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SHORT COMMUNICATIONS

Synthesis of New Pyrazole Derivatives from Benzylidenemalononitrile

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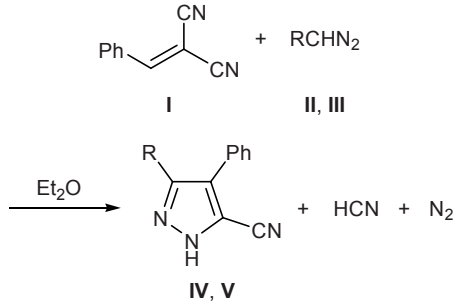
1,3-Dipolar cycloaddition of diazoalkanes to acetylenes [1] or styrenes [2] activated by electron-withdrawing substituents underlies a traditional procedure for the synthesis of pyrazoles. For example, 1-bromo-1-nitro-2-phenylethene reacts with diazomethane in diethyl ether to give 5-bromo-5-nitro-4,5-dihydro-1*H*-pyrazole, and treatment of the latter with hydrochloric acid or a solution of sodium hydrogen carbonate leads to the formation of 5-bromo- or 5-nitro-4-phenyl-1*H*-pyrazole, respectively [3].

With a view to study competing effects of functional groups in an analog of 1-nitro-2-phenylethene, benzylidenemalononitrile (**I**), we examined its reactions with diazomethane (**II**) and diazoethane (**III**). The cycloaddition of diazoalkanes **II** and **III** to dipolarophile **I** occurred under mild conditions (in diethyl ether at –5 to 5°C), and the products were the corresponding 4-phenyl-1*H*-pyrazole-5-carbonitriles **IV** and **V** (Scheme 1).

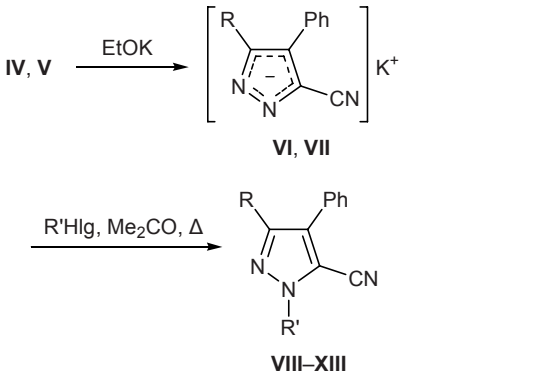
Scheme 1.



II, **IV**, R = H; **III**, **V**, R = Me.

In the IR spectra of compounds **IV** and **V** we observed an absorption band at 3550 cm^{-1} due to stretching vibrations of the NH group, and the NH signal appeared in their ^1H NMR spectra as a broadened singlet at δ 10.8–10.9 ppm. The presence of a labile hydrogen atom on the nitrogen in molecules **IV** and **V** opens prospects in further functionalization of these compounds, e.g., via alkylation of the corresponding potassium salts **VI** and **VII**. The latter were prepared *in situ* by treatment of 4-phenyl-1*H*-pyrazole-5-carbonitriles **IV** and **V** with potassium ethoxide. The alkylation of potassium salts **VI** and **VII** with chloromethyloxirane, phenacyl bromide, and 4-toluenesulfonyl chloride resulted in the formation of previously unknown alkylation products **VIII**–**XI** and N-sulfonyl derivatives **XII** and **XIII** (Scheme 2) whose structure was confirmed by spectral data and elemental analyses. The IR spectra of **X** and **XI** contained an absorption band at 1705 cm^{-1} due to stretching vibrations of the carbonyl group, while compounds **XII** and **XIII** displayed absorption bands at 1150 and 1300 cm^{-1} belonging, respectively, to antisymmetric and symmetric

Scheme 2.



VI, **VIII**, **X**, **XII**, R = H; **VII**, **IX**, **XI**, **XIII**, R = Me; **VIII**, **IX**, R′ = oxiran-2-ylmethyl; **X**, **XI**, R′ = $PhCOCH_2$; **XII**, **XIII**, R′ = 4-$MeC_6H_4SO_2$; Hlg = Cl, Br.

stretching vibrations of the SO_2 group. The ^1H NMR spectra of **VIII**–**XIII** were consistent with the assumed structures, and they resembled those reported for structurally related compounds [4, 5]. Protons in the oxirane ring of compounds **VIII** and **IX** resonated in the ^1H NMR spectra at δ 2.65–3.07 ppm. The ^1H NMR spectra of phenacyl and sulfonyl derivatives **X**–**XIII** contained signals typical of methylene protons in the NCH_2CO fragment (δ 6.44–6.45 ppm; compounds **X**, **XI**) or protons in the *p*-tolyl substituent (**XII**, **XIII**).

Thus the described reactions open a synthetic route to functionally substituted pyrazoles having various pharmacophoric groups on the nitrogen atom, which are difficult to obtain by other methods.

Diazomethane [6], diazomethane [7], and phenacyl bromide [8] were prepared according to known procedures.

Reaction of benzylidenemalononitrile (I) with diazoalkanes II and III (*general procedure***).** A solution of diazoalkane **II** or **III** was added under stirring to a solution of 8 mmol of benzylidenemalononitrile (**I**) in 30 ml of anhydrous diethyl ether at –5 to 5°C until nitrogen no longer evolved. The mixture was then kept for 24 h at 25°C and evaporated under reduced pressure, and the oily residue was subjected to chromatography in a 250 × 10-mm column charged with activated silica gel (Silicagel 100–400 μm) using carbon tetrachloride as eluent.

4-Phenyl-1*H*-pyrazole-5-carbonitrile (IV). Yield 44%, mp 154–156°C. IR spectrum, ν, cm^{-1}: 3550 (NH), 2230 (CN). ^1H NMR spectrum, δ, ppm: 7.35 m (H_{arom}), 7.58 s (CH), 10.9 br.s (NH). Found, %: C 70.74; H 4.03; N 24.58. $C_{10}H_7N_3$. Calculated, %: C 71.01; H 4.14; N 24.85.

3-Methyl-4-phenyl-1*H*-pyrazole-5-carbonitrile (V). Yield 46%, mp 162–164°C. IR spectrum, ν, cm^{-1}: 3550 (NH), 2230 (CN). ^1H NMR spectrum, δ, ppm: 2.35 s (CH_3), 7.34 m (H_{arom}), 10.8 br.s (NH). Found, %: C 7.95; H 4.78; N 22.74. $C_{11}H_9N_3$. Calculated, %: C 72.13; H 4.92; N 22.95.

1-Substituted 4-phenyl-1*H*-pyrazole-5-carbonitriles VIII–XIII (*general procedure***).** A solution of 6 mmol of compound **IV** or **V** in 20 ml of ethanol was cooled to 0±5°C, 6 mmol of potassium ethoxide was added, the mixture was kept for 0.5 h at 5°C, and the precipitate was filtered off, washed with cold ethanol, and dried. Pyrazole potassium salt **VI** or **VII** thus obtained was dispersed in 100 ml of acetone, 6 mmol of chloromethyloxirane or phenacyl bromide or a solution of 6 mmol of *p*-toluenesulfonyl chloride in ethanol was added, and the mixture was heated for 2 h under reflux. The mixture was then kept for 3 days at 25°C and evaporated under reduced pressure, the residue was treated with diethyl ether (3 × 10 ml), the extract was evaporated, and the residue was subjected to chromatography in a 500 × 10-mm column charged with activated silica gel (Silicagel, 100–400 μm) using benzene (compounds **VIII**, **IX**) or chloroform (**X**–**XIII**) as eluent.

1-(Oxiran-2-ylmethyl)-4-phenyl-1*H*-pyrazole-5-carbonitrile (VIII). Yield 62 %, mp 105–108°C. ^1H NMR spectrum, δ, ppm: 2.65 d (CH_2), 3.06 m (CH), 4.23 d (CH_2), 7.38 m (H_{arom}), 7.59 s (CH). Found, %: C 69.10; H 4.68; N 18.51. $C_{13}H_{11}N_3O$. Calculated, %: C 69.33; H 4.89; N 18.67.

3-Methyl-1-(oxiran-2-ylmethyl)-4-phenyl-1*H*-pyrazole-5-carbonitrile (IX). Yield 64%, mp 118–120°C. ^1H NMR spectrum, δ, ppm: 2.35 s (CH_3), 2.64 d (CH_2), 3.05 m (CH), 4.21 d (CH_2), 7.35 m (H_{arom}). Found, %: C 70.05; H 5.27; N 17.38. $C_{14}H_{13}N_3O$. Calculated, %: C 70.29; H 5.44; N 17.57.

1-(2-Oxo-2-phenylethyl)-4-phenyl-1*H*-pyrazole-5-carbonitrile (X). Yield 72%, mp 141–143°C. IR spectrum, ν, cm^{-1}: 2230 (CN). 1705 (C=O). ^1H NMR spectrum, δ, ppm: 6.44 s (CH_2), 7.33–7.45 m (H_{arom}), 7.58 s (CH). Found, %: C 75.05; H 4.34; N 14.42. $C_{18}H_{13}N_3O$. Calculated, %: C 75.26; H 4.53; N 14.63.

3-Methyl-1-(2-oxo-2-phenylethyl)-4-phenyl-1*H*-pyrazole-5-carbonitrile (XI). Yield 74%, mp 152–153°C. IR spectrum, ν, cm^{-1}: 2230 (CN), 1705 (C=O). ^1H NMR spectrum, δ, ppm: 2.34 s (CH_3), 6.45 s (CH_2), 7.36–7.44 m (H_{arom}). Found, %: C 75.56; H 4.77; N 13.74. $C_{19}H_{15}N_3O$. Calculated, %: C 75.75; H 4.98; N 13.95.

1-(4-Methylphenylsulfonyl)-4-phenyl-1*H*-pyrazole-5-carbonitrile (XII). Yield 71%, mp 172–174°C. IR spectrum, ν, cm^{-1}: 2230 (CN); 1300, 1150 (SO_2). ^1H NMR spectrum, δ, ppm: 2.32 s (CH_3), 7.11–7.52 m (H_{arom}), 7.57 s (CH). Found, %: C 62.94; H 3.86; N 12.83. $C_{17}H_{13}N_3O_2S$. Calculated, %: C 63.16; H 4.02; N 13.00.

3-Methyl-1-(4-methylphenylsulfonyl)-4-phenyl-1*H*-pyrazole-5-carbonitrile (XIII). Yield 75%, mp 180–183°C. IR spectrum, ν, cm^{-1}: 2230 (CN); 1300, 1150 (SO_2). ^1H NMR spectrum, δ, ppm: 2.32 s (CH_3), 2.35 s (CH_3), 7.12–7.54 m (H_{arom}). Found, %: C 63.86; H 4.27; N 12.31. $C_{18}H_{15}N_3O_2S$. Calculated, %: C 64.09; H 4.45; N 12.46.

The IR spectra were recorded on an IKS-29 spectrometer from solutions in chloroform with a concentration of 40 mg/ml (cell path length l = 0.1 mm). The ^{1}H NMR spectra were measured from solutions in acetone-d_6 on a Tesla BS-487C spectrometer (80 MHz) relative to hexamethyldisiloxane as internal reference. The progress of reactions and the purity of products were monitored by ascending TLC on Silufol UV-254 plates using acetone–hexane (2 : 3) as eluent; spots were visualized by treatment with iodine vapor.

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