Facile and Inexpensive Synthesis of 4-Oxoalkanoic Acids from Primary Nitroalkanes and Acrolein

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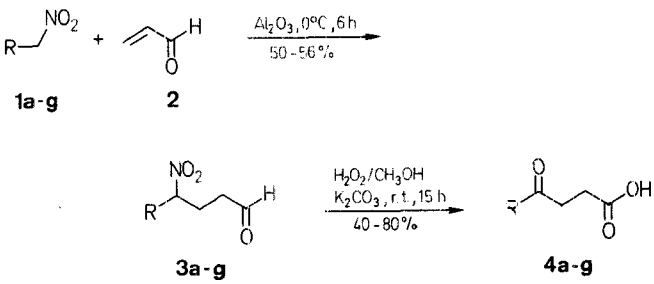
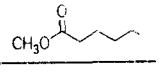
4-Oxoalkanoic acids, useful organic compounds, are easily prepared by conjugate addition of primary aliphatic nitro compounds to acrolein on alumina surface, in the absence of a solvent, and subsequent oxidation with hydrogen peroxide/potassium carbonate.

4-Oxoalkanoic acids represent an interesting class of organic compounds. They can be used to prepare cyclic products such as lactones[1,2,3], β-lactam antibiotics[4], isoquinolines[5], and lactonic sex pheromones[6], they are also used without further transformation[7,8,9]. Several methods (some of which are patents) to prepare 4-oxoalkanoic acids have been developed[10–19]; however, these procedures often exhibit some disadvantages such as the use of difficulty available starting materials, drastic reaction conditions, or very low temperature. The object of the research outlined herein is the development of a new simple and inexpensive method to obtain functionalized 4-oxoalkanoic acids.

Our method (Scheme A) consists of the conjugate addition of primary nitrocompounds (**1a–g**) to propenal (acrolein, **2**) on alumina surface in the absence of a solvent[20] and oxidation of the 4-nitroalkanals (**3a–g**) thus obtained with hydrogen peroxide (The conversion of nitroalkanes into aldehydes or ketones by the oxidation method used by us has already been reported[21]).

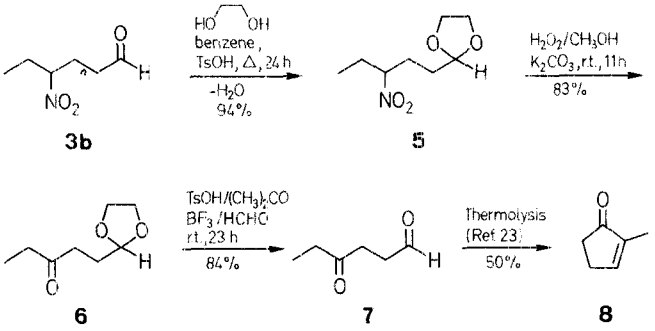


1/3/4	R
a	CH_3
b	C_2H_5
c	n-C_4H_9
d	n-C_5H_{11}

1/3/4	R
e	
f	
g	

Scheme A

We also report the application of our procedure to the synthesis of 2-methyl-2-cyclopentenone (**8**), an important starting material for the synthesis of cyclopentenoid natural products[22]. The whole sequence leading to product **8** consists of acetalization of 4-nitrohexanal (**3b**) with 1,2-ethanediol, oxidation of the resultant 4-nitrohexanal 1,2-ethanediyl acetal (**5**) with hydrogen peroxide to give 4-oxoalkanal 1-(1,2-ethanediyl acetal) (**6**), acetal cleavage of **6**, and thermal intramolecular cyclocondensation of 4-oxohexanal (**7**) using the procedure of Lit.[23] (Scheme **B**).



Scheme B

Microanalyses were performed by using a C,H,N Analyzer Model 185 from Hewlett-Packard Co. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. ^{1}H-NMR spectra were recorded at 90 MHz on a Varian EM 390.

Acrolein, nitroethane, 1-nitropropane, 1-nitropentane, and 1-nitrohexane are commercial materials. 3,3-(1,2-Ethanediyldioxy)-1-nitrobutane (**1e**) is prepared from butenone[27]. 4,4-(1,2-Ethanediyldioxy)-1-nitrobutane (**1f**) is prepared from acrolein according the procedure of Lit.[28]. Methyl 6-nitrohexanoate (**1g**) is prepared by ring cleavage of 2-nitrocyclohexanone[29].

4-Nitroalkanals (3a–g); General Procedure:

A 100 ml two-necked flask equipped with a mechanical stirrer is charged with the nitro compound **1** (0.05 mol) and cooled with an ice-water bath. Acrolein (2804 g, 0.05 mol) is added and the mixture stirred for 5 min. Chromatographic alumina (Carlo Erba RS, actity I according to Brockmann; 10 g) is added and stirring is continued for 6 h. The reaction progress is monitored by TLC (ethyl acetate/hexane (2:8) as eluent) or by GLC analysis [Carlo Erba Fractovap 4160; column: OV1 duran glass, 25 × 0.3 mm; film thickness 0.4–0.45 μm; injector temperature: 300 °C; detector flame ionization: 300 °C; carrier: nitrogen at 3 ml/min; column temperature: 65 °C; programme: 3 min at 65 °C, then from 65 °C to 300 °C at 15 °C/min and held]. At the end of the reaction, the alumina is washed with ether (4 × 50 ml) and the filtered extract is evaporated at reduced pressure, and purified by distillation or by chromatography over silica gel (0.063–0.200 mm) with ethyl acetate/hexane (2:8) as eluent.

4-Oxoalkanoic Acids (4a–g). General Procedure:

Aqueous 30% hydrogen peroxide (30 ml) is added to a cooled (0 °C) and stirred solution of the 4-nitroalkanal **3** (0.015 mol) in methanol (70 ml). To the resultant solution, potassium carbonate (12 g) is added, and stirring is continued for 15 h at room temperature. The solution is then acidified with 2 normal hydrochloric acid and extracted with dichloromethane (3 × 40 ml). The organic layer is washed with water (40 ml), and dried with magnesium sulfate. The solvent is removed under vacuum to leave the crude product which can be used without further purification. The pure 4-oxoalkanoic acids can be obtained by distillation or by column chromatography over silica gel (0.063–0.200 mm) using ethyl acetate/hexane (4:6) as eluent.

4-Nitrohexanal 1,2-Ethanediyl Acetal (5):

4-Nitrohexana (**3b**; 3.6 g, 0.025 mol) is placed in a 100 ml three-necked flask equipped with a Dean Stark apparatus and condenser. Benzene (50 ml), ethanediol (12.3 g, 0.198 mol), and p-toluensulfonic acid (0.95 g, 0.005 mol) are added and the solution is refluxed for 24 h with azeotropic removal of water. The mixture is cooled and saturated sodium hydrogen carbonate solution (30 ml) is added. The

Table 1. 4-Nitroalkanals **3** Prepared

3	Yield[a] [%]	b.p. [°C/torr]	Molecular Formula[b]	IR [cm^{-1}][c] $\nu_{C=O}$	IR [cm^{-1}][c] ν_{NO_2}	^{1}H-NMR ($CDCl_3$)[d] δ [ppm]
a	50	71/0.4	$C_5H_9NO_3$ (131.1)	1720	1545	1.56 (d, 3H, J = 7.0 Hz); 1.92–2.76 (m, 4H); 4.68 (m, 1H, J = 7.0 Hz); 9.88 (s, 1H)
b	54	90/0.5	$C_6H_{11}NO_3$ (145.2)	1720	1545	0.98 (t, 3H, J = 7.5 Hz); 1.64–2.72 (m, 6H); 4.24–4.72 (m, 1H); 9.88 (s, 1H)
c	51	88/0.3	$C_8H_{15}NO_3$ (173.2)	1725	1545	0.94 (t, 3H, J = 7.9 Hz); 1.00–2.64 (m, 10H); 4.1–4.65 (m, 1H); 9.75 (s, 1H)
d	50	103/0.3	$C_9H_{17}NO_3$ (187.2)	1720	1545	0.92 (t, 3H, J = 6.4 Hz); 1.04–2.76 (m, 12H); 4.28–4.80 (m, 1H); 9.84 (s, 1H)
e	56	oil[e]	$C_9H_{15}NO_5$ (217.2)	1720	1550	1.32 (s, 3H); 1.64–2.88 (m, 6H); 4.00 (m, 4H); 4.52–5.00 (m, 1H); 9.84 (s, 1H)
f	50	oil[e]	$C_9H_{15}NO_5$ (217.2)	1720	1545	1.44–2.76 (m, 8H); 3.72–4.20 (m, 4H); 4.36–5.04 (m, 2H); 9.84 (s, 1H)
g	53	oil[e]	$C_{10}H_{17}NO_5$ (231.2)	1725	1545	1.00–2.72 (m, 12H); 3.72 (s, 3H); 4.36–4.80 (m, 1H); 9.88 (s, 1H)

[a] Yield of pure, isolated product. At least 98% pure according to GLC analysis.
[b] Microanalyses were performed using a C, H, N, – Analyzer Model 185, Hewlett-Packard Co.: C ±0.21, H ±0.17, N ±0.26.
[c] Recorded on a Perkin-Elmer 297 spectrometer.
[d] Recorded at 90 MHz using a Varian EM 390 spectrometer.
[e] Purified by chromatography over silica gel (0.063–0.200 mm) with Ethyl acetate/hexane (2 : 8) as eluent.

Table 2. 4-Oxoalkanoic Acids **4** Prepared

4	Yields[a] [%]	b.p. [°C/torr] or m.p. [°C]	Molecular Formula[b] or Lit. Data	IR [cm^{-1}][c] ν_{O-H}	IR [cm^{-1}][c] $\nu_{C=O}$	^{1}H-NMR ($CDCl_3$)[d] δ [ppm]
a	62	b.p. 120/10	b.p. 245/760[24]	3200	1710	2.24 (s, 3H); 2.44–3.08 (m, 4H); 8.84 (br. s, 1H)
b	70	b.p. 113/3	b.p. 143/16[25]	3200	1710	1.03 (t, 3H, J = 7.5 Hz); 2.48 (q, 2H, J = 7.5 Hz); 2.67 (m, 2H); 10.4 (br. s, 1H)
c	78	b.p. 95/0.3	b.p. 155/10[26]	3200	1715	0.92 (t, 3H, J = 6.8 Hz); 1.6–2.92 (m, 10H); 8.96 (br. s, 1H)
d	80	m.p. 66–8[e]	m.p. 66[14]	3200	1705	0.88 (t, 3H, J = 6.3 Hz); 1.00–2.84 (m, 12H); 9.75 (br. s, 1H)
e	56	oil[e]	$C_9H_{14}O_5$ (202.2)	3180	1710	1.4 (s, 3H); 2.44–3.00 (m, 6H); 3.88–4.12 (m, 4H); 7.48 (br. s, 1H)
f	57	oil[e]	$C_9H_{14}O_5$ (202.2)	3200	1720	1.44–3.00 (m, 8H); 3.4–4.16 (m, 4H); 4.96 (t, 1H, J = 4.0 Hz); 7.48 (br. s, 1H)
g	40	oil[e]	$C_{10}H_{16}O_5$ (216.2)	3200	1715	1.2–3.00 (m, 12H); 3.64 (s, 3H); 8.48 (br. s, 1H)

[a] Yield of pure, isolated product.
[b] Microanalyses were performed using a C, H, N – Analyzer Model 185, Hewlett-Packard Co.: C ±0.16, H ±0.23.
[c] Recorded on a Perkin-Elmer 297 spectrometer.
[d] Recorded at 90 MHz using a Varian EM 390 spectrometer.
[e] Purified by chromatography over silica gel (0.063–0.200 mm) with ethyl acetate/hexane (1 : 1).

organic layer is separated and washed with saturated sodium chloride solution (3 × 20 ml). The aqueous phase is extracted with chloroform (3 × 20 ml) and the combined organic phase is dried with sodium sulfate. The solvent is removed at reduced pressure and the residue is distilled in vacuum to give the pure product **5**; yield: 4.23 g (94%); b.p. 100 °C/0.4 torr.

$C_8H_{15}NO_4$ (189.2) calc. C 50.78 H 7.99 N 7.40
found 50.89 8.14 7.61

IR (neat) ν = 1545 (NO_2) cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ = 0.96 (t, 3H, J = 7.5 Hz); 1.44–2.32 (m, 6H); 3.76–4.08 (m, 4H); 4.8–5.0 (m, 1H); 4.28–4.68 ppm (m, 1H).

4-Oxohexanal 1-(1,2-Ethanediyl Acetal) (6):
To a stirred solution of compound **5** (1 g, 0.0053 mol) in methanol (30 ml) cooled to 0 °C is added 30% hydrogen peroxide (10.6 ml), followed by a solution of potassium carbonate (4.2 g) in water (15 ml). Stirring is continued for 11 h at room temperature, the solution then acidified with 2 normal hydrochloric acid and extracted with dichloromethane (3 × 20 ml). The combined organic layers are dried with sodium sulfate, and evaporated. The residue is distilled in vacuum to afford the pure product **6**; yield: 0.68 g (83%); b.p. 92 °C/3 torr.

$C_8H_{14}O_3$ (158.2) calc. C 60.74 H 8.92
found 60.82 9.10

IR (neat) ν = 1710 (CO) cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ = 1.03 (t, 3H, J = 7.5 Hz); 1.8–2.18 (m, 2H); 2.28–2.75 (m, 4H); 3.8–4.1 (m, 4H); 4.28–5.00 ppm (m, 1H).

4-Oxohexanal (7):
Compound **6** (0.5 g, 0.0031 mol) is dissolved in acetone (20 ml), distilled boron trifluoride etherate (0.76, 0.0054 mol), *p*-toluenesulfonic acid (0.15 g, 0.0008 mol), and aqueous 37% formaldehyde solution (2.23 ml, 0.03 mol) are added. The mixture is stirred at room temperature for 15 h and aqueous 37% formaldehyde (1 ml) is added. Stirring is continued for 8 h, the solution then evaporated at reduced pressure, the residue diluted with ether (30 ml), and the

organic layer dried with sodium sulfate. The solvent is removed at reduced pressure and the residue distilled in vacuo (Kugelrohr) to give product **7**; yield: 0.3 g (84%); b.p. 150°C (bath)/11 torr.

$C_6H_{10}O_2$ (114.1) calc. C 63.13 H 8.83
found 63.00 9.01

IR (neat) ν = 2740 (CHO); 1710 (CO) cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ = 1.05 (t, 3H, J = 7.5 Hz); 2.5 (q, 2H, J = 7.5 Hz); 2.72 (s, 4H); 9.82 ppm (s, 1H).

2-Methyl-2-cyclopentenone (8):
Compound **7** can be converted into compound **8** using the procedure of Lit.[23]; yield: 50%.

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[1] Muys, G.T., Van der Ven, B., de Jonge, A.P. *Brit. Patent* 916 822 (1963), Unilever Ltd.; *C.A.* **1963**, 58, 9601.
[2] Ravid, U., Iverstein, R.M., Smith, L.R. *Tetrahedron* **1978**, *34*, 1449.
[3] May, W.A., Peterson, R.S., Chang, S.S. *J. Food Sci.* **1978**, *43*, 1248.
[4] Edwards, M.L., Bambury, R.E., Ritter, H.W. *J. Med. Chem.* **1976**, *19*, 330.
[5] Kigasawa, K., Hiiragi, M., Ishimaru, H., Haga, S. *Jap. Patent* 75 111 098 (1975), Grelan Pharmaceutical Co.; *C.A.* **1976**, *84*, 135496.
[6] Naoshima, Y., Ozawa, H., Xondo, H., Hayashi, S. *Agric. Biol. Chem.* **1983**, *47*, 1431.
[7] Robach, M.C. *U.S. Patent* 4 356 204 (1982), Monsanto Co.; *C.A.* **1983**, *98*, 15734.
[8] Mayr, H.H., Presoly, E., Rittmeyer, G. *Z. Pflanzenernähr. Bodenkd.* **1977**, *140*, 463; *C.A.* **1977**, *87*, 113000.
[9] Reynolds, R.S. *Neth. Appl.* 6 516 702 (1966) Tobacco Co.; *C.A.* **1967**, *66*, 53041.
[10] Takeda, A., Takahasi, K., Moriwake, T. *J. Org. Chem.* **1966**, *31*, 616.
[11] Haage, K., Reinheckel, H. *German Patent (East)* 51 309 (1966); *C.A.* **1967**, *66*, 65114.
[12] Haage, K., Reinheckel, H. *Brit. Patent* 1 081 234 (1967), Deutsche Akademie der Wissenschaften; *C.A.* **1967**, *67*, 108235.
[13] Reinheckel, H., Haage, K., Gensike, R. *German Patent* 1 284 961 (1968), Deutsche Akademie der Wissenschaften; *C.A.* **1969**, *70*, 67629.
[14] Steglich, W., Gruber, P. *Angew. Chem.* **1971**, *83*, 727; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 655.
[15] Syroezhko, A.M., Potekhin, V.M., Proskuryakov, V.A. *Zh. Prikl. Khim. (Leningrad)* **1973**, *46*, 2694; *C.A.* **1974**, *80*, 59382.
[16] Fuentes, L.M., Larson, G.L. *Tetrahedron Lett.* **1982**, *23*, 271.
[17] Miyashita, M., Yamaguchi, R., Yoshikoshi, A. *Chem. Lett.* **1982**, 1505.
[18] Kamashima, M., Fijisawa, T. *Chem. Lett.* **1984**, *10*, 185.
[19] Miyashita, M., Yamaguchi, R., Yoshikoshi, A. *J. Org. Chem.* **1984**, *49*, 2857.
[20] Rosini, G., Marotta, E., Ballini, R., Petrini, M. *Synthesis* **1986**, 237.
[21] Olah, G.A., Arvanaghi, M., Vankar, Y.D., Prakash, G.K.S. *Synthesis* **1980**, 662.
[22] Funk, R.L., Vollhardt, K.P.C. *Synthesis* **1980**, 118; and references cited therein.
[23] Cavill, G.W.K., Goodrich, B.S., Laig, D.G. *Aust. J. Chem.* **1970**, *23*, 83.
[24] Aldrich Catalog 1985/1986, p. 672.
[25] Noltes, A.W., Kogl, F. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1334.
[26] Taylor, H.T. *J. Chem. Soc.* **1958**, 3922.
[27] Rosini, G., Ballini, R., Sorrenti, P. *Tetrahedron* **1983**, *39*, 4127.
[28] Miyakoshi, T., Saito, S. *Oil Chemistry* **1982**, 231.
[29] Duranleau, R.G., Kablaoui, M.S., Love, R.F. *U.S. Patent* 3 796 734 (1974), Texaco Inc.; *C.A.* **1974**, *80*, 120320.