A ONE STEP SYNTHESIS OF 4-CYANOPYRAZOLES

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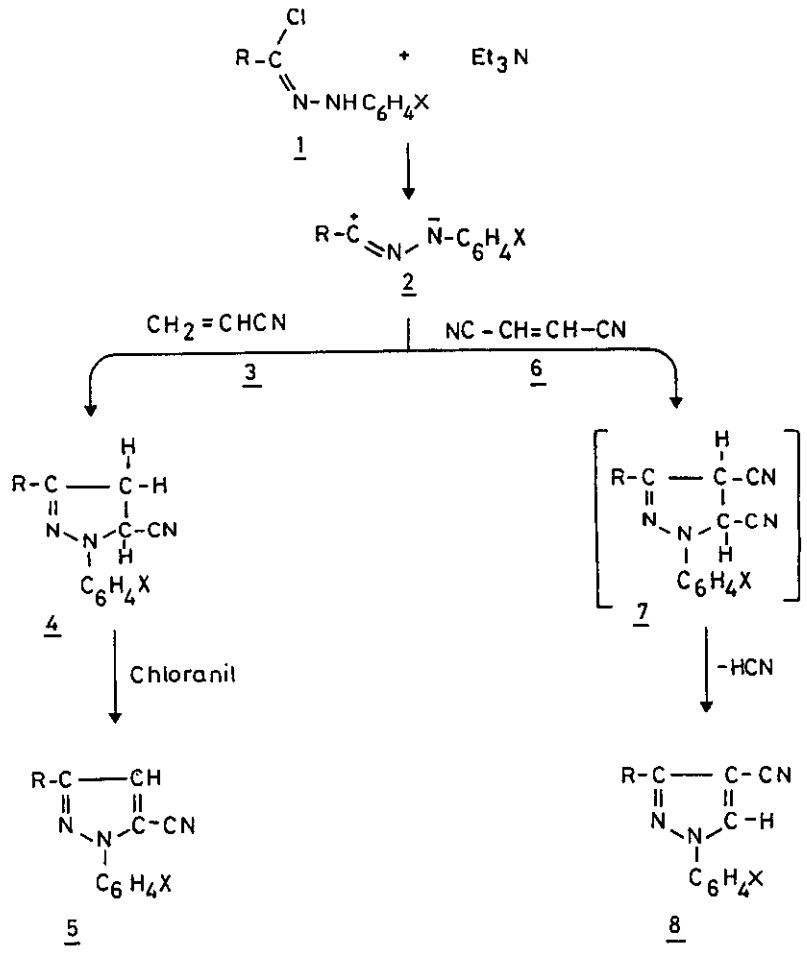
Abstract - Reaction of nitrilimines 2 with fumaronitrile 6 yielded 4-cyanopyrazoles 8 in good yields. The structures of 8 were substantiated by comparison with their regioisomers 5-cyanopyrazoles 5, prepared by addition of 2 to acrylonitrile followed by oxidation of the 2-pyrazoline cycloadducts 4.

1,3-Dipolar cycloaddition of nitrilimines 2 to acrylonitrile 3 is known to be regioselective yielding 5-cyano-2-pyrazolines 4 exclusively[1-8] (Scheme 1). Oxidation of 4 affords the corresponding 5-cyanopyrazole derivatives 5. We now wish to report one step synthesis for their regioisomers, 4-cyanopyrazoles 8 via the reaction of 2 with fumaronitrile 6 (Scheme 1). The principle upon which this synthesis is based is that hydrogen cyanide was reported to be eliminated readily from nitrogen heterocycles having a cyano group in the α-position with respect to the hetero-nitrogen atom and an acidic β-hydrogen atom.[9-11]

Reaction of 2a-h, generated in situ by treatment of the corresponding hydrazidoyl halides 1a-h with triethylamine in chloroform, with fumaronitrile 6 gave in each case one product as evidenced by thin layer chromatographic analysis. The products obtained were identified as 1,3-disubstituted 4-cyanopyrazoles 8a-h (Scheme 1). Their structures were assigned on the basis of elemental analyses and spectral data. The ^{1}H nmr spectra of 8a-h showed in each case a characteristic singlet signal near δ8.35 ppm assignable to the 5-CH of pyrazole ring residue.[12] In their infrared spectra the products 8a-h exhibit a nitrile absorption band near 2230 cm^{-1}. It seems probable that the intermediate cycloadducts 7a-h have undergone elimination of hydrogen cyanide as soon as they are formed to give 8a-h (Scheme 1) since the crude reaction mixture revealed the absence of the doublet signals expected for the 4-CH and 5-CH of the 2-pyrazoline ring residue of intermediates 7a-h. The elimination of hydrogen cyanide from 7 is analogous to the elimination of benzenesulfinic acid, hydrazoic acid and benzaldehyde from 5-benzenesulfonyl-, 5-azido- and 5-benzoyl substituted 2-pyrazolines, respectively.[13-15]



5	R / X
a	CH_3CO / H
b	C_2H_5OCO / H
c	C_2H_5OCO / 4-CH_3
d	C_6H_5 / H

8	R / X
e	C_6H_5 / 4-NO_2
f	C_6H_5NHCO / H
g	C_6H_5NHCO / 4-CH_3
h	$C_6H_5CH=CH$ / H

Scheme 1

The identity of the products 8a-h was further substantiated by comparison with authentic samples of their regioisomers namely 5-cyanopyrazoles 5a-h. The latters were prepared by the reaction of 2a-h with acrylonitrile 3 and oxidation of the resulting 5-cyano-2-pyrazoline cycloadducts 4a-h. The structures of the unreported 5-cyano substituted 2-pyrazolines 4 and pyrazoles 5 were confirmed by their elemental analyses and spectrtal data. For example, the nitrile absorption was either absent or very weak in the ir spectra of 4a-h. This is similar to the case of aliphatic nitriles activated by a nitrogen atom or an oxygen atom in the α-position.[16] In their ^{1}H nmr spectra the cycloadducts 4a-h exhibit an A_2X pattern: a triplet near δ 5.00 ppm (5-CH) and a doublet near δ 3.40 ppm (4-CH_2). Compounds 5a-h exhibit a nitrile absorption near 2220 cm^{-1} and a characteristic singlet near δ 7.30 ppm (4-CH) in their infrared and ^{1}H nmr spectra, respectively.

EXPERIMENTAL

All melting points were determined on Bockmonoscop hot stage apparatus and are uncorrected. Infrared spectra (KBr) were recorded on Perkin Elmer 257 Spectrophotometer. ^{1}H Nmr spectra in deuterated chloroform and DMSO were recorded on a Varian T60-A Spectrometer using tetramethylsilane as an internal reference. Elemental analyses were carried out at the Microanalytical Laboratory at the University of Cairo, Giza, Egypt.

1,3-Disubstituted 4-cyanopyrazoles 8a-h. General Method - To a solution of the appropriate hydrazidoyl chloride 1 (5 mmol) and fumaronitrile (0.40 g, 5 mmol) in chloroform (40 ml) was added triethylamine (0.7 ml, 5 mmol) while stirring at room temperature. The mixture was refluxed for 4 h, then cooled. The reaction mixture was washed with water and the organic layer was collected and dried over anhydrous sodium sulfate, then filtered. The solvent was removed under reduced pressure and the residue was triturated with methanol where it solidified. The crude product was collected and crystallised from ethanol to yield the corresponding 4-cyanopyrazole derivatives 8.

Compound 8a had mp 162°C, yield 75 %, δ ($CDCl_3$) 2.6 (s, 3H), 7.4-7.8 (m, 5H), 8.4 (s, 1H) ppm; $\tilde{\nu}$(KBr) 2220 (C≡N), 1700 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89 Found: C 68.11; H, 4.11; N, 19.72.

Compound 8b had mp 145°C, yield 70 %, δ($CDCl_3$) 1.45 (t, J = 7Hz, 3H), 4.5 (q, J = 7Hz, 2H), 7.3-7.7 (m, 5H), 8.4 (s, 1H); ν (KBr) 2220 (C≡N), 1720 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.56; N, 17.42. Found: C, 64.55; H, 4.41; N, 17.13.

Compound 8c had mp 134°C, yield 72 %, δ($CDCl_3$), 1.4 (t, J = 7Hz, 3H), 2.35 (s, 3H), 4.4 (q, J = 7Hz, 2H), 7.1-7.6 (m, 4H), 8.4 (s, 1H), $\tilde{\nu}$ (KBr) 2230 (C≡N); 1720 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.61; H, 5.02; N, 16.33.

Compound 8d had mp 136°C, yield 85 %, δ ($CDCl_3$) 7.0-7.9 (m, 10H), 8.6 (s, 1H) ppm; $\tilde{\nu}$ (KBr) 2210 (C≡N), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.21; H, 4.41; N, 17.10.

Compound 8e had mp 225°C, yield 76 %, δ ($CDCl_3$) 7.0-7.9 (m, 5H), 7.2 (d, J = 9Hz, 2H), 8.2 (d, J = 9Hz, 2H), 8.6 (s, 1H) ppm; $\bar{\nu}$ (KBr) 2220 (C≡N), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47; N, 19.51. Found: C, 66.11; H, 3.34; N, 19.71.

Compound 8f had mp 191-193°C, yield 70 %, δ ($CDCl_3$) 7.2-8.0 (m, 10H), 8.3 (s, 1H), 8.5 (s, 1H) ppm; $\bar{\nu}$(KBr) 3300 (NH), 2230 (C≡N), 1680 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{17}H_{12}N_4O$: C, 71.37; H, 4.66; N, 18.69. Found: C, 71.42; H, 4.82; N, 18.62.

Compound 8g had mp 203-204°C, yield 77 %, δ ($CDCl_3$) 2.4 (s, 3H), 7.0-7.7 (m, 9H), 8.25 (s, 1H), 8.5 (s, 1H) ppm; $\bar{\nu}$ (KBr) 3300 (NH), 2230 (C≡N), 1680 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.37; H, 4.66; N, 18.69. Found: C, 71.42; H, 4.23; N, 18.46.

Compound 8h had mp 144°C, yield 80 %, δ ($CDCl_3$) 6.8-7.8 (m, 12H), 8.5 (s, 1H) ppm; $\bar{\nu}$ (KBr) 2220 (C≡N), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.82; N, 15.48. Found: C, 80.0; H, 4.60; N, 15.52.

1,3-Disubstituted 5-cyano-2-pyrazolines 4a-h. General Method: To a stirred solution of hydrazidoyl halide 1 (5 mmol) and acrylonitrile (15 ml) in chloroform (40 ml) was added triethylamine (0.7 ml, 5 mmol) at room temperature. The mixture was refluxed for 10 h, then cooled. Work up of the reaction mixture as above afforded the corresponding 2-pyrazoline derivatives 4.

Compound 4a had mp 124-125°C, yield 68 %, (lit. mp 110-112°C)[7]; δ ($CDCl_3$) 2.5 (s, 3H), 3.4 (d, J = 8Hz, 2H), 5.0 (t, J = 8Hz, 1H), 7.0-7.5 (m, 5H) ppm; $\bar{\nu}$ (KBr) 1660 (C=O), 1590 (C=N) cm^{-1}.

Compound 4b had mp 96°C, yield 65 %, (lit. mp 86°C)[6], δ ($CDCl_3$) 1.4 (t, J = 7Hz, 3H), 3.5 (d, J = 8Hz, 2H), 4.4 (q, J = 7Hz, 2H), 5.0 (t, J = 8Hz, 1H), 6.9-7.4 (m, 5H), ppm; $\bar{\nu}$ (KBr) 1720 (C=O), 1600 (C=N) cm^{-1}.

Compound 4c had mp 112-114°C, yield 70 %, (lit. mp 103°C)[6]; δ ($CDCl_3$) 1.4 (t, J = 7Hz, 3H), 2.3 (s, 3H), 3.6 (d, J = 8Hz, 2H), 4.3 (q, J = 7Hz, 2H), 5.1 (t, J = 8Hz, 1H), 6.8-7.5 (m, 4H) ppm; $\bar{\nu}$(KBr) 1725 (C=O), 1600 (C=N) cm^{-1}.

Compound 4d had mp 136°C, yield 80 %, (lit. mp 138-140°C)[1], δ ($CDCl_3$) 3.4 (d, J = 7Hz, 2H), 4.9 (t, J = 7Hz, 1H), 6.9-7.8 (m, 10H) ppm; $\bar{\nu}$(KBr) 1600 (C=N) cm^{-1}.

Compound 4e had mp 216-217°C, yield 65 %, δ (DMSO) 3.4 (d, J = 7Hz, 2H), 4.9 (t, J = 7Hz, 1H), 7.2 (d, J = 9Hz, 2H), 7.0-7.9 (m, 5H), 8.1 (d, J = 9Hz, 2H) ppm; $\bar{\nu}$ (KBr) 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47; N, 19.51. Found: C, 66.71; H, 3.50; N, 19.72.

Compound 4f had mp 149-150°C, yield 70 %, (lit. mp 146-147°C)[7]; δ ($CDCl_3$) 3.5 (d, J = 8Hz, 2H), 4.9 (t, J = 8Hz, 1H), 6.9-7.6 (m, 10H), 8.35 (s, 1H), ppm; $\bar{\nu}$ (KBr) 3300 (NH), 1670 (C=O), 1600 (C=N) cm^{-1}.

Compound 4g had mp 137-139°C, yield 72 %, δ ($CDCl_3$) 2.3 (s, 3H), 3.5 (d, J = 8Hz, 2H), 4.9 (t, J = 8Hz, 1H), 6.9-7.6 (m, 9H), 8.35 (s, 1H) ppm; $\bar{\nu}$ (KBr) 3300 (NH), 1670 (C=O), 1600 (C=N) cm^{-1}; Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.37; H, 4.66; N, 18.69. Found: C, 71.41; H, 4.25; N, 18.44.

Compound 4h had mp 139-140°C, yield 75 %, δ ($CDCl_3$) 3.6 (d, J = 8Hz, 2H), 5.0 (t, J = 8Hz, 1H), 7.0-8.0 (m, 12H) ppm; $\bar{\nu}$ (KBr) 1590 (C=N) cm^{-1}. Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.10; H. 5.53; N, N, 15.37. Found: C, 80.00; H, 5.50; N, 15.52.

1,3-Disubstituted-5-cyanopyrazoles 5a-h. General Method. To a solution of the appropriate 2-pyrazoline derivative 4 (3 mmol) in dry xylene (30 ml) was added chloranil (4 mmol) and the reaction mixture was refluxed for 20 h, and cooled. The reaction mixture was washed with sodium hydroxide solution (1 M, 100 ml) three times and dried over anhydrous sodium sulfate. The solvent was distilled off and the residue was triturated with petroleum ether (40/60°). The curde solid was collected and crystallised from ethanol or acetic acid to yield the corresponding pyrazole derivatives 4.

Compound 5a had mp 95°C, yield 72 %, δ ($CDCl_3$) 2.45 (s, 3H), 7.0-7.5 (m, 6H) ppm; $\bar{\nu}$ (KBr) 2210 (C≡N), 1660 (C=O), 1590 (C=N) cm^{-1}. Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.89; H, 4.30; N, 19.71.

Compound 5b had mp 95°C, yield 70 %, δ ($CDCl_3$) 1.4 (t, J = 7Hz, 3H), 4.4 (q, J = 7Hz, 2H), 6.9-7.7 (m, 6H) ppm; $\bar{\nu}$ (KBr) 2210 (C≡N), 1720 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, C, 64.72; H, 4.56; N, 17.42. Found: C, 65.50; H, 4.81; N, 17.31.

Compound 5c had mp 104°C, yield 70 %, δ ($CDCl_3$), 1.4 (t, J = 7Hz, 3H), 2.35 (s, 3H), 4.3 (q, J = 7Hz, 2H), 6.8-7.5 (m, 5H) ppm; $\bar{\nu}$ (KBr) 2210 (C≡N), 1720 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46, Found: C, 65.41; H. 5.01; N, 16.30.

Compound 5d had mp 136°C, yield 80 %, (lit. mp 133-5°C)[1], δ ($CDCl_3$) 7.0-8.0 (m, Ar-H); $\bar{\nu}$ (KBr) 2210 (C≡N), 1590, (C=N) cm^{-1}.

Compound 5e had mp 162-164°C, yield 75 %, δ ($CDCl_3$), 7.2 (d, J = 9Hz, 2H), 7.0-7.9 (m, 6H), 8.2 (d, J = 9Hz, 2H) ppm; $\bar{\nu}$ (KBr) 2215 (C≡N) 1590 (C=N) cm^{-1}; Anal. Calcd for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47; N, 19.51. Found: C, 66.11; H, 3.22; N, 19.41.

Compound 5f had mp 123°C, yield 80 %, δ ($CDCl_3$); 6.9-7.8 (m, 11H), 8.4 (s, 1H) ppm; $\bar{\nu}$ (KBr) 3350 (NH), 2210 (C≡N) 1660 (C=O), 1600 (C=N) cm^{-1}. Anal. Calcd for $C_{17}H_{12}N_4O$: C, 71.37; H, 4.66; N, 18.69. Found: C, 71.20; H, 4.51; N, 18.77.

Compound 5g had mp 115°C, yield 72 %, δ ($CDCl_3$); 2.3 (s, 3H), 6.9-7.8 (m, 10H), 8.45 (s, 1H) ppm; $\bar{\nu}$ (KBr) 3350 (NH), 2115 (C≡N), 1660 (C=O), 1590 (C=N) cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.37; H, 4.66; N, 18.69. Found: C, 71.61; H, 4.80; N, 18.62.

Compound 5h had mp 102°C, yield 75 %, δ ($CDCl_3$) 7.0-7.90 (m, Ar-H) ppm; $\bar{\nu}$ (KBr) 2110 (C≡N), 1590 (C=N) cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.82; N, 15.48. Found: C, 79.80; H, 4.60; N, 15.61.

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