Communication

Liquid-Phase Synthesis of 2-Methyl-2-aryloxypropanoic Acid Derivatives from Poly(ethylene glycol) Supported 2-Bromo-2-methylpropanoate

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An efficient liquid-phase synthesis of 2-methyl-2-aryloxypropanoic acid derivatives with good yields and high purity on soluble polyethylene glycol (PEG) has been developed by treatment of PEG-bound 2-bromo-2-methylpropanoate with phenoxides in the presence of a catalytic amount of NBu_4I and KI, and subsequent cleavage from the PEG.

Keywords: Liquid-phase synthesis; PEG-Bound 2-bromo-2-methylpropanoate; 2-Methyl-2-aryloxypropanoic acid derivatives; Alkylation; PPAR agonist.

The polymer-supported liquid-phase organic synthesis (LPOS) of small organic molecules has been a subject of intense research activity recently.[1] It profits from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena and ease of analysis without following the cleavage-and-check technique) and of solid-phase methods (use of excess reagents and easy isolation and purification of products). Among the various soluble polymers, polyethylene glycol (PEG) is the most useful and promising polymer, which is soluble in many solvents, such as CH_2Cl_2, $CHCl_3$, THF, CH_3OH or H_2O at room temperature and can be precipitated from a solution by addition of diethyl ether, *tert*-butyl methyl ether, propan-2-ol or hexane.[2] Furthermore, the PEG-bound intermediate products can be adequately characterized by TLC analysis, ^{1}H NMR or IR spectroscopy.

In the last decade, many organization and pharmaceutical companies have carried out extensive research and development on the PPAR agonists,[3] major therapeutic candidates for the treatment of human metabolic diseases. An important functionality common to many of the PPAR agonists and earlier pharmaceuticals developed to treat dislipidemia such as Clofibrate[4] and Fenofibrate,[5] is the 2-methylpropanoic moiety (Fig. 1). There are a limited number of methods for the preparation of 2-methyl-2-aryloxypropanoic acid derivatives in the literature.[4b,5,6] The alkylation reaction of phenols with ethyl 2-bromo-2-methylpropanoate (and other esters) and the Bargellini reaction using materials of 1,1,1-trichloro-2-propanol and phenols are two common procedures among those methods. However, these methods involved difficulties such as laborious manipulation, low overall yields and safety issues. To our knowledge, a liquid-phase synthesis of 2-methyl-2-aryloxypropanoic acids using PEG as the support has not yet been reported. Herein we wish to report a novel liquid-phase synthesis of this derivatives using PEG as soluble support (Scheme I).

As shown in Scheme I, esterification of commercially available difunctional PEG (MW = 4,000) with 2-bromo-2-methylpropanoic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in anhydrous CH_2Cl_2 at room temperature for 24 h readily

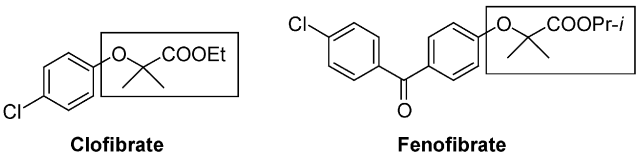
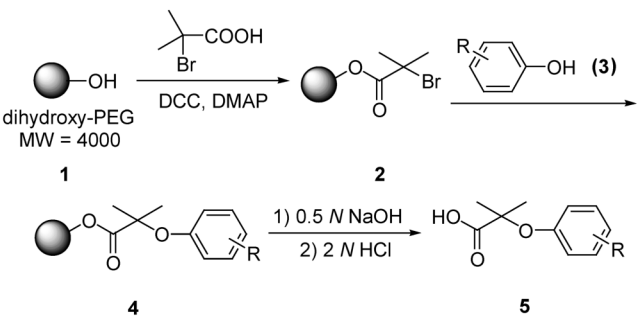


Fig. 1. 2-Methyl-2-aryloxypropanoic acid derivatives.

Scheme I



gave rise to the corresponding PEG bound 2-bromo-2-methylpropanoate **2**. The conversion of terminal hydroxyl groups on PEG was determined by ^{1}H NMR analysis to be quantitative. The loaded resin **2** showed complete disappearance of the hydroxyl OH stretch and the appearance of a C=O stretch at 1735 cm^{-1}. With the resin **2** in hand, the preparation of phenolic ethers resin **4**, the key for the success of this protocol was investigated. Conversion of resin **2** into resin **4** under standard conditions (phenol, NaH, THF, rt) was first attempted; the conversion yield after 2 days was calculated to be 56% from the ^{1}H NMR spectrum, but the reaction never reached completion even by warming up to 50 °C for 2 days. To our delight, when a catalytic amount of NBu_4I/KI in DMF was added to the mixture, the reaction went to almost completion over 12 h and gave a high yield of the corresponding PEG-bound resin **4**. Followed by hydrolysis of resin **4** using sodium hydroxide aqueous solution and subsequently acidified with hydrochloric acid solution, 2-methyl-2-aryloxypropanoic acids **5** was obtained in good yields (81-91%) with excellent purity (> 90% by HPLC analysis) of the crude products, and the results are summarized in Table 1. It should be noted, in some cases, a trace amount of the PEG residue might contaminate the final products **5**. But this problem could be easily solved by passing the crude product through a pad of silica gel column (acetone-methanol as the eluent, 1:1).

On the other hand, resin **4** cleaved with another method was further investigated as shown in Scheme II. For example, treatment of the resin **4b** with 0.1 N EtONa in ethanol at room temperature for 8 h afforded Clofibrate **6b** in 90% yield and 95% HPLC purity.[7] This methodology also could be used for preparation of the other corresponding esters.

In summary, we have developed a novel liquid-phase methodology for the synthesis of 2-methyl-2-aryloxypropanoic acid derivatives on soluble PEG support with satisfactory yields and high purity. The mild reaction conditions ensure the applicability of this procedure to combinatorial chemistry library synthesis.

EXPERIMENTAL SECTION

Melting points were determined on an X_4 melting point apparatus and are uncorrected; ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer; IR spectra were determined on a Perkin-Elmer SP One FT-IR spectrophotometer; Microanalyses were performed with a PE 2400 elemental analyzer. All the chemicals were used without further purification.

General procedure for preparation of PEG-bound 2-bromo-2-methylpropanoate 2

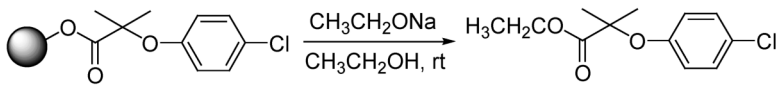
To a stirred solution of PEG (5.0 g, 2.5 mmol) in dichloromethane (20 mL) were added 2-bromo-2-methylpropanoic acid (1.67 g, 10 mol), DCC (2.06 g, 10 mol) and DMAP (0.305 g, 2.5 mol). After the mixture was stirred at

Table 1. Synthesis of 2-methyl-2-aryloxypropanoic acids

Entry	Phenol (**3**)	Product	Yield (%)[a]	Purity (%)[b]
1	C_6H_5OH (**3a**)	**5a**	86	94
2	*p*-ClC_6H_4OH (**3b**)	**5b**	91	97
3	*o*-ClC_6H_4OH (**3c**)	**5c**	84	94
4	*p*-BrC_6H_4OH (**3b**)	**5d**	90	95
5	*p*-$MeOC_6H_4OH$ (**3d**)	**5e**	83	95
6	*p*-MeC_6H_4OH (**3d**)	**5f**	84	95
7	*p*-$F_3CC_6H_4OH$ (**3e**)	**5g**	81	93
8	*p*-(4-$ClC_6H_4CO)C_6H_4OH$ (**3f**)	**5h**	90	95

[a] Isolated yield based on loading of original HO-PEG-OH.
[b] Purity determined by HPLC analysis of the crude products before purification.

Scheme II



4b **6b (Clofibrate)**

r.t. for 24 h, the precipitate was removed by filtration and the polymer was precipitated by addition of diethyl ether (200 mL) to the filtrate. For completion of the precipitation, the suspension was left at 0 °C for another 30 min. The white precipitate was collected and washed several times with diethyl ether, and then dried in vacuo to afford the PEG bound ester **2** as a white power: ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H), 3.65-3.75 (m, PEG CH_2), 4.33 (t, J = 4.98 Hz, 2H, PEG-OCH_2CH_2OCO); IR (KBr) ν 2887, 1735, 1646, 1567, 1467, 1360, 1280, 1242, 1147, 1116, 1062, 964, 842 cm^{-1}.

General procedure for preparation of 2-methyl-2-aryloxypropanoic acids 5

To a solution of phenol (**3**) (8 mmol) in anhydrous THF (10 mL) and DMF (3 mL) was added NaH (60% dispersion in mineral oil, 320 mg, 8.0 mmol) under nitrogen atmosphere at r.t. After stirring at 50 °C for 30 min, the mixture was cooled to r.t. and the PEG-bound ester **2** (1.0 mmol), n-Bu_4NI (0.1 mmol), KI (1.5 mmol) was added. The mixture was stirred at 50 °C for 12 h. After accomplishment of the reaction, the reaction mixture was cooled and the diethyl ether (60 mL) was added to allow the precipitation of PEG-bound product **4**, which was collected by filtration and washed with diethyl ether three times. The obtained product **4** was dissolved in 2 mL of 0.5 N NaOH aqueous solution and stirred for 12 h at room temperature. Then the solution was acidified to PH 2-3 using 2 N HCl and the final crude product was precipitated. After filtration, the collected solids were redissolved in a small amount of methanol/acetone (1/1) mixed solvent, and the solution was allowed to pass through a pad of silica gel column using acetone-methanol (1:1) as the eluent. The combined filtrate was evaporated under reduced pressure to give the products **5a**-**5h**.

2-Phenoxy-2-methylpropanoic acid (5a)

Colorless solid; mp 45-46 °C (Lit.[5a] mp 46-48 °C); ^{1}H NMR ($CDCl_3$) δ 13.12 (s, 1H), 7.31-7.26 (m, 3H), 6.96-6.93 (m, 2H), 1.60 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 154.5, 129.3, 123.1, 120.4, 79.4, 25.1; IR (KBr) ν 3010, 2907, 1698, 1597, 1489, 1381, 1294, 1240, 1151, 1081, 976, 930, 754, 690 cm^{-1}; Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.71; H, 6.78.

2-(4-Chlorophenoxy)-2-methylpropanoic acid (5b)

Colorless solid; mp 120-121 °C (Lit.[8] mp 120-122 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 7.32 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 1.51 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.5, 154.9, 129.6, 126.0, 120.9, 79.4, 25.5; IR (KBr) ν 3010, 2910, 1700, 1600, 1489, 1379, 1295, 1240, 1150, 1080, 975, 930, 824, 756, 690 cm^{-1}; Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17. Found: C, 56.01; H, 5.20.

2-(2-Chlorophenoxy)-2-methylpropanoic acid (5c)

Colorless solid; mp 75-76 °C (Lit.[6] mp 72 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.18 (s, 1H), 7.41 (dd, J = 7.5, 1.6 Hz, 1H), 7.20 (ddd, J = 8.0, 7.5, 1.2 Hz, 1H), 7.05 (dd, J = 8.5, 1.2 Hz, 1H), 7.02 (ddd, J = 8.5, 8.0, 1.6 Hz, 1H), 1.63 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 150.6, 130.6, 127.8, 127.5, 124.5, 121.7, 81.4, 25.2; IR (film) ν 3000, 2908, 1699, 1600, 1490, 1376, 1296, 1243, 1152, 1079, 975, 928, 776, 689 cm^{-1}; Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17. Found: C, 56.02; H, 5.23.

2-(4-Bromophenoxy)-2-methylpropanoic acid (5d)

Colorless solid; mp 132-133 °C (Lit.[6] mp 135 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 7.41 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.2, 154.6, 129.3, 125.8, 120.2, 79.2, 25.4; IR (KBr) ν 3010, 2910, 1701, 1601, 1490, 1382, 1295, 1242, 1152, 1079, 978, 933, 825, 760, 691 cm^{-1}; Anal. Calcd for $C_{10}H_{11}BrO_3$: C, 46.36; H, 4.28. Found: C, 46.43; H, 4.36.

2-(4-Methoxyphenoxy)-2-methylpropanoic acid (5e)

Beige solid; mp 58-59 °C (Lit.[4a] mp 57 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.15 (s, 1H), 6.94 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 1.53 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.7, 155.3, 149.6, 121.6, 114.9, 79.4, 55.8, 25.6; IR (KBr) ν 3006, 2908, 1698, 1600, 1490, 1378, 1294, 1240, 1150, 1080, 980, 935, 822, 760 cm^{-1}; Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.78; H, 6.69.

2-(4-Methylphenoxy)-2-methylpropanoic acid (5f)

Colorless solid; mp 65-67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.13 (s, 1H), 6.92 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 2.35 (s, 3H), 1.53 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.5, 155.1, 149.5, 121.2, 114.4, 79.2, 25.5, 20.5; IR (KBr) ν 3000, 2908, 1698, 1495, 1376, 1295, 1242, 1151, 1082, 981, 936, 824, 760 cm^{-1}; Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.12; H, 7.36.

2-(4-Trifluoromethylphenoxy)-2-methylpropanoic acid (5g)

Colorless solid; mp 103-104 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 1.56 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.0, 159.1, 127.5, 122.1, 118.5, 79.4, 25.6; IR (KBr) ν 3000, 2905, 1701, 1497, 1379, 1300, 1245, 1152, 1084, 982, 938, 826, 763 cm^{-1}; Anal. Calcd for $C_{11}H_{11}FO_4$: C, 53.23; H, 4.47. Found: C, 53.19; H, 4.53.

2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid (5h)

Colorless solid; mp 179-180 °C (Lit.[5a] mp 185 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.8, 175.0, 160.1, 137.7, 136.8, 132.4, 131.8, 130.0, 129.2, 117.6, 79.4, 25.5; IR (KBr) ν 3000, 2910, 1700, 1665, 1600, 1500, 1378, 1297, 1245, 1154, 1090, 985, 940, 832, 765 cm^{-1}; Anal. Calcd for $C_{17}H_{15}ClO_4$: C, 64.06; H, 4.74. Found: C, 64.10; H, 4.50.

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