Synthesis of Methoxythiazolidine Fused Heterocycles

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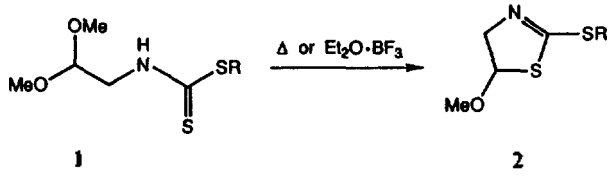
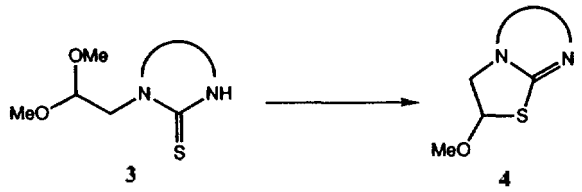
During the course of our research to develop new cephalosporin antibiotics we needed various heterocyclic thiols. We have recently reported[1] that 2-alkylthio-4,5-dihydro-5-methoxythiazoles **2** is prepared by theremal or diethyl ether-boron trifluoride mediated intramolecular cyclization of the corresponding *N*-(2,2-dimethoxylethyl) 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[2] 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[3,4] 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[5] from the methyl *N*-(2,2-dimethoxyethyl) dithiocarbamate[4] 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



1 **2**

Scheme 1



3 **4**

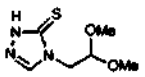
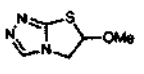
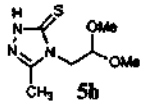
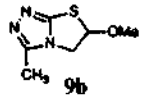
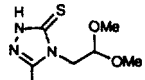
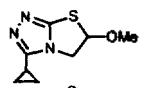
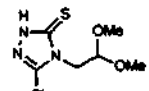
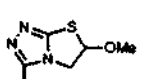
Scheme 2

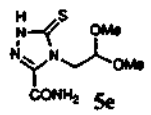
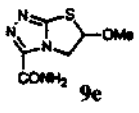
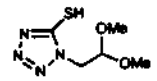
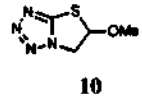
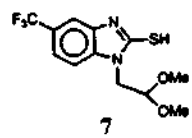
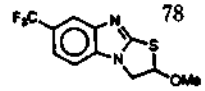
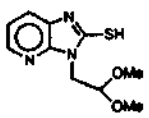
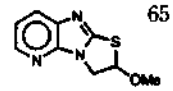
aminoacetaldehyde dimethylacetal and reduced with sodium hydrosulfite and further treatment with *O*-ethylxanthic acid, potassium salt, respectively.[6]

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 etherboron trifluoride (2.2-3.3 equiv.)[7] 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 ($NaHCO_3$) work-up and purification by recrystallization afforded the product. Table 1 gives the list of compounds studied

Table 1. Methoxythiazolidine Fused Heterocycles Prepared

Reactant	$Et_2O\cdot BF_3$ (equiv)	Time (min)	Product	Yield[a] (%)	Mp.(℃) (solvent)	Molecular formula	^{1}H-NMR (DMSO-d_6/TMS)[b] δ, J (Hz)	MS (70 eV)[c] m/z (%)
 **5a**	2.2	30	 **9a**	89	148-150 (THF)	$C_5H_7N_3OS$ (157.0)	3.36 (s, 3H, OCH_3), 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^+, 84), 127 (29), 126 (100), 114 (36), 71 (36)
 **5b**	2.2	10	 **9b**	93	117-118 (EtOAc)	$C_6H_9N_3OS$ (171.1)	2.33 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 4.32 (d, 2H, J=2.8, H-5), 6.22 (t, 1H, J=2.8, H-6)	171 (M^+, 35), 140 (100), 115 (12), 99 (20), 97 (33)
 **5c**	2.2	10	 **9c**	91	73-74 (EtOAc)	$C_8H_{11}N_3OS$ (197.1)	1.07 (m, 4H, CH_2-cyclopropyl), 1.74 (m, 1H, CH-cyclopropyl), 3.44 (s, 3H, OCH_3, 4.27 (d, 2H, J=2.5, H-5), 5.97 (t, 1H, J=2.5, H-6)	197 (M^+, 77), 196 (70), 182 (14), 166 (100), 141 (15), 97 (27)
 **5d**	2.2	10	 **9d**	86	171-172 (EtOAc)	$C_{11}H_{11}N_3OS$ (233.1)	3.39 (s, 3H, OCH_3), 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, $5H_{aromatic}$)	233 (M^+, 40), 202 (94), 146 (12), 103 (100), 99 (23), 97 (28)

 5e	2.2	20	 9e	81	161-163 (THF/ EtOAc)	$C_6H_8N_4O_2S$ (200.2)	3.39 (s, 3H, OCH_3), 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_2)	200 (M^+, 18), 169 (100), 156 (21), 152 (21)
 6	3.3	60	 10	72	72-73 (EtOAc)	$C_4H_6N_4OS$ (158.2)	3.51 (s, 3H, OCH_3), 3.73 (d, 2H, J=3.0, H-6), 6.28 (t, 1H, J=3.0, H-5)	158 (M^+, 29), 97 (27), 76 (20), 72 (13), 58 (100)
 7	2.2	10	 11	78	162 (EtOAc)	$C_{11}H_{19}F_3N_2OS$ (274.3)	3.49 (s, 3H, OCH_3), 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 $1H_{aromatic}$), 7.90 (s, $1H_{aromatic}$)[d]	274 (M^+, 40), 243 (100), 231 (24), 229 (14), 187 (19)
 8	2.2	30	 12	65	210	$C_9H_9N_3OS$ (207.2)	3.49 (s, 3H, OCH_3), 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, $1H_{aromatic}$), 7.86 (dd, J=8.0, 1.4, $1H_{aromatic}$), 8.21 (dd, J=5.0, 1.4, $1H_{aromatic}$)[d]	207 (M^+, 45), 176 (100), 164 (29), 135 (30), 108 (12)

[a] Yield of isolated product. [b] Recorded on a Bruker AM-200 spectrometer. [c] Recorded on a Hewlett Packard model 5985 B spectrometer. [d] Recorded on a Varian Gemini 300 spectrometer ($CDCl_3$).

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-nitrobenzotrifuoride and 2-chloro-3-nitropyridine, respectively.
7. Treatment of **5a-e** with 5 equiv. of $MeSO_3H$ (CH_2Cl_2, r.t., 2-5 h) and subsequent saturated aqueous $NaHCO_3$ work-up gave similar results.

Selectivity in the Lactone Formation *via* C-H Insertion Reaction of Diazoacetoacetates

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It is now well established that rhodium (II) catalyzed intramolecular C-H insertion reactions of α-diazo-β-ketocarboxylic acid methyl esters result in the formation of cyclopentanones.[1] Under similar conditions, α- diazoketones,[2,3] α-diazo-β-ketosulfones[4] and α-diazo-β-ketophosphonates[5] are also converted into five-membered carbocyclic systems. In these reactions, electron withdrawing substituents decrease the reactivity of the adjacent C-H bonds[1c,2] and the insertion reaction is promoted at the C-H bond adjacent to ether oxygens.[3] 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[3], and subtler electronic factors may provide enough impetus for more favorable formation of cyclo-