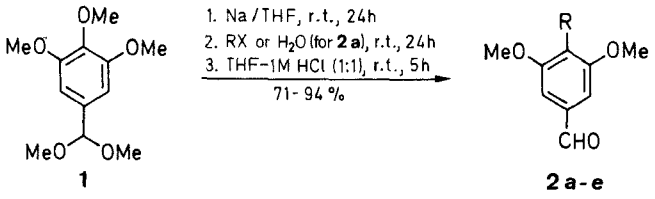
Regioselective Reductive Alkylation of 3,4,5-Trimethoxybenzaldehyde Dimethylacetal: A New Synthesis of 4-Alkyl-3,5-dimethoxybenzaldehydes and 2,5-Dialkyl-1,3-dimethoxybenzenes

Ugo Azzena,* Sergio Cossu, Teresa Denurra, Giovanni Melloni, Anna Maria Piroddi
Dipartimento di Chimica, Universita' di Sassari, Via Vienna 2, I-07100 Sassari, Italy

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;[1] however, there are few reported syntheses of such compounds,[1,2] 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-trimethyoxybenzene and of its 5-methyl-substituted homolog with an alkyl group.[3] As a continuation of our research on the demethoxylation of aromatic substrates under reductive electron-transfer conditions we have extended this reaction to other 5-alkyl substituted 1,2,3-trimethoxybenzenes;[4] however, poor yields (10–20%) of the corresponding products were obtained.[5]

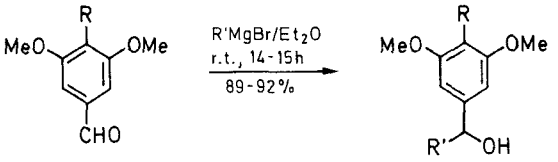


1 → 2a-e

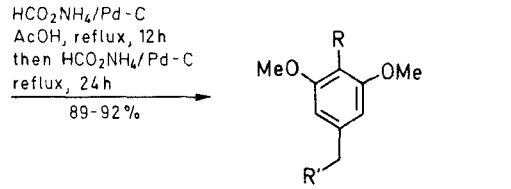
2	R	2	R
a	H	d	Bu
b	Me	e	n-C_6H_{13}
c	Et		

We then examined the use of the inexpensive reagent, 3,4,5-trimethoxybenzaldehyde, with the carbonyl group appropriately protected towards reduction by the alkali metal. Reaction of 3,4,5-trimethoxybenzaldehyde dimethylacetal (**1**)[6] with 3 equivalents of sodium metal in tetrahydrofuran at room temperature for 24 hours afforded, after aqueous workup and acid hydrolysis, 3,5-dimethoxybenzaldehyde (**2a**) in almost quantitative yield.

The reductive alkylation of **1** with primary alkyl halides was successful;[7] under the above reaction conditions, 4-methyl-3,5-dimethoxybenzaldehyde (**2b**), 4-ethyl-3,5-dimethoxybenzaldehyde (**2c**), 4-butyl-3,5-dimethoxybenzaldehyde (**2d**), and 4-hexyl-3,5-dimethoxybenzaldehyde (**2e**) were obtained in good yields by alkylation of the intermediate arylsodium derivative with iodomethane, bromoethane, 1-bromobutane, and 1-bromohexane, respectively (Table).



2d, e → 3d, e



4d R = R' = Bu
e R = n-C_6H_{13}, R' = Et

This was applied to a new synthesis of 1,3-dimethoxy-2-butyl-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.[1] 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,[8] 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. HCO_2NH_4, $HC(OMe)_3$, Et_3N, NH_4Cl, Na and 10% Pd-C were purchased from Janssen. 3,4,5-Trimethoxybenzaldehyde (Janssen) was dried in vacuo before use. Et_2O and THF were dried and distilled over Na. MeOH was dried and distilled over Mg. Boiling and melting points are uncorrected. ^{1}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 N_2 to a suspension of NH_4Cl (150 mg, 3 mmol) in a solution of $HC(OMe)_3$ (20 mL) in MeOH (20 mL), and the mixture is stirred at reflux for 3 h. After cooling to r.t., Et_3N (1.5 mL, 7 mmol) is added, followed, after a few minutes stirring, by H_2O (50 mL). The mixture is extracted with Et_2O (3 × 30 mL), and the organic phase is washed with sat. aq $NaHCO_3$ (30 mL), H_2O (30 mL), and dried (Na_2SO_4). The solvent is evaporated and the crude product **1** is purified by distillation to give a colorless oil which solidifies upon standing; yield: 10.3 g (83%); bp 180°C/10 Torr.

$C_{12}H_{18}O_5$ (242.3) calc. C 59.48 H 7.50 found 59.17 7.38

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.98 (s, 6H, $CH(OCH_3)_2$), 3.80 (s, 3H, OCH_3), 3.87 (s, 6H, OCH_3), 4.57 (br s, 1H, CH), 6.73 (br s, 2H_{arom}).

3,5-Dimethoxybenzaldehyde (2a):
A solution of **1** (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 N_2. The mixture is stirred at r.t. for 24 h, then cooled to 0°C, and quenched by very careful dropwise addition of H_2O (10 mL). Et_2O (20 mL) is added, and the

Table. 4-Alkyl-3,5-dimethoxybenzaldehydes, **2b–e**; 1-(4-Alkyl-3,5-dimethoxyphenyl)alkanols, **3d–e**; and 2,5-Dialkyl-1,3-dimethoxybenzenes, **4d,e** Prepared

Product	Yield (%)	bp (°C)/Torr or mp (°C) solvent	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
2b	71	93–4 (acetone)	$C_{10}H_{12}O_3$ (180.2)	2.10 (s, 3H, CH_3), 3.90 (s, 6H, OCH_3), 6.98 (s, $2H_{arom}$), 9.67 (s, 1H, CHO)
2c	75	68–9 (*i*-PrOH/H_2O)	$C_{11}H_{14}O_3$ (194.3)	1.12 (t, 3H, $J = 7$, CH_3), 2.77 (q, $2H_{benzylic}$, $J = 7$), 3.97 (s, 6H, OCH_3), 7.10 (s, $2H_{arom}$), 9.50 (s, 1H, CHO)
2d	86	60–1 (*i*-PrOH/H_2O)	$C_{13}H_{18}O_3$ (222.3)	0.9–1.11 (m, 3H, CH_3), 1.23–1.67 (m, $4H_{aliph}$), 2.73 (t, $2H_{benzylic}$, $J = 7$), 3.93 (s, 6H, OCH_3), 7.12 (s, $2H_{arom}$), 9.83 (s, 1H, CHO)
2e	84	52–3 (*i*-PrOH/H_2O)	$C_{15}H_{22}O_3$ (250.4)	0.87–1.06 (m, 3H, CH_3), 1.17–1.56 (m, $6H_{aliph}$), 2.63 (br t, $2H_{benzylic}$), 3.90 (s, 6H, OCH_3), 6.95 (s, $2H_{arom}$), 9.80 (s, 1H, CHO)
3d	89	40–1 (*i*-PrOH/H_2O)	$C_{17}H_{28}O_3$ (280.5)	0.75–0.9 (m, 6H, CH_3), 1.10–1.76 (m, $10H_{aliph}$), 2.16 (br s, 1H, OH), 2.33–2.70 (m, $2H_{benzylic}$), 3.72 (s, 6H, OCH_3), 4.43 (t, $1H_{benzylic}$, $J = 6$), 6.40 (s, $2H_{arom}$)
3e	92	64–5 (pentane)	$C_{17}H_{28}O_3$ (280.5)	0.77–1.06 (m, 6H, CH_3), 1.17–1.77 (m, $10H_{aliph}$), 2.32 (br s, 1H, OH), 2.33–2.73 (n, $2H_{benzylic}$), 3.80 (s, 6H, OCH_3), 4.48 (t, $1H_{benzylic}$, $J = 6$), 6.40 (s, $2H_{arom}$)
4d	92	131/2	$C_{17}H_{28}O_2$ (264.5)	0.75–1.08 (m, 6H, CH_3), 1.15–1.73 (m, $10H_{aliph}$), 2.40–2.80 (m, $4H_{benzylic}$), 3.80 (s, 6H, OCH_3), 6.28 (s, $2H_{arom}$)
4e	89	120/1.5	$C_{17}H_{28}O_2$ (264.5)	0.78–1.09 (m, 6H, CH_3), 1.14–1.75 (m, $10H_{aliph}$), 2.38–2.79 (m, $4H_{benzylic}$), 3.77 (s, 6H, OCH_3), 6.23 (s, $2H_{arom}$)

[a] Satisfactory microanalyses: C ± 0.41; H ± 0.25.

organic phase is washed with H_2O (20 mL) and evaporated. The crude acetal is dissolved in THF/1 N HCl (1:1, 20 mL) and stirred at r.t. for 5 h. The mixture is extracted with Et_2O (3 × 30 mL), and the organic phase washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and evaporated to afford crude **2a** which is purified by distillation to afford a colorless solid; yield: 0.9 g (90%); bp 142°C/10 Torr; mp 46–48°C (from Et_2O/pentane); (Lit.[9] bp 151°C/16 Torr; Lit.[10] mp 46.5–47°C).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.83 (s, 6H, OCH_3), 6.67 (d, $1H_{arom}$, $J = 3$), 7.00 (d, $2H_{arom}$, $J = 3$), 9.83 (s, 1H, CHO).

4-Alkyl-3,5-dimethoxybenzaldehydes 2b–e; General Procedure:
A solution of **1** (4 g, 17 mmol) in anhydrous THF (20 mL) is added dropwise to a mixture of freshly cut Na (1.2 g, 52 mmol) in THF (60 mL) chilled at 0°C under dry N_2. The mixture is stirred at r.t. for 24 h, then cooled to 0°C, and the appropriate alkyl halide (25 mmol) is added dropwise. After 24 h stirring at r.t., the reaction mixture is quenched by careful dropwise addition of H_2O (20 mL). Et_2O (30 mL) is added, and the organic phase is washed with H_2O (20 mL) and evaporated. The crude product (purity ≥ 95%, according to GC) is dissolved in THF/1 N HCl (1:1, 50 mL) and stirred at r.t. for 5 h. The mixture is extracted with Et_2O (3 × 30 mL), and the organic phase washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and evaporated to afford the crude product **2** which is purified by recrystallization (Table).

1-(4-Alkyl-3,5-dimethoxyphenyl)alkanols 3d, e; General Procedure:
The appropriate aldehyde **2** (11 mmol), dissolved in dry Et_2O (15 mL), is added dropwise to a suspension of alkylmagnesium bromide, freshly prepared from the appropriate 1-bromoalkane (13 mmol) and Mg turnings (0.33 g, 13 mmol) in Et_2O (13 mL). The mixture is stirred overnight at r.t., and then quenched by dropwise addition of a solution of NH_4Cl (1.5 g, 30 mmol) in H_2O (5 mL). The mixture is filtered and the precipitate thoroughly washed with Et_2O (3 × 10 mL); the filtrate is washed with H_2O (2 × 20 mL) and dried (Na_2SO_4). Evaporation of the solvent affords the crude product **3** which is purified by recrystallization (Table).

2,5-Dialkyl-1,3-dimethoxybenzenes 4d,e; General Procedure:
The appropriate alkanol **3** (3.6 mmol) is added to a suspension of HCO_2NH_4 (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_2NH_4 (0.2 g, 3 mmol) and 10% Pd-C (50 mg) are added, and the reaction mixture is stirred at reflux for 24 h. The catalyst is filtered off under N_2, and washed with AcOH (10 mL) and CH_2Cl_2 (2 × 20 mL). The filtrate is washed with H_2O (2 × 50 mL), sat. aq $NaHCO_3$ (2 × 30 mL), and H_2O (2 × 30 mL), and dried (Na_2SO_4). Evaporation of the solvent affords the crude product **4** which is purified by distillation (Table).

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(1) Achenbach, H.; Kohl, W.; Kunze, B. *Chem. Ber.* **1979**, *112*, 1841; and references therein.
(2) Rasmussen, M.; Ridley, D.D.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* **1968**, *21*, 2989; and references therein.
(3) Azzena, U.; Cossu, S.; Denurra, T.; Melloni, G.; Piroddi, A.M. *Tetrahedron Lett.* **1989**, *30*, 1689.
(4) Azzena, U.; Denurra, T.; Melloni, G.; Rassu, G. *Synthesis* **1989**, 28.
(5) Azzena, U.; Denurra, T.; Melloni, G.; Piroddi, A.M. unpublished 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 **1** with Na followed by addition of 2-iodopropane and workup, afforded **2a** in 92% yield; see also ref. 3.
(8) Ram, S.; Spicer, L.D. *Tetrahedron Lett.* **1988**, *29*, 3741; and references therein.
(9) Mauthner, F. *J. Prakt. Chem.* **1920**, *100*, 176.
(10) Ridley, D.D.; Ritchie, E.; Taylor, W.C. *Aust. J. Chem.* **1968**, *21*, 2979.