N-Amination of Pyrazoles: a General Approach

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A general approach to *N*-amination of pyrazoles, allowing the synthesis of previously inaccessible *N*-aminopyrazoles with electron-acceptor substituents in the ring, has been proposed, consisting of treatment of the pyrazoles with hydroxylamine-*O*-sulfonic acid in aqueous media at controlled pH depending on pK_a of the pyrazole.

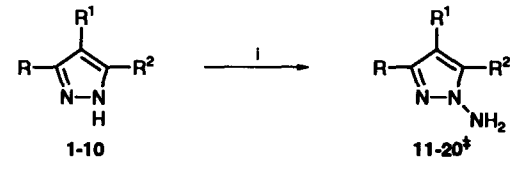
A method has already been described[1,2] for the *N*-amination of pyrazoles at the cyclic nitrogen atom by the acton of hydroxylamine-*O*-sulfonic acid (HOSA) in an aqueous alkaline solution. The method produces good results for alkyl- and aryl-substituted pyrazoles. However, we failed to expand this approach to pyrazoles containing electron-acceptor groups in the nucleus (NO_2, CN, *etc*). Thus, with nitropyrazoles as an example we found that amination of such compounds according to the known procedures, devised for *N*-amination of pyrazole and its alkyl- and aryl-substituted derivatives, either proceeds in very low yields† or does not proceed at all. In our opinion, the reason for these failures is the fact that during the amination with HOSA in an alkali medium two processes are taking place: the amination of substrate (pyrazolate anions in our case) and the well-known hydrolytic decomposition of HOSA under the action of an alkali.[4] The presence of electron-acceptor substituents in the nucleus of pyrazoles leads to a decrease in nucleophilicity of their anions, while in the case of nitropyrazoles the amination rate seems to become lower than that of HOSA decomposition in the alkali medium.

Hydrolysis of HOSA leads to consumption of hydroxyl ions,[4] thus decomposition of HOSA in water can be retarded by lowering the pH of the reaction medium to a minimum acceptable level. This level is determined by the acidity at which the aminated pyrazole exists completely (or mostly) in the reactive anionic form. Nitropyrazoles have NH-acidity[5] sufficient to form anions at pH 7–11. We carried out reactions of the sodium salt of HOSA with sodium salts of 3-nitro-4-cyanopyrazole and 3,5-dinitro-4-chloropyrazole in an aqueous medium. The medium on mixing the reagents was nearly neutral. However, acidification of the medium then took place very quickly (5–10 min), and the pyrazoles transformed into the inactive NH-form, so *N*-aminopyrazoles did not form.

As mentioned above, hydrolytic decomposition of HOSA occurs with consumption of hydroxyl ions; therefore, in the absence of excess alkali the hydrolysis of even a small fraction of HOSA leads to a decrease in pH, which in our case of an initially neutral solution causes rapid acidification of the reaction mixture. It was deduced from the results obtained that *N*-amination with HOSA should be carried out at a fixed optimum pH at which hydrolysis of HOSA occurs slower than *N*-amination and at which the reaction mixture is not acidified.

We have developed a procedure for *N*-amination in water at monitored solution pH. In this case the *N*-amination of pyrazoles bearing nitro- and other electron-acceptor groups in the pyrazole ring proceeds readily at 60 °C to give *N*-aminopyrazoles, chiefly in 45–95% yields, Scheme 1.

As we have found, in order to achieve the highest yields of *N*-aminopyrazoles,§ the reaction mixture pH must be maintained 1–2 units higher than the pK_a of the pyrazole in order to be aminated. For the compounds **1–8** (pK_a between 8 and 11) the optimum pH is 10–11. For the more acidic compounds **9** and **10**, the pH may be lowered to 7–8.



1-10 **11-20‡**

1,11 R = R² = H; R¹ = NO_2
2,12a R = NO_2; R¹ = R² = H
12b R = R¹ = H; R² = NO_2
3,13a R = NO_2; R¹ = H; R² = Me
13b R = Me; R¹ = H; R² = NO_2
4,14a R = Me; R¹ = NO_2; R² = H
14b R = H; R¹ = NO_2; R² = Me
5,15a R = H; R¹ = NO_2; R² = NH_2
15b R = NH_2; R¹ = NO_2; R² = H
6,16 R = H; R¹ = CN; R² = NH_2
7,17 R = CO_2H; R¹ = NO_2; R² = H
8,18 R = $CONH_2$; R¹ = NO_2; R² = H
9,19 R = NO_2; R¹ = CN; R² = H
10,20 R = R² = NO_2; R¹ = Cl

Scheme 1 *Reagents and conditions*: i, H_2NOSO_2OH, H_2O, pH 7–8 or 10–11, 4 h

In the case of unsymmetric pyrazoles **3–5**, two isomers are formed (**12a,b–15a,b**), but in the case of similar unsymmetric **6–9**, only one isomer is formed (*N*-aminopyrazoles **16–19**).

All the compounds obtained were characterized by a combination of spectral methods (IR and mass spectrometry and ^1H, ^{13}C and ^{15}N NMR spectroscopy).

The method of *N*-amination of pyrazoles at monitored pH is a general method. For every pyrazole an optimum pH of the reaction mixture can be selected at which the amination proceeds faster than decomposition of HOSA, and at which *N*-aminopyrazole is formed in maximum yield. The amination of alkyl- and aryl-substituted pyrazoles at high pK_a (> 13) described in the literature[1,2] requires an excess of alkali to obtain a pH of not less than 14. In this case the high rate of *N*-amination causes the process to be successful, even in a strong alkali medium.

Our data expand the range of pyrazoles that can be aminated to include the region of medium and low pK_a values.

The method developed is probably suitable for other NH-azoles. In fact, 4-nitro-1,2,3-triazole (pK_a = 4.8[6]) is aminated with HOSA at pH 7 to form 1-amino- and 2-amino-4-nitro-1,2,3-triazoles in a total yield of *ca.* 40%.

References

1 U. Neunhoeffer, M. Clausen, H. D. Voeter, H. Ohl, C. Krueger and K. Angermund, *Liebigs Ann. Chem.*, 1985, 1732.
2 A. Ohsawa, H. Arai, H. Ohnishi and H. Igeta, *J. Chem. Soc., Chem. Commun.*, 1980, 1182.
3 R. J. Harder, US Pat., 3207763, 1965 (*Chem. Abstr.*, 1965, **63**, 18096c.)
4 E. Schmitz, R. Ohme and G. Korakiewier, *Z. Anorg. Chem.*, 1965, 44.
5 J. Catalan, J. L. M. Abboud and J. Elguero in *Adv. Heterocycl. Chem.*, ed. A. R. Katritzky, Academic Press, New York, 1987, **41**, 187.
6 S. Majorana, D. Pocar and P. D. Croce, *Tetrahedron Lett.*, 1966, 6043.

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† Patent [3] reports on *N*-amination of 4-nitropyrazole with HOSA in an alkali medium to form 1-amino-4-nitropyrazole in 13% yield.

‡ M.p. (from H_2O): **11** 98 °C; **12a** 132 °C; **13a** 125 °C; **14a** 149 °C; **15a** 290 °C; **16** 256 °C; **17** 201 °C; **18** 213 °C; **19** 135 °C; **20** 122 °C.

§ NaOH (0.8 g, 0.02 mol), 4-nitropyrazole (0.57 g, 0.005 mol) and HOSA (1.7 g, 0.015 mol) were added in a boric buffer (25 ml) at pH 11. The reaction mixture was heated for 4 h at 60 °C then cooled and extracted with Et_2O (4 × 15 ml). The ethereal extract was washed with a 5% aqueous solution of NaOH and then water. Ether was evaporated and the residue was crystallized from H_2O. Yield 0.56 g (78%).