ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 11, pp. 2663–2664. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © V.I. Rstakyan, A.A. Saakyan, H.S. Attaryan, A.G. Hasratyan, 2015, published in Zhurnal Obshchei Khimii, 2015, Vol. 85, No. 11, pp. 1924–1926.

LETTERS TO THE EDITOR

Chloromethylation of Pyrazole Ring

V. I. Rstakyan, A. A. Saakyan, H. S. Attaryan, and A. G. Hasratyan

Institute of Organic Chemistry, Scientific and Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia, ave. Azatutyan 26, Yerevan, 0014 Armenia
e-mail: vrstakyan@gmail.com

Received July 7, 2015

Keywords: chloromethylated pyrazole, 1-phenyl-3,5-dimethylpyrazole

DOI: 10.1134/S1070363215110262

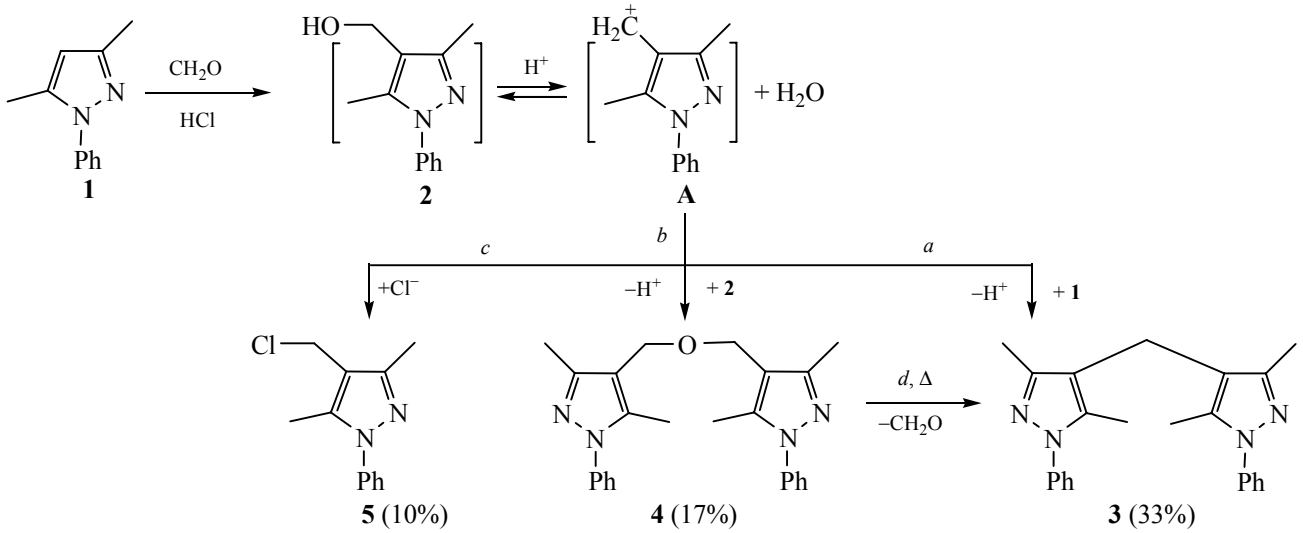
It is known that chloromethylation of 1,3,5-trimethyl-1*H*-pyrazole with paraformaldehyde in the presence of concentrated HCl is competed by formation of methane-4,4'-diylbis(1,3,5-trimethyl-1*H*-pyrazole) [1]. However, chloromethylation of 1,3,5-triphenyl-1*H*-pyrazole has afforded the corresponding chloromethyl derivative as the only reaction product [1]. In addition, methanediylbis(1*H*-pyrazole) derivatives have not been obtained when the pyrazole ring contains aromatic and heteroaromatic substituents in positions 1 and 4 [2]. That was explained by the stabilizing effect of the substituents.

In the present study we investigated chloromethylation of pyrazoles containing methyl and phenyl substituents. Chloromethylation of 3,5-dimethyl-1-phenyl-1*H*-pyrazole **1** proceeded as electrophilic substitution.

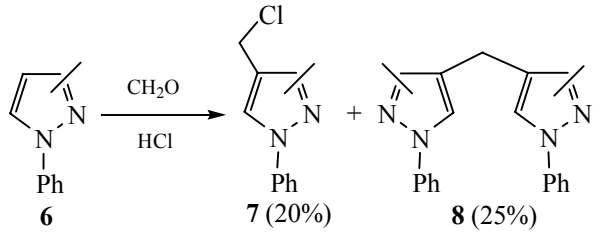
The reaction did not stop at the stage of (3,5-dimethyl-1-phenyl-1*H*-pyrazol-3-yl)methanol **2** formation. In the presence of hydrochloric acid, the alkylation occurred at the position 4 of pyrazole ring of compound **1** (route *a*) to form methane-4,4'-diylbis-(3,5-dimethyl-1*H*-pyrazole) **3**. Alkylation of alcohol **2** (route *b*) yielded the symmetrical ester **4**; the latter underwent elimination of formaldehyde upon distillation to form bispirazolylmethane **3** (route *d*) [3]. Reaction of the intermediate pyrazolecarbinol **2** with concentrated HCl resulted in formation of 3,5-dimethyl-1-phenyl-4-(chloromethyl)-1*H*-pyrazole **5** (route *c*) (Scheme 1).

Similarly, chloromethylation of 3(5)-methyl-1-phenyl-1*H*-pyrazole **6** yielded 3(5)-methyl-1-phenyl-4-

Scheme 1.



Scheme 2.



(chloromethyl)-1*H*-pyrazole **7** and methanediylbispyrazole **8** (Scheme 2).

Since all the above reactions proceeded via carbocation **A** formation, the stabilizing effect of substituents [2] as well as the substrate nucleophilicity affected the reaction route.

Nucleophilicity of 1,3,5-trimethyl-1*H*-pyrazole was somewhat higher compared with that of 3,5-dimethyl-1-phenyl- (**1**) and 3(5)-methyl-1-phenyl-1*H*-pyrazole (**6**); therefore, bispyrazolylmethane formation was the predominant reaction pathway.

To conclude, increasing the number of methyl substituents in the pyrazole ring prevented chloromethylation reaction, and the presence of phenyl substituents had the opposite effect.

Hydroxymethylation of 3,5-dimethyl-1-phenyl-1*H*-pyrazole (1). *a*. A mixture of 17.1 g (0.1 mol) of 3,5-dimethyl-1-phenyl-1*H*-pyrazole **1**, 3 g of paraformaldehyde, and 50 mL of conc. HCl was refluxed during 1.5 h. The reaction mixture was neutralized with NaOH solution. The reaction products were extracted with butanol. The extract was dried over $MgSO_4$ and concentrated. The residue was distilled in vacuum to give 3,5-dimethyl-1-phenyl-4-chloromethyl-1*H*-pyrazole **5** in yield of 2.2 g (10%), bp 140°C (1 mmHg), n_D^{20} 1.5844. IR spectrum, ν, cm^{-1}: 1540 (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 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.

On top of that, **methane-4,4'-diylbis(3,5-dimethyl-1-phenyl-1*H*-pyrazole) 3** was isolated with 60% yield (10.6 g), bp 260°C (1 mmHg), mp 118°C (water–acetone). IR spectrum, ν, cm^{-1}: 1550 (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 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.

b. The reaction was performed similarly. The products were extracted with butanol, and 15 mL of pyridine was added to capture the 4-(chloromethyl) derivative. The resulting quaternary salt was filtered off. After removal of butyl alcohol, the residue crystallized. The crystals were filtered off and washed with petroleum ether to yield **methane-4,4'-diylbis-(3,5-dimethyl-1-phenyl-1*H*-pyrazole) 3** (5.8 g, 33%). After removal of petroleum ether, 3.2 g (17%) of **oxydimethane-4,4'-diylbis(3,5-dimethyl-1-phenyl-1*H*-pyrazole 4** (viscous liquid, n_D^{20} 1.5485) was isolated. IR spectrum, ν, cm^{-1}: 1100 (CH_2OCH_2), 1540 (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.21 s (6H, 3-CH_3), 2.30 s (6H, 5-CH_3), 4.26 s (4H, $O(CH_2)_2$), 7.28–7.47 m (10H, $2C_6H_5$).

Hydroxymethylation of 3(5)-methyl-1-phenyl-1*H*-pyrazole 6 was carried out similarly. **4-Chloromethyl-3(5)-methyl-1-phenyl-4-chloromethyl-1*H*-pyrazole (7).** Yield 4.1 g (20%), bp 130–135°C (1 mmHg), n_D^{20} 1.5835. IR spectrum, ν, cm^{-1}: 1530 (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.20 s (3H, 3-CH_3), 2.32 s (3H, 5-CH_3), 4.28 s (2H, CH_2Cl), 7.19 s (1H, H^3), 7.30 s (1H, H^5), 7.40 m (5H, C_6H_5). Found, %: C 63.49; H 5.85; Cl 17.4; N 13.2. $C_{11}H_{11}ClN_2$. Calculated, %: C 63.92; H 5.32; Cl 17.19; N 13.59.

Bis[3(5)-methyl-1-phenylpyrazol-4-yl]methane (8). Yield 4.0 g (25%), bp 245–250°C (1 mmHg), viscous liquid, n_D^{20} 1.5428. IR spectrum, ν, cm^{-1}: 1580 (ring). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.98 s (6H, 3-CH_3), 2.0 s (6H, 5-CH_3), 3.31 s (2H, CH_2), 7.21 s (1H, H^3), 7.31 s (1H, H^5), 7.45 m (10H, $2C_6H_5$). Found, %: C 76.99; H 6.48; N 17.31. $C_{21}H_{20}N_4$. Calculated, %: C 76.82; H 6.09; N 17.07.

IR spectra were obtained with a Nexus Thermo Nicolet spectrometer. ^1H NMR spectra were registered using a Varian Mercury instrument (300 MHz).

REFERENCES

1. Grandberg, I.I., Vasina, L.G., and Kost, A.N., *Zh. Obshch. Khim*., 1960, vol. 30, no. 10, p. 3324.
2. Bratenko, M.K., Chernyuk, I.N., and Vovk, M.B., *Russ. J. Org. Khim*., 1997, vol. 33, no. 9, p. 1368.
3. Attaryan, H.S., Gevorkyan, A.A., Antanosyan, S.K., and Matsoyan, S.G., *Russ. J. Gen. Chem*., 2007, vol. 77, no. 6, p. 1139. DOI: 10.1134/S1070363207060345.