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A convenient route to 1-benzyl 3-aminopyrrolidine and 3-aminopiperidine

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Abstract—1-Benzyl 3-aminopyrrolidine **1** and 1-benzyl 3-aminopiperidine **2** were prepared rapidly mainly in aqueous conditions in 55 and 75% yields, respectively, on a multi-gram scale starting from inexpensive and commercially available starting materials. The key step involved the Curtius rearrangement mediated by sodium nitrite and trifluoroacetic acid of the appropriate acylhydrazides. All the reactions (except LAH reductions) were performed in water.

The well-known 3-aminopyrrolidine and 3-aminopiperidine heterocycles have become attractive synthetic targets[1] due to the increasing demand as building blocks in bioactive compounds (i.e. receptor ligands of the central nervous system,[2] quinolone antibacterials,[3] and antitumoral compounds[4]). The optically active forms of their 1-substituted derivatives have been successfully used as chiral ligands,[5] and their complexes with transition metals have been sometimes characterized.[6] In our continuing interest for studying serotoninergic and cholinergic neurotransmission,[7] we were interested in those two building blocks **1** and **2**, especially the 3-aminopiperidine (Fig. 1).

A variety of syntheses have been reported for these compounds. However, each has one or more drawbacks: (1) Syntheses via direct cyclization of a *N*-protected amino acid[8] or related compounds[9] are multi-step and remain cumbersome to reproduce, thus lacking in practicability for a multi-gram production. (2) Preparations involving functional transformations of a 3-substituted pyrrolidine[10,11] or piperidine[12] require expensive starting materials. (3) Hydrogenation of pyridine derivatives[13] suffers from low yields. (4) Nucleophilic substitution with ring enlargement of 2-substituted pyrrolidines[14] yields mixtures of five- and six-membered ring heterocycles. Only one industrial synthesis of the five-membered ring amine seems attractive although it involves a high pressure reaction.[15] Herein we report on a simple and practical synthesis of 1-benzyl 3-aminopyrrolidine **1** and 1-benzyl 3-aminopiperidine **2** from commercially available lactam **3** and nipecotate **4a**, respectively. Cost, practicability, speed, waste disposal and simplicity of purification have all been factors considered in the choice of methods, reagents and solvents.

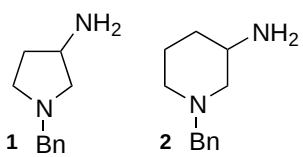

Fig. 1.

The strategy we envisaged was based on the well-known Hofmann[16] and Curtius[17] rearrangements of acid derivatives into primary amines (with one less carbon atom). Amide **5**[18] was prepared in 72% yield by treatment of the methyl ester **3**[19] with aqueous ammonia (Scheme 1). The Hofmann rearrangement was studied under different conditions (Table 1). Using standard reagents, i.e. NaOH and Br_2[16] (entry 1) or NaOCl in the presence of NaOH[16] (entry 2), aminolactam **6** was obtained in 47 and 50% yields, respectively. Attempts to carry out the reaction with *N*-bromosuccinimide and DBU[20] (entry 3) failed. Due to the waste generated on large scale reactions, lead tetraacetate[21] was not chosen as a possible reagent for the rearrangement.

Over the past 25 years hypervalent iodine reagents have often found use in the Hofmann rearrangement,[22] par-

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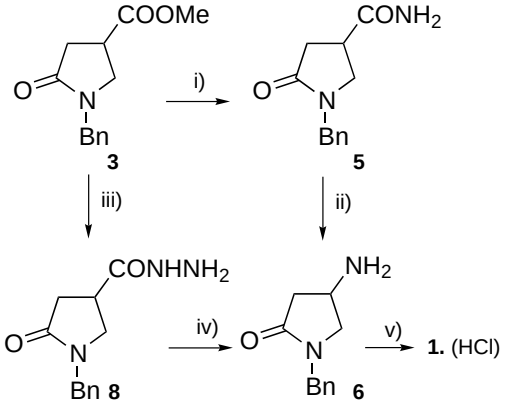
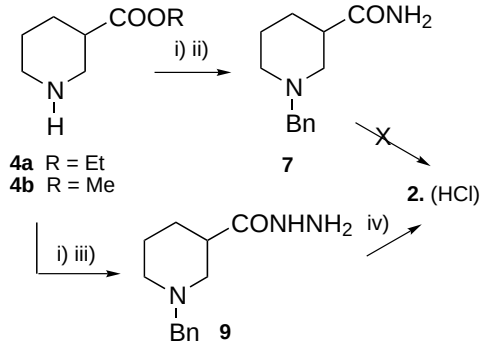


Scheme 1. *Reagents and conditions*: (i) NH_4OH (28%), 12 h, 72%; (ii) $PhI(OAc)_2$, H_2O/MeCN (1/1), rt, 1 h, 75%; (iii) $NH_2NH_2{\cdot}H_2O$ (10 equiv.), MeOH, reflux, 2 h, 99%; (iv) $NaNO_2$, TFA, H_2O, 0°C, 1 h, then 80°C, 1 h, 70%; (v) $LiAlH_4$, THF, reflux, 3 h, 80%. Compound **1** was isolated as its monohydrochloride (recrystallized from iPrOH/iPr$_2$O).

ticularly bis(trifluoroacetoxy)iodobenzene (referred to as PIFA) sometimes in combination with pyridine as a catalyst.[23] Phenyliododiacetate (PIDA)[24] was shown to be synthetically equal to PIFA but superior in terms of cost, stability, use in milder acidic conditions, and avoidance of pyridine. The treatment of amide **5** with PIDA (entry 4) afforded the aminolactam **6** (hydrochloride form) in 70–77% reproducible yield.[25]

By comparison, the use of PIFA led to a complete recovery of the starting material **5** (entry 5). Pyridine activation was not attempted since this amine complicates the final purification. Reduction of **6** with lithium aluminum hydride[26] (80% yield) completed the rapid three-step preparation of 1-benzyl-3-aminopyrrolidine **1**, in an overall yield of 43% from methyl ester **3**.

Application of the same methodology (Scheme 2) to the synthesis of 1-benzyl 3-aminopiperidine **2** was limited by the availability of the amide **7**. Indeed, reactions of a concentrated methanolic solution of ammonia (7N) onto the ethyl ester **4a** in the presence of NaCN[27] gave a 1/1 mixture of the expected amide **7** and of the methyl ester **4b**. Treatment of the crude material with aqueous ammonia (28%) afforded amide **7** as the sole product in



Scheme 2. *Reagents and conditions*: (i) $PhCH_2Br$, Na_2CO_3, CH_2Cl_2/H_2O (2/1), reflux, 3 h, 95%; (ii) NH_3 (7N), MeOH, NaCN, 55°C, 2 days, then NH_4OH (28%), 14 h, 50%; (iii) $NH_2NH_2{\cdot}H_2O$ (10 equiv.), MeOH, reflux, 4 h, 99%; (iv) $NaNO_2$, TFA, H_2O, 0°C, 1 h, then 80°C, 1 h, 80%. Compound **2** was isolated as its monohydrochloride (precipitated from Et_2O).

50% yield. Attempts to carry out the Hofmann rearrangement on amide **7** with PIDA as described above failed.

Curtius rearrangement is a good alternative to the Hofmann rearrangement to prepare primary amines from carboxylic acids. Reaction of sodium azide onto the acid chloride is often the most satisfactory method.[17] This procedure is usually carried out in an inert solvent (toluene or chloroform) to isolate the isocyanate or in an alcohol, to afford the corresponding carbamate. The hydrolysis of these intermediates give the expected primary amines. If yields are generally high, this multi-step sequence has the major drawbacks of requiring an organic solvent, anhydrous conditions and being lengthy.

With the aim of simplicity of the synthetic process, we reinvestigated Curtius rearrangement under the original conditions,[28] using the acylhydrazides **8** and **9**. These latter compounds were quantitatively prepared from the corresponding methyl and ethyl esters, respectively, **3** and **4a**.[29] The rearrangement was studied under hydrolytic conditions using sodium nitrite in the presence of different aqueous acids, in order to isolate directly the primary amines. Relevant results are shown in Table 2.

Table 1. Hofmann rearrangement of amide **5**

Entry	Reagents (equiv.)	Conditions		Yields[a] (%)
		Solvent(s) ratio (v/v)	Temp. (°C), time (h)	
1	NaOH (6), Br_2 (1.2)	H_2O	0–70, 3	47
2	NaOCl[b] (1.9), NaOH (4)	H_2O	60, 24	50
3	NBS (2), DBU (3)	H_2O/MeCN (2:1)	Reflux, 0.25	[c]
4	$PhI(OAc)_2$ (1.33)	H_2O/MeCN (1:1)	rt, 1	75[d]
5	$PhI(OCOCF_3)_2$ (1.33)	H_2O/MeCN (1:1)	rt, 12	[c]

[a] Isolated yield.
[b] 12.5% NaOCl.
[c] Starting material.
[d] Average of four runs.

Table 2. Curtius rearrangement of acylhydrazides **8** and **9**

Entry	Substrate	Conditions[a]		Yield[b] (%)
		Reagents (equiv.)	Temp. (°C), time (h)	
1	**8**	$NaNO_2$ (4), H_2SO_4 (2.4)	60, 14	50
2	**8**	$NaNO_2$ (1.1), H_2SO_4 (1.1)	50, 14	68
3	**8**	$NaNO_2$ (1.5), TFA (3)	80, 1	70[c]
4	**9**	$NaNO_2$ (1.5), HCl (3)	80, 1	57
5	**9**	$NaNO_2$ (1.5), H_2SO_4 (2.1)	80, 1	45
6	**9**	$NaNO_2$ (1.5), TFA (3)	80, 1	74
7	**9**	$NaNO_2$ (1.5), TFA (3)	80, 1	80[d]

[a] The reactions were carried out in H_2O (concentration of **8** or **9**: 0.4 M). Sodium nitrite and the acid were added at 0°C and the resulting mixture was stirred for 1 h at rt before heating until gas evolution ceased.
[b] Isolated (average of three runs).
[c] The same yield was obtained on a 10 g scale reaction.
[d] The reaction was carried out on a 10 g scale in H_2O (concentration of **9**: 0.8 M).

Formation of 1-benzyl 4-aminopiperidine from the corresponding hydrazide was previously reported with a 43% yield.[13] Under the described conditions for the 3-substituted piperidine acylhydrazide **9** using hydrochloric acid (Table 2, entry 4), we obtained the 3-aminopiperidine **2** in 57% yield. No improvement was observed if HCl was substituted for sulfuric acid (45%, entry 5). The highest yields of aminopiperidine **2** (74%, average of three runs) were obtained using sodium nitrite in conjunction with trifluoroacetic acid.[30]

From substrate **8**, comparable results were obtained using the different acidic conditions. The combination $NaNO_2$/TFA proved to be a superior reagent to carry out the Curtius rearrangement (Table 2, entries 6 and 7). On a 10 g scale, aminolactam **6** and amine **2** were isolated as their monohydrochloride salts in 70 and 80%, respectively (entries 3 and 7). It appears that trifluoroacetic acid improves the yield significantly. To the best of our knowledge this acid has never been employed for the Curtius rearrangement. No reaction occurred with acetic acid (data not shown). The three-step hydrazide rearrangement sequence allowed us to synthesize pyrrolidine **1** and piperidine **2** on a preparative scale. It should be pointed out that each reaction, including the rearrangement step, affords a very clean product (>95% pure by ^1H NMR) and no purification is required to perform the next reaction.

In summary, this study has proven to be a potent addition to the existing methods for the synthesis of important building blocks for medicinal chemistry: 1-benzyl-3-aminopyrrolidine **1**, 1-benzyl-4-amino-2-pyrrolidone **6** and 1-benzyl-3-aminopiperidine **2**. This work provides full characterizations of compounds (including synthetic intermediates). The major benefits of this synthetic approach include amounts of the compounds prepared from inexpensive starting materials and reagents, less than 2 days work, very simple three-step sequence taking place in 55, 70, 75% yields, respectively, the easiness of isolation and the conditions safe for the environment. The use of PIDA for the Hofmann rearrangement can be advantageous when the starting amide is easily available. Finally, reassessment of the Curtius rearrangement under the original aqueous conditions showed that trifluoroacetic acid/sodium nitrite is the tailor-made couple to perform the reaction in high yields for a straightforward isolation of primary amines.

Acknowledgements

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    1-Benzyl-5-oxo-pyrrolidine-3-carboxamide **5**: A mixture of ester **3** (10 g, 43 mmol) was stirred overnight with ammonium hydroxide (46 ml, 28%) at rt. Filtration yielded amide **5** as a white solid (6.8 g, 72%); mp 166°C ($MeOH/Et_2O$); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.69 (dd, $J=9.7$, 16.9 Hz, 1H), 2.79 (dd, $J=8.0$, 16.9 Hz, 1H), 3.09 (qt, $J=8.8$ Hz, 1H), 3.43 (dd, $J=9.9$, 8.8 Hz, 1H), 3.54 (dd, $J=7.0$, 9.9 Hz, 1H), 4.38 (d, $J=14.7$ Hz, 1H), 4.56 (d, $J=14.7$ Hz, 1H), 5.6 (br s, NH_2), 7.24–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 35.2, 37.3, 47.0, 49.3, 128.2, 128.6, 129.2, 136.3, 172.7, 174.4; IR (KBr): 3340, 3168, 1676, 1636, 1444, 1292 cm^{-1}; MS m/z (rel. int.): 218 (18), 190 (18), 146 (36), 118 (55), 106 (30), 91 (100), 86 (98). Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.48; H, 6.54; N, 12.72%.
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    4-Amino 1-benzylpyrrolidin-2-one **6**:
    From hydrazide **8**: To a solution of hydrazide **8** (13 g, 55.7 mmol) in water (100 ml) was added successively trifluoroacetic acid (13 ml, 167.2 mmol) and $NaNO_2$ (5.8 g, 83.6 mmol) at 0°C. The mixture was gradually heated at 80°C until gas evolution ceased. Aqueous sodium hydroxide (30 ml, 6N) was then added to the mixture. The aqueous layer was extracted with CH_2Cl_2 (2×150 ml), then EtOAc (3×150 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford **6** as a yellow oil (7.4 g, 70 %); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (br s, NH_2), 2.21 (dd, $J=4.7$, 16.9 Hz, 1H), 2.73 (dd, $J=7.5$, 16.9 Hz, 1H), 2.94 (dd, $J=4.0$, 10.0 Hz, 1H), 3.47 (dd, $J=6.6$, 10.0 Hz, 1H), 3.66 (m, 1H), 4.46 (s, 2H), 7.24–7.53 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 40.3, 44.0, 45.6, 54.9, 127.8, 128.1, 135.6, 172.7; IR (NaCl): 3428, 1684, 1442, 1210, 1134 cm^{-1}; MS m/z (rel. int.): 190 (12), 120 (28), 91 (41), 59 (28), 58 (24), 45 (100). Anal. calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.11; H, 7.50; N, 15.06%.
    From amide **5**: $PhI(OAc)_2$ (982 mg, 3.05 mmol) was added to a solution of amide **5** (500 mg, 2.29 mmol) in H_2O (20 ml) and MeCN (20 ml). The mixture was stirred for 1 h at rt before adding H_2O (10 ml), then HCl (2 ml, 37%). The aqueous layer was washed with CH_2Cl_2 and water was removed under vacuum to give the hydrochloride of **6** (407 mg, 78 %); mp 200°C; ^1H NMR (D_2O, 400 MHz): δ 2.55 (dd, $J=3.4$, 18.1 Hz, 1H), 2.98 (dd, $J=18.1$, 8.6 Hz, 1H), 3.38 (dd, $J=3.0$, 12.0 Hz, 1H), 3.74 (dd, $J=12.0$, 7.4 Hz, 1H), 4.03 (m, 1H), 4.32 (d, $J=15$ Hz, 1H), 4.52 (d, $J=15$ Hz, 1H), 7.23–7.43 (m, 5H); ^{13}C NMR (D_2O, 62.5 MHz): δ 36.0, 43.8, 46.8, 51.3, 128.6, 129.4, 135.4, 173.8; IR (KBr): 3046, 2938, 2878, 1680 cm^{-1}.
26. 1-Benzyl-pyrrolidin-3-ylamine **1**: A solution of amide **6** (11 g, 57.8 mmol) in dry THF (330 ml) was added slowly at rt to a suspension of $LiAlH_4$ (4.4 g, 115.6 mmol) in dry THF (330 ml). The mixture was refluxed for 3 h under N_2, cooled to rt, and carefully treated with water (4.4 ml), aqueous sodium hydroxide (15%, 4.4 ml) and water (13.2 ml). The mixture was dried over Na_2SO_4 and concentrated under reduced pressure to afford **1** as a yellow oil (8 g, 80%). ^1H NMR ($CDCl_3$, 400 MHz) was identical to the one previously described.[11] The monohydrochloride of **1** was recrystallized from iPrOH/$(i$Pr$)_2O$. **1**·HCl: ^1H NMR (D_2O, 400 MHz): δ 1.72 (m, 1H), 2.22 (m, 1H),

2.60 (m, 1H), 2.80 (m, 1H), 3.07 (m, 1H), 3.72 (m, 1H), 3.76 (br s, 2H), 7.10–7.35 (m, 5H); ^{13}C NMR (D_2O, 62.5 MHz): δ 28.3, 48.1, 52.7, 55.5, 58.9, 129.8, 130.1, 130.6, 130.7.

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1-Benzyl-5-oxo-pyrrolidine-3-carbohydrazide **8**: Methyl 1-benzyl-5-oxo-pyrrolidine-3-carboxylate **3** (15 g, 64 mmol), hydrazine monohydrate (30 ml, 640 mmol) and methanol (20 ml) were stirred under reflux for 2 h. After cooling, the solvent and excess of hydrazine were removed under vacuum to afford **8** as a white solid (14.9 g, 99%); mp 150°C (from MeOH/Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.65 (dd, J=9.6, 16.8 Hz, 1H), 2.78 (dd, J=8.1, 16.8 Hz, 1H), 3.00 (qt, J=8.5 Hz, 1H), 3.40 (dd, J=9.6, 8.9 Hz, 1H), 3.45 (br s, NH_2), 3.50 (dd, J=7.1, 9.7 Hz, 1H), 4.37 and 4.55 (AB, J_{AB}=14.7 Hz, 1H), 7.2–7.4 (m, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 35.0, 36.2, 47.0, 49.3, 128.2, 128.5, 129.2, 136.2, 172.6, 173.3; IR (KBr): 3298, 3188, 3164, 1644, 1624 cm^{-1}; MS m/z (rel. int.): 233 (32), 217 (6), 173 (7), 145 (15), 91 (100). Anal. calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found C, 61.78; H, 6.52; N, 17.86.

1-Benzyl-piperidine-3-carbohydrazide **9**: The same procedure, starting from ester **4a** (23 g, 93 mmol) and using ethanol as the solvent, afforded hydrazide **9** as a viscous oil (20.5 g, 95%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.51–1.68 (m, 3H), 1.83 (br s, 1H), 2.24 (m, 1H), 2.33 (m, 1H), 2.50 (m, 1H), 2.66–2.70 (m, 2H), 3.41 (d, J=6.4 Hz, 1H), 3.49 (d, J=6.4 Hz, 1H), 3.86 (br s, NH_2), 7.24–7.34 (m, 5H), 9.01 (br s, NH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 23.0, 26.8, 40.9, 53.7, 54.6, 59.8, 63.3, 127.3, 128.1, 129.1, 137.5, 175.2; IR (NaCl): 3292, 1654, 1626 cm^{-1}; MS m/z (rel. int.): 233 (40), 217 (35), 202 (10), 174 (15), 142 (20), 106 (15), 91 (100). HRMS calcd for $C_{13}H_{19}N_3O$: 233.1528. Found: 233.1530.

30. 1-Benzyl-piperidin-3-ylamine **2**: To a solution of hydrazide **9** (9.5 g, 40.7 mmol) in water (50 ml) was added successively trifluoroacetic acid (9.4 ml, 122.1 mmol) and $NaNO_2$ (4.2 g, 61.1 mmol) at 0°C. The mixture was gradually heated until gas evolution ceased. Aqueous sodium hydroxide (22 ml, 6N) was then added to the mixture. The aqueous layer was extracted with CH_2Cl_2 (2×100 ml), then EtOAc (3×150 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford **2** as a yellow oil (6.2 g, 80 %); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (m, 1H), 1.53 (m, 1H), 1.68 (m, 1H), 1.80 (m, 1H), 1.94 (m, 1H), 2.08 (m, 1H), 2.56 (m, 1H), 2.63 (br s, NH_2), 2.72 (br d, $J\sim$9.6 Hz, 1H), 2.91 (m, 1H), 3.45 and 3.49 (AB, J_{AB}=13.2 Hz, 2H), 7.21–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 23.3, 33.1, 47.8, 53.4, 61.7, 63.0, 126.9, 128.1, 129.0, 138.3; IR (NaCl): 3350, 3278, 2934, 2796 cm^{-1}; MS m/z (rel. int.): 190 (5), 172 (14), 147 (21), 134 (16), 91 (100). The monohydrochloride of **2** was precipitated from Et_2O. **2**·HCl: mp 160°C; ^{1}H NMR (D_2O, 400 MHz): δ 1.29 (m, 1H), 1.49 (m, 1H), 1.91 (m, 1H), 2.11 (m, 2H), 2.81 (br d, $J\sim$11.8 Hz, 1H), 2.99 (br d, $J\sim$10.1 Hz, 1H), 3.12 (m, 1H), 3.61 and 3.63 (AB, J_{AB}=12.8 Hz, 2H), 7.3–7.4 (m, 5H); ^{13}C NMR (D_2O, 62.5 MHz): δ 20.9, 26.3, 45.7, 51.9, 52.3, 61.7, 128.2, 129.7, 130.9, 131.7; IR (KBr): 3422, 2930, 2872, 2750, 1610, 1530 cm^{-1}. Anal. calcd for $C_{12}H_{19}ClN_2$: C, 63.56; H, 8.45; N, 12.35. Found: C, 63.76; H, 8.46; N, 12.14%.