A Facile and Efficient Synthesis of (*o*-Hydroxyaryl)-glycolic Acid Derivatives[1]

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It is well known that a mixture of products can be obtained in the reaction of phenols with carbonyl derivatives under acidic conditions, and the aromatic substitution generally occurs in the *para* position to the phenolic oxygen atom[2-6].

We report here the reaction of α-keto esters **1** with phenols **2** in the presence of a Lewis acid (mainly chlorides of metals in high oxidation state such as e.g. tetravalent titanium, zirconium or tin or, less efficiently, trivalent boron or aluminium)[6], affording in high yields (*o*-hydroxyaryl)-glycolic acid derivatives **3** (Table 1). These compounds are useful inter-

Table 1. *ortho*-Hydroxyalkylation of Phenols **2** by α-Keto Esters or Acids **1** in the Presence of Lewis Acids

Product No.	R^1	R^2	R^3	R^4	R^5	ML_n	Method	Reaction Conditions temperature [°C]/ time [h]	Yield[a] [%]	m.p. [°C] or n_D^{20}	Molecular formula[b] or Lit.[14], n_D^{20}
3a	H	CH_3	H	H	H	$TiCl_4$	B	0°/1.5	75	137–140°	$C_9H_{10}O_4$ (182.2)
3b	C_2H_5	CH_3	H	H	H	$TiCl_4$	B	0–25°/1	92	1.5193	1.5198
						$TiCl_2(OR)_2$[c]	A	25°/20	60	oil	
						$TiCl_4$	A	0–25°/8	80	oil	
						$AlCl_3$	A	0°/3	52[d]	oil	
3c	C_2H_5	CH_3	CH_3	H	H	$TiCl_4$	B	0°/1	92	1.5207	1.5209
3d	C_2H_5	CH_3	H	CH_3	H	$TiCl_4$	A	0°/0.2	75	oil	$C_{12}H_{16}O_4$ (224.3)
						$TiCl_4$	B	0°/0.2	88	oil	
						$ZrCl_4$	B	0°/1	84	oil	
3e	C_2H_5	CH_3	H	H	CH_3	$TiCl_4$	B	0°/2	90	oil	$C_{12}H_{16}O_4$ (224.3)
3f	C_2H_5	CH_3	H	H	*c*-C_6H_{11}	$TiCl_4$	B	0°/2	80	oil	$C_{17}H_{24}O_4$ (292.4)
3g	C_2H_5	CH_3	H	*i*-C_4H_9	H	$TiCl_4$	B	0°/1	83	oil	$C_{15}H_{22}O_4$ (266.3)
3h	C_2H_5	CH_3	H	OH	H	$TiCl_4$	B	−20°/1	80	glass	glass
3i	C_2H_5	CH_3	H	OH	$C_6H_5CH_2$	$TiCl_4$	B	−50°/0.2	86	oil	$C_{18}H_{20}O_5$ (316.4)
3j	C_2H_5	CH_3	H	OCH_3	H	$TiCl_4$	A	0°/1	93	oil	$C_{12}H_{16}O_5$ (240.3)
3k	C_2H_5	CH_3	H	H	OCH_3	$TiCl_4$	A	25°/8	70	1.5209	1.5208
3l	H	CH_3	H	OCH_3	H	$TiCl_4$	B	0°/1.5	70	111–113°	$C_{10}H_{12}O_5$ (212.2)
3m	C_2H_5	CH_3	H	$OCOCH_3$	H	$TiCl_4$	B	0°/0.5	79	oil	$C_{13}H_{16}O_6$ (268.3)
3n	C_2H_5	CH_3	H	H	OC_6H_5	$TiCl_4$	B	40°/40	49	oil	$C_{17}H_{18}O_5$ (302.3)
3o	C_2H_5	CH_3	H	H	SCH_3	$TiCl_4$	B	25°/14	89	oil	$C_{12}H_{16}O_4S$ (256.3)
3p	C_2H_5	H	H	H	SCH_3	$TiCl_4$	B	25°/12	71	oil	$C_{11}H_{14}O_4S$ (242.3)
3q	C_2H_5	CH_3	H	H	C_6H_5	$TiCl_4$	B	25°/3	80	oil	$C_{17}H_{18}O_4$ (286.3)
3r	C_2H_5	CH_3	H	H	2′,4′-di-F—C_6H_3	$TiCl_4$	B	0–20°/20	70	oil	$C_{17}H_{17}F_2O_4$ (322.3)
3s	C_2H_5	CH_3	Cl	H	H	$TiCl_4$	B	40°/5	35	oil	$C_{11}H_{13}ClO_4$ (244.7)
3t	C_2H_5	CH_3	H	H	Cl	$TiCl_4$	B	25°/30	52	1.5253	1.5255
3u	C_2H_5	CH_3	H	Br	H	$TiCl_4$	B	25°/1	75	oil	$C_{11}H_{13}BrO_4$ (289.1)
3v	C_2H_5	CH_3	H	phthalimide	H	$TiCl_4$	B	25°/12	45	oil	$C_{19}H_{17}NO_6$ (355.4)
3w	C_2H_5	CH_3	—(CH=CH)$_2$—		H	$TiCl_4$	B	−40°/0.2	98	1.5862	1.5860
						$SnCl_4$	B	−30°/0.2	73	oil	
3x	C_2H_5	H	—(CH=CH)$_2$—		H	$TiCl_4$	B	−40°/0.5	70	oil	$C_{14}H_{14}O_4$ (246.3)
3y	C_2H_5	*c*-C_6H_{11}	—(CH=CH)$_2$—		H	$TiCl_4$	B	−30°/0.5	75	oil	$C_{20}H_{24}O_4$ (328.4)
3z	CH_3	C_6H_5	—(CH=CH)$_2$—		H	$TiCl_4$	B	−30°/0.5	78	oil	$C_{19}H_{16}O_4$ (308.3)
3aa	C_2H_5	$C_6H_5CH_2$	—(CH=CH)$_2$—		H	$TiCl_4$	B	−30°/0.2	70	oil	$C_{21}H_{20}O_4$ (336.4)
3bb	C_2H_5	CH_3	—(CH=CH)$_2$—		Cl	$TiCl_4$	B	−50°/0.5	90	oil	$C_{15}H_{15}ClO_4$ (294.7)
3cc	C_2H_5	CH_3	—CH=CH—C(OCH$_3$)=CH—		H	$TiCl_4$	B	−40°/0.2	85	oil	$C_{16}H_{18}O_5$ (290.3)
3dd	C_2H_5	$COOC_2H_5$	H	H	H	$TiCl_4$	B	0–25°/2.5	76	oil	$C_{13}H_{16}O_6$ (268.3)
3ee	C_2H_5	$COOC_2H_5$	H	*i*-C_4H_9	H	$TiCl_4$	B	0°/1	85	63–64°	$C_{17}H_{24}O_6$ (324.4)
3ff	C_2H_5	$COOC_2H_5$	H	CH_3	H	$TiCl_4$	B	0°/0.5	85	oil	$C_{14}H_{18}O_6$ (282.3)
3gg	C_2H_5	$COOC_2H_5$	H	H	OC_6H_5	$TiCl_4$	B	0–25°/4	70	oil	$C_{19}H_{20}O_7$ (360.4)
3hh	C_2H_5	$COOC_2H_5$	H	H	SCH_3	$TiCl_4$	B	25°/12	81	60–61°	$C_{14}H_{18}O_6S$ (314.4)
3ii	C_2H_5	$COOC_2H_5$	—(CH=CH)$_2$—		H	$TiCl_4$	B	−50°/1	80	59–60°	$C_{17}H_{18}O_6$ (318.3)
3jj	C_2H_5	$COOC_2H_5$	—CH=CH—C(OCH$_3$)=CH—		H	$TiCl_4$	B	−40°/0.2	73	73°	$C_{18}H_{20}O_7$ (348.4)

[a] Isolated yield.

[b] Satisfactory microanalyses obtained: C ±0.13, H ±0.11, Br −0.35, Cl +0.2, N +0.08, S ±0.08.

[c] R = *i*-C_3H_7.

[d] The presence of a small quantity of *para* derivative (≅ 10%) was observed.

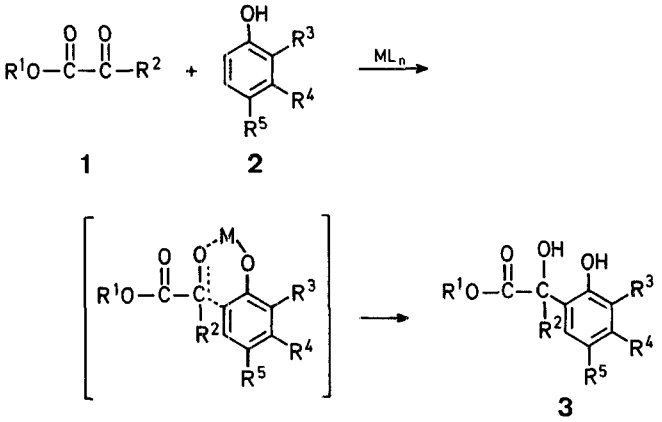
Table 2. ^{1}H-N.M.R.-Spectral Data of New Compounds **3** prepared

Product No.	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
3a	7.70–6.70 (m, 4H$_{arom}$); 5.33 (s, 3H, Ar—OH, C—OH, COOH); 1.90 (s, 3H, CH_3)
3d	8.50 (s, 1H, Ar—OH); 7.15 (m, 1H$_{arom}$); 6.67 (m, 2H$_{arom}$); 4.50 (s, 1H, C—OH); 4.25 (q, 2H, CH_2); 2.23 (s, 3H, Ar—CH_3); 1.70 (s, 3H, C—CH_3); 1.20 (t, 3H, CH_2—CH_3)
3e	8.30 (s, 1H, Ar—OH); 7.03 (m, 1H$_{arom}$); 6.97 (m, 1H$_{arom}$); 6.70 (m, 1H$_{arom}$); 4.60 (s, 1H, C—OH); 4.22 (q, 2H, CH_2); 2.23 (s, 3H, Ar—CH_3), 1.78 (s, 3H, C—CH_3), 1.20 (t, 3H, CH_2—CH_3)
3f	7.50 (s, 1H, Ar—OH); 6.55–5.90 (m, 3H$_{arom}$); 4.05–3.55 (m, 3H, CH_2, C—OH); 2.30–0.90 (m, 17H, c-C_6H_{11}, CH_3, CH_2—CH_3)
3g	8.32 (s, 1H, Ar—OH); 7.05–6.55 (m, 3H$_{arom}$); 4.30 (s, 1H, C—OH); 4.10 (q, 2H, CH_2CH_3); 2.30 (d, 2H, Ar—CH_2); 1.70 (m, 1H, CH); 1.70 (s, 3H, C—CH_3); 1.10 (t, 3H, CH_2—CH_3), 0.80 [d, 6H, $CH(CH_3)_2$]
3j	8.60 (s, 1H, Ar—OH); 7.33 (m, 1H$_{arom}$); 6.45 (m, 2H$_{arom}$); 4.35 (s, 1H, C—OH); 4.27 (q, 2H, CH_2); 3.95 (s, 3H, OCH_3); 1.80 (s, 3H, C—CH_3); 1.20 (t, 3H, CH_2—CH_3)
3l	9.35 (s, 1H, COOH); 7.25 (d, 1H$_{arom}$); 6.50–6.30 (m, 2H$_{arom}$); 3.75 (s, 3H, OCH_3); 1.78 (s, 3H, C—CH_3)
3m	8.20 (s, 1H, Ar—OH); 7.20 (m, 1H$_{arom}$); 6.55 (m, 2H$_{arom}$); 6.25 (s, 1H, C—OH); 4.20 (q, 2H, CH_2); 2.20 (s, 3H, O—CO—CH_3); 1.70 (s, 3H, C—CH_3); 1.20 (t, 3H, CH_2—CH_3)
3n	8.10 (s, 1H, Ar—OH); 7.20–6.50 (m, 8H$_{arom}$); 4.45 (s, 1H, C—OH); 4.00 (q, 2H, CH_2); 1.60 (s, 3H, C—CH_3); 1.15 (t, 3H, CH_2—CH_3)
3o	8.55 (s, 1H, Ar—OH); 7.30–6.70 (m, 3H$_{arom}$); 4.50–4.00 (m, 3H, CH_2—CH_3, C—OH); 2.40 (s, 3H, SCH_3); 1.93 (s, 3H, C—CH_3); 1.24 (t, 3H, CH_2—CH_3)
3p	7.72 (s, 1H, Ar—OH); 7.25–6.60 (m, 3H$_{arom}$); 5.25 (d, 1H, C—OH); 4.50 (d, 1H, CH); 4.20 (q, 2H, CH_2); 2.36 (s, 3H, SCH_3); 1.18 (t, 3H, CH_2—CH_3)
3q	8.70 (s, 1H, Ar—OH); 7.50–6.80 (m, 8H$_{arom}$); 5.81 (s, 1H, C—OH); 4.20 (q, 2H, CH_2); 1.87 (s, 3H, C—CH_3); 1.16 (t, 3H, CH_2—CH_3)
3r	8.60 (s, 1H, Ar—OH); 7.35–6.50 (m, 6H$_{arom}$); 4.45–3.95 (m, 3H, CH_2, C—OH); 1.82 (s, 3H, C—CH_3); 1.20 (t, 3H, CH_2—CH_3)
3s	8.10 (s, 1H, Ar—OH); 7.40–6.70 (m, 3H$_{arom}$); 4.25 (q, 2H, CH_2—CH_3); 3.60 (s, 1H, C—OH); 1.80 (s, 3H, C—CH_3); 1.32 (t, 3H, CH_2—CH_3)
3t	8.85 (s, 1H, Ar—OH); 7.40–6.80 (m, 3H$_{arom}$); 4.60 (s, 1H, C—OH); 4.23 (q, 2H, CH_2); 1.80 (s, 3H, C—CH_3); 1.23 (t, 3H, CH_2—CH_3)
3v	8.10 (s, 1H, Ar—OH); 7.25 (m, 4H$_{arom}$); 6.75 (m, 1H$_{arom}$); 6.40 (m, 2H$_{arom}$); 4.45 (s, 1H, C—OH); 3.88 (q, 2H, CH_2); 1.65 (s, 3H, C—CH_3); 1.12 (t, 3H, CH_2CH_3)
3x	8.40 (s, 1H, Ar—OH); 8.40–7.15 (m, 6H$_{arom}$); 5.48 (s, 1H, C—OH); 4.20 (q + s, 3H, CH_2, CH); 1.22 (t, 3H, CH_2—CH_3
3y	8.40–7.20 (m, 6H$_{arom}$); 4.72 (s, 1H, C—OH); 4.28 (q, 2H, CH_2—CH_3); 2.20 (m, 1H, CH); 1.90–1.00 (t + m, 13H, CH_2, CH_3)
3z	9.28 (s, 1H, Ar—OH); 8.40–6.90 (m, 11H$_{arom}$); 4.90 (s, 1H, C—OH); 3.80 (s, 3H, CH_3)
3aa	9.98 (s, 1H, Ar—OH); 8.40–6.68 (m, 11H$_{arom}$); 4.20 (q, 2H, CH_2—CH_3); 3.70 (s, 1H, C—OH), 3.50 (dd, 2H, Ar—CH_2); 1.20 (t, 3H, CH_2—CH_3)
3bb	9.30 (s, 1H, Ar—OH); 8.00–7.50 (m, 3H$_{arom}$); 7.25–6.80 (m, 3H$_{arom}$); 4.70 (s, 1H, C—OH); 3.90 (q, 2H, CH_2); 1.65 (s, 3H, C—CH_3); 1.00 (t, 3H, CH_3)

Table 2. Continued

Product No.	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
3cc	9.60 (s, 1H, Ar—OH); 8.20 (d, 1H$_{arom}$); 7.30–7.00 (m, 4H$_{arom}$); 4.60 (s, 1H, C—OH); 4.22 (q, 2H, CH_2—CH_3); 3.83 (s, 3H, OCH_3); 1.85 (s, 3H, C—CH_3); 1.20 (t, 3H, CH_2—CH_3)
3dd	7.52 (s, 1H, Ar—OH); 7.00–6.25 (m, 4H$_{arom}$); 4.85 (s, 1H, C—OH); 4.00 (q, 4H, CH_2); 1.05 (t, 6H, CH_2—CH_3)
3ee	7.20–6.40 (m, 3H$_{arom}$); 5.40 (s, 2H, Ar—OH, C—OH); 4.30 (q, 4H, CH_2); 2.40 (d, 2H, Ar—CH_2); 1.95 (m, 1H, CH); 1.25 (t, 6H, CH_2—CH_3); 0.90 [d, 6H, $CH(CH_3)_2$
3ff	7.80 (s, 1H, Ar—OH); 7.18 (d, 1H$_{arom}$); 6.74 (s, 1H$_{arom}$); 6.70 (d, 1H$_{arom}$); 4.80 (s, 1H, C—OH); 4.33 (q, 4H, CH_2); 2.25 (s, 3H, Ar—CH_3); 1.28 (t, 6H, CH_2—CH_3)
3gg	7.60 (s, 1H, Ar—OH); 7.20–6.70 (m, 8H$_{arom}$); 5.00 (s, 1H, C—OH); 4.20 (q, 4H, CH_2); 1.20 (t, 6H, CH_2—CH_3)
3hh	8.73 (s, 1H, Ar—OH); 7.38–6.73 (m, 3H$_{arom}$); 5.69 (s, 1H, C—OH); 4.30 (q, 4H, CH_2); 2.40 (s, 3H, SCH_3); 1.28 (t, 6H, CH_2—CH_3)
3ii	9.18 (s, 1H, Ar—OH); 8.47–7.25 (m, 6H$_{arom}$); 5.10 (s, 1H, C—OH); 4.33 (q, 4H, CH_2); 1.28 (t, 6H, CH_2—CH_3)
3jj	9.10 (s, 1H, Ar—OH); 8.10 (d, 1H$_{arom}$); 7.35–6.90 (m, 4H$_{arom}$); 5.65 (s, 1H, C—OH); 4.35 (q, 4H, CH_2); 3.90 (s, 3H, O—CH_3); 1.32 (t, 6H, CH_2—CH_3)

mediates[7] for the preparation of 2,3-dihydrobenzofuran-2-ones, a new and interesting class of antiinflammatory agents[8–11].



The reaction conditions, temperature and time, are largely dependent on the susceptibility of the phenol derivate to electrophilic substitution, varying from to −60 °C to +40 °C and from few h (or min) to 40 h. The only limitations for this reaction under the employed conditions, are the presence of deactivating substituents on the phenol ring and, of course, the instability of carbonyl derivatives to the acidic conditions. The high regioselectivity for the *ortho*-position, found in this reaction, implies that in the transition state the metal M is tightly bonded to phenolic and carbonyl oxygen atoms and probably also to carbonyl of the ester group (depending on the metal).

The metal phenolates, that are obtained *in situ* by direct reaction of phenols and metal salts[12] and the described pericyclic transition state[13] are probably involved also in the synthesis of **3** carried out very recently under unusual Friedel-Crafts conditions[14]. It is noteworthy, however, that in the latter

case, reaction conditions are reported to be quite strict and the yield of **3** highly dependent on alkaline salts and on the nature of Lewis acid[14].

The process described here can be considered as a Lewis acid-catalysed aldol reaction, where the metal salt of the phenol functions as the enol form of one of two carbonyl derivatives. Hence, it will be possible to realise other highly efficient *ortho*-selective C—C bond formations of phenol derivatives, the only limitation being the stability of the reagents and products to the acidic medium.

(*o*-Hydroxyaryl)-glycolic Acid Derivatives 3; Typical Procedures:

Method A: To a stirred solution of *m*-cresol (500 mg, 4.6 mmol) and ethyl pyruvate (534 mg, 4.6 mmol) in dichloromethane (20 ml) at 0 °C, titanium tetrachloride (873 mg, 4.6 mmol) is added slowly within 10 min. After 10 min, the reaction is quenched with water (10 ml) and extracted with ether (3 × 30 ml). The ether phase is washed with water (3 × 30 ml), dried with sodium sulfate and evaporated. The oily residue is chromatographed on silica gel with *n*-hexane/ethyl acetate (8:2) to give ethyl α-(2-hydroxy-4-methylphenyl)-lactate (**3d**); yield: 775 mg (75%).

Method B: To a solution of *m*-cresol (500 mg, 4.6 mmol) in dichloromethane (20 ml) maintained at 0 °C is added titanium tetrachloride (873 mg, 4.6 mmol) and the mixture is stirred at 0 °C for 30 min. A solution of ethyl pyruvate (534 mg, 4.6 mmol) in dichloromethane (5 ml) is then added slowly to the mixture. After maintaining the mixture for 10 min at 0 °C, the reaction is worked up as given for Method A to give **3d**; yield: 910 mg (81%).

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