Asian Journal of Chemistry; Vol. 25, No. 12 (2013), 6545-6549

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.14353

$Bi(NO_3)_3 \cdot 5H_2O$: An Efficient and Green Catalyst for Synthesis of 1,5-Benzodiazepines and β-Amino Carbonyl Compounds

JASPREET KAUR RAJPUT* and GAGANDEEP KAUR

Department of Chemistry, Dr. B.R. Ambedkar National Institute of Technology, Jalandhar-144 011, India

*Corresponding author: E-mail: rajputj@nitj.ac.in; gagandeepnit@gmail.com

(*Received*: 20 July 2012; *Accepted*: 20 May 2013) AJC-13518

Bismuth nitrate pentahydrate is found to be an efficient catalyst for the synthesis of 1,5-benzodiazepines and β-amino carbonyl compounds using condensation of *o*-phenylenediamine with ketones and one pot three component Mannich reaction, respectively under solvent free conditions at room temperature. This method offers a simple, solvent free, room temperature, environment friendly synthesis of 1,5-benzodiazepines and β-amino carbonyl compounds. The products are isolated by column chromatography and recrystallization, respectively and were characterized by their melting point, IR and ^{1}H NMR spectroscopy.

Key Words: 1,5-Benzodiazepines, β-Amino carbonyl compounds, $Bi(NO_3)_3 \cdot 5H_2O$, Solvent free conditions.

INTRODUCTION

The development of solvent free organic synthesis has become important research area, aiming to make the synthesis simpler, to prevent hazardous solvent waste, to save energy and toxicity in chemical processes. Many organic solvents are ecologically harmful and their use should be minimized as far as possible or should be avoided altogether[1,2].

Benzodiazepines are very important biologically active compounds as these are used as anticonvulsant, antianxiety, antiinflammatory, analgesic, hypnotic, antidepressive and sedative agents[3]. Inspite of their biological importance, benzodiazepines have application in industries such as dyes for acrylic fibres in photography[4]. Additionally, 1,5-benzodiazepines are useful synthons for the preparation of other fused ring compounds such as triazolo-[5-7], oxadiazolo-[8-10], oxazino[11] and furano-benzodiazepines[12]. Mannich reaction is important in carbon-carbon bond forming reaction in organic synthesis[13-15], as it provides β-amino carbonyl compounds which are important synthetic intermediates for various nitrogen containing natural products and pharmaceutical[16,17]. The increasing popularity of Mannich reaction has been fuelled by the ubiquitous nature of nitrogen-containing compounds in drugs and natural products[18].

1,5-Benzodiazepines are prepared by condensation reaction of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds[19], β-haloketones[20], β-diketones[21], chalcones[22] or ketones using variety of catalysts such as $BF_3 \cdot OEt_2$[23], $NaBH_4$[24], Al_2O_3-P_2O_5 under microwave[25], HOAc microwave[26], $InBr_3$[27], $FeCl_3$[28], zeolite[29], $Sc(OTf)_3$[30], ceric ammonium nitrate[31], ionic liquid[32], kaolin[33], $NbCl_5$[34], keggin hetropolyacids[35]. Whereas the synthesis of β-amino carbonyl compounds involves the three-component one pot reaction using aromatic aldehydes, aromatic ketones and aromatic amines. Several methods have been reported in the literature and few catalysts, including conc. HCl[36], $NbCl_5$[37], $Al(CH_3SO_3)_3 \cdot 4H_2O$[38], dodecylbenzenesulfonic acid[39], $SnCl_2$[40], ionic liquid[41], $InCl_3$[42] and polymer-support sulphonic acid[43], GuHCl[44], Me_2SBr_2[45] *etc.*, have been developed. However, most of these methods suffer from disadvantages such as strong acids or expensive catalysts, longer reaction time, elevated reaction temperature, toxic reagents, low yield. Hence there is an increasing interest in developing environmentally benign reactions and atom-economic catalytic processes for the synthesis of 1,5-benzodiazepines and β-amino carbonyl compounds.

Recently, bismuth(III) salts are used as Lewis acid catalysts[46-49] in organic synthesis because of low cost, easy handling and friendly ecological behaviour. In continuation to our work on green synthesis[50] we report a rapid synthesis of 1,5-benzodiazepines and β-amino carbonyl compounds in presence of $Bi(NO_3)_3 \cdot 5H_2O$ because it is non-toxic, cheaper, easy available and stable in air.

EXPERIMENTAL

Melting points were recorded on gallen kamp apparatus and are uncorrected. ^{1}H NMR (400 MHz) spectra were determined with a Brucker Advance 400 spectrometer ($CDCl_3$) using tetramethylsilane (TMS) as internal standard. Infrared spectra

(cm^{-1}) were measured with Perkin Elmer spectrometer. All reactions were carried out using reagent-grade solvents and the reagents were purchased from local suppliers.

General procedure for synthesis of 1,5-benzodiazepines: To a mixture of *o*-phenylenediamine (1 mmol) and ketone (2.2 mmol), catalyst Bi $(NO_3)_3 \cdot 5H_2O$ (0.05 mmol or 5 mol %) was added and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After the completion of reaction catalyst was removed by filtration and then reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give crude product. Then crude product was purified by silica gel columm chromatography using hexane:ethyl acetate as an eluent to afford the desired compound in pure form.

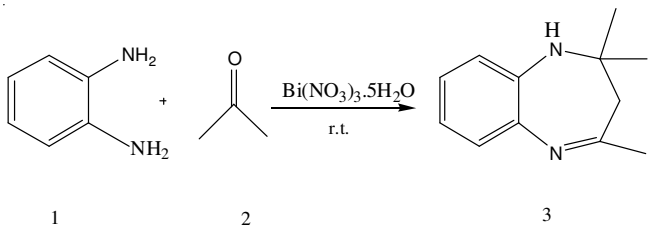
General procedure for synthesis of β-amino carbonyl compounds: To the mixture of acetophenone (1 mmol), aldehyde (1 mmol) and aniline (1 mmol) catalyst $Bi(NO_3)_3 \cdot 5H_2O$ (0.1 mmol or 10 mol %) was added and the mixture was stirred at room temperature until the completion of reaction as indicated by TLC. The catalyst was removed by filtration. Then the resulting mixture was washed with water. The crude product was purified by recrystallization from ethanol to give corresponding pure compound.

2,2,4-Trimethyl -2,3-dihydro-1*H*-1,5-benzodiazepines (3a): m.p. 135-137 ºC, IR (KBr, ν_{max}, cm^{-1}): 3293.3, 1632.3, ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm (*J*, Hz): 1.34 (6H, s); 2.25 (2H, s); 2.36 (3H, s); 2.95 (1H, NH, br, s); 6.71-7.14 (4H, m).

1, 3-Diphenyl-3-(phenylamino) propan-1-one (4a): m.p. 142-143 ºC, IR (KBr, ν_{max}, cm^{-1}) : 3384.8, 2917.8, 1671, 1291.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ: ppm (*J*, Hz): 357-3.58 (d, 2H), 5.01- 5.042 (m, 1H), 6.64-6.66 (d, 2H), 6.74 (t, 1H), 7.10-7.60 (m, 10H), 7.91-7.92 (d, 2H).

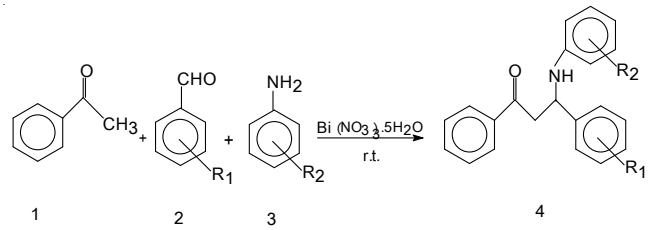
RESULTS AND DISCUSSION

In this paper we report a facile, efficient and practical method for the synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamine with ketones and β-amino carbonyl compounds by one pot three component reaction of aromatic aldehydes, aromatic ketones and aromatic amines using $Bi(NO_3)_3 \cdot 5H_2O$ as catalyst (**Schemes I** and **II**).



Scheme-I: Synthesis of 1,5-benzodiazepines using $Bi(NO_3)_3 \cdot 5H_2O$ as a catalyst at room temperature under solvent free conditions

Initially, the optimized reaction conditions were screened by conducting the reaction with different catalyst amount at room temperature for the preparation of 1,5-benzodiazepines (Table-1, Fig. 1). At first stage, reaction was investigated with *o*-phenylenediamine, acetone and $Bi(NO_3)_3 \cdot 5H_2O$ (5 mol %) under solvent free conditions at room temperature. The reaction occurred in 15 min and product was obtained in 85 % yield.



Scheme-II: Synthesis of β-amino carbonyl compounds using $Bi(NO_3)_3 \cdot 5H_2O$ as a catalyst at room temperature under solvent free conditions

TABLE-1
EFFECT OF THE AMOUNT OF THE CATALYST ON THE YIELD OF 1,5-BENZODIAZEPINES AND β-AMINO CARBONYL COMPOUNDS

Entry	Amount of catalyst (mmol or mol %)	Yield (%)	
		1, 5-Benzodiazepines	β-Amino carbonyl compounds
1	2	65	65
2	5	92	75
3	7	85	80
4	10	83	85
5	12	81	79

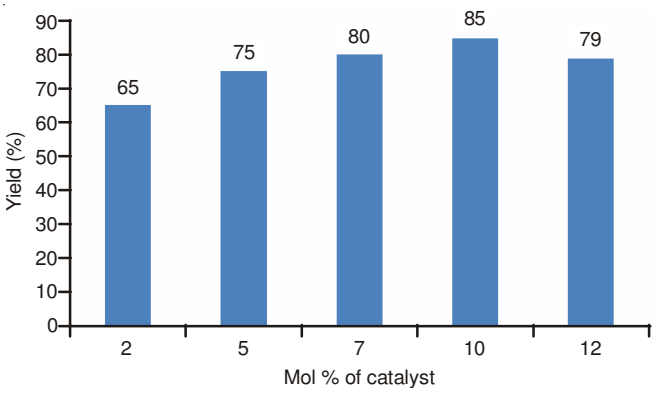


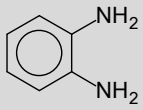
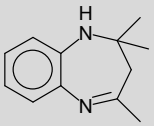
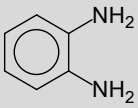
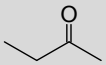
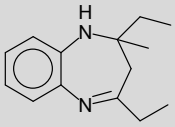
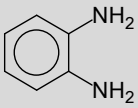
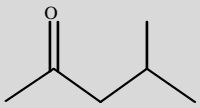
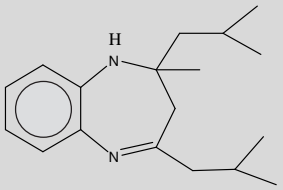
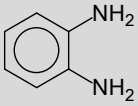
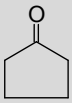
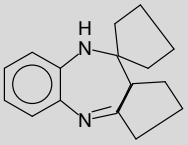
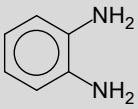
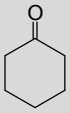
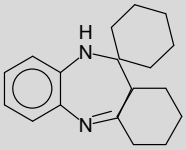
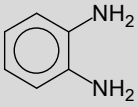
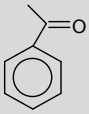
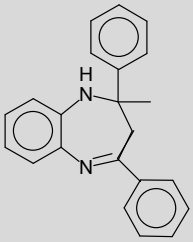
Fig. 1. Effect of amount of catalyst on the yield of 1,5-benzodiazepines

Further the optimized amount of catalyst was screened by taking *o*-phenylenediamine and acetone as model reactants. Using less amount of catalyst *i.e.*, 2 and 4 mol % resulted in the decrease of yield and by increasing the amount of catalyst up to 12 mol % did not improve the yield. However in the absence of catalyst the reaction did not proceed. It was found that reaction occurs in short time producing high yields of products. Further it was screened that 5 mol % of catalyst is sufficient for carrying out the synthesis of 1,5-benzodiazepines. An increase in the amount of catalyst did not improve the yield.

To show the feasibility of reaction method the reaction was explored by carrying out the reaction using various substrates (Table-2) with optimized amount of catalyst at room temperature under solvent free conditions. Both the acyclic and cyclic ketones gave excellent yields of products. It was observed that both primary and secondary ketones such as methyl ethyl ketones and methyl *iso*-butyl ketones were reacted and less hindered primary ketone is involved in cyclisation to give the product. The products are formed successfully under ambient condition within 10-30 min.

The efficiency of the present method and catalytic activity of catalyst was compared with the reported procedures and

TABLE-2
$Bi(NO_3)_3·5H_2O$ CATALYZED SYNTHESIS OF 1,5-BENZODIAZEPINES USING *o*-PHENYLENEDIAMINE AND VARIOUS KETONES AT ROOM TEMPERATURE

S. No.	Diamine	Ketone	Product	Time (min)	Yield (%)	m.p. (ºC) observed	m.p. (ºC) reported
a				15	92	134-136	137-139
b				15	80	135-137	137-139
c				25	79	117-119	118-120
d				14	83	135-138	137-139
e				5	87	134-136	138-139
f				25	90	110-111	107-109

catalysts. Condensation of *o*-phenylenediamine with acetone afforded 96 % yield after 3 h at 50 ºC in hexane in the presence of $NbCl_5$ (5 mol %)[34]. Kaolin[33] catalysed condensation of *o*-phenylenediamine with acetone gave 90 % yield in dichloroethane after 3 h. While in case of $Sc(OTf)_3$ (5 mol %)[30], reaction proceeded in 3 h at room temperature afforded 96 % yield. The reaction in presence of $InBr_3$[27] provided the 96 % yield in 0.5 h. Compared to above methods and catalysts $Bi(NO_3)_3·5H_2O$ catalyzed condensation of *o*-phenylenediamine with acetone gave 92 % yield in 15 min at room temperature under solvent free conditions.

After the successful application of $Bi(NO_3)_3·5H_2O$ as catalyst in the synthesis of 1,5-benzodiazepines, we tried to explore its activity in synthesis of β-amino carbonyl compounds using various aromatic aldehydes, aromatic ketones and aromatic amines at room temperature under solvent free conditions.

In this reaction, optimization of amount of catalyst was also screened (Table-1, Fig. 2). The yield of the product was poor with low amount of catalyst and there was gradual increase in the yield of product with increase in amount of catalyst. Maximum yield was obtained when the 10 mol % of catalyst was used. Further increase of catalyst did not improve the yield.

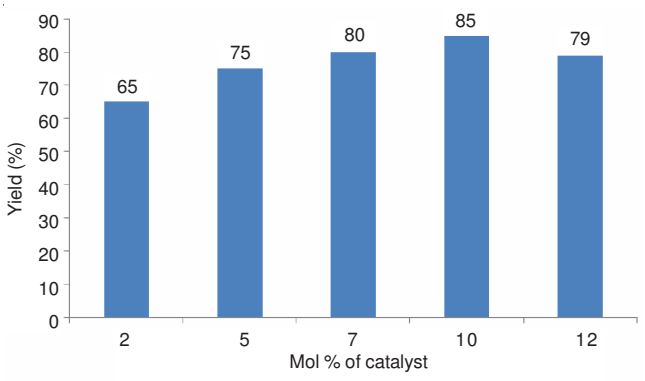


Fig. 2. Effect of amount of catalyst on the yield of β-amino carbonyl compounds

TABLE-3
$Bi(NO_3)_3·5H_2O$ CATALYZED SYNTHESIS OF β-AMINO CARBONYL COMPOUNDS USING AROMATIC KETONE, SUBSTITUTED AROMATIC ALDEHYDES AND SUBSTITUTED AROMATIC AMINES AT ROOM TEMPERATURE

Entry	R_1	R_2	Product	Time (min)	Yield (%)	m.p. (ºC) (observed)	Ref. m.p. (ºC) (reported)
1	H	H	**4a**	30	85	142-144	143-144
2	H	4-NO_2	**4b**	60	61	180-182	184-186
3	H	4-Cl	**4c**	45	78	168-170	170-171
4	H	4-OCH_3	**4d**	90	74	119-121	124-125
5	H	4-F	**4e**	20	64	158-160	162-163
6	H	2-CH_3	**4f**	360	Trace	–	–
7	H	3-CH_3	**4g**	30	76	129–130	131-132
8	H	2-OCH_3	**4h**	300	Trace	–	–
9	H	2-Cl	**4i**	120	43	112-114	–
10	H	2-NO_2	**4j**	180	48	101-103	–
11	4-OCH_3	H	**4k**	105	72	142-145	147–149
12	4-OCH_3	4-Cl	**4l**	25	62	155-156	158-160
13	4-OCH_3	4-OCH_3	**4m**	10	62	145-146	–
15	4-OCH_3	2-Cl	**4o**	360	Trace	–	–
16	4-OCH_3	2-NO_2	**4p**	420	Trace	–	–
17	4-OCH_3	2-CH_3	**4q**	450	Trace	–	–
18	4-Cl	H	**4r**	60	64	110-111	114-115
19	4-Cl	4-Cl	**4s**	90	69	115-116	118-119

A series of β-amino carbonyl compounds were prepared from various aromatic aldehydes, aromatic ketones and aromatic amines (Table-3). The scope of the reaction was examined by reacting various substituted aldehydes and substituted amines. All the reactions proceeded well in the presence of $Bi(NO_3)_3·5H_2O$ (10 mol %) at room temperature to give corresponding products in moderate to good yields. It was observed that the substituted aldehydes with electon-withdrawing (-Cl) and electron-donating (-OCH_3) groups gave good results. Further it was seen that the substituted amines with both electon-withdrawing and electron-donating groups at the *meta* and *para* positions gave the product in good yields, but the *ortho* substituted amines gave very low or trace amount of yield.

To check the efficiency of the present method it was compared with the reported methods. The Mannich reaction of benzaldehyde, acetophenone and aniline afforded 83 % yield after 12 h at 25 ºC in the presence of ionic liquid (2.5 g)[41] and 86 % yield after 8 h in ethanol using $Al(CH_3SO_3)_3·4H_2O$ (5 mol %)[38] $SnCl_2$[40] catalyzed reaction (93 % yield in ethanol in 10 h), GuHCl, (10 mol %)[44] as catalyst (80 % yield in 4 h) and Me_2SBr_2[45] (80 % yield in 3 h). But by using $Bi(NO_3)_3·5H_2O$, β-amino carbonyl compounds was obtained in 87 % yield after 0.5 h at room temperature in solvent free conditions.

Conclusion

We have demonstrated the simple, an efficient and green synthesis of biologically active 1,5-benzodiazepines and β-amino carbonyl compounds using an efficient catalyst $Bi(NO_3)_3·5H_2O$ at room temperature in solvent free conditions. The present protocol has attractive features such as: (a) simple procedure; (b) cheap, non-toxic, oxygen and moisture tolerant catalyst; (c) solvent free synthesis; (d) shorter reaction time; (e) high yielding of products; (f) environment friendly method. The 1,5-benzodiazepines and β-amino carbonyl compounds are smoothly obtained in mild conditions.

ACKNOWLEDGEMENTS

The authors are thankful to SAIF (Panjab University, Chandigarh for NMR and IR. One of the authors (G.K.) is thankful to MHRD and NIT Jalandhar for giving the fellowship.

REFERENCES

1. K. Tanaka and F. Toda, *Chem. Rev*., **100**, 1025 (2000).
2. S. Bhagat and A.K. Chakraborti, *J. Org. Chem*., **72**, 1263 (2007).
3. J.K. Landquist, A.R. Katritzky and C.W. Ress, In Comprehensive Heterocyclic Chemistry, Pergamon: Oxford (1984); (b) L.O. Randall, B. Kappel and E. Mussini, Benzodiazepines, Raven Press: New York (1973).
4. R.C. Harries and J.M. Straley, Cationic Polymethine Dyes for Acrylic Fibers, US Patent 1,537,757 (1968); *Chem. Abstr.*, **73**, 100054w (1970).
5. M. Essaber, A. Baouid, A. Hasnaoui, A. Benharref and J.P. Lavergne, *Synth. Commun*., **28**, 4097 (1998).
6. N. Bennamane, R. Kaoua, L. Hammal and B. Nedjar-Kolli, *Org. Commun*., **1**, 62 (2008).
7. A. Boudina, A. Baouid, A. Hasnaoui and M. Essaber, *Synth. Commun*., **36**, 573 (2006).
8. J.X. Xu, H.T. Wu and S. Jin, *Chin. J. Chem*., **17**, 84 (1999).
9. X.Y. Zhang, J.X. Xu and S. Jin, *Chin. J. Chem*., **17**, 404 (1999).
10. K. Nabih, A. Baouid, A. Hasnaoui and A. Kenz, *Synth. Commun*., **34**, 3565 (2004).
11. A.M. El-Sayed, H. Abdel-Ghany and A.M.M. El-Saghier, *Synth. Commun*., **29**, 3561 (1999).
12. K.V.V. Reddy, P.S. Rao and D. Ashok, *Synth. Commun*., **30**, 1825 (2000).
13. M. Arend, B. Westermann and N. Risch, *Angew. Chem. Int. Ed*., **37**, 1044 (1998).
14. S. Kobayashi and H. Ishitani, *Chem. Rev*., **99**, 1069 (1999).
15. M.M.B. Marques, *Angew. Chem. Int. Ed*., **45**, 348 (2006).
16. R. Muller, H. Goesmann and H. Waldmann, *Angew. Chem. Int. Ed*., **38**, 184 (1999).
17. H. Bohme and M. Haake, In ed.: E.C. Taylor, Advances in Organic Chemistry, John Wiley and Sons, New York, p. 107 (1976).
18. W. Notz, F. Tanka, S.I. Watanable, N.S. Chowdari, J.M. Turner, R. Thayumanavan and C.F. Barbas, *J. Org. Chem*., **68**, 25 (2003).
19. P. Stahlofen and W. Ried, *Chem. Ber*., **90**, 815 (1957).
20. W. Ried and E. Torinus, *Chem. Ber*., **92**, 2902 (1959).
21. C. Gallardo, A. Trujillo, M. Fuentealba, A. Vega, D. Carrillo and C. Manzur, *J. Chilean Chem. Soc*., **52**, 1266 (2007).
22. M. Kodomari, T. Noguchi and T. Aoyama, *Synth. Commun*., **34**, 1783 (2004).

23. J.A. Herbert and H. Suschitzky *J. Chem. Soc., Perkin Trans I*, 2657 (1974).
24. H.R. Morales, A. Bulbarela and R. Contreras, *Heterocycles*, **24**, 135 (1986).
25. B. Kaboadin and K. Navaee, *Heterocycles*, **55**, 1443 (2001).
26. M. Pozarentzi, J.S. Stephanatou and C.A. Tsoleridis, *Tetrahedron Lett*., **43**, 1755 (2002).
27. J.S. Yadav, B.V.S. Reddy, S.P. Kumar and K. Nagaiah, *Synthesis*, 480 (2005).
28. M.A. Chari and K. Syamasunder, *Catal. Commun*., **6**, 67 (2005).
29. M. Tajbakhsh, M.M. Heravi, B. Mohajerani and A.N. Ahmadi, *J. Mol. Catal. A*, **247**, 213 (2006).
30. S.K. De and R.A. Gibbs, *Tetrahedron Lett*., **46**, 1811 (2005).
31. R. Varala, R. Enugala, S. Nuvula and S.R. Adapa, *Synlett*, 1009 (2006).
32. V.D. Jarikote, A.S. Siddiqui, R. Rajagopal, D. Thomas, J.R. Lahoti and V.K. Srinivasan, *Tetrahedron Lett*., **44**, 1835 (2003).
33. M.M. Heravi, F. Derikvand, L. Ranjbar and H.A. Oskooie, *Heteroatom Chem*., **19**, 2 (2008).
34. S.T. Gao, W.H. Liu, J.J. Ma, C. Wang and Q. Liang, *Synth. Commun*., **39**, 3278 (2009).
35. R. Kaoua, N. Bennamane, S. Bakhta, S. Benadji, C. Rabia and B.N. Koli, *Molecules*, **16**, 92 (2011).
36. L. Yi, H.S. Lei, J.H. Zou and X.J. Xu, *Synthesis*, 717 (1991).
37. R. Wang, B.G. Li, T.K. Huang, L. Shi and X.X. Lu, *Tetrahedron Lett*., **48**, 2071 (2007).
38. M. Wang, Z.G. Song and H. Jiang, *Org. Prep. Proc. Int*., **41**, 315 (2009).
39. K. Manabe and S. Kobayashi, *Org. Lett*., **1**, 1965 (1999).
40. M. Wang, Z.G. Song, X. Wan and S. Zhao, *Monatsh. Chem*., **140**, 1205 (2009).
41. G. Zhao, T. Jiang, H. Gao, B. Han, J. Huang and D. Sun, *Green Chem*., **6**, 75 (2004).
42. T.P. Loh, S.B.K.W. Liung, K.L. Tan and L.L. Wei, *Tetrahedron*, **56**, 3227 (2000).
43. S. Iimura, D. Nobutou, K. Manabe and S. Kobayashi, *Chem. Commun*., 1644 (2003).
44. M.M. Heravi, M. Zakeri and N. Mohammadi, *Chin. Chem. Lett*., **22**, 797 (2011).
45. M. Shailaja, A. Manjula and B.V. Rao, *Indian J. Chem*., **49B**, 482 (2010).
46. B.K. Banik and M. Cardona, *Tetrahedron Lett*., **47**, 7385 (2006).
47. A. Banik, S. Batta, D. Bandyopadhyay and B.K. Banik, *Molecules*, **15**, 8205 (2010).
48. M.A. Chari, D. Shobha, T.K. Kumar and P.K. Dubey, *Arkivoc*, 74 (2005).
49. N. Srivastava and B.K. Banik, *J. Org. Chem*., **68**, 2109 (2003).
50. J.K. Rajput and G. Kaur, *Tetrahedron Lett*., **53**, 646 (2012).