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Methyl 8-Nitrooctanoate as Reagent for 7-Methoxycarbonylheptyl Anion Synthon: New Syntheses of Methyl 9-Oxodecanoate and Methyl 9-Oxo-12-tridecenoate

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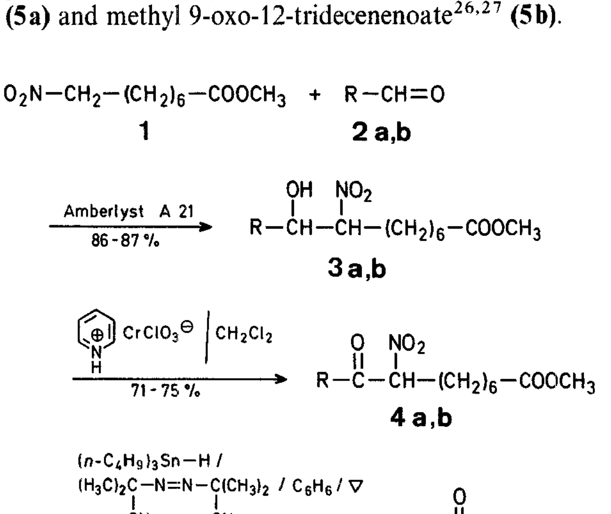
Primary nitroalkane derivatives play an important role in developing new methodologies in organic synthesis[1-19]. Recently we have devised a simple, general synthesis of 1,4-dicarbonyl compounds[16,17] including key intermediates for (*Z*)-jasmonoids and prostaglandins, via nitroaldol condensation, oxidation and direct or indirect denitration.

In course of our previous work we used 2-methyl-2-(2-nitroethyl)-1,3-dioxolane[16] and 2-(2-nitroethyl)-1,3-dioxolane[17] as reagents for 3-oxobutyl and 3-oxopropyl anion synthons, respectively. We have now successfully employed our procedure for the synthesis of two important prostanoid building blocks[20]: methyl 9-oxodecanoate[21-25] (**5a**) and methyl 9-oxo-12-tridecenenoate[26,27] (**5b**).



2,5	a	b
R	CH3	H2C=CH–CH2–CH2–

Methyl 8-nitrooctanoate (**1**) is used as a common starting material for the synthesis of both compounds. The ω-nitro ester **1** is readily available in good yield by methanolic cleavage of α-nitrocyclooctanone[28]. Methyl 8-nitrooctanoate (**1**) when treated with aldehydes **2a, b** in the presence of Amberlyst A 21 without solvent at room temperature gives nitroalkanols **3a, b** in good yields. Subsequent oxidation with pyridinium chlorochromate[29] in dichloromethane affords α-nitroketones **4a, b** which by reaction with tri-*n*-butyltin hydride and catalytic amounts of azobisisobutyronitrile in refluxing benzene[3] are denitrated. Methyl 9-oxodecanoate (**5a**) and methyl 9-oxo-12-tridecenenoate (**5b**) are obtained in about 46% overall yield. Thus, this procedure represents a very simple and efficient route to **5a, b** starting from methyl 8-nitrooctanoate (**1**) as reagent for 7-methoxycarbonylheptyl anion synthon.

At present we are continuing our efforts in exploring the utilization of primary nitroalkyl derivatives in synthetic transformations.

^{1}H-N.M.R. spectra were recorded at 90 MHz on a Varian EM 390. I.R. spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Microanalyses were performed by using a C,H,N Analyzer Model 185 from Hewlett-Packard Co. Vapor-phase chromatographic analyses were performed on a Carlo Erba Fractovap 4160 HRGC instrument using capillary column (25 m × 0.3 mm) of fused silica (0.4–0.45 μm) with Carbowax 20 M. Tri-*n*-butyltin hydride, azobisisobutyronitrile (AIBN), Amberlyst A 21, and pyridinium chlorochromate are commercial materials. 4-Pentenal (**2b**) was prepared by pyridinium chlorochromate oxidation of 4-penten-1-ol[30], which was obtained from tetrahydrofuryl alcohol according to Ref.[31].

1-Acetoxycyclooctene:

Cyclooctanone (22.42 g, 0.178 mol) is added to a solution of acetic anhydride (36.4 g, 0.357 mol) and *p*-toluenesulfonic acid (103 mg, 0.6 mmol). The solution is heated to 175 °C (bath temperature) and the acetic acid generated removed by distillation. After 3 h, the solution is cooled to room temperature, and dichloromethane (100 ml) is added; the resulting solution is washed with water (2 × 60 ml), 5% aqueous sodium carbonate (2 × 60 ml), and dried with magnesium sulfate. The solvent is removed under vacuum to leave a residue which is distilled; yield: 22.7 g (76%); b.p. 60–62 °C/0.4 torr.

$C_{10}H_{16}O_2$	calc.	C 71.39	H 9.59
(168.2)	found	71.48	9.47

I.R. (neat): ν = 1683, 1745 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS): δ = 1.25–2.60 (m + s, 15H); 5.25 ppm (t, 1H, J = 8.25 Hz).

2-Nitrocyclooctanone:

To a solution of 1-acetoxycyclooctene (10.9 g, 64.9 mmol), acetic anhydride (19.5 ml), dichloromethane (20 ml) and three drops of concentrated sulfuric acid cooled at 0 °C, is added over a period of 30 min a mixture of glacial acetic acid (3.25 ml) and concentrated nitric acid (4.55 ml, 0.07 mol). The inner temperature is maintained below 6 °C by external cooling. The resulting mixture is stirred at 0–5 °C for 1 h, then at room temperature for 2 h. Acetic acid is removed as completely as possible under vacuum at 40 °C and the residue is dissolved in ether (100 ml); the solution is washed with water (2 × 60 ml). The ether solution is dried with magnesium sulfate and the solvent removed under vacuum to give an oil which, on T.L.C. analysis (silica gel; *n*-hexane/ethyl acetate), is pure; yield: 8.76 g (79%); b.p. 58–60 °C/0.08 torr.

$C_8H_{13}NO_3$	calc.	C 56.12	H 7.65	N 8.18
(171.2)	found	55.97	7.80	8.06

I.R. (neat): ν = 1720 (C=O), 1555 cm^{-1} (NO$_2$).

^{1}H-N.M.R. (CDCl$_3$/TMS): δ = 1.00–3.00 (m, 12H); 5.45 ppm (dd, 1H, J = 6.0 Hz, 6.0 Hz).

Methyl 8-Nitrooctanoate (1):

To a solution of 2-nitrocyclooctanone (5.1 g, 3.0 mmol) in absolute methanol (100 ml) potassium fluoride dihydrate (2 g, 21.2 mmol) is added at room temperature. The solution is refluxed for 48 h and then evaporated. The residue is treated with water (50 ml) and extracted with ether (3 × 30 ml). The extracts are washed with brine (2 × 30 ml), dried with sodium sulfate, filtered, and evaporated. Compound **1** is obtained as an oily residue, pure according to G.L.C.; yield: 4.3 g (71 %).

$C_9H_{17}NO_4$	calc.	C 53.19	H 8.43	N 6.89
(203.2)	found	53.08	8.50	6.77

I.R. (neat): ν = 1735 (C=O); 1550 cm^{-1} (NO_2).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.15–2.20 (m, 10H); 2.35 (t, 2H, J = 6.75 Hz); 3.65 (s, 3H); 4.38 ppm (t, 2H, J = 6.75 Hz).

2-Nitroalkanols 3a, b; General Procedure:

A 100 ml-two necked flask equipped with a mechanical stirrer is charged with compound **1** (1.5 g, 7.4 mmol). After cooling with an ice bath, the aldehyde **2a, b** (7.4 mmol) is added and the mixture stirred for 5 min. Amberlyst A 21 (3 g) is added and the mixture stirred at room temperature for 3 h and then allowed to stand for 16 h. The Amberlyst resin is washed with dichloromethane (3 × 40 ml) and the filtered extract evaporated at reduced pressure to give **3a, b** as oily residues.

Methyl 8-Nitro-9-hydroxydecanoate (**3a**); yield: 86 %.

$C_{11}H_{21}NO_5$	calc.	C 53.42	H 8.56	N 5.66
(247.3)	found	53.49	8.63	5.58

I.R. (neat): ν = 3450 (OH); 1725 (C=O); 1545 cm^{-1} (NO_2).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.1–2.1 (m, 13H); 2.32 (t, 2H, J = 7.5 Hz); 3.65 (s, 3H); 4.00–4.55 ppm (m, 2H).

Methyl 8-Nitro-9-hydroxy-12-tridecenoate (**3b**); yield: 87 %.

$C_{14}H_{25}NO_5$	calc.	C 58.51	H 8.77	N 4.87
(287.4)	found	58.62	8.83	4.94

I.R. (neat): ν = 3470 (OH); 1725 (C=O); 1545 cm^{-1} (NO_2).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.10–2.50 (m + t, 16H); 3.63 (s, 3H); 3.80–4.15 (m, 1H); 4.30–4.60 (m, 1H); 4.90–5.25 (m, 2H); 5.55–6.10 ppm (m, 1H).

α-Nitroketones 4a, b; General Procedure:

A 100 ml-two necked flask equipped with a mechanical stirrer is charged with pyridinium chlorochromate (1.8 g, 8.4 mmol) in anhydrous dichloromethane (20 ml) in the presence of molecular sieves (3 g, 3 Å). The alcohol **3a, b** (5.59 mmol) is added in one portion. The mixture is stirred at room temperature for 24 h. A further portion of pyridinium chlorochromate (0.9 g, 4.2 mmol) is added and the mixture stirred at room temperature for additional 12 h. The mixture is diluted with ether (40 ml) and the supernatant liquid decantated. The organic solution is passed through a short pad of Florisil to give a clear solution which after evaporation of the solvents affords the α-nitroketones **4a, b** as oils.

Methyl 8-Nitro-9-oxodecanoate (**4a**); yield: 71 %.

$C_{11}H_{19}NO_5$	calc.	C 53.86	H 7.81	N 5.71
(245.3)	found	53.94	7.90	5.68

I.R. (neat): ν = 1740 (C=O); 1555 cm^{-1} (NO_2).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.18–2.50 (m + s, 15H); 3.65 (s, 3H); 5.00–5.28 ppm (m, 1H).

Methyl 8-Nitro-9-oxo-12-tridecenoate (**4b**); yield: 75 %.

$C_{14}H_{23}NO_5$	calc.	C 58.93	H 8.13	N 4.91
(285.4)	found	58.80	8.21	4.83

I.R. (neat): ν = 1730 (C=O); 1640 (C=C); 1555 cm^{-1} (NO_2).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.20–2.90 (m, 16H); 3.65 (s, 3H); 4.90–5.35 (m, 3H); 5.58–6.05 ppm (m, 1H).

Denitration of α-Nitroketones 4a, b; General Procedure:

A dried, nitrogen flushed 100 ml flask with a septum inlet and a magnetic stirring bar is charged with the α-nitroketone **4a, b** (1.2 mmol) and azobisisobutyronitrile (78 mg, 0.48 mmol) in dry benzene (10 ml). Tri-*n*-butyltin hydride (0.52 g, 1.80 mmol) is added by a syringe and the resulting solution refluxed for 4 h. The reaction progress is monitored by G.L.C. analysis (detector: flame ionization, 300 °C; carrier: nitrogen at 3 ml/min; column temperature: 3 min 65 °C with subsequent increase to 300 °C with a rate of 15 °C/min). After completion of the reaction, the solvent is evaporated and the crude product purified by short column chromatography on silica gel with ethyl acetate/cyclohexane (1/4) as eluent.

Methyl 9-Oxodecanoate (**5a**); yield: 75 %; b.p. 77 °C/0.6 torr (Ref.[23], b.p. 98–100 °C/3 torr).

$C_{11}H_{20}O_3$	calc.	C 65.97	H 10.07
	found	66.03	9.99

I.R. (neat): ν = 1735, 1710 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.15–1.90 (m, 10H); 2.13 (s, 3H); 2.10–2.65 (m, 4H); 3.65 ppm (s, 3H).

All physical data agreed with these reported in Ref.[23].

Methyl 9-Oxo-12-tridecenoate (**5b**); yield: 69 %; b.p. 100 °C/0.05 torr (Ref.[26], b.p. 108–110 °C/0.05 torr).

$C_{14}H_{24}O_3$	calc.	C 69.96	H 10.07
	found	69.81	10.00

I.R. (neat): ν = 1740, 1720 (C=O); 1645 cm^{-1} (C=C).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.05–1.85 (m, 10H); 2.15–2.70 (m, 8H); 3.63 (s, 3H); 4.88–5.18 (m, 2H); 5.58–6.10 ppm (m, 1H).

All physical data agreed with these reported in Ref.[26].

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