

다마스콘 및 관련 향료물질의 합성 : 베타다마스콘*

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Synthesis of Damascones and Related Flavoring Compound: β -Damascone

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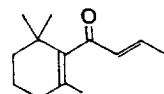
요약. 방향을 지니는 천연물인 베타다마스콘(I)을 2,2,6-트리메틸시클로헥산온(II)으로부터 출발하여 합성하였다. 아세틸렌의 THF 포화용액을 2차 부틸리튬으로 처리하여 얻은 모노아세틸화 음이온을 -78°C 에서 (II)와 반응시켜 에틴일화하고, 이때 생긴 에틴일카르비놀(III)을 옥살산 또는 포름산과 함께 끓여서 이성질화시켜 일종의 아세틸시클로헥산(IV)을 얻었다. (IV)를 2차 부틸리튬으로 처리하여 생성되는 엔올화 음이온을 잘 건조시킨 아세트알데히드와 반응시켜서 생성되는 베타히드록시케톤(V)을 파라톨루엔술폰산으로 탈수하여 트랜스-2,2,6-트리메틸-1-크로톤일-1-시클로헥센 즉, 다마스콘(I)을 합성하였다.

ABSTRACT. The synthesis of β -damascone(I), an odoriferous natural product, was investigated from 2,2,6-trimethylcyclohexanone(II); (II) was ethynylated by the action of monoacetylide anion prepared from acetylene and sec-butyllithium at -78°C , to give an ethynylcarbinol(III), which was isomerized to an acetylcyclohexene(IV) by refluxing in aqueous oxalic or formic acid. (IV) was treated with sec-butyllithium, the enolate was reacted with freshly dried acetaldehyde, and the resultant β -hydroxyketone(V) was dehydrated by TsOH to β -damascone, *trans*-2,2,6-trimethyl-1-crotonyl-1-cyclohexene(I).

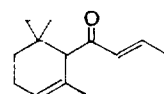
1. INTRODUCTION

The damascones and damascenones are natural products with characteristic fragrance and flavoring properties. They are significant constituents of Bulgarian rose oil and raspberry aroma¹. β -Damascone is a member of this group of compounds, and has also been detected in vari-

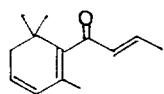
ous brands of tobacco^{2~5} and tea⁶ as well as rose oil.



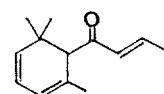
β -damascone
(1)



α -damascone
(2)



β -damascenone
(3)

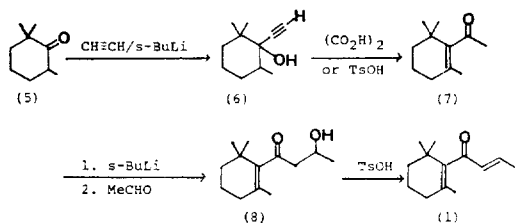


α -damascenone
(4)

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Since the recognition of β -damascone as a useful material for the creation of modern fragrances, its chemical synthesis has been received much attention. Several syntheses of β -damascone have been reported in previous communications, starting from β -cyclocitral^{7~10}, β -ionone^{11,12}, β -ionol^{11,13}, prenyl phenyl sulfone¹⁴, 2, 2, 6-trimethylcyclohexanone^{11,15~18}.

This paper provides a new synthetic procedure of β -damascone using 2, 2, 6-trimethylcyclohexanone(5) as a starting material, which was synthesized by one of the known methods^{19~22}. The trimethylcyclohexanone(5) was ethynylated with monoacetylide anion which could be produced from acetylene and sec-butyllithium, to give a tertiary ethynylcarbinol(6). The 1-ethynyl-2, 2, 6-trimethylcyclohexanol(6) was converted, by refluxing in oxalic acid, into 1-acetyl-2, 6, 6-trimethyl-1-cyclohexene(7). The acetylcyclohexene(7) was treated with sec-butyllithium to give an enolate ion which was reacted with acetaldehyde to produce an aldol condensation product, β -hydroxyketone(8). Dehydration of the hydroxyketone(8) gave the β -damascone(1) of fragrant odour.



2. EXPERIMENTAL

All operations involving organometallic reagents were carried out with well-dried vessels and solvents under nitrogen. Tetrahydrofuran was dried by refluxing for hours in the presence of sodium metal and benzophenone, followed by distillation under nitrogen. The boiling point of liquid products were unmeasured. The tlc

was taken with DC-Plastikfolien Kieselgel, Art 5735, 60F₂₅₄ (Merck). Ir spectra were recorded on Analect FT IR, Model FX 6160 (Analect, USA), nmr spectra were taken on a Varian EM 360A spectrometer, and Mass spectra were obtained on a Hewlett Packard (USA) Model 5985B or Shimadzu-LKB 9000GC/MS system.

2.1 Ethynylation of 2, 2, 6-Trimethylcyclohexanone(5). In a 250ml three-necked round-bottomed flask fitted with a dropping funnel and a magnetic stirrer, was added under nitrogen 50ml of freshly dried tetrahydrofuran, and the flask was cooled in a dry ice-acetone bath. Dry acetylene gas was bubbled with stirring to the tetrahydrofuran for 10min. To the saturated solution of acetylene, was added dropwise with stirring 25ml of 1.4M sec-butyllithium (45 mmoles) through a syringe, while bubbling acetylene during the addition. A solution of 2.0g (14 mmoles) of 2, 2, 6-trimethylcyclohexanone in 2~3ml of tetrahydrofuran was added dropwise with stirring to the resultant acetylide under nitrogen. After stirring 1.5hr, cooling was removed and 50ml of water was added followed by adding a few drops of dilute hydrochloric acid. Tetrahydrofuran was removed on a rotary evaporator, and the reaction mixture was extracted with diethyl ether, washed with water, dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent gave a pale yellow liquid product which showed only one spot on tlc. This product, 1-ethynyl-2, 2, 6-trimethylcyclohexanol(6), being pure, could be used in subsequent experiment. The yield 75~83%. This compound was deemed to have *trans*-configuration²³. When the reaction was carried out with n-butyllithium instead of sec-butyllithium, the yield was reduced and a mixture of *cis* and *trans* isomer was produced in a ratio of about 1 : 7, which could be able to separate on a silica gel column.

Trans form (equatorial C₆-methyl, equatorial OH). IR(neat); 3500(broad, OH), 3300(sharp, ≡CH), 2100cm⁻¹(weak, C≡C). NMR(CDCl₃); δ 0.95(s, 3H, CH₃), δ 1.03(s, 3H, CH₃), δ 1.10(s, 3H, CH₃), 1.30-1.60(m, 6H, 3CH₂), 1.80(s, 1H, OH), 2.40(s, 1H, ≡CH).

Cis-form (equatorial C₆-methyl, axial OH). IR(neat); 3600(broad, OH), 3300(sharp, ≡CH), 2100cm⁻¹(weak, C≡C). NMR(CDCl₃); δ 1.07(d, 3H, CH₃), δ 1.08(s, 6H, 2CH₃), δ 1.70(s, 1H, OH), δ 1.20-1.60(m, 6H, 3CH₂), δ 2.30(s, 1H, ≡CH).

Mass spectrum: m/e 166(M⁺), 151, 133, 125, 110, 95, 82, 77, 67, 55, 41.

2.2 Isomerization of 1-Ethyl-2,2,6-trimethylcyclohexanol(6). The tertiary ethynylcarbinol(6) was isomerized to an acetylcyclohexene(7) by refluxing in oxalic or formic acid, where hydration to acetylene and dehydration proceeded simultaneously.

A mixture of 0.9g (54mmoles) of the tertiary ethynylcarbinol(6) and 15ml of 40~50% oxalic acid was refluxed for 3hr. The reaction mixture was cooled to room temperature, 40ml of cold water was added and neutralized with aqueous sodium carbonate. The mixture was extracted with ether, washed with aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated the solvent under reduced pressure. The crude product was purified on a silica gel column to give a yellow liquid product, 1-acetyl-2,6,6-trimethyl-1-cyclohexene(7). The yield was 46~75%. This conversion could also be performed with 85% formic or with sulfuric acid containing mercuric oxide.

IR(neat); 2900, 1690(C=O), 1650cm⁻¹(C=C). NMR(CDCl₃); δ 1.03(s, 6H, 2CH₃), δ 1.02-2.0(m, 6H, 3CH₂), 1.60(s, 3H, =C-CH₃), 2.21(s, 3H, COCH₃). MS; m/e 166(M⁺), 123, 109, 81, 41.

2.3 3-Hydroxy-1-(2,6,6-trimethylcyclohexen-1-yl)-1-butanone(8). A β-hydroxyketone (8) was obtained by the action of an enolate of the acetylcyclohexene(7) on acetaldehyde to give an aldol condensation product.

A solution of 500mg (3 mmoles) of the acetylcyclohexene(7) in 5ml of dry tetrahydrofuran was added under nitrogen to a 250ml two-necked round-bottomed flask. The flask was cooled in a dry ice-acetone bath, 3.3ml of sec-butyllithium(1.4M in cyclohexane) was added by a syringe with stirring, and stirred for additional 10 min. To this enolate solution, was added with stirring at -78°C a solution of 132mg (3 mmole) of freshly distilled, dry acetaldehyde in 2 ml of tetrahydrofuran and stirred 50 min, allowing the reaction mixture to warm to room temperature. To this reaction mixture, one equivalent of acetic acid was added, stirred 10 min, and 30 ml of water was added. After 30min stirring, the mixture was extracted with ether, washed with aqueous sodium bicarbonate and then saline solution, dried over anhydrous magnesium sulfate, and evaporated the solvent under reduced pressure to give a crude product, which was chromatographed on silica gel column obtaining a pale yellow liquid product of a hydroxyketone(8). This condensation reaction could also be done using LDA instead of sec-butyllithium. The yield 55~67%.

IR(neat): 3550(broad, OH), 1715cm⁻¹(C=O). NMR(CDCl₃): δ 3.7(two s, 2H, OH and tert. H), δ 2.8(d, 2H, COCH₂), δ 2.0(t, 2H, =C-CH₂), δ 1.5-1.67(m, 7H, CH-CH₂, C=C-CH₃), δ 1.2(d, J=6Hz, 3H), δ 1.1(s, 6H, 2CH₃). MS; m/e 210(M⁺).

2.4 β-Damascone(1). In a 250ml two-necked round-bottomed flask fitted with a Dean-Stark trap, 500mg of the hydroxyketone(8) and a small (catalytic) amount of *p*-toluenesulfonic acid was dissolved in benzene, and the mixture

was refluxed for a few hours. Benzene was removed at reduced pressure, water was added, extracted with ether, washed with aqueous sodium carbonate and then saline water, and dried over anhydrous magnesium sulfate. Evaporation of solvent gave a almost pure, deep yellow liquid product, β -damascone(1), which was purified by chromatography. The yield 90~95 %.

IR(neat) : 1621, 1646 and 1678($C=C-O$), 974($CH=CH$, *trans*), $730cm^{-1}$ ($CH=CH$, *cis*). The glc showed that the product was a mixture of *cis* and *trans* isomers in a ratio of about 1 : 4. NMR($CDCl_3$) : δ 6.70(d/q, 1H, $J=16$ Hz, $MeCH=$), δ 6.10(d/q, 1H, $J=16$ Hz, $COCH=$), 1.90(d/d, 3H, $J=6.5$ Hz, $CH_3CH=$), 1.50(s, 3H, $CH_3C=C$), δ 1.05(s, 6H, CH_3-CH-H_3). MS : m/e 192(M^+), 177, 123, 107, 91, 81, 69, 41.

3. RESULTS AND DISCUSSION

A new synthetic procedure of β -damascone starting from 2, 2, 6-trimethylcyclohexanone was reported in this paper. In this investigation, some progress have been made in organic reactions frequently applicable in organic synthesis. The one is the ethynylation of carbonyl compound, the other is the Rupe rearrangement of acetylenic tertiary alcohols.

In previous communications, the addition of acetylene to ketone was carried out usually with alkali-metal acetylide^{24, 25} in liquid ammonia or with lithium acetylide prepared from acetylene and n-butyllithium²⁶. The authors could prepare the monoacetylide anion by the reaction of sec-butyllithium with acetylene in THF at $-78^\circ C$, with which 2, 2, 6-trimethylcyclohexanone could be ethynylated in good yield to give an ethynylcarbinol. By this technique, *trans* product (equatorial C_6-CH_3 , equatorial OH) of 1-ethynyl-2, 2, 6-trimethylcyclohexanol(6) was

almost exclusively formed. When the n-butyllithium was used in place of sec-butyllithium however, the product was a mixture of *cis* and *trans* isomers in a *ratio* of 1 : 7.

In addition the authors developed a new method in the Rupe rearrangement. The conversion of acetylene-to-ketone has usually been carried out in sulfuric acid containing mercuric salt^{27, 28} as catalyst or in formic acid^{29, 30}. However, the Rupe rearrangement^{31~34} of the ethynylcarbinol(6) to the corresponding α , β -unsaturated ketone(7) could also be accomplished by refluxing in aqueous oxalic acid or *p*-toluenesulfonic acid in pretty good yield.

In the condensation of 1-acetyl-2, 6, 6-trimethyl-1-cyclohexene(7), Olah³⁶ *et. al.* treated the acetylcyclohexene(7) with N-methylanilinomagnesium bromide to obtain an enolate. The authors could obtain the lithium enolate by simply treating the α , β -unsaturated ketone(7) with sec-butyllithium at $-78^\circ C$, which was then condensed with well-dried acetaldehyde to give a β -hydroxyketone(8).

The target compound β -damascone, *trans*-6, 6-trimethyl-1-crotonyl-1-cyclohexene(1), was obtained as a yellow liquid product, the structure of which could be determined by spectroscopic analysis^{37, 38}.

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