Conversions of 2-aminopyridines into 5-substituted derivatives mediated by 1-hydroxymethylbenzotriazole

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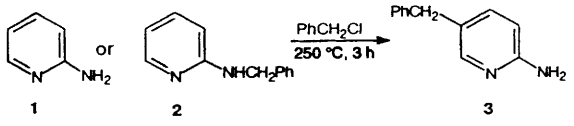
2-Aminopyridines are benzotriazolylmethylated at the 5-position by 1-hydroxymethylbenzotriazole. The methylene group of 2-amino-5-(benzotriazolylmethyl)pyridines **6** can be mono- or di-lithiated and subsequently substituted by various electrophiles. The benzotriazole moiety in both the primary products **6**, and in their methylene-substituted derivatives **8** and **9**, is displaced by alkyl and aryl anions derived from Grignard reagents, or by alkoxide and thioalkoxide anions. Moreover, the derivative **8a** undergoes smooth elimination of benzotriazole under basic conditions to generate the 5-vinyl-substituted 2-aminopyridine **12**. These approaches allow the synthesis of many new types of 5-substituted 2-aminopyridines.

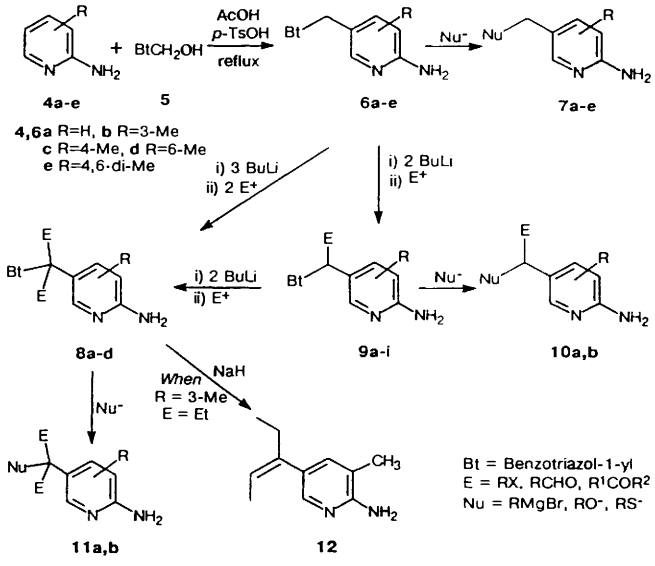
While the direct electrophilic alkylation of the pyridine ring is intrinsically unfavourable due to the pyridine nitrogen deactivating effect,[1] electron-donating groups such as amino or hydroxy activate electrophilic substitution at the *ortho* and *para* positions as in other aromatic systems. Nitrations and sulfonations of hydroxy- and amino-pyridines are well known, but few electrophilic Friedel–Crafts type *C*-alkylations have been reported. 3-Ethoxypyridine was alkylated by benzyl chloride or chlorocyclohexane at high temperature (180 °C) in the presence of anhydrous aluminium chloride to give 2-benzyl-3-ethoxypyridine and 5-cyclohexyl-3-ethoxypyridine in 90% and 60% yields, respectively.[2] Alkylations of 2-pyridones with triphenylchloromethane without a catalyst or with triphenylmethanol in the presence of sulfuric acid at 250 °C yield 5-triphenylmethyl-2-pyridones in 45–60% yields.[3] *N*-Benzylpyridinium cations can undergo thermolytic rearrangement to give *C*-benzylpyridines.[4] Kowalski reported the preparation of 2-amino-5-benzylpyridine **3** in 48% yield by heating 2-aminopyridine **1** with benzyl chloride at 250 °C and, in unspecified yield, by intermolecular rearrangement of 2-benzylaminopyridine **2** in the presence of benzyl chloride.[5,6] For an MO study of these reactions see ref. 7. Direct alkylations of 2,6-diaminopyridine with benzyl chloride,[8] and thermal,[9] acid-catalysed (Hofmann–Martius reaction)[10] and Lewis acid-catalysed ($AlCl_3$)[11] rearrangements of *N*-mono- and *N*,*N*′-bis(arylmethyl)-2,6-diaminopyridines into 3- and 3,5-substituted derivatives have also been reported, but in all cases, the alkylating reagents were limited to those of the benzylic type and the yields varied (14–77%).



Previous work in our laboratory has demonstrated the versatility of benzotriazole as a synthetic auxiliary in organic synthesis.[12–14] The benzotriazole anion is a good activating and leaving group, and has been utilized in many transformations of organic compounds. In particular, benzotriazole-mediated methods for the alkylation of phenylamines have been developed in this laboratory;[15–17] anilines, *N*-alkylanilines and *N*,*N*-dialkylanilines are readily alkylated by 1-(hydroxymethyl)-1*H*-benzotriazole at the *para* position to give 4-(benzotriazol-1-ylmethyl)-substituted derivatives. The active methylene group in 4-(benzotriazol-1-ylmethyl)anilines undergoes smooth lithiation and substitution by electrophiles. The subsequent displacement of benzotriazole from the parent compounds or their substituted products by carbanions derived from Grignard reagents, by hydride from lithium aluminium hydride ($LiAlH_4$), or by aromatic nucleophiles, leads to a variety of 4-substituted derivatives. This reaction concept has now been extended to 2-aminopyridines to provide a new and general synthetic approach for the preparation of 5-substituted 2-aminopyridines.

Results and discussion

2-Aminopyridines **4a–e** reacted with 1-hydroxymethylbenzotriazole **5** in acetic acid in the presence of a catalytic amount of toluene-*p*-sulfonic acid to afford the corresponding 5-substituted products **6a–e** in 53–73% yields (Scheme 1 and Table 1).



Scheme 1

Thus, heating a mixture of **4a** and 1-hydroxymethylbenzotriazole under reflux for 72 h gave 5-benzotriazolylmethyl-2-aminopyridine **6a** in 53% yield. Compounds **6b–e** were prepared similarly. Aminopyridines **6** were readily purified by recrystallization from ethanol except in the case of **6a** which was purified by column chromatography. The presence of toluene-*p*-sulfonic acid in these reactions is essential.

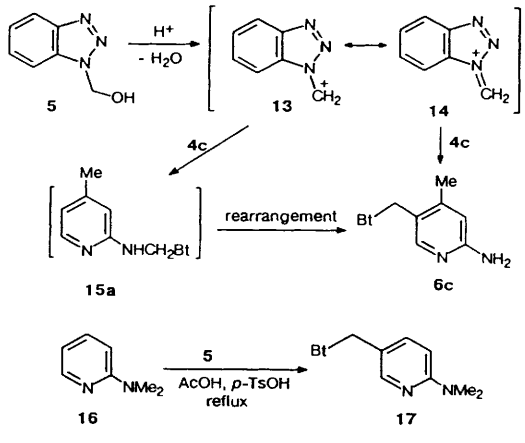
The reactions described above involve protonation of the

Table 1 Preparative data of compounds **6a–e**, **7a–e**, **8a–d**, **9a–i**, **10a–b** and **11a–b**

Product	R	E	Nu	Yield (%)	Mp (°C)	Found (%) (Required) C	H	N
6a	H	—	—	53	183–185	64.3 (63.99)	4.9 (4.92)	30.7 (31.09)
6b	3-Me	—	—	73	174–175	64.9 (65.26)	5.5 (5.48)	29.5 (29.27)
6c	4-Me	—	—	60	213–214	65.6 (65.26)	5.6 (5.48)	29.5 (29.27)
6d	6-Me	—	—	62	208–210	65.5 (65.26)	5.5 (5.67)	28.9 (29.27)
6e	4,6-Me_2	—	—	61	247–249		254.1418/254.1406[a]	
7a	3-Me	—	Bu	77	oil	74.45 (74.11)	10.25 (10.18)	15.3 (15.71)
7b	6-Me	—	Ph	49	113–114	79.1 (78.75)	7.3 (7.21)	13.9 (14.13)
7c	4-Me	—	SPh	94	110–111	67.7 (67.79)	6.1 (6.13)	12.0 (12.16)
7d	3-Me	—	SBu	48	34–36	63.0 (62.81)	8.7 (8.63)	13.3 (13.32)
7e	6-Me	—	OBu	70	45–47		195.1520/195.1497[a]	
8a	3-Me	Et	—	85	161–162	69.4 (69.13)	7.2 (7.17)	23.8 (23.76)
8b	4-Me	3-Me-Bu	—	78	180–181		380.2769/280.2814[a]	
8c	3-Me	C_8H_{17}	—	81	100–101	75.45 (75.12)	9.95 (9.78)	15.1 (15.10)
8d	3-Me	Et, Pr	—	60	78–81		310.1973/310.2032[a]	
9a	3-Me	Et	—	60	152–153	67.7 (67.39)	6.6 (6.41)	26.1 (26.20)
9b	3-Me	Pr^i	—	78	192–193	68.2 (68.30)	6.8 (6.81)	24.9 (24.89)
9c	3-Me	3-Me-Bu	—	61	136–137	70.05 (69.87)	7.6 (7.49)	22.6 (22.63)
9d	3-Me	C_8H_{17}	—	65	106–107	71.6 (71.63)	8.45 (8.32)	19.55 (19.92)
9e	4,6-Me_2	Et	—	59	183–184	68.7 (68.30)	7.0 (6.81)	24.7 (24.89)
9fI	3-Me	PhCH(OH)	—	36	223–225	69.4 (69.55)	5.6 (5.54)	20.2 (20.28)
9fII	3-Me	PhCH(OH)	—	17	262–264	69.7 (69.55)	5.6 (5.54)	20.3 (20.28)
9g	3-Me	$Ph_2C(OH)$	—	72	280–281	74.3 (74.09)	5.65 (5.50)	16.4 (16.2)
9h	3-Me	$Me_2C(OH)$	—	69	237–230	64.8 (64.63)	6.5 (6.44)	23.5 (23.55)
9i	4-Me	$Me_2C(OH)$	—	66	103–105	64.4 (64.63)	6.5 (6.44)	23.3 (23.55)
10a	3-Me	Et	Bu	65	oil		206.1782/206.1783[a]	
10b	3-Me	$Ph_2C(OH)$	Bu	70	168–170	79.6 (79.96)	7.9 (7.83)	8.1 (7.77)
11a	3-Me	Et	Bu	83	34–36		234.2036/234.2096[a]	
11b	3-Me	Et	OEt	72	44–46	70.3 (70.23)	9.7 (9.97)	13.0 (12.60)

[a] HRMS data.

hydroxy group of **5** under the strongly acidic conditions, followed by loss of a water molecule to generate the reactive cation **13**↔**14**,[12] which attacks the pyridine ring directly to yield the 5-substituted derivatives **6**. Alternatively, cation **13**↔**14** reacts with the amino group to form *N*-substituted intermediates of type **15** which subsequently rearrange to **6** (Hofmann–Martius reaction). The dual pathway mechanism depicted in Scheme 2 is supported by the following: (i) under



Scheme 2

similar acidic conditions, heating 2-[(benzotriazol-1-ylmethyl)amino]-4-methylpyridine **15a**, prepared from **4c** and 1-hydroxymethylbenzotriazole **5** in refluxing ethanol, resulted in formation of the same 2-amino-5-(benzotriazolylmethyl)-pyridine **6c** as prepared by the direct reaction of **4c** with **5**, and (ii) 2-dimethylamino)pyridine was also benzotriazolylmethylated upon treatment with 1-hydroxymethylbenzotriazole **5** in refluxing acetic acid for 60 h to give 2-(dimethylamino)-5-(benzotriazol-1-ylmethyl)pyridine **17** in 56% yield. As mentioned above, this type of rearrangement (Hofmann–Martius reaction) was previously observed for *N*-benzylated 2,6-diaminopyridines.[10] The fact that benzotriazolylmethylation occurred exclusively at the *para* position relative to the amino group, is also consistent with the aniline cases.[15–17] Steric effects play an important role in these reactions.

2-Amino-5-(benzotriazol-1-ylmethyl)pyridines **6b**, **6c** and **6e** readily underwent lithiation with butyllithium to form deep greenish blue solutions, which decolourized immediately on addition of the appropriate electrophiles (alkyl halide, aldehyde or ketone) to give derivatives **9a–i**. Thus, treatment of compound **6b** with 2 equiv. of BuLi in THF at −78 °C for 15 min followed by the addition of ethyl bromide afforded **9a** in 60% yield. Compounds **9b–e**,**g–i** were similarly obtained in 59–78% yields. In the case of **9f** in which an aldehyde was employed as the electrophile, two diastereoisomers (**9fI** and **9fII**) were obtained due to the existence of two chiral centres, and were separated to give yields of 36% and 17%, respectively.

When 3 equiv. of BuLi and 2 equiv. of the electrophile were used, the disubstituted products **8a–c** were prepared in 78–85% yields. When alkyl halides were used as the electrophiles, an alternative procedure both in the mono- and di-lithiation could be employed with identical results: the 'reversal procedure'. The electrophile was added to the reaction solution before the addition of BuLi. The anions formed by deprotonation immediately reacted with the alkyl halides to give the methylene-alkylated product. In the case of **8d**, a stepwise treatment, *i.e.* addition of two equivalents of BuLi and one equivalent of ethyl bromide, followed by addition of one further equivalent of BuLi and propyl bromide, afforded the bis-alkylated product containing two different substituents. This approach allows the convenient introduction of various functionalities into the molecule. Since two equivalents (in the cases of **9a–i**) or three equivalents (in the cases of **8a–d**) of BuLi are used, the amino group of the 2-aminopyridines is still present in the molecule as the lithium amide after reaction with

the electrophile. Therefore, the reactions should be quenched with water at −78 °C to avoid decomposition of the lithium salt which could occur at higher temperatures.

The benzotriazolyl group in the primary compounds **6b,d** and alkylated products **8a** and **9a,g** is now shown to be displaced efficiently by Grignard reagents to give the substituted derivatives. Thus, heating **6b** with an excess of butylmagnesium bromide in tetrahydrofuran under reflux for 8 h gave 2-amino-5-pentylpyridine **7a** in 77% yield. The reactions with Grignard reagents are expected to be general, as phenylmagnesium bromide also succeeded and other Grignard reagents have been used in related work. Compounds **7b**, **10a,b** and **11a** were similarly obtained in 49–83% yields. The benzotriazole generated in these reactions was readily extracted into the aqueous solution under basic conditions during work up; the desired compounds were easily purified by flash column chromatography.

Displacement of the benzotriazolyl group by nucleophilic alcohols and thiols was investigated. Thus, refluxing a mixture of **6c** and NaSPh in Bu'OH for 72 h gave the expected product **7c** in 94% yield. Compounds **7d,e** and **11b** were similarly prepared by treatment of the benzotriazole adducts **6b**, **6d** or **8a** with the corresponding alcohol or thiol in good yields. Treatment of compound **8a** with sodium hydride in refluxing THF for 4 h afforded 2-amino-5-(1-ethylprop-1-enyl)-3-methylpyridine **12** in 58% yield.

The structures of all intermediates and final products were confirmed by ^{1}H NMR, ^{13}C NMR, and elemental analysis or HRMS. The methylene groups in 2-amino-5-(benzotriazol-1-ylmethyl)pyridines **6a–e** show proton signals in the region of δ 5.79–5.80 and carbon signals between δ 45.8–48.9 respectively. A substituent in the mono-lithiated derivatives shifts both the corresponding protons and carbon downfield as shown in the cases of **9a–i**. Similarly, the carbon signals shifted downfield in the cases of **8a–d**. The displacement products **7a–e**, **10a,b**, **11a,b** and **12** clearly show the disappearance of the characteristic benzotriazolyl signals.

In summary, a new and versatile method has been developed for the conversion of 2-aminopyridines into 5-substituted derivatives. Novel examples of electrophilic substitutions of pyridine rings were provided. The present method utilizes readily available starting materials, relatively mild reaction conditions, and short sequences, thus providing a convenient approach for the synthesis of 5-substituted 2-aminopyridines.

Experimental

General

Melting points were determined with a Köfler hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer; *J* values are given in Hz. High resolution mass measurements were recorded on an AEI MS-30 mass spectrometer. Elemental analyses were performed on a Carlo Erba-1106 instrument. Tetrahydrofuran and diethyl ether were predried and freshly distilled from sodium and benzophenone. Column chromatography was carried out on MCB silica gel (230–400 mesh).

General procedure for the alkylation of 2-aminopyridines 4a–e and 2-(dimethylamino)pyridine 16. Preparation of compounds 6a–e and 17

A mixture of 1-(hydroxymethyl)-1*H*-benzotriazole **5** (3.75 g, 25 mmol), the corresponding 2-aminopyridine (25 mmol) and a catalytic amount of toluene-*p*-sulfonic acid (30 mg) in acetic acid (25 cm^3) was heated under reflux for 72 h. The acetic acid was removed under reduced pressure, and to the residue was added aqueous Na_2CO_3 (10% w/v, 50 cm^3). The product was extracted with ethyl acetate (4 × 80 cm^3), washed with aqueous sodium hydroxide (10%, 50 cm^3), then water (80 cm^3), and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the solid was recrystallized or chromatographed as indicated below, to give the pure products **6a–e** and **17**. Melting points, elemental analyses and preparative data are given in Table 1.

2-Amino-5-(benzotriazol-1-ylmethyl)pyridine 6a. The crude product from 2-aminopyridine was chromatographed with chloroform–ethyl acetate (10:1), δ_H(DMSO) 5.81 (2 H, s), 6.10 (2 H, s), 6.43 (1 H, d, *J* 8.3), 7.38–7.42 (2 H, m), 7.54 (1 H, t, *J* 7.5), 7.92 (1 H, d, *J* 8.3), 8.07 (1 H, d, *J* 8.4) and 8.14 (1 H, s); δ_C(DMSO) 48.7, 107.9, 110.7, 118.8, 119.1, 123.9, 127.3, 132.3, 137.2, 145.4, 147.8 and 159.7.

2-Amino-5-(benzotriazol-1-ylmethyl)-3-methylpyridine 6b. The crude product from 2-amino-3-methylpyridine was crystallized from ethanol, δ_H(DMSO) 2.00 (3 H, s), 5.79 (2 H, s), 5.88 (2 H, s), 7.28 (1 H, s), 7.40 (1 H, t, *J* 8.2), 7.55 (1 H, t, *J* 8.0), 7.90 (1 H, d, *J* 8.3), 8.03 (1 H, s) and 8.07 (1 H, d, *J* 8.3); δ_C(DMSO) 17.0, 48.8, 110.8, 116.1, 119.2, 119.5, 124.1, 127.4, 132.4, 137.0, 145.2, 145.5 and 158.4.

2-Amino-5-(benzotriazol-1-ylmethyl)-4-methylpyridine 6c. The crude product from 2-amino-4-methylpyridine was crystallized from ethanol, δ_H(DMSO) 2.11 (3 H, s), 5.82 (2 H, s), 6.00 (2 H, s), 6.29 (1 H, s), 7.40 (1 H, t, *J* 7.4), 7.53 (1 H, t, *J* 7.1), 7.81 (1 H, d, *J* 8.4), 8.05 (1 H, s) and 8.06 (1 H, d, *J* 7.3); δ_C(DMSO) 18.6, 47.5, 108.9, 110.8, 117.9, 119.2, 124.0, 127.3, 132.6, 145.3, 147.0, 149.0 and 160.1.

2-Amino-5-(benzotriazol-1-ylmethyl)-6-methylpyridine 6d. The crude product from 2-amino-6-methylpyridine was recrystallized from ethanol, δ_H(DMSO) 2.32 (3 H, s), 5.80 (2 H, s), 6.00 (2 H, s), 6.30 (1 H, d, *J* 8.6), 7.35 (1 H, d, *J* 8.5), 7.39 (1 H, t, *J* 6.7), 7.52 (1 H, t, *J* 6.7), 7.77 (1 H, d, *J* 8.4) and 8.07 (1 H, d, *J* 8.4); δ_C(DMSO) 21.6, 48.9, 105.2, 110.7, 116.1, 119.2, 123.9, 127.2, 132.5, 138.8, 145.3, 155.1 and 159.1.

2-Amino-5-(benzotriazol-1-ylmethyl)-4,6-dimethylpyridine 6e. The crude product from 2-amino-4,6-dimethylpyridine was crystallized from ethanol, δ_H(DMSO) 2.13 (3 H, s), 2.30 (3 H, s), 5.78 (2 H, s), 5.88 (2 H, s), 6.20 (1 H, s), 7.38 (1 H, t, *J* 7.5), 7.52 (1 H, t, *J* 7.5), 7.66 (1 H, d, *J* 8.4) and 8.04 (1 H, d, *J* 8.3); δ_C(DMSO) 19.3, 22.1, 45.8, 106.8, 110.5, 115.1, 119.2, 123.8, 127.2, 132.7, 145.0, 147.8, 156.0 and 158.8.

5-(Benzotriazol-1-ylmethyl)-2-(dimethylamino)pyridine 17. The crude product from 2-(dimethylamino)pyridine was crystallized from ethanol (56%), mp 164–165 °C (Found: M$^+$, 253.1334. $C_{14}H_{15}N_5$ requires *M*, 253.1405); δ_H($CDCl_3$) 3.08 (6 H, s), 5.73 (2 H, s), 6.45 (1 H, d, *J* 8.8), 7.30–7.45 (4 H, m), 8.05 (1 H, d, *J* 8.2) and 8.29 (1 H, d, *J* 2.5); δ_C($CDCl_3$) 38.0, 49.8, 106.0, 109.8, 117.4, 120.0, 123.8, 127.3, 132.3, 137.0, 146.4, 147.4 and 159.3.

General procedure for the lithiation of compounds 6b, 6c and 6e. Preparation of 8a–d and 9a–i

To a solution of 2-amino-5-(benzotriazol-1-ylmethyl)pyridines **6b**, **6c** or **6e** (5 mmol) in THF (100 cm^3) at −78 °C was added butyllithium (for **8a–d**, 15 mmol; for compounds **9a–i**, 10 mmol) under nitrogen. The mixture developed an intense greenish blue colour immediately. The solution was stirred for 15 min at this temperature and the appropriate electrophile (for **8a–d**, 10 mmol; for compounds **9a–i**, 5 mmol) was added. The mixture was kept at this temperature for a further 15 min. Water (50 cm^3) was then added to the mixture at −78 °C, and the solution was extracted with diethyl ether (3 × 150 cm^3), washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed on silica gel with methylene chloride and hexane (1:1) as the eluent. In the case of **8d**, the lithiation was carried out in a stepwise procedure: 2 equiv. of BuLi were added to the solution of **6b** and 1 equiv. of ethyl bromide. After 15 min, a further 1 equiv. of BuLi and 1

equiv. of propyl bromide were added. The temperature for the whole process was kept at −78 °C and the workup was as described above. Melting points, elemental analyses and preparative data are given in Table 1. The electrophiles used were: **8a**, EtBr; **8b**, 3-Me-BuBr; **8c**, $C_8H_{17}Br$; **8d**, EtBr and PrBr; **9a**, EtBr; **9b**, Pr^{i}Br; **9c**, 3-Me-BuBr; **9d**, $C_8H_{17}Br$; **9e**, EtBr; **9f**, PhCHO; **9g**, PhCOPh; **9h**, acetone; **9i**, acetone.

2-Amino-5-[1-(benzotriazol-1-yl)-4-methyl-1-(3-methylbutyl)pentyl]-4-methylpyridine 8b. $\delta_H(CDCl_3)$ 0.76 (6 H, d, *J* 6.2), 0.80 (6 H, d, *J* 6.6), 1.00–1.03 (2 H, m), 1.29 (3 H, s), 1.44–1.48 (2 H, m), 2.58–2.64 (4 H, m),4.50 (2 H, s), 6.16 (1 H, s), 6.84 (1 H, d, *J* 8.4), 7.16 (1 H, t, *J* 7.4), 7.27 (1 H, t, *J* 7.3), 8.05 (1 H, d, *J* 8.3) and 8.30 (1 H, s); $\delta_C(CDCl_3)$ 19.4, 22.5, 28.0, 32.2, 32.7, 69.1, 111.6, 112.0, 119.9, 123.7, 126.2, 126.5, 132.2, 146.5, 146.8, 147.9 and 158.0.

2-Amino-5-[1-(benzotriazol-1-yl)-1-octylnonyl]-3-methylpyridine 8c. $\delta_H(CDCl_3)$ 0.85 (6 H, t, *J* 7.2), 1.12–1.30 (24 H, m), 2.02 (3 H, s), 2.40–2.52 (2 H, m), 2.65–2.75 (2 H, m), 4.62 (2 H, s), 6.85 (1 H, d, *J* 8.6), 6.89 (1 H, s), 7.20 (1 H, t, *J* 7.4), 7.27 (1 H, t, *J* 7.4), 7.96 (1 H, d, *J* 2.2) and 8.07 (1 H, d, *J* 8.2): $\delta_C(CDCl_3)$ 14.0, 17.2, 22.5, 23.0, 29.2, 29.6, 31.7, 36.3, 69.1, 112.3, 116.8, 120.0, 123.5, 126.4, 128.8, 132.1, 136.1, 143.3, 146.9 and 156.6.

2-Amino-5-[1-(benzotriazol-1-yl)-1-ethylbutyl]-3-methylpyridine 8d. $\delta_H(CDCl_3)$ 0.64 (3 H, t, *J* 7.2), 0.80–0.90 (4 H, m), 1.20–1.22 (1 H, m), 1.25 (3 H, s), 2.50–2.80 (4 H, m), 4.84 (2 H, s), 6.19 (1 H, s), 6.86 (1 H, d, *J* 8.4), 7.16 (1 H, t, *J* 7.2), 7.28 (1 H, t, *J* 7.2), 8.03 (1 H, d, *J* 8.3) and 8.28 (1 H, s); $\delta_C(CDCl_3)$ 7.7, 14.1, 16.6, 19.2, 27.8, 36.4, 69.3, 111.5, 111.9, 119.7, 123.6, 125.6, 126.4, 132.1, 146.4, 146.6, 147.7 and 158.1.

2-Amino-5-[1-(benzotriazol-1-yl)propyl]-3-methylpyridine 9a. $\delta_H(CDCl_3)$ 0.94 (3 H, t, *J* 7.4), 2.03 (3 H, s), 2.50 (1 H, m), 2.71 (1 H, m), 4.63 (1 H, br s), 5.60 (1 H, t, *J* 7.1), 7.35 (4 H, m) and 8.05 (2 H, d, *J* 4.9); $\delta_C(CDCl_3)$ 11.1, 17.0, 27.7, 62.8, 109.7, 117.0, 119.9, 123.8, 124.8, 127.0, 132.5, 136.2, 144.1, 146.1 and 157.3.

2-Amino-5-[1-(benzotriazol-1-yl)-2-methylpropyl]-3-methylpyridine 9b. $\delta_H(CDCl_3)$ 0.87 (3 H, d, *J* 6.5), 1.01 (3 H, d, *J* 6.7), 2.06 (3 H, s), 3.17 (1 H, m), 4.54 (2 H, s), 5.13 (1 H, d, *J* 10.7), 7.33 (1 H, t, *J* 7.1), 7.46 (1 H, t, *J* 7.1), 7.53 (1 H, d, *J* 8.4), 7.56 (1 H, s), 8.03 (1 H, d, *J* 8.4) and 8.06 (1 H, s); $\delta_C(CDCl_3)$ 17.1, 20.2, 20.4, 32.6, 68.0, 109.4, 117.1, 119.9, 123.8, 124.4, 127.1, 133.0, 136.8, 144.9, 145.7 and 157.3.

2-Amino-5-[1-(benzotriazol-1-yl)-2-methylpentyl]-3-methylpyridine 9c. $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.6), 1.13 (1 H, m), 1.30 (1 H, m), 1.62 (1 H, m), 2.16 (3 H, s), 2.47 (1 H, m), 2.65 (1 H, m), 4.57 (2 H, s), 6.00 (1 H, t, *J* 6.6), 6.30 (1 H, s), 7.30 (3 H, m), 8.04 (1 H, d, *J* 7.8) and 8.29 (1 H, s); $\delta_C(CDCl_3)$ 19.0, 22.4, 27.7, 31.3, 35.7, 59.6, 110.1, 120.0, 122.6, 123.7, 127.0, 132.0, 146.4, 146.8, 147.8 and 158.3.

2-Amino-5-[1-(benzotriazol-1-yl)nonyl]-3-methylpyridine 9d. $\delta_H(CDCl_3)$ 0.85 (3 H, t, *J* 6.5), 1.20 (12 H, m), 2.04 (3 H, s), 2.45 (1 H, m), 2.70 (1 H, m), 4.62 (2 H, br s), 5.65 (1 H, t, *J* 6.9), 7.40 (4 H, m), 8.03 (1 H, s) and 8.06 (1 H, d, *J* 8.3); $\delta_C(CDCl_3)$ 14.0, 17.0, 22.5, 26.4, 29.0, 29.2, 31.7, 34.5, 61.2, 109.7, 117.1, 119.9, 123.8, 125.1, 127.0, 132.5, 136.3, 144.0, 146.1 and 157.3.

2-Amino-5-[1-(benzotriazol-1-yl)propyl]-4,6-dimethylpyridine 9e. $\delta_H(CDCl_3)$ 1.17 (3 H, t, *J* 7.4), 1.93 (3 H, s), 2.32 (3 H, s), 2.52 (1 H, m), 3.21 (1 H, m), 4.63 (2 H, s), 5.85 (1 H, t, J 7.1), 6.16 (1 H, s), 6.95 (1 H d, J 8.6), 7.30 (2 H, m) and 8.04 (1 H, d, J 8.7); $\delta_C(CDCl_3)$ 11.5, 19.8, 22.8, 25.6, 61.2, 109.0, 110.1, 119.7, 120.7, 123.7, 126.9, 133.1, 146.3, 147.7, 155.0 and 157.1.

2-Amino-5-[1-(benzotriazol-1-yl)-2-hydroxy-2-phenylethyl]-3-methylpyridine 9f-I. δ_H(DMSO) 2.07 (3 H, s), 5.71 (1 H, dd, *J* 9.3, 4.6), 5.83 (2 H, s), 5.95 (1 H, d, *J* 4.7), 6.08 (1 H, d, *J* 9.6), 7.00–7.12 (3 H, m), 7.20–7.40 (4 H, m), 7.71 (1 H, s), 7.84 (1 H, d, *J* 7.7), 7.88 (1 H, d, *J* 7.7) and 8.19 (1 H, s); δ_C(DMSO) 17.2, 64.8, 74.0, 110.5, 115.4, 118.7, 121.6, 123.7, 126.8, 126.9, 127.3, 127.6, 132.5, 136.9, 142.3, 144.4, 145.8 and 158.1.

2-Amino-5-[1-(benzotriazol-1-yl)-2-hydroxy-2-phenylethyl]-3-methylpyridine 9f-II. δ_H(DMSO) 1.92 (3 H, s), 5.69 (2 H, s), 5.79–5.82 (2 H, m), 6.07–7.12 (1 H, m), 7.16–7.30 (3 H, m), 7.37 (1 H, t, *J* 7.2), 7.45–7.56 (4 H, m), 7.87 (1 H, s), 8.03 (1 H, d, *J* 8.5) and 8.19 (1 H, d, *J* 8.3); δ_C(DMSO) 17.0, 65.9, 74.5, 111.3, 115.3, 118.8, 120.7, 123.7, 126.8, 127.5, 127.6, 127.9, 133.5, 136.7, 142.0, 144.9, 145.5 and 157.9.

2-Amino-5-[1-(benzotriazol-1-yl)-2-hydroxy-2,2-diphenylethyl]-3-methylpyridine 9g. δ_H(DMSO) 1.87 (3 H, s), 5.64 (2 H, s), 6.24 (1 H, s), 6.99 (1 H, d, *J* 7.2), 7.04–7.16 (3 H, m), 7.22–7.37 (4 H, m), 7.45 (1 H, s), 7.50–7.60 (3 H, m), 7.74 (2 H, d, *J* 7.3), 7.92 (1 H, s), 7.94 (1 H, d, *J* 8.3) and 8.24 (1 H, d, *J* 8.4); δ_C(DMSO) 17.2, 65.4, 81.0, 111.6, 114.6, 118.9, 119.8, 124.2, 125.1, 126.1, 126.6, 127.4, 127.7, 127.8, 133.2, 137.7, 144.1, 146.0, 146.5 and 157.6.

2-Amino-5-[1-(benzotriazol-1-yl)-2-hydroxy-2-methylpropyl]-3-methylpyridine 9h. δ_H(DMSO) 1.19 (3 H, s), 1.26 (3 H, s), 2.01 (3 H, s), 4.93 (1 H, s), 5.78 (2 H, s), 5.85 (1 H, s), 7.38 (1 H, t, *J* 8.0), 7.53 (1 H, t, *J* 7.0), 7.76 (1 H, s), 8.03 (1 H, d, *J* 8.1), 8.06 (1 H, d, *J* 8.0) and 8.16 (1 H, s); δ_C(DMSO) 17.3, 26.9, 27.8, 68.5, 72.5, 111.5, 114.8, 118.8, 120.7, 123.8, 126.9, 133.9, 138.1, 144.3, 146.3 and 158.0.

2-Amino-5-[1-(benzotriazol-1-yl)-2-hydroxy-2-methylpropyl]-4-methylpyridine 9i. $\delta_H(CDCl_3)$ 1.37 (3 H, s), 1.40 (3 H, s), 2.42 (3 H, s), 4.50 (2 H, br s), 5.83 (1 H, s), 6.33 (1 H, s), 7.32–7.42 (1 H, m), 7.46–7.49 (2 H, m), 8.10 (1 H, d, *J* 8.2) and 8.55 (1 H, s); $\delta_C(CDCl_3)$ 20.0, 27.0, 28.9, 65.0, 74.3, 109.1, 109.9, 120.1, 120.7, 124.2, 127.7, 133.5, 145.2, 147.0, 149.8 and 157.9.

General procedure for the preparation of compounds 7a,b, 10a,b and 11a

To a solution of benzotriazole adducts **6b,d**, **8a** or **9a,g** (5 mmol) in THF (50 cm^3) under nitrogen was added the appropriate Grignard reagents (BuMgBr or PhMgBr; 1 mol dm^{-3} in diethyl ether; 20 cm^3 2 mmol). The diethyl ether was distilled off and the mixture was refluxed for 8 h. The reaction was monitored by TLC until the starting material had been consumed. After the reaction mixture was cooled, poured into ice–water (30 cm^3) and acidified to pH 9 with 2 mol dm^{-3} HCl, the solution was extracted with diethyl ether (3 × 60 cm^3). The solution was washed with saturated aqueous $NaHCO_3$ (2 × 100 cm^3) and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography (hexane–CH_2Cl_2 1:1). Melting points, elemental analyses and preparative data are given in Table 1.

2-Amino-3-methyl-5-pentylpyridine 7a. $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.8), 1.20–1.35 (4 H, m), 1.49–1.60 (2 H, m), 2.09 (3 H, s), 2.43 (2 H, t, *J* 7.4), 4.40 (2 H, br s), 7.09 (1 H, s) and 7.76 (1 H, s); $\delta_C(CDCl_3)$ 13.9, 17.0, 22.4, 31.1, 31.2, 31.9, 116.2, 128.3, 138.1, 144.6 and 155.2.

2-Amino-5-benzyl-6-methylpyridine 7b. $\delta_H(CDCl_3)$ 2.30 (3 H, s), 3.80 (2 H, s), 4.40 (2 H, br s), 6.27 (1 H, d, *J* 8.0) and 7.08–7.28 (6 H, m); $\delta_C(CDCl_3)$ 22.0, 37.8, 106.0, 123.5, 126.0, 128.3, 128.4, 139.6, 140.3, 155.0 and 156.4.

2-Amino-5-(2-ethylpentyl)-3-methylpyridine 10a. $\delta_H(CDCl_3)$ 0.77 (3 H, t, *J* 7.4), 0.84 (3 H, t, *J* 7.0), 1.17 (2 H, m), 1.30 (2 H, m), 1.47 (2 H, m), 1.63 (2 H, m), 2.13 (3 H, s), 2.27 (1 H, m), 4.37 (2 H, br s), 7.07 (1 H, s) and 7.71 (1 H, s); $\delta_C(CDCl_3)$ 12.0, 13.9, 17.2, 22.7, 29.5, 29.7, 36.0, 44.3, 116.4, 131.5, 136.8, 144.9 and 155.4.

2-Amino-5-{1-[hydroxy(diphenyl)methyl]pentyl}-3-methylpyridine 10b. $\delta_H(CDCl_3)$ 0.78 (3 H, t, *J* 6.9), 1.14 (4 H, m), 1.72 (2 H, m), 1.99 (3 H, s), 2.69 (1 H, br s), 3.54 (1 H, t, *J* 7.7), 4.21 (2 H, s), 7.02 (1 H, d, *J* 7.3), 7.05 (1 H, s), 7.10 (2 H, t, *J* 5.2), 7.22–7.28 (3 H, m), 7.35 (2 H, t, *J* 7.3), 7.55 (2 H, d, *J* 7.2) and 7.57 (1 H, s); $\delta_C(CDCl_3)$ 14.0, 17.1, 22.6, 29.8, 30.1, 50.9, 81.0, 115.7, 125.7, 126.1, 126.3, 126.7, 127.7, 128.1, 139.2, 146.0, 146.3, 146.9 and 155.4.

2-Amino-5-(1,1-diethylpentyl)-3-methylpyridine 11a. δ_H($CDCl_3$) 0.67 (6 H, t, *J* 7.4), 0.77 (3 H, t, *J* 7.4), 0.86 (2 H, t, *J* 7.2), 0.95–1.05 (2 H, m), 1.20–1.40 (2 H, m), 1.61 (4 H, q, *J* 7.4), 2.13 (3 H, s), 4.30 (2 H, br s), 7.21 (1 H, s) and 7.87 (1 H, s); δ_C($CDCl_3$) 7.8, 12.1, 14.1, 17.4, 23.4, 25.6, 28.8, 36.0, 41.6, 115.8, 133.1, 136.6, 144.0 and 154.6.

General procedure for the preparation of compounds 7c,d

To 2-methylpropan-2-ol (50 cm^3) was added sodium metal (1.15 g, 50 mmol). On complete dissolution of the metal, benzenethiol or BuSH (10 mmol) and benzotriazole adduct **6b** or **6c** (1.20 g, 5 mmol) were added and the mixture refluxed for the appropriate time (for **7c**, 72 h; for **7d**, 8 h). Evaporation of the solvent gave a residue which was dissolved in water (50 cm^3) and extracted with ethyl acetate (3 × 60 cm^3). The organic extracts were washed with water (50 cm^3) and dried over $MgSO_4$. Evaporation of the solvent gave the pure compounds. Analytical samples were obtained by column chromatography (hexane–CH_2Cl_2; 10:1).

2-Amino-4-methyl-5-phenylsulfanylmethylpyridine 7c. δ_H($CDCl_3$) 2.28 (3 H, s), 3.96 (2 H, s), 4.45 (2 H, br s), 6.30 (1 H, s), 7.15–7.32 (5 H, m) and 7.68 (1 H, s); δ_C($CDCl_3$) 18.8, 34.6, 109.7, 121.4, 126.7, 128.8, 130.7, 135.9, 147.8, 148.2 and 157.9.

2-Amino-5-butylsulfanylmethyl-3-methylpyridine 7d. δ_H($CDCl_3$) 0.88 (3 H, t, *J* 7.2), 1.30–1.40 (2 H, m), 1.48–1.58 (2 H, m), 2.12 (3 H, s), 2.39 (2 H, t, *J* 7.2), 3.56 (2 H, s), 4.60 (2 H, br s), 7.30 (1 H, s) and 7.80 (1 H, s); δ_C($CDCl_3$) 13.6, 17.0, 21.9, 30.8, 31.2, 32.9, 116.8, 124.2, 138.4, 144.9 and 156.2.

General procedure for the preparation of compounds 7e and 11b

To butanol or ethanol (20 cm^3) was added sodium metal (2.3 g, 100 mmol). On complete dissolution of the metal, the benzotriazole adduct **6d** or **8a** (5 mmol) was added in one portion and the solution was refluxed for 5 h. Evaporation of the solvent gave a residue which was dissolved in water (50 cm^3) and extracted with ethyl acetate (3 × 60 cm^3). The organic extracts were washed with water (50 cm^3) and dried over $MgSO_4$. Evaporation of the solvents gave a residue, which was chromatographed (hexane–CH_2Cl_2, 1:1) to give the desired product. Melting points, elemental analyses and preparative data are given in Table 1.

2-Amino-5-butoxymethyl-6-methylpyridine 7e. δ_H($CDCl_3$) 0.94 (3 H, t, *J* 7.3), 1.35–1.45 (2 H, m), 1.52–1.62 (2 H, m), 2.40 (3 H, s), 3.45 (2 H, t, *J* 6.5), 4.36 (2 H, s), 4.55 (2 H, br s), 6.31 (2 H, d, *J* 8.2) and 7.34 (1 H, d, *J* 8.2); δ_C($CDCl_3$) 13.9, 19.4, 21.3, 31.8, 70.0, 70.2, 105.5, 121.5, 139.2, 155.8 and 157.3.

2-Amino-5-(1-ethoxy-1-ethylpropyl)-3-methylpyridine 11b. δ_H($CDCl_3$) 0.96 (6 H, t, *J* 7.4), 1.40 (3 H, t, *J* 7.0), 2.06 (4 H, m), 2.39 (3 H, s), 3.39 (2 H, q, *J* 7.0), 4.61 (2 H, br s), 7.57 (1 H, s) and 8.15 (1 H, s); δ_C($CDCl_3$) 7.4, 15.6, 17.3, 28.2, 56.3, 79.9, 115.9, 130.6, 136.6, 143.8 and 155.7.

Preparation of 2-amino-5-(1-ethylprop-1-enyl)-3-methylpyridine 12

To a solution of 2-amino-5-[1-(benzotriazol-1-yl)-1- ethylpropyl]-3-methylpyridine **8a** (1.50 g, 5 mmol) in THF (40 cm^3) was added NaH (0.24 g, 10 mmol) in one portion. The solution was refluxed for 4 h, cooled to room temperature and water (30 cm^3) added. The solution was extracted with ethyl acetate (3 × 30 cm^3), washed with aqueous $NaHCO_3$ (10% w/v, 50 cm^3), and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed (hexane–CH_2Cl_2, 3:1) to give an oil (0.5 g, 58%) (Found: C, 75.1; H, 9.5; N, 15.5. $C_{11}H_{16}N_2$ requires C, 74.96; H, 9.15; N, 15.89%); δ_H($CDCl_3$) 0.97 (3 H, t, *J* 7.5), 1.77 (2 H, d, *J* 6.9), 2.14 (3 H, s), 2.46 (2 H, q, *J* 7.4), 4.40 (2 H, br s), 5.61 (1 H, q, *J* 6.9), 7.27 (1 H, s) and 7.94 (1 H, s); δ_C($CDCl_3$) 13.1, 13.7, 17.2, 22.4, 115.9, 120.5, 135.9, 143.0 and 155.7.

Preparation of 2-[(benzotriazol-1-ylmethyl)amino]-4-methylpyridine 15a

A mixture of 1-hydroxymethylbenzotriazole **5** (3.75 g, 20 mmol) and 2-amino-4-methylpyridine **4c** (2.70 g, 25 mmol) was heated in ethanol (50 cm^3) under reflux for 20 h. The solvent was distilled off, and the solid product was recrystallized from ethanol (5.4 g, 90%), mp 163 °C (lit.,[18] 157–158 °C) (Found: C, 64.95; H, 5.5; N, 29.5. $C_{13}H_{13}N_5O$ requires C, 65.26; H, 5.48; N, 29.27%); δ_H($CDCl_3$) 2.18 (3 H, s), 6.16 (1 H, t, *J* 7.1), 6.34 (1 H, d, *J* 7.2), 6.38 (1 H, s), 6.51 (1 H, d, *J* 4.4), 7.32 (1 H, t, *J* 6.9), 7.42 (1 H, t, *J* 6.9), 7.96 (1 H, d, *J* 8.3), 8.02 (1 H, d, *J* 8.3) and 8.05 (1 H, d, *J* 5.2); δ_C($CDCl_3$) 20.9, 54.4, 109.0, 111.3, 116.5, 119.4, 123.9, 127.2, 132.7, 146.0, 147.3, 149.0 and 156.4.

Rearrangement of 2-[(benzotriazol-1-ylmethyl)amino]-4-methylpyridine 15a to 6c

2-[(Benzotriazol-1-ylmethyl)amino]-4-methylpyridine **15a** (5 mmol) was heated under reflux in acetic acid (25 cm^3) with a catalytic amount of toluene-*p*-sulfonic acid (30 mg) for 72 h. The acetic acid was removed under reduced pressure, and to the residue was added aqueous Na_2CO_3 (10%, 50 cm^3). The product was extracted with ethyl acetate (4 × 80 cm^3), washed with aqueous sodium hydroxide (10%, 50 cm^3) then water (100 cm^3), and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed (CH_2Cl_2) to give pure product **6c** in 40% yield.

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