LiBr as an Efficient Catalyst for One-pot Synthesis of Hantzsch 1,4-Dihydropyridines under Mild Conditions

Yadav, D. K.[a] Patel, R.[b] Srivastava, V. P.[b] Watal, G.[a] Yadav, L. D. S.*[,b]

[a] *Alternative Therapeutics Unit, Drug Development Division, Medicinal Research Lab, Department of Chemistry, University of Allahabad, Allahabad 211002, India*

[b] *Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211002, India*

A simple, inexpensive and efficient one-pot synthesis of 1,4-dihydropyridines has been accomplished via lithium bromide-catalyzed Hantzsch three-component condensation reaction of an aldehyde, *α*,*β*-ketoester and ammonium acetate in acetonitrile at room temperature in good to excellent yields. The present protocol is applicable to wide range of substrates including aliphatic, aromatic and heterocyclic aldehydes affording 1,4-dihydropyridines.

Keywords Hantzsch reaction, 1,4-dihydropyridines, lithium bromide, cyclization, one-pot procedure, multicomponent reactions

Introduction

Multicomponent reactions (MCRs) are one-pot processes that combine three or more substrates simultaneously.[1] Such processes are of great interest in diversity-oriented synthesis, especially to generate compound libraries for screening purposes. Hantzsch 1,4-dihydropyridines (1,4-DHPs) and their derivatives have gained considerable importance in the field of organic and medicinal chemistry since they display a fascinating array of pharmacological properties.[2-5] The 1,4-dihydropyridine skeleton is common in many drugs such as nifedipine, nicardipine, amlodipine and others, which have been found to be useful as calcium channel blockers,[6] and are used most frequently as cardiovascular agents for the treatment of hypertension (Figure 1).[7]

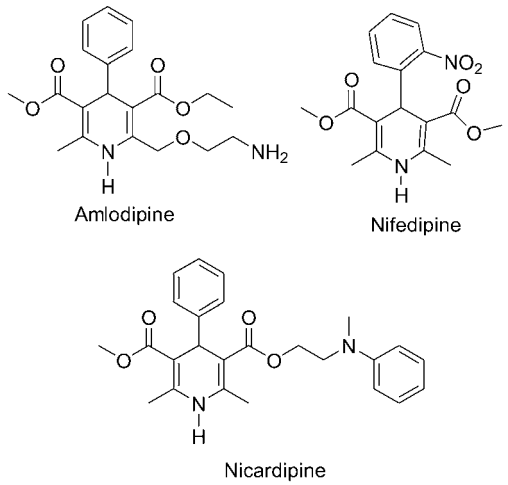


Figure 1 Examples of 1,4-DHPs in clinical use.

Moreover, studies have discovered that 1,4-DHPs exhibit diverse medical functions such as neuroprotectants, platelet antiaggregators, chemosensitizers and are important in Alzheimer's disease as antiischaemic agents.[8] Furthermore, the 1,4-dihydropyridine skeleton is common in many vasodilator, bronchodilator, antiatherosclerotic, antitumour, antidiabetic, geroprotective and hepatoprotective agents.[9] Among 1,4-DHPs, there are also examples of drug-resistance modifiers,[10] antioxidants[11] and a drug for the treatment of urinary urge incontinence.[12] Interest in 1,4-dihydropyridines is also sustained by their structural similarity to nicotinamide dinucleotide, a cofactor used by many reductases in metabolism.[10,13] Beyond their diverse pharmaceutical applications, Hantzsch-derived 1,4-dihydropyridines are also useful synthetic tools as organo-reducing agents in organic synthesis.[14] These examples clearly demonstrate the remarkable potential of novel DHP derivatives as a source of valuable drug candidates. A recent computational analysis of the comprehensive medicinal chemistry database found the 1,4-DHP framework to be among the most prolific chemotypes found. Thus, the synthesis of this heterocyclic nucleus is of continuing interest. The success of these calcium antagonists has led to the development of new synthetic strategies to improve their classical methods of preparation. The preparation of dihydropyridines was first reported by Hantzsch via the one-pot condensation of ethyl acetoacetate and acetaldehyde with ammonia in refluxing alcohol or acetic acid.[15] Owing to the modest yield reported, numerous improvements on this method have been developed involving also the use of preformed Knoevenagel adducts between aldehyde and the ketoester or the use of preformed enaminoesters that en-

* E-mail: ldsyadav@hotmail.com
Received April 8, 2010; revised September 9, 2010; accepted September 16, 2010.

CHINESE JOURNAL OF CHEMISTRY

hance the yields of the product but lack the simplicity of the one-pot, one-step synthesis.[16] Other procedures comprise the use of microwaves,[17] ionic liquids,[18] boronic acids,[10,19] metal triflates,[20] TMSCl-NaI,[21a] $CeCl_3$•$7H_2O$,[21b] molecular iodine,[21c] ceric ammonium nitrate,[21d] iron(III) trifluoroacetate,[21e] *in situ* generated HCl,[22a] and silica-supported acids,[22b] Na- and Cs-Norit carbons,[22c] tetrabutylammonium hydrogen sulfate,[13] fermenting Baker's yeast[22d] and organocatalysts.[23] Very recently, Debache *et al.* have introduced triphenylphosphine as a Lewis base catalyst for one-step synthesis of Hantzsch 1,4-dihydropyridines.[24]

Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as high reaction temperatures, expensive metal precursors, use of catalysts that are harmful to environment, spending longer reaction times and unsatisfactory yields. Thus, the development of a simple, efficient and versatile method for the synthesis of 1,4-dihydropyridines remains of interest and there is a scope for further renovation toward milder reaction conditions and better yields.

Considering the above valid points and in continuation of our effort towards the development of newer and 'greener' synthetic methodologies,[25] we set out to find out a simple and improved protocol for the preparation of 1,4-dihydropyridines using a readily available, cheap and non-toxic catalyst. Lithium bromide is a stable, relatively safe and readily available low cost reagent having unique mild Lewis acid properties. It has a wide variety of utility in different chemical transformations including Biginelli condensation, Knoevenagel condensation, Ehrlich-Sachs reaction, Friedel-Crafts reaction, rearrangement of epoxides and preparation of acylals and xanthenes.[26] In most of these reported reactions, LiBr is almost neutral[27] and also does not form any corrosive or harsh by-products during aqueous workup, unlike strong and expensive catalysts.

Experimental

General procedure

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (300 MHz) FT spectrometer in $CDCl_3$ using TMS as internal reference. Mass spectra (MS) were recorded under electron impact at 70 eV on an LC-MSD instrument (Agilent Technologies). All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was for TLC.

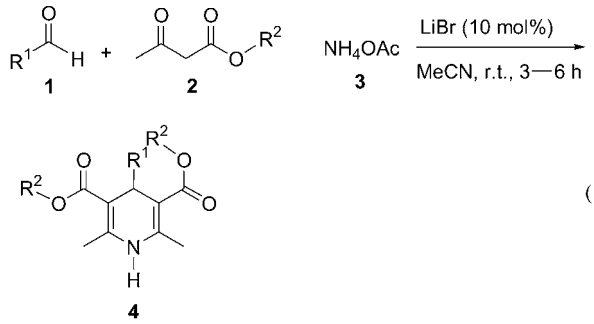
General procedure for the synthesis of Hantzsch 1,4-dihydropyridines

A mixture of an aldehyde (1 mmol), α,β-ketoester (2 mmol), NH_4OAc (1.1 mmol), and LiBr (0.1 mmol) was stirred at room temperature in acetonitrile for an appropriate time (Table 2). After completion of the reaction, as indicated by TLC, acetonitrile was removed and ethyl acetate was added to the residue. The resulting suspension was washed with water followed by brine solution and dried over Na_2SO_4. After evaporation of the solvent, the crude yellow products were purified by crystallization from ethanol to afford 1,4-dihydropyridines **4** in 81%—94%. The structure of the products was confirmed by comparison of their m.p., TLC, IR and ^{1}H NMR data with authentic samples prepared by the literature methods (Table 2).

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4b) m.p. 157—159 ℃; ^{1}H NMR ($CDCl_3$ 300 MHz) δ: 1.30 (t, J=8.2 Hz, 6H), 2.22 (s, 6H), 4.09 (q, J=8.2 Hz, 4H), 5.02 (s, 1H), 5.90 (brs, 1H), 7.24—7.36 (m, 5H); IR (KBr) ν_{max}: 3344, 2958, 1705, 1652, 1497 cm^{-1}; EIMS *m*/*z*: 329 (M^+).

Results and discussion

Herein, we report a mild and efficient protocol for the preparation of 1,4-dihydropyridines derivatives by three-component condensation of an aldehyde, a β-ketoester and ammonium acetate at room temperature using LiBr as catalyst (Eq. 1).

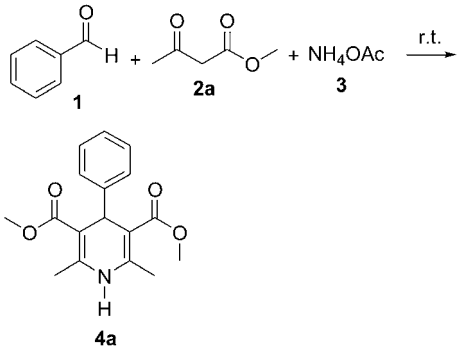


(1)

Our initial work commenced with screening of solvent and catalyst loading so as to obtain optimal reaction conditions for the synthesis of 1,4-dihydropyridines. Compiled in Table 1 are the results of the model study using benzaldehyde, methyl acetoacetate and ammonium acetate as substrates under various reaction conditions. The catalytic activity of LiBr was found to be the best with 10 mol% catalyst loading in acetonitrile as the solvent (Table 1, Entry 1) in terms of yield and reaction time among all the other tested solvents, namely, ethanol, THF, water (Table 1, Entries 3—5). There was no improvement in the reaction rate and yield on increasing the catalyst loading from 10 mol% to 20 mol% (Table 1, Entries 1 and 7). In the absence of a catalyst, the product 1,4-dihydropyridine **4a** was obtained in only 25% yield after 16 h demonstrating the efficiency of our catalyst (Table 1, Entry 8). Neat conditions furnished the product **4a** in 68% yield. Furthermore, the reaction in the presence of other catalysts was also examined. When $LiClO_4$•$3H_2O$ and $FeCl_3$•$6H_2O$ were used as the catalyst, the reaction required longer time and afforded the desired product in significantly lower yields than

that in the case of LiBr (Table 1, Entries 1, 9 and 10).

Table1 Optimization of conditions for LiBr-catalyzed Hantzsch synthesis of 1,4-dihydropyridine **4a**[a]



Entry	Catalyst	Mol%	Solvent[b]	Time/h	Yield[c]/%
1	LiBr	10	CH_3CN	3.0	90
2	LiBr	5	CH_3CN	5.0	79
3	LiBr	10	EtOH	5.0	81
4	LiBr	10	THF	8.0	38
5	LiBr	10	H_2O	8.0	20
6	LiBr	10	Neat	6.0	68
7	LiBr	20	CH_3CN	3.0	90
8	—	—	CH_3CN	16	25
9	$LiClO_4$•$3H_2O$	10	CH_3CN	8.0	70
10	$FeCl_3$•$6H_2O$	10	CH_3CN	10	72

[a] Reaction conditions: Benzaldehyde (1 mmol), methyl acetoacetate (2 mmol), ammonium acetate (1.1 mmol). [b] 2 mL was used. [c] Yields of the isolated pure compounds.

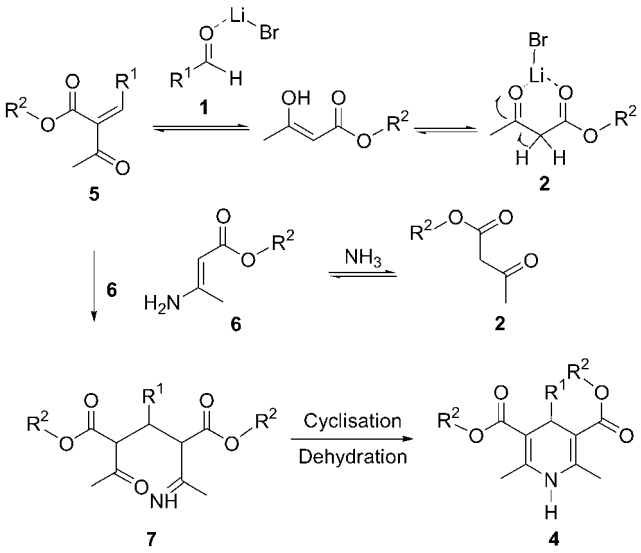
Under these optimized conditions, the reactions between various aliphatic, aromatic, heterocyclic aldehydes and *β*-ketoesters (ethyl acetoacetate and methyl acetoacetate) in the presence of ammonium acetate were investigated and the results are summarized in Table 2, which clearly demonstrate the generality and scope of the present methodology. It was found that all the reactions proceeded smoothly to give the corresponding 1,4-dihydropyridines in good to excellent yields 81%—94% (Table 2). Both aromatic aldehydes bearing electron-donating substituents such as 4-methoxybenzaldehyde (giving **4e**, 89%; **4f**, 84%) and electron-withdrawing groups such as 4- or 3-nitrobenzaldehyde (giving **4j**, 91%; **4k**, 81%; **4l**, 90%) gave excellent yields.

The procedure worked well for heterocyclic aldehydes (giving **4m**, 90%; **4n**, 93%) as well as aliphatic aldehydes (giving **4o**, 88%; **4p**, 84%) in addition to aromatic aldehydes. The mildness of the procedure makes it very selective, as it tolerates a variety of functionalities, including chloro, bromo, methoxy and nitro groups. In all cases, crude products were obtained by extracting the reaction mixtures with ethyl acetate and were then purified by crystallization from ethanol. The products were characterized by IR, ^{1}H NMR and mass spectroscopy, and also by comparison with authentic samples.

The generality and superiority of the present protocol over existing methods can be seen by comparing our results with those of some recently reported procedures, as shown in Table 3. The reaction of benzaldehyde **1a**, ethyl acetoacetate **2b** and ammonium acetate for the preparation of 2,6-dimethyl-3,5-dicarbomethoxy-4-(phenyl)-1,4-dihydropyridine **4b** (Table 2) was chosen as a model reaction and the comparison is in terms of mol% of the catalysts used, reaction times, reaction conditions and percentage yields (Table 3).

From a mechanistic point of view, the first step of this reaction can be visualized as the LiBr-catalyzed formation of Knoevenagel product **5**. A second key intermediate is ester enamine **6**, produced by condensation of the second equivalent of the *β*-ketoester with ammonia. Condensation of these two fragments gives intermediate **7**, which subsequently cyclizes to afford 1,4-dihydropyridine **4** (Scheme 1).

Scheme 1



Conclusion

In conclusion, we have reported for the first time lithium bromide as a novel and highly efficient catalyst for the synthesis of a variety of 4-substituted-1,4-dihydropyridines via one-pot three-component condensation of an aldehyde, *α*,*β*-ketoester and ammonium acetate in acetonitrile. The present remarkably improved Hantzsch reaction is applicable to wide range of substrates including aliphatic, aromatic and heterocyclic aldehydes affording 1,4-dihydropyridines in good to excellent yields at room temperature. This methodology offers several advantages such as reduced reaction times, milder conditions, elevated product yields, compatibility with various functional groups and economic viability of the catalyst, compared with conventional methods and other catalyst.

Table 2 LiBr-catalyzed Hantzsch synthesis of 1,4-dihydropyridine **4**

Compound	R^1	R^2	Time/h	Yield[a,b]/%	m.p./℃	
					Measured	Reported
4a	C_6H_5	CH_3	3.0	90	194—196	196—198[17d]
4b	C_6H_5	C_2H_5	3.0	93	157—159	158—160[28]
4c	4-MeC_6H_4	CH_3	3.5	82	175—177	174—176[17d]
4d	4-MeC_6H_4	C_2H_5	4.0	91	137—139	135—137[17a]
4e	4-$MeOC_6H_4$	CH_3	4.0	89	187—188	186—188[17d]
4f	4-$MeOC_6H_4$	C_2H_5	3.5	84	159—161	161—163[28]
4g	4-ClC_6H_4	CH_3	4.0	87	195—196	196—198[17d]
4h	4-ClC_6H_4	C_2H_5	4.0	94	146—148	147—148[28]
4i	4-BrC_6H_4	C_2H_5	4.5	86	159—160	162—164[24]
4j	4-$NO_2C_6H_4$	C_2H_5	5.0	91	130—132	129—131[28]
4k	3-$NO_2C_6H_4$	CH_3	5.5	81	210—211	210—212[17d]
4l	3-$NO_2C_6H_4$	C_2H_5	5.0	90	161—163	162—164[28]
4m	2-Furyl	CH_3	4.0	90	191—193	192—194[17d]
4n	2-Furyl	C_2H_5	4.5	93	158—160	160—161[28]
4o	$(CH_3)_2CH$	C_2H_5	5.0	88	95—96	96—97[21b]
4p	$(CH_3)_2CHCH_2$	CH_3	6.0	84	120—122	122—124[17d]

[a] Product were characterized by comparison of their m.p., TLC, IR, and ^{1}H NMR data with those of authentic samples. [b] Yields of the isolated pure compounds.

Table 3 Comparison of results for the synthesis of 1,4-dihydropyridine **4b** (Table 2) via Hantzsch reaction using other catalysts

Catalyst	Mol/%	Time/h	Temp./℃	Yield[a]/%	Ref.
$CeCl_3$•$7H_2O$	10	3.0	r.t.	80	21b
PPh_3	20	5.0	78	72	24
$PhB(OH)_2$	10	4.0	78	90	19
SiO_2SO_3H	12	5.5	60	90	22b
LiBr	10	3.0	r.t.	93	This work

[a] Yield of the isolated pure product.

Acknowledgement

We sincerely thank SAIF, Punjab University, Chandigarh for providing microanalyses and spectra.

References

1 (a) Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron Asymmetry* **2007**, *18*, 693.
(b) Domling, A. *Chem. Rev.* **2006**, *106*, 17.
(c) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. Org. Chem.* **2004**, 4957.
(d) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.

2 Kawase, M.; Shah, A.; Gaveriya, H.; Motohashi, N.; Sakagami, H.; Varga, A.; Molnar, J. *Bioorg. Med. Chem.* **2002**, *10*, 1051.

3 Suarez, M.; Verdecia, Y.; Illescas, B.; Martinez-Alvarez, R.; Avarez, A.; Ochoa, E.; Seoane, C.; Kayali, N.; Martin, N. *Tetrahedron* **2003**, *59*, 9179.

4 Shan, R.; Velazquez, C.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 254.

5 (a) Ryabokon, N. I.; Goncharova, R. I.; Duburs, G.; Rzeszowska-Wolny, J. *Mutat. Res.* **2005**, *587*, 52.
(b) Yamamoto, T.; Niwa, S.; Ohno, S.; Onishi, T.; Matsueda, H.; Koganei, H.; Uneyama, H.; Fujita, S.; Takeda, T.; Kito, M.; Ono, Y.; Saitou, Y.; Takahara, A.; Iwata, S.; Shoji, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 798.

6 (a) Janis, R. A.; Triggle, D. J. *J. Med. Chem.* **1983**, *26*, 775.
(b) Boecker, R. H.; Guengerich, F. P. *J. Med. Chem.* **1986**, *29*, 1596.

7 (a) Buhler, F. R.; Kiowski, W. *Hypertens* **1987**, *5*, S3.
(b) Reid, J. L.; Meredith, P. A.; Pasanisi, F. *J. Cardiovasc. Pharmacol.* **1985**, *7*, S18.

8 (a) Klusa, V. *Drugs Future* **1995**, *20*, 135.
(b) Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. *Am. J. Kidney Dis.* **1983**, *21*, 53.
(c) Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. *Drugs Future* **1992**, *17*, 465.

9 (a) Saushins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269.
(b) Mager, P. P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J.; Rothe, H. *Drug Des. Discovery* **1992**, *8*, 273.
(c) Mannhold, R.; Jablonka, B.; Voigt, W.; Schoanfinger, K.; Schraven, E. *Eur. J. Med. Chem.* **1984**, *27*, 229.

10 Sridhar, R.; Perumal, P. T. *Tetrahedron* **2005**, *61*, 2465.

11 Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. *Tetrahedron Lett.* **2005**, *46*, 2775.

12 Moseley, J. D. *Tetrahedron Lett.* **2005**, *46*, 3179.

13 Tewari, N.; Dwivedi, N.; Tripathi, R. P. *Tetrahedron Lett.* **2004**, *45*, 9011.

14 (a) Kang, Q.; Zhao, Z. A.; You, S. L. *Org. Lett.* **2008**, *10*, 2031.
(b) Ouellet, S. G.; Walji, A. M.; MacMillan, D. W. *Acc. Chem. Res.* **2007**, *40*, 1327.

(c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, W. C. *J. Am. Chem. Soc*. **2006**, *128*, 84.
(d) Tuttle, J. B.; Ouellet, S. G.; MacMillan, W. C. *J. Am. Chem. Soc*. **2006**, *128*, 12662.
15 Hantzsch, A. *Justus Liebigs Ann. Chem*. **1882**, *215*, 1.
16 (a) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem*. **1996**, *61*, 924.
(b) Breitenbucher, J. G.; Figliozzi, G. *Tetrahedron Lett*. **2000**, *41*, 4311.
17 (a) Khadikar, B. M.; Gaikar, V. G.; Chitnavis, A. A. *Tetrahedron Lett*. **1995**, *36*, 8083.
(b) Ohberg, L.; Westman, J. *Synlett* **2001**, 1296.
(c) Agarwal, A.; Chauhan, P. M. S. *Tetrahedron Lett*. **2005**, *46*, 1345.
(d) Salehi, H.; Guo, Q.-X. *Synth. Commun*. **2004**, *34*, 4349.
18 Ji, S.-J.; Jiang, Z.-Q.; Lu, J.; Loh, T.-P. *Synlett* **2004**, 831.
19 Debache, A.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Synlett* **2008**, 509.
20 Wang, L. M.; Sheng, J.; Zhang, L.; Han, J.-W.; Fan, Z.-Y.; Tian, H.; Qian, C.-T. *Tetrahedron* **2005**, *61*, 1539.
21 (a) Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett*. **2003**, *44*, 4129.
(b) Sabitha, G.; Arundhathi, K.; Sudhakar, K.; Sastry, B. S.; Yadav, J. S. *Synth. Commun*. **2009**, *39*, 2843.
(c) Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. *Tetrahedron Lett*. **2005**, *46*, 5771.
(d) Ko, S.; Yao, C.-F. *Tetrahedron* **2006**, *62*, 7293.
(e) Adibi, H.; Samimi, H. A.; Beygzadeh, M. *Catal. Commun*. **2007**, *8*, 2119.
22 (a) Sharma, G. V. M.; Reddy, K. L.; Lakshmi, P. S.; Krishna, P. R. *Synthesis* **2006**, 55.
(b) Gupta, R.; Paul, S.; Loupy, A. *Synthesis* **2007**, 2835.
(c) Perozo-Rondon, E.; Calvino-Casilda, V.; Martin-Aranda, R. M.; Casal, B.; Duran-Valle, C. J.; Rojas-Cervantes, M. L. *Appl. Surf. Sci*. **2006**, *252*, 6080.
(d) Lee, J. H. *Tetrahedron Lett*. **2005**, *46*, 7329.
23 Kumar, A.; Maurya, R. A. *Tetrahedron* **2007**, *63*, 1946.
24 Debache, A.; Ghalem, W.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett*. **2009**, *50*, 5250.
25 (a) Yadav, L. D. S.; Singh, S.; Rai, V. K. *Green Chem.* **2009**, *11*, 878.
(b) Yadav, L. D. S.; Patel, R.; Srivastava, V. P. *Tetrahedron Lett*. **2009**, *50*, 1335.
(c) Yadav, L. D. S.; Yadav, B. S.; Rai, V. K. *J. Heterocyclic Chem*. **2008**, *45*, 1315.
(d) Yadav, L. D. S.; Rai, A.; Rai, V. K.; Awasthi, C. *Tetrahedron* **2008**, *64*, 1420.
26 (a) Ono, F.; Negoro, R.; Sato, T. *Synlett* **2001**, 1581.
(b) Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *Helv. Chim. Acta* **1991**, *74*, 1102.
(c) Prajapati, D.; Lekhok, K. R.; Sandhu, J. S.; Ghosh, A. C. *J. Chem. Soc., Perkin Trans 1* **1996**, 959.
(d) Laskar, D. D.; Prajapati, D.; Sandhu, J. S. *Synth. Commun*. **2001**, *31*, 1427.
(e) Baruah, P. P.; Gadhwal, S.; Prajapati, D.; Sandhu, J. S. *Chem. Lett*. **2002**, 1038.
(f) Saini, A.; Kumar, S.; Sandhu, J. S. *Synlett* **2006**, 1928.
(g) Mojtahedi, M. M.; Akbarzadeh, E.; Sharifi, R.; Abaee, M. S. *Org. Lett*. **2007**, *9*, 2791.
(h) Maiti, G.; Kundu, P.; Guin, C. *Tetrahedron Lett*. **2003**, *44*, 2757.
(i) Rudrawar, S. *Synlett* **2005**, 1197.
27 Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58.
28 Eynde, J. J. V.; Delfosse, F.; Mayence, A.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 6511.

(E1004084 Cheng, F.; Lu, Z.)

