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Comparison of Iodination of Methoxylated Benzaldehydes and Related Compounds using Iodine/Silver Nitrate and Iodine/Periodic Acid

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Abstract: Iodination of the three methoxybenzaldehydes, four dimethoxybenzaldehydes, vanillin, and piperonal by two methods were compared. Iodine and periodic acid gave better yields for iodination for the methoxybenzaldehydes, whereas iodine and silver nitrate generally gave better yields for the rest of the compounds.

Keywords: benzaldehydes, iodination, periodic acid, silver nitrate

Previously, we reported a high-yield iodination of 2,5-dimethoxybenzaldehyde, **1d**, to produce 4-iodo-2,5-dimethoxybenzaldehyde, **2d**, using iodine and silver nitrate.[1] In contrast, iodination with iodine and periodic acid[2] gave a mixture of iodinated products. We decided to compare these two methods of iodination for other methoxylated benzaldehydes and related compounds. The reaction is shown in Scheme 1.

As can be seen in Table 1, both methods succeeded well for the methoxybenzaldehydes, **1a**–**1c**, although the iodine and periodic acid method gave somewhat higher yields. For the dimethoxybenzaldhydes, **1d**–**g**, iodine and silver nitrate gave fair to good yields, whereas iodine and periodic acid gave variable results: In some cases, mixtures of the desired product and iododeformylated product, as shown in Scheme 2. Iododeformylation has been

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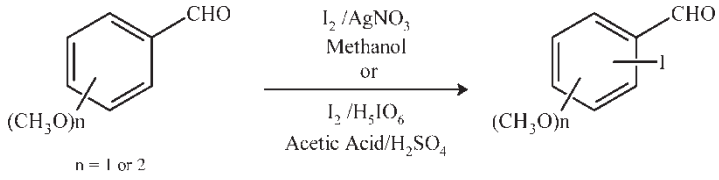


Scheme 1.

previously reported[3] for some related benzaldehydes. The iododeformylation reaction is being investigated further.

The iodination of 2,3-dimethoxybenzaldehyde, **1e**, to form 5-iodo-2,3-dimethoxybenzaldehyde, **2e**, in 51% yield is notable, because the previously reported synthesis of **2e** required five steps from 2-hydroxy-3-methoxybenzaldehyde.[4] Iodination of vanillin, **1h**, proceeded in fair yield using iodine and silver nitrate, although the yield is not as good as using sodium iodide, iodine, and sodium hydroxide.[5] The yield for iodination of piperonal, **1i**, was also low, but this procedure is simple and has one step to form a single product, 6-iodopiperonal, **2i**, as opposed to the three-step procedure previously reported.[6]

In conclusion, iodine and silver nitrate can be used to iodinate a wide variety of methoxylated benzaldehydes in fair to excellent yields. For monomethoxybenzaldehydes, however, iodine and periodic acid gives somewhat higher yields. In all cases, except for iodination of some dimethoxybenzaldehydes with iodine and periodic acid, monoiodination products free of other isomers were obtained.

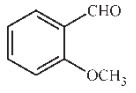
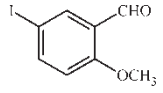
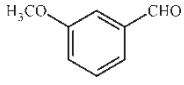
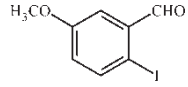
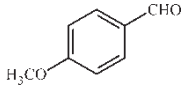
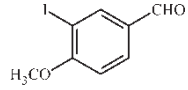
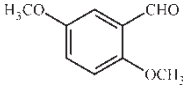
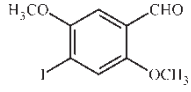
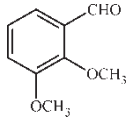
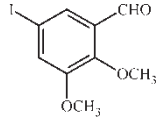
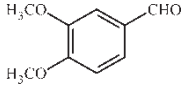
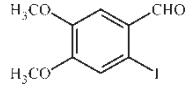
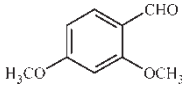
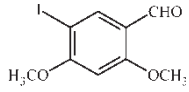
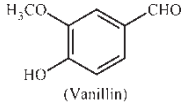
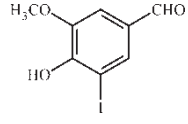
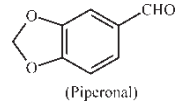
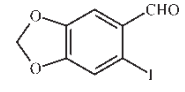
EXPERIMENTAL PROCEDURES

NMR spectra were recorded on a Bruker DPX-300, using $CDC1_3$ as a solvent. GC-mass spectra were obtained with a Thermo-Electron/Finnigan Trace GC Ultra-Polaris Q GC-MS. IR spectra were recorded on a Thermo-Electron Nexus 670 FT-IR with a Smart Endurance ATR accessory. Melting ranges are reported in degree Celsius.

Example Procedure for Iodination with Periodic Acid (H_5IO_6) and Iodine

To 100 mL of acetic acid, 5.77 g (40 mmol) *m*-anisaldehyde, 4.71 g (18 mmol) of iodine, and 1.40 g (6 mmol) of periodic acid were added, followed by 20 mL of water and 3 mL of sulfuric acid. A dark purple solution resulted. The mixture was heated and stirred at 65–70°C overnight. After the reaction was cooled, saturated sodium bisulfite solution was added to remove the dark color. A yellow precipitate formed upon pouring the solution into ice water. The precipitate was filtered off and recrystallized in 95% ethanol to yield 6.53 g (67%) of 2-iodo-5-methoxybenzaldehyde.

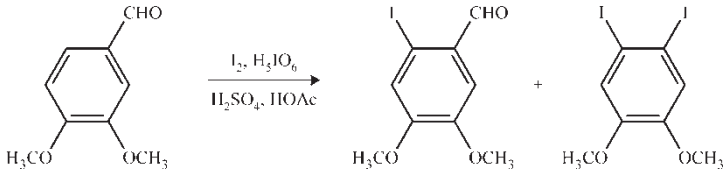
Table 1. Yields of iodinated products under two different iodination conditions

Starting material		Product		I_2/H_5IO_6	$AgNO_3/I_2$
1a		**2a**		97%	95%
1b		**2b**		67%	47%
1c		**2c**		83%	66%
1d		**2d**		Mixture of products	84%
1e		**2e**		6%	51%
1f		**2f**		Mixture of products	78%
1g		**2g**		81%	42%
1h	 (Vanillin)	**2h**		NR[a]	35%
1i	 (Piperonal)	**2i**		NR	16%

[a]NR-means no solid product formed upon workup of the reaction.

Example Procedure for Iodination with Silver Nitrate and Iodine

A mixture of 1.68 g (10 mmol) of 3,4-dimethoxybenzaldehyde, 1.71 g (10 mmol) of silver nitrate, and 2.80 g (11 mmol) of iodine in 65 mL of methanol was stirred overnight at room temperature under nitrogen. The yellow precipitate of silver iodide that formed was filtered off and washed



Scheme 2.

with methanol. Excess iodine was reduced with sodium bisulfite solution. The methanol was removed on a rotary evaporator; the solid was suspended in 30 mL water for several minutes and then filtered. The product was recrystallized in 95% ethanol to yield 2.30 g (78%) of 2-iodo-4,5-dimethoxybenzaldehyde.

Data

5-Iodo-2-methoxybenzaldehyde, **2a**

Mp 140–141, literature mp 140–142.[7] ^{1}H NMR (ppm): 10.3 (1H, s), 8.1 (1H, d, $J = 2.4$ Hz), 7.8 (1H, dd, $J = 8.8$ Hz & 2.4 Hz), 6.8 (1H, d, $J = 8.8$ Hz), 3.9 (3H, s). ^{13}C NMR (ppm): 188.3, 161.4, 144.1, 137.0, 126.4, 114.2, 83.0, 55.9. EI-GCMS (relative abundance): 262 (M^+, 100), 63 (38), 263 (34), 244 (28), 118 (15), 62 (12), 77 (12), 92 (11), 64 (10), 75 (10). IR (cm^{-1}): 3071, 3009, 2874, 1666, 1584, 1267, 1243, 1176, 817.

2-Iodo-5-methoxybenzaldehyde, **2b**

Mp 105–106, literature mp 112–113.[8] ^{1}H NMR (ppm): 10.0 (1H, s), 7.8 (1H, d, $J = 8.7$ Hz), 7.4 (1H, d, $J = 3.2$ Hz), 6.9 (1H, dd, $J = 8.7$ Hz & 3.2 Hz), 3.9 (3H, s). ^{13}C NMR (ppm): 195.7, 160.2, 141.0, 135.6, 123.5, 113.5, 89.9, 55.7. EI-GCMS (relative abundance): 262 (M^+, 100), 63 (60), 134 (47), 261 (30), 62 (15), 64 (12), 74 (11), 262 (10), 92 (10). IR (cm^{-1}): 3003, 2947, 2860, 1667, 1593, 1276, 1243, 932, 817.

3-Iodo-4-methoxybenzaldehyde, **2c**

Mp 101–102, literature mp 106–107.[9] ^{1}H NMR (ppm): 9.8 (1H, s), 8.3 (1H, d, $J = 2.0$ Hz), 7.9 (1H, dd, $J = 8.5$ & 2.0 Hz), 6.9 (1H, d, $J = 8.5$ Hz), 4.0 (3H, s). ^{13}C NMR (ppm): 189.4, 162.7, 141.0, 132.1, 131.4, 110.5, 86.5, 56.8. EI-GCMS (relative abundance): 262 (M^+, 100), 261 (77), 63 (22), 77 (16), 119 (16), 51 (14), 76 (13), 62 (12), 92 (12), 76 (12), 105 (12). IR (cm^{-1}): 3004, 2936, 2829, 1669, 1591, 1562, 1274, 1243, 1196, 818.

5-Iodo-2,3-dimethoxybenzaldehyde, **2d**

Mp 97–98, literature mp 101–102.[4] ^{1}H NMR (ppm): 10.3 (1H, s), 7.7 (1H, d, $J = 2.0$ Hz), 7.4 (1H, d, $J = 2.0$ Hz), 4.0 (3H, s), 3.9 (3H, s). ^{13}C NMR (ppm): 188.6, 153.7, 152.6, 130.9, 128.2, 126.6, 87.0, 62.4, 56.3. EI-GCMS (relative abundance): 292 (M^+, 100), 293 (37), 51 (31), 274 (29), 245 (23), 94 (22), 121 (20), 79 (19), 63 (17), 66 (16). IR (cm^{-1}): 3078, 2936, 2864, 1680, 1567, 1237, 1170, 988, 827.

2-Iodo-4,5-dimethoxybenzaldehyde, **2e**

Mp 140–141, literature mp 145–146.[10] ^{1}H NMR (ppm): 9.9 (1H, s), 7.4 (1H, s), 7.3 (1H, s), 4.0 (3H, s), 3.9 (3H, s). ^{13}C NMR (ppm): 194.9, 154.5, 149.7, 128.4, 121.8, 111.1, 92.8, 56.5, 56.1. EI-GCMS (relative abundance): 292 (M^+, 100), 164 (38), 136 (37), 291 (34), 51 (31), 94 (18), 293 (14), 121 (14), 79 (14), 66 (13). IR (cm^{-1}): 3006, 2936, 2850, 1671, 1579, 1498, 1261, 1212, 1016, 861.

4-Iodo-2,5-dimethoxybenzaldehyde, **2f**

Mp 137–139, literature mp 136–137.[11] ^{1}H NMR (ppm): 10.4 (1H, s), 7.5 (1H, s), 7.2 (1H, s), 3.90 (3H, s), 3.88 (3H, s). ^{13}C-NMR (ppm): 189.1, 156.2, 152.7, 125.0, 123.7, 108.0, 95.9, 56.9, 56.4. EI-GCMS (relative abundance): 292 (M^+, 100), 246 (40), 274 (33), 276 (31), 53 (24), 51 (23), 63 (20), 79 (20), 77 (19), 107 (19). IR (cm^{-1}):2938, 2876, 2843, 1670, 1591, 1569, 1380, 1268, 1213, 1041, 711.

5-Iodo-2,4-dimethoxybenzaldehyde, **2g**

Mp 172–173, literature mp 172–173.[12] ^{1}H NMR (ppm): 10.2 (1H, s), 8.2 (1H, s), 6.4 (1H, s), 3.97 (3H, s), 3.95 (3H, s). ^{13}C NMR (ppm): 187.0, 164.1, 163.8, 139.2, 120.3, 94.8, 75.6, 56.7, 55.9. EI-GCMS (relative abundance): 292 (M^+, 100), 274 (58), 148 (41), 246 (40), 275 (40), 291 (21), 293 (11), 135 (10). IR (cm^{-1}): 2966, 2937, 2871, 2831, 1654, 1590, 1455, 1271, 1210, 1024, 810, 683.

4-Hydroxy-3-iodo-5-methoxybenzaldehyde, **2h**

Mp 175–177, literature mp 180.[13] ^{1}H NMR (ppm): 9.8 (1H, s), 7.9 (1H, d, $J = 1.7$ Hz), 7.4 (1H, d, $J = 1.7$ Hz), 6.7 (1H, br s), 4.0 (3H, s). ^{13}C NMR (ppm): 189.6, 151.4, 146.5, 136.2, 131.1, 108.6, 80.5, 56.5. EI-GCMS (relative abundance): 278 (M^+, 100), 277 (58), 51 (21), 235 (15), 135 (15), 79 (13), 279 (11), 53 (10), 107 (9), 136 (9). IR (cm^{-1}): 3151 (broad), 2845, 1664, 1571, 1415, 1256, 1142, 1039, 852, 782, 669.

6-Iodopiperonal, **2i**

Mp 108–110, literature mp 108–110.[6] ^{1}H NMR (ppm): 9.9 (1H, s), 7.37 (1H, s), 7.34 (1H, s), 6.1 (2H, s). ^{13}C NMR (ppm): 194.5, 153.6, 149.2, 129.7, 119.5, 108.9, 102.7, 93.4. EI-GCMS (relative abundance): 276 (M^+, 100), 148 (60), 120 (52), 275 (37), 62 (35), 63 (21), 119 (18), 61 (16), 149 (14), 69 (12). IR (cm^{-1}): 2894, 2857, 1661, 1608, 1592, 1383, 1247, 1166, 1110, 925, 872, 847, 783.

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