A Convenient Synthesis of 2-Alkylthio-4,5-dihydro-5-methoxythiazoles

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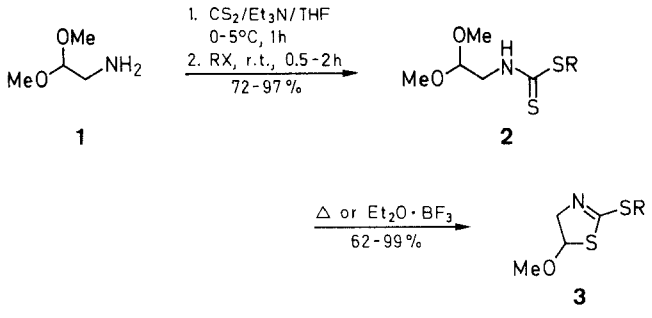
A series of 2-alkylthio-4,5-dihydro-5-methoxythiazoles **3** were prepared by thermal or diethyl ether–boron trifluoride mediated intramolecular cyclization of the corresponding *N*-(2,2-dimethoxyethyl)dithiocarbamic acid esters **2**. Methyl *N*-(2,2-dimethoxyethyl)dithiocarbamate **(2b)** and 4,5-dihydro-5-methoxy-2-methylthiothiazole **(3b)** were converted by a two-step sequence to methyl 2-methyl-3-thioxo-1,2,3,4-tetrahydro-1,2,4-triazine-4-carbodithioate **(6)**.

Dithiocarbamates have been used extensively in organic synthesis, especially for the construction of heterocyclic structures.[1–5] Recently, we have reported that methyl *N*-(2,2-dimethoxyethyl)dithiocarbamate **(2b)** is an excellent intermediate in the synthesis of 1,2,4-triazolo[4,3-*a*]pyrazines.[6] Continuing our studies on the synthesis of heterocyclic compounds, we have found that 2-alkylthio-4,5-dihydro-5-methoxythiazoles **3** could be formed very effectively from *N*-(2,2-dimethoxyethyl)dithiocarbamic acid esters **2** by intramolecular cyclization. Generally, intramolecular ring closure between sulfur and a reactive carbon atom bearing a good leaving group is a well-known route for the synthesis of the 4,5-dihydrothiazole ring system.[7,8] *N*-Allylthioureas can also undergo an acid-catalyzed cyclization to give 4,5-dihydrothiazoles.[9]

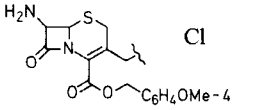
We now describe a new general method for the synthesis of the hitherto unknown 2-alkylthio-4,5-dihydro-5-methoxythiazoles **3** based on the thermal elimination or Lewis acid mediated cyclization of dithiocarbamates **2** (Scheme **1**). Similar cyclizations have been reported in the literature, e.g. thiobenzamidoacetaldehyde diethyl acetal under mild acidic conditions giving 4,5-dihydro-5-ethoxy-2-phenylthiazole, and under more vigorous conditions giving 2-phenylthiazole,[10] and the reaction of β-amino ketones with carbon disulfide providing 4,5-dihydro-5-hydroxythiazole-2-thiones.[11]

The starting compounds, dithiocarbamates **2** were obtained by treatment of aminoacetaldehyde dimethyl acetal **(1)** with carbon disulfide in the presence of triethylamine and further treatment with an alkyl halide in tetrahydrofuran (Table 1). Whilst attempting to purify the product by distillation *in vacuo* (1–15 mbar), we found that the product was 4,5-dihydro-5-methoxy-2-methylthiothiazole **(3b)** and not the expected methyl *N*-(2,2-dimethoxyethyl)dithiocarbamate **(2b)**. We were able to synthesize several dihydrothiazoles **3b–e** by thermally induceded intramolecular cyclization in this manner, starting from the corresponding dithiocarbamate **2**. The cyclization could also be performed using diethyl ether–boron trifluoride with greater facility and mildness (Table 2). This method is of general applicability and was used for the synthesis of the novel cephalosporin derivative **3h** in high yield.

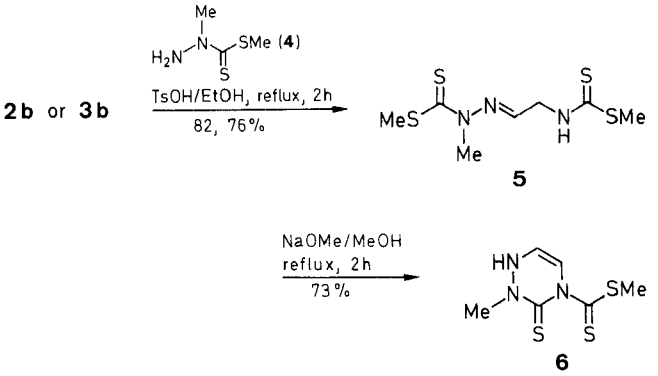
The condensation reaction of **3b** with methyl 2-methyldithiocarbazate **(4)** was carried out with *p*-toluenesulfonic acid as the catalyst in ethanol at reflux temperature.[12] It proceeded regioselectively, with cleavage of the C–O and C–S bonds, to afford the methyl *N*-[2-(2-methyl-2-methylthiothiocarbonylhydrazono)ethyl]dithiocarbamate **(5)** in good yield. Alternatively, the same compound **5** could also be obtained from the reaction of methyl *N*-(2,2-dimethoxyethyl)dithiocarbamate **(2b)** with **4**. Cyclization of **5** with sodium methoxide in refluxing methanol gave the methyl 2-methyl-3-thioxo-1,2,3,4-tetrahydro-1,2,4-triazine-4-carbodithioate **(6)** (Scheme **2**).



1 **2** **3**

2,3	R	X	2,3	R	X
a	H	Cl	**e**	$HC{\equiv}CCH_2$	Br
b	Me	I	**f**	$PhCH_2$	Cl
c	Et	Br	**g**	2-pyridylmethyl	Cl
d	$H_2C{=}CHCH_2$	Br	**h**		Cl

Scheme **1**



5 **6**

Scheme **2**

All compounds were characterized by their ^{1}H-NMR and mass spectra as well as by their microanalytical data. Our simple method starting from very common and easily available dithiocarbamate **2** appears as an attractive route to new derivatives **3** and **6**, which are of potential biological interest.

Table 1. *N*-(2,2-Dimethoxyethyl)dithiocarbamic Acid Esters **2** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	0.5	72	oil	$C_5H_{11}NO_2S_2$ (181.3)	3.41 (s, 6H, OCH_3), 3.57 (d, 2H, J = 5.2, CH_2), 4.47 (t, 1H, J = 5.0, CH), 6.19 (brs, 1H, NH)
2b	1	95	oil	$C_6H_{13}NO_2S_2$ (195.3)	2.63 (s, 3H, SCH_3), 3.40 (s, 6H, OCH_3), 3.87 (t, 2H, J = 5.1, CH_2), 4.60 (t, 1H, J = 5.1, CH), 7.57 (brs, 1H, NH)
2c	2	95	oil	$C_7H_{15}NO_2S_2$ (209.3)	1.33 (t, 3H, J = 7.5, CH_3), 3.27 (q, 2H, J = 7.5, SCH_2), 3.43 (s, 6H, OCH_3), 3.87 (t, 2H, J = 5.0, CH_2), 4.57 (t, 1H, J = 5.0, CH), 7.33 (brs, 1H, NH)
2d	0.5	96	oil	$C_8H_{15}NO_2S_2$ (221.3)	3.43 (s, 6H, OCH_3), 3.80–4.03 (m, 4H, $SCH_2 + CH_2$), 4.60 (t, 1H, J = 5.0, CH), 5.07–5.53 (m, 2H, $=CH_2$), 5.67–6.23 (m, 1H, =CH), 7.43 (brs, 1H, NH)
2e	0.5	92	oil	$C_8H_{13}NO_2S_2$ (219.2)	2.29 (t, 1H, J = 2.5, ≡CH), 3.47 (s, 6H, OCH_3), 3.89 (t, 2H, J = 5.7, CH_2), 4.09 (d, 2H, J = 2.5, SCH_2), 4.67 (t, 1H, J = 5.5, CH), 7.42 (brs, 1H, NH)
2f	2	97	oil	$C_{12}H_{17}NO_2S_2$ (271.4)	3.40 (s, 6H, OCH_3), 3.90 (t, 2H, J = 5.1, CH_2), 4.55 (t, 1H, J = 5.1, CH), 4.57 (s, 2H, SCH_2), 7.23–7.53 (brs, 6H, $5H_{arom}$ + NH)
2g	2	95	53 (Et_2O)	$C_{11}H_{16}N_2O_2S_2$ (272.4)	3.44 (s, 6H, OCH_3), 3.93 (t, 2H, J = 5.5, CH_2), 4.30 (s, 2H, SCH_2), 5.68 (t, 1H, J = 5.5, CH), 7.13–8.69 (m, 5H, $4H_{pyridyl}$ + NH)
2h	0.5	92	50 (CH_2Cl_2/ Et_2O)	$C_{21}H_{27}N_3S_3O_6$ (513.6)	1.81 (s, 2H, NH_2), 3.41 (s, 6H, OCH_3), 3.58 (brs, 2H, H-2), 3.80 (s, 3H, $ArOCH_3$), 3.91 (dd, 2H, J = 6.2, 5.3, CH_2), 4.34, 4.44 (2d, each 1H, J = 13.9, SCH_2), 4.57 (t, 1H, J = 5.3, CH), 4.72 (d, 1H, J = 5.0, H-6), 4.90 (d, 1H, J = 5.0, H-7), 5.18, 5.26 (2d, each 1H, J = 11.9, CH_2Ar), 6.88, 7.34 (2d, $4H_{arom}$, J = 8.7), 7.70 (t, 1H, J = 5.3, NH)[c]

[a] Yield of crude product. Low yield of **2a** is presumably due to its instability.
[b] Satisfactory microanalyses obtained: C ±0.19, H ±0.07, N ±0.29.
[c] Recorded on a Bruker AM-200 spectrometer.

All reactions were carried out in dry N_2 atmosphere. CH_2Cl_2 and THF were dried and distilled from CaH_2 and $LiAlH_4$, respectively. Silica gel EM 7747 for column chromatography was used throughout for product separation. Melting points were measured using an Electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Perkin-Elmer 240 DS element analyzer. Mass spectra were obtained using a Hewlett Packard model 5985 B spectrometer. ^{1}H-NMR spectra were measured on either a Bruker AM-200 **(3a–h, 2h)** or a Jeol PMX-60SI **(2a–g)** spectrometer.

7-Amino-3-chloromethlycephalosporanic acid *p*-methoxybenzyl ester, hydrochloric acid salt was purchased from Otsuka Chemical Co. Methyl 2-methyldithiocarbazate **(4)**[13] was prepared following the literature procedure.

N-(2,2-Dimethoxyethyl)dithiocarbamic Acid Esters 2; General Procedure:

To a stirred solution of aminoacetaldehyde dimethyl acetal (**1**; 10.5 g, 100 mmol) in THF (100 mL) are added dropwise Et_3N (12.2 g, 120 mmol) and CS_2 (8.4 g, 110 mmol) at 0–5 °C. The mixture is stirred for 1 h at r.t., then RX (100 mmol) is added. After stirring for the time indicated in Table 1 at r.t., the precipitated solid ($Et_3N \cdot HX$) is filtered, the filtrate is concentrated under reduced pressure, and the residual oil is dissolved in EtOAc (100 mL). This solution is subsequently washed with sat. aq $NaHCO_3$ (20 mL), brine (20 mL), water (20 mL), and dried ($MgSO_4$). The solvent is stripped off to give the crude product **2**, which is used for the next reaction without further purification. An analytical sample is prepared by column chromatography on silica gel (hexane/EtOAc) (Table 1).

2-Alkylthio-4,5-dihydro-5-methoxythiazoles 3; General Procedure:

Method A, *Thermal Elimination (for* **3b–e***):* The *N*-(2,2-dimethoxyethyl)dithiocarbamic acid ester **2b–e** (50 mmol) is simply distilled at reduced pressure (1–15 mbar, bath temperature 190–260 °C) and the major fraction corresponding to **3b–e** is collected (Table 2).

Method B, *$BF_3 \cdot OEt$ Mediated Cyclization (for* **3a–h***):* To a stirred solution of *N*-(2,2-dimethoxyethyl)dithiocarbamic acid **(2a)** or ester **2b–h** (25 mmol) in CH_2Cl_2 (50 mL) is added dropwise $Et_2O \cdot BF_3$ (3.38 mL, 27.5 mmol) at 0–5 °C.[14] After stirring for 20 min at r.t., the mixture is neutralized with sat. aq $NaHCO_3$ (pH = 8 ~ 9). CH_2Cl_2 (50 mL) is then added and the organic phase is separated, washed with H_2O (25 mL), and dried ($MgSO_4$). The solvent is evaporated and the residual oil is purified by short-column chromatography on silica gel (hexane/EtOAc) to give **3** (Table 2).

Methyl *N*-[2-(2-methyl-2-methylthiothiocarbonylhydrazono)ethyl]-dithiocarbamate (5):

To a stirred solution of 4,5-dihydro-5-methoxy-2-methylthiothiazole (**3b**; 6.53 g, 40 mmol) or methyl *N*-(2,2-dimethoxyethyl)dithiocarbamate (**2b**, 7.81 g, 40 mmol) in EtOH (50 mL) are added methyl 2-methyldithiocarbazate (**4**; 5.45 g, 40 mmol) and a catalytic amount of TsOH. The mixture is heated at reflux temperature for 2 h then allowed to cool to r.t. The precipitated crystalline solid is separated by filtration and recrystallized from EtOH to give **5** as colorless crystals; yield: 8.14 g (76%), 8.77 g (82%), respectively; mp 93 °C (EtOH).

$C_7H_{13}N_3S_4$ (267.4) calc. C 31.44 H 4.90 N 15.71
found 31.61 4.94 15.62

MS (70 eV): m/z = 219, 141, 132, 91, 88, 14, 12.

^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ = 2.49 (s, 3H, SCH_3), 2.60 (s, 3H, SCH_3), 3.80 (s, 3H, NCH_3), 4.57 (t, 2H, J = 4.5 Hz, CH_2), 7.38 (t, 1H, J = 4.5 Hz, CH), 9.47 (br s, 1H, NH).

Methyl 2-Methyl-3-thioxo-1,2,3,4-tetrahydro-1,2,4-triazine-4-carbodithioate (6):

To a stirred solution of dithiocarbamate **5** (2.67 g, 10 mmol) in MeOH (50 mL) is added NaOMe (0.54 g, 11 mmol). The mixture is stirred at reflux temperature for 2 h. After cooling, the mixture is neutralized with 5% HCl (pH = 6), then extracted with $CHCl_3$ (2 × 50 mL). The extract is dried ($MgSO_4$), and concentrated under

Table 2. 2-Alkylthio-4,5-dihydro-5-methoxythiazoles **3** Prepared

Product	Yield[a] (%)	mp(°C) (solvent) or bp(°C)/mbar	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
3a[c]	74	77 (Et_2O)	$C_4H_7NOS_2$ (149.2)	3.40 (s, 3H, OCH_3), 4.05 (dd, 1H, J = 14.0, 0.9, H-4), 4.19 (dd, 1H, J = 13.0, 5.2, H-4), 5.54 (dd, J = 5.0, 0.9, H-5), 8.79 (brs, 1H, NH)	149 (M^+, 86), 120 (11), 118 (100), 101 (12), 76 (47)
3b	98 (75)	118/15	$C_5H_9NOS_2$ (163.3)	2.53 (s, 3H, SCH_3), 3.26 (s, 3H, OCH_3), 4.04 (dd, 1H, J = 16.2, 5.6, H-4), 4.45 (d, 1H, J = 16.2, H-4), 5.62 (d, 1H, J = 5.6, H-5)	163 (M^+, 79), 132 (14), 116 (9), 91 (15), 87 (99), 72 (100)
3c	96 (70)	104/6	$C_6H_{11}NOS_2$ (177.3)	1.35 (t, 3H, J = 7.4, CH_3), 3.09, 3.11 (2q, each 1H, J = 7.4, SCH_2), 3.25 (s, 3H, OCH_3), 4.08 (dd, 1H, J = 16.1, 5.5, H-4), 4.43 (d, 1H, J = 16.1, H-4), 5.60 (d, 1H, J = 5.4, H-5)	177 (M^+, 33), 149 (100), 118 (34), 116 (26), 101 (37), 72 (74)
3d	99 (62)	110/4	$C_7H_{11}NOS_2$ (189.3)	3.27 (s, 3H, OCH_3), 3.78 (m, 2H, SCH_2), 4.11 (dd, 1H, J = 16.2, 5.6, H-4), 4.47 (d, 1H, J = 16.2, H-4), 5.14 (d, 1H, J_{cis} = 8.7, $=CH_2$), 5.28 (d, 1H, J_{trans} = 17.1, $=CH_2$), 5.62 (d, 1H, J = 5.6, H-5), 5.84–6.00 (m, 1H, CH=)	189 (M^+, 8), 175 (10), 174 (100), 159 (23), 131 (21), 72 (99)
3e	98 (72)	169/3	$C_7H_9NOS_2$ (187.3)	2.27 (t, 1H, J = 2.6, ≡CH), 3.27 (s, 3H, OCH_3), 3.83, 3.95 (2dd, each 1H, J = 16.3, 2.6, SCH_2), 4.11 (dd, 1H, J = 16.3, 5.5, H-4), 4.48 (d, 1H, J = 16.3, H-4), 5.67 (d, 1H, J = 5.4, H-5)	187 (M^+, 0.8), 158 (11), 156 (100), 129 (14), 72 (52)
3f	97	oil[d]	$C_{11}H_{13}NOS_2$ (239.4)	3.20 (s, 3H, OCH_3), 4.05 (dd, 1H, J = 16.2, 5.4, H-4), 4.29, 4.30 (2d, each 1H, J = 13.0, SCH_2), 4.45 (d, 1H, J = 16.2, H-4), 5.54 (d, 1H, J = 5.4, H-5), 7.20–7.35 (m, $5H_{arom}$)	239 (M^+, 43), 121 (14), 91 (100), 77 (16), 72 (32)
3g	97	oil[d]	$C_{10}H_{12}N_2OS_2$ (240.3)	3.38 (s, 3H, OCH_3), 4.23 (dd, 1H, J = 16.2, 5.5, H-4), 4.60 (d, 1H, J = 16.2, H-4), 4.56–4.72 (m, 3H, H-4 + SCH_2), 5.75 (d, 1H, J = 5.5, H-5), 7.25–7.78, 8.64–8.67 (m, $4H_{pyridyl}$)	240 (M^+, 3), 207 (23), 182 (15), 164 (100), 125 (15), 124 (51), 106 (51), 92 (78), 72 (68)
3h	97	53–54 (CH_2Cl_2/Et_2O)	$C_{20}H_{23}N_3O_5S_3$ (481.6)	1.86 (brs, 2H, NH_2), 3.27 (s, 3H, OCH_3), 3.53, 3.66 (2d, each 1H, J = 20.1, H-2'), 3.80 (s, 3H, $ArOCH_3$), 4.06 (dd, 1H, J = 17.9, 5.2, H-4), 4.41 (d, 1H, J = 17.9, H-4), 4.42, 4.55 (2d, each 1H, J = 13.5, SCH_2), 4.70 (d, 1H, J = 5.0, H-6'), 4.88 (d, 1H, J = 5.0, H-7'), 5.23 (s, 2H, CH_2Ar), 5.61 (d, 1H, J = 5.2, H-5), 6.88, 7.35 (2d, each $2H_{arom}$, J = 8.5)	269 (33), 149 (10), 139 (11), 121 (100), 118 (20), 109 (36), 77 (50)

[a] Yield of isolated product. Yield of thermal elimination method is given in parenthesis.
[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.06, N ±0.25.
[c] Exists in the thiazolidene-2-thione form.
[d] Decomposes during distillation.

reduced pressure to give a crystalline solid **6**. An analytical sample is prepared by recrystallization from EtOH as colorless crystals; yield: 1.62 g (74%); mp 224–226°C.

$C_6H_9N_3S_3$ (219.3) calc. C 32.85 H 4.14 N 19.16
found 32.80 4.11 19.21

MS (70 eV): m/z = 219 (M^+), 171, 100, 99, 91, 88, 73, 72, 71.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.47 (s, 3H, SCH_3), 3.67 (s, 3H, NCH_3), 7.03 (d, 1H, J = 2.4 Hz, H-6), 7.36 (d, 1H, J = 2.0 Hz, H-5), 12.60 (br s, 1H, NH).

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