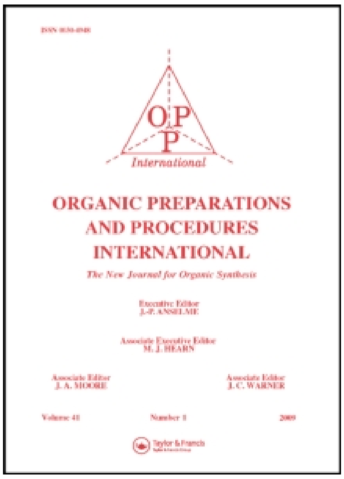

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AN IMPROVED SYNTHESIS OF 2,3-bis(BROMOMETHYL)-1,4-DIMETHOXYBENZENE

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AN IMPROVED SYNTHESIS OF 2,3-bis(BROMOMETHYL)-1,4-DIMETHOXYBENZENE

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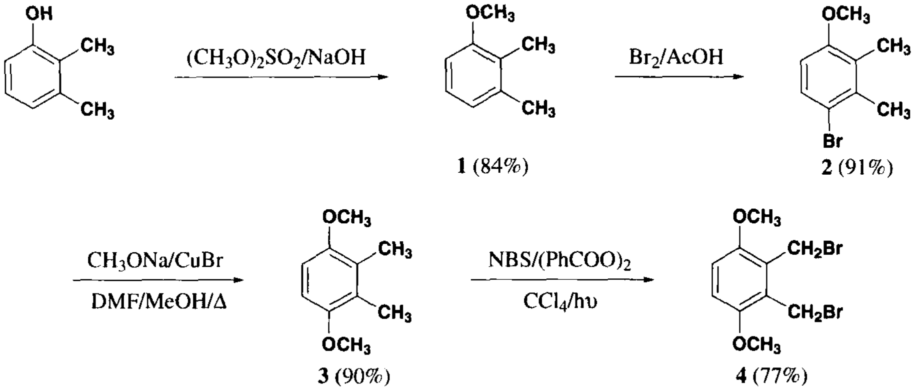
In connection with a project on the synthesis of new types of discotic liquid crystals,[1] large amounts of 2,3-bis(bromomethyl)-1,4-dimethoxybenzene (**4**) were needed. This compound has also been utilized in the synthesis of compounds such as fredericamycin A,[2] anthracycline derivatives,[3,4] xestoquinone,[5] idarubicin analogs,[6] daunomycin,[7] thiochromanones,[8] unnatural aminoacids[9,10] and supramolecular structures.[11,12] Apart from one method,[12] all the previously published procedures start from 2,3-dimethyl-1,4-benzoquinone,[13] which is synthesized in three steps from 2,3-dimethylphenol by coupling with diazotized sulfanilic acid followed by reduction with sodium dithionite to 4-amino-2,3-dimethylphenol, which is finally oxidized to the quinone with $FeCl_3$. The quinone is then reduced and methylated to give 1,4-dimethoxy-2,3-dimethylbenzene, which is brominated under radical conditions to give **4**.[14]



Our procedure which is shown in the Scheme, is based on the nucleophilic substitution of aromatic bromides with methoxide in the presence of Cu(I) in DMF/MeOH, and is simple to perform on a large scale. However, we found that the yield in the final side-chain bromination step was very sensitive to the purity of the NBS used. The best (and reproducible) yields were obtained with either NBS crystallized from water or with commercial grade NBS dried *in vacuo* (0.03 mmHg) for 8 hours prior to use, thus confirming the findings of Chapman and Williams[16] on the side-chain bromination of methylnaphthalene.

EXPERIMENTAL SECTION

The chemicals used were obtained from Aldrich, Fluka and Acros, and were used without further purification unless otherwise noted. NMR spectra were recorded with a Bruker AM 250-MHz or a Varian Unity 400-MHz spectrometer, and all chemical shifts are relative to TMS. GC-MS were recorded with a Hewlett-Packard 5890 Series II instrument with a 5972 series detector, fitted with a 30 m x 0.25 mm HP, 5 M.S. (0.25 mm, crosslinked 5% Ph Me Silicone) column. All melting points are uncorrected.

2,3-Dimethylmethoxybenzene (1).- To a solution of sodium hydroxide (48 g, 1.20 mol) in water (480 mL) was added 2,3-dimethylphenol (114.3 g, 0.84 mol) with stirring. The mixture was cooled to 0° and dimethylsulphate (110 mL, 1.14 mol) was added over 10 minutes. The cooling bath was removed after an additional 30 minutes, and the mixture was allowed to reach room temperature. The mixture was refluxed for 1.5 hour, cooled to room temperature and extracted with ether. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was distilled in vacuum to give 106.9 g (84%) of the pure compound as a nearly colorless oil, bp. 102-107° (100-120 mmHg), *lit.*[17] bp. 73-74° (10 mmHg). ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (t, J = 7.9 Hz, 1 H); 6.81 (d, J = 7.5 Hz, 1 H); 6.74 (d, J = 8.2 Hz, 1 H); 3.84 (s, 3 H); 2.31 (s, 3 H); 2.19 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4; 137.7; 125.6; 122.2; 112.4; 107.7; 55.4; 19.9; 11.4. GC-MS: m/z (intensity): 136 (100%); 105 (18%); 91 (66%); 77 (46%).

4-Bromo-2,3-dimethylmethoxybenzene (2).- A solution of bromine (50 mL, 0.97 mol) in acetic acid (500 mL) was added with stirring to a solution of **4** (113.6 g, 0.83 mol) in acetic acid (1000 mL) over 1 hour. Water (4 L) was added to the mixture followed by a little Na_2SO_3 to destroy excess bromine. The product was extracted by stirring with CH_2Cl_2 (400 mL) for 5 minutes followed by separation of the organic phase. The organic phase was placed in an Erlenmeyer flask and washed free of acids by stirring with aqueous 2M NaOH containing a little phenolphthaleine. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 163.8 g (91%) of product as a pale yellow oil, bp. 145-148° (29 mmHg), *lit.*[18] bp. 140-143° (18 mmHg). ^1H NMR (250 MHz, $CDCl_3$): δ 7.36 (d, J = 8.8 Hz, 1 H); 6.60 (d, J = 8.8 Hz, 1 H); 3.81 (s, 3 H); 2.39 (s, 3 H); 2.23 (s, 3 H). ^{13}C NMR (62 MHz, $CDCl_3$): δ 155.5; 136.7; 129.4; 116.2; 109.2; 55.5; 19.6; 12.7. GC-MS m/z (intensity): 214 (100%); 199 (48%); 135 (22%); 91 (66%).

1,4-Dimethoxy-2,3-dimethylbenzene (3).- To a solution of sodium methoxide in CH_3OH prepared by dissolving Na (20.3 g, 0.88 mol) in CH_3OH (200 mL) was added DMF (200 mL), compound **2** (79.0 g, 0.37 mol) and CuI (4.7 g, 6.7 mol%). The mixture was refluxed for 24 hours or until the disappearance of the starting material on TLC (Silicagel/CH_2Cl_2). Water (500 mL) was added, and the product was steam distilled out of the mixture to give 67.7 g (90%) of **3** as nearly colorless crystals, mp. 79.2-80.1°, *lit.*[15] mp. 78-79°. ^1H NMR (250 MHz, CD_3COCD_3): δ 6.70 (s, 2 H); 3.74 (s, 6 H); 2.11 (s, 6 H). ^{13}C NMR (62 MHz, CD_3COCD_3): δ 152.1; 126.1; 108.1; 55.1; 11.5. GC-MS: m/z (intensity): 151 (100%); 121 (18%); 91 (29%); 77 (23%).

2,3-bis(Bromomethyl)-1,4-dimethoxybenzene (4).- To a refluxing, mechanically stirred mixture of **3**

(18.3 g; 0.11 mol) and NBS (either from the bottle and freshly dried for 8 hours at 0.03 mmHg or freshly crystallized from water followed by drying *in vacuo.*) (42.2 g, 0.23 mol) in CCl_4 (500 mL) was added a solution of benzoyl peroxide (0.4 g) in CCl_4 (10 mL) over 1 hour. When the reaction was complete (typically after 1.5 hour), the reaction mixture was filtered while hot to remove the precipitated succinimide. The solvent was then removed *in vacuo*, and the impurities were washed out of the product with methanol to give 27.5 g (77%) pure **4** as a pale yellow powder, mp. 150-151°, *lit.*[14] mp. 152.2°. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.83 (s, 2 H); 4.73 (s, 6 H); 3.84 (s, 6 H). ^{13}C NMR (62 MHz, $CDCl_3$): δ 151.7; 126.3; 112.1; 56.1; 23.8. GC-MS: m/z (intensity): 324 (20%); 243 (95%); 164 (100%); 149 (50%).

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