Unusual Friedel–Crafts Reactions. Part 7.[1] Synthesis of α-(2-Hydroxyphenyl)ethyl Lactates and Their Reductive Cyclization to 3-Methyl-2,3-dihydrobenzofuran-2-ols

Giovanni Casiraghi, Giovanni Sartori,* Giuseppe Casnati, and Franca Bigi
Istituto di Chimica Organica dell'Università, Via M. D'Azeglio 85, I-43100 Parma, Italy

A mild procedure has been developed where α-(2-hydroxyphenyl)ethyl lactates (3), obtained *via* aluminium trichloride-promoted *ortho*-specific alkylation of lithium phenolates (1) with ethyl pyruvate (2), are reductively cyclized to racemic 3-methyl-2,3-dihydrobenzofuran-3-ols (4) in high yields and purity.

Direct alkylation of phenols at the *ortho*-position using reactants carrying an additional electrophilic reaction centre is one of the most promising methods for the synthesis of oxygen heterocycles. After nuclear alkylation of the phenol, ring closure generally takes place under the reaction conditions or *via* subsequent annelation of *ortho*-substituted intermediates. However, the application of this route is often limited because of the low selectivity of the *ortho*-alkylation step and the competition of side-reactions involving the multifunctional reactants.

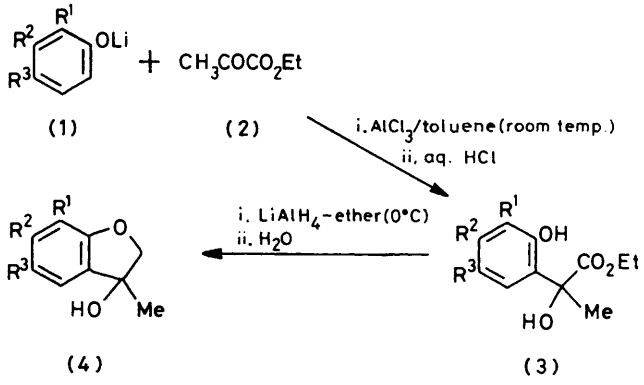
Continuing our synthetic studies on metal ion-driven *ortho*-specific alkylations of metal phenolates and related annelation processes [1,2] we describe here a mild regiospecific synthesis of α-(2-hydroxyphenyl)ethyl lactates (3) and their reductive annelation to the little known 3-methyl-2,3-dihydrobenzofuran-3-ols (3-methylcoumaran-3-ols) (4).

Treatment of lithium phenolates (1), prepared *in situ* from n-butyl-lithium and the corresponding phenol, with ethyl pyruvate (2) (1 mol equiv.) in toluene solution at room temperature in the presence of aluminium trichloride (1 mol equiv.) followed by acidic quenching and chromatographic separation gave racemic α-(2-hydroxyphenyl)ethyl lactates (3) as sole reaction products in 42—61% yield and >83% selectivity. Table 1 lists the lactates (3) synthesized *via* this approach.

Optimum reaction conditions are quite strict. When lithium phenolate was treated with ethyl pyruvate in toluene or benzene solutions in the presence of tin or titanium tetrachloride, instead of aluminium chloride, (3a) was produced in slightly diminished yield (20 and 30% respectively), but when sodium or potassium phenolates, ether solvents or other Lewis acid-catalysts were used under otherwise similar conditions (3a) was not detected.

Aryl lactates (3) on treatment in diethyl ether at 0 °C with lithium aluminium hydride (5 mol equiv.) gave the corresponding racemic coumaranols (4) in high yields, probably *via* reduction of the carboxylate group and subsequent base-promoted cyclization of the carbinol formed. Aqueous quenching and removal of the solvent gave (4) directly which, if necessary, could be easily purified by silica-gel chromatography. The yields and physical data of the coumaranols (4) obtained are collected in Table 2.

The structures of all the foregoing products were supported by their n.m.r. spectra. For derivatives (3) (Table 3), the proton spectra reveal two hydroxy signals near δ 4.5 and 8.5, two methyl signals at δ 1.2 (triplet) and 1.8, and one methylene signal at δ 4.2 (quartet). For coumaranols (4) (Table 4) the important ^{1}H n.m.r. characteristics are the two doublets near δ 3.4 and 3.8 (*J* 12 Hz) for protons of the 2-methylene group (AB system), the sharp singlet near δ 1.5 of the 3-methyl group, and the broad signal between δ 3.8 and 5.5 for the benzylic hydroxyl.



Scheme 1.

The ^{13}C n.m.r. spectra of the parent compound (3a) and (4a) were also in accord with their structures. The ring carbons form a six-line pattern characteristic of *ortho*-substituted phenol derivatives: 117 p.p.m. (CH-*ortho*), 119 p.p.m. (CH-*para*), 126 and 129 p.p.m. (CH-*meta*), 125 p.p.m. (C-*ortho*), and 155 p.p.m. (C–O). The structural assignments for (3) and (4) were also substantiated by i.r. and u.v. spectroscopy, and elemental analysis (see Tables). The purity was checked by t.l.c. on silica-gel plates with hexane–ethyl acetate mixtures for development. Compounds (3) gave characteristic green or red spots when sprayed with aqueous iron trichloride and then warmed, while annelated compounds (4) gave very intense blue-violet spots. Compounds (3) and (4), in the pure form, are quite stable at room temperature but extensively decomposed during distillation.

As far as the reaction mechanism is concerned, we propose for this *ortho*-specific process a substrate–reagent molecular complex, such as depicted in Scheme 2, to account for the activation of both the reagents in the transition state (by increasing the effective molarity of the reactants) and for the orientation of the reaction partners which brings the reactive sites, *i.e.* carbonyl and *ortho*-phenoxy carbons, into a favourable spatial proximity.

In conclusion, we have described herein a mild completely selective approach to hydroxylated arylpropionic esters (3) *via* template-driven *ortho*-specific Friedel-Crafts alkylation of phenols with ethyl pyruvate. Compounds (3) represent versatile, potentially useful phenolic intermediates. It can be, for example, transformed into pharmaceutically interesting phenylpropionic acid derivatives [3] by selective reduction of their carbinol function or into hydroxylated coumarans by reductive ring closure. We also believe that the high-yield room-temperature synthesis of coumaran-3-ols in this study offers an attractive entry into this class of compounds.

Table 1. α-(2-Hydroxyphenyl)ethyl lactates (3)

Compd.	R^1	R^2	R^3	Yield (%) [a]	n^{20}	Found (%) C	Found (%) H	Formula	Calc. (%) C	Calc. (%) H
(3a)	H	H	H	45 (95)	1.5198	62.95	6.65	$C_{11}H_{14}O_4$	62.84	6.71
(3b)	Me	H	H	48 (98)	1.5209	64.4	7.05	$C_{12}H_{16}O_4$	64.27	7.19
(3c)	H	H	Cl	42 (98)	1.5255	53.85	5.4	$C_{11}H_{13}ClO_4$	53.99	5.35 [b]
(3d)	H	H	OMe	50 (95)	1.5208	59.8	6.7	$C_{12}H_{16}O_5$	59.99	6.71
(3e)	$-(CH=CH)_2-$		H	55 (90)	1.5860	69.4	6.1	$C_{15}H_{16}O_4$	69.21	6.20
(3f)	H	OH	H	61 (85)	Glass	58.45	6.2	$C_{11}H_{14}O_5$	58.40	6.24
(3g)	H	OMe	OMe	45 (83)	1.5305	57.85	6.6	$C_{13}H_{18}O_6$	57.77	6.71

[a] Actual yield of pure isolated compounds. Values in parentheses refer to yield based on unrecovered starting phenol. [b] Found: Cl, 14.6; Calc. 14.51%.

Table 2. 3-Methylcoumaran-3-ols (4)

Compd.	R^1	R^2	R^3	Yield (%) [a]	n^{20}	Found (%) C	Found (%) H	Formula	Calc. (%) C	Calc. (%) H
(4a)	H	H	H	98	1.5595	71.9	6.75	$C_9H_{10}O_2$	71.98	6.71
(4b)	Me	H	H	97	1.5494	73.25	7.35	$C_{10}H_{12}O_2$	73.14	7.37
(4c)	H	H	Cl	94	1.5643	58.4	5.05	$C_9H_9ClO_2$	58.54	4.91 [b]
(4d)	H	H	OMe	90	Oil	66.8	6.6	$C_{10}H_{12}O_3$	66.65	6.71
(4e)	$-(CH=CH)_2-$		H	90	Glass	77.85	6.2	$C_{13}H_{12}O_2$	77.98	6.04

[a] Actual yield of pure isolated compounds. [b] Found: Cl, 19.14; Calc. 19.22%.

Table 3. I.r., u.v., and ^1H n.m.r. data for α-(2-hydroxyphenyl)ethyl lactates (3)

Compd.	ν_{max}(neat)/cm^{-1}	λ_{max}(EtOH)/nm (log ε)	δ ($CDCl_3$/$SiMe_4$)
(3a)	3 350, 2 983, 1 730, 1 460, 1 240, 1 128 754	213 (3.76), 275 (3.29), 279 (3.28)	1.23 (3 H, t, OCH_2CH_3), 1.76 (3 H, s, CH_3), 4.18 (2 H, q, OCH_2), CH_3 4.44 (1 H, s, OH), 6.5—7.3 (4 H, m, ArH), 8.39 (1 H, s, ArOH)
(3b)	3 380, 2 990, 1 730, 1 475, 1 260, 1 135, 750	218 (3.95), 280 (3.38)	1.21 (3 H, t, OCH_2CH_3), 1.77 (3 H, s, CH_3), 2.18 (3 H, s, CH_3), 4.14 (2 H, q, OCH_2CH_3), 4.39 (1 H, s, OH), 6.4—7.3 (3 H, m, ArH), 8.47 (1 H, s, ArOH)
(3c)	3 350, 2 980, 1 725, 1 485, 1 270, 1 130, 822	229 (3.96), 284 (3.32), 288 (3.30)	1.25 (3 H, t, OCH_2CH_3), 1.78 (3 H, s, CH_3), 4.20 (2 H, q, OCH_2CH_3), 4.56 (1 H, bs, OH), 6.6—7.4 (3 H, m, ArH), 8.46br (1 H, bs, ArOH)
(3d)	3 370, 2 980, 1 730, 1 500, 1 260, 1 130	225 (3.79), 295 (3.49)	1.22 (3 H, t, OCH_2CH_3), 1.80 (3 H, s, CH_3), 3.73 (3 H, s, OCH_3), 4.16 (2 H, q, OCH_2CH_3), 4.56br (1 H, s, OH), 6.5—6.9 (3 H, m, ArH), 7.96 (1 H, bs, ArOH)
(3e)	3 300, 2 980, 1 728, 1 470, 1 258, 1 124, 812, 758	214 (4.54), 238 (4.47), 299 (3.64), 311 (3.56), 327 (3.51)	1.08 (3 H, t, OCH_2CH_3), 1.86 (3 H, s, CH_3), 4.05 (2 H, q, OCH_3CH_3), 4.82 (1 H, s, OH), 6.8—8.5 (6 H, m, ArH), 9.66 (1 H, s, ArOH)
(3f)	3 360, 3 200, 1 780, 1 450, 1 265, 1 170, 840	220 (3.97), 280 (3.51), 283 (3.48)	1.22 (3 H, t, OCH_2CH_3), 1.82 (3 H, s, CH_3), 4.06br (1 H, s, OH), 4.12 (2 H, q, OCH_2CH_2), 6.1—7.0 (3 H, m, ArH), 8.24 (1 H, s, ArOH), 8.62 (1 H, s, ArOH)
(3g)	3 400, 2 980, 1 730, 1 450, 1 255, 1 205, 1 127	225 (3.84), 291 (3.67)	1.26 (3 H, t, OCH_2CH_3), 1.80 (3 H, s, CH_3), 3.82 (6 H, s, OCH_3), 4.24 (2 H, q, OCH_2CH_3), 4.57br (1 H, s, OH), 6.45 and 6.80 (2 H, 2s, ArH), 8.42br (1 H, s, ArOH)

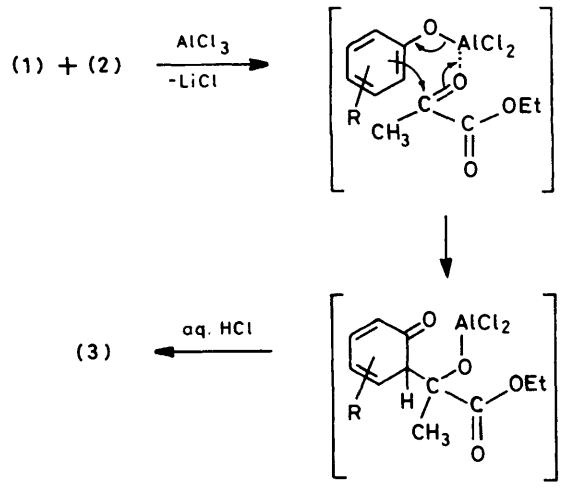
Table 4. I.r., u.v., and ^1H n.m.r. data for 3-methylcoumaran-3-ols (4)

Compd.	ν_{max}(neat)/cm^{-1}	λ_{max}(EtOH)/nm (log ε)	δ ($CDCl_3$/$SiMe_4$)
(4a)	3 340, 2 980, 1 585, 1 454, 1 235, 1 036, 752	212 (3.76), 275 (3.25)	1.46 (3 H, s, 3C-H_3), 3.42 and 3.73 (2 H, 2d, *J* 12 Hz, 2-CH_2), 5.56 (1 H, s, OH), 6.4—7.3 (4 H, m, ArH)
(4b)	3 340, 2 930, 1 470, 1 250, 1 040, 745	215 (3.79), 277 (3.30)	1.48 (3 H, s, 3-CH_3), 2.16 (3 H, s, 7-CH_3), 3.37 and 3.76 (2 H, 2d, *J* 12 Hz, 2-CH_2), 5.30br (1 H, s, OH), 6.3—7.2 (3 H, m, ArH)
(4c)	3 340, 2 980, 1 485, 1 240, 1 042, 820	229 (3.84), 286 (3.30)	1.48 (3 H, s, 3-CH_3), 3.46 and 3.80 (2 H, 2d, *J* 12 Hz, 2-CH_2), 5.40br (1 H, s, OH), 6.5—7.3 (3 H, m, ArH)
(4d)	3 370, 2 940, 1 485, 1 222, 1 035, 870, 810	227 (3.71), 293 (3.43)	1.53 (3 H, s, 3-CH_3), 3.47 and 3.83 (2 H, 2d, *J* 12 Hz, 2-CH_2), 3.72 (3 H, s, OCH_3), 5.10br (1 H, s, OH), 6.2—6.9 (3 H, m, ArH)
(4e)	3 390, 2 930, 1 467, 1 285, 1 042, 804, 745	211 (4.47), 237 (4.46), 299 (3.56), 315 (3.45)	1.60 (3 H, s, CH_3), 3.54 and 3.94 (2 H, 2d, *J* 12 Hz, 2-CH_2), 3.80br (1 H, s, OH), 6.7—8.5 (6 H, m, ArH)

Advantages of this method over the few existing ones [4] include two simple steps, short reaction times, readily available starting materials, and flexibility to incorporate alkyl, alkoxy, or hydroxy-groups at the aromatic ring by varying the phenolic reagent.

Experimental

For general remarks, see ref. 2*b*. Ethyl pyruvate was purchased from E. Merck Darmstadt (Germany); phenols, metal halide-catalysts, n-butyl-lithium, and solvents were also commercially available and were used without further purification.



Scheme 2.

α-(2-*Hydroxyphenyl*)*ethyl lactates* (3a): *Typical Procedure*.—To a suspension of lithium phenolate [prepared *in situ* from phenol (0.94 g, 10 mmol) and n-butyl-lithium (6.25 ml of 1.6 molar hexane solution)] in anhydrous toluene (50 ml) aluminium chloride (1.33 g, 10 mmol) was added with stirring at room temperature. The slurry was heated under reflux with stirring for 15 min, while a stream of dry nitrogen was passed through it. The resulting suspension was cooled to room temperature and a solution of ethyl pyruvate (1.16 g, 10 mmol) in toluene (10 ml) was added dropwise with stirring. The reaction mixture was stirred for 4 h at room temperature and then quenched with 10% aqueous hydrochloric acid (40 ml) and extracted with diethyl ether. After drying (sodium sulphate), the solvent was removed under reduced pressure and the residual oil chromatographed on silica gel [hexane–ethyl acetate, 8 : 2 (v : v)] to give pure α-(2-hydroxyphenyl)-ethyl lactate (3a); the yield was 0.946 g (45% on phenol), n^{20} 1.5198; δ_C ($CDCl_3$) 174.63 (CO_2Et), 155.04 (CO-1), 129.48 (CH-3), 126.32 (CH-5), 125.68 (C-2), 119.69 (CH-4), 117.29 (CH-6), 77.32 (C-OH), 62.49 (OCH_2CH_3), 25.93 (CH_3), and 13.92 (OCH_2CH_3). I.r., u.v., and ^1H n.m.r. data are collected in Table 3.

The other α-(2-hydroxyphenyl)ethyl lactates (3b—g) listed in Table 1 were prepared in a similar way.

3-*Methyl*-2,3-*dihydrobenzofuran*-3-*ol* (4a): *Typical Procedure*.—To a stirred suspension of lithium aluminium hydride (0.95 g, 25 mmol) in diethyl ether (20 ml) a solution of α-(2-hydroxyphenyl)ethyl lactate (3a) (1.05 g, 5 mmol) in anhydrous diethyl ether (20 ml) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min and then quenched by careful addition of 5% aqueous hydrochloric acid. The organic layer was separated and the solvent was removed to give a yellow oil which was chromatographed on silica gel [hexane–ethyl acetate, 8 : 2 (v : v)] to give pure 3-methyl-2,3-dihydrobenzofuran-3-ol (4a); the yield was 0.73 g (98%), n^{20} 1.5595, δ_C ($CDCl_3$) 155.79 (CO-8), 128.96 (CH-4), 128.57 (C-9), 126.10 (CH-6), 119.64 (CH-5), 117.38 (CH-7), 77.85 (C-3), 69.06 (CH_2-2), and 24.78 (CH_3). I.r., u.v., and ^1H n.m.r. data are collected in Table 4.

The other 3-methyl-2,3-dihydrobenzofuran-3-ols (4b—e) listed in Table 2 were prepared in a similar way.

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