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Convenient Method for the *ortho*-Formylation of Phenols

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Phenolic derivatives are formylated selectively *ortho* to the hydroxy group by paraformaldehyde with magnesium dichloride–triethylamine as base. With alkyl-substituted phenols excellent yields of the corresponding salicylaldehyde derivatives were obtained. Similar results were obtained with chloro-substituted phenols and with 3-and 4-methoxyphenol, while 2-methoxyphenol was unreactive. A good yield of methyl 3-formyl-4-hydroxybenzoate was obtained by this method as well, but generally phenols with electron-attracting groups reacted sluggishly; the long reaction times required caused the formation of by-products, particularly MOM-derivatives of the phenols.

Formylation of aromatic compounds is a classical reaction in organic chemistry, and numerous methods are available.[1] Some years ago Casiraghi *et al.* reported that the reaction of paraformaldehyde and magnesium phenoxides, formed from the respective phenol and ethylmagnesium bromide in benzene as solvent and in the presence of stoichiometric amounts of HMPTA resulted in monoformylation exclusively at the *ortho* position.[2] Apparently the magnesium ion plays an essential role in this reaction, which led us to consider using a combination of magnesium dihalide–triethylamine as base. This combination is a considerably stronger base than triethylamine alone and has been used for a variety of base-induced reactions such as acylations of malonates[3] and phosphonoacetates,[4] condensation of ketones with isocyanates,[5] α-carboxylations of ketones,[6] and Dieckman-type cyclisations.[7] It is also known that magnesium dibromide–triethylamine promotes Michael additions to enamines.[8] To our knowledge this particular base system has not previously been used in combination with paraformaldehyde for the formylation of aromatic compounds; however, a formylation reaction of phenols with paraformaldehyde using magnesium methoxide as base and toluene as solvent furnished good yields of salicylaldehydes.[9] In the present paper we describe a simplified version of the Casiraghi formylation method in which the Grignard reagent is replaced by the anhydrous magnesium dichloride–triethylamine base system. Our method gives improved yields, fewer by-products and renders the use of the metal complexing agent hexamethylphosphoric triamide (HMPTA) superfluous. The latter, being a strong carcinogen, should be avoided if possible.

Results and discussion

The reactions were generally performed on a 20 mmol scale by adding an excess of dry paraformaldehyde to the magnesium phenoxide, formed from the phenol and a 1:2.5 molar mixture of magnesium dichloride and triethylamine in acetonitrile as solvent, and heating the reaction mixture under reflux for 2–4 h in most cases. Some of the results are summarized in Table 1.

The large excess of paraformaldehyde was used in order to maintain a reasonable reaction time; for example the reaction of 2-*tert*-butylphenol gave the same result (Table 1) but at a slower rate using a 3:1 ratio of paraformaldehyde to phenol. The yields are based on isolated product and they are not optimized. With the exception of methyl 3-formyl-4-hydroxybenzoate (**1**) and 5-cyanosalicylaldehyde (**2**) the aldehydes recorded in Table 1 are known compounds which were identified by comparison with authentic samples or with spectral data and other physical properties recorded in the literature. The effect of solvent on the reaction time and yield of aldehyde was examined briefly using phenol as substrate. Under the general reaction conditions, but with THF as solvent and 1.5 h of reflux, salicylaldehyde was obtained in 74% yield, while with dichloromethane as solvent the aldehyde was obtained in 89% yield after 48 h of reflux; however, in benzene solution reaction rates similar to those in acetonitrile were observed only in the presence of HMPTA as co-solvent.

The effect of substituents seems to follow the pattern

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Table1. Formylation of phenolic derivatives with paraformaldehyde using $MgCl_2$–triethylamine as base and acetonitrile as solvent.

Phenol	Aldehyde	Yield (%)	*t*/h
Phenol	Salicylaldehyde	83[a]	1.5
2-Naphthol	2-Hydroxy-1-naphthaldehyde	73	17
2-Methylphenol	3-Methylsalicylaldehyde	99	1.5
3-Methylphenol	4-Methylsalicylaldehyde	70	4
	6-Methylsalicylaldehyde	12	
4-Methylphenol	5-Methylsalicylaldehyde	90	4
2-*tert*-Butylphenol	3-*tert*-Butylsalicylaldehyde	83	3
3-Methoxyphenol	4-Methoxysalicylaldehyde	91	2
	6-Methoxysalicylaldehyde	5	
4-Methoxyphenol	5-Methoxysalicylaldehyde	97	2
2-Chlorophenol	3-Chlorosalicylaldehyde	87	3.5
3-Chlorophenol	4-Chlorosalicylaldehyde	63	2
	6-Chlorosalicylaldehyde	15	
4-Chlorophenol	5-Chlorosalicylaldehyde	78	3.5
Methyl-4-hydroxybenzoate	Methyl-3-formyl-4-hydroxybenzoate (**1**)	88[b]	21
4-Cyanophenol	5-Cyanosalicylaldehyde (**2**)	24[c]	44

[a]THF as solvent, 22h, 83% yield. [b]73% conversion. [c]58% conversion.

expected for an electrophilic aromatic substitution reaction. Electron-donating substituents promote the reaction while the opposite is true for electron-withdrawing groups. The alkyl-substituted phenols afford high yields of the corresponding *ortho*-substituted aldehydes. The reactions of 3- and 4-methoxyphenol furnished good yields of the corresponding aldehydes as well, but with 2-methoxyphenol as substrate only traces of the aldehyde were formed even after prolonged reaction time. The ethers 2-methoxymethylphenol[10] and 2-methoxymethyl-6-methylphenol (**3**)[11] were identified as minor (<2%) by-products from reactions of phenol and 2-methylphenol, respectively. A similar compound became a significant by-product in the reaction of 2-naphthol which in addition to the aldehyde formed 1-methoxymethyl-2-naphthol (**4**) in 9% yield.

When the formylation method was applied to phenols containing electron-attracting groups, mixed results ensued. As expected the chlorophenols undergo the formylation reaction, and at rates not much slower than that of phenol; good yields of the corresponding aldehydes were obtained without significant amounts of by-products. Similarly, the reaction of methyl 4-hydroxybenzoate furnished the corresponding aldehyde **1** in excellent yield. On the other hand, all the other phenols with electron attracting substituents that were used as substrates reacted sluggishly, and complete conversion of starting material was not achieved even after long reaction times. The reactions gave low yields of the corresponding salicylaldehydes, the respective MOM derivatives of phenols being the major by-products in most cases. Under the general conditions 4-hydroxyacetophenone was converted into products to an extent of only 62% after 41 h of reflux; a complex mixture resulted from which 5-acetylsalicylaldehyde (**5**) was isolated in 20% yield together with a small amount (4%) of the MOM-derivative, 4-methoxymethoxyacetophenone (**6**). Using isobutyronitrile as solvent the reaction of

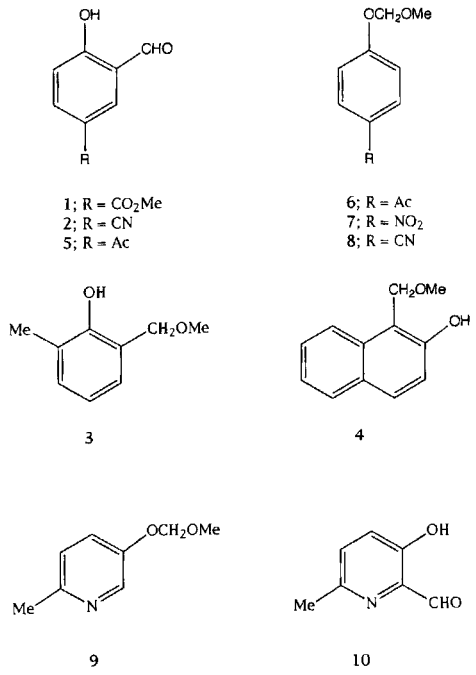


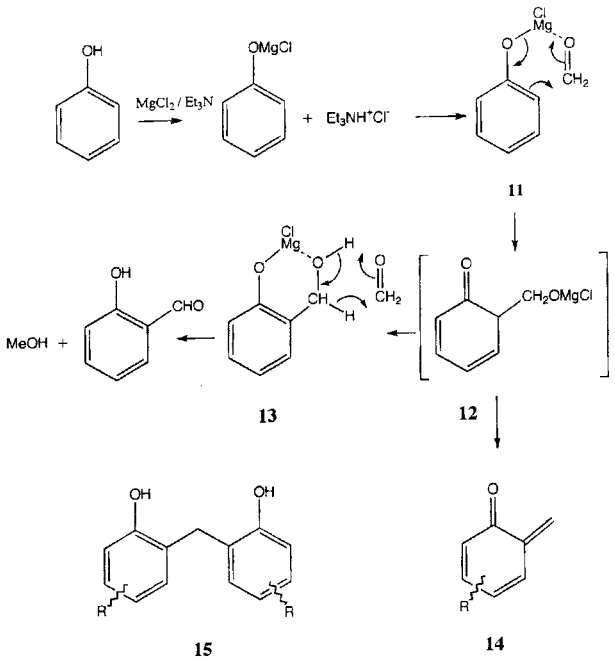
Fig. 1.

4-hydroxyacetophenone went to completion after being heated under reflux for 96 h, but the yield of aldehyde **5** was not improved. Reaction of 4-nitrophenol by the general method gave 38% conversion after 45 h of reflux in acetonitrile. From the product mixture 5-nitrosalicylaldehyde and 4-methoxymethoxy-1-nitrobenzene (**7**) were obtained in 12 and 11% yields, respectively. Changing the solvent to isobutyronitrile and the time to 96 h of reflux the reaction was still incomplete (77%); however, the main component of the complex product mixture was the MOM-derivative **7**, which was isolated in 57% yield, and only a small amount of the aldehyde was present. Similar results were obtained with

4-cyanophenol which had only partially reacted even after 44 h of reflux in acetonitrile, furnishing a 24% yield of 5-cyanosalicylaldehyde (**2**) accompanied by an almost equal amount of 4-methoxymethoxybenzonitrile (**8**). Hence, with electron poor phenol derivatives the degree of formylation was not improved by either prolonged heating under reflux or the use of a higher boiling solvent such as isobutyronitrile.

The reaction of 3-hydroxypyridine by the general method gave no aldehyde even after heating under reflux for 22 h, but under similar conditions 6-methyl-3-hydroxypyridine afforded as part of a complex product mixture 6% of 6-methyl-3-hydroxy-2-formylpyridine (**10**) and 10% of 3-methoxymethoxy-6-methylpyridine (**9**). Furthermore, when thiophenol was the substrate no formylation of the aromatic ring took place; a mixture of compounds was obtained from which the phenylthioacetal of formaldehyde and phenyl methoxymethyl sulfide were identified as the main components.

The reaction path pictured in Scheme 1 is similar to that proposed by Casiraghi *et al.*[2a] and accommodates the selective *ortho*-formylation of the phenols.



Scheme 1.

Paraformaldehyde is depicted as monomeric formaldehyde, which is most probably the reactive species at the temperatures employed. The reaction as exemplified with phenol is initiated by the base system providing the salt **11**, which is depicted as the phenoxymagnesium chloride but could very well be diphenoxymagnesium. The magnesium salt is a requirement for further reaction; no reaction occurred when a solution of phenol, paraformaldehyde and triethylamine in acetonitrile was heated under reflux for 48 h. Moreover, when the amine was omitted no reaction took place in the presence of magnesium dichloride. The intermediate **11** reacts with formaldehyde through the cyclohexadienone structure **12** furnishing, as the primary product, the magnesium salt of salicyl alcohol **13**. This intermediate subsequently takes part in a redox reaction with formaldehyde in which salicylaldehyde is formed together with methanol. In a separate experiment it was shown that salicyl alcohol is rapidly oxidized under the prevailing reaction conditions. Accordingly, the formylation reaction requires two moles of formaldehyde for each mole of phenol. As depicted in Scheme 1 the first step demands coordination between the magnesium atom and the formaldehyde oxygen. The magnesium atom of the salt of 2-methoxyphenol is most probably coordinated to the neighbouring methoxy oxygen and thus less available for coordination to the formaldehyde oxygen; this explains why only traces of formylation product were indicated from the reaction of 2-methoxyphenol. With 3-substituted phenols *ortho*-formylation may yield two regioisomers. In the three cases investigated mixtures of the two isomers were actually formed with the less sterically crowded isomer as major component. This result is expected from the above reaction scheme. It is interesting to note that the uncatalysed reaction of phenols with paraformaldehyde in xylene as solvent and in the presence of dimethoxyethane gives excellent yields of the corresponding salicyl alcohols and no aldehydes;[12] however,without dimethoxyethane only low yields of alcohols were obtained, the main product being 2,2′-dihydroxydiphenylmethanes (**15**).[13] Evidently a Lewis acid–base system is essential only for the redox reaction.

The MOM derivatives and the ethers have not previously been reported as by-products from similar formylation reactions. The formation of the MOM acetals of the phenols are most probably catalysed by the Lewis acids present in the reaction mixture, e.g. triethylamine hydrochloride and magnesium dichloride. It is unlikely that similar catalysis accounts for the ether formation from the intermediate salicyl alcohols (**13** of Scheme 1), although methanol seems essential for this reaction; when methanol was deliberately added at the outset of the formylation reaction of 2-naphthol under otherwise general conditions, the yield of the 1-methoxymethyl derivative **4** increased from 9 to 17%. It has been reported that salicyl alcohols are converted into such ethers when heated in methanol in the presence of ferrous or ferric chloride.[10]

The Michael addition of methanol to the quinomethane intermediate **14** was offered as an explanation for the ether formation; on the other hand, it has also been suggested that the same intermediate **14** is responsible for the formation of 2,2′-dihydroxydiphenylmethanes **15**, which have been reported as major by-products from similar formylation reactions of phenols.[2,9] Although we did not detect diphenylmethane derivatives in the product of any of our reactions, the quinomethane **14** seems a likely intermediate in the reaction path to the benzyl methyl ethers.

Experimental

General. The NMR spectra were recorded on a Varian Gemini 200 instrument using $CDCl_3$ as both solvent and internal standard. IR spectra were recorded on a Nicolet Magna IR spectrometer 550. MS spectra were recorded on a Fison Instrument VG ProSpec Q.

General procedure. Dry (P_2O_5) paraformaldehyde (135 mmol) was added to a mixture of the phenolic derivative (20 mmol), commercially available (Norsk Hydro) anhydrous magnesium dichloride (30 mmol) and dry (Na) triethylamine (75 mmol) in acetonitrile (100 ml; distilled over CaH_2), and the mixture heated under reflux for the reaction time recorded in Table 1. The mixture was cooled to room temperature after which 5% aq. HCl was added and the product extracted with ether. The dried ($MgSO_4$) extract was evaporated and the residue purified by flash chromatography on silica gel.

Aldehydes. Salicylaldehyde, 5-chlorosalicylaldehyde, 4-methoxysalicylaldehyde, 5-methoxysalicylaldehyde, 5-nitrosalicylaldehyde and 2-hydroxy-1-naphthaldehyde were identified by comparison with commercial samples, and the following aldehydes were characterized by comparison with spectral data given in the literature: 3-chlorosalicylaldehyde,[14] 4-chlorosalicylaldehyde,[14] 6-chlorosalicylaldehyde,[14] 3-methylsalicylaldehyde,[14] 4-methylsalicylaldehyde,[9] 5-methylsalicylaldehyde,[14] 6-methylsalicylaldehyde,[9] 6-methoxysalicylaldehyde,[14] 3-*tert*-butylsalicylaldehyde.[15]

Methyl 3-formyl-4-hydroxybenzoate (**1**). M.p. 82–83 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.80 (s, 3 H), 6.87 (d, *J* 8.8 Hz, 1 H), 8.02(dd, *J* 8.8, 2.2 Hz, 1 H), 8.17 (d, *J* 2.2 Hz, 1 H), 9.82 (s, 1 H), 11.26 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.2, 117.0, 119.2, 121.3, 135.1, 136.6, 163.6, 164.1, 194.8. IR (film): 1713, 1651, 1587 cm^{-1}. MS (EI): *m/z* 180 (M^+),149 (100), 121, 93, 65. Anal. (HRMS). Found: 180.042 426. Calc. for $C_9H_8O_4$: 180.042 259.

5-Cyanosalicylaldehyde (**2**). M.p. 148–149 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.98 (d, *J* 8.8 Hz, 1 H), 7.63 (dd, *J* 8.8, 2.2 Hz, 1 H), 7.89 (d, *J* 2.2 Hz, 1 H), 9.92 (s, 1 H), 11.27 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 103.2, 117.1, 118.6, 120.2, 137.0, 138.4, 163.1, 193.2. IR (film): 3187, 2852, 2226, 1669, 1572 cm^{-1}. MS (EI): *m/z* 147 (M^+), 146 (100), 129, 118, 101, 90, 63. Anal. (HRMS). Found: 147.032 284; Calc. for $C_8H_5NO_2$: 147.032 028.

2-Methoxymethyl-6-methylphenol (**3**).[11] ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.29 (s, 3 H), 3.46 (s, 3 H), 4.68 (s, 2 H), 6.78 (dd, *J* 7.4, 7.4 Hz, 1 H), 6.89 (br d, *J* 7.4 Hz, 1 H), 7.12 (br d, *J* 7.4 Hz, 1 H), 7.63 (s, 1 H).

1-Methoxymethyl-2-naphthol (**4**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.58 (s, 3 H), 5.21 (s, 2 H), 7.16–7.20 (m, 1 H), 7.34–7.55 (m, 2 H), 7.72–7.84 (m, 3 H), 8.65 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 58.2, 70.7, 111.6, 118.9, 120.8, 122.8, 126.4, 128.4, 128.5, 129.5, 131.5, 154.1. IR (film): 3300, 1615, 1590 cm^{-1}. MS (EI): *m/z* 188, 156, 128 (100). Anal. (HRMS). Found: 188.083 432; Calc. for $C_{12}H_{12}O_2$: 188.083 730.

5-Acetylsalicylaldehyde (**5**). M.p. 84–85 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.61 (s, 3 H), 7.06 (d, *J* 8.8 Hz, 1 H), 8.15 (dd, *J* 8.8, 2.2 Hz, 1 H), 8.25 (d, *J* 2.2 Hz, 1 H), 9.98 (s, 1 H), 11.42 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.8, 117.5, 119.4, 129.0, 134.2, 136.0, 164.1, 194.0, 195.0. IR (film): 3190, 2853, 1679, 1655, 1586 cm^{-1}. Anal. (HRMS). Found: 164.045 818; Calc. for $C_9H_8O_3$: 164.047 344.

4-Methoxymethoxyacetophenone (**6**).[16] ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.55 (s, 3 H), 3.47 (s, 3 H), 5.23 (s, 2 H), 7.06 (d, *J* 9.0 Hz, 2 H), 7.92 (d, *J* 9.0 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.5, 56.3, 93.9, 115.5, 130.0, 160.8, 196.5. IR (film): 1665, 1590 cm^{-1}. MS (EI): *m/z* 180, 135, 45 (100). Anal. (HRMS). Found: 180.080 213; Calc. for $C_{10}H_{12}O_3$: 180.078 644.

4-Methoxymethoxynitrobenzene (**7**).[17] ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.49 (s, 3 H), 5.26 (s, 2 H), 7.10 (d, *J* 9.0 Hz, 2 H), 8.19 (d, *J* 9.0 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.7, 94.0, 115.5, 125.1, 141.4, 161.2. IR (film): 1580 cm^{-1}. MS (EI): *m/z* 183, 45 (100). Anal. (HRMS). Found: 183.053 223; Calc. for $C_8H_9NO_4$: 183.053 158.

4-Methoxymethoxybenzonitrile (**8**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.46 (s, 3 H), 5.21 (s, 2 H), 7.08 (d, *J* 9.0 Hz, 2 H), 7.57 (d, *J* 9.0 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.3, 94.0, 104.9, 116.6, 119.0, 133.8, 160.4. IR (film): 2200, 1595 cm^{-1}. GC–MS (EI): *m/z* 163, 132, 102, 90, 45 (100). Anal. (HRMS). Found: 163.064 166; Calc. for $C_9H_9NO_2$: 163.063 329.

2-Formyl-3-hydroxy-6-methylpyridine (**10**). ^{1}H NMR (200 MHz, CD_2Cl_2): δ 2.53 (s, 3 H), 7.27 (d, *J* 8.8 Hz, 1 H), 7.33 (s, *J* 8.8 Hz, 1 H), 9.99 (s, 1 H), 10.60 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.0, 125.8, 129.7, 134.8, 150.1, 155.9, 197.1. IR (film): 3358, 2853, 1725, 1659, 1633 cm^{-1}. GC–MS (EI): *m/z* 137 (M^+), 109, 80 (100), 53. Anal. (HRMS). Found: 137.047 888; Calc. for $C_7H_7NO_2$: 137.047 679.

3-Methoxymethoxy-6-methylpyridine (**9**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3 H), 3.44 (s, 3 H), 5.12 (s, 2 H), 7.02 (d, *J* 8.4 Hz, 1 H), 7.24 (dd, *J* 2.9, 8.4 Hz, 1 H), 8.25 (d, *J* 2.9 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.5, 56.0, 94.7, 123.1, 123.6, 138.5, 151.2, 151.3. IR (film): 1590, 1570 cm^{-1}. GC–MS (EI): *m/z* 153 (M^+), 123, 108, 92, 80, 65, 53, 45 (100). Anal. (HRMS). Found: 153.080 306; Calc. for $C_8H_{11}NO_2$: 153.078 979.

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