http://www.e-journals.net

ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
2011, **8(3),** 1339-1345

ZnO as an Efficient and Inexpensive Catalyst for One Pot Synthesis of 2, 4, 5 -Triphenyl-1*H* - imidazole Derivatives at Room Temperature

BABASAHEB P. BANDGAR*, BALIRAM S. HOTE,
BALAJI L. KORBAD and SACHIN A. PATIL

*Medicinal Chemistry Research Laboratory
School of Chemical Sciences, Solapur University, Solapur, India
Organic Chemistry Research Laboratory, School of Chemical Sciences
Swami Ramanand Teerth Marathwada University, Nanded, India
bandgar_bp@yahoo.com

Received 3 November 2010; Accepted 20 January 2011

Abstract: An improved and rapid one pot synthesis of 2,4,6-triphenyl-1*H*-imidazoles on condensation with benzil, aromatic aldehyde and NH_4OAc has been carried out using ZnO as an efficient and inexpensive catalyst in high yield at room temperature. The short reaction time, good yields (60-93%), environmental friendly procedure, mild reaction condition and convenient operation are important advantage of these synthetic methods.

Keywords: Benzil, NH_4OAc, Aromatic aldehyde, ZnO, One pot synthesis

Introduction

The importance of imidazoles in biological systems has attracted much interest due to their chemical and biochemical properties. Compounds with imidazole ring system have many pharmacological properties and play an important role in biochemical process[1]. The structures of trisubstituted imidazoles are prevalent in natural products and pharmacologically active compounds, such as p38 kinase inhibitor I (SB 203580)[2] and cyclooxygenase-2 (COX-2) inhibitor II, (Figure 1)[3] fungicides and herbicides[4], plant growth regulators[5] and therapeutic agents[6]. Recent advances in green chemistry and organometallic chemistry have extended the boundary of imidazoles to the synthesis and application of a large class of imidazoles as ionic liquids and imidazole related *N*-heterocyclic carbenes (NHC)[7,8].

There are several methods reported in literature for the synthesis of imidazoles such as hetero-cope rearrangement[9], four component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin[10], reaction of *N*-(2-oxo)-amides with ammonium

trifluroacetate[11], 1,2-aminoalcohols in the presence of PCl_5[12], diketones, aldehyde, amine and ammonium acetate in phosphoric acid[13], in acetic acid[14], organo catalyst in acetic acid[15] as well as H_2SO_4[16], DMSO[17]. Several microwave (MW) assisted syntheses of imidazoles from 1, 2-diketones and aldehydes in the presence of a variety of catalysts have been recently reported. These include MW/silica-gel[18], MW/silica-gel/ H-Y[19], MW/Al_2O_3[20], MW/CH_3COOH[21], in DMF[22]. The condensation of α-hydroxy ketones with aldehydes and ammonium acetate on solid supported silica gel or alumina in the presence of MW has been reported recently[23].

Designing of new specific catalysts and exploring their catalytic activity has caused profound effects in optimizing the efficiency of a wide range of organic synthesis. Development of such catalysts has resulted in more economical and environmentally friendly chemistry through replacing nonselective, unstable, or toxic catalysts[24]. Surface of metal oxides exhibit both lewis acid and lewis base characters. This is characteristic of many metal oxides, especially TiO_2, Al_2O_3, ZnO, *etc.* and they are excellent adsorbents for a wide variety of organic compounds and increase reactivity of the reactants[25]. ZnO is certainly one of the most interesting of metal oxides, because it has surface properties which suggest that a very rich organic chemistry may occur there[26].

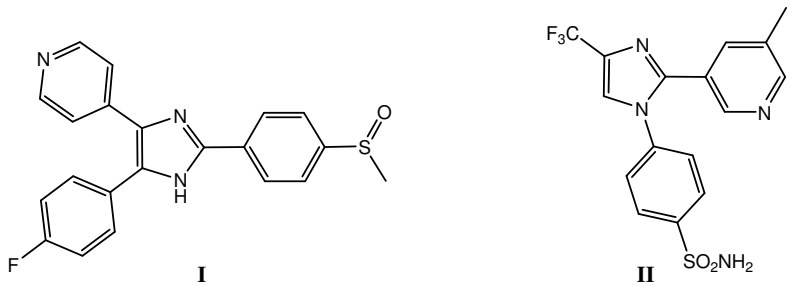
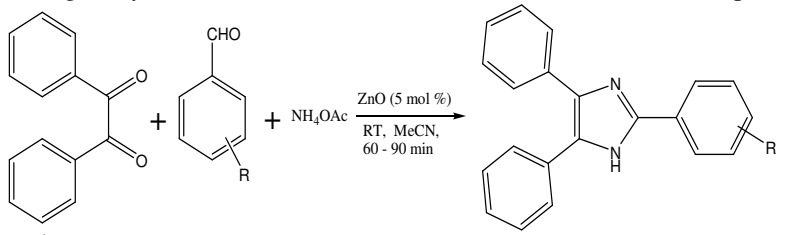


Figure 1

Many of the synthetic protocols for imidazoles reported so far suffer from one or more disadvantages such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous and often expensive acid catalysts. Moreover, the syntheses of these heterocycles have been usually carried out in polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed off.



3a: R = H	3b: R = 4 - Me	3c: R = 4 - Br
3d: R = 2 - Cl	3e: R = 4 - Cl	3f: R = 3 - NO_2
3g: R = 2 - OH	3h: R = 4 - OMe	3i: R = 4 - OH
3j: R = 3, 4 - $(OMe)_2$	3k: R = 2 - NO_2	3l: R = 4 - NO_2
3m: R = 2 - F	3n: R = 4 - F	3o: R = 2 - Me

Scheme 1

Experimental

Melting points were recorded in open capillaries with super fit melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on 300 MHz Bruker FT-NMR spectrometer using tetramethylsilane as internal standard and chemical shifts are reported in δ units and the coupling constant (*J*) are reported in hertz. ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer. Mass spectra were recorded on Bruker daltonics data analysis 3.4. All chromatographic purification was performed with silica gel (100 - 200 mesh), whereas all TLC (silica gel) developments were performed on silica gel (Merck Kiesel $60F_{254}$, 0.2 mm thickness) sheets. All reagents and solvents were of commercial quality and were used as supplied unless otherwise stated. Yields reported are isolated yield of the compounds.

*General procedure for synthesize of 2,4,5–triphenyl-1H-imidazole derivatives (**3a-j**)*

A mixture of benzil (1 mmol), aldehyde (1 mmol), NH_4OAc (5 mmol) and ZnO (5 mol%) in acetonitrile (10 mL) was stirred at room temperature. After completion of the reaction (TLC analysis), it was diluted with water (10 mL) and extracted with dichloromethane (25 mL). The organic layer was dried (Na_2SO_4), evaporated and purified by chromatography by using chloroform to give the products in 60 - 93% yields.

Selected spectral data of the products

2,4,5-Triphenyl-1H-imidazole (Table 2 entry 1)

Solid; m.p. 267-269 ^{o}C; IR (KBr) ν = 3434, 2993, 2470, 1638, 1216 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.61 (s, 1H), 7.42 - 8.12 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 136.53, 129.14, 128.95, 127.23, 122.14; EIMS: *m/z* = 296. Anal. Calcd. for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.13; H, 5.28; N, 9.35.

4,5–Dipheny-2-p-tolyl-1H-imidazole (Table 2 entry 2)

Solid; m.p. 230-231 ^{o}C; IR (KBr) ν = 3405, 3033, 1602, 1493, 1449 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.60 (s, 1H), 7.98 (d, 2H, *J* = 8.4 Hz), 7.20 - 7.56 (m, 12H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 145.53, 137.65, 136.82, 135.24, 131.14, 129.23, 128.65, 128.35, 128.32, 127.65, 127.65, 127.08, 126.43, 125.35, 20.81; EIMS: *m/z* = 310. Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.83; N, 9.03. Found: C, 85.17; H, 5.85; N, 9.06.

2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole (Table 2 entry 3)

Solid; m.p. 248-250 ^{o}C; IR (KBr) ν = 3400, 3060, 1601, 1482, 1450, 1429 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.79 (s, 1H), 8.04 (d, 2H, *J* = 8.4 Hz), 7.68 (d, 2H, *J* = 8.4 Hz), 7.55 - 7.23 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 144.34, 137.34, 134.90, 131.61, 130.83, 129.62, 128.64, 128.33, 128.10, 127.63, 127.13, 126.14, 121.33; EIMS: *m/z* = 385 (M+1). Anal. Calcd. for $C_{21}H_{15}BrN_2$: C, 67.21; H, 4.03; Br, 21.29; N, 7.47. Found: C, 67.25; H, 4.08; Br, 21.31; N, 7.45.

2-(2–Chlorophenyl)-4,5–diphenyl-1H-imidazole (Table 2 entry 4)

Solid; m.p. 186-188 ^{o}C; IR (KBr) ν = 3434, 2993, 2470, 1638, 1216 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.5 (s, 1H), 8.03 (dd, 1H, *J* = 8.7 Hz), 7.58 (d, 2H, *J* = 8 Hz), 7.47 (dd, 1H, *J* = 9 Hz), 7.27 - 7.37 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 142.25, 130.54, 130.15, 129.67, 128.83, 128.65, 128.47, 127.23, 126.90, 126.51, 125.62, 125.44; EIMS: *m/z* = 340 (M+1). Anal. Calcd. for $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.57; Cl, 10.72; N, 8.47. Found: C, 76.27; H, 4.62; Cl, 10.68; N, 8.52.

2-(4–Chlorophenyl)-4,5–diphenyl–1H-imidazole (Table 2 entry 5)

Solid; m.p. 248-250 °C; IR (KBr) ν = 3405, 3060, 1603, 1485, 1448, 1433 cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.79 (s, 1H), 7.21 - 7.56 (m, 12H), 8.11 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$): δ 144.33, 137.24, 134.92, 132.54, 130.84, 130.81, 129.14, 128.73, 128.54, 128.40, 128.31, 128.14, 127.06, 126.55, 126.24; EIMS: *m/z* = 340 (M+1). Anal. Calcd. for $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.57; Cl, 10.72; N, 8.47. Found: C, 76.28; H, 4.60; Cl, 10.68; N, 8.50.

2-(3-Nitrophenyl)-4,5-diphenyl–1H-imidazole (Table 2 entry 6)

Solid; m.p. 252-254 °C;IR (KBr) ν = 3382, 3064, 1605, 1519, 1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 13.10 (s, 1H), 8.96 (t, 1H, *J* = 2.0 Hz), 8.50 - 8.55 (m, 1H), 8.15-8.25 (m, 1H), 7.78 (t, 1H, *J* = 8 Hz), 7.24 - 7.60 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 148.36, 143.25, 137.55, 134.52, 131.14, 130.53, 130.32, 129.03, 128.64, 128.30, 128.21, 128.00, 127.62, 122.55, 119.44; EIMS: *m/z* = 350. Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31; O, 9.97. Found: C, 73.94; H, 4.46; N, 12.29; O, 9.94.

2-(4,5–Diphenyl-1H–imidazol–2-yl)phenol (Table 2 entry 7)

Solid; m.p. 117-119 °C; IR (KBr) ν = 3438, 2985, 2970, 1625, 1226 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.62 (s, 1H), 8.03 (dd, 2H, *J* = 8.7 Hz), 7.59 (d, 2H, *J* = 8 Hz), 7.49 (s, 1H), 7.27 - 7.34 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 147.62, 133.15, 130.25, 129.53, 128.17, 121.95, 118.56, 116.48; EIMS: *m/z* = 321 (M+1). Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97; O, 5.12. Found: C, 80.78; H, 5.14; N, 9.02; O, 5.14.

2-(4-Methoxyphenyl)-4,5–diphenyl-1H-imidazole (Table 2 entry 8)

Solid; m.p. 220-222 °C; IR (KBr) ν = 3428, 2893, 2465, 1636, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.52 (s, 1H), 8.03 (d, 2H, *J* = 8.8 Hz), 7.55 - 7.59 (m, 10H), 6.94 (d, 2H, *J* = 8.8 Hz), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.17, 145.75, 132.83, 127.64, 127.45, 126.53, 126.34, 122.73, 113.27, 54.63; EIMS: *m/z* = 326. Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58; O, 4.90. Found: C, 80.99; H, 5.59; N, 8.56; O, 4.93.

4-(4,5-Diphenyl-1H–imidazol–2-yl)phenol (Table 2 entry 9)

Solid; m.p. 202-204 °C; IR (KBr) ν = 3428, 3215, 1602, 1532 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.51 (s, 1H), 7.2 - 7.52 (m, 10H), 6.99 (d, 2H, *J* = 7.8 Hz), 6.89 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$): δ 156.55, 145.46, 129.18, 128.37, 127.93, 126.92, 124.74, 119.08, 116.54, 112.82. EIMS: *m/z* = 321. Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97; O, 5.12. Found: C, 80.80; H, 5.19; N, 9.03; O, 5.17.

2-(3,4-Dimethoxyphenyl)-4,5-diphenyl-1H-imidazole (Table 2 entry 10)

Solid; m.p. 210-212 °C; IR (KBr) ν = 3431, 2987, 2893, 2465, 1636, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.48 (s, 1H), 8.05 (d, 2H, *J* = 8.7 Hz), 7.28. - 7.61 (m, 10H), 6.95 (d, 1H), 3.85 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 150.35, 147.64, 144.82, 129.57, 129.33, 129.30, 129.34, 128.83, 128.81, 127.58, 127.56, 133.14, 124.21, 120.83, 115.81 112.34, 56.24; EIMS: *m/z* = 356. Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86; O, 8.98. Found: C, 77.56; H, 5.69; N, 7.90; O, 8.94.

Results and Discussion

Having established the advantages of ZnO as catalyst, bearing in mind that solvents can also effect the chemical reaction, we continued to optimize the process by varying the solvents.

such as acetonitrile, THF, ethanol, THF/water (1/1), acetonitrile/water (1/1), ethanol/water (1/1) and toluene (shown in Table 1) were chosen as the medium for a comparison. It was found that compound **1** (1 mmol), **2** (1 mmol) and NH_4OAc were mixed together with ZnO (5 mol%) and solvent (5 mL) stirred at room temperature. It was found that acetonitrile (entry 1, Table 1) gave the highest yield of the desired product. When other mentioned solvents (Table 1) were used, the reaction suffered many disadvantages such as more reaction time and lower yields.

Table 1. Optimization of reaction condition for synthesis of 2, 4, 5-triphenyl 1*H*-imidazole derivatives using 5 mol% ZnO catalyst

Entry	Solvent	Time, h	Yields[a], %
1	Acetonitrile	1	93
2	THF	4	60
3	Ethanol	6	54
4	THF/Water	5	46
5	Acetonitrile/Water	4	58
6	Ethanol/Water	6	68
7	Toluene	9	39

[a]*Isolated yields*

The progress of reaction by using solvents revealed that when the reaction was performed in acetonitrile, it proceeded much faster than in other solvents; to afford entry 3 in 93% yield (Table 2). A similar reaction was also carried out in solvents toluene in (Table 1), in this case, the reaction took longer reaction time with less yields.

Table 2. Synthesis of 2,4,5-tripheny-1*H*-imidazole derivatives in the presences of ZnO catalyst

Entry	R	Product	Time, min	Yield[b], %
1	H	**3a**	65	75
2	4-Me	**3b**	75	63
3	4-Br	**3c**	60	93
4	2-Cl	**3d**	62	84
5	4-Cl	**3e**	64	89
6	3-NO2	**3f**	70	85
7	2-OH	**3g**	80	71
8	3-OMe	**3h**	90	69
9	4-OH	**3i**	85	68
10	3,4-(OMe)2	**3j**	78	70
11	2-NO2	**3k**	62	74
12	4- NO2	**3l**	65	74
13	2-F	**3m**	60	81
14	4-F	**3n**	58	78
15	2-Me	**3o**	93	65

[b]*All yields refer to isolated products*

The synthetic strategy is based on the condensation of 1, 2-diphenylethanedienones with variety of aldehydes and amines in the presence of an excess of NH_4OAc, resulting in 2, 4, 5-tripheny l-1*H* - imidazole derivatives **3a-o** by using 5 mol% of ZnO catalyst. Initially, benzil **1** in acetonitrile was treated with an equimolar quantity of variety of aromatic banzaldehyde, excess of NH_4OAc stirred at room temperature for 60 - 90 min to furnish 2, 4, 5 - triphenyl -1*H* - imidazole derivatives, **3a-o** (Table 2) in 63 - 93% yields.

To examine the scope and limitations of this reaction, we carried out the reaction of various aromatic aldehydes including both electron donating and electron withdrawing substituents in *ortho*, *meta* and *para* positions of benzaldehyde (Table 2). We found that the reaction proceeded very efficiently in all cases and the reaction time decreased for aldehydes containing electron withdrawing substitutents. The best result was obtained with 4-bromobenzaldehyde (93% yield, entry 3, Table 2) and the least yield (63%) was obtained from 4-methyl benzaldehyde after stirring for 75 min (Table 2, entry 2).

Conclusion

We have reported an efficient procedure for the synthesis of 2,4,5-triphenyl-1*H*-imidazole **3a-o** derivatives using ZnO as a reusable, non-toxic, non-corrosive, inexpensive and commercially available heterogeneous catalyst. The method also offers some other advantages such as clean reaction, low loading of catalyst, high yields of products, short reaction times and use of various substrates, which make it a useful and attractive strategy for the synthesis of 2,4,5-triphenyl-1*H*-imidazole derivatives.

Acknowledgment

BSH acknowledges the Council of Scientific and Industrial Research (CSIR), New Delhi, India for financial support.

References

1. (a) Lambardino J G and Wiseman E H, *J Med Chem*., 1974, **17,** 1182-1188; (b) Philips A P, White H L and Rosen S, *Eur Pat Appl*., 1982, EP, 58890.
2. Adams J L and Lee D, *Curr Opin Drug Discov Dev*., 1999, **2,** 96-109.
3. Khanna I K, Yu Y, Huff R M, Weier R M, Xu X D, Koszyk F J, Collins P W, Cogburn J N, Isakson P C, Kobolt C M, Masferrer J L, Perkins W E, Seibert K, Veenhuizen A W, Yuan J, Yang D and Zhang Y Y, *J Med Chem.*, 2000, **43,** 3168.
4. Maier T, Schmierer R, Bauer K, Bieringer H, Buerstell H and Sachse B, *Chem Abstr*., 1989, **111,** 19494.
5. Schmierer R, Mildenberger H and Buerstell H, *Chem Abstr*., 1988, **108,** 37838.
6. Heeres J, Backx L J J, Mostmans J H and Van Custem J, *J Med Chem*., 1979, **22,** 1003.
7. (a) Welton T, *Chem Rev*., 1999, **99,** 2071; (b) Wasserscheid P and Keim W, *Angew Chem Int Ed Engl.*, 2000, **39,** 3772-3789.
8. (a) Hermann W A and Kocher C, *Angew Chem Int Ed Eng*., 1997, **36,** 2162; (b) Zhang C, Huang J, Trudell M L and Nolan S P, *J Org Chem*., 1999, **64,** 3804; (c) Bourissou D, Guerret O, Gabbai F P and Bertrand G, *Chem Rev*., 2000, **100,** 39-91.
9. Lantos I, Zhang W Y, Shiu X and Eggleston D S, *J Org Chem*., 1993, **58,** 7092.
10. Zhang C, Moran E J, Woiwade T F, Short K M and Mjalli A M M, *Tetrahedron Lett*., 1996, **37,** 751.
11. Claiborne C F, Liverton N J and Nguyen K T, *Tetrahedron Lett.*, 1998, **39,** 8939-8942.
12. Bleicher K H, Gerber F, Wuthrich Y, Alanine A and Capretta A, *Tetrahedron Lett*., 2002, **43,** 7687-7690.
13. Liu J P, Chen J B, Zhao J F, Zhao Y H, Li L and Zhang H B, *Synthesis,* 2003, 2661-2666.
14. Sarshar S, Siev D and Mjalli A M M, *Tetrahedron Lett.*, 1996, **37,** 835.
15. Frantz D E, Morency L, Soheili A, Murry J A, Grabowski E J J and Tillyer R D, *Org Lett*., 2004, **6(5),** 843.

16. Weinmann H, Harre M, Koeing K, Merten E and Tilstam U, *Tetrahedron Lett.*, 2002, **43,** 593.
17. Clark N G and Cawkill E, *Tetrahedron Lett*., 1975, **16,** 2717.
18. Balalaie S, Hashemi M M, Akhbari M A, *Tetrahedron Lett*., 2003, **44,** 1709.
19. Balalaie S and Arabanian A, *Green Chem*., 2000, 2, 274-276.
20. Usyatinsky A Y and Khemelnitsky Y L, *Tetrahedron Lett*., 2000, **41,** 5031-5034.
21. Wolkenberg S E, Wisnoski D D, Leister W H, Wang Y, Zhao Z and Lindsley C W, *Org Lett*., 2004, **6,** 1453-1456.
22. Cobb J M, Grimster N, Khan N, Lai J Y Q, Payne Nee Gold H J, Payne L J, Raynham T and Taylor J, *Tetrahedron Lett.*, 2002, **43(42),** 7557.
23. Xu L, Wan Li -F, Salehi H, Deng W and Guo Q X, *Hetrocycles*, 2004, **63,** 1613.
24. (a) Singh R, Kissling M R, Letellier A M and Nolan P S, *J Org Chem.*, 2004, **69,** 209; (b) Anastas T P, Bartlett B L, Kirchhof M M and Williamson C T, *Catal Today*, 2000, **55,** 11.
25. Tanabe K, Solid Acids and Bases, Academic Press, New York, 1970.
26. (a) Tamaddom F, Amrollahi A M and Sharafat L, *Tetrahedron Lett.*, 2005, **46,** 7841; (b) Gupta M, Paul S, Gupta R and Loupy A, *Tetrahedron Lett.*, 2005, **46**, 4957; (c) Hosseini-Sarvari M and Sharghi H, *J Org Chem.*, 2006, **71(17)**, 6652-6654; (d) Hosseini-Sarvari M and Sharghi H, *Tetrahedron*, 2005, **61(46),** 10903-10907; (e) Sharghi H and Hosseini-Sarvari M, *Synthesis*, 2002, **8,** 1057; (f) Hosseini-Sarvari M, *Synthesis*, 2005, **5,** 787-790; (g) Hosseini-Sarvari M, Sharghi H, *Phos Silicon Sulf.*, 2007, **182(9),** 2125-2130; (h) Hosseini-Sarvari M, *Synth Commun.*, 2008, **16,** 832; (i) Hosseini-Sarvari M and Etemad S, *Tetrahedron*, 2008, **64(23),** 5519-5523; (j) Hosseini-Sarvari M, Sharghi H and Etemad S, *Helv Chim Acta.,* 2008, **91,** 715-724.