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Aq. Ammonium chloride induced one pot efficient synthesis of bioactive quinoxalines

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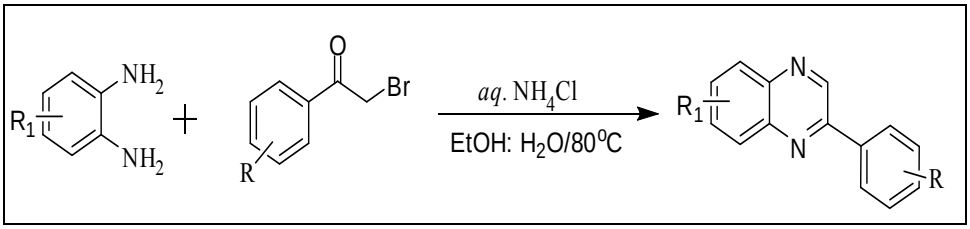
Abstract
In the current protocol, we have developed a highly efficient, mild, simple, acid-free, metal-free, cost-effective and eco-benign catalyst system to generate quinoxalines at reflux temperature in ethanol: water. *Aq*. ammonium Chloride was successfully utilized to carry out the current conversion giving the product in good to excellent amount of yield of the product within shorter reaction times.

Keywords: o-phenylenediamines, Substituted Phenacyl Bromide, *Aq.* Ammonium Chloride, Quinoxalines

1. Introduction
Quinoxaline substituted quinoxalines, and their derivatives are important nitrogen-containing heterocyclic compounds possessing potent biological as well as pharmaceutically valued activities [1]. In addition, they also constitute a unique building block, & intermediate for a variety of medicinally important heterocyclic nucleus showing antifungal, antibacterial, anticancer, antitubercular, antileishmanial, antimalarial and antidepressant activities [2]. In addition, some of the derivatives are known to show potent antimicrobial, antithrombotic, anti-pain anti-inflammatory activities. In addition to these potential applications majority of quinoxaline and their derivatives have shown to possess unique applications for their use in semiconductors, organic ligands, DNA cleaving agents, cavitands, dyes, chemically controllable switches, dehydroannulenes, anion receptors, & electroluminescent materials [3].
Quinoxalines can be synthesized by a different traditional method that involves a condensation reaction between aryl 1,2-diamines with 1,2-dicarbonyl compound [4], 1,4-addition of 1,2-diamines to diazenylbutens [5], and oxidation trapping of α-hydroxy ketones with 1,2-diamines [6]. Thus in the above routine methods, there is a need of strong acidic media in addition to severe reaction conditions.
In recent times, we have been witnessing a reaction of differently substituted phenacyl bromides and 1, 2-diaminoarenes as an alternative approach [7] for the synthesis of bioactive quinoxalines. Recently, under this heading various researchers across the globe have accomplished the synthesis of quinoxaline by the reaction of phenacyl bromides with 1, 2-diamines in solid phase [8], β-cyclodextrin (b-CD) [9], $HClO_4$–SiO_2 as a heterogeneous catalyst[10], sodium hexafluorophosphate-Amberlite[11], KF-alumina [12], $CeCl_3.7H_2O$ [13], Polyethylene glycol (PEG-400) [14], cetyltrimethylammonium ammonium bromide (CTAB) [15], Sodium tetrachlorocuprate(III) dehydrate [16], TMSCl-water [17], tetrabutylammonium bromide in basic media [18], DMSO in solvent free conditions [19], microwave irradiation [20], DABCO[21] were successfully used methods reported in the literature. Although the methods reported in the literature has mentioned superior merits over their counterparts that includes mainly, shorter reaction time with a good yield of products and substrate scope. But the majority of synthetic protocols suffers from certain drawbacks that include mainly longer reaction time, tedious workup procedure, use of toxic, air sensitive, excessive and expensive metal catalyst, the poorer yield of products, industrial scale-up problems, generation of toxic wastes and solvents that can hamper long-term environment issues. All these countable demerits enlightened us to devise an efficient straightforward synthetic approach that can bypass all these major notable demerits for the synthesis of diverse quinoxalines and their derivatives.
In current era due to stringent environmental safety regulations, the development of cost-effective, methods with the use of non-metals along with eco- benign catalytic systems [22] are gained surmount popularity and trust among the various methods under the ageism of organic

synthesis. Hence to advocate and propagate this heading we thought of recruiting Ammonium Chloride [23] (NH_4Cl) as an easily available, inexpensive, eco-friendly & non-carcinogenic catalyst to carry out the reaction. Ammonium chloride has been employed successfully to bring and promote synthesis of various organic compounds, that includes mainly Ugi four-component reactions, four-component synthesis of pyrrolo [3,4-b] pyridinones, to carry aliphatic Claisen rearrangement, reduction of azo compounds to their corresponding hydrazines, Biginelli synthesis of 3,4-dihydropyrimidinones, reduction of nitrophenols in aqueous media, and under ultrasound, reductive cleavage of azo compounds, synthesis of diindolylmethane, and the thia-Michael addition reaction [24]. To the best of our knowledge, there is no report on the synthesis of quinoxalines using *Aq*. Ammonium chloride. Thus to address all these issues and develop an eco-benign protocol we thought of presenting and devising a simple, environmentally sustainable method for the construction of quinoxaline heterocyclic compounds have been disclosed in this current paper. Under this heading synthesis of structurally diverse quinoxalines are achieved by the reaction of o-phenylenediamines with phenacyl bromides in the presence of aq. Ammonium chloride in ethanol: water solvent under reflux conditions at 80 ^{0}C temperature for 0.5 hr to yield the product in good to excellent amount of yield. (Scheme 1).



Scheme 1: *Aq.* Ammonium Chloride Induced Synthesis of Quinoxalines

2. Results and Discussion

Our study was initiated by the reaction of phenacyl bromide with o-phenylenediamines in the presence of *aq.* ammonium chloride in water at room temperature. The reaction worked well to give the desired product in 6 hrs of time. Thereon we studied the effect of solvent on the rate of reaction and yield of product by making different solvent system combination like in dichloromethane, acetonitrile, 1,4-dioxane, ethanol, ethanol: water yielded the product in 30%, 37% 45% 65% & 91% yield of the quinoxaline in 5 hr of reaction time (Table-1).

Further, we have studied the effect of temperature on the reaction and we carried out the two component reaction under different conditions ranging from 40 ^{o}C, 60 ^{o}C, 80 ^{o}C and 100 ^{o}C (Table: 2). From the above different scale of temperature, we got the highest yield of desired product at an 80 ^{o}C in 92%. So Thus we have finalized the reaction conditions by utilizing ethanol: water solvent system at 80 ^{o}C. In addition to above solvent system and temperature optimization conditions, we have also carried out the amount of catalyst utilized to carry out the above-said reaction.

Table 1: Synthesis of quinoxaline *2,3-diphenylquinoxaline* (3a) in the presence of a catalytic amount of NH_4Cl (20 mol%) in various solvents at Room temperature.

Entry	Solvent	Reaction time (h)	Yield (%)
1	Dichloromethane	6	35
2	Acetonitrile	6	37
3	1,4-dioxane	6	45
4	ethanol,	6	65
5	ethanol: water	5	91
6	water	6	89

Table 2: Synthesis of quinoxaline *2,3-diphenyl quinoxaline* (3a) in the presence of a catalytic amount of NH_4Cl (20 mol%) in ethanol: water at various temperature.

Entry	Temperature (^{o}C)	Reaction time (h)	Yield (%)
1	40	2	80
2	60	1.5	85
3	80	0.5	92
4	100	0.5	90

To optimize this, we have utilized the different amount of mole % of ammonium chloride ranging from 10, 20, 30, 40, 50 mole % of catalyst yielding the quinoxaline in 85, 92, 90, 85, 82% yield of product (Table-3) within 0.5 h of reaction time.

Finally, we have the optimized conditions in hand, we continued our studies of the electronic effects of the substituents on phenacyl bromide and *o-phenylenediamines*. The effect of electron releasing and electron with drawing substituent on the aromatic ring of phenacyl bromides on the reaction was investigated. The results are summarized in Table 4, which demonstrates that electron releasing groups and electron withdrawing groups did not affect significantly on the yields and the reaction times. While with the use of 1,2-diamines possessing electron-withdrawing substituent took longer reaction times and the yields were lower in comparison to their counter parts.

Table 3: Study of synthesis of quinoxaline *2,3-diphenyl quinoxaline* (3a) in the presence of a different amount of mole % of NH_4Cl in ethanol: water at 80 ^{o}C temperature.

Entry	Mole% of catalyst	Reaction time (h)	Yield (%)
1	10	2	85
2	20	1.5	92
3	30	0.5	90
4	40	0.5	85
6	50	0.5	80

3. Experimental

3.1. General

All chemicals, unless otherwise specified, were purchased from commercial sources (Aldrich, Spectrochem, and SD Fine chemicals) and were used without any further purification. All the products were characterized by comparison of their physical data with those of known samples and by their spectral data. Melting points were measured in open capillaries & are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded at ambient temperature on a BRUKER AVANCE 300 MHz using CDCl3 or DMSO-d_6 as the solvent and using TMS as an internal standard. FT-IR and

Mass spectra were recorded on a Bruker Alpha spectrometer in KBr and Shimadzu LC-MS/MS respectively. Further, the progress of the reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F254 aluminum sheets and visualized by UV light.

3.2. General procedure for the preparation of quinoxalines:

To a stirred mixture of phenacyl bromide (1 mmol) and pyridine (0.1 mmol) in THF (2 mL) was added 1,2-diamine (1 mmol) slowly at room temperature and continued for a period of specific time (Table 4). The progress of the reaction was monitored by thin layer chromatography. After completion of the

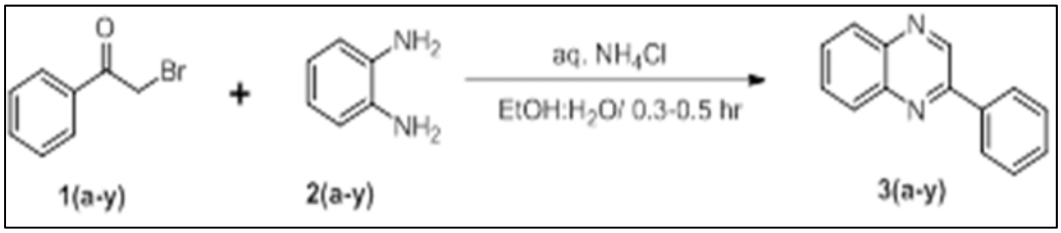


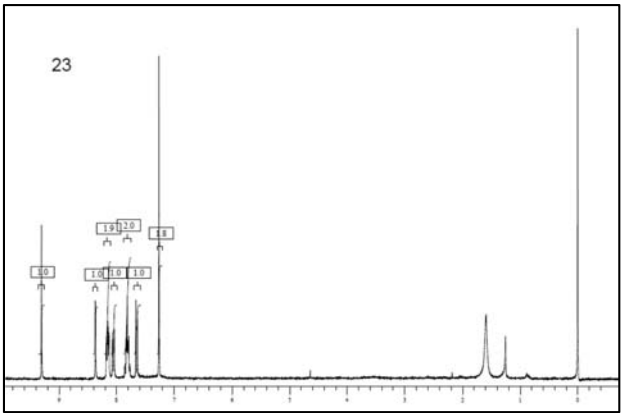
Table 4: Synthesis of various Substituted Quinoxalines utilizing *Aqueous* NH_4Cl in ethanol: water solvent system at 80 °C

Entry	Phenacyl Bromide	1, 2-diamine	Product	Time (h)	Yield (%)[Ref]
1.	Phenacyl bromide-1a	o-phenylene diamine	3a	0.5	92[21]
2.	Phenacyl bromide-1b	4-methylbenzene-1,2-diamine	3b	0.5	90[21]
3	Phenacyl bromide-1c	4,5-dimethylbenzene-1,2-diamine	3c	0.5	88[21]
4.	Phenacyl bromide-1d	4-nitrobenzene-1,2-diamine	3d	0.5	82[21]
5.	Phenacyl bromide-1e	4-methoxybenzene-1,2-diamine	3e	0.5	86[21]
6.	p-chloro-phenacyl bromide-1f	o-phenylene diamine	3f	0.5	84[21]
7.	p-chloro-phenacyl bromide-1g	4-methylbenzene-1,2-diamine	3g	0.5	85[14]
8.	p-chloro-phenacyl bromide-1h	4,5-dimethylbenzene-1,2-diamine	3h	0.5	88[14]
9.	p-chloro-phenacyl bromide-1i	4-nitrobenzene-1,2-diamine	3i	0.5	80[14]
10.	p-chloro-phenacyl bromide-1j	4-methoxybenzene-1,2-diamine	3j	0.5	87[14]
11.	3,4-dichloro-phenacyl bromide-1k	o-phenylene diamine	3k	0.5	88
12.	p-bromo-phenacyl bromide-1l	o-phenylene diamine	3l	0.5	86[21]
13.	p-bromo-phenacyl bromide-1m	4-methylbenzene-1,2-diamine	3m	0.5	8[21]
14.	p-bromo-phenacyl bromide-1n	4,5-dimethylbenzene-1,2-diamine	3n	0.5	88[21]
15.	p-bromo-phenacyl bromide-1o	4-nitrobenzene-1,2-diamine	3o	0.5	80[14]
16.	p-bromo-phenacyl bromide-1p	4-methoxybenzene-1,2-diamine	3p	0.5	85[21]
17.	p-Fluro-phenacyl bromide-1q	o-phenylene diamine	3q	0.5	82[14]
18.	p-nitro-phenacyl bromide-1r	o-phenylene diamine	3r	0.5	87[14]
19.	p-nitro-phenacyl bromide-1s	4-methylbenzene-1,2-diamine	3s	0.5	84[14]
20.	p-nitro-phenacyl bromide-1t	4,5-dimethylbenzene-1,2-diamine	3t	0.5	88[21]
21.	p-methoxy-phenacyl bromide-1u	o-phenylene diamine	3u	0.5	90[21]
22.	p-methyl phenacyl bromide-1v	o-phenylene diamine	3v	0.5	89[21]
23.	p-methyl phenacyl bromide-1w	4-methylbenzene-1,2-diamine	3w	0.5	90[14]
24.	p-methyl phenacyl bromide-2x	4,5-dimethylbenzene-1,2-diamine	3x	0.5	91[14]
25.	p-methyl phenacyl bromide-2y	4-nitrobenzene-1,2-diamine	3y	0.5	88[14]

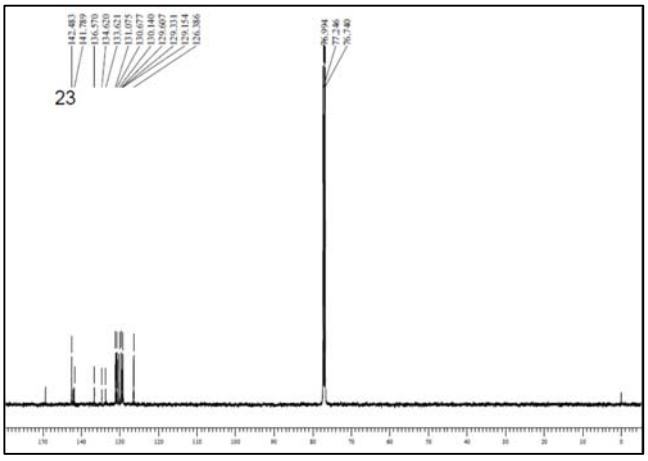
the reaction, as indicated by TLC, the reaction mixture was poured on crushed ice. The reaction residue was filtered and washed with water (3X10 mL). The product was then recrystallized in hot ethanol to yield the product in pure form. All the pure products were identified by their IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry data. In addition, the known compounds data were compared with their reported data in the literature.

Spectral data for some of the representative compound is given as follows:

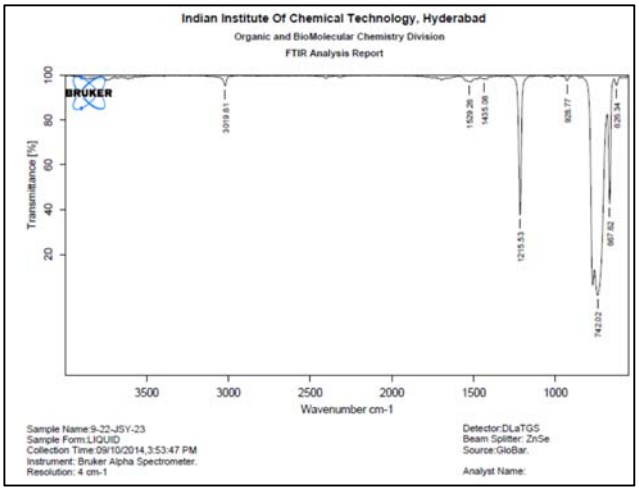
Compound 3k: M.P. 190-192 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.65 (d, 1H, J = 8.36 Hz), 7.80 (m, 2H), 8.12 (d, 1H, J = 8.3 Hz), 8.20 (m, 2H), 8.40 (s, 1H), 9.35 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 126.3, 129.1, 129.3, 129.6, 130.1, 130.6, 131, 133.6, 134.6, 136.5, 141.7, 142.4, IR (KBr, v/cm): 626, 667, 742, 928, 1215, 1453, 1529, 3019; ESI-MS: 275 (M+1).



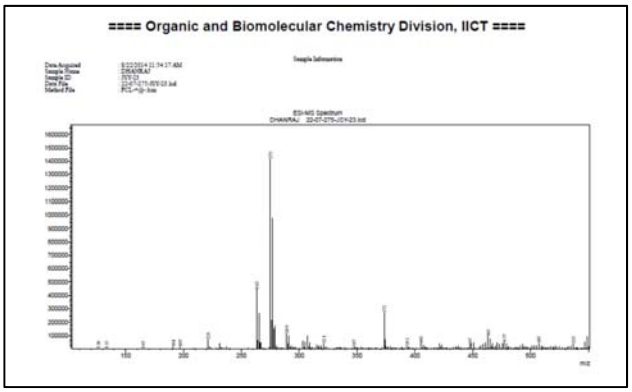
^{1}H NMR Spectrum of compound 3k



^{13}C NMR Spectrum of compound 3k



IR Spectrum of compound 3k



ESI-MS Spectrum of Compound 3k

4. Conclusions

In conclusion, the current paper highlights a most straightforward, convenient and efficient process for the synthesis of diverse quinoxaline and their derivatives by use of aqueous ammonium chloride. This present protocol offers some of the most promising features that include the use of a cheap, non-toxic catalyst, with the simple experimental procedure, shorter reaction times giving higher yields of product. In addition to all these merits, it has proven its applicability in organic synthesis fulfilling the concept of eco-benign approach.

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