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Grau de Química

Treball Final de Grau

An approach to direct and catalyzed alkylation reaction: Synthesis of *N*-acyl-1,3-thiazinane-2-thiones and *N*-acyl-1,3-thiazolidine-2-thiones.

Una aproximació a la reacció d'alquilació directa i catalitzada: Síntesi de *N*-acil-1,3-tiazinan-2-tiones i *N*-acil-1,3-tiazolidin-2-tiones.

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Universitat de Barcelona

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If you can't, you must,
and if you must, you can.
Anthony Robbins

Primer de tot agrair a en Fèlix per supervisar tot el projecte, ajudar-me i aconsellar-me en l'escriptura de la memòria. També per fer-me veure la importància de tenir criteri i així fer-me créixer i millorar com a futura química.

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Y, sobre todo a ti, allí donde estés, esto va por ti.

REPORT

CONTENTS

1. SUMMARY

Stereoselective construction of carbon-carbon bonds is the key step in the synthesis of natural products with biological activity. Therefore, the reactions involving metal enolates, capable of reacting with a wide range of electrophiles to generate new C-C bonds, occupy a preeminent position in organic synthesis. Thus, in last decades, stereoselective methodologies have been developed that use metal enolates in alkylation, aldol and Michael reactions. In most synthetic approaches, stereochemical control has gone through substrate control or the use of chiral auxiliaries. However, in both methodologies, the reactions take place in stages -first the enolization and then the reaction with the electrophile- and stoichiometric amounts of metal are always required. In this context, the emergence of asymmetric catalysis has paved the way for direct and catalytic reactions using chiral metal complexes to generate enolates. However, very few of these complexes can promote the selective enolization of an activated carboxylic acid derivative and provide a suitable environment for reacting enantioselectively with electrophiles.

In recent years, our group has developed a new methodology in which chiral complexes of Ni(II) are used to catalyze direct and enantioselective alkylation reactions of *N*-acyl-1,3-thiazinane-2-thiones with electrophiles. Initially, the formation of a single stereocenter was studied, using electrophiles activate with TESOTf to generate oxocarbenium cations and also stable carbocations. The asymmetric formation of two chiral centers is currently being evaluated by direct catalytic reactions with acetals and aldehydes, in both cases activated with a Lewis acid.

In this context, this project aims to obtain 1,3-thiazinane-2-thione on a large scale and to carry out a wide range of acylation reactions with this platform and also with 1,3-thiazolidin-2-thione, to prepare different *N*-acylthiomides, which may be used in the above-mentioned reactions. Finally, a first assay of a direct alkylation reaction was also performed with a commercial and aquiral nickel catalyst and methyl orthoformate activated with TESOTf as an electrophile.

Keywords: direct enantioselective reactions, enolates, asymmetric catalysis, nickel catalyst, scaffold.

2. RESUM

La construcció estereoselectiva d'enllaços carboni-carboni és l'etapa clau en la síntesi de productes naturals amb activitat biològica. Per això, les reaccions que involucren els enolats metàl·lics, capaços de reaccionar amb molts electròfils per generar nous enllaços C-C, ocupen una posició preeminent en la síntesi orgànica. Així, en les darreres dècades, s'han desenvolupat metodologies estereoselectives que empren els enolats metàl·lics en reaccions d'alquilació, aldòliques i de Michael. Habitualment, el control estereoquímic ha passat per control del substrat o l'ús d'auxiliars quirals. Ara bé, en ambdues metodologies, les reaccions tenen lloc per etapes - primer l'enolització i després la reacció amb l'electròfil- i sempre calen quantitats estequiomètriques de metall. Ara bé, l'emergència de la catàlisi asimètrica ha obert el camí a reaccions directes i catalítiques emprant complexos metàl·lics quirals per generar enolats. Tot i això, molt pocs complexos poden promoure l'enolització selectiva d'un derivat activat d'un àcid carboxílic i proporcionar un entorn adequat per reaccionar enantioselectivament amb electròfils.

En els darrers anys, el nostre grup ha desenvolupat una nova metodologia en la qual s'utilitzen complexos quirals de Ni(II) per catalitzar reaccions d'alquilació directes i enantioselectives de *N*-acil-1,3-tiazinan-2-tiones amb electròfils. Inicialment, es va estudiar la formació d'un únic estereocentre, emprant com electròfils precursors de cations oxocarbeni activats amb TESOTf i carbocations estables. Ara mateix, s'està avaluant la formació asimètrica de dos centres quirals, mitjançant reaccions directes amb acetals i aldehids.

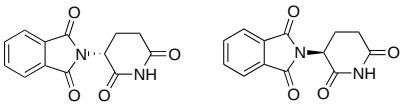
En aquest context, en aquest projecte es pretén obtenir a gran escala l'1,3-tiazinan-2-tiona i portar a terme un ampli ventall de reaccions d'acilació amb aquesta plataforma i també amb l'1,3-tiazolidin-2-tiona, per preparar diferents *N*-acil tiomides, que podran ser utilitzades en les reaccions abans esmentades. Finalment, s'ha fet un primer assaig d'una reacció d'alquilació directa amb un catalitzador de níquel aquiral i ortoformiat de metil activat amb TESOTf.

Paraules clau: reaccions enantioselectives directes, enolats, catàlisi asimètrica, catalitzador de níquel, scaffold.

3. INTRODUCTION

Stereoselectivity has been a topic of remarkable interest in organic chemistry in the last decades. The structure of a compound and its spatial distribution led to specific physicochemical properties. This fact implies that a change, even simple, in the spatial distribution of a compound can lead to completely different effects on the human's body. There is a growing interest in the pharmaceutical industry to obtain enantiomerically pure drugs. This is because one enantiomer may have different pharmacological behavior than the other enantiomer. For example, one enantiomer can be biologically active for a determined use and the other can be biologically inactive, or active for a different use. Having a single enantiomer drug can lead to higher efficiency and fewer side effects. Also, some drugs can be administrated in its racemic form without any contraindications, but others not because one of the enantiomers is toxic. For this reason, in recent years some racemic drugs have been changed to their pure enantiomeric form.[1]

A clear example of the importance of being able to obtain enantiomerically pure drugs is the case of thalidomide. This compound was sold in its racemic form in the late 1950s and was used to treat the effects of morning sickness during pregnancy. Shortly after being commercialized, it was shown that the children of pregnant women who had taken this drug were born with limb malformations and with a fairly high mortality rate. This drug was a racemic mixture, and the *R* enantiomer was therapeutically active, whereas the *S* enantiomer was responsible for teratogenic deformities in children born after their mothers used it during pregnancies (Figure 1).[2]



(R)-thalidomide *(S)*-thalidomide

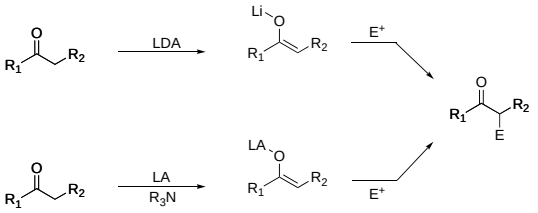
Figure 1. Thalidomide structure.

This growing interest in obtaining enantiomerical pure molecules has led to the development of new methods that allow asymmetric synthesis. One of the fields of interest is the stereoselective formation of carbon-carbon bonds, which has great importance in organic synthesis.[3]

3.1. REACTIONS OF ENOLATES

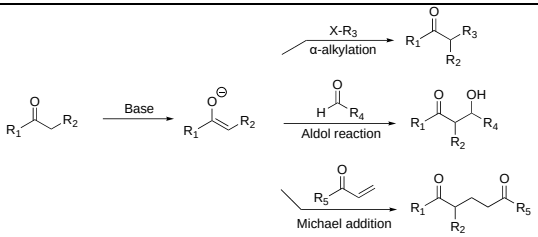
One of the most important methods to construct carbon-carbon bonds is the reaction between an enolate and an electrophilic species. For the stereoselective construction of the carbon-carbon bonds, one of the achievements is to form a metal enolate and then carry out an alkylation, an aldol reaction, or a Michael addition.

Classical methodologies are based on the stoichiometric preformation of the enolate species, with a strong base, such as LDA or NaHMDS, followed by the addition of the electrophilic species. Another approach, the soft enolization, consists of the preformation of the enolate using a Lewis acid, such as $TiCl_4$ or Bu_2BOTf, and a tertiary amine, as a base, followed by the addition of the electrophilic specie in a second step as before (Scheme 1).



Scheme 1. Two-steps reaction.

There are a great variety of electrophilic species and depending on their nature, different types of reactions take place. There are three main categories: alkylation reaction, aldol reaction and Michael addition. The alkylation uses alkyl halides as the electrophilic species. The aldol reaction uses aldehydes as an electrophiles and β-hydroxy carbonyl compounds (or aldols) are obtained. Finally, Michael additions, which use an α,β-unsaturated carbonyl compound as the electrophile, lead to the formation of new bonds at the β position of the carbonyl affording 1,5-dicarbonyl compounds (Scheme 2).



Scheme 2. Types of enolate reactions.

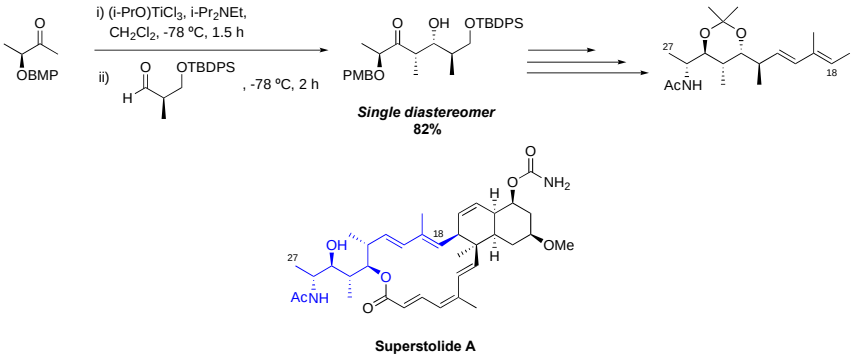
3.2. STEREOCHEMICAL CONTROL IN THE C-C BOND FORMATION REACTION WITH ENOLATES

Generally, the stereochemical control in the formation of carbon-carbon bonds can be classified in two different ways: substrate-controlled synthesis and diastereoselective induction using chiral auxiliaries.[3]

3.2.1. Substrate control

Substrate-controlled reactions are based on the control of the stereochemistry by the use of reactants that have chiral elements in their structure, with a specific configuration. Then chiral substrate undergoes a sequence of selective reactions, transforming certain parts of the molecule whilst retaining the desired chiral aspect to yield the enantiopure product. All chirality is mapped from the starting material either maintaining it, manipulating or using it to propagate further chiral centers. These kinds of reactions are simple and also more economically and environmentally attractive than using chiral auxiliaries or catalysts, but low selectivities are obtained for some types of products.[4]

One example of this kind of reactions is the highly stereoselective approach directed toward the synthesis of the C18-C27 fragment of superstolide A, taking an aldehyde and a ketone as the only sources of chirality (Scheme 3).[5]



Scheme 3. Synthesis of the fragment C18-C27 of superstolide A.

3.2.2. Chiral auxiliaries

Another way to control the stereoselectivity of a large number of chemical transformations, such as carbon-carbon bond formation reactions, is by using chiral auxiliaries. This approach attaches to the carboxyl group a chiral auxiliary, which is easily removable, that generates a chiral substrate able to control the stereochemical outcome in the following reactions, giving rise to the desired stereoisomer. Once the desired product is obtained the chiral auxiliary is removed. Many examples of chiral auxiliaries can be found, such as the ones described by Evans, Nagao/Fujita and Crimmins (Figure 2).[6-9]

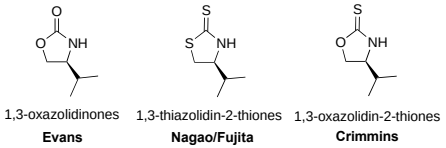
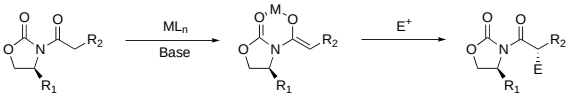


Figure 2. Chiral auxiliaries.

The first approaches were two-steps processes, as was mentioned before. Firstly, the enolate was formed using a strong base or a Lewis acid and a tertiary amine. In the alkylation reaction, the metal of the enolate chelates to the carboxyl group of the chiral auxiliary. This chelation forces a planar structure and it is the chiral center which blocks one of the faces of the enolate (Figure 3), favoring the approach of the electrophile from the opposite face (Scheme 4).[10,11]



Scheme 4. Metal enolate formation using chiral auxiliaries.

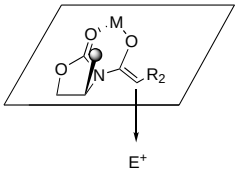
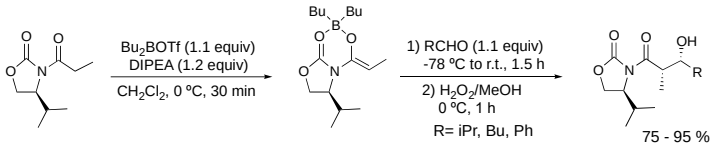


Figure 3. Stereocontrol approach of chelated enolates.

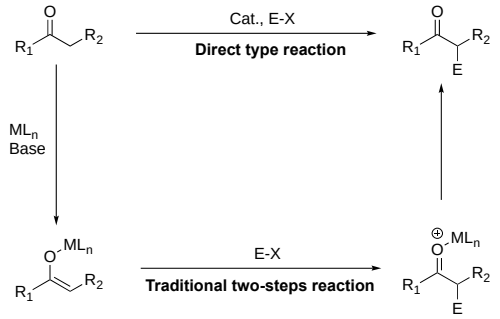
One example of this strategy is a classical aldol reaction described by Evans, which implies an aldol reaction of a boron enolate of a chiral *N*-propanoyl-1,3-ozaxolidine-2-one with different aldehydes. These types of reactions provide high yields and high stereoselectivities (Scheme 5).[12]



Scheme 5. Stereoselective aldol reaction with chiral auxiliaries.

3.3. DIRECT REACTIONS

So far, we have been describing two-step processes, which are currently used methods. Asymmetric catalytic reactions have been developing over the past years, leaving aside traditional reactions. This leads to the possibility of performing one-step reactions, which are considered direct reactions, in which the enolate is generated catalytically and the electrophilic specie is added in the same step.[13] These types of procedures include the use of species in substoichiometric quantities for the enolate generation (Scheme 6).[10] One of the advantages is that these methodologies follow the terms of the atom economy.[14]

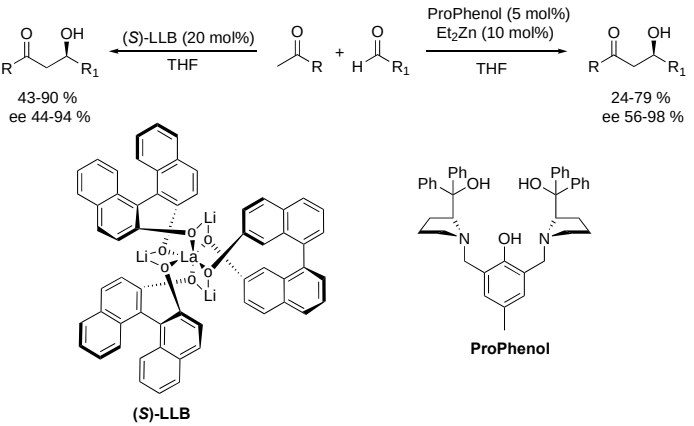


Scheme 6. Direct type reaction *versus* traditional two-steps reaction.

3.3.1. Metal enolates

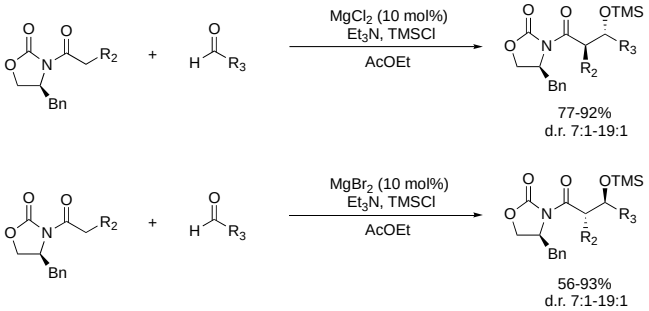
There are methods that are based on the use of metal complexes to catalyze asymmetric and direct aldolic reactions. The metal complex is coordinated to the carbonyl group of the starting species, thus increasing the acidity of the alpha proton and thus being able to generate an enolate able to react with the electrophile. Today this methodology is still being investigated so there are not a large number of methodologies available.

Two of the most important methods are described by Trost and Shibasaki, who developed metallic catalysts to carry out aldol reactions.[15] In the case of Shibasaki, large amounts of catalyst and aldehydes were needed and moderate to high enantioselectivities and yields were obtained.[16-18] Trost developed the ProPhenol catalyst, which is a bimetal catalyst based in a dinuclear zinc complex that gives low or moderate yields and better enantioselectivities (Scheme 7).[19-22]



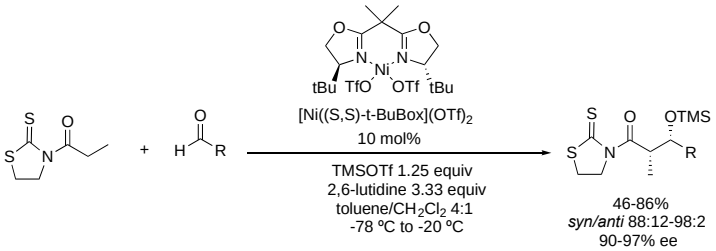
Scheme 7. Direct catalytic asymmetric reaction promoted by BINOL and ProPhenol catalysts.

Evans studied the catalytic approach of an aldol reaction, controlling the stereochemistry by using their classical Evans chiral auxiliaries and magnesium halides ($MgCl_2$ or $MgBr_2 \cdot OEt_2$) as catalysts in presence of stoichiometric amounts of trimethylsilyl chloride (TMSCl) and Et_3N, affording the two *anti* aldol adducts with good yields and high stereoselectivity (Scheme 8).[15,23,24]



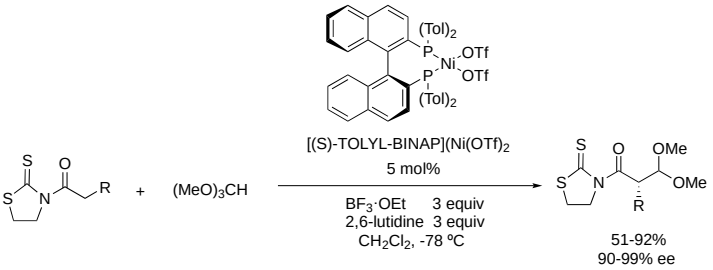
Scheme 8. Catalytic aldol reaction based on chiral auxiliaries.

Evans also reported a catalytic approach of the aldol reaction using an achiral scaffold, the 1,3-thiazolidine-2-thione, and using a Ni(II) chiral complex under silylating conditions, obtaining the *syn* aldol adduct (Scheme 9). The methodology has a wide scope, and several aldehydes have been used including aromatic and aliphatic aldehydes. The main drawback is the difficulty to prepare and handle the chiral catalyst containing the triflate ligands.[15]



Scheme 9. Direct asymmetric aldol reaction with chiral Ni(II) catalyst.

Evans also explored these approaches using a similar Ni(II) chiral catalysts to carry out alkylations with trimethyl orthoformate as electrophile, with great enantioselectivities and high yields (Scheme 10).[15]

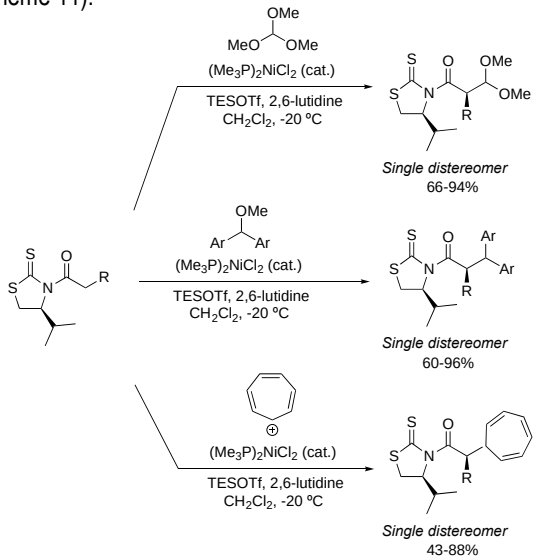


Scheme 10. Direct asymmetric alkylation reaction catalyzed with Ni(II) complex.

3.4. ALKYLATION REACTIONS BASED ON NI(II) CATALYSTS

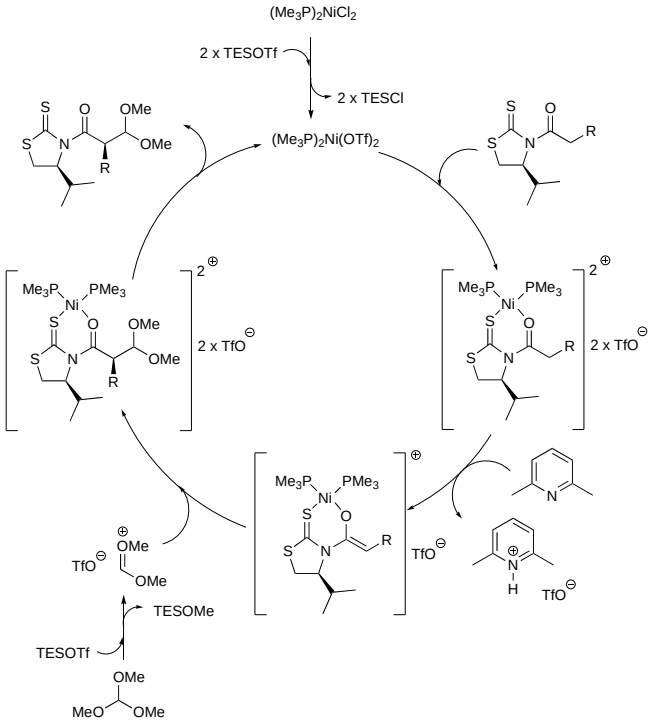
3.4.1. Achiral Ni(II) complexes

Inspired by precedent works described by Evans, our group has developed direct, diastereoselective and catalytic alkylation reactions of chiral *N*-acyl-1,3-thiazolidine-2-thiones using Ni(II) achiral catalysts. In this approach, it is the chiral auxiliary that controls the stereochemical outcome of these alkylation reactions. The chiral *N*-acyltiomides derived from L-valine react with different electrophiles, such as trimethyl orthoformate, diarylmethyl methyl ethers and stable carbocationic salts, in presence of an achiral Ni(II) catalyst, TESOTf as a Lewis acid and 2,6-lutidine as a base to afford the S_N1 alkylated compound in high yield and excellent diastereoselectivity (Scheme 11).[25-27]



Scheme 11. Catalytic alkylation of chiral *N*-acyl thiazolidinethiones with electrophiles.

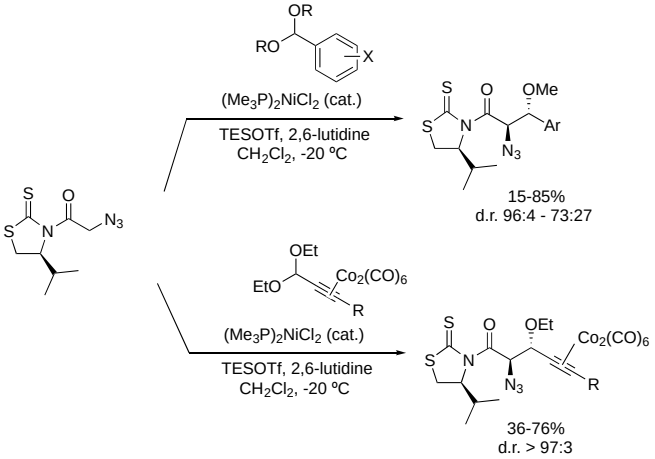
In these reactions, the alkylation proceeds by an S_N1-mechanism in which the electrophiles are carbenium and oxonium ions generated in the reaction mixture by the reaction of the electrophiles species with the Lewis acid (TESOTf). Moreover, the TESOTf is responsible of activating the pre-catalyst to from the real catalyst, which contains two triflate ligands. The function of the real catalyst consists of the formation of the chelate Ni(II) enolate by the coordination of the Ni(II) complex to the N-acyl thioamide creating a chelated system that reacts with the 2,6-lutidine to from the Z-enolate, which have one of the faces blocked by the isopropyl group from the chiral auxiliary (Scheme 12).[10]



Scheme 12. Catalytic cycle of the alkylation of chiral *N*-acyl thiazolidinethiones.

The previously mentioned reaction can create just one stereoisomer, but our approach can be able of creating simultaneously up to new stereocenters just moving to a different electrophile. Therefore, our group studied electrophiles based on acetals which could be used to generate the

chiral adducts with good selectivities and yields in the reaction of N-azidocetyltiomide (Scheme 13).[28]



Scheme 13. Catalytic alkylation of chiral *N*-acyl thiazolidinethiones to form two stereocenters.

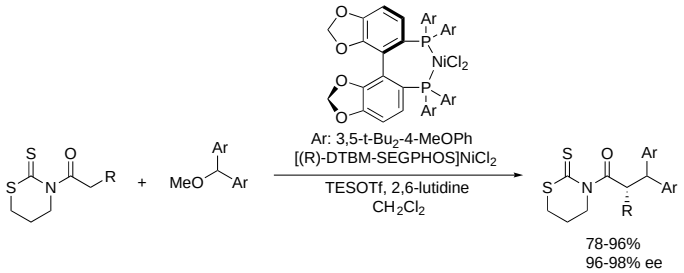
Although these types of reactions are robust, they present some impediments. One of them is that stoichiometric amounts of chiral auxiliaries are required as well as the addition of two more steps in the process due to the initial incorporation and elimination of the auxiliary, which affect the performance of the reaction. For this reason, the group studied new alternative methodologies where stereochemistry is controlled with a chiral Ni(II) catalyst.

3.4.2. Chiral Ni(II) complexes

To overcome the aforementioned impediments, instead of using chiral auxiliaries to control stereochemistry, nickel catalysts were used. The stereochemistry of the final product depends on the configuration of the ligands that the Ni(II) catalyst has. This methodology makes possible to obtain the two enantiomers of the final product starting from the same substrate, only by changing the configuration of the catalyst ligands. This presents a considerable difference with chiral auxiliaries, with which only one of the enantiomers could be obtained. In any case, heterocyclic auxiliaries continued to be used due to the need to create the metal chelate, so that the reaction could take place.

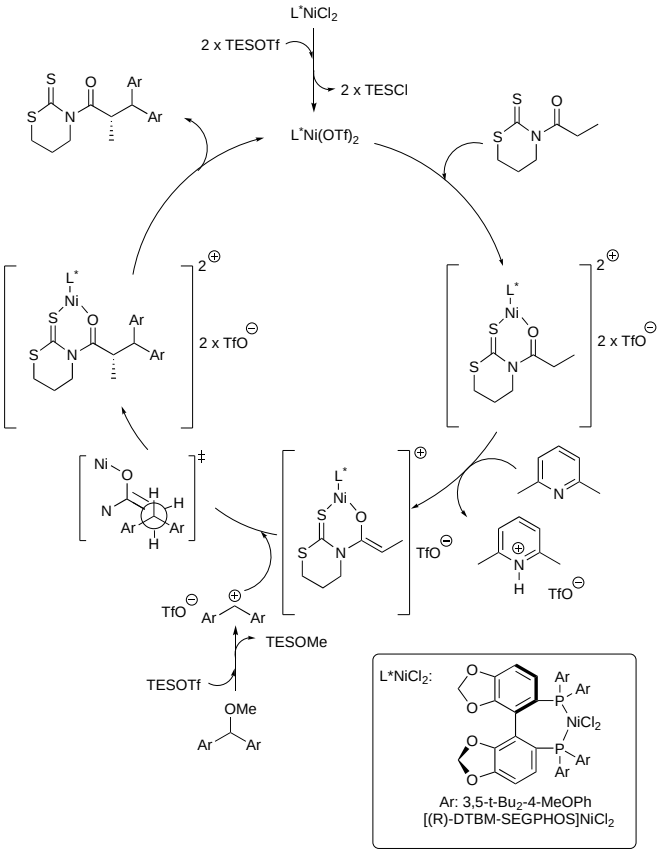
Inspired by the Evans and Kumagai and Shibasaki works, the group has been carrying out these types of direct and enantioselective reactions using chiral Ni(II) catalysts and heterocyclic

auxiliaries with different types of electrophiles. One of the latest studies of the group, *N*-acyl-1,3-thiazinane-2-thione was reacted with a carbenium electrophile in presence of TESOTf as a Lewis acid and using the chiral catalyst (*R*)-DTBM-SEGPHOS]$NiCl_2$, which blocks on of the faces of the enolate to afford with high yields and enantiomeric excess (Scheme 14).[29]



Scheme 14. Catalytic alkylation controlled by a chiral Ni(II) catalyst.

In this case, the Lewis acid (TESOTf) again activates the pre-catalyst to form the real catalyst with two triflates ligands, and then it coordinates with the acylated scaffold to forming a six-membered ring and facilitate the formation of the chelate enolate. Also, the TESOTf reacts with the electrophile producing the carbocation that will be added to the enolate (Scheme 15).[29] Afterwards, the catalyst is liberated to start a new catalytic cycle.



Scheme 15. Catalytic cycle of *N*-acyl thiazinanethione catalyzed by a chiral Ni(II) catalyst.

4. OBJECTIVES

The first objective of this project will be to prepare large quantities of 1,3-thiazinane-2-thione following an experimental procedure described previously by the research group trying to obtain similar yields in order to demonstrate that the synthetic protocol is reproducible for an no fully trained chemist.

The second objective will be to perform acylation reactions to obtain *N*-acyl-1,3-thiazinane-2-thione and *N*-acyl-1,3-thiazolidin-2-thiones with different carboxylic acids acyl chlorides following different synthetic methodologies to use them as starting materials to carry out different types of direct reactions, such as aldol or alkylations reactions.

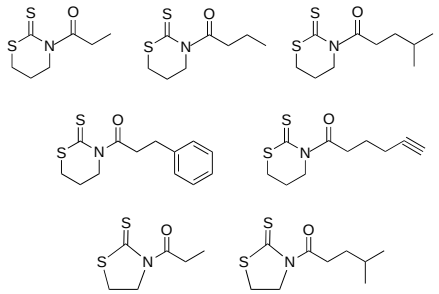
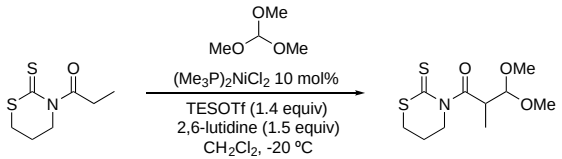


Figure 4. *N*-acyl-1,3-thiazinane-2-thione and *N*-acyl-1,3-thiazolidin-2-thiones generated

The last part consisted to perform a direct alkylation reaction of the previously prepared *N*-propanoyl-1,3-thiazinane-2-thione using an achiral Ni(II) catalyst and trimethyl orthoformate activate with TESOTf to obtain the alkylated adduct.



Scheme 16. Direct alkylation reaction of N-propanoyl-1,3-thiazinane-2-thione

5. RESULTS AND DISCUSSION

5.1. SYNTHESIS OF THE SCAFFOLD

As mentioned before, one of the main objectives of this project has been to synthesize the 1,3-thiazinane-2-thione (**3**), one of the scaffolds that have been used by our research group in the last research projects, at a large scale following a synthetic procedure described very recently and trying to reproduce and to secure the yields and the purity described previously. Then, the scaffold has been acylated with different acyl groups. Various side chains have been used to acylate scaffolds in order to later be able to use them to carry out other types of reactions and to analyze the robustness and limitations of the acylation methods used.

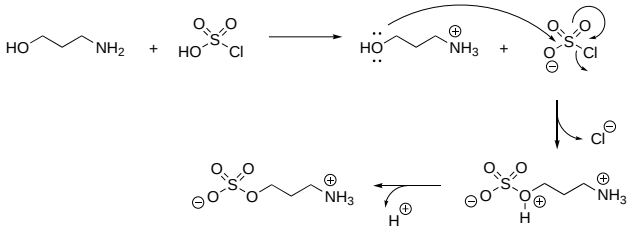
5.1.1. Synthesis of 1,3-thiazinane-2-thione (3)

In previous studies of the group, different scaffolds, which are five- and six-membered heterocyclic ring auxiliary groups, have been synthesized and analyzed. Different heteroatoms were tested for the auxiliaries and it was found that those with oxygen did not lead to any conversion and were therefore discarded. 1,3-Thiazinane-2-thione was found to give the best results in terms of enantioselectivity in the alkylation reactions. The 1,3-thiazolidin-2-thione scaffold also gave good results but lower than 1,3-thiazinane-2-thione.[29]

The synthesis of the scaffold 1,3-thiazinane-2-thione is a two-step reaction. As we have mentioned before, one of the main objectives of this project was to obtain this auxiliary in a large scale following the experimental procedure described and submitted to publish by our group to prove the yields previously obtained and the feasibility of the procedure.

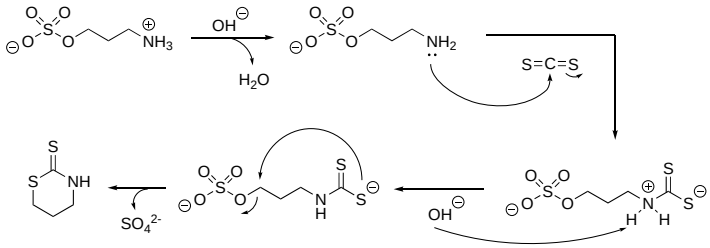
The first step consisted in the reaction of a solution of 3-amino-1-propanol (**1**) in CH_2Cl_2 with chlorosulfonic acid at 0 ºC in order to achieve 3-ammoniopropylsulfate (**2**). The reaction of 3-amino-1-propanol (**1**) with chlorosulfonic acid is an acid-base reaction followed by a nucleophilic attack. The nucleophilic species is 3-amino-1-propanol, which has two groups that can act as nucleophiles, the hydroxyl group and the amino group. Broadly speaking, the amino group, being

the most basic group, is a better nucleophile than the alcohol group, which is less basic. However, it is observed that the group that attacks the electrophile is the alcohol group. This is due to the fact that as we have a strong acid in the medium, the chlorosulfonic acid, and the amino group reactions with the proton giving ammonia salt and loses its nucleophilia (Scheme 17).



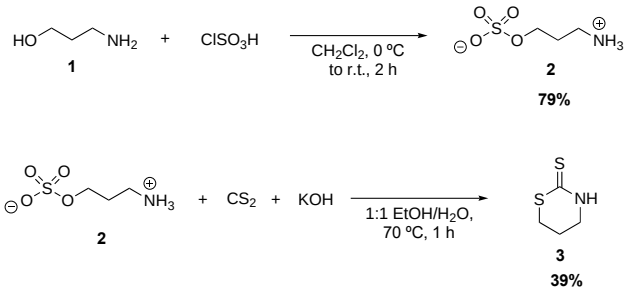
Scheme 17. Mechanism for obtaining 3-ammoniopropylsulfate (**2**).

Then, 3-ammoniopropylsulfate (**2**) was dissolved in ethanol and carbon disulfide and a solution of KOH in ethanol/water was added to the solution in order to neutralize the amine group of 3-ammoniopropylsulfate (**2**) to make it able to react with the carbon disulfide at 70 ºC to form a thiocarbamate, which cyclizes to from the 1,3-thiazinane-2-thione (**3**) (Scheme 18).



Scheme 18. Mechanism for obtaining 1,3-thiazinane-2-thione (**3**).

As it summarizes in Scheme 18, following the described procedures the 3-ammoniopropylsulfate (**2**) was obtained with a high yield (79%) and 1,3-thiazinane-2-thione (**3**) was obtained in a lower yield (39%). The yield obtained in this project for 3-ammoniopropylsulfate is very similar to the one reported by our group (87-89%). In the case of 1,3-thiazinane-2-thione, the reported yield in the paper is 62% and the obtained is lower. However, we can say that the procedure is reproducible and feasible and, in this project, the two-step synthesis affords an acceptable 31% overall yield.

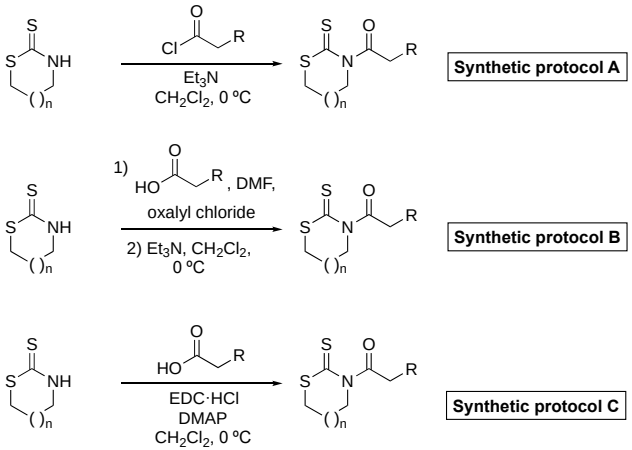


Scheme 19. Synthesis of 1,3-thiazinane-2-thione (**3**).

5.2. SYNTHESIS OF *N*-ACYL-1,3-THIAZINANE-2-THIONES AND *N*-ACYL-1,3-THIAZOLIDINE-2-THIONES

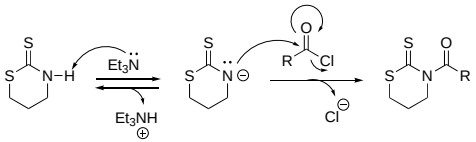
Various alkyl chains have been tested in the acylation reactions, from very simple ones, like the propionyl chain, to more complex ones like the 3-phenylpropanoyl chain. The propionyl chain is the least likely to present steric hindrance and, therefore, it is the most suitable to check the feasibility of the synthesis process published by the group. To go further, chains with more steric hindrance have been tested, in order to analyze the yields obtained using the synthesis method proposed by the group. Also, 1,3-thiazolidine-2-thione scaffold has been acylated with simple alkyl chains, such as the propynyl chain and the methylpentanoyl chain, to compare the results obtained with the results of acylating 1,3-thiazinane-2-thione scaffold with the same alkyl chains. These results are summarized in Table 1.

Three different synthetic protocols have been used to acylate 1,3-thiazinane-2-thione (3) and 1,3-thiazolidine-2-thione (**4**) summarized in Scheme 20.



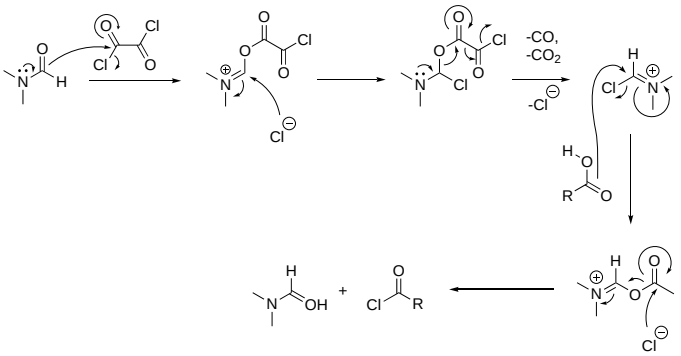
Scheme 20. Synthetic protocols to obtain *N*-acyl-1,3-thiazinane-2-thiones and *N*-acyl-1,3-thiazolidine-2-thiones.

The first one consists of the reaction of the scaffold with an acid chloride using a tertiary amine (Scheme 20, synthetic protocol A). In this case the tertiary amine is triethylamine and acts as a base that deprotonates the scaffold and starts the reaction of addition-elimination to form the desired *N*-acyl derivative (Scheme 21).



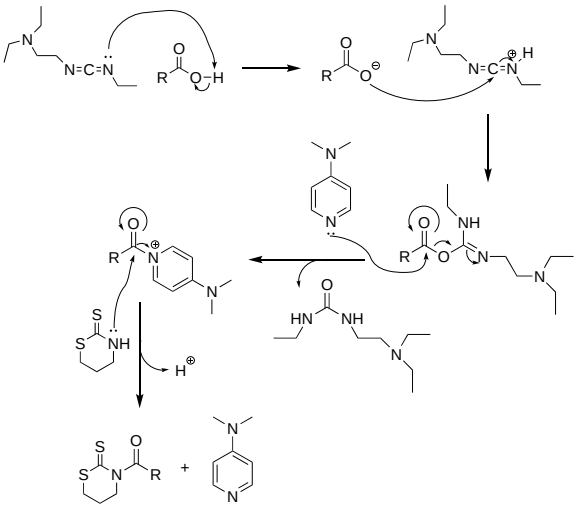
Scheme 21. Mechanism for obtaining N-acyl-1,3-thiazinane-2-thiones following the synthetic protocol A.

The second protocol is similar to the described previously implying also the acylating with carboxylic acids activated as acyl chlorides. However, in this procedure, the acyl chloride should be prepared previously using oxalyl chloride and DMF (Scheme 20, synthetic protocol B). In this reaction, the DMF acts as a catalyst and reacts with oxalyl chloride to form a more nucleophilic species, that will attack the carboxylic acid to obtain the acyl chloride, as described in Scheme 22.



Scheme 22. Mechanim of the preparation of acyl chloride with oxalyl chloride and DMF.

The last protocol is based on the reaction of a carboxylic acid with a coupling reagent, such as EDC·HCl, in presence of a catalyst, DMAP (Scheme 20, synthetic protocol C). The carboxylic acid reacts with the EDC to form an active ester that, in presence of DMAP, forms an *N*-acylpyridinium salt, a more electrophilic species and, therefore, a more reactive specie able of being attacked by the scaffold (Scheme 23).



Scheme 23. Mechanism of the acylation with EDC and DMAP

The results obtained in these reactions have been summarized in Table 1.

Entry	Scaffold	R	Synthetic protocol	t (h)	Product	Yield (%)
1	3	Me	A	2	5	65
2	3	Et	A	72	6	70
3	3	iBu	C	72	7	27
4	3	$PhCH_2$	C	48	8	55
5	3	$(CH_2)_2CH{\equiv}CH$	B	48	9	58
6	4	Me	A	4	10	83
7	4	iBu	B	4	11	65

Table 1. Synthesis of *N*-acyl-1,3-thiazinane-2-thiones and *N*-thiazolidine-2-thiones.

In general, the synthetic protocols A and B, based in the acylation reaction using an acyl chloride, afforded higher yields than protocol C, which uses a carbodiimide to activate the carboxylic acid

We also observed that for the five-membered ring scaffold, 1,3-thiazolidine-2-thione, we obtained higher yields than for the six-membered ring scaffold, 1,3-thiazinane-2-thione (compare entry 1 and 6 in Table 1).

The *N*-acyl thiomide **7** was particularly difficult to prepare and to purify using protocol C. The acylation reaction using the 4-methylpentanoic acid was checked by TLC to observe if there was

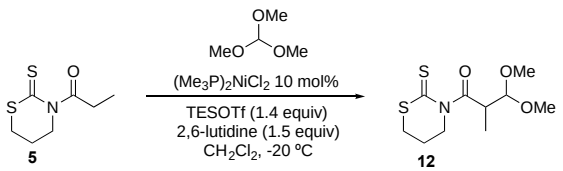
any starting material left in the reaction mixture and if the product had been formed. The reaction was controlled at 48 h, but it was observed that there was still starting material, so it was left 24 hours more reacting. At 74 h it was checked again, and it was observed that there was still starting material, but we decided to stop the reaction anyway. Also, we had difficulties to purify the compound, and we had to readjust the column conditions in order to properly separate the desired product from some impurities. Two *flash* column chromatography had to be carried out under different conditions to obtain the pure product. For these reasons, a lower yield (27%) was obtained as has been summarized in entry 3 of Table 1.

To prepare the *N*-acyl thioimide **11**, as we had obtained low yields for N-acyl thiomide **7** acylating with the same electrophile, we decided to perform an alternative protocol. Instead of following protocol C we followed protocol B, using the methylpentanoyl chloride prepared from the 4-metilpentanoic acid by reaction with oxalyl chloride and DMF cat. We also had problems to purify the product and two flash chromatography in different conditions had to be carried out to obtain the pure compound, however, a higher yield (65%) was obtained (Table 1, entry 7).

5.3. DIRECT AND CATALYZED ALKYLATION REACTION OF *N*-PROPANOYL-1,3-THIAZINANE-2-THIONE (5)

After obtaining the starting material *N*-propanoyl-1,3-thiazinane-2-thione (**5**) a direct and catalyzed alkylation reaction was carried out using very a simple and not expensive achiral catalyst commercially available, $(Me_3P)_2NiCl_2$, to obtain the racemic mixture of the desired alkylated compound.

The alkylation reaction was performed with 10 mol% of the achiral catalyst $(Me_3P)_2NiCl_2$ and was carried out at -20 ºC. The electrophile used was trimethyl orthoformate activated with TESOTf and using 2,6-lutidine as a base (Scheme 24).



Scheme 24. Direct alkylation reaction with trimethyl orthoformate.

The alkylation reaction was followed by TLC. After 24 hours, the reaction was stopped because there was apparently no evolution. However, the reaction was not complete, and the

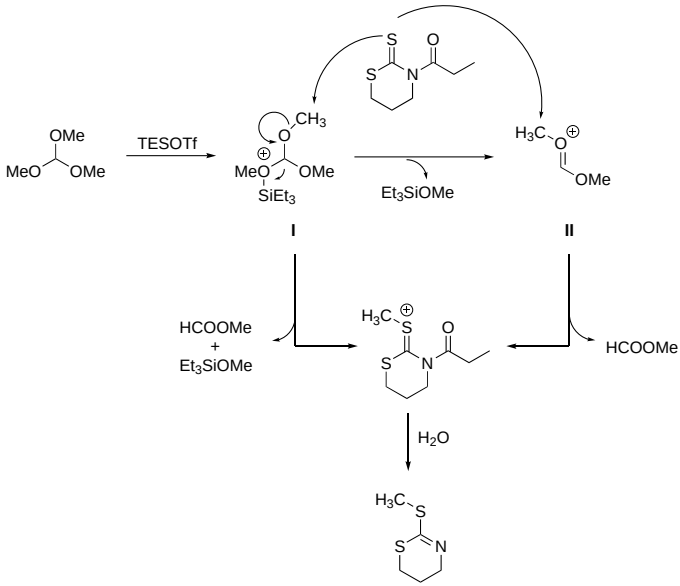
conversion of the reaction was only 53%, as it had been calculated by NMR of the crude mixture. It was observed that we had the *N*-acyl thiomide **5**, the desired product and a by-product in the reaction mixture. The tree compounds were difficult to separate and purify. The first *flash* column chromatography carried out did not work to separate the different substances and, therefore, the pure product was not obtained. After a great effort to find conditions to be able to carry out the separation, it was possible to isolate the *N*-acyl tioimide **5** (30%) from the by-product and the alkylated adduct **12**. After analyzing the fraction of the by-product **13** with the adduct **12** by NMR, we can assume that the by-product is a secondary product due to the alkylation of the sulfur of the scaffold (Figure 5).

13

Figure 5. Alkylation on the sulphur by-product.

Due to the low conversion of the reaction, the isolation of a by-product and the problems derived from purification, a low yield was obtained for the racemic mixture of the desired product. A 17% yield of *N*-[(*S*)-(3,3-dimethoxy-2-methylpropanoyl)]-1,3-thiazinane-2-thione (**12**) and 8% of the by-product **13** were obtained.

The formation of the by-product **13** rests on the nucleophilicity of the C=S. Indeed, the sulfur atom could attack either the coordinated complex **I** or the oxonium cation **II** (see Scheme 25). After deacylation and/or hydrolysis, **13** may be obtained.



Scheme 25. Mechanism of by-product **13** generation.

In conclusion, in order to obtain a higher conversion and avoid the formation of the by-product, the reaction should be carried out at a lower temperature, at -40 ºC. In order to obtain higher conversion in the alkylation reaction, a chiral catalyst more active could also be used, instead of the less active achiral catalyst used, since even having had a high amount of it in the reaction medium, the reaction has not been completed.

6. EXPERIMENTAL SECTION

6.1. MATERIALS AND METHODS

All reactions were conducted in oven-dried glassware and under N_2 atmosphere in anhydrous solvents. When necessary, the solvents and reagents were dried and purified according to standard procedures.[30] Otherwise, commercially available reagents were used as received.

Analytical thin layer chromatography (TLC) were carried out on Merck silica gel 60 F_{254} plates and analyzed by UV (254 nm) and stained with solutions of *p*-anisaldehyde. Column chromatography was carried out using low pressure (*flash*) and performed on SDS silica gel 60 (35-75 μm). Eluents are indicated in brackets in each case and R_f values are approximate.

IR spectra (Attenuated Total Reflectance, ATR) were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer. Only the most representative frequencies (n) are reported in cm^{-1}.

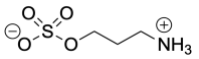
^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded at room temperature on Varian Mercury 400 or a Brüker 400 spectrometer. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ 0.00 for ^1H NMR) and $CDCl_3$ (δ 77.0 for ^{13}C NMR). Data are reported as follows: chemical shift (multiplicity, coupling constant(s), number of protons); multiplicity is reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, quintet; m, multiplet; coupling constants (*J*) are quoted in Hz.

High resolution mass spectra HRMS (+ESI) were obtained with Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses (CCiTUB), Universitat de Barcelona.

6.2. SYNTHESIS OF 3-AMMONIOPROPYLSULFATE (2)

An oven-dried single-necked 100 mL round-bottomed flask, equipped with a 2,5 cm magnetic stir bar, was charged with 3-amino-1-propanol (11.5 mL, 150 mmol, 1 equiv) and 35 mL of anhydrous dichloromethane using syringes. Then, a 50 mL pressure-relieving addition funnel equipped with a $CaCl_2$ tube was attached to the single-necked 100 mL round-bottomed flask and then was charged with chlorosulfonic acid (10.5 mL, 158 mmol, 1.05 equiv) using a glass

measuring cylinder. The flask was immersed in an ice bath and the solution was stirred for 5 minutes. Then, the chlorosulfonic acid was added dropwise over 30 minutes, allowing the fumes to escape. During the addition of chlorosulfonic acid, a white solid was formed. When the addition was complete, the reaction was stirred for 20 minutes maintaining the ice bath. Then, the ice bath was removed, and the reaction mixture was stirred at room temperature overnight. A fluffy white solid was formed, and the resulting mixture was filtered using a 70 mm diameter Number 3 glass filter with a Buchner setup. The product was retired from the flask walls using methanol. The mixture in the filter funnel was triturated with methanol a few times, using a spatula to break up the lumps each time. The resulting white solid was grounded to a fine white powder using a glass mortar and then transferred to a 100 mL round-bottomed flask. The flask was placed on a rotatory evaporator (40 °C, 12 mmHg pressure) for 1 hour. Then the flask was dried on a high vacuum line (room temperature, 0,1 mmHg pressure) for 2 hours. The fine white powder compound obtained corresponds to 3-ammoniopropylsulfate (**2**) (18.27 g, 118 mmol, 79% yield).



White solid; mp 196-198 °C; IR (ATR): 3123, 3066, 2974, 1622, 1527, 1192, 1166, 1030 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.68 (s, 3H, NH_3); 3.82 (t, J = 6.1 Hz, 2H, NH_3CH_2), 2.88-2.83 (m, 2H, SO_4CH_2), 1.84-1.77 (m, 2H, $NH_3CH_2CH_2$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 63.4 (CH_2), 36.9 (CH_2), 27.3 (CH_2).

6.3. SYNTHESIS OF 1,3-THIAZINANE-2-THIONE (3)

An oven-dried single-necked 250 mL round-bottomed flask, equipped with a 4 cm magnetic stir bar, was charged with 3-ammoniopropylsulfate (18.27 g, 118 mmol, 1 equiv) and 15 mL of absolute ethanol. The mixture was stirred for a couple of minutes at room temperature. Then, neat carbon disulfide (9.25 mL, 153 mmol, 1.3 equiv) was rapidly added using a syringe.

Meanwhile, separately, a KOH solution was prepared. KOH beads (14.91 g, 265 mmol, 2.2 equiv) were weighed in a 250 mL conical flask equipped with a 4 cm magnetic stirrer. A solution of ethanol/water 1:1 (100 mL) was added to the flask and the mixture was stirred at room temperature until all the KOH dissolved. The mixture was transferred to a 250 mL pressure relieved addition funnel previously attached to the 250 mL round-bottomed flask. The pressure relieved addition funnel was sealed with a rubber septum and the system was purged with N_2 flow for 5 minutes. Then, a N_2 filled balloon was attached to the rubber septum. The KOH solution was added dropwise to a round-bottomed flask over 30 minutes at room temperature. The formation

of a white precipitate and a strong green/black solution was observed. The addition funnel was replaced by a reflux condenser sealed with a rubber septum and an N_2 balloon was attached to it. The reaction mixture was heated to reflux (70 °C) for 1 hour, under N_2 atmosphere. The fluffy white precipitate obtained was left in the refrigerator overnight.

The mixture was filtered using a 70 mm diameter Number 3 glass filter funnel with a Buchner setup. The flask was rinsed with deionized cold water and the washings were added to the filter funnel. A part of the fluffy white precipitate was filtrated with the solution in the receiving flask, so it was changed and filtrated again. The white fluffy precipitated was dried in vacuo for 15 minutes. The receiving flask was changed again for a new one and then the solid was cleaned with dichloromethane a few times, each time breaking up the solids with a spatula and mixing before applying the vacuum. This organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure on a rotatory evaporator (40 °C). A pure crystalline powder of 1,3-thiazinane-2-thione was obtained (1.20 g).

The remaining solid from the filter funnel was transferred to a 250 mL round-bottomed flask equipped with a 4 cm magnetic stir bar. Then, 150 mL of dichloromethane were charged to the flask. A reflux condenser sealed with rubber septum was attached to the flask and the system was purged under N_2 atmosphere for a couple of minutes. Then a N_2 charged balloon was attached to the rubber septum. The solution was heated to reflux and stirred over 1 hour. Then it was filtered with a 70 mm diameter Number 3 glass filter funnel with a Buchner setup whilst warm. The solid was washed with dichloromethane, each time breaking up the solids with a spatula and mixing thoroughly before applying the vacuum. The filtrates were dried with $MgSO_4$, filtered, and concentrated under reduced pressure on a rotatory evaporator (40 °C). The second portion of pure 1,3-thiazinane-2-thione was obtained (4.88 g). The combined products weigh 6.08 g (39% overall yield).

Crystalline white solid; m.p. 130-133 °C; R_f 0.3 (hexane/EtOAc 6:4); IR (ATR): 3164, 3088, 2946, 1565, 1461, 1309, 1226, 1154, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.70 (br s, 1H, N<u>H</u>), 3.50-3.46 (m, 2H, NHC<u>H</u>$_2$), 3.01-2.98 (m, 2H, SC<u>H</u>$_2$), 2.21-2.16 (m, 2H, NHCH$_2$C<u>H</u>$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 194.6 (C); 44.3 (CH_2), 30.0 (CH_2), 20.5 (CH_2); HRMS (+ESI) *m/z* calc. For $C_4H_8NS_2$ $[M + H]^+$ 134.0093, found 134.0093.

6.4. SYNTHESIS OF *N*-ACYL-1,3-THIAZINANE-2-THIONE AND *N*-ACYL-1,3-THIAZOLIDINE-2-THIONE

6.4.1. Acylation with acid chlorides. General procedure

An oven-dried single-necked 25 mL round-bottomed flask, equipped with a magnetic stir bar, was charged with 1,3-thiazinane-2-thione or 1,3-thiazolidine-2-thione (1 equiv). The system was flushed with N_2 and an N_2 filled balloon was left attached to the system. The flask was charged with anhydrous dichloromethane (5 mL), immersed in an ice bath, and stirred for a few minutes. Distilled triethylamine (1.3 equiv) was added dropwise. The solution was stirred for a few minutes. Afterward, acyl chloride (1.2 equiv) was added dropwise. The ice bath was removed, and the reaction was warmed up to room temperature and was left stirring until apparent completion, followed by TLC. On apparent completion, the reaction mixture was cooled with an ice bath and quenched with a saturated solution of NH_4Cl (5 mL) and left to stir for a few minutes.

The mixture was rinsed with 20 mL of water and extracted with dichloromethane (4x10 mL). The combined organic extracts were washed with 2 M NaOH (60 mL), dried over $MgSO_4$, and filtered. The organic solution was dried with $MgSO_4$ and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography column on silica gel to obtain the pure *N*-acyl-1,3-thiazinane-2-thione or *N*-acyl-1,3-thiazilidine-2-thione.

6.4.2. Acylation with carboxylic acids. General procedure

An oven-dried single-necked 25 mL round-bottomed flask, equipped with a magnetic stir bar, was charged with 1,3-thiazinane-2-thione or 1,3-thiazolidine-2-thione (1 equiv), EDC·HCl (1.3 equiv) and DMAP (0.2 equiv). The system was flushed with N_2 and an N_2 filled balloon was left attached to the system. The flask was charged with anhydrous dichloromethane (10 mL), immersed in an ice bath, and stirred for a few minutes. Then, the carboxylic acid (1.2 equiv) was added dropwise. The reaction was warmed up to room temperature and it was followed by TLC. On apparent completion, it was quenched with 5 mL of a saturated solution of NH_4Cl.

The reaction mixture was rinsed with 20 mL of water and extracted with dichloromethane (3x8 mL). The resulting organic solution was rinsed with 35 mL of Et_2O and washed with 2M NaOH (3x25 mL) and with 2M HCl (3x25 mL). Then the organic phase was dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure on a rotatory evaporator. The resulting crude

was purified by flash chromatography column on silica gel to obtain the pure *N*-acyl-1,3-thiazinane-2-thione or *N*-acyl-1,3-thiazilidine-2-thione

6.4.3. Acylation with carboxylic acids activated as acyl chlorides. General procedure

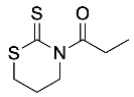
An oven-dried single-necked 25 mL round-bottomed flask, equipped with a magnetic stir bar, was charged with carboxylic acid (1 equiv). The system was flushed with N_2 and an N_2 filled balloon was left attached to the system. The flask was charged with anhydrous dichloromethane (15 mL). Then, two drops of DMF were added dropwise and the mixture was immersed in an ice bath and stirred for a few minutes. Then, oxalyl chloride (1.2 equiv) was added dropwise. Then, the reaction mixture was warmed up to room temperature and stirred overnight. Afterwards, the volatiles were removed under reduced pressure.

A solution of 1,3-thiazinane-2-thione or 1,2-thizolidine-2-thione (1 equiv) in anhydrous CH_2Cl_2 was immersed in an ice bath and stirred for a few minutes. Distilled triethylamine (1.3 equiv) was added dropwise. The solution was stirred for a few minutes. Afterwards, the acyl chloride previously prepared was added dropwise with a cannula. The ice bath was removed, and the reaction was warmed up to room temperature and left stirring until apparent completion, followed by TLC. The resulting reaction mixture was cooled with an ice bath and quenched with a saturated solution of NH_4Cl (5 mL) and left to stir for a few minutes.

The mixture was rinsed with 20 mL of water and extracted with dichloromethane (4x10 mL). The combined organic extracts were washed with 2 M NaOH (3x20) and 2M HCl (3x20 mL), dried over $MgSO_4$, and filtered. The solution was concentrated under reduced pressure. on a rotatory evaporator. The resulting crude was purified by flash chromatography column on silica gel to obtain the pure *N*-acyl-1,3-thiazinane-2-thione or *N*-acyl-1,3-thiazilidine-2-thione

6.4.4. *N*-Propanoyl-1,3-thiazinane-2-thione (5)

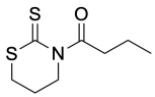
Following the general procedure 3.1, 1,3-thiazinane-2-thione (669 mg, 5 mmol, 1 equiv) was dissolved in 5 mL of anhydrous dichloromethane. Then, distilled triethylamine (0.9 mL, 6.5 mmol, 1.3 equiv) and propionyl chloride (0.52 mL, 6 mmol, 1.2 equiv) were added. The solution was stirred for 2 hours and quenched with 5 mL of NH_4Cl and left stirring overnight. The organic phase was extracted, dried, filtered and concentrated under reduced pressure (following the general procedure 3.1.). The obtained crude was purified by flash chromatography (90:10 hexanes/ethyl acetate). A yellow oil was obtained (616 mg, 65% yield).



Yellow oil; R_f: 0.3 (hexanes/EtOAc 8:2); IR (ATR): 2974, 2933, 2873, 1698, 1470, 1347, 1302, 1289, 1125, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.94-3.91 (m, 2H, NCH_2), 3.09 (q, *J* = 7.3 Hz, 2H, $COCH_2$), 3.05 (t, *J* = 6.7 Hz, 2H, SCH_2), 2.28-2.22 (m, 2H, SCH_2CH_2), 1.22 (t, *J* = 7.3 Hz, 3H, $COCH_2CH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 202.8 (C), 178.9 (C), 46.4 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 22.8 (CH_2), 10.0 (CH_3).

6.4.5. *N*-Butanoyl-1,3-thiazinane-2-thione (6)

Following the general procedure 3.1, 1,3-thiazinane-2-thione (669 mg, 5 mmol, 1 equiv) was dissolved in 5 mL of anhydrous dichloromethane. Then, distilled triethylamine (0.9 mL, 6.5 mmol, 1.3 equiv) was added. The solution was left stirring for 5 minutes. Butyryl chloride (0.6 mL, 6 mmol, 1.2 equiv) was added dropwise over 5 minutes. The solution was left stirring 72 hours. The reaction was followed by TLC. On apparent completion the reaction was quenched with 5 mL of a saturated solution of NH_4Cl and left stirring for 5 minutes. The reaction mixture was extracted, dried, filtered and concentrated under reduced pressure (following the general procedure 3.1.). The obtained crude was purified by flash chromatography (90:10 hexanes/Ethyl acetate) and concentrated under reduced pressure. A yellow oil was obtained (711 mg, 70% yield).

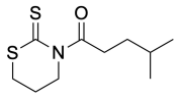


Yellow oil; R_f: 0.3 (hexanes/EtOAc 8:2); IR (ATR): 1705, 1472, 1306, 1287, 1133, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.94-3.91 (m, 2H, NCH_2), 3.07-3.01 (m, 4H, SCH_2, $COCH_2$), 2.28-2.23 (m, 2H, SCH_2CH_2), 1.79-1.69 (m, *J* = 7.4, 2H, $COCH_2CH_2$), 0.95 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 203.4 (C), 177.9 (C), 46.3 (CH_2), 41.0 (CH_2), 32.1 (CH_2), 23.0 (CH_2), 19.6 (CH_2), 13.6 (CH_3).

6.4.6. *N*-(4-Methylpentanoyl)-1,3-thiazinane-2-thione (7)

Following the general procedure 3.2, 1,3-thiazinane-2-thione (668 mg, 5 mmol, 1 equiv), EDC·HCl (1.246 g, 6.5 mmol, 1.3 equiv) and DMAP (132 mg, 1 mmol, 0.2 equiv) were dissolved in 10 mL of anhydrous dichloromethane. Then, 4-methylpentanoic acid (0.75 mL, 6 mmol, 1.2 equiv) were added dropwise and the reaction mixture was stirred for 72 h. The reaction was followed by TLC. On apparent completion, the reaction was quenched with 5 mL of a saturated solution of NH_4Cl. The reaction mixture was extracted, washed, dried, filtered and concentrated under reduced pressure (following the general procedure 3.2.). The obtained crude was purified

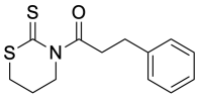
by flash chromatography (80:20 hexanes/EtOAc) twice. A yellow oil was obtained (313 mg, 27% yield).



Yellow oil; R_f: 0.3 (hexanes/EtOAc 8:2); IR (ATR): 2953, 2927, 2867, 1702, 1287, 1133, 1107, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.93-3.90 (m, 2H, NCH_2), 3.09-3.01 (m, 4H, SCH_2, $COCH_2$), 2.28-2.21 (m, 2H, SCH_2CH_2), 1.64-1.54 (m, 3H, CH, $COCH_2CH_2$), 0.90 (d, *J* = 6.3 Hz, 6H, CH_3, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 203.35 (C), 178.58 (C), 46.60 (CH_2), 37.37 (CH_2), 34.92 (CH_2), 32.20 (CH_2), 27.86 (CH), 23.10 (CH_2), 22.41 (CH_3); HRMS (+ESI) *m/z* calcd for $C_{10}H_{18}NOS_2$ $[M + H]^+$ 232.0824, found 232.0826.

6.4.7. *N*-(3-Phenylpropanoyl)-1,3-thiazolidine-2-thione (8)

Following the general procedure 3.2, 1,3-thiazinane-2-thione (668 mg, 5 mmol, 1 equiv), EDC·HCL (1.246 g, 6.5 mmol, 1.3 equiv) and DMAP (129 mg, 1 mmol, 0.2 equiv) were dissolved in 10 mL of anhydrous dichloromethane. Then 3-phenylpropanoic acid (0.66 mL, 6 mmol, 1.2 equiv) were added dropwise. The solution was stirred for 48 h. The reaction was followed by TLC. On apparent completion, the reaction was quenched with 5 mL of a saturated solution of NH_4Cl. The reaction mixture was extracted, washed, dried, filtered and concentrated under reduced pressure (following the general procedure 3.2). The obtained crude was purified by flash chromatography (60:40 CH_2Cl_2/Hexanes). A yellow oil was obtained (728 mg, 55% yield).



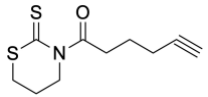
Yellow oil; R_f: 0.44 (Hexanes/EtOAc 8:2); IR (ATR): 1816, 1755, 1731, 1682, 1603, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.30-7.26 (m, 2H, ArH), 7.21-7.18 (m, 3H, ArH), 3.77-3.74 (m, 2H, NCH_2), 3.39 (t, *J* = 7.4, 2H, $COCH_2$), 3.04 (t, *J* = 7.4, 2H, $COCH_2CH_2$), 2.83 (t, *J* = 6.8, 2H, SCH_2), 2.02-1.96 (m, 2H, SCH_2CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 203.8 (C), 177.4 (C), 140.3 (C), 128.5 (CH), 126.3 (CH), 46.3 (CH_2), 40.7 (CH_2), 32.6 (CH_2), 31.8 (CH_2), 22.8 (CH_2).

6.4.8. *N*-(5-Hexynoyl)-1,3-thiazolidine-2-thione (9)

Following the general procedure 3.3, 5-hexynoic acid (0.757mL, 7 mmol) was dissolved in 15 mL of anhydrous CH_2Cl_2 and cooled to 0 ºC in an ice bath. Then Oxalyl chloride was (0.72 mL, 8.4 mmol) added dropwise and then, two drops of DMF were added. The solution was left stirring

4 h at room temperature. The volatiles were removed under reduced pressure to obtain pure 5-hexynoyl chloride.

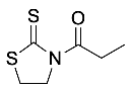
Then, 1,3-thiazinane-2-thione (669 mg, 5 mmol, 1 equiv) was dissolved in 15 mL of anhydrous CH_2Cl_2 and cooled to 0 ºC in an ice bath. Triethylamine (0.9 mL, 6.5 mmol, 1.3 equiv) was added dropwise. Then, 5-hexynoyl chloride was added. The solution was left stirring for 48 h. The reaction was quenched with 5 mL of a saturated solution of NH_4Cl. The reaction mixture was extracted, washed, dried, filtered and concentrated under reduced pressure (following the general procedure 3.3). The obtained crude was purified by flash chromatography (hexanes/EtOAc from 90:10 to 70:30). A yellow oil was obtained (657 mg, 58% yield).



Yellow oil; R_f: 0.4 (Hexanes/EtOAc 8:2); IR (ATR): 3284, 3132, 3039, 2922, 1813, 1742, 1702, 1123, 1040, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.94-3.92 (m, 2H, NCH_2), 3.21 (t, *J* = 7.3, 2H, $COCH_2$), 3.03 (t, *J* = 6.8, 2H, SCH_2), 2.29-2.22 (m, 4H, SCH_2, $COCH_2CH_2CH_2$), 1.99-1.85 (m, 3H, $COCH_2CH_2$, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 203.96 (C), 177.19 (C), 83.35 (C), 69.44 (CH), 46.43 (CH_2), 37.89 (CH_2), 32.20 (CH_2), 24.76 (CH_2), 23.16 (CH_2), 17.85 (CH_2); HRMS (+ESI) *m/z* calcd for $C_{10}H_{13}NOS_2$ $[M + H]^+$ 228.0511, found 288.0512.

6.4.9. *N*-Propanoyl-1,3-thiazolidine-2-thione (10)

Following the general procedure 3.1, 2-thiazolidine-2-thione (596 mg, 5 mmol, 1 equiv) was dissolved in 5 mL of anhydrous dichloromethane. Then, distilled triethylamine (0,9 mL, 6.5 mmol, 1.3 equiv) and propionyl chloride (0.52 mL, 6 mmol, 1.2 equiv) were added. The solution was stirred for 4 hours and quenched with 5 mL of a saturated solution of NH_4Cl. The organic phase was extracted, dried, filtered and concentrated under reduced pressure (following the general procedure 3.1.). The obtained crude was purified by flash chromatography (90:10 hexanes/EtOAc) and concentrated under reduced pressure. A yellow oil was obtained (724 mg, 83% yield).

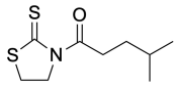


Yellow oil; R_f: 0.3 (hexanes/EtOAc 9:1); IR (ATR): 2978, 2935, 1692, 1455, 1396, 1347, 1264, 1147, 1042, 1026, 1000 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.60 (t, *J* = 7.5 Hz, 2H, NCH_2), 3.31-3.24 (m, 4H, SCH_2, $COCH_2$), 1.19 (t, *J* = 7.2 Hz, 3H, CH_3).

6.4.10. *N*-(4-Methylpentanoyl)-1,3-thiazolidine-2-thione (11)

Following the general procedure 3.3, 4-methylpentanoic acid (0.75 mL, 6 mmol) was dissolved in 15 mL of anhydrous CH_2Cl_2 and cooled to 0 ºC in an ice bath. Then Oxalyl chloride was (0.62 mL, 7.2 mmol) added dropwise and then, two drops of DMF were added. The solution was left stirring overnight at room temperature. The volatiles were removed under reduced pressure to obtain pure 4-methylpentanoic chloride.

Afterwards, 1,3-thiazolidine-2-thione (596 mg, 5 mmol, 1 equiv) was dissolved in 15 mL of anhydrous CH_2Cl_2 and cooled to 0ºC in an ice bath. Triethylamine (0.9 mL, 6.5 mmol, 1.3 equiv) was added dropwise and then, 4-methylpentanoic chloride was added. The solution was left stirring for 4 h. The reaction was quenched with 5 mL of a saturated solution of NH_4Cl. The reaction mixture was extracted, washed, dried, filtered and concentrated under reduced pressure (following the general procedure 3.3). The obtained crude was purified by flash chromatography (hexanes/EtOAc 90:10). The product was purified further with flash chromatography (hexanes/CH_2Cl_2 70:30). A yellow oil was obtained (716 mg, 65% yield).



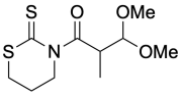
Yellow oil; R_f: 0.47 (hexanes/EtOAc 8:2); IR (ATR): 2953, 2868, 1693, 1463, 1363, 1276, 1218, 1148, 1123, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.58 (t, *J* = 7.5 Hz, 2H, $NC\underline{H_2}$), 3.30-3.24 (m, 4H, $SC\underline{H_2}$, $COC\underline{H_2}$), 1.67-1.55 (m, 3H, $COCH_2C\underline{H_2}$, $C\underline{H}$), 0.92 (d, *J* = 6.4 Hz, 6H, $C\underline{H_3}$).

6.5. FIRST ATTEMPT OF DIRECT AND CATALYZED ALKYLATION REACTION

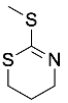
6.5.1. *N*-[(3,3-Dimethoxy-2-methylpropanoyl)]-1,3-thiazinane-2-thione (12)

An oven-dried single necked 10 mL round-bottomed flask, equipped with a magnetic stir bar, was charged with *N*-propanoyl-1,3-thiazinane-2-thione (202 mg, 1 mmol, 1 equiv) and $(Me_3P)_2NiCl_2$ (28 mg, 0.1 mmol, 10 mol%). The round-bottomed flask was sealed with a septum and the system was purged with N_2 for a few minutes. Then, a N_2-filled balloon was attached to the system. Anhydrous dichloromethane (2 mL) was added to the mixture. Then, trimethyl orthoformate (0.13 mL, 1.2 mmol, 1.2 equiv) was added. The mixture was stirred and cooled to -20 ºC with an ice/methanol bath. Then, triethylsilyl triflate (0.32 mL, 1.4 mmol, 1.4 equiv) was added and the mixture was stirred for 5 minutes. Finally, 2,6-lutidine (0.17 mL, 1.5 mmol, 1.5 equiv) was added. The resulting mixture was left stirring overnight at -20 ºC.

The reaction was quenched with a saturated solution of NH_4Cl (2 mL). The reaction mixture was extracted with CH_2Cl_2 and the flask was washed with deionized water. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure on a rotatory evaporator. The resulting residue was purified by flash chromatography column on silica gel (from CH_2Cl_2/Hexanes 50:50 to 80:20). The alkylated compound 12 was obtained as a yellow oil (47 mg, 17% yield), the methylated scaffold 13 was isolated as an oil (13 mg, 8% yield) and it was recovered *N*-propanoyl-1,3-thiazinane-2-thione (61 mg, 30% yield).



Yellow oil; R_f: 0.36 (hexanes/EtOAc 8:2); IR (ATR): 2936, 2823, 1704, 1460, 1374, 1344, 1289, 1127, 1096, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.41 (d, *J* = 8.2 Hz, 1H, C<u>H</u>$(OMe)_2$), 4.13 (dt, *J* = 13.3, 5.0 Hz, 1H, NC<u>H</u>), 3.97-3.92 (m, 1H, COC<u>H</u>), 3.51-3.44 (m, 1H, NC<u>H</u>), 3.33 (s, 3H, OC<u>H_3</u>), 3.30 (s, 3H, OC<u>H_3</u>), 3.10-2.99 (m, 2H, SC<u>H_2</u>), 2.31-2.19 (m, 2H, SCH_2C<u>H_2</u>), 1.3 (d, *J* = 6.7 Hz, 3H, COCHC<u>H_3</u>); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 201.1 (C), 181.4 (C), 107.4 (CH), 55.2 (CH_3), 52.0 (CH_3), 47.6 (CH_2), 45.8 (CH), 31.8 (CH_2), 22.5 (CH_2), 13.8 (CH_3).



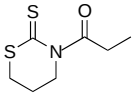
Oil; R_f: 0.14 (hexanes/EtOAc 8:2); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.76-3.74 (m, 2H, NC<u>H_2</u>), 3.02-2.99 (m, 2H, SC<u>H_2</u>), 2.38 (s, 3H, SC<u>H_3</u>), 1.94-1.88 (m, 2H,SCH_2CH_2).

7. CONCLUSIONS

The first objective of this project was to prepare large quantities of 1,3-thiazinane-2-thione. This scaffold has been synthetized at a scale of 120 mmol and it was obtained a 39% overall yield, very near to the described previously by the group (55%).

39%

The second objective was to perform various acylation reactions with different electrophiles to obtain *N*-acyl-1,3-thiazinane-2-thione and *N*-acyl-1,3-thiazolidin-2-thiones that they will be used as starting materials for further reactions. As different methodologies were performed, we obtained very different yields for each product, some were very low but for most of the compounds were obtained with good yields.



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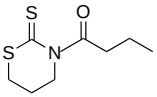

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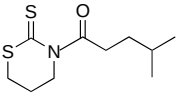

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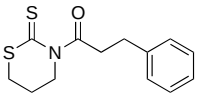

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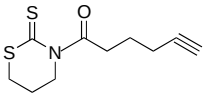

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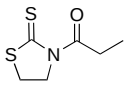

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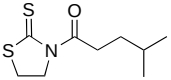

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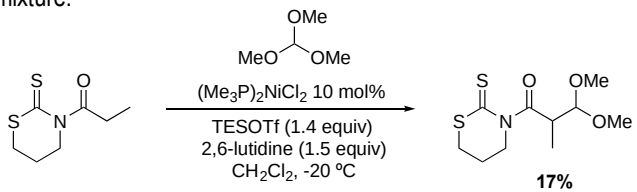
Finally, one attempt of a direct and catalyzed alkylation reaction with methyl orthoformate activated with TESOTf was performed at 1 mmol scale using the *N*-propanoyl-1,3-thiazinane-2-thione previously synthetized. However, the reaction afforded low conversion (53%) and the *N*-[(3,3-dimethoxy-2-methylpropanoyl)]-1,3-thiazinane-2-thione was obtained in a very low yield (17%) as racemic mixture.



17%

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9. ACRONYMS

ATR	Attenuated Total Reflectance
br	Broad
Bu_2BOTf	Dibutylboron triflate
$CDCl_3$	Deuterated chloroform
δ	Chemical shift
d.r.	Diastereomeric ratio
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
E^+	Electrophile
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
Equiv	Equivalent(s)
ESI	Electrospray ionization
Et	Ethyl
Et_3N	Triethylamine
EtOAc	Ethyl acetate
HRMS	High resolution mass spectrometry
iBu	Isobutyl
IR	Infrared spectroscopy
LA	Lewis acid
LDA	Lithium diisopropylamide
Me	Methyl

m.p.	Melting point
NaHMDS	Sodium bis(trimethylsilyl)amide
NMR	Nuclear magnetic resonance
Ph	Phenyl
ppm	Parts per million
r.t.	Room temperature
R_f	Retention factor
TESOTf	Triethylsilyl trifluoromethanesulfonate
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride