



# 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.<sup>1</sup> 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.<sup>2</sup>

As part of our research interest in synthetic transformations involving allylic bromides **1** with ambident compounds,<sup>3</sup> 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.

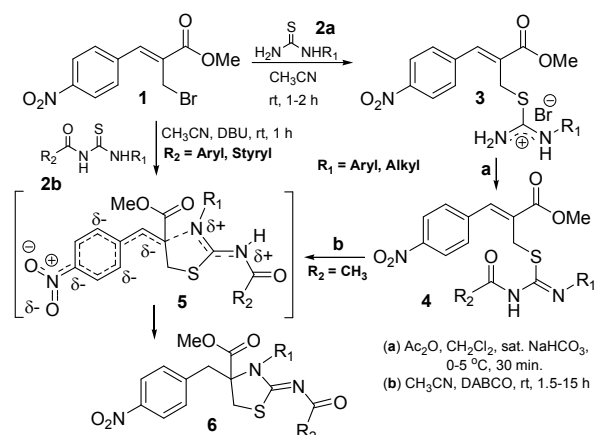
## RESULTS AND DISCUSSION

Allylic bromides **1** were obtained in high yields by treating  $\alpha$ -methylene- $\beta$ -hydroxyesters (Morita-Baylis-Hillman adducts) with LiBr/H<sub>2</sub>SO<sub>4</sub> in acetonitrile (75-90% yield).<sup>4</sup>

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<sup>3b</sup> where **4** was the major product (60-80%, conversion, determined by <sup>1</sup>H NMR 400 MHz, CDCl<sub>3</sub>, Scheme 1).

Monoacetylated isomer **4a** (R<sub>1</sub> = C<sub>6</sub>H<sub>5</sub>, R<sub>2</sub> = CH<sub>3</sub>) 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  $\alpha$ -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 isothiuronium salts **3**.

<b>6</b> <sup>a</sup>	R <sub>1</sub>	Time (h)	Yield (%) <sup>b</sup>	Mp (°C)
<b>6a</b>	C <sub>6</sub> H <sub>5</sub>	1.5	73	151.5-153.0
<b>6b</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4	47	174.5-176.0
<b>6c</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	4	30	167.5-168.5
<b>6d</b>	CH <sub>3</sub>	15	54	135.0-136.0
<b>6e</b>	CH <sub>2</sub> =CHCH <sub>2</sub>	4.5	70	126.5-127.5

<sup>a</sup> R<sub>2</sub> = CH<sub>3</sub>. <sup>b</sup> Isolated yield.

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

<b>6</b>	R <sub>1</sub>	R <sub>2</sub>	Yield (%) <sup>a</sup>	Mp (°C)
<b>6a</b>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	95	234.0-235.0
<b>6b</b>	(CH <sub>3</sub> ) <sub>2</sub> CH	C <sub>6</sub> H <sub>5</sub>	84	131.5-133.5
<b>6c</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	91	179.5-180.5
<b>6d</b>	CH <sub>2</sub> =CHCH <sub>2</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	88	141.0-142.0
<b>6e</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH	82	152.5-154.5

<sup>a</sup> Isolated yield.

## CONCLUSION

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

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