Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 1992, **2**(**3**), 120–121

Mendeleev
Communications

A New Regiospecific Synthesis of Isomeric 3(4)-Aryl-4(3)-nitro-1,2,5-oxadiazole 2-Oxides

Vladimir G. Dubonos, Igor V. Ovchinnikov, Nina N. Makhova* and Lenor I. Khmel'nitskii

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation. Fax: +7 095 135 5328

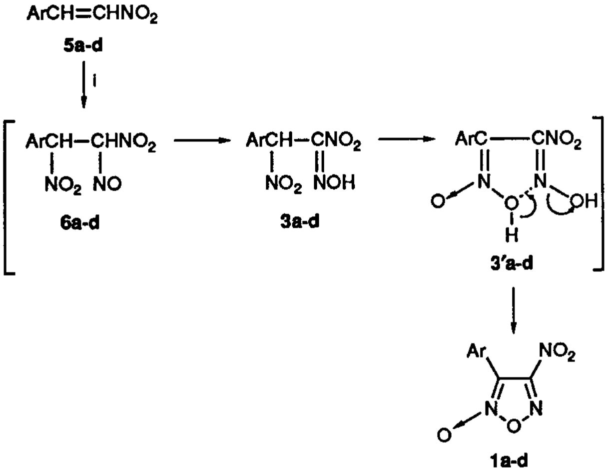
New general, regiospecific methods of synthesis of isomeric 3(4)-aryl-4(3)-nitro-1,2,5-oxadiazole 2-oxides are suggested based on the cyclization of nitro-substituted α-nitrooximes; these methods involve the action of nitrosylating reagents on β-nitrostyrenes and 2-aryl-2-oximino-1,1-dinitroethanes, respectively.

A limited number of examples of the synthesis of 3(4)-aryl-4(3)-substituted nitrofuroxans (1,2,5-oxadiazole 2-oxides) **1** and **2** is known,[1–5] and the methods reported are not of a general nature. The 3-nitro-derivatives **2** in particular are difficult to obtain. Here we suggest new regiospecific methods for synthesis of **1** and **2**. An assumption about the possibility of furoxan ring closure in Ar- and NO_2-substituted α-nitrooximes forms the basis of these methods. The synthesis of arylalkyl-1,2,5-oxadiazole 2-oxides using the dehydration of arylalkyl-substituted α-nitrooximes has been reported.[6–9] The position of the NO_2-group in the starting α-nitrooxime determined the regiospecificity of this cyclization reaction: the oxygen atom in the NO moiety in the product always appeared on the same side as the substituent that was adjacent to the NO_2-group in the starting α-nitrooxime. Stabilization of the oxime fragment (in the absence of the NO-form) and conversion of the NO_2-group into the *aci*-nitro form were found to be the important conditions for the dehydration process. It seemed likely that for α-nitrooxime **3** (in this case it has been synthesized) these conditions could be realized, but that the conversion of the NO_2-group into the *aci*-nitro form could be hindered.

An addition reaction of N_2O_3 to the C=C bond of β-nitrostyrenes **5** was used to obtain **3** and at once 3-aryl-4-nitro-1,2,5-oxadiazole 2-oxides **1** were obtained. Analogously to refs. 7–10 it might be supposed that the process occurs *via* the pseudonitrosite **6**, α-nitrooxime **3** and its *aci*-nitro form according to Scheme 1.†

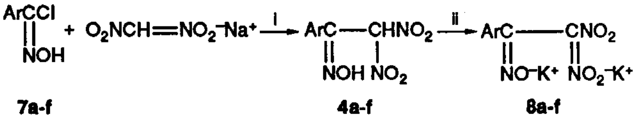
α-Nitrooximes **4** were obtained by the interaction of hydroxamic acid derivatives **7** and dinitromethane sodium salt (*cf.* ref. 11) as dipotassium salts **8** (Scheme 2). Compound **4a** had been reported previously as a monopotassium salt.[11]†

The possibility of achieving the *aci*-nitro form of α-nitrooximes **4** and its ability to cyclize to form the furoxan ring were investigated in two ways using **8e**: by adding dry HCl in diethyl ether to the reaction mixture and by treatment with concentrated H_2SO_4 with heating. As expected from the work in ref. 12 the transformation of *aci*-nitro form obtained from **8e** into the nitro derivative **4e** appeared to be more preferable than the cyclization process leading to the formation of **2e**, which was obtained in low yields in both cases (Scheme 3).†



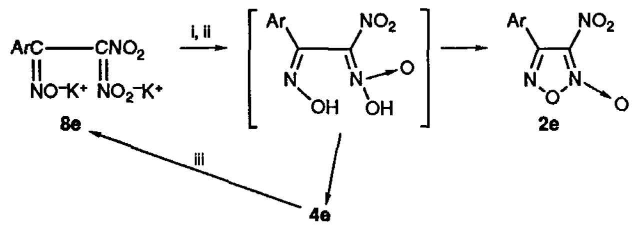
a; Ar = Ph
b; Ar = *o*-$NO_2C_6H_4$
c; Ar = *m*-$NO_2C_6H_4$
d; Ar = *p*-$NO_2C_6H_4$
e; Ar = 3,5-$(NO_2)_2$-4-$MeOC_6H_2$
f; Ar = *p*-BrC_6H_4

Scheme 1 *Reagents and conditions*: i, $NaNO_2$ (10–15 moles), AcOH, 20–25°C, 72 h; **1a** 50%, **1b** 21%, **1c** 26%, **1d** 22%

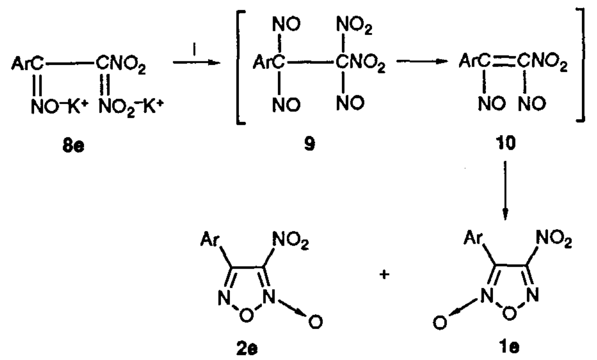


Scheme 2 *Reagents and conditions*: i, *N*,*N*-dimethylformamide (DMF), −10→0°C, 15 h; 20°C, 3 h; ii, AcOK, MeOH, 10°C, 82–87%

Mendeleev Commun., 1992, 2(3), 120–121



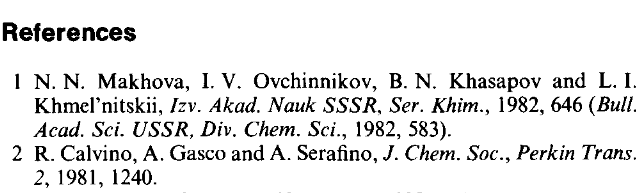
Scheme 3 *Reagents and conditions*: i, HCl, diethyl ether, 20°C (**2e** 4%); ii, H_2SO_4, 0°C, 0.5 h, 60–70°C, 0.5 h (**2e** 14%); iii, AcOK, MeOH, 10°C (**4e**, **8e** 90 and 80%, respectively)



Scheme 4 *Reagents and conditions*: i, N_2O_4 (5 moles), $CHCl_3$, 10°C (**1e** + **2e** 26%)

The cyclization of **4** to form 4-aryl-3-nitro-1,2,5-oxadiazole 2-oxides **2** was successfully carried out by the interaction of nitrosylating reagents and **8**. A mixture of **1e** and **2e** was obtained by the interaction of **8e** and N_2O_4, and on treatment of **8e** with $NaNO_2$ in AcOH only compound **2e** was isolated. Probably, both anionic centres are nitrosylated on treatment of **8e** with N_2O_4, forming the intermediate **9**. The latter is transformed into cyclic compounds **1e** and **2e** with equal probability after elimination of nitrogen oxides *via* intermediate **10**. This result indicates that the process may be free radical in character (Scheme 4).†

The regiospecificity of the cyclization of compound **8**, according to Scheme 5, allows us to propose that in this case the first step of this process is nitrosylation of the dinitromethyl anion moiety of compound **8**, and the oxygen atom of the oxime group in the intermediate **11** attacks the nitrogen atom of the nitroso group. The fact that the yields of compounds **2** increased from 50–55% to 68–80% when AcOK was added to the reaction mixture before carrying out the nitrosylation procedure supports this scheme. According to pK_a data for **4e** (determined by UV spectroscopy) and AcOH (pK_a of the dinitromethyl fragment 2.25, of the oxime fragment 4.45 and of AcOH 7.75), the quantity of the anionic form **11** in the reaction mixture must be increased as a result of such action. The participation of the oxime moiety in the ring closure was confirmed by the synthesis of ^{15}N-labelled compound **2′f** from the corresponding **7′f**. ^{15}N and ^{13}C NMR spectroscopy showed that the label was completely transferred from the starting compound to **2′f**. All compounds **2** were easily isomerized to **1** on heating in toluene (Scheme 5).†



Scheme 5 *Reagents and conditions*: i, AcOK, $NaNO_2$, AcOH, 15–20°C, (**2a** 74%, **2b** 78%, **2c** 79%, **2d** 80%, **2e** 68%, **2f** 56%, **2′f** 50%); ii, toluene, reflux, 3 h (**1** 78–85%)

References

1 N. N. Makhova, I. V. Ovchinnikov, B. N. Khasapov and L. I. Khmel'nitskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 646 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, 583).

2 R. Calvino, A. Gasco and A. Serafino, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1240.

3 H. Wieland, *Liebigs Ann. Chem.*, 1903, **328**, 154.

4 O. A. Rakitin, V. A. Ogurtsov, T. I. Godovikova and L. I. Khmel'nitskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 1620 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, 1469).

5 A. Kunai, T. Doi, T. Nagaoka, H. Yagi and K. Sasaki, *Bull. Soc. Chem. Jpn*, 1990, **63**, 1843.

6 A. Agneli, *Gazz. Chim. Ital.*, 1892, **22**, 325.

7 H. Wieland, *Liebigs Ann. Chem.*, 1903, **329**, 225.

8 H. Schechter, *Rec. Chem. Progr.*, 1964, **25**, 55.

9 L. I. Khmel'nitskii, S. S. Novikov and T. I. Godovikova, *Khimiya Furoksanov. Stroenie i sintez* (Chemistry of Furoxans. Structure and Synthesis), Nauka, Moscow, 1981 (in Russian).

10 H. Becker, *Einführung in die Elektronentheorie Organisch-chemischer Reaktionen*, VEB Deutscher Verlag der Wissenschaften, Berlin, 1974 (in German).

11 S. A. Shevelev, V. I. Erashko and A. A. Fainzilberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1976, 2725 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1976, 2535).

12 G. I. Oleneva, A. I. Ivanov, V. A. Shlyapochnikov and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1972, 638 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1972, 601).

Received: *Moscow, 27th January 1992*
Cambridge, 26th March 1992; *Com. 2/00549B*

---

† All new compounds synthesized gave satisfactory elemental analyses and were characterized by ^{1}H NMR, ^{13}C NMR, ^{14}N NMR, ^{15}N NMR and mass spectra.

1b: m.p. 91–92°C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.96 (m, 3H, Ar), 8.35 (m, 1H, Ar); ^{13}C NMR [$(CD_3)_2SO$] δ 109.24 (C^3 of furoxan ring), 158.20 (C^4 of furoxan ring); MS *m/z* (relative intensity %) M^+ absent, 176 (15), 148 (44), 134 (30), 102 (100).

1c: m.p. 92–93°C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.35 (m, 3H, Ar), 8.63 (m, 1H, Ar); MS *m/z* 252 (M^+, 3%), 222 (50), 176 (100), 148 (60), 130 (26), 118 (4), 102 (90).

1d: m.p. 101–102°C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.98, 8.36 (H, Ar, $^{3}J_{AB}$ 9.6 Hz); MS *m/z* M^+ absent, 194 (28%), 176 (3), 148 (60), 118 (70), 102 (100).

1e: m.p. 126–127°C; ^{1}H NMR [$(CD_3)_2SO$] δ 4.1 (s, 3H, MeO), 8.73 (s, 2H, Ar); MS *m/z* 327 (M^+, 9%), 311 (2), 297 (8), 281 (20), 267 (3), 251 (100), 223 (88).

1f: m.p. 56.3–57.5°C; ^{1}H NMR ($CDCl_3$) δ 7.72 (s).

1′f: m.p. 56.0–57.5°C; ^{13}C NMR [$CDCl_3$, $^{n}J(^{13}C-^{15}N)/Hz$] δ 108.7 (ring C^3 ^{1}J 24.5), 157.7 (ring C^4), 118.4 (i-C, Ar, ^{2}J 1.0), 130.3 (*o*-C, Ar, ^{3}J 1.5), 132.6 (*m*-C, Ar), 126.7 (*p*-C, Ar, ^{5}J 0.5); ^{15}N NMR ($CDCl_3$) ($MeNO_2$) δ −16.2 (N^2); ^{14}N NMR ($CDCl_3$) ($MeNO_2$) δ −35.4 (NO_2).

2b: m.p. 127–128°C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.0 (m, 3H, Ar), 8.45 (m, 1H, Ar); ^{13}C NMR [$(CD_3)_2SO$] δ 119.58 (i-C, Ar), 146.9 (CNO_2, Ar), 125.23, 133.18, 133.40, 135.24 (Ar), 127.20 (ring C^3), 150.09 (ring C^4); MS *m/z* 252 (M^+, 13%), 222 (68), 206 (100), 160 (15), 130 (17), 106 (34).

2c: m.p. 117–118°C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.35 (m, 3H, Ar), 8.50 (s, 1H, Ar); MS *m/z* 252 (M^+, 24%), 222 (63), 176 (90), 148 (59), 130 (36), 102 (100).

2d: m.p. 132–133°C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.98, 8.36 (Ar, H, $^{3}J_{AB}$ 9.6 Hz); ^{13}C NMR [$(CD_3)_2SO$] δ 130.91 (i-C, Ar), 123.87 (*m*-C, Ar), 131.33 (*o*-C, Ar), 149.55 (*p*-C, Ar), 128.17 (ring C^3), 151.49 (ring C^4); MS *m/z* 252 (M^+, 33%), 236 (5), 222 (100), 206 (14), 176 (100), 160 (12).

2e: m.p. 149–150°C; ^{1}H NMR [$(CD_3)_2SO$] δ 4.08 (s, 3H, Me), 8.70 (s, 2H, Ar); ^{13}C NMR [$(CD_3)_2SO$] δ 64.75 (MeO), 120.82 (i-C, Ar), 130.99 (*o*-C, Ar), 144.53 (*m*-C, Ar), 149.36 (*p*-C, Ar), 127.8 (ring C^3), 140.36 (ring C^4); MS *m/z* 327 (M^+, 16%), 311 (3), 297 (10), 281 (31), 267 (3), 251 (100), 222 (21).

2f:m.p. 80.0–81.3°C; ^{1}H NMR (CD Cl_3) ι 7.72(s).

2′f: m.p. 80.5–81.3°C;^{13}C NMR [$CDCl_3$, ^{n}J ($^{13}C-^{15}N$)/Hz] δ 126.1 (ring C^3), 150.5 (ring C^4 ^{1}J 2.6), 122.4 (C^i, Ar, ^{2}J 6.2), 130.5 (*o*-C, Ar, ^{3}J 2.0), 132.5 (*m*-C, Ar), 127.3 (*p*-C, Ar, ^{5}J 0.6); ^{15}N NMR ($CDCl_3$) ($MeNO_2$) δ −12.0 (N^5); ^{14}N NMR ($CDCl_3$) ($MeNO_2$) δ −39.7 (NO_2).

8a–f: IR ν/cm^{-1} 1300–1380 (NO_2 s), 1500–1550 (NO_2 as).