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## Formylation of Phenols with Electron-withdrawing Groups in Strong Acids. Synthesis of Substituted Salicylaldehydes

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Salicylaldehydes with electron-withdrawing groups, *i.e.*, 2-hydroxy-5-nitrobenzaldehyde (**2a**), methyl 3-formyl-4-hydroxybenzoate (**2b**), methyl 5-chloro-3-formyl-2-hydroxybenzoate (**2c**), 3,5-dichloro-2-hydroxybenzaldehyde (**2d**), 5-cyano-2-hydroxybenzaldehyde (**2e**), and 5-fluoro-2-hydroxybenzaldehyde (**2f**), were synthesized by the formylation of the corresponding phenols (**1a–f**) with hexamethylenetetramine in 75% polyphosphoric acid, methanesulfonic acid, or trifluoroacetic acid. The yields of these reactions were better than those of the Duff reaction.

**Keywords**—Duff reaction; formylation; hexamethylenetetramine; methanesulfonic acid; phenol; polyphosphoric acid; salicylaldehyde trifluoroacetic acid

The formylation of phenols with electron-withdrawing groups is, in general, difficult. However, Duff and other workers have reported that phenols with carboxyl,<sup>1)</sup> carbamoyl,<sup>2)</sup> alkoxycarbonyl,<sup>3)</sup> bromo,<sup>4)</sup> or chloro groups<sup>4)</sup> react with hexamethylenetetramine (HMT) in acidic media to yield the salicylaldehydes. This characteristic reaction is called the Duff reaction.

In this work, we describe the synthesis of salicylaldehydes which have electron-withdrawing groups, such as nitro, methoxycarbonyl, cyano, chloro, and fluoro groups, by the formylation of the corresponding phenols with HMT in acidic media. We tried to formylate 4-nitrophenol with HMT in acetic acid or boric acid, but without success; the formylations of such phenols were achieved by using 75% polyphosphoric acid (PPA), methanesulfonic acid (MSA), or trifluoroacetic acid (TFA) as acidic medium.

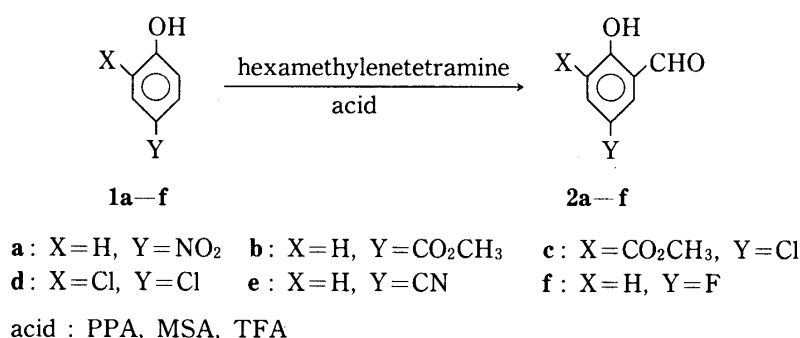


Chart 1

The formylations of 4-nitrophenol (**1a**), methyl 4-hydroxybenzoate (**1b**), methyl 5-chloro-2-hydroxybenzoate (**1c**), 2,4-dichlorophenol (**1d**), 4-cyanophenol (**1e**), and 4-fluorophenol (**1f**) were performed with HMT in 75% PPA, MSA, or TFA. 2-Hydroxy-5-nitrobenzaldehyde (**2a**), methyl 3-formyl-4-hydroxybenzoate (**2b**), methyl 5-chloro-3-formyl-2-hydroxybenzoate (**2c**), 3,5-dichloro-2-hydroxybenzaldehyde (**2d**), 5-cyano-2-hydroxybenzaldehyde (**2e**), and 5-fluoro-

2-hydroxybenzaldehyde (**2f**) were obtained in the yields shown in Table I. The melting point of **2a**, **2b**, **2d**, and **2f** were consistent with those given in the literature.<sup>5-7)</sup> Compound (**2e**) was reported<sup>8)</sup> but **2c** is new. The structures of these compounds (**2a—f**) were confirmed by infrared (IR), mass, and proton-nuclear magnetic resonance (<sup>1</sup>H-NMR) spectroscopy.

TABLE I. Formylation of Phenols (**1a—f**) by Using Hexamethylenetetramine (HMT) in Strong Acidic Media (PPA, MSA, and TFA)<sup>a)</sup>

Starting material	HMT (mmol)	Acidic media	Bath temp. (°C)	Time (h)	Yield of <b>2a—f</b> (%)
<b>1a</b>	10	PPA	100	2	69
	20	MSA	100	2	57
	20	TFA	100	6	35
<b>1b</b>	10	PPA	100	0.75	61
	20	MSA	100	0.33	51
	20	TFA	80	3	30
<b>1c</b>	10	PPA	100	5	6
	20	MSA	130	5	77
	20	TFA	100	5	Trace <sup>b)</sup>
<b>1d</b>	10	PPA	100	1.5	5
	20	MSA	100	2	50
	20	TFA	100	2	16
<b>1e</b>	10	PPA	100	1	— <sup>c)</sup>
	20	MSA	r.t. <sup>d)</sup>	1	— <sup>c)</sup>
	20	TFA	100	7	41
<b>1f</b>	10	PPA	100	0.5	14
	20	MSA	r.t. <sup>d)</sup>	1	4
	20	TFA	100	2	16

a) PPA=75 % polyphosphoric acid; MSA=methanesulfonic acid; TFA=trifluoroacetic acid.

b) The starting material was almost entirely recovered.

c) An insoluble solid was obtained.

d) After the addition of HMT, the mixture was stirred at room temperature.

The salicylaldehydes **2a** and **2b** were synthesized in yields of 69 and 61%, respectively, by the reaction of phenols **1a** and **1b** in 75% PPA. The yields of those reactions were better than when MSA and TFA were used as acidic media. Compounds **2a—d** were synthesized in yields of 57, 51, 77, and 50%, respectively, by the reactions of phenols **1a—d** in MSA. The synthesis of **2d** in the yield of 7% in boric acid has been reported.<sup>1c)</sup> When MSA was used as an acidic medium, the reaction was vigorously exothermic. Accordingly, the addition of HMT has to be controlled with care so that the temperature can be kept within the range of 80—90°C.

The reaction of **1e** with HMT in TFA gave **2e** in 41% yield. However, the formylation in PPA and MSA gave an insoluble solid material, and the desired compound was not obtained. The synthesis of **2f** proceeded, but with poor yields, in PPA, MSA, and TFA.

It was found that the synthesis of the salicylaldehydes was facilitated by the use of the present methods in the reactions of various phenols with electron-withdrawing groups. Better yields of these compounds were obtained than when the Duff reaction was used.

### Experimental

The IR spectra were recorded with a Hitachi 260-10 spectrometer, the mass spectrum (MS), with a JEOL JMS-D300 spectrometer, and the <sup>1</sup>H-NMR spectra, with a JEOL FX100 spectrometer. The melting points were measured with a Yanagimoto micromelting-point apparatus and are uncorrected.

**Formylation in Polyphosphoric Acid**—HMT (1.4 g, 10 mmol) was added in portions to a stirred mixture of a phenol (**1a—f**, 10 mmol) and 75% PPA (8 ml) at 100°C on an oil bath. The stirring was continued at 100°C for the time shown in Table I. After the reaction, cold H<sub>2</sub>O (40 ml) was added, and the mixture was allowed to cool to room temperature while being stirred. The corresponding salicylaldehyde (**2a—d** or **2f**)

was separated from the reaction mixture by extraction or filtration. The product was purified by column-chromatography over silica gel, using  $\text{CH}_2\text{Cl}_2$ , or by recrystallization.

**Formation in Methanesulfonic Acid**—HMT (2.8 g, 20 mmol) was added in portions to a mixture of a phenol (1a—f, 10 mmol) and MSA (8 ml), with stirring. The reaction mixture was carefully maintained at 80—90°C (these reactions were accompanied by a vigorous heat evolution). After the heat evolution had ceased, the stirred reaction mixture was heated on the oil bath at a definite temperature. After the reaction, conc. HCl (2 ml) and  $\text{H}_2\text{O}$  (30 ml) were added, and the mixture was stirred for 30 min. Then, the corresponding salicylaldehyde (2a—d or 2f) was obtained as has been described above.

In the formylations of 1e and 1f, the reaction mixture was stirred without heating for 1 h after the addition of HMT.

**Formylation in Trifluoroacetic Acid**—HMT (2.8 g, 20 mmol) was added all at once to a stirred mixture of a phenol (1a—f, 10 mmol) and TFA (8 ml). After the heat evolution had ceased, the reaction mixture was heated with stirring. The reaction mixture was then cooled on the ice bath, and 50%  $\text{H}_2\text{SO}_4$  (5 ml) and  $\text{H}_2\text{O}$  (30 ml) were added; the stirred mixture was maintained for 30 min at room temperature. The corresponding salicylaldehyde (2a—f) was then obtained in the manner described above.

2-Hydroxy-5-nitrobenzaldehyde (2a): Colorless prisms; mp 128°C (aq. ethanol); lit.<sup>5)</sup> mp 133—134°C.

Methyl 3-Formyl-4-hydroxybenzoate (2b): Colorless needles; mp 78—80°C (aq. methanol); lit.<sup>6)</sup> mp 80—81°C.

Methyl 5-Chloro-3-formyl-2-hydroxybenzoate (2c): Colorless prisms; mp 129—130°C (aq. methanol). IR (KBr): 1684  $\text{cm}^{-1}$ . MS  $m/e$ : 214 ( $\text{M}^+$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 11.33 (1H, s, OH), 10.38 (1H, s, CHO), 7.99 (1H, d,  $J=2.9$  Hz, aromatic H), 7.91 (1H, d,  $J=2.9$  Hz, aromatic H), 3.99 (1H, s,  $\text{OCH}_3$ ). Anal. Calcd for  $\text{C}_9\text{H}_7\text{ClO}_4$ : C, 50.37; H, 3.29. Found: C, 50.10; H, 3.35.

3,5-Dichloro-2-hydroxybenzaldehyde (2d): Pale yellow prisms; mp 92°C (acetic acid); lit.<sup>1a)</sup> mp 95°C.

5-Cyano-2-hydroxybenzaldehyde (2e):<sup>8)</sup> Colorless plates; mp 147°C (aq. methanol). IR (KBr): 2210 ( $\text{C}\equiv\text{N}$ ), 1655 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ . MS  $m/e$ : 147 ( $\text{M}^+$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 11.40 (1H, s, OH), 9.88 (1H, s, CHO), 7.90 (1H, d,  $J=2.1$  Hz, aromatic H), 7.73 (1H, dd,  $J=2.1$  and 8.7 Hz, aromatic H), 7.07 (1H, d,  $J=8.7$  Hz, aromatic H).

5-Fluoro-2-hydroxybenzaldehyde (2f): Colorless plates; mp 82°C (aq. methanol); lit.<sup>7)</sup> mp 82—84°C.

#### References and Notes

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