Organic LETTERS

Letter

pubs.acs.org/OrgLett

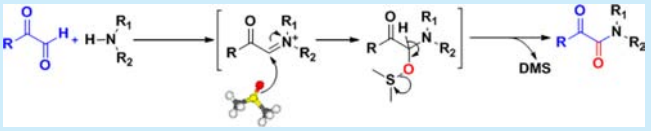
Metal-Free Oxidative Amidation of 2-Oxoaldehydes: A Facile Access to α-Ketoamides

Nagaraju Mupparapu,[†,‡] Shahnawaz Khan,[†,‡] Satyanarayana Battula,[†,‡] Manoj Kushwaha,[§] Ajai Prakash Gupta,[§] Qazi Naveed Ahmed,*[,†,‡] and Ram A. Vishwakarma*[,†,‡]

[†]Medicinal Chemistry Division, [‡]Academy of Scientific and Innovative Research (AcSIR), [§]Quality Control and Quality Assurance (QC & QA), Indian Institute of Integrative Medicine (IIIM), Jammu, Jammu and Kashmir 180016, India

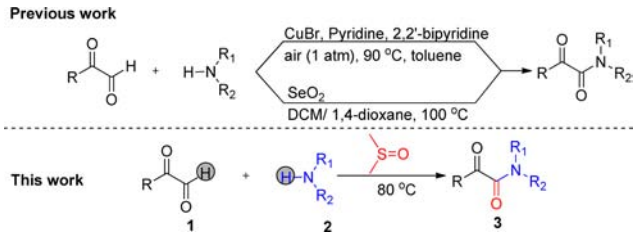
Supporting Information

ABSTRACT: A novel and efficient method for the synthesis of α-ketoamides, employing a dimethyl sulfoxide (DMSO)-promoted oxidative amidation reaction between 2-oxoaldehydes and amines under metal-free conditions is presented. Furthermore, mechanistic studies supported an iminium ion-based intermediate as a central feature of reaction wherein C_1-oxygen atom of α-ketoamides is finally derived from DMSO.



α-Ketoamides, a well-known structural element of many natural products, pharmaceuticals and synthetic agents, have attracted considerable attention for their synthesis using different starting materials.[1−8] Not only have these compounds been optimized for their remarkable biological and pharmacological activities, but also they are known with wide application in a wide variety of functional group transformations as well.[9,10] Consequently, a number of synthetic methods for construction of this important unit have been established in the past decades. Nevertheless, most of these methods described synthesis under (1) harsh conditions (use strong oxidizing conditions) or (2) metal salt catalytic conditions. Recently chemistry around 2-oxoaldehyde (OA) has been explored by two different groups for the construction of α-ketoamides (Scheme 1).[7] It is a well familar

Scheme 1. 2-Oxoaldehyde-Based Methods for Synthesis of α-Ketoamides



fact that OA possessing adjacent aldehyde and ketone functional groups with different reactivity shows interesting chemical properties. The higher reactivity of aldehyde of OA in comparison to normal aldehyde is attributed to existence of an electron-withdrawing ketone group and has been well explored to produce different important structures.[11] Because of the importance of α-ketoamides and broad synthetic applications of OA, we developed a unique, alternative, convenient, and efficient method to access α-ketoamides using a metal-free oxidative amidation approach (Scheme 1).

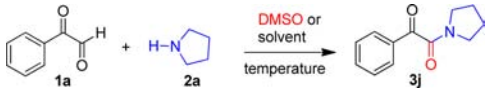
The present method employing a dimethyl sulfoxide (DMSO) promoted oxidative amidation reaction between OA and amine under metal-free conditions has clearly demonstrated the unusual behavior of OA toward amine in a DMSO environment.

Interestingly, it was observed that reaction of phenylglyoxal **1a** with pyrrolidine **2a** in DMSO at 60 °C for 12 h afforded the desired product **3j** in 10% yield (entry 1, Table 1). Same reaction when kept for 24 h could not increase the yields to that extent (12%, entry 2). To improve upon the yields of α-ketoamides, a preliminary set of reaction between **1a** and pyrrolidine **2a** under different condition has been carried out (entry 3−22). The effects of reaction temperature on the yields of **3j** at different time intervals (pyrrolidine taken at 0.75 mmol) were subsequently examined. A higher conversion rate was obtained when the reaction was performed at 80 °C for 1.5 h (80%, entry 4). No further increase in yield was observed when the reaction temperature was >80 °C and time more than 1.5 h. The same reaction when tried at 45 °C for 48 h failed to produce desired product (entry 8 and 9). Next, various concentrations of amine were screened at 80 °C (entry 10−16). 0.97 mmol of pyrrolidine **2a** was subsequently determined as the best concentration for the reaction. Finally as observed, the optimal reaction conditions for the reaction turned out to be phenylglyoxal **1a** (0.75 mmol) with pyrrolidine **2a** (0.97 mmol) at 80 °C in DMSO (95%, entry **11**). Since the reaction was carried out in air atmosphere, it was necessary to perform reaction in different solvent conditions so as to ascertain the role of DMSO (entry 17−22). Reaction of **2a** with **1a** in different solvents under reflux conditions failed to produce desired product. Furthermore test reaction between **1a** and **2a** failed to produce α-ketoamides in DMSO/THF solution (DMSO taken in 10 equiv) as well. These results clearly

Received: January 3, 2014
Published: February 3, 2014

   dx.doi.org/10.1021/ol5000204 | *Org. Lett.* 2014, 16, 1152−1155

Table 1. Optimization Studies for Synthesis of α-Ketoamides[a]



entry	solvent	amine (mmol)	temp (°C)	time (h)	yield (%)[b]
1	DMSO	0.75	60	12	10
2	DMSO	0.75	60	24	12
3	DMSO	0.75	80	1	76
4	DMSO	0.75	80	1.5	80
5	DMSO	0.75	80	12	80
6	DMSO	0.75	80	24	80
7	DMSO	0.75	120	1	82
8	DMSO	0.75	45	1	0
9	DMSO	0.75	45	48	0
10	DMSO	0.97	80	1	90
11	DMSO	0.97	80	1.5	95
12	DMSO	0.97	80	2	95
13	DMSO	0.97	120	1.5	95
14	DMSO	1.125	80	1	94
15	DMSO	1.5	80	1	95
16	DMSO	3.75	80	1	93
17	ACN	0.97	80	12	trace
18	MeOH	0.97	65	12	0
19	H2O	0.97	100	12	0
20	DMF	0.97	120	12	trace
21	THF	0.97	66	12	0
22	DMSO in THF[c]	0.97	80	12	0

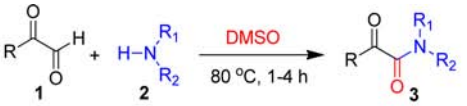
[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.97 mmol), and DMSO (3 mL) were heated for 1.5 h. [b]Yields of the isolated product. [c]DMSO taken at 10 equiv in THF.

revealed the unusual role of DMSO as oxidant in these conditions.

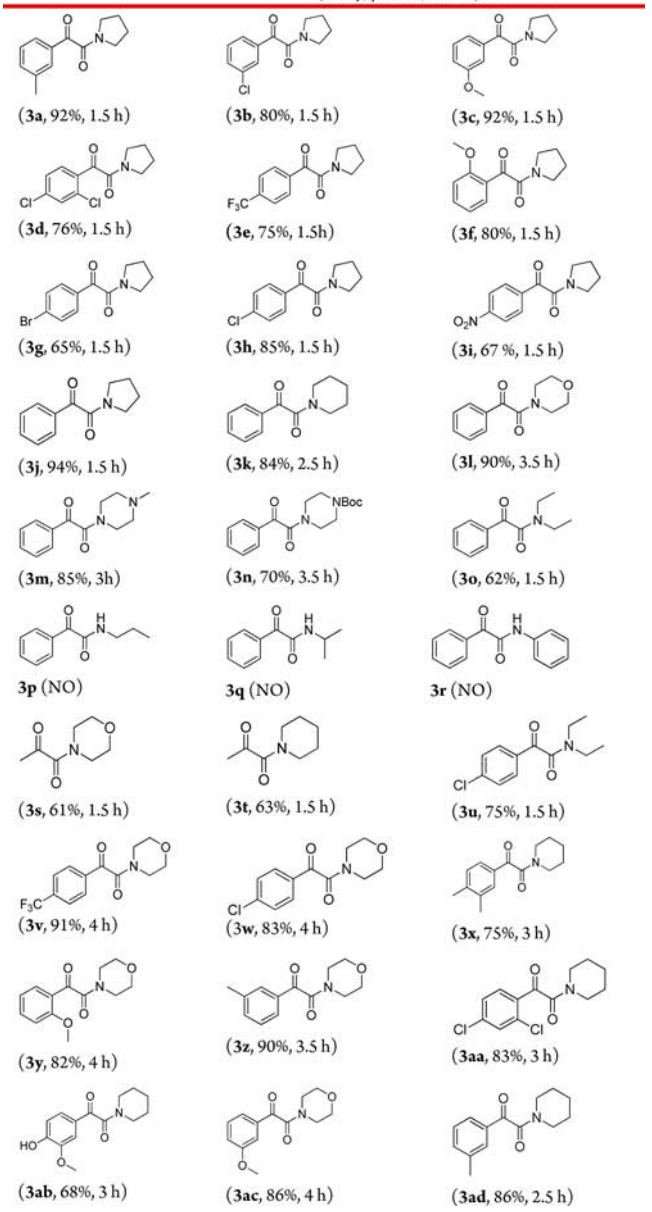
Following these optimized procedure, different sets of experiments were carried out to investigate the scope and limitations of this reaction. In one set of experiments reaction was performed between different 2-oxoaldehyde **1** and pyrrolidine **2a** (entry **3a**−**3j**, Scheme 2). It was observed that both electron rich and electron-deficient OA could be smoothly transformed into α-ketoamides. Furthermore, substituents at different positions of the arene group and their electronic nature do not affect the efficiency of the reaction. Both electron-donating and electron-withdrawing groups attached to the phenyl rings of substrates could afford the corresponding product in moderate to good yields (65−92%).

Another set of experiments was performed between different amines **2** and phenylglyoxal (entry **3j**−**3r**) for the preparation of different α-ketoamides. Yields were generally good for all secondary amines tested (entry **3j**−**3o**). However primary amines including anilines (entry **3p**−**3r**) when tested failed to produce desired product even if tried for days under refluxed conditions. According to the above experimental results it is quite clear that this method is applicable with secondary amines only as supported by stark enamine reaction, wherein iminium ion intermediate is being produced by the reaction of secondary amine with carbonyl substrate.[12] After having established the scope and limitation of the reaction, a small library of different α-ketoamides was also generated by assembling the building blocks shown in Scheme 2 (entry **3s**−**3ad**). In addition, for

Scheme 2. DMSO-Promoted Oxidative Amidation of 2-Oxoaldehyde (1) and Amine (2)[a]



(**entry**, yield %, time h)



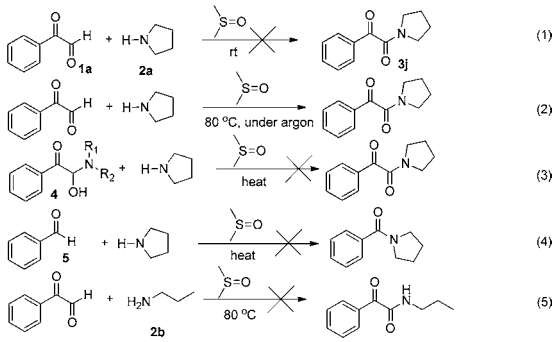
[a]Reaction conditions: **1a** (0.75 mmol), **2** (0.97 mmol), and DMSO (3 mL) were heated for 1.5−4 h. Yields given for isolated products after chromatography. NO: Not observed.

certain moderate yielding reactions (entry **3g**, **3i**, and **3ab**), we also observed minor quantity of hydroxy compound **4**.

In order to have mechanistic insight into the unusual functioning of DMSO as oxidant, experiments 17−22 (Table 1) and few additional reactions were keenly observed.

In reaction 1, a reaction was tried between pyrrolidine **2a** and phenylglyoxal **1a** at rt (room temperature). Absence of product in the reaction revealed that this reaction is feasible only at higher temperature. Experiments 17−22 (Table 1) demonstrated that the reaction of substrates in different solvent

dx.doi.org/10.1021/ol5000204 | Org. Lett. 2014, 16, 1152−1155



conditions failed to produce desired product. These facts clearly pointed toward the importance of DMSO environment for bringing some transition state in to existence. In further investigation, reaction of substrates in argon atmosphere produced desired product in good yield, thereby ruling out the probability of aerobic oxidation (reaction 2). To exclude the role of compound **4** as an intermediate, a reaction was tried between **4** and pyrrolidine **2a** under optimized conditions (reaction 3). No product was observed in ^{1}H NMR, which clearly revealed nonparticipation of **4**. Further reaction between benzaldehyde **5** and pyrrolidine **2a** failed to produce desired amide (reaction 4). This observation clearly pointed toward role of electron-withdrawing ketone in OA to α-ketoamides synthesis. In addition, absence of product formation in case of reaction between phenylglyoxal **1a** and *n*-propylamine **2b** (reaction 5) supported the role of some intermediate toward product formation.

On the basis of the above results, the only plausible route for synthesis of α-ketoamides can be visualized by the presence of iminium ion as an intermediate (Figure 1). Monohydrate form

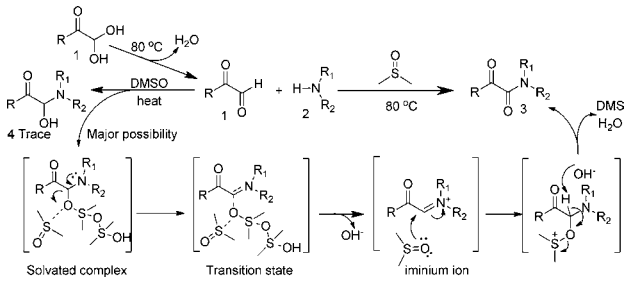


Figure 1. Proposed mechanism for direct transformation.

of OA on heating undergoes dehydration to produce 2-oxoaldehyde **1**.[11] Reaction of OA **1** with amine **2** at 80 °C in DMSO environment facilitated formation of iminium ion as a reactive intermediate. Generation of iminium ion is expected through DMSO solvated complex promoted by the carbonyl group of OA, which on reaction with DMSO at electrophilic carbon, through elimination of water and dimethyl sulfide (DMS), produced the desired product in good yields. This proposed mechanism perhaps shows unusual behavior of two reactants in DMSO environment at heating condition wherein the C_1-oxygen atom of **3** is derived from DMSO.

In order to support our mechanism, an O-labeled DMSO experiment was performed between phenylglyoxal **1a** and morpholine **2c** under optimized conditions (Figure 2). Mass analysis (Supporting Information, page 9) of desired product **^{18}O3l** clearly indicated that DMSO served as the oxidant in this transformation. Further confirmation of mechanism was

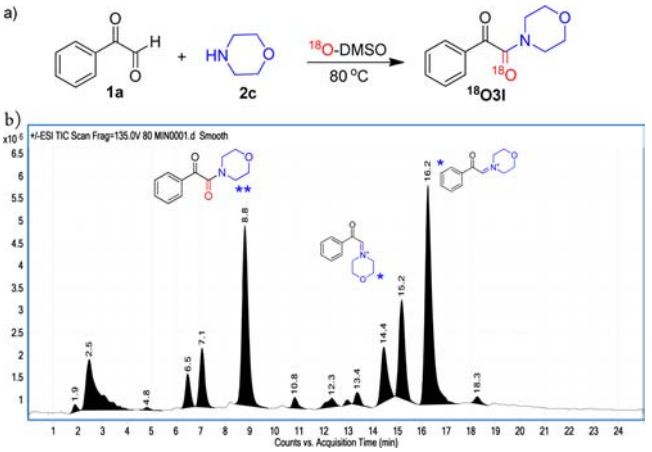
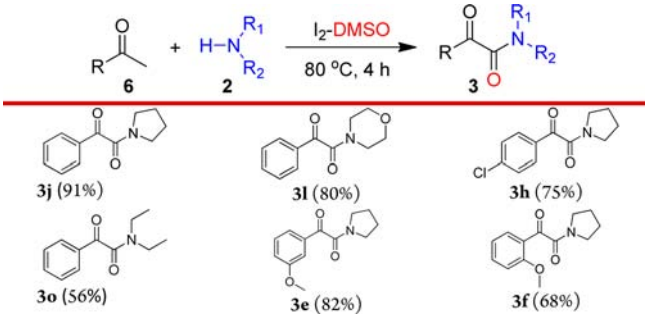


Figure 2. (a) DMSO O-labeled experiment. (b) LC-ESI-MS analysis of reaction mixture (entry **3l**) at 80 min to investigate reaction mechanism. *Iminium ion peak (both syn and anti). **Product ion peak.

achieved by analyzing three different sets of LC-ESI-MS analysis experiments performed between **1** and **2** at different time intervals (for detail, see Supporting Information page 3). On the basis of these observations, we speculated that reaction is only feasible through iminium ion facilitated by carbonyl group of OA and promoted by DMSO environment at heating conditions.

Further application of our method was extended in developing a one-pot method for synthesis of α-ketoamides employing acetophenones as source of 2-oxoaldehyde. For this a reaction was carried out between acetophenones and iodine in DMSO at 80 °C for initial generation of OA[13] followed by addition of respective amine to produce desired product in comparable yields (Scheme 3).

Scheme 3. One-Pot Synthesis of α-Ketoamides Employing Acetophenones (6)



In conclusion we have successfully demonstrated a unique DMSO-promoted oxidative amidation approach for synthesis of α-ketoamides. This method is perhaps an efficient approach wherein DMSO plays a dual role both as solvent and as oxidant. This protocol has additional uniqueness, as it is also applicable for synthesis of aliphatic α-ketoamides. Furthermore, mechanism studies revealed that the carbonyl group of OA plays a vital role as a directing/stabilizing group in the DMSO environment at heating conditions (temperature $\geq$ 80 °C) to facilitate iminium ion formation, which on DMSO-mediated oxidation results in synthesis of α-ketoamides having a C_1-oxygen atom derived from DMSO. In addition, we successfully

dx.doi.org/10.1021/ol5000204 | *Org. Lett.* 2014, 16, 1152−1155

applied the same method employing acetophenones as source of 2-oxoaldehydes for synthesis of α-ketoamides.

■ ASSOCIATED CONTENT

Supporting Information

Experiment details and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: naqazi@iiim.ac.in.
*E-mail: ram@iiim.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge CSIR/DST for the award of Senior Research Fellowship and AcSIR for Ph.D. registration. This work was generously supported by network project through Grant No. BSC0108. IIIM/1593/2014.

■ REFERENCES

(1) (a) Feng-Tian, D.; Ji, J.-X. *Chem. Sci.* **2012**, *3*, 460. (b) Lamani, M.; Prabhu, K. R. *Chem.—Eur. J.* **2012**, *18*, 14638. (c) Mai, W.-P.; Wang, H.-H.; Li, Z.-C.; Yuan, J.-W.; Xiao, Y.-M.; Yang, L.-R.; Mao, P.; Qu, L.-B. *Chem. Commun.* **2012**, *48*, 10117. (d) Wei, W.; Shao, Y.; Hu, H.; Zhang, F.; Zhang, C.; Xu, Y.; Wan, X. *J. Org. Chem.* **2012**, *77*, 7157. (e) Zhang, X.; Wang, L. *Green Chem.* **2012**, *14*, 2141. (f) Zhao, Q.; Miao, T.; Zhang, X.; Zhou, W.; Wang, L. *Org. Biomol. Chem.* **2013**, *11*, 1867.

(2) (a) Bouma, M.; Masson, G.; Zhu, J. *J. Org. Chem.* **2010**, *75*, 2748. (b) Chen, J.; Cunico, R. F. *J. Org. Chem.* **2004**, *69*, 5509.

(3) (a) Zhang, C.; Xu, Z.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11088. (b) Song, B.; Wang, S.; Sun, C.; Deng, H.; Xu, B. *Tetrahedron Lett.* **2007**, *48*, 8982. (c) Shanmugapriya, D.; Shankar, R.; Satyanarayana, G.; Dahanukar, V. H.; Kumar, U. K. S.; Vembu, N. *Synlett* **2008**, *19*, 2945.

(4) (a) Hua, R.; Takeda, H.-a.; Abe, Y.; Tanaka, M. *J. Org. Chem.* **2004**, *69*, 974. (b) Chiou, A.; Markidis, T.; Kokotou, V. C.; Verger, R.; Kokotus, G. *Org. Lett.* **2000**, *2*, 347.

(5) (a) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2003**, *68*, 6063. (b) Dinoiu, V. *Rev. Roum. Chim.* **2007**, *52*, 219. (c) Zhang, X.; Yang, W.; Wang, L. *Org. Biomol. Chem.* **2013**, *11*, 3649. (d) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Biomol. Chem.* **2013**, *11*, 4573. (e) Li, D.; Wang, M.; Liu, J.; Zhao, Q.; Wang, L. *Chem. Commun.* **2013**, *49*, 3640.

(6) (a) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (b) Xu, C.-F.; Xu, M.; Jia, Y.-X.; Li, C.-Y. *Org. Lett.* **2011**, *13*, 1556. (c) Al-Rashid, Z. F.; Johnson, W. L.; Hsung, R. P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* **2008**, *73*, 8780.

(7) (a) Shaw, A. Y.; Denning, C. R.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 4151. (b) Zhang, C.; Zong, X.; Zhang, L.; Jiao, N. *Org. Lett.* **2012**, *14*, 3280.

(8) (a) Kaïm, L. E.; Gamez-Montaño, R.; Grimaud, L.; Ibarra-Rivera, T. *Chem. Commun.* **2008**, 1350. (b) Grassot, J.-M.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 947. (c) Mossetti, R.; Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2010**, *12*, 820. (d) Liu, J.; Zhang, R.; Wang, S.; Sun, W.; Xia, C. *Org. Lett.* **2009**, *11*, 1321. (e) Murphy, E. R.; Martinelli, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1734. (f) Uozumi, Y.; Arii, T.; Watanabe, T. *J. Org. Chem.* **2001**, *66*, 5272. (g) Iizuk, M.; Kondo, Y. *Chem. Commun.* **2006**, 1739.

(9) (a) Dubowchik, G. M.; Ditta, J. L.; Herbst, J. J.; Bollini, S.; Vinitsky, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 559. (b) Knust, H.; Nettekoven, M.; Pinard, E.; Roche, O.; Rogers-Evans, M. PCT Int. Appl. WO 2009016087, 2009. (c) Patel, D. V.; Gless, R. D. J.; Webb, H.; Heather, K.; Anandan, S. K.; Aavula, B. R. PCT Int. Appl. WO 2008073623, 2008. (d) Crowley, C. A.; Delaet, N. G. J.; Ernst, J.; Grove, C. G.; Hepburn, B.; King, B.; Larson, C. J.; Miller, S.; Pryor, K.; Shuster, L. J. WO2007146712, 2007. (e) Li, Z.; Ortega-Vilain, A.-C.; Patil, G. S.; Chu, D.-L.; Foreman, J. E.; Eveleth, D. D.; Powers, J. C. *J. Med. Chem.* **1996**, *39*, 4089. (f) Sheha, M. M.; Mahfouz, N. M.; Hassan, H. Y.; Youssef, A. F.; Mimoto, T.; Kiso, Y. *Eur. J. Med. Chem.* **2000**, *35*, 887. (g) Chen, Y.-H.; Zhang, Y.-H.; Zhang, H.-J.; Liu, D.-Z.; Gu, M.; Li, J.-Y.; Wu, F.; Zhu, X.-Z.; Li, J.; Nan, F.-J. *J. Med. Chem.* **2006**, *49*, 1613. (h) Alvarez, S.; Alvarez, R.; Khanwalkar, H.; Germain, P.; Lemaire, G.; Rodríguez-Barrios, F.; Gronemeyer, H.; Lera, A. R. d. *Bioorg. Med. Chem. Lett.* **2009**, *17*, 4345. (i) Chatterjee, S.; Dunn, D.; Tao, M.; Wells, G.; Gu, Z.-Q.; Bihovsky, R.; Ator, M. A.; Siman, R.; Mallamo, J. P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2371.

(10) (a) Zhang, Z.; Zhang, Q.; Ni, Z.; Liu, Q. *Chem. Commun.* **2010**, *46*, 1269. (b) Jesuraj, J. L.; Sivaguru, J. *Chem. Commun.* **2010**, *46*, 4791. (c) Sai, K. K. S.; Esteves, P. M.; Penha, E. T. d.; Klumpp, D. A. *J. Org. Chem.* **2008**, *73*, 6506. (d) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946. (e) Yang, L.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Am. Chem. Soc.* **2009**, *131*, 10390. (f) Coffinier, D.; Kaim, L. E.; Grimaud, L. *Org. Lett.* **2009**, *11*, 1825. (g) Liu, Q.; Perreault, S. p.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066. (h) Yang, L.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Am. Chem. Soc.* **2009**, *131*, 10390. (i) Natarajan, A.; Wang, K.; Ramamurthy, V.; Scheffer, J. R.; Patrick, B. *Org. Lett.* **2002**, *4*, 1443.

(11) Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* **2013**, *113*, 2958.

(12) (a) Zhang, S.-L.; Xie, H.-X.; Zhu, J.; Li, H.; Zhang, X.-S.; Li, J.; Wang, W. *Nat. Commun.* **2011**, *2*, 211. (b) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, 12. (c) Hunter, L. *Beilstein J. Org. Chem.* **2010**, 38.

(13) (a) Gao, Q.-H.; Fei, Z.; Zhu, Y. P.; Lian, M.; Jia, F. C.; Liu, M. C.; She, N. F.; Wu, A. X. *Tetrahedron* **2013**, *69*, 22−28. (b) Zhu, Y. P.; Fei, Z.; Liu, M. C.; Jia, F. C.; Wu, A. X. *Org. Lett.* **2013**, *15* (2), 378−381.