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LETTERS TO THE EDITOR

Addition of Azoles to Methyl Vinyl Ketone by the Aza-Michael Reaction

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The capability of azoles to react with compounds containing activated double bond allows to prepare a variety of their derivatives [1–7]. The conjugate addition of azoles to methyl vinyl ketone in most cases occurs in the presence of acidic catalysts [8–11] or any other agents (ethylamine [12], molecular iodine on alumina [13], imidazolium salts [14]). There are some examples of the addition in dimethyl sulfoxide [15]. Only two papers described the addition of imidazole and pyrazole to methyl vinyl ketone in the absence of any catalysts and solvents; the target adducts were isolated in 63–74% yields [16, 17].

In the present work, we studied the interaction of pyrazole **I**, 3(5)-methylpyrazole **II**, 3,5-dimethylpyrazole **III**, 1,2,4-triazole **IV**, imidazole **V** and tetrazole **VI** with methyl vinyl ketone in the absence of a catalyst and a solvent (Scheme 1).

The introduction of hetero atoms in the azole ring enhances the reactivity of the corresponding heterocycles in nucleophilic addition reactions [18, 19].

We found that the addition of pyrazoles **I**–**III** to methyl vinyl ketone proceeded in 0.5–3 h. The reaction rate depends on the acidity of pyrazoles. By the reaction rate, the studied pyrazoles can be arranged in the following sequence: pyrazole **I**) (pK_a 20.4 [20]) > 3(5)-methylpyrazole **II** pK_a 21.0 [20]) > 3,5-dimethylpyrazole **III** (pK_a 22.0 [20]).

The introduction of an electron-donor methyl substituents into the pyrazole ring affects the deprotonation, thus decreasing the rate of the reaction. In the case of tetrazole **VI** (pK_a 4.89 [21]), the reaction was completed in 15 min.

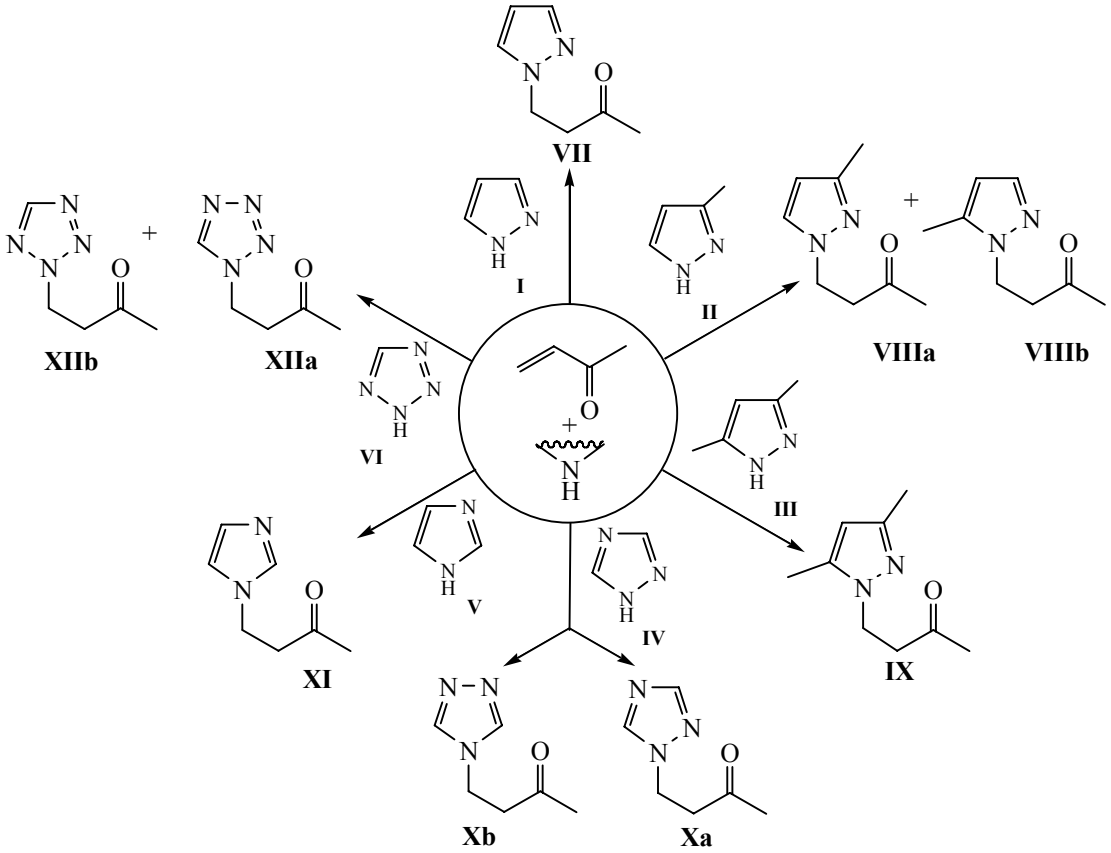
Addition of 1,2,4-triazole **IV** (pK_a 15.4 [22]) and imidazole **V** (pK_a 14.52 [22]) to methyl vinyl ketone took place analogously to pyrazole **I**. Hence, in a series of pyrazoles **I**–**III** the presence of electron-donor substituents in the positions 3 and 5 of the the pyrazole ring affects the rate of the reaction, and an increase in the number of N atoms in the azole ring accelerates the reaction.

In the case of addition of 3-methylpyrazole **II** the final product represents a mixture of two isomers **VIIIa** and **VIIb** in a ratio of 3 : 1.

The reaction of 1,2,4-triazole **IV** with methyl vinyl ketone proceeded stereoselectively to afford only isomer **Xa** [23].

The interaction of tetrazole **VI** with methyl vinyl ketone took place with the formation of 1- and 2-substituted isomers **XIIa** and **XIIb** in a ratio of 1 : 2. After the removal of the excess of the methyl vinyl ketone, the product of ~96% purity was obtained (according to NMR data). Despite the high yields the separation and characterisation of individual isomers was impossible due to their high instability at higher temperatures. The identification of isomers was done according to the position of signals of ring hydrogens in NMR spectra. In the isomer (**XIIb**) the signal of the ring proton is revealed in the stronger field compared to the proton of isomer (**XIIa**) [24].

Scheme 1.



In summary, aza-addition of azoles can be performed in the absence of a catalyst and a solvent at heating with 10% excess of methyl vinyl ketone.

4-(1*H*-Pyrazol-1-yl)butan-2-one (VII). A mixture of 3.4 g (0.05 mol) of pyrazole **I** and 3.85 g (0.055 mol) of methyl vinyl ketone was heated in an oil bath at 110°C for 0.5 h. After cooling, the reaction mixture was distilled in a vacuum. Yield 5.70 g (83%), mp 79°C (3 mmHg), n_D^{20} 1.4841. IR spectrum, ν, cm^{-1}: 1520 (ring), 1720 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.21 s (3H, 3-CH_3), 2.93 t (2H, CH_2C=O, *J* 6.6), 4.11 t (2H, NCH_2, *J* 6.6), 6.15 d.d (1H, 4H, *J* 2.3), 7.34 d.d (1H, 3H, *J* 1.8), 7.54 d.d (1H, 5H, *J* 2.3). Found, %: C 60.35; H 7.80; N 20.56. $C_7H_9N_3$. Calculated, %: C 60.85; H 7.30; N 20.28.

4-(3-Methyl-1*H*-pyrazol-1-yl)butan-2-one (VIIIa, VIIIb) (mixture of isomers) was prepared similarly from 4.75 g (0.05 mol) of 3(5)-methylpyrazole **II** by heating for 1.5 h. Yield 6.69 g (88%), bp 103°C (5 mmHg), n_D^{20} 1.4760. IR spectrum, ν, cm^{-1}: 1530 (ring), 1720 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.21 s (**a**) and 2.22 s (**b**) [3H, 3(5)-CH_3], 2.94–3.5 m (2H, CH_2C=O), 4.15–4.22 m (2H, NCH_2), 6.20 d (1H, H^4, *J* 2.3), 7.30 d (**a**) (1H, H^5, *J* 2.3), 7.19 d (**b**) (1H, H^3, *J* 2.3). Found, %: C 63.55; H 7.35; N 18.85. $C_8H_{12}N_2O$. Calculated, %: C 63.13; H 7.95; N 18.41.

4-(3,5-Dimethyl-1*H*-pyrazol-1-yl)butan-2-one (IX) was prepared similarly from 4.8 g (0.05 mol) of 3,5-dimethylpyrazole **III** by heating for 3 h. Yield 6.97 g (84%), bp 112°C (5 mmHg), n_D^{20} 1.4831. IR spectrum, ν, cm^{-1}: 1540 (ring), 1720 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.22 s (3H, 3-CH_3), 2.26 s (3H, 5-CH_3), 2.96 t (2H, CH_2C=O, *J* 6.6), 4.15 t (2H, NCH_2, *J* 6.6), 6.25 s (1H, 4H). Found, %: C 65.48; H 8.79; N 16.34. $C_9H_{14}N_2O$. Calculated, %: C 65.03; H 8.49; N 16.85.

4-(1*H*-1,2,4-Triazol-1-yl)butan-2-one (Xa) was prepared similarly from 3.45 g (0.05 mol) of 1,2,4-triazole **IV**. Yield 6.26 g (90%), bp 120°C (2 mmHg), n_D^{20} 1.4701. IR spectrum, ν, cm^{-1}: 1510 (ring), 1720 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.13 s (3H, CH_3), 3.03 t (2H, 2H, CH_2C=O, *J* 6.6), 4.36 t (2H, NCH_2, *J* 6.6), 7.71 s (1H, CH). Found, %: C 51.48; H 6.85; N 30.49. $C_6H_9N_3O$. Calculated, %: C 51.79; H 6.52; N 30.20.

4-(1*H*-Imidazol-1-yl)butan-2-one (XI) was prepared similarly from 3.4 g (0.05 mol) of imidazole **V**. Yield 5.87 g (85%), bp 146°C (7 mmHg), n_D^{20} 1.4838. IR spectrum, ν, cm^{-1}: 1540 (ring), 1720 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.11 s (3H, CH_3), 2.94 t (2H, $CH_2C{=}O$, *J* 6.6), 4.16 t (2H, NCH_2, *J* 6.6), 6.78 m (1H, CH), 6.94 m (1H, CH), 7.42 m (1H, CH). Found, %: C 60.39; H 7.85; N 20.54. $C_6H_7N_2O$. Calculated, %: C 60.85; H 7.30; N 20.28

4-(1*H*-Tetrazol-1-yl)butan-2-one (XIIa, XIIb) (mixture of isomers, 1 : 2) was prepared similarly from 3.5 g (0.05 mol) of tetrazole **VI** and 3.85 g (0.055 mol) of methyl vinyl ketone by heating under the conditions for preparation of compound (**VII**) within 15 min. After cooling, an excess of methyl vinyl ketone was removed under reduced pressure to give 6.8 g of a mixture of isomers **XIIa**,**b** in a ratio of 1 : 2 (by ^1H NMR). Yield 6.8 g (97%). IR spectrum, ν, cm^{-1}: 1500 (ring), 1720 (C=O). ^1H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): isomer **XIIa**, 2.19 s (3H, CH_3), 3.25 t (2H, CH_2C, *J* 6.7), 4.83 t (2H, NCH_2, *J* 6.7), 8.57 s (1H, CH); isomer **XIIb**, 2.15 s (3H, CH_3), 3.17 t (2H, CH_2C, *J* 6.5), 4.62 t (2H, NCH_2, *J* 6.5), 9.09 s (1H, CH).

IR spectra were obtained on a Nexus spectrometer (Thermo Nicolet Corporation, USA). ^1H NMR spectra were recorded on Varian Mercury instrument (300 MHz) in DMSO–CCl_4, 1 : 3. Elemental analysis was performed on a Korshun–Klimov apparatus.

REFERENCES

1. Grandberg, I.I. and Kost, A.N., *Russ. J. Gen. Chem.*, 1961, vol. 31, no. 11, p. 3700.
2. Darbinyan, E.G., Matsoyan, M.S., Oganesyan, K.G., Mitardzanyan, Yu.B., Saakyan, A.A., and Matsoyan, S.G., *Byull. Izobret.,* 1979, no. 36.
3. Itoh, H., Kameyama, A., and Nishikubo, T., *Polym. Sci. Polym. Chem*., 1997, vol. 35, no. 15, p. 3217. DOI: 10.1002/(SICI)1099-0518(19971115)35:15<3217::AID-POLA14> 3.0.CO;2-E.
4. Stohr, A. and Strohrigl, P., *Macromol. Chem. Phys*., 1998, vol. 199, no. 5, p. 751. DOI: 10.1002/(SICI)1521-3935(19980501)199:5<751::AID-MACP751>3.0.CO;2-3.
5. Attaryan, O.S., Baltayan, A.O., Badalyan, K.S., Minasyan, G.G., and Matsoyan, S.G., *Russ. J. Gen. Chem*., 2006, vol. 76, no. 7, p. 1131. DOI: 10.1134/S1070363206070218.
6. Attaryan, O.S., Baltayan, A.O., and Matsoyan, S.G., *Russ. J. Gen. Chem*., 2007, vol. 77, no. 2, p. 297. DOI: 10.1134/S10703632o702017X.
7. Attaryan, O.S., *Khim. Zh. Armenii*, 2010, vol. 49, no. 1, p. 161.
8. Bartoli, G., Bartolacci, M., Giuliani, A., Marcantoni, E., Massaccesi, M., and Torregiani, E., *J. Org. Chem*., 2005, vol. 70, no. 1, p. 169. DOI: 10.1021/jo048329g.
9. Firouzabadi, H., Iranpoor, N., and Jafari, A.A., *Adv. Synth. Catal*., 2005, vol. 347, no. 5, p. 655. DOI: 10.1002/adsc.200404348.
10. Saidi, M.R., Pourshojaei, Y., and Aryanasab, F., *Synth. Commun*., 2009, vol. 39, no. 6, p. 1109. DOI: 10.1080/00397910802499559.
11. Kawatsura, M., Aburatani, S., and Uenishi, J., *Tetrahedron*, 2007, vol. 63, no. 19, p. 4172. DOI: 10.1016/j.tet.2007.02.091.
12. Weintraub, P.M., Tiernan, P.L., and Huffman, J.C., *J. Heterocycl. Chem*., 1987, vol. 24, no. 3, p. 561. DOI: 10.1002/jhet. 5570240305.
13. Saikia, M., Kakati, D., Joseph, M.S., and Sarma, J.C., *Lett. Org. Chem*., 2009, vol. 6, no. 8, p. 654. DOI: 10.2174/ 157017809790442961.
14. Schneiders, K., Boesmann, A., Schulz, P.S., and Wasserscheid, P., *Adv. Synth. Catal*., 2009, vol. 351, no. 3, p. 432. DOI: 10.1002/adsc.200800569.
15. Bo, K.L., Wu, Q., Xue, Q.Q., De, S.L., and Xian, F.L., *Synthesis*, 2007, no. 17, p. 2653. DOI: 10.1055/s-2007-983816.
16. Ferroni, R., Milani, L., Simoni, D., Orlandini, P., and Guarner, M., *Farmaco*, 1989, vol. 44, no. 5, p. 495.
17. Reimlinger, H. and Oth, J.F.M., *Chem. Ber*., 1964, vol. 97, no. 2, p. 331. DOI: 10.1002/cber.19640970205.
18. Baltayan, A.O., *Khim. Zh. Armenii*, 2007, vol. 60, no. 3, p. 527.
19. Attaryan, O.S., Baltayan, A.O., Sagatelyan, R.E., and Takmazyan, K.Ts., *Russ. J. Gen. Chem*., 2007, vol. 77, no. 12, p. 2176. DOI: 10.1134/S1070363207120158.
20. Ivanskii, V.I., *Khimiya geterotsiklicheskikh soedinenii* (Chemistry of Heterocyclic Compounds), Moscow: Vysshaya Shkola, 1978, p. 560.
21. Katritzky, A.R., *Physical Methods in Heterocyclic Chemistry*, New York: Academic Press, 1960–1972.
22. Terekhova, M.I., Petrov, E.S., and Rokhlina, E.M., *Khim. Geterotsikl. Soed.*, 1979, no. 8, p. 1104.
23. Greagh, L.T. and Truitt, P., *J. Org. Chem*., 1968, vol. 33, no. 7, p. 2956. DOI: 10.1021/jo01271a076.
24. Belousov, A.M., Gareev, G.A., Kirillova, L.P., and Verschagin, L.I., *Zh. Org. Khim.,* 1980. vol. 16, no. 12, p. 2622.