Studies on Pyrazines. Part 22.[1] Lewis Acid-Mediated Cyanation of Pyrazine *N*-Oxides with Trimethylsilyl Cyanide: New Route to 2-Substituted 3-Cyanopyrazines

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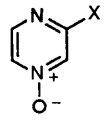
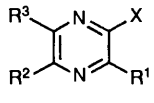
Reaction of 3-substituted pyrazine 1-oxides with trimethylsilyl cyanide in the presence of triethylamine in acetonitrile gave the corresponding cyanopyrazines, yields of which depended remarkably on the substituent. Electron-donating groups enhanced the cyanation with high regioselectivity to 2-substituted 3-cyanopyrazines, while a chloro substituent suppressed the conversion. Addition of zinc halide to the reaction mixture, in most cases, increased the reactivity and improved the regioselectivity. On the other hand, the *N*-oxides carrying an electron-withdrawing methoxycarbonyl or *N*-butylcarbamoyl group underwent the cyanation, without need for the Lewis acid, to provide a mixture of nearly equal amounts of 2-substituted 3- and 5-cyanopyrazines. The latter compound was exclusively obtained when 3-methoxycarbonyl- or 3-cyanopyrazine 1-oxide was treated with diethoxyphosphoryl cyanide.

Owing to their versatility as synthetic intermediates, especially for chemotherapeutically useful pyrazinecarboxamide derivatives,[2] cyanopyrazines are attracting considerable attention in pyrazine chemistry. A common method of introducing a cyano group into the pyrazine nucleus relied on nucleophilic displacement of bromopyrazines with copper(I) cyanide compounds.[3–6] This methodology, however, suffers from certain disadvantages, including the relative inaccessibility of such reactive halogenopyrazines and the requirement for the cyanation to be conducted under harsh reaction conditions in most cases. Although the Reissert–Henze-type reactions, which involve treatment of heteroaromatic *N*-oxides with acid chlorides and a cyanide nucleophile, are efficient methods of the preparation for cyano derivatives of a variety of heterocycles,[7,8] so far as is known pyrazine *N*-oxides have resisted those cyanation conditions. On the other hand, a divergent procedure for the preparation of the corresponding cyano compound from pyridine,[9,10] pyrimidine[11] and quinoxaline *N*-oxides[12] consists of treatment with trimethylsilyl cyanide in the presence of triethylamine in refluxing acetonitrile or dimethylformamide (DMF) at 100–110 °C. In our studies directed towards development of functionalization of pyrazine *via* the *N*-oxide, we have also reported a new synthesis of 2-amino-3-cyanopyrazine **2a** from 3-aminopyrazine 1-oxide **1a** by the above cyanation in the latter solvent.[13] Success in the regiospecific preparation prompted us to extend the cyanation to other substituted pyrazine *N*-oxides. In this paper we describe how a nearly exclusive synthesis of 2-substituted 3-cyanopyrazines is achieved by Lewis acid-mediated cyanation of 3-substituted pyrazine 1-oxides **1** with trimethylsilyl cyanide (TMSCN), as well as two examples of regiospecific conversion, **1h** and **1j**, into the 2-substituted 5-cyanopyrazines by treatment with diethoxyphosphoryl cyanide (DEPC).

In terms of toxicity and cost of the reagent, the procedure in which TMSCN was generated *in situ* from trimethylsilyl chloride and sodium cyanide in DMF appeared to be more convenient than the procedure using TMSCN itself. A careful work-up on our earlier synthesis of compound **2a**, however, revealed that a considerable amount (12%) of cyanation product **2a** underwent further condensation with the solvent to afford 2-cyano-3-[(dimethylaminomethylene)amino]pyrazine **5**. When compound **1b** was treated under the same conditions, no pyrazine compounds could be obtained, probably because of extensive decomposition. A most surprising outcome was seen

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1–4 **a**; X = NH_2
b; X = OMe
c; X = Ph
d; X = Me
e; X = H
f; X = Cl
g; X = CONHBu
h; X = CO_2Me
i; X = CO_2H
j; X = CN

2 R^1 = CN, R^2 = R^3 = H
3 R^1 = R^3 = H, R^2 = CN
4 R^1 = R^2 = H, R^3 = CN
5 X = N=CHNMe$_2$, R^1 = CN, R^2 = R^3 = H
6 X = NMe_2, R^1 = CN, R^2 = R^3 = H

in the cyanation reaction of compound **1f**, which yielded 2-cyano-3-(dimethylamino)pyrazine **6**. Presumably this compound came from the initial formation of intermediate **2f**, followed by displacement of the chloro substituent, perhaps facilitated by the adjacent electron-withdrawing cyano group, by the solvent. Indeed, independent treatment of compound **2f** in DMF under the similar conditions gave compound **6** in 58% yield.

Instead of the above reagent/solvent system, direct treatment with TMSCN in acetonitrile was performed in order to avoid the intense solvent effect of DMF. Reflux of compound **1a** with 3.5 mol equiv. of TMSCN in MeCN for 6 h in the presence of triethylamine (TEA) led, after work-up with ethanol, to a mixture of compound **2a** and the 6-cyano regioisomer **4a** in 93 and 6% yield, respectively. To establish the structure of the second product, we carried out an alternative synthesis of compound **4a** from 6-aminopyrazinecarboxamide.[14] Conveniently, the isomeric disubstituted pyrazines were unambiguously distinguished by their coupling constants between the ring proton in the ^1H NMR spectrum.[2a] In this manner, the identity of cyanation products from other substituted *N*-oxides was confirmed.

Inspection of Table 1 shows the clear substituent effect on reactivity. Electron-donating groups facilitate the cyanation

Table 1 Cyanation of pyrazine *N*-oxides **1** with TMSCN, DEPC or diethylaluminium cyanide

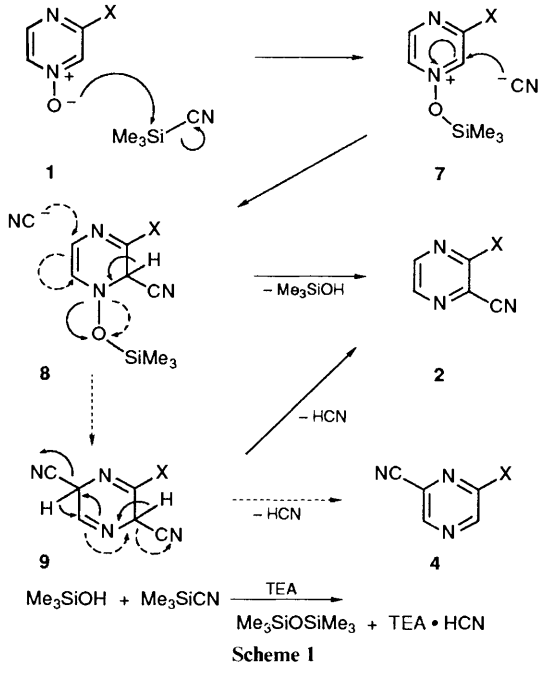
Substrate	Method[a]	Time (*t*/h)	Product and yield (%)[b] 2	3	4
1a	A	6	98[c,d]	0	0
	B	6	93[d]	0	6
	C	6	81	0	0
	D	18	49	0	0
	E	6	24	0	0
1b	A	18	0	0	0
	B	6	43	0	19[e]
	C	6	76	0	0
	D	18	34	0	0
	E	6	35	0	0
1c	B	6	46	7	0[f]
	C	18	65	11	0
	D	18	5	1	0
1d	B	18	38[g]	2	2[h]
	C	18	51[g]	3	0
	D	18	0	0	0
1e	B	18		19	
	C	18		18	
	D	18		0	
1f	A	18	12[i]	0	0
	B	18	0	0	0[j]
	B[k]	18	0	0	0
	C	18	68	0	~0
	D	18	0	0	0
	E	18	0	0	0
1g	B	18	25[l]	26	0[m]
	D	18	0	0	0
1h	B	18	28	32	0
	C	18	21	33	0
	D	18	0	63	0
	E	18	0	0	0
1i	B	18	0	0	0
1j	B[n]	6	~1	24	0
	D[n]	6	0	48	0

[a] A: With TMSCN in DMF at 100–110 °C. B: With TMSCN in refluxing MeCN. C: With TMSCN and 2 mol equiv. of $ZnBr_2$ in refluxing MeCN. D: With DEPC in refluxing MeCN. E: With diethylaluminium cyanide in refluxing benzene. [b] Unless otherwise noted, yields of each component were isolated by column chromatography. [c] This yield includes 12% of by-product **5**. [d] The yields were determined by GLC using a 2% OV-275 column (2 m) at 180–260 °C. [e] Recovered starting material: 16%. [f] 35%. [g] The relative ratios were determined from the ^1H NMR spectrum. [h] Recovered starting material, 34%. [i] This material was compound **6**. [j] Recovered starting material, 71%. [k] DBU was used instead of TEA. [l] Obtained as a mixture with 31% yield of *N*-butylpyrazinecarboxamide.[1] [m] Recovered starting material, 7%. [n] At room temperature.

Table 2 Cyanation of **1f** with TMSCN in the presence of Lewis acid[a]

Lewis acid	Molar equiv.	Product and yield (%) 2f	4f	Unchanged substrate recovered **1f** (%)
$ZnCl_2$	1	27	2	17
$ZnBr_2$	0.1	12	0	33
	1	68	2	14
	2	76	1	1
	2	68[b]	~0	1[b]
	2[c]	11	0	78
ZnI_2	1	74	1	9
	1	61[b]	~0	9[b]
	2	67	0	2
$SnCl_4$	1	19	0	5
$TiCl_4$	1	0	0	0

[a] The yields of components were determined by HPLC using a C_{18} column eluted with water MeCN (9:1), unless otherwise noted. [b] These are isolated yields by column chromatography. [c] In the absence of TEA.



Scheme 1

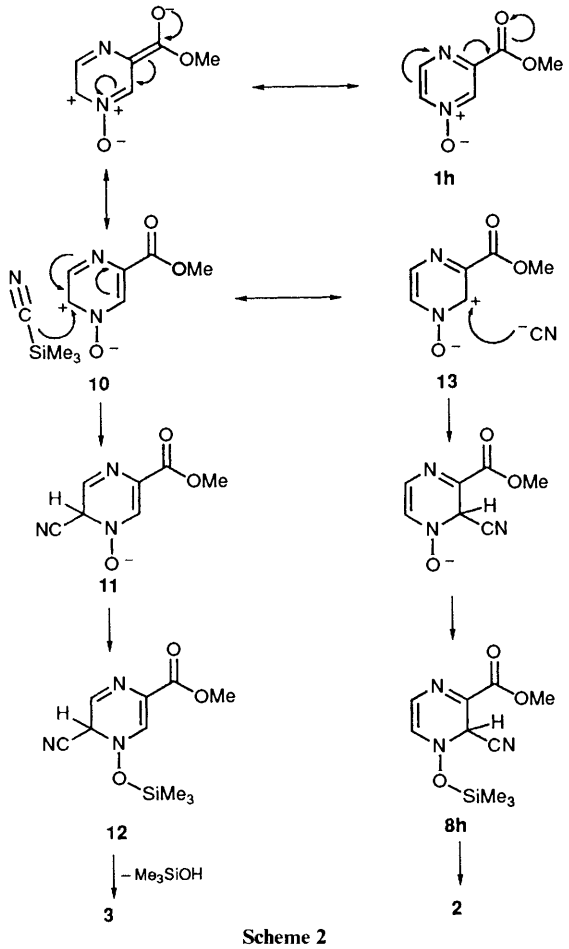
more easily than does the parent *N*-oxide **1e**, while a chloro substituent suppresses the substitution reaction. The use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which sufficed as the base (instead of TEA) for the cyanation of the less reactive 3-chloroquinoxaline 1-oxide,[12] was not as effective in the reaction of compound **1f**. Another feature in the cyanation of the substituted pyrazine *N*-oxides is a high regioselectivity for the substitution on the carbon α to the *N*-oxide function, unlike the case of non-regioselective chlorination with phosphoryl trichloride.[15] On the basis of work previously reported from this laboratory,[15] a mechanism for the formation of products **2** and **4** is outlined in Scheme 1. The key step is the second nucleophilic attack by the cyanide ion at the C-5 carbon of intermediate **8** to form the common intermediate **9**, which undergoes competitive dehydrocyanation to give the β- and α-cyanated products. The predominance of α-substitution in the present cyanation is caused by the reduced second attack of the cyanide ion on species **8** because of its shorter lifetime. In other words, elimination of hydrogen from intermediate **8** is more enhanced by the more strongly electron-withdrawing cyano group than by the chloro substituent.

By analogy with the well defined mechanism from kinetic studies of the reaction of pyridine *N*-oxides with acetic anhydride,[16] including their behaviour in the Reissert–Henze reaction,[7,8] the sequence to intermediate **8** will be initiated by the reversible formation of *N*-(trimethylsiloxy)pyrazinium salt **7**, followed by the rate-determining nucleophilic attack of the cyanide ion at the electron-deficient carbon α to the *N*-oxide function, leading to species **8**. Conceivably, the electron-withdrawing substituent could enhance the cyanation because the resulting electron-deficient intermediate **7** should be more susceptible to nucleophilic attack. The logical deduction, however, is clearly opposite to the observed reactivity so that the preceding process to intermediate **7** is concluded to be the rate-determining step. Namely, the nucleophilicity of the *N*-oxide oxygen governs the cyanation in a different manner from that of pyridine *N*-oxides. The inertness of the pyrazine series results from the combined electron-attracting effect of both the substituent and the additional ring nitrogen atom *para* to the *N*-oxide function.

The above mechanism suggested that activation of the *N*-oxide oxygen in substrate **1f** is the key effect on the cyanation. Addition of Lewis acid to the reaction mixture resulted in the

formation of compound **2f**. It is obvious from Table 2 that the cyanation proceeds stoichiometrically with a weaker Lewis acid in the presence of TEA in contrast to the zinc iodide-catalysed addition of TMSCN to aldehydes and ketones giving cyanohydrin trimethylsilyl ethers.[17] The best yield was obtained by using 2 mol equiv. of zinc bromide. This procedure successfully improved the yields of the cyanation products from substrates **1b–d**. In comparison with cyanation by TMSCN alone, the Lewis acid-mediated reactions are distinguished by complete suppression of displacement on carbon β to the *N*-oxide function. This aspect is attributed to prohibition of the second attack by cyanide anion on the intermediate **8**, resulting in exclusive formation of α-cyanopyrazines *via* the direct pathway.

An electron-withdrawing group should reduce the nucleophilicity of the *N*-oxide oxygen more than does a chloro substituent. Nevertheless, achievement of the cyanation in substrates **1g**, **1h** and **1j** even under conditions without a Lewis acid was rationalized to the α-carbons suffering a strong electron-deficiency induced by both their substituent and the ring nitrogen atoms as shown in Scheme 2 for the case of



Scheme 2

substrate **1h**. Therefore, cyanation on the ring carbon precedes trimethylsilylation of the *N*-oxide oxygen, the reverse of the sequence shown in Scheme 1. This clearly explains the curious regioselectivity shown on cyanation of substrates **1g** and **1h**. Namely, an initial cyanation occurs only at the C-5 carbon, intermediate **10**, and this gives anion **11** since interaction at C-3 with the bulkier TMSCN is strongly impeded by the adjacent substituent. Trimethylsilanol as the leaving group from siloxamine **12** undergoes condensation with another molecular of TMSCN to furnish, in the presence of TEA, hexamethyldisiloxane and triethylammonium cyanide (see the final equation in Scheme 1). The anion of the latter salt is a smaller species than TMSCN and can attack the reactive carbon C-3 in the form of zwitterion **13** without steric problems resulting in nearly equal formation of products **2** and **3**. Conversely, formation of compounds **3c** and **3d** is probably attributed to steric interruption by a phenyl or methyl group on the attack of cyanide ion on the intermediate **7**, taking account of the progress of cyanation which depends on the nucleophilicity of the *N*-oxide oxygen.

Pyrazinecarboxylic acid *N*-oxide **1i**, which was expected to be cyanated *via* the trimethylsilyl ester, led to the formation of only a tar-like material on treatment with TMSCN. Despite complete consumption at room temperature after 6 h, cyanopyrazine *N*-oxide **1j** afforded 2,5-dicyanopyrazine **3j**, in only 24% yield; however, the product was almost pure. This enhanced regioselectivity results from a marked difference in reactivity, probably owing to the strong electronic effect of the cyano group of substrate **1j**, between the C-3 and C-5 carbons.

Although improvements were achieved in the cyanation of substrates **1b–d** and **1f**, the addition of Lewis acid had no effect on their yield in the reaction of compounds **1e** and **1h**. Numerous examinations with other cyanide compounds showed that diethylaluminium cyanide and DEPC[18] were effective for the cyanation of compounds **1a**, **1b**, **1h** and **1j** as seen in Table 1, whereas benzoyl cyanide, tributyltin cyanide, and toluene-*p*-sulphonyl cyanide failed to achieve the transformation. Because of its synthetic utility, DEPC is the reagent of choice for regiospecific formation of compounds **3h** and **3j**, which should be formed in a similar fashion to that postulated for cyanation with TMSCN. However, here the leaving group is diethylphosphoric acid, which must be directly trapped with TEA without reacting with other species. Consequently, the secondary cyanation to yield product(s) **2** is completely suppressed, probably by the absence of reacting cyanide ion in the reaction medium. The exclusive cyanation observed in the case of substrate **1b** is caused by promoted abstraction of hydrogen from the corresponding intermediate **8** due to the stronger reinforcing effect of the diethyl phosphate group. As a cyanation reagent, TMSCN is found to be the most powerful nucleophile; DEPC is less reactive than TMSCN and can give regiospecific cyanation; and diethylaluminium cyanide shows poor reactivity as can be seen in Table 1. Finally, investigation by molecular orbital (MO) calculations in order to explain the observed regiochemistry is now in progress and will be reported at a later date.

Experimental

M.p.s were determined using a Büchi 535 apparatus and are uncorrected. B.p.s are uncorrected. IR spectra were recorded on a JASCO IR-810 spectrometer. NMR spectra were obtained with a JEOL JNM FX-90Q (90 MHz ^{1}H, 22.5 MHz ^{13}C) and a EX270 (270 MHz ^{1}H, 67.8 MHz ^{13}C) instrument with solutions in $(CD_3)_2SO$, unless otherwise noted, containing Me_4Si as internal standard. *J*-Values are given in Hz.

2-Amino-6-cyanopyrazine **4a**.—Phosphoryl trichloride (0.2 cm^3, 2.1 mmol) was added to a stirred solution of 6-aminopyrazinecarboxamide[14] (0.1 g, 0.72 mmol) in dry DMF (3.0 cm^3) and the resulting mixture was stirred and heated at 50–60 °C for 45 min. After cooling to room temperature, the mixture was evaporated and the residue was suspended in water (3 cm^3). The slurry was refluxed for 1 h, during which time it became a solution. The precipitates which formed on cooling was filtered off, dried (in air), and sublimed at 180 °C/1 mmHg to give *compound* **4a** (0.48 g, 55%) as yellow tiny needles, m.p. 201–203 °C (from EtOH) (Found: C, 49.5; H, 3.3; N, 46.4. $C_5H_4N_4$ requires C, 50.0; H, 3.4; N, 46.6%); ν_{max}(KBr)/cm^{-1} 2230 (C≡N); δ_H 7.17 (2 H, br s), 8.10 (1 H, s) and 8.15 (1 H, s); δ_C 116.64, 126.29, 135.01, 137.45 and 155.54.

N-*Butylpyrazinecarboxamide* 4-*Oxide* **1g**.—A slurry of methylpyrazinecarboxylate 4-oxide **1h** (2.32 g, 0.015 mol) in butylamine (45 cm^3) was stirred and refluxed until a clear solution had been formed (0.5 h). After the mixture had been heated for a further 0.5 h, the solvent was removed and the residue was recrystallized from propan-2-ol to afford *compound* **1g** (2.74 g, 93%) as imbricate crystals, m.p. 156 °C (Found: C, 55.3; H, 6.7; N, 21.6. $C_9H_{13}N_3O_2$ requires C, 55.4; H, 6.7; N, 21.5%); ν_{max}(KBr)/cm^{-1} 3310 (N–H) and 1660 (C=O); δ_H($CDCl_3$) 0.97 (3 H, t), 1.42 (2 H, sextet), 1.63 (2 H, quintet), 3.48 (2 H, q), 7.80 (1 H, br s), 8.17 (1 H, dd, *J* 1.7 and 4.0), 8.39 (1 H, d, *J* 4.0) and 8.84 (1 H, d, *J* 1.7); δ_C($CDCl_3$) 13.71, 20.11, 31.50, 39.44, 133.78, 135.42, 145.64, 149.77 and 160.93.

General Procedure of Cyanation of Pyrazine N-*Oxides* **1** *with TMSCN or DEPC*.—(A) *In DMF*. A mixture of an *N*-oxide **1** (1 mmol) and freshly powdered 97% NaCN (0.15 g, 3 mmol) in dry DMF (6 cm^3) containing TEA (0.7 cm^3, 5 mmol) was purged by passage of argon, and trimethylsilyl chloride (0.51 cm^3, 4 mmol) was added *via* a syringe at below 30 °C. The reaction mixture was stirred and heated at 100–110 °C for the period given in Table 1 and was then concentrated to give a dark oil. The residue from substrate **1a** was only stirred in EtOH (10 cm^3) for 0.5 h at room temperature and the mixture was then evaporated. The products were separated by chromatography on SiO_2 and elution with hexane–ethyl acetate (6:1 to 2:1). The proportions of product isomers were determined by the method shown in Table 1.

(B) *In MeCN*. TMSCN (0.48 cm^3, 3.5 mmol) was added under argon to a mixture of a substrate **1** (1 mmol) in dry MeCN (6 cm^3) containing TEA (0.7 cm^3, 5 mmol) in the previously described manner. The mixture was refluxed and stirred for the time given in Table 1. The solvent was evaporated off and the residue was worked up in the above manner.

(C) *In MeCN in the presence of* ZnX_2. A mixture of a substrate **1** (1 mmol) and ZnX_2 (0.1, 1 or 2 mmol) was purged by passage of argon after evacuation of air, and then MeCN (6 cm^3), TEA (0.7 cm^3), and finally TMSCN (0.48 cm^3, 3.5 mmol) were added. The slurry was worked up in the previously described manner.

(D) *In MeCN with DEPC*. The procedure was the same as the above method (B) except for the use of DEPC in place of TMSCN.

The following compounds were obtained by the above procedure.

2-Amino-3-cyanopyrazine **2a**. As pale yellow needles, m.p. 192 °C (from water) (lit.,[13] 192 °C); ν_{max}(KBr)/cm^{-1} 2225 (C≡N); δ_H 7.34 (2 H, br s), 7.98 (1 H, d, *J* 2.2) and 8.34 (1 H, d); δ_C 111.61, 115.89, 133.71, 147.25 and 157.06.

2-Cyano-3-methoxypyrazine **2b**. As needles, m.p. 55 °C (from hexane) (lit.,[13] 55–56 °C); ν_{max}(KBr)/cm^{-1} 2230 (C≡N); δ_H 4.08 (3 H, s), 8.44 (1 H, d, *J* 2.4) and 8.61 (1 H, d); δ_C 54.88, 114.47, 118.32, 137.98, 145.78 and 164.33.

2-*Cyano*-6-*methoxypyrazine* **4b**. As tiny needles, m.p. 80 °C (from hexane) (Found: C, 51.4; H, 3.6; N, 30.1. $C_6H_5N_3O{\cdot}\frac{1}{4}H_2O$ requires C, 51.6; H, 4.0; N, 30.1%); ν_{max}(KBr)/cm^{-1} 2230 (C≡N); δ_H 3.98 (3 H, s), 8.66 (1 H, d, *J* 0.7) and 8.79 (1 H, d); δ_C 54.34, 115.83, 124.87, 140.64, 140.80 and 159.49.

2-Cyano-3-phenylpyrazine **2c**. As needles, m.p. 96–97 °C (from hexane) (lit.,[19] 94–96 °C); ν_{max}(KBr)/cm^{-1} 2230 (C≡N); δ_H($CDCl_3$) 7.57–7.59 (3 H, m), 7.98–8.01 (2 H, m), 8.65 (1 H, d, *J* 2.3) and 8.84 (1 H, d); δ_C($CDCl_3$) 116.39, 127.98, 129.02, 131.14, 134.34, 142.98, 146.48 and 157.10.

2-Cyano-3-methylpyrazine **2d**. B.p. 105 °C/30 mmHg (Kugelrohr) (lit.,[5] 125–126 °C/50 mmHg); ν_{max}(neat)/cm^{-1} 2220 (C≡N); δ_H 2.74 (3 H, s), 8.70 (1 H, d, *J* 2.4) and 8.86 (1 H, d); δ_C 21.41, 115.78, 129.16, 142.86, 147.86 and 157.49.

2-Cyanopyrazine **2e** (≡**3e**≡**4e**). As a liquid, b.p. 100–101 °C/17 mmHg (lit.,[5] 116–117 °C/50 mmHg); ν_{max}(KBr)/cm^{-1} 2240 (C≡N); δ_H 8.90 (1 H, dd, *J* 1.3, 2.3), 9.00 (1 H, d, *J* 2.3) and 9.26 (1 H, d, *J* 1.3); δ_C 115.96, 129.83, 145.84, 148.30 and 148.73.

2-Chloro-3-cyanopyrazine **2f**. As tiny needles, m.p. 48 °C (from hexane) (lit.,[20] 48 °C); ν_{max}(KBr)/cm^{-1} 2240 (C≡N); δ_H 8.85 (1 H, d, *J* 2.3) and 8.88 (1 H, d); δ_C 114.39, 129.61, 143.99, 147.71 and 150.40.

N-*Butyl*-3-*cyanopyrazinecarboxamide* **2g**. As needles, m.p. 100–101 °C (from hexane) (Found: C, 58.7; H, 5.9. $C_{10}H_{12}N_4O$ requires C, 58.8; H, 5.9%); ν_{max}(KBr)/cm^{-1} 3210 (N–H) and 1740 (C=O); δ_H($CDCl_3$) 0.97 (3 H, t), 1.43 (2 H, sextet), 1.78 (2 H, quintet), 3.98 (2 H, q), 8.81 (1 H, d, *J* 2.6), 8.89 (1 H, d) and 9.42 (1 H, br s); δ_C($CDCl_3$) 13.71, 20.18, 30.35, 38.85, 122.89, 144.51, 147.72, 148.28 and 163.74.

N-*Butyl*-5-*cyanopyrazinecarboxamide* **3g**. As needles, m.p. 71–72 °C (from hexane) (Found: C, 58.8; H, 5.9; N, 27.7. $C_{10}H_{12}N_4O$ requires C, 58.8; H, 5.9; N, 27.4%); ν_{max}(KBr)/cm^{-1} 3300 (N–H), 2240 (C≡N) and 1660 (C=O); δ_H($CDCl_3$) 0.97 (3 H, t), 1.43 (2 H, sextet), 1.65 (2 H, quintet), 3.52 (2 H, q), 7.76 (1 H, br s), 8.86 (1 H, d, *J* 1.3) and 8.51 (1 H, s); δ_C($CDCl_3$) 13.71, 20.09, 31.48, 39.51, 115.02, 132.65, 144.98, 145.86, 146.02 and 161.17.

Methyl 3-*cyanopyrazinecarboxylate* **2h**. As tiny needles, m.p. 76 °C (from hexane) (Found: C, 51.3; H. 3.1; N, 25.9. $C_7H_5N_3O_2$ requires C, 51.5; H, 3.1; N, 25.8%); ν_{max}(KBr)/cm^{-1} 2240 (C≡N); δ_H($CDCl_3$) 4.13 (3 H, s), 8.90 (1 H, d, *J* 2.3) and 8.91 (1 H, d); δ_C 53.15, 115.27, 129.74, 145.41, 146.86, 147.54 and 162.24.

Methyl 5-*cyanopyrazinecarboxylate* **3h**. As pale yellow flakes, m.p. 95 °C (from hexane) (Found: C, 51.4; H, 3.1; N, 25.7%); δ_H($CDCl_3$) 4.10 (3 H, s), 9.04 (1 H, d, *J* 1.3) and 9.41 (1 H, d); δ_C 53.21, 115.62, 131.98, 144.82, 145.84, 148.23 and 161.96.

2,5-Dicyanopyrazine **3j**. As prisms, m.p. 193 °C (from EtOAc) (lit.,[21] 188–189 °C); ν_{max}(KBr)/cm^{-1} 2240 (C≡N); δ_H($CDCl_3$) 9.04 (2 H, s); δ_C($CDCl_3$) 114.01, 132.72 and 148.17.

The following materials could not be isolated or obtained in sufficient quantity for analysis so that only their NMR spectral data are given.

2-Cyano-5-phenylpyrazine **3c**. δ_H($CDCl_3$) 7.5–7.6 (3 H, m), 8.08–8.11 (2 H, m), 8.94 (1 H, d, *J* 1.3) and 9.14 (1 H, d); δ_C($CDCl_3$) 115.83, 127.62, 128.82, 129.45, 131.64, 134.54, 142.50, 147.62 and 154.84.

2-Cyano-5-methylpyrazine **3d**. δ_H 2.61 (3 H, s), 9.01 (1 H, d, *J* 1.4) and 9.06 (1 H, d).

2-Cyano-6-methylpyrazine **4d**. δ_H 2.66 (3 H, s), 8.77 (1 H, s) and 8.89 (1 H, s).

2-*Cyano*-3-[(*dimethylaminomethylene*)*amino*]*pyrazine* **5**.—A mixture of compound **2a** (49 mg, 0.4 mmol) in DMF dimethyl acetal (1 cm^3) was refluxed and stirred for 20 min. After cooling to room temperature, the mixture was evaporated. The residue which solidified upon storage was recrystallized to give compound **5** (47 mg, 66%) as tiny plates, m.p. 86 °C (from EtOH) (lit.,[22] 86 °C) (Found: C, 54.7; H, 5.2; N, 39.9. Calc. for $C_8H_9N_5$: C, 54.9; H, 5.2; N, 40.0%); ν_{max}(KBr)/cm^{-1} 2225 (C≡N); δ_H 3.09 (3 H, s), 3.18 (3 H, s), 8.09 (1 H, d, *J* 2.2), 8.32 (1 H, d) and 8.56 (1 H, s); δ_C 34.57, 40.64, 116.54, 122.22, 137.61, 146.44, 157.12 and 159.60.

2-*Cyano*-3-(*dimethylamino*)*pyrazine* **6**.—A mixture of compound **2f** (0.425 g, 3 mmol) and TEA (2.1 cm^3, 15 mmol) in dry DMF (18 cm^3) was heated at 100 °C for 18 h and then evaporated to dryness. The residue was subjected to flash chromatography on SiO_2 with hexane–ethyl acetate (7:1) as the eluent to afford an unidentified material (2 mg), δ_H($CDCl_3$) 1.29 (9 H, t), 1.58 (6 H, s), 3.73 (4 H, q), 7.88 (1 H, d, *J* 2.0) and 8.20 (1 H, d); δ_C($CDCl_3$) 13.33, 29.72, 44.02, 132.86 and 145.35.

Compound **6** was obtained as the second fraction (0.261 g, 58%), m.p. 46 °C (from hexane) (Found: C, 56.6; H, 5.3; N, 37.7. $C_7H_8N_4$ requires C, 56.7; H, 5.4; N, 37.8%); ν_{max}(KBr)/cm^{-1}

2200 (C≡N); δ_H 3.25 (3 H, s), 3.36 (3 H, s), 8.00 (1 H, d, *J* 2.2) and 8.38 (1 H, d); δ_C 39.28, 39.49, 111.00, 117.88, 133.32, 145.62 and 155.37.

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