Synthesis of some *N*-methyl-1,2,3,4-tetrahydroisoquinolines by Friedel–Crafts cyclisation using benzotriazole auxiliary

Cornelia Locher and Naseem Peerzada

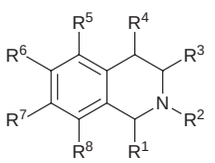
Faculty of Science, Northern Territory University, Darwin N.T. 0909, Australia

Received (in Cambridge) 28th September 1998, Accepted 18th November 1998

1-Hydroxymethylbenzotriazole reacts with phenylethylamines to give the respective *N*,*N*-bis(benzotriazol-1-ylmethyl)phenylethylamines, which are then subject to an intramolecular Friedel–Crafts cyclisation at room temperature to yield *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines. These crystalline UV- and oxygen-stable products can be reduced at room temperature to the corresponding *N*-methyl-1,2,3,4-tetrahydroisoquinolines using $NaBH_4$. The method offers an elegant approach to a wide range of *N*-methylated 1,2,3,4-tetrahydroisoquinolines since it can be applied not only for the synthesis of 1,2,3,4-tetrahydroisoquinolines with electron-donating substituents on the aromatic moiety, but also for deactivated derivatives. All steps involved work under very mild conditions in high to excellent yields.

Introduction

Isoquinoline alkaloids represent one of the largest groups of alkaloids and have attracted a great deal of interest over the decades due to their potent biological activities.[1–3] In recent years, research has often focused on the role of endogenously derived tetrahydroisoquinolines in peripheral and central mechanisms and their possible therapeutic applications.[4–6] In this context various structures are discussed including the 1,2,3,4-tetrahydroisoquinolines of general type **1** as inhibitors



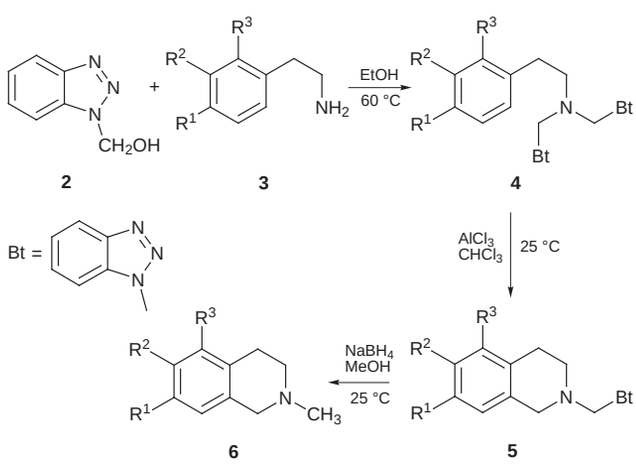
1

R^1, R^3, R^4 = H or C_1–C_2 alkyl group
R^2 = H or CH_3 group
R^5–R^8 = H or electron-withdrawing groups

of the enzyme phenylethanolamine *N*-methyltransferase.[7,8] The Bischler–Napieralski,[9–11] Pictet–Spengler[12,13] and Pomeranz–Fritsch[14,15] reactions as well as the Bobbitt variation[14] of the latter are well-known, generally suitable methods for the synthesis of 1,2,3,4-tetrahydroisoquinolines *in vitro*. These methods are, however, often restricted to tetrahydroisoquinolines with electron-donating substituents on the aromatic part of the structure or produce poor yields when applied to the synthesis of isoquinolines with electron-withdrawing groups.[16–19] An interesting approach, suitable for the synthesis of deactivated 1,2,3,4-tetrahydroisoquinolines, was introduced by Deady and co-workers[20] but imposed difficulties, as claimed by Mendelson *et al.*,[7] in regard to its reproducibility. A more recent method by Stokker[17] is exclusively applicable to 1,2,3,4-tetrahydroisoquinolines with electron-withdrawing substituents, but it produces only moderate yields for unsubstituted 1,2,3,4-tetrahydroisoquinoline and fails completely for activated derivatives. There continues to be a lack of general methods for the synthesis of a wide range of 1,2,3,4-tetrahydroisoquinolines independent from the nature of their substituents on the aromatic moiety of the structure.

This paper reports the use of benzotriazole, a very versatile synthetic auxiliary in heterocyclic chemistry and excellent leaving group,[21–23] to establish a new synthesis routine for a wide range of *N*-substituted 1,2,3,4-tetrahydroisoquinolines. The method can be applied to the preparation of derivatives with electron-donating groups but also to the synthesis of deactivated 1,2,3,4-tetrahydroisoquinolines producing high to excellent yields under very mild synthesis conditions. Furthermore, the crystalline intermediate products of the reaction are very stable derivatives which can easily be transformed on a need basis into various, often UV- and oxygen-sensitive, *N*-substituted 1,2,3,4-tetrahydroisoquinolines, hence providing ideal storage intermediates.

The synthesis (Scheme 1) first involves the reaction of



2 **3** **4** **5** **6**

	R^1	R^2	R^3
a	H	H	H
b	Cl	H	H
c	H	H	Cl
d	Cl	H	Cl
e	OCH_3	H	H
f	OCH_3	OCH_3	H

Scheme 1

1-hydroxymethylbenzotriazole **2** with a phenylethylamine **3** to give the respective *N*,*N*-bis(benzotriazol-1-ylmethyl)phenylethylamine **4**. The crystalline product is the precursor for the subsequent Friedel–Crafts ring closure to the corresponding *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinoline **5** by removal of one benzotriazolyl moiety using a Lewis acid

Table 1 *N*,*N*-Bis(benzotriazol-1-ylmethyl)phenylethylamines **4**

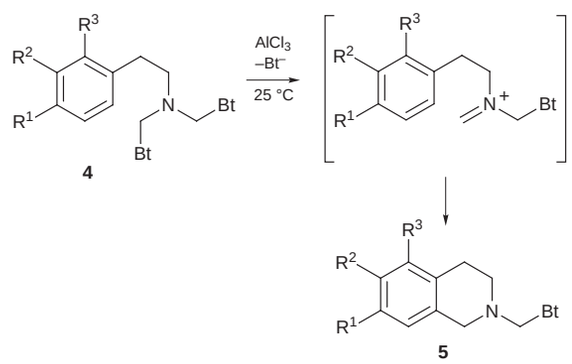
Compound (Formula)	R^1	R^2	R^3	Yield (%)	Mp/°C (EtOH)	Found (Required) (%) C	H	N	δ (Bt-CH_2-N)
4a[a] ($C_{22}H_{21}N_7$)	H	H	H	92	123–124	68.8 (68.9)	5.6 (5.5)	25.5 (25.6)	5.62 (s, 4H)
4b ($C_{22}H_{20}N_7Cl$)	Cl	H	H	92	149–150	63.0 (63.2)	4.9 (4.8)	23.4 (23.5)	5.62 (s, 4H)
4c ($C_{22}H_{20}N_7Cl$)	H	H	Cl	80	116–118	63.2 (63.2)	4.9 (4.8)	23.1 (23.5)	5.68 (s, 4H)
4d ($C_{22}H_{19}N_7Cl_2$)	Cl	H	Cl	88	125–126	58.7 (58.4)	4.5 (4.2)	21.9 (21.7)	5.68 (s, 4H)
4e ($C_{23}H_{23}N_7O$)	OCH_3	H	H	95	97–99	67.2 (66.8)	5.9 (5.6)	23.9 (23.7)	5.62 (s, 4H)
4f ($C_{24}H_{25}N_7O_2$)	OCH_3	OCH_3	H	76	91–93	64.2 (65.0)	5.7 (5.7)	22.1 (22.1)	5.64 (s, 4H)

[a] Lit.,[25] mp 122–124 °C, δ (N-CH_2-N) 5.71 (s).

Table 2 *N*-Benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines **5** by intramolecular cyclisation with $AlCl_3$

Compound (Formula)	R^1	R^2	R^3	*t*/h	Yield (%)	Mp/°C (EtOH)	Found (Required) (%) C	H	N	δ [Bt-CH_2-N]	δ [Ar-CH_2-N]
5a ($C_{16}H_{16}N_4$)	H	H	H	4	87	155–157	72.6 (72.7)	6.2 (6.1)	21.2 (21.2)	5.64 (s, 2H)	3.86 (s, 2H)
5b ($C_{16}H_{15}N_4Cl$)	Cl	H	H	8	88	146–148	64.2 (64.3)	5.1 (5.1)	18.4 (18.8)	5.62 (s, 2H)	3.80 (s, 2H)
5c ($C_{16}H_{15}N_4Cl$)	H	H	Cl	68	14	144–145[a]	64.1 (64.3)	5.1 (5.1)	18.6 (18.8)	5.61 (s, 2H)	3.81 (s, 2H)
5d ($C_{16}H_{14}N_4Cl_2$)	Cl	H	Cl	140	NR[b]						
5e ($C_{17}H_{18}N_4O$)	OCH_3	H	H	4	83	128–130	69.2 (69.4)	6.1 (6.2)	18.9 (19.0)	5.62 (s, 2H)	3.82 (s, 2H)
5f ($C_{18}H_{20}N_4O_2$)	OCH_3	OCH_3	H	4	94	137–140	66.6 (66.7)	6.3 (6.2)	16.9 (17.3)	5.63 (s, 2H)	3.77–3.84 (m, 8H)[c]

[a] Repeated recrystallisation from EtOH and EtOAc. [b] No reaction. [c] Signal overlaps with those from OCH_3.



Scheme 2

whereby the reaction proceeds *via* an iminium ion (Scheme 2). Replacement of the second benzotriazolyl group leads to a wide range of *N*-substituted 1,2,3,4-tetrahydroisoquinolines, in this case *N*-methyl-1,2,3,4-tetrahydroisoquinolines **6**.

Results and discussion

Reaction of 1-hydroxymethylbenzotriazole with phenylethylamines

1-Hydroxymethylbenzotriazole **2** was produced following its established literature synthesis by reaction of benzotriazole and formaldehyde which was shown to yield the 1-substituted isomer.[24] Various phenylethylamines **3a**–**f** were reacted with 1-hydroxymethylbenzotriazole **2** with the ratio of starting material being 1:2,[25] yielding good to excellent quantities of *N*,*N*-bis(benzotriazol-1-ylmethyl)phenylethylamines **4a**–**f** (Table 1).

Cyclisation of *N*,*N*-bis(benzotriazol-1-ylmethyl)phenylethylamines

When the intermediate precursors *N*,*N*-bis(benzotriazol-1-ylmethyl)phenylethylamines **4a**–**f** were treated with excess of anhydrous $AlCl_3$ in a molar ratio of 1:4 in $CHCl_3$ at room temperature, one benzotriazolyl moiety was eliminated from the molecule, yielding *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines **5a**–**f**. During the reaction the resultant iminium ion (Scheme 2) reacted intramolecularly with the aromatic ring, with the rate of this electrophilic cyclisation being influenced by the number and nature of the substituents on the benzene ring. The intramolecular ring-closure, however, not only produced very high yields with activated (**4e**,**f**) or unsubstituted (**4a**) structures, but was also applicable to phenylethylamines with electron-withdrawing substituents (**4b**,**c**) on the aromatic ring (Table 2).

The only reaction showing somewhat different behaviour was the ring closure of *N*,*N*-bis(benzotriazol-1-ylmethyl)-2-chlorophenylethylamine **4c**. When reacted for 4–8 h at room temperature, the characteristic peak at δ 3.81 for Ar-CH_2-N, indicating a successful ring closure, could be detected in the crude product by ^{1}H NMR analysis; the reaction, however, was found to be incomplete and required a substantially longer reaction time. After work-up the synthesis yielded a viscous yellow oil which crystallised slowly. It afforded only low quantities of **5c** after repeated recrystallisation with EtOH–EtOAc.

A more successful approach to the cyclisation of **4c** appears to be the use of conc. H_2SO_4, a method already employed for the synthesis of 1-aryl-1,4-dihydroisoquinolin-3(2*H*)-ones.[26] Compound **4c** was added to conc. H_2SO_4 at 0 °C with stirring. The mixture was slowly brought to room temperature, basified and extracted with CH_2Cl_2. The solution yielded an oily residue which slowly crystallised (yield 71%) to **5c**.

The ring closure of *N*,*N*-bis(benzotriazol-1-ylmethyl)-2,4-dichlorophenylethylamine **4d**, however, failed with both methods and starting material was recovered even if the reaction times were substantially increased. Deactivation of the aromatic ring by the electron-withdrawing chloro substituents reduced the electron availability on it for the required electrophilic cyclisation to occur.

N-Methylation of *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines

The crystalline, UV- and oxygen-stable products **5** can easily be converted into a wide range of *N*-substituted-1,2,3,4-tetrahydroisoquinolines by replacing the remaining benzotriazolyl moiety with a variety of nucleophiles. Benzotriazole has been demonstrated to be easily replaced by different alkyl substituents, using Grignard reagents or organozinc compounds,[27–29] which leads to various *N*-alkylated compounds. Employing

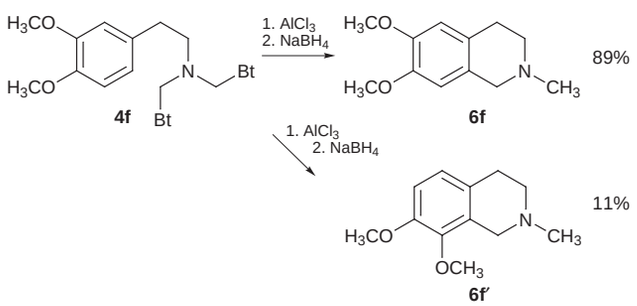
Table 3 *N*-Methyl-1,2,3,4-tetrahydroisoquinolines **6**

Compound (Formula)	R^1	R^2	R^3	Yield (%)	Mp/°C (EtOH)	Mp (picrate)/ °C (EtOH)	δ [N-CH_3]
6a ($C_{10}H_{13}N$)	H	H	H	70	liquid	150–153[a]	2.44 (s, 3H)
6b ($C_{10}H_{12}NCl$)	Cl	H	H	60	liquid	167–169	2.44 (s, 3H)
6c ($C_{10}H_{12}NCl$)	H	H	Cl	55	liquid	176–178	2.43 (s, 3H)
6e ($C_{11}H_{15}NO$)	OCH_3	H	H	95	liquid	140–142[b]	2.42 (s, 3H)
6f ($C_{12}H_{17}NO_2$)	OCH_3	OCH_3	H	67	74–75[c]	154–156[d]	2.43 (s, 3H)

[a] Lit.,[36] 148–150 °C. [b] Lit.,[37] 142–143 °C. [c] Lit.,[33] 69–70 and 82 °C (hemihydrate). [d] Lit.,[33] 160 °C.

alcohols or thiols yields the respective *N*-alkoxymethyl derivatives and their thio analogues under very mild conditions.[30] The benzotriazolyl moiety can also easily be reduced with $NaBH_4$,[29,31] in this case yielding the respective *N*-methylated derivatives.

The latter conversion has been used to synthesise various *N*-methyl-1,2,3,4-tetrahydroisoquinolines **6**. The respective *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinolines **5a**–**f** were reduced with $NaBH_4$ at room temperature. After work-up the corresponding *N*-methyl-1,2,3,4-tetrahydroisoquinolines **6a**–**f** were obtained in generally good yields (Table 3). The purity of the products was analysed by GC/MS and in all cases a single peak was observed. The yield of the conversion of compound **5e** into 7-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline **6e**, although not optimised, is comparable with the traditional synthesis by Mirza from 7-methoxy-1,2,3,4-tetrahydroisoquinoline methiodide.[32] The procedure has been applied to the synthesis of the natural occurring 6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (*N*-methylheliamine) **6f**, found in *Pachycereus weberi*, *Thalictrum dioicum*, *T. polygamum*, *Backebergia militaris*, *Nelumbo nucifera*, *Pilosocereus guerreronis* and *Papaver bracteatum*.[33] Theoretically two isomers, the 6,7-dimethoxy- **5f** as well as the 7,8-dimethoxy-substituted isomer **5f′**, could be expected from the cyclisation of *N*,*N*-bis(benzotriazol-1-ylmethyl)-3,4-dimethoxyphenylethylamine **4f**. The preferred isomer was isolated in high yield and, after reduction with $NaBH_4$, ^{1}H NMR analysis presented two singlets at δ 6.59 and 6.50 for the aromatic protons, confirming 6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline **6f** as the product. After reduction of the crude cyclised intermediate, GC/MS analysis of the crude product detected two compounds, **6f** and **6f′**, with the same molecular weight (*m*/*z* 207) in a ratio of approximately 8 : 1 (Scheme 3). This demonstrated the high



Scheme 3

regioselectivity of the intramolecular ring closure, which can be explained by steric hindrance of the electrophilic attack at the position *ortho* to the methoxy substituent on the aromatic structure, manifesting the *para*-directing effect of alkoxy groups.[34] This phenomenon is also well-documented for *m*-methoxy-substituted β-arylamines which cyclise to the 6-methoxy regioisomer as the major, often even exclusive, product.[35]

Conclusion

Using benzotriazole as auxiliary, the Friedel–Crafts cyclisation presented in this paper offers a new approach to a wide range of *N*-alkylated 1,2,3,4-tetrahydroisoquinolines. Under very mild synthesis conditions it is possible to produce not only activated or unsubstituted 1,2,3,4-tetrahydroisoquinolines which are also easily accessible by more traditional routines, but 1,2,3,4-tetrahydroisoquinolines with electronegative substituents on the aromatic moiety for which only a limited number of syntheses have been reported. As demonstrated, the intermediates of the reaction are ideal storage forms for various *N*-methylated tetrahydroisoquinolines, but the very nature of benzotriazole as auxiliary undoubtedly also allows the transformation of these intermediates into a wide range of other *N*-substituted 1,2,3,4-tetrahydroisoquinolines.

Experimental

General

All reagents used were AR grade. Melting points were determined on a Gallenkamp Melting Point Apparatus and are uncorrected. FTIR spectra were taken on a Mattson Polaris FTIR-Spectrophotometer in Nujol and UV/VIS data on a Varian DMS 200 UV Visible Spectrophotometer, using ethanol as solvent. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 (200 MHz) in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal reference. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm), $\delta_{TMS} = 0.00$) and ^{13}C NMR results (in ppm) are referenced to $CDCl_3$ (δ 77.0 for centerline). Coupling patterns are indicated as s (singlet), d (doublet), q (quartet) and m (multiplet). GC/MS spectra were obtained on a Varian Star 3400 CX spectrometer with a SGE 30QC2.5/BPX1.0 column. Elemental analyses were performed in the Research School of Chemistry, Australian National University, Canberra, Australia.

General procedure for compounds 4a–f: *N*,*N*-bis(benzotriazol-1-ylmethyl)phenylethylamine 4a

Phenylethylamine **3a** (3.45 g, 28.5 mmol) was added to 1-hydroxymethylbenzotriazole **2** (8.50 g, 57.0 mmol) while stirring. The mixture was heated and ethanol added dropwise until everything dissolved. The material was refluxed for 30 min and then kept at −5 °C to promote crystallisation. The white crystals **4a** (10.05 g, 92%) were recrystallised from EtOH. Mp 123–124 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 207 (31821), 259 (10245) and 276 (7756); ν_{max}(Nujol)/cm^{-1} 1205, 1160, 1145, 1075, 990, 745; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.09 (2H, d, *J* 5), 7.53–7.38 (6H, m), 7.17 (3H, d, *J* 3), 7.03 (2H, t, *J* 3), 5.62 (4H, s, NCH_2N), 3.17 (2H, t, *J* 5, NCH_2CH_2), 2.83 (2H, t, *J* 5, NCH_2CH_2); δ_C(50 MHz; $CDCl_3$) 33.9 ($ArCH_2$), 52.1 (NCH_2CH_2), 64.3 (NCH_2N), 109.9, 120.1, 124.3, 126.5, 128.0, 128.6, 133.3, 138.8, 146.2.

***N*,*N*-Bis(benzotriazol-1-ylmethyl)-4-chlorophenylethylamine 4b.** 1-Hydroxymethylbenzotriazole **2** (7.51 g, 50.4 mmol) was reacted with 4-chlorophenylethylamine **3b** (3.93 g, 25.4 mmol) for one hour. Crystallisation started almost immediately to yield compound **4b** (9.68 g, 92%) as a fine, white powder. Mp 149–150 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 208

(34641), 259 (12838) and 274 (10127); ν_{max}(Nujol)/cm^{-1} 1200, 1145, 980, 960, 750, 725, 670, 630, 575, 525; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.10 (2H, d, *J* 5), 7.51–7.39 (6H, m), 7.06 (2H, d, *J* 5), 6.88 (2H, d, *J* 5), 5.62 (4H, s, NCH_2N), 3.12 (2H, t, *J* 6, NCH_2CH_2), 2.78 (2H, t, *J* 6, NCH_2CH_2); δ_C(50 MHz; $CDCl_3$) 33.0 ($ArCH_2$), 51.6 (NCH_2CH_2), 64.4 (NCH_2N), 109.7, 120.2, 124.4, 128.1, 128.6, 129.9, 132.2, 133.2, 137.2, 146.2.

***N*,*N*-Bis(benzotriazol-1-ylmethyl)-2-chlorophenylethylamine 4c.** 1-Hydroxymethylbenzotriazole **2** (2.80 g, 18.8 mmol) and 2-chlorophenylethylamine **3c** (1.46 g, 9.4 mmol) were reacted for one hour. Crystallisation occurred very quickly to give product **4c** (3.13 g, 80%) as a fine, white powder. Mp 116–118 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 216 (7619), 257 (9287) and 273 (8657); ν_{max}(Nujol)/cm^{-1} 1220, 1190, 1160, 1120, 1050, 970, 740; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.10 (2H, d, *J* 5), 7.62–7.37 (6H, m), 7.21 (1H, s), 7.05–6.97 (3H, m), 5.68 (4H, s, NCH_2N), 3.19 (2H, t, *J* 7, NCH_2CH_2), 2.96 (2H, t, *J* 7, NCH_2CH_2); δ_C(50 MHz; $CDCl_3$) 31.8 ($ArCH_2$), 50.4 (NCH_2CH_2), 64.4 (NCH_2N), 109.8, 118.4, 120.1, 124.3, 127.0, 128.0, 129.5, 130.9, 133.3, 133.9, 136.3, 146.2.

***N*,*N*-Bis(benzotriazol-1-ylmethyl)-2,4-dichlorophenylethylamine 4d.** The reaction between 1-hydroxymethylbenzotriazole **2** (2.02 g, 13.6 mmol) and 2,4-dichlorophenylethylamine **3d** (1.29 g, 6.8 mmol) for one hour yielded compound **4d** (2.70 g, 88%) as fine white crystals. Mp 125–126 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 207 (43597), 259 (13417) and 277 (9809); ν_{max}(Nujol)/cm^{-1} 1275, 1200, 1150, 990, 890, 845, 795, 740; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.10 (2H, d, *J* 4), 7.53–7.41 (6H, m), 7.14 (1H, s), 6.84 (2H, q, *J* 12), 5.68 (4H, s, NCH_2N), 3.11 (2H, t, *J* 8, NCH_2CH_2), 2.89 (2H, t, *J* 8, NCH_2CH_2); δ_C(50 MHz; $CDCl_3$) 30.9 ($ArCH_2$), 49.7 (NCH_2CH_2), 64.5 (NCH_2N), 109.6, 120.2, 124.4, 127.2, 128.1, 129.2, 131.5, 133.0, 133.2, 134.4, 134.9, 146.2.

***N*,*N*-Bis(benzotriazol-1-ylmethyl)-4-methoxyphenylethylamine 4e.** 1-Hydroxymethylbenzotriazole **2** (2.16 g, 14.5 mmol) was reacted with 4-methoxyphenylethylamine **3e** (1.09 g, 7.2 mmol) for one hour to yield fine needles of product **4e** (2.83 g, 95%). Mp 97–99 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 208 (35963), 225 (16361), 260 (13597) and 273 (11850); ν_{max}(Nujol)/cm^{-1} 1255, 1195, 1150, 1040, 830, 745; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.10 (2H, d, *J* 5), 7.52–7.39 (6H, m), 6.92 (2H, d, *J* 5), 6.70 (2H, d, *J* 5), 5.62 (4H, s, NCH_2N), 3.75 (3H, s, OCH_3), 3.13 (2H, t, *J* 8, NCH_2CH_2), 2.77 (2H, t, *J* 8, NCH_2CH_2); δ_C(50 MHz; $CDCl_3$) 33.0 ($ArCH_2$), 52.3 (NCH_2CH_2), 55.1 (OCH_3), 64.4 (NCH_2N), 109.9, 113.9, 120.1, 124.3, 128.0, 129.6, 130.8, 133.3, 146.3, 158.3.

***N*,*N*-Bis(benzotriazol-1-ylmethyl)-3,4-dimethoxyphenylethylamine 4f.** Product **4f** (2.42 g, 76%) was obtained as white crystals from the reaction of 1-hydroxymethylbenzotriazole **2** (2.12 g, 14.2 mmol) and 3,4-dimethoxyphenylethylamine **3f** (1.30 g, 7.2 mmol). Mp 91–93 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 210 (33945), 231 (14038), 264 (16640) and 280 (15200); ν_{max}(Nujol)/cm^{-1} 1140, 1075, 1025, 820, 745; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.10 (2H, d, *J* 5), 7.53–7.38 (6H, m), 6.64 (1H, d, *J* 5), 6.56 (1H, d, *J* 5), 6.45 (1H, s), 5.64 (4H, s, NCH_2N), 3.82 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.15 (2H, t, *J* 7, NCH_2CH_2), 2.76 (2H, t, *J* 7, NCH_2CH_2); δ_C(50 MHz; $CDCl_3$) 33.6 ($ArCH_2$), 52.3 (NCH_2CH_2), 55.6 (OCH_3), 64.5 (NCH_2N), 109.8, 111.1, 111.6, 120.1, 120.5, 124.4, 128.0, 131.3, 133.2, 146.2, 147.7, 149.0.

General procedure for compounds 5a–f: *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinoline 5a

N,*N*-Bis(benzotriazol-1-ylmethyl)phenylethylamine **4a** (2.57 g, 6.7 mmol) was dissolved in $CHCl_3$ (25 ml). Anhydrous $AlCl_3$ (3.58 g, 26.9 mmol) was slowly added with stirring. The mixture was stirred at 25 °C for 4 h with a drying tube (anhydrous $CaCl_2$) attached. The product was then poured onto crushed ice (approx. 25 g) and NaOH (2 M, 75 ml) was added to pH 14. The organic and aqueous layer were separated and the aqueous material was extracted with $CHCl_3$ (3 × 30 ml). The combined organic extracts were rewashed with NaOH (2 M, 90 ml), dried with anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to yield compound **5a** as a slightly yellow, oily product (1.54 g, 87%) which crystallised rapidly and was recrystallised from EtOH. Mp 155–157 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 206 (27060), 253 (6970) and 273 (5808); ν_{max}(Nujol)/cm^{-1} 1260, 1210, 1150, 1090, 1050, 955, 940, 740; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.08 (1H, d, *J* 4), 7.68 (1H, d, *J* 4), 7.52 (1H, t, *J* 7), 7.38 (1H, t, *J* 7), 7.10–6.90 (4H, m), 5.64 (2H, s, NCH_2N), 3.86 (2H, s, $ArCH_2N$), 2.96–2.91 (4H, m, $ArCH_2CH_2N$); δ_C(50 MHz; $CDCl_3$) 29.0 ($ArCH_2CH_2N$), 48.4 ($ArCH_2N$), 52.3 ($ArCH_2CH_2N$), 69.1 (NCH_2N), 110.1, 118.4, 120.1, 124.1, 125.9, 126.4, 126.6, 127.7, 128.9, 133.6, 134.0, 146.1.

***N*-Benzotriazol-1-ylmethyl-7-chloro-1,2,3,4-tetrahydroisoquinoline 5b.** *N*,*N*-Bis(benzotriazol-1-ylmethyl)-4-chlorophenylethylamine **4b** (2.51 g, 6.0 mmol) was reacted with $AlCl_3$ (3.58 g, 26.9 mmol) for 8 h. Product **5b** was obtained as white crystals (1.58 g, 88%). Mp 146–148 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 207 (40498), 254 (11264) and 273 (9923); ν_{max}(Nujol)/cm^{-1} 1205, 1150, 1055, 960, 780, 770, 750; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.07 (1H, d, *J* 4), 7.67 (1H, d, *J* 4), 7.51 (1H, t, *J* 7), 7.37 (1H, t, *J* 7), 7.04–6.98 (3H, m), 5.62 (2H, s, NCH_2N), 3.80 (2H, s, $ArCH_2N$), 2.93 (2H, d, *J* 2, $ArCH_2CH_2N$), 2.86 (2H, d, *J* 2, $ArCH_2CH_2N$); δ_C(50 MHz; $CDCl_3$) 28.5 ($ArCH_2CH_2N$), 48.2 ($ArCH_2N$), 51.9 ($ArCH_2CH_2N$), 68.8 (NCH_2N), 109.9, 120.2, 124.1, 126.5, 126.6, 127.8, 130.2, 131.5, 132.1, 134.0, 135.5, 146.1.

***N*-Benzotriazol-1-ylmethyl-5-chloro-1,2,3,4-tetrahydroisoquinoline 5c.** *Method A.* *N*,*N*-Bis(benzotriazol-1-ylmethyl)-2-chlorophenylethylamine **4c** (1.01 g, 2.4 mmol) and $AlCl_3$ (1.29 g, 9.7 mmol) were reacted for 68 h to give an orange oil which crystallised slowly (0.69 g, 96% yield of crude product). Repeated recrystallisation from EtOH–EtOAc yielded compound **5c** as slightly beige crystals (0.10 g, 14%). Mp 144–145 °C (EtOH–EtOAc); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 206 (35164), 253 (8761) and 275 (7092); ν_{max}(Nujol)/cm^{-1} 1205, 1150, 1050, 955, 750; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.07 (1H, d, *J* 4), 7.67 (1H, d, *J* 4), 7.51 (1H, t, *J* 7), 7.37 (1H, t, *J* 7), 7.16 (1H, d, *J* 4), 7.03 (1H, t, *J* 8), 6.90 (1H, d, *J* 4), 5.61 (2H, s, NCH_2N), 3.81 (2H, s, $ArCH_2N$), 2.95 (2H, d, *J* 2, $ArCH_2CH_2N$), 2.89 (2H, d, *J* 2, $ArCH_2CH_2N$); δ_C(50 MHz; $CDCl_3$) 27.3 ($ArCH_2CH_2N$), 48.2 ($ArCH_2N$), 52.3 ($ArCH_2CH_2N$), 68.8 (NCH_2N), 110.0, 120.1, 124.1, 125.1, 126.9, 127.2, 127.8, 131.9, 133.9, 134.4, 136.0, 146.1.

Method B. Compound **4c** (0.53 g, 1.3 mmol) was added to conc. H_2SO_4 (3 ml) at 0 °C while stirring. The mixture was brought to room temperature and stirred at 25 °C for a further 2 h, poured onto crushed ice (approx. 5 g) and basified with NaOH (10 M, 15 ml) to pH 14. CH_2Cl_2 (15 ml) was added and the layers separated. The aqueous material was extracted with CH_2Cl_2 (5 × 5 ml) and the combined organic extracts were rewashed with NaOH (2 M, 25 ml), dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The solution yielded an oily residue which slowly crystallised to give product **5c** (0.27 g, 71%).

***N*-Benzotriazol-1-ylmethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline 5e.** The reaction of *N*,*N*-bis(benzotriazol-1-ylmethyl)-4-methoxyphenylethylamine **4e** (1.23 g, 3.0 mmol) and $AlCl_3$ (1.59 g, 11.9 mmol) for 4 h gave compound **5e** as white crystals (0.77 g, 83%). Mp 128–130 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3

mol^{-1} cm^{-1}) 206 (34251), 224 (12818), 259 (7997) and 278 (8585); ν_{max}(Nujol)/cm^{-1} 1610, 1505, 1325, 1225, 1150, 1040, 975, 845, 775, 745; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.08 (1H, d, *J* 4), 7.70 (1H, d, *J* 4), 7.51 (1H, t, *J* 7), 7.38 (1H, t, *J* 7), 6.98 (1H, d, *J* 4), 6.71 (1H, d, *J* 4), 6.53 (1H, s), 5.62 (2H, s, NCH_2N), 3.82 (2H, s, $ArCH_2N$), 3.73 (3H, s, OCH_3), 2.94 (2H, d, *J* 2, $ArCH_2CH_2N$), 2.85 (2H, d, *J* 2, $ArCH_2CH_2N$); δ_C(50 MHz; $CDCl_3$) 28.2 ($ArCH_2CH_2N$), 48.7 ($ArCH_2N$), 52.4 ($ArCH_2CH_2N$), 55.1 (OCH_3), 69.0 (NCH_2N), 110.1, 111.1, 113.0, 120.0, 124.1, 125.6, 127.7, 129.8, 134.0, 134.7, 146.1, 157.9.

***N*-Benzotriazol-1-ylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 5f.** *N*,*N*-Bis(benzotriazol-1-ylmethyl)-3,4-dimethoxyphenylethylamine **4f** (1.02 g, 2.3 mmol) was reacted with $AlCl_3$ (1.23 g, 9.2 mmol) for 4 h. Product **5f** (0.70 g, 94%) was obtained as a yellow oil which rapidly crystallised. Mp 137–140 °C (EtOH); λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1}) 207 (44096), 220 (12798) and 281 (10433); ν_{max}(Nujol)/cm^{-1} 1605, 1515, 1375, 1225, 1140, 1110, 1020, 995, 855, 830, 740; δ_H(200 MHz; $CDCl_3$; Me_4Si) 8.08 (1H, d, *J* 4), 7.70 (1H, d, *J* 4), 7.52 (1H, t, *J* 7), 7.38 (1H, t, *J* 7), 6.55 (1H, s), 6.48 (1H, s), 5.62 (2H, s, NCH_2N), 3.84–3.77 (8H, m, $ArCH_2N$ + OCH_3), 2.94 (2H, d, *J* 2, $ArCH_2CH_2N$), 2.85 (2H, d, *J* 2, $ArCH_2CH_2N$); δ_C(50 MHz; $CDCl_3$) 28.4 ($ArCH_2CH_2N$), 48.4 ($ArCH_2N$), 51.8 ($ArCH_2CH_2N$), 55.7 (OCH_3), 69.0 (NCH_2N), 109.2, 110.0, 111.3, 120.0, 124.0, 125.4, 126.5, 127.6, 133.9, 146.0, 147.4, 147.7.

General procedure for compounds 6a–f: *N*-methyl-1,2,3,4-tetrahydroisoquinoline 6a

$NaBH_4$ (0.31 g, 8.2 mmol) was dissolved in MeOH (25 ml) and *N*-benzotriazol-1-ylmethyl-1,2,3,4-tetrahydroisoquinoline **5a** (0.87 g, 3.3 mmol) was added in small amounts with stirring. The solution was stirred at 25 °C for 7 h with a drying tube (anhydrous $CaCl_2$) attached. The solvent was then removed under reduced pressure to yield a slightly yellow, oily residue. CH_2Cl_2 (10 ml) as well as NaOH (2 M, 10 ml) were added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 ml) and the combined organic extracts rewashed with NaOH (2 M, 30 ml). The organic solution was dried with anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to yield product **6a** (0.34 g, 70%) as a pale yellow oil with a strong ammoniacal odour. δ_H(200 MHz; $CDCl_3$; Me_4Si) 7.11–6.98 (4H, m, ArH), 3.57 (2H, s, $ArCH_2N$), 2.91 (2H, t, *J* 6, $ArCH_2CH_2N$), 2.67 (2H, t, *J* 6, $ArCH_2CH_2N$), 2.44 (3H, s, CH_3N); δ_C(50 MHz; $CDCl_3$) 28.9 ($ArCH_2CH_2N$), 45.9 (NCH_3), 52.7 ($ArCH_2CH_2N$), 57.7 ($ArCH_2N$), 125.7, 126.2, 126.5, 128.7, 133.8, 134.6; *m*/*z* 148 (17%), 147 (M$^+$, 22), 146 (100), 144 (8), 131 (7), 130 (4), 118 (4), 117 (4), 115 (5), 104 (20), 103 (14), 78 (11), 77 (6). Picrate: mp 150–153 °C (EtOH) (lit.,[36] 148–150 °C).

7-Chloro-*N*-methyl-1,2,3,4-tetrahydroisoquinoline 6b. *N*-Benzotriazol-1-ylmethyl-7-chloro-1,2,3,4-tetrahydroisoquinoline **5b** (0.30 g, 1.0 mmol) was reduced with $NaBH_4$ (0.10 g, 2.6 mmol) and yielded product **6b** (0.11 g, 60%) as a slightly yellow oil; δ_H(200 MHz; $CDCl_3$; Me_4Si) 7.08–7.00 (3H, m, ArH), 3.53 (2H, s, $ArCH_2N$), 2.87 (2H, t, *J* 6, $ArCH_2CH_2N$), 2.67 (2H, t, *J* 6, $ArCH_2CH_2N$), 2.44 (3H, s, CH_3N); δ_C(50 MHz; $CDCl_3$) 28.5 ($ArCH_2CH_2N$), 45.8 (NCH_3), 52.5 ($ArCH_2CH_2N$), 57.4 ($ArCH_2N$), 126.4, 130.1, 131.2, 132.4, 136.7; *m*/*z* 183 (10%), 182 (63), 181 (M$^+$, 22), 180 (100), 178 (6), 145 (6), 144 (7), 140 (5), 138 (15), 115 (5), 103 (44), 102 (9), 77 (7). Picrate: mp 167–169 °C (EtOH). Anal. calc. for $C_{16}H_{15}N_4O_7Cl$: C, 46.8; H, 3.7; N, 13.6; Found: C, 46.8; H, 3.7; N, 13.6%.

5-Chloro-*N*-methyl-1,2,3,4-tetrahydroisoquinoline 6c. *N*-Benzotriazol-1-ylmethyl-5-chloro-1,2,3,4-tetrahydroisoquinoline **5c** (0.18 g, 0.6 mmol) was reduced with $NaBH_4$ (0.06 g, 1.6 mmol) and gave product **6c** (0.06 g, 55%) as a colourless oil. δ_H(200 MHz; $CDCl_3$; Me_4Si) 7.18 (1H, d, *J* 4, ArH), 7.05 (1H, t, *J* 7, ArH), 6.91 (1H, d, *J* 4, ArH), 3.54 (2H, s, $ArCH_2N$), 2.88 (2H, t, *J* 6, $ArCH_2CH_2N$), 2.69 (2H, t, *J* 6, $ArCH_2CH_2N$), 2.43 (3H, s, CH_3N); δ_C(50 MHz; $CDCl_3$) 27.3 ($ArCH_2CH_2N$), 45.7 (NCH_3), 52.5 ($ArCH_2CH_2N$), 57.8 ($ArCH_2N$), 124.9, 126.6, 126.9, 132.2, 134.4, 137.1; *m*/*z* 184 (19%), 183 (12), 182 (91), 181 (M$^+$, 18), 180 (100), 178 (5), 146 (15), 145 (6), 144 (8), 103 (29), 102 (7). Picrate: mp 176–178 °C (EtOH). Anal. calc. for $C_{16}H_{15}N_4O_7Cl$: C, 46.8; H, 3.7; N, 13.6; Found: C, 46.8; H, 3.6; N, 13.6%.

7-Methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline 6e. *N*-Benzotriazol-1-ylmethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline **5e** (0.35 g, 1.2 mmol) was reduced with $NaBH_4$ (0.12 g, 3.2 mmol). Product **6e** was obtained as a colourless oil (0.20 g, 95%); δ_H(200 MHz; $CDCl_3$; Me_4Si) 7.00 (1H, d, *J* 5, ArH), 6.69 (1H, d, *J* 5, ArH), 6.55 (1H, s, ArH), 3.75 (3H, s, CH_3O), 3.53 (2H, s, $ArCH_2N$), 2.83 (2H, t, *J* 7, $ArCH_2CH_2N$), 2.65 (2H, t, *J* 7, $ArCH_2CH_2N$), 2.42 (3H, s, CH_3N); δ_C(50 MHz; $CDCl_3$) 28.1 ($ArCH_2CH_2N$), 45.9 (NCH_3), 53.0 ($ArCH_2CH_2N$), 55.1 (CH_3O), 58.0 ($ArCH_2N$), 111.1, 112.5, 126.0, 129.6, 135.8, 157.7; *m*/*z* 178 (11%), 177 (M$^+$, 38), 176 (100), 161 (6), 146 (7), 135 (11), 134 (100), 133 (10), 132 (12), 131 (7), 119 (9), 118 (5), 117 (7), 105 (13), 104 (26), 103 (14), 91 (35), 79 (5), 78 (25), 77 (11), 65 (11). Picrate: mp 140–142 °C (EtOH) (lit.,[37] 142–143 °C).

6,7-Dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline 6f. *N*-Benzotriazol-1-ylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **5f** (0.21 g, 0.6 mmol) was reduced with $NaBH_4$ (0.07 g, 1.9 mmol) to yield product **6f** (0.09 g, 67%) as a white residue. Mp 74–75 °C (EtOH); δ_H(200 MHz; $CDCl_3$; Me_4Si) 6.59 (1H, s), 6.50 (1H, s), 3.82 (6H, s, CH_3O), 3.49 (2H, s, $ArCH_2N$), 2.83 (2H, t, *J* 5, $ArCH_2CH_2N$), 2.65 (2H, t, *J* 5, $ArCH_2CH_2N$), 2.43 (3H, s, CH_3N); δ_C(50 MHz; $CDCl_3$) 28.5 ($ArCH_2CH_2N$), 45.9 (NCH_3), 52.8 ($ArCH_2CH_2N$), 55.7 (CH_3O), 57.4 ($ArCH_2N$), 109.2, 111.3, 125.7, 126.6, 147.2, 147.5; *m*/*z* 208 (23%), 207 (M$^+$, 29), 206 (100), 192 (9), 191 (7), 190 (16), 165 (8), 164 (68), 162 (7), 149 (25), 148 (5), 121 (25), 103 (10), 93 (8), 91 (16), 77 (16). Picrate: mp 154–156 °C (EtOH) (lit.,[33] 160 °C).

Acknowledgments

C. L. is grateful for the receipt of a NTU Postgraduate Research Scholarship and N. P. would like to thank A. R. Katritzky for a short training in Benzotriazole chemistry.

References

1 K. W. Bentley, *The Isoquinoline Alkaloids*, Harwood Academic Publishers, Amsterdam, 1998.
2 *Isoquinolines*, ed. F. G. Kathawala, G. M. Coppola and H. F. Schuster, Wiley, New York, 1990.
3 M. Shamma, *The Isoquinoline Alkaloids: Chemistry and Pharmacology*, Academic Press, New York, 1972.
4 K. S. P. Mcnaught, C. Altomare, S. Cellamare, A. Carotti, U. Thull, P. A. Carrupt, B. Testa, P. Jenner and C. D. Marsden, *NeuroReport*, 1995, **6**, 1105.
5 T. Fukuda, *Brain Res.*, 1994, **639**, 325.
6 H. Rollema, E. A. Johnson, R. G. Booth, P. Caldera, P. Lampen, S. K. Youngster, A. J. Trevor, N. Naiman and N. Castagnoli Jr., *J. Med. Chem.*, 1990, **33**, 2221.
7 W. L. Mendelson, C. B. Spainhour Jr., S. S. Jones, B. L. Lam and K. L. Wert, *Tetrahedron Lett.*, 1980, **21**, 1393.
8 W. E. Bondinell, F. W. Chapin, G. R. Girard, C. Kaiser, A. J. Krog, A. M. Pavloff, M. S. Schwartz, J. S. Silvestri, P. D. Vaidya, B. L. Lam, G. R. Wellman and R. G. Pendleton, *J. Med. Chem.*, 1980, **23**, 506.
9 J. Gal, R. J. Wienkam and N. Castagnoli Jr., *J. Org. Chem.*, 1974, **39**, 418.

10 G. Fodor, J. Gal and B. A. Phillips, *Angew. Chem.*, *Int. Ed. Engl.*, 1972, **11**, 919.
11 W. M. Whaley and T. R. Govindachari, *Org. React.*, 1951, **6**, 74.
12 E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797.
13 W. M. Whaley and T. R. Govindachari, *Org. React.*, 1951, **6**, 151.
14 J. M. Bobbitt, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1973, p. 99.
15 W. J. Gensler, *Org. React.*, 1951, **6**, 191.
16 T. J. N. Watson, *J. Org. Chem.*, 1998, **63**, 406.
17 G. E. Stokker, *Tetrahedron Lett.*, 1996, **37**, 5453.
18 N. Sotomayor, E. Domínguez and E. Lete, *Tetrahedron*, 1995, **51**, 12159.
19 A. Kubo, N. Saito, N. Kawakami, Y. Matsuyama and T. Miwa, *Synthesis*, 1987, **9**, 824.
20 L. W. Deady, N. Pirzada and R. D. Topsom, *J. Chem. Soc.*, *Chem. Commun.*, 1971, 799.
21 A. R. Katritzky, X. Lan, J. Z. Yang and O. V. Denisko, *Chem. Rev.*, 1998, **98**, 409.
22 A. R. Katritzky, X. Lan and W.-Q. Fan, *Synthesis*, 1994, **5**, 445.
23 A. R. Katritzky, S. Rachwal and G. J. Hitchings, *Tetrahedron*, 1991, **47**, 2683.
24 J. H. Burckhalter, V. C. Stephens and L. A. R. Hall, *J. Am. Chem. Soc.*, 1952, **74**, 3868.
25 A. R. Katritzky, S. Rachwal and B. Rachwal, *J. Chem. Soc.*, *Perkin Trans. 1*, 1987, 799.
26 A. R. Katritzky, X. Lan and Z. Zhang, *J. Heterocycl. Chem.*, 1993, **30**, 381.
27 A. R. Katritzky and X. Lan, *Chem. Soc. Rev.*, 1994, **23**, 363.
28 A. R. Katritzky, H. Lang and X. Lan, *Tetrahedron*, 1993, **49**, 2829.
29 A. R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala and L. Urogdi, *J. Chem. Soc.*, *Perkin Trans. 1*, 1989, 225.
30 A. R. Katritzky, W.-Q. Fan and Q.-H. Long, *Synthesis*, 1993, **2**, 229.
31 A. R. Katritzky, S. Rachwal and R. Ollmann, *J. Heterocycl. Chem.*, 1994, **31**, 775.
32 M. Okamoto and M. Yamada, *Chem. Pharm. Bull.*, 1963, **11**, 554.
33 *Dictionary of Alkaloids*, ed. I. W. Southon and J. Buckingham, Chapman and Hall, London, 1989.
34 M. Schlosser, G. Simig and H. Geneste, *Tetrahedron*, 1998, **54**, 9023.
35 R. M. Williams, P. P. Ehrlich, W. Zhai and J. Hendrix, *J. Org. Chem.*, 1987, **52**, 2615.
36 *Dictionary of Organic Compounds*, ed. J. Buckingham, Chapman and Hall, New York, 1982.
37 Ochiai and Nakagome, *Yakugaku Zasshi*, 1958, **78**, 1438 (*Chem. Abstr.*, 1959, 8138).

Paper 8/07543C