

Appendix - II:

Abstract and the paper presented at
the sixty ninth session of the Indian
Science Congress held at Mysore 1982.

**Part 9. Studies in the Synthesis of Sesquiterpenes : Synthesis of 4'-methoxy
2'-methyl propiophenone.**

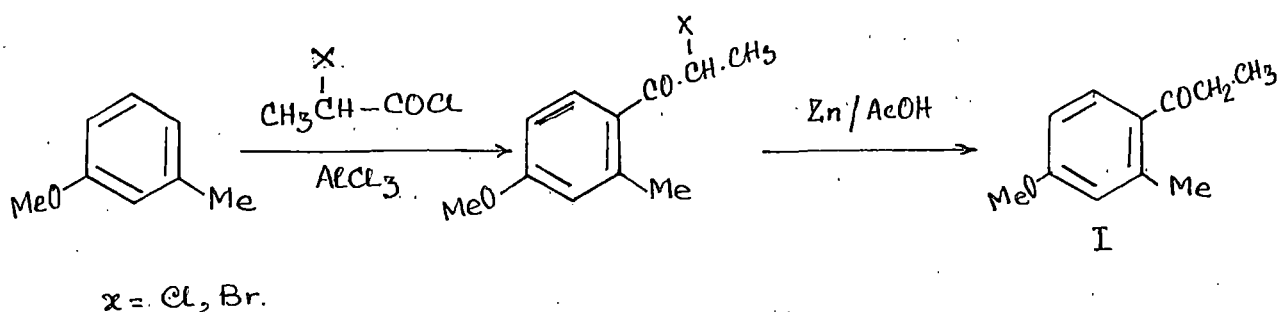
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4'-Methoxy-2'-methyl propiophenone and 2'-methoxy-4'-methyl propiophenone have been prepared by Friedel Crafts acylation reaction of m-cresol methyl ether with propionyl chloride/propionic anhydride. 4'-methoxy-2'-methyl propiophenone has also been prepared by the reaction of m-cresol methyl ether with propionic acid in presence of phosphoric anhydride and calcium carbonate. Both the compounds have been identified through their derivatives. The p.m.r. spectra of the compounds have been recorded.

STUDIES IN THE SYNTHESIS OF SESQUITERPENES - SYNTHESIS OF
4'-METHOXY 2'-METHYL PROPIOPHENONE

In connection with our studies in the synthesis of sesquiterpenes 4'-methoxy-2'-methyl propiophenone (I) was needed. Auwers¹ had prepared this compound by Friedel Crafts reaction of m-cresol methyl ether with α -chloro (or α -bromo) propionyl chloride followed by dehalogenation with Zinc - Acetic acid.

(Scheme I)

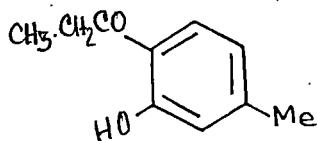


Scheme I

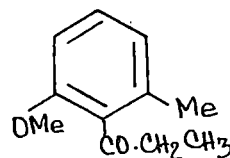
In addition to the propiophenone (I) a small quantity of 2'-hydroxy-4'-methyl propiophenone (II) was isolated by him. It is significant to note that neither the methoxy derivative of (II)

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nor the isomeric 2'-methoxy-6'-methyl propiophenone (III) was isolated by Auwers..

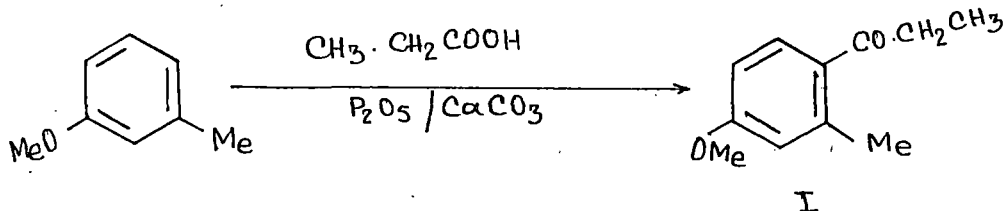


II



III

We considered some alternative methods for the preparation of the title compound. Aryl ethers are so sensitive that acylation may occur in the presence of catalysts less powerful than Aluminium chloride; even the free carboxylic acids have been used as acylating agents. Kosolapoff² acetylated anisole by treating it with a mixture of glacial acetic acid and phosphoric anhydride. In view of the extreme simplicity of this procedure and the reported high yields, we attempted to prepare (I) by this method. (Scheme II)

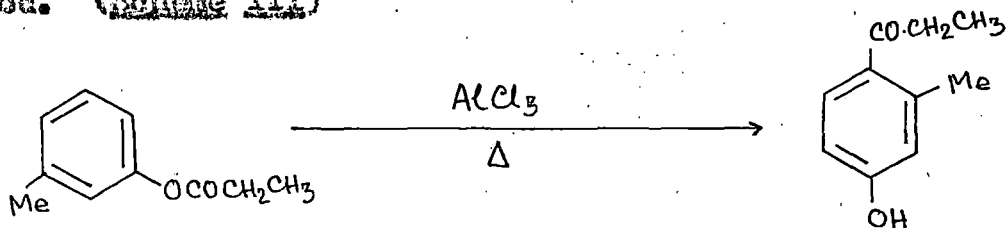


Scheme II

On refluxing a mixture of *m*-cresol methyl ether, phosphoric anhydride with continuous stirring in presence of calcium carbonate for 75 minutes, the compound (I) could be isolated in approximately 10%

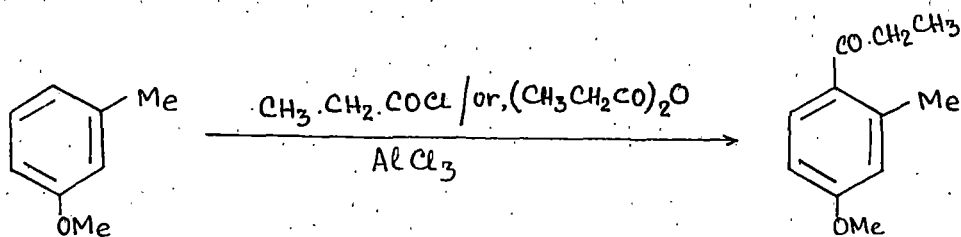
yield. Increase in the reaction time did not materially affect the yield.

Fries rearrangement³ of phenolic esters is one of the important methods of preparing phenolic ketones. However, in view of the extremely poor yields, - even in the simple case of phenyl acetate, the reported yield is about 30% - we did not consider this method. (Scheme III)



Scheme III

We therefore considered the obvious but hitherto unreported Friedel Crafts acylation of *m*-cresol methyl ether with propionyl chloride/propionic anhydride and found that this is the best preparative method for this compound (I). (Scheme IV)



Scheme IV

In addition to 4'-methoxy-2'-methyl propiophenone, we could isolate 4'-hydroxy-2'-methyl propiophenone and 2'-hydroxy-4'-methyl propio-

phenone. It has been found that the use of the aromatic substrate, propionyl chloride and anhydrous aluminium chloride in the molar ratio 1:1:2 gave the best yields. 4'-hydroxy compound could be almost quantitatively methylated to the 4'-methoxy compound.

4'-Methoxy-2'-methyl propiophenone was identified through its melting point -43°C , and by its oxidation to 4'-methoxy phthalic acid, m.p. $168 - 69^{\circ}$. The 2:4 dinitrophenyl hydrazone derivative m.p. $142-45^{\circ}$ and the oxime $94-95^{\circ}$ have also been prepared. The p.m.r spectrum of the compound was in accordance with the structure.

2'-methoxy-4'-methyl propiophenone was identified through its m.p. $85-87/5$ mm, 2,4-dinitrophenyl hydrazone 167° , and oxidation to methoxy terephthalic acid m.p. 380° . The compound (II) has been converted to 2,3,7 trimethyl - 1:4 benzopyrone following the method of Robertson, Waters and Jones.⁴

The non-formation of 2'-methoxy-6'-methyl propiophenone is most probably due to steric factors. This is evident from the demethylation studies of Robertson *et al*⁴ who found that the attempted demethylation of 2-methoxy-6'-methyl propiophenone led to the formation of normal demethylated product along with significant quantities of 4'-hydroxy-2'-methyl propiophenone. The demethylation of 4'-methoxy and 2'-methoxy compounds was studied by us. We found that the latter compound gave 4'-hydroxy compound along with the normal product.

Moreover, the demethylation was faster compared to the 4'-methoxy isomer.

E X P E R I M E N T A L

4'-Methoxy-2'-methyl propiophenone (Kosalopoff's method)

A mixture of *m*-cresol methyl ether (22 g), phosphoric anhydride (13 g) and calcium carbonate (0.6 g) was taken up in dry benzene (50 ml) and was treated with propionic acid (6 g) over a period of 15 minutes with gentle reflux and vigorous stirring. Usual working up gave 3.5 g of 4'-methoxy-2'-methyl propiophenone b.p. 130 - 35° m.p. 42 - 43°;

D.M.R. 1.1.12 δ (3H, Triplet, J, 6 ppm), 2.91 - 2.99 δ (2H, q, J, 9p pm) 2.42 δ (3H, s) : 2:4 dinitrophenylhydrazone 142 - 43°, oxime 97 - 98°

Friedel Crafts method:

To a well cooled solution of *m*-cresolmethyl ether (84.5 g) and freshly prepared propionyl chloride (64 g) in dry carbon disulphide (400 ml) was added with stirring anhydrous aluminium chloride (100 g) over a period of 2 hours. After the addition was over, the reaction mixture was stirred for a further period of two hours and left over night. The dark pasty mass was decomposed with

inorganic hydrochloric acid and the ~~inorganic~~ layer was separated. The aqueous layer was extracted with benzene. The combined organic layers were washed dried and concentrated. The residue was subjected to steam distillation. From the distillate was isolated 2'-hydroxy-4'-methyl propiophenone m.p. 42° (Lit⁴ 42.5), Dinitrophenylhydrazone 197 - 98°, oxime 103°^{1.4} (Lit 103.4°)

The residue after steam distillation was taken up in benzene and washed with 10% sodium hydroxide solution to remove any phenolic component and then with water until neutral, dried and concentrated. Distillation under reduced pressure afforded 4'-methoxy-2'-methyl-propiofenone 47 g. The sodium hydroxide wash on acidification followed by extraction etc gave 4-hydroxy compound (5 g). 2'-methoxy-4-methyl propiophenone was prepared by methylation of the 2'-hydroxy compound with dimethyl sulphate by standard procedure b.p. 85 - 87/5 mm, 2:4 dinitrophenylhydrazone m.p. 167°. Oxidation of 2-methoxy-4'-methyl propiophenone with alkaline potassium permanganate for 10 hours gave the methoxy terephthalic acid m.p. 280° Permanganate oxidation of 4-methoxy-2'-methyl propiophenone gave 4'-methoxy phthalic acid⁵ which responded to phthalein test. m.p. 168 - 169°.

2:3:7 Trimethyl, 1:4 benzopyrone

A mixture of 2'-hydroxy-4'-methyl propiophenone (2 g), anhydrous sodium acetate (2 g) and acetic anhydride (20 ml) was refluxed at 170 - 75 for two hours and then at 200° for 19 hours. The

hot solution was poured onto 200 ml brine and left overnight. The aqueous solution was extracted with ether, washed, dried, concentrated and distilled under reduced pressure. The fraction boiling at 140 - 45°/2 mm was found to be 2:3:7 trimethyl 1:4 benzopyrone m.p. 85 - 86° (Lit 86°⁴)

Demethylation of 4'-methoxy-2'-methyl propiophenone and 2'-methoxy-4'-methyl propiophenone:

A mixture of the propiophenone and anhydrous aluminium chloride in approximately 1:1 molar ratio was taken in dry carbon disulphide and refluxed. After usual work up the products were isolated by standard procedure. The results are summarised in Table I

Table I

Compound	Wt of the Compound gms	Wt of AlCl ₃	Time hrs	Products		Starting material recovered gms
				4-OH gm	2-OH gm	
4-MeO	8	8	6	3.9	-	3.6
"	8	8	12	5.0	-	2.4
"	8	8	18	6.3	-	0.8
"	8	8	24	6.2	-	0.8
"	8	8	36	6.2	-	0.8
2-MeO	8	8	6	0.5	6.5	-
"	8	8	12	1.3	6.6	-
"	8	8	18	2.2	4.5	-
"	8	8	24	2.5	4.5	-
"	8	8	36	2.5	4.5	-

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R E F E R E N C E S.

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