

## Synthesis of Methoxythiazolidine Fused Heterocycles

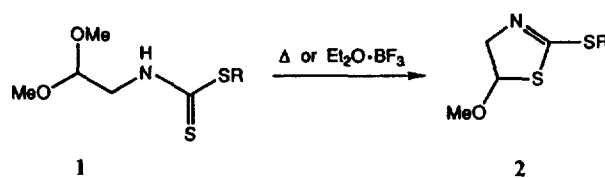
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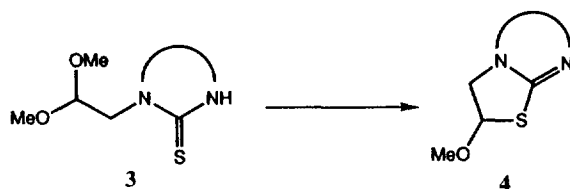
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During the course of our research to develop new cephalosporin antibiotics we needed various heterocyclic thiols. We have recently reported<sup>1</sup> that 2-alkylthio-4,5-dihydro-5-methoxythiazoles **2** is prepared by thermal or diethyl ether-boron trifluoride mediated intramolecular cyclization of the corresponding *N*-(2,2-dimethoxyethyl) dithiocarbamic acid esters **1** (Scheme 1). Continuing our studies on the synthesis of heterocyclic compounds, we have investigated its possibility for the conversion of heterocyclic compounds **3**, which possess acetal and thiol moieties, into the corresponding fused ring monothioacetals **4** (Scheme 2). Although there is a growing number of methods for effecting intermolecular monothioacetalization<sup>2</sup> between acetals and thiols, we here report intramolecular monothioacetalization using various heterocyclic thioureidoacetals **3** with Lewis acid.

The starting 4-(2,2-dimethoxyethyl)-5-thioxo-1,2,4-triazoles **5a-e** used in this study are readily prepared<sup>3,4</sup> from the corresponding 4-(2,2-dimethoxyethyl)-3-(acyl) thiosemicarbazide by treatment with aqueous sodium hydrogen carbonate, and the 1-(2,2-dimethoxyethyl)-5-mercaptotetrazole (**6**) is prepared<sup>5</sup> from the methyl *N*-(2,2-dimethoxyethyl) dithiocarbamate<sup>4</sup> with sodium azide. Also, 2-mercaptobenzimidazole **7** or 3H-imidazo[4,5-*b*]pyridine **8** is obtained by treatment of 4-chloro-3-nitrobenzotrifluoride or 2-chloro-3-nitropyridine with



Scheme 1



Scheme 2

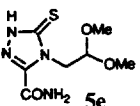
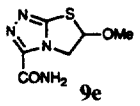
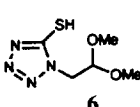
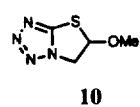
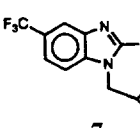
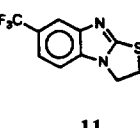
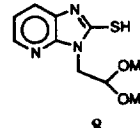
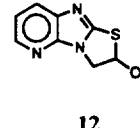
aminoacetaldehyde dimethylacetal and reduced with sodium hydrosulfite and further treatment with *O*-ethylxanthic acid, potassium salt, respectively.<sup>6</sup>

These heterocyclic mercaptoacetals **5-8** undergo the Lewis acid mediated intramolecular cyclization to give methoxythiazolidine fused heterocycles, *i.e.*, 6-methoxy-5,6-dihydrothiazolo[2,3-*c*]-1,2,4-triazoles **9a-e**, 5-methoxy-5,6-dihydrothiazolo[3,2-*d*]tetrazole (**10**), 2-methoxy-7-trifluoromethyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole (**11**), and 2-methoxy-2,3-dihydrothiazolo[2',3':2,3]imidazo[4,5-*b*]pyridine (**12**) in good yields.

The general procedure involved addition of diethyl ether-boron trifluoride (2.2-3.3 equiv.)<sup>7</sup> to a stirred solution of mercaptoacetal **5-8** (1.0 equiv.) in dry dichloromethane at room temperature. The mixture was stirred at ambient temperature for the time indicated in Table 1. Aqueous basic (NaHCO<sub>3</sub>) work-up and purification by recrystallization afforded the product. Table 1 gives the list of compounds studied

Table 1. Methoxythiazolidine Fused Heterocycles Prepared

Reactant	Et <sub>2</sub> O·BF <sub>3</sub> (equiv)	Time (min)	Product	Yield <sup>a</sup> (%)	Mp.(°C) (solvent)	Molecular formula	<sup>1</sup> H-NMR (DMSO- <i>d</i> <sub>6</sub> /TMS) <sup>b</sup> δ, J (Hz)	MS (70 eV) <sup>c</sup> m/z (%)
	2.2	30		89	148-150 (THF)	C <sub>5</sub> H <sub>7</sub> N <sub>3</sub> OS (157.0)	3.36 (s, 3H, OCH <sub>3</sub> ), 4.41 (d, 2H, J=2.9, H-5), 6.17 (t, 1H, J=2.9, H-6), 8.49 (s, 1H, H-3)	157 (M <sup>+</sup> , 84), 127 (29), 126 (100), 114 (36), 71 (36)
	2.2	10		93	117-118 (EtOAc)	C <sub>6</sub> H <sub>9</sub> N <sub>3</sub> OS (171.1)	2.33 (s, 3H, OCH <sub>3</sub> ), 3.39 (s, 3H, OCH <sub>3</sub> ), 4.32 (d, 2H, J=2.8, H-5), 6.22 (t, 1H, J=2.8, H-6)	171 (M <sup>+</sup> , 35), 140 (100), 115 (12), 99 (20), 97 (33)
	2.2	10		91	73-74 (EtOAc)	C <sub>8</sub> H <sub>11</sub> N <sub>3</sub> OS (197.1)	1.07 (m, 4H, CH <sub>2</sub> -cyclopropyl), 1.74 (m, 1H, CH-cyclopropyl), 3.44 (s, 3H, OCH <sub>3</sub> ), 4.27 (d, 2H, J=2.5, H-5), 5.97 (t, 1H, J=2.5, H-6)	197 (M <sup>+</sup> , 77), 196 (70), 182 (14), 166 (100), 141 (15), 97 (27)
	2.2	10		86	171-172 (EtOAc)	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> OS (233.1)	3.39 (s, 3H, OCH <sub>3</sub> ), 4.51 (d, 1H, J=12.6, H-5), 4.80 (dd, 1H, J=12.5, 4.7, H-5), 6.30 (d, 1H, J=4.6, H-6), 7.52-7.85 (m, 5H <sub>aromatic</sub> )	233 (M <sup>+</sup> , 40), 202 (94), 146 (12), 103 (100), 99 (23), 97 (28)

	2.2	20		81	161-163 (THF/ EtOAc)	$C_6H_8N_4O_2S$ (200.2)	3.39 (s, 3H, OCH <sub>3</sub> ), 4.55 (d, 2H, J=2.8, H-5), 6.26 (t, 1H, J=2.7, H-6), 7.88, 8.24 (s, each 1H, NH <sub>2</sub> )	200 (M <sup>+</sup> , 18), 169 (100), 156 (21), 152 (21)
	3.3	60		72	72-73 (EtOAc)	$C_4H_6N_4OS$ (158.2)	3.51 (s, 3H, OCH <sub>3</sub> ), 3.73 (d, 2H, J=3.0, H-6), 6.28 (t, 1H, J=3.0, H-5)	158 (M <sup>+</sup> , 29), 97 (27), 76 (20), 72 (13), 58 (100)
	2.2	10		78	162 (EtOAc)	$C_{11}H_{19}F_3N_2OS$ (274.3)	3.49 (s, 3H, OCH <sub>3</sub> ), 4.40 (dd, 1H, J=11.7, 4.9, H-3), 4.49 (dd, 1H, J=11.7, 1.1, H-3), 5.98 (dd, 1H, J=4.9, 1.1, H-2), 7.29, 7.46 (two d, J=8.3, each 1H <sub>aromatic</sub> ), 7.90 (s, 1H <sub>aromatic</sub> ) <sup>d</sup>	274 (M <sup>+</sup> , 40), 243 (100), 231 (24), 229 (14), 187 (19)
	2.2	30		65	210	$C_9H_9N_3OS$ (207.2)	3.49 (s, 3H, OCH <sub>3</sub> ), 4.44 (dd, 1H, J=12.1, 5.2, H-3), 4.67 (dd, 1H, J=12.1, 1.0, H-3), 5.99 (dd, 1H, J=5.2, 1.0, H-2), 7.15 (dd, J=8.0, 5.0, 1H <sub>aromatic</sub> ), 7.86 (dd, J= 8.0, 1.4, 1H <sub>aromatic</sub> ), 8.21 (dd, J=5.0, 1.4, 1H <sub>aromatic</sub> ) <sup>d</sup>	207 (M <sup>+</sup> , 45), 176 (100), 164 (29), 135 (30), 108 (12)

<sup>a</sup>Yield of isolated product. <sup>b</sup>Recorded on a Bruker AM-200 spectrometer. <sup>c</sup>Recorded on a Hewlett Packard model 5985 B spectrometer. <sup>d</sup>Recorded on a Varian Gemini 300 spectrometer (CDCl<sub>3</sub>).

and the yields of isolated product, together with spectral identification data.

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6. The 2-mercaptobenzimidazole **7** and 3H-imidazo[4,5-b]pyridine **8** were prepared in 46, 60% overall yield from 4-chloro-3-nitrobenzotrifluoride and 2-chloro-3-nitropyridine, respectively.
7. Treatment of **5a-e** with 5 equiv. of MeSO<sub>3</sub>H (CH<sub>2</sub>Cl<sub>2</sub>, r.t.,

2-5 h) and subsequent saturated aqueous NaHCO<sub>3</sub> work-up gave similar results.

## Selectivity in the Lactone Formation via C-H Insertion Reaction of Diazoacetates

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It is now well established that rhodium (II) catalyzed intramolecular C-H insertion reactions of  $\alpha$ -diazo- $\beta$ -ketocarboxylic acid methyl esters result in the formation of cyclopentanones.<sup>1</sup> Under similar conditions,  $\alpha$ -diazoketones,<sup>2,3</sup>  $\alpha$ -diazo- $\beta$ -ketosulfones<sup>4</sup> and  $\alpha$ -diazo- $\beta$ -ketophosphonates<sup>5</sup> are also converted into five-membered carbocyclic systems. In these reactions, electron withdrawing substituents decrease the reactivity of the adjacent C-H bonds<sup>1c,2</sup> and the insertion reaction is promoted at the C-H bond adjacent to ether oxygens.<sup>3</sup> The propensity for the formation of five-membered carbocycles can sometimes be overcome: the dominating factor of ether activation may prevail and cyclohexanone derivatives may be formed<sup>3</sup>, and subtler electronic factors may provide enough impetus for more favorable formation of cyclo-