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Oxazolidine-2-thiones and Thiazolidine-2-thiones as Nucleophiles in Intermolecular Michael Additions

Laura Munive,[†] Veronica M. Rivas,[†,§] Aurelio Ortiz,[‡] and Horacio F. Olivo*[,†]

Division of Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, Iowa 52242, United States, and Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Puebla 72570, Mexico

horacio-olivo@uiowa.edu

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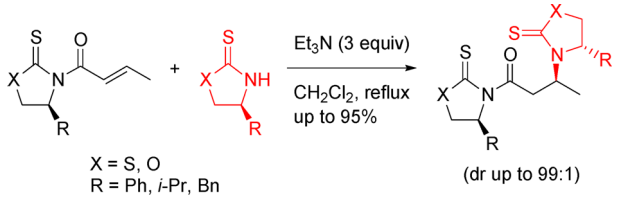
ABSTRACT



Conjugate addition of thiazolidinethiones and oxazolidinethiones to *N*-crotonylthiazolidinethiones and -oxazolidinethiones was observed in the presence of excess triethylamine in dichloromethane. The addition takes place by the nitrogen of the heterocycle with high diastereoselectivity. It was observed that the stereoselective addition occurs on the *anti*-s-*cis* conformation of the *N*-enoyl sulfur-containing heterocycle.

There has been a growing interest in the use of chiral 1,3-thiazolidine-2-thione and 1,3-oxazolidine-2-thione auxiliaries in several asymmetric transformations because they are easy to prepare, promote high diastereoselectivities, and are easier to cleave than more common oxazolidinone analogues.[1,2] These thiocarbonyl-containing chiral auxiliaries have been particularly useful in the acetate–aldol reaction where chiral oxazolidinones failed to give any diastereoselectivity.[3] In addition, three of the four possible propionate–aldol products can be accessed from the same chiral thiazolidinethione, only by modifying the number of base-equivalents or the nature of the Lewis acid.[4]

It is well-known that thiazolidinethiones and oxazolidinethiones undergo *N*-acylation with a carboxylic acid by DCC/4-DMAP coupling or employing an acyl chloride in the presence of triethylamine.[5] In contrast, alkylation of thiazolidinethiones and oxazolidinethiones with various primary alkyl halides and sodium hydride or triethylamine at room temperature deliver the corresponding thioalkylthiazoline or -oxazoline.[6] These thioalkyl products undergo a rearrangement to the corresponding *N*-alkylated product when heated.[6b]

N-Enoylthiazolidinethiones and -oxazolidinethiones can undergo a stereoselective intramolecular conjugate addition in the presence of Lewis and Bronsted acids to yield β-mercapto oxazolidinones.[7] The sulfur atom of the thiocarbonyl group reacts internally with the enoyl group. The intermediate thus formed is hydrolyzed to yield *N*-acyl-β-mercaptooxazolidinones. Another interesting

[†] The University of Iowa.
[‡] Benemérita Universidad Autónoma de Puebla.
[§] Departamento de Química Analítica, Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, NL, Mexico.

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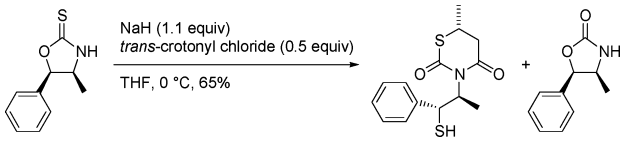
reaction particular to these chiral auxiliaries is the tandem intramolecular Michael addition followed by an aldol addition and cyclization, which occurs when a benzaldehyde is present delivering complex tricyclic molecules with high diastereoselectivity.[8] We have recently reported on the diastereoselective Michael addition of organocuprates to *N*-enoyloxazolidinethiones.[9]

During the coupling of (1*R*,2*S*)-norephedrine-derived oxazolidinethione with *trans*-crotonyl chloride, Ortíz et al. observed a side-product which resulted from addition of an oxazolidinethione thiolate to *N*-crotonyl oxazolidinethione on C-5 position, followed by a cyclization assisted by the known intramolecular sulfur rearrangement and hydrolysis, Scheme 1.[10] This side product was observed only when the oxazolidinethione had a phenyl substituent on the C-5 position.

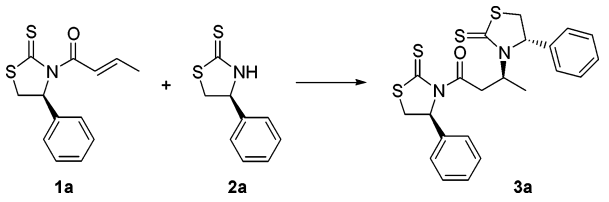
Scheme 1. Addition of a Thiolate to Oxazolidinethione, Cyclization, and Hydrolysis



Interestingly, we observed side products during a similar coupling of 4-benzyloxy-butenoyl chloride with both 4-phenyl-oxazolidinethione and thiazolidinethione that appeared to be Michael addition products.[11] We noticed that both sulfur-containing heterocycles underwent conjugate additions with the corresponding *N*-enoyl imides. In this paper, we describe an investigation of the new reactivity observed in these *N*-enoyl oxazolidinethiones and thiazolidinethiones.

We started by investigating conditions to obtain the Michael adduct in good yield, Table 1. We selected *N*-crotonyl-4-phenylthiazolidinethione **1a** as the Michael acceptor and the same 4-phenylthiazolidinethione **2a** as the nucleophile. One single diastereomeric product was observed in good yield until an excess of triethylamine was added to the reaction mixture (entries 1−5). We determined that the nucleophilic addition of the auxiliary took place by the nitrogen, and not the sulfur, because of the characteristic thiocarbonyl signals of thiazolidinethiones observed by ^{13}C NMR (203.0 and 198.1 ppm). The stereochemistry of the newly created center was determined unambiguously by single-crystal X-ray analysis.[12] Decomposition was observed when DBU was used as base (entry 6), and a low conversion occurred when NaH was used as base in THF (entry 7). The highest conversion was obtained when the reaction was heated to reflux for 5 h (entry 8).

Table 1. Exploration of Conditions for Michael Addition[a]



entry	solvent	temp (°C)	time (h)	base (equiv)	conv[b] (%)
1	CH_2Cl_2	rt	24		NR
2	CH_2Cl_2	0	24	Et_3N (1)	NR
3	CH_2Cl_2	rt	24	Et_3N (2)	35
4	CH_2Cl_2	rt	24	Et_3N (3)	85
5	CH_2Cl_2	rt	24	Et_3N (4)	85
6	CH_2Cl_2	rt	24	DBU (3)	dec
7	THF	rt	16	NaH (1)	32
8	CH_2Cl_2	reflux	5	Et_3N (3)	90

[a] Equimolar amounts of **1a** and **2a** were employed at 0.1 M concentration in the indicated solvent. [b] Determined by ^1H NMR peak integrations with crude product.

A plausible model to rationalize the stereochemical control of the conjugate addition is depicted in Figure 1. *N*-Crotonylimide **1a** could adopt four different conformations depending on the reagents present in the reaction mixture. Lithium amides are known to react in a conjugate fashion with (*E*)-α,β-unsaturated acceptors in the *anti*-s-*cis* conformation.[13] Attack of the nucleophile on the less hindered Si face of C3 of imide **1a** provides the preferred diastereomer **3a** as illustrated.

Having found satisfactory conditions for the conjugate addition, we proceeded to investigate the addition of chiral auxiliaries with three chiral thiazolidinethiones and oxazolidinethione analogues, Table 2. The best diastereoselectivity obtained was when the 4-substituent was the phenyl ring (entry 1). The lowest diastereoselectivity was obtained

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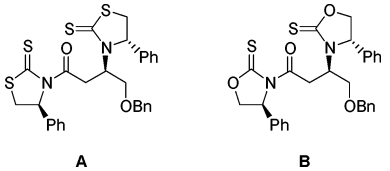
(11) The Michael addition products were characterized as:



(12) CCDC 879664 contains the supplementary crystallographic data for **3a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

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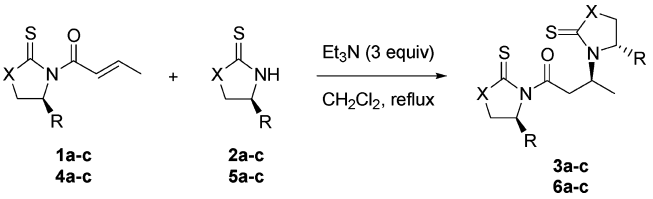
Table 2. Michael Addition of Chiral Thiazolidinethiones and Oxazolidinethiones[a]



1a-c 4a-c | 2a-c 5a-c | 3a-c 6a-c

entry	R	X	acceptor	nucleophile	time (h)	product	yield (%)[b]	dr[c]
1	Ph	S	**1a**	**2a**	5	**3a**	90	99:1
2	*i*-Pr	S	**1b**	**2b**	9	**3b**	71	7:3
3	Bn	S	**1c**	**2c**	8	**3c**	80	6:4
4	Ph	O	**4a**	**5a**	5	**6a**	84	99:1
5	*i*-Pr	O	**4b**	**5b**	8	**6b**	83	99:1
6	Bn	O	**4c**	**5c**	5	**6c**	83	7:3

[a] See the experimental details (Supporting Information). [b] Isolated yield after chromatography. [c] Determined by ^{1}H NMR analysis of unpurified mixture.

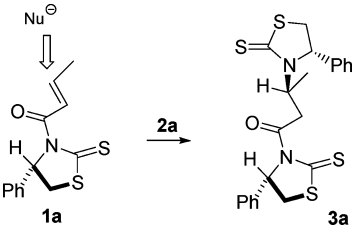


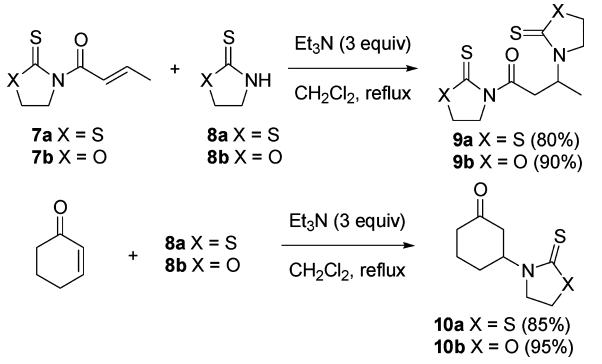
Figure 1. Model to rationalize the observed stereochemistry.

when the substituent was a benzyl group (entry 3). When thiazolidinethione **2b** was added to *N*-crotonylimide **1a**, a complex mixture of products was obtained (not shown). This mixture was probably due to *trans*-acylation of the *N*-crotonyl group from imide **1a** to form imide **1b**.

Next, we investigated the Michael addition of three chiral oxazolidinethiones (entries 4–6). The Michael addition of oxazolidinethiones **5a**–**c** to *N*-crotonyloxazolidinethiones **4a**–**c** worked in good yields (80–84%). Again, the highest diastereoselectivity was observed when the substituent was a phenyl ring (entry 4). Also, excellent diastereoselectivity was observed with the isopropyl substituent (entry 5). Poor diastereoselectivity was observed with the benzyl substituent (entry 6). Michael adduct **6a** showed two characteristic signals for the oxazolidinethione thiocarbonyl on ^{13}C NMR (187.3 and 185.4 ppm) indicating that it was the nitrogen atom reacting on the conjugate addition. Again, when *N*-crotonyl imide **4a** was reacted with oxazolidinethione **5b** a complex mixture was obtained as in the case of mixed thiazolidinethiones (not shown).

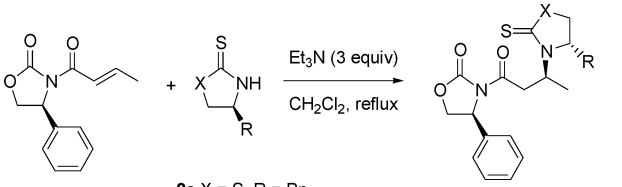
Michael addition of nonsubstituted thiazolidinethione **8a** to *N*-crotonylimide **7a** gave adduct **9a**, Scheme 2.[14] Michael adduct **9a** showed the characteristic two signals for the thiazolidinethione thiocarbonyl on ^{13}C NMR (202.5 and 196.6 ppm). While addition of oxazolidinethione **8b** to *N*-crotonyl imide **7b** gave the corresponding adduct **9b**. Michael adduct **9b** presented the two ^{13}C NMR signals corresponding to the oxazolidinethione thiocarbonyl (187.2 and 185.8 ppm). In order to explore the scope of this newly observed reactivity, cyclohexenone was also employed as a Michael acceptor. Addition of unsubstituted thiazolidinethione **8a** and oxazolidinethione **8b** to cyclohexenone occurred in very good yields.

Scheme 2. Michael Additions of Nonsubstituted Thiazolidinethione and Oxazolidinethione



N-Acylthiazolidinethiones and -oxazolidinethiones are easier to cleave than the corresponding *N*-acyloxazolidinones. In this context, we explored the conjugate addition of the sulfur-containing heterocycles **5b** and **2c** to *N*-crotonyloxazolidinone **11**, Scheme 3. In contrast to the previous additions of thiazolidinethiones and oxazolidinethiones, no *trans*-acylation was observed between imide **11** and sulfur-containing heterocycles. Addition of 4-substituted thiazolidinethiones **2c** to *N*-crotonyl imide **11** yielded exclusively diastereomer **12b** in good yields. In the same manner, addition of oxazolidinethione **5b** to *N*-crotonylimide **11** gave again only addition product **12c**. These experiments showed the capability of the sulfur-containing heterocycles to act as good nucleophiles in Michael additions and the robustness of the *N*-acyloxazolidinones.

Scheme 3. Conjugate Addition of Thiazolidinethiones and Oxazolidinethiones to *N*-Crotonyloxazolidinone



In summary, we showed that thiazolidinethiones and oxazolidinethiones undergo an unprecedented conjugate addition to *N*-enoylimides in good yields and high diastereoselectivity. We showed that, in these conjugate additions, the nitrogen is responsible for the nucleophilic attack and not the sulfur as it was the case in the addition to the *N*-crotonylnorephedrine-derived oxazolidinethione.[10] This nucleophilicity of thiazolidinethiones and oxazolidinethiones should find potential applications in heterocyclic chemistry. Our research group is currently investigating the match/mismatch conjugate addition of the chiral sulfur-containing heterocycles to chiral oxazolidinones and will be reported in due time.

(14) A similar reaction was reported by Ortíz (ref 8). ^{1}H and ^{13}C NMR spectra of adduct **9b** were identical to those of compound **5** in ref 10.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds and copies of ^{1}H and ^{13}C NMR and 2D spectra. X-ray data for compound **3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.