Organic LETTERS
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

Regioselective Ring Expansion of Isatins with *In Situ* Generated α-Aryldiazomethanes: Direct Access to Viridicatin Alkaloids

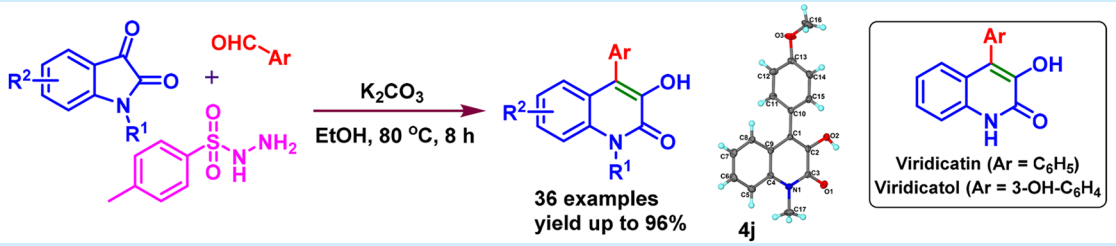
Yellaiah Tangella,[†,§] Kesari Lakshmi Manasa,[†,∥] Namballa Hari Krishna,[†,∥] B. Sridhar,[‡] Ahmed Kamal,*[,§,⊥] and Bathini Nagendra Babu*[,†,§,∥]

[†]Fluoro-Agrochemicals and [‡]Centre for X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

[§]Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India

[∥]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad 500 037, India

Supporting Information



ABSTRACT: A novel efficient one-pot regioselective ring-expansion reaction of isatins with *in situ* generated α-aryl/heteroaryldiazomethanes for the construction of viridicatin alkaloids has been described under metal-free conditions. The utility of this protocol is further demonstrated in the synthesis of naturally occurring viridicatin, viridicatol, and substituted 3-*O*-methyl viridicatin and their scale up.

Heterocyclic compounds have attracted burgeoning attention over the past decade as the most valuable leads in the area of synthetic and medicinal chemistry, due to their potential to create a huge number of chemical libraries against various life-threatening diseases.[1] Among them, the quinolinone skeleton has been recognized as a valuable scaffold in numerous natural products that exhibit a wide range of pharmacological properties.[2] In particular, 4-arylquinolin-2(1*H*)-ones and 3-hydroxyquinolin-2(1*H*)-ones have been found to possess profound biological activities, including selective inhibition of HIV-1 reverse transcriptase, neuroprotection, antibacterial by opening the maxi-K channel, as well as D-amino acid oxidase (DAAO) inhibitory activity.[3−6] For example, tipifarnib (**I**), a 4-arylquinolin-2(1*H*)-one derivative which is a potent orally active antineoplastic agent, acts by inhibiting farnesyltransferase,[7] whereas natural products such as viridicatin[8] (**II**), viridicatol[9] (**III**), and 3-*O*-methyl viridicatin[10] (**IV**) are promising anti-inflammatory agents[11] and are also capable of inhibiting TNF-α-induced HIV replication (Figure 1).[12]

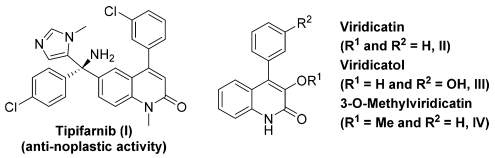


Figure 1. Representative biologically active 4-arylquinolin-2(1*H*)-one and 3-hydroxyquinolin-2(1*H*)-one scaffolds.

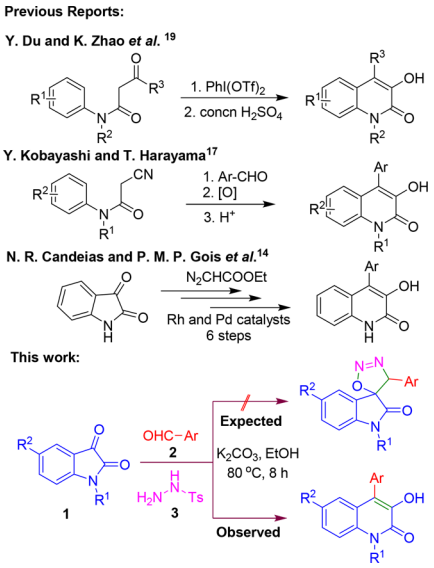
Consequently, various synthetically feasible protocols have evolved for the construction of these important and attractive scaffolds.[13−20] Traditional strategies for the synthesis of 4-arylquinolin-2(1*H*)-ones include ring expansion of isatins with either diazomethanes[13]/EDA under the catalysis of NHC-dirhodium(II)[14]/TMS-diazomethane in the presence of TFA,[15] followed by C-4 arylation using conventional coupling reactions. They can also be synthesized by (i) Diels−Reese reaction,[16] (ii) Knoevenagel condensation/epoxidation, followed by decyanative epoxide-arene cyclization of cyanoacetanilides,[17] (iii) decarboxylative rearrangement of cyclopenin and cyclopenol,[18] and (iv) $PhI(OCOCF_3)_2$-mediated α-hydroxylation, followed by acid-promoted intramolecular annulation of *N*-phenylacetoacetamide (Scheme 1).[19]

Although the existing methodologies have their own advantages, unfortunately, they are associated with certain limitations such as usage of expensive transition metals, inaccessible substrates, poor breadth of functional group tolerance, and multistep syntheses coupled with lower yields. Therefore, alternative, simple, flexible, and straightforward strategies for the construction of these scaffolds from commercially available starting materials are strongly needed.

Received: May 4, 2018

DOI: 10.1021/acs.orglett.8b01417
Org. Lett. XXXX, XXX, XXX−XXX

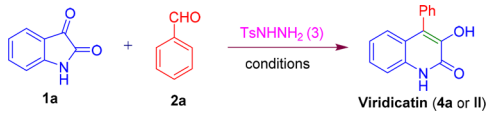
Scheme 1. Comparison of Our Work with the Previous Reports for the Synthesis of 3-Hydroxy-4-arylquinolin-2(1*H*)-ones



As part of our interest in developing novel synthetic strategies for structurally/biologically interesting heterocyclic compounds,[20] we envisioned to assemble an oxadiazole ring onto isatin in a spiroannulation manner by treating with α-aryldiazomethanes generated *in situ* from *N*-tosylhydrazones[21] via 1,3-dipolar cycloaddition. Unexpectedly, ring expansion occurred, resulting in the formation of 3-hydroxy-4-arylquinolin-2(1*H*)-ones (viridicatin alkaloids). This unanticipated regioselective one-pot ring-expansion reaction of isatins with α-aryldiazomethanes was described herein, which represents a valuable complement to the existing elegant strategies.

In order to evaluate the optimal reaction conditions for the unanticipated strategy, we commenced our investigation by treating isatin (**1a**) with benzaldehyde (**2a**) and *p*-toluenesulfonylhydrazide (**3**), employing DBU (2.0 equiv) in MeCN under refluxing temperatures. To our delight, ring-expanded product **4a** (natural product viridicatin) was obtained in 70% yield (Table 1, entry 1). The structure of the compound was unambiguously confirmed by spectroscopic and X-ray crystallographic analysis. This interesting outcome further encouraged us to optimize the reaction parameters such as base, solvent, and temperature (Table 1). Performing a reaction at room temperature failed to deliver **4a**, even after 24 h (Table 1, entry 2). There was no noticeable enhancement in yield of **4a**, with the increase in the stoichiometry of base (Table 1, entry 3). K_2CO_3 proved to be a superior base among a set of screened bases such as Et_3N, DMAP, DIPEA, ^tBuONa, Na_2CO_3, and K_2CO_3, providing the highest conversion of isatin (**1a**) to product **4a** (Table 1, entries 4−9). Further, a survey was conducted on alternative solvents such as EtOH, THF, DMF, DMSO, PhMe, and 1,4-dioxane, which revealed that EtOH was the optimal solvent of choice (Table 1, entries 10−15). A decent decrease in the yield was observed at lower temperatures (Table 1, entry 16). A control experiment lacking either base or *p*-toluenesulfonylhydrazide (**3**) did not deliver any product, even after prolonged reaction times (Table 1, entries 17 and 18). Hence, after a brief screening, the optimal conditions to be concluded are **1a** (1 mmol), **2a** (1 mmol), **3** (1 mmol), and

Table 1. Optimization of Reaction Conditions[a−d]



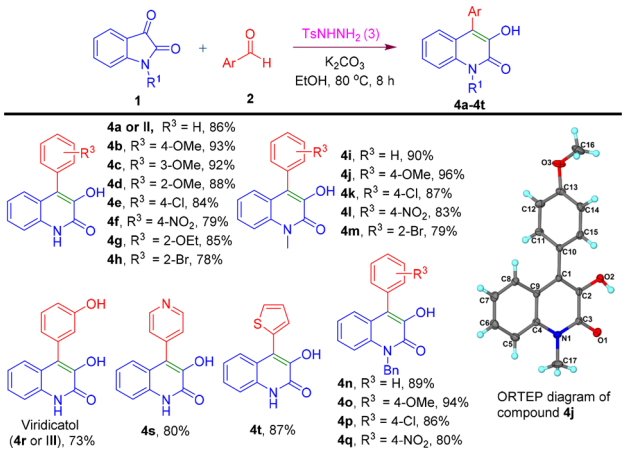
entry	base	solvent	temp (°C)	time (h)	yield (%)[b]
1	DBU	MeCN	80	12	70
2	DBU	MeCN	rt	24	-
3[c]	DBU	MeCN	80	12	71
4	Et_3N	MeCN	80	12	27
5	DMAP	MeCN	80	12	trace
6	DIPEA	MeCN	80	12	36
7	Na_2CO_3	MeCN	80	12	43
8	K_2CO_3	MeCN	80	12	78
9	^tBuONa	MeCN	80	12	67
10	K_2CO_3	THF	80	12	65
11	K_2CO_3	DMF	80	12	69
12	K_2CO_3	DMSO	80	12	62
13	K_2CO_3	PhMe	80	12	70
14	**K_2CO_3**	**EtOH**	**80**	**8**	**86**
15	K_2CO_3	dioxane	80	12	63
16	K_2CO_3	EtOH	50	16	55
17	-	EtOH	80	24	-
18[d]	K_2CO_3	EtOH	80	24	-

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3** (1 mmol), and base (2 mmol) stirred in open air atmosphere. [b]Isolated yield. [c]3 mmol of base is used. [d]Reaction performed in the absence of *p*-toluenesulfonylhydrazide (**3**).

K_2CO_3 (2 mmol) in ethanol under refluxing temperature, i.e., 80 °C.

Having identified the optimal reaction parameters, the generality and substrate scope of both isatin and aldehyde partners were examined. Initially, a wide array of aldehydes substituted with different functional groups were screened, which underwent ring expansion smoothly and provided the corresponding viridicatin derivatives in good to excellent yields (73−96%). Comparably better yields were obtained with aldehydes bearing electron-donating groups (Scheme 2, **4b**−

Scheme 2. Substrate Scope of Aldehydes to the Synthesis of 3-Hydroxyquinolin-2(1*H*)-ones[a,b]



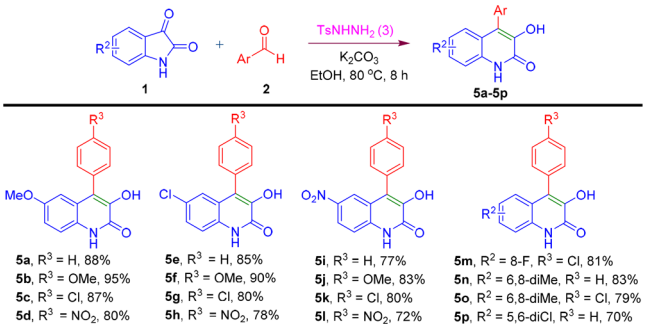
[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), and K_2CO_3 (2 mmol) in EtOH was stirred in an open air atmosphere at 80 °C for 8 h. [b]Isolated yield.

DOI: 10.1021/acs.orglett.8b01417
Org. Lett. XXXX, XXX, XXX−XXX

4d, **4g**, **4j**, and **4h**) than the electron-withdrawing groups (Scheme 2, **4e**, **4f**, **4h**, **4k**, **4l**, **4m**, **4p**, and **4q**). As expected, the position of the substituent on the aryl aldehyde partner had a considerable influence on the reaction efficacy, where *ortho*-substituted aldehydes (OMe, OEt, and Br) delivered corresponding products in relatively lesser yields than the *meta*- and *para*-substituted aldehydes (Scheme 2, **4b**, **4c**, and **4j**). This may be possibly due to steric hindrance imparted by the ortho substituents (Scheme 2, **4d**, **4g**, **4h**, and **4m**). It is worth mentioning that synthetically useful halo substituents such as Cl or Br are stable under the optimized reaction conditions, which are useful for further functional group interconversions such as metal-catalyzed coupling reactions. Notably, hydroxyl-substituted aldehyde was also amenable for this transformation and provided the corresponding product (**4r** or **III**) in 73% yield, which is a naturally occurring alkaloid, viridicatol. Besides aryl aldehydes, even heteroaryl aldehydes such as 4-pyridinecarboxaldehyde and 2-thiophenecarboxaldehyde were also compatible with this protocol and delivered corresponding products **4s** and **4t** in 80% and 87% yield, respectively (Scheme 2). To the best of our knowledge, utilization of heteroaromatic aldehydes for the synthesis of 3-hydroxy-4-heteroarylquinolin-2(1*H*)-ones has not been explored extensively. In contrast, aliphatic aldehydes were found to be incompatible with this transformation and did not yield any product, even after stirring for more than 12 h, leaving the isatin unreacted. N-Protected isatins afforded the corresponding products in slightly higher yields than the unprotected isatins (Scheme 2).

With these fruitful results, we next turned our attention to broadening the substrate scope of isatins. As summarized in Scheme 3, a diverse range of isatins substituted with electron-

Scheme 3. Substrate Scope of Isatins to the Synthesis of 3-Hydroxy-4-arylquinolin-2(1*H*)-ones[a,b]

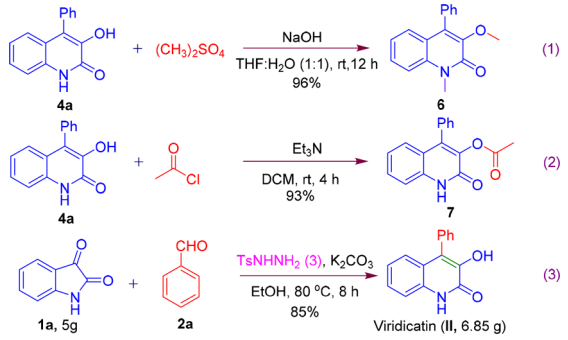


[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), and K_2CO_3 (2 mmol) in EtOH were stirred in an open air atmosphere at 80 °C for 8 h. [b]Isolated yield.

donating (OMe) as well as electron-withdrawing (Cl and NO_2) substituents at the fifth position of the aromatic ring reacted smoothly to deliver the corresponding products in good to excellent yields (**5a**–**5l**). Later, the effect of the position of substitution was also studied where 4,5-dichloro, 7-fluoro, and 5,7-dimethyl isatins were also amenable for this transformation and provided corresponding products **5m**–**5p** in good yields irrespective of their electronic nature. Similar to aldehyde partners, variation in the electronic nature has the discriminable impact on the reaction efficacy where isatins bearing electron-donating substituents yielded corresponding products comparably in higher yields than the electron-withdrawing substituents (Scheme 3).

In addition, to substantiate the synthetic applicability of the current protocol, several transformations were conducted. Initially, we were fascinated to investigate the functionalization of phenolic–OH and amide–NH, which provide a library of novel viridicatin derivatives. Accordingly, the synthesized viridicatin was protected as its N- and O-methylated derivative **6** in excellent yield by treating with dimethyl sulfate in the presence of NaOH (Scheme 4, eq 1). In addition, the

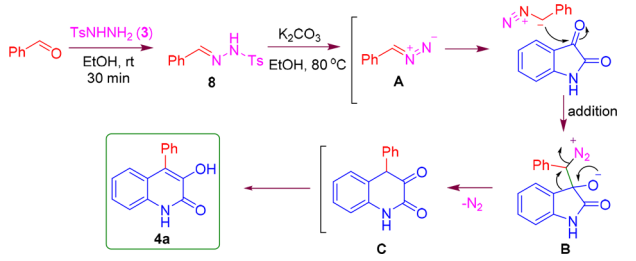
Scheme 4. Synthetic Applicability of the Current Protocol



acetylation of viridicatin with acetyl chloride provided the corresponding 2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl acetate (**7**) in 93% yield (Scheme 4, eq 2). Furthermore, the practical utility of this protocol was also extended by executing a gram-scale synthesis. Natural product viridicatin (**4a**) was prepared in 6.85 g from isatin (**1a**, 34 mmol) and benzaldehyde (**2a**, 34 mmol) under the optimized conditions (Scheme 4, eq 3) in one pot in 85% yield.

Based on the literature reports[22] and our observations, a plausible reaction mechanism has been proposed for the present protocol (Scheme 5). Initially, benzaldehyde condenses

Scheme 5. Plausible Reaction Mechanism



with *p*-toluenesulfonylhydrazide to generate the corresponding hydrazone intermediate **8**, which subsequently transforms into diazomethylbenzene intermediate **A** in the presence of base under elevated temperatures. Intermediate **A** then adds onto carbonyl carbon of isatin (**1a**) in a nucleophilic addition manner to yield intermediate **B**, which is assumed to undergo cyclization via intramolecular ring expansion by the elimination of N_2 to deliver intermediate **C**. Intermediate **C** after subsequent aromatization delivers the desired product **4a**.

In summary, an efficient regioselective ring expansion reaction of isatins with aldehydes promoted by *p*-toluenesulfonylhydrazide has been developed to construct various pharmaceutically important 3-hydroxy-4-arylquinolin-2(1*H*)-ones in one step, which proceeds via an *in situ* generated *α*-

DOI: 10.1021/acs.orglett.8b01417
Org. Lett. XXXX, XXX, XXX–XXX

aryl/heteroaryldiazomethane. The present protocol has advantages such as commercially available substrates, one-pot reaction with higher yields, utilization of greener solvent with simple workup, and broad functional group tolerance. We believe that this metal-free and milder approach may open the door to access new bioactive 3-hydroxy-4-arylquinolin-2(1*H*)-ones. Moreover, this protocol provides a convenient access to various naturally occurring bioactive alkaloids such as viridicatin, viridicatol, substituted 3-*O*-methyl viridicatin, and its derivatives. The synthetic feasibility is also extended by performing a gram-scale synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01417.

Detailed experimental procedures, crystal data, and spectral data for all compounds (PDF)

Accession Codes

CCDC 1832714 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: bathini@iict.res.in.

*E-mail: ahmedkamal915@gmail.com.

ORCID

Ahmed Kamal: 0000-0002-4107-1775

Bathini Nagendra Babu: 0000-0001-7378-0878

Present Address

[⊥]School of Pharmaceutical Education and Research (SPER), Jamia Hamdard University, New Delhi 110062, India.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Council of Scientific and Industrial Research (CSIR), and Y.T. is thankful to UGC for a research fellowship (IICT Comm. No. IICT/Pubs/2018/153).

■ REFERENCES

(1) (a) Alvarez-Builla, J.; Vaquero, J. J. *Modern Heterocyclic Chemistry*; Wiley-VCH: Weinheim, Germany, 2011. (b) Quin, L. D.; Tyrell, J. A. *Fundamentals of heterocyclic chemistry: Importance in Nature and in the synthesis of pharmaceuticals*; Wiley: Hoboken, NJ, 2010. (c) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. *Org. Biomol. Chem.* **2016**, *14*, 6611.

(2) (a) Maiti, A.; Reddy, P.; Sturdy, M.; Marler, L.; Pegan, S.; Mesecar, A.; Pezzutto, J.; Cushman, M. *J. Med. Chem.* **2009**, *52*, 1873. (b) Cheng, P.; Zhang, Q.; Ma, Y.-B.; Jiang, Z.-Y.; Zhang, X.-M.; Zhang, F.-X.; Chen, J.-J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3787. (c) Angibaud, P. R.; Venet, M. G.; Filliers, W.; Broeckx, R.; Ligny, Y. A.; Muller, P.; Poncelet, V. S.; End, D. W. *Eur. J. Org. Chem.* **2004**, *3*, 479. (d) Aoki, Y.; Ishiwara, M.; Koda, A.; Takagaki, H. *Eur. J. Pharmacol.* **2000**, *409*, 325.

(3) (a) Gioiello, A.; Venturoni, F.; Marinozzi, M.; Natalini, B.; Pellicciari, R. *J. Org. Chem.* **2011**, *76*, 7431. (b) Toum, J.; Moquette, A.; Lamotte, Y.; Mirguet, O. *Tetrahedron Lett.* **2012**, *53*, 1920. (c) He, J.; Lion, U.; Sattler, I.; Gollmick, F. A.; Grabley, S.; Cai, J.; Meiners, M.; Schunke, H.; Schaumann, K.; Dechert, U.; Krohn, M. *J. Nat. Prod.* **2005**, *68*, 1397. (d) Chen, M. H.; Fitzgerald, P.; Singh, S. B.; O'Neill, E. A.; Schwartz, C. D.; Thompson, C. M.; O'Keefe, S. J.; Zaller, D. M.; Doherty, J. B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2222. (e) Hewawasam, P.; Fan, W.; Knipe, J.; Moon, S. L.; Boissard, C. G.; Gribkoff, V. K.; Starrett, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1779.

(4) Suchaud, V.; Bailly, F.; Lion, C.; Tramontano, E.; Esposito, F.; Corona, A.; Christ, F.; Debyser, Z.; Cotelle, P. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3988.

(5) Sit, S. Y.; Meanwell, N. A. U.S. Patent 5,892,045, 1999.

(6) Duplantier, A. J.; Becker, S. L.; Bohanon, M. J.; Borzilleri, K. A.; Chrunyk, B. A.; Downs, J. T.; Hu, L. Y.; El-Kattan, A.; James, L. C.; Liu, S.; Maklad, N.; Mansour, M. N.; Mente, S.; Piotrowski, M. A.; Sakya, S. M.; Sheehan, S.; Steyn, S. J.; Strick, C. A.; Williams, V. A.; Zhang, L. *J. Med. Chem.* **2009**, *52*, 3576.

(7) (a) Kraus, J.; Verlinde, C.; Karimi, M.; Lepesheva, G.; Gelb, M.; Buckner, F. *J. Med. Chem.* **2009**, *52*, 1639. (b) Kraus, J.; Tatipaka, H.; McGuffin, S.; Chennamaneni, N.; Karimi, M.; Arif, J.; Verlinde, C.; Buckner, F.; Gelb, M. *J. Med. Chem.* **2010**, *53*, 3887.

(8) (a) Cunningham, K. G.; Freeman, G. G. *Biochem. J.* **1953**, *53*, 328. (b) Bracken, A.; Pocker, A.; Raistrick, H. *Biochem. J.* **1954**, *57*, 587. (c) Luckner, M.; Mothes, K. *Tetrahedron Lett.* **1962**, *3*, 1035.

(9) (a) Luckner, M.; Mothes, K. *Arch. Pharm.* **1963**, *296*, 18. (b) Mohammed, Y. S.; Luckner, M. *Tetrahedron Lett.* **1963**, *4*, 1953. (c) Wei, M.-Y.; Yang, R.-Y.; Shao, C.-L.; Wang, C.-Y.; Deng, D.-S.; She, Z.-G.; Lin, Y.-C. *Chem. Nat. Compd.* **2011**, *47*, 322.

(10) Austin, D. J.; Meyers, M. B. *J. Chem. Soc.* **1964**, *1*, 1197.

(11) Heguy, A.; Cai, P.; Meyn, P.; Houck, D.; Russo, S.; Michitsch, R.; Pearce, C.; Katz, B.; Bringmann, G.; Feineis, D.; Taylor, D. L.; Tyms, A. S. *Antiviral Chem. Chemother.* **1998**, *9*, 149.

(12) Ribeiro, N.; Tabaka, H.; Peluso, J.; Fetzer, L.; Nebigil, C.; Dumont, S.; Muller, C. D.; Désaubry, L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5523.

(13) (a) Greibrokk, T.; Undheim, K.; et al. *Acta Chem. Scand.* **1971**, *25*, 2935. (b) Johnsen, B. A.; Undheim, K.; et al. *Acta Chem. Scand.* **1984**, *38*, 109.

(14) Paterna, R.; André, V.; Duarte, M. T.; Veiros, L. F.; Candeias, N. R.; Gois, P. M. P. *Eur. J. Org. Chem.* **2013**, *28*, 6280.

(15) Sagong, H. Y.; Parhi, A.; Bauman, J. D.; Patel, D.; Vijayan, R. S.; Das, K.; Arnold, E.; LaVoie, E. J. *ACS Med. Chem. Lett.* **2013**, *4*, 547.

(16) Huntress, E. H.; Bornstein, J.; Hearon, W. M. *J. Am. Chem. Soc.* **1956**, *78*, 2225.

(17) Kobayashi, Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603.

(18) (a) White, J. D.; Dimsdale, M. J. *J. Chem. Soc. D* **1969**, 1285. (b) Martin, P. K.; Rapoport, H.; Smith, H. W.; Wong, J. L. *J. Org. Chem.* **1969**, *34*, 1359. (c) Smith, H. W.; Rapoport, H. *J. Am. Chem. Soc.* **1969**, *91*, 6083. (d) Terada, A.; Yabe, Y.; Miyadera, T.; Tachikawa, R. *Chem. Pharm. Bull.* **1973**, *21*, 807.

(19) Yuan, Y.; Yang, R.; Zhang-Negrerie, D.; Wang, J.; Du, Y.; Zhao, K. *J. Org. Chem.* **2013**, *78*, 5385.

(20) (a) Nagarsenkar, A.; Prajapti, S. K.; Guggilapu, S. D.; Babu, B. N. *Org. Lett.* **2015**, *17*, 4592. (b) Manasa, K. L.; Sastry, K. N. V.; Tangella, Y.; Babu, B. N. *ChemistrySelect* **2018**, *3*, 2730. (c) Manasa, K. L.; Tangella, Y.; Ramu, G.; Babu, B. N. *ChemistrySelect* **2017**, *2*, 9162. (d) Guggilapu, S. D.; Guntukub, L.; Reddy, T. S.; Nagarsenkar, A.; Sigalapallia, D. K.; Naidu, V. G. M.; Bhargava, S. K.; Babu, B. N. *Eur. J. Med. Chem.* **2017**, *128*, 1. (e) Nagarsenkar, A.; Guntuku, L.; Prajapti, S. K.; Guggilapu, S. D.; Sonar, R.; Naidu, G. V. M; Babu, B. N. *New J. Chem.* **2017**, *41*, 12604.

(21) (a) Kamal, A.; Sastry, K. N. V.; Chandrasekhar, D.; Mani, G. S.; Adiyala, P. R.; Nanubolu, J. B.; Singarapu, K. K.; Maurya, R. A. *J. Org. Chem.* **2015**, *80*, 4325. (b) Xia, Y.; Wang, J. *Chem. Soc. Rev.* **2017**, *46*, 2306. (c) Fu, R.; Li, Z. *Org. Lett.* **2018**, *20*, 2342.

(22) Allwood, D. M.; Blakemore, D. C.; Ley, S. V. *Org. Lett.* **2014**, *16*, 3064.

DOI: 10.1021/acs.orglett.8b01417
Org. Lett. XXXX, XXX, XXX−XXX