**Dialkylaminoacetonitrile Derivatives as Amide Synthons. A One-Pot Preparation of
Heteroaryl Amides *via* a Strategy of Sequential S_NAr Substitution and Oxidation**

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General Procedures: Preparation of Compound 8c

General procedure for the preparation of heteroaryl amides using TMSO-OTMS: NaHMDS (8.2 mL, 1.0 M in THF, 8.2 mmol) was added to a solution of 2-chloro-benzoxazole (0.4 mL, 3.5 mmol) and *N,N*-diethylamino-acetonitrile (0.55 mL, 4.2 mmol) in dry THF (50 mL). After stirring for 10 h at room temperature, TMSO-OTMS (1.4 g, 7.8 mmol) was added and the mixture stirred a further 10 h at room temperature. The reaction mixture was quenched with saturated Na₂SO₃ solution, the aqueous layer extracted with EtOAc (3 x 50 mL) and the combined organic layers dried over MgSO₄. Concentration *in vacuo* afforded a residue which was purified by silica gel chromatography to provide benzoxazole-2-carboxylic acid, diethylamide **8c** (420 mg, 55%).

General procedure for the preparation of heteroaryl amides using NiO₂-H₂O: NaHMDS (12 mL, 1.0 M in THF, 12 mmol) was added to a solution of 2-chloro-benzoxazole (0.57 mL, 5.0 mmol) and *N,N*-diethylamino-acetonitrile (0.84 mL, 6.5 mmol) in dry THF (80 mL). After stirring for 10 h at room temperature, NiO₂-H₂O (2.2 g, 20 mmol) was added and the mixture stirred a further 10 h at room temperature. Insoluble solids were filtered off and washed with MeOH. Concentration of filtrate *in vacuo* afforded a residue which was purified by silica gel chromatography to provide benzoxazole-2-carboxylic acid, diethylamide **8c** (720 mg, 66%).

HRMS Results

Compound Number	Formula [M+H]	Theoretic m/z.	Observed m/z	Deviation in ppm
8a	C ₉ H ₁₃ ClN ₃ O	214.0747	214.0742	2.6
8b	C ₁₂ H ₁₅ N ₂ OS	235.0905	235.0915	-4.2
8c	C ₁₂ H ₁₅ N ₂ O ₂	219.1134	219.1130	1.7
8d	C ₁₃ H ₁₆ N ₃ O	230.1293	230.1289	2.1
8e	C ₁₄ H ₁₇ N ₂ O	229.1341	229.1343	-0.7
8f	C ₁₀ H ₁₇ N ₄ O ₃	241.1301	241.1294	2.6
8g	C ₁₂ H ₁₆ N ₅ O	246.1355	246.1356	-0.4
8h	C ₁₀ H ₁₄ BrN ₂ O	257.0289	257.0277	4.8
8i	C ₁₃ H ₁₆ NO ₂	218.1181	218.1177	1.7
8j	C ₁₇ H ₂₀ N ₃ O	282.1606	282.1606	0.3
8k	C ₁₂ H ₁₆ NO	190.1232	190.1234	-1.0
8l	C ₁₈ H ₁₈ NO ₄	312.1236	312.1238	-0.8
Compound Number	Formula [M-H]	Theoretic m/z.	Observed m/z	Deviation in ppm
7a	C ₁₀ H ₁₂ ClN ₄	223.0750	223.0756	-2.5

Supporting Material: Spectra

(3-Chloro-pyrazin-2-yl)-diethylamino-acetonitrile, 7a

^1H NMR (500 MHz, CDCl_3) δ 8.52 (d, 1H, $J = 2.37$ Hz), 8.39 (d, 1H, $J = 2.36$ Hz), 5.37 (s, 1H), 2.74 (m, 2H), 2.55 (m, 2H), 1.02 (t, 6H, $J = 7.22$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 149.0, 148.5, 144.0, 141.5, 114.7, 57.8, 45.5, 12.9; HRMS m/z : (M-H) $^+$ calcd. for $\text{C}_{10}\text{H}_{14}\text{ClN}_4$: 223.0750. Found 223.0756.

3-Chloro-pyrazine-2-carboxylic acid diethylamide, 8a

^1H NMR (500 MHz, CDCl_3) δ 8.50 (d, 1H, $J = 2.43$ Hz), 8.41 (d, 1H, $J = 2.43$ Hz), 3.58 (q, 2H, $J = 7.12$ Hz), 3.14 (q, 2H, $J = 7.06$ Hz), 1.28 (t, 3H, $J = 7.07$ Hz), 1.12 (t, 3H, $J = 7.10$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 164.9, 149.6, 146.0, 144.2, 142.1, 43.1, 39.8, 13.9, 12.5; HRMS m/z : (M+H) $^+$ calcd. for $\text{C}_9\text{H}_{13}\text{ClN}_3\text{O}$: 214.0747. Found 214.0742.

Benzothiazole-2-carboxylic acid diethylamide, 8b

^1H NMR (500 MHz, CDCl_3) δ 8.03 (d, 1H, $J = 8.50$ Hz), 7.88 (d, 1H, $J = 7.50$ Hz), 7.46 (m, 1H), 7.41 (m, 1H), 4.01 (q, 2H, $J = 7.00$ Hz), 3.55 (q, 2H, $J = 7.00$ Hz), 1.26 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.2, 160.7, 153.4, 136.3, 126.5, 126.4, 124.7, 121.8, 43.3, 42.4, 14.6, 12.8; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{OS}$: 235.0905. Found 235.0915.

Benzoxazole-2-carboxylic acid diethylamide, 8c

^1H NMR (500 MHz, CDCl_3) δ 7.77 (d, 1H, $J = 7.77$ Hz), 7.58 (d, 1H, $J = 8.18$ Hz), 7.40 (m, 2H), 3.82 (q, 2H, $J = 7.03$ Hz), 3.58 (q, 2H, $J = 7.10$ Hz), 1.27 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.3, 155.4, 150.0, 140.4, 127.0, 125.2, 121.4, 111.5, 43.6, 41.5, 14.6, 12.6; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_2$: 219.1134. Found 219.1130.

Quinoxaline-2-carboxylic acid diethylamide, 8d

^1H NMR (500 MHz, CDCl_3) δ 9.11(s, 1H), 8.11 (d, 1H, $J = 2.90$ Hz), 8.05 (d, 1H, $J = 5.20$ Hz), 7.78 (m, 2H), 3.60 (q, 2H, $J = 7.04$ Hz), 3.58 (q, 2H, $J = 6.97$ Hz), 1.28 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.5, 149.0, 144.8, 142.1, 140.5, 131.1, 130.7, 129.8, 129.2, 43.7, 40.9, 14.6, 12.9; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}$: 230.1293. Found 230.1289.

Quinoline-2-carboxylic acid diethylamide, 8e

^1H NMR (500 MHz, CDCl_3) δ 8.30 (d, 1H, $J = 8.40$ Hz), 8.15 (d, 1H, $J = 8.52$ Hz), 7.86 (d, 1H, $J = 8.18$ Hz), 7.77 (t, 1H, $J = 7.04$ Hz), 7.62 (m, 2H), 3.61 (q, 2H, $J = 7.08$ Hz), 3.39 (q, 2H, $J = 7.00$ Hz), 1.31 (t, 3H, $J = 7.16$ Hz), 1.20 (t, 3H, $J = 7.10$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 168.3, 153.9, 146.0, 138.1, 130.7, 128.9, 128.1, 127.9, 127.8, 120.2, 43.6, 40.6, 14.3, 12.8; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}$: 229.1341. Found 229.1343.

4,6-Dimethoxy-[1,3,5]triazine-2-carboxylic acid diethylamide, 8f

^1H NMR (500 MHz, CDCl_3) δ 4.01 (s, 6H), 3.46 (q, 2H, $J = 7.13$ Hz), 3.16 (q, 2H, $J = 7.06$ Hz), 1.19 (t, 3H, $J = 7.16$ Hz), 1.13 (t, 3H, $J = 7.02$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 173.1, 172.8, 55.7, 42.9, 39.4, 14.1, 12.6; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{10}\text{H}_{17}\text{N}_4\text{O}_3$: 241.1301. Found 241.1294. Note: The Et_3N impurity shown on page S18 originated from eluting co-solvents (hexane / EtOAc / Et_3N) during silica gel chromatography.

1-Phenyl-1H-tetrazole-5-carboxylic acid diethylamide, 8g

^1H NMR (500 MHz, CDCl_3) δ 7.52 (m, 5H), 3.48 (q, 2H, $J = 7.14$ Hz), 3.23 (q, 2H, $J = 7.11$ Hz), 1.13 (t, 3H, $J = 7.21$ Hz), 1.08 (t, 3H, $J = 7.17$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 157.0, 148.5, 133.9, 130.5, 129.8, 123.7, 43.6, 40.5, 14.3, 12.5; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_5\text{O}$: 246.1355. Found 246.1356.

5-Bromo-pyridine-2-carboxylic acid diethylamide, 8h

^1H NMR (500 MHz, CDCl_3) δ 8.62 (s, 1H), 7.90 (d, 1H, $J = 8.26$ Hz), 7.48 (d, 1H, $J = 8.27$ Hz), 3.51 (q, 2H, $J = 7.09$ Hz), 3.35 (q, 2H, $J = 6.96$ Hz), 1.26 (t, 3H, $J = 7.21$ Hz), 1.08 (t, 3H, $J = 7.05$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 167.8, 153.0, 149.4, 139.8, 124.7, 121.7, 43.5, 42.5, 14.3, 12.7; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{10}\text{H}_{14}\text{BrN}_2\text{O}$: 257.0289. Found 257.0277. Note: The Et_3N impurity shown on page S20 originated from eluting co-solvents (hexane / EtOAc / Et_3N) during silica gel chromatography.

1-Morpholin-4-yl-3-phenyl-propenone, 8i

^1H NMR (500 MHz, CDCl_3) δ 7.66 (d, 1H, $J = 15.50$ Hz), 7.48 (m, 2H), 7.35 (m, 3H), 6.80 (d, 1H, $J = 15.50$ Hz), 3.69 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.6, 144.2, 134.9, 130.1, 129.0, 128.0, 116.1, 66.8; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{13}\text{H}_{16}\text{NO}_2$: 218.1181. Found 218.1177.

(4-Benzyl-piperazin-1-yl)-pyridin-3-yl-methanone, 8j

^1H NMR (500 MHz, CD_3OD) δ 8.80 (m, 2H), 8.22 (d, 1H, $J = 8.00$ Hz), 7.77 (m, 1H), 7.50 (m, 5H), 4.40 (s, 2H), 3.98-3.30 (m, 8H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.6, 150.6, 147.6, 139.0, 132.5, 131.5, 130.5, 129.9, 126.1, 61.8, 52.3; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_3\text{O}$: 282.1606. Found 282.1606.

Phenyl-piperidin-1-yl-methanone, 8k

^1H NMR (500 MHz, CDCl_3) δ 7.34 (m, 5H), 3.67 (b, 2H), 3.32 (b, 2H), 1.64 (b, 4H), 1.48 (b, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 135.0, 130.0, 128.6, 126.8, 49.1, 43.8, 26.5, 25.6, 24.4; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{12}\text{H}_{16}\text{NO}$: 190.1232. Found 190.1234.

2-Benzoyl-6,7-dimethoxy-3,4-dihydro-2H-isoquinolin-1-one, 8l

^1H NMR (500 MHz, $\text{CD}_3\text{OD} + \text{CDCl}_3$) δ 7.59 - 7.38 (m, 6H), 6.87 (s, 1H), 4.09 (t, 2H, J = 6.50 Hz), 3.90 (s, 3H), 3.82 (s, 3H), 3.14 (t, 2H, J = 6.50 Hz); ^{13}C NMR (125 MHz, $\text{CD}_3\text{OD} + \text{CDCl}_3$) δ 176.4, 167.5, 155.6, 149.9, 137.8, 137.0, 132.9, 129.5, 129.4, 121.4, 112.4, 111.3, 57.2, 57.0, 46.2, 29.3; HRMS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{18}\text{H}_{18}\text{NO}_4$: 312.1236. Found 312.1238.

***N,N*-Diethyl-*N'*-propyl-benzothiazole-2-carboxamidine, 14**

^1H NMR (500 MHz, CDCl_3) δ 8.11 (d, 1H, J = 8.50 Hz), 7.91 (d, 1H, J = 8.50 Hz), 7.51 (m, 1H), 7.41 (m, 1H), 3.24 (m, 4H), 2.99 (t, 2H, J = 7.00 Hz), 1.50 (m, 2H), 1.12 (q, 3H, J = 7.00 Hz), 0.79 (t, 3H, J = 7.50 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 161.0, 152.8, 152.0, 135.2, 126.4, 125.9, 124.0, 121.8, 52.5, 41.9, 25.5, 13.4, 11.9; MS m/z : $(\text{M}+\text{H})^+$ calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_3\text{S}$: 276.15. Found 276.19.