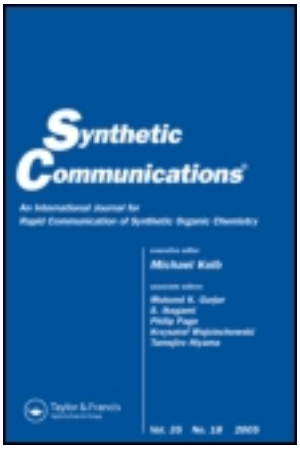

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Improved Synthesis of C_2-Symmetric 4,4′-α,ω-Alkylenedioxy-bis(3-meth

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Improved Synthesis of C_2-Symmetric 4,4′-α,ω-Alkylenedioxy-*bis*(3-methoxybenzaldehydes)

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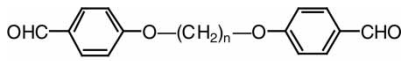
Abstract: An improved Williamson synthesis of C_2-symmetric 4,4′-(α,ω-alkylenedioxy)-*bis*(3-methoxybenzaldehydes) from vanillin is described. These dialdehydes are often insoluble in cold acetone, which renders their purification especially facile.

Keywords: C_2 symmetry, dialdehydes, phenols, Williamson synthesis

INTRODUCTION

The incorporation of the C_2 symmetry element into molecules designed for use as liquid crystals often confers unusual and useful properties on those molecules. Many of these compounds are based on a C_2-symmetric 4,4′-alkylenedioxy-*bis*(arene) carbon skeleton, for which the C_2-symmetric 4,4′-alkylenedioxy-*bis*(benzaldehydes) (e.g., **1**) can provide a useful starting material.



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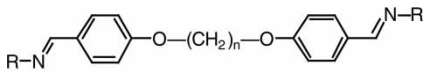
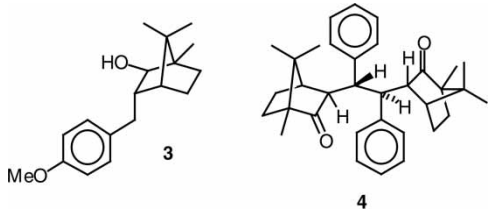
Similar compounds have been used by Date and coworkers in their synthesis of thermotropic liquid crystals (e.g., **2**),[1,2] and such compounds have been widely used in the synthesis of other useful liquid crystalline materials.[3–7]



2

In our own laboratories, we had prepared 3-*endo*-(*p*-methoxybenzyl)isoborneol (**3**) as a chiral alcohol with potential for use in the alkylation of ester lithium enolates.[8] The conformation of the *p*-nitrobenzoate ester of the alcohol[9] suggested that this alcohol would be an excellent chiral auxiliary for this and other reactions of esters, but, in a study of the alkylation of the lithium enolate of its propionate ester,[10,11] it proved to be of marginal utility, giving diastereomeric excesses only in the 24–40% range.[11] One way to improve the levels of asymmetric induction generated by this auxiliary would be to increase the steric bulk at the 3 position while keeping the equivalent weight constant. We attempted to do so by generating C_2-symmetric dimeric analogs by the reductive dimerization of (*E*)-3-benzylidenecamphor.[12] The reaction gave homoacylaoin condensation products as the major products, but the yields were low, and the major product of a complex mixture (**4**) lacked the C_2 symmetry.



3 **4**

We concluded that intramolecular reductive dimerization of a series of C_2-symmetric α,ω-alkylene-*bis*-(3-benzylidenecamphors) might constrain the reaction to occur with C_2 symmetry. Moreover, these compounds might, conceivably, result in the formation of compounds containing a chiral cavity into which the prochiral precursor might bind. Therefore, a series of C_2-symmetric dialdehydes was required for condensation with (1*R*)-(+)-camphor.

RESULTS AND DISCUSSION

The obvious method for the synthesis of these dialdehydes was by the Williamson ether synthesis from a phenolic aldehyde and an α,ω-dihalide with potassium carbonate in acetone.[13] Using vanillin as the model

phenolic aldehyde, we carried out several syntheses of C_2-symmetric dialdehydes. We were surprised, however, to find that on carrying out the reaction with 1,6-dibromohexane according to well-established literature precedent, the product was obtained in only a minute yield ($<2\%$) and was badly contaminated with the excess vanillin. In his studies with *p*-hydroxybenzaldehyde, Wiegel[14] has found that this problem may be partially circumvented by the use of cesium carbonate as the base, but even under these circumstances, the yield is low.

The solution to this problem became apparent when the reaction was checked for mass balance. When this was done, it was found that the majority of the mass was present in the solid recovered by filtration, and that very little of the reaction mass was left in the filtrate—the apparent problem was due to the unexpected solubility characteristics of the product dialdehydes. The majority of the C_2-symmetric dialdehydes, we have subsequently found, are almost insoluble in cold acetone and precipitate with the insoluble inorganic salts. The only dialdehydes that we found to have appreciable solubility in acetone are those whose α,ω-alkylenedioxy chain is based on a poly(ethylene oxide) backbone or those with long α,ω-alkylenedioxy chains. This characteristic solubility is fortuitous, for it permits the extremely facile purification of the C_2-symmetric dialdehydes: the excess phenol and/or alkylene dihalide is removed during the filtration of the acetone solution, and the *bis*(benzaldehyde) is then recovered pure by recrystallization of the acetone-insoluble material from toluene. In this way, the dialdehydes are obtained in typical yields of 50–75%.

It must be pointed out that there is evidence that the scope of this improved synthesis may still be limited: the analytical data obtained for the products obtained when 1,8-dibromooctane and 1,3-dibromopropoane were used are both more consistent with other reactions having occurred. Thus, the propylene compound is consistent with being a CO_2 insertion product that has ether and carbonate ester functionalities, and the octylene compound has a microanalysis and spectroscopic data consistent with an *ansa* lactone derived from a CO_2 adduct of the aldehyde functioning as an intramolecular nucleophile displacing the ω-bromo group of the bromooctylaldehyde, followed by a Cannizzarro-type oxidation to the lactone; neither compound exhibits the observed solubility in acetone of the C_2-symmetric dialdehydes, and neither is obtained in high yield.

EXPERIMENTAL

General

Melting points were measured on a Fisher–Johns hot-stage melting point apparatus and are uncorrected. Infrared spectra were determined as KBr

pellets using a Nicolet 5DXC FT-IR spectrometer. ^{1}H NMR spectra were recorded as $CDCl_3$ solutions using a JEOL Eclipse NMR spectrometer operating at 400 MHz; peak positions are reported as δ (ppm) downfield from internal Me_4Si. ^{13}C NMR spectra were recorded as $CDCl_3$ solutions at 100 MHz; peak positions are reported in ppm relative to the center peak of $CDCl_3$ (77.1 ppm). Vanillin was used as obtained from Fisher Chemical Company; all other reagents and solvents were used as obtained from Aldrich Chemical Company. Microanalyses were performed by Robertson–Microlit Laboratories, Rahway, NJ.

General Procedure

To a stirred solution of the α,ω-dibromide (1.0 eq.) and vanillin ($\geq$2.05 eq.) in acetone ($\approx$20 mL per mmol dihalide) was added potassium carbonate ($\geq$2.1 eq.). The reaction mixture was heated under reflux for 18–24 h, after which time the solids were collected by vacuum filtration. The solids were boiled with approximately 2–3 times their volume of toluene, and the mixture was filtered hot. The 4,4′-(α,ω-alkylenedioxy)-*bis*(3-methoxybenzaldehyde) was obtained as colorless crystals upon cooling the filtrate.

4,4′-(1,4-butylenedioxy)-*bis*(3-methoxybenzaldehyde) was prepared by procedure A from vanillin (15.7 g, 0.102 mol), 1,4-dibromobutane (9.01 g, 0.042 mol), and potassium carbonate (14.2 g, 0.103 mol) in acetone ($\approx$100 mL). The product (7.10 g, 47%) was obtained as white crystalline plates, mp 160–163°C. ν_{max} (cm^{-1}): 2956 (w), 2936 (w), 2839 (w), 2831 (w), 2763 (w), 2736 (w), 1693 (m), 1674 (s), 1596 (m), 1584 (s), 1508 (s), 1276 (s), 1261 (s), 1133 (s), 1001 (m), 812 (m), 731 (m). ^{1}H NMR (δ ppm): 9.85 (2H, s, C**H**=O), 7.43 (2H, d J = 1.8 Hz of d J = 8.1 Hz, C5′–**H**), 7.41 (2H, d J = 1.8 Hz, C2′–**H**), 6.99 (2H, d J = 8.1 Hz, C6′–**H**), 4.22 (4H, br. t, O–C**H$_2$**), 3.90 (6H, s, OC**H$_3$**), 2.12 (4H, br. t, O–CH$_2$C**H$_2$**). ^{13}C NMR (δ ppm): 191.0 (**C**=O), 154.0, 149.9, 130.0, 126.8, 111.4, 109.3, 68.7, 56.0, 25.8. Found C, 66.78; H 6.15%. $C_{20}H_{22}O_6$ requires C, 67.03; H, 6.19%.

4,4′-(1,6-hexylenedioxy)-*bis*(3-methoxybenzaldehyde) was prepared by procedure A from vanillin (15.4 g, 0.101 mol), 1,6-dibromohexane (11.7 g, 0.048 mol), and potassium carbonate (14.4 g, 0.103 mol) in acetone ($\approx$100 mL). The product (10.4 g, 57%) was obtained as white crystalline plates, mp 162.5–164°C. ν_{max} (cm^{-1}): 2951 (w), 2934 (w), 2874 (w), 2829 (w), 2760 (w), 2731 (w), 1696 (m), 1681 (s), 1593 (s), 1585 (s), 1507 (s), 1277 (s), 1262 (s), 1134 (s), 1011 (s), 733 (m). ^{1}H NMR (δ ppm): 9.85 (2H, s, C**H**=O), 7.43 (2H, dd J = 1.8, 8.1 Hz, C5′–**H**), 7.41 (2H, d J = 1.8 Hz, C2′–**H**), 6.96 (2H, d J = 8.1 Hz, C6′–**H**), 4.12 (4H, t J = 6.6 Hz, O–C**H$_2$**), 3.92 (6H, s, OC**H$_3$**), 1.93 (4H, br. pentet J = 6.9 Hz, O–CH$_2$C**H$_2$**), 1.59 (4H, br. m, O–CH$_2$CH$_2$C**H$_2$**). ^{13}C NMR (δ ppm): 191.0, 154.2, 149.9, 130.0, 126.8, 111.4, 109.4, 69.0, 56.1, 28.9, 25.8. Found C, 68.31; H, 6.94%. $C_{22}H_{26}O_6$ requires C, 68.38; H, 6.78%.

4,4′-[(1,4-phenylenedimethylene)dioxy]-*bis*(3-methoxybenzaldehyde) was prepared by Procedure A from vanillin (9.15 g, 60 mmol), 1,4-*bis*(bromomethyl)-benzene (6.81 g, 26 mmol), and potassium carbonate (8.34 g, 60 mmol) in acetone (≈100 mL). The product (7.12 g, 66%) was obtained as white crystalline needles, mp 150–153°C. ν_{max} (cm^{-1}): 3070 (w), 2934 (w), 2853 (w), 2829 (w), 2713 (w), 1681 (s), 1595 (s), 1584 (s), 1506 (s), 1267 (s), 1237 (s), 1132 (s), 1016 (s), 803 (m), 731 (m). ^{1}H NMR (δ ppm): 9.84 (2H, s, C**H**═O), 7.46 (4H, s, *p*–C$_6$**H$_4$**), 7.43 (2H, d $J = 1.8$ Hz, C2′–**H**), 7.39 (2H, dd $J = 1.8$, 8.1 Hz, C5′–**H**), 6.98 (2H, d $J = 8.1$ Hz, C6′–**H**), 5.24 (4H, s, OC**H$_2$**), 3.95 (6H, s, OC**H$_3$**). ^{13}C NMR (δ ppm): 190.9, 153.5, 150.1, 136.2, 130.5, 127.7, 126.6, 112.5, 109.5, 70.6, 56.1. Found C, 70.75; H, 5.20%. $C_{24}H_{22}O_6$ requires C, 70.92; H, 5.46%.

4,4′-[(1,2-phenylenedimethylene)dioxy]-*bis*(3-methoxybenzaldehyde) was prepared by procedure A from vanillin (15.24 g, 100 mmol), 1,2-*bis*(bromomethyl)benzene (13.44 g, 50.9 mmol), and potassium carbonate (13.92 g, 101 mmol) in acetone (≈100 mL). The product (13.86 g, 68%) was obtained as white crystalline needles, mp 153–154°C. ν_{max} (cm^{-1}): 3074 (w), 3000 (w), 2936 (w), 2829 (w), 2753 (w), 2720 (w), 1679 (s), 1586 (s), 1512 (s), 1268 (s), 1136 (s), 1031 (m), 732 (m). ^{1}H NMR (δ ppm): 9.82 (2H, s, C**H**═O), 7.49 (2H, m, C$_6$**H$_4$**), 7.4–7.3 (4H, m, Ar**H**), 7.03 (2H, d $J = 8.8$ Hz, Ar**H**), 5.38 (4H, s, OC**H$_2$**), 3.89 (6H, s, OC**H$_3$**). ^{13}C NMR (δ ppm): 190.9, 153.4, 150.1, 134.3, 130.5, 129.0, 128.8, 126.5, 112.4, 109.4, 69.4, 56.0. Found C, 70.90; H, 5.33%. $C_{24}H_{22}O_6$ requires C, 70.92; H, 5.46%.

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