OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

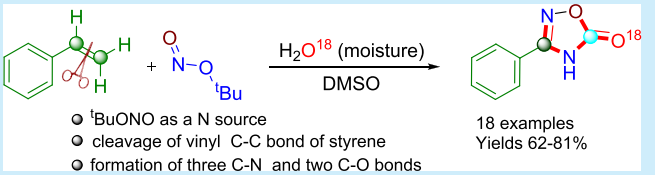
tert-Butyl Nitrite Mediated Synthesis of 1,2,4-Oxadiazol-5(4*H*)-ones from Terminal Aryl Alkenes

Prasenjit Sau, Amitava Rakshit, Tipu Alam, Hemant Kumar Srivastava,* and Bhisma K. Patel*

Department of Chemistry, Indian Institute of Technology Guwahati, North Guwahati 781039, India

Supporting Information

ABSTRACT: *tert*-Butyl nitrite (TBN) mediated synthesis of 3-aryl-1,2,4-oxadiazol-5(4*H*)-ones has been accomplished using terminal aryl alkenes via a biradical reaction intermediate. Three consecutive sp^2 C−H bond functionalizations of styrenes afforded 3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones via the formation of new C═N, C═O, C−O, and two C−N bonds. Both of the N atoms originate from TBN, while the carbonyl oxygen is from the water (moisture) the other oxygen from the N═O part of the TBN.



Nitrogen-containing heterocyclic frameworks are ubiquitous and found in many naturally occurring and synthetic compounds exhibiting remarkable biological and medicinal properties.[1] Among the *N*-containing heterocycles, 1,2,4-oxadiazol-5(4*H*)-one is an integral constituent of many pharmaceutically and biologically active molecules (Figure 1).[2a−d] Thus, considerable attention has been devoted to exploring newer routes and especially one-pot synthetic strategies for these *N*-heterocycles and their derivatives. In this regard, only a few methods are available for the synthesis of 3-phenyl-1,2,4-oxadiazol-5(4*H*)-one.[3] However, all of the existing strategies involve condensation of amidoximes with carboxylic acid esters or carbonyldiimidazole. The amidoximes often need additional reaction steps for their preparation, thus affecting the overall efficacy. Therefore, it is pertinent to design an efficient and reliable strategy for the synthesis of 3-phenyl-1,2,4-oxadiazol-5(4*H*)-one and its derivatives.

The oxidative C−H bond functionalizations are reliable and valuable tools in synthetic organic chemistry, providing sustainable synthetic methodologies with minimum steps and waste.[4] Amidst the significant C−H bond functionalization process, the derivatization of alkenes using *tert*-butyl nitrite is a powerful yet simple route for the creation of *N*-containing heterocycles in a single operation.[5] Recently, Maiti et al. reported a radical intermediate generated in the reaction of styrene with ^{t}BuONO in which the nitroalkane radical was trapped with the help of a scavenger such as TEMPO (Scheme 1a).[6] During the oxysulfenylation of aromatic terminal alkenes reported by Gao et al. utilizing ammonium iodide, DMSO, and alcohol, a radical pathway was associated with the generation of a methylthiyl radical (MeS$^\bullet$) from DMSO (Scheme 1b).[7] Taking a cue from above, we were inquisitive to examine whether the reaction of styrene with *tert*-butyl nitrite in the presence of DMSO will offer similar difunctionalized product or a complete different reactivity would be observed leading to the formation of some other product (Scheme 1c).

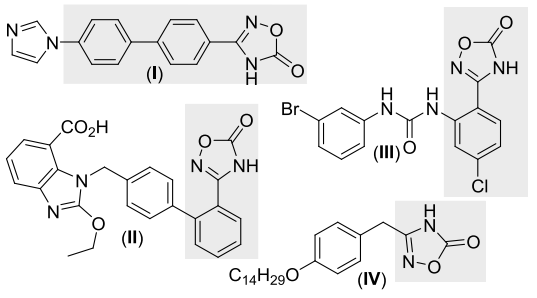
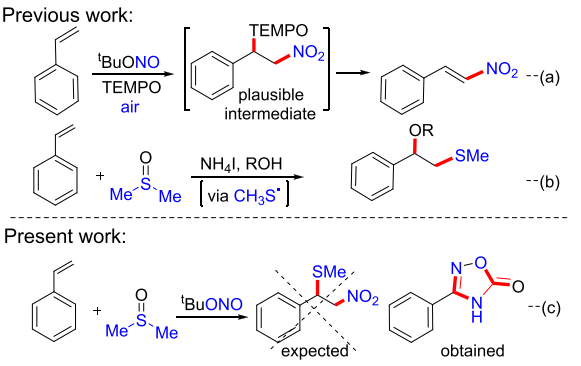


Figure 1. Representative examples of clinically relevant 1,2,4-oxadiazoles.

Scheme 1. C−H Functionalization of Alkene to 1,2,4-Oxadiazole

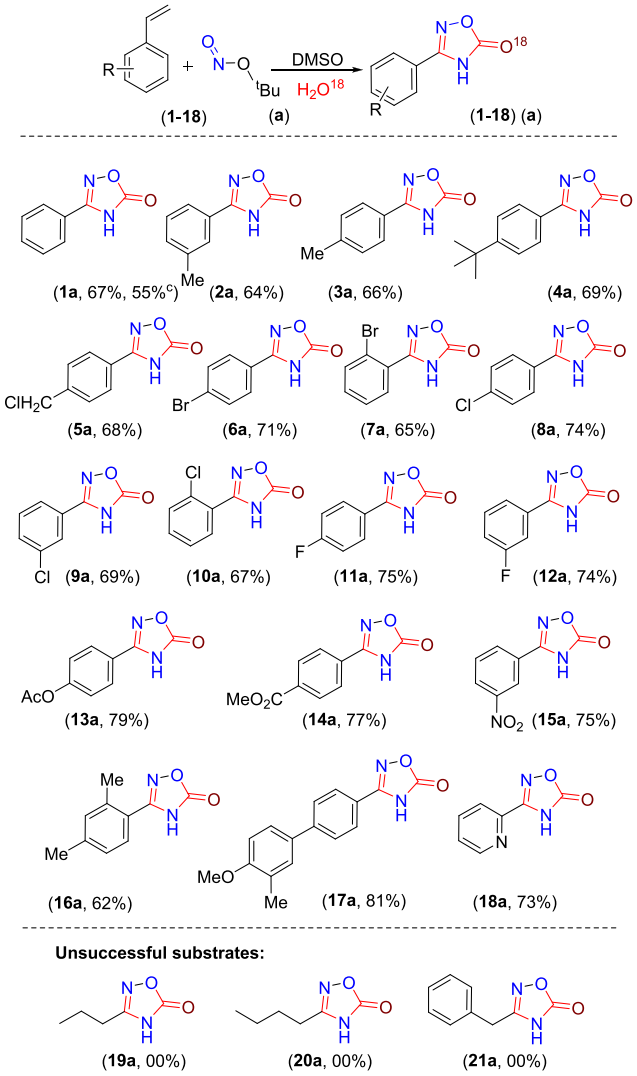


With this assumption, we commenced our investigation by reacting styrene (**1**) with *tert*-butyl nitrite (^{t}BuONO) (**a**, 3.0 equiv) and $Sc(OTf)_3$ catalyst (10 mol %) at 80 °C using DMSO as the solvent. Fortuitously, the reaction provided 3-phenyl-1,2,4-oxadiazol-5(4*H*)-one (**1a**) in 47% yield, the

Received: April 25, 2019

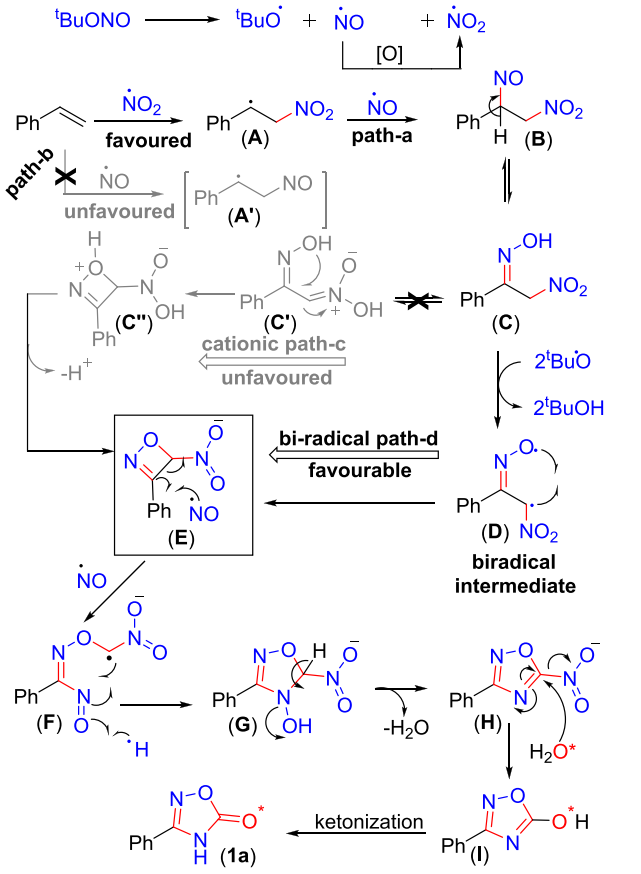
DOI: 10.1021/acs.orglett.9b01430
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope for Synthesis of 1,2,4-Oxadiazoles from Aryl Alkenes[a,b]



[a]Reaction conditions: alkene (**1**−**18**) (0.25 mmol), *tert*-butyl nitrite (**a**) (1 mmol) at 80 °C in DMSO. [b]Yield after 6 h. [c]Gram-scale reaction.

Scheme 3. Proposed Reaction Pathway for the Formation of 1a



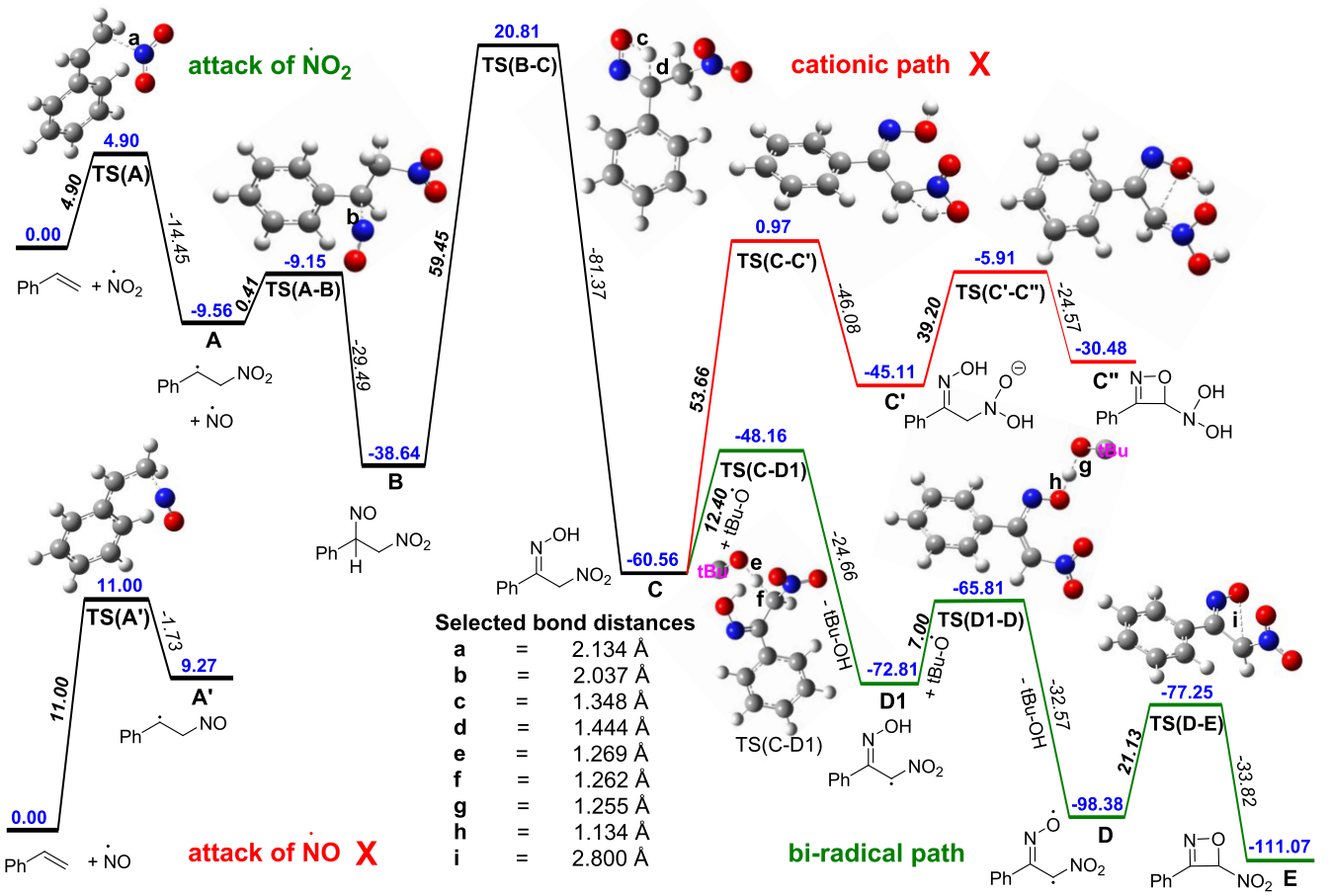
structure of which was ascertained by standard spectroscopic investigations (Scheme 1c). The synthesis of 1,2,4-oxadiazole was realized via the snapping of a vinylic C═C bond with concurrent construction of three C−N and two C−O bonds. It was observed that here the two N atoms in the oxadiazole moiety originated from TBN while the oxygen can originate either from the TBN, water, or oxygen.

Encouraged by the above outcome, further optimization of the reaction was carried out by varying various reaction parameters. At first, polar aprotic solvents such as DMSO, DMF, DMA, CH_3CN, and DCE were tested (Table S1, entries 1−5). Among the solvents examined, DMSO was found to be an effective solvent providing the product in 47% yield. When $Cu(OTf)_3$ (10 mol %) was used in lieu of $Sc(OTf)_3$ (10 mol %) under otherwise identical conditions, a diminished product yield (41%) was observed (Table S1, entry 6). Interestingly, the reaction proceeds better in the absence of any catalyst, giving the product **1a** in 59% yield (Table S1, entries 7). This result suggested that the catalyst has no role in the transformation. By increasing the *tert*-butyl nitrite loading from 3 to 4 equiv, the yield of the product **1a** improved to 67% (Table S1, entry 8). No significant improvement in the product yield was noticed when 5 equiv of TBN was employed in the reaction (Table S1, entry 9). Increasing the reaction temperature to 100 °C or decreasing it to 60 °C decreased the product yield to 51% and 57%, respectively. The optimized conditions were found to be using 4 equiv of TBN at 80 °C in DMSO.

The scope of the methodology was examined with a variety of aromatic terminal aryl alkenes (Scheme 2) under the optimized reaction condition. Styrenes bearing moderately electron-donating substituents on the aromatic ring such as *m*-Me (**2**), *p*-Me (**3**), *p*-^{t}Bu (**4**), and *p*-CH_2Cl (**5**) yielded the corresponding 1,2,4-oxadiazoles **2a**, **3a**, **4a**, and **5a** in 64−69% yields (Scheme 2). The single-crystal X-ray diffraction measurement reconfirmed the structure of the product **3a** (Figure S1). Vinyl arenes possessing moderately electron-withdrawing groups such as *p*-Br (**6**), *o*-Br (**7**), *p*-Cl (**8**), *m*-Cl (**9**), *o*-Cl (**10**), *p*-F (**11**), and *m*-F (**12**) on the aromatic ring provided the corresponding 1,2,4-oxadiazoles **6a** (71%), **7a** (65%), **8a** (74%), **9a** (69%), **10a** (67%), **11a** (75%), and **12a** (74%) in moderate yields (Scheme 2). However, vinyl arenes having strong electron-withdrawing substituents such as *p*-OAc (**13**), *p*-CO_2Me (**14**), and *m*-nitro (**15**), also reacted smoothly, affording the corresponding 1,2,4-oxadiazoles **13a** (79%), **14a** (77%), and **15a** (75%) in modest yields (Scheme 2). Other aromatic terminal alkenes such as 2,4-dimethylstyrene (**16**), 4-phenyl styrene (**17**), and 2-vinylpyridine (**18**) underwent the

DOI: 10.1021/acs.orglett.9b01430
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Energy Profile Diagram of the Reaction[a]



[a]Relative energy (blue color), activation barrier (italic bold) and stabilization gained (italic normal) are given in kcal/mol and calculated at M06/6-31+G(d,p) level of DFT. The "tertiary-butyl" radical is shown as "*t*-Bu" for clarity in representation. The biradical path (shown in green color) is preferred over the cationic path (shown in red color). The cross sign in red color (X) indicates the unfavorable reaction with higher activation barrier and lower stabilization. Selected interatomic distances of the transition states are given in angstroms.

reactions successfully to produce the 1,2,4-oxadiazoles **16a**, **17a**, and **18a** in 62%, 81%, and 73% yields, respectively, as shown in Scheme 2. During the synthesis of 1,2,4-oxadiazoles, similar yields were obtained from styrenes irrespective of the nature of the substituents (electron-donating or electron-withdrawing) present in the aryl rings. The possible reason for this could be the higher reactivity of the reaction intermediate.

However, employing aliphatic alkenes such as pent-1-ene (**19a**) but-1-ene (**20a**), and allylbenzene (**21a**) in the reaction failed to react with *tert*-butyl nitrite, which might be due to the instability of the radical produced during the reaction (Scheme 2). A successful demonstration of a gram-scale reaction using styrene (**1**) (12 mmol, 1.25 g) and *tert*-butyl nitrite (**a**) (48 mmol, 4.94 g) under the standard reaction conditions giving the product **1a** in 55% isolated yield conveyed the synthetic potential of this strategy.

To illustrate a probable reaction pathway for this one-pot synthesis of 1,2,4-oxadiazole, some control experiments were carried out. At first, to ascertain the origin of keto oxygen in the product **1a**, the reaction between styrene (**1**) and *tert*-butyl nitrite (**a**) was performed in the presence of $H_2{}^{18}O$ under otherwise identical conditions. Incorporation of ^{18}O-labeled product suggested that the oxygen from water (moisture from DMSO) is the possible source of oxygen in keto group of the product and the other oxygen is originating from TBN (see the Supporting Information). To confirm the radical nature of this transformation, a reaction was performed in the presence of a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv) under otherwise identical conditions. The desired product (**1a**) was obtained in <3%, suggesting the radical nature of the reaction. From the HRMS analysis of the reaction mixture at various time points, many possible reaction intermediates were detected, based on which a reaction mechanism can be inferred (Scheme 3).

The thermal decomposition of *tert*-butyl nitrite generates a $^{\bullet}NO$ radical, which under aerobic condition is oxidized to a nitro radical ($^{\bullet}NO_2$).[8] Subsequently, the attack of $^{\bullet}NO_2$ radical at the nonbenzylic terminal sp^2-carbon generates the nitroalkane radical intermediate **A**. Although both $^{\bullet}NO$ and $^{\bullet}NO_2$ radicals coexist in the medium, only the later attacks at the terminal carbon and the former at the benzylic position to generate an intermediate (**B**) (path a, Scheme 3),[5a] and no reverse attack (path b, Scheme 3) was observed in the literature.[5a] To understand this, DFT calculations were carried out and modeled the reaction profile at the M06/6-31+G(d) level of theory. The activation barrier for the attack of $^{\bullet}NO_2$ at the terminal carbon is around 6 kcal/mol lower compared to the attack of $^{\bullet}NO$ radical (Scheme 4). Moreover, $^{\bullet}NO_2$ attack

DOI: 10.1021/acs.orglett.9b01430
Org. Lett. XXXX, XXX, XXX−XXX

leads to the generation of a comparatively stable intermediate (**A**). Formation of C-nitroso intermediate **B** through the TS(A−B) is a quick reaction with an activation barrier of only 0.41 kcal/mol and stabilization of more than 38 kcal/mol. The intermediate **B** rearranges to an α-nitroxime **C** through TS(B−C), and this has an activation barrier of 59.45 kcal/mol and stabilization of more than 80 kcal/mol. From the intermediate **C**, the reaction may either proceed via a biradical path through TS(C−D1) and TS(D1−D) to generate the intermediate **D** or via a cationic path through TS(C−C′) to form the intermediate **C**′. As evident from Scheme 4, the activation barrier for the formation of **C**′ (53.66 kcal/mol) is much higher compared to the barrier for the formation of **D1** (12.40 kcal/mol). The formation of a biradical species is a two-step process. The first step is the abstraction of one hydrogen atom from the hydroxyl group by a *tert*-butoxy radical to give intermediate **D1**, while the second step is the abstraction of one hydrogen atom from the nitro group by another *tert*-butoxy radical to form the biradical intermediate **D**. Both of these steps have a lower activation barrier and higher stabilization and may proceed easily to form a biradical species **D**. This biradical species cyclizes to a four-membered 4*H*-1,2-oxazete (**E**) intermediate through TS(D−E), and the process has an activation barrier of 21.13 kcal/mol and stabilization of 33.82 kcal/mol. On the other hand, the formation of intermediates **C**′ and **C**″ through TS(C−C′) and TS(C′−C″) via a cationic path shows much higher activation barrier, and also the stabilization is lower compared to the barrier. Thus, the biradical path is preferred over the cationic path. As expected, all of the steps from $^{\bullet}NO_2$ attack followed by $^{\bullet}NO$ attack, rearrangement, attack of two *tert*-butoxy radicals, and ring closure to generate intermediate **E** are favorable with reasonable activation barriers, and they lead to the generation of stable intermediates. Formation of a similar four-membered ring has been proposed in the literature.[9] Because of the ring strain, the four-membered ring intermediate **E** undergoes ring-opening reaction with $^{\bullet}NO$ through transition TS(E−F) to generate intermediate **F** (Scheme S1). The activation barrier for this reaction is 28.64 kcal/mol, and stabilization is more than 100 kcal/mol. This reactive radical intermediate **F** undergoes cyclization through TS(F−G) to intermediate **G**. Formation of **G** is also a favorable reaction with an activation barrier of 29.49 kcal/mol and stabilization of more than 80 kcal/mol. Dehydration of intermediate **G** to intermediate **H** through TS(G−H) seems a slow reaction with an activation barrier of 98.14 kcal/mol. However, the reaction is feasible as the stabilization is much more than the activation barrier for the formation of **H** (Scheme S1). This is possibly the rate-determining step. Now the intermediate **H** is hydrolyzed by moisture available in the solvent/atmosphere through TS(G−H) to form the intermediate **I**. The activation barrier and stabilization for this transformation is 56.70 and 67.46 kcal/mol, respectively. Finally, the intermediate **I** undergoes ketonization through TS(I−1a) to form the desired and stable product (**1a**). All of the steps are given in Scheme 4, and Scheme S1 is feasible and leads to a stable complex formation as the activation barrier is always lower than the stabilization. Generation of intermediates **A**, **B**, **C**, and **F** has been identified by the HRMS analysis of reaction mixtures, thereby supporting the proposed pathway (see the Supporting Information).

In summary, an efficient protocol for the synthesis of 3-phenyl-1,2,4-oxadiazol-5(4*H*)-ones from aromatic terminal alkenes using *tert*-butyl nitrite has been developed. A range of aryl arenes reacted successfully with TBN to generate the heterocycle in good yields. However, the method is not successful for aliphatic terminal alkenes. On the basis of control experiments and detection of intermediates and from the DFT calculations a biradical reaction pathway has been suggested. This work is not only important from a mechanistic point of view but has a potential opportunity for easy access to many biologically active compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01430.

Experimental procedures; spectral and analytical data of all products; DFT calculations (PDF)

Accession Codes

CCDC 1911236 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E mail: hemants@iitg.ac.in.
*E mail: patel@iitg.ac.in.

ORCID

Hemant Kumar Srivastava: 0000-0001-6589-6854
Bhisma K. Patel: 0000-0002-4170-8166

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

B.K.P. acknowledges the support of this research by the Department of Science and Technology (DST/SERB) (EMR/2016/007042), T.A. and A.R. thank IIT Guwahati for fellowships. H.K.S. thanks DST/SERB SB/S2/RJN/004-2015 and Param-Ishan supercomputing facility at IIT Guwahati. CIF, IIT Guwahati, is highly acknowledged.

■ DEDICATION

Dedicated to Professor H. Ila on the occasion of her 75th birthday.

■ REFERENCES

(1) (a) Patel, R. V.; Park, S. W. *Eur. J. Med. Chem.* **2014**, *71*, 24. (b) Shang, X. F.; Natschke, S. L. M.; Liu, Y. Q.; Guo, X.; Xu, X. S.; Goto, M.; Li, J. C.; Yang, G. Z.; Lee, K. H. *Med. Res. Rev.* **2018**, *38*, 1. (c) Huang, C. Y.; Kavala, V.; Kuo, C. W.; Konala, A.; Yang, T. H.; Yao, C. F. *J. Org. Chem.* **2017**, *82*, 1961. (d) Iranshahy, M.; Quinn, R. J.; Iranshahi, M. *RSC Adv.* **2014**, *4*, 15900. (e) Kumar, S.; Bawa, S.; Gupta, H. *Mini-Rev. Med. Chem.* **2009**, *9*, 1648. (f) Ager, I. R.; Barnes, A. C.; Danswan, G. W.; Hairsine, P. W.; Kay, D. P.; Kennewell, P. D.; Matharu, S. S.; Miller, P.; Robson, P.; Rowlands, D. A.; Tully, W. R.; Westwood, R. *J. Med. Chem.* **1988**, *31*, 1098. (g) Kemnitzer, W.; Kuemmerle, J.; Jiang, S.; Zhang, H. Z.; Sirisoma, N.; Kasibhatla, S.; Grundy, C. C.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6259. (h) Enguehard-Gueiffier, C.; Musiu, S.; Henry, N.;

DOI: 10.1021/acs.orglett.9b01430
Org. Lett. XXXX, XXX, XXX−XXX

Véron, J. B.; Mavel, S.; Neyts, J.; Leyssen, P.; Paeshuyse, J.; Gueiffier, A. *Eur. J. Med. Chem.* **2013**, *64*, 448.
(2) (a) Gharat, L. A.; Muthukaman, N.; Tondlekar, S.; Khairatkar, J. N.; Shah, D. M.; Kadam, S. R. PCT Int. Appl. 2016046782, 2016, CODEN: PIXXD2. (b) Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. *J. Med. Chem.* **1996**, *39*, 5228. (c) Valgeirsson, J.; Nielsen, E. Ø.; Peters, D.; Mathiesen, C.; Kristensen, A. S.; Madsen, U. *J. Med. Chem.* **2004**, *47*, 6948. (d) Dong, C. Z.; Ahamada-Himidi, A.; Plocki, S.; Aoun, D.; Touaibia, M.; Meddad-Bel Habich, N.; Huet, J.; Redeuilh, C.; Ombetta, J.-E.; Godfroid, J.-J.; Massicot, F.; Heymans, F. *Bioorg. Med. Chem.* **2005**, *13*, 1989.
(3) (a) Bhat, S. V.; Robinson, D.; Moses, J. E.; Sharma, P. *Org. Lett.* **2016**, *18*, 1100. (b) Charton, J.; Cousaert, N.; Bochu, C.; Willand, N.; Deprez, B.; Deprez-Poulain, R. *Tetrahedron Lett.* **2007**, *48*, 1479. (c) Baykov, S.; Sharonova, T.; Shetnev, A.; Rozhkov, S.; Kalinin, S.; Smirnov, A. V. *Tetrahedron* **2017**, *73*, 945.
(4) (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (c) Colby, D.; Bergman, A. R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (e) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (f) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (g) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058.
(5) (a) Sau, P.; Santra, S. K.; Rakshit, A.; Patel, B. K. *J. Org. Chem.* **2017**, *82*, 6358. (b) Sau, P.; Rakshit, A.; Modi, A.; Behera, A.; Patel, B. K. *J. Org. Chem.* **2018**, *83*, 1056. (c) Mir, B. A.; Singh, S. J.; Kumar, R.; Patel, B. K. *Adv. Synth. Catal.* **2018**, *360*, 3801. (d) Qi, Z.; Jiang, Y.; Wang, Y.; Yan, R. *J. Org. Chem.* **2018**, *83*, 8636. (e) Chen, F.; Huang, X.; Li, X.; Shen, T.; Zou, M.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 10495. (f) Prateeptongkum, S.; Jovel, I.; Jackstell, R.; Vogl, N.; Weckbecker, C.; Beller, M. *Chem. Commun.* **2009**, *15*, 1990. (g) Chen, R.; Zhao, Y.; Fang, S.; Long, W.; Sun, H.; Wan, X. *Org. Lett.* **2017**, *19*, 5896. (h) Peng, X.-X.; Deng, Y.-J.; Yang, X.-L.; Zhang, L.; Yu, W.; Han, B. *Org. Lett.* **2014**, *16*, 4650. (i) Yuan, B.; Zhang, F.; Li, Z.; Yang, S.; Yan, R. *Org. Lett.* **2016**, *18*, 5928. (j) Wang, F.; Hu, B.-L.; Liu, L.; Tu, H.-Y.; Zhang, X.-G. *J. Org. Chem.* **2017**, *82*, 11247. (k) Yedage, S. L.; Bhanage, B. M. *J. Org. Chem.* **2017**, *82*, 5769.
(6) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384.
(7) Gao, X.; Pan, X.; Gao, J.; Jiang, H.; Yuan, G.; Li, Y. *Org. Lett.* **2015**, *17*, 1038.
(8) (a) Taniguchi, T.; Yajima, A.; Ishibashi, H. *Adv. Synth. Catal.* **2011**, *353*, 2643. (b) Kilpatrick, B.; Heller, M.; Arns, S. *Chem. Commun.* **2013**, *49*, 514. (c) Taniguchi, T.; Sugiura, Y.; Hatta, T.; Yajima, A.; Ishibashi, H. *Chem. Commun.* **2013**, *49*, 2198. (d) Wu, X. F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun.* **2011**, *47*, 12462. (e) Galliker, B.; Kissner, R.; Nauser, T.; Koppenol, W. H. *Chem. - Eur. J.* **2009**, *15*, 6161.
(9) Dutta, U.; Lupton, D. W.; Maiti, D. *Org. Lett.* **2016**, *18*, 860.

DOI: 10.1021/acs.orglett.9b01430
Org. Lett. XXXX, XXX, XXX−XXX