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The Study of Some Potential New Synthetic Routes to LLM-105 (2,6-Diamino-3,5-dinitropyrazine 1-oxide)

Anthony J. BELLAMY

Cranfield University, Defence Academy of the United Kingdom, Shrivenham, Swindon SN6 8LA, UK
E-mail: A.J.Bellamy@cranfield.ac.uk

Peter GOLDING

AWE Aldermaston, Reading RG7 4PR, UK

Abstract: The synthesis of LLM-105 (2,6-diamino-3,5-dinitropyrazine 1-oxide) via the direct nitration of 2,6-diaminopyrazine 1-oxide is reported. Two synthetic routes to the starting material 2,6-diaminopyrazine 1-oxide have been investigated. The synthesis of 2,6-diamino-3,5-dinitropyrazine by nitration of 2,6-diaminopyrazine and 2,6-diacetamidopyrazine has also been studied. Whilst mono-nitration of 2,6-diaminopyrazine is very selective, further nitration leads to mixtures of 2,6-diamino-3,5-dinitropyrazine, 6-amino-2-keto-3,5-dinitropyrazine and tetraketopiperazine, the latter predominating in many cases. It was shown that tetraketopiperazine is formed by further reaction of the initially formed 2,6-diamino-3,5-dinitropyrazine. Nitration of 2,6-diacetamidopyrazine does furnish 2,6-diamino-3,5-dinitropyrazine, but the yield is poor.

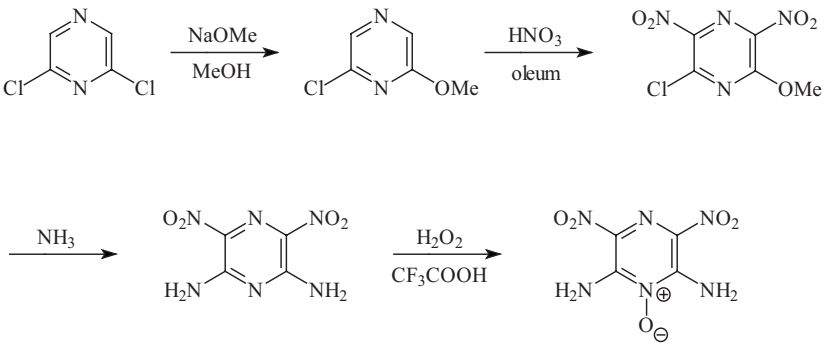
Keywords: LLM-105, 2,6-diamino-3,5-dinitropyrazine 1-oxide, 2,6-diamino-pyrazine, 2,6-diaminopyrazine 1-oxide, nitration

Introduction

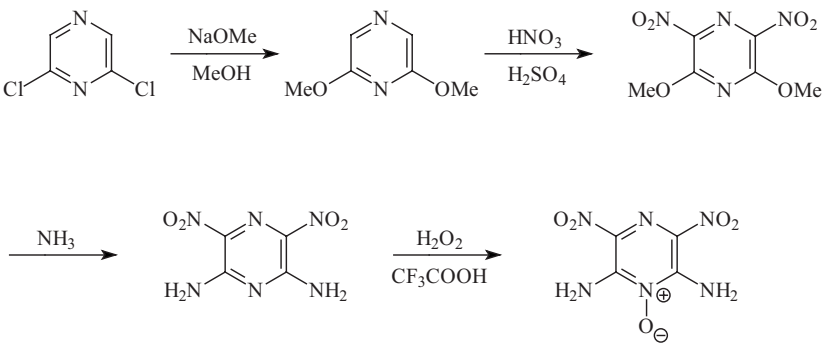
LLM-105 (2,6-diamino-3,5-dinitropyrazine 1-oxide) is of considerable interest as a replacement for TATB (1,3,5-triamino-2,4,6-trinitrobenzene). Although its synthesis is not so direct as that for TATB (4 or 5 steps vs 2), it has the advantage of being more energetic [V_{calc} TATB 7870 m s^{-1}, LLM-105 8730 m s^{-1};

P_{calc} 278 and 359 kbar respectively; density 1.93 and 1.92 g cm^{-3} respectively; decomposition 350 and 354 °C respectively] and for some applications more easily initiated [1].

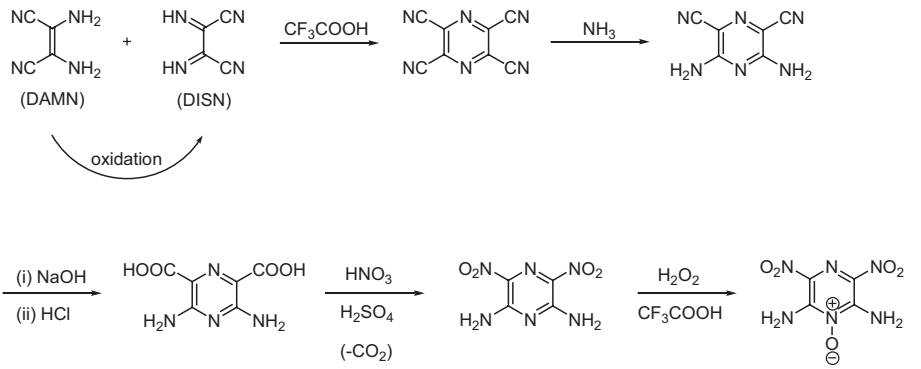
To date there are three published routes for the synthesis of 2,6-diamino-3,5-dinitropyrazine 1-oxide (LLM-105). The first [1-4], and the one that appears to be the most widely used, involves a 4-step synthesis from the expensive 2,6-dichloropyrazine (see Scheme 1), via 6-chloro-2-methoxypyrazine, 6-chloro-2-methoxy-3,5-dinitropyrazine and 2,6-diamino-3,5-dinitropyrazine. The overall yield is ~47%. The second route [4] (see Scheme 2) is closely related to the first and involves the replacement of both Cl atoms by MeO groups, generating an intermediate, 2,6-dimethoxypyrazine, that is easier to nitrate due to the double activation by the MeO groups. The subsequent steps are essentially the same as route 1, the overall yield being ~50%. The third route [1] (see Scheme 3), a 5-step synthesis developed by du Pont for other purposes, which uses a much cheaper starting material, 2,3-diaminomaleonitrile, and creates the pyrazine ring itself in step 1, has been tested by the Lawrence Livermore group [1] and rejected due to (unspecified) difficulties in scale-up. In this case the overall yield is ~30%. The final step in all three synthetic routes involves the oxidation of N-1 of the pyrazine ring in 2,6-diamino-3,5-dinitropyrazine to the N-oxide. The precipitation of the latter during the oxidation can lead to unoxidised material becoming trapped inside the particles of the product.



Scheme 1. Route 1 to LLM-105.



Scheme 2. Route 2 to LLM-105.



Scheme 3. Route 3 to LLM-105.

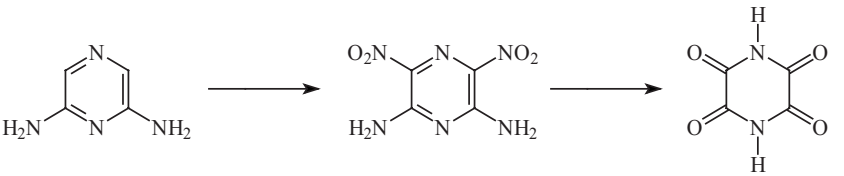
It is clear from these known routes to LLM-105, that the sequence in which the various substituents on the pyrazine ring are introduced may be varied in order to facilitate subsequent reactions. Routes 1 and 2 leave amination until the penultimate step whilst route 3 has nitration (nitrodecarboxylation) of a 2,6-diaminopyrazine as the penultimate step. In the latter case the amine groups are stable to the nitration conditions.

In order to explore the potential of sequence ordering further, and possibly to reduce the number of synthetic steps, we have now studied the direct nitration of 2,6-diaminopyrazine itself, its *N,N'*-diacetyl derivative, and of 2,6-diaminopyrazine 1-oxide. The latter was suggested [5] as a route avoiding the problems associated with the N-1 oxidation of 2,6-diamino-3,5-dinitropyrazine (see above).

Results and Discussion

Nitration of 2,6-diaminopyrazine

The synthesis of 2,6-diaminopyrazine will be described in a later section. Direct nitration of 2,6-diaminopyrazine was attempted using a variety of reagents (i) N_2O_5/HNO_3 (ii) HNO_3 alone (iii) HNO_3/H_2SO_4. Treatment with both N_2O_5/HNO_3 and HNO_3 alone gave tetraketopiperazine (in yields up to 26%) as the only isolated product. The desired 2,6-diamino-3,5-dinitropyrazine was also found to be converted into tetraketopiperazine on treatment with N_2O_5/HNO_3, suggesting that the transformation from diaminopyrazine to tetraketopiperazine may proceed via the dinitro derivative (Scheme 4).

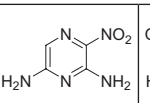
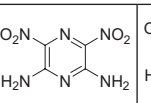
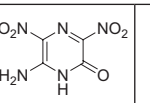
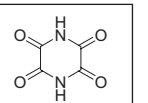


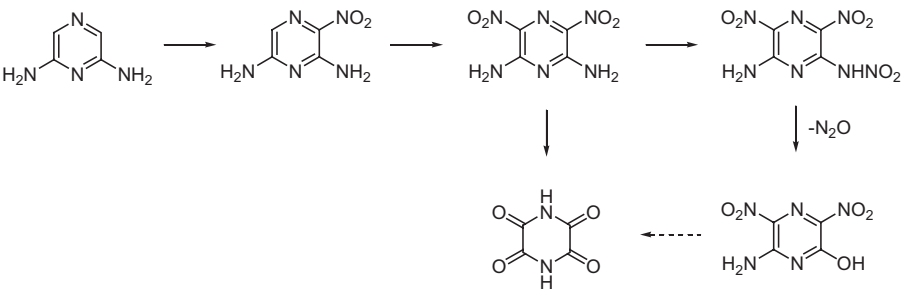
Scheme 4. Nitration of 2,6-diaminopyrazine.

Nitration of 2,6-diaminopyrazine with HNO_3/H_2SO_4 gave a variety of products [2,6-diamino-3-nitropyrazine, 2,6-diamino-3,5-dinitropyrazine, 6-amino-2-keto-3,5-dinitropyrazine, tetraketopiperazine], the relative amounts of which were dependent upon the number of equivalents of HNO_3 used (see Table 1).

With 2 equivalents of HNO_3, the distribution of products was: 2,6-diamino-3,5-dinitropyrazine (59-70%), 6-amino-2-keto-3,5-dinitropyrazine (28-39%), tetraketopiperazine (0-9%), plus gaseous products [N_2O, NO, CO and CO_2, with some O_2 consumed]. With 4 equivalents of HNO_3, the same products were obtained in 22, 48 and 31% respectively. However when the amount of HNO_3 was limited to 1 equivalent, 2,6-diamino-3-nitropyrazine was the only product (73%). Treatment of the 2,6-diamino-3-nitropyrazine with a further 1 equivalent of HNO_3 gave a mixture of 2,6-diamino-3,5-dinitropyrazine (82%) and 6-amino-2-keto-3,5-dinitropyrazine (18%), plus some tetraketopiperazine which slowly separated from the filtrate. In a further experiment, 2,6-diaminopyrazine in H_2SO_4 was treated with two separate 1 equivalent amounts of HNO_3, separated by 22 h. In this case the product was a mixture of 2,6-diamino-3,5-dinitropyrazine, 6-amino-2-keto-3,5-dinitropyrazine and tetraketopiperazine (variable composition 88:12:0 - 58:27:15 respectively).

Table 1. Nitration of 2,6-diaminopyrazine

					
Nitrating agent		Percent composition of product			
N_2O_5/HNO_3 (equivalents)	Yield (mg) from 79 mg				
5.5	13 (12%)				100
3.0	21 (20%)				100
Dinitrodiamino-pyrazine + 3.0	(55%)				100
HNO_3	27 (26%)				100
	27 (26%)				100
HNO_3/H_2SO_4 (equivalents of HNO_3)	Yield (mg) from 55 mg				
4.0	17	0	22	48	31
2.0	24	0	70	28	0
1.0	52	100	0	0	0
1.0 + 1.0	34	0	88	12	0



Scheme 5. Pathways for the nitration of 2,6-diaminopyrazine.

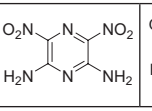
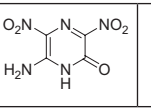
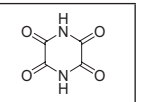
Thus direct nitration of 2,6-diaminopyrazine with two or more equivalents of the reagents (i) N_2O_5/HNO_3, (ii) HNO_3 alone, or (iii) HNO_3/H_2SO_4, is unselective and gives either tetraketopiperazine alone (reagents i and ii), or a mixture of 2,6-diamino-3-nitropyrazine, 2,6-diamino-3,5-dinitropyrazine, 6-amino-2-keto-3,5-dinitropyrazine and tetraketopiperazine (reagent iii) (Scheme 5). However stepwise treatment with two 1 equivalent portions of HNO_3 in H_2SO_4 is rather

more selective, leading to the isolation of a product, albeit in poor yield, containing only 2,6-diamino-3,5-dinitropyrazine and 6-amino-2-keto-3,5-dinitropyrazine, with the former predominating. Treatment with only 1 equivalent of HNO_3 in H_2SO_4 gives pure 2,6-diamino-3-nitropyrazine. We therefore concluded that initial nitration to the mono-nitro derivative is very selective, but further nitration is less so. The identification of 6-amino-2-keto-3,5-dinitropyrazine was based on its spectroscopic properties being similar to those of 6-amino-2-keto-3,5-dinitropyridine, the by-product from the nitration of 2,6-diaminopyridine to give 2,6-diamino-3,5-dinitropyridine [6].

Nitration of 2,6-diacetamidopyrazine

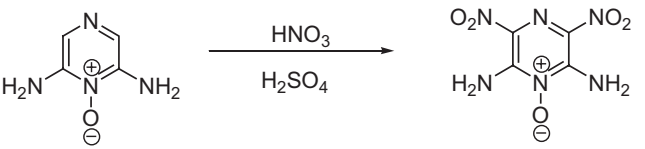
Since the direct nitration of 2,6-diaminopyrazine was found to be rather unselective, attention was directed to the nitration of the *N*-protected diaminopyrazine, 2,6-diacetamidopyrazine, which was prepared from diaminopyrazine by treatment with acetic anhydride at 20 °C. Its nitration was attempted using the same range of conditions as was used for the unprotected system viz N_2O_5/HNO_3 and HNO_3/H_2SO_4, and with HNO_3/Ac_2O. In all cases the *N*-acetyl groups were hydrolysed off, before or during work-up. N_2O_5/HNO_3 gave a low yield of tetraketopiperazine, whilst HNO_3/Ac_2O gave a mixture of products, none of which was the desired 2,6-diamino-3,5-dinitropyrazine. However, mixed acid conditions, with 2 or more equivalents of HNO_3, did give 2,6-diamino-3,5-dinitropyrazine, but in low yield. Less than 1 equivalent of HNO_3 gave a low yield of a mixture of the mono- and the di-nitro derivatives. The results are presented in Table 2.

Table 2. Nitration of 2,6-diacetamidopyrazine

				
Nitrating agent	Yield (mg) from 55 mg	Percent composition of product		
N_2O_5/HNO_3 (equivalents)				
5.5	16	0	0	100
HNO_3/H_2SO_4 (equivalents of HNO_3)				
4.0	13	100	0	0
2.0	15	95	0	0

Nitration of 2,6-diaminopyrazine 1-oxide

The synthesis of 2,6-diaminopyrazine 1-oxide will be described in a later section. Mixed acid nitration of 2,6-diaminopyrazine 1-oxide does give 2,6-diamino-3,5-dinitropyrazine 1-oxide (LLM-105, Scheme 6), albeit in disappointing yield. This reaction was investigated using mixed acids with (i) varying equivalents of HNO_3 in 98% H_2SO_4, (ii) 4 equivalents of HNO_3 in varying concentrations of H_2SO_4 (90-100%), (iii) varying equivalents of KNO_3 in H_2SO_4, (iv) HNO_3 or KNO_3 in 4.36% or 30% oleum, and (v) N_2O_5 in HNO_3. The results are presented in Table 3 page 47. The highest yields (~50%) were obtained using HNO_3 (4 eq) in 100% H_2SO_4 and 4.36% oleum (4.36% oleum should be capable of reacting with all liberated water, assuming that the reaction is quantitative).



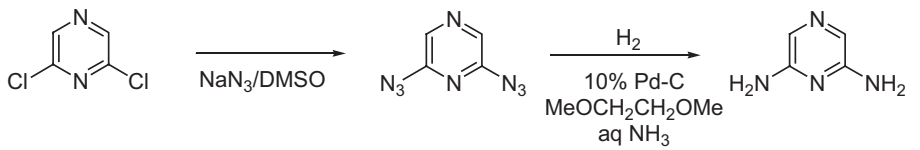
Scheme 6. Nitration of 2,6-diaminopyrazine 1-oxide.

As judged by ^1H NMR, the LLM-105 obtained using HNO_3/H_2SO_4 usually contained small amounts (<3%) of by-products, whilst those derived using KNO_3/H_2SO_4 were pure. All products appeared to be pure LLM-105 by FTIR.

LLM-105 was also obtained by nitrating (HNO_3/H_2SO_4 or KNO_3/H_2SO_4) 2,6-diacetamidopyrazine 1-oxide, but the yields were no better than when the unacetylated compound was used.

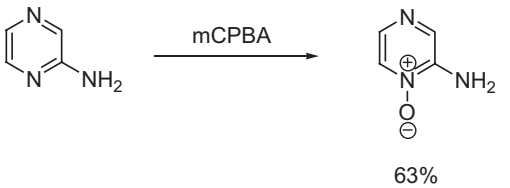
Synthesis of 2,6-diaminopyrazine and 2,6-diaminopyrazine 1-oxide

2,6-Diaminopyrazine may be fairly readily prepared from 2,6-dichloropyrazine by azide substitution followed by hydrogenation (Scheme 7) [7]. The yield of 2,6-diazidopyrazine was reported to be 84%, and the yield of 2,6-diaminopyrazine 83%; our overall yield of 2,6-diaminopyrazine was ~74%. If the hydrogenation catalyst is not sufficiently active e.g. due to age, then the product is contaminated with the half-reduced intermediate, 2-amino-2-azidopyrazine which exists as 5-aminotetrazolo[1,5a]pyrazine.

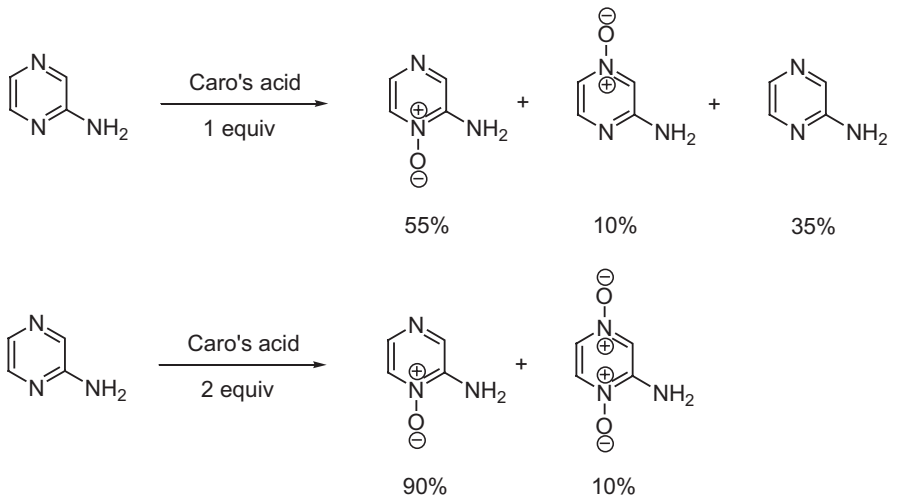


Scheme 7. Synthesis of 2,6-diaminopyrazine.

The direct N-oxidation of 2,6-diaminopyrazine has not been reported, but both *m*-chloroperbenzoic acid (*m*CPBA, Scheme 8) [8] and Caro's acid (Oxone, $2KHSO_5.KHSO_4.K_2SO_4$; Scheme 9) [9] have previously been used to selectively oxidise 2-aminopyrazine to 2-aminopyrazine 1-oxide.



Scheme 8. *m*CPBA oxidation of 2-aminopyrazine.



Scheme 9. Caro's acid oxidation of 2-aminopyrazine.

The *m*-CPBA method has been improved to give 99% yield of 2-aminopyrazine 1-oxide by performing the reaction in DMF-MeOH in the presence of HF [10].

The oxidation of 2,6-diaminopyrazine itself was investigated using both *m*-CPBA and Oxone. The oxidation of 2,6-diaminopyrazine using *m*CPBA (1 eq), in both acetone and dimethoxyethane (DME), gave only 20-25% conversion to *N*-oxides, the remainder being unchanged starting material. The products appeared to be identical to products 1 and 3 from the Oxone oxidation (see below) i.e. the 4- and the 1-oxide respectively, with the latter predominating. The results of these and further experiments with larger amounts of *m*CPBA are shown in

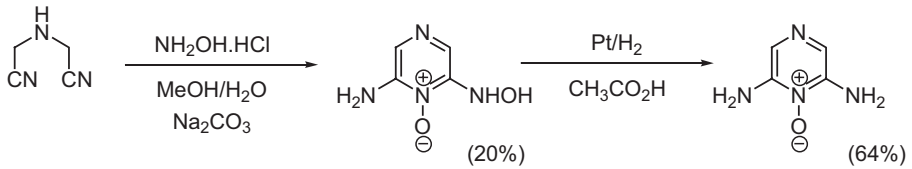
Table 4 page 49. Isolation of the 1-oxide by continuous extraction with $CHCl_3$ was complicated by the co-extraction of *m*-chlorobenzoic acid. In the presence of HF, *m*CPBA gave a mixture of products which could not be identified.

The use of Oxone gave results which appeared to be similar to those obtained with 2-aminopyrazine [9], which was reported to give: 35% starting material, 10% 4-oxide and 55% 1-oxide with 1 equivalent of Oxone, and 90% 1-oxide and 10% 1,4-dioxide with 2 equivalents of Oxone. 2,6-Diaminopyrazine, when treated with 0.5 equivalents of Oxone, gave a mixture of starting material (61%) and three products, product 1 (5%, 4-oxide, identical to the oxide obtained by the hydrolysis of the 2,6-diacetamidopyrazine 4-oxide – see below), product 2 (3%, 1,4-dioxide) and product 3 (31%, 1-oxide). Increasing amounts of Oxone (1-3 equivalents) reduced the proportion of starting material and increased the proportion of the 1-oxide, with the 4-oxide disappearing and 1,4-dioxide increasing slightly (see Table 4 page 49). These results indicate that N-1 is more reactive than N-4 in 2,6-diaminopyrazine, and N-1 in 2,6-diaminopyrazine 4-oxide is more reactive than N-4 in 2,6-diaminopyrazine 1-oxide, most of the 1,4-dioxide being generated by further oxidation of the 4-oxide.

In order to facilitate isolation of the 1-oxide from the mixture of 1-oxide and 1,4-dioxide obtained using 3 equivalents of Oxone, the original work-up procedure [9] was modified (see Experimental). Continuous $CHCl_3$ extraction of an aqueous solution of the mixture gave pure 1-oxide, the 1,4-dioxide having a greater affinity for water. Extraction of the dry oxidation mixture gave less pure 1-oxide. The purified 1-oxide was recrystallised from water and its spectroscopic properties compared with those reported for 2,6-diaminopyrazine 1-oxide synthesised from iminodiacetonitrile (see below) [11]. Although the ^1H NMR spectra were in reasonable agreement, comparison of some of the other reported physical properties (m.p., IR) was not entirely convincing. The m.p. of our product was 272 °C (DSC onset, 10 K/min; immediately followed by decomposition at 283 °C) whilst the reported [11] value was 294-295 °C (dec). This discrepancy may be attributed to the presence of a few percent of the 1,4-dioxide in our sample. The main concern was that the IR spectrum (KBr) of our product did not agree with that reported (Nujol) [11]. In order to clarify this major discrepancy a single crystal structure was obtained (Dr Mary Mahon, University of Bath). This showed conclusively that our material was indeed 2,6-diaminopyrazine 1-oxide (as its trihydrate; see Figure 2 page 52). We concluded that the wrong IR spectrum may have been reported [11]. It was shown later (see below and Experimental) that the product obtained from iminodiacetonitrile did have an IR spectrum (KBr) identical to the product obtained from the Oxone oxidation of 2,6-diaminopyrazine.

Synthesis of 2,6-diaminopyrazine 1-oxide from iminodiacetonitrile

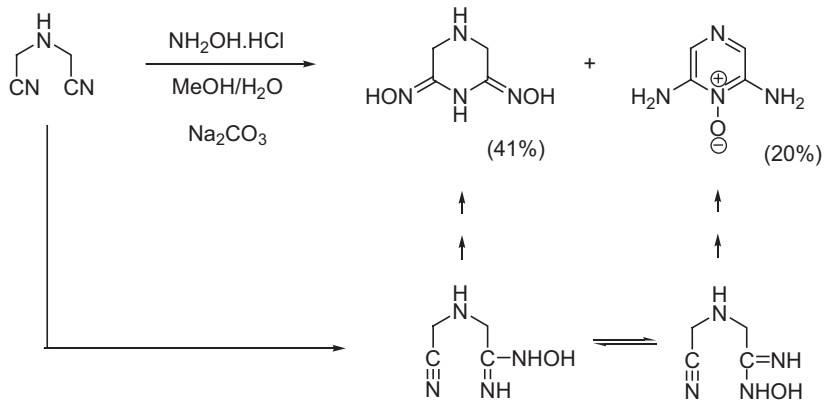
The synthesis of 2,6-diaminopyrazine 1-oxide from iminodiacetonitrile [11] involves reaction with hydroxylamine, followed by hydrogenation of the resulting 2-amino-6-hydroxyaminopyrazine 1-oxide (Scheme 10).



Scheme 10. Synthesis of 2,6-diaminopyrazine 1-oxide from iminodiacetonitrile.

2-Amino-6-hydroxyaminopyrazine 1-oxide is not the only product isolated, the major product being a hydrated complex between 2,6-bishydroxyiminopiperazine and hydroxylamine hydrochloride, $(C_4H_8N_4O_2)_2.(NH_2OH.HCl).H_2O$ (complex C).

These two products probably arise by alternative modes of cyclisation of the initial adduct of hydroxylamine to one of the cyano groups of iminodiacetonitrile, cyclisation involving the N-atom of the added hydroxylamine leading to the pyrazine 1-oxide and cyclisation involving the N-atom of the attacked cyano group leading to the piperazine (see Scheme 11).



Scheme 11. Reaction of iminodiacetonitrile with hydroxylamine.

In attempting to synthesise 2-amino-6-hydroxyaminopyrazine 1-oxide following Barot and Elvidge's recipe [11], we encountered a number of difficulties (see Experimental) which required modification of the process.

Specifically, the slurry obtained by mixing aqueous Na_2CO_3 and methanolic $NH_2OH.HCl$ was too thick to achieve a controlled rate of addition. Nevertheless, both reported products, the hydrated complex 2,6-bishydroxyiminopiperazine/ hydroxylamine hydrochloride and 2-amino-6-hydroxyaminopyrazine 1-oxide, were isolated. The latter was found to be complexed with variable amounts of NH_4Cl (NH_3 is a by-product of the reaction) and removal of the NH_4Cl was rather tedious. Hydrogenolysis of 2-amino-6-hydroxyaminopyrazine 1-oxide gave 2,6-diaminopyrazine 1-oxide as reported [11].

Oxidation of 2,6-diacetamidopyrazine

The oxidation of 2,6-diacetamidopyrazine was attempted with a variety of reagents viz H_2O_2/CF_3CO_2H, H_2O_2/CH_3CO_2H, CH_3CO_3H. In all cases the product appeared to be a mixture of NH_4NO_3 and one other component. When H_2O_2/CH_3CO_2H was used, the organic product separated as a white solid and was filtered off. Single crystal XRD (Dr Mary Mahon, University of Bath) identified it as 2,6-diacetamidopyrazine 4-oxide. Hydrolytic removal of the acetyl groups (2.5 M HCl/100 °C) gave a 2,6-diaminopyrazine oxide which was identical with product 1 from the Oxone oxidation of 2,6-diaminopyrazine, and which therefore identifies product 1 as the 4-oxide.

Conclusions

The synthesis of LLM-105 (2,6-diamino-3,5-dinitropyrazine 1-oxide) via the direct nitration of 2,6-diaminopyrazine 1-oxide has been achieved, although the yield (~50%) is rather disappointing. Two synthetic routes to the starting material 2,6-diaminopyrazine 1-oxide have been investigated. The route starting from the expensive 2,6-dichloropyrazine, via 2,6-diaminopyrazine, appears to be the least problematic, although it may be possible to improve the iminodiacetonitrile route.

The synthesis of 2,6-diamino-3,5-dinitropyrazine by nitration of 2,6-diaminopyrazine and 2,6-diacetamidopyrazine has also been studied. Whilst mono-nitration of 2,6-diaminopyrazine is very selective, further nitration leads to mixtures of 2,6-diamino-3,5-dinitropyrazine, 6-amino-2-keto-3,5-dinitropyrazine and tetraketopiperazine, the latter predominating in many cases. It has been shown that tetraketopiperazine is formed by further reaction of the initially formed 2,6-diamino-3,5-dinitropyrazine. Nitration of 2,6-diacetamidopyrazine does furnish 2,6-diamino-3,5-dinitropyrazine, but the yield is poor.

Experimental

Nitration of 2,6-diaminopyrazine

(i) With N_2O_5/HNO_3

2,6-Diaminopyrazine (79 mg) was dissolved in 99.5 wt% HNO_3 (0.50 ml) at 0 °C and N_2O_5 in HNO_3 (0.56 ml – 3 eq; 9.42 g N_2O_5 dissolved in 18.8 ml HNO_3 → total volume 23 ml) was added. After 94 h at RT the separated solid was filtered off (not washed). Yield 21 mg (20%) of tetraketopiperazine. With 5.5 eq N_2O_5 the yield was 13 mg (12%). Similar treatment of 2,6-diamino-3,5-dinitropyrazine (18 mg) with 3 eq N_2O_5 also gave tetraketopiperazine (7mg).

(ii) With HNO_3

2,6-Diaminopyrazine (79 mg) was added to 99.5 wt% HNO_3 (0.50 ml) at 0 °C and stirred during 72 h at RT. The separated solid was filtered off (not washed). Yield 27 mg (26%) of tetraketopiperazine.

(iii) With HNO_3/H_2SO_4

(a) 2,6-Diaminopyrazine (55 mg, 0.5 mmol) was dissolved in conc. H_2SO_4 (0.55 ml) with cooling in ice-water and 99.5 wt% HNO_3 [(a) 0.088 ml - 4 eq, (b) 0.044 ml - 2 eq or (c) 0.022 ml - 1 eq)] was added. After 1h at 0 °C, the solution was stirred during 20-24 h at RT. The solution was added to ice (2.5g; gas evolved), the precipitated solid was filtered off and washed with water (3X). Yield: (a) 17 mg [2,6-diamino-3,5-dinitropyrazine (22%), 6-amino-2-keto-3,5-dinitropyrazine (48%), tetraketopiperazine (31%)] (b) 24 mg [2,6-diamino-3,5-dinitropyrazine (70%) , 6-amino-2-keto-3,5-dinitropyrazine (28%)] (c) 52 mg [2,6-diamino-3-nitropyrazine (100%)].

(b) 2,6-Diamino-3-nitropyrazine (77 mg, 0.5 mmol) was dissolved in conc. H_2SO_4 (0.55 ml) with cooling in ice-water and 99.5 wt% HNO_3 (0.022 ml - 1 eq) was added. After 1 h at 0 °C, the solution was stirred during 22 h at RT. The solution was added to ice (2.5g; gas evolved), the precipitated solid was filtered off and washed with water (3X). Yield 29 mg [2,6-diamino-3,5-dinitropyrazine (82%), 6-amino-2-keto-3,5-dinitropyrazine (18%), tetraketopiperazine (0%)]. More solid (9 mg) slowly separated from the filtrate [2,6-diamino-3,5-dinitropyrazine (2%) , 6-amino-2-keto-3,5-dinitropyrazine (24%), tetraketopiperazine (74%)].

(c) 2,6-Diaminopyrazine (55 mg, 0.5 mmol) was dissolved in conc. H_2SO_4 (0.55 ml) with cooling in ice-water and 99.5 wt% HNO_3 (0.022 ml - 1 eq) was added. After 1 h at 0 °C, the solution was stirred during 22 h at RT.

More 99.5 wt% HNO_3 (0.022 ml - 1 eq) was added at 0°C. After 1 h at 0 °C, the solution was stirred during 24 h at RT The solution was added to ice (2.5 g; gas evolved), the precipitated solid was filtered off and washed with water (3X). Yield 34 mg [2,6-diamino-3,5-dinitropyrazine (88%), 6-amino-2-keto-3,5-dinitropyrazine (12%), tetraketopiperazine (0%)]. In a larger scale experiment, 2,6-diaminopyrazine (220 mg, 2.0 mmol) gave 108 mg of initial product [2,6-diamino-3,5-dinitropyrazine (58%), 6-amino-2-keto-3,5-dinitropyrazine (27%), tetraketopiperazine (15%)], with more solid (27 mg) separating from the filtrate/washings on standing [2,6-diamino-3,5-dinitropyrazine (6%), 6-amino-2-keto-3,5-dinitropyrazine (24%), tetraketopiperazine (70%)].

The composition of the various products was determined by ^{1}H NMR spectroscopy (DMSO-d_6). The individual components exhibited the following properties.

Tetraketopiperazine: ^{1}H 12.54 ppm; ^{13}C 155.3 ppm [Further characterized by FTIR (KBr) 3201, 2834, 1767, 1730, 1699, 1510, 1419, 1362, 1329, 1291, 869, 809, 788, 767cm^{-1}; DSC (10 K/min) endotherm max 406.5 °C, onset 381 °C; single crystal XRD (Dr Mary Mahon, University of Bath) – recrystallised from water].

6-Amino-2-keto-3,5-dinitropyrazine: ^{1}H 8.16 (br s, NH), 8.92 (br s, NH), 12.54 ppm (br s, NH); ^{13}C 119.7, 131.7, 148.9, 150.0 ppm [FTIR (KBr) 1701 cm^{-1}]. The structure was assigned on the basis of the similarity of the NMR data with that of the corresponding pyridine derivative [6].

2,6-Diamino-3,5-dinitropyrazine: ^{1}H 8.22 and 8.61 ppm (4H, NH); ^{13}C 125.5, 151.1 ppm

2,6-Diamino-3-nitropyrazine: ^{1}H 7.19 (1H, CH), 7.66 and 7.78 ppm (4H, NH); ^{13}C 122.7 (CH), 128.3 (C), 151.3 (C), 157.3 ppm (C) [recrystallised from water and further characterized by FTIR (KBr); DSC (10 K/min) melting onset 332 °C, decomposition max 338 °C; CHN analysis : Found (0.9 mg sample) C 30.9, 30.8; H 3.17, 3.13; N 45.0, 45.4% (3.18 mg sample) C 30.9; H 3.23, N 44.9%. $C_4H_5N_5O_2$ requires C 30.97, H 3.25, N 45.16%].

Preparation of 2,6-diacetamidopyrazine

2,6-Diaminopyrazine (200 mg) was dispersed in acetic anhydride (16 ml) and stirred at 20 °C. At no stage was the system homogeneous. NMR analysis of a sample filtered off after 1.5 h indicated that it was a mixture of mono- and di-acetylated products (56:44 respectively). After 4 h the ratio was 35:65, and after 90 h it was 5:95. After this time the product was filtered off (not washed) and dried. Yield 336 mg (95%). The diacetamidopyrazine was largely insoluble

in most solvents. NMR spectra were recorded in CF_3COOH solution using an acetone-d_6/TMS probe. ^1H: 1.96 (s, 6.23H, CH_3), 8.98 (s, 2.00H, CH), 9.24 ppm (s, 2.02H, NH); ^{13}C 22.4 (CH_3), 122.3 (CH), 150.4 (CN), 175.7 ppm (CO). An analytical sample was recrystallised from acetic acid. DSC (10 K/min) onset 383 °C, decomposition peak 390.6 °C. $C_8H_{10}N_4O_2$ requires C 49.5, H 5.19, N 28.9%. Found C 49.4, 49.1, H 5.26, 5.20, N 29.0, 29.0%. The mono-acetyl derivative (admixed with the di-acetyl derivative) exhibited: ^1H 7.52 (s, 1H, CH), 8.17 ppm (s, 1H, CH); ^{13}C 114.1 (CH), 121.0 (CH), 148.4 (CN), 155.1 ppm (CN). The ^1H and ^{13}C signals of the CH_3CO group were obscured.

Nitration of 2,6-diacetamidopyrazine

(i) With N_2O_5/HNO_3

2,6-Diacetamidopyrazine (49 mg) was dissolved in 99.5% HNO_3 (0.18 ml), cooled in ice and N_2O_5 in HNO_3 (0.132 ml – 2 eq; 9.42 g N_2O_5 dissolved in 18.8 ml HNO_3, total volume 23 ml) was added. A white solid had begun to separate after 1h. After 23 h at 20 °C the solid was filtered off (not washed) and dried. Yield 16 mg (26%) of tetraketopiperazine. No solid separated on adding the filtrate to ice (5 g).

(ii) With HNO_3/Ac_2O

Ac_2O (0.50 ml) was cooled in ice and 99.5% HNO_3 (0.025 ml, 2 eq) was added followed by 2,6-diacetamidopyrazine (55 mg). After 24 h at 20 °C the mixture was evaporated to dryness. The orange foam (73 mg) was a mixture of unidentified products (by NMR); no 2,6-diamino-3,5-dinitropyrazine was present.

(iii) With HNO_3/H_2SO_4

2,6-Diacetamidopyrazine (55 mg) was dissolved in conc. H_2SO_4 (0.55 ml) at 0 °C. 99.5% HNO_3 (0.025 ml, 2 eq) was added at 0°C and the solution was stirred at 20 °C during 23 h. The solid which formed on adding to ice (5 g) was filtered off and washed with ice-water (3 x 1.0 ml). The product (15 mg) was largely 2,6-diamino-3,5-dinitropyrazine (~95%). Only small amounts of tetraketopiperazine and 6-amino-2-keto-3,5-dinitropyrazine were present.

With 1 eq HNO_3 the product (12 mg) was a black solid which contained 2,6-diamino-3,5-dinitropyrazine (~78%) and 2,6-diamino-3-nitropyrazine (~22%). With 4 eq HNO_3 the product (12 mg) was pure 2,6-diamino-3,5-dinitropyrazine. The yield was not increased by extending the reaction period from 21 to 67 h.

General recipe for the mixed acid nitration of 2,6-diaminopyrazine 1-oxide

2,6-Diaminopyrazine 1-oxide (8.0 mg) was treated at 0 °C with conc. sulphuric acid (0.11 ml; did not dissolve) and variable amounts of 99.5% nitric acid (0.0025 ml ≡ 1 eq). Addition of the nitric acid caused the solid to dissolve. The solution was kept at 0 °C during 1 h and room temperature during 20 h. Crushed ice (1.5 g) was added and a yellow solid separated. The latter was filtered off, washed with water and dried. See Table 3 for results. Similar experiments were performed using KNO_3 instead of HNO_3, and N_2O_5 in HNO_3 (see Table 3).

Typical NMR data (DMSO-d_6):
^{1}H 8.78 (br s), 9.02 ppm (br s); ^{13}C 124.8, 144.6 ppm
LLM-105 exhibits:
^{1}H 8.78 (br s), 9.03 ppm (br s); ^{13}C 124.8, 144.6 ppm

Table 3. Nitration of 2,6-diaminopyrazine 1-oxide

Nitration conditions (0-20 °C)	Equivalents of nitrating agent	Yield (%) of LLM-105
99.5% HNO_3/98% H_2SO_4	2	45*
99.5% HNO_3/98% H_2SO_4	4	29 (3 h), 35 (20 h)
99.5% HNO_3/98% H_2SO_4	6	36
99.5% HNO_3/4.36% oleum	4	52
99.5% HNO_3/100% H_2SO_4	4	50, 54
99.5% HNO_3/96% H_2SO_4	4	38
99.5% HNO_3/90% H_2SO_4	4	15
KNO_3/98% H_2SO_4	2	46
KNO_3/98% H_2SO_4	3	45
KNO_3/98% H_2SO_4	4	42
KNO_3/100% H_2SO_4	4	45, 45
KNO_3/30% oleum	4	31*
KNO_3/4.36% oleum	4	47
N_2O_5/HNO_3	4	0

* contains ~4% mono-nitro derivative and other impurities

Some LLM-105 product samples exhibited a low intensity ammonium triplet (7.07 ppm) and/or a low intensity singlet at 8.52 ppm. The mother liquor from the HNO_3 (4 eq)/100% H_2SO_4 nitration exhibited no ^{13}C absorptions. The mother liquor from a KNO_3 (2+3 eq)/98% H_2SO_4 nitration exhibited ^{13}C absorption at 161.5 ppm (tetraketopiperazine exhibits 155.7 ppm).

Acetylation of 2,6-diaminopyrazine 1-oxide

2,6-Diaminopyrazine 1-oxide (67 mg) was treated with acetic anhydride (2.5 ml) during 3 days. The resultant solid was filtered off, washed with ethanol and dried to give 2,6-diacetamidopyrazine 1-oxide (58 mg). NMR (DMSO-d_6) ^{1}H 2.30 (s, 6.49H), 9.10 (s, 2.00H, CH) and 10.56 ppm (s, 2.04H, NH), in reasonably good agreement with the data reported by Barot and Elvidge [11]; ^{13}C 24.0 (CH_3), 130.2 (CH), 139.4 (C), 169.7 ppm (CO). The FTIR spectrum (KBr) did not correspond to that reported by Barot and Elvidge (Nujol) [11].

Nitration of 2,6-diacetamidopyrazine 1-oxide

2,6-Diacetamidopyrazine 1-oxide (13.0 mg) was treated at 0 °C with a solution of HNO_3 in conc. H_2SO_4 (0.12 ml, 4 eq; from 0.417 ml HNO_3 diluted to 5.00 ml with conc. H_2SO_4) The solution was kept at 0 °C during 1 h and room temperature during 20 h. Crushed ice (1.5 g) was added and a yellow solid separated. The latter was filtered off, washed with water and dried to give LLM-105 (5.6 mg, 41%). A similar experiment was performed using KNO_3 (4 eq) instead of HNO_3. This gave LLM-105 (4.8 mg, 35%).

Synthesis of 2,6-diazidopyrazine

2,6-Dichloropyrazine (2.40 g) was dissolved in DMSO (32 ml) and NaN_3 (1.04 g) was added. The mixture was slowly heated to 60 °C, kept at 60 °C during 15 min and then more NaN_3 (1.04 g) was added in portions. The resultant solution was kept at 60-65 °C during 2.5 h and then added to ice-water (30 ml). The solid was filtered off, washed with water and dried. Yield 2.29 g (88%). NMR (DMSO-d_6) ^{1}H 8.17 ppm.

Hydrogenation of 2,6-diazidopyrazine to 2,6-diaminopyrazine

2,6-Diazidopyrazine (4.54 g) was dissolved in dimethoxyethane (62 ml) and 10% Pd/C catalyst (3.31 g; Johnson-Matthey Type 39 paste, 58% water) was added, followed by 0.88 ammonia (3.69 ml). The mixture was hydrogenated at 5 bar pressure during 24 h. For the first 7 h, the system was re-flushed with hydrogen every hour in order to remove the generated nitrogen. The final mixture was heated to boiling, filtered hot and the catalyst washed with boiling dimethoxyethane (3×10 ml). Evaporation of the solvent gave 2,6-diamino-pyrazine (2.55 g, 83%). The solid darkened on storage, even when sealed and in the absence of light, but the darkened material (after several months) still appeared to be pure by NMR analysis. The material was also unchanged (with no further darkening) after exposure to air and light during 20 h. NMR (DMSO-d_6) ^{1}H 5.70 (br s, 3.98H, NH), 7.02 ppm (s, 2.00H, CH); ^{13}C 118.4 (CH), 154.7 ppm.

Oxidation of 2,6-diaminopyrazine with *m*-chloroperbenzoic acid

(i) Following the *m*-CPBA recipe used for 2-aminopyrazine [8b]. 2,6-Diaminopyrazine (55 mg) was added to acetone (1.00 ml – largely insoluble) followed by *m*-CPBA (95 mg, 1eq). The mixture became slightly warm. After 23 h at 20 °C, the mixture was rotary evaporated to give a dark solid. Na_2CO_3 (60 mg) and water (0.3 ml) were added and the mixture was again evaporated. The dark residue was extracted (Soxhlet) with $CHCl_3$ overnight. The extract was concentrated to give a light brown oil (49 mg). NMR analysis suggested that this was a mixture of starting material (81%) and an *N*-oxide [19%, mainly 1-oxide; ^{1}H NMR (D_2O) 7.44 ppm (s)].

(ii) As (i) but using 1,2-dimethoxyethane (DME) as the solvent; the same solvent as used in the synthesis of 2,6-diaminopyrazine. Yield of beige solid (44 mg). NMR analysis: starting material (79%) and an *N*-oxide [21%, mainly 1-oxide; ^{1}H NMR (D_2O) 7.44 ppm (s)]. Similar oxidations were performed using 2 and 4 equivalents of oxidant (see Table 4).

Table 4. Oxidation of 2,6-diaminopyrazine

Component (Identity)	Product 1 (4-oxide)	Starting material	Product 2 (1,4-dioxide)	Product 3 (1-oxide)
^{1}H NMR chemical shift of CH*	7.09	7.22	7.42	7.60
^{13}C NMR chemical shift of CH* and C*	111.9 159.7	122.6 156.6		117.8 159.1
Equivalents of *m*CPBA	Product distribution (%)			
1.0 (acetone)	3	81	**	19
1.0 (DME)	3	79	**	21
2.0 (DME)	8	50	**	43
4.0 (DME)	6	7	12	75
Equivalents of Oxone	Product distribution (%)			
0.5	5	61	3	31
1.0	0	34	7	59
1.0	8	31	7	54
2.0	0	3	19	78
3.0	0	5	13	82

* in D_2O with DSS as reference

** not detected

(iii) Using a modified procedure for *m*-CPBA [10]. 2,6-Diaminopyrazine (55 mg) was dissolved in DMF (7.2 ml) and MeOH (2.4 ml). 48% HF (0.024 ml, 1.2 eq) was added followed by *m*-CPBA (215 mg, 2.1 eq). After stirring at 20 °C during 1 h the solution was added to water (50 ml). No precipitate formed. The aqueous solution was rotary evaporated to dryness. The residue was a complex mixture of products.

Oxidation of 2,6-diaminopyrazine with Oxone and isolation of 2,6-diaminopyrazine 1-oxide

(i) 2,6-Diaminopyrazine (440 mg, 4.0 mmol) was dissolved in 0.5 M KOH (40 ml) and Oxone (3.696 g, 6.0 mmol, 3.0 eq) was added in portions. After 24 h at 20 °C the solution was neutralised with conc. HCl (1.6 ml) and then basified with Na_2CO_3 (1.272 g). Rotary evaporation of a 0.5 ml sample and ^{1}H NMR (in D_2O) analysis of the residue indicated that it was a mixture of the 1-oxide (80.3%), the 4-oxide (1.5%), the 1,4-dioxide (17.2%) and starting material (1.0%), plus inorganic material. The remaining aqueous solution was then continuously extracted with $CHCl_3$. After 3 days the concentrated extract was 141 mg (pure 1-oxide; Figure 1 illustrates the change in ^{1}H NMR spectrum on purification). Further extraction (4 days) gave 40 mg of material [1-oxide (94.3%), 4-oxide (1.9%) and 1,4-dioxide (3.8%)]. Due to solid inorganic material having separated in the extractor, the whole was dissolved in water, rotary evaporated and then redissolved in water (40 ml). Further continuous extraction (4 days) gave 12 mg of material [1-oxide (78.9%), 4-oxide (5.7%) and 1,4-dioxide (15.4%). The total recovered yield of the 1-oxide was 199 mg (~40% yield). Rotary evaporation of the remaining aqueous phase gave a brown residue (5.47 g) which contained no 1-oxide; only 1,4-dioxide (70%) and an unknown (30%) as the organic components.

(ii) A similar oxidation on half the scale was worked up by dry extraction i.e. the whole aqueous solution (after basification with Na_2CO_3) was evaporated to dryness, crushed and continuously extracted with $CHCl_3$ in a Soxhlet extractor. Before extraction the solid was a mixture of the 1-oxide (62.1%) and the 1,4-dioxide (37.9%), plus inorganic material. After 20 h the concentrated extract was 65 mg [1-oxide (90.9%), 1,4-dioxide (9.1%)], and after another 24 h a further 10 mg [1-oxide (71.1%), 1,4-dioxide (28.9%)]. The solid mass was then dried, recrushed and the continuous extraction continued. This gave 25 mg after 24 h [1-oxide (28.0%), 1,4-dioxide (72.0%)], 23 mg after a further 24 h [1-oxide (58.7%), 1,4-dioxide (41.3%)], and 33 mg after a further 72 h [1-oxide (30.3%), 1,4-dioxide (69.7%)].

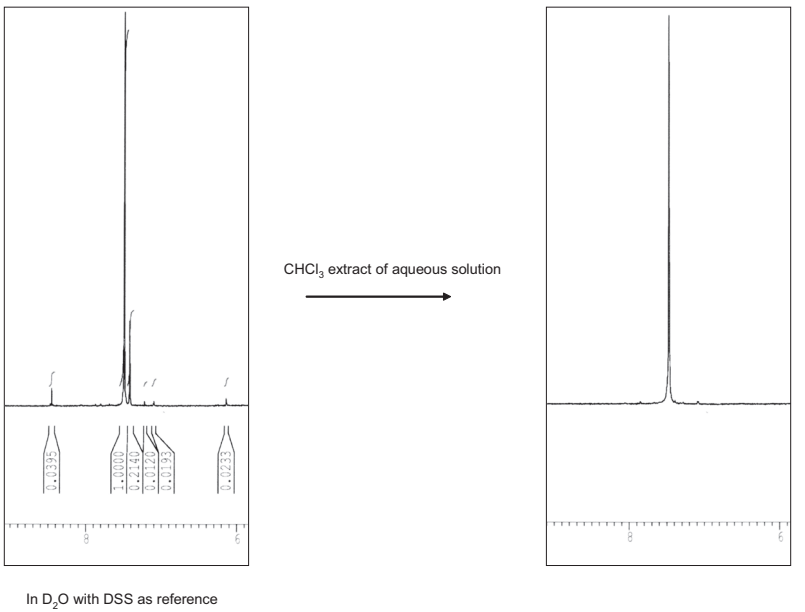


Figure 1. Purification of 2,6-diaminopyrazine 1-oxide as indicated by ^{1}H NMR spectroscopy.

A sample of pure 2,6-diaminopyrazine 1-oxide from the first extraction in preparation (i) was recrystallised from water (as needles) for single crystal XRD (Figure 2), DSC, TG and FTIR. DSC (10 K/min) of an air dried sample: melting onset 275 °C, decomposition onset 279 °C. TG (10 K/min) of an air dried sample: decomposition onset 276 °C, inflection point of step 291 °C, mass loss 47.1%; mass loss between 70 and 150 °C 2.5%. NMR (DMSO-d_6) ^{1}H 6.69 (br, 4.05H, 2xNH_2), 7.32 ppm (s, 2.00H, 3- and 5-H); ^{13}C 117.5 (C-3, C-5), 145.7 ppm (C-2, C-6); NMR (D_2O) ^{1}H 7.48 ppm (s, 3- and 5-H); ^{13}C 121.4 (C-3, C-5), 148.9 ppm (C-2, C-6). FTIR (KBr) 3402, 3265, 3204, 3128, 1613, 1566, 1545, 1486, 1464, 1406, 1395, 1313, 1267, 1233, 1163, 1072, 1025, 851, 839, 812, 734, 712, 668, 607, 551, 493, 411 cm^{-1}. Reference 11 reports: m.p. 294-295 °C (decomp.), needles from water; ^{1}H NMR (DMSO-d_6) 6.6 (br, 2xNH_2), 7.33 ppm (s, 3- and 5-H). Although the XRD indicated that the recrystallised material was a trihydrate, air drying of the crystals left no evidence of water being present (DSC, TG, FTIR).

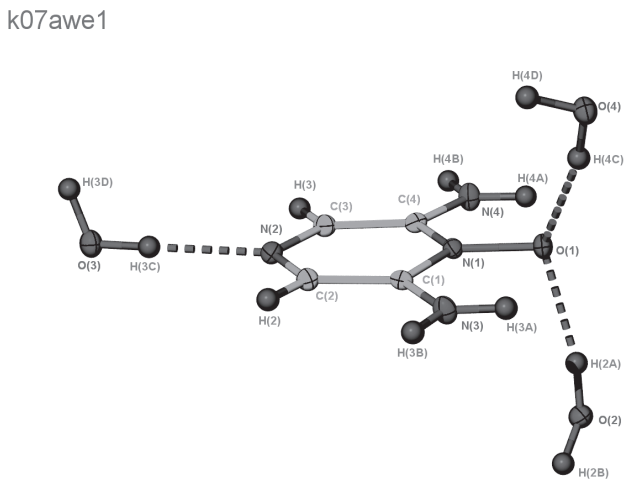


Figure 2. XRD structure of 2,6-diaminopyrazine 1-oxide trihydrate.

Crystal data: $C_4H_{12}N_4O_4$, M = 180.18, 0.25x0.20x0.20 mm^3, monoclinic, space group $C2/c$, a = 24.9520(7), b = 10.3500(4), c = 6.7590(3) Å, β = 103.346(1)°, V = 1698.39(11) Å^3, Z = 8, Dc = 1.409 g/cm^3, F(000) = 768, MoKα radiation, λ = 0.71073 Å, T = 150(2) K, 2θmax = 30º, 15911 reflections collected, 2476 unique (Rint = 0.0856). Goodness of Fit = 0.997, R1 = 0.0499, wR2 = 0.1084, [R indices based on 1329 reflections with I >2σ(I) (refinement on F^2)], 145 parameters, 14 restraint, μ = 0.153 mm^{-1}.

CCDC 652120 contains the supplementary crystallographic data for 2,6-diaminopyrazine 1-oxide trihydrate. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-366033; or deposit@ccdc.cam.ac.uk.

Oxone oxidations of 2,6-diaminopyrazine using 0.5, 1.0 and 2.0 equivalents of oxidant were performed as (i) above. 2,6-Diaminopyrazine present in under-oxidised mixtures appeared to slowly undergo aerial oxidation to the 1-oxide.

Synthesis of 2-amino-6-hydroxyaminopyrazine 1-oxide

The procedure given by Barot and Elvidge [11] is as follows:

"Hot solutions of hydroxylamine hydrochloride (111.2 g, 1.6 mol) in methanol (120 ml) and sodium carbonate (21 g, 0.2 mol) in water (80 ml) were mixed and slowly added to iminodiacetonitrile (38 g, 0.4 mol) in boiling methanol (160 ml) under nitrogen. When half had been added (0.5 h), an exothermic

reaction began, the solution darkened, and product started separating: heating and addition were then controlled to maintain gentle reflux. After a further 1h, the solid was collected (27 g, 41%) and washed with methanol to give complex C. On treating the filtrate with charcoal (2×) and then partially evaporating it by bubbling nitrogen through for 1h, needles separated (11.65 g, 20.5%) of the monohydrate of 2-amino-6-hydroxyaminopyrazine 1-oxide, m.p. 161 °C (decomp.) (from MeOH-H_2O). ^{1}H NMR (DMSO-d_6) 6.79 (br s, NH_2), 7.51 (s, H-3), 7.56 (s, H-5), 9.08 ppm (br, NHOH)."

This procedure was found to be deficient in a number ways: (a) Whilst Na_2CO_3 dissolved in the specified amount of hot water, $NH_2OH.HCl$ only partially dissolved in the methanol. On mixing, the resulting paste was very thick and caused problems in maintaining a uniform addition. The only way this could be reliably achieved was by using a plastic disposable pipette (3.0 ml capacity), ~2 ml portions being added every minute (half-scale run). The slurry was too thick to be added by peristaltic pump without further dilution with more water-methanol (2:3 by volume) (b) Collection of the primary product and washing with methanol. It is not stated if the washings are added to the filtrate (mother liquor) (c) Treatment with charcoal. The amount of charcoal is unspecified, as is the temperature. It was assumed that boiling was intended (d) Partial evaporation. No temperature is specified (assumed to be room temperature) and the rate of nitrogen flow is unspecified.

Attempts to repeat Barot and Elvidge's experiment (all at half-scale) were as follows:

Run A. Addition of the slurry was achieved using a plastic pipette. The slurry was maintained hot and stirred. The addition was probably too fast and not particularly uniform. Yield of Complex C 25.12 g. Nitrogen was passed through the filtrate until the total volume had been halved. Yield of 2-amino-6-hydroxyaminopyrazine 1-oxide (as a complex with NH_4Cl) 4.67 g.

Run B. Addition of the slurry (agitated at room temperature) was achieved using a peristaltic pump. However in order to transfer all of the solid it was necessary to add a further quantity of water-methanol (2:3 by volume, 50 ml). Yield of Complex C ~17.4 g. Nitrogen was passed through the filtrate for 2 h, after which time the volume had decreased only a little, but solid had separated. Yield of 2-amino-6-hydroxyaminopyrazine 1-oxide (as a complex with NH_4Cl) 6.74 g. A further quantity of solid (1.89 g) had separated after passing nitrogen for a further 3 h.

Run C. Addition of the slurry was achieved using a plastic pipette through a wide-bore tap attached directly to the reaction vessel, and adding ~2 ml every minute. Total addition time 67 min. More methanol (15 ml) was used to complete the addition of all the solid. The vigorous reaction commenced after

~25 min. Nitrogen was passed through the filtrate for 1h only. Yield of 2-amino-6-hydroxyaminopyrazine 1-oxide (as a complex with NH_4Cl) 3.13 g.

Analysis of the various products:

Complex C: NMR (DMSO-d_6) ^1H 3.43 (s, 4.00H), 7.81 (br s) and 8.23 (s, overlapped peaks, 11.16H), 10.01 ppm (s, 1.73H); ^{13}C 43.9 (CH_2), 142.7 ppm (C).

2-Amino-6-hydroxyaminopyrazine 1-oxide: all samples consisted of a mixture of the pyrazine 1-oxide and NH_4Cl, with variable NH_4Cl content (run A 84 mol%, run B 89 mol%, run C 40 mol% NH_4Cl). NMR (DMSO-d_6) ^1H 6.82 (s, 2.00H, NH_2), 7.52 (s, 0.98H, CH), 7.57 (s, 1.03H, CH), 9.11 (s, 1.02H), 9.17 ppm (s, 0.99H); the broad triplet of NH_4^+ was superimposed on the above, 7.32 ppm (J ~50Hz) ; ^{13}C 117.0 (CH), 120.6 (CH), 145.5 (C), 148.0 ppm (C).

The second crop (1.89 g) from run B was most probably a mixture/complex of 2,6-bishydroxyiminopiperazine and ammonia from its NMR and mixed NMR spectra: (DMSO-d_6) ^1H 3.94 (s, 4.00H), 7.45 (t, 2.85H, J 50Hz), 8.34 (s, 0.95H), 10.44 (br s, 1.92H), 10.76 ppm (s, 2.04H); ^{13}C 40.9 (CH_2), 137.9 ppm (C).

Purification of crude 2-amino-6-hydroxyaminopyrazine 1-oxide.

After exploring various methods for removing the NH_4Cl, most of which involved neutralisation with base and loss of NH_3, the following procedure was adopted. The combined product from runs A, B and C was dissolved in MeOH (1.00 g/50 ml) and stirred overnight with a slight excess (~25%) of the amount of $NaHCO_3$ required to neutralise the NH_4Cl. The residue obtained after filtration and evaporation still contained 50-65 mol% NH_4Cl. Portions (200 mg) of this material were purified by:

(a) washing with water – 200 mg was sonicated with water (1.0 ml) and then filtered off. The solid was then washed with water (0.5 ml in three portions) and dried. Yield 51 mg. This material appeared to be free of NH_4Cl.

(b) recrystallisation from MeOH-water - 200 mg was heated in boiling water (1.0 ml) and MeOH (0.5 ml) was added until the solid had completely dissolved. The solution was allowed to cool (to 0 °C), the solid was filtered off, washed with ice-cold water-MeOH (0.5 ml) and then dried. Yield 45 mg. This material appeared to be free of NH_4Cl. DSC (10 K/min) endotherm onset 106 °C, peak 131 °C (loss of water of crystallisation), decomposition exotherm onset 164.4 °C {lit [11] m.p. 161 °C (decomp.)}.

The bulk of the dry material (~7.5 g) obtained by stirring with $NaHCO_3$/MeOH was further purified by continuous extraction with portions of $CHCl_3$ (150-200 ml). Evaporation of the extracts gave essentially pure 2-amino-6-hydroxyaminopyrazine

1-oxide as a beige powder: after 24 h, 0.64 g; after a further 24 h, 0.39 g; after a further 24 h, 0.47 g; after a further 48 h, 0.54 g; after a further 72 h, 0.26 h. Total material extracted: 2.30 g. The unextracted residue contained no more pyrazine oxide.

Hydrogenation of 2-amino-6-hydroxyaminopyrazine 1-oxide to 2,6-diaminopyrazine 1-oxide

As described by Barot and Elvidge [11]. PtO_2 (10 mg) was dispersed in acetic acid (4.0 ml) and pre-reduced by stirring in hydrogen. Purified 2-amino-6-hydroxyaminopyrazine 1-oxide (100 mg) was added and the mixture was stirred in hydrogen (at atmospheric pressure) at 20-25 °C during 24 h. The catalyst was filtered off (dark filtrate – Barot and Elvidge treated this with decolorising charcoal) and the solvent was rotary evaporated to give a dark paste containing clusters of crystals (140 mg). ^{1}H and ^{13}C NMR (DMSO-d_6 and D_2O) indicated that this was a mixture of 2,6-diaminopyrazine 1-oxide and acetic acid (69 mol% acetic acid).

The above procedure was repeated but using 10% Pd/C Johnson-Matthey type 39 paste catalyst (112 mg ≡ Pt used above). The catalyst was filtered off (yellow solution – the charcoal in the catalyst appeared to have effected decolourisation) and the solvent was rotary evaporated to give a dark paste (215 mg). ^{1}H NMR (DMSO-d_6) indicated that this was a mixture of 2,6-diaminopyrazine 1-oxide and acetic acid (85 mol% acetic acid). The acetic acid content was reduced by sequentially (a) storing in a vacuum desiccator containing solid KOH (final mass 127 mg), and (b) digesting with $CHCl_3$ (final mass 78 mg, 46 mol% acetic acid). Apart from the acetic acid present, the FTIR spectrum (KBr) of the latter material exhibited good agreement with that of 2,6-diaminopyrazine 1-oxide prepared by Oxone oxidation of 2,6-diaminopyrazine.

A larger scale hydrogenation using purified 2-amino-6-hydroxyaminopyrazine 1-oxide (1.00 g), 10% Pd/C catalyst (1.12 g) and acetic acid (40 ml), gave a dark paste (2.25 g, 85 mol% acetic acid).

Oxidation of 2,6-diacetamidopyrazine

2,6-Diacetamidopyrazine (200 mg) was dispersed in CH_3COOH (10.0 ml) and 30% H_2O_2 (10.0 ml) was added. After heating at 60 °C during 6 h the white solid (121 mg, 56%) was filtered off (not washed) and dried. NMR (in CF_3COOH with acetone-d_6 probe): ^{1}H 1.91 (s, 6.02H, CH_3), 8.68 (s, 2.00H, CH), 8.92 ppm (s, 1.93H, NH); ^{13}C 22.4 (*C*H_3CO), 121.6 (CH), 148.8 (CN), 175.4 ppm (CO). Samples were recrystallised from hot NMP and hot DMSO. DSC (10 K/min) onset of decomposition 355.5 °C, max 362 °C. The crystal for single crystal XRD was obtained by recrystallisation from hot DMSO (Figure 3).

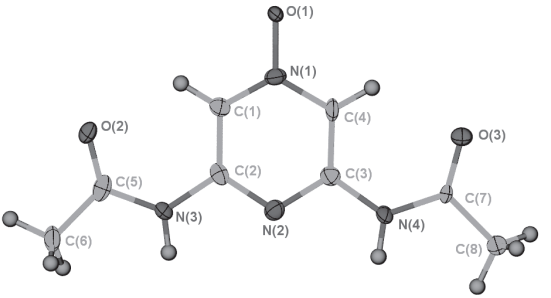


Figure 3. XRD structure of 2,6-diacetamidopyrazine 4-oxide.

Crystal data: $C_{16}H_{20}N_8O_6$, M = 420.38, 0.25x0.15x0.05 mm^3, monoclinic, space group $P2_1/a$, a = 6.5150(5), b = 11.9450(9), c = 23.7700(18) Å, β = 82.044(9)°, V = 1832.02 Å^3, Z = 4, Dc = 1.524 g/cm^3, F(000) = 880, MoKα radiation, λ = 0.71073 Å, T = 150(2) K, 2θmax = 24.99º, 15476 reflections collected, 3148 unique (Rint = 10.84). Goodness of Fit = 1.08, $R1$ = 0.0625, $wR2$ = 0.1323, [R indices based on 1549 reflections with I >2σ(I) (refinement on F^2)], 276 parameters, 35 restraint, μ = 0.120 mm^{-1}.

CCDC 652119 contains the supplementary crystallographic data for 2,6-diacetamidopyrazine 4-oxide. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-366033; or deposit@ccdc.cam.ac.uk.

Hydrolysis of 2,6-diacetamidopyrazine 4-oxide

The conditions used were those that were reported [12] for the hydrolysis of 2-acetamidopyrazine 1-oxide. The 'oxide' (20 mg) was heated with 2.5 M HCl (0.11 ml) at 100 °C during 10min. The very dark mixture was neutralized with saturated $NaHCO_3$ and then concentrated to give a black solid. This was continuously extracted with boiling $CHCl_3$ to give a cream solid. NMR (D_2O) ^{1}H 7.08 ppm (s); ^{13}C 111.9 (CH), 159.7 ppm (C-N). Unlike 2.6-diaminopyrazine 1-oxide, this material did not give a blue coloration with $FeCl_3$ solution (test for amino adjacent to ring N-O [12]). It was identical (by ^{1}H and ^{13}C NMR) to product 1 observed in the Oxone oxidation of 2,6-diaminopyrazine.

Acknowledgments

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