Improved Method for the Synthesis of 2-Methyl-2-Aryloxypropanoic Acid Derivatives

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Abstract: An improved method for the formation of 2-methyl-2-aryloxypropanoic acid derivatives, an important class of compounds for the potential treatment of type II diabetes, is reported. This method offers several advantages over the existing chemistry for this transformation.

Key words: 2-methyl-2-aryloxypropanoic acid, PPAR agonist, alkylation, fibric acid

In the last decade, both within our organization as well as other pharmaceutical companies, extensive research and development has focused on the PPAR agonists,[1] major therapeutic candidates for 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[2] and Fenofibrate,[3] is the 2-methylpropanoic acid moiety. (Figure 1).

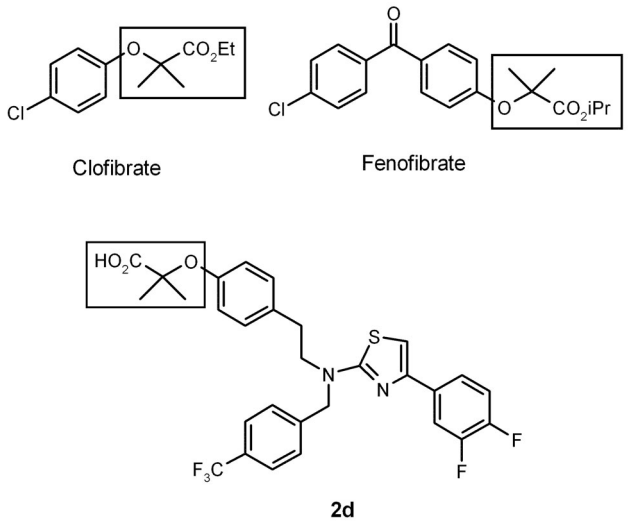

Figure 1 2-Methyl-2-aryloxypropanoic acid derivatives

There are a limited number of methods in the literature for the preparation of 2-methyl-2-aryloxypropanoic acid derivatives, each with disadvantages. To support the development of clinical candidates, we required a general, safe and efficient method for the preparation of 2-methylpropanoic acid derivatives.

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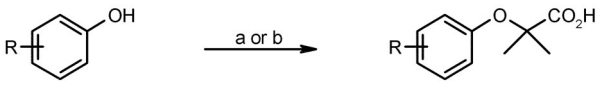
There are two common methods reported in the literature to introduce the 2-methylpropanoic acid functionality (Scheme 1). One is the use of ethyl 2-bromo-2-methylpropanoate (and other esters), alternatively, the Bargellini[4] reaction, using 1,1,1-trichloro-2-methyl-2-propanol (the condensation product of $CHCl_3$ and acetone), may be employed.



a) $BrC(CH_3)_2CO_2R^1$ (R^1 = alkyl), base, solvent b) $HOC(CH_3)_2CCl_3$, MOH, acetone (equivalent to $CHCl_3$, MOH, acetone)

Scheme 1

The use of ethyl 2-bromo-2-methylpropanoate followed by hydrolysis is well recognized in the literature. The alkylation of phenols with this reagent affords high yields and has been demonstrated as suitable for research scale synthesis. The major issue in using this reagent is the formation of ethyl methacrylate and its attended polymerization. Although polymerization may not be an issue on small-scale synthesis, it does become an issue on industrial scale both from a quality and engineering perspective with respect to polymer coating of equipment.

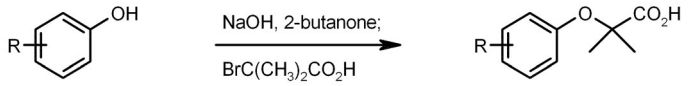
The use of the Bargellini reaction offers the advantage of avoiding the formation of ethyl methacrylate, thus reducing polymerization issues. There is also one less step since hydrolysis of an ester is not required. This methodology has been employed in several industrial scale processes[2b,3,5] including projects within our organization. The main disadvantages with the Bargellini reaction are safety issues resulting from the exothermic nature of the reaction,[6] the potential for regeneration of $CHCl_3$, and the formation of mesityl oxide (from acetone condensation), which may pose a quality issue of the final drug product. It should be noted that other solvents are inferior to acetone in the Bargellini reaction.

To avoid the various issues with the methods previously described, we have developed an alternative method, in which 2-bromo-2-methylpropanoic acid is used as the alkylating reagent.[7,8] While we postulate that the α-lactone[9] is the reactive intermediate, all our efforts to prove this intermediacy by IR spectroscopy were unsuccessful. We had noted very few applications for the alkyl-

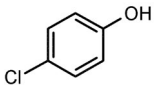
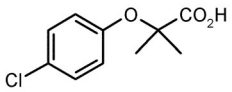
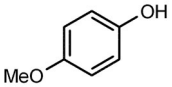
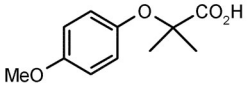
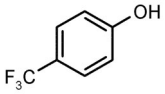
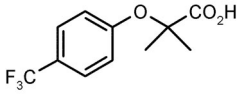
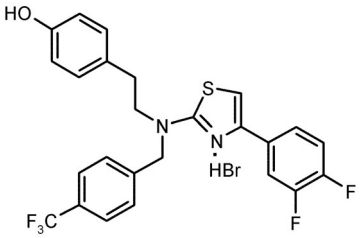
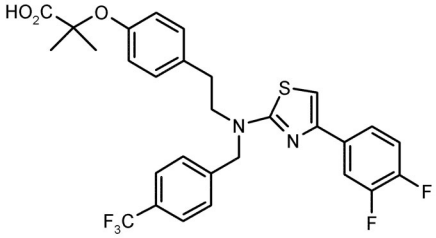
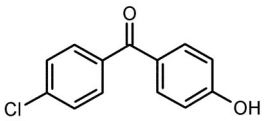
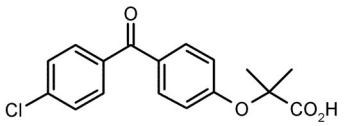
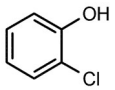
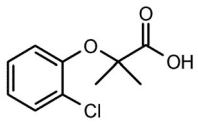
ation of phenols using this reagent,[10] all lacking complete experimental detail. This reagent offers several advantages over the use of 2-bromo-2-methylpropanoates and the Bargellini reaction. Polymerization issues are minimized, as small amounts of the water-soluble poly(methacrylic acid) formed are removed in the aqueous work-up. Exposure safety concerns related to $CHCl_3$ regeneration and mesityl oxide formation are eliminated. Exotherm control is no longer a factor, as the addition of 2-bromo-2-methylpropanoic acid to the phenoxide is significantly less exothermic[11] (ca. one-third of the total heat generated and one-third of the heat output rate) than the addition of 1,1,1-trichloro-2-methyl-2-propanol, as used in the Bargellini reaction. In addition, solvents are no longer limited to acetone.

We have applied this chemistry on multi-kilogram scales to several candidates within our organization. We have also extended this methodology on smaller scales to selected commercially available phenols. (Table 1) The reaction itself is very straightforward; the phenoxide, preformed in the reaction with NaOH, is treated with a solution of 2-bromo-2-methylpropanoic acid in a suitable solvent, in our case, 2-butanone is the preferred solvent. The choice of 2-butanone offers the additional advantage of purification during work-up. A water wash of the 2-butanone suspension after the reaction is complete removes the salts and excess hydroxide base, sodium methacrylate formed during the reaction, and any poly(sodium methacrylate) which may have formed. The sodium salt of the product remains in the organic layer during the water

Table 1 Alkylation of Selected Phenol Substrates (**1a**–**f**)



1 2

Entry		Phenol	Time (h)		Product	Yield (%)[a]
1	**1a**		1.5	**2a**		87
2	**1b**		0.5	**2b**		75
3	**1c**		2.0	**2c**		72
4	**1d**		2.5	**2d**		81
5	**1e**		16[b]	**2e**		87
6	**1f**		2	**2f**		77

[a] Isolated yields.
[b] After 2.5 h, ca 4% starting material remained. Additional $BrC(CH_3)_2CO_2H$ (0.2 equiv) and NaOH (0.2 equiv) were added and the reaction was stirred overnight.

wash. The 2-methyl-2-aryloxypropanoic acid derivative is isolated after work-up and crystallization in 72–87% yield with high purity (>98% AUC).

In summary, an alternative method for the synthesis of 2-methyl-2-aryloxypropanoic acid derivatives using the reagent, 2-bromo-2-methylpropanoic acid, was developed. This method has been successfully applied on multi-kilogram scales and avoids the process safety and quality issues observed in the current methods available.

Melting points were determined on an Electrothermal IA9100 melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained with Varian 300/400 MHz instruments while ^{13}C NMR spectra were obtained exclusively with a Varian 400 MHz instrument. Elemental analyses were performed by Atlantic Microlabs, Inc. All reagents and solvents with the exception of **1d** were purchased from commercial sources and were used without further purification. The compound, **1d**, was synthesized in-house from commercial starting materials.

2-({4-[2-([4-(3,4-Difluorophenyl)-1,3-thiazol-2-yl]{[4-(trifluoromethyl)phenyl]methyl}amino)ethyl]phenyl}oxy)-2-methylpropanoic Acid (2d); General Procedure

A suspension of phenol **1d** (1.0 kg, 1.75 mol) and 20–40 mesh NaOH (0.385 kg, 9.63 mol) in 2-butanone (6 L) was heated to 50 °C over 0.5 h. The mixture was stirred at 50°C for 1 h. A solution of $BrC(CH_3)_2CO_2H$ (0.438 kg, 2.63 mol) in 2-butanone (1 L) was added over 1 h. The resultant suspension was stirred an additional 2.5 h at 50 °C monitoring by HPLC. After the reaction was deemed complete, H_2O (4 L) was added and the bi-phasic solution was cooled to 20 °C. The aqueous layer, containing excess base and small amounts of methacrylic acid, was separated and discarded. EtOAc (5 L) was added to the 2-butanone solution followed by 0.5 M HCl (3.5 L). After discarding the aqueous layer, the organic layer was washed with H_2O (4 L) and reduced to 3 L via distillation under reduced pressure. After solvent exchange to *iso*-octane, the product was isolated via filtration and dried under vacuum at 55–60 °C to give **2d** as an off-white solid; yield: 809 g (81%); mp 113–114 °C.

^{1}H NMR [400 MHz, $(CD_3)_2CO$]: δ = 11.29 (br s, 1 H, CO_2H), 7.84 (ddd, *J* = 12.0, 7.6, 2.0 Hz, 1 H, ArH), 7.56 (ddd, *J* = 8.4, 4.0, 2.0 Hz, 1 H, ArH), 7.70 (d, *J* = 8.4 Hz, 2 H, ArH), 7.59 (d, *J* = 8.4 Hz, 2 H, ArH), 7.33 (dt, *J* = 10.4, 8.4 Hz, 1 H, ArH), 7.19 (d, *J* = 8.4 Hz, 2 H, ArH), 7.14 (s, 1 H, thiazole-H), 6.86 (d, *J* = 8.4 Hz, 2 H, ArH), 4.87 (s, 2 H, $ArCH_2$), 3.77 (t, *J* = 7.2 Hz, 2 H, $ArCH_2$), 3.00 (t, *J* = 7.2 Hz, 2 H, R_2NCH_2), 1.54 (s, 6 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.8, 169.7, 154.5, 149.1, 148.2, 143.2, 133.1, 132.4, 130.2, 128.7, 128.4, 126.1, 126.0, 123.0, 119.4, 118.4, 118.2, 115.2, 115.0, 103.7, 79.0, 54.0, 32.5, 25.7.

Anal. Calcd for $C_{29}H_{25}F_5N_2O_3S$: C, 60.41; H, 4.37; O, 8.32. Found: C, 60.22; H, 4.40; O, 8.32.

2-(4-Chlorophenoxy)-2-methylpropanoic Acid (Clofibric acid, 2a)

Colorless solid; yield: 14.5 g (87%); mp 120–121 °C (Lit.[12] mp 119–120 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.14 (s, 1 H, CO_2H), 7.33 (d, *J* = 9.0 Hz, 2 H, ArH), 6.85 (d, *J* = 9.0 Hz, 2 H, ArH), 1.51 (s, 6 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.4, 154.9, 129.7, 126.1, 120.8, 79.5, 25.6.

Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17; O, 22.36. Found: C, 55.98; H, 5.21; O, 22.44.

2-(4-Methoxyphenoxy)-2-methylpropanoic Acid (2b)

Beige solid; yield: 1.28 g (75%); Mp 58–59 °C (Lit.[2a] mp 57 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 8.8 Hz, 2 H, ArH), 6.82 (d, *J* = 8.8 Hz, 2 H, ArH), 3.78 (s, 3 H, OCH_3), 1.54 (s, 6 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.8, 155.2, 149.4, 121.7, 114.9, 79.5, 55.9, 25.6.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71; O, 30.44. Found: C, 62.67; H, 6.68; O, 30.44.

2-(4-Trifluoromethylphenoxy)-2-methylpropanoic Acid (2c)

Colorless Solid; yield: 9.6 g (72%); mp 104–105 °C (Lit.[13] 95 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.26 (s, 1 H, CO_2H), 7.62 (d, *J* = 8.8 Hz, 2 H, ArH), 6.94 (d, *J* = 8.8 Hz, 2 H, ArH), 1.55 (s, 6 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.1, 159.1, 127.4, 122.0, 118.4, 79.5, 25.6.

Anal. Calcd for $C_{11}H_{11}F_3O_3$: C, 53.23; H, 4.47; O, 19.34. Found: C, 53.09; H, 4.44; O, 19.48.

2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic Acid (Fenofibric Acid) (2e)

Colorless solid; yield: 6.07 g (87%); mp 179–180 °C (Lit.[3a] mp 185 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.4 Hz, 2 H, ArH), 7.71 (d, *J* = 8.4 Hz, 2 H, ArH), 7.44 (d, *J* = 8.4 Hz, 2 H, ArH), 6.94 (d, *J* = 8.4 Hz, 2 H, ArH), 1.70 (s, 6 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.9, 175.1, 160.2, 137.7, 136.9, 132.5, 131.9, 130.0, 129.2, 117.7, 79.5, 25.7.

Anal. Calcd for $C_{17}H_{15}ClO_4$: C, 64.06; H, 4.74; O, 20.08. Found: C, 64.02; H, 4.78; O, 19.95.

2-(2-Chlorophenoxy)-2-methylpropanoic Acid (2f)

Colorless solid; yield: 1.9 g (77%); mp 76–77 °C (Lit.[14] 72 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, *J* = 7.6, 1.6 Hz, 1 H, ArH), 7.19 (ddd, *J* = 8.0, 7.6, 1.2 Hz, 1 H, ArH), 7.07 (dd, *J* = 8.4, 1.2 Hz, 1 H, ArH), 7.04 (ddd, *J* = 8.4, 8.0, 1.6 Hz, 1 H, ArH), 1.64 (s, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 150.9, 130.7, 127.7, 127.6, 124.6, 121.7, 81.6, 25.1.

Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17; O, 22.36. Found: C, 56.03; H, 5.24; O, 22.27.

Acknowledgment

We would like to thank Bill Hinkley for obtaining reaction calorimetry data on the Bargellini reaction and the reaction using 2-bromo-2-methylpropanoic acid.

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(6) The alkylation of one of our compounds using conditions reported by Bargellini was monitored by reaction calorimetry with a Metler Toledo RC1 unit. The total heat generated during the addition (1 h addition time) of the 1,1,1-trichloro-2-methyl-2-propanol was measured at 2180 kJ/kg. The average heat output rate for the duration of the addition was measured at 550 W/kg. Based on the reaction calorimetry, an adiabatic temperature rise of 58 °C was calculated.
(7) We thank Prof. Barry Trost, Stanford University, for first suggesting this reagent to us.
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(11) The alkylation of the compound noted in ref.[6] with 2-bromo-2-methylpropanoic acid was monitored by reaction calorimetry with a Metler Toledo RC1 unit. The total heat generated during the addition (1 h addition time) of the 2-bromo-2-methylpropanoic acid was measured at 669 kJ/kg. The average heat output rate for the duration of the addition was measured at 141 W/kg. Based on the reaction calorimetry, an adiabatic temperature rise of 35 °C was calculated.
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