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Regioselective synthesis of 3-(heteroaryl)-iminothiazolidin-4-ones

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Abstract—Cyclization of unsymmetrical thioureas affords 3-(heteroaryl)-iminothiazolidin-4-ones with excellent levels of regiocontrol. In the absence of base, 2-(pyridylmethyl) and 2-(aminomethyl)benzimidazolyl substituents on the thiourea scavenge acid that is generated upon sulfur alkylation with bromoesters. The resulting conjugate acid plays an important role in influencing the regiochemical outcome and overall rate of the reaction.

The thiazolidinone ring system has been widely employed in the investigation of pharmacologically active heterocyclic compounds,[1] perhaps most notably as a common structural motif in the glitazone class of PPAR-γ agonists (**1**, Fig. 1).[2] In contrast, imino derivatives of thiazolidinones are less common, despite the clear opportunity to introduce an additional handle for chemical diversity and thus enable exploration of unmapped regions of a thiazolidinone-based pharmacophore (region B, **2**). One reason might be the lack of efficient synthetic methods to prepare iminothiazolidinones, in particular with distinct substitution patterns on each of the nitrogen atoms. We report here one approach to this heterocyclic ring system that reliably installs diverse functionality around the iminothiazolidinone core.

A common synthetic strategy to construct iminothiazolidinones relies on cyclization of thioureas with

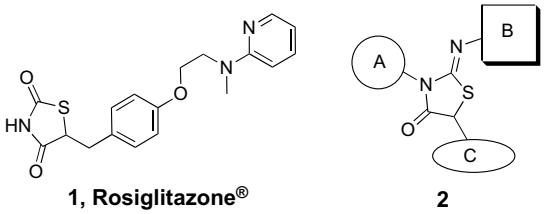
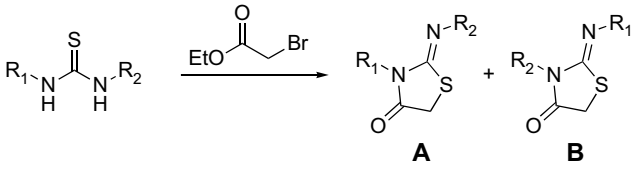


Figure 1. Thiazolidinone (**1**) and iminothiazolidinone (**2**) ring systems.

α-halo esters or acids in the presence of an inorganic base (i.e., NaOAc) in polar solvents such as ethanol or acetic acid. For unsymmetrical thioureas ($R_1 \neq R_2$, Eq. 1), regiocontrol in the cyclization step is typically influenced by electronic factors that predispose electron-withdrawing substituents (i.e., aryl or heteroaryl) to maintain conjugative stabilization with the imine nitrogen (i.e., R_2 in structure **A**). This electronic preference allows the regioselective cyclization of a thiourea bearing one alkyl and one aryl substituent or two aryl groups having dramatically different electronic properties.[3] However, in the absence of an electronic bias (i.e., $R_1 = R_2 =$ alkyl), the reaction of an unsymmetrical thiourea with an α-halo ester or acid is expected to proceed with minimal regioselectivity.



(1)

Indeed, the reaction of 1-benzyl-3-(3-chlorobenzyl)-thiourea with ethyl bromoacetate and 2.0 equiv of NaOAc in EtOH (80 °C, 16 h) afforded a 1:1 mixture of regioisomeric iminothiazolidinone products. We wondered whether this poor selectivity could be improved by the replacement of one of the arylmethyl thiourea substitutents with a heteroarylmethyl group. While we expected no electronic bias to influence the regiochemical outcome of the cyclization, we hoped that a potential hydrogen bond between a protonated heterocycle and

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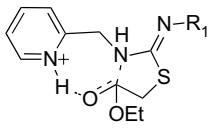
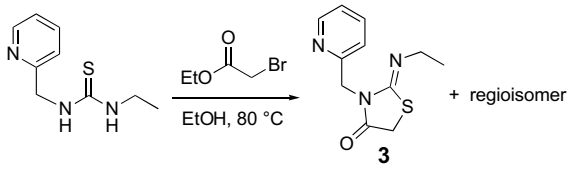


Figure 2. Selective cyclization via intramolecular hydrogen bond.

the reacting carbonyl ester might predispose the proximal thiourea nitrogen to cyclize (Fig. 2).

We elected to omit NaOAc from the thiourea cyclization conditions to maximize the effect of the proposed hydrogen bond. To test this hypothesis, the unsymmetrical thiourea prepared from 2-(aminomethyl)pyridine and ethyl isothiocyanate was treated with 1.0 equiv of ethyl bromoacetate in EtOH at 80 °C for 2 h. Under these 'acidic' conditions (no exogenous base), the predicted 2-ethylimino-3-pyridin-2-ylmethyl-thiazolidin-4-one (**3**, Eq. (2)) was generated with 16:1 regioselectivity, whereas a completely non-selective cyclization occurred when 2.0 equiv of NaOAc was present during the reaction.



(2)

The regiochemistry of **3** was established unequivocally by heteronuclear multiple bond correlation (HMBC) between the benzylic C–H bonds and both the C=O and C=N ring carbons. Single crystal X-ray analysis confirmed this connectivity, and also established the imine geometry of **3** (Fig. 3). As one might predict based on steric considerations, the ethyl group is oriented away from the ring nitrogen substituent with a measured torsion angle S1–C1–N2–C4 = 2.3°.[4]

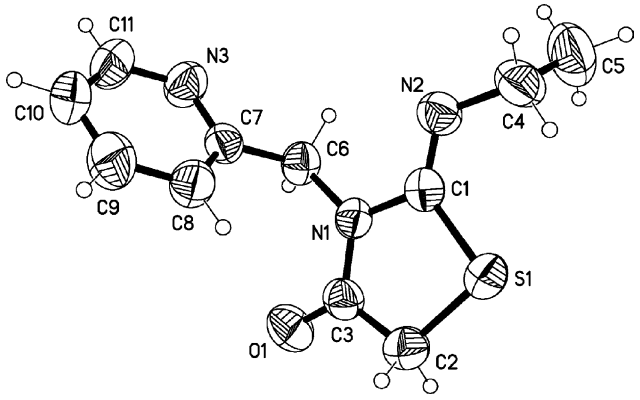


Figure 3. Thermal ellipsoid plot (50% probability) of **3** using crystallographic numbering.

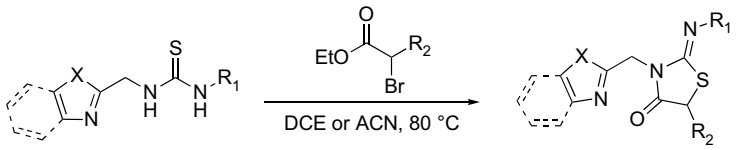
The corresponding 3- and 4-(aminomethyl)pyridine thioureas were also prepared to probe the role of the protonated pyridine nitrogen in preorganizing the transition state assembly. As expected, these thioureas afforded equimolar mixtures of iminothiazolidinone regioisomers, regardless of whether NaOAc was added (data not shown). These data collectively suggest that the excellent levels of regiocontrol are a direct consequence of an intramolecular hydrogen bond between the conjugate acid of the heteroaryl-substituted thiourea and the reacting ester carbonyl moiety.

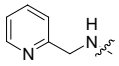
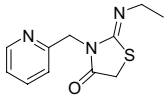
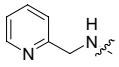
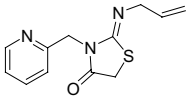
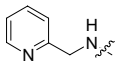
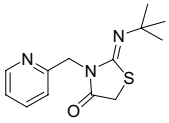
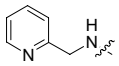
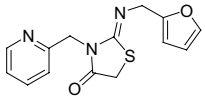
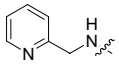
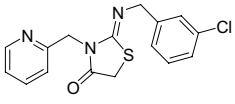
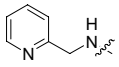
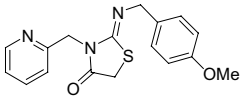
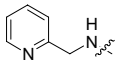
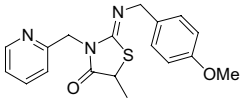
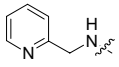
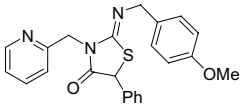
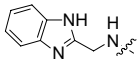
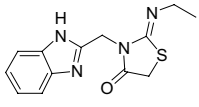
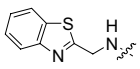
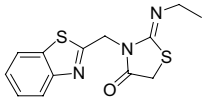
Iminothiazolidinone **3** was the predominant isomer obtained when the cyclization was performed in other solvents (ACN, THF, DCE, toluene), suggesting that a protic medium was not required for the H bond directing effect of the protonated heterocycle. To rapidly investigate a diverse set of imine substitution patterns, we developed a one-pot procedure[5] for thiourea formation and subsequent cyclization that proved to be robust and highly regioselective (Table 1). Aliphatic substituents ranging from allyl to *t*-butyl could be efficiently installed as the imine substituent of the iminothiazolidinone (entries 1–3). Arylmethyl groups emanating from the imine nitrogen could also be selectively prepared, including the iminothiazolidinone derived from 3-chlorobenzyl isothiocyanate (entry 5), which in the absence of a H bond directing effect was completely unselective in the cyclization event (vide supra). It is interesting that the pyridine nitrogen is also responsible for a significant rate acceleration, as the phenyl version of the thiourea cyclization requires overnight heating in DCE to go to completion, whereas all of the pyridylmethyl-substituted thioureas are consumed within 2 h. Thus in addition to influencing the regiochemical outcome of the cyclization, the pyridinium conjugate acid plays an important role in activating the carbonyl ester towards nucleophilic attack.

Substitution on the bromo ester component was also feasible, although the initial displacement of the bromide by thiourea required a more polar solvent like acetonitrile to drive the reaction to completion (entries 7 and 8). In general, all of the 2-(aminomethyl)pyridyl thioureas investigated reacted with excellent efficiency (isolated yields 64–90%) and regioselectivity (>15:1) to afford iminothiazolidinone cores that were decorated with up to three aryl-containing functionalities.[6] Our investigation of other heterocycles identified benzimidazole as an equally effective directing group (entry 9). However, the benzothiazole moiety was less competent as a directing group, and afforded the corresponding iminothiazolidinone with low regioselectivity (2.4:1, entry 10).

Based on our model, one would expect a 2-pyridyl thiourea that lacks the intervening methylene spacer to perform as well if not better than the (aminomethyl) pyridyl group in terms of its directing ability, as the resulting hydrogen bond would be placed in a six-membered cyclic arrangement. Unfortunately, when the cyclization of 1-phenyl-3-pyridyl thiourea was investigated under 'acidic' conditions, only a trace amount of

Table 1. Regioselective cyclization of unsymmetrical thioureas

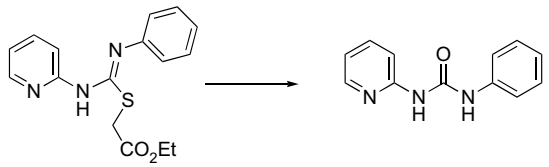


Entry	Heterocycle	R_1	R_2	Product	Ratio[a]	Yield (%)[b]
1		Et	H		94:6	80
2		Allyl	H		98:2	90
3		*t*-Butyl	H		>99:1	85
4		2-Furylmethyl	H		>99:1	68
5		3-Cl-Benzyl	H		96:4	80
6		4-MeO-Benzyl	H		98:2	85
7		4-MeO-Benzyl	Me[c]		96:4	64
8		4-MeO-Benzyl	Ph[c]		97:3	84
9		Et	H		94:6	73
10		Et	H		71:39	51

[a] Ratio of regioisomers as measured by HPLC analysis of crude reaction mixtures.
[b] Isolated yield.
[c] Acetonitrile used as reaction solvent.

iminothiazolidinone was observed. Instead, the majority of the thiourea was degraded under the reaction conditions to the corresponding urea, a result which may be explained by the poor nucleophilicity of the anilinic thiourea nitrogen atom or the reduced basicity of the pyridine nitrogen. Either (or both) of these factors

presumably slow the rate of cyclization and allow other reaction pathways (i.e., hydrolysis) to intervene (Eq. 3).



(3)

In summary, we have developed a highly efficient cyclization protocol of unsymmetrical thioureas that relies on internal hydrogen bonding to influence the regiochemistry and overall rate of the reaction. While it is perhaps counterintuitive to omit an acid scavenger from a reaction where strong acid is produced, the acidic nature of the reaction media clearly has a profound impact on the selectivity of this transformation. This methodology allows the vectoral display of unique substitution patterns on the iminothiazolidinone core, and should enable a more thorough exploration of this as well as other heterocyclic pharmacophores.

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References and notes

1. Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175–203.
2. (a) Van Gaal, L.; Scheen, A. J. *Diabetes/Metabolism Res. Rev.* **2002**, *18*(Suppl. 2), S1–S4; (b) Hulin, B.; McCarthy, P. A.; Gibbs, E. M. *Curr. Pharm. Design* **1996**, *2*, 85–102.
3. (a) Sahu, M.; Garnaik, B. K.; Behera, R. K. *Ind. J. Chem.* **1987**, *26B*, 779–781; (b) Mandhare, P. N.; Rindhe, S. S.; Patil, L. R.; Mane, R. A. *Ind. J. Heterocylic. Chem.* **2003**, *12*, 209–212.
4. Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC reference number 223830). Copies of the data can be obtained free of charge via the internet at http://www.ccdc.cam.ac.uk.
5. General procedure: A scintillation vial was charged with 2-(aminomethyl)pyridine (0.108 mL, 1.0 mmol) and 4 mL of solvent (DCE or ACN). To this solution was added the appropriate isothiocyanate (1.0 mmol), and the reaction was stirred for 2 h. Ethyl bromoacetate (1.0 mmol) was then added by syringe, and the reaction was heated to 80 °C for 2 h. The reaction was then cooled, partitioned between DCM and saturated $NaHCO_3$ solution, and the organic extracts were dried. The iminothiazolidinone products were then purified by silica gel flash chromatography (0–5% MeOH/DCM).
6. All compounds were characterized by ^1H and ^{13}C NMR, HRMS, and IR and found to be single imine isomers. For example, analytical data for **3**: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.48 (d, 1H, $J = 4.8$ Hz), 7.58 (m, 1H), 7.15 (d, 1H, $J = 7.6$ Hz), 7.11 (dd, 1H, $J = 7.0$, 1.8 Hz), 5.01 (s, 2H), 3.85 (s, 2H), 3.24 (q, 2H, $J = 7.3$ Hz), 1.08 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 155.3, 151.2, 149.1, 136.9, 122.4, 121.7, 47.4, 46.6, 32.7, 15.6; IR (KBr) 1706, 1657, 1645 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{13}N_3OS$ $[M+H]^+$: 236.0857, found: 236.0855.