Enhanced Catalytic Activity and Selectivity in Oxidation of α-Isophorone to Ketoisophorone with Phosphomolybdic Acid

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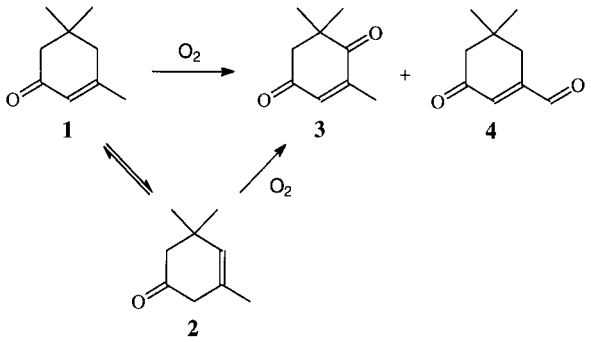
Abstract: Aerobic allylic oxidation of α-isophorone with phosphomolybdic acid as catalyst in combination with DMSO and potassium *tert*-butoxide provides ketoisophorone in unprecedented high yield. This study suggests that the solvent can play a pivotal role in directing selectivity in allylic oxidations of highly substituted cyclic olefins.

Key words: isophorone, oxidations, catalysis, oxygen, DMSO

Selective aerobic allylic oxidation of cyclic olefins is a synthetically useful and environment-friendly conversion which currently attracts considerable attention.[1] Catalytic allylic oxidations are, however, characterized by the formation of product mixtures containing allylic ketones, alcohols and competitive epoxidation products. The difficulties encountered are highlighted in the allylic oxidation of the isophorone isomers (**1** and **2**), in particular, α-isophorone (**1**) to ketoisophorone (**3**) (Scheme). Interest in this conversion stems from the availability of isophorone as starting material and the fact that ketoisophorone (**3**) is a versatile intermediate for the preparation of various flavoring and fragrance fine chemicals.[2] Ketoisophorone (**3**) is currently obtained in >90% yield via homogeneous liquid phase oxidation of β-isophorone (**2**).[3,4] On the other hand, investigations of the catalytic oxidation of α-isophorone (**1**) using known allylic oxidation catalysts provided ketoisophorone (**3**) in poor yields.[5-10] Given the interest in ketoisophorone (**3**), an effective direct oxidation of α-isophorone (**1**) to this product, eliminating the intermediate isomerization step (Scheme),[11] is intrinsically attractive. In the present contribution we report that phosphomolybdic acid (PMA) in combination with a highly polar aprotic solvent (DMSO) and a strong base (KOBu^t) gives almost quantitative conversion of α-isophorone (**1**) under relatively mild reaction conditions while providing ketoisophorone (**3**) in good yield.

Results for the phosphomolybdic acid (PMA) catalyzed allylic oxidation of α-isophorone (**1**) (α-IP) to ketoisophorone (**3**) in DMSO, based on GC-MS analysis of the reaction mixtures, are summarized in Table 1. In all cases, subsequent work-up of the reactions gave isolated yields 2−6% lower than those determined by GC-MS analysis. With PMA/DMSO/KOBu^t almost quantitative conversion of α-isophorone (**1**) is achieved in remarkably short reaction times (24 h versus 95 h) simultaneously providing approx. 70% yield of ketoisophorone (**3**) (entry 1) as



Scheme Catalytic oxidation of isophorone to ketoisophorone with dioxygen

compared to 45% in the solvent-free system.[6] At low α-isophorone (**1**) conversion, the selectivity to ketoisophorone (**3**) is high (approx. 90%) and decreases to 70% as the reaction proceeds. Small amounts of formylisophorone (**4**) (entry 2), formed by competitive allylic oxidation at the α-methyl group, were detected at short reaction times and appeared to further react probably via a pinacol cross-coupling of the aldehyde as the reaction progressed.[12] The reduction in selectivity on addition of DMSO to the catalyst-free autoxidation of α-isophorone (**1**) (entries 4, 5) is compensated for by the introduction of KOBu^t to the α-IP/DMSO mixture (entry 3). Importantly, addition of DMSO to catalytic oxidations with α-IP/PMA more than doubles conversion accompanied by a significant increase in selectivity to ketoisophorone (**3**) (entries 6, 7). An extensive study of alternative solvents showed that oxidation was not observed in low boiling point solvents (< 90 °C). In benzonitrile, for example, conversion and selectivity were significantly reduced (entry 9). Based on the observations that only negligible amounts of ketoisophorone (**3**) (< 1.0%) were observed under catalytic reaction conditions in the absence of oxygen, and that the addition of DMSO did not influence conversion in the autoxidation of α-isophorone (**1**) (entry 4), it seems unlikely that DMSO is directly involved in oxygen transfer to α-isophorone (**1**). Small amounts of methyl sulfide detected by GC-MS analysis during ketoisophorone (**3**) synthesis may be a result of a reaction of DMSO with phosphomolybdic acid. Therefore, the significant role of DMSO in the α-isophorone oxidation may be attributed to its high proton solvating power.[13] Following proton abstraction from α-isophorone (**1**), the oxidation of the enolate inter-

Table 1 Allylic Oxidation of α-Isophorone (**1**) to Ketoisophorone (**3**) using Phosphomolybdic Acid (PMA) under Various Conditions

Entry	System	Catalyst Mol %	Temp. °C	Time h	X{**1**}[a] %	S{**3**}[b] %	S{**4**}[b] %
1	α-IP/DMSO/KOBu^t/PMA	0.43	115	24	99.1	70.3	0
2	α-IP/DMSO/KOBu^t/PMA	0.43	115	8	62.1	88.4	1.9
3	α-IP/DMSO/KOBu^t	0	115	24	19.8	89.4	5.5
4	α-IP/DMSO	0	115	24	21.4	60.5	2.6
5	α-IP	0	115	24	22.2	80.3	3.4
6	α-IP/PMA	0.43	115	24	41.2	44.4	0
7	α-IP/DMSO/PMA	0.43	115	24	97.5	61.5	0
8	α-IP/KOBu^t/PMA	0.43	115	24	59.3	50.3	1.0
9	α-IP/PhCN/KOBu^t/PMA	0.43	115	24	52.4	30.0	1.9

[a] X{**1**} conversion of α-isophorone (**1**) (α-IP).
[b] S{**3**}/S{**4**)} selectivity to ketoisophorone (**3**)/formylisophorone (**4**) as determined by GC-MS analysis.

mediate formed probably proceeds via a mechanism similar to that described by Costantini and coworkers for β-isophorone (**2**) oxidation.[3]

The α-isophorone oxidation presented has several advantages over previously reported methods.[5–10] Firstly, our one-pot allylic oxidation of α-isophorone (**1**) to ketoisophorone (**3**) eliminates the isomerization step involved in the conversion of α-isophorone (**1**) to β-isophorone (**2**), currently used as the starting material.[11] Previously, oxidation of α-isophorone required reaction temperatures in the range 100−150 °C with reaction times up to 6 days.[5–10] Here, we demonstrate that phosphomolybdic acid in combination with DMSO/KOBu^t provides almost quantitative conversion of α-isophorone (**1**) at 115 °C in just 24 h.

Finally, in order to determine the applicability of the solvent/base combination, several known allylic oxidation catalysts were investigated for the oxidation of α-isophorone (**1**) in combination with DMSO/KOBu^t (Table 2). In all cases (Table 2), the addition of DMSO enhanced conversion over the solvent-free oxidations[5–10] accompanied, however, by low selectivity to ketoisophorone (**3**). Interestingly, α-isophorone (**1**) was previously described as unreactive to allylic oxidation under conditions employed for β-isophorone (**2**) oxidation with tetraphenylphorphyrinmanganese chloride (TPPMnCl).[4] The combined results presented here therefore highlight the uniqueness of the phosphomolybdic acid catalyzed oxidation of α-isophorone (**1**) in DMSO with KOBu^t and simultaneously confirm the unique status of α-isophorone (**1**) oxidation in the class of cyclic olefin allylic oxidation.[1]

In conclusion, the combination of DMSO/KOBu^t with phosphomolybdic acid provides an attractive one-pot synthesis of ketoisophorone (**3**) via allylic oxidation of the more accessible α-isophorone (**1**) isomer. Appropriate choice of the solvent/base afforded an approx. 25% increase in ketoisophorone (**3**) yield over the solvent-free system with greatly reduced reaction times.[6]

α-Isophorone (**1**) was supplied by F. Hoffmann-La Roche Ltd. Analytical grade solvents, phosphomolybdic acid and potassium *tert*-butoxide (KOBu^t) were used as supplied by Fluka. Quantitative analysis of product mixtures was carried out using a HP 5890A/HP

Table 2 Allylic Oxidation Catalysts Investigated for α-Isophorone (**1**) Oxidation in DMSO/KOBu^t

System	Mol %	Temp. °C	Time h	X{**1**}[a] %	S{**3**}[b] %	S{**4**}[b] %
α-IP/DMSO/KOBu^t/$VO(acac)_2$	8.68	115	24	88.0	31.0	0.6
α-IP/DMSO/KOBu^t/$Na_2V_2O_5$	8.68	115	24	71.9	22.0	0.7
α-IP/DMSO/KOBu^t/$Cr(acac)_3$	8.68	115	24	17.8	45.2	2.1
α-IP/DMSO/KOBu^t/TPPMnCl[c]	0.43	115	24	47.6	26.3	0.4

[a] X{**1**} conversion of α-isophorone (**1**) (α-IP).
[b] S{**3**}/S{**4**} selectivity to ketoisophorone (**3**)/formylisophorone (**4**) as determined by GC-MS analysis.
[c] TPPMnCl = tetraphenylphorphyrinmanganese chloride.

5972 GC/MS system fitted with a HP 50+column (50% Ph/Me siloxane, 30 m, 0.25 μm). α-Isophorone (**1**) conversion (X{**1**}) and selectivity to ketoisophorone (**3**) (S{**3**}) were determined by GC-MS analysis using tetralin as standard. NMR spectra were recorded on a Bruker 300 MHz spectrometer with TMS as internal standard (δ ppm).

Ketoisophorone (3)

α-Isophorone (**1**) (23.08 g, 167 mmol), $KOBu^t$ (0.11 g, 1 mmol), and DMSO (25 mL) were stirred under O_2 (1 bar) in a 100 mL conical flask, fitted with condenser and magnetic stirring. Phosphomolybdic acid (1.30 g, 0.72 mmol) was added and the mixture was heated to 115 °C for 24 h. The reaction mixture was then allowed to cool to r.t. and analyzed by GC-MS. Distillation of the reaction mixture to dryness at reduced pressure (110 °C, 12 mm Hg) afforded approx. 40 mL of a pale-yellow liquid. IR analysis of the solid residue showed that some ketoisophorone (**3**) remained. Soxhlet extraction of this residue with Et_2O improved yields of ketoisophorone (**3**) slightly. Careful distillation of the pale-yellow distillate afforded a fraction (bp 94−7 °C, 12 mm Hg) comprising ketoisophorone (**3**) (17.2 g, 67.7% yield) with negligible amounts of α-isophorone (**1**)/DMSO (< 0.5 mol%).

IR: ν = 2969, 1746, 1680, 1613, 1470, 1387, 1279, 1187 cm^{-1}.

^1H NMR (d_6-DMSO, 300 MHz): δ = 1.14 (s, 6H), 1.90−1.94 (m, 3H), 2.49−2.76 (m, 2H), 6.64−6.66 (m, 1H).

^{13}C NMR (d_6-DMSO, 75 MHz): δ = 203.6, 198.2, 148.6, 137.3, 51.5, 45.0, 26.1, 16.6.

MS: *m/z* = 152 (M^+).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.08; H, 8.01.

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