Oxidation of β,γ-Unsaturated Ketones with Molecular Oxygen Catalyzed by Metal Phthalocyanines and Porphyrins: A Practical Synthesis of Oxophorone

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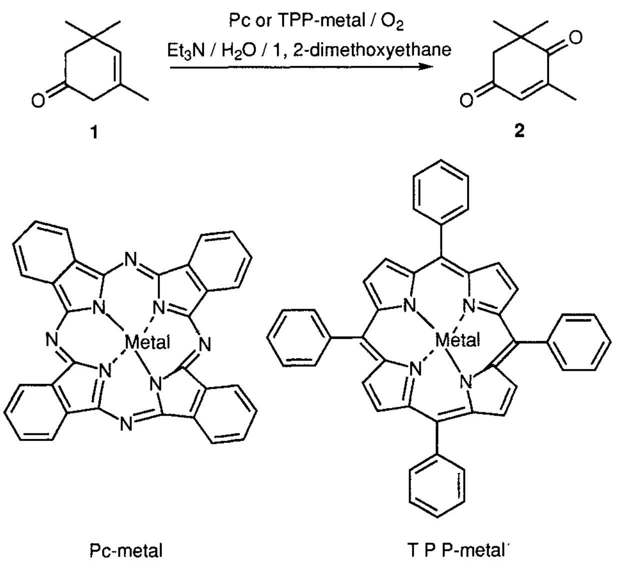
Oxidation of 3,5,5-trimethylcyclohex-3-en-1-one (**1**) with molecular oxygen catalyzed by metal phthalocyanines (Pc) and 5,10,15,20-tetraphenylporphyrins (TPP) including Mn(II), Mn(III), Fe(II), Fe(III), Co(II), Cu(II), and Ru(II) to 3,5,5-trimethylcyclohex-2-ene-1,4-dione (**2**) was studied. TPPMn(III)Cl showed an excellent catalytic activity, affording **2** in 93 % yield and 12500 turnover number.

A number of transition metal phthalocyanines and porphyrins are known to activate molecular oxygen by reversibly bonding to the metal center.[1] Such oxygen carrier metal complexes have been worthy of remark not only as catalyst for oxidation of organic compounds, but also as models for oxygenase enzymes.[2,3] In the oxidation reactions, much attention has been focused on the epoxidation of olefins and hydroxylation of alkenes using transition metal phthalocyanines and porphyrins.[4] However, little is known about other efficient and practically useful oxidation reactions.[5]

3,5,5-Trimethylcyclohex-2-ene-1,4-dione (oxophorone, **2**) is well known as an important key intermediate for the syntheses of carotenoids[6] and flavoring substances.[7] During the course of our synthetic study of natural products, a substantial quantity of oxophorone (**2**) was required because of limited amount of supply from natural sources.[8] One obvious and direct approach to this problem would be oxidation of isophorone and the other would be oxidative transformation of 3,5,5-trimethylcyclohex-3-en-1-one (β-isophorone, **1**), which is readily available in large quantities by imidazoline-catalyzed deconjugation of isophorone.[9] However, the former oxidation was difficult and the latter transformation employing some oxygen carrier metal complexes as a catalyst suffered from poor yield and low turnover of catalyst.[10] Now we disclose herein that oxidative transformation of β-isophorone (**1**) into oxophorone (**2**) is greatly enhanced by the use of 5,10,15,20-tetraphenylporphyrinatomanganese (TPPMn) as the oxygen carrier catalyst.

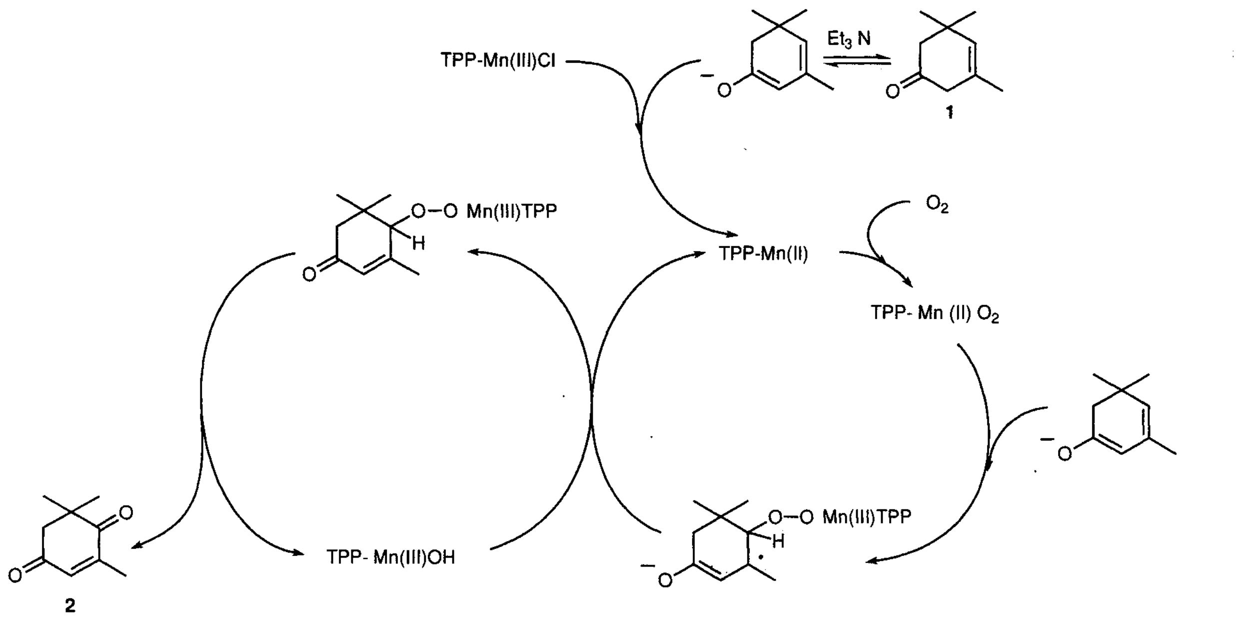
Oxidation of β-isophorone (**1**) was effected with molecular oxygen catalyzed by a variety of metal phthalocyanines (Pc) and 5,10,15,20-tetraphenylporphyrins (TPP) in the presence of triethylamine and water[11] in 1,2-dimethoxyethane (Scheme 1).[12] The product yields were quantitatively determined by GC using an internal standard. The results obtained are summarized in the Table. TPP-V(IV)=O, Pc -and TPP-metal [metal Ni(II) and Cu(II)] were less active (Entries 3,4,13 and 15) or inactive (Entry 12), except 1,2,3,4,8,9,10,11,15,16,17,18,22,23,24,25-hexadecachlorophthalocyanine Cu(II) [Cl_{20}PcCu(II)] (Entry 6). Better catalytic activity of Cl_{20}PcCu(II) may be attributable to the chlorinated electron-poor phthalocyanine ligand. PcMn(II), PcFe(II), PcCo(II), TPPRu(II)C=O, TPPCo(II) and TPPFe(III)Cl showed moderate catalytic activity (Entries 1,2,5,10,11 and 14). Among metal complexes employed, TPPMn(III)Cl was most effective for this oxidative transformation (Entries 7 and 8). In Entry 8, the turnover number reached 12500 and the isolated yield of **2** is 92 %. The same result was obtained in the presence of TPPMn(II)[13] (Entry 9).



Scheme 1

In the present oxidation, trivalent TPP-metal complexes such as TPPMn(III)Cl and TPPFe(III)Cl showed catalytic activity in the absence of reducing agents. In the oxidation using a O_2/TPP-metal(III)Cl system, the initial reduction of the TPP-metal(III) to TPP-metal(II) is usually achieved by addition of reducing agents such as H_2-Pt,[4] superoxide(O_2-),[14] $NaBH_4$,[13] because it is known that divalent metal complexes are active species in these catalytic cycles.[15] A plausible reaction pathway is shown in Scheme 2, assuming the initial electron-transfer to TPP-Mn(III) from an extended dienolate anion generated from β-isophorone (**1**) and triethylamine to generate the TPP-Mn(II).

Alternative trivalent manganese complex, chloro-*N*, *N'*-bis(salicylidene)ethylenediiminomanganese [Mn(III)Cl-salen][16] also catalyzed oxidation of **1** to give **2** in 81 % yields (Entry 16). The mode of present oxidation would be analogous to that of oxidation with *N*, *N'*-bis(salicyl-



Scheme 2

Table. Oxidation of β-Isophorone (**1**) to Oxophorone (**2**) with Molecular Oxygen Catalyzed by Pc Transition Metal and TPP Transition Metal Complexes[a]

Entry	Catalyst	Mol% of Catalyst Used	Time (h)	Yield of **2**[b] (%)
1	PcMn(II)	0.33	6.5	59
2	PcFe(II)	1.3	8	55
3	PcNi(II)	3.3	6.5	7
4	PcCu(II)	3.3	6.5	9
5	PcCo(II)	3.3	6.5	28
6	$Cl_{20}PcCu(II)$	3.3	6.5	48
7	TPPMn(III)Cl	0.04	2	91
8	TPPMn(III)Cl	0.008	9	93 (92)[c]
9	TPPMn(II)	0.04	2	93
10	TPPCo(II)	3.3	6.5	52
11	TPPFe(III)Cl	3.3	6.5	46
12	TPPNi(II)	3.3	6.5	0
13	TPPCu(II)	3.3	6.5	10
14	TPPRu(II)C=O	3.3	6.5	44
15	TPPV(IV)=O	3.3	6.5	8
16	Mn(III)Cl-Salen	0.06	2.5	81

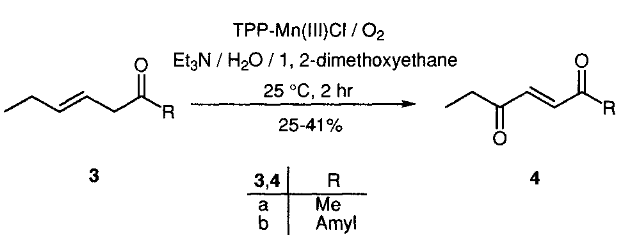
[a] Oxidation of **1** (0.82 mol/L) was carried out at 25 °C under oxygen atmosphere in the presence of Et_3N (0.32 mol/L) and H_2O (2.3 mol/L) in 1,2-dimethoxyethane.

[b] Yields by gas chromatographic quantitative analyses.

[c] Isolated yield by column chromatography.

idene)ethylenediiminomanganese [Mn(II)-salen] by Costantini and his co-workers.[15]

Our oxidative transformation was applied to hept-4-en-2-one (**3a**) and undec-3-en-6-one (**3b**) in order to understand the generality of the oxidation. On treatment with TPPMn(III)Cl (0.5 mol%) in 1,2-dimethoxyethane/H_2O/Et_3N under oxygen atmosphere, although the starting materials were consumed completely, the yields of the oxidation products were moderate; hept-3-en-2,5-dione (**4a**) and undec-4-en-3,6-dione (**4b**) were obtained from **3a** and **3b** in 25 and 41 % yields, respectively (Scheme 3). The compound **4a** is known as aggression controlling substance in bees.[17]



Scheme 3

The ^1H NMR spectra of **4a** and **4b** exhibited singlets at $\delta = 6.92$ and 6.88, respectively, indicating the geometry of the double bond to be *trans*, since the olefinic proton of diethyl fumarate is more deshielded ($\delta = 6.87$) than that of diethyl maleate ($\delta = 6.25$).[18]

In summary, among the studies on oxidation of β-isophorone (**1**) with molecular oxygen catalyzed by metal phthalocyanines and porphyrins, TPPMn(III)Cl revealed the excellent catalytic activity, giving oxophorone (**2**) in 93 % yield with a turnover number of 12500. The present method is practically useful for the synthesis of **2**, because TPPMn(III)Cl is commercially available and stable to handle under atmospheric oxygen, as well as the simplicity of operation an high yield.

β-Isophorone (**1**), [9] (*E*)-hept-4-en-2-one (**3a**),[19] (*E*)-undec-3-en-6-one (**4a**),[19] TPPMn(II)[13] and Mn(III)-salen[16] were prepared according to the literature procedures. $Cl_{20}PcCu(II)$ was purchased from Tokyo Kasei Co. Other metal phthalocyanines and porphyrins were purchased from Aldrich Co. These catalysts were used without purification. Melting points were determined with a Mettler FP62 hot stage apparatus and were uncorrected. IR spectra were recorded on a JASCO FT/IR-7000 spectrophotometer. ^{1}H NMR spectra were obtained in $CDCl_3$ with JOEL LA-400 (400 MHz) and Hitachi R-24B (60 MHz) instruments with TMS as an internal standard. J-Values are given in Hz. Mass spectra were run on Hewlett Packard 5992B and Hitachi M-80B spectrometers with a Hitachi MO101 data system. Gas chromatographic quantitative analyses were carried out on a Hitachi 263-30 gas chromatograph equipped with 2 m 5% FFAP packed column with a temperature program of 100–200 °C (5 °C/min).

Oxidation of β-Isophorone (1); Typical Procedure:

To a solution of β-isophorone (**1**; 500.0 mg, 3.62 mmol), Et_3N (142 mg, 1.42 mmol) and H_2O (182 mg, 10 mmol) in 1,2-dimethoxyethane (4.4 mL) was added a solution of TPPMn(III)Cl (0.195 mg, 0.29 μmol) in 1,2-dimethoxyethane (0.2 mL). The mixture was exposed to oxygen atmosphere under vigorous stirring for 9 h at r.t. The mixture was evaporated to give 790.1 mg of a crude oil. The quantitative analysis of oxophorone (**2**) formed was achieved by adding ethyl phenylacetate (103.5 mg) as an internal standard to the crude oil (153.4 mg) and diluting with EtOAc (2 mL). The resulting solution was analyzed by GC; GC yield of oxophorone (**2**): 93 %. The crude product (636.7 mg) was chromatographed on silica gel using EtOAc/hexane (1:3) as an eluent to give pure **2** (408.2 mg, 92 %); mp 24–25 °C; Lit.[7] mp 15–16 °C.

IR (film): ν = 2980 (C—H), 1678 (C=O), 1621 (C=C), 1280 cm^{-1}.

^{1}H NMR: δ = 1.18 [6 H, s, $(CH_3)_2C$], 1.92 (3 H, d, J = 2, CH_3), 2.58 (2 H, s, 6-H), 6.40 (1 H, br s, 2-H).

MS: m/z (%) = 152 (M^+, 38), 137 (3), 109 (10), 96 (78), 68 (100), 55 (2), 39 (35).

(*E*)-Hept-3-ene-2,5-dione (4a):

To a solution of **3a** (66 mg, 0.59 mmol), Et_3N (24 mg, 0.24 mmol) and H_2O (31 mg, 1.7 mmol) in 1,2-dimethoxyethane (0.75 mL) was added TPPMn(III)Cl (2.0 mg, 0.003 mmol). The resulting solution was exposed to oxygen atmosphere under vigorous stirring for 2 h at r.t. The mixture was evaporated and the crude product was chromatographed on silica gel using EtOAc/hexane (3:1) as an eluent to afford **4a** (19 mg, 25 %); oil.

IR (film): ν = 3045, 2970 (C—H), 1678 (C=O), 1618 (C=C), 1358 cm^{-1}.

^{1}H NMR: δ = 1.13 (3 H, t, J = 7, CH_3CH_2), 2.38 (3 H, s, CH_3CO), 2.72 (2 H, q, J = 7, 6-H), 6.92 (2 H, s, CH=CH).

MS: m/z (%) = 126 (M^+, 16), 111 (4), 98 (12), 97 (100), 83 (43), 67 (27), 57 (21), 43 (85).

(*E*)-Undec-4-ene-3,6-dione (4b):

Following the procedure described above for the preparation of **4a**, a mixture of **3b** (54 mg, 0.32 mmol), TPPMn(III)Cl (1.1 mg, 0.0016 mmol), Et_3N (13 mg, 0.13 mmol), H_2O (17 mg 0.94 mmol) and 1,2-dimethoxyethane (0.41 mL) was stirred under oxygen for 2 h. Workup followed by purification of the oily product by chromatography on silica gel (EtOAc/hexane, 5:1) gave **4b** (24 mg, 41 %); mp 37–38 °C.

IR (film): ν = 3045, 2980 (C—H), 1665 (C=O), 1160 cm^{-1}.

^{1}H NMR: δ = 0.90 (3 H, br t, J = 7, 11-CH_3), 1.13 (3 H, t, J = 7.6, 1-CH_3), 1.25–1.38 (4 H, m, 9- and 10-H), 1.61–1.68 (2 H, m, 8-H), 2.62–2.71 (4 H, m, 2- and 7-H), 6.88 (2 H, s, CH=CH).

MS: m/z (%) = 182 (M^+, 1) 153 (18), 125 (48), 111 (33), 97 (100), 83 (32), 55 (67), 43 (34), 29 (41).

HRMS: Found: M^+, 182.1333; $C_{11}H_{18}O_2$ requires M, 182.1361.

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