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A Study of the Synthesis and Amination of 2,6-Dialkoxy-3,5-dinitropyrazines

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Abstract: A series of 2,6-dialkoxy-3,5-dinitropyrazines (R = Me, Et, Pr) has been synthesized and subjected to amination. The yield and purity of the generated 2,6-diamino-3,5-dinitropyrazine was found to be independent of the alkoxy group present in the precursor. This contrasts with the behaviour of 1,3,5-trialkoxy-2,4,6-trinitrobenzene (R = Me, Et, Pr), where the purity of the 1,3,5-triamino-2,4,6-trinitrobenzene (TATB) produced by amination was very dependent upon the alkoxy group.

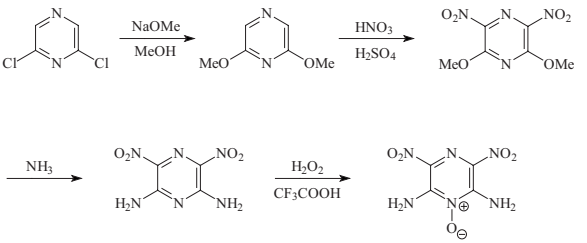
Keywords: LLM-105, 2,6-dialkoxy-3,5-dinitropyrazine, 2,6-dialkoxy-pyrazine, nitration, amination

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 7870ms^{-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

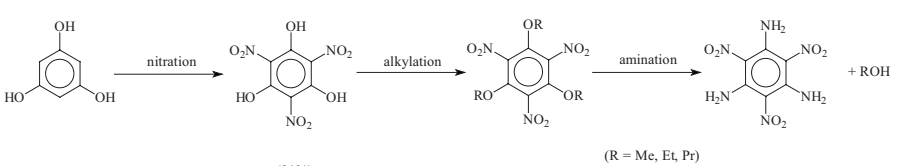
easily initiated [1].

One [4] of the four published routes for the synthesis of 2,6-diamino-3,5-dinitropyrazine 1-oxide (LLM-105) [1-5] involves the replacement of both Cl atoms in 2,6-dichloropyrazine by MeO groups, generating an intermediate, 2,6-dimethoxypyrazine, that is easier to nitrate to the dinitro derivative than the analogous mono-methoxy derivative [1-4] due to the double activation by the MeO groups. Subsequent steps involve replacement of the methoxy groups by amino groups (aminodemethoxylation) and oxidation of N-1 (Scheme 1). The overall yield is ~50%.



Scheme 1. A variant of the common route to LLM-105.

This route is analogous to one variant of the new route to TATB [6, 7] (see Scheme 2), in which the methoxy substituents in 1,3,5-trimethoxy-2,4,6-trinitrobenzene are replaced by amino groups. Work on the TATB synthesis has shown that whilst the trimethoxy derivative does give TATB in excellent yield, better quality TATB, as judged by its decomposition temperature, is obtained if the replaced substituents are ethoxy or propoxy [8-10] [DSC exotherm onset at 10 K min^{-1}: 346, 357 and 374 °C for TATB derived from trimethoxy-, triethoxy- and tripropoxy-trinitrobenzene respectively, the latter being very close to that of TATB derived from trichlorotrinitrobenzene (375 °C)]. This is probably due to a side reaction in which NH_3 attacks the methyl carbon in the methoxy substituent (liberating methylamine) in competition with the desired attack at the methoxy bearing ring carbon [9]. This side reaction appears to be less significant with the ethoxy and propoxy substituents.



Scheme 2. A new synthetic route to TATB.

Since the ethoxy and propoxy derivatives in the benzene series gave better quality TATB than the methoxy derivative, it was envisaged that this pattern might be followed in the pyrazine system too. Consequently 2,6-dimethoxy-, 2,6-diethoxy- and 2,6-dipropoxy-3,5-dinitropyrazine were prepared and subjected to amination.

Results and Discussion

Synthesis of 2,6-dialkoxypyrazines

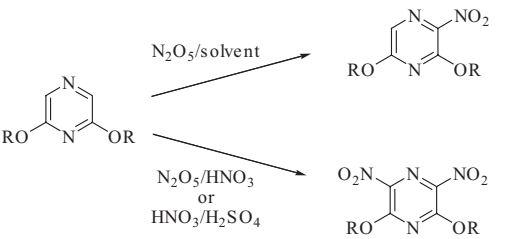
2,6-Dimethoxypyrazine was prepared from 2,6-dichloropyrazine by reaction with excess NaOMe in MeOH according to literature procedures [11, 12]. The diethoxy and dipropoxy derivatives were synthesized analogously.

Nitration of 2,6-dialkoxypyrazine

Various nitration conditions were explored using the dimethoxy derivative as substrate.

The conditions used for the nitration of 2-chloro-6-methoxypyrazine, namely HNO_3/20% oleum at 75 °C/4 h [2] gave the di-nitro derivative, but in poor yield (11%).

N_2O_5 in organic solvents (CH_2Cl_2, CH_3CN) gave only the mono-nitro derivative plus an unidentified by-product. No di-nitro derivative was formed. However N_2O_5 in HNO_3 was more effective and gave pure 2,6-dimethoxy-3,5-dinitropyrazine in 40% yield (Scheme 3).



R = Me, Et, Pr

Scheme 3. N_2O_5 nitration of 2,6-dialkoxypyrazines.

Nitration with HNO_3/H_2SO_4 and KNO_3/H_2SO_4 gave the pure di-nitro derivative in around 48% yield. In both cases, extraction of the mother liquor with ethyl acetate afforded more di-nitro derivative, but this was heavily contaminated with unidentified by-products.

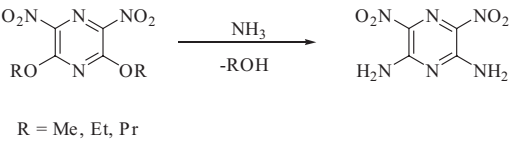
Nitration of the diethoxy- and dipropoxy-pyrazines was also investigated using the same nitrating agents. Almost pure 2,6-diethoxy-3,5-dinitropyrazine (55%, 2 mol% impurity) was obtained using N_2O_5/HNO_3. In this case too, extraction of the mother liquor gave a mixture of the di-nitro derivative and an unidentified by-product. With HNO_3/H_2SO_4, a 40% yield of the di-nitro derivative was obtained, contaminated with 2-3 mol% of the mono-nitro derivative. If, instead of filtering off the di-nitro derivative after quenching, the entire quench mixture was extracted with EtOAc, the product was the di-nitro derivative contaminated with the same by-product (20 mol%) that was observed in the filtered product from N_2O_5/HNO_3 nitration.

Nitration of 2,6-dipropoxypyrazine with N_2O_5/HNO_3 gave a product that was gum-like and could not be filtered off. After decantation of the mother liquor and washing with water, the dried product was 2,6-dipropoxy-3,5-dinitropyrazine (60%) contaminated with 5-10 mol% of an unidentified by-product. The latter could be removed by sonication of the mixture in water to give the pure di-nitro derivative which could be filtered off. Nitration with HNO_3/H_2SO_4 under normal conditions gave a product that was a mixture of the di-nitro and the mono-nitro derivatives (~15 mol% of the latter). Halving the proportion of dipropoxypyrazine gave complete nitration. Extraction of either the mother liquor or the entire quench mixture from these mixed acid nitrations gave mixtures that contained one (or possibly more) further unidentified by-product(s) (21 mol% from a normal nitration, 33 mol% when a greater proportion of mixed acid was used). When a pure sample of 2,6-dipropoxy-3,5-dinitropyrazine was dissolved in the mixed acid and then immediately isolated by quenching in ice and extracting with EtOAc, the di-nitro derivative was recovered quantitatively. However if the work-up was delayed for 24 h, then the isolated material consisted of the di-nitro derivative and the same by-product(s) as were observed in the mixed acid nitration of 2,6-dipropoxypyrazine, but in different proportions. Thus the by-product(s) are not formed by hydrolysis during work-up but by further nitration of the primary product.

Amination of 2,6-dialkoxy-3,5-dinitropyrazines

The purified 2,6-dialkoxy-3,5-dinitropyrazines were subjected to various amination conditions viz. in acetonitrile or the corresponding alcohol at ambient temperature with aqueous 35 wt% NH_3, or in toluene, acetonitrile or the corresponding alcohol at ambient temperature with gaseous NH_3 at 8 bar. In all cases the product was pure 2,6-diamino-3,5-dinitropyrazine (Scheme 4). Unlike the 1,3,5-trialkoxy-2,4,6-trinitrobenzene aminations, the alkoxy group had little or no effect on the decomposition temperature of the product as measured

by DSC (see Table 1), the onset temperature range being 354.7-358.2 °C and the peak maximum range being 357.6-363.4 °C for all three alkyl groups, with 355.9-357.6 and 358.3-360.7 °C respectively for the methyl derivative, 354.7-358.2 and 357.6-361.8 °C respectively for the ethyl derivative, and 356.1-357.2 and 359.3-363.4 °C respectively for the propyl derivative. The yields ranged from 89.5 to 99%, with essentially no correlation with alkoxy group or amination conditions.



Scheme 4. Amination of 2,6-dialkoxy-3,5-dinitropyrazines.

For 1,3,5-trimethoxy-2,4,6-trinitrobenzene it was found that amination with gaseous ammonia at higher temperatures favoured the formation of ammonium 3,5-diaminopicrate by attack of NH_3 on the methyl carbon instead of the alkoxy bearing ring carbon [8, 9]. However amination of 2,6-dimethoxy-3,5-dinitropyrazine at ~110 °C still gave pure 2,6-diamino-3,5-dinitropyrazine, with yield and thermal decomposition properties falling within the same narrow ranges as aminations performed at ambient temperature.

Conclusions

A series of 2,6-dialkoxy-3,5-dinitropyrazine (R = Me, Et, Pr) has been synthesized and subjected to amination. The yield and purity of the generated 2,6-diamino-3,5-dinitropyrazine was independent of the alkoxy group present in the precursor. This contrasts with the behaviour of 1,3,5-trialkoxy-2,4,6-trinitrobenzene (R = Me, Et, Pr), where the purity of the 1,3,5-triamino-2,4,6-trinitrobenzene (TATB) produced by amination was very dependent upon the alkoxy group. We conclude that attack by NH_3 at the α-carbon of the alkyl group instead of the alkoxy bearing ring carbon is not important in the pyrazine series.

Table 1. Yield and DSC data for 2,6-diamino-3,5-dinitropyrazine formed by amination of 2,6-dialkoxy-3,5-dinitropyrazines

Alkyl group / Method	Yield (%)	DSC onset (°C)	DSC maximum (°C)
Methyl / A	94	357.3, 356.8	360.4, 359.7
Ethyl / A	89.5	357.7	361.6
Propyl / A	92	357.2, 356.3	363.4, 359.0
Methyl / B	94	357.2	359.6
Ethyl / B	96.5	357.8	360.8
Propyl / B	96.5	356.1, 357.6	359.6, 360.7
Methyl / C	96.5	355.9 (358.2*)	358.3 (362.6*)
Ethyl / C	96.5	354.7 (356.5*)	357.6 (361.1*)
Propyl / C	99	356.5 (357.0*)	359.3 (364.0*)
Methyl / D	94	357.1	361.5
Ethyl / D	92	358.2	361.8
Propyl / D	94	357.1	359.9
Methyl / E	96.5	357.6	360.7
Ethyl / E	94	356.0	359.8
Propyl / E	92	357.1	360.5
Methyl / F	96.5	356.6	359.4

Method A: in acetonitrile, aqueous 35 wt% NH_3
Method B: in corresponding alcohol, aqueous 35 wt% NH_3
Method C: in toluene, NH_3 at 8 bar
Method D: in acetonitrile, NH_3 at 8 bar
Method E: in corresponding alcohol, NH_3 at 8 bar
Method F: in toluene at 110 °C, NH_3 at 8 bar
DSC conditions: 10 K min^{-1}, unsealed pan, sample ~1 mg [(*) results ~2 mg]. Duplicate figures are from the same batch.

Experimental

Synthesis of 2,6-dialkoxypyrazines

2,6-Dimethoxypyrazine

2,6-Dichloropyrazine (4.73 g, 32 mmol) was added to a mixture of 30 wt% NaOMe in MeOH (28.8 g, 0.16 mol, 5 eq) and dry MeOH (46 ml). The solution was heated under reflux during 8 h and then left overnight. The mixture was then poured into water (195 ml) and the product was extracted with Et_2O (6X50 ml). The combined extracts were dried (Na_2SO_4), concentrated through a Vigreux column and then rotary evaporated at room temperature. The residue was finally pumped under high vacuum. Yield of low melting white solid (lit. m.p. 48-49 °C [11], 31-31.5 °C [12]) which sublimed onto the walls of the flask on standing: 4.30 g (97%). NMR (acetone-d_6): ^{1}H 3.96 (s, 6.15H, CH_3), 7.76 ppm (s, 2.00H, ArH); ^{13}C 53.8 (CH_3), 125.2 (CH), 159.9 ppm (C).

2,6-Diethoxypyrazine

Sodium (1.94 g, 84 mmol, 5 eq) was dissolved in AnalaR (MeOH and PrOH free) EtOH (42 ml). 2,6-Dichloropyrazine (2.50 g, 16.8 mmol) was added at RT (addition at 80 °C caused vigorous boiling) and the solution was then heated at 80 °C during 22 h. The dark suspension was poured into water (100 ml) and the product was extracted with Et_2O (6X25 ml). The combined extracts were washed with saturated brine (25 ml), dried (Na_2SO_4) and concentrated to give a residue that slowly crystallised to a low melting solid (lit. m.p. 27-27.5 °C [12]). Yield 2.78 g (98%). NMR (acetone-d_6): ^{1}H 1.38 (t, 6.33H, CH_3), 4.37 (q, 4.12H, CH_2), 7.71 ppm (s, 2.00H, ArH); ^{13}C 14.8 (CH_3), 62.7 (CH_2), 125.3 (CH), 159.5 ppm (C).

2,6-Dipropoxypyrazine

Sodium (1.15 g, 50 mmol, 5 eq) was dissolved in PrOH (25 ml). 2,6-Dichloropyrazine (1.48 g, 10 mmol) was added at RT and the solution was then heated at 80 °C during 23 h. The dark suspension was poured into water (60 ml) and the product was extracted with Et_2O (6X15 ml). The combined extracts were washed with saturated brine (15 ml), dried (Na_2SO_4) and concentrated to give a solid residue. Yield 2.01 g (100%). NMR (acetone-d_6): ^{1}H 0.97 (t, 6.30H, CH_3), 1.75 (m, 4.20H, CH_2), 4.23 (t, 4.24H, CH_2), 7.81 ppm (s, 2.00H, ArH); ^{13}C 10.2 (CH_3), 21.7 (CH_2), 67.4 (CH_2), 124.0 (CH), 158.1 ppm (C).

Nitration of 2,6-dialkoxypyrazines

NB. In the analysis of the NMR spectra of the nitration products, it was assumed that unidentified products that contained alkoxy groups had 2 identical alkoxy groups. Should it be subsequently shown that a product contained only 1 alkoxy group, or 2 non-identical alkoxy groups, then product distributions would have to be recalculated taking this into account.

2,6-Dimethoxypyrazine

(i) Conditions used for the nitration of 2-chloro-6-methoxypyrazine viz. HNO_3/oleum [2]. The nitration mixture was prepared by adding 30% oleum (23.0 ml, 43.4 g) to 99.5% HNO_3 (9.9 ml, 14.85 g) and 98% H_2SO_4 (11.8 ml, 21.7 g) with external cooling. 2,6-Dimethoxypyrazine (0.49 g) was added during 10 min to the nitration mixture (2.75 ml, 5.01 g) cooled in ice/water. The solution became very dark. It was allowed to warm to RT (no exotherm) and then heated slowly to 70 °C. After 4 h at 75 °C the dark upper layer which had initially formed had largely disappeared. The mixture was added to ice (50 g), the resultant cream solid was filtered off and was washed with water. Some solid appeared to dissolve as the ice melted and possibly during washing. Yield of fairly pure 2,6-dimethoxy-3,5-dinitropyrazine 43 mg (5.3%). The pale yellow filtrate (~75 ml) was extracted with EtOAc (2X30 ml), the extracts were combined and washed with saturated brine (3X10 ml). Evaporation of the solvent gave more product (46 mg, 5.7%). Total yield 89 mg (11%).

(ii) With N_2O_5 in organic solvents

N_2O_5 (4 eq) in the reaction solvent (~0.9 ml) was added, with ice-water cooling, to 2,6-dimethoxypyrazine (50 mg) in the reaction solvent (1.5 ml). The temperature was maintained at 0 °C during 3 h. The reaction was then worked-up as follows:

(a) Solvent CH_2Cl_2: Water (1.5 ml) was added, the organic layer was separated and the aqueous phase was extracted with more CH_2Cl_2 (1.5 ml). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (1.5 ml), water (1.5 ml) and saturated brine (1.0 ml). The residue (23 mg) after rotary evaporation of the CH_2Cl_2 solution was an oil. ^1H NMR analysis (acetone-d_6) indicated that it did not contain any dinitro derivative. It consisted of starting material (73%), mononitro derivative (17%) and an unknown (10%) - see below for NMR data on the latter 2 products.

(b) Solvent CH_3CN: Water (3.0 ml) was added and gave a cloudy precipitate. The mixture was rotary evaporated to remove most of the CH_3CN and then extracted with CH_2Cl_2 (2X2.0 ml). The combined extracts were washed with saturated aqueous $NaHCO_3$ (1.5 ml), water (1.5 ml) and saturated brine (1.0 ml). The residue (13 mg) after rotary evaporation of the CH_2Cl_2 solution was an oil. ^1H NMR analysis (acetone-d_6) indicated that it did not contain any dinitro derivative. It consisted of starting material (36%), mononitro derivative (53%) and one other unidentified component exhibiting 2 methyl signals (11%). NMR data for the mononitro derivative: ^1H 4.03 (s, CH_3), 4.08 (s, CH_3), 7.75 ppm (s, ArH); ^{13}C 53.9 (CH_3), 54.5 (CH_3), 123.6 (CH), 154.8, 158.0, 163.5, 168.8 ppm. : ^1H NMR data for the unidentified component 4.14 (s), 4.17 ppm (s).

(iii) N_2O_5 in HNO_3

(a) 2,6-Dimethoxypyrazine (100 mg) was added in portions with ice/water cooling to a solution of N_2O_5 in HNO_3 (0.79 ml, ~4.2 eq; from 9.42 g N_2O_5 and 18.8 ml HNO_3 → ~23 ml). The reaction was fairly vigorous. After 23 h at RT the solution was added to ice (10 g). The white precipitate was filtered off, washed with water (3X) and dried. Yield: 65 mg (40%) of pure (by NMR) 2,6-dimethoxy-3,5-dinitropyrazine.

On a larger scale (845 mg) and using 3eq N_2O_5, the yield of pure 2,6-dimethoxy-3,5-dinitropyrazine was 58% (801 mg).

(b) A solution of N_2O_5 in HNO_3 (0.56 ml, ~3 eq; same solution as above) was added to a solution of 2,6-dimethoxypyrazine (100 mg) in HNO_3 (0.50 ml) with external cooling and then allowed to warm to RT. Samples (0.3 ml) were removed at intervals, added to ice (5 g) and worked up as above. Yield of pure 2,6-dimethoxy-3,5-dinitropyrazine: 4 h 25 mg, 8 h 26 mg, 24 h 29 mg.

(iv) Using HNO_3/H_2SO_4

(a) 2,6-Dimethoxypyrazine (200 mg, 1.43 mmol) was added, with ice/water cooling, to 99.5% HNO_3 (0.25 ml, 5.95 mmol, ~4 eq) in 98% H_2SO_4 (0.90 ml) during 5 min. After 30 min at 0 °C, the mixture was allowed to warm to RT and kept at RT during 5 h. The mixture was added to ice (10 g), the cream solid was filtered off, washed with ice-cold water (3X1 ml) and dried. Yield of pure (by NMR) 2,6-dimethoxy-3,5-dinitropyrazine: 125 mg (38%). The combined filtrate and washings were extracted with EtOAc (3X5 ml), the combined extracts were washed with saturated brine (3X2 ml) and evaporated to give a crystalline

residue (23 mg). ^{1}H NMR analysis indicated that this consisted of some dinitro derivative, but mainly other products (starting material was absent).

(b) As (a) but the dimethoxypyrazine was dissolved in H_2SO_4 before adding the HNO_3. Yield of solid product 128 mg (39%).

(c) As (a) but the reaction was continued for 22 h. There was essentially no foaming during the reaction. Instead of filtering off the solid the whole was extracted with EtOAc. Yield 119 mg (contained ~79 mol% dinitro derivative).

(d) As (a) on 800 mg scale. Reaction time 23 h. Yield of pure 2,6-dimethoxy-3,5-dinitropyrazine (isolated as a white solid by filtration) 630 mg (48%).

(v) Using KNO_3/H_2SO_4

As (iv-a above) but using KNO_3 (601 mg) instead of HNO_3. Some foaming occurred. Reaction time 20 h. Yield of pure 2,6-dimethoxy-2,5-dinitropyrazine (as a white solid) 154 mg (47%). EtOAc extraction of the filtrate and washings gave 21 mg of residue containing ~50 mol% dinitro derivative; there was no starting material and essentially no mono-nitro derivative. NMR (acetone-d_6) analysis showed the presence of other minor methoxy-substituted products in the EtOAc extract: ^{1}H 3.83, 3.86, 3.92 ppm; ^{13}C 53.4, 53.9, 54.1 ppm. These were also present in the EtOAc extract from iv-a and iv-c. No aromatic H was detected i.e. no mono-nitro derivative was present.

2,6-Dimethoxy-3,5-dinitropyrazine (from iv-a) was recrystallised from MeOH. DSC (10 K min^{-1}) melting endotherm onset 163.1 °C, decomposition onset ~270 °C. CHN analysis: Found C 31.1, H 2.60, N 24.1%. $C_6H_6N_4O_6$ requires C 31.3, H 2.63, N 24.5%. NMR (acetone-d_6): ^{1}H 4.34 ppm (s, OCH_3); ^{13}C 57.6 (OCH_3), 131.6 (v.w., CNO_2), 156.0 ppm ($COCH_3$).

2,6-Diethoxypyrazine

(i) N_2O_5 in HNO_3

2,6-Diethoxypyrazine (970 mg) was added slowly to 99.5% HNO_3 (4.1 ml) with external cooling. A solution of N_2O_5 in HNO_3 (4.67 ml, ~3 eq; from 9.42 g N_2O_5 and 18.8 ml HNO_3 → ~23 ml) was then added dropwise. After 1 h at 0 °C and 23 h at RT, the solution was added to ice (80 g). The cream precipitate was filtered off, washed with ice-cold water (3X) and dried. Yield: 814 mg (55%) of

2,6-diethoxy-3,5-dinitropyrazine (contaminated with ~2 mol% of an unidentified component – neither starting material nor mono-nitro derivative were present since no ArH was observed). The filtrate was extracted with EtOAc (3X40 ml), the combined extracts were washed with saturated brine (3X8ml) and concentrated. The residue (690 mg) contained a considerable amount of EtOAc. NMR (acetone-d_6) analysis indicated that it contained less than 10 mol% di-nitro derivative.

(ii) HNO_3/H_2SO_4

(a) 2,6-Diethoxypyrazine (240 mg, 1.43 mmol) was added to 99.5% HNO_3 (0.25 ml, 5.95 mmol, ~4 eq) in 98% H_2SO_4 (0.90 ml) with external cooling. After 1 h at 0 °C, the solution was left at RT during 22 h, before being added to ice (10 g). The solid was filtered off, washed with water (3X2 ml) and dried. Yield of 2,6-diethoxy-3,5-dinitropyrazine (contaminated with ~2-3 mol% mono-nitro derivative) 148 mg (40%). NMR data (acetone-d_6) for the mono-nitro derivative: ^{1}H 1.42 (t), 4.58 (overlapping quartets), 7.65 ppm (s).

(b) As (a). There was considerable foaming, even towards the end of the reaction period (22 h). Instead of filtering off the solid, the whole was extracted into EtOAc (3X5 ml). The combined extracts were washed with saturated brine (3X2 ml) before concentration to give a pale yellow solid (169 mg). NMR analysis indicated that this was mainly 2,6-diethoxy-3,5-dinitropyrazine contaminated with the same by-product (20 mol%) as was the major by-product in (i) viz. NMR ^{1}H 1.38 (t), 4.38 ppm (q); ^{13}C 14.1 (CH_3CH_2), 64.1 ppm (OCH_2CH_3).

2,6-Diethoxy-3,5-dinitropyrazine (from i) was recrystallised from EtOH. DSC (10 K min^{-1}) melting endotherm onset 140.9 °C, max 142.0 °C, decomposition onset 282 °C. CHN analysis: Found C 37.8, 37.3, H 4.04, 4.06, N 21.5, 21.7%. $C_8H_{10}N_4O_6$ requires C 37.2, H 3.90, N 21.7%. NMR (acetone-d_6): ^{1}H 1.51 (t, 6.00H, CH_3), 4.78 ppm (q, 4.01H, OCH_2); ^{13}C 14.4 (CH_3), 67.5 (OCH_2), 131.6 (v.w., CNO_2), 155.5 ppm (*C*OEt).

2,6-Dipropoxypyrazine

(i) N_2O_5/HNO_3

(a) 2,6-Dipropoxypyrazine (140 mg, 0.72 mmol) was dissolved, with cooling, in 99.5% HNO_3 (0.50 ml) and a solution of N_2O_5 in HNO_3 (0.56 ml, 3 eq; from 9.42 g N_2O_5 and 18.8 ml HNO_3 → ~23 ml) was added dropwise. The solution was maintained at 0 °C during 1 h and the RT during 22 h (no visible gas evolution)

before being added to ice (10 g). The suspension was allowed to coagulate, the supernatant liquor was decanted and the residue was washed with water and dried. Yield: 113 mg (55%). NMR analysis (acetone-d_6) indicated that this was 2,6-dipropoxy-3,5-dinitropyrazine contaminated with ~5 mol% of an unidentified component A (possible compounds excluded: propan-1-ol, propan-1-ol nitrate, 2,6-dipropoxypyrazine).

(b) As (a) on 2,6-dipropoxypyrazine (1188 mg). Yield: 1048 mg (60%). This product was contaminated with the same impurity (~9 mol%) as in (a).

Sonication of this material (812 mg) in water (60 ml) during 30 min gave a solid which was filtered off, washed with water (3X) and dried. The resultant cream solid was pure 2,6-dipropoxy-3,5-dinitropyrazine (731 mg, 90%). Extraction of the filtrate with EtOAc (30 ml) and washing the extract with saturated brine (15 ml) gave a residue (28 mg) which consisted predominantly of the di-nitro derivative and the impurity A, with slightly more of the latter. NMR data (acetone-d_6) for the unidentified component A: ^{1}H 0.97 (t, J 6.6Hz, 2.85H, CH_3), 1.72 (m, 2.12H, $CH_2CH_2CH_3$), 4.22 ppm (t, 2.00H, OCH_2); ^{13}C 10.5 (CH_3), 22.4 ($CH_2CH_2CH_3$), 68.2 (OCH_2), 159.5 (C), 161.7 ppm (C). The relative intensities of the ^{13}C peaks suggest that A contains only one propoxy group.

(ii) HNO_3/H_2SO_4

(a) 2,6-Dipropoxypyrazine (280 mg, 1.43 mmol) was added to 99.5% HNO_3 (0.25 ml, 5.95 mmol, ~4 eq) in 98% H_2SO_4 (0.90 ml) with external cooling. After 1 h at 0 °C, the solution was left at RT during 22 h, before being added to ice (10 g). The liquor was decanted from the waxy solid and the latter was washed with water (3X). Yield after drying: 162 mg (40%). The product was a mixture of 2,6-dipropoxy-3,5-dinitropyrazine (84 mol%) and the mono-nitro derivative (16 mol%).

(b) As (a) but 48 h reaction period. Yield: 148 mg (36%). Di-nitro derivative (86 mol%) + mono-nitro derivative (14 mol%).

(c) As (a) but only 5 h reaction period. A cream solid had separated before the reaction was terminated, but this had redissolved by 5 h. Foaming was observed. The reaction mixture was added to ice (10 g). This gave a cream precipitate which became liquid as the temperature rose. The whole was extracted with EtOAc (3X5 ml), the combined extracts were washed with saturated brine (3X2 ml) and concentrated to give a golden liquid (328 mg). This was a mixture of di-nitro

derivative (60 mol%), mono-nitro derivative (19 mol%) and an unidentified by-product B (21mol%). NMR data (acetone-d_6) for the mono-nitro derivative: ^{1}H 4.49 (2 overlapped triplets, 4.00H, OCH_2), 7.66 ppm (s, 1.12H, ArH); other absorptions were obscured by absorptions from the di-nitro derivative; ^{13}C 10.6 (CH_3), 22.7 ($CH_2CH_2CH_3$), 70.5 (OCH_2), 70.6 (OCH_2), 123.6 ppm (CH). NMR data (acetone-d_6) for the unknown by-product B: ^{1}H 0.96-1.01 (m), 1.76 (m), 4.20-4.29 ppm (overlapped multiplets).

The product was re-dissolved in EtOAc (15 ml) and washed sequentially with saturated $NaHCO_3$ (2X2 ml) and saturated brine (2X2 ml). Concentration gave a residue (217 mg). NMR analysis indicated that the unidentified by-product B had been reduced to 8 mol%, with the ratio of the other components remaining unchanged. This material became largely crystalline on standing during 3 months. The crystalline portion contained only the di- and mono-nitro derivatives (84 and 16 mol% respectively).

(d) As (c) but 20 h reaction period. There was a precipitate after <1 h, but this had redissolved before work-up. Although the final precipitated product was more solid than in (c), it was still extracted into EtOAc. Yield: 283 mg. NMR analysis indicated that the products were: di-nitro derivative (66 mol%), mono-nitro derivative (16 mol%), unidentified by-product B (18 mol%).

(e) The pure dinitro derivative (45 mg) was dissolved in a solution of 99.5% HNO_3 (0.125 ml) in 98% H_2SO_4 (0.45 ml) with external cooling. The light yellow solution was immediately added to ice (5 g), generating a white precipitate. The mixture was extracted with EtOAc (3X2.5 ml) and the combined extracts were washed with saturated brine (3X1 ml). Evaporation of the solvent gave an oil (43 mg) which crystallized. The product was still pure 2,6-dipropoxy-3,5-dinitropyrazine.

(f) The pure product from (e) (43 mg) was dissolved in a solution of 99.5% HNO_3 (0.125 ml) in 98% H_2SO_4 (0.45 ml) with external cooling. The light yellow solution was kept at room temperature during 24 h. The solution was then added to ice (5 g), generating a white precipitate. The mixture was extracted with EtOAc (3X2.5 ml) and the combined extracts were washed with saturated brine (3X1 ml). Evaporation of the solvent gave an oil (20 mg). In this case the product was a mixture of the dinitropyrazine (32%) and the unidentified by-product(s) (68%) observed before.

2,6-Dipropoxy-3,5-dinitropyrazine (from ib) was recrystallised from PrOH. M.p. 48-49 °C. DSC (10K/min) melting endotherms onset 42.4 °C, max 45.3 °C,

onset 48.4 °C, max 50.2 °C (both disappeared after heating and pumping during 4 h and therefore are probably loss of PrOH), decomposition onset 274.1 °C, max 297.2 °C. CHN analysis: Found C 41.8, 41.8, H 5.00, 4.96, N 19.5, 19.3%. $C_{10}H_{14}N_4O_6$ requires C 42.0, H 4.93, N 19.6%. NMR (acetone-d_6): ^{1}H 1.07 (t, 6.02H, CH_3), 1.92 (m, 3.97H, $CH_2CH_2CH_3$), 4.68 ppm (q, 4.00H, OCH_2); ^{13}C 10.6 (CH_3), 22.6 ($CH_2CH_2CH_3$), 72.8 (OCH_2), 131.5 (v.w., CNO_2), 155.6 ppm (*C*OPr).

HPLC analysis of 2,6-dialkoxy-3,5-dinitropyrazines used for amination studies

Conditions: InertSil ODS2, 25 cm, ID 4.6 mm; mobile phase CH_3CN:H_2O (50:50), 1 ml min^{-1}.

	Retention time (min)	Absorbance (λ_{max})	Purity (%)
Dimethoxy	6.77	287.5, 331.4 nm	~100
Diethoxy	12.26	289.9, 333.8 nm	~100
Dipropoxy	26.81	289.9, 334.9 nm	97.7

Amination of 2,6-dialkoxy-3,5-dinitropyrazines to 2,6-diamino-3,5-dinitropyrazine

(i) With aqueous 35wt% NH_3 – general procedure

The dialkoxydinitropyrazine (0.22 mmol) in either acetonitrile (1 ml) or the corresponding alcohol (2 ml) was treated with aqueous 35wt% NH_3 (0.20 ml) at room temperature during 24 h. The yellow solid was filtered off, washed with either acetonitrile or the corresponding alcohol and dried (see Table 1 for results).

(ii) With gaseous NH_3 at 8 bar – general procedure

The dialkoxydinitropyrazine (0.22 mmol) in either toluene (5 ml), acetonitrile (2 ml) or the corresponding alcohol (2 ml) was sealed in a pressure vessel which was then pressurised (8 bar) with NH_3 at room temperature during 24 h. The dissolved NH_3 was allowed to evaporate and the yellow solid was filtered off, washed with either toluene, acetonitrile or the corresponding alcohol and dried (see Table 1 for results). The ^{1}H NMR spectra of the products precipitated from

toluene indicated that small amounts of toluene were present [from: dimethoxy 0.51 wt% toluene, diethoxy 2.2 wt%, dipropoxy 0.58 wt%], but loss of this was not apparent from the DSC data.

(iii) With gaseous NH_3 at 110 °C

Dimethoxydinitropyrazine (50 mg, 0.22 mmol) in toluene (5 ml) was sealed in a pressure vessel and heated to 105 °C. The vessel was then pressurised (8 bar) with NH_3 and the temperature was maintained at 110 °C during 3.5 h. It was then allowed to cool (overnight), the dissolved NH_3 was allowed to evaporate and the yellow solid was filtered off, washed with toluene and dried. Yield of 2,6-diamino-3,5-dinitropyrazine 42 mg (96.5%). Evaporation of the filtrate and washings gave no residue.

Typical data for the isolated 2,6-diamino-3,5-dinitropyrazine:

NMR (DMSO-d_6): ^{1}H (Figure 1) 8.25 (br s, 2.03H, 2NH), 8.65 ppm (br s, 2.00H, 2NH) (non-equivalence of NH_2 hydrogens due to H-bonding of one H with O of the adjacent nitro group); ^{13}C (Figure 2) 125.5 (C.NO_2), 151.1 ppm (C.NH_2).

FTIR (KBr): 3465, 3350, 3302 (-NH_2), 1553, 1318 (-NO_2), 1641, 1623, 1493 cm^{-1} (-NH_2, C=C and/or C=N); lit. [13] 3472, 3367, 3322, 1558, 1319, 1647, 1626, 1495 cm^{-1}. All product samples had essentially identical IR spectra.

Decomposition temperature: a typical DSC of a sample produced in this work is shown in Figure 3. See also data in Table 1. Lit. [13] 356 °C.

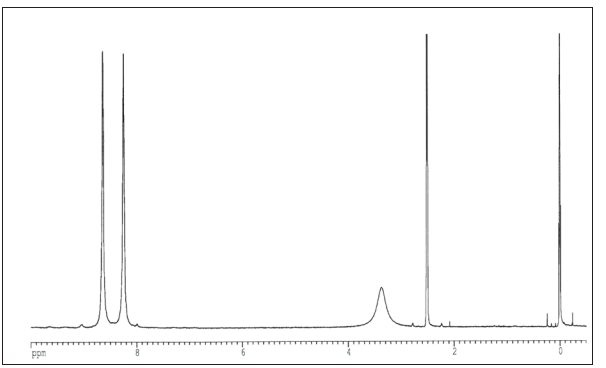


Figure 1. ^{1}H NMR (DMSO-d_6) of 2,6-diamino-3,5-dinitropyrazine.

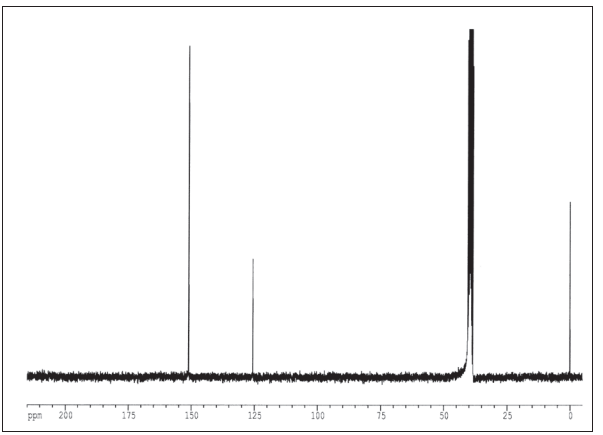


Figure 2. ^{13}C NMR (DMSO-d_6) of 2,6-diamino-3,5-dinitropyrazine.

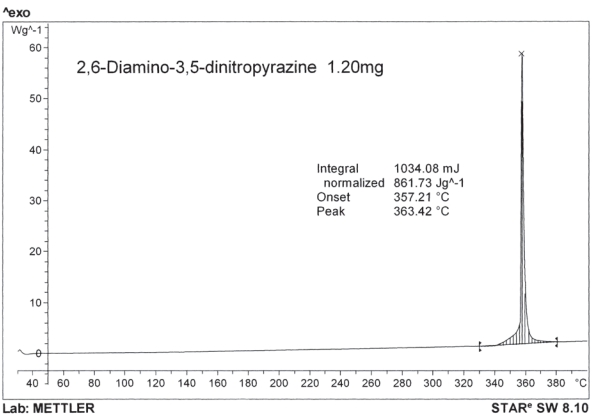


Figure 3. Typical DSC of 2,6-diamino-3,5-dinitropyrazine.

Acknowledgments

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