Nitration reactions in the manufacture of pharmaceutical intermediates

Nitration chemistry provides an excellent tool for accessing complex pharmaceutical molecules.

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The pharmaceutical intermediates sector of the chemical industry uses a diverse range of materials, manufactured to exacting standards, in order to provide the selection of life-enhancing and life-saving medicines that constitute the weapons in the armoury of the modern physician. This short article covers the area of nitration chemistry, as used in the manufacture of pharmaceutical intermediates; this is a broad area and so we can only skim the surface of this fascinating and diverse subject.

Overview of nitration

Nitration is simply defined as the introduction of the nitro functionality, -NO₂, into a molecule - most frequently by the electrophilic action of the nitronium ion (NO₂⁺). This type of nitration chemistry has been practised on an industrial scale for over 100 years in the manufacture of a variety of materials ranging from explosives, through dyestuffs, to active pharmaceutical compounds.

The formation of the nitronium ion occurs by disproportionation of nitric acid, which is promoted by the presence of a second (strong) acid. Most commonly, this second acid is either sulphuric acid or oleum, but may include organic acids such as acetic acid (Table 1). The selection of an appropriate second acid to promote the formation of the nitronium ion will be influenced by factors including the power needed to bring about the nitration, the sensitivity of the substrate molecule to strong (mineral) acids and - of course - health, safety and environmental factors.

Ionic nitration, though, is not limited to the electrophilic mechanism; nucleophilic substitution is well known, although it has not been well studied in comparison with its electrophilic cousin.

Nitronium ion source | Acid catalyst(s)
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Nitric acid | Sulphuric acid, Oleum, (Poly)phosphoric acid, Perchloric acid, Acetic acid, Hydrogen halides, Lewis acids, Sulphonic acids, Lewis acids, Trifluoroacetic acid.
Metal nitrates | Sulphuric acid, Lewis acids.
Alkyl nitrates | Sulphuric acid, Lewis acids.
Acyl nitrates | Lewis acids.
Oxides of nitrogen | Sulphuric acid, Lewis acids.
Nitrosyl halides | Lewis acids.

Table 1. Some examples of electrophilic nitrating agents (1).
practised nucleophilic nitrations is the substitution of a halide by sodium nitrite.

Whilst nitration chemistry relies to a large extent on well practised chemistry, it would be unfair to suggest that there have been no developments in this area. The use of exotic nitration species including dinitrogen pentoxide ($\text{N}_2\text{O}_5$), together with nitration using lanthanide triflate catalysts and nitronium tetrafluoroborate, and transfer nitrations using alkyl nitrates have been documented. There has also been research into nitration by radical species derived from the oxides of nitrogen.

The most common form of nitration is that of C-nitration, particularly of aromatic systems. However, it is also possible to carry out derivatisations of oxygen and nitrogen functionalities using nitration chemistry. For example, the formation of nitrate esters is well documented, and nitroglycerine (used as a vasodilator in the treatment of acute angina, as well as being one of the most famous explosives in the world) is manufactured by the nitration of glycerine using a traditional mixed acid reaction. N-nitration is usually followed by rearrangement of the nitramine intermediate formed by the reaction of the amine substrate with the nitronium ion.

There are several excellent texts available (1,2,3) to which the reader is referred for a more in-depth review of nitration chemistry.

**Processing**

The specialised fine chemicals industry makes much use of traditional batch reactors for the manufacture of most of its products (4). Batch reactors find use in virtually every form of chemistry practised on an industrial scale in the world today - including nitration. However, no matter how efficient the process, the flow of materials through a batch reactor is always disrupted by non-productive activities such as heating, cooling, transfer, isolations and so on. The productive time spent in a batch reactor may, in fact, be as little as one-third of the total plant residence time, representing a significant under-utilisation of what may be a very costly set of equipment.

However, where the volume of product is large or the process is particularly energetic, batch reactors may not be well suited to manufacture - incurring relatively high costs, particularly in terms of the labour associated with operation of even the most advanced plants. At a time when there is a real drive towards cost-effective plant operation, it comes as no surprise to learn that there is an increasing tendency to consider continuous manufacturing. Continuously operated plants are not new, and have been utilised within the petrochemical industry for many years. With the advantages that continuous processing can afford,
it is starting to attract the attention of the fine chemicals industry.

Within the chemical industry, the need for the safe operation of plant is paramount. This is especially so in the case of nitrination chemistry, where prolonged residence time can lead to undesirable poly-nitrination, competitive reactions (for example, O- versus C- versus N-nitrination) and so on, and here continuous processing can afford some distinct advantages over batch manufacture.

Consider as an example the manufacture of nitroglycerine, which has been successfully practised by the exchem group for about 100 years. The safety of the process has been radically improved by moving from a batch - to a continuous process. The glycerine and the nitrating acid are mixed by a venturi effect, and the reaction mixture is then allowed to flow along a tube to completion. In this fashion, the residence time for the reaction can be cut by a factor of 50 or more, whilst maintaining a lower inventory within the reactor system. In particular, the use of a tubular reactor, as described above, avoids the use of stirrers and reduces the risk of detonation as a result of shear on the reaction mixture.

Another example is provided by the nitration of amides and esters, both of which are particularly prone to competitive side reactions, when the conditions used to bring about the nitration employ acidic media. In particular for esters - such as those of 5-nitro-isophthalic acid (used as intermediates in the manufacture of X-ray contrast media) - the heat liberated during the reaction can lead to competitive hydrolysis of the ester function. This can liberate an alcohol (typically short-chained), which may in turn be prone to O-nitrination to form nitrate esters, which are well documented as explosives. Also of potential concern is the formation of NO\textsubscript{x} from the nitrating medium; this becomes more problematic as the temperature of the reaction mixture is increased. With its ability to act as an oxidant, generation of NO\textsubscript{x} can accelerate thermal runaway, with the uncontrollable evolution of permanent gas as, for example, nitrogen and oxides of carbon. Indeed, it is this evolution of permanent gas that makes nitrated compounds so useful as high explosives.

According to legislation enacted by the British Parliament in 1990, the chemical industry is mandated to employ the Best Available Techniques (BAT) for processes to eliminate waste wherever possible. Where this cannot be achieved, recycling of materials to minimise waste-streams becomes a viable strategy. It is also necessary to give due consideration to the use of energy in the process, and optimisation of the same. Improvement in energy utilisation per unit of production is made possible by the use of a series of heat-exchange systems. In general terms, waste-streams from a
continuous process are easily recycled within the process, and this can lead to significantly less waste-intensive processes. It is also practical to design a process such that the waste-stream may be re-utilised for a second and even third reaction.

Generally speaking, the inventory of reactants in a continuous process is lower than in its batch reactor analogue. This can present its own advantages in terms of reduced financial risk in the case of a process failure. This effect can be further enhanced by the use of ever more readily available automated monitoring techniques; these may be employed to improve the process by the use of control loops and so on. Data from such automated monitoring systems may be used to form the basis of statistical process control, potentially making supply chain management more cost-effective.

Of particular concern to the pharmaceutical industry is the requirement for a consistent (im)purity profile for a given product. Batch operations are variable by virtue of the number of changeable factors that routinely occur in most chemical processes, and problems can stem from many potential sources. Continuous processes - by their very nature - exist in a steady state and this can present significant advantages in the area of product profile.

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Nitration as a tool in synthesis

The nitro functionality, introduced via the act of nitration, represents an extremely versatile substituent in itself. Consider as examples the molecules 4-nitrobenzyl alcohol, p-NBA [(1) in Scheme 1] and 4-methyl-3-nitroaniline [(2) in Scheme 2].

p-NBA has two functionalities present, both of which allow for the preparation of a wide variety of 1,4-disubstituted molecules by modification of the molecule along the oxidation chain (5). Relatively simple, practical chemistry will allow for the benzylic alcohol to be oxidised to its benzaldehyde (used in the manufacture of chloramphenicol) or further to its corresponding benzoic acid. Simple reduction of the nitro- function will afford the corresponding aminobenzyl alcohol, from which a starburst of products can be envisaged; these may be accessed by, for example, alkylation, acylation, diazotisation and so on. Partial reduction of the nitro- function can afford the corresponding hydroxylamine, from which again a variety of products can be envisaged. By altering the conditions used for reduction, or by including a carbonyl compound in the reaction mixture, reductive alkylation can be brought about. This affords an alkylaminobenzyl alcohol, which could in turn be modified to form heterocyclic compounds.
such as substituted oxindoles and quinolines.

It is, however, as a protecting group that p-NBA finds its greatest use in pharmaceutical manufacture. The carbapenem class of antibacterials, exemplified by imipenem and meropenem, requires the use of a protecting group in the synthetic pathway to the product itself. These products, which act by interfering with cell-wall growth, find use in the treatment of bacterial infections where the infective agent has built up a partial resistance to conventional antibiotics of the penicillin class.

The carbapenem antibacterials are based on the thienamycin structure \((3)\) in Figure 1\) and it is in the preparation of this that p-NBA finds its most significant use as a protecting group. Reaction of the p-NBA with, for example, diketene will produce the corresponding 4-nitrobenzyl aceto-acetate, which is reacted onward to form the thienamycin or its nitrated derivative \((4)\) in Figure 1\).

These 4-nitrobenzyl esters are reported to be more stable to acidic hydrolyses (by for example HBr) than their 4-chlorobenzyl analogues and, as such, have been recommended for terminal carboxylic acid protection in solid-phase peptide synthesis.

![Figure 1. The structures of Thienamycin (3) and p-Nitrobenzyl Thienamycin (4).](image)
Cleavage of the 4-nitrobenzyl esters to be found in penicillin, carbapenem and cephalosporin syntheses is easily achieved under mild conditions by using sodium sulphide in aqueous acetone at around 0°C, in reported yields of 75-85%. Electrolytic cleavage at a potential of -1.2 V has been reported in the literature, as has a reductive cleavage.

Of course, the use of p-NBA as a protecting group is not limited to the masking of carboxylic acids as their esters; the use of alcohols to form acetals and ketals is well documented, and the use of nitrobenzyl ethers in synthesis has also been reported. Use may also be made of the 4-nitrobenzyl group to protect amines as their 4-nitrobenzylidene derivatives, in order to impart resistance to attack from a variety of reagents.

4-Nitrocinnamyl carbamate (Noc), which may be derived from p-NBA, has been developed as a protecting group for amino acids (6), with the advantage that the Noc functionality is not isomerised by the action of Wilkinson’s catalyst [chlorotris(triphenylphosphine)rhodium]. This allows for the selective removal of the allylic ester, presenting some synthetic advantages.

As an intermediate, 4-methyl-3-nitroaniline (2) may be employed to introduce additional functionality using, for example, diazotisation chemistry, halogenation, phosphoramidate chemistry and so on, as shown in Scheme 2.

Within the pharmaceutical sector, 4-methyl-3-
nitroaniline may be derivatised to afford sulphonamides (7), and cyclic ketones such as thioxanthone dioxides (8) of interest in the treatment of various allergies.

Nitration provides a convenient route by which nitrogenous functionality can be introduced; this is particularly useful for the preparation of heterocyclic compounds, such as imidazoles, indazoles and indoles. Products from these classes find uses in a variety of pharmaceutical products including NO synthase inhibitors, vasodilators, beta-blockers and so on. Here, for example, 4-methyl-3-nitroaniline has also found ready application in the preparation of a variety of 6-substituted indoles (9) [Scheme 3].

The modification of the nitro function need not be limited to its inclusion in the final molecule, and considerable use has been made of the ability of the nitrite ion (NO$^-$_2) to act as a leaving group. This is exemplified by preparation of the anti-ulcer proton pump inhibitor, omeprazole (10). In the preparation of this molecule, the nitro group is displaced from the pyridine-N-oxide to form the methoxy compound [(5) and (6) as shown in Scheme 4].

Another interesting transformation relying on “elimination” of the nitro group is the Nef reaction (11). Here, nitroalkanes may be converted into carbonyl compounds via the formation of the aci form, and subsequent hydrolysis of the resulting carbon-nitrogen double bond. Variations of the Nef reaction give access to molecules such as acetals, ketal and hydroxamic acids (12).

Conclusion

The area of nitration chemistry is huge, providing an excellent tool for accessing complex molecules - by both acting as a method of introducing nitrogenous functionality and providing a good leaving group for onward transformation (13).

References


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