ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ

ΤΜΗΜΑ ΤΕΧΝΟΛΟΓΙΚΩΝ ΚΑΙ ΘΕΤΙΚΩΝ ΣΠΟΥΔΩΝ

ΤΜΗΜΑ ΧΗΜΕΙΑΣ

Study of the Asinger Reaction and its combination with other multicomponent reactions (MCRs)

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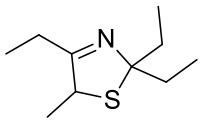
Abstract

The aim of this project was the synthesis of 3-thiazolines from the modified Asinger Reaction, the combination of the Asinger/Ugi reaction using as starting materials the synthesized 3-thiazoline ring and the cyclization of the Ugi product with NaH. However, as a result of the pandemic Covid-19 it wasn't possible the completion of the experimental research, therefore, it was carried out bibliographic study of the reaction. The aim of the bibliographic study was to write a review about the history, the different types of reactions and the post modification of the Asinger Reaction. Some points of the review will also be mentioned in the present project.

1. Introduction

Multicomponent Reactions (MCRs) are reactions where more than two starting materials react to form a product. The product includes all the atoms of the educts.[1] MCRs can categorize for example, according to the reactions mechanisms, the components that involved, or their intrinsic variability.[2] Depending, on the number of the components MCRs can be classified as 3CR, 4CR, etc. However, the main classification of the MCRs is based on the isocyanide scaffold. So, there are two categories; the isocyanide-based MCRs (IMCRs) and the non isocyanide-based MCRs (non IMCRs). In the IMCRs are included mainly the Ugi reaction and its variations. In the non IMCRs are included a diversity of reactions such as the Mannich, Gewald and Asinger reaction, etc.

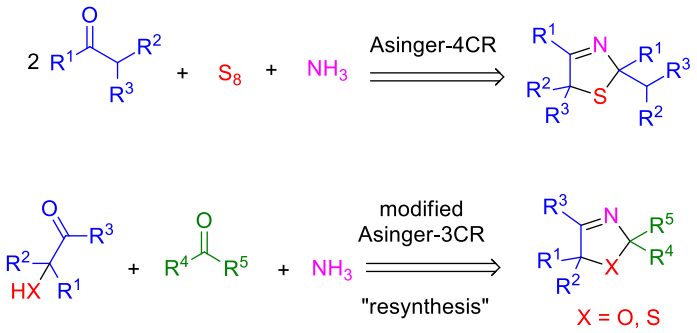
Friedrich Asinger (1907-1999) after years in exile in the Soviet Union and studies on rocket fuels in 1956 illustrated the structure of a novel one-pot three component reaction. It was the reaction of elemental sulfur, gaseous ammonia and penta-3-one at room temperature in normal pressure.[3] Asinger, just had discovered access to the Δ^3-thiazolines (Figure 1), which until that time only one compound of this class had been reported, that was the degradation product from uscharin.[4] The Asinger reaction belongs to the non IMCRs and is one of the rare reactions of elemental sulfur with other components in Organic Chemistry. Other reactions that are use sulfur are the Willgerodt-Kindler[5] and Gewald reaction.[6]



01, 85%
(bp 96°, 12 Torr)

Figure 1. The first 3-thiazoline discovered by Asinger.

There are mainly two variations of the Asinger Reaction, which both of them were discovered from Asinger. The first variation is the classical Asinger four-component reaction ("pseudo" 4CR with the collaboration of two molecules of the same oxocomponent). The second variation is the modified Asinger three-component reaction, known as "resynthesis" which is mainly based on the reaction of α-sulfanyl ketones and a second oxocomponent (Scheme 1).



Scheme 1. The classical 4CR and modified 3CR Asinger Reaction.

The 3-thiazolines can be found as intermediates in a plethora of pharmaceutically active molecules.[4] They can also be converted into a large number of different products by functionalizing their reactive C=N double bond[7,8,9]. Usually, the 3-thiazolines are used as precursors for the synthesis of other active molecules.[10–14]
The alkyl-substituted 3-thiazolines usually are colorless liquids with fusty odor. As the molecular weight of the scaffold increases, the odor becomes similar to that of terpene and finally almost completely disappears.[8] A remarkable exception is the 3-thiazoline that is synthesized using as starting material the cyclohexanone. This scaffold is crystalline and almost odorless.[15] However, the 3-thiazolines that are formed by cyclopentanone[16] and from the reaction of α-mercaptocyclopentanone with cyclopentanone and ammonia[16] are again liquids. The 3-thiazolines that are formed from aromatic substrates are frequently obtained in a crystalline form.[8] Usually, the heterocyclic scaffolds have melting point between 90 and 150 °C. It is worth mentioning that the 3-thiazolines are insoluble in water but soluble in alcohols, chlorinated hydrocarbons, ether, benzene and petroleum ether.[8]

2. Asinger Reaction

In general, the Asinger MCR especially the modified one has a great scope, giving rise but not limited to diverse thiazoline derivatives. In Figure 2 a brief description of the different components that are used are presented

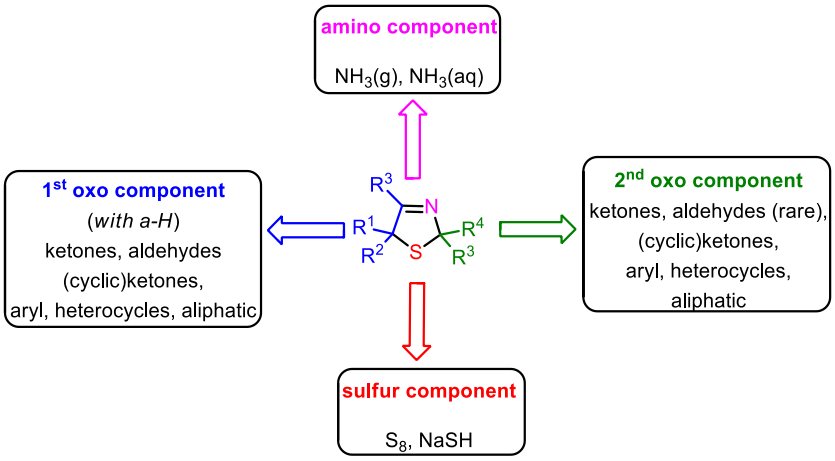
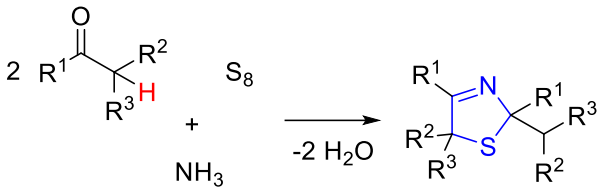


Figure 2. The oxo, sulfur and amino components used for the synthesis of the 3-thiazolines.

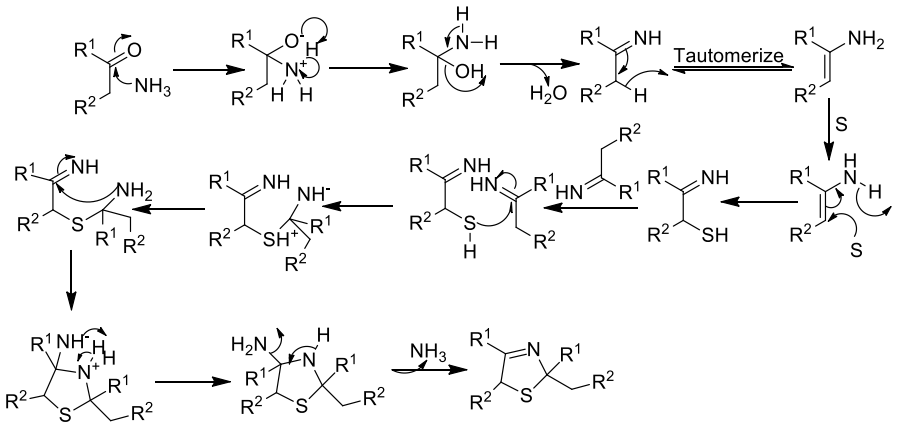
2.1 Asinger classical four-component reaction (A-4CR)

The combination of elemental sulfur, gaseous ammonia and a variety of carbonyl compounds with at least one α-H atom to the carbonyl group yields substituted Δ^3-thiazolines, in good yields.[3,8] (Scheme 2)



Scheme 2. The 3-thiazolines that arise from the A-4CR.

F. Asinger, proposed a mechanism that contained two steps; the first step is an α-thiolation catalyzed by an amine for the formation of an α-sulfhydryl ketone. The second step is an α-aminoalkylation of an SH acid and subsequent stabilization by a ring closure with elimination of water. However, there were two limitations with that mechanism. Firstly, NH_3 is not strong enough to abstract an α-proton from the ketone and moreover there were not given any details about the formation of the final 3-thiazolines. Therefore, an alternative mechanism is proposed, as shown in Scheme 3.[8,17]



Scheme 3. The mechanism followed for the synthesis of the 3-thiazolines.

A typical experimental procedure for the synthesis of A-4CR 3-thiazolines is at it follows; excess of ammonia is added into a well-stirred suspension of ketone and sulfur at room temperature. The temperature often rises to about 60°C, the reaction mixture then becomes brown, while the reaction is completed after 3-4 hours.[8] Depending on the ketone that is used the experimental conditions may vary in order for the product to be produced at maximum yields. For example, when the oxocomponent is the methyl isopropyl ketone[18] the reaction is carried out in anhydrous benzene. In the case of the 7-tridecanone[19] the reaction is carried out in pyridine at 60°C. Generally, the Asinger reaction is depended of the exact nature of the oxocomponent (pKa, lipophilicity, solubility, etc.). The diversity that can therefore be achieved is based on the oxocomponent. The variety of them than can be used

are aliphatic, alicyclic, mixed aliphatic-alicyclic and heretocyclic ketones with at least one α-H atom to the carbonyl group.[8]

The aliphatic ketones that have been used are mainly acyclic such 3-pentanone[20], ethyl-6-oxoheptanoate[21] (compounds **2** and **3,** respectively) or cyclic such as cyclohexanone[15] and cyclooctanone[22] (compounds **4** and **5**, respectively Figure 3). Also, the heterocyclic ketones 1-thia-4-cyclohexanone[22] and 1-methyl-4-piperidone[23] have been reported as substrates in the A-4CR.

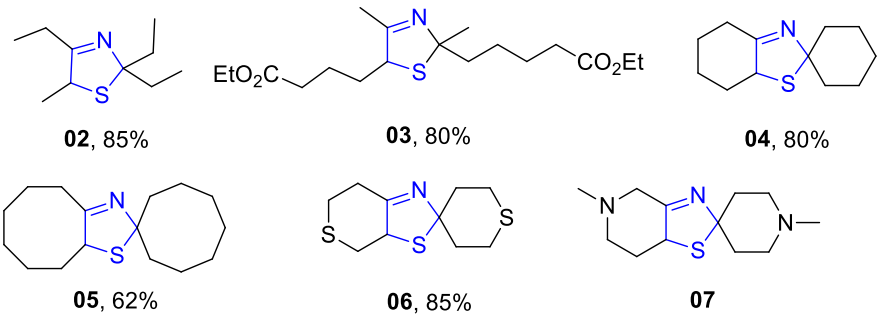
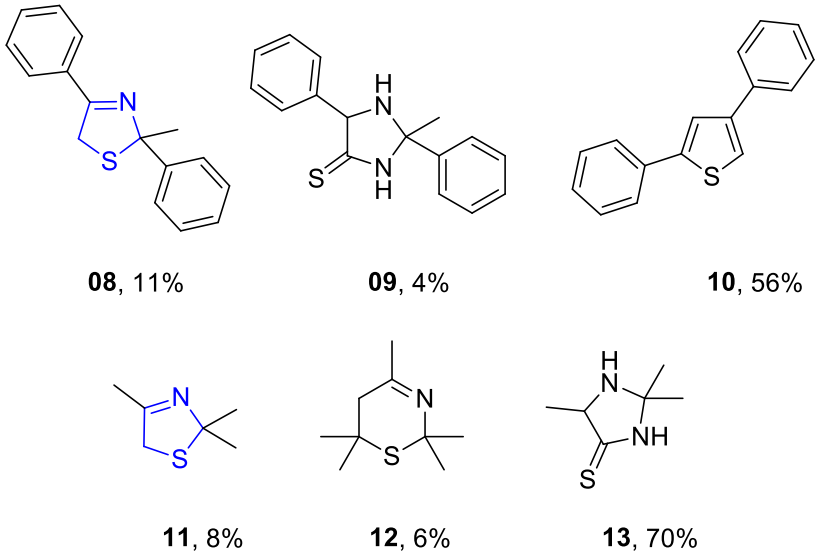


Figure 3. Some of the 3-thiazolines synthesized by an A-4CR.

Ketones with α-methyl group, due to di- or trithiolation, give multiple adducts along with the expected ones. For example, the classical Asinger reaction of acetophenone[24] besides the Asinger thiazoline (**8**), the 2-methyl-2,4-diphenyl-3-imidazoline-5-thione (**9**)[8,24–26] and the thiophene (**10**)[8] are also obtained as minor adducts.[4] Under optimized conditions all compounds could be obtained in good yields. refs Other interesting example is acetone, as the Asinger product (**11**) is obtained only in 8% yield together with the by-products 2,2,4,6,6-pentamethyl-1,3-dihydrothiazine (6% yield, **12**). Under optimized conditions, the 2,2,4-trimethyl-3-imidazoline-5-thione (**13**) is formed in yields up to 70%, as a result of trithiolation.[4,8,27]

Reaction with asymmetric ketones with at least one thiolatable H atom in each of the positions α to the carbonyl group can give two isomeric α-mercapto ketones on thiolation. The ring-closure step thereafter produces two isomeric Δ^3-thiazolines. Studies on asymmetric ketones had shown that the direction of the thiolation was strongly dependent of the temperature. For example, in 20 ^{o}C: CH_2>>CH>CH_3 and in 80 ^{o}C: CH_2>CH_3>CH.[8,28]

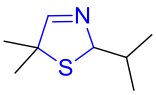


08, 11% **09**, 4% **10**, 56%

11, 8% **12**, 6% **13**, 70%

Figure 4. The products and by-products formed from the A-4CR of acetophenone and acetone.

However, the classical Asinger thiazoline synthesis has its restrictions, for example, cyclopentanone give polymeric by-products. Also, it has not been yet described the formation of Δ^3-thiazolines from camphor, stearone and isophorone.[8,29]
Other carbonyl compounds such as keto acids and their esters produce 3-thiazolines only when the keto group and the carbonyl group are so far apart that they do not affect each other (e.g. 6-oxohexanecarboxylic acid and its esters).[21]
The Asinger reaction with aldehydes using the same conditions with ketone gives products in poor yields (10% maximum). However, a remarkable exception is isobutyraldehyde, which reacts very smoothly and forms the 2-isopropyl-5,5-dimethyl-3-thiazoline, but in the case of other aldehydes 2,3,5-trialkylated pyridines are formed as by-products in yields 20-35%[8]. It is mentioning that 2-isopropyl-5,5-dimethyl-3-thiazoline is the starting material for the Asinger Reaction of D-penicillamine[30,31] further, analysis will presented below.



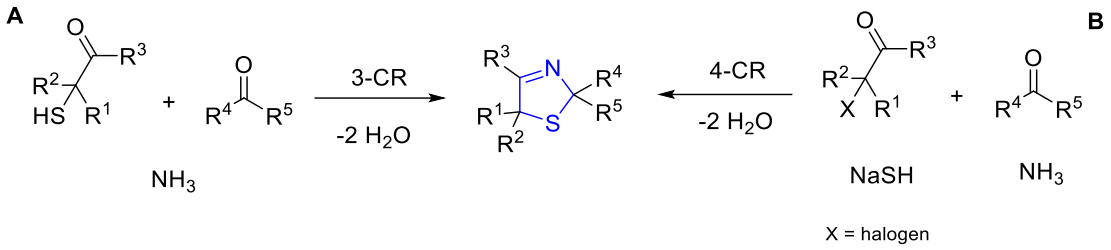
14, 80%

Figure 5. 3-thiazoline is the precursor of the D-penicillamine.

2.2 Modified Asinger ("resynthesis") reaction

The modified Asinger reaction is based on the reaction of α-mercapto-ketones or aldehydes (either isolated or *in situ*) with ammonia and an oxocomponent. This class of the Asinger reaction includes greatly the diversity and complexity of the produced scaffolds and overcomes the restrictions of the classical Asinger reaction.[4] In the "resynthesis", generally any α-mercapto oxocomponent, ammonia and carbonyl compound that has a variety of functional substituents can be utilized and because of that today this is the most used variation of the Asinger reaction (Scheme 4).

The α-mercapto oxocomponents can be accessed by two different methods. At first, they can either be prepared and isolated by the reaction of α-halogeno carbonyl compound with sodium hydrogen sulfide in alcoholic solution (Scheme 4A),[32,33] or can either be formed *in situ* in a four component MCR setup (Scheme 4 B). Otherwise, hydrolysis of any 3-thiazoline derivative can produce the desired a-mercapto aldehyde or ketone which can be further be converted to another 3-thiazoline derivative via a new or second Asinger multicomponent reaction.[34]



Scheme 4. Methods to access the α-mercapto oxocomponents.

A typical experimental procedure followed for the synthesis of 3-thiazolines using as starting materials sodium hydrogen sulfide hydrate, acetone, 2-chloro-2-methylpropanal and gaseous ammonia is; in a suspension of sodium hydrogen sulfide hydrate at dry dichloromethane a solution of acetone and 2-chloro-2-methylpropanal was added under argon atmosphere. After, that the suspension was cooled to –15°C, gaseous ammonia was added dropwise in the reaction mixture for 15 min. The suspension was warmed up to room temperature and stirred for 12 h. Water was added and the aqueous layer was extracted with three portions of dichloromethane. The combined organic layers were dried with magnesium sulfate and the solvent was removed with the help of a rotary evaporator.[35,36]

Similarly to the classical A-4CR, in the modified A-3CR is equally important the nature of the oxocomponent. The choice of the substituents is easier compared to the classical version because the α-halogeno carbonyl compounds can be easily synthesized.[37,38] It is noteworthy, that Asinger and Offermanns synthesized almost 180 3-thiazolines[8], in order to show the potential of the resynthesis. The ketones and aldehydes that they used are formaldehyde[39], propionaldehyde[29], cyclohexanecarboxaldehyde[39],butanone[40], cyclohexanone[39] and benzaldehyde.[33] Here are presented indicatively, six of them (Figure 6).

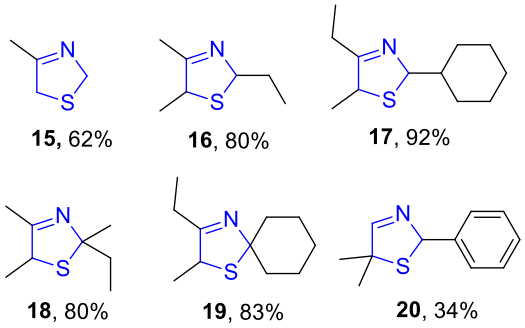


Figure 6. Some of the modified 3-thiazolines synthesized by Asinger and Offermanns.

Aliphatic ketones produce 3-thiazolines in high yields also, in the modified Asinger reaction. Furthermore, acetone and acetophenone are also used as starting materials in the "resynthesis". The cyclic ketones, cyclopentanone and cyclohexanone produce 3-thiazolines in higher yields compared to the A-4CR[8] (Figure 7). Heterocyclic ketones such as tetrahydro-*4H*-pyran-4-one and 1-thia-4-cyclohexanone have been used in both classical and modified Asinger reaction[8] (Figure 7). It is worth mentioning that the 3-thiazolines **24** and **26** didn't isolated and they were used in post modification procedures.[41,42]

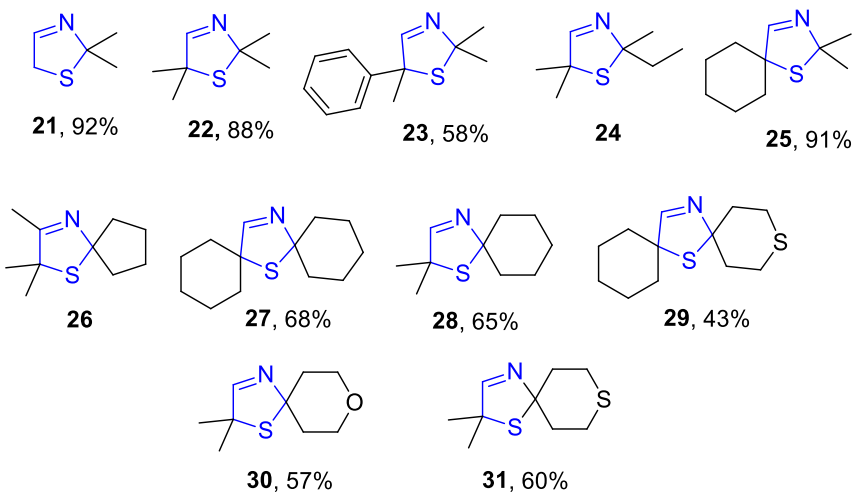


Figure 7. Some of the ketones used for the "resynthesis".

On the contrary to the classical Asinger, here aldehydes successfully participate in the reaction; aliphatic ones such as acetaldehyde, propionaldehyde[8,29] and even formaldehyde[8,39]. Moreover, pivalaldehyde,[13] cyclohexyl formaldehyde[8,39] and isobutyraldehyde[13] have also been reported. Regarding aromatic aldehydes, benzaldehyde[8,33] has been used as starting material (Figure 8).

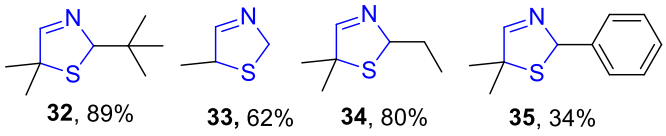


Figure 8. 3-thiazolines produced using as starting materials aldehydes.

For the synthesis of 3-thiazolines using as starting materials aldehydes[13,43,44] the experimental procedure is at follows; sodium hydrosulfide monohydrate, ammonia-solution and aldehyde are mixed and cooled to 0°C. α-Chlorinated aldehyde is dissolved in dichloromethane and added to the yellow mixture, keeping the temperature under 10°C. The reaction mixture is stirred overnight at room temperature, phases are separated, and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over magnesium sulfate; the solvent is extracted with a rotary evaporator and the crude product is purified by flash column chromatography.

Enantiomerically pure 3-thiazolines have been also synthesized using chiral carbonyl compounds such as (*R*)-citronellal (**compound 36**), tartaric acid derivative(**compound 37**)[45], protected (*R*)-glyceraldehyde (**compound 38**)[46] and a galactose derivative (**compound 39**) [47] as starting materials (**compounds 36-39,** Figure 9).

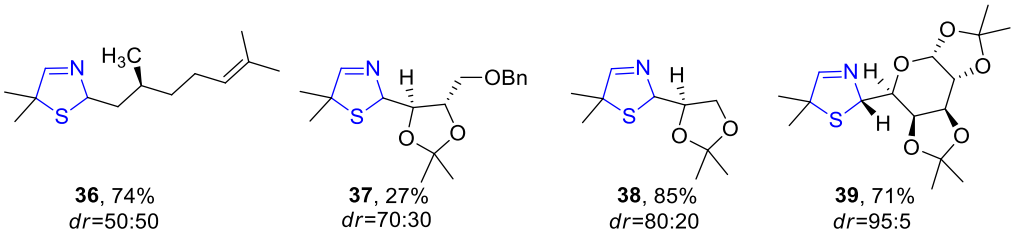


Figure 9. Some of the enantiomerically pure 3-thiazolines that have been synthesized.

In the most studies that "resynthesis" is used the α-halogenated aldehyde is the 2-chloro-2-methylpropanal[10,11,52,53,12,13,35,47–51], (*R*,*S*)-2-chloro-2-phenylpropanal,[10] 1-chlorohexanecarbaldehyde[12,48–52,54,55], 3-chloro-3-methyl-2-one,[42,41] 2-bromo-2-methylpropanal[56] or chloroacetaldehyde[44] (Figure 6-9).

The crystal structure of the 3-thiazoline bearing a galactose moiety **39** is shown below

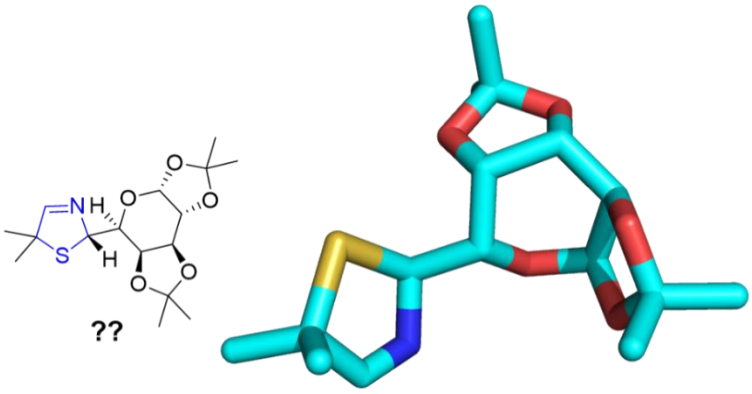


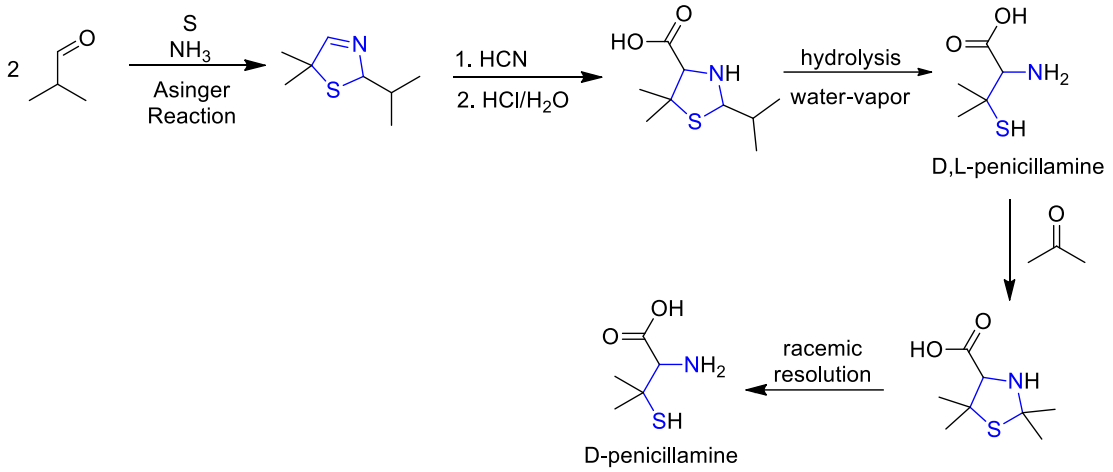
Figure 10. The X-ray structure of compound 39 (CCDC 146345).

3. Post-modification of the Asinger Reaction

3.1 Industrial synthesis of the D-penicillamine.

The most famous application of the Asinger Reaction in the industry is the synthesis of the D-penicillamine.[31] As it shown in the Scheme 5,[57] two molecules of the isobutyraldehyde react with sulfur and ammonia to provide access to the 3-thiazoline scaffold, in which the imine bond is added by hydrogen cyanide for introducing a cyano group to be converted into the carboxylic acid group with hydrolysis. The synthesized 2-isopropyl-5,5-dimethylthiazolidine-4-carboxylic acid is further

hydrolyzed with the help of a water-vapor providing access to the racemic penicillamine. The racemic penicillamine then react with acetone in order to form the 2,2,5,5-tetramethylthiazolidine-4-carboxylic acid. After, it is held racemic resolution with chiral agents such as L-lysine, (-)-norephedrine and (-)-pseudonorephedrine for the synthesis of the D-penicillamine. The L-penicillamine can be re-racemized and the aforementioned racemic resolution is repeated to give the D-penicillamine. It is worth mentioning that the Asinger reaction is a ''green'' chemical procedure that exhibits high efficiency in the use of atoms in the reagents.[58]



Scheme 5. Synthesis of the D-penicillamine.

3.2 Reduction of Thiazolidine scaffold

It is worth mentioning that some of the 3-thiazolines when they react with BF_3 produce stable adducts[8]. When the 3-thiazolines reacts with $LiAlH_4$ they can be hydrogenated (hydrogenation of the azomethine bond), and they can also form N-substituted cystamines **(40)**.[59]

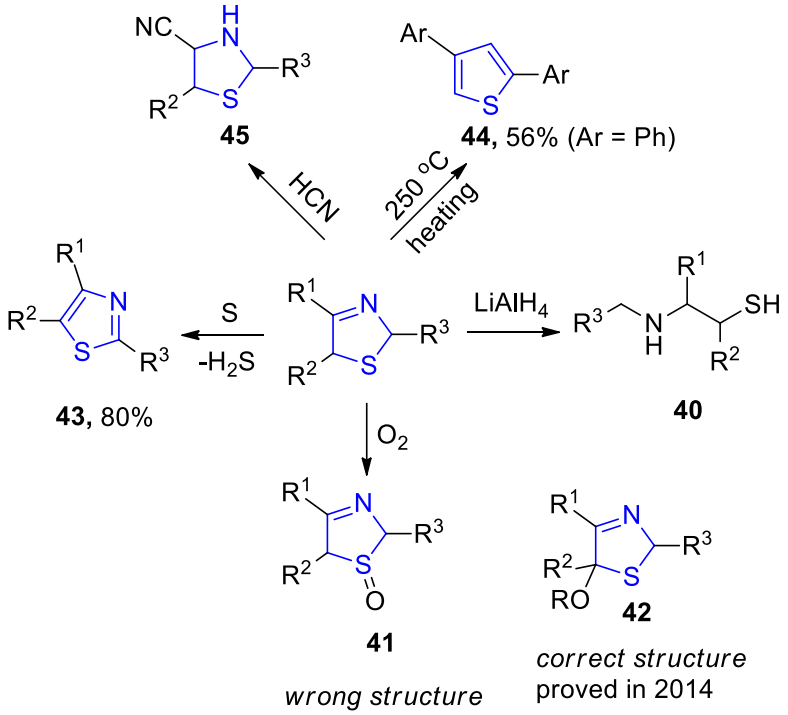
Because, 3-thiazolines are stable they can be stored for long periods without distortion. However, the derivatives from the cycloaliphatic ketones can be synthesize with air the 3-thiazoline *S*-oxides **(41)**.[22] The 3-thiazolines that are synthesized from alkylcyclohexanones and 2,2-pentamethylene-4,5-tetramethylene-3-thiazoline are used as antioxidants for polyolefins.[8] The predominance of their properties contrasted with those of other molecules that contain sulfur is because these thiazolines can be easily autoxidize to form *S*-oxides. However, the structure that Asinger found was wrong. In 2014 Brockmeyer *et al.*[60] found the correct structure (**41**) during the regioselective air oxidation of sulfides to *O,S*-acetals with the use of a bubble column starting from 3-thiazolines.

The derivatives 3-thiazolines from primary or secondary α-mercapto ketones or aldehydes, aldehydes and ammonia, which have C-H bonds in positions 2 and 5 can be dehydrogenated to thiazoles **(42)**, preferably by heating with sulfur at 130°C[61–63], $FeCl_3$, $K_3[Fe(CN)_6]$, K_2Cr_2O and hydrogen peroxide are less suitable than sulfur powder for this novel thiazole synthesis. The yields are about 80%.

It is worth mentioning that the 3-thiazolines that produced from acetophenone and ring-substituted acetophenones with sulfur and ammonia[8] can be pyrolysed by heating at 250°C for to 5 to 15 hours; the observed products are the 2,4-diarylthiophenes.[8] When the R^2 or R^3 is Ar-C_6H_5 the yield is 56% **(43)**.

When the anhydrous hydrogen cyanide reacts with the 3-thiazoline ring at room temperature the azomethine bond is hydrogenated.[64] The produced thiazolidine-4-carbonitriles **(44)** are more or less stable, depending on their purity and on the nature and number of substituents in positions 2 and 4; however, they are always stable in the form of their hydrochlorides. No relationship could be found between structure and stability. Thiazolidine-4-carbonitriles that are not quite pure decompose much more rapidly.

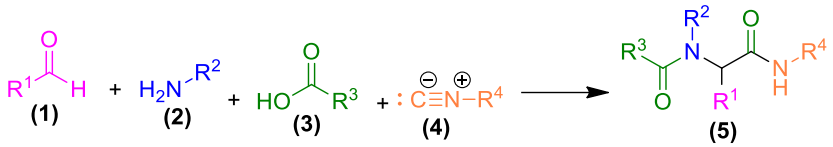
It is worth mentioning that 3-thiazolines can undergo hydrolysis with aqueous acids with formation of α-mercapto ketones or aldehydes, oxo compounds and ammonium salts (reversal ring formation).[34] The rate of hydrolysis is depending of the nature and position of the substituents of the thiazole ring.



Scheme 6. Reactions of the thiazoline ring.

4. Ugi Reaction

The Ugi Reaction was discovered by Ivar Ugi in 1959[65], and it is an isocyanide-based multicomponent reaction.[66] The reaction has a result the synthesis of an α-N-acylamino amide (Scheme 7).

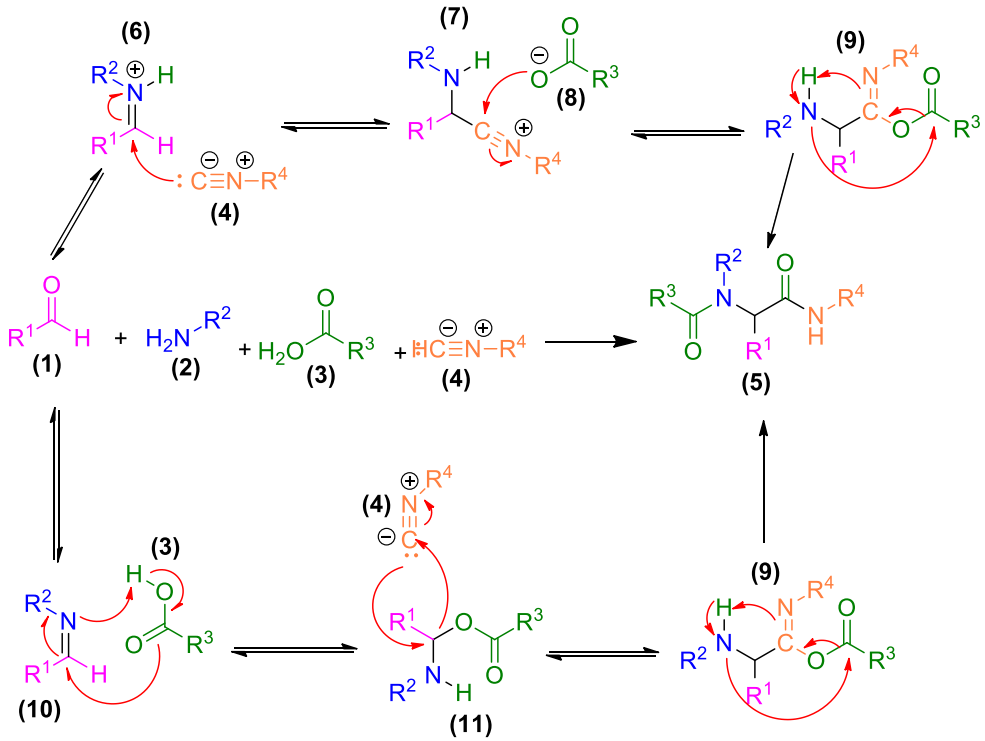


Scheme 7. The Ugi reaction.

The reaction is performed in the presence of a polar protic solvent such as methanol. It has been also used water, having successful results.[67] However, the reaction has been adequately studied in the last 20 years because; there was limited availability of isocyanides and poor stereocontrol. It is worth mentioning that in the mid 1900's only a few isocyanides were available, these days about 380 isocyanides are commercially available.[68]

Development of stereocontrol has been difficult due to incomplete knowledge of the reaction mechanism. The control of the enantioselectivity in the Ugi reaction involves Lewis acids catalysts and chiral auxiliaries.

Two possible mechanisms for the Ugi reaction have been proposed.[69] The first step, in both mechanisms includes condensation of the aldehyde **(1)** and the amine **(2)**, followed by protonation of the imine by **(3),** (Scheme 8). The discuss is whether the follow step includes introduction of the carboxylic acid to **(10)** causing the isocyanide **(4)** to react with the **(11)** via an SN_2 mechanism or whether the isocyanide **(4)** first undergoes nucleophilic addition to the imine **(6)**, followed by the addition of the carboxylate **(8)** to the **(7)** (Scheme 8).

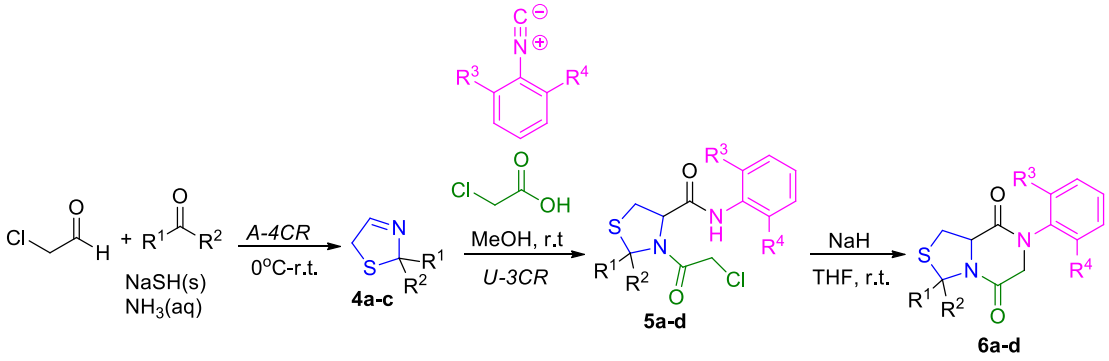


Scheme 8. The two proposed mechanisms of the Ugi reaction.

Experiments supporting the formation of the intermediate **(7)** versus the **(11)** have not been yet performed.[70]

5. Results and Discussion

Our primary target was to synthesize the fused thiazolo-piperazine derivatives **6** (Scheme 9). Thus, we first synthesized different 3-thiazoline derivatives **4** via a modified Asinger-4CR (Scheme 12). Then, we employed the 3-thiazolines as starting materials in Ugi-Jullié (Scheme 13). At the end, we performed cyclization of the Ugi products with NaH (Scheme 9, 14).



Scheme 9. General procedure that was followed in this project.

5.1 Chlorination

During the Asinger-4CR, the chloroacetaldehyde was used as starting material, however, in order to investigate more of the Asinger-4CR the chlorination of other aldehydes was attempted (Figure 10). Although there were used two different synthetic routes[37,38] and aldehydes for the chlorination, in both case the desirable product wasn't obtained.

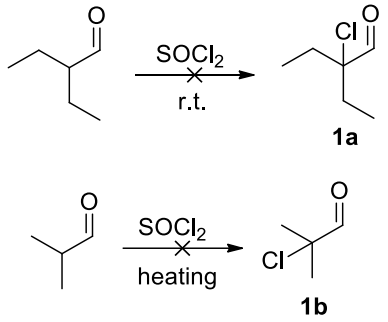
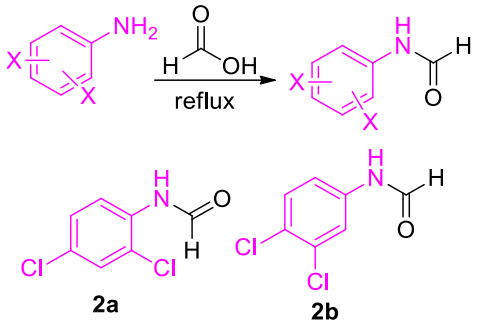


Figure 11. Chlorination of the aldehydes.

5.2 Formylation-Synthesis of the Formamides

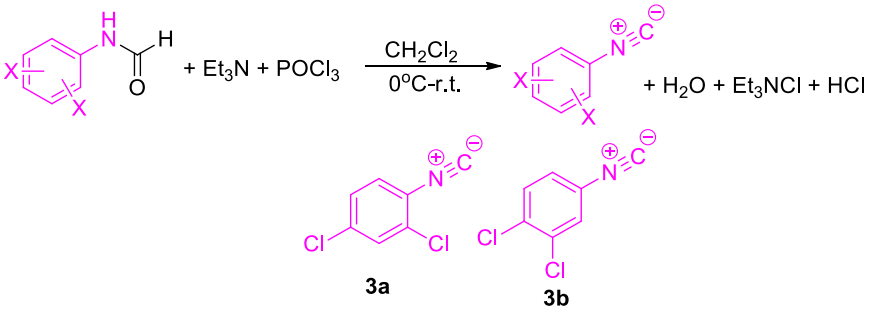
In order to synthesize the isocyanides that shown in Scheme 11, we performed the formylation of the 2,4-dichlroananiline and the 3,4-dichloroaniline with formic acid (Scheme 10).



Scheme 10. Formylation with formic acid.

5.3 Synthesis of the Isocyanides

2-isocyano-1,3-dimethylbenzene was used as starting material for the Ugi-3CR. In order to further investigate the Ugi-3CR, two more isocyanides were synthesized from the formamides that synthesized according to Scheme 10. However, due to the covid-19 pandemic it wasn't possible to held the Ugi-3CR using as starting materials the synthesized isocyanides.



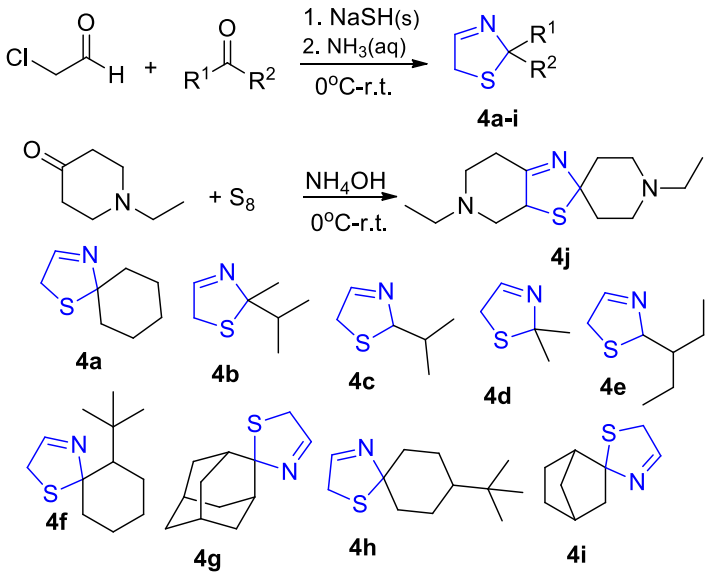
Scheme 11. Synthesis of the isocyanides.

5.4 Asinger Reaction-Synthesis of the 3-thiazolines

The main purpose of this project was the thorough study of the Asinger-4CR. As it seems in Scheme 12, the following 3-thiazolines **4a-i** were synthesized from various aldehydes, ketones, chloroacetaldehyde, NaSH and ammonia solution (aqueous). As mentioned above it was attempted unsuccessfully to chlorinate other aldehydes in order to use them as starting materials in A-4CR. However, not all the ketones obtained the desirable products. For example, in case of the 2-adamantone, the 4-tert-butylcyclohexanone, the bicyclo[2.2.1]heptan-2-one, 1-ethyl-4-piperidone and the 2-tert-butylcyclohexanone the desirable products were not observed. The 3-thiazolines **4f-i** weren't synthesized because of solubility issues of the ketones that were employed.

After 3-thiazolines were synthesized they were not purified with column chromatography due to their instability in acidic conditions and they were used directly utilized as starting materials in the Ugi-3CR. However, in certain 3-thiazolines

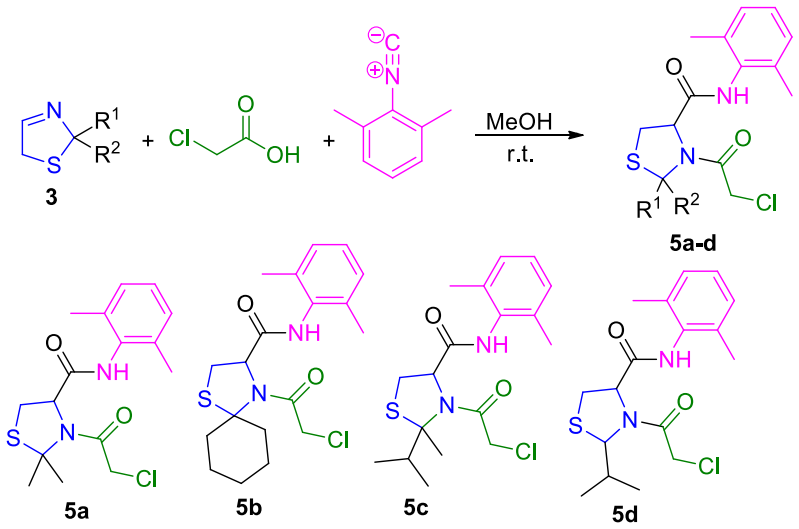
(these from cyclohexanone **4a** and isobutyraldehyde **4c**), it was decided to be filtrated through silica pad before further used in the Ugi-3CR.



Scheme 12. The A-4CR and the A-3CR reaction.

5.5 Ugi Reaction

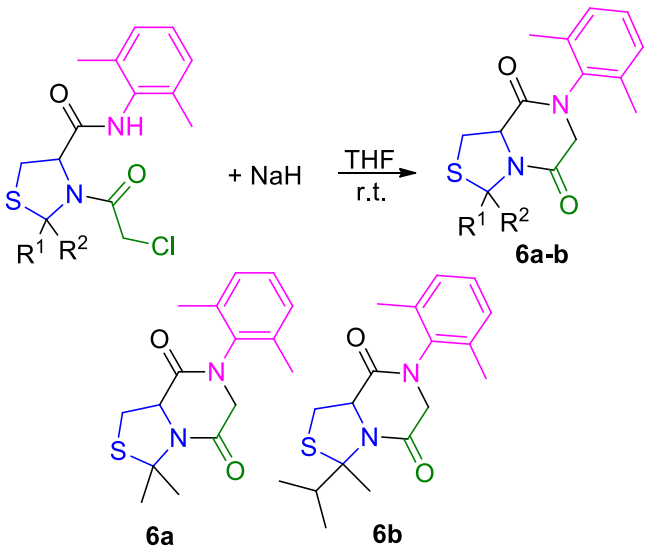
For the Ugi-3CR they were used as starting materials the synthesized imines **4**, the 2-isocyano-1,3-dimethylbenzene and chloroacetic acid, MeOH as solvent while the reaction was performed in room temperature (Scheme 12). Usually in the Ugi MCR are used polar and protic solvents (e.g., methanol, ethanol, or trifluoroethanol). The preferences for protic solvents rely on the fact that the intermediates noted in the general mechanism (Scheme 8) are polar derivatives (prone to H-bond formation) that are consequently stabilized in these solvents.[71]



Scheme 13. The Asinger/Ugi combination reaction.

5.6 NaH cyclization

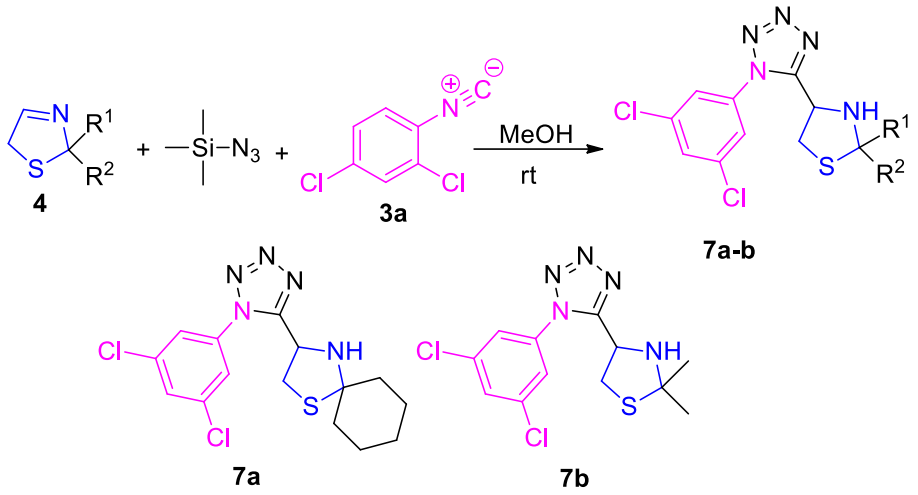
The final step of the reactions that were performed for this project is the cyclization of the Ugi product with NaH using THF as solvent towards the targeted thiazolo-piperazine derivatives. Unfortunately, due to the COVID-19 pandemic, the work had to be stopped. Therefore, the final adducts were not purified, although we verified their synthesis in crude NMRs. Moreover, we didn't synthesize large number of different products. In future we will perform all the necessary purifications and build a large library of compounds **6**.



Scheme 14. Cyclization of the Ugi products.

5.7 Tetrazoles

Another object of this project was the synthesis of tetrazoles scaffolds using the Asinger-Ugi tetrazole union (Scheme 15), from the synthesized 3-thiazoline **4** by the A-4CR. The reaction which was held in methanol at room temperature resulted only traces of the product according to the ^{1}H NMR spectroscopy. It is worth mentioning that union of an Asinger reaction with other MCRs is known to be low yielding.[72,73] Therefore due to the limited time that existed for the completion of the project this object was abandoned. It is worth mentioning that because the products were detected in traces they were not purified with column chromatography therefore their yield and purity isn't known.



Scheme 15. Synthesis of the tetrazoles using the Asinger-Ugi tetrazole union.

6. Experimental Section

General Procedure for the chlorination of the aldehydes[37, 36]

For the chlorination of the aldehydes two different experimental procedures were followed.

1. In a flask equipped with a dropping funnel, stirrer and reflux condenser, 1 equiv of the isobutyraldehyde was placed. To the aldehyde, 1 equiv of freshly distilled $SOCl_2$ was added slowly with agitation at room temperature. After the addition was completed, the reaction was heated for 2h, and the stirring was continued for another 2h. The reaction mixture was stirred at room temperature overnight. Afterwards the reaction mixture was diluted with CH_2Cl_2 and H_2O. The two phases were separated (each one washed twice) and the organic phase was collected. It was then dried over with $MgSO_4$, filtrated and concentrated with the use of a rotatory evaporator. According to ^1H NMR spectroscopy the desired product wasn't obtained.[37]

2. To the neat aldehyde (2 equiv), in a flask equipped with an air cooler, was added thionyl chloride (2,10 equiv). The reaction mixture stirred at room temperature for three hours. After, the reaction was completed the resulting mixture was then poured into water and the phases were separated. The aqueous phase was extracted with DCM three times. The combined organic fractions were washed with water and dried over sodium sulfate. The solvent was removed with a rotatory evaporator. According to ^1H NMR spectroscopy the desired product wasn't obtained.[38]

General Procedure for the Formylation

In a flask equipped with a stirrer the formic acid and the amine (10 g, 1 equiv) were added. The reaction mixture then was placed in an oil bath and left stirring and

heating at 120 ^{o}C in reflux conditions. The reaction completed after two hours. According to NMR ^{1}H spectroscopy the desirable product was obtained.

Notes

1. The reaction mixture was left heating because the formic acid has boiling point 100,8^{o}C.
2. The formamides were dark brown solids.
3. When the formed formamide comes in contact with the room temperature is solidifies.

General Procedure for the synthesis of the isocyanides

In a flask equipped with a stirrer and dropping funnel, the formamide (**2a-b**, 5 g, 1 equiv), 50 ml of CH_2Cl_2, and triethylamine (18,35 ml, 5 equiv) were added. Next was added dropwise the phosphoryl chloride (3,05ml, 1equiv). The reaction mixture placed in an ice bath and left stirring for a 1 hour, then, the pH checked if it was basic. The reaction mixture was left stirring at room temperature overnight. After, the reaction was completed, the pH checked again for basicity and then the reaction mixture transferred in a conical flask. In the conical flask were added a suspension of $NaHCO_{3(s)}$, water, ice and the reaction mixture, they were left stirring for approximately 30 minutes. Afterwards, the reaction mixture, passed from vacuum filtration in order for the Et_3Cl to be removed. Water was added and the aqueous layer was extracted with two portions of dichloromethane. The combined organic layers were dried with magnesium sulfate and the drier was removed with vacuum filtration. The solvent was removed the rotary evaporator. The residue was stored in the fridge so that it can be used in following experiments. According to NMR ^{1}H spectroscopy the desirable product was obtained.

Notes

1. The ice was added because the reaction was exothermic, also, with parallel stirring the reaction mixture was brought in room temperature.
2. The formed isocyanides have strong odor and are colored solids.

General Procedure for the synthesis of the 3-thiazolines 4 using as starting material ketones

In a flask equipped with a stirrer, a suspension of sodium hydrogen sulfide hydrate (0,56 g, 1 equiv), solution of ammonium hydroxide (25% in water, 3,84 ml, 2 equiv), and ketone (2 equiv) were added. The reaction mixture was cooled to ~0 °C and the chloroacetaldehyde (1,29 ml, 1 equiv) was added dropwise over the course of 10 minutes. The reaction mixture was left stirring for 45 minutes in room temperature. After, water was added and the aqueous layer was extracted with two portions of dichloromethane. The combined organic layers were dried with magnesium sulfate and the solvent was removed a rotary evaporator. The residue was stored in the fridge so that it can be used following experiments. In case that it’s left out of the fridge there is a risk of polymerization.

General Procedure for the synthesis of the 3-thiazolines 4 using as starting material aldehydes[13,43,44]

Sodium hydrosulfide monohydrate (0,56g, 1 equiv), ammonia-solution (25% in water, 3,84 ml, 2 equiv), and aldehyde (2 equiv) are mixed and cooled to 0°C. The chloroacetaldehye (1,29 ml, 1 equiv) was dissolved in dichloromethane and was added to the yellow mixture, keeping the temperature under 10°C. The reaction mixture was left stirring overnight at room temperature. Then the phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over with magnesium sulfate; the solvent was removed with rotatory evaporator. The residue was stored in the fridge so that it can be used following experiments. In case that it's left out of the fridge there is a risk of polymerization.

Notes

1. In some cases when the organic phase was washed with water an emulsion was formed (possible formation due to vigorous shaking). In order, to dissolve it saturated NaCl was added.
2. All the 3-thiazolines smell like garlic and they are colored liquids.
3. The desirable products were obtained with NMR ^{1}H spectroscopy.
4. 2-adamantanone was used as starting material twice however both times the desirable product didn't obtained.

General Procedure for the synthesis of the 3-thiazoline 4 using as starting material the 1-ethyl-4-piperidone[23]

First an ice-bath solution of 1-ethyl-4-piperidone (1,72 equiv) was prepared. Sulfur was added and the ammonia was added dropwise. As more ammonia was added, the more the viscosity of the 1-ethyl-4-piperidone was lowered, plus the sulfur becoming more soluble. The mixture was left stirring at room temperature overnight. Then, the reaction mixture was washed with diethyl ether and the two phases were separated and washed twice with ether and water. The organic phase dried over with $MgSO_4$ and concentrated with the use of the rotatory evaporator.

Notes

1. The obtained product was a yellow solid.
2. According to the ^{1}H NMR spectroscopy the desirable product wasn't obtained.

Purification of the 3-thiazolines with vacuum filtration

At first the filter funnel (Gooch filter) was filled with SiO_2. Then the 3-thiazoline was added and washed with petroleum ether (3:1 and 1:1). The product was separated in fractions and with the use of the TLC chromatography and the ^{1}H NMR spectroscopy was determined in which fraction the impurities were left and where the 3-thiazoline was remained.

General Procedure for the Ugi CR

In a solution of the respective imine **4** (1 equiv) in anhydrous MeOH (1.0 ml per mmol of imine) were added the chloroacetic acid (1 equiv) and the respective isocyanide (1 equiv). The reaction mixture was left stirring for 2 days in room temperature. Each day the reaction was checked with TLC chromatography if it was completed. The solvent was removed by rotary evaporator. The residue was stored in the fridge so that it can be used following experiments. The desirable products were obtained with NMR ^{1}H spectroscopy.

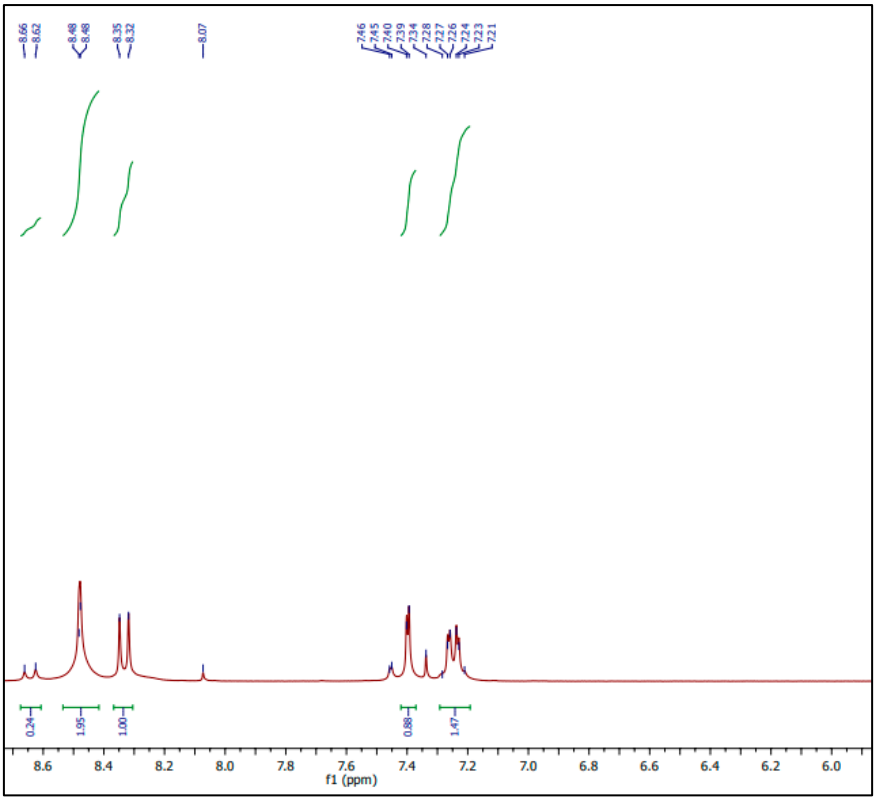
General Procedure for the NaH cyclization

To a suspension of the respective Ugi product **5** (1 equiv), which was dissolved in THF was added the NaH (1 equiv). The reaction mixture was left stirring overnight at room temperature. Water was added and the aqueous layer was extracted with three portions of dichloromethane. The combined organic layers were dried with magnesium sulfate and the solvent was removed with the rotatory evaporator. The residue was stored in the fridge.

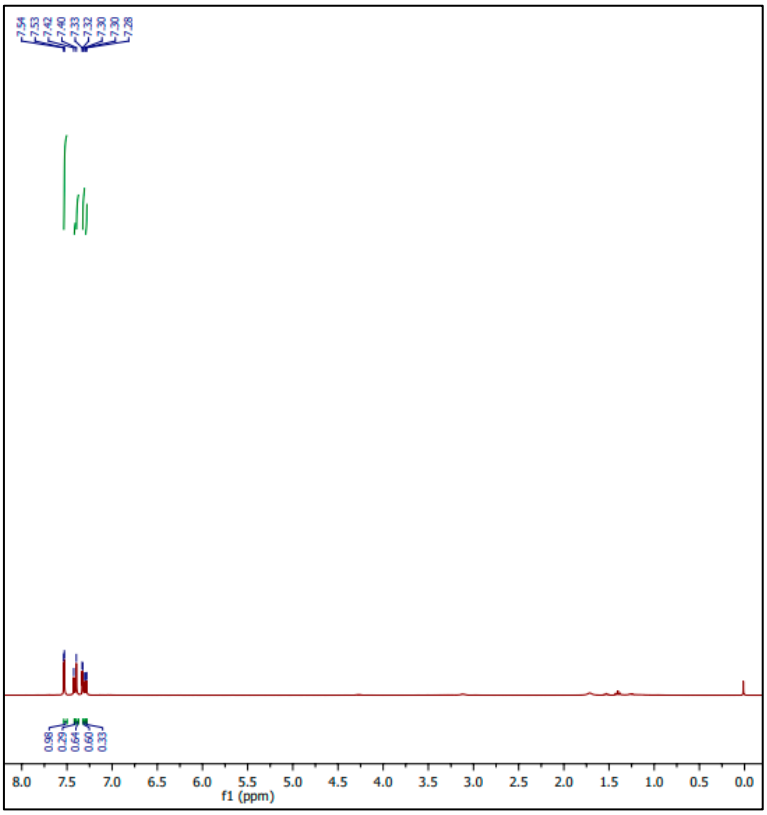
General Procedure for the synthesis of the tetrazoles

At first the 1 equiv thiazoline **4** was dissolved in 1 equiv MeOH. After, 5 min 1 equiv of the isocyanide **3a** was added and the reaction mixture was left stirring for 10 min at room temperature. Then 1 equiv of TMS azide was added and the reaction mixture was left stirring at room temperature for 2 days. Each day the reaction was checked with TLC chromatography if it was completed. The reaction mixture was diluted with CH_2Cl_2 and H_2O; the two phases were separated (each one washed twice) and the organic phase was collected. It was then dried over with $MgSO_4$, filtrated and then concentrated with the use of a rotatory evaporator.

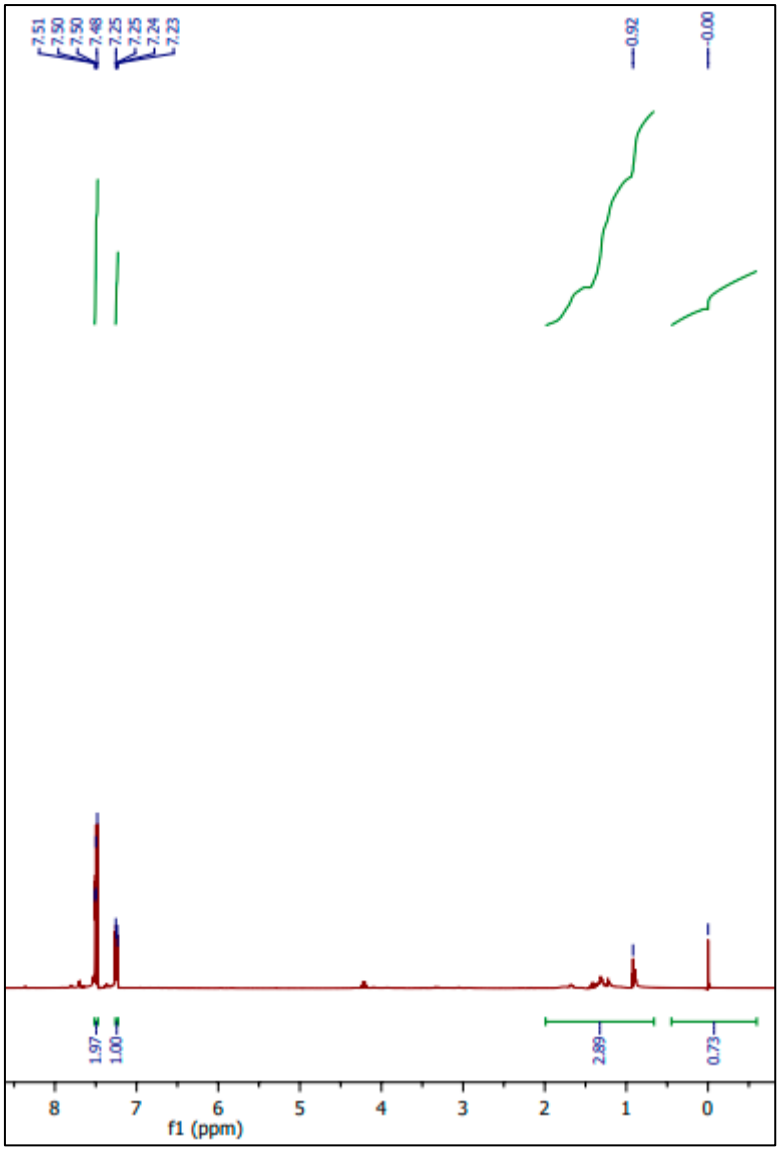
NMR Spectrums of the products



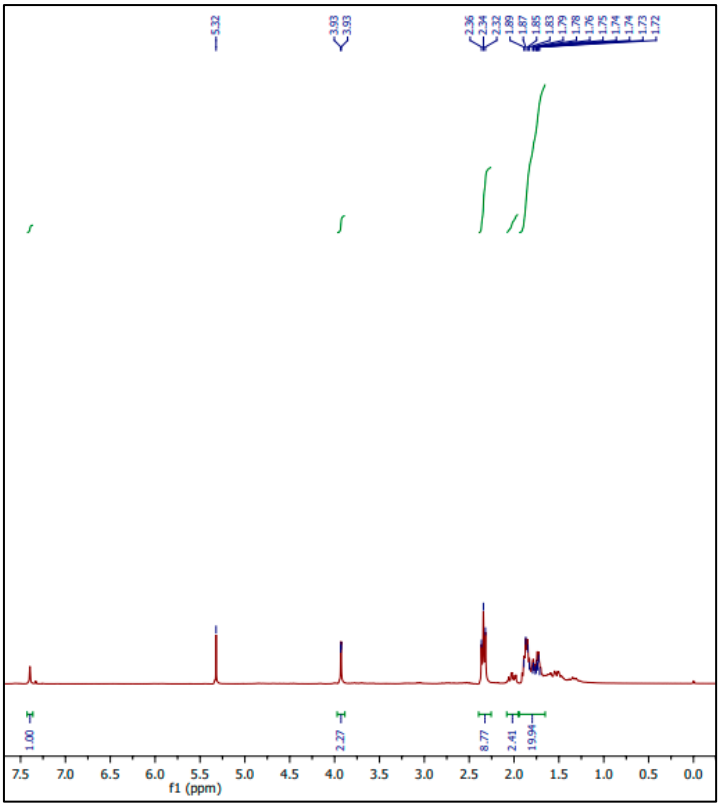
Scheme 16. The NMR spectra of the product 2a.



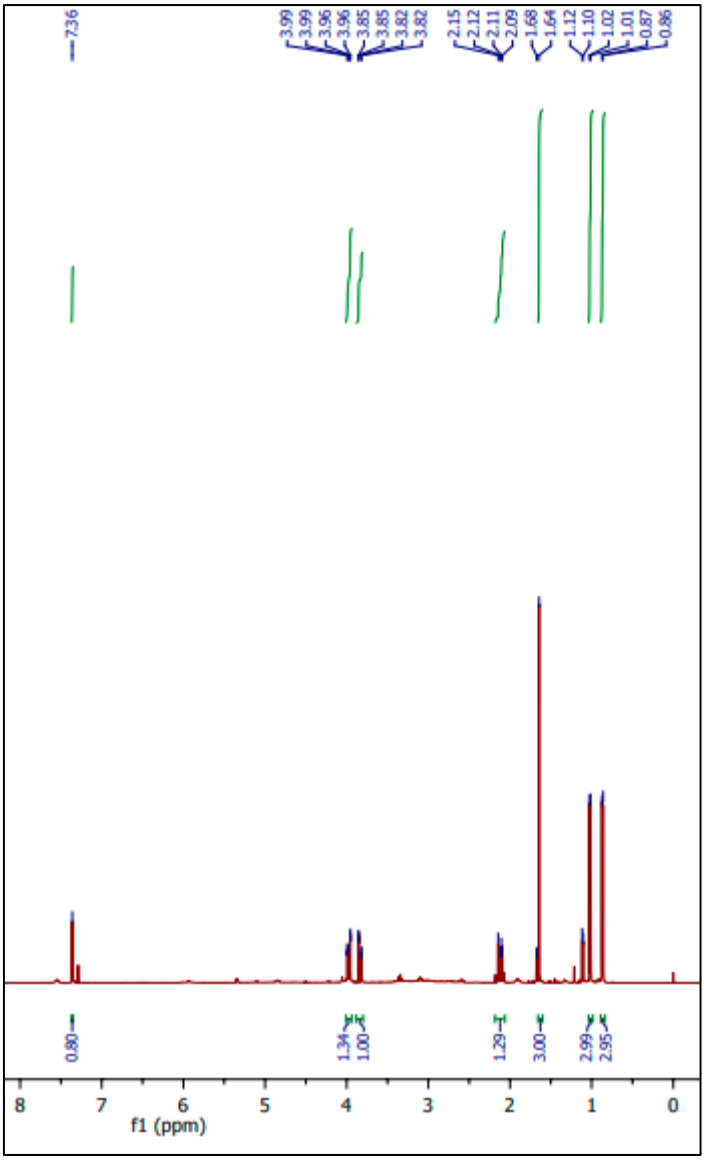
Scheme 17. The NMR spectra of the product 3a.



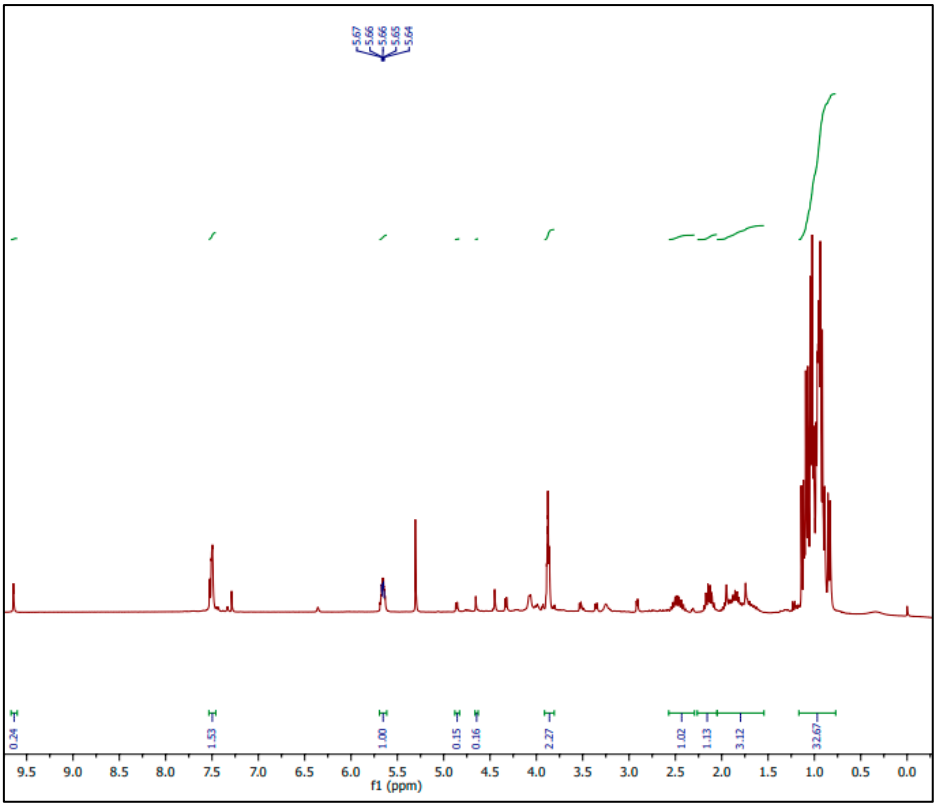
Scheme 18. The NMR spectra of the product 4b.



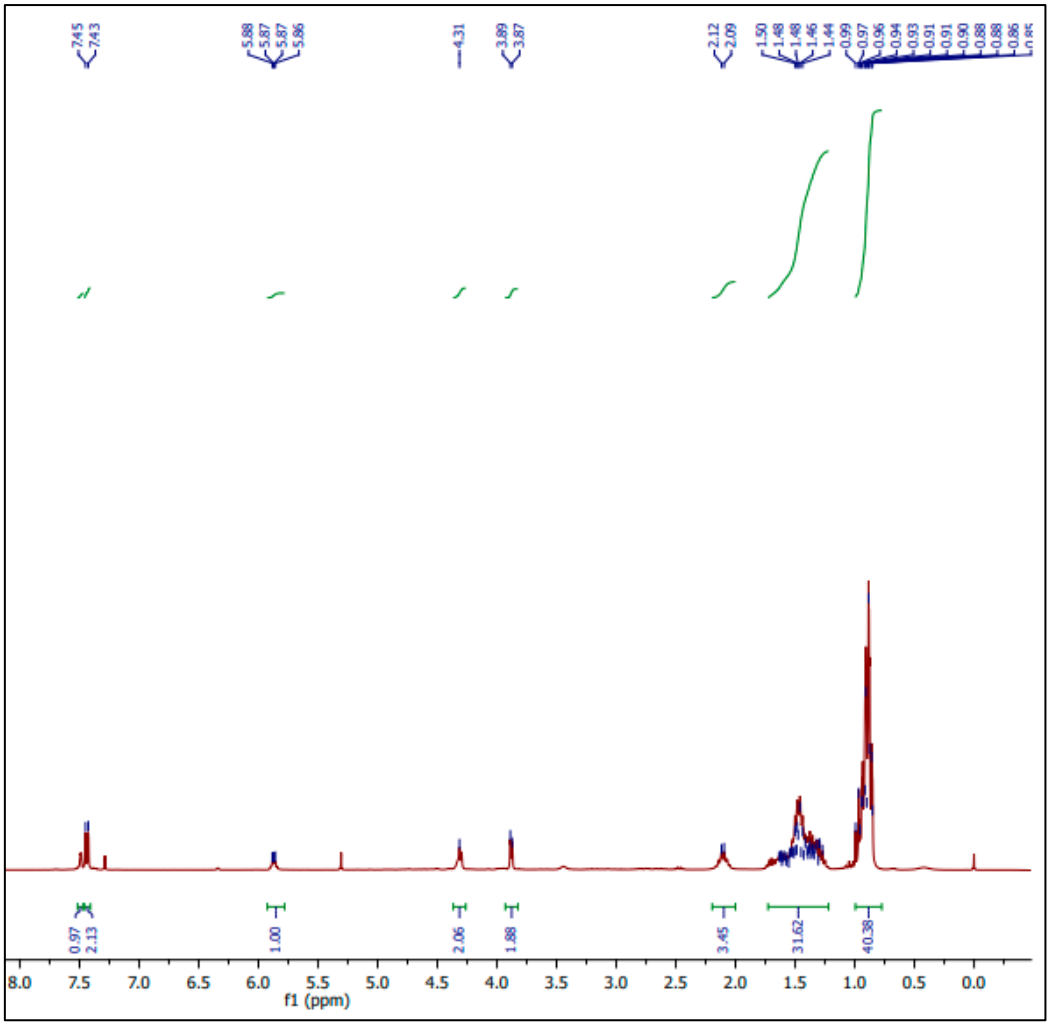
Scheme 19. The NMR spectra of the product 4a.



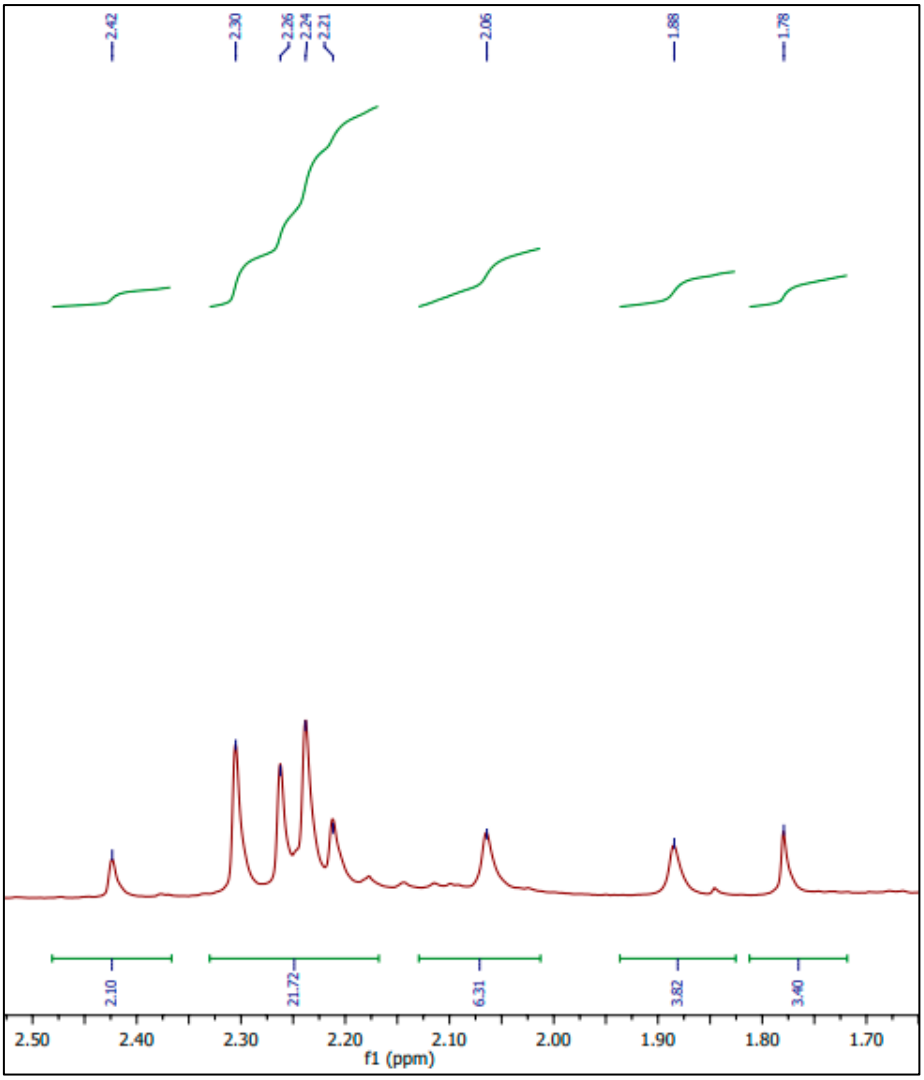
Scheme 20. The NMR spectra of the product 4b.



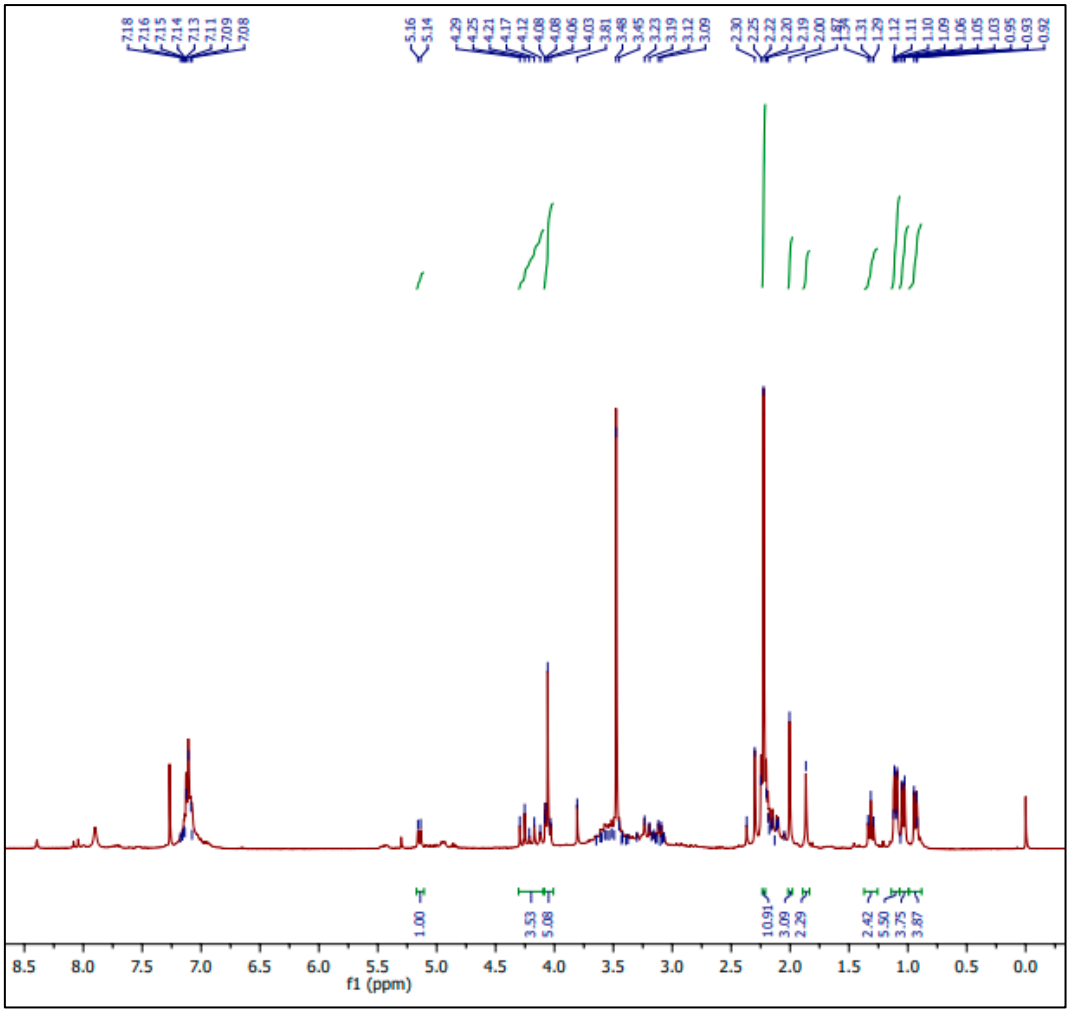
Scheme 21. The NMR spectra of the product 4c.



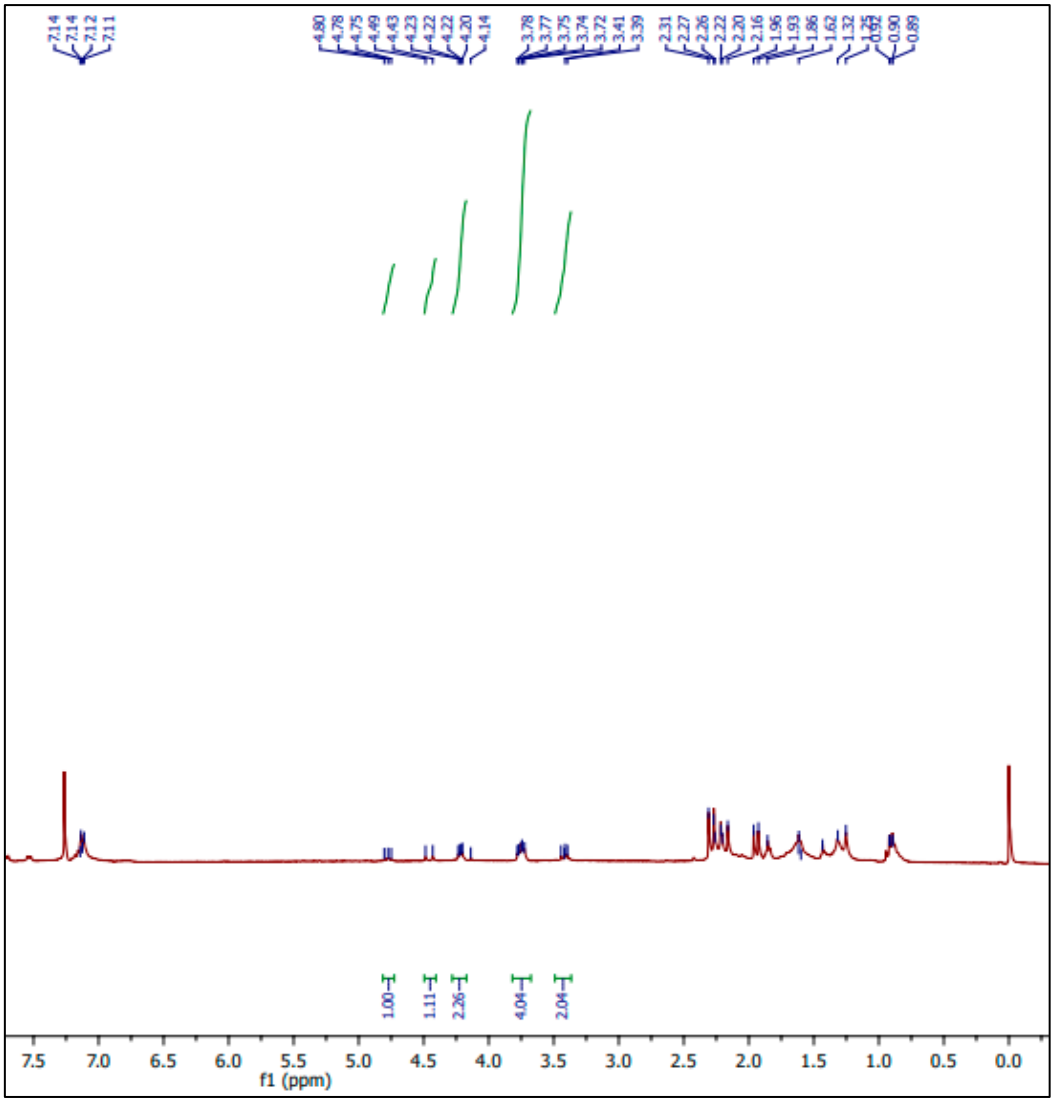
Scheme 22. The NMR spectra of the product 4e.



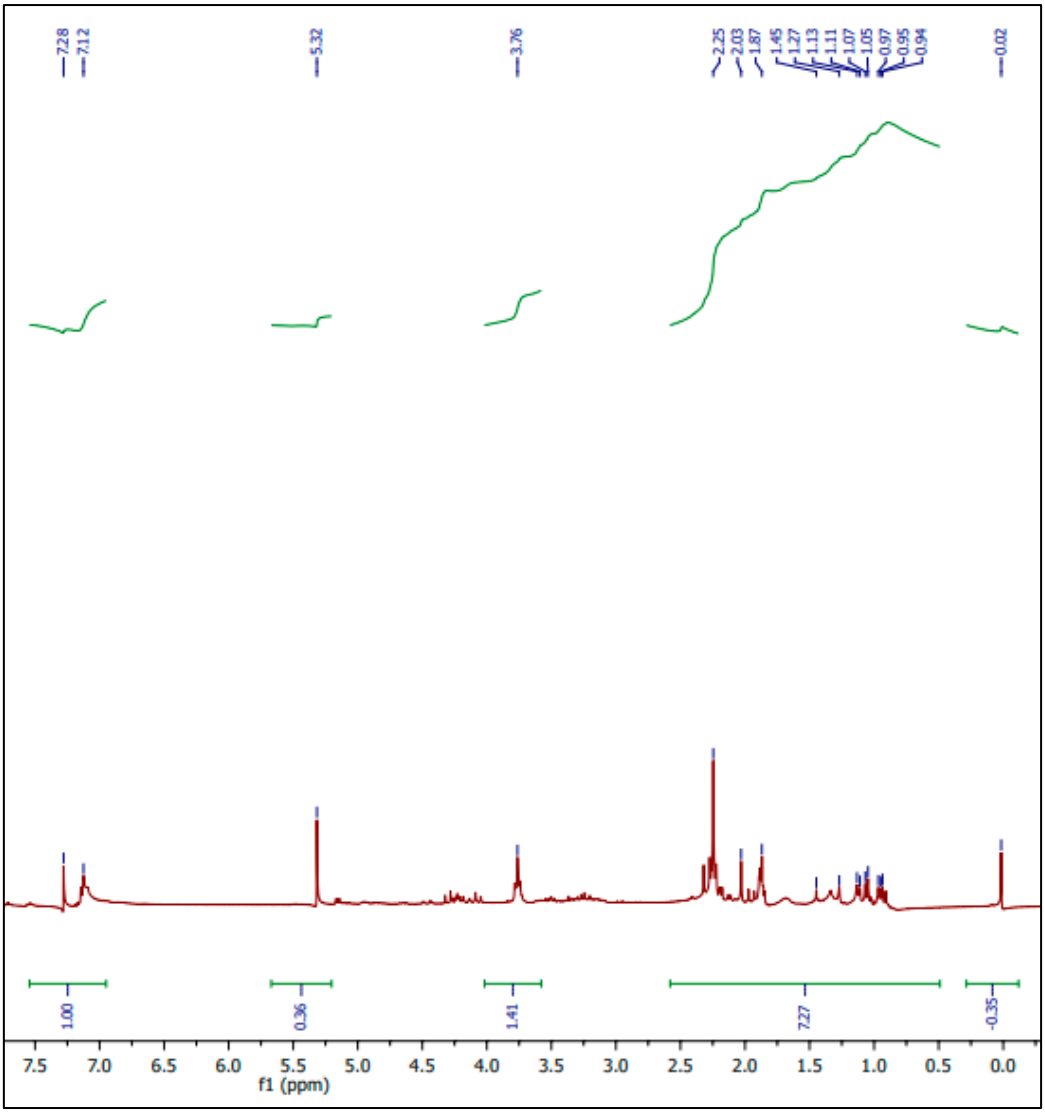
Scheme 23. The NMR spectra of the product 5a.



Scheme 24. The NMR spectra of the product 5c.



Scheme 25. The NMR spectra of the product 6a.



Scheme 26. The NMR spectra of the product 6b.

Conclusions

Based on what has been reported in the present project it is observed that the Asinger reaction can be used alone or in combination with other reactions such as the Ugi reaction. It was found that the reaction products are widely used, especially in pharmaceutical chemistry. A typical example is the industrial composition of the D-penicillamine. As for the substrates that can be used for the Asinger reaction, it has been observed that stereochemically inhibited ketones such as 2-tertbutylcyclohexanone do not lead to a successful reaction. It was also observed that the 3-thiazoline ring can for example hydrogenate and dehydrogenated. Part of the project was successfully completed; synthesis of the 3-thiazoline ring, combination of the Asinger/Ugi reaction using as starting materials the synthesized 3-thiazolines and finally the cyclization of the Ugi product with NaH. However, due to the covid-19 pandemic the purification of the finals products wasn't possible.

References

(1) Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry †. *Chem. Rev.* **2006**, *106* (1), 17–89. https://doi.org/10.1021/cr0505728.

(2) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. Asymmetric Isocyanide-Based MCRs. In *Multicomponent Reactions*; Wiley Online Books; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, FRG, 2005; pp 1–32. https://doi.org/10.1002/3527605118.ch1.

(3) Romanides. Über Die Gemeinsame Einwirkung von Schwefel Und Ammoniak Auf Ketone, Prof. Dr.-Ing. Habil. F. Asinger, 68. Jahry. 1956 Nr. 12 Https://Doi.Org/10.1002/Ange.19560681209. **1956**, *147004*, 1–21.

(4) Keim, W.; Offermanns, H. Friedrich Asinger (1907–1999): A Mediator between Basic and Applied Research. *Angew. Chemie Int. Ed.* **2007**, *46* (32), 6010–6013. https://doi.org/10.1002/anie.200700904.

(5) Asinger, F.; Schäfer, W.; Halcour, K.; Saus, A.; Triem, H. The Course of the Willgerodt-Kindler Reaction of Alkyl Aryl Ketones. *Angew. Chemie Int. Ed. English* **1964**, *3* (1), 19–28. https://doi.org/10.1002/anie.196400191.

(6) Gewald, K. Methods for the Synthesis of 2-Aminothiophenes and Their Reactions (Review). *Chem. Heterocycl. Compd.* **1976**, *12* (10), 1077–1090. https://doi.org/10.1007/BF00945583.

(7) Ugi, I.; Offermann, K. Isonitrile, XVIII. Hydantoin-Imide-(4). *Chem. Ber.* **1964**, *97* (8), 2276–2281. https://doi.org/10.1002/cber.19640970825.

(8) Asinger, F.; Offermanns, H. Syntheses with Ketones, Sulfur, and Ammonia or Amines at Room Temperature. *Angew. Chemie Int. Ed. English* **1967**, *6* (11), 907–919. https://doi.org/10.1002/anie.196709071.

(9) Kintscher, J.; Martens, J. Vereinfachte Peptidsynthese Mit Schutzgruppenfreien Aminosäure-Hydrochloriden Nach Dem Prinzip Der Vierkomponenten-Kondensation. *Synthesis (Stuttg).* **1992**, *1992* (09), 837–838. https://doi.org/10.1055/s-1992-26240.

(10) Stalling, T.; Brockmeyer, F.; Kroeger, D.; Schwaeblein, A.; Martens, J. ChemInform Abstract: 2,5-Dihydro-1,3-Thiazoles as Scaffolds in the Synthesis of O,N-Diacyl O,N-Acetals in a One-Pot Reaction. *ChemInform* **2013**, *44* (7), no-no. https://doi.org/10.1002/chin.201307109.

(11) Sehlinger, A.; Stalling, T.; Martens, J.; Meier, M. A. R. Oxa- and Thiazolidine-Containing Polymers Derived via the Asinger Four-Component Reaction: The Ring Matters. *Macromol. Chem. Phys.* **2014**, *215* (5), 412–420. https://doi.org/10.1002/macp.201300716.

(12) Schlüter, T.; Frerichs, N.; Schmidtmann, M.; Martens, J. Consecutive Multicomponent Reactions: Synthesis of 3-Acyl-4-Alkynyl-Substituted 1,3-Thiazolidines. *Synthesis (Stuttg).* **2018**, *50* (05), 1123–1132. https://doi.org/10.1055/s-0036-1591873.

(13) Zumbrägel, N.; Wagner, K.; Weißing, N.; Gröger, H. Biocatalytic Reduction of 2-Monosubstituted 3-Thiazolines Using Imine Reductases. *J. Heterocycl. Chem.* **2019**, *56* (3), 788–794. https://doi.org/10.1002/jhet.3437.

(14) Kröger, D.; Schlüter, T.; Fischer, M.; Geibel, I.; Martens, J. Three-Component Reaction toward Polyannulated Quinazolinones, Benzoxazinones, and Benzothiazinones. *ACS Comb. Sci.* **2015**, *17* (3), 202–207. https://doi.org/10.1021/co500165a.

(15) Asinger, F.; Thiel, M.; Kaltwasser, H. Über Die Gemeinsame Einwirkung Von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone II Die Gemeinsame Einwirkung Von Schwefel Und Ammoniak Auf Cyclohexanon. *Justus Liebigs Ann. Chem.* **1957**, *606* (1), 67–74. https://doi.org/10.1002/jlac.19576060107.

(16) Asinger, F.; Thiel, M.; Usbeck, H.; Gröbe, K.-H.; Grundmann, H.; Tränkner, S. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XXV. Die Gemeinsame Einwirkung von Schwefel Und Ammoniak Auf Cyclische Ketone, II. *Justus Liebigs Ann. Chem.* **1960**, *634* (1), 144–163. https://doi.org/10.1002/jlac.19606340115.

(17) Asinger Reaction. In *Comprehensive Organic Name Reactions and Reagents*; Major Reference Works; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2010; pp 107–110. https://doi.org/10.1002/9780470638859.conrr025.

(18) Thiel, M.; Asinger, F.; Reckling, G. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone IX. Die Gemeinsame Einwirkung von Schwefel Und Ammoniak Auf Methyl-Isopropylketon. *Justus Liebigs Ann. Chem.* **1958**, *611* (1), 131–138. https://doi.org/10.1002/jlac.19586110114.

(19) Asinger, F.; Schäfer, W.; Herkelmann, G.; Römgens, H.; Reintges, B. D.; Scharein, G.; Wegerhoff, A. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XXXIX. Einwirkung von Schwefel Und Ammoniak Auf Tridecanon-(7) Und Pentanone-(2). Thiazoline-Δ3 Aus α-Mercapto-Oxoverbindungen Und Oxoverbindungen in Gegenwart Vo. *Justus Liebigs Ann. Chem.* **1964**, *672* (1), 156–178. https://doi.org/10.1002/jlac.19646720112.

(20) Asinger, F.; Thiel, M.; Pallas, E. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone I. Die Gemeinsame Einwirkung von Schwefel Und Ammoniak Auf Diäthylketon. *Justus Liebigs Ann. Chem.* **1957**, *602* (1), 37–49.

https://doi.org/10.1002/jlac.19576020104.

(21) Asinger, F.; Thiel, M.; Sedlak, H.; Hampel, O.; Sowada, R. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone XIV. Die Gemeinsame Einwirkung Von Schwefel Und Ammoniak Auf Ketocarbonsäuren Bzw. Deren Ester. *Justus Liebigs Ann. Chem.* **1958**, *615* (1), 84–93. https://doi.org/10.1002/jlac.19586150114.

(22) Asinger, F.; Schäfer, W.; Baumann, M.; Römgens, H. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XXXVII. Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Cyclische Ketone, IV. *Justus Liebigs Ann. Chem.* **1964**, *672* (1), 103–133. https://doi.org/10.1002/jlac.19646720110.

(23) Lyle, R. E.; Munk, R.; Ladd, L. The Asinger Reaction with 1-Methyl-4-Piperidone. *J. Org. Chem.* **1965**, *30* (1), 293–294. https://doi.org/10.1021/jo01012a505.

(24) Asinger, F.; Thiel, M.; Püchel, P.; Haaf, F.; Schäfer, W. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XXXV. Einwirkung von Schwefel Und Ammoniak Auf Acetophenon, I. *Justus Liebigs Ann. Chem.* **1962**, *660* (1), 85–97. https://doi.org/10.1002/jlac.19626600110.

(25) Asinger, F.; Schäfer, W.; Baumgarte, G.; Müting, P. F. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XXXVI. Einwirkung von Schwefel Und Ammoniak Auf Acetophenon, II Synthese von Imidazolin-Δ3-Thionen-(5). *Justus Liebigs Ann. Chem.* **1963**, *661* (1), 95–110. https://doi.org/10.1002/jlac.19636610108.

(26) Asinger, F.; Thiel, M.; Peschel, G.; Heinz Meinicke, K. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XVI Die Gemeinsame Einwirkung von Schwefel Und Ammoniak Auf Methylketone. *Justus Liebigs Ann. Chem.* **1958**, *619* (1), 145–160. https://doi.org/https://doi.org/10.1002/jlac.19586190115.

(27) Thiel, M.; Asinger, F. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone IV. Die Gemeinsame Einwirkung Von Schwefel Und Ammoniak Auf Aceton. *Justus Liebigs Ann. Chem.* **1957**, *610* (1), 17–24. https://doi.org/10.1002/jlac.19576100103.

(28) Asinger, F.; Schäfer, W.; Reintges, B. D.; Wegerhoff, A.; Scharein, G. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XLII Das Isomerenverhältnis Der Aus Unsymmetrischen Aliphatischen Ketonen, Schwefel Und Ammoniak Entstehenden Thiazoline-Δ3. *Justus Liebigs Ann. Chem.* **1965**, *683* (1), 121–131. https://doi.org/10.1002/jlac.19656830115.

(29) Danckwerts, P. V. Angewandte Chemie. *Chem. Eng. Sci.* **1962**, *17* (11), 955. https://doi.org/10.1016/0009-2509(62)87032-8.

(30) Eigenschaften, D. H.; Weigert, V. W. M.; Offermanns, H. D-Penkillamin - Herstellung Und Eigenschaften. **1975**.

(31) Weigert, W. M.; Offermanns, H.; Degussa, P. S. D-Penicillamine?Production and Properties. *Angew. Chemie Int. Ed. English* **1975**, *14* (5), 330–336. https://doi.org/10.1002/anie.197503301.

(32) Vorbrüggen, H. The Synthesis of 3-Acyl-2,3-Dihydro-2,2-Dimethyl-1,3-Thiazoles. *Helv. Chim. Acta* **1991**, *74* (2), 297–303. https://doi.org/10.1002/hlca.19910740206.

(33) Thiel, M.; Asinger, F.; Schmiedel, K. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone VIII. Die Kondensation von α-Mercaptoaldehyden Mit Oxo-Verbindungen Und Gasförmigem Ammoniak Zu Thiazolinen-Δ. *Justus Liebigs Ann. Chem.* **1958**, *611* (1), 121–131. https://doi.org/10.1002/jlac.19586110113.

(34) Asinger, F.; Schäfer, W.; Herkelmann, G. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XL. Hydrolyse-Geschwindigkeit von Thiazolinen-Δ. *Justus Liebigs Ann. Chem.* **1964**, *672* (1), 179–193. https://doi.org/10.1002/jlac.19646720113.

(35) Watzke, M.; Schulz, K.; Johannes, K.; Ullrich, P.; Martens, J. First Synthesis of Bi- and Tricyclic α,β-Unsaturated δ-Oxacaprolactams from Cyclic Imines via Ring-Closing Metathesis. *European J. Org. Chem.* **2008**, *2008* (22), 3859–3867. https://doi.org/10.1002/ejoc.200800254.

(36) Köpper, S.; Lindner, K.; Martens, J. Die Anlagerung von Mercaptocarbonsäuren an 3-Thiazoline Und Anschließende Lactamisierung. *Tetrahedron* **1992**, *48* (47), 10277–10292. https://doi.org/10.1016/S0040-4020(01)88333-2.

(37) Stevens, C. L.; Gillis, B. T. Epoxyethers. XI. O→O Acyl Migrations with α-Hydroxyacylals. *J. Am. Chem. Soc.* **1957**, *79* (13), 3448–3451. https://doi.org/10.1021/ja01570a036.

(38) Masschelein, K. G. R.; Stevens, C. V. Synthesis of 1,1-Bisphosphono-2-Aza-1,3-Dienes, a New Class of Electron-Deficient Azadienes. *Tetrahedron Lett.* **2008**, *49* (28), 4336–4338. https://doi.org/10.1016/j.tetlet.2008.05.031.

(39) Asinger, F.; Thiel, M.; Esser, G. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone VI. Die Herstellung Von Thiazolinen-Δ3 Durch Gemeinsame Einwirkung Von Ammoniak Und Oxo-Verbindungen Auf α-Mercaptoketone. *Justus Liebigs Ann. Chem.* **1957**, *610* (1), 33–49. https://doi.org/10.1002/jlac.19576100105.

(40) Asinger, F.; Thiel, M.; Kalzendorf, I. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone V. Die Gemeinsame Einwirkung Von Schwefel Und Ammoniak Auf Methyläthylketon. *Justus Liebigs Ann. Chem.* **1957**, *610* (1), 25–32.

https://doi.org/10.1002/jlac.19576100104.
(41) Zumbrägel, N.; Gröger, H. One-Pot Synthesis of a 3-Thiazolidine through Combination of an Asinger-Type Multi-Component-Condensation Reaction with an Enzymatic Imine Reduction. *J. Biotechnol.* **2019**, *291*, 35–40. https://doi.org/10.1016/j.jbiotec.2018.12.009.
(42) Zumbrägel, N.; Gröger, H. Merging Heterocyclic Chemistry and Biocatalysis in One-Pot Processes through Compartmentalization of the Reaction Steps. *Bioengineering* **2018**, *5* (3). https://doi.org/10.3390/bioengineering5030060.
(43) Reiners, I.; Gröger, H.; Martens, J. A New Enantioselective Synthetic Approach to β-Aminothio-Compoundsvia Enantioselective Reduction OfN,S-Heterocyclic Imines. *J. für Prakt. Chemie/Chemiker-Zeitung* **1997**, *339* (1), 541–546. https://doi.org/10.1002/prac.19973390197.
(44) Martens, J.; Offermanns, H.; Scherberich, P. Facile Synthesis of Racemic Cysteine. *Angew. Chemie Int. Ed. English* **1981**, *20* (8), 668–668. https://doi.org/10.1002/anie.198106681.
(45) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. Synthesis of Saccharides and Related Polyhydroxylated Natural Products. 1. Simple Alditols. *J. Org. Chem.* **1982**, *47* (7), 1373–1378. https://doi.org/10.1021/jo00346a051.
(46) Suzuki, T.; Sato, E.; Unno, K.; Kametani, T. Enantioselective Synthesis of Trans-Octahydro-1,6-Dioxoinden-4-Ylpropionic Acid from (R)-2,3-O-Isopropylideneglyceraldehyde by Tandem Orthoester Claisen Rearrangement. *J. Chem. Soc. Perkin Trans. 1* **1986**, No. 0, 2263–2268. https://doi.org/10.1039/P19860002263.
(47) Schlemminger, I.; Janknecht, H.-H.; Maison, W.; Saak, W.; Martens, J. Synthesis of the First Enantiomerically Pure 3-Thiazolines via Asinger Reaction. *Tetrahedron Lett.* **2000**, *41* (38), 7289–7292. https://doi.org/10.1016/S0040-4039(00)01266-1.
(48) Kröger, D.; Schlüter, T.; Fischer, M.; Geibel, I.; Martens, J. Three-Component Reaction toward Polyannulated Quinazolinones, Benzoxazinones, and Benzothiazinones. *ACS Comb. Sci.* **2015**, *17* (3), 202–207. https://doi.org/10.1021/co500165a.
(49) Brockmeyer, F.; Kröger, D.; Stalling, T.; Ullrich, P.; Martens, J. A Manifold Three-Step Synthetic Route to Polycyclic Annulated Hydantoins via Cyclic Imines. *Helv. Chim. Acta* **2012**, *95* (10), 1857–1870. https://doi.org/10.1002/hlca.201200441.
(50) Brockmeyer, F.; Morosow, V.; Martens, J. A New Multicomponent Reaction: Unexpected Formation of Derivatizable Cyclic α-Alkoxy Isothioureas. *Org. Biomol. Chem.* **2015**, *13* (11), 3341–3346. https://doi.org/10.1039/C4OB02608J.
(51) Kröger, D.; Franz, M.; Schmidtmann, M.; Martens, J. Sequential Multicomponent Reactions and a Cu-Mediated Rearrangement: Diastereoselective Synthesis of Tricyclic Ketones. *Org. Lett.* **2015**, *17* (23), 5866–5869. https://doi.org/10.1021/acs.orglett.5b03057.
(52) Kröger, D.; Stalling, T.; Martens, J. The Concept of Sequential Multicomponent Reactions: A Short Synthesis of Thiazolo- and Oxazolo[1,4]Benzodiazepine-2,5-Diones. *Synth.* **2016**, *48* (23), 4189–4198. https://doi.org/10.1055/s-0035-1562457.
(53) Johannes, K.; Watzke, M.; Martens, J. Synthesis of α,β-Unsaturated Caprolactams Starting from Heterocyclic Imines. *J. Heterocycl. Chem.* **2010**, *47* (3), n/a-n/a. https://doi.org/10.1002/jhet.381.
(54) Brockmeyer, F.; van Gerven, D.; Saak, W.; Martens, J. Two Sequential Multicomponent Reactions: Synthesis of Thiazolidin-4-Yl-1,3,4-Oxadiazoles under Mild Conditions. *Synthesis (Stuttg).* **2014**, *46* (12), 1603–1612. https://doi.org/10.1055/s-0033-1341043.
(55) Hatam, M.; Tehranfar, D.; Martens, J. A Novel and Convenient Route to Phosphono-Oligopeptides Derived from 1,3-Oxazolines, 1,3-Oxazines and 1,3-Thiazolines. *Synth. Commun.* **1995**, *25* (11), 1677–1688. https://doi.org/10.1080/00397919508015852.
(56) Xin, S.; Dengfeng, Z.; Jiangtao, S. Practical, Efficient Synthesis of N-Mono-Substituted β-Amino Tertiary Thiols via Reductive Ring-Opening of 3-Thiazolines. *Res. Chem. Intermed.* **2013**, *39* (2), 767–770. https://doi.org/10.1007/s11164-012-0705-8.
(57) Liu, Z.-Q. Two Neglected Multicomponent Reactions: Asinger and Groebke Reaction for Constructing Thiazolines and Imidazolines. *Curr. Org. Synth.* **2015**, *12* (1), 20–60. https://doi.org/10.2174/1570179411999141112144441.
(58) Andraos, J. Unification of Reaction Metrics for Green Chemistry II: Evaluation of Named Organic Reactions and Application to Reaction Discovery. *Org. Process Res. Dev.* **2005**, *9* (4), 404–431. https://doi.org/10.1021/op050014v.
(59) Thiel, M.; Asinger, F.; Häussler, K.; Körner, T. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XXII.: Mercaptoamine Durch Reduktion von Thiazolinen-Δ3 Oder Dihydro-Metathiazinen-Δ3 Mit Lithiumalanat. *Justus Liebigs Ann. Chem.* **1959**, *622* (1), 107–116. https://doi.org/10.1002/jlac.19596220117.
(60) Brockmeyer, F.; Martens, J. Regioselective Air Oxidation of Sulfides to O,S -Acetals in a Bubble Column. *ChemSusChem* **2014**, *7* (9), 2441–2444. https://doi.org/10.1002/cssc.201402310.
(61) Asinger, F.; Thiel, M.; Schröder, L. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone VII. Die Dehydrierung Von Thiazolinen-Δ3 Zu Thiazolen. *Justus Liebigs Ann. Chem.* **1957**, *610* (1), 49–56. https://doi.org/10.1002/jlac.19576100106.

(62) Thiel, M.; Asinger, F.; Fedtke, M. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone XIII. Die Gemeinsame Einwirkung von Schwefel Und Ammoniak Auf Methylbenzylketon. *Justus Liebigs Ann. Chem.* **1958**, *615* (1), 77–84. https://doi.org/10.1002/jlac.19586150113.

(63) Asinger, F.; Schröder, L.; Hoffmann, S. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, XXXII. Die Umsetzung von α-Mercaptoketonen Mit β-Aminovinylketonen. *Justus Liebigs Ann. Chem.* **1961**, *648* (1), 83–95. https://doi.org/10.1002/jlac.19616480113.

(64) Asinger, F.; Witte, E.-C.; Schäfer, W. Über Die Gemeinsame Einwirkung von Elementarem Schwefel Und Gasförmigem Ammoniak Auf Ketone, LV. Thiazolidin-Nitrile-(4), -(Thio)Amide-(4), -Carbonsäuren-(4) Und Penicillamin-Derivate Aus Thiazolinen-Δ3. *Justus Liebigs Ann. Chem.* **1966**, *697* (1), 140–157. https://doi.org/10.1002/jlac.19666970110.

(65) Ugi, I. The ?-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions. *Angew. Chemie Int. Ed. English* **1962**, *1* (1), 8–21. https://doi.org/10.1002/anie.196200081.

(66) Kanizsai, I.; Szakonyi, Z.; Sillanpää, R.; Fülöp, F. A Comparative Study of the Multicomponent Ugi Reactions of an Oxabicycloheptene-Based β-Amino Acid in Water and in Methanol. *Tetrahedron Lett.* **2006**, *47* (51), 9113–9116. https://doi.org/10.1016/j.tetlet.2006.10.069.

(67) Lehnhoff, S.; Goebel, M.; Karl, R. M.; Klösel, R.; Ugi, I. Stereoselective Syntheses of Peptide Derivatives with 2-Acetamido-3,4,6-Tri-O-Acetyl-1-Amino-2-Deoxy-β-D-Glucopyranose by Four-Component Condensation. *Angew. Chemie Int. Ed. English* **1995**, *34* (10), 1104–1107. https://doi.org/10.1002/anie.199511041.

(68) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. Massive Parallel Catalyst Screening: Toward Asymmetric MCRs. *Org. Lett.* **2003**, *5* (22), 4021–4024. https://doi.org/10.1021/ol035010u.

(69) Ugi, I.; Offermann, K. Asymmetric 1,3-Induction during the ?-Addition of Immonium Ions and Carboxylate Anions onto Isonitriles. *Angew. Chemie Int. Ed. English* **1963**, *2* (10), 624–624. https://doi.org/10.1002/anie.196306241.

(70) Ugi, I.; Heck, S. The Multicomponent Reactions and Their Libraries for Natural and Preparative Chemistry. *Comb. Chem. High Throughput Screen.* **1970**, *4* (1), 1–34. https://doi.org/10.2174/1386207013331291.

(71) Rocha, R. O.; Rodrigues, M. O.; Neto, B. A. D. Review on the Ugi Multicomponent Reaction Mechanism and the Use of Fluorescent Derivatives as Functional Chromophores. *ACS Omega* **2020**, *5* (2), 972–979. https://doi.org/10.1021/acsomega.9b03684.

(72) Kehagia, K.; Dömling, A.; Ugi, I. The Formation of β-Lactam Derivatives and a C3-Symmetrical Heterocycle from 5,6-Dihydro-2H-1,3-Oxazines. *Tetrahedron* **1995**, *51* (1), 139–144. https://doi.org/10.1016/0040-4020(94)00958-W.

(73) Gröger, H.; Hatam, M.; Martens, J. Synthese Totalgeschützter, Nichtproteinogener α-Aminosäuren Und Oligopeptide Aus 2H-1,3-Oxazinen Und 2H-1,3-Benzoxazinen via Ugi-Reaktion. *Tetrahedron* **1995**, *51* (26), 7173–7180. https://doi.org/10.1016/0040-4020(95)00365-F.