Reductive One Batch Synthesis of *N*-Arylpiperidines From Primary Amines and Glutaraldehyde

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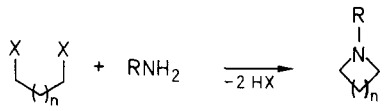
The construction of the piperidine ring about an aromatic nitrogen atom, by a 5C + N reductive condensation reaction, using glutaraldehyde (pentanedial) and sodium borohydride in acidic water/methanol medium is described. The reaction is fast, affords good to excellent yields and appears insensitive to electronic effects and severe steric hindrance; it is found to be compatible with a large variety of aryl substituents, including nitro and oxo groups.

In principle, the methods to produce cyclic amines can be distinguished by the types and sizes of the fragments to be joined, and by the type of reaction employed to perform the cyclization.[1]

The synthesis of middle sized cyclic amines, an important endeavor in many synthetic fields for which a number of procedures are available,[2-6] is performed by the nC + 1N scheme from a reactive C_n molecule suitably functionalized at both ends and a primary amine by a displacement reaction (Gabriel synthesis) and variations thereof.



This route is particularly convenient because a large selection of amines can be made available to yield *N*-substituted piperidines (n = 5). If the terminal carbons exhibit a higher oxidation state the process must be either a condensative–reductive or a redutive–condensative one.

We have decided to apply our *N*-permethylation procedure,[7-8] with any necessary adaptation, to piperidine ring synthesis, using a primary amine function of aromatic amines bearing a variety of substituents. The expectation was that aromatic amines, with a wide range of nitrogen and ring reactivity, would provide the most challenging substrate for experimentation. Previous methods applying the glutaraldehyde condensation–reduction approach were: a multistep synthesis;[9] a procedure using iron pentacarbonyl in a carbon monoxide atmosphere;[10] and another employing sodium cyanoborohydride.[11]

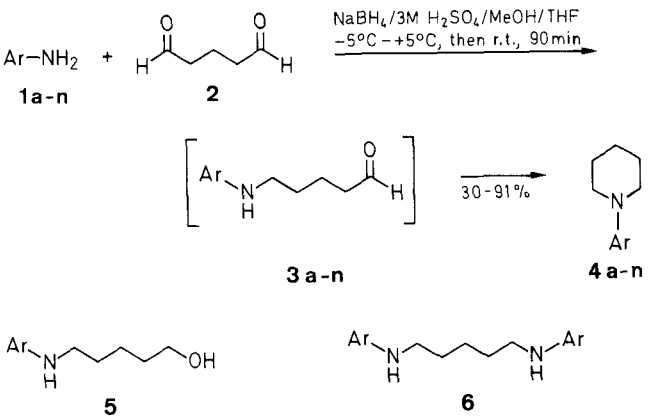
The reaction was tested on the simplest system, i.e. benzeneamine **(1a)** using the cheap and readily available glutaraldehyde **(2)**, which is commercially available in the form of a concentrated aqueous solution (titre: 25% or 50%). Table 1 gathers the results obtained by a very narrow parametrization of the experimental variables. The "best" conditions, as appearing in the experiment 17 of Table 1, were directly applied to the preparative reactions collected in Table 2 without any further systematic individual attempt of improving either the yields or other reaction variables. The reaction was remarkably successful, free of any experimental complications and fast. A preliminary investigation of the side products did not evidence the presence of any 5-(arylamino)-1-pentanol **5**, but of *N,N'*-diaryl-1,5-pentanediamine **6**, which confirmed the high rate at which imines are formed and reduced in this reactive environment.

It was reported that a reductive route using **2** and tetracarbonylhydridoferrate gave yields of *N*-arylpiperidines in the range 77–89% with aromatic amines as reactive partners with the notable exception of the complete failure with 2-chlorobenzeneamine,[10] but no amine with electron-withdrawing groups in any position was shown to undergo the reaction, which required long reaction times and a carbon monoxide blanket. Our reaction performed invariably well with any type of substituent of widely different electronic effect and was totally indifferent to very severe steric hindrance, i.e. **4d**.

Table 1. Preparation of 1-Phenylpiperidine (**4a**)

Run[a]	$NaBH_4$[b] (mmol)	3M H_2SO_4 (mmol)	**2** (25%, mmol)	Solvent (mL)	Temp.[c] (°C)	Time[d] (min)	Yield[e] (%)
1	21	27	7.8	THF (25)	−10	30	76
2	21[f]	27	7.8	THF (25)	−10	30	68
3	21	27	7.8	THF (25)	−10	90	81
4	21	27	7.8	THF (25)	−5–(+)5	30	75
5	21[g]	27	7.8	THF (25)	−10	30	65
6	21[h]	27	7.8	THF (25)	−10	30	51
7	26	27	7.8	THF (25)	−10	30	77
8	21	27	10.0	THF (25)	−10	30	76
9	21	27	7.8	THF (50)	−10	30	77
10	21	27	7.8	THF (25)	−20	30	64
11	21	27	7.8	Et_2O (25)	−10	30	67
12	21	26.8[i]	7.8	THF (25)	−10	30	64
13	21	13.5[j]	7.8	THF (25)	−10	30	67
14	21	32.4[k]	7.8	THF (25)	−10	30	68
15	21	27	7.8	THF/MeOH 10/15)	−10	30	79
16	21	27	7.8	THF/MeOH (10/15)	−5–(+)5	30	80
17	21	27	7.8	THF/MeOH (10/15)	−5–(+)5	90	94

[a] In all the experiments 5.38 mmol of aniline (**1a**) dissolved in THF (10 mL) was used. For the full procedure see experimental part.
[b] Unless otherwise stated $NaBH_4$ in pellet form was used.
[c] Temperature of addition of the solution of **2**.
[d] Time of reaction at r.t. after mixing of reactants.
[e] GC yields based on amine **1a**.
[f] All of the $NaBH_4$ was present from the beginning of the addition of **2**.
[g] Finely powdered $NaBH_4$ was used.
[h] The inverse addition procedure (**1a** and powdered $NaBH_4$ slurry in THF to the **2**/H_2SO_4/THF solution) was followed.
[i] In this run 6M H_2SO_4 (26.8 mmol) was used.
[j] In this run 1.5M H_2SO_4 (13.5 mmol) was used.
[k] In this run 37% HCl (32.4 mmol) was used.



1–4	Ar	**1–4**	Ar
a	Ph	**h**	4-$MeO_2CC_6H_4$
b	4-MeC_6H_4	**i**	2-$MeO_2CC_6H_4$
c	2-MeC_6H_4	**j**	4-$MeOCC_6H_4$
d	2,6-*i*-$Pr_2C_6H_3$	**k**	4-CNC_6H_4
e	4-$MeOC_6H_4$	**l**	4-$O_2NC_6H_4$
f	4-BrC_6H_4	**m**	3-$O_2NC_6H_4$
g	2-ClC_6H_4	**n**	2-$O_2NC_6H_4$

A few general conclusive remarks seem convenient. Reported procedures to make *N*-arylpiperidines from piperidine require either the presence of activated halogens (ar-S_N2)[20,22,25,28,30–35] or the activation of the nucleophile used as an alkali salt excess on aryl halides (ar-S_N2 and/or benzyne reactions).[12,29,36–38] Whereas the limitations of the scope of the former reactions are obvious, the latter is beleaguered by the unavoidable occurrence of isomers, the incidence of redox reactions and other inconveniences. The route 5C + N in the 1,5-dibromopentane version is definitively disappointing in quantitative terms, linked to a sufficient basicity of the amine and is very sensitive to steric hindrance.[16,19] None of these problems affect our procedure, which is very convenient from the points of view of costs, reagents availability and handling, product yield and recovery, and reaction conditions. A time consuming procedure directly using 1,5-pentanediol on an activated catalyst at very high temperatures to yield moderate yields of substituted alkyl aromatic piperidines was found to be incompatible with the presence of halogens in the ring.[39] An improvement of the cyclization of 1,5-pentanediol about a few aliphatic and aromatic amines was achieved by the use of a sacrificial ruthenium catalyst,[13] but an oxygen free atmosphere, special equipment, high temperatures and long reaction times characterize the procedure.

All the aromatic amines **1** used in this work, $NaBH_4$ pellets (8 mm diameter) and powder, were purchased from Aldrich Chimica S.r.l., Milano, Italy. Compound **2** (25% aqueous solution) was obtained from Fluka Chemie AG, Buchs, Switzerland. All solvents used were laboratory grade and were used without any purification. Alumina (neutral) was purchased from BDH Italia S.r.l., Milano, Italy.

Gas chromatographic (GC) analyses were performed with a fused silica capillary column (30 m long, 0.32 mm i.d., Supelchem® SE-54, film thickness 0.25 μm) assembled on a Perkin–Elmer Sigma 10 gas chromatograph, using the ion source of the mass spectrometer as a detector. GC quantitative determinations were performed by means of suitable internal standard after independent determination of

Table 2. 1-Arylpiperidines **4**[a] Prepared

Product	Yield[b] (%)	mp[c] (°C) or bp[c] (°C)/Pa	Lit. mp (°C) or bp (°C)/Pa	IR (KBr or neat) ν (cm^{-1})	^{1}H-NMR($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
4a	90	117/1700	99/27,[10] 119–120/1729,[12] 81/120[13]	2914, 2830, 2778, 1597, 1498, 1450, 1382, 1235, 1220, 1130, 1120, 1022, 917, 753, 689	1.35–1.90 (m, 6H), 2.94–3.28 (m, 4H), 6.66–7.42 (m, 5H)	161 (M^+, 75), 160 (100), 132 (33), 120 (46), 105 (66), 104 (64), 91 (28), 77 (63), 51 (39)
4b	82	127/1520	56/93,[10] 130.5–131/1596,[12] 140.8–142/2128[14]	2910, 2840, 2780, 1615, 1510, 1450, 1371, 1235, 1210, 1130, 920, 857, 808	1.43–1.91 (m, 6H), 2.25 (s, 3H), 2.93–3.21 (m, 4H), 6.75–7.18 (m, 4H)	175 (M^+, 87), 174 (100), 160 (7), 146 (16), 134 (29), 119 (54), 118 (37), 105 (13), 91 (49), 65 (20)
4c	79	117/1340	44/27,[10] 115–116/1330[15]	2900, 2820, 2770, 1598, 1488, 1448, 1376, 1225, 1121, 1103, 1050, 1024, 920, 755, 720	1.40–1.90 (m, 6H), 2.29 (s. 3H), 2.70–2.99 (m, 4H), 6.83–7.28 (m, 4H)	175 (M^+, 85), 174 (100), 146 (48), 132 (38), 119 (44), 118 (82), 91 (67), 65 (50)
4d	40[d] 85[d,e]	96/21		2940, 2910, 2840, 2770, 1440, 1383, 1337, 1267, 1235, 1195, 1120, 1050, 978, 805, 758	1.19 (d, 12H, J = 7.03), 1.51–1.89 (m, 6H), 2.89–3.18 (m, 4H), 3.48 (sept, 2H, J = 6.88), 7.08 (s, 3H)	245 (M^+, 96), 244 (100), 230 (35), 202 (26), 190 (86), 188 (36), 177 (33), 176 (77), 160 (19), 146 (52), 132 (43), 91 (20), 84 (23), 41 (29)
4e	69	36	37[16]	2910, 2830, 2800, 2765, 1505, 1440, 1380, 1270, 1240, 1178, 1037, 1022, 915, 820, 791	1.40–1.96 (m, 6H), 2.89–3.18 (m, 4H), 3.76 (s, 3H), 6.76–6.97 (m, 4H)	191 (M^+, 95), 190 (62), 176 (100), 162 (3), 150 (8), 135 (17), 134 (9), 120 (22)
4f	86	77	77,[17] 76[18]	2920, 2840, 2800, 1587, 1490, 1440, 1340, 1278, 1240, 1220, 1121, 1020, 912, 855, 802	1.37–1.88 (m, 6H), 2.96–3.14 (m, 4H), 6.77 (d, 2H, J = 9.04), 7.30 (d, 2H, J = 9.28)	241 (M^+, 84), 240 (94), 239 (M^+, 88), 238 (100), 200 (20), 198 (21), 185 (39), 184 (35), 183 (39), 182 (30), 157 (20), 155 (20), 130 (11), 76 (19)
4g	85	120/920	125/931[19]	2915, 2830, 2780, 1587, 1478, 1450, 1440, 1381, 1231, 1128, 1108, 1037, 1024, 751, 741	1.40–1.94 (m, 6H), 2.76–3.12 (m, 4H), 6.75–7.44 (m, 4H)	197 (M^+, 41), 196 (73), 195 (M^+, 71), 194 (100), 154 (25), 141 (24), 140 (41), 139 (66), 138 (63), 125 (15), 111 (38)
4h	90	100	92–95[20]	2920, 2810, 1700, 1605, 1432, 1388, 1355, 1281, 1245, 1187, 1105, 958, 912, 824, 767, 690	1.49–1.92 (m, 6H), 3.20–3.45 (m, 4H), 3.85 (s, 3H), 6.83 (d, 2H, J = 9.27), 7.89 (d, 2H, J = 9.04)	219 (M^+, 87), 218 (100), 204 (6), 190 (11), 188 (37), 178 (29), 163 (23), 162 (11), 132 (55), 104 (12), 77 (21)
4i	86	94/20	218/101 080[21]	2918, 1725, 1597, 1488, 1447, 1380, 1296, 1250, 1227, 1212, 1113, 1080, 1050, 1025, 757	1.40–1.89 (m, 6H), 2.86–3.12 (m, 4H), 3.87 (s, 3H), 6.80–7.78 (m, 4H)	219 (M^+, 52), 204 (100), 190 (36), 188 (25), 186 (76), 158 (82), 148 (30), 132 (38), 105 (27), 84 (32), 77 (65)
4j	90	89	87–88,[20] 78–80[22]	2900, 2815, 1651, 1600, 1420, 1385, 1351, 1280, 1260, 1242, 1221, 1192, 1125, 913, 815	1.45–1.88 (m, 6H), 2.49 (s, 3H), 3.18–3.52 (m, 4H, 6.81 (d, 2H, J = 9.03), 7.84 (d, 2H, J = 9.03)	203 (M^+, 91), 202 (85), 188 (100), 174 (9), 162 (15), 146 (9), 132 (48), 104 (10), 91 (9), 77 (18), 43 (18)
4k	89	56	54–55,[20] 52–54[22]	2910, 2820, 2782, 2100, 1620, 1507, 1445, 1380, 1247, 1220, 1178, 1120, 910, 810	1.47–1.98 (m, 6H), 3.08–3.58 (m, 4H), 6.81 (d, 2H, J = 9.03), 7.44 (d, 2H, J = 9.27)	186 (M^+, 81), 185 (100), 171 (9), 157 (21), 145 (49), 131 (21), 130 (66), 129 (68), 116 (18), 102 (62), 75 (15), 55 (16)
4l	91	104	103–103.5,[23] 102–103,[24] 105[25]	2910, 1595, 1505, 1471, 1305, 1241, 1195, 1105, 815, 750	1.40–1.92 (m, 6H), 3.15–3.71 (m, 4H), 6.76 (d, 2H, J = 9.40), 8.07 (d, 2H, J = 9.40)	206 (M^+, 88), 205 (100), 165 (22), 159 (35), 150 (25), 120 (13), 119 (10), 104 (9), 77 (18)
4m	90	142/80	140/80[26,27]	2910, 2820, 2790, 1618, 1525, 1487, 1450, 1385, 1347, 1240, 1132, 990, 950, 870, 751, 732	1.35–1.97 (m, 6H), 3.06–3.39 (m, 4H), 7.03–7.78 (m, 4H)	206 (M^+, 87), 205 (100), 177 (6), 165 (31), 160 (19), 159 (40), 150 (36), 119 (11), 104 (27), 92 (10), 77 (29)
4n	30 69[e]	80	81,[28] 77.5–78.5[29]	2910, 2830, 2790, 1604, 1515, 1485, 1448, 1380, 1341, 1295, 1231, 1128, 924, 850, 747	1.40–2.01 (m, 6H), 2.84–3.17 (m, 4H), 6.81–7.86 (m, 4H)	206 (M^+, 21), 189 (100), 171 (18), 159 (49), 158 (50), 144 (27), 130 (31), 119 (15), 104 (40)

[a] Reaction condition as in experiment 17, Table 1.
[b] Yield of pure isolated product.
[c] Melting and boiling points are not corrected.
[d] Satisfactory microanalyses obtained: C, H, N ±0.20.
[e] Twice the amount of **2** was used in this experiment.

area/weight calibration factor. Mass spectra (MS) in the electronic impact positive ions mode were obtained with a Finnigan 1020 mass spectrometer equipped with a conventional source operating at 70 eV, a quadrupole filter and detector of ions, data system and library. IR spectra were recorded on a JASCO Infrared Spectrophotometer mod. DS-702G. ^{1}H-NMR spectra were obtained from a Bruker WP-80 SY spectrometer. Table 2 collects relevant physical and MS data of all amines **4** prepared.

N-Arylpiperidine (4); General Procedure:

The cyclization reaction is essentially carried out for all the amines studied as follows. A MeOH/THF (25 mL; 3:2) solution of **2** (25%; 3.0 mL, 7.8 mmol) and 3 M H_2SO_4 (9 mL, 27 mmol) is added dropwise to an open vessel containing a solution of the appropriate amine **1** (5.38 mmol) in THF (10 mL) and some $NaBH_4$ pellets, more of which (to a total of approximately 0.80 g, 21 mmol) are added, as soon as the former are consumed, under vigorous magnetic stirring at 0°C (± 5°C). The mixture is then allowed to warm up to r.t. during 90 min, then it is diluted with H_2O (10 mL) and made strongly alkaline with NaOH pellets (cooling). A *t*-BuOMe extract of the mixture (3 × 30 mL) is dried (Na_2SO_4), the solvents are removed by distillation and the residue is conveniently (distillation and/or recrystallization and/or absorption chromatography on neutral alumina, using mixtures of hexane/CH_2Cl_2) treated for product separation. Preliminary acid–base separation of amines from neutral compounds was not very convenient and led to material lossess; in some cases the dried ether extract might instead be treated with gaseous HCl in a dry atmosphere to obtain the corresponding ammonium salts, from which the free amines can be released. Scaling the reaction, up to larger amounts did not pose any particular problem.

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