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Preparation of α-damascone

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α-Damascone is widely used in perfumes. However, the manufacture of α-damascone remains challenging owing to the limitations of current production processes. Herein, α-damascone was successfully synthesized from α-ionone using a new route involving only four steps, namely oximization, epoxidation, dehydration, and reduction. The total yield was 54.9% with a final chemical purity of 97% (by GC). Only water, cyclohexane, and ethanol were used in the reactions except in the purification step, and all solvents could be recycled. The structures of the intermediates and target compound were identified by ^{1}H NMR and ^{13}C NMR analyses and MS experiments. This route is a simple and successful method for the industrial preparation of α-damascone.

Keywords: α-damascone, α-ionone, preparation.

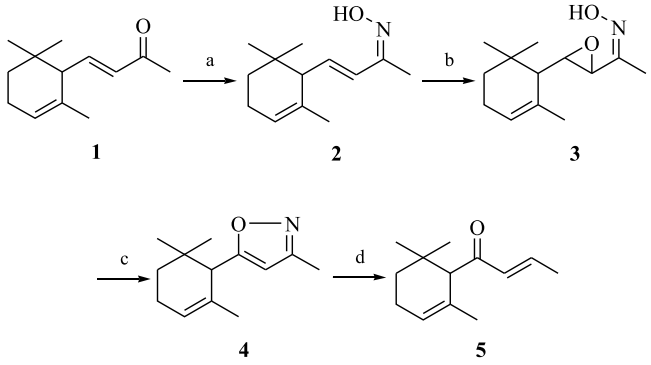
INTRODUCTION

Owing to the delicate fragrance it gives to certain roses, fruits, and nicotiana tabacum[1], α-damascone is used as a flavoring agent in high-end cosmetics, foods, and other applications. It is also a rare spice that has been developed in recent decades. Accordingly, α-damascone has received much research attention recently. α-Damascone can be extracted from black tea[2] or tobacco[3]. However, the amount of α-damascone that can be extracted from natural sources is low, and market demand remains far from being met owing to its complex synthesis. Therefore, the current price of α-damascone is high, resulting in limited applications.

The synthesis of α-damascone in several reaction steps has previously been reported from α-ionone, an inexpensive and readily available starting material. α-Damascone was successfully synthesized by Ohloff[4] in the early 1970s in three steps using a Wharton rearrangement reaction, but the result was poor owing to numerous cyclization byproducts. Serra and Fuganti[5] utilized a base-mediated elimination of 7-oxy-dihydroionol acetate to obtain α-damascone. Boulin, B.[6], Luis A.S.[7], Gosselin, P.[8], also reported methods of preparation of α-Damascone respectively. However, the reaction conditions were harsh and expensive, and the yield was low. Another synthetic route was reported[9] involving transforming an oxime into an isoxazole derivative and α-damascone was obtained *via* a reduction reaction. However, preparation of the isoxazole derivative consumed huge amounts of iodine reagents, which was costly, and presented decolorization problems. We now report a feasible new route, involving the epoxidation of an oxime, followed by isoxazole preparation *via* dehydration with strong acid, as shown in Scheme 1, to avoid the aforementioned synthetic problems.

EXPERIMENTAL

General experimental procedures. NMR analyses were performed using an Avance 500 instrument (Bruker, USA) at 500 and 125 MHz for ^{1}H and ^{13}C spectra, respectively. Spectra were recorded in deuterated solvents containing tetramethylsilane as an internal reference standard. ESI-MS data were obtained on an Agilent 6530 Q-TOF instrument (Agilent, Singapore). α-Ionone (**1**) was purchased from Haihang Industry Co., Ltd.



Scheme 1. Synthesis of α-damascone
Reagents and conditions: a. $NH_2OH{\cdot}HCl$, NaOAc, $EtOH/H_2O$, 55°C, 99.6%; b. H_2O_2/H_2O, CTAOH, LiOH, H_2O, 15°C, 96.1%; c. HCl/H_2O, cyclohexane, 35°C, 79.5%; d. Na, C_2H_5OH, cyclohexane, 35°C, 72.4%

α-Ionone oxime (2). Hydroxylamine hydrochloride (3.8 g, 0.06 mol) and sodium acetate (6.4 g, 0.07 mol) were dissolved in water (15 mL) and the solution was added dropwise to a solution of α-ionone (**1**) (10.0 g, 0.052 mol) in ethanol (20 mL). The reaction was then stirred for 4 h at 55°C. The mixture was cooled to room temperature, diluted with water (60 mL), and extracted with EtOAc (80 mL × 3). The organic phase was washed with saturated $NaHSO_3$ (100 mL), dried with $MgSO_4$, and concentrated *in vacuo* to afford **2** (9.3 g, 99.6% yield, 98% chemical purity by GC, a mixture of two cis/trans isomers) as a sticky orange oil. $C_{13}H_{21}NO$; mass spectrum (ESI), *m/z* 207 $[M]^+$. These diastereoisomers were used in the next steps without purification or separation.

Isomer **2a** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 6.12 (d, J = 15.8 Hz, 1H), 5.86 (dd, J = 15.7, 9.5 Hz, 1H), 5.42 (s, 1H), 2.22 (d, J = 9.4 Hz, 1H), 2.00 (s, 5H), 1.55 (s, 3H), 1.51 – 1.34 (m, 1H), 1.18 (d, J = 13.2 Hz, 1H), 0.89 (s, 3H), 0.81 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ_C 155.7, 136.5, 132.8, 127.9, 120.9, 53.9, 31.7, 30.9, 28.2, 27.0, 26.3, 22.2, 9.3.

Isomer **2b** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 6.84 (d, J = 16.0 Hz, 1H), 6.17 – 5.78 (m, 1H), 5.44 (s, 1H), 2.25 (t, J = 12.5 Hz, 1H), 2.10 – 1.82 (m, 5H), 1.56 (s, 3H), 1.47 – 1.36 (m, 1H), 0.98 (d, J = 19.4 Hz, 1H), 0.90 (s, 3H),

0.81 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ_C 152.4, 140.8, 132.4, 121.2, 119.9, 53.9, 31.7, 30.9, 27.0, 26.3, 22.4, 22.2, 9.3.

α-Ionone oxime epoxide (3). α-Ionone oxime **2** (5.1 g, 0.025 mol, a mixture of two cis/trans isomers obtained in step 1) and 10 wt% CTAOH aqueous solution (3.7 mL) were dissolved in water (70 mL) at 0°C. H_2O_2 (35 mL, 30% in water) and LiOH aqueous solution (5 mL, 6 mol/L) were mixed and was slowly added at below 15°C. After 15 h, the reaction mixture was extracted with CH_2Cl_2 (50 mL × 3), dried with $MgSO_4$, and condensed to provide **3** (4.9 g, 96.1% yield, 97% chemical purity by GC, a mixture of multiple diastereoisomers) as a sticky oil. $C_{13}H_{21}NO_2$; mass spectrum (ESI), *m/z* 223 $[M]^+$. These diastereoisomers were used in the next steps without purification or separation.

Isomer **3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 (s, 1H), 3.42 (m, 1H), 2.84 (dd, *J* = 15.9, 8.7 Hz, 1H), 2.04 (s, 3H), 1.89 (m, 1H), 1.80 (m, 1H), 1.71 (d, *J* = 5.1 Hz, 3H), 1.56 (m, 1H), 1.42 (d, *J* = 8.7 Hz, 1H), 1.25 (m, 1H), 1.11 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 155.4, 130.3, 123.5, 56.4, 56.1, 51.7, 32.6, 31.9, 31.3, 26.7, 23.0, 22.4, 7.6.

Isomer **3b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 (s, 1H), 3.43 (s, 1H), 2.84 (t, *J* = 12.4 Hz, 1H), 2.04 (s, 3H), 1.83 (m, 1H), 1.71 (d, *J* = 5.7 Hz, 3H), 1.55 (m, 1H), 1.42 (d, *J* = 8.8 Hz, 1H), 1.40 – 1.12 (m, 2H), 1.11 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 155.4, 130.3, 123.5, 56.4, 56.0, 51.7, 31.9, 31.3, 26.7, 26.4, 23.1, 22.4, 7.6.

α-Ionone isoxazole (4). HCl (1.5 mL, 35% in water) was added dropwise to a solution of **3** (2.0 g, 0.009 mol) in cyclohexane (20 mL) at 35°C. After addition was complete, the mixture was stirred under reflux for 6 h. The reaction mixture was then diluted with water (50 mL), extracted with CH_2Cl_2 (70 mL × 3), neutralized with 10% NaOH aqueous solution, and the organic layer was collected and condensed to provide **4** (1.59 g, 79.5% yield, 92% chemical purity (GC)) as a sticky oil. $C_{13}H_{19}NO$; mass spectrum (ESI), *m/z* 205 $[M]^+$.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (s, 1H), 5.50 (s, 1H), 2.91 (s, 1H), 2.20 (s, 3H), 2.03 (m, 2H), 1.50 (s, 3H), 1.15 (m, 2H), 0.94 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 173.9, 158.7, 130.8, 122.2, 102.5, 48.8, 32.2, 32.1, 30.2, 27.3, 25.9, 22.2, 10.8.

α-Damascone (5). Sodium (1.1 g, 0.5 mol) was added to a solution of α-ionone isoxazole **4** (2.1 g, 0.010 mol) in cyclohexane (40 mL) and absolute ethanol (5 mL) at 35°C. When the sodium was completely dissolved, the mixture was heated at reflux for 8 h. NH_4Cl (16 mL, 20% in water) were then added to the reaction mixture, which was then cooled to room temperature. The mixture was extracted with EtOAc (70 mL × 3) and the organic phase was washed with saturated $NaHCO_3$ (50 mL), dried with $MgSO_4$, concentrated *in vacuo* to give the crude product. After distillation, α-damascone (1.52 g, 72.4% yield, 97% chemical purity (GC)) was obtained as a sticky oil. $C_{13}H_{20}O$; mass spectrum (ESI), *m/z* 192 $[M]^+$.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (m, 1H), 6.30 (d, *J* = 15.4 Hz, 1H), 5.59 (m, 1H), 2.88 (s, 1H), 2.07 (dt, *J* = 20.3, 15.3 Hz, 2H), 1.87 (t, *J* = 11.4 Hz, 3H), 1.68 (m, 1H), 1.54 (m, 3H), 1.14 (dt, *J* = 19.8, 10.0 Hz, 1H), 0.93 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 201.6, 141.6, 131.6, 129.9, 122.9, 60.7, 31.8, 30.7, 27.4, 27.3, 22.6, 22.0, 17.5.

RESULTS AND DISCUSSION

In this synthesis, α-ionone oxime was prepared from α-ionone and hydroxylamine hydrochloride in water and ethanol. And in the key epoxidation reaction (b), water, which is an important environmentally friendly solvent, was used as the solvent instead of an organic solvent[10]. Furthermore, hydrogen peroxide was used as oxidant with cetyltrimethylammonium hydroperoxide (CTAOH) as the catalyst for the epoxidation reaction so only water was the byproduct for this reaction. The diastereomeric ratios was not analyzed because all of the diastereoisomers of compound **2** and **3** would product the same product (compound **4**) after the next steps.

After α-ionone oxime epoxide was converted to α-ionone isoxazole in cyclohexane, the final reduction step was achieved using sodium in ethanol, which greatly reduced the reaction time, number of steps, and operational costs. The overall yield was 54.9%, which is higher than those reported (from 23.3% to 41.5%).

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