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A NOVEL SYNTHESIS OF THIENO[2,3-C]PYRAZOLE

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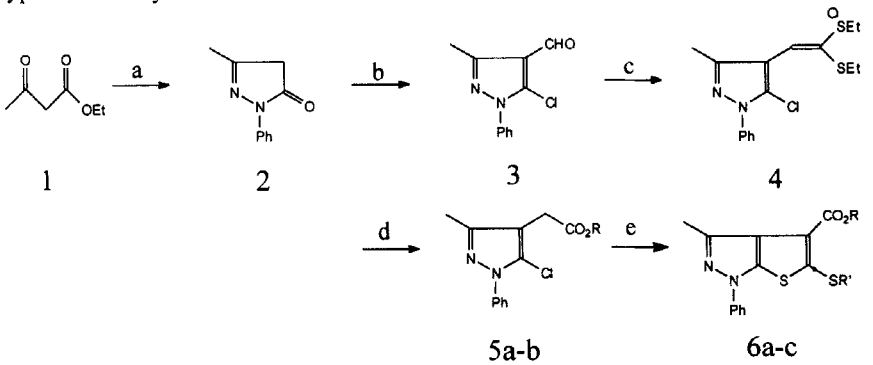
Abstract: A new method was found for the synthesis of pyrazoleacetate esters from pyrazolaldehyde. By a new tandem reaction, in which 4-pyrazoleacetate esters reacted with carbon disulfide and iodomethane, thieno[2,3-c]pyrazole was synthesized. This was an easy method for the synthesis of this type of heterocycles.

In our study on new pharmaceuticals and agrochemicals, the application of heterocycles is a very important method, which can improve the biological activities. In reviewing the recent reported pesticide patents, we found that the heterocyclic compounds occupied a dominant position in pesticide research. In our study on this type of compounds, we found[1] that thieno[2,3-c]pyrazole had good biological activities. The synthesis of thieno[2,3-c]pyrazole was studied by Kvitko[2,3], who prepared 3-methyl-1-phenyl-5-thieno[2,3-c]pyrazolecarboxylic acid from 5-chloro-3-methyl-1-phenyl-4-pyrazolaldhyde and thioglycolic acid. They[4] 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 reacted with N-phenylthioacetamide to afford 4-amino-3-methyl-1-phenyl-5-

phenylaminocarbonylthieno[2,3-c]pyrazole[5].Brown[6]used dithiodipyrazolaldhyde to react with nitromethane to afford 3-methyl-5-nitro-1-phenylthieno[2,3-c]pyrazole. In our recent studies, we found a new method for the synthesis of this type of heterocycles.



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

Scheme

Compound **2** was prepared by treatment of ethyl acetoacetate with phenylhydrazine[7]. Compound **3** was prepared by Vilsmeier-Haack reaction from Compound **2**[8-11]. Using the method of Ogura[12-14], compound **4** was prepared, which was then converted to compounds **5(a-b)**. This was a new method for the synthesis of pyrazoleacetate esters from pyrazolaldehyde. Compounds **5(a-b)**, CS_2, KOH and DMSO are stirred overnight at room temperature and then RX is added to give the ring-closed products **6(a-d)**.

Experimental section:

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. ^1H NMR spectra were recorded on a Bruker AC-P200(200MHz) Spectrometer using tetramethylsilane (TMS) as an internal standard an $CDCl_3$ as the solvent. Mass spectra were recorded on a Hewlett-Packard 5988 instrument.

Preparation of compound **4**:

With the protection of N_2, FAESO[15] (1.5 g, 10 mmol) was added dropwise to a stirred mixture of sodium hydride (50%, 0.6 g, 12 mmol) and 40mL of dry THF. After stirring at room temperature for 1hour, compound **3** (2.2 g, 10 mmol) was added in the reaction mixture. The mixture was then refluxed for 3hours. When the mixture cooled, 30 mL of water and 50 mL of ether were added. The separated water layer was extracted with 50 mL of ether. The combined ether extracts were washed with water (30 mL×2), and dried with $MgSO_4$. After evaporation of ether, 2.9 g of a yellow thick liquid was obtained which was purified by flash column chromatography (petroleum/acetone=10:1), 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(ppm): 1.1-1.3(m,6H), 2.34(s,3H), 2.6-3.2(m,4H), 7.3-7.6(m,5H)

Preparation of compound **5a**(R=Me):

Dry HCl gas was vigorously bubbled into a solution of compound **4** (6.5 g, 18 mmol) in 50 mL of dry methanol, the temperature rose rapidly to reflux. When the temperature dropped to 60℃, the introduction of HCl was stopped. The solution was poured into 200 mL ice-water and extracted with ether (50 mL×3). The combined ether extracts were washed with water (80 mL×2) and dried with $MgSO_4$. After the evaporation of ether, 3.9 g of a colorless liquid was obtained which was purified by flash column chromatography (petroleum/acetone=10:1), 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(ppm): 2.20(s, 3H), 3.40(s, 2H), 3.75(s, 3H), 7.3-7.6(m, 5H)

Compound **5b** (R=Et), 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(ppm): 1.27(t, 3H,*J*=7.0Hz), 2.28(s, 3H), 3.46(s, 2H), 4.17(q, 2H, *J*=7.0Hz), 7.3-7.7(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%, power, 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 again. The mixture

was poured into 100 mL of water. 1.5 g of a solid was collected, yield=94%, mp: 138-139℃(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(ppm): 2.60(s, 6H), 3.92(s,3H), 7.2-7.7(m,5H). MS(m/z): 318(M^+), 303, 287,271, 243, 232, 202, 186, 171, 159, 143, 115, 100

Compounds **6(b-c)** were prepared in the same method.

Compound **6b** (R=Et, R'=Me): yield = 85%, mp: 115-117℃(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(ppm): 1.43(t, 3H, *J*=6.9Hz), 2.61(s, 3H), 2.64(s, 3H), 4.42(q, 2H, *J*=6.9Hz), 7.2-7.8(m, 5H).

Compound **6c** (R=Et, R'=MeO_2CCH_2): yield = 63%, mp: 126-128℃(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(ppm): 1.44(t, 3H, *J*=7.4Hz), 2.61(s, 3H), 3.73(s, 3H), 3.79(s, 2H), 4.44(q, 2H, *J*=7.4Hz), 7.2-7.7(m, 5H)

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