Synthesis of 2- and 3-Nitrooxypropanol by Chemoselective Reduction of Methyl 2- and 3-Nitrooxypropionoate

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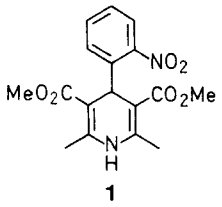
Highly chemoselective reduction of methyl 2- and 3-nitrooxypropionate (**9**) and (**12**) with calcium borohydride was accomplished to give the desired 2- and 3-nitrooxypropanols (**6** and **13**) in good yields without affecting the nitrooxy group.

Nitrate compounds such as nitroglycerin, nicorandil and nipradiol are clinically useful drugs.[1] In this context, we examined the preparation of 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates **3**[2] possessing nitrooxy groups. These compounds are expected to be the potentially active Ca^{++} channel antagonists similar to nifedipine (**1**)[3] and nicardipine hydrochloride (**2**).[4]



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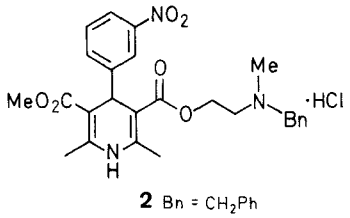
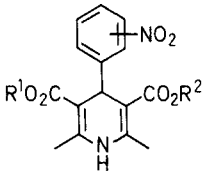


2 Bn = CH_2Ph



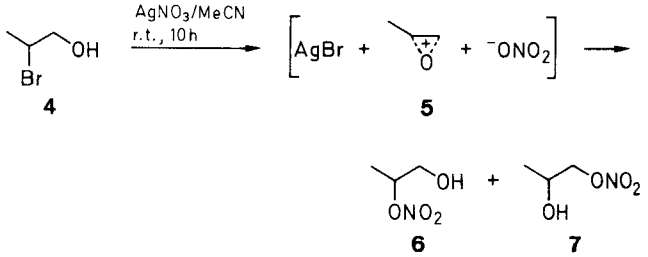
3

R^1 = alkyl, $CH_2CH(ONO_2)CH_3$

R^2 = $CH_2CH(ONO_2)CH_3$, $CH_2CH_2CH_2ONO_2$, $CH(CH_2ONO_2)_2$

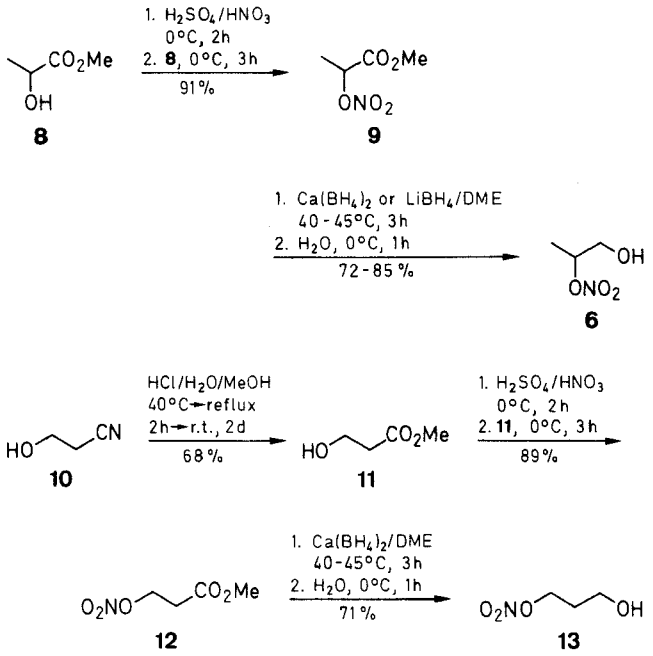
For the preparation of **3** by esterification of 4-phenyl-1,4-dihydropyridine-3-carboxylic acid, it was necessary to synthesize nitrooxyalkanol derivatives. We examined two methods, for the synthesis of nitrooxypropanols **6** and **13**; displacement of bromine in a bromohydrin by nitrate and chemoselective reduction of nitrooxyalkanoates.

The synthesis of 2-nitrooxypropanol (**6**) from bromohydrin **4** by treatment of **4** with silver nitrate[5] failed to give **6** selectively, resulting in a 4:3 mixture of **6** and **7**. The observed nonregioselectivity can be explained by the formation of an oxonium intermediate **5** and the subsequent attack by nitrate anion (Scheme **A**).



Scheme **A**

Next, we attempted the chemoselective reduction of the methyl 2-nitrooxypropionate (**9**), which was obtained by nitration[6] of methyl 2-hydroxypropionate (**8**) with nitric acid/sulfuric acid at 0 °C. Reduction of **9** with lithium aluminum hydride gave propane-1,2-diol while reduction with sodium borohydride gave starting material only. Use of Vitride as reducting agent afforded **6** in 45% yield. In order to improve the yield, reduction of **9** with other hydrides was examined. The use of calcium borohydride, prepared from calcium chloride/sodium borohydride *in situ* in 1,2-dimethoxyethane (DME), gave **6** in 85% yield. Reduction of **9** with lithium borohydride, prepared *in situ* from lithium chloride/sodium borohydride in 1,2-dimethoxyethane also afforded **6** in 72% yield (Scheme **B**).



Scheme **B**

Table 1. Chemoselective Reduction of Methyl 2- and 3-Nitrooxypropionates (**9**) and (**12**) with $NaBH_4$/Metal Salts (MX_n)

Substrate	Metal Salt (MX_n)	Reaction Conditions			Yield[a] (%)
		Solvent	Temperature (°C)	Time (h)	
9	$CaCl_2$	DME	45	3	85
9	LiCl	DME	40	3	72
12	$CaCl_2$	EtOH	0	2	21
12	$CaCl_2$	diglyme	30	1	28
12	$CaCl_2$	THF	25	3	–[b]
12	$CaCl_2$	DME	45	3	71
12	$MgCl_2$	Et_2O	30	1	26
12	$MgCl_2$	diglyme	30	1	22
12	$MgCl_2$	DME	45	5	39
12	LiCl	diglyme	30	1	17
12	LiCl	DME	40	3	55

[a] Isolation yield of **6** and **13**.
[b] No reaction.

Table 2. 2- and 3-Nitrooxypropionates **9**, **12** and Nitrooxypropanols **6**, **13** Prepared

Product	bp (°C)/Torr	Molecular Formula[a] or Lit. bp (°C)/Torr	IR[b] (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)	MS-CI[d] m/z (%)
9	38–39/1.2	$C_4H_7NO_5$ (149.1)	1280, 1646, 1757	1.56 (d, 3H, J = 7), 3.82 (s, 3H), 5.26 (q, 1H, J = 7)	150 (M^+ + 1, 20), 90 (20), 59 (47), 46 (100)
12	59–62/0.5	$C_4H_7NO_5$ (149.1)	1285	2.77 (t, 2H, J = 6), 3.75 (s, 3H), 4.74 (t, 2H, J = 6)	150 (M^+ + 1, 20), 103 (5), 87 (15), 59 (23), 46 (100)
6	52–54/0.2	50–52/1[f,g]	1278, 1625, 3368	1.37 (d, 3H, J = 7), 2.48 (br s, 1H)[e], 3.68 (dd, 1H, J = 12.5, 7), 3.80 (dd, 1H, J = 12.5, 4), 5.20 (m, 1H)	122 (M + 1, 3), 104 (8), 90 (5), 75 (10), 59 (100), 46 (88)
13	56–58/0.15	$C_3H_7NO_4$ (121.1)	1283, 1634, 3368	1.77 (s, 1H)[e], 1.99 (quint, 2H, J = 6), 3.78 (t, 2H, J = 6), 4.62 (t, 2H, J = 6)	122 (M + 1, 10), 104 (16), 75 (17), 59 (27), 46 (100)

[a] Microanalyses: C ±0.1, H ±0.1, N ±0.5. It was difficult to get correct elemental analysis data for compound **9**, probably due to its volatility.
[b] Recorded on a Perkin-Elmer 1760 FI-IR Spectrometer.
[c] Recorded on a Varian VXR-200 Spectrometer.
[d] Recorded on a JEOL JMS-SX102 Spectrometer.
[e] Treatment with D_2O caused the signal to disappear.
[f] Isomeric mixtures.

Similarly, we could prepare 3-nitrooxypropanol **(13)** by chemoselective reduction of methyl 3-nitrooxypropionate **(12)**. Treatment of 3-hydroxypropanenitrile **(10)** with hydrogen chloride in aqueous methanol, according to the modified procedure of Fein and Fisher,[7] yielded methyl 3-hydroxypropionate **(11)**; this was subsequently converted to methyl 3-nitrooxypropionate **(12)** by treatment with nitric acid/sulfuric acid. The results of reduction of **12** with calcium borohydride, lithium borohydride, magnesium borohydride, in various solvents such as 1,2-dimethoxyethane, ethanol, diglyme, tetrahydrofuran, and diethyl ether are summarized in Table 1.

Again the use of calcium borohydride in dimethoxyethane gave the best results, giving **13** in 71% yield.

Methyl 3-Hydroxypropionate (11):
Dry HCl (980 g, 26.88 mol) is passed through a mixture of MeOH (2 L) and H_2O (320 g, 17.76 mol) in an ice bath. Cyanohydrin **10** (1050 g, 14.77 mol) is added dropwise with stirring at 40 °C, the mixture is refluxed for 2 h and then stirred at r.t. for 2 h. $NaHCO_3$ (785 g, 9.34 mol) is added with stirring, the precipitate is filtered off. The filtrate is evaporated at reduced pressure to furnish the crude ester **11**, which is purified by distillation; yield: 1046 g (68%); bp 71–73 °C/9 Torr (Lit.[7], bp 70 °C/10 Torr).

Methyl 2- and 3-Nitrooxypropionates (9,12); General Procedure:
Fuming HNO_3 (114 mL, 2.70 mol) is added dropwise to an ice cold solution of H_2SO_4 (152 mL, 2.70 mol) with stirring. After 2 h at 0 °C, **8** or **11** (2.10 mol) is added dropwise at the same temperature and the mixture is stirred for 3 h. The mixture is poured into ice-water (2 L) and extracted with Et_2O (1 L). The organic layer is washed with sat. $NaHCO_3$ (5 × 100 mL) and H_2O (2 × 100 mL), dried (Na_2SO_4), and evaporated. The remaining crude product is distilled to provide the pure nitrooxypropionates, **9**; yield: 285 g (91%), **12**; yield: 279 g (89%) (Table 2).

2- and 3-Nitrooxypropanols (6,13); General Procedure:
To a solution of $Ca(BH_4)_2$, prepared from $CaCl_2$ (0.41 mol) and $NaBH_4$ (0.82 mol) in dry DME (600 mL) under N_2-atmosphere, is added methyl nitrooxypropionate (1.09 mol) dropwise at 40 °C. The mixture is stirred at 45 °C for 3 h and then at r.t. for 10 h. After cooling to 0 °C H_2O (163 mL) is added and the mixture is subsequently stirred at r.t. for another 1 h. The precipitated salt is filtered off, the filtrate is extracted with Et_2O (3 × 400 mL), and the combined organic extracts are washed with brine and dried (Na_2SO_4). The solvent is evaporated and the residue is distilled to provide the pure alcohol; **6**; yield: 112 g (85%), **13**; yield: 94 g (71%) (Table 2).

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