Tetrahedron Letters 51 (2010) 3944–3950

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Room temperature synthesis of tri-, tetrasubstituted imidazoles and bis-analogues by mercaptopropylsilica (MPS) in aqueous methanol: application to the synthesis of the drug trifenagrel

Chhanda Mukhopadhyay [a,*], Pradip Kumar Tapaswi [a], Michael G. B. Drew [b]

[a] Department of Chemistry, University of Calcutta, 92 APC Road, Kolkata 700009, India
[b] Department of Chemistry, The University, Whiteknights, Reading RG 6 6AD, UK

ARTICLE INFO

Article history:
Received 17 April 2010
Revised 20 May 2010
Accepted 22 May 2010
Available online 27 May 2010

Keywords:
Mercaptopropylsilica (**MPS**)
Heterogeneous catalyst
Recyclable
Room temperature
2,4,5-Tri- and 1,2,4,5-tetrasubstituted imidazoles
Aqueous methanol
Bis-imidazoles
Trifenagrel

ABSTRACT

The heterogeneous solid catalyst, mercaptopropylsilica (**MPS**), has been prepared by a modified procedure in water and its structure confirmed by solid state carbon-13 CP-MAS NMR spectrum. This catalyst has been efficiently utilized for the synthesis of a wide variety of tri-, tetrasubstituted imidazoles and their bis-analogues at room temperature. The protocol was further explored for the synthesis of the drug trifenagrel.

1. Introduction

A major area of research in present organic synthesis is the application of solid catalysts in generating environmentally benign methodologies which prove highly advantageous for both academia and industry.[1] Although a number of solid catalysts have been developed for varieties of useful synthetic transformations, a majority of them possess several drawbacks including long hours of reaction and rough reaction protocols. In addition, most of these methodologies are sensitive towards moisture and not recoverable. Such problems can be easily overcome by switching over to silica chain possessing covalently anchored organic spacer to produce organic–inorganic hybrid catalysts. In such catalysts, the reactive centres are highly mobile similar to homogeneous catalysts, in addition, possessing the recyclability like the heterogeneous catalysts. On this basis, we decided to utilize a silica-bonded solid acid catalyst preparing it by a modified procedure maintaining a green protocol for the construction of a very important organic heterocycle, the substituted imidazoles and bis-imidazoles.

2. Results and discussion

In continuation of our studies on the synthesis of various pharmacologically important chromophores,[1c] we chose the substituted imidazoles as it is a core molecule in many biological systems such as biotin, histamine, histidine as well as active component in potential drug molecules such as trifenagrel[2] (Fig. 1) and several pesticides.[3] Various substituted imidazoles possess antiallergic,[4] analgesic[5] and anti-inflammatory activities.[6] Of particular interest is the 4,5-diaryl imidazoles which act as potential inhibitors of p38 MAP kinase,[7] B-Raf kinase, transforming growth factor β1 (TGF-β1), type 1 activin receptor-like kinase (ALK-5) and cyclooxygenase-2 (COX-2). This moiety is also a significant intermediate in the biosynthesis of interleukin-1 (IL-1).[8]

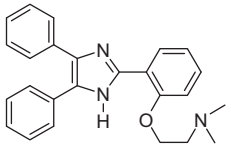
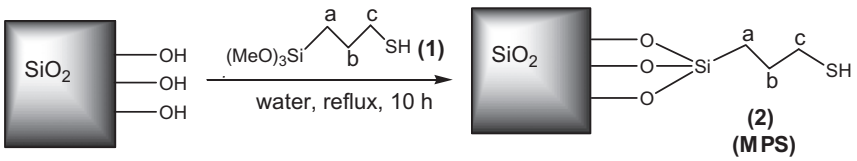


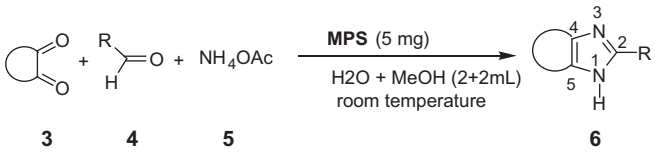
Figure 1. Trifenagrel.

* Corresponding author. Tel.: +91 33 23371104; fax: +91 33 23519755.
E-mail address: cmukhop@yahoo.co.in (C. Mukhopadhyay).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.102



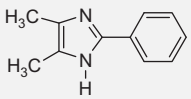
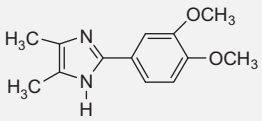
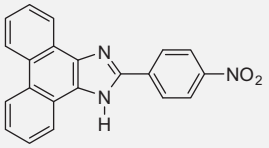
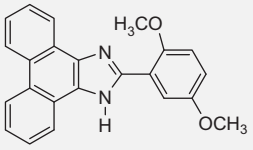
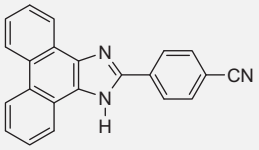
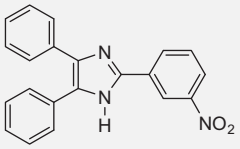
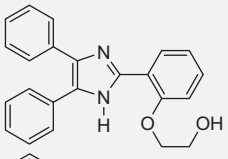
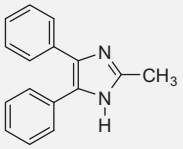
Scheme 1. Preparation of the catalyst: mercaptopropylsilica (**MPS**) (**2**) in water.



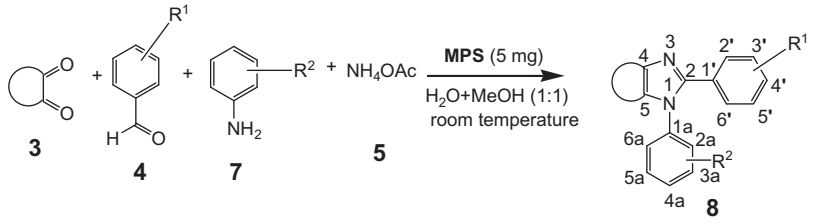
Scheme 2. Synthesis of 2,4,5-trisubstituted imidazoles with MPS* (5 mg) per mmol of starting aldehyde.

Recent advancements in organometallic catalysis and green chemistry have extended the applicability of substituted imidazoles as ionic liquids.[9] Such wide applicability of tetrasubstituted imidazoles, in particular the 4,5-diaryl ones, triggered us to undertake the synthesis of these systems. The existing methodologies for the synthesis of the tetrasubstituted imidazoles are mostly multi-step processes or derived from trisubstituted 1*H*-imidazole.[5] The important point that needs mentioning is that all the earlier reported methods for the synthesis of the tetrasubstituted imidazoles require high temperatures with catalysts such as ionic liquids,[10] acetic

Table 1
Synthesis of 2,4,5-trisubstituted imidazoles at room temperature

Entry	Products (**6**)	Time (h)	Yield (%) (isolated)	Reference
1		2	65	20
2		2.5	61	–
3		3	92	21
4		3	90	–
5		3	88	–
6		3	90	17
7		3	96	–
8		3	56	18

Reaction conditions: aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (3 mmol) and catalyst **MPS** (5 mg) in (water + methanol) (2 + 2 mL) at rt.



Scheme 3. Synthesis of 1,2,4,5-tetrasubstituted imidazoles.

Table 2
Synthesis of 1,2,4,5-tetrasubstituted imidazoles with **MPS**[a] at room temperature

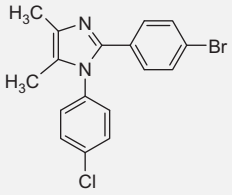
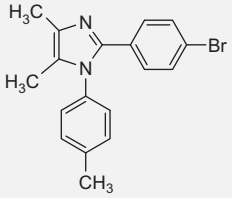
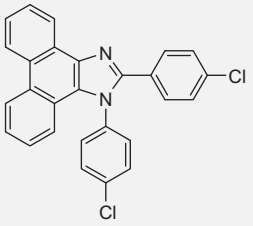
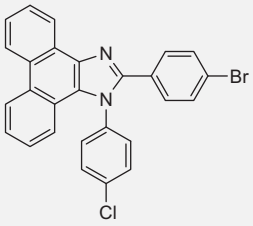
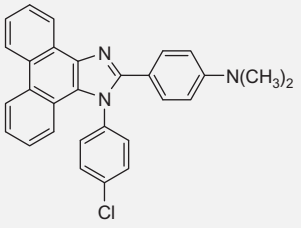
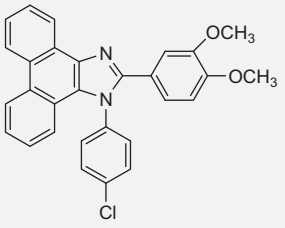
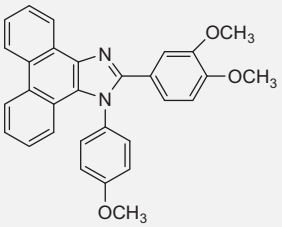
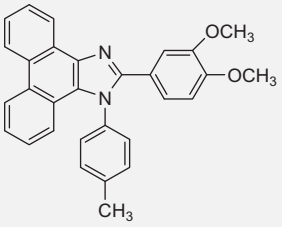
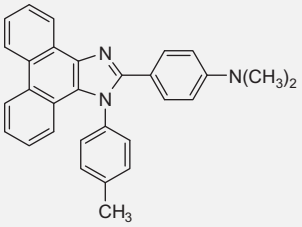
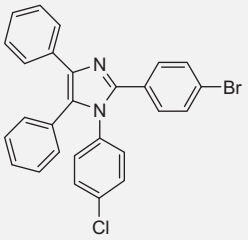
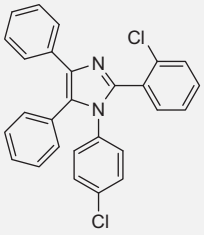
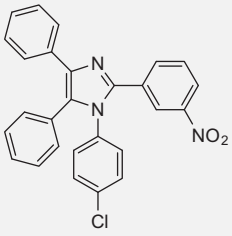
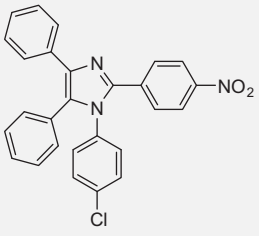
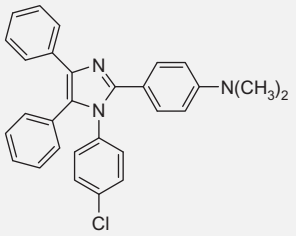
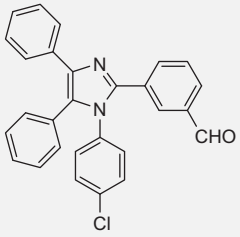
Entry	Products	Time (h)	Yield (%) (isolated)	Reference
1		4	65	–
2		4	68	–
3		5	89	–
4		5	89	–
5		6	92	–
6		7	91	–

Table 2 (*continued*)

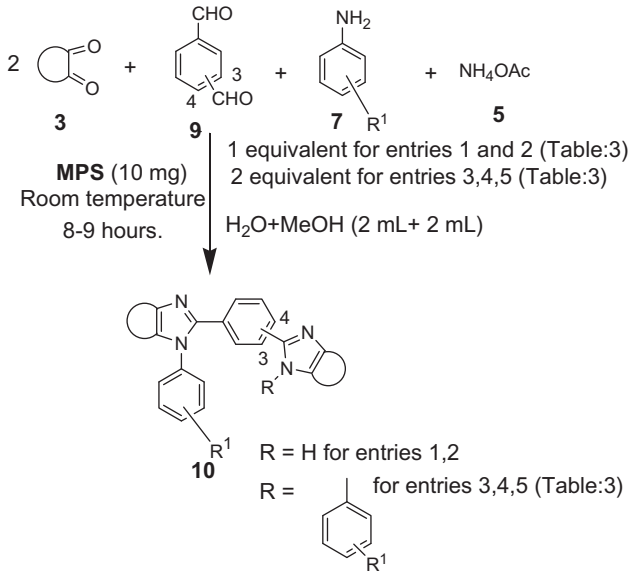
Entry	Products	Time (h)	Yield (%) (isolated)	Reference
7		6	92	–
8		6	93	–
9		5	92	–
10		4	87	–
11		5	90	–
12		4	84	–
13		4	85	–

(*continued on next page*)

Table 2 (*continued*)

Entry	Products	Time (h)	Yield (%) (isolated)	Reference
14		5	92	–
15		6	89	–

[a] Reaction conditions: aldehyde (1 mmol), benzil (1 mmol), aromatic amine (1 mmol) ammonium acetate (1.5 mmol) and catalyst **MPS** (5 mg) in (water + methanol) (2 + 2 mL) at rt.



Scheme 4. Synthesis of tetra–tri and tetra–tetra bis-imidazoles with **MPS**.

acid,[11] silica–sulfuric acid[12] or $NiCl_2$–$6H_2O$/Al_2O_3,[13] $HClO_4$–SiO_2,[14] heteropolyacid[15] and silica gel/$NaHSO_4$[16]. There is only one report till date, for the synthesis of the substituted imidazoles at room temperature, that too using indium chloride,[17] the recyclability of which is rather difficult. A very recent paper[18] for the synthesis of the substituted imidazoles employs L-proline as catalyst and does not include the synthesis of the bis-imidazoles.

We have very efficiently prepared the known heterogeneous solid acid catalyst (mercaptopropylsilica, **MPS**) (**1**) (Scheme 1) by a modified procedure in water and employed it for the synthesis of the tri-/tetrasubstituted imidazoles and their corresponding bis-analogues in excellent yields at room temperature with easy regeneration and recyclability of the catalyst. In addition, this is the first report of the preparation of the catalyst in aqueous medium in a shorter time.

The prepared catalyst mercaptopropylsilica (**MPS**) (**2**) was characterized by comparing the solid state carbon-13 CP-MAS NMR spectrum of the prepared catalyst mercaptopropylsilica (**MPS**) (**2**) and the normal solution phase carbon-13 NMR spectrum of 3-(mercaptopropyl)-trimethoxysilane (**1**). The normal solution phase carbon-13 NMR spectrum of (**1**) showed peaks at δ 50.3 (OCH_3), 27.3 (b,c) and 8.0 (a). When the catalyst was prepared, the peak at 50.3 vanished as the bonding took place through the methoxy groups while the remaining two peaks remained with slight deviations at δ 27.1 (b,c) and 10.6 (a). Thus, there is no ambiguity regarding structural proof of **MPS** (**2**). Earlier,[19] the structure of **MPS** has never been confirmed by solid state carbon-13 NMR spectrum. The elemental analysis of **MPS** was also done which showed the carbon content to be 2.49%.

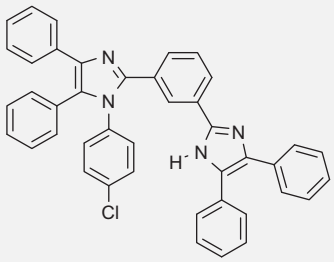
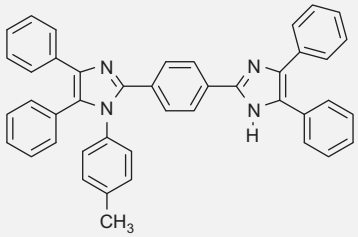
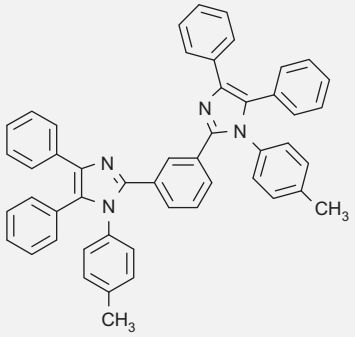
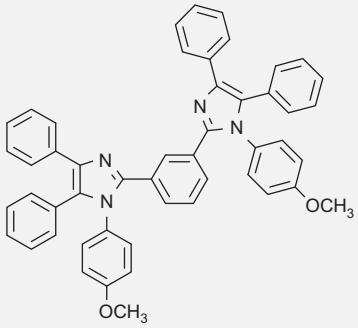
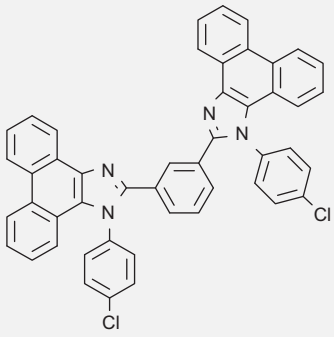
In order to optimize the amount of the catalyst per mmol of aldehyde, the synthesis of 2,4,5-triphenyl imidazole was chosen as a model reaction. It was seen that **MPS** (**2**) is a highly effective catalyst for this transformation and in the absence of this catalyst the reaction proceeded to give trace amounts of product after 24 h. The optimum loading was 5 mg of **MPS** per mmol of aldehyde in terms of isolated yield and reaction time although a lower catalyst loading (1 mg of **MPS**) could be used to furnish the reaction in much lower yields. The model reaction was also studied in the presence of **MPS** (5 mg per mmol of aldehyde) in various solvents such as water, methanol, aqueous methanol (various percentages), DCM, ACN and THF or even under solvent-free conditions. It was observed that by using 50% aqueous methanol, the yield of the reaction was highest and the reaction time shortest. The addition of water has some positive effect on the yield of the reaction as it probably helps in the hydrolysis of ammonium acetate to ammonium hydroxide and acetic acid both of which are required for the reaction.

Once the optimum conditions were standardized, a variety of 2,4,5-trisubstituted imidazoles (**6**) were synthesized (Scheme 2, Table 1) using this methodology in excellent yields.

On examination of Table 1 we find that almost all the 2,4,5-trisubstituted imidazoles (except entry 8) were produced in high yields. This methodology was also applicable on an aliphatic aldehyde (Table 1, entry 8). It is important to mention that the reaction is carried out at room temperature. In almost all the earlier reported procedures,[18,20,21] high temperature is required for the synthesis of the imidazole moiety.

After the initial studies, the methodology was applied for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (Scheme 3) using structurally different aldehydes and primary amines (Table 2).

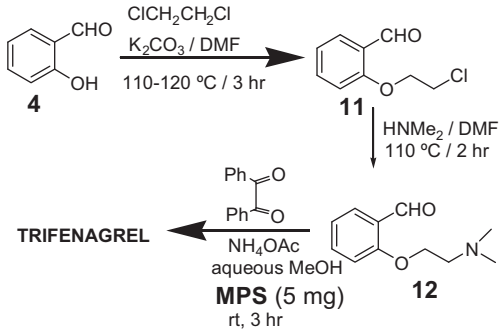
Table 3
Synthesis of tetra–tri- and tetra–tetrasubstituted bis-imidazoles with **MPS**[a] at room temperature

Entry	Products	Time (h)	Yield (%) (isolated)	Reference
1		8	75	–
2		8	74	–
3		8	78	–
4		9	78	–
5		9	80	–

[a] Reaction conditions: aldehyde (1 mmol), benzil (2 mmol), aromatic amine (1 mmol for entries 1, 2 and 2 mmol for entries 3–5) ammonium acetate (4.5 mmol for entries 1, 2 and 3 mmol for entries 3–5) and catalyst **MPS** (10 mg) in (water + methanol) (2 + 2 mL) at rt.

On examination of Table 2, it is obvious that the utility of this catalyst for the synthesis of tetrasubstituted imidazoles is quite general with variations in all the three components. This is the first report of the synthesis of tetrasubstituted imidazoles with phenanthraquinone.

The mechanism of formation of tri- and tetrasubstituted imidazoles involves protonation (probably due to proton exchange property of the SH group in the catalyst) of the aldehydic carbonyl, diimine formation of the corresponding diketo compound with either only ammonium acetate or ammonium acetate and aromatic



Scheme 5. Synthesis of trifenagrel (overall yield: 91%).

amine, cyclization involving aromatic aldehydes and finally loss of water and ammonia to produce the final products. The more stable diimine with aromatic amines is responsible for the selective formation of tetrasubstituted imidazoles rather than trisubstituted ones even in the presence of ammonium acetate. The X-ray structural analysis of a single crystal of 2-(4′-bromophenyl)-1-(4a-chlorophenyl)-4,5-diphenylimidazole (Table 2, entry 10) (given in Supplementary data) further confirms its structure.

Once our catalyst was successful towards the synthesis of 2,4,5-tri- and 1,2,4,5-tetrasubstituted imidazoles, we turned our attention towards the synthesis of the corresponding bis-analogues. We could efficiently synthesize tetra–tri- and tetra–tetrasubstituted bis-analogues by simply varying the mole ratio of the aromatic amine (Scheme 4, Table 3).

The most important aspect of our methodology besides being room temperature synthesis is that we have successfully tuned the formation of tetra–tri- and tetra–tetrasubstituted bis-imidazoles. The final confirmation for the structure of a bis-analogue comes from the X-ray crystal structure analysis of a single crystal of 1-(4a-chlorophenyl)-2-[3′-(4,5-diphenyl-1*H*-imidazol-2-yl)-phenyl]-4,5-diphenyl-1*H*-imidazole (Table 3, entry 1) (given in Supplementary data).

The cavities shown in the X-ray crystal structure are important sources for encapsulation which could be utilized for further reactions such as DNA-binding studies. Moreover, the formation of such bis-analogues is very rare in the literature.

It has been already reported that the drug trifenagrel (Figure 1) is a chemically novel potent inhibitor of arachidonate and collagen-induced aggregation of platelets. We then started its synthesis from salicaldehyde, the phenolic-OH group alkylated to obtain the desired starting aldehyde,[2] and simple application of our solid heterogeneous catalyst **MPS** at room temperature (Scheme 5) produced trifenagrel.[2]

To rule out the contribution of homogeneous catalysts towards the synthesis of 2,4,5-triphenyl imidazole, the reaction of benzil, benzaldehyde and ammonium acetate was carried out at room temperature in the presence of **MPS** (**2**) until the conversion was 30% (by crude ^{1}H NMR) and at that point, the solid was filtered off. The liquid phase in (water/methanol) (2 mL + 2 mL) was allowed to react, but no further conversion was observed. This proves that **MPS (2)** is the active catalyst for this reaction. We observed that the two most important points regarding the heterogeneous catalysts is their deactivation in addition to reusability which shows their high stability. The recycled catalyst was reused ten times without any other treatment.

In conclusion, we have prepared **MPS** by a modified methodology in aqueous medium. The catalyst has been utilized very efficiently for the synthesis of a large number of tri- and tetrasubstituted imidazoles at room temperature. This methodology has also been very efficiently applied towards the synthesis of the corresponding bis-analogues in addition to the drug trifenagrel which is a chemically novel potent inhibitor of arachidonate and collagen-induced aggregation of platelets.

Acknowledgements

One of the authors (P.K.T.) thanks the University Grants Commission, New Delhi, for his fellowship (SRF). We thank the CAS Instrumentation Facility, Department of Chemistry, University of Calcutta, for spectral data. We also acknowledge grant received from UGC funded Major project, F. No. 37-398/2009 (SR) dated 11-01-2010. Moreover, NMR Research Centre, IISc, Bangalore 560012, is gratefully acknowledged for the solid state carbon-13 CP-MAS NMR spectrum.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.102.

References and notes

1. (a) Chaudhary, D.; Paul, S.; Gupta, R.; Clark, J. H. *Green Chem.* **2008**, *8*, 479; (b) Karimi, B.; Abedi, S.; Clark, J. H.; Budarin, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 4776; (c) Mukhopadhyay, C.; Tapaswi, P. K. *Tetrahedron Lett.* **2008**, *49*, 6237.
2. Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453.
3. Mjalli, A. M. M.; Sarshar, S. U.S. Patent, 1997, U.S. 5700826, p 19. *Chem. Abstr.* **1998**, *128*, 88918a.
4. Blank, J. W.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R. *Nature* **1974**, *248*, 65.
5. Ucucu, U.; Karaburun, N. G.; Iskdag, I. *Il Farmaco* **2001**, *56*, 285.
6. Suzuki, F.; Kuroda, T.; Tamura, T.; Sato, S.; Ohmori, K.; Ichikawa, S. *J. Med. Chem.* **1992**, *35*, 2863.
7. Murray, J. A. *Curr. Opin. Drug Discov. Dev.* **2003**, *6*, 945.
8. Lange, J. H. M.; Van Stuivenberg, H. H.; Coolen, H. K. A. C.; Adolfs, T. J. P.; MoCreary, A. C.; Keizer, H. G.; Wals, H. C.; Veerman, W.; Borst, A. J. M.; de Loof, W.; Verveer, P. C.; Kruse, C. G. *J. Med. Chem.* **2005**, *48*, 1823.
9. Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363.
10. Sparks, R. B.; Combs, A. P. *Org. Lett.* **2004**, *6*, 2473.
11. Wang, J.; Mason, R.; Derveer, D. V.; Feng, K.; Bu, X. R. *J. Org. Chem.* **2003**, *68*, 5415.
12. Shaabani, A.; Rahmati, A. *J. Mol. Catal. A: Chem.* **2006**, *249*, 246.
13. Heravi, M. M.; Bakhtiari, K.; Oskooie, H. A.; Taheri, S. J. *J. Mol. Catal. A: Chem.* **2007**, *263*, 279.
14. Kantevari, S.; Vuppalapati, S. V. N.; Biradar, D. O.; Nagarapu, L. *J. Mol. Catal. A: Chem.* **2007**, *266*, 109.
15. Heravi, M. M.; Derikvand, F.; Bamoharram, F. F. *J. Mol. Catal. A: Chem.* **2007**, *263*, 112.
16. Karimi, A. R.; Alimohammadi, Z.; Azizian, J.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Catal. Commun.* **2006**, *7*, 728.
17. Das Sharma, S.; Hazarika, P.; Konwar, D. *Tetrahedron Lett.* **2008**, *49*, 2216.
18. Samui, S.; Nandi, G. C.; Singh, P.; Singh, M. S. *Tetrahedron* **2009**, *65*, 10155.
19. (a) Karimi, B.; Khalkhali, M. *J. Mol. Catal. A: Chem.* **2005**, *232*, 113; (b) Niknam, K.; Saberi, D.; Sefat, M. N. *Tetrahedron. Lett.* **2009**, *50*, 4058.
20. Chuanming, Y.; Min, L.; Weike, S.; Yuanyan, X. *Synth. Commun.* **2007**, *37*, 3301.
21. Behmadi, H.; Roshani, M.; Saadati, S. M. *Chin. Chem. Lett.* **2009**, *20*, 5.