Synthesis of N-arylsubstituted pyrrolidines and piperidines by reaction of anilines with α,ω-diols catalyzed by $FeCl_3 \cdot 6H_2O$ in carbon tetrachloride

Ravil I. Khusnutdinov,* Alfiya R. Bayguzina, Rigina S. Asylbaeva, Rishat I. Aminov and Usein M. Dzhemilev

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, 141 Prospekt Oktyabrya, Ufa 450075, Russia
E-mail: khusnutdinov@anrb.ru

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Abstract

N-Arylpyrrolidines and N-arylpiperidines were synthesized in 20-88% yields by the reaction of aniline and aniline derivatives with 1,4-butane- and 1,5-pentanediols in the presence of Fe-containing catalysts and carbon tetrachloride. 1,4-Butane- and 1,5-pentanediols are partially chlorinated under the reaction conditions to give chlorohydrins, which subsequently undergo N-heterocyclization with anilines to give N-arylpyrrolidines and N-arylpiperidines.

Keywords: N-heterocyclization, anilines, 1,4-butane- and 1,5-pentanediols, N-arylpyrrolidines, *N*-arylpiperidines, $FeCl_3 \cdot 6H_2O$, chlorohydrin, catalysis, carbon tetrachloride

Introduction

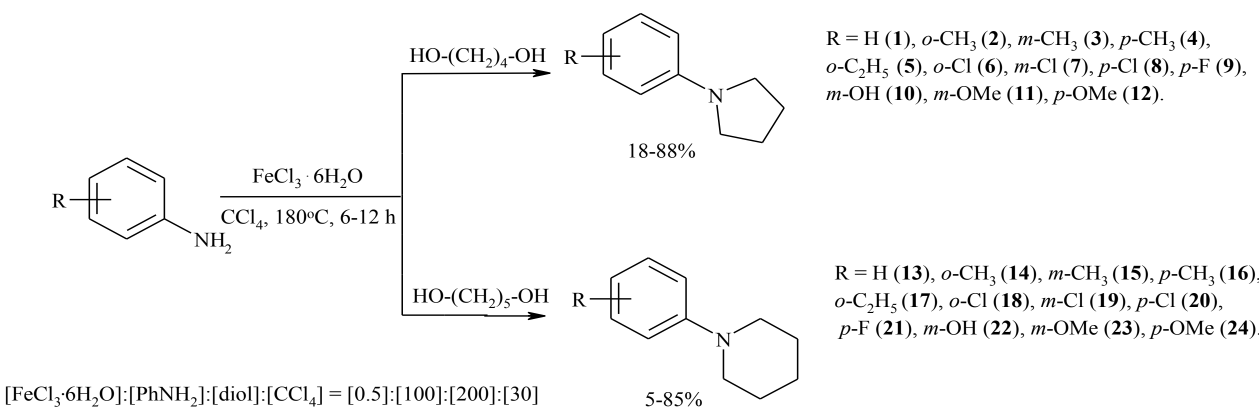
Pyrrolidines and piperidines form a highly important class of secondary amines; they are present as structural parts in many pharmaceuticals, herbicides, fungicides, and dyes.[1] A known method for the synthesis of cyclic amines of the pyrrolidine and piperidine series is based on aniline heterocyclization with α,ω-diols catalyzed by Ru metal complexes to give high yields of the target products.[2-6] Presumably, the reaction mechanism includes dehydrogenation of one OH group of the diol to give the [Ru]-hydroxyaldehyde-H_2 complex, which then condenses with aniline to give the Schiff base. The latter is hydrogenated affording amino alcohol, which undergoes intramolecular cyclization to yield N-substituted cyclic amine.[2]

Another publication[7] describes the synthesis of N-phenylpyrrolidines by the reaction of anilines with 1,4-butanediol catalyzed by the iridium complex $Ir[C_5(CH_3)_5]$ in the presence of $NaHCO_3$ as a base.

In this study, we ascertained that iron compounds and complexes serve as efficient catalysts for the synthesis of cyclic amines, N-arylpyrrolidines and *N*-arylpiperidines, by reactions of anilines with 1,4-butane- and 1,5-pentanediols. The reaction proceeds in carbon tetrachloride in the presence of the following iron compounds: $FeCl_3$, $FeBr_2$, $FeCl_3{\cdot}6H_2O$, $Fe(acac)_3$, $Fe_2(CO)_9$, the catalyst of choice being $FeCl_3{\cdot}6H_2O$.

Results and Discussion

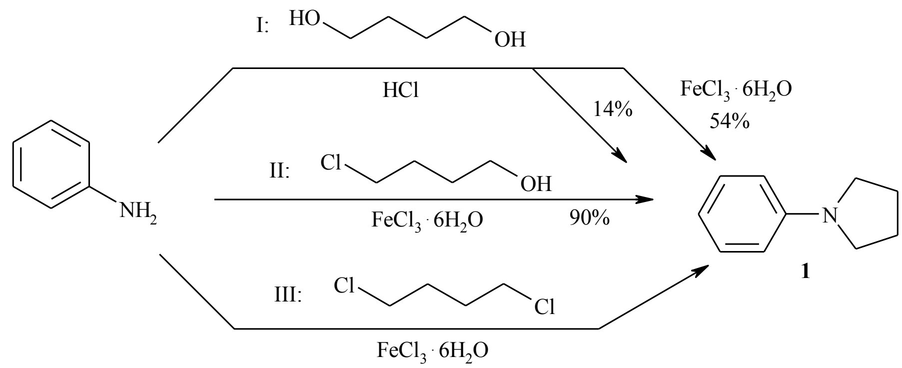
It was found experimentally that the optimal catalyst and reactant molar ratios are as follows: $[FeCl_3{\cdot}6H_2O]$:$[RC_6H_4NH_2]$:[diol]:$[CCl_4]$ = 0.5:100:200:30. At 180 ^oC over a period of 6 h, the reactions give N-arylpyrrolidines **1-12** and N-arylpiperidines **13-24** in 5-88% yields. The highest yields of 88% and 85% were observed for unsubstituted aniline-derived products **1** and **13**. Aniline derivatives were less active in this reaction irrespective of the electron-donating or electron-withdrawing properties of substituents. Therefore, our attempt to establish a correlation between the basicity (pK_a) and reactivity of substituted anilines was not a success. Most difficult was heterocyclization of 1,4-butane- and 1,5-pentanediols with *p*-anisidine (the yields were 18% for **12** and 5% for **24**), the basicity of which (pK_a = 5.29) differs little from the basicity of *p*-toluidine (pK_a = 5,12), which forms cyclic amines **4** and **16** in 75 and 61% yields, respectively (Scheme 1).



Scheme 1

The abnormal behavior of *p*-anisidine may be due to the possibility of complex formation with the central atom of the catalyst involving the ether group or chelation by NH_2- and OMe-groups.

Note that in the absence of carbon tetrachloride, no reaction occurs. It is evident that CCl_4 is not only a solvent but also a reactant. Taking into account the probable participation of CCl_4, three reaction pathways leading to *N*-phenylpyrrolidine can be conceived and are shown in the chart (Scheme 2).



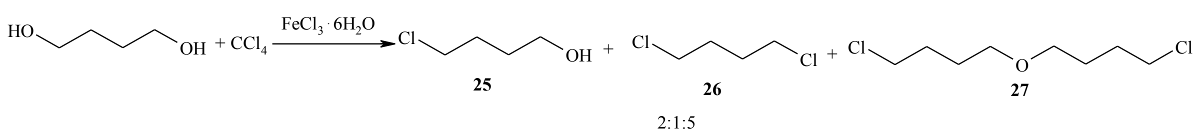
Scheme 2

First, CCl_4 can be hydrolyzed under the reaction conditions to give HCl, which can subsequently catalyze the reaction (pathway I – acid catalysis) (Scheme 3).

$$CCl_4 + 2H_2O \longrightarrow 4HCl + CO_2$$

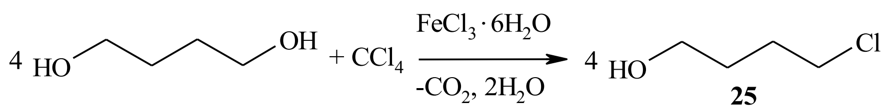
Scheme 3

This assumption was verified by experiments with authentic hydrochloric acid taken in a concentration of 15% comparable with the concentration released upon the formation of *N*-phenylpyrrolidine **1** from 1,4-butanediol, aniline, and CCl_4 under the action of the catalyst. As shown by the experiment, in the presence of HCl without a catalyst in the reaction mixture, the yield of *N*-phenylpyrrolidine **1** was only 14%. Hence, this pathway is unlikely.
According to gas chromatography/mass spectrometry analysis data, the reaction mixture contained 4-chlorobutanol **25**, 1,4-dichlorobutane **26**, and 4,4'-di(chlorobutyl) ether **27**, which may participate in the formation of *N*-phenylpyrrolidine **1** (pathways II and III) (Scheme 4).



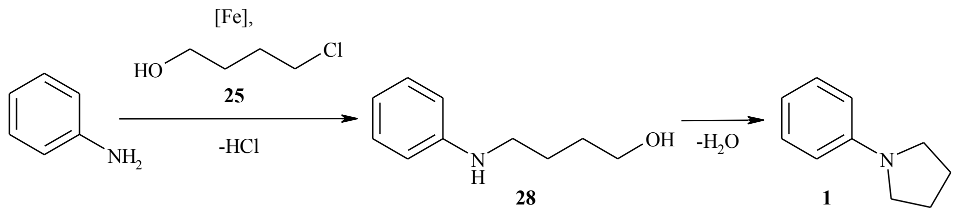
Scheme 4

In view of the presence of 4-chloro-1-butanol **25** and considering published data,[8] the process starts, most likely, with partial chlorination of 1,4-butanediol with CCl_4 to give chlorohydrin **25**. The evolution of CO_2 was detected by test reaction with a calcium hydroxide solution (Scheme 5).



Scheme 5

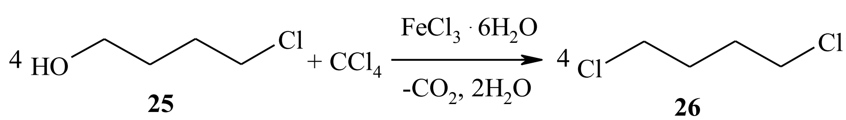
The next step is the reaction of chlorohydrin **25** with aniline under the action of $FeCl_3{\cdot}6H_2O$ to give 4-(*N*-phenylamino)-1-butanol **28**, which then undergoes intramolecular dehydration with evolution of 1 mole of water to afford *N*-phenylpyrrolidine **1** (Scheme 6).



Scheme 6

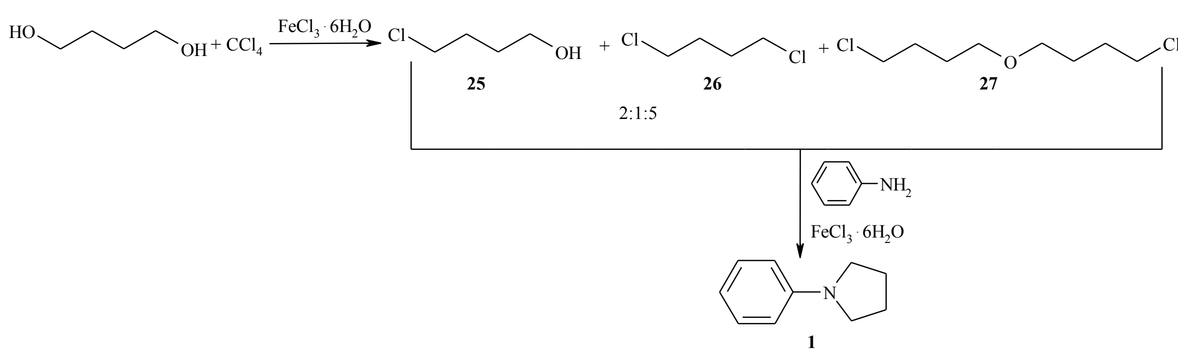
A control experiment with authentic chlorohydrin **25** in the presence of the $FeCl_3{\cdot}6H_2O$ catalyst resulted in the formation of *N*-phenylpyrrolidine **1** in a quantitative yield.

Note that under the reaction conditions a part of the formed chlorohydrin **25** that has not reacted with aniline can subsequently react with carbon tetrachloride yielding 1,4-dichlorobutane **26** and giving off two moles of water (Scheme 7).



Scheme 7

The second pathway is supported by the results of control experiment with aniline and a mixture of 4-chlorobutanol, 1,4-dichlorobutane, and 4,4'-dichlorodibutyl ether (2:1:5) carried out in the presence of the $FeCl_3{\cdot}6H_2O$ catalyst at 180 ^{o}C within 4 h. It was found that only 4-chloro-1-butanol **25** was consumed for the formation of *N*-phenylpyrrolidine (Scheme 8).



Scheme 8.

Conclusions

We propose a readily available catalyst, $FeCl_3{\cdot}6H_2O$, for N-heterocyclization of anilines with 1,4-butane- and 1,5-pentanediols in the presence of CCl_4 giving *N*-aryl-substituted pyrrolidines and piperidines.

Experimental Section

General. ^1H, ^{13}C and ^{19}F NMR spectra were measured on a Bruker Avance-400 spectrometer (400.13, 100.62 and 376.5 MHz, respectively) in $CDCl_3$, the chemical shifts are referred to TMS. Mass spectra were run on a Shimadzu GCMS-QP2010Plus GC/MS spectrometer (an SPB-5 capillary column, 30 m × 0.25 mm, helium as a carrier gas, temperature programming from 40 to 300 °C at 8 °C/min, evaporation temperature 280 °C, temperature of the ion source 200 °C, ionization energy 70 eV). Chromatographic analysis was carried out on a Shimadzu GC-9A, GC-2014 instrument [2 m × 3 mm column, silicone SE-30 (5%) on Chromaton N-AW-HMDS as the stationary phase, temperature programming from 50 to 270 °C at 8 °C/min, helium as the carrier gas (47 mL/min)]. The elemental composition of the samples was determined on a Karlo Erba 1106 elemental analyzer.

N-Arylpyrrolidines and N-arylpiperidines. General procedure. The reactions were carried out in a glass ampoule (V = 10 mL), placed in a stainless-steel micro autoclaves (V = 17 mL) under constant stirring and controlled heating.

The ampoule was charged with $FeCl_3{\cdot}6H_2O$ (2.9 mg, 0.01 mmol), aniline (0.2 mL, 2.15 mmol), diol (1,4-butanediol 0.38 mL and 1,5-pentanediol 0.45 mL, 4.30 mmol) and carbon tetrachloride (0.06 mL, 0.65 mmol) in an argon flow. The sealed ampoule was placed in an autoclave. The autoclave was air-tightly closed and heated at 160-180 °C for 6-12 h under continuous stirring. After completion of the reaction, the autoclave was cooled to room temperature, the ampoule was opened, and the reaction mixture was treated with diluted (10%) hydrochloric acid. The water layer was separated, neutralized with 10% solution of sodium hydroxide, and extracted with dichloromethane. The organic layer was filtered and the solvent was distilled off. The residue was distilled in a vacuum or recrystallized from hexane.

***N*-Phenylpyrrolidine (1).**[3] Yield 88%; colorless, oily liquid; bp 89-90 °C/1 mm (lit.[3] 86 °C/1 mm). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.34 (m, 2H, $C^{3,5}H$), 6.78 (m, 1H, C^4H), 6.69 (d, *J* 8 Hz, 2H, $C^{2,6}H$), 3.38 (m, 4H, $C^{2',5'}H_2$), 2.09 (m, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 148.06 (C^1), 129.22 ($C^{3,5}$), 115.53 (C^4), 111.81 ($C^{2,6}$), 47.72 ($C^{2',5'}$), 25.56 ($C^{3',4'}$); MS (EI, 70 eV): *m/z* (%) 147 (94) [M+], 146 (100), 119 (9), 104 (25), 91 (72), 77 (46), 65 (7), 51 (19).

***N*-(2-Methylphenyl)pyrrolidine (2).**[9] Yield 50%; light yellow oily liquid; bp 121-123 °C/10 mm (lit.[10] 55 °C/0.38 mm). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.20 (m, 1H, C^3H), 7.05 (m, 1H, C^5H), 6.93 (m, 1H, C^6H), 6.70 (m, 1H, C^4H), 3.32 (m, 4H, $C^{2',5'}H_2$), 2.44 (s, 3H, C^7H_3), 2.04 (m, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 148.14 (C^1), 131.92 (C^3), 129.20 (C^5), 126.56 (C^4), 121.68 (C^2), 116.59 (C^6), 49.74 ($C^{2',5'}$), 24.52 ($C^{3',4'}$), 20.35 (C^7).

***N*-(3-Methylphenyl)pyrrolidine (3).**[9] Yield 63%; colorless, oily liquid; bp 85-86 °C/1 mm (lit.[10] 70 °C/0.64 mm). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.24 (m, 1H, C^5H), 6.63 (d, *J* 8 Hz, 1H, C^4H), 6.53 (s, 1H, C^2H), 6.52 (d, *J* 8 Hz, 1H, C^6H), 3.39 (m, 4H, $C^{2',5'}H_2$), 2.45 (s, 3H, C^7H_3), 2.09 (m, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 148.15 (C^1), 138.83 (C^3), 129.11 (C^5), 116.61 (C^4), 112.53 (C^2), 109.14 (C^6), 47.79 ($C^{2',5'}$), 25.55 ($C^{3',4'}$), 21.98 (C^7); MS (EI, 70 eV): *m/z* (%) 161 (72) [M+], 160 (100), 118 (22), 105 (69), 91 (56), 77 (14), 65 (34), 51 (11).

***N*-(4-Methylphenyl)pyrrolidine (4).**[11] Yield 75%; yellow solid; mp 38-40 °C (lit.[12] 40–42 °C). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.07 (d, *J* 8 Hz, 2H, $C^{3,5}H$), 6.56 (d, *J* 8 Hz, 2H, $C^{2,6}H$), 3.27 (m, 4H, $C^{2',5'}H_2$), 2.28 (s, 3H, C^7H_3), 2.02 (m, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 145.85 (C^1), 129.68 ($C^{3,5}$), 124.98 (C^4), 112.19 ($C^{2,6}$), 48.26 ($C^{2',5'}$), 25.39 ($C^{3',4'}$), 20.36 (C^7); MS (EI, 70 eV): *m/z* (%) 161 (76) [M+], 160 (100), 118 (31), 105 (79), 91 (64), 89 (16), 77 (18), 65 (38), 51 (13).

***N*-(2-Ethylphenyl)pyrrolidine (5).** Yield 47%; yellow oily liquid; bp 88-90 °C/0.8 mm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.22 (m, 1H, C^3H), 7.16 (m, 1H, C^5H), 6.99 (m, 1H, C^6H), 6.95 (m, 1H, C^4H), 3.20 (br s, 4H, $C^{2',5'}H_2$), 2.75 (q, *J* 7.2 Hz, 2H, C^7H_2), 1.97 (br s, 4H, $C^{3',4'}H_2$), 1.29 (t, *J* 7.2 Hz, 3H, C^8H_3); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 135.50 (C^1), 129.39 (C^3), 128.35 (C^5), 126.18 (C^4), 120.97 (C^2), 116.66 (C^6), 51.62 ($C^{2',5'}$), 25.33 ($C^{3',4'}$), 24.93 (C^7), 14.39 (C^8); MS (EI, 70 eV): *m/z* (%) 175 (80) [M+], 174 (100), 160 (7), 146 (12), 134 (15), 119 (35), 91 (37), 65 (16); Anal. Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99%. Found: C, 82.11; H, 9.83; N, 8.06%.

***N*-(2-Chlorophenyl)pyrrolidine (6).**[10] Yield 51%; colorless, oily liquid; bp 78-80 °C/1 mm (lit.[10] 54 °C/0.20 mm). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.29 (m, 1H, C^3H), 7.17 (m, 1H, C^5H), 7.00 (m, 1H, C^6H), 6.82 (m, 1H, C^4H), 3.41 (br s, 4H, $C^{2',5'}H_2$), 1.97 (br s, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 146.98 (C^1), 131.29 (C^3), 127.29 (C^5), 126.44 (C^4), 123.59 (C^2), 120.91 (C^6), 51.26 ($C^{2',5'}$), 25.20 ($C^{3',4'}$); MS (EI, 70 eV): *m/z* (%) 181 (85) [M+], 183 (23), 182 (42), 180 (100), 140 (24), 138 (64), 125 (69), 111 (49), 91 (27).

***N*-(3-Chlorophenyl)pyrrolidine (7).**[9] Yield 50%; yellow oily liquid; bp 92-93 °C/0.8 mm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.06 (m, 1H, C^5H), 6.55 (d, *J* 8 Hz, 1H, C^4H), 6.46 (s, 1H, C^2H), 6.37 (d, *J* 8 Hz, 1H, C^6H), 3.19 (br s, 4H, $C^{2',5'}H_2$), 1.96 (br s, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 148.83 (C^1), 134.78 (C^3), 129.98 (C^5), 114.95 (C^4), 111.27 (C^2), 109.89 (C^6), 47.57 ($C^{2',5'}$), 25.41 ($C^{3',4'}$).

***N*-(4-Chlorophenyl)pyrrolidine (8).**[10] Yield 60%; white solid; mp 83-85 °C (lit.[13] 84–85 °C). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.14 (d, *J* 8 Hz, 2H, $C^{3,5}H$), 6.46 (d, *J* 8 Hz, 2H, $C^{2,6}H$), 3.25 (m, 4H, $C^{2',5'}H_2$), 2.02 (m, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 146.51 (C^1), 128.90 ($C^{3,5}$), 120.04 (C^4), 112.73 ($C^{2,6}$), 47.78 ($C^{2',5'}$), 25.56 ($C^{3',4'}$); MS (EI, 70 eV): *m/z* (%) 181 (88) [M+], 183 (23), 182 (30), 180 (100), 138 (37), 127 (17), 125 (66), 110 (46), 91 (16), 89 (19), 75 (20).

***N*-(4-Fluorophenyl)pyrrolidine (9).**[14] Yield 45%; yellow oily liquid; bp 82-84 ^oC/1mm (lit.[14] 130–132 ^oC/13 mm). ^1H NMR (400.13 MHz, $CDCl_3$): δ 6.96 (m, 2H, $C^{3,5}H$), 6.50 (m, 2H, $C^{2,6}H$), 3.25 (m, 4H, $C^{2',5'}H_2$), 2.02 (m, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 154.83 (d, C^4, *J* 232 Hz), 144.83 (C^1), 115.43 (d, $C^{2,6}$, *J* 8 Hz,), 112.14 (d, $C^{3,5}$, *J* 22 Hz,), 48.18 ($C^{2',5'}$), 25.53 ($C^{3',4'}$); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -130.73; MS (EI, 70 eV): *m/z* (%) 165 (94) [M+], 164 (73), 136 (11), 122 (63), 109 (100), 95 (10).

***N*-(3-Hydroxyphenyl)pyrrolidine (10).**[15] Yield 42%; white solid; mp 134-135 °C (lit.[16] 134 ^oC). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.07 (m, 1H, C^5H), 6.19 (m, 1H, C^4H), 6.18 (s, 1H, C^2H), 6.08 (m, 1H, C^6H), 3.25 (m, 4H, $C^{2',5'}H_2$), 1.99 (m, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.84 (C^3), 149.52 (C^1), 130.02 (C^5), 104.61 (C^4), 102.77 (C^6), 98.90 (C^2), 47.70 ($C^{2',5'}$), 25.40 ($C^{3',4'}$); MS (EI, 70 eV): *m/z* (%) 163 (93) [M+], 162 (100), 134 (17), 120 (17), 107 (55), 93 (21), 77 (10), 65 (30).

***N*-(3-Methoxyphenyl)pyrrolidine (11).**[15] Yield 24%; colorless, oily liquid; bp 109-110 ^oC/1 mm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.18 (m, 1H, C^5H), 6.30 (m, 1H, C^4H), 6.18 (s, 1H, C^2H), 6.11 (m, 1H, C^6H), 3.85 (s, 3H, C^7H_3), 3.32 (m, 4H, $C^{2',5'}H_2$), 2.03 (m, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 160.74 (C^3), 149.50 (C^1), 129.97 (C^5), 105.08 (C^6), 100.60 (C^4), 98.02 (C^2), 55.14 (C^7), 47.72 ($C^{2',5'}$), 25.46 ($C^{3',4'}$); MS (EI, 70 eV): *m/z* (%) 177 (82) [M+], 176 (100), 121(99), 107 (35), 92 (45), 77 (78), 64 (57), 41 (80), 39 (62).

***N*-(4-Methoxyphenyl)pyrrolidine (12).**[9] Yield 18%; white solid; mp 44-46 °C. ^1H NMR (400.13 MHz, $CDCl_3$): δ 6.87 (d, *J* 8 Hz, 2H, $C^{3,5}H$), 6.57 (d, *J* 8 Hz, 2H, $C^{2,6}H$), 3.77 (s, 3H, C^7H_3), 3.23 (m, 4H, $C^{2',5'}H_2$), 2.01 (m, 4H, $C^{3',4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 150.81 (C^4), 143.24 (C^1), 115.04 ($C^{2,6}$), 112.70 ($C^{3,5}$), 56.02 (C^7), 48.31 ($C^{2',5'}$), 25.36 ($C^{3',4'}$); MS (EI, 70 eV): *m/z* (%) 177 (75) [M+], 162 (100), 134 (10), 120 (15), 92 (6), 77 (8), 65 (5), 55 (7).

***N*-Phenylpiperidine (13).**[2] Yield 85%; colorless oil; bp 73-74 ^oC/0.4 mm (lit.[3] 86 ^oC/1 mm). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.30 (m, 2H, $C^{3,5}H$), 7.00 (d, *J* 8 Hz, 2H, $C^{2,6}H$), 6.88 (m, 1H, C^4H), 3.21 (m, 4H, $C^{2',6'}H_2$), 1.76 (m, 4H, $C^{3',5'}H_2$), 1.64 (m, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 152.22 (C^1), 129.04 ($C^{3,5}$), 119.36 (C^4), 116.66 ($C^{2,6}$), 50.81 ($C^{2',6'}$), 25.88 ($C^{3',5'}$), 24.34 ($C^{4'}$).

***N*-(2-Methylphenyl)piperidine (14).**[17] Yield 42%; light yellow oily liquid; bp 60-61 ^oC/0.6 mm (lit.[18] 44 ^oC/0.2 mm). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.19 (m, 1H, C^3H), 7.14 (m, 1H, C^5H), 6.98 (m, 1H, C^6H), 6.87 (m, 1H, C^4H), 2.99 (br s, 4H, $C^{2',6'}H_2$), 2.41 (s, 3H, C^7H_3), 1.86 (br s, 4H, $C^{3',5'}H_2$), 1.60 (m, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 149.87 (C^1), 132.41 (C^3), 131.56 (C^5), 126.74 (C^4), 124.31 (C^2), 119.32 (C^6), 54.08 ($C^{2',6'}$), 25.74 ($C^{3',5'}$), 23.76 ($C^{4'}$), 18.31 (C^7); MS (EI, 70 eV): *m/z* (%) 175 (86) [M+], 174 (100), 146 (28), 132 (18), 118 (86), 91 (38).

***N*-(3-Methylphenyl)piperidine (15).**[19] Yield 47%; light yellow oily liquid; bp 95-97 ^oC/0.5 mm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.17 (m, 1H, C^5H), 6.88 (d, *J* 8 Hz, 1H, C^4H), 6.53 (s, 1H, C^2H), 6.51 (m, 1H, C^6H), 3.25 (m, 4H, $C^{2',6'}H_2$), 2.33 (s, 3H, C^7H_3), 2.22 (m, 4H, $C^{3',5'}H_2$), 1.63 (m, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 148.34 (C^1), 139.45 (C^3), 129.32 (C^5), 124.56 (C^4), 119.90 (C^2), 115.62 (C^6), 53.49 ($C^{2',6'}$), 24.69 ($C^{3',5'}$), 23.18 ($C^{4'}$), 21.64 (C^7); MS (EI, 70 eV): *m/z* (%) 175 (81) [M+], 174 (100), 160 (7), 146 (12), 134 (15), 119 (36), 91 (38), 65 (16).

***N*-(4-Methylphenyl)piperidine (16).**[12] Yield 61%; light yellow solid; mp 264-266 °C (lit.[12] 265-267 °C). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.56 (d, *J* 8 Hz, 1H, $C^{3,5}$H), 7.11 (d, *J* 8 Hz, 1H, $C^{2,6}$H), 3.30 (m, 4H, $C^{2',6'}H_2$), 2.24 (s, 3H, C^7H_3), 2.07 (m, 4H, $C^{3',5'}H_2$), 1.69 (m, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 142.18 (C^1), 137.94 ($C^{3,5}$), 129.92 (C^4), 120.42 ($C^{2,6}$), 56.15 ($C^{2',6'}$), 23.17 ($C^{3',5'}$), 21.94 ($C^{4'}$), 20.86 (C^7); MS (EI, 70 eV): *m/z* (%) 175 (98) [M+], 174 (100), 160 (12), 146 (9), 134 (13), 119 (32), 91 (29), 64 (10).

***N*-(2-Ethylphenyl)piperidine (17).** Yield 38%; yellow oily liquid; bp 75-77 °C/1mm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.27 (m, 1H, C^3H), 7.19 (m, 1H, C^5H), 7.11 (m, 1H, C^6H), 7.06 (m, 1H, C^4H), 2.77 (m, 4H, $C^{2',6'}H_2$), 2.57 (m, 2H, C^7H_2), 1.80 (m, 4H, $C^{3',5'}H_2$), 1.61 (m, 2H, $C^{4'}H_2$), 1.30 (m, 3H, C^8H_3); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 152.29 (C^1), 139.29 (C^3), 128.87 (C^5), 126.36 (C^4), 123.62 (C^2), 119.85 (C^6), 54.36 ($C^{2',6'}$), 26.61 ($C^{3',5'}$), 24.66 (C^7), 24.36 ($C^{4'}$), 14.89 (C^8); Anal. Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40%. Found: C, 82.61; H, 10.04; N, 7.35%.

***N*-(2-Chlorophenyl)piperidine (18).** Yield 33%; light yellow oily liquid; bp 89-90 °C/0.6 mm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.39 (m, 1H, C^3H), 7.26 (m, 1H, C^5H), 7.08 (m, 1H, C^6H), 7.00 (m, 1H, C^4H), 3.02 (m, 4H, $C^{2',6'}H_2$), 1.79 (m, 4H, $C^{3',5'}H_2$), 1.63 (m, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 150.66 (C^1), 130.53 (C^3), 128.00 (C^2),127.45 (C^5), 123.15 (C^4), 120.49 (C^6), 52.92 ($C^{2',6'}$), 26.31 ($C^{3',5'}$), 24.32 ($C^{4'}$); Anal. Calcd. for $C_{11}H_{14}NCl$: C, 67.51; H, 7.21; N, 7.16%. Found: C, 67.62; H, 7.39; N, 7.03%.

***N*-(3-Chlorophenyl)piperidine (19).**[9] Yield 35%; light yellow oily liquid; bp 82-83 °C/0.5 mm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.15 (m, 1H, C^5H), 7.04 (d, *J* 8 Hz, 1H, C^4H), 6.92 (s, 1H, C^2H), 6.79 (d, *J* 8 Hz, 1H, C^6H), 3.18 (m, 4H, $C^{2',6'}H_2$), 1.71 (m, 4H, $C^{3',5'}H_2$), 1.60 (m, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 152.80 (C^1), 134.85 (C^3), 130.26 (C^5), 118.95 (C^4), 116.16 (C^2), 114.49 (C^6), 50.34 ($C^{2',6'}$), 25.52 ($C^{3',5'}$), 24.14 ($C^{4'}$).

***N*-(4-Chlorophenyl)piperidine (20).**[20] Yield 40%; light yellow solid; mp 45-47 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.21 (d, *J* 8 Hz, 2H, $C^{3,5}$H), 6.60 (d, *J* 8 Hz, 2H, $C^{2,6}$H), 3.14 (m, 4H, $C^{2',6'}H_2$), 1.75 (m, 4H, $C^{3',5'}H_2$), 1.60 (m, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 144.90 (C^1), 128.95 ($C^{3,5}$), 123.07 (C^4), 118.11 ($C^{2,6}$), 51.19 ($C^{2',6'}$), 25.46 ($C^{3',5'}$), 23.94 ($C^{4'}$); MS (EI, 70 eV): *m/z* (%) 195 (91) [M+], 197 (36), 196 (41), 194 (100), 154 (25), 139 (42), 125 (14), 111 (50); Anal. Calcd. for $C_{11}H_{14}NCl$: C, 67.51; H, 7.21; N, 7.16%. Found: C, 67.38; H, 7.46, N, 7.23%.

***N*-(4-Fluorophenyl)piperidine (21).**[14] Yield 35%; yellow oily liquid; bp 65-67 °C/1.5 mm (lit.[14] 110-112 °C/16 mm). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.46 (br s, 2H, $C^{3,5}$H), 6.95 (br s, 2H, $C^{2,6}$H), 3.22 (br s, 4H, $C^{2',6'}H_2$), 1.93 (br s, 4H, $C^{3',5'}H_2$), 1.59 (br s, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 160.09 (d, C^4, *J* 244 Hz), 143.02 (C^1), 121.47 (d, $C^{2,6}$, *J* 8 Hz), 116.28 (d, $C^{3,5}$, *J* 22 Hz), 55.00 ($C^{2',6'}$), 24.20 ($C^{3',5'}$), 22.35 ($C^{4'}$); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -116.13.

***N*-(3-Hydroxyphenyl)piperidine (22).**[21] Yield 24%; white solid; mp 122-123 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.10 (m, 1H, C^5H), 6.54 (d, *J* 8 Hz, 1H, C^4H), 6.44 (s, 1H, C^2H), 6.33 (m, 1H, C^6H), 3.14 (m, 4H, $C^{2',6'}H_2$), 1.71 (m, 2H, $C^{4'}H_2$), 1.60 (m, 4H, $C^{3',5'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.77 (C^3), 153.40 (C^1), 129.88 (C^5), 108.99 (C^4), 106.64 (C^6), 103.84

(C^{2}), 50.71 ($C^{2',6'}$), 25.58 ($C^{3',5'}$), 24.25 ($C^{4'}$); MS (EI, 70 eV): *m/z* (%) 177 (61) [M+], 176 (86), 121 (99), 93 (55), 65 (87), 55 (54), 41 (73), 39 (100).

***N*-(3-Methoxyphenyl)piperidine (23).**[22] Yield 7%; light yellow oily liquid; 103-104 °C/0.4 mm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.08 (m, 1H, C^{5}H), 6.52 (d, *J* 8 Hz, 1H, C^{4}H), 6.45 (s, 1H, C^{2}H), 6.33 (m, 1H, C^{6}H), 3.81 (s, 3H, $C^{7}H_3$), 3.15 (m, 4H, $C^{2',6'}H_2$), 1.70 (m, 4H, $C^{3',5'}H_2$), 1.59 (m, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 160.45 (C^{3}), 153.51 (C^{1}), 130.01 (C^{5}), 108.86 (C^{6}), 106.44 (C^{4}), 103.69 (C^{2}), 55.16 (C^{7}), 50.58 ($C^{2',6'}$), 25.64 ($C^{3',5'}$), 24.29 ($C^{4'}$); MS (EI, 70 eV): *m/z* (%) 191 (68) [M+], 190 (100), 135 (62), 92 (44), 77 (58), 65 (39), 55 (38), 41 (66), 39 (54).

***N*-(4-Methoxyphenyl)piperidine (24).**[11] Yield 5%; white solid; mp 64-65 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.95 (d, *J* 8 Hz, 1H, $C^{3,5}$H), 6.83 (d, *J* 8 Hz, 1H, $C^{2,6}$H), 3.78 (s, 3H, $C^{7}H_3$), 3.03 (m, 4H, $C^{2',6'}H_2$), 1.74 (m, 4H, $C^{3',5'}H_2$), 1.56 (m, 2H, $C^{4'}H_2$); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 153.90 (C^{4}), 147.63 (C^{1}), 115.35 ($C^{3,5}$), 113.74 ($C^{2,6}$), 57.82 (C^{7}), 50.87 ($C^{2',6'}$), 26.93 ($C^{3',5'}$), 24.14 ($C^{4'}$); MS (EI, 70 eV): *m/z* (%) 191 (57) [M+], 190 (34), 176 (74), 135 (44), 120 (100), 92 (48), 77 (46), 65 (43), 55 (36), 41 (90), 39 (54).

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