

Silyl Nitronates in Organic Synthesis. Silylation of Secondary Nitro Compounds. Preparation of Nitroso Compounds and α,β -Unsaturated Aldehydes

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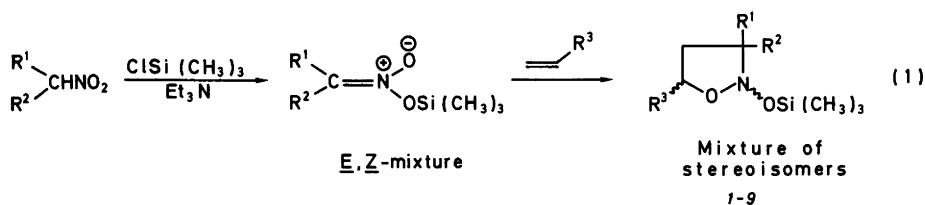
Secondary nitro compounds can be silylated by triethylamine and chlorotrimethylsilane in acetonitrile as solvent. The silyl nitronates add to olefins forming 3,3-disubstituted isoxazolidines, which can be rearranged to tertiary nitroso compounds. Addition of the secondary nitronates to acrylonitrile and subsequent treatment with fluoride ion leads to β,β -disubstituted α,β -unsaturated aldehydes.

Simple primary nitro compounds are easily silylated by chlorotrimethylsilane and triethylamine in benzene at room temperature.^{1,2} Higher homologues or sterically hindered primary nitro compounds react sluggishly with this silylating agent. Use of *N,O*-bis(trimethylsilyl)acetamide³ (BSA) or lithium diisopropylamide-chlorotrimethylsilane⁴ forces the reaction to completion. We have now found that addition of acetonitrile (which forms a complex with chlorotrimethylsilane) to the reaction

medium promotes the reaction considerably. Primary and several secondary nitro compounds undergo complete conversion to silyl nitronates with the chlorotrimethylsilane-triethylamine couple in acetonitrile, or in acetonitrile-benzene or toluene mixtures. *N*-Trimethylsilyloxyisoxazolidines are formed directly when the silylation is carried out in the presence of a dipolarophile (1). Secondary nitro compounds such as 2-nitropropane and nitrocyclopentane are easily silylated and add in high yields to acrylonitrile and methyl acrylate, while dimethyl 4-nitroheptandioate and methyl 4-nitropentanoate require refluxing for a few h in acetonitrile-toluene. 5-Nitrohexan-2-one and 2-nitrocyclooctanone give poor yields of isoxazolidines, 6 and 9, respectively, by the $\text{ClSi}(\text{CH}_3)_3/(\text{C}_2\text{H}_5)_3\text{N}$ method. The yield of 9 was increased considerably by using BSA, as were those of 7 and 8.

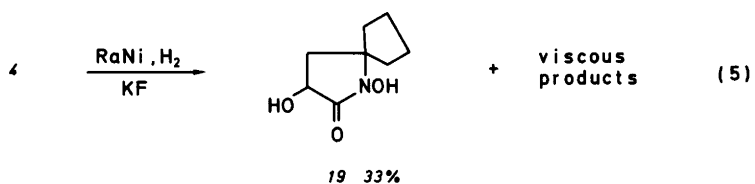
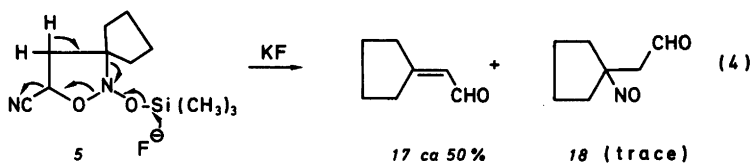
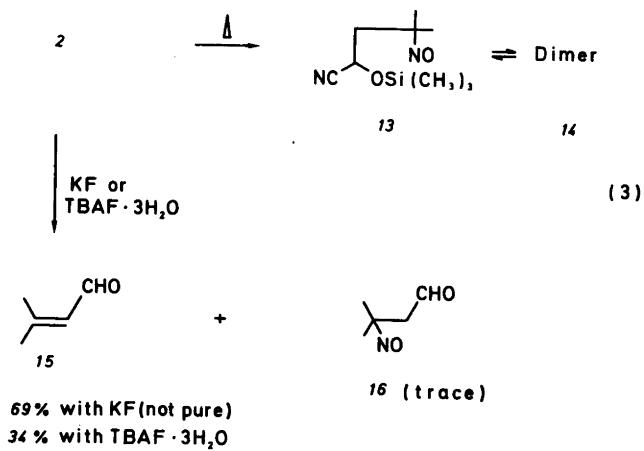
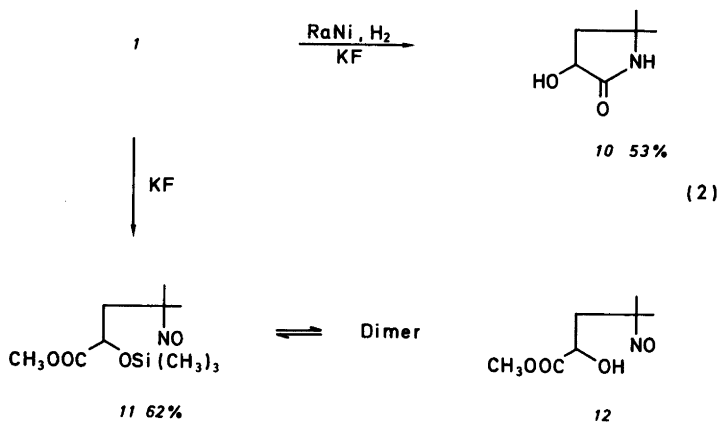
The inversion barrier of the tetrahedral nitrogen in compounds 1-9 is high, which results in formation of stereoisomeric mixtures of isoxazolidines

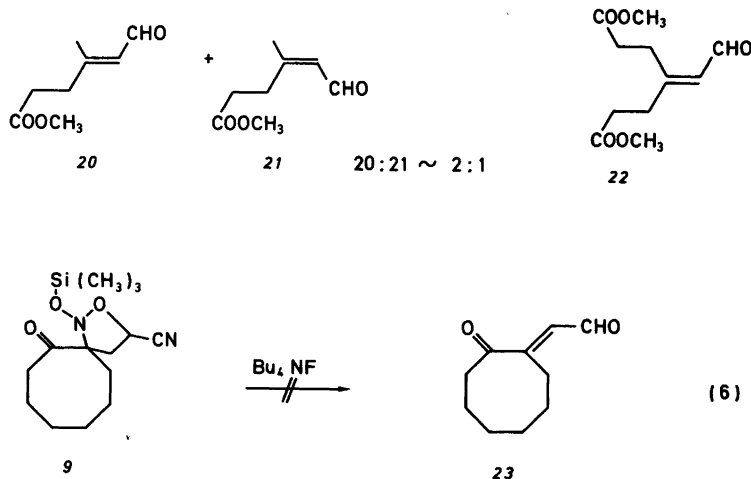
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1. $\text{R}^1 = \text{R}^2 = \text{CH}_3, \text{R}^3 = \text{COOCH}_3$
2. $\text{R}^1 = \text{R}^2 = \text{CH}_3, \text{R}^3 = \text{CN}$
3. $\text{R}^1 = \text{R}^2 = \text{CH}_3, \text{R}^3 = \text{CHO}$
4. $\text{R}^1, \text{R}^2 = (\text{CH}_2)_4, \text{R}^3 = \text{COOCH}_3$
5. $\text{R}^1, \text{R}^2 = (\text{CH}_2)_4, \text{R}^3 = \text{CN}$

6. $\text{R}^1 = \text{CH}_3, \text{R}^2 = \text{CH}_2\text{CH}_2\text{COCH}_3, \text{R}^3 = \text{CN}$
7. $\text{R}^1 = \text{CH}_3, \text{R}^2 = \text{CH}_2\text{CH}_2\text{COOCH}_3, \text{R}^3 = \text{CN}$
8. $\text{R}^1 = \text{R}^2 = \text{CH}_2\text{CH}_2\text{COOCH}_3, \text{R}^3 = \text{CN}$
9. $\text{R}^1, \text{R}^2 = (\text{CH}_2)_6\text{CO}, \text{R}^3 = \text{CN}$





(1). The *N*-trimethylsilyloxyisoxazolidines are unstable oils, which decompose on standing for a few weeks.

Catalytic hydrogenation of **1** gives the pyrrolidone, **10** (2). The more sterically hindered **4** gives the *N*-hydroxypyrrolidone, **19** (5) as the only product identified. When **1** was heated with potassium fluoride it rearranged to the deep blue nitroso derivative, **11**, and small amounts of the desilylated derivative, **12**. The fluoride ion cleaves the Si–O bond of **1** and forms trimethylfluorosilane and an α -hydroxy- γ -nitroso ester which then is resilylated to **11**. The cyano derivative, **2**, rearranged to the corresponding nitroso derivative, **13**, simply on heating. **13** crystallized slowly on standing, forming a colourless dimer, **14**, which again turned blue on heating indicating dissociation to the monomeric form (**3**).

When the cyano derivatives **2** and **5** were heated with potassium fluoride without any solvent the reaction took a different course. Trimethylsilanol, hydrocyanic acid and the nitroso group were eliminated and 3-methylbutenal (senecioaldehyde), **15**, and cyclopentylideneacetaldehyde, **17**, were obtained in good yields. They were contaminated by small amounts of blue nitroso compounds, presumably **16** and **18**. The yield was lower when the reaction was carried out in refluxing 1,2-dichloroethane or methylene chloride and with Bu₄NF · 3H₂O as catalyst. It appears that the fluoride ion decomposes the α,β -unsaturated aldehyde formed and removal of the aldehyde by distillation when formed improves the yield. The mechanism of the rearrangement is depicted in (4). This reaction seems to be a

convenient procedure for the preparation of 3-methylbutenal from acrylonitrile and 2-nitropropane. Since the reaction could have some synthetic value for transformation of secondary nitro compounds into α,β -unsaturated aldehydes the investigation was extended to a few other secondary nitro compounds. Crude **7** and **8** were treated with tetrabutylammonium fluoride trihydrate at 80 °C for ca. 25 min in 1,2-dichloroethane as solvent. The corresponding aldehydes, **20**–**22**, were obtained in a yield of ca. 20%. The cyclic derivative, **9**, did not give any detectable amount of the aldehyde **23** (6).

EXPERIMENTAL

2-Trimethylsilyloxy-3,3-dimethyl-5-carbomethoxyisoxazolidine, **1**. To 2-nitropropane (5.0 g, 0.055 mol), triethylamine (6.68 g, 0.07 mol), and methyl acrylate (4.73 g, 0.055 mol) in dry acetonitrile (20 ml) chlorotrimethylsilane (5.96 g, 0.055 mol) was added dropwise at room temperature. The mixture was stirred for 30 min at room temperature and then for 1 h at 50 °C. The solution was filtered and the solvent evaporated *in vacuo*. The product was taken up in chloroform, and washed with water, dried over anhydrous Na₂SO₄, filtered, evaporated, and distilled *in vacuo*, b.p. 60 °C 10 mmHg, blue-green liquid. The yield of **1** was 12.2 g, 93%. The NMR spectrum showed the presence of two isomers. ¹H NMR, major isomer, (CDCl₃): δ 0.16 (9 H, s), 1.18 (3H, s), 1.26 (3H, m), 1.9–2.8 (2H, m), 3.76 (3H, s), 4.92 (1H, dd, *J* 10.4, 4.6 Hz). The blue colour indicates the presence of a nitroso compound, presumably **11**.

3-Hydroxy-5,5-dimethyl-2-pyrrolidone, 10. **1** (2.4 g, 0.01 mol) was hydrogenated at room temperature over RaNi (1.5 g, slurry) in ethanol (20 ml) and acetic acid (2.0 ml) in the presence of potassium fluoride (50 mg). The hydrogen absorption stopped after 48 h. The catalyst was filtered off and the solution evaporated. A viscous oil was obtained, from which a white solid, **10**, separated after a few days. It was filtered and crystallized from methanol (0.78 g, 53 %) m.p. 178–180 °C. ¹H NMR (D₂O): δ 1.24 (3H, s), 1.30 (3H, s), 1.78 (1H, dd, *J* 12.8, 8.8 Hz), 2.4 (1H, dd, *J* 12.8, 8.4 Hz, ABX spectrum), 4.50 (1H, t, 8.6 Hz), 4.7 (H₂O, s). IR (KBr): 1100 (s), 1680 (br. s), 3280 (br. s) cm⁻¹.

Methyl 2-trimethylsilyloxy-4-nitroso-4-methyl-pentanoate, 11. Finely powdered potassium fluoride (40 mg) was mixed thoroughly with **1** (1.0 g, 0.004 mol) and distilled *in vacuo*. A deep blue liquid b.p. 106–108 °C/14 mmHg was obtained. The crude yield was 0.62 g (62 %). ¹H NMR (CDCl₃): δ 0.1 (9H, s), 1.08 (3H, s), 1.13 (3H, s), 2.1–2.9 (2H, m), 3.71 (3H, s), 4.19 (1H, dd, *J* 9.2, 4.8 Hz). IR (film): 852 (s), 1260 (s), 1752 (s), 2965 (m) cm⁻¹. The NMR spectrum indicated the presence of minor amounts of the hydroxy derivative **12**.

2-Trimethylsilyloxy-3,3-dimethyl-5-cyanoisoxazolidine, 2. Chlorotrimethylsilane (8.94 g, 0.090 mol) was added dropwise at room temperature to a mixture of 2-nitropropane (7.5 g, 0.084 mol), triethylamine (8.08 g, 0.080 mol) and acrylonitrile (4.38 g, 0.082 mol) in dry acetonitrile (20 ml). The mixture was stirred for 30 min at room temperature and then for 2 h at 50 °C. The solution was filtered, to remove the ammonium salt and evaporated *in vacuo*. The product was taken up in methylene chloride and washed with water, dried over anhydrous Na₂SO₄, filtered, evaporated and distilled *in vacuo*. A blue liquid, **2**, b.p. 56 °C/0.5 mmHg was obtained. The yield of **2** was 16.78 g (96 %). ¹H NMR (CDCl₃): δ 0.14 (9H, s), 1.26 (6H, s), 2.22 and 2.63 (2H, *J* 11.8, 10.0, 4.2 Hz, ABX spectrum), 4.94 (1H, dd, *J* 10.0, 4.2 Hz). The blue colouration originates from minor amounts of the nitroso compound, **13**.

1-Trimethylsilyloxy-1-cyano-3-nitroso-3-methyl-butane, **13**, and its dimer, **14**. Distillation of **2** (1.0 g) at 11 mmHg gave a green liquid, **13**, b.p. 102–104 °C (0.72 g, 72 %), which soon solidified. It was contaminated by some unrearranged starting material, **2**. The solid was recrystallized from ether giving colourless crystals of **14**, m.p. 82 °C. ¹H NMR (CDCl₃) **13**: δ 0.14 (9H, s), 1.12 (3H, s), 1.18 (3H, s), 2.56 and 2.87 (2H, *J* 14.6, 7.9, 4.9 Hz, ABX spectrum), 4.41 (1H, dd, *J* 7.9, 4.9 Hz). IR (CHCl₃): 850 (s), 1250 (s), 1560 (s), 2980 (s) cm⁻¹. (Found: C 50.12; H 8.43. Calc. for C₉H₁₈N₂O₂Si: C 50.46; H 8.41). The dimer **14** had a more complicated ¹H NMR spectrum with multiplets at δ ≈ 1.5, 2.4 and 4.4.

3-Methyl-2-butenal, **15**. *Method A*. To **2** (6.0 g, 0.03 mol), powdered potassium fluoride (2 g) was added and the mixture was stirred well and distilled *in vacuo* at 36 mmHg. **15** (1.6 g, 69 %) b.p. ca. 70 °C was obtained, contaminated by some blue nitroso compound, **16**. Pure **15** was obtained by repeating the distillation over potassium fluoride at 35 mmHg. ¹H NMR (CDCl₃): δ 1.83 (3H, s), 2.03 (3H, s), 5.70 (H, br.d, *J* 8.0 Hz), 9.76 (1H, d, *J* 8.0 Hz).

Method B. Tetrabutylammonium fluoride trihydrate (500 mg) was added to **2** (500 mg, 2.3 mmol) in 1,2-dichloroethane (10 ml). The colour of the solution changed to deep green. The mixture was refluxed for 25 min, cooled and diluted with light petroleum. The solution was decanted from the precipitated oily material which was extracted with light petroleum. The combined organic phases were dried with anhydrous Na₂SO₄ and evaporated. The residue (130 mg, crude) contained **15** (spectroscopic yield ca. 34 %).

2-Trimethylsilyloxy-5-carbomethoxy-isoxazolidine-3-spirocyclopentane, **4**. To nitrocyclopentane (3.4 g, 0.03 mol), triethylamine (4.04 g, 0.04 mol) and methyl acrylate (3.87 g, 0.04 mol) in dry acetonitrile (20 ml) chlorotrimethyl silane (3.30 g, 0.03 mol) was added slowly at room temperature with stirring. The mixture was then heated at 50 °C for 2.5 h. Usual work-up gave **4** as blue liquid, b.p. 98–102 °C/0.2 mmHg (7.86 g, 96 %). ¹H NMR (CDCl₃): δ 0.18 (9H, s), 1.4–2.0 (8H, m), 2.23 (1H, dd, *J* 11.4, 3.8 Hz), 2.70 (1H, dd, *J* 11.4, 10.7 Hz), 3.83 (3H, s), 4.86 (1H, dd, *J* 10.7, 3.8 Hz).

1,3-Dihydroxy-2-pyrrolidone 5-spirocyclopentane, **19**. **4** (2.0 g) was hydrogenated over RaNi (0.50 g, slurry) in ethanol) at 2 atm. and 25 °C in ethanol (25 ml) and acetic acid (2.5 ml) in presence of potassium fluoride (0.050 g). After 48 h the hydrogen absorption had stopped. Filtration and evaporation *in vacuo*, gave a brown oil. Addition of chloroform precipitated **19** (0.41 g, 33 %), m.p. 186–188 °C from methanol. The compound gave an intense blue colouration with Fe³⁺, indicating the hydroxamic acid function. ¹H NMR (D₂O): δ 1.4–1.9 (9H, m), 2.5 (1H, dd, *J* 8.2, 13.3 Hz), 4.41 (1H, t, *J* 8 Hz), 4.7 (br.s). IR (KBr): 1050 (m), 1680 (s), 2950 (m), 3350 (s) cm⁻¹. MS: 171 (M⁺). Evaporation of the chloroform solution gave a viscous liquid, which could not be crystallized.

2-Trimethylsilyloxy-5-cyano-isoxazolidine 3-spirocyclopentane, **5**. To nitrocyclopentane (3.45 g, 0.03 mol), triethylamine (3.03 g, 0.03 mol) and acrylonitrile (1.80 g, 0.03 mol) in dry acetonitrile (20 ml), chlorotrimethylsilane (3.24 g, 0.03 mol) was added dropwise at room temperature. The mixture was then stirred at 50 °C for 1 h. Usual work-up gave **5** as a green liquid b.p. 92–94 °C/0.1 mmHg. The yield of **5** was (7.09 g, 98 %). ¹H NMR (CDCl₃):

δ 0.2 (9H, s), 1.7 (8H, m), 2.30 (1H, dd, J 12.3, 3.6 Hz), 2.82 (1H, dd, J 12.0, 9.4 Hz), 4.91 (1H, dd, J 9.4, 3.6 Hz).

Cyclopentylidene acetaldehyde, 17. Finely powdered potassium fluoride (3 g) was mixed with 5 (7.0 g, 0.03 mol) and distilled *in vacuo* at 14 mmHg. 17 (2.4 g) distilled into the receiver at ca. 64 °C (lit.⁵ 53–56 °C/12 mmHg). It was contaminated by a blue nitroso compound, presumably 18. Redistillation gave colourless 17. ¹H NMR (CDCl₃): δ 1.5–3.0 (8H, m), 5.98 (1H, d, quint, J 8.0, 1.0 Hz), 9.83 (1H, d, J 8.0 Hz). 17 was formed in a yield of ca. 50 % (as determined by NMR) by heating 5 with one equivalent of Bu₄NF · 3H₂O in dichloroethane for 30 min at 80 °C.

2-Trimethylsilyloxy-3,3-dimethyl-5-formyl-isoxazolidine, 3. To 2-nitropropane (5.0 g, 0.05 mol), triethylamine (6.06 g, 0.06 mol) in dry benzene (20 ml) and dry acetonitrile (10 ml), chlorotrimethylsilane (11.92 g, 0.10 mol) was added dropwise with stirring at room temperature. After addition stirring was continued for 30 min and the solution was filtered. Acrolein (6.2 g, 0.11 mol) was slowly added to the filtrate with stirring at room temperature. After ca. 1 h the solution was evaporated *in vacuo*. Usual work-up gave 3, (yield 60 %) as a colourless liquid, b.p. 50–52 °C/0.3 mmHg, contaminated by some, *4-methyl-4-nitropentanal*, formed by Michael addition of 2-nitropropane to acrolein. ¹H NMR (CDCl₃): δ 0.2 (9H, s), 1.15 (3H, s), 1.26 (3H, s), 2.0–2.4 (2H, m), 4.43 (1H, ddd, J 8.8, 6.8 and 1 Hz), 9.76 (1H, d, J 1 Hz). 3 decomposes slowly on standing.

2-Trimethylsilyloxy-3-methyl-3-(β -carbomethoxyethyl)-5-cyano-isoxazolidine, 7 and *E* and *Z* methyl *4-methyl-5-formyl-4-pentenoate* 20, 21. A mixture of methyl 4-nitropentanoate (1.61 g, 0.01 mol), BSA (3.0 g, 0.015 mol), acrylonitrile (0.79 g, 0.015 mol) and a few drops of triethylamine in benzene (7.5 ml) and acetonitrile (2.5 ml) was refluxed for 3 h. The solution was extracted several times with water, dried over sodium sulfate and evaporated *in vacuo*. The crude yield of 7 was 2.6 g (85 %). ¹H NMR (CDCl₃): δ 0.18 (9H, s), 1.23 (3H, s), 1.8–2.7 (6H, m), 3.65 (3H, s), 4.9 (1H, m). A somewhat less pure product was obtained by refluxing the nitro compound and acrylonitrile with one equivalent of (CH₃)₃SiCl/Et₃N in toluene–acetonitrile (3:1) for 1–2 h.

The isoxazolidine 7 (2.4 g, 0.0077 mol) was rearranged to a mixture of the *E* and *Z* aldehydes, 20 and 21, by heating with tetrabutylammonium fluoride trihydrate (1.5 g, 0.0048 mol) in dichloroethane (50 ml) at 80 °C for 25 min. The reaction mixture was washed with water, evaporated *in vacuo* and purified by preparative TLC (SiO₂, CHCl₃). 0.32 g (21 %) of a mixture of 20 and 21 (2:1) was obtained as an oil. ¹H NMR (CDCl₃):

δ 1.98 (3H, d, J 1 Hz, isomer 21), 2.19 (3H, d, J 1 Hz, isomer 20), 2.2–2.9 (4H, m), 3.67 (3H, s), 5.82 (1H, br.d. J 8 Hz), 10.0 (1H, d, J 8 Hz).

2-Trimethylsilyloxy-3,3-(bis- β -carbomethoxyethyl)-5-cyano-isoxazolidine, 8, and *3,3-bis(2-carbomethoxyethyl)propenal*, 22, were prepared according to the same method as 7, 20 and 21, respectively. ¹H NMR (CDCl₃): δ 0.18 (9H, s), 1.7–2.7 (10 H, m), 3.69 (6H, s), 4.98 (1H, m). 22: δ 2.3–2.9 (8H, m), 3.66 (6H, s), 5.81 (1H, d, J 7.7 Hz), 9.98 (1H, d, J 7.6 Hz). The crude yield of 8 was 60 %, and the yield of 22, purified by TLC, oil, was ca. 20 %. MS 22: (M⁺ + 1) 209. ¹H NMR (CDCl₃): δ 2.1–3.0 (8H, m), 3.64 (3H, s), 5.81 (1H, d, J 7.7 Hz), 10.0 (1H, d, J 7.7 Hz).

9 was obtained from 2-nitrocyclooctanone, acrylonitrile and BSA (1.5 eqv.) according to the method described for 7 in a practically quantitative yield (crude). ¹H NMR (CDCl₃): δ 0.2 (9H, m), 1.2–3.3 (14 H, m), 4.91 (1H, m). 23 could not be detected when 9 was treated with tetrabutylammonium fluoride in the same ways as 7.

Tetrabutylammonium fluoride trihydrate. A solution of potassium hydroxide (5.6 g, 0.1 mol) and potassium fluoride (11.5 g, 0.2 mol) in water (15 ml) was extracted with a solution of tetrabutylammonium hydrogen sulfate (34.0 g, 0.1 mol) in methylene chloride (100 ml) in a separating funnel. The mixture was filtered and the layers were separated. The organic phase was washed with a solution of potassium fluoride (5.0 g) in water (6 ml) and evaporated. Tetrabutylammonium fluoride was obtained as a viscous oil in a crude yield of ca. 90 %. This procedure is similar to the one described for the preparation of tetrabutylammonium chloride.⁶

5-Nitrohexan-2-one,⁷ *methyl 4-nitropentanoate*,⁸ *dimethyl 4-nitroheptandioate*⁹ and *2-nitrocyclooctanone*¹⁰ were prepared according to the literature.

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