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New Twists in the Chemistry of Thioureas: 1,3-Thiazolidines as a Vector of Sustainability

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This study introduces a sustainable and pioneering cascade synthesis of 1,3-thiazolidine derivatives under eco-friendly conditions. The methodology transcends traditional approaches yielding complex novel compounds with unique *N,S*-heterocyclic structures. By operating at room temperature, utilizing green solvents, and minimizing excess of reactants, this procedure offers an innovative pathway for sustainable chemical development. Notably, this method not only prioritizes sustainability but also delivers high-purity products with exceptional yields. The simplicity of the process, requiring only a simple filtration and featuring short reaction times, underscores its efficiency and utility.

Introduction

The search for new and effective drugs to treat a variety of diseases has led to the exploration of a wide range of chemical structures, such as thioureas and derivatives. Thioureas are very versatile and well-known compounds that have demonstrated a diversity of biological activities, including antifungal,[1] antimicrobial,[2] herbicidal,[3] antiviral,[4] anti-inflammatory[5] and anticancer properties.[6] Moreover, one of the latest works of our group pointed out the promising cytotoxic activities that thiourea-metal complexes – gold(I) and silver(I) – can achieve in different cancer cell lines in a synergic way.[7]

Although the specific properties of each thiourea depend on the unique features of its structure,[8] the common **N**–**C(S)**–**N** core suggests that the principal cellular uptake is related to it.

Therefore, introducing this motif into compounds other than thioureas could potentially enhance the biological properties of other targets. Examples of species that share this interesting structural core are 2-imino-1,3-thiazolidines, many of them with interesting biological activities (Figure 1). Variations over this structural core also confer interesting properties to the final substrates. For example, the main light-emitting molecule responsible for bioluminescence in fireflies – firefly luciferin –, contains two 1,3-thiazoline rings (Figure 1, **II**).

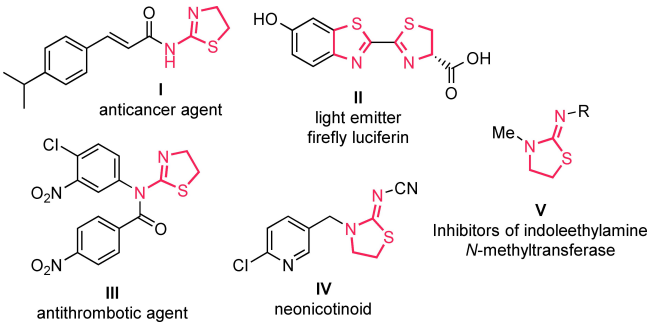

Figure 1. Interesting 1,3-thiazolidine derivatives: **I**,[9] **II**, **III**,[10] **IV**,[11] and **V**.[12]

Because of the presence of 1,3-thiazolidine rings in natural structures, their interest in Medicinal Chemistry has increased in the last decades. For example, some thiazolidinedione drugs (TZDs), based on the 1,3-thiazolidine structure, are used in the treatment of type 2 diabetes, such as the pioglitazone hydrochloride – under the commercial name Actos –[13] and rosiglitazone – under the commercial name Avandia – .[14] Other drugs based on this motif are ralitoline – an anticonvulsant –,[15] etolozin – a loop diuretic –[16] and many synthetic compounds with anti-inflammatory,[17] anti-HIV,[18] antifungal,[19] antiparasitic[20] and anticancer[21] activities, among others.

As a result, numerous approaches for synthesizing functionalized 1,3-thiazolidin-2-imines and derivatives have been described in the literature. For example, using ethanolamine and different isothiocyanates allows obtaining 2-imino-1,3-thiazolidines. However, the process undergoes under high temperatures and acid conditions to remove the alcohol group. Other alternatives often have low atom economies and need an excess of some reactants. Moreover, these stop-and-go processes, or low atom economy cascade processes, need chromatographic techniques to purify their final products, which could result in a lack of sustainability.[22] Herein, we describe a simpler, straightforward, and greener protocol for the obtainment of 1,3-thiazolidin-2-imines **4** (Scheme 1).

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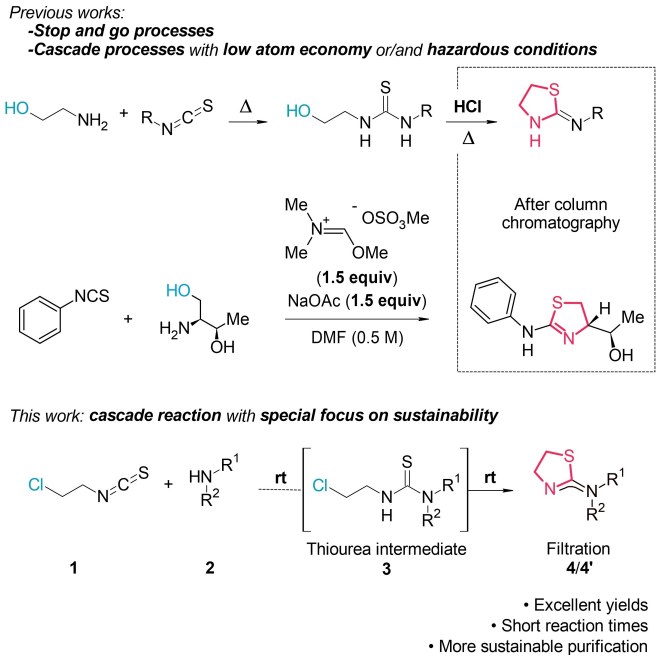


Scheme 1. Hypothesis of work.

Results and Discussion

Although there are some precedents for similar transformations, this work achieves excellent yields and reaction times, making an extra effort to *greenify* the syntheses of these biological cores. The scope of this methodology points out its versatility and ease of use. Besides, it also offers two different reaction pathways, avoiding some usual trouble related to these processes, and making this article a "1,3-thiazoli(di)ne all-in-one-box" ready for any scientist who wants to study sustainably this promising structural motif.

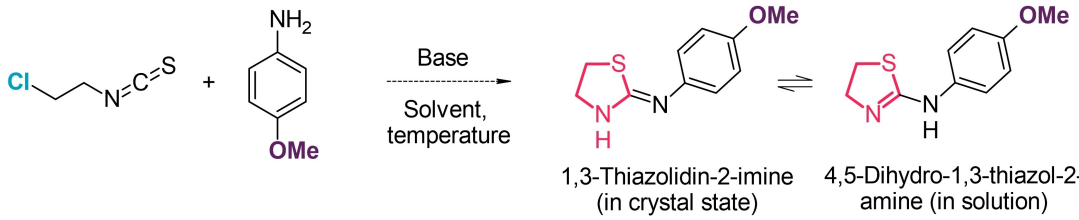
Therefore, a new synthetic route affording 1,3-thiazoli(di)ne derivatives is described here, starting from isothiocyanates **1** and amines **2** in 1:1 equivalence, in green and safe solvents, such as ethyl-L-lactate[23] and ethanol, at room temperature, and using a cascade process (Scheme 1).

Using an isothiocyanate **1**, containing a good leaving group, allows obtaining thioureas **3**. Some thiourea intermediates were isolated to confirm the reaction pathway despite the cascade nature of the process (see supporting information, Table S2). Then, addition of a weak base, like K_2CO_3, leads to an *in situ* cyclization of the intermediate and the formation of the 1,3-thiazolidin-2-imines **4** (characterized in crystal state) and 4,5-dihydro-1,3-thiazol-2-amines **4'** (characterized in solution) after a simple filtration. To compare the process – as a more sustainable option – different conditions were tested before establishing the optimal ones. The tested variables were solvent, temperature, molar ratio between reagents **1** and **2**, and the base. A screening of the process is disclosed in Table 1.

The reaction was carried out in four solvents: DCM, as a common solvent in synthetic chemistry, and ethanol, ethyl-L-lactate, and cyclopentyl methyl ether as significantly more sustainable options.[24]

DCM and ethanol were tested with and without a base to check the background of the reaction (entries 1–3 and 5). The conclusion is that the process needs the presence of a base.

Table 1. Screening of the reaction conditions to obtain 4,5-dihydro-1,3-thiazol-2-amine **4a'**.[a]



1 **2a** **4a** **4a'**

Entry	Solvent (mL)	Temp. (°C)	**1**:**2a** (mmols)	Base (equivs.)	Time (h)	Yield **4a'** (%)[b]
1	CH_2Cl_2 (0.5 mL)	rt	2.0:1.0	–	53	–
2	CH_2Cl_2 (0.5 mL)	rt	2.0:1.0	K_2CO_3 (1.0)	53	82
3	Ethanol (0.5 mL)	rt	2.0:1.0	–	54	–
4	Ethanol (0.5 mL)	rt	2.0:1.0	NaOH (2.0)	53	52
5	Ethanol (0.5 mL)	rt	2.0:1.0	K_2CO_3 (1.0)	54	87
6	Ethanol (0.5 mL)	60	2.0:1.0	K_2CO_3 (1.0)	54	86
7	**Ethyl-L-lactate (0.5 mL)**	**rt**	**1.0:1.0**	**K_2CO_3 (1.0)**	**6**	**94**
8	Cyclopentyl methyl ether (0.5 mL)	rt	1.0:1.0	K_2CO_3 (1.0)	6	90

[a] To a solution of 1.0 mmol of 4-anisidine (**2a**) in the indicated solvent, the corresponding amount of 2-chloroethyl isothiocyanate (**1**) is added. The reaction mixture is left stirring at different temperatures and its course is followed by thin layer chromatography (TLC) (*n*-hexane/ethyl acetate 7:3). Once the reaction is finished and the TLC does not show any rest of amine (the limiting reactant), the base is added under stirring and the reaction is again followed by TLC (*n*-hexane/ethyl acetate 5:5). [b] Isolated yield by filtration.

Moreover, the yield in ethanol was slightly better than in DCM (entries 5 and 2, respectively).

To improve its efficiency, a stronger base, such as NaOH, was tested in ethanol. However, the yield did not progress more than 52% in 53 h (entry 4). Heating to 60 °C (entry 6) did not show better results than at room temperature (entry 5).

The uptick of the procedure came with the use of renewable solvents such as ethyl-L-lactate and cyclopentyl methyl ether. Its use allowed for increasing the speed velocity and reducing isothiocyanate **1** equivalence to 1.0 (entries 7 and 8). Although the yields were similar under both conditions, the ease of operation with ethyl-L-lactate established it as the best solvent.

On the base of the previous results shown in Table 1, the best conditions were found using 0.5 mL of ethyl-L-lactate *per* mmol, a stoichiometric amount of the isothiocyanate **1** and 4-anisidine **2a**, and K_2CO_3 in 1:1:1 molar ratio (entry 7, Table 1). These results deserve special attention due to the excellent yields obtained of final products **4/4'** by direct and simple filtration from the reaction crude, as example of sustainable conditions with the shortest reaction time.

The process is conducted in a synthetic cascade and followed by TLC (*n*-hexane/ethyl acetate 7:3). Once there is only thiourea in the medium, K_2CO_3 is added. The presence of the base triggers the subsequent cyclization reaction. At the same time, it is expected that the HCO_3^- formed in the cyclization process neutralizes the formed acid because of the protonation of the leaving group – HCl – . The proposal of these equilibria is supported by the observation of gas release after base addition – CO_2 from the decomposition of carbonic acid –.

This new methodology was tested with different amines **2** to evaluate the scope of the process (*route A* depicted in Scheme 2).

The procedure allowed obtaining a good number of thiazolidines **4** with excellent results. Interestingly, six compounds – **4s**, **4t**, **4u'**, **4v'** and **4w** – were obtained following a different approach. For these examples, the leaving group is located at the end of the primary amine **6b**, while the aromatic moiety is on the isothiocyanate group **5** (*route B* reported in Scheme 3).

Although the reaction seems similar, the connotations are different. The aliphatic rest of the amines **6** makes the nitrogen atom a better nucleophile, while the activated isothiocyanate **5** is a better electrophile. Therefore, the proposal involved two new reagents: 2-chloroethylamine hydrochloride (**6a**) and 2-bromoethylamine hydrobromide (**6b**). In this situation, K_2CO_3 is added from the beginning since amines **6a** and **6b** are ammonium salts. Thus, a basification of the medium is required before the first addition. In contrast, route A could be more convenient when amine **2** bears aromatic rings with electron-donating groups. Synthesized thiazolidines **4/4'** with the reaction times and yields are shown in Schemes 2 and 3. All the products were characterized in solution by NMR: ^{1}H, ^{13}C-APT{^{1}H}, additional experiments: COSY, HSQC, and HMBC to elucidate the structures; and ^{19}F{^{1}H} for the corresponding species. Some representative examples of relevant compounds were crystallized and measured by X-ray diffraction (Schemes 2 and 3).[25]

From the interpretation of the above results (Schemes 2 and 3), there are some conclusions that can be extracted: 1) Reactions that involve electron-donating groups (**EDG**) in the amine **2** render very good – even excellent – yields in short reaction times. On the other hand, amines with electron-withdrawing groups (**EWG**) needed longer reaction times – even days – to afford comparable yields. 2) 2-Pyridyl and 3-pyridyl derivatives, **4r** and **4q'**, respectively, afforded the double insertion of isothiocyanate in the same thiazolidine molecule. Both species have two thiazolidine rings instead of just one, as the rest of the species. 3) A similar behavior is observed for **4s** and **4t** through route B (Scheme 3), but in this case, it resulted in an insertion of a new thiourea moiety instead of an additional thiazolidine ring. 4) Additionally, in solution, the characterized tautomer of some of the compounds is the 4,5-dihydro-1,3-thiazole derivative **4'**, while in the crystal structure the tautomer **4** was found (see for instance, **4g**, **4j**, **4r**, **4s**, **4t** and **4w**). 5) The reaction between 4-nitroaniline (**2w**) and 2-chloroethyl isothiocyanate (**1**) following route A leads to neither formation of thiazolidine **4w** nor to the thiourea **3w**, in ethyl-L-lactate. Although after four days, the reaction yielded **4w** in 68% using ethanol. In contrast, an 87% yield was afforded in 1.5 h using the reaction pathway B.

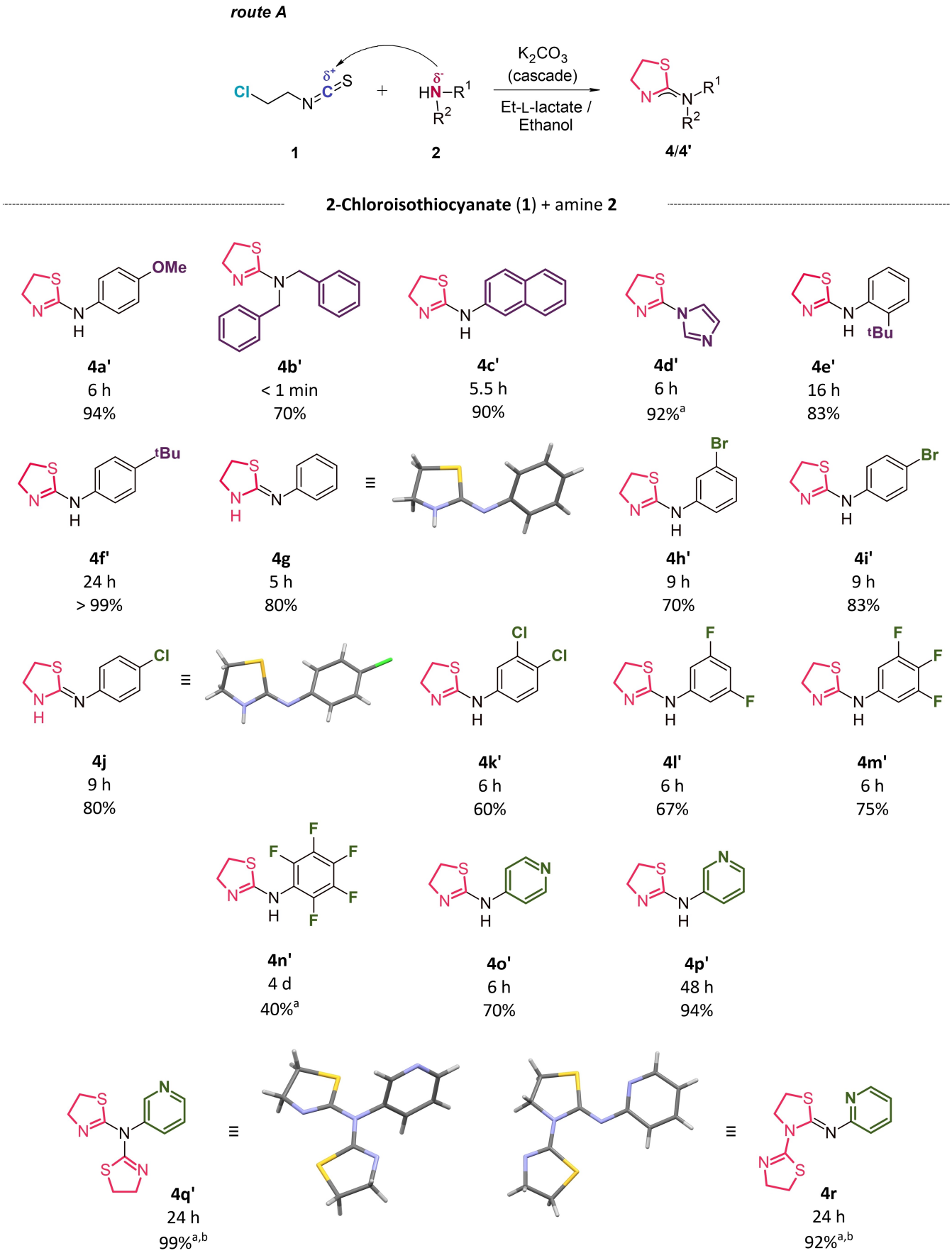
Remarkably, compound **4v'** was obtained through a higher-scale process (10 mmol, 2.61 g) after 2 hours of reaction, with a yield of 86%. This demonstrates the efficiency, simplicity, and scalability of the methodology.

Tautomeric Discussion in Solution and Crystal-State

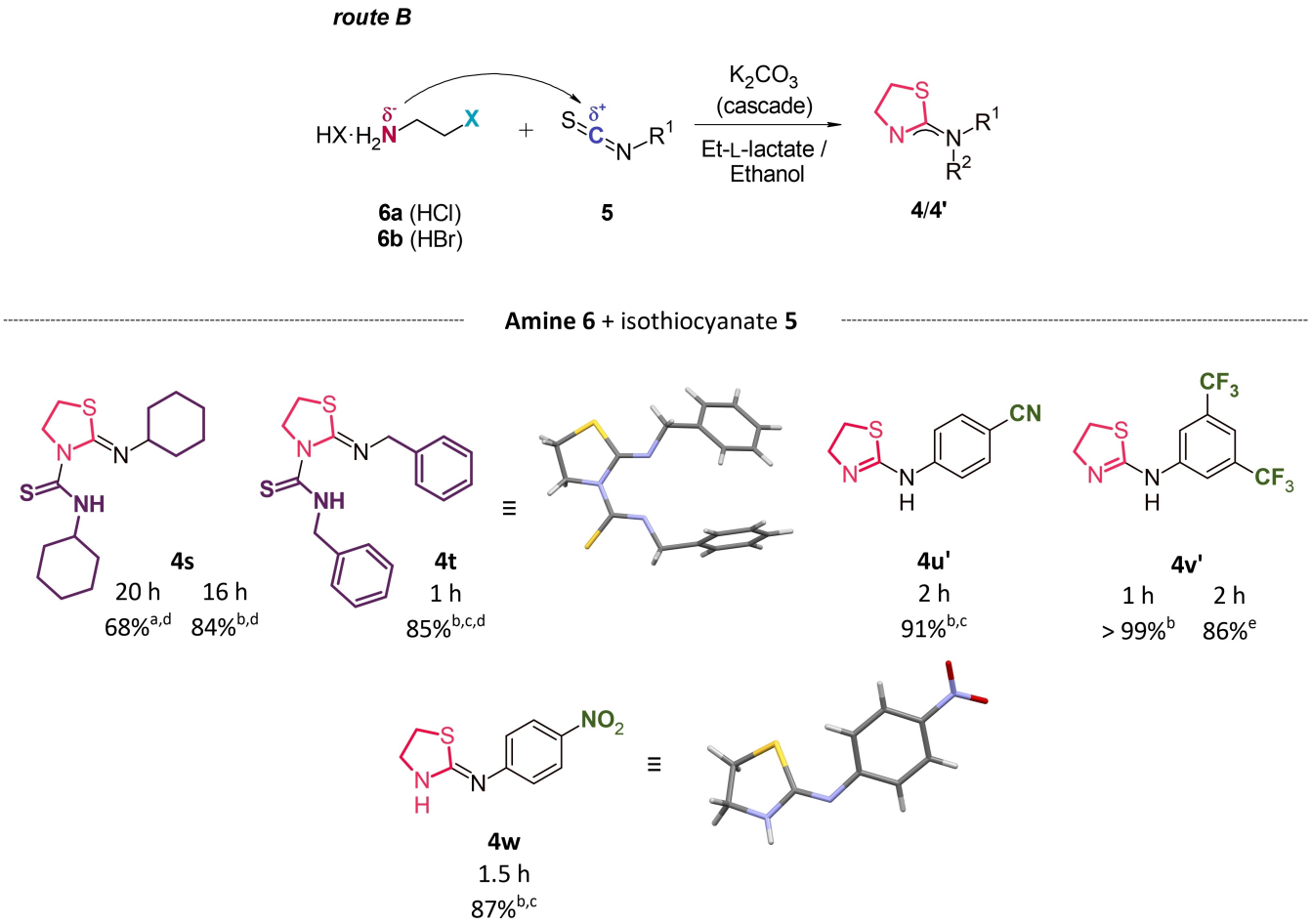
It exists a tautomeric equilibrium between the thiazolidine-2-imine **4** and the 4,5-dihydrothiazol-2-amine **4'**. We have observed that in solution the characterized structures correspond to **4'** (Figure 2, A). An NMR ^{1}H-^{13}C HMBC experiment (Heteronuclear Multiple Bond Correlation) was performed to observe interactions between the NH and its closest carbon. This interaction is key in determining where the NH is located. If the NH is inside the five-membered cycle, a coupling signal corresponding to C_2 would be expected (the aliphatic carbon next to the N atom in the thiazolidine ring). However, if the NH is outside the ring, an interaction between the NH and C_5 is predicted (Figure 2, B).

As anticipated in the second case, there is a correlation between NH and C_5. This signal provides evidence of the presence of a hydrogen atom in the off-cycle nitrogen and a double bond inside. In other words, for the 3,4-dichloro derivative, the characterized tautomer in solution is the *N*-(3,4-dichlorophenyl)-4,5-dihydrothiazol-2-amine (**4k'**).

The explanation proposal for this phenomenon is the energetic barrier between solution and solid-state. While in other tautomeric equilibria the typical situation is a mixture between tautomeric forms, in this case – as we reported for six-membered rings –,[26] the energetic difference among tautomers for these *N,S*-heterocycles seems to be enough to stabilize one



Scheme 2. Route A for the synthesized and characterized products **4** and **4'** with their reaction times and yields. [a] No K_2CO_3 needed. [b] Isothiocyanate/amine molar proportion is 2:1 while still in equivalence.



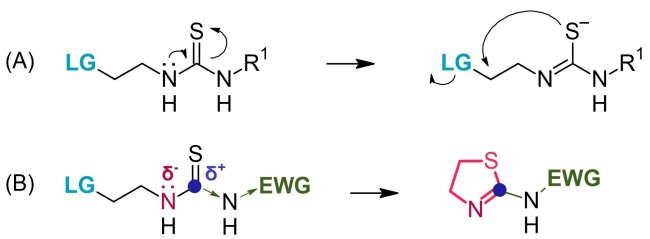
Scheme 3. Route B for the synthesized and characterized products **4** and **4'** with their reaction times and yields. [a] Starting from 2-chloroethylamine hydrochloride (**6a**) and the corresponding isothiocyanate **5**. [b] Starting from 2-bromoethylamine hydrobromide (**6b**) and the corresponding isothiocyanate **5**. [c] Performed in ethanol. [d] Isothiocyanate/amine molar proportion is 2:1 while still in equivalence. e) 10 mmol scale, 2 h, 2.61 g obtained.

of them against the other in certain solvents and the crystallization process. Controlling this equilibrium by changing the reaction medium opens the door to using them like a divergent building block.

Mechanistical and Practical Considerations

The progression from the starting reagents **1**, **2**, **5**, and **6** – Schemes 2 and 3, both routes A and B – to the final thiazoli(di)ne **4**/**4'** products go through a thiourea intermediate **3**, as already stated. Most species above described afforded first to the corresponding thiourea **3** in the lack of base. However, *N*-imidazole, pentafluorophenyl-, 2-pyridyl-, 3-pyridyl- and 4-nitrophenyl- derivatives – **4d'**, **4n'**, **4r, 4q'** and **4w**, respectively – do not need K_2CO_3 to directly drive to the cyclization step. We postulate that the electronic density – in terms of electro-negativity – on the core carbon is key to the stability of the thiourea **3**.

The next mechanism proposal is based on two data: the influence of the substituent on the cyclization rate, and the characterized tautomer in solution. There is an equilibrium in solution between the thiourea and the isothiourea tautomers (Scheme 4, A), and it is the latter that carries out the nucleophilic attack to the activated carbon. Depending on which nitrogen supports the double bond, there are also two isothiourea tautomers. The final thiazoli(di)nes are also in a tautomeric situation. Thus, it seems a reasonable hypothesis to use Occam's razor: the isothiourea tautomer will drive the reaction to the thiazoli(di)ne tautomer. Moreover, strongest **EWG**s activate the core carbon to the isothiourea formation, speeding up the cyclization (Scheme 4, B).



Scheme 4. From thiourea to isothiourea and the cyclization mechanism proposal.

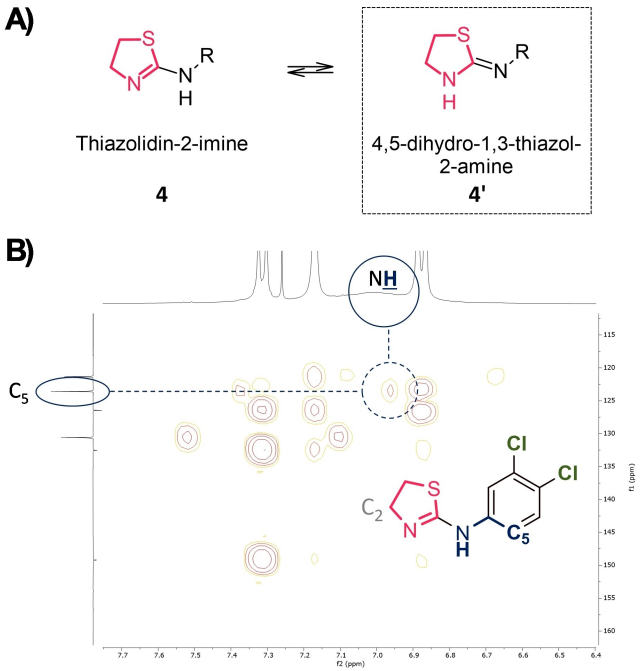


Figure 2. A) Tautomeric equilibrium between the thiazolin-2-imine **4** and the 4,5-dihydrothiazol-2-amine **4'**. B) ^{1}H-^{13}C HMBC NMR (400 MHz, 101 MHz, $CDCl_3$) spectrum for **4k'**.

Therefore, unless the substituent manifests a strong electronic-withdrawing effect – 4-nitro- or pentafluoro- groups –, in which the base is not necessary, without the addition of a base the reaction stops at the thiourea **3**. To prove this hypothesis, thioureas **3a** and **3k** were purified before the K_2CO_3 introduction. Two NH signals in ^{1}H NMR and a thiourea carbon signal in $^{13}C\{^{1}H\}$-APT NMR confirmed the presence of the thiourea **3k** (see supporting information, Figures S79–S82). An analogous experiment led to the characterization of **3a** (see supporting information, Figures S74–S78). The addition of 1 eq. of K_2CO_3 to the thiourea in the same conditions (room temperature, same solvent, and volume) promoted the subsequent cyclization, affording the thiazolines **4a'** and **4k'** with quantitative yields and always in short reaction times.

There are three conclusions that can be extracted from the procedure splitting into two steps: First, the cascade process consists of two different reactions with dissimilar electronic requirements: The first step, the thiourea formation, is a nucleophilic attack from the amine **2/6** nitrogen to the isothiocyanate **1/5** carbon. Hence, the more electronic density that nitrogen has, the short the reaction time and the best yield will achieve. Nevertheless, cyclization has opposite electronic needs. The lowest electronic density that the same nitrogen presents, the more unstable the thiourea **3** is. The cyclization can even be a spontaneous process – without base addition –.

Second, the reaction rate-determining step seems to be the formation of the thiourea **3**. It is because cyclization times are significatively shorter than in the previous attack of the aniline to the isothiocyanate.

Third, the alternative synthetic route – Scheme 2, route B – is a more suitable option in terms of reactivity. Both steps show similar electronic requirements. **EWG**s in the isothiocyanate conduct to best thiourea **3** formation and its further conversion to the thiazolidine **4**.

Conclusions

A new sustainable methodology for synthesizing 1,3-*N,S*-heterocycles – 1,3-thiazolidine-2-imines **4** and 4,5-dihydrothiazol-2-amines **4'** – has been developed.

Emphasizing sustainability addresses a critical need in the industry and represents a significant advancement in producing pharmacologically relevant compounds.

This innovative approach offers considerable shorter reaction times with higher yields, reduced energy consumption, and the elimination of hazardous chemicals. Moreover, the process is scalable, as demonstrated by the reaction conducted on a 10 mmol scale.

Each step of the process has been designed with sustainable considerations in mind. For instance, all compounds were isolated through precipitation and a simple filtration, thereby minimizing the use of large quantities of petroleum-derived organic solvents. All the described compounds are potential building blocks in organic and pharmaceutical synthesis. An exhaustive characterization and structural elucidation of the phase-dependent tautomeric equilibria of the compounds was performed. The conclusions of this discussion were that stabilization of one tautomer allows using it as an isolated building block, and *vice versa.*

Understanding the reaction mechanism allowed for the optimization of conditions, achieving very high yields within just a few hours.

Due to this, the synthesis of novel 1,3-thiazolidine-2-imine derivatives from a sustainable perspective is an unexplored field with great potential to discover. The versatility of this process, combined with the best times and yields reported in the literature, supposes the most advanced example in this area nowadays. Additionally, the preparation of six- and seven-membered rings is an ongoing development in our laboratory and will be published in due course.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Cascade · Isocyanate · Sustainability · 1,3-thiazolines · 1,3-thiazolidines

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