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Stereoselective Nitration of Olefins with ^{t}BuONO and TEMPO: Direct Access to Nitroolefins under Metal-free Conditions

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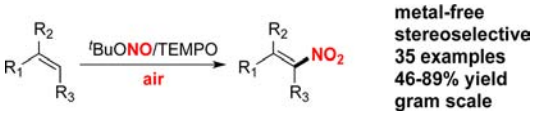
ABSTRACT



Nitroolefins are essential elements for both synthetic chemistry and medicinal research. Despite significant improvements in nitration of olefin an efficient *metal-free* synthesis remains elusive so far. Herein, we disclose a new set of reagents to access nitroolefins in a single step under metal-free conditions. A wide range of olefins with diverse functionalities has been nitrated in synthetically useful yields. This transformation is operationally simple and exhibits excellent *E*-selectivity. Furthermore, site selective nitration in a complex setup makes this method advantageous.

Nitroolefins are a prominent class of synthetic intermediates, which have found application in the preparation of a wide variety of biorelevant compounds and pharmaceuticals.[1] These are usually synthesized by Henry reaction, involving base mediated condensation of nitroalkanes with aldehydes or ketones followed by subsequent dehydration.[2] An alternative and relatively simple approach relies upon widely available olefins as the starting material, wherein a nitro group directly replaces olefin hydrogen. This convenient and step economical process has drawn significant attention in recent decades. To date, a number of methods have been developed with different metal based and gaseous nitrating agents (Scheme 1).[3] These methods while offering significant improvements in direct nitration of olefins often have several drawbacks. Problematic issues include the tendency to form an undesired mixture of *E*/*Z* isomers,[3a,b] lack of functional group tolerance,[3e,g] and harsh reaction conditions among others.[3d,g] Further, stereoselective nitration of olefins with an easy-to-handle *metal-free* reagent is yet to be developed.

Notably, from a practical aspect, metal-free syntheses[4] are preferred, as the removal of metal contamination can render a process quite expensive.[5] In particular, nitration under metal-free conditions would be of great significance due to its close association with the pharmaceutical industry. Our lab has been involved in developing a

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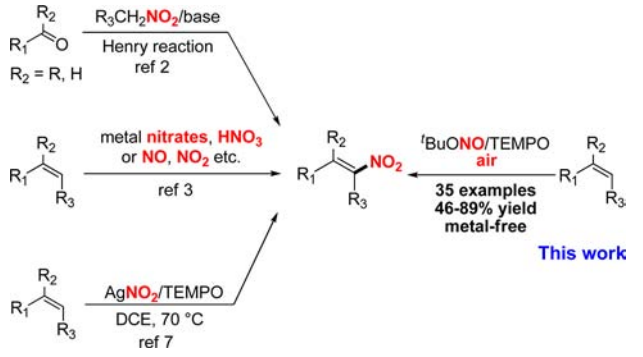
nitration reaction with nitro radicals generated from shelf-stable reagents.[6,7] Recently, we have reported a stereoselective nitration of olefins with $AgNO_2$ and TEMPO (Scheme 1).[7]

Scheme 1. Different Approaches To Synthesize Nitroolefins

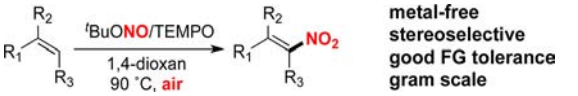


A related set of transformations would be of tremendous interest, if it can be carried out under metal-free conditions without compromising the efficiency of the reaction. Herein, we disclose our findings to report the metal-free nitration of olefins in a stereoselective way with *tert*-butyl nitrite (^{t}BuONO) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (Scheme 2). This newly developed method is operationally simple, functional group tolerant, high yielding, and scalable.

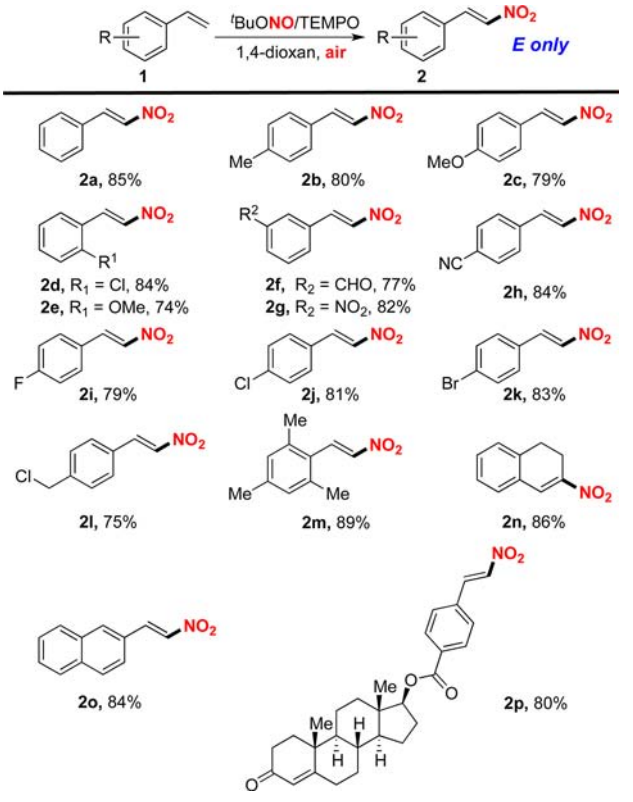
Within the realm of nitrating agents, nitric oxide (NO)[8] can be envisaged as a metal-free alternative for nitration of olefin since it can generate a NO_2 radical in the presence of air.[3b,e,h]

However, difficulties associated with handling of gaseous reagents limited its application in everyday laboratory setup. We hypothesized that a safe and easily storable nonmetallic reagent capable of generating a NO radical would solve the problem. A preliminary set of experiments with *tert*-butyl nitrite in different solvents confirmed the validity of our hypothesis, as nitroolefin was obtained in good yield with only 1 equiv of nitrating agent.[9] By further optimizing the amount of reagents, temperature, concentration, and reaction time, we discovered that 2 equiv of ^{t}BuONO and 0.2−0.4 equiv of TEMPO in 1,4-dioxan at 90 °C could provide the optimal yield of the desired nitro product. Remarkably, no change in outcome was observed while performing the reaction under aerobic conditions in either a sealed vessel or in an open flask.[9]

Scheme 2. Nitration of Olefin under *Metal-free* Conditions



Scheme 3. Nitration of Styrene Derivatives[a]



[a] Isolated yields. Reaction mixture was analyzed by GC-MS/^{1}H NMR to determine the *E*/*Z* ratio. Reaction conditions: Olefin (0.5 mmol, 1 equiv), ^{t}BuONO (2 equiv), TEMPO (0.4 equiv), 90 °C, 1,4-dioxan (2 mL), 12 h.

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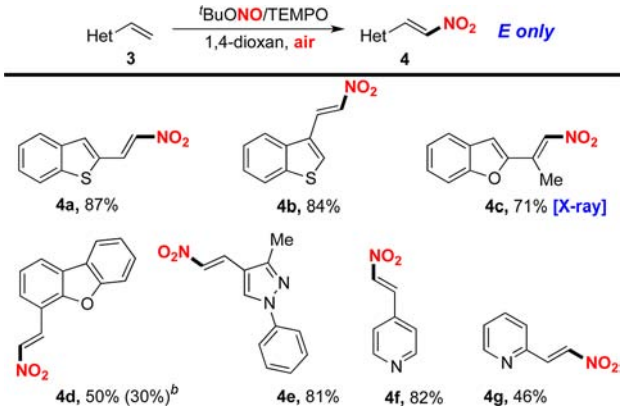
(9) See Supporting Information for detailed description.

With the fully optimized reaction conditions, we explored the scope and limitations of the method. The simplest of the nitroolefins, β-nitrostyrene, was obtained in an excellent 85% isolated yield with complete *E*-selectivity (Scheme 3, **2a**). Substituents regardless of their electronic properties had no effect on the yields of the products (**2b**−**2m**, 74−89%). Even styrenes containing strong electron-withdrawing −CHO, $-NO_2$ and −CN groups reacted wth the electrophilic nitro radical with equal ease (**2f**−**2h**). Presumably the high reactivity of this protocol was responsible for overcoming this electronic constraint. Likewise, different halogen substituted styrenes were also well tolerated in the transformation (**2i**−**2k**, 79−83%). An aromatic $-CH_2Cl$ moiety, which was oxidized to aldehyde in our previous method,[7a] remains intact under the present conditions (**2l**, 75%). A potential telomerase inhibitor 2-(2-nitrovinyl) naphthalene (NVN) was obtained in 84% isolated yield (**2o**).[1f] Sterically challenging *o*-substituted styrene derivatives provided excellent yields under usual conditions (**2d**, **2e**, and **2m**). Although the steric requirement of the reaction center in 1,2-dihydronaphthalene is considerably high due to the presence of a substituent at the β-position, this internal olefin afforded an 86% isolated yield of the desired nitro product (**2n**). Notably, the nitro group cannot be incorporated on such a moiety by a traditional Henry reaction.

Scheme 4. Nitration of Heteroaromatic Olefins[a]

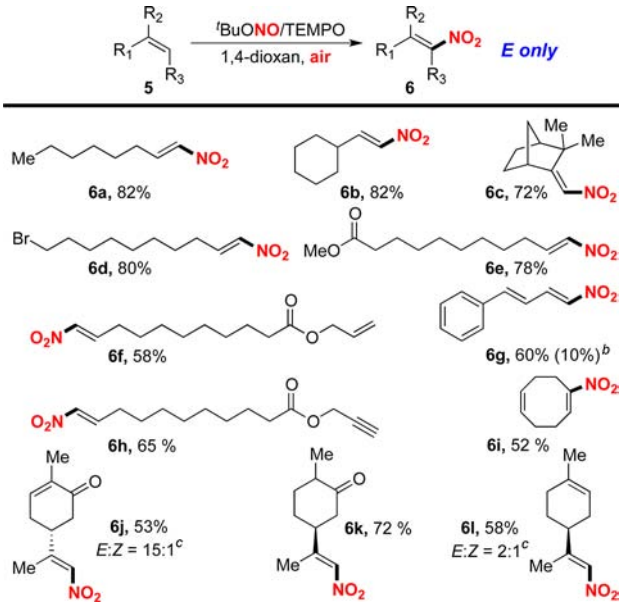


[a] Isolated yields. Reaction conditions: Olefin (0.5 mmol, 1 equiv), ^{t}BuONO (2 equiv), TEMPO (0.4 equiv), 90 °C, 1, 4-dioxan (2 mL), 12 h. [b] Recovered starting material in parentheses; reaction at 70 °C.

The generality of the protocol was further verified with different heteroaryl olefins (Scheme 4). Olefins attached to electron-rich thiophenes and furans were nitrated in excellent yields and selectivities (**4a**−**4d**, 71−87%). The presence of two heteroatoms in pyrazole-based olefin did not alter the expected outcome of the reaction (**4e**, 81%). Even electron-deficient vinyl pyridines, which were found to be problematic under previous reaction conditions,[7a,c] underwent successful nitration in good to excellent yields (**4f** and **4g**).

After evaluating the scope of the reaction with styrene derivatives and heteroaromatic olefins, we applied our optimal conditions on a number of aliphatic olefins of stereoelectronic diversity (Scheme 5). Simple unsubstituted 1-octene produced the nitro product in an excellent 82% isolated yield, and only the *E*-isomer was detected (**6a**). Substituted terminal olefins with distant bromo and ester groups were nitrated with complete regio- and stereoselectivity (**6d** and **6e**). Vinyl cyclohexane exhibited comparable reactivity (**6b**, 82%) with its aromatic counterpart (**2a**, 85%). Further investigation on reactivity revealed that a terminal olefin could be selectively nitrated in the presence of a cyclic internal olefin (**6l**).

Scheme 5. Nitration of Aliphatic Olefins[a]



[a] Isolated yields. In no case was double nitration of olefin observed. Reaction conditions: Olefin (0.5 mmol, 1 equiv), ^{t}BuONO (2 equiv), TEMPO (0.4 equiv), 90 °C, 1,4-dioxan (2 mL), 12 h. [b] Recovered starting material in parentheses. [c] *E*/*Z* ratios were determined by ^{1}H NMR.

Alkenes within close proximity of electron-withdrawing carbonyl groups are presumably deactivated for nitration. Accordingly, nitration of *only* distal olefins was observed in case of (−)-carvone (**6j**) and a substrate derived from 10-undecenoic acid and allyl alcohol (**6f**). Selective nitration of a terminal alkene was observed in the presence of an alkyne (**6h**). Even a conjugated olefin was nitrated in a preparatively useful yield under the metal-free conditions (**6g**). Notably, such an example is unprecedented in literature with other direct nitration methods.[7,10]

Next, we sought to explore the synthetic applicability of the method. With electronically unbiased substrate styrene, the reaction was successfully scaled up to 1 g, without any significant decrease in the efficiency (82% vs 85% in 0.5 mmol scale; Scheme 6).

The gram-scale reaction was performed in the usual laboratory setup with a two-neck round-bottomed flask

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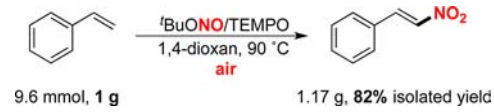
Scheme 6. Synthetic Application: Gram-Scale Reaction



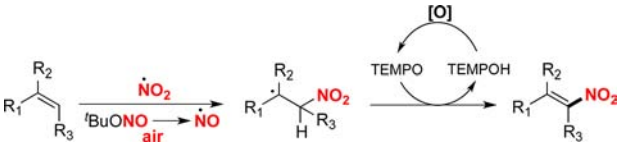
fitted with a reflux condenser.[9] This example clearly demonstrates the practical aspect of this newly developed method.

A single crystal X-ray diffraction study (in addition to analytical studies) of compound **4c** further confirmed the *trans*-geometry of nitroolefin generated by employing this ^{t}BuONO/TEMPO method.[11]

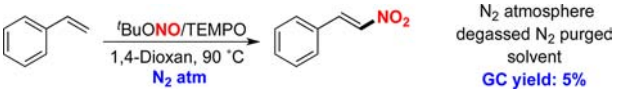
We predicted that this transformation proceeded through a pathway involving the NO_2 radical (Scheme 7).[12]

Indeed, generation of NO from *tert*-butyl nitrite and its conversion to the NO_2 radical under aerobic conditions has strong literature precedent.[12b−f,13] To validate this hypothesis, the reaction was performed under a nitrogen atmosphere with dry and degassed solvent purged with N_2 gas. It was observed that the reaction was inhibited in the absence of air (Scheme 8).[9]

Scheme 7. Plausible Mechanism of Nitration



Scheme 8. Preliminary Mechanistic Investigation



The in situ generated nitro radical can attack olefin to generate a nitroalkane radical intermediate. TEMPO[14] is likely responsible for the radical abstraction of hydrogen from this intermediate. Under aerobic conditions, TEMPOH could be oxidized back to TEMPO to continue the cycle.[15] Even with a reduced TEMPO loading, nitration proceeded successfully albeit in a lower yield (e.g., 40 mol % TEMPO, **2a** 92% vs 5 mol % TEMPO, **2a** 65%). Reactions with radical inhibitors resulted in a considerable decrease in yields of the product.[9] A detailed mechanistic investigation is currently underway in our laboratory.

In summary, we have developed a new set of reagents for stereoselective nitration of olefin under metal-free conditions. A wide array of aromatic, aliphatic, and heteroaromatic olefins was nitrated in excellent yields with commercially available, easy-to-handle nonmetallic reagents. The site of nitration was exclusively determined on the basis of inherent steric and electronic properties of the olefins. The method is operationally simple and can be performed under aerobic conditions in the usual laboratory setup.[16] Excellent *E*-selectivity, a broad substrate scope, and tolerance of a wide variety of functional groups are some noteworthy features of this newly developed method.

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Supporting Information Available. Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(11) Experimental details of the structure determination can be found in the Supporting Information. CCDC-932098 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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(16) A notification on potential hazards regarding usage of ^{t}BuONO: *tert*-butyl nitrite is known to undergo highly exothermic decomposition (−1200 J/g) starting from 110 °C (see Bretherick's Handbook of Reactive Chemical Hazards Vol. II and MSDS of ^{t}BuONO, for additional details). It is advisable to perform the reaction in a heater−stirrer fitted with a temperature sensor so that the temperature of the oil bath does not exceed the aforementioned limit (EKT Hei-Con with MR-Hei Standard, Heidolph was used in our laboratory). After performing the reaction, the screw-capped tube should be opened inside the reaction hood to evacuate the NO_X formed in the reaction. Although we did not take any special care to perform these reactions at 90 °C, careful handling is advisable. Notably, no unfortunate event with ^{t}BuONO was encountered in our laboratory while performing the reaction even in gram scale.