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A NOVEL METHOD FOR THE SYNTHESIS OF PYRAZOLO[5,1-b]THIAZOLE

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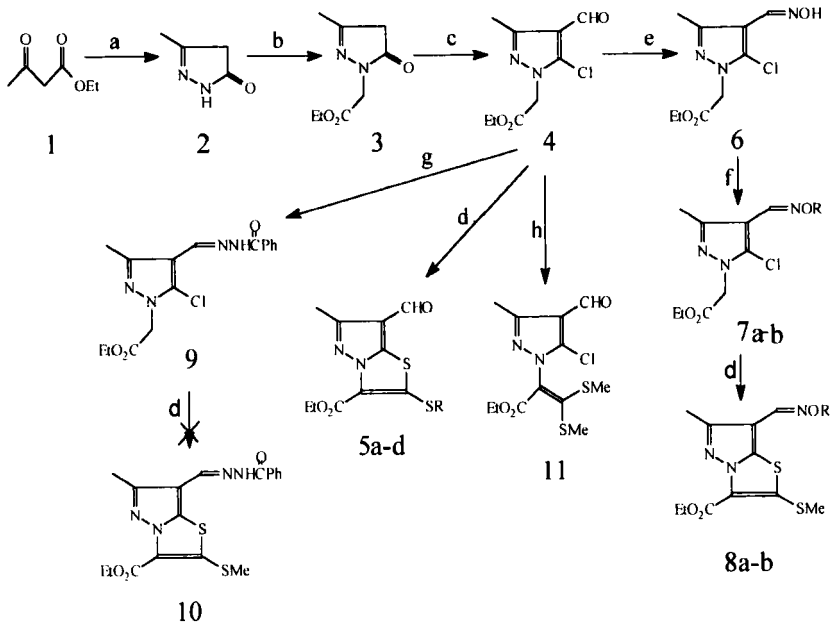
Abstract: By a new tandem reaction, in which ethyl 1-pyrazolacetate reacted with carbon disulfide and iodomethane, pyrazolo[5,1-b]thiazole was synthesized. This was an easy method for the synthesis of this type of heterocyles.

In study on new pharmaceuticals and agrochemicals, the application of heterocycles is a very important method, which can improve the biological activities. In these years, more and more new agrochemicals have been synthesized which have the structures containing heterocycles, especially pyrazole. In our study on this type of compounds, we found [1] that pyrazolo[5,1-b]thiazole had good biological activities. We are also interested in its synthesis. Pyrazolo[5,1-b]thiazole was studied few before our study. Molina [2][3] synthesized 3,6-diphenyl-7-mercaptopyrazolo[5,1-b]thiazole, 7-benzoyl-3,6-diphenylpyrazolo[5,1-b]thiazole and 6-amino-3,7-diphenylpyrazolo[5,1-b]thiazole from 3-amino-4-phenyl-4-thiazolin-2-thione and its analogue.

Some other methods had been reported, and imines [4][5], ketones [6][7] and dihydro derivatives [8] of pyrazolo[5,1-b]thiazole were synthesized.

In Molina's methods, the thiazole ring was constructed first. In our studies, we found a new route for the synthesis of pyrazolo[5,1-b]thiazole, in which the pyrazole was constructed before the thiazole ring system (**scheme**).



a.$N_2H_4\,H_2O$;**b**.$BrCH_2CO_2Et$;**c**.DMF/$POCl_3$;**d**.Method **A**:1,CS_2/KOH/DMSO;2, RX; Method **B**:1,CS_2/NaH/DMA/Ether;2,MeI;**e**.$NH_2OH{\cdot}HCl$/ $NaHCO_3$;**f**.RX/K_2CO_3;**g**. $PhCONHNH_2$/Ethanol;**h**.CS_2/MeI/KOH/DMSO

Scheme

Pyrazolone **2** was prepared from ethyl acetoacetate and hydrazine [9]. Ethyl 1-pyrazolacetate **3** was prepared by heating **2** and ethyl bromoacetate [10][11]. By the Vilsmeier-Haack reaction, compound **4** was prepared. By a tandem reaction, compounds **5(a-d)** were synthesized. In the preparation of **5(a-d)**, two methods were used (**A** and **B**). In method **A,** potassium hydroxide was used as the base in DMSO. In method **B**, sodium hydride was used as the base in dry ether and with the catalysis of DMA. Method **A** was better, because it had more convenient reaction condition and could be treated easier. In the synthesis of **5a** (method **A**), compound **4,** carbon disulfide and potassium hydroxide were stirred overnight, and then iodomethane was added to give the ring-closed product. When carbon disulfide, potassium hydroxide and iodomethane were mixed together and stirred

overnight, the product was **11**, instead of **5a**. However, in the synthesis of compound **5a** in method **B**, a mixture of compound **4**, carbon disulfide, sodium hydride and DMA in dry ether was stirred overnight, and then iodomethane was added. Compounds **5(b-d)** were prepared in method **A**. Ester **4** reacted with hydroxylamine to afford compound **6**, which was then alkylated to afford compound **7(a-b)**. Compound **7a** reacted with carbon disulfide (method **A**) to afford compound **8a** easily. But only trace of **8b** was observed in GC-MS, in which **5a** was also observed (M^+=284). A ring-closed try of compound **9** was failed, in which the reaction mixture was complicated and the desired compound **10** was not observed in GC-MS.

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

Compound **2** was prepared by treatment of ethyl acetoacetate with $N_2H_4 H_2O$ in ethanol, yield=87%, mp: 231-233 ℃ (literature [8]: mp: 231-232 ℃).

Preparation of compound **3**:

3-methyl-2-pyrazolin-5-one (compound **2**) (29.4 g, 0.30 mol) and ethyl bromoacetate (50.4 g, 0.30 mol) were stirred under reflux for 5 hours. After the addition of 50 mL of water, the mixture was neutralized with 50% KOH (pH=7). 25.0 g of white power was collected, yield=45%, mp: 154-156 ℃ (ethanol). Calcd. for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.56; N, 15.21. Found: C, 52.13; H, 6.46; N, 15.10. ^{1}H NMR (ppm): 1.25 (t, 3H, J=7.4 Hz), 2.09 (s, 3H), 3.23 (s, 2H), 4.19 (q, 2H, J=7.4 Hz), 4.39 (s, 2H)

Preparation of compound **4**:

With mechanic stirring, fresh phosphorus oxylchloride (154 mL, 1.61 mol) was added dropwise to dry N,N-dimethylformide (51.5 g, 0.68 mol) (t<5 ℃).

After the addition of phosphorus oxylchloride, the reaction mixture was slowly heated to 102 ℃, and kept for 6 hours. The mixture was then cooled and poured into a mixture of ice and water (1200 mL), and extracted with ether (200 mL×3). The combined ether extracts were washed with water (200 mL×2) and dried with $MgSO_4$. After evaporation of ether, 31.5 g of yellow solid was obtained, yield=60%, mp: 66-68 ℃ (petroleum/ether).

Calcd. for $C_9H_{11}ClN_2O_3$: C, 46.87; H, 4.81; N, 12.14. Found: C, 46.72; H, 4.60; N, 12.09. ^{1}H NMR (ppm): 1.28 (t, 3H, J=7.2 Hz), 2.45 (s, 3H), 4.24 (q, 2H, J=7.2 Hz), 4.86 (s, 2H), 9,86 (s, 1H)

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

Method **A**:

Compound **4** (1.2 g, 5.0 mmol), carbon disulfide (0.5 g, 6.6 mmol), potassium hydroxide (80%, power, 0.8 g, 12.0 mmol) and 20 mL of DMSO were mixed and stirred overnight at room temperature. Iodomethane (0.9 g, 6.0 mmol) was then added in and the mixture was stirred overnight again. The mixture was poured into 100 mL of cooled water. 1.0 g of solid was obtained, yield=73%, mp: 147-149 ℃ (acetone).

Calcd. for $C_{11}H_{12}N_2O_3S_2$: C, 46.46; H, 4.25; N, 9.85. Found: C, 46.49; H, 4.14; N, 9.90. ^{1}H NMR (ppm): 1.44 (t, 3H, J=7.2 Hz), 2.61 (s, 3H), 2.64 (s, 3H), 4.49 (q, 2H, J=7.2 Hz), 9.86 (s, 1H). MS (m/z): 284 (M^+), 269, 255, 239, 210, 197, 167, 140, 126

Compounds **5(b-d)** were prepared in the same method.

Compound **5b** (R=$PhCH_2$): yield=72%, mp: 110-111 ℃ (acetone).

Calcd. for $C_{19}H_{16}N_2O_3S_2$: C, 56.65; H, 4.47; N, 7.77. Found: C, 56.74; H, 4.51; N, 7.56. ^{1}H NMR (ppm): 1.43 (t, 3H, J=7.2 Hz), 2.64 (s, 3H), 4.23 (s, 2H), 4.48 (q, 2H, J=7.2 Hz), 7.25-7.35 (m, 5H), 9.86 (s, 1H)

Compound **5c** (R=EtO_2CCH_2): yield=22%, mp: 129-130 ℃ (acetone)

Calcd. for $C_{14}H_{16}N_2O_5S_2$: C, 47.18; H, 4.53; N, 7.86. Found: C, 47.08; H, 4.49; N, 7.60. ^{1}H NMR (ppm): 1.26 (t, 3H, J=7.3 Hz), 1.45 (t, 3H, J=7.3 Hz), 2.64 (s, 3H), 3.78 (s, 2H), 4.21 (q, 2H, J=7.3Hz), 4.51 (q, 2H, J=7.3 Hz), 9.86 (s, 1H)

Compound **5d** (R=MeO_2CCH_2): yield=35.3%, mp: 123-124 ℃ (acetone)
Calcd. for $C_{13}H_{14}N_2O_5S_2$: C, 45.60; H, 4.12; N, 8.18. Found: C, 45.47; H, 4.20; N, 7.87. ^{1}H NMR (ppm): 1.44 (t, 3H, *J*=7.3 Hz), 2.64 (s, 3H), 3.75 (s, 2H), 3.78 (s, 3H), 4.51 (q, 2H, *J*=7.3 Hz), 9.98 (s, 1H)

Method **B**:

5 mL of dry N,N-dimethylacetamide was added dropwise to a mixture of compound **4** (1.2 g, 5.0 mmol), carbon disulfide (0.5 g, 6.0 mmol), sodium hydride (80%, 0.4 g, 12 mmol) and 25 mL of dry ether in an ice bath. The mixture was stirred overnight at room temperature, iodomethane (0.9 g, 6 mmol) in 10 mL of dry N,N-dimethylacetamide was added dropwise. After stirred overnight at room temperature again, the mixture was poured into a mixture of 100 mL of water and 20 mL of ether. After the separation of the ether layer, the water layer was extracted with 50 mL of ether. The combined ether extracts were washed with water (50 mL × 3) and dried with $MgSO_4$. After the evaporation of ether, 1.9 g of yellow solid was obtained, yield=76%.

Preparation of compound **6**:

Compound **4** (6.9 g, 30 mmol), hydroxylamine hydrochloride (2.8 g, 40 mmol), sodium bicarbonate (3.4 g, 40 mmol) and 60 mL of anhydrous ethanol were stirred overnight at room temperature and refluxed for 1 hour, and filtered. After the evaporation of part of the solvent of the filtrate, 6.4 g of white crystal was obtained from the cool solution, yield=88%, mp: 125-126 ℃ (ethanol).
Calcd. for $C_9H_{12}ClN_3O_3$: C, 44.00; H, 4.92; N, 17.10. Found: C, 43.91; H, 4.84; N, 16.84. ^{1}H NMR (ppm): 1.27 (t, 3H, *J*=7.1 Hz), 2.36 (s, 3H), 4.22 (q, 2H, *J*=7.1 Hz), 4.86 (s, 2H), 7.80 (br, 1H), 8.02 (s, 1H)

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

Compound **6** (1.1 g, 5 mmol), dimethyl sulfate (0.7 g, 5 mmol), potassium carbonate (1.0 g, 7 mmol) and 30 mL of acetone were stirred for 6 hours at reflux, and filtered. After the evaporation of the solvent of the filtrate, 0.9 g of yellow solid was obtained, yield=80%, mp: 62-63 ℃ (petroleum/ether)
Calcd. for $C_{10}H_{14}ClN_3O_3$: C,46.25; H, 5.43; N, 16.18. Found: C, 46.37; H, 5.53; N, 15.88. ^{1}H NMR (ppm): 1.24 (t, 3H, *J*=7.2 Hz), 2.37 (s, 3H), 3.90 (s, 3H), 4.21 (q, 2H, *J*=7.2 Hz), 4,82 (s, 2H), 7.94 (s, 1H)

Compound **7b** (R=MeO_2CCH_2) was prepared in the same method from compound **6** and methyl bromoacetate, yield=90%, mp: 66-67 ℃ (petroleum/ether)
Calcd. for $C_{12}H_{16}ClN_3O_5$: C, 45.36; H, 5.08; N, 13.23. Found: C, 45.49; H, 4.92; N, 13.02. ^{1}H NMR (ppm): 1.25 (t, 3H, J=7.0 Hz), 2.33 (s, 3H), 3.76 (s, 3H), 4.22 (q, 2H, J=7.0 Hz), 4.66 (s, 2H), 4.82 (s, 2H), 8.09 (s, 1H). MS (m/z): 317 (M+), 244, 228, 200, 154, 142, 120

Compound **8a** was prepared in the same method as method **A** for the preparation of **5a**, yield=83%, mp: 148-150 ℃ (acetone)
Calcd. for $C_{12}H_{15}N_3O_3S_2$: C, 45.67; H, 4.82; N, 13.41. Found: C, 45.88; H, 4.72; N, 13.25. ^{1}H NMR (ppm): 1.44 (t, 3H, J=7.2 Hz), 22.44 (s, 3H), 2.61 (s, 3H), 3.91 (s, 3H), 4.49 (q, 2H, J=7.2 Hz), 8.07 (s, 1H)

Preparation of compound **9**:

Compound **4** (3.6 g, 15 mmol), benzoxyl hydrazine (2.0 g, 15 mmol) and 30 mL of ethanol was refluxed for 10 hours. After the reaction mixture was cooled, 2.8 g of yellow solid was collected, yield=52%, mp: 155-157 ℃ (ethanol)
Calcd. for $C_{16}H_{17}ClN_4O_3$: C, 55.10; H, 4.91; N, 16.06. Found: C, 54.85; H, 4.63; N, 15.92. ^{1}H NMR (ppm): 1.25 (t, 3H), 2.45 (s, 3H), 4.21 (q, 2H), 4.82 (s, 2H), 7.27-8.00 (m, 5H), 8.25 (s, 1H), 9.25 (s, 1H)

Preparation of compound **11**:

Compound **4** (1.2 g, 5 mmol), carbon disulfide (0.5 g, 6.6 mmol), potassium hydroxide (82%, power, 2.1 g, 15 mmol), iodomethane (2.1 g, 15 mmol) and 20 mL of DMSO were stirred for 2 days at room temperature. The mixture was poured into 100 mL of cooled water and extracted with ether (50 mL×2). The combined ether extracts were washed with water (50 mL×2) and dried with $MgSO_4$. After the evaporation of ether, 1.5 g of yellow liquid was obtained. With flash column chromatograph, 0.9 g of colorless crystal was obtained, yield=54%, mp: 100-101 ℃.
Calcd. for $C_{12}H_{15}ClN_2O_3S_2$: C, 43.04; H, 4.52; N, 8.37. Found: C, 42.96; H, 4.33; N, 8.22. ^{1}H NMR (ppm): 1.17 (s, 3H, J=7.1 Hz), 2.25 (s, 3H), 2.49 (s, 3H), 2.57 (s, 3H), 4.18 (q, 2H, J=7.1 Hz), 9.98 (s, 1H). MS (m/z): 334 (M^+), 299, 273, 253, 238, 213, 199, 183, 157, 145, 132, 103, 91

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