Reductive and Catalytic Monoalkylation of Primary Amines Using Nitriles as an Alkylating Reagent

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Supporting Information

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Purification method of nitriles.[1] Each nitrile purchased from Aldrich, Nacalai, TCI and Wako (98-99.8% purity) was washed with conc HCl and brine, then dried over K_2CO_3. The organic layer was fractionally distilled from P_2O_5.

General procedure for reductive alkylation of aromatic amines. After two vacuume/H_2 cycles to remove air from the reaction tube, the stirred mixture of the aromatic amine (1.0 or 0.5 mmol), 10% Pd/C (10 wt% of the amine) and the nitrile (5 equiv) in MeOH (1 mL) was hydrogenated at ordinary pressure (balloon) and temperature (ca. 20°C) for appropriate time (see Table 1, 2 and 3). The reaction mixture was filtrated using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated under reduced pressure. The ratio of the primary (**1**), secondary (**2**) and tertiary amines (**3**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$. The crude mixture was purified by flash silica gel column chromatography, if necessary.
When NH_4OAc was used as an additive, the residue was partitioned between ether (10 mL) and water (10 mL). The aqueous layer was extracted with ether (10 mL×3), then combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

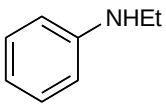
Procedure for reductive cyclization of 2-aminobenzylnitrile (7) (equation 1) After two vacume/H_2 cycles to remove air from the reaction tube, the stirred mixture of the 2-aminobenzylcyanide (**7**) (81.1 mg, 0.5 mmol), 10% Pd/C (8.1 mg, 10 wt% of the substrate) in MeOH (1 mL) was hydrogenated at ordinary pressure (balloon) and temperature (ca. 20°C) for 22 h. The reaction mixture was filtrated using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ether 20:1) to afford indole (**8**) (62.4 mg, 98% yield) as a white solid.

General procedure for preparation of *mono*-alkylaniline derivatives from nitrobenzene (9). After two vacuume/H_2 cycles to remove air from the reaction tube, the stirred mixture of the nitrobenzene (**9**) (61.6 mg, 0.5 mmol), 10% Pd/C (6.2 mg, 10 wt% of the amine) and nitrile (5 equiv) in MeOH (1 mL) was hydrogenated at ordinary pressure (balloon) and at temperature (ca. 20°C) for the appropriate time (see Table 4). The reaction mixture was filtrated using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and filtrate was concentrated under reduced pressure. The ratio of the primary (**1**), secondary (**2**) and tertiary amines (**3**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$. The crude mixture was purified by flash silica gel column chromatography, if

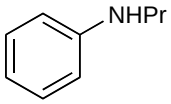
necessary.
When NH_4OAc was used as an additive, the residue was partitioned between ether (10 mL) and water (10 mL). The aqueous layer was extracted with ether (10 mL×3), then combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

General procedure for reductive alkylation of aliphatic amines. After two vacuume/H_2 cycles to remove air from the reaction tube, the stirred mixture of the aliphatic amine (1.0 mmol), 10% Pd/C or 5% Rh/C (10 wt% of the amine) and a nitrile (5 equiv or 2 equiv) in MeOH (1 mL) was hydrogenated at ordinary pressure (balloon) and temperature (ca. 20°C) for the appropriate time (see Table 5). The reaction mixture was filtrated using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and filtrate was concentrated under reduced pressure. The ratio of the primary (**10**), secondary (**11**) and tertiary amines (**12**) was confirmed by ^1H NMR of the crude mixture in $CDCl_3$. The crude mixture was purified by flash silica gel column chromatography, if necessary.
When NH_4OAc was used as an additive, the residue was partitioned between ethylacetate (10 mL) and water (10 mL). The aqueous layer was extracted with ether (10 mL×3), then combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

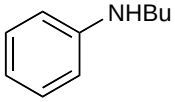
Procedure for synthesis of *N*-ethyl-*N*-propyl-2-phenylethylamine (15). After two vacuume/H_2 cycles to remove air from the reaction tube, the stirred mixture of the 2-phenylethylamine (**13**) (121.2 mg, 1.0 mmol), 5% Rh/C (24.2 mg, 20 wt% of the amine) and acetonitrile (261 μl, 5.0 mmol) in MeOH (1 mL) was hydrogenated under ambient pressure (balloon) and at room temperature (ca. 20°C) for 28 h. The reaction mixture was filtrated using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and filtrate was concentrated under reduced pressure. The reaction mixture and distilled propionitrile (357 μl, 5.0 mmol) in MeOH was hydrogenated in the presence of 10% Pd/C (16.3 mg) and ammonium acetate (77.1 mg, 1.0 mmol) under ambient temperature and pressure for 7 h. The reaction mixture was filtrated using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL×3), then combined the organic phases were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford *N*-ethyl-*N*-propyl-2-phenylethylamine[2] (89.5 mg, 94%).



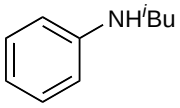
***N*-Ethylaniline** (Table 1, entry 3 and Table 2, entry 1, commercially available)



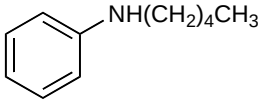
***N*-Propylaniline** (Table 2, entry 2, commercially available)



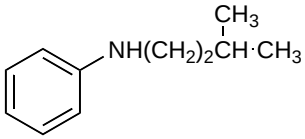
***N*-Butylaniline** (Table 2, entry 4 and Table 4, entry 1, commercially available)



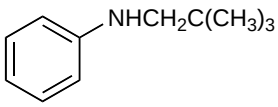
***N*-*iso*-Butylaniline**[3] (Table 2, entry 6 and Table 4, entry 2)



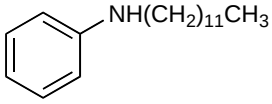
***N*-Pentylaniline** (Table 2, entry 7 and Table 4, entry 3, commercially available)



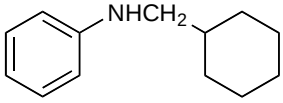
***N*-(3-Methylbutyl)aniline** (Table 2, entry 8 and Table 4, entry 4) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.17 (t, *J*=7.6 Hz, 2H), 6.69 (t, *J*=7.6 Hz, 1H), 6.61 (d, *J*=7.6 Hz, 2H), 3.54 (brs, NH), 3.12 (t, *J*=7.3 Hz, 2H), 1.74-1.69 (m, 1H), 1.52 (q, *J*=7.3 Hz, 2H), 0.95 (d, *J*=6.4 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 148.5, 129.2, 117.1, 112.7, 42.1, 38.6, 26.0, 22.6. MS (EI) *m/z* 163 (M^+, 20%), 106 (100), 77 (14). HRMS (EI) Calcd for $C_{11}H_{17}N$ (M^+) 163.1354. Found 163.1361.



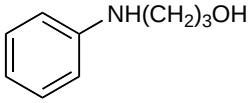
***N*-(2,2-Dimethylpropyl)aniline** (Table 2, entry 10) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.16 (t, *J*=7.4 Hz, 2H), 6.67 (t, *J*=7.4 Hz, 1H), 6.62 (d, *J*=7.4 Hz, 2H), 3.62 (brs, NH), 2.89 (s, 2H), 0.99 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 149.1, 129.2, 116.9, 112.6, 55.8, 31.8, 22.7. MS (EI) *m/z* 163 (M^+, 15%), 106 (100), 77 (13). HRMS (EI) Calcd for $C_{11}H_{17}N$ (M^+) 163.1365. Found 163.1361.



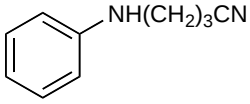
***N*-Dodecylaniline** (Table 2, entry 12 and Table 4, entry 5, commercially available)



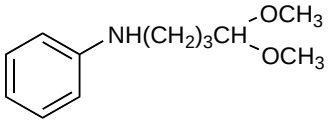
***N*-(Cyclohexylmethyl)aniline**[4] (Table 2, entry 13)



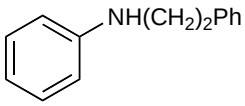
***N*-(3-Hydroxypropyl)aniline**[5] (Table 2, entry 14)



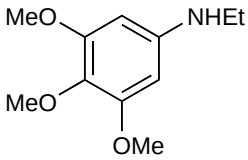
***N*-(3-Cyanopropyl)aniline** (Table 2, entry 15) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.19 (t, *J*=7.3 Hz, 2H), 6.74 (t, *J*=7.3 Hz, 1H), 6.62 (d, *J*=7.3 Hz, 2H), 3.69 (brs, NH), 3.32 (t, *J*=6.7 Hz, 2H), 2.48 (t, *J*=6.7 Hz, 2H), 2.00-1.94 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 147.5, 129.4, 119.3, 118.0, 112.8, 42.3, 25.3, 14.8. MS (EI) *m/z* 160 (M^+, 25%), 106 (100), 77 (15). HRMS (EI) Calcd for $C_{10}H_{12}N_2$ (M^+) 160.0992. Found 160.1001.



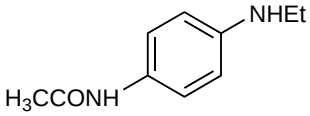
***N*-(4,4-Dimethoxybutyl)aniline** (Table 2, entry 16) The procedure afforded the mixture (680.0 mg) of the title compound and nitrile. The structure was determined by ^{1}H NMR and HRMS data of the crude mixture.



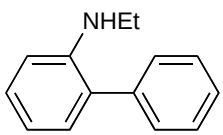
***N*-(2-Phenylethyl)aniline**[6] (Table 2, entry 15)



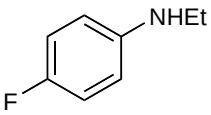
***N*-Ethyl-3,4,5-trimethoxyaniline** (Table 3, entry 1) Dark blue oil. ^{1}H NMR ($CDCl_3$): δ 5.85 (s, 2H), 3.83 (s, 6H), 3.76 (s, 3H), 3.13 (t, *J*=7.1 Hz, 2H), 1.26 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 153.9, 145.2, 130.0, 90.3, 61.1, 55.9, 38.9, 14.8. MS (EI) *m/z* 211 (M^+, 40%), 196 (100). HRMS (EI) Calcd for $C_{11}H_{17}NO_3$ (M^+) 211.1196. Found 211.1209.



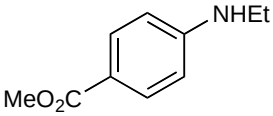
4-Ethylaminoacetanilide (Table 3, entry 2) White solid. Mp 123-124°C. ^{1}H NMR ($CDCl_3$): δ 7.25 (d, *J*=8.5 Hz, 2H), 6.55 (d, *J*=8.5 Hz, 2H), 3.50 (brs, NH), 3.12 (q, *J*=7.1 Hz, 2H), 2.11 (s, *3*H), 1.25 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 168.3, 145.6, 128.1, 122.4, 112.8, 38.7, 24.1, 14.8. MS (EI) *m/z* 167 (M^+, 100%), 163 (40), 121 (65). Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found C, 67.39; H, 8.08; N, 15.67.



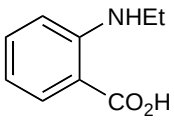
2-Ethylaminobiphenyl[7] (Table 3, entry 3)



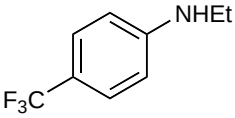
***N*-Ethyl-4-fluoroaniline** (Table 3, entry 4) Brown oil. ^{1}H NMR ($CDCl_3$): δ 6.93-6.86 (m, 2H), 6.55-6.52 (m, 2H), 3.41 (brs, NH), 3.11 (q *J*=7.1 Hz, 2H), 1.25 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.9, 154.6, 144.8, 115.7, 155.5, 113.5, 113.5, 39.1, 14.9. MS (EI) *m/z* 139 (M^+, 38%), 124 (100). HRMS (EI) Calcd for $C_8H_{10}FN$ (M^+) 139.0797. Found 139.0792.



4-Ethylaminobenzoic acid (Table 3, entry 5) White solid. Mp 179-180°C. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, *J*=8.8 Hz, 2H), 6.55 (d, *J*=8.8 Hz, 2H), 3.23 (q, *J*=7.1 Hz, 2H), 1.29 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 171.7, 152.6, 132.3, 117.1, 111.3, 37.9, 14.6. MS (EI) *m/z* 165 (M^+, 45%), 150 (100). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found C, 65.22; H, 6.67; N, 8.32.

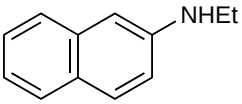


***N*-Ethylanthranilic acid** (Table 3, entry 6) Light brown solid. Mp 156-157°C. ^{1}H NMR ($CDCl_3$): δ 7.96 (d, *J*=8.0 Hz, 1H), 7.39 (t, *J*=8.0 Hz, 1H), 6.69 (d, *J*=8.0 Hz, 1H), 6.60 (t, *J*=8.0 Hz, 1H), 3.26 (q, *J*=7.1 Hz, 2H), 1.32 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 173.0, 151.8, 135.5, 132.6, 114.5, 111.3, 108.5, 37.4, 14.5. MS (EI) *m/z* 165 (M^+, 50%), 132 (100), 150 (25), 77 (19), 57 (15). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found C, 65.58; H, 6.65; N, 8.26.

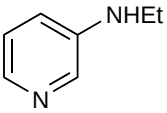


***N*-Ethyl-4-trifluoromethylaniline** (Table 3, entry 8) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.39 (d, *J*=8.5 Hz, 2H), 6.58 (t, *J*=8.5 Hz, 2H), 3.89 (brs, NH), 3.22-3.15 (m, 2H), 1.27 (t, *J*=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 150.8, 126.7, 126.6, 126.6, 111.7, 38.1, 14.6. MS (EI) *m/z* 189 (M^+, 30%), 174 (100). HRMS (EI) Calcd for $C_9H_{10}F_3N$ (M^+) 189.0765.

Found 189.0771.



***N*-Ethyl-β-naphthylamine** (Table 3, entry 9) Brown oil. ^{1}H NMR ($CDCl_3$): δ 7.65 (d, *J*=8.0 Hz, 1H), 7.61 (d, *J*=8.0 Hz, 2H), 7.35 (t, *J*=8.0 Hz, 1H), 7.18 (t, *J*=8.0 Hz, 1H), 6.86 (d, *J*=8.0 Hz, 1H), 6.80 (s, 1H), 3.71 (brs, NH), 3.26 (q, *J*=7.2 Hz, 2H), 1.32 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 146.6, 135.3, 128.9, 127.6, 127.5, 126.3, 125.9, 121.8, 118.0, 104.3, 38.5, 14.8. MS (EI) *m/z* 171 (M^+, 75%), 156 (100), 127 (40). HRMS (EI) Calcd for $C_{12}H_{13}N$ (M^+) 171.1048. Found 171.1038.



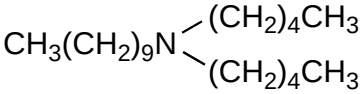
***N*-Ethyl-3-aminopyridine**[8] (Table 3, entry 10)

$CH_3(CH_2)_9NEt_2$

***N,N*-Diethyldecylamine** (Table 5, entry 1) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.51 (t, *J*=7.2 Hz, 4H), 2.40 (t, *J*=7.8 Hz, 2H), 1.47-1.42 (m, 2H), 1.38-1.20 (m, 14H), 1.02 (t, *J*=7.2 Hz, 6H), 0.88 (t, *J*=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 53.1, 46.9, 31.9, 29.6, 29.6, 29.3, 27.8, 27.0, 22.7, 14.1, 11.7. MS (FAB, Gly) *m/z* 214 (M^++H, 17%). HRMS (FAB, Gly) Calcd for $C_{14}H_{32}N$ (M^++H) 214.2535. Found 214.2530.

$CH_3(CH_2)_9NBu_2$

***N,N*-Dibutyldecylamine** (Table 5, entry 2) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.40-2.36 (m, 6H), 1.44-1.37 (m, 6H), 1.33-126 (m, 18H), 0.93-0.86 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 54.3, 54.0, 31.9, 29.6, 29.2, 27.7, 27.0, 22.6, 20.8, 14.1. MS (FAB, NBA) *m/z* 270 (M^++H, 52%). HRMS (EI) Calcd for $C_{18}H_{40}N$ (M^++H) 270.3161. Found 270.3158.



***N,N*-Dipentyldecylamine** (Table 5, entry 3) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.37 (t, *J*=7.6 Hz, 6H), 1.46-1.20 (m, 14H), 0.89-0.86 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 54.1, 31.9, 29.8, 29.6, 29.3, 27.6, 26.9, 22.6, 14.1. MS (FAB, Gly) *m/z* 298 (M^++H, 95%). HRMS (FAB, Gly) Calcd for $C_{20}H_{44}N$ (M^++H) 298.3468. Found 298.3474.

$CH_3(CH_2)_9NHEt$

***N*-Ethyldecylamine** (Table 5, entry 4) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.64(q, *J*=7.2 Hz, 2H), 2.59 (t, *J*=7.1 Hz, 2H), 1.48-1.46 (m, 2H), 1.28-1.26 (m, 14H), 1.11 (t, *J*=7.2 Hz, 3H), 0.88 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 50.0, 44.2, 31.9, 30.3, 29.6, 29.3, 27.4, 22.6, 15.4, 14.1. MS (FAB, NBA) *m/z* 186 (M^++H, 20%). HRMS (FAB, NBA) Calcd for $C_{12}H_{27}N$ (M^++H) 186.2228. Found 186.2222.

$CH_3(CH_2)_9NHBu$

***N*-Butyldecylamine** (Table 5, entry 5) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.62-2.58 (m, 4H), 1.52-1.44 (m, 4H), 1.39-1.26 (m, 16H), 0.92 (t, *J*=7.3 Hz, 3H), 0.88 (t, *J*=7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 49.9, 49.5, 31.9, 31.8, 29.7, 29.6, 29.3, 27.4, 22.6, 20.5, 14.1, 13.9. MS (FAB, NBA) *m/z* 214 (M^++H, 15%). HRMS (FAB, NBA) Calcd for $C_{14}H_{32}N$ (M^++H) 214.2535. Found 214.2543.

$CH_3(CH_2)_9NH(CH_2)_4CH_3$

***N*-Pentyldecylamine** (Table 5, entry 6) Colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.58 (t, *J*=7.1 Hz, 4H), 1.52-1.45 (m, 4H), 1.36-1.26 (m, 18H), 0.90 (t, *J*=7.1 Hz, 3H), 0.88 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 50.2, 31.9, 30.2, 29.9, 29.6, 29.3, 27.4, 22.6, 14.0. MS (EI) *m/z* 227 (M^+, 10%), 170 (100), 100 (100). HRMS (EI) Calcd for $C_{15}H_{33}N$ (M^+) 227.2613. Found 227.2600.

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