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Ionic liquid mediated safer synthetic routes for schiff bases and 1,3,4-oxadiazoles

Vasant B. Jagrut*[a], Wamanrao N. Jadhav[b], Dinesh L. Lingampalle[c] and Ramrao A. Mane[d]

[a]Lal Bahadur Shastri. Sr. College, Partur(MS), India
[b]Research Center Dnyanopasak College, Parbhani(MS), India
[c]Vivekanand College, Aurangabad(MS), India
[d]Dept. of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad(MS), India

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ABSTRACT

*An efficient and greener synthetic protocol for the synthesis of 1,3,4-oxadiazoles, N-{4-[4-acetyl-5-(4-substituted-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl}-4-methyl-benzenesulfonamide (**6a-g**) has been developed using 4-amino benzoic acid (**1**) as starting material. Attempts were made to synthesize required precursors by employing green tools. The route is found to be rapid, eco-friendly, easier to work and gives better yields of the intermediates and titled products.*

Key words: Sulfonamide, Schiff bases, Oxadiazole, Ionic liquid, Green synthesis.

INTRODUCTION

The concept of green chemistry is now widely adopted to meet the fundamental challenges of protecting the human health and environment while simultaneously achieving commercial viability [1]. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes. The target is to explore alternative reaction conditions[2] and reaction media to accomplish the desired chemical transformations with minimum byproducts or waste generation, as well as to eliminate the use of conventional organic solvents. The use of alternative reaction media such as supercritical fluids, polyethylene glycol (PEGs) and ionic liquids (ILs) is gaining increasing popularity as well[3].

Organic synthesis in an ionic liquid medium is a lucrative research area considering its cost, safety and significance to environmentally benign process development[4-7]. Ionic liquids (ILs) have become omnipresent in the recent chemical literature, for they can be used as highly customizable solvents for almost any synthetic purpose[8]. Especially in the industry, their application goes beyond their use as solvents. The highly diverse properties of these materials make possible a surprising number of applications. In organic reactions, although ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties like nonvolatility, nonflammability, thermal stability, and controlled miscibility, today they have marched far beyond this boundary, showing their significant role in controlling reactions as solvents or catalysts[8]. It is well-known that the microenvironment generated by a solvent can change the outcome of a reaction, in terms of both equilibria and rates[9].

Schiff bases are one of the precursors for generating biodynamic heterocycles and find great use in organic synthesis. These compounds are useful building blocks in four and five membered heterocycles. Conventionally Schiff bases have been prepared by refluxing mixture of the amines and the carbonyl compounds in organic solvent using acid or base catalyst. The conventional method has been modified to obtain high yields of the schiff bases by using aprotic

non-polar solvents, azotropic removal of water using Dean-Stark apparatus, and by adding suitable dehydrating agents. Environmentally benign synthetic methods have been receiving considerable attention and some solvent-free protocols have also been developed. Grinding together anilines and benzaldehydes yielded various kinds of benzylidenes.

Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products. Among the heterocyclic compounds 1,3,4-oxadiazoles are non naturally occurring five membered aromatic heterocycles. Compounds containing 1,3,4-oxadiazole nucleus have a broad spectrum of biological activities including antiinflamatory[10], antibacterial[11], antitumor[12], cyctotoxic[13], antihypertensive[14], obesity and diabetes[15]. Moreover, oxadiazole bearing compounds Raltegravir and Zibotenta are used as a medicament for the treatment of antiretroviral[16], anticancer[17] agent respectively.

The commonly used synthetic route for 1,3,4-oxadiazoles include reaction of acid hydrazides (or hydrazine) with acid chlorides,/carboxylic acids and direct cyclization of diacylhydrazines using variety of dehydrating agents such as thionyl chlorides, phosphorous pentaoxide, phosphorous oxychloride, triflic anhydride and polyphosphoric acid. Solid-phase syntheses of these compounds were also reported. It is also revealed that there is scanty information on the synthesis of 1,3,4-oxadiazoles from N-acylhydrazones, the reaction of N-acylhydrazones with acetic anhydride by refluxing became one of the most popular methods for the preparation of 1,3,4-oxadiazoles[18]. Recently, Guin and his coworkers[19] reported a direct route to both symmetrical and unsymmetrical 2,5-disubstituted-1,3,4-oxadiazoles from N-arylidenearoylhydrazides using $Cu(OTf)_2$ as catalyst at 110 ^oC for 12-24 h. in DMF. Li and He[20] synthesized compounds 2-(anthracen-9-yl)-5-(p-tolyl)-1,3,4-oxadiazoles in 75 % yield from oxidative cyclization of N-acylhydrazone using chloramines-T by refluxing in ethanol for 4 h. In 2009 we have reported[21] an efficient synthesis of 1,3,4-oxadiazoles under reflux condition using CH_3CN for 3 h.

It is observed that the reported methods, used for this condensations & cyclocondensations are having one or other kind of drawback such as longer reaction times, high temperature, low yields, and media used are found to be carcinogenic and hazardous. These reaction conditions are also suffer from environmental concerns. In view of the above drawbacks and in continuation with our earlier interest[22] we have developed safer and greener synthetic route for schiff bases and 1,3,4-oxadiazoles using greener media, ionic liquid.

MATERIALS AND METHODS

General procedures. All chemicals were obtained from commercial sources and used without any further purification. The melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a FT-IR (JASCO FT- IR) Japan. The ^1H NMR was measured on Bruker DRX-300, 300 MHZ FT NMR with low and high temperature in DMSO using TMS as internal reference. Mass spectra were recorded on an Ieo SX 102/DA-600 mass spectrometer.

Synthesis of N-methyl pyridinium tosylate (Ionic liquid).
Pyridine (1.1 mol) was added to a methyl-4-toulene sulphonate (1 mol) at 0-10 ^oC. After completion of addition, the reaction mass was stirred at room temperature for 1 h. the solid appeared N-methyl pyridinium tosylate was filtered. The product was then washed with ethyl acetate to remove unreacted reactants and then dried. The physical parameter of the ionic liquid is in good agreement with those reported in the literature[23].

Synthesis of 4-(toluene-4-sulfonylamino)-benzoic acid (2).
4-Aminobenzoic acid (0.01 mol, 1.37 g), *p*-toluenesulfonyl chloride (0.01 mol, 1.9 g) and pyridine (0.01 mole, 0.8 mL) were added to in an ionic liquid (2 g). The reaction mixture was stirred at. 120 ^oC. for 2.5 h. the reaction was monitored by TLC. After completion, the reaction mass was poured in ice cold water and was extracted with EtOAc. The solvent was removed and crude product was crystallized from aqueous ethanol. Yield 87%, mp 230 ^oC.

Synthesis of 4-(toluene-4-sulfonylamino)-benzoic acid ethyl ester (3).
4-(Toluene-4-sulfonylamino)-benzoic acid ethyl ester were prepared from the corresponding acid according to the literature [21] procedure.

Synthesis of *N*-(4-hydrazinocarbonylphen-yl)-4-methyl benzenesulfonamide (4).
4-(Toluene-4-sulfonylamino)benzoic acid ethyl ester (0.01 mol, 3.19 g) and hydrazine hydrate (0.03 mol, 1.5 mL) was added to an in ionic liquid (2 g) and the reaction mixture was stirred at 120 ^oC. for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was poured in ice cold water and was extracted with EtOAc. The solvent wa removed and crude product was crystallized from methanol Yield 90 %, mp 236 ^oC.

Mps and structures of compounds (**2**), (**3**) & (**4**) were confirmed by comparison of the IR, ^{1}HNMR, mass analyses with those authentic materials and are in good agreements[21].

Synthesis of N^1-(4-substitutedbenzylidene)-4-(tosylamino)benzohydrazide (5a-g).
N-(4-hydrazinocarbonylphene-yl)-4-methyl-benzene sulfonamide (0.002 mol) and aromatic aldehyde (0.002 mol) was added to in an ionic liquid (0.4 g) and the reaction mixture was stirred for 3 h. at 120 ^{o}C. The progress of the reaction was monitored on TLC plate using hexane: ethyl acetate. After completion, the reaction mass was poured into ice cold water and was extracted with EtOAc. The solvent was removed and crude product was subjected to column chromatography to obtained pure schiff bases. The ionic liquid was recovered from the aqueous layer. The physical parameters of the product are incorporated in Table 1.1

Synthesis of 1,3,4-oxadiazoles, N-{4-[4-acetyl-5-(4-substituted-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl}-4-methyl-benzenesulfonamide (6a-g).
N^1-(4-substitutedbenzylidene)-4-(tosylamino)benzohydrazi- de (0.002) and acetic anhydride (5 mL) was added to in an ionic liquid (0.4 g) and the reaction mixture was stirred for 1 h. at 120 ^{o}C. The progress of the reaction was monitored on TLC plate using hexane: ethyl: acetate (7:3). After completion, the mixture was poured into cold water and was extracted with EtOAc. The solvent was removed and crude product was subjected to column chromatography to obtained pure 1,3,4-oxidiazoles. The ionic liquid was recovered from the aqueous layer. The physical parameters of the product are incorporated in Table 1.2

The new compounds have been characterized by IR, ^{1}H NMR and Mass analyses. Characteristic absorption of (**6f**) and (**6g**) has been presented bellow. Compound (**6f**), MS (m/z): 494 (M^+ +1). IR (KBr) cm^{-1} 3069 (N-H, str.), 1765 (C=O, str.$OCOCH_3$), 1668 (C=O, str. $NCOCH_3$), 1509 (C=N, str.), 1278 (C-O-C, str.) and 1366 and 1169 (SO_2, asymmetric and symmetric stretching, respectively) ^{1}H NMR (DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 2.49 (s, 3H, $OCOCH_3$), 7.18 (d, 2H, Ar-H), 7.25 (s, 1H, oxadiazole), 7.47 (d, 2H, Ar-H), 7.54 (d, 2H, Ar-H) 7.83 (d, 2H, Ar-H), 7.95 (d, 2H, Ar-H), 8.04 (d, 2H, Ar-H), 10.70 (s, 1H, NH, SO_2NH exchange with D_2O).

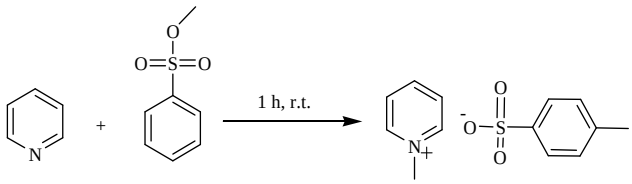
Compound (**6g**), MS (m/z): 479 (M^+ +1). IR (KBr) cm^{-1} 3049 (N-H, str.), 1701 (C=O, str. $NCOCH_3$), 1512 (C=N, str.), 1264 (C-O-C, str.) and 1365 and 1167 (SO_2, asymme- tric and symmetric stretching, respectively) ^{1}H NMR (DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 2.51 (s, 3H, $COCH_3$), 2.81 (s, 6H, $(CH_3)_2$), 6.90 (d, 2H, Ar-H), 7.01 (s, 1H, oxadiazoles), 7.22 (d, 2H, Ar-H), 7.27 (d, 2H, Ar-H) 7.43 (d, 2H, Ar-H), 7.65 (d, 2H, Ar-H), 7.76 (d, 2H, Ar-H), 9.98 (s, 1H, NH, SO_2NH exchange with D_2O).

RESULTS AND DISCUSSION

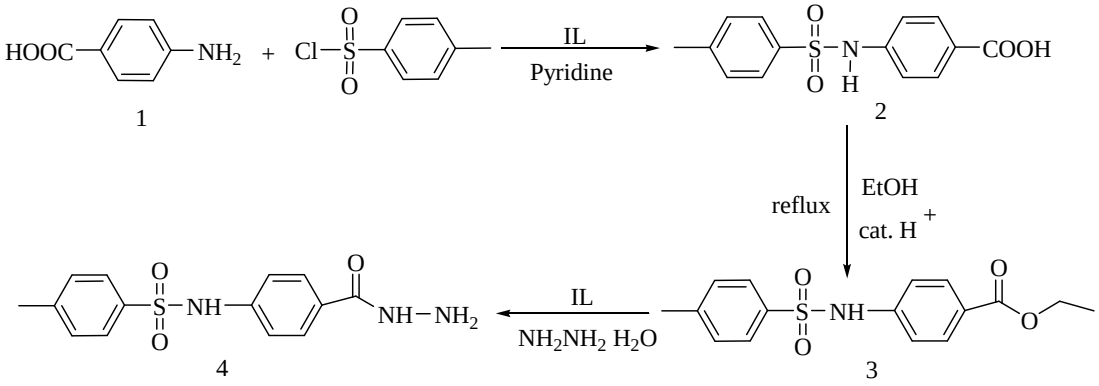
Attempts were made to synthesize the target heterocycles from readily available precursors. The key intermediates required for these syntheses were synthesized by employing green tools. 4-Aminobenzoic acid (**1**) was subjected with p-toulenesulfonyl chloride in an ionic liquid, N-methyl pyridinium tosylate at 120 ^{o}C in the presence of pyridine. Using this method we obtained excellent yields of the 4-(toluene-4-sulfonylamino)benzoic acid (**2**). Esterification of (**2**) with ethanol in an acidic medium afforded ester (**3**). Treatment of 4-(toluene-4-sulfonylamino)-benzoic acid ethyl ester (**3**) with hydrazine hydrate in the ionic liquid at 120 ^{o}C furnished the corresponding hydrazide (**4**) with good yield. It was observed that, theses condensation was completed within 4 h. and avoided excesses use of hydrazine hydrate. Compounds (**5a-g**) were prepared by condensing compound (**4**) with aromatic aldehydes in the ionic liquid. It was noticed that these condensation was completed within 3 h. with moderate yield. The intermediates, N^1-(4-substituted benzylidene)-4-(tosylamino)benzohydrazide (**5a-g**) in subsequent step when cyclocondensed with acetic anhydride in the ionic liquid at 120 ^{o}C gave high yield of the titled products N-{4-[4-acetyl-5-(4-substituted-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl}-4-methyl benzene sulfonamide (**6a-g**). The cyclocondensation was found to be completed within 1 h. The ionic liquid, N-methyl pyridinium tosylate used in the worked was freshly prepared following literature procedure[23].

The rate acceleration of condensation & cyclocondensation can be attributed to homogeneity of all the reactants in the ionic liquid forming initial high concentration of the reactants. The deployment of ionic liquid eliminates the use of catalyst, dehydrating agents, Dean-Stark apparatus and provides high yielding ecofriendly route for schiff bases (**5a-g**). As reaction of acid hydrazide with aromatic aldehydes is being carried at 120 ^{o}C using air condenser the water found in the reaction could be escaping as water vapor through the condenser helping to shift the reaction course. The reaction sequence is outlined in Scheme 1, 2 & 3

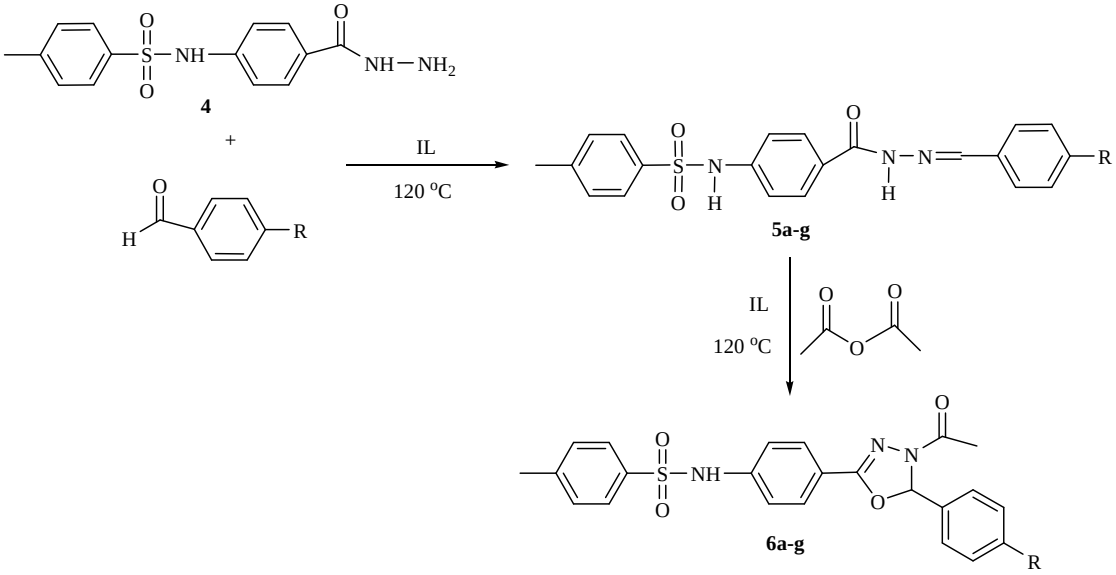
This method reduce environmental pollution, thus considered as green chemistry, and offers significant advantages over the reported method including i) reaction is relatively rapid. ii) gives better yields of intermediates and products, iii) medium are recyclable and non toxic iv) nontedious workup.



Scheme 1. Synthesis of N-methyl pyridinium tosylate (ILs)



Scheme 2. Synthesis of *N*-(4-hydrazinocarbonylphen-yl)-4-methylbenzenesulfonamide



Scheme 3. Synthesis of *N*-{4-[4-acetyl-5-(4-substituted-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl}-4-methyl-benzene sulfonamide

Table 1.1 Physical data of schiff bases (5a-g).

Product	R	Yield[a] (%)	Mp (°C)	
			Obs	Lit[24]
5a	H	93	224-225	223-224
5b	OCH_3	92	272-274	272-274
5c	Cl	92	281-282	282-284
5d	F	92	277-278	277-278
5e	Br	91	248-250	248-250
5f	$OCOCH_3$	92	233-234	235-236
5g	$N(CH_3)_2$	90	246-247	246-247

[a] Isolated yields based on acid hydrazide.
*Structures were confirmed by comparison of the IR, ^{1}H NMR and mass analyses with those authentic materials[24].

Table 1.2 Physical data of 1,3,4-oxadiazoles (6a-g).

Product	R	Yield[a] (%)	Mp (°C)	
			Obs	Lit[21]
6a	H	85	126-128*	126-128
6b	OCH_3	88	206-208*	208-210
6c	Cl	82	150-152*	150-152
6d	F	80	112-114*	110-112
6e	Br	87	162-164*	164-166
6f	$OCOCH_3$	82	170-172#	_
6g	$N(CH_3)_2$	83	137-139#	_

[a] Isolated yields based on schiff bases.
[b] Structures were confirmed by comparison of the IR, ^{1}H NMR and mass analyses with those authentic materials[21].
#Newly synthesized compounds.

CONCLUSION

In conclusion, Ionic liquid, N-methyl pyridinium tosylate was successfully first time employed as an alternative

green solvent in the synthesis of schiff bases and 1,3,4-oxadiazoles bearing sulfonamido pharmacophore. The clean and eco-friendly nature of the conversion, shorter reaction times, non tedious workup and considerable high yields are excellent features of the work

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REFERENCES

[1] P.T. Anastan, J.C. Warner, *Green Chemistry,* Theory and Practice; Oxford University Press: Oxford, NY, **1998**.
[2] J.D. Holbrey, M.B. Turner, R.D. Rogres, *Ionic Liquids as Green solvent*, ACS Symposium Series 856, American Chemical Society Washington, DC, **2003**.
[3] (a) P. Wasserscheid, T. Welton, *Ionic Liquid in Synthesis*, Eds.; Verlag & Co KGaA: Weinhein, Germany, **2003.** (b) A. A. Clifford, C. M. Rayer, *Tetrahedron Leet*., **2001**, 42, 323. (c) P. Wentworth, K. D. Janda, *Chem.* Commun., **1999**, 1917. (d) Chandrasekhar, S.; Narsihmula, Ch.; Shameem, S, S.; Reddy, N. R. *Org. Lett*. **2002**, *4*, 4399.
[4] (a) Karthikeyan, G.; Perumal, P.T. *Journal of Heterocyclic Chemistry* **2004**, *41*, 1039. (b) Jorapur, Y.R.; Chi, D.Y. *Bull. Korean Chem. Soc*. **2006**, 27, 345.
[5] Martins, M.A.P.; Frizzo, C.P.; Moreira, D.N.; Zanatta, N. Bonacorso, H.G. *Chemical Reviews* **2008**, 108, 2015.
[6] Moreira, D.N.; Frizzo, C.P.; Longhi, K.; Zanatta, N.; Bonacorso, H.G.; Martins, M.A.P. Monatsheft fur Chemie 2008, 139, 1049.
[7] Moreira, D.N.; Longhi, K.; Frizzo, C.P.; Bonacorso, H.G.; Zanatta, N.; Martins, M.A.P. *Catalysis Communications*, **2010**, *11*, 476.
[8] Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*,Wiley-VCH, Weinheim, **2008**.
[9] Pârvulescu, V.I.; Hardacre, C. *Chemical Reviews* **2007**, *107*, 2615.
[10] Manjunatha, K.; Poojary, B.; Lobo, P.L.; Fernandes, J.; Kumari, N.S. *Eur. J. Med. Chem.* **2010**, *45*, 5225
[11] Kumar, R.; Kumar, A.; Jain, S.; Kaushik, D. *Eur. J. Med. Chem.* **2011**, *46*, 3543.
[12] Liu, K.; Lu, X.; Zhang, H.-J.; Sun, J.; Zhu, H.-L. *Eur. J. Med .Chem.* **2012**, *47*, 473.
[13] Puthiyapurayil, P.; Poojary, B.; Chikkanna, C.; Buridipad, S.K. *Eur. J. Med. Chem.* **2012**, *53*, 203
[14] Bankar, G.R.; Nampurath, G.K.; Nayak, P.G.; Bhattcharya, S. *Chem. Biol. Interact* **2010**, *183*, 327
[15] McCoull, W.; Addie, M.S.; Birch, A.M.; Birtles, S.; Bucett L.K.; Butlin, R.J.; Bowker, S. S.; Boyd, S.; Chapmn, S.; Davies, R.D.M.; et al. Bioorg. Med. Chem. Lett. 2012, 22, 3873.
[16] Savarino, A. *Expert Opin. Investig. Drugs **2006**, 15, 1507.*
[17] James, N.D.; Growcott, J.W. Zibotentan. *Drugs Future* **2009**, *34*, 624. J. Med. Chem. 2010,45, 2063.
[18] Kumar, G.V.S.; Rajendraprasad, Y.; Mallikarjuna, B.P.; Chandrashekar, S.M.; Kistayya, C. *Eur.*
[19] Guin, S.; Ghosh, T.; Rout, S.K.; Banerjee, A.; Patel, B.K *Org. Lett.* **2011**, *13*, 5976.
[20] Li, X.; He, D. *Dyes Pigm.* **2012**, *93*, 1422.
[21] Jagrut, V. B.; Netankar, P. D.; Jawale, D. V.; Mane, R. A.; Jadhav, W. N. *Bull. Korean Chem. Soc*.**2009**, *30*, 2812.
[22] (a) Jagrut, V.B.; Waghmare, R.A.; Jawale, D.V.; Mane, R.A.; Jadhav, W.N. *Int.J. ChemTech Res*. **2011**, 3, 1592. (b) Jagrut, V. B.; Lingampalle, D.L.; Phase, R.P.; Jadhav W.N.J. Chem Bio. *Phy. Sci. Sec*. A. **2012**, *2*, 1166. (c) Jagrut, V.B.; Lingampalle, D.L.; Netankar, P.D.; Jadhav, W.N. *Der Pharma Chemica* **2013,** *5*, 8.
[23] Lingampalle, D.L.; Jawale, D.V.; Waghmare, R.A.; Mane, R.A. *Synthetic Communications* **2010,** 2397.
[24] Jagrut, V.B.; Netankar, P.D.; Mane, R.A.; Jadhav, W.N. *Int. J. Chem. Sci*. **2012**, 10, 1705.