Selectivity in Reactions between Metal Phenolates and Trichloroacetaldehyde; A Mild Synthesis of 2-(2,2,2-Trichloro-1-hydroxyethyl)-phenols

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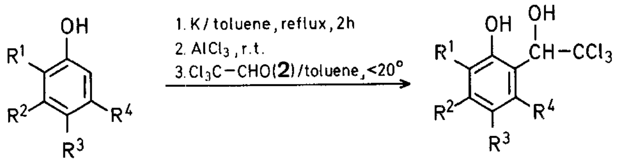
The Lewis acid-catalyzed reaction of electrophilic agents with aromatic compounds is one of the most widely studied processes of organic chemistry[1]. A preponderance of literature on the subject concerns reactions of neutral substrates. Reports of Lewis acid-promoted reactions involving aromatic anion salts are rare[2].

In a recent paper, we have described the use of aluminum chloride as an effective catalyst in the *C-ortho* site-specific isoprenylation of metal phenolates[3]. We now wish to report on an extension of that work as applied to the reaction between trichloroacetaldehyde (**2**) and phenols **1**[4,5].



1 **3**

It was found that a 1:1:1 mixture of the phenol **1**, its potassium salt, and aluminum chloride in toluene reacts cleanly with anhydrous trichloroacetaldehyde (**2**) at room temperature to give 2-(2,2,2-trichloro-1-hydroxyethyl)-phenols **3** in one step with virtually complete *ortho*-selectivity, as illustrated in Table 1 (*o*:*p* ratio ≥98:2 as determined by G.L.C., conditions: SE-30, 5% on Chromosorb W). Structure **3** has been assigned to the products on the bases of microanalytical, I.R., U.V., and ^{1}H-N.M.R. spectral data (Table 2).

The synthesis outlined in this report appears to constitute an efficient method for the *C-ortho* site-specific introduction of trichloro-hydroxyethyl group into a variety of phenol nuclei[5]. The yield exceeds 90% in all cases and the method avoids the use of strong conditions or tedious workup procedures.

Further synthetically useful applications of this unusual aluminum chloride-catalyzed electrophilic substitution using metal phenolates are currently being explored.

2-(2,2,2-Trichloro-1-hydroxyethyl)-phenol (3a); Typical Procedure: A dry 500-ml three-necked, round bottomed flask containing a magnetic stirring bar, equipped with a reflux condenser and a pressure-equalizing dropping funnel fitted with a gas-inlet tube, is throughly purged with dry, oxygen-free nitrogen. To the flask are added potassium pellets (1.95 g, 0.05 mol), phenol (9.4 g, 0.1 mol), and anhydrous toluene (200 ml). The mixture is heated under reflux with stirring until all of the potassium has dissolved (~2 h). The slurry is cooled to room temperature and aluminum chloride (6.6 g, 0.05 mol) is then added. The slurry is heated under reflux with stirring for 10 min, while a stream of dry nitrogen is passed through the apparatus. The resulting opalescent solution is cooled to/or below 20° and a solution of anhydrous trichloroacetaldehyde (**2**; 14.8 g; 0.1 mol) in toluene (100 ml) added dropwise over a period of ~15 min. After the addition is complete, the mixture is allowed to stand overnight, then diluted with a saturated aqueous ammonium chloride solution and extracted with ether. The organic layer is washed with water and dried with anhydrous magnesium sulphate. Removal of the solvent affords crude **3a** as a viscous liquid which solidifies on cooling; yield: 23.8 g. This solid is recrystallized from hexane/benzene, 8:2 to give pure **3a**; colourless needles; yield: 22.1 g (92% based on introduced phenol); m.p. 58–59°; Lit. [5], m.p. 60°.

Financial support from C.N.R., Rome, Italy, is gratefully acknowledged.

Received: June 25, 1979

0039-7881/79/1032-0824 $ 03.00

Table 1. 2-(2,2,2-Trichloro-1-hydroxyethyl)-phenols **3a-k** Prepared

Product No.	R^1	R^2	R^3	R^4	Yield[a] [%]	m.p.[b] (solvent)	Molecular formula[c] or Lit. m.p.	
3a	H	H	H	H	92	58-59° (8:2 hexane/benzene)	60°[5]	
3b	H_3C	H	H	H	94	91-92° (8:2 hexane/benzene)	$C_9H_9Cl_3O_2$	(255.3)
3c	H	H	H_3C	H	95	148° (PE)	147.5°[4c]	
3d	H	H	Cl	H	95	138-140° (benzene)	$C_8H_6Cl_4O_2$	(275.9)
3e	H	HO	H	H	90	176° (benzene)	176°[4b]	
3f	t-C_4H_9	H	H	H	98	89-90° (PE)	$C_{12}H_{15}Cl_3O_2$	(297.6)
3g	H	$(H_3C)_2N$	H	H	91	110° dec. (benzene)[d]	$C_{10}H_{12}Cl_3NO_2$	(284.5)
3h	H	H	C_8H_{17}[e]	H	97	108-109° (7:3 hexane/benzene)	$C_{16}H_{23}Cl_3O_2$	(353.4)
3i	t-C_4H_9	H	H_3C	H	95	61-62° (hexane)	$C_{13}H_{17}Cl_3O_2$	(311.4)
3k	H	H	CH_2-CH_2-		98	133° dec. (benzene)	$C_{12}H_9Cl_3O_2$	(291.4)

[a] Yield of recrystallized product based on 1; purity >98% as determined by ^{1}H-N.M.R. and T.L.C. on silica gel plates with hexane/ethyl acetate, 8:2 as eluent.

[b] Uncorrected; in open capillary tubes.

[c] The microanalyses were in good agreement with the calculated values (C ±0.25, H ±0.16, Cl ±0.22, N ±0.02).

[d] Decomposition without melting.

[e] 1,1,3,3-Tetramethylbutyl.

Table 2. Characteristic I.R., U.V., and ^{1}H-N.M.R. Spectroscopic Data of Products **3a-k**

Product	I.R. (KBr)[a] ν [cm^{-1}]	U.V. (C_2H_5OH)[b] λ_{max} [nm] (ε)	^{1}H-N.M.R.[c,d] δ [ppm]
3a	3030, 1570, 1430, 1220, 1060, 750	220 (6035), 283 (3018)	5.35 (bs, 1H, $C\underline{H}OH$); 5.80 (bs, 1H, $CHO\underline{H}$); 6.5-7.5 (m, $4H_{arom}$); 8.18 (bs, 1H, OH)
3b	3005, 1551, 1430, 1207, 1054, 733	222 (6768), 287 (3639)	2.21 (s, 3H, CH_3); 5.22 (bs, 1H, $C\underline{H}OH$); 5.81 (bs, 1H, $CHO\underline{H}$); 6.5-7.2 (m, $3H_{arom}$); 8.25 (s, 1H, OH)
3c	3012, 1550, 1424, 1205, 1050, 743	222 (6749), 290 (3624)	2.30 (s, 3H, CH_3); 5.27 (bs, 1H, $C\underline{H}OH$); 5.80 (bs, 1H, $CHO\underline{H}$); 6.5-7.6 (m, $3H_{arom}$); 8.20 (s, 1H, OH)
3d	3250, 1580, 1400, 1220, 1050, 735	230 (6769), 291 (2994)	5.52 (d, 1H, $C\underline{H}OH$, $J=3$ Hz); 7.20 (d, 1H, $CHO\underline{H}$, $J=3$ Hz); 6.7-7.6 (m, $3H_{arom}$); 10.15 (s. 1H, OH)
3e	3040, 1550, 1430, 1200, 1050, 765	225 (7690), 294 (9473)	5.50 (bs, 1H, $C\underline{H}OH$); 5.86 (bs, 1H, $CHO\underline{H}$); 6.5-7.5 (m, $3H_{arom}$); 8.19 and 9.01 (s, 1H, OH)
3f	3300, 1580, 1440, 1225, 1054, 755	224 (5617), 287 (3209)	1.40 (s, 9H, CH_3); 4.05 (d, 1H, $CHO\underline{H}$, $J=3$ Hz); 5.25 (d, 1H, $C\underline{H}OH$, $J=3$ Hz); 6.6-7.4 (m, $3H_{arom}$); 8.00 (s, 1H, OH)
3g	3200, 1540, 1440, 1250, 1070, 765	226 (11 095), 267 (11692), 295 (6245)	2.87 (s, 6H, CH_3); 5.48 (bs, 1H, $C\underline{H}OH$); 6.65 (bs, 1H, $CHO\underline{H}$); 7.2-7.6 (m, $3H_{arom}$); 9.40 (s, 1H, OH)
3h	2830, 2645, 1420, 1236, 1041, 722	221 (8223), 288 (2799)	0.77 (s, 9H, CH_3); 1.35 (s, 6H, CH_3); 1.76 (s, 2H, CH_2); 4.83 (bs, 1H, $CHO\underline{H}$); 5.70 (bs, 1H, CHOH); 6.6-7.7 (m, $3H_{arom}$); 8.66 (s, 1H, OH)
3i	3100, 2742, 1453, 1290, 1070, 760	219 (7567), 292 (3347)	1.42 (s, 9H, CH_3); 2.21 (s, 3H, CH_3); 4.86 (bs, 1H, $CHO\underline{H}$); 5.31 (bs, 1H, $C\underline{H}OH$); 7.02 (m, $2H_{arom}$); 8.07 (s, 1H, OH)
3k	3124, 1610, 1580, 1220, 1080, 745	239 (15120), 281 (5223), 336 (3161)	6.25 (d, 1H, $C\underline{H}OH$, $J=3.5$ Hz); 7.30 (d, 1H, $CHO\underline{H}$, $J=3.5$ Hz); 6.9-7.9 (m, $5H_{arom}$); 8.86 (m, $1H_{arom}$); 10.22 (s, 1H, OH)

[a] Recorded on a Perkin-Elmer 257 spectrometer.

[b] Recorded on a Perkin-Elmer 475 spectrophotometer.

[c] Recorded on a Varian EM 360 instrument at 60 MHz with TMS as internal standard; solvent, $CDCl_3$ except **3d, 3g,** and **3k** in DMSO-d_6.

[d] These alcohols failed to give the expected multiplicities for the hydroxy and methine resonances, except **3d, 3f,** and **3k** (Ref. [6]).

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