Dealkoxylation of N-alkoxyamides without an external reductant

driven by Pd/Al cooperative catalysis

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Supporting Information

General. All reactions were carried out with standard Schlenk techniques under an argon or nitrogen atmosphere. Column chromatography was carried out on Wakogel[®] C-200 (75–150 μ m). Preparative thin-layer chromatography (TLC) was performed on Wakogel[®] B-5F. Proton chemical shifts were referenced to residual CHCl₃ signal at 7.26 ppm. Carbon chemical shifts were referenced to CDCl₃ at 77.0 ppm.

Materials. *N*-Methoxy-*N*-methylamides were prepared by the literature method.¹ All other reagents and solvents were obtained from commercial sources and used without further purification.



N-Methoxy-*N*,3,4-trimethylbenzamide (1d). Colorless oil; ¹H NMR (400 MHz, CHCl₃) δ : 7.45 (1H, s), 7.41 (1H, dd, *J* = 7.8, 1.8 Hz), 7.14 (1H, d, *J* = 8.2 Hz), 3.57 (3H, s), 3.34 (3H, s), 2.29 (6H, s); ¹³C NMR(CDCl₃, 75.57 MHz) δ : 170.2, 139.5, 136.2, 131.5, 129.3, 129.1, 125.6, 60.9, 33.9, 19.7, 19.6; IR (neat, cm⁻¹): 2970, 2936, 1645, 1569, 1455, 1418, 1373, 1177, 1124, 1005; HRMS (ESI) calcd for C₁₁H₁₅NNaO₂⁺ [M + Na]⁺, found 216.0995.

General Procedure for Dealkoxylation of *N*-Methoxy-*N*-Methylamides 1. To a Schlenk tube was added Pd(dba)₂ (6.9 mg, 12 μ mol) and DPPBz (5.4 mg, 12 μ mol), and the tube was evacuated and backfilled with argon. CPME (1.0 mL) was injected to the tube, and the solution was heated at 50 °C for 15 min. After the catalyst preparation, *N*-methoxy-*N*-methylamide 1 (0.300 mmol) and Al*i*-Bu₃ (30 μ L, 1.0 M in hexane) were added. The mixture was heated at 150 °C with stirring for 6 h. After cooling to room temperature, the solution was filtered through a plug of Florisil[®] washing with AcOEt, and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC to afford the desired secondary amide 2.

A Gram Scale Reaction for Dealkoxylation of *N*-Methoxy-*N*-Methylbenzamides 1a. To a 100 mL two-neck round-bottom flask was added $Pd(dba)_2$ (230 mg, 0.400 mmol) and DPPBz (179 mg, 0.401 mmol), and the flask was evacuated and backfilled with argon. Diglyme (33.0 mL) was injected to the flask, and the solution was heated at 50 °C for 15 min. After the catalyst preparation, *N*-methoxy-*N*-methylbenzamide 1a (1.57 g, 9.50 mmol) and Al*i*-Bu₃ (1.0 mL, 1.0 M in hexane) were added. The mixture was heated at 150 °C with stirring for 18 h. After cooling to room temperature, the crude reaction mixture was diluted with AcOEt (30 mL) and H₂O (30 mL). The aqueous layer was extracted with AcOEt (30 mL × 3), and the combined organic layer was washed with H₂O (30 mL × 3) and brine (30 mL × 1). The solution was dried over anhydrous Na₂SO₄, filtered and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (Hexane:AcOEt = 1:1) to afford the desired secondary amide **2a** (1.00 g, 7.40 mmol, 78%).



N-Methylbenzamide (2a). The general procedure was followed using 1a (49.6 mg, 0.300 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded 2a (40.2 mg, 0.297 mmol, 99%) as a white solid. Mp 80–81 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.77–7.75 (2H, m), 7.47–7.33 (3H, m), 6.74 (1H, br s), 2.95 (3H, d, *J* = 4.8 Hz). The spectral data matched those reported in the literature.²



N,4-Dimethylbenzamide (2b). The general procedure was followed using 1b (53.8 mg, 0.300 mmol; 54.9 mg, 0.306 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded 2a (40.0 mg, 0.268 mmol, 89%; 38.8 mg, 0.260 mmol, 85%) as a white solid. Mp 145–146 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.65 (2H, d, *J* = 8.3 Hz), 7.22 (2H, d, *J* = 8.3 Hz), 6.19 (1H, s), 3.01 (3H, d, *J* = 4.8 Hz), 2.39 (3H, s). The spectral data matched those reported in the literature.²



N,3-Dimethylbenzamide (2c). The general procedure was followed using 1c (53.8 mg,

0.300 mmol; 53.2 mg, 0.297 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded **2a** (42.8 mg, 0.287 mmol, 94%; 40.6 mg, 0.272 mmol, 92%) as pale yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ : 7.58 (1H, s), 7.55–7.52 (1H, m), 7.27–7.24 (2H, m), 6.71 (1H, br s), 2.95 (3H, d, J = 4.8 Hz), 2.33 (3H, s). The spectral data matched those reported in the literature.²



N,3,4-Trimethylbenzamide (2d). The general procedure was followed using 1d (57.0 mg, 0.295 mmol; 57.1 mg, 0.295 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded 2d (46.5 mg, 0.285 mmol, 97%; 45.1 mg, 0.276 mmol, 94%) as a white solid. Mp 107–109 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.55 (1H, d, *J* = 2.1 Hz), 7.46 (1H, dd, *J* = 7.9, 2.1 Hz), 7.16 (1H, d, *J* = 7.6 Hz), 6.19 (1H, br s), 2.99 (3H, d, *J* = 4.8 Hz), 2.28 (6H, s). The spectral data matched those reported in the literature.³



N,2-Dimethylbenzamide (2e). The general procedure was followed using Pd(dba)₂ (13.8 mg, 24 µmol) and DPPBz (10.7 mg, 24 µmol), Al*i*-Bu₃ (60 µL, 1.0 M in hexane) and 1e (54.9 mg, 0.306 mmol; 52.6 mg, 0.293 mmol) for 20 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded 2e (37.4 mg, 0.251 mmol, 82%; 33.6 mg, 0.225 mmol, 77%) as a white solid. Mp 78–79 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.29–7.23 (2H, m), 7.17–7.11 (2H, m), 6.09 (1H, br s), 2.90 (3H, d, *J* = 4.8 Hz), 2.38 (3H, s). The spectral data matched those reported in the literature.²



4-Methoxy-*N*-methylbenzamide (2f). The general procedure was followed using 1f (59.5 mg, 0.305 mmol; 58.2 mg, 0.298 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded 2f (44.9 mg, 0.272 mmol, 89%; 45.0 mg, 0.272 mmol, 91%) as a white solid. Mp 117–120 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.74 (2H, d, *J* = 8.6 Hz), 6.91 (2H, d, *J* = 8.6 Hz), 6.08 (1H, br s), 3.84 (3H, s), 2.99 (3H, d, *J* = 4.8 Hz). The spectral data matched those reported in the literature.²



3-[(*tert***-Butyldimethylsilyl)oxy]-***N***-methylbenzamide (2g). The general procedure was followed using 1g** (88.0 mg, 0.298 mmol; 88.6 mg, 0.300 mmol) for 18 h. Purification by preparative TLC (hexane:AcOEt = 3:1) yielded **2f** (75.6 mg, 0.285 mmol, 96%; 77.5 mg, 0.292 mmol, 97%) as a colorless liquid. ¹H NMR (CDCl₃, 500 MHz) δ : 7.33–7.30 (2H, m), 7.23 (1H, dd, *J* = 8.0, 7.4 Hz), 6.93 (1H, dd, *J* = 7.4, 1.7 Hz), 6.81 (1H, br s), 2.95 (3H, d, *J* = 4.6 Hz), 0.97 (9H, s), 0.19 (6H, s); ¹³C NMR(CDCl₃, 500 MHz) δ : 168.0, 155.7, 136.0, 129.3, 122.8, 119.5, 118.8, 26.7, 25.5, 18.0, -4.6; IR (neat, cm⁻¹): 3328, 2956, 2931, 2859, 1644, 1580, 1550, 1304, 1253, 1136, 949; HRMS (ESI) calcd for C₁₄H₂₃NO₂SiNa⁺ [M + Na]⁺ 288.1390, found 288.1378.

N-Methyl-4-(trifluoromethyl)benzamide (2h). The general procedure was followed

using **1h** (76.1 mg, 0.326 mmol; 70.1 mg, 0.301 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded **2h** (58.8 mg, 0.289 mmol, 88%; 57.0 mg, 0.281 mmol, 93%) as a white solid. Mp 157–158 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.87 (2H, d, *J* = 7.9 Hz), 7.69 (2H, d, *J* = 8.6 Hz), 6.25 (1H, s), 3.04 (3H, d, *J* = 4.8 Hz). The spectral data matched those reported in the literature.⁴

4-Fluoro-*N***-methylbenzamide (2i).** The general procedure was followed using **1i** (57.1 mg, 0.312 mmol; 58.5 mg, 0.319 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded **2i** (44.5 mg, 0.291 mmol, 93%; 45.9 mg, 0.300 mmol, 94%) as a white solid. Mp 128–129 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.78–7.75 (2H, m), 7.10 (2H, t, J = 8.6 Hz), 6.18 (1H, br s), 3.00 (3H, d, J = 5.2 Hz). The spectral data matched those reported in the literature.⁵

4-Chloro-*N***-methylbenzamide (2j).** The general procedure was followed using Pd(dba)₂ (13.8 mg, 24 µmol) and DPPBz (10.7 mg, 24 µmol), Al*i*-Bu₃ (60 µL, 1.0 M in hexane) and **1j** (60.0 mg, 0.301 mmol; 59.0 mg, 0.296 mmol) for 20 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded **2j** (25.4 mg, 0.150 mmol, 50%; 27.1 mg, 0.160 mmol, 54%) as a white solid. Mp 155–156 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.70 (2H, d, *J* = 8.7 Hz), 7.40 (2H, d, *J* = 8.7 Hz), 6.13 (1H, br s), 3.01 (3H, d, *J* = 5.0 Hz). The spectral data matched those reported in the literature.²



N-Methylisonicotinamide (2k). The general procedure was followed using 1k (46.0 mg, 0.296 mmol; 48.0 mg, 0.309 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 2:1, Et₃N 5%) yielded 2k (26.2 mg, 0.192 mmol, 65%; 29.2 mg, 0.214 mmol, 69%) as a white solid. Mp 99–102 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 8.65 (2H, d, *J* = 6.2 Hz), 7.60 (2H, d, *J* = 6.2 Hz), 7.03 (1H, br s), 2.97 (3H, d, *J* = 4.8 Hz). The spectral data matched those reported in the literature.⁶



N-Methylnicotinamide (21). The general procedure was followed using 11 (47.0 mg, 0.303 mmol; 46.8 mg, 0.302 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 2:1, Et₃N 5%) yielded 21 (33.6 mg, 0.247 mmol, 81%; 32.4 mg, 0.238 mmol, 79%) as a brown solid. Mp 112–113 °C ¹H NMR (CDCl₃, 300 MHz) δ : 9.01 (1H, d, *J* = 2.1 Hz), 8.67 (1H, dd, *J* = 4.8, 1.7 Hz), 8.14 (1H, dt, *J* = 7.9, 2.1 Hz), 7.35 (2H, m), 3.00 (3H, d, *J* = 4.8 Hz). The spectral data matched those reported in the literature.⁶



N-Methylpicolinamide (2m). The general procedure was followed using 1m (46.1 mg, 0.297 mmol; 47.0 mg, 0.303 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 2:1, Et₃N 5%) yielded 2m (26.1 mg, 0.192 mmol, 65%; 24.6 mg, 0.180 mmol, 60%) as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ : 8.54 (1H, dq, *J* = 4.7, 0.9 Hz), 8.20 (1H, dt, *J* = 7.8, 1.0 Hz), 8.06 (1H, s), 7.84 (1H, dt, *J* = 1.7, 7.7Hz), 7.42 (1H, ddd, *J* = 7.7, 4.7, 1.1 Hz),

3.04 (3H, d, J = 5.2 Hz). The spectral data matched those reported in the literature.⁷

N-Methylfuran-2-carboxamide (2n). The general procedure was followed using 1n (47.5 mg, 0.306 mmol; 46.7 mg, 0.301 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded 2n (30.0 mg, 0.240 mmol, 78%; 30.7 mg, 0.245 mmol, 82%) as a pale yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ : 7.42 (1H, dd, *J* = 1.5, 0.9 Hz), 7.10–7.09 (1H, m), 6.49–6.48 (1H, m), 6.37 (1H, br s), 2.98 (3H, d, *J* = 4.8 Hz). The spectral data matched those reported in the literature.⁸



N-Methylthiophene-2-carboxamide (20). The general procedure was followed using 10 (51.7 mg, 0.302 mmol; 52.0 mg, 0.304 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded 20 (40.4 mg, 0.286 mmol, 95%; 39.2 mg, 0.278 mmol, 91%) as a white solid. Mp 116–117 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.54 (1H, d, *J* = 3.8 Hz), 7.40 (1H, d, *J* = 3.8 Hz), 7.00 (1H, dd, *J* = 4.8, 3.8 Hz), 6.74 (1H, br s), 2.93 (3H, d, *J* = 4.8 Hz). The spectral data matched those reported in the literature.⁶



N-Methylcinnamamide (2p). The general procedure was followed using Pd(dba)₂ (13.8 mg, 24 μ mol) and DPPBz (10.7 mg, 24 μ mol), Al*i*-Bu₃ (60 μ L, 1.0 M in hexane) and **1p** (60.9 mg, 0.318 mmol; 58.6 mg, 0.306 mmol) for 20 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded **2p** (34.6 mg, 0.215 mmol, 67%; 35.7 mg, 0.221 mmol, 72%) as

a white solid. Mp 110–111 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.63 (1H, d, J = 15.5 Hz), 7.50 (2H, dd, J = 6.5, 3.1 Hz), 7.40–7.33 (3H, m), 6.39 (1H, d, J = 15.5 Hz), 5.71 (1H, s), 2.95 (3H, d, J = 4.8 Hz). The spectral data matched those reported in the literature.⁵



N-Methyl-3-phenylpropanamide (2q). The general procedure was followed using Pd(dba)₂ (13.8 mg, 24 µmol) and DPPBz (10.7 mg, 24 µmol), Al*i*-Bu₃ (60 µL, 1.0 M in hexane) and 1q (58.0 mg, 0.300 mmol; 58.1 mg, 0.301 mmol) for 20 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded 2q (40.0 mg, 0.245 mmol, 82%; 38.2 mg, 0.234 mmol, 78%) as a white solid. Mp 58–59 °C; ¹H NMR (CDCl₃, 300 MHz) δ : 7.28–7.20 (5H, m), 5.79 (1H, s), 2.96 (2H, t, *J* = 7.7 Hz), 2.76 (3H, d, *J* = 4.8 Hz), 2.47 (2H, t, *J* = 7.9 Hz). The spectral data matched those reported in the literature.⁶



N-Methyl-4-phenoxybutanamide (2r). The general procedure was followed using Pd(dba)₂ (13.8 mg, 24 µmol) and DPPBz (10.7 mg, 24 µmol), Al*i*-Bu₃ (60 µL, 1.0 M in hexane) and 1r (67.3 mg, 0.301 mmol; 67.4 mg, 0.302 mmol) for 20 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded 2r (49.4 mg, 0.256 mmol, 85%; 49.3 mg, 0.255 mmol, 84%) as a white solid. Mp 81–83 °C; ¹H NMR (CDCl₃, 500 MHz) δ : 7.27–7.23 (2H, m), 6.93–6.90 (1H, m), 6.86 (2H, dd, *J* = 5.7, 3.4 Hz), 6.28 (1H, br s), 3.96 (2H, t, *J* = 6.0 Hz), 2.76 (3H, d, *J* = 4.6 Hz), 2.36 (2H, t, *J* = 7.4 Hz), 2.09 (2H, dt, *J* = 15.8, 5.2 Hz); ¹³C NMR (CDCl₃, 500 MHz) δ : 173.1, 158.6, 129.3, 120.5, 114.2, 66.7, 32.6, 26.0, 25.1; IR (neat, cm⁻¹): 3338, 2963, 2909, 2875, 1644, 1543, 1504, 1476, 1228, 1039; HRMS (ESI) calcd for C₁₁H₁₅NO₂Na⁺ [M + Na]⁺ 216.0995, found 216.1005.



N-Methylcyclohexanecarboxamide (2s). The general procedure was followed using $Pd(dba)_2$ (13.8 mg, 24 µmol) and DPPBz (10.7 mg, 24 µmol), Al*i*-Bu₃ (60 µL, 1.0 M in hexane) and 1s (54.0 mg, 0.315 mmol; 52.0 mg, 0.304 mmol) for 20 h. Purification by column chromatography (hexane:AcOEt = 2:1) yielded 2s (35.4 mg, 0.251 mmol, 80%; 33.8 mg, 0.239 mmol, 79%) as a white solid. Mp 112–113 °C ¹H NMR (CDCl₃, 300 MHz) δ : 5.92 (1H, br s), 2.74 (3H, d, *J* = 4.8 Hz), 2.05 (1H, tt, *J* = 11.7, 3.4 Hz), 1.82–1.61 (5H, m), 1.37–1.20 (5H, m). The spectral data matched those reported in the literature.⁹



N,4-Dimethylbenzenesulfonamide (4). The general procedure was followed using **3** (64.1 mg, 0.298 mmol; 64.4 mg, 0.299 mmol) for 6 h. Purification by preparative TLC (hexane:AcOEt = 3:1) yielded **4** (45.7 mg, 0.247 mmol, 83%; 49.0 mg, 0.265 mmol, 88%) as a white solid. Mp 163–164 °C; ¹H NMR (CDCl₃, 400 MHz) δ : 7.73 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.6 Hz), 4.90 (1H, br s), 2.60 (3H, d, *J* = 5.5 Hz), 2.41 (3H, s). The spectral data matched those reported in the literature.¹⁰



Diphenyl methylphosphoramidate (6). The general procedure was followed using **5** (86.0 mg, 0.293 mmol; 84.9 mg, 0.290 mmol) for 20 h. Purification by preparative TLC (hexane:AcOEt = 1:1) yielded **6** (51.7 mg, 0.185 mmol, 63%; 47.6 mg, 0.170 mmol, 59%) as a pale yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ : 7.35–7.23 (8H, m), 7.18–7.13 (2H, m), 3.53

(1H, s), 2.70 (3H, dd, J = 12.7, 2.8 Hz). The spectral data matched those reported in the literature.¹¹

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