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NOTE

One Step Synthesis of Vanillin d_3 (4-hydroxy-3-(methoxy d_3)-benzaldehyde)

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SUMMARY

A simple one step synthesis of deuteriated vanillin from 3,4-dihydroxybenzaldehyde and iodomethane-d_3 in strongly basic medium is described.

Key-words

3,4-dihydroxybenzaldehyde, iodomethane-d_3, vanillin d_3.

INTRODUCTION

Studies of the biosynthesis and/or biodegradation of lignin requires the utilization of precursors labelled either by radioactive[1] or stable[2] isotopes. Vanillin is the starting material for the synthesis of more complex molecules such as coniferyl alcohol[3] or lignin model compounds[4]. This explains the various synthesis of labelled vanillin described either on the aldehyde (^{14}C)[5], the methoxy group (^{13}C)[4], (CD_3)[6] or on the aromatic ring (5-^{14}C)[5].

Markey and coworkers[6] have described a three step synthesis of vanillin d_3 starting from 3,4-dihydroxybenzaldehyde **1** in an overall yield of 18%. The diphenol **1** is first protected by benzylation of the para position, then methylated and deprotected. We wish to report here the ortho methylation of 3,4-dihydroxybenzaldehyde **1** without protection and in a higher yield.

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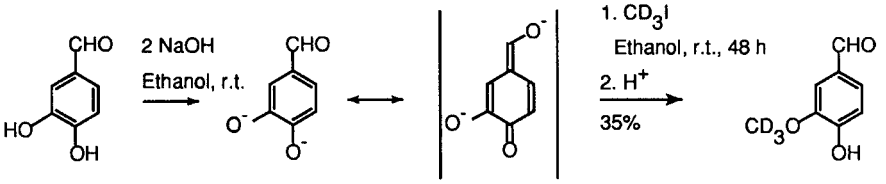
RESULTS AND DISCUSSION

As reported 3,4-dihydroxybenzaldehyde **1** is alkylated at the para position under moderately basic condition[6]. When diphenol **1** is dissolved in ethanol containing two equivalents of base, the colour of the solution immediately turns to dark red/black indicating the formation of the dianion **2**. In dianion **2**, the meta oxygen, conjugated only with the aromatic ring, is more basic than the para oxygen, conjugated with the aromatic ring and with the electroattractive aldehyde group. The difference in basicity beetwen the two oxygen atoms allows selective monoalkylation of dianion **2** mainly on the meta position[7,8,9].



1 2 3

In order to check the influence of the counter-ion, sodium hydroxide, potassium hydroxide and lithium hydroxide in absolute ethanol have been used as base. The best result has been obtained using sodium hydroxide. In this case GC/MS showed that up to 90% of ortho-methylation has been obtained, contaminated by only 2% of 3-hydroxy-4-methoxy-benzaldehyde (isovanillin) and 7% of dimethylated product (3,4-dimethoxy-benzaldehyde). Potassium hydroxide gave about 70% of vanillin, lithium hydroxide 80%. On the other hand sodium ethanolate in absolute ethanol gave a mixture of vanillin d_3 (55%), dimethylated product (40%) and isovanillin (5%); NaOH in DMF gave also a poorer yield. Vanillin d_3 is obtained analytically pure without chromatography by recrystallization of the crude product from dichloromethane / pentane at -18°C. The overall yield is 35%. Analysis of ^{1}H NMR and mass spectrometry spectra[10] agree wih a content of deuterium of 97.5%.

EXPERIMENTAL

The melting point, determined on a Buchi 510 apparatus, is uncorrected. Proton ^{1}H and carbon ^{13}C spectra were obtained using a Brucker 250 MHz and a Brucker 400 MHz spectrometer respectively. Chemical shifts are reported in ppm from acetone d_6 relative to internal tetramethylsilane. Coupling constants

(J) are expressed in Hertz (Hz). GC-MS experiments were carried out with a fused silica capillary column CPSIL5 (50m, 0.3mm internal diameter; programm 100-300 °C, 5°C/mn) from Chrompack company (Nederlands) on a Nermag R10-10C instrument using chemical ionization CI and electronic impact IE. Infrared (IR) spectra was recorded on a Perkin-Elmer 599 instrument. Microanalyses was performed by the "Service de microanalyse" of the University Paris VI.

3,4-Dihydroxybenzaldehyde (Aldrich), iodomethane d_3 (99% *d* from CEA, Saclay) and absolute ethanol (Aldrich) were used without further purification. The reaction was carried out under an atmosphere of dry argon.

4-Hydroxy-3-(methoxy d_3)-benzaldehyde (3)

3,4-Dihydroxybenzaldehyde (2.70 g, 20 mmol) is dissolved in ethanol NaOH 2N (20 ml). Iodomethane-d_3 (2.76 g, 19 mmol), diluted in ethanol (20 ml) is added dropwise in about 45 minutes; the reaction mixture is stirred at room temperature for 48 hours. The red solution is concentrated on a rotary evaporator under vacuum (15mm Hg) in order to avoid emulsion, diluted with a large excess of water (200 ml) and extracted with dichloromethane (3 x 20 ml) in order to remove the dimethylated compound. The water layer is acidified with HCl 5% and extracted with dichloromethane (4 x 50 ml). The organic layer is washed with water, dried over $MgSO_4$ and evaporated. The crude product (1.41 g) is purified by two recrystallizations in dichloromethane / pentane at -18°C, affording 1.10 g (7.1 mmol) of pure vanillin d_3 (35% yield based on iodomethane).

Mp.: 78.5 - 79.5°C (lit.:[6] 75-77°C).

^1H NMR (250 MHz, CD_3COCD_3): δ = 7.04 (d, 1H, J_{HH} = 7.8 Hz, C_2H), 7.46 (d, 1H, J_{HH} = 1.5 Hz, C_5H), 7.49 (dd, 1H, J_{HH} = 7.8 Hz and J_{HH} = 1.5 Hz, C_6H), 8.72, (s, 1H, OH), 9.85 (s, 1H, CHO).

^{13}C NMR (400 MHz, CD_3COCD_3)(assigned according to ref 11): δ = 189.5 (s, 1C, CHO), 151.7 (s, 1C, C_1), 147.1 (s, 1C, C_2), 128.8 (s, 1C, C_4), 125.3 (s, 1C, C_6), 114.1 (s, 1C, C_3), 109.0 (s, 1C, C_5), 53.7 (m, 1C, OCD_3).

GC/ MS (EI, 70 eV): m/z (relative intensity) = 156 (8.9), 155 (94.1), 154 (100.0), 126 (11.3), 109 (21.9), 108 (10.3), 81 (39.0), 80 (10.6), 79 (13.8), 66 (8.2), 63 (8.1), 62 (5.1), 53 (16.6), 52 (18.0), 51 (17.6), 50 (9.9). GC/MS (CI, NH_3): m/z = 190 ($M + NH_4^+ + NH_3$), 173 ($M + NH_4^+$), 156 ($M + H^+$).

IR (KBr): 3650-2900 (OH), 1670 (CO) cm^{-1}. $C_8H_5D_3O_3$ (155.1) calc.: C 61.92, H and D 5.19 found 61.98, 5.09.

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