Organic LETTERS

Letter

pubs.acs.org/OrgLett

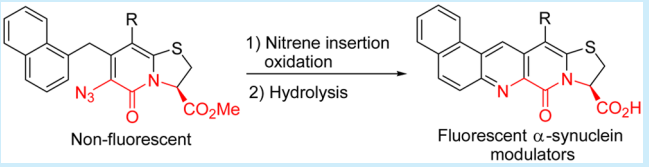
Synthesis of Multiring Fused 2-Pyridones via a Nitrene Insertion Reaction: Fluorescent Modulators of α-Synuclein Amyloid Formation

Pardeep Singh,[†] Erik Chorell,[†] K. Syam Krishnan,[§] Tomas Kindahl,[†] Jörgen Åden,[†] Pernilla Wittung-Stafshede,[†,‡] and Fredrik Almqvist*[,†]

[†]Umeå University, Department of Chemistry, 90187 Umeå, Sweden

Supporting Information

ABSTRACT: An efficient, straightforward method for the synthesis of thiazolo-2-pyridone embedded peptidomimetic polyheterocycles via a catalyst-free, microwave-assisted, intramolecular C−H amination reaction is reported. All the synthesized polyheterocycles were evaluated for their fluorescent properties and effect on α-synuclein amyloid formation.



Polyheterocycles are found in a number of biologically important synthetic and natural products.[1,2] Furthermore, aiming at biologically active compounds, the construction of polyheterocycles around privileged substructures has attracted considerable attention.[3] This approach requires a bioactive substructure which can be easily equipped with reactive centers and subsequently transformed into polyheterocyclic structures. One such moiety is the 2-pyridone scaffold, which has contributed significantly in pharmaceutical, polymer, and material chemistry.[4] 2-Pyridone derived polyheterocycles are present in many natural products, for example, camptothecin, **1**, and sempervilam, **2** (Figure 1), and are associated with interesting biological and pharmacological activities.[5]

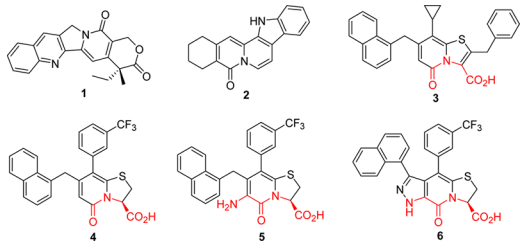


Figure 1. 2-Pyridone containing natural products (**1** and **2**), pilicide (**3**), curlicide (**4**), and α-synuclein inhibitors (**5** and **6**).

Thiazolo-2-pyridones are bicyclic peptidomimetic scaffolds known for their ability to inhibit bacterial virulence. Some derivatives, termed pilicides[6a−d] (**3**, Figure 1, peptidomimetic backbone highlighted in red), interfere with pili biogenesis in uropathogenic *E. coli*, while others with larger substituents (e.g., *m*-CF_3-phenyl, **4**) inhibit formation of the bacterial amyloid known as curli and Alzheimer β-peptides[7a−c] (**4**, Figure 1). Recently, we have disclosed that these amyloid inhibitors also act as modulators for the fiber formation of α-synuclein, an amyloid forming protein involved in Parkinson's disease.[7d,e] For example, compound **4** templates the formation of α-synuclein fibers, but compounds **5** and **6** (Figure 1), with an extended peptidomimetic backbone, are inhibitors. Thus, it is evident from the previous studies that the nature of the substituents on the central fragment is crucial to the biological effect. Thiazolo-2-pyridones have served as versatile substrates for the construction of structurally diverse tricyclic to polyheterocyclic skeletons.[8a−f]

Aware of the optical properties of our previously reported polyheterocyclic 2-pyridones[8f] and the biological role played by scaffolds with an extended peptidomimetic backbone,[7d] we became interested in 2-pyridone based bioactive fluorophores. We envisioned that intramolecular C−N bond formation via nitrene insertion would be an attractive way to synthesize fluorescent 2-pyridone annulated polyheterocycles with an extended peptidomimetic backbone (Figure 2).

In recent years, azides have been utilized as convenient starting materials in the synthesis of *N*-heterocycles via nitrene insertion.[9] Thermal,[10] photo-,[11] or transition metal catalyzed[12] decomposition of an azide generates a nitrene which has the potential to accomplish C−H insertion, forming a carbon−nitrogen bond.

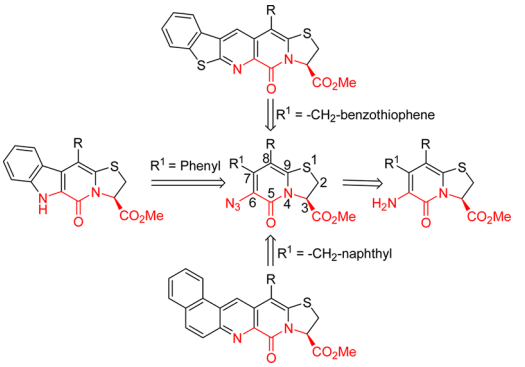


Figure 2. Outlined approach to polyheterocycles.

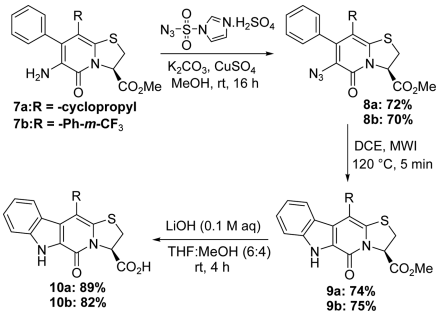
Received: November 4, 2015

DOI: 10.1021/acs.orglett.5b03190
Org. Lett. XXXX, XXX, XXX−XXX

Although nitrene insertion reactions of azido-2-pyridones for the construction of isoxazolo[4,3-*c*]pyridones,[13] pyrido[2,3-*b*]-[1,5]benzodiazepines,[14] and indolo[2,3:4,5] pyrido[2,3-*d*]-pyrimidines[15] have been reported, their potential in the synthesis of 2-pyridone based peptidomimetic polyheterocycles have not been previously explored. In the present work, we report a microwave-assisted synthesis of indole/benzoquinoline/benzothienopyridine-2-pyridone annulated peptidomimetics via a transition-metal-free nitrene insertion reaction. The utilized protocol allows access to diverse bioactive and fluorescent polyheterocycles from readily available azido-2-pyridones.

The synthesis of the intermediate 6-amino-2-pyridones **7a** and **7b** was accomplished using previously reported procedures.[16] Using these intermediates, 6-azido-2-pyridones **8a** and **8b** could be synthesized in good yields by treatment of 6-amino-2-pyridones **7a** and **7b** with the sulfuric acid salt of imidazole-1-sulfonyl azide[17] in the presence of K_2CO_3 and $CuSO_4$ at room temperature (Scheme 1).

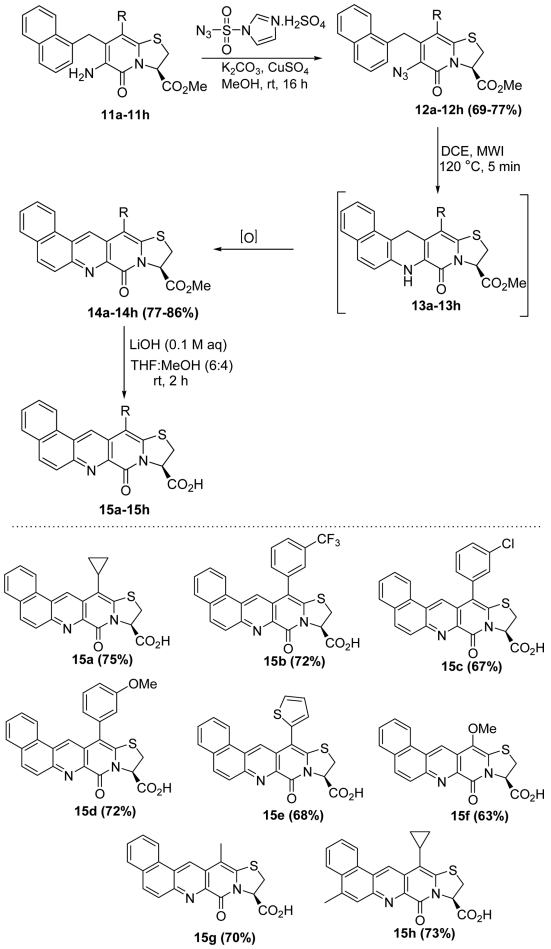
Scheme 1. Synthesis of Indole Annulated 2-Pyridones



Nitrene insertion chemistry has been used extensively for the synthesis of indole or polyfused indole rings,[18] and we accordingly first investigated the possibility of building an indole ring fused 2-pyridone system by the thermolysis of azido-2-pyridone **8**. The generation of nitrenes from azides usually requires harsh conditions and/or metal catalysts. However, thermolysis of pyridone **8a** and **8b** in 1,2-dichloroethane (DCE) by heating under microwave irradiation at 120 °C for 5 min delivered polyheterocycle **9a** and **9b** in good yields. In all our previous studies of amyloid modulators it was shown that the carboxylic acid was essential for activity;[7d,e] thus, the esters **9a** and **9b** were hydrolyzed with LiOH followed by acidic workup to the corresponding carboxylic acids **10a** and **10b**.

Having succeeded in constructing the five-membered ring, we turned our attention toward the possibility of forming a six-membered ring to rigidify our previously studied amyloid modulators (e.g., **4** and **5**, Figure 1). Thus, a series of azido-pyridones **12a−12h** were synthesized from the corresponding amino-pyridones **11a−11h** following the same conditions as developed for the indole fused analogues. The substituent at position C-8 (see Figure 2 for numbering) on the pyridone ring was varied from alkyl to aryl, heteroaryl, and an alkoxy group to establish the substrate scope of the reaction and to establish initial structure−activity relationship information in the subsequent testing for their ability to modulate α-synuclein fiber formation. We were pleased to see that our reaction conditions proved general as thermolysis of azido-pyridones **12a−12h** furnished benzoquinoline annulated 2-pyridones **14a−h** in 77−86% yield (Scheme 2).

Scheme 2. Synthesis of Benzoquinoline Annulated 2-Pyridones



The reaction is believed to proceed through the formation of a nitrene, which undergoes insertion into the naphthyl C−H bond to form intermediates **13a−13h**, which next oxidize spontaneously to the target compounds **14a−14h**. The nature of the substituents did not affect the outcome of the reaction significantly and excellent yields were obtained in all cases. Finally, compounds **14a−14h** were hydrolyzed to the corresponding acids **15a−15h** in good yields.

To further probe the scope of our method we attempted the cyclization onto a benzothiophene ring. The azido-pyridones **16a** and **16b** were synthesized from the corresponding amines as previously. Subsequent thermolysis of compounds **16a** and **16b** resulted in polyheterocycles **17a** and **17b** in 65% and 69% yield (Scheme 3), respectively. Hydrolysis of **17a** and **17b** gave carboxylic acids **18a** and **18b**.

The fluorescent properties of the 2-pyridone annulated polyheterocycles were then examined (Table 1). The benzoquinoline annulated 2-pyridones **15a−15h** generally showed quantum yields around 20% except for **15e** and **15f** that displayed lower quantum yields, 2% and 1% respectively.

Benzothienopyridine annulated 2-pyridones **18a** and **18b** also showed lower quantum yields (7% and 6% respectively) compared to the benzoquinoline annulated 2-pyridones **15a** and **15b** (19% and 21% respectively), thus emphasizing the importance of the structure of the polycyclic backbone on the fluorescent properties. The indole annulated 2-pyridone **10a** showed a quantum yield of 11%, but interestingly, its analogue

DOI: 10.1021/acs.orglett.5b03190
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of Benzothienopyridine Annulated 2-Pyridones

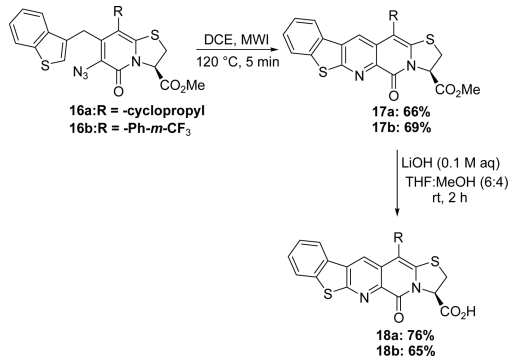


Table 1. Quantum Yield of Fluorescence (Φ_f) and Fluorescence Lifetime (τ_f) of 2-Pyridone Annulated Polyheterocycles When Dissolved in Ethanol at 20 °C

compound	em_{max} (nm)	Φ_f[a]	τ_f (ns)[c]
10a	420	0.11	2.1[d]
10b	420	0.04	0.6[d]
15a	510	0.19	12.1
15b	505	0.21	11.7
15c	510	0.24	12.4
15d	515	0.23	14.0
15e	550	0.02	1.9
15f	580	0.01	0.7
15g	515	0.19	12.9
15h	510	0.18	10.9
18a	505	0.07[b]	7.2
18b	500	0.06[b]	4.7

[a] λ_{ex} = 355 nm. [b] λ_{ex} = 335 nm. [c] λ_{ex} = 404 nm. [d] λ_{ex} = 375 nm.

10b with *m*-CF_3−Ph at position C-8 only showed a quantum yield of 4%. The fluorescence lifetime of the compounds follows the same trend as the quantum yields, with generally long lifetimes (11−14 ns) for benzoquinoline annulated 2-pyridones but with **15e** and **15f** as exceptions (1.9 and 0.7 ns respectively). Compounds **18a** and **18b** showed lifetimes of 7.2 and 4.7 ns, respectively. The lifetime was also short for the indole annulated polyheterocycles i.e. 2.1 and 0.6 ns for **10a** and **10b** respectively. Analogous polyheterocyclic 2-pyridones with similar photophysical properties as **15c**, **15d**, **15g**, and **15h** have previously proven to be useful in biological systems,[8f] thus indicating that these benzoquinoline annulated 2-pyridones can be used as fluorescent probes or tags in biological systems.

Finally, all compounds were evaluated for their ability to affect α-synuclein amyloid formation as measured by increased ThT fluorescence upon amyloid formation. Interestingly, compounds **15d**, **18b**, and **15b** proved to accelerate α-synuclein amyloid formation almost as efficiently as the previously most effective accelerating compound FN075 (**4**, Figure 1). Compounds **15f**, **15g**, and **18a** on the other hand significantly reduced the rate of α-synuclein amyloid formation (Figure 3), but the other compounds did not significantly effect this system (see Supporting Information). We have previously shown that small variations on the central fragment can result in drastic changes in the effect of the compounds on α-synuclein amyloid formation.[7d] In all previous examples[7d,e] where we have studied bicyclic or tricyclic 2-pyridones, a larger C-8 substituent has been essential to see any amyloid modulating properties. Interestingly, in this

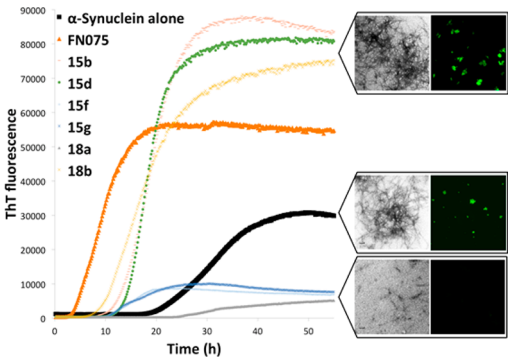


Figure 3. Affect on α-synuclein aggregation.

study we concluded that benzoquinoline fused 2-pyridones or benzothienopyridines fused 2-pyridones in combination with smaller C-8 substituents (i.e., Me-, MeO-, and cyclopropyl) may also be inhibitors. However, all accelerators identified in this study are equipped with a larger substituent (i.e., *m*-CF_3Ph or *m*-OMePh in C-8).

To ensure that the observed effect in the ThT assay actually correlated with α-synuclein amyloid formation and was not an effect of fluorescence disturbance or ThT binding, we analyzed the end products from the ThT assay by using fluorescence microscopy and EM. The fluorescence microscopy did not show any fluorescent amyloid deposits when inhibitory compounds were used, whereas fluorescent amyloid deposits were clearly visible when accelerating compounds were used (Figure 3). Also, the EM samples showed no or only small amounts of α-synuclein amyloid fibers in the case of inhibitors, but large deposits of intertwined α-synuclein amyloid fibers in the case of accelerators (Figure 3). These data support the ThT assay data, showing both compounds that can accelerate and others that can reduce the rate of α-synuclein amyloid formation, depending on their C-8 substituent.

In conclusion, we have developed methods to synthesize new peptidomimetic polyheterocycles using an intramolecular C−N bond formation via a metal-free nitrene insertion reaction under microwave conditions. The protocol results in a clean and efficient reaction with easy purifications and excellent yields that can be used to synthesize new fluorescent and biologically interesting polyheterocycles. As an example, we synthesized a set of rigidified analogues of our previously published amyloid modulators. Biological evaluation of these multiring fused 2-pyridones revealed both fluorescent accelerators and fluorescent inhibitors of α-synuclein amyloid formation depending on the C-8 substituents. Interestingly, the rigidification of the central fragment for the first time resulted in inhibitory analogues with smaller C-8 substituents (i.e., methyl, methoxy, cyclopropyl). This knowledge will be important in the design of future improved α-synuclein modulators. More detailed investigations will be undertaken in the future to understand how the difference in substitution pattern and central fragment constitution affect the biological activity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03190.

DOI: 10.1021/acs.orglett.5b03190
Org. Lett. XXXX, XXX, XXX−XXX

Experimental procedure; spectroscopic and analytical data for all new compounds; absorption and emission spectra for final carboxylic acids (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: Fredrik.almqvist@umu.se.

Present Addresses

‡Chalmers University of Technology, Department of Biology and Biological Engineering, Division of Chemical Biology, 41296 Göteborg, Sweden.

§Department of chemistry, Mannam Memorial NSS College, Kottiyam, Kollam, 691571 Kerala, India.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

F.A. is grateful to the Swedish Research Council (621-2010-4730), the Knut and Alice Wallenberg Foundation, the Göran Gustafsson Foundation, the Swedish Foundation for Strategic Research, and the Michael J. Fox Foundation for financial support. P.S. postdoctoral scholarship was supported by the Umeå Centre for Microbial Research, and K.S.K. was supported by the J. C. Kempe Foundation. P.W.S. is grateful to the Swedish Research Council and the Knut and Alice Wallenberg Foundation for funding.

REFERENCES

(1) See, for example: (a) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825−1838. (b) Pilli, R. A.; De Oliveira, M. C. F. *Nat. Prod. Rep.* **2000**, *17*, 117−127. (c) Kornienko, A.; Evidente, A. *Chem. Rev.* **2008**, *108*, 1982−2014. (d) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264−287. (e) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080−3098. (f) Pilli, R. A.; Rosso, G. B.; De Oliveira, M. C. F. *Nat. Prod. Rep.* **2010**, *27*, 1908−1937. (g) Sridharan, V.; Suryavanshi, P. A.; MenØndez, J. C. *Chem. Rev.* **2011**, *111*, 7157−7259. (h) Hu, J.-F.; Fan, H.; Xiong, J.; Wu, S.-B. *Chem. Rev.* **2011**, *111*, 5465−5491.

(2) For recent reviews of heterocycles in drug molecules, see: (a) Dua, R.; Shrivastava, S.; Sonwane, S. K.; Shrivastava, S. K. *Adv. Biol. Res.* **2011**, *5*, 120−144. (b) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265−2319. (c) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274. (d) Hussain, H.; Al-Harrasi, A.; Al-Rawahi, A.; Green, I. R.; Gibbons, S. *Chem. Rev.* **2014**, *114*, 10369−10428.

(3) Kim, J.; Kim, H.; Park, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 14629−14638.

(4) (a) Margrey, K. A.; Hazzard, A. D.; Scheerer, J. R. *Org. Lett.* **2014**, *16*, 904−907 and references cited therein. (b) Hibi, S.; Ueno, K.; Nagato, S.; Kawano, K.; Ito, K.; Norimine, Y.; Takenaka, O.; Hanada, T.; Yonaga, M. *J. Med. Chem.* **2012**, *55*, 10584−10600. (c) Hagimori, M.; Temma, T.; Mizuyama, N.; Uto, T.; Yamaguchi, Y.; Tominaga, Y.; Mukai, T.; Saji, H. *Sens. Actuators, B* **2015**, *213*, 45−52.

(5) (a) Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478−4479. (b) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888−3890. (c) Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757−1779.

(6) (a) Åberg, V.; Almqvist, F. *Org. Biomol. Chem.* **2007**, *5*, 1827−1834. (b) Pinkner, J. S.; Remaut, H.; Buelens, F.; Miller, E.; Åberg, V.; Pemberton, N.; Hedenström, M.; Larsson, A.; Seed, P.; Waksman, G.; Hultgren, S. J.; Almqvist, F. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 17897−17902. (c) Greene, S. E.; Pinkner, J. S.; Chorell, E.; Dodson, K. W.; Shaffer, C. L.; Conover, M. S.; Livny, J.; Hadjifrangiskou, M.; Almqvist, F.; Hultgren, S. J. *mBio* **2014**, *5*, e02038-14. (d) Chorell, E.; Pinkner, J. S.; Phan, G.; Edvinsson, S.; Buelens, F.; Remaut, H.; Waksman, G.; Hultgren, S. J.; Almqvist, F. *J. Med. Chem.* **2010**, *53*, 5690−5695.

(7) (a) Åberg, V.; Norman, F.; Chorell, E.; Westermark, A.; Olofsson, A.; Sauer-Eriksson, A. E.; Almqvist, F. *Org. Biomol. Chem.* **2005**, *3*, 2817−2823. (b) Cegelski, L.; Pinkner, J. S.; Hammer, N. D.; Cusumano, C. K.; Hung, C. S.; Chorell, E.; Åberg, V.; Walker, J. N.; Seed, P. C.; Almqvist, F.; Chapman, M. R.; Hultgren, S. J. *Nat. Chem. Biol.* **2009**, *5*, 913−919. (c) Andersson, E. K.; Bengtsson, C.; Evans, M. L.; Chorell, E.; Sellstedt, M.; Lindgren, A. E. G.; Hufnagel, D. A.; Bhattacharya, M.; Tessier, P. M.; Wittung-Stafshede, P.; Almqvist, F.; Chapman, M. R. *Chem. Biol.* **2013**, *20*, 1245−1254. (d) Horvath, I.; Weise, C. F.; Andersson, E. K.; Chorell, E.; Sellstedt, M.; Bengtsson, C.; Olofsson, A.; Hultgren, S. J.; Chapman, M. R.; Wolf-Watz, M.; Almqvist, F.; Wittung-Stafshede, P. *J. Am. Chem. Soc.* **2012**, *134*, 3439−3444. (e) Horvath, I.; Sellstedt, M.; Weise, C.; Nordvall, L.-M.; Prasad, G. K.; Olofsson, A.; Larsson, G.; Almqvist, F.; Wittung-Stafshede, P. *Arch. Biochem. Biophys.* **2013**, *532*, 84−90.

(8) (a) Pemberton, N.; Jakobsson, L.; Almqvist, F. *Org. Lett.* **2006**, *8*, 935−938. (b) Sellstedt, M.; Almqvist, F. *Org. Lett.* **2009**, *11*, 5470−5472. (c) Sellstedt, M.; Almqvist, F. *Org. Lett.* **2011**, *13*, 5278−5281. (d) Sellstedt, M.; Almqvist, F. *Org. Lett.* **2008**, *10*, 4005−4007. (e) Bengtsson, C.; Almqvist, F. *J. Org. Chem.* **2011**, *76*, 9817−9825. (f) Sellstedt, M.; Nyberg, A.; Rosenbaum, E.; Engstrom, P.; Wickstrom, M.; Gullbo, J.; Bergstrom, S.; Johansson, L. B. A.; Almqvist, F. *Eur. J. Org. Chem.* **2010**, *2010*, 6171−6178.

(9) (a) Hajos, G.; Riedl, Z. *Curr. Org. Chem.* **2009**, *13*, 791−809. (b) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191−5194. (c) Shen, M.; Driver, T. G. *Org. Lett.* **2008**, *10*, 3367−3370. (d) Dong, H.; Latka, R. T.; Driver, T. G. *Org. Lett.* **2011**, *13*, 2726−2729.

(10) (a) Sundberg, R. J.; Gillespie, D. W.; DeGraff, B. A. *J. Am. Chem. Soc.* **1975**, *97*, 6193−6196. (b) Sundberg, R. J.; Russell, H. F.; Ligon, W. V.; Lin, L.-S. *J. Org. Chem.* **1972**, *37*, 719−724. (c) Smith, P. A. S.; Hall, J. H. *J. Am. Chem. Soc.* **1962**, *84*, 480−485. (d) Smith, P. A. S.; Brown, B. B. *J. Am. Chem. Soc.* **1951**, *73*, 2435−2437.

(11) (a) Von, E.; Doering, W.; Odum, R. A. *Tetrahedron* **1966**, *22*, 81−93. (b) Swenton, J. S.; Ikeler, T. J.; Williams, B. H. *J. Am. Chem. Soc.* **1970**, *92*, 3103−3109. (c) Albini, A.; Bettinetti, G.; Minoli, G. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2803−2808. (d) Isomura, K.; Kobayashi, S.; Taniguchi, H. *Tetrahedron Lett.* **1968**, *9*, 3499−3502.

(12) (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297−368. (b) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240.

(13) Khattab, A. F. *Liebigs Ann.* **1996**, *1996*, 393−395.

(14) Mekheimer, R. A.; El-Hameid, A. M.; Sadek, K. U. *J. Heterocycl. Chem.* **2008**, *45*, 97−101.

(15) Dang, V. T.; Stadlbauer, W. *Molecules* **1997**, *1*, 201−206.

(16) Åberg, V.; Sellstedt, M.; Hedenstrom, M.; Pinkner, J. S.; Hultgren, S. J.; Almqvist, F. *Bioorg. Med. Chem.* **2006**, *14*, 7563−7581.

(17) Fischer, N.; Goddard-Borger, E. D.; Greiner, R.; Klapötke, T. M.; Skelton, B. W.; Stierstorfer, J. *J. Org. Chem.* **2012**, *77*, 1760−1764.

(18) (a) Tollari, S.; Cenini, S.; Rossi, A.; Palmisano, G. *J. Mol. Catal. A: Chem.* **1998**, *135*, 241−248. (b) Grubbs, A. W.; Artman, G. D.; Williams, R. M. *Tetrahedron Lett.* **2005**, *46*, 9013−9016. (c) Matyus, P.; Maes, B. U. W.; Riedl, Z.; Hajos, G.; Lemiere, G. L. F.; Tapolcsanyi, P.; Monsieurs, K.; Elias, O.; Dommisse, R. A.; Krajsovszky, G. *Synlett* **2004**, *7*, 1123−1139. (d) Krajsovszky, G.; Matyus, P.; Riedl, Z.; Csanyi, D.; Hajos, G. *Heterocycles* **2001**, *55*, 1105−1111. (e) Riedl, Z.; Monsieurs, K.; Krajsovszky, G.; Dunkel, P.; Maes, B. U. W.; Tapolcsanyi, P.; Egyed, O.; Boros, S.; Matyus, P.; Pieters, L.; Lemiere, G. L. F.; Hajos, G. *Tetrahedron* **2006**, *62*, 121−129. (f) Blake, A. J.; Clark, B. A. J.; McNab, H.; Sommerville, C. C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1605−1608.

DOI: 10.1021/acs.orglett.5b03190
Org. Lett. XXXX, XXX, XXX−XXX