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Facile Synthesis of 3-(p-Alkoxyphenyl)-3-Methyl-2-Butanones

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FACILE SYNTHESIS OF 3-(p-ALKOXYPHENYL)-3-METHYL-2-BUTANONES

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Abstract: A novel procedure for the preparation of 3-(p-hydroxyphenyl)-3-methyl-2-butanone,in excellent yield, is described *via* a simple $AlCl_3$ catalysed rearrangement of p-ethoxy-pivalophenone. Various 3-(p-alkoxyphenyl)-3-methyl-2-butanones have been synthesised by the O-alkylation of the phenolic compound.

In the course of our investigations to develop new cost effective methodologies for the synthesis of the new generation synthetic pyrethroids, e.g. MTI-800[1], we have achieved a simple synthesis of the 3-(p-alkoxyphenyl)-3-methyl-2-butanones, which are the required precursors.

A survey of the literature revealed that 3-(p-methoxyphenyl)-3-methyl-2-butanone has been obtained by the pinacol rearrangement of 1-(p-methoxyphenyl)-1,2,2-trimethylethylene glycol with concentrated sulphuric acid in 30% overall yield, after a tedious four step procedure[2]. Thus, ethyl-(p-methoxyphenyl)glyoxylate[3] obtained from anisole and ethyl-chloroglyoxylate, was treated with methylmagnesium iodide to yield predominantly 3-hydroxy-3-(p-methoxyphenyl)-2-butanone. The latter on treatment with either methyllithium or

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ethylmagnesium iodide gave 1-(p-methoxyphenyl)-1,2,2-trimethylethylene glycol, which on pinacol rearrangement furnished 3-(p-methoxyphenyl)-3-methyl-2-butanone, **3.**

In another method, a stepwise alkylation of 3-(p-methoxyphenyl)acetone[4] was carried out first with methyl iodide/sodium isopropoxide to yield 3-(p-methoxyphenyl)-2-butanone and then with methyl iodide/potassium-t-butoxide to yield 3-(p-methoxyphenyl)-3-methyl-2-butanone, in 42% overall yield.

We report here the synthesis of 3-(p-hydroxyphenyl)-3-methyl-2-butanone **2** by a novel method, in which aluminium chloride rearrangement of 1-(p-ethoxyphenyl)-2,2-dimethyl-1-propanone **1** is the key step. Various 3-(p-alkoxyphenyl)-3-methyl-2-butanones **3 a-j** were obtained by simple O-alkylation of **2**.

Secondary and tertiary alkyl ketones have been prepared from carboxylic acid chlorides and lithium phenylthio(alkyl)cuprate reagents[5]. The simple Friedel-Crafts acylation of aromatic hydrocarbons with pivaloylchloride using a variety of catalysts such as $AlCl_3$[6], CF_3SO_3H[7], perfluorinated sulfonic acid resins such as $CF_3(CF_2)_nSO_3H$ (n = 0,3,7)[8], 2,4,6-$(NO_2)_3$-$C_6H_5SO_3H$[9] and diphenylborylhexachloro antimonate (p-$OMeC_6H_4)_2$-$BSbCl_6$[10] has also been used for the synthesis of alkyl aryl ketones.

In our work, 1-(p-ethoxyphenyl)-2,2-dimethyl-1-propanone **1** needed, was prepared in 78% yield by the Friedel-Crafts reaction of phenetole and pivaloyl chloride in dry light petroleum ether (bp 60-80°C) using aluminium chloride as the catalyst according to the method reported by E.Rothstein *et al*[7] for the synthesis of 1-(p-methoxyphenyl)-2,2-dimethyl-1-propanone.

The isomerisation of the pivalophenones to the benzyl ketones using $AlCl_3$ and benzene under reflux conditions[11] has been reported. No detailed procedure, however, is available for this conversion. In our procedure (described under experimental), the rearrangement of 1-(p-ethoxyphenyl)-2,2-dimethyl-1-

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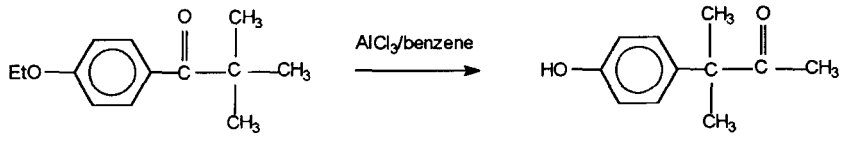
propanone **1** with $AlCl_3$ proceeds under mild conditions. A concomitant de-O-alkylation also occurs to yield 3-(p-hydroxy-phenyl)-3-methyl -2-butanone **2.** The overall yield is reasonably good. The de-O-alkylation of ether groups during aluminium chloride rearrangements is well documented in the literature[12].

The rearranged product was also obtained in a one pot reaction, in which, after carrying out the Friedel-Crafts acylation reaction in hexane, the solvent was removed and the resulting complex was suspended in benzene and stirred at room temperature for 45 minutes. The yield was 76% yield. The yield was improved to 92% by adding excess $AlCl_3$ along with benzene to the complex.

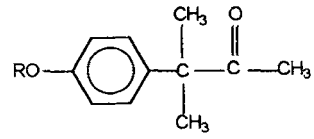
The phenolic compound **2** on O- alkylation with various alkylating agents yielded the corresponding alkoxy compounds **3 a-j** in moderate to excellent yields.



1 **2**

RX

Compd No.	R
3a	CH_3
3b	C_2H_5
3c	C_3H_7
3d	C_4H_9
3e	C_5H_{11}
3f	$CH(CH_3)_2$
3g	$CH_2CH{=}CH_2$
3h	$CH_2C(CH_3){=}CH_2$
3i	C_7H_{15}
3j	C_8H_{17}



3a-j

In conclusion, our method provides a facile preparation of 3-(p-alkoxyphenyl)-3-methyl-2-butanones in two simple steps.

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EXPERIMENTAL SECTION

1-(p-Ethoxyphenyl)-2,2-dimethyl-1-propanone 1:

Using phenetole (20g, 160 mmol) in hexane(50mL), pivaloyl chloride (12.1g, 100mmol) in hexane(50mL) and $AlCl_3$ (18.6g, 140mmol) in hexane (100mL), **1** was obtained following the the procedure of E.Rothstein *et al*[7]; yield 26.1g (77.3%); bp 108-112°C/0.5mm; IR cm^{-1}(C=O) 1680; ^{1}H-NMR (CCl_4/TMS, 60MHz): 7.3 (dd,4H), 3.97 (q,2H), 1.31 (s,9H), 1.21 (t,3H); MS (m/e): 206 (M^+).

3-(p-Hydroxyphenyl)-3-methyl-2-butanone 2:

A suspension of $AlCl_3$(133.4g, 1000mmol) in benzene(300mL) was stirred at room temperature for fifteen minutes..To this slurry, 1-(p-ethoxyphenyl)-2,2-dimethyl-1-propanone(103g,500mmol) in benzene(300mL) was added at room temperature dropwise over a period of one hr. Stirring was continued for another 3 hrs. The reaction mixture was poured onto crushed ice (500 mL) and extracted with ethyl acetate (2X400mL). The ethylacetate layer was washed with NaOH(2x250mL, 30%solution). The basic solution was neutralised with cold dilute hydrochloric acid and the separated phenolic compound extracted with ethylacetate (2x300 mL) and dried (Na_2SO_4). Removal of the solvent and distillation under vacuum yielded 3-(p-hydroxyphenyl)-3-methyl-2-butanone; yield 68.4 g (80%); bp 202-204°C/0.5mm; IR cm^{-1} (C=O): 1718; ^{1}HNMR(CCl_4/TMS, 60 MHz): 6.9(dd,4H), 1.84(s,3H), 1.37(s,6H); HRMS (M^+): 178.09749 (observed), 178.09938 (calculated).

One pot synthesis of 3-(p-Hydroxyphenyl)-3-methyl-2-butanone 2:

a. After the Friedel-Crafts reaction using phenetole (3.05g, 25mmol) in hexane (30mL), pivaloyl chloride (3g, 25mmol) in hexane (30 mL) and $AlCl_3$ (5 g, 37.5 mmol) in hexane (50 mL) , in the above experiment the solvent was removed

TABLE I

Alkylation of 3-(p-hydroxyphenyl)-3-methyl-2-butanone

S. No.	Alkylating agent	Product	Isolated yield %	B.Pt °C/ 0.5 mm
1	Dimethylsulphate	**3a**	84	94*
2	Diethylsulphate	**3b**	80	108
3	1-Bromopropane	**3c**	62	130
4	1-Iodobutane	**3d**	80	136
5	1-Iodopentane	**3e**	79	142
6	Isopropyl bromide	**3f**	65	120
7	Allyl bromide	**3g**	63	130
8	Methallyl chloride	**3h**	53	134
9	1-Bromoheptane	**3i**	72	160
10	1-Bromooctane	**3j**	69	162

*Lit. B.Pt. 109-114° C/2.5 mm

in vacuo and benzene (60 mL) added and the reaction mixture stirred at room temperature for 45 minutes. Work up as above gave **2**; 3.4 g (76%).

b. In the previous experiment addition of $AlCl_3$ (5 g, 37.5 mmol) along with benzene, stirring at room temperature for 45 minutes and usual work up gave **2**; yield 4.1 g (92%).

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TABLE II
SPECTRAL DATA OF COMPOUNDS 3a-j

Compd No.	IR[a] C=O cm^{-1}	H-1 NMR (CCl_4)[b] chemical shift in δ ppm	Molecular formula	HRMS M^+ observed mass (calculated mass)
3a	1710	6.95 (dd, 4H), 3.74 (s, 3H), 1.82 (s,3H), 1.39 (s,6H).	$C_{12}H_{16}O_2$	192[c] (192.11503)
3b	1712	6.53 (dd, 4H), 3.96 (q, 2H), 1.80 (s, 3H), 1.41 s, 6H), 0.97 (t, 3H).	$C_{13}H_{18}O_2$	206.13336[d] (206.13068)
3c	1715	6.9 (dd, 4H), 3.86 (t, 2H), 1.80 (s, 3H), 1.77 (sextet, 2H), 1.41 (s, 6H), 1.03 (t, 3H).	$C_{14}H_{20}O_2$	220.14469[d] (220.14633)
3d	1710	6.9 (dd, 4H), 3.97 (t, 2H), 1.93 (s, 3H), 1.58 -2.50 (m,4H), 1.37 (s, 6H), 1.21 (t, 3H).	$C_{15}H_{22}O_2$	234.16052[d] (234.16198)
3e	1716	6.9 (dd, 4H), 3.91 (t, 2H), 1.51 - 2.50 (m, 6H), 1.80 (s, 3H), 1.37 (s, 6H), 1.00 (t, 3H).	$C_{16}H_{24}O_2$	248.17870[d] (248.17763)
3f	1712	6.9 (dd, 4H), 4.4 (septet, 1H) 1.80 (s, 3H), 1.5 (s, 3H), 1.33 (s,6H), 1.2 (s, 3H).	$C_{14}H_{20}O_2$	220.14907[d] (220.14633)
3g	1710	6.9 (dd, 4H), 5.2 (d, 2H), 4.4 (d, 2H), 1.80 (s, 3H), 1.35 (s, 6H), 1.00 (t, 1H).	$C_{14}H_{18}O_2$	218[c] 218.13068
3h	1712	7.00 (dd, 4H), 5.05 (s, 2H), 4.42 (s, 2H), 2.01 (s, 3H), 1.88 (s, 3H), 1.33 (s, 6H).	$C_{15}H_{20}O_2$	232[c] 232.14633
3i	1725	6.97 (dd, 4H), 3.89 (t, 2H), 1.53 - 2.50 (m, 10H), 1.82 (s, 3H), 1.41 (s, 6H), 0.90 (t, 3H).	$C_{18}H_{28}O_2$	276.20654[d] 276.20893)
3j	1720	6.95 (dd, 4H), 3.87 (t, 2H), 1.56 - 2.50 (m, 12H), 1.82 (s, 3H), 1.39 (s, 6H) 0.88 (t, 3H).	$C_{19}H_{30}O_2$	290.22681[d] (290.22458)

a. IR spectra were recorded using BRUKER FT-IR; b.NMR spectra were recorded using a HITACHI 60 MHz instrument with TMS as standard; c. LRMS were recorded using SHIMADZU GCMS-QP1000A mass spectrometer; d. HRMS were recorded using a FINNIGAN MAT 8230 mass spectrometer with perfluoro kerosene as reference sample.

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3-(p-Alkoxyphenyl)-3-methyl-2-butanones 3 a-j

The p-methoxy and the p-ethoxy compounds **3a** and **3b** were prepared using dimethyl sulfate and diethyl sulfate respectively and NaOH in aqueous solution. The other 3-(p-alkoxyphenyl)-3-methyl-2-butanones **3c-3j** were prepared using the appropriate alkyl halide as the alkylating agent and potassium carbonate in acetone, followed by usual work-up. The compounds were purified by distillation under reduced pressure.

3-(p-Methoxyphenyl)-3-methyl-2-butanone 3a:

Reaction of 3-(p-hydroxyphenyl)-3-methyl-2-butanone **2** (5.34g,30mmol) with dimethyl sulphate(3.78g, 30mmol; 2.8mL, d=1.340) and 10.5%solution of NaOH(1.26g, 30mmol) yielded **3a** after usual workup.

3-(p-Ethoxyphenyl)-3-methyl-2-butanone 3b:

Reaction of 3-(p-hydroxyphenyl)-3-methyl-2-butanone **2** (5.34g,30mmol) with diethyl sulphate (4.6g,30mmol; 3.9mL, d=1.177) and 10.5%solution of NaOH(1.26g,30mmol) yielded **3b** after usual workup.

Typical procedure for the preparation of 3-(p-Alkoxyphenyl)-3-methyl-2-butanones 3c-3j:

3-(p-Propoxyphenyl)-3-methyl-2-butanone 3c:

Reaction of 3-(p-hydroxyphenyl)-3-methyl-2-butanone(5.34g,30 mmol) with 1-bromo-propane (3.69g,30mmol;2.5mL,d=1.435),anhydrous potassium carbonate(5g,36mmol) and acetone(50mL) under refluxion for 24-30 hours on a water-bath, yielded 3-(p-propoxyphenyl)-3-methyl-2-butanone **3c** after usual workup.

The isolated yields with the respective boiling points for the O-alkylation reactions are presented in **TABLE I** and the spectral data of the compounds **3a-j** in **TABLE II.**

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