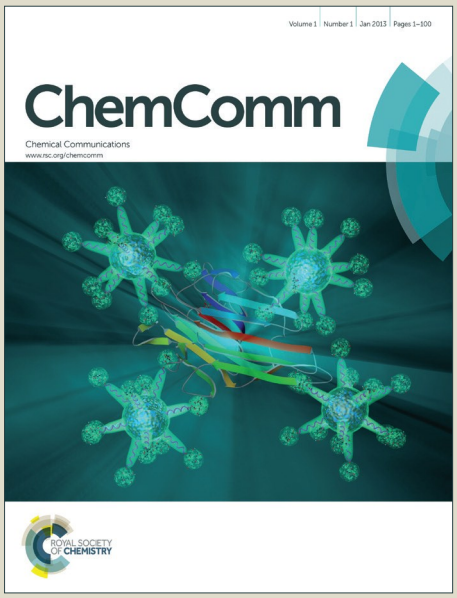
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. K. Laha, K. V. Patel, K. S. S. T. and N. Dayal, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC04259G.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C6CC04259G

Journal Name

COMMUNICATION

Formation of amides, their intramolecular reactions to the synthesis of *N*-heterocycles, and preparation of a marketed drug, Sildenafil: A comprehensive coverage

Received 00th January 20xx,
Accepted 00th January 20xx

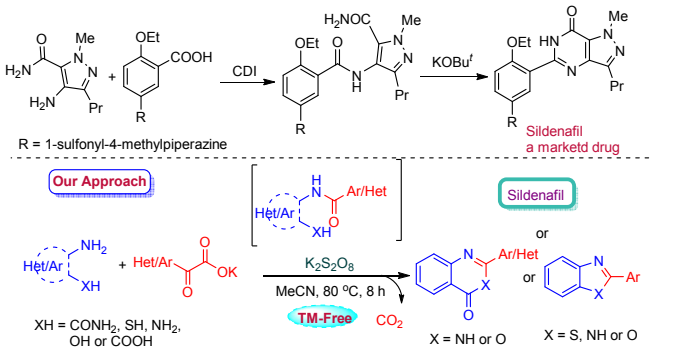
DOI: 10.1039/x0xx00000x

www.rsc.org/

Joydev K. Laha,* Ketul V. Patel, K. S. Satyanarayana Tummalapalli, and Neetu Dayal

A unified approach to the tandem preparation of diverse nitrogen heterocycles via decarboxylative acylation of *ortho*-substituted amines with α-oxocarboxylic acids and subsequent intramolecular cyclizations has been developed. The key features of this work include: first example of transition-metal-free decarboxylative amidation of α-oxocarboxylic acids with *ortho*-substituted amines, realization of intramolecular cyclization of amides employing nucleophiles that have previously been unexplored, mechanistic investigation of an unprecedented $K_2S_2O_8$ promoted amide formation and its subsequent intramolecular cyclizations, and application to the synthesis of a best-selling marketed drug.

Benz-amidine/oxazine heterocyclic structures are privileged molecular scaffolds ubiquitously found in natural products, pharmaceuticals, and performance materials.[1] Because of their wide prevalence in chemical entities that demonstrate heralds of pharmacological and biological activities, an impressive armory of diverse synthetic routes have been developed for the synthesis of these nitrogen heterocycles.[2] Among the various tools executed for the synthesis of these heterocycles, intramolecular reactions of secondary aryl amides with another amide group juxtaposed to the original amide leading to the synthesis of quinazolin-4-ones is especially alluring.[3] Despite the great potential, as demonstrated in the preparation of a pharmaceutical drug Sildnafil,[4] the intramolecular cyclization of amides is rarely practiced largely because of the difficulty in preparation of starting amides using classical approaches, poor reactivity of amides, and ineffective cyclizations with a variety of nucloephiles under basic conditions (Scheme 1). Remarkably, α-oxocarboxylic acids have been demonstrated to serve as acyl surrogates in contemporary amide synthesis[5] via decarboxylative acylaton of hydroxylamines,[6a] and aliphatic[6b] or aromatic amines[6c] under reagent-free conditions, I_2, or visible-light mediated transition-metal-catalysis. However, a strategy integrating amide preparation and subsequent intramolecular cyclizations to the synthesis of diverse benz-amidine/oxazine heterocycles is yet to be realized.



Scheme 1. Amide preparation and subsequent intramolecular cyclizations to benz-amidine/oxazine heterocycles.

A defined objective with a focus to develop a) amide formation from α-oxocarboxylic acids and amines, especially under transition-metal-free conditions, b) subsequent intramolecular cyclizations of amides with an internal nucleophile present at the appropriate position, c) a novel tandem approach involving both reactions in the presence of one set of reagents, and d) a general protocol for the synthesis of benz-amidine/oxazine while attractive would be a daunting challenge. Earlier, we demonstrated a tandem oxidative conversion of 10,11-dihydro-*5H*-dibenzo [*b*,*e*][1,4]diazepines to phenazines[7] and an intramolecular oxidative nitrogenation/oxygenation of benzylic C(sp^3)-H bond using cheap, environment-friendly oxidant $K_2S_2O_8$.[8] Leveraging our previous experiences on the synthesis of nitrogen heterocycles,[9] we describe herein development of a unified tandem approach to the synthesis of nitrogen heterocycles via decarboxylative acylation of amines with α-oxocarboxylic acids and subsequent intramolecular cyclizations. The reactions of readily available *ortho*-substituted aryl or heteroaryl amines and α-oxocarboxylic acids occur in the presence of $K_2S_2O_8$ affording a diverse nitrogen heterocycles in good to excellent

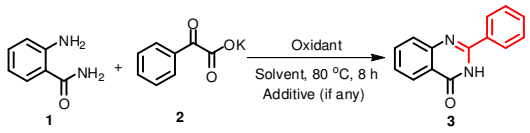
[a] *Department of Pharmaceutical Technology (Process Chemistry)*
National Institute of Pharmaceutical Education and Research
S. A. S. Nagar, Punjab 160062, India; E-mail: jlaha@niper.ac.in

Electronic Supplementary Information (ESI) available: [Supporting information for this article is given via a link]. See DOI: 10.1039/x0xx00000x

View Article Online DOI: 10.1039/C6CC04259G

yields. The distinctive features of this work include a) realization, for the first time, of a transition-metal-free decarboxylative amidation of α-oxocarboxylic acids with *ortho*-substituted aromatic amines, b) event of intramolecular cyclization of amides without any requirement of additional reagents, c) $K_2S_2O_8$ promoted unprecedented amide formation and subsequent intramolecular cyclizations appealing a mechanistic debate, and d) practical application to the synthesis of a top-selling marketed drug.

Table 1. Optimization of the reaction conditions[a]



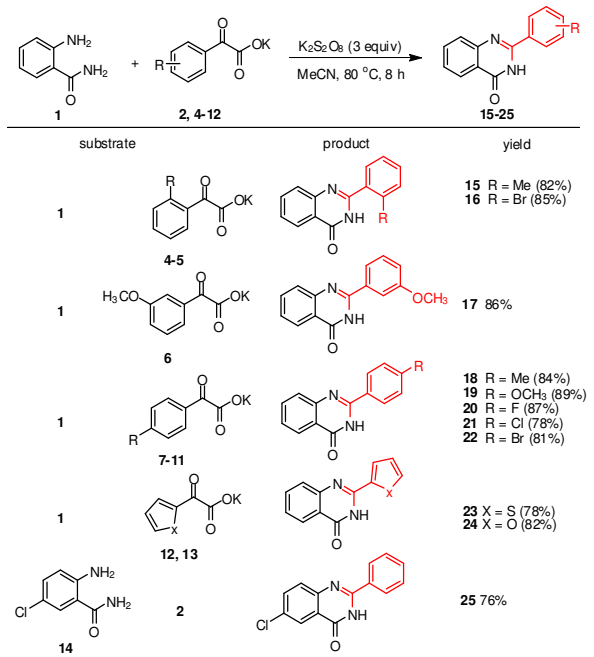
1 2 3

Entry	Oxidant (equiv)	Additive	Solvent	Yield[b] (%)
1	$K_2S_2O_8$ (3)		MeCN/H_2O	35
2	$K_2S_2O_8$ (3)		MeOH	30
3	$K_2S_2O_8$ (3)		MeCN	95
4	$K_2S_2O_8$ (1)		MeCN	80
5			MeCN	0
6	$Na_2S_2O_8$ (3)		MeCN	73
7	Oxone (3)		MeCN	67
8[c]	$K_2S_2O_8$ (3)		MeCN	64
9	$K_2S_2O_8$ (3)		DMF	81
10[d]	$K_2S_2O_8$ (3)	$AgNO_3$	MeCN	77
11[e]	$K_2S_2O_8$ (3)	BHT	MeCN	76
12[e]	$K_2S_2O_8$ (3)	TEMPO	MeCN	78

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), oxidant (3 equiv), solvent (2 mL) 80 °C, 8 h. [b] Isolated yield. [c] Solvent (4 mL) used. [d] $AgNO_3$ (20 mol%) used. [e] BHT or TEMPO (10 equiv) used.

Our initial investigations on the reactions of 2-aminobenzamide **1** and salt of α-oxocarboxylic acid **2** were largely focused on exploring a condition that could promote a tandem amide formation and intramolecular cyclizations to yield 2-aryl-quinazolinone **3**. Heating a solution of **1** and **2** in a mixture of solvents [CH_3CN/H_2O (1:1)] in the presence of 3 equiv of $K_2S_2O_8$ at 80 °C gave **3** in 35% yield (Table 1, entry 1). Changing the solvent to MeOH gave **3** in a comparable yield (entry 2). However, a substantial improvement in the yield was observed in the absence of any polar protic solvent [H_2O or MeOH]. Thus, an optimized reaction conditions entailed heating **1** and **2** in CH_3CN in the presence of $K_2S_2O_8$ at 80 °C for 8 h, which afforded **3** in 95% yield (entry 3). A subordinate amount of $K_2S_2O_8$ was somewhat detrimental (entry 4). Without $K_2S_2O_8$, the reaction did not give even a trace amount of **3** suggesting the crucial role of $K_2S_2O_8$ in this tandem reaction (entry 5). Other oxidants, such as $Na_2S_2O_8$ or oxone had adverse effects on the tandem reaction (entries 6-7). The tandem reaction conducted at higher dilution proved deleterious (entry 8). The effect of a polar aprotic solvent DMF is comparable to that of CH_3CN (entry 9). Interestingly, a Ag-catalyzed condition produced inferior results (entry 10). Remarkably, a free radical quencher, such as BHT or TEMPO did not affect the yield of **3** significantly (entries 11-12). Central to this investigation was to identify $K_2S_2O_8$ as the sole reagent that could promote tandem amide formation and subsequent intramolecular cyclizations.

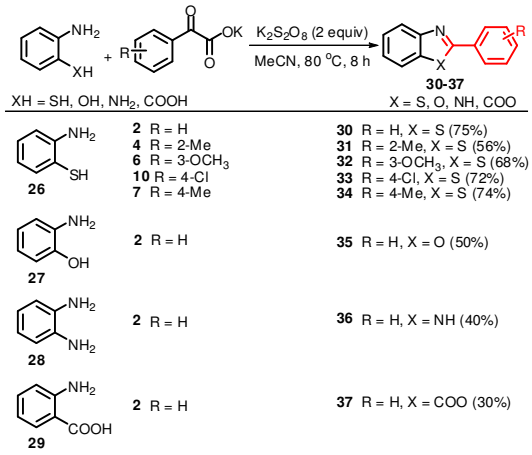
Next, we investigated the scope of both substrates that could participate in tandem decarboxylative amidation/intramolecular cyclizations for the synthesis of quinazolin-4-ones (Scheme 2). An α-oxocarboxylic acid with an electron-donating group at 2-position delivered quinazolin-4-one **15** in 82% yield. An α-oxocarboxylic acid containing an OMe group at 3-position also worked well affording **17** in 86% yield. The α-oxocarboxylic acids containing an electron-donating group at 4-postion worked eventfully affording quinazolin-4-ones **18-19** in 84-89% yield. The tandem transformation also exhibited tolerance for halogen groups at 2- or 4-positions. 4-Fluorophenyl glyoxylate also reacted with **1** under the optimized conditions affording **20** in 87% yield. Furthermore, extended substrate scope was explored with heterocycles containing an α-oxocarboxylic acid group. Thus, thiophene or furan **12-13** was compatible under the reaction conditions yielding **23-24** in 78-82% yield. 5-Chloro-2-aminobenzamide **14** is also a viable substrate yielding 6-chloro-2-phenylquinazolin-4-one **25** in 76% yield. The chloro substituent in the product could be a synthetic handle for further functionalizations.



Scheme 2. Substrate scope to quinazolin-4-ones synthesis.

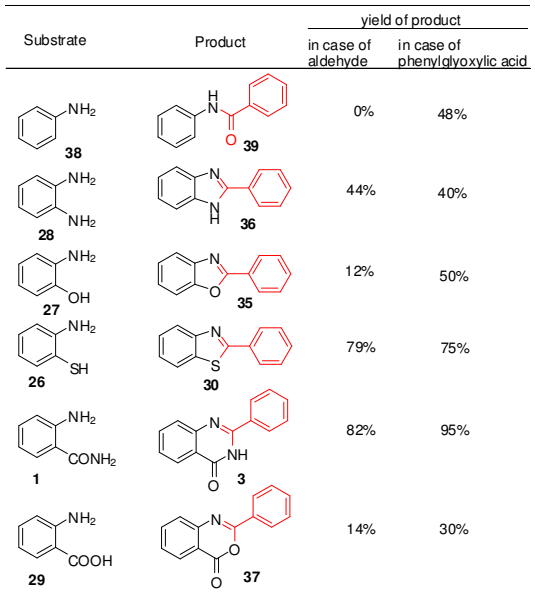
To demonstrate the general applicability of our protocol to the synthesis of diverse benz-amidine/oxazine heterocycles, we next investigated the tandem reactions of α-oxocarboxylic acids and different *ortho*-substituted amines under the optimized conditions. Intriguingly, 2-aminothiophenol **26** gave 2-arylbenzo[*d*]thiazoles **30-34** in good 56-75% yields (Scheme 3). To our delight, 2-aminophenol **27** gave benzoxazole **35** in 50% yield. *o*-Phenylenediamine **28** reacted with phenylglyoxylate to give mono-acylated product, which upon subsequent intramolecular cyclization gave (NH)-benzimidazole **36** in 40% yield. 2-Aminobenzoic acid **29**

reacted similarly with phenylglyoxylate to give benzoxazine **37** in 30% yield. Pivotal to this investigation was to uncover intramolecular cyclizations of amides with a variety of nucleophiles including NH_2, SH, OH, and CO_2H, which have previously been unexplored.



Scheme 3. Substrate scope to 2-aryl benzazoles.

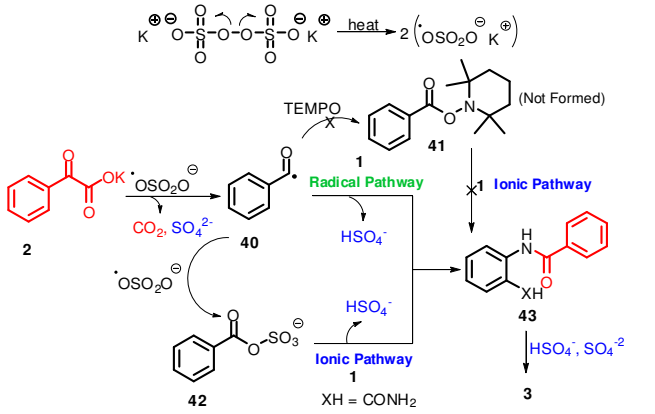
Interestingly, reactions of *ortho*-substituted amines and benzaldehyde also gave the corresponding nitrogen heterocycles under the optimized conditions (Scheme 4). A comparison of the reactivity of phenylglyoxylate and benzaldehyde towards reaction with amines is apparent.



Scheme 4. Comparative study with aldehyde.

While the yields for the formation of quinazolinone **3**, benzothiazole **30**, or benzimidazole **36** were comparable, benzaldehyde reacted very sluggishly with 2-aminophenol and 2-aminobenzoic acid affording benzoxazole **35** and benzoxazine **37** only in 12% and 14% yields, respectively. Perhaps most importantly, the reaction of phenylglyxolate and aniline only gave benzamide **39**. Conclusively, these experiments do not support the formation of aldehydes from α-oxocarboxylic acids in our study. Thus, our tandem protocol is clearly distinct from the approach, which involves imine formation and subsequent intramolecular cyclization, commonly used for the synthesis of benz-amidine/oxazine heterocycles.

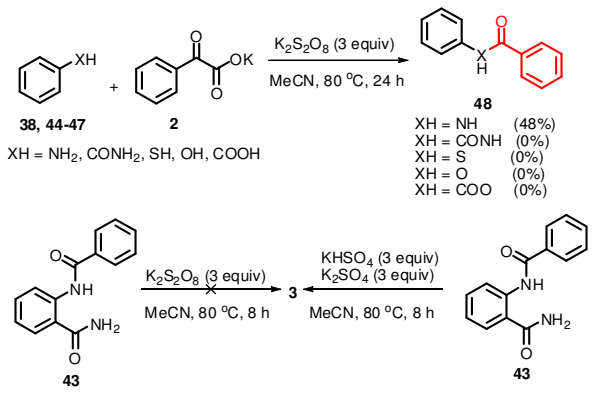
The possible reaction pathways of the tandem reaction are shown in Scheme 5. Initially, homolytic cleavage of $K_2S_2O_8$ under thermal conditions could generate a sulfate radical anion ($SO_4^{\cdot-}$),[10] which upon reaction with phenylglyoxylate could produce acyl radical **40** via decarboxylation. The formation of amide **43** could occur via two pathways. The acyl radical **40** could react with 2-aminobenzamide **1** to form amide **43** via a radical pathway.[6c] Upon capture of a sulfate radical anion ($SO_4^{\cdot-}$), the acyl radical **40** could form benzoyl sulfate **42**, which could undergo nucleophilic substitution with **1** to give **43** via anionic pathway. In the case of TEMPO as additive, the compound **43** could also form via nucleophilic substituion of a TEMPO adduct **41** with **1** (see ESI for a detailed discussion). Furthermore, intramolecular nucleophilic addition of the primary amide group to the secondary amide in amide **43** in the presence of bases (HSO_4^-, SO_4^{-2}) generated *in situ* could give quinazolinone **3**.



Scheme 5. Possible reaction pathways.

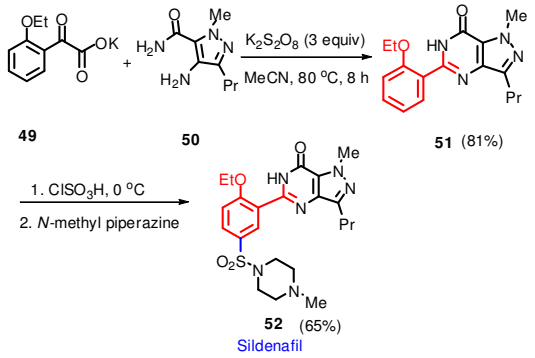
Some control experiments were performed to gain insights into the reaction mechanism (Scheme 6). To understand whether a regioselective decarboxylative acylation takes place in 2-aminobenzamides, we carried out two reactions involving phenylglyoxylate and aniline or benzamide under the optimized conditions. While the reaction of benzamide and phenylglyoxylate did not afford any product, the reaction of aniline and phenylglyoxylate gave the corresponding amide **39** in 48% yield. These experiments may rule out the possibility of decarboxylative *N*-acylation of the amide group in 2-aminobenzamides. Furthermore, attempted decarboxylative acylations of thiophenol, phenol, or benzoic acids under the optimized conditions were not successful. These experiments suggest that regioselective mono-acylation of amino group occur in the presence of another nucleophile present at the *ortho*-position (*vide supra*, Scheme 3). Collectively, these experiments support the formation of an amide compound in our tandem reaction. Further evidence was conceived from the experiments carried out with isolated pure sample of 2-(benzoylamino)benzamide **43** prepared

independently. When **43** was exposed to our optimized conditions, the desired compound **3** was not obtained. However, compound **43** when subjected to heating in the presence of $KHSO_4$ and K_2SO_4, the desired product **3** was obtained. This experiment suggests that HSO_4^- and SO_4^{-2} anions, generated *in situ* from $K_2S_2O_8$, could facilitate the intramolecular cyclizations of amide to give quinazolinone **3**.



Scheme 6. Control experiments.

To demonstrate a translational application of our laboratory concept, we prepared a marketed drug, Sildenafil (Viagra™).[11] Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5) used in the treatment of male erectile dysfunction.[12]



Scheme 7. Synthesis of sildenafil.

Treatment of 2-ethoxy phenylglyoxylate **49** with the commercially available pyrrazole **50** under the optimized conditions gave quinazolin-4-one **51** in 81% yield. In the commercial production of the drug, quinazolin-4-one **51** is prepared by coupling of 2-ethoxybenzoic acid and pyrrazole **50** in the presence of CDI followed by intramolecular cyclization of the amide in the presence of *t*-BuOK. Distinct from the commercial preparation, our protocol delivers the quinazolin-4-one **51** in a single step using $K_2S_2O_8$ as the only reagent in a comparable yield. Chlorosulfonation of **51** followed by reaction with *N*-methylpiperazine gave sildenafil (Scheme 7).[13]

In conclusion, the study described herein includes a comprehensive package of new amide formation, their unexplored intramolecular reactions to the synthesis of diverse nitrogen heterocycles, and applications to the synthesis of a marketed drug. A detailed understanding of the mechanism, preparation of new analogues of sildenafil, and process development of sildenafil citrate encompassing the key quinazolin-4-one preparation are currently underway.

View Article Online
DOI: 10.1039/C6CC04250C

Acknowledgements

The financial support from the SERB, New Delhi is greatly appreciated.

Notes and references

1 M. Smist and H. Kwiecien, *Curr. Org. Synth*., 2014, **11**, 676.
2 (a) T. Hisano, M. Ichikawa, A. Nakagawa and M. Tsuji, *Chem. Pharm. Bull.*, 1975, **23**, 1910; (b) A. Ben-Alloum, S. Bakkas and M. Soufiaoui, *Tetrahedron Lett*., 1997, **38**, 6395; (c) B. C. Ranu, R. Jana and S. S. Dey. *Chem. Lett.,* 2004, **33**, 274; (d) A. K. Chakraborti, C. Selvam, G. Kaur and S. Bhagat, *Synlett*, 2004, 851; (e) Y. Mitobe, S. Ito, T. Mizutani, T. Nagase, N. Sato and S. Tokita, *Bioorg. Med. Chem. Lett*., 2009, **19**, 4075; (f) J. Zhou and J. Fang, *J. Org. Chem*., 2011, **76**, 7730; (g) H. Hikawa, Y. Ino, H. Suzuki and Y. Yokoyama, *J. Org. Chem*., 2012, **77**, 7046; (h) T. B. Nquyen, L. Ermolenko and A. Al-Mourabil, *Green Chem*., 2013, **15**, 2713; (i) D. Zhao, T. Wang and J. -X. Li, *Chem. Commun.,* 2014, **50**, 6471; (j) L. He, H. Li, H. Neumann, M. Beller and X. -F. Wu, *Angew. Chem. Int. Ed*., 2014, **53**, 1420.
3 (a) R. Soliman, F and S. G. Soliman, *Synthesis,* 1979, 803; (b) J. Hanusek, M. Sedlak, P. Simunek and V. Sterba, *Eur. J. Org. Chem.,* 2002, 1855.
4 D. J. Dale, P. J. Dunn, C. Golightly, M. L. Hughes, P. C. Levett, A. K. Pearce, P. M. Searle, G. Ward and A. S. Wood, *Org. Process Res. Dev.,* 2000, **4**, 17.
5 (a) E. Valeur and M. Bradley, *Chem. Soc. Rev.,* 2009, **38**, 606; (b) V. R. Pattabiraman and J. W. Bode, *Nature,* 2011, **480**, 471; (c) C. L. Allen and J. M. J.Williams, *Chem. Soc. Rev.,* 2011, **40**, 3405.
6 (a) J. W. Bode, R. M. Fox and K. D. Baucom, *Angew. Chem. Int. Ed*., 2006, **45**, 1248; (b) C. -C. Cho, J. -N. Liu, C. -H. Chien, J. -J. Shie, Y. -C. Chen and J. -M. Fang, *J. Org. Chem*., 2009, **74**, 1549; (c) J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan and A. Lei, *Angew. Chem. Int. Ed.,* 2014, **53**, 502.
7 J. K. Laha, K. S. S. Tummalapalli and A. Gupta, *Org. Lett.,* 2014, **16**, 4392.
8 J. K. Laha, K. S. S. Tummalapalli, A. Nair and N. Patel, *J. Org. Chem.,* 2015, **80**, 11351.
9 (a) J. K. Laha, N. Dayal, R. Jain and K. Patel, *J. Org. Chem.,* 2014, **79**, 10899; (b) J. K. Laha, N. Dayal, K. P. Jethava and D. V. Prajapati, *Org. Lett*., 2015, **17**, 1296; (c) J. K. Laha and N. Dayal, *Org. Lett.,* 2015, **17**, 4742; (d) J. K. Laha, K. P. Jethava and S. Patel, *Org. Lett.,* 2015, **17**, 5890; (e) J. K. Laha, K. S. S. Tummalapalli and K. P. Jethava, *Org. Biomol. Chem.* 2016, **14**, 2473; (f) J. K. Laha, R. A. Bhimpuria, D. Prajapati, N. Dayal and S. Sharma, *Chem. Commun.,* 2016, **52**, 4329.
10 (a) Y. -M. Li, X. -H. Wei, X. -A. Li and S. -D. Yang, *Chem. Commun.,* 2013, **49**, 11701; (b) Z. Zhang, S. Fang, Q. Liu and G. *J.* Zhang, *Org. Chem.,* 2012, **77**, 7665.
11 P. J. Dunn, S. Galvinb and K. Hettenbach, *Green Chem.,* 2004, **6**, *43.*
12 N. K. Terrett, A. S. Bell, D. Brown and P. Ellis, *Bioorg. Med. Chem. Lett.,* 1996, **6**, 1819.
13 A. S. Bell, D. Brown and N. K. Terrett, EP0463756A1, 1992.