Improved Carbonylation of Heterocyclic Chlorides and Challenging Aryl Bromides

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I. General

General Methods. ^{1}H NMR and ^{13}C NMR were recorded at ambient temperature on a Bruker DPX 400 at a frequency of 400.13 and 100.61 MHz, respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ (δ = 7.27) for proton and $CDCl_3$ (δ = 77.0) for carbon. The data are reported as follows: proton multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and app = apparent), coupling constants, and integration. Microanalyses were performed by Quantitative Technologies, Inc. Melting points are reported uncorrected. Flash chromatography was performed using the indicated solvent system on EM Reagents silica gel (SiO_2) 60 (230–400 mesh).

Materials. MeOH and triethylamine were used as received. All reagents used were commercially available from Aldrich Chemical Co.

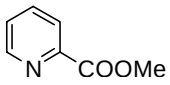
II. General Procedure for Carbonylation of Heterocyclic Chlorides and Aryl Bromides to Esters

An autoclave vessel was charged with chloride or bromide substrate (3 mmol), (BINAP)$PdCl_2$ 24 mg (1 mol%), and triethylamine 0.9 mL (1.3 eq) in 15 mL of methanol. Vessel was tested for leaks using nitrogen, then purged with nitrogen three times and carbon monoxide three times. Vessel was pressurized to 50 psig with carbon monoxide and heated to 100^0C. The reaction was thus allowed to progress until completion, then allowed to cool to room temp and sampled. Reaction was judged to be complete when 2%LCAP or less of starting material remained. When cool, the reaction solution was filtered through Solka-Floc, and cake rinsed with methanol, and filtrate concentrated, and purified by silica gel chromatography to provide the products listed in Table 2 and Table 3.

Heterocyclic Chlorides to Esters

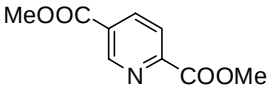
The known chloride substrates in Table 2: 2-chloropyridine, 2,5-dichloropyridine, 2,3-dichloropyridine, 3-chloropyridine, 3-chloro-2-fluoro-5-trifluoromethylpyridine, 2-chloropyrazine, and 1-chloroanthraquinone were commercially available from Sigma-Aldrich. Entry 8 substrate naphthyridone chloride was synthesized.[1]

Representative Procedure for the Carbonylation of Chlorides to Esters (Table 2).
2-Chloropyridine.



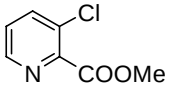
An autoclave vessel was charged with 2-chloropyridine 340mg (3 mmol), (BINAP)$PdCl_2$ 24 mg (1 mol%), and triethylamine 0.9 mL (1.3 eq) in 15 mL of methanol. Vessel was tested for leaks using nitrogen, then purged with nitrogen three times and carbon monoxide three times. Vessel was pressurized to 50 psig with carbon monoxide and heated to 100^0C. The reaction was thus allowed to progress until completion, then allowed to cool to room temp and sampled. Reaction was judged to be complete when 2%LCAP or less of starting material remained. When cool, the reaction solution was filtered through Solka-Floc, and cake rinsed with methanol, and filtrate concentrated. Assay yield of **methyl picolinate** was determined by HPLC analysis of the reaction mixture referenced to authentic (Sigma-Aldrich) **methyl picolinate** (407 mg, 99%).

Dimethyl 2,5-dicarboxypyridine.[2]



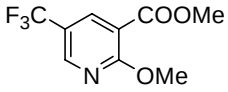
Using the general procedure with **2,5-dichloropyridine** (444 mg, 3 mmol) afforded **dimethyl 2,5-dicarboxypyridine**, after purification by flash chromatography (10% EtOAc in hexanes), as a white solid (573 mg, 98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99 (s, 3H), 4.04 (s, 3H), 8.20 (dd, *J*=8.2, 0.8 Hz, 1H), 8.42 (dd, *J*=8.2, 2.1 Hz, 1H), 9.30 (dd, *J*=2.0, 0.7 Hz, 1H). ^{13}C NMR δ 49.0, 49.5, 120.9, 124.9, 134.6, 147.0, 147.1, 161.1, 161.2.

Methyl 3-chloro-2-carboxypyridine. [3]



Using the general procedure with **2,3-dichloropyridine** (444 mg, 3 mmol) afforded **methyl 3-chloro-2-carboxypyridine**, after purification by flash chromatography (10% EtOAc in hexanes), as a white solid (443 mg, 86%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.88 (s, 3H), 7.28 (dd, *J*=8.1, 4.7 Hz, 1H), 7.69 (dd, *J*=8.1, 1.5 Hz, 1H), 8.44 (dd, *J*=4.7, 1.4 Hz, 1H). ^{13}C NMR δ 52.8, 126.3, 130.9, 138.6, 147.1, 147.15, 164.5.

Carbonylation of 2-fluoro-3-chloro-5-(trifluoromethyl)pyridine. Using the general procedure with **2-fluoro-3-chloro-5-(trifluoromethyl)pyridine** (600mg, 3 mmol) afforded two products, separated by flash chromatography (5-15% EtOAc in hexanes):
Methyl 2-methoxy-5-(trifluoromethyl)nicotinate.



Collected as fraction #1, white solid, (426 mg, 60%): mp 52ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (s, 3H), 4.10 (s, 3H), 8.37, (d, *J*=2.7, 1H), 8.57 (m, 1H). ^{13}C NMR δ 52.5, 54.8, 113.8, 119.5 (q, J_{CF}=271.5

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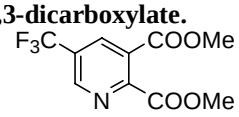
[1] Springfield, S.; Marcantonio, K.; Ceglia, S.; Albaneze-Walker, J.; Dormer, P.; Nelson, T.; Murry J. *J. Org. Chem.* **2003**, *68*, 4598-4599.
[2] Jokela, R. *Magn. Res Chem.* **1992**, *30*, 681-683.
[3] Epsztajn, J.; Plotka, M.; Grabowska, A. *Synth. Comm.* **1997**, *27*, 1075-1086.

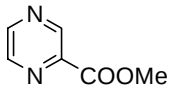
Hz), 123.0 (q, J_{CF}=33.6 Hz), 138.4, 148.0, 164.0 (C=O). Anal Calcd for $C_9H_8F_3NO_3$: C, 45.97; H, 3.43; F, 24.24; N, 5.96. Found: C, 45.92; H, 3.11; F, 24.57; N, 5.86. Anal Calcd for $C_9H_8F_3NO_3$: C, 45.97; H, 3.43; F, 24.24; N, 5.96. Found: C, 45.92; H, 3.11; F, 24.57; N, 5.86.

Dimethyl 5-(trifluoromethyl)pyridine-2,3-dicarboxylate.



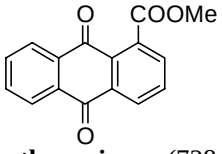
Collected as fraction #2, colorless oil (79 mg, 10%): ^{1}H NMR δ 3.97 (s, 3H), 4.01 (s, 3H), 8.44 (s, 1H), 9.00 (s, 1H). ^{13}C NMR δ 53.20, 53.24, 122.4 (q, J_{CF}=273.1 Hz), 126.5, 127.7 (q, J_{CF}=34.4 Hz), 135.1, 148.6, 153.9, 164.0 (C=O), 165.6(C=O). Anal Calcd for $C_{10}H_8F_3NO_4$: C, 45.64; H, 3.06; F, 21.66; N, 5.32. Found: C, 45.45; H, 2.86; F, 21.80; N, 5.29.

Methyl carboxypyrazine. [4]



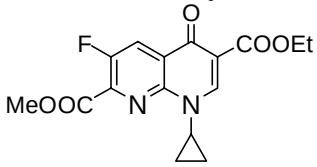
Using the general procedure with **chloropyrazine** (344 mg, 3 mmol) afforded **methyl carboxypyrazine**, after purification by flash chromatography (5% EtOAc in hexanes), as a white solid (410 mg, 99%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.04 (s, 3H), 8.72 (dd, *J*=2.4, 1.7 Hz, 1H), 8.77 (d, *J*=2.4 Hz, 1H), 9.31 (d, *J*=1.5 Hz, 1H). ^{13}C NMR δ 53.0, 143.2, 144.3, 146.2, 147.6, 164.3.

Methyl 1-carboxyanthraquinone. [5]



Using the general procedure with **1-chloroanthraquinone** (728 mg, 3 mmol) afforded **methyl 1-carboxyanthraquinone** [32114-46-8], after purification by flash chromatography (5% EtOAc in hexanes), as a white solid (487 mg, 61%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.02 (s, 3H), 7.83-7.86 (m, 2H), 8.32-8.37 (m, 2H), 8.40 (d, *J*=8.2 Hz, 1H), 8. (dd, *J*=8.44, 1.6 Hz, 1H), 8.96 (d, *J*=1.8 Hz, 1H). ^{13}C NMR δ 52.7, 127.2, 127.3, 127.4, 128.5, 133.2, 133.3, 133.4, 134.3, 134.4, 134.5, 135.0, 136.0, 165.4, 182.1, 182.4.

6-Ethyl-2-methyl-8-cyclopropyl-2-fluoro-5-oxo-5,8-dihydro-1,8-naphthyridine-2,6-dicarboxylate.[1]



Using the general procedure with **6-Ethyl-2-chloro-8-cyclopropyl-2-fluoro-5-oxo-5,8-dihydro-1,8-naphthyridine-6-carboxylate** (932 mg, 3 mmol) afforded **6-ethyl-2-methyl-8-cyclopropyl-2-fluoro-5-oxo-5,8-dihydro-1,8-naphthyridine-2,6-dicarboxylate**, after purification by flash chromatography (20% EtOAc in hexanes), as a white solid, (632 mg, 63%): mp 226ºC. ^{1}H NMR δ 1.07 (m, 2H), 1.32 (m, 2H), 1.41 (t, *J*=7.1 Hz, 3H), 3.75 (sept, *J*=3.9 Hz, 1H), 4.06 (s, 3H), 4.41 (q, *J*=7.1 Hz, 2H), 8.52 (d, J_{HF}=9.1 Hz, 1H), 8.73 (s, 1H). ^{13}C NMR δ 7.6, 14.3, 34.3, 53.2, 61.1, 111.5, 124.5 (d, J_{CF}=21.6 Hz), 126.5, 139.6 (d, J_{CF}=14.4 Hz), 145.9, 149.6, 156.1 (d, J_{CF}=267.5 Hz), 162.7, 164.7, 173.1. Anal Calcd for $C_{16}H_{15}FN_2O_5$: C, 57.49; H, 4.52; F, 5.68; N, 8.38. Found: C, 56.99; H, 4.34; F, 5.90; N, 8.22.

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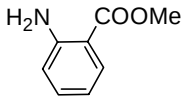
[4] Takeuchi, R.; Suzuki, K.; Sato, N. *Synthesis*, **1990**, 923-4.
[5] Gore, P.; Rahim, A.; Waters, D. *J. Chem. Soc. (B)* **1971**, 202-204.

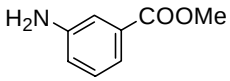
Aryl Bromides to Esters

Representative Procedure for the the Carbonylation of Bromides to Esters (Table 3).
Methyl 2-aminobenzoate. [6]



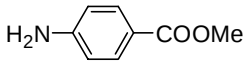
An autoclave vessel was charged with **2-bromoaniline** 172 mg (1 mmol), (BINAP)$PdCl_2$ 24 mg (3 mol%), and triethylamine 0.42 mL (1.3 eq) in 7 mL of methanol. Vessel was tested for leaks using nitrogen, then purged with nitrogen three times and carbon monoxide three times. Vessel was pressurized to 50 psig with carbon monoxide and heated to 100^0C. The reaction was thus allowed to progress until completion, then allowed to cool to room temp and sampled. Reaction was judged to be complete when 2%LCAP or less of starting material remained. When cool, the reaction solution was filtered through Solka-Floc, and cake rinsed with methanol, and filtrate concentrated to afford **methyl 2-aminobenzoate**, after purification by flash chromatography (10% EtOAc in hexanes), as a colorless oil (134 mg, 92%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.88 (s, 3H), 5.50 (br s, 2H), 6.63-6.69 (m, 2H), 7.25-7.30 (m, 1H), 7.86 (dd, *J*=8.0, 1.6, 1H). ^{13}C NMR δ 51.4, 110.8, 116.3, 116.7, 131.1, 134.0, 150.2, 168.5.

Methyl 3-aminobenzoate. [7]



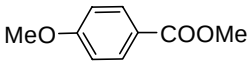
Using the general procedure with **3-bromoaniline** (172 mg, 1 mmol) afforded **methyl 3-aminobenzoate**, after purification by flash chromatography (25% EtOAc in hexanes), as a white solid (148 mg, 98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.55 (br s, 2H), 3.90 (s, 3H), 6.87 (ddd, *J*=8.0, 2.4, 0.8, 1H), 7.21 (t, *J*=7.8, 1H), 7.36 (t, *J*=2.1, 1H), 7.43 (dt, *J*=8.1, 09., 1H). ^{13}C NMR δ 52.0, 115.8, 119.4, 119.7, 129.2, 131.0, 146.2, 167.2.

Methyl 4-aminobenzoate. [6]



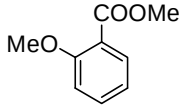
Assay yield of **methyl 4-aminobenzoate** was determined by HPLC analysis of the reaction mixture referenced to authentic (Acros) **methyl 4-aminobenzoate** (76 mg, 50%).

Methyl 4-methoxybenzoate.[7]



Using the general procedure with **4-bromoanisole** (172 mg, 1 mmol) afforded **methyl 4-methoxybenzoate**, after purification by flash chromatography (3% EtOAc in hexanes), as a white solid (160 mg, 96%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H), 3.87 (s, 3H), 6.89 (d, *J*=9.0, 2H), 7.98 (d, *J*=8.9, 2H). ^{13}C NMR δ 51.7, 55.3, 113.5, 122.5, 131.5, 163.2, 166.7.

Methyl 2-methoxybenzoate. [6]



Using the general procedure with **2-bromoanisole** (172 mg, 1 mmol) afforded **methyl 2-methoxybenzoate**, after purification by flash chromatography (5% EtOAc in hexanes), as a white solid

[6] *The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra*; Aldrich Chemical Company, Inc.: Milwaukee, 1993; Ed 1.
[7] Budesinsky, M.; Exner, O. *Magn. Res Chem*. **1989**, *27*, 585-591.

(164 mg, 99%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (s, 3H), 3.09 (s, 3H), 6.96-7.00 (m, 2H), 7.44-7.49 (m, 1H), 7.79 (dd, *J*=8.0, 1.6, 1H). ^{13}C NMR δ 51.9, 55.9, 111.9, 119.9, 120.0, 131.6, 133.4, 159.0, 166.6.