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Reactions of β-(Lithiomethyl)azines with Nitriles as a Route to Pyrrolo-pyridines, -quinolines, -pyrazines, -quinoxalines and -pyrimidines

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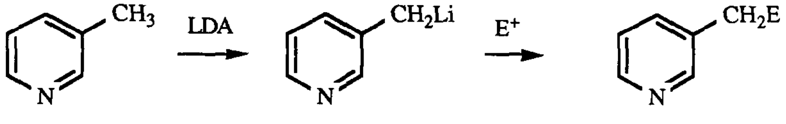
Key Words: β-methylazines and diazines, deprotonation, nitriles, cyclisation, pyrrolopyridines and related heterocycles.

Abstract: *Deprotonation of 3-methylpyridine, followed by reaction with benzonitile, gives an intermediate which, on treatment with additional strong base, cyclises to give 2-phenyl[1H]-pyrrolo[2,3-*b*]pyridine. The application of this type of reaction to a variety of nitriles and β-methylazines (pyridines, quinolines, pyridines, quinoxalines and pyrimidines) is described.*

Analogues of purines, in which ring-nitrogen atoms are replaced by CH (deazapurines) or in different positions, display a variety of potentially useful biological activities.[1] In this paper we describe a method for synthesising such ring systems starting from readily available β-methylazines such as β-picoline.

Although β-picoline is much less acidic than α- or γ-picoline, the methyl group may be deprotonated by lithium di-isopropylamide (LDA), and functionalised by subsequent reaction with electrophiles (Scheme 1); in our hands the presence of hexamethylphosphoramide[2] was not necessary.



Scheme 1

We envisaged that on heating, the intermediate from the reaction with benzonitrile might undergo an intramolecular Chichibabin-type reaction (Scheme 2). However, the few reported examples of intramolecular Chichibabin reactions required harsh conditions and gave at best modest yields,[3] and our initial trials were

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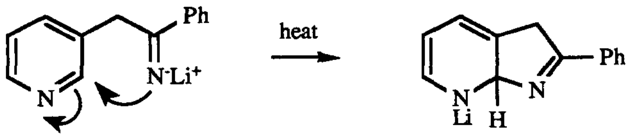
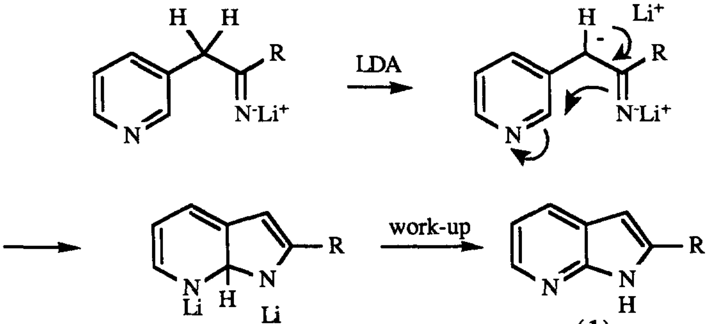
discouraging: a maximum yield of 2-phenyl-[1*H*]pyrrolo[2,3-*b*]pyridine (1, R = Ph) of 63% was obtained, but required heating in a Carius tube at 100° for 36 h.



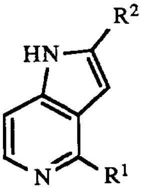
Scheme 2

Nevertheless, we can now report that under appropriate conditions it is possible to achieve such cyclisations under much milder conditions, and sometimes in high yields. The key to our success is the use of an excess of strong base. We suggest that removal of a second α-proton aids the cyclisation step as shown in Scheme 3. The final steps may involve elimination of lithium hydride or oxidation on work-up.≠ Where R = Ph, yields of up to 90% were achieved. In a few experiments, traces of the isomer, 2-phenyl-[1*H*]pyrrolo[3,2-*c*]pyridine (2) R^1 = H, R^2 = Ph) derived from cyclisation on to the pyridine 4-position, were also obtained.



(1)

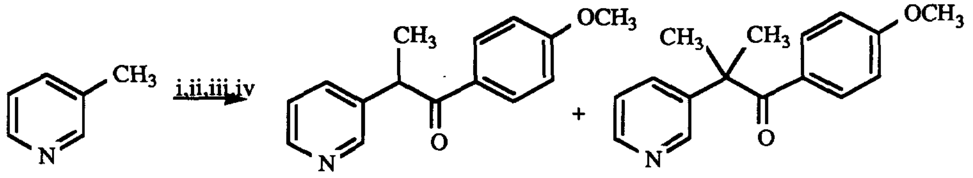
Scheme 3



(2)

≠ We have not studied this aspect of the reaction in detail, but yields were not improved by treatment of the reaction mixture with oxygen, permanganate, or nitrobenzene.

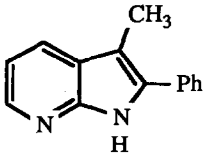
Some evidence for a second deprotonation (whether simultaneous or sequential (cf. ref. 4), was provided by trapping with iodomethane (Scheme 4).



Reagents: i 2LDA, ii 4-$CH_3OC_6H_4CN$, iii 4MeI, iv H_3O^+

Scheme 4

The results of our investigation of the scope of this type of reaction are summarised in Tables 1 and 2. It should be noted that although many of the reactions have been repeated several times, they have not been systematically optimised; yields higher than those reported, which are of isolated products, may well be achievable.



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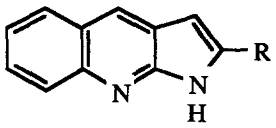

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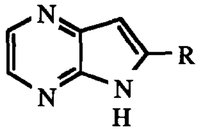

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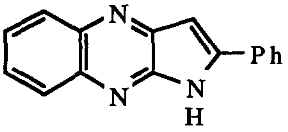

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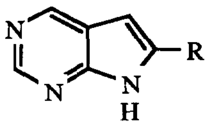
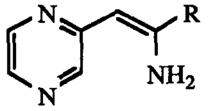
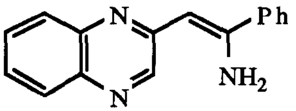


(7)



(8)

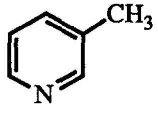
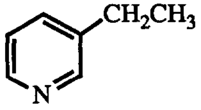
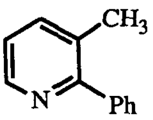


(9)

As noted above, cyclisation on to the 4-position of the pyridine ring is possible. When the 2-position is blocked, this mode of cyclisation gives pyrrolo[3,4-*c*]pyridines **2**.

Table 1

Synthesis of pyrrolopyridines

Starting material	Nitrile RCN R	Cyclised Product	Yield %	m.p. [°C]
	C_6H_5	2-phenyl-[1*H*]-pyrrolo[2,3-*b*]pyridine (**1**, R = Ph)	90	202-3[a]
	$4\text{-}CH_3OC_6H_6$	2-(4-methoxyphenyl)[1*H*]-pyrrolo[2,3-*b*]-pyridine (**1**, R = 4-MeOC$_6$H$_4$)	72	205-6
	$4\text{-}ClC_6H_4$	2-(4-chlorophenyl)[1*H*]-pyrrolo[2,3-*b*]-pyridine (**1**, R = 4-ClC$_6$H$_4$)	3	dec > 300
	CH_3	none		
	$(CH_3)_3C$	2-*t*-butyl[1*H*]-pyrrolo[2,3-*b*]pyridine (**1**, R = Bu^t)	90	198-9
	$(CH_3)_2CH$	2-isopropyl[1*H*]pyrrolo[2,3-*b*]pyridine (**1**, R = Pr^i)	50[b]	84
	Cl_3C	none		
	C_6H_5	3-methyl-2-phenyl[1*H*]pyrrolo[2,3-*b*]-pyridine (**3**)	25[c]	193.5-194
	$(CH_3)_3C$	[d]		
	C_6H_5	2,4-diphenyl[1*H*]pyrrolo[3,2-*c*]pyridine (**2**, R^1 = R^2 = Ph)	61	230-1
	$4\text{-}CH_3OC_6H_4$	2-(4-methoxyphenyl)-4-phenyl[1*H*]pyrrolo-[3,2-*c*]pyridine (**2**, R^1 = Ph, R^2 = 4-MeOC$_6$H$_4$)	76	219.5
	$(CH_3)_3C$	2-*t*-butyl-4-phenyl[1*H*]pyrrolo[3,2-*c*]pyridine (**2**, R^1 = Ph, R^2 = Bu^t)	67	231-2

[a] Lit. 204-5° [8]; together with 3,3-dimethyl-1-(3-pyridyl)butan-2-one (trace).

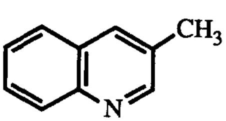
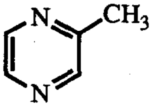
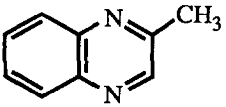
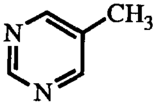
[b] Together with 3-methyl-1-(3-pyridyl)butan-2-one (28%).

[c] Addition of iodomethane before work-up gave 1,3-dimethyl-2-phenyl[1*H*]pyrrolo[2,3-*b*]pyridine (9%).

[d] Products were (**10**) and (**11**); see text.

Table 2

Synthesis of pyrrolo-quinolines, -pyrazines, -quinoxalines and -pyrimidines

Starting material	Nitrile, RCN R =	Cyclised Product	Yield %	m.p. [°C]
	C_6H_5	2-Phenyl[1*H*]pyrrolo[2,3-*b*]quinoline (**4**, R = Ph)	14	199.5-200
	4-$MeOC_6H_4$	2-(4-methoxyphenyl)[1*H*]pyrrolo[2,3-*b*]quinoline (**4**, R = 4-$MeOC_6H_4$)	32	206-7
	Bu^t	2-(*t*-butyl(1*H*]pyrrolo[2,3-*b*]quinoline (**4**, R = Bu^t)	41	145
	C_6H_5	2-phenyl[1*H*]pyrrolo[2,3-*b*]pyrazine (**5**, R = Ph)	62[a]	215-6
	4-$MeOC_6H_4$	2-(4-methoxyphenyl) (**5**, R = 4-$MeOC_6H_4$)	40[b]	238-40 dec.
	4-ClC_6H_4	2-(4-chlorophenyl) (**5**, R = 4-ClC_6H_4)	43[c]	dec. *ca* 250
	Bu^t	2-*t*-butyl[1*H*]pyrrolo[2,3-*b*]pyrazine (**5**, R = Bu^t)	55	238
	C_6H_5	2-phenyl[1*H*]pyrrolo[2,3-*b*]quinoxaline (**6**)	21[d]	dec. *ca* 233
	C_6H_5	2-phenyl[1*H*]pyrrolo-[2,3-*d*]pyrimidine (**7**, R = Ph)	15	245-6 dec.
	4-$MeOC_6H_4$	2-(4-methoxyphenyl)[1*H*]pyrrolo[2,3-*d*]pyrimidine (**7**, R = 4-$MeOC_6H_4$)	12	dec. *ca* 160
	Bu^t	2-*t*-butyl[1*H*]pyrrolo[2,3-*d*]pyrimidine (**7**, R = Bu^t)	15	200

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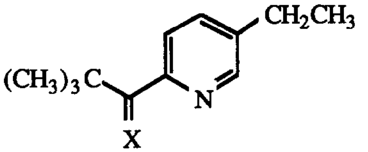
[a] Together with 1-amino-1-phenyl-2-(pyrazin-2-yl)ethene (**8**, R = Ph) (31%), m.p. 116.5-117.5°

[b] Together with 1-amino-1-(4-methoxyphenyl)-2-(pyrazin-2-yl)ethene (**8**, R = 4-$MeOC_6H_4$) (13%), m.p. 104 - 105°.

[c] Together with 1-amino-1-(4-chlorophenyl)-2-(pyrazin-2-yl)ethene (**8**, R = 4-ClC_6H_4), (34%), m.p. 120-1°

[d] Together with 1-amino-1-phenyl-2-(quinoxalin-2-yl)ethene (**9**) *ca.* 80% (impure) dec. *ca* 265°.

Reactions of β-picoline with aromatic nitriles were successful, though an electron-withdrawing substituent in the nitrile resulted in low yields. The reaction was also successful with pivalonitrile (no α-hydrogen) and isobutyronitrile. It failed with acetonitrile (presumably because of α-deprotonation) and trichloroacetonitrile (which gave a mixture of unidentified products). The yield from 3-ethylpyridine was poor; evidently reaction at the ring competes with reaction at the side-chain, as the imine **10** and its hydrolysis product **11** were obtained from a reaction with pivalonitrile.



(10) X = NH

(11) X = O

The reactions of methyl derivatives of other heterocycles, summarised in Table 2, all gave the required products **4** to **7**, though in variable yields. The noteworthy feature of the reactions of methylpyrazine and 2-methylquinoxaline is the formation of significant proportions of uncyclised products **8**, **9**, although the pyrazine ring should be **more** susceptible to intramolecular nucleophilic attack. (Similar results, though with even lower proportions of cyclised products, had been obtained in a similar study by Vierfond *et al.*[5]) A possible explanation is that in the intermediate, lithium-bonding to a ring nitrogen tends to hold the side-chain in a conformation unfavourable for cyclisation (Fig. 1). The n.m.r. spectra of the uncyclised products were consistent with the enamine tautomers **8**, **9**. These compounds were very moisture-sensitive, and elemental analyses were consistently 1-2% low in nitrogen, owing to partial hydrolysis.

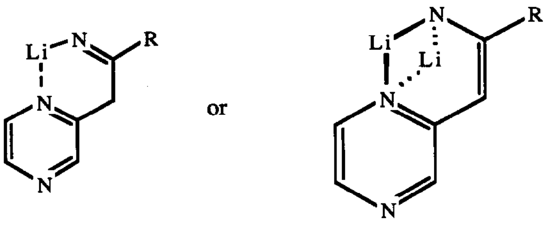
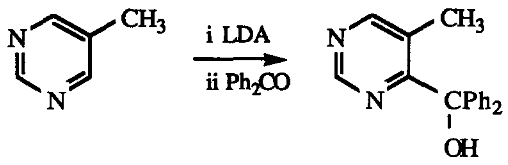


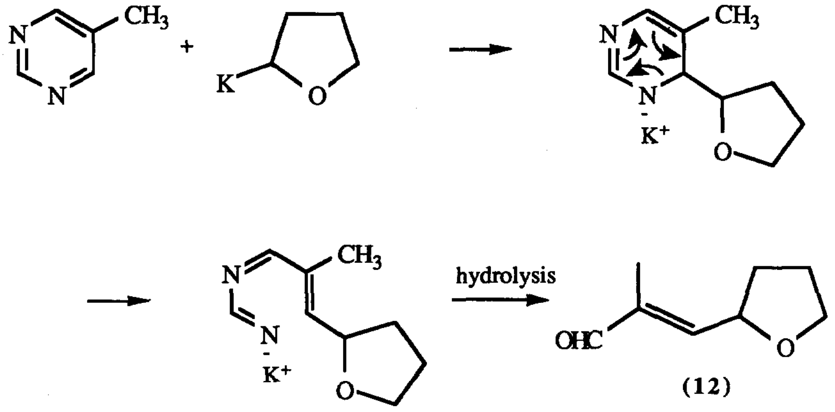
Fig. 1

Reactions of 5-methylpyrimidine were of particular interest, since the expected cyclised products were deazapurines **7**. Initial experiments were unsuccessful, and we confirmed the report that lithiation with LDA occurs at the 4- rather than the α-position (Scheme 5)[6].



Scheme 5

Attempts to achieve metallation at very low temperature were also unsuccessful. For example, from a reaction with butyllithium-potassium *t*-butoxide (a reagent system which metallates pyridine)[7] in THF at -100°, followed by reaction with iodomethane, the only product identified, in low yield, was the aldehyde **12**. A conceivable mechanism involving attack on the solvent and ring-opening is shown in Scheme 6.



Scheme 6

Surprisingly, in view of these observations, the reactions with nitriles under the conditions described in the Experimental section did give the required pyrrolopyrimidines **7**, albeit in modest yields.

Experimental

All experiments involving butyllithium or lithium diisopropylamide (LDA) were carried out in dried apparatus under an atmosphere of dry, oxygen-free nitrogen. Tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone ketyl. Diisopropylamine was distilled from calcium hydride and stored over potassium hydroxide pellets. β-Picoline was distilled from, and stored over, calcium hydride. Other methyl-heterocycles were distilled and stored over molecular sieves.

Butyllithium was supplied by FMC Lithium Division as an approximately 1.5*M* solution in hexanes and was assayed by titration against diphenylacetic acid.

Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded for thin films from evaporation of solutions in $CDCl_3$ on a Perkin Elmer 1712 FTIR instrument; only selected absorptions are reported. ^1H n.m.r. spectra were recorded at 300 MHz using a Bruker AC 300 spectrometer. Low resolution mass spectra were recorded using a Finnigan-4000 instrument, and accurate mass measurement was carried out on a Kratos Concept instrument. Elemental analyses were performed by Butterworth Laboratories Limited.

Column (flash) chromatography was carried out using Merck 9385 Kieselgel, and thin layer chromatography using Polygram silica-coated plastic plates (Camlab) or Kieselgel 60F-254 glass plates.

Preparation of LDA

A solution of diisopropylamine (0.35 ml, 2.5 mmol) in THF (10 ml) was cooled to -10°C and stirred as butyllithium (2.5 mmol) was added dropwise, the temperature being kept below 5°C. The solution was stirred at 0°C for 30 min.

Preparation of pyrrolo-pyridines, -quinolines, -pyrazines, -quinoxalines, and -pyrimidines: general procedure

(The proportions of the reagents used for individual preparations are listed in Table 3.)

A solution of LDA was prepared as described above, or using an excess of diisopropylamine, and the appropriate methyl azine was added dropwise. The resulting suspension was stirred at 0°C for 30 min. The nitrile was added dropwise (*exothermic reaction*) at such a rate that the temperature did not rise above 10-15°C. Stirring was continued for 60-90 min at 0°C. Further LDA solution (prepared as described above) was added, and stirring was continued at the temperature and for the times listed in Table 3.

The final reaction mixture was allowed to cool (if necessary) and ice-water (50 ml) was added. The mixture was extracted with dichloromethane (3 x 20 ml) and the combined extracts were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The residue was subjected to flash chromatography.* The yields and m.p.s of the products are recorded in Tables 1 and 2. Spectroscopic and analytical data follow.

1, R = Ph δ ($CDCl_3$ + DMSO-d_6) 6.81 (1H, s; H-3), 7.00 (1H, dd, J 8, 4.5 Hz; H-5), 7.29 (1H, m; ArH), 7.41 (2H, "t", 7 Hz; ArH), 7.85-7.9 (3H, m; ArH + H-4), 8.19 (1H, dd, J 4.5, 1.5 Hz; H-6), 12.1 (1H, br s; H-1). for m.p. see Table 1).

2, R^1 = H, R^2 = Ph m.p. 274-276°C (lit.[8] m.p. 282-283°C), δ (DMSO-D_6 + $CDCl_3$) 6.98 (1H, s; H-3), 7.5 (4H, m; H-7 + ArH), 7.93 (2H, m; ArH), 8.25 (1H, d; H-6), 8.9 (1H, s; H-4), 11.8 (1H, br s; H-1).

1, R = 4-$CH_3OC_6H_4$ δ ($CDCl_3$ + DMSO-d_6) 3.79 (3H, s; OCH_3), 6.63 (1H, s; H-3), 6.9 (3H, m; *M*-ArH + H-5), 7.8 (3H, m; *o*-ArH + H-4), 8.10 (1H, d, J 4.5 Hz, H-6), 11.9 (1H, br s; H-1). Found: C, 74.7; H, 5.25; N, 12.4. $C_{14}H_{12}N_2O$ requires C, 75.0; H, 5.35; N, 12.5%.

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* In a few cases part of the product was recovered by crystallisation.

Table 3
Conditions for cyclisation reactions

Target compound	Initial LDA (mmol)	Methyl azine (mmol)	Nitrile (mmol)	Further LDA (mmol)	Time (h)	Temp. (°C)
1, R = Ph	5	3	3	5	4	40
1, R = 4-CH$_3$OC$_6$H$_4$	2.5[a]	2.5	2.5	2.5[a]	17	r.t.
1, R = 4-ClC$_6$H$_4$	5	5	5	5	4	80
1, R = Bu^t	10	6	6	10	5	60
1, R = Pr^i	10	6	6	10	3.5	60
3	5	5	5	5	3.75	75-80
2, R^1 = R^2 = Ph	5	3	3	5	1.5	50
2, R^1 = Ph, R^2 = 4-MeOC$_6$H$_4$	5	6	5	10	1.5	50
2, R^1 = Ph, R^2 = Bu^t	5	3	3	5	1.5	50
4, R = Ph	10	6[b]	6	10	4-5	60
4, R = 4-MeOC$_6$H$_4$	5	3[b]	3	5	4	60
4, R = Bu^t	10	6[b]	6	0	3	60
5, R = Ph	5	3	3	5	3	40
5, R - 4-MeOC$_6$H$_4$	5	3	3	5	4.5	40-50
5, R = 4-ClC$_6$H$_4$	5	3	3	5	1 + 4	60 50
5, R = Bu^t	5	3	3	5[c]	5	60
6	5	3	3	5	4	50
7, R = Ph	10	6	6	10	7	60
7, R = 4-MeOC$_6$H$_4$	5	3	3	5	15	60
7, R = Bu^t	15	9	9	0	15	60

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[a] Or with the second portion of LDA formed *in situ*: see text.

[b] Added at -40°C

[c] Plus TMEDA (3 mmol)

1, R = 4-ClC_6H_4 (slightly impure), δ ($DMSO\text{-}d_6$ + $CDCl_3$) 6.7 (1H, s; H-3), 6.94 (1H, dd, J 8,4.5 Hz; H-5), 7.22 (2H, d, J 8.5 Hz; ArH), 7.8 (3H, m; ArH + H-4), 8.2 (1H, m, H-6), 11.7 (1H, br s; H-1).
Found: $(M+ 1)^+$ at *m/z* 229.0530 $C_{13}H_{10}{}^{35}ClN_2$ requires 229.0532.

3,3-Dimethyl-1-(3-pyridyl)butan-2-one, oil, δ ($CDCl_3$) 0.9 (9H, s; Bu^t), 3.5 (2H, s; CH_2), 6.9 (dd, J 7.7, 4.8 Hz; pyridyl H-5), 7.2 (1H, d, J 7.7 Hz; pyridyl H-4), 8.2 (1H, dd, J 4.8, 1.4 Hz; pyridyl H-6. ν_{max} 1710 cm^{-1}. Found: $(M + 1)^+$ at *m/z* 178.1227. $C_{11}H_{16}NO$ requires 178.1232.

1, R = $(CH_3)_3C$ δ ($CDCl_3$) 1.51 (9H, s; Bu^t), 6.21 (1H, d, J 1 Hz; H-3), 7.05 (1H, m; H-5), 7.86 (1H, d, J 7.8 Hz; H-4), 8.30 (1H, dd, J 3.8, 1 Hz; H-6), 12.3 (1H, br s; H-1).
Found: C, 76.0; H, 8.2; N, 16.0. $C_{11}H_{14}N_2$ requires C, 75.8; H, 8.1; N, 16.1%.

1, R = $(CH_3)_2CH$ δ ($CDCl_3$) 1.45 (6H, d, J 7 Hz; $CH(CH_3)_2$, 3.21 (1H, septet, J 7 Hz; $CH(CH_3)_2$), 6.0 (1H, s; H-3), 7.04 (1H, dd, J 8, 4.5 Hz; H-5), 7.84 (1H, dd, J 8, 1.3 Hz; H-4), 8.24 (1H, dd, J 4.5, 1.2 Hz; H-6), 12.5 (1H, br s; H-1) Found: M^+ at *m/z* 160.1005 $C_{10}H_{12}N_2$ requires 160.1000.

3-Methyl-1-(3-pyridyl)butan-2-one, oil δ ($CDCl_3$) 0.80 (6H, d, J 7 Hz; $CH(CH_3)_2$), 2.41 (1H, septet, J 7 Hz; $CH(CH_3)_2$), 6.91 (1H, dd, J 8, 3 Hz; pyridyl H-5), 7.21 (1H, m; pyridyl H-4), 8.11 (1H, d, J 2 Hz; pyridyl H-2), 8.14 (1H, m, pyridyl H-6) ν_{max} 1718 cm^{-1} $(M + 1)^+$ at *m/z* 164.

3 δ ($CDCl_3$) 2.46 (3H, s; CH_3), 7.06 (1H, dd, J 8, 5 Hz; H-5), 7.49 (1H, m; ArH), 7.5-7.7 (3H, m; ArH), 7.89 (1H, d, J 8 Hz; ArH), 8.75 (2H, m; H-4, 6), 12.0 (1H, br s; H-1). (Found: C, 80.8; H, 5.8; N, 13.45 $C_{14}H_{12}N_2$ requires C, 80.7; H, 5.8; N, 13.4%.

1,3-Dimethyl-2-phenyl(1*H*)pyrrolo[2,3-*b*]pyridine δ ($CDCl_3$) 2.27 (3H, s; 3-CH_3), 3.72 (3H, s; N-CH_3), 7.05 (1H, dd, J 7.7, 4.7 Hz; H-5); 7.3-7.5 (5H, m; Ph), 7.85 (1H, dd, J 7.7, 1.5 Hz; H-4), 8.34 (1H, dd, J 4.7, 1.5 Hz; H-6). Found: M^+ at *m/z* 222.1144 $C_{15}H_{14}N_2$ requires 222.1157.

10, m.p. 134-5°C, δ ($CDCl_3$) 1.16 (9H, s; Bu^t), 1.26 (3H, t, J 8 Hz; CH_2CH_3), 2.25 (2H, quartet, J 8 Hz; CH_2 CH_3), 7.09 (1H, d, J 8 Hz; pyridyl H-3), 7.53 (1H, dd, J 8, 2 Hz; pyridyl H-4), 8.51 (1H, d, J 2 Hz; pyridyl H-6), 8.88 (1H, br s; NH). ν_{max} 3305 cm^{-1} Found: M^+ at *m/z* 190.1478 $C_{12}H_{18}N_2$ requires 190.1470.

11, oil δ ($CDCl_3$) 1.17 (3H, t, J 8 Hz; CH_2CH_3), 1.36 (9H, s; Bu^t), 2.59 (2H, quartet, J 8 Hz, CH_2CH_3), 7.50 (1H, dd, J 8, 2 Hz; pyridyl H-3), 7.76 (1H, d; J 8 Hz; pyridyl H-4), 8.36 (1H, d, J 2 Hz, pyridyl H-6) ν_{max} 1683 cm^{-1} Found: $(M + 1)^+$ at *m/z* 192.1396 $C_{12}H_{18}NO$ requires 192.1388.

2, $R^1 = R^2$ = Ph δ ($CDCl_3$) 7.07 (1H, s; H-3), 7.14 (1H, d, J 5.5 Hz; H-7), 7.3-7.5 (6H, m; ArH), 7.8 (2H, m; ArH), 8.0 (2H, d, J 7 Hz; ArH), 8.28 (1H, d, J 5.5 Hz; H-6), 10.6 (1H, br s; H-1). Found: C, 83.8; H, 5.4; N, 10.4. $C_{19}H_{15}N_2$ requires C, 84.4; H, 5.2; N, 10.3%.

2, R^1 = Ph, R^2 = 4-$CH_3OC_6H_4$ δ ($CDCl_3$ 3.81 (3H, s; OCH_3), 6.90 (2H, d; J 8 Hz; ArH), 6.97 (1H, s; H-3), 7.15 (1H, d, J 6 Hz; H-7), 7.4-7.5 (3H, m; ArH), 7.60 (2H, d, J 8 Hz; ArH), 8.00 (2H, d, J 7 Hz; ArH), 8.31 (1H, d, J 6 Hz; H-6), 9.8 (1H, br s; H-1) Found: $(M + 1)^+$ at *m/z* 301.1341 $C_{20}H_{17}N_2O$ requires 301.1341.

2, R^1 = Ph, R^2 = $(CH_3)_3C$ δ ($CDCl_3$) 1.29 (9H, s; Bu^t), 6.48 (1H, d, J 1.5 Hz; H-3), 7.08 (1H, d, J 6 Hz; H-7), 7.4-7.7 (3H, m; ArH), 8.0 (2H, m; ArH), 8.26 (1H, d, J 6 Hz; H-6), 10.5 (1H, br s; H-1) Found: C, 81.1; H, 7.3; N, 11.1 $C_{17}H_{18}N_2$ requires C, 81.55; H, 7.25; N, 11.2%.

4, R = Ph δ ($CDCl_3$) 6.92 (1H, s; H-3), 7.3-7.9 (9H, m; ArH), 8.40 (1H, s; H-4), 10.8 (1H, br s; H-1). Found: M^+ at *m/z* 244.1005 $C_{17}H_{12}N_2$ requires 244.1000.

4, R = 4-$CH_3OC_6H_4$ δ ($CDCl_3$) 3.83 (3H, s; OCH_3), 6.77 (1H, s; H-3), 6.91 (2H, d, J 8.8 Hz; *meta*-H), 7.39 (1H, dt, J 7, 1.3 Hz, H-7 or H-6), 7.54 (1H, dt, J 7, 1.3 Hz; H-6 or H-7), 7.68 (2H, d, J 8.8 Hz; *ortho*-H), 7.9 (2H, m; H-5, H), 8.32 (1H, s; H-4), 10.5 (1H, br s; H-1). Found: M^+ at *m/z* 274.1099 $C_{18}H_{14}N_2O$ requires 274.1106.

4, R = $(CH_3)_3C$ δ ($CDCl_3$) 1.35 (9H, s; Bu^t), 6.27 (1H, d, J 1.5 Hz; H-3), 7.39 (1H, dt, J 7, 1.2 Hz; H-6), 7.60 (1H, dt, J 7, 1.5 Hz; H-7), 7.90 (1H, dd, J 8, 1.2 Hz; H-5), 8.03 (1H, d, J 8 Hz; H-8), 8.23 (1H, s; H-4), 10.5 (1H, br s; H-1). Found: $(M + 1)^+$ at *m/z* 225.1394 $C_{15}H_{17}N_2$ requires 225.1392.

5, R = Ph R_f 0.15 (2:1 light petroleum:ethyl acetate) δ (DMSO-d_6) 7.02 (1H, d, J 1.9 Hz; H-3), 7.3-7.5 (3H, m; ArH), 7.95 (2H, m; ArH), 8.13 (1H, d, J 2.4 Hz; H-5 or H-6), 8.30 (1H, d, J 2.4 Hz; H-6 or H-5). Found: C, 73.45; H, 4.7; N, 21.3% $C_{12}H_9N_3$ requires C, 73.8; H, 4.65; N, 21.5%.

8, R = Ph R_f 0.4 (2:1 light petroleum:ethyl acetate) δ ($CDCl_3$) 5.48 (1H, s; =CH), 6.8 (2H, br; NH_2), 7.4 (3H, m; ArH), 7.6 (2H, m; ArH), 8.03 (1H, d, J 2.6 Hz; pyrazinyl H), 8.3 (2H, m; pyrazinyl H) Found: M^+ at *m/z* 197.0953 $C_{12}H_{11}N_3$ requires 197.0953.

5, R = 4-$CH_3OC_6H_4$. R_f 0.06 (2:1 light petroleum:ethyl acetate). δ($CDCl_3$ + DMSO-d_6) 3.39 (3H, s; OCH_3), 7.02 (1H, d, J 2 Hz; H-3), 7.07 (2H, d, J 9 Hz; *meta*-H), 7.90 (2H, d, J 9 Hz; *ortho*-H), 8.15 (1H, d, J 2.5 Hz; H-5 or H-6), 8.31 (1H, d, J 2.5 Hz; H-5 or H-6), 12.5 (br s, H-1). Found: M^+ at *m/z* 225.0905 $C_{13}H_{11}N_3O$ requires 225.0902.

8, R = 4-$CH_3OC_6H_4$ R_f 0.25 (2:1 light petroleum:ethyl acetate). δ ($CDCl_3$) 3.83 (3H, s; OCH_3), 5.44 (1H, s; =CH), ca. 6.7 (2H, br s; NH_2), 6.92 (2H, d, J 9 Hz; *meta*-H), 7.55 (2H, d, J 9 Hz; *ortho*-H), 8.00 (1H, d, J 2.6 Hz; pyrazinyl H), 8.3 (2H, m; pyrazinyl H). Found: M^+ at *m/z* 227.1056 $C_{13}H_{13}N_3O$ requires 227.1059.

5, R = 4-ClC_6H_4 R_f 0.15 (2:1 light petroleum:ethyl acetate). δ ($CDCl_3$ + DMSO-d_6) 7.17 (1H, s; H-3), 7.55 (2H, d; *ortho*-H), 8.03 (2H, d; *meta*-H), 8.21 (1H, d, J 2.6 Hz; H-5 or H-6), 8.36 (1H, d, J 2.6 Hz; H-5 or H-6), 12.5 (1H, br; H-1). Found: C, 62.7; H, 3.6; N, 18.0 $C_{12}H_8ClN_3$ requires C, 62.9; H, 3.5; N, 18.3%.

8, R = 4-ClC_6H_4 R_f 0.37 (2:1 light petroleum:ethyl acetate). δ ($CDCl_3$) 5.45 (1H, s; =CH), 6.7 (2H, br s; NH_2), 7.37 (2H, d, J 8.6 Hz; *ortho*-H), 7.54 (2H, d, J 8.6 Hz; *meta*-H), 8.05 (1H, d, J 2.5 Hz; pyrazinyl H), 8.3 (2H, m; pyrazinyl H). Found: M^+ at *m/z* 230.0489 $C_{12}H_{10}N_3Cl$ requires 230.0485.

5, R = $(CH_3)_3C$ δ ($CDCl_3$) 1.51 (9H, s; Bu^t), 6.46 (1H, d, J 2.2 Hz; H-3), 8.16 (1H, d, J 2.6 Hz; H-5 or H-6), 8.41 (1H, d, J 2.6 Hz; H-5 or H-6), 11.9 (1H, br s; H-1). Found: C, 68.6; H, 7.8; N, 24.2. $C_{10}H_{13}N_3$ requires C, 68.5; H, 7.5; N, 24.0%.

6, δ (DMSO-d_6) 7.29 (1H, s; H-3), 7.5-7.7 (5H, m; ArH), 8.1-8.3 (4H, m; ArH), 12.5 (1H, brs; H-1). Found: M^+ at *m/z* 245.0957 $C_{16}H_{11}N_3$ requires 245.0953.

9, δ ($CDCl_3$) 5.64 (1H, s; =CH), 7.1-7.5 (2H, br; NH_2), 7.4-7.7 (7H, m; ArH), 7.81 (1H, d, J 8 Hz; quinoxalinyl H-4 or H-7), 7.92 (1H, d, J 8 Hz; quinoxalinyl H-4 or H-7), 8.5 (1H, s; quinoxalinyl H-1). Found: M^+ at *m/z* 247.1111 $C_{16}H_{13}N_3$ requires 247.1109.

7, R = Ph δ ($CDCl_3$) 6.81 (1H,s; H-3), 7.5 (3H, m; ArH), 7.83 (2H, 'd'; *ortho*-H), 8.80 (1H, s; H-4), 8.95 (1H, s; H-6), 12.5 (1H, br s; H-1) Found: M^+ at *m/z* 196.0878 $C_{12}H_9N_3$ requires 196.0875.

7, R = 4-$CH_3OC_6H_4$ δ ($CDCl_3$) 3.86 (3H, s; OCH_3), 6.71 (1H, d, J 1.2 Hz; H-3), 7.04 (2H, d, J 8.7 Hz; *meta*-H), 7.78 (2H, d, J 8.7 Hz; *ortho*-H), 8.84 (1H, s, H-4 or H-6), 8.95 (1H, s, H-4 or H-6), 12.3 (1H, brs; H-1) Found: M^+ at *m/z* 225.0899. $C_{13}H_{11}N_3O$ requires 225.0902.

7, R = $(CH_3)_3C$ δ ($CDCl_3$) 1.48 (9H, s; Bu^t), 6.27 (1H, s; H-3), 8.88 (1H, s; H-4 or H-6), 8.89 (1H, s; H-4 or H-6), 12.5 (1H, br s; H-1) Found: C, 68.2; H, 7.3; N, 23.8 $C_{10}H_{13}N_3$ requires C, 68.5; H, 7.5; N, 24.0%.

1-(4-Methoxybenzoyl)-1-(3-pyridyl)ethane and 2-(4-methoxybenzoyl)-2-(3-pyridyl)propane

To a stirred solution of LDA (5 mmol) in THF (10 ml) was added β-picoline (0.24 ml, 2.5 mmol). To the resulting suspension was added a solution of 4-methoxybenzonitrile (0.33 g, 2.5 mmol) in THF (5 ml). The mixture was stirred for 1 h at 0°C. Iodomethane (0.6 ml, 10 mmol) was added. The mixture was worked up as described above. Elution with 5:1 light petroleum: ethyl acetate gave i) 1-(4-methoxybenzoyl)-1-(3-pyridyl)-

ethane (63 mg, 5%), yellow oil, R_f 0.24 (4:1 light petroleum:ethyl acetate), δ 1.6 (3, d; CHC*H*$_3$), 3.7 (3H, s; OCH$_3$), 4.6 (1H, q; C*H*CH$_3$), 6.8 (2H, d; aroyl *m*-H), 7.1 (1H, m; pyridyl H-5), 7.6 (1H, m, pyridyl H-4); 7.86 (2H, d, J 8 Hz, aroyl *o*-H), 8.35 (1H, dd, J 4.82 Hz, pyridyl H-6), 8.50 (1H, d, J 2.2 Hz, pyridyl 2-H), MS (CI, NH$_3$) *m/z* 259 $(M + NH_4)^+$ 242 $(M + H)^+$.

ii) 2-(4-methoxybenzoyl)-2-(3-pyridyl)propane (272 mg, 45%), brown oil, R_f 0.07, δ 1.62 (6H, s; C-CH$_3$), 3.74 (3H, s; OCH$_3$), 6.70 (2H, d, J 9 Hz; aroyl *m*-H), 6.95 (1H, ddd, J 8, 4.5 and 2 Hz; pyridyl 5-H), 7.5 (3H, m; aroyl *o*-H and pyridyl 4-H), 8.49 (1H, dd, J 4.5, 2 Hz; pyridyl 6-H), 8.60 (1H, d, J 2 Hz; pyridyl 2-H); MS (CI, NH$_3$) *m/z* 273 $(M + NH_4)^+$, 256 $(M + H)^+$.

Metallation of 5-methylpyrimidine

a) With LDA. Reaction of 5-methylpyrimidine with LDA, followed by benzophenone, was carried out as described by McNamara[9] to give (5-methylpyrimidin-4-yl) diphenylmethanol, 10%, m.p. 178-180°C (lit.[6,9] m.p. 182°C).

b) With "butylpotassium". To a stirred mixture of butyllithium (4 mmol) and potassium *t*-butoxide (4 mmol) in THF (15 ml) at -60°C was added a solution of 5-methylpyrimidine (0.28 g, 3 mmol) in THF (15 ml). The mixture was stirred at -60°C for 20 min. Iodomethane (0.25 ml, 4 mmol) was added, and stirring was continued as the mixture warmed to room temperature and for a further 4 h. Water (40 ml) was added. The resulting mixture was extracted with ether (3 x 30 ml), and the combined extracts dried and the solvents evaporated. Flash chromatography of the residue gave 3-(tetrahydrofuran-2-yl)-2-methylpropenal **12** (90 mg, 22%) (*E:Z ca.* 10:1), oil, δ (CDCl$_3$) for *E*-isomer 1.6 (1H, m, tetrahydrofuryl H-4 or 3), 1.71 (3H, d, J 1.3 Hz; CH$_3$), 1.95 (2H, m; tetrahydrofuryl H-3 or 4), 2.97 (1H, m; tetrahydrofuryl H-3 or 4), 3.79 (1H, ddd, J 8, 6.9, 1.4 Hz, tetrahydrofuryl H-5a), 3.89 (1H, ddd, J 8, 6.9, 1.4 Hz; tetrahydrofuryl H-5b), 4.71 (1H, "quartet", J 7.5, tetrahydrofuryl H-2), 6.43 (1H, dd, J 7.5, 1.3 Hz, H-3), 9.36 (1H, s; CHO). Found: M^+ at *m/z* 140.0865 $C_8H_{12}O_2$ requires 140.0837.

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