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Synthesis of *N*-hydroxypyrazoles with electron-accepting substituents in the ring

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A method for the synthesis of *N*-hydroxynitropyrazoles by oxidation of pyrazolate anions with $KHSO_5$ in aqueous solution at constant pH has been developed.

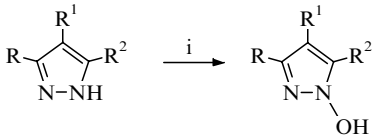
N-Hydroxypyrazoles are of considerable interest due to their extensive synthetic possibilities (see, *e.g.*, refs. 1 and 2). However, only a few of them, synthesized by partial reduction of 1-hydroxypyrazole-2-oxides obtained by cyclization of oximes, have been described in the literature to date.[3–7]

Direct *N*-hydroxylation of *N*-unsubstituted pyrazoles can be an appropriate method for the preparation of *N*-hydroxypyrazoles. Although several patents on *N*-hydroxylation of pyrazoles[8–10] have appeared recently, that paper which describes the synthesis of *N*-hydroxypyrazole by oxidation of pyrazole with 3-chloroperbenzoic or performic acids was published only in 1995.[1] Taking into account the very low basicity of the pyrazole ring, especially those containing electron-accepting substituents,† this approach probably cannot serve as a general method for the synthesis of *N*-hydroxypyrazoles with various substituents in the ring.

The use of reactions of pyrazolate anions as nucleophiles with electrophilic hydroxylating or acyloxylating agents seems more attractive. The paper addressing this problem also appeared only in 1995.[2] In this work, it was shown that pyrazole sodium salts and their methyl- and 4-halogeno-derivatives, under the action of benzoyl peroxide, give the corresponding *N*-hydroxypyrazoles.

These results prompted us to publish our data on the *N*-hydroxylation of pyrazoles containing the nitro group as well as some other electron-accepting substituents (CN, CO_2Me) in the ring. No *N*-hydroxypyrazoles with a nitro group in the ring were known before the present work. This work continues our studies on *N*-functionalization of pyrazoles (see refs. 13–15).

First of all we studied the action of several oxidants on *N*-unsubstituted nitropyrazoles. It turned out that nonionized nitropyrazoles do not react with Caro's acid, organic peracids (CH_3CO_3H, CF_3CO_3H), dibenzoyl peroxide, bis-4-nitrophenylsulfonyl peroxide, or even with such a strong oxidant as bis-fluorosulfonyl peroxide (FSO_2OOSO_2F). As for nitropyrazolate anions, *N*-hydroxynitropyrazoles are not formed under the action of dibenzoyl peroxide (under the conditions in ref. 2), potassium persulfate, bis-nitrophenylsulfonyl peroxides or bis-fluorosulfonyl peroxide on alkaline salts of nitropyrazoles (in the latter case, nitropyrazole completely decomposes).



1–7 **1a–7a**§

1 R = CO_2Me, R^1 = NO_2, R^2 = H;
2 R = NO_2, R^1 = H, R^2 = CO_2Me;
3 R = CO_2Me, R^1 = NO_2, R^2 = CO_2Me;
4 R = NO_2, R^1 = CN, R^2 = H;
5 R = NO_2, R^1 = NO_2, R^2 = Me;
6 R = NO_2, R^1 = H, R^2 = NO_2;
7 R = NO_2, R^1 = NO_2, R^2 = H

i: solution of $KHSO_5$ in phosphate buffer at pH = 6–8

We found that $KHSO_5$ is an appropriate oxidant for the *N*-hydroxylation of nitropyrazolate anions. The method developed for the synthesis of *N*-hydroxypyrazoles involves the treatment of salts of *N*-unsubstituted pyrazoles with $KHSO_5$ in an aqueous solution at constant medium pH. A phosphate buffer is used to create and maintain the necessary acidity of the solution. Reagents (initial NH-pyrazole and $KHSO_5$‡) are mixed at ~20 °C in a phosphate buffer with pH from 6 to 8, and the mixture is stirred for 5 h. The optimum acidity of the solution depends on the pyrazole chosen: pH of the medium should provide not less than 50% formation of the pyrazolate anion from NH-pyrazole, *i.e.*, the value of pH should be equal to, or little higher than, the pK_a of NH-pyrazole.

Nitropyrazoles **1–7** with pK_a lower than 9 readily engage in reaction to form the corresponding products in 30–60% yields. Conversion of the initial nitropyrazole is about 90%.

† For pyrazole, 4-nitropyrazole, 3(5)-nitropyrazole, and 3,4-dinitropyrazole, pK_{BH^+} = 2.52 (ref. 11), −1.96 (ref. 11), −4.66 (ref. 11), and −8.06, respectively (the latter value was determined spectrophotometrically by the known procedure[12]).

Table 1 Yields and NMR data for compounds **1a**–**7a** and **10a**.

Compounds	Yield (%)	NMR (in [$^2H_6$]acetone)[a]			
		^1H (δ_{TMS})	^{13}C (δ_{TMS})	^{15}N (δ_{MeNO_2})	^{17}O[b] (δ_{D_2O})
1a	44	3.88 s (3H, CH_3), 8.51 s (1H, H-5)	53.2 q (CH_3, J = 148.9), 124.3 d (C-5, J = 205.4), 131.9 d (C-4, J = 5.0), 132.9 d (C-3, J = 6.6), 160.8 q (CO, J = 4.2)	−23.6 (NO_2)	149.0 (OH), 371.7 (CO), 592.4 (NO_2)
2a	43	3.91 s (3H, CH_3), 7.29 s (1H, H-4)	53.2 q (CH_3, J = 149.4), 105.5 d (C-4, J = 191.5), 129.2 d (C-5, J = 6.5), 148.0 s (C-3), 158.1 q (CO, J = 4.0)		143.6 (OH), 260.2 (OMe), 351.8 (CO), 585.6 (NO_2)
3a	38	3.85 c (3H, CH_3), 3.91 s (3H, CH_3), 11.73 br.s (1H, OH)	53.07 q (CH_3, J = 147.9), 53.8 q (CH_3, J = 149.7), 123.3 s (C-5), 128.3 s (C-3), 134.1 s (C-4), 156.3 q (CO, J = 3.9), 159.4 q (CO, J = 3.9)		147.5 (OH), 275.0 (OMe), 358.8 (CO), 632.6 (NO_2)
4a[c]	64	8.51 s (H-3)	87.4 d (C-4, J = 7.1), 110.8 s (CN), 132.1 d (C-5, J = 206.7), 148.1 d (C-3, J = 9.6)	−136.9 d (N-1, J = 1.74), −114.3 s (CN), −85.0 s (N-2), −27.0 d (NO_2, J = 1.0))	159.2 (OH), 587.0 (NO_2)
5a[c]	52	2.44 s (3H, CH_3), 12.8 (OH)	9.92 q (CH_3, J = 132.0), 122.4 s (C-4), 135.7 q (C-5, J = 7.2), 141.6 s (C-3)	−145.7 q (N-1, J = 3.3), −94.5 s (N-2), −26.5 s, −25.6 s (3-NO_2, 4-NO_2)	146.0 (OH), 598.0, 617.7 (3-, 4-NO_2)
6a	20[d]	7.77 s (H-4)			
7a	48	8.98 s (H-5)	125.5 d (C-4, J = 8.1), 125.9 d (C-5, J = 208.0), 142.2 d (C-3, J = 5.0)		
10a	38	8.60 s (H-5), 12.6 s (OH)	139.2 d (C-5, J = 224.4), 156.9 d (C-3, J = 18.5)	−140.0 d (N-1, J = 12.6), −134.6 d (N-4, J = 7.0), −91.6 s (N-2), −27.7 s (NO_2)	145.4 (OH), 589.4 (NO_2)

[a] NMR spectra were recorded on a Bruker AM-300 instrument (300 MHz). [b] In CD_3CN. [c] In [$^2H_6$]DMSO. [d] The yield was determined from the ^1H NMR spectrum.

Pyrazoles with pK_a > 9, for example, 4-nitropyrazole **8** (pK_a = 9.64, ref. 11) and 3(5)-methyl-5(3)-nitropyrazole **9** (pK_a = 10.25, ref. 11) do not react under these conditions. This testifies to the fact that the pyrazolate anions, which are formed in insignificant quantities in the case of pyrazoles **8** and **9** at pH 8, react. *N*-Hydroxylation of weakly acidic pyrazoles is possible in a more alkaline medium (pH = 10); however, yields of products are very low (for example, 1-hydroxy-5-methyl-3-nitropyrazole **9a** determined by the ^1H NMR spectrum is formed in 5% yield). It is likely that a decrease in yield as pH increases is related to a decrease in the concentration of the active form of the oxidant, which yields the unreactive $S_2O_8^{2-}$ dianion under strongly alkaline conditions.

Oxidation by $KHSO_5$ is inappropriate for pyrazoles containing the amino group.

N-Hydroxylation of the nonsymmetric nitropyrazoles studied is regioselective: one isomer is formed, and the hydroxylation occurs on the nitrogen atom of the ring, which is the most remote from the most electron-accepting substituent.

All isolated compounds were characterized by ^1H, ^{13}C and ^{15}N and ^{17}O NMR data (Table 1) and IR spectroscopy. The ^{17}O NMR spectra (Table 1) provide direct evidence for the existence of the hydroxy group at the cyclic nitrogen atom of the pyrazole ring. The chemical shift (δ_{D_2O}) of the signal of the N–OH group ranges from 140 to 160 ppm.

All *N*-hydroxynitropyrazoles obtained are strong organic acids: they are several orders of magnitude stronger than the initial NH-pyrazoles, which makes it possible to readily separate them from unreacted NH-pyrazoles. An ether extract of the reaction mixture is washed several times with 5% aqueous sodium acetate in order to transfer *N*-hydroxypyrazoles to the aqueous phase as a salt. After acidification of the aqueous phase, *N*-hydroxynitropyrazoles are isolated by extraction with ether.

The method developed is appropriate for hydroxylation of other azoles with electron-accepting substituents. For example, 3-nitro-1,2,4-triazole **10** gives 1-hydroxy-3-nitro-1,2,4-triazole **10a** in 38% yield under the reaction conditions.

References

1 M. Begtrup and Per Vedso, *J. Chem. Soc., Perkin Trans. 1*, 1995, 243.
2 W. Reuther and U. Baus, *Liebigs Ann.*, 1995, 1563.
3 J. P. Freeman and J. J. Gannon, *J. Heterocycl. Chem.,* 1966, **3**, 544.
4 J. P. Freeman and J. J. Gannon, *J. Org. Chem.,* 1969, **34**, 194.
5 J. P. Freeman, J. J. Gannon and D. L. Surbey, *J. Org. Chem.,* 1969, **34**, 187.
6 J. F. Hansen and D. E. Vietti, *J. Org. Chem.,* 1976, **41**, 2871.
7 A. Kotali and P. G. Tsoungas, *Heterocycles*, 1989, **29**, 1615.
8 U. Baus, W. Rreuther and R. Fikentscher, *Ger. Off.*, 1989, 3820738 (*Chem. Abstr.*, 1990, **113**, 59171).
9 U. Baus, W. Rreuther and E. Hahn, *Ger. Off.*, 1989, 3820739 (*Chem. Abstr.*, 1990, **113**, 23904).
10 F. Schuetz, H. Sauter, S. Brand, B. Wenderoth, U. Baus, W. Reuther, G. Lorenz and E. Ammermann, *Ger. Off.*, 1990, 3905948 (*Chem. Abstr.*, 1991, **114**, 81823).
11 J. Catalan, J. L. M. Abboud and J. Elguero, *Adv. Heterocycl. Chem.*, 1987, **41**, 187.
12 A. Albert and E. Seargeant, *Konstanty ionizatsii kislot i osnovanii* (*Ionization Constants of Acids and Bases*), Khimiya, Moscow, 1964 (in Russian).
13 S. A. Shevelev, V. M. Vinogradov, I. L. Dalinger, B. I. Ugrak and V. I. Filippov, *Mendeleev Commun.,* 1993, 14.
14 V. M. Vinogradov, I. L. Dalinger and S. A. Shevelev, *Mendeleev Commun.,* 1993, 111.
15 I. L. Dalinger, V. M. Vinogradov, V. S. Kuz'min and S. A. Shevelev, *Mendeleev Commun.*, 1996, 13.

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