Pd(0)-Catalyzed PMHS Reductions of Aromatic Acid Chlorides to Aldehydes

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Materials and Methods: All reactions were carried out with magnetic stirring, and monitored by thin-layer chromatography with 0.25-mm precoated silica gel plates or capillary GC with a fused silica column, unless otherwise noted. THF was freshly distilled from sodium/benzophenone under nitrogen. Tris(dibenzylideneacetone)dipalladium (0), tri-2-furylphosphine, anhydrous A.C.S grade potassium fluoride, polymethylhydrosiloxane (PMHS), and tetrabutylammonium fluoride (1M solution in THF) were purchased and used without purification unless otherwise mentioned. 2-Thiophenecarbonyl chloride,¹ and 3,4,5-trimethoxybenzoyl chloride² were prepared following literature procedures and used after distillation. The remaining acid chlorides were purchased and used without purification. Flash chromatography was performed with silica gel 60 Å (230–400 mesh). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ¹H NMR and ¹³C NMR spectra were recorded on a 300 MHz spectrometer (300 MHz for ¹H, respectively, and 75 MHz for ¹³C, respectively) with chemical shifts reported relative to the residue peaks of solvent chloroform (δ 7.24 for ¹H and δ 77.0 for ¹³C). Melting points were measured on a capillary melting point apparatus and are uncorrected.

General Procedure for Reductions with Me₃SnCl/PMHS/KF/Pd(0): Pd₂dba₃ (0.01 mmol, 9.2 mg) and trifurylphosphine (TFP) (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, acid chloride (1 mmol), Me₃SnCl (0.1–1.0 mmol), PMHS (1.5 mmol, 0.09 mL), aq KF (1.5 mmol, 87.3 mg in 1 mL H₂O) and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt until the reduction was judged complete by GC (~0.5 to 1 h). At that time, the reaction was diluted with saturated aq KF (3 mL) and stirred for 0.5 h. The reaction was then extracted with Et₂O and the aqueous phase was back extracted with Et₂O. The combined organics were dried over MgSO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (10% Et₂O/pentane) to afford the aldehyde.

General Procedure for Reductions with PMHS/KF/Pd(0): Pd₂dba₃ (0.01 mmol, 9.2 mg) and trifurylphosphine (TFP) (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, acid chloride (1 mmol), PMHS (3.0 mmol, 0.18 mL), aq. KF (3.0 mmol, 174.5 mg in 1 mL H₂O) and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt until the reduction was complete by GC monitoring (~1 h). At that time, the reaction was extracted with Et₂O and the aqueous phase back extracted with Et₂O. The combined organics were dried over MgSO₄,

(1) DeVries, V. G.; Bloom, J. D.; Dutia, M. D.; Katocs, A. S., Jr.; and Largis, E. E. *J. Med. Chem.* **1989**, *32*, 2318–2325.

(2) Azzena, U.; Denurra, T.; Melloni, G.; and Rassu, G. *J. Chem. Soc., Chem. Commun.* **1987**, 1549–1550.

filtered, and concentrated. The resulting residue was purified by silica gel chromatography (10% Et₂O/pentane) to afford the aldehyde.

Experimental Details and Spectroscopic Data:

Benzaldehyde (Table 2, entry 1): Subjection of benzoyl chloride (**1**) (1.0 mmol, 0.141 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.105 g (99%) of benzaldehyde (**2**) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 9.98 (s, 1H), 7.85 (dd, *J* = 8.0, 1.1 Hz, 2H), 7.62 (m, 1H), 7.51 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 192.2, 136.3, 134.3, 129.6, 128.9. Physical and spectral data were consistent with those obtained from a commercial sample.

2-Methylbenzaldehyde (Table 2, entry 2): Subjection of 2-methyl-benzoyl chloride (**3**) (1.0 mmol, 0.155 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.100 g (83%) of 2-methyl-benzaldehyde (**4**) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 10.24 (s, 1H), 7.78 (d, *J* = 7.4 Hz, 1H), 7.48 (m, 1H), 7.35 (m, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 2.64 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 192.8, 140.6, 134.2, 133.6, 132.0, 131.7, 126.3, 19.5. Physical and spectral data were consistent with those obtained from a commercial sample.

4-tert-Butylbenzaldehyde (Table 2, entry 3): Subjection of 4-tert-butyl-benzoyl chloride (**5**) (1.0 mmol, 197 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.161 g (99%) of 4-tert-butylbenzaldehyde (**6**) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 9.96 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 1.32 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 191.9, 158.4, 134.1, 129.6, 125.9, 35.3, 31.0. Physical and spectral data were consistent with those obtained from a commercial sample.

4-Methoxybenzaldehyde (Table 2, entry 4): Subjection of 4-methoxy-benzoyl chloride (**7**) (1.0 mmol, 0.171 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.124 g (91%) of 4-methoxybenzaldehyde (**8**) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 9.84 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 190.7, 164.6, 131.9, 129.9, 114.3, 55.5. Physical and spectral data were consistent with those obtained from a commercial sample.

3-Methoxybenzaldehyde (Table 2, entry 5): Subjection of 3-methoxybenzoyl chloride (**9**) (1.0 mmol, 0.171 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.133 g (98%) of 3-methoxybenzaldehyde (**10**) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 9.92 (s, 1H), 7.40 (m, 2H), 7.33 (s, 1H), 7.14 (m, 1H), 3.81 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 192.0, 160.1, 137.7, 129.9, 123.4, 121.4, 112.0, 55.3. Physical and spectral data were consistent with those obtained from a commercial sample.

3,4,5-trimethoxybenzaldehyde (Table 2, entry 6): Subjection of 3,4,5-trimethoxybenzoyl chloride (**11**) (1.0 mmol, 231 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.160 g (82%) of 3,4,5-trimethoxybenzaldehyde (**12**) as white crystals. ¹H NMR (300 MHz, CDCl₃): δ 9.84 (s, 1H), 7.01 (s, 2H), 3.91 (s, 3H), 3.90 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 191.0, 153.6, 143.7, 131.7, 106.7, 61.0, 56.3; mp 71–72 °C. Physical and spectral data were consistent with those obtained from a commercial sample.

1-Naphthaldehyde (Table 2, entry 7): Subjection of 1-naphthoyl chloride (**13**) (1.0 mmol, 0.191 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.134 g (86%) of 1-naphthaldehyde (**14**) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 10.36 (s, 1H), 9.25 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.67 (t, *J* = 8.5 Hz, 1H), 7.59 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 193.3, 136.5, 135.1, 133.6, 131.3, 130.4, 128.9, 128.4, 126.8, 124.7 (2C). Physical and spectral data were consistent with those obtained from a commercial sample.

2-Naphthaldehyde (Table 2, entry 8): Subjection of 2-naphthoyl chloride (**15**) (1.0 mmol, 0.191 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.126 g (81%) of 2-naphthaldehyde (**16**) as white crystals. ¹H NMR (300 MHz, CDCl₃): δ 10.12 (s, 1H), 8.30 (s, 1H), 7.95–7.85 (m, 4H), 7.63–7.52 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 191.8, 136.1, 134.1, 133.7, 132.3, 129.1, 128.7 (2C), 127.7, 126.7, 122.4; mp 57–58 °C. Physical and spectral data were consistent with those obtained from a commercial sample.

2-Thiophenecarboxaldehyde (Table 2, entry 9): Subjection of 2-thiophenecarbonyl chloride (**17**) (1.0 mmol, 0.147 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.103 g (92%) of 2-thiophenecarboxaldehyde (**18**) as a colorless liquid. ¹H NMR

(300 MHz, CDCl₃): δ 9.90 (s, 1H), 7.75 (m, 2H), 7.19 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 182.9, 144.0, 136.2, 135.0, 128.2. Physical and spectral data were consistent with those obtained from a commercial sample.

4-Bromobenzaldehyde (Table 2, entry 10): Subjection of 4-bromo-benzoyl chloride (**19**) (1.0 mmol, 220 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et₂O/pentane) 0.126 g (68%) of 4-bromobenzaldehyde (**20**) as white crystals. ¹H NMR (300 MHz, CDCl₃): δ 9.93 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 190.9, 135.0, 132.4, 130.9, 129.7; mp 54–56 °C. Physical and spectral data were consistent with those obtained from a commercial sample.

S9

S11

S12

S13

S15

S17

S18

S19

ppm

1

2

3

4

5

6

7

8

9

10

S20

S21

S23

S24