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Recyclable Zinc (II) Ionic Liquid Catalyzed Synthesis of Quinoxaline by Direct Condensation of Phenacyl Bromide and o-Phenylene Diamines at Room Temperature

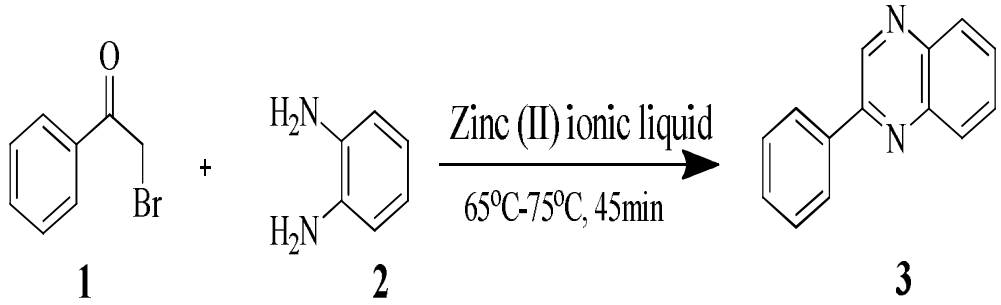
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Abstract: ***Using zinc (II) ionic liquid on silica as recyclable catalyst we have developed methodology for the synthesis of quinoxalines by condensation of phenacyl bromides and o-phenylene diamines in presence of zinc (II) ionic liquid . The Zinc (II) ionic liquid catalyst can be reused for three successive runs with slight decrease in yield.***
Keywords: Zinc (II) ionic liquid; quinoxaline; ambient temperature.

I. INTRODUCTION

Organic synthesis is a broad area that requires more efficient chemical methods and synthetic routes.[1] Quinoxaline and its derivatives are very important in various fields of science like chemical, pharmaceutical and material industries.[2] Quinoxalines and its frame-works continue to play an important role in nitrogen heterocyclic chemistry. Molecules that are contain quinoxaline subunits posses some interesting biological activities including anticancer, antimicrobial, anathematic, antidepressant and antifungal activities.[3] Various antibiotics such as echinomycin, levomycin and actinomycin[4] having quinoxaline moieties leads to inhibit the growth of gram positive bacteria and are active against several trans plantable tumors. They have been employed as dyes,[5] organic semiconductors,[6] chemically controllable switches,[7] efficient electroluminescent materials.[8] Quinoxaline derivatives are generally synthesized by condensation of 1, 2-diamines with α-diketones in MeOH under microwave irradiation,[9] oxidative coupling of epoxides with ene-1,2-diamines.[10] Additionally synthesis of quinoxalines by using solid-phase synthesis,[11] β-cyclodextrin (β-CD),[12] DABCO[13] oxidation trapping of α-hydroxy ketones with 1,2 diamines. The above methods suffer from limitations, preparations of starting materials, long reactions, unsatisfactory yields, expensive metal precursors and harsh reaction conditions, and difficult experimental procedures. Therefore, development of efficient and versatile procedure for the synthesis of quinoxaline derivatives still remains strongly desirable.

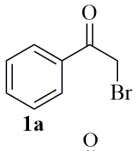
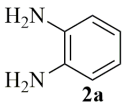
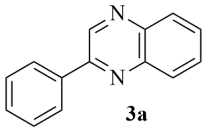
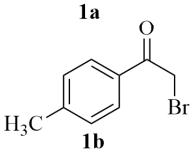
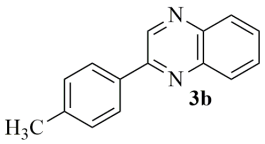
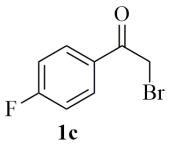
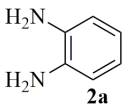
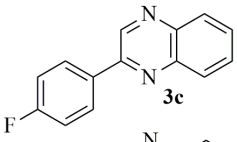
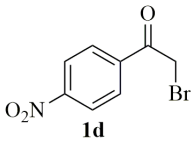
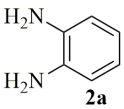
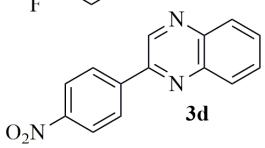
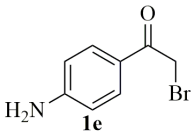
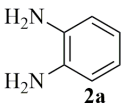
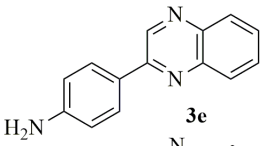
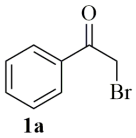
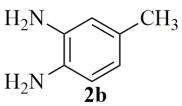
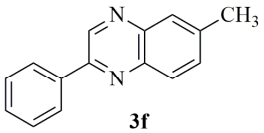
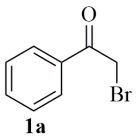
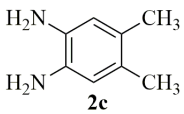
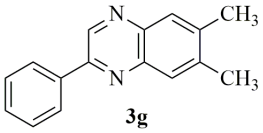
Silica is broadly used as inorganic space filler. Based on this we can transform the surface of silica with various inorganic or an organic moieties leads to many organic transformations. Additionally heterogeneous catalysts have gained considerable importance because of environmentally friendly alternative to the more wasteful traditional catalysts, easy to handle, not moisture sensitive and economic considerations. We have observed that zinc (II) ionic liquid is very suitable to catalyze the synthesis of quinoxalines. It can be easily recovered from the reaction mixture by simple filtration and can be re-used. Also it can be reused four successive runs with slight decrease in yield and slight increase in reaction time. Here we report the utilization of a heterogeneous catalyst for the preparation of quinoxalines from phenacyl bromide and phenylene diamines.



Scheme 1. Zinc (II) ionic liquid catalyzed synthesis of quinoxaline

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Table I: Zinc (II) ionic liquid catalyzed synthesis of quinoxalines[a]

Entry	Phenacyl bromide (1)	o-phenylenediamine (2)	Product (3)	Time(min)	Yield(%)[b]
(1)	 1a	 2a	 3a	65	95
(2)	 1b	 2a	 3b	60	95
(3)	 1c	 2a	 3c	70	90
(4)	 1d	 2a	 3d	80	85
(5)	 1e	 2a	 3e	75	90
(6)	 1a	 2b	 3f	64	96
(7)	 1a	 2c	 3g	59	98

Reaction conditions: a Phenacyl bromide (1.0 mmol), *o*-phenylene diamine (1.1 mmol), Zinc (II) ionic liquid (5mol %),); b yield.

II. RESULTS AND DISCUSSION

A model reaction using phenacyl bromide and o-phenylenediamine was carried out in the Acetonitrile in presence of Zinc (II) ionic liquid to investigate best reaction condition as shown in Table 1. The reaction was carried out at 80^{o}C the resultant compound formed with good yield but at room temperature slows down the reaction resulting in incomplete reaction with lower yield. It was clear that phenacyl bromides bearing electron-donating groups completed the reaction in shorter time than those bearing electron-withdrawing groups. The couplings of electron-rich 2-bromo-4'-methylacetophenonewith diamines provided the product in 95% yield in 60 min, (Table 1, entry 2). In the case of electron-poor 2-bromo-4'-nitroacetophenone, the corresponding products rapidly in low yield (Table 1, entry 4), which were also far more efficient than those in reported recyclable catalytic systems. It was worth noting that using electron rich *o*-phenylenediamine as the coupling partner, resulted in formation of desired product in good yield (Table 1, entries 6 and 7).

One of the main aims of our revise was to examine the reuse and recycling the catalyst. To conclude, we explored the reusability of the Zinc (II) ionic liquid catalytic system using the reaction of phenacyl bromide and *o*-phenylenediamine as the model reaction. After the completion of the reaction, add solvent to isolate the product. And separate the ionic liquid and reused directly under the conditions mentioned above. The results listed in Table 2 and showed the catalytic system could be reused up to 4 runs while retain the catalytic activity.

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Table 2: Reuse of catalytic system for the synthesis of quinoxaline by the reaction of phenacyl bromide and *o*-phenylenediamine[a]

Run	1	2	3	4
Yield(%)[b]	95	93	92	90

[a]Reaction conditions: Phenacyl bromide (1.0 mmol), *o*-phenylene diamine (1.1 mmol), Zinc (II) ionic liquid (5 mol %), [b]Isolated yield.

A. Experimental Procedure

Product purification by column chromatography by using Merck silica gel 60-120 mesh was performed. Melting points (mp) were determined in capillary tubes with a veego model: VMP-DS apparatus (heating rate 50C/min) and are given uncorrected. Infrared spectra (IR) were recorded using Thermo Nicole Nexus 670 FT-IR spectrometer. NMR spectra were recorded on either a Bruker Advance 300 or Advance 400 spectrometer. Chemical shifts (d) are given in ppm using internal references or TMS as external reference for $CDCl_3$. Mass spectra were recorded on Finnigan MAT 1020 mass spectrometer operating at 70 eV.

B. General Procedure

The phenacyl bromide 1a (1 mmol) and *o*-phenylenediamine 2a (1 mmol) the were added in 5 mL of Zinc (II) ionic liquid at room temperature then it was stirred at 80^{o}C for 60 min. After completion of the reaction monitered by TLC the reaction add solvent to seperate the qionoxaline from ionic liquid. The catalyst was washed with Et_2O 2-3 times for reuse. The filtrate was concentrated and the residue was subjected to column chromatography (Hexane–EtOAc) to obtain pure quinoxaline 3a. The recovered catalyst was reused for the synthesis of quinoxaline.

(3a) 2-phenylquinoxaline:[15] Milky white colour solid; mp 75-78^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.61-7.40 (m, 3H, Ar-H), 7.82-7.66 (m, 2H, Ar-H), 8.16-8.06 (m, 2H, Ar-H), 8.25-8.17 (m, 2H, Ar-H), 9.31 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 127.3, 129.0, 129.1, 129.5, 129.6, 130.1, 130.2, 136.7, 141.5, 142.2,143.3, 151.7; MS (ESI) m/z 207 $(M+H)^+$; HRMS (ESI) Calcd for $C_{14}H_{10}N_2$ $(M+H)^+$ 207.0922, found 207.0929.

(3b) 2-p-tolylquinoxaline: Brown colour solid; mp 90-92^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.45 (s, 3H, Ar-CH_3), 7.37-7.29 (m, 2H, Ar-H), 7.77-7.64 (m, 2H, Ar-H), 8.14-8.04 (m, 4H, Ar-H), 9.28 (s, 1H, Ar-H); ^{13}C NMR (75 MHz,$CDCl_3$) δ (ppm) 21.4, 127.4, 129.0, 129.2, 129.5, 129.8, 130.1, 133.9, 140.4, 141.4, 142.2, 143.2, 151.7; MS (ESI) m/z: 220 $(M+H)^+$; HRMS (ESI) Calcd for $C_{15}H_{12}N_2$ $(M+H)^+$ 220.1080, found 220.1083.

(3c) 2-(4-fluorophenyl) quinoxaline:[16] Yellow colour solid; mp: 120-122^{o}C; ^{1}H NMR (JCAMP, $CDCl_3$) δ (ppm) 7.18-7.28 (m, 2H, Ar-H), 7.67-7.82 (m, 2H, Ar-H), 8.06-8.12 (td, 2H, Ar-H), 8.18-8.27 (m, 2H, Ar-H), 9.27 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 116.0, 116.3, 129.1, 129.4, 129.5, 129.5, 130.3, 132.9, 142.8, 150.6, 165.8; MS (ESI) m/z 225 $(M+H)^+$; HRMS (ESI) Calcd for $C_{14}H_9FN_2$ $(M+H)^+$ 225.0924, found 225.0929.

(3d) 2-(4-nitro-phenyl)-quinoxaline: Yellow colour solid; mp 187-189^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77-7.85 (m, 2H, Ar-H), 8.11-8.18 (m, 2H, Ar-H), 8.40 (s, 4H, Ar-H), 9.36 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 127.7, 128.4, 129.2, 130.1, 130.8, 131.4, 133.0,138.6, 142.8, 147.0, 149.1; MS (ESI) m/z 252$(M+H)^+$; HRMS (ESI) Calcd for $C_{14}H_9N_3O_2$ $(M+H)^+$ 252.0756, found 252.0766.

(3e) 4-quinoxalin-2-yl-aniline: Black colour solid; mp 167-169^{o}C; ^{1}H NMR (500MHz, $CDCl_3$) δ (ppm) 6.76 (dd, 1H, $J_{(1,2)}$ = 8.9, $J_{(1,3)}$ = 3.0, Ar-H), 7.29 (t, 1H, J =7.9, Ar-H), 7.45-7.58 (m, 2H), 7.64-7.79 (m, 2H, Ar-H), 8.09 (t, 2H, J = 10.8, Ar-H), 9.25 (s, 1H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$) δ (ppm) 113.7, 116.9, 117.6, 129.0, 129.3, 129.4, 129.9, 130.1, 137.7, 141.4, 142.1, 143.4, 147.2; MS (ESI) m/z 222 $(M+H)^+$; HRMS (ESI) Calcd for $C_{16}H_{11}N_3$ $(M+H)^+$ 222.1392, found 242.1410.

(3f) 6-methyl-2-phenylquinoxaline: White colour solid; mp 134-136^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.62 (s, 3H, Ar-CH_3), 7.61-7.42 (m, 4H, Ar-H), 8.03-7.82 (m, 2H, Ar-H), 8.18 (m, 2H, Ar-H), 9.24 (d, J =7.3MHz, 1H, Ar-H); ^{13}C NMR (75MHz, $CDCl_3$) δ (ppm) 20.1, 127.2, 127.9, 128.4, 128.8, 129.6, 136.9, 139.9, 140.3, 140.6, 140.9, 142.2, 150.8; MS (ESI) m/z 220 $(M+H)^+$; HRMS (ESI) Calcd for $C_{15}H_{12}N_2$ $(M+H)^+$ 220.1082, found 220.1085.

(3g) 6,7-dimethyl-2-phenylquinoxaline: Light yellow colour solid; mp 122-124^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.51 (s, 6H, Ar-CH_3), 7.56-7.41 (m, 3H, Ar-H), 7.89-7.79 (m, 2H, Ar-H), 8.20-8.12 (m, 2H, Ar-H), 9.19 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75MHz) δ (ppm) 20.3, 20.4, 127.3, 128.1, 128.6, 129.0, 129.8, 140.1, 140.8, 142.4; MS (ESI) m/z 234 $(M+H)^+$; HRMS (ESI) Calcd for $C_{16}H_{14}N_2$ $(M+H)^+$ 234.1220, found 234.1223.

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III. CONCLUSIONS

We have demonstrated that Zinc (II) ionic liquid catalyst was proved to be highly efficient for the synthesis of quinoxaline. Furthermore, the Zinc (II) ionic liquid catalyst can be easily separated and recovered from the reaction mixture by filtration and reused for up to 4 runs without noticeable losing activities. This method has several advantages, such as low cost, short reaction time, excellent yield, simple experimental as well as isolation procedures. This greener methodology will be useful in synthesis of libraries of compounds having such different bioactivities as pharmaceuticals and agrochemicals.

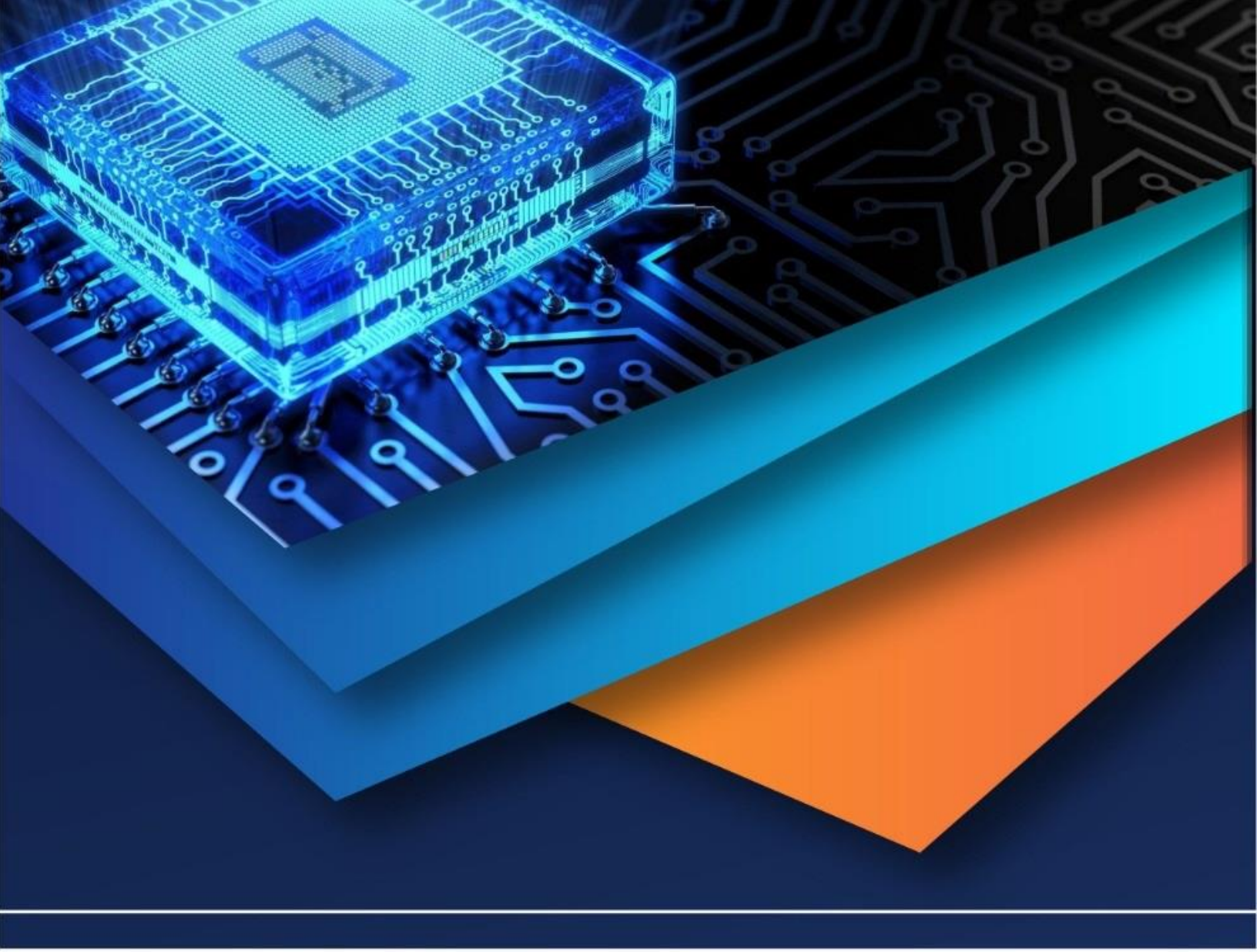
IV. ACKNOWLEDGEMENTS

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