Unusual Friedel–Crafts Reactions. Part 8.[1] Synthesis of 2-Hydroxyarylglyoxylic Acids *via ortho*-Specific Oxaloylation of Phenols with Oxalyl Chloride

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2-Hydroxyarylglyoxylic acids (**6**) are readily prepared from the bromomagnesium salts of phenols (**2**) and oxalyl chloride (**3**) in toluene at room temperature. This procedure bypasses some of the inherent difficulties in the conventional Friedel–Crafts acylation procedures.

The regiospecific oxaloylation of phenols with oxalyl chloride leading to 2-hydroxyarylglyoxylic acids (**6**) presented here is part of a series of extensive investigations on chelation-directed electrophilic substitution of non-transition metal phenolates conducted in this laboratory. Previous work[1,2] involved alkylation and cycloalkylation of bromomagnesium, zinc(II), aluminium(III), tin(IV), and titanium(IV) phenolates providing ready access to a number of *ortho*-substituted phenols and five- and six-membered cyclic ethers. Additional studies reported to date have involved the magnesium-assisted chromenylation of phenols[3] and the boron trichloride-promoted α-chloroacetylation of phenols.[4] Such investigations emphasized the pivotal role played by the co-ordinating metal in the activation of the reacting species, providing regiospecificity by bringing the phenolic *ortho*-carbon into the proximity of the electrophile.

2-Hydroxyarylglyoxylic acids (**6**) are interesting intermediates which can easily be transformed into powerful anti-inflammatory agents such as 2,3-dihydrobenzofuran-2-ones and 2-hydroxyphenylacetic acids.[5,6] The synthesis of compounds (**6**) by direct oxaloylation of the phenols with oxalyl chloride has been previously reported, but this procedure, which commonly used aluminium chloride as the Friedel–Crafts promoter, is limited in scope because of extensive competition from bis-arylation, *para*-acylation, and decarbonylation side-processes.[7]

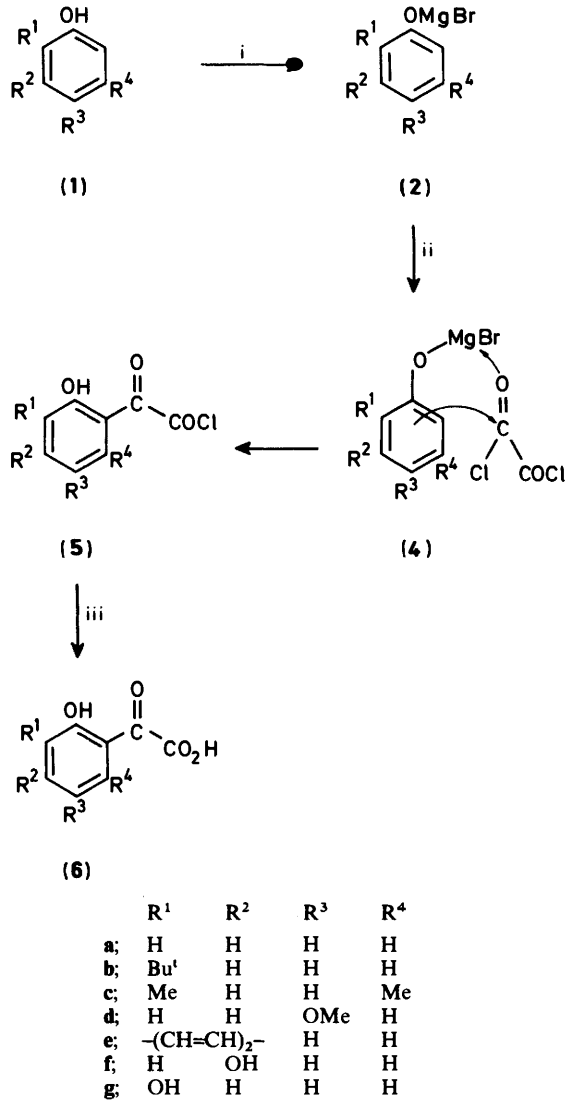
The primary goal of this investigation is to try to develop a procedure with mild conditions which would allow us to control the course of the reaction, circumventing the difficulties of the conventional procedures.

The reaction of the phenol (**1a**) with oxalyl chloride (**3**) indicates that the results can be controlled by varying the catalytic species involved and the solvents. We first repeated the reaction between the phenol (**1a**) and (**3**) under the usual Friedel–Crafts conditions, *viz.* aluminium chloride in methylene dichloride.[5] After quenching with water, 2-hydroxyphenylglyoxylic acid (**6a**) (20%) was isolated, along with 2,2′-dihydroxybenzil (13%) and 2,4′-dihydroxybenzil (7%). No starting phenol was recovered, but the reaction is not selective since several unidentified compounds accounting for 35—40% of the product mixture were also formed.

Unsatisfactory results were also obtained using tin and zircon tetrachloride under similar conditions, or dichloroaluminium phenolate in toluene solution. In contrast, when bromomagnesium phenolate was allowed to react at ambient temperature in toluene with compound (**3**), a clean reaction was observed yielding the product (**6a**) (44%), along with recovered phenol (45%).

One equivalent of magnesium relative to phenol (complete salt formation) was required to give the maximum yield; the yield fell off rapidly when less than the stoicheiometric amount of the magnesium salt was employed. Titanium tetraphenolate, which can easily be prepared *in situ* from titanium tetraisopropoxide and phenol, also behaved selectively, but the phenol was converted to a smaller extent (35%) than in the reaction involving the magnesium derivative (55%).

We next extended the reaction to a variety of mono- and di-hydric phenols in order to evaluate the synthetic potential of this methodology. All the reactions were conducted at ambient temperature using phenol salts in toluene solution. After



	R^1	R^2	R^3	R^4
a;	H	H	H	H
b;	Bu^t	H	H	H
c;	Me	H	H	Me
d;	H	H	OMe	H
e;	–(CH=CH)$_2$–		H	H
f;	H	OH	H	H
g;	OH	H	H	H

Scheme. *Reagents and conditions:* i, EtMgBr, ether, room temperature; ii, $(CO)_2Cl_2$ (**3**), toluene, room temperature; iii, H_2O–NH_4Cl

Table 1. 2-Hydroxyarylglyoxylic acids (**6a**—**g**)

Compound	Yield (%)	M.p. (°C)	Found (%) C	Found (%) H	Formula	Calc. (%) C	Calc. (%) H
(**6a**)	44	Oil	57.7	3.9	$C_8H_6O_4$	57.83	3.64
(**6b**)	60	46—49	64.8	6.4	$C_{12}H_{14}O_4$	64.85	6.35
(**6c**)	40	131—133[a]	61.9	5.25	$C_{10}H_{10}O_4$	61.85	5.19
(**6d**)	56	128—130[a]	55.1	4.2	$C_9H_8O_5$	55.10	4.11
(**6e**)	71	144—147[a]	66.5	3.8	$C_{12}H_8O_4$	66.67	3.73
(**6f**)	70	146—148[a]	52.7	3.4	$C_8H_6O_5$	52.75	3.32
(**6g**)	68	54—55[a]	52.8	3.25	$C_8H_6O_5$	52.75	3.32

[a] Decomposes on melting.

Table 2. I.r., u.v., ^{13}C n.m.r., and mass spectral data for compounds (**6a**—**g**)

Compound	$\nu_{max.}$/cm^{-1} [a]	$\lambda_{max.}$(EtOH)/nm (log ε)	δ_C/p.p.m.[b]	*m/z* (rel. int.%)
(**6a**)	3 448, 1 739, 1 626, 1 198	213 (3.88), 257 (3.86), 328 (3.49)	117.14 (C-3), 119.30 (C-1), 119.49 (C-5), 129.96 (C-6), 136.49 (C-4), 159.62 (C-2), 166.60 (CO_2H), 189.00 (CO)	166 (M^+, 20), 121 (100)
(**6b**)	3 460, 3 120, 2 940, 1 818, 1 730, 1 590, 1 413, 1 190	213 (4.22), 265 (3.99), 340 (3.54)	28.85 (CH_3), 34.37 (CCH_3), 115.11 (C-1), 119.2 (C-5), 130.02 (C-6), 134.74 (C-4), 137.77 (C-3), 161.72 (C-2), 164.31 (CO_2H), 194.85 (CO)	222 (M^+, 7), 176 (50), 161 (100), 148 (40), 133 (86), 106 (72)
(**6c**)	3 420, 2 920, 1 820, 1 722, 1 588, 1 250, 1 135, 1 035	218 (4.10), 269 (3.91), 345 (3.45)	15.93 (3-CH_3), 19.80 (6-CH_3), 120.38 (C-5), 129.47 (C-1), 123.16 (C-3), 132.32 (C-4), 135.11 (C-6), 155.99 (C-2), 170.37 (CO_2H), 190.08 (CO)	194 (M^+, 5), 148 (64), 120 (95), 105 (24), 91 (100)
(**6d**)	3 460, 3 200, 2 950, 1 740, 1 640, 1 485, 1 170, 1 032	224 (4.03), 261 (3.64), 289 (3.15), 360 (3.36)	57.29 (OCH_3), 116.35 (C-6), 117.53 (C-3), 120.48 (C-1), 126.27 (C-4), 152.80 (C-2), 153.84 (C-5), 168.92 (CO_2H), 191.33 (CO)	196 (M^+, 17), 151 (48), 124 (89), 109 (100)
(**6e**)	3 060, 1 718, 1 614, 1 210, 1 040	216 (4.37), 260 (4.37), 295 (3.89), 371 (3.70)	110.91 (C-2), 119.50 (C-4), 124.16 (C-9), 123.55, 124.71, 126.37, 127.70, and 132.72 (5 ArC), 137.24 (C-10), 161.68 (C-1), 165.31 (CO_2H), 191.47 (CO)	216 (M^+, 36), 171 (100), 143 (22), 115 (69)
(**6f**)	3 430, 3 170, 1 745, 1 620, 1 430, 1 230	209 (4.13), 228 (3.83), 284 (3.98), 310 (3.81)	102.41 (C-3), 109.10 (C-5), 110.53 (C-1), 132.87 (C-6), 163.28 (C-2), 165.63 (CO_2H), 166.40 (C-4), 187.91 (CO)	182 (M^+, 10), 137 (100)
(**6g**)	3 360, 1 735, 1 632, 1 460, 1 270, 1 050	216 (4.08), 272 (3.92), 346 (3.28)	119.36 (C-5), 119.88 (C-6), 120.61 (C-1), 121.24 (C-4), 146.04 (C-3), 149.14 (C-2), 166.46 (CO_2H), 189.66 (CO)	182 (M^+, 31), 137 (100)

[a] KBr disks, except (**6a**) neat. [b] For solutions in $(CD_3)_2SO$, relative to Me_4Si.

quenching of the reaction mixture with water, the 2-hydroxyarylglyoxylic acids (**6a**—**g**) were separated from the unchanged starting phenols by extraction with aqueous sodium hydrogen carbonate, acidification, extraction with methylene dichloride, and removal of the solvent. The results are illustrated in Table 1.

The carboxylic acids (**6**) are generated from the arylglyoxyl chloride intermediates (**5**) during the quenching procedure. When the reaction mixtures were quenched with reactants other than water, *e.g.* an amine or an alcohol, the final products incorporated the corresponding residue; *e.g.*, treatment of the reaction mixture from 2-t-butylphenol and oxalyl chloride with dimethylamine or isopropyl alcohol resulted in the production of 2-hydroxy-*N*,*N*-dimethyl-3-t-butylphenylglyoxylamide and isopropyl 2-hydroxy-3-t-butylphenylglyoxylate, respectively, in 60 and 76% isolated yields.

The structure elucidation was mainly based on the spectroscopic data (Table 2). The salient features of compounds (**6**) include the carbonyl absorption at 1 720—1 745 cm^{-1} in the i.r. spectra, and the three low-field absorptions (s) at δ 188—195 (C=O), 164—170 (CO_2H), and 145—161 p.p.m. (phenoxy carbon) in the ^{13}C n.m.r. spectra.

Mechanistically, it is reasonable to consider that compounds (**6**) in this *ortho*-specific acylation are formed by the intramolecular collapse of a magnesium chelate intermediate involving the aromatic substrate, the metal, and the acylating reactant. A molecular complex such as (**4**), in which the carbonyl carbon is in the proximity of the phenolic *ortho*-carbon, provides a rational model for this intermediate.

In conclusion, these results herein conform to our basic expectations: namely, that only those metal ions which are located at the phenolic hydroxy and which then produce metal-bonded electrophilic species may force a selective encounter of the reacting sites. In sharp contrast, if positive species (acylium ions, acid halide–oxonium complexes) freely react with the aromatic substrate,[7] then multidirectional and somewhat complicated reactions may occur.

Experimental

General points and methods for the preparation of metal phenolates are described in the preceding papers of this series.[1,2]

Preparation of 2-Hydroxyarylglyoxylic Acids (**6a**—**g**). *General Procedure.*—To a slurry of the appropriate bromomagnesium phenolate (**2**) (20 mmol, prepared from phenol and ethylmagnesium bromide) in toluene (50 ml), a solution of oxalyl chloride (**3**) (20 mmol) in toluene (20 ml) was added dropwise during 20 min. As oxalyl chloride was added the slurry became deep red, but the colour faded as the reaction

proceeded. The mixture was stirred for 7 h at room temperature under dry nitrogen, then quenched with water. After extraction with aqueous sodium hydrogen carbonate, the solution was acidified with hydrochloric acid (pH 1—2) and re-extracted with methylene dichloride. The extract was dried (sodium sulphate) and evaporated to dryness to afford the almost pure 2-hydroxyarylglyoxylic acids (**6**) as yellow solids. The purity of compounds (**6**) was checked by t.l.c. on silica gel plates using benzene–ethanol–ammonium hydroxide (28 : 57 : 14) as the eluant (intense dark-green spots with ferric chloride).

Preparative data and significant spectroscopic data for all synthesized arylglyoxylic acids (**6a–g**) are given in Tables 1 and 2.

Isopropyl 2-Hydroxy-3-t-butylphenylglyoxylate.—A mixture of 2-t-butylphenoxymagnesium bromide (20 mmol) and oxalyl chloride (20 mmol) in toluene (70 ml) was allowed to react at room temperature for 7 h. Anhydrous isopropyl alcohol (6.0 g, 100 mmol) in toluene (10 ml) was then added, and the mixture was stirred for 2 h. After aqueous quenching the reaction mixture was extracted with diethyl ether and the organic extracts were dried (Na_2SO_4) and evaporated to give a yellow oil (5.1 g). This residue was chromatographed on silica gel (500 g) and the column was eluted with ethyl acetate–hexane (10%) to give *isopropyl 2-hydroxy-3-t-butylphenylglyoxylate* (4.0 g, 76% on starting phenol); yellow oil, n_D^{16} 1.5286 (Found: C, 68.3; H, 7.9. $C_{15}H_{20}O_4$ requires C, 68.1; H, 7.63%); *m/z* 264 (M^+), and 177 (base, $M^+ - C_4H_7O_2$); $\nu_{max.}$ 3 450, 2 940, 1 730, and 1 610 cm^{-1}; δ 1.36 (6 H, d, *J* 2 Hz), 1.40 (9 H, s), 5.21 (1 H, hept., *J* 6 Hz), 6.6—7.6 (3 H, m), and 11.88 (1 H, s); $\lambda_{max.}$(ethanol) 213 (log ε 4.22), 265 (3.95), and 340 nm (3.48).

2-Hydroxy-N,N-dimethyl-3-t-butylphenylglyoxylamide.—A mixture of 2-t-butylphenoxymagnesium bromide (20 mmol) and oxalyl chloride (20 mmol) in toluene (70 ml) was allowed to react at room temperature for 7 h. A solution of *N,N*-dimethylamine (100 mmol) in toluene (10 mmol) was then added, and the mixture was stirred for 2 h. Work-up as above yielded *2-hydroxy-N,N-dimethyl-3-t-butylphenylglyoxylamide* (2.98 g, 60% on starting phenol) as a yellow viscous oil, n_D^{16} 1.5520 (Found: C, 67.3; H, 8.0; N, 5.5. $C_{14}H_{19}NO_3$ requires C, 67.44; H, 7.68; N, 5.62%); *m/z* 249 (M^+), and 177 (base, $M^+ - C_3H_6NO$); $\nu_{max.}$ 3 310, 2 960, and 1 660 cm^{-1}; δ 1.40 (9 H, s), 2.95 (3 H, s), 3.08 (3 H, s), 6.6—7.6 (3 H, m), and 12.05 (1 H, s); $\lambda_{max.}$(ethanol) 216 (log ε 4.27), 265 (4.09), and 338 nm (3.56).

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