Nitrodeiodination of Polyiodopyrazoles: a Convenient Synthesis of 4-Nitroiodopyrazoles

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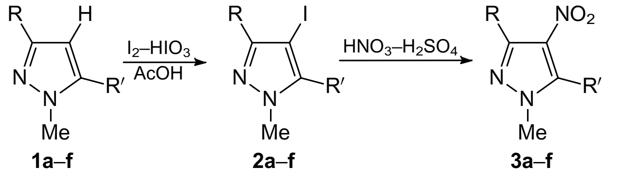
A number of 3,4-, 4,5-diiodo- and 3,4,5-triiodo-1-methylpyrazoles **2a–f** have been converted into the corresponding almost inaccessible 3-, 5-iodo- and 3,5-diiodo-1-methyl-4-nitropyrazoles **3a–f** by nitration with an HNO_3–H_2SO_4 mixture.

Intramolecular cyclization of functionally substituted vicinal aromatic acetylenic compounds has recently become increasingly important as a method for the synthesis of heterocyclic condensed systems.[1] The use of pyrazoles containing an iodine atom and functional groups (NO_2, NH_2) could provide a route to inaccessible bicyclic compounds which bear aromatic or non-aromatic and pyrazole rings. Furthermore, this could give additional information on the reasons for the different reaction pathways in the heterocyclization of functionally substituted acetylenic derivatives of benzene and pyrazole.[2–4] Only vicinal iodonitropyrazoles form such functionally substituted acetylenylpyrazoles, because on the one hand, only iodo- (but not chloro- or bromo-) derivatives of pyrazoles react with the acetylenic moiety, and on the other hand, the nitro group may be readily converted into amino and then diazo groups. The fact that the oxidative iodination of 1-methylpyrazoles using I_2–HIO_3 is an efficient method allows us to prepare some iodo-derivatives containing even electron-withdrawing substituents in the ring.[5–7] However, attempts to iodinate the pyrazole ring with a nitro, amino or acetylamino group in the 4-position proved unsuccessful.[5] A general synthetic approach to iodo-4-nitro-1-methylpyrazoles is still unknown.

In the present communication we report a convenient synthetic procedure for the preparation of the iodonitropyrazoles by means of exhaustive iodination of a pyrazole ring[†] with subsequent nitration (Scheme 1).

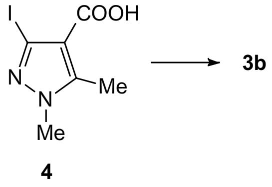


	R	R′
a	Me	I (H)
b	I (H)	Me
c	I (H)	CO_2H
d	CO_2H	I (H)
e	NO_2	I (H)
f	I (H)	I (H)

Scheme 1

We examined 4,5-diiodo-1,3- and 3,4-diiodo-1,5-dimethylpyrazoles **2a** and **2b**, respectively, in order to determine the general applicability of *ipso* nitration. The replacement of the iodine atom proceeded smoothly at 50 °C in a solution of concentrated (or fuming) nitric acid in 94% sulfuric acid in yields of 90–93%.[‡] As to the literature data, Grimmett[8] and Stepanov[9,10] reported on the nitrodebromination of 4-bromo-1-methylpyrazoles, while the nitrodeiodination of 4-iodo-1-methylpyrazoles as reported has failed.[11]

Determination of the nitro group position in **3a** was based on both the difference in the reactivity towards electrophiles of the 4- and other positions of the ring, and a comparison of the physical and spectroscopic data of **3a** with the known 5-iodo-1,3-dimethyl-4-nitropyrazole.[3] In addition, the reduction of **3a** gave 4-amino-5-iodo-1,3-dimethylpyrazole[3] rather than 5-amino-4-iodo-1,3-dimethylpyrazole.[5] Iodonitropyrazole **3b** was also obtained by nitrodecarboxylation of 3-iodo-1,5-dimethylpyrazole-4-carboxylic acid **4**,[12] which unambiguously proved its structure (Scheme 2).[§]



Scheme 2

As expected, the nitration of 3,4,5-triiodo-1-methylpyrazole **2f** requires more time. The yield of 3,5-diiodo-1-methyl-4-nitropyrazole **3f** was rather good (74%).

Taking into account the fact that 4-chloro- and 4-bromo-1-methylpyrazolecarboxylic acids failed to undergo *ipso* nitration[9,11] it is interesting to clarify the possibility of nitrodeiodination in the presence of a carboxylic group. We have found that both 3,4-diiodo- **2c** and 4,5-diiodopyrazolecarboxylic acid **2d** give iodo-4-nitropyrazolecarboxylic acids **3c,d** in 51–68% yields.

In order to establish the generality of nitrodeiodination and its applicability to the synthesis of iododinitropyrazoles, we nitrated 4,5-diiodo-1-methyl-3-nitropyrazole **2e**. It has been demonstrated that even the vicinal nitro group did not prevent *ipso* substitution of the iodine atom in the 4-position of pyrazole. Moreover, surprisingly, TLC testing of the reaction mixture after it had been heated at 50 °C for 10 min showed the absence of starting material. Work-up gave 5-iodo-3,4-dinitro-1-methylpyrazole **3e** in 94% yield. The reasons for the acceleration of nitrodeiodination in this case

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[†] In a typical experiment, 0.01 mol of **1a–f**, 2.03 g (0.008 mol) of I_2 and 0.7 g (0.004 mol) of HIO_3 in a mixture of 40 ml of AcOH, 4 ml of 30% H_2SO_4 and 5 ml of CCl_4 were heated at 80–85 °C for 2.5 h (**1a–d,f**) or 40 h (**1e**) until the iodine colour disappeared, after which the mixture was diluted with 150 ml of water, the precipitate was filtered and washed with a saturated solution of Na_2SO_3 and with water. Recrystallisation of the residue from ethanol–water gave diiodo-derivatives **2a–d,f**. 3,4,5-Triiodo-1-methylpyrazole **2e** was synthesised in a similar manner except for the fact that we used 3 equiv. of iodinating mixture, 3.05 g (0.012 mol) of I_2 and 1.06 g (0.006 mol) of HIO_3.[5]

[‡] General method for the preparation of iodo-4-nitropyrazoles **3a–f**. A mixture of fuming nitric acid (10 ml) and 94% sulfuric acid (10 ml) was added dropwise to 7.76 mmol diiodopyrazole **2a–f** in 94% sulfuric acid (30 ml). The mixture was heated at 50 °C for the period of time indicated in Table 1 (TLC), then poured into ice (70–80 g). The cold (0–5 °C) suspension was filtered out and the solid was washed with a saturated solution of Na_2SO_3 and with water. Recrystallisation of the residue gave 4-nitroiodopyrazoles **3a–f**. The results are summarised in Tables 1 and 2.

§ A mixture of fuming nitric acid (13.5 ml) and 98% sulfuric acid (13.5 ml) was added dropwise to 8 g (30 mmol) **4** in 98% sulfuric acid (4.5 ml). The mixture was heated at 70–80 °C for 1 h, then poured into ice. The cold (0–5 °C) suspension was filtered and the solid washed with water. Recrystallisation of the residue from EtOH gave 4.7 g (58.7%) of the 4-nitroiodopyrazole **3b**.

Table 1 Reaction times, yields and melting points of 4-nitroiodopyrazoles **3a**–**f**.

No	Time/min	Yield (%)	M.p./°C (crystallisation solvent)	Formula
3a	40	92.7	149–151[a] (EtOH–H_2O 10:1)	–
3b	40	90.3	134–135 ($CHCl_3$)	$C_5H_6N_3O_2I$
3c	180	51.5	194–194.5 (C_6H_6–$CHCl_3$ 1:1)	$C_5H_4N_3O_4I$
3d	180	68.4	224–225 (decomp.) (C_6H_6–$CHCl_3$ 1:1)	$C_5H_4N_3O_4I$
3e	10	93.6	77–78 (hexane–C_6H_6 3:1)	$C_4H_3N_4O_4I$
3f	90	74.2	226–226.5 (decomp.) (EtOH)	$C_4H_3N_3O_2I_2$

[a] Ref. 3: 150–151 °C (tetrachloromethane).

as well as for an extension of the synthesis by the above route are currently being investigated.

In all cases studied only one product was isolated. This presents an excellent route to iodo-4-nitropyrazoles, which are useful synthons.

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Table 2 Analytical and characteristic IR spectral data.

No	Calc./Found (%) C	Calc./Found (%) H	Calc./Found (%) I	IR ($CHCl_3$): ν_{max}/cm^{-1}
3b	$\frac{20.47}{20.49}$	$\frac{2.33}{2.26}$	$\frac{47.46}{47.52}$	1332, 1555
3c	$\frac{20.22}{20.26}$	$\frac{1.36}{1.31}$	$\frac{42.73}{42.71}$	1310, 1330, 1410, 1540, 1760, 3540
3d	$\frac{20.22}{20.30}$	$\frac{1.36}{1.23}$	$\frac{42.73}{42.70}$	1320, 1330, 1405, 1540, 1770, 3530
3e	$\frac{16.12}{16.16}$	$\frac{1.01}{1.09}$	$\frac{42.58}{42.60}$	1330, 1360, 1560, 1570
3f	$\frac{12.68}{12.84}$	$\frac{0.80}{0.73}$	$\frac{66.99}{66.87}$	1330, 1500

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