Studies of Novel Nitro-Substituted Nitrogen Heterocyclic Compounds

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1. Abstract

Extensive nitration studies have been carried out towards the preparation of a series of high energy insensitive explosives. Systems investigated include quinoxalines, quinazolines and pyrazines. A novel candidate explosive, 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) has been produced via a novel nitration of the precursor dialkoxypyrazine compound. Oxidation of ANPZ-i towards the di-N-oxide derivative was studied but no degree of oxidation could be achieved.

A range of benzodiazines (quinazolines and quinoxalines) were nitrated giving a series of novel nitro-substituted compounds. 2,4-Diamino-6,8-dinitroquinazoline was both oxidised and aminated successfully, but it was found in general that a high level of functionalisation of the heterocyclic rings was difficult to attain.

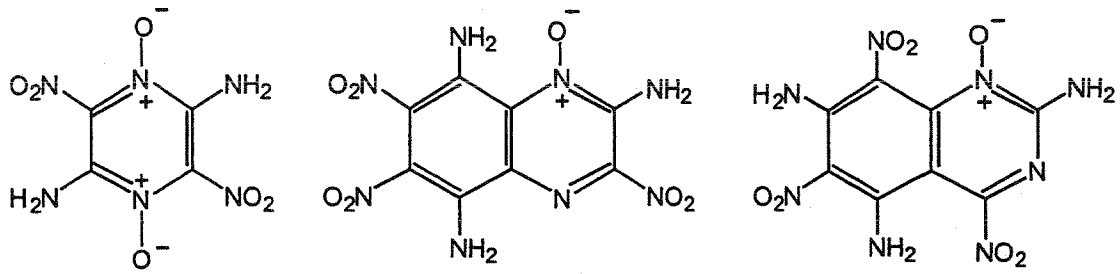
In summary a novel candidate explosive has been prepared, along with a series of novel nitro-explosive precursor compounds. It is hoped that this work can feed into future research into high energy insensitive fillers.

2. Introduction

Existing explosives such as RDX or HMX are very powerful, but suffer from a high sensitivity (thermal and mechanical). Several approaches can be adopted in order to render the system insensitive, e.g. by the use of inert and energetic binders. An alternative approach is the incorporation of amino groups into the explosive; for example TATB is very insensitive, however lacks sufficient power output. It has been postulated that the insensitivity in TATB arises from intramolecular hydrogen bonding between adjacent amino and nitro groups.

The aim of this project was therefore to prepare high energy compounds, with a similar performance to RDX, but with also a high insensitivity. Consequently, the synthesis of energetic nitro substituted nitrogen heterocyclic compounds, principally pyrazines (**1**), quinoxalines (**2**) and quinazolines (**3**), was investigated. This work was carried out within DERA Chemical Technology Department, where highly integrated research is carried out drawing from disciplines such as molecular modelling, physical and chemical characterisation, hazard assessment, formulation, scale-up and of course bench synthetic chemistry. High explosive compounds were envisaged with nitro, amino and N-oxide functionalisation of the ring systems. *Figure 1* shows some of the nitrogen heterocyclic

target molecules. Molecular modelling of these target molecules was carried out and this information is shown in *Table 1*. Existing nitrogen heterocyclic explosives which have nitro, amino and N-oxide functionalisation include PZO and CL-14.



1 **2** **3**

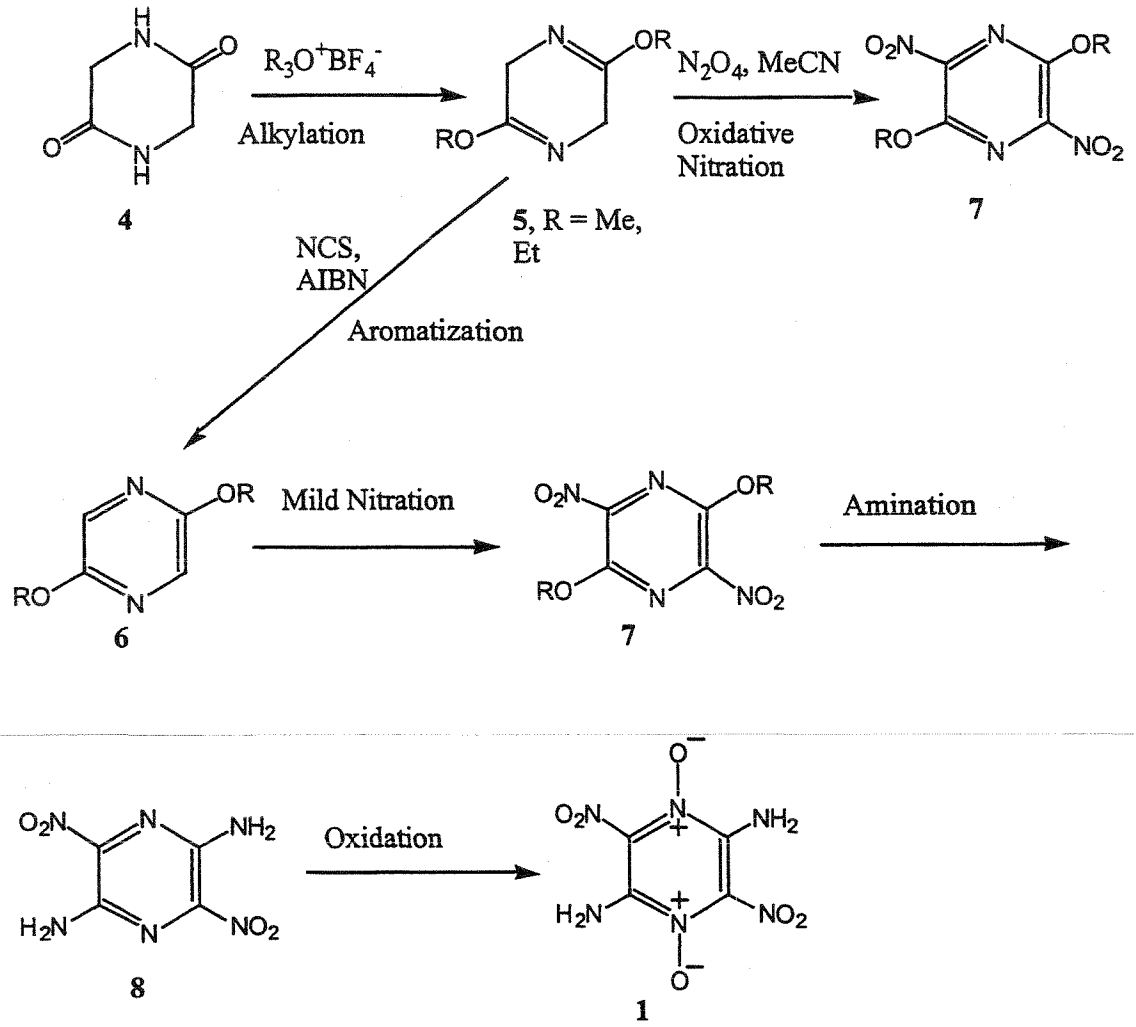
Figure 1: Nitrogen Heterocyclic Target Molecules

Compound	*Calculated Performance Data (From Molecular Modelling)*
1	$V_D = 9.04$ km.s^{-1}, $P_{C\text{-}J} = 40.4$ GPa (at density = 1.92 g.cm^{-3})
2	$V_D = 7.86$ km.s^{-1}, $P_{C\text{-}J} = 27.1$ GPa (at density = 1.79 g.cm^{-3})
3	$V_D = 8.00$ km.s^{-1}, $P_{C\text{-}J} = 28.7$ GPa (at density = 1.81 g.cm^{-3})
	Empirical Performance Data
TATB	$V_D = 7.62$ km.s^{-1}, $P_{C\text{-}J} = 25.9$ GPa (at density = 1.85 g.cm^{-3})
RDX	$V_D = 8.64$ km.s^{-1}, $P_{C\text{-}J} = 33.8$ GPa (at density = 1.77 g.cm^{-3})

Table 1: Comparison of Calculated Performance Data of Target Molecules Against Empirical Performance Data of TATB and RDX

3. Pyrazine Reactions

The preparation of PZO (2,6-diamino-3,5-dinitropyrazine-N-oxide) has been reported by researchers at LLNL, Livermore, California (USA) [1]. The synthesis of this explosive molecule was found to be relatively straightforward. Consequently, it was decided that the dioxide isomer of PZO; 2,5-diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) would be an attractive target explosive molecule (*Scheme 1*).



Scheme 1: Proposed Preparation of 2,5-Diamino-3,6-dinitropyrazine-1,4-dioxide

Initially, the ethylation of piperazine-2,5-dione (**4**) was found to be problematic [2]. It is thought that commercially available triethyloxonium tetrafluoroborate or Meerwein's salt is contaminated with fluoroboric acid. The fluoroboric acid protonates **4** forming an unreactive salt.

Triethyloxonium tetrafluoroborate was therefore generated *in situ*, by the reaction between epichlorohydrin and boron trifluoride diethyl etherate, and then used in the alkylation of piperazine-2,5-dione. It is essential that the Meerwein's salt is prepared in dry conditions and therefore all the reagents were freshly distilled and the reaction was kept under nitrogen at all times. The Meerwein's salt is formed in quantitative yield and is kept in the reaction vessel where it is used to alkylate **4** in dichloromethane solvent again in very high yield. Aromatization of 2,5-diethoxy-3,6-dihydropyrazine (**5**) also proceeds very smoothly and 2,5-diethoxypyrazine (**6**) is produced in high yield [3].

3.1 Nitration of 2,5-Diethoxypyrazine (6)

The electrophilic nitration of **6** was attempted under a wide range of conditions (*Table 2*). Mixed acid nitration of **6** resulted in an extremely violent reaction where decomposition of the starting material was instantaneous above a specific temperature (*c.* -10°C). Therefore, it was thought that a milder nitrating agent would be more effective for the nitration of this highly activated aromatic species.

No.	*Nitrating System*	*Result*
1	c. HNO_3, 30% oleum, r.t.	Violent decomposition
2	c. HNO_3, c. H_2SO_4, 0°C	Decomposition
3	69% aq. HNO_3, 0°C	Decomposition
4	c. HNO_3, -10°C	Decomposition
5	N_2O_5, CH_2Cl_2, -20°C < T < +10°C	Several breakdown products
6	100% HNO_3, Ac_2O	No reaction
7	100% HNO_3, AcOH	Decomposition
8	*i*-Pr-ONO_2,	No reaction
9	$NO_2^+BF_4^-$, NO_2Me	No reaction
10	$NaNO_2$, aq. HCl, 2 h, 0°C	Decomposition
11	BzCl, $AgNO_3$, MeCN	Decomposition
12	$NO_2^+BF_4^-$, sulpholane (high concentration)	Decomposition
13	$NO_2^+BF_4^-$, sulpholane (0.5M commercial grade)	Successful dinitration
14	$NO_2^+SbF_6^-$, sulpholane	Successful dinitration

Table 2: Nitrating Systems Employed in the Attempted Nitration of 2,5-Diethoxypyrazine

The use of nitronium tetrafluoroborate in sulpholane was found to be effective in dinitrating **6**, typically with a yield of 30-40%. The optimisation of this reaction was studied under a range of conditions (*Table 3*), however, the optimum yield appears to be *c.* 35-40%. It is thought that the relatively low reaction yield with the tetrafluoroborate salt may be due to decomposition of the salt.

No.	*Reaction length*	*Reaction Temperature (°C)*	*Stoichiometry (substrate: salt)*	*Reaction yield (%)*
1	15 h	r.t.	1:2	30 - 35
2	5 d	r.t.	1:2	35
3	2 - 5 d	40	1:2	35 - 40
4	3 d	r.t.	1:4	< 5
5	2 - 3 h	100	1:2	20
6	15 h	75	1:2	20

Table 3: Reaction Conditions Used in the $NO_2^+BF_4^-$/Sulpholane Nitration of 2,5-Diethoxypyrazine

2,5-Diethoxypyrazine was also successfully nitrated using nitronium hexafluoroantimonate (V) in dry sulpholane with a reaction yield of ~35%, however a large excess of the nitrating agent was required in order to achieve this reaction yield.

3.2 Oxidative Nitration of 2,5-Diethoxy-3,6-dihydropyrazine (5) [4]

The oxidative nitration of **5** was attempted a number of times using N_2O_4. For each reaction a decomposition product was obtained and it is the authors' opinion that this reaction is not repeatable.

3.3 Amination of 2,5-Diethoxy-3,6-dinitropyrazine (7)

The amination of 2,5-diethoxy-3,6-dinitropyrazine (**7**) was attempted using aq. ammonia in acetonitrile at atmospheric pressure, however, unreacted starting material was recovered. Therefore, amination of the substrate was attempted with an ammonia saturated solution of methanol under autoclave conditions; 2,5-diamino-3,6-dinitropyrazine (**8**) was obtained in 95% yield.

Both HPLC and IR analysis indicated the presence of a pure compound and the 60 MHz ^{1}H NMR spectrum showed only the presence of amino protons, which collapsed and formed a doublet on D_2O addition, with no ethoxy proton signals present. ^{13}C NMR analysis has also been carried out.

Detonics studies using MOLPAK and Cheetah calculations have given the following predicted data for ANPZ-i:

$V_D = 8.63$ km.s^{-1}

$P_{C\text{-}J} = 34.9$ GPa

(at a density of 1.88 g.cm^{-3}).

Therefore, ANPZ-i has a predicted performance equal to RDX but is expected to show higher insensitivity to impact.

3.4 N-Oxidation of 2,5-Diamino-3,6-dinitropyrazine (8)

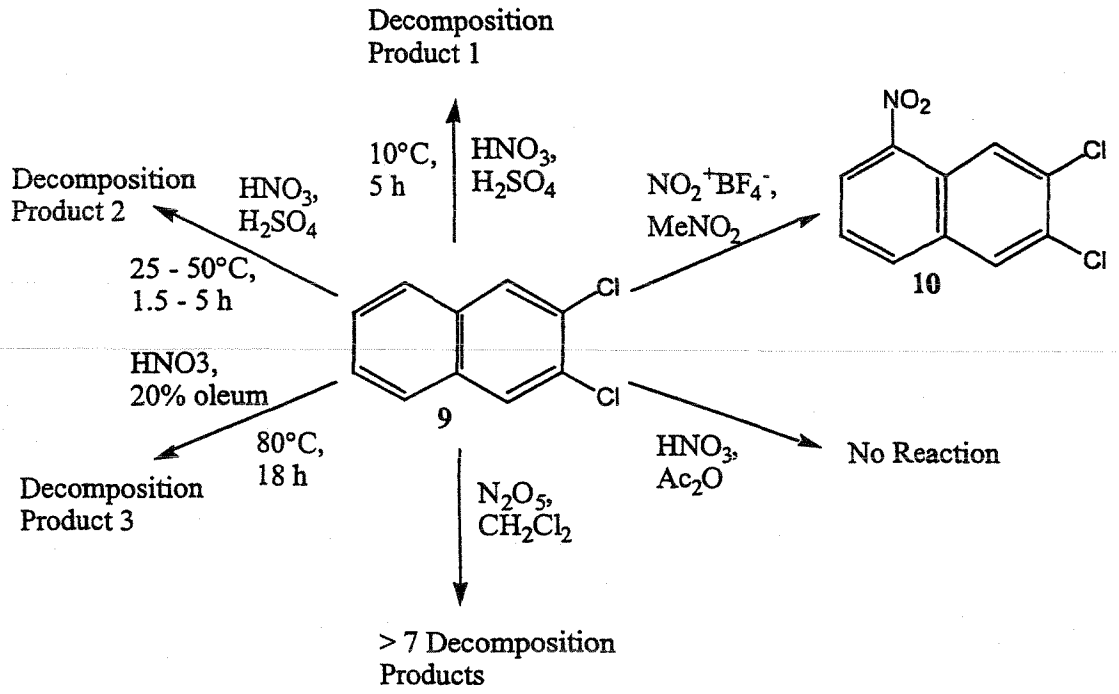
A number of attempted oxidations of 2,5-diamino-3,6-dinitropyrazine (also known as ANPZ-i) (**8**) have been carried out using 30% hydrogen peroxide and trifluoroacetic acid (*in situ* generation of trifluoroperacetic acid) Typically upon work-up of the reaction mixture no product could be obtained since the starting material/product could not be extracted from the aqueous acidic layer. Also, no positive ferric chloride test was observed. Further oxidation systems were used in the attempted oxidation of **8** including; MCPBA (*meta*-chloroperbenzoic acid), DMD (dimethyldioxirane) and HF/MCPBA all without success.

By comparison of the structures of ANPZ and ANPZ-i, the former is readily oxidised to the mono-N-oxide since the oxide is flanked by two amino groups and hence stabilised by intramolecular hydrogen bonding. Conversely, with the structure of ANPZ-i, both mono- and di-oxidation leads to an N-oxide group being flanked by one amino group and one

nitro group. It is suspected that this change in electronic environment of the oxide group is responsible for the difficulty in oxidising ANPZ-i when compared to ANPZ.

4. Quinoxaline Reactions

2,3-Dichloroquinoxaline (**9**) was chosen as a suitable starting material for functionalisation to an energetic quinoxaline compound. The first reaction in the proposed synthetic sequence was nitration of the benzenoid ring, this reaction did however prove to be very difficult. Many nitrating systems were used in the attempted nitration of 2,3-dichloroquinoxaline (**9**), some of which are summarised in *Scheme 3*.



Scheme 3: Attempted Nitrations of 2,3-Dichloroquinoxaline

In the attempted nitration of **9** a series of decomposition products were obtained with mixed acid media. It was hoped that nitration using the milder and selective dinitrogen pentoxide (N_2O_5) would be successful, however, more than 7 decomposition products were obtained. LC-MS of the reaction mixture did indicate the presence of small amounts of the mono-nitro product but not in any appreciable yield. Reaction with nitric acid and acetic anhydride (*in situ* generation of acetyl nitrate) resulted only in recovery of starting material.

Initially, reaction with nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in dichloromethane again resulted in recovery of starting material, although this is thought to be due to the low solubility of both the nitronium salt and starting material in the solvent. Therefore, the reaction was carried out in nitromethane, which has a greater solvating power for both the salt and the starting material, and this time the reaction resulted in production of 2,3-dichloro-8-nitroquinoxaline (**10**) in 70-80% yield.

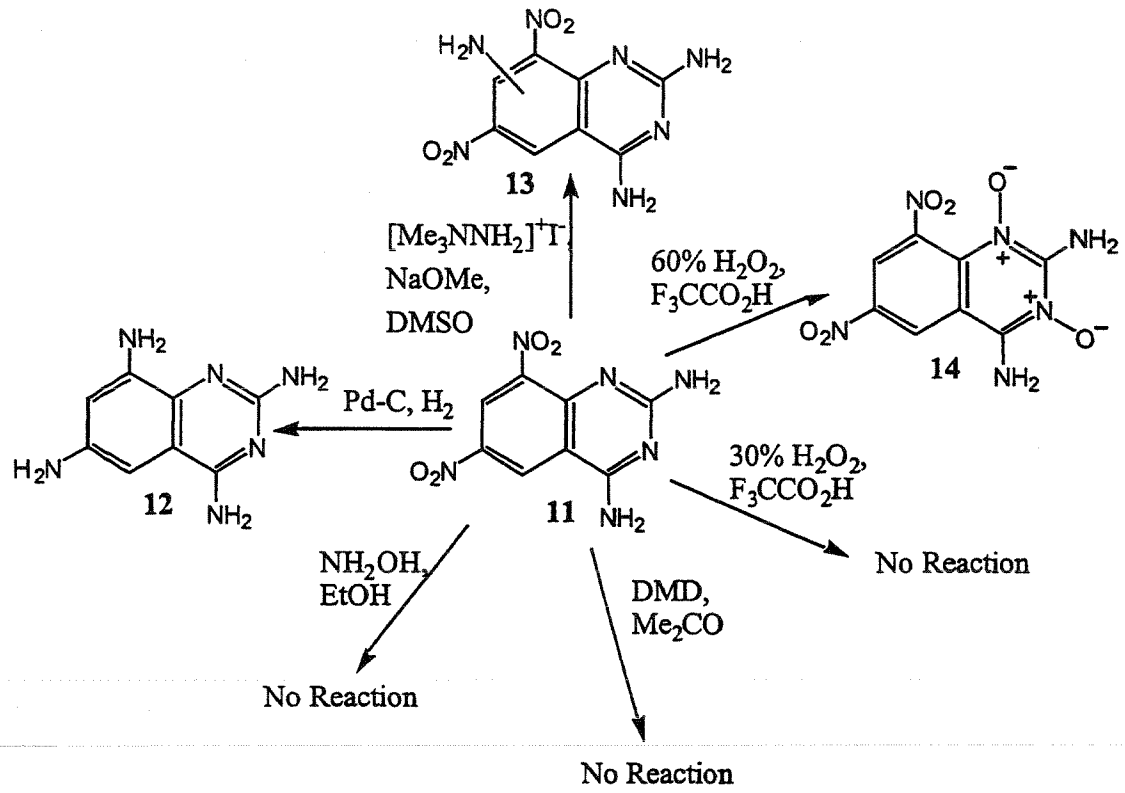
A number of other fundamental quinoxaline nitrations were carried out including; mixed acid dinitration of 2,3-dihydroxyquinoxaline, mixed acid mononitration of 2,3,6-trichloroquinoxaline, $NO_2^+BF_4^-$ (in sulpholane) mononitration of 2-hydroxyquinoxaline and $NO_2^+BF_4^-$ (in sulpholane) mononitration of 2-hydroxy-3-methylquinoxaline. The $NO_2^+BF_4^-$ (in sulpholane) nitration of both 2-methylquinoxaline and quinoxaline-2-carboxylic acid resulted in decomposition of the starting material with the former substrate reacting violently.

A number of quinoxaline aminations were also attempted. It was found that ammmonia saturated solutions of both methanol and acetonitrile were not capable of aminating chloroquinoxalines at atmospheric pressure. Consequently, 2,3-dichloroquinoxaline was successfully aminated to give the 2,3-diamino derivative using methanolic ammonia at high pressure and temperature in an autoclave. Subsequent nitration of 2,3-diaminoquinoxaline again resulted in decomposition of the starting material.

5. Quinazoline Reactions

Initially, quinazoline synthesis studies were centred on the nitration of 2,4-dichloroquinazoline, which was obtained via the dichlorination of benzoylene urea, but again decomposition products were obtained. Therefore, an alternative strategy was employed which involved the preparation of 2,4-diamino-6,8-dinitroquinazoline via the dinitration of 2-methoxybenzonitrile and its subsequent ring closure effected by guanidine [5].

2,4-Diamino-6,8-dinitroquinazoline was then used as a synthetic platform for several attempted functionalisations (*Scheme 4*).



Scheme 4: Attempted Functionalisations of 2,4-Diamino-6,8-dinitroquinazoline

The catalytic hydrogenation (Pd-C, hydrogen) of 2,4-diamino-6,8-dinitroquinazoline (**11**) resulted in successful dihydrogenation, yielding 2,4,6,8-tetra-aminoquinazoline (**12**) in good yield (75-80%). The subsequent mixed acid nitration of **12** resulted in decomposition of the strating material. Consequently, a number of further nitrations, using milder reagents were carried out. Additionally, the protective acetylation of **12** was also attempted.

A number of aminations of **11** were attempted including the use of hydroxylamine which resulted in recovery of starting material. Initially, the use of the vicarious nucleophilic substitution (VNS) reagent; 1,1,1-trimethylhydrazinium iodide $[Me_3NNH_2]^+T$ did not result in any degree of amination of **11**. However, when a large excess of the reagents was employed a monoamino product (**13**) was obtained in 20% yield.

Attempted conversion of the amino groups in **11** to nitro groups via oxidation with dimethyldioxirane (DMD) in acetone was not successful. Attempted N-oxidation of **11** with 30% hydrogen peroxide in trifluoroacetic acid (TFA) also resulted in recovery of starting material. However, when the same reaction was repeated but with 60% hydrogen peroxide the di-N-oxide derivative (**14**) was obtained. The presence of the dioxide was detected by mass spectral analysis.

6. Conclusions

2,5-Diamino-3,6-dinitropyrazine (ANPZ-i), which is a novel explosive compound, has been prepared and fully characterised. ANPZ-i was prepared via the electrophilic nitration of 2,5-diethoxypyrazine using nitronium tetrafluoroborate in sulpholane and subsequent diamination under autoclave conditions. The N-oxidation of ANPZ-i was not achieved despite the use of a wide selection of oxidation systems.

Molecular modelling of ANPZ-i has shown it to have equal performance to RDX but with an envisaged higher insensitivity. It is hoped that in the future larger amounts of ANPZ-i can be produced for hazard testing.

A number of reactions have been carried out on the functionalisation of 2,4-diamino-6,8-dinitroquinazoline. Successful catalytic hydrogenation, VNS (vicarious nucleophilic substitution) amination and N-oxidation reactions have all been achieved. It was hoped that 2,4-diamino-6,8-dinitroquinazoline could act as a platform for functionalisation on to a range of high energy insensitive explosive compounds. The difficulty in reacting this substrate is thought to be largely due to to its insolubility.

A range of novel nitrations of various pyrazine, quinazoline and quinoxaline compounds have also been achieved. In particular, the nitration of 2,3-dichloroquinoxaline with nitronium tetrafluoroborate in sulpholane. In the nitration of nitrogen heterocyclic compounds this reagent has often been found to be far more superior to other systems such as mixed acid or dinitrogen pentoxide.

In summary, extensive investigations have been carried out towards the preparation of novel nitrogen heterocycles for application as high energy insensitive explosives. Difficulties were found in nitrating the heterocyclic rings as well as obtaining a high degree of functionality on the rings. It is believed that with continued studies further candidate explosive compounds can be obtained.

7. References

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