Facile preparation of acetals and enol ethers derived from 1-arylpiperidin-4-ones

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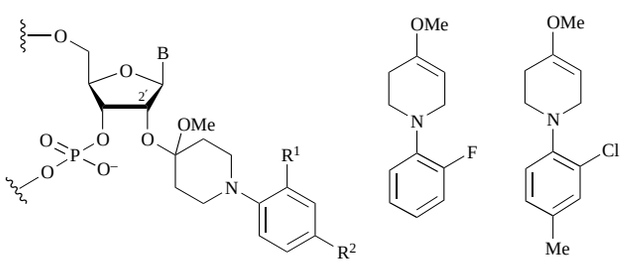
When primary aromatic amines 6 are heated under reflux with slight excesses each of crude 1,5-dichloropentan-3-one 4 and toluene-4-sulfonic acid monohydrate in dry methanol solution, and an excess of trimethyl orthoformate is then added to the reactants, the corresponding 1-arylpiperidin-4-one dimethyl acetals 9 are obtained in good (74–81%) overall yields. The dimethyl acetals 9 undergo hydrolysis in formic acid–water (9 : 1 v/v) at room temperature to give the parent 1-arylpiperidin-4-ones 8 in virtually quantitative yields. When the dimethyl acetals 9 are allowed to react with an excess each of *N*,*N*-diisopropylethylamine and boron trifluoride–diethyl ether complex in dichloromethane solution at 0 °C they are converted in good yields into the corresponding enol ethers 10, which are required as reagents in the solid phase synthesis of oligoribonucleotides.

Introduction

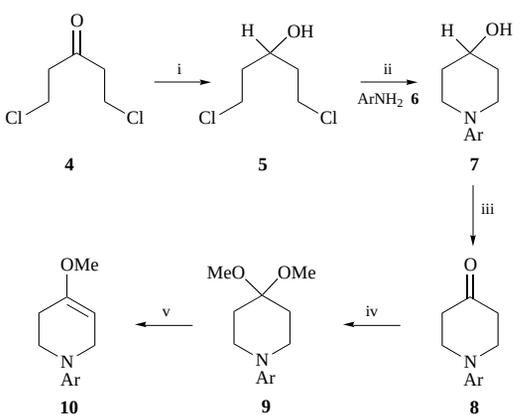
We have developed an automated solid phase synthesis of oligo- and poly-ribonucleotides (RNA sequences)[1–3] in which the 2′-hydroxy functions of the ribonucleoside residues are protected with 1-aryl-4-methoxypiperidin-4-yl groups,[4] such as the 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl (Fpmp)[5] and 1-(2-chloro-4-methylphenyl)-4-methoxypiperidin-4-yl (Ctmp)[4] groups (as in **1a** and **1b**, respectively).



1a R^1 = F, R^2 = H
b R^1 = Cl, R^2 = Me

2 **3**

The reagents required[4,5] for the introduction of these acetal protecting groups are 1-(2-fluorophenyl)- and 1-(2-chloro-4-methylphenyl)-4-methoxy-1,2,5,6-tetrahydropyridines (**2** and **3**, respectively). As no completely general method was available for the preparation of 1-arylpiperidin-4-ones **8** when we started our work on synthesis of RNA sequences, we developed[5] the procedure indicated in outline in Scheme 1. We showed[6] many years ago that 1,5-dichloropentan-3-one **4** can be prepared in virtually quantitive yield by allowing 3-chloropropionyl chloride to react with ethylene in the presence of aluminium chloride in dichloromethane solution. 1,5-Dichloropentan-3-one **4** is a relatively unstable compound which tends to decompose on distillation;[6] however, the crude material can be reduced with sodium borohydride to give[5,7] 1,5-dichloropentan-3-ol **5**, which is a stable distillable liquid, in good yield. In the presence of potassium carbonate and sodium iodide, 1,5-dichloropentan-3-ol **5** reacts[5] with a variety of primary aromatic amines ($ArNH_2$ **6**) in DMF solution at 100 °C to give the corresponding 1-arylpiperidin-4-ols **7** in satisfactory to good yields. The latter compounds **7** can be converted[5,8] into 1-arylpiperidin-4-ones **8** by Moffatt oxidation.[9] When the corresponding dimethyl acetals **9**, which are prepared[4,5] from the ketones **8** in the usual way, are heated with a catalytic



Scheme 1 *Reagents and conditions:* i, $NaBH_4$, EtOH, H_2O; ii, K_2CO_3, NaI, DMF, 100 °C; iii, DCC, CF_3CO_2H, Me_2SO, C_5H_5N, C_6H_6; iv, $CH(OMe)_3$, $TsOH.H_2O$, MeOH, reflux; v, TsOH (*ca.* 1.0 mol%), 150 °C, *ca.* 20 mmHg

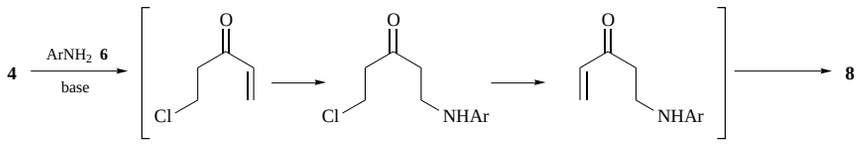
quantity of toluene-4-sulfonic acid (TsOH), the required enol ether reagents **10** (*e.g.* **2** and **3**) are obtained.[4,5]

Results and discussion

We have always believed that, if the right experimental conditions could be found, it should be possible to shorten the above enol ether synthesis (Scheme 1) by two steps [*i.e.* the reduction and oxidation steps; steps (i) and (iii), respectively]. We have now succeeded in avoiding the reduction and oxidation steps, and report a one pot conversation of primary aromatic amines **6** into 1-arylpiperidin-4-one dimethyl acetals **9** in very good overall yields. We also describe a much improved procedure for the conversion of the dimethyl acetals **9** into the enol ether reagents **10**.

We first tried to react 1,5-dichloropentan-3-one[6] **4** with a primary aromatic amine in the presence of a relatively strongly basic tertiary amine (*e.g.* triethylamine) in the hope of effecting a series of two elimination and two Michael addition reactions according to Scheme 2. However, under such basic conditions, considerable darkening occurred and none of the desired 1-arylpiperidin-4-one **8** could be detected in the products.

The situation was quite different when the primary aromatic amine and 1,5-dichloropentan-3-one **4** were heated together in the absence of an additional base. After some preliminary



Scheme 2

Table 1 Preparation of 1-arylpiperidin-4-one acetals **9**, ketones **8** and enol ethers **10**[a]

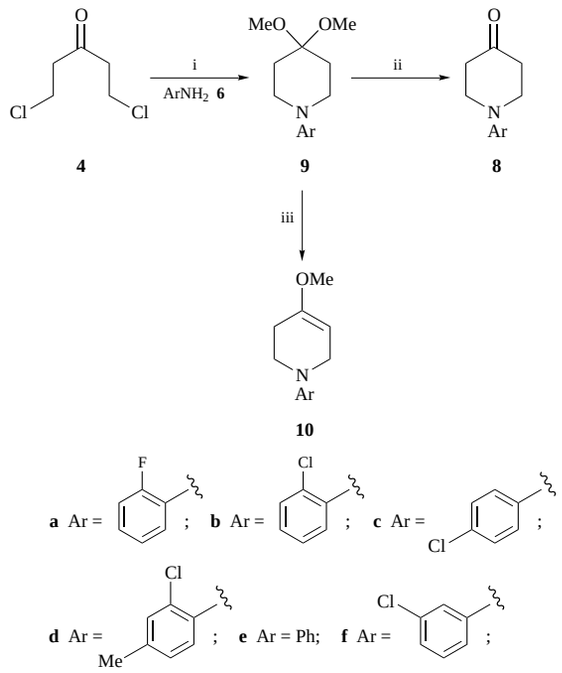
Entry	Starting material	Product	Yield (%)	Mp(bp)/°C
1	**6a**	**9a**	81	72–73
2	**6b**	**9b**	74	67–68
3	**6c**	**9c**	77	109–111
4	**6d**	**9d**	81	62–63
5	**6e**	**9e**	75	34–36 (136–138 at 34–36 1 mmHg)
6	**6f**	**9f**	76	— (148–150 at 1 mmHg)
7	**9a**	**8a**	99	67–68
8	**9c**	**8c**	99	57–58
9	**9e**	**8e**	99	38–39
10	**9a**	**10a** (≡ **2**)	83	30–31
11	**9d**	**10d** (≡ **3**)	85	55–57
12	**9f**	**10f**	72.5	— (153–156 at 1 mmHg)

[a] See Scheme 3 and Experimental section for full experimental details.

experiments, it was found that when the primary aromatic amine was heated, under gentle reflux, with a *ca.* 10% excess each of crude 1,5-dichloropentan-3-one **4** and toluene-4-sulfonic acid monohydrate in dry methanol for 2-4 h, a mixture of 1-arylpiperidin-4-one **8** and its dimethyl acetal **9** was obtained. An excess of trimethyl orthoformate was then added (Scheme 3) and heating was continued for a further period of 1 h. Little or no darkening of the reaction solution was observed and the 1-arylpiperidin-4-one dimethyl acetal **9** was obtained as virtually the sole product. Indeed, the overall isolated yields of the mainly crystalline dimethyl acetals **9** were 74–81% (Table 1), based on the primary aromatic amines **6** as starting materials. Thus our original procedure[5] (Scheme 1) for the preparation of the dimethyl acetals **9** has essentially been shortened by three steps and the overall yields have been increased considerably.

The preparation of the dimethyl acetals **9a-f** (Table 1, entries 1–6) was carried out on a 0.1 molar scale but could be easily scaled up; thus these compounds have become readily accessible and relatively inexpensive provided that the primary aromatic amine starting materials **6** themselves are also inexpensive. Preliminary experiments have indicated[10] that if methanol and trimethyl orthoformate [Scheme 3, step (i)] are replaced by ethanol and triethyl orthoformate, 1-arylpiperidin-4-one diethyl acetals are obtained, also in very good yields. If the parent 1-arylpiperidin-4-ones **8** themselves are required, we believe that they are best prepared by first isolating the pure dimethyl acetals **9** and then subjecting them to acidic hydrolysis [Scheme 3, step (ii)]. Thus when dimethyl acetals **9a**, **9c** and **9e** were dissolved in formic acid–water (9:1 v/v) and the solutions were stirred at room temperature for 2 h, the corresponding ketones **8a**, **8c** and **8e** were obtained and isolated as colourless crystalline solids in virtually quantitive yields (Table 1, entries 7–9).

Our main purpose for undertaking the present study was to make the enol ethers **10** [particularly **10a** (≡**2**) and **10d** (≡**3**)], required for oligoribonucleotide synthesis,[1–3] more readily accessible.We had previously prepared[5] these reagents **10** by heating the corresponding dimethyl acetals **9** with a catalytic quantity of toluene-4-sulfonic acid at 150 °C under reduced pressure [Scheme 1, step (v)].These reaction conditions are rather drastic and often the enol ether **10** obtained was contaminated both with ketone **8** and starting material **9**. Gassman



Scheme 3 *Reagents and conditions:* i, $TsOH·H_2O$, MeOH, reflux, 2–4 h, then $CH(OMe)_3$, reflux, 1 h; ii, $HCO_2H–H_2O$ (9:1 v/v), room temp., 2 h; iii, Pr^i_2NEt, $Et_2O–BF_3$, CH_2Cl_2, 0 °C, 2–4 h

and his co-workers[11,12] have shown that when acetals are allowed to react with a slight (usually less than twofold) excess each of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and *N,N*-diisopropylethylamine (Hünig's base) in dichloromethane solution at a relatively low temperature (−20 to 25 °C), the corresponding enol ethers are obtained in high yields. This reaction appears to be general. Unfortunately, TMSOTf is an expensive reagent and its use would considerably increase the overall cost of preparing the enol ethers [such as **10a** (≡**2**) and **10d** (≡**3**)], which are required for oligoribonucleotide synthesis. We now report that boron trifluoride–diethyl ether complex, which on a molar basis is some 50–100 times cheaper than TMSOTf, is equally effective in the conversion of 1-arylpiperidin-4-one dimethyl acetals **9** into the corresponding enol ethers **10**.

We have prepared the three enol ethers **10a** (≡**2**), **10d** (≡**3**) and **10f** (Table 1, entries 10–12) that we believe at present[13] to be the most useful reagents for the introduction of 2′-protecting groups in the solid phase synthesis of RNA sequences. In each case, we started with 0.2 mol of the appropriate primary aromatic amine **6** which was converted [Scheme 3, step (i)] into the corresponding 1-arylpiperidin-4-one dimethyl acetal **9**. The crude acetals were then dissolved in dichloromethane and the resulting solutions were treated first with 2.4 molar equivalents (with respect to aromatic amine **6**) of Hünig's base followed by 2.0 molar equivalents of boron trifluoride–diethyl ether complex at 0 °C. The reactions [Scheme 3, step (iii)] were allowed to proceed for 2–4 h, and the enol ethers **10a** (≡**2**), **10d** (≡**3**) and **10f** (Table 1, entries 10–12) were all obtained in good yields. Furthermore, the enol ethers were all isolated in a higher state of purity than they had been obtained by the acid-catalysed extrusion procedure[4,5] [Scheme 1, step (v)]. There would appear to be little doubt that the Hünig's base/boron trifluoride–diethyl ether complex procedure for the conversation of

1-arylpiperidin-4-one dimethyl acetals **9** into the corresponding enol ethers **10** could readily be scaled up. It also seems likely that this procedure might find more general use in the conversion of acetals into enol ethers.

Experimental

Melting points were measured with a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 360 MHz with a Bruker AM 360 spectrometer; ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. Chemical shifts δ are given in ppm relative to tetramethylsilane and J values are given in Hz. Merck silica gel 60 F_{254} plates were developed in a solvent system consisting of light petroleum (bp 40–60 °C)–ethyl acetate (7:1 v/v). Triethylamine and *N,N*-diisopropylethylamine were dried by heating, under reflux, over calcium hydride, and were then distilled; dichloromethane was dried by distillation over phosphorus pentaoxide.

Preparation of 1-aryl-4,4-dimethoxypiperidines 9

Toluene-4-sulfonic acid monohydrate (20.92 g, 0.11 mol) and crude 1,5-dichloropentan-3-one[6] (17.05 g *ca*. 0.11 mol) were added to a stirred solution of primary aromatic amine **6** (0.10 mol) in dry methanol (100 cm^3). The reactants were then heated under gentle reflux. After an appropriate time (2 h for **6a–d**, 4 h for **6e** and 3 h for **6f**), trimethyl orthoformate (32.8 cm^3, 0.30 mol) was added, and the reactants were again heated under reflux. After a further period of 1 h, the products were cooled (ice–water bath) and triethylamine (46 cm^3, 0.33 mol) was added. The resulting mixture was evaporated under reduced pressure and the residue was partitioned between light petroleum (bp 40–60 °C, 150 cm^3) and saturated aqueous sodium hydrogen carbonate (150 cm^3). The organic layer was separated and the aqueous layer was back-extracted with light petroleum (bp 40–60 °C, 2 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give a crude product.

(a) The residual crude 1-aryl-4, 4-dimethoxypiperidines **9a–d**, derived from 2-fluoroaniline **6a**, 2-chloroaniline **6b**, 4-chloroaniline **6c** and 2-chloro-4-methylaniline **6d**, respectively, were dissolved in dry methanol (100 cm^3) and the solution was evaporated under reduced pressure. After this process had been repeated, the residue was redissolved in methanol (200 cm^3) at room temperature. Water (150 cm^3) was added dropwise over a period of 1 h, with stirring, to the resulting solution. Crystallisation was allowed to occur overnight at room temperature and then for a further period of 1 h at 0 °C (ice–water bath). The crystalline precipitates were then collected by filtration, washed with methanol–water (1:1 v/v) and dried *in vacuo* over sodium hydroxide pellets.

(b) Tridodecylamine (0.25 g, 0.48 mmol) was added to each of the crude 1-aryl-4,4-dimethoxypiperidines **9e** and **9f**, derived from aniline **6e** and 3-chloroaniline **6f**, respectively, and the crude materials were purified by distillation under reduced pressure (oil pump).

1-(2-Fluorophenyl)-4,4-dimethoxypiperidine 9a. Compound **9a** was obtained as a pale yellow crystalline solid (Found, from colourless material recrystallised from aqueous methanol and dried *in vacuo* over sodium hydroxide pellets: C, 65.21; H, 7.66; N, 5.70. Calc. for $C_{13}H_{18}FNO_2$: C, 65.25; H, 7.58; N, 5.85%) (19.45 g, 81%), mp 72–73 °C (lit.,[5] mp 69–70 °C); R_f 0.62; $\delta_H(CDCl_3)$ 1.95 (4 H, m), 3.10 (4 H, m), 3.24 (6 H, s), 6.89–7.07 (4 H, m); $\delta_C(CDCl_3)$ 32.7, 47.6, 47.9 (d, $J_{C,F}$ 3.3), 98.2, 116.1 (d, $J_{C,F}$ 20.9), 119.4 (d, $J_{C,F}$ 2.9), 122.3 (d, $J_{C,F}$ 7.9), 124.4 (d, $J_{C,F}$ 3.5), 140.3 (d, $J_{C,F}$ 8.5), 155.8 (d, $J_{C,F}$ 245.8).

1-(2-Chlorophenyl)-4,4-dimethoxypiperidine 9b. Compound **9b** was obtained as a pale yellow crystalline solid (Found, from colourless material recrystallised from aqueous methanol and dried *in vacuo* over sodium hydroxide pellets: C, 60.96; H, 7.01; N, 5.27. $C_{13}H_{18}ClNO_2$ requires: C, 61.05; H, 7.09; N, 5.48%) (18.97 g, 74%), mp 67–68 °C; R_f 0.68; $\delta_H(CDCl_3)$ 1.95 (4 H, m), 3.03 (4 H, m), 3.24 (6 H, s), 6.94 (1 H, m), 7.05 (1 H, m), 7.19 (1 H, m), 7.34 (1 H, m); $\delta_C(CDCl_3)$ 32.9, 47.6, 48.6, 98.4, 120.7, 123.5, 127.5, 129.0, 130.6, 149.6.

1-(4-Chlorophenyl)-4,4-dimethoxypiperidine 9c. Compound **9c** was obtained as a pale yellow crystalline solid (Found, from colourless material recrystallised from aqueous methanol and dried *in vacuo* over sodium hydroxide pellets: C, 61.07; H, 7.18; N, 5.30. $C_{13}H_{18}ClNO_2$ requires: C, 61.05; H, 7.09; N, 5.48%) (19.76 g, 77%), mp 109–111 °C; R_f 0.45; $\delta_H(CDCl_3)$ 1.88 (4 H, m), 3.20 (4 H, m), 3.23 (6 H, s), 6.85 (2 H, m), 6.89 (2 H, m); $\delta_C(CDCl_3)$ 32.1, 46.7, 47.6, 98.3, 117.7, 124.2, 128.9, 149.7.

1-(2-Chloro-4-methylphenyl)-4,4-dimethoxypiperidine 9d. Compound **9d** was obtained as a pale yellow crystalline solid (Found, from colourless material recrystallised from aqueous methanol and dried *in vacuo* over sodium hydroxide pellets: C, 62.30; H, 7.36; N, 5.05. $C_{14}H_{20}ClNO_2$ requires: C, 62.33; H, 7.47; N, 5.19%) (21.92 g, 81%), mp 62–63 °C; R_f 0.69; $\delta_H(CDCl_3)$ 1.94 (4 H, m), 2.26 (3 H, s), 2.99 (4 H, m), 3.23 (6 H, s), 6.97 (2 H, m), 7.17 (1 H, m); $\delta_C(CDCl_3)$ 20.8, 33.3, 47.9, 49.2, 98.8, 120.8, 128.4, 129.0, 131.3, 133.8, 147.5.

1-Phenyl-4,4-dimethoxypiperidine 9e. Compound **9e** was obtained as a pale yellow oil (16.65 g, 75%), bp 136–138 °C at 1 mmHg. This material was dissolved in light petroleum (bp 40–60 °C, 150 cm^3) and the solution was filtered through a short column of silica gel (20 g). The column was then washed with light petroleum (bp 40–60 °C)–ethyl acetate (98:2 v/v). The combined filtrate and washings were evaporated under reduced pressure, and the residue was redissolved in methanol (100 cm^3). The solution was cooled (ice–water bath) until crystallisation commenced. Water (100 cm^3) was then added dropwise over a period of 1 h to the stirred mixture at room temperature. Crystallisation was allowed to occur at room temperature overnight and then for a further period of 1 h at 0 °C (ice–water bath). The colourless crystalline precipitate of 1-*phenyl*-4,4-*methoxypiperidine* was collected by filtration and washed with cold methanol–water (1:1 v/v) (Found, from material dried *in vacuo* over sodium hydroxide pellets: C, 70.44; H, 8.63; N, 6.35. $C_{13}H_{19}NO_2$ requires: C, 70.56; H, 8.65; N, 6.33%), mp 34–36 °C; R_f 0.51; $\delta_H(CDCl_3)$ 1.89 (4 H, m), 3.22 (10 H, m), 6.82 (1 H, m), 6.93 (2 H, m), 7.24 (2 H, m); $\delta_C(CDCl_3)$ 32.4, 46.9, 47.8, 98.7, 116.7, 119.6, 129.3, 151.3.

1-(3-Chlorophenyl)-4,4-dimethoxypiperidine 9f. Compound **9f** was obtained as a pale yellow oil (HRMS: found M^+, 255.1028. $^{12}C_{13}{}^1H_{18}{}^{35}Cl^{14}N^{16}O_2$ requires *M*, 255.1026) (19.44 g, 76%), bp 148–150 °C at 1 mmHg; R_f 0.55; $\delta_H(CDCl_3)$ 1.86 (4 H, m), 3.22 (10 H, m), 6.77 (2 H, m), 6.88 (1 H, m), 7.13 (1 H, m); $\delta_C(CDCl_3)$ 32.0, 46.2, 47.6, 98.4, 114.3, 116.1, 118.9, 130.0, 134.9, 152.1.

Preparation of 1-arylpiperidin-4-ones 8

A solution of pure 1-aryl-4, 4-dimethoxypiperidine **9** (10 mmol) in formic acid–water (9:1 v/v; 10 cm^3) was stirred at room temperature. After 2 h, the products were evaporated to dryness under reduced pressure. The residue was evaporated under reduced pressure first with toluene (2 × 10 cm^3) and then with acetonitrile (2 × 10 cm^3), and was then crystallised from aqueous methanol.

1-(2-Fluorophenyl)piperidin-4-one 8a. Compound **8a** was obtained as colourless crystals (Found: C, 68.19; H, 6.09; N, 7.18. Calc. for $C_{11}H_{12}FNO$: C, 68.38; H, 6.26; N, 7.25%) (1.92 g, 99%), mp 67–68 °C (lit.,[5] 64 °C); R_f 0.44; $\delta_H(CDCl_3)$ 2.62 (4 H, t, *J* 6.1), 3.40 (4 H, t, *J* 6.0), 6.95–7.10 (4 H, m); $\delta_C(CDCl_3)$ 41.7, 50.8 (d, $J_{C,F}$ 3.0), 116.4 (d, $J_{C,F}$ 20.6), 119.7 (d, $J_{C,F}$ 2.3), 123.2 (d, $J_{C,F}$ 8.0), 124.6 (d, $J_{C,F}$ 3.5), 139.2 (d, $J_{C,F}$ 8.9), 155.7 (d, $J_{C,F}$ 245.7), 208.2.

1-(4-Chlorophenyl)piperidin-4-one 8c. Compound **8c** was obtained as colourless crystals (Found: C, 62.99; H, 5.64; N, 6.55. Calc. for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68%)

(2.07 g, 99%), mp 57–58 °C (lit.,[5] 55–56 °C); R_f 0.24; $\delta_H(CDCl_3)$ 2.54 (4 H, t, *J* 6.1), 3.57 (4 H, t, *J* 6.1), 6.89 (2 H, m), 7.24 (2 H, m); $\delta_C(CDCl_3)$ 40.6, 48.8, 117.1, 124.7, 129.3, 147.8, 207.8.

1-Phenylpiperidin-4-one 8e. Compound **8a** was obtained as colourless crystals (Found: C, 75.35; H, 7.45; N, 8.18. Calc. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%) (1.75 g, 99%), mp 38–39 °C (lit.,[14] 37–38 °C); R_f 0.32; $\delta_H(CDCl_3)$ 2.53 (4 H, t, *J* 6.2), 3.58 (4 H, t, *J* 6.1), 6.87 (1 H, m), 6.96 (2 H, m), 7.28 (2 H, m), $\delta_C(CDCl_3)$ 40.8, 48.7, 115.9, 119.9, 129.5, 149.2, 208.3.

Preparation of 1-aryl-4-methoxy-1,2,5,6-tetrahydropyridines 10

1-Aryl-4,4-dimethoxypiperidines **9** were prepared as above but on double the scale (*i.e.* from 0.20 mol of the primary aromatic amine **6**). After the addition of triethylamine, the products were evaporated under reduced pressure and then partitioned between light petroleum (bp 40–60 °C, 300 cm^3) and saturated aqueous sodium hydrogen carbonate (300 cm^3). The organic layer was separated, and the aqueous layer was back-extracted with light petroleum (bp 40–60 °C, 2 × 75 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was evaporated with toluene (2 × 50 cm^3) under reduced pressure and then dissolved in dichloromethane (300 cm^3). The solution obtained was cooled to 0 °C (ice–water bath) in an atmosphere of argon. Dry *N,N*-diisopropylethylamine (53.6 cm^3, 0.48 mol) was added, and then boron trifluoride–diethyl ether complex (49.2 cm^3, 0.40 mol) was added dropwise over a period of 5 min to the stirred solution maintained at 0 °C. After 2–4 h (3 h in the preparation of **10a**, 2 h in the preparation of **10d** and 4 h in the preparation of **10f**), the products were allowed to warm up to room temperature and were washed with saturated aqueous sodium hydrogen carbonate (500 cm^3). The organic layer was separated and the aqueous layer was back-extracted with dichloromethane (2 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Light petroleum (bp 40–60 °C, 300 cm^3) was added to the residue, and the resulting suspension was filtered through a bed of silica gel (20 g). The silica gel was washed with light petroleum (bp 40–60 °C)–ethyl acetate (98:2 v/v; 3 × 75 cm^3). The combined filtrate and washings were concentrated under reduced pressure, and the residue was co-evaporated with methanol (2 × 50 cm^3).

1-(2-Fluorophenyl)-4-methoxy-1,2,5,6-tetrahydropyridine 10a. The residue was dissolved in methanol (200 cm^3) and the solution was cooled to 0 °C (ice–water bath). After crystallisation had commenced, water (200 cm^3) was added slowly over a period of 2 h to the stirred, cooled suspension. After a further period of 4 h, pale yellow crystals of 1-(2-*fluorophenyl*)-4-*methoxy*-1,2,5,6-*tetrahydropyridine* **10a** (34.5 g, 83%) were collected by filtration and washed with cold methanol–water (1:1 v/v) (HRMS: found M^+, 207.1048. Calc. for $^{12}C_{12}{}^{1}H_{14}{}^{19}F{}^{14}N{}^{16}O$, 207.1059), mp 30–31 °C; R_f 0.85; $\delta_H(CDCl_3)$ 2.32 (2 H, m), 3.30 (2 H, t, *J* 5.8), 3.56 (3 H, s), 3.67 (2 H, m), 4.69 (1 H, m), 6.87–7.06 (4 H, m); $\delta_C(CDCl_3)$ 28.4, 48.1 (d, $J_{C,F}$ 3.1), 54.2, 91.4, 116.1 (d, $J_{C,F}$ 20.7), 119.4 (d, $J_{C,F}$ 2.7), 122.2 (d, $J_{C,F}$ 8.0), 124.4 (d, $J_{C,F}$ 3.4), 139.8 (d, $J_{C,F}$ 8.7), 154.2, 155.8 (d, $J_{C,F}$ 245.6).

1-(2-Chloro-4-methylphenyl)-4-methoxy-1,2,5,6-tetrahydropyridine 10d. The residue was recrystallised from methanol–water (1:1 v/v) in the same way as **10a** to give 1-(2-*chloro*-4-*methylphenyl*)-4-*methoxy*-1,2,5,6-*tetrahydropyridine* **10d** (40.7 g, 85%) (Found: C 65.51; H, 6.68; N, 5.75. Calc. for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; N, 5.89%) as pale yellow crystals, mp 55–57 °C; R_f 0.91; $\delta_H(CDCl_3)$ 2.26 (3 H, d, *J* 0.5), 2.33 (2 H, m), 3.21 (2 H, m), 3.56 (3 H, s), 3.61 (2 H, m), 4.70 (1 H, m), 6.99 (2 H, m), 7.18 (1 H, m); $\delta_C(CDCl_3)$ 20.6, 28.7, 48.9, 49.4, 54.4, 91.9, 120.6, 128.2, 128.6, 131.3, 133.6, 146.6, 154.5.

1-(3-Chlorophenyl)-4-methoxy-1,2,5,6-tetrahydropyridine 10f. Distillation of the residue gave 1-(3-*chlorophenyl*)-4-*methoxy*-1,2,5,6-*tetrahydropyridine* **10f** (32.48 g, 72.5%) (HRMS: found M^+, 223.0765. $^{12}C_{12}{}^{1}H_{14}{}^{35}Cl{}^{14}N{}^{16}O$ requires *M*, 223.0764) as pale yellow liquid, bp 153–156 °C at 1 mmHg; R_f 0.82; $\delta_H(CDCl_3)$ 2.29 (2 H, m), 3.39 (2 H, t, *J* 5.8), 3.53 (3 H, s) 3.71 (2 H, m), 4.64 (1 H, m), 6.75 (2 H, m), 6.85 (1 H, m), 7.12 (1 H, m); $\delta_C(CDCl_3)$ 28.2, 45.4, 46.5, 54.3, 90.8, 113.3, 115.0, 118.4, 130.1, 135.0, 151.7, 154.1.

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