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An environmentally benign protocol for the synthesis of quinoxaline derivatives under ultrasound irradiation

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In continuation of our efforts to develop green synthetic routes for the formation of biologically active quinoxalines, we report oxidative cyclization of *o*-phenylenediamine and α-bromo ketones. The efficacy of this reaction is illustrated by the compatibility with chloro, bromo, nitro, methoxy, furyl, *etc.* groups. All the new compounds have been characterized by IR, NMR and elemental analysis. The foremost feature of this methodology is environmentally benign reaction, simple work-up, mild reaction conditions and less reaction time.

Keywords: Quinoxaline, Oxidative cyclization, Environmentally benign, Ultrasound

Quinoxalines and their derivatives are most vital class of compounds showing a variety of biological activities (Fig. 1) including antiviral[1], antibacterial[2], anticancer[3], anti inflammatory[4], analgesic[5], antifungal[6], antioxidant[7], anti depressant activities[8] *etc.* Additionally quinoxalines have numerous applications in dyes[9], organic semiconductors[10], chemically controllable switches[11], and building blocks for the synthesis of anion receptors[12], cavitands1[3], and DNA cleaving agents[14], which show that they are an essential class of N-containing heterocycles in organic synthesis. Because of these numerous advantages, a number of methods have been developed for the synthesis of quinoxaline scaffold. The condensation of o-phenyldiamine with 1,2-dicarbonyl compounds[15-18], 1,4-addition of 1,2-diamine to diazenylbutenls[19], oxidative cyclization of α -hydroxy ketones and 1,2-diamines[20-22], oxidative coupling of epoxides with ene-1,2-diamines[23], cyclization-oxidation of phenacyl bromides with 1,2-diamines by $HClO_4.SiO_2$[24] are some of the reported synthetic methods. Nevertheless most of these methods suffer from drawbacks such as expensive reagents, harsh reaction condition and low product yield. Considering these hurdles, clean approaches are highly desirable goal in organic synthesis.

Ultrasound assisted organic synthesis is a powerful technique that is being used to accelerate organic reactions[25]. Over the year's protection of environment and waste prevention-reduction have been increasingly emphasized by researchers. For this reason, ultrasound is more convenient as compared with traditional thermal methods because they provide broad area for research and can be carried out in higher yield product, purity of product, product selectivity. In conclusion, we have developed an eco-friendly synthesis of quinoxaline by oxidative cyclization under ultrasound irradiation as shown in Scheme 1.

Results and Discussion

Initial study was focused to optimize the reaction conditions. The reaction was studied in different solvents such as DMF, THF, DMSO, which are aprotic solvents and MeOH, EtOH, H_2O which are protic solvents. Efforts were directed towards the evaluation of the synthesis of quinoxaline, however all the solvents provide good yield except water but ethanol was the solvent of choice in terms of yield and reaction time (Table 1).

A typical experiment was performed by choosing various symmetric diamines with substituted α-bromo ketones to explore the scope of the reaction to synthesize the desired product which are summarized in Table 2. The reaction proceeded effortlessly in the presence of electron withdrawing as well as electron donating substituents on α-bromo ketones. It was observed that substituted α-bromo ketones undergo condensation with 1,2-diamine well to afford the corresponding products in moderate to excellent yields.

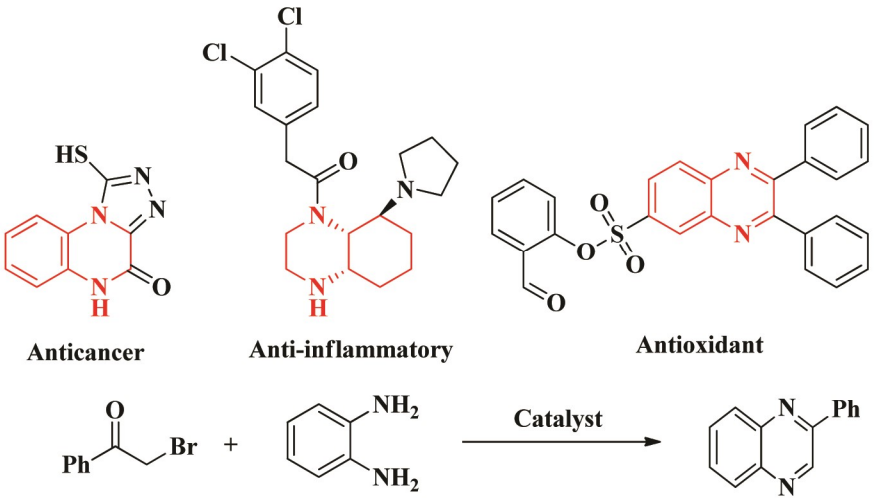
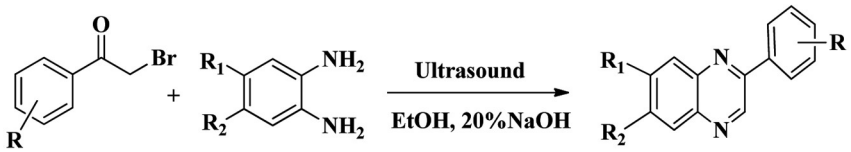


Fig. 1 — Biological active compounds of Quinoxalines



Scheme 1 — Synthesis of 2-phenylquinoxaline

Table 1 — Effects of solvents on the reaction of 1, 2- diamine and α-bromo ketones under ultrasound irradiation.

Entry	Solvent	Yield (%)
1	DMF	84
2	THF	85
3	DMSO	92
4	MeOH	96
5	EtOH	98
6	H_2O	42

Based on the observation, a plausible reaction mechanism is envisaged for the synthesis of quinoxaline. Initially on α-bromo ketone a nucleophilic substitution occurs to afford the intermediate 3. After cyclization, intermediate 4 undergoes aromatization to form the final product (Fig. 2).

The reaction of *o*-phenylenediamine with α-bromo ketones resulted in high yields of substituted quinoxaline. In case of 4-methyl and 4-nitro bromo ketone (Entries 4, 6) steric factors played a key role by affecting the rate of reaction. On the other hand, sterically hindered diamine (Entries 8-12) afforded the product in moderate yield (Table 2).

Materials and Methods

All the chemicals used were of research grade (purchased from Sigma Aldrich and TCI) and used without further purification. The melting points of all compounds were determined on a Toshniwal apparatus in capillary and uncorrected. IR spectra were recorded on a Shimadzu FT IR- 8400S spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained using $CDCl_3$ as solvent on a JEOL JNM LA-200 spectrometer (200 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR). The ^{1}H NMR data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm), chemical shift (multiplicity) and the ^{13}C NMR data in ppm (δ) from the internal standard (TMS, 0.0 ppm). Mass spectra were obtained using Waters Xevo G2S instrument.

General procedure for the synthesis of compounds

In order to achieve simple, ecofriendly approach for the synthesis of quinoxaline derivatives reaction between α-bromo ketones and *o*-phenylenediamine was carried out in the presence of ethanol and 20% sodium hydroxide under ultrasound irradiation. The formation of the product was checked by TLC. The product was poured into a beaker containing crushed ice and acidified by dil. HCl. The crude product was filtered, dried and recrystallized to furnish product from 1 to 12 (Ref. 27).

2-Phenylquinoxaline, 1

Solid, m.p. 74–76°C (lit.33 75–76°C); ^{1}H NMR (300 MHz, $CDCl_3$): d 7.56–7.59 (m, 3H), 7.77–7.81

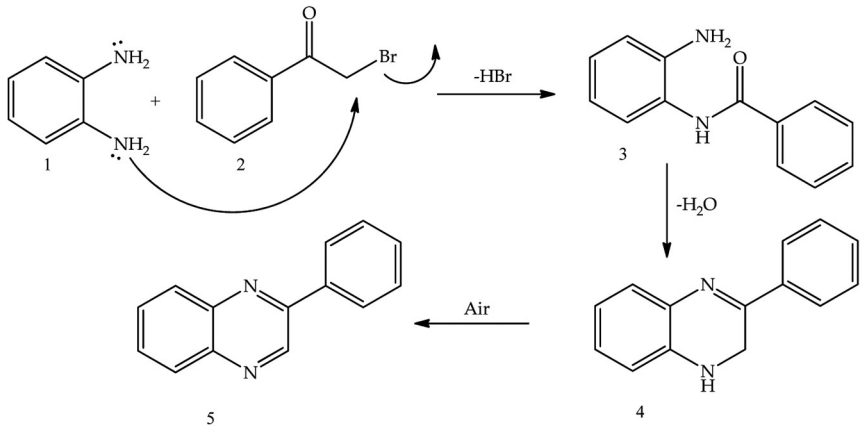
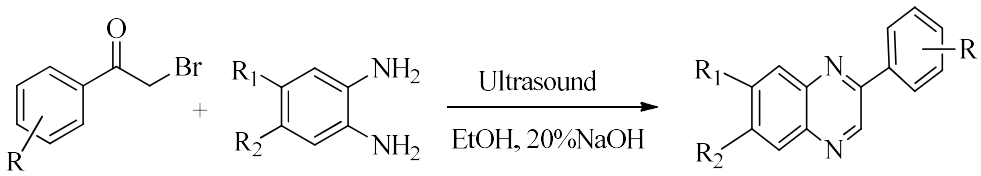
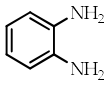
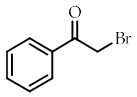
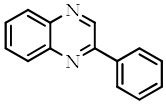
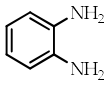
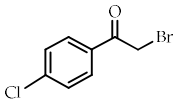
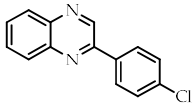
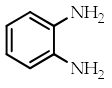
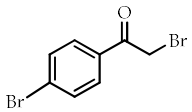
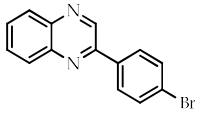
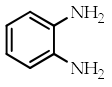
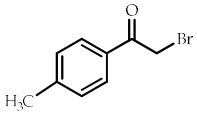
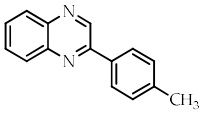
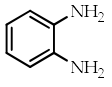
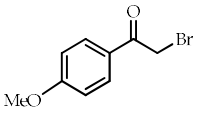
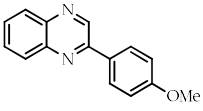
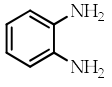
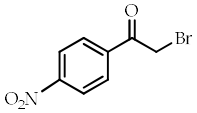
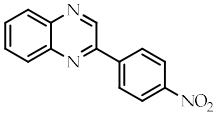
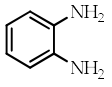
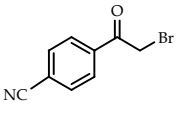
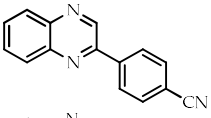
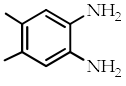
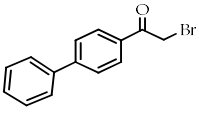
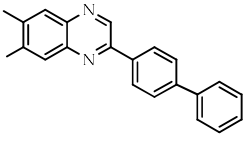


Fig. 2 — Plausible reaction mechanism

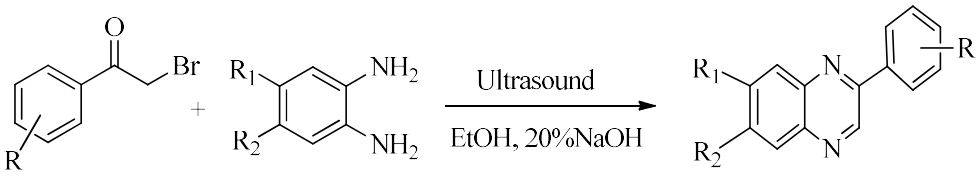
Table 2 — Synthesis of quinoxaline under ultrasound irradiation

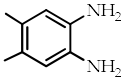
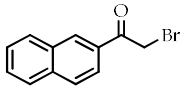
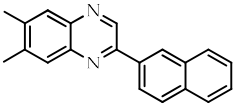
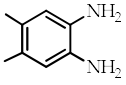
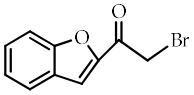
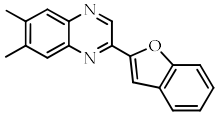
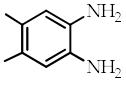
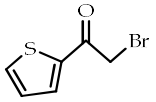
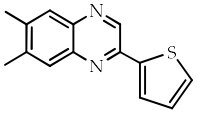
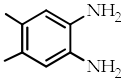
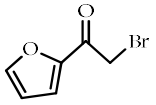
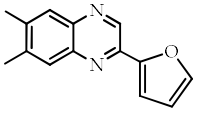


Entry	O-phenylenediamine	α-bromo ketones	Product	Isolated Yield(%)	Ref.
1				90	[26]
2				90	[26]
3				90	[26]
4				87	[26]
5				92	[26]
6				83	[26]
7				90	[26]
8				87	-

(*Contd*.)

Table 2 — Synthesis of quinoxaline under ultrasound irradiation — (*Contd.*)



Entry	O-phenylenediamine	α-bromo ketones	Product	Isolated Yield(%)	Ref.
9				89	-
10				85	-
11				89	-
12				84	-

(m, 2H), 8.13–8.23 (m, 4H), 9.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 127.4, 127.7, 129.0, 129.3, 129.5, 130.0, 130.1, 136.5, 141.4, 142.1, 143.2, 151.5; MS (ESI): m/z 207$(M+H)^+$.

2-(4-Chlorophenyl)quinoxaline, 2

Solid, m.p. 125–128°C (not reported); ^{1}H NMR (300 MHz, $CDCl_3$): d 7.53–7.56 (m, 2H), 7.56– 7.81 (m, 2H), 8.11–8.18 (m, 2H), 9.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 128.7, 129.1, 129.4, 129. 6, 129.7, 130.4, 135.1, 136.6, 141.6, 142.2, 142.8, 150.5; MS (ESI): m/z 241 $(M+H)^+$.

2-(4-Bromophenyl)quinoxaline, 3

Solid, m.p. 136–139°C (not reported); ^{1}H NMR (300 MHz, $CDCl_3$): d 7.63–7.66 (m, 2H), 7.74– 7.76 (m, 2H), 8.02–8.11 (m, 2H), 9.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 124.91, 128.89, 129.09, 129.51, 129.73, 130.40, 132.25, 135.47, 141.57, 142.10, 142.70, 150.48; MS (ESI): m/z 285 $(M+H)^+$.

2-(4-Methylphenyl)quinoxaline, 4

Solid, m.p. 93–94°C (lit.33 90–91°C); ^{1}H NMR (300 MHz, $CDCl_3$): d 2.44 (s, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.71–7.77 (m, 2H), 8.09–8.16 (m, 4H), 9.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 21.3, 127.3, 129.0, 129.2, 129.4, 129.8, 130.1,133.8, 140.4, 141.3, 142.2, 143.2, 151.7; MS (ESI): m/z 221 $(M+H)^+$.

2-(4-Methoxyphenyl)quinoxaline, 5

Solid, m.p. 100–101°C (lit.33 99–100°C); ^{1}H NMR (300 MHz, $CDCl_3$): d 3.88 (s, 3H), 7.05–7.08 (m, 2H), 7.71–7.75 (m, 2H), 8.07–8.18 (m, 4H), 9.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 55.4, 114.5, 128.9, 129.0, 129.0, 129.2, 129.3, 130.1, 141.2, 142.3, 143.0, 151.3,161.4; MS (ESI): m/z 237 $(M+H)^+$.

2-(4-Nitrophenyl)quinoxaline, 6

Solid, m.p. 188–191°C (not reported); ^{1}H NMR (300 MHz, DMSO-d6): d 7.90–7.93 (m, 2H), 8.13–8.16 (m, 2H), 8.39–8.42 (m, 2H), 8.56–8.59 (m, 2H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d6) d 124.6, 129.2, 129.36, 129.9, 131.4, 131.5, 141.8, 142.0, 142.4, 144.4, 148. 9, 149.4; MS (ESI): m/z 252 $(M+H)^+$.

4-(Quinoxalin-2-yl)benzonitrile, 7

Pale yellow solid; yield 90%; mp 193–195°C; Rf (20% EtOAc/n-hexane) 0.28; ^{1}H NMR (200 MHz, $CDCl_3$) d 7.82–7.88 (m, 4H, ArH), 8.13–8.20 (m, 2H, ArH), 8.33–8.36 (d, J = 8.309, 2H, ArH), 9.35 (s, 1H, C_3–H); ^{13}C NMR (75 MHz, $CDCl_3$) d 113.8, 118.4, 127.5, 128.0, 129.0, 129.8, 130.7, 130.9, 132.9, 140.6, 141.6, 142.3, 142.3, 149.6; MS (ESI): m/z 252 $(M+H)^+$.

2-Biphenyl-4-yl-6,7-dimethyl-quinoxaline, 8

Pale yellow solid, mp 130-131°C; Rf (20% EtOAc/n-Hexane) 0.46; ^{1}H NMR (200MHz, $CDCl_3$) δ

2.35-2.39 (s, 6H), 7.22- 7.33 (m, 3H), 7.48-7.58 (m, 6H), 7.85-7.94 (s, 2H), 9.26 (s, 1H, C_3-H) ; ^{13}C NMR (75MHz, $CDCl_3$ ppm) δ 20.3,127.4, 127.8, 127.9, 128.2, 129.0, 135.0, 136.6, 141.1, 144.0, 145.4; MS (ESI): m/z 311 (M+H)+.

6,7-Dimethyl-2-naphthalen-2-yl-quinoxaline, 9

Dark yellow solid, mp 165-168°C; Rf (20% EtOAc/n-Hexane) 0.45; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.35-2.39 (s, 6H), 7.22-7.33 (m, 3H), 7.48-7.58 (m, 6H), 7.85-7.94 (s, 2H), 9.26 (s, 1H, C_3-H); ^{13}C NMR (75MHz, $CDCl_3$) δ20.2, 125.0, 126.5, 128.0, 128.2, 128.5, 133.0, 133.6, 141.0, 144.0, 145.2; MS (ESI): m/z 285.13 (M+H)+.

2-Benzofurane-2-yl-6,7-dimethyl-quinoxaline, 10

Dark yellow solid, mp 102-105°C; Rf (20% EtOAc/n-Hexane) 0.47; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.35-2.39 (s, 6H), 7.8-7.12 (s, 2H), 7.2-7.7 (m, 5H), 9.26 (s, 1H, C_3-H), ^{13}C NMR (75MHz, $CDCl_3$) δ 20.3, 120.1,122.0, 123.8, 124.0, 124.2, 128.0,139.2, 140.0, 141.2, 143.0, 144.0; MS (ESI): m/z 291.09 (M+H) +.

6,7-Dimethyl-2-thiophene-2-yl-quinoxaline, 11

Pale yellow solid, mp 130-135°C; Rf (20% EtOAc/n-Hexane) 0.48; ^{1}H NMR (200MHz, $CDCl_3$) δ 2.35-2.39 (s, 6H), 7.8-7.12 (s, 2H), 7-7.2 (m, 2H), 7.4 (d, 1H), 9.26 (s, 1H, C_3-H); ^{13}C NMR (75MHz, $CDCl_3$) δ 20.2, 122.0, 125.4, 127.6, 128.0, 141.0, 142.7, 144.0; MS (ESI): m/z 241.08 (M+H)+.

2-Furane-2-yl-6,7-dimethyl-quinoxaline, 12

Yellow solid, mp 95-98°C, Rf (20% EtOAc/n-Hexane) 0.45, ^{1}H NMR (200MHz, $CDCl_3$) δ 2.35-2.39 (s, 6H), 7.8-7.12 (s, 2H), 6.2-6.7 (m, 2H), 7.4 (d, 1H), 9.26 (s, 1H, C_3-H); ^{13}C NMR (75MHz, $CDCl_3$) δ 20.2, 105.2, 111.0, 128.0, 141.0, 142.7, 144.0, 154.0; MS (ESI): m/z 225.10 (M+H)+.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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Conclusions

In summary, we successfully synthesized and evaluated new quinoxaline derivatives from *o*-phenylene-diamine and α-bromo ketones using ultrasound. This method follows the mechanism of oxidative cyclization. It has many advantages such as high product yield under mild conditions, an inexpensive green method, *etc.* These advantages make this method a green chemical process for the preparation of quinoxaline.

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