Synthesis of 3-Nitropropanol Homologues

James K. Addo,[a] Paul Teesdale-Spittle,[b] John O. Hoberg*[c]

[a] School of Chemical and Physical Sciences, Victoria University of Wellington, Wellington, New Zealand

[b] School of Biological Sciences, Victoria University of Wellington, Wellington, New Zealand

[c] Department of Chemistry, University of Wyoming, Laramie, WY 82071, USA
Fax +1(307)7662807; E-mail: hoberg@uwyo.edu

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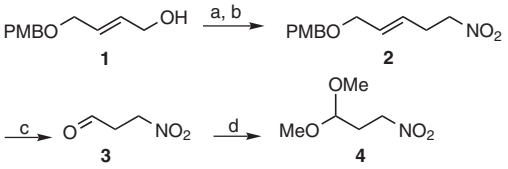
Abstract: Several high yielding routes to oxygenated nitropropanes have been developed that include a palladium catalyzed nitro allylation of allylic carbonates, nitration of brominated compounds and a nitro aldol condensation/hydrogenation sequence.

Key words: nitroaldol, 3-nitropropanol, 3-nitropropanal, 3-nitropropanoic acid, ethyl glyoxylate

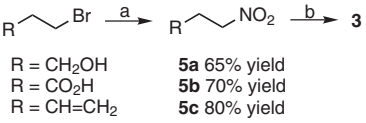
Organonitro compounds are valuable compounds in synthetic organic chemistry as they are easily transformed into a wide variety of functionality, allowing access to target molecules such as amines, hydroxylamines, imines and oximes.[1–3] Oxygenated nitroalkenes and nitroalkanes are particularly versatile synthetic intermediates as both functional groups are capable of being further elaborated.[4,5] We recently required access to 3-nitropropanals and 3-nitropropanols and have investigated routes to these compounds. Described herein are several routes to homologues of 3-nitropropanols from commercially available or readily available starting materials. These routes include a palladium catalyzed nitromethane allylation using allylic carbonates,[6] nitration of bromated compounds[7] and a nitro aldol condensation/hydrogenation sequence.[5,8–10]

The traditional method for preparing these compounds is from acrolein,[11] however the toxicity of acrolein detracts from its use and often limits its availability due to shipping restrictions. We therefore investigated the palladium catalyzed allylation of nitromethane using allylic carbonates, which has garnered considerable attention recently,[6] and was envisioned to give access into our target intermediates after subsequent elaboration of the resulting olefinic moiety (Scheme 1). Thus, treatment of **1**[12,13] with ethyl chloroformate gave the allylic carbonate, which underwent palladium catalyzed reaction to give nitroalkene **2** in good overall yield. The 1,5 N-O relationship formed in **2** is a common relationship and thus is useful in itself.[14] For our purpose, subsequent ozonolysis of **2** gave crude **3**, which was converted to the acetal **4**, in reasonable overall yield.

An alternative to the above strategy involves nitration of brominated substrates (Scheme 2). Although the addition of $AgNO_2$ to 3-bromopropanol has been reported, no experimental conditions were given.[15] Thus, we began with the optimization of this reaction and found that refluxing conditions are required for the formation of 3-nitropropanol (**5a**). Encouraged by the simplicity of this reaction, we treated 3-bromopropanoic acid under identical conditions to give **5b** in good yield. This series can be completed by the formation of nitrobutene **5c** followed by ozonolysis to give 3-nitropropanal (**3**) in good overall yield.



Scheme 1 a) $ClCO_2Et$, Py, CH_2Cl_2, 95%; b) $MeNO_2$, $Pd_2(dba)_3$, Ph_3P, CH_2Cl_2, 61%; c) O_3, CH_2Cl_2, –78 °C, then Me_2S; d) $HC(OMe)_3$, MeOH, 52% two steps.



Scheme 2 a) $AgNO_2$, Et_2O, reflux; b) O_3, CH_2Cl_2, –78 °C, then Me_2S, 55%.

Finally, we investigated the Henry reaction using ethyl glyoxylates (Scheme 3). Aldol reaction of nitromethane with acetaldehyde dimethyl acetal or ethyl glyoxylate gave the corresponding nitro alcohols, which underwent elimination via a mesylation/silica gel sequence to give **6a** and **6b**, respectively.[16,17] Hydrogenation with Pd/C gave the reduced nitroalkanes **4** and **7b** in good overall yields. Similarly, treatment of ethyl glyoxylate with nitroethane provided nitroalkene **6c**, which also is easily reduced.[18] Asymmetric reduction was also attempted using (*S*,*S*)-Me-DUPHOS-Rh as the ligand under transfer hydrogenation conditions with ammonium formate. However, we obtained only a 25% yield and equally poor enantiomeric excess. Efforts at optimizing this reaction are underway; however, Carreira has just recently reported a highly efficient enantioselective reduction of nitroalkenes using JOSIPHOS and CuF_2.[19]

In conclusion, several high yielding routes to oxygenated nitropropanes have been developed that alleviate the need

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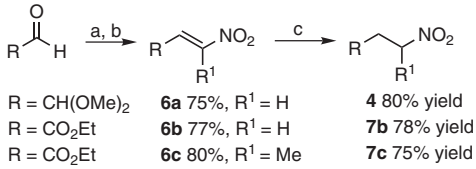

Scheme 3 a) $MeNO_2$ or $EtNO_2$, H_2O, alumina; b) MsCl, *i*-Pr_2EtN, CH_2Cl_2, silica; c) H_2, Pd/C, EtOAc

for toxic acrolein. The ease, simplicity and cost of these routes provide for straightforward access into this series of compounds.

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian spectrometer with chemical shifts reported relative to $CDCl_3$ (δ = 7.23 and 77.3 ppm, respectively). All solvents were dried prior to use, standard syringe techniques were used for handling air-sensitive reagents, and all reactions were carried out under Ar.

1-*p*-Methoxybenzyloxy-5-nitro-2-pentene (2)
To a solution of alcohol **1** (3.00 g, 16.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added pyridine (2.72 mL, 34.0 mmol) followed by dropwise addition of ethyl chloroformate (1.61 mL, 16.8 mmol). The reaction was allowed to warm to r.t. and stirred until TLC indicated complete reaction. The reaction mixture was quenched by addition of sat. NH_4Cl and extracted with Et_2O (3 × 15 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated in vacuo to give a residue, which was chromatographed on silica gel (10% EtOAc–hexanes) to give ethyl 4-*p*-methoxybenzyloxy-2-butene-1-carbonate as an oil (4.48 g, 95% yield).

^1H NMR: δ = 7.26 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 5.89 (m, 2 H), 4.63 (d, *J* = 4.8 Hz, 2 H), 4.46 (s, 2 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.02 (d, *J* = 4.5 Hz, 2 H), 3.80 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 159.2, 154.9, 131.7, 130.1, 129.3, 125.8, 113.7, 71.9, 69.3, 67.4, 64.0, 55.2, 14.2.

HRMS: *m/z* [M + NH_4] calcd for $C_{15}H_{24}NO_5$: 298.1654; found: 298.1649.

To a degassed solution of PPh_3, (186.2 mg, 10 mol%) and $Pd_2(dba)_3$ (162.5 mg, 2.5 mol%, 0.178 mmol) in CH_2Cl_2 was added nitromethane (5 mL, 92.4 mmol). After stirring for 5 min, the above carbonate (2.00 g, 7.10 mmol) was added. The resulting mixture was stirred at r.t. for 2 h and concentrated in vacuo. The crude product was directly purified by flash chromatography on silica gel (10% EtOAc–hexanes) to give **2** as an oil (1.03 g, 61% yield).

^1H NMR: δ = 7.26 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.70 (m, 2 H), 4.43 (s, 2 H), 4.42 (t, *J* = 7.2 Hz, 2 H), 3.95 (d, *J* = 5.1 Hz, 2 H), 3.80 (s, 3 H), 2.76 (m, 2 H).

^{13}C NMR: δ = 159.5, 131.3, 130.4, 129.7, 126.7, 114.1, 75.1, 72.2, 70.0, 55.5, 30.3.

HRMS: *m/z* [M + NH_4] calcd for $C_{13}H_{21}N_2O_4$: 269.1501; found: 269.1495.

3-Nitropropanal Dimethyl Acetal (4)
Compound **2** (2.37 g, 10.00 mmol) was dissolved in CH_2Cl_2 (15 mL). The solution was cooled to –78 °C with stirring and then treated with ozone for 5 min. The reaction was quenched with dimethyl sulfide (1 mL), left to stir at –78 °C for 1 h and then evaporated at reduced pressure to give crude 3-nitropropanal (**3**). The oil was dissolved in MeOH (15 mL), then trimethyl orthoformate (698 mg, 6.58 mmol) and *p*-TsOH·H_2O (20 mg) were added. The mixture was stirred at r.t. for 3.5 h and the solvent was removed under vacuum. Flash chromatography (15% EtOAc–hexanes) gave **4** as an oil (774 mg, 52% overall yield from **2**).

^1H NMR: δ = 4.48 (m, 3 H), 3.39 (s, 6 H), 2.21 (m, 2 H).

^{13}C NMR: δ = 102.1, 71.3, 54.2, 30.6.

Reaction of Silver Nitrite with Bromides; General Procedure
Anhydrous Et_2O (40 mL) was added to a mixture of $AgNO_2$ (13.68 g, 89.0 mmol) and the bromide (29.6 mmol) in a flask protected from light. The reaction mixture was refluxed overnight, cooled and filtered, then purified by distillation or crystallization.

3-Nitropropanol (5a)
Yield: 65%.

^1H NMR: δ = 4.53 (t, *J* = 7.2 Hz, 2 H), 3.75 (t, *J* = 5.9 Hz, 2 H), 2.23 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 72.7, 59.1, 30.0.

3-Nitropropionic Acid (5b)
Yield: 70%.

^1H NMR: δ = 4.65 (t, *J* = 6.1 Hz, 2 H), 3.05 (t, *J* = 6.1, 2 H).

^{13}C NMR ($CDCl_3$): δ = 175.6, 69.3, 30.8.

4-Nitro-1-butene (5c)
Yield: 80%.

^1H NMR: δ = 5.75 (m, 1 H), 5.12 (m, 2 H), 4.42 (t, *J* = 6.1 Hz, 2 H), 2.76 (m, 2 H).

^{13}C NMR: δ = 132.0, 119.0, 74.9, 31.5.

3-Nitropropanal (3)
Nitropropene **5c** (1.00 g, 9.98 mmol) was dissolved in CH_2Cl_2 (15 mL). The solution was cooled to –78 °C with stirring and treated with ozone for 5 min. The reaction was quenched with dimethyl sulfide (1 mL), stirred at –78 °C for 1 h and then evaporated at reduced pressure to give **3** as an analytically pure oil (560 mg, 55% yield). As noted in the literature,[11b] compound **3** is unstable and should be used immediately upon formation.

Formation of 6a–c; General Procedure
Neutral alumina (10 g) was added to a solution of aldehyde (48.0 mmol) dissolved in nitromethane (10 mL, 145.0 mmol) (or nitroethane). The resulting cloudy suspension was stirred at r.t. overnight then filtered and washed with EtOAc (3 × 15 mL). The combined filtrate was concentrated in vacuo to give an oil, which was purified via flash chromatography (10% EtOAc–hexanes) to give the corresponding nitroalcohol. Spectral data were identical to that reported previously.[16,20] The nitroalcohol was dissolved in CH_2Cl_2 (20 mL) and cooled to –78 °C. Then MsCl was added dropwise followed by a solution of *N*,*N*-diisopropylethylamine (9.69 g, 75.0 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at –78 °C for 2 h and allowed to warm to r.t. After TLC indicated the reaction was over, the reaction mixture was poured onto ice-cold water and extracted with CH_2Cl_2. The organic phase was washed with H_2O, brine, dried with $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed on silica gel (5% EtOAc–hexanes) to give the corresponding nitroalkene.

3-Nitro-2-propenal Dimethylacetal (6a)
^1H NMR: δ = 7.20 (d, *J* = 13.5 Hz, 1 H), 7.02 (dd, *J* = 13.2, 3.2 Hz, 1 H), 5.15 (d, *J* = 3.4 Hz, 1 H), 3.39 (s, 6 H).

^{13}C NMR: δ = 142.7, 136.7, 98.2, 53.2.

Ethyl 3-Nitroacrylate (6b)
^1H NMR: δ = 7.68 (d, *J* = 13.6 Hz, 1 H), 7.09 (d, *J* = 13.6 Hz, 1 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR: δ = 162.9, 149.1, 127.9, 62.6, 14.1.

Ethyl 3-Methyl-3-nitroacrylate (6c)
^{1}H NMR: δ = 7.0 (s, 1 H), 4.2 (q, *J* = 7.2 Hz, 2 H), 2.5 (s, 3 H), 1.2 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 164.2, 160.0, 121.5, 61.8, 14.1, 14.0.

Hydrogenation of 6a–c; General Procedure
A suspension of nitroalkene (6.89 mmol) and 10% Pd/C (300 mg) in CH_2Cl_2 (10 mL) was hydrogenated at r.t. under a balloon of H_2 for 2 h. The mixture was filtered, concentrated in vacuo and the residue chromatographed on silica gel with 5% EtOAc–hexanes to give the corresponding nitroalkane.

Ethyl 3-Nitropropionate (7b)
^{1}H NMR: δ = 4.68 (t, *J* = 6.1 Hz, 2 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 2.99 (t, *J* = 6.1 Hz, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR: δ = 169.8, 69.9, 61.5, 31.1, 14.1.

HRMS: *m/z* [M + H] calcd for $C_5H_{10}NO_4$: 148.0609; found: 148.0790.

Ethyl 3-Nitrobutanoate (7c)
Alternatively, a mixture of ethyl-3-methyl-3-nitroacrylate (100 mg, 0.628 mmol), (*S*,*S*)-Me-DUPHOS-Rh (0.42 mg, 0.000628 mmol, 0.1 mol%), NH_4CO_2 (119 mg, 1.88 mmol) in CH_2Cl_2 (15 mL) in a flask previously evacuated with hydrogen was allowed to stir overnight. The mixture was filtered through celite and the combined filtrate evaporated in vacuo and directly chromatographed on silica with 5% EtOAc–hexanes as eluent.

^{1}H NMR: δ = 4.93 (m, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.17 (dd, *J* = 8.7, 12.2 Hz, 1 H), 2.72 (dd, *J* = 5.1, 12.2 Hz, 1 H), 1.62 (d, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR: δ = 169.4, 78.7, 61.5, 38.7, 19.6, 14.3.

HRMS: *m/z* [M + H] calcd for $C_6H_{12}NO_4$: 162.0766; found: 162.0731.

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