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Received July 6, 1992

4,5-Dimethyl-1,2-dithiole-3-thione **1** reacts with primary amines and formaldehyde to give the *mono*-, *retro*-, *bis*-Mannich bases in moderate yield.

*J. Heterocyclic Chem.*, **30**, 545 (1993).

The mobility of the protons of the methyl group at position 5 of 4,5-dimethyl-1,2-dithiole-3-thione **1** has been previously reported [1,2]. This methyl group is activated by the presence of the thione group. An enol-type delocalisation, corresponding to the thiono  $\alpha\beta$  ethylenic moiety, may occur. Reactions of **1** with various heterocyclic aldehydes afford 4-methyl-5-substituted-1,2-dithiole-3-thiones [1,2]. This particular reactivity has not been extensively explored though **1** may constitute a very high lipophilic [4] and an efficient electron-withdrawing group. Selective oxidation of the 5-methyl group has also been observed [5].

In this report we described the reactivity of **1** in the Mannich reaction in the hope to synthesize *bis*-Mannich bases **4**. These kinds of molecules have received recent attention in anti-leukemic research [3]. In the course of exploratory work in this area we observed the formation of the three main types of products: *mono*-Mannich bases **2**, *retro*-Mannich bases **3** and *bis*-Mannich bases **4** in various percentage yields. This work was extended to different primary amines.

The synthesis was carried out at reflux temperature in absolute alcohol with formaldehyde equivalent (trioxane) and the amine and **1** in the ratio 2/1:5/1. A large excess of formaldehyde and amine seems to influence the course of the reaction. In the case of the morpholine (**a**), for the ratio 5/4/1, the yield of **2a** became negligible but the amount of **4a** was greatly increased. Structure assignments of the products are based on spectral studies. Typically, for instance in the pmr spectrum of **2a**, **3a**, **4a** signals at  $\delta$  2.30 ppm are due to the methyl protons at position 5 (3H singlet) and at  $\delta$  2.65 (4H, CH<sub>2</sub>, 1'), 3.80 (4H, CH<sub>2</sub>, 2') ppm for the protons of morpholine ring (AA'BB' system) are observed. For **2a**, there are two  $\alpha$ -CH<sub>2</sub> and the two  $\beta$ -CH<sub>2</sub> groups which appear at  $\delta$  3.10 and 2.75 as triplets ( $J = 6$ ). For **3a**, a singlet at  $\delta$  3.10 corresponding to the  $\beta$ -CH<sub>2</sub> group and a two-singlets (5.45, 5.55) corresponding to the CH<sub>2</sub> = group are observed. In **4a**, signals at  $\delta$  2.70 ppm (d, 4H,  $\beta$ -CH<sub>2</sub>) and at  $\delta$  3.50 ppm (q, 1H,  $\alpha$ -CH) are characteristic. The <sup>13</sup>C nmr spectra of all compounds **4** synthesized are listed in Table 2. Shifts near  $\delta$  43 ppm for  $\alpha$ -CH and  $\delta$

## Scheme

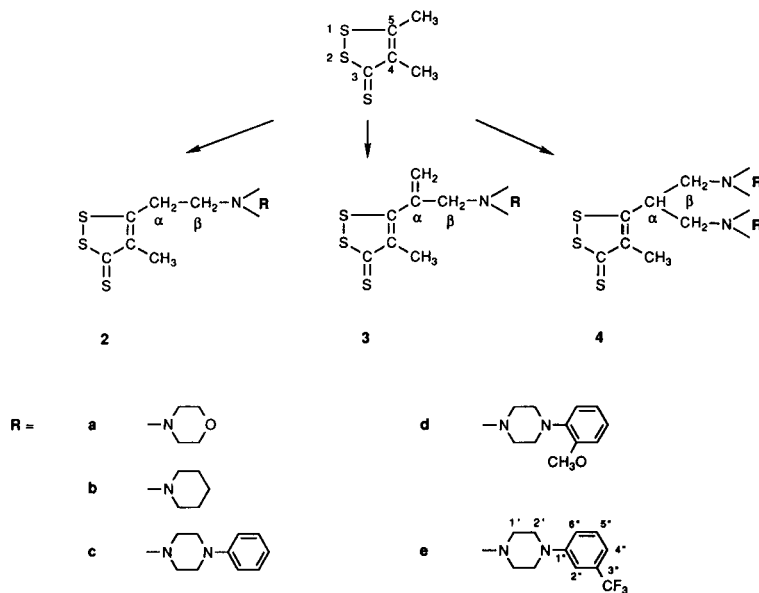


Table 1  
Analytical Data for Compounds **2a**, **3a**, **4a**

Compound	Yield % [a]	Mp °C	Molecular Formula	Analysis, %		
				Calcd./Found	C	H
<b>2a</b>	22 (trace) [b]	119-120	C <sub>10</sub> H <sub>15</sub> NOS <sub>3</sub>			
		diethyl ether	261.4	45.94	5.78	5.35
<b>3a</b>	trace (4) [b]	133-134	C <sub>11</sub> H <sub>15</sub> NOS <sub>3</sub>			
		petroleum ether	273.4	45.59	6.00	5.67
<b>4a</b>	21 (40) [b]	102-103	C <sub>15</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> S <sub>3</sub>			
		petroleum ether	360.5	48.32	5.53	5.12
<b>2b</b>	6	104-105	C <sub>11</sub> H <sub>17</sub> NS <sub>3</sub>			
		diisopropyl ether	259.5	48.16	5.86	5.32
<b>3b</b>	27	99-100	C <sub>12</sub> H <sub>17</sub> NS <sub>3</sub>			
		petroleum ether	271.5	49.97	6.71	7.77
<b>3c</b>	9	105-107	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> S <sub>3</sub>			
		cyclohexane	348.5	49.93	6.33	7.66
<b>4c</b>	8	180-181	C <sub>27</sub> H <sub>34</sub> N <sub>4</sub> S <sub>3</sub>			
		petroleum ether	510.8	50.92	6.60	5.40
<b>2d</b>	9	164-165	C <sub>17</sub> H <sub>12</sub> N <sub>2</sub> OS <sub>3</sub>			
		diethyl ether	366.6	51.34	6.83	5.43
<b>4d</b>	18	137-138	C <sub>29</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub> S <sub>3</sub>			
		petroleum ether	570.8	53.09	6.31	5.16
<b>4e</b>	13	157-158	C <sub>29</sub> H <sub>32</sub> N <sub>4</sub> S <sub>3</sub> F <sub>6</sub>			
		cyclohexane	646.8	53.07	6.32	5.16

[a] Yields are not optimized and are calculated from the starting material **1**. [b] Yields in parentheses correspond to a large excess of amine and trioxane.

Table II  
<sup>13</sup>C NMR Spectral Data for Compounds **4**

Compound	(C=S)	C4	C5	(CH <sub>3</sub> ) <sub>4</sub>	(CH) A	(CH <sub>2</sub> )	R
<b>4a</b>	215.25	142.39	172.70	16.28	42.19	60.29	54.28 (C 1'), 66.72 (C 2')
<b>4c</b>	215.47	142.53	172.78	16.49	42.98	59.76	49.17, 54.04 (C 1', C 2') 116.16, 129.17 (C 2", C 3") 119.97 (C 4"), 151.12 (C 1")
<b>4d</b>	215.33	142.50	173.25	16.42	42.97	59.87	50.51, 54.22 (C 1', C 2'), 55.34 (CH <sub>3</sub> O) 112.23, 118.20, 120.98, 123.01 (C 3", C 4", C 5", C 6") 141.06 (C 2"), 162.22 (C 1")
<b>4e</b>	215.39	142.54	172.50	16.50	42.92	59.76	48.73, 53.83 (C 1', C 2') 112.24 (q, C 2", J = 3.4), 116.10 (q, C 4", J = 3.4) 118.86 (C 2"), 124.26 (q, CF <sub>3</sub> , J = 273.9), 129.58 (C 6") 131.66 (q, C 3", J = 31.8), 151.21 (C 1")

60 ppm for  $\beta$ -CH<sub>2</sub> groups are commonly observed. In the other two series, for example **2b**,  $\delta$  32.04 and 55.32 are due to  $\alpha$ -CH<sub>2</sub> and  $\beta$ -CH<sub>2</sub> groups, respectively. In the case of **3b**, absorptions at  $\delta$  63.87, 122.62 and 139.85 are due to  $\beta$ -CH<sub>2</sub>, C=CH<sub>2</sub> and C=CH<sub>2</sub>, respectively. Assignments were made in accordance with the literature [6,7].

## EXPERIMENTAL

The <sup>1</sup>H (80.13 MHz) and <sup>13</sup>C (20.15 MHz) nmr spectra were recorded on a Bruker WP 80 spectrometer in deuteriochloroform. The <sup>13</sup>C nmr spectra were recorded in the proton-noise decoupled (BB). Tetramethylsilane was used as the internal standard. Chemical shifts are in  $\delta$  (ppm); coupling constants (absolute

value) are expressed in Hz. Deuterated solvents provided the internal lock signal. Melting points were measured with a Büchi SMP-20 capillary melting point apparatus and are uncorrected. Combustion analysis were performed by the C.N.R.S. (Vernaison). Samples were obtained through preparative separations performed on a Jobin-Yvon Modulprep hplc system with the R.I. Iota detector, Spectro Monitor D variable wavelength detector LDC Milton-Roy ( $\lambda = 280$  nm) and with a 40 mm  $\Phi$  column of silica gel (10-40  $\mu$ m) as the stationary phase and toluene/methanol (0 to 5%) as eluent. Thin layer chromatography (tlc) was performed on silica gel plates. The following solvent systems were used: toluene, toluene/petroleum ether (40-60°), toluene/methanol (various percentages); uv detection was at  $\lambda = 254$  and 366 nm.

#### General Procedure.

A mixture of formaldehyde (0.02 mole, as trioxane, 0.6 g, 0.066 mole), 4,5-dimethyl-1,2-dithiole-3-thione **1** (1.60 g, 0.01 mole) and primary amine (0.015 mole) in absolute alcohol (25 ml) is refluxed three days. The kinetics of the reactions were followed by thin layer chromatography (tlc). At the end of the reaction the solution was evaporated to dryness. The residue was resolved into its com-

ponents by preparative hplc. The resulting fractions were evaporated under vacuum to dryness. The product crystallised by addition of cold petroleum ether (40-60°). The purity of each fraction was controlled by tlc. The physical data are collected in Table 1.

#### REFERENCE AND NOTES

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