Efficient and Practical Protocol for the Synthesis of Pyridopyrazines, Pyrazines and Quinoxalines Catalyzed by $La(OAc)_3$ in Water

Rezanejade Baradajee, Ghasem*+; Mohamadi, Ali

Department of Chemistry, Payame Noor University, P.O. Box 19395-3697 Tehran, I.R. IRAN

ABSTRACT: *$La(OAc)_3$ has been used as an efficient catalytic system for the synthesis of quinoxalines. This method provides several advantages over methods that are currently employed such as a simple work-up, mild reaction conditions, good to excellent yields, and a process to recover and reuse the catalyst for five cycles with consistent activity.*

KEY WORDS: *$La(OAc)_3$, 1,2-Diamines, 1,2-Diketones, Quinoxalines, Water.*

INTRODUCTION

Quinoxalines, an important class of fused heterocyclic compounds [1,2], have attracted much synthetic attention because of their wide range of pharmacological and therapeutic activities such as anticancer [3], anti-inflammatory [4], anti-depressant [5], anti-HIV [6], and anti-viral [7]. In addition to the medicinal applications, they have been used as dyes [8] and important intermediates in the synthesis of organic semiconductors [9], chemically controllable switches [10], building blocks for the synthesis of anion receptors [11], cavitands [12], and dehydoannulenes [13]. The most common approach for the preparation of quinoxalines involves the condensation of 1,2-aryldiamine with 1,2-diketone in refluxing ethanol or acetic acid [14]; but, there are many reports which has been focused on finding new catalysts to improve the yield of this condensation reaction. Many catalysts including I_2 [15,16], SA [17], Montmorillonite K-10 [18], SSA [19], $H_6P_2W_{18}O_{62}.24H_2O$ [20], $InCl_3$ [21], $MnCl_2$ [22], $CuSO_4.5H_2O$ [23], Zn/L-Proline [24], and CAN [25] have been explored. However, most of these procedures have significant drawbacks such as long reaction times, low yields of the products, harsh reaction conditions, difficult work-up, and the use of expensive and environmentally toxic catalysts, reagents, or media. In addition, some of the starting materials have to be synthesized and purified first, hence these methods are time-consuming. Thus, the development of new catalytic methods is highly desirable. In this article, we report an efficient protocol for the synthesis of quinoxaline derivatives in good to excellent yields by the condensation of 1,2-diamines with 1,2-diketones catalyzed by $La(OAc)_3$ in water.

EXPERIMENTAL SECTION

Chemicals and instrumental analysis

Commercial grade 1,2-diamines and 1,2-ketones were purchased from Merck or Aldrich. The solvents were of analytical grade and were used as received. Silica gel

** To whom correspondence should be addressed.*
+ E-mail: rezanejad@pnu.ac.ir
1021-9986/13/3/61 7/$/2.70

(Merck, grade 9385, 230-400 mesh, 60 A°) for column chromatography was used as received. The course of the synthesis and the purity of the products were followed by TLC on silica gel plates (Merck F60254, 20110, 0.2 mm, ready-to-use), using ethyl acetate/ n-hexane (1:4) as eluent. The eluent for column chromatography was the same as the TLC eluent. Melting points were recorded using a Buchi B540 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AC 400 and 500 MHz spectrometers using $CDCl_3$ or DMSO-d_6 as the NMR solvents. ^{1}H NMR spectra are referenced to tetramethylsilane (0.00 ppm) and ^{13}C NMR spectra are referenced from the solvent central peak (for example, 77.23 ppm for $CDCl_3$). Chemical shifts are given in ppm.

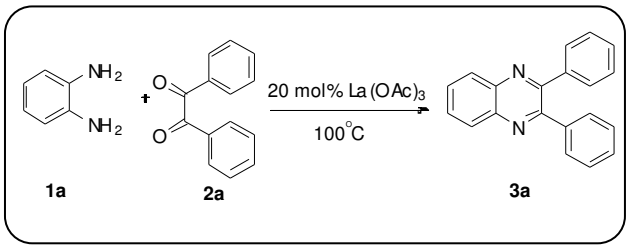
GC-MS (EI), 70 ev, HP6890 Column: HP-5 (30 m × 0.25mm × 0.2 umL MSD: HP5793) were used to record the mass spectra. IR spectra were taken as KBr pellets o n an ABB Bomem MB-100 FT-IR spectrophotometer. IR is reported as characteristic bands (cm^{-1}) at their maximum intensity.

General procedure for the synthesis of quinoxaline derivatives (Table 2, entries 1-19)

To a stirred solution of of an appropriate 1,2-diketone (1 mmol) and 1,2-diamine (1 mmol) in water (5 mL), a catalytic amount of $La(OAc)_3$ (20 mol %) was added, and the mixture was stirred at 100 °C (reflux) for an appropriate time (Table 2). After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, the product was recrystallized from EtOH and collected by filtration or purified by column chromatography on silica gel using ethylacetate/ n-Hexane (1:4 v/v) as the eluent to give the analytically pure quinoxalines.

*2,3-bis(4-fluorophenyl)pyrido[3,4-b]pyrazine (**3d**)*

^{1}H NMR (500 MHz, $CDCl_3$), δ 9.58 (s, 1H), 8.83 (d, *J* = 5.5 Hz, 1H), 7.97 (d, *J* = 6.0, 1H), 7.51-7.57 (m, 4H), 7.06-7.09 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.3, 165.2, 162.0, 161.8, 156.6, 154.4, 154.0, 147.5, 143.5, 136.2, 134.1, 132.0, 131.8, 131.8, 131.7, 121.2, 115.9, 115.6.; IR (υ (cm^{-1})): 3049, 1597, 1509, 1381, 1325, 1230, 835; MS m/z (%) 319.09 (100.0%), 320.10 (20.7%), 321.10 (2.0%), 320.09 (1.1%); Anal. Calcd for $C_{19}H_{11}F_2N_3$: C, 71.47; H, 3.47; F, 11.90; N, 13.16. Found: C, 71.50; H, 3.46; F, 11.90; N, 13.14.



Scheme 1: Model reaction.

*2,3-bis(4-fluorophenyl)pyrido[2,3-b]pyrazine (**3h**)*

^{1}H NMR (500 MHz, $CDCl_3$), δ 8.32 (d, *J* = 2.4, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.74 (m, 4H), 6.30 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 161.9, 161.8, 154.4, 154.2, 152.8, 149.2, 137.7, 135.8, 134.3, 134.2, 132.0, 132.0, 131.9, 131.8, 125.8, 115.3, 115.1, 115.0; IR (υ (cm^{-1})): 2925, 1728, 1597, 1548, 1508, 1446, 1386, 1331, 1226, 832; Anal. Calcd for $C_{19}H_{11}F_2N_3$ (319.3): C, 71.47; H, 3.47; N, 13.16. Found: C, 71.64; H, 3.59; N, 13.38.

*2,3-di(pyridin-4-yl)pyrido[2,3-b]pyrazine (**3o**)*

^{1}H NMR (500 MHz, $CDCl_3$), 8.94 (d, *J* = 4.1 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.14 (dd, *J* = 9.7, 4.8 Hz, 1H), 7.68-7.81 (m, 5H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8, 1H), 7.29 (m, 2H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 154.2, 154.1, 152.7, 148.8, 148.7, 148.4, 138.6, 138.5, 136.3, 136.3, 128.1, 127.5, 125.7, 125.5, 125.2, 125.0.; MS m/z (%) 285.10 (100.0%), 286.10 (20.2%), 287.11 (1.6%).

RESULTS AND DISCUSSION

In order to get the best experimental results, we have considered the model reaction of *o*-phenylenediamine and benzil (Scheme 1) in different solvents and catalysts amount (Table 1). Reactions in EtOH and MeOH gave low yield of products in 120 min (Table 1, entries 3 and 4), while DMF and DMSO gave moderate yield of products within 60 min (Table 1, entries 1 and 2). Reactions in H_2O provided desired product in 94% yield (Table 1, entry 5).

Because of high product yield, being environmentally benign, and good availability, water was chosen as a solvent for further reaction optimization. In the study of catalyst loading, 10%, 15%, and 20 mol % of $La(OAc)_3$ were tested, with 20 mol % of catalyst gave quantitative yield in 60 min (Table 1, entry 5), whereas 10% and 15 mol % catalyst

Table 1: $La(OAc)_3$-catalyzed condensation of o-phenylenediamine 1a and benzil 2a.

Entry[a]	Solvent	$La(OAc)_3$ (%)	Time (min)	Yield[b] (%)
1	DMSO	20	60	71
2	DMF	20	60	78
3	EtOH	20	120	52
4	MeOH	20	120	55
5	H_2O	20	60	94
6	H_2O	15	60	67
7	H_2O	10	60	49
8	H_2O	none	200	0

a) all reactions performed at 100°C. b) Isolated Yield.

Table 2: Heterocyclic derivatives from the reaction of 1,2-diamines and 1,2-diketones catalyzed by 20 mol % $La(OAc)_3$.

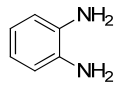
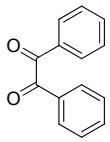
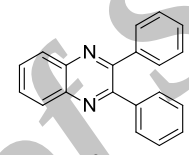
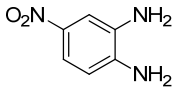
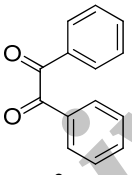
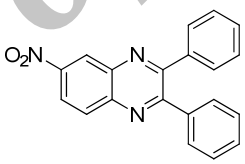
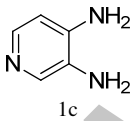
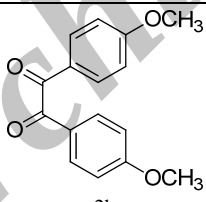
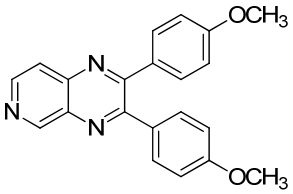
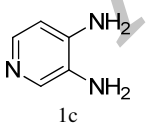
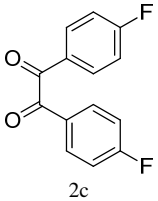
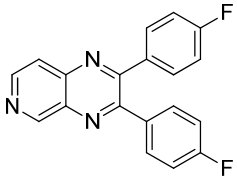
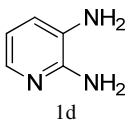
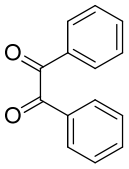
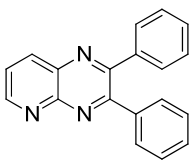
Entry	1,2- Diamine	1,2- Diketone	Product	Yield[a] (%)	Time (h)	Ref.
1	 1a	 *2a*	 3a	94	1	[20]
2	 1b	 2a	 3b	92	2.5	[20]
3	 1c	 2b	 3c	89	3	[26]
4	 1c	 2c	 3d	90	2.5	b
5	 1d	 2a	 3e	89	2.5	[27]

Table 2:

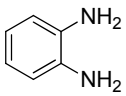
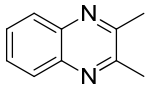
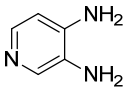
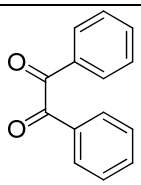
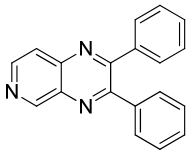
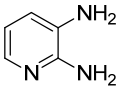
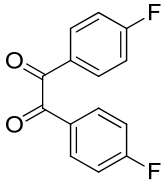
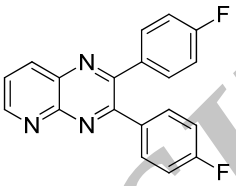
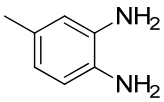
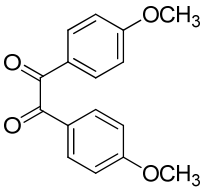
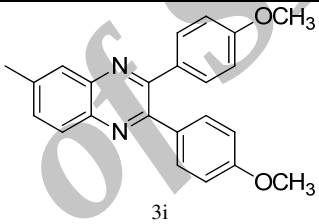
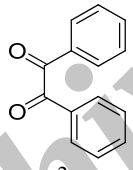
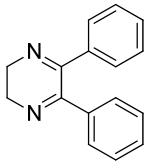
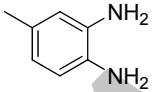
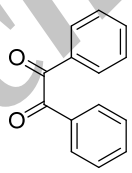
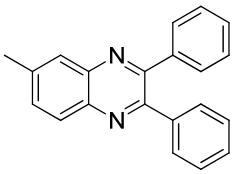
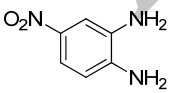
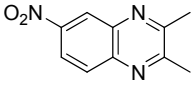
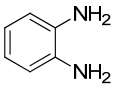
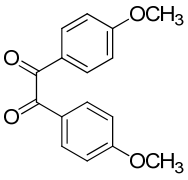
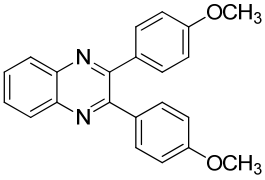
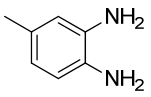
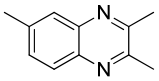
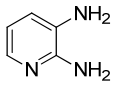
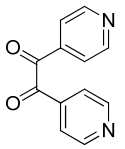
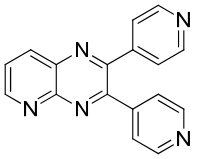
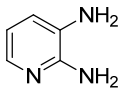
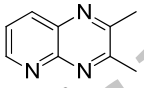
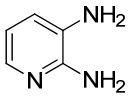
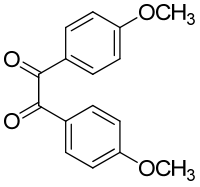
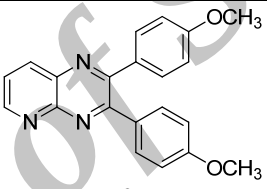
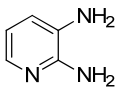
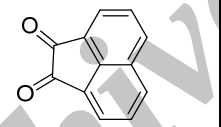
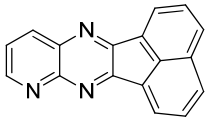
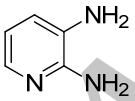
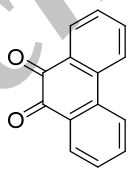
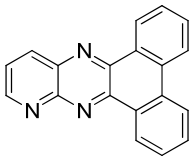
6	 1a	 2d	 3f	95	0.5	[27]
7	 1c	 2a	 3g	90	2.5	[28]
8	 1d	 2c	 3h	95	2.5	b
9	 1e	 2b	 3i	93	2.5	[27]
10	 1f	 2a	 3j	96	2	[29]
11	 1e	 2a	 3k	94	1	[29]
12	 1b	 2d	 3l	95	0.5	[27]
13	 1a	 2b	 3m	91	2.5	[27]

Table 2:

14	 1e	 2d	 3n	97	0.5	[27]
15	 1d	 2e	 3o	86	2.5	b
16	 1d	 2d	 3p	96	0.5	[27]
17	 1d	 2b	 3q	92	2.5	[27]
18	 1d	 2f	 3r	86	2	[30]
19	 1d	 2g	 3s	86	2	[30]

a) Isolated Yield. B) Their spectroscopic data have been reported in Experimental Section.

loading only gave 49% and 67% yields respectively at reaction time of 60 min (Table 1, entries 6 and 7). When the same reaction was carried out in the absence of catalyst, the reaction did not yield the product even after 200 min, which indicates that catalyst is obviously necessary for the reaction (Table 1, entry 8). To clarify the catalytic role of La^{3+} ions, we used NaOAc (20 mol%) as the catalyst for the model reaction under optimized conditions in the absence of $La(OAc)_3$, and no product was obtained (yield = 0 %). In this regard, we can attribute the catalytic activity of $La(OAc)_3$ to the La^{3+} ions.

Using the optimized reaction conditions, a range of substituted quinoxalines were synthesized (Table 2). It can be seen that in all cases, the difference in reactivity of diamines or diketones can be compensated by changing the reaction times. For example, the less reactive systems including substituted 1,2-phenylenediamines bearing electron-withdrawing groups (EWG) (Table 2, entry 2)

Table 3: Comparison of our results with some previously reported data for the synthesis of compound 3q.

Method	Temperature (°C)	Time (h)	Yield[a] (%)	Ref.
Uncatalysed reactions in mixture of EtOH and AcOH	Reflux	16	97	[30]
$ZrCl_4$	20	4	95	[27]
Silica-supported stannous chloride	20	3	94	[31]
$La(OAc)_3$	100	2.5	92	This work

a) Isolated Yield.

and diaminopyridines (Table 2, entries 3-5) were more slowly condensed and needed longer reaction times to reach quantitative conversion to the desired products.

We compared some previously reported data for the synthesis of **3q** (Table 2, entry 17) with our protocol (Table 3). As one can see our results show a very good comparability with previously reported data in terms of yields and reaction times.

CONCLUSIONS

To sum up a $La(OAc)_3$-promoted synthesis of quinoxaline derivatives has been developed. High yields, short reaction times, and neat conditions are the important advantages of this protocol.

Acknowledgements

We are grateful to the PNU for funding this work.

Received : Mar. 7, 2012 ; Accepted : Dec. 26, 2012

REFERENCES

[1] Katritzky A.R., Rees C.W., "Comprehensive Heterocyclic Chemistry", Pergamon, Oxford (1984).

[2] (a) Sherman D., Kawakami J., He H.Y., Dhun F., Rios R., Liu H., Pan W., Xu Y.J., Hong S.P., Arbour M., Labelle M., Duncton M.A.J., Synthesis of Unsymmetrical and Regio-Defined 2,3,6-Quinoxaline and 2,3,7-Pyridopyrazine Derivatives, *Tetrahedron Lett*., **48**, p.8943 (2007).

(b) Shaabani A., Maleki A., A Fast and Efficient Method for the Synthesis of 1,5-Benzodiazepine Derivatives Under Solvent-Free Conditions, *Iran. J. Chem. Chem. Eng.*, **26**(4), p. 93 (2007).

[3] Lindsley C.W., Zhao Z., Leister W.H., Robinson R.G., Barnett S.F., Defeo-Jones D., Jones R.E., Hartman G.D., Huff J.R., Huber H.E., Duggan M.E., Allosteric Akt (PKB) Inhibitors: Discovery and SAR of Isozyme Selective Inhibitors, *Bioorg. Med. Chem. Lett.*, **15**, p.761 (2005).

[4] Kim Y.B., Kim Y.H., Park J.Y., Kim S.K., Synthesis and Biological Activity of New Quinoxaline Antibiotics of Echinomycin Analogues, *Bioorg. Med. Chem. Lett*., **14**, p.541 (2004).

[5] Sarges R., Howard H.R., Browne R.G., Lebel L.A., Seymour P.A., Koe B.K., 4-Amino[1,2,4]triazolo[4,3-a]quinoxalines. A Novel Class of Potent Adenosine Receptor Antagonists and Potential Rapid-Onset Antidepressants, *J. Med. Chem*., **38**, p.2240 (1990).

[6] Hui X., Desrivot J., Bories C., Loiseau P.M., Franck X., Hocquemiller R., Figadere B., Synthesis and Antiprotozoal Activity of Some New Synthetic Substituted Quinoxalines, *Bioorg. Med. Chem. Lett.*, **16**, p.815 (2006).

[7] Loriga M., Piras S., Sanna P., Paglietti G., Quinoxaline Chemistry. Part 7. 2-[Aminobenzoates]- and 2-[Aminobenzoylglutamate]-quinoxalines as Classical Antifolate Agents. Synthesis and Evaluation of in Vitro Anticancer, Anti-HIV and Antifungal Activity, *Farmaco*., **52**, p.157 (1997).

[8] (a) Kumar A., Kumar S., Saxena A., De A., Mozumdar S., Ni-nanoparticles: An Efficient Catalyst for the Synthesis of Quinoxalines, *Catal. Commun.*, p.778 (2008).

(b) Jaung J.Y., Synthesis and Halochromism of New Quinoxaline Fluorescent Dyes, *Dyes and Pigments*, **71**, p.45 (2006).

[9] Dailey S., Feast W.J., Peace R.J., Sage I.C., Till S., Wood E.L., Synthesis and Device Characterisation of Side-Chain Polymer Electron Transport Materials for Organic Semiconductor Applications, *J. Mater. Chem*., **11**, p.2238 (2001).

[10] Crossley M.J., Johnston L.A., Laterally-extended Porphyrin Systems Incorporating a Switchable Unit, *Chem. Commun*., p.1122 (2002).

[11] Kazunobu T., Ryusuke O., Tomohiro M., Molecular Design and Evaluation of Quinoxaline-Carbohydrate Hybrids as Novel and Efficient Photo-Induced GG-Selective DNA Cleaving Agents, *Chem. Commun*., p. 212 (2002).

[12] Sessler J.L., Maeda H., Mizuno T., Lynch V.M., Furuta H., Quinoxaline-bridged Porphyrinoids, *J. Am. Chem. Soc*., **124**, p.13474 (2002).

[13] Sascha O., Rudiger F., Quinoxalinodehydroannulenes: A Novel Class of Carbon-rich Materials, *Synlett*, p. 1509 (2004).

[14] Pan X.Q., Zou J.P., Huang Z.H., Zhang W., $Ga(OTf)_3$-Promoted Condensation Reactions for 1,5-Benzodiazepines and 1,5-Benzothiazepines, *Tetrahedron Lett*., **49**, p.5302 (2008).

[15] Bhosale R.S., Sarda S.R., Ardhapure S.S., Jadhav W.N., Bhusare S.R., Pawar R.P., An Efficient Protocol for the Synthesis of Quinoxaline Derivatives at Room Temperature Using Molecular Iodine as the Catalyst, *Tetrahedron Lett*., **46**, p.7183 (2005).

[16] More S.V., Sastry M.N.V., Wang C.C., Yao C.F., Molecular Iodine: A Powerful Catalyst for the Easy and Efficient Synthesis of Quinoxalines, *Tetrahedron Lett.*, **46**, p.6345 (2005).

[17] Darabi H.R., Mohandessi S., Aghapoor K., Mohsenzadeh F., A Recyclable and Highly Effective Sulfamic Acid/Meoh Catalytic System for the Synthesis of Quinoxalines at Room Temperature, *Catal. Commun*., **8**, p.389 (2007).

[18] Huang T.K., Wang R., Shi L., Lu X.X., Montmorillonite K-10: An efficient and Reusable Catalyst for the Synthesis of Quinoxaline Derivatives in Water., *Catal. Commun*., **9**, p. 1143 (2008).

[19] Srinivas C., Kumar C.N.S.S.P., Rao V.J., Palaniappan S., Efficient, Convenient and Reusable Polyaniline-sulfate Salt Catalyst for the Synthesis of Quinoxaline Derivatives, *J. Mol. Catal. A: Chem.*, **265**, p. 227 (2007).

[20] Heravi M.M., Bakhtiari K., Bamoharram F.F., Tehrani M.H., Wells-Dawson Type Heteropolyacid Catalyzed Synthesis of Quinoxaline Derivatives at Room Temperature, *Monatsh. Chem*., **138**, p.465 (2007).

[21] Hazarika P., Gogoi P., Konwar D., A Simple and Convenient Synthesis of Pyrazinones, *Synth. Commun*., **37**, p. 3447 (2007).

[22] Heravi M.M., Bakhtiari K., Oskooie H.A., Taheri S., $MnCl_2$-promoted Synthesis of Quinoxaline Derivatives at Room Temperature, *Heteroat. Chem.*, **19**, p. 218 (2008).

[23] Heravi M.M., Taheri S., Bakhtiari K., Oskooie H.A., On Water: A Practical and Efficient Synthesis of Quinoxaline Derivatives Catalyzed by $CuSO_4$ $5H_2O$, *Catal. Commun*., **8**, p. 211 (2007).

[24] Heravi M.M., Tehrani M.H., Bakhtiari K., Oskooie H.A., Zn[(I)proline]: A Powerful Catalyst for the Very Fast Synthesis of Quinoxaline Derivatives at Room Temperature, *Catal. Commun*., **8**, p. 1341 (2007).

[25] More S.V., Sastry M.N.V., Yao C.F., Cerium (IV) Ammonium Nitrate (CAN) as a Catalyst in Tap Water: A Simple, Proficient and Green Approach for the Synthesis of Quinoxalines, *Green Chem*., **8**, p. 91 (2006).

[26] Antoine M., Czech M., Gerlach M., Günther E., Schuster T., Marchand P., Preparation of Novel 2,3,8-Trisubstituted Pyrido[3,4-b]Pyrazines and Pyrido[2,3-b]pyrazines, *Synthesis*, **5**, p. 794 (2011).

[27] Aghapoor K., Darabi H.R, Mohsenzadeh F., Balavar Y., Daneshyar H., Zirconium(IV) Chloride as Versatile Catalyst for the Expeditious Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines under Ambient Conditions, *Transit. Metal Chem.*, **35**, p. 53 (2010).

[28] Duarte F.F., Popp F.D., Reissert Compound Studies. LXVII. The Pyrido[3,4-b]pyrazine Reissert Compound, *J. Heterocylic Chem*., **31**, p.819 (1994).

[29] Cai J.J., Zou J.P., Pan X.Q., Zhang W., Gallium(III) Triflate-catalyzed Synthesis of Quinoxaline Derivatives, *Tetrahedron Lett*., **49**, p. 7386 (2008).

[30] Yeo B.R., Hallett A.J., Kariuki B.M., Pope S.J.A., The Re(I) Coordination Chemistry of a Series of Pyrido[2,3-b]pyrazine-derived Ligands: Syntheses, Characterisation and Crystal Structures, *Polyhedron*, **29**, p. 1088 (2010).

[31] Darabi H.R., Aghapoor K., Mohsenzadeh F., Jalili M.R., Talebian S., Ebadi-Nia L., Khatamifar E., Aghaee A., Heterogeneous $SnCl_2/SiO_2$ Versus Homogeneous $SnCl_2$ Acid Catalysis in the Benzo[N,N]-Heterocyclic Condensation, *B. Korean Chem. Soc*., **32**, p. 213 (2011).