An Efficient Method for the Synthesis of Alkyl 2-(4-Benzoylphenoxy)-2-Methyl Propanoates

[1]M. Z. REHMAN*, [1]A. A. KAZI, [2]H. L. SIDDIQUI, [3]M. A. KASHMIRI AND [4]V. U. AHMAD
[1]Applied Chemistry Research Centre, PCSIR Labs Complex, Ferozpur Road, Lahore, 54600, Pakistan.
[2]Institute of Chemistry, University of the Punjab, Lahore-54590, Pakistan.
[3]Department of Chemistry, Government College University, Lahore-54000, Pakistan.
[4]HEJ Research Institute of Chemistry, Karachi-75270, Pakistan.

(Received 22nd January 2007, Revised 22nd February 2007)

Summary: A new generalized method for the synthesis of various anticholesteramic and antilipemic alkyl 2-(4-benzoylphenoxy)-2-methylpropanoates has been described. Different 2-methyl-2-phenoxy-propanoates synthesized from phenol are coupled with substituted benzoyl chlorides to yield the title compounds in overall good yields. Also, a mechanism for the synthesis of 2-methyl-2-phenoxy-propanoates from phenol is proposed.

Introduction

Hyperlipidemia in body results in increasing levels of triglycerides (TG), total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) and in decreasing levels of high density lipoprotein cholesterol (HDL-C) and Apo A [1]. Change in these levels from normal values results in dyslipoproteinemia [2] and dyslipidemia. PPAR antagonists [3] have been proposed for use in therapy of excessive cholesterol and triglyceride levels and in this connection ethyl 2-(4-chlorophenoxy)-2-methylpropanoate (Clofibrate) [4] was developed. It has since been found that many new compounds of related structure are more effective in their cholesterol reducing effect such as Fenofibrate, Ciprofibrate and Clobuzarit [5]. 2-Methylpropanoic acid moiety (Fig 1) has been commonly found in many of the PPAR antagonists but only a limited number of methods are found in literature for its preparation. One of the methods involves the alkylation of phenols with alkyl 2-bromo-2-methylpropanoates and is well recognized in literature [6], for affording high yields. But its major disadvantage is the formation of alkyl methacrylates and their polymerization products.

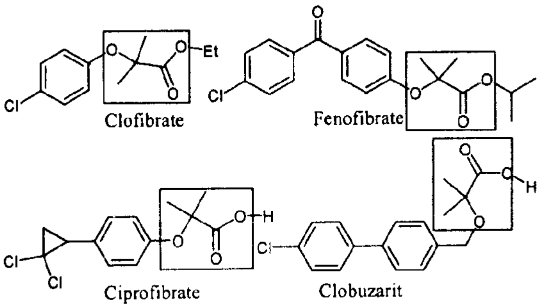


Fig.1. Fibrates possessing 2-methyl-2-propanoic acid moiety

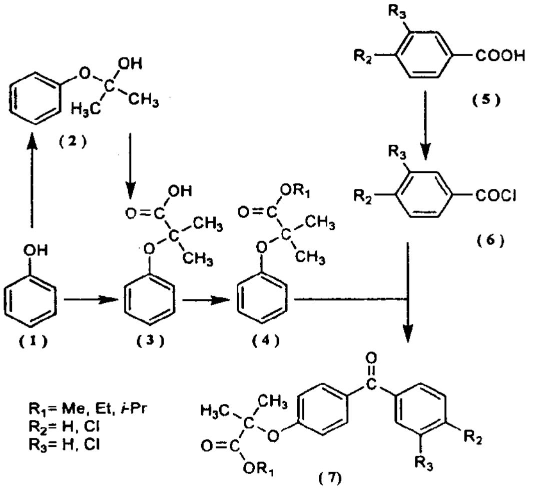
Recently, to overcome this problem, the use of 2-bromo-2-methylpropanoic acid has been reported for the synthesis of 2-methyl-2-aryloxy propanoic acid functionality involving the alkylation of phenols in basic medium (perhaps involving the α-lactones as a reactive intermediate which could not be proved by the authors). It however involves an additional step of conversion of (4-chlorophenyl) (4-methoxyphenyl) methanone to (4-chlorophenyl) (4-hydroxyphenyl) methanone [7]. Here, we are reporting an efficient and simple method for the preparation of 2-methyl-2-aryloxypropanoic acid derivatives in a generalized way.

Results and Discussion

For the synthesis of 2-methyl-2-phenoxypropanoic acid (**3**), phenol was reacted with a mixture of acetone and chloroform in the presence of potassium hydroxide in anhydrous conditions (Scheme 1).

---

*To whom all correspondence should be addressed.



Scheme-1. Route for the synthesis of *p*-carbonyl phenoxy iso-butyrates

Reaction takes place through an intermediate 2-phenoxypropane-2-ol (2), which subsequently reacts with dichlorocarbene generated *in situ* by the action of excess base with chloroform. Dichlorocarbene converts the alcohol into 2-methyl-2-phenoxy propanoyl chloride through an intramolecular rearrangement which is later on converted to corresponding sodium salt from which carboxylic acid is liberated by dilute acid treatment. A proposed mechanism for the reaction is given in Fig. 2. In order to confirm the above proposed mechanism, phenol was reacted with acetone in anhydrous, basic conditions followed by acidic hydrolysis, thus isolating the intermediate 2-phenoxypropane-2-ol (2), which gave the same product (3) when reacted with chloroform under basic (KOH) anhydrous conditions. Moreover, failure of the reaction upon addition of a small amount of water supports the proposed mechanism; dichlorocarbene gets converted to formic acid.

Use of inert atmosphere improves the yield by minimizing the production of Mesityl oxide (an unwanted by-product) due to self-condensation of acetone. Better exothermic control of the reaction has been achieved by the addition of chloroform after an interval following the addition of acetone. Finally, 2-methyl-2-phenoxypropanoates (4 a-c) obtained by esterification of carboxylic acid (3) [Table-1] are coupled with benzoyl chlorides (6 a-e) to get the corresponding 2-(4-benzoyl phenoxy)-2-methylpropanoate (7 a-e) by the well-known Friedel Crafts acylation method. [Table- 2] Carbon disulphide proves to be a better solvent due to its low boiling point; yields diminish with high boiling solvents as the ester gets hydrolyzed considerably in the presence of acid during work-up at high temperatures.

Table-1.Esterification of 2-Methyl-2-phenoxy propanoic acid.

S.No.	Alcohol/ phenol	Product	Reaction time	Yield (%)[1]
1	Methyl alcohol	4-a	5 hrs	94
2	Ethyl alcohol	4-b	5 hrs	93
3	Isopropyl alcohol	4-c	6 hrs	91

[1] Isolated yields based on 2-methyl-2-phenoxy propanoic acid.

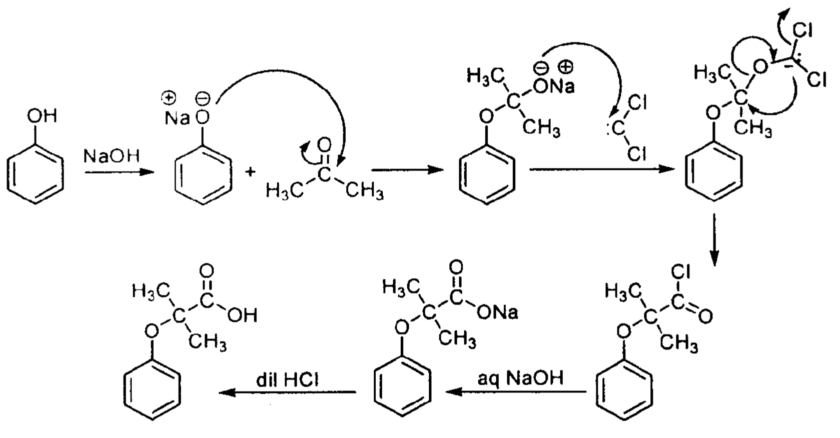


Fig.2. Proposed mechanism of carboxylic acid formation from phenol.

Table- 2. Yields and general information of various alkyl 2-(4-benzoyl henoxy)-2-methyl propanoates

Product	R_1	R_2	R_3	R_4	R_5	MP (°C)	Reaction time	Yield (%)
7-a	CH_3	H	H	Cl	H	89	4 hrs	68
7 -b	C_2H_5	H	H	Cl	H	79	4 hrs	70
7 -c	$CH(CH_3)_2$	H	H	Cl	H	82	4 hrs	75
7 -d	$CH(CH_3)_2$	H	Cl	H	H	79	4.5 hrs	69
7 -e	$CH(CH_3)_2$	H	Cl	Cl	H	69	6 hrs	72

[1] Isolated yields based on respective 2-methyl-2-phenoxy propanoate.

In conclusion, we have developed an efficient alternative method for the synthesis of various alkyl 2-(4-benzoyl phenoxy)-2-methyl propanoates which is devoid of various associated issues such as the formation of alkyl methacrylates, their polymers and Mesityl oxide. Moreover, it avoids an additional step of deprotection (methoxy to hydroxyl) of (4-chlorophenyl) (4-methoxyphenyl) methanone to (4-chlorophenyl) (4-hydroxyphenyl) methanone described in literature [8-9].

Experimental

Apparatus

Melting points were taken on Gallenkamp melting point apparatus and are uncorrected. ^1H NMR spectra were taken on the BRUKER NMR spectrometer at 100 MHz and chemical shifts given in ppm downfield from TMS as the internal standard. IR spectra were recorded in the spectral range of 4000- 400 Cm^{-1} on Hitachi spectrometer, model 270-30. Mass spectra were taken on Jeol JMS-HX110 spectrometer. All the chemicals used were from E. Merck, BDH or Fluka and were used without purification. However, solvents were purified through distillation.

Synthesis of 2-Methyl, 2-phenoxy propanoic acid (2)

A mixture of phenol (14.68 g; 0.156 moles), acetone (74.82; 2.58 moles), and sodium hydroxide (30.0 g; 0.75 moles) was stirred and refluxed under nitrogen atmosphere for a period of thirty minutes. To it, chloroform (25.33 g; 0.212 moles) was added and the reaction mixture was refluxed for four more hours. Contents were cooled after evaporation of the solvents under vacuum and acidified to Congo red with dilute hydrochloric acid. Oil was separated which was solidified in 15 minutes to get the crude product. It was washed with sodium bicarbonate solution and extracted in chloroform; lower layer was separated, dried and filtered. Evaporation of solvent and crystallization from petroleum ether afforded II (22.45 g, 80 %): m.p. 96°C. IR cm^{-1} (KBr): 3550-2800, 1690, 1038, ^1H NMR (DMSO-d_6) δ1.61 (s, 6H's of two methyl groups), 6.77 - 6.88 (m, 5H), 12.8 (s, 1H); EIMS *m/z* 180 (M^+), 163 (M^+ - OH), 135 (M^+- COOH), 93 (M^+- $C(CH_3)_2COOH$). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; O, 24.71; Found: C, 67.96; H, 7.34; O, 24.67.

General Procedure for the Synthesis of Alkyl 2-methyl-2-phenoxypropanoates.

A mixture of 2-phenoxy 2-methyl propanoic acid (0.1 moles), alcohol (150 ml), and para toluene sulphonic acid (0.01 moles) was refluxed for a period of six hours. Alcohol was then distilled off at a slow rate to a volume *c.a.* 35 ml. Contents were cooled and extracted with dichloromethane (3 x 50 ml); organic layers were washed with sodium bicarbonate solution and dried over anhydrous magnesium sulphate. Evaporation of chloroform under vacuum afforded the ester.

Methyl 2-methyl-2-phenoxypropanoate (4-a)

Viscous liquid; IR (Neat): 1720, 1240, 1138 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.63 (s, 6H), 3.72 (s, 3H), 6.92 - 7.12 (m, 5H). EIMS *m/z*: 194 [M^+], 163 [M^+ - OCH_3]. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; O, 24.71; Found: C, 67.96; H, 7.34; O, 24.68.

Ethyl 2-methyl-2-phenoxypropanoate (4-b)

Viscous liquid; IR (Neat): 1718, 1236, 1141 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.24 (t, 7.2 Hz, 3H), 1.53 (s, 6H), 3.98 (q, 7.2 Hz, 2H), 6.89 - 7.20 (m, 5H). EIMS *m/z*: 208 [M$^+$}, 163 [M$^+$ - OC_2H_5]. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; O, 23.05; Found: C, 69.30; H, 7.68; O, 22.99.

Isopropyl 2-methyl-2-phenoxypropanoate (4-c)

Viscous liquid; IR (Neat): 1720, 1238, 1140 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.12 (d, 6.8 Hz, 6H), 1.49 (s, 6H), 2.37 (m, 1H), 6.94-7.28 (m, 5H). EIMS *m/z*: 222 [M$^+$], 163 [M$^+$ - OC_3H_7]. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; O, 21.59; Found: C, 70.31; H, 8.09; O, 23.05.

General Reaction for the Synthesis of Alkyl 2-(4-benzoylphenoxy)-2-methyl propanoates

Benzoyl chloride (0.05 moles) in carbon disulfide (25.0 ml) was added cautiously to a mixture of alkyl 2-methyl-2-phenoxypropanoate (0.05 moles), dichloromethane (50.0 ml) and anhydrous aluminium chloride (0.11 moles) while keeping the reaction temperature at 0 °C. Contents were then refluxed (For reaction conditions please see Table- 1) and poured on to a mixture of ice cold water and HCl. Crude product was obtained by extraction with dichloromethane thrice and was recrystallized from isopropyl alcohol.

Methyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate (7-a)

White solid; mp 89 °C. IR (KBr): 1728, 1650, 1260 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.65 (s, 6H), 3.82 (s, 3H), 6.91 - 7.46 (m, 8H). EIMS *m/z*: 334 [M$^+$+2], 331 [M$^+$], 232 [M$^+$ -$(CH_3)_2CHOCOCH(CH_3)_2$]. HREIMS Calcd: 332.0815, Found: 332.0821.

Ethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate (7-b)

Off white solid; mp 79 °C; (Lit. mp 79 °C) [9]; IR (KBr): 1724, 1656, 1254 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.31 (t, 7.2 Hz, 3H), 1.52 (s, 6H), 4.34 (q, 7.2 Hz, 2H), 6.93-7.44 (m, 8H). EIMS *m/z*: 348 [M$^+$+2], 346 [M$^+$], 231 [M$^+$ - $(CH_3)_2CHOCOCH(CH_3)_2$]. HREIMS Calcd: 346. 0972, Found: 346.0967.

Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate (7-c)

Cream coloured crystalline solid; mp 82 °C; (Lit. mp 79-80 °C) [10]. IR (KBr): 1725, 1647, 1258 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.20 (d, 6.8 Hz, 6H), 1.68 (s, 6H), 2.32 (m, 1H), 6.88 - 7.39(m, 8H). EIMS *m/z*: 362 [M$^+$ + 2], 360 [M$^+$], 231 [M$^+$ - $(CH_3)_2$ $CHOCOCH(CH_3)_2$]. HREIMS Calcd: 360. 1128, Found: 360.1123.

Isopropyl 2-[4-(3-chlorobenzoyl)phenoxy]-2-Methylpropanoate (7-d)

Off white solid; mp 79 °C. IR (KBr): 1723, 1651, 1261 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.18 (d, 6.8 Hz, 6H), 1.66 (s, 6H), 2.26 (m, 1H), 6.91-7.49 (m, 8H). EIMS *m/z*: 362 [M$^+$ + 2], 360 [M$^+$], 231 [M$^+$-$(CH_3)_2CHOCOCH(CH_3)_2$]. HREIMS Calcd: 360. 1128, Found: 360.1137.

Isopropyl 2-[4-(3,4-dichlorobenzoyl)phenoxy]-2-methylpropanoate (7-e)

White solid; mp 70 °C; (Lit. mp 69 °C) [9]. IR (KBr): 1720, 1645, 1266 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.24 (d, 6.8 Hz, 6H), 1.64 (s, 6H), 2.27 (m, 1H), 6.87-7.41 (m, 7H). EIMS *m/z*: 399 [M$^+$+4], 397 [M$^+$+2], 395 [M$^+$], 265 [M$^+$ - $(CH_3)_2CHOCOCH(CH_3)_2$]. HREIMS Calcd: 394. 0739, Found: 394.0744.

References

1. J. Najib, *Clinical Therap.*, **24**, 2022 (2002).
2. B. G. Katzung, *Basic and clinical pharmacology*, 6th ed., Prentice-Hall International Inc. (1995).
3. T. M. Wilson, P. J. Brown, D. D. Sternbach and B. R. Henke, *J. Med. Chem.*, **43**, 527 (2000).
4. M. Chevais, *Therapie*, **35**, 5 (1980).
5. R. Sornay, J. Gurrieri, C. Tourne, F. J. Renson, B. Majoie and E. Wulfert, *Arzenium-Forch.*, **26**, 885 (1976).
6. J. P. Bougogne and R. Sorney, *Eur. Patent Appl.* 245156 (1987).
7. D. D. Roman, N. F. Russ and G. Jiasheng,

Synthesis, 1959 (2004).

8. F. G. Klein and J. T. Banchero, *Ind. Eng. Chem.* **48**, 1278 (1956).
9. A. Mieville, *U.S. Patent*, 4058552 (1977).
10. S. Budavari, *The Merck Index*, 11th ed.; Merck & Co. Inc. Rahway, N.J., USA. p 624. (1989).