Synthesis of 4-hydroxy-4-methylcyclohex-2-en-1-one

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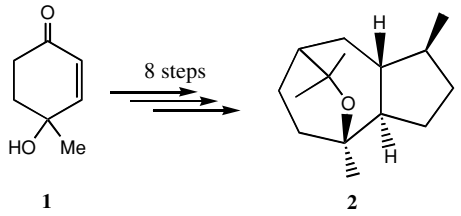
4-Hydroxy-4-methylcyclohex-2-en-1-one was synthesised from 4-methylanisole. The key step is the regioselective reaction of singlet oxygen with 4-methylcyclohex-3-en-1-one.

Keywords: singlet oxygen, hydroxycyclohexenones, hydroperoxides, ene reactions

4-hydroxy-4-methylcyclohex-2-en-1-one **1**, has been used as a synthon in the preparation of biologically important compounds, such as compactin, dienedynes, and diverse carbocycles.[1] 4-Hydroxy-4-methylcyclohex-2-en-1-one **1** has been isolated as a volatile compound from natural oils, and it has been used as an additive in food and cosmetics.[5] Booker-Milburn *et al*.[2] used **1** to generate the natural product kessane **2** (Scheme 1) which was isolated from *Valeriana officinalis* and a detailed structural assignment was performed by van Beek *et al*.[3,4]

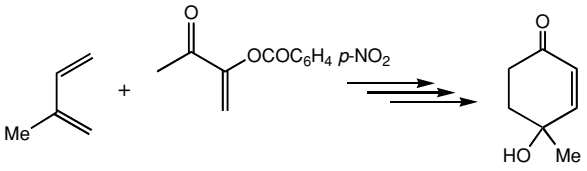
Many synthetic methods to prepare **1** are known. For example Tamariz and co-workers[6] reported the regioselective synthesis of 4-hydroxy-4methylcyclohex-2-en-1-one (**1**) using 3-*p*-nitrobenzoyloxy-3-buten-2-one (**5**) as a ketene equivalent in a Diels-Alder reaction with isoprene (**4**) in moderate yield (Scheme-2).

We report here a simple synthesis of 4-hydroxy-4-methylcyclohex-2-en-1-one starting from 4-methylanisole (**6**). Our synthetic strategy is based on a four-step sequence, and takes advantage of the fact that compound **8** is susceptible to reaction with singlet oxygen to form the intermediate **9** in high yield.



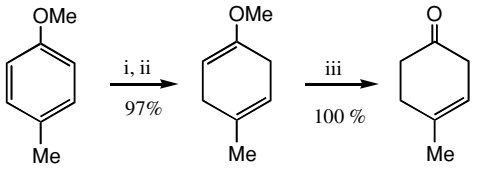
1 **2**

Scheme 1



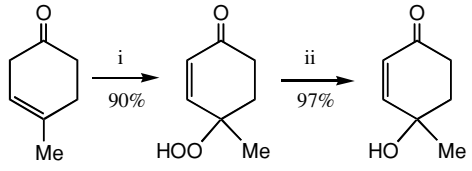
4 **5** **1**

Scheme 2



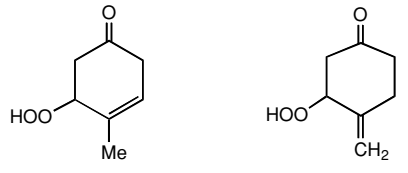
6 **7** **8**

Scheme 3 *Reagents*: i, Li/NH_3, -60°C; ii, EtOH; iii, $(CO_2H)_2/H_2O$, 15°C



8 **9** **1**

Scheme 4 *Reagents*: i, O_2, TPP, Hv, r.t. $CHCl_3$; ii, DMS/$Ti(OiPr)_4$, $CHCl_3$, r.t., 10 min



10 **11**

Results and discussion

For the synthesis of **9** we selected the known compound **8** of which the synthesis is shown in Scheme 3. Birch reduction [7,8a,b] of **6** with Li in liquid ammonia gave compound **7** followed by acid hydrolysis in the presence of oxalic acid which yielded the key compound **8**.

The photo-oxygenation of olefins with singlet oxygen provides a convenient and effective route to allylic hydroperoxides.[9,10] Much effort has been expended to achieve regiocontrol in this ene reaction.

Tetraphenylporphyrin-sensitised photo-oxygenation of 4-methylcyclohex-3-en-1-one (**8**) in chloroform at room temperature formed the allylic hydroperoxide as sole product. Careful NMR studies did not reveal any trace of the alternative products **10** and **11.** The formation of the conjugated α, β-unsaturated system is the only driving force for the formation of **9**. The structure of the hydroperoxide **9** was assigned based on its ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum of hydroperoxide **9** displays an AB system, which corresponds to olefinic protons. The seven-line ^{13}C NMR spectrum is decisive. IR displays a bond at 3360 cm^{-1} for hydroperoxy group. Reduction of the peroxide linkage[11-12] in **9** was performed with dimethyl sulfide[13] / $Ti(Oi\text{-}Pr)_4$ under very mild conditions to give 4-hydroxy-4-methylcyclohex-2-en-1-one (**1**) in 97% yield (Scheme 4).

In summary, we have achieved an efficient and regioselective synthesis of γ-hydroxycyclohexenone **1**. This methodology may be of value in the preparation of a variety of functionalised γ-hydroxycyclohexenone derivatives.

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Experimental

IR spectra were recorded on a Mattson 1000 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini-200 (200 MHz) with $CDCl_3$ as solvent and TMS as internal standard. Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyser. All column chromatography was performed on silica gel (60 mesh, Merck).

4-methylcyclohex-3-en-1-one (**8**): To a magnetically stirred solution of **7**[8], 15 g (0.12 mol) in 150 ml of diethyl ether, was added a solution of 2M oxalic acid (100 ml) in water at room temperature. After complete addition (10 min), the mixture was stirred for 1.5 h. The organic phase was separated, washed with 150 ml of water and then dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (130–135 g, hexane / $CHCl_3$, 95:5) to give 14.9 g (100%) of **8** as a yellow oil. IR ($CHCl_3$): 2978, 2927, 2876, 1727, 1676, 1472, 1421, 1344, 1268, 1217, 1191, 1093 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.28 (bs, olefin, 1H), 2.12–2.66 (m, methylene, 6H), 1.62 (s, CH_3, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.2, 136.5, 131.6, 41.4, 40.2, 32.2, 24.7.

4-hydroperoxy-4-methylcyclohex-2-en-1-one (**9**)**:** Ketone **8** (2 g, 18.2 mmol) in chloroform (150 ml) containing tetraphenylporphyrin (50 mg) was irradiated using a projector lamp (500 W) while a slow stream of dry oxygen was continuously passed through. The progress of the photo-oxygenation was monitored by ^1H NMR spectroscopy until complete consumption of the starting material (5 h). The solvent was roto-evaporated at room temperature. Chromatography of the crude product on silica gel (65 g) with ether – hexane (25 : 75) as eluent yielded the allylic hydoperoxide **9** (90%). IR ($CHCl_3$) 3336, 3004, 2953, 2825, 1676, 1472, 1421, 1395, 1370, 1293, 1142, 1089 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.80 (d, A-part of AB-system, 1H, J = 10.2, olefin), 5.86 (d, B-part of AB-system, 1H, J = 10.2 Hz, olefin), 1.30 (s, 3H, methyl), 1.8–2.6 (m, 4H, methylenic). ^{13}C NMR (50 MHz, $CDCl_3$): δ 202.3, 155.0, 131.5, 81.5, 36.5, 33.5, 24.5. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.27; H, 8.02.

4-hydroxy-4-methylcyclohex-2-en-1-one (**1**): To a magnetically stirred solution of **9** 1.0 g (7 mmol) in 100 ml of dichloromethane was added dimethyl sulfite (0.87 g, 14 mmol) and titanium tetra-isopropoxide (19 mg, 0.065 mmol) at –5°C. After complete addition, the mixture was stirred for 10 min. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (60 g, hexane / ether, 85:15) to give 0.85 g (97%) of **1** as a pale yellow oil. IR ($CHCl_3$): 3336, 3029, 2978, 2953, 2876, 1702, 1676, 1446, 1395, 1293, 1191, 1089 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.55 (d, A-part of AB-system, 1H , J = 10.3 Hz, olefin), 5.55 (d, B-part of AB-system, 1H, J = 10.3 Hz, olefin), 1.92–2.49 (m, 4H, methylenic), 1.28 (s, 3H, methyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ 201.9, 158.0, 128.3, 70.0, 38.9, 36.8, 28.9.

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