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A New Method for the Synthesis of Thieno[2,3-c]pyrazoles

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ABSTRACT: *A new method has been found for the synthesis of pyrazoleacetate esters from pyrazolaldehyde. By a new tandem reaction, in which methyl 4-pyrazoleacetate was reacted with carbon disulfide and iodomethane, thieno[2,3-c]pyrazole was synthesized. This was an easy method for the synthesis of this type of heterocycle.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 303–305, 1999

INTRODUCTION

In a study on new pharmaceuticals and agrochemicals, the application of heterocycles is a very important consideration that can improve the biological activity. In recent years, many new agrochemicals have been synthesized that have structures containing heterocyclic rings, especially pyrazole. In our study on this type of compound, we have found that thieno[2,3-c]pyrazole exhibited good biological activity. We are therefore interested in its synthesis. Thieno[2,3-c]pyrazoles were studied by few chemists before our study. Kvitko and coworkers [1,2] prepared 3-methyl-1-phenyl-5-thieno[2,3-c]pyrazolecarboxylic acid by treatment of 5-chloro-3-methyl-1-phenyl-4-pyrazolaldehyde with thioglycolic acid. Kvitko and Tarasenko [3] also prepared this compound by the reaction of 4-dimethyaminomethylene-3-methyl-1-phenyl-5-thiopyrazolone with chloroacetic acid. 5-Chloro-3-methyl-1-phenyl-4-cyanopyrazole was reacted with *N*-phenylthioacetamide to afford 4-amino-3-methyl-1-phenyl-5-phenylaminocarbonylthieno[2,3-c]pyrazole [4]. Brown and Otto [5] used dithiodipyrazolaldehyde to react with nitromethane to afford 3-methyl-5-nitro-1-phenylthieno[2,3-c]pyrazole.

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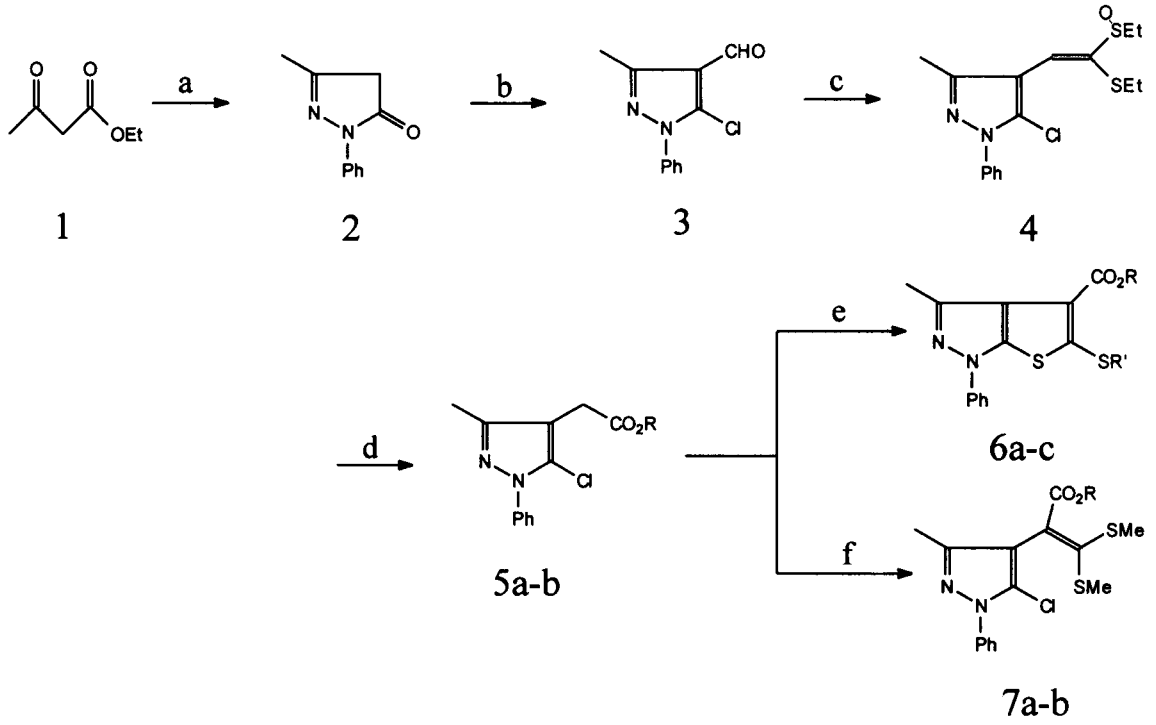
RESULTS AND DISCUSSION

In our study, we found a new method for the synthesis of these types of heterocycles (Scheme). Pyrazolone **2** was prepared by treatment of ethyl acetoacetate with phenylhydrazine [6]. The pyrazolaldehyde **3** was prepared by a Vilsmeier–Haack reaction from **2** [7–10]. By use of the method of Ogura and coworkers [11–13], compound **4** was prepared, which was then converted to esters **5(a–b)**. This was a new method for the synthesis of pyrazoleacetate esters from pyrazolaldehyde. Compounds **5(a–b)**, CS_2, KOH (power), and DMSO were stirred overnight at room temperature, and then RX was added. The ring-closed products **6(a–d)** were thusly synthesized. When iodomethane (RX = MeI) was mixed with compounds **5**, CS_2, KOH, and DMSO and stirred overnight at room temperature, the products were **7(a–b)**, instead of **6(a–b)**.

EXPERIMENTAL

All melting points were determined on a micromelting-point apparatus and were uncorrected. Elemental analysis data were obtained by use of a Yanaco CHN Corder MR-3 apparatus. ^{1}H NMR spectra were recorded on a Bruker AC-P200(200 MHz) Spectrometer using tetramethylsilane (TMS) as an internal



SCHEME 1 **a**. $PhNHNH_2$; **b**. $DMF/POCl_3$; **c**. FAESO/NaH/THF; **d**. dry HCl/ROH; **e**. 1, CS_2/KOH/DMSO; 2, R′X; **f**. CS_2/MeI/KOH/DMSO

standard and $CDCl_3$ as the solvent. Mass spectra were recorded on a Hewlett-Packard 5988 instrument.

Preparation of Compound **4**

Under a nitrogen atmosphere, formaldehyde, diethyl dithioacetal S-oxide (FAESO) [14] (1.5 g, 10 mmol) was added dropwise to a mixture of sodium hydride (50%, 0.6 g, 12 mmol) and 40 mL of dry THF with stirring. After the mixture had been stirred at room temperature for 1 hour, compound **3** (2.2 g, 10 mmol) was added. The mixture was then refluxed for 3 hours. When the mixture had cooled, 30 mL of water and 50 mL of ether were added. The separated water layer was extracted with an additional 50 mL of ether. The combined ether extract was washed with water (30 mL × 2) and dried with $MgSO_4$. After evaporation of the ether, 2.9 g of yellow thick liquid was obtained by flash column chromatography, yield = 80%. Calcd for $C_{16}H_{19}ClN_2OS_2$: C, 54.15; H, 5.40; N, 7.89. Found: C, 53.81; H, 5.50; N, 7.62. ^{1}H NMR: δ = 1.08–1.33 (m,6H), 2.34 (s,3H), 2.60–3.22 (m,4H), 7.30–7.60 (m,5H).

Preparation of Compound **5a** (*R* = *Me*)

Dry HCl gas was vigorously bubbled into a solution of **4** (6.5 g, 18 mmol) in 50 mL of dry methanol. The temperature rose rapidly, and the solution began to reflux. When the temprature dropped to 60°C, the introduction of HCl was stopped. The solution was poured into 200 mL of ice water and extracted with ether (50 mL × 3). The combined ether extract was washed with water (80 mL × 2) and dried with $MgSO_4$. After evaporation of the ether, 3.9 g of colorless liquid was obtained by flash column chromatography, yield = 80%. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.98; H, 4.95; N, 10.59. Found: C, 58.70; H, 4.80; N, 10.30. ^{1}H NMR: δ = 2.20 (s, 3H), 3.40 (s, 2H), 3.75 (s, 3H), 7.25–7.62 (m, 5H).

Compound **5b** (R = Et) was prepared by the same method, yield = 80%. Calcd for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05. Found: C, 60.31; H, 5.54; N, 9.87. ^{1}H NMR: δ = 1.27 (t, 3H, J = 7.0 Hz), 2.28 (s, 3H), 3.46 (s, 2H), 4.17 (q, 2H, J = 7.0 Hz), 7.30–7.66 (m, 5H).

Preparation of Compound **6a** (*R,R′* = *Me*)

Compound **5a** (1.3 g, 5 mmol), carbon disulfide (0.5 g, 6.6 mmol), potassium hydroxide (82%, powder, 1.2 g, 12 mmol) and 20 mL of methyl sulfoxide were stirred overnight at room temperature. Iodomethane (1.0 g, 7 mmol) was added, and the mixture was stirred overnight at room temperature. The mixture was poured into 100 ml of water; 1.5 g of solid was

collected, yield = 94%, mp 138–139°C (acetone). Calcd for $C_{15}H_{14}N_2O_2S_2$: C, 56.58; H, 4.43; N, 8.80. Found: C, 56.63; H, 4.14; N, 8.61. ^{1}H NMR: δ = 2.60 (s, 6H), 3.92 (s,3H), 7.20–7.70 (m,5H). MS (m/z): 318 (M^+), 303, 287, 271, 243, 232, 202, 186, 171, 159, 143, 115, 100.

Compounds **6(b–d)** were prepared by the same method. Compound **6b** (R = Et, R′ = Me): yield = 85%, mp 115–117°C (acetone). Calcd for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; H, 4.85; N, 8.43. Found: C, 58.03; H, 4.74; N, 8.55. ^{1}H NMR: δ = 1.43(t, 3H, J = 6.9 Hz), 2.61 (s, 3H), 2.64 (s, 3H), 4.42 (q, 2H, J = 6.9 Hz), 7.22–7.80 (m, 5H).

Compound **6c** (R = Et, R′ = MeO_2CCH_2): yield = 63%, mp 126–128°C (acetone). Calcd for $C_{18}H_{18}N_2O_4S_2$: C, 55.37; H, 4.65; N, 7.17. Found: C, 55.56; H, 4.60; N, 7.32.^{1}H NMR: δ 1.44 (t, 3H, J = 7.4 Hz), 2.61 (s, 3H), 3.73 (s, 3H), 3.79 (s, 2H), 4.44 (q, 2H, J = 7.4 Hz), 7.22–7.71 (m, 5H).

Preparation of Compound **7a** (*R* = *Me*)

Compound **5a** (1.3 g, 5 mmol), carbon disulfide (0.5 g, 6.6 mmol), potassium hydroxide (82%, powder, 1.2 g, 12 mmol), iodomethane (1.7 g, 12 mmol), and 20 mL of methyl sulfoxide were stirred at room temperature for 2 days. The mixture was poured into 100 mL of water and extracted with ether (50 mL × 3). The ether layer was dried with $MgSO_4$. After evaporation of the ether, 1.0 g of a thick liquid was obtained by flash column chromatography, yield = 50%. Calcd for $C_{15}H_{17}ClN_2O_2S_2$: C, 50.48; H, 4.80; N, 7.85. Found: C, 50.86; H, 4.79; N, 7.53. ^{1}H NMR: δ = 2.21 (s, 3H), 2.2 4(s, 3H), 2.48 (s, 3H), 3.74 (s, 3H), 7.28–7.66 (m, 5H). MS (m/z): 368 (M^+), 353, 318, 303, 290, 262, 235, 215, 205, 171, 159, 144, 103, 94.

Compound **7b** (R = Et) was prepared as a yellow thick liquid by the same method, yield = 68%. Calcd for $C_{16}H_{19}ClN_2O_2S_2$: C, 51.81; H, 5.16; N, 7.55. Found: C, 52.15; H, 5.05; N, 7.90. ^{1}H NMR: δ = 1.26 (t, 3H, J = 6.9 Hz), 2.21 (s, 3H), 2.24 (s, 3H), 2.46 (s, 3H), 4.21 (q, 2H, J = 6.9 Hz), 7.22–7.62 (m, 5H).

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