Selective Reactions between Phenols and Formaldehyde. A Novel Route to Salicylaldehydes

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Treatment of phenols (1) with 2 mol equiv. of paraformaldehyde in aprotic and poorly electron-donating solvents in the presence of selected metal halides coupled with suitable bases produces salicylaldehydes (3) in high yields. The route is highly selective for *ortho*-formylation and also specific towards monoformylation. The crucial role of added bases is emphasized.

SALICYLALDEHYDES and their simple derivatives are a class of substances of great synthetic and industrial significance.[1] Thus, much interest has been directed towards the search for new and convenient approaches to these compounds as well as to the improvement of their classical synthesis.

In 1965 one of us,[2] utilizing phenoxymagnesium bromide and triethyl orthoformate as formylating agent, reported a selective synthesis of salicylaldehydes while a second and more efficient route was reported recently by us.[3] In the latter case the strategy is based on form-aldehyde as a formylating agent and, once more, on magnesium phenoxides as *ortho*-directive substrates. Although this synthesis is *ortho*-specific and general, its applicability on a large scale is seriously restrained both by the need to use a considerable amount of toxic hexamethylphosphoramide (HMPA) and the troublesome preparation of magnesium phenolates.

A more extensive investigation has now been undertaken, directed towards a method of real synthetic and industrial utility. The present report describes a new convenient synthesis of salicylaldehydes.†

RESULTS AND DISCUSSION

The first system studied was the tin(IV) tetrachloride-catalysed condensation between phenol (1a) and para-formaldehyde. Table 1 shows that using tin(IV) tetra-chloride [0.1 mol per mol of (1a)] in toluene at 100 °C (12 h), a very low yield (*ca.* 2%) of salicylaldehyde (3a) was obtained, whereas the bulk of the reaction product was a glassy resin.‡ On the other hand, using 0.1 mol of tin(IV) tetrachloride combined with 0.4 mol of an amine such as tri-n-octylamine, (3a) could be obtained, free from polymeric materials, in a high yield with virtually complete selectivity. Low concentrations of amine gave a resin containing less of (3a). The maximum yield was reached using 4 mol per mol of tin(IV) tetrachloride, when (3a) was the sole reaction product. With >4 mol per mol a progressive decrease of phenol conversion was observed until no reaction occurred. A similar result was obtained using tin(II) or iron(III) chloride, whereas

aluminium trichloride or copper(II) bromide were found to be much less efficient catalysts.

In further experiments we examined the influence of basic additives on the yield of (3a). Table 2 shows the yield in the run with trimethylamine to be much poorer than that using trioctylamine. A similar but more remarkable difference in the yields was shown in the runs with pyridine and 2,6-lutidine. Most probably, steric

TABLE 1

Lewis-acid-catalysed reactions between phenol (1a) and paraformaldehyde in the presence of varied amounts of trioctylamine [a]

Run	Catalyst	Trioctylamine (mmol)	Conversion (%) [b]	Yield of (3a) (%) [b]
1	SnCl$_4$	None	94	2 [c]
2	SnCl$_4$	10	86	14 [d]
3	SnCl$_4$	20	80	44
4	SnCl$_4$	40	78	78
5	SnCl$_4$	60	59	52
6	SnCl$_4$	100	5	ND [e]
7	SnCl$_2$	40	76	70
8	FeCl$_3$	40	60	50
9	AlCl$_3$	40	30	14
10	CuBr$_2$	40	15	5

[a] Reaction conditions: (1a) (100 mmol), paraformaldehyde (220 mmol), catalyst (10 mmol), toluene (200 ml) at 100 °C for 8 h. [b] By g.l.c. analyses, using an internal standard. [c] 9.3 g of a glassy resin also formed. [d] 7.1 g of a glassy resin also formed. [e] (3a) not detected.

requirements of bases play an important role in this reaction, so that more hindered compounds are more efficient than less hindered ones.

We also tested other additives such as tributyl phosphite, dimethoxyethane, and glyme. While these reactions proceeded well, they failed to offer very much in either yield or selectivity, indicating that weak bases are much less efficient than stronger ones.

Next, the effect of a different solvents was tested. As shown in Table 3, the donating strength of the solvent has a substantial influence on the yield of (3a). While aprotic poorly donating compounds such as aromatic and aliphatic hydrocarbons are good solvents, strong donors cause a sharp drop in reactivity.

These observations lead us to postulate the mechanis-

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† The method described in this paper has been patented (G. Casnati, G. Casiraghi, G. Puglia, G. Sartori, G. Terenghi, *Ital. Pat. Appl.* 26,270 A/76/1976; *Ger. Offen* 2,736,523/1977; G. Casiraghi, G. Casnati, G. Sartori, and L. Bolzoni, *Ital. Pat. Appl.* 20,139 A/78/1978).

‡ Accurate [13]C n.m.r. analysis showed that this resin was essentially a mixture of randomly linked methylene polyphenol derivatives (E. Dradi, G. Casiraghi, and G. Casnati, *Chem. and Ind.*, 1978, 627).

tic pathway depicted in the Scheme for the tin(IV) tetra-chloride + tertiary-amine-catalysed condensation of phenol with paraformaldehyde. Initially [equation (a)], the phenol (1a) reacts with tin(IV) tetrachloride giving the phenoxide intermediate (4). The resulting hydrogen

TABLE 2

Influence of additive on the yield of salicylaldehyde (3a) [a]

Run	Additive	Yield of (3a) (%) [b]
1	Me₃N	58 (84)
2	Bu₃N	59 (94)
3	Trioctylamine	78 (100)
4	Pyridine	40 (81)
5	α-Picoline	68 (90)
6	2,6-Lutidine	80 (99)
7	P(Bu)₃	28 (60)
8	Dimethoxyethane	15 (34)
9	Glyme	14 (33)

[a] Reaction conditions: (1a) (100 mmol), paraformaldehyde (220 mmol), tin(IV) tetrachloride (10 mmol), additive (40 mmol), toluene (200 ml) at 100 °C for 8 h. [b] By g.l.c. analysis; values in parentheses refer to yields based on unrecovered (1a).

chloride which could bring about uncontrolled acid-catalysed phenol–formaldehyde condensation, is trapped by the tertiary amine. In support of this assumption, addition of 4 molar equivalents of trioctylamine to trap the hydrogen chloride liberated in the reaction between phenol and tin(IV) tetrachloride raised the yield of (3a) dramatically as shown by comparing runs 1 and 4 in Table 1. The second stage [equation (b)] is the inter-action between (4) and formaldehyde giving an active oriented complex (5), in which the metal atom serves as a link between the reaction partners. Such interaction has probably two main consequences: (i) simultaneous activation of both reaction partners (formaldehyde by co-ordination with the metal atom and phenol by en-hancing nucleophilicity of the nucleus itself) and (ii) orientation and close contact of partners enabling the formaldehyde to enter easily into the ortho-position of the phenolic ring. The formation of such an oriented π

TABLE 3

Influence of solvent on the yield of salicylaldehyde (3a) [a]

Run	Solvent	DN/kcal mol⁻¹ [b]	Yield of (3a) (%) [c]
1	Benzene [d]	0.1	76 (100)
2	Toluene		78 (100)
3	Decalin		63 (90)
4	Acetonitrile [d]	14.1	21 (73)
5	Dioxan [d]	14.8	20 (71)
6	Dimethoxyethane	24.0	Traces
7	Dimethylformamide	27.0	ND [e]
8	HMPA	35.8	ND [e]

[a] Reaction conditions: (1a) (100 mmol), paraformaldehyde (220 mmol), tin(IV) tetrachloride (10 mmol), trioctylamine (40 mmol), solvent (200 ml), at 100 °C for 8 h. [b] Donor Number values are taken from V. Gutman, Coord. Chem. Rev., 1976, 18, 225. [c] By g.l.c. analysis; values in parentheses refer to yields based on unrecovered (1a). [d] Experiments were carried out in sealed ampoules with stirring. [e] (3a) not detected.

complex has been proposed to explain similar ortho-specific electrophilic substitutions involving metal phenolates,[3,4] anilides,[5] and benzyl–metal derivatives.[6]

The subsequent intramolecular collapse of (5)

[equation (c)] leads to the saligenol derivative (2) prob-ably via the dienone (6). At this point we would emphasize the unique role played by added amines, as illustrated in Table 2. Since donor agents which could compete with formaldehyde for co-ordination sites of the metal atom do not favour the formation of the active species (5), one can say with confidence that bases which form more stable complexes with (4) are less effective donor agents and vice versa. The trioctylamine–(4) and 2,6-lutidine–(4) complexes are considered to be unstable due to steric strain.[7] Whereas the comparatively stable
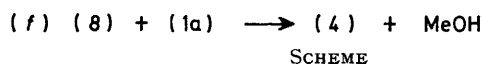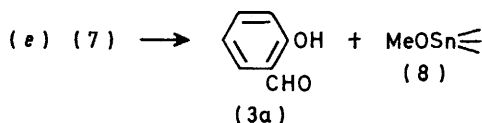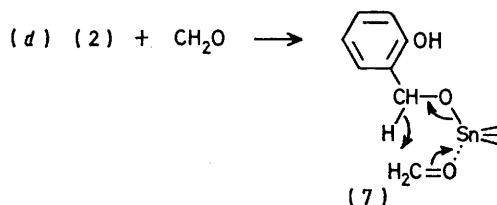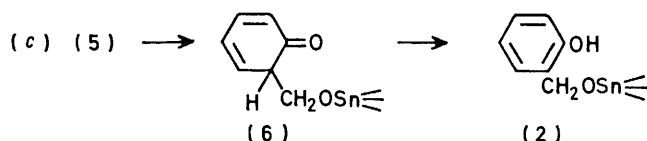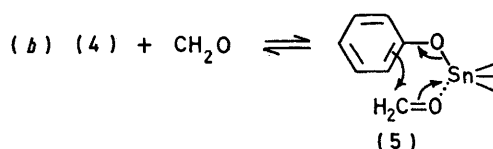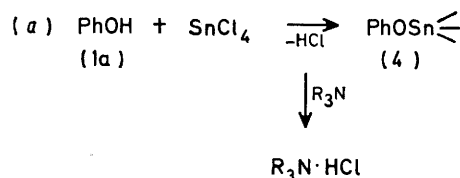
trimethylamine–(4) and pyridine–(4) complexes possess very poor Lewis acidity for reaction with formaldehyde, unstable complexes may dissociate or have Lewis acidity sufficient to form the transient metal phenolate–form-aldehyde complex (5) via amine exchange. Moreover, trioctylamine or 2,6-lutidine can trap the hydrogen chloride evolved in the first stage of the reaction. Thus, bases which poorly co-ordinate with (4), but can trap hydrogen chloride, are essential ingredients. Tri-octylamine and 2,6-lutidine fully satisfy this criterion as shown in Table 2 (runs 3 and 6).*

* A similar effect of added bases was recently reported by Sugasawa and his co-workers [5] for reactions between secondary anilinodichloroboranes and benzaldehydes.

The solvent effects in Table 3 can be interpreted analogously. While donor agents which can strongly solvate the phenolate metal counter-ion retard the process, compounds which are poor donors and do not interfere in the formation of the active intermediate (5) are favourable. The next stages [equations (d) and (e)] apparently involve a redox process between the phenol (2) and formaldehyde leading to salicylaldehyde (3a) and tin(IV) methoxide (8). In order to explain the process, a detailed study of tin(IV) alkoxide-promoted hydride transfer reactions between alcohols and carbonyl compounds was undertaken.[8] On the basis of kinetic evidence and isotope labelling measurements we conclude that the process involves direct hydride transfer from the alkoxide group of the phenol to the co-ordinated

As shown in Table 4, this reaction is generally applicable to a variety of substituted phenols. Typically, to a stirred solution of a phenol (1 mol) in an appropriate solvent was added a mixture of 0.1 mol of tin(IV) tetrachloride and 0.4 mol of an appropriate base at room temperature. After 20 min * paraformaldehyde (2.2 mol) was added to the resulting slurry, which presumably contains the active species (4). Within a few minutes, the slurry turned into a clear yellowish solution which was then heated at ca. 100 °C for 8 h. Work-up involving acidic quenching, extraction, drying, and removal of solvent gave the desired products (3) which were purified by conventional procedures (see Experimental section). The yields of (3) amount to 80—99% based on recovered starting phenol (50—91% isolated yield).
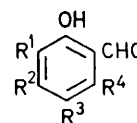
TABLE 4

Synthesis of salicylaldehydes (3a—q)

Compd.	R^1	R^2	R^3	R^4	Yield (%) a	Yield (%) b	M.p. or b.p. (°C)/Torr Found	Reported c
(3a)	H	H	H	H	74	99	198/ambient	197/760
(3b)	Me	H	H	H	87	96	211/ambient	208/760
(3c)	H	Me	H	H	80 d	91	60—61	60
(3d)	H	H	Me	H	86	98	55—56	56
(3e)	Me	H	Me	H	91	99	12—14	11
(3f)	Me	H	H	Me	87	96	63—64	62—63
(3g)	cyclo-C_6H_{11}	H	H	H	85	94	150/16	e
(3h)	n-C_9H_{19}	H	H	H	80	96	173/16	e
(3i)	Bu^t	H	Me	H	86	99	128—130/16	e
(3j)	Pr^i	H	H	H	82	95	128—130/16	130/15
(3k)	Ph	H	H	H	64	93	47—48	e
(3l)	H	H	OMe	H	51	85	51—52	50—52
(3m)	Cl	H	H	H	69	93	54—55	54
(3n)	H	H	Cl	H	74	96	98—99	99
(3o)	H	H	NHAc	H	60	80	185—186	e
(3p)	H	H	OH	H	50	91	99	99
(3q)	H	H	—C_4H_4—		91	98	82	82

a Isolated actual yield of reported products. b Values refer to yield based on consumed starting phenol. c Values are taken from ref. 3. d 5% of 2-hydroxy-6-methylbenzaldehyde is obtained as by-product. e Elemental analyses [C, H (N)] consistent with structures.

carbonyl compound in a concerted reaction, as shown for (7). The last stage of the proposed catalytic cycle is considered to be the alcoholysis of (8) with (1a) leading to methanol with re-formation of the active species (4). In accord with this postulate, the reaction between tin(IV) tetramethoxide and phenol (4 mol equiv.) in toluene at 100 °C to produce (4) and methanol is shown to be rapid and quantitative.

Two special experimental observations also support the proposed mechanistic scheme: (i) a mixture of phenol (1a) (60 mmol) and tin(IV) tetraphenoxide (4) reacts with formaldehyde (220 mmol) under the usual reaction conditions to give (3a) in fair yield, indicating that a metal phenoxide such as (4) could be considered as an active catalyst in our process; and (ii) salicyl alcohol may be converted quantitatively into (3a) by heating (toluene, 100 °C) with paraformaldehyde (1 mol equiv.) in the presence of tin(IV) tetrachloride (0.1 mol) and trioctylamine (0.4 mol), suggesting that the saligenol derivative (2) could be a reaction intermediate.

This simple method can be successfully applied to phenols bearing electron-donating or weak electron-withdrawing substituents, but when substituents such as Cl or OMe are situated ortho to the hydroxy-function of the phenol ring the reaction does not proceed. This effect may be attributed to the intramolecular co-ordination of the substituents reducing the Lewis acidity of the metal phenoxide intermediate (4). Moreover, attempts to apply this reaction to phenols bearing strong electron-withdrawing substituents (NO_2, COMe, CO_2Me) failed.

To summarize, this process provides a widely applicable exclusive ortho-formylation of phenols with formaldehyde through an easily viable route. In most instances the procedure is a marked improvement over existing methods for laboratory-scale preparations of

* The mode of addition had a marked effect on the yield of isolated products. When paraformaldehyde was simultaneously added with other reactants, a remarkable lack of specificity was observed.

salicylaldehydes.[9] We believe also that this method can compete in efficiency and economy with widely used *ortho*-formylation processes of industrial interest such as the aluminium phenoxides-catalysed carbonylation of phenols [10] and catalytic oxidation of salicyl alcohols.[11]

Such an unusual *ortho*-specific Friedel–Crafts reaction is unique in that ordinary Lewis-acid-catalysed phenol–formaldehyde condensation processes in non-aqueous media are known to give predominantly methylene-bridged polyphenolic compounds (novolac resins) with a variable degree of *ortho*-specificity.[12]

EXPERIMENTAL

Vapour-phase chromatography was carried out with a Varian Aerograph 2700 by using a 1.5-m analytical column packed with Carbowax 20 M on Chromosorb W or a 1.5-m column packed with Apiezon L. All starting materials used in this work were commercially available in generally 98% or higher purity and used without further purification. Solvents were distilled once before use. Tin(IV) tetraethoxide was prepared from tin(IV) tetrachloride and anhydrous ethanol as previously described.[8] Tin(IV) phenoxide was prepared from phenol and tin(IV) tetraethoxide.[13] All reactions were carried out under dry nitrogen. Microanalyses were performed by Istituto di Chimica Farmaceutica, Università di Parma, Italy.

General Procedure for Preparation of Salicylaldehydes (3a—q).—To a four-neck round-bottom flask (2.5 l) equipped with a reflux condenser, mechanical stirrer, thermometer, and a nitrogen source was added anhydrous toluene (200 ml), the appropriate phenol (1.0 mol), tin(IV) tetrachloride (26 g, 0.1 mol), and tri-n-butylamine (54 g, 0.4 mol). The mixture was stirred for 20 min at room temperature, then para-formaldehyde (66 g, 2.2 mol) was added. The resulting yellowish solution was heated at 100 ± 0.5 °C for 8 h. After cooling, the reaction mixture was poured into water (5 l), acidified to pH 2 with 2N-hydrochloric acid, and extracted with ether. The ether extract was washed with a saturated sodium chloride solution, dried (Na_2SO_4), and concentrated to leave crude salicylaldehydes. Products (3a—j) were purified by steam distillation and, if necessary, by subsequent distillation. Products (3k—n) were recrystallized from light petroleum (b.p. 40—60 °C), products (3o—q) from benzene. Yields and physical data for all aldehydes (3a—q) are collected in Table 4.

2-Hydroxybenzaldehyde (3a) [*Tin*(IV) *Phenoxide as Catalyst*].—A mixture of phenol (5.6 g, 60 mmol), tin(IV) phenoxide (4.9 g, 10 mmol), and paraformaldehyde (6.6 g, 220 mmol) in dry toluene (200 ml) was stirred under nitrogen at 100 °C for 8 h. After the usual work-up the crude oil

obtained on removal of the solvent was distilled on a short-path column to give pure (3a) (8.5 g, 70%), b.p. 198 °C (ambient), identical (spectra) with an authentic specimen.

2-Hydroxybenzaldehyde (3a) (*from* *2-Hydroxybenzyl Alcohol*).—A mixture of salicyl alcohol (12.4 g, 100 mmol), tin(IV) tetrachloride (2.6 g, 10 mmol), and tri-n-octylamine (5.4 g, 40 mmol) in dry toluene (200 ml) was stirred under nitrogen for 20 min at room temperature. Paraformaldehyde (3.6 g, 110 mmol) was added to the slurry and the resulting pale yellow solution was heated at 100 °C with stirring for 8 h. Work-up as described in the preceding experiment gave (3a) (11.8 g, 96%), b.p. 198 °C (ambient), identical with an authentic specimen.

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