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Efficient Synthesis of Quinoxaline Derivatives Using ACamforsulfonic Acid As An Organocatalyst

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ABSTRACT: Camforsulfonic acid is an efficient organocatalyst for a one pot synthesis of quinoxaline derivatives in ethanol at ambient temperature. A series of quinoxaline derivatives were efficiently synthesized in excellent yields by the reaction of 1,2-diaminesand 1,2-dicarbonyl compounds catalyzed by camforsulfonic acid in ethanol as green solvent at room temperature under aerobic conditions. The main advantages of this protocol include practical simplicity, high yields, metalfree recyclable catalysts, green solvent and ambient temperature.

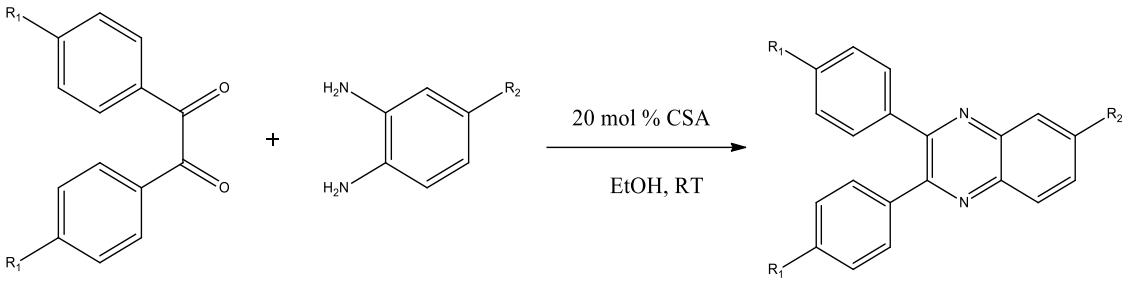
KEYWORDS: organocatalyst,ambient temperature, quinoxaline, green solvent etc.

I. INTRODUCTION

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles, and they constitute useful intermediates in organic synthesis. Quinoxaline derivatives are well known in the pharmaceutical industry[1].Quinoxalines and its derivatives have shown a broad spectrum of biological activities such as antiviral[2], antibacterial[3], anti-inflammatory[4] and anticancer[5] which have made them privileged structures in pharmacologically active compounds. Besides this, they are well known for their application in dyes[6], efficient electroluminescent materials[7], organic semiconductors[8,9]and organic synthons[10-12].Quinoxaline, N-heterocyclic scaffold, is well known for being a key structural motif in many biocides[13], pharmaceuticals[14] and various bio-functional molecules[15] .Various methods have been reported for synthesis of quinoxaline derivatives catalyzed by zeolites[16], $CuSO_4$ $5H_2O$[17], cerium ammonium nitrate[18], montmorillonite K-10[19], $Yb(OTf)_3$[20], Pd $(OAc)_2$[12], MnO_2[22], $InCl_3$[23], $MnCl_2$[24], $MnFe_2O_4$ nano-material[25] and $ZrOCl_2.8H_2O$ [26].

All these conventional methodologies have came across certain drawbacks such as, critical product isolation procedures , prolonged reaction times, unsatisfactory product yields, tedious catalyst preparation,expensive and detrimental metal precursors and, use of toxic solvents, harsh reaction conditionsand workup. The chemical industry is a major contributor to environmental pollution due to the use of several hazardous organic solvents, flammables, explosives, carcinogens, etc.

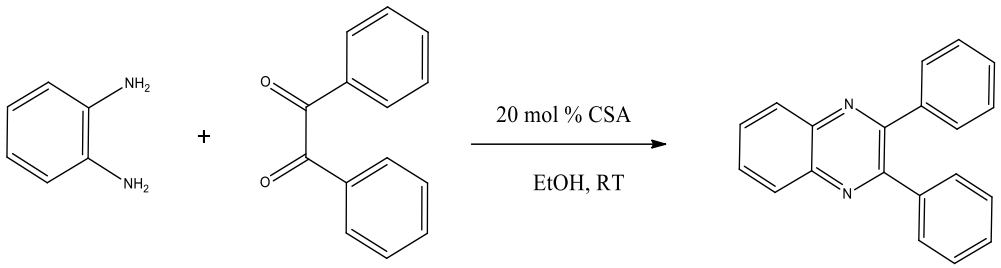
However the development of an efficient method , easy work up procedure, simple, environmentally benign protocol using a metal-free catalyst and green solvent for the synthesis of quinoxalinederivatives is still desirable and in demand. There is increasing interest in developing organocatalytic green reactions for the synthesis of quinoxaline by the reaction of 1,2-diaminesand 1,2-dicarbonyl compounds in recent years.The development of organocatalyzed reactions in which the reactions are catalyzed by organic molecules is an important area for green synthesis.camphor-10-sulfonic acid (CSA) is an inexpensive and easy to handle organo-catalyst that has been used in various organic transformations. Recently, it was observed that CSA is a highly efficient catalyst for the activation of imines in the Mannich type reaction of enolizable ketones[27] and the synthesis of fused quinoline and benzoquinoline derivatives [28]. As part of our research work in synthetic organic chemistry to develop green methods for organic synthesis using eco-friendly materials as catalysts, we have developed the synthesis of quinoxaline derivatives by the reaction of 1,2-diaminesand 1,2-dicarbonyl compounds in the presence 20 mol % CSA in ethanol at room temperature **(Scheme 1) .**



Scheme 1 CSA catalyzed synthesis of quinoxaline derivatives

II. RESULTS AND DISCUSSION

In a model reaction, benzil,o-phenylenediamine and 20 mol% CSA in ethanol stirred at room temperature **(Scheme 2)**.



Scheme 2 : CSA catalyzed synthesis of 2,3-diphenyl quinoxalines

To optimize the reaction conditions, we initially carried out the model reaction for the synthesis of 2,3-diphenylquinoxalineby the reaction of o-phenylenediamine (1 mmol) and benzil (1 mmol) in the presence of various solvents and concentrations of catalyst . Condensation reaction catalyzed by CSA in various solvents including methanol, acetonitrile, ethanol/water, and ethanol,higher yields were obtained when the reaction was carried out in EtOH. From the evaluation of different solvents, Ethanol which is a standard green medium,obviously the best choice for this reaction.Thus, EtOH was selected and used as reaction media for all reactions **Table 1**.

Table 1:Effects of solvents on the synthesis of 2,3-diphenylquinoxaline [a]

Entry	Solvent	Time(h)	Yield (%)[b]
1	Methanol	2	50
2	Acetonitrile	2	65
3	Ethanol/Water	2	85
4	**Ethanol**	**2**	**98**

[a]**Reaction conditions :** o-phenylenediamine (1 mmol), benzil (1 mmol), and 20 mol% CSA in solvent (5 mL) at room temperature.[b]Isolated yields.

The effect of the amounts of CSA on the yields of condensation reaction in ethanol has been shown in **Table 2**.It showed that when a mixture of 1 mmolbenzil, and 1 mmol o-phenylenediamine was stirred for 8 h in the absence of CSA, no product was detected, which showed that the catalyst should be necessary for this condensation reaction. Afterward, we selected 5 mol% of CSA to catalyze the model reaction and found that the desired quinoxaline was obtained in 50% yield, (Table 2,Entry 1). The reaction worked well when the amount of CSA was increased to 20 mol% (Table 2, Entry 4). When the amount of catalyst increased to 30%, the yields did not increase noticeably (Table 2, Entry 5). Thus, 20 mol% CSA was chosen as the optimum amount of catalyst.

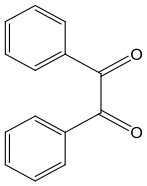
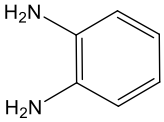
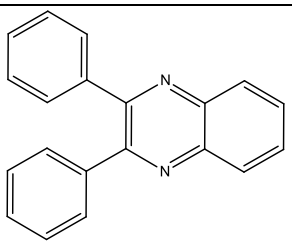
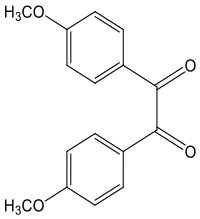
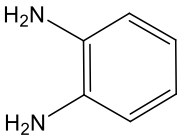
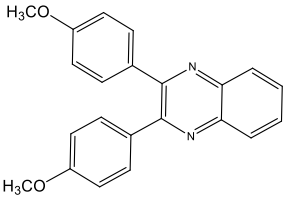
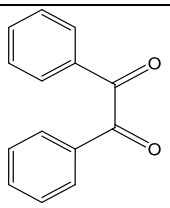
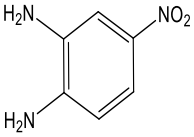
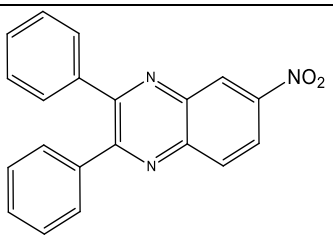
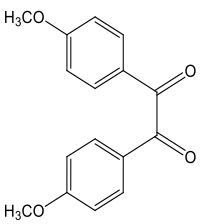
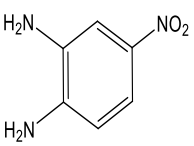
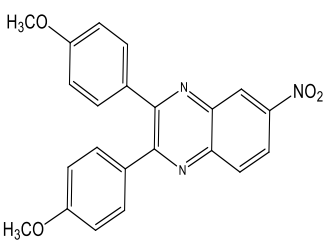
Table 2Effects of amount of CSA on the reaction times and yields [a]

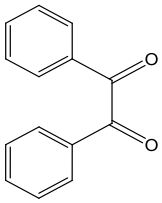
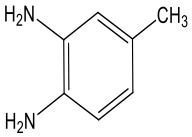
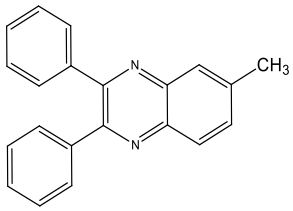
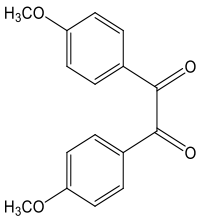
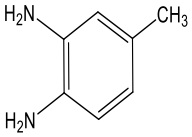
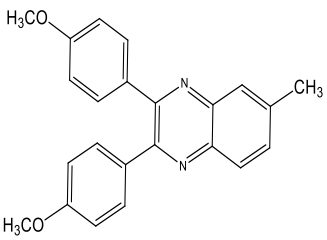
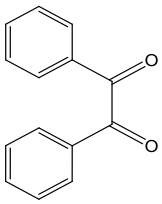
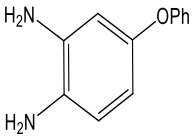
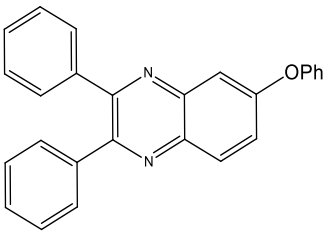
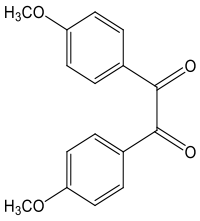
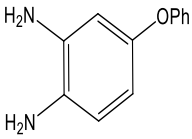
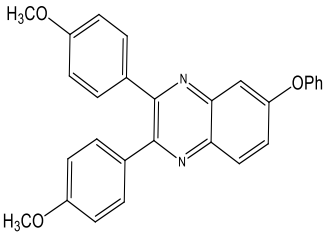
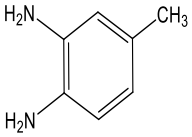
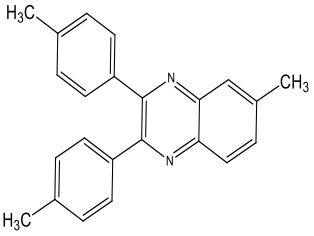
Entry	Catalyst concentration	Time (h)	Yield (%)[b]
1	5	2	50
2	10	2	65
3	15	2	85
4	**20**	**2**	**98**
5	30	2	98

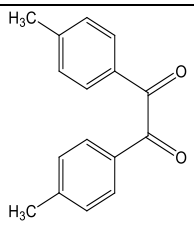
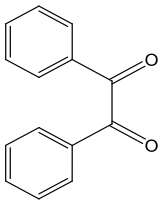
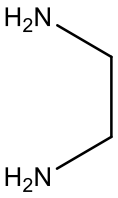
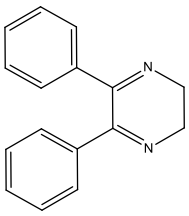
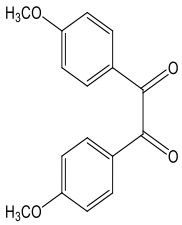
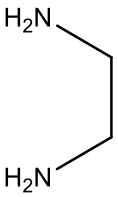
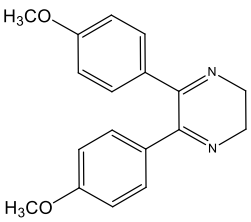
[a]**Reaction conditions :** o-phenylenediamine (1 mmol), benzil (1 mmol), and 20 mol% CSA in solvent (5 mL) at room temperature temperature,[b]Isolated yields.

Encouraged by the above results, we examined the applications and scope of our method with varying 1,2- diamines and 1,2-dicarbonyl compounds using 20 mol% of CSA in ethanol at room temperature. All the results are compiled in **Table 3**. It is observed that, 1,2- diaminewith electron-donating as well as electron-withdrawing substituents reacted efficiently with equal chemical reactivity. The formation of the desired product was confirmed with the help of FT-IR, ^{1}H NMR, and ^{13}C NMR.

Table 3 Synthesis of quinoxaline derivatives using CSA as an organocatalyst[a]

Entry	1,2-dicarbonyl compounds	1,2-diamines	Product	M.P.	Time (h)	Yield[b] (%)	Ref.
1				124-125	2	98	29
2				153-154	2	96	29
3				191-192	4	92	29
4				190-191	3	90	29

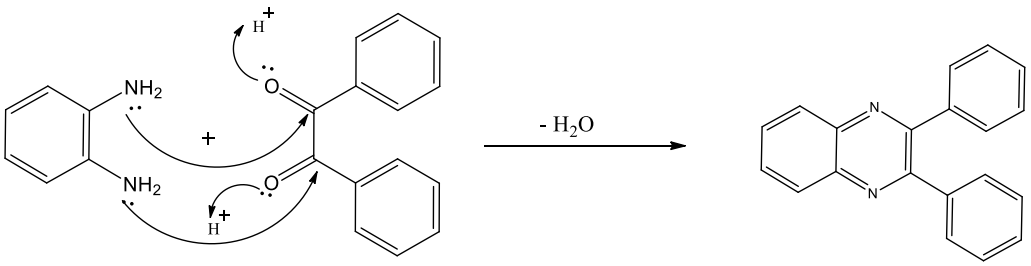
5				115-116	3	95	30
6				124-125	3	96	30
7				135-136	5	98	30
8				132-133	5	94	30
9				137	2	90	18

							
10				154-155	7	94	26
11				114-115	8	54	26

[a]**Reaction conditions:** o-phenylenediamine (1 mmol), benzil (1 mmol), and 20 mol% CSA in solvent (5 mL) at room temperature [b] Isolated yield of purified products

Plausible mechanism for the synthesis of quinoxalines

The plausible reaction mechanism for the green formation of quinoxaline products can be presented in **Scheme 3**. 1,2-dicarbonyl compounds stabilized via protonation of carbonyl group by CSA, then by the partial polarization of carbonyl group reacts readily with o-phenylenediamine. The resultant amino-1,2-diol undergoes dehydration to give quinoxaline as the end product[31].



Scheme 3: Plausible mechanism for the synthesis of quinoxalines in the presence of CSA

We have carried out the model reaction using different amounts of catalyst. The catalyst screening results are summarized in **Table 4**. The reaction proceeded smoothly yielding 98 – 90% of the product at room temperature for five successive runs. The result indicates that activity of the catalyst was not much affected upon recycling at least for five times.

Table 4 Reusability of the catalyst[a]

Entry	No.of cycles	Time (min)	Yield (%)[b]
1	1	2	98
2	2	2	96
3	3	2	94
4	4	2	92
5	5	2	90

[a]**Reaction conditions :** o-phenylenediamine (1 mmol), benzil (1 mmol), and 20 mol% CSA in solvent (5 mL) at room temperature,[b]Isolated yields.

III. EXPERIMENTAL SECTION

3.1 General

All the chemicals were obtained from Sigma Aldrich and Spectrochem and used without further purification. All reactions were performed in the borosil round bottom flask, volume 25 mL. Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F_{254} Merck (20 × 20 cm). TLC plates were visualized by exposing to UV light. Melting points were taken in an open capillary and are uncorrected. IR Spectra were recorded withPerkin-Elmerinstrument.^{1}H NMR and ^{13}C spectra were recorded with AV 400 Bruker 400 MHz NMR instrument. Chemical data for protons are reported in parts per million (ppm, scale) downfield from Tetramethylsilane (TMS) and are referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.2).

3.2General procedure for the synthesis of quinoxaline

A solution of 1,2-dicarbonyl compounds (1 mmol), 1,2-diamines (1 mmol) in 5 mL EtOH was stirred for 2 - 8 hrs in the presence of 20 mol% camforsulfonic acid (CSA)at room temperature.After completion of the reaction as indicated by TLC, cold water (5 mL) was added and stirring was continued until a free-flowing solid resulted in the reaction mixture. The resultant pure solid was filtered, washed with water and then dried. Further solid was recrystallized from a suitable solvent like ethanol. The pure product was characterized by spectroscopic methods.

3.3Data and values for Representative compound

[Table 3, entry 1]2,3-diphenylquinoxaline**:** ^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.36 – 7.38 (m, 6 H), 7.52 – 7.55 (dd, 4H, 7.6*Hz*),7.77 -7.79 (dd, 2 H, J= 3.6 *Hz*& 6.4 *Hz*), 8.19 – 8.21 (dd, 2 H, J= 2.8 *Hz*& 6.4 *Hz*), ; ^{13}CNMR (100 MHz, $CDCl_3$): δ = 153.5, 141.2, 139.0, 130.0, 129.8, 129.2, 128.8, 128.3 ; IR (KBr) cm^{-1}: 3057, 1440,1346,1222,1056,763,694.

[Table 3, entry 3] 6-nitro-2,3-diphenylquinoxaline**:** ^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 7.38-7.42 (dd, 4 H, J= 8.0 *Hz*& 7.6 *Hz*), 7.44 (m, 2H), 7.56-7.58(dd, 4 H ,J = 3.2 Hz & 2.0 Hz), 8.32 (d, 1H, J= 9.2 *Hz*), 8.55 (d, 1H, J= 9.2 Hz), 9.09 (s,1H), ; ^{13}C-NMR (100 MHz,$CDCl_3$):δ= 156.3,155.7,147.8,143.6,139.9, 138.0,134.9,130.8, 129.9, 129.6,129.0,128.5,125.7,123.3,; IR (KBr) cm^{-1}: 3053,1516, 1334, 1209, 1053, 767,696.

IV. CONCLUSION

The ambient conditions , the use of an organocatalyst, practical simplicity, high yields, eco-friendly solvent, atom economy and ease of isolation of the product., not only make this methodology an alternative platform to the conventional acid/base catalyzed thermal processes, but it also becomes significant under the umbrella of environmentally greener and safer processes.

V. ACKNOWLEDGMENTS

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