Regioselective 4-Demethoxylation of 1-n-Alkyl-3,4,5-trimethoxybenzenes: a Key Step in the Synthesis of Olivetol and its Homologues

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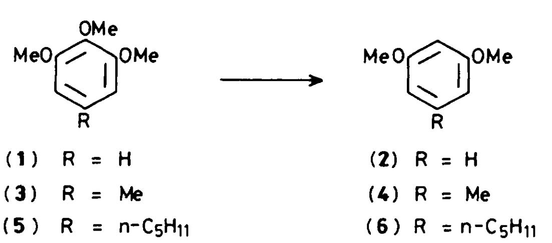
Selective removal of the 4-methoxy group in 1-n-alkyl-3,4,5-trimethoxybenzenes was performed under electron-transfer conditions; a new synthesis of olivetol dimethyl ether is described.

Among the different approaches to the synthesis of 5-n-alkylresorcinols [particularly olivetol (1-n-pentyl-3,5-dihydroxybenzene)],[1–8] significant intermediates in the synthesis of cannabinoids,[9] those which are attractive from an economic point of view[4,10] use readily available and cheap starting materials such as 3,4,5-trimethoxybenzoic acid. The key step of such procedures is the selective removal of the 4-methoxy group. This has been accomplished hitherto under electron-transfer conditions by dissolving metal reduction, using a large excess of sodium in t-butyl alcohol for 3,4,5-trimethoxy-substituted aryl ketones[1] and the corresponding benzyl alcohols.[2] This method, however, presents some drawbacks,



Scheme 1. *Reagents and conditions*: K, THF, room temp., 24 h.

$$\underset{(7)}{RCO_2H} \xrightarrow{i} \underset{(8)}{RCOCl} \xrightarrow{ii} \underset{(9)}{RCO[CH_2]_3Me} \xrightarrow{iii} \underset{(5)}{R[CH_2]_4Me}$$

R = 3,4,5-trimethoxyphenyl

Scheme 2. *Reagents and conditions:* i, $SOCl_2$, reflux, 5 h, 92%; ii, $Me[CH_2]_3MgBr$, $ZnCl_2$ in benzene, room temp., 12 h, 90%; iii, NH_2NH_2 in EtOH, reflux, 5 h, then KOH, 180 °C, 1 h, 75%.

e.g. the large amount of sodium metal necessary (up to 40 : 1 molar ratio) and the poor quality of the product(s). On the other hand, alternative procedures based on the reductive elimination of a diethyl phosphate ester group in 1-alkyl-3,5-dimethoxy-4-hydroxyphenyl diethyl phosphates[5,11] suffer from the high cost of the starting material, *i.e.* 2,6-dimethoxyphenol; several related procedures for the deoxygenation of phenol derivatives are also available.[12]

In the course of our research on the electron-transfer reduction of models for the monomeric units of lignin,[13] we have found a simple method of selective demethoxylation of 1,2,3-trimethoxybenzene (**1**) in weakly polar solvents under rigorously aprotic conditions. In a typical experiment, compound (**1**) (10.0 g, 60 mmol), dissolved in anhydrous tetrahydrofuran (THF) (60 ml),† was treated at room temperature with finely divided potassium metal (5.9 g, 0.15 g atom) under nitrogen with efficient stirring for 24 h. After cooling to 0 °C, the reaction mixture was quenched by careful dropwise addition of anhydrous ethanol under nitrogen in an efficient hood, followed by addition of water after disappearance of all the potassium residues. Standard work-up afforded resorcinol dimethyl ether (**2**) (7.0 g, 85% yield). Secondary products were 2,3- and 2,6-dimethoxyphenol, easily removed from the reaction mixture during work-up. Extension of the reaction to 1-methyl-3,4,5-trimethoxybenzene (**3**) afforded dimethylorcinol (3,5-dimethoxytoluene) (**4**) in 87% yield (Scheme 1).

The procedure was further extended to the demethoxylation of 1-n-pentyl-3,4,5-trimethoxybenzene (**5**), prepared in 62% overall yield through the sequence of reactions reported in Scheme 2. Selective demethoxylation of (**5**) under the conditions reported for (**1**) and (**3**) afforded olivetol dimethyl ether (**6**) in 82% yield, from which olivetol was obtained by known procedures.[10,11]

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† Similar results were obtained in n-heptane or iso-octane (2,2,4-trimethylpentane).

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