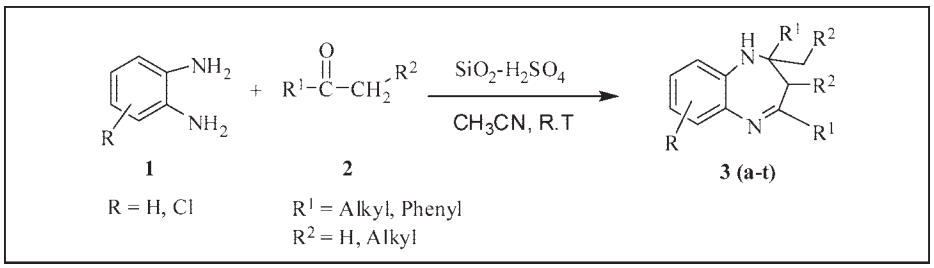
Silica Gel-Supported Sulfuric Acid Catalyzed Synthesis of 1,5-Benzodiazepine Derivatives

D. Shobha,[a,b] M. Adharvana Chari,[b]* K. Mukkanti,[a] and K. H. Ahn[b]

[a]Department of Chemistry, Institute of Science and Technology, Jawaharlal Nehru Technological University, Hyderabad, Andhra Pradesh 500072, India
[b]Department of Chemistry, Kyung Hee University, Seoul, South Korea
*E-mail: drmac_s@yahoo.com

Received January 16, 2009
DOI 10.1002/jhet.174
Published online 2 September 2009 in Wiley InterScience (www.interscience.wiley.com).



Silica gel-supported sulfuric acid has been found to be an efficient catalyst for the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and ketones in acetonitrile solvent. This method is simple, effective, and environmentally friendly and gives better yields. Compared to the classical reaction conditions, this new method consistently has the advantage of excellent yields (80–97%) and short reaction time (30–150 min) at room temperature.

J. Heterocyclic Chem., **46**, 1028 (2009).

INTRODUCTION

Benzodiazepines are pharmacologically active compounds having anti-inflammatory [1], antianxiety, anticonvulsant, and hypnotic activity [2,3]. Because of the broad biological significance, the syntheses of these compounds have received a great deal of attention. Benzodiazepines have been synthesized by the condensation of *o*-phenylenediamines with β-unsaturated carbonyl compounds, β-haloketones, or ketones. This condensation has been carried out using different reagents, such as BF_3-etherate [4], polyphosphoric acid [5], $NaBH_4$ [6], SiO_2 [5], $MgO/POCl_3$ [7], $Yb(OTf)_3$ [8], $Ga(OTf)_3$ [9], lead nitrate [10], L-proline [11], acetic acid under microwave conditions [12], molecular iodine [13], and in ionic liquids [14]. Recently, this condensation is reported using different acid catalysts [15–22]. Many of these processes suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious workup procedure. Therefore, the search continues for a better catalyst for the synthesis of 1,5-benzodiazepines in terms of mild reaction conditions.

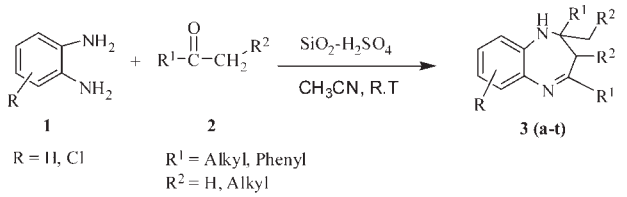
Recently, the use of heterogeneous catalysts [23–26] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of catalysts. Among the various heterogeneous catalysts, particularly, silica gel-supported sulfuric acid [27] has advantages of low cost, ease of preparation, and catalyst recycling. As the reaction is heterogeneous in nature, the catalyst can conveniently be separated by simple filtration. In view of recent surge in the use of heterogeneous catalysts, we wish to report a simple, convenient, and efficient method for the preparation of 1,5-benzodiazepines under acetonitrile solvent using silica gel-supported sulfuric acid (10 mol %) as a catalyst. This catalyst is easy to handle, thermally robust, nonvolatile, nonexplosive, eco-friendly, and recyclable for a variety of organic transformations.

RESULTS AND DISCUSSION

Initially, we studied the catalytic properties of silica gel-supported sulfuric acid for the synthesis of 1,5-benzodiazepines at room temperature using *o*-phenylenediamine (**1**) and the ketone (**2**) (Scheme 1) and varying the mol % of silica gel-supported sulfuric acid (Table 1). Among the results obtained, use of 10 mol % silica gel-supported sulfuric acid gave better yield (97%) in 30 min for the synthesis of **3a**.We achieved good yield when compared with our earlier report (90% in 30 min) [16].

We investigated the reaction of a series of symmetrical and unsymmetrical ketones with *o*-phenylenediamine to get the corresponding 1,5-benzodiazepinederivatives in 80–97% yield under acetonitrile conditions. All

Scheme 1



synthesized derivatives were characterized using IR, ^{1}H NMR, and mass spectral analysis and also by comparison with authentic samples. The reactions of various ketones with *o*-phenylenediamine in the presence of silica gel-supported sulfuric acid are superior in terms of yields and reaction times (Table 2) than the previously reported methods. Especially, with *p*-chloroacetophenone (Table 2, entry 9), we have obtained 95% yield in 50 min, whereas previously reported was less than 95% in 50 min [17,18].

Chloro-substituted *o*-phenylenediamine and substituted ketones have been used with similar success to provide the corresponding benzodiazepines in high yields, which are also of much interest with regard to biological activity. The efficiency of the recovered catalyst was verified with the reaction of *o*-phenylenediamine and ketone (entry 1). Using the fresh catalyst, the yield of product (**3a**) was 97%, whereas using the recovered catalyst in the three subsequent recyclization, the yields were 94, 92, and 90, respectively.

In summary, we have developed a new methodology for the synthesis of various 1,5-benzodiazepines by using substituted *o*-phenylenediamine and substituted ketones in the presence of catalytic amount of silica gel-supported sulfuric acid catalyst at room temperature. Thus, this method is a simple, high yielding, time saving, and eco-friendly process. The catalyst can be prepared from available inexpensive reagents and can be easily recycled, which is heterogeneous and nonhazardous. Hence, the utility of silica gel-supported sulfuric acid catalyst for the synthesis of 1,5-benzodiazepines would be a valuable addition to available methods.

EXPERIMENTAL

All chemicals were AR grade obtained from Qualigens, India. All the solvents were purified by standard techniques. Column chromatographic separations were carried out on silica gel 100–200 mesh size. IR spectra were scanned on FT/IR-4200 Type A, spectrophotometer with potassium bromide optics. NMR spectra were recorded on a 300 MHz and mass spectra were recorded on a LC-MS.

Preparation of the catalyst. The catalyst was prepared by mixing silica gel (10 g, 200–400 mesh) in dry diethyl ether (50 mL), with sulfuric acid (3 mL). The resulting mixture was stirred for 30 min to absorb sulfuric acid on the surface of silica gel. After the removal of solvent in a rotary evaporator, the solid powder was dried at 120°C for 2–3 h under reduced pressure.

General procedure for the synthesis of 1,5-benzodiazepines. A mixture of *o*-phenylenediamine (**1**) (1 mmol), ketone (**2**) (2.5 mmol), and silica gel-supported sulfuric acid (0.1 mmol) was stirred in acetonitrile at room temperature until thin layer chromatography indicated that the reaction was complete. After the completion of reaction, 20 mL of ethyl acetate was added to the reaction mixture, and the catalyst was recovered by filtration. The organic layer was concentrated, and the crude product was purified by silica gel column chromatography using ethyl acetate–*n*-hexane (1:9) as eluent to afford the desired product (**3**). Entry **1–5** and **11** spectral data [20], entry **7**, **8** spectral data [21], and entry **9**, **10**, and **13** spectral data [22] are in full agreement with the reported literature, and the new compounds spectral data are given later.

Entry 6 (3f). Yellow solid, m.p. 140–142°C, IR(KBr): ν_{max} 3341, 1674, 1589 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92–0.98 (m, 6H, $2CH_3$), 1.13 (s, 3H, CH_3), 1.18–1.36 (m, 4H, $2CH_2$), 1.52–1.62 (m,1H, CH^a), 2.10–2.20 (m, 1H, CH^b), 2.51–2.59 (m, 4H, $2CH_2$), 3.05 (br s,1H, NH), 6.70–6.73 (m, 1H, Ar—H), 6.95–6.98 (m, 2H, Ar—H), 7.12–7.14 (m, 1H, Ar—H). EIMS: *m/z* [M$^+$] = 244. *Anal.* Calcd for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.50; H, 9.85; N, 11.36.

Entry 12 (3l). Yellow solid, m.p. 94–96°C, IR(KBr): ν_{max} 3424, 1595, 1499 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, CH_3), 1.24–1.25 (m, 6H, $2CH_3$), 1.60–1.65 (m, 2H, CH_2), 2.22 (m, 2H, CH_2), 2.50–2.68 (q, 2H, J = 3.23 Hz, CH_2), 3.00–3.20 (br s,1H, NH), 6.62–6.71 (m, 1H, Ar—H), 6.88–6.93 (m, 1H, Ar—H), 7.04–7.14 (m, 1H, Ar—H). EIMS: *m/z* [M$^+$] = 250, *Anal.* Calcd for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64; N, 11.17. Found: C, 67.00; H, 7.54; N, 11.10.

Entry 14 (3n). Light yellow solid, m.p.140–142°C, IR(KBr): ν_{max} 3197, 1623, 1590 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98–1.02 (m, 12H, $4CH_3$), 1.25 (m, 2H, 2CH), 1.30 (s, 3H, CH_3), 1.70–1.73 (m,2H, $2CH_2$), 2.15–2.20 (m, 2H, CH_2), 2.40 (d, 2H, CH_2), 3.50 (br s,1H, NH), 6.60–6.673 (m, 1H, Ar—H), 6.86–6.94 (m, 1H, Ar—H), 7.04–7.13 (m, 1H, Ar—H). EIMS: *m/z* [M$^+$] = 306. *Anal.* Calcd for $C_{18}H_{27}ClN_2$: C, 70.45; H, 8.87; N, 9.13. Found: 70.35; H, 8.76; N, 9.09.

Entry 15 (3o). Yellow crystalline solid, m.p.156–158°C, IR(KBr): ν_{max} 3344, 1647, 1603 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88–2.10 (m, 12H, $6CH_2$), 2.90–2.95 (d, 1H, CH), 3.90–4.25 (m, 2H, CH_2), 3.05 (br s, 1H, NH), 6.63–6.64 (m, 1H, Ar—H), 6.73–6.77 (m, 1H, Ar—H), 7.87–7.90 (m, 1H,

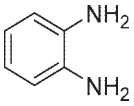
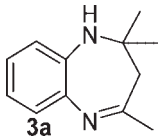
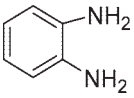
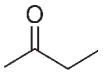
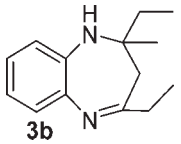
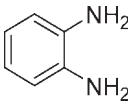
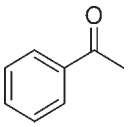
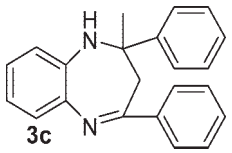
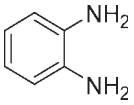
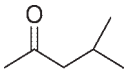
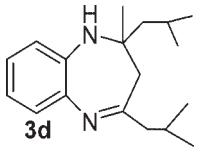
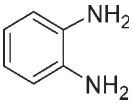
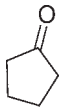
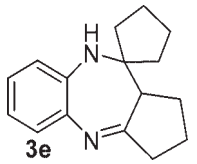
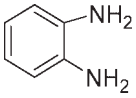
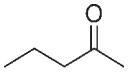
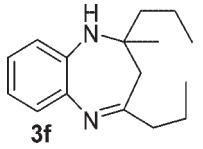
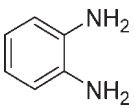
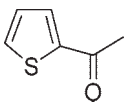
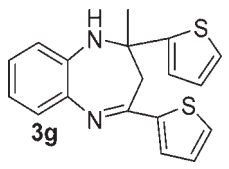
Table 1

Optimization of reaction conditions and the concentration of silica gel-supported sulfuric acid for the synthesis of **3a**.

H_2SO_4/Silica gel (mol %)	Reaction time (min)	Yield (%)
2.5	110	85
5	80	89
10	30	97
15	30	97
20	30	97

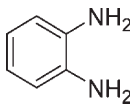
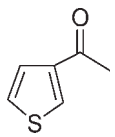
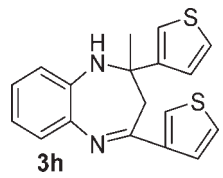
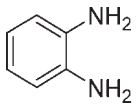
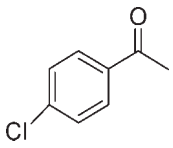
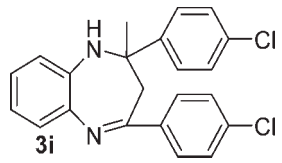
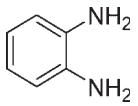
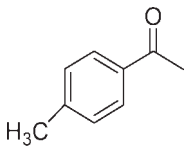
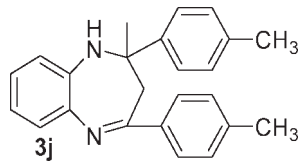
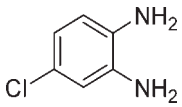
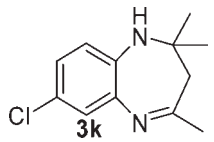
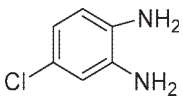
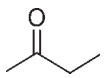
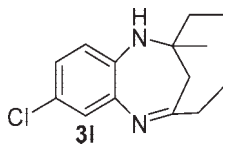
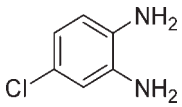
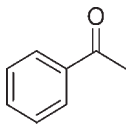
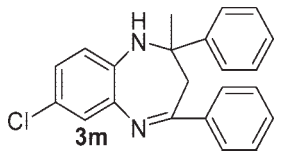
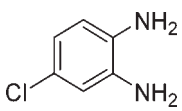
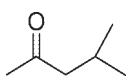
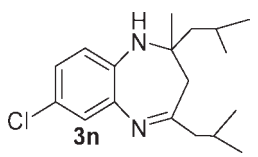
Table 2

Silica gel-supported sulfuric acid catalyzed synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines.

Entry	Diamine	Ketone	Product	Time (min)	Yield (%)
1			 **3a**	30	97
2			 **3b**	40	95
3			 **3c**	40	92
4			 **3d**	60	94
5			 **3e**	60	92
6			 **3f**	50	90
7			 **3g**	120	86

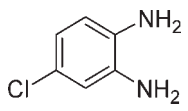
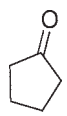
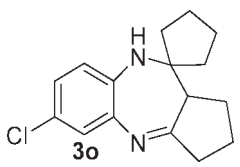
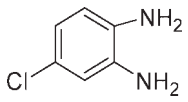
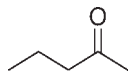
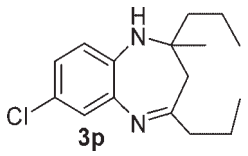
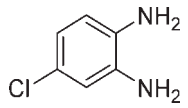
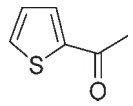
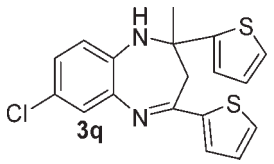
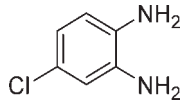
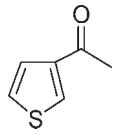
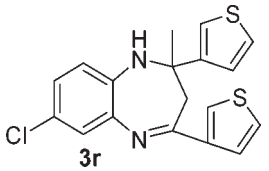
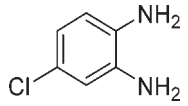
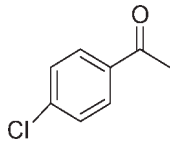
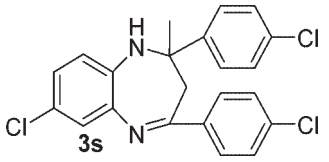
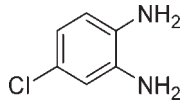
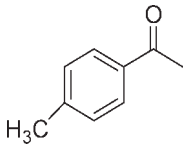
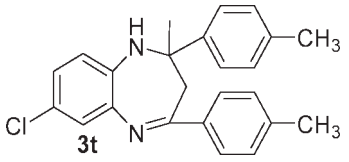
(*Continued*)

Table 2
(*Continued*)

Entry	Diamine	Ketone	Product	Time (min)	Yield (%)
8			 **3h**	120	82
9			 **3i**	50	95
10			 **3j**	50	96
11			 **3k**	50	94
12			 **3l**	60	92
13			 **3m**	120	90
14			 **3n**	90	88

(*Continued*)

Table 2
(*Continued*)

Entry	Diamine	Ketone	Product	Time (min)	Yield (%)
15			 **3o**	90	86
16			 **3p**	120	88
17			 **3q**	140	82
18			 **3r**	150	80
19			 **3s**	120	85
20			 **3t**	120	90

Ar—H). EIMS: *m/z* [M^+] = 274. *Anal*. Calcd for $C_{16}H_{19}ClN_2$: C, 69.93; H, 6.97; N, 10.19. Found: C, 69.83; H, 6.87; N, 10.09.

Entry 16 (3p). Reddish yellow solid, m.p. 160–162°C, IR(KBr): ν_{max} 3338, 1638, 1591 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.82–0.92 (m, 6H, $2CH_3$), 1.15 (s, 3H, CH_3), 1.23–1.49 (m, 4H, $2CH_2$), 1.58–1.68 (m, 2H, CH_2), 2.02–2.10 (m, 2H, CH_2), 2.39–2.45 (m, 2H, CH_2), 3.10 (br s, 1H, NH), 6.51–6.60 (m, 1H, Ar—H), 6.77–6.82 (m, 1H, Ar—H), 6.93–7.02 (m, 1H, Ar—H). EIMS: *m/z* [M^+] = 278. *Anal*. Calcd for $C_{16}H_{23}ClN_2$: C, 68.92; H, 8.31; N, 10.05. Found: C, 68.83; H, 8.21; N, 10.00.

Entry 17 (3q). Yellow solid, m.p. 130–132°C, IR(KBr): ν_{max} 3303, 1599, 1471 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 3H, CH_3), 2.99 (d, 1H, J = 13.20 Hz, CH_2), 3.08 (d, 1H, J = 13.20 Hz, CH_2), 3.58 (br s, 1H, NH), 6.79–6.82 (m,

1H, Ar—H), 6.90–6.93 (m, 2H, Ar—H), 7.01–7.10 (m, 4H, Ar—H), 7.30–7.40 (m, 1H, Ar—H), 7.63–7.69 (m, 1H, Ar—H). EIMS: *m/z* [M^+] = 358. *Anal*. Calcd for $C_{18}H_{15}ClN_2S_2$: C, 60.24; H, 4.21; N, 7.81. Found: C, 60.14; H, 4.15; N, 7.71.

Entry 18 (3r). Light yellow crystalline solid, m.p.120–122°C, IR(KBr): ν_{max} 3320, 1602, 1490 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.73 (s, 3H, CH_3), 2.86 (d, 1H, *J* = 13.20 Hz, CH_2), 2.93 (d, 1H, *J* = 13.20 Hz, CH_2), 3.43 (br s, 1H, NH), 6.70–6.79 (m, 1H, Ar—H), 6.99–7.01 (m, 2H, Ar—H), 7.10–7.17 (m, 1H, Ar—H), 7.20–7.30 (m, 5H, Ar—H). EIMS: *m/z* [M^+] = 358. *Anal*. Calcd for $C_{18}H_{15}ClN_2S_2$: C, 60.24; H, 4.21; N, 7.81. Found: 60.14; H, 4.15; N, 7.71.

Entry 19 (3s). Yellow solid, m.p. 145–147°C, IR(KBr): ν_{max} 3267, 1646, 1562 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, 3H, CH_3), 2.86 (d, 1H, *J* = 12.80 Hz, CH_2), 3.14 (d, 1H, *J* = 12.80 Hz, CH_2), 3.50 (br s, 1H, NH), 6.74–6.84 (m, 1H, Ar—H), 6.98–7.06 (m, 1H, Ar—H), 7.19–7.29 (m, 5H, Ar—H), 7.42–7.52 (m, 4H, Ar—H). EIMS: *m/z* [M^+] = 415. *Anal*. Calcd for $C_{22}H_{17}Cl_3N_2$: C, 63.56; H, 4.12; N, 6.74. Found: C, 63.46; H, 4.06; N, 6.64.

Entry 20 (3t). Pale yellow solid, m.p. 138–140°C, IR(KBr): ν_{max} 3320, 1602, 1567 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 3H, CH_3), 2.17 (s, 2H, CH_2), 2.33 (s, 6H, $2CH_3$) 3.00 (br s, 1H, NH), 6.80–6.81 (m, 1H, Ar—H), 7.06–7.10 (m, 5H, Ar—H), 7.42–7.53 (m, 5H, Ar—H). EIMS: *m/z* [M^+] = 374. *Anal*. Calcd for $C_{24}H_{23}ClN_2$: C, 76.89; H, 6.18; N, 7.47. Found: C, 76.79; H, 6.08; N, 7.37.

REFERENCES AND NOTES

[1] (a) De Baun, J. R.; Pallos, F. M.; Baker, D. R. U.S. Pat. 3,978,227 (1976); (b) De Baun, J. R.; Pallos, F. M.; Baker, D. R. Chem Abstr 1977, 86, 5498d.

[2] (a) Schultz, H. Benzodiazepines; Springer: Heidelberg, 1982; (b) Smiley, R. K. Comprehensive Organic Chemistry; Pergamon: Oxford, 1979; (c) Landquist, J. K. Comprehensive Heterocyclic Chemistry, Vol.1; Pergamon: Oxford, 1984; p 166, 170.

[3] Randall, L. O.; Kappel, B. In Benzodiazepines; Garattini, S., Mussini, E., Eds.; Raven Press: New York, 1973.

[4] Herbert, J. A.; Suschitzky, L. H. J Chem Soc Perkin Trans 1974, 1, 2657.

[5] Morales, H. R.; Bulbarela, A.; Contreras, R. Heterocycles 1986, 24, 135.

[6] Jung, D. I.; Choi, T. W.; Kim, Y. Y.; Kim, I. S.; Park, Y. M.; Lee, Y. G.; Jung, D. H. Synth Commun 1999, 29, 1941.

[7] Balakrishna, M. S.; Kaboudin, B. Tetrahedron Lett 2001, 42, 1127.

[8] Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. Tetrahedron Lett 2001, 42, 3193.

[9] Pan, X.-Q.; Zou, J.-P.; Hauang, Z.-H.; Zhang, W. Tetrahedron Lett 2008, 49, 5302.

[10] Kumar, R.; Chaudhary, P.; Nimesh, S.; Verma, A. K.; Chandra, R. Green Chem 2006, 8, 519.

[11] Sivamurugan, V.; Deepa, K.; Palanichamy, M.; Murugesan, V. Synth Commun 2004, 34, 3833.

[12] Minothora, P.; Julia, S. S.; Constantinos, A. T. Tetrahedron Lett 2002, 43, 1755.

[13] Chen, W. Y.; Lu, J. Synlett 2005, 1337.

[14] Jarikote, D. V.; Siddiqui, S. A.; Rajagopal, R.; Thomas, D.; Lahotiands, R. J.; Srinivasan, K. V. Tetrahedron Lett 2003, 44, 1835.

[15] (a) Bandgar, B. P.; Patil, A. V.; Chavan, O. S. J Mol Catal A: Chem 2006, 256, 99; (b) Heravi, M. M.; Zadsirjan, V.; Behbahani, F. K. J Mol Catal A: Chem 2006, 259, 201; (c) Xia, M.; Lu, Y. D. Heteroatom Chem 2007, 18, 354.

[16] Chari, M. A.; Shobha, D.; Syamasundar, K. J Heterocycl Chem 2007, 44, 929.

[17] Sangshetti, J. N.; Kokare, N. D.; Shinde, D. B. Chin Chem Lett 2007, 18, 1305.

[18] Hegedu, A.; Hell, Z.; Potor, A. Catal Lett 2005, 105, 229.

[19] Xia, M.; Lu, Y.-D. Heteroatom Chem 2007, 18, 354.

[20] Suryakiran, N.; Rajesh, K.; Prabhakar, P.; Jon paul Selvam, J.; Venkateswarlu, Y. Catal Commun 2007, 8, 1635.

[21] Kuo, C.-W.; More, S. V.; Yao, C.-F. Tetrahedron Lett 2006, 47, 8523.

[22] Varala, R.; Enugala, R.; Adapa, S. R. J Braz Chem Soc 2007, 18, 291.

[23] Chari, M. A.; Syamasundar, K. Catal Commun 2005, 6, 67.

[24] Breton, G. W. J Org Chem 1997, 62, 8952.

[25] Gupta, R.; Paul, S.; Gupta, R. J Mol Catal A: Chem 2007, 266, 50.

[26] Jain, S. L.; Prasad, V. V. N.; Sain, B. Catal Commun 2008, 9, 499.

[27] Roy, B.; Mukopadhya, B. Tetrahedron Lett 2007, 48, 3783.