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A concise approach for the synthesis of 6-methoxy-2-tetralone

Abstract

A three-step synthesis of 6-methoxy-2-tetralone, a potential intermediate for many terpenoids and steroidal compounds, has been developed.

Keywords: 6-methoxy-1-tetralone, 2,4-pentanediol, MCPBA, PTS, hydroboration-oxidation

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Abbreviations: MCPBA, chloroperbenzoic acid; p-TsOH, p-toluenesulphonic acid; FT, fourier transform; MS, mass spectra; TLC, layer chromatography

Introduction

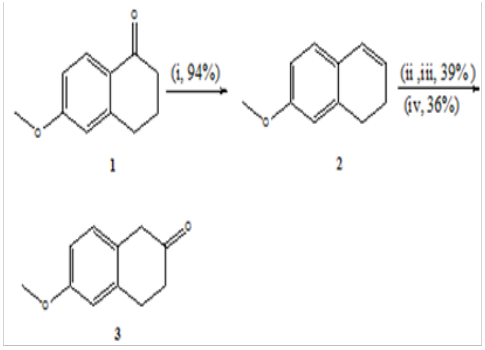
6-methoxy-2-tetralone has been selected as starting material for the synthesis of many steroidal compounds[1–3] 2-aminotetalin derivatives[4] which exhibit antifungal activities, tetrahydro benzocycloheptane[5] and many terpenoid compounds.[6] 6-methoxy-2-tetralone is more expensive, difficult to synthesize and unstable in comparison to 6-methoxy-1-tetralone. Therefore 6-methoxy-2-tetralone has attracted an array of impressive synthetic efforts.[7–13] The draw backs of the published methods are

(i) Use of flammable material like trimethylsilyl cyanide and corrosive product like zinc iodide[7]

(ii) Use of bad smelling product like ethyl mercaptied[14]

(iii) Long steps and complicated experimental procedure.[8,9]

The overall yield of the most of the published procedures range from 39 to 42%. The importance of 6-methoxy 2-tetralone in organic synthesis encouraged us to develop an alternative approach of the same. The present paper describes the results of our efforts towards the synthesis of the title compound. The synthetic route is depicted in Scheme 1.



Scheme 1 (i) 2,4-pentane diol, PTs; (ii) MCPBA, CH_2Cl_2; (iii) Et OH, 10% H_2SO_4; (iv) $BF_3.OEt_2$

Results and discussion

The commercially available 6-methoxy-1-tetralone 1 was converted[15] into the olefin 2 in 94% yield by heating under reflux with 2,4-pentanediol and a catalytic amount of p-toluenesulphonic acid (p-TsOH) who's spectroscopic properties perfectly agree with structure assigned. The olefin 2 was also previously synthesized by different routes[14,16] but the yield was not high compared with the present procedure. Epoxidation of the olefin 2 was performed with m-chloroperbenzoic acid (MCPBA) in dichloromethane and without purification the resulting epoxide was heated under reflux for 3 hours with ethanolic sulfuric acid (10%) to afford the tetralone 3 in 39% yield (overall yield 36%). The reaction was attempted several times using different reaction conditions which included change of temperature, time of heating, amount of sulfuric acid etc., (Table 1) however the yield could not be further improved. The spectroscopic data (NMR and MS) lent support to the assigned structure. An attempt was made to purify the epoxides by column chromatography but could not be isolated due to tendency of decomposition as exhibited in TLC.

Table 1 Brief description of conditions for experiments of compound 3

Time of heating	Amount of H_2SO_4	Changes of temperature	Yield
1.5 hours	1mL (15%)	40–45°	12%
2 hours	2mL (15%)	50–60°	18%
3 hours	3mL (25%)	60–70°	20%
3 hours	3mL (10%)	Reflux	39%

The cleavage of the crude epoxide was also tried with freshly distilled borontrifluoride etherate [($BF_3.Et_2O$)] at room temperature. The tetralone 3 was obtained in 36% (overall yield 35%). The opening of the epoxide was also attempted with sodium cyanoborohydride and borontrifluoride etherate.[17] A mixture of four products were obtained (evidenced by TLC) which on the basis of spectral data contained little if any of the desired product. In order to improve the yield, the olefin 2 was subjected to hydroboration-oxidation[18] reaction. As expected a mixture of alcohols were obtained as evidenced by ^1H NMR spectroscopy. Oxidation with Jones reagent[18,19] followed by

purification afforded the 2-tetralone in very poor yield. The tetralone, obtained in major proportion was identified as 1-tetralone 1.

Experimental

Unless otherwise stated, IR spectra were taken on a Nicolet –Fourier Transform (FT) instrument, Bruker AM 300MHz spectrometers in $CDCl_3$ were employed for the determination of ^1H and ^{13}C NMR spectra, with deuteriochloroform as solvent. Mass spectra (MS) were determined on a Dupont 21-492B. Column chromatography was performed on silica gel 60 (Merck). Thin layer chromatography (TLC) plates were coated with silica gel and the spots visualized using ultraviolet light. All melting points are uncorrected and were determined on an electrothermal melting point apparatus. All organic solvents were dried over anhydrous $MgSO_4$ and solvents were evaporated *in vacuo*. Elemental analyses were performed on a Carlo-Erba 1108 Elemenal Analyser.

6-Methoxy-3,4-dihydronaphthalene (2)

To a solution of the tetralone 1 (1g; 5.7mmol) in toluene (95mL) was added p-toluenesulphonic acid (250mg, 1.45mmol) and 2, 4-pentanediol (2.42mL, 22.3 mmol) and then heated under reflux for 24 hours. Using a Dean-Stark apparatus. The reaction mixture was cooled, diluted with sodium bicarbonate solution (5%) and extracted three times with ether. The combined extracts were washed with brine, dried, evaporated and chromatographed over silica gel (eluent hexane) to obtain the dihydronaphthalene 2 as oil (861mg, 94%). lit. b.p 85-95° (1mm);[16] m/z 161 (M^+1); ^1H NMR: δ7.06 (d, 1H, J=9Hz, H-7), 6.81 (m, 2H, H-5, H-8), 6.56 (d, 1H, J=10.2Hz, H-1), 6.01 (m, 1H, H-2), 3.86 (s, 3H, OMe), 2.91 (t, 2H, J=0.31Hz, J=16.8Hz, H-4), 2.41 (m, 2H, H-3); ^{13}C NMR: δ158. 43 (C6), 136 .92 (C10), 127.15 (C9), 127.04 (C2), 126 .67 (C1), 125.57 (C8), 113.62 (C5), 110.82 (C7), 54.83 (C11), 27.84 (C4), 22.83 (C3). Anal. Calcd. for $C_{11}H_{12}O$, C,82.46; H, 7.55. Found: C, 82.68; H, 7.69.

6- Methoxy-2-tetralone (3)

First Procedure: To a suspension of MCPBA (1.5g, 8.7mmol) in dry dichloromethane (16mL), cooled in ice, was added dihydronaphthalene 2 (616mg, 3.8mmol) dissolved in dichloromethane (2mL). The reaction mixture was stirred overnight, filtered, diluted with dichloromethane, washed with a solution of sodium bicarbonate (5%), brine, dried and evaporated to obtain an oil (591mg), which without purification was dissolved in ethanol (3mL) and treated with sulfuric acid (3mL, 10%) and heated under reflux for 3 hours. The reaction mixture was cooled, diluted with water and extracted three times with chloroform. The organic extracts were washed with brine, dried and evaporated to obtain an oil which on purification (eluent hexane: ether 7:3) afforded the teralone 3 (264mg, 39%); lit b.p 117-119° (0.5mm);[13] m/z 177 [M^++H], υ_{max} 1671.3cm^{-1} (C0); ^1H NMR: δ7.01 (d, 1H, J=8.04Hz, H-7), 6.76 (s, 1H, H-4), 6.73 (d, 1H, J=2.72Hz, H-6), 3.79 (s, 3H, H-11), 3.51 (s, 1H, H-10), 3.01 (t, 2H, J=6.61Hz, H-3), 2.52 (t, 2H, J=6.61Hz, H -2); ^{13}C NMR: δ2.10.91 (C-1), 1.58.51 (C-5), 137.88(C-9), 129.10 (C-7), 125.17 (C-8), 112.38 (C-6), 112.31 (C-4), 55.31 (C-11), 44.22 (C-10), 38.14 (C-2), 28.62 (C-3). Anal: Calcd for $C_{11}H_{12}O_2$ C, 74.97; H, 6.86. Found: C, 75.15; H, 6.98.

Second procedure

To the oily epoxide, prepared by the above mentioned procedure, from dihydronaphthalene 2 (616mg, 3.8mmol), in dichloromethane (15mL) was added freshly distilled borontrifluoride etherate (0.7mL, 5.7mmol) at room temperature and stirred for 10min. The organic extract was separated, dried and evaporated to yield an oil which on chromatographic purification (eluent: hexane: ether 7:3) afforded the tetralone 3 (246mg, 36%) %); lit. b.p. 117-119° (0.5mm);[13] whose spectroscopic data was almost identical with tetralone 3 prepared by the first procedure.

Conclusion

In conclusion a concise approach for the synthesis of 6-methoxy-2-tetralone was developed with an overall yield of 36%. We believe the present approach is a valuable addition to the known methods for the synthesis of the 6-methoxy-2-tetralone.

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Conflict of interest

The author declares no conflict of interest.

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