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Tandem approach for the synthesis of imidazo[1,2-*a*]pyridines from alcohols

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ABSTRACT

Propylphosphonic anhydride (®T3P) is shown to be an effective and mild reagent for the one-pot synthesis of imidazo[1,2-*a*]pyridines from a variety of alcohols. Alcohols are oxidized in situ to aldehydes under mild conditions, which in turn undergo a three-component reaction with various 2-aminopyridines and isocyanides to afford imidazo[1,2-*a*]pyridines in excellent yields. ®T3P acts as an activator for both DMSO in oxidation reaction and the Schiff base in nucleophilic addition reaction with isocyanides.

The imidazo[1,2-*a*]pyridine scaffold is present in a large number of compounds showing an impressive variety of biological properties,[1] such as antibacterial, antifungal, anthelmintic, antiviral, antiprotozoal, anti-inflammatory, anticonvulsant, anxiolytic, hypnotic, gastrointestinal, antiulcer, and immunomodulatory activities.[2,3] Furthermore, imidazo[1,2-*a*]pyridine scaffold forms the core structure of several drug molecules[4] like zolpidem used in the treatment of insomnia, alpidem, as an anxiolytic agent, olprinone for the treatment of acute heart failure, minodronic acid useful for the treatment of osteoporosis, and zolimidine used for the treatment of peptic ulcer (Fig. 1).

Several methods are available for the preparation of 2- or 3-substituted imidazo[1,2-*a*]pyridines.[5a–g] Among these, the three-component coupling of 2-aminopyridine, aldehyde, and alkyne is one of the most common methods for the synthesis of imidazo[1,2-*a*]pyridines. Another approach is the three-component reaction (3-CR) of aromatic amidines with aromatic aldehyde and isocyanide.[6] Numerous catalysts are being used over the years such as $Sc(OTf)_3$[7], solid supported *p*-toluenesulfonic acid,[8a] glyoxylic acid,[8b] $ZnCl_2$,[9] and ionic liquid.[10] Recently, Adib et al. (2011) reported the synthesis of imidazo[1,2-*a*]pyridine scaffolds by a modified three-component coupling (3-CR) of aromatic amidines, benzyl halides, and isocyanides in the presence of DMSO and K_2CO_3 (Scheme 1).[11a]

Adib et al. (2007) reported a catalyst-free, simple, and environmentally friendly approach for the synthesis of imidazo[1,2-*a*]pyridines[11b] using aldehydes as one of the substrates in water at 70 °C. Some of the methods entail such demerits as the requirement of expensive and excess amounts of catalysts, prolonged reaction times, difficulties in work-up procedure, and harsh reaction conditions. Though these protocols are quite useful, there is still a need to develop new methodologies which might work under milder reaction conditions. So far, there is no report on the one-pot synthesis of imidazo[1,2-*a*]pyridines directly from alcohols. Recently, propylphosphonic anhydride (®T3P) has received increased attention as a coupling agent and as a water scavenger,[12] offering several advantages such as high yields, purity, low toxicity, broad functional group tolerance, and easy work-up when compared to traditional reagents.[12,13] Though, ®T3P has been identified as a mild water scavenger, the wider scope and synthetic utility of this reagent for oxidization and cyclodehydration have not been explored.

In continuation of our work on the development of the useful synthetic methodologies,[14–17] we have recently reported, a novel and straight forward approach for the one-pot synthesis of benzimidazoles and benzothiazoles using ®T3P/DMSO.[18] In the present work, the method used involves an in situ oxidation–cyclocondensation sequence starting from alcohols. Thus, under mild oxidative conditions, alcohols reacting with propylphosphonicanhydride and DMSO in ethyl acetate as a solvent at room temperature get converted into the corresponding aldehydes (Scheme 2). Subsequently, the in situ formed aldehyde is condensed with 2-aminopyridine followed by treatment with isocyanide at room temperature which resulted in the corresponding imidazo[1,2-*a*]pyridines.

In order to explore the scope and optimal conditions (Table 1) for ®T3P/DMSO catalyzed synthesis of imdiazo[1,2-*a*]pyridine, alcohol **1b** was selected as a model. With reaction of **1b** (1.0 equiv),

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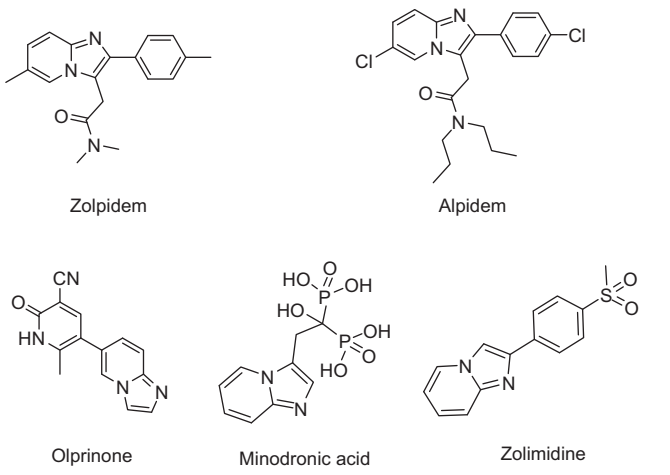


Figure 1. Examples of imidazo[1,2-*a*]pyridine containing drugs and biologically active compounds.

DMSO (2.0 equiv), 2-amino-5-fluoropyridine **1a** (1.0 equiv), isocyanide **1c** (1.5 equiv), ®T3P (1.0 equiv, 50% solution in EtOAc), in 10 volumes of EtOAc at room temperature for 24 h, the desired product was obtained in a trace yield. Upon increasing the equivalent of ®T3P, the formation of the desired product was improved (Table 1, entry 2). At 2.5 equiv of ®T3P, the yield was 72% (Table 1, entry 4). These results suggested that ®T3P played a vital role in various stages of the reaction. The effect of temperature was the next parameter to be investigated (Table 1, entries 6–7), and we found that the room temperature was the most effective. The role of DMSO and of the solvents on the synthesis of imidazo[1,2-*a*] pyridine **1d**, was then studied. We found that the reaction of alcohol **1b** (1.0 equiv), 2-amino-5-fluoropyridine **1a** (1.0 equiv), isocyanide **1c** (1.5 equiv), ®T3P (2.5 equiv) without DMSO, did not take place both at room temperature and under reflux condition. This makes the obvious point that DMSO is needed as an oxidizing agent to convert alcohol into aldehyde. However, increasing the amount of DMSO with respect to ethyl acetate in the ratio (EtOAc/DMSO) 1:1, 1:2, 1:3, and 1:4 did not improve the yield. Solvents other than ethyl acetate such as THF, DMF, toluene, acetonitrile, acetone, and benzene did not make a difference. Then ethyl acetate was chosen as the preferred solvent.

Using the optimized reaction conditions (Table 1, entry 4), we subsequently explored the reaction scope by using aminopyridines, aromatic or heterocyclic alcohols, and isocyanides to afford imidazo[1,2-*a*]pyridine products in 72–94% yields (Table 2).

Table 1
Optimization of reaction conditions

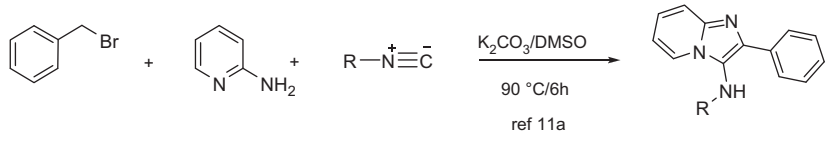
No.	T3P[a] (equiv)	Time (h)	Temperature	Yield (%)
1	1.0	24	RT	Trace
2	1.5	24	RT	44
3	2.0	8	RT	68
4	2.5	4.5	RT	72
5	3.0	4.0	RT	69
6	2.5	3	35 °C	68
7	2.5	3	45 °C	62

[a] 50% solution in ethyl acetate.

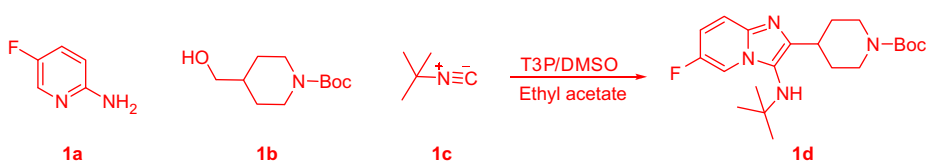
A variety of aromatic alcohols containing electron donating and electron withdrawing substituents such as *p*-methoxy (table 2, entry 8b), *p*-isopropyl (Table 2, entry 2b), *p*-bromo (Table 2, entry 4b), and *p*-cyano (Table 2, entry 5b), *p*-fluoro (Table 2, entry 14b), and *p*-nitrobenzyl alcohol (Table 2, entry 10b), participate well in this three component reaction. Notably, even sterically hindered alcohols such as (Table 2, entry 11b) and heterocyclic alcohols (Table 2, entry 6b, 7b, 12b, 13b) proved to be effective to afford the respective imidazo[1,2-*a*]pyridines. In addition, sensitive functionalities like Boc (Table 2, entry 1b), chloro (Table 2, entry 2a, 5a, and 7a), cyano (Table 2, entry 5b) etc. are tolerated. The scope and generality of this procedure are demonstrated for various isocyanides as well *t*-butyl isocyanide, benzyl isocyanide, *n*-pentylisocyanide participate in the three-component reaction to give the corresponding imidazo[1,2-*a*]pyridines. Then this protocol provides an opportunity for further chemical elaborations in getting various functionalized products. Several therapeutically active moieties can be incorporated into N-fused imidazo[1,2-*a*]pyridines at ease by this method.

All synthesized compounds were adequately characterized by the physical and spectral data which are in good agreement with the structures of the products.

A possible mechanism of the oxidative and dehydrative cyclization to get imidazo [1,2-*a*]pyridine is suggested in Scheme 3. DMSO **1** gets activated by T3P **2** to give an electrophilic sulfur species **3**, which then reacts with alcohol **4** to give an aryloxysulfonium salt **6**. The hydrolyzed T3P obtained as byproduct **5** acts as a base to pull out H of aryloxysulfonium salt **6** to form aldehyde **7**. *P*,*P*′,*P*″-Tripropyltriphosphonic acid **5a** and dimethyl sulfide formed as the byproduct. The second step in the probable mechanism is the T3P catalyzed condensation of aminopyridine with aldehyde to afford aminol intermediate **9**, which undergoes elimination to form the imine intermediate **10**. The byproduct, *P*,*P*′,*P*″-tripropyltriphosphonic acid **5a** protonates the imine to give the activated form **11**. The stage is now set for nucleophilic addition of isocyanide **12** to



Scheme 1. Synthesis of imidazo[1,2-*a*]pyridines from benzyl halides.

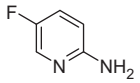
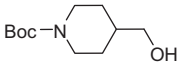
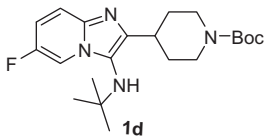
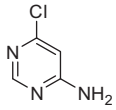
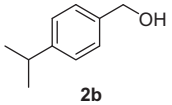
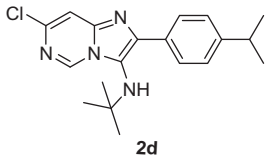
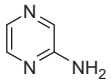
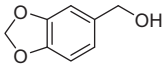
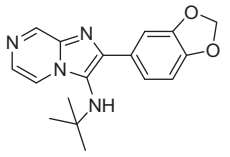
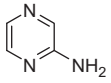
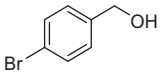
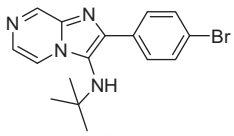
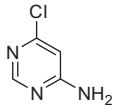
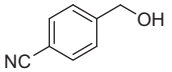
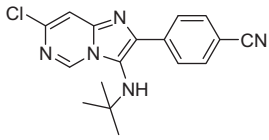
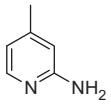
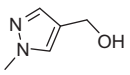
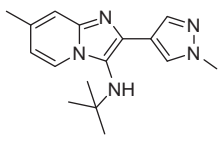
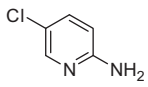
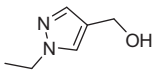
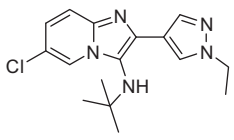
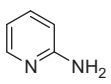
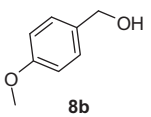
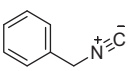
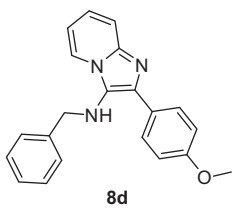
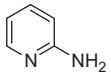
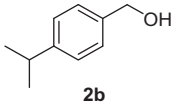
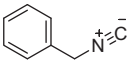
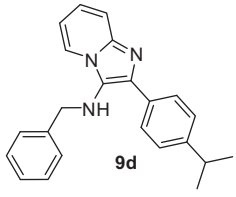


Scheme 2. Synthesis of imidazo[1,2-*a*]pyridines from alcohols.

yield the isonitrilium intermediate **13**, which cyclizes to the key intermediate **14**. Prototrophic tautomerization of **14** yields the final imidazo[1,2-*a*]pyridine **15**.

In conclusion, we have developed an efficient and simple one-pot strategy for the synthesis of imidazo[1,2-*a*]pyridines by in situ oxidation of alcohols to aldehydes followed by the three-

Table 2
Synthesis of imidazo[1,2-*a*]pyridines from alcohols via 3 cc reaction

Amino pyridine	Alcohol	Isocyanide	Product	Yield (%)	Time (h)
 **1a**	 **1b**	 **1c**	 **1d**	72	4.5
 **2a**	 **2b**	 **1c**	 **2d**	82	5
 **3a**	 **3b**	 **1c**	 **3d**	85	5
 **3a**	 **4b**	 **1c**	 **4d**	89	4
 **2a**	 **5b**	 **1c**	 **5d**	94	4
 **4a**	 **6b**	 **1c**	 **6d**	84	5
 **5a**	 **7b**	 **1c**	 **7d**	80	5
 **6a**	 **8b**	 **2c**	 **8d**	78	4
 **6a**	 **2b**	 **2c**	 **9d**	81	4

(*continued on next page*)

Table 2 (*continued*)

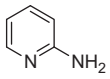
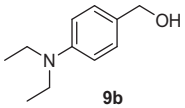
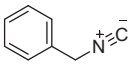
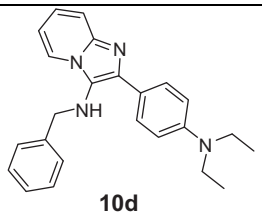
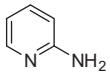
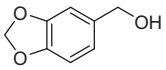
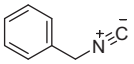
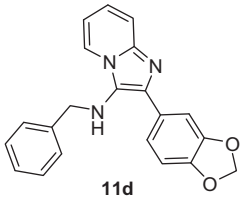
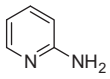
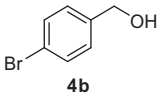
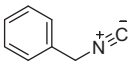
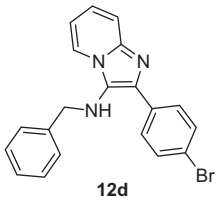
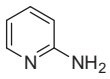
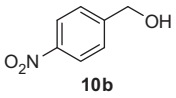
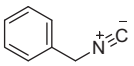
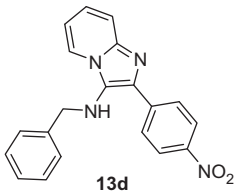
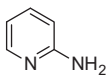
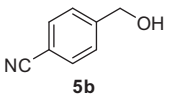
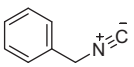
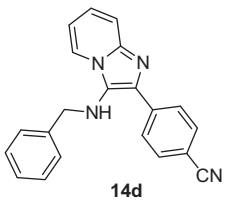
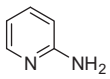
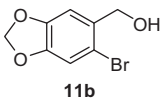
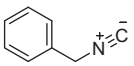
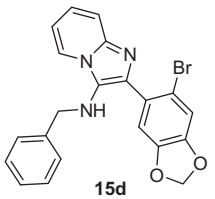
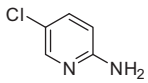
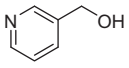
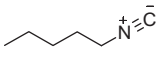
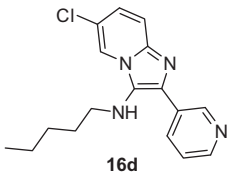
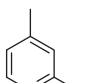
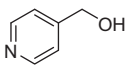
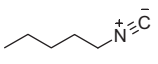
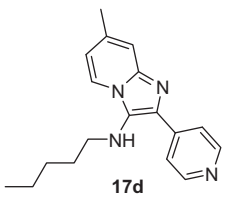
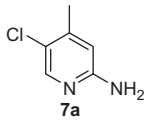
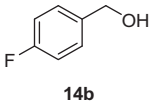
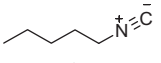
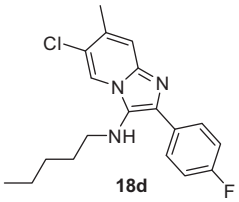
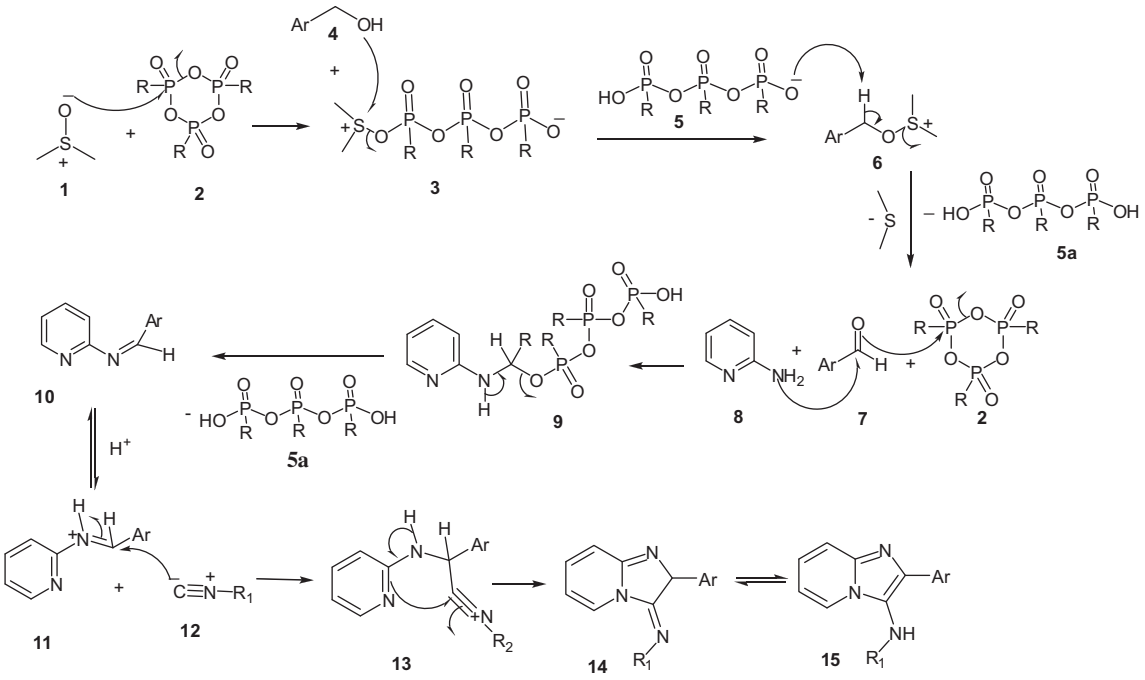
Amino pyridine	Alcohol	Isocyanide	Product	Yield (%)	Time (h)
 **6a**	 **9b**	 **2c**	 **10d**	86	4
 **6a**	 **3b**	 **2c**	 **11d**	81	4.5
 **6a**	 **4b**	 **2c**	 **12d**	90	4
 **6a**	 **10b**	 **2c**	 **13d**	93	4
 **6a**	 **5b**	 **2c**	 **14d**	92	3.5
 **6a**	 **11b**	 **2c**	 **15d**	87	5
 **5a**	 **12b**	 **3c**	 **16d**	76	5
 **4a**	 **13b**	 **3c**	 **17d**	75	5

Table 2 (*continued*)

Amino pyridine	Alcohol	Isocyanide	Product	Yield (%)	Time (h)
 **7a**	 **14b**	 **3c**	 **18d**	92	3.5



Scheme 3.

component coupling of aldehyde, 2-aminopyridine, and isocyanide. Excellent yield, tandem nature, mild conditions, simple and convenient work-up are the highlights of this reaction. The method provides an easy access to a diverse array of medicinally-relevant N-fused heterocycles.

Typical procedure for the synthesis of (**4d**): To the solution of alcohol **4b** (0.50 g, 2.67 mmol) and DMSO (0.41 g, 5.34 mmol) in ethyl acetate (5 ml) was added ®T3P (1.84 g, 6.68 mmol, 2.5 equiv, 50% solution in ethyl acetate) at 0 °C. The resulting mixture was allowed to warm to RT and stirred for 1 h. Pyrazine-2-amine **3a** (0.254 g, 2.67 mmol) was added to the above mixture and stirred for 15 min, which was followed by the addition of isocyanide **1c** (0.33 g, 4.01 mmol) at room temperature and stirring for 4 h. Progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was diluted with ethyl acetate and neutralized with aqueous sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (25 mL × 2), the combined organic phases were washed with water, brine solution, dried over anhydrous sodium sulfate, and concentrated under vacuum to afford a crude product, which was purified on silica gel using ethyl acetate and petroleum ether.

Analytical data for some representative compounds: Compound **4d**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.92 (s, 1H), 8.40 (d, J = 3.30, 1H), 8.15 (d, J = 8.13, 2H), 7.85 (d, J = 4.08, 1H), 7.60 (d, J = 8.12, 2H), 4.83 (s, 1H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.15, 139.57, 137.10, 134.19, 131.55, 130.24, 128.93, 126.27, 121.46, 117.75, 56.77, 30.43; MS (ES) m/z (M+2) = 346.1; Compound **11d**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.13 (d, J = 6.31, 1H), 7.68 (s, 2H), 7.08–7.40 (m, 7H), 6.96 (d, J = 8.19, 1H), 6.75 (t, J = 6.2, 1H), 6.03 (s, 2H), 5.26 (s, 1H), 4.05 (d, J = 5.44, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.86, 146.70, 140.70, 140.23, 134.83, 129.24, 128.64, 127.47, 126.14, 124.15, 123.49, 120.76, 116.96, 111.56, 108.76, 107.28, 101.32, 51.62; MS (ES) m/z (M+1) = 344.3; Compound **14d**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.30 (d, J = 8.05 Hz, 2H), 8.17 (d, J = 6.66 Hz, 1H), 7.84 (d, J = 7.92 Hz, 2H), 7.44 (d, J = 8.87 Hz, 1H), 7.15–7.42 (m, 6H), 6.80 (t, J = 6.44 Hz, 1H), 5.53 (d, J = 5.73 Hz, 1H), 4.08 (d, J = 5.82 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 141.27, 139.93, 139.68, 132.75, 132.67, 128.71, 128.68, 127.58, 127.25, 125.12, 123.85, 119.67, 117.50, 112.12, 109.25, 51.75; MS (ES) m/z (M+1) = 325.2.

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Supplementary data

Supplementary data (relevant spectra LCMS, ^{1}H, ^{13}C NMR for all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.112.

References and notes

1. (a) Lhassani, M.; Chavignon, O.; Chezal, J.-M.; Teulade, J.-C.; Chapat, J.-P.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271; (b) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 347; (c) Trapani, G.; Franco, M.; Latrofa, A.; Ricciardi, L.; Carotti, A.; Serra, M.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **1999**, *42*, 3934.
2. Howard, A. S. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. V. F., Eds.; Pergamon Press: London, 1996; Vol. 8,. Chapter 10, pp 262–274, and references therein.
3. Couty, F.; Evano, G. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. V. F., Taylor, R. J. K., Eds.; Elsevier Science, Oxford, 2008; Vol. 11,. Chapter 10, pp 409–492, and references therein.
4. Enguehard-Gueiffier, C.; Gueiffier, A. *Mini Rev. Med. Chem.* **2007**, *7*, 888.
5. (a) Ueno, M.; Nabana, T.; Togo, H. *J. Org. Chem.* **2003**, *68*, 6424; (b) Adib, M.; Mahdavi, M.; Abbasi, A.; Jahromi, A. H.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2007**, *48*, 3217; (c) Parenty, A. D. C.; Cronin, L. *Synthesis* **2008**, 1479; (d) Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synthesis* **2009**, 271; (e) Adib, M.; Shebani, E.; Zhu, L.-G.; Mirzaei, P. *Tetrahedron Lett.* **2008**, *49*, 5108; (f) Guchhait, S. K.; Madaan, C. *Org. Biomol. Chem.* **2010**, *8*, 3631; (g) Shaabani, A.; Soleimani, E.; Maleki, A.; Moghimi, J. *Synth. Commun.* **2008**, *38*, 1090.
6. (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661; (b) Blackburn, C. *Tetrahedron Lett.* **1998**, *39*, 5469; (c) Bienayme, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234.
7. Ireland, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2003**, *44*, 4369.
8. (a) Chen, J. J.; Golebiowski, A.; McClenaghan, J.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett.* **2001**, *42*, 2269; (b) Lyon, M. A.; Kercher, T. S. *Org. Lett.* **2004**, *6*, 4989.
9. Rousseau, A. L.; Matlaba, P.; Parkinson, C. J. *Tetrahedron Lett.* **2007**, *48*, 4079.
10. Shaabani, A.; Soleimani, E.; Maleki, A. *Tetrahedron Lett.* **2006**, *47*, 3031.
11. (a) Adib, M.; Sheikhi, E.; Rezaei, N. *Tetrahedron Lett.* **2011**, *52*, 3191; (b) Adib, M.; Mahdavi, M.; Noghani, M. A.; Mirzaei, P. *Tetrahedron Lett.* **2007**, *48*, 7263.
12. (a) Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 1191; (b) Zumpe, F. L.; Melanie, F.; Schmitz, K.; Lender, A. *Tetrahedron Lett.* **2007**, *48*, 1421; (c) Basavaprabhu, N. N.; Ravi, S. L.; Sureshbabu, V. V. *Tetrahedron Lett.* **2010**, *51*, 3002.
13. (a) Augustine, J. K.; Atta, R. N.; Ramappa, B. K.; Boodappa, C. *Synlett* **2009**, 3378; (b) Augustine, J. K.; Vairaperumal, V.; Narasimhan, S.; Alagarsamy, P.; Radhakrishnan, A. *Tetrahedron* **2009**, *65*, 9989; (c) James M. Crawforth, J. M.; Paoletti, M. *Tetrahedron Lett.* **2009**, *50*, 4916; (d) Augustine, J. K.; Bombrun, A.; Venkatachaliah, S. *Tetrahedron Lett.* **2011**, *52*, 6814; (e) Poojari Subba; ParameswarNaik, P.; Krishnamurthy, G. *Tetrahedron Lett.* **2012**, *53*, 4639.
14. Chandrappa, S.; Vinaya, K.; Ananda Kumar, C. S.; Rangappa, K. S. *Tetrahedron Lett.* **2010**, *51*, 6493.
15. Raghavendra, G. M.; Harsha, K. B.; Vinaya, K.; Mantelingu, K.; Rangappa, K. S. *Synth. Commun.* **2011**, *41*, 2296.
16. Chandrappa, S.; Vinaya, K.; Ramakrishanappa, T.; Rangappa, K. S. *Synlett* **2010**, 3019.
17. Chandrappa, S.; Umashankara, M.; Vinaya, K.; Ananda Kumar, C. S.; Rangappa, K. S. *Tetrahedron Lett.* **2012**, *53*, 2632.
18. Raghavendra, G. M.; Ramesha, A. B.; Revanna, C. N.; Nandeesh, K. N.; Mantelingu, K.; Rangappa, K. S. *Tetrahedron Lett.* **2011**, *52*, 5571.