Organic LETTERS

Letter

pubs.acs.org/OrgLett

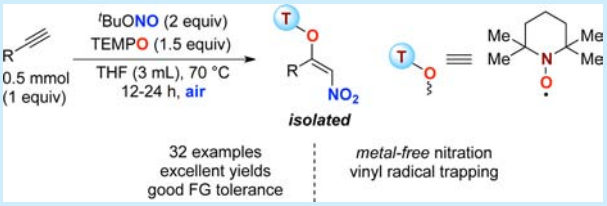
Aerobic Oxynitration of Alkynes with ^{t}BuONO and TEMPO

Uttam Dutta, Soham Maity, Rajesh Kancherla, and Debabrata Maiti*

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

Supporting Information

ABSTRACT: An efficient method for stereoselective nitroaminoxylation of alkyne has been reported. The reaction enjoys a broad substrate scope, good functional group tolerance, and high yields. Synthetically useful α-nitroketones can be accessed through these products in a single step.



Olefins and alkynes are considered as feedstock chemicals in organic chemistry. Synthetic transformations of these unsaturated systems under mild aerobic conditions are of utmost importance. In this context, development of sustainable radical reactions seems to be the key to achieve such a purpose.[1]

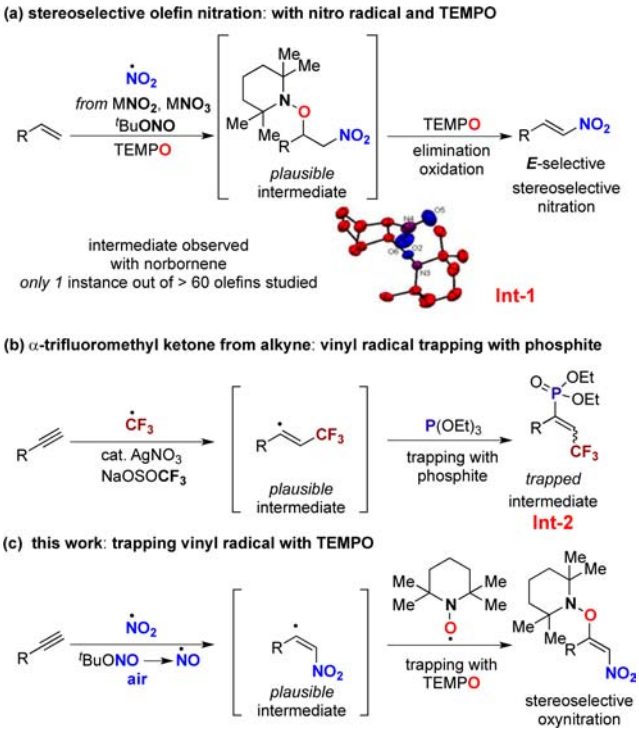
Recently we reported a series of radical based stereoselective nitration of olefins with TEMPO as the oxidizing agent.[2] Nitro radicals derived from shelf-stable precursors are likely to interact with the olefin to generate a nitroalkane radical intermediate.[3] Such transient radical species might be trapped with a 'persistent radical' such as TEMPO (plausible intermediate, Scheme 1a).[4] However, among more than 60 olefins studied, we observed such an intermediate only with a strained olefin, norbornene (**Int-1**, Scheme 1a). In other cases, subsequent oxidation proceeded faster to give olefin nitration in a stereoselective manner.[2a]

This observation was followed by a related development wherein an incipient trifluoromethyl radical[5] from $NaOSOCF_3$ reacted with an alkyne to afford a highly reactive vinyl radical, which in the presence of $P(OEt)_3$ underwent an Arbuzov type[6] reaction to give intermediate 2 (**Int-2**, Scheme 1b).[7] This result showed us that selective functionalization of alkynes could be performed without having the Glaser−Hay homocoupling product.[8] Furthermore, a highly reactive vinyl radical (σ radical) with a lower lifetime could be trapped in the laboratory setup to provide a bis-functionalized product.[9]

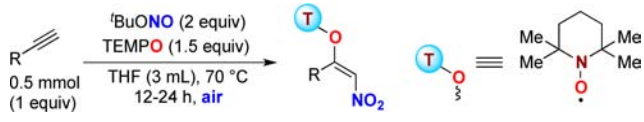
These observations motivated us to explore further, and we decided to apply our previously established *metal-free* nitration conditions on terminal alkynes.[2b,10] Interestingly, ^{t}BuONO provided the desired oxynitro product in considerable synthetic yield. The careful choice of solvents, temperature, and more importantly nitro radical source consisted of optimized reaction conditions where a slight excess of TEMPO provided the nitro product in excellent yields (Scheme 2).

Next, we started to explore the scope and limitation of this reaction. Phenylacetylene gave the product in 90% isolated yield (GC 95%; Scheme 3, **2a**). Differentially substituted alkynes with 4-Me (**2b**, 86%) and 4-F (**2d**, 82%) groups did

Scheme 1. Our Previous Work with Unsaturated Systems and Functional Group Radicals



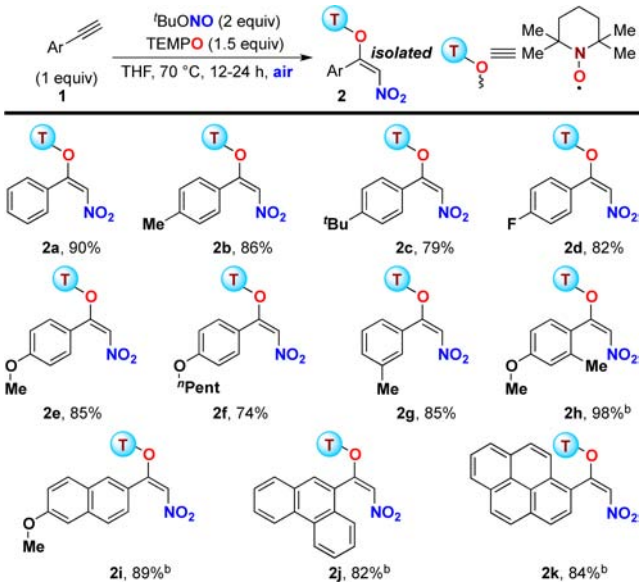
Scheme 2. Oxynitration of Alkynes with ^{t}BuONO and TEMPO



Received: October 15, 2014
Published: November 17, 2014

   dx.doi.org/10.1021/ol503025n | *Org. Lett.* 2014, 16, 6302−6305

Scheme 3. Scope with Aromatic Terminal Alkynes[a]

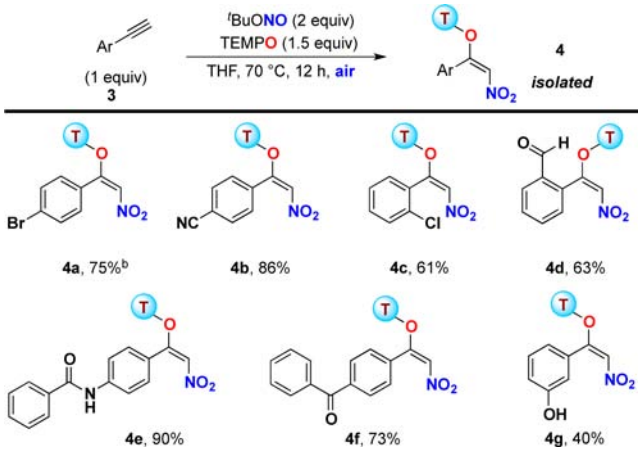


[a]General reaction condition: alkyne (0.5 mmol), tBuONO (1 mmol), TEMPO (0.75 mmol), THF (3 mL), 70 °C, 24 h. [b] 12 h.

not alter the outcome of the reaction. Likewise, a 4-OMe (**2e**, 85%) and a 4-alkoxy group (**2f**, 74%) were well tolerated. *Meta*- and *ortho*- substituted phenylacetylenes also underwent the reaction successfully (**2g** and **2h**). Notably, alkynes based on naphthalene (**2i**, 89%), phenanthrene (**2j**, 82%), and pyrene (**2k**, 84%) gave the desired products in excellent yields.

A number of functionalized terminal alkynes underwent successful oxynitration under standard conditions (Scheme 4).

Scheme 4. Scope with Functionalized Aromatic Terminal Alkynes[a]

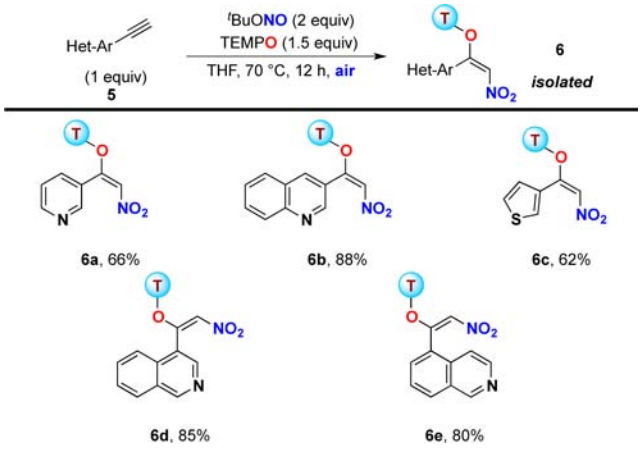


[a]General reaction condition: alkyne (0.5 mmol), tBuONO (1 mmol), TEMPO (0.75 mmol), THF (3 mL). [b] 24 h.

The 4-bromo phenylacetylene gave the product in 75% yield (**4a**). Similarly, a cyano group at the *para*- position was found to be compatible under this tBuONO/TEMPO condition (**4b**, 86%). Sterically congested 2-Cl (**4c**, 61%) and 2-CHO (**4d**, 63%) substituted phenylacetylene provided the desired product. Likewise, a NHCO- (**4e**, 90%) and a keto- (**4f**, 73%) moiety remained intact while undergoing oxynitration. Moreover, a 3-OH group was also tolerated (**4g**, 40%). Note that a minor amount of ring nitration product was detected in this case.[11]

Next, the scope of this reaction was extended to heteroaromatic alkynes, which reacted efficiently in usual conditions (Scheme 5). Quinoline (**6b**) and isoquinoline

Scheme 5. Scope with Heteroaromatic Terminal Alkynes[a]

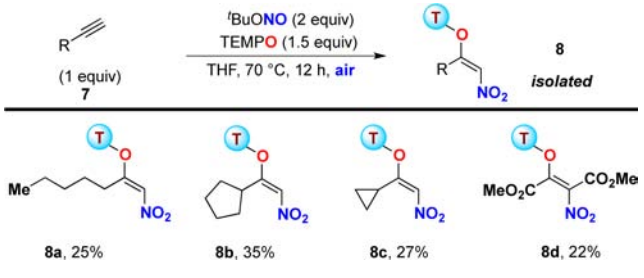


[a]General reaction conditions: alkyne (0.5 mmol), tBuONO (1 mmol), TEMPO (0.75 mmol), THF (3 mL).

derivatives (**6d** and **6e**) were particularly interesting as excellent yields were obtained with the corresponding alkynes (80−88%). With pyridine 3-alkyne, a slight decrease in yield was observed (**6a**, 66%). On the other hand, thiophene gave the desired product in synthetically useful yield (**6c**, 62%).

Aliphatic alkynes are distinct from their aromatic counterpart. Particularly in the radical mechanism, the electronic difference often plays a major role in terms of reactivity. Nevertheless, we investigated a number of such alkynes under the standard conditions (Scheme 6). An aliphatic terminal

Scheme 6. Scope with Aliphatic Terminal Alkynes[a]



[a]General reaction conditions: alkyne (0.5 mmol), tBuONO (1 mmol), TEMPO (0.75 mmol), THF (3 mL).

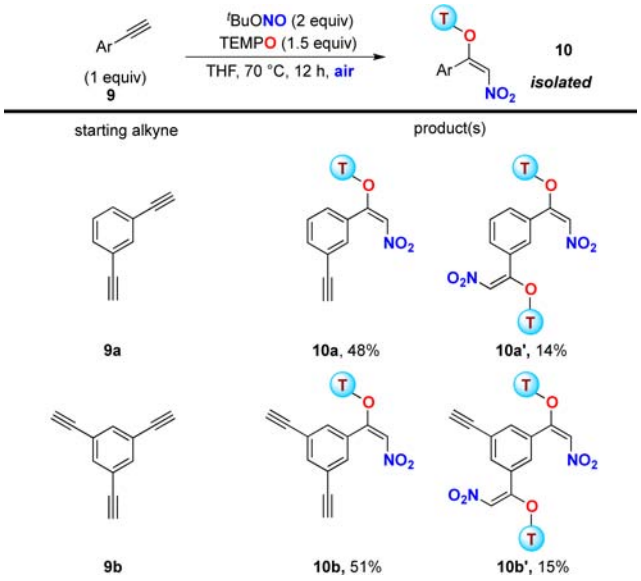
alkyne such as 1-heptyne reacted with the ensuing nitro radical although the reactivity was diminished significantly (**8a**, 25%). This might be attributed to the lack of stabilization of the vinyl radical in the absence of an aromatic system. Interestingly, both cyclopentyl (**8b**, 35%) and cyclopropyl (**8c**, 27%) acetylene gave the usual oxynitro product. The absence of any rearrangement or allene type product indeed suggests that the TEMPO trapping step is fast. Isolation of unreacted TEMPO from the reaction mixture further indicated the lack of undesired reactions in these cases. Notably, internal alkyne

dx.doi.org/10.1021/ol503025n | Org. Lett. 2014, 16, 6302−6305

dimethylacetylene dicarboxylate underwent successful oxynitration under the standard conditions (**8d**).

Another interesting class of substrates is *bis*- and *tris*-alkynes (Scheme 7). Under the usual conditions, preference for

Scheme 7. Substrates with Multiple Triple Bonds[a]

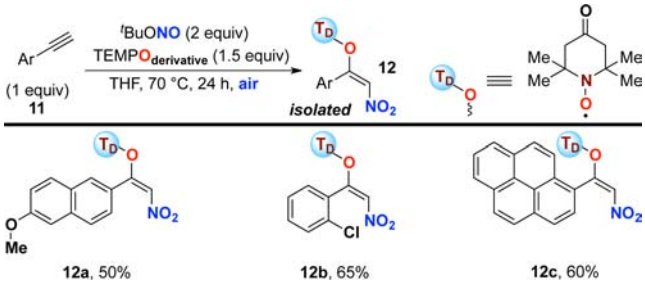


[a]General reaction conditions: alkyne (0.5 mmol), tBuONO (1 mmol), TEMPO (0.75 mmol), THF (3 mL).

monofunctionalization was evident in 1,3-diethynylbenzene and 1,3,5-triethynylbenzene. In the case of *tris*-alkyne only a trace amount of trifunctionalized product was detected.

We next investigated the reaction with 4-oxo TEMPO (Scheme 8). The 6-methoxynaphthalene can be coupled in

Scheme 8. Scope of 4-oxo TEMPO Derivatives[a]



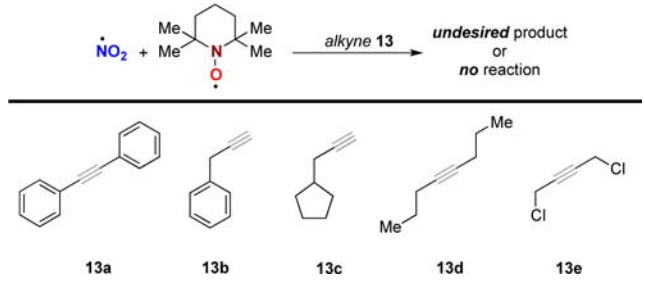
[a]General reaction conditions: alkyne (0.5 mmol), tBuONO (1 mmol), TEMPO derivative (0.75 mmol), THF (3 mL).

50% yield (**12a**). Similarly, 2-chlorophenylacetylene (**12b**, 65%) and 1-ethynylpyrene (**12c**, 60%) provided the desired product in preparatively useful yields.

The present method is not without limitation. We realized that internal alkynes such as diphenyl acetylene (**13a**) and 4-octyne (**13d**) did not produce the expected oxynitration compounds (Scheme 9). In the case of diphenyl acetylene, 20% of benzil was isolated without a trace of the desired nitro compound.

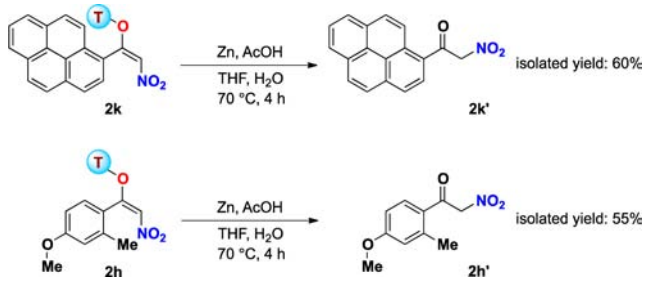
The nitroaminoxylated products in Schemes 3−8 can be easily converted to useful α-nitroketones in high yields and purity in a single step (Scheme 10). These examples further

Scheme 9. Unsuccessful Substrates



signify the synthetic utility of nitroaminoxylated products derived through this present method.

Scheme 10. Synthetic Applications: Synthesis of α-Nitro Ketones



We confirmed the formation of (*E*)-product by X-ray crystallographic characterization of compounds **2i** (CCDC 1029301) and **4b** (CCDC 1029302) (Figure 1). Interestingly,

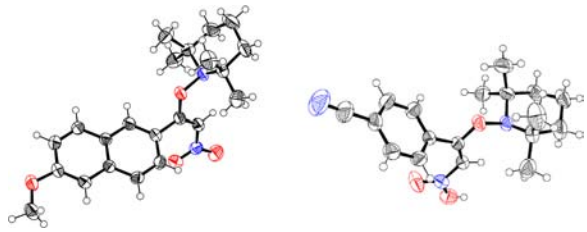


Figure 1. ORTEP diagram of compounds **2i** and **4b**.

these compounds are containing aryl rings perpendicular to the plane of olefin double bonds and hence to the plane of the vinyl radical. This might attribute to the relatively longer lifetime of vinyl radical which is sufficient in this case for trapping with TEMPO to get the anticipated nitroaminoxylated product.

In conclusion, we have developed an efficient method for oxynitration of simple unactivated alkynes. Generation of the nitro radical, reaction with alkyne, and subsequent trapping of the vinyl radical with TEMPO comprise the reaction sequence. This newly developed process is tolerant of a wide variety of functional groups, and excellent yields have been obtained in most of the cases. Even aliphatic alkynes can be functionalized albeit in low yield. Owing to its mild nature and broad substrate scope, this method is expected to find applications in academic and industrial settings.

dx.doi.org/10.1021/ol503025n | Org. Lett. 2014, 16, 6302−6305

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dmaiti@chem.iitb.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This activity is supported by DRDO, India (ARMREB/HEM/2014/159). Financial support received from CSIR (S.M.) and DST under Fast Track Scheme (R.K.) is gratefully acknowledged. We sincerely thank Dr. Saikh M. Mobin (IIT Indore) for insightful discussions.

■ REFERENCES

(1) (a) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433. (b) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. (c) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (d) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593. (e) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (f) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234. (g) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647. (h) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (i) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (j) Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592. (k) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581. (l) Maji, A.; Rana, S.; Akanksha; Maiti, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 2428. (m) Modak, A.; Dutta, U.; Kancherla, R.; Maity, S.; Bhadra, M.; Mobin, S. M.; Maiti, D. *Org. Lett.* **2014**, *16*, 2602. (n) Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maiti, D. *Org. Lett.* **2012**, *14*, 1736.

(2) (a) Maity, S.; Manna, S.; Rana, S.; Naveen, T.; Mallick, A.; Maiti, D. *J. Am. Chem. Soc.* **2013**, *135*, 3355. (b) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384. (c) Naveen, T.; Maity, S.; Sharma, U.; Maiti, D. *J. Org. Chem.* **2013**, *78*, 5949. (d) Gemotes, H. P. L.; Hessel, V.; Noel, T. *Org. Lett.* **2014**, DOI: dx.doi.org/10.1021/ol502910e. (e) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851.

(3) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Synlett* **2014**, *25*, 603.

(4) (a) Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267. (b) Hartmann, M.; Li, Y.; Studer, A. *J. Am. Chem. Soc.* **2012**, *134*, 16516. (c) Li, Y.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8221.

(5) (a) Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9747. (b) Patra, T.; Deb, A.; Manna, S.; Sharma, U.; Maiti, D. *Eur. J. Org. Chem.* **2013**, 5247.

(6) (a) Ganapathy, S.; Sekhar, B. B. V. S.; Cairns, S. M.; Akutagawa, K.; Bentrude, W. G. *J. Am. Chem. Soc.* **1999**, *121*, 2085. (b) Jiao, X. Y.; Bentrude, W. G. *J. Am. Chem. Soc.* **1999**, *121*, 6088. (c) Jiao, X. Y.; Bentrude, W. G. *J. Org. Chem.* **2003**, *68*, 3303.

(7) Maji, A.; Hazra, A.; Maiti, D. *Org. Lett.* **2014**, *16*, 4524.

(8) (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2633. (b) Bedard, A.-C.; Collins, S. K. *J. Am. Chem. Soc.* **2011**, *133*, 19976. (c) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (d) Peng, H.; Xi, Y.; Ronaghi, N.; Dong, B.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2014**, *136*, 13174.

(9) (a) Sargent, G. D.; Browne, M. W. *J. Am. Chem. Soc.* **1967**, *89*, 2788. (b) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. W. *J. Am. Chem. Soc.* **2013**, *135*, 11481.

(10) Manna, S.; Jana, S.; Saboo, T.; Maji, A.; Maiti, D. *Chem. Commun.* **2013**, *49*, 5286.

(11) Koley, D.; Colon, O. C.; Savinov, S. N. *Org. Lett.* **2009**, *11*, 4172.