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Formal [3+2] Annulation Involving Allylic Bromides and Thioureas. Synthesis of 2-Iminothiazolidines through a Base-Catalyzed Intramolecular *anti*-Michael Addition

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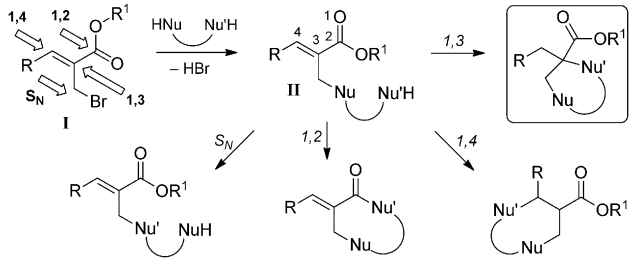
Abstract: A simple and efficient protocol was developed for the synthesis of 2-iminothiazolidines through a base-mediated [3+2] annulation involving substituted thioureas and allylic bromides bearing electron-withdrawing groups. This domino process consists of nucleophilic displacement, followed by intramolecular *anti*-Michael addition of the preformed allylic isothiourea under mild conditions to give the thiazolidine core.

Keywords: 2-iminothiazolidines; allylic compounds; annulations; *anti*-Michael addition; N-heterocycles

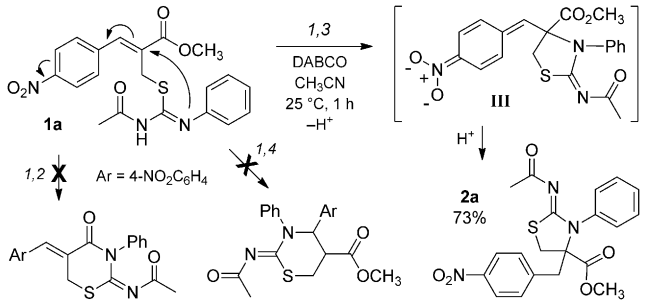


Scheme 1. Cyclization modes for allylic bromides **I** and derivatives **II**.

The development of efficient synthetic methods, where structural diversification is selectively assembled at the molecular level from multifunctional small molecules through several bond-forming and bond-breaking processes in a single reaction vessel,[1] constitutes one of the key paradigms of modern organic chemistry. Toward this endeavor, tandem and domino processes[2] have found widespread applications due to the reduced number of laboratory operations and purification procedures. Their superior practicability and economical feasibility are obvious advantages compared to conventional multistep synthesis.

Allylic bromides **I**, derived from the Morita–Baylis–Hillman (MBH) reaction, are versatile building blocks, mainly due to their widespread use in heterocycle synthesis[3] (Scheme 1). The multifaceted reactivity of allylic bromides **I** is largely justified by the existence of three electrophilic centers that are capable to selectively react with nucleophiles to give products of either nucleophilic displacement (S_N-mode) or addition (1,2- or 1,4-mode). Therefore, carbo- and heterocyclic frameworks can be readily constructed by combining derivatives of the MBH reaction, such as the allylic bromides **I**, with ambident nucleophiles to give products of "normal" 1,2- as well as "conjugated" 1,4-addition (Michael-type additions)[4] from the common intermediate **II**. However, despite the known behavior of α,β-unsaturated carbonyl compounds containing strongly electron-withdrawing groups at the β-position to participate in nucleophilic α-addition (1,3- or *anti*-Michael addition),[5] as far as we know, cyclic products generated from intramolecular 1,3-addition have not yet been developed for allylic compounds **I** or **II**.

During the development of the intramolecular 1,2-addition of allylic isothiouronium salts and analogues to access the thiazin-4-one core,[6] we found that the 4-nitroaryl-substituted isothiourea **1a** furnished the unexpected 2-iminothiazolidine **2a** (possibly through the intermediacy of **III**, Scheme 2) in good isolated yield, without any trace of the expected adducts from 1,2- or 1,4-addition. Due to the novel reactivity of **1a** and the importance of 2-iminothiazolidines as pharmacologically privileged structural motifs with a diverse biological activity[7] (including their use as antitumor, anti-inflammatory, insecticide and radioprotection agents), we decided to investigate the scope of this intramolecular *anti*-Michael addition with the aim of developing a simple methodology for the synthesis of multisubstituted 2-iminothiazolidines.



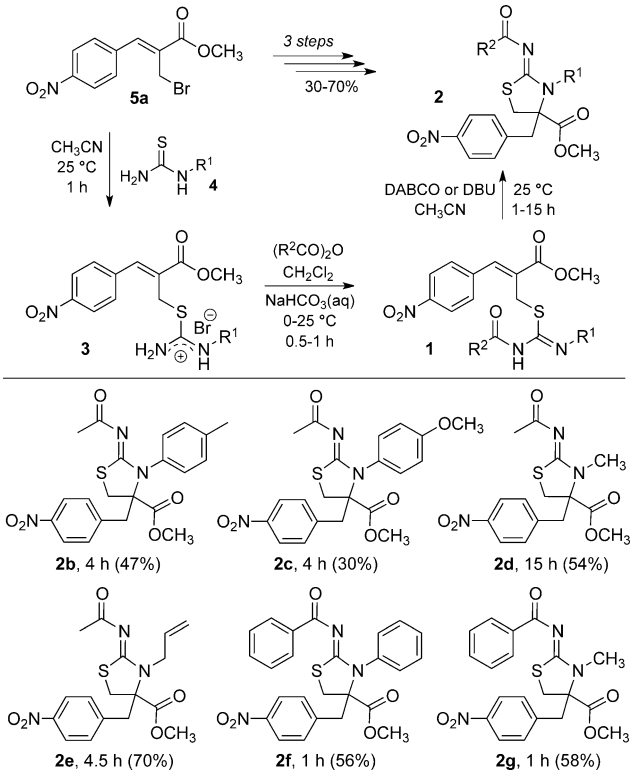
Scheme 2. Formation of the thiazolidine (1,3-addition) *versus* the thiazine (1,2- or 1,4-addition) core.

The preparation of the required isothiouronium salts **3** was readily achieved by combining a variety of *N*-substituted thioureas **4** with the 4-nitroaryl-substituted allylic bromide **5a** (which was obtained in high yield by treating the corresponding α-methylene-β-hydroxyester with $LiBr/H_2SO_4$)[8] in acetonitrile at rt in 66–97% yield (Scheme 3). Subsequent base-mediated acetylation of *N*-substituted salts **3a–d** using acetic anhydride under a biphasic medium furnished the expected products as a mixture of monoacetylated isothioureas,[6b] with the *N*-acetyl-*N*′-substituted isomers **1a–d** being the major products. On the other hand, the *N*-allyl-substituted isothiouronium salt **3e** was found to be an exception, as only isomer **1e** was formed in the acetylation step. Similarly, the benzoylation of salts **3a,d** using benzoic anhydride under the stated conditions gave the corresponding *N*-benzoylated isothioureas **1f,g** as the sole isomers (Scheme 3).

Each acylated isothiourea **1** could be purified by chromatography before being submitted to the base-catalyzed intramolecular *anti*-Michael addition. However, better results were obtained when the crude *N*-acylated products **1** were treated with DABCO or DBU in acetonitrile at rt for 1–15 h to give either the acetylated or benzoylated 2-iminothiazolidines **2a–g** with moderate to good overall yields (three steps from the allylic bromide **5a**, Scheme 3). Remarkably, the formation of any product coming from competitive 1,2- or 1,4-addition was not detected in the crude reaction.

While this simple three-step methodology to access structurally diverse 2-iminothiazolidines **2** from the allylic bromide **5a** was useful and potentially amenable to scale-up (as only one chromatographic purification is required), the number of work-up and separation procedures limited its broader application and also may have a negative impact on the overall yields for particular substrates. In addition, this three-step strategy (as depicted in Scheme 3) did not work well with substrates containing electron-withdrawing groups other than 4-nitro (see discussion below).

Therefore, we envisioned a more convergent synthetic approach wherein 2-iminothiazolidines **2** could

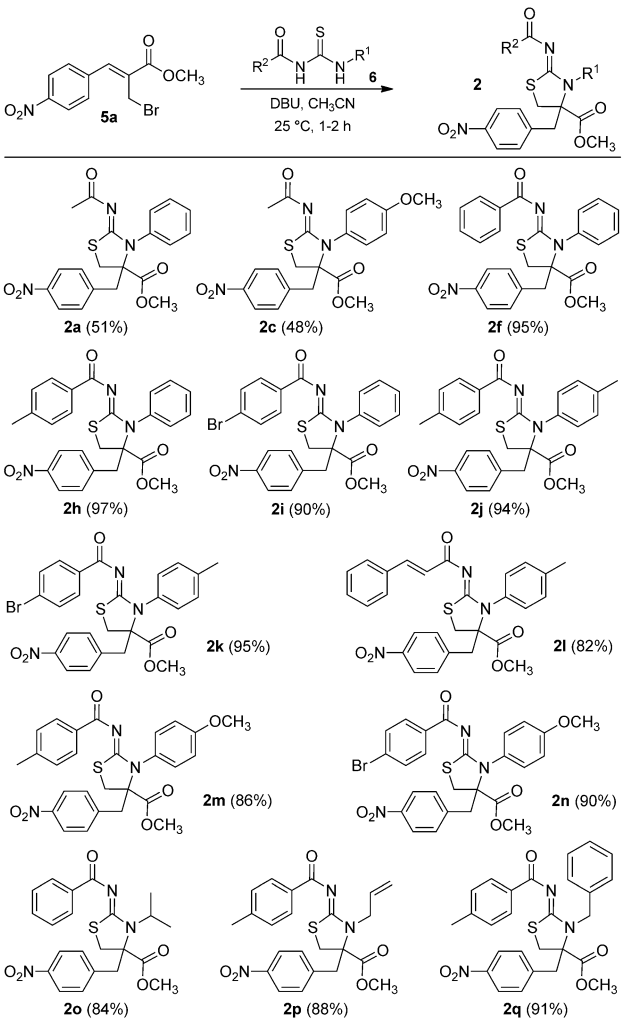


Scheme 3. Base-mediated intramolecular *anti*-Michael addition from *N*-acylated isothioureas **1** (isolated yields).

be directly obtained by a formal [3+2] annulation involving the reaction of allylic bromide **5a** with *N*-acyl-*N*′-substituted thioureas **6** in the presence of a suitable base (Scheme 4). By combining **5a** and *N*-acyl thioureas containing different substitution patterns in the presence of DBU in acetonitrile at rt, the reaction cleanly furnished the expected 2-iminothiazolidines **2**. Other combinations of base (DABCO, DIPEA, K_2CO_3) and solvent (THF, MeOH) were also tried, but they all gave inferior results (slower reaction rates and competitive formation of side products) compared to DBU in acetonitrile.

This [3+2] annulation proved to have general application and was also tolerant to a variety of functional groups. Similarly to the three-step method displayed in Scheme 3, acetyl-derived 2-iminothiazolidines **2a,c** could not be obtained in high isolated yields, while the aroylated products **2f, h–k, m–q**, as well as the cinnamoyl derivative **2l**, were readily obtained in excellent yields as crystalline solids. In addition, the substitution at the nitrogen in the 3-position of the ring does not seem to cause any deleterious effect, as both *N*-aryl- (**2a,c,f, h–n**) and *N*-alkyl-substituted (**2o-q**) 2-iminothiazolidines were isolated in high yields.

To investigate the scope of this base-mediated [3+2] annulation, the reaction of acylthioureas **6** with allylic bromides **5** containing different electron-withdrawing groups attached to the aryl ring was per-

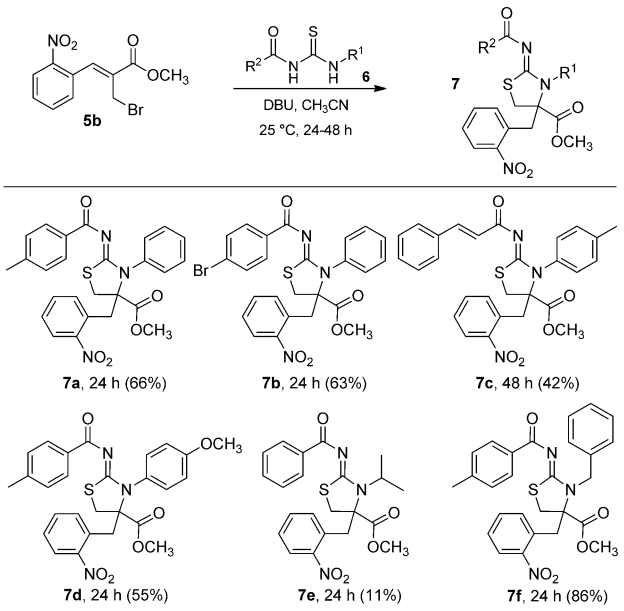


Scheme 4. Base-mediated [3+2] annulation involving allylic bromide **5a** and *N*-acylthioureas **6** (isolated yields).

formed (Scheme 5). Thus, allylic bromide **5b**, with a nitro group at the 2-position, was also able to drive the cyclization through the corresponding 2-iminothiazolidines **7a–f** in good yields, except for **7e** (11 %). In this case, this disappointing yield was largely due to an inefficient chromatographic separation of the main product **7e** from other side products present in the crude reaction.

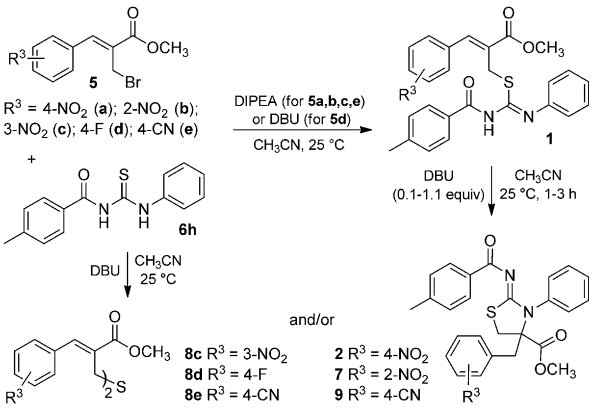
Compared to the reaction carried out with 4-nitro-substituted bromide **5a** (Scheme 4), which was completed in 1–2 h, the transformation involving the 2-nitro analogue **5b** was much slower (24–48 h, Scheme 5). This lower reactivity might be related to the formation of competitive side products observed in a few cases.

Notably, the activation mode of the nitro group was completely lost if it was attached to the 3-position of the aryl ring, with no desired 2-iminothiazolidine **7** being observed in the crude reaction mixture after treating the 3-nitro-substituted allylic bromide **5c**



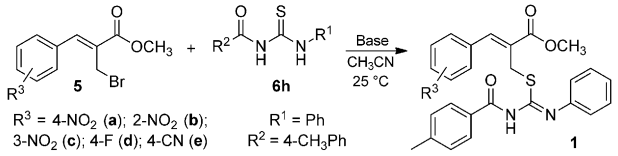
Scheme 5. Base-mediated [3+2] annulation involving allylic bromide **5b** and *N*-acylthioureas **6** (isolated yields).

with a proper acylthiourea **6h** in the presence of DBU. Instead, cleavage of the S-CN bond took place to give the symmetric sulfide **8c** in high yield[9] (Scheme 6). Due to the well-known propensity of isothioureas to undergo cleavage of the amidino group through alkaline solvolysis to generate thiolates,[6b,10] the intermediacy of this nucleophilic species should be considered to explain the formation of sulfide **8c**. Similar behavior was observed for the reaction of the 4-fluoro-substituted allylic bromide **5d** with acylthiourea **6h** and DBU, with variable mixtures of isothiourea **1t** and sulfide **8d** being noticed in all reactions under study (Scheme 6 and Table 1). Additionally, no cyclization product was ever detected in the crude reaction, even after prolonged periods.



Scheme 6. Isothioureas **1**, 2-iminothiazolidines **2**, **7**, and **9** and sulfides **8** from bromides **5** and thiourea **6h**.

Table 1. Preparation of isothioureas **1** from bromides **5**.[a]



#	R^3	Base	Time [h]	Yield [%][b]
5a	4-NO_2	DIPEA	2	**1h** (98)[c]
5b	2-NO_2	DIPEA	24	**1r** (86)
5c	3-NO_2	DIPEA	24	**1s** (85)
5d	4-F	DBU	2	**1t** (94)
5e	4-CN	DIPEA	24	**1u** (90)[c]

[a] Conditions: **5** (1.0 mmol), **6** (0.95 mmol), base (1.1 mmol), CH_3CN (6 mL).
[b] Isolated yields after chromatography.
[c] Isolated yields after crushing the solid in ethyl ether.

In the case of the cyano-substituted allylic bromide **5e**, the reaction with acylthiourea **6h** mediated by DBU led to the formation of the corresponding 2-iminothiazolidine **9**, together with sulfide **8e** and other side products. The presence of **9** was noted by the appearance of two characteristic pairs of doublets in the ^{1}H NMR of the crude reaction, which are related to each diastereotopic methylene group (CH_2S and CH_2Ar). However, given the difficulties associated with the chromatographic separation at this time, another strategy to obtain cyclization products was explored, which involved the intermediacy of isothioureas **1**.

As stated above, among the bases tested for this [3+2] annulation, DBU (1.1 equiv) gave the best results in all cases, while the use of DABCO or K_2CO_3 led to slow reaction rates and formation of side products. On the other hand, the bulky diisopropylethylamine (DIPEA) was not able to mediate the cyclization step; instead, the corresponding isothiourea **1h** was the only product observed in the reaction medium after reacting bromide **5a** with thiourea **6h** (Scheme 6 and Table 1). Similarly, representative isothioureas **1r–u** containing electron-withdrawing groups attached to the aryl ring were prepared by treating the corresponding bromides **5b,c,e** with thiourea **6h** and DIPEA (or DBU, in the case of the less reactive fluoro-substituted bromide **5d**).

For the more reactive 4-nitro-substituted isothiourea **1h**, a catalytic amount of DBU (0.1 equiv) led to 100% conversion of the starting material to the corresponding 2-iminothiazolidine **2h** after 1 h.

Therefore, as anticipated from the study involving the three-step method depicted in Scheme 3, the isothioureas **1** are clearly the key intermediates for the subsequent base-catalyzed intramolecular *anti*-Michael attack to give the 2-iminothiazolidines **2** in high yields.

On the other hand, the treatment of the 3-nitro-substituted isothiourea **1s** with DBU did not result in the formation of the expected 2-iminothiazolidine, with the only isolable compound being the symmetric sulfide **8c**, albeit in low yield (Scheme 6). Similar results were observed for the 4-fluoro-substituted isothiourea **1d**, where no product coming from the intramolecular *anti*-Michael cyclization was ever detected.

Applying the same strategy for the cyano-substituted isothiourea **1u** (prepared from the corresponding allylic bromide **5e** and acylthiourea **6h** using DIPEA) led to the formation of a mixture containing the 2-iminothiazolidine **9** and the sulfide **8e** (Scheme 6), which were fully characterized after being separated by chromatography (see the Supporting Information). Therefore, the cyano group was partially capable of controlling the intramolecular *anti*-Michael step toward cyclization to the 2-iminothiazolidine **9**, although it is less reactive than the 2- and 4-nitro-substituted analogues, with the latter being the most reactive of all substrates tested.

In conclusion, we developed a straightforward methodology for the synthesis of a variety of 2-iminothiazolidines **2**, **7** and **9**, from a base-mediated [3+2] annulation starting from readily available allylic bromides **5** and acylthioureas **6**. Prior preparation of the *N*-acylisothiourea intermediates **1** with subsequent cyclization through intramolecular *anti*-Michael addition was also successfully explored. This process is remarkably modular, operationally simple, and tolerates a variety of functional groups, thus demonstrating its general applicability.

Experimental Section

Representative Procedure for the Synthesis of 2-Iminothiazolidines 2 from Allylic Bromide 5a

To a stirred suspension of *N*-acyl-*N'*-substituted thiourea **6** (1.1 mmol) in acetonitrile (3.0 mL) at 25 °C was added DBU (1.1 mmol) followed by a solution of allylic bromide **5a** (1.0 mmol) in acetonitrile (3.0 mL). After stirring for 1–2 h, the final mixture was diluted with CH_2Cl_2 and the organic extract was washed with 0.1 M HCl, H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (7:3 hexane/ethyl acetate) to give the corresponding 2-acyliminothiazolidines **2a,c,f,h–q**. For products **2a,c** the solid obtained after the chromatography was crushed in ethyl ether and filtrated to give pure 2-acyliminothiazolidines.

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