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Thermolysis of Geminal Diazides: Reagent-Free Synthesis of 3-Hydroxypyridines

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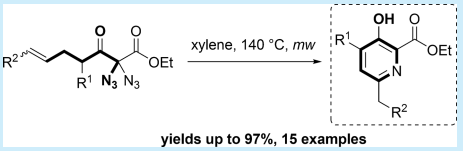
Supporting Information

ABSTRACT: An operationally simple protocol for the rapid and efficient construction of highly substituted 3-hydroxypyridines is presented. The thermally induced cyclization of easily constructed geminal diazides derived from β-ketoesters having an additional olefin moiety affords the title compounds in yields up to 97% under reagent-free conditions. The new method allows for the synthesis of preparative quantities of material. Additionally, the synthetic utility of the pyridine products for the synthesis of valuable heterocycles is described.



The intriguing chemical nature of the pyridine heterocycle in combination with its prominence in natural products[1] and pharmaceuticals[2] has inspired chemists to develop new and efficient methodologies toward its synthesis.[3] In particular, 3-hydroxypyridines have recently attracted attention due to their promising biological activity (Figure 1). The motif can be

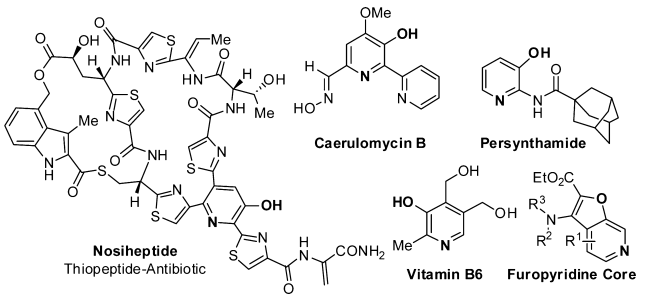
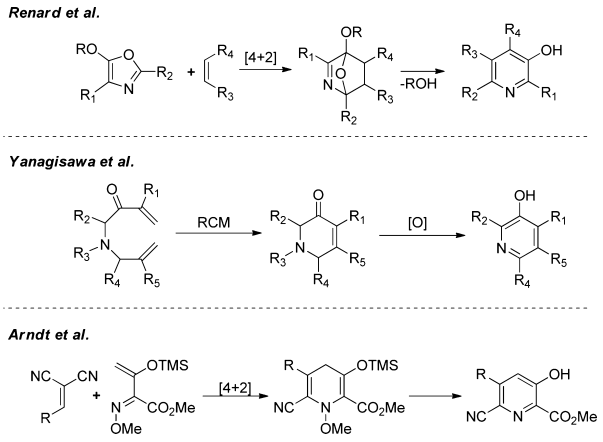


Figure 1. 3-Hydroxyypridines in nature and medicinal chemistry.

found in nosiheptide[4] and nocathiacine,[5] both of which exhibit antibiotic activity and are valuable entries to the family of thiopeptide antibiotics. The 3-hydroxypyridine core is also part of caerulomycin B[6] isolated from *Streptomyces caeruleus* and persynthamide.[7] Arguably the most known representative is vitamin B6, an essential cofactor of the amino acid metabolism.[8] 3-Hydroxypyridines are also valuable starting materials for the synthesis of furopyridines, many of which are promising B-Raf inhibitors.[9]

Several methods for the synthesis of 3-hydroxypyridines have been developed,[10] some of which are depicted in Scheme 1. In particular, questions regarding the regioselective construction of this heterocyclic core are still an ongoing important synthetic challenge. For example, Renard and co-workers contributed to this area via Kondrat'eva cycloaddition and subsequent cleavage of the resulting oxabicyclic products.[11] Yanagisawa and co-workers utilized ring-closing metathesis for the construction of pyridinones, which afforded 3-hydroxypyridines upon oxidation.[12] Moreover, Arndt and co-workers achieved the synthesis

Scheme 1. Strategies for the Synthesis of 3-Hydroxypyridines



of dihydropyridines through highly regioselective hetero-Diels–Alder cycloaddition followed by aromatization to the 3-hydroxypyridine core.[13]

We came in contact with this field of heterocyclic chemistry as part of our ongoing efforts to employ geminal diazides as valuable synthetic intermediates.[14] More recently, we have reported methods for the synthesis of geminal triazides[15a] and geminal diazides derived from 1,3-dicarbonyls.[16] We also used geminal diazides for the synthesis of azidomethylenebistriazoles and their corresponding geminal tristriazoles.[17] The thermolysis of geminal diazides became of particular interest: Early studies hinted at a great, but still undisclosed, potential for the synthesis of nitrogen-containing heterocycles.[18] By expansion of the works by Rank and Ogilvie,[18c] we showed that geminal diazides are powerful starting materials for the preparation of 1,3,4-oxadiazoles through thermolysis, as exemplified in eq 1.[19]

To our surprise, conventional heating of geminal diazide **1a** with an additional olefin moiety in xylene did not provide the

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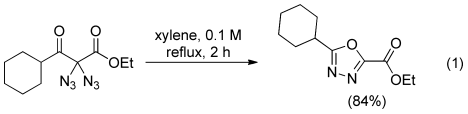
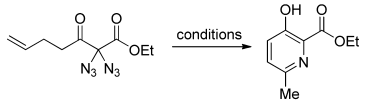


(1)

oxadiazole core. Instead, 3-hydroxypyridine **2a** was isolated in 58% yield (Table 1, entry 1). The originally expected 1,3,4-oxadiazole was not formed under the reaction conditions. We now report that a promising range of 3-hydroxypyridines can be generated from 2,2-diazido-3-oxohept-6-enoates through simple and reagent-free thermolysis. The method will likely become a useful alternative to existing methods for the synthesis of 3-hydroxypyridines, since the diazide starting materials were previously found to be remarkably stable and are easily accessed when the dicarbonyl precursors are stirred with iodine and sodium azide in aqueous DMSO at room temperature.[16a]

Table 1. Optimization of the Reaction Conditions for 2a



1a **2a**

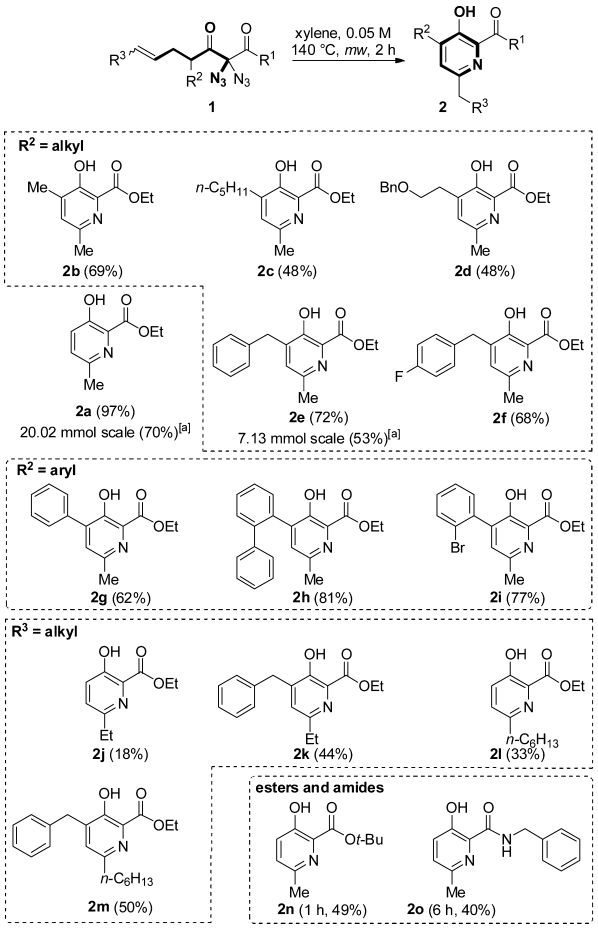
entry	solvent	c (mol/L)	temp (°C)	yield[a] (%)	comment
1	xylene	0.1	138	58	
2	xylene	0.1	138	54	+ $NaHCO_3$
3	toluene	0.1	111	59	
4	1,2-$Cl_2C_6H_4$	0.1	180	11	
5	benzene	0.1	80	23	
6	*n*-octane	0.1	126	47	
7	xylene	0.1	25		*hν*[b]
8	NMP	0.1	130		dec
9	MeCN	0.1	82	12	
10	Ph_2O	0.1	130	33	
11	**xylene**	**0.05**	**140**	**97**	**MW**[c]
12	xylene	0.05	138	70	

[a]Isolated yields. [b]254 nm irradiation. [c]Microwave irradiation.

Intrigued by our initial results on the formation of 3-hydroxypyridine **2a**, we conducted an expanded screening experiment in various solvents and under different reaction temperatures, as shown in Table 1. It was found that addition of sodium bicarbonate to intercept possible acidic byproducts had no influence on the product yield (entry 2). The use of toluene gave rise to **2a** in 59% (entry 3). 1,2-Dichlorobenzene led to a unclean conversion at a reaction temperature of 180 °C and afforded the product in poor 11% yield (entry 4). Benzene and *n*-octane as well had no positive effect on the transformation (entries 5 and 6). It is worth mentioning that geminal diazide **2a** rapidly undergoes decomposition when stirred in xylene under irradiation with light of a wavelength of 254 nm (entry 7). NMP showed no traces of the desired product (entry 8), whereas MeCN and Ph_2O afforded the product in 12% and 33% yield, respectively (entries 9 and 10). A major increase in yield was observed when the reaction was carried out in xylene at 140 °C with a concentration of 0.05 mol/L under microwave conditions to afford the product in 97% isolated yield in a remarkably clean reaction (entry 11). Conventional heating of a 0.05 M solution yielded **2a** in 70% (entry 12). As a general trend, we noticed that microwave irradiation led, in a stipulated time, to a significantly enhanced consumption of the starting material, in comparison to traditional heating at the same temperature. In addition, microwave irradiation resulted in a marked decrease of decomposition, as judged from TLC controls. We also note that unspecific intermolecular side reactions may cause lowered yields at concentrations above 0.1 M;[20] however, highly diluted reaction mixtures (<0.05 M) were impractical due to the volume limitations we faced in our microwave reactor with sealed 20 mL vials.

With the optimized reaction conditions at hand (Table 1, entry 11), we further investigated the substrate scope of the method and found that a good variety of substituted *β*–ketoesters can be transformed into the corresponding 3-hydroxypyridines in moderate to excellent yields (Scheme 2).

Scheme 2. Scope of the Thermolysis



[a]The reactions were carried out by refluxing a 0.05 M solution of the corresponding geminal diazide under conventional heating for 2 h.

The presence of alkyl substituents at C4 (R^2 = alkyl), as shown with the examples of **2b** and **2c**, is well tolerated and led to 69% and 48% yield, respectively. Benzyl ether **2d** was obtained in 48% yield. As demonstrated by the formation of **2e** in 72% and **2f** in 68%, aromatics are fine under the reaction conditions, too. Notably, the presented method allows for the preparation of biphenyls (R^2 = aryl) as it was exemplified by the formation of **2g** and **2h**, which have been obtained in 62% and 81% yield. Gratifyingly, bromo-substituted biphenyl **2i** was accessed in 77% yield. When switching from terminal to internal olefins with alkyl substituents (R^3 = alkyl), the yields dropped significantly. Pyridine **2j**, for example, was obtained in poor 18% yield. Benzylated pyridine **2k** was afforded in acceptable

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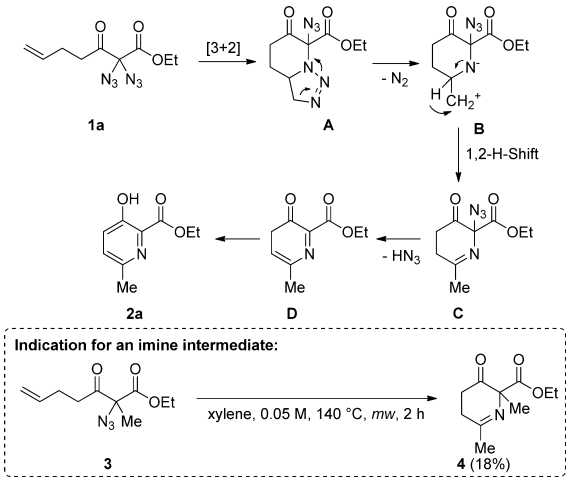
44% yield. The related heterocycles **2l** and **2m** were formed in 33% and 50% isolated yield. The synthesis of 3-hydroxypyridines was also possible with *tert*-butyl esters (e.g., **2n**) and amides (e.g., **2o**), albeit with lower yields compared to the analogous ethyl esters. We like to point out that all transformations proceeded in an extraordinarily clean manner. The isolation of the 3-hydroxypyridines was directly possible by removing the solvent after completion of the reaction followed by purification through column chromatography over silica. Because of the reagent-free protocol, no aqueous workup was necessary.

To show that the method allows for the synthesis of preparative useful amounts of substance, the synthesis of **2a** and **2e** was carried out with 5.05 and 2.44 g under conventional heating and gave rise to the products in 70% and 53% isolated yield. The reactions proceeded smoothly and without any kind of hazardous or vigorous behavior in every case, thus rendering the presented method safe and underlining the stable and easy to handle nature of the geminal diazide starting materials.[21,16a]

A rationale for the reaction was proposed and is depicted in Scheme 3. We reasoned that the geminal diazide undergoes

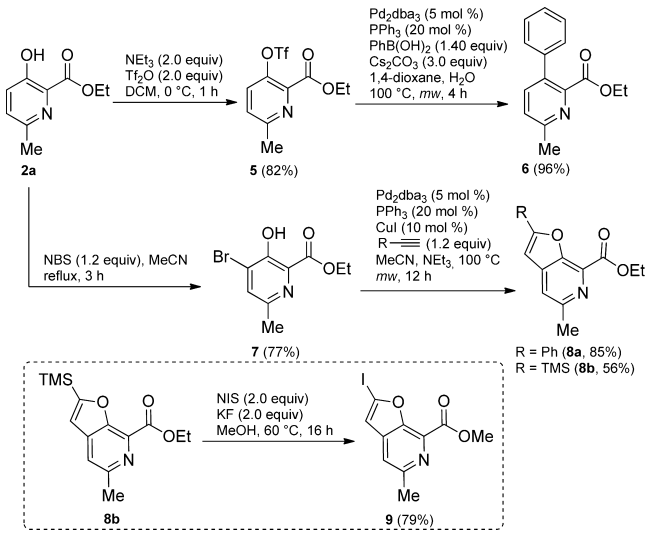
Scheme 3. Rationale for the Formation of 3-Hydroxypyridines



intramolecular [3 + 2]-Huisgen cycloaddition to form 1,2,3-Δ^2-triazoline **A**.[22] The unstable nature of **A**[23] then allows for the elimination of elemental nitrogen, thus forming **B** by a 1,2-hydride shift to give imine **C**. Finally, elimination of hydrazoic acid may lead to **D**, which after tautomerization gives rise to the aromatic title compound. A strong indication for the participation of an imine intermediate was found by conducting the thermolysis of monoazide **3**. In the absence of the second azide functionality acting as a leaving group, the only product that was detectable was the imine **4**; the sequence was stopped at this stage without the possibility of reacting under aromatization. On further notice, all reactions were accompanied by the smooth evolution of gas bubbles which can be rationalized by the loss of nitrogen during the formation of intermediate **B**. After the reaction had reached completion, no IR-signal characteristic for azides was present in the crude mixture, thus implying a complete degeneration of all azide units (including the possibly formed hydrazoic acid) under the reaction conditions.

To provide insight into the use of the obtained 3-hydroxypyridines, we then engaged in subsequent studies to show their value as starting points for the facile synthesis of attractive chemical entities (Scheme 4). Suzuki cross-coupling

Scheme 4. Selected Modifications of 3-Hydroxypyridines



of **5**, which was accessed from **2a** in 82% yield with Tf_2O and NEt_3, allowed for the synthesis of biphenyl **6** in 96% yield. Furthermore, bromination of **2a** with NBS gave rise to 4-bromopyridine **7** in 77% yield. Subsequent Sonogashira cross-coupling with an appropriate alkyne followed by intramolecular cyclization turned out to be an excellent tool for the synthesis of furo[2,3-*c*]pyridines (e.g., **8a** with R = Ph in 85% and **8b** with R = TMS in 56% yield).[24] We would like to highlight the possibility for iododesilylation of compound **8b** to furnish **9** in 79% yield (under concomitant replacement of the ethyl ester with methanol).[25] The furo[2,3-*c*]pyridines are interesting compounds in medicinal chemistry due to their promising activity as HIV-1 non-nucleoside reverse-transcriptase inhibitors[26] and human toll-like receptor agonists.[27] We consider **9** to be an attractive building block for biological studies due to its ease of construction and vast possibilities for diversification.

In conclusion, we have presented a new method for the rapid synthesis of highly substituted 3-hydroxypyridines by the simple heating of geminal diazides. The ease of accessing the diazide starting materials renders this method a flexible tool for the generation of a broad range of the title compounds, including pyridine cores with aliphatic, benzylic, and aromatic groups. Hopefully, this methodological addition to the chemistry of nitrogen-rich organic molecules inspires chemists to continue research on the field of polyazidated compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03475.

Experimental and spectral details for all new compounds and all reactions (PDF)

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Pinder, A. R. *Nat. Prod. Rep.* **1990**, *7*, 447.
(2) Goetz, A.; Garg, N. K. *Nat. Chem.* **2012**, *5*, 54.
(3) For reviews on the synthesis of multisubstituted pyridines, see: (a) Hill, M. D. *Chem. - Eur. J.* **2010**, *16*, 12052. (b) Allais, C.; Grassot, J.-M.; Rodriguez, J.; Constantieux, T. *Chem. Rev.* **2014**, *114*, 10829.
(4) Pascard, C.; Ducruix, A.; Lunel, J.; Prangé, T. *J. Am. Chem. Soc.* **1977**, *99*, 6418.
(5) Constantine, K. K.; Mueller, J.; Huang, S.; Abid, S.; Lam, K. S.; Li, W.; Leet, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 7284.
(6) McInnes, A. G.; Smith, D. G.; Wright, J. L. C.; Vining, L. C. *Can. J. Chem.* **1977**, *55*, 4159.
(7) Stern, H. M.; Murphey, R. D.; Shepard, J. L.; Amatruda, J. F.; Straub, C. T.; Pfaff, K. L.; Weber, G.; Tallarico, J. A.; King, R. W.; Zon, L. I. *Nat. Chem. Biol.* **2005**, *1*, 366.
(8) Eliot, A. C.; Kirsch, J. F. *Annu. Rev. Biochem.* **2004**, *73*, 383.
(9) (a) Cailly, T.; Lemaître, S.; Fabis, F.; Rault, S. *Synthesis* **2007**, *2007*, 3247. (b) Buckmelter, A. J.; Ren, L.; Laird, E. R.; Rast, B.; Miknis, G.; Wenglowsky, S.; Schlachter, S.; Welch, M.; Tarlton, E.; Grina, J.; Lyssikatos, J.; Brandhuber, B. J.; Morales, T.; Randolph, N.; Vigers, G.; Martinson, M.; Callejo, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1248.
(10) (a) Chubb, R. W. J.; Bryce, M. R.; Tarbit, B. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 1853. (b) Leditschke, H. *Chem. Ber.* **1952**, *85*, 202. (c) Gruber, W. *Chem. Ber.* **1955**, *88*, 178. (d) Gruber, W. *Chem. Ber.* **1955**, *88*, 178. (e) Leditschke, H. *Chem. Ber.* **1953**, *86*, 612. (f) Lipinski, C. A.; LaMattina, J. L.; Oates, P. J. *J. Med. Chem.* **1986**, *29*, 2154.
(11) Sabot, C.; Oueis, E.; Brune, X.; Renard, P.-Y. *Chem. Commun.* **2012**, *48*, 768.
(12) Yoshida, K.; Kawagoe, F.; Hayashi, K.; Horiuchi, S.; Imamoto, T.; Yanagisawa, A. *Org. Lett.* **2009**, *11*, 515.
(13) (a) Lu, J.-Y.; Keith, J. A.; Shen, W.-Z.; Schürmann, M.; Preut, H.; Jacob, T.; Arndt, H.-D. *J. Am. Chem. Soc.* **2008**, *130*, 13219. (b) Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205.
(14) For a comprehensive review regarding the synthesis and reactivity of geminal di- and triazides, see: (a) Häring, A. P.; Kirsch, S. F. *Molecules* **2015**, *20*, 20042. For an excellent review regarding the chemistry of organic azides in general, see: (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
(15) (a) Klahn, P.; Erhardt, H.; Kotthaus, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 7913. For tetraazidomethane, see: (b) Banert, Kl; Joo, Y.-H.; Rüffer, T.; Walfort, B.; Lang, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1168.
(16) (a) Erhardt, H.; Häring, A. P.; Kotthaus, A.; Roggel, M.; Tong, M. L.; Biallas, P.; Jübermann, M.; Mohr, F.; Kirsch, S. F. *J. Org. Chem.* **2015**, *80*, 12460. (b) Harschneck, T.; Hummel, S.; Kirsch, S. F.; Klahn, P. *Chem. - Eur. J.* **2012**, *18*, 1187.
(17) (a) Erhardt, H.; Mohr, F.; Kirsch, S. F. *Chem. Commun.* **2016**, *52*, 545. (b) Erhardt, H.; Kirsch, S. F. *Synthesis* **2016**, *48*, 1437.
(18) (a) Moriarty, R. M.; Serridge, P. *J. Am. Chem. Soc.* **1971**, *93*, 1534. (b) Kappe, T.; Lang, G.; Pongratz, E. *J. Chem. Soc., Chem. Commun.* **1984**, 338. (c) Ogilvie, W.; Rank, W. *Can. J. Chem.* **1987**, *65*, 166. (d) Kappe, C. O.; Färber, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, *5*, 1342.
(19) Erhardt, H.; Mohr, F.; Kirsch, S. F. *Eur. J. Org. Chem.* **2016**, 5629.
(20) We were not able to identify any side products in the course of the thermolysis reaction.
(21) Although we never encountered any problems when heating the geminal diazides **1**, we point out that diazide compounds are potentially hazardous compounds that should always be handled with great care and appropriate safety equipment.
(22) The intramolecular [3 + 2]-cycloaddition of an azide with an alkene under the formation of imines is known. For representative examples, see: (a) de Miguel, I.; Herradón, B.; Mann, E. *Adv. Synth. Catal.* **2012**, *354*, 1731. (b) Hui, B. W. Q.; Chiba, S. *Org. Lett.* **2009**, *11*, 729. (c) Zhou, Y.; Murphy, P. V. *Org. Lett.* **2008**, *10*, 3777. (d) Kim, S.; Lee, Y. M.; Lee, J.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D. *J. Org. Chem.* **2007**, *72*, 4886.
(23) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Wolff, L. *Justus Liebigs. Ann. Chem.* **1912**, *394*, 23.
(24) Chartoire, A.; Comoy, C.; Fort, Y. *Tetrahedron* **2008**, *64*, 10867.
(25) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, *2002*, 453.
(26) (a) Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. *J. Org. Chem.* **1998**, *63*, 7851. (b) Wishka, D. G.; Graber, D. R.; Kopta, L. A.; Olmsted, R. A.; Friis, J. M.; Hosley, J. D.; Adams, W. J.; Seest, E. P.; Castle, T. M.; Dolak, L. A.; Keiser, B. J.; Yagi, Y.; Jeganathan, A.; Schlachter, S. T.; Murphy, M. J.; Cleek, G. J.; Nugent, R. A.; Poppe, S. M.; Swaney, S. M.; Han, F.; Watt, W.; White, W. L.; Poel, T. J.; Thomas, R. C.; Voorman, R. L.; Stefanski, K. J.; Stehle, R. G.; Tarpley, W. G.; Morris, J. *J. Med. Chem.* **1998**, *41*, 1357.
(27) Salunke, D. B.; Yoo, E.; Shukla, N. M.; Balakrishna, R.; Malladi, S. S.; Serafin, K. J.; Day, V. W.; Wang, X.; David, S. A. *J. Med. Chem.* **2012**, *55*, 8137.

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