Supporting Online Material

An Efficient and Simple Aqueous *N*-heterocyclization of Aniline

Derivatives: Microwave-assisted Synthesis of *N*-Aryl Azacycloalkanes

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Experimental procedures:

All starting aniline derivatives and alkyldihalides were obtained from Aldrich Chemical Company and were used as such. The crude products were identified by GC/MS qualitative analysis using an HP 6890 GC system with an HP 5872 Mass selective detector, a Supelco Equity-5 capillary GC column (30 m X 0.32 mm, ID 0.25 μ m) was used. The identities were further confirmed by ^1H and ^{13}C NMR spectra that were recorded for the pure products in chloroform-*d* (CDCl_3) with TMS as internal reference using a Bruker Biospin 300 MHz NMR spectrometer. High resolution mass spectra data were obtained using electrospray ionization from a Quadrupole-Time-of-flight (Q-Tof II) mass spectrometer (Micromass Manchester, U. K.).

A representative azacycloalkane preparation is as follows: 1.0 mmol aniline (0.093 g), 1.1 mmol 1,4-dibromobutane (0.237 g) and 1.2 mmol potassium carbonate (0.165 g) in 2 mL distilled water were placed in a 10 mL crimp-sealed thick-wall reaction tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed in a CEM Discover Focused Microwave Synthesis System, operated at 120 ± 5 $^\circ\text{C}$ (measured by an Infrared temperature sensor) for 20 mins with a 3 mins ramp time, power 80-100 Watt and pressure 65-80 psi for 20 minutes. The typical reaction conditions are shown in Figure 1. After completion of the reaction, the organic portion

was extracted into ethyl acetate. Removal of the solvent under reduced pressure and flash column chromatography using hexane/ethyl acetate (90/10) as eluent to afford 0.131 g 1-phenyl-pyrrolidine (89%) as a light yellow oil. Satisfactory ^1H and ^{13}C NMR data was consistent with those found in literature.

Figure 1. Typical MW reaction condition profile

Characterizations of products:

1-Phenyl-azetidine (3a).¹ The reaction of aniline (1.0 mmol, 0.093 g), 1,3-dichloropropane (1.1 mmol, 0.123 g) was carried out as described earlier and produced 0.072 g (54%) of 1-phenyl-azetidine as a yellow oil. ^1H NMR (300 MHz, CDCl_3/TMS) δ

ppm 7.11 (m, 2H), 6.57 (m, 3H), 3.58 (t, 2H, $J = 6.6$ Hz), 3.26 (t, 2H, $J = 6.5$ Hz), 1.99 (m, 2H); ^{13}C NMR (75.5 MHz, CDCl_3/TMS) δ ppm 147.8, 129.2, 117.9, 113.0, 43.0, 41.3, 32.4; MS (EI) m/z (relative intensity, %) 133 (M , 63), 105 (100), 104 (78), 77 (37), 51 (11).

1-Phenylpyrrolidine (3b).² The reaction of aniline (1.0 mmol, 0.093 g), 1,4-dibromobutane (1.1 mmol, 0.238 g) was carried out as described earlier and produced 0.131 g (89%) of 1-phenylpyrrolidine as a yellow oil. ^1H NMR (300 MHz, CDCl_3/TMS) δ ppm 7.19 (t, 2H, $J = 7.5$ Hz), 6.62 (d, 1H, $J = 7.3$ Hz), 6.53 (d, 2H, $J = 8.0$ Hz), 3.23 (t, 4H, $J = 5.5$ Hz), 1.94 (t, 4H, $J = 4.6$ Hz). ^{13}C NMR (75.5 MHz, CDCl_3/TMS) δ ppm 147.9, 129.0, 115.3, 111.6, 47.4, 25.3. MS (EI) m/z (relative intensity, %) 147 (85), 146 (M^+ , 100), 119 (15), 104 (26), 91 (83), 77 (59), 51 (26).

1-Phenylpyrrolidine (3c).² The reaction of aniline (1.0 mmol, 0.093 g), 1-chloro-4-iodobutane (1.1 mmol, 0.240 g) was carried out as described earlier and produced 0.112 g (76%) of 1-phenylpyrrolidine as a yellow oil. Same as **2b**.

1-Phenylpyrrolidin-3-ol (3d).³ The reaction of aniline (1.0 mmol, 0.093 g), 1,4-dibromo-2-butanol (1.1 mmol, 0.255 g) was carried out as described earlier and produced 0.067 g (42%) of 1-phenylpyrrolidin-3-ol as a yellow oil. ^1H NMR (300 MHz, CDCl_3/TMS) δ ppm 7.17 (dd, 2H, $J = 8.3, 6.8$ Hz), 6.62 (t, 1H, $J = 7.2$ Hz), 6.50 (d, 2H,

$J = 8.1$ Hz), 4.51 (s, 1H), 3.43 (dd, 1H, $J = 15.1, 7.2$ Hz), 3.27 (d, 2H, $J = 15.0$ Hz), 2.03 (d, 2H, $J = 20.0$ Hz), 1.62 (m, 2H); ^{13}C NMR (75.5 MHz, CDCl_3/TMS) δ ppm 147.7, 129.2, 116.1, 111.8, 71.4, 56.3, 45.5, 34.2; MS (EI) m/z (relative intensity, %) 163 (M , 76), 119 (45), 104 (15), 91 (100), 77 (25),

1-[4-(2-Methyl-1-pyrrolidinyl)-phenyl]-ethanone (3e). The reaction of 1-(4-aminophenyl)-ethanone (1.0 mmol, 0.135 g), 1,4-dibromo-pentane (1.1 mmol, 0.253 g) was carried out as described earlier and produced 0.132 g (70%) of 1-[4-(2-methyl-1-pyrrolidinyl)-phenyl]-ethanone as a light yellow solid. ^1H NMR (300 MHz CDCl_3/TMS) δ ppm 7.76 (d, 2H, $J = 9.0$ Hz), 6.43 (d, 2H, $J = 9.0$ Hz), 3.91 (dd, 1H, $J = 12.0, 6.1$ Hz), 3.41 (m, 1H), 3.21 (m, 1H), 2.41 (s, 3H), 1.99 (m, 2H), 1.68 (m, 2H), 1.11 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (75.5 MHz CDCl_3/TMS) δ ppm 196.2, 149.9, 130.7, 124.8, 110.8, 53.7, 47.8, 32.8, 25.8, 23.0, 18.8; MS (EI) m/z (relative intensity, %) 203 (M , 23), 189 (13), 188 (100), 146 (5), 91 (3); HR-MS (ESI): calcd ($M+\text{H}$) $^+$ for $\text{C}_{13}\text{H}_{17}\text{NO}$: 204.1388 ($\text{C}_{13}\text{H}_{18}\text{NO}^+$), found ($M+\text{H}$) $^+$ 204.1381.

1-Indan-5-yl-pyrrolidine (3f).⁴ The reaction of indanyl-5-amine (1.0 mmol, 0.133 g), 1,4-dibromobutane (1.1 mmol, 0.238 g) was carried out as described earlier and produced 0.180 g (96%) of 1-indan-5-yl-pyrrolidine as a yellow oil. ^1H NMR (300 MHz CDCl_3/TMS) δ ppm 6.99 (d, 1H, $J = 7.9$ Hz), 6.41 (s, 1H), 6.30 (d, 1H, $J = 7.80$ Hz), 3.16 (t, 4H, $J = 5.5$ Hz), 2.81-2.71 (tt, 4H, $J = 7.1$ Hz), 2.16-1.80 (m, 6H); ^{13}C NMR (75.5

MHz CDCl₃/TMS) δ ppm 147.2, 145.2, 131.0, 124.6, 110.0, 107.8, 48.0, 33.5, 32.4, 25.8, 25.4; MS (EI) m/z (relative intensity, %) 187 (M , 69), 186 (M^+ , 100), 144 (5), 131 (21), 117 (9), 115 (15).

3-Pyrrolidinyl benzoic acid ethyl ester (3g). The reaction of 3-aminobenzoic acid ethyl ester (1.0 mmol, 0.165 g), 1,4-dibromobutane (1.1 mmol, 0.238 g) was carried out as described earlier and produced 0.204 g (93%) of 3-pyrrolidinyl benzoic acid ethyl ester as a yellow oil. ¹H NMR (100 MHz CDCl₃/TMS) δ ppm 7.32-7.21 (m, 3H), 6.68 (d, 1H, J = 8.1 Hz), 4.35 (q, 2H, J = 6.6 Hz), 3.32 (t, 4H, J = 7.8 Hz), 1.97 (t, 4H, J = 7.5 Hz), 1.37 (t, 3H, J = 6.9 Hz); ¹³C NMR (75.5 MHz CDCl₃/TMS) δ ppm 167.1, 147.5, 130.9, 128.7, 116.2, 115.6, 112.2, 60.5, 47.5, 25.2, 14.2; MS (EI) m/z (relative intensity, %) 219 (M , 100), 218 (M^+ , 72), 190 (41), 174 (54), 163 (25), 146 (11), 135 (7); HR-MS (ESI): calcd ($M+H$)⁺ for C₁₃H₁₇NO₂: 220.1338 (C₁₃H₁₈NO₂⁺), found ($M+H$)⁺ 220.1327.

1,4-Dipyrrolidinyl-benzene (3h).⁵ The reaction of benzene-1,4-diamine (1.0 mmol, 0.108 g), 1,4-dibromobutane (2.2 mmol, 0.576 g) was carried out as described earlier and produced 0.206 g (95%) of 1,4-dipyrrolidinyl-benzene as a yellow solid. ¹H NMR (300 MHz CDCl₃/TMS) δ ppm 6.60 (s, 4H), 3.22 (m, 8H), 1.98-1.94 (tt, 8H, J = 3.4, 4.0); ¹³C NMR (75.5 MHz CDCl₃/TMS) δ ppm 140.6, 136.7, 48.6, 25.1; MS (EI) m/z (relative intensity, %) 217 ($M+H^+$ 16), 216 (M , 100), 215 (M^+ , 68), 187 (10), 160 (9), 118 (6).

1-Phenyl-piperidine (3i).⁶ The reaction of aniline (1.0 mmol, 0.093 g), 1,5-dibromopentane (1.1 mmol, 0.253 g) was carried out as described earlier and produced 0.155 g (96%) of 1-phenyl-piperidine as a yellow oil. ¹H NMR (300 MHz CDCl₃/TMS) δ ppm 7.27 (t, 2H, *J* = 7.4 Hz), 6.89 (d, 2H, *J* = 7.8 Hz), 6.75 (t, 1H, *J* = 7.3 Hz), 3.13 (t, 4H, *J* = 6.7 Hz), 1.62 (m, 4H), 1.45 (t, 2H, *J* = 4.8 Hz); ¹³C NMR (75.5 MHz CDCl₃/TMS) δ ppm 151.6, 129.7, 19.2, 116.6, 51.4. 25.2, 24.0; MS (EI) *m/z* (relative intensity, %) 161 (*M*, 69), 160 (*M*⁺, 100), 120 (13), 105 (27), 104 (21), 77 (18).

1-(4-Bromophenyl)-azepane (3j). The reaction of 4-bromoaniline (1.0 mmol, 0.172 g), 1,6-dibromohexane (1.1 mmol, 0.268 g) was carried out as described earlier and produced 0.165 g (65%) of 1-(4-bromophenyl)-azepane as a yellow solid. ¹H NMR (300 MHz CDCl₃/TMS) δ ppm 7.18 (d, 2H, *J* = 9.0 Hz), 6.66 (d, 2H, *J* = 9.2 Hz), 3.39 (t, 4H, *J* = 12.1 Hz), 1.58-1.36 (m, 8H); ¹³C NMR (75.5 MHz CDCl₃/TMS) δ ppm 148.0, 129.2, 117.1, 112.7, 52.9, 29.6, 27.2; MS (EI) *m/z* (relative intensity, %) 255 (*M*, 97), 253 (*M*, 100), 226 (77), 224 (80), 200 (21), 198 (23), 184 (37), 171 (25), 169 (25); HR-MS (ESI): calcd (*M*+H)⁺ for C₁₂H₁₆BrN: 254.0544 (C₁₂H₁₇BrN⁺), found (*M*+H)⁺ 254.0538.

1-(4-Ethylphenyl)-azepane (3k). The reaction of 4-ethylaniline (1.0 mmol, 0.121 g), 1,6-dibromohexane (1.1 mmol, 0.268 g) was carried out as described earlier and produced 0.177 g (87%) of 1-(4-ethylphenyl)-azepane as a yellow oil. ¹H NMR (300

MHz CDCl₃/TMS) δ ppm 6.99 (d, 2H, $J = 8.9$), 6.48 (d, 2H, $J = 9.2$ Hz), 3.15 (t, 4H, $J = 9.1$ Hz), 2.54 (q, 2H, $J = 9.8$ Hz), 1.52 (m, 4H), 1.28 (s, 3H), 1.18 (t, 3H, $J = 9.6$); ¹³C NMR (75.5 MHz CDCl₃/TMS) δ ppm 146.4, 131.1, 128.5, 112.2, 51.2, 27.7, 27.3, 27.0, 16.0; MS (EI) m/z (relative intensity, %) 203 (M , 100), 202 (M^+ , 29), 188 (65), 174 (64), 160 (47), 148 (19), 118 (22); HR-MS (ESI): calcd ($M+H$)⁺ for C₁₄H₂₁N: 204.1752 (C₁₄H₂₂N⁺), found ($M+H$)⁺ 204.1747.

1-Phenyl-azetidine

1-Phenyl-pyrrolidine

1-Phenyl-pyrrolidin-3-ol

1-[4-(2-Methyl-1-pyrrolidinyl)-phenyl]-ethanone

1-Indan-5-yl-pyrrolidine

3-Pyrrolidinyl benzoic acid ethyl ester

1,4-Dipyrrolidinyl-benzene

1-Phenylpiperidine

1-(4-Bromophenyl)-azepane

1-(4-Ethylphenyl)-azepane

Supporting Information

References:

1. (a) Bottini, A. T.; Nash, C. P. *J. Am. Chem. Soc.* **1962**, *84*, 734-739. (b) Cerichelli, G.; Galli, C.; Lillocci, C.; Luchetti, L. *J. Chem. Soc. Perkin Trans. 2*, **1985**, 725-728.
2. (a) Horning, C. H.; Bergstrom, F. W. *J. Am. Chem. Soc.* **1945**, *67*, 2110-2111. (b) Collins, C. J.; Singaram, B. *ARKIVOC* **2001**(iv), 59-75.
3. Huang, Y.- L.; Lin, C.- F.; Lee, Y.- J.; Li, W.- W.; Chao, T.- C.; Bacherikov, V. A.; Chen, K.-T.; Chen, C.- M.; Su, T.- L. *Bioorg. Med. Chem.* **2003**, *11* (1), 145 - 158.
4. Tsuji, Y.; Yokoyama, Y.; Huh, K.- T.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60* (9), 3456-3458.
5. Christensen, J. B.; Schioedt, N.- C.; Bechgaard, K.; Buch-Rasmussen, T. *Acta Chem. Scand.* **1996**, *50* (11), 1013-1019.
6. (a) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677 - 8681. (b) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403-1412.