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Selective Preparation of 4-(Bromo or lodo)-2,5dimethoxybenzonitrile and 2-(Bromo or lodo)-3,6dimethoxybenzonitrile from 2,5-Dimethoxybenzaldehyde

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## SELECTIVE PREPARATION OF 4-(BROMO OR IODO)-2,5-DIMETHOXYBENZONITRILE AND 2-(BROMO OR IODO)-3,6-DIMETHOXYBENZONITRILE FROM 2,5-DIMETHOXYBENZALDEHYDE

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**Abstract**: By use of appropriate reactions and sequence of steps, 2,5dimethoxybenzaldehyde can be converted either to 4-(bromo or iodo)-2,5dimethoxybenzonitrile or 2-(bromo or iodo)-3,6-dimethoxybenzonitrile.

In the course of other work, we needed to prepare either 4-bromo-2,5dimethoxybenzonitrile or 4-iodo-2,5-dimethoxybenzonitrile. Neither of these compounds had been previously reported in the literature. Two possible pathways to these compounds were pursued, both of which began with 2,5dimethoxybenzaldehyde, <u>1</u>.

In the first pathway, 1 was brominated to form 4-bromo-2,5-

dimethoxybenzaldehyde, 2, using either the procedure of Barfknecht and Nichols

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(1), or by treatment with bromine in acetic acid. Neither of these procedures worked in high yield. Treatment of  $\underline{2}$  with hydroxylamine hydrochloride and sodium hydroxide in ethanol yielded the oxime, which was converted to the 4-bromo-2,5-dimethoxybenzonitrile,  $\underline{3}$ , with acetic anhydride (2).



Iodination of  $\underline{1}$  using a similar procedure as for bromination was unsuccessful. Use of iodine monochloride had also been reported not to work (3). Using stoichiometric amounts of iodine and silver nitrate in methanol (4) gave an 85% yield of 4-iodo-2,5-dimethoxybenzaldehyde,  $\underline{4}$ . This was converted to 4iodo-2,5-dimethoxybenzonitrile,  $\underline{5}$ , in the same manner as the bromo compound.



Since bromination of  $\underline{1}$  did not occur in good yield,  $\underline{1}$  was converted to 2,5dimethoxybenzonitrile,  $\underline{6}$ , and bromination of  $\underline{6}$  was investigated. Bromination in acetic acid did not occur in the 4-position to form  $\underline{3}$ , but rather in the 6-position to form (using correct numbering) 2-bromo-3,6-dimethoxybenzonitrile,  $\underline{7}$ , in low yield. Exhaustive extraction of the reaction mixture did not yield more product. The proton NMR spectrum of  $\underline{7}$  showed a pair of doublets with a 9 Hz coupling in the aromatic region, in contrast to the spectrum of  $\underline{3}$ , which showed a pair of singlets. Bromination as in reference 1 yielded a mixture of  $\underline{3}$  and  $\underline{7}$ , by proton NMR.



Iodination of  $\underline{6}$  yielded only 2-iodo-3,6-dimethoxybenzonitrile,  $\underline{8}$ , in low yield, by either of two methods (4,5). No  $\underline{5}$  could be detected in the crude products by proton NMR.

In conclusion, 4-(bromo or iodo)-2,5-dimethoxybenzonitrile and 2-(bromo or iodo)-3,6-dimethoxybenzonitrile have been prepared by simple three-step procedures from 2,5-dimethoxybenzaldehyde. Although the overall yields are not

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high in some cases, pure products are readily obtained by recrystallization of the crude reaction products.

### **Experimental Procedures:**

NMR spectra were recorded on a Bruker DPX-300, using CDCl<sub>3</sub> as a solvent. IR spectra were recorded as KBr pellets on a Perkin-Elmer Spectrum 1000 FT-IR. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ, and were within  $\pm 0.4\%$  of the calculated values.

4-Bromo-2,5-dimethoxybenzaldehyde, 2.

To a solution of 5.0 g of 2,5-dimethoxybenzaldehyde, <u>1</u>, in 20 mL of acetic acid was added 1.8 mL of bromine dropwise. The solution was allowed to stir for 4 hours. TLC (silica gel, ethyl acetate:hexane (1:1)) indicated starting material was still present, so 1.0 mL of bromine was added, and the solution stirred overnight. The reaction mixture was poured into water, and treated with 5% sodium bisulfite solution to remove the excess bromine. The solid was filtered and washed with water. The solid was recrystallized from methanol to yield 3.45 g (46.9%) of **2**, mp 122-4, literature mp 132-3 (1). Proton NMR: 10.39 ppm (1H, s), 7.34 ppm (1H, s), 7.24 ppm (1H, s), 3.90 ppm (3H, s), 3.89 ppm (3H, s).

4-Bromo-2,5-dimethoxybenzonitrile, 3.

Following the procedure in reference 2, 2.0 g of  $\underline{2}$  was converted to the 1.69 g (81.2%) of the oxime. Refluxing 1.07 g of the oxime in 5 mL of acetic anhydride for six hours, followed by dilution with ice water, suction filtration, and recrystallization from methanol, yielded 0.865 g (76.6%) of  $\underline{3}$ , mp 175-7. Proton NMR: 7.22 ppm (1H, s), 7.05 ppm (1H, s), 3.91 ppm (3H, s), 3.88 ppm (3H, s). IR: 3115, 2942, 2848, 2227, 1602, 1567, 1490, 1380, 1279, 1226, 1040, 1024, 854, 788 cm<sup>-1</sup>. Elemental analysis: C - 44.6%, H - 3.3%, N - 5.6%; Calculated: C - 44.7%, H - 3.3%, N - 5.8%.

#### 4-Iodo-2,5-dimethoxybenzaldehyde, 4.

A mixture of  $\underline{1}$  (5.10 g, 0.0307 moles), silver nitrate (5.60 g, 0.033 moles), and iodine (8.10 g, 0.032 moles) in 125 mL of methanol was stirred under nitrogen for seven hours. The yellow precipitate was filtered and washed with methanol. The filtrate was treated dropwise with just enough saturated sodium bisulfite solution to reduce the remaining iodine, and the solvent was removed on a rotary evaporator. The solid was suspended with 50 mL of water, filtered, and recrystallized from 95% ethanol to yield 7.62 g (84.9%) of <u>4</u>, mp 137-9, literature mp 136-7 (3). Proton NMR: 10.39 ppm (1H, s), 7.47 ppm (1H, s), 7.22 ppm (1H, s), 3.90 ppm (3H, s), 3.88 ppm (3H, s).

## 4-Iodo-2,5-dimethoxybenzonitrile, 5.

A solution of 4 (7.30 g, 0.025 moles) in 125 mL warm 95% ethanol was prepared on a steam bath. Hydroxylamine hydrochloride (2.08 g, 0.030 moles) was dissolved in 15 mL of water, and added to the aldehyde solution. Sodium hydroxide (1.60 g, 0.040 moles) was dissolved in 15 mL of water, and added to the aldehyde solution. The solution was heated on the steam bath for 3 hours. The volume of solution was reduced to about 75 mL on the rotary evaporator, and the solution cooled to yield 3.97 g of off-white crystals of the oxime. Further reduction of volume of the filtrate to about 40 mL yielded another 2.47 g, for a total yield of 6.44g (84.0%) of the oxime. The oxime (5.0 g) was dissolved in 25 mL of acetic anhydride, and heated at reflux for 6 hours. The reaction mixture was cooled and diluted with water. The precipitated solid was filtered, washed with water, and recrystallized from methanol to yield 4.11g (87.3%) of 5, mp 153-5. Proton NMR: 7.42 ppm (1H, s), 6.92 ppm (1H, s), 3.89 ppm (3H, s), 3.85 ppm (3H, s). IR: 3104, 2970, 2940, 2844, 2224, 1594, 1487, 1438, 1373, 1277, 1221, 1035, 858, 781, 705 cm<sup>-1</sup>. Elemental analysis: C - 37.6%, H - 2.6%, N - 4.7%; Calculated C - 37.4%, H - 2.8%, N - 4.6%.

## 2,5-dimethoxybenzonitrile 6.

Using the same procedure as that in reference 2, <u>6</u> was prepared from <u>1</u> in 60% overall yield, mp 77-9, literature mp 82 (6). Proton NMR (CDCl<sub>3</sub>): 7.09 ppm (1H, dd, J = 9Hz and 3Hz), 7.05 ppm (1H, d, J = 3Hz), 6.91 ppm (1H, d, J = 9Hz), 3.89 ppm (3H, s), 3.78 ppm (3H, s).

2-Bromo-3,6-dimethoxybenzonitrile, 7.

To a mixture of <u>6</u> (3.50g, 0.021 moles) in 15 mL of warm acetic acid was added bromine (1.2 mL, 0.024 moles) dropwise with stirring. The reaction was stirred at room temperature overnight, poured into 80 mL of water, and the solid filtered by suction. The solid was recrystallized from methanol to yield 1.122g (22.1%) of <u>7</u>, mp 150-2. Proton NMR: 7.09 ppm (1H, d, J = 9Hz), 6.89 ppm (1H, d, J = 9Hz), 3.91 ppm, (3H, s), 3.89 ppm (3H, s). IR: 3081, 2928, 2837, 2229, 1568, 1483, 1435, 1269, 1196, 1067, 1033, 805, 713 cm<sup>-1</sup>. Elemental analysis: C - 45.0%, H -3.3%, N - 5.7%; Calculated C - 44.7%, H - 3.3%, N - 5.8%.

2-Iodo-3,6-dimethoxybenzonitrile, 8.

Following the procedure in reference 5,  $\underline{6}$  (1.82g, 0.0122 moles), iodine (1.275g, 0.00479 moles), periodic acid (0.365g, 0.0016 moles), 0.5 mL of sulfuric acid, 15 mL of acetic acid, and 5 mL of water were stirred and heated at 60° overnight. The reaction was cooled and diluted with water. The excess iodine was removed by treatment with sodium bisulfite solution, and the solid filtered, then recrystallized from methanol to yield 0.575g (17.7%) of **8**, mp 167-9. Proton NMR (CDCl<sub>3</sub>): 7.00 ppm (1H, d, J = 9Hz), 6.93 ppm (1H, d, J = 9Hz), 3.90 ppm (3H, s), 3.87 ppm (3H, s). IR: 3081, 2224, 1566, 1474, 1429, 1265, 1065, 1019, 810, 710 cm<sup>-1</sup>. Elemental analysis: C - 37.6%, H - 2.6%, N - 4.8%; Calculated C - 37.4%, H - 2.8%, N - 4.8%.

To a solution of  $\underline{6}$  (1.0g, 6.0 mmoles) in 50 mL of methylene chloride was added silver nitrate (2.04g, 12.0 mmoles) and iodine (3.10g, 12.0 mmoles). The solution was stirred under nitrogen overnight. The silver iodide was filtered, and the methylene chloride solution was washed with 2 × 50 mL of 5% sodium bisulfite solution and then with 50 mL of water. The methylene chloride was dried over magnesium sulfate, then removed under reduced pressure to yield a yellow solid, which was recrystallized from methanol to yield 0.58g (33.4%) of §, mp 168-170. The proton NMR spectrum was identical to that of the material produced by the preceding procedure.

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