Zn-Proline Catalyzed Selective Synthesis of 1,2-Disubstituted Benzimidazoles in Water

Varala RAVI, Enugala RAMU, Kotra VIJAY, and Adapa SRINIVAS RAO*

Indian Institute of Chemical Technology; Hyderabad-500 007, India. Received January 4, 2007; accepted May 17, 2007

Zn-proline (5 mol%) performs as a *novel water-soluble and recyclable Lewis acid catalyst* for the selective synthesis of 1,2-disubstituted benzimidazoles from wide range of substituted *o*-phenylenediamines and aldehydes in moderate to excellent isolated yields (42—92%) using water as solvent at ambient temperature.

Key words benzimidazole; zinc proline; water; recyclability

The development of efficient and environmentally benign chemical processes for the preparation of new biologically relevant molecules constitutes a major challenge for chemists in organic synthesis. The benzimidazole core is classified by medicinal chemists as one of the 'privileged sub-structures' for drug design, in light of the affinity they display towards a variety of enzymes and protein receptors.[1)] Interest in benzimidazole containing structures stems from their widespread occurrence in molecules that exhibit significant activity against several viruses such as HIV, herpes (HSV-1), RNA, influenza, and human cytomegalovirus (HCMV).[2—6)] In addition, benzimidazole derivatives have been used to act as topoisomerase inhibitors, selective neuropeptide YY1 receptor antagonists, angiotensin II inhibitors, 5-HT_3 antagonists in isolated guinea pig ileum, potential antitumor agents, antimicrobial agents, smooth muscle cell proliferation inhibitors, a treatment for interstitial cystitis, as factor Xa inhibitors, and in diverse areas of chemistry.[7—12)]

In view of the tremendous biological activities of substituted benzimidazoles, their preparation has gained considerable attention in recent years. The traditional synthesis of benzimidazoles involves the reaction between an *o*-phenylendiamine and a carboxylic acid or its derivatives (nitriles, amidates, orthoesters) under harsh dehydrating conditions.[13—18)] The most popular strategies for their synthesis utilise *o*-nitroanilines as intermediates or resort to direct *N*-alkylation of an unsubstituted benzimidazole.[19—22)] Another method for the synthesis of these compounds is the reaction of *o*-phenylenediamine with aldehydes in the presence of acidic catalysts under various reaction conditions.[23—28)] Many of these methods suffer from one or more limitations, such as low yields, use of expensive reagents, harsh organic solvents, a special oxidation process or long reaction times, tedious work-up procedures, co-occurrence of several side reactions and poor selectivity. Very recently, we have reported L-proline catalyzed efficient synthesis of 1,2-disubstituted benzimidazoles in chloroform at ambient temperature.[29)] Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles in terms of operational simplicity, economic viability, greater selectivity and in particular using green solvent such as water as media.

Water emerged as a useful alternative solvent for several organic reactions owing to many of its potential advantages such as safety, economy, readily available, nontoxic and environmental concern.[30—32)] Reactions in water have been very useful to the synthetic chemist for many years and their utility is reflected by the many studies to discover new processes with which they can be performed catalytically and chemoselectively.

Since the exploration of water soluble $Zn(proline)_2$-complex by Darbre's group[33—37)] in effecting various asymmetric aldol type transformations as chiral catalyst; only two reports have so far appeared employing zinc proline as an efficient recyclable and inexpensive Lewis acid (LA) catalyst for the preparation of Hantzch 1,4-dihydropyridine derivatives and 1,5-benzodiazepines under microwave conditions.[38,39)] There is still lot of scope to further explore the catalyst for its application in forming various heterocycle rings. In continuation of our recent efforts to develop novel synthetic routes for carbon–carbon and carbon-heteroatom bond formations and heterocycles,[40—42)] in the present study, we wish to broaden the scope of $Zn(proline)_2$-complex as an efficient LA catalyst for the selective synthesis of 1,2-disubstituted benzimidazoles (2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles) and the results from our study are presented herein (Chart 1).

Results and Discussion

Initially, we have studied the efficacy of $Zn(proline)_2$-complex (5 mol%) for the model reaction using *o*-PD (1 mmol) and benzaldehyde (2 mmol) in water (2 ml), being stirred at ambient temperature.

To our surprise, the reaction proceeded smoothly during 2 h and resulted in the formation of corresponding product **3** in excellent yield (92%, entry 1, Table 1). The optimum yields of the product were obtained when a ratio of *o*-PD to aldehyde (1 : 2) is used. 5 mol% of catalyst was sufficient to

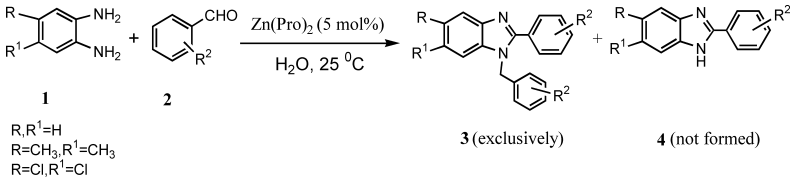
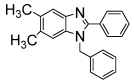
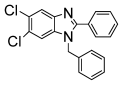
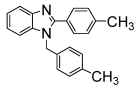
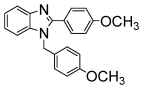
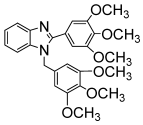
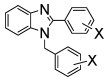
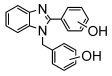
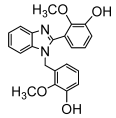
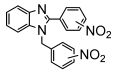
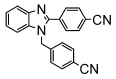
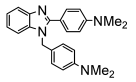
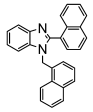


Chart 1

* To whom correspondence should be addressed. e-mail: rvarala_iict@yahoo.co.in

Table 1. Zn-Proline-Catalyzed Synthesis of 1,2-Disubstituted Benzimidazoles in Water

Entry[Ref.]	Product		Time (h)	Yield (%)[a)]
1[26]		**3a**	2.0	92/90/90/88[b)]
2[new]		**3b**	8.5	55
3[new]		**3c**	5.0	87
4[26]		**3d**	2.5	90
5[26]		**3e**	2.0	88
6[new]		**3f**	4.5	65
7[28]		X=*o*-F	3.5	62
8[28]		*p*-F	2.5	78
9[26]		X=*o*-Cl	4.0	70
10[26]		*p*-Cl	2.5	84
11[20]		X=*m*-Br	5.5	72
12[19]		*p*-Br	4.0	82
13[new]		*o*-OH	8.0	42
14[new]		*o*-OH	8.0	55
15[new]		**3o**	6.5	68
16[26]		*o*-NO_2	3.5	85
17[26]		*p*-NO_2	3.0	90
18[new]		**3r**	2.5	88
19[26]		**3s**	4.0	83
20[20]		**3t**	4.5	85
21[27]		**3u**	6.0	78
22[26]		**3v**	6.5	75

a) Yields refer to the isolated pure products. *b*) Yield after third recycle.

carry forward the reaction in order to get the optimum yield in less reaction time. As less as 3 mol% of catalyst is also sufficient to catalyze the reaction to the same extent, but needs prolonged reaction times (2.5 h). The present Zn(proline)$_2$-catalysis is highly selective. Under the optimized reaction conditions, in all cases the yields are high and **3** (1,2-disubstituted product) was formed selectively rather than **4** (2-substituted product) as depicted in Chart 1. This selectivity could be useful in synthesizing a mini library of biologically relevant 1,2-disubstituted benzimidazoles in moderate to excellent yields. To the best of our knowledge, there are no earlier reports on the preparation of benzimidazoles using zinc proline as an efficient recyclable and inexpensive Lewis acid catalyst.

The reaction of benzaldehyde (2 mmol) and *o*-PD (1 mmol) in the presence of zinc proline (5 mol%) in water (2 ml) was taken as model reaction for recycling studies. After the reaction is over as specified in Table 1, the crude product was extracted in dichloromethane and simple separation from aqueous phase and organic phase to recover the catalyst. The catalyst present in aqueous medium was used for the subsequent cycle. The same procedure was adopted for all recycling studies (entry 1). The results reveal that the catalyst exhibited good catalytic activity upto three cycles. The scope of the reaction was further investigated with a wide range of electronically divergent aromatic aldehydes and *o*-PD's to afford the corresponding 1,2-disubstituted benzimidazoles selectively, in the presence of zinc proline as catalyst. The results are summarized in Table 1. In all cases, the 1,2-disubstituted benzimidazoles were the sole products obtained and the rest of the material was essentially starting material. All products (entries 1—22) were well characterized by using instrumental techniques.

A large variety of functionalities were tolerated including phenolic group, halogen, and nitriles under the present reaction conditions. The present protocol is equally effective for aromatic aldehydes bearing either electron-donating or electron-withdrawing substituents (entries 4—19). Steric factors played a vital role in affecting the rate of reaction. In general the aromatic aldehyde bearing a group on *o*-substitution requires a longer reaction time and yields are also less in compared to the group on *p*-substitution (entries 6—17). However, aldehydes containing –OH groups gave moderate yields upon stirring for longer reaction times (entries 13—15). Furthermore, α-naphthaldehyde (entry 20) and heteroaromatic aldehydes including pyridine-2-carbaxaldehyde, furfural (entries 21, 22) gave their corresponding benzimidazoles in good yields.

The proposed mechanism for the zinc proline-catalyzed synthesis of 1,2-disubstituted benzimidazoles, may tentatively be visualized to occur *via* a tandem sequence of reactions as depicted in Chart 2 as follows: Initially, coordination of the carbonyl oxygen to the acidic metal center and subsequent formation of imine with proline; followed by nucleophilic attack of *o*-PD to the imine, forming dibenzylidene-*o*-PD, which then following the usual steps (i) protonation of the dibenzylidene-*o*-PD by acidic proton and ring closure leading to a five membered ring either a sequential or concerted manner, (ii) 1,3-hydride transfer and (iii) deprotonation, to form the desired 1,2-disubstituted benzimidazoles.

Conclusion

In summary, we report an efficient procedure for the selective synthesis of 1,2-disubstituted benzimidazole derivatives from various electronically divergent aromatic aldehydes and *o*-PDs using 'easily preparable, stable, inexpensive and recyclable' Zn(proline)$_2$-complex as an efficient LA catalyst in

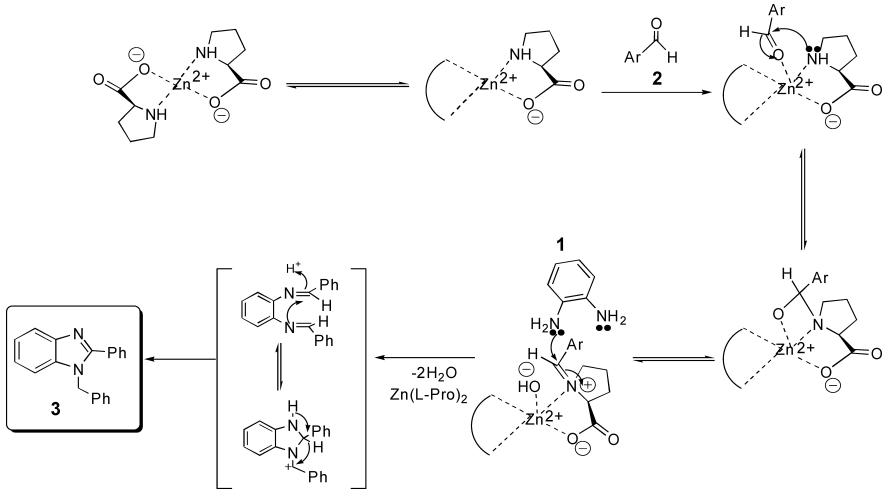


Chart 2. Proposed Mechanism for Zn(L-Pro)$_2$-Catalyzed Synthesis of 1,2-Disubstituted Benzimidazoles

'green solvent,' water. The present protocol has several advantages: mild reaction conditions (at room temperature), operational and experimental simplicity, study of wide range of electronically divergent aldehydes and *o*-PDs. We believe that this zinc proline promoted methodology will be a valuable addition to the existing processes and further expansion of zinc-proline catalysis for the formation of other biologically relevant heterocycles is being progress in our laboratory and will be reported elsewhere.

Experimental

General Procedure All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography were distilled before use. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) instruments, in $CDCl_3$. Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as internal standard. Electron-impact (EI) mass spectra were recorded on a VG 7070H Micromass mass spectrometer at 200 °C, 70 eV. Elemental analyses were performed by Elementar analyzer Vario EL. The IR spectra were obtained with Perkin Elmer 240-C instrument using potassium bromide pellets/neat. Melting points were checked using Electrothermal Melting Point Apparatus. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on glass). Column chromatography was performed using Acme silica gel (100—200 mesh).

General Procedure for the Synthesis of 1,2-Disubstituted Benzimidazoles To a solution of Zn(proline)$_2$ (5 mol%) in water (2 ml) were added successively *o*-phenylenediamine (1 mmol) and aldehyde (2 mmol) at room temperature for the time specified in Table 1. After completion of the reaction, the crude product was extracted with dichloromethane, dried over anhydrous $MgSO_4$, concentrated under reduced pressure to furnish the crude product, which was further purified by silica gel chromatography using EtOAc/hexane (1 : 5), to afford corresponding product. All compounds gave satisfactory spectroscopic data in accordance to their proposed structures (see Table 1).

Recovered the catalyst by simple separation from aqueous phase and organic phase. The catalyst present in aqueous medium was used for the subsequent cycle. The same procedure was adopted for all recycling studies. The reaction time and yield for different cycles are presented in entry 1, Table 1 as model substrate for recycling studies.

Spectral Data for New Compounds 1-Benzyl-5,6-dimethyl-2-phenyl-1*H*-benzo[*d*]imidazole (Entry 2, **3b**): White solid. mp 183—184 °C. IR (KBr) cm^{-1}: 3043, 2996, 2986, 2860, 1464. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (6H, s), 5.40 (2H, s), 7.25—7.63 (10H, m), 7.85—8.01 (2H, m). EI-MS *m/z*: 312 (M^+). *Anal.* Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.54; H, 6.47; N, 9.01.

1-Benzyl-5,6-dichloro-2-phenyl-1*H*-benzo[*d*]imidazole (Entry 3, **3c**): Cream solid. mp 162—163 °C. IR (KBr) cm^{-1}: 3040, 2947, 1463, 734. ^{1}H-NMR ($CDCl_3$) δ: 5.44 (2H, s), 7.09 (2H, d, J=8.31 Hz), 7.27—7.50 (6H, m), 7.94 (2H, s), 8.01—8.19 (2H, m). EI-MS *m/z*: 353 (M^+). *Anal.* Calcd for $C_{20}H_{14}Cl_2N_2$: C, 68.00; H, 3.99; N, 7.93. Found: C, 67.98; H, 4.02; N, 7.91.

1-(3,4,5-Trimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)-1*H*-benzo[*d*]imidazole (Entry 6, **3f**): White solid. mp 262—263 °C. IR (KBr) cm^{-1}: 3032, 2988, 2962, 1614, 1509, 1441, 1248. ^{1}H-NMR ($CDCl_3$) δ: 3.85 (6H, s), 3.91 (6H, s), 3.93 (6H, s), 5.38 (2H, s), 6.32 (2H, s), 7.25—7.31 (5H, m), 7.88 (1H, d, J=7.55 Hz). FAB-MS *m/z*: 465 (M^++H). *Anal.* Calcd for $C_{26}H_{28}N_2O_6$: C, 67.23; H, 6.08; N, 6.03. Found: C, 67.18; H, 6.15; N, 5.99.

2-[1-(2-Hydroxybenzyl)-1*H*-benzo[*d*]imidazol-2-yl]phenol (Entry 13, **3m**): Yellow solid. mp 207—208 °C. IR (KBr) cm^{-1}: 3358, 3260, 3041, 2930, 1558, 1463. ^{1}H-NMR ($CDCl_3$+DMSO) δ: 5.54 (2H, s), 6.81—7.05 (3H, m), 7.11—7.46 (5H, m), 7.56—7.62 (2H, m), 7.95 (2H, d, J=7.6 Hz), 10.86 (2H, br s, OH). FAB-MS *m/z*: 317 (M^++H). *Anal.* Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.88; H, 5.18; N, 8.91.

2-[1-(4-Hydroxybenzyl)-1*H*-benzo[*d*]imidazol-2-yl]phenol (Entry 14, **3n**): Pale yellow solid. mp 254—256 °C. IR (KBr) cm^{-1}: 3361, 3257, 3045, 2928, 1561, 1461. ^{1}H-NMR ($CDCl_3$+DMSO) δ: 5.51 (2H, s), 6.68—7.01 (4H, m), 7.09—7.57 (6H, m), 7.95 (2H, d, J=7.6 Hz). FAB-MS *m/z*: 317 (M^++H); *Anal.* Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.88; H, 5.18; N, 8.91.

3-[1-(3-Hydroxy-2-methoxybenzyl)-1*H*-benzo[*d*]imidazol-2-yl]-2-methoxyphenol (Entry 15, **3o**): Viscous liquid. IR (KBr) cm^{-1}: 3364, 3039, 2981, 2931, 1614, 1439, 1284, 1061. ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s), 4.01 (3H, s), 5.37 (2H, s), 6.67—6.71 (1H, m), 6.84—6.99 (4H, m), 7.11—7.32 (3H, m), 7.62—7.85 (2H, m). EI-MS *m/z*: 376 (M^+). *Anal.* Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.17; H, 5.41; N, 7.45.

2-[1-(4-Cyanobenzyl)-1*H*-benzo[*d*]imidazol-2-yl]phenol (Entry 18, **3r**): Pale yellow solid. mp 187—188 °C. IR (KBr) cm^{-1}: 3345, 3063, 2930, 2142, 2098, 1565, 1453. ^{1}H-NMR ($CDCl_3$) δ: 5.56 (2H, s), 7.12 (1H, dd), 7.31—7.42 (4H, m), 7.79—7.90 (3H, m), 8.21—8.29 (4H, m). EI-MS *m/z*: 334 (M^+). *Anal.* Calcd for $C_{22}H_{14}N_4$: C, 79.02; H, 4.22; N, 16.76. Found: C, 78.98; H, 4.31; N, 16.70.

Acknowledgments Ravi Varala thanks DIICT, Dr. J. S. Yadav and Council of Scientific Industrial Research (CSIR, India) for financial support.

References

1) Mason J. S., Morize I., Menard P. R., Cheney D. L., Hume C., Labaudiniere R. F., *J. Med. Chem.*, **42**, 3251—3264 (1999).
2) Tebbe M. J., Spitzer W. A., Victor F., Miller S. C., Lee C. C., Sattelberg T. R., Mckinney E., Tang C. J., *J. Med. Chem.*, **40**, 3937—3946 (1997).
3) Porcari A. R., Devivar R. V., Kucera L. S., Drach J. C., Townsend L. B., *J. Med. Chem.*, **41**, 1252—1262 (1998).
4) Roth M., Morningstar M. L., Boyer P. L., Hughes S. H., Bukheit R. W., Michejda C. J., *J. Med. Chem.*, **40**, 4199—4207 (1997).
5) Migawa M. T., Giradet J. L., Walker J. A., Koszalka G. W., Chamberlain S. D., Drach J. C., Townsend L. B., *J. Med. Chem.*, **41**, 1242—1251 (1998).
6) Tamm I., *Science,* **126**, 1235—1236 (1957).
7) Kim J. S., Gatto B., Yu C., Liu A., Liu L. F., Lavioe E., *J. Med. Chem.*,

39, 992—998 (1996).
8) Zarrinmayeh H., Zimmerman D. M., Cantrell B. E., Schober D. A., Bruns R. F., *Bioorg. Med. Chem. Lett.*, **9**, 647—652 (1999).
9) Kohara Y., Kubo K., Imamiya E., Wada T., Inada Y., Naka T., *J. Med. Chem.*, **39**, 5228—5235 (1996).
10) Lopez M. L. R., Benhamu B., Morcillio M. J., Tejada I. D., Orensanz L., Alfaro L., Martin M. I., *J. Med. Chem.*, **33**, 814—819 (1999).
11) Forseca T., Gigante B., Gilchrist T. L., *Tetrahedron*, **57**, 1793—1799 (2001) and references cited therein.
12) Zhao J., Arnaiz B., Griedel B., Sakata J., Dallas M., Whitlow L., Trinh D., Post J., Liang A., Morrissey M., Shaw K., *Bioorg. Med. Chem. Lett.*, **10**, 963—966 (2000).
13) Preston P. N., "Chemistry of Heterocyclic Compounds," Vol. 40, ed. by Weissberger A., Taylor E. C., John Wiley and Sons (1981).
14) Sun Y.-C., Chi C.-M., *Synlett*, **2000**, 591—594 (2000).
15) Huang W., Scarborough R. M., *Tetrahedron Lett.*, **40**, 2665—2668 (1999).
16) Dudd L. M., Venardou E., Garcia-Verdugo E., Licence P., Blake A. J., Wilson C., Poliako M., *Green Chem.*, **5**, 187—192 (2003).
17) Wu Z., Rea P., Wickam G., *Tetrahedron Lett.*, **41**, 9871—9874 (2000) and references cited therein.
18) Mazurov A., *Bioorg. Med. Chem. Lett.*, **10**, 67—70 (2000).
19) Kim B. H., Han R., Kim J. S., Jun Y. M., Baik W., Lee B. M., *Heterocycles*, **63**, 41—54 (2004).
20) Itoh T., Nagata K., Ishikawa H., Ohsawa A., *Heterocycles*, **63**, 2769—2783 (2004).
21) Tumelty D., Cao K., Holmes C. P., *Org. Lett.*, **3**, 83—86 (2001).
22) Kilburn J. P., Lau J., Jones R. C. F., *Tetrahedron Lett.*, **41**, 5419—5421 (2000) and references cited therein.
23) Pertry R. J., Wilson B. D., *J. Org. Chem.*, **58**, 7016—7021 (1993).
24) Anastasiou D., Campi E. M., Chaouk H., Jackson W. R., *Tetrahedron*, **48**, 7467—7468 (1992).
25) Brain C. T., Brunton S. A., *Tetrahedron Lett.*, **43**, 1893—1895 (2002).
26) Perumal S., Mariappan S., Selvaraj S., *Arkivoc*, **8**, 46—51 (2004).
27) Salehi P., Dabiri M., Zolfigol M. A., Otokesh S., Baghbanzadeh M., *Tetrahedron Lett.*, **47**, 2557—2560 (2006).
28) Sun P., Hu Z., *J. Heterocyclic Chem.*, **43**, 773—775 (2006).
29) Varala R., Nasreen A., Ramu E., Adapa S. R., *Tetrahedron Lett.*, **48**, 69—72 (2007).
30) Narayan S., Muldoon J., Fin M. G., Folkin V. V., Kolb H. C., Sharpless K. B., *Angew. Chem., Int. Ed.*, **44**, 3275—3279 (2005).
31) Lindstrom U. M., *Chem. Rev.*, **102**, 2751—2772 (2002) and references cited therein.
32) Li C. J., *Chem. Rev.*, **105**, 3095—3166 (2005).
33) Darbre T., Machuqueiro M., *Chem. Commun.*, **2003**, 1090—1091.
34) Kofoed J., Machuqueiro M., Reymond J.-L., Darbre T., *Chem. Commun.*, **2004**, 1540—1541.
35) Kofoed J., Reymond J.-L., Darbre T., *Org. Biol. Chem.*, **2005**, 1850—1855.
36) Ruben F.-L., Kofoed J., Machuqueiro M., Darbre T., *Eur. J. Org. Chem.*, **2005**, 5268—5275.
37) Kofoed J., Darbre T., Reymond J.-L., *Chem. Commun.*, **2006**, 1482—1484.
38) Sivamurugan V., Vinu A., Palanichamy M., Murugesan V., *Heteroatom Chemistry*, **17**, 267—271 (2006).
39) Sivamurugan V., Deepa K., Palanichamy M., Murugesan V., *Synth. Commun.*, **34**, 3833—3846 (2004).
40) Varala R., Sreelatha N., Adapa S. R., *J. Org. Chem.*, **71**, 8283—8286 (2006).
41) Varala R., Sreelatha N., Adapa S. R., *Synlett*, **10**, 1549—1553 (2006) and references cited therein.
42) Varala R., Ramu E., Adapa S. R., *Synthesis*, **22**, 3825—3830 (2006).