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A Simple Synthesis of (±)-α-Cuparenone*

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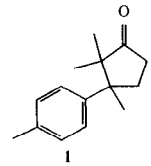
Abstract

A short and simple synthesis of (±)-α-cuparenone from 4-methyl-acetophenone *via* acid catalyzed decomposition of a β,γ-unsaturated-α–diazoketone is described.

Keywords: *Diazocompounds; Addition reaction; Cyclopentenones; Terpenes and terpenoids*

Introduction

(±)-α-Cuparenone **1** was isolated from *Thuja Orientalis*[1, 2] (Mayurpankhi tree) by Sukh Dev and co-workers. This bicyclic terpene along with its isomers present a synthetic challenge to organic chemists by virtue of the presence of two contiguous quaternary centers in a cyclopentane ring. A variety of approaches are reported for its synthesis.[3-33]



1

α-Cuparenone

Results

In continuation of our interest in cyclopentanoid natural products,[34] we have studied routes to and reported an efficient synthesis of (±)-α-cuparenone.[35] A recent report by Cossy[36] on the synthesis of (±)-α-cuparenone using a preformed cyclopentenone ring prompts us to disclose our contribution towards the same synthesis using efficient methodology for formation of the cyclopentanoid ring. Central to this strategy of construction of a substituted cyclopentenone is the acid-catalyzed decomposition of a β,γ-unsaturated-α–diazoketone.[37-39]

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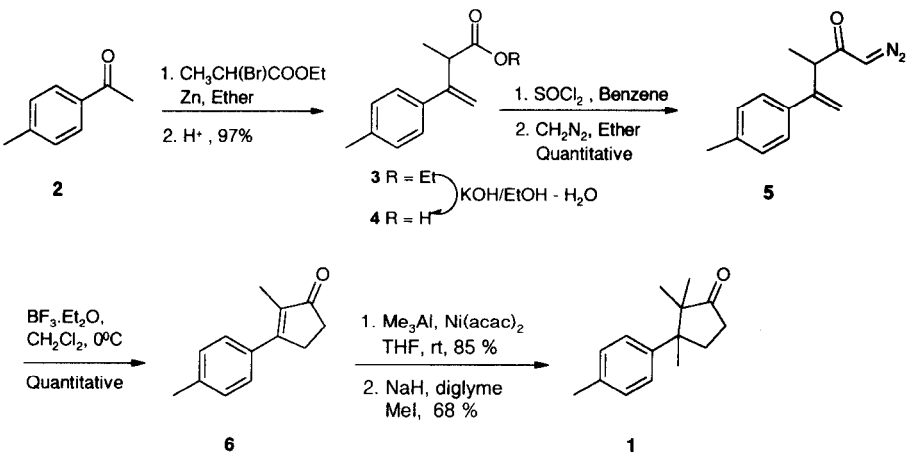
The 2-methyl-3-*p*-tolylcyclopentenone thus obtained is a common intermediate in ours and Cossy's[36] strategy resulting in a simple and short synthesis of (±)-α-cuparenone, whereas it is a key intermediate in Salaun's[40] for the synthesis of laurene.

Discussion

Reformatsky reaction of 4-methylacetophenone **2** and ethyl 2-bromopropionate furnished the β,γ-unsaturated ester **3** in 97% yield. The α,β-unsaturated ester though apparently more stable is not formed. Although the exact reason for this is not very clear, this may possibly be ascribed to the "peri" interaction of the aliphatic methyl with the ortho aromatic proton. Saponification of the ester (KOH/EtOH) at ambient temperature followed by treatment with $SOCl_2$ in benzene gave the corresponding acid chloride. Reaction of the acid chloride with diazomethane gave β,γ-unsaturated diazoketone **5** in quantitative yield. The crucial $BF_3.Et_2O$ catalyzed cyclization[38, 39] of **5** resulted in quantitative formation of 2-methyl-3-*p*-tolylcyclopentenone **6**. Several attempts to induce 1,4-conjugate addition to this enone employing a variety of reagents failed in our hands. However, 1,4-conjugate addition with trimethylaluminium,[41] in the presence of $Ni(acac)_2$ followed by alkylation[42] furnished (±)-α-cuparenone **1**. (±)-α-Cuparenone **1** thus obtained had identical spectral properties to those reported for natural α-cuparenone.[33, 36]



Thus (±)-α-Cuparenone **1** was obtained, in a very simple and high yielding reaction sequence starting from the commercially available 4-methylacetophenone.

Conclusion

Even though the acid promoted diazoketone decomposition has been known for many years it is under exploited for the synthesis of cyclopentenones. We have demonstrated that β,γ-unsaturated-β–aryl substituted α-diazoketones can serve as substrates for the synthesis of

substituted cyclopentenones and this concept has been utilized for a simple synthesis of (±)-α-cuparenone.

Experimental

General information: Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin- Elmer model 683 grating infrared spectrometer. Proton and ^{13}C NMR spectra were recorded on Bruker AC-200, 500 NMR, WH-90, Varian FT80A spectrometer. The chemical shifts are reported in parts per million (δ) with tetramethyl silane as an internal standard. Mass spectra were recorded with a Finnigan MAT-1020-B-70eV mass spectrometer. Elemental analysis were carried out on a Carlo Erba CHNS-O analyzer.

2-Methyl-3-p-tolylbut -3-enoic acid ethyl ester (3)

This ester **3** was prepared using a general Reformatsky reaction. To a mixture of 4-methylacetophenone **2** (14.8 g, 0.11 mole) and ethyl bromopropionate (22.5 g, 0.12 mole) in dry ether (200 mL) was added Zn (9 g, excess) and iodine crystals to catalyze the reaction while gentle reflux was maintained by external heating. The reaction was monitored by TLC. After 3 hr. the reaction mixture was treated with 50% HCl (20 mL) for 10 min. and extracted with ether (200 x 3). The extract was dried over anhydrous sodium sulfate and the solvent was removed on rotary evaporator to afford viscous oil. Purification of the residue by column chromatography (2% EtOAc/hexane), furnished title compound **3** (23.5 g, 97%) as colourless oil. [Found: C, 76.7; H, 8.2. $C_{14}H_{18}O_2$ requires C, 77.06; H, 8.25%]; ν_{max} (Neat): 2980, 1730, 1410, 1360, 1320, 1180 $cm.^{-1}$; δ_H (90 MHz $CDCl_3$) 7.10-7.46 (4H, m, Ar), 5.28 (1H, s, C=C$\underline{H_a}H_b$), 5.10 (1H, s, C=C$H_a\underline{H_b}$), 4.05 (2H, q, J = 7 Hz, -O$\underline{CH_2}CH_3$), 3.62 (1H, q, J = 7 Hz, CH_3-$\underline{CH}$CO), 2.28 (3H, s, Ar$\underline{CH_3}$), 1.34 (3H, d, J = 7 Hz, $\underline{CH_3}$-CHCO) 1.13 (3H, t, J = 7Hz, -$OCH_2\underline{CH_3}$); δ_C (50 MHz $CDCl_3$) 174.1, 147.9, 138.0, 137.0, 128.8, 126.2, 112.8, 60.3, 44.4, 20.8, 16.8, 13.9; *m/z* 218 (M^+, 20%), 203 (30), 175 (20), 145 (25), 135 (100), 129 (20), 119 (60), 105 (30), 91 (70), 74 (25), 65 (20), 56 (5).

2-Methyl-3-p-tolylbut-3-enoic acid (4)

The ester **3** (23.5 g, 0.107 mole) was added to the solution of KOH (6.0 g, 0.107 mole) in water (150 mL), ethanol (150 mL) and stirred at room temperature for 2 hr. The ethanol was removed at reduced pressure. The aqueous layer was then neutralized with dil. HCl (10 mL, 50%) and extracted with ethyl acetate. The ethyl acetate layer was then extracted with a saturated solution of $NaHCO_3$ (3 x 100 mL). The aqueous layer was neutralized with dil. HCl (30 mL, 50%) and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate and the solvent was removed at reduced pressure to afford *title acid* **4** (20.4 g, quantitative) as a colorless oil Found: C, 75.50; H, 6.94% $C_{12}H_{14}O_2$ requires: C,

75.7; H, 7.36%. ν_{max} ($CHCl_3$): 3100 (broad), 2900, 1720, 1640, 1520, 1460, 1420 cm^{-1}. δ_H (80 MHz $CDCl_3$) 10 (1H, broad, -OH), 7.24 –7.34 (4H, m, Ar), 5.42 (1H, s, C=CH), 5.28 (1H, s, C=CH), 3.69 (1H, d, J = 6 Hz, CH_3CHCO), 2.35 (3H, s, $ArCH_3$), 1.39 (3H, d, J = 6 Hz, CH_3CHCO); δ_C (50 MHz $CDCl_3$) 180.7, 147.1, 137.7, 129.0, 126.2, 124.7, 113.6, 44.2, 21.0, 16.9; *m/z*. 190 (M^+, 100%), 175 (60), 144 (40), 129 (60), 115 (70), 105 (60), 91 (60), 77 (40), 44 (40), 39 (40).

2-Methyl-1-oxo-3-p-tolylbut-3-ene-1-diazonium (5)

Thionyl chloride (0.85 g, 7 mmol) was added at 0°C to a stirred solution of acid **4** (1.10 g, 5.7 mmol) in benzene (25 mL) followed by a catalytic amount of DMF (1 drop). The reaction mixture was stirred at room temperature for 2 hr. After removal of excess of thionyl chloride and benzene (approx.25 mL) the acid chloride was taken up in dry ether (20 mL). The acid chloride in dry ether (20 mL) was slowly added at –78°C to a solution of triethylamine (0.575 g, 5.7 mmol) and an ethereal solution of diazomethane prepared from nitrosomethylurea (4.5 g, 43.7 mmol) KOH (15 mL, 50%)[CAUTION] in ether (100 mL) and then stirred at room temperature for 2 hr. Removal of ether at low pressure and temperature afforded β,γ-unsaturated diazoketone **5** (1.23 g, quantitative) as a yellow oil. ν_{max} (CCl_4): 2900, 2100, 1730, 1640, 1500, 1440, 1350, 1140, 800 cm^{-1}. δ_H (200 MHz $CDCl_3$) 7.17 - 7.27 (4H, m, Ar),. 5.5 (1H, s, $C=CH_aH_b$), 5.33 (1H, s, $-CHN_2$), 5.23 (1H, s, $C=CH_2$), 3.64 (1H, d, J = 7 Hz, CH_3CH-), 2.36 (3H, s, $ArCH_3$), 1.40 (3H, d, J = 7 Hz, CH_3CH-); δ_C (50 MHz, $CDCl_3$) 196.5, 147.8, 137.8, 137.6, 129.3, 126.3, 114.2, 50.2, 46.4, 21.1, 16.6.

2-Methyl-3-p-tolylcyclopent-2-enone (6)

A solution of β,γ-unsaturated diazoketone **5** (0.75 g, 3.5 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere, was cooled to 0°C. To this, $BF_3.Et_2O$ (0.5 mL, 3.5 mmol) was added slowly and a vigorous evolution of nitrogen was observed. After 30 min. saturated $NaHCO_3$ (2 mL) was added slowly and the mixture was extracted with CH_2Cl_2 (10 x 3). The combined extracts were washed with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulfate and concentrated under reduced pressure to furnish the *title compound* **6** (0.65 g, quantitative) as a yellowish solid. Recrystallization from hexane (5 mL) furnished yellowish needles. m.p.: 80°C [Found: C, 83.67; H, 7.85%. $C_{13}H_{14}O$ requires C, 83.87; H, 7.52%] UV λ_{max} (MeOH) 296 nm; ε = 9309; ν_{max} (Nujol) 2900, 1700, 1620, 1520, 1450, 800 $cm.^{-1}$; δ_H (200 MHz $CDCl_3$) 7.20 - 7.50 (4H, m, Ar), 2.90-3.00 (2H, m, $-CH_2CH_2$-CO), 2.60-2.70 (2H, m, $-CH_2CH_2$-CO), 2.4 (3H, s, $ArCH_3$), 2.0 (3H, s, $CH_3C=C$); δ_C (50 MHz $CDCl_3$,) 209.7, 166.5, 139.8, 135.9, 133.6, 129.4, 127.6, 34.0, 29.2, 21.4,10.0; *m/z* 186 (M^+, 75%), 171 (100), 143 (40), 128 (45), 115 (35), 89 (15), 75 (20), 63 (15), 51 (20).

2-3-Dimethyl-3-p-tolylcyclopentanone

Trimethylaluminium (10% solution in hexane, 0.7 mL, 0.65 mmol) was added to a magnetically stirred solution of $Ni(acac)_2$ (7.8 mg, 0.03 mmol) and enone **6** (117 mg, 0.63 mmol) in anhydrous THF (1 mL) at 0°C. A slightly exothermic reaction occurred and the green colored mixture turned black. After stirring for 19 hr. at room temperature the reaction mixture was diluted with hexane (15 mL) and quenched by careful addition of saturated NH_4Cl solution (1.5 mL). Stirring was continued for 2 hr. and the resulting solid was filtered through a sintered glass funnel. The residue was washed with THF (3 x 10 mL). Evaporation of solvent and flash chromatography on silica gel using 10% ethyl acetate-pet. ether as the eluent, afforded epimeric mixture of ketone as 1:1 diastereomeric mixture from chemical shifts, (101 mg 85%). The ketone exhibited the same spectral properties as reported in literature.[36, 40] ν_{max} ($CHCl_3$) 3020, 1733, 1508, 1215, 1020, 759 $cm.^{-1}$;δ_H (200 MHz $CDCl_3$) 7.1 - 7.3 (4H, m, Ar), 2.70-2.50 (2H, m, $-CH_2\underline{CH_2}CO$), 2.50-2.40 (2H, m, $-\underline{CH_2}CH_2CO$), 2.30 (3H, s, $Ar\underline{CH_3}$), 1.43 (1.5H, s, Tol-C-$\underline{CH_3}$), 1.21 (1.5H, s, Tol-C-$\underline{CH_3}$), 1.1 (1.5 H, d, J = 7 Hz, $\underline{CH3}CHCO$), 0.8 (1.5 H, d, J = 7 Hz, $\underline{CH_3}CHCO$).

(±)-α-Cuparenone (1)

A solution of the above ketone (40 mg; 0.19 mmol) in dry diglyme (0.1 mL) was added to a cold suspension of NaH (11.5 mg; 50% dispersion in mineral oil; 0.24 mmol) in dry diglyme (0.2 mL). After evolution of gas had ceased, methyl iodide (106 mg; 0.75 mmol) was added over 30 minutes and the reaction was allowed to stand overnight at room temperature. Excess of methyl iodide was removed by applying vacuum at 40°C and the residue was extracted with ether (20 mL x 3). The organic layer was washed with water (10 mL), brine

(10 mL) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure to give crude product, which was purified by column chromatography (10% EtOAc/pet ether) to give (±) α-cuparenone **1** (40 mg, 68%) as low melting solid, MP 47 ^{0} C.(Found: C,83.28; H,9.32%. C15H20O requires C,83.33; H,9.26%) ν_{max} (neat) 2960, 1735, 1510, 1460, 815 cm^{-1}; δ_H (200 MHz $CDCl_3$) 7.20-7.30 (4H, m,Ar), 2.75 -2.60- (1H, m, -$\underline{CH_2}CH_2CO$-),. 2.55-2.45 (2H, m, -$\underline{CH_2}\underline{CH_2}CO$), 2.3 (3H, s, $Ar\underline{CH_3}$), 1.85-1.95 (1H, m, -$CH_a\underline{H_b}CH_2CO$-), 1.30 (3H, s, $C\underline{CH_3}$), 1.20 (3H, s, $C\underline{CH_3}$), 0.60 (3H, s, $C\underline{CH_3}$); δ_C (75.4 MHz $CDCl_3$) 222.6, 141.9, 135.8, 128.9, 126.4, 53.2, 48.34, 33.8, 29.7, 25.9, 22.1, 20.8, 18.4; *m/z* 216 (M^+, 75%), 201 (20), 183 (10), 173 (15), 159 (18), 144 (100) 131 (40) 115 (20), 105 (10), 91 (10), 70 (5).

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