Organic Chemistry

Alkylation of salts of *N*-nitrohydroxylamines with chloromethylnitramines

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The reactions of Ag-salts of *N*-nitrohydroxylamines with *N*-methyl-*N*-chloromethylnitramine afford mainly products of *O*-alkylation, whereas the reactions of the corresponding Li-, Na-, K-, Mg-, and NH_4-salts in the presence of tetrabutylammonium bromide (TBAB) give mainly products of *N*-alkylation. The reactions of the corresponding NH_4-salts with bis-(chloromethyl)nitramine in the presence of TBAB lead solely to products of *O*-alkylation. Increasing in the amount of TBAB results in the appearance of the *N*-isomer.

Key words: alkylation, salts of *N*-nitrohydroxylamines, chloromethylnitramines.

Earlier we developed methods for the synthesis of *N*-nitrohydroxylamines (NHA), $MeN(NO_2)OR$, where R are radicals with different electronegativities.[1–3] The possibility of synthesing NHA with electron-accepting substituents in the radical at the N atom is studied in this work. As part of this study the reactions of the salts of NHA **1**—**3** with chloromethylnitramines **4** and **5** were investigated.

$[RON(NO_2)]^-M^+$

1: R = $MeN(NO_2)CH_2$

2: R = Me

$ClCH_2N(NO_2)CH_3$

4

$[^+M^-N(NO_2)O]_2CH_2$

3

$ClCH_2N(NO_2)CH_2Cl$

5

Like nitramines, which are close analogs to NHA, ambident anions **1**—**3** can be alkylated at the N or O atoms. As a rule, alkylation proceeds at both centers. Therefore, one should expect the formation of the product of *N*-alkylation (*N*-isomer) and geometric isomers of the product of *O*-alkylation (*O*-isomer).[4] To identify the products, analytical criteria are needed that allow one to carry out the analysis without isolating the individual compounds. This analysis can be done using the spectral data on the *N*- and *O*-isomers. In order to obtain this criteria, the reactions of the Ag-salts of **1** and **3** with methyl iodide were studied, the products were isolated, and their ^1H and ^{13}C NMR spectra were studied. The choice of Ag-salts is explained by the fact that within the nitramine series, they primarily give products of *O*-alkylation. Products of the *N*-methylation of **1** and **3** are known.[3] The Ag-salt of **2** was not studied since it was impossible to isolate the corresponding product of its *N*-methylation, $MeN(NO_2)OMe$, due to its high volatility.[3]

The reaction of the Ag salt of **1** with MeI results in the formation of products **6a**—**c** in a ratio **6a** : **6b,c** ≈ 1 : 7. The product of *N*-methylation, **6a**, has been previously synthesized[3] by substitution nitration.* Com-

* Here and hereafter the *N*-isomers were identified by the addition of *N*-isomers obtained by an independent method to the tube of the NMR spectrometer.

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pounds **6b,c** are the *cis-trans*-isomers of the *O*-methylation product. By analogy with *O*-isomers of nitramines[5] it can be assumed that *trans*-isomer **6b** prevails in the mixture (**6b** : **6c** ≈ 11 : 1).

$$\underset{\mathbf{1}}{[MeN(NO_2)CH_2ON(NO_2)]^-Ag^+} + MeI \longrightarrow$$

$$\longrightarrow \underset{\mathbf{6a}}{MeN(NO_2)CH_2ON(NO_2)Me} +$$

$$+ \underset{\mathbf{6b,c}}{MeN(NO_2)CH_2ON{=}N(O)OMe}$$

The ^1H and ^{13}C NMR spectral data for products **6a—c** are given in Tables 1—4.

The reaction of the Ag-salt of **3** with MeI afforded a mixture of five products. Generally, this reaction can give six components, the *N,N'*-dimethylation product (**7a**), two isomers of the *N,O*-dimethylation product (**7b**), and three stereoisomers of the *O,O'*-dimethylation product (**7c**).

$$\underset{\mathbf{3}}{[N(NO_2)OCH_2ON(NO_2)]^{2-}2Ag^+} + MeI \longrightarrow$$

$$\longrightarrow \underset{\mathbf{7a}}{MeN(NO_2)OCH_2ON(NO_2)Me} +$$

$$+ \underset{\mathbf{7b}}{MeN(NO_2)OCH_2ON{=}N(O)OMe} + \underset{\mathbf{7c}}{[MeON(O){=}NO]_2CH_2}$$

The ^1H NMR spectrum of the product isolated consists of three groups of signals (A, B, and C): five singlets at δ 5.6—5.8, which correspond to OCH_2O groups (A), two singlets near δ 4 belonging to CH_3O groups (B), and three singlets near δ 3.5 corresponding to $CH_3(NO_2)N$ groups (C). The ratio of the intensities of the signals of group A to the sum of the intensities of the signals of groups B and C is 1 : 3, indicating that all these signals correspond to dimethylation products. The ratio of the intensities of the signals of group C to the sum of the intensities of the signals of groups B and C is 0.26; therefore the fraction of the *N*-methylation products is 26 %. The fraction of compound **7a**, which has been obtained earlier,[4] in the mixture is ~6 % (Table 1). Among isomers **7b**, the predominant one has chemical shifts at 5.79 and 3.45, and the minor isomer has shifts at 5.67 and 3.47 (OCH_2O and $MeN(NO_2)$ groups, respectively). In addition, group A contains two more signals

Table 1. ^1H NMR spectral data of the *N*-isomers (DMSO-d_6, δ)

Compound	MeN	CH_2	MeO
6a	3.43 3.45	5.72	
7a	3.49	5.59	
8a	3.35 3.37	5.79 5.72	
9a	3.32	5.53	3.78
10	3.50	5.58 5.60	
13		5.73	3.76

Table 2. ^{13}C NMR spectral data of the *N*-isomers (DMSO-d_6, δ)

Compound	MeN—O	MeN—C	NCH_2N	NCH_2O	MeO	OCH_2O
6a	44.36	37.09	—	81.81	—	—
7a	45.85	—	—	—	—	101.75
8a	— —	38.59 39.32	71.60 —	81.39 —	— —	— —
9a	—	39.38	71.25	—	64.59	—
10	—	—	71.25	—	—	101.49
13	—	—	71.44	—	64.26	—

Table 3. ^1H NMR spectral data of the *O*-isomers (DMSO-d_6, δ)

Compound	CH_2	MeON	MeN
6b	5.84	3.96	3.42
6c	5.81	3.95	3.42
8b,c	5.88 6.06	— —	3.42 3.43
9b	5.80	3.90	3.35
10	5.87 6.13	— —	— 3.39
12	6.09	3.89	—

Table 4. ^{13}C NMR spectral data of the *O*-isomers (DMSO-d_6, δ)

Compound	$NCH_2ON{=}$	$=N(O)CH_2$	$MeON(O){=}$	$MeN(NO_2)$	$MeON{=}$
6b	80.88	—	57.85	38.32	—
6c	80.87	—	56.76	38.50	—
8b	79.50	74.00	—	37.68	—
8c	80.41	78.50	—	36.56	—
9b	—	77.06	—	38.59	62.15
11	81.11	76.17	—	38.15	—
12	—	78.76	—	—	61.63

with approximately equal intensities (at δ 5.71 and 5.88), which are attributed to the OCH_2O groups of the two *O,O'*-dimethylation products **7c**. Product **7a** is the only one that can be identified with certainty in the ^{13}C NMR spectrum (Table 2). It should be noted that three signals (at δ 57.67, 57.59, and 56.73) of MeO groups are also observed. A comparison of the data of Tables 1—4 shows that the chemical shifts of the carbon atom, which was the reaction center of the alkylating agent, in the alkylation products, as well as the chemical shifts of the protons at this carbon atom, are sufficiently reliable criterion to attribute the product to the *N*- or *O*-series (for the *O*-isomers, these signals are located at weaker fields).

The reaction of the Ag-salt of **1** with chloride **4** results in the formation of *N*-alkylation product **8a** (in ~8 % yield) and two isomers of the *O*-alkylation product **8b,c** in the ratio **8b** : **8c** ≈ 12 : 1 (Tables 1—4).

$$[MeN(NO_2)CH_2ON(NO_2)]^-Ag^+ + ClCH_2N(NO_2)Me \longrightarrow$$

$$\longrightarrow \underset{\textbf{8a}}{MeN(NO_2)CH_2ON(NO_2)CH_2N(NO_2)Me} +$$

$$+ \underset{\textbf{8b,c}}{MeN(NO_2)CH_2ON{=}N(O)OCH_2N(NO_2)Me}$$

It should be noted that unstable compounds are present in this mixture and the NMR spectra contains weak non-identified signals.

The reaction of the Ag-salt of **2** with chloride **4** affords a mixture of two compounds (**9a** and **9b**) in the ratio **9a** : **9b** ≈ 1 : 9. Judging from the NMR spectral data, compound **9a** is the *N*-isomer and **9b** is the *O*-isomer (Tables 1—4).

$$[MeON(NO_2)]^-Ag^+ + ClCH_2N(NO_2)Me \longrightarrow$$

$$\longrightarrow \underset{\textbf{9a}}{MeON(NO_2)CH_2N(NO_2)Me} +$$

$$+ \underset{\textbf{9b}}{MeON{=}N(O)CH_2N(NO_2)Me}$$

Thus, we established that the alkylation of the Ag-salts of NHA in acetonitrile occurs mainly at the oxygen atom of the nitro group.

We studied the influence of a metal cation on the course of the alkylation using the reactions of the salts of **1** and **2** containing alkaline and alkaline-earth cations (NH_4, Li, Na, K, Mg) with chloride **4**. The reactions were carried out in DMSO, in which these salts are readily soluble. The reactions of the Ag-salts were carried out in acetonitrile but the alkaline and alkaline-earth salts of **1** and **2** are poorly soluble in this solvent and their reaction with chloride **4** for all intents and purposes does not proceed in this solvent. The reaction was monitored by TLC (Silufol UV-250, eluent $CHCl_3$: MeOH, 20 : 1). The reaction was considered to be complete when the spot of chloride **4** disappeared from the chromatogram. The reaction products were isolated and analyzed by ^1H and ^{13}C NMR spectroscopy. We found that under these reaction conditions, the *N*-alkylation products **8a** and **9a** are isolated in a practically pure state. The results obtained are given in Table 5.

Table 5. Alkylation of the NHA salts with chloride **4**

M^+	Salt **1**		Salt **2**	
	Time/h	Yield (%)	Time/h	Yield (%)
Li	0.3	34.0	0.5	42
Na	1.0	58.7	0.5	55
K	1.0	39.5	1.0	32
Mg	1.0	65.0	0.5	61
NH_4	—	—	4.0	42

As can be seen from Table 5, the highest yields of **8a** and **9a** are observed with the magnesium salts. However, these salts are not very convenient since they are highly hygroscopic. In addition, chloride **4** is probably not completely inert in DMSO and gives an acidic reaction with litmus. Therefore, it was useful to develop a method for the alkylation of NHA salts without using DMSO or magnesium salts of NHA.

We found that alkylation of the ammonium salts of **1** and **2** with chloride **4** proceeds readily in acetonitrile in the presence of a phase transfer catalyst, tetrabutylammonium bromide (TBAB), to afford **8a** and **9a** in 70 % and 73 % yields, respectively, *i.e.*, the yield is even higher than in the case of the magnesium salts of **1** and **2** in DMSO. The same results were obtained using triethylbenzylammonium bromide as the catalyst. It should be noted that the analysis of the ^1H NMR spectra showed the formation of ~20 % *O*-isomer **9b** in the reaction of compounds **2** and **4**, but *O*-isomers **8b,c** were not found in the reaction of compounds **1** and **4**.

The reaction of the diammonium salt of **3** with chloride **4** in the presence of TBAB results in the isolation of solely the product of *N*-alkylation **10** (Tables 1 and 2), $[MeN(NO_2)CH_2N(NO_2)O]_2CH_2$, however, the yield was only 25 %. An increase in the acidity of the medium was observed in the course of the reaction. In order to bind the acids, which may destroy[3] NHA, we carried out this reaction in the presence of Na_2CO_3 and isolated NHA **10** in 81 % yield.

An unexpected result was obtained in the alkylation of the ammonium salts of **1** and **2** with dichloride **5** in the presence of TBAB. The reaction afforded solely the products of *O*-alkylation, **11** and **12**, respectively, as one isomer each, in practically quantitative yields (Tables 3 and 4).

$$[MeN(NO_2)CH_2ON(NO_2)]^-NH_4^+ + ClCH_2N(NO_2)CH_2Cl \xrightarrow{TBAB}$$

$$\longrightarrow [MeN(NO_2)CH_2ON{=}N(O)OCH_2]_2NNO_2$$

11

$$[MeON(NO_2)]^-NH_4^+ + ClCH_2N(NO_2)CH_2Cl \xrightarrow{TBAB}$$

$$\longrightarrow [MeON{=}N(O)OCH_2]_2NNO_2$$

12

It is known[6] that in the alkylation of ambident enolate anions, the ratio of free ions and ionic pairs in solution affects the ratio of *C*- and *O*-products, as well as the ratio of *cis-trans*-isomers in the *O*-product. For example, *O*-alkylation with the formation of the *trans*-product is observed for free anions, and *C*-alkylation and the formation of the *cis*-product of an *O*-isomer proceeds mainly with contact ionic pairs. Taking into account these data, one may assume that the alkylation of the salts of NHA **1** and **2** with chloride **4** proceeds mainly with contact ion pairs, and the reaction with dichloride **5** proceeds with free anions. These different states of the salts of **1** and **2** can result from the fact that a significantly larger amount of salt passes into solution in the case of chloride **4** than in dichloride **5**. This means that the presence of an alkylating agent in the solution affects the solvent action of acetonitrile. Such influence is probable if we take into account the fact that the mass ratio between the alkylating agent and acetonitrile is 16 % for compound **4** and 20 % for compound **5** under the conditions used (see Experimental). If the assumption of the influence of the concentrations of the salts **1** and **2** in solution on the ratio of the products of *N*- and *O*-alkylation is true, the amount of TBAB used in these reactions should also affect these ratios, *i.e.*, increasing the amount of TBAB should result in an increase in the concentration of the salts in solution and, hence, an increase in concentration of contact ionic pairs and, as a result, to the increase in the fraction of the *N*-alkylation product.

To check this proposal, we have carried out the reaction of the salt of **2** with chloride **4** with a decreased amount of TBAB, and the reaction of the salt of **2** with dichloride **5** with an increased amount of TBAB. It should be noted that all the results given above were obtained using 20 mol % TBAB with respect to the salts of **1** and **2**. The reaction of the salt of **2** with chloride **4** in the presence of 5 % TBAB afforded a product with the ratio of *N*-(**9a**) and *O*-isomers (**9b**) 9 : 11 (this ratio was equal to 4 : 1 in the presence of 20 % TBAB). For the reaction of the salt of **2** with dichloride **5**, increasing the amount of TBAB resulted in the formation of the *N*-alkylation product **13**, $[MeON(NO_2)]_2CH_2NNO_2$ (see Tables 1 and 2). The fraction of **13** in the reaction product was ~25 % for 45 % TBAB and ~50 % for the equimolar amount of TBAB.

Thus, we have proved experimentally that the ratio of the products of *N*- and *O*-alkylation in the reaction of the ammonium salts of NHA with chloromethylnitramines depends on the amount of the phase transfer catalyst, *i.e.*, increasing this amount results in an increase in the ratio of the *N*-isomer.

Experimental

^1H and ^{13}C NMR spectra were obtained on a Bruker WM 250 instrument.

Alkaline and alkaline-earth salts of 1 and 2. The ammonium salt **1** or **2** (M = NH_4) (0.003 g-equiv.) was added to a solution of metal (Li, Na, K, Mg) (0.003 g-equiv.) in abs. MeOH (4 mL). The solution was stirred until the ammonium salt was completely dissolved, MeOH was concentrated to 1/3 of the initial volume, abs. ether (5 mL) was added, and the mixture was stirred at 20 °C. The white precipitate that formed was filtered off and dried *in vacuo* to afford the salt in quantitative yield.

Silver salt of *N*-nitro-*O*-(2-nitrazapropyl)hydroxylamine. An aqueous solution (2 mL) of the ammonium salt of **1** (0.4 g, 2.18 mmol) was mixed with an aqueous solution of $AgNO_3$ (0.38 g, 2.24 mmol). EtOH (20 mL) was added to the solution. The precipitate that formed was filtered off, washed with cooled EtOH (2×5 mL), and dried *in vacuo* to afford 0.5 g (84 %) of the silver salt of **1**.

Silver salt of *N*-nitro-*O*-methylhydroxylamine. An aqueous solution (1 mL) of the ammonium salt of **2** (0.4 g, 3.67 mmol) was mixed with an aqueous solution (2 mL) of $AgNO_3$ (0.62 g, 3.71 mmol). EtOH (20 mL) was added to the solution, and the solution was cooled at −10 to −12 °C for 2 h. The precipitate that formed was filtered off, washed with cooled EtOH (2×5 mL) and ether, and dried *in vacuo* to afford 0.56 g (76.7 %) of the Ag salt of **2**.

Disilver salt of methylene-*O,O'*-bis-*N*-nitrohydroxylamine. An aqueous solution (3 mL) of the diammonium salt of **3** (0.5 g, 2.47 mmol) was mixed with an aqueous solution (2 mL) of $AgNO_3$ (0.85 g, 5 mmol). The precipitate that formed was filtered off, washed with water, MeOH, and ether, and dried *in vacuo* to afford 0.77 g (81.7 %) of the disilver salt of **3**.

Alkylation of the silver salt of 1 with methyl iodide. A suspension of the Ag-salt of **1** (0.3 g, 1.1 mmol) in abs. ether (8 mL) and methyl iodide (0.17 g, 1.2 mmol) was stirred at 20 °C for 8 h. The precipitate that formed was filtered off and washed with ether, and the filtrate was evaporated *in vacuo* to afford 0.19 g (92.5 %) of a mixture of **6a—c** as a colorless liquid. Found (%): N, 29.75. $C_3H_8N_4O_5$. Calculated (%): N, 30.21.

Alkylation of the silver salt of 3 with methyl iodide. A mixture of the Ag salt of **3** (0.77 g, 2 mmol) and methyl iodide (0.62 g, 474 mmol) in abs. MeCN (5 mL) was stirred at 20 °C for 5 h. The precipitate that formed was filtered off, washed with MeCN, and concentrated *in vacuo* to afford 0.35 g (89 %) of a mixture of **7a—c** as an oil. Found (%): N, 28.30. $C_3H_8N_4O_6$. Calculated (%): N, 28.57.

Alkylation of the silver salt of 1 with chloride 4. A solution of chloride **4** (0.19 g, 1.52 mmol) in abs. MeCN (1 mL) was added dropwise to a solution of the Ag salt of **1** (0.4 g, 1.47 mmol) in abs. MeCN (3 mL). The mixture was stirred for 2 h at 20 °C, and ethyl acetate (10 mL) was then added. The precipitate that formed was filtered off and washed with ethyl acetate. The filtrate was washed with water, dried with a mixture of $CaSO_4$ and $NaHCO_3$ at 0 °C, and concentrated

in vacuo to 1/3 of the initial volume to afford 0.2 g (54 %) of a crystalline mixture of **8—c**, t. dec. 90–91 °C. The product is unstable and decomposes after 2 days at 20 °C.

Alkylation of the silver salt of 2 with chloride 4. A solution of chloride **4** (0.2 g, 1.69 mmol) in abs. MeCN (1 mL) was added dropwise to a solution of the Ag salt of **2** (0.32 g, 1.61 mmol) in abs. MeCN (2 mL). The mixture was stirred for 2 h at 20 °C. The precipitate that formed was filtered off and washed with MeCN (2×3 mL). The filtrate was concentrated to 1/3 of the initial volume, diluted with water, and extracted with ether. The ethereal extracts were dried with Na_2SO_4, and the solvent was distilled off to afford 0.24 g (82.8 %) of a mixture of **9a,b** as an oil. Found (%): N, 29.88. $C_3H_8N_4O_5$. Calculated (%): N, 30.22.

Reaction of alkaline and alkaline-earth salts of 1 and 2 with chloride 4. General procedure. A solution of NHA salt (0.003 g-equiv.) and chloride **4** (0.003 g-equiv.) in anhydrous DMSO (1.5 mL) was stirred at 20 °C until the reaction was completed (monitored by TLC), and 15 mL of water was added to the solution. In the case of the reaction with the salt of **1**, the precipitate that formed was filtered off, washed with water, and reprecipitated from acetone with water. In the case of the reaction with the salt of **2**, the oil that formed was extracted with chloroform, and the extract was washed with water and dried with $MgSO_4$. The solvent was distilled off, and the residual oil crystallized on cooling. The yields and the reaction times are given in Table 5. Compound **8a**, m.p. 78 °C (reprecipitated from acetone with water). Found (%): C, 19.02; H, 4.00; N, 32.95. $C_4H_{10}N_6O_7$. Calculated (%): C, 18.90; H, 3.97; N, 33.07. Compound **9a**, m.p. 51 °C (from ether). Found (%): C, 20.18; H, 4.62; N, 31.05. $C_3H_8N_4O_5$. Calculated (%): C, 20.00; H, 4.48; N, 31.11.

Alkylation of the ammonium salts of NHA with chloromethylnitramines 4 and 5 in the presence of TBAB. General procedure. A suspension of NHA salt (0.005 g-equiv.), TBAB (20 mol % with respect to the NHA salt), and chloromethylnitramine (0.005 g-equiv.) in abs. MeCN (5 mL) was stirred at 20 °C until the reaction was completed (monitored by TLC on silufol, eluent $CHCl_3$: MeOH, 20 : 1). The reaction mixture was then poured into a saturated aqueous solution of NaCl (20 mL). If crystals were formed, they were filtered off and dried in the air. If the product formed as an oil, it was extracted with ethyl acetate (20 mL), the extract was washed with a saturated aqueous solution of NaCl (4×5 mL) and dried with $MgSO_4$. The solvent was distilled off, and the product was purified by column chromatography on silica gel (LC 100/160, eluent chloroform. Compound **11**, yield 96 %, m.p. 94–96 °C (with decomp.). Found (%): C, 17.38; H, 3.40; N, 33.35. $C_6H_{14}N_{10}O_{12}$. Calculated (%): C, 17.23; H, 3.37; N, 33.49. Compound **12**, yield 98 %, very viscous mass. Found (%): C, 17.87; H, 3.90; N, 31.10. $C_4H_{10}N_6O_8$. Calculated (%): C, 17.87; H, 3.90; N, 31.

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