An efficient synthesis of imidazolines and benzimidazoles using Lanthanum (III) nitrate hexahydrate

***V. B. NINGDALE[1], S. B. LOMATE[1], S. K. TUPE[2]**

Dept. of Chemistry[1] and Physics[2]
Kalikadevi Art's, Commerce and Science College, Shirur (Ka.) Dist. Beed [M. S.]-India
*E-mail: vijay_orgchem@yahoo.co.in / 02442-259590

ABSTRACT

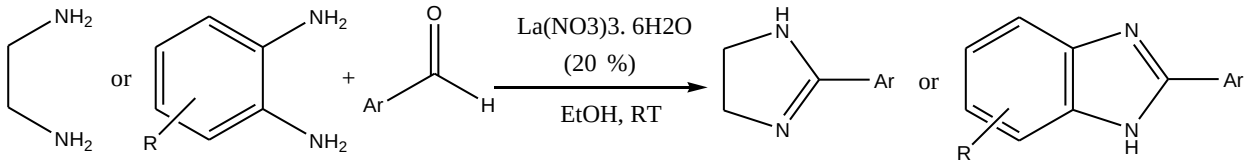
Imidazolines and Benzimidazoles have been efficiently synthesized in high yields by treatment of 1,2-diamine with aldehydes using catalytic amount of $La(NO_3)_3.H_2O$ under mild reaction conditions The key advantages of this protocol are short reaction time, high to excellent yields, simple work up, inexpensive catalyst and simple separation of pure product.

KEYWORDS: *Aldehydes; imidazolines; benzimidazoles; Lanthanum (III) nitrate hexahydrate.*

INTRODUCTION

The development of simple, efficient and general synthetic method for biological active compounds from readily available catalyst is one of the major challenges in organic synthesis.
The importance of imidazolines and benzimidazloes units arises, because they are found in many biologically active compounds.[1-2] Imidazolines are biologically active pharmacophore and synt heticintermediates in medicinal chemistry.[3-5] They are also used as chiral catalysts,[6] chiral auxiliaries [7] and ligands for asymmetric catalysis.[8-9] As a continuation of our interest in the synthesis of imidazolines due to its broad spectrum of biological activities including antihyperglycemic, [10-11] antiinflammatory [12-13] antihypertensive, [14-15] anticancer [16] and antihypercholesterolemic [17] agents. In addition, the benzimidazol moiety shown excellent biological activity like antiulcers, antihypertensives, antivirals, antifungals, anticancers, antihistaminics, antibacterial, antitubercular, antiasthmatic, antidiabetic and antiprotozoal.[18-26] Recently, several methods have been developed, for the synthesis of benzimidazoles in presence of various catalyst such as sulfur/ultrasonic,[27] homogeneous Lewis acids,[28] I_2, /KI/K_2CO_3, H_2O_2 ,[29] pyridinium-p-toluenesulfonate,[30] ionic liquids, [31] polyaniline-sulfate,[32] (bromodimethyl)sulfonium bromide [33] , Zeolite [34] and $LaCl_3$ [35]. However, all of the synthetic protocols reported so far suffer from disadvantages such as, use of organic solvents, [28,30-32] harsh reaction conditions, [29-33] excess temperature,[29] prolonged reaction times,[30-32] use of expensive reagents. [28-31] Therefore, there is a strong demand for a highly efficient and environmentally benign method.

Lanthanum (III) nitrate have recently attracted much attention in organic transformations due to its high acidity, thermal stability, low toxicity, low cost and good stability, Furthermore, current literature reveals that Lanthanum (III) nitrate has been utilized as an effective catalyst in the synthesis of 4-(3H)-quinazolinones under solvent-free conditions, chiral tetrahydroquinolino pyranose derivatives, chemoselective deprotection of acetonides, chemoselective protection of amines as N-benzyloxycarbonyl derivatives, acetylation of alcohols, phenols and amines with acetic anhydride and synthesis of α-amino nitriles.[45-50]



A **B** **C**

Scheme 1: Synthesis of imidazolines and benzimidazoles (A, B → Reactants and C→ Product)

EXPERIMENTAL

Materials and Apparatus

The chemicals and solvents were purchased from commercial suppliers (Merck, S.D. fine and Spectrochem) and they were used without purification prior to use. Melting points were recorded by open tube capillary method and are uncorrected. The progress of the reaction and the purity of the compounds were monitored by thin layer chromatography (TLC), using analytical silica gel plates (Merck 60 F250). ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 and 100 MHz, respectively. NMR spectra were obtained in DMSO-d_6 solutions and are reported as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard and the coupling constants (J) are expressed in Hertz (Hz).

GENERAL PROCEDURE FOR THE SYNTHESIS OF IMIDAZOLINES / BENZIMIDAZOLINES

La(NO3)36H2O (15 mol%) was added to a stirred solution of the mixture of substituted 1,2 diamine (1.1 mmol), aldehyde (1 mmol) in ethanol (5 mL) and the mixture was stirred at room temperature for appropriate time (Table 2). The progress of the reaction was monitored by thin layer chromatography (TLC) (Hexane: Ethyl acetate). After the reaction was completed, the pure products were isolated by filtration. The solid product was purified by recrystallization from ethanol.

Selected spectral data of compounds are given below.

2-(4-Bromophenyl)imidazoline: IR (KBr,cm^{-1}): Solid; 243-245^{o}C ν 3187 (NH), 2961 and 2941 (CH), 1608;^{1}HNMR (DMSO-d_6,400 MHz): δ 7.81–7.70 (m, 4H), 4.31 (br, 1H), 3.85 (s, 4H).

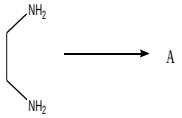
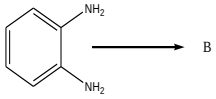
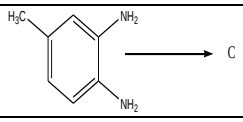
2-(p-Tolyl)-1H-benzimidazole: Solid; mp 264–266◦C ^{1}H NMR (DMSO-d_6,400 MHz) δ12.83 (s, 1H), 8.08 (d,J=7.8Hz,2H),7.59(s,2H), 7.37 (d ,J =7.8Hz,2H),7.21–7.19(m,2H),2.39(s,3H).

RESULT AND DISCUSSION

To explore the use of Lanthanum (III) nitrate hexahydrate as a catalyst, a reaction of benzaldehyde B and 1, 2 diamine A was conducted as a standard model reaction for the preparation of imidazolines and benzimidazoles (Scheme 1).The reaction in the absence of catalyst did not give any desired product. To determine the exact amount of the catalyst, we investigated the model reaction using different concentrations of Lanthanum (III) nitrate hexahydrate (Table 1). During this study, we observed that15 mol% Lanthanum (III) nitrate hexahydrate was proved to be an efficient catalyst to conduct the reaction smoothly. With these optimized reaction conditions, effect of different solvents such as methanol, dichloromethane, acetonitrile, THF, ethanol, aqueous ethanol and water was investigated**.** Among the tested solvents, ethanol was found to be superior over the other tested solvents in terms of both yield and reaction time for this transformation. Encouraged by this result, in order to build the generality of the reaction, various aromatic aldehydes, possessing electron-donating and electron-withdrawing groups were converted to 2-arylbenzothiazole derivatives in good to excellent yields. All the results are summarized in Table 1. In order to understand the efficiency and greenness of the method, we compared our results on the synthesis of imidazolines and benzimidazoles with the well known data from the literature. Many of the previously reported methodologies suffer from one or more disadvantages such

as requirement of excess amount of catalyst, high temperature, ultrasound irradiation, prolonged reaction time, and use of volatile and toxic organic solvents. Thus, the present method avoids the disadvantages of the previously reported methodologies.

Table 1: Synthesis of imidazolines and benzimidazoles

Entry	1,2-diamines	Aldehyde	Product (a-i)	Yield %	mp (^{o}C)
1		R-C_6H_4-CHO	a 4-NO_2; b 4-CH_3; c 4-Br	96 93 91	228-231 179-181 243-245
2		R-C_6H_4-CHO	d 4-CH_3; e H; f 4-OCH_3	94 89 97	274-276 293-295 222-225
3		R-C_6H_4-CHO	g H; h 4-NO_2; i 3-F	95 97 96	235-236 240-242 174-176

CONCLUSION

In summary, we have developed a facile, efficient and green method for the synthesis of imidazolines and benzimidazoles through condensation of aromatic aldehydes with 1,2 diamine in the presence of Lanthanum (III) nitrate hexahydrate under mild reaction conditions. Compare with the previously reported methodologies, the present protocol features simple work up, environmentally benign, high yields and use of catalytic amount of a cheap catalyst.

AKNOWLEDGEMENT

Authors wish to thanks Principal, Kalikadevi ACS College, Shirur (Ka.) Dist. Beed for providing necessary laboratory facilities.

REFERENCES

[1] Preston, P. N.,*Chem. Rev*.1974, 74, 279–314
[2] Rondu, F.; Bihan, G. L.;Tounian, A. P.;Wang, X.; Lidy, S.; Touboul, E.; Lamouri, A.;Dive, G. J. H.; Pfeiffer, B.; Renard, P.;Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J.J., *J. Med. Chem*.1997, 40, 3793–3803.
[3] Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.*1996, 37, 4969-4972;
[4] Jung, M. E.; Huang, A.,*Org. Lett*. 2000,2, 2659–2661:
[5] Lin, Y. R.; Zhou, X. T.; Dai, L.X.; Sun, J., *J. Org. Chem*.1997,62, 1799–1803.
[6] Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T., *Chem. Commun*. 2001, 243–244.
[7] Langlois, Y.; Dalko, P. I., *J. Org. Chem.*1998, 63, 8107–8117.
[8] Menges, F.; Neuburger, M.; Pfaltz, A.,*Org. Lett*. 2002,4, 4713–4716;
[9] Boland, N. A.; Casey, M.; Hynes, S. J.; Matthews, J. W.; Muller-Bunz, H.; Wilkes, P., *Org. Biomol. Chem*. 2004, 2, 1995–2002.
[10] Doyle, M. E.; Egan, J. M., *Pharmacol*. *Rev*.2003, 55 ,105-131
[11] Meidute-Abaraviciene, S.; Mosen, H.; Lundquist, I.; Salehi, A., *Acta Physiol.* 2009,195, 375-383.

[12] Ueno, M.; Imaizumi, K.; Sugita, T.; Takata, I.; Takeshita, M., *Int. J. Immunopharmacology*.1995, 17,597-603;
[13] Kahlon, D. K.; Lansdell, T. A.; Fisk, J. S.; Tepe, J. *J.,Bioorg. Med. Chem*. 2009, 17, 3093-3103.
[14] Touzeau, F.; Arrault, A.; Guillaumet, G.; Scalbert, E.; Pfeiffer, B.; Rettori, M. C.; Renard, P.; Merour, J. Y., *J. Med. Chem*. 2003,46 , 1962–1979;
[15] Masajtis-Zagajewska, A.; Majer, J.; Nowicki, M., *Hypertens. Res.* 2010, 33, 348–353.
[16] Sun, M.; Wu, X. Chen, J.; Cai, J.; Cao, M.; Ji, M., *Eur. J. Med. Chem*. 2010,45, 2299-2306.
[17] Li, H.Y.; Drummond, S.; DeLucca, I.; Boswell, G. A., *Tetrahedron*, 1996, 52, 11153-11162.
[18] Scott, L. J.; Dunn, C. J.; Mallarkey, G.; Sharpe, M. Esomeprazole, *Drugs* 2002, 62, 1503.
[19] Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A. , *Pharm. Chem. J.*, 1999,33, 232.
[20] Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J., *J. Med. Chem*. 1996,39, 992.
[21] Navarrete-Vázquez, G.; Rojano-Vilchis, M. M.; Yépez-Mulia, L.; Meléndez, V.; Gerena, L.;Hernández-Campos, A.; Castillo, R.; Hernández-Luis, F., Eur. *J. Med. Chem*. 2006, 41,135-141.
[22] Mirkhani, V.; Moghadam, M.; Tangestaninejad, S.; Kargar, H.,*Tetrahedron Lett*.2006,47, 2129.
[23] Curini, M.; Epifano, F.; Montanari, F.; Rosati, O.; Taccone, S. *Synlett* 2004, 1832.
[24] Gogoi, P.; Konwar, D. *Tetrahedron Lett*. 2006 , 47, 79.
[25] Hornberger, K. R.; Adjabeng, G. M.; Dickson, H. D.; Davis-Ward, R. G., *Tetrahedron Lett.* 2006, 47, 5359.
[26] Nadaf, R. N.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V., *J. Mol. Catal. A: Chem.* 2004, 214, 155.
[27] Srinivas, U.; Srinivas, C.; Narender, P.; Rao, V. J.; Palaniappan, S., *Catal. Commun*.2007, 8, 107.
[28] Das, B.; Holla, H.; Srinivas, Y.,*Tetrahedron Lett*. 2007, 48, 61.
[29] Hegedüüs, A.; Hell, Z.; Potor, A., *Synth Commun*. **2006**, 36, 3625–3630.
[30] Yekkirala V.; Sudhagani R. K.; Panuganti L.; *Org. and Med. Chemistry Lett.*, 2013,3:7