



SYNTHESIS OF 2,5-DIMETHYL-7-METHOXY TETRALONE

D. V. Awale

Department of Chemistry, Gopal Krishna Gokhale College, Kolhapur-416012, M. S. India
awale2010@rediffmail.com

Abstract :

Natural products is the important class of the organic compounds and their synthesis is always a challenging task. Natural products like terpenes and sesquiterpenes can be synthesized by using 2,5-dimethyl-7-methoxy tetralone as an intermediate. We report, the synthesis of same intermediate using 5-methyl-7-methoxy-1-tetralone as a substrate. The substrate is formylated to obtain hydroxymethylene derivative, converted in to its thioether followed by Mozingo desulphurization with W-2 Raney nickel to yield desired 2,5-dimethyl-7-methoxy tetralone.

Keywords: Tertralone, Terpene, Sesquiterpene, W-2 Raney nickel.

Introduction

For the methylation, various methods have been reported in the literature [1]. These methods involve use of sodium hydride and methyl iodide [2] which may yield the desired monomethylated ketone along with undesired bis-alkylated product. The conversion of tetralone into its enamine followed by alkylation was another option but reported yield was poor [3].

Number of methods has been used to improve selectivity in the alkylation in high yields and to reduce the amount of polyalkylation. One of the widely used methods is to introduce an activating group temporarily at alpha position to stabilise the corresponding enolate anion. This group is removed after the alkylation has been effected. Common activating groups used for this purpose are ethoxycarbonyl, ethoxyoxalyl and formyl group. Thus, for example to prepare 2-methyl cyclohexanone from cyclohexanone, the best procedure is to go through the 2-ethoxycarbonyl derivative which is easily obtained from the ketone by the reaction with ethyl carbonate or by condensation with diethyl oxalate followed by decarboxylation. Now, the conversion into enolate ion with a base such as sodium ethoxide takes place exclusively at the doubly activated position. Methylation of such 2-ethoxy carbonyl derivative with the methyl iodide and removal of beta-keto ester group with the acid or base gives 2-methyl cyclohexanone free from polyalkylated products.

Another technique is to acylate the ketone with ethyl formate and to transform the resulting formyl group or hydroxymethylene substituent into a group that is stable to base such as enamine, enol-ether or an enol thioether.

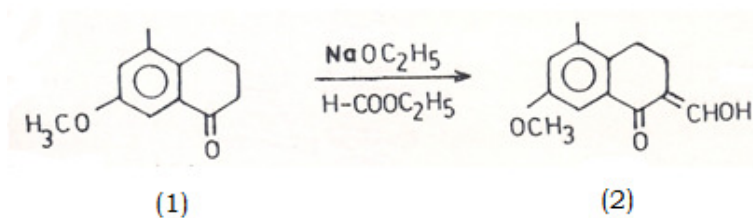
The enol thioether on reduction with Raney nickel gives exclusively monoalkylated product. Instead of one, if two alpha positions are available, one of the alpha positions can be blocked by the same technique of conversion to an enol thioether. This group is then removed after alkylation is effected at other alpha position. We planned the conversion of tetralone (1) by formylation to its hydroxymethylene derivative (2) then into its enol thioether (3) followed by Mozingo desulphurisation with W-2 Raney nickel [4] to get the methylated ketone (4)[5].

Experimental

All the chemicals used were of analytical grade and used without further purification. The products synthesized were characterized by infrared (IR) and proton magnetic resonance (PMR) spectroscopic techniques.

1. Synthesis of 2-hydroxymethylene-5-methyl-7-methoxy-1-tetralone

To an ice cold suspension of sodium methoxide (0.27 mole) in dry benzene (120 mL) under nitrogen atmosphere was added drop wise with stirring the above tetralone (0.031 mole) in benzene (10 mL) followed by ethyl formate (0.31 mole). The mixture was stirred overnight and diluted with water. The separated benzene layer was washed with water and then with 5% sodium hydroxide. The combined alkaline extract on acidification furnished the hydroxymethylene tetralone (1). It was extracted with ether, washed with water, dried over anhydrous sodium sulphate and then the ether is removed to yield hydroxymethylene tetralone (5.6 g). The product solidifies on cooling and examination of thin layer chromatography (TLC) showed it to be almost pure m.p.68-69 °C. The reaction is represented as below:

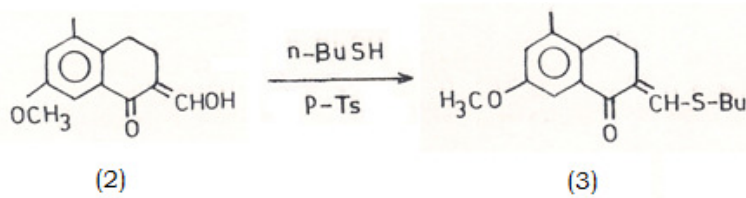


The PMR spectrum (Fig. 1) of hydroxymethylene tetralone exhibited two singlets for aromatic methyl and methoxy groups at 2.3 and 3.9 δ respectively. It also showed two clear triplets ($J=7$ Hz) for homobenzylic methylene at 2.55 δ and for benzylic methylene at 2.8 δ . Two aromatic meta coupled protons appeared as two sharp doublets ($J=2$ Hz) at 6.95 δ and 7.4 δ . A broad singlet at 8.2 δ was due to the olefinic proton and a highly deshielded enolic proton appeared at 14.6 δ .

2. Synthesis of 2-butylthiomethylene-5-methyl-7-methoxy-1-tetralone

To the solution of above hydroxymethylene tetralone (0.025 mole) in dry

benzene (50 mL) was added n-butylmercaptan (0.031 mole) and a trace of p-toluenesulphonic acid. The reaction mixture was refluxed azeotropically till no more water gets collected (6 hrs). The cooled reaction mixture was diluted with benzene and the benzene extract was washed with water, dilute sodium hydroxide, again with water, dried over anhydrous sodium sulphate and benzene is removed initially on water bath and then under vacuum to get expected thioether (4.8 g), m.p. 67 $^{\circ}\text{C}$. The reaction is represented as below:



IR spectrum (Fig. 2) of thioether showed peaks at 1650 cm^{-1} for ketone carbonyl group and at 1560 cm^{-1} for thiomethylene group.

PMR spectrum (Fig. 3) exhibited a triplet at 0.9 δ ($J=7$ Hz) for aliphatic methyl group (from butyl chain), a multiplet for six protons (four from butyl chain and two from homobenzylic methylene group) appeared at 1.6 δ , a multiplet at 2.7-3.0 δ is due to four protons (two from benzylic methylene and two from thiomethylene group), two sharp singlets at 2.3 and 3.9 δ were due to aromatic methyl and methoxy group respectively, two doublets ($J=2$ Hz) 7.0 and 7.5 δ are due to two aromatic meta coupled protons respectively and a singlet at 7.8 δ is due to olefinic proton.

3. Synthesis of 2,5-dimethyl-7-methoxy-1-tetralone

3.1 Preparation of W-2 Raney-nickel

To a solution of sodium hydroxide (195 g in 800 ml of distilled water) in a beaker equipped with mechanical stirrer and cooled to 10 $^{\circ}\text{C}$ was added nickel-aluminium alloy (160 g) in small portions maintaining the temperature at 30 $^{\circ}\text{C}$ (within 3 hrs). When evolution of hydrogen becomes slow, the beaker was heated on steam bath for 8 hrs. During this heating, the volume of the solution was maintained constant by frequent addition of

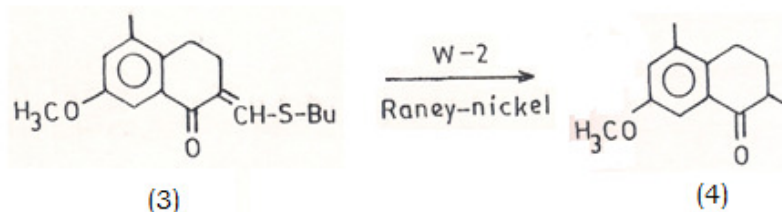
distilled water. After heating, nickel was allowed to settle down and most of the supernatant liquid was decanted. To it, 10% sodium hydroxide (250 mL) was added and mixture stirred for five minutes and allowed to settle. The alkali was decanted and the spongy nickel obtained was washed by suspension in distilled water and decantation method repeatedly until washings are neutral to litmus. It was further washed with distilled water for twenty to thirty times so as to remove alkali completely from nickel surface. Then it was washed with 95% ethanol (3x150 mL) and finally kept suspended in absolute ethanol (80 mL) [6].

3.2 Conversion of 2-butylthiomethylene-5-methyl-7-methoxy-1-tetralone to 2,5-dimethyl-7-methoxy-1-tetralone

To a suspension of W-2 Raney nickel (80 g) absolute alcohol (80 mL) was added the above thioether (4.5 g) in absolute ethanol (20 mL) the mixture was rapidly heated with stirring to 65-70 $^{\circ}\text{C}$ for 1 hr. The catalyst was filtered using Gooch crucible and then washed with boiling ethanol (3x50 mL). From the combined alcohol extract, alcohol was removed under vacuum and the residue was taken up in ether. The ether extract was washed with water, dried over anhydrous

sodium sulphate and finally ether was evaporated to obtain the desired methylated ketone (4.2 g). The product was chromatographed over column of silica gel (100 g) and elution with

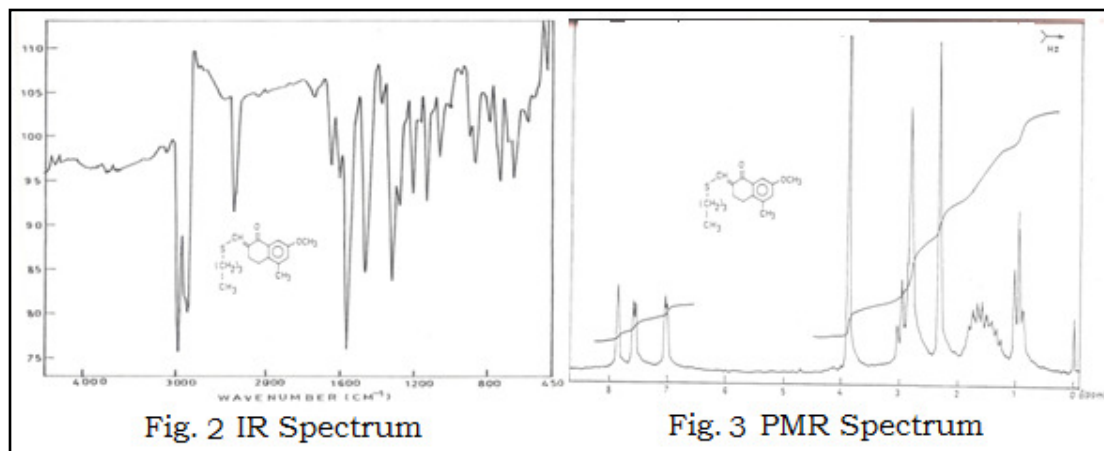
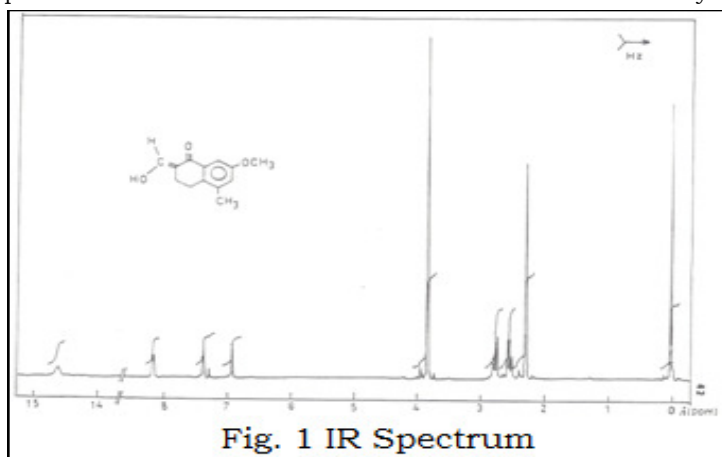
benzene gave pure methylated ketone (2.8 g) m. p. 50 °C (lit.51-52 °C) [7]. The reaction is represented as below:

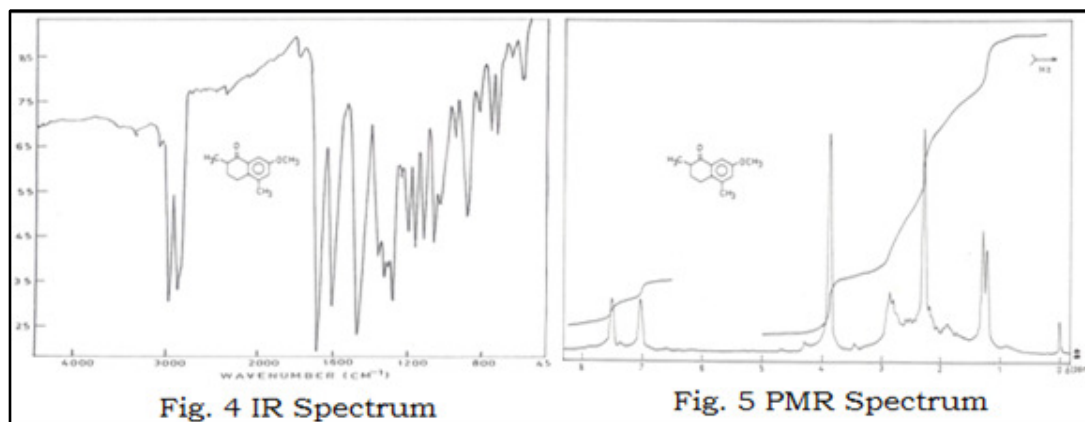


IR spectrum (Fig. 4) showed a peak at 1680 cm^{-1} for ketone carbonyl group.

PMR spectrum (Fig. 5) indicated two singlets at 2.2 and 3.9 δ for aromatic methyl and methoxy group respectively, a characteristic doublet for secondary methyl group appeared at 1.25 δ , a multiplet at 1.9 δ was due to

homobenzylic methylene and that in between 2.5-3.0 was due to benzylic methylene and methane proton. Two broad singlets at 7.0 and 7.5 δ were due to aromatic protons ortho and para to methyl group respectively. The appearance of doublet at 1.25 δ clearly indicates the formation of monomethylated product (4).





Conclusions

In conclusion, we have successfully, methylated the tetralone (1) using different methylating strategy in which the tetralone was successively formylated, converted into thio-ether followed by Mozingo desulphurisation by W-2 Raney nickel to obtain the desired 2,5-dimethyl-7-methoxy-1-tetralone the structures of these products have been confirmed by IR and PMR spectroscopic techniques. This compound could be used as an intermediate in the synthesis of terpenes and sesquiterpenes.

References

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