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Reactions of 3,5-Dimethyl-1-phenyl-1*H*-pyrazole with Electrophiles

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Abstract—Reactions of 3,5-dimethyl-1-phenyl-1*H*-pyrazole with various electrophilic reagents were studied. Electrophilic attack occurred regioselectively at the C^4 atom in the pyrazole ring.

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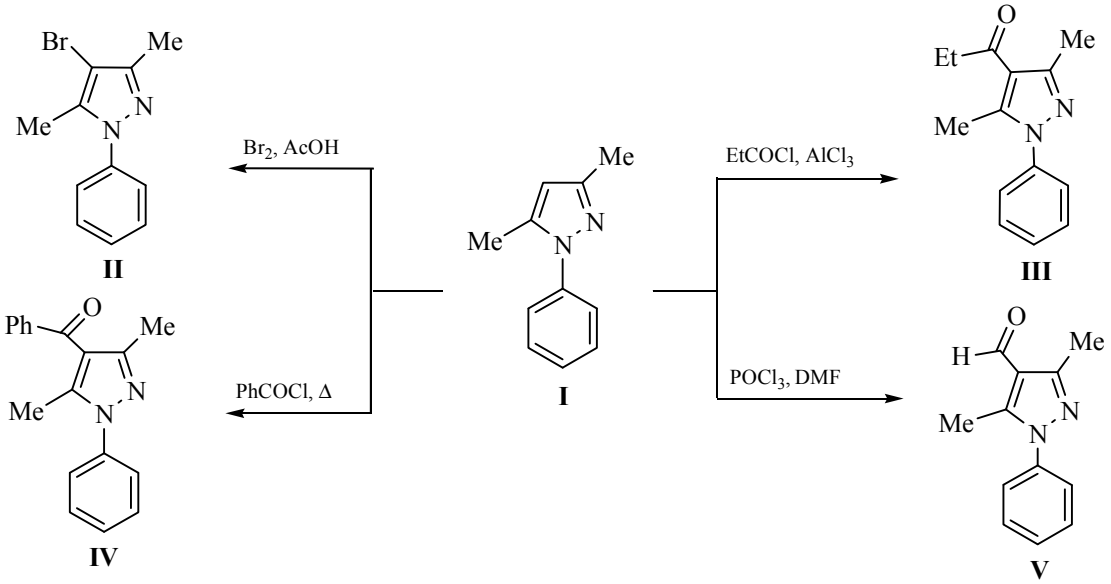
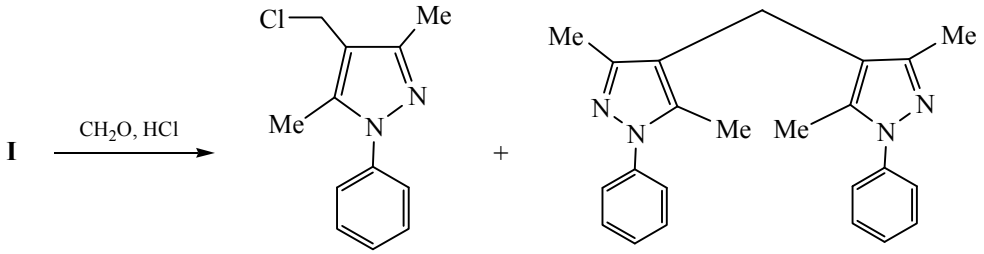
Growing interest in the pyrazole chemistry and methods of its functionalization is related to extension of application of its derivatives in the design of new materials. Pyrazole possesses many properties intrinsic to aromatic compounds [1]. Unlike pyrrole whose aromaticity is determined by the presence of an sp^2-hybridized nitrogen atom in the ring [2], the presence of two nitrogen atoms in pyrazole molecule reduces its reactivity toward electrophiles [3]. Electrophilic attack on pyrazole ring is generally directed at the 4-position which is characterized by the maximal π-electron density [4]. The reactivity of pyrazole at C^4 is intermediate between the reactivities of phenol and benzene [5]. However, no detailed studies were performed with a view to compare the ease of substitution in pyrazole ring and other aromatic systems.

Taking the above stated into account, it was interesting to compare the reactivities of the pyrazole and benzene rings in 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**I**); in addition, it should be kept in mind that pyrazolium cation is less reactive than benzenium [5]. Initially, we performed bromination of compound **I**, which is a common method for the preparation of bromo derivatives of pyrazole requiring no catalyst [1]. The bromination of pyrazole **I** in acetic acid gave 4-bromo-3,5-dimethyl-1-phenyl-1*H*-pyrazole (**II**) which was isolated from the reaction mixture in 70% yield.

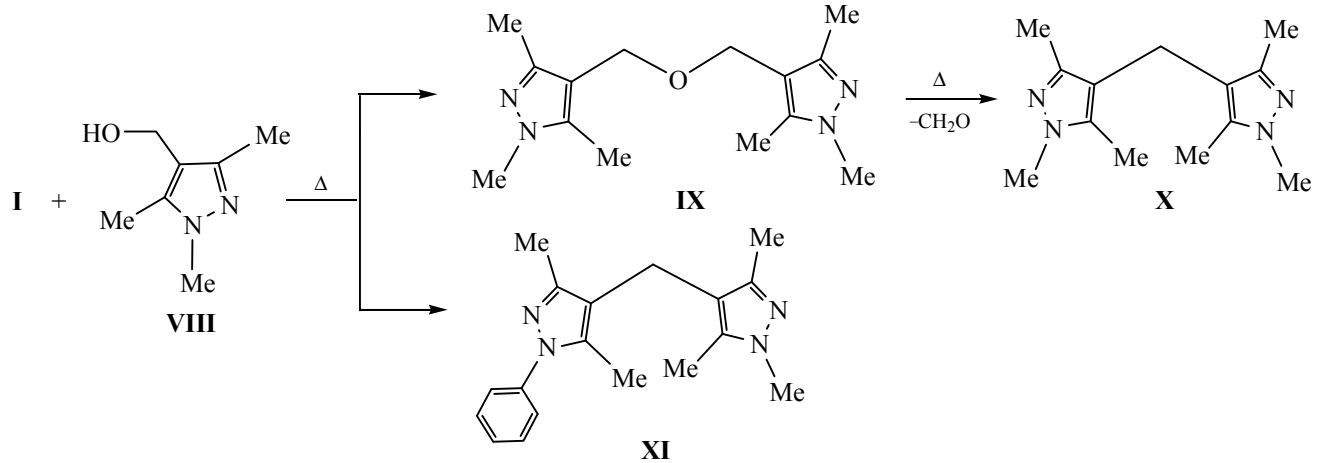


The product structure was assigned on the basis of its ^{1}H NMR spectrum which contained no 4-H signal, and the intensity of signals from protons in the phenyl group was very consistent with structure **II**. Friedel–Crafts acylation of 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**I**) with propionyl chloride [6] afforded 4-propionyl-substituted pyrazole **III**. 4-Benzoyl derivative **IV** was synthesized in 68% yield by heating compound **I** in benzoyl chloride in the absence of aluminum chloride. In no case substitution in the benzene ring was observed. We also examined formylation of 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**I**) with dimethylformamide in the presence of $POCl_3$ (Vilsmeier–Haack reaction [7]). It may be expected that, like aromatic amines, the benzene ring in molecule **I** will react more readily than the pyrazole ring [8]. However, the reaction involved exclusively the pyrazole ring with formation of aldehyde **V**.



VI **VII**

By chloromethylation of 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**I**) with paraformaldehyde and hydrogen chloride we obtained a mixture of 10% of 4-chloromethyl-3,5-dimethyl-1-phenyl-1*H*-pyrazole (**VI**) and 60% of bis(1-phenyl-3,5-dimethylpyrazol-4-yl)methane (**VII**). We previously showed [9] that heating of 1,3,5-trimethyl-1*H*-pyrazol-4-ylmethanol (**VIII**) in the presence of phenol leads to C-alkylation of the aromatic ring in the latter. The reaction of **VIII** with pyrazole **I** involved not only C-alkylation of the pyrazole ring in **I** but also intermolecular dehydration of alcohol **VIII** with formation of symmetric ether **IX**. In the course of distillation, the latter lost formaldehyde molecule, thus being converted into bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)methane (**X**). The formation of compound **X** was studied by us in detail previously [10–12].

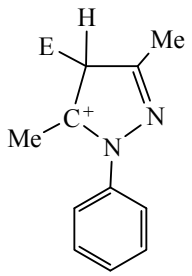


VIII **IX** **X** **XI**

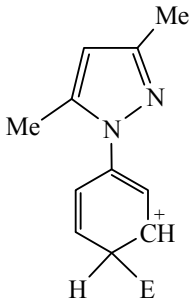
Our results in combination with the data of [13] allowed us to conclude that methyl groups in the pyrazole ring stabilize σ-complex **XII** rather than alternative structure **XIII**; therefore, substitution in the pyrazole ring is more favorable.

EXPERIMENTAL

The IR spectra were measured on a Specord 75-IR spectrometer from thin films. The ^{1}H NMR spectra were recorded on a Varian Mercury instrument at 300 MHz from solutions in DMSO-d_6.



XII



XIII

E stands for electrophile.

4-Bromo-3,5-dimethyl-1-phenyl-1*H*-pyrazole (II). A solution of 6 ml of bromine in 10 ml of acetic acid was added dropwise under stirring over a period of 1 h at room temperature to a mixture of 17.0 g of 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**I**), 20.0 g of sodium acetate, and 70 ml of water. The mixture was neutralized with a solution of sodium carbonate and extracted with chloroform (3 × 50 ml), the extracts were dried over magnesium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure. Yield 17.6 g (70%), bp 133°C (1 mm), n_D^{20} = 1.5940. IR spectrum: ν 1530 cm^{-1} (ring). ^1H NMR spectrum (DMSO-d_6), δ: 2.11 s (3H, 3-CH_3), 2.35 s (3H, 5-CH_3), 7.45 m (5H, C_6H_5). Found, %: C 52.26; H 4.71; Br 31.26; N 11.65. $C_{11}H_{11}BrN_2$. Calculated, %: C 52.58; H 4.38; Br 31.87; N 11.15.

1-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)propan-1-one (III). A mixture of 54.0 g of $AlCl_3$ and 200 ml of CCl_4 was cooled to –5 to –10°C, 17.0 g of pyrazole **I** was added dropwise under stirring, 18.0 g of propionyl chloride was then added, and the mixture was stirred for 2 h at 15–20°C and left to stand for 24 h. The mixture was treated with ice water and aqueous sodium carbonate, and the precipitate was filtered off. The filtrate was extracted with diethyl ether, the extract was dried over $MgSO_4$ and evaporated, and the residue was distilled under reduced pressure. Yield 7.3 g (32%), bp 160°C (1 mm), n_D^{20} = 1.5800. IR spectrum, ν, cm^{-1}: 1550 (ring), 1670 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.14 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.2), 2.46 s (3H, 3-CH_3), 2.51 s (3H, 5-CH_3), 2.76 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.2), 7.37–7.53 m (5H, C_6H_5). Found, %: C 73.21; H 6.39; N 12.68. $C_{14}H_{16}N_2O$. Calculated, %: C 73.68; H 7.01; N 12.28.

(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone (IV). A mixture of 17.2 g of pyrazole **I** and 9.8 g of benzoyl chloride was heated for 10 h under reflux. The mixture was neutralized with a solution of sodium carbonate and extracted with chloroform. The solvent was distilled off from the extract, and the residue was distilled under reduced pressure. Yield 19 g (68.8%), bp 210°C (1 mm), mp 99–100°C (from petroleum ether [14]). IR spectrum, ν, cm^{-1}: 1530, 1580 (ring); 1670 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.16 s (3H, 3-CH_3), 2.26 s (3H, 5-CH_3), 7.38–7.59 m (8H) and 7.70–7.74 m (2H) (C_6H_5). Found, %: C 78.64; H 5.21; N 9.69. $C_{18}H_{16}N_2O$. Calculated, %: C 78.26; H 5.79; N 10.14.

3,5-Dimethyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (V). A mixture of 17.0 g of pyrazole **I** and 50 ml of DMF was heated under stirring to 110°C, and 31.0 g of $POCl_3$ was added at the same temperature. After cooling, the mixture was neutralized with aqueous sodium hydroxide, maintaining the temperature below 20°C, and extracted with chloroform, the extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was distilled under reduced pressure. Yield 14.6 g (73.0%), bp 170°C (1 mm), mp 121–122°C. IR spectrum, ν, cm^{-1}: 1540 (ring), 1680 (C=O). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ, ppm: 2.45 s (3H, 3-CH_3), 2.57 s (5H, 3-CH_3), 7.40–7.54 m (5H, C_6H_5), 9.95 s (1H, CHO). Found, %: C 72.41; H 6.34; N 13.86. $C_{12}H_{12}N_2O$. Calculated, %: C 72.00; H 6.00; N 14.00.

4-Chloromethyl-3,5-dimethyl-1-phenyl-1*H*-pyrazole (VI). A mixture of 17.0 g of pyrazole **I**, 3 g of paraformaldehyde, and 50 ml of concentrated hydrochloric acid was heated for 1.5 h under reflux. The mixture was neutralized with aqueous sodium hydroxide and extracted with butanol, the extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was distilled under reduced pressure. Yield 2.2 g (10%) bp 140°C (1 mm), n_D^{20} = 1.5844. IR spectrum: ν 1540 cm^{-1} (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.21 s (3H, 3-CH_3), 2.36 s (3H, 5-CH_3), 4.61 s (2H, CH_2Cl), 7.42 m (5H, C_6H_5). Found, %: C 65.81; H 5.44; Cl 16.35; N 12.24. $C_{12}H_{13}ClN_2$. Calculated, %: C 65.30; H 5.89; Cl 16.09; N 12.69.

In addition, bis(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)methane (**VII**) was isolated from the reaction mixture. Yield 10.6 g (60%), bp 260°C (1 mm), mp 118°C (from aqueous acetone). IR spectrum: ν 1550 cm^{-1} (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.1 s (6H, 3-CH_3), 2.23 s (6H, 5-CH_3), 3.52 s (2H, CH_2), 7.27–7.46 m (10H, C_6H_5). Found, %: C 77.21; H 6.96; N 15.38. $C_{23}H_{24}N_4$. Calculated, %: C 77.52; H 6.74; N 15.73.

Bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)methane (X) and 4-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)-1,3,5-trimethyl-1*H*-pyrazole (XI). A mixture of 17.2 g of pyrazole **I** and 3 g of 1,3,5-trimethyl-1*H*-pyrazol-4-ylmethanol (**IX**) was heated for 4–5 h under reflux. Excess pyrazole **I** was distilled off, the residue was dissolved in 30 ml of petroleum ether, the solution was cooled, and the precipitate was filtered off. Yield of bis(1,3,5-trimethyl-1*H*-pyrazol-4-yl)methane (**X**) 0.9 g (38%), mp 67–68°C. IR spectrum: ν 1540 cm^{-1} (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.96 s (6H, 3-CH_3), 2.05 s (6H, 5-CH_3), 3.35 s (2H, CH_2), 3.65 s (6H, NCH_3). Found, %: C 67.58; H 8.36; N 24.56. $C_{13}H_{20}N_4O$. Calculated, %: C 67.24; H 8.62; N 24.14.

The filtrate was evaporated, and the residue was distilled under reduced pressure. Yield of 4-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)-1,3,5-trimethyl-1*H*-pyrazole (**XI**) 2.5 g (42.5%), bp 230°C (1 mm), n_D^{20} = 1.5740. IR spectrum: ν 1560 cm^{-1} (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.20 s (6H, 3-CH_3), 2.32 s (6H, 5-CH_3), 3.41 s (2H, CH_2), 3.65 s (3H, NCH_3), 7.22–7.40 m (5H, C_6H_5). Found, %: C 73.18; H 7.21; N 19.44. $C_{18}H_{22}N_4$. Calculated, %: C 73.46; H 7.48; N 19.04.

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