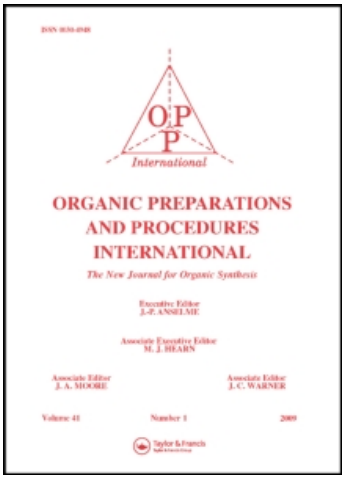

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IMPROVED SYNTHESIS OF 1,2-DIMETHOXY-3-ISOPROPYLBENZENE AND GENERAL SYNTHESIS OF 3-SUBSTITUTED-1,2-DIMETHOXYBENZENES

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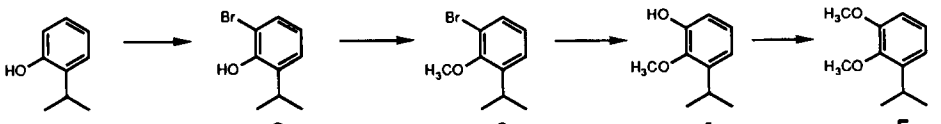
The 3-substituted o-catechol configuration is common in natural products. The laboratory synthesis of some of these natural products and their analogs starts with a 3-substituted-1,2-dimethoxybenzene from which the methyl groups are later removed. The syntheses of gossypol[1] and at least one other natural product of recent interest, taxodione[2], use 1,2-dimethoxy-3-isopropylbenzene (**5**) as the starting material. The first step in Adams' route to **5** was the Kolbe-Schmidt reaction on guaiacol (**6**) to form 3-methoxysalicylic acid in 33% yield and the overall yield for the six-step synthesis was about 11%. Others have improved this synthesis[3] or synthesized **5** from 2-isopropylphenol[4] (**1**), but the basic problem of efficiently attaining the 3-substituted-1,2-dimethoxybenzene configuration was not solved.

A new approach was needed to prepare **5** and other 3-substituted-1,2-dimethoxybenzenes in the quantities required for starting materials in synthesis of natural products. The method of Pearson and coworkers[5] for o-bromination of phenols provided a selective route for substitution of both **1** and **6**. Applied to **1**, it gave 2-bromo-6-isopropylphenol (**2**) in 89% yield. Compound **2** was converted to 1-bromo-3-isopropyl-2-methoxybenzene (**3**) with dimethyl sulfate in alkaline methanol in 90% yield. Compounds **2** and **3** do not appear to have been previously reported.

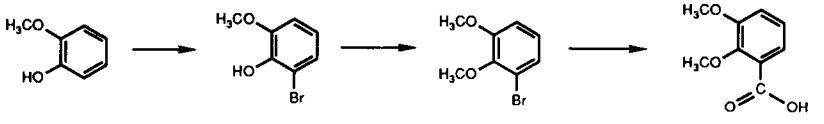
Treatment of **3** with magnesium in the presence of diborane[6] followed by basic hydrogen peroxide[7] yielded 3-isopropyl-2-methoxyphenol (**4**). Methylation of **4** with dimethyl sulfate afforded **5** in 88% overall yield from **3**. This approach should



1 **2** **3** **4** **5**

provide a convenient laboratory preparation for 3-alkylated-1,2-dimethoxybenzenes in cases where the appropriate 2-substituted phenol is readily available, as is 2-isopropylphenol.

Similar bromination of guaiacol (**6**) afforded a 63% yield of 2-bromo-6-methoxyphenol (**7**). Methylation of **7** gave 1-bromo-2,3-dimethoxybenzene (**8**) in 85% yield. This compound forms a Grignard reagent in the presence of one mole of ethyl bromide.



6 **7** **8** **9**

Reaction of this Grignard reagent with carbon dioxide yielded 2,3-dimethoxybenzoic acid (**9**, 70%) which had previously been converted to **5** in four steps.[3] This approach to the synthesis of 3-substituted-1,2-dimethoxybenzenes from guaiacol is more general than the synthesis from 2-alkylated phenols but not as convenient for the preparation of 1,2-dimethoxy-3-isopropylbenzene.

EXPERIMENTAL SECTION

The mps were taken in capillary tubes and are uncorrected. IR spectra were obtained on a Beckman IR-33 spectrophotometer. NMR spectra were recorded on a Varian FT-80A spectrometer (80 MHz) or a General Electric 350 MHz spectrometer using TMS as an internal standard.

2-Bromo-6-isopropylphenol (**2**).- A solution of t-butylamine (16 ml, 0.152 mol) in 400 ml of toluene was cooled to -30° and

bromine (4 ml, 0.078 mol) was added dropwise over a period of 10 min. The reaction mixture was cooled to -70° and a solution of isopropylphenol (10 g, 0.074 mol) in 50 ml of CH_2Cl_2 was added. The reaction mixture was allowed to come to room temperature and stand for 5 hr. The toluene solution was washed with dilute HCl and then water and dried over $MgSO_4$. The toluene was removed by rotary evaporation, and the residual oil was distilled (bp. 101-103° 10 mm) to give 14.2 g (89%) of **2**. IR (neat): 3530, 2980-2880, 1600, 1475, 1445, 1385, 1365, 1325, 1270, 1235, 1205, 1175, 1150, 1110, 1045, 895, 820, 765 and 730 cm^{-1}; NMR (350 MHz, $CDCl_3$): δ 1.23 (d, 6H, J = 7 Hz), 3.31 (septet, 1H, J = 7 Hz), 5.58 (s, 1H), 6.75 (t, 1H, J = 7.8 Hz), 7.12 (q, 1H, J1 = 7.8 Hz, J2 = 1.5 Hz), 7.26 (q, 1H, J1 = 7.8 Hz, J2 = 1.5 Hz).

Anal. Calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.16
Found: C, 50.53; H, 5.28

1-Bromo-3-isopropyl-2-methoxybenzene (**3**).- To a solution of **2** (20 g, 0.093 mol) in 25 ml of methanol was added KOH (5.2 g, 0.093 mol) in 25 ml of methanol. Dimethyl sulfate (11.8 g, 0.093 mol) was added slowly with stirring. The mixture was refluxed for 1 hr., another one half equivalent of KOH and dimethyl sulfate were added and refluxing was continued for another 0.5 hr. If gas chromatography showed a significant amount of starting phenol, another aliquot of base and dimethyl sulfate were added and the reaction mixture refluxed again. This procedure was continued until only traces of phenol remained. Excess KOH was added to destroy the dimethyl sulfate and most of the methanol was removed on a rotary evaporator. The product was extracted with ether and the ether layer washed with dilute HCl and water and dried over $MgSO_4$. The ether and then the product were distilled (bp. 105-106° 10 mm) to give 19.2 g (90%) of **3**. IR (neat): 3080-2840, 1565, 1470, 1455, 1425, 1390, 1370, 1340, 1260, 1235, 1180, 1110, 1090, 1050, 1005, 900, 800, 775 and 750 cm^{-1}; NMR (350 MHz, $CDCl_3$): δ 1.22 (d, 6H, J = 6.9 Hz), 3.35 (septet, 1H, J = 6.9 Hz), 3.81 (s,3H),

6.94 (t, 1H, J = 7.8 Hz), 7.18 (q, 1H, J1 = 7.8 Hz, J2 = 1.3 Hz), 7.35 (q, 1H, J1 = 7.8 Hz, J2 = 1.3 Hz).

Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72
Found: C, 52.44; H, 5.58

3-Isopropyl-2-methoxyphenol (**4**).- Magnesium (2.7 g, 0.11 mol), 100 ml of 1M BH_3 in THF and compound **3** (22 g, 0.096 mol), were placed in a 500 ml round bottom flask equipped with a reflux condenser. The reaction mixture was allowed to come to reflux and the reaction rate was controlled with an ice bath as necessary. After the reaction was nearly complete, the mixture was refluxed with external heat for 1 hr. Water was added dropwise with stirring until hydrogen evolution ceased. One hundred ml of 1M NaOH were added and then 15 ml of 30% H_2O_2 were added dropwise. After stirring for 1 hr., the reaction mixture was acidified, the organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried over $MgSO_4$ and most of the solvent was removed on a rotary evaporator. The best overall yield was obtained when this material was methylated without further purification. On distillation (bp. 71-74° 1.0 mm) the nearly pure phenol solidified on standing for a few hr.; mp. 61-62°, lit.[4] 63-64°. IR (KBr): 3300, 3020-2840, 1580, 1500, 1465, 1360, 1320, 1295, 1235, 1200, 1160, 1045, 990, 955, 855, 780 and 745 cm^{-1}; NMR (80 MHz, $CDCl_3$): δ 1.23 (d, 6H, J = 6.4 Hz), 3.27 (septet, 1H, J = 6.4 Hz), 3.78 (s, 3H), 5.62 (s, 1H), 6.71-7.24 (m, 3H).

1,2-Dimethoxy-3-isopropylbenzene (**5**).- Compound **4** obtained from 22 g of **3** without purification was treated with KOH and dimethyl sulfate in methanol by the same procedure used to make **3** except that this methyl ether formed more readily. The reaction was complete after the addition of 1.5 equivalents of KOH and dimethyl sulfate. The product was distilled (bp. 62-65° 10 mm, lit.[1] 119-121° 24 mm) to give 15.3 g (88% from **3**) of **5**. IR (neat): 3100-2840, 1610, 1590, 1485, 1440, 1390, 1370, 1345, 1305, 1280, 1230, 1175, 1105, 1070, 1015, 930, 845, 790 and 745 cm^{-1}; NMR (80 MHz $CDCl_3$): δ 1.21 (d, 6H, J = 7.0 Hz), 3.36

(septet, 1H, J = 7.0 Hz), 3.81 (s, 3H), 3.82 (s, 3H), 6.6-7.1 (m, 3H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.11; H, 8.99

2-Bromo-6-methoxyphenol (**7**).- A solution of t-butylamine (8.5 ml, 0.081 mol) in 300 ml of toluene was cooled to -30° and bromine (2.2 ml, 0.043 mol) was added dropwise over a period of 10 min. The reaction mixture was cooled to -70° and a solution of guaiacol (5 g, 0.04 mol) in 25 ml of CH_2Cl_2 was added. The reaction mixture was allowed to come to room temperature and stand for 5 hr. The toluene solution was washed with dilute acid and then water and dried over $MgSO_4$. The toluene was removed by rotary evaporation and the residual solid recrystallized from ligroin to give 5.3 g (63%) of **7**, mp. 62-63°, lit.[8] 62-63°. IR (KBr): 3425, 3010-2865, 1610, 1495, 1475, 1450, 1360, 1290, 1240, 1205, 1150, 1075, 1025, 810, and 760 cm^{-1}; NMR (80 MHz, $CDCl_3$): δ 3.88 (s, 3H), 5.91 (s, 1H), 6.5-7.1 (m, 3H).

Anal. Calcd for $C_7H_7BrO_2$: C, 41.41; H, 3.48
Found: C, 41.47; H, 3.50

1-Bromo-2,3-dimethoxybenzene (**8**).- To compound **7** (5 g, 0.025 mol) in 30 ml of methanol was added 4 ml of dimethyl sulfate and 1.7 g of KOH in 10 ml of methanol. The reaction mixture was refluxed for 3 hr. and allowed to cool. Water was added and the product was extracted with ether. The ether was boiled off and the product was distilled (bp. 90-95° 2 mm, lit.[9] 70° 0.5 mm) to give 4.6 g (85%) of **8**. IR (neat): 3020-2870, 1590, 1490, 1440, 1305, 1275, 1245, 1200, 1180, 1160, 1090, 1045, 1010, 775 and 740 cm^{-1}; NMR (80 MHz, $CDCl_3$): δ 4.07 (s, 3H), 4.08 (s, 3H), 7.0-7.5 (m, 3H).

Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18
Found: C, 44.34; H, 4.29

2,3-Dimethoxybenzoic Acid (**9**).- Compound **8** (3.4 g, 0.0157 mol) and ethyl bromide (1.75 g, 0.016 mol) in 15 ml of dry THF were added dropwise to 0.8 g (0.033 mol) of magnesium in 20 ml of dry THF. The reaction mixture was refluxed for 1 hr. with external heat and then cooled. Dry CO_2 was bubbled into the reaction

mixture with stirring for 2.5 hr. The mixture was acidified with dilute HCl and extracted with ether. The ether layer was washed with water, dried over $MgSO_4$ and the ether was evaporated. The residual solid was recrystallized from ethyl acetate to give 2 g (70%) of **9**, mp. 120-121° lit.[1] 120-122°. IR (KBr): 3400, 3010-2840, 1680, 1600, 1580, 1490, 1470, 1440, 1350, 1315, 1285, 1230, 1195, 1140, 1020, 800, and 750 cm^{-1}; NMR (80 MHz, $CDCl_3$): δ 3.92 (s, 3H), 4.06 (s, 3H), 7.14 - 7.67 (m, 3H), 10.9 (s, 1H).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53
Found: C, 59.32; H, 5.56

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