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Eco-Friendly Synthesis of Quinoxaline Derivatives Catalysed By Zinc Triflate

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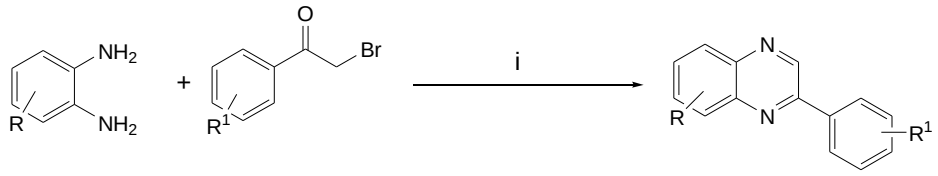
ABSTRACT

Quinoxaline nucleus based nitrogen containing compounds have wide applications in pharmaceutical and paint industries. Some antibiotic structures constitute the quinoxaline moiety. For the synthesis of such important class of derivatives, a simple and efficient method is developed. The reaction between substituted phenacyl bromide and benzene 1,2 diamine catalysed by Zinc triflate in water solvent. The method is eco-friendly; require mild reaction condition, easy work up procedure and good yield are the main features of the method.



1 2 3a-3x

Scheme 1: *Reagent and conditions*: (i) 10 mol% $Zn(OTf)_2$, 5 mL water, 70-80^{0}C.

Keywords: quinoxaline, phenacyl bromide, benzene 1, 2 diamine, zinc triflate.

I. INTRODUCTION

Quinoxaline based heterocyclic compounds constitute a versatile class of nitrogen containing compounds. Quinoxaline moiety is useful intermediate in organic synthesis & medicinal chemistry. They are well known for their wide range of biological activities including anti-bacterial[1a], anti-viral[1b], anti-inflammatory[1c], anti-cancer[1d], anti HIV[1e]etc. Quinoxaline derivatives also have a variety of applications in dyes, fluorescent materials, semiconductors[2a], insecticides, fungicides and herbicides[2b]. Some examples are shown in **Figure 1**. For example, Quinacillin is highly effective in penicillin sensitive or strains of staphyllococcusaureus which produces penicillinase. Brimonidine is used for the treatment of open-angle glaucoma, as eye drops or applied to the skin. Varenicline is used to treat nicotine addiction. This scaffold was also well- known in bioacids,[3] organic synthons,[4] electroluminescent materials,[5] organic semiconductors,[6] cavitands,[7] dehydroannulenes[8] and ligands in coordination chemistry[9].The quinoxaline nucleus is the main constituent of some antibiotics such as Levomycin, Actinoleutin and Echinomycin[10]. Therefore attention is made for the synthesis of quinoxaline derivatives.

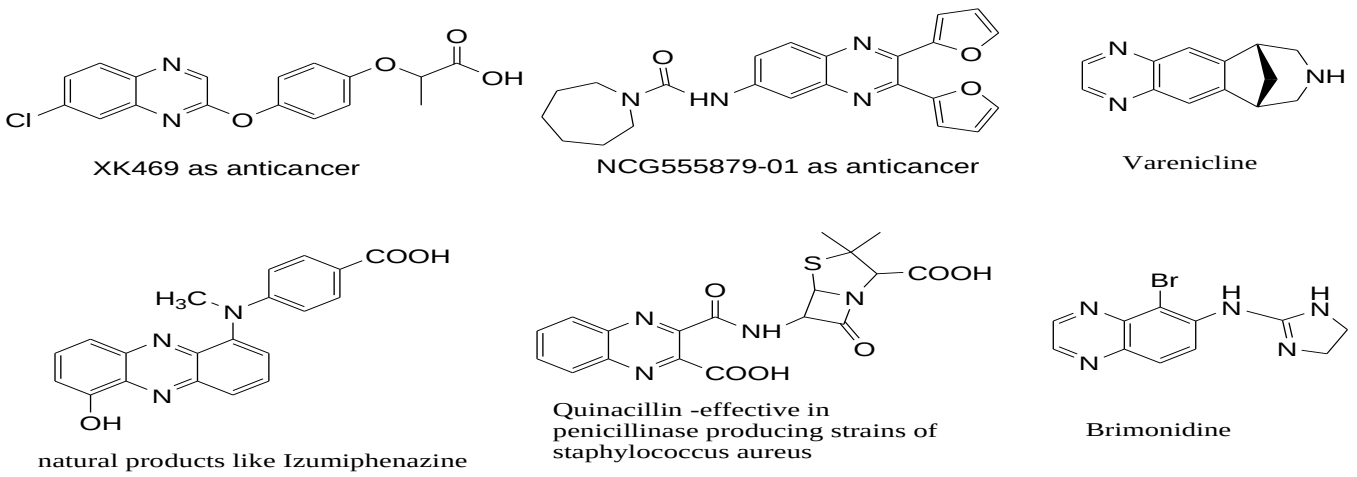


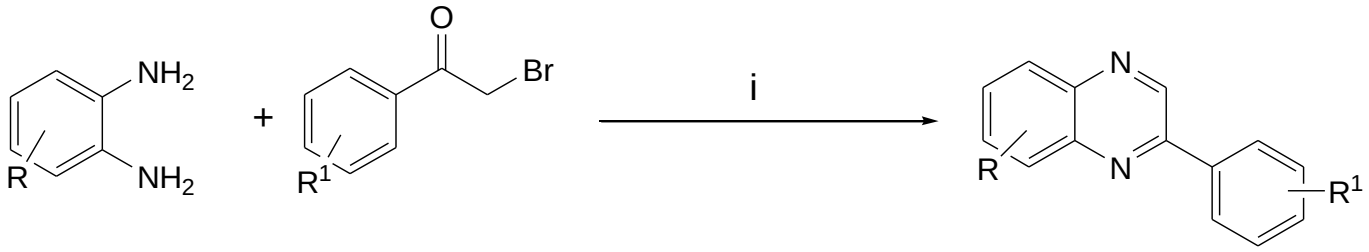
Figure 1. Examples of bioactive compounds having quinoxaline scaffold.

In recent years there is a considerable interest in developing environmentally benignreactions.[11, 12].For this purpose, the use of solid heterogeneous acid catalysts in organic synthesis is extensively carried out. Heterogeneous solid acid catalysts are superior to the conventional homogeneous acid catalysts due to their low cost, operational simplicity, low toxicity and environmental compatibility. Moreover, they can easily be recovered from reaction mixtures by filtration and reused for making the process economically viable.

The reactions catalysed by zinc are found to be sustainable alternative to use of more precious or toxic transition metals.[13] Zinc triflate [$Zn(OTf)_2$] is an inexpensive catalyst having thermal stability, ease of availability, low cost and addresses problem associated with the toxicity of metals up to a great extent. It is known as an efficient catalyst used in various chemical transformations[14-16].

Numerous common synthetic methods involve double condensation reactions between o-phenylene diamine and α-diketones[17-21] with or without the presence of catalyst in various solvents. Synthesis of quinoxaline derivatives is carried out from diketone and 1,2 diamine using zinc triflate in acetonitrile.[22] Alternative methods are also proposed which includes oxidative trapping of α-hydroxy ketones with o- phenylene diamine[19], oxidative trapping of α-hydroxy ketones with o- phenylenediamine in presence of transition metal complexes such as Mn, Pd, Cu, Pb[23-25]. Reaction of 2-bromo acetophenone with o-phenylenediamine or α-hydroxy ketones or from arynes[26-35], Cu (II) [36], microwave irradiation [37, 41], $RuCl_2(PPh_3)$ [38], $HClO_4.SiO_2$[39], $Ga(OTf)_3$[40], SSA[42], K 10 clay[43], Amberlite IR-120H[44] and $VOSO_4$[45,46].

The above reported methodologies for synthesis of quinoxaline derivatives have shown good results in many instances. However, some of the synthetic strategies also have limitations in terms of expensive reagents, long reaction time, environmentally hazardous, harsh reaction conditions, tedious work-up procedure and unsatisfactory yield. Therefore, in order to overcome these disadvantages of previous methods I have developed a simple, highly efficient and environmentally benign method for the synthesis of quinoxalines catalysed by zinc triflate [$Zn(OTf)_2$] in solvent water. The product can be separated by filteration of the reaction mixture after completion of the reaction Hence, this method provides a green and much improved protocol over the existing methods. Thus, herein I report a green and simple approach for the synthesis of quinoxaline derivatives from various 2-bromo acetophenones and 1,2-diamines catalyzed by zinc triflate [$Zn(OTf)_2$] **(Scheme 1)**.



1(a-c) 2(a-i) 3a-3x

Scheme 1: *Reagent and conditions*: (i) 10 mol% $Zn(OTf)_2$, 5 mL water, 70-80^{0}C.

II. EXPERIMENTAL

2.1. General details

All chemicals were purchased from Sigma Aldrich and Spectrochem companies and used without further purification. The reactions were monitored by TLC using aluminum sheets 20 x 20 cm, Silica gel 60 F_{254} ,Merck grade. Products were characterized by ^{1}H and ^{13}C NMR spectra recorded on a Bruker spectrometer using $CDCl_3$& DMSO-d_6 as a solvent and tetramethylsilane as an internal standard. Mass spectrometric data was recorded by an electron spray ionisation (EST) technique on a Q-tof-micro quadruple mass spectrometer (Micro mass). Melting points were determined on DBK-programmable melting point apparatus.

2.2. General procedure for the synthesis of quinoxalines

In a 25 mL round bottom flask 1,2-diamine (1 mmol), 2-bromo acetophenone (1 mmol), 5mL water and Zinc triflate (10 mol%) were heated at 70-80^{0}C for 35 to 60 minutes. The progress of reaction was monitored by TLC. After completion of reaction; confirmed by thin-layer chromatography (TLC) using eluent petroleum ether–ethyl acetate (7:3), the reaction mixture was cooled and filtered. The product as residue was washed with water thrice. The crude product obtained was recrystallised using ethanol to afford the products in good yields. The structure of the product was confirmed by Mass and ^{1}H NMR specta.

III. RESULT AND DISCUSSION

Herein, I reported synthesis of quinoxaline derivatives in good to excellent yields via one pot reaction between o-phenylenediamines and various substituted bromo acetophenones. All reactions were performed by the use of zinc triflate $Zn(OTf)_2$ as catalyst in water under reflux. The products were obtained in good to excellent yields.

To determine the suitable reaction conditions, a solvent-free reaction of 2, 4-dibromo acetophenone (1 mmol) and o-phenylenediamine (1 mmol) was performed at room temperature (entry 1, **Table 1**). Low yield was observed in this case. Then, the reaction mixture was heated for 4 h and 50% yield was found. So, we studied the effect of solvent and various amounts of zinc triflate catalyst on the model reaction **(Scheme1).** The reaction was performed by using different solvents such as CH_2Cl_2, EtOH and CH_3CN under heat for about 40-90^{0}C with more time and low yield **(entry 1-4, Table 1).** The same reaction was performed in presence of 10 mol% at 70-80^{0}C water (**entry 5, Table 1**). More result was obtained using 10 mol% of the catalyst (**entry 5-7, Table 1**).

Table 1: Optimization of reaction condition for the synthesis of quinoxaline derivatives.

Entry	Solvent	Catalyst (mol%)	Temperature (^{0}C)	Time (min.)	Yield (%)
1	None	-	70-80	240	50
2	CH_2Cl_2	10	RT	85	68
3	EtOH	10	70-80	40	78
4	CH_3CN	10	80-90	70	72
5	**H_2O**	**10**	**70-80**	**35**	**88**
6	H_2O	5	70-80	42	78
7	H_2O	20	70-80	35	87

Thereafter, a series of reactions was carried out using diversely substituted 2-bromo acetophenone under identical reaction conditions. All these reactions afforded good to excellent yields of 2-Phenyl quinoxaline derivatives (3a-3p), **(entries 1-16, Table 2).** Methyl and chloro substituted o-phenylene diamines were used which produced selectively one product with various substituted 2-bromo acetophenones bearing both electron donating and withdrawing groups. All these reactions resulted in good to excellent yields (**Table 2**).

Table 2 : One pot synthesis of quinoxaline derivatives in 1:1 water - ethanol mixture Using zinc triflate $Zn(OTf)_2$ [a].

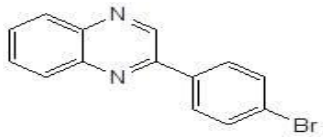
Entry	1,2diamine 1(a-c)	2-bromo acetophenone 2(a-i)	Product 3 (a-x)	Time (min.)	Yield[b] (%)
1	O-phenylene diamine	4-Br	3a	28	88
2	O-phenylene diamine	4-OCH_3	3b	46	85
3	O-phenylene diamine	4-CH_3	3c	42	88
4	O-phenylene diamine	4-Cl	3d	40	88
5	O-phenylene diamine	4-NO_2	3e	34	90
6	O-phenylene diamine	3,4-dichloro	3f	43	85
7	O-phenylene diamine	4-F	3g	35	87
8	O-phenylene diamine	4-CN	3h	38	89
9	O-phenylene diamine	4-H	3i	40	86
10	4-methyl o-phenylene diamine	4-Br	3j	41	88
11	4-methyl o-phenylene diamine	4-OCH_3	3k	53	90
12	4-methyl o-phenylene diamine	4-CH_3	3l	50	91
13	4-methyl o-phenylene diamine	4-Cl	3m	48	84
14	4-methyl o-phenylene diamine	4-NO_2	3n	46	91
15	4-methyl o-phenylene diamine	4-F	3o	52	86
16	4-methyl o-phenylene diamine	4-CN	3p	55	88

17	4-methyl o-phenylene diamine	4-H	3q	58	87
18	4-chloro o-phenylene diamine	4-OCH_3	3r	64	84
19	4-chloro o-phenylene diamine	4-CH_3	3s	60	85
20	4-chloro o-phenylene diamine	4-Cl	3t	58	82
21	4-chloro o-phenylene diamine	4-NO_2	3u	53	84
22	4-chloro o-phenylene diamine	4-F	3v	58	83
23	4-chloro o-phenylene diamine	4-CN	3w	60	82
24	4-chloro o-phenylene diamine	4-H	3x	63	86

[a]Substitutedo-phenylenediamine (1 mmol), substituted 2-bromo acetopenone (1.0 mmol), H_2O (5 mL), under reflux.

[b]isolated yield

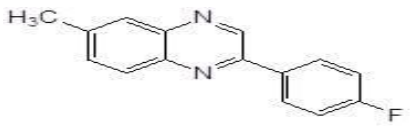
IV. CHARACTERISATION DATA



2-(4-bromophenyl)quinoxaline (entry 1, 3a, Table 2): MP- 138-140^0C[12] :

^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) 7.7-7.782 (m, 2H, Ar), 7.788-7.830 (m, 2H, Ar), 8.126-8.130 (s, 2H, Ar), 8.152-8.158 (s, 2H, Ar), 9.344 (s, 1H, Ar);

ESI-MS: m/z = found-285 (M+1), exact-284 for $C_{14}H_9BrN_2$.



2-(4-fluorophenyl) 6-methyl quinoxaline (entry 15, 3o, Table 2) MP-141-143^0C **:**

IR (Cm^{-1})779, 881, 927, 960, 1047, 1134, 1161, 1222, 1267, 1377, 1436, 1467, 1496, 1541, 1599, 1620, 1656, 1870, 1907, 2337, 2360, 2856, 2918, 3059.

^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) 2.6 (s, 3H, CH_3), 7.109 (s, 1H, Ar), 7.15 (s, 1H, Ar), 7.3 (m, 1H, Ar), 7.85 (m,1H, Ar), 8.0 (m, 1H, Ar), 8.1 (s, 2H, Ar), 9.1 (s, 1H, Ar)

^{13}C NMR (500 MHz, DMSO d_6):δ (ppm) 21.23, 78.61, 116.02, 127.52, 128.31, 129.49, 131.92, 132.67, 139.69, 140.98, 149.81, 162.52, 164.50.

ESI-MS: m/z = found-239 (M+1), exact-238 for $C_{15}H_{11}FN_2$.

V. CONCLUSION

In summary, I report an efficient synthesis of 2-phenyl quinoxaline derivatives by the reaction of various benzene 1,2 diamine and substituted phenacyl bromides using zinc triflate $Zn(OTf)_2$ catalyst. Non-hazardous reaction condition and the use of water as the reaction solvent makes the present protocol an environmentally benign and green approach for the synthesis of 2-phenyl quinoxaline derivatives.

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