



Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 11(2), 2015 [059-065]

Micellar dispersion assisted green synthesis of β -enaminones

Pallavi M.More, Madhuri S.Barge, Arjun S.Kumbhar, Satyanarayan M.Arde, Rajashri S.Salunkhe*

Department of Chemistry, Shivaji University, Kolhapur, 416004, M. S., (INDIA)

E-mail : rsschem1@gmail.com

ABSTRACT

An extremely efficient, straightforward and green protocol for the synthesis of β -enaminones has been developed as a consequence of pursuing the emerging routes towards sustainable growth. The green synthesis of β -enaminones was carried out by using natural surfactant solution as a reaction medium. We have employed the aqueous extract of mesocarp of fruit of *Balanites roxburghii* plant which contained natural surfactant as a major component. A variety of β -enamino ketones are synthesized in quantitative yield under the influence of micelles at room temperature. The reaction proceeds effortlessly in a short reaction time with easy product formation and via environmentally benign method with economic benefits.

© 2015 Trade Science Inc. - INDIA

KEYWORDS

Aqueous medium;
Balanites roxburghii;
 β -enaminones;
 Green;
 Micelle;
 Natural surfactant.

INTRODUCTION

Enaminones are enamines of β -dicarbonyl compounds and their chemistry has been extensively reviewed.^[1] These are very resourceful structural motifs synthesized by using numerous methods and used as pharmaceutical drugs with antiepileptic, anticonvulsant,^[2] anti-inflammatory^[3] and antitumor^[4] properties. A series of enaminone derivatives bearing the aniline, benzylamine and various aromatic hydrocarbons such as pyridine, phenothiazines and isoxazole nucleus are renowned potent and orally active class of compounds showing anticonvulsant activity.^[5] In addition these are considered as admirable starting materials in organic synthesis and used as versatile building blocks for the synthesis of important heterocyclic compounds, and naturally occurring alkaloids. They act as very useful intermediates for the synthesis of diverse compounds like aminoesters, α , β -aminoacids, peptides, quinolines and azo compounds and imidazolone derivatives.

^[6,7] Generally β -enaminones are synthesized by condensation of β -dicarbonyl compounds with amines in the presence of various catalysts and reaction conditions such as Bi (TFA)₃ in aqueous medium,^[8] LaCl₃,^[9] InBr₃,^[10] silica supported Fe (HSO₄)₃,^[11] P₂O₅,^[12] and perchloric acid^[13] under solvent free conditions, silver nanoparticles,^[14] and silica sulfuric acid^[15] etc. In regardless of availability of several methods for the synthesis of β -enaminones, some of them are hampered by routine drawbacks like long reaction times, low yields, use of hazardous reagents and solvents, requirement of far-reaching condition, tedious experimental procedure etc.

The phenomenon of dissolution of solid in liquid phase to form a homogeneous system is known as solubility and it is an essential parameter for organic reaction to be initiated. In order to carry out the aqueous mediated organic synthesis, there is necessity to improve solubilization of poor water soluble organic compounds. A range of methodologies are employed for this pur-

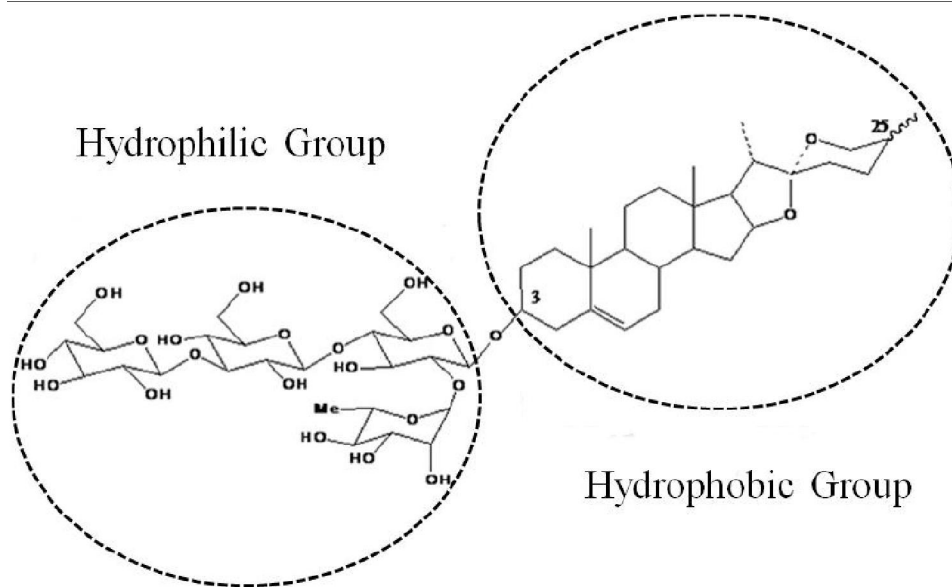


Figure 1 : Balanitiscin A

pose like micellar solubilization, hydrotropy, chemical modification, pH adjustment, micronization, solid dispersion, complexation, co-solvency *etc.* Out of which micellar solubilization by using surfactant (SURFace ACTIVE Agent) was preferred for our study because it is simple, rapid, non-toxic and non-expensive and also organic transformations can be carried out in aqueous medium avoiding use of hazardous volatile organic solvents. It is reported that surfactants enhance the solubility by lowering the surface tension as well as by formation of micelles with hydrophobic tail and hydrophilic head under ambient conditions. The use of micellar surfactant (chemical) as catalyst is widespread and has been investigated in detail for various organic reactions in aqueous solution.^[16]

Recently a good number of research work has been done involving plant material for chemical transformations as well as for synthesis of nanoparticles.^[17,18] Hence we thought of using plant material which is having surfactant contents. Natural surfactant is a surface active agent derived from a natural source which may be of plant origin or animal origin. *Balanites roxburghii* is one of the sources of plant origin which we have employed in the present work and is known by several names such as desert date, Hingota *etc.* It is broadly dispersed in the various arid zones of Asia and Africa.^[19] Its fruits, roots and bark contain steroidal saponins.^[20] Balanitiscin A (Figure 1) is one of the saponins present

in the different parts of *Balanites roxburghii* plant and its structure which consists of hydrophobic group (aglycone part) and hydrophilic group (sugar moiety), was confirmed by D. C. Jain^[21] in the year 1987. The IUPAC name for Balanitiscin A is (25 R and S) - spirost-5-en-3 β -ol; 3-O-[α -L-rhamnopyranosyl(1'2)]-[β -D-glucopyranosyl(1'3)- β -D-glucopyranosyl(1'4)]- β -D-glucopyranoside. Due to chain length of the hydrophobic group, the solubility of substrates is increased while the buffering property *i.e.* ability to resist the pH change on addition of small amount of acid or base is exhibited due to hydrophilic group. *Balanites roxburghii* holds its own importance in the nature because almost every part of the plant is useful to human being. The fruit is used as digestive, anthelmintic, analgesic, antidiarrhetic, to treat ulcers, skin diseases and snakebites. Bark is used as a purgative and also exhibits hepatoprotective activity.^[22]

In continuation with our work dedicated to green chemistry concept, we have developed for the first time a new, highly competent and green method for synthesizing β -enaminones through the reactions of dimedone with variety of amines in aqueous extract of mesocarp of fruit of *Balanites roxburghii* plant. The natural surfactant concurrently acts as a catalyst to promote the reactions and as a surfactant to increase the solubility of organic substrates. To the best of our acquaintance, the application of the present protocol for the synthesis

of β -enaminones has not been investigated so far. The method offers number of advantages such as short reaction times, high yields, mild reaction conditions, simple experimental procedure and use of a cost effective catalyst to boost the solubilization of starting materials. The present protocol is totally free from hazardous chemical reagents as well as organic solvents which are waste producing elements.

EXPERIMENTAL

Materials

All commercial reagents were used as received without purification. The reaction was monitored by Thin Layer Chromatography using 0.25 mm Merck silica gel 60 F₂₅₄ precoated plates, which were visualized with UV light. Melting points were recorded in open capillaries. The IR spectra were recorded on Perkin-Elmer FT-IR spectrometer using KBr discs. The ¹H NMR and ¹³C NMR were recorded on Bruker Avon spectrometer at 300 and 75 MHz respectively. Chemical shifts are reported in ppm downfield from TMS as an internal standard; coupling constants *J* are given in Hertz. LCMS analyses were carried out on Q-exactiveThermoscientific LCMS instrument.

Methods

(1) General procedure for the preparation of aqueous extract of mesocarp of fruit of *Balanites roxburghii* plant

Dried fruits of *Balanites roxburghii* plant were purchased from local market and authenticated from Department of Botany, Shivaji University, Kolhapur-416004 (India). Aqueous extract of fruits was prepared by soaking 3-4 g powder of mesocarp of fruit in 100 mL distilled water for twelve hours. The material was smashed and then the resultant solution was filtered through Whatman filter paper No. 42. The wine red coloured filtrate was used as the biocatalyst *i.e.* aqueous extract of mesocarp of fruit of *Balanites roxburghii* plant. It was stored below 5 °C and its activity remained unaffected for more than three months.

(2) General procedure for the synthesis of β -enaminone derivatives:

A mixture of dimedone (0.140 g, 1mmol), amine

(1mmol) and 5 mL of diluted aqueous extract of *Balanites roxburghii* plant was stirred at room temperature for the felicitous time till the completion of reaction as monitored by Thin Layer Chromatography (Pet ether: Ethyl acetate, 8:2). The product was filtered, washed with distilled water, dried and recrystallized from ethyl alcohol.

Spectral data of synthesized compounds

3-phenylamino-5,5-dimethylcyclohexen-2-enone (TABLE 2, entry 1)

Pale yellow solid; m.p. 184 °C; FT-IR (KBr): ν cm⁻¹ = 3233, 2943, 1594, 1542, 1268, 707; ¹H NMR (TMS, 300 MHz, CDCl₃): δ = 1.082 (s, 6H), 2.175 (s, 2H), 2.358 (s, 2H), 5.548 (s, 1H), 7.110 (d, 3H), 7.265 (t, 2H), 7.407 (s, 1H) ppm; ¹³C NMR (TMS, 75 MHz, CDCl₃): δ = 28.3, 32.7, 43.3, 50.1, 98.2, 123.7, 125.3, 129.2, 138.3, 160.7, 197.0 ppm.

3-(4-chlorophenylamino)-5,5-dimethylcyclohexen-2-enone (TABLE 2, entry 2)

Off white solid; m.p. 218 °C; FT-IR (KBr): ν cm⁻¹ = 3257, 2953, 1595, 1563, 1274, 727; ¹H NMR (TMS, 300 MHz, CDCl₃): δ = 1.091 (s, 6H), 2.211 (s, 2H), 2.380 (s, 2H), 5.514 (s, 1H), 7.078 (d, 2H, *J* = 8.7Hz), 7.264 (t, 2H, *J* = 4.8Hz), 7.5 (brs, 1H) ppm; ¹³C NMR (TMS, 75 MHz, CDCl₃): δ = 28.2, 32.8, 43.2, 49.8, 98.3, 125.1, 129.4, 136.4, 136.7, 161.9, 197.4 ppm.

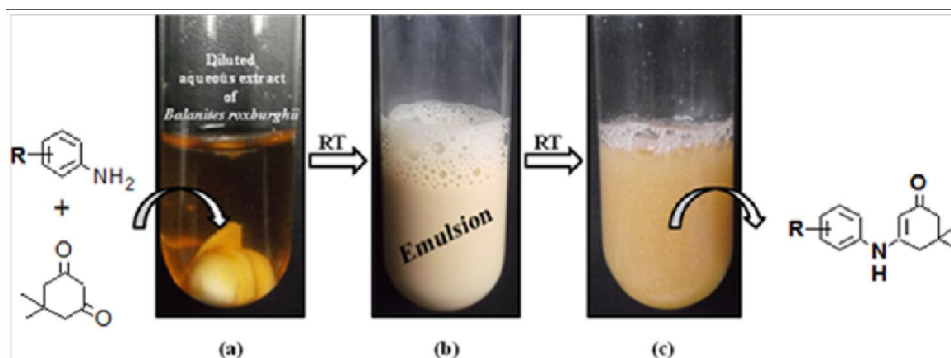
4-[(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino]benzoic acid (TABLE 2, entry 5)

White solid; m.p. 316 °C; FT-IR (KBr): ν cm⁻¹ = 3237, 3177, 2961, 1704, 1610, 1578, 1264, 706; ¹H NMR (TMS, 300 MHz, d₆-DMSO): δ = 1.091(s, 6H), 2.081 (s, 2H), 2.344 (s, 2H), 5.584 (s, 1H), 7.170 (d, 2H, *J* = 8.7 Hz), 7.850 (d, 2H, *J* = 8.7 Hz), 8.881 (s, 1H), 11.281 (s, 1H) ppm; ¹³C NMR (TMS, 75 MHz, d₆-DMSO): δ = 28.3, 32.6, 42.7, 50.3, 99.2, 121.4, 126.0, 130.8, 143.7, 159.7, 167.4, 197.4 ppm; LCMS: 259.90.

3-(3-chlorophenylamino)-5,5-dimethylcyclohex-2-enone (TABLE 2, entry 7):

Cream solid; m.p. 154 °C; FT-IR (KBr): ν cm⁻¹ = 3181, 2962, 1598, 1530, 1258, 729; ¹H NMR (TMS, 300 MHz, CDCl₃): δ = 1.091(s, 6H), 2.196

Full Paper



Scheme 1 : Micelle Assisted Synthesis of β -enaminones in aqueous extract of *Balanites roxburghii*; (a) at the start of reaction; (b) after emulsion formation and (c) at the end of reaction.

(s, 2H), 2.373 (s, 2H), 5.560 (s, 1H), 7.135 (m, 3H), 7.221 (t, 1H), 7.641 (s, 1H) ppm; ^{13}C NMR (TMS, 75 MHz, CDCl_3): δ = 28.3, 32.8, 50.1, 98.7, 121.6, 123.6, 125.3, 130.1, 134.9, 139.7, 160.6, 197.7 ppm; LCMS: 249.96.

3-(3-hydroxyphenylamino)-5,5-dimethylcyclohex-2-enone (TABLE 2, entry 9)

Light brown solid; m.p. 244 °C; FT-IR (KBr): ν cm^{-1} = 3302, 2813, 2685, 1599, 1507, 1269, 703; ^1H NMR (TMS, 300 MHz, d_6 -DMSO): δ = 1.041 (s, 6H), 2.055 (s, 2H), 2.321 (s, 2H), 5.444 (s, 1H), 6.472 (dd, 2H), 6.598 (d, 1H), 7.043 (t, 1H), 7.379 (s, 1H), 9.208 (s, 1H) ppm; ^{13}C NMR (TMS, 75 MHz, d_6 -DMSO): δ = 28.4, 32.6, 42.7, 50.3, 97.5, 110.4, 113.9, 129.7, 140.2, 158.3, 161.0, 196.0 ppm; LCMS: 232.05.

RESULTS AND DISCUSSION

Natural surfactant played a significant role in synthesis of β -enaminones in water. The proper workout of the reaction was planned in order to study the versatility of the natural surfactant. Initially a model reaction was carried out between aniline and dimedone by using 5 mL of wine red coloured aqueous extract of mesocarp of fruit of *Balanites roxburghii* plant at room temperature. The reaction mixture became turbid white in colour indicating emulsion formation which turned into a pale yellow coloured solution after completion of reaction. It was observed that it required short reaction time with excellent yield. Further the reaction was carried out by using 5 mL diluted aqueous extract which was almost colourless (Scheme 1). Surprisingly we

TABLE 1 : Effect of different surfactants on synthesis of β -enaminones^a

Entry	Chemical Surfactant	Amount	Time (h)	Yield ^b (%)	Price/100 g (INR)
1	CTAB	10 mol %	10	47	792
2	SDS	10 mol %	10	65	1,759
3	Triton X 100	10 mol %	10	27	542
4	Tween 80	10 mol %	10	30	565
5	Natural Surfactant	Diluted solution	15min	85	40

^aReaction conditions- Aniline (0.09 mL, 1mmol) and dimedone (0.140 g, 1mmol) in diluted catalytic solution (5 mL) at room temperature for 15 min

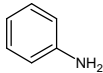
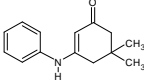
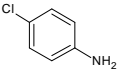
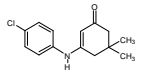
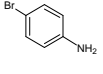
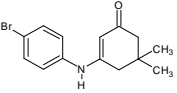
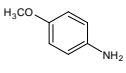
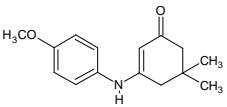
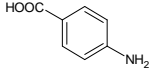
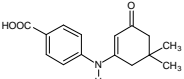
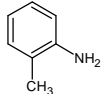
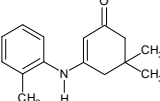

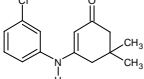
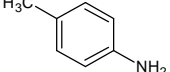
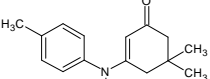

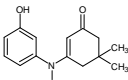
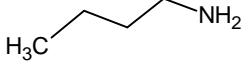
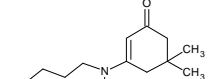
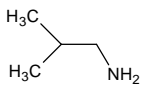
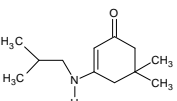
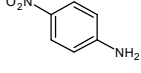
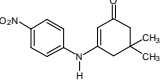

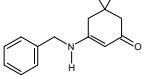

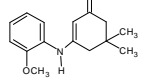
^bIsolated yields after purification.

found that the yield of the product and pH (4.85) of the catalytic solution remain unaffected even after dilution. This indicates that our natural surfactant exhibits buffering action because of which the reaction proceeds in excellent mode shifting the present protocol progressively towards green approach. In control experiment, there was no product formation in the absence of natural surfactant even after prolonged reaction time (12h).

To evaluate the efficiency of natural surfactant, we compared the effect of different chemical surfactants on the model reaction as shown in TABLE 1. From the results it is revealed that the natural surfactant is more effectual in terms of reaction time, catalytic activity and yield of the product. The cost efficiency of the present protocol can be explained by comparing the prices (Indian Rupees *i.e.* INR) of chemical surfactants (Alfa Aesar) with that of natural surfactant.

To study the generality of the natural surfactant,

TABLE 2 : Synthesis of β -enaminone derivatives by using aqueous extract of mesocarp of fruits of *Balanites roxburghii* plant as a natural surfactant^a

Entry	Amines	Product	Time (min.)	Yield ^b %	M.P. °C [Lit.] ^c
1			15	85	184-186 [184-185] ¹⁶
2			10	90	188-190 [190-192] ¹¹
3			10	88	222-224 [219-220] ¹²
4			10	90	188-190 [192-194] ¹⁶
5			20	80	314-316
6			20	86	110-112 [108-110] ¹³
7			10	90	154-156
8			15	88	198-200 [195-196] ¹¹
9			25	90	244-246
10			20	84	114-116 [117-119] ¹⁶
11			20	86	110-112 [113-115] ¹³
12			30	82	190-192 [193-195] ¹³
13			20	86	120-122 [124-126] ¹⁶
14			10	86	130-132 [126-128] ¹⁶

^aReaction conditions- Aniline (0.09 mL, 1mmol) and dimedone (0.140 g, 1mmol) in diluted catalytic solution (5 mL) at room temperature for 15 min.

^b Isolated yields. ^c Literature values in parentheses.

Full Paper

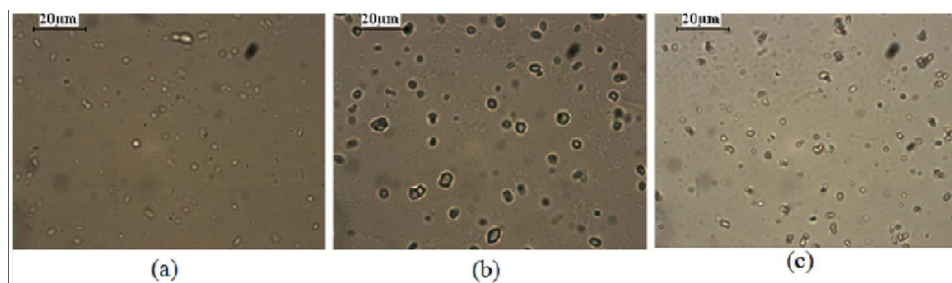


Figure 2 : Optical micrographs of the reaction mixture of aniline with dimedone in the presence of natural surfactant at room temperature; (a) at the start of the reaction; (b) after emulsion formation and (c) at the end of reaction.

we selected a variety of structurally different amines including aliphatic and aromatic amines for condensation with dimedone. The results are summarized in TABLE 2. Newly synthesized (TABLE 2, entries 5, 7 and 9) and some reported (TABLE 2, entry 1 and 2) products were characterized by IR, ^1H NMR, ^{13}C NMR, and LCMS analyses.

The results showed that the amines containing electron donating groups (TABLE 2, entries 2, 3, 4, 8 and 9) gave better yield within shorter reaction time as compared to amines containing electron withdrawing groups (TABLE 2, entries 5 and 12) and this is attributed to the availability of lone pair on Nitrogen. The reaction goes in forward direction due to acidic pH (4.85) of the aqueous extract and formation of micelles.

Formation of micelle is indicated by turbid emulsion on stirring the reaction mixture for few minutes. Optical micrograph (Figure 2) of the reaction mixture after turbidity is used to confirm the formation of spherical droplets in water. This Figure 2 clarifies that amine and dimedone, both being hydrophobic, are forced within the hydrophobic core of micelle due to which reaction is promoted appreciably in forward direction with removal of water molecule.

Reusability of the catalyst is the most momentous factor as far as green chemistry approach is considered. The natural surfactant can be reused for number of subsequent reactions with the identical starting materials without any further treatment with no change in yield of the products.

CONCLUSIONS

In conclusion, we have developed a new, highly competent and green method in which aqueous extract of mesocarp of fruit of *Balanites roxburghii*

plant is explored as the green source. The results presented in this work demonstrated a novel, very mild and efficient method which offers several merits including mild reaction conditions, enhanced reaction rates, clean reaction profile, small quantity of inexpensive and biodegradable catalyst, operational and experimental simplicity. A simple procedure combined with low toxicity and reusability of the catalyst; make this protocol an economic and waste-free green process for the synthesis of biologically active β -enaminone in pharmaceutical industry.

ACKNOWLEDGEMENT

We gratefully acknowledge the financial support from the Department of Science Technology and University Grants Commission, New Delhi, India for FIST and SAP respectively. One of the authors Pallavi More thanks the Department of Science Technology, New Delhi, India for the award of PURSE fellowship.

REFERENCES

- [1] J.V.Greenhill; Chem. Soc. Rev., 277 (1977).
- [2] (a) B.Malawska; Curr. Top. Med. Chem., 69 (2005); (b) N.D.Eddington, D.S.Cox, R.R.Roberts, R.J.Butcher, I.O.Edafiogho, J.P.Stables, N.Cooke, A.M.Goodwin, C.A.Smith, K.R.Scott; Eur. J. Med. Chem., 635 (2002).
- [3] A.El-Hashim, S.Yousefi, I.Edafiogho, R.Raghu-pathy, M.Yousif, H-U Simon; Eur. J. Pharmacol., 73, (2010).
- [4] A.S.Shawali, T.A.Farghaly, A.R.Al-Dahshoury, Arkivoc, 88 (2009).
- [5] (a) J.C.Garro, M.P.R.Duchowicz, M.R.Estrada, G.N.Zamarbide, E.A.Castro; Int. J. Mol. Sci., 9354 (2011); (b) K.R.Scott, I.O.Edafiogho, E.L.Richardson, V.A.Farrar, J.A.Moore, E.I.Tietz,

- C.N. Hinko, H.Chang, M.El-Assadi, J.M.Nicholson; *J. Med. Chem.*, 1947 (1993).
- [6] M.Zhang, A.Abdukader, Y.Fu, C.Zhu; *Molecules*, 2812 (2012).
- [7] J.Bezensek, U.Groselj, K.Stare, J.Svete, B.Stanovnik; *Tetrahedron*, 516 (2012).
- [8] A.R.Khosropour, M.M.Khodaei, M.Kookha-zadeh; *Tetrahedron Lett.*, 1725 (2004).
- [9] R.Lenin, R.M.Raju; *Arkivoc*, 204 (2007).
- [10] Z.H.Zhang, L. Yin, Y.Wang; *Adv. Synth. Catal.*, 184 (2006).
- [11] H.Ishghi, S.M.Sayedi, E.Safaei, M.Vakili, A.Farhadipour, M.Bayat-Mokhtari; *J. Mol. Cat. A: Chem.*, 430, (2012).
- [12] M.R.Mohammadizadeh, A.Hasaninejad, M.Bahramzadeh, Z.S.Khanjalow; *Syn. Comm.*, 1152 (2009).
- [13] B.Das, K.Venkateswarlu, A.Majhi, M.R.Reddy, K.N.Reddy, Y.K.Rao, K.Ravikumar, B.Sridhar; *J. Mol. Cat. A: Chem.*, 276 (2006).
- [14] K.D.Bhatte, P.J.Tambade, K.P.Dhake, B.M.Bhannage; *Catal. Commun.*, 1233 (2010).
- [15] A.Hasaninejad, A.Zare, M.R.Mohammadizadeh, M.Shekouhy, A.R.Moosavi-Zare; *E-J. Chem.*, 1546 (2010).
- [16] (a)K.Bahrami, M.M.Khodaei, A.Nejati, *Green Chem.*, 1237 (2010); (b) K.Manabe, X.M.Sun, S.Kobayashi; *J. Am. Chem. Soc.*, 10101 (2001).
- [17] (a)A.M.Fonseca, F.J.Q.Monte, M.da Concei, F.de Oliveira, M.C.de Mattos, G.A.Cordell, R.Braz-Filho, T.L.G.Lemos, *J. Mol. Cat. B: Enzym.*, 78 (2009); (b)A.Mironowicz, *Phytochemistry*, 1531 (1998); (c)J.S.Yadav, P.T.Reddy, S.Nanda, A.B.Rao; *Tetrahedron: Asymmetry*, 3381 (2001); (d)L.H. Andrade, R.S.Utsunomiya, A.T.Omori, A.L.M.Porto, J.V.Comasseto, *J. Mol. Cat. B: Enzym.*, 84 (2006).
- [18] (a)V.Kumar, S.K.Yadav; *J. Chem. Technol. Biotechnol.*, 151 (2009); (b) A.K.Mondal, S.Mondal (Parui), S.Samanta, S.Mallick; *Adv. Biores.*, 122 (2011); (c)A.Saxena, R.M.Tripathi, R.P.Singh; *Dig. J. Nanomater. Bios.*, 427 (2010).
- [19] V.N.Deshmukh; *Int. J. of Universal Pharmacy and Life Sciences*, 318 (2011).
- [20] S.B.Mahato, A.N.Ganguly, N.P.Sahu; *Phytochemistry*, 959 (1982).
- [21] D.C.Jain; *Phytochemistry*, 2223 (1987).
- [22] B.Jaiprakash, A.Rajkumar, R.V.Karadi, R.V.Sa-vadi, V.L.Hukkeri; *J. Natural Remedies*, 205 (2003).