Supporting Information

Synthesis of Primary Aromatic Amides by Aminocarbonylation of Aryl Halides using Formamide as an Ammonia Synthon

Anita Schnyder, Matthias Beller, Gerald Mehlretter, Thomas Nsenda, Martin Studer, Adriano F. Indolese

Experimental

**General Considerations.** For the carbonylation experiments a 250 ml glass autoclave equipped with a magnet-driven hollow shaft stirrer was used. The reactions were carried out under non-isobaric conditions, and the course of the reactions was followed by measuring the pressure in the autoclave. CO gas (purity 99.97 %) was purchased from Carbagas Chemical Co.

Commercially obtained materials were used as received without further purification. Aryl halides, ligands, reagents and solvents were purchased from Fluka Chemical Co. except 4-bromobenzotrifluoride (Aldrich Chemicals Co.) and 3-bromobenzotrifluoride (Novartis AG). Anhydrous dioxane (stored over molecular sieves) was used. Pd(OAc)$_2$ was purchased from Fluka Chemical Co., PdCl$_2$ (20 % Pd in hydrochloric acid) from Degussa AG, and PdCl$_2$(PPh$_3$)$_2$ from Avocado Chemical Co. Dpephos was prepared according to a literature procedure.$^1$
1H and 13C{1H} NMR spectra were recorded on a Bruker dpx 300 spectrometer. Chemical shifts (δ) are given in ppm and refer to TMS as internal standard. IR spectra were recorded on a Perkin Elmer 1710 spectrometer. Melting points were measured with a Büchi 520 apparatus, and were not corrected. Gas chromatography was performed on a Fisons GC 8000 with a DB-17 column and helium as the carrier gas using di(ethylene glycol) di-n-butyl ether as the internal standard. The combustion analyses were carried out by Solvias AG, Switzerland.

**Typical Procedure for the Preparative Carbonylation Experiments (Table 3)**

**3-Trifluoromethylbenzamide (Table 3, Entry 1).** The autoclave was charged with 3-bromobenzotrifluoride (8.01 g, 35.6 mmol), 4-dimethylaminopyridine (4.74 g, 38.0 mmol), formamide (3.12 g, 69.1 mmol), PdCl2(PPh3)2 (243 mg, 0.35 mmol, 1 mol-%) and 1,4-dioxane (25 ml). The autoclave was purged three times with nitrogen (6 bar), charged with 5 bar CO, and the reaction mixture was heated to 120 °C. After 20 h and cooling to room temperature, the solvent was evaporated in vacuo. The residue was partitioned between dichloromethane and water, and the aqueous layer was extracted twice with additional dichloromethane. The organic phases were combined, dried (Na2SO4), and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, EtOAc/hexane as eluent). 4.8 g (25 mmol, 71 %) of the title compound was obtained as colorless crystals. Rf = 0.24 (EtOAc:hexane 1:1); mp.: 121.5-122.0 °C (Lit.: 122-123 °C); 1H NMR (300.1 MHz, dms-406, 297 K) δ 8.25 (s (br), 1H), 8.22-8.17 (m, 2H), 7.89 (dd, J = 7.8 Hz, 0.7 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.64 (s (br), 1H); 13C{1H} NMR (75.5 MHz, dms-406, 297 K) δ 167.2, 136.0, 132.3, 130.3, 130.0 (q, J(C-F) = 32 Hz), 128.6 (q, J(C-F) = 4 Hz), 124.9 (q, J(C-F) = 4 Hz), 124.8 (q, J(C-F) = 272 Hz); IR (KBr, cm⁻¹) 3333, 3152, 1667, 1628, 1588, 1400; Anal. Calcd for C₈H₆F₃NO: C, 50.80; H, 3.20; N, 7.41. Found: C, 50.83; H, 3.21; N, 7.19.
For experiments under different conditions of temperature or CO pressure, or with other ligands and bases, the conditions given in the respective tables were used.

**Isolation of the Reaction Intermediates 5-9 (Fig. 2).** The experiment was carried according the typical procedure. After two hours at 120 °C, the reaction was stopped, and the mixture was cooled to room temperature. The reaction mixture was worked up as described, and the products were purified by column chromatography (silica gel, EtOAc/hexane 1:2 as eluent).

**3-Trifluoromethylbenzamide (4)** was obtained as colorless crystals (3.3 g, 17.5 mmol, 49 %).

**N-Formyl-3-trifluoromethylbenzoylimide (5)** was obtained as colorless crystals (650 mg, 3.0 mmol, 8 %). \( R_f = 0.54 \) (EtOAc:hexane 1:2); mp.: 130.0-130.5 °C; \(^1\)H NMR (300.1 MHz, dms-\( d_6 \), 297 K) \( \delta \) 11.96 (d, \( J = 8.6 \) Hz, 1H), 9.28 (d, \( J = 8.4 \) Hz, 1H), 8.34 (s, 1H), 8.30 (d, \( J = 7.9 \) Hz, 1H), 8.03 (dd, \( J = 7.8 \) Hz, 0.7 Hz, 1H), 7.79 (t, \( J = 7.8 \) Hz, 1H); \(^1^3\)C\{\(^1\)H\} NMR (75.5 MHz, dms-\( d_6 \), 297 K) \( \delta \) 167.2, 165.2, 133.6, 133.3, 130.8, 130.6 (q, \( J(C-F) = 4 \) Hz), 130.3 (q, \( J(C-F) = 32 \) Hz), 125.9 (q, \( J(C-F) = 4 \) Hz), 124.6 (q, \( J(C-F) = 272 \) Hz); IR (KBr, cm\(^{-1}\)) 3246, 1740, 1678, 1469; Anal. Calcd for C\(_6\)H\(_4\)F\(_3\)NO\(_2\): C, 49.78; H, 2.79; N, 6.45; F, 26.25; O, 14.74. Found: C, 49.89; H, 2.83; N, 6.27; F, 26.08; O, 14.75.

**Bis-(3-trifluoromethylbenzoylimide (6)** was obtained as colorless crystals (210 mg, 0.6 mmol, 3 %). \( R_f = 0.50 \) (EtOAc:hexane 1:1); mp.: 177-178 °C; \(^1\)H NMR (300.1 MHz, dms-\( d_6 \), 297 K) \( \delta \) 11.72 (s, 1H), 8.27 (s, 2H), 8.21 (d, \( J = 7.9 \) Hz, 2H), 8.01 (d, \( J = 7.8 \) Hz, 2H), 7.78 (t, \( J = 7.8 \) Hz, 2H); \(^1^3\)C\{\(^1\)H\} NMR (75.5 MHz, dms-\( d_6 \), 297 K) \( \delta \) 167.4, 135.7, 133.6, 130.6, 129.5 (q, \( J(C-F) = 26 \) Hz), 129.8, 126.1 (q, \( J(C-F) = 4 \) Hz), 124.7 (q, \( J(C-F) = 272 \) Hz); IR (KBr, cm\(^{-1}\)) 3267, 1719, 1528, 1336; Anal. Calcd for C\(_{16}\)H\(_4\)F\(_6\)NO\(_2\): C, 53.20; H, 2.51; N, 3.88. Found: C, 53.13; H, 2.58; N, 3.87.
7 was obtained as colorless crystals (120 mg, 0.21 mmol, 2%). \( R_f = 0.48 \)
(EtOAc:hexane 1:2); \(^1 \)H NMR (300.1 MHz, dmso-\( d_6 \), 297 K) \( \delta 9.46 \) (d, \( J = 6.1 \) Hz, 3H),
8.28 (s, 3H), 8.23 (d, \( J = 7.8 \) Hz, 3H), 7.96 (dd, \( J = 7.8 \) Hz, 0.6 Hz, 3H), 7.77 (t, \( J = 7.8 
\) Hz, 3H), 7.38 (q, \( J = 6.1 \) Hz, 1H); \(^{13}\)C{\(^1 \)H} NMR (75.5 MHz, dmso-\( d_6 \), 297 K) \( \delta 
165.2 \) (3C), 135.4 (3C), 132.7 (3C), 130.6 (3C), 129.9 (q, \( J(C-F) = 32 
\) Hz, 3C), 129.1 (q, \( J(C-F) = 4 
\) Hz, 3C), 125.8 (q, \( J(C-F) = 272 
\) Hz, 3C), 125.1 (q, \( J(C-F) = 4 
\) Hz, 3C), 64.4.

8 and 9 were obtained as a mixture of colorless crystals, consisting of 80 \% of 8 (520 mg, 1.2 mmol, 8\%) and 20 \% of 9 (130 mg, 0.5 mmol, 1\%).

8: \(^1 \)H NMR (300.1 MHz, dmso-\( d_6 \), 297 K) \( \delta 9.50 \) (d, \( J = 6.2 \) Hz, 2H), 8.94 (dd, \( J = 7.0 
\) Hz, 1.3 Hz, 1H), 8.26 (s, 2H), 8.20 (d, \( J = 7.8 \) Hz, 2H), 8.09 (dd, \( J = 1.3 \) Hz, 0.8 Hz, 
1H), 7.95 (dd, \( J = 7.8 \) Hz, 0.7 Hz, 2H), 7.75 (t, \( J = 7.8 \) Hz, 2H), 7.38 (q, \( J = 6.2 \) Hz, 1H).

Additional signals for 9: \( \delta 9.50 \) (d, \( J = 6.2 \) Hz, 1H), 8.43-8.41 (m, 2H), 6.97-6.90 (m, 1H).

4-Trifluoromethylbenzamide (Table 3, Entry 2). The reaction of 4-bromobenzotri fluoride (4.01 g, 17.8 mmol) was effected using the general procedure to
afford 2.35 g (12.4 mmol, 70 \%) of the title compound as a colorless solid. \( R_f = 0.50 
\) (EtOAc:hexane 4:1); mp.: 184.5-185 °C (Lit.\(^2\): 180-181 °C); \(^1 \)H NMR (300.1 MHz, dmso-\( d_6 \), 297 K) \( \delta 8.21 \) (s (br), 1H), 8.07 (d, \( J = 8.1 
\) Hz, 2H), 7.83 (d, \( J = 8.2 
\) Hz, 2H), 7.64 (s (br), 1H); \(^{13}\)C{\(^1 \)H} NMR (75.5 MHz, dmso-\( d_6 \), 297 K) \( \delta 
167.6, 138.9, 132.0 \) (q, \( J(C-F) = 32 
\) Hz), 129.2 (2C), 126.1 (q, \( J(C-F) = 4 
\) Hz, 2C), 124.8 (q, \( J(C-F) = 272 
\) Hz); IR (KBr, cm\(^{-1}\)) 3374, 3178, 1654, 1627, 1323, 1139; Anal. Calcd for C\(_9\)H\(_8\)F\(_3\)NO: C, 50.80; H, 3.20; N, 7.41; Found: C, 50.91; H, 3.20; N, 7.35.

4-Acetylbenezamide (Table 3, Entry 3). The reaction of 4-bromoacetophenone (3.44 g, 17.3 mmol) was effected using the general procedure to afford 960 mg (5.9 mmol, 34 \%)
\) of the title compound as a colorless solid. \( R_f = 0.10 \) (EtOAc:hexane 1:10); mp.: 194-195.5 °C; \(^1 \)H NMR (300.1 MHz, dmso-\( d_6 \), 297 K) \( \delta 8.15 \) (s (br), 1H), 8.02 (d, \( J = 8.9 
\) Hz,
2H), 7.99 (d, J = 7.9 Hz, 2H), 7.57 (s (br), 1H), 2.62 (s, 3H); $^{13}$C{¹H} NMR (75.5 MHz, dmso-$d_6$, 297 K) δ 198.6, 168.0, 139.5, 139.0, 128.9 (2C), 128.6 (2C), 27.8; IR (KBr, cm⁻¹) 3399, 3188, 1678, 1660, 1415, 1267; Anal. Calcd for C₉H₈NO₂: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.23; H, 5.63; N, 8.59.

2-Pyridinecarboxamide (Table 3, Entry 4). The reaction of 2-bromopyridine (2.73 g, 17.3 mmol) was effected using the general procedure to afford 1.37 g (11.2 mmol, 66 %) of the title compound as a colorless solid. $R_f = 0.40$ (EtOAc:hexane 4:1); mp.: 101-105 °C (Lit.²: 107-108 °C); $^1$H NMR (300.1 MHz, dmso-$d_6$, 297 K) δ 8.63 (dt, J = 4.8 Hz, 1.1 Hz, 1 H), 8.14 (s (br), 1H), 8.05 (dd, J = 6.8 Hz, 1.0 Hz, 1H), 7.98 (td, J = 7.6 Hz, 1.7 Hz, 1H), 7.67 (s (br), 1H), 7.58 (ddd, J = 7.2 Hz, 4.8 Hz, 1.4 Hz, 1H); $^{13}$C{¹H} NMR (75.5 MHz, dmso-$d_6$, 297 K) δ 166.9, 151.2, 149.3, 138.5, 127.3, 122.8; IR (KBr, cm⁻¹) 3420, 3180, 1661, 1390; Anal. Calcd for C₉H₈N₂O: C, 59.01; H, 4.95; N, 22.94. Found: C, 58.97; H, 4.99; N, 22.71.

2-Pyridinecarboxamide (Table 3, Entry 5). The reaction of 2-chloropyridine (3.92 g, 34.6 mmol) was effected using the general procedure, but with additional triphenylphosphine (272 mg, 1.0 mmol), to afford 3.30 g (27.0 mmol, 78 %) of the title compound as a colorless solid. $R_f = 0.24$ (EtOAc:dichloromethane 2:3); mp.: 104-105 °C (Lit.²: 107-108 °C); spectroscopic data see above.

p-Toluamide (Table 3, Entry 6). The reaction of 4-bromotoluene (5.91 g, 34.6 mmol) was effected using the general procedure to afford 3.85 g (28.5 mmol, 82 %) of the title compound as a colorless solid. $R_f = 0.29$ (EtOAc:hexane 7:3); mp.: 159.5-160 °C (Lit.²: 158-160 °C); $^1$H NMR (300.1 MHz, dmso-$d_6$, 297 K) δ 7.91 (s (br), 1H), 7.79 (d, J = 8.1 Hz, 2H), 7.29 (s (br), 1H), 7.24 (d, J = 8.0 Hz, 2H), 2.34 (s, 3H); $^{13}$C{¹H} NMR (75.5 MHz, dmso-$d_6$, 297 K) δ 168.7, 141.9, 132.3, 129.6 (2C), 128.4 (2C), 21.8; IR (KBr, cm⁻¹) 3344, 3168, 1672, 1618, 1412, 1398; Anal. Calcd for C₈H₈NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 69.98; H, 6.65; N, 10.21.
4-t-Butylbenzamide (Table 3, Entry 7). The reaction of 4-bromo-t-butylbenzene (3.68 g, 17.3 mmol) was effected using the general procedure, but with additional triphenylphosphine (272 mg, 1.0 mmol), to afford 2.26 g (12.7 mmol, 74%) of the title compound as a colorless solid. $R_f$ = 0.33 (EtOAc:dichloromethane 2:3); mp.: 169.5-171.5 °C (Lit.²: 172-174 °C); $^1$H NMR (300.1 MHz, dmoso-$d_6$, 297 K) δ 7.91 (s (br), 1H), 7.81 (d, $J$ = 8.4 Hz, 2H), 7.45 (d, $J$ = 8.4 Hz, 2H), 7.29 (s (br), 1H), 1.29 (s, 9H); $^{13}$C{¹H} NMR (75.5 MHz, dmoso-$d_6$, 297 K) δ 168.7, 154.8, 132.4, 128.2 (2C), 125.8 (2C), 35.4, 31.8 (3C); IR (KBr, cm⁻¹) 3398, 3220, 2959, 1650, 1612, 1414; Anal. Calcd for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.60; H, 8.41; N, 7.64.

4-Methoxybenzamide (Table 3, Entry 8). The reaction of 4-bromoanisole (6.46 g, 17.3 mmol) was effected using the general procedure, but with additional triphenylphosphine (272 mg, 1.0 mmol), to afford 3.60 g (23.8 mmol, 69%) of the title compound as a colorless solid. $R_f$ = 0.19 (EtOAc:hexane 7:1); mp.: 166.5-167.0 °C (Lit.²: 164-167 °C); $^1$H NMR (300.1 MHz, dmoso-$d_6$, 297 K) δ 7.86 (d, $J$ = 8.8 Hz, 3H), 7.21 (s (br), 1H), 6.97 (d, $J$ = 8.8 Hz, 2H), 3.80 (s, 3H); $^{13}$C{¹H} NMR (75.5 MHz, dmoso-$d_6$, 297 K) δ 168.3, 162.4, 130.2 (2C), 127.4, 114.2 (2C), 56.1; IR (KBr, cm⁻¹) 3390, 3167, 1645, 1617, 1394; Anal. Calcd for C₈H₇NO₂: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.41; H, 6.08; N, 9.38.

Cinnamide (Table 3, Entry 9). The reaction of β-bromostyrene (6.52 g, 35.6 mmol) was effected using the general procedure to afford 3.80 g (25.8 mmol, 73%) of the title compound as a colorless solid. $R_f$ = 0.38 (EtOAc:hexane 4:1); mp.: 147-148 °C (Lit.²: 146-148 °C); $^1$H NMR (300.1 MHz, dmoso-$d_6$, 297 K) δ 7.58-7.55 (m, 3H), 7.46-7.37 (m, 4H), 7.14 (s (br), 1H), 6.62 (d, $J$ = 15.9 Hz, 1H); $^{13}$C{¹H} NMR (75.5 MHz, dmoso-$d_6$, 297 K) δ 167.5, 140.0, 135.7, 130.3, 129.8 (2C), 128.4 (2C), 123.2; IR (KBr, cm⁻¹) 3373, 3168, 1663, 1609, 1398; Anal. Calcd for C₉H₇NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.38; H, 6.23; N, 9.37.
2-Thiophenecarboxamide (Table 3, Entry 10). The reaction of 2-bromothiophene (2.82 g, 17.3 mmol) was effected using the general procedure, but with additional triphenylphosphine (272 mg, 1.0 mmol), to afford 1.87 g (14.7 mmol, 85%) of the title compound as a colorless solid. \( R_f = 0.58 \) (EtOAc); mp.: 169-175 °C (decomp.) (Lit.: 181-183 °C); \(^1\)H NMR (300.1 MHz, dmso-\( d_6 \), 297 K) \( \delta \) 7.95 (s (br), 1H), 7.76-7.72 (m, 2H), 7.39 (s (br), 1H), 7.13 (dd, \( J = 5.0 \) Hz, 3.7 Hz, 1H); \(^{13}\)C\(^{\{1\}H} \) NMR (75.5 MHz, dmso-\( d_6 \), 297 K) \( \delta \) 163.7, 150.0, 131.8, 129.5, 128.7; IR (KBr, cm\(^{-1}\)) 3367, 3175, 1654, 1607, 1433.

N-Methyl-3-trifluoromethylbenzamide (Table 3, Entry 12). The reaction of 3-bromobenzotri fluoride (8.01 g, 35.6 mmol) with N-methylformamide (3.12 g, 69.1 mmol) was effected using the general procedure, but with additional triphenylphosphine (377 mg, 1.42 mmol), to afford 5.63 g (27.7 mmol, 78%) N-methyl-3-trifluoromethylbenzamide as colorless crystals. \( R_f = 0.32 \) (EtOAc:hexane 1:1); mp.: 81.0-81.5 °C; \(^1\)H NMR (300.1 MHz, dmso-\( d_6 \), 297 K) \( \delta \) 8.58 (s (br), 1H), 8.04-8.00 (m, 2H), 7.75 (d, \( J = 7.8 \) Hz, 1H), 7.58 (tt, \( J = 7.8 \) Hz, 0.6, 1H), 2.69 and 2.68 (2s, 3H); \(^{13}\)C\(^{\{1\}H} \) NMR (75.5 MHz, dmso-\( d_6 \), 297 K) \( \delta \) 165.9, 136.2, 132.0, 130.4, 130.0 (q, \( J(C-F) = 32 \) Hz), 128.4 (q, \( J(C-F) = 4 \) Hz), 124.8. (q, \( J(C-F) = 272 \) Hz), 124.5 (q, \( J(C-F) = 4 \) Hz), 27.1; IR (KBr, cm\(^{-1}\)) 3348, 1639, 1551, 1447, 1407, 1335; Anal. Calcd for C\(_3\)H\(_2\)F\(_3\)NO: C, 53.21; H, 3.97; N, 6.89; F, 28.05; O, 7.88. Found: C, 53.28; H, 3.96; N, 6.75; F, 27.80; O, 8.19.

N,N-Dimethyl-3-trifluoromethylbenzamide (Table 3, Entry 13). The reaction of 3-bromobenzotri fluoride (8.01 g, 35.6 mmol) with DMF was effected using the general procedure, with imidazole (2.59 g, 38.0 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (486 mg, 0.70 mmol, 2 mol-%), triphenylphosphine (0.377 g, 1.42 mmol), and DMF (25 ml) as the solvent. 6.88 g (31.7 mmol, 78%) of N,N-dimethyl-3-trifluoromethylbenzamide was obtained as a colorless oil. \( R_f = 0.12 \) (EtOAc:hexane 2:1); \(^1\)H NMR (300.1 MHz, dmso-\( d_6 \), 297 K) \( \delta \) 7.70-7.50 (m, 4H), 3.15 (s, 3H), 2.95 (s, 3H); \(^{13}\)C\(^{\{1\}H} \) NMR (75.5 MHz, dmso-\( d_6 \), 297
K) $\delta$ 170.1, 137.4, 131.7, 130.5 (q, $J(C-F) = 32$ Hz), 129.1 (q, $J(C-F) = 4$ Hz), 126.4 (q, $J(C-F) = 4$ Hz), 124.3, 124.1 (q, $J(C-F) = 272$ Hz), 39.5, 35.4; IR (neat, cm$^{-1}$) 2935, 1644, 1397, 1332; Anal. Calcd for C$_{10}$H$_{10}$F$_3$NO: C, 55.30; H, 4.64; N, 6.45. Found: C, 55.04; H, 4.75; N, 6.44.

References


(2) Lancaster Catalogue, 93/94.