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K$_2$S$_2$O$_8$ mediated C-3 arylation of quinoxalin-2(1H)-ones under metal-, photocatalyst- and light-free conditions†

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Two facile and effective C-3 arylation protocols of quinoxalin-2(1H)-ones with arylhydrazines and aryl boronic acids respectively *via* free radical cross-coupling reactions under metal-, photocatalyst- and light-free conditions have been unveiled. K$_2$S$_2$O$_8$ has been used as an efficient oxidant to generate aryl radicals from arylhydrazines and aryl boronic acids under two different reaction conditions. The generated aryl radicals undergo a free radical coupling reaction at the C-3 position of quinoxalin-2(1H)-ones producing 3-arylquinoxalin-2(1H)-ones in good to excellent yields. The involvement of radicals in the course of the reaction has been demonstrated by radical trapping experiments with 2,2,6,6-tetramethylpiperidine-1-oxyl.
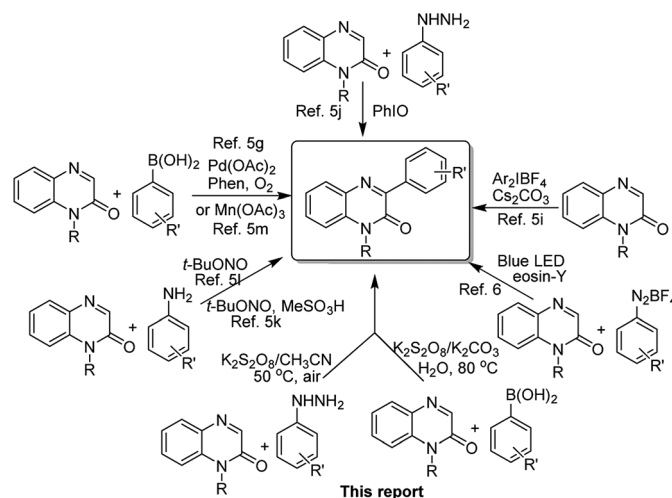
Introduction

Quinoxalin-2(1H)-ones have emerged as an important class of heterocyclic compounds because of their broad biological activities and other chemical properties.[1] More specifically, the skeleton of 3-arylquinoxalin-2(1H)-one is found in a variety of potential biological entities, and they exhibit a broad spectrum of pharmaceutical properties.[2] Anti-tryposomal,[3a] anti-plasmodial,[3b] anti-histamine,[3c] anticancer,[3d] anti-viral,[3e,f] antitumor and antimicrobial,[3g] CFTR activators,[3h] FXa coagulation inhibitors[2b] and PDGF-βR inhibitor[2c] are a few of them reported in the literature. Besides, polymers obtained from these compounds can be used as semiconductors which also sets up their importance in the field of materials science.[4]

Owing to their broad biological properties, synthetic and medicinal chemists all over the world are putting effort into developing easy-to-handle and practical methods for the synthesis of 3-arylquinoxalin-2(1H)-ones. Generally, the arylation of quinoxalin-2(1H)-ones with versatile aryl source under suitable reaction conditions produces 3-arylquinoxalin-2(1H)-ones in a single step chemical process. Recently, several research groups have highlighted the importance of this skeleton and also reported a handsome number of synthetic methodologies.[5] Most of these methods undergo the radical

C–C bond formation reaction at C-3 position of quinoxalin-2(1H)-ones by involving different aryl radical sources such as arylboronic acids, diaryliodonium salts, arylhydrazine/ iodosobenzene, and aniline/alkyl nitrite. Very recently, Kim's group used the technique of visible light-mediated redox catalysis to obtain 3-arylquinoxalin-2(1H)-ones from arylquinoxalin-2(1H)-ones by using arenediazonium salt as an aryl radical source.[6] Although these methods have their own merits, there is a need for further improvement concerning the practical and operational simplicity as well as the use of non-toxic oxidant (previous reports, Scheme 1).

It has been well established that compared to the classical cross-coupling methods to form carbon–carbon and carbon-
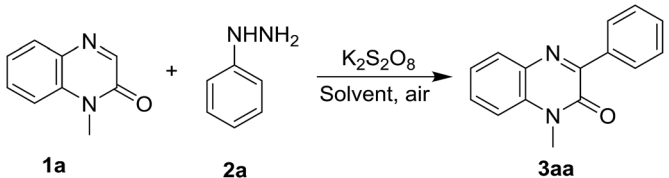
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† Electronic supplementary information (ESI) available: Experimental data of all new compounds; ^{1}H and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/d0ra00013b

Scheme 1 C-3 arylation of quinoxalin-2(1H)-ones.

Table 1 Reaction optimization studies[a]

Entry	PhNH$_2$NH$_2$ (equiv.)	K$_2$S$_2$O$_8$ (equiv.)	Solvent	Time (h)	Yields[b] (%)
1	1.2	—	CH$_3$CN	6	n.r.
2	1.5	—	CH$_3$CN	6	n.r.
3	1.2	1.5	CH$_3$CN	6	49
4	1.5	2.0	CH$_3$CN	6	57
5	1.5	3.0	CH$_3$CN	6	61
6	2.0	3.0	CH$_3$CN	6	62
7	1.5	3.0	ClCH$_2$H$_2$Cl	6	Complex mixture
8	1.5	3.0	ClCH$_2$CH$_2$Cl–H$_2$O	6	Trace
9	1.5	3.0	THF	6	Complex mixture
10	1.5	3.0	Acetone	6	n.r.
11[c]	1.5	3.0	CH$_3$CN	6	81
12[c]	1.5	2.0	CH$_3$CN	6	53
13[d]	1.5	3.0	CH$_3$CN	6	78
14[e]	1.5	3.0	CH$_3$CN	6	61
15[e]	1.5	3.0	DMSO–H$_2$O	6	61
16[f]	1.5	3.0	CH$_3$CN	6	Trace
17[g]	1.5	3.0	CH$_3$CN	6	Trace

[a] Reaction conditions: a mixture of **1a** (0.2 mmol) and **2a** in the presence of K$_2$S$_2$O$_8$ was stirred as mentioned above in the table. [b] Isolated yields. [c] Reaction is carried out at 50 °C. [d] Additive K$_2$CO$_3$ was used. [e] NH$_4$S$_2$O$_8$. [f] Mn(OAc)$_3$·2H$_2$O. [g] PhI(OCOCF$_3$)$_2$ were used instead of K$_2$S$_2$O$_8$.

heteroatom bonds, the coupling reactions involving free-radicals have emerged as modern synthetic methods in organic and medicinal chemistry.[7] Generally, bromo- and iodoarenes are used as traditional aryl radicals sources for various arylation reaction under different metal-catalyzed conditions.[8] In recent years, back to back publications establish arylhydrazine as a readily available aryl radical source in the presence of either an oxidizing agent or a base which undergoes C–H functionalization reaction at an active C-centre of different organic compounds.[9] However, the use of excess bases and toxic transition metals, longer reaction hours and low yield of the desired products are a few major drawbacks of these reported methods. Recently, Akamanchi's group has published a series of articles where they used the mixture of arylhydrazine and iodoxybenzoic acid as an aryl radical source for the arylation reaction of different organic compounds.[10] Similarly, arylboronic acids are also used as aryl radical sources under different metal as well as metal-free reaction conditions for the arylation of different organic compounds such as naphthoquinone, benzoquinone, quinazoline, quinoline, quinoxalin-2(1H)-ones, imidazopyridines, etc.[11] Additionally, stability, as well as easy availability in different substituted forms, makes aryl boronic acids more convenient and practical to use as aryl radical counterparts for synthesizing versatile building blocks and structural scaffolds. Even, several important organic transformations involving aryl boronic acids can be performed in water which proves their water stability as well.[12] Among

different organic and inorganic oxidants, potassium persulfate (K$_2$S$_2$O$_8$) has come out as a suitable oxidant for many oxidative transformations since the discovery of Minisci reaction.[13,14] Because of inexpensive, readily available and easy-to-handling properties it has been widely used as an oxidant in both laboratory experiments and industrial processes.[14] Although several reports on the synthesis of 3-arylquinoxalin-2(1H)-ones are known in the literature, there is no such report on the use of arylhydrazine and arylboronic acid in the presence of the oxidizing agent K$_2$S$_2$O$_8$ as aryl radical source for the C-3 arylation reaction of quinoxalin-2(1H)-ones. Again, the reagent system arylhydrazine/K$_2$S$_2$O$_8$ has been utilized for the first time for any arylation reaction.

In continuation of our ongoing research program on the synthesis of various heterocycles,[15] we, herein, report two new methods for the synthesis of 3-arylquinoxalin-2(1H)-ones via the radical coupling reaction of quinoxalin-2(1H)-ones with arylhydrazines and arylboronic acids as radical counterparts in the presence of sole oxidant K$_2$S$_2$O$_8$ (this report, Scheme 1).

Results and discussion

To find the optimal reaction conditions for the synthesis of 3-arylquinoxalin-2(1H)-one derivatives, we first attempted the cross-coupling reaction of quinoxalin-2(1H)-one (**1a**, 0.2 mmol) with phenylhydrazine (**2a**, 0.24 mmol) in acetonitrile at room temperature under open-air atmosphere. No reaction was
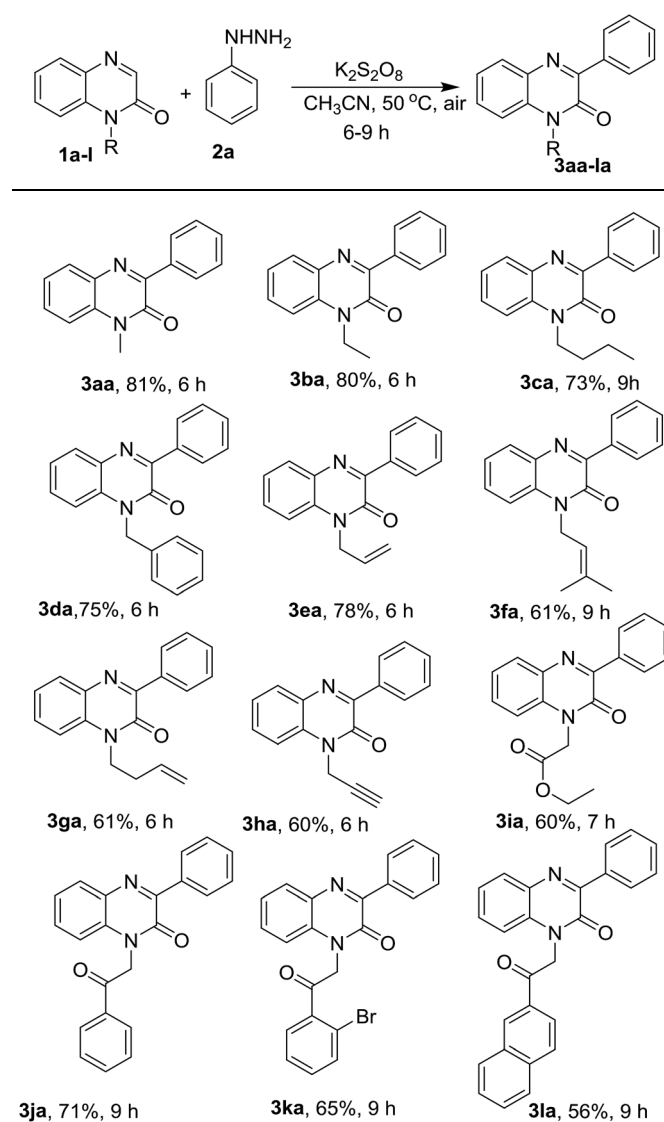
perceived as both starting materials remained unchanged after 6 h of reaction time (Table 1, entry 1). We also performed the same reaction by adding 1.5 equiv. of **2a**, but the same result was obtained (Table 1, entry 2). When the reaction was carried out in the presence of 1.5 equiv. of $K_2S_2O_8$, after 6 hours of reaction, a new spot above the starting compound **1a** was noticed in the TLC which was isolated in 49% yield and confirmed as the product **3aa** by ^1H and ^{13}C NMR spectral analysis as well as by comparing with the known spectral data (Table 1, entry 3). To improve the yield of the reaction, the ratio of $K_2S_2O_8$ and phenylhydrazine were increased; and accordingly, two sets of the same reaction were performed by using 1.5 equiv. of phenylhydrazine in the presence of 2.0 and 3.0 equiv. of $K_2S_2O_8$. As expected, both the reactions smoothly underwent affording the product in 57% and 61% yield (Table 1, entry 4 & 5). Again, use 2.0 equiv. of **2a** with 3.0 equiv. of $K_2S_2O_8$ did not significantly enhance the yield of the reaction, and we obtained the product in 62% yield (Table 1, entry 6). Other solvents like DCE, 1 : 1 mixture of DCE: water, THF, and acetone were also employed, but none of them were successful (Table 1, entry 7, 8, 9, 10). Therefore, we selected acetonitrile as the solvent of choice. Surprisingly, when we warmed the reaction up to 50 °C, a significant enhancement of the yield was perceived and an 81% yield of the product was obtained (Table 1, entry 11). In a further improvement of the yield of **3aa**, an additive like K_2CO_3 was also used, but we did not notice any increment (Table 1, entry 13). Instead of $K_2S_2O_8$ we also used $(NH_4)_2S_2O_8$ as an oxidant and performed the same reaction in two different solvent systems *viz.* acetonitrile and 1 : 1 mixture of DMSO and water, but both experiments failed to give a better yield of **3aa** (Table 1, entry 14 & 15). Oxidants like $Mn(OAc)_3 \cdot 2H_2O$ and $PhI(OCOCF_3)_2$ have also been screened for the same reaction under the optimized reaction conditions, however, they only produced a trace amount of **3aa** (Table 1, entry 16 & 17). Thus, the optimized reaction conditions involve the simple stirring of quinoxalin-2(1H)-one (**1a**, 1.0 equiv.) with phenylhydrazine (**2a**, 1.5 equiv.) in the presence of $K_2S_2O_8$ (3.0 equiv.) in acetonitrile at 50 °C for 6 h under open-air atmosphere (Table 1, entry 11).

With optimized conditions in hand, we first examined the scope and general applicability of different N-substituted quinoxalin-2(1H)-one with the radical counterpart phenylhydrazine (**2a**). Different N-substituted quinoxalin-2(1H)-ones such as N-ethyl (**1b**), N-n-butyl (**1c**), N-benzyl (**1d**), N-allyl (**1e**), N-prenyl (**1f**) and N-homoallyl (**1g**) quinoxalin-2(1H)-ones smoothly underwent the reaction producing the respective 3-phenylquinoxalin-2(1H)-ones **3ba**–**3ga** in very good to excellent yields. Other substituents like ethoxycarbonylmethyl and phenacyl groups at the N-1 position of quinoxalin-2(1H)-one were also well tolerated under the optimized reaction conditions and the respective N-substituted quinoxalin-2(1H)-ones (**1i** & **1j**) produced the 3-phenylated products **3ia** & **3ja** in good yields. It was observed that the substituents present at the N-1 atom showed a significant variation of the yield of the product under the reaction conditions. For example, N-substituted quinoxalin-2(1H)-ones bearing N-alkyl groups like methyl, ethyl, benzyl and allyl (**1a**, **1b**, **1d** & **1e**) gave more yield of the respective phenylated products (**3aa**, **3ba**, **3da** & **3ea**) rather than those bearing little

bulky groups namely n-butyl, prenyl, homoallyl, ethoxycarbonylmethyl and phenacyl groups (**1c**, **1f**, **1g** & **1i–j**). Further, we noticed that quinoxalin-2(1H)-ones bearing more bulky groups such as 2'-bromophenacyl (**1k**) and naphthalene-2-acyl (**1l**) at the N-1 position also afforded the respective products **3ka** & **3la** in good yields. It would be worth mentioning that quinoxalin-2(1H)-one having N-propargyl group (**1h**) also took place in the reaction and produced the product **3ha** in 60% yield (Table 2).

After exemplification of our protocol with different N-substituted quinoxalin-2(1H)-one, we explored the scope of N-unsubstitued quinoxalin-2(1H)-one with a variety of phenylhydrazines. We first performed the reaction of quinoxalin-2(1H)-one (**1m**) with phenylhydrazine (**2a**) under the standard

Table 2 Scope of N-substituted quinoxalin-2(1H)-one.^{a,b}

3aa, 81%, 6 h

3ba, 80%, 6 h

3ca, 73%, 9 h

3da, 75%, 6 h

3ea, 78%, 6 h

3fa, 61%, 9 h

3ga, 61%, 6 h

3ha, 60%, 6 h

3ia, 60%, 7 h

3ja, 71%, 9 h

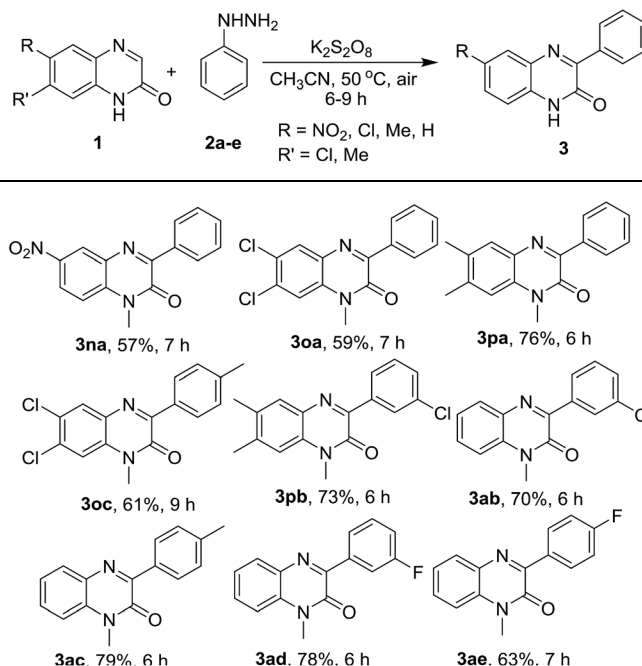**3ka**, 65%, 9 h

3la, 56%, 9 h

^{a} Reaction condition: a mixture of **1** (0.5 mmol) and **2a** (0.75 mmol) in the presence of $K_2S_2O_8$ (1.5 mmol) was stirred in acetonitrile at 50 °C for 6–9 hours under air exposure. ^{b} Isolated yields.

Table 3 Scope of *N*-unsubstituted quinoxalin-2(1*H*)-one with diverse phenylhydrazines.[a,b]

Table 4 Scope of *N*-methyl quinoxalin-2(1*H*)-ones with diverse phenylhydrazines.[a,b]
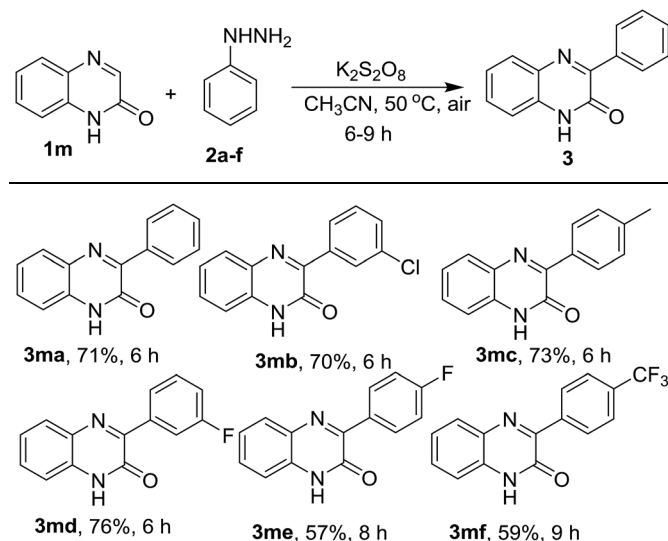
[a] Reaction conditions: a mixture of **1m** (0.5 mmol) and **2a–f** (0.75 mmol) in the presence of K₂S₂O₈ (1.5 mmol) was stirred in acetonitrile at 50 °C for 6–9 hours under air exposure. [b] Isolated yields.

[a] Reaction conditions: a mixture of **1** (0.5 mmol) and **2a–e** (0.75 mmol) in the presence of K₂S₂O₈ (1.5 mmol) was stirred in acetonitrile at 50 °C for 6–9 hours under air exposure. [b] Isolated yields.

reaction conditions. Unexpectedly, the reaction smoothly underwent affording the corresponding product **3ma** in very good yield (71%). To prove the efficacy of the protocol, a variety of substituted phenylhydrazines were also reacted with **1m** under the optimized reaction conditions, and all the reactions underwent smoothly affording the respective products **3mb**–**3mf** in very good yields. In contrary to the earlier reports, this protocol is equally suitable for *N*-unsubstitued quinoxalin-2(1*H*)-one and we obtained 3-arylated products in very good yields. The results were presented in Table 3.

Next, we checked the compatibility of our developed protocol with a variety of quinoxalin-2(1*H*)-one with unsubstituted and substituted phenylhydrazines (Table 4). Different arene ring-substituted 1-methylquinoxalin-2(1*H*)-one for example 6-nitro-1-methylquinoxalin-2(1*H*)-one (**1n**), 6,7-dichloro-1-methyl-quinoxalin-2(1*H*)-one (**1o**), 6,7-dimethyl-1-methylquinoxalin-2(1*H*)-one (**1p**) also underwent the reaction with **2a** producing the respective phenylated products **3na, 3oa** & **3pa** in very good yields. Quinoxalin-2(1*H*)-one bearing electron-donating group (**1p**) gave higher yields than those bearing electron-withdrawing groups (**1n** & **1o**). In further exploration, a variety of phenyl-hydrazines bearing electron-withdrawing and electron-donating groups in the arene ring (**2b, 2c, 2d** & **2e**) were reacted with different 1-methylquinoxalin-2(1*H*)-one **1a, 1o** & **1p**. As expected, all the reactions proceeded well and afforded the respective products **3oc, 3pb, 3ab, 3ac, 3ad** & **3ae** in good to very good yields (Table 4). Arylhydrazines having an electron-donating group at *para*-position (**2c**) and electron-withdrawing groups at *meta*-position (**2b** & **2d**) worked better and produced
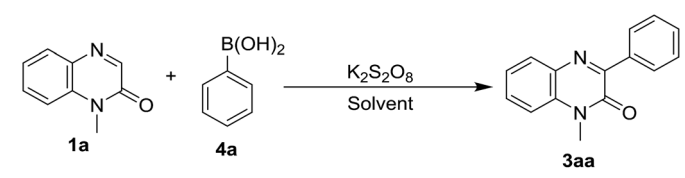
higher yields than that having an electron-withdrawing group at *para*-position (**2e**).

Once the exploration of our protocol with a variety of phe-nylhydrazines was completed, we next examined the efficacy of the arylation reaction of quinoxalin-2(1*H*)-ones with different aryl boronic acid. Accordingly, we performed the reaction of **1a** with phenyl boronic acid (**4a**) in acetonitrile at room tempera-ture under the optimized reaction conditions of Table 1. The reaction did not yield the product **3aa** and both the starting materials **1a** & **4a** remained intact in the reaction mixture (Table 5, entry 1). As is known from the literature that aryl boronic acids form aryl radicals in the presence of excess K₂S₂O₈ at higher temperature, hence we checked the feasibility of the reaction at a little higher temperature.[16] Accordingly, we carried out the same reaction at 80 °C. This time, a very little conversion was observed in TLC, but we were not able to isolate the product **3aa** (Table 5, entry 2). In further optimization, the effect of solvent on the yield of the product was also examined and accordingly, we performed the same reaction in different solvents like dichloroethane and a 1 : 1 mixture of dichloro-ethane and water at 80 °C. Surprisingly, a significant improve-ment of the yield was observed in the 1 : 1 mixture of dichloroethane and water (Table 5, entry 4). To further improve the yield, we also added a base K₂CO₃ in different amounts. To our delight, an addition of 1.0 equiv. of K₂CO₃ to the reaction mixture considerably enhanced the yield (Table 5, entry 6). Given curiosity, we also performed the same reaction in pure

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**Table 5** Reaction optimization studies with phenylboronic acid.[a,b]

Entry	Solvent	Additive	Temp (°C)	Time (h)	Yield[b] (%)
1	CH_3CN	—	30	12	n.r.
2	CH_3CN	—	80	12	—[c]
3	$ClCH_2CH_2Cl$	—	80	6	—[c]
4	$ClCH_2CH_2C–H_2O$	—	80	6	40
5	$ClCH_2CH_2Cl–H_2O$	K_2CO_3 (0.25 mmol)	80	6	57
6	$ClCH_2CH_2Cl–H_2O$	K_2CO_3 (0.50 mmol)	80	6	66
7	$ClCH_2CH_2C–H_2O$	K_2CO_3 (0.75 mmol)	80	6	67
8	H_2O	K_2CO_3 (0.50 mmol)	80	2	80
9[d]	H_2O	K_2CO_3 (0.50 mmol)	80	6	n.r.

[a] Reaction conditions: a mixture of **1a** (0.5 mmol), **4a** (0.75 mmol) and $K_2S_2O_8$ (1.0 mmol) in solvent was stirred as mentioned in the table above. [b] Isolated yield. n.r.: no reaction. [c] Product **3aa** could not be isolated. [d] Reaction was performed without $K_2S_2O_8$.

water keeping the other conditions unchanged and surprisingly, the reaction underwent very smoothly producing 80% yield of **3aa** (Table 5, entry 8). Thus the optimized reaction conditions involve the stirring of the reaction mixture of *N*-methylquinoxalin-2(1*H*)-ones (**1a**, 0.5 mmol) and phenylboronic acid (**4a**, 0.75 mmol) in the presence of 2.0 equiv. of $K_2S_2O_8$ and 1.0 equiv. of K_2CO_3 in water (5 mL) at 80 °C for 2 h (Table 5, entry 8). However, no reaction took place in the absence of $K_2S_2O_8$ under standard reaction conditions and the starting compounds remained unchanged (Table 5, entry 9).

After optimization of the reaction conditions with phenylboronic acid, we engaged different aryl boronic acids bearing both electron-donating and -withdrawing substituents in the arene ring to react with quinoxalin-2(1*H*)-ones (Table 6). Accordingly, a series of experiments were conducted by reacting **1a** with a variety of aryl boronic acids such as 3-fluorophenylboronic (**4d**), 4-methoxylphenylboronic acid (**4g**), 3-methylphenylboronic acid (**4h**), 4-chlorophenylboronic acid (**4i**) and 4-bromophenylboronic acid (**4j**); and all the reaction underwent smoothly producing the respective arylated quinoxalin-2(1*H*)-ones **3aa**, **3ad**, **3ag**, **3ah**, **3ai** & **3aj** in very good to excellent yields. Aryl boronic acid bearing electron-withdrawing group in *meta*-position (**4d**) gave a better yield than those of *para*-position (**4i** & **4j**). Similarly, aryl boronic acid with electron-donating group in *para*-position (**4g**) afforded a better yield than that of *meta*-position (**4h**). *N*-Benzyl and *N*-ethylcarboxymethyl quinoxalin-2(1*H*)-ones (**1d** & **1i**) were also reacted with **4a** under the optimized reaction conditions and both substrates produced the corresponding 3-phenylquinoxalin-2(1*H*)-ones **3da** & **3ia** in very good yields. In the next couple of experiments, we also examined the efficacy of *N*-unsubstituted quinoxalin-2(1*H*)-one **3m** and performed the reaction of **3m** with **4a**, **4h** & **4j**. Surprisingly, we obtained very good yields of the respective products **3ma**, **3mh** & **3mj**.

Table 6 Substrate scope with variation of quinoxalin-2(1*H*)-one and arylboronic acids.[a,b]
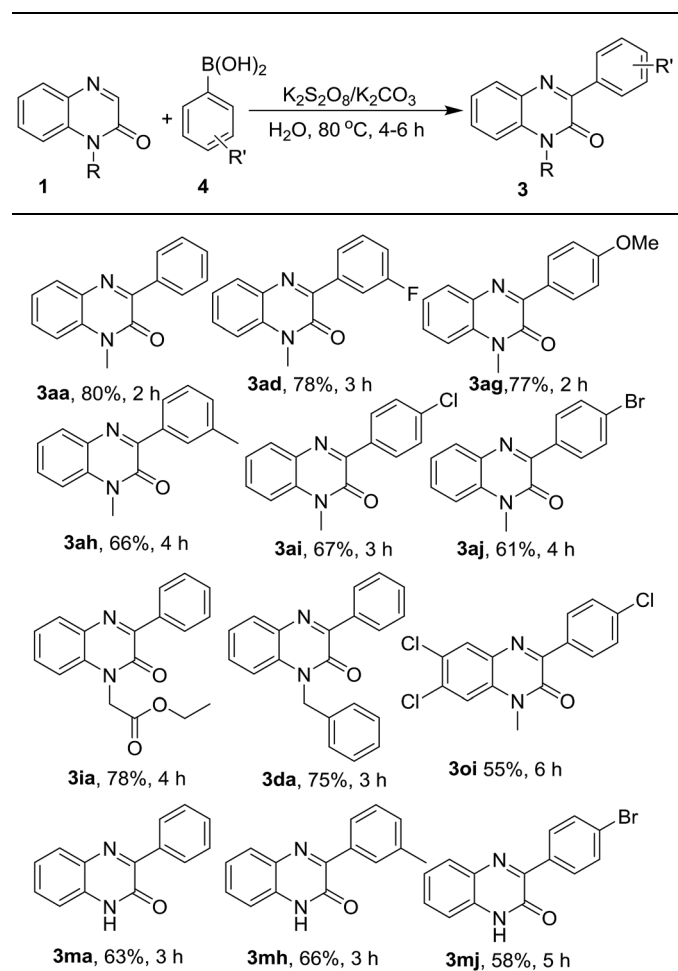
[a] Reaction conditions: a mixture of **1** (0.5 mmol), **4** (0.75 mmol), $K_2S_2O_8$ (1.5 mmol) and K_2CO_3 (0.5 mmol) in H_2O was stirred at 80 °C for 2–6 hours. [b] Isolated yield.
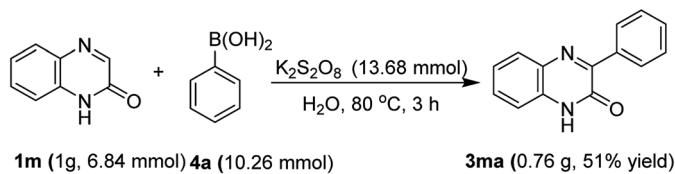
Scheme 2 Gram-scale synthesis of **3ma**.

In another experiment, the robustness of the above protocol was proved by performing a gram-scale reaction with quinoxalin-2(1H)-one (**3m**) and phenylboronic acid (**4a**) under optimal reaction conditions. As expected, the product **3ma** was obtained in 51% yield which is comparable to the yield obtained in the small scale preparation (Scheme 2).

To find out a plausible reaction mechanism, a radical scavenger effect was explored by performing the arylation reaction of quinoxalin-2(1H)-one (**1a**) with phenylhydrazine (**2a**) in the presence of a radical trapping reagent 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) under the standard reaction conditions. As expected, the yield of the product **3aa** sharply reduced from 81% to 19% on the addition of 2.0 equiv. of TEMPO. The same reaction was also repeated at room temperature to trap the radical, but we could not isolate the radical trapping product, however, the yield of **3aa** was drastically affected affording only a 10% yield. Another radical trapping experiment was performed by reacting TEMPO with 2,4-dinitrophenylhydrazine (**2g**) under the optimized reaction conditions, this furnished the TEMPO adduct 1-(2,4-dinitrophenoxy)-2,2,6,6-tetramethylpiperidine (**5**) in 67% yield. The above experiments proved the involvement of radicals in the course of the reaction (Scheme 3).

Based on the above result as well as literature's supports,[17] a plausible mechanism has been proposed in Scheme 4. The reaction commences with the decomposition of persulfate
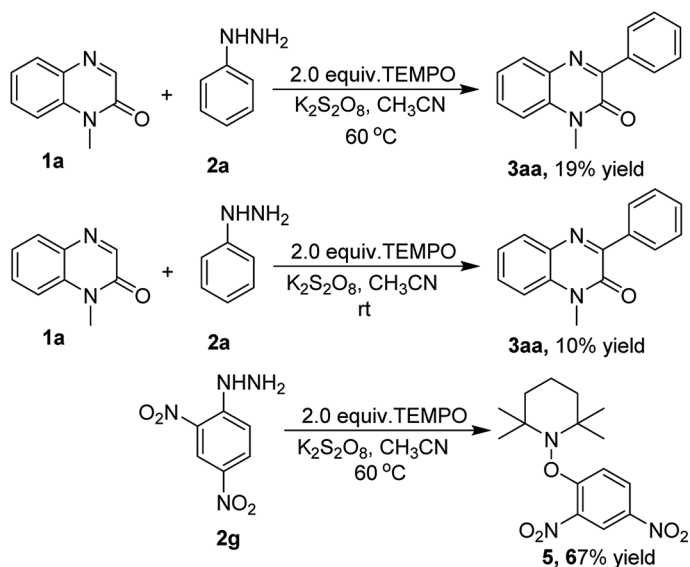

Scheme 3 Radical scavenger effect.
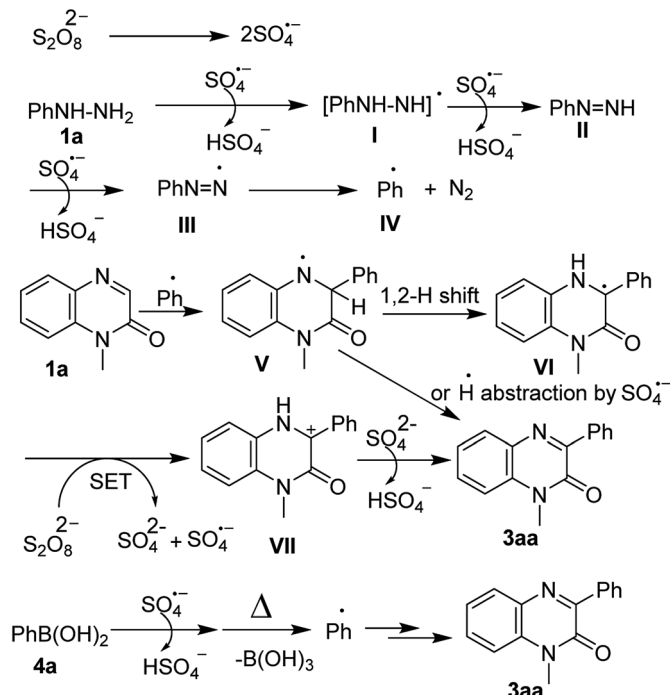
Scheme 4 Plausible reaction mechanism.

$S_2O_8{}^{2-}$ to the sulfate radical anion $SO_4{}^{\bullet-}$ which reacts with phenylhydrazine to form the phenylhydrazine radical **I**. Again, one more sulfate anion radical reacts with **I** to give phenyldiazene **II**, which in turn reacts with another sulfate anion radical and forms **III**. The removal N_2 gas from **III** produces the phenyl radical **IV** which undergoes Minisci-type[13] radical addition reaction on to C-3 position of quinoxalin-2(1H)-one (**1a**), thus affording the nitrogen radical intermediate **V**. The formed intermediate **V** undergoes 1,2-hydrogen shift and produces the carbon radical **VI** which is again oxidized by persulfate via SET to form the carbon cation intermediate **VII**. Finally, the abstraction of β-H from intermediate **VII** by $SO_4{}^{2-}$ produces the desired product **3aa**. In an alternative path, H• radical abstraction by $SO_4{}^{\bullet-}$ from **V** could also furnish **3aa**. Similarly, aryl boronic acid also forms aryl radical which undergoes the radical addition reaction and finally produces the 3-arylquinoxalin-2(1H)-one (Scheme 4).[11f]

In view of the importance of 1,2,3-triazoles compounds and their uses as linkers for various applications in diverse areas of chemistry such as medicinal chemistry, agrochemistry, and material chemistry,[18] we, herein, attempted to synthesize quinoxalinone linked triazole derivative and accordingly, we carried out the reaction between **3ha** and commercially available 1-azidoadamantane (**6**) under standard reaction conditions of Huisgen [2 + 3]-cycloaddition reaction.[19] The reaction smoothly underwent furnishing the product **7** in 82% yield (Scheme 5).

A comparison of our both protocols with the reported methods in terms of yield, reaction temperature and time has been given in Table 7. From the data presented in Table 7, it can be concluded that both methodologies show tremendous potential over earlier reported methods. These two protocols
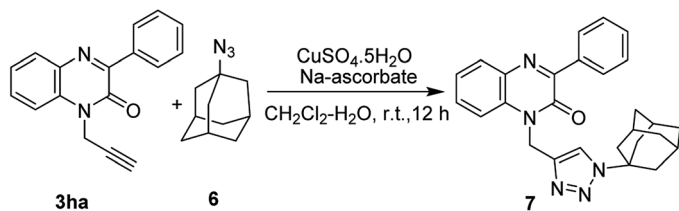
Scheme 5 Synthesis of 3-phenylquinoxalin-2(1H)-one linked triazole.

have not used any hazardous organic or inorganic oxidants like PhIO and Mn(OAc)$_3$, transition metal catalyst *viz.* Pd(OAc)$_2$, extremely corrosive and explosive reagent *t*-BuONO (used in 6 equiv.), strong Brønsted acid such as methane sulfonic acid and very high temperature, *etc.* Again, PhIO and Ar$_2$IBF$_4$ are not commercially available reagents. Use of cheap, readily available and non-toxic oxidant K$_2$S$_2$O$_8$, mild reaction conditions (50–80 °C), shorter reaction hours (2–9 h) and environmentally benign solvents make these two transformations an alternative methodology for the construction of various 3-arylquinoxalin-2(1H)-ones from readily available starting materials.

Conclusions

In conclusion, we have established the reagent system comprising of arylhydrazine and K$_2$S$_2$O$_8$ as a versatile reagent system for the first time to promote the free radical arylation reaction on to C-3 position of quinoxalin-2(1H)-ones. Similarly, K$_2$S$_2$O$_8$/arylboronic acid has also been found to be an efficient reagent system to drive the same arylation reaction. In both the methods K$_2$S$_2$O$_8$ took part in the reaction as a sole oxidant producing aryl radicals from arylhydrazines and aryl boronic acids under metal-, photocatalyst- and light-free conditions in environmentally benign solvents acetonitrile and water respectively. Both the methodologies are operationally very simple and robust, and they do not require any dry reaction conditions and special reaction set up. A wide range of N-substituted quinoxalin-2(1H)-ones bearing both electron-donating and withdrawing

substituents in the arene ring have undergone the arylation reaction with various arylhydrazines and aryl boronic acids producing 3-arylquinoxalin-2(1H)-ones in very good to excellent yields. N-Unsubstituted quinoxalin-2(1H)-ones also work well under the optimized conditions of both protocols. Huisgen [2 + 3]-cycloaddition reaction on 3-arylquinoxalin-2(1H)-one derived alkyne was also accomplished to reveal its synthetic application. Further applications of these two reactions are under investigation in our laboratory.

Experimental section

General experimental details

^{1}H NMR and ^{13}C NMR spectra were recorded in CDCl$_3$, DMSO-d_6 on 500, 400 and (125, 100) MHz NMR spectrometer, respectively, using TMS as internal standard. HRMS (ESI) data were recorded on Mass spectrometer. All the commercially available reagents were used without further purification. All experiments were monitored by thin layer chromatography using aluminium pre-coated silica gel TLC plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Column chromatography was performed on silica gel (100–200 mesh) eluting appropriate ethyl acetate–hexane mixture.

Preparation of starting materials

The starting compounds quinoxalin-2(1H)-one (**1a–1p**) were prepared in accordance with literature methods.[2c,5g]

General procedure for the preparation of compound 3 with arylhydrazines. To a solution of quinoxalin-2(1H)-one (1, 0.5 mmol) and arylhydrazine 2 (0.75 mmol) in acetonitrile (5 mL) was added K$_2$S$_2$O$_8$ (1.5 mmol). Then the reaction mixture was stirred at 50 °C for 6–9 hours under air exposure. After completion of the reaction (as monitored by TLC) water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (1 × 10 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated under rotary evaporator and column

Table 7 Comparison of our protocols *vs.* reported methods for the preparation of **3aa**

Entry	Reagent system	Temp. (°C)	Time (h)	Yield (%)	Ref.
1	ArB(OH)$_2$/Pd(OAc)$_2$/phenanthroline/O$_2$	100	20	85	5g
2	ArB(OH)$_2$/Mn(OAc)$_2$.	120	12	80	5m
3	Ar$_2$IBF$_4$/Cs$_2$CO$_3$	r. t.	72	80	5i
4	ArNHNH$_2$/PhIO	r. t.	9	81	5j
5	ArNH$_2$/t-BuONO/CH$_3$SO$_3$H	r. t.	1.5	81	5k
6	ArNH$_2$/t-BuONO	r. t.	48	89	5l
7	ArN$_2$BF$_4$/Eosin-Y/blue LED	r. t.	3	71	6
8	ArNHNH$_2$/K$_2$S$_2$O$_8$	50	6	81	This report
9	ArB(OH)$_2$/K$_2$S$_2$O$_8$/K$_2$CO$_3$	80	2	80	This report

chromatographed on silica gel (100–200 mesh) using 2 : 8 ethyl acetate–hexane as the eluent to get the pure 3-aryl quinoxalin-2(1*H*)-ones 3. Products **3aa, 3ba, 3da, 3ea, 3ia, 3ma, 3mc, 3me, 3nd, 3oa, 3pa, 3ab, 3ac, 3ad & 3ae** are known in the literature[5,6] and the spectral data of unknown compounds **3ca, 3fa, 3ga, 3ha, 3ja, 3ka, 3la, 3mb, 3md, 3mf, 3oc, 3pb, 5 & 7** have been given here.

1-Butyl-3-phenylquinoxalin-2(1H)-one (3ca). Orange liquid, 73% yield. IR (CHCl₃): 3057.5, 2959.1, 1652.0, 1603.5, 1465.3, 1295.3, 1180.7, 763.5, 692.2, 426.7 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ 8.30 (dd, 2H, *J* = 7.0, 3.5 Hz), 7.95 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.56 (t, 1H, *J* = 8.5 Hz), 7.47–7.46 (m, 3H), 7.36–7.32 (m, 2H), 4.32 (t, 2H, *J* = 8.0 Hz), 1.81 (p, 2H, *J* = 7.5 Hz), 1.55 (sextet, 2H, *J* = 7.5 Hz), 1.02 (t, 3H, *J* = 7.5 Hz). ¹³C NMR (CDCl₃, 125 MHz): δ 154.3, 154.0, 135.9, 133.2, 132.4, 130.5, 130.16, 130.12, 129.4, 127.9, 123.4, 113.4, 42.3, 29.2, 20.2, 13.7. HRMS (ESI): calculated *m/z* for C₁₈H₁₈N₂O [M + H]⁺: 279.1492, found: 279.1493.

1-(3-Methylbut-2-enyl)-3-phenylquinoxalin-2(1H)-one (3fa). Orange solid, mp 97.9–115.2 °C, 61% yield. IR (CHCl₃): 3295.8, 2916.7, 1652.0, 1604.4, 1466.3, 1293.8, 1178.5, 762.3, 692.1, 425.2 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ 8.31–8.29 (m, 2H), 7.95 (dd, 1H, *J* = 7.5, 1.0 Hz), 7.55–7.52 (m, 1H), 7.48–7.45 (m, 3H), 7.36–7.29 (m, 2H), 5.23–5.20 (m, 1H), 4.96 (d, 2H, *J* = 6.5 Hz), 1.92 (s, 3H), 1.74 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 154.2, 154.1, 137.2, 136.0, 133.2, 132.5, 130.4, 130.1, 130.0, 129.4, 127.9, 123.4, 117.8, 113.8, 40.8, 25.5, 18.3.

1-(But-3-enyl)-3-phenylquinoxalin-2(1H)-one (3ga). Yellow liquid, 61% yield. IR (CHCl₃): 3075.0, 2976.6, 1651.9, 1602.8, 1465.3, 1295.7, 919.1, 762.9, 692.1, 428.4 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ 8.31–8.29 (m, 2H), 7.96 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.57–7.54 (m, 1H), 7.49–7.46 (m, 3H), 7.37–7.32 (m, 2H), 5.96–5.87 (m, 1H), 5.17–5.09 (m, 2H), 4.40 (t, 2H, *J* = 8.0 Hz), 2.58 (q, 2H, *J* = 7.0 Hz). ¹³C NMR (CDCl₃, 125 MHz): δ 154.2, 154.0, 135.9, 133.8, 133.2, 132.3, 130.6, 130.2, 130.1, 129.4, 127.9, 123.5, 117.6, 113.4, 41.7, 31.4. HRMS (ESI): calculated *m/z* for C₁₈H₁₆N₂O [M + H]⁺: 277.1335, found: 277.1346.

3-Phenyl-1-(prop-2-ynyl) quinoxalin-2(1H)-one (3ha). Yellow solid, mp 139.9–143.2 °C, 60% yield. IR (CHCl₃): 3282.6, 1651.3, 1603.4, 1464.3, 1173.9, 1029.8, 753.8, 427.0 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 8.31 (dd, 2H, *J* = 6.4, 2.0 Hz), 7.96 (dd, 1H, *J* = 8.4, 1.6 Hz), 7.61–7.57 (m, 1H), 7.48–7.46 (m, 4H), 7.41–7.37 (m, 1H), 5.12 (d, 2H, *J* = 2.8 Hz), 2.30 (t, 1H, *J* = 2.4 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 154.1, 153.8, 135.8, 133.9, 131.9, 130.7, 130.6, 130.5, 129.6, 128.2, 124.2, 114.1, 76.9, 73.2, 31.7. HRMS (ESI): calculated *m/z* for C₁₇H₁₂N₂O [M + H]⁺: 261.1022, found: 261.1032.

1-(2-Oxo-2-phenylethyl)-3-phenylquinoxalin-2(1H)-one (3ja). Brownish yellow solid, mp 198.1–201.3 °C, 71% yield. IR (CHCl₃): 3058.5, 1691.3, 1648.6, 1446.9, 1227.4, 989.1, 754.6, 423.5 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ 8.33–8.30 (m, 2H), 8.10 (dd, 2H, *J* = 8.0, 0.5 Hz), 7.99 (dd, 1H, *J* = 8.0, 1.0 Hz), 7.69 (tt, 1H, *J* = 7.5, 2.0 Hz), 7.57 (t, 2H, *J* = 8.0 Hz), 7.49–7.44 (m, 4H), 7.37–7.33 (m, 1H), 6.99 (dd, 1H, *J* = 8.5, 1.0 Hz), 5.79 (s, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 191.2, 154.4, 153.8, 135.8, 134.6, 134.3, 133.3, 132.8, 130.7, 130.43, 130.4, 129.6, 129.0,

128.2, 128.1, 123.9, 113.4, 48.6. HRMS (ESI): calculated *m/z* for C₂₂H₁₆N₂O₂ [M + H]⁺: 341.1292, found: 341.1285.

1-(2-(2-Bromophenyl)-2-oxoethyl)-3-phenylquinoxalin-2(1H)-one (3ka). Yellow solid, mp 168.6–172.5 °C, 65% yield. IR (CHCl₃): 3059.5, 2949.1, 1960.7, 1711.9, 1648.6, 1440.2, 1217.1, 986.5, 763.6, 430.9 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ 8.31–8.29 (m, 2H), 7.99 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.72–7.67 (m, 2H), 7.56–7.52 (m, 1H), 7.49–7.44 (m, 4H), 7.41–7.37 (m, 2H), 7.23 (dd, 1H, *J* = 8.5, 1.0 Hz), 5.67 (s, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 195.1, 154.2, 153.7, 138.6, 135.6, 133.8, 133.2, 132.68, 132.62, 130.6, 130.4, 130.3, 129.4, 128.0, 127.7, 123.9, 118.9, 113.4, 51.2. HRMS (ESI): calculated *m/z* for C₂₂H₁₅BrN₂O₂ [M + H]⁺: 419.0390, found: 419.0392.

1-(2-(Naphthalen-2-yl)-2-oxoethyl)-3-phenylquinoxalin-2(1H)-one (3la). Brown solid, mp 207.0–219.4 °C, 56% yield. IR (KBr): 3245.5, 2938.3, 2220.9, 1650.5, 1601.5, 1464.1, 1241.0, 1176.6, 750.5, 693.7, 534.2 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ 8.67 (s, 1H), 8.33 (dd, 2H, *J* = 6.0, 2.5 Hz), 8.10 (dd, 1H, *J* = 9.0, 2.0 Hz), 8.03–7.98 (m, 3H), 7.93 (d, 1H, *J* = 8.0 Hz), 7.68–7.59 (m, 2H), 7.49–7.45 (m, 4H), 7.38 (t, 1H, *J* = 7.5 Hz), 7.05 (dd, 1H, *J* = 8.5, 1.0 Hz), 5.94 (s, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 191.1, 154.4, 153.7, 135.9, 135.7, 133.2, 132.7, 132.3, 131.8, 130.6, 130.3, 130.0, 129.6, 129.4, 129.3, 129.0, 128.9, 127.9, 127.8, 127.1, 123.8, 123.3, 123.0, 113.7, 113.4, 48.6. HRMS (ESI): calculated *m/z* for C₂₆H₁₈N₂O₂ [M + H]⁺: 391.1441, found: 391.1450.

3-(3-Chlorophenyl) quinoxalin-2(1H)-one (3mb). Brown solid, mp 233.6–237.7 °C, 70% yield. IR (KBr): 3421.8, 2926.4, 1667.3, 1610.8, 1417.9, 1116.5, 902.2, 754.6, 618.5 cm⁻¹. ¹H NMR (DMSO-*d₆*, 500 MHz) δ 12.67 (s, 1H), 8.38 (s, 1H), 8.30 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.87 (d, 1H, *J* = 7.5 Hz), 7.59–7.52 (m, 3H), 7.36 (d, 2H, *J* = 7.0 Hz). ¹³C NMR (DMSO-*d₆*, 125 MHz): δ 154.8, 152.7, 137.8, 132.9, 132.5, 132.2, 131.1, 130.28, 130.21, 129.2, 129.1, 128.0, 123.8, 115.5. HRMS (ESI): calculated *m/z* for C₁₄H₉ClN₂O [M + H]⁺: 257.0476, found: 257.0486.

3-(3-Fluorophenyl) quinoxalin-2(1H)-one (3md). Brownish yellow solid, mp 225.6–227.5 °C, 76% yield. IR (KBr): 3433.8, 3068.5, 2848.7, 1668.5, 1607.8, 1475.1, 1246.5, 896.9, 783.0, 555.4 cm⁻¹. ¹H NMR (DMSO-*d₆*, 500 MHz) δ 12.66 (s, 1H), 8.20–8.31 (m, 2H), 7.86 (dd, 1H, *J* = 8.0, 2.5 Hz), 7.58–7.52 (m, 2H), 7.38–7.32 (q, 3H, *J* = 6.5 Hz). ¹³C NMR (DMSO-*d₆*, 125 MHz): δ 162.9 (d, *J* = 240.625 Hz), 154.8, 152.7, 138.1 (d, *J* = 8.125 Hz), 132.5, 132.1, 131.1, 130.2 (d, *J* = 8.0 Hz), 129.2, 125.5 (d, *J* = 2.625 Hz), 123.8, 117.4 (d, *J* = 21.0 Hz), 116.1 (d, *J* = 23.375 Hz), 115.5. HRMS (ESI): calculated *m/z* for C₁₄H₉FN₂O [M + H]⁺: 241.0772, found: 241.0775.

3-(4-(Trifluoromethyl) phenyl) quinoxalin-2(1H)-one (3mf). Brown solid, mp 291.7–294.7 °C, 59% yield. IR (KBr): 3434.6, 2850.5, 1663.3, 1610.8, 1330.1, 1114.8, 906.5, 760.1, 618.6 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d₆*) δ 12.70 (s, 1H), 8.51 (d, 2H, *J* = 8.5 Hz), 7.86 (d, 3H, *J* = 8.5 Hz), 7.59 (t, 1H, *J* = 8.0 Hz), 7.36–7.33 (m, 2H). ¹³C NMR (DMSO-*d₆*, 125 MHz): δ 154.8, 153.1, 139.6, 132.6, 132.2, 131.3, 130.2, 129.3, 125.1, 125.0, 123.9, 115.5. HRMS (ESI): calculated *m/z* for C₁₅H₉F₃N₂O [M + H]⁺: 291.0740, found: 291.0750.

6,7-Dichloro-1-methyl-3-p-tolylquinoxalin-2(1H)-one (3oc). Brown solid, mp 180.9–183.4 °C, 61% yield. IR (CHCl₃): 3394.4,

2919.5 1661.6, 1417.7, 1294.6, 94.2, 883.3, 427.0 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.22 (d, 2H, J = 8.5 Hz), 7.95 (s, 1H), 7.36 (s, 1H), 7.27 (d, 2H, J = 7.5 Hz), 3.67 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 154.7, 154.1, 141.4, 133.9, 132.6, 132.5, 132.1, 130.8, 129.6, 128.9, 127.3, 114.9, 29.5, 21.5. HRMS (ESI): calculated m/z for C$_{16}$H$_{12}$Cl$_2$N$_2$O [M + H]$^+$: 319.0399, found: 319.0407.

3-(3-Chlorophenyl)-1,6,7-trimethylquinoxalin-2(1H)-one (**3pb**). Yellow solid, mp 172.0–173.8 °C, 73% yield. IR (CHCl$_3$): 3366.3, 2919.5 1637.7, 1419.4, 1298.8, 1011.1, 677.0, 431.0 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.34 (t, 1H, J = 2.0 Hz), 8.26 (dt, 1H, J = 7.5, 1.5 Hz), 7.67 (s, 1H), 7.43–7.37 (m, 2H), 7.08 (s, 1H), 3.72 (s, 3H), 2.42 (s, 3H), 2.35(s, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 154.5, 151.0, 140.9, 137.9, 134.0, 132.9, 131.47, 131.40, 130.5, 129.9, 129.4, 129.2, 127.6, 114.1, 29.2, 20.7, 19.2. HRMS (ESI): calculated m/z for C$_{17}$H$_{15}$ClN$_2$O [M + H]$^+$: 299.0946, found: 299.0958.

1-(2,4-Dinitrophenoxy)-2,2,6,6-tetramethylpiperidine (**5**). Yellow liquid, 67% yield. IR (CHCl$_3$): 3115.7, 2977.2, 2938.4, 1602.1, 1533.0 (N–O stretch), 1470.2, 1365.5(N–O stretch), 1271.3, 426.9 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.06 (dd, 1H, J = 2.5, 2.0 Hz), 8.36 (dd, 1H, J = 9.5, 3.0 Hz), 8.09 (d, 1H, J = 9.5 Hz), 1.68–1.65 (m, 6H), 1.31 (s, 6H), 1.02 (s, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 161.4, 139.6, 135.1, 128.6, 121.1, 118.3, 61.7, 39.4, 31.8, 20.7, 16.5.

General procedure for the preparation of compound 3 with arylboronic acid. To a solution of quinoxalin-2(1H)-one **1**, (0.5 mmol) and arylboronic acid **4** (0.75 mmol) in water (3 mL) in a reaction vial was added K$_2$S$_2$O$_8$ (1.0 mmol) and K$_2$CO$_3$ (0.5 mmol). Then the reaction vial was screwed and stirred at 80 °C for 2–6 hours. After completion of the reaction (as monitored by TLC) water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (1 × 10 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated under rotary evaporator and column chromatographed on silica gel (100–200 mesh) using 2 : 8 ethyl acetate–hexane as the eluent to get the pure 3-aryl quinoxalin-2(1H)-ones **3**. Products **3aa**, **3ad**, **3ag**, **3ah**, **3ai**, **3aj**, **3ia**, **3ja**, **3oi**, **3ma**, **3mh** & **3mj** are known in the literature.[5]

Procedure for the preparation of the compound 7. Compound **3ha** (0.138 mmol) and 1-azidoadamantane (**6**, 0.138 mmol) were taken in CH$_2$Cl$_2$ and H$_2$O (2 mL, 1 : 1) system in a 25 mL round-bottomed flask and stirred for 5 min. CuSO$_4$·5H$_2$O (0.150 mmol) and sodium ascorbate (2.8 mmol) were added and the reaction mixture was stirred at r.t. for 12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude mixture was partitioned between H$_2$O (15 mL) and CH$_2$Cl$_2$ (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over anhydrous sodium sulphate and concentrated under rotary evaporator and column chromatographed on silica gel (100–200 mesh) using 2 : 8 ethyl acetate–hexane as the eluent to get the pure compound **7**. Yellow liquid, 82% yield. IR (CHCl$_3$): 3400.8, 2911.7, 1651.8, 1604.2, 1444.4, 1101.1, 911.3, 733.2, 462.8 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.31 (dd, 2H, J = 7.0, 3.5 Hz), 8.01 (dd, 1H, J = 8.5, 1.0 Hz), 7.92

(dd, 1H, J = 8.0, 1.5 Hz), 7.75 (s, 1H), 7.60–7.56 (m, 1H), 7.49–7.48 (m, 3H), 7.36–7.33 (m, 1H), 5.58 (s, 2H), 2.20–2.16 (m, 9H), 1.76–1.70 (m, 6H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 154.4, 153.8, 141.3, 135.8, 133.1, 132.4, 130.5, 130.2, 130.1, 129.3, 128.0, 123.8, 120.2, 114.8, 59.7, 42.7, 38.3, 35.7, 29.2. HRMS (ESI): calculated m/z for C$_{27}$H$_{27}$N$_2$O [M + H]$^+$: 438.2288, found: 438.2293.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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