Organic LETTERS

Letter

pubs.acs.org/OrgLett

Acid-Mediated N−H/α,β-C(sp^3)−H Trifunctionalization of Pyrrolidine: Intermolecular [3 + 2] Cycloaddition for the Construction of 2,3-Dihydro-1*H*-Pyrrolizine Derivatives

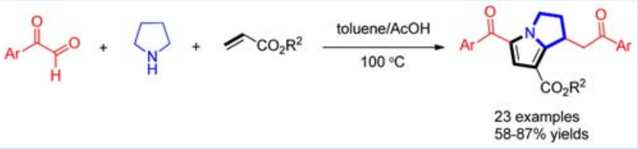
Kai-Lu Zheng,[†] Wen-Ming Shu,[†] Jun-Rui Ma,[†] Yan-Dong Wu,*[,†] and An-Xin Wu*[,†,‡]

[†]Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, Hubei 430079, P. R. China

[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

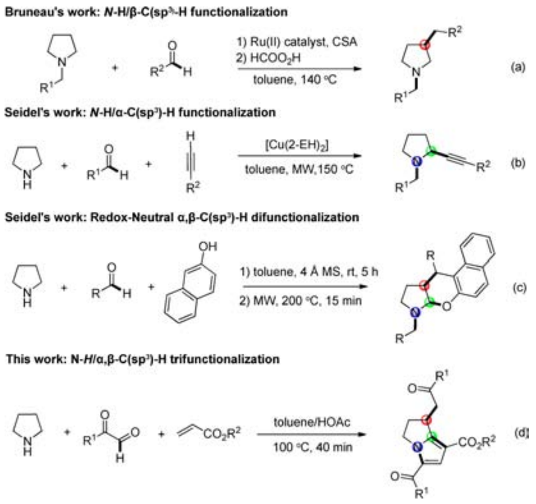
Supporting Information

ABSTRACT: A one-pot acid-mediated reaction has been developed for the N−H/α,β-C(sp^3)−H trifunctionalization of pyrrolidine without any metallic reagents or external oxidants. This reaction involves the intermolecular [3 + 2] cycloaddition of in situ-generated azomethine ylides with acrylic esters to provide facile access to 2,3-dihydro-1*H*-pyrrolizine derivatives in high yields under mild conditions.



There has recently been a considerable increase in the development of new reactions for the preparation of cyclic amines and related alkaloids because of their potential pharmaceutical value and synthetic applications.[1] Reactions between amines and aldehydes are widely used for the functionalization of cyclic amines, and significant progress has been made during the past decade toward the functionalization of cyclic amines at their N-, α-, and β-positions. N-Functionalization of cyclic amines can be achieved via reductive amination or oxidative amidation of the amine with an aldehyde.[2,3] Several strategies have also been developed for α-functionalization of cyclic amines with aldehydes using redox-neutral approaches.[4] However, because the β-C(sp^3)−H bonds of cyclic amines are inert, the preparation of β-functionalized cyclic amines always require a multistep process, and the direct functionalization of amines at the β-position remains rare.[5,6] For example, Bruneau and colleagues reported a Ru(II)-catalyzed sequential dehydrogenation process to realize the β-alkylation of N-protected pyrrolidines that proceeds via an azomethine ylide intermediate (Scheme 1a).[7] To further exploit the use of azomethine ylides as intermediates for the intermolecular functionalization of amines, Seidel's group developed a Cu(II)-catalyzed three-component coupling reaction to produce N-alkylated/α-alkynylated pyrrolidines via a redox-neutral approach (Scheme 1b).[8] The same group subsequently disclosed an appealing redox-neutral reaction for the α,β-difunctionalization of N-functionalized pyrrolidines via a transient in situ-generated enamine. Notably, the N-alkylation/α,β-difunctionalization of pyrrolidine could be performed as a two-stage/one-pot procedure (Scheme 1c).[9] Herein we report the use of acrylates to capture the azomethine ylides generated in situ from phenylglyoxal monohydrate and pyrrolidine to develop a new reaction for the acid-mediated N−H/α,β-C(sp^3)−H trifunctionalization of pyrrolidine. This new reaction provides a straightforward and efficient process for the construction of structurally diverse pyrrolizine derivatives, which are the basic skeletons in many alkaloids and exhibit a range of diverse biological and pharmacological activities,[10] including anti-inflammatory,[11] antitumor,[12] and CNS activities.[13]

Scheme 1. Models of Functionalization of Pyrrolidine



We initially explored the reaction of phenylglyoxal monohydrate (**1a**) with pyrrolidine (**2**) and ethyl acrylate (**3a**) in toluene at 80 °C in the presence of PhCO$_2$H, which afforded the desired product **4aa** in 65% yield. We subsequently evaluated the use of several different acids, solvents, and reaction temperatures to further optimize the reaction conditions, and the results of these experiments are

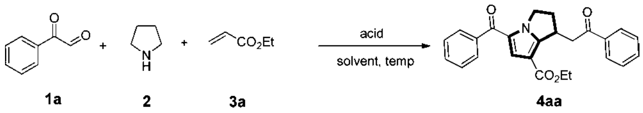
Received: May 11, 2016
Published: July 11, 2016

ACS Publications

DOI: 10.1021/acs.orglett.6b01369
Org. Lett. 2016, 18, 3526−3529

summarized in Table 1. The results revealed that the nature of the acid had a significant effect on the outcome of the reaction (Table 1, entries 1–8). For example, the use of MsOH or TfOH failed to afford any of the desired product (entries 2 and 3). Furthermore, TsOH, HCl, TFA, and PivOH gave much lower yields of the desired product (Table 1, entries 4–7). Remarkably, the yield of **4aa** increased to 70% when the reaction was carried out in the presence of AcOH (Table 1, entry 8). Several different solvents were also investigated (e.g., DMSO, 1,4-dioxane, DMF, DCE, NMP, and EA), and the results revealed that toluene is the optimal solvent for this reaction (Table 1, entries 9–15). Varying the reaction temperature from 70 to 110 °C showed that 100 °C is optimal for this protocol (Table 1, entries 16–19).

Table 1. Optimization of the Reaction Conditions[a]

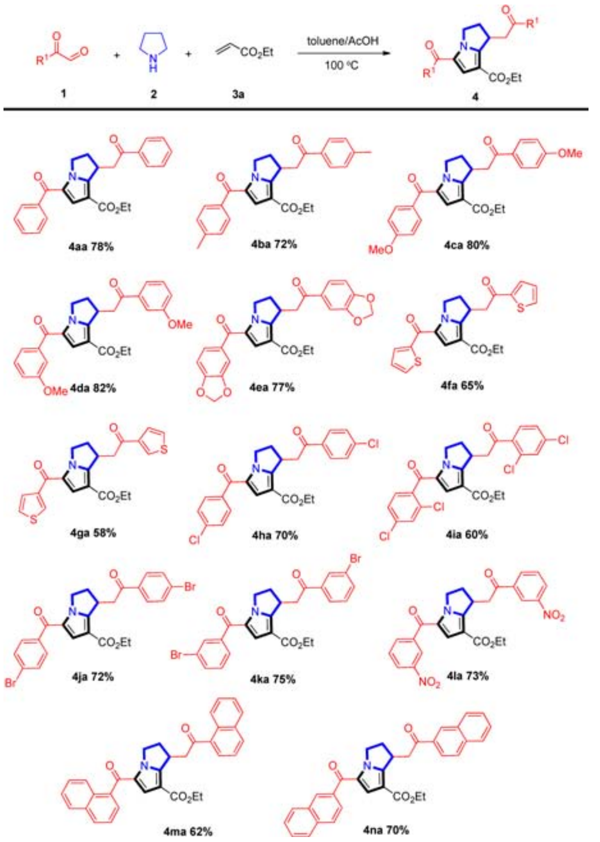


entry	solvent	acid	temp (°C)	yield (%)[b]
1	toluene	$PhCO_2H$	80	65
2	toluene	MsOH	80	–
3	toluene	TfOH	80	–
4	toluene	TsOH	80	12
5	toluene	HCl	80	10
6	toluene	PivOH[c]	80	30
7	toluene	TFA	80	15
8	toluene	AcOH	80	70
9	EG	AcOH	80	20
10	DMSO	AcOH	80	56
11	1,4-dioxane	AcOH	80	60
12	DMF	AcOH	80	62
13	DCE	AcOH	80	32
14	NMP	AcOH	80	47
15	EA	AcOH	80	28
16	toluene	AcOH	70	38
17	toluene	AcOH	90	72
18	toluene	AcOH	100	78
19	toluene	AcOH	110	40

[a] Reaction conditions: **1a** (0.2 mmol, 2.0 equiv), **2** (0.2 mmol, 2.0 equiv), **3a** (0.1 mmol, 1.0 equiv), acid (0.2 mL), and solvent (2 mL) for 40 min. [b] Isolated yields. [c] Piv = pivaloyl.

With the optimal reaction conditions in hand, we proceeded to explore the substrate scope of arylglyoxal monohydrates **1**, as shown in Scheme 2. The electronic properties of the substituents on the aromatic ring system were shown to have little influence on the efficiency of this reaction. For example, phenylglyoxal monohydrates bearing an electron-neutral (H) or electron-donating (e.g., 4-Me, 4-OMe, 3-OMe, or 3,4-OCH_2O) group reacted smoothly to give the corresponding products in good to excellent yields (72–82%; **4aa–ea**). Several heteroaromatic substrates also reacted smoothly to give the desired products in moderate yields (58–65%; **4fa–ga**). Satisfactory yields were also observed for substrates bearing a halogen group (e.g., 4-Cl, 2,4-di-Cl, 4-Br, or 3-Br) on the benzene ring (60–75%; **4ha–ka**). Notably, electron-withdrawing (3-NO_2) and sterically hindered (1-naphthyl and 2-naphthyl) substrates reacted well to afford the expected products in moderate to good yields (62–73%; **4la–na**). The structure of **4ca** was unambiguously confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information).

Scheme 2. Scope of Arylglyoxal Monohydrates[a]

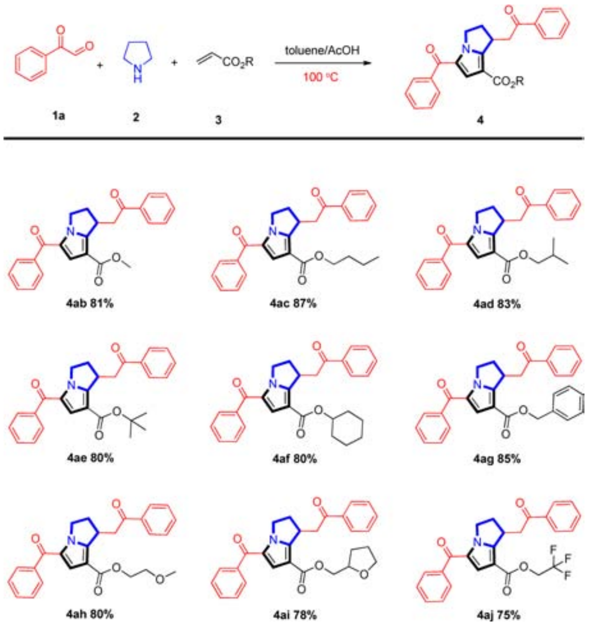


[a] Reactions were carried out with **1** (2.0 mmol, 2.0 equiv), **2** (2.0 mmol, 2.0 equiv), **3a** (1.0 mmol, 1.0 equiv), and AcOH (0.5 mL) in toluene (5 mL) at 100 °C for 40 min. Isolated yields are shown.

The scope of this reaction was subsequently expanded to a variety of substituted acrylates (Scheme 3). When readily available aliphatic acrylates were subjected to the optimal reaction conditions, the reaction proceeded smoothly and produced the corresponding products in excellent yields (80–87%; **4ab–ae**). Notably, butyl acrylate reacted a little more efficiently than isobutyl or *tert*-butyl acrylate, suggesting that steric hindrance plays a role in this transformation. Cyclohexyl acrylate and benzyl acrylate were also well-tolerated under the optimal reaction conditions, affording the corresponding products **4af** and **4ag** in 80% and 85% yield, respectively. Furthermore, 2-methoxyethyl acrylate, (tetrahydrofuran-2-yl)-methyl acrylate, and 2,2,2-trifluoroethyl acrylate reacted smoothly to give the corresponding products in high yields (75–80%; **4ah–aj**).

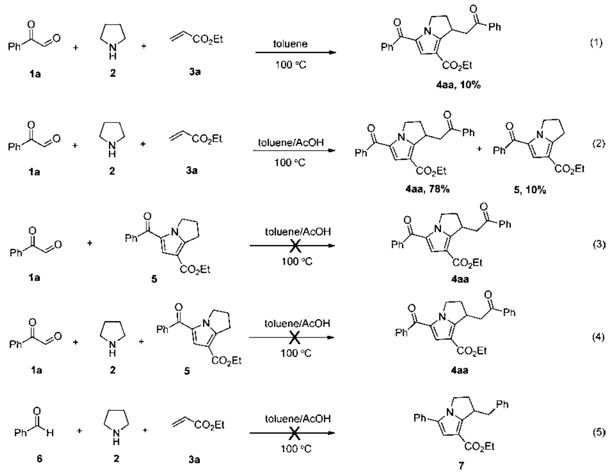
To gain insight into the mechanism of this new reaction for the N–H/α,β-C(sp^3)–H trifunctionalization of pyrrolidine, we conducted several control experiments (Scheme 4). When the model substrates **1a**, **2**, and **3a** were reacted in the absence of AcOH in toluene at 100 °C, we obtained the product **4aa** in only 10% yield, demonstrating that AcOH plays an important role in this reaction (eq 1). Under the standard conditions, the cycloaddition product **5** was obtained in 10% yield (eq 2). Furthermore, the reaction of **5** with **1a** failed to afford **4aa** (eqs 3 and 4), demonstrating that **5** is not formed as an intermediate in this reaction. The reaction of **6** with **2** and **3a** under the

Scheme 3. Scope of Acrylic Esters[a]



[a]Reactions were carried out with **1** (2.0 mmol, 2.0 equiv), **2** (2.0 mmol, 2.0 equiv), **3a** (1.0 mmol, 1.0 equiv), and AcOH (0.5 mL) in toluene (5 mL) at 100 °C for 40 min. Isolated yields are shown.

Scheme 4. Control Experiments[a]

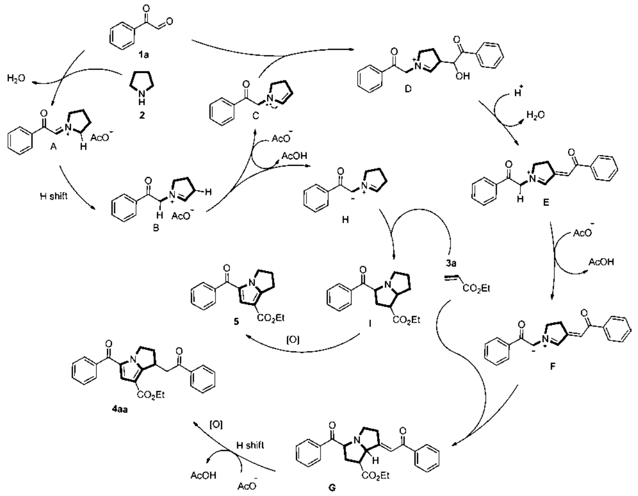


[a]Isolated products.

standard conditions did not result in the formation of **7**, indicating that the phenylglyoxal group is essential for this reaction (eq 5).

Taken together with previous results from the literature,[14] the above results have led us to propose a plausible mechanism for this reaction, which is depicted in Scheme 5 using **4aa** as a representative example. Phenylglyoxal monohydrate (**1a**) would initially react with pyrrolidine (**2**) to give iminium ion **A**, which would undergo a [1,3] hydride shift in the presence of AcOH to give the corresponding iminium ion **B**.[7a,14a,b] Subsequent deprotonation of **B** would afford azomethine ylide **H**, which would undergo a 1,3-dipolar cycloaddition with **3a** to give **I**, and finally, compound **I** would be oxidized to give **5**. Alternatively, the deprotonation of **B** could afford the key enamine intermediate **C**, which would undergo an aldol-type reaction with **1a** to give **D**.[7a] Dehydration of **D** would give iminium ion **E**, which would be deprotonated to give azomethine ylide **F**.[14c] The subsequent reaction of **F** with ethyl acrylate (**3a**) would afford the cycloaddition product **G**, which would undergo a hydrogen shift and oxidation process to give the desired product **4aa**.[14b]

Scheme 5. Possible Mechanism



In conclusion, we have developed an acid-mediated N−H/α,β-C(sp^3)−H trifunctionalization reaction for the synthesis of 2,3-dihydro-1*H*-pyrrolizine derivatives from pyrrolidine via an intermolecular [3 + 2] cycloaddition of in situ-generated azomethine ylides with acrylic esters. In contrast to previous approaches, this method is more atom-economical, efficient, and direct because it avoids the requirement of prefunctionalization of the substrates. Furthermore, the wide range of available starting materials, simple reaction conditions, and broad substrate scope make this protocol very practical and attractive. Further studies toward the application of this methodology are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01369.

Crystallographic data for **4ca** (CIF)
Experimental procedures, product characterizations, crystallographic data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chwuyd@mail.ccnu.edu.cn.
*E-mail: chwuax@mail.ccnu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (Grants 21272085 and 21472056) and the Fundamental Research Funds for the Central Universities (CCNU15ZX002 and CCNU16A05002) for financial support.

REFERENCES

(1) (a) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795−813. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795−3892. (c) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713−1760.

(2) (a) Mizuta, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 2195−2199. (b) Bhanushali, M. J.; Nandurkar, N. S.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2007**, *48*, 1273−1276. (c) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2008**, *73*, 3885−3891. (d) Lee, O.-Y.; Law, K.-L.; Yang, D. *Org. Lett.* **2009**, *11*, 3302−3305.

(3) (a) Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 13064−13065. (b) Seo, S.; Marks, T. J. *Org. Lett.* **2008**, *10*, 317−319. (c) Li, J.; Xu, F.; Zhang, Y.; Shen, Q. *J. Org. Chem.* **2009**, *74*, 2575−2577. (d) Zhu, M.; Fujita, K.-i.; Yamaguchi, R. *J. Org. Chem.* **2012**, *77*, 9102−9109. (e) Miyamura, H.; Min, H.; Soulé, J.-F.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 7564−7567.

(4) (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416−417. (b) Zhang, C.; Das, D.; Seidel, D. *Chemical Science* **2011**, *2*, 233−236. (d) Jurberg, I. D.; Peng, B.; Wöstefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 1950−1953. (e) Rahman, M.; Bagdi, A. K.; Mishra, S.; Hajra, A. *Chem. Commun.* **2014**, *50*, 2951−2953. (f) Mahato, S.; Haldar, S.; Jana, C. K. *Chem. Commun.* **2014**, *50*, 332−334. (g) Seidel, D. *Acc. Chem. Res.* **2015**, *48*, 317−328.

(5) (a) Xia, X.-F.; Shu, X.-Z.; Ji, K.-G.; Yang, Y.-F.; Shaukat, A.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2010**, *75*, 2893−2902. (b) Yuan, K.; Jiang, F.; Sahli, Z.; Achard, M.; Roisnel, T.; Bruneau, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8876−8880. (c) Boudiar, T.; Sahli, Z.; Sundararaju, B.; Achard, M.; Kabouche, Z.; Doucet, H.; Bruneau, C. *J. Org. Chem.* **2012**, *77*, 3674−3678. (d) Millet, A.; Larini, P.; Clot, E.; Baudoin, O. *Chemical Science* **2013**, *4*, 2241−2247. (e) Jiang, F.; Achard, M.; Bruneau, C. *Chem. - Eur. J.* **2015**, *21*, 14319−14323. (g) Mandal, S.; Mahato, S.; Jana, C. K. *Org. Lett.* **2015**, *17*, 3762−3765. (h) Affron, D. P.; Bull, J. A. *Eur. J. Org. Chem.* **2016**, *2016*, 139−149.

(6) (a) Horwell, D. C.; Howson, W.; Naylor, D.; Wilems, H. M. G. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1445−1450. (b) Zhou, Z.-L.; Keana, J. F. W. *J. Org. Chem.* **1999**, *64*, 3763−3766. (c) Fleck, T. J.; McWhorter, W. W., Jr.; DeKam, R. N.; Pearlman, B. A. *J. Org. Chem.* **2003**, *68*, 9612−9617. (d) Yamada, S.; Jahan, I. *Tetrahedron Lett.* **2005**, *46*, 8673−8676.

(7) (a) Sundararaju, B.; Tang, Z.; Achard, M.; Sharma, G. V. M; Toupet, L.; Bruneau, C. *Adv. Synth. Catal.* **2010**, *352*, 3141−3146. (b) Sundararaju, B.; Achard, M.; Sharma, G. V. M; Bruneau, C. *J. Am. Chem. Soc.* **2011**, *133*, 10340−10343.

(8) Das, D.; Sun, A. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3765−3769.

(9) Chen, W.; Kang, Y.; Wilde, R. G.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5179−5182.

(10) (a) Smith, L. W.; Culvenor, C. C. J. *J. Nat. Prod.* **1981**, *44*, 129−152. (b) Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357−7358. (c) Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* **2013**, *113*, 2958−3043. (d) Belal, A.; El-Gendy, B. E.-D. M. *Bioorg. Med. Chem.* **2014**, *22*, 46−53.

(11) (a) Narayanan, N. K.; Nargi, D.; Attur, M.; Abramson, S. B.; Narayanan, B. A. *Anticancer Res.* **2007**, *27*, 2393−2402. (b) Tavolari, S.; Bonafè, M.; Marini, M.; Ferreri, C.; Bartolini, G.; Brighenti, E.; Manara, S.; Tomasi, V.; Laufer, S.; Guarnieri, T. *Carcinogenesis* **2008**, *29*, 371−380.

(12) (a) Anderson, W. K.; Dean, D. C.; Endo, T. *J. Med. Chem.* **1990**, *33*, 1667−1675. (b) Atwell, G. J.; Fan, J.-Y.; Tan, K.; Denny, W. A. *J. Med. Chem.* **1998**, *41*, 4744−4754. (c) Kakadiya, R.; Dong, H.; Lee, P.-C.; Kapuriya, N.; Zhang, X.; Chou, T.-C.; Lee, T.-C.; Kapuriya, K.; Shah, A.; Su, T.-L. *Bioorg. Med. Chem.* **2009**, *17*, 5614−5626. (d) Gouda, A. M.; Abdelazeem, A. H.; Arafa, E.-S. A.; Abdellatif, K. R. A. *Bioorg. Chem.* **2014**, *53*, 1−7.

(13) (a) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2004**, *45*, 1567−1570. (b) Portevin, B.; Tordjman, C.; Pastoureau, P.; Bonnet, J.; De Nanteuil, G. *J. Med. Chem.* **2000**, *43*, 4582−4593.

(14) (a) Burrows, W. D.; Burrows, E. P. *J. Org. Chem.* **1963**, *28*, 1180−1182. (b) Oda, M.; Fukuchi, Y.; Ito, S.; Thanh, N. C.; Kuroda, S. *Tetrahedron Lett.* **2007**, *48*, 9159−9162. (c) Deb, I.; Das, D.; Seidel, D. *Org. Lett.* **2011**, *13*, 812−815.