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LETTERS TO THE EDITOR

Alkylation of Pyrazoles with Ethyl Chloroacetate under Phase-Transfer Catalysis and Hydrolysis of the Esters Obtained

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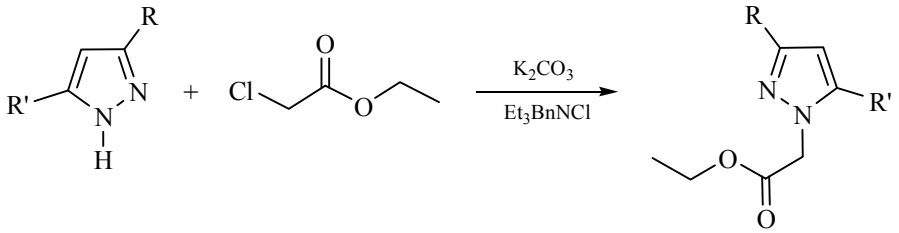
Phase-transfer catalyzed reactions of the esters of haloacetic acids with pyrazoles have not been studied so far, although alkylation of pyrazoles with bromoacetates has been known [1]. The approach towards synthesis of (3,5-dimethyl-1*H*-pyrazol-1-yl)acetic acid via condensation of ethyl hydrazinylacetate hydrochloride and acetylacetone followed by hydrolysis has been reported [2]. However, this method is laborious due to ethyl hydrazinylacetate hydrochloride instability of; yield of the target compounds does not exceed 65%.

In [3] the authors have proposed the alkylation of 3,5-dimethylpyrazole with chloroacetic acid in aqueous medium followed by neutralization of hydrochloric acid with sodium formate, making possible to isolate amphoteric (3,5-dimethyl-1*H*-pyrazol-1-yl)-acetic acid with yield of 84%. Numerous attempts to obtain 1*H*-pyrazol-1-yl-acetic acid by reacting pyrazole with chloroacetic acid have failed, as the pyrazole basicity (pK_a 2.53) is significantly different from the basicity of 3,5-dimethylpyrazole (pK_a 4.3). This method has also proved to be inappropriate for synthesis of the individual isomers of 3-methyl- and (5-methyl-1*H*-pyrazol-1-yl)acetic acids.

Extending our previous findings on the synthesis of 1-substituted azoles [4, 5], herein we report the interaction of pyrazoles **I** and **III** with ethyl chloroacetate under phase-transfer catalysis conditions (Scheme 1).

The alkylation was carried out in acetone medium using triethylbenzylammonium chloride (Et_3BnNCl) as catalyst and K_2CO_3 as base. The highest yields (45–63%) of **IV**–**VI** were achieved at the ratios of pyrazole : ethyl chloroacetate : K_2CO_3 equal to 1 : 2 : 2.5

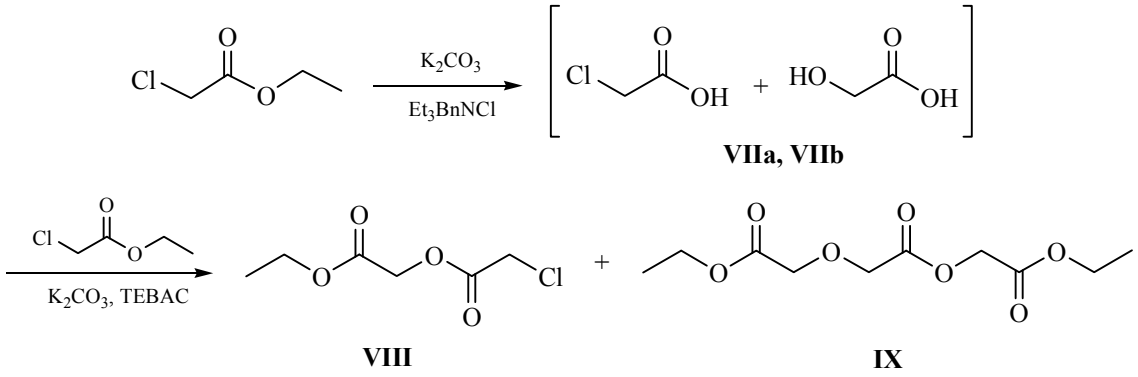
Scheme 1.



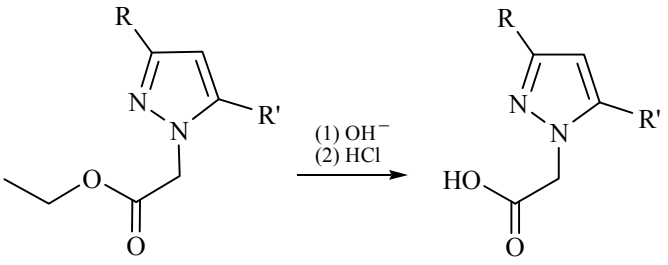
I–**III** **IV**–**VI**

I, IV, R = R' = H; **II**, R = CH_3, R' = H or R = H, R' = CH_3; **Va**, R = CH_3, R' = H; **Vb**, R = H, R' = CH_3; **III, VI**, R = R' = CH_3.

Scheme 2.



Scheme 3.



IV, X, R = R' = H; Va, **XIa**, R = CH_3, R' = H; **Vb, XIb**, R = H, R' = CH_3; **VI, XII**, R = R' = CH_3.

and 1 : 1 : 1.5. Low yields of the desired products were caused by side reactions occurring. In particular, alkylation of pyrazoles **I**–**III** in the presence of excess of ethyl chloroacetate resulted in **IV**–**VI** along with the side products **VIII** and **IX**, whose formation was most likely rationalized by partial hydrolysis of ethyl chloroacetate to **VIIa** and **VIIb** followed by alkylation (Scheme 2).

In addition, partial hydrolysis of **IV**–**VI** occurred presumably under the action of K_2CO_3 [6]; potassium salts of pyrazoleacetic acids remained in the reaction mixture. That suggestion was supported by the fact that the product yield in the alkylation reaction of pyrazole **I** was reduced from 45 to 30% when the reaction time was up from 5 h to 10 h (Scheme 3).

As expected, alkylation of 3,5-dimethylpyrazole **III** proceeded slower (within 10 h) compared to that of pyrazole **I** (within 5 h), likely due to steric hindrances [6, 7]; 3(5)-methylpyrazole **II** was an intermediate case.

Alkylation of 3(5)-methylpyrazole **II** afforded isomeric mixture of pyrazoles **Va** and **Vb** [8] in the 3 : 2 ratio (^{1}H NMR) with the overall yield of 60%. Attempts to separate them by fractionation at 150°C (1 mmHg) failed due to the partial hydrolysis yielding **XIa** and **XIb**.

Hydrolysis of the esters **IV**–**VI** was carried out with an aqueous NaOH solution at room temperature to obtain acids **X**–**XII** in yields of 78–80%.

Ethyl (1*H*-pyrazol-1-yl)acetate (IV). A mixture of 6.8 g (0.1 mol) of pyrazole **I**, 24.5 g (0.3 mol) of ethyl chloroacetate, 1 g Et_3BnNCl, 27.6 g (0.2 mol) K_2CO_3, and 150 mL of acetone was stirred during 4 h at 50–55°C, then cooled, and filtered. After the solvent removal, the residue was distilled in vacuum. The resulting condensate [a mixture of ethyl pyrazolylacetate **IV** with esters **VIII** and **IX**] was treated with 10% aqueous hydrochloric acid (100 mL). Compounds **VIII** and **IX** were extracted with diethyl ether. The aqueous layer was basified to pH 8, and the ester **IV** was extracted with chloroform (3 × 50 mL). The extract was dried over magnesium sulfate and evaporated. The residue was distilled in vacuum. Yield 6.9 g (45.0%), bp 95–98°C (1 mmHg), n_D^{20} 1.4690. IR spectrum, ν, cm^{-1}: 1510 (ring), 15710 (C=O). ^{1}H NMR

spectrum (DMSO-d_6–CCl_4, 1 : 4, 300 MHz), δ, ppm (*J*, Hz): 1.29 t (3H, $CH_2\underline{CH_3}$, *J* 7.1), 4.79 s (2H, $\underline{CH_2}CH_3$, *J* 7.1), 4.94 s (2H, NCH_2), 6.21 d.d (1H, H^4, *J* 1.8, 2.4), 7.37 d.d (1H, H^3, *J* 1.8, 0.7), 7.58 d.d (1H, H^5, *J* 2.4, 0.7). Found, %: C 54.29; H 6.85; N 18.37. $C_7H_{10}N_2O_2$. Calculated, %: C 54.54; H 6.49; N 18.18.

Ethyl [3(5)-methyl-1*H*-pyrazol-1-yl]acetate (Va, Vb) was obtained similarly from 3(5)-methylpyrazole **II** (8.2 g, 0.1 mol), reaction time 6 h. Yield 9.2 g (55%), bp 104–105°C (3 mmHg). IR spectrum, ν, cm^{-1}: 1520 (ring), 1700 (C=O). Found, %: C 57.45; H 7.35; N 16.38. $C_8H_{12}N_2O_2$. Calculated, %: C 57.14; H 7.14; N 16.66.

Ethyl (3,5-dimethyl-1*H*-pyrazol-1-yl)acetate (VI) was obtained similarly from 3,5-dimethylpyrazole **III** (9.6 g, 0.1 mol), reaction time 10 h. Yield 11.4 g (63%), bp 110–115°C (3 mmHg), n_D^{20} 1.4700. IR spectrum, ν, cm^{-1}: 1550 (ring), 1750 (C=O). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1 : 4, 300 MHz), δ, ppm (*J*, Hz): 1.30 t (3H, $\underline{CH_3}CH_2O$, *J* 7.1), 2.12 s (3H, 3-CH_3, *J* 7.1), 2.18 s (3H, 5-CH_3), 4.19 q (2H, $O\underline{CH_2}CH_3$, *J* 7.1), 4.72 s (2H, NCH_2), 5.73 br.s (1H, H^4). Found, %: C 59.68; H 7.32; N 15.71. $C_9H_{14}N_2O_2$. Calculated, %: C 59.34; H 7.69; N 15.38.

Ethoxycarbonymethyl chloroacetate (VIII). ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 1.3 t (3H, $CH_2\underline{CH_3}$, *J* 7.1), 4.14 s (2H, OCH_2), 4.23 q (2H, $\underline{CH_2}CH_3$, *J* 7.1), 4.65 s (2H, CH_2Cl).

Ethyl ethoxycarbonylmethoxycarbonylmethoxyacetate (IX). ^{1}H NMR spectrum (DMSO-d_6, 300 MHz), δ, ppm (*J*, Hz): 1.3 t (6H, CH_3, *J* 7.1), 4.18 s (6H, OCH_2), 4.20 q (4H, $\underline{CH_2}CH_3$, *J* 7.1).

1*H*-Pyrazole-1-ylacetic acid (X). 15.4 g (0.1 mol) of **IV** was added dropwise upon stirring to a solution of 6 g (0.15 mol) of sodium hydroxide in 50 mL of water, maintaining the temperature in the range of 20–30°C. The reaction mixture was stirred during 3 h. Then non-polar organic residues were extracted with chloroform (1×50 mL). After distilling off 2/3 of the aqueous solution, potassium pyrazol-1-ylacetate was treated with hydrochloric acid. White crystals were filtered off and dried. Yield 10 g (80%), mp 175°C [6].

[3(5)-Methyl-1*H*-pyrazol-1-yl]acetic acid (XIa, XIb) was obtained similarly from 16.8 g (0.1 mol) of ethyl 3(5)-methylpyrazol-1-ylacetate **Va, Vb**. Yield 11.5 g (82%), mp 160–168°C [6].

(3,5-Dimethyl-1*H*-pyrazol-1-yl) acetic acid (XII) was obtained similarly from 18.2 g (0.1 mol) of ethyl 3,5-dimethylpyrazol-1-yl-acetate **VI**. Yield 12.3 g (80%), mp 188–190°C [6].

IR spectra were obtained with the Nexus spectrometer (Thermo Nicolet Corporation, USA). ^{1}H NMR spectra (DMSO-d_6–CCl_4 or D_2O–CF_3COOH) were recorded with the Varian Mercury spectrometer (300 MHz). TLC analysis was performed using Silufol UV-254 plates, eluting with a benzene-acetone (4 : 1) mixture and developing with iodine vapor.

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