A Simple Route to Benzofuran-2(3*H*)-ones[1,†]

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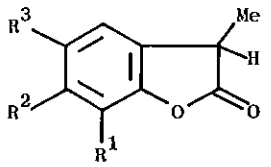
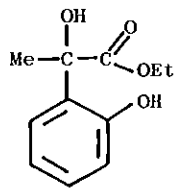
We report a simple route to benzofuran-2(3*H*)-ones by reductive cyclization of 2-hydroxy-2-(2-hydroxyaryl)-alkanoic esters.

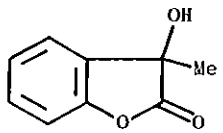
Benzofuran-2(3*H*)-ones (1) are a new and promising class of drugs showing anti-flammatory, antipyretic, and edema-inhibiting activities.[2–5] Other derivatives of this class of compounds have been patented as intermediates in the preparation of pharmaceuticals.[6–8]



(1)	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	H	H	Me
d	H	Bu^i	H
e	H	H	Ph
f	H	H	2,4-$C_6H_3F_2$
g	H	OMe	H
h	H	H	OPh
i	H	H	SMe
j	H	OH	CH_2Ph
k	CH=CH-CH=CH		H
l	CH=CH-CH(OMe)=CH		H



(2)



(3)

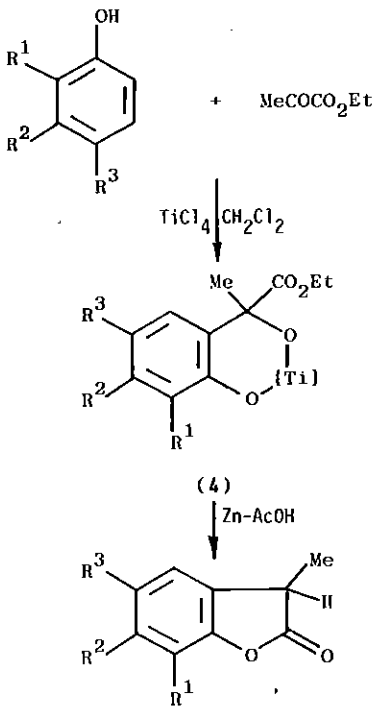
A general route to (1) is the acid-catalysed cyclization of *o*-hydroxyaryl alkanoic acids.[9] These, however, are not readily available compounds.

We recently reported a facile synthesis of 2-hydroxy-2-(2-hydroxyaryl)alkanoic acids or esters[10] and decided to utilize these compounds for preparing (1). Our attempts to remove the benzylic alcohol by hydrogenolysis with zinc in acetic acid were unsuccessful, the only products being 3-hydroxybenzofuran-2(3*H*)-one derivatives. However, reaction proceeded smoothly to (1) in the presence of catalytic quantities of titanium salts (0.01–1.00 molar ratio to the substrate); Table 1 reports the results of Zn–AcOH hydrogenolysis of ethyl 2-(2-hydroxyphenyl)lactate (2) both in the absence and presence of $TiCl_4$ to give (1a) or 3-hydroxy-3-methyl-benzofuran-2(3*H*)-one (3). An efficient one-pot synthesis of (1) has also been obtained by reduction of the crude titanium(IV) complex (4) (Scheme); the yields

Table 1 Reduction of ethyl 2-(2-hydroxyphenyl)lactate (2) by zinc[a]

$TiCl_4$ (mmol)	Zn (mol)	*t*/h	Yield (%) (3)	Yield (%) (1a)
0	0.474	12	80	<1
13.0–47.5	0.137	3	—	100
0.50–4.60	0.137	12–24	—	100
4.60	0.047	24	—	100

[a] *General reaction conditions.* To the ester (2) (10 g, 47.5 mmol) and the reported amount of $TiCl_4$ in CH_2Cl_2 (50 ml) were added Zn and AcOH (100 ml) at room temperature and the mixture was heated at 90 °C, distilling off the CH_2Cl_2.



(4)

(1)

Scheme

*To receive any correspondence.
†This is a Short Paper as defined in the Instructions for Authors [*J. Chem. Research (S)*, 1985, Issue 1, p. iv]; there is therefore no corresponding material in *J. Chem. Research (M)*.
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Table 2 Physical data for compounds (1)[a]

Compound	Yield (%)	M.p. or (B.p./mmHg) (°C)	δ/ppm ($CDCl_3$)	m/e (70 eV)	Found (required) (%) C	H
(1a)	81	54(81/1)	7.20 (4 H, m, ArH), 3.70 (1H, q, $CHCH_3$), 1.52 (3 H, d, $CHCH_3$)	148 (M^+, 100) 120 (92)	72.7 (72.96)	5.5 (5.44)
(1b)	75	39(76/0.3)	7.20–6.72 (3 H, m, ArH), 3.58 (1 H, q, $CHCH_3$), 2.35 (3 H, s, CH_3), 1.50 (3 H, d, $CHCH_3$)	162 (M^+, 82) 134 (100)	74.4 (74.05)	6.1 (6.22)
(1c)	80	(72/0.2)	7.05 (3 H, m, ArH), 3.68 (1 H, q, $CHCH_3$), 2.33 (3 H, s, CH_3), 1.52 (3 H, d, $CHCH_3$)	162 (M^+, 76) 134 (100)	74.3 (74.05)	6.15 (6.22)
(1d)	70	(83/0.07)	7.10–6.56 (3 H, m, ArH), 3.50 (1 H, q, $CHCH_3$), 2.40 (2 H, d, CH_2), 2.10–1.20 [4 H, m + d, $CH(CH_3)_2$, $CHCH_3$], 0.90 [6 H, d, $CH(CH_3)_2$]	204 (M^+, 80) 133 (100)	76.2 (76.44)	7.8 (7.90)
(1e)	76	89	7.70–7.10 (8 H, m, ArH), 3.80 (1 H, q, $CHCH_3$), 1.60 (3 H, d, $CHCH_3$)	224 (M^+, 68) 196 (100)	80.5 (80.34)	5.45 (5.39)
(1f)	60	83	7.55 (6 H, m, ArH), 3.85 (1 H, q, $CHCH_3$), 1.65 (3 H, d, $CHCH_3$)	260 (M^+, 100) 232 (60)	69.3 (69.23)	3.95 (3.87)
(1g)	65	oil	7.95 (1 H, s, ArH), 6.70 (2 H, m, ArH), 3.83 (3 H, s, OCH_3), 3.68 (1 H, q, $CHCH_3$), 1.50 (3 H, d, $CHCH_3$)	178 (M^+, 78) 150 (100)	66.45 (66.65)	6.8 (6.71)
(1h)	50	oil	7.36 (8 H, m, ArH), 3.51 (1 H, q, $CHCH_3$), 1.38 (3 H, d, $CHCH_3$)	240 (M^+, 62) 212 (100)	74.8 (74.99)	5.1 (5.03)
(1i)	80	49.5	7.35–6.90 (3 H, m, ArH), 3.68 (1 H, q, $CHCH_3$), 2.45 (3 H, s, SCH_3), 1.45 (3 H, d, $CHCH_3$)	194 (M^+, 92) 166 (100)	61.6 (61.82)	16.5 (16.47)
(1j)	60	67.5	7.45–7.15 (5 H, m, ArH), 6.95 (1 H, m, ArH), 6.65 (1 H, m, ArH), 3.95 (2 H, s, CH_2), 3.60 (2 H, m, OH + $CHCH_3$), 1.45 (3 H, d, $CHCH_3$)	254 (M^+, 100) 226 (83)	75.8 (75.57)	5.5 (5.55)
(1k)	82	79	8.00–7.00 (6 H, m, ArH), 3.88 (1 H, q, $CHCH_3$), 1.63 (3 H, d, $CHCH_3$)	198 (M^+, 100) 170 (90)	78.9 (78.67)	5.0 (5.09)
(1l)	80	135.5	8.00–7.00 (5 H, m, ArH), 4.03–3.56 (4 H, s + q, OCH_3 + $CHCH_3$), 1.58 (3 H, d, $CHCH_3$)	228 (M^+, 75) 200 (100)	73.65 (73.67)	5.4 (5.30)

[a]*General reaction conditions.* To the reaction mixture, prepared from the phenol derivative (0.106 mol), $TiCl_4$ (0.106 mol), and ethyl pyruvate (0.106 mol) in CH_2Cl_2 (200 ml)[10] were added Zn (0.16 mol) and AcOH (80 ml) at room temperature. The mixture was refluxed for 3 h, distilling off the CH_2Cl_2, then cooled, filtered and concentrated under vacuum to 20 ml. The residue was poured into 10% HCl and diethyl ether (100 ml) and the mixture stirred for 3 h. The organic phase was washed with water and concentrated and the residue was distilled and crystallized [light petroleum (b.p. 40–50 °C)–diethyl ether] or purified by flash chromatography.

are good and are usually determined by the condensation step. The results, obtained by using ethyl pyruvate and some phenols, are reported in Table 2 along with the n.m.r. and mass spectra of the new compounds (1).

Preliminary measurements of the anti-inflammatory activity of the new compounds (1), determined *in vivo* by the carrageenin edema test,[11] have shown that compounds (1d, h, and l) show an activity comparable with that of the structurally related known anti-inflammatory drugs Ibuprofen, Phenoprofen, and Naproxen.[12]

Investigations on both the improvement and the synthetic implications of the titanium-catalysed hydrogenolysis reaction of the benzylic alcohol group are currently being conducted. Similar catalytic activities have been obtained in the conversion of alkyl esters of 4'-hydroxymandelic acid into the corresponding alkyl esters of 4-hydroxyphenylacetic acid.[13]

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[1]The method described in this paper has been patented (Ital. P. Appl. 24817/1982).
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