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Nitration of Primary Amines to Form Primary Nitramines (Review)

Daniel McAteer, Jean-François Pons, Ian Wilson, Hamish Cavaye

Centre for Defence Chemistry, Cranfield University, Defence Academy of the United Kingdom, Shrivenham, SN6 8LA

d.mcateer@cranfield.ac.uk

Abstract: The nitration of primary amines to form primary nitramines is a rarely reported synthetic procedure which proceeds through a minimum of two steps. This is in stark contrast to the nitration of alcohols and secondary amines which is readily achievable by a number of methods in a single step. In general the primary amine must initially be activated to nitration as direct exposure to nitrating media tends to result in the formation of an ionic nitrate salt. This activation may be achieved through the use of a multitude of protecting groups that are stable to the nitrating conditions used thereafter. The review presented here is an attempt to bring together the published literature on this often overlooked synthetic procedure in energetic materials chemistry.

Keywords: N-nitration; primary nitramine; literature review;

1 Introduction

The synthesis of primary nitramines is a much neglected area of energetic materials chemistry. This is due to the limited use of primary nitramines in explosive compounds and the apparent difficulty in their synthesis. The difficulty faced in the formation of nitramines from their corresponding amines is linked to several hurdles. Firstly, most nitration reactions occur in acidic media which quickly forms an unreactive ammonium salt. A second difficulty lies in the instability of primary aliphatic nitramines under acidic conditions [1, 2] (Figure 1). Alternative routes are generally multistep approaches which are often long and inefficient.

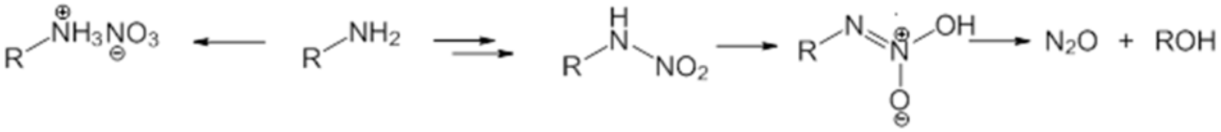


Figure 1: Difficulties observed in direct nitration of amines [3].

2 Results and Discussion

2.1 Traditional Mixed Acid Nitration

The traditional route to primary nitramines has been via the nitramide analogue. For example in the case of methylnitramine [3], a dangerous and unstable explosive, the nitramide is prepared by nitration of any one of a number of amines activated to nitration with either neat nitric acid or mixed acid (Figure 2). The nitramide is then isolated by hydrolysis in aqueous base or by ammonolysis followed by work-up in acid.

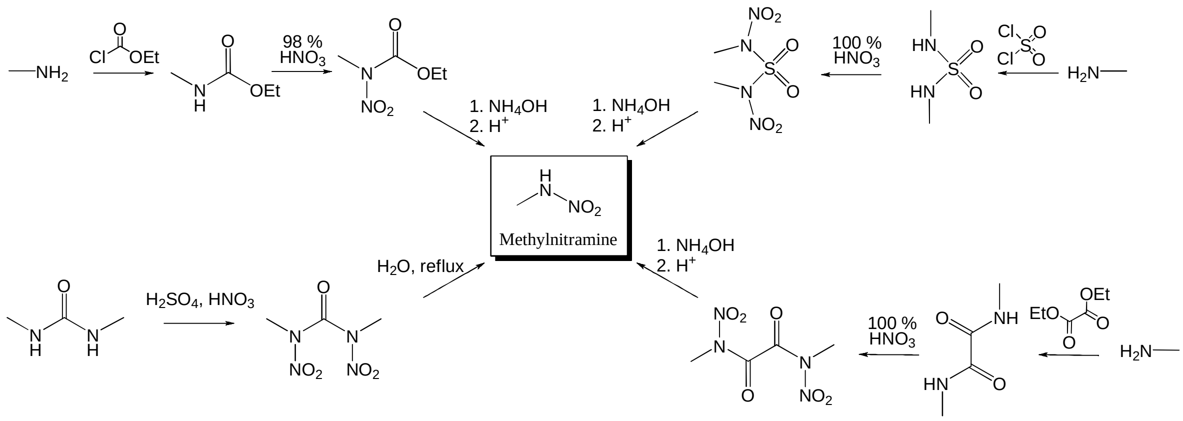


Figure 2: Syntheses of methylnitramine [3]

This process, which has been used widely for over a century [4-8], is still the commonly used route to form primary nitramines (Figure 3) as shown by Klapötke et al. in their recent paper [9].

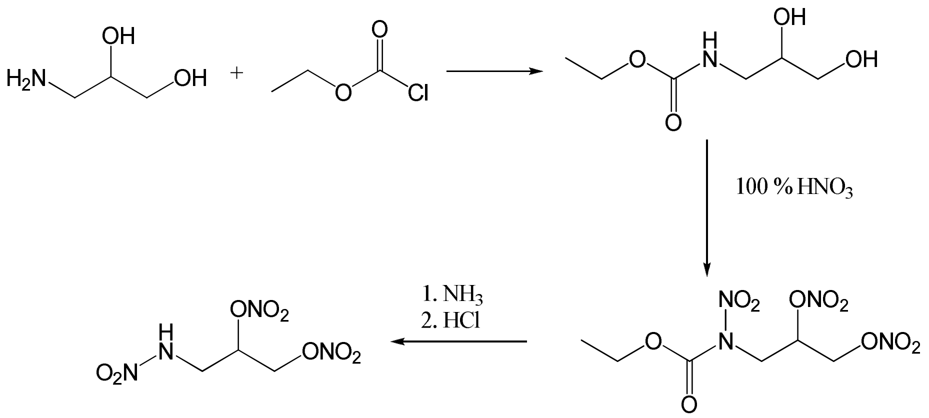


Figure 3: Multistep synthesis of NG-N1.

In the syntheses of aliphatic nitramines there are no direct routes from the amine precursor. This contrasts to the nitration of the amino-functionalized aromatic heterocycles (Figure 4**:** Aromatic nitramine). In these cases the basic nature of the amines is reduced by the delocalization of electrons into the aromatic system and treatment with nitric acid yields the nitramine directly rather than the quaternary ammonium salt [10-13].

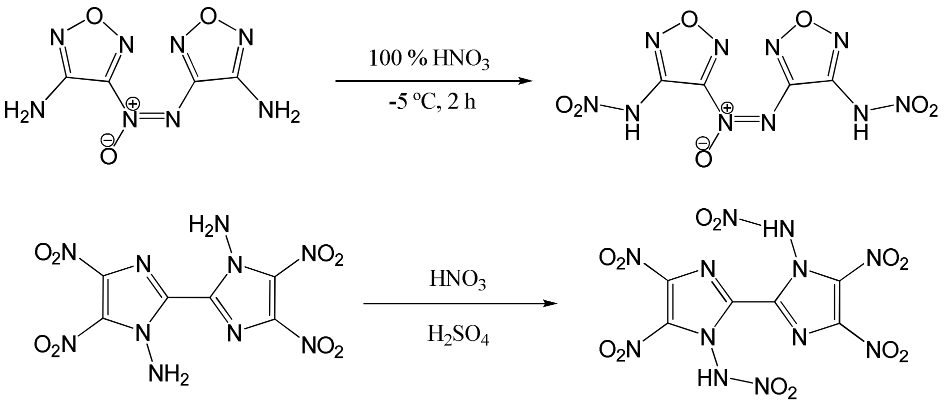


Figure 4: Aromatic nitramine formation

The involvement of the aromatic systems in the nitration of the amine of a 1,2,3-triazole system (Figure 5) is particularly well illustrated by the thermal ellipsoid plot yielded by X-ray crystallography, which clearly shows that the acidic proton of the nitramine resides on the heterocycle and that the structure is stabilized as a zwitterion [13].

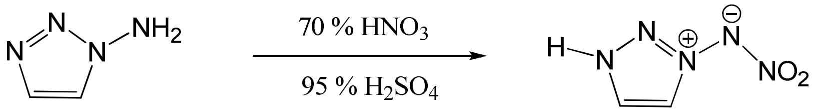


Figure 5: Example of aromatic nitramine

In addition to the nitrations under strong acidic conditions, a number of reagents have been used or developed for nitrations under milder or neutral pH (Figure 6). These are particularly valuable for the direct formation of nitramines from their corresponding amines.

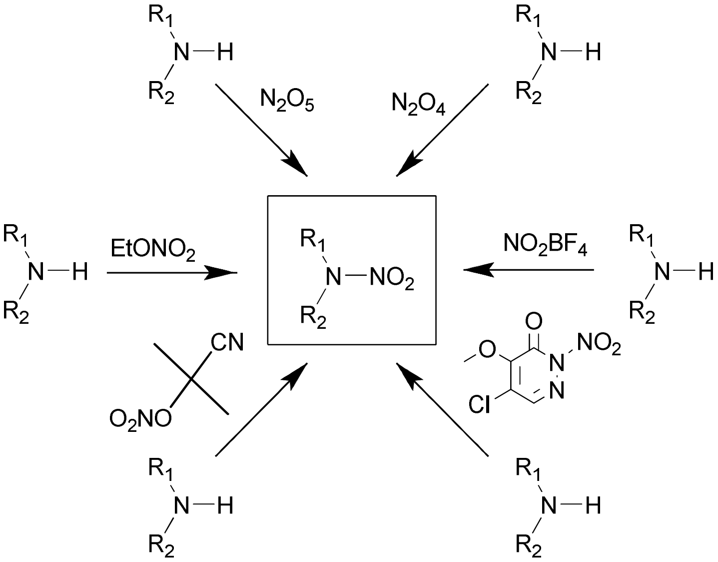
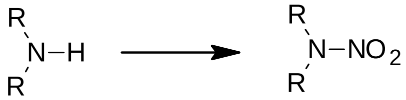


Figure 6: Nitrating agents

2.2 Aprotic Nitration

The use of N_2O_5 as a nitrating agent of aromatic amines is well known but it was Emmons et al. who first reported its use on aliphatic amines (Table 1) [14]. This work was a striking contrast from nitro-transfer reagents (such as cyanohydrin nitrate [15] which will be discussed later) as they highlighted the excellent conversion of hindered secondary amines and cyclic amines to their corresponding nitramines. However, this methodology seemed to be only applicable to the nitration of secondary alkyl amines.

Table 1: Nitramine using N_2O_5



Amine 1	Nitramine (Yield)
Pyrrolidine	91%
Piperidine	64%
Morpholine	91%
Diethylamine	81%
Dipropylamine	84%
Diisopropylamine	91%
Diisobutylamine	97%

The reaction with a primary amine, exemplified with n-octylamine, led almost exclusively to octylnitrate (Figure 7); the authors speculated that the primary nitramine decomposed under the reaction conditions.

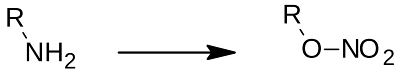
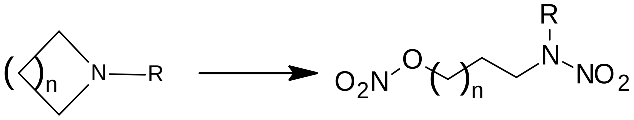


Figure 7: Reaction of N_2O_5 with primary amines

Golding et al. showed that small nitrogen containing rings would ring open to form the corresponding nitramine nitrate ester (Table 2) [16]. This technique was described for N-alkylated azetidines and aziridines, however, larger rings sizes such as N-methylpyrrolidine did not yield the desired nitramine.

Table 2: Reaction of N_2O_5 on cyclic amine



Amine	Product (Yield)
Aziridine	56-82%
Azetidine	41-88%
Pyrrolidine	0%

Millar et al. also described the use of N_2O_5, converting N-silylamine to the nitramine via a nitrodesilylation (Figure 8**:** Amine activation) [17]. This methodology will be described in more detail in a later section.

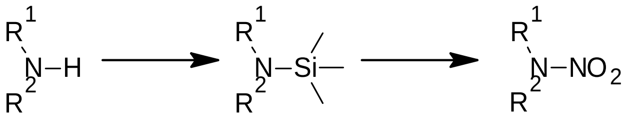
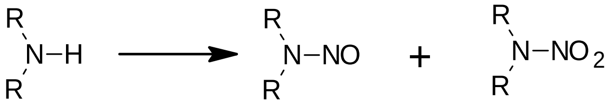


Figure 8: Amine activation

White et al. presented the versatility of N_2O_4 [18], where nitramines and nitrosamines were prepared selectively by careful monitoring of the temperature and the solvent (Table 3).

Table 3: Nitramine using N_2O_4



Amine	Temperature / Solvent	Nitrosamine (Yield)	Nitramine (Yield)
Diethylamine	0°C / DCM	98%	0%
	-80°C / DCM	0%	97%
	-80°C / Ether	39%	59%
Hexylamine	-80°C / DCM	0%	53%
Octanol	*-80°C / DCM*	*93%**	*0%***
Sodium butoxide	*-80°C / DCM*	*26%**	*56%***

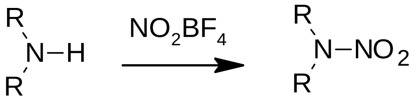
*nitrite isolated; **nitrate ester isolated

It was hypothesised that the basicity of the nucleophile also played a role in the chemoselectivity of the reaction. This was particularly highlighted when alcohol and alkoxides were used.

Several nitronium salts have also been used (BF_4^-, PF_6^-, SbF_6^-, AsF_6^-, PtF_6^-, ClO_4^- *etc.*) [19] NO_2BF_4 and NO_2PF_6 being probably the most common due to their ease of handling and their commercial availability.

These salts were first described by Hantzsch [20], their structure was revised by Goddard [21] and preparations presented by Woolf [22]. However, their first use in nitrations was described on aromatic systems and alcohols by Olah et al. [23, 24]. Olah presented a number of salts, their stability and ease of use, highlighting the superiority of the BF_4^- salt. Yet, it was Olsen et al. [25] who first reported the use of NO_2BF_4 to form nitramine (Table 4). They presented the conversion of secondary amines in moderate yields while the primary n-butylamine led to the n-butyl nitrate in low yield. Interestingly, the nitration of amides and imides were the least effective while the nitration of ethyl butyl carbamate showed the highest conversion. The authors also highlighted the importance of the solvent, as the nitramines were isolated in DCM but not in MeCN.

Table 4: Nitramine using NO_2BF_4



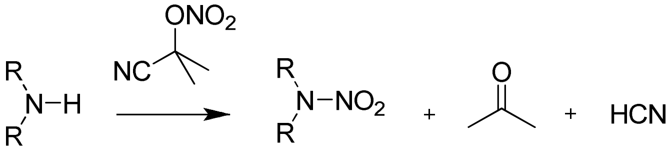
Amine	Product (Yield)
Di butylamine	54%
Morpholine	72%
Ethyl butyl carbamate	91%
Succinimide	43%
Butyl acetamide	40%
Acetamide	12.5%
Benzamide	52.5%
Picramide	85%

Other nitration reagents involving the transfer of the nitro group have also been exemplified, such as N-nitro imidazole [26] or nitropyridazine reagent [27] and will be discussed in the following section.

2.3 Nitronium Transfer

An alternative approach, particularly useful in the case of amines that are sensitive to acidic conditions, is the use of organic transfer reagents in basic media. Emmons [15] described the formation of both primary and secondary nitramines from the corresponding amines via reaction with cyanohydrin nitrate (Table 5).

Table 5: Cyanohydrin nitrate nitro-transfer

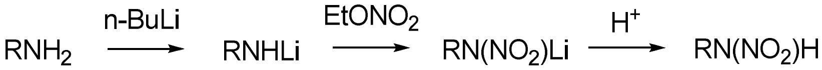


Amine	Product (Yield)
Dimethylamine	76%
Diethylamine	60%
Di-*n*-propylamine	42%
Di-*n*-butylamine	54%
Diisobutylamine	60%
Diisoamylamine	64%
Piperazine	55%
Piperidine	62%
Morpholine	81%
Pyrrolidine	60%
n-Propylamine	50%
n-Butylamine	52%
Isobutylamine	54%
n-Amylamine	55%
Isoamylamine	54%

Although the range of nitramines prepared was fairly broad, it was noted that aromatic amines and aliphatic amines containing branching on the α–carbon were not nitrated under these conditions. It was hypothesised that the lack of reactivity of branched amines was due to steric interactions between substrate and reagent. β-Substitution was not observed to adversely affect reactivity.

Primary aliphatic nitramines may also be prepared via formation of the conjugate base followed by reaction with ethyl nitrate, as described by Winters [28]. The primary amine is deprotonated using butyllithium, and then reacted with a nitronium transfer agent in a one-pot process. Ethyl nitrate was selected as the transfer agent as it was noted that the performance was superior to cyanohydrin nitrate when nitrating sterically hindered amines. Two drawbacks of this procedure are the use of strong base, which limits the species to which the transformation may be applied, and the poor to moderate yields obtained (Table 6).

Table 6: Ethylnitrate nitro-transfer



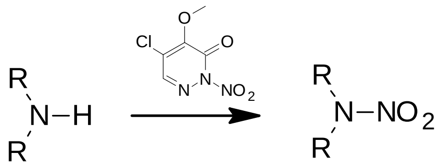
$$RNH_2 \xrightarrow{n\text{-BuLi}} RNHLi \xrightarrow{EtONO_2} RN(NO_2)Li \xrightarrow{H^+} RN(NO_2)H$$

Amine	Product (Yield)
Methylamine	35%
Isopropylamine	58%
n-Butylamine	49%
s-Butylamine	45%
t-Butylamine	37%
n-Decylamine	46%

This approach to nitramines, via the deprotonation of the parent amine, has also been fairly widely reported for the preparation of aryl nitramines. Bamberger [29] used potassium ethoxide and ethyl nitrate, while White [30] introduced the concept of using phenyllithium as the deprotonating agent. A recent example of this methodology appears in Fukuzumi's synthesis of *ortho*-phenylenebis(guanidine) derivatives [31], where butyllithium is used to deprotonate alkylated anilines which are subsequently reacted with *iso*-butylnitrate to afford primary aryl nitramines.

Park et al. presented a new pyridazine nitro-transfer reagent [27] capable of N-nitration of aliphatic secondary amines (Table 7). They presented the preparation and the reactivity of a series of N-nitro pyridazinone.

Table 7: N-nitro pyridazinone nitro-transfer



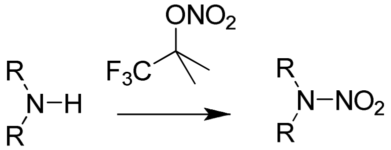
Amine	Product (Yield)
Diethylylamine	90%
Morpholine	92%
Dicyclohexylamine	28%
Homopiperazine	86% (82%)*
3-Pyrroline	82%

*bis nitration when using 2 equivalents of reagent

The reaction with the more hindered dicyclohexylamine yielded 28% of the nitramine analogue and 39% of the corresponding nitrosamine. Interestingly, using 1 or 2 equivalents of the nitrating agent with homopiperazine, led almost exclusively to the mono nitramine (86%) or dinitramine (82%) respectively. However, under the same conditions, aromatic amines, primary amines and amides did not lead to the desired nitramines.

The problem of nitrosamine formation, a common side-reaction in the preparation of secondary nitramines, was tackled by Bottaro [32]. It was demonstrated that the use of 2-(trifluoromethyl)-2-propyl nitrate as a transfer agent afforded secondary nitramines in moderate to excellent yield with no nitrosamine side-products detected (Table 8).

Table 8: 2-(trifluoromethyl)-2-propyl nitrate nitro-transfer



Amine	Product (Yield)
Piperidine	75%
Morpholine	72%
N-benzylmethamine	75%
Pyrrolidine	100%
Diethylamine	58%

An alternative transfer agent described in the same report, 2,2-bis(chloromethyl)propane-1,3-diol dinitrate, was also found to give the desired nitramines under mild conditions, although yields were slightly lower and small amounts of nitrosamines were formed in certain reactions.

2.4 Activation/Protecting Group Chemistry

Nitramines are commonly produced by first protecting or activating the target amine. The use of amide and carbamate protection has already been mentioned in the sections above but these methods have some problems. A prime example is that of the reaction of a secondary amide with nitric acid. This reaction can indeed afford the desired secondary nitramine however a co-produced acyl nitrate is also formed, which may be difficult or dangerous to remove and dispose of. Various alternatives have been designed to avoid these problems.

As mentioned in the previous section, Millar et al. successfully nitrated a variety of secondary amines, secondary cyclic amines and diamines, as well as amides by first forming the silylamine [17, 33]. The substrates are then subjected to a nitrodesilylation, forming the nitramine and nitramide products (Figure 9**:** Tin and silicon activation).

In a similar manner Nielsen et al. performed a nitrodestannylation in order to convert the cyclic secondary diamine 1,3-bis(trimethylstannyl)hexahydropyrimidine to 1,3-dinitrohexyhydropyramidine by reaction with NO_2BF_4 in acetonitrile at 50°C in a yield of 31% [34]. Of course the use of organotin reagents can lead to other problems with toxicity and waste disposal.

Figure 9: Tin and silicon activation

Continuing this theme, Bottaro et al. reported the cleavage of a P-N bond to synthesise N,N-dimethylnitramine from hexamethylphosphoramide (HMPA) with phosphoric acid as a byproduct [35]. The reaction required just nitric acid but did still produce a 12% yield of the known carcinogen N,N-dimethylnitrosamine.

The authors of this paper could find no reports in the literature of nitrodesilylation, nitrodestannylation, or nitrodephosphorylation reactions being performed on primary amines. Nitration of primary amines was achieved by Highsmith and co-workers by activation via chloramine functionality [36]. By reaction of diethylene triamine with sodium hypochlorite the trichloramine was formed, which was activated towards conventional nitration with nitric acid in acetic anhydride. Finally a dechlorination step with sodium hydroxide afforded the diethylene trinitramine with an overall yield of 45% (Figure 10).

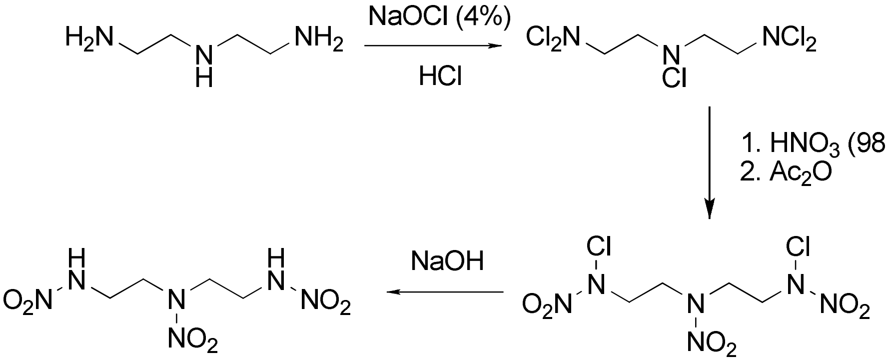


Figure 10: Nitramines from chloramines

3 Conclusions

This review highlights the difficulties encountered when preparing aliphatic nitramines and in particular targeting primary aliphatic nitramines. There are no reported direct methods to nitrate a primary aliphatic amine and only a small set of conditions described for secondary amines. It would therefore be of great interest to develop a new methodology to fill the knowledge-gap regarding primary nitramine production and thus pave the way for further research into this much neglected family of energetic materials.

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McAteer, Daniel

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