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Harnessing Autoxidation of Aldehydes: *In Situ* Iodoarene Catalyzed Synthesis of Substituted 1,3,4-Oxadiazole, in the Presence of Molecular Oxygen

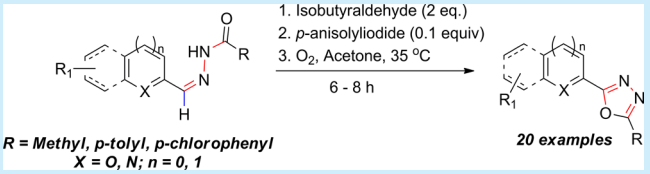
Jyoti Chauhan,[†] Mahesh K Ravva,[‡] and Subhabrata Sen*[,†]

[†]Department of Chemistry, School of Natural Sciences, Shiv Nadar University, Dadri, Chithera, Gautambudh Nagar, Uttar Pradesh 201314, India

[‡]Department of Chemistry, SRM University-AP, Amaravati, Andhra Pradesh 522502, India

Supporting Information

ABSTRACT: Isobutyraldehyde underwent auto-oxidation in the presence of molecular oxygen to generate an acyloxy radical under a "metal-free" environment. They were subsequently exploited *in situ* to afford hypervalent iodines with *p*-anisolyl iodide which generated substituted 1,3,4-oxadiazoles in moderate to excellent yields from *N*′-arylidene acetohydrazides. The reaction strategy tolerated diverse substitution on the hydrazide substrates. Control experiments and literature precedence supported the formation of an *in situ* iodosylarene complex that facilitates the formation of products.



Heterocycles/heteroaromatics play an integral role in drug discovery.[1a−i] They have been widely used as new chemical entities (NCE), active pharmaceutical ingredients (API), and pharmaceutical building blocks.[2a,b] Each of these molecules by virtue of their structural, electronic, and functional attributes impose a unique modulation to the biological systems. Among a myriad of such compounds, oxadiazole is an interesting class of compounds implicated as remedies in various physical ailments involving antibacterial, antifungal, antiviral, antitumoral, and anti-inflammatory activities.[2c−e] Typically oxadiazoles are synthesized by treating arylketone acylhydrazones with a stoichiometric quantity of (diacetoxy)iodobenzene (PIDA) and a few other hypervalent reagents and bases.[3] An interesting example, reported in 2013, involved reaction of a carboxylic acid with thiosemicarbazide in the presence of a coupling reagent to afford the desired oxadiazole.[4] In the recent past Fang et al. demonstrated a palladium catalyzed synthesis of 2-aminooxadiazoles from hydrazides and isocyanides.[5] Gao et al. recently reported direct annulation of hydrazides with methyl ketones in the presence of iodine and potassium carbonate.[6] In 2017, Tokumaru et al. reported a convergent synthesis of 1,3,4-oxadiazoles from acyl hydrazide under semiaqueous conditions.[7]

Hypervalent iodine has been ubiquitously utilized in diverse organic reactions, including oxidation of alkenes, alkynes, alcohols, and phenols; α-functionalization of carbonyl compounds; and oxidative transformations to generate various heterocycles.[8] Its application in organic transformations began as reagents and gradually evolved as catalysts.[9]

In the past decade, facile strategies for *in situ* generation of hypervalent iodines in the presence of commercially available oxidants such as *m*-CPBA (*meta*-chloroperbenzoic acid), hydrogen peroxide, peracetic acid, sodium perborate, etc. have gained immense popularity.[10] However, there is always scope for developing greener strategies for transformations involving *in situ* generated hypervalent iodine.[11] Oxygen is envisioned as an appropriate alternative.[12] Autoxidation of aldehydes in the presence of oxygen is a chemistry developed in the 19th century by Wöhler and Leibeg.[12a] Later in 1927 Backström elucidated the radical chain mechanism associated with the transformation.[12b] In recent decades various organic transformations are facilitated through the radical chain pathway of atutoxidation of aldehydes in the presence of oxygen.[12c−e] In the recent past Miyamoto and Powers harnessed the strategy to generate hypervalent iodine species.[12f−h] Inspired by this century old chemistry, we envisaged a metal devoid catalytic strategy for a facile synthesis of substituted 1,3,4-oxadiazoles from *N*′-arylidene acetohydrazides (*N*-acetyl aldehyde hydrazone) by using *p*-iodoanisole (as a source for generating *in situ* hypervalent iodine species) in the presence of oxygen and an appropriate aldehyde.

Accordingly, preliminary investigation with sterically bulky isobutyraldehyde at 35 °C under O_2 (1 atm) in acetone afforded peracid **A** after 1 h, which could be generated from the acyl peroxy radical $\mathbf{A_2}$ (Scheme 1). $\mathbf{A_2}$ in turn could lose an oxygen to generate acyloxy radical $\mathbf{A_3}$ which subsequently reacted with iodobenzene to generate a mixture of hypervalent iodine compounds in 6 h as observed by the NMR kinetics experiment.[12i] Similar reactions with acetaldehyde and benzaldehyde were not as clean as it was with isobutyraldehyde. After about 8 h, the reaction started to turn turbid at which point, it was stopped and the turbid product was

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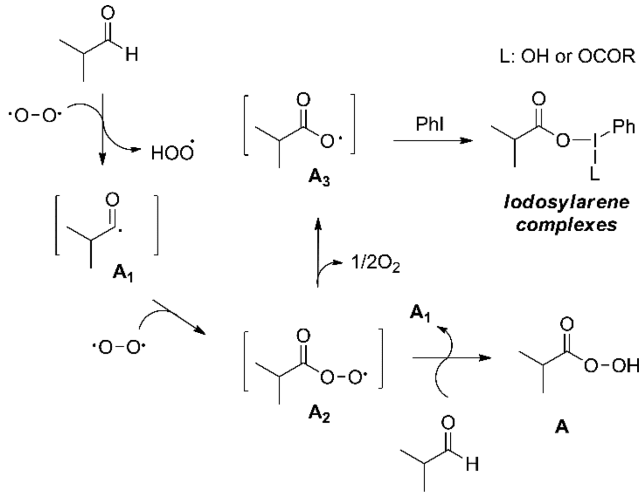
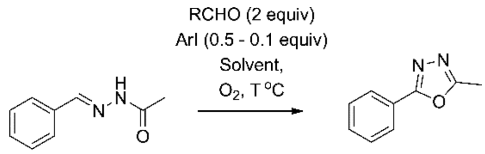
Scheme 1. Mechanism of Autoxidation of Aldehydes and Formation of Iodoarenes Complexes *in Situ*



isolated and characterized to be an hypervalent iodine compound (refer to SI).

Encouraged by these results, **1a** (synthesized by condensation of benzaldehyde and acetylhydrazide in ethanol at rt) was reacted with 0.5 equiv of iodobenzene (PhI) in various solvents such as acetone, 1,2-dichoroethane (DCE), acetonitrile (ACN), and ethanol at 35 to 90 °C in the presence of isobutyraldehyde (Table 1, entries 1−4). The reaction with acetone afforded the desired product **2a** in the best yield of 80% (Table 1, entry 1). Furthermore, with acetone as solvent, a variety of aryl iodides were screened as catalysts, starting from *p*-anisolyl iodide, *p*-tolyl iodide, *o*-tolyl iodide, 2,4-dimethyl iodobenzene, and *p*-nitro iodobenzene (Table 1, entries 5−9). The yields of **2a** with these new iodides ranged from 33% to 96%. The best yield was obtained with *p*-anisolyl iodide (Table 1, entry 5). The fact that *p*-nitro iodobenzene provided **2a** in the poorest yield (33%) proved that electron-withdrawing moieties on the aryl iodides is not tolerated by our system (Table 1, entry 9). The average reaction time were ∼6−8 h. In a bid to assess the catalytic ability of our protocol, the next two experiments were conducted in the presence of 0.3 and 0.1 equiv of *p*-anisolyl iodide (Table 1, entries 10 and 11). To our utmost gratification both the reactions went smoothly to afford **2a** in 84% and 92% yield respectively (Table 1, entries 10 and 11). To ascertain the role of oxygen in the protocol, the reaction was conducted in the presence of an inert atmosphere (argon) and as expected did not provide the desired product (Table 1, entry 12). Reactions with acetaldehyde and benzaldehyde under the same conditions afforded **2a** in a lower yield compared to isobutyraldehyde (Table 1, entries 13 and 14). This further established our initial hypothesis about usage of a bulky aldehyde like isobutyraldehye to facilitate the transformation. It was noteworthy that reactions with a lower loading of *p*-iodoanisole (0.05 and 0.01 equiv) than 0.1 equiv (Table 1, entries 15 and 16) provided the desired products in a much lower yield. Hence from this preliminary optimization study, 0.1 equiv of *p*-anisolyl iodide to catalyze reaction was selected (Table 1, entry 11) as the most suitable protocol for conversion of *N*′-arylidene acetohydrazides, **1a**, to their corresponding substituted 1,3,4-oxadiazoles, **2a**.

Table 1. Reaction Optimization for Aryl Iodide Mediated Conversion of *N*′-Arylidene Acetohydrazides to Substituted 1,3,4-Oxadiazole



entry	ArI (equiv)	solvent	*T* (°C)	yield[a]
1	PhI (0.5)	Acetone	35	80%
2	″	DCE	80	78%
3	″	EtOH	40	68%
4	″	CH_3CN	90	72%
5	*p*-anisolyl iodide (0.5)	Acetone	35	96%
6	*p*-tolyl iodide (0.5)	″	″	81%
7	*o*-tolyl iodide (0.5)	″	″	84%
8	2,4-dimethyl iodobenzene (0.5)	″	″	80%
9	*p*-nitroiodobenzene (0.5)	″	″	33%
10	*p*-anisolyl iodide (0.3)	″	″	84%
11	″ (0.1)	″	″	92%
12[b]	″	″	″	0%
13[c]	″	″	″	63%
14[d]	″	″	″	54%
15	″ (0.05)	″	″	74%
16	″ (0.01)	″	″	39%

[a]Isolated (After 10 h). [b]Solvent degassed and under an argon atmosphere. [c]With acetaldehyde. [d]With benzaldehyde. DCE: 1, 2-dichloroethane. CH_3CN: Acetonitrile. EtOH: Ethanol.

With the optimized conditions in hand we embarked on assessing the generic nature of the protocol. The synthetic sequence began by reacting 1 equiv of the appropriate aromatic aldehyde (diverse aromatic and heteroaromatic) with 1 equiv of acetyl, tolyl, or *p*-chlorobenzoyl hydrazide in ethanol at rt, to afford the desired hydrazone **1a−r** which precipitated from the reaction mixture. Compounds **1a−r** were pure enough to subject it for further reaction. Under optimized conditions they afforded the desired products **2a−r** in 49−95% yield (Scheme 2). Various electron-withdrawing and electron-donating groups at the aromatic moiety were tolerated by the reaction conditions (Scheme 2). The desired compounds were isolated by flash column chromatography with ethyl acetate and hexane as eluents. The structures of the compounds were confirmed by generating the single crystal X-ray structure of compound **1f**. The protocol was well tolerant toward *N*′-heteroarylidene acetohydrazide compounds **1g**, **k**, and **q** to afford the desired oxadiazoles in 49%−79% yield, respectively (Scheme 2). Product **2p** was formed in 71% yield. The drug isoniazid (INH) or isonicotinyl hydrazide is a potent antimycobacterial agent.[13,13a] Unfortunately in the recent past nearly 10% of TB disease cases have been detected with nonmultidrug resistant (MDR) INH.[13b] To circumvent this threat, serious endeavors are in progress to modify the drug. Accordingly we utilized our optimized strategy to convert INH to corresponding 1,3,4-oxadizole which are also reported as potential antitubercular agents.[13c] To our greatest satisfaction, two compounds **2s** and **t** were prepared from the corresponding hydrazone **1s** and **t**, containing the isoniazid moiety in excellent yield (84% and 91%, respectively).

The optimized reaction condition was robust enough to tolerate the conversion of aliphatic hydrazone like **1p** to the desired

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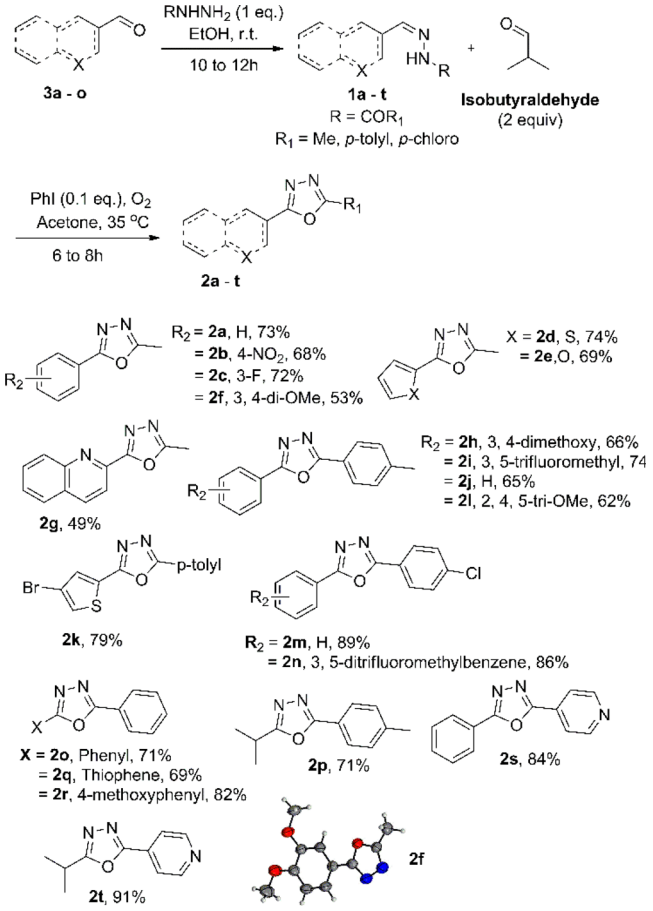
Scheme 2. Synthesis of Aromatic Oxadiazole 2a−r



From the literature report, our hypothesis, and initial proof-of-concept studies, the mechanism of transformation of **1a** → **2a** is postulated and is depicted in Scheme 3. The transformation is envisioned to be segregated into two aspects. The preliminary stage involved autoxidation of isobutyraldehyde, which is assumed to be a bimolecular reaction between the aldehyde and oxygen to afford the peracid **III** via the acyl and acyl peroxy radicals **I** and **II**, respectively (Scheme 3). From literature precedence we believe that acyl peroxy radical **II** generates acyloxy radical **IV** which probably enacts the role of oxidant and in the next stage reacts with *p*-anisolyl iodide to afford *in situ* the hypervalent iodosyl arene complex **V** (Scheme 3).[12i] **V** reacts with **1a** to afford **VI**. It is worth mentioning that there is a chance of formation of **Va** as an alternative hypervalent iodine species, but we were unable to isolate it. Eventually **VI** cyclizes to **VII** which aromatizes to afford **2a** and in the course regenerates *p*-anisolyl iodide which continues the catalytic cycle.

Next to assess the robustness of the protocol, a scale up reaction was conducted, where a 5 g scale of *N*′-benzylidene acetohydrazides, **1a**, under optimized conditions generated the desired compound **2a** in 76% yield.

In conclusion we have successfully demonstrated O_2 as a primary and an acyloxy radical as the terminal oxidant for facile synthesis of substituted 1,3,4-oxadiazole. We leveraged the autoxidation of isobutyraldehyde in an O_2 atmosphere. The final transformation involved reaction of *N*′-arylidene acetohydrazides **1** substrates with isobutyraldehyde and catalytic *p*-anisolyl iodide under 1 atm of O_2 at 35 °C in acetone. An *in situ* generated hypervalent iodine is the key player in this transformation. This strategy is replicated in gram scale and displayed exceptional functional group tolerance. Control experiment and literature precedence provided a preliminary insight into the mechanism of the reaction. Investigation to expand the scope and further elucidate the mechanism through DFT studies is in progress in our lab.

■ ASSOCIATED CONTENT

Supporting Information

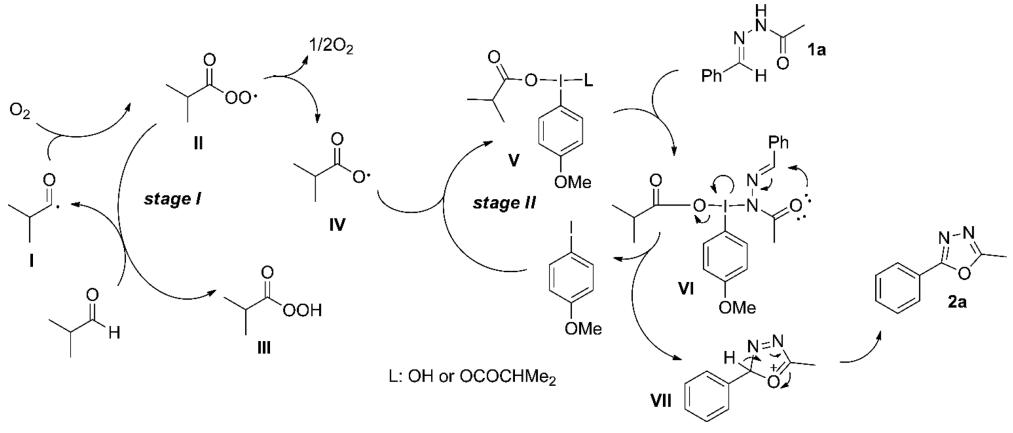
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02542.

NMR spectra (PDF)

Accession Codes

CCDC 1889823 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.

Scheme 3. Putative Mechanism for the Formation of Substituted 1,3,4-Oxadiazole 2a−r



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AUTHOR INFORMATION

Corresponding Author

*E-mail: subhabrata.sen@snu.edu.in; subhabrata.s@srmap.edu.in.

ORCID

Mahesh K Ravva: 0000-0001-9619-0176
Subhabrata Sen: 0000-0002-4608-5498

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Lesokhin, A. M.; Callahan, M. K.; Postow, M. A.; Wolchok, J. D. *Sci. Transl. Med.* **2015**, *7*, 280sr1. (b) Chen, T.-T. *J. Immunother. Cancer* **2013**, *1*, 18. (c) Suntharalingam, G.; Perry, M. R.; Ward, S.; Brett, S. J.; Castello-Cortes, A.; Brunner, M. D.; Panoskaltsis, N. *N. Engl. J. Med.* **2006**, *355*, 1018. (d) Adams, J. L.; Smothers, J.; Srinivasan, R.; Hoos, A. *Nat. Rev. Drug Discovery* **2015**, *14*, 603. (e) Iyer, V. V. Anti-Cancer Agents. *Anti-Cancer Agents Med. Chem.* **2015**, *15*, 433. (f) Weinmann, H. *ChemMedChem* **2016**, *11*, 450. (g) Dhanak, D.; Edwards, J. P.; Nguyen, A.; Tummino, P. *J. Cell Chem. Biol.* **2017**, *24*, 1148. (h) Lin, D. Y.-W.; Tanaka, Y.; Iwasaki, M.; Gittis, A. G.; Su, H.-P.; Mikami, B.; Okazaki, T.; Honjo, T.; Minato, N.; Garboczi, D. N. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 3011. (i) Huck, B. R.; Kötzner, L.; Urbahns, K. *Angew. Chem., Int. Ed.* **2018**, *57*, 4412.

(2) (a) *IUPAC Gold Book—Heterocyclic Compounds*. Available online: http://goldbook.iupac.org/H02798.html (accessed on 26 May 2015). (b) Gomtsyan, A. *Chem. Heterocycl. Compd.* **2012**, *48*, 7. (c) Shivi, B.; Gupta, M. *J. Chem. Pharm. Res.* **2011**, *3*, 137. (d) Farshori, N. N.; Banday, M. R.; Ahmad, A.; Khan, A. U. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1933. (e) Yathirajan, H. S.; Mayekar, A. N.; Narayana, B.; Sarojini, B. K.; Kumari, S. *Int. J. Chem.* **2010**, *2*, 38.

(3) Patel, K. D.; Prajapati, S. M.; Panchal, S. N.; Patel, H. D. *Synth. Commun.* **2014**, *44*, 1859.

(4) Yang, S.-J.; Lee, S.-H.; Kwak, H.-H.; Gong, Y.-D. *J. Org. Chem.* **2013**, *78*, 438.

(5) Fang, T.; Tan, Q.; Ding, Z.; Liu, B.; Xu, B. *Org. Lett.* **2014**, *16*, 2342.

(6) Gao, Q.; Liu, S.; Wu, X.; Zhang, J.; Wu. *Org. Lett.* **2015**, *17*, 2960.

(7) Tokumaru, K.; Johnston, J. N. *Chem. Sci.* **2017**, *8*, 3187.

(8) (a) Wirth, T. *Angew. Chem.* **2001**, *113*, 2893; *Angew. Chem., Int. Ed.* **2001**, *40*, 2812. (b) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (c) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, *2008*, 467. (d) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086. (e) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261. (f) Fuchigami, T.; Fujita, T. *J. Org. Chem.* **1994**, *59*, 7190. (g) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233. (h) Zhdankin, V. V.; Smart, J. T.; Zhao, P.; Kiprof, P. *Tetrahedron Lett.* **2000**, *41*, 5299. (i) Zhdankin, V. V.; Koposov, A. Y.; Netzel, B. C.; Yashin, N. V.; Rempel, B. P.; Ferguson, M. J.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 2194. (j) Zhdankin, V. V.; Litvinov, D. N.; Koposov, A. Y.; Luu, T.; Ferguson, M. J.; McDonald, R.; Tykwinski, R. R. *J. Org. Chem.* **2005**, *70*, 6484.

(9) (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596. (c) Yusubov, M. S.; Zhdankin, V. V. *Res-Eff. Technol.* **2015**, *1*, 49. (d) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244. (e) Zhdankin, V. V.; Crittell, C. M.; Stang, P. J.; Zefirov, N. S. *Tetrahedron Lett.* **1990**, *31*, 4821.

(10) (a) Zhdankin, V. V. *Hypervalent Iodine Chemistry*; John Wiley & Sons: New York, 2014. (b) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328. (c) *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Topic in Current Chemistry, *373*; Springer: Berlin, 2016. (d) Hussain, H.; Green, I. R.; Ahmed, I. *Chem. Rev.* **2013**, *113*, 3329.

(11) (a) Milas, N. A.; McAlevy, A. *J. Am. Chem. Soc.* **1934**, *56*, 1221. (b) Silbert, L. S.; Siegel, E.; Swern, D. *Org. Synth.* **1964**, *44*, 81. (c) Meyers, A. I.; Schwartzman, S.; Olson, G. L.; Cheung, H.-C. *Tetrahedron Lett.* **1976**, *17*, 2417. (d) King, R. B.; Douglas, W. M.; Efraty, A. *Org. Synth.* **1977**, *56*, 1.

(12) (a) Wöhler, F.; Liebig, J. *Liebigs Ann.* **1832**, *3*, 249. (b) Bäckstrom, H. L. T. *J. Am. Chem. Soc.* **1927**, *49*, 1460. (c) Nam, W.; Kim, H. J.; Kim, S. H.; Ho, R. Y. N.; Valentine, J. S. *Inorg. Chem.* **1996**, *35*, 1045. (d) Shapiro, N.; Kramer, M.; Goldberg, I.; Vigalok, A. *Green Chem.* **2010**, *12*, 582. (e) Das, P.; Saha, D.; Saha, D.; Guin, J. *ACS Catal.* **2016**, *6*, 6050. (f) Miyamoto, K.; Yamashita, J.; Narita, S.; Sakai, Y.; Hirano, K.; Saito, T.; Wang, C.; Ochiai, M.; Uchiyama, M. *Chem. Commun.* **2017**, *53*, 9781. (g) Maity, A.; Hyun, S.-M.; Powers, C. D. *Nat. Chem.* **2018**, *10*, 200. (h) Maity, A.; Hyun, S.-M.; Wortman, A. K.; Powers, D. C. *Angew. Chem.* **2018**, *130*, 7323. (i) Hyun, S.-M.; Yuan, M.; Maity, A.; Gutierrez, O.; Powers, D. C. *Chem.* **2019**, *5*, 1.

(13) (a) Mitchison, D. A. *Int. J. Tuberc. Lung Dis.* **2000**, *4*, 796−806. (b) Stagg, H. R.; Lipman, M. C.; McHugh, T. D.; Jenkins, H. E. *Int. J. Tuberc. Lung Dis.* **2017**, *21*, 129. (c) Vosátka, R.; Krátký, M.; Svarcová, M.; Janoušek, J.; Stolaříková, J.; Madacki, J.; Huszár, S.; Mikušová, K.; Korduláková, J.; Trejtnar, F.; Vinšová, J. *Eur. J. Med. Chem.* **2018**, *151*, 824.

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