Nitroalkane chemistry

Nitroalkanes offer a strategic tool for cost reduction in pharmaceutical syntheses.

David Green and Thomas Johnson, Angus Chemical Company

The pharmaceutical industry is moving through a period of great change. Not only are the global players consolidating, but companies are fundamentally changing the way they approach the market. "Big Pharma" has learned to focus on what it does best - that is, the discovery and marketing of new products. All other endeavours are increasingly being out-sourced to a growing number of support laboratories and pharmaceutical intermediate manufacturers. In fact, pharmaceutical companies that once took a vested interest in undertaking their own manufacturing are now taking the view that internal production is actually alien to their key business interests.

As the pharmaceutical industry concentrates internally upon drug discovery, it is making much greater demands upon its suppliers for a broad range of complex intermediates and bulk actives. Successful intermediate suppliers have developed the ability rapidly to scale up a broad range of traditional processes, as well as innovative new chemistries - and all of this while holding the line on manufacturing costs.

Nitroalkane chemistry offers the pharmaceutical industry a strategic tool for success in this endeavour. Nitroalkanes - specifically nitromethane, nitroethane, 1-nitropropane and 2-nitropropane - are extremely versatile, inexpensive synthetic feedstocks (Figure 1). Although some highly successful pharmaceuticals - such as ranitidine, methyldopa and ethambutol - are based on nitroalkane chemistry, the full potential of this novel class of compounds has yet to be realised.

The usefulness of nitroalkanes lies in their ability to provide new, cost-effective synthetic routes to existing compounds, as well as highly efficient routes to new compounds. While they are most recognised as a means of adding nitro or amino functionality to a molecule, their exceptional versatility offers synthetic chemists numerous other benefits. Nitroalkane chemistry can, for instance, provide a vehicle for connecting two halves of a complex molecule. It can also provide synthetic chemists with a set of unique tools to place a variety of functional groups at specific locations on a given compound. This nitroalkane chemistry is actually quite different from what many people are familiar with when they think of nitro compounds.

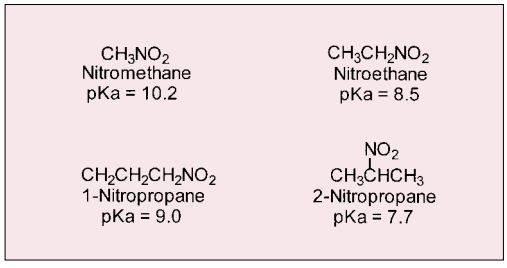


Figure 1. Commercially available nitroalkanes.

… the full potential of this novel class of compounds has yet to be realised

Acidity/reactivity

One unique feature of nitroalkanes is their high degree of acidity (1). As seen in Figure 2, a nitro group is greater than ten orders of magnitude more effective than a single carbonyl or cyano group, and 10-1,000 times more effective than *two* cyano or ester groups in stabilising a carbanion. This trait is explained by the structure of the nitronate anion,

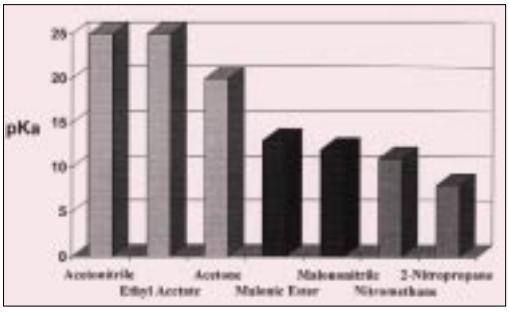


Figure 2. Acidity of carbon acids. Comparison of activating groups.

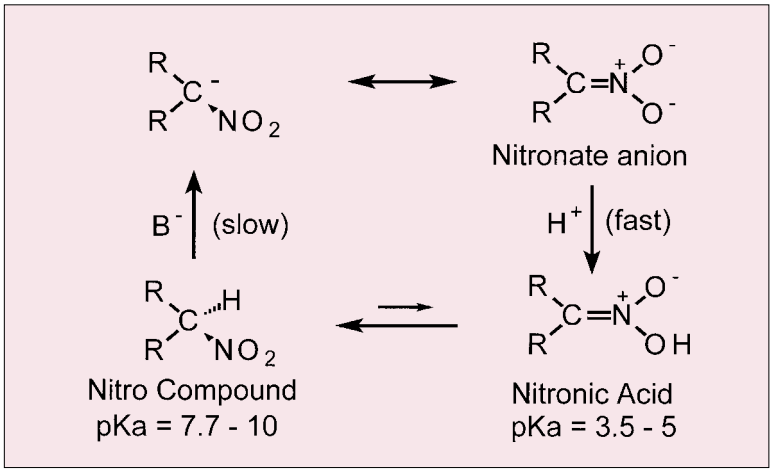


Figure 3. Acidity characteristics of nitroalkanes

unusually slow. Once nearly full deprotonation is achieved, the nitronate anion flattens into a classic sp^2 hybridised system, allowing the negative charge to be delocalised out into the nitro group. The result of this late transition state during deprotonation is that base-catalysed nitroalkane reactions often exhibit induction periods of many seconds, or even minutes, before a significant rate is obtained.

The high acidity of nitroalkanes provides two significant advantages in the design of synthetic routes. First, nitroalkane carbanion chemistry can be performed with mild bases (for example, amines, fluoride ion, carbonates and hydroxide ion). This allows chemistry to be performed in the presence of epimerisable centres or highly labile functional groups. Often, these reactions can also be conducted in environmentally friendly solvents, such as water or alcohols. A second advantage of

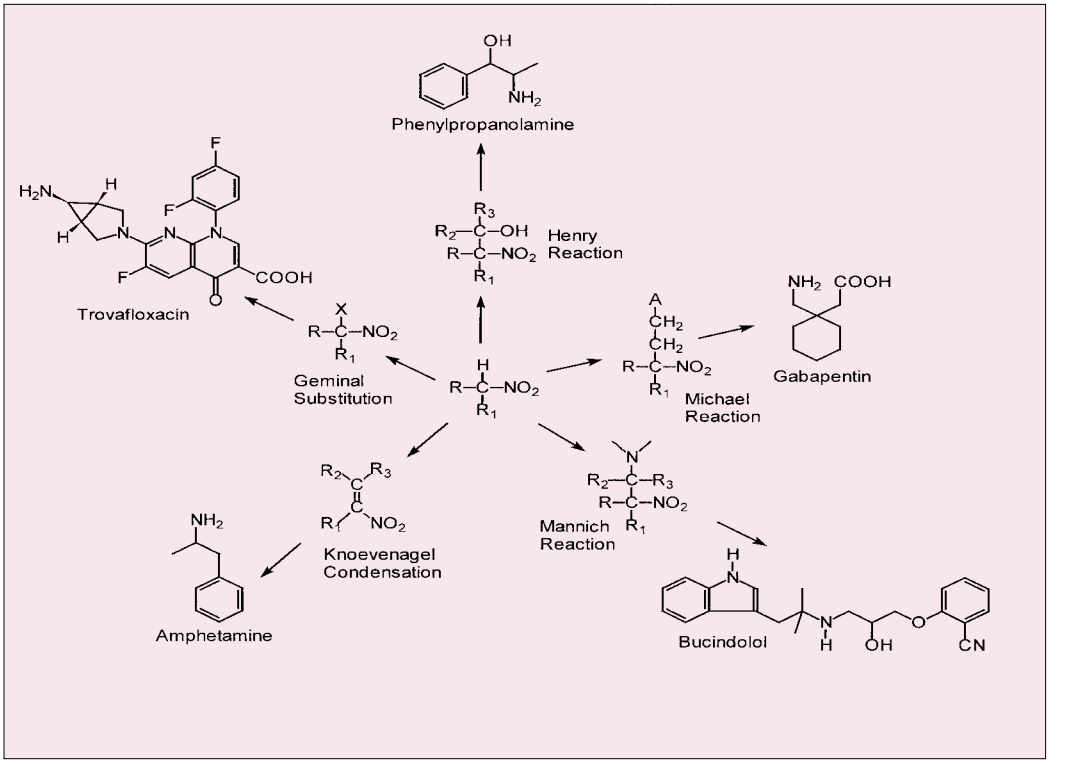


Figure 4. Nitroalkanes in pharmaceutical applications.

where the negative charge is delocalised onto a pair of oxygen atoms, analagous to the structure of a carboxylate anion. Figure 3, depicting the charge delocalisation and acidity characteristics of nitroalkanes, helps explain another unusual feature of nitroalkane acidity - namely, slow deprotonation. The large degree of charge build-up on carbon during deprotonation, aided essentially by induction effects alone, causes this step to be

nitroalkane acidity is molecular economy. For example, bis-activated carbon acids, such as malonic esters, are often used when high acidity is required in a synthetic route. This usually necessitates a decarboxylation step subsequent to the desired bond-forming reaction. Unfortunately, this adds an extra processing step and discards a portion of the product molecule. With the mono-activated nitroalkanes, the advantage of acidity is achieved without the need for decarboxylation or removal of an activating group, resulting in greater molecular economy.

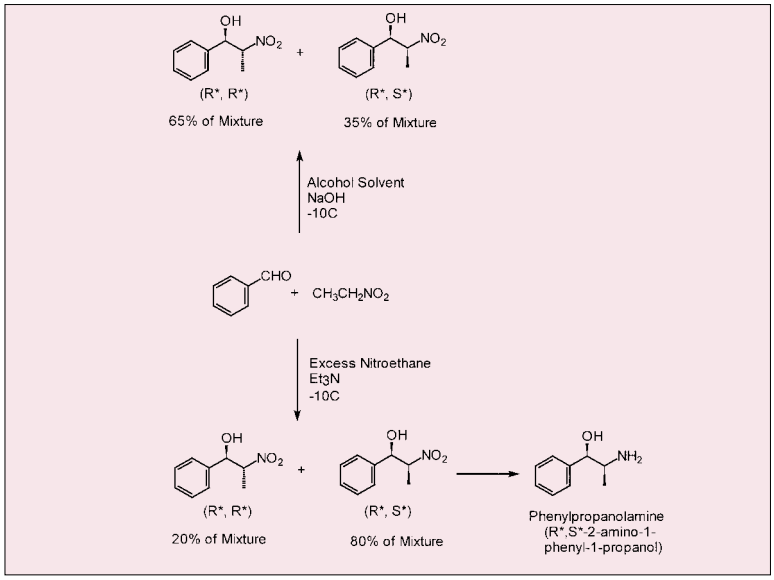


Figure 5. Control of phenylpropanolamine diastereoselectivity.

functional moiety. Brief descriptions of the most common carbon bond forming reactions of the nitroalkanes - the Henry reaction, Michael reaction and Mannich reaction - are given below.

Henry reaction The Henry reaction, also known as the nitroaldol reaction, has been known for over 100 years (2). This is a mild base-catalysed reaction of nitroalkanes with aldehydes or ketones to yield 1,2-nitroalcohols. Because this reaction is equilibrium controlled, it is very useful for most aldehydes but requires equilibrium displacement to obtain useful yields for highly hindered aldehydes or ketones. This can often be achieved by the use of a stoichiometric amount of base, as the more

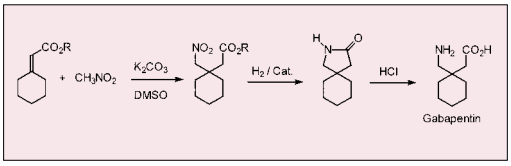


Figure 7. Nitromethane based synthesis of gabapentin.

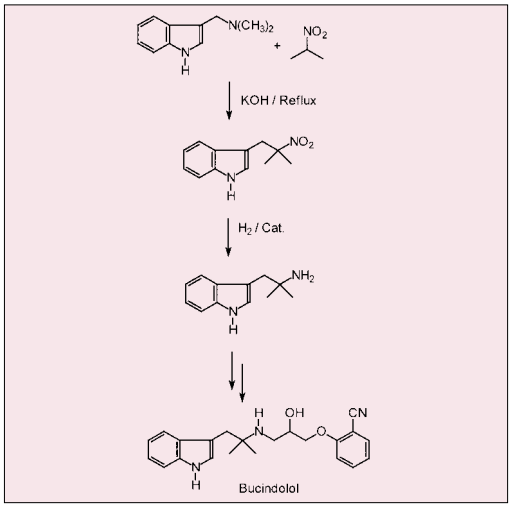


Figure 6. Michael adduct cyclisation products.

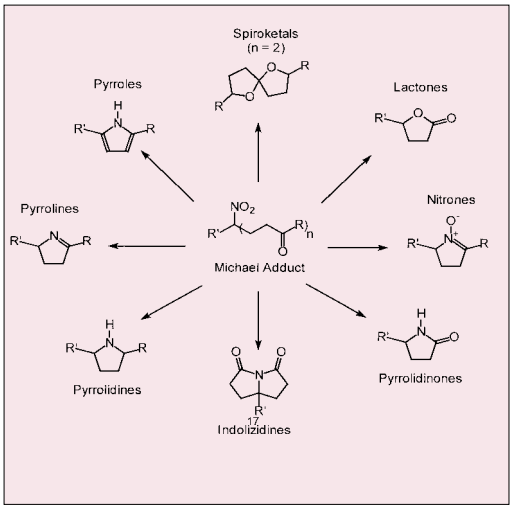


Figure 8. Nitroalkane route to bucindolol. A vinylogous Mannich reaction.

Carbon-carbon bond forming reactions

Nitroalkanes undergo a wide variety of carbon-carbon bond forming reactions. A collection of several commercially relevant examples can be seen in Figure 4. Addition reactions yielding geminally substituted products, as well as 1,2 and 1,4 substituted products, are known. Thus, the commercial availability of only four nitroalkanes as feedstocks is not a limiting factor as essentially any acyclic nitro compound, including nitrocyclohexanes, is readily available from these four "basics". Often, the nitroalkanes are used as coupling agents, connecting two or more molecular "wings", followed by transformation of the nitro group into another highly substituted product is more acidic than is the starting nitroalkane (another unusual feature of nitroalkane acidity).

The Henry reaction was the original route used for the manufacture of phenylpropanolamine, a widely-used vasoconstrictor found in many cold and allergy medications. This preparation required the separation of two diastereomers formed in equilibrium concentrations that did not favour the correct isomer. A recent patent from the Amvac Chemical Corporation, however, gives an improved procedure by which the Henry reaction can be performed under kinetic control to

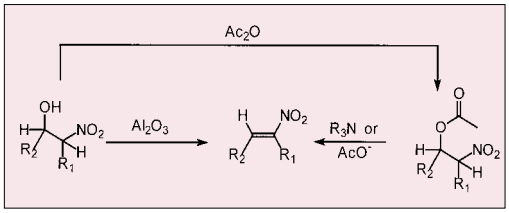


Figure 9. Formation of nitroalkenes.

selectively prepare the desired diastereomer of phenylpropanolamine (3). The effect of kinetic versus thermodynamic control of the Henry reaction is seen in Figure 5. Angus Chemical Company practices the Henry reaction on a large scale in the production of nitroalcohols (and aminoalcohols) from each of the four basic nitroalkanes in combination with formaldehyde.

Michael reaction The Michael addition of nitroalkanes to electron-deficient alkenes follows the normal regiochemistry for 1,4-conjugate additions. The only unusual aspect of the chemistry is the mild conditions required - a catalytic amount of fluoride ion is often the base of choice (4). The 1,4-difunctional products are ideally suited for making either nitrogen- or oxygen-containing five membered heterocycles, as seen in Figure 6. Goedecke AG exploited this chemistry to prepare the key spirolactam intermediate for gabapentin, a new anticonvulsant from Parke-Davis, shown in Figure 7 (5). Additions to alkyne derivatives have also been exploited (6).

Mannich reaction The Mannich reaction of nitroalkanes is very useful and provides high yields of 1,2-nitroamines (7). Simply mixing the nitroalkane, an aldehyde and an amine together in water or alcohol with gentle warming forms the products. The use of ammonia or primary amines with a primary nitroalkane leads to good yields of either hexahydropyrimidines or 1,3-oxazines depending on the reagent stoichiometry. In an extension of this chemistry, Krieghbaum and Comer published a route to bucindolol using gramine as the Mannich base precursor and 2-nitropropane as the nucleophile (8). This example, demonstrating the utility of nitroalkanes for coupling two large molecular fragments, is seen in Figure 8.

Nitroalkenes

As seen in Figure 9, dehydration of the Henry reaction products, 1,2-nitroalcohols, leads to the formation of nitroalkenes (9). This dehydration may be carried out *in situ,* without isolating the intermediate nitroalcohol, or in a subsequent step. Typical dehydrating agents - such as

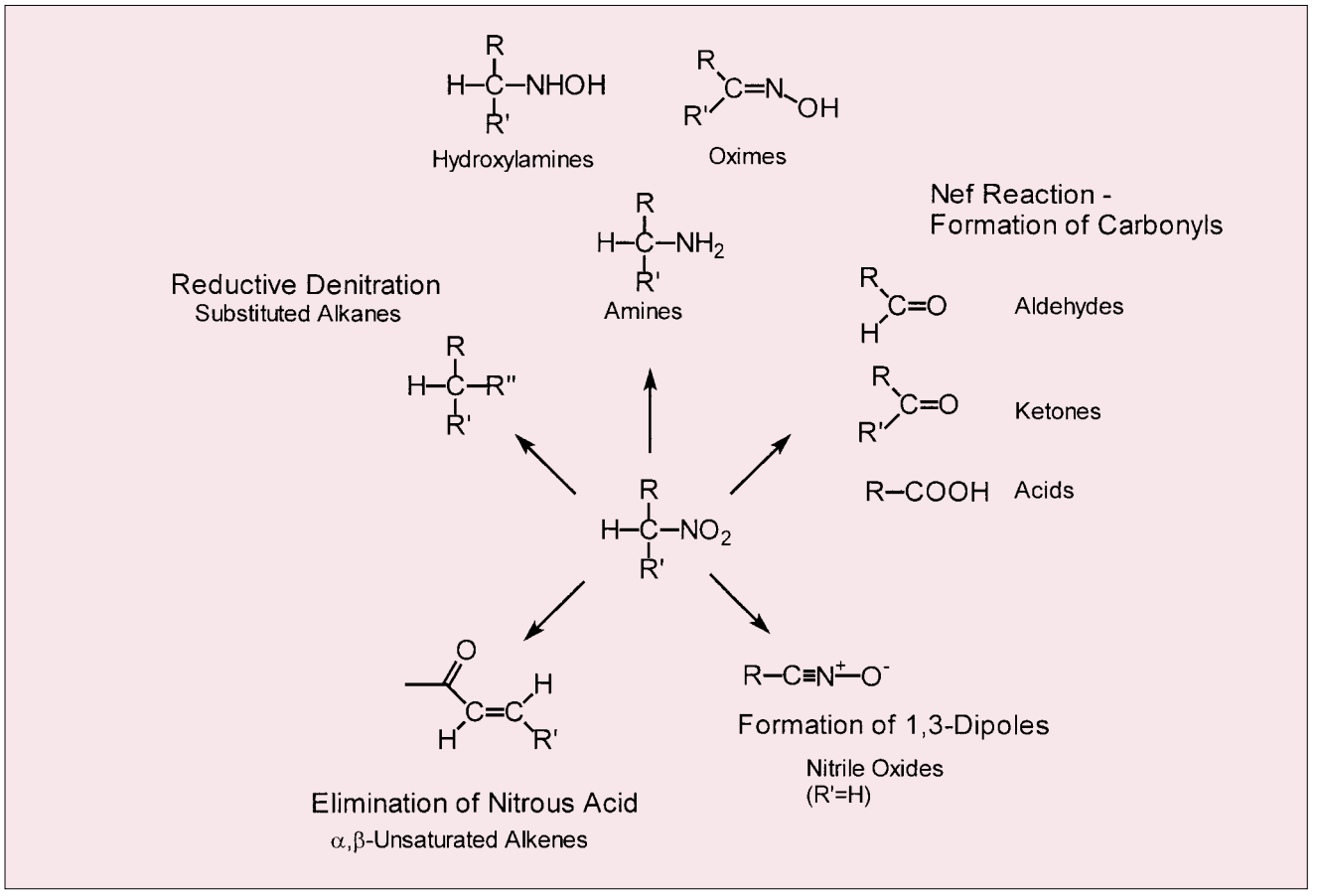


Figure 10. Transformations of the nitro group.

Other bond-forming reactions involving nitroalkanes … are alkylations, acylations and geminal substitution reactions

dicyclohexylcarbodiimide and acid anhydrides - are quite effective. Alternatively, due to the relatively high reactivity of low molecular weight nitroalkenes, a precursor molecule, such as the acetate ester of a nitroalcohol, may be used to generate the nitroalkene *in situ*. Treatment of the nitroesters with mild bases - for example, acetate salts - induces elimination of acetic acid to form the nitroalkene in a controlled fashion.

Nitroalkenes undergo reactions typical of electron deficient alkenes. Michael additions of nitroalkenes with salts of alcohols or thiols provide nitro-(thio)ethers in good yields (10). Hydroxylamines have also been used as nucleophiles with nitroalkenes yielding 1,2-diamines after reduction (11). Carbon nucleophiles can also be employed - Grignard reagents, organocuprates and even other nitroalkanes have been successfully used to form chain extended products (12, 13, 14).

Nitroalkenes are also capable of undergoing Diels Alder additions in both normal and inverse electron demand scenarios. In the normal Diels Alder reaction, the nitro group is a powerful activator and often allows the reaction to be run under mild conditions, forming nitrocyclohexenes in good yield. Additionally the nitro group controls - over cyano, carbonyl or sulfonyl groups - the regiochemistry of additions to the alkene (15). Conversely, inverse electron demand Diels Alder reactions occur between nitroalkenes and vinyl ethers or enamines forming, initially, cyclic nitronic esters (16, 17). The cyclic esters may then be hydrolysed to provide 1,4-nitroketones or aldehydes, or hydrogenated to provide pyrrolidines. A significant amount of work using the cyclic nitronic esters as 1,3-dipoles for further cycloaddition reactions has also been published (18).

Other bond-forming reactions involving nitroalkanes that have found use in pharmaceutical applications are alkylations, acylations and geminal substitution reactions. While current reviews detailing these chemistries have not been published, a collection of recent examples may be found in the references (19).

Transformations of the nitro group

The ability to transform an aliphatic nitro group into a wide variety of functional moieties provides another key example of the versatility of nitroalkanes. Figure 10 demonstrates a few selected examples where the nitro group has been transformed into groups as diverse as unsubstituted alkanes, amines and carboxylic acids.

The Nef reaction - the conversion of a nitro group into an aldehyde, ketone or carboxylic acid - is the basis for employing nitroalkanes as carbonyl anion synthons. While this reaction has been known for over 100 years, research in the last two decades has transformed the traditionally harsh reaction conditions of the Nef reaction into those mild enough to be useful in complex molecular syntheses (20). A very mild, high yield, nitrite/acetic acid induced conversion of primary nitroalkanes to carboxylic acids has also been described (21).

Dehydrating conditions - typically either an isocyanate or acid anhydride mixed with a catalytic amount of base - can be used to generate nitrile oxides from primary nitroalkanes. Alternatively, silyl nitronates may be formed via O-silylation of a nitronate anion with trimethylsilyl chloride. While both intermediates form the same 1,3-dipolar cycloaddition products with alkenes, the silyl nitronates are inherently less reactive and can offer enhanced selectivity in certain cases (22).

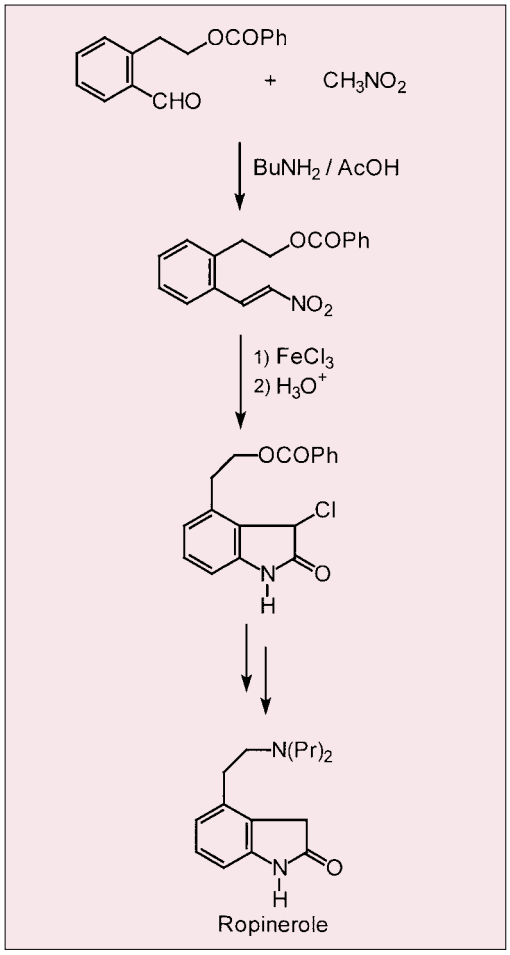


Figure 11. Ropinerole via the Royer reaction.

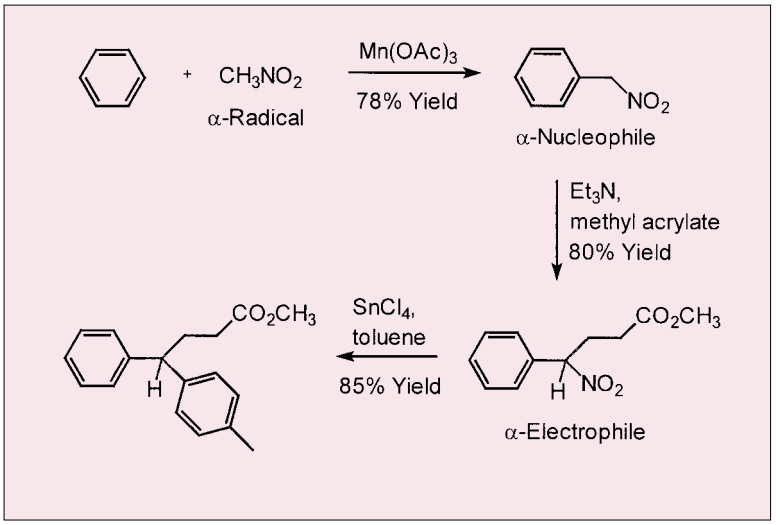


Figure 12. Mechanistic versatility of nitroalkanes.

… this chemistry can provide cost-savings in the synthesis of a vast number of existing drugs, as well as compounds in development

Reduction of the nitro group can lead to the direct generation of oximes, hydroxylamines or amines via catalytic or chemical means (23). Angus Chemical Company makes a wide variety of aminoalcohols via catalytic reduction of nitroalcohols and has recently commercialised isopropylhydroxylamine (IPHA).

The nitro group may be eliminated from an organic backbone via either radical or ionic mechanisms. The use of tributyltin hydride with AIBN or thiolate anions can be used to reductively replace a nitro group with a hydrogen atom (24, 25). Nitroalkanes bearing an acidic proton beta to the nitro group undergo elimination of the elements of nitrous acid, HONO, to form alkenes under basic conditions (26). Both palladium catalysts and tin tetrachloride have been used with allylic nitroalkanes to generate allyl cations that were subsequently alkylated with typical reagents (27, 28).

The Royer reaction is a little known transformation of aromatic nitroalkenes. Treatment of β-nitrostyrene derivatives with anhydrous ferric chloride followed by an acidic hydrolysis provides a facile route to 3-chlorooxindoles. As seen in Figure 11, SmithKline Beecham has utilised this methodology in their highly efficient commercial synthesis of ropinerole (29).

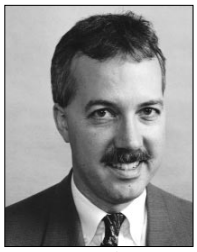
Mechanistic flexibility

As a powerful example of how nitroalkanes can be used as molecular coupling agents utilising radical, anionic and cationic mechanisms, the synthesis of methyl-(4-phenyl-4-p-tolyl)-butyrate is shown in Figure 12. An electrophilic nitromethyl radical may be generated from nitromethane using manganese triacetate (30). In the presence of reactive aromatic systems, this intermediate provides an entry into substituted α-nitrotoluenes. In the second reaction, Michael addition of the α-nitrotoluene anion to methyl acrylate leads to methyl-(4-nitro-4-phenyl)-butyrate. Finally, the tin tetrachloride mediated removal of the nitro group as nitrite anion yields a reactive benzylic cation that was used to alkylate toluene (28). Thus as a direct result of the nitro group, in three subsequent reactions, the nitroalkane was used as a radical, an anion and as a cation for coupling three molecular wings to a central carbon atom.

In summary, nitroalkanes demonstrate excellent versatility as an efficient way to achieve carbon skeleton build-up and to add useful functionality to an existing molecule. Angus Chemical Company has identified over two dozen chemical families and literally thousands of specific compounds which can be created from these basic building blocks. The potential benefit to the pharmaceutical industry is enormous, as this chemistry can provide cost-savings in the synthesis of a vast number of existing drugs, as well as compounds in development. More importantly, the versatility of nitroalkane chemistry offers pharmaceutical manufacturers an excellent tool with which to streamline complex synthetic routes, and thus bring highly sophisticated new productss to the market in record time.

Note: To help customers further optimise their processes, Angus offers in-depth product knowledge and handling expertise, as well as educational seminars on the use of "Nitroalkanes as versatile synthetic intermediates". For more information regarding nitroalkanes, contact Angus Chemical Company in the US: Tel (800) 362-2580 (toll-free), Fax (847) 808 3710.

Dr David Green received a bachelors degree from Indiana University in 1982, followed by a PhD in Organic Chemistry from the University of Arizona in 1986. After working in the corporate R&D labs of Allied Signal for ten years, he joined Angus Chemical Company in 1996. As Manager of the Product Development Group, he is responsible for finding and developing new opportunities for nitroalkane-based chemistry. The utility of nitroalkane chemistry in pharmaceutical applications has been the focus of his recent efforts.



Thomas Johnson holds a bachelors degree in Chemistry, as well as a masters in Business Administration. He has held numerous positions in Applications R&D, Technical Service and Business Management over his 20-year career in the specialty chemicals industry. He currently holds the position of Senior Manager, Commercial Development, at Angus Chemical Company, with responsibility for bringing new nitroalkane derivatives to the market.

References

1. a) Lewis E, The Chemistry of Functional Groups, Supplement F, Part 2. Chapter 16, Patai (Ed). b) Guthrie J (1997). J Am Chem Soc, 119, 1151. c) Bernasconi C, Wenzel (1997). J Am Chem Soc, 119, 4008. d) Kingsbury C (1998). J Org Chem, 63, 3838.
2. a) Robertson G (1995). Contemp Org Syn, 5, 357. b) Rosini G (1991). Comprehensive Organic Synthesis, Pergamon, Oxford, Chapter 1.10, "The Henry (Nitroaldol) Reaction".
3. Baxter E, US Patent 5,750,802.
4. Feuer H, Nielsen A (eds) (1990). VCH Publishers Inc, "Nitro Compounds: Recent Advances in Synthesis and Chemistry".
5. Geibel W, Hartenstein J, Hermann W, Witzke J, EP O414274 A2.
6. Anderson D, Hwu J (1990). J Org Chem, 55 (2), 511.
7. Urbanski T (1974). Synthesis, (9) 613.
8. Kreighbaum W, Comer W, US Patent 4,234,595.
9. a) Feuer H, Hirschfeld A (1968). Tetrahedron, 24, 1187. b) Ballini R, Castagnani R (1992). J Org Chem, 57 (7) 2160. c) Bandgar B, Zirange M (1996) SynLett, 149.
10. Hwu J, Wang N (1988). Syn Comm, 18 (1), 21.
11. Imagawa K, Hata E (1996). Chem Lett, 291.
12. Yao C, Chen W (1996). Tetrahedron Lett, 37, 35, 6339.
13. Terang N, Mehta B (1998). Tetrahedron, 54, 12973.
14. Alcantara M, Gomez-Sanchez A (1996). Synthesis, 64.
15. a) Ono N, Kamimura A (1986). J Org Chem, 51, 2139. b) Seebach D, Knochel P (1984). Helv Chim Acta, 67, 261. c) Ono N, Miyake H (1982). J Chem Soc, Chem Commun, 33.
16. Felluga F, Valentin E (1989). Tetrahedron, 45, 17, 5667.
17. Denmark S, Thorarensen A (1996). Chem Rev, 96, 137.
18. Denmark S, Parker D (1997). J Org Chem, 62, 435.
19. For selected alkylation reactions of nitroalkanes, see: a) Sawamura M, Ito Y (1996). J Org Chem, 61, 9090. b) Linker M, Reuter G (1998). J Prak Chem, 340, 63. c) Vanelle P, Terne T (1998). Syn Lett, 1067. d) Roubad C, Vanelle P (1995). Tetrahedron, 51, 35, 9643. For acylations see: e) Pal B, Ram S, US Patent 5,475,138. f) Yuasa Y, Tsuruta J (1998). Syn Comm, 28 (3), 395. g) Quirk J, Carter C, US Patent 4,873,358. For geminal substitution reactions see: h) Prakash G, Olah G (1997). J Org Chem, 62, 1872. i) Hiskey M, Coburn M, US Patent 5,336,784. j) Olah G, Ramaiah P (1993). J Org Chem, 58, 763.
20. a) Sandefur L, World Patent Application, WO 98/55437. b) Seebach D, Colvin E (1979). Chemia 33 (1), 1. c) Hergovich E, Speier G (1996). Chem Lett, 573.
21. Mioskowski C, Matt C (1997). J Org Chem, 62,234.
22. a) Narayanan I, Hassner A (1997). J Org Chem, 62, 485. b) Duffy J, Kurth M (1994). J Org Chem, 59, 3783.
23. For a review on nitroalkane/nitroalkene reductions, see: Croce P (1992). Semin Org Synth, Summer Sch, "A Corbella", 17th, 163.
24. Tormo J, Fu G (1998). J Org Chem, 63, 5296.
25. Kornblum N, Carlson S, Smith R (1978). J Am Chem Soc, 100, 289.
26. a) Ballini R, Rinaldi A (1994). Tetrahedron Lett, 35 (49) 9247. b) Ballini R, Bosica G (1996), Liebigs Ann, 2087.
27. a) Tamura R, Ono N (1991). Synthesis, 423. b) Tamura R, Kai Y (1986). J Org Chem, 51, 4375.
28. Ono N, Yanai T (1986). J Chem Soc, Chem Commun, 1285.
29. Hayler J, Howie S, Giles R, *et al.* (1998). Org Proc Res Develop, (2), 3.
30. Kurz M, Chen T (1978). J Org Chem, 43 (2), 239.