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# Vilsmeier Reaction of Phenols. I. Synthesis of Aryl Formates[1)]

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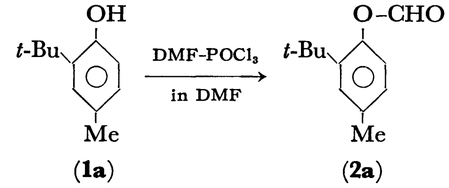
**Synopsis** The reaction of phenol and *o*-*t*-butylphenols with *N*,*N*-dimethylformamide–phosphoryl chloride complex in dimethylformamide afforded the corresponding formates in fairly good yields. The scope and limitation of *o*-formylation of highly sterically hindered phenols with the complex were also examined.

Vilsmeier reagents have been shown to be effective in formylating the benzene nuclei of phenol derivatives. For example, the preparation of vanillin by the formylation of guaiacol with *N*-methylformanilide–phosphoryl chloride complex has been disclosed in an early patent.[2)] Furthermore, it has been shown that the hydroxyl group of picric acid is replaced by a chlorine atom when treated with (chloromethylene)dimethylammonium chloride.[3)] However, examples of formylation of the phenolic hydroxyl group by Vilsmeier reagent have not yet been reported. During the course of our study on the hindered phenol-type antioxidants, we have found that dimethylformamide–phosphoryl chloride (DMF–POCl$_3$) complex reacts with phenol derivatives to afford the formates in fairly good yields.

When 2-*t*-butyl-*p*-cresol (**1a**) was treated with DMF–POCl$_3$ complex in DMF at 80 °C for 5 h, the formate (**2a**) was obtained in 78% yield after hydrolysis of the reaction mixture. No product arising from the formylation of the benzene nucleus was isolated. The structure of **2a** was confirmed by the satisfactory analytical values and the following spectral data. The IR spectrum did not show OH absorption but exhibited the characteristic absorption at 1750 cm$^{-1}$ for the ester carbonyl group. The NMR spectrum indicated the presence of three aromatic protons.



*o*-*t*-Butylphenols, **1b**—**g**, listed in the Table 1 also gave the corresponding formates, **2b**—**g**, when treated with DMF–POCl$_3$ complex. In the case of 6-*t*-butyl-*m*-cresol (**1d**), formation of the formate (**2d**) accompanied the production of 6-*t*-butyl-4-formyl-*m*-cresol (**3d**) as the minor product. The aldehyde **3d** showed carbonyl and hydroxyl absorptions at 1667 and 3320 cm$^{-1}$ respectively in the IR spectrum, and the NMR spectrum exhibited two singlets at 7.50 and 7.28 ppm due to the isolated aromatic protons. Bis(5-*t*-butyl-4-hydroxy-2-methylphenyl sulfide (**1f**) is less reactive toward the complex, and a considerable amount of monoformate (**3f**) was obtained together with the diformate (**2f**) even when the reaction period was extended up to 24 h.

Further reactions with *o*,*o*'-disubstituted phenols such as 6-*t*-butyl-2,4-xylenol (**1h**) and 2,6-di-*t*-butyl-*p*-cresol (**1i**) were investigated in order to examine the limitation of the present method of formylation. The former phenol (**1h**) gave the formate (**2h**) in a low yield, whereas the latter (**1i**) was recovered after being treated with DMF–POCl$_3$ complex for 20 h at 85—95 °C. Employment of drastic reaction conditions (25 h at 120—125 °C) on the above reaction of **1i** resulted in the elimination of the *t*-butyl group, giving 2-*t*-butyl-4-methylphenyl formate (**2a**) in 76% yield.

6-*t*-Butyl-4-formyl-*m*-cresol (**3d**) was not formylated by DMF–POCl$_3$ complex. The inertness of this phenol is probably based on the deactivation due to the electron-

Table 1. Reaction of DMF–POCl$_3$ complex with phenols

| Phenol | Reactant ratio (phenol: complex) (molar ratio) | React. temp (°C) | React. time (h) | Product | Yield (%) |
|---|---|---|---|---|---|
| 2-*t*-Butyl-*p*-cresol (**1a**) | 1 : 1.5 | 78—80 | 5 | Formate (**2a**) | 78 |
| 4,6-Di-*t*-butyl-*m*-cresol (**1b**) | 1 : 1.5 | 80—90 | 3 | Formate (**2b**) | 82 |
| 2,4-Di-*t*-butylphenol (**1c**) | 1 : 1.5 | 90—95 | 9 | Formate (**2c**) | 58 |
| 6-*t*-Butyl-*m*-cresol (**1d**) | 1 : 1.5 | 70—80 | 3 | Formate (**2d**) | 83 |
| | | | | 6-*t*-Butyl-4-formyl-*m*-cresol (**3d**) | 10 |
| 1,1-Bis(5-*t*-butyl-4-hydroxy-2-methylphenyl)butane (**1e**) | 1 : 3.0 | 95—100 | 8 | Diformate (**2e**) | 68 |
| Bis(5-*t*-butyl-4-hydroxy-2-methylphenyl)sulfide (**1f**) | 1 : 3.0 | 95—100 | 24 | Diformate (**2f**) | 38 |
| | | | | Monoformate (**3f**) | 45 |
| 1,1,3-Tris(5-*t*-butyl-4-hydroxy-2-methylphenyl)butane (**1g**) | 1 : 5.0 | 85—90 | 8 | Triformate (2**g**) | 71 |
| 6-*t*-Butyl-2,4-xylenol (**1h**) | 1 : 1.5 | 85—90 | 20 | Formate (**2h**) | 10 |
| 2,6-Di-*t*-butyl-*p*-cresol (**1i**) | 1 : 1.5 | 120—125 | 25 | **2a** | 76 |
| Phenol (**1j**) | 1 : 1.5 | 75—80 | 4 | Formate (**2j**) | 59 |

TABLE 2. PHYSICAL CONSTANTS AND ANALYTICAL DATA OF FORMATES

| Compd | Mp (°C) [Bp (°C/Torr)] | Molecular formula | Found (Calcd) | |
|---|---|---|---|---|
| | | | C% | H% |
| **2a** | 39.5—40.5 | $C_{12}H_{16}O_2$ | 75.04<br>(74.97) | 8.42<br>(8.39) |
| **2b** | 78—79 | $C_{16}H_{24}O_2$ | 77.28<br>(77.37) | 9.66<br>(9.74) |
| **2c** | [112—115/3.5] | $C_{15}H_{22}O_2$ | 76.79<br>(76.88) | 9.40<br>(9.46) |
| **2d** | [93—94/3.5] | $C_{12}H_{16}O_2$ | 74.91<br>(74.97) | 8.43<br>(8.39) |
| **3d** | 168—169 | $C_{12}H_{16}O_2$ | 75.11<br>(74.97) | 8.36<br>(8.39) |
| **2e** | 77—78 | $C_{28}H_{38}O_4$ | 76.66<br>(76.67) | 8.67<br>(8.73) |
| **2f** | 90—91 | $C_{24}H_{30}O_4S$ | 69.48<br>(69.54) | 7.36<br>(7.30) |
| **3f** | 144—165 | $C_{23}H_{30}O_3S$ | 71.38<br>(71.48) | 7.89<br>(7.82) |
| **2g** | 153.5—154.5 | $C_{40}H_{52}O_6$ | 76.52<br>(76.40) | 8.30<br>(8.34) |
| **2h** | [103.5—104.5/3.5] | $C_{13}H_{18}O_2$ | 75.72<br>(75.69) | 8.74<br>(8.80) |
| **2j** | [87—88/24] | $C_7H_6O_2$ | 68.70<br>(68.84) | 4.87<br>(4.95) |

withdrawing formyl function.

In connection with the formation of the formates from the hindered phenols, the formylation of phenol (**1j**) was also investigated. It had previously been reported that *p*-hydroxybenzaldehyde (**3j**) was obtained in a low yield when **1j** was heated with an equimolar mixture of DMF and $POCl_3$.[4] In the present work, the reaction was carried out using excess DMF as the solvent, and phenyl formate (**2j**) was obtained in 59% yield. The aldehyde, **3j**, was not isolated.

The formates of hindered phenols prepared in this work were shown to be useful for preventing the degradation of several synthetic polymers.[5]

## Experimental

*Reaction of DMF–$POCl_3$ Complex with Phenols (**1a**—**1i**).* An example is cited for the reaction with 2-*t*-butyl-*p*-cresol (**1a**). Similar procedures were used in the reactions with other phenols. The products, **2b**, **3d**, and **2f**, were purified by recrystallization from ethanol, and **2e**, **3f**, and **2g** from benzene. Purification of the oily products, **2c**, **2d**, and **2i** was effected by distillation under reduced pressure. Results of elemental analyses of the products are given in Table 2. To a stirred solution of 16.4 g (0.1 mol) of **1a** in 40 ml of DMF, 22.6 g (0.15 mol) of $POCl_3$ added dropwise at 0—5 °C. After being stirred for 1 h at room temp, the mixture was heated slowly to 80 °C and kept at 78—80 °C for 5 h. To this reaction mixture were added 300 ml of hexane and then 240 ml of 10% aqueous sodium acetate at 0—5 °C with stirring. The hexane solution was separated, washed successively with clod aqueous $NaHCO_3$ and ice-water, and dried over $Na_2SO_4$. The solvent was removed under reduced pressure at temp below 50 °C, and the residue was recrystallized from ether to give 14.4 g (78%) of the formate, **2a**, mp 39.5—40.5 °C. IR (Nujol) 1750 $cm^{-1}$ (C=O). NMR ($CCl_4$) $\delta$ 1.35 (s, 9H, $-\mathrm{C}(\mathrm{C}\underline{\mathrm{H}}_3)_3$), 2.32 (s, 3H, $-\mathrm{C}\underline{\mathrm{H}}_3$), 6.84 (d, $J$=8.0 Hz, 1H, $\mathrm{C}_6$-$\underline{\mathrm{H}}$), 7.06 (d-d, $J$=8.0 and 2.0 Hz, 1H, $\mathrm{C}_5$-$\underline{\mathrm{H}}$), 7.22 (d, $J$=2.0 Hz, 1H, $\mathrm{C}_3$-$\underline{\mathrm{H}}$), 8.29 (s, 1H, $-\mathrm{C}\underline{\mathrm{H}}\mathrm{O}$).

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