A Synthesis of 1-Alkyl-3,5-dimethoxybenzenes

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The reaction of 3,4,5-trimethoxybenzaldehyde or 3,4,5-trimethoxyphenyl methyl ketone with alkyl magnesium halides gives secondary or tertiary carbinols. These are converted in good yields into 1-alkyl-3,5-dimethoxybenzenes by reaction with dissolving sodium in alcohols.

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Les réactions du triméthoxy-3,4,5 benzaldéhyde ou de la triméthoxy-3,4,5 phényl méthyl cétone avec les halogénures de méthylmagnésium conduisent aux alcools secondaires ou tertiaires correspondants. La réaction de ces derniers avec du sodium dissous dans les alcools conduit avec de bons rendements aux alkyl-1 diméthoxy-3,5 benzène.

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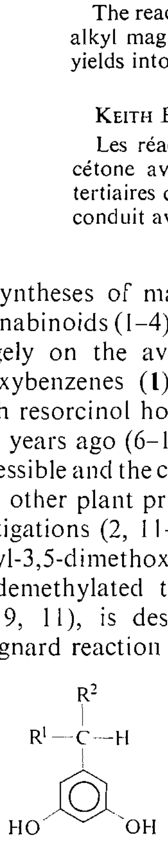
Syntheses of many plant products including cannabinoids (1–4) and their homologues depend largely on the availability of 1-alkyl-3,5-dihydroxybenzenes (**1**) (5). Although syntheses of such resorcinol homologues were described several years ago (6–10), they remain somewhat inaccessible and the current interest in cannabinoids and other plant products has spurred further investigations (2, 11–13). A simple synthesis of 1-alkyl-3,5-dimethoxybenzenes (**2**), which are readily demethylated to the 3,5-dihydroxybenzenes (2, 9, 11), is described here. It involves the Grignard reaction of an alkyl magnesium halide with 3,4,5-trimethoxybenzaldehyde or 3,4,5-trimethoxyphenyl methyl ketone (which are more readily available than their 3,5-dimethoxy counterparts) to give a carbinol (**3**; R^1 = H or CH_3) which is simultaneously 4-demethoxylated and reduced in the side chain to give the dimethoxybenzenes (**2**; R^1 = H or CH_3) by the action of dissolving sodium in *t*-butanol. The last step is an extension and improvement of a reaction described by Asahina (6) in which dimethoxybenzenes (**2**; R^1 = H) were prepared from 3,4,5-trimethoxyphenyl alkyl ketones with dissolving sodium in alcohol. If the resorcinol derivatives (**1**) are desired, it is not generally necessary to purify the intermediates **2** and **3**. Typical procedures are described in the Experimental section.



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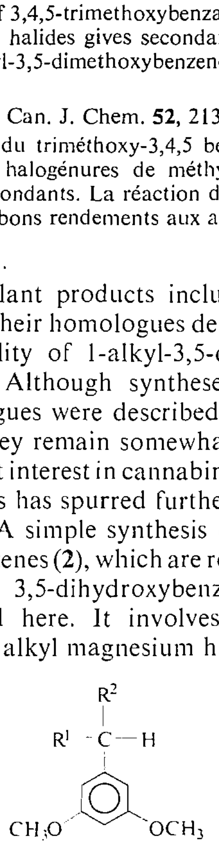

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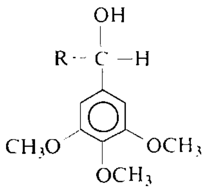

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When the reaction was first investigated, Asahina's procedure (6) (add sodium pieces and ethanol or isopropanol to 3,4,5-trimethoxyphenyl alkyl ketones) was applied to the carbinol. A number of 1-alkyl-3,5-dimethoxybenzenes were prepared (**2**; R^1 = H, R^2 = CH_3; R^1 = H, R^2 = n-C_3H_7; R^1 = H, R^2 = n-C_4H_9; R^1 = H, R^2 = n-C_5H_{11}; R^1 = H, R^2 = C_6H_5; R^1 = CH_3, R^2 = n-C_3H_7; R^1 = CH_3, R^2 = n-C_4H_9; R^1 = CH_3, R^2 = n-C_6H_{13}; R^1 = CH_3, R^2 = cyclohexyl; R^1 = CH_3, R^2 = C_6H_5) but the yields were only fair (about 75% isolated, about 60% pure). A more satisfactory practice (see

TABLE 1. Effect of change in alcohol on reduction* of 3 (R^1 = H, R^2 = n-C_5H_{11})

Alcohol	Isolated crude yield (%)	Purity (%)
Methanol	99	77
Ethanol	83	67
i-Propanol	92	85
t-Butanol	92	93

*For conditions, see Experimental; purity was estimated by g.l.c. assuming equal response factors.

TABLE 2. Effect of change in proportion of sodium on reduction* of 3 (R^1 = H, R^2 = n-C_5H_{11})

Quantity of 3 (mmol)	Quantity of sodium (mmol)	Crude yield (%)	Purity (%)
1.2	43	83	98
2.4	43	92	93
5.0	43	97	61

*See footnote, Table 1.

TABLE 3. Yields of 2 on reduction* of different carbinols 3

3	Crude yield 2 (%)	Purity of 2 (%)
R^1 = H, R^2 = n-C_3H_7	89	86
R^1 = H, R^2 = n-C_5H_{11}	92	93
R^1 = H, R^2 = cyclohexyl	100	54
R^1 = H, R^2 = C_6H_5	93	84
R^1 = CH_3, R^2 = cyclohexyl	89	50
R^1 = CH_3, R^2 = C_6H_5	96	57

*See footnote, Table 1.

Experimental) was to generate sodium sand (14), cover it with a little benzene, add the carbinol, and then the alcohol. The effect of changing the alcohol on the reduction of 3 (R^1 = H, R^2 = n-C_5H_{11}) was investigated with the results shown in Table 1. t-Butanol had the advantage of a good yield of material which was sufficiently pure for subsequent transformation. The effects of changing the ratio of sodium to carbinol are shown in Table 2; a molar ratio of about 20:1 (about half that employed by Asahina (6)) afforded a good yield of reasonably pure product. Yields of **2** from different carbinols (**3**) are shown in Table 3. Starting materials of approximately 95% purity, estimated by gas–liquid chromatography (g.l.c.) were employed in investigating the yields presented in the tables.

A frequent by-product of the synthesis of **3** was the olefin corresponding to its dehydration. Investigations on 1-(3,4,5-trimethoxyphenyl)-hexene as an example showed that it was converted into **2** (R^1 = H, R^2 = n-C_5H_{11}) under the reduction conditions and so in practical syntheses the crude Grignard product (**3**) was usually used without purification.

The progress of the reduction of the carbinols was monitored by g.l.c. and the formation of an "intermediate" was noted. A small amount was isolated by column chromatography of the products from the reduction of **3** (R^1 = H, R^2 = n-C_5H_{11}) and identified spectroscopically and by comparison with material synthesized from 3,5-dimethoxybenzaldehyde as the 4-demethoxylated product **2** (R^1 = OH, R^2 = n-C_5H_{11}). (These products can be converted into **2** by dehydration (refluxing xylene) followed by hydrogenation or into **1** by simultaneous demethylation and dehydration with pyridine hydrochloride (2) followed by hydrogenation.)

Experimental

Proton magnetic resonance (p.m.r.) spectra were determined at 60 MHz for solutions in deuteriochloroform containing tetramethylsilane as internal reference, with a Varian A60A spectrometer. Infrared (i.r.) spectra were determined on natural films or Nujol mulls with a Unicam SP1000 spectrophotometer. Gas–liquid chromatography was performed on a Varian Aerograph 1520 with 6 ft long × 3/16 in. i.d. glass columns containing 5% OV-7 on 80–100 mesh Chromosorb W, injection port, and flame ionization detector at 275°, nitrogen flow 30 ml/min, and an appropriate oven temperature (175–225°, depending on retention time).

Preparation of Carbinols (3)

Typically, magnesium turnings (1.725 g, 0.0725 mol) were covered with dry ether (25 ml) and bromoalkane (1 g) was added to initiate formation of the Grignard reagent. The bromoalkane (to total 0.075 mol) in dry ether (25 ml) was then added and the mixture heated under reflux with stirring until no magnesium remained. A solution of 3,4,5-trimethoxybenzaldehyde or 3,4,5-trimethoxyphenyl methyl ketone (0.05 mol) in dry benzene (75 ml) was added dropwise and the mixture was stirred under reflux for 2 h and then allowed to cool. Hydrochloric acid (1.5 *N*, 50 ml) was added cautiously. The aqueous layer was separated and extracted with benzene (50 ml) and the organic phases were combined, dried ($MgSO_4$), and concentrated to furnish the carbinol (**3**). In the case of **3** (R^1 = H), the products were usually of reasonable purity (*ca.* 90%) and were used in the reduction step (6). For the purposes of quantitative investigation, carbinols **3** (R^1 = H, R^2 = cyclohexyl, and R^1 = CH_3, R^2 = C_6H_5) were purified by recrystallization from mixtures of hexane with chloroform and **3** (R^1 = CH_3, R^2 = cyclohexyl) was purified by adsorption onto a column of silica gel and elution with chloroform. The carbinols **3** (R^1 = H or CH_3) had very similar i.r. spectra with absorption at *ca.* 3450, 1590, 1505, 1415, 1325, 1235, 1130, 1005, and 935 cm^{-1}. Their p.m.r. bands included δ *ca.* 3.9 (OCH_3) and for **3** (R^1 = H) at 6.55 (Ar*H*) and *ca.* 4.3–4.6 (benzylic *H*, multiplicity and position depending on R^2) and for **3** (R^1 = CH_3) at 6.67 (Ar*H*) and 1.57 (benzylic CH_3) p.p.m.

Reduction of Carbinols (3)

Typically, sodium sand (1 g, 43 mmol) was prepared (14) in a round bottom flask and covered with dry benzene (5 ml). The carbinol (2.5 mmol) was added. A two-neck adaptor with a condenser and dropping funnel were fitted. The mixture was stirred magnetically and kept at 80–85° on an oil bath. The alcohol (15 ml) was added (methanol or ethanol were added dropwise to keep the ensuing reaction moderate but *t*-butanol could be added safely in one steady portion). The mixture was stirred at 80–85° for 3–4 h (extended periods did not significantly improve the yields), inspected for the disappearance of all sodium, and then poured into water (300 ml). The mixture was acidified (HCl) and extracted with ether (3 × 50 ml). The extract was dried ($MgSO_4$) and concentrated. The products **2** (R^1 = H or CH_3) had similar i.r. spectra with absorption bands at *ca.* 1605, 1595, 1200, 1150, 1060, and 830 cm^{-1} (by-products **2**; R^1 = OH, had ν_{max} 3400, 1605, 1595, 1200, 1150, 1060, and 840 cm^{-1}). Their p.m.r. bands included δ 6.33 (Ar*H*), 3.77 (OCH_3), *ca.* 2.3–2.6 (benzylic protons, multiplicity and position depending on R^1 and R^2) and for **2** (R^1 = CH_3) 1.20 (doublet, benzylic CH_3) p.p.m. (by-products **2**; R^1 = OH, had δ *ca.* 6.50 (Ar*H* at 2 and 6), 6.38 (Ar*H* at 4), 3.78 (OCH_3) and *ca.* 4.5 (benzylic proton, multiplicity and position depending on R^2) p.p.m.).

In experiments where the proportion of sodium was changed, the volume of *t*-butanol was kept constant. The products **2** could be purified by adsorption on to silica gel and elution with chloroform in hexane, and their conversion into **1** accomplished with pyridine hydrochloride (2).

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