Direct iodination of 3- and 4-nitropyrazoles with a reagent based on iodine monochloride and silver sulfate

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The reagent obtained from iodine monochloride and silver sulfate in sulfuric acid easily iodinates 1-methyl-3-nitropyrazole under mild conditions to give 4-iodo or 4,5-diiodo derivatives. 1-Methyl-4-nitropyrazole was also directly iodinated with this reagent for the first time.

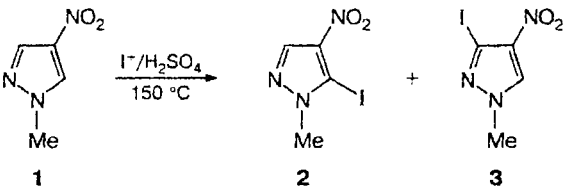
Key words: iodination, iodine monochloride, methylnitropyrazoles, iodomethylnitropyrazoles.

In the previous papers,[1,2] it was shown that vicinal iodonitro-1-methylpyrazoles are promising intermediates because the halogen atom and the nitro group can be easily transformed into other functional groups, and their vicinal arrangement allows various reactions of intramolecular cyclization to occur.[3–5] However, the synthesis of iodonitropyrazoles is believed to be a nontrivial problem.[6] First of all, this relates to 3-iodo-4-nitro- and 5-iodo-4-nitro-1-methylpyrazoles.

Earlier, we described the preparation of some iodopyrazoles by oxidative iodination in an I_2—HIO_3—H_2SO_4 system, but this method has limitations. With certain acceptor-type substituents (CHO, COOH, and COPh) at position 4 of the pyrazole ring, *ipso*-iodination occurs, while the acetyl group is iodinated at the methyl group.[7] In the case of 4-nitropyrazole, no traces of iodinated derivatives are detected even after heating at 80 °C for 80 h, and the initial 4-nitropyrazole is recovered in quantitative yield. Previously,[1,2] it was proposed to synthesize iodo-4-nitropyrazoles by exhaustive iodination of 1-methylpyrazole derivatives with subsequent *ipso*-nitration of the pyrazole ring in position 4. Thus, direct iodination of 4-nitropyrazoles is unknown.

In this work, we attempted to iodinate nitropyrazoles directly, with the use of the recently described superelectrophilic iodinating reagent (reagent "I^+") formed in the reaction of iodine chloride with silver sulfate in sulfuric acid.[8,9] Because both free positions in 1-methyl-4-nitropyrazole (**1**) are strongly deactivated, iodination at relatively low temperatures (80—100 °C), at which this substrate has been iodinated earlier[7] with the I_2—HIO_3—H_2SO_4 system, did not give iodonitropyrazoles despite high electrophilicity of the reagent "I^+". However, at 120 °C, two isomers, namely, 5-iodo-1-methyl-4-nitropyrazole (**2**) and 3-iodo-1-methyl-4-nitropyrazole (**3**), were detected in nearly equal ratio (TLC) after 3 h (Scheme 1).

Scheme 1



1 **2** **3**

At 150 °C, the reaction time is reduced to 1.5 h, and the degree of conversion of the initial nitropyrazole **1** into iodinated products **2** and **3** increases. However, even in this case, the preparative yields of iodonitropyrazoles **2** and **3** after chromatographic purification were only 16 and 18%, respectively. An increase in temperature to 170 °C and in the substrate-to-reagent ratio from 1 : 2 to 1 : 4, as well as longer reaction time (4 h), did not result in higher yields of iodinated products.

In 1,3-dimethyl-4-nitropyrazole (**4**), position 5 is even more deactivated. Iodine could not be introduced into compound **4** under the conditions for the synthesis of iodopyrazoles **2** and **3** (despite the presence of the electron-donating methyl group in position 3 of the pyrazole ring). Only at 200 °C, did direct iodination afford, for the first time, 5-iodo-1,3-dimethyl-4-nitropyrazole (**5**) in 17% yield (Scheme 2).

Supposedly, the completion of the reaction is partly hampered by decomposition of the reagent "I^+" to iodine at high temperature, which decelerates the process. Sepa-

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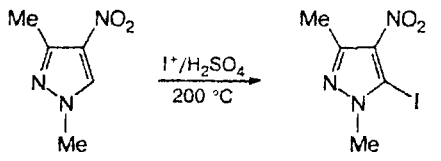
Scheme 2

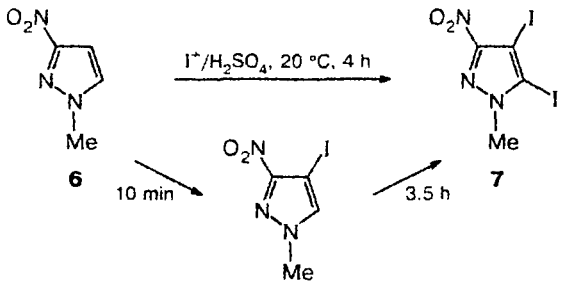


4 **5**

ration of the mixture of the reaction products and re-iodination of the unconsumed nitropyrazoles **1** and **4** increase the yields of products **2**, **3**, and **5**. The best result was obtained after chromatographic recovery and re-iodination of the initial compounds. After two cycles, the yield of iodinated compounds **2**, **3**, and **5** was ~25%.

The proposed reagent "I^+" and the I_2—HIO_3—H_2SO_4 system were compared in efficiency when iodinating 1-methyl-3-nitropyrazole (**6**). With I_2—HIO_3—H_2SO_4 in AcOH, monoiodination occurs at 80 °C over 1.5 h, while the second iodine atom can be introduced under these conditions over 40 h, the conversion of substrate **6** into 4,5-diiodo-1-methyl-3-nitropyrazole (**7**) being only 50%.[10] The reagent "I^+" monoiodinated pyrazole **6** at room temperature (20 °C) within 10 min to give 4-iodo-1-methyl-3-nitropyrazole (**8**) (Scheme 3).

Scheme 3



Gradual addition of reagent "I^+" to substrate **6** allows one to obtain purer product **8**. Iodination of iodopyrazole **8** at 20 °C for 3.5 h gives diiodo derivative **7** in 82% yield. Direct synthesis of this compound from the starting compound **6** takes place in the presence of a double amount of reagent "I^+" and takes 4 h to be completed.

Experimental

The course of the reaction was monitored and the purity of the products obtained was checked by TLC on Silufol UV-254 plates in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) with HMDS as the internal standard. IR spectra were recorded on a UR-20 instrument. GLS/MS analysis was performed on HP-5972 and HP-5890 instruments. No depression of the melting points was observed for the samples prepared upon mixing the products obtained with authentic samples.

Iodination of 1-methyl-4-nitropyrazole (1). Compound **1** (0.64 g, 5 mmol) was dissolved with stirring in 5 mL of 90% H_2SO_4 and heated to 150 °C. Reagent "I^+" (19 mL) obtained from ICl and Ag_2SO_4 according to the published procedure[8,9] (substrate-to-reagent molar ratio was 1 : 1.5 with respect to the iodine chloride used for preparing reagent "I^+") was added dropwise at the same temperature for 30 min. The reaction mixture was heated at 150 °C for an additional 1 h, cooled, and poured into 50 mL of water. The products were extracted with chloroform, and compounds **2** and **3** were isolated by column chromatography (20×1.5 cm, silica gel L 40/100, $CHCl_3$ as the eluent). **5-Iodo-1-methyl-4-nitropyrazole (2)**, yield 0.21 g (16%), m.p. 110—112 °C (from EtOH). IR, ν/cm^{-1}: 1165, 1335, 1421, 1558, 2980, 3150. ^1H NMR ($CDCl_3$), δ: 3.82 (s, 3 H, NCH_3); 7.60 (s, 1 H, H(3)). Found (%): C, 19.07; H, 1.87; I, 49.95. $C_4H_4IN_3O_2$. Calculated (%): C, 18.99; H, 1.59; I, 50.16.

3-Iodo-1-methyl-4-nitropyrazole (3), yield 0.23 g (18%), m.p. 210—212 °C (from EtOH). IR, ν/cm^{-1}: 1177, 1307, 1404, 1427, 1483, 1508, 2947, 3127. ^1H NMR (CD_2Cl_2), δ: 4.05 (s, 3 H, NCH_3); 8.20 (s, 1 H, H(5)). MS, m/z (I_{rel} (%)): 254.9 $[M + 2]^+$ (1.21), 253.8 $[M + 1]^+$ (11.18), 252.8 $[M]^+$ (100.0), 236.8 $[M - O]^+$ (2.79), 222.9 $[M - NO]^+$ (6.61). Found: m/z 252.9341 $[M]^+$. $C_4H_4IN_3O_2$. Calculated: M = 252.9348.

The unconsumed pyrazole **1** (0.36 g) was separated from products **2** and **3** and iodinated again. Chromatographic separation of the reaction products was performed as described above. The overall yields of compounds **2** and **3** after two cycles were 0.29 g (22%) and 0.32 g (24%), respectively.

5-Iodo-1,3-dimethyl-4-nitropyrazole (5) was obtained analogously at 200 °C. Product **5** was isolated by column chromatography (10×1.5 cm, SiO_2, $CHCl_3$ as the eluent). Yield 0.21 g (17%), m.p. 147—149 °C (EtOH—H_2O, 10 : 1) (*cf.* Ref. 1: m.p. 149—151 °C).

The unconsumed compound **4** was iodinated again, and the reaction product was purified by column chromatography. The overall yield of iodopyrazole **5** was 0.31 g (25%).

Iodination of 1-methyl-3-nitropyrazole (6). 4-Iodo-1-methyl-3-nitropyrazole (8). Reagent "I^+" (25 mL) was added to a solution of pyrazole **6** (0.64 g) in 5 mL of 90% H_2SO_4 at 20 °C for 30 min (substrate-to-reagent molar ratio was 1 : 2 with respect to ICl) . The reaction mixture was stirred at this temperature for an additional 10 min and poured into 50 mL of water. Products were extracted with $CHCl_3$, and the solvent was removed. Purification by column chromatography (20×1.5 cm, silica gel L 40/100, $CHCl_3$ as the eluent) gave compound **8** (0.57 g, 45%), m.p. 169—170 °C (EtOH) (*cf.* Ref. 10: m.p. 171—172 °C).

4,5-Diiodo-1-methyl-3-nitropyrazole (7). Reagent "I^+" (50 mL) was added to a solution of nitropyrazole **6** (0.64 g) in 5 mL of 90% H_2SO_4 at 20 °C over 0.5 h (substrate-to-reagent molar ratio was 1 : 4), and the reaction mixture was kept for an additional 3.5 h.

Analogously, the reaction of iodopyrazole **8** (0.63 g) with 25 mL of reagent "I^+" gave diiodopyrazole **7**. In this case, the total reaction time was 3.5 h. After the iodination was completed, the reaction mixture was poured into 50 mL of water, the product was extracted with $CHCl_3$, and the solvent was removed.

The yields of product **7** were 1.55 g (82%) (from substrate **6**) and 0.8 g (85%) (from iodopyrazole **8**), m.p. 222—224 °C (dioxane) (*cf.* Ref. 10: m.p. 226—227 °C).

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