A Novel Selective Oxidation of 5-Substituted 2-Hydroxy-3-hydroxymethylbenzaldehydes

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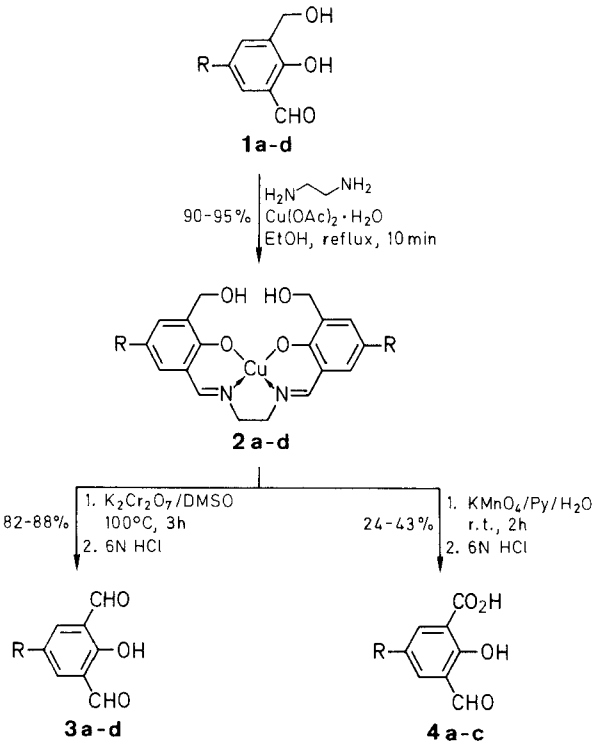
5-Substituted 2-hydroxy-1,3-benzenedicarbaldehydes **3** and 5-substituted 3-formyl-2-hydroxybenzoic acids **4** were prepared by selective oxidation of 5-substituted 2-hydroxy-3-(hydroxymethyl)-benzaldehydes **1** in a one-pot reaction. Compounds **1** were reacted with ethylenediamine and copper acetate to produce the complexes **2** as intermediates, in which formyl and phenolic hydroxy groups were protected in the subsequent oxidation step.

The derivatives of 2-hydroxy-1,3-benzenedicarbaldehyde (**3**, R = H) and 3-formyl-2-hydroxybenzoic acid (**4**, R = H) have been frequently used as starting materials in the synthesis of macrocyclic compounds,[1-3] and as ligands in transition metal multinuclear complexes.[4,5] However, the synthesis of these compounds remained cumbersome and furnished low yields only.[6-9]

We present here a novel synthesis of 5-substituted 2-hydroxy-1,3-benzenedicarbaldehydes **3** and 5-substituted 3-formyl-2-hydroxybenzoic acids **4**, respectively, by selective oxidation of 5-substituted 2-hydroxy-3-(hydroxymethyl)benzaldehydes **1**. The compounds **1** were obtained by the selective partial oxidation of the 4-substituted 2,6-bis(hydroxymethyl)phenols.[10,11]

The aldehydes **1** were reacted with ethylenediamine and copper acetate to furnish the complexes **2**. The structure of **2** has been established by elemental analyses and spectral data,[12] indicating that nitrogen atoms and the oxygen atoms of the phenolic hydroxy groups are coordinated to the copper atom, whereas the aliphatic hydroxy groups remain in an uncoordination state. Thus, aldehyde and phenolic functions are protected by template formation in the subsequent oxidation step.



1–4	a	b	c	d
R	Cl	Br	Me	OMe

Oxidation of **2a–2d** with potassium dichromate in dimethyl sulfoxide, followed by hydrolysis with aqueous hydrochloric acid yielded the dialdehydes **3a–3d**, whereas oxidation using a solution of potassium permanganate in aqueous pyridine provided the carboxylic acid aldehydes **4a–4c**. However, the methoxy derivative **2d** failed to afford the corresponding carboxylic acid aldehyde **4d**.

The synthesis of compounds **3** and **4**, respectively, were also accomplished, in an one-pot procedure without isolation of the intermediate complexes **2**.

All melting points are uncorrected and measured with a Yanaco MP-500 apparatus. IR spectra were recorded on a Nicolet FT-IR 170 SX spectrophotometer, ^{1}H-NMR spectra on a Varian FT-80 spectrometer and mass spectra on a ZAB-HS spectrometer.

5-Substituted 2-Hydroxy-3-hydroxymethylbenzaldehydes 1; Typical Procedure:[11]

4-Substituted 2,6-bis(hydroxymethyl)phenols (R = Cl, Br, Me, OMe) (10 g, ~0.05 mol) is stirred with a suspension of active MnO_2 (50 g, 0.57 mol) in $CHCl_3$ (300 mL) at r.t. for 5–16 h. The mixture is filtered and the filtrate evaporated to give **1** as yellow needles ($EtOH/H_2O$); yield: 40–68%; mp[10] 87–88°C, 100–101°C, 75–76°C, 89–91°C for **1a–d** respectively.

***N,N'*-Ethylenbis(5-chloro-3-hydroxymethylsalicylaldimino)copper (2a); General Procedure:**

To a stirred solution of **1a** (1.87 g, 10 mmol) in anhydrous EtOH (80 mL), is added ethylenediamine (0.35 g, 6 mmol). The mixture is refluxed for 10 min followed by addition of $Cu(OAc)_2 \cdot H_2O$ (2.0 g, 10 mmol) in H_2O (20 mL) and stirred for an additional 1 h at reflux temperature. The separated solid is filtered hot, washed with hot EtOH (2 × 20 mL) to give **2a** as brown needles; yield: 2.18 g (95%) (Table 1).

Table 1. Complexes **2** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})
2a	95	>250	$C_{18}H_{16}Cl_2CuN_2O_4$ (458.8)	3380, 1627, 1295, 592, 496, 476
2b	92	>250	$C_{18}H_{16}Br_2CuN_2O_4$ (547.7)	3363, 1624, 1294, 591, 492, 471
2c	90	>250	$C_{20}H_{22}CuN_2O_4$ (418.0)	3391, 1626, 1285, 587, 497, 478
2d	90	>250	$C_{20}H_{22}CuN_2O_6$ (450.0)	3426, 1610, 1298, 594, 515, 474

[a] Satisfactory microanalyses obtained: C, H, N ±0.3, Cu ±0.5.

5-Chloro-2-hydroxy-1,3-benzenedicarbaldehyde (3a); Typical Procedure:

A mixture of the complex **2a** (2.3 g, 5 mmol) and $K_2Cr_2O_7$ (2.94 g, 10 mmol) in DMSO (50 mL) is stirred at 100°C for 3 h. The mixture is acidified with 6 N aq HCl (100 mL), then refluxed for 5 min, cooled to r.t. and extracted with Et_2O (3 × 50 mL). The combined extracts are washed with H_2O (2 × 50 mL) and dried

(Na_2SO_4). Evaporation of the solvent affords the crude product, which is recrystallized from $EtOH/H_2O$; yield: 1.57 g (85%) (Table 2).

Table 2. Compounds **3** and **4** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C)
3a	87 (85)	122–123	122–124[8]
3b	85 (86)	137–138	137–139[8]
3c	80 (82)	132–133	132–133[8]
3d	90 (88)	137–139	138–139[8]
4a	35 (40)	222–224	$C_8H_5ClO_4$ (200.6)
4b	40 (43)	204–206	$C_8H_5BrO_4$ (245.0)
4c	25 (25)	180–182	$C_9H_8O_4$ (180.2)

[a] Isolated yields. The yields given in the parenthesis refer to products from the procedures in which the complexes **2** were separated.

[b] Satisfactory microanalyses obtained: C, H ±0.3.

5-Chloro-3-formyl-2-hydroxybenzoic Acid (4a); Typical Procedure:
To a stirred solution of the complex **2a** (2.3 g, 5 mmol) in pyridine/H_2O (5:1, 180 mL), is added powdered $KMnO_4$ (6.32 g, 40 mmol) and the mixture is stirred for 2 h at r.t. An aqueous solution of $NaHSO_3$ is added until the pinkish color of the mixture has disappeared. The mixture is acidified with 6N aq HCl to pH = 2, refluxed for 5 min, cooled to r.t. extracted with Et_2O (3 × 50 mL), and dried (Na_2SO_4). The solvent is evaporated and the residue is recrystallized from $EtOH/H_2O$ to afford pure **4a**; yield: 0.80 g (40%) (Tables 2 and 3).

Table 3. Spectral Data of New Compounds **4a–c**

Product	IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS), δ	MS (70 eV) m/z (%)
4a	3450, 3060, 2880, 1670, 1595, 930	5.64 (s, 1H, ArOH), 7.81–8.01 (m, $2H_{arom}$), 10.28 (s, 1H, CHO)	200 (M^+, 52), 172 (M^+–28, 56), 154 (M^+–46, 100)
4b	3450, 3070, 2880, 1665, 1559, 927	5.13 (s, 1H, ArOH), 7.96–8.13 (m, $2H_{arom}$), 10.27 (s, 1H, CHO)	244 (M^+, 40), 216 (M^+–28, 37), 194 (M^+–46, 100)
4c	3497, 1715, 1665, 1660, 915	5.71 (s, 1H, ArOH), 7.69–7.88 (m, $2H_{arom}$), 10.32 (s, 1H, CHO)	180 (M^+, 28), 152 (M^+–28, 27), 134 (M^+–46, 100)

One-Pot Preparation of 3a and 4a; Typical Procedures:

5-Chloro-2-hydroxy-1,3- benzenedicarbaldehyde (**3a**): To a solution of **1a** (1.78 g, 10 mmol) and ethylenediamine (0.30 g, 5 mmol) in DMSO (20 mL) is added a solution of $Cu(OAc)_2 \cdot H_2O$ (1.1 g, 5.5 mmol) in DMSO (20 mL) and the mixture is stirred at r.t. for 30 min. A solution of $K_2Cr_2O_7$ (2.94 g, 10 mmol) in DMSO (30 mL) is then added, the mixture is stirred at 100°C for 3 h and worked up as above for the preparation of **3a** from the complex **2a**; yield: 1.60 g (87%) (Table 2).

5-Chloro-3-formyl-2-hydroxybenzoic Acid (**4a**): To a solution of **1a** (1.78 g, 10 mmol) and ethylenediamine (0.30 g, 5 mmol) in pyridine (150 mL) is added a solution of $Cu(OAc)_2 \cdot 2H_2O$ (1.1 g, 5.5 mmol) in H_2O (30 mL) and the mixture is stirred at r.t. for 30 min. Then powdered $KMnO_4$ (6.32 g, 40 mmol) is added, the mixture stirred for 2 h and worked up as above for the preparation of **4a** from the complex **2a**; yield: 0.70 g (35%) (Tables 2 and 3).

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