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Synthesis of (-)-3-Carene-2,5-dione via Allylic Oxidation of (+)-3-Carene

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Activated carbon-supported CuCl₂ (CuCl₂/AC) is a heterogeneous catalyst for the liquid-phase selective allylic oxidation of (+)-3-carene with tert-butyl hydroperoxide (TBHP) and O₂ to produce (-)-3-carene-2,5-dione. The possible reaction mechanism and the effects of different factors on the allylic oxidation were investigated. The optimal conditions are as follows: reaction temperature, 45 °C; molar ratio of CuCl₂ to (+)-3-carene, 1%; volume ratio of (+)-3-carene to TBHP, 1:3; and reaction time, 12 h. Under the optimal conditions, the conversion of (+)-3-carene reached 100%, whereas the selectivity for (-)-3-carene-2,5-dione reached 78%. The CuCl₂/AC catalyst was characterized via X-ray diffraction, and the chemical structure of the target compound was identified via infrared spectroscopy, proton nuclear magnetic resonance spectroscopy, mass spectrometry, and optical analysis.

Keywords: Activated carbon-supported CuCl₂; (-)-3-Carene-2,5-dione; (+)-3-Carene; Allylic oxidation; Mechanism.

INTRODUCTION

Allylic oxidation is an important and useful reaction in many areas of organic synthesis.¹ (-)-3-Carene-2,5-dione, one of the products of allylic oxidation of (+)-3-carene[(1S,6R)-3,7,7-trimethylbicyclo[4.1.0]hept-3-ene] often serves as the starting material for the synthesis of fragrances and flavors, as well as of synthetic intermediates and chiral building blocks.² (+)-3-Carene is an interesting substrate for oxidation reactions because it can undergo several different modes of attack by the oxidant, such as, e.g. epoxidation or oxidative cleavage of the double bond, or the oxidation of allylic C-H bonds. Different catalysts and oxidants can be used in the allylic oxidation of (+)-3carene to synthesize the desired product selectively. For example, Robles-Dutenhefner³ used sol-gel Co/SiO₂ as a catalyst for the allylic oxidation of (+)-3-carene with oxygen under solvent-free conditions, achieving only 10% selectivity. Catir⁴ reported the allylic oxidation of (+)-3-carene to (-)-3-carene-2,5-dione with a system of bis(trifluoroacetoxyiodo)benzene and tert-butyl hydroperoxide (TBHP), achieving high conversion (90%) but low selectivity (35%). In these two studies, (-)-3-carene-2,5-dione was obtained with very low selectivity. Shing⁵ was able to obtain high selectivity (60%) in the mild manganese(III) acetate-catalyzed allylic oxidation of (+)-3-carene to (-)-3-carene-2,5dione after 48 h reaction time. Lempers⁶ reported the use of chromium-substituted aluminophosphate (CrAPO-5) as an active, selective catalyst for the allylic oxidation of (+)-3carene with either oxygen or TBHP as the oxidant, obtaining 51% selectivity after 48 h. The major drawback of these systems is the overly long reaction time. Oliveira' reported that the PdCl-catalyzed allylic oxidation of (+)-3-carene with H₂O₂ in CH₃CN solutions has a conversion of 47% after 10 h. Although the reaction time is not very long, the conversion is quite low, and the oxidant, H₂O₂, is highly explosive. In addition, because of the serious environmental problems associated with chromium- and selenium-containing effluents, attention has focused on environmentally safe catalysts for the allylic oxidation of (+)-3-carene. Carbon-supported Cu-based catalysts can be used in vapor phase reactions,^{8–12} with oxygen as one of the oxygenants. Thus, a novel catalyst composed of activated carbon-supported CuCl₂ (denoted as CuCl₂/AC) was prepared and characterized via powder X-ray diffraction (XRD). The allylic oxidation of (+)-3-carene to (-)-3-carene-2,5-dione by an O2-TBHP system using CuCl2/AC as an active, selective, and recyclable catalyst is also reported. Not only was the reaction time reduced, but the selectivity of the (-)-3carene-2,5-dione product was also enhanced.

EXPERIMENT

Instruments and raw materials

Most of the chemicals were purchased from China Medicine (Group) Shanghai Chemical Reagent Corp., except for (+)-3-Carene, CuCl₂, and activated carbon, which were purchased from Sigma-Aldrich. The Panalytical PW

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3040/60 X'Pert PRO diffractometer was used to characterize the catalyst. The GC-9790 II gas chromatograph was used to monitor the oxidation reaction and analyze the reaction product qualitatively and quantitatively. The Bruker AVANCE III 500 MHz spectrometer, Agilent 5973N mass spectrometer (MS), Magana-IR 500 Fourier transform infrared (FT-IR) spectrometer, and Rudolph Autopol III polarimeter were all used to characterize the oxidation product.

Catalyst preparation

The activated carbon support and CuCl₂ used for catalyst preparation were commercial products of chemically pure grade. The CuCl₂/AC catalysts were prepared via the conventional impregnation method. Activated carbon and CuCl₂ were dried in vacuum to remove water. A copper chloride solution was prepared by dissolving $CuCl_2$ (1 g, 5.8 mmol) in ethanol (10 g). The activated carbon particles (3 g, 0.25 mol) were then impregnated with the copper chloride solution. The resulting solution was stirred for 24 h under a nitrogen gas flow at room temperature, followed by drying under nitrogen at 150 °C for 2 h. The dried samples were then cooled to room temperature. Calcination was performed by heating the powdered catalyst to 300 °C at a rate of 1 °C/min in a stream of nitrogen, and the temperature was held at 300 °C for 10 h. Morphological analysis of the catalyst was conducted via XRD.

Catalyst characterization

The XRD patterns were recorded on a Panalytical PW 3040/60 X'Pert PRO diffractometer with Cu K α radiation. The diffraction patterns at 40 kV and 40 mA were recorded within the 5° to 80° Bragg angle (2 θ) range at a rate of 5°/ min.

Two activated carbon peaks were detected at $2\theta = 26.6^{\circ}$ and 54.7° (Fig. 1). This peak pattern is in accordance



Fig. 1. X-ray diffraction (XRD) patterns of fresh activated carbon (AC), pure CuCl₂, and activated carbon-supported CuCl₂ (CuCl₂/AC).

with the XRD spectra of fresh activated carbon. A number of peaks for CuCl₂/AC were detected at $2\theta = 16.2^{\circ}$, 21.9° , 28.88° , and 33.9° , thereby confirming its successful preparation.

Synthesis of (-)-3-carene-2,5-dione

The allylic oxidation of (+)-3-carene was conducted in a 25 mL round-bottomed flask connected to a condenser and a magnetic stirrer. (+)-3-Carene (1.7 g, 0.0125 mol), TBHP (6 mL), acetonitrile (MeCN, 10 mL), and CuCl₂/AC (0.067 g, 12.5 mmol) were added into the flask, and the reaction mixture was heated at 45 °C under an oxygen flow. The reactions were analyzed using a gas chromatograph (GC) equipped with a flame ionization detector and fitted with an SE-54 capillary column ($30 \text{ m} \times 0.53 \text{ mm}$). The GC conditions were as follows: initial temperature, 80 °C (1 min); temperature rate, 5 °C/min; final temperature, 200 °C; injector temperature, 80 °C; and detector temperature, 200 °C. The amount of each compound in the reaction mixture was estimated from the corresponding chromatographic peak areas using chlorobenzene as the internal standard, and by comparing with the corresponding calibration curves. These calibration curves were constructed using authentic samples or isolated compounds from the reaction solution. The retention times were compared with those of commercially available or previously synthesized products. The experimental results showed that the main oxidation products are (-)-3-carene-2,5-dione and (+)-3carene-5-one by a 10:1 ratio or better.

Pure (-)-3-carene-2,5-dione was obtained through silica column chromatography [eluting with a mixture of ethyl acetate: petroleum ether (10:90)] as a pale yellow needle crystal. $[\alpha]_{D}^{23} = -9.428$ (c 0.308, EtOH); ¹H NMR (CDCl₃, 500 MHz) δ : 1.33 and 1.33 (2s, 2×3 H, H-8, 9), 1.98 (s, 3H, H-10), 2.32–2.35 (m, 2H, H-1, 6), and 6.51 (q, 1H, H-4); IR (KBr) υ : 3434, 3038, 2981, 2955, 2926, 1652, and 1622 cm⁻¹; MS (70 eV) *m/z* (relative intensity %): 164 (M⁺, 57), 128 (100), 121 (55), 91 (50), 93 (69), 77 (41), 67 (44), and 53 (44). The data are in accordance with experimental results reported in literature.¹³

As a byproduct of oxidation of the (+)-3-carene, (+)-3-carene-5-one was obtained through silica column chromatography as an orange oily material. $[\alpha]_{D}^{23} = +153.51^{\circ}$ (c 0.101 g/100 mL, AcOEt); ¹H NMR (CDCl₃, 500 MHz) δ : 1.03 (s, 3H), 1.19 (s, 3H), 1.45 (t, 1H), 1.57 (d, 1H), 1.87 (s, 3H), 2.32 (d, 1H), 2.64 (d, 1H), and 5.83 (s, 1H). IR (KBr) v (cm⁻¹): 2959, 1658, 1440, 1379 cm⁻¹. MS (EI) *m/z* (relative intensity %): 150 (M⁺⁺, 100), 135 (9.21), 121 (13.33), 107 (11.34), 93 (100), 91 (53.38), 79 (37.74), 43 (35.69), 41 (34.69), 77 (33.98), 92 (31.17), 80 (29.04). The data are in accordance with the results reported in literature.¹³

RESULTS AND DISCUSSION

Effect of the reaction temperature

The reaction is a gas-liquid-solid three-phase reaction; thus, the temperature is the crucial factor that affects the reaction. Therefore, the effect of the reaction temperature on the yield was investigated. Fig. 2 shows that the best results were obtained at 45 °C. When the temperature increases, the yield of the target product drops, and more byproducts are formed. When the temperature is increased, the oxygen content in the solution is reduced, and the reaction becomes inhibited. Therefore, 45 °C was determined as the optimal reaction temperature.

Effect of the reaction time

The reaction processes were monitored via GC. Fig. 3



Fig. 2. Effect of the reaction temperature on the product yield (%). Conditions: 1.7 g (+)-3-Carene; 0.067 g CuCl₂/AC; 6.0 mL tert-butyl hydroperoxide (TBHP); 10.0 mL acetonitrile (MeCN); reaction time: 8 h; oxygen.



Fig. 3. Effect of the reaction time on product yield (%). Conditions: 1.7 g (+)-3-carene; 0.067 CuCl₂/ AC; 6.0 mL TBHP; 10.0 mL MeCN; temperature: 45 °C; oxygen.

shows that the best result was obtained after 12 h reaction time. When the reaction time is increased to 18 h, numerous unidentified by-products are formed, and the product yield decreases.

Effect of the catalyst concentration

The previously determined optimized conditions were applied to the experimental reactions using different amounts of the catalyst to determine the optimal catalyst amount. Fig. 4 shows that the best result was obtained at a 1% to 3% mole ratio of CuCl₂/AC to (+)-3-carene. When the catalyst amount is greater than 3%, the (-)-3-carene-2,5-dione yield slightly changes, and excess amounts of the catalyst leads to the decomposition of the product. Fig. 4 also shows that a catalyst amount between 1% and 3% has negligible effect on the product yield. Therefore, 1% catalyst was determined as the optimal amount.

Effect of the volume ratio of TBHP to (+)-3-carene

The amount of TBHP has significantly affects the reaction rate. The effect of the volume ratio of TBHP to (+)-3-carene on the reaction was determined. Fig. 5 shows that 3:1 is the best volume ratio of TBHP to (+)-3-carene. Side reactions are likely to happen when an excess amount of TBHP is present, resulting in reduced selectivity for (-)-3carene-2,5-dione. Therefore, 3:1 was determined as the optimal volume ratio of TBHP to (+)-3-carene.

Effect of oxygen

Fig. 5 shows that some of the raw materials are oxidized even when no TBHP is added to the reaction. This observation indicates the presence of another oxidant in the reaction. This oxidant is oxygen. Therefore, the effect of oxygen was determined through a pair of controlled experiments, with one reaction conducted in the presence of oxygen, and the other with no oxygen present. The reaction



Fig. 4. Effect of the catalyst amount on the product yield (%). Conditions: 1.7 g (+)-3-carene; 6.0 mL TBHP; 10.0 mL MeCN; temperature: 45 °C; reaction time: 12 h; oxygen.

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processes were monitored via GC within 14 h. The results (Fig. 6) show that oxygen is an important factor in the reaction.

Reaction mechanism

The proposed reaction mechanism is as follows (Scheme I). According to the type of oxidant (t-BuOOH and CuCl₂) and the proportion of alcohol and ketone (higher selectivity for ketone), we considered that that the reaction is one of the Gif oxidation system, namely GoChAgg^{II}. The mechanism is similar to that proposed for other Gif-typ reactions.¹⁴⁻¹⁵

Oxidation of $\alpha\mbox{-pinene}$ and cyclohexene

Under the same optimal conditions, verbenone was also synthesized via the allylic oxidation of α -pinene, with a yield of 28%; cyclohexenone was also synthesized via the allylic oxidation of cyclohexene, with a yield of 13.8%



Fig. 5. Effect of the volume ratio of TBHP to (+)-3-carene on the product yield (%). Conditions: 1.7 g (+)-3-carene; 0.067 g CuCl₂/AC; 10.0 mL MeCN; temperature: 45 °C; reaction time: 12 h; oxygen.



Fig. 6. Effect of oxygen on the product yield (%). The red and black lines indicate the yield in the presence and absence of oxygen, respectively. Conditions: 1.7 g (+)-3-carene; 0.067 g CuCl₂/ AC; 10.0 mL MeCN; temperature: 45 °C.

Scheme I Mechanism of allylic oxidation of (+)-3carene



(Scheme II). Moreover, when the temperature is increased to 70 $^{\circ}$ C, the yields of verbenone and cyclohexenone increase to 76.7% and 23.1%, respectively.

Verbenone was characterized via ¹H NMR. (500.15 MHz, CDCl₃) δ: 1.02 (s, 3H); 1.46 (s, 3H); 2.00 (s, 3H);



2.41 (t, 2H); 2.65 (t, 1H); 2.83 (m, 1H); and 5.71 (s, 1H). Cyclohexenone was characterized via MS. *m*/*z*: 96 (M⁺), 81, 68, 55, 39, and 27.

CONCLUSIONS

(-)-3-Carene-2,5-dione can be synthesized via the allylic oxidation of (+)-3-carene with CuCl₂/AC, TBHP, and O₂ in a solution of MeCN. Single-factor experiments were designed to optimize the synthesis conditions and obtain the desired yield. The optimal conditions are as follows: reaction temperature, 45 °C; molar ratio of CuCl₂ to (+)-3carene, 1%; volume ratio of (+)-3-carene to TBHP, 1:3; and reaction time, 12 h. Under these optimal conditions, the conversion of (+)-3-carene reached 100%, and the selectivity for (-)-3-carene-2,5-dione can reach 78%.

In summary, a mild, efficient, facile, environment-

friendly, and highly economical method of preparing (-)-3-carene-2,5-dione has been developed in this study.

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