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Sodium Bromate/Sodium Hydrogen Sulfite: A New Catalyst for the Synthesis of Quinoxaline Derivatives

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Abstract: Treatment of 1,2-phenylenediamine with benzil analogs in the presence of a mixture of sodium bromate/ sodium hydrogen sulfite in water gave the corresponding quinoxalines in high yields. The method is eco-friendly due to use of water instead of other hazardous organic solvents.

Keywords: Eco-friendly chemistry, high yield, quinoxaline, $NaBrO_3/NaHSO_3$ in water.

INTRODUCTION

Quinoxaline is an important nitrogen-containing heterocyclic class of compounds whose analogs exhibit a wide spectrum of biological activities, this class of compounds making a privileged structure for pharmaceutical use as antifungal and antibacterial agents [1], a key structural component for semiconductors [2], electrical and photochemical material [3], anticancer and kinase inhibitors [4-7], pesticides [8], herbicides [9], as part of other receptor antagonists [10], antitumor agent [11]. Some quinoxaline analogs has been reported as picomolar inhibitors of bc_1 Q_o sites [12].

Complexes of quinoxaline derivatives with indium and europium have been found to enhance fluorescence properties through the transformation of ligand to metal and find their use as imaging agents [13-15]. Functionalized quinoxalines can be accessed by various synthetic methods such as iodine catalysis [16], polyanilinesulfate salt [17], Bi/DMSO [18], $MnCl_2$ at room temperature [19], and iron catalysis [20]. A stereospecific synthesis of tetrahydroquinoxaline has been reported, starting from anhydro-sugars [21]. However, all of these methodologies suffer from several limitations such as, long multi-step route, low yields, tedious work-up, long reaction times, limited or no selectivity, and the need to use large amounts of a catalysts resulting in the production of toxic waste. Considering these drawbacks, we have developed an eco-friendly and good yielding method for the synthesis of quinoxalines.

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RESULTS AND DISCUSSION

The significance of the $NaBrO_3/NaHSO_3$ reagent system was extensively studied by our group in recent years [22-25]. Earlier, this reagent system efficiently used as bromohydroxylation agent for alkenes, alkynes and allylic alcohol [26, 27]. This mixture system has also been used for the oxidation of ethers and diols [28, 29], primary alcohols [30], and the α-bromination of alkyl and allyl benzenes [31, 32]. The syntheses of γ-lactones from corresponding *o*-alkylbenzoic acids [25], disulfides from thiols [23], and esters from aromatic carboxylic acids and substituted toluenes by this reagent are also reported by our research group [24]. In addition, we have broadened the scope of this reagent in our laboratory by developing various practical effective approaches in organic synthesis.

In current study, we found that quinoxalines can easily be prepared by reacting 1,2-phenylenediamines with benzils in the presence of 10% catalytic amounts of the $NaBrO_3/NaHSO_3$ reagent system in water at room temperature producing derivatives **1**-**10** (Table **1**). The main advantages of this method are that neither toxic organic solvent nor high temperatures are used. The products were obtained rapidly and the method has overall eco-friendly profile. The structures of synthetic derivatives **1**-**10** were elucidated by using ^{1}HNMR and mass spectroscopy. In addition, the assigned structures of compounds **1**-**4** were further confirmed by single crystal x-ray diffraction studies (Fig. **1**). The experimental crystallographic data of compounds **1**-**4** is summarized in (Table **2**).

The reaction conditions for our newly methodology were optimized by varying the amount of catalyst (sodium bromate/sodium bisulfite mixture). It was found that with 10% aqueous mixture of catalyst the reaction precedes smoothly giving desired products in good yields. Increasing

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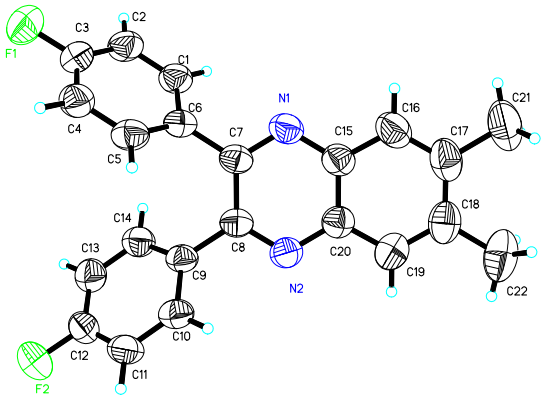
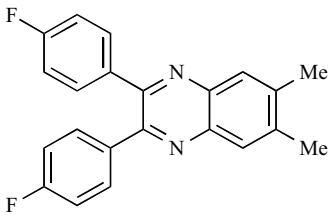
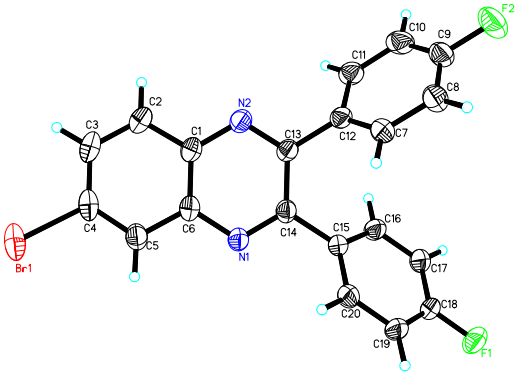
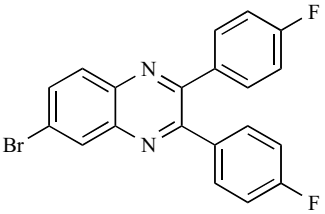


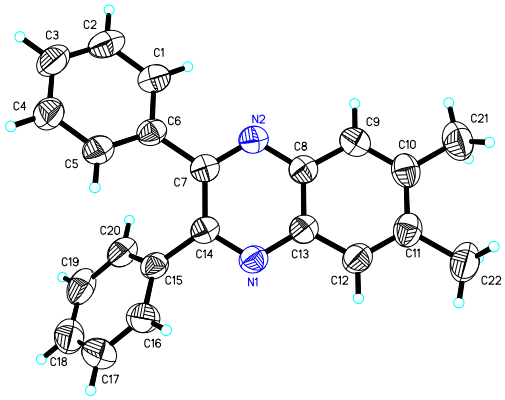


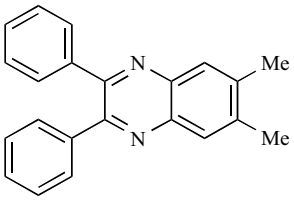
2,3-*Bis*(4-fluorophenyl)-6,7-dimethylquinoxaline (**1**)



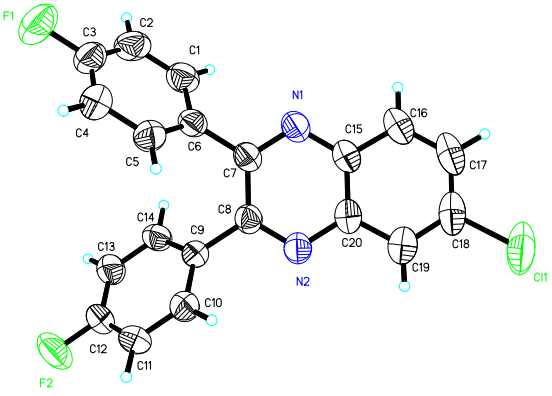


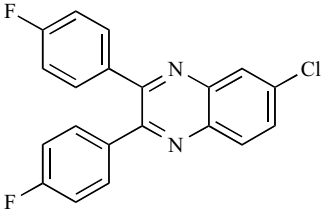
6-Bromo-2,3-*Bis*(4-fluorophenyl)quinoxaline (**2**)





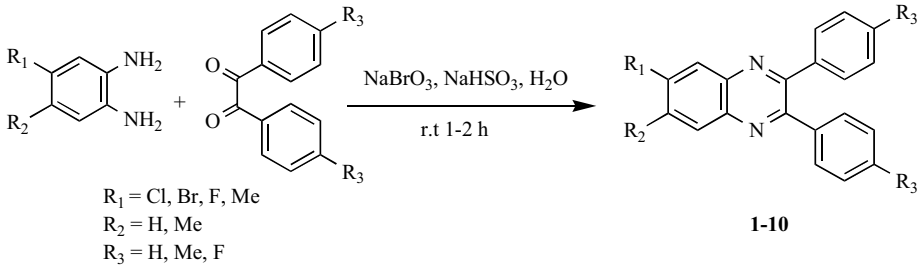
6,7-Dimethyl-2,3-diphenylquinoxaline (**3**)





6-Chloro-2,3-*bis*(4-fluorophenyl)quinoxaline (**4**)

Fig. (1). ORTEP diagrams of compounds 1-4 along with their chemical structures.



R_1 = Cl, Br, F, Me
R_2 = H, Me
R_3 = H, Me, F

1-10

Scheme 1.

Table 1. Synthesis of quinoxaline derivatives 1-10.

Entry	R_1	R_2	R_3	Yield (%)
1	Me	Me	F	94
2	Br	H	F	89
3	Me	Me	H	81
4	Cl	H	F	85
5	F	H	H	80
6	Cl	H	H	80
7	F	H	Me	81
8	Br	H	Me	82
9	Me	H	Me	85
10	Cl	H	Me	89

Table 2. Crystal data for compounds 1-4.

	Compound 1	Compound 2	Compound 3	Compound 4
Empirical formula	$C_{22}H_{16}F_2N_2$	$C_{21}H_{11}BrF_2N_2$	$C_{22}H_{18}N_2$	$C_{20}H_{11}ClF_2N_2$
Formula weight	346.37	397.22	310.38	352.76
Temperature	273(2)	273(2)	273(2)	273(2)
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	P21/c	P21/n	Pbca	P21/n
A	11.0017(7) Å	13.7780(17) Å	8.0111(5) Å	13.524(3) Å
B	12.1567(12) Å	7.6925(10) Å	19.9996(14) Å	7.7043(17) A
C	9.6409(7) Å	16.303(2) Å	20.8495(14) Å	16.438(4) Å
a	90°	90°	90°	90°
b	101.305(2)°	105.501(3)°	90°	105.456(4)°
g	90°	90°	90°	90°
Volume	1484.4(2) A^3	1665.1(4) A^3	3340.5(4) A^3	1650.8(6) A^3
Z	4	4	8	4
Calculated density	1.289 mg/m^3	1.585 mg/m^3	1.234 mg/m^3	1.419 mg/m^3

Table 2. Contd…..

	Compound 1	Compound 2	Compound 3	Compound 4
Absorption coefficient	0.091 mm^{-1}	2.493 mm^{-1}	0.073 mm^{-1}	0.256 mm^{-1}
F(000)	720	792	1312	720
Crystal size	0.59 x 0.22 x 0.07 mm	0.54 x 0.23 x 0.10 mm	0.46 x 0.20 x 0.13 mm	0.59 x 0.24 x 0.12 mm
qrange	1.89 to 25.50°	1.72 to 25.50°	1.95 to 25.50°	1.74 to 25.50°
Reflections Collected	10461	9457	18355	8857
Reflections Unique	3313	3104	3097	3040
(R_{int})	0.0294	0.0247	0.0357	0.0316
R_1 with I > 2s(I)	0.0434	0.0386	1.041	0.0445
R_2 with I > 2s(I)	0.0996	0.1065	0.0432	0.0990
R_1 for all data	0.0718	0.0610	0.1015	0.0724
R_2 for all data	0.1063	1186	0.0622	0.1118
Goodness of fit	1.030	1.043	0.1035	1.012
max / min ρeA^{o-3}	0.133 and -0.151	0.449 and -0.567	0.109 and -0.174	0.179 and -0.187
CCDC numbers	948545	948547	948544	948546

Table 3. Impact of catalyst amount in overall yields and reaction times.

Entry	Amount of Catalyst %	Reaction Time (h)	Yield %
1	5	2.10	70
2	10	2.10	94
3	15	2.15	74
4	20	2.40	73
5	25	3.00	69
6	Sodium Bromate	3.00	00
7	Sodium bisulfite	3.00	00
8	Without catalyst	3.00	00

the amount of catalyst from 10% to 25% had a negative yield outcome and the reaction requires longer times for completion. This may be due to poising of reaction but actual reason is unknown. To ensure the utility of sodium bromate/sodium bisulfite as a catalyst for this reaction, we performed three reactions. First, a blank reaction was carried out in same reaction conditions without using sodium bromate or sodium bisufite, however, no product was obtained. Second, using only sodium bromate as a catalyst in same reaction conditions but no product was observed. Third, only sodium bisulfite was used, however, it didn't yield any product which clearly indicates that combination of sodium bromate/sodium bisulfite mixture behaves as catalyst for this reaction (Table **3**).

Since the esterification of tolyl or benzyl group with carboxylic acids also takes place by sodium bromate/sodium bisulfate [24, 25]. Therefore, it was considered that the tolyl or benzyl containing moieties may condense with diamine to form secondary amine in the same reaction conditions instead of quinoxaline formation. To eliminate this possibility, sodium bromate/sodium bisulfite was used deliberately for entries 7-10 which contain tolyl groups and it was observed that it is quite selective in the presence of tolyl functionality and methyl group remain intact even after the completion of the reaction. No any side product was found in any reaction.

CONCLUSION

Conclusively, we have developed a new method for the synthesis of quinoxalines using a sodium bromate/sodium hydrogen sulfite mixture as a catalyst in water. The reaction is eco-benign, efficient, easy to handle and high yielding. The newly developed method may be used as an alternative method for the synthesis of quinoxalines.

GENERAL EXPERIMENTAL

A Bruker Smart APEX II single-crystal X-ray diffractometer fitted with a CCD detector was used to collect the data [33]. Data was reduced and solved by was using the SAINT program and direct methods, respectively [34]. Finally, the structural atomic arrangement was solved using the SHELXL97 program by using full-matrix least-square calculation on F^2 [35,36]. The figures were plotted using the ORTEP program. The crystallographic data is available free of charge from the Cambridge crystallographic data centre by using the CCDC numbers. (http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/Requestastructure.aspx).

The experimental data of compounds **1**-**4** is summarized in (Table **2**).

General Synthetic Procedure for Quinoxaline Derivatives 1-10

Generally, to a stirring mixture of different substituted 1,2-phenylenedine (2 mmol) and substituted benzils (2 mmol) in water, sodium bromate and sodium hydrogen sulfite (10%) were added and stirred for 2-3 h. The progress of reaction was monitored by TLC. After the completion of reaction, 20 mL ethyl acetate was added to reaction mixture, the organic layer was separated by a separating funnel. The quinoxaline derivatives **1-10** were obtained in high yields. Pure products were obtained by recrystallization from ethanol and in some cases through column chromatography (silica gel) using 2:8 ethyl acetate and *n*-hexane as eluent.

The structures of compounds were confirmed by using various spectroscopic techniques, including ^{1}H NMR, EI mass, and X-ray spectroscopy.

2,3-*Bis*(4-fluorophenyl)-6,7-dimethylquinoxaline (1)

Yield: 0.57 g (90%); M.P: 221°C, white crystal, ^{1}H-NMR (400 MHz, Acetone): δ 7.88 (s, 2H, H-5, H-8), 7.55 ((m, 4H, 2 x H-3, H-5), 7.55 (m, 4H, 2 x H-3, H-5), 7.14 (m, 4H, 2 x H-2, H6), 2.53 (s, 6H, 2 x $ArCH_3$); EI-MS *m/z* (rel. abund. *%*): 446 (M+, 100), 445 (99), 103(48).

6-Bromo-2,3-bis(4-fluorophenyl)quinoxaline (2)

Yield: 0.53 g (89%); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.15 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5), 8.02 (d, 1H, $J_{8,7}$ = 11.4 Hz, H-8), 7.96 (dd, 1H, $J_{7,5}$ = 2.2 Hz, $J_{7,8}$ =10.6 Hz, H-7), 8.16(m, 4H, H-3, H-5, 2 x H-3'/5'), 7.87 (m, 4H, H-2, H-6, 2 x H-2'/6'), EI-MS m/z (rel. abund.*%*): 398 (M^++2, 92), 396 (M^+, 100), 396 (65), 91(54).

2,3-Bis(4-methylphenyl)quinoxaline (3)

Yield: 0.43 g (70%); M.P: 243 °C, white crystal, ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.14 (m, 2H, H-5, H-8), 7.84 (m, 2H, H-6, H-7), 7.37 (d, 4H, $J_{3',2'/5',6'}$ = 9.76 Hz, 2 x H-3'/5'), 7.17 (br d, 4H, $J_{2',3'/6',5'}$ = 8.00 Hz, 2 x H-2'/6'), 2.49 (s, 6H, 2 x $ArCH_3$); EI-MS *m/z* (rel. abund. *%*): 310 (M^+, 78), 309 (32), 91(31).

6-Chloro-2,3-bis(4-fluorophenyl)quinoxaline (4)

Yield: 0.48 g (71%); M.P: 234 °C, white crystal, ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.65 (d, 1H, $J_{5,7}$ =2.0 Hz, H-5), 8.53 (d, 1H, $J_{8,7}$ = 12.0 Hz, H-8), 8.61 (dd, 1H, $J_{7,5}$ = 2.2 Hz, $J_{7,8}$ = 10.2 Hz, H-7), 8.23 (m, 4H, 2 x H-3, 2 x H-5, 2 x H-3'/5'), 7.76 (m, 4H, H-2, H-6, 2 x H-2'/6'), EI-MS *m/z* (rel. abund.*%*): 354 (M+2, 24), 353 (M+1, 21), 352 (M+, 100), 21 225 (43), 123(96).

6-Fluoro-2,3-diphenylquinoxaline (5)

Yield: 0.43 g (70%); M.P: 226 °C, Yellowish solid, ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.24 (m, 1H, H-5), 7.96 (dd, 1H, $J_{7,8}$ = 9.6 Hz, $J_{7,5}$ = 2.8 Hz, H-7), 7.46 (m, 4H, 2 x H-2, H-6), 7.83 (m, 6H, 2 x H-3, 2 x H-4, 2 x H-5); EI-MS *m/z* (rel. abund. *%*): 299.2 (M+, 100), 197 (100), 150 (35.7), 103 (12.5).

6-Chloro-2,3-diphenylquinoxaline (6)

Yield: 0.42 g (76%); M.P: 235 °C, light brown solid, ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.25 (s,0 1H, H-5), 8.18 (d, $J_{8,7}$ = 8.8 Hz, H-8), 7.91 (1H dd, 1H, $J_{7,8}$ = 9.2, $J_{7,5}$ = 2.4 Hz, H-7), 7.46 (m 4H, 2 x H-2, H-6), 7.37 (m, 6H, 2 x H-3, 2 x H-4, 2 x H-5); EI-MS *m/z* (rel. abund. *%*): 318 (M+2, 34), 317 (M+1, 44), 316 (M+, 100), 314.87 (71.5), 177 (24.1), 212.9 (21.7).

6-Fluoro-2,3-bis(4-methylphenyl)quinoxaline (7)

Yield: 0.49 g (75%); M.P: 248 °C, brown solid, ^{1}H-NMR (400 MHz, DMSO-d6): 8.20 (m, 1H, H-5), 8.18 (dd, $J_{7,8}$ = 9.6, $J_{7,5}$ = 2.8 Hz, H-7), 7.77 (m, 1H, H-8), 7.37 (m 4H, 2 x H-2, H-6), 7.17 (m, 4H, 2 x H-3, 2 x H-5), 2.49 (s, 6H, 2 x $ArCH_3$); EI-MS *m/z* (rel. abund. *%*): 328 (M^+, 100), 327.2 (73.6), 313.2 (94), 120.1 (19.4).

6-Bromo-2,3-bis(4-methylphenyl)quinoxaline (8)

Yield: 0.56 g (73%); M.P: 256 °C, white solid, ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.35 (s, 1H, H-5), 8.04 (d, $J_{8,7}$ = 8.8 Hz, H-8), 7.96 (dd, 1H, $J_{7,5}$ = 2.0 Hz, $J_{7,8}$ = 8.8 Hz, H-7), 7.36 (d, 4H, $J_{2,3}$ = 8.0 Hz, 2 x H-2, H-6), 7.17 (d 4H, $J_{3,2}$ / $J_{5,6}$ = 8 .0 Hz, 2 x H-3, H-5), 7.17 (d, 4H, $J_{2,3}$/ $J_{6,5}$ = 6.8 Hz, 2 x H-2, H-6), 2.32 (s, 6H, 2 x $ArCH_3$); EI-MS *m/z* (rel. abund. *%*): 390 (M+2, 58), 388 (M+, 56), 192 (35), 90 (42).

6-Methyl-2,3-bis(4-methylphenyl)quinoxaline (9)

Yield: 0.46 g (72%); M.P: 243 °C, yellow solid, ^{1}H-NMR (400 MHz, DMSO-d6): δ 7.96 (d, 1H, $J_{8,7}$ = 8.2 Hz, H-8), 7.87 (s, 1H, H-5), 7.85 (dd, 1H, $J_{7,5}$ = 2.0 Hz, $J_{7,8}$ = 11.2 Hz, H-7), 7.43 (dd, 4H, $J_{2,6}$ = 2.4 Hz, $J_{2,3}$ = 10.8 Hz, 2 x H-2, H-6), 7.16 (br d, 4H, $J_{3',2'/5',6'}$ = 10.4 Hz, 2 x H-3'/5'); 2.60 (s, 3H, $ArCH_3$), 2.348 (s, 6H, 2 x $ArCH_3$) EI-MS *m/z* (rel. abund. *%*): 323 (M+, 100), 316 (32), 90(38).

6-Chloro-2,3-bis(4-methylphenyl)quinoxaline (10)

Yield: 0.45 g (66%); M.P: 238 °C, white solid, ^{1}H-NMR (400 MHz, DMSO-d6): δ 8.35 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5), 8.06 (d, 1H, $J_{8,7}$ = 12.0 Hz, H-8), 7.98 (dd, 1H, $J_{7,5}$ = 2.8 Hz, $J_{7,8}$ = 12.0 Hz, H-7), 7.34 (br d, 4H, $J_{2',3'/6',5'}$ = 10.8 Hz, 2 x H-2'/6'), 7.17 (d, 4H, $J_{3',2'/5',6'}$ = 10.4 Hz, 2 x H-3'/5'), 2.49 (s, 6H, 2 x $ArCH_3$), EI-MS *m/z* (rel. abund. *%*): 346 (M+2, 26), 345 (M+1, 18), 344 (M+, 87), 301 (100), 91 (37).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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