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C-Alkyl-4-nitropyrazoles from 5-Chloro-4-nitropyrazoles

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Abstract—5-Chloro-4-nitro-1*H*-pyrazoles reacted with arylsulfonyl-, cyano-, and acetylacetic acid esters in DMSO in the presence of potassium carbonate to give 5-[alkoxycarbonyl(acetyl, cyano, or arylsulfonyl)-methyl]-substituted 4-nitropyrazoles which may be promising from the viewpoint of preparation of other functionalized pyrazole derivatives and bicyclic ensembles.

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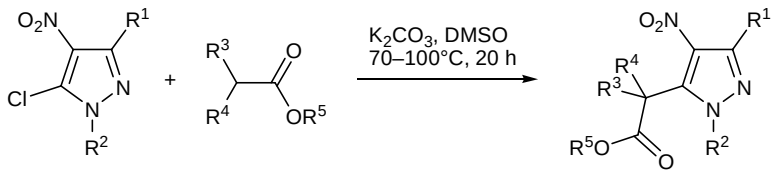
Pyrazole derivatives are widely used in medicine, industry, and agriculture. Methods for the preparation and functionalization of these compounds are extensively developed [1]. While continuing studies in the field of 4- and 5-chloro(bromo)pyrazole chemistry [2–5], we proposed a procedure for the preparation of 5-chloro-4-nitropyrazoles by nitration of 1,3-alkyl(or aryl)-substituted 5-chloropyrazoles in 65% oleum or polyphosphoric acid [6]; as a result, we obtained a series of chloronitropyrazoles which are interesting as substrates for further chemical transformations and functionalization.

The halogen atom in chloropyrazoles is weakly reactive toward N-, O-, S-, and C-centered nucleophiles, but introduction of a strongly electron-acceptor nitro group into position *4* of the pyrazole ring allowed us to effect reactions of 5-chloro-4-nitropyrazoles **Ia** and **Ib** with CH acids **IIa**–**IIe**. These reactions gave 60–65% of C-alkylated pyrazoles **IIIa**–**IIIe** (Scheme 1) containing various pharmacophoric groups. As CH acids we used acetyl-, arylsulfonyl-, and cyanoacetic acid esters, including those additionally substituted at the α-position.

We examined the effect of temperature, solvent nature, base, and reaction time on the yield of compounds **IIIa**–**IIIe**. The latter were not formed when the reactions were performed in alcohols in the presence of alkali or alkali metal alkoxide, regardless of the reaction temperature. No C-alkylation products were obtained in DMSO or DMF at room temperature in the presence of alkali metal hydroxides or sodium methoxide. When the reaction mixture was heated for 1–6 h at 90°C, the yield of pyrazoles **IIIa**–**IIIc** did not exceed 10%, and the initial reactants remained mostly unchanged. Compounds **IIIa**–**IIIe** were obtained in 60–65% yield by heating chloronitropyrazoles **Ia** and **Ib** with C-centered nucleophiles **IIa**–**IIe** in anhydrous DMSO in the presence of anhydrous potassium carbonate for 18–20 h at 70–100°C. Shortening of the reaction time resulted in incomplete conversion. For

Scheme 1.



Ia, **Ib** **IIa–IIe** **IIIa–IIIe**

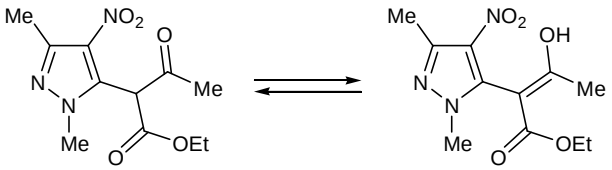
I, $R^1 = R^2 =$ Me (**a**); $R^1 =$ Me, $R^2 =$ Pr (**b**); **II**, $R^4 =$ H, $R^5 =$ Me, $R^3 = 4\text{-}ClC_6H_4SO_2$ (**a**), $PhSO_2$ (**b**); $R^3 = 4\text{-}MeC_6H_4SO_2$, $R^4 = PhCH_2$, $R^5 =$ Me (**c**); $R^4 =$ H, $R^5 =$ Et, $R^3 =$ CN (**d**), Ac (**e**); **III**, $R^1 = R^2 = R^5 =$ Me, $R^4 =$ H, $R^3 = 4\text{-}ClC_6H_4SO_2$ (**a**), $PhSO_2$ (**b**); $R^1 =$ Pr, $R^2 = R^5 =$ Me, $R^3 = PhSO_2$, $R^4 = PhCH_2$ (**c**), $R^3 =$ CN, $R^5 =$ Et (**d**), $R^3 =$ Ac, $R^5 =$ Et (**e**).

example, heating of a mixture of **Ib** and **IIc** under the above conditions for 9 h gave only 30% of **IIIc**.

Compounds **IIIa**–**IIIc** are colorless odorless crystalline powders. Compound **IIIe** was isolated as a very viscous oily substance. The structure of pyrazoles **IIIa**–**IIIe** was proved by the IR and ^{1}H and ^{13}C NMR spectra and elemental analyses. The IR spectra of **IIIa**–**IIIe** contained strong broadened absorption bands belonging to the nitro (1525–1520 and 1350–1325 cm^{-1}) and carbonyl groups (1755–1710 cm^{-1}). Stretching vibration bands due to C=C bonds in the pyrazole and benzene rings are partially overlapped by the NO_2 absorption. Ethyl cyano(1,3-dimethyl-4-nitro-1*H*-pyrazol-5-yl)acetate (**IIId**) displayed an absorption band at 2250 cm^{-1} which corresponds to the cyano group.

In the ^{1}H NMR spectra of nitropyrazoles **IIIa**–**IIIe** we observed signals from protons in the alkyl substituents on N^1 and C^3. The chemical shift of the methyl protons at the nitrogen changed only slightly on replacement of the chlorine atom in position *5* by functionally substituted methyl groups. The NCH_3 signal in the ^{1}H NMR spectrum of initial 5-chloro-1,3-dimethyl-4-nitro-1*H*-pyrazole (**Ia**) in $CDCl_3$ appeared at δ 3.84 ppm [6], while in the spectra of **IIIa** and **IIIc**–**IIIe** (DMSO-d_6) the corresponding signal was located in the δ range from 3.66 to 4.04 ppm. Only pyrazole **IIIb** in acetone-d_6 showed an appreciable downfield shift of the NCH_3 signal (δ 4.44 ppm). According to the ^{1}H and ^{13}C NMR data, pyrazole **IIIe** in $CDCl_3$ exists as a mixture of two tautomers, enol and ketone (Scheme 2).

Scheme 2.



IIIe

It should be noted that compounds **IIIa**–**IIIe** are stable to hydrolysis. They remained unchanged on heating in an aqueous solution of sodium carbonate or hydroxide under the conditions ensuring transformation of methyl arylsulfonylacetates into the corresponding acids [7].

Studies on reactions of chloronitropyrazoles with both C- and N-, O-, and S-centered nucleophiles and binucleophiles, as well as on the chemical properties of their C-alkylation products, are now in progress.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.13 for ^{1}H and 100.61 MHz for ^{13}C using HMDS as internal reference. The IR spectra were measured in KBr on a Specord 75IR instrument. Esters **IIa**–**IIe** were synthesized by the procedure described in [7]. Dimethyl sulfoxide was preliminarily dried over molecular sieves.

Ethyl cyano(1,3-dimethyl-4-nitro-1*H*-pyrazol-5-yl)acetate (IIId). Finely powdered calcined potassium carbonate, 0.59 g (6 mmol), was added to a solution of 0.55 g (3 mmol) of 5-chloro-1,3-dimethyl-4-nitro-1*H*-pyrazole (**Ia**) and 0.34 g (3 mmol) of ethyl cyanoacetate (**IId**) in 20 ml of anhydrous DMSO. The mixture was stirred for 9 h at 70°C, cooled, diluted with 30 ml of water, and acidified with hydrochloric acid, and the precipitate was filtered off, washed with water, and dried. Yield 0.5 g (65%), mp 81–82°C. IR spectrum, ν, cm^{-1}: 3000, 2970, 2900 (C–H); 2250 (CN); 1745 (C=O); 1570 (C=C, NO_2); 1360 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.16 s (1H, CH), 4.38 q (2H, CH_2, J = 7.2 Hz), 3.97 s (3H, CH_3), 2.56 s (3H, CH_3), 1.38 t (3H, CH_3, J = 7.2 Hz), ^{13}C NMR spectrum, δ_C, ppm: 161.28 (C=O), 146.38 (C^3), 130.28 (C^5), 116.00 (C^4), 111.50 (CN), 64.47 (CH_2), 38.12 (CH), 33.41 (CH_3), 30.66 (CH_3), 13.70 (CH_3). Found, %: C 47.60; H 4.82; N 22.23. $C_{10}H_{12}N_4O_4$. Calculated, %: C 47.62; H 4.80; N 22.21.

Methyl (4-chlorophenylsulfonyl)(1,3-dimethyl-4-nitro-1*H*-pyrazol-5-yl)acetate (IIIa) was synthesized in a similar way from 0.37 g (2 mmol) of 5-chloro-1,3-dimethyl-4-nitro-1*H*-pyrazole (**Ia**) and 0.5 g (2 mmol) of methyl (4-chlorophenylsulfonyl)acetate (**IIa**) in 20 ml of DMSO in the presence of 0.4 g (4 mmol) of K_2CO_3; the reaction mixture was heated for 20 h at 65°C. Yield 0.45 g (60%), mp 150–153°C. IR spectrum, ν, cm^{-1}: 3085 (=C–H); 2960, 2920 (CH_3); 1755 (C=O); 1570 (C=C, NO_2); 1350 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.86 d (2H, H_{arom}, J = 8.7 Hz), 7.53 d (2H, H_{arom}, J = 8.7 Hz), 6.80 (1H, CH), 4.05 s (3H, CH_3), 3.81 s (3H, CH_3), 2.51 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 162.28 (C=O), 146.81 (C^3), 141.84 (C^p), 136.81 (C^i), 131.66 (C^5), 130.00 (C^4), 130.41 and 129.53 (C^o, C^m), 64.88 (CH), 53.77 (OCH_3), 40.04 (CH_3), 14.12 (CH_3). Found, %: C 43.93; H 3.65; Cl 9.13; N 9.81; S 8.35. $C_{14}H_{14}ClN_3O_6S$. Calculated, %: C 43.36; H 3.64; Cl 9.14; N 10.84; S 8.27.

Methyl (1,3-dimethyl-4-nitro-1*H*-pyrazol-5-yl)-(phenylsulfonyl)acetate (IIIb) was synthesized in

a similar way from 0.18 g (1 mmol) of 5-chloro-1,3-dimethyl-4-nitro-1*H*-pyrazole (**Ia**) and 0.21 g (1 mmol) of methyl (4-methylphenylsulfonyl)acetate (**IIb**) in the presence of 0.2 g (1.5 mmol) of K_2CO_3; the mixture was heated for 20 h at 110°C. Yield 0.21 g (60%), mp 105°C. IR spectrum, ν, cm^{-1}: 3085 (=C–H); 2920, 2850 (CH_3); 1745 (C=O); 1535 (C=C, NO_2); 1350 (NO_2). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 7.96–7.73 m (5H, H_{arom}), 4.44 s (1H, CH), 3.67 (3H, CH_3), 3.17 (3H, OCH_3), 2.46 (3H, CH_3). Found, %: C 47.63; H 4.30; N 11.85; S 9.00. $C_{14}H_{15}N_3O_6S$. Calculated, %: C 47.59; H 4.28; N 11.89; S 9.07.

Methyl 2-(1-methyl-4-nitro-3-propyl-1*H*-pyrazol-5-yl)(phenylsulfonyl)-2-(4-methylphenylsulfonyl)-3-phenylpropionate (IIIc) was synthesized in a similar way from 0.29 g (1.4 mmol) of 5-chloro-1-methyl-4-nitro-3-propyl-1*H*-pyrazole (**Ib**) and 0.45 g (1.4 mmol) of methyl 2-(4-methylphenylsulfonyl)-3-phenylpropionate (**IIc**) in the presence of 0.4 g (3 mmol) of K_2CO_3; the mixture was heated for 10 h at 40°C. After appropriate treatment, a mixture of 0.4 g of compound **IIIc** with initial pyrazole **Ib** and ester **IIc** was isolated. According to the ^{1}H NMR data, the fraction of pyrazole **IIIc** was 30%. The IR and ^{1}H NMR spectral parameters of **IIIc** were determined from the spectra of the product mixture. IR spectrum, ν, cm^{-1}: 3070, 3030 (=C–H); 2970, 2945 (Alk); 1735 (C=O); 1575 (C=C, NO_2); 1370 (NO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.76 d (2H, H_{arom}, J = 7.7 Hz), 7.46 d (2H, H_{arom}, J = 7.7 Hz), 7.15 m (5H, C_6H_5), 4.04 (3H, CH_3), 3.59 (3H, OCH_3), 3.29 (2H, CH_2), 2.71 t (2H, CH_2, J = 7.3 Hz), 2.40 (3H, CH_3), 2.38 (3H, NCH_3), 1.58 m (2H, CH_2, J = 7.3 Hz), 0.89 t (3H, CH_3, J = 7.3 Hz).

Ethyl 2-(1,3-dimethyl-4-nitro-1*H*-pyrazol-5-yl)-3-oxobutanoate (IIIe) was synthesized in a similar way from 0.1 g (0.57 mmol) 5-chloro-1,3-dimethyl-4-nitro-1*H*-pyrazole (**Ia**) and 0.08 g (0.6 mmol) of ethyl acetoacetate in 10 ml of DMSO in the presence of 0.12 g (0.85 mmol) of K_2CO_3; the reaction mixture was heated for 27 h at 70°C. Yield 0.1 g (65%), viscous oil. IR spectrum, ν, cm^{-1}: 3400 br (OH); 2910, 2845 (C–H); 1710, 1705, 1645, 1600 (C=O, C=N, C=C); 1550, 1355 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 13.42 (1H, OH), 4.19 q (2H, CH_2, J = 7.1 Hz), 3.66 s (3H, CH_3), 2.55 (3H, CH_3), 1.89 (3H, CH_3, enol), 1.17 t (3H, CH_3, J = 7.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 178.47 (C=O), 170.39 (C=**C**OH), 146.45 (C^3), 136.87 (C^5), 119.69 (C^4), 91.19 (**C**=COH), 61.52 (CH_2), 36.83 (NCH_3), 29.75 (C=C**C**H_3), 19.92 (CH_3), 14.21 (CH_3). Found, %: C 52.20; H 6.01; N 16.57. $C_{11}H_{15}N_3O_4$. Calculated, %: C 52.17; H 5.97; N 16.59.

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