IJISET - International Journal of Innovative Science, Engineering & Technology, Vol. 1 Issue 6, August 2014.
www.ijiset.com

ISSN 2348 – 7968

A Greener Chemistry Approach for Synthesis of 2,3-diphenyl quinoxaline

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ABSTRACT

The objective of present research work is to provide green technique for synthesis of 2,3-diphenyl quinoxaline. Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities. Highly efficient and simple methods have been described in this manuscript for the synthesis with competent yields. Present synthesis complies with principle of Green chemistry. As part of current studies, we here in report economical practical techniques like- ultrasonic wave organic synthesisand by application of green solvents. On completion of reaction the products were characterized by IR, NMR and Mass Spectra. These methods are more convenient and reactions can be carried out in higher yield (94-97%), shorter reaction time (08mins-20mins) and milder conditions, without generation of pollution and safer to analyst.

Keywords: *Ultrasonic irradiation, Green chemistry, Green solvents, Organic synthesis Ecofriendly, Efficient.*

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1. INTRODUCTION

Quinoxaline derivatives are an important class of nitrogen containing benzo heterocyclic compounds containing a ring complex made up of a benzene ring and a pyrazine ring[1]; for medicinal chemists, since it has wide range of therapeutic uses and potential activities; acting as antimicrobial agents[2,3], cytotoxic agents, anti-tubercular, anxiolytic, anti-HIV, antioxidant[3], anti-inflammatory[4,5], antimalarial, anticancer, antidepressant[2], antibacterial, antifungal[4]. antibiotics, such as echinomycin, levomycin and actinoleutin that are known to inhibit growth of gram positive bacteria and are active against various transplantable tumors[5,6], as well as rheumatoidarthritis, hemangioma and Kaposi's sarcoma, which are related to vasculogenesis and angiogenesis[7,8].

They are also used in the agricultural field as fungicides, herbicides and insecticides[8], pesticides[9,10].as well as their application in dyes, efficient electroluminescent materials, organic semiconductors, chemical controllable switches, corrosion inhibitor[9,10],building blocks for the synthesis of anion receptor, cavitands, dehydroannulenes, and DNA cleaving agents[8,11].Because of their diverse pharmacological and biological properties, they have emerged as privileged structures in combinatorial drug discovery libraries[12].

Heterocycles are used in many various industries. However most of these compounds aren't extracted from natural source, but are synthesized. Consequently, many methods have been developed for the synthesis of quinoxaline[10], despite the progress, the synthesis of these compounds remains less than ideal. Thus, the development of environmentally friendly benign (*Green Chemistry*), high-yielding and clean approaches for the yield of quinoxaline derivatives still remains a highly desired goal in organic synthesis. Performing organic reactions in water has attracted much attention over the past decades due to its numerous advantages such as being considerably safe, nontoxic, environmentally friendly, and cheap. In addition, reactions in water can facilitate access to different reactivity and selectivity patterns compared with those observed in common organic solvents [13].

Development of a mild and eco-friendly one-pot synthetic protocol for these highly significant classes of compounds is desirable. Now a days recognition for the development of green synthetic protocols is increasing.[14]

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Numerous methods are available for the synthesis of quinoxaline derivatives which involve condensation of 1,2-diamines with α-diketones,[15,16] 1,4-addition of 1,2-diamines to diazenylbutenes,[17] cyclization–oxidation of phenacyl bromides [18,19] and oxidative coupling of epoxides with ene-1,2-diamines.[20] 2,3-Disubstituted quinoxalines have also been prepared *via* the Suzuki–Miyaura coupling reaction,[21] condensation of *o*-phenylenediamines with 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation,[22] and iodine catalyzed cyclocondensation of 1,2-dicarbonyl compounds with substituted *o*-phenylenediamines in DMSO[23] or CH_3CN [24].Also, α-hydroxy ketones react with *o*-phenylenediamines in the presence of transition metals such as Mn, Pd, Ru and Cu, Pb to give quinoxalines.[20, 25-37]

Improved methods have been reported for the synthesis of quinoxaline derivatives including a bi-catalyzed oxidative coupling method [20],a microwave procedure [22] ,and the use of $RuCl_2$-$(PPh_3)_3$-TEMPO [25], Manganese dioxide[26],$POCl_3$ [30],zeolites [23], iodine [31],cerium ammonium nitrate [32],$CuSO_4.5H_2O$ [33],Montmorillonite K-10 [34], $H_6P_2W_{18}O_{62}.24H_2O$; Wells-Dawson[35] and SA/MeOH[36]as a catalyst.

Recently, Juncai and co-workers [38]used *o*-phenylenediamines and α-hydroxy ketones as reactants in the synthesis of quinoxaline derivatives. A variety of catalysts were tested in synthesis reactions such as acetic acid [8], iodine [24], $CuSO_4.5H_2O$ [33], nickel nanoparticles [39]gallium(III)triflate[40], montmorillonite K10 [34], ionic liquids [41], Nano-TiO_2[42], sulfated TiO_2[43], $Pd(OAc)_2$[15], $RuCl_2$-(PPh_3)3-2,2,6,6-tetramethylpiperidine 1-oxyl(TEMPO) [15], MnO_2[15], Al_2O_3[44], zirconium(IV)-modified silica gel [45], nanocrystallineCuO[46], cerium(IV) ammonium nitrate [32], iron exchanged molybdophosphoric acid [47], silica-bonded S-sulfonic acid [48].

Different reaction media were used to perform this synthesis such as the use of acetonitrile[24] or DMSO[49] as solvents, or even cleaner ways as the solvent-free reaction [44,50,] with various ways to give energy to the substrate, such as microwave radiation [44,50], ultrasound [46] or even room temperature [43,48,36.]many of these processes suffer from one or more limitations such as drastic reaction conditions, low product yields, tedious work-up procedures, the use of toxic metal salts as catalysts, and relatively expensive reagents. which has resulted in their reduced commercial attractiveness . In view of the disadvantages, there remains a scope for the development of facile and green method for the synthesis of the quinoxaline derivatives.

In view of the above shortcomings, development of a mild and eco-friendly protocol for these highly significant classes of compounds was investigated, here we used ultrasonic radiations to complete the reaction; ethanol employed as a solvent was not only inexpensive but also environmentally benign,.

2. MATERIALS AND METHODS

Melting points of the synthesized heterocycle was determined on Gallenkamp's apparatus, Model No. IC0949 and were uncorrected. The purification of synthesized compounds was performed by washing with appropriate solvent system. Nuclear Magnetic Resonance spectra were recorded withBruker-Avance-III, 400MHz, Switzerland. Infrared spectra were recorded on FTIR spectrophotometer Bruker-Tensor 27, Germany. Mass spectra were recorded in Bruker-MicrOTOFQ-II, Germany. All spectral analysis was performed in ambient condition.

Materials: All the Chemicals and reagents used for the study were of analytical grade, O-phenylenediamine,Benzil, p-TSA were procured from Lobachem, Mumbai. Ethanol, was procured from MERCK, Germany. Water used in the study was extra pure double distilled.

2.1 General scheme for the synthesis

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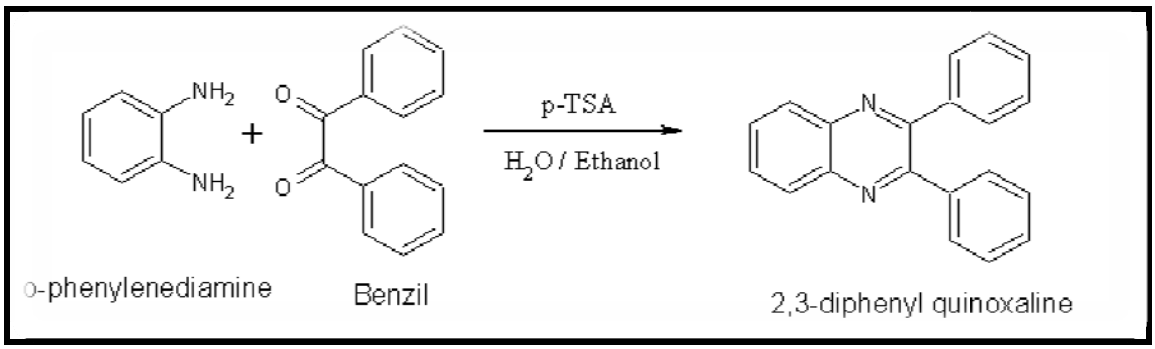

2,3-diphenyl quinoxalinewas prepared following a general reaction as stated above. The various experimental routes followed for the synthesis is as given below:

Method A: O-phenylenediamine (0.108 gm, 0.001 mol) and Benzil (0.210 gm, 0.001 mol) were taken in flat bottom flask, dissolved in ethanol (5 ml) and then p-TSA (0.034gm, 0.002mol) was added to this mixture. The mixture was sonicated for 8 minutes (Approximately). After completion of reaction, reaction mass was poured on crushed ice. It was stirred for 10 minutes. The solid separated was filtered, washed with water, dried in oven and crystallised in ethanol **.**

Method B:O-phenylenediamine (0.108 gm, 0.001 mol), Benzil (0.210 gm, 0.001 mol) and p-TSA (0.034gm, 0.002mol) were taken in flat bottom flask, dissolved in ethanol (5 ml).The mixture was stirred for 10 minutes (Approximately). After completion of reaction, reaction mass was poured on crushed ice. It was stirred again for 10 minutes. The solid separated was filtered, washed with water, dried in oven and crystallised in ethanol **.**

Method C: O-phenylenediamine (0.108 gm, 0.001 mol), Benzil (0.210 gm, 0.001 mol) p-TSA (0.034gm, 0.002mol) were taken in flat bottom flask, dissolved in water (10 ml). The mixture was stirred for 20 minutes (Approximately). After completion of reaction, solid separated was filtered, washed with water, dried in oven and crystallised in ethanol.

3. RESULTS

IR: Characteristic IR (KBr)bands found at:1665.51, 1585.40, 1446.19, 1317.39, 1210.31, 1167.94, 1069.76, 995.32, 873.21, 786.54, 716.79, 639.85(cm^{-1}). The absorption bands at 1665 cm^{-1} and 1585.40 cm^{-1} are due to C-C stretching of aromatic ring (phenyl nucleus), at 1210.31 cm^{-1} due to plain bending of C-H in aromatic phenyl ring, weak absorption band at 3061 cm^{-1} due to aromatic -C-H stretching, strong absorption band at 716.79 cm^{-1} and 786.54 cm^{-1} indicate mono substituted benzene ring. The weak absorption band at 1446 cm^{-1} is due to –C=N stretching.

1H-NMR: (400MHz, $CDCl_3$), δ ppm :8.01, 7.99, 7.69, 7.67, 7.65, 7.54, 7.53, 7.51.

MS (m/z) : Anal. Calcd for **$C_{20}H_{14}N_2$**282.33 (calc.), 283.13 (exp.)

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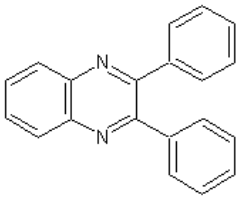
Table 1.Comparison between traditional synthesis and green techniques

Sr. No.	Compound	Parameter	Traditional method	Green Techniques		
				A	B	C
1	 2,3-diphenylquinoxaline	Time Required	1 hr	08 min	10 min	20 min
2		% Yield	75	97	95	94
3		Melting point	125-127	126	125	127

4. DISCUSSION

Heravi et al. [51]and More et al. [32]reported greener methods for the synthesis of quinoxaline derivatives in green solvents ($EtOH/H_2O$), using copper sulphate pentahydrate and cerium (IV) ammonium nitrate as catalysts, respectively. Though the above mentioned methods are greener in approach for small scale synthesis, but the toxic nature of these catalysts (copper sulphate a mutagenic agent and cerium (IV) ammonium nitrate a skin corrosive, irritant and mild explosive; owning to the oxidizing property) restricts their use in large scale or long term synthesis.Radhakrishnan et al., [2]reporteda rapid and green synthetic approach for the synthesis of quinoxaline derivatives from o-phenylenediamines and 1,2-dicarbonyl compounds in the presence of nontoxic, cheap and edible citric acid as a catalyst in ethanolic medium, the reaction was completed in less than 1 min with 94% yield.

Conventional Method of synthesis:1.26 gm of benzil was dissolved in 8 ml of warm rectified spirit and transferred into 100 ml round bottomed flask containing 1.08 gm of O-Phenylenediamine dissolved in 8 ml of rectified spirit. The mixture was refluxed for 1 hour on a boiling water bath. Then, water was added until slight cloudiness persists. The crude product was filtered and recrystallised from rectified spirit (75% yield, 1-1.5hrs)[52,53]. Significant yield improvement at a shorter reaction time was observed when we synthesized the same compound with the help of ultrasound (97%, 8 minutes).

Joshi et al.[54], synthesized 2,3-Diphenyl quinoxaline by microwave irradiation of benzil (0.01M), o-phenylenediamine (0.01M) and ethanol (16ml) which gave 60% yield in a reaction time of 55 seconds, while we achieved 97% yield after 8 minutes of sonication. The yield of our compound was found to be significantly higher than the conventional method of synthesis which led to 51% yield at a reaction time of 0.5 hrs[54]. Although the reaction time by Joshi et al.[54] was less, the yield could be increased by modifying the technique and slightly varying the reaction time.

Jyotidas and Sarkar[41]synthesised quinoxalines in aqueous medium in the presence of tetraethylammonium bromate. They found spectral data of 2,3-Diphenylquinoxaline^{1}H NMR: (300MHz, CDCl3) ∂ 8.193(t, 2H, J1=2.7 Hz, J2=3.6 Hz, ArH),7.77-7.803(m, 2H, ArH), 7.519-7.544(m, 4H, ArH), 7.344-7.365(m, 6H, ArH).13C NMR: (75MHz, CDCl3) ∂ 153.43, 141.17, 138.99, 129.95, 129.79,129.15, 128.78, 128.25.IR (cm^{-1}): 3057.17, 3028.24, 1548.84. The yield was found to be as high as 92% [11]synthesized 2,3diphenyl quinoxaline applying efficient practical techniques like- sonication (sonochemistrysythesis), UV radiations and simple mechanochemistry using mortal-pastel method. The overall progress of the reaction was monitored by TLC and characterized by IR and NMR. Compared with traditional methods, these methods are more convenient and reactions lead to higher yield (95.8-98.3%), shorter reaction time (10, 15, 17 minutes) and milder conditions, without generation of pollution and safer to analyst. The melting point of the compound observed by Bendale et al., [11]was in the range 122-124°C, whereas we observed the melting point to be between 125-127°C. The spectroscopic studies revealedλmax: 292 nmIR: Characteristic IR (KBr) bands found at: 3065, 1441, 1395, 768, (vmax/cm-1).1H NMR: (500 MHz, Chloroform) δ 8.06, 8.06, 8.01, 8.01, 8.01, 8.01, 7.53, 7.53, 7.43, 7.43, 7.43, 7.43, 7.41, 7.41.MS (m/z): 282.12 (100.0%), 283.12 (21.8%), 284.12 (2.4%). Our observation of MS was (m/z): 283.13. As observed by Bendale et al.,[11] we also found that in comparison with traditional methods our methods are more convenient and reactions can becarried out in higher yield (94-97%), shorter reaction time (8-20

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minutes) and milder conditions (sonication and stirring at room temperature), without generation of pollution and safer to analyst.

Jesus et al.,[7] reported microwave assisted synthesis of quinoxalines and found reactions that involved at least one liquid reagent showed shorter reaction times than those involving two solid reagents. The reaction time under microwave irradiation was reduced to 180 seconds with 90% yield of the compound. On analysis they found that melting point was between 128–129 °C which was closer to that observed by us. They concluded that Solvent-free and microwave-assisted synthesis provides an easy, fast and eco-friendly methodology for the preparation of some 6-substituted quinoxalines and pyrido[2,3*b*]pyrazines derivatives from *α*-dicarbonyl derivatives with substituted *o*-phenylenediamines.

Seyed Mohammad Vahdat and SaeedBaghery[6] studied the effect of Solvent in the synthesis of 2,3-diphenylquinoxaline under conditions involving; *o*-phenylenediamine, benzil, ionic liquid catalystand solvent. They observed that when water and ethanol were used as solvent the reaction time required was less, while the yield of compound was increased; 94 and 95% with water and ethanol respectively (reaction time 25 and 23 minutes) whereas under solvent free conditions the yield decreased to 51% and the reaction time increased to 40 minutes. Mina Saeediet al. [55] Synthesized quinoxaline derivatives in aqueous media, via reaction of 1,2-phenylenediamine derivatives with 1,2-diketones employing Bakers' yeast as a catalyst. They found that the reactions proceed rapidly and the products are obtained in good yields. On performing spectral analysis they observed Melting point of 2,3-Diphenylquinoxaline in the range 124-125 °C; IR (KBr, cm^{-1}): 1664, 1591, 1473; ^{1}H NMR (500 MHz, CDCl3): δ= 7.30- 8.23 (m, 14H); MS, *m/z*: 282 (M, 100%). 2,3-Diphenylquinoxaline was isolated in 85% yield after 10 min.

To investigate the role of ultrasonic irradiation in our method, the reactions were carried out in the presence of p-TSA, dissolving O-phenylenediamine and benzil in EtOH; sonicating the above mixture at room temperature. From the results it is clear that, under the same reaction conditions, reactions under ultrasonic irradiation led to relatively higher yields and shorter reaction times.It is presumed that the efficiency using ultrasound irradiation is due to the cavitation phenomena. An ultrasonic wave is a pressure wave with alternate compressions and rarefactions which is able to break the intermolecular forces maintaining the cohesion of the liquid and produces a cavity in the rarefaction section of the wave. The chemical and physical effects of ultrasound derive primarily from acoustic cavitation which includes formation, growth and collapse of the cavity[56,57,58.] Bubble collapse in liquids results in an enormous concentration of energy from the conversion of kinetic energy of liquid motion into heating of the contents of the bubble. The high local temperatures and pressures produced by cavitation lead to a diverse set of applications of ultrasound such as accelerating the rate of the reaction, changing the reaction pathway, enhancing chemical reactivity and important uses in synthetic organic compounds[59.] Catalyst regeneration is essential for industrial production.

The discovery of the piezoelectric effect in the 1880s provided the basis for the construction of modern ultrasonic devices. Piezoelectric materials generate mechanical vibrations in response to an applied alternating electrical potential. If the potential is applied at sufficiently high frequency, ultrasonic waves are generated. The phenomenon responsible for the beneficial effects of ultrasound on chemical reactions is cavitation. Ultrasonic waves are propagated via alternating compressions and rarefactions induced in the transmitting medium through which they pass. During the rarefaction cycle of the sound wave, the molecules of the liquid are separated, generating bubbles that subsequently collapse in the compression cycle. These rapid and violent implosions generate short-lived regions with local temperatures of roughly 5000 °C, pressures of about 1000 atm and heating and cooling rates that can exceed 10 billion °C per second. Such localized hot spots can be thought of as micro reactors in which the mechanical energy of sound is transformed into a useful chemical form. In addition to the generation of such hot spots, there can also be mechanical effects produced as a result of the violent collapse[60].

The two main sources of ultrasound in organic synthesis are ultrasonic cleaning baths and ultrasonic immersion probes, which typically operate at frequencies of 40 and 20 kHz, respectively[61]. The former are more commonly employed in organic synthesis simply because they are less expensive and hence more widely available to chemists, even though the amount of energy transferred to the reaction medium is lower than that of ultrasonic probe systems, which deposit the acoustic energy directly into the reaction medium.

Compared with traditional method, our method is more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of pollution and safer to analyst. From these features present methods can be correlated for safer and efficient synthesis of other products.This new

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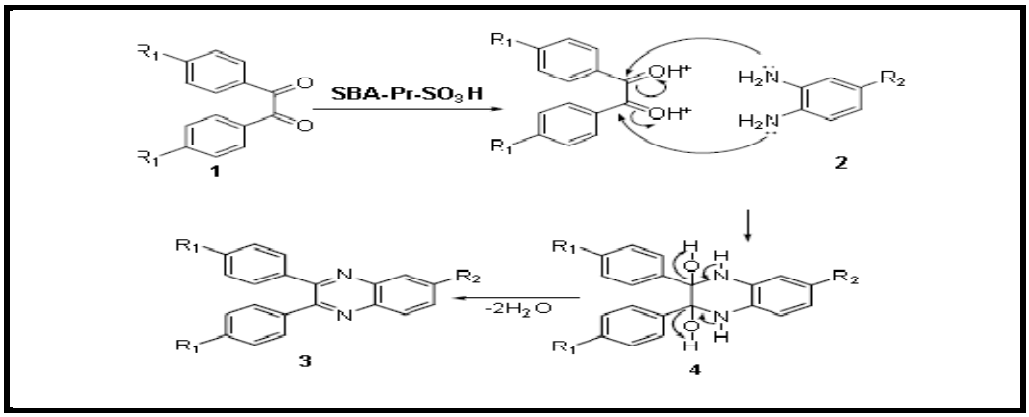
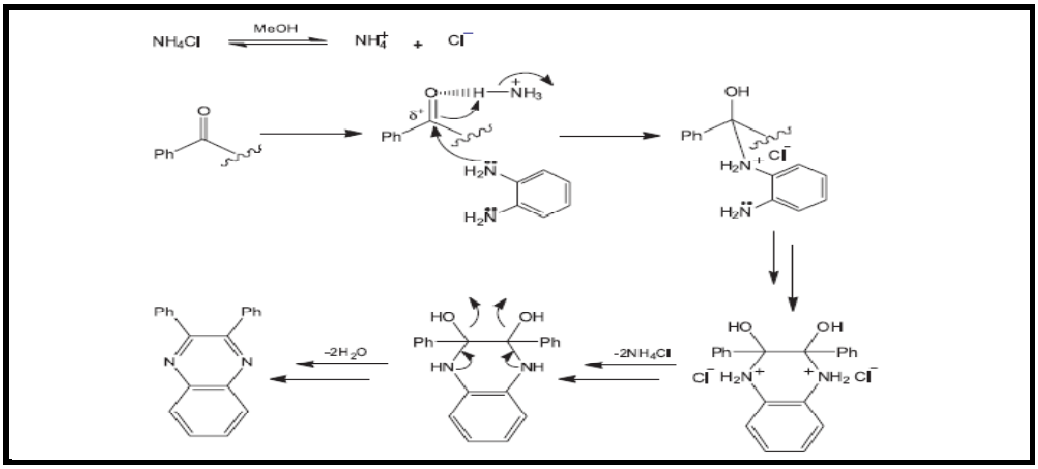
strategy has several advantages, such as excellent yield, short reaction time, low cost, simple experimental as well as isolation procedures, and finally, it is in agreement with the green chemistry protocols.

Darabiet al.[36]have proposed a mechanism for NH_4Cl catalysed synthesis of quinoxalines as given below. **(Scheme-2)**



Scheme-2

Another mechanism was proposed by Ziarani et al. [62].(**Scheme-3)**



Scheme-3

5. CONCLUSION

Ultrasonicwave technique is advantageous over conventional methods due to shorter reaction times, avoiding the use of harmful solvents, cleaner reactions, easy work up, and minimization of waste products for synthesis of 2,3-diphenyl quinoxaline. Compared with traditional methods, the applied methods are more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of pollution and safer to analyst. It can be concluded that the ultrasonication method is an efficient, fast, simple and environment friendly method for the synthesis of a large number of organic heterocyclic molecules. In addition there is an increase in the yield. Hence it is a viable and feasible method for performing the synthesis of drug, intermediates and chemicals. However, these efforts do not mean that everything is known, and there is still a lot to learn about this fascinating and useful reaction.

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