Reactions of *N*-methoxydiazen-*N'*-oxidoacetic acid derivatives with electrophilic reagents

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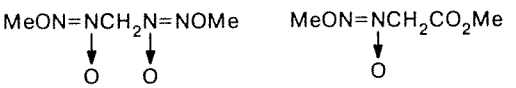
Bromination, methylation, and nitration of *N*-methoxydiazen-*N'*-oxidoacetic acid derivatives were investigated. The results of the reactions depended significantly on both the type of the starting compound and the electrophilic reagent.

Key words: *N*-methoxydiazen-*N'*-oxidoacetic acid, electrophilic reagents, nitration, bromination, methylation.

N-Alkyl-*N'*-alkoxydiazen-*N*-oxides (AADO) have been studied insufficiently although they are known for a long time.[1] The AADO containing α-protons in the *N*-substituent can undergo deuterium exchange under the action of bases, which makes possible the synthesis of different α-derivatives. Earlier it has been shown that methylenebis(*N'*-methoxydiazen-*N*-oxide) (**1**) and methyl *N*-methoxydiazen-*N'*-oxidoacetate (**2**) are readily methylated[2] on treatment with NaH followed by MeI.

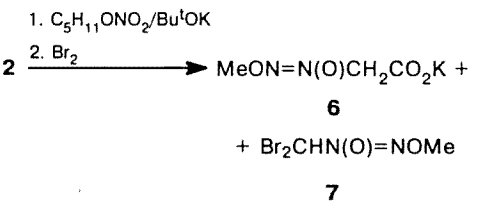


1 **2**

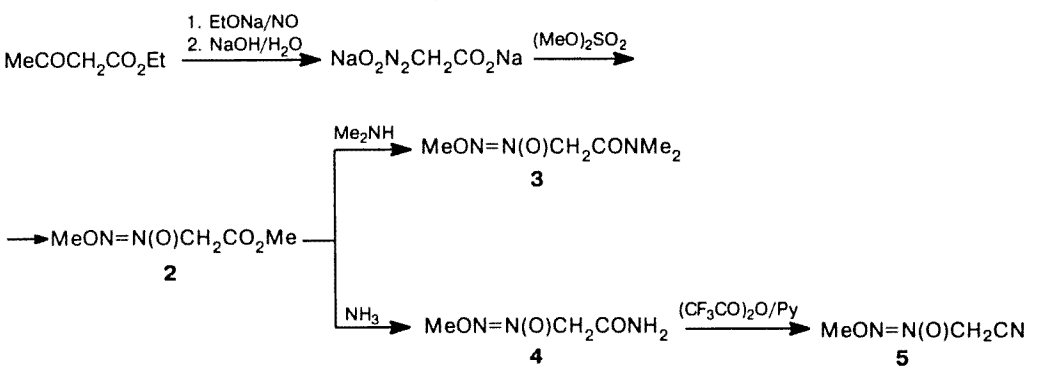
Compound **1** is smoothly chlorinated and brominated in the presence of alkali.[3] It is interesting that permethylation and perhalogenation proceed in all these cases.

However, our attempts to carry out nitration and nitrosation of compound **1** under the action of alkyl nitrates, tetranitromethane, or nitrogen oxides in alkaline medium were unsuccessful. We assumed that the substitution of one of the methoxydiazen-*N*-oxide groups in the compound **1** by an ester, amide, or nitrile group will facilitate the formation of AADO anions and the reaction as a whole. In this connection, we studied the reactions of some derivatives of *N*-methoxydiazen-*N'*-oxidoacetic acid with electrophilic reagents. Methyl ester **2**, dimethylamide (**3**), and nitrile (**5**) were obtained according to Scheme 1.

The possibility of nitration of compound **2** was studied using its reaction with $C_5H_{11}ONO_2$ in the presence of Bu^tOK as an example. Since α-nitroesters are often unstable, the reaction mixture obtained was treated with bromine with the aim of obtaining a more stable α-bromo-α-nitro derivative. However, potassium salt (**6**) and *N*-dibromomethyl-*N'*-methoxydiazen-*N*-oxide (**7**) were isolated instead of the expected product.



Scheme 1



Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 4. pp. 913—915, April, 1996.

1066-5285/96/4504-0868 $15.00

The formation of **7** may be explained by bisbromination of ester **2** followed by saponification and decarboxylation in the isolation.

Bromination of amide **3**, which is more stable to hydrolysis, afforded monobromide (**8**) in 26 % yield. This may be accounted for by the fact that the amide group activates the α-position to a lesser extent.

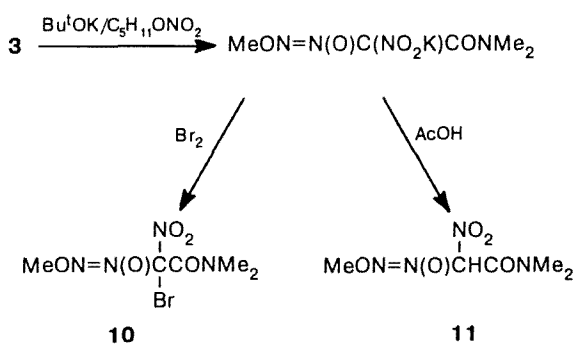
$$3 \xrightarrow{Bu^tOK/Br_2} MeON{=}N(O)CHBrCONMe_2$$
8

The treatment of amide **3** with Bu^{t}OK (1.8 equiv.) in THF followed by the addition of MeI (1.5 equiv.) afforded the product of monomethylation (**9**) in quantitative yield.

$$3 \xrightarrow{Bu^tOK/MeI} MeON{=}N(O)CHMeCONMe_2$$
9

The nitration of **3** followed by bromination gave the bromonitro derivative (**10**) in 30 % yield (Scheme 2).

Scheme 2



When the reaction mixture after completion of the nitration was acidified with a solution of AcOH in THF at −60 °C, we succeeded in isolating the free nitro derivative (**11**), a rather stable crystalline compound, in a low yield (~5 %).

In the study of nitrosation of **3**, a positive result was obtained only with methyl nitrite in the presence of MeONa, and the product of nitrosation (**12**) was isolated in a very low yield (~1 %).

$$3 \xrightarrow{MeONO/MeONa} MeON{=}N(O)C(=NOH)CONMe_2$$
12

Treatment of nitrile **5** with Bu^{t}OK followed by treatment with MeI led to the formation of a mixture of products of mono- and dimethylation (**13** and **14**) in a 1 : 1 ratio.

$$5 \xrightarrow{Bu^tOK/MeI} MeON{=}N(O)CHMeCN + MeON{=}N(O)CMe_2CN$$
13 **14**

Attempts to use alkyl nitrates for nitration of **5** were unsuccessful.

Experimental

IR spectra were recorded on a UR-20 instrument in thin layers or in KBr pellets, ^{1}H NMR spectra were recorded on an R-12 instrument (60 MHz) using HMDS as the internal standard, and mass spectra (EI, 70 eV) were obtained on a Varian CH-C instrument.

Methyl *N*-methoxydiazen-*N'*-oxidoacetate (2) was obtained using the modified procedure of Ref. 1. $MeCOCH_2CO_2Et$ (60 g, 0.46 mol) was added to a solution of EtONa obtained from 23 g of Na (1 g-at.) and EtOH (680 mL), and a uniform flow of NO was passed through the solution formed for 4 h. The precipitate formed was filtered off, washed with EtOH (2×50 mL), and dissolved in H_2O (100 mL). Then a 10 % solution of NaOH (100 mL) was added and the solution was carefully heated until the liberation of gas ceased. Water was distilled off *in vacuo*, the residue was treated with EtOH (500 mL), and the precipitate formed was filtered off and washed with EtOH and Et_2O to afford 65.8 g (89 %) of $NaO_2N_2CH_2CO_2Na$. A mixture of this salt (10 g, 61 mmol), acetone (100 mL), H_2O (30 mL), and Me_2SO_4 (17 mL, 183 mmol) was heated at 55 °C for 1.5 h with stirring. The mixture was then cooled, aqueous NH_3 was added to pH 8, and the solution was filtered and concentrated. The residue was extracted with $CHCl_3$ (3×50 mL), and the extract was dried with $MgSO_4$ and concentrated. The residue was distilled at 92—93 °C (3 Torr) to give 3.27 g (36 %) of **1** as an oil which crystallizes on storage into lamellar crystals with m.p. 36 °C. Found (%): C, 32.43; H, 5.42; N, 19.60. $C_4H_8N_2O_4$. Calculated (%): C, 33.43; H, 5.44; N, 18.91. IR, ν/cm^{-1}: 1760 (C=O); 1510, 1330 (N_2O_2). ^{1}H NMR ($CDCl_3$), δ: 3.36 (s, 3 H, MeOC); 4.5 (s, 3 H, MeON); 4.7 (s, 2 H, CH_2).

***N'*, *N'*-Dimethyl *N*-methoxydiazen-*N'*-oxidoacetamide (3).** A mixture of **2** (2 g, 13.5 mmol) and Me_2NH (1.6 g, 133 mmol) in MeOH (50 mL) was heated at 50 °C for 2 h. The solvent was distilled off and the residue was crystallized from ethanol to give 1.88 g (87 %) of **3**, m.p. 68—70 °C. IR, ν/cm^{-1}: 1680 (C=O); 1510, 1330 (N_2O_2). ^{1}H NMR ($CDCl_3$), δ: 2.99 (d, 6 H, Me_2, Δν = 2.67 Hz); 4.06 (s, 3 H, MeO); 4.93 (s, 2 H, CH_2).

***N*-Methoxydiazen-*N'*-oxidoacetamide (4).** A mixture of **2** (3.5 g, 24 mmol) and NH_3 (5 g, 290 mmol) in MeOH (50 mL) was heated for 3 h at 50 °C, concentrated, and the residue was crystallized from EtOH to give 1.93 g (61.5 %) of **4**, m.p. 142—143 °C (*cf.* Ref. 4: m.p. 142 °C). IR, ν/cm^{-1}: 3400—3500 (NH); 1700 (C=O); 1520, 1310 (N_2O_2). ^{1}H NMR (DMSO-d_6), δ: 3.9 (s, 3 H, MeO); 4.66 (s, 2 H, CH_2); 7.42 (d, 2 H, NH_2, Δν = 15 Hz).

***N*-Methoxydiazen-*N'*-oxidoacetonitrile (5).** Pyridine (2.3 g, 29 mmol) was added to a suspension of amide **4** (1.93 g, 145 mmol) in THF (20 mL), the mixture was cooled to 0 °C, and $(CF_3CO)_2O$ (3.0 g, 14.5 mol) was added dropwise. The mixture was warmed up to ~20 °C, stirred for 4 h, and concentrated. The residue was dissolved in $CHCl_3$ (100 mL), washed with H_2O (2×10 mL), and dried with $MgSO_4$. After the solvent was removed, the residue was distilled *in vacuo* at 97 °C (3 Torr) to give 1.01 g (60.5 %) of **5** as an oil. Found (%): C, 31.00; H, 4.27; N, 36.44. $C_3H_5N_3O_2$. Calculated (%): C, 31.33; H, 4.38; N, 36.51. IR, ν/cm^{-1}: 1515, 1310 (N_2O_2); 2280 (vw, CN). ^{1}H NMR ($CDCl_3$), δ: 4.09 (s, 3 H, MeO); 5.13 (s, 2 H, CH_2).

Potassium *N*-methoxydiazen-*N'*-oxidoacetate (6) and *N*-dibromomethyl-*N'*-methoxydiazen-*N*-oxide (7). A solution of **2** (1 g, 6.75 mmol) in THF (10 mL) was added dropwise to a solution of Bu^{t}OK (1.25 g, 10 mmol) in abs. THF (20 mL) at −30 °C. Then a solution of pentyl nitrate (0.9 g, 6.75 mmol) in THF (15 mL) was added to the mixture. The mixture was warmed up to ~20 °C, then a solution of bromine in hexane was added untill the absorption of bromine ceased. The residue was filtered off to afford **6** as a mixture with KBr. IR, ν/cm^{-1}: 1725 (C=O); 1490, 1310 (N_2O_2). ^{1}H NMR (D_2O), δ: 4.02 (s, 3 H, MeO); 4.64 (s, 2 H, CH_2). The filtrate was concentrated and the residue was crystallized from MeOH to give 0.1 g (6 %) of **7**, m.p. 98—100 °C. IR, ν/cm^{-1}: 3000, 2950 (CH); 1490, 1250 (N_2O_2). ^{1}H NMR (acetone-d_6), δ: 4.04 (s, 3 H, MeO); 8.00 (s, 1 H, $HCBr_2$). MS, *m/z*: 245, 247, 249 [M^+]; 230, 232, 234 [M^+−Me]; 200, 202, 204 [M^+−NOMe]; 170, 172, 174 [$M^+-N_2O_2Me$]; 91, 93 [$M^+-N_2O_2Me-Br$].

***N'',N''*-Dimethyl *N*-methoxydiazen-*N'*-oxidobromoacetamide (8).** A solution of Bu^{t}OK (0.64 g, 5.7 mmol) in THF (20 mL) was cooled to −60 °C and a solution of **3** (0.5 g, 3.1 mmol) in THF (30 mL) was added dropwise. The mixture was warmed up to ~20 °C, kept for 30 min at this temperature, and then cooled to −5 °C. A solution of bromine in hexane was added to the mixture until the absorption of bromine ceased. The residue was filtered off and the filtrate was concentrated. Chromatography of the residue on silica gel (ethyl acetate, R_F 0.21) afforded 0.2 g (26.8 %) of **8**, m.p. 69—71 °C. IR, ν/cm^{-1}: 1680 (C=O); 1490, 1250 (N_2O_2). ^{1}H NMR ($CDCl_3$), δ: 3.04 (d, 6 H, Me_2N, Δν = 6 Hz); 4.13 (s, 3 H, MeO); 6.51 (s, 1 H, HCBr).

***N'',N''*-Dimethyl 2-(*N*-methoxydiazen-*N'*-oxido)propionamide (9).** A solution of **3** (0.5 g, 3.1 mmol) in THF (30 mL) was added dropwise to a solution of Bu^{t}OK (0.64 g, 5.7 mmol) in THF (20 mL) at −60 °C. The mixture was warmed to ~20 °C and kept at this temperature for 30 min. A solution of MeI (0.66 g, 4.6 mmol) in THF was then added dropwise to the mixture at 10 °C. The solution was filtered and the filtrate was concentrated. Chromatography of the residue on silica gel (acetone, R_F 0.57) afforded 0.54 g of **9** as an oil in quantitative yield. IR, ν/cm^{-1}: 1680 (C=O); 1510, 1300 (N_2O_2). ^{1}H NMR ($CDCl_3$), δ: 1.64 (d, 3 H, Me, *J* = 9.33 Hz); 3.01 (d, 6 H, Me_2N, Δν = 6 Hz); 4.09 (s, 3 H, MeO); 5.18 (q, 1 H, HC, *J* = 9.33 Hz).

***N'',N''*-Dimethyl (*N*-methoxydiazen-*N'*-oxido)bromonitroacetamide (10).** A solution of **3** (0.5 g, 3.1 mmol) in THF (20 mL) was added dropwise to a solution of Bu^{t}OK (0.54 g, 4.8 mmol) in THF (20 mL) at −60 °C. The mixture was warmed to ~20 °C, kept at this temperature for 15 min, cooled to −40 °C, and a solution of $C_5H_{11}ONO_2$ (1 g, 7.5 mmol) in THF (10 mL) was added dropwise. The mixture was again warmed to ~20 °C, kept at this temperature for 30 min, and cooled to −5 °C. Then a solution of bromine in hexane was added until the color remained unchanged. The precipitate formed was filtered off and the filtrate was concentrated. TLC of the residue on silica gel (ethyl acetate, R_F 0.46) afforded 0.12 g (16 %) of **8** and 0.25 g (28 %) of **10**, m.p. 145—146 °C. Found (%): C, 20.82; H, 3.12; N, 19.67. $C_5H_9N_4O_5Br$. Calculated (%): C, 21.07; H, 3.18; N, 19.66. IR, ν/cm^{-1}: 1680 (C=O); 1600 (NO_2); 1480, 1330 (N_2O_2). ^{1}H NMR ($CDCl_3$), δ: 4.07 (s, 3 H, MeO); 2.9 (d, 6 H, Me_2N, Δν = 2.67 Hz). MS, *m/z*: 238, 240 [M^+-NO_2], 166, 168 [$M^+-NO_2-CONMe_2$].

***N'',N''*-Dimethyl *N*-methoxydiazen-*N'*-oxidonitroacetamide (11).** A solution of **3** (0.5 g, 3.1 mmol) in THF (20 mL) was added dropwise to a solution of Bu^{t}OK (0.54 g, 4.8 mmol) in THF (20 mL) at −60 °C. The mixture was warmed to ~20 °C, kept at this temperature for 15 min, and cooled to −40 °C, and a solution of $C_5H_{11}ONO_2$ (1 g, 7.5 mmol) in THF (10 mL) was added dropwise. The mixture was again warmed to ~20 °C, kept at this temperature for 30 min, and cooled to −60 °C, and a solution of $MeCO_2H$ in THF was added to pH 5. The residue was filtered off and the solution was concentrated. Chromatography of the residue on silica gel (ethyl acetate, R_F 0.26) afforded 30 mg (5 %) of **11** in the form of colorless crystals, m.p. 92—93 °C. Found (%): C, 29.47; H, 4.93; N, 26.28. $C_5H_{10}N_4O_5$. Calculated (%): C, 29.13; H, 4.89; N, 27.18. IR, ν/cm^{-1}: 1700 (C=O); 1600 (NO_2); 1500, 1370 (N_2O_5). ^{1}H NMR (CD_3CN), δ: 2.68 (d, 6 H, Me_2N, Δν = 2.67 Hz); 4.07 (s, 3 H, MeO); 7.27 (s, 1 H, $HCNO_2$). MS, *m/z*: 160 [M^+-NO_2], 88 [$M^+-NO_2-NMe_2$], 85 [$M^+-NO_2-N_2O_2$].

***N'',N''*-Dimethyl *N*-methoxydiazen-*N'*-oxidohydroxyiminoacetamide (12).** Compound **3** (0.5 g, 3 mmol) was added dropwise to a suspension of MeONa (0.18 g, 4 mmol) in anhydrous DMF (10 mL) at −5 °C, then a solution of $MeONO_2$ (0.2 g, 3 mmol) in DMF (5 mL) was added dropwise to the mixture. The mixture was kept at −5 °C for 2 h and left overnight. The solution was concentrated, the residue was dissolved in H_2O (3 mL), and the solution was acidified with a solution of NH_4Cl and concentrated. The residue was extracted with $CHCl_3$, and the extract was dried with $MgSO_4$ and concentrated. Chromatography of the residue (0.3 g) on silica gel (acetone, R_F 0.64) afforded 7 mg (1 %) of **12**, m.p. 172—174 °C. Found (%): C, 31.41; H, 6.06; N, 27.88. $C_5H_{10}N_4O_4$. Calculated (%): C, 31.58; H, 5.30; N, 29.46. IR, ν/cm^{-1}: 1350, 1520 (N_2O_2); 1680 (C=N); 3400 (OH). ^{1}H NMR ($CDCl_3$), δ: 4.02 (s, 3 H, MeO); 2.96 (d, 6 H, Me_2N, Δν = 2.67 Hz).

2-(*N*-Methoxydiazen-*N'*-oxido)propiononitrile (13) and 2-(*N*-methoxydiazen-*N'*-oxido)isobutyronitrile (14). A solution of **5** (0.3 g, 2.6 mmol) in THF (10 mL) was added dropwise to a solution of Bu^{t}OK (0.3 g, 0.28 mmol) in THF (20 mL) at −60 °C. The mixture was then warmed to ~20 °C, and a solution of MeI (0.5 g, 3.5 mmol) in THF (10 mL) was added dropwise. The mixture was kept at this temperature for 10 min, the precipitate was filtered off, and the filtrate was concentrated. Chromatography of the residue on silica gel (CH_2Cl_2) afforded 0.2 g of a mixture of **13** and **14** in a 1 : 1 ratio as an oil. **13**. ^{1}H NMR ($CDCl_3$), δ: 1.84 (d, 3 H, MeCH, *J* = 8.0 Hz); 4.04 (s, 3 H, MeO); 5.02 (q, 1 H, CH, *J* = 8.0 Hz). **14**. ^{1}H NMR ($CDCl_3$), δ: 1.89 (s, 6 H, Me_2C); 4.04 (s, 3 H, MeO).

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Received June 13, 1995;
in revised form November 15, 1995