A New Route to 5-Substituted Resorcinols

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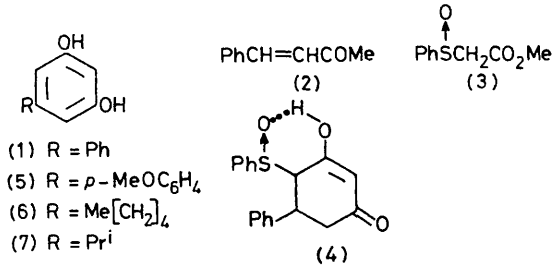
Summary A simple two-step synthesis of a range of 5-substituted resorcinols is described.

5-SUBSTITUTED resorcinol residues occur in a wide variety of natural products,[1] although sources of such substituted aromatic systems are limited. Current methods for obtaining such derivatives include modification of 3,5-dimethoxybenzoic acid,[2] substitution into pyrogallol systems followed by reductive elimination of the 2-hydroxy group,[3] and total syntheses.[4]

Herein we describe a short and versatile method for the total synthesis of such systems. The previously described methods, such as that described by Marmor,[5] suffer from the need to aromatise cyclohexanedione systems using oxidants such as bromine[4a] or copper(II) bromide.[5] In our method the oxidant is incorporated into the initial cyclisation product. The method is exemplified by the synthesis of the phenyl derivative (**1**).

Addition of benzylidenacetone (**2**) to a solution of methyl (phenylsulphinyl)acetate (**3**) and magnesium methoxide (8 equiv.) in methanol at room temperature and stirring the mixture for 16 h resulted, after removal of solvent, acidification, and extraction into ether, in formation of a mixture of isomeric products (**4**). This was best purified by extraction from the ether solution into aqueous sodium hydrogen carbonate, reacidification, and extraction into ethyl acetate. Evaporation afforded (**4**) as an unstable solid, shown to be a mixture of stereoisomers by ^{1}H n.m.r. spectroscopy. Heating a solution of this mixture in benzene at reflux for 2—3 h converted it into one major product, 5-phenylresorcinol (**1**); purification (preparative t.l.c.) gave a 43% yield of crystalline material, m.p. 155—157 °C (lit.[6] m.p. 157 °C).



The formation of the resorcinol is envisaged to proceed by base-catalysed Michael addition and condensation between the reactants. Thermal elimination of phenylsulphenic acid produces the resorcinol. In the base-catalysed step between 4 and 8 equiv. of magnesium methoxide appear to be optimal.

In a similar manner 5-(4-methoxy)phenylresorcinol (**5**) was obtained in 60% yield, m.p. 152—153 °C (lit.,[7] m.p. 158—159 °C). The reaction scheme can also be applied to the preparation of 5-alkyl-substituted resorcinols. In this manner both olivetol (**6**) (m.p. 45 °C; 45%)[4a] and 5-isopropylresorcinol (**7**) (oil; 30%)[8] were obtained.

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