# Intramolecular Aza-Anti-Michael Addition for the Synthesis of 2-Iminothiazolidines

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## INTRODUCTION

Allylic bromides **1** (derived from the Morita-Baylis-Hillman adducts) are versatile intermediates for the preparation of cyclic compounds.[1] In addition, substituted thioureas **2** are widely used in reactions with molecules having more than one electrophilic center allowing the synthesis of heterocycles with biological properties.[2]

As part of our research interest in synthetic transformations involving allylic bromides **1** with ambident compounds,[3] herein we report the intramolecular aza-anti-Michael reaction of allylic bromides **1** with thioureas **3** as a new methodology for the synthesis of 2-iminothiazolidine derivatives.

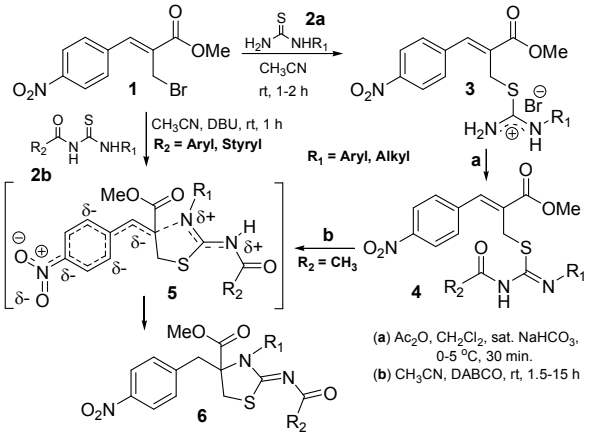
## RESULTS AND DISCUSSION

Allylic bromides **1** were obtained in high yields by treating α-methylene-β-hydroxyesters (Morita-Baylis-Hillman adducts) with $LiBr/H_2SO_4$ in acetonitrile (75-90% yield).[4]

The reaction of allylic bromides **1** with *N*-substituted thioureas **2a** in acetonitrile furnished isothiuronium salts **3** (66-97%, Scheme 1). Subsequent acetylation reactions of *N*-substituted salts **4** with acetic anhydride under basic medium at low temperature furnished a mixture of monoacetylated isomers[3b] where **4** was the major product (60-80%, conversion, determined by $^1H$ NMR 400 MHz, $CDCl_3$, Scheme 1).

Monoacetylated isomer **4a** ($R_1 = C_6H_5$, $R_2 = CH_3$) was purified by column chromatography. Subsequent treatment of **4a** with base (DABCO) in acetonitrile allowed the unexpected formation of 2-iminothiazolidine **6a** through the conjugate addition at the α-position of the alkenoate acceptor known as the anti-Michael reaction (91% yield). Complete structural elucidation of compound **6a** was achieved by X-ray crystallography analysis (Scheme 1, Table 1). Cyclization reaction of crude mixtures of *N*-acetylated products **4** in basic medium without prior purification also furnished the corresponding 2-iminothiazolidines **6** in reasonable yields (Scheme 1, Table 1).

In a more convergent synthetic approach, 2-iminothiazolidines **6** could also be obtained in good yields from a one-step reaction of *N*-benzoyl-*N'*-substituted thioureas **2b** with allylic bromides **1** in the presence of DBU (Scheme 1, Table 2).




**Scheme 1**

**Table 1.** 2-Iminothiazolidines **6** from isothiouronium salts **3**.

| 6 [a] | $R_1$ | Time (h) | Yield (%) [b] | Mp (°C) |
|---|---|---|---|---|
| **6a** | $C_6H_5$ | 1.5 | 73 | 151.5-153.0 |
| **6b** | $4\text{-}CH_3C_6H_4$ | 4 | 47 | 174.5-176.0 |
| **6c** | $4\text{-}CH_3OC_6H_4$ | 4 | 30 | 167.5-168.5 |
| **6d** | $CH_3$ | 15 | 54 | 135.0-136.0 |
| **6e** | $CH_2{=}CHCH_2$ | 4.5 | 70 | 126.5-127.5 |

[a] $R_2 = CH_3$. [b] Isolated yield.

**Table 2.** 2-Iminothiazolidines **6** from allylic bromides **1**.

| 6 | $R_1$ | $R_2$ | Yield (%) [a] | Mp (°C) |
|---|---|---|---|---|
| **6a** | $C_6H_5$ | $C_6H_5$ | 95 | 234.0-235.0 |
| **6b** | $(CH_3)_2CH$ | $C_6H_5$ | 84 | 131.5-133.5 |
| **6c** | $C_6H_5CH_2$ | $4\text{-}CH_3C_6H_4$ | 91 | 179.5-180.5 |
| **6d** | $CH_2{=}CHCH_2$ | $4\text{-}CH_3C_6H_4$ | 88 | 141.0-142.0 |
| **6e** | $4\text{-}CH_3C_6H_4$ | $C_6H_5CH{=}CH$ | 82 | 152.5-154.5 |

[a] Isolated yield.

## CONCLUSION

A simple protocol for the synthesis of 2-iminothiazolidines **6** in goods yields via intramolecular aza-anti-Michael addition of Morita-Baylis-Hillman derivatives under mild conditions was developed.

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CAPES, CNPq, INCT-Catálise

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