Novel and Versatile Photosensitized Oxygenation Reaction of α -Cedrene

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> **Abstract:** Three types of photosensitized oxygenations of α -cedrene (CED) were investigated, including: rose bengal(RB)-sensitized photooxygenation of α -cedrene in acetonitrile produced one major stereospecific product (cedr-8exoen-9 α -ol), in which the double bond migrated to an adjacent position, this result demonstrated the singlet oxygen process; 9,10-dicyanoanthrathene (DCA) sensitized photooxygenation led to the formation of cedr-8-en-10 β -ol; benzyl (BZ)-sensitized photoepoxidation furnished a stereospecific 8 α ,9 α -cedrene epoxide, this reaction includes radical reaction mechanism.

Keywords: Sensitized photooxygenation, α -cedrene, singlet oxygen, electron transfer, regioselectivity.

1. INTRODUCTION

It is established that the photochemical synthesis of terpenoids and natural products etc. has become a useful platform for methodological and synthetic studies [1]. Particularly, application of the photooxygenation for a variety of organic compounds, including olefins, heterocycles and natural products etc., has been extensively studied in recent years [2]. The photooxygenation provides an efficient and convenient method in organic synthesis, in which versatile oxygen-containing functional groups were introduced into the target molecules and the reactions frequently proceed in stereocontrolled manner to furnish the stereospecific selectivity. The photooxygenations also make important contribution to the green chemistry [3]. On the other hand, biologically active molecules such as amino acid, protein, nucleic acid and hormone etc. were found to undergo the photochemical damage through photooxygenation [4]. Therefore, both theoretical and applied studies on the photooxygenation are of significance.

Cedrene and its oxygenated derivatives such as sesquiterpenoids are major components of perfume essentials, flavors and some pharmaceuticals [5]. They are also attractive topics of total synthesis [6]. Abraham and coworkers [7] reported that Corynespora cassicola DSM 62474 and Rhodococcus rhodochrous ATCC 999 converted α -cedrene (Scheme 1) to a number of oxygenated products, such as 3hydroxy- and 12-hydroxy- α -cedrenes and cedrenone and 10methoxy- α -cedrene, but the biotransformations of α -cedrene require a long cultivation time and the product yields were extremely low. The epoxidation of the acid sensitive (+)-8(15)-cedren-9-ol with sulfonyl imidazolides / H₂O₂ / OH⁻ gave the corresponding cedrene epoxide as a single diastereoisomer [8]. Each of these prior art, cedrenol and cedrenone production processes, has disadvantages, where it requires not only a prolonged period of reaction time but also complicated byproducts that require extensive separation processes for the resulting cedrenol and cedrenone. There is no effective chemical method to synthesize the cedrenol and the cedrenone.

In this paper, three types of sensitized photooxygenations of α -cedrene involving the ene reaction by singlet oxygen $({}^{1}O_{2})[9]$, electron transfer (ET) and free radical reaction were explored. The results showed that these syntheses are effective and convenient to furnish stereospecific products, cedrenol, cedrenone and cedrene epoxide in high and moderate yields.

2. RESULTS AND DISCUSSION

RB Sensitized Photooygenation of α -cedrene

The rose bengal (RB) sensitized photooxygenation of α cedrene (CDE) 1 was carried out in acetonitrile under continuous bubbling of O_2 . The reaction gave rise to a single stereospecific enol, Cedr-8-exoen-9 α -ol 3[10], in high yield (88.8 %) after the reduction of the unstable 9-allylic hydroperoxide 2 by PPh₃. Obviously, the reaction proceeded via the ene reaction of singlet oxygen ($^{1}O_{2}$) according to the C=C shift manner and formation of the allylic hydroxyl group. RB is well known as a typical sensitizer for the formation of ¹O₂ $(\Phi = 0.76)$ [11]. Upon excitation, the triplet RB can convert oxygen to ${}^{1}O_{2}$ efficiently. The branched 8-methyl group in α cedrene led to the migration of C=C to the adjacent 8-exo position when the mild electrophilic ${}^{1}O_{2}$ attacked the more nucleophilic 9-position of 8-C=C bond from the α orientation and the formation of 9α -allylic hydroperoxide 2 via the suprafacial H shift.

This stereospecific phenomenon known as the 'cis effect' was first recognized in enol ethers by Conia [12] and Foote [13]. The cyclohexene and its derivatives show no cis effect, only gave the anti ene addition.

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Scheme 1. RB-sensitized photooxygenation of α -cedrene.



Scheme 2. DCA sensitized photooxygenation of α -cedrene.



Scheme 3. DCA/BP co-sensitized photooxygenation of α -cedrene.

This mechanism is also verified by our experiments. The attack of ¹O₂ at the C(8)=C(9) bond in α -cedrene yields only 9 α -allylic hydroperoxide **2**.

DCA Sensitized and DCA/BP Co-sensitized Photooxy-genation of α -cedrene

It was found that 9, 10-dicyanoanthrathene (DCA) sensitized photooxygenation of α -cedrene showed different product distribution pattern as compared with that in Rose bengal-sensitized photooxygenation of α -cedrene (see Scheme 1). As shown in Scheme 2, the reaction initially led to the formation of the major product, cedr-8-en-10 β hydroperoxide 4, and minor product, cedr-8-exoen-9 α hydroperoxide 2. Similarly, the reduction by PPh₃ was followed to give the corresponding enols, cedr-8-en-10 β -ol 5, in 45 % yield, and cedr-8-exoen-9 α -ol 3, in 30 % yield. DCA is a electron-deficient sensitizer. Upon excitation, the singlet state of DCA will be obtained.

To demonstrate above DCA-sensitized ET reaction postulate, the DCA/biphenyl (BP) cosensitized photooxygenation of CDE was further carried out. The result showed that the reaction led to the formation of two cedr-8-en-10-ol epimers, cedr-8-en-10 β -ol **5** and cedr-8-en-10 α -ol **6**. This regioselectivity is consistent with the major product of cedr-8en-10 β -ol **5** for the DCA sensitized photooxygenation of CDE and no formation of C=C-shifted cedr-8-exoen-9 α -ol **3** was observed. In addition, the reaction was greatly accelerated and completed in 14 min, shortened about 20 folds as compared with that for DCA-sensitized reaction.

It was well established that DCA/BP co-sensitization could efficiently enhance the ET reaction of less reactive substrates (S) via the secondary (or indirect) ET process [14], i.e. BP $^+$ + S \rightarrow BP + S $^+$. In our case, therefore, CDE can be regarded as such substrate and suggested to undergo the following ET photooxygenation:

$$DCA + BP \longrightarrow DCA^{-.} + BP^{+.}$$

$$BP^{+.} + CDE \longrightarrow BP + CDE^{+.}$$

$$DCA^{-.} + O_2 \longrightarrow DCA + O_2^{-.}$$

$$CDE^{+.} + O_2^{-.} \longrightarrow 5 + 6$$

BZ Sensitized Photoepoxidation of α-cedrene

When the photosensitized oxygenation reaction of α cedrene was performed under the photosensitization of benzil (BZ), cedrene epoxide was obtained (Scheme 4) in total yield of 60.6 %, which was further isolated to give two stereoisomers, minor 8β ,9 β - cedrene epoxide (7) and major 8α , 9 α -cedrene epoxide 8 in the ratio of 0.43 : 1. This reaction could be illustrated by the Bartlett reaction [15], in which the photoxidation of benzil produces benzoylperoxy radicals which can transfer an oxygen atom effectively to olefins producing the stereospecific α -epoxides. Furthermore, 8, 9-epoxycedrane can be easily transformed into cedran-9-one 9 through the isomerization with boron trifluoride ether complex (BF₃·OEt₂).

3. EXPERIMENTAL PROCEDURES

3.1. Rose Bengal-sensitized Photooxygenation of α -cedrene

 α -cedrene (1.05 g, 5.0 mmol) and Rose Bengal (0.11 g) were dissolved in 80 ml of acetonitrile. The solution was irradiated under continuous bubbling of O₂ with medium pressure mercury lamp (500 w) for 4 h and the reaction was followed by TLC until the reaction was completed. 1.51 g of triphenylphosphine (PPh₃) was then added to the solution with vigorous stirring for 1 h. After removal of solvent, the mixture was isolated by column chromatography on silica gel with eluant of petroleum: ethyl acetate (26 : 1). Cedr-8-

exoen-9α-ol **3** (0.95 g) was obtained as a white, crystalline solid, m.p. 123-125 °C; $[α]^{20}_{589}$ +8.5, (*c* 1, CHCl₃) [16]. The yield was 88.8 %. ¹H NMR(400Mz, CDCl₃):δ4.99 (t, 1H, *J* = 2.4 Hz), 4.75 (t, 1H, *J* = 2.4 Hz), 4.34 (m, 1H), 2.35 (d, 1H, *J* = 4.2 Hz), 1.72-1.92 (m, 3H), 1.51-1.61 (m, 2H), 1.16-1.47 (m, 4H), 0.97 (s, 3H), 0.94 (s, 3H), 0.86 (d, 3H, *J* = 6.9 Hz); ¹³C NMR (100Mz, CDCl₃):δ154.0, 106.6, 70.0, 60.4, 57.0, 54.9, 45.0, 44.9, 42.3, 41.6, 36.7, 26.7, 26.1, 25.8, 15.5; MS (m/z, %): 220 (24), 205 (26), 187 (23), 177 (47), 162 (60), 159 (59), 136 (56), 135 (66), 118 (54), 109 (54), 91 (59), 69 (100), 41 (53).

3.2. DCA Sensitized Photooxygenation of α -cedrene

89 mg of α -cedrene and 7.8 mg of DCA were added in 80 mL of acetonitrile. The solution was irradiated under continuous bubbling of O₂ with medium pressure mercury lamp (500 W) for 4 h and the reaction was followed by TLC. 130 mg of triphenylphosphine (PPh₃) was then added to the solution with stirring for 30 min. After removal of solvent, the mixture was isolated by column chromatography on silica gel with eluent of petroleum/ ethyl acetate (8 : 1). Two components were obtained: 43.4 mg of the major product, Cedr-8-en-10β-ol 5, yield 45%, m.p. 88-90 °C and 28.5 mg of minor product, Cedr-8-exoen-9a-ol 3, yield 30 %, m.p. 123-125 °C. Spectral data for 5, IR (cm⁻¹) 3246, 2946, 2932, 2843, 1457, 1056, 998, 892. ¹H NMR(400Mz, CDCl₃):δ5.37 $(1H, dd, J = 4.2 Hz 10\alpha H), 3.86 (1H, d, J = 4.0 Hz 9-H),$ 1.52-1.93 (m, 9H), 1.13-1.49 (m, 4H), 0.98 (s, 3H), 0.92 (s, 3H), 0.80 (d, 3H, J = 7.0 Hz); ¹³C NMR (100Mz, CDCl₃):8144.3, 124.2, 72.3, 60.2, 54.5, 51.9, 45.7, 38.6, 35.2, 33.9, 28.5, 25.7, 25.0, 23.8, 14.9; MS (m/z, %): 220 (11), 202 (12), 187(27), 177(51), 159 (84), 136 (51), 118 (68), 105 (2), 91 (61), 69 (100). Spectral data for **3** were the same as that in above rose bengal-sensitized photooxygenation of α -cedrene.

3.3. DCA-BP Co-sensitized Photooxygenation of α -cedrene

99 mg of α -cedrene, 6.3 mg of DCA and 523 mg of biphenyl were dissolved in 80 ml of acetonitrile. The solu-



Scheme 4. BZ-sensitized photoepoxynation of α -cedrene.

tion was irradiated under continuous bubbling of O₂ with medium pressure mercury lamp (500 W) for 20 h and the reaction was followed by TLC until the reaction was completed. After removal of solvent, the mixture was isolated by column chromatography on silica gel with eluent of petroleum/ ethyl acetate (8 : 1). 32.5 mg of the component was obtained as Cedr-8-en-10-ol. HPLC analysis indicated the component was consist of equal amount of two epimers, Further separation by column chromatography on silica gel with eluent of petroleum/ ethyl acetate (8 : 1) to give two epimers, 16.2 mg Cedr-8-en-10α-ol 6(15.2%) and 16.2 mg Cedr-8-en-10β-ol 5(15.2%). IR (cm⁻¹) 3246, 2946, 2932, 2843, 1457, 1056, 998, 892. ¹H NMR(400Mz, CDCl₃): δ 5.37 (1H, dd, J = 4.2 Hz 10 α H), 3.86 (1H, d, J = 4.0 Hz 9-H), 1.52-1.93 (m, 9H), 1.13-1.49 (m, 4H), 0.98 (s, 3H), 0.92 (s, 3H), 0.80 (d, 3H, J = 7.0 Hz); ¹³C NMR (100Mz, CDCl₃): δ 144.3, 124.2, 72.3, 60.2, 54.5, 51.9, 45.7, 38.6, 35.2, 33.9, 28.5, 25.7, 25.0, 23.8, 14.9; MS (m/z, %): 220 (11), 202 (12), 187(27), 177(51), 159 (84), 136 (51), 118 (68), 105 (2), 91 (61), 69 (100).

3.4. Photooxygenation of α-cedrene with Benzyl

α-cedrene (2.0 g, 11.0 mmol) and benzil (1.2 g) were dissolved in 80 ml of benzene. The solution was irradiated under O₂ with medium pressure mercury lamp(500 W) for 15 h and the reaction was followed by TLC. After removal of solvent, the mixture was isolated by column chromatography on silica gel with eluent of petroleum/ ethyl acetate (120:1) to give 1.15 g of 8,9-epoxycedrane **7**, **8** as a pale yellow oil, the yield was 48 %. ¹H NMR(400Mz, CDCl₃): δ 3.01 (d, 1H, J = 4.8Hz), 1.75-1.95 (m, 4H), 1.52-1.69 (m, 4H), 1.41 (s, 3H), 1.21-1.36 (m, 3H), 1.18 (s, 3H), 0.99 (s, 3H), 0.81 (d, 3H, J = 4.2Hz); ¹³C NMR(100Mz, CDCl₃): δ60.6, 60.4, 57.7, 53.4, 51.7, 42.7, 41.2, 36.5, 35.6, 35.5, 29. 8, 27.2, 24.7, 23.4, 15.3; MS (m/z, %): 220(M⁺, 6), 150(61), 135(71), 121(100 %), 107(30), 93(33), 91(31), 43(33), 41(35).

3.5. Synthesis of cedran-9-one

1 mL of boron trifluoride ether complex $(BF_3 \cdot O(C_2H_5)_2)$ was added dropwise to a stirred solution of the 2 g 8,9epoxycedrane in 80 ml of benzene at 0 °C. After stirring for 1 h, the reaction mixture was filtrated. The filtrate was washed with brine (10 ml). The organic layer was dried (MgSO₄) and evaporated. The residue was purified by column chromatography with petroleum/ethyl acetate (60:1) to furnish the cedran-9-one 9 as orange yellow oil (1.4 g, 70%), $\left[\alpha\right]_{589}^{20}$ -78.9 (c 1,CHCl₃) [17]. ¹H NMR (400Mz, CDCl₃):82.66(q, 1H, J=7.2Hz), 2.36(d, 1H, J=16.2Hz), 2.20(d, 1H, J=16.2Hz), 1.82-1.91(m, 3H), 1.73(m, 1H), 1.67(m, 1H), 1.53-1.61(m, 1H), 1.25-1.48(m, 3H), 1.11(d, 3H, J=7.2Hz), 0.97(s, 3H), 0.95(s, 3H), 0.83(d, 3H, J=6.6Hz); ¹³C NMR(100Mz, CDCl₃):8216.5, 58.5, 55.7, 55.2, 49.7, 46.9, 42.7, 41.6, 37.6, 36.8, 26.9, 26.9, 25.7, 18.1, 15.3; MS (m/z, %): 220(M⁺, 53), 205(100 %).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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