Reductive One Batch Synthesis of *N*-Substituted Pyrrolidines from Primary Amines and 2,5-Dimethoxytetrahydrofuran

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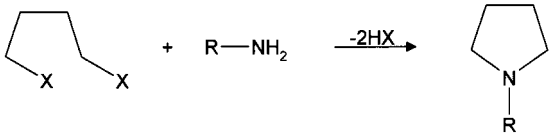
Abstract: The construction of the pyrrolidine ring about a nitrogen of a primary amine by a reductive condensation reaction using 2,5-dimethoxytetrahydrofuran and sodium borohydride in acidic water medium is described. The reaction is fast, affords good to excellent yields and appears insensitive to electron effects and severe steric hindrance; it is found to be compatible with a large variety of aryl substituents, including nitro and oxo groups. The reaction allows the introduction of two deuterium atoms, with label conservation, in both the α-positions of the pyrrolidine ring by the use of sodium borodeuteride instead of sodium borohydride.

Key words: pyrrolidine, 2,5-dimethoxytetrahydrofuran, sodium borohydride, sodium borodeuteride, reductive alkylation

In principle, the methods to build up cyclic amines can be distinguished by the type and size of the fragments to be joined and by the type of reactions employed to perform the cyclization.

The synthesis of *N*-substituted pyrrolidines, an important endeavour in many synthetic fields, has been studied extensively and a number of procedures are available.[1] A versatile synthetic way, also for a large scale utilisation, is the reaction between tetrahydrofuran and the appropriate primary amine in the presence of water-splitting catalysts such as Al_2O_3[2] or other oxides[3] (i.e. TiO_2, ThO_2, Fe_2O_3, MoO_3) at elevated temperatures (300–500 °C). This method has been utilised both with aromatic and aliphatic amines, but it is not suitable for medium scale or laboratory preparation due to the need of special equipment.

The pyrrolidine skeleton may be also obtained by the 4C+1N scheme from a reactive C4 molecule suitably functionalized at both ends and a primary amine via a displacement reaction.



The reactive C4 molecule may be a 1,4-dihalide[4] (X = Cl or Br) or 1,4-diol.[5] This route, even if particularly convenient, suffers from some disadvantages: with the former substrate the reaction is very sensitive to steric hindrance[6] and to the basicity of the amine: in some cases, a catalyst ($ZnCl_2$, $AlCl_3$)[7] or long reaction times are needed. With the latter, a catalyst [$RuCl_2(PPh_3)_3$, Al_2O_3 or aluminosilicate] and very high temperatures are requested. The esterification of the two hydroxyl groups with sulfonic acids derivatives[8] allowed milder reaction conditions.

Of particular synthetic value are reactions which permit selective functionalization of otherwise unactivated atoms. The oldest representative of such a process is the Hofmann–Löffler–Freytag reaction.[9] In this reaction secondary *N*-haloamines, in which one alkyl group has a hydrogen in the 4-position, are heated with H_2SO_4 to give *N*-alkylpyrrolidines.

Reported procedures to make *N*-arylpyrrolidines from pyrrolidine require either the presence of activated halogens (ar-S_N2)[10] or the activation of the nucleophile as an alkali salt (ar-S_N2 and/or benzyne reactions).[11]

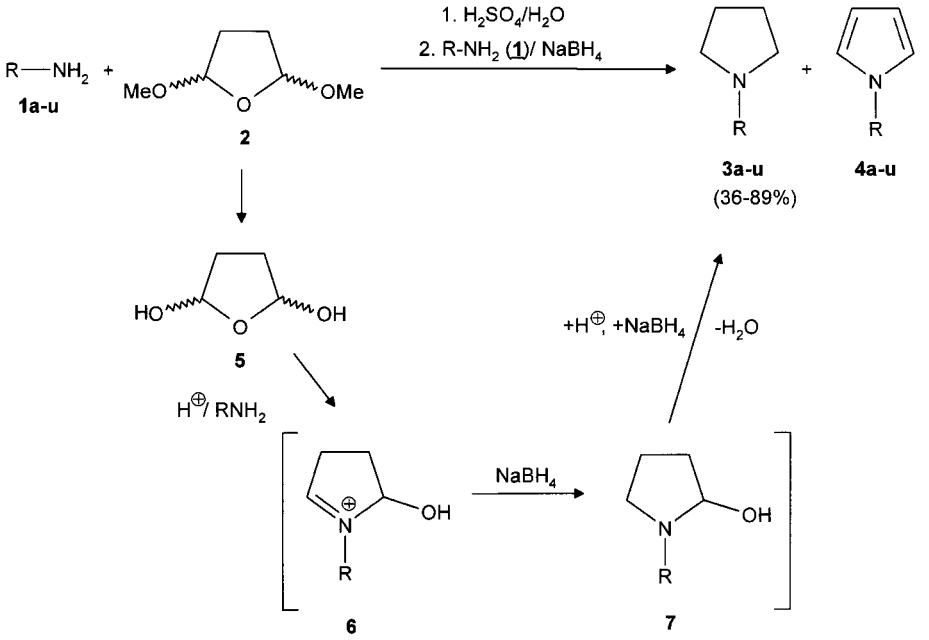
Examples of reduction of *N*-substituted 2,5-dioxopyrrolidines with $LiAlH_4$[12] and 2-oxopyrrolidines with catalytic hydrogenation[13] or $NaBH_4$ in presence of $POCl_3$[14] are reported in the literature. The catalytic hydrogenation has been extensively used for the reduction of *N*-substituted pyrroles[15] with some limitations for *N*-aryl pyrroles because of concomitant hydrogenation of the aromatic ring.

Little attention, however, has been paid to the reductive alkylation of amines using succinaldehyde derivatives. We applied our reductive *N*-alkylation procedure[16] using a primary amine (**1**) and 2,5-dimethoxytetrahydrofuran (**2**). We used $NaBH_4$ in H_2SO_4–water–methanol as the reducing agent for the intermediate condensation products (Scheme 1). R groups are listed in Table 1.

Previous methods applying the reductive 2,5-dimethoxytetrahydrofuran (**2**) condensation-reaction approach were a procedure using tetracarbonylhydroferrate under carbon monoxide atmosphere[17] and another employing sodium cyanoborohydride to convert *N*-aminopiperidine to *N*-piperidylpyrrolidine.[18]

The method described here is very simple, fast and cheap, both in handling and equipment. We have successfully applied our procedure not only to aromatic amines bearing substituents of widely different electronic effect and very severe steric hindrance, i.e. **1e** and **1n**, but also to aliphatic ones, i.e. **1t** and **1u** (see Table 1).

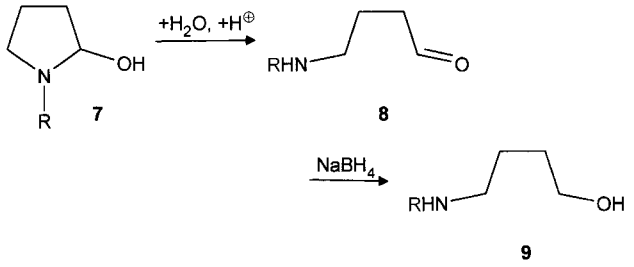
GCMS analysis of the crude reaction mixtures after neutralisation showed the presence ca. 5–6% of the corresponding *N*-substituted pyrrole (**4**) as the only side product (Scheme 1). We confirmed the structures of **4a–u** by the comparison of their GC retention times and mass spectra with those of authentic samples prepared according to a known procedure.[19]



Scheme 1

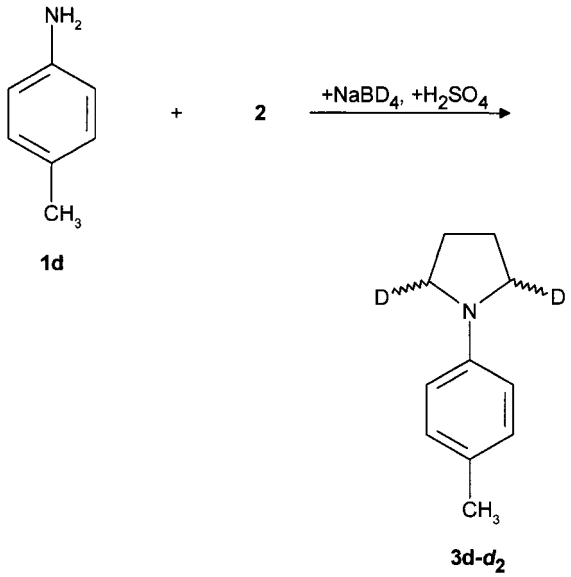
The amount and the concentration of H_2SO_4 are important in order to reduce the formation of **4** and the proper conditions depend on the nature of the amine **1**. In general, we used a lesser amount of acid and a greater amount of water than in the previously reported reductive alkylation procedure.[16]

We noticed that also the form of the $NaBH_4$ used was very important for the good proceeding of the reaction. $NaBH_4$ as pellets (diameter 11 mm) or half-broken caplets have to be preferred to $NaBH_4$ powder that favours the formation of the alcohol **9** as a side product.



When $NaBD_4$ was used instead of $NaBH_4$, two deuterium atoms were introduced to the 2- and 5-position of the pyrrolidine ring: the procedure applied on 4-methylbenzenamine (**1d**) gave 2,5-dideuterio-1-(4'-methyl-phenyl)-pyrrolidine (**3d**-d_2) in high yield.

There was some consideration on the ^{13}C NMR spectrum of 1-(2,6-diisopropylphenyl)pyrrolidine (**3e**): it can be seen that the Ar–C_1 chemical shift is located in the usual region for benzenamines, whereas Ar–C_4 appears to be deshielded (δ = 126.2 ppm) in comparison with benzenamine (δ = 119.0 ppm) and *N*,*N*-dimethylbenzenamine (δ = 116.7 ppm), showing a value quite close to that of toluene and isopropylbenzene (δ = 125.6 and δ = 126.0 ppm, respectively) and 1-(2',6'-diisopropylphenyl)piperidine



(**11**, δ = 126.1 ppm).[20] This observation can be taken as an indication of the lack of conjugation between the nitrogen lone pair and the ring, as a consequence of the mutual "orthogonal" position of the two rings as we already saw in **11**.[20] This conformational situation in **3e** may explain its resistance to iodination, in fact, while it was easy to synthesise 4-iodo-2,6-diisopropylbenzenamine (**1n**) from **1e**, the same reaction proved to be ineffective on **3e** in order to synthesise **3n**.

Data pertinent to the synthesised 1-substituted pyrrolidines (**3**) are collected on Table 2.

With the exception of 4-iodo-2,6-diisopropylbenzenamine (**1n**), which was prepared as described,[21] the other amines **1a–m** and **1o–u** used in this work, 2,5-dimethoxytetrahydrofuran (**2**), $NaBH_4$ pellets (11 mm diameter) and $NaBD_4$ powder (96 atom% D) were purchased from Aldrich, Italy, Milan. $NaBH_4$ (Venpure) caplets were kindly offered by Morton International S.p.A. (Mozzate, Como).

Table 1 Yields and Some Properties of 1-Substituted Pyrrolidines **(3)**

Product	R	Separated yield (%)	mp[a] (°C) or bp[a] (°C)/ mbar	Lit. mp (°C) or bp (°C)/ mbar	Formula	Elemental analysis	
						Calcd.	Found
3a	C_6H_5	87	58/0.30[f]	100/7.98,[8b] 37-8/0.13,[13a] 70/0.77[17a]			
3b	2-MeC_6H_4	80	60/0.60[f]	114/14.6,[6a] 55/0.51[17a]			
3c	3-MeC_6H_4	83	60/0.40[f]	70/0.85[17a]			
3d	4-MeC_4H_4	83	69/0.42[f]	120/10.6,[15b] 64/0.19[17a]			
3d-*d*$_2$		72	71/0.42[f]		$C_{11}H_{13}D_2N$	C: 80.53, H: 7.38, N: 9.40	C: 80.06, H: 7.33, N: 9.23
3e	2,6-*i*-$Pr_2C_6H_3$	58; 80[b]	70/0.15[f]		$C_{16}H_{25}N$	C: 83.06, H: 10.89, N: 6.05	C: 83.15, H: 10.84, N: 6.12
3f	3-$MeOC_6H_4$	78	85/0.42[g]	174/26.6[6a]			
3g	4-$MeOC_6H_4$	81	41[c]	86/0.43[17a]			
3h	2,3,4-$F_3C_6H_2$	79	74/1.0[f]		$C_{10}H_{10}F_3N$	C: 59.70, H: 5.01, N: 6.96	C: 59.62, H: 4.93, N: 6.87
3i	3-$CF_3C_6H_4$	82	73/0.41[f]	60-2/0.36[5e]			
3j	2-ClC_6H_4	85	78/0.80[f]	54/0.27[17a]			
3k	3-ClC_6H_4	83	119/0.70[f]		$C_{10}H_{12}ClN$	C: 66.12, H: 6.66, N: 7.71	C: 66.08, H: 6.72, N: 7.65
3l	4-ClC_6H_4	86	86[d]	85-6[17a]			
3m	3-BrC_6H_4	79	95/0.20[f]		$C_{10}H_{12}BrN$	C: 53.12, H: 5.35, N: 6.19	C: 53.17, H. 5.42, N: 6.23
3n	2,6-*i*-Pr_2-4-I-C_6H_2	43; 72[b]	121[d]		$C_{16}H_{24}lN$	C: 53.79, H: 6.77, N: 3.92	C: 53.72, H: 6.72, N: 4.02
3o	2-$MeO_2CC_6H_4$	77[b]	105/0.30[f]		$C_{12}H_{15}NO_2$	C: 70.22, H: 7.37, N: 6.82	C: 70.15, H: 7.43, N: 6.88
3p	4-$MeOCC_6H_4$	87	126[d]		$C_{12}H_{15}NO$	C: 76.16, H: 7.99, N: 7.40	C: 76.02, H: 7.92; N: 7.34
3q	2-$NO_2C_6H_4$	32; 65[b]	34[h]	105–7/0.13[10c]			
3r	3-$NO_2C_6H_4$	87	100[e]	98–100[10e]			
3s	4-$NO_2C_6H_4$	89	177[c]	167–8,[10b] 169-71,[10d] 178-9[10e]			
3t	$C_6H_5CH_2$	40	42/0.38[f]	95/7.98,[2b] 82/6.65,[8b] 44/0.43[17a]			
3u	C_6H_{11}	36	40/0.22[f]	200-10/1013[5a]			

[a] Uncorrected.
[b] Yield obtained after a second treatment on the reaction mixture.
[c] Recrystallized from MeOH/H_2O.
[d] Recrystallized from MeOH.
[e] Recrystallized from Et_2O.
[f] Purified by distillation.
[g] Purified by absorption chromatography on alumina (eluent: hexane).
[h] Purified by absorption chromatography on alumina (eluent: hexane-Et_2O 90:10).

Alumina (active neutral, Brokmann Grade I) was obtained from BDH (Milan, Italy). Thin layer chromatography was performed on alumina (Aluminiumoxid 60 F_{254} neutral, Merck, Darmstadt, Germany) and hexane–Et_2O (60:40) were used as eluents. Solvents were used as received. GCMS analyses were performed with a Fisons TRIO 2000 gas chromatograph–mass spectrometer, working in the positive ion 70 eV electron impact mode. Spectra were recorded in the range 35–450 u. Injector temperature was kept at 250 °C and the column (Supelco SPB™-5, 30 m long, 0.25 mm I.D.) temperature was programmed from 60 °C to 300 °C with a gradient of 10 °C/min. IR spectra were obtained with a Nicolet FT-IR Magna 550 spectrophotometer using KBr technique for solids and recorded in the range 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at r.t. on a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively. NMR peak locations are reported as δ-values from TMS (^1H NMR) and the central peak of $CDCl_3$ (^{13}C NMR).

Table 2 Infrared, ^{1}H and ^{13}C NMR Spectra and Electron Impact Mass Spectra of 1-Substituted Pyrrolidines (**3**)

Product	IR (Kbr or neat) (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$); δ	MS (70 eV) *m/z* (%)
3d-d_2	3019, 2980, 2868, 1619, 1522, 1365, 1189, 1169, 801	1.90–1.97 (m, 4H, CH_2), 2.24 (s, 3H, CH_3), 3.16–3.24 (m, 2H, N-CHD), 6.47 (*app* d, 2H, H_{arom}, J = 8.5), 7.02 (*app* d, 2H, H_{arom}, J = 8.5)	20.2, 25.2, 47.4 (t, J = 20.76), 111.7, 124.3, 129.5, 146.0	163(M^+, 89), 162(100), 161(63), 160(9), 159(4), 135(5), 120(5), 119(10), 118(11), 106(37), 91(13)
3e	2960, 2867, 1653, 1622, 1447, 1383, 1286, 1174, 1102	1.21 (d, 12H, CH_3), 1.95–2.05 (m, 4H, CH_2), 3.12–3.35 (m, 6H, N-CH_2+CH), 7.03–7.15 (m, 3H, H_{arom})	24.5, 26.6, 28.0, 52.7, 123.8, 126.2, 142.8, 150.0	231(M^+, 74), 230(53), 216(20), 190(100), 188(22), 146(27), 144(8), 132(15), 130(8), 91(7)
3f	2964, 1608, 1573, 1502, 1487, 1373, 1220, 1166, 1082, 1052	1.92–2.00 (m, 4H, CH_2), 3.22–3.30 (m, 4H, N-CH_2), 3.78 (s, 3H, CH_3O), 6.00–6.27 (m, 3H, H_{arom}), 7.05–7.27 (m, 1H, H_{arom})	25.3, 47.5, 55.0, 97.8, 100.4, 104.8, 129.7, 149.2, 160.6	177(M^+, 75), 176(100), 174(4), 149(6), 148(6), 134(8), 121(21), 107(5), 92(7), 77(5)
3h	2973, 2877, 1519, 1498, 1463, 1358, 1280, 1000	1.90–2.05 (m, 4H, CH_2), 3.30–3.45 (m, 4H, N-CH_2), 6.22–6.36 (m, 1H, H_{arom}), 6.70–6.86 (m, 1H, H_{arom})	25.0, 49.6 (d, J = 4.2), 107.5 (m), 110.6 (dd, J_1 = 18.3, J_2 = 3.1), 135.1 (m), 138.5 (*app* t, J = 14.8), 140.7 (*app* dd, J_1 = 10.4, J_2 = 3.2), 143.4 (*app* t, J = 14.8), 145.5 (*app* dd, J_1 = 10.2, J_2 = 2.2)	201(M^+, 80), 200(100), 199(12), 198(11), 197(7), 169(6), 159(13), 158(72), 145(76), 138(10), 138(10), 131(26)
3k	2968, 2873, 1591, 1480, 1354, 1297, 1146, 1111, 1037, 743	1.95–2.05 (m, 4H, CH_2), 3.18–3.32 (m, 4H, N-CH_2), 6.41 (ddd, 1H, H_{arom}, J_1 = 6.0, J_2 = 2.4, J_3 = 0.8), 6.51 (t, 1H, H_{arom}, J = 2.2), 6.61 (ddd, 1H, H_{arom}, J_1 = 5.0, J_2 = 1.1, J_3 = 0.8), 7.1 (*app* t, 1H, H_{arom}, J = 8.0)	25.4, 47.5, 109.8, 111.4, 115.0, 130.0, 135.0, 148.8	183(M^+, 25), 182(32), 181 (M^+, 54), 180(87), 146(24), 140(18), 139(10), 138(47), 127(38), 125(100), 117(12), 113(11), 111(29), 77(12), 75(17)
3m	2969, 2843, 1653, 1622, 1593, 1552, 1495, 1458s, 1371, 1246, 1170, 1090, 982	1.90–2.02 (m, 4H, CH_2), 3.15–3.25 (m, 4H, N-CH_2), 6.42 (ddd, 1H, H_{arom}, J_1 = 8.3, J_2 = 2.4, J_3 = 0.9), 6.64 (t, 1H, H_{arom}, J = 2.0), 6.73 (*app* ddd, 1H, H_{arom}, J_1 = 8.0, J_2 = 2.0, J_3 = 0.9), 7.02 (*app* t, 1H, H_{arom}, J = 8.0)	25.3, 47.5, 110.2, 114.2, 117.9, 123.2, 130.2, 148.9	227(M^+, 68), 226(95), 225(M^+, 70), 224(100), 199(4), 197(4), 184(8), 182(8), 171(17), 169(17), 157(8), 155(8), 117(7), 91(4), 90(5)
3n	2973, 2874, 2821, 1568, 1455, 1368, 1330, 1170, 1061	1.18 (d, 12H, CH_3), 1.95–2.05 (m, 4H, CH_2), 3.05–3.25 (m, 6H, N-CH_2+CH), 7.38 (s, 2H, H_{arom})	24.3, 26.5, 28.0, 52.6, 92.2, 133.4, 142.9, 152.9	357(M^+, 91), 356 (54), 342(19), 316(100), 314(25), 301(16), 187(48), 173(17), 172(26), 158(15), 144(15), 139(10), 115(10), 43(8)
3o	2975, 2875, 1712, 1600, 1500, 1450, 1369, 1299, 1229, 1130, 1084	1.85–1.95 (m, 4H, CH_2), 3.15–3.25 (m, 4H, N-CH_2), 3.84 (s, 3H, CH_3), 6.67 (*app* dt, 1H, H_{arom}, J_1 = 8.0, J_2 = 1.0), 6.74 (*app* dd, 1H, H_{arom}, J_1 = 8.5, J_2 = 0.7), 7.21–7.32 (m, 1H, H_{arom}), 7.55 (dd, 1H, H_{arom}, J_1 = 7.8, J_2 = 1.7)	25.5, 50.5, 51.6, 113.6, 115.3, 116.7, 130.7, 131.4, 147.6, 169.2	205(M^+, 55), 201(10), 190(100), 177(40), 174(24), 172(15), 170(12), 154(44), 146(17), 145(40), 117(13), 105(28), 91(14), 77(34)
3p	2966, 1656, 1603, 1524, 1466, 1405, 1286vs, 1186	1.95–2.05 (m, 4H, CH_2), 2.50 (s, 3H, CH_3), 3.28–3.38 (m, 4H, N-CH_2), 6.48 (*app* d, 2H, H_{arom}, J = 8.8), 7.84 (*app* d, 2H, H_{arom}, 2H, H_{arom}, J = 8.8)	25.3, 47.4, 110.5, 124.7, 130.5, 150.8, 196.1	189(M^+, 52), 188(25), 174(100), 146(20), 145(8), 144(8), 133(17), 132(9), 118(10), 117(10), 105(10), 104(9), 91(11), 77(8)
3q	2976, 1602, 1573, 1522, 1464, 1405, 1344, 1292, 1252, 1158, 1109	1.90–2.05 (m, 4H, CH_2), 3.13–3.25 (m, 4H, N-CH_2), 6.65–6.75 (m, 1H, H_{arom}), 6.89 (dd, 1H, H_{arom}, J_1 = 8.8, J_2 = 1.2), 7.31–7.41 (m, 1H, H_{arom}), 7.72 (dd, 1H, H_{arom}, J_1 = 8.3, J_2 = 1.7)	25.6, 50.2, 115.3, 115.8, 126.6, 132.8, 136.9, 142.6	192(M^+, 34), 175(55), 158(5), 157(9), 145(94), 144(100), 131(9), 119(17), 117(23), 104(42), 91(13), 77(18)
3r	2979, 1627, 1614, 1522, 1481, 1381, 1345, 1312, 1250, 1150	1.95–2.10 (m, 4H, CH_2), 3.22–3.35 (m, 4H, N-CH_2), 6.74 (ddd, 1H, H_{arom}, J_1 = 8.3, J_2 = 2.4, J_3 = 0.8), 7.20–7.30 (m, 2H, H_{arom}), 7.40 (ddd, 1H, H_{arom}, J_1 = 8.1, J_2 = 2.1, J_3 = 0.9)	25.4, 47.7, 105.5, 109.6, 117.2, 129.4, 148.1, 149.2	192(M^+, 82), 191(100), 164(7), 146(21), 145(30), 144(8), 136(36), 130(5), 117(7), 104(11), 91(8), 90(10), 77(9)

Table 2 (continued)

Product	IR (Kbr or neat) (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$); δ	MS (70 eV) *m/z* (%)
3s	2976, 1602, 1573, 1522, 1464, 1405, 1362, 1292, 1194, 1109, 1044	2.00–2.12 (m, 4H, CH_2), 3.30–3.42 (m, 4H, N-CH_2), 6.44 (*app* d, 2H, H_{arom}, *J* = 9.3), 8.07 (*app* d, 2H, H_{arom}, *J* = 9.3)	25.4, 47.9, 110.4, 126.2, 136.4, 151.8	192(M^+, 95), 191(100), 176(5), 164(11), 162(18), 146(20), 145(50), 144(10), 136(31), 130(6), 120(5), 117(7), 106(9), 90(5)
3u	2936, 2850, 1620, 1454, 1388, 1137, 1077	1.10–1.30 (m, 6H, CH_2), 1.55–2.05 (m, 8H, CH_2), 2.50–2.63 (m, 5H, N-CH_2+N-CH)	23.0, 25.0, 25.9, 32.0, 51.3, 63.6	153(M^+, 76), 152(15), 124(11), 111(37), 110(100), 108(6), 97(30), 96(31), 84(13), 70(20), 69(13), 68(8), 55(7)

Some ^1H multiplets are characterised by the term *app* (apparent): this refers only to their appearance and may be an oversimplification. Elemental analysis were performed with a Carlo Erba Mod. 1106 elemental analyser and were in satisfactory agreement with calculated values. Mps were determined with an automatic Mettler (Mod. FP61) and are not corrected. Boiling points refer to the central cut of small distillations and are uncorrected.

_N_-Substituted Pyrrolidines (3); General Procedure

A THF (25 mL) solution of 2,5-dimethoxytetrahydrofuran (**2**, 2.99 mL, 23.1 mmol) and 2.5M H_2SO_4 (17.80 mL, 44.5 mmol) was added dropwise (ca. 20 min) to an open vessel containing a solution of the appropriate amine **1** (17.8 mmol) in MeOH/THF (40 mL; 1:1) and some $NaBH_4$ pellets or half-broken caplets (one every ca. 4 min, to a total of approximately 2.70 g, 71 mmol) were added under vigorous magnetic stirring at ca. 10 °C. The mixture, under stirring, was then allowed to warm up to r.t. over 90 min, then it was diluted with H_2O (30 mL), made strongly alkaline (cooling) with NaOH pellets (3.0 g) and extracted with Et_2O (3 × 30 mL). Preliminary acid-base treatment of the residue removed pyrrole **4**: the combined extracts were treated with a 6M aq HCl (30 mL). The aqueous phase, containing the hydrochloride of **3**, was washed with Et_2O (2 × 15 mL), basified and extracted with Et_2O (3 × 20 mL) from which the product **3** was recovered after washing with brine (30 mL) and drying (Na_2SO_4). Final purification yielded products as specified in Table 1.

In the case of alkyl amines **1t** and **1u**, the procedure was the same, but the amount and concentration of the acid were varied: 3M H_2SO_4 (11.9 mL, 35.6 mmol) was used.

$NaBD_4$ pellets (prepared by us from the powder using the same procedure as for KBr pellets in IR analysis) instead of $NaBH_4$ were used in the synthesis of 2,5-dideuterio-1-(4'-methylphenyl)pyrrolidine (**3d**-d_2). The ^1H NMR spectrum of **3d**-d_2 showed a percentage of deuteration identical with the purity of $NaBD_4$ used (96%).

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References

(1) Coleman, G. H.; Nicholas, G.; Martens, T. F.; *Org. Synth. Col.*; Vol. III, 1955, p 159.
Livingston, R. In *Rodd's Chemistry of Carbon Compounds*; Coffey, S., Ed.; Elsevier: Amsterdam, 1973; Vol. IVa, p 379.
Bird, C. W.; Cheeseman, G. W. H.; Synthesis of Five-membered Rings with One Heteroatom. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C.W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 89.

(2) (a) Farbenind, I. G. *Ger. Pat.* 637730/1936 (*Chem. Abstr.* **1937**, *31*, 2616[1]).
(b) Yur'ev, Yu. K.; Tronova, V. A.; L'vova, N. A.; Bukshpan, Z. Ya. *J. Gen. Chem.* **1941**, *11*, 1128.
(c) Walkup, R. E.; Searles, S. Jr. *Tetrahedron* **1985**, *41*, 101.

(3) Farbenind, I. G. *Fr. Pat.* 851178/1940 (*Chem. Abstr.* **1942**, *36*, 1957[2]).
Yur'ev, Yu. K.; Levi, I. S. *Vestnik Moskov. Univ., Ser. Mat. Mekh., Astron., Fiz. i Khim.* **1956**, *11*, 153 (*Chem. Abstr.* **1958**, *52*, 355c).
Hargis, D. C. *U.S. Pat.* 4626592/1986 (*Chem. Abstr.* **1987**, *106*, 156270f).
Hargis, D. C. *U.S. Pat.* 4721810/1988 (*Chem. Abstr.* **1988**, *108*, 186309j).

(4) Elderfield, R. C.; Hageman, H. A. *J. Org. Chem.* **1949**, *14*, 605.
Badische Anilin- & Soda- Fabrik *Ger. Pat.* 803903/1951 (*Chem. Abstr.* **1951**, *45*, 8046h).
Murayama, K.; Morimura, S. *Ann. Rept. Takamine Lab.* **1954**, *6*, 6.
Hillers, S.; Vasserman, Kh. M.; Venter, K. K. *Voprosy Ispol'zovan. Pentozansoderzhashachego Syr'ya, Trudy Vsesoyuz. Soveshchaniya, Riga* **1955**, 393 (*Chem. Abstr.* **1959**, *53*, 15075i).
Wellcome Foundation Ltd. *Belg. Pat.* 616609/1962 (*Chem. Abstr.* **1963**, *58*, 11335e).
Philips A. P.; Burrows, R. B. *U.S. Pat.* 3075975/1963 (*Chem. Abstr.* **1963**, *59*, 1603f).

(5) (a) Reppe, W.; Schuster, C.; Weiss, E. *U.S. Pat.* 2421650/1947 (*Chem. Abstr.* **1947**, *41*, 5552d).
(b) Yur'ev, Yu. K.; Korobitsyna, I. K.; Ben-Yakir, R. D.; Savina, L. A.; Akishin, P. A. *Vestnik Moskov. Univ. 6, No. 2, Ser. Fiz.-Mat. i Estestven. Nauk* **1951**, *1*, 37 (*Chem. Abstr.* **1953**, *47*, 124f).
(c) Yur've, Yu. K.; Arbatskii, A. V.; Korobitsyna, I. K.; Andreev, V. M. *Zhur. Priklad. Khim.* **1955**, *28*, 781.
(d) Yur've, Yu. K.; Arbatskii, A. V.; Korobitsyna, I. K.; Andrev, V. M. *J. Appl. Chem. U.S.S.R.* **1955**, *28*, 745.
(e) Tsuji, Y.; Yokoyama, Y.; Huh, K. T.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3456.

(6) (a) Sommers, A. H. *J. Am. Chem. Soc.* **1956**, *78*, 2439.
(b) Shapiro, S. L.; Freedman, L.; Soloway, H. *U.S. Pat.* 3218328/1965 (*Chem. Abstr.* **1966**, *64*, 5044g).

(7) Badische Anilin- & Soda- Fabrik *Ger. Pat.* 812552/1951 (*Chem. Abstr.* **1953**, *47*, 3352i).

(8) (a) Reynolds, D. D.; Kenyon, W. O. *J. Am. Chem. Soc.* **1950**, *72*, 1597.

(b) Reynolds, D. D.; Kenyon, W. O. *U.S. Pat.* 2581443/1952 (*Chem. Abstr.* **1952**, *46*, 7125h).
(9) March, J. In *Advanced Organic Chemistry – Reactions, Mechanisms, and Structure*; Third ed.; John Wiley & Sons: New York, 1985; p 1043 and references cited therein.
(10) (a) Späth, E.; Kuffner, F.; Platzer, N. *Ber.* **1935**, *68B*, 935.
(b) LuValle, J. E.; Glass, D. B.; Weissberger, A. *J. Am. Chem. Soc.* **1948**, *70*, 2223.
(c) Nair, M. D.; Adams, R. *J. Am. Chem. Soc.* **1961**, *83*, 3518.
(d) Farhat, K. *U.S. Pat.* 3480617/1969 (*Chem. Abstr.* **1970**, *72*, 31647g).
(e) Ibata, T.; Isogami, Y.; Toyoda, J. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 42.
(f) Ibata, T.; Shang, M.; Demura, T. *Heterocycl. Commun.* **1995**, *1*, 241.
(11) Suga, K.; Watanabe, S.; Pan, T. P.; Fujita, T. *Chem. Ind.* **1969**, 78.
Suga, K., Watanabe, S., Fujita, T., Pan, T. P. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3606.
Bhaskar Kanth, J. V.; Periasamy, M. *J. Org. Chem.* **1993**, *58*, 3156.
(12) Rice, L. M.; Reid, E. E.; Grogan, C. H. *J. Org. Chem.* **1954**, *19*, 884.
Vystrcil, A.; Cerny, J. *Chem. Listy* **1958**, *52*, 494.
Schreiber, K. C.; Fernandez, V. P. *J. Org. Chem.* **1961**, *26*, 1744.
(13) (a) Bocz, A. K. *Chem. Ber.* **1966**, *99*, 1923.
(b) Mitsubishi Petrochemical Co., Ltd. *Jpn. Kokai Tokkyo Koho JP 59* 88464/1984 (*Chem. Abstr.* **1984**, *101*, 171087s).
(c) Mori, S.; Minafuji, M.; Nomura, Y. *Jpn. Kokai Tokkyo Koho JP 63* 27486/1988 (*Chem. Abstr.* **1988**, *109*, 110248p).
(d) Champion, D. H.; Knifton, J. F.; Su, W. Y. *U.S. Pat.* 4892959/1990 (*Chem. Abstr.* **1991**, *115*, 49388q).
(14) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* **1977**, *42*, 2082.
(15) (a) Wibaut, J. P. *Rec. Trav. Chim.* **1925**, *44*, 1101.
(b) Craig, L. C.; Hixon, R. M. *J. Am. Chem. Soc.* **1931**, *53*, 187.
(c) Yur'ev, Yu. K.; Shen'yan, F. F. *J. Gen. Chem. U.S.S.R.* **1934**, *4*, 1258.
(d) Signaigo, F. K.; Adkins, H. *J. Am. Chem. Soc.* **1936**, *58*, 709.
(e) Adkins, H.; Coonrad, H. L. *J. Am. Chem. Soc.* **1941**, *63*, 1563.
(16) Giumanini, A. G.; Verardo, G.; Gei, M. H.; Lassiani, L. *J. Labelled Compd. Radiopharm.* **1987**, *24*, 255.
Verardo, G.; Giumanini, A. G.; Favret, G.; Strazzolini, P. *Synthesis* **1991**, *6*, 447.
Verardo, G.; Giumanini, A. G.; Strazzolini, P.; Poiana, M. *Synthesis* **1993**, *1*, 121.
Verardo, G.; Giumanini, A. G.; Strazzolini, P. *Synth. Commun.* **1994**, *24*, 609.
Verardo, G.; Toniutti, N.; Giumanini, A. G. *Tetrahedron* **1997**, *53*, 3707.
(17) (a) Shim, S. C.; Huh, K. T.; Park, W. H. *Tetrahedron* **1986**, *42*, 259.
(b) Shim, S. C.; Woo, B. W.; Doh, C. H.; Choi, K. N.; Yeo, Y. K. *Taehan Hwahakoe Chi* **1990**, *34*, 641 (*Chem. Abstr.* **1991**, *114*, 206928).
(18) Nelsen, S. F.; Weisman, G. R. *Tetrahedron. Lett.* **1973**, 2321.
(19) Wollweber, H.; Stoltefuss, J.; Berschauer, F.; De Jong, A.; Scheer, M. *Eur. Pat.* 289850 A2/1988 (*Chem. Abstr.* **1989**, *110*, 154143).
(20) Giumanini, A. G.; Verardo, G.; Bruckner, S.; Malpezzi, L.; Cerioni, G. *J. Mol. Struct.* **1994**, *232*, 139.
(21) Vogel, A. In *Vogel's Textbook of Practical Organic Chemistry, including Quantitative Organic Analysis*, 4th ed.; revised by Furniss, B. S., Hannaford, A. J., Roger, V., Smith, P. W. G., Tatchell, A. R.; Longman: New York, 1978; p 909.