Phosphomolybdic acid promoted Kabachnik–Fields reaction: an efficient one-pot synthesis of α-aminophosphonates from 2-cyclopropylpyrimidine-4-carbaldehyde

Pogula Sreekanth Reddy, Peddiahgari Vasu Govardhana Reddy, Sura Mallikarjun Reddy

PII: S0040-4039(14)00665-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.04.053
Reference: TETL 44515

To appear in: *Tetrahedron Letters*

Received Date: 28 February 2014
Revised Date: 10 April 2014
Accepted Date: 15 April 2014

Please cite this article as: Reddy, P.S., Vasu Govardhana Reddy, P., Reddy, S.M., Phosphomolybdic acid promoted Kabachnik–Fields reaction: an efficient one-pot synthesis of α-aminophosphonates from 2-cyclopropylpyrimidine-4-carbaldehyde, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.04.053

Tetrahedron Letters

Graphical Abstract

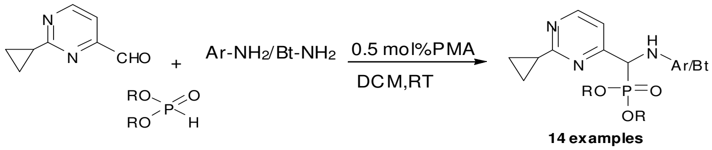
To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Phosphomolybdic acid promoted Kabachnik–Fields reaction: an efficient one-pot synthesis of α-aminophosphonates from 2-cyclopropylpyrimidine-4-carbaldehyde

Leave this area blank for abstract info.

Pogula Sreekanth Reddy[a], Peddiahgari Vasu Govardhana Reddy[a]* and Sura Mallikarjun Reddy[b]

2-Cyclopropylpyrimidin-4-yl-aryl/benzothiazole derived α-aminophosphonates were synthesized in a simple and efficient method from the three-component condensation reaction of 2-cyclopropylpyrimidin-4-carbaldehyde, various anilines/ benzothiazole amines and different phosphites by using 0.5 mol % of phosphomolybdic acid.



Tetrahedron Letters
journal homepage: www.elsevier.com

Phosphomolybdic acid promoted Kabachnik–Fields reaction: an efficient one-pot synthesis of α-aminophosphonates from 2-cyclopropylpyrimidine-4-carbaldehyde

Pogula Sreekanth Reddy[a], Peddiahgari Vasu Govardhana Reddy[a*] and Sura Mallikarjun Reddy[b]

[a] *Department of Chemistry, Yogi Vemana University, Kadapa-516003, Andhra Pradesh, India.*
[b] *Department of Chemistry, Vellore Institute of Technology, Vellore-632014, Tamil Nadu, India.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Phosphomolybdic acid
2-Cyclopropylpyrimidine 4-carbaldehyde
α-Aminophosphonates
Kabachnik-Fields reaction

ABSTRACT

2-Cyclopropylpyrimidin-4-yl-aryl/benzothiazole derived α-aminophosphonates were synthesized in a simple and efficient method from a three-component condensation reaction of 2-cyclopropylpyrimidin-4-carbaldehyde, various anilines/ benzothiazole amines and different phosphites by using 0.5 mol % of phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) in dichloromethane at room temperature in good to excellent yields with short reaction times.

Significant efforts have been made to improve the biological features of organophosphorus compounds[1-4] wherein α-aminophosphonates constitutes an important class of compounds in pharmaceutical chemistry with potential biological effectives and medicinal importance due to structure analogues of amino acid.[5] Apart from this, their potential usage as anticancer agents,[6a-c] herbicides,[6d] peptide mimetics,[6e] enzyme inhibitors,[6f] fungicides,[6g] bactericides,[6h] and antiviral agents[6i,6j] is of significant importance. Because of their versatile biological activities, a number of methods for the synthesis of α-aminophosphonates have been developed during the past two decades. Of these methods, three-component Kabachnik- Fields reaction starting from aldehydes, amines and phosphites catalyzed by nano catalysts,[7a-c] heterogeneous catalysts,[7d] metal triflates,[7e, 7f] Lewis acids,[7g-i] and Brønsted acids[7j] are common strategic catalytic systems for the synthesis of α-aminophosphonates. But most of them suffer from at least one of the following disadvantages: harsh reaction conditions, air sensitivity, use of stoichiometric, toxic and relatively expensive reagents or catalysts, poor product yields, long reaction times and tedious separation procedures. To compensate for these deficiencies, numerous endeavors have been made giving rise to satisfactory results in terms of efficiency and rate of the reaction. Therefore, the development of a simple, convenient, and an efficient protocol using inexpensive and readily available reagents would extend the scope of the synthesis of α-amino phosphonates. Recently, the use of heteropoly acids (HPAs) has received great attention in organic synthesis, owing to their commercial viability, high catalytic activity and ease of handling. They are low-toxic and allow cleaner reactions when compared to conventional catalysts, hence they are regarded as green catalysts. Moreover, heteropoly acids are potent solid acids and act as bifuncional catalysts in homogeneous as well as heterogeneous conditions.[8a-c] Among various heteropoly acids, phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) is one of the less expensive and commercially available solid acid catalysts.

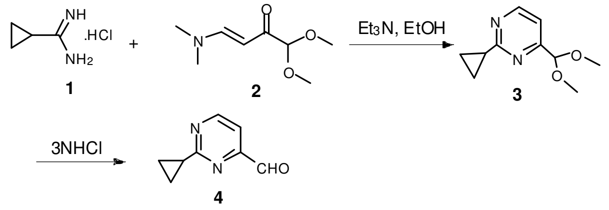
Though several works focused on the synthesis and biological tests of α-aminophosphonates have been reported, the preparation of α-aminophosphonates from the reaction of heterocyclic aldehydes and heterocyclic amines is limited. Owing to their synthetic and biological values, there is a need to find new, accessible, cheaper, and more efficient approaches to the synthesis of *α*-aminophosphonates. Heterocyclic skeletons serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs. Among them, pyrimidine derivatives play an important role in several biological and pharmacologically active substances such as antimicrobial and antitumor agents.[9a-c, 10] In view of this research and our desire to develop *α*-aminophosphonate structures, we have designed and synthesized a series of new α-aminophosphonates containing 2-cyclopropylpyrimidine moiety. Herein, we report for first time the finding of our investigations for the synthesis of new *α*-aminophosphonates by three-component coupling (3CC) of 2-cyclopropylpyrimidin-4-carbaldehyde with amines and phosphites in the presence of phosphomolybdic acid ($H_3PMo_{12}O_{40}$), further the reaction conditions like optimization of catalyst and solvent were carried out and listed in the Table 1.

Initially, we have examined the preparation of 2-cyclopropyl pyrimidine-4-carbaldehyde (**4**) by following the reported literature with some modifications in order to introduce cyclopropyl moiety to pyramidine-4-carbaldehyde at second position.[10] In this connection, the reaction of cyclopropane carboxamidine hydrochloride (**1**)[11] and (*E*)-4-(dimethylamino)-

---

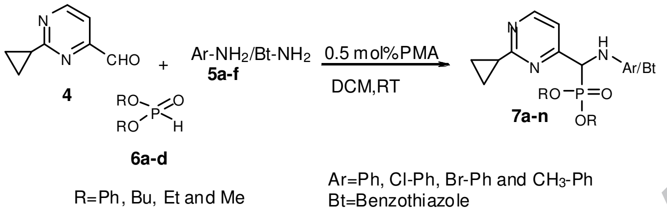
[*] Corresponding Author. Tel:+91-8562-225410, e-mail: pvgr@yogivemanauniversity.ac.in (P. V. G. Reddy)

1,1-dimethoxybut-3-en-2-one (2)[10] in the presence of Et_3N base resulted in the production of 2-cyclopropyl-4-(dimethoxymethyl)pyrimidine (**3**). It was later treated with 3N hydrochloric acid to obtain the 2-cyclopropyl pyrimidine 4-carbaldehyde (**4**) (Scheme 1).



Scheme1: Synthesis of 2-cyclopropyl pyrimidine-4-carbaldehyde

In this article, we report an efficient and environmentally benign protocol for the synthesis of α-aminophosphonates via Kabachnik-Fields reaction approach from 2-cyclopropylpyrimidin-4-carbaldehyde, anilines/ benzothiazole amines, and aromatic and alkylphosphites in the presence of catalytic amount (0.5 mol %) of PMA in dichloromethane at room temperatures (Scheme 2).



Scheme 2. Synthesis of α-aminophosphonates from 2-cyclopropyl pyrimidine-4-carbaldehyde.

We also screened different common Lewis acids for their ability to catalyze the three-component Kabachnik–Fields reaction and 2-cyclopropylpyrimidin-4-carbaldehyde, aniline, and diphenyl phosphite were selected as models. As shown in Table 1, the common Lewis acids such as $AlCl_3$, $FeCl_3$ and $ZnCl_2$ afforded the desired product **7a** but only in moderate yield (Table 1, entries a–c). Encouraged by these initial findings, we began a systematic screening of various catalysts in order to improve the conversion. The results reveal that, solid acids such as Amberlyst-15, cellulose sulfuric acid and Al_2O_3-SiO_2 also afforded the product **7a** with moderate yield (Table 1, entries d–f). After screening several catalysts, the best conversions were achieved with 2 mol % of phosphomolybdic acid ($H_3PMo_{12}O_{40}$) (Table 1, entry m). No change was observed when we decreased the amount of catalyst from 2 to 0.5 mol %. The results are summarized in Table 1. Subsequently, we examined the effect of various solvents such as dichloromethane, methanol, toluene and CH_3CN. Of these, dichloromethane appeared to give the best results.

Inspired by the above results, we further extended this process for other amines and phosphites. The scope of the reaction is illustrated with respect to various amines and phosphites and the results are summarized in Table 2. Interestingly, diphenyl phosphite (**6a**) underwent a smooth coupling with 2-cyclopropylpyrimidin-4-carbaldehyde (**4**) under similar conditions to afford the corresponding α-aminophosphonate (**7g**) in 96 % yield (entry g, Table 2). Similarly, effective reaction was observed with other phosphites such as dibutyl, diethyl and dimethyl phosphites in the combination of 2-cyclopropylpyrimidin-4-carbaldehyde (**4**) and various amines to obtain the respective α-amino phosphonates in good yields (Table 2). The reaction works not only with aniline but also with chloroaniline, *p*-toulidine, benzo[*d*]thiazol-5-amine and benzo[*d*]thiazol-6-amine. All the products were characterized by IR, (^1H, $^{13}C\{^1H\}$ &^{31}P) NMR and mass spectral analysis. This method provides a wide range of α-aminophosphonate derivatives from 2-cyclopropylpyrimidin-4-carbaldehyde in good to excellent yields. We observed that the physical state of the title compounds (**7a-n**), in which some of them (**7a-f)** obtained as solids when the aromatic phosphite moiety is attached to the system while the other compounds (**7g-n**) were obtained as liquids since the system has alkyl phosphite moiety.

Table1: Influence of the catalyst and solvent on the synthesis of α-minophosphonate (**7a**)[a]

Entry	Catalyst (mol %)	Solvent	Time (min)	Yield (%)[b]
a	$AlCl_3$(10)	Toluene	180	60
b	$FeCl_3$(10)	Toluene	150	63
c	$ZnCl_2$(10)	Toluene	180	62
d	Amberlyst-15[c]	Toluene	120	68
e	CellSA[c]	Toluene	90	70
f	Al_2O_3-SiO_2[c]	Toluene	90	75
g	$H_3PWo_{12}O_{40}$(2)	Toluene	60	90
h	$H_3PMo_{12}O_{40}$(2)	Toluene	25	92
I	$H_3PMo_{12}O_{40}$(1)	Toluene	25	92
J	$H_3PMo_{12}O_{40}$(0.5)	Toluene	25	92
k	$H_3PMo_{12}O_{40}$(0.5)	MeOH	25	88
l	$H_3PMo_{12}O_{40}$(0.5)	CH_3CN	25	82
m	$H_3PMo_{12}O_{40}$(0.5)	DCM	20	95

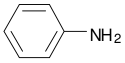
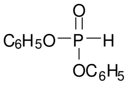
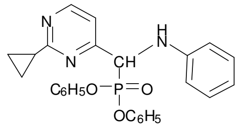
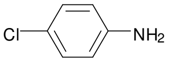
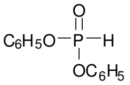
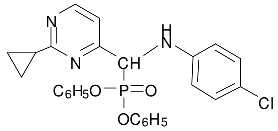
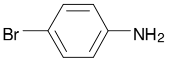
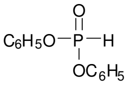
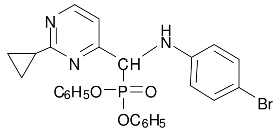
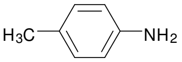
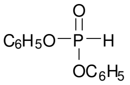
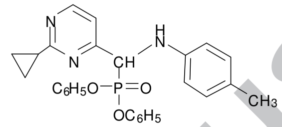
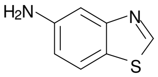
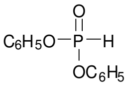
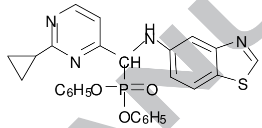
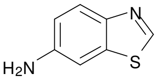
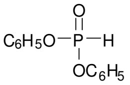
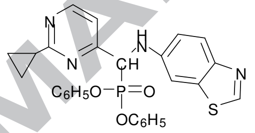
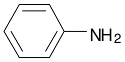
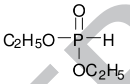
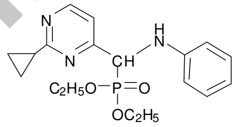
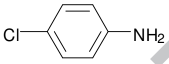
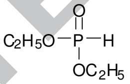
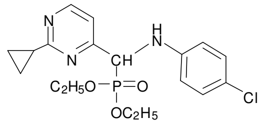
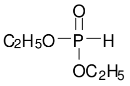
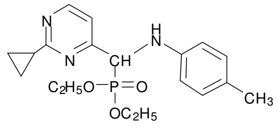
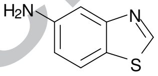
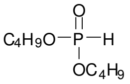
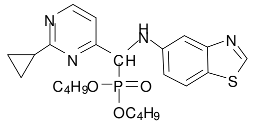
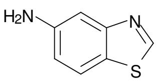
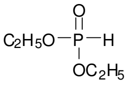
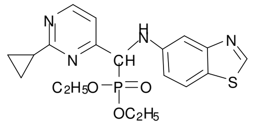
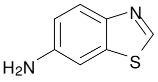
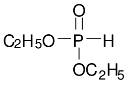
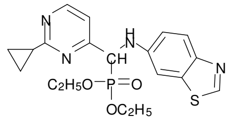
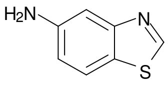
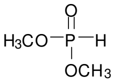
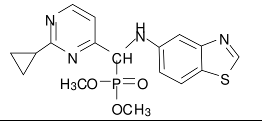
[a]Reaction of 2-cyclopropylpyrimidin-4-carbaldehyde (**4**) (1 mmol), aniline (**5a)** (1 mmol) and diphenyl phosphate (**6a**) (1 mmol) in various solvents.
[b]Isolated yields.
[c]Catalyst loaded by 20 mg

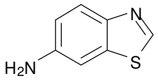
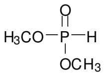
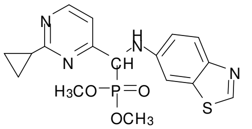
The reusability of the phosphomolybdic acid (PMA) catalyst was also examined. After each run, the product was filtered, the solvent was evaporated, and the catalyst residue was washed with dichloromethane and reused. For example, the reaction of 2-cyclopropylpyrimidin-4-carbaldehyde, aniline and diphenyl phosphite in the presence of PMA gave the corresponding α-aminophosphonate **7a** in 95%, 93%, 92%, and 90% yields over four cycles. These results indicate that the PMA catalyst is highly efficient for the synthesis of α-aminophosphonates and could avoid the necessity of anhydrous conditions, highly expensive and toxic reagents, and moisture sensitive Lewis acids. The developed methodology is simple and a substantial contribution in the field of α-aminophosphonates.

2-Cyclopropylpyrimidin-4-yl-aryl/ benzothiazole derived α-aminophosphonates were obtained as racemates as evidenced by 1:1 ratio peaks in chiral HPLC (**7f**).

In summary, we have demonstrated promising ability of heteropoly acid as a solid catalyst for the synthesis of potent α-aminophosphonates by the Kabachnik-Fields reaction of 2-cyclopropylpyrimidin-4-carbaldehyde, amines and phosphites. The salient features of PMA-promoted Kabachnik-Fields reaction are short reaction times, high conversions, and the use of easily recyclable catalyst without loss of considerable catalytic activity. Moreover, the use of phosphomolybdic acid ($H_3PMo_{12}O_{40}$) makes this method simple, convenient, and may be practical for the large scale synthesis. Furthermore, studies are under progress on the synthesis of chiral α-aminophosphonates by our newly synthesized chiral Brønsted acids from the camphor for the same racimates.

Table 2: Synthesis of α-aminophosphonates from 2-cyclopropyl pyrimidine-4-carbaldehyde in the presence of 0.5 mol% of PMA in dichloromethane.

Entry	Amine (**5a-f**)	Phosphite (**6a-d**)	Product (**7a-n**)	Yield (%)[d]	Mp (°C)
a		 $C_6H_5O-\underset{OC_6H_5}{\overset{O}{P}}-H$		95	76-78
b		 $C_6H_5O-\underset{OC_6H_5}{\overset{O}{P}}-H$		92	80-82
c		 $C_6H_5O-\underset{OC_6H_5}{\overset{O}{P}}-H$		93	78-80
d		 $C_6H_5O-\underset{OC_6H_5}{\overset{O}{P}}-H$		92	76-78
e		 $C_6H_5O-\underset{OC_6H_5}{\overset{O}{P}}-H$		94	134-136
f		 $C_6H_5O-\underset{OC_6H_5}{\overset{O}{P}}-H$		92	130-132
g		 $C_2H_5O-\underset{OC_2H_5}{\overset{O}{P}}-H$		96	oil
h		 $C_2H_5O-\underset{OC_2H_5}{\overset{O}{P}}-H$		91	oil
i		 $C_2H_5O-\underset{OC_2H_5}{\overset{O}{P}}-H$		93	oil
j		 $C_4H_9O-\underset{OC_4H_9}{\overset{O}{P}}-H$		89	oil
k		 $C_2H_5O-\underset{OC_2H_5}{\overset{O}{P}}-H$		93	oil
l		 $C_2H_5O-\underset{OC_2H_5}{\overset{O}{P}}-H$		87	oil
m		 $H_3CO-\underset{OCH_3}{\overset{O}{P}}-H$		91	oil

n		 $H_3CO-\overset{O}{\underset{OCH_3}{P}}-H$		94	oil

[d]Isolated yields

Acknowledgements
This project was supported by the Department of Science and Technology (DST), New Delhi, India (grant SR/FT/CS-013/2010) and is gratefully acknowledged.

Supplementary Material
Supplementary material of all experimental data, ^1H, ^{13}C {^1H} & ^{31}P NMR, HRMS spectra and chiral HPLC (**7f**) associated with this article can be found in the online version, at

References and Notes

1. Vebrugghen, T.; Vandurm, P.; Pouyez, J.; Maes, L.; Wouters, J.; Calenbergh, V. *J. Med. Chem.* **2013**, *56*, 376-380.
2. Queffélec, C.; Petit, M.; Janvier, P.; Knight, A.; Bujoli, B. *Chem. Rev.* **2012**, *112*, 3777-3807.
3. Reddy, P.V.G.; Balakrishna, A.; Reddy, M. V. N.; Annar, S. K.; Reddy, C. S. *J. Chem. Res.* **2009**, 65-67.
4. Reddy, P.V.G.; Kiran, Y.B.; Reddy, C.S.; Reddy, C.D. *Chem. Pharm. Bull.* **2004**, *52*, 307-310.
5. Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **2003**, *46*, 2641-2655.
6. (a) Gu, L.; Jin, C. *Org. Biomol. Chem.* **2012**, *10*, 7098–7102; (b) Jin, L.; Song, B.; Zhang, G.; Xu, R.; Zhang, S.; Gao, X.; Hu, D.; Song, Y. *Bioorg. Med. Chem. Lett.* **2006,** *16*, 1537-1543; (c) Kafarski, P.; Lejczak, B. *Curr. Med. Chem: Anti Cancer Agents.* **2001**, *1*, 301-312; (d) Bonarska, D.; Sarapuk, J.; Kleszczyn´ska, H. *Pol. J. Food Nutr. Sci.* **2003**, *12/53*, 17-19; (e) Lejczak, B.; Kafarski, P.; Sztajer, H.; Mastarlerz, P. *J. Med. Chem.* **1986**, *29*, 2212–2217; (f) De Lombaert, S.; Blanchard, L.; Tan, T.; Sakane, Y.; Berry. C.; Ghai, R. D. *Bioorg. Med.Chem. Lett.* **1995**, *5*, 145–150; (g) Reddy, M. V. N.; Sivakumar, B.; Balakrishna, A.; Reddy, C. S.; Naik, S. K.; Reddy, C. D. *Arkivoc.***2007**, 246-254; (h) Shafakat, S.; Ali, N.; Zakhr, S.; Patel, M.; Farooqui, M. *Eur. J. Med. Chem.* **2012**, *50*, 39-43; (i) Long, N.; Cai, X.-J.; Song, B.-A.; Yang, S.; Chen, Z.; Bhaduri, P. S.; Hu, D.-Y.; Jin, L.-H.; Xue, W. *J. Agric. Food Chem.***2008**, *56*, 5242-5246; (j) Zhou, J.; Fan, B.-A. Song, L.-H. Jin, P.S. Bhaduri, D.-Y. Hu, S. Yang, H.-T. *Phosphorous, Sulphur Silicon Relat. Elem.* **2010**, *186*, 81-87.
7. (a) Saberi, D.; Cheragi, S.; Mahdudi, S.; Akbari, J.; Heydari, A. *Tetrahedron Lett.* **2013**, *54*, 6403-6406; (bSubba Reddy,) B. V.; Siva Krishna, A.; Ganesh, A. V.; Narayana Kumar, G. G. K. S. *Tetrahedron Lett.* **2011**, *52*, 1359–1362; (c) Agawane, S.M.; Nagarkar, J. M.; *Tetrahedron Lett.* **2011**, *52,* 3499–3504 (d) Heydari, A.; Hamadi, H.; Pourayoubi, M. *Catal. Commun.* **2007**, *8*, 1224–1226; (e) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, 2692-2696; (f) Paraskar, A. S.; Sudalai, A. *Arkivoc* **2006**, 183-192; (g) Reddy, M. V. N.; Dindulkar, S. D.; Jeong, Y. T. *Tetrahedron Lett.* **2011**, *52*, 4764-4767; (h) Rezaei, Z.; Firouzabadi, H.; Iranpoor, N. ; Ghaderi, A.; Reza Jafari, M.; Jafari, A. A.; Reza Zare, H. *Eur. J. Med. Chem.* **2009**, *44*, 4266-4275 (i) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263-1270; j) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744-5758.
8. (a) Subba Reddy, B. V.; Narasimhulu, G.; Subbalakshumma, P.; Vikram Reddy, Y.;. Yadav, J.S.; *Tetrahedron Lett.* **2012**, *53,* 1776–1779; (b) Yadav, J. S.; Subba Reddy, B. V.; Chaya, D. N.; Narayana Kumar, G. G. K. S.; Naresh, P.; Jagadeesh, B. *Tetrahedron Lett.* **2009**, *50,* 1799–1802; (c) Yadav, J. S.; Subba Reddy, B. V.; Pandurangam, T.; Raghavendra Rao, K. V.; Praneeth, K.; Narayana Kumar, G. G. K. S.; Madavi, C.; Kunwar. A. C. *Tetrahedron Lett*. **2008**, *49*, 4296-4301.
9. (a) Talukdar, A.; Breen, M.; Bacher, A.; Illarionov, B.; Fischer, M.; Georg, G.; Ye, Q.-Z.; Cushman, M. *J. Org. Chem.* **2009**, *74*, 5123-5134; (b) Chen, X.; Adrian, J.; Cushing, T. Di Maio, H.; Liang L.; Mayorga, V.; Miao, S.; Peterson, M. G.; Powers, J. P.; Spector, F.; Stein, C.; Wright, M.; Xu, Ye, D. Q.; Jaen, J. *Bio Org. Med. Chem. Lett.* **2007**, *17*, 2188-2192; (c) Mallikarjun Reddy, S.; Vasu Govardhana Reddy, P.; Rajendraprasad Reddy, B.; and Ramakrishna, V. *J. Heterocyclic Chem.* **2013**, *50*, 1395-1399.
10. Subramanyam, C.; Wager, T. T. US Patent Application (US.2011/0098272A1, Dated: Apr 28, 2011).
11. Ueda, S.; Nagasawa, H. *J. Am.Chem. Soc.* **2009**, *131*, 15080-15081.