Studies on Pyrazines. Part 27.[1] A New Deoxidative Nucleophilic Substitution of Pyrazine *N*-Oxides; Synthesis of Azidopyrazines with Trimethylsilyl Azide

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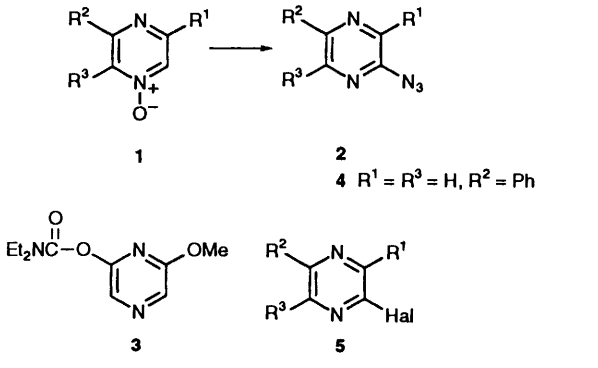
Azidopyrazines bearing amino, methoxy and/or phenyl groups have been synthesized by reaction of pyrazine *N*-oxides with trimethylsilyl azide in the presence of diethylcarbamoyl chloride in refluxing acetonitrile. In most cases, the azidation occurs only at the carbon α to the *N*-oxide function, and 3-substituted pyrazine 1-oxides gave 2-azido-3-substituted pyrazines. Conversely, methyl, chloro and methoxycarbonylpyrazine *N*-oxides did not undergo azidation. The electronic and steric effects of the substituent on the reactivity are discussed.

Azidopyrazines **2**, or rather the tautomeric tetrazolo[1,5-*a*]pyrazines, have, until now, been prepared by nucleophilic substitution of halogenopyrazines with sodium azide[2–4] or nitrosation of hydrazinopyrazines with sodium nitrite.[3] In our efforts directed towards the functionalization of the pyrazine ring, we envisioned the synthesis of azidopyrazines by deoxidative nucleophilic substitution of pyrazine *N*-oxides. A literature search provided only two reports[5,6] for such a conversion, starting from pyridine and quinoline *N*-oxides, which involved thermolysis of the *N*-oxides with arenesulfonyl azide[5] or their treatment with trimethylsilyl azide in the presence of methanesulfonyl chloride in refluxing acetonitrile.[6] Although attempted conversion of a selection of pyrazine *N*-oxides **1** employing the latter procedure, which was expected to be more practical, failed to yield azidopyrazines **2**, use of diethylcarbamoyl chloride instead of methanesulfonyl chloride did induce the conversion (Scheme 1). In this paper, we present



1 **2**

4 $R^1 = R^3 = H$, $R^2 = Ph$

3 **5**

1, 2, 5a $R^1 = NH_2$, $R^2 = R^3 = H$
b $R^1 = NH_2$, $R^2 = H$, $R^3 = Me$
c $R^1 = OMe$, $R^2 = R^3 = H$
d $R^1 = OMe$, $R^2 = Ph$, $R^3 = H$
e $R^1 = Ph$, $R^2 = R^3 = H$
f $R^1 = H$, $R^2 = R^3 = Ph$
g $R^1 = R^2 = Ph$, $R^3 = H$
h $R^1 = H$, $R^2 = OMe$, $R^3 = Ph$
i $R^1 = OMe$, $R^2 = R^3 = Ph$
j $R^1 = R^3 = Me$, $R^2 = H$
k $R^1 = Cl$, $R^2 = R^3 = H$
l $R^1 = CO_2Me$, $R^2 = R^3 = H$
m $R^1 = R^2 = H$, $R^3 = NH_2$
n $R^1 = R^2 = H$, $R^3 = OMe$

Scheme 1

the details of this azidation, particularly the reactivity dependence on the substituent of the starting *N*-oxide and the comparison of mechanism with the previously verified cyanation[7] and thiation[8] reactions.

Results and Discussion

It has been established that in the presence of diethylcarbamoyl chloride pyridine *N*-oxides[9] or pyrazine *N*-oxides[8] undergo thiation with a thiol. In the azidation described here the acid chloride also effected the conversion, *i.e.* quantitative formation of 2-amino-3-azidopyrazine **2a** was achieved by treating 3-aminopyrazine 1-oxide **1a** with 1.2 equiv. each of trimethylsilyl azide (TMSA) and diethylcarbamoyl chloride in refluxing acetonitrile for 18 h. Under identical conditions, 5-amino-2-methylpyrazine 1-oxide **1b** gave the azide **2b** (59%) although some (31%) of the starting *N*-oxide was recovered. With a longer reaction time (30 h) consumption of the *N*-oxide **1b** was complete and the yield of product was improved (84%). Quantitative conversion of **1b** into **2b** was achieved with a doubling (2.4 equiv.) of the reagents employed and an 18 h reflux period. In the absence of the acid chloride no azidation occurred.

Similarly, 3-methoxypyrazine 1-oxide **1c** gave 2-azido-3-methoxypyrazine **2c** (63%) when treated with 2.4 equiv. each of the reagents in acetonitrile for 18 h; surprisingly, 2-diethylcarbamoyloxy-6-methoxypyrazine **3** was formed as a by-product (established by elemental analysis and ^1H and ^{13}C NMR). Although the presence of zinc bromide has proved effective in promoting the thiation of pyrazine *N*-oxides with 4-methoxytoluene-α-thiol and diethylcarbamoyl chloride,[8] it gave a decreased yield of the azide **2c**. This decreased yield is probably ascribable to rapid consumption of TMSA as a result of acylation by the carbamoyl chloride in the presence of zinc bromide.

Sodium azide instead of TMSA could also be used for the azidation. For example, the pyrazine *N*-oxides **1a** and **1c**, when treated with 1.2 equiv. of sodium azide in refluxing acetonitrile for 18 h gave the corresponding azides **2a** (32%) and **2c** (38%), respectively. Alternatively, compounds **2a** and **2c** could be prepared by the classical procedure[4] from the corresponding halogenopyrazines **5a** and **5c** employing sodium azide in dimethylformamide at 120 °C for 5 h in 77 and 20% yields, respectively. In terms of synthetic utility, TMSA is the choice for synthesis of these azides, because of the accessibility of the starting material, yields and ease of isolation of the products.

The identity of the azido compounds **2a** and **2c** was confirmed through independent synthesis from the halogenopyrazines **5** as just described. Conveniently, the isomeric disubstituted pyrazines were unambiguously distinguished by the ^1H NMR coupling constants between their ring protons.[7,8] The 2,3-isomers usually have a coupling constant of 2.4–2.9 Hz[10] whilst the azido pyrazines **2a** and **2c** have values of 4.3–4.6 Hz in [$^2H_6$]dimethyl sulfoxide. In contrast, the isomeric 2-azido-5-substituted pyrazine **4** has a typical coupling constant of 1.7 Hz.[10] The same values for each coupling constant of the

Table 1 Reaction of pyrazine *N*-oxides **1** with TMSA in the presence of diethylcarbamoyl chloride[a]

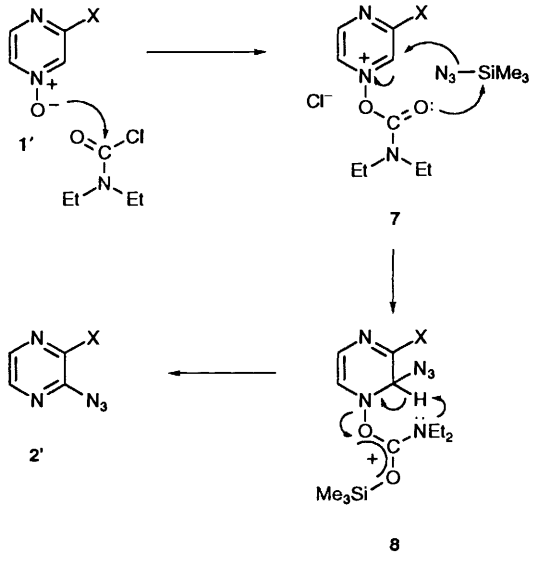
Substrate	TMSA[b] (mol equiv.)	Reaction time (*t*/h)	Products (% ratio)[c]	Yield of azide (%)	Recovered *N*-oxide **1** (%)
1a	1.2	18	**2a**	99	0
1b	1.2	18	**2b**	59	31
	1.2	30	**2b**	84	0
	2.4	18	**2b**	100	0
1c	1.2	18	**2c**[d]	36	28
	2.4	18	**2c**[e]	63	2
1d	1.2	18	**2d**	79	16
	2.4	18	**2d**	99	0
1e	1.2	18	**2e** (62), **4** (38)	53	46
	1.2	30	**2e** (64), **4** (36)	54	41
	2.4	18	**2e** (71), **4** (29)	85	6
	2.4	30	**2e** (72), **4** (28)	90	4
1f	1.2	30	**2f**	69	24
	2.4	18	**2f**	85	5
1g	1.2	24	**2g**	82	17
	2.4	18	**2g**	100	0
1h	1.2	18	**2h**[f]	25	10

[a] Yields given here are those of reaction carried out on 1.0 mmol scale. [b] The same mol equiv. of diethylcarbamoyl chloride was used. [c] Ratios were determined by ^{1}H NMR spectroscopy. [d] Compound **3** was also formed in 20% yield. [e] Compound **3** was also formed in 28% yield. [f] This compound was contaminated with the isomeric 2-azido-6-methoxy-5-phenylpyrazine. Other products were 2-diethylcarbamoyl-5-methoxy-6-phenyl- and -6-methoxy-5-phenylpyrazines (27%), and 2-methoxy-3-phenylpyrazine (37%).

5,6- and 3,6-hydrogens were observed in the spectrum of 2-azidopyrazine[2] existing in the form of the tetrazolo[1,5-*a*]-pyrazine **6** as deduced from IR and UV evidence.

A variety of substituted pyrazine *N*-oxides were similarly treated, with the successful examples collected in Table 1. From the results it is clear that azidation proceeded only with pyrazine *N*-oxides bearing electron-donating (NH_2, MeO, Ph) groups, and that compounds containing a weak electron-donating (Me) and electron-withdrawing (2,5-Me_2, 3-Cl and 3-MeO_2C) substituents did not undergo the reaction. Thus, compounds **1j–l** were mostly recovered upon work-up, the desired azide not being isolated although some indication of its formation was indicated by TLC. Similarly, the 2-substituted pyrazine 1-oxides **2m** and **2n** did not react with TMSA.

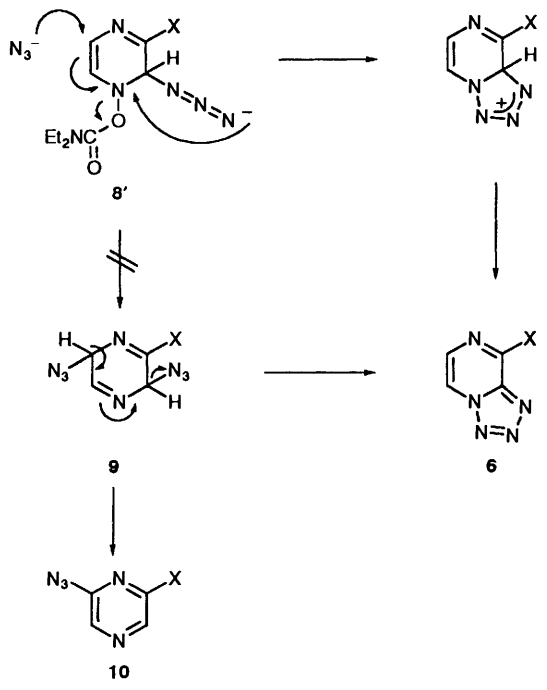
The reactivity sequence for the azidation is evident from a comparison of the results for reactions in which 1.2 equiv. each of the reagents was used (see Table 1). The trend in the substituent effect resembles that in the cyanations and thiations examined earlier.[7,8] Based on the explanation given then, the mechanism of azidation is exhibited in Scheme 2. The use of diethylcarbamoyl chloride promotes the dehydration in the final step by the built-in diethylamine group[8,9] (see Scheme 2). The generation of the azide ion from TMSA is probably caused by nucleophilic attack by the carbonyl oxygen of the *N*-diethylcarbamate intermediate **7**, owing to the strong affinity between silicon and oxygen atoms. However, the electron-withdrawing substituent on the pyrazine ring decreases the nucleophilic capacity of the carbonyl oxygen. This is believed to be a reason why the *N*-oxides having such an electron-withdrawing group failed in the azidation, whereas they underwent thiation using the same auxiliary reagent, diethylcarbamoyl chloride. A further reason for the lower reactivity is the azide ion having weaker nucleophilicity than the thiol.



Scheme 2

By comparing the yields of substitution products and the recovered amount of the starting *N*-oxide, it is evident that a substituent R^3 adjacent to the *N*-oxide group inhibits the attack of the *N*-oxide oxygen onto TMSA to some degree. The second step of introducing the azide group is more strongly hindered by an additional substituent R^1 adjacent to where the azidation occurs. The steric impediment is clearly exemplified in the reaction of 2,3-diphenyl-5-methoxypyrazine 1-oxide **1i**, which provided a 70% yield of the deoxygenated product of 2,3-diphenyl-5-methoxypyrazine and 21% recovery of the starting *N*-oxide. Since the deoxygenation step follows the formation of the *N*-diethylcarbamoyloxy pyrazine (intermediate **7**), this accounts for the difficulty in substitution by the azide ion due to the steric effect of the 3-methoxy substituent. This aspect presents a striking contrast to the reaction of 2,3-diphenylpyrazine 1-oxide **1f**, which, under identical conditions, forms 69% of the azido product and a similar recovery of the starting *N*-oxide (24%). Consequently, the first step is governed mostly by the nucleophilicity of the *N*-oxide oxygen and the succeeding processes are strongly influenced by steric factors.

A further noteworthy feature of the azidation in the 3-substituted pyrazine 1-oxides **1a**, **1c** and **1e** is the lack of formation of 6-azido-2-substituted pyrazines **10** arising from substitution at the carbon β to the *N*-oxide function. Such β-substituted compounds are formed as minor to major products in the substitutions explored before. A plausible pathway to such a derivative **10** is shown in Scheme 3. However, the azido group of the intermediate **8'** is likely to attack the N-1 ring nitrogen to produce tetrazolo[1,5-*a*]pyrazine **6**. This rapid intramolecular reaction prohibits the second attack of azido ion on the intermediate **8'**, thus preventing formation of the β-



Scheme 3

substituted compound **10**. In contrast, the azidation of *N*-oxides **1h** provided a mixture of the α- and β-azidopyrazines in 25% combined yields. This regiochemical inconsistency in the azidation of 3-substituted pyrazine 1-oxides is probably attributable to the interference with cyclization to the tetrazole ring by the steric effect of the 6-substituent, allowing a second nucleophilic attack to yield the β-substituted product.

Also of mechanistic interest is the formation of diethylcarbamoyloxypyrazine **3**. Further investigation into the acetoxylation of pyrazine *N*-oxides is now in progress and the results will be reported in the near future.

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 EX270 (270 MHz ^{1}H, 67.8 MHz ^{13}C) instrument with solutions in $CDCl_3$, unless stated otherwise, containing Me_4Si as internal standard. *J* Values are given in Hz.

Preparation of Pyrazine N-*Oxides* **1**.—The following pyrazine *N*-oxides were prepared according to reported literature procedures: **1a**,[11] **1b**,[1] **1c**, **1n**,[12] **1h**,[13] **1j**,[14] **1k**,[15] **1l**[16] and **1m**.[17]

3-*Methoxy*-5-*phenylpyrazine* 1-*oxide* **1d**. A mixture of 3-chloro-5-phenylpyrazine 1-oxide[18] (2.04 g, 10 mmol) in methanolic sodium methoxide, which was prepared from dry MeOH (30 cm^3) and sodium (0.28 g, 25 mmol), was stirred under reflux for 20 h and then evaporated under reduced pressure. To the residue was added water (20 cm^3), and the solution was extracted with $CHCl_3$ (3 × 20 cm^3). The combined extracts were washed (H_2O), dried ($MgSO_4$) and evaporated to afford the title compound **1d** (1.72 g, 86%), which was recrystallized from EtOH to afford needles, m.p. 147–148 °C (Found: C, 65.4; H, 5.2, N, 13.95. $C_{11}H_{10}N_2O_2$ requires C, 65.3; H, 5.0; N, 13.85%); ν_{max}(KBr)/cm^{-1} 1610, 1530, 1430, 1180 and 690; δ_H 4.10 (3 H, s), 7.49–7.52 (3 H, m), 7.74 (1 H, d, *J* 1.3), 7.93–7.96 (2 H, m) and 7.22 (1 H, d).

3-*Phenylpyrazine* 1-*oxide* **1e**. A solution of 2-phenylpyrazine[18] (3.13 g, 20 mmol) and 87% *m*-chloroperbenzoic acid (4.76 g, 24 mmol) in 1,2-dichloroethane (60 cm^3) was stirred at room temperature for 24 h and then evaporated under reduced pressure. The residue was treated with $CHCl_3$ (50 cm^3), and the mixture was washed with aqueous sodium carbonate to remove *m*-chlorobenzoic acid. After being washed twice with water and dried ($MgSO_4$), the solution was evaporated and the residue was subjected to chromatography in SiO_2 (20 g) eluting with hexane–AcOEt (1 : 1) to give the title compound **1e** (2.91 g, 85%), which was recrystallized from EtOH to provide flakes (2.57 g, 75%); m.p. 137.5–138 °C (lit.,[18] 141–142 °C); δ_H 7.51–7.54 (3 H, m), 7.92–7.96 (2 H, m), 8.05 (1 H, dd, *J* 4.0, 1.3), 8.52 (1 H, dd, *J* 4.0, 0.7) and 8.54 (1 H, dd, *J* 1.3, 0.7).

2,3-*Diphenylpyrazine* 1-*oxide* **1f** *and* 2,6-*diphenylpyrazine* 1-*oxide* **1g**. A solution of diphenylpyrazine (1.16 g, 5.0 mmol) and 87% *m*-chloroperbenzoic acid (1.20 g, 6.0 mmol) in 1,2-dichloroethane (15 cm^3) was stirred and heated at 65 °C (bath temperature) for 3 h and then worked up as described above. Compound **1f** was obtained as needles (65%), m.p. 179.5–180 °C (from EtOH) (lit.,[19] 171–172 °C); δ_H 7.25–7.38 (10 H, m), 8.22 (1 H, d, *J* 4.3) and 8.50 (1 H, d). Compound **1g** was obtained as needles (73%), m.p. 206–206.5 °C [from hexane–AcOEt (1 : 1)] (Found: C, 77.3; H, 4.5; N, 11.2. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.9; N, 11.3%); ν_{max}(KBr)/cm^{-1} 3070, 1590, 1580, 1220 and 680; δ_H 7.52–7.57 (6 H, m), 8.05–8.09 (4 H, m) and 8.50 (2 H, s).

2,3-*Diphenyl*-5-*methoxypyrazine* 1-*oxide* **1i**. A solution of 2-chloro-5,6-diphenylpyrazine[20] (2.67 g, 10 mmol) and 87% *m*-chloroperbenzoic acid (2.07 g, 12 mmol) in 1,2-dichloroethane (30 cm^3) was stirred and heated at 65 °C for 15 h and then additional peracid (0.52 g, 4 mmol) was added to the mixture. The resulting mixture was then heated for 9 h and worked up as described above to furnish 5-chloro-2,3-diphenylpyrazine 1-oxide, which was recrystallized from EtOH to give needles (2.34 g, 83%), m.p. 124–126 °C (Found: C, 67.7; H, 4.0; N, 9.55. $C_{16}H_{11}ClN_2O$ requires C, 68.0; H, 3.9; N, 9.9%); ν_{max}(KBr)/cm^{-1} 3060, 1550, 1420, 1340, 970 and 690; δ_H 7.22–7.38 (10 H, m) and 8.28 (1 H, s). A solution of the above *N*-oxide (1.415 g, 5.0 mmol) in dry MeOH (20 cm^3) containing sodium (0.25 g, 11 mmol) was stirred under reflux for 12 h, and the resulting mixture was worked up as described above to afford the title compound **1i** (1.279 g, 92%), which was recrystallized from hexane to yield pale yellow needles, m.p. 159.5–162.5 °C (Found: C, 73.2; H, 5.0; N, 9.75. $C_{17}H_{14}N_2O_2$ requires C, 73.4; H, 5.1; N, 10.1%); ν_{max}(KBr)/cm^{-1} 3050, 1530, 1360, 1230, 1220 and 690; δ_H 4.07 (3 H, s), 7.18–7.35 (10 H, m) and 7.93 (1 H, s).

General Procedure of Deoxidative Azidation of Pyrazine N-*Oxides* **1**.—Samples of the *N*-oxides **1** (1 mmol) were purged by passage of argon after evacuation of air, and MeCN (8 cm^3), trimethylsilyl azide (0.17 cm^3, 1.2 mmol or 0.34 cm^3, 2.4 mmol) and finally diethylcarbamoyl chloride (0.16 cm^3, 1.2 mmol or 0.32 cm^3, 2.4 mmol) were added *via* a syringe. The mixture was stirring under reflux for the time given in Table 1 and then evaporated under reduced pressure. The residue was subjected to chromatography on SiO_2 (20 g) eluting with hexane–AcOEt (10 : 1 to 3 : 1).

The following compounds were obtained by the above procedure.

2-*Amino*-3-*azidopyrazine* **2a**. As microcrystallites; m.p. 225 °C (decomp.) (from EtOH) (Found: C, 35.2; H, 2.8; N, 61.5. $C_4H_4N_6$ requires C, 35.3; H, 3.0; N, 61.7%); ν_{max}(KBr)/cm^{-1} 3300, 3150, 1670, 1550 and 620; δ_H[$(CD_3)_2SO$] 7.63 (1 H, d, *J* 4.6), 8.02 (2 H, br s), and 8.45 (1 H, d).

2-*Amino*-3-*azido*-5-*methylpyrazine* **2b**. As microcrystallites; m.p. 225 °C (decomp.) (from EtOH) (Found: C, 40.0; H, 3.7; N, 56.1. $C_5H_6N_6$ requires C, 40.0; H, 4.0; N, 56.0%); ν_{max}(KBr)/cm^{-1} 3300, 1685, 1560 and 1210; δ_H[$(CD_3)_2SO$] 3.33 (3 H, d, *J* 1.1), 7.49 (1 H, d) and 7.72 (2 H, br s).

2-*Azido*-3-*methoxypyrazine* **2c**. As microcrystallites; m.p.

143–144 °C [from hexane–AcOEt (4:1)] (Found: C, 39.7; H, 3.5; N, 46.2. $C_5H_5N_5O$ requires C, 39.7; H, 3.3; N, 46.3%); ν_{max}(KBr)/cm^{-1} 1540, 1490, 1360, 1180 and 960; δ_H 4.28 (3 H, s), 7.77 (1 H, d, *J* 4.6) and 8.40 (1 H, d).

2-*Azido*-3-*methoxy*-5-*phenylpyrazine* **2d**. As tiny needles; m.p. 208.5–209.5 °C (from EtOH) (Found: C, 58.2; H, 4.0; N, 30.9. $C_{11}H_9N_5O$ requires C, 58.15; H, 4.0; N, 30.8%); ν_{max}(KBr)/cm^{-1} 1550, 1450, 1365, 1220, 965 and 760; δ_H 4.38 (3 H, s), 7.50–7.57 (3 H, m), 7.99–8.02 (2 H, m) and 8.75 (1 H, s).

2-*Azido*-3-*phenylpyrazine* **2e**. As yellow needles; m.p. 221–222 °C (decomp.) (from AcOEt) (Found: C, 60.9; H, 3.6; N, 35.7. $C_{10}H_7N_5$ requires C, 60.9; H, 3.6; N, 35.5%); ν_{max}(KBr)/cm^{-1} 3100, 1595, 1510, 1465, 790 and 690; δ_H 7.61–7.64 (3 H, m), 8.38 (1 H, d, *J* 4.6), 8.70 (1 H, d) and 8.86–8.90 (2 H, m).

2-*Azido*-5-*phenylpyrazine* **4**. As pale yellow prisms; m.p. 178–179 °C (decomp.) (from C_6H_6) (Found: C, 61.3; H, 3.7; N, 35.3. $C_{10}H_7N_5$ requires C, 60.9; H, 3.6; N, 35.5%); ν_{max}(KBr)/cm^{-1} 1470, 1310, 1080, 780 and 690; δ_H 7.47–7.61 (3 H, m), 8.01–8.06 (2 H, m), 9.09 (1 H, d, *J* 1.7) and 9.73 (1 H, d).

2-*Azido*-5,6-*diphenylpyrazine* **2f**. As pale yellow needles; m.p. 166–167 °C (from EtOH) (lit.,[3] 171–173 °C) (Found: C, 70.1; H, 3.7; N, 25.5. $C_{16}H_{15}N_5$ requires C, 70.3; H, 4.1; N, 25.6%); ν_{max}(KBr)/cm^{-1} 1465, 1440, 1350, 1080, 760 and 700; δ_H 7.27–7.57 (10 H, m) and 9.71 (1 H, s).

2-*Azido*-3,5-*diphenylpyrazine* **2g**. As needles; m.p. 162–163 °C (from EtOH) (lit.,[4] 170–171 °C) (Found: C, 70.0; H, 4.15; N, 25.3. $C_{16}H_{11}N_5$ requires C, 70.3; H, 4.1; N, 25.6%); ν_{max} (KBr)/cm^{-1} 1520, 1460, 1440, 750 and 690; δ_H 7.57–7.67 (8 H, m), 8.13–8.17 (2 H, m) and 9.02 (1 H, s).

2-*Diethylcarbamoyloxy*-6-*methoxypyrazine* **3**. As an oil; b.p. 105 °C/4 mmHg (Kugelrohr) (Found: C, 52.5; H, 6.6; N, 18.4. $C_{10}H_{15}N_3O_3 \cdot 0.2H_2O$ requires C, 52.5; H, 6.8; N, 18.4%); δ_H 1.23 (3 H, t, *J* 7.3), 1.28 (3 H, t, *J* 7.3), 3.41 (2 H, q), 3.48 (2 H, q), 3.95 (3 H, s), 8.04 (1 H, s) and 8.10 (1 H, s); δ_C 13.1, 14.1, 42.1, 42.2, 53.8, 128.7, 131.4, 152.6, 152.7 and 159.2.

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