Regioselective Reductive Alkylation of 3,4,5-Trimethoxybenzaldehyde Dimethylacetal: A New Synthesis of 4-Alkyl-3,5-dimethoxybenzaldehydes and 2,5-Dialkyl-1,3-dimethoxybenzenes

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The regioselective replacement of the 4-methoxy group of 3,4,5-trimethoxybenzaldehyde dimethylacetal by an alkyl group under reductive electron-transfer conditions has been employed as a key step in a new synthesis of 2,5-dialkyl-1,3-dimethoxybenzenes via the corresponding 4-alkyl-3,5-dimethoxybenzaldehydes.

2,5-Dialkylresorcinols are an important class of natural products with significant biological and pharmacological properties; however, there are few reported syntheses of such compounds, in comparison, for instance, with the variety of synthetic procedures reported for 5-alkylresorcinols (olivetol and homologs).

We have recently reported a synthetic procedure allowing the regioselective replacement of the 2-methoxy group of 1,2,3-trimethoxybenzene and of its 5-methyl-substituted homolog with an alkyl group. As a continuation of our research on the demethylation of aromatic substrates under reductive electron-transfer conditions we have extended this reaction to other 5-alkyl substituted 1,2,3-trimethoxybenzenes; however, poor yields (10-20%) of the corresponding products were obtained.

This was applied to a new synthesis of 1,3-dimethoxy-2-butylyl-5-pentylbenzene (4d) and 1,3-dimethoxy-2-hexyl-5-propylbenzene (4e), from which the corresponding resorcinols, the natural antibiotics stemphol and DB 2073, respectively, can be easily obtained.

Reaction of aldehyde 2d with freshly prepared butylmagnesium bromide in diethyl ether afforded the carbinol 3d (89%); catalytic hydrogenolysis of the latter with 10% palladium on carbon in refluxing acetic acid, using ammonium formate as a hydrogen donor, afforded 4d (92%). Likewise, 4e was prepared through the sequence 2e → 3e (92%) → 4e (89%).

All reagents were of the highest commercial quality from freshly opened containers. HCOONH₄, HCl(OMe)₂, Et₃N, NH₄Cl, Na and 10% Pd-C were purchased from Janssen. 3,4,5-Trimethoxybenzaldehyde (Janssen) was dried in vacuo before use. Et₂O and THF were dried and distilled over Na. MeOH was dried and distilled over Mg. Boiling and melting points are uncorrected.

H-NMR spectra were recorded on a Varian T-60 spectrometer.

3,4,5-Trimethoxybenzaldehyde Dimethylacetal (1): 3,4,5-Trimethoxybenzaldehyde (10 g, 51 mmol) is added under N₂ to a suspension of NH₄Cl (150 mg, 3 mmol) in a solution of HC(O Me)₂ (20 mL) in MeOH (20 mL), and the mixture is stirred at reflux for 3 h. After cooling to r.t., Et₃N (1.5 mL, 7 mmol) is added, followed, after a few minutes stirring, by H₂O (30 mL). The mixture is extracted with Et₂O (3 x 30 mL), and the organic phase is washed with sat. aq NaHCO₃ (30 mL), H₂O (30 mL), and dried (Na₂SO₄). The solvent is evaporated and the crude product is purified by distillation to give a colorless oil which solidifies upon standing; yield: 10.3 g (83%); bp 180°C/10 Torr.

C₇H₁₄O₃ calc. C 59.48 H 7.50
(242.3) found 59.17 7.38

H-NMR (CDCl₃/TMS): δ = 2.98 (s, 6 H, CH(OCH₃)₂), 3.80 (s, 3 H, OCH₃), 3.87 (s, 6 H, OCH₃), 4.57 (br s, 1 H, CH), 6.73 (br s, 2 H, arom).

3,5-Dimethoxybenzaldehyde (2a): A solution of I (1.5 g, 6 mmol) in anhydrous THF (6 mL) is added dropwise to a mixture of freshly cut Na (0.43 g, 18 mmol) in THF (15 mL) chilled at 0°C under dry N₂. The mixture is stirred at r.t. for 24 h, then cooled to 0°C, and quenched by very careful dropwise addition of H₂O (10 mL). Et₂O (20 mL) is added, and the
organic phase is washed with H$_2$O (20 mL) and evaporated. The crude acetal is dissolved in THF/1 N HCl (1:1, 20 mL) and stirred at rt. for 5 h. The mixture is extracted with Et$_2$O (3 × 30 mL), and the organic phase is washed with H$_2$O (2 × 20 mL), dried (Na$_2$SO$_4$), and evaporated to afford crude 2a which is purified by distillation to afford a colorless solid; yield: 0.9 g (90%); br. s 142°C/10 Torr; mp 46–48°C (from Et$_2$O/pentane); (Lit.$^9$ bp 151°C/16 Torr; Lit.$^{10}$ mp 46.5–47°C).

2.5-Dialkyl-1,3-dimethoxybenzenes 4d,e; General Procedure: The appropriate alkanol 3 (3.6 mmol) is added to a suspension of HCO$_2$NH$_2$ (0.9 g, 14 mmol) and 10% Pd-C (0.2 g) in glacial AcOH (40 mL) under dry N$_2$. The reaction mixture is stirred at reflux for 12 h, then again HCO$_2$NH$_2$ (0.2 g, 3 mmol) and 10% Pd-C (50 mg) are added, and the reaction mixture is stirred at reflux for 2 h. The catalyst is filtered off under N$_2$, and washed with AcOH (10 mL) and CH$_2$Cl$_2$ (2 × 20 mL). The filtrate is washed with H$_2$O (2 × 20 mL), sat. aq NaHCO$_3$ (2 × 20 mL), and H$_2$O (2 × 30 mL), and dried (Na$_2$SO$_4$). Evaporation of the solvent affords the crude product 4 which is purified by distillation (Table).

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(5) Azzena, U.; Denurra, T.; Mellonii, G.; Pirotto, A. M. un-published results; see also ref. 1.

(6) Although mentioned, the synthesis and the characterization of compound 1 have never been reported; see, for example, Torii, S.; Inokuchi, T.; Takagishi, S.; Horike, H.; Kuroda, H. Bull. Chem. Soc. Jpn. 1987, 60, 2173.

(7) Reduction of I with Na followed by addition of 2-iodopropane and workup, afforded 2a in 92% yield; see also ref. 3.

