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Bismuth (III) Chloride: A Facile and Efficient Catalyst for the Synthesis of Quinoxalins.

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ABSTRACT

A facile and efficient approach for the synthesis of quinoxaline derivatives was achieved with excellent yields by the Oxidative-condensation of *ortho*-phenylene-diamines with *α*-halo ketones in presence of catalytic amount of bismuth Chloride ($BiCl_3$) under room temperature condition.
Keywords: Quinoxaline derivatives, *ortho*-phenylenediamines, α-haloketones, bismuth Chloride.

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INTRODUCTION

Quinoxaline moiety is recurrently employed as a significant pharmacophore in the field of drug discovery. These derivatives serve as useful building blocks for the development of molecules that play a crucial role in medicinal chemistry [1-4]. Moreover, some characteristic examples of quinoxaline skeleton bearing drug molecules are given in **Figure 1**. These derivatives have been used as functional units for the synthesis of organic semiconductors [5,6] and also applied in the process of extraction of metal cations [7]. Quinoxaline corresponds to a substantial class of biologically active nitrogen compounds demonstrating a number of principal biological properties, such as antifungal [8], antimycobacterial [9], anthelmintic [10], antitumor [11] and antidepressant [12]. Additionally, quinoxaline derivatives perform a crucial role in the field of bio-organic medicinal chemistry with potential applications in the advancement of several antibiotic drugs like Echinomycin, Levomycin, and Actinoleutin that are known to hinder the growth of Gram positive bacteria [13-14] as well as active against several transplantable tumors [15].

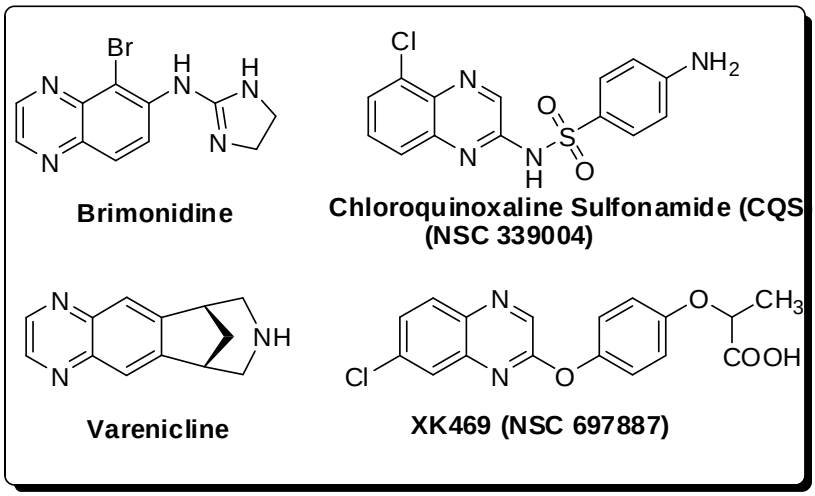

Figure 1: Biologically Active Quinoxaline Molecules

Various approaches have been exploited for the synthesis of quinoxaline derivatives such as cyclization of diketones with diamines in using K10-montmorillonite [16], gallium triflate [17], silica gel [18], copper(II) sulfate [19], iodine [20], indium(III) chloride [21], phosphorusoxychloride [22], o-iodoxy-benzoic acid [23], cericammonium nitrate [24] however on the other hand oxidative coupling of α-hydroxyketones with *o*-phenylenediamines (OPDA) *via* a tandem oxidation process by using various metal catalysts [25-29], 1,4-addition of 1,2-diamines to diazenyl-butenes [30], cetyltrimethyl ammonium bromide (CTAB) [31], solid-phase synthesis [32-33],condensation of 1,2-diamines and 1,2-dicarbo-nyl compounds[34-36], cyclization of phenacyl bromides with 1,2-diamines by $HClO_4.SiO_2$ [37], sodium hexafluorophosphate-Amberlite [38], Copper catalyst with *α*-hydroxy ketones [39], KF-alumina [40], $CeCl_3.7H_2O$ with diamine and haloketones [41] and by using *β*-cyclodextrin, polyethylene glycol (PEG-400) catalyzed with phenyl diamines and phenylacyl bromides[42-43].

Nevertheless, a lot of the stated means experience somelimitations such as harsh reaction conditions, long reaction time, unsatisfactory yields, tedious workup procedures, incomplete conversions, and the isolation of products and use of expensive catalysts. For that reason, the development of a proficient chemical procedure is a major challenge for the chemists in organic synthesis. In the recent times, bismuth chloride has come to light as a capable Lewis acid owing to its speedy availability at a low price, comparatively low toxicity and tolerance to trace amounts of water. Thus, bismuth Chloride has been considered as an ideal Lewis acid in order to deal with some of the drawbacks put forward by the established processes.

As a part of our research curriculum to expand unique methodologies, herein we have exploited a well-organized and easy protocol for the synthesis of quionoxaline derivatives under easygoing reaction conditions by using bismuth chloride as a catalyst. In this, we have revealed effective $BiCl_3$catalyzed synthesis of quinoxalins.

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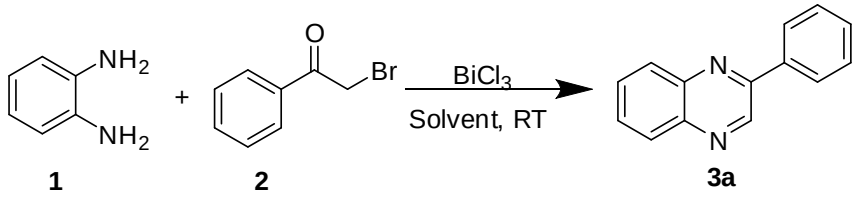
RESULTS AND DISCUSSIONS

In the current study, we have reported a novel protocol for the synthesis of quinoxalins by means of cyclization of phenacylbromides with *ortho*-phenylene-diamines using a catalytic amount of bismuth chloride. Accordingly, we have initially carried out the reaction between phenyldiamine and phenacyl-bromide using 10 mol% $BiCl_3$ in acetonitrile. The reaction has been progressed at room temperature in acetonitrile and the desired product, 2-Phenylquinoxaline **3a**, was obtained in 94% yield (**Scheme 1**). From this we can found to be $BiCl_3$ is an excellent catalyst to carry forward the reaction in terms of rate of the reaction, and product yield and the corresponding results were shown in **Table 1**.

Further, we have observed the effect of different solvents such as acetonitrile, tetrahydrofuran, methanol, ethyl acetate, dichloromethane, DMF and water using the same reaction conditions, as shown in **Table 1.** The yield of the product varied with the nature of the solvent and it was observed that the dielectric constant of the solvent has a significant role on the rate of the reaction. The reactivity increased with increase in dielectric constant of the solvent. The high dielectric constant of water made the reactants less soluble affording poor yields. Acetonitrile facilitated the reaction as indicated from the yields obtained.



Scheme 1

Table 1: Effect of solvents for the preparation quinoxalins

Entry	Solvent	Time (Hr)	Yield (%)
1	CH_3CN	2	94
2	CH_3OH	3	85
3	CH_3COOEt	5	64
4	DMF	2	90
5	THF	4	72
6	DCM	5	60
7	H_2O	6	35

By encouraging the above result, later we have carried out the reaction with various combinations of α-halo ketones with substituted 1,2-phenylenediamine and the results are displayed in **Table 2** (**Scheme 1**). Phenacylbromides bearing electron donating and weak electron withdrawing groups such as Cl, Br all afforded good to excellent yields at room temperature. Although phenacylbromides having electron withdrawing groups successfully reacted with 1,2-phenylenediamines to afford good yields of the corresponding quinoxalins, the rate of the reaction is relatively slow. It might be attributed to high eutectic point for the mixture of o-phenylenediammine and 4-nitrophenacylbromide. All the products were confirmed by their proton nuclear magnetic resonance (^{1}H NMR), infrared (IR), and mass spectroscopy data.

EXPERIMENTAL SECTION

Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded On a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr disk. ^{1}H NMR-Spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure for the synthesis of quinoxalins

A mixture of phenyldiamine (0.108 g, 1 mmol) and 2-bromo carbonyl compound (0.198 g, 1 mmol) was stirred in presence of $BiCl_3$ (10%mol) in acetonitrile (8 mL) at room temperature. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction as indicated by TLC,

the solvent was removed under reduced pressure. The residue was extracted with chloroform (2x10 mL). The combined filtrates were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using silica gel 60-120 mesh to afford the desired quinoxalins (Ethyl acetate; Hexane, 2:8). All the pure products were identified by their spectroscopy data.

Spectral data for compounds

2-phenylquinoxaline (3a): Bright yellow solid. Mp 75-78 °C; IR (neat): υ 3448, 3059, 2922, 2852, 1631, 1544, 1487, 1313, 1224, 1027, 956, 768 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$) *δ:* 7.66-7.56 (m, 3H, ArH), 7.83-7.73 (m, 2H, ArH), 8.22-8.13 (m, 4H, ArH), 9.33 (s, 1H, C3-H). MS (ESI): *m/z* 207 (M+H) $^+$.

2-(4-methylphenyl)quinoxaline (3b): Pale yellow solid,Mp 92-93 ^{O}C. IR (neat): υ 3053, 2855, 2764, 1606, 1512, 1462, 1298, 1201, 1011, 942, 748 cm^{-1}; ^{1}HNMR($CDCl_3$) : 2.44 (s, 3H), 7.36 (dd, 2H, *J* = 0.8, 8.8 Hz,), 7.81-7.71 (m, 2H, ArH), 8.18-8.10 (m, 4H, ArH), 9.32 (s, 1H, C3-H); MS (ESI): *m/z* 221 (M+H) $^+$.

2-(4-bromophenyl)quinoxaline (3c): Yellow Solid. Mp. 133-134 ^{O}C; IR (neat): υ 3421, 2927, 1633, 1583, 1534, 1475, 1418, 1101, 1073, 955, 830, 759 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.78-7.69 (m, 4H, ArH), 8.20-8.10 (m, 4H, ArH), 9.31 (s, 1H, C3-H).; MS (ESI): *m/z* 286 (M+H) $^+$.

2-(4-chlorophenyl)quinoxaline (3d); Pale yellow solid,Mp 134-136 ^{O}C,; IR (neat): υ 3056, 2360, 1612, 1545, 1521, 1452, 1399, 1097, 1053, 955, 822, 760 cm^{-1}; ^{1}HNMR ($CDCl_3$): 7.55-7.52 (m, 2H, ArH), 7.82-7.74 (m, 2H, ArH),8.16-8.11 (m, 4H, ArH), 9.30 (s, 1H, C3-H); MS (ESI): *m/z* 241 (M+H) $^+$.

2-(naphthalen-2-yl)quinoxaline (3e): Yellow Solid. Mp. 140-142 ^{O}C. IR (neat): υ 3448, 2925, 2855, 1631, 1594, 1190, 964, 855, 819, 746 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 7.60-7.50 (m, 2H, ArH), 7.82-7.70 (m, 2H, ArH), 8.01-7.84 (m, 3H, ArH), 8.20-8.10 (m, 2H, ArH), 8.40 (d, 1H, *J* = 8.0 Hz, ArH), 8.65 (s, 1H, ArH), 9.65 (s, 1H, C3-H).; EIMS: *m/z* (%): 257 (M+H) $^+$.

2-(4-methoxyphenyl)quinoxaline (3f): Light yellow solid,Mp 97-98 ^{O}C. IR (neat): υ 3057, 2899, 2815, 1622, 1576, 1098, 972, 855, 759 cm^{-1}; ^{1}HNMR($CDCl_3$) : 3.90 (s, 3H, -OCH_3), 7.09 (dd, 2H, *J* = 2.0, 6.8Hz, ArH), 7.77-7.68 (m, 2H, ArH), 8.09 (t, 2H, *J* = 8.0 Hz, ArH), 8.18-8.15 (m, 2H, ArH), 9.28 (s, 1H, C3-H); EIMS: *m/z* (%): 237 (M+H) $^+$.

2-(4-fluorophenyl) quinoxaline (3g): yellow solid,Mp 119-120 ^{O}C. IR (neat): υ 3048, 2815, 2785, 2361, 1652, 1545, 1112, 967, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$): 7.28-7.22 (m, 2H, ArH), 7.81-7.72 (m, 2H, ArH), 8.14-8.11 (m, 2H, ArH), 8.24-8.18 (m, 2H, ArH), 9.29 (s, 1H, C3-H); EIMS: *m/z* (%): 225 (M+H) $^+$.

2-(4-nitrophenyl) quinoxaline (3h): pale yellow solid,Mp 185-189 ^{O}C. IR (neat): υ 3066, 2877, 2799, 2454, 1631, 1544, 1487, 1313, 1224, 1027, 965, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$): 7.86-7.82 (m, 2H, ArH), 8.22-8.17 (m, 2H, ArH), 8.38 (s, 4H,ArH), 9.36 (s, 1H, C3-H); EIMS: *m/z* (%): 252 (M+H) $^+$.

4-(quinoxalin-2-yl)benzonitrile(3i): Pale yellow solid.Mp.194-196°C.; IR (neat): υ 3548, 2867, 1629, 1475, 1114, 1018, 978, 864, 775 cm.$^{-11}$HNMR ($CDCl_3$) *δ*: 7.88-7.82 (m, 4H, ArH), 8.20-8.13 (m, 2H, ArH), 8.36-8.33 (d, 2H, *J*=8.3Hz, ArH), 9.35 (s, 1H, C3-H); EIMS: *m/z* (%): 232 (M+H) $^+$.

2 (Furan2yl) quinoxaline(**3k**): Solid.Mp 95-98 °C; IR (neat): υ 3548, 3036, 2855, 1631, 1597, 1533, 1265, 1034, 964, 855, 756 cm.$^{-11}$HNMR ($CDCl_3$) *δ*: 6.62-6.60 (m, 1H, ArH), 7.28 (d, 1H,*J* = 4.0 Hz, Furan H), 7.72-7.64 (m, 3H, ArH), 8.06-8.01 (m,2H, Furan H), 9.56 (s, 1H, C3-H); EIMS: *m/z* (%): 197 (M+H) $^+$.

2-methylquinoxaline (3l): colorless oil;bp 125-126 ^{O}C; IR (neat): υ 1574, 1506, 1447, 1425, 1388, 989 cm-1; ^{1}HNMR ($CDCl_3$) *δ*: , 2.72 (s, 3H, CH_3), 7.76-7.67 (m, 2H, ArH, 8.08-8.01 (m, 2 H, ArH), 8.75 (s, 1 H, C3-H; EIMS: *m/z* (%): 144(M^+).

6,7-dimethyl-2-phenylquinoxaline (3m): Yellow Solid; mp 107-109°C; IR (neat): υ 3041, 2822, 2742, 1596, 1488, 1402, 1276, 1204, 1043, 951, 728 cm^{-1};^{1}H NMR ($CDCl_3$): *δ* 2.56 (s, 6H, -CH_3), 7.60-7.52 (m, 3H, ArH), 7.81 (d, 2H, ArH), 8.14-8.11 (m, 2H, ArH), 9.32 (s, 1H, C3-H),; EIMS: *m/z* (%): 235 (M+H) $^+$.

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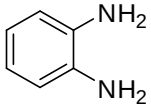
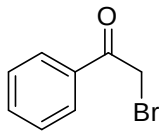
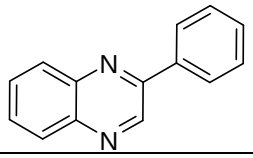
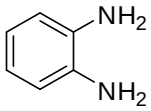
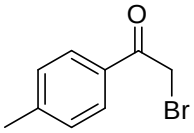
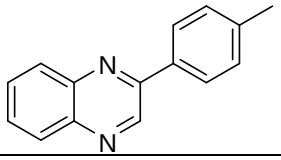
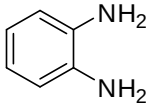
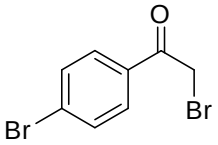
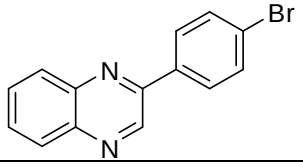
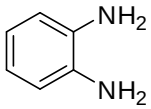
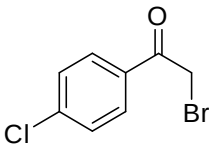
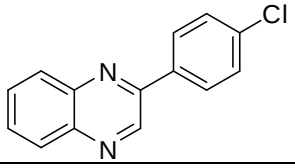
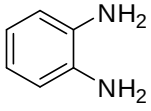
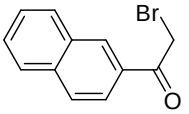
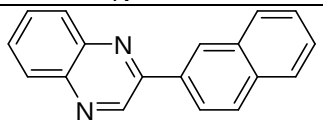
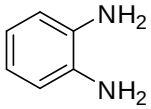
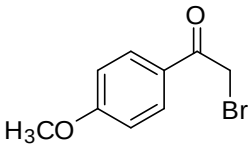
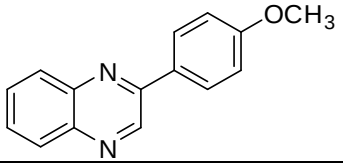
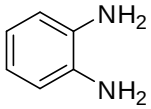
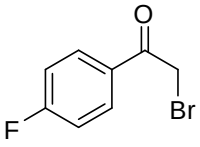
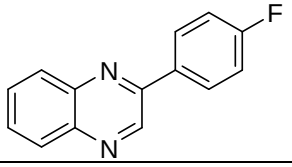
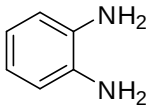
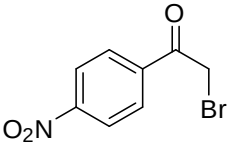
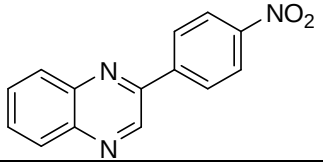
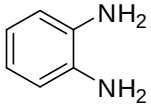
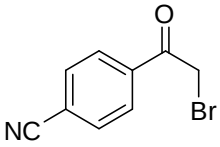
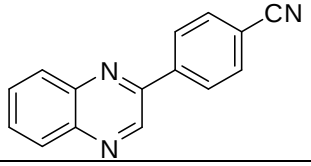
2-(4-Chlorophenyl)-6,7-dimethylquinoxaline (3n): pale yellow Solid; mp 148-150°C;IR (neat): υ 3085, 2456, 1665, 1584, 1488, 1443, 1376, 1115, 1086, 974, 845, 772 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.52 (s, 6H, $-CH_3$), 7.56-7.52 (m, 2H, ArH), 8.16-8.13 (m, 2H, ArH), 7.87 (d, 2H, ArH), 9.32 (s, 1H, C3-H); EIMS: *m/z* (%): 269 $(M+H)^+$.

6,7-Dimethyl-2-(*p*-tolyl)quinoxaline (3o): Yellow Solid; mp 107-110°C; IR (neat): υ 3044, 2825, 2752, 1615, 1542, 1488, 1265, 1196, 1025, 956, 757 cm^{-1};
^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 2.52 (s, 6H), 7.38 (d, 2H, *J* = 8.0Hz, ArH), 8.09 (d, 2H, *J* = 8.2 Hz, ArH), 7.88 (d, 2H, *J* = 16.0Hz, ArH), 9.22 (s, 1H, C3-H),; EIMS: *m/z* (%): 249$(M+H)^+$.

Table 2: $BiCl_3$ catalyzed synthesis of quinoxaline derivatives

Entry	Diamines	Phenacyl bromides	Product 3 (a-n)	Time (hr)	Yield (%)
a				2	94
b				2	92
c				3	89
d				3	90
e				3.5	91
f				2.5	88
g				3	87
h				5	84
I				4.5	86

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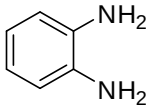
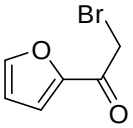
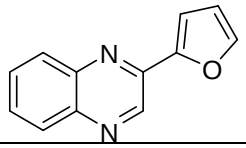
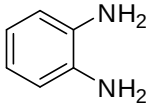
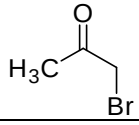
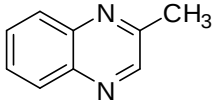
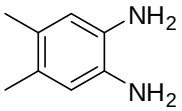
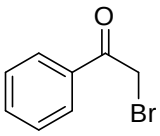
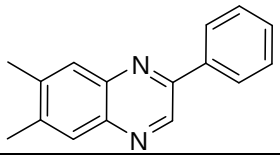
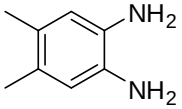
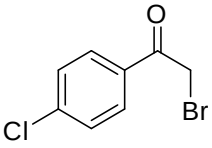
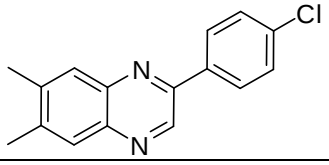
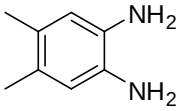
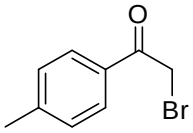
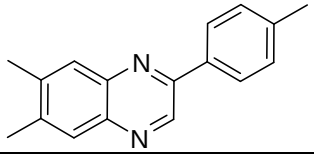
J				4	89
K				3	95
I				2.5	91
m				4	89
n				3	90

CONCLUSION

In conclusion, we were extremely succeeded in developing a simple, economically feasible, and eco-friendly methodology for the preparation of quinoxalins from phenylenediamine with several phenacyl-bromides using $BiCl_3$as catalyst in acetonitrile at room temperature. However, owing to this means, admirable percentage of yields was reported. The exciting benefits of this method include that the reaction conditions were extremely mild as well as the products separation was exceptionally effortless. This simple methodology may be expected to achieve widespread applications in synthetic, organic and medicinal chemistry fields.

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