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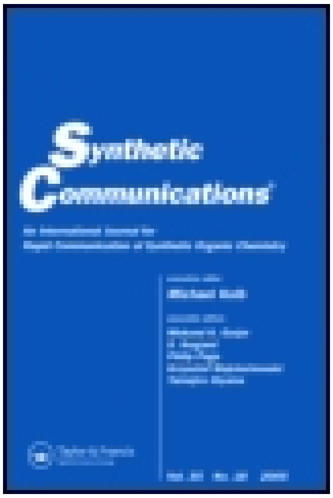

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Alternative Route for the Synthesis of 6-Methoxy-5-methyl-α-tetralone and 6-Methoxy-2,5-dimethyl-α-tetralone

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Alternative Route for the Synthesis of 6-Methoxy-5-methyl-α-tetralone and 6-Methoxy-2,5-dimethyl-α-tetralone

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Abstract: The ketoesters **3** and **4**, obtained by the condensation of 2-cyclohexanone carboxylate and 1-chloro-3-pentanone, were heated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to yield the dienones **5** and **6**, which on hydrolysis with potassium t-butoxide and dimethyl sulfoxide afforded tetralin **8**. These were converted to tetralone **10** by methylation and oxidation respectively. Further methylation of **10** yielded tetralone **11**.

Keywords: annelation, aromatization, dehydrogenation, hydrolysis, tetralone

INTRODUCTION

Martin and Robinson[1] reported the synthesis of tetralin **8** and its conversion into tetralone **10** for the construction of the fundamental skeleton of steroid–hormone analogs. On methylation[2] this yielded the dimethyl-α-tetralone **11** which proved to be useful as an intermediate for the synthesis[3] of cloven-3-one and epiclovane-3-one. The published synthesis[1] of tetralin **8** consists of reductive cleavage of methylene dinaphthol, followed by catalytic hydrogenation with Raney-nickel at l00°C/100 atm. We believe that this method requires modification, because the hydrogenation with Raneynickel at high

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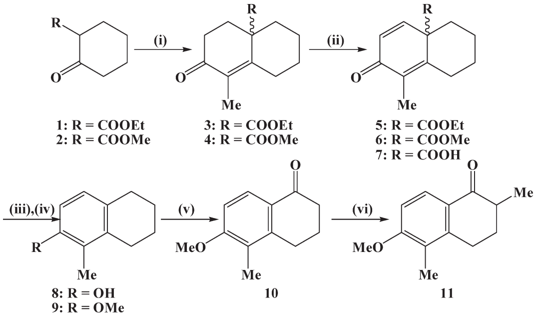

Scheme 1. Reagents: (i) $ClCH_2CH_2COCH_2CH_3$,C_6H_6, PTS; (ii) DDO, dioxane; (iii) C_4H_9OK, DMSO; (iv) Me_2SO_4, K_2CO_3, Me_2CO; (v) CrO_3, MeCOOH; (vi) MeI, NaH, Et_3B, THE.

temperature may be hazardous, and if the alkalinity of the reaction mixture is not controlled,[4] alcohol instead of phenol is obtained in major yield.

Therefore we devised a practical method for the synthesis of the tetralin **8** and its conversion into tetralones **10** and **11**. The synthetic route is described in Scheme 1.

RESULTS AND DISCUSSION

The condensation of the commercially available ethyl 2-cyclohexanonecarboxylate **1** (mixed with methyl 2-cyclohexane carboxylate **2**) (60:40) with l-chloro-3-pentanone under Dean–Stark conditions in benzene in the presence of a catalytic amount of p-toluene-sulfonic acid yielded a mixture of α,β-unsaturated ketoesters **3** and **4** in 72% as oil. The spectral data (IR and MS) gave strong support in favor of the structures of **3** and **4**. Its ^{1}H and ^{13}C NMR were difficult to interpret because of the mixture of two esters. However, no attempt was made to separate the ketoesters **3** and **4** and determine their percentage in the reaction mixture as the completion of the synthesis did not require their separations. This mixture of ketoesters **3** and **4** was heated with 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) in dioxane[5] to obtain the dienones **5** and **6** in 66% yield. The dienone mixtures were subjected to hydrolysis[6] with potassium t-butoxide in dimethylsulfoxide, and we expect to obtain the acid **7.** The spectroscopic data of the resulting product indicated the formation of tetralin **8** instead. Its IR spectrum exhibited a hydroxyl band at 3423 cm^{-1} and molecular ion peak at 162 (M$^+$) in the mass spectrum. The signals at δ 6.56 (d, $J = 8$ Hz, 1H) and 6.79 (d, $J = 8$ Hz, lH) (two aromatic protons) as well as 2.6l (t, $J = 6$ Hz, 2H) and 2.69 (t, $J = 6$ Hz, 2H) (benzylic protons at C-1 and C-4) 4.57 (s, 1H, OH) nicely supported the structure of tetralin **8**. Its melting point was identical with that reported.[1] On methylation with dimethylsufate, this produced compound **9** which was oxidized[7] with chromic acid in acetic acid to yield tetralone **10** in 76% yield. Its metting point was identical with that reported.[1] Its spectral data agreed with the assigned structure.

Tetralone **10** was methylated[8] with methyl iodide in the presence of sodium hydride and triethylborane in tetrahydrofuran to obtain the dimethyltetralone **11** in 71% yield. This one-step methylation procedure has this advantage over the published procedure,[2] which require three steps.

In conclusion, we have developed a simple and efficient synthesis of 6-methoxy-5-methyl-α-tetralone and 6-methoxy-2,5-dimethyl-α-tetralone. The experimental procedures are simple, and the yields are very satisfactory.

EXPERIMENTAL

Unless otherwise stated, IR spectra were taken on Nicolet FT instrument. ^{1}H NMR and ^{13}C spectra were recorded on Brucker AM 300- Hz instrument in $CDCl_3$. Mass spectra were run on gas chromatograph Hewlett Packard 5890 Quadrupolar 5972 series S. Melting points were recorded on an electrothermal melting-point apparatus. The expression *workup* indicates that the solution was diluted with water, extracted with ether, washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography was performed on silica gel (Merck grade 60, 70–230 mesh). The spectral and analytical data of all new compounds have been reported in the Experimental section. Microanalyses were carried out at the Chemistry Department, IVIC, Caracas, Venezuela.

10-Carboethoxy-4-methyl-3-oxo-octahydronaphthalene 3 and 10-Carbomethoxy-4-methyl-3-oxo-octahydronaphthalene 4

A mixture containing cyclohexanone carboxylate **1** and **2** (4.35 g), 1-chloro-3-pentanone (11.21 g, 93.05 mmol), and p-toluenesulfonic acid (351 mg, 1.89 mmol) in toluene (100 mL) was refluxed for 30 h under a Dean–Stark trap. The reaction mixture was cooled, washed with 10% aqueous sodium bicarbonate solution followed by brine, dried, evaporated, and purified on silica gel (hexane–diethyl ether 8:2) to obtain ketoesters **3** and **4** (4.52 g); m/z 236 (M^+), l62 (M^+-EtCOOH), 222 (M^+), l62 (M^+-MeCOOH); ν_{max} 1727(CO), 1667 cm^{-1}(CO).

10-Carboethoxy-4-methyl-3-oxo-hexahydrophenanthrene 5 and 10-Carboethoxy-4-methyl-3-oxo-hexahydrophenanthrene 6

To a solution of ketoesters **3** and **4** (481 mg) in freshly distilled dry dioxane (100 mL), 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (2.3l g, 10.16 mmol) was added. The resulting solution was refluxed under N_2 for 72 h. The reaction mixture was cooled, filtered, concentrated, and purified on silica gel (hexane–ether 85:15) to yield dienones **5** and **6** (357 mg); m/z 234 (M^+), 160 (M^+-EtCOOH), 220 (M^+), 160 (M^+-EtCOOH); ν_{max} 1731, 1660 cm^{-1} (CO).

6-Hydroxy-5-methyltetralin 8

To a solution of dienones **5** and **6** (181 mg) in dry dimethylsulfoxide (35 ml), freshly prepared potassium t-butoxide (3.71 g, 33 mmol) was added and heated in an oil bath (90°C) for 40 min. The resulting dark solution was diluted with water and extracted with ether. The ethereal extract was dried, evaporated, and purified on silica gel (hexane–diethylether 14:1) to give tetralin **8** (115 mg, 92%); mp 113–114°C (from hexane) (lit.[1] 113.5–114.5°C); m/z 162 (M^+); ν_{max} 3229 cm^{-1}. (OH): ^{1}H NMR: δ 1.75–1.85 (m, 4H, C-2 and C-3), 2.11 (s, 3H, Me, C-5), 2.61 (t, 2H, $J = 6$ Hz), 2.69 (t, 2H, $J = 7$ Hz) (C-1 and C-4), 4.57 (s, OH, C-5), 6.56 (d, 1H, $J = 8$ Hz), 6.79 (d, 1H, $J = 8$ Hz) (C-7 and C-8); ^{13}C: δ 29.9 (C-1), 23.3 (C-2), 22.8 (C-3), 27.1 (C-4), 121.8 (C-5), 151.1 (C-6), 112.3 (C-7), 126.9 (C-8), 129.5 (C-9), 136.7 (C-10), 10.9 (C-11). Found: C, 81.66; H, 8.88. $C_{11}H_{14}O$ requires C, 81.44%; H, 8.70%.

6-Methoxy-5-methyltetralene 9

To a solution of tetralin **8** (301 mg, 1.85 mmol) in dry acetone (10 mL), dimethyl sulphate (3.13 mL, 32.98 mmol) and potassium carbonate (301 mg, 3.15 mmol) were added and heated under reflux for 5 h. The solution was concentrated, diluted with water, and extracted with ether. The extracts were washed, dried, evaporated, and purified on silica gel (hexane) to obtain 6-methoxy-5-methyltetralene **9** (172 mg; 88%), mp 48–50°C (from hexane); m/z 176 (M^+); ^{1}H δ 1.81–1.86 (m, 4H, C-2 and C-3), 2.14 (s, 3H, Me, C-5), 2.68 (t, 2H, $J = 6$ Hz), 2.76 (t, 2H, $J = 6$ Hz), (C-1 and C-4), 3.84 (s, 3H, C-6), 6.71 (d, 1H, $J = 8$ Hz), 6.93 (d, 1H, $J = 8$ Hz) (C-7 and C-8); ^{13}C: δ 29.2 (C-1), 23.1 (C-2), 22.6 (C-3), 26.8 (C-4), 124.3 (C-5), 155.1 (C-6), 107.8 (C-7), 126.3 (C-8), 129.1 (C-9), 136.3 (C-10), 10.6 (C-11), 55.4 (C-12). Found: C, 82.06; H, 9.33. $C_{12}H_{16}O$ requires C, 81.77%; H, 9.15%.

6-Methoxy-5-methyl-α-tetralone 10

To a stirred solution of methoxymethyltetralin **9** (950 mg, 0.54 mmol) in acetic acid (1.4 mL, 24.5 mmol), a solution (2.24 mL) of 10% aqueous chromic–acetic acid solution was added dropwise over a period of 30 min. The reaction temperature was maintained at 15–20°C, and the reaction was allowed to proceed to completion (2 h) as evidenced by thin-layer chromatography (TLC). The reaction mixture was diluted with water, extracted with ether, washed with saturated aqueous solution of sodium bicarbonate, dried, and purified (hexane–diethyl ether 19:1) to yield methoxymethyltetralin **10** (779 mg; 76%), mp 112–112.5°C (from hexane) (lit.[1] 112–113°C); m/z 190 (M^+); ν_{max} 1678 cm^{-1} (CO); ^{1}H: δ 2.13 (m, 2H, C-3), 2.16 (s, 3H, Me, C-5), 2.61 (t, 2H, $J = 7$ Hz), 2.88 (t, 2H, $J = 7$ Hz), (C-2 and C-4), 3.91 (s, 3H, OMe), 6.85 (d, 1H, $J = 9$ Hz), 8.0l (d, 1H, $J = 9$ Hz) (aromatic protons); ^{13}C δ 197.9 (C-1), 38.4 (C-2), 22.7 (C-3), 26.9 (C-4), 123.6 (C-5), 161.3(C-6), 108.2 (C-7), 126.2 (C-8), 127.1 (C-9), 144.2 (C-10), 11.2 (C-11), and 55.5 (C-12). Found: C, 75.95; H, 7.54. $C_{12}H_{14}O_2$ requires C, 75.76%; H, 7.42%.

6-Methoxy-2,5-dimethyl-α-tetralone 11

To a suspension of sodium hydride (52 mg) in tetrahydrofuran (3 mL) triethylborane (0.034 mL, 0.31 mmol) was added and stirred for 3 min. Tetralone **10** (43 mg, 0.24 mmol) dissolved in dry tetrahydrofuran (3 mL) was then added. The resulting solution was stirred for 1 h at room temperature, methyl iodide (0.017 mL, 0.27 mmol) was added, and it was stirred for 30 min at room temperature. To the resulting dark brown solution, hydrochloric acid (4 mL, 10%) was slowly added, and the mixture was extracted with ether. The combined extracts were washed, dried, and purified (hexane) to give the dimethyl tetralone **11** (32.6 mg; 71%), mp 112–113°C (from hexane) (lit.[2] mp 111–113°C); m/z 204 (M^+); ν_{max} l660 cm^{-1} (CO) ^{1}H: δ 1.23 (d, 3H, $J = 7$ Hz) (C-2), 2.01 (m, 1H) (C-3), 2.13 (s, 3H) (C-5), 2.51 (m, 1H) (C-2), 2.79-2.99 (m, 2H) (C-4), 3.81 (s, 3H) (C-6), 6.81 (d, 1H, $J = 9$ Hz), 7.96 (d, 1H, J = 9 Hz) (C-7 and C-8); ^{13}C: δ 200.2 (C-1), 41.5 (C-2), 30.7 (C-3), 26.2 (C-4), 123.5 (C-5), 161.1 (C-6), 108.3 (C-7), 125.9 (C-8), 127.1 (C-9), 143.8 (C-10), 11.1 (C-11), 55.5 (C-12) and 15.3 (C-13). Found: C, 76.66; H, 8.08. $C_{13}H_{16}O_2$ requires C, 76.44%; H, 7.90%.

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