One-Step Synthesis of 5-Mercaptopyrazoles from 2-Methylene-1,3-dithietanes

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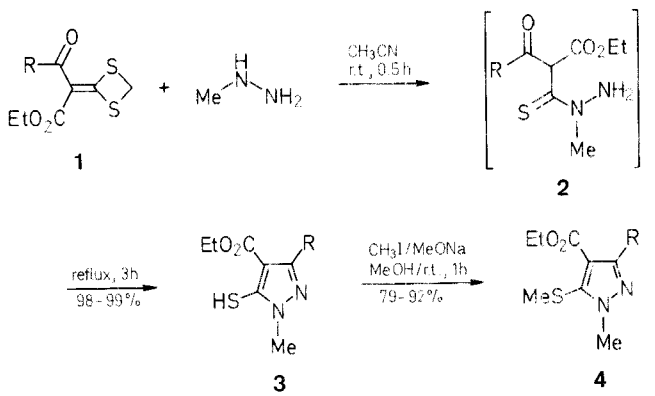
2-Methylene-1,3-dithietanes bearing electron-withdrawing groups on the sp^2 carbon afford 5-mercaptopyrazole derivatives by the reaction with methylhydrazine.

The 5-mercaptopyrazoles **3** are of value as a key intermediate of potent herbicide.[1] The hitherto reported synthetic methods of them can be classified in two groups. One[2] involves the transformation of 5-hydroxypyrazoles into the objective compounds via chlorination and subsequent thiolation, and the other[1,3] consists of their preparation from 5-aminopyrazoles by the Sandmeyer reaction. However, both methods are not satisfactory with respect to the total yield and versatility.

In a series of studies on four-membered heterocycles, the authors have found that 2-(acetylethoxycarbonyl)methylene-1,3-dithietane **(1a)** on treatment with amines underwent facile ring-opening to yield thioamides, and the latter on treatment with bromine were cyclized to 3-isothiazolones.[4]

The authors report here a new one-pot preparation of 3,4-disubstituted 5-mercapto-1-methylpyrazoles from the dithietanes **1a, b** by treating with methylhydrazine. On refluxing with excess methylhydrazine in acetonitrile, 2-methylene-1,3-dithietanes **1a, b** were directly converted into the 5-mercaptopyrazoles **3a, b** in almost quantitative yield. However, attempts to condense the dithietanes **1a, b** with excess phenylhydrazine were unsuccessful. On methylation, 5-mercaptopyrazoles **3** were converted to 5-methylthiopyrazoles[5] **4**.



1 **2** **3** **4**

1–4	R
a	CH_3
b	Ph

The compounds prepared were characterized by IR- and ^{1}H-NMR spectra which were consistent with the proposed structure. 2-Methylene-1,3-dithietanes **1a, b** were prepared by the reaction of ethyl α-acylacetates with carbon disulfide in the presence of a base followed by cyclization with dibromomethane in 52–74% overall yields.[6,7]

The melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadzu IR-420 spectrophotometer. ^{1}H-NMR spectra were determined with a Varian EM-390 (90 MHz) spectrometer with TMS as internal standard.

4-Ethoxycarbonyl-5-mercapto-1,3-dimethylpyrazole (3a):
To a solution of 2-methylene-1,3-dithietane (**1a**, 8.0 g, 36 mmol) in CH_3CN (50 mL) is added dropwise methylhydrazine (3.5 g, 71 mmol) at r.t. over 30 min. The reaction mixture is refluxed for 3 h, and the contents are concentrated under reduced pressure. After addition of H_2O (50 mL) to the residual mixture the contents are acidified with 1 N HCl to pH 2 and extracted with EtOAc (50 mL). The organic layer is dried over anhydrous Na_2SO_4, evaporated to dryness, and the residue is chromatographed on a silica gel column with hexane/EtOAc (2:1) as eluent to give **3a**; yield: 3.7 g (99%); mp 64–66°C.

$C_8H_{12}N_2O_2S$ (200.3) calc. C 47.98 H 6.04 N 13.99
found 47.88 6.00 14.05

IR (Nujol): ν = 1670 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.35 (t, 3H, J = 7 Hz); 2.37 (s, 3H); 3.67 (s, 3H); 4.30 (q, 2H, J = 7 Hz); 6.55 (br s, 1H).

4-Ethoxycarbonyl-5-mercapto-1-methyl-3-phenylpyrazole (3b):
Yield: 2.3 g (98%) from **1a** (2.0 g, 9 mmol), brown oil.

$C_{13}H_{14}N_2O_2S$ (262.3) calc. C 59.52 H 5.38 N 10.68
found 59.60 5.40 10.70

IR (liquid): ν = 1670 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.15 (t, 3H, J = 7 Hz); 3.85 (s, 3H); 4.20 (q, 2H, J = 7 Hz); 7.20–7.60 (m, 5H).

4-Ethoxycarbonyl-1,3-dimethyl-5-methylthiopyrazole (4a):
To a solution of 5-mercaptopyrazole (**3a**, 0.5 g, 2.5 mmol) in MeOH (50 mL) is added dropwise MeONa (2.5 mmol) and then MeI (0.4 g, 2.5 mmol) at r.t.. The reaction mixture is stirred at r.t. for 1 h, and concentrated under reduced pressure. After addition of H_2O (30 mL), the solution is acidified with 1 N HCl to pH 2 and extracted with CH_2Cl_2 (50 mL). The organic layer is dried over anhydrous Na_2SO_4 and evaporated to dryness to give **4a**; yield: 0.5 g (92%); mp 33–34°C.

$C_9H_{14}N_2O_2S$ (214.3) calc. C 50.45 H 6.59 N 13.07
found 50.44 6.70 13.11

IR (Nujol): ν = 1710, 1510, 1250 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.40 (t, 3H, J = 7 Hz); 2.45 (s, 6H); 3.92 (s, 3H); 4.35 (q, 2H, J = 7 Hz).

4-Ethoxycarbonyl-1-methyl-5-methylthio-3-phenylpyrazole (4b):
Yield: 1.9 g (79%) from **3b** (2.3 g, 8.8 mmol), yellow oil.

$C_{14}H_{16}N_2O_2S$ (276.4) calc. C 60.85 H 5.84 N 10.14
found 60.88 5.84 10.15

IR (liquid): ν = 1710 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.18 (t, 3H, J = 7 Hz); 2.50 (s, 3H); 4.00 (s, 3H); 4.24 (q, 2H, J = 7 Hz); 7.20–7.60 (m, 5H).

Received: 1 August 1988; revised: 9 January 1989

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(5) The reason why the formation of the 3-mercapto isomer was excluded is as follows. 4-Ethoxycarbonyl-1,3-dimethyl-5-methylthiopyrazole which was synthesized from 5-amino-4-ethoxycarbonyl-1,3-dimethylpyrazole (**4a**) was prepared alternatively by methylthioation of 5-chloro-4-ethoxycarbonyl-1,3-dimethylpyrazole (**5**) by the Sandmeyer reaction.[1,3] 5-Aminopyrazole **5** was prepared from methylhydrazine and ethyl 2-cyano-3-ethoxycrotonate.[8] On this reaction the formation of 3-aminopyrazole was excluded.[9,10]
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