
Synthesis of 5-Alkylaminomethyland 5-(Alkyl-N-nitroaminomethyl)-3-nitroisoxazolidines

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Abstract—5-Halomethyl-3-nitrooxazolidines react with alkylamines to give 5-alkylaminomethyl-3-nitrooxazolidines which are readily nitrated at the exocyclic nitrogen atom.

The present work continues our systematic studies in the field of synthesis and reactivity of *N*-nitrooxazolidines [1]. It was aimed at developing a procedure for synthesizing a series of functionally substituted 5-alkylaminomethyl-3-nitrooxazolidines **I** and converting them into the corresponding *N*-nitroamines. For this purpose, we examined the reaction of various amines with 5-chloromethyl-3-nitrooxazolidine (**IIa**). The reactions were carried out with excess amine at 120–130°C (2–6 h). As a result, the corresponding amino derivatives **Ia–Id** were obtained in up to 90% yield (Scheme 1). The products were isolated by fractional distillation (Table 1).

Scheme 1.

$$O_2N$$
 O_2N
 O_2N

I, RR'N = morpholino (**a**); R = H, R' = CH₂CH₂OH (**b**), CH₂CH(OH)CH₃ (**c**), Bu (**d**), Me (**e**); **II**, Hlg = Cl (**a**), I (**b**).

However, we failed to synthesize compound **Ie** in such a way. Therefore, we have developed a more complex scheme: initially, chloromethyl derivative **IIa** was treated with 6 equiv of sodium iodide in DMF for 14 h at 75–80°C to obtain 5-iodomethyl-3-nitrooxazolidine (**IIb**) (Scheme 2).

Scheme 2.

Compound **IIb** was then brought into reaction with methylamine in methanol or acetonitrile at 50–55°C (reaction time 38 h). The target compound (**Ie**) was thus obtained in approximately the same yield as in the reaction of **IIa** with the other amines.

Compounds **Ib–Ie** were nitrated to the corresponding 5-(alkyl-*N*-nitroaminomethyl)-3-nitrooxazolidines **IIIb–IIIe** (Scheme 3). The nitration was effected with a mixture of nitric and acetic acids at 0–5°C. The yields of crystalline *N*-nitroamino derivatives **III** ranged from 30 to 90% (Table 1).

Scheme 3.

$$O_2N \xrightarrow{N} CH_2NHR \xrightarrow{HNO_3/Ac_2O} O_2N \xrightarrow{N} CH_2N-R$$

$$Ib-Ie \qquad IIIb-IIIe$$

I, $R = CH_2CH_2OH$ (b), $CH_2CH(OH)CH_3$ (c), Bu (d), Me (e); III, $R = CH_2CH_2ONO_2$ (b), $CH_2CH(ONO_2)CH_3$ (c), Bu (d), Me (e).

In addition, we tried to replace the iodine atom in **IIb** by other nucleophilic groups (Scheme 4). The reaction of methyl-*N*-nitroamine sodium salt with

Scheme 4.

IIIe, $X = CH_3NNO_2$; IV, $X = ONO_2$.

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Comp.	Yield, %	mp, °C, or bp, °C (p, mm)	Found, %			F 1	Calculated, %		
			С	Н	N	Formula	С	Н	N
Ia	90	140–143 (1.0–1.2)	44.77	7.16	_	C ₈ H ₁₅ N ₃ O ₄	44.23	6.96	_
Ib	85	165–166 (0.9–1.1)	37.67	6.80	21.98	$C_6H_{13}N_3O_4$	37.69	6.85	21.98
Ic	90	52 153–155 (0.8–1.0)	41.18	7.47	20.69	$C_7H_{15}N_3O_4$	40.97	7.37	20.48
Id	90	109–111 (0.9–1.1)	47.85	8.46	20.35	$C_8H_{18}N_3O_3$	47.28	8.43	20.67
Ie	72 ^a	93–94 (0.8–1.0)	_	_	20.84	$C_5H_{11}N_3O_3^b$	_	_	21.26
IIb	87	30–31 108–109 (0.7–0.9)	19.34	2.90	10.97	$C_4H_7IN_2O_3$	18.62	2.73	10.86
IIIb	77	58.5–59.5	26.09	4.00	25.73	$C_6H_{11}N_5O_8$	25.63	3.94	24.91
IIIc	91	95.5–96.5	28.50	4.47	24.00	$C_7H_{13}N_5O_8$	28.48	4.44	23.72
IIId	70	Oily substance	_	_	22.77	$C_8H_{17}N_4O_5$	_	_	22.57
IIIe	30 67 ^a	110–111 162–163 (0.8–1.0) ^c	29.82	5.02	27.18	$C_5H_{10}N_4O_5$	29.13	4.89	27.18
IV	71	Oily substance	_	_	21.76	$C_4H_7N_3O_6$	_	=	21.76

Table 1. Yields, melting or boiling points, and elemental analyses of oxazolidines Ia-Ie, IIb, IIIb-IIIe, and IV

iodide **IIb** gave 67% of compound **IIIe** which was identical to the product obtained by nitration of **Ie**. It should be emphasized that methyl-*N*-nitroamine anion adds mainly through its nitrogen atom. Treatment of compound **IIb** with silver nitrate led to formation of 3-nitro-5-nitroxymethyloxazolidine (**IV**) in 71% yield (Scheme 4).

Thus we have developed a general procedure for synthesizing functionally substituted 5-(alkylaminomethyl)-3-nitrooxazolidines **I** and 5-(alkyl-*N*-nitroaminomethyl)-3-nitrooxazolidines **III** based thereon, starting from 5-halomethyl-3-nitrooxazolidines **II**.

EXPERIMENTAL

The ¹H NMR spectra were recorded on Bruker WM-250 (250.13 MHz) and Bruker AM-300 instruments (300.13 MHz, compound **IIb**) in (CD₃)₂CO using HMDS as internal reference (Table 2).

5-(2-Hydroxyethylaminomethyl)-3-nitrooxazolidine (Ib). A solution of 3.4 g (20 mmol) of 5-chloromethyl-3-nitrooxazolidine (**Ha**) in 3.6 g (60 mmol) of 2-aminoethanol was heated for 5 h at 120–125°C, and the mixture was then evaporated under reduced pressure. The residue was dissolved in 50% ethanol, and the solution was adjusted to pH 12.1–12.3 (with

KOH) and evaporated under reduced pressure. The residue was treated with ethyl acetate $(3 \times 10 \text{ ml})$, the combined extracts were evaporated under reduced pressure, and the residue was subjected to fractional distillation. Yield 3.23 g.

Compounds Ia, Ic, and Id were synthesized in a similar way.

5-Methylaminomethyl-3-nitrooxazolidine (Ie). Compound **IIb**, 5.06 g (19.6 mmol), was added to a solution of 3 g (100 mmol) of methylamine in 52.5 ml of acetonitrile. The mixture was heated for 38 h at 50–55°C in an ampule and was evaporated under reduced pressure. The residue was dissolved in 50% ethanol, and the solution was adjusted to pH 12.1–12.3 (KOH) and evaporated under reduced pressure. The residue was extracted with benzene (3×15 ml), the combined extracts were evaporated under reduced pressure, and the residue was subjected to fractional distillation. Yield 2.25 g.

5-Iodomethyl-3-nitrooxazolidine (**IIb**). A solution of 3.35 g (20.1 mmol) of compound **IIa** in 40 ml of DMF was heated to 85–90°C, 23 g (124 mmol) of NaI·2H₂O was added, and the mixture was stirred for 15 h. It was then poured into 120 ml of water and extracted with benzene $(4 \times 25 \text{ ml})$, the combined extracts were washed with water $(7 \times 30 \text{ ml})$ and

^a From **IIb**.

^b The data of elemental analysis are given for the corresponding hydrochloride, mp 128-130°C.

^c Decomposes during distillation.

Table 2. ¹H NMR spectra of compounds Ia-Ie, IIb, IIIb-IIIe, and IV

Comp.	Chemical shifts δ , ppm (J, Hz)						
Ia	2.64 m (6H, CHC \mathbf{H}_2 N, CH $_2$ NCH $_2$), 3.55 d.d [1H, N(NO $_2$)C \mathbf{H}_2 CH, $J=-10.6$, 8.0], 3.72 m (4H, CH $_2$ OCH $_2$, $J=4.3$, 4.3), 4.14 d.d [1H, N(NO $_2$)C \mathbf{H}_2 CH, $J=-12.2$, 6.9], 4.56 m (1H, CHO), 5.14 d (1H, NCH $_2$ O, $J=-6.4$], 5.46 d (1H, NCH $_2$ O, $J=-6.4$)						
Ib	2.80 m (2H, NC \mathbf{H}_2 CH ₂ OH), 3.00 m (2H, CHC \mathbf{H}_2 NCH ₂ CH ₂ OH), 3.60 d.d [1H, N(NO ₂)C \mathbf{H}_2 CH, $J=-11.0$, 6.0], 3.80 t (2H, NCH ₂ C \mathbf{H}_2 OH, $J=5.5$), 4.10 d.d [1H, N(NO ₂)C \mathbf{H}_2 CH, $J=-11.0$, 5.5], 4.42 m (1H, CHO), 5.10 d (1H, NCH ₂ O, $J=-6.6$)						
Ic	1.06 d (3H, CHCH ₃ , $J=4.1$), 2.55 m (2H, NCH ₂ CHCH ₃), 2.85 m (2H, CH ₂ NCH ₂ CHCH ₃), 3.72 m (2H, CHCH ₃ , OCH ₂ NCH ₂), 4.05 d.d (1H, OCH ₂ NCH ₂ , $J=-7.7$, 4.6), 5.07 d (1H, NCH ₂ O, $J=-5.1$), 5.40 d (1H, NCH ₂ O, $J=-5.1$)						
Id	0.87 t (3H, CH ₂ C H ₃ , $J = 6.0$), 1.38 m (4H, CH ₂ C H ₂ C H ₂ CH ₃), 2.62 t (2H, NC H ₂ CH ₂ CH ₂ , $J = 6.0$), 2.84 d (2H, C H ₂ NCH ₂ CH ₂ , $J = 3.0$), 3.76 d.d [1H, N(NO ₂)C H ₂ CH, $J = -9.5$, 6.0], 4.04 d.d [1H, N(NO ₂)C H ₂ CH, $J = -9.5$, 6.0], 4.40 m (1H, CHO), 5.07 d (1H, NCH ₂ O, $J = -5.4$), 5.41 d (1H, NCH ₂ O, $J = -5.4$)						
Ie	2.41 s (3H, NCH ₃), 2.82 d (2H, CH ₂ NCH ₃ , $J = 5.1$), 3.75 d.d [1H, N(NO ₂)CH ₂ CH, $J = -10.2$, 8.5], 4.08 d.d [1H, N(NO ₂)CH ₂ CH, $J = -10.2$, 8.5], 4.43 m (1H, CHO), 5.12 d (1H, NCH ₂ O, $J = -6.8$), 5.45 d (1H, NCH ₂ O, $J = -6.8$)						
IIb	3.50 m (2H, CH ₂ I), 3.72 d.d (1H, NCH ₂ CH, $J = -12.0$, 8.2), 4.23 d.d (1H, NCH ₂ CH, $J = -12.0$, 7.6), 4.43 m (1H, NCH ₂ CH), 5.21 d (1H, NCH ₂ O, $J = -7.1$), 5.50 d (1H, NCH ₂ O, $J = -7.1$)						
IIIb	3.77 d.d [1H, N(NO ₂)C \mathbf{H}_2 CH, $J = -11.8$, 7.1], 4.30 m [5H, N(NO ₂)C \mathbf{H}_2 CH, C \mathbf{H}_2 N(NO ₂)C \mathbf{H}_2 CH ₂], 4.75 m (1H, CHO), 4.92 t (2H, CH ₂ ONO ₂ , $J = 3.5$), 5.20 d [1H, N(NO ₂)CH ₂ O, $J = -7.1$], 5.50 d [1H, N(NO ₂)CH ₂ O, $J = -7.1$]						
IIIc	1.42 d (3H, CH ₃ , $J = 6.4$), 3.77 d.d [1H, OCH ₂ N(NO ₂)C H ₂ , $J = -10.5$, 6.4], 4.22 m [5H, OCH ₂ N(NO ₂)C H ₂ , C H ₂ N(NO ₂)C H ₂ CHCH ₃], 4.75 m (1H, CHO), 5.17 d [1H, N(NO ₂)CH ₂ O, $J = -5.1$], 5.45 d [1H, N(NO ₂)CH ₂ O, $J = -5.1$], 5.62 m (1H, CHONO ₂)						
IIId	0.92 t (3H, CH ₃ , $J = 7.0$), 1.20–1.70 m [4H, N(NO ₂)CH ₂ CH ₂ CH ₂ CH ₃], 3.40–4.25 m [6H, OCH ₂ N(NO ₂)CH ₂ , CH ₂ N(NO ₂)CH ₂], 4.75 m (1H, CHO), 5.17 d [1H, N(NO ₂)CH ₂ O, $J = -7.0$], 5.45 d [1H, N(NO ₂)CH ₂ O, $J = -7.0$]						
IIIe	3.45 s (3H, CH ₃), 3.78 d.d [1H, OCH ₂ N(NO ₂)CH ₂ , $J = -12.1$, 7.3], 4.22 m [3H, OCH ₂ N(NO ₂)CH ₂ , CH ₂ N(NO ₂)CH ₂], 4.75 m (1H, CHO), 5.20 d [1H, N(NO ₂)CH ₂ O, $J = -6.5$], 5.50 d [1H, N(NO ₂)CH ₂ O, $J = -6.5$]						
IV	3.90 d.d [1H, N(NO ₂)C \mathbf{H}_2 CHO, $J = -12.6$, 8.1], 4.22 d.d [1H, N(NO ₂)C \mathbf{H}_2 CHO, $J = -12.6$, 8.1], 4.40 m (1H, CHO), 4.77 m (2H, CH ₂ ONO ₂), 5.20 d [1H, N(NO ₂)CH ₂ O, $J = -6.8$], 5.45 d [1H, N(NO ₂)CH ₂ O, $J = -6.8$]						

evaporated under reduced pressure, and the residue was recrystallized from ether. Yield 4.53 g.

3-Nitro-5-(N-nitro-2-nitroxyethylaminomethyl)-**oxazolidine (IIIb).** 5-(2-Hydroxyethylaminomethyl)3-nitrooxazolidine (**Ib**), 1.26 g (6.63 mmol), was added at 0°C to a mixture of 3.5 ml of 97% HNO₃, 11.5 ml of Ac_2O , 3 ml of 2-nitropropane, and 0.12 g (1.78 mmol) of $MeNH_2 \cdot HCl$. The mixture was stirred for 40 min, poured into 50 ml of an ice—water mixture, and extracted with ethyl acetate (3×15 ml). The extract was washed with water and a solution of

sodium carbonate and evaporated under reduced pressure. The residue was recrystallized from ethanol. Yield 1.44 g.

Compounds **IIIc** and **IIId** were synthesized in a similar way. Product **IIId** was purified by vacuum sublimation at 120°C (1 mm).

5-(Methyl-*N***-nitroaminomethyl)-3-nitrooxazolidine (IIIe).** Methyl-*N*-nitroamine, 0.5 g (6.58 mmol), was added to a solution of 1.29 g (5 mmol) of compound **IIb** and 0.70 g (6.58 mmol) of Na₂CO₃ in 15 ml of DMF, heated to 85–90°C. The mixture was

stirred for 8 h, poured into 40 ml of water, and treated with benzene $(4 \times 10 \text{ ml})$. The extract was washed with water $(7 \times 10 \text{ ml})$ and evaporated under reduced pressure, and the residue was recrystallized from ethanol. Yield 0.69 g.

3-Nitro-5-(nitroxymethyl)oxazolidine (IV). Silver nitrate, 1.40 g (8.24 mmol), was added to a solution of 1 g (3.88 mmol) of compound **IIb** in 10 ml of DMF, heated to 75–80°C, and the mixture was stirred for 1 h. It was then filtered from the precipitate

of AgI, and the filtrate was poured into 30 ml of water and extracted with benzene (5×10 ml). The extract was washed with water (7×15 ml) and evaporated under reduced pressure. Yield 0.53 g.

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