Oxidation of 2-Nitroalkanols under Phase Transfer Conditions: A Mild and Efficient Synthesis of Linear α-Nitro Ketones

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Open-chain α-nitro ketones **4** are useful intermediates in organic synthesis. However, their synthetic application is restricted due to difficulties involved in their preparation. Although a significant improvement has been achieved in the C-acylation of 1-nitroalkanes[1,2], the most widely employed method is based on the oxidation of 2-nitroalkanols **3**, readily available by the nitro-aldol (or Henry) reaction[3]. Recently, we have reported that pyridinium chlorochromate can be used to oxidize complex or polyfunctional 2-nitroalkanols **3** without affecting several functional or protecting groups[4]. The only shortcoming of this procedure are the long reaction times (30–36 h). In this communication we report on an improvement obtained by applying the phase transfer technique[5] to this kind of oxidation.

The reactions are carried out by slow addition at −10 to −5 °C of potassium dichromate or potassium chromate and 30% sulfuric acid to a solution of 2-nitroalkanols **3** and tetra-*n*-butylammonium hydrogen sulfate (0.1 mol per mol **3**) in dichloromethane. The reaction proceeds smoothly to completion within 2 h. Under the phase transfer conditions, acid-labile protecting groups are retained and good yields of products **4** are obtained (Table).

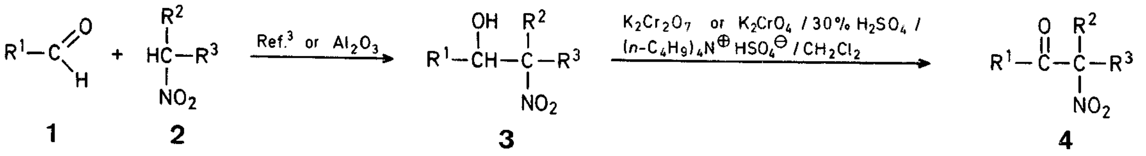
Furthermore, a one-pot synthesis consisting of a solvent-free nitro-aldol reaction (**1** + **2** → **3**) on alumina followed by *in situ* oxidation to **4** under phase transfer conditions has been developed. We expect that this procedure will give ready access to this class of compounds.

α-Nitro Ketones 4 by Phase Transfer Oxidation of 2-Nitroalkanols 3; General Procedure:

To a mechanically stirred solution of 2-nitroalkanol **3** (0.05 mol) and tetra-*n*-butylammonium hydrogen sulfate (1.7 g, 0.005 mol) in dichloromethane (90 ml) is added, slowly and simultanously at −10 °C, 30% sulfuric acid (60 ml) and potassium dichromate or potassium chromate (0.065 mol). After further stirring for 2 h at −10 °C, 10% aqueous iron(II) sulfate (50 ml) is added and the layers are separated. The organic phase is dried with sodium sulfate and passed through a bed of Florisil (30 g). The solvent is removed under reduced pressure to afford the α-nitro ketones **4** (Table).

One-Pot Synthesis of α-Nitro-Ketones (4g–i); General Procedure:

A mixture of the aldehyde **1** (0.05 mol) and the nitroalkane **2** (0.05 mol) is mechanically stirred for 2–3 min and then cooled in an ice-bath. After the addition of chromatographic alumina (Carlo Erta RS, activity I according to Brockmann;) and stirring at 20 °C for 3 h, the mixture is allowed to stand for 20 h. Dichloromethane (90 ml) and tetra-*n*-butylammonium hydrogen sulfate (1.7 g, 0.005 mol) are added. Under stirring and cooling to −10 °C, 30% sulfuric acid (60 ml) and potassium dichromate (19.1 g, 0.065 mol) are simultanously added, keeping the inner temperature at −10° to −5 °C. After stirring for 2 h at −10 °C, the mixture is worked-up as above. The following yields are obtained; **4g**: 80%, **4h**: 72%; **4i**: 72%.



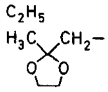
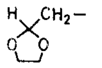
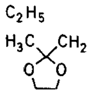
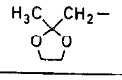
3,4	R^1	R^2	R^3	3,4	R^1	R^2	R^3
a	CH_3	C_2H_5	H	**g**	$C_6H_5-CH_2-CH_2-$	CH_3	H
b	CH_3		H	**h**	$H_2C=CH-CH_2-CH_2-$	CH_3	H
c	*i*-C_3H_7	C_2H_5	H	**i**	*n*-C_6H_{13}		H
d	*n*-C_6H_{13}	C_2H_5	H				
e	*n*-C_6H_{13}		H	**j**	*n*-C_6H_{13}	$H_3CO-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-$	H
f	$H_2C=CH-CH_2-CH_2-$	CH_3	CH_3	**k**	$C_6H_5-CH_2-CH_2-$		H

Table. α-Nitro Ketones **2a–k** prepared

Product	Oxidant	Yield[a] [%]	b.p. [°C]/torr or m.p. [°C]	Molecular formula[b] or Lit. data	I.R. [cm^{-1}][c]		^{1}H-N.M.R. (CDCl$_3$/TMS)[d] δ [ppm]
					$\nu_{C=O}$	ν_{NO_2}	
4a	$K_2Cr_2O_7$ K_2CrO_4	83 68	50–55°/1.5	50–55°/1.5[4]	1725	1549	1.03 (t, 3H, J = 7.5 Hz); 2.0–2.4 (m, 5H); 5.09–5.29 (dd, 1H, J = 6.0 Hz, 6.0 Hz)
4b	$K_2Cr_2O_7$	72	59–60°	59–60°[4]	1730	1558	1.33 (s, 3H); 2.30 (s, 3H); 2.5–2.8 (m, 2H); 3.96 (s, 4H); 5.35 (m, 1H)
4c	$K_2Cr_2O_7$	70	68–70°/1.6	55–58°/0.4[4]	1730	1560	1.0–1.4 (m, 9H); 2.0–2.4 (m, 2H); 2.9 (m, 1H); 5.38 (m, 1H)
4d	$K_2Cr_2O_7$	83	94–95°/1.1	$C_{10}H_{19}NO_3$ (201.3)	1730	1550	0.7–1.85 (m, 14H); 2.0–2.4 (m, 2H); 2.6 (t, 2H, J = 7.5 Hz); 5.05–5.25 (dd, 1H, J = 6.0 Hz, 6.0 Hz)
4e	$K_2Cr_2O_7$	95	oil	$C_{13}H_{22}NO_5$ (273.3)	1725	1550	0.87 (t, 3H, J = 6.0 Hz); 1.1–1.8 (m + s, 11H); 2.35–2.85 (m, 4H); 3.8–4.05 (m, 4H); 5.25–5.45 (m, 1H)
4f	$K_2Cr_2O_7$	77	oil	$C_8H_{13}NO_3$ (171.2)	1725	1542	1.48–1.9 (m, 6H); 2.15–2.8 (m, 4H); 4.83–5.3 (m, 2H); 5.55–6.1 (m, 1H)
4g	$K_2Cr_2O_7$	93	oil	$C_{11}H_{13}NO_3$ (207.2)	1730	1550	1.6 (d, 3H, J = 7.5 Hz); 2.88 (s, 4H); 5.2 (q, 1H, J = 7.5 Hz); 7.0–7.95 (m, 5H)
4h	$K_2Cr_2O_7$	84	75–77°/1.5	$C_7H_{11}NO_3$ (157.2)	1730	1553	1.58 (d, 3H, J = 6.3 Hz); 2.12–2.55 (m, 4H); 4.9–5.22 (m, 2H); 5.3 (q, 1H, J = 6.3 Hz); 5.57–6.05 (m, 1H)
4i	$K_2Cr_2O_7$	82	oil	$C_{12}H_{21}NO_5$ (259.3)	1730	1550	0.8 (t, 3H, J = 6.0 Hz); 1.15–1.45 (m, 8H); 2.3 (m, 2H); 2.5–2.6 (t, 2H, J = 7.5 Hz); 3.85 (m, 4H); 5.00 (m, 1H); 5.3–5.5 (m, 1H)
4j	K_2CrO_4	85	145–148°/6	$C_{12}H_{21}NO_5$ (259.3)	1725	1545	0.76–1.08 (m, 3H); 1.1–1.86 (m, 8H); 2.00–2.74 (m, 6H); 3.70 (s, 3H); 5.3–5.5 (m, 1H)
4k	K_2CrO_4	71	oil	$C_{15}H_{19}NO_5$ (293.3)	1730	1550	1.30 (s, 3H); 2.4–2.75 (m, 2H); 2.9 (s, 4H); 3.75–4.05 (m, 4H); 5.2–5.4 (m, 1H); 7.05–7.43 (m, 5H)

[a] Yields of isolated pure products. The purity of the liquid products was > 97%; by G.L.C. analysis with a Carlo Erba Fractovap 4160 (column: OV1 duran glass; film thickness 0.4–0.45 μm; injector temperature: 300 °C, flame ionization detector: 300 °C; carrier: N_2 at 3 ml/min; programme: 3 min at 60 °C, then from 60–290 °C at 15°/min and held).

[b] Microanalysis were performed using a C,H,N-Analyzer Model 185, Hewlett Packard. Satisfactory microanalysis obtained: C ±0.18, H ±0.14, N ±0.25; except **4k**: H ±0.49.

[c] Recorded on a Perkin-Elmer 297 spectrometer.

[d] Recorded at 90 MHz using a Varian EM 390 spectrometer.

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