IITB-Monash Research Academy

Indian Institute of Technology Bombay | MONASH University

An Indian-Australian research partnership

Project Title:	**Metal Mediated Synthesis of Nitroalkanes, Nitroolefins and Nitroaromatics**
Project Number	**IMURA0367** *(will be inserted by The Academy)*
Monash Supervisor(s)	Main Supervisor: Dr David W. Lupton Associate Supervisor: NA
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IITB Department:	Department of Chemistry

Research Academy Themes:

Highlight which of the Academy's Theme(s) this project will address?

(*Feel free to nominate more than one. For more information, see www.iitbmonash.org)*

1. Advanced computational engineering, simulation and manufacture
2. Infrastructure Engineering
3. **Clean Energy**
4. Water
5. Nanotechnology
6. Biotechnology and Stem Cell Research

The research problem

Nitro-compounds are ubiquitous in explosive materials, racing fuel, dyes, plastics and pharmaceuticals and. Commonly nitration is done by mixed acid reagent, or with gaseous nitrating agent like dinitrogen pentoxide. Consequently, these methods suffer from both functional group tolerance and regioselectivity. Also due to the harsh reaction condition, these methods are not applicable in large-scale industrial set-up. In this context development of efficient, regioselective and practical methods of nitration by radical reaction is being proposed.

Project aims

The proposed project is mainly based on the development of methods for nitration of aromatic, heteroaromatic compounds and olefins. These methods will utilize economical and environment friendly metal salts as the nitrating agent. By these methods aliphatic, aromatic, heteroaromatic compounds and olefins are expected to undergo nitration in very mild and easy to handle condition. We will also focus on developing a user-friendly procedure for nitroalkane synthesis. We plan to overcome this problem by applying our methodology in two different ways: a) by generating heteroaromatic radicals from boronic acids and carboxylic acids and b) by producing radicals from activated C–H bonds followed by nitration with nitro radical generated in the reaction medium. It is expected that these proposed reactions can be performed in a mild condition without use of strong acids. We intend to concentrate on an appropriate mixture of practical and basic research. We will utilize a combination of mechanistic and fundamental approaches that will correlate synthetic and mechanistic studies. Mechanistic studies will include kinetic isotope effect (KIE), deuterium labeling experiments, DFT calculations, and rate of reaction in terms of Hammett plots, effect of electronic and steric variation on the substrates.

Expected outcomes

The proposed project is expected to find application both in academia and in industry. Also we expect that our protocol will be beneficial in further progress regarding nitration, which in turn will be reflected by cost reduction in developing fuel grade nitroalkanes, pharmaceuticals and related nitro products.

How will the project address the Goals of the above Themes?

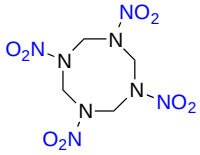
Nitro compounds are well known as fuel and explosives. Nitroalkane compounds (especially nitromethane) are used as fuel in rocket, drag racers. In this context an efficient method for preparing nitro-organic compounds in environment friendly pathway can contribute a major impact in the research of “clean enrgy”.

Nitration is one of the most widely studied reactions in synthetic chemistry as nitro group is present ubiquitously in dyes, plastics, pharmaceuticals and explosive materials (Scheme 1). [1-12] We are interested in developing synthetic methodologies that will provide nitration protocols of aromatic, heteroaromatic compounds and olefinic double bonds in a regioselective and practical way. As our first strategy, we plan to explore the possibility to generate nitro radical from bench stable metal nitrates and radical based oxidizing agents. We will then react these nitro radical with various olefins by following a new approach (*vide infra*-Scheme 2). To impose regioselectivity on aromatic and heteroaromatic compounds, *ipso* substitution strategy will be employed on widely used and commercially available boronic acids and carboxylic acids. A stable radical will be produced from these substrates, which is expected to react with nitro radical generated under the applied condition. As a result, nitro compounds will be produced with complete regioselectivity without formation of any side product. We also plan to synthesize nitroolefins in both stereoselective as well as stereospecific manner. Aliphatic, benzylic and heteroaromatic nitroolefins will also be prepared following our protocols.

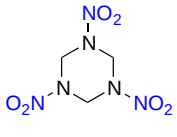
Nitration of heteroaromatics is particularly problematic as their chemistry is significantly different and no efficient method is reported so far.[13-18] We plan to overcome this problem by applying our methodology in two different ways: a) by generating heteroaromatic radicals from boronic acids and carboxylic acids and b) by producing radicals from activated C–H bonds followed by nitration with nitro radical generated in the reaction medium. It is expected that these proposed reactions can be performed in a mild condition without use of strong acids.

We intend to concentrate on an appropriate mixture of practical and basic research. We will utilize a combination of mechanistic and fundamental approaches that will correlate synthetic and mechanistic studies. Mechanistic studies will include kinetic isotope effect (KIE), deuterium labeling experiments, DFT calculations, and rate of reaction in terms of Hammett plots, effect of electronic and steric variation on the substrates.

Scheme 1. Nitro group containing explosive materials

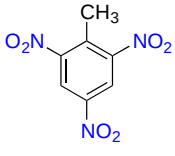


HMX



RDX

FOX-7



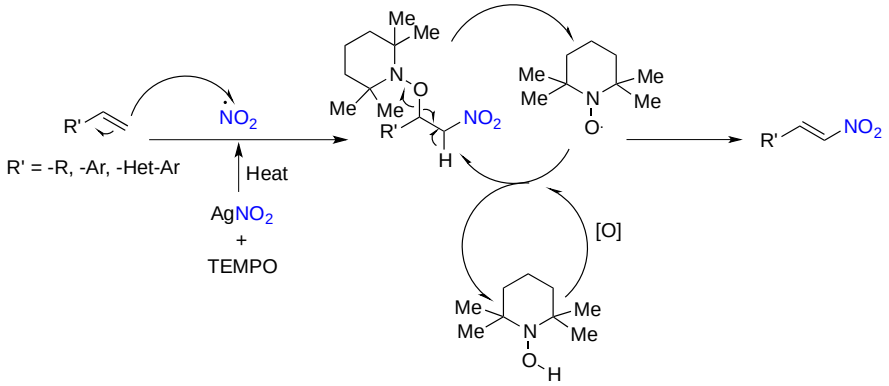
TNT

Nitroolefins are building blocks for generating molecules of biological and pharmaceutical relevance.[1-3,11] They are used in different carbon-carbon bond forming reactions like Michael reaction,[19-22] cycloaddition reactions[4,5,23-26], Morita-Baylis-Hillman reaction[27,28] and for the generation of oximes,[29] hydroxylamines, nitroalkanes,[30] aliphatic amines and nitroso compounds.[4,5] Nitroolefins are conventionally synthesized by Henry reaction[6,31] which relies upon base mediated condensation of an aldehyde or ketone with a

nitroalkane. However, synthesis of nitroolefin via incorporation of a nitro group directly into the olefin by the replacement of a hydrogen atom is a powerful and preferred class of reaction.[32-40] In this context, regio– and stereoselective nitration of olefin, if successful, would provide an opportunity to install nitro functionalities at a late stage.[41] Such a strategy will reduce the problems related to an early stage nitration that changes the electronic properties of the substrate and also require careful selection of reagents to keep the nitro group intact in subsequent steps.

Despite progresses in the discovery of catalytic methods for olefin nitration,[32-40] nitroolefin synthesis is eluded by severe limitations. Most importantly nitration of olefins almost invariably formed undesirable mixture of *E*/*Z* isomers. In addition, prior methods either employ harsh or complex reaction condition and/or suffer from poor substrate scope. Further, nitration of heterocyclic olefins and olefins in complex settings has not been explored. One of the approaches to solve these problems lies in discovering a nitration protocol that is highly reactive, yet selective by distinguishing subtle steric and electronic differences between olefins and is general enough for a broad range of olefins (Scheme 2).

Scheme 2. Proposed catalytic pathway for nitroolefin synthesis from olefins



Recently, we reported an *ipso*-nitration strategy in which nitro radical is generated from bench stable nitrate salt.[42] Following this concept, we envisioned that if an olefin is reacted under this condition, nitro radical would generate a carbon centered radical which can be further oxidized to give the corresponding nitroolefin (Scheme 2). This carbon centered radical is expected to form at the more substituted (or benzylic position) thereby determining regioselectivity of the reaction solely in terms of stability of the radical. We further predicted that if an exogenous radical, *e.g.* 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)[43-46] could intercept the carbon-centered radical; anti-elimination would result in stereoselective nitration of olefin. We propose to develop an efficient and user-friendly reaction condition by using silver nitrite ($AgNO_2$) in combination with TEMPO to effect highly selective nitration of olefins (Scheme 1). Site of nitration may be predicted in complex settings with multiple olefins on the basis of electronic and steric environment of the olefin.

References

(1) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms (Organic Nitro Chemistry)*; Wiley-Interscience; 1 edition (October 2, 1989).
(2) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751.
(3) Bui, T.; Syed, S.; Barbas, C. F. *J. Am. Chem. Soc.* **2009**, *131*, 8758.
(4) March, J. *Advanced Organic Chemistry*; 3rd ed.; John Wiley & Sons: New York, 1985.
(5) Larock, R. C. *Comprehensive Organic Transformaions*; VCH: New York, 1989.
(6) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press, 2005.
(7) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA.
(8) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*; 2nd ed.; Pergamon: New York, 2000.
(9) Agrawal, J. P.; Hodgson, R. *Organic Chemistry of Explosives*; 1st ed., Wiley, 2007.
(10) Haines, A. H. *Methods for the Oxidation of Organic Compounds: Alcohols, Alcohol Derivatives, Alkyl Halides, Nitroalkanes, Alkyl Azides, Carbonyl Compounds, Hydrox (Best synthetic methods)* Academic Pr, December 1988.
(11) Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. A. *Nitroalkenes: Conjugated Nitro Compounds*; John Wiley & Sons; 1 edition (August 1994).
(12) Ono, N. *The Nitro Group in Organic Synthesis*, 2001.
(13) Salzbrunn, S.; Simon, J.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **2000**, 1485.
(14) Prakash, G. K. S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2004**, *6*, 2205.
(15) Saito, S.; Koizumi, Y. *Tetrahedron Lett.* **2005**, *46*, 4715.
(16) Wu, X. F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun.* **2011**, *47*, 12462.
(17) Yang, H. J.; Li, Y.; Jiang, M.; Wang, J. M.; Fu, H. *Chem. Eur. J.* **2011**, *17*, 5652.
(18) Prakash, G. K. S.; Mathew, T. *Angew. Chem. Int. Ed.* **2010**, 1726.
(19) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.
(20) Huang, H. B.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170.
(21) Tripathi, C. B.; Kayal, S.; Mukherjee, S. *Org. Lett.* **2012**, *14*, 3296.
(22) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583.
(23) Albrecht, L.; Dickmeiss, G.; Acosta, F. C.; Rodriguez-Escrich, C.; Davis, R. L.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543.
(24) Liu, Y. K.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212.

(25) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338.
(26) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.
(27) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447.
(28) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2012**, *14*, 4580.
(29) Corma, A.; Serna, P.; Garcia, H. *J. Am. Chem. Soc.* **2007**, *129*, 6358.
(30) Martin, N. J. A.; Ozores, L.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 8976.
(31) Fioravanti, S.; Pellacani, L.; Tardella, P. A.; Vergari, M. C. *Org. Lett.* **2008**, *10*, 1449.
(32) Tinsley, S. W. *J. Org. Chem.* **1961**, *26*, 4723.
(33) Corey, E. J.; Estreicher, H. *J. Am. Chem. Soc.* **1978**, *100*, 6294.
(34) Sy, W. W.; By, A. W. *Tetrahedron Lett.* **1985**, *26*, 1193.
(35) Campos, P. J.; Garcia, B.; Rodriguez, M. A. *Tetrahedron Lett.* **2000**, *41*, 979.
(36) Jovel, I.; Prateeptongkum, S.; Jackstell, R.; Vogl, N.; Weckbecker, C.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2493.
(37) Mukaiyama, T.; Hata, E.; Yamada, T. *Chem. Lett.* **1995**, 505.
(38) Suzuki, H.; Mori, T. *J. Org. Chem.* **1997**, *62*, 6498.
(39) Kancharla, P. K.; Reddy, Y. S.; Dharuman, S.; Vankar, Y. D. *J. Org. Chem.* **2011**, *76*, 5832.
(40) Taniguchi, T.; Fujii, T.; Ishibashi, H. *J. Org. Chem.* **2010**, *75*, 8126.
(41) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199.
(42) Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maiti, D. *Org. Lett.* **2012**, *14*, 1736.
(43) Vogler, T.; Studer, A. *Synthesis-Stuttgart* **2008**, 1979.
(44) Tebben, L.; Studer, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 5034.
(45) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901.
(46) He, Z. H.; Kirchberg, S.; Frohlich, R.; Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 3699.

Capabilities and Degrees Required

Degree Requirement:	BSc: 1st class in Chemistry as Major (Hons.) subject. MSc: 70% marks (or CPI 8.0) in Chemistry (Hons.)
CSIR/UGC clearance:	Students with valid CSIR/UGC rank (research).
Research Experience:	Minimum 1 year experience (including MSc project)

Students having prior experience in working with nitro compounds will be preferred.