2-Formylbenzenesulphonyl Chloride as a Reagent for the Protection of Phenols

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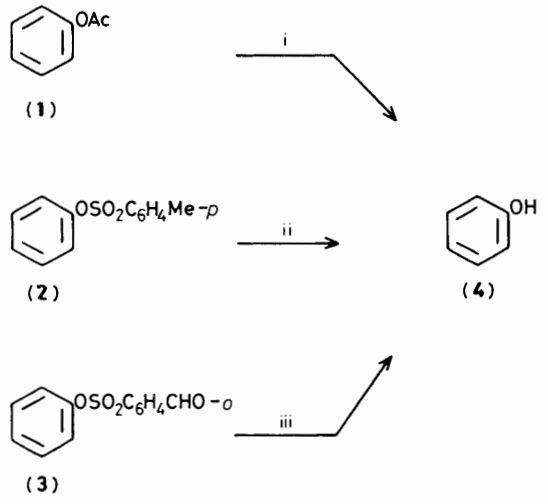
2-Formylbenzenesulphonate esters of phenols are rapidly cleaved by alkali leaving carboxylate esters untouched.

Methods for the protection of phenolic hydroxy functions usually involve formation of alkyl ethers or esters. Groups such as acetyl,[1] pivolyl,[2] vinylcarboxy,[3] and fluoren-9-ylcarboxy[4] are among the most commonly used carboxylic acid groups. Although sulphonyl esters show a far greater stability to acidic conditions,[5] they are not commonly used because of the difficulty in removing them. Long reaction times and strongly basic conditions are required.[6]

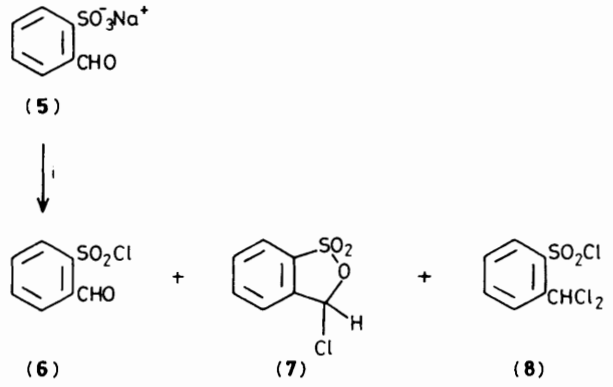
During a study of neighbouring group effects,[7] particularly of keto participation, we found that phenyl 2-formylbenzenesulphonates are hydrolysed about 10^6 times faster than the corresponding 4-formyl derivatives. The application of this result for synthetic purposes is demonstrated in the present communication.

Scheme 1 compares the conditions required for the hydrolysis of phenyl acetate (**1**), phenyl toluene-*p*-sulphonate (**2**), and phenyl 2-formylbenzenesulphonate (**3**) to phenol (**4**). The conditions required for the hydrolysis of (**3**) are even milder than those required for the hydrolysis of (**1**) owing to the presence of the γ-carbonyl group.

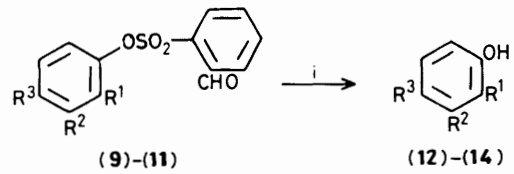
2-Formylbenzenesulphonyl chloride[8] (**6**) can be prepared by refluxing commercially available sodium 2-formylbenzenesulphonate (**5**) (5 g) with thionyl chloride (15—20 ml) for 3 min in the presence of a catalytic amount of dimethylformamide (DMF) (Scheme 2). Quenching the reaction mixture with ice and extraction with methylene chloride gives a mixture of products, consisting of (**6**), its pseudo isomer[9] (**7**), and 2-dichloromethylbenzenesulphonyl chloride (**8**). Extrac-



Scheme 1. *Reagents and conditions:* i, aqueous MeOH, saturated $NaHCO_3$, 40 min 25 °C; ii, aqueous EtOH, 0.6 M NaOH, 65 min reflux; iii, aqueous Me_2CO, 0.05 M NaOH, 5 min 25 °C.

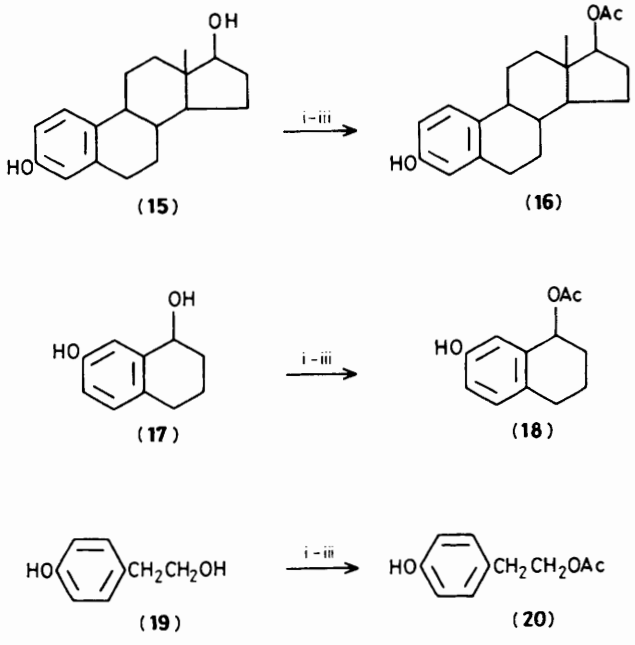


Scheme 2. i, $SOCl_2$–DMF, 3 min reflux.



(**9**),(**12**) $R^1 = R^2 = H$, $R^3 = CH_2CO_2Me$ 93%
(**10**),(**13**) $R^2 = R^3 = H$, $R^1 = CO_2Me$ 93%
(**11**),(**14**) $R^1 = R^3 = H$ $R^2 = OCOMe$ 83%

Scheme 3. i, Base, aqueous Me_2CO, 5 min 25 °C.



Scheme 4. *Reagents:* i, (**6**), NEt_3; ii, MeCOCl, NEt_3; iii, NaOH, Me_2CO.

tion of the mixture with pentane leaves behind (**7**) as a residue. Compounds (**6**) and (**8**) can then be separated by silica gel column chromatography.

Sulphonates (**9**), (**10**), and (**11**)† were prepared by the reaction of (**6**) with phenols (**12**), (**13**), and (**14**) respectively, in the presence of triethylamine. Hydrolysis of these sulphonates to the corresponding phenol showed that the carboxylic acid esters remain unaffected under the conditions used for the hydrolysis of the sulphonate moiety (Scheme 3). The sulphonate (1 mmol) was dissolved in acetone (10 ml). An aqueous solution of sodium hydroxide (0.1 M) was added over a period of 2—3 min with stirring [sodium carbonate was used in the case of (**11**)]. After stirring for 2—3 min, the reaction mixture was acidified (HCl) and saturated with sodium chloride. The product was obtained by extraction with diethyl ether.

Selective esterification of an alcoholic hydroxy group in the presence of a phenolic hydroxy group could be achieved indirectly (Scheme 4). The phenolic function of estradiol (**15**) was protected as the 2-formylbenzenesulphonate derivative. A solution of (**6**) (0.102 g) in dry diethyl ether (3 ml) was added dropwise with stirring to a solution of (**15**) (0.12 g in 10 ml diethyl ether) and triethylamine (0.06 g) over a period of 1 h. Stirring was continued for 4 h. The reaction mixture was diluted with diethyl ether and washed with dilute hydrochloric acid and water and then dried. The solid product obtained (m.p. 61—62 °C, $\nu_{max.}$ 1700 cm^{-1}) was acetylated with acetyl chloride (0.05 g) in the presence of triethyl amine (0.1 g) in dry diethyl ether. The product so obtained (gummy solid; $\nu_{max.}$ 1740, 1700 cm^{-1}) was hydrolysed as in the case of (**9**). Monoacetate (**16**) was purified by passing through a short column of silica gel. Overall yield 70%, m.p. 213—214 °C (lit.[10] m.p. 217 °C), $\nu_{max.}$ 3500—3300, 1720 cm^{-1}.

† All the n.m.r. spectra were recorded in $CDCl_3$ solution. I.r. spectra of solids were recorded as Nujol mulls and of liquids as neat films.

Selected data: (**9**): m.p. 75—76 °C; $\nu_{max.}$ 1740, 1700 cm^{-1}; ^1H n.m.r. δ 3.6 (s, 2H), 3.75 (s, 3H), 6.8—7.4 (q, 4H), 10.6 (s, 1H).

(**10**) M.p. 112—113 °C; $\nu_{max.}$ 1720, 1690 cm^{-1}; ^1H n.m.r. δ 3.8 (s, 3H), 7.0—8.4 (m, 8H), 10.7 (s, 1H).

(**11**): Gum; $\nu_{max.}$ 1760, 1690 cm^{-1}; ^1H n.m.r. δ 2.3 (s, 3H), 6.7—8.3 (m, 8H), 10.6 (s, 1H).

(**18**): Liquid; $\nu_{max.}$ 3600—3300, 1730 cm^{-1}; ^1H n.m.r. δ 1.6—2.9 (m, 6H and OH), 2.05 (s, 3H), 5.9 (t, 1H), 6.6—7.3 (m, 3H).

(**20**) Liquid: $\nu_{max.}$ 3600—3200, 1730 cm^{-1}; ^1H n.m.r. δ 2.05 (s, 3H), 2.8 (t, 2H), 4.2 (t, 2H), 6.6—7.2 (q, 4H and OH).

Employing similar reaction sequences, diols (**17**) and (**19**) could be converted into the monoacetates† (**18**) (68%) and (**20**) (61%) respectively. They are freely soluble in aqueous sodium hydroxide.

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