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LETTERS TO THE EDITOR

Catalytic Addition of Pyrazoles to But-3-enenitrile

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Recently, we have shown that pyrazoles react with but-3-enenitrile under rigid conditions (200–220°C, pressure reactor) [1]. It was assumed that at 200–220°C the presence of basic pyrazoles (pK_a = 20.4–22.0 [2]) causes isomerization of but-3-enenitrile into but-2-enenitrile, which further facilitates the nucleophilic addition at the β-carbon atom of the conjugated double bond.

Taking into account the data obtained, we assumed that the basicity of pyrazole is not sufficient to ensure non-conjugated double bond isomerization, so the reaction should be carried out under rigid conditions.

To test our hypotheses, we have carried out a similar reaction involving cyclic amines of higher basicity: morpholine (pK_a = 8.36), piperidine (pK_a = 11.22) and pyrrolidine (pK_a = 11.27) [3].

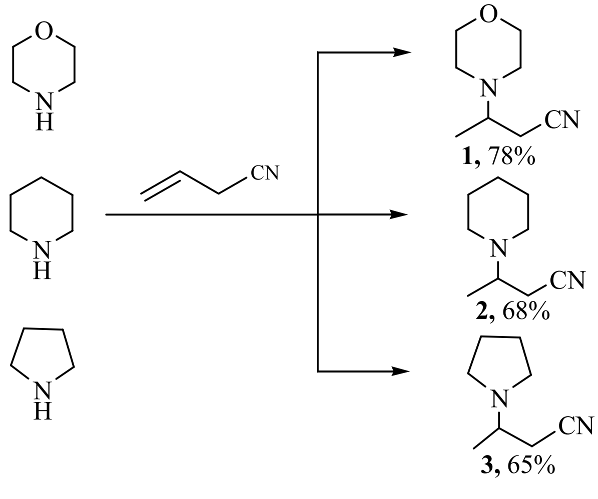
We found that the selected amines reacted with but-3-enenitriles at moderate heating. This fact confirmed our assumption that the formation of the double bond adducts includes a two stage process: first isomerization and further aza-addition of a nucleophile to the conjugated system (Scheme 1).

We concluded that the addition of pyrazoles **4**–**6** to but-3-enenitrile can be carried out under conditions supporting isomerization of but-3-enenitrile into but-2-enenitrile. For this purpose we have chosen acetone–water mixture as a solvent and KOH as a catalyst of the isomerization [4, 5]. Compared with non-catalytic thermal process (200–220°C), KOH-catalyzed reactions of pyrazoles **4**–**6** with but-3-enenitrile occurred readily at 20–25°C within 24 h to form the corresponding adducts **7**–**9** (Scheme 2).

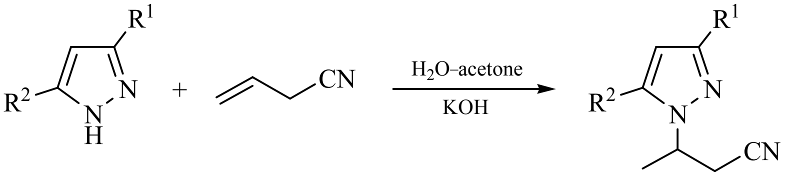
The reaction time was reduced approximately 2-fold with increasing temperature from 20 to 40°C. Further increase in temperature led to decrease in the yield of the target compounds due to the occurrence of a by-processes, in particular, acetone self-condensation [6].

The use of alkali metal alcoholates as catalysts had no special advantages. Performing the reaction under phase transfer catalysis using triethylbenzylammonium chloride led to the predominant formation of by-products due to acetone self-condensation, which caused a decrease in the yield of the target compounds as well as made their isolation difficult.

Scheme 1.



Scheme 2.



4–6 **7–9**, 47–74%

R^1 = R^2 = H (**4**, **7**); R^1 = H, R^2 = CH$_3$ (**5a**, **8a**); R^1 = CH$_3$, R^2 = H (**5b**, **8b**); R^1 = R^2 = CH$_3$ (**6**, **9**).

Unlike thermal process [1], in the case of the catalytic addition of pyrazoles **4–6** to but-3-enenitrile the adduct yield decreased when passing from pyrazole **4** to 3,5-dimethylpyrazole **6**. Probably, the base promotes the isomerization of but-3-enenitrile as well as pyrazole anion generation. Introduction of donor methyl substituents into the pyrazole ring complicates deprotonation [7, 8], thereby slowing down the addition reaction.

3-(Morpholin-4-yl)butanenitrile (1). A mixture of 4.3 g (0.05 mol) of morpholine and 5.0 g (0.075 mol) of but-3-enenitrile was heated on a water bath for 6 h. After cooling, the reaction mixture was distilled under a reduced pressure. Yield 6 g (78%), bp 129°C (4 mmHg), n_D^{20} 1.4690, d_4^{20} 1.0291. IR spectrum, ν, cm^{-1}: 2200 (CN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.16 d (3H, CH$_3$, *J* 6.7), 2.45 d.d (1H, CH$_2$, *J* 16.8, 7.0), 2.46–2.51 m [4H, N(CH$_2$)$_2$], 2.55 d.d (1H, CH$_2$, *J* 16.8, 5.9), 2.83–2.94 m (1H, C$\underline{H}$CH$_2$), 3.56–3.62 m [4H, O(CH$_2$)$_2$]. Found, %: C 62.85; H 9.80; N 18.56. $C_8H_{14}N_2$. Calculated, %: C 62.31; H 9.15; N 18.17.

3-(Piperidin-1-yl)butanenitrile (2) was prepared similarly from 8.5 g (0.1 mol) of piperidine and 10.1 g (0.15 mol) of but-3-enenitrile. Yield 10.4 g (68%), bp 95°C (4 mmHg), n_D^{20} 1.4660, d_4^{20} 0.9375. IR spectrum, ν, cm^{-1}: 2220 (CN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 d (3H, CH$_3$, *J* 6.7), 1.39 m (2H, CH$_2$), 1.50–1.59 m (4H,CH$_2$), 2.38 d.d (1H, NCH$_2$, *J* 16.6, 7.3), 2.42–2.46 m [4H, N(CH$_2$)$_2$], 2.50 d.d (1H, NCH$_2$, *J* 16.6, 6.0), 2.87–2.98 m (1H, CH). Found, %: C 71.75; H 10.29; N 18.55. $C_9H_{16}N_2$. Calculated, %: C 71.01; H 10.59; N 18.40.

3-(Pyrrolidin-1-yl)butanenitrile (3) was prepared similarly from 2.1 g (0.03 mol) of pyrrolidine and 3.4 g (0.05 mol) of but-3-enenitrile. Yield 2.7 g (65%), bp 84°C (2 mmHg), n_D^{20} 1.4645, d_4^{20} 0.9419. IR spectrum, ν, cm^{-1}: 1500 (ring), 2250 (CN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 d (3H, CH$_3$, *J* 6.4), 1.75–1.84 m (4H, NCH$_2$C$\underline{H}_2$), 2.41 d.d (1H, CH$_2$CN, *J* 16.6, 7.7), 2.56–2.61 m [5H, N(CH$_2$)$_2$, CH$_2$CN], 2.65–2.75 m (1H, CH). Found, %: C 64.42; H 10.52; N 20.55. $C_8H_{16}N_2$. Calculated, %: C 64.52; H 10.21; N 20.27.

3-(1*H*-Pyrazol-1-yl)butanenitrile (7). To a solution of 2.8 g (0.05 mol) KOH in 7 mL of water and 25 mL of acetone was added with stirring at 40°C 3.4 g (0.05 mol) of pyrazole **4** and 5.4 g (0.08 mol) of but-3-enenitrile. The reaction mixture was stirred for 12 h, then cooled. Acetone was removed under a reduced pressure; the residue was extracted with benzene. The extract was dried with MgSO$_4$ and evaporated. The residue was distilled under a reduced pressure. Yield 4.9 g (74%), bp 93°C (1 mmHg), n_D^{20} 1.4852, d_4^{20} 1.0462 [1].

3-[3(5)-Methyl-1*H*-pyrazol-1-yl]butanenitrile (8a, 8b) was prepared similarly from 8.2 g (0.1 mol) of 3(5)-methylpyrazole **5** and 10.1 g (0.15 mol) of but-3-enenitrile. Yield 9 g (61%), bp 102°C (2 mmHg), n_D^{20} 1.4812, d_4^{20} 1.0109 [1].

3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)butanenitrile (9) was prepared similarly from 9.6 g (0.1 mol) of 3,5-dimethylpyrazole **6** and 10.1 g (0.15 mol) of but-3-enenitrile. Yield 7.7 g (47%), bp 123°C (1 mmHg), n_D^{20} 1.4802, d_4^{20} 0.9765 [1].

IR spectra were recorded on a Nexus instrument (Thermo Nicolet Corporation, USA). ^{1}H NMR spectra were obtained on a Varian Mercury spectrometer (300 MHz) in DMSO–CCl$_4$ (1 : 3). Elemental analysis was performed on a Korshun–Klimova instrument. But-3-enenitrile was produced in "Ariak."

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REFERENCES

1. Khachatryan, H.N., Hayotsyan, S.S., Attaryan, H.S., and Hasratyan, G.V., *Russ. J. Gen. Chem.*, 2015, vol. 85, no. 4, p. 996. DOI: 10.1134/S1070363215040404.
2. Ivanskii, V.I., *Khimiya geterotsiklicheskikh soedinenii* (Chemistry of Heterocyclic Compounds), Moscow: Vysshaya Shkola, 1978.
3. Savarimuthu, P.A., Varughese, S., and Draper, S.M., *Chem. Commun.*, 2009, no. 48, p. 7500. DOI: 10.1039/B914027A.
4. Shekhirev, Yu.P., Lopatinskii, V.P., Sutyagin, V.M., and Tuzovskaya, S.A., *Chem. Heterocycl. Comp.,* 1983, vol. 19, no. 11, p. 1192. DOI: 10.1007/BF00515355.
5. Attaryan, H.S., Asratyan, G.V., Darbinyan, E.G., and Matsoyan, S.G., *Zh. Org. Khim.*, 1988, vol. 24, no. 6, p. 1339.
6. Elin, I.O., Pesin, L.M., and Gemfer, E.L., Author's Certificate 195439, 1967, USSR; *Byull. Izobret.*, 1967, no. 10.
7. Attaryan, H.S., Baltayan, A.O., Badalyan, K.S., Minasyan, G.G., and Matsoyan, S.G., *Russ. J. Gen. Chem.*, vol. 76, no. 7, p. 1131. DOI: 10.1134/S1070363206070218.
8. Hayotsyan, S.S., Khachatryan, H.N., Baltayan, A.O., Attaryan, H.S., and Hasratyan, G.V., *Russ. J. Gen. Chem.*, 2015, vol. 85, no. 4, p. 993. DOI: 10.1134/S1070363215040398.