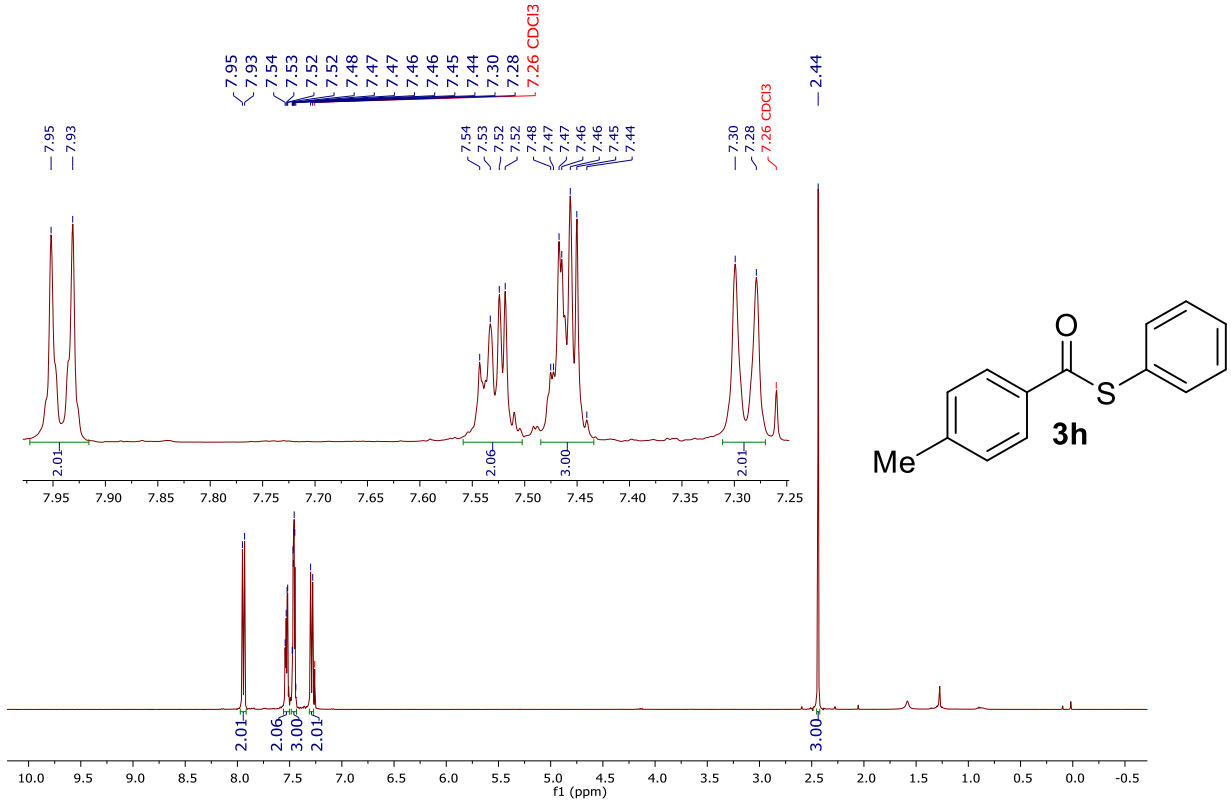

Figure 31. ^{1}H NMR spectrum of compound **3h** (400 MHz, $CDCl_3$).

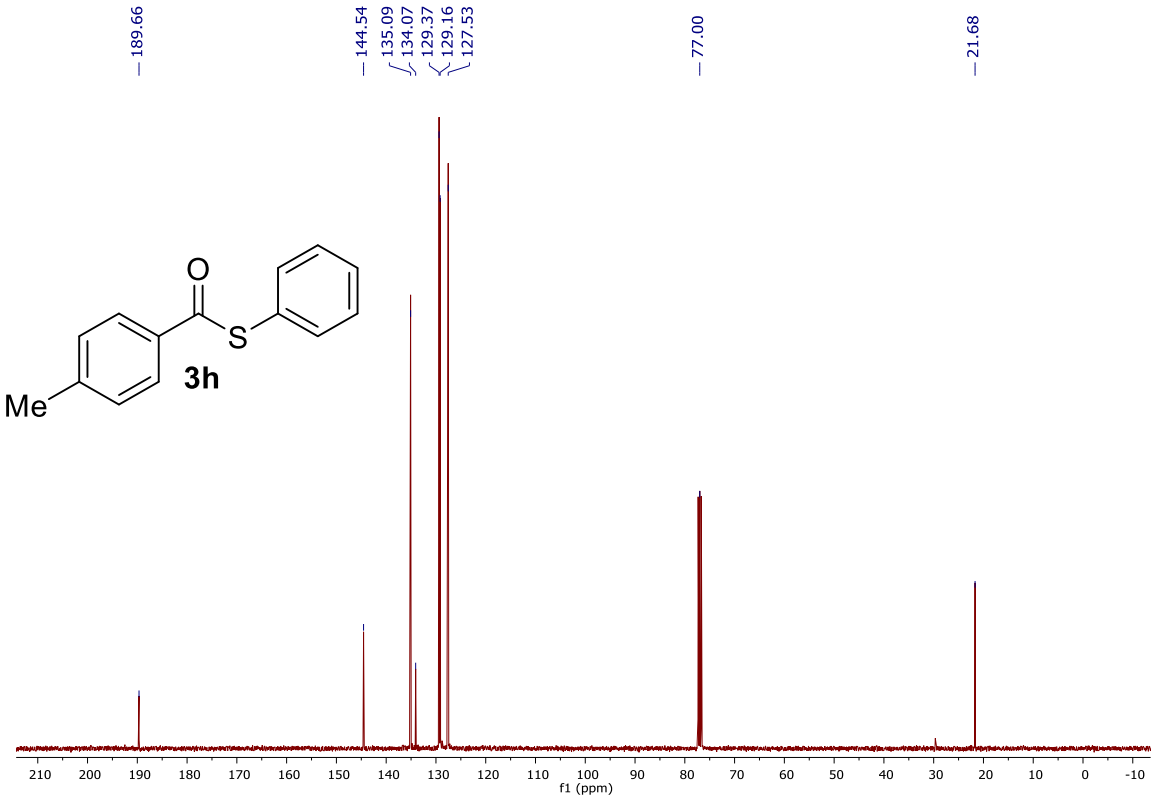

Figure 32. ^{13}C NMR spectrum of compound **3h** (100 MHz, $CDCl_3$).

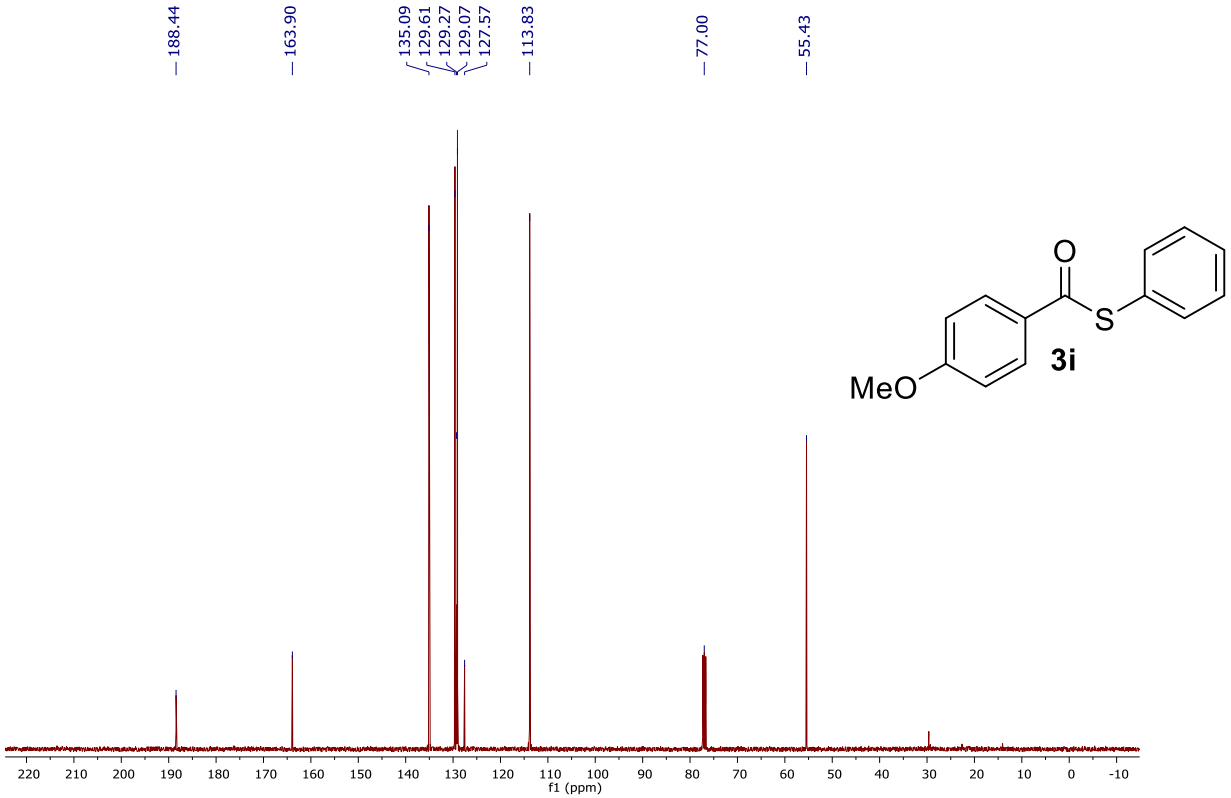

Figure 33. ^{1}H NMR spectrum of compound **3i** (400 MHz, $CDCl_3$).

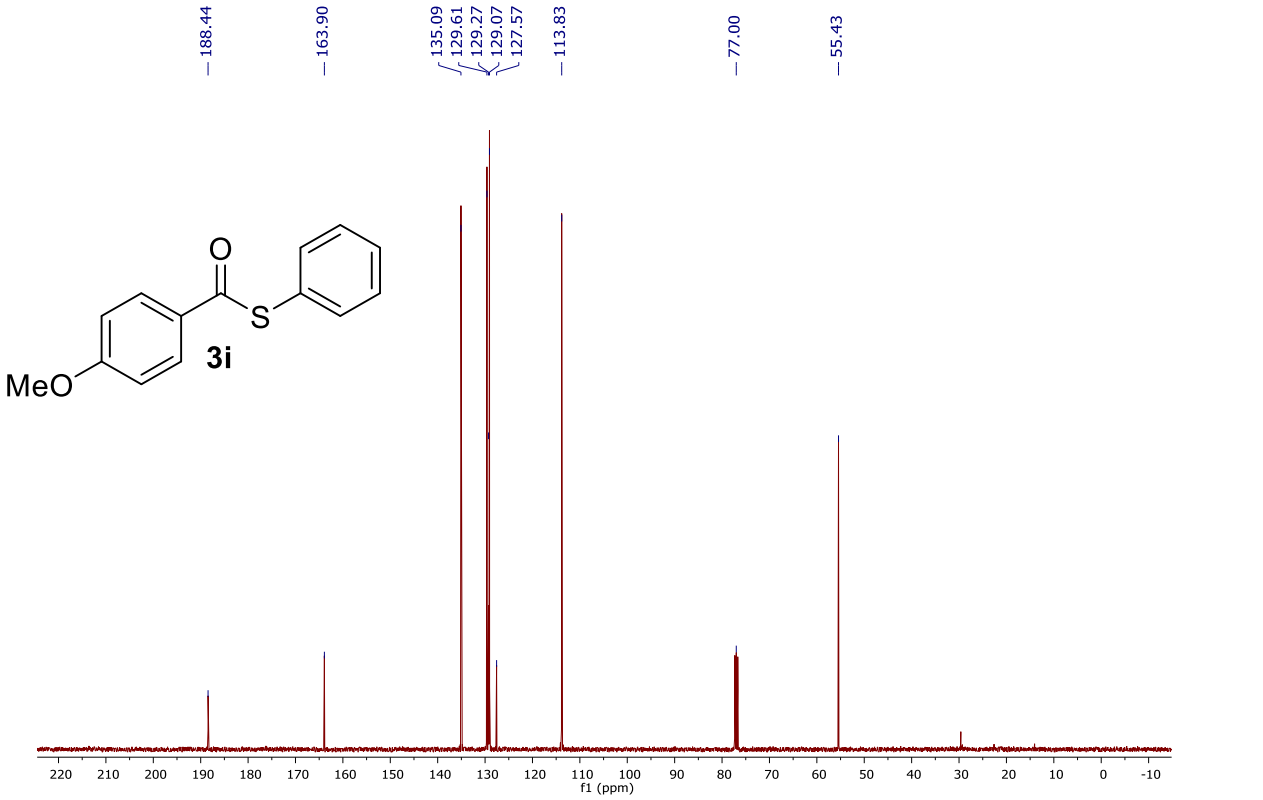

Figure 34. ^{13}C NMR spectrum of compound **3i** (100 MHz, $CDCl_3$).