# Nitrodeiodination of 4-iodo-1-methylpyrazoles

*E. V. Tret'yakov and S. F. Vasilevsky**

*Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 3 ul. Institutckaya, 630090 Novosibirsk, Russian Federation. Fax: 007 (383 2) 35 2350. E-mail: vasilev@kinetics.nsk.su*

4-Iodo-1-methylpyrazoles react with a nitrating mixture at 55 °C to give the corresponding 4-nitro-1-methylpyrazoles. The qualitative dependence of the nitrodeiodination rate on the structure of the heterocycles and the reaction conditions was considered.

**Key words:** nitrodehalogenation, iodo-*N*-alkylpyrazoles, nitro-*N*-alkylpyrazoles, oxidative iodination.

According to the literature data, 4-nitro-[1–6] or 3- and/or 5-nitrosubstituted pyrazoles[4,5] can dominate among the products of the nitration of 4-halopyrazoles, depending on the structure of the 4-bromo- and 4-chloroderivatives and the reaction conditions (temperature, duration, and the content of water in the nitrating mixture). In certain cases, the formation of both products occurs in parallel.[4,6] It has also been reported that 4-iodopyrazolecarboxylic acids undergo oxidative destruction under the conditions of nitration.[7]

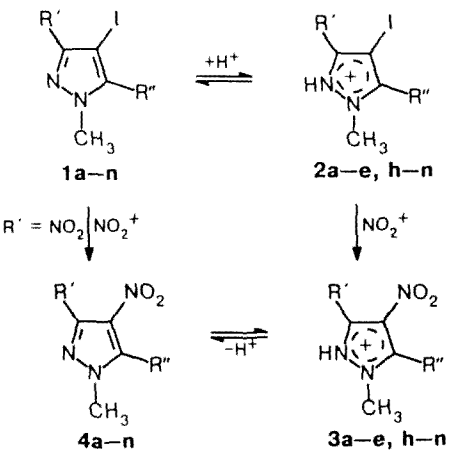
In the preliminary publication[8] we reported the successful nitrodeiodination of polyiodopyrazoles, thus proposing a convenient method for the synthesis of not easily accessible 3- and 5-iodo-4-nitropyrazoles. In that article we noted that an $NO_2$ group, which strongly hampers electrophilic substitution, accelerates the nitrolysis of 4,5-diiodo-1-methyl-3-nitropyrazole (**1g**). In the literature one can find cases where nitration of the pyrazole ring was accelerated by introducing a nitro group, *e.g.*, into the *N*-phenyl substituent. It was shown that this effect was due to the fact that the substrate was nitrated with a mixture of nitric and sulfuric acids in the form of a free base and not in the protonated form (through intermediate compounds **2** and **3**).[9,10]

To determine the causes of this acceleration in our case and to find out whether the nitrodeiodination is of a similar character, we carried out a systematic study of the *ipso*-nitration of a series of mono-, di-, and triiodopyrazoles, including derivatives with donor and acceptor substituents (Scheme 1, the R′ and R″ are indicated in Table 1).

The presence of substrates with both types of substituents appears to be important owing to the significant influence of their nature and position in the ring on the reaction pathway in the series of 4-bromo- and 4-chloropyrazoles.[1,2,4,7]

We assumed that the failure to nitrolyze 4-iodo-1-methylpyrazole-3- (**1d**) and 4-iodo-1-methylpyrazole-5-carboxylic acid (**1e**) (their destruction) described in

**Scheme 1**




Ref. 7 was due to the drastic conditions in which the reaction was carried out. That is why we first optimized the nitrodeiodination conditions: 20% oleum was replaced by 94% $H_2SO_4$, and the reaction temperature was decreased. This allowed us to conduct the nitrolysis of a large number of 4-iodopyrazoles in 54—94% yields.

A qualitative comparison of the influence of substituents on the reactivity of nitrating agents was carried out by correlating the nitrolysis duration (under standard conditions) of 4-iodo-1-methylpyrazole (**1a**) with the corresponding derivatives of 4-iodopyrazole having both donor and acceptor substituents at position 3 and/or 5 of the ring.

The end of the reaction was determined by the disappearance of the starting iodopyrazoles (TLC). As would be expected, the introduction of a donor substituent ($CH_3$) into position 3 (**1c**) or position 5 (**1d**) led to an increase in the rate of *ipso*-nitration over that of unsubstituted 4-iodopyrazole **1a**. The reaction durations were 35, 20, and 45 min, respectively. In contrast, the

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 2722—2725, November, 1996.

**Table 1.** Reaction duration (τ, at 55 °C), constants, and yields of 1-methyl-4-nitropyrazoles **4a—n**

| Compound | R′ | R″ | τ/min | Yield[a] (%) | M.p./°C (solvent)[b] |
|---|---|---|---|---|---|
| **4a** | H | H | 45 | 82.7 | 90—92 (H—B)[11] |
| **4b** | $CH_3$ | H | 35 | 74.6 | 74—75 (H—B)[12] |
| **4c** | H | $CH_3$ | 20 | 70.9 | 111—113 (H—B)[12] |
| **4d** | COOH | H | 360 | 58.3 | 173—174 (Ch)[12] |
| **4e** | H | COOH | 780 | 54.1 | 163—164 (Ch)[2] |
| **4f** | $NO_2$ | H | 20[c] | 88.4 | 20—25 (H)[11] |
| **4g** | $NO_2$ | I | 10[c] | 93.6 | 77—78 (H—B)[8] |
| **4h**[d] | I | H | 10 | 87.3 | 148—149 (B—Ch) |
| **4i** | I | $CH_3$ | 5 | 90.3 | 134—135 (Ch)[8] |
| **4j** | $CH_3$ | I | 5 | 93.7 | 149—151 (Ch)[13] |
| **4k** | I | I | 3 | 89.4 | 226—226.5 (A)[8] |
| **4l** | COOH | I | 35 | 71.2 | 224—225 (B—Ch)[8] |
| **4m** | I | COOH | 180 | 61.8 | 194—194.5 (B—Ch)[8] |
| **4n**[e] | $CH_3$ | COOH | 60 | 61.0 | 146—147 (Ch) |

[a] One product forms in all cases. The decrease in the yield of 4-nitropyrazolecarboxylic acids is due to their high solubility in water.

[b] A — alcohol, B — benzene, Ch — chloroform, and H — hexane.

[c] Nitrolysis was carried out at 30 °C.

[d] Found (%): C, 19.07; H, 1.87; I, 49.95. $C_4H_4N_3O_2I$. Calculated (%): C, 18.99; H, 1.59; I, 50.16. IR ($CHCl_3$), ν/cm$^{-1}$: 1335, 1558 ($NO_2$). $^1$H NMR ($CDCl_3$), δ: 3.82 (s, 3 H, NCH$_3$), 7.6 (s, 1 H, 5-H).

[e] Found (%): C, 38.92; H, 3.81; N, 22.70. $C_6H_7N_3O_4$. Calculated (%): C, 38.96; H, 3.75; N, 22.78. $^1$H NMR ($CDCl_3$), δ: 2.65 (s, 3 H, 3-$CH_3$), 3.95 (s, 3 H, $NCH_3$), 7.6 (br. s, 1 H, COOH).

presence of a COOH group significantly slowed down nitrodeiodination. Thus, the reaction duration was 360 min for 3-carboxy derivative **1d** and 780 min for isomeric 5-carboxypyrazole **1e**. In contrast to the data of Ref. 7, we were able to carry out the nitrolysis of isomeric 4-iodopyrazolecarboxylic acids to obtain 4-nitropyrazolecarboxylic acids **4d** (58%) and **4e** (54%). As might be expected, the introduction of a donor substituent ($CH_3$) leads to an increase in the nitrodeiodination rate, and the duration of reaction **1n** was 60 min.

As can be seen from Table 1, activating substituents at position 5 of the ring accelerate nitrolysis to a greater extent and moderately deactivating substituents decelerate nitrolysis to a greater extent than similar groups located at position 3 of pyrazole.

The presence of a strongly deactivating nitro group at position 3 of the ring sharply increases the reaction rate. Since the reactivity of 4-iodo-1-methyl-3-nitropyrazole (**1f**) is high, the nitrolysis was carried out at a lower temperature (30 °C), and the reaction duration was 20 min. It is probable that the high rate of the nitrolysis of iodide **1f** is due to the significant decrease in the basicity of the substrate produced by the strongly deactivating nitro group, which causes the substrate to enter the reaction predominantly in the form of a free base, and not in the protonated form as it does for methyl and carboxy derivatives of pyrazole. Both possibilities, as applied to the nitration of 4-halopyrazoles, are discussed in Ref. 4.

This supposition was additionnally confirmed by a direct experiment, a comparison between the rates of the nitration of 4-iodo-1,3-dimethyl- (**1b**) and 4-iodo-3-nitro-1-methylpyrazole (**1f**) under conditions where the substrates react in the basic form.[14] The nitration was carried out in a mixture of acetic anhydride and nitric acid at 25 °C. The nitrodeiodination of compound **1b** was completed after 10 min, whereas, in the case of iodide **1f**, no traces of its nitrolysis product were yet detected after 24 h of exposure, which is in full agreement with the influence of donor and acceptor substituents on the rate of electrophilic substitution.

Thus, one can believe that there is a great degree of probability that the anomalous acceleration of the nitrolysis of iodide **1f**, affected by the nitro group at position 3 of the ring, is related to the fact that a higher concentration of the substrate is in the form of a free base than in the case of methyl and carboxy derivatives, which predominantly react in the form of a conjugated acid.

A comparison of the rates of the nitrolysis of 3-nitroiodide **1f** (20 min) and 3-nitrodiiodide **1g** (10 min) (though obtained under conditions that somewhat differed[8]) suggested a certain acceleration of the reaction due to the additional iodine atom in the pyrazole molecule.

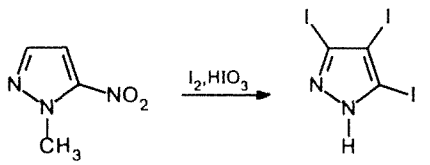
This induced us to compare the rates of the nitrolysis of compounds **1f** and **1g** under standard optimized conditions as well as the reactivity of monoiodide **1a** with that of vicinal diiodides both in the presence of donor and acceptor substituents and in their absence.

It was determined that the introduction of an additional iodine atom into position 3 or 5 of the pyrazole ring caused a significant acceleration of the reaction.

Thus, the completion of the nitrodehalogenation of 4-iodopyrazole **1a**, 3,4-diiododerivative **1h**, and 3,4,5-triiodide **1k** takes 45, 10, and only 3 min, respectively. These regularities are also valid for vicinal 3,4- and 4,5-diiodopyrazoles with both donor and acceptor type substituents. As would be expected, the former additionally accelerate nitrolysis, while the latter decelerate it, and the influence of groups at position 5 is somewhat greater than that of the same groups at position 3 (as in the case of 4-monoiodides).

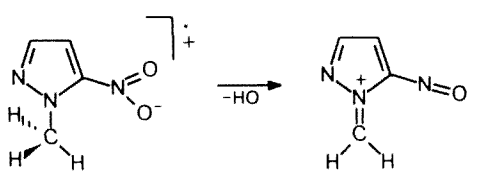
It is probable that the acceleration of the reaction by the neighboring iodine atoms at positions 3 and 5 of the ring is due to the fact that the bulky substituents favor the displacement of the iodide cation from position 4 of the ring in the intermediate σ-complex.[15]

Unfortunately, we failed to synthesize 3,4-diiodo-1-methyl-5-nitropyrazole because an unexpected product, 3,4,5-triiodopyrazole **6**, was obtained in 60% yield under the conditions of the oxidative iodination of 1-methyl-5-nitropyrazole **5** ($I_2$—$HIO_3$, $CH_3COOH$, 80 °C, 30% $H_2SO_4$).




**5** **6**

This is the first case of the elimination of an *N*-methyl group under these reaction conditions from a number of known examples of the oxidative iodination of different *N*-methylpyrazoles.[16,17] One can assume that the elimination of the methyl group occurs *via* its oxidation to a carboxylic group followed by decarboxylation, which, in turn, is due to the steric proximity of the $NO_2$ and $CH_3$ groups. The oxygen atom is introduced at the C—H bond, then the intermediate *N*-hydroxymethyl-5-nitrosopyrazole is oxidized to the *N*-carboxy derivative by $HIO_3$ with subsequent or simultaneous decarboxylation and exhaustive iodination, including the *ipso*-substitution of the $NO_2$ group. The ease of the cleavage of the N—O and C—H bonds in the methyl group of compound **5** (according to the data of mass spectrometry) indirectly confirms the possibility of this scheme.[18]

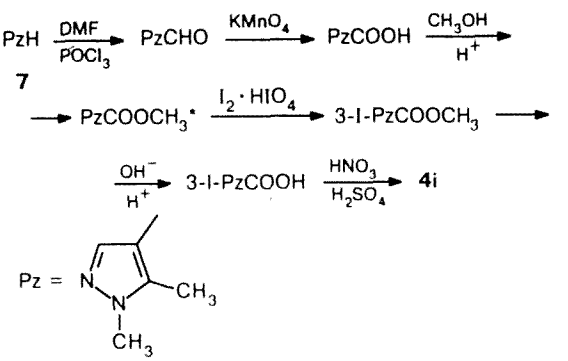



The results obtained by us and the literature data allow one to draw some generalizations concerning the behavior of 4-halopyrazoles during nitration. The nitrolysis of 4-chloropyrazoles does not occur in a mixture of 99% $HNO_3$—20% oleum (1 : 5).[7] The interaction of the nitrating mixture with 4-bromopyrazoles results either in products of nitration at free positions 3 and/or 5 of the ring or in 4-nitropyrazoles, depending on the reaction conditions and the structure of the substrate. *ipso*-Nitration does not occur at all in the case of 4-bromopyrazoles with acceptor carboxylic groups, but in certain cases, nitrodecarboxylation products form.[7] The nitration of the simplest 4-bromo-*N*-alkylpyrazoles is accompanied by some complications,[4,6] and a mixture of nitration and *ipso*-nitration products forms. An increase in the relative amount of the latter involves the presence of water (in order to facilitate the elimination of the $Br^+$ cation).[4]

A particular feature of the nitrodeiodination of 4-iodo-1-methylpyrazoles found by us is that this reaction knows no limits (at least, in the range of the starting compounds selected by us) and proceeds under mild conditions, in high yields, and selectively (there was no case in which we found nitrodeprotonation and nitrodecarboxylation products).

It is worthy of special note that the technique of the *ipso*-nitration of 4-iodopyrazoles elaborated by us is especially important for the synthesis of not easily accessible 3- and/or 5-iodo-4-nitropyrazoles. The advantages of this technique can be illustrated by comparing two ways of synthesizing 3-iodo-1,5-dimethyl-4-nitropyrazole (**4i**) from the same initial compound, 1,5-dimethylpyrazole (**7**). Previously, compound **4i** was obtained by us in six stages in a total yield of 10.8% (Scheme 2).[19]

**Scheme 2**




Using the technique proposed by us in this paper, the synthesis of compound **4i** was carried out in two stages, exhaustive iodination of pyrazole **7** followed by nitrodeiodination. The yield of the target product (with respect to compound **7**) amounts to 80.8%.

* The direct iodination of the acid PzCOOH is not possible owing to decarboxylation followed by the formation of PzI.

## Experimental

$^1H$ NMR (in $CDCl_3$) and $^{13}C$ NMR (in $(CD_3)_2CO$) spectra were recorded on a Jeol FX90Q spectrometer at 25 °C. IR spectra were recorded on a UR-20 instrument.

**4-Iodo-1-methylpyrazole (1a).** 1-Methylpyrazole (0.82 g, 0.01 mol) was iodinated with $I_2$ and $HIO_3$ according to a procedure described earlier.[16] The reaction mixture was then poured into ice, the mineral acid was neutralized with $Na_2CO_3$, and the precipitate was filtered off and washed with water. 1.86 g (89.4%) of compound **1a** was obtained, m.p. 63—64 °C (from hexane).[20]

Substituted *N*-methylpyrazoles were synthesized analogously. Iodo-, diiodo-, and triiodopyrazoles **1a—n** were obtained in 87—95% yields.[16]

**Iodination of 1-methyl-5-nitropyrazole (5).**[15] Nitropyrazole **5** (1.5 g, 0.012 mol),[16] $I_2$ (3.81 g, 0.015 mol), and $HIO_3$ (3.17 g, 0.018 mol) in a mixture of 20 mL of glacial AcOH, 0.3 mL of $H_2SO_4$, 1.1 mL of water, and 3 mL of $CCl_4$ were refluxed at 80 °C for 30 h until the iodine color disappeared. Isolation performed according to the above procedure yielded 3,4,5-triiodopyrazole (**6**) (3.21 g, 60.0%), m.p. 225—226 °C (hexane—$CHCl_3$).[21] $^{13}C$ NMR, δ: 93(C-4); 150(C-3); 179(C-5).

**Preparative nitration in sulfuric acid.** A mixture of 2 mL of $HNO_3$ (*d* 1.54) and 2 mL of $H_2SO_4$ was added to a solution of 4-iodo-1-methylpyrazole (**1a**) (420 mg, 20 mmol) in 16 mL of 96% $H_2SO_4$ at 55 °C and the resulting mixture was stirred at the same temperature. After the reaction was completed (45 min, TLC), the mixture was poured out into crushed ice, and the precipitate that formed was filtered off, dried in the air, and recrystallized from a hexane-benzene mixture. 1-Methyl-4-nitropyrazole (**4a**) was obtained (210 mg, yield 82,7%), m.p. 90—92 °C.[11]

The nitrolysis of iodopyrazoles **1b—n** was carried out analogously (see Table 1).

**Preparative nitration in acetic anhydride.** A mixture of 2 mL of $HNO_3$ and 20 mL of $Ac_2O$ was added to a solution of 4-iodo-1,3-dimethylpyrazole (**1b**) (440 mg, 20 mmol) in 5 mL of $Ac_2O$ and stirred at 25 °C. After the reaction was completed (15 min, TLC), the reaction mixture was poured out into 100 mL of water and extracted with $CHCl_3$ (3×30 mL). The extract was filtered through an $Al_2O_3$ layer, and the solvent was removed. The residue was recrystallized from a hexane-benzene mixture. The yield of 1,3-dimethyl-4-nitropyrazole (**4b**) was 220 mg (78%), m.p. 76—77 °C.[12]

An attempt at the nitrolysis of 4-iodo-1-methyl-3-nitropyrazole (**1f**) was carried out analogously. The starting compound **1f** (440 mg, 87%) was isolated after 160 h, m.p. 20—25 °C (from hexane).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 95-03-08928a).

## References

1. M. A. Andreeva, M. I. Bolotov, Sh. G. Isaev, R. Ya. Mushii, V. P. Perevalov, V. I. Seraya, and B. I. Stepanov, *Zh. Obshch. Khim.*, 1980, **50**, 2116 [*J. Gen. Chem. USSR*, 1980, **50** (Engl. Transl.)].
2. V. P. Perevalov, M. A. Andreeva, L. I. Baryshnenkova, Yu. A. Manaev, G. S. Yamburg, B. I. Stepanov, and V. A. Dubrovskaya, *Khim. Geterosikl. Soedin.*, 1983, 1676 [*Chem. Heterocycl. Compd.*, 1983, **19** (Engl. Transl.)].
3. R. H üttel and M. R. Bü chele, *Chem. Ber.*, 1955, **88**, 1586.
4. K. C. Clang, M. R. Grimmett, D. D. Ward, *Austral. J. Chem.*, 1979, **32**, 1727.
5. M. Coburn, *J. Het. Chem.*, 1971, **8**, 153.
6. M. A. Andreeva, M. I. Bolotov, Sh. G. Isaev, V. P. Perevalov, and B. I. Stepanov, *Khim. Geterosikl. Soedin.*, 1980, 1561 [*Chem. Heterocycl. Compd.*, 1980, **16** (Engl. Transl.)].
7. Yu. A. Manaev, M. A. Andreeva, V. P. Perevalov, B. I. Stepanov, V. A. Dubrovskaya, and V. I. Seraya, *Zh. Obshch. Khim.*, 1982, **52**, 2592 [*J. Gen. Chem. USSR*, 1982, **52** (Engl. Transl.)].
8. E. V. Tretyakov and S. F. Vasilevsky, *Mendeleev Commun.*, 1995, 233.
9. A. G. Burton, A.R. Katritzky, M. Konya, and H. O. Tarhan, *J. Chem. Soc., Perkin Trans. 2*, 1974, 389.
10. A. R. Katritzky, B. Terem, E. V. Scriven, S. Clementi, and H. O. Tarhan, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1600.
11. M. R. Grimmett and K. H. R. Lim, *Aust. J. Chem.*, 1978, **31**, 689.
12. V. Papesch and R. M. Dodson, *J. Org. Chem.*, 1965, **30**, 199.
13. S. F. Vasilevsky, T. V. Anisimova, and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 688 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1983, **32**, 626 (Engl. Transl.)].
14. M. R. Grimmett, S. R. Hartshorn, K. Schofield, and J. B. Weston, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1654.
15. C. L. Perrin, *J. Org. Chem.*, 1971, **36**, 420.
16. S. F. Vasilevsky and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1980, 1071 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1980, **29**, 778 (Engl. Transl.)].
17. S. F. Vasilevsky, A. I. Belov, and M. S. Shvartsberg, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1985, 100 (in Russian).
18. J. H. Boer, in *Organic Nitro Chemistry. Nitroazoles. The C-Nitro Derivatives of Five-membered N- and N,O-Heterocycles*, VCH, Deerfield Beach, 1986, 186.
19. S. F. Vasilevsky, D. Sc. (Chem.) Thesis, Institute of Chemical Kinetics and Burning, Siberian Branch of RAS, Novosibirsk, 1986, pp. 66 (in Russian).
20. R. Hüttel, O. Schäfer, and P. Jochum, *Lieb. Ann. Chem.*, 1955, **593**, 200.
21. D. Giles, E. W. Parnell, and I. D. Rerwick, *J. Chem. Soc. (C)*, 1966, 1179.

*Received April 23, 1996;*
*in revised form June 3, 1996*