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"Dark" Singlet Oxygenation of β-Citronellol: A Key Step in the Manufacture of Rose Oxide

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Abstract:

We describe the development of a scalable process for the "dark" singlet oxygenation of β-citronellol as a key step in the manufacture of the fragrance compound, rose oxide. This process, based on catalytic disproportionation of hydrogen peroxide into singlet oxygen and water, has been carried out on production scale in 10 m^3 reactors.

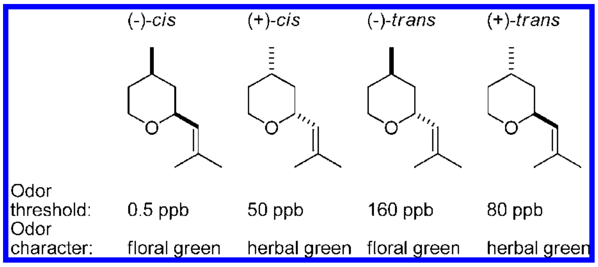
Introduction

(2*S*, 4*R*)-4-Methyl-2-(2-methylprop-1-enyl)tetrahydro-2*H*-pyran or (−)-*cis*-rose oxide is a major natural fragrance compound that is not only present in roses, but also contributes to the aroma of other flowers, fruits (e.g., lychee), or fruit-derived products (e.g., Gewürztraminer wine).[1] The aroma of (−)-*cis*-rose oxide is described as "floral; green". Commercially, natural rose oxide is isolated as fragrant oil from Bulgarian roses. This natural (−)-*cis*-rose oxide is expensive, since about 3000 kg of rose blossoms are needed to obtain 1 kg of rose oil.[2] Therefore, it finds limited applications in high-value perfumes. Synthetic rose oxide is produced on a much larger scale as a mixture of the four (−)-*cis*-, (+)-*cis*-, (−)-*trans*-, and (−)-*trans*-stereoisomers (rose oxide inactive), which still has a desirable rosy aroma profile like the natural and most fragrant (−)-*cis*-rose oxide stereoisomer (Chart 1). It finds application as a perfumery and flavour component.

A key step in the manufacture of synthetic rose oxide[3] is the peroxidation of β-citronellol by singlet oxygen[4] through an ene-type mechanism (Scheme 1).

Most commonly, this is done by photooxidation with triplet oxygen ($^3O_2$) in the presence of a sensitizer to achieve the required intersystem crossing to generate singlet oxygen ($^1O_2$).[5] The combination of organics, oxygen, and light entails problems with respect to safe processing on large scale, whereas economic processing suffers from the lack of economy of scale caused by the required photoreactors. In addition, such dedicated photoreactors are rarely available in a multipurpose plant chemicals production environment. These disadvantages can be overcome by generating $^1O_2$ in a "dark" way through catalytic disproportionation of hydrogen peroxide (Scheme 2).[6]

Chart 1. **Stereoisomers of rose oxide and their odor characteristics**



Such a "dark" singlet oxygenation (DSO) can be carried out in commonly available stirred tank reactors. This contribution

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(3) Among the various other methods reported for the preparation of rose oxide, especially worth mentioning is work from Takasago on "dark" production of rose oxide from citronellol based on bromination. These researchers also reported an elegant study on the odor properties of each of the four individual stereoisomers of rose oxide (see Chart 1). Yamamoto, T.; Matsuda, H.; Utsumi, Y.; Hagiwara, T.; Kanisawa, T. *Tetrahedron Lett.* **2002**, *43*, 9077.

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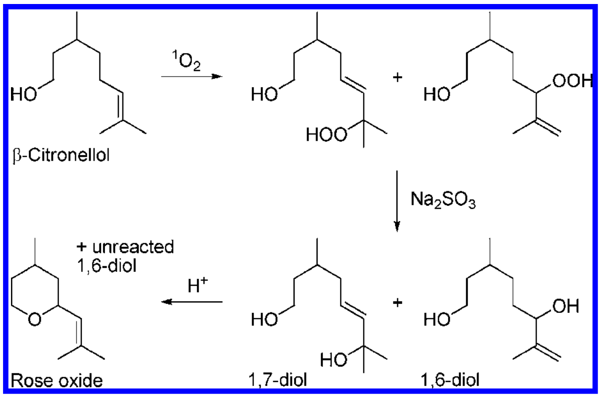
Scheme 1. **Synthesis of rose oxide via singlet oxygenation of *β*-citronellol**



Scheme 2. **Reaction sequence of "dark" singlet oxygenation**

$$2\ H_2O_2 \xrightarrow{\text{catalyst}} 2\ H_2O + {}^1O_2$$

$${}^1O_2 + \text{alkene} \longrightarrow \text{peroxide}$$

describes the process research and development of the DSO of *β*-citronellol carried out in 10 m^3 reactors. Background information on DSO can be found in earlier papers.[6]

The following scalability issues had to be taken into account in order to arrive at process implementation:

- choice of the catalyst
- suitable reaction medium with respect to chemical performance and safety
- prevention of H_2O_2 accumulation in the reaction mixture
- organic peroxide stability and reductive workup
- product isolation and catalyst recycling

These issues will be discussed below.

Choice of the Catalyst. Molybdate anions, MoO_4^{2-}, efficiently disproportionate hydrogen peroxide into singlet oxygen.[6] Thus, simple sodium molybdate, for example, is a very efficient homogeneous catalyst for DSO in polar media, with a quantitative $^1O_2$ yield in water. Molybdate can also be immobilized through anion exchange on layered double hydroxides (LDH),[7] Since the active species for $^1O_2$ generation is also anionic (viz., the triperoxomolybdate $[MoO(O_2)_3]^{2-}$),[6c] immobilization is preserved during the reaction. This species completely converts back into molybdate at low H_2O_2 concentration (i.e., at the end of the reaction). Accordingly, the original molybdate on LDH catalyst can be easily recycled after the DSO by simple filtration, thus avoiding problems arising from too high molybdate concentrations in aqueous waste streams. Besides this recycling advantage, use of heterogeneous molybdate on LDH instead of homogeneous Na_2MoO_4 as catalyst also offers advantages related to catalyst activity, solvent scope, and synthetic scope.[7] On the down side, H_2O_2 efficiency is lower (so a larger excess of H_2O_2 is required) because of $^1O_2$ loss through quenching by the LDH support. Because of this, and because homogeneous Na_2MoO_4 works well for DSO of *β*-citronellol, we chose to use Na_2MoO_4 as DSO catalyst, with catalyst recycling being enabled by a proper choice of the solvent (see below).

Suitable Reaction Medium with Respect to Chemical Performance and Safety. Molybdate-catalyzed H_2O_2 disproportionation proceeds most efficiently in terms of rate and $^1O_2$ yield in water as the solvent, in which *β*-citronellol is insoluble. Use of a two-phase aqueous H_2O_2/organic solvent system to deal with substrate insolubility does not work for DSO, since $^1O_2$ generated from H_2O_2 in the aqueous phase under molybdate catalysis is quenched by water to $^3O_2$ before it is able to diffuse from the aqueous layer to the organic layer, where it could react with *β*-citronellol. The problem of substrate inaccessibility arising from the short lifetime of $^1O_2$ in water (~3 μs) can be efficiently solved by working in water-in-oil microemulsions as medium, for which the aqueous droplet diameter is much smaller than the mean travel distance of $^1O_2$ before quenching.[8] Proper formulation of the microemulsion medium partially relieves problems related to the scalability of such systems, in particular those arising from the large amount of surfactant (~15%) required to generate a microemulsion.[9] More recently, three-liquid-phase microemulsion systems based on balanced catalytic surfactants have been developed.[9d] They are obtained with lower amounts of surfactants compared to conventional microemulsions (~3−5%), and they allow an easier recovery of oxidation product and catalyst, but they require the preparation of the catalyst. Despite these solutions, a straightforward single-phase reaction medium based on a water-miscible organic solvent would be preferred from a large-scale implementation point of view. An extensive screening of polar organic solvents revealed that lower alcohols, in particular methanol, are acceptable for sufficiently reactive substrates, such as *β*-citronellol. Although the $^1O_2$ yield from H_2O_2 disproportionation in methanol is reduced to 82% compared to the quantitative yield in water, this negative effect is counterbalanced by an enhanced $^1O_2$ lifetime in MeOH (10 μs) compared to that in water (3 μs).[6l] Thus, despite loss of $^1O_2$ caused by quenching, the overall trapping efficiency of $^1O_2$ by sufficiently reactive substrates is still high enough to allow almost full conversion without an economically unfeasible amount of H_2O_2.

Although methanol is the most convenient water-miscible solvent for lab-scale preparative DSO, its use on large scale is hampered by unfavorable safety data. In particular, its oxygen

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limit concentration (OLC)[10] is very low (8 vol %), and this parameter is of prime importance when dealing with the unavoidable partial loss of $^1O_2$ via quenching to triplet oxygen which escapes into the headspace of the reactor. Therefore, we chose to use ethylene glycol for further development towards implementing DSO of β-citronellol, since the OLC of ethylene glycol is much higher (50 vol %). Thus, safety prevailed over chemical performance, because the latter is reduced compared to methanol as a result of a lower $^1O_2$ yield from H_2O_2 disproportionation (70%) and a shorter $^1O_2$ lifetime (7.5 μs) in ethylene glycol.[6l] Near quantitative conversion of β-citronellol could be achieved, however, with a modest H_2O_2 excess (3 molar equiv. 50% aqueous H_2O_2; 150% relative to the stoichiometry of H_2O_2 disproportionation). In order to ensure that the headspace of the reactor maintained an oxygen concentration well below the OLC, nitrogen was sparged into the reaction mixture from the bottom of the reactor. Typically, the DSO of β-citronellol was run with 4 mol % Na_2MoO_4 as catalyst.

Prevention of H_2O_2 Accumulation in the Reaction Mixture. Besides avoiding accumulation of oxygen in the headspace of the reactor, safe processing also requires that no accumulation to dangerous levels of H_2O_2 in the reaction mixture occurs.[11] Preferably, H_2O_2 should be added at such a rate that a very low stationary-state concentration is maintained throughout the reaction at the chosen temperature. This requires insight in the mechanism and kinetics of the molybdate-catalyzed H_2O_2 disproportionation into $^1O_2$ and water. The prevalent peroxomolybdate species $Mo(O_2)_nO_{4-n}{}^{2-}$ with $n = 1, 2, 3, 4$ present in the reaction mixture depends on the H_2O_2 concentration and the pH. In our case, the DSO was carried out without pH adjustment, i.e. at natural pH (slightly alkaline conditions). Since $^1O_2$ is formed by decomposition of triperoxomolybdate $[MoO(O_2)_3]^{2-}$ whereas tetraperoxomolybdate $Mo(O_2)_4{}^{2-}$ does not generate $^1O_2$ and diperoxomolybdate $MoO_2(O_2)_2{}^{2-}$ is much less active in $^1O_2$ generation,[6c] H_2O_2 should be added at such a rate that formation of triperoxomolybdate is favored. Accordingly, there is an optimum H_2O_2 addition rate. This optimum can be monitored visually in practice by maintaining the orange colour of the triperoxomolybdate throughout the reaction and avoiding too fast addition causing the deep-red colour of the tetraperoxomolybdate $[Mo(O_2)_4]^{2-}$ or too slow addition favoring the yellow diperoxomolybdate $[MoO_2(O_2)_2]^{2-}$. Although molybdate-catalyzed DSO can be carried out at room temperature, on large scale the DSO of β-citronellol was carried out at 55 °C in order to avoid H_2O_2 accumulation and increase the space-time yield of the process. This elevated temperature was within the safe processing window as determined by DSC measurements to be discussed below.

Organic Peroxide Stability and Reductive Work-Up. Whereas most oxidations with H_2O_2 result in an oxygen atom transfer from the oxidant to the substrate with an overall reduction of peroxide in the reaction mixture, peroxide functionalities are partly preserved during DSO,[12] which generates an organic peroxide arising from incorporation of both H_2O_2 oxygen atoms by the substrate. Safe processing requires insight into the thermochemical behaviour of this organic peroxide product. DSO of β-citronellol in ethylene glycol generates a 1/1 mixture of the expected tertiary and secondary hydroperoxides, the tertiary hydroperoxide being the desired one for further transformation into rose oxide (Scheme 1).[5] A DSC measurement of the isolated hydroperoxide 1/1 isomer mixture indicated a highly exothermic decomposition (1309 J/g), with an onset temperature of 68 °C and a peak at 136 °C. The DSC showed a slight shoulder at 115 °C, indicative of the hydroperoxide isomer mixture. The onset of hydroperoxide decomposition shifted to much higher temperatures (110 °C) well above the reaction temperature of 55 °C when measured by DSC in aqueous ethylene glycol as obtained by DSO of β-citronellol (160 g/L ethylene glycol; hydroperoxide decomposition in aqueous ethylene glycol: 119 J/g). Thus, the reaction could be carried out safely at 55 °C.

Hydroperoxide reduction was carried out by introducing the reaction mixture to an aqueous solution of Na_2SO_3 at 60 °C. Reverse addition of Na_2SO_3 to the reaction mixture should be avoided since the hydroperoxide reduction is highly exothermic and evolution of heat in a mixture containing large amounts of the thermally labile hydroperoxides may lead to runaway conditions. Formed Na_2SO_4 precipitated largely during the reduction process and was removed by filtration. The Na_2MoO_4 catalyst, however, remains in solution and is present in the filtrate.

Product Isolation and Catalyst Recycling. The filtrate obtained after hydroperoxide reduction was extracted with MTBE to isolate the isomeric diol products derived from β-citronellol (Scheme 1). Simple evaporation of the solvent afforded the diols with sufficient purity for further processing to rose oxide via acid-catalyzed cyclization of the tertiary hydroperoxide. By distillation, water was largely removed from the aqueous ethylene glycol phase left after product extraction with MTBE. To the concentrated ethylene glycol solution that also contained the Na_2MoO_4 catalyst was added a new batch of β-citronellol, followed by dosing of H_2O_2 (3 molar equiv) at 55 °C. Work-up as described above afforded a new batch of isomeric diols in almost the same yield as obtained in the first run. Thus, use of ethylene glycol not only secured safe processing but also enabled easy and efficient catalyst recycling.[13]

Summary and Conclusions

DSO provides a scalable alternative for conventional photooxidation of β-citronellol as the key step in the manufacture of rose oxide. Safe processing was achieved by working in ethylene glycol as the solvent at elevated temperature (55 °C)

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(12) Peroxide functionalities are preserved only partly during DSO because only one molecule of $^1O_2$ is generated from two molecules of H_2O_2 through hydrogen peroxide disproportionation, in which one H_2O_2 molecule is reduced to water, whereas another H_2O_2 molecule is oxidized to O_2.

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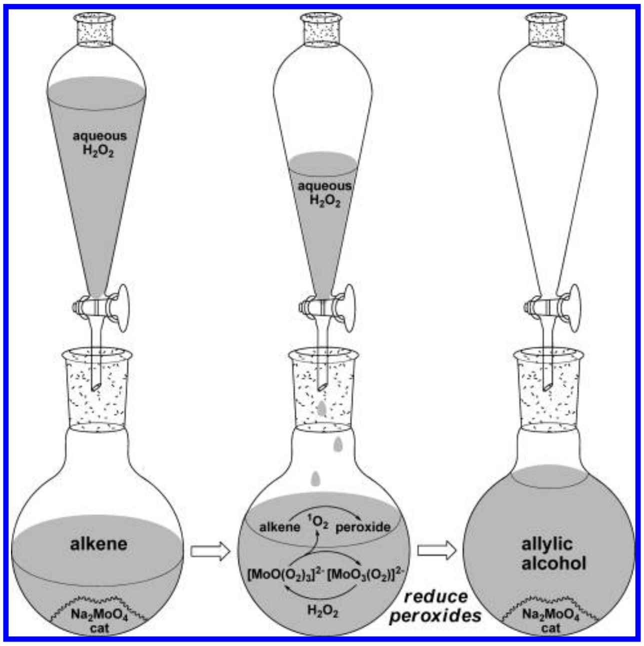

Figure 1. **"Dark" singlet oxygenation in practice.**

to avoid H_2O_2 accumulation. This solvent also allowed easy catalyst recycling and product isolation by simple extraction with MTBE. Ultimately, rose oxide obtained via DSO showed the same olfactory properties as rose oxide obtained via photooxidation of β-citronellol. DSO is also an easily applicable laboratory method that can be readily carried out using nothing more than a dropping funnel and a round-bottom flask, as shown in Figure 1, illustrating its use for the conversion of alkenes into allylic alcohols through an ene/Diels−Alder type singlet oxygenation.

Experimental Section

The following 1.5 mol scale procedure is analogous to the large-scale production carried out in 10 m^3 stirred tank reactors, except that no nitrogen was blown into the reaction mixture when the DSO was carried out in lab glassware without risk of ignition by spark formation.

A double-walled reactor equipped with a stirrer was charged with β-citronellol (240.0 g; 1.54 mol), $Na_2MoO_4 \cdot 2H_2O$ (16.7 g; 0.07 mol), water (30 mL), and ethylene glycol (1500 mL). After heating to 55 °C, 50% aqueous H_2O_2 (313.1 g; 4.60 mol) was added over a period of 6 h (43.5 mL/h). After the reaction was complete, the reaction mixture was introduced into a solution of Na_2SO_3 (193.5 g; 1.54 mol) in water (550 mL) at 60 °C at such a rate that the temperature did not increase. Na_2SO_4 was filtered off and the filtrate was extracted with MTBE (4 × 500 mL). Evaporation of MTBE afforded a 1/1 mixture of 3,7-dimethyloct-7-ene-1,6-diol and 3,7-dimethyloct-5-ene-1,7-diol (266.0 g; 1.54 mol; 100% yield).[14]

Catalyst Recycling. Water was removed from the aqueous ethylene glycol phase by distillation. A double-walled reactor equipped with a stirrer was charged with β-citronellol (240.0 g; 1.54 mol) and the concentrated ethylene glycol phase (1556 g) containing the catalyst. After heating to 55 °C, 50% aqueous H_2O_2 (313.1 g; 4.60 mol) was added over a period of 6 h (43.5 mL/h), and the reaction was worked up as described above to afford a 1/1 mixture of 3,7-dimethyloct-7-ene-1,6-diol and 3,7-dimethyloct-5-ene-1,7-diol (258.0 g; 1.54 mol; 97% yield).

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Supporting Information Available

Preparation of rose oxide by acid-catalyzed diol cyclization. This material is available free of charge via the Internet at http://pubs.acs.org/.

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