Supporting Information

The Direct Preparation of Amides from Amine Hydrochloride Salts and Orthoesters: A Synthetic and Mechanistic Perspective

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General information

All solvents and reagents were obtained from commercial suppliers. With the exception of methylamine hydrochloride and ethylamine hydrochloride, all amine hydrochlorides were prepared by treatment of the amine free bases with ammonium chloride (see general procedure for the preparation of amine hydrochloride salts **2c-2r**). Pyrrolidine, piperidine, and morpholine were distilled prior to conversion to their hydrochloride salts but all the other amines were used without further purification. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of acetamides **3a-3r** and tetrafluoroborate salt **6** were recorded on a Bruker Avance DPX 300 spectrometer in CDCl_3 with TMS as the internal standard. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra of acetamides **3s-3u** were recorded on a Bruker Avance 400 spectrometer in CDCl_3 with TMS as the internal standard. Chemical shifts are reported in ppm (δ) and J values are in Hz. Reactions heated via microwave irradiation were performed on a Biotage Initiator™ Sixty EXP Microwave Synthesis System.

General procedure for the preparation of amine hydrochloride salts **2c-2r**

To a 25-mL round-bottomed flask containing ammonium chloride (0.54 g, 10 mmol) was added ethanol (3 mL) followed by the requisite amine (10 mmol). The mixture was magnetically stirred and refluxed for 2 h. The solvent was then removed by rotary evaporation affording the hydrochloride salt as a solid invariably in quantitative yield.

General procedure for the preparation of acetamides **3a-3u** (conventional thermal reaction)

The amine hydrochloride (0.010 mol) and trimethyl orthoacetate (2.0 mL, 1.5 eq) were combined in a round bottom flask and heated under gentle reflux while being stirred for 2-4 h. The homogeneous solution was evaporated under reduced pressure to yield essentially pure acetamide.

General procedure for the preparation of acetamides **3a-3u** (via microwave irradiation)

To a solution of 1.5 eq trimethyl orthoacetate in 2 mL MeOH was added amine hydrochloride (0.0015 mol). After heating via microwave irradiation to 135 °C for 15 minutes, the product was isolated by concentration *in vacuo* to give essentially pure acetamides. In general, these reactions were accompanied by an expected but slight increase in pressure – none exceeded the pressure limits of the instrument.

Experimental procedure and ^1H and ^{13}C NMR spectral data for acetamides **3a-3u**

N-Methylacetamide (**3a**).^[1] Methylamine hydrochloride (0.68 g, 0.010 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The homogeneous solution was then evaporated under reduced pressure to yield 0.66 g (91%) of a clear liquid. ^1H NMR δ 6.46 (br, 1H), 2.78 (d, 3H, $J_{\text{CH-NH}}$ = 4.8 Hz), 1.99 (s, 3H); ^{13}C NMR δ 171.0, 26.2, 22.8.

N-Ethylacetamide (**3b**).^[1] Ethylamine hydrochloride (0.82 g, 0.010 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The homogeneous solution was then evaporated under reduced pressure to yield 0.69 g (85%) of a clear liquid. ¹H NMR δ 6.42 (br, 1H), 3.22-3.31 (m, 2H), 1.98 (s, 3H), 1.11-1.16 (m, 3H); ¹³C NMR δ 169.5, 33.7, 22.4, 14.0.

N-Isopropylacetamide (**3c**).^[2] Isopropylamine hydrochloride (0.96 g, 0.010 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The homogeneous solution was then evaporated under reduced pressure to yield 0.94 g (93%) of a colorless oil. ¹H NMR δ 6.15 (br, 1H), 4.02-4.09 (m, 1H), 1.96 (s, 3H), 1.15 (d, 6H, *J* = 6.6 Hz); ¹³C NMR δ 169.3, 41.3, 23.2, 22.6.

N-*tert*-butylacetamide (**3d**).^[2] *tert*-Butylamine hydrochloride (1.50 g, 0.014 mol) and trimethyl orthoacetate (3.36 g, 0.028 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2.5 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.42 g (90%) of a white solid. ¹H NMR δ 5.55 (br, 1H), 1.91, (s, 3H), 1.34 (s, 9H); ¹³C NMR δ 169.4, 51.1, 28.8, 24.4.

N-Benzylacetamide (**3e**).^[3] Benzylamine hydrochloride (1.43 g, 0.010 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.46 g (98%) of a clear oil that solidified to a yellowish solid. ¹H NMR δ 7.23-7.34 (m, 5H), 6.24 (br, 1H), 4.38 (d, 2H, *J* = 5.7 Hz), 1.97; ¹³C NMR δ 170.4, 138.5, 128.7, 127.8, 127.4, 43.7, 23.1.

N-α-Methylbenzylacetamide (**3f**).^[4] α-Methylbenzylamine hydrochloride (1.07 g, 0.0066 mol) and trimethyl orthoacetate (1.18 g, 0.0098 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.05 g (97%) of an off white solid. ¹H NMR δ 7.20-7.24 (m, 5H), 6.45 (br, 1H), 5.03-5.13 (m, 1H), 1.92 (s, 3H), 1.44 (d, 3H, *J* = 6.9 Hz); ¹³C NMR δ 169.2, 143.4, 128.6, 127.2, 126.3, 126.2, 48.8, 23.2, 21.8.

N-3-Phenylpropylacetamide (**3g**).^[5] 3-Phenylpropylamine hydrochloride (1.52 g, 0.0089 mol) and trimethyl orthoacetate (2.13 g, 0.018 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2.5 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.58 g (100%) of a yellow oil. ¹H NMR δ 7.14-7.34 (m, 5H), 6.18 (br, 1H), 3.21-3.28 (m, 2H), 2.63 (t, 2H, *J* = 7.5 Hz), 1.92 (s, 3H), 1.77-1.87 (m, 2H); ¹³C NMR δ 170.2, 141.5, 128.4, 128.3, 126.0, 39.3, 33.3, 31.1, 23.1.

N-Cyclohexylacetamide (**3h**).^[6] Cyclohexylamine hydrochloride (1.36 g, 0.010 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The

homogeneous solution was then evaporated under reduced pressure to yield 1.35 g (96%) of a tan solid. ^1H NMR δ 5.70 (br, 1H), 3.69-3.76 (m, 1H), 1.95 (s, 3H), 1.87-1.95 (m, 2H), 1.60-1.68 (m, 3H), 1.28-1.42 (m, 2H), 1.05-1.19 (m, 3H); ^{13}C NMR δ 169.0, 48.2, 33.1, 25.5, 24.8, 23.4.

N-1-Adamantylacetamide (**3i**).^[7] 1-Adamantylamine hydrochloride (1.51 g, 0.0080 mol) and trimethyl orthoacetate (1.45 g, 0.012 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 3 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.54 g (99%) of a white solid. ^1H NMR δ 5.36 (br, 1H), 2.06 (m, 3H), 1.99-2.00 (m, 6H), 1.91 (s, 3H), 1.66-1.68 (m, 6H); ^{13}C NMR δ 169.2, 51.8, 41.7, 36.4, 29.5, 24.6.

N-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)acetamide (**3j**).^[8] 2,2-Dimethyl-1,3-dioxolane-4-methanamine hydrochloride (1.23 g, 0.0074 mol) and trimethyl orthoacetate (1.32 g, 0.011 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 3 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.15 g (90%) of a clear oil. ^1H NMR δ 6.08 (br, 1H), 4.13-4.18 (m, 1H), 3.95-4.00 (dd, 1H), 3.45-3.59 (m, 2H), 3.13-3.22 (m, 1H), 1.94 (s, 3H), 1.36 (s, 3H), 1.27 (s, 3H); ^{13}C NMR δ 170.5, 109.2, 74.5, 66.8, 41.8, 26.7, 25.1, 22.8.

N,N-Diethylacetamide (**3k**).^[9] Diethylamine hydrochloride (1.63 g, 0.015 mol) and trimethyl orthoacetate (3.57 g, 0.030 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 4 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.53 g (88%) of a clear oil. ^1H NMR δ 3.28-3.41 (m, 4H), 2.08, (s, 3H), 1.09-1.21 (m, 6H); ^{13}C NMR δ 169.4, 42.7, 39.8, 21.1, 14.0, 12.9.

N,N-Dipropylacetamide (**3l**).^[10] Dipropylamine hydrochloride (1.37 g, 0.010 mol) and trimethyl orthoacetate (2.76 g, 0.023 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 4 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.42 g (99%) of a light brown oil that solidified to a yellowish solid. ^1H NMR δ 3.17-3.30 (m, 4H), 2.08 (s, 3H), 1.49-1.66 (m, 4H), 0.86-0.95 (m, 6H); ^{13}C NMR δ 170.0, 50.4, 47.2, 22.0, 21.2, 20.8, 11.2, 11.0.

N,N-Diisobutylacetamide (**3m**).^[9] Diisobutylamine hydrochloride (1.65 g, 0.010 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 3.5 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.56 g (94%) of a light brown oil. ^1H NMR δ 3.18 (d, 2H, J = 7.6 Hz), 3.08 (d, 2H, J = 7.6 Hz), 2.10 (s, 3H), 1.89-2.06 (m, 2H), 0.85-0.93 (m, 12H); ^{13}C NMR δ 170.0, 55.7, 52.2, 27.1, 25.8, 21.1, 19.5, 19.4.

N-Acetylpyrrolidine (**3n**).^[11] Pyrrolidine hydrochloride (1.08 g, 0.010 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 3 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.11 g (98%) of a pale oil. ^1H NMR δ 3.41-3.48 (m, 4H), 2.06 (s, 3H), 1.83-2.02 (m, 4H); ^{13}C NMR δ 169.1, 47.3, 45.4, 26.0, 24.5, 22.3.

N-Acetylpiperidine (**3o**).^[12] Piperidine hydrochloride (1.00 g, 0.0083 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 4 hours. The homogeneous solution was then evaporated under reduced pressure to yield 0.95 g (90%) of a pale oil. ¹H NMR δ 3.54 (t, 2H, *J* = 6.9 Hz), 3.39 (t, 2H, *J* = 6.9 Hz), 2.09 (s, 3H), 1.47-1.69 (m 6H); ¹³C NMR δ 168.8, 47.4, 42.5, 26.4, 25.4, 24.4, 21.3.

N-Acetylmorpholine (**3p**).^[13] Morpholine hydrochloride (1.24 g, 0.010 mol) and trimethyl orthoacetate (2.30 g, 0.019 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.22 g (95%) of a pale oil. ¹H NMR δ 3.60-3.70 (m, 6H), 3.45-3.49 (m, 2H), 2.10 (s, 3H); ¹³C NMR δ 169.1, 66.7, 66.5, 46.6, 41.8, 20.9.

N-Acetylhexamethyleneimine (**3q**).^[14] Hexamethyleneimine hydrochloride (1.36 g, 0.010 mol) and trimethyl orthoacetate (1.80 g, 0.015 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.40 g (99%) of a pale oil. ¹H NMR δ 3.52 (t, 2H, *J* = 6.0 Hz), 3.42 (t, 2H, *J* = 6.0 Hz), 2.10 (s, 3H), 1.56-1.73 (m, 8H); ¹³C NMR δ 168.7, 47.4, 42.4, 26.3, 25.4, 24.4, 21.2.

N-Acetyl-1,2,3,4-tetrahydroisoquinoline (**3r**).^[15] 1,2,3,4-Tetrahydroisoquinoline hydrochloride (1.27 g, 0.0075 mol) and trimethyl orthoacetate (1.35 g, 0.011 mol) were combined in a 25 mL round bottomed flask and heated under gentle reflux while being stirred for 2 hours. The homogeneous solution was then evaporated under reduced pressure to yield 1.27 g (97%) of a viscous oil. ¹H NMR (2 rotamers) δ 2.16, 2.17 (s, 3H), 2.81-2.90 (m, 2H), 3.64 (t, 1.16H, *J* = 5.8 Hz), 3.79 (t, 0.84H, *J* = 6.0 Hz), 4.59 (s, 0.84H), 4.70 (s, 1.12H), 7.09-7.20 (m, 4H); ¹³C NMR δ 44.0, 43.9, 39.4, 29.4, 29.5, 21.8, 21.5.

Acetanilide (**3s**).^[8] Aniline hydrochloride (0.65 g, 0.0050 mol) and trimethyl orthoacetate (0.66 g, 0.0055 mol) were combined in a 10 mL round bottomed flask and heated under gentle reflux while being stirred for 1 hour. The homogeneous solution was then evaporated under reduced pressure to yield the crude product that was crystallized from H₂O/EtOH affording colorless plates (83%). ¹H NMR δ 2.18, (s, 3H), 7.12 (t, 1H, *J* = 7.3 Hz), 3.32 (t, 2H, *J* = 7.6 Hz), 7.53 (d, 2H, *J* = 8 Hz), 7.78 (s, 1H).

N-Acetyl-*p*-toluidine (**3t**).^[16] *p*-Toluidine hydrochloride (0.72 g, 0.0050 mol) and trimethyl orthoacetate (0.66 g, 0.0055 mol) were combined in a 10 mL round bottomed flask and heated under gentle reflux while being stirred for 1 hours. The homogeneous solution was then evaporated under reduced pressure to yield crude product that was crystallized from H₂O/EtOH affording white needles (84%). ¹H NMR δ 2.16, (s, 3H), 2.32 (s, 3H), 7.12 (d, 2H, *J* = 8.0 Hz), 7.40 (d, 2H, *J* = 8.2 Hz), 7.81 (s, 1H), 7.78.

N-Acetyl-*p*-anisidine (**3u**).^[17] *p*-Anisidine hydrochloride (0.80 g, 0.0050 mol) and trimethyl orthoacetate (0.66 g, 0.0055 mol) were combined in a 10 mL round bottomed flask and heated under gentle reflux while being stirred for 1 hours. The homogeneous solution was

then evaporated under reduced pressure to yield crude product that was crystallized from H₂O/EtOH affording colorless plates (78%). ¹H NMR δ 2.16, (s, 3H), 3.80 (s, 3H), 6.86 (d, 2H, *J* = 8.9 Hz), 7.41 (d, 2H, *J* = 8.9 Hz), 7.58 (s, 1H).

Copies of ^1H and ^{13}C NMR spectra for acetamides 3a-3u

Copies of ^1H , ^{13}C , and DEPT-135 NMR spectra for imidate salt **6**

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