A New, Modulated, Oxidative Ring Cleavage of α-Nitrocycloalkanones by Oxone®: Synthesis of α,ω-Dicarboxylic Acids and α,ω-Dicarboxylic Acid Monomethyl Esters

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Dedicated to the memory of Prof. Paolo Ceccherelli

Received 11 May 1998

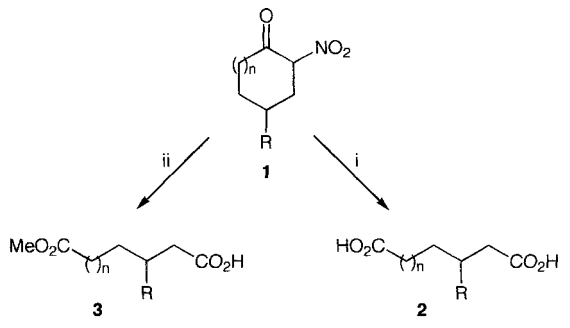
Abstract: By the appropriate choice of the reaction conditions Oxone® produces the ring cleavage of α-nitrocycloalkanones affording good yields of α,ω-dicarboxylic acids and α,ω-dicarboxylic acid monomethyl esters, respectively, regardless the ring size and/or the presence of an alkyl group as substituent.

α-Nitrocycloalkanones are an important class of compounds commercially available and/or easily accessible from the corresponding ketones or olefins by several nitrating processes.[1-5]

The C-C bond between the carbonyl group and the nitro substituted atom of cyclic α-nitro ketones undergoes cleavage by internal[6] or external nucleophiles,[1,7-16] the former gives macrocyclic compounds by the ring enlargement, and the latter gives α,ω-disubstituted molecules.

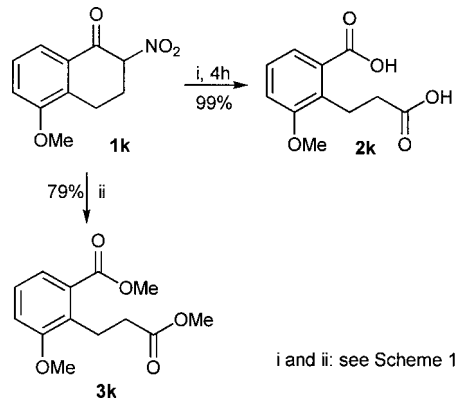
During our studies on the oxidative cleavage[11,13,16] of the title compounds we discovered that treatment of α-nitrocycloalkanones with aqueous 30% hydrogen peroxide[11] produces α,ω-dicarboxylic acids, while potassium persulfate oxidation,[16] in methanol and in the presence of sulfuric acid at 80 °C, provides α,ω dicarboxylic acid dimethyl esters. In the last years commercially available Oxone® (potassium hydrogen persulfate) has found extensive synthetic application in organic chemistry. Among these particularly are the preparation of dioxiranes,[17] the oxidation of sulphides to sulphoxides and sulphones,[18] of selenides to selenones,[19] of alkenes to epoxides.[20] Besides, Oxone® has been successfully used to perform Bayer-Villiger oxidation of ketones,[21] and carbonyl regeneration from thioketals.[22] Recently we found that Oxone® can be employed to oxidize nitrocompounds to carbonyl derivatives,[23] and oxime to *gem*-chloronitrocompounds.[24]

Now we found that, by the appropriate choice of the reaction conditions Oxone® can be conveniently used for a new oxidative cleavage of cyclic α-nitro ketones **1** (Scheme 1) affording high yields of α,ω-dicarboxylic acids[25] **2**, and/or α,ω-dicarboxylic acid monomethyl esters[26] **3**, alternatively. Thus, reaction of **1**, in a solution of 0.5 M Na_2HPO_4 and 1 N NaOH, with 2.5 moles of Oxone® affords high yields (78-99%) of



i: a) MeOH, 0.5 M Na_2HPO_4, 1 M NaOH, 70 °C; b) Oxone®, H_2O, r. t.;
ii: a) MeOH, KOH, 65 °C; b) 0.5 M Na_2HPO_4, 1 M NaOH, Oxone®, H_2O, r. t.

Scheme 1



Scheme 2

Table 1. α,ω-Dicarboxylic Acids and α,ω-Dicarboxylic Acids Monomethyl Esters Prepared

Entry	R	n	Yield[a] % of **2** (Reaction times, h)	Yield[a] % of **3**
a	H	1	93 (1)	89
b	$C(CH_3)_3$	1	99 (4)	99
c	CH_3	1	88 (4)	90
d	H	7	87 (4)	82
e	Ph	1	78 (4)	92
f	H	2	94 (4)	91
g	H	6	99 (4)	93
h	H	5	98 (4)	84
i	H	10	98 (4)	84
j	H	3	99 (4)	86

[a]All the products were characterized by analytical and spectroscopic data

(entry **3b,c,e,l**) which are hard to obtain by the regioselective monomethyl esterification of the corresponding dicarboxylic acids.

In conclusion our procedure represents an important method for an high efficient synthesis of both α,ω-dicarboxylic acids and α,ω-dicarboxylic acid monomethyl esters, from the easily available α-nitrocycloalkanones, by the appropriate modulation of the reaction conditions. Moreover, this method appears as a further evidence of the high versatility of cyclic nitro ketones and extends their application in organic synthesis.

Acknowledgements. The support for this investigation by Italian MURST and Italian C.N.R. is gratefully acknowledged.

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(25) **General procedure for the preparation of α,ω-dicarboxylic acids** (**2**) is as follows: To a solution of α-nitro ketone (0.7 mmol) in MeOH (4.2 ml), 25 ml of 0.5 M Na_2HPO_4 in a 1 N of NaOH were added and the resulting mixture was heated at 70 °C for 1-4 h, then Oxone® (1.75 mmol) in water (3 ml) was added to the cold solution (r. t.). After 4 h the mixture was diluted with brine (10 ml), acidified to pH=2 with a 10% solution of HCl and extracted with EtOAc (3 x 20 ml). The combined organic layers were washed with brine (10 ml), dried over Na_2SO_4 and evaporated to yield pure dicarboxylic acid **2**.

(26) **General procedure for the preparation of α,ω-dicarboxylic acid monomethyl esters** (**3**) is as follows: To a solution of α-nitro ketone (0.7 mmol) in MeOH (2 ml), 6 ml of a solution of KOH (1.75 mmol) in MeOH were added and the resulting mixture was heated at 65 °C for 4 h, then 17 ml of a 0.5 M of Na_2HPO_4 in a 1 N solution of NaOH and Oxone® (2.1 mmol) in water (5 ml) were added to the cold solution r.t.). After 4 h the mixture was diluted with water (20 ml) and a 5% solution of $NaHCO_3$ (5 ml), washed with CH_2Cl_2 (1 x 10 ml), acidified to pH=2 with a 1% solution of HCl and extracted with EtOAc (3 x 20 ml). The combined layerswere washed with brine 10 ml), dried over Na_2SO_4 and evaporated yielding the pure compound **3**.

(27) Selected analytical data for the compounds **3b,c,e**:
3b: IR (CH_2Cl_2): ν = 2890, 1730 and 1709 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.88 (s, 9H), 1.28-2.47 (m, 7H), 3.62 (s, 3H), 9.20-9.80 (s *br*, 1H). Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.17; H, 9.40.
3c: IR (CH_2Cl_2): ν = 2890, 1740 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.85-0.97 (d, 3H, *J* = 5.9 Hz), 1.35-2.45 (m, 7H), 3.62 (s, 3H), 8.75-9.45 (s *br*, 1H). Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.09; H, 8.16.
3e: IR (CH_2Cl_2): ν = 2890, 1733 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.78-2.22 (m, 4H), 2.55-2.62 (d, 2H, *J* = 7.3 Hz), 2.96-3.08 (m, 1H), 3.53 (s, 3H), 7.10-7.27 (m, 5H), 9.25-9.75 (s *br*, 1H). Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.82. Found: C, 66.17; H, 6.90.