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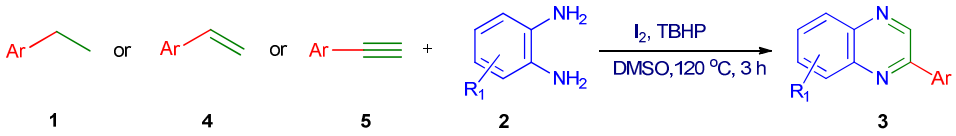
View Article Online
DOI: 10.1039/C4RA08589B

I_2 Catalyzed Tandem Protocol for Synthesis of Quinoxalines *via* sp^3, sp^2 and sp C-H Functionalization

An efficient metal-free tandem protocol for the synthesis of quinoxalines *via* sp^3, sp^2 and sp C-H functionalization has been developed.



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I_2 Catalyzed Tandem Protocol for Synthesis of Quinoxalines *via* sp^3, sp^2 and sp C-H Functionalization

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Abstract:

One-pot, atom-economic synthesis of quinoxalines has been achieved through generation of arylglyoxal from easily available ethylarenes, ethylenearenes and ethynearenes, and subsequent condensation with *o*-phenylenediamines. Use of catalytic I_2 with TBHP as an oxidant in DMSO is the system of choice for this domino reaction involving C-H functionalization/oxidative cyclization. This metal-free, mechanistically distinct and functional group tolerant tandem approach could be a powerful complement to traditional approaches for the synthesis of quinoxalines.

Keywords: C-H Functionalization, Metal-free synthesis, Quinoxalines, Iodine, *tert*-Butyl hydroperoxide (TBHP), Kornblum oxidation

Introduction

Quinoxaline is a widely explored nitrogen heterocyclic compound owing to it's presence in numerous compounds and has promising applications in dyes,[1,2] organic semiconductors,[3] electroluminescent materials[4] and anionic receptors.[5] Furthermore, quinoxaline derivatives exhibit a broad range of biological activities such as antiviral, antibacterial, anti-inflammatory, anti-protozoal and kinase inhibitors.[6] In addition, these are used as anticancer, antifungal, insecticidal and anthelmintic agents.[7] Notably, quinoxaline is a key constituent of antibiotics such as echinomycin, levomycin and actinomycin.[8] Quinoxaline derivatives also have promising applications in cavitands, chemically controllable switches and DNA cleaving agents.[9]

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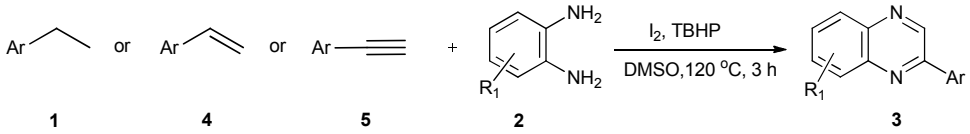
In view of the wide range of applications, various methods have been developed for the synthesis of quinoxaline derivatives. A highly explored method amongst these is the acid catalyzed condensation of 1,2-diaminobenzenes with 1,2-dicarbonyl compounds.[10] Quinoxaline derivatives are also prepared by reaction of 1,2-diaminobenzenes with α-hydroxy ketones,[11] epoxides,[12] α-haloketones,[13] α-tosyloxy ketones,[14] α-ketocarboxylic acids,[15] oxalic acid,[16] diazenyl butenes,[17] hydroxy acetylenes,[18] alkynes,[19] vicinal diols[20] or diazoketones.[21] A wide range of catalysts, e.g. molecular sieves,[22] $HClO_4/SiO_2$,[23] β-cyclodextrin,[24] Me_3SiCl,[25] DABCO,[26] transition metals (Mn, Ru, Pd and Cu),[27] $Ga(ClO_4)_3$,[28] ion-exchanged molybdophosphoric acid,[29] KF-alumina[30] and microwave irradiation[31] have been employed, for these reactions.

However, many of these catalysts cannot be widely used owing to environmental and /or economical issues, including requirement of heavy metal catalysts, use of stoichiometric amounts, an excess amount of base, high temperature, incompatibility with functionalized substrates, long reaction time, low yield of products and multi step synthesis.

Therefore, development of economically viable procedures for the synthesis of quinoxaline derivatives from easily available multiform starting materials still continues to be a challenging task. In this context, summarizing the practical advantages of domino strategy of synthesis and continuation in our efforts towards development of facile, efficient, environment and eco-friendly synthetic protocols,[32] herein we describe the synthesis of quinoxalines using I_2/TBHP and DMSO in one step from ethylarenes (**1**), ethylenearenes (**4**) and ethynearenes (**5**) (Scheme 1). The method encompasses three primary processes- C-H functionalization, oxidation and condensation.



1 **4** **5** **2** **3**

Scheme 1. Tandem metal-free synthesis of quinoxalines from ethylarenes or ethylenearenes or ethynearenes and *o*-phenylenediamines

We first studied the action of I_2/TBHP and DMSO on ethylbenzene (**1a**) for C-H functionalization and generation of phenylglyoxal, followed by *in situ* condensation with *o*-phenylenediamine.

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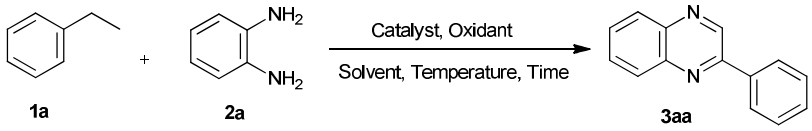
Table 1. Optimization of reaction conditions for tandem metal-free synthesis of quinoxaline from ethylbenzene and *o*-phenylenediamine[a]



1a 2a 3aa

Entry	Catalyst (equiv.)	Oxidant (equiv.)	Solvent	Time (h)	Temp. (°C)	Yield (%)[g]
1	I_2 (1.0)	TBHP (2)	DMSO	3.0	80	28
2	I_2 (1.0)	TBHP (3)	DMSO	3.0	80	39
3	I_2 (1.0)	TBHP (3)	DMSO	3.0	100	54
4	I_2 (1.0)	TBHP (3)	DMSO	3.0	120	67
5	I_2 (0.5)	TBHP (3)	DMSO	3.0	120	75
6	I_2 (0.3)	TBHP (3)	DMSO	3.0	120	84
7	I_2 (0.2)	TBHP (3)	DMSO	3.0	120	90
8	I_2 (0.1)	TBHP (3)	DMSO	3.0	120	85
9	I_2 (0.2)	TBHP (3)	-	0.5	120	63
10	I_2 (0.2)	TBHP (3)	-	1.0	120	95
11	I_2 (0.2)	TBHP (3)	-	1.5	120	76
12	I_2 (0.2)	TBHP (3)	-	2.0	120	57
13	I_2 (0.2)	TBHP (3)	DMSO	1.0	120	71
14	I_2 (0.2)	TBHP (3)	DMSO	2.0	120	90
15	I_2 (0.2)	TBHP (3)	DMSO	3.0	120	82
16	I_2 (0.2)	TBHP (3)	DMSO	0.5	120	45
17	I_2 (0.2)	TBHP (3)	DMSO	1.0	120	59
18	I_2 (0.2)	TBHP (3)	DMSO	1.5	120	73
19	I_2 (0.2)	TBHP (3)	DMSO	2.0	120	90
20	I_2 (0.2)	TBHP (3)	DMSO	3.0	120	84
21	I_2 (0.2)	TBHP (3)	DMSO	3.0	120	Trace
22	I_2 (0.2)	DTBP (3)	DMSO	3.0	120	0
23	I_2 (0.2)	IBX (3)	DMSO	3.0	120	41
24	I_2 (0.2)	DMP (3)	DMSO	3.0	120	Trace
25	I_2 (0.2)	DIB (3)	DMSO	3.0	120	Trace
26	I_2 (0.2)	HTIB (3)	DMSO	3.0	120	Trace
27	I_2 (0.2)	DDQ (3)	DMSO	3.0	120	Trace
28	I_2 (0.2)	$K_2S_2O_8$ (3)	DMSO	3.0	120	Trace
29	I_2 (0.2)	O_2 (1 atm)	DMSO	3.0	120	0
30	-	TBHP (3)	DMSO	3.0	120	-
31	NIS (0.2)	TBHP (3)	DMSO	3.0	120	26
32	KI (0.2)	TBHP (3)	DMSO	3.0	120	19
33	CuI (0.2)	TBHP (3)	DMSO	3.0	120	23
34	TBAI (0.2)	TBHP (3)	DMSO	3.0	120	35
35	I_2 (0.2)	TBHP (3)	DMF	3.0	120	-
36	I_2 (0.2)	TBHP (3)	1,4-dioxane	3.0	120	-
37	I_2 (0.2)	TBHP (3)	THF	3.0	120	-
38	I_2 (0.2)	TBHP (3)	Toluene	3.0	120	-

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[a]Reaction conditions: **1a** (1.0 mmol), catalyst and oxidant was heated for 1.0 h in sealed tube, **2a** (1.0 mmol) in solvent (3.0 mL) was added and heating continued for 2.0 h. [b]Reaction conditions (entries 9-12): **1a** (1.0 mmol), I_2 (0.2 mmol) and TBHP (3.0 mmol) was heated for 0.5-2.0 h in sealed tube. [c]Reaction conditions (entries 13-15): **1a** (1.0 mmol), I_2 (0.2 mmol), TBHP (3.0 mmol) and DMSO (3.0 mL) was heated for 1.0-3.0 h in sealed tube. [d]Reaction conditions (entries 16-20): **1a** (1.0 mmol), I_2 (0.2 mmol) and TBHP (3.0 mmol) was heated for 1.0 h in sealed tube, **2a** (1.0 mmol) in DMSO (3.0 mL) was added and heating continued for 0.5-3.0 h. [e]Reaction condition (entry 21): **1a** (1.0 mmol), **2a** (1.0 mmol), I_2 (0.2 mmol) and TBHP (3.0 mmol) was heated in DMSO (3.0 mL) in sealed tube at 120 °C for 3.0 h. [f]Reaction condition (entry 30): **1a** (1.0 mmol) and TBHP (3.0 mmol) was heated in sealed tube at 120 °C for 1.0 h, **2a** (1.0 mmol) in DMSO (3.0 mL) was added and heating continued for 2.0 h. [g]Isolated yield. DTBP = Di-*tert*-butyl peroxide, IBX = *o*-Iodoxy-benzoic acid, TBHP = *tert*-Butyl hydroperoxide, DMP = 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, DIB = (Diacetoxyiodo)benzene, HTIB = [Hydro(tosyloxy)iodo]benzene, DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, $K_2S_2O_8$= Potassium persulfate

Initially, the reaction of ethylbenzene (**1a**) with 1.0 equiv. I_2 and 2.0 equiv. TBHP as an oxidant was carried out at 80 ^oC temperature for 1.0 h. *o*-Phenylenediamine (1.0 equiv.) in DMSO (3.0 mL) was added and heating was continued for 2.0 h to afford quinoxaline (**3aa**) in 28% yield (Table 1, entry 1). Use of 3.0 equiv. of TBHP resulted in slightly higher yield (39%, Table 1, entry 2). The reaction was then carried out at 100 and 120 ^oC, whereupon yields of 54 and 67% were obtained (Table 1, entries 3 and 4), thereby indicating a significant role played by temperature in this reaction. We next varied the iodine concentration from 0.5 equiv. to 0.1 equiv. in DMSO (3.0 mL) as a solvent with 3.0 equiv. of TBHP at 120 ^oC. The reaction with 0.5 equiv. of I_2 led to 75% yield of product (Table 1, entry 5), whereas a higher yield of 84% was achieved with 0.3 equiv. of I_2 (Table 1, entry 6). Use of 0.2 equiv. of I_2 and 3.0 equiv. of TBHP in DMSO (3.0 mL) at 120 ^oC was found to be optimal resulting in 90% yield (Table 1, entry 7). A slight drop in the yield (85%) was observed when I_2 concentration was reduced to 0.1 equiv. (Table 1, entry 8). In order to optimize the time required for formation of α-iodo acetophenone (**B**) from ethylbenzene (**1a**), few experiments (Table 1, entries 9-12) were carried out with varying time by using 0.2 equiv. of I_2 and 3.0 equiv. of TBHP. The reaction time of 1.0 h was

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found to be the optimal time for this conversion. Similarly, few reactions (Table 1, entries 13-15) were performed to optimize the time needed for conversion of ethylbenzene (**1a**) to phenylglyoxal (**C**) with DMSO as a solvent. It was observed that reaction took 2.0 h for completion and formed phenylglyoxal (**C**) in 90% yield. Beside this we conducted some experiments (Table 1, entry 16-20) for optimization of the time necessary to form quinoxaline (**3aa**) after addition of *o*-phenylenediamine (**2a**) in DMSO. It was noticed that the reaction was completed in 2.0 h to afford quinoxaline (**3aa**) in 90% yield. We also tried simultaneous addition of all reaction components but it afforded the product only in trace amount thus proving the importance of sequential addition of the reactants (Table 1, entry 21). The other common oxidants namely DTBP, IBX, DMP, DIB, HTIB, DDQ, $K_2S_2O_8$, molecular O_2 were also screened, but TBHP was found to be the most effective oxidant for this transformation (Table 1, entries 22-29). The reaction in absence of I_2 was also attempted but it failed to give the desired product thereby highlighting the key role of I_2 as a catalyst in this reaction (Table 1, entry 30). We screened catalysts such as NIS, KI, CuI and TBAI but all of these attempts resulted in low yields (19 to 35%, Table 1, entries 31-34). I_2, therefore, is the most efficient catalyst for this reaction. No product was obtained when we conducted the reaction by using solvents such as DMF, 1,4-dioxane, THF, and toluene. These results confirm the dual role of DMSO in this reaction, as a solvent and a co-oxidant (Table 1, entries 35-38).

With the optimized reaction conditions in hand, we explored the scope and limitations of this transformation by using substituted ethylarenes. To our delight, the reaction was found to be robust and unaffected by the nature as well as the position of the substituent present in the aromatic ring. Ethylarenes bearing halogen substituents such as -F, -Cl and -Br at the ortho and para positions reacted smoothly with *o*-phenylenediamine to offer the corresponding quinoxalines **3ba**, **3ca** and **3da** in yields ranging from 85-92%. The reaction of ethylarenes with electron donating substituents such as -Me, -OMe proceeded easily with *o*-phenylenediamine furnishing the corresponding quinoxalines **3ea**, **3fa** and **3ga** in good yields (82-86%). The reaction of ethylarenes bearing an electron withdrawing substituent such as $-NO_2$ with *o*-phenylenediamine resulted in formation of quinoxaline **3ha** in excellent yield (91%).

Table 2. I_2/TBHP catalyzed synthesis of quinoxalines from ethylarenes and *o*-phenylenediamines[a,b]

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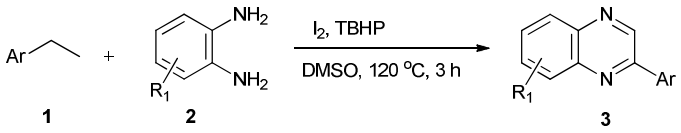

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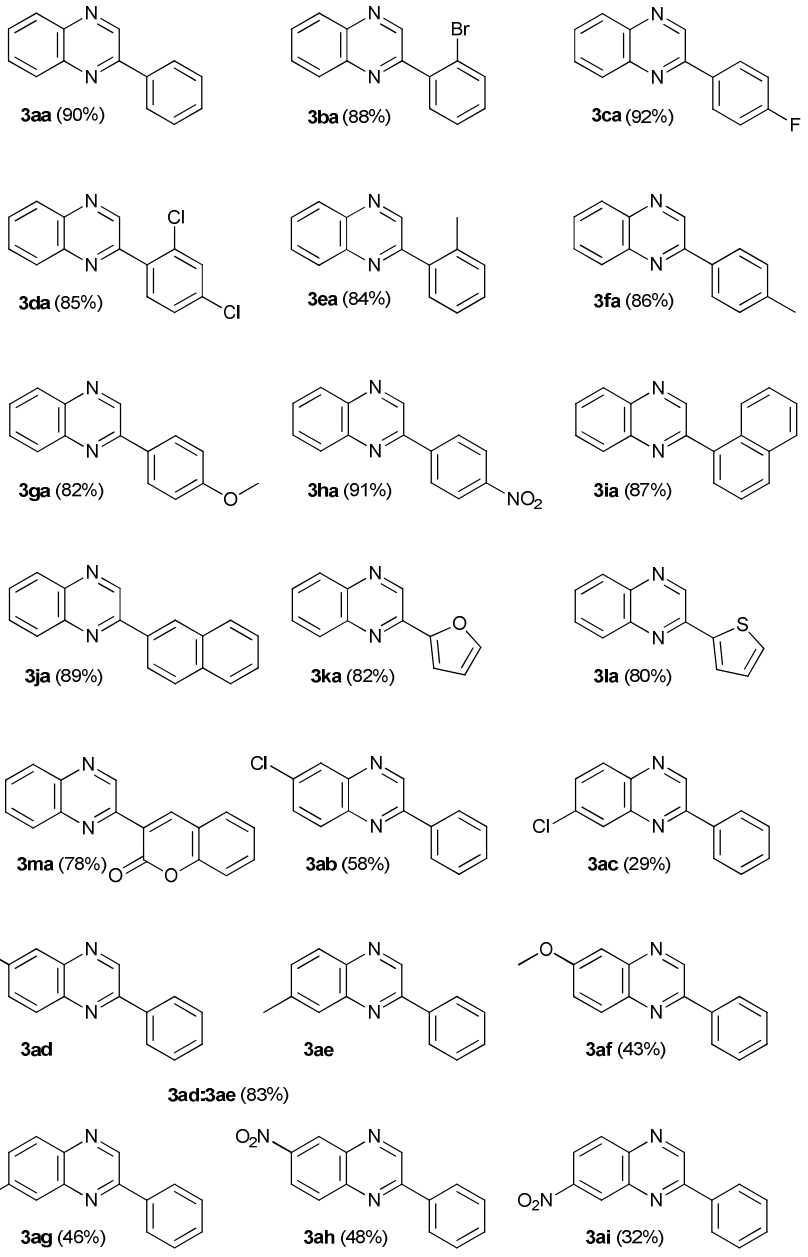

[a]Reaction conditions: **1** (1.0 mmol), I_2 (0.2 mmol) and TBHP (3.0 mmol) was heated for 1.0 h at 120 °C in sealed tube, **2** (1.0 mmol) in DMSO (3.0 mL) was added and heating continued for 2.0 h. [b]Isolated yield.

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Similarly, 1-ethylnaphthalene and 2-ethylnaphthalene also offered the corresponding quinoxalines **3ia** and **3ja** in 87 and 89% respectively. Notably, heteroarylethanes such as 2-ethylfuran, 2-ethylthiophene and 3-ethyl-2*H*-benzopyran-2-one afforded the corresponding quinoxalines **3ka**, **3la** and **3ma** in quantitative yields. To investigate the effect of substituent on reactivity and regioselectivity, different *o*-phenylenediamines such as 4-chloro, 4-methyl, 4-methoxy and 4-nitro-*o*-phenylenediamine were reacted with ethylbenzene (**1a**). The reaction of 4-chloro-*o*-phenylenediamine with ethylbenzene (**1a**) formed regioisomers **3ab** and **3ac** in 2:1 ratio with a combined yield of 87% while 4-methyl-*o*-phenylenediamine produced inseperable mixture of regioisomers **3ad** and **3ae** in 1:4 ratio which is confirmed by ^{1}H NMR with 83% overall yield. 4-Methoxy-*o*-phenylenediamine reacted smoothly with ethylbenzene (**1a**) and offered regioisomers **3af** and **3ag** in 1:1 ratio with a total yield of 89%. 4-Nitro-*o*-phenylenediamine on reaction with ethylbenzene (**1a**) resulted in formation of regioisomers **3ah** and **3ai** in 3:2 ratio with 80% overall yield.

Having obtained encouraging results with ethylarenes, we turned our attention to C-H functionalization of ethylenearenes followed by oxidative cyclization with *o*-phenylenediamines. When we reacted styrene (**4a**) with *o*-phenylenediamine (**2a**) under optimized conditions, C-H functionalization followed by oxidative cyclization occurred smoothly to offer quinoxaline **3aa** in 92% yield. Ethylenearenes bearing halogen substituents such as -Cl and -Br at the meta and para positions also reacted smoothly with *o*-phenylenediamine to form the corresponding quinoxalines **3na** and **3oa** in excellent yields (90 and 93% respectively). The reaction of ethylenearenes with electron donating substituents -Me, -OMe proceeded to furnish the respective quinoxalines **3fa** and **3pa** in good yields (88 and 78% respectively). The reaction of ethylenearenes bearing an electron withdrawing substituent (-NO_2) with *o*-phenylenediamine afforded quinoxaline **3ha** in excellent yield (92%).

Likewise, 1-ethylenenaphthalene also produced the corresponding quinoxaline **3ia** with 89% yield whereas, the reaction of heteroarylethylenes such as 2-vinylfuran and 3-vinyl-2*H*-benzopyran-2-one formed quinoxalines **3ka** and **3ma** in 84 and 80% yield respectively. Next, we studied the effect of substituted *o*-phenylenediamines on reactivity and regioselectivity. 4-Chloro-*o*-phenylenediamine reacted easily with styrene (**4a)** to form regioisomers **3ab** and **3ac** in 2:1 ratio with an overall yield of 91%. The reaction of 4-methoxy-*o*-phenylenediamine with styrene (**4a**) produced regioisomers **3af** and **3ag** in 1:1 ratio with a combined yield of 93%. 4-

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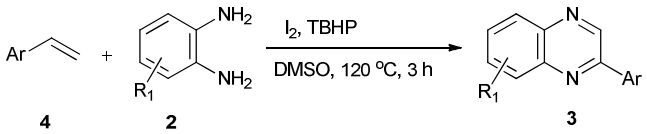
Nitro-*o*-phenylenediamine reacted smoothly with styrene (**1a**) to offer regioisomers **3ah** and **3ai** in 3:2 ratio with a total yield of 84%.

Table 3. I_2/TBHP catalyzed synthesis of quinoxalines from ethylenearenes and *o*-phenylenediamines[a,b]



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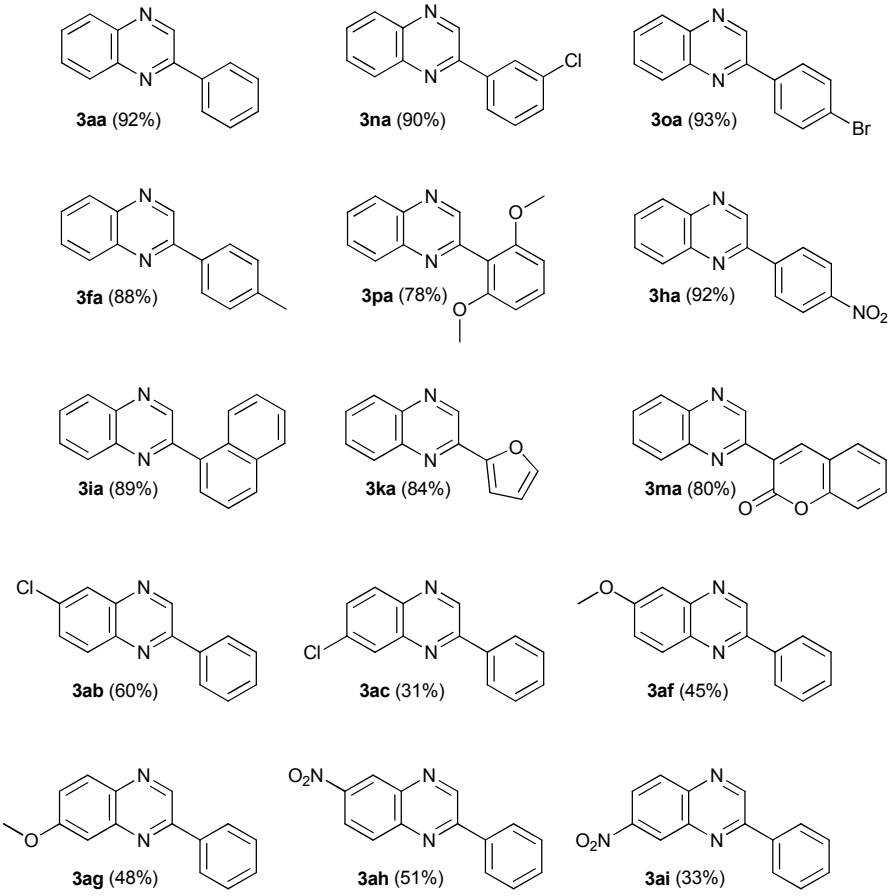

[a]Reaction conditions: **4** (1.0 mmol), I_2 (0.2 mmol) and TBHP (3.0 mmol) was heated for 1.0 h at 120 °C in sealed tube, **2** (1.0 mmol) in DMSO (3.0 mL) was added and heating continued for 2.0 h. [b]Isolated yield.

With results of ethylarenes and ethylenearenes in hand, we conducted the reaction of phenylacetylene (**5a**) with *o*-phenylenediamine (**2a**) under optimized reaction conditions and obtained quinoxaline **3aa** in excellent yield (89%). We also found that substituted (halogens, Me,

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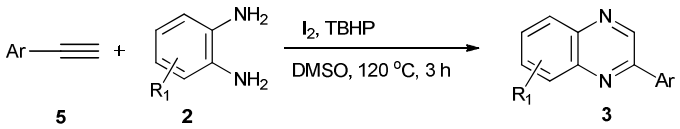
OMe and NO_2) ethynearenes reacted smoothly and afforded the corresponding quinoxalines in good to excellent yields (81-90%). 2-Ethynylnaphthalene gave quinoxaline **3ja** in 85% yield. To study the reaction scope of *o*-phenylenediamines, we carried out the reaction of 4-chloro-*o*-phenylenediamine with phenylacetylene (**5a)**. Notably, a mixture of regioisomers **3ab** and **3ac** in 2:1 ratio was obtained with an overall yield of 79%. The reaction of 4-methyl-*o*-phenylenediamine with phenylacetylene (**5a**) showed higher regioselectivity and formed regioisomers **3ad** and **3ae** in 1:4 ratio with a total yield of 85%. 4-Methoxy-*o*-phenylenediamine reacted with phenylacetylene (**5a**) to produce regioisomers **3af** and **3ag** in 1:1 ratio with a combined yield of 91%. 4-Nitro-*o*-phenylenediamine reacted smoothly with phenylacetylene (**5a**) to afford regioisomers **3ah** and **3ai** in 3:2 ratio with total yield of 81%.

Table 4. I_2/TBHP catalyzed synthesis of quinoxalines from ethynearenes and *o*-phenylenediamines[a,b]



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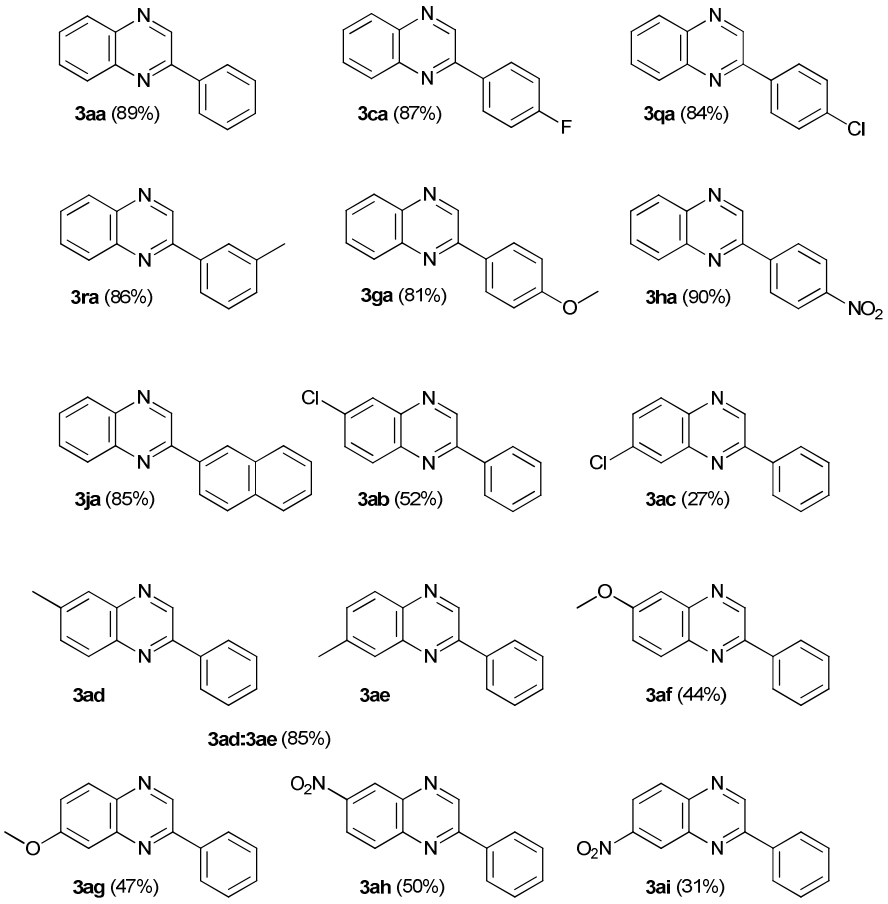

[a]Reaction conditions: **5** (1.0 mmol), I_2 (0.2 mmol) and TBHP (3.0 mmol) was heated for 1.0 h at 120°C in sealed tube, **2** (1.0 mmol) in DMSO (3.0 mL) was added and heating continued for 2.0 h. [b]Isolated yield.

A few controlled experiments (Scheme 2) were performed in order to support our proposed mechanism. To demonstrate the involvement of TBHP in the formation of α-iodoacetophenone (**B**), a key intermediate, ethylbenzene (**1a**) or styrene (**4a**) or phenylacetylene (**5a**) were reacted with I_2 and DMSO at 120 ^oC (Scheme 2a). These reactions failed to produce the α-iodoacetophenone (**B**), proving that TBHP plays a crucial role in the formation of α-iodoacetophenone (**B**) through radical intermediates. When ethylbenzene (**1a**) or styrene (**4a**) or phenylacetylene (**5a**) were treated with I_2/TBHP in absence of DMSO (Scheme 2b), the reaction solely formed α-iodoacetophenone (**B**). Compound **1a** on reaction with I_2/TBHP (Scheme 2c) resulted in successive formation of acetophenone (**A**) and α-iodoacetophenone (**B**), an important intermediate, which is also obtained from compound **4a** and **5a** (Scheme 2d). α-Iodoacetophenone (**B**) was finally converted into phenylglyoxal (**C**) in presence of DMSO. It

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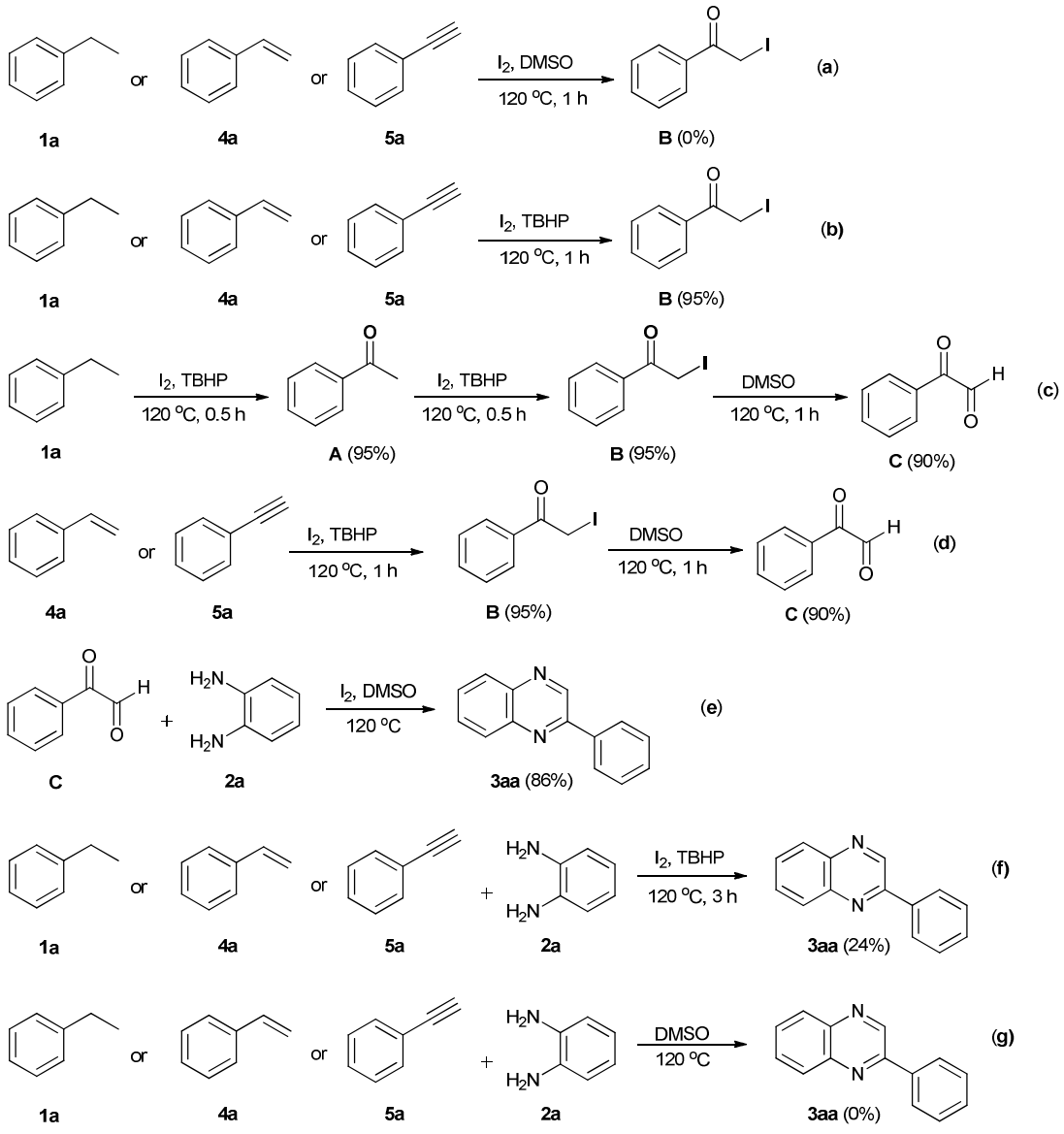
ascertained the requirement of DMSO as a solvent and a co-oxidant. Phenylglyoxal (**C**) reacted with *o*-phenylenediamine (**2a**) in presence of I_2 and DMSO to form quinoxaline (**3aa**) exclusively (Scheme 2e). The reaction of compound **1a**, **4a** and **5a** with *o*-phenylenediamine (**2a**) in presence of I_2 and TBHP gave quinoxaline **3aa** in low yield (scheme 2f). Ethylbenzene (**1a**), styrene (**4a**) and phenylacetylene (**5a**) did not react with *o*-phenylenediamine (**2a**) in DMSO thereby clearly highlighting the role of I_2/TBHP in C-H functionalization (Scheme 2g).



Scheme 2. Control experiment

A plausible mechanism for this transformation is presented in Scheme 3. Ethylbenzene (**1a**) is oxidized to acetophenone (**A**) by I_2/TBHP *via* a radical mechanism with 1-phenylethanol as an

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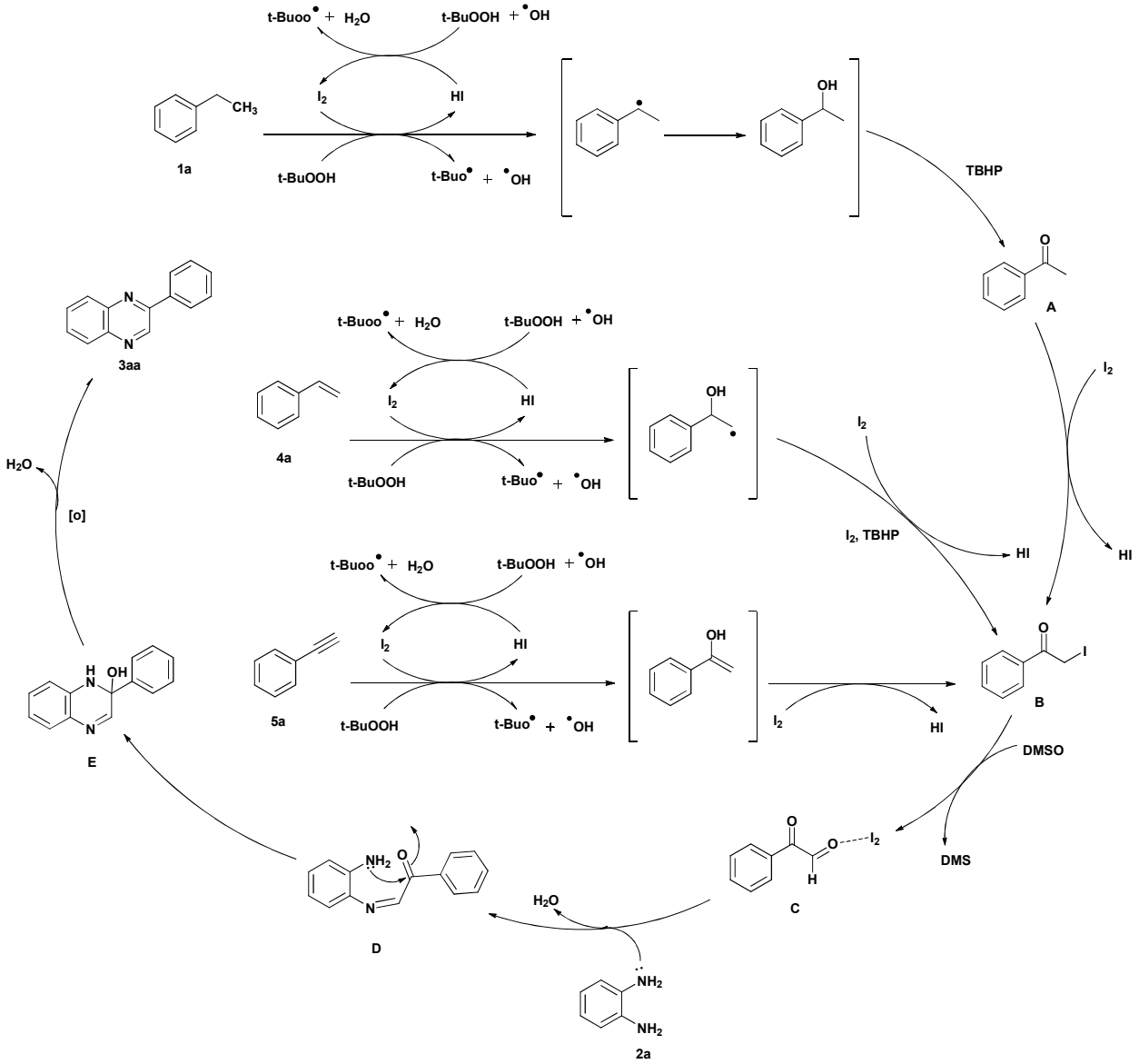
intermediate product. Formation of acetophenone was confirmed by TLC, GC-MS and ^{1}HNMR. Acetophenone (**A**) on iodination is converted into α-iodoacetophenone (**B**). This key intermediate is also produced from styrene (**4a**) and phenylacetylene (**5a**) by oxidation/iodination with I_2/TBHP as depicted in scheme 3. α-Iodoacetophenone (**B**) is further transformed *via* Kornblum oxidation into phenylglyoxal (**C**) which on reaction with *o*-phenylenediamine (**2a**) gives intermediate **D**. Cyclization of **D** followed by oxidation offer quinoxaline (**3aa**).



Scheme 3. Plausible reaction mechanism

Experimental section

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General information

Chemical reagents were obtained from commercial companies. All reactions were performed in a sealed tube and monitored by TLC performed on aluminum plates (0.25 mm, E. Merck) precoated with silica gel Merck 60 F-254. Developed TLC plates were visualized under a short-wavelength UV lamp. Yields refer to spectroscopically (^{1}H, ^{13}C NMR) homogeneous material obtained after column chromatography performed on silica gel (100–200 mesh size) supplied by S. D. Fine Chemicals Limited, India. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution with Brüker 400, Agilent 500 and 600 MHz spectrometers. Coupling constants (J) were measured in Hertz. Chemical shifts (δ) are quoted in ppm, relative to $SiMe_4$ (δ = 0) as an internal standard. The number of protons (n) for a given resonance is indicated by nH. High resolution mass spectra (HRMS) were obtained by using positive electronspray ionization (ESI) by Time of Flight (TOF) method. Melting points were recorded on a standard melting point apparatus from Sunder Industrial Product, Mumbai and uncorrected.

General experimental procedure for synthesis of quinoxalines:

A sealed tube equipped with magnetic stirring bar was charged with ethylarene (**1**) or ethylenearene (**4**) or ethynearene (**5**) (1.0 mmol), I_2 (0.2 mmol) and *tert*-butyl hydroperoxide (TBHP, 3.0 mmol, 70% aq. solution) at room temperature. The resulting mixture was heated to 120 ℃ and maintained at 120 ^{o}C for 1.0 h. After disappearance of the reactant (monitored by TLC), substituted *o*-phenylenediamine **2** (1.0 mmol) in DMSO (3.0 mL) was added and heating continued at 120 ^{o}C for 2.0 h. After completion of the reaction, 20 mL of water was added to the reaction mixture and it was extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with 10% $Na_2S_2O_3$ solution (20 mL) and brine solution (20 mL) successively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on 100:200 mesh silica gel using *n*-hexane:ethyl acetate (8:2) as eluent to obtain the corresponding quinoxaline **3**.

Product characterization data

2-Phenylquinoxaline (3aa). White solid; MP 76-78 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.53 (t, J = 7.8, 7.2 Hz, 1H), 7.58 (t, J = 7.8, 7.2 Hz, 2H), 7.76 (t, J = 7.8, 6.6 Hz, 1H), 7.80 (t, J = 7.2 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 7.2 Hz, 2H), 9.34 (s, 1H);

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^{13}C NMR (150 MHz, $CDCl_3$): δ = 127.53, 129.08, 129.14, 129.54, 129.59, 130.17, 130.29, 136.74, 141.52, 142.28, 143.33, 151.85; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{11}N_2$: 207.0923; found: 207.0925.

2-(2-Bromophenyl)quinoxaline (3ba). White solid; MP 116-118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.38 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.81-7.84 (q, *J* = 3.2 Hz, 2H), 8.17 (d, *J* = 3.2 Hz, 2H), 9.19 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 122.05, 128.10, 129.32, 129.67, 130.24, 130.39, 130.99, 131.95, 133.51, 138.57, 141.41, 142.16, 146.21, 153.69; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}BrN_2$: 285.0028; found: 285.0030.

2-(4-Fluorophenyl)quinoxaline (3ca). White solid; MP 120-122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.22-7.28 (m, 2H), 7.74-7.82 (q, *J* = 9.6, 8.0, 6.8 Hz, 2H), 8.13 (t, *J* = 8.0, 6.8 Hz, 2H), 8.20-8.23 (distorted q, *J* = 6.4, 5.6, 2.0 Hz, 2H), 9.30 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 116.15, 116.37, 129.18, 129.50, 129.58, 129.62, 130.43, 132.99, 133.02, 141.55, 142.25, 142.97, 150.81, 163.05, 165.54; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}FN_2$: 225.0829; found: 225.0833.

2-(2,4-Dichlorophenyl)quinoxaline (3da). White solid; MP 144-146 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.46-7.83 (m, 5H), 8.17 (s, 2H), 9.20 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 128.00, 129.35, 129.66, 130.16, 130.45, 130.52, 132.96, 133.40, 135.11, 136.37, 141.49, 142.33, 145.90, 151.35; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_9Cl_2N_2$: 275.0144; found: 275.0146.

2-(*o*-Tolyl)quinoxaline (3ea). White solid; MP 88-90 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.47 (s, 3H), 7.37 (s, 3H), 7.55 (d, *J* = 6.8 Hz, 1H), 7.80 (distorted t, *J* = 3.6, 3.2 Hz, 2H), 8.16 (d, *J* = 6.8 Hz, 2H), 9.02 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 20.43, 126.42, 129.22, 129.51, 129.63, 129.84, 130.08, 130.35, 131.30, 136.66, 137.20, 141.08, 142.11, 145.98, 155.09; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2$: 221.1079; found: 221.1083.

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2-(*p*-Tolyl)quinoxaline (3fa). White solid; MP 92-94 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.74 (t, *J* = 7.8, 7.2 Hz, 1H), 7.78 (t, *J* = 7.8, 7.2 Hz, 1H), 8.10-8.12 (m, 3H), 8.15 (d, *J* = 8.4 Hz, 1H), 9.32 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 21.32, 127.37, 129.03, 129.48, 129.54, 129.77, 129.98, 133.96, 140.47, 141.42, 142.31, 143.35, 151.81; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2$: 221.1079; found: 221.1081.

2-(4-Methoxyphenyl)quinoxaline (3ga). White solid; MP 98-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.91 (s, 3H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.70-7.78 (m, 2H), 8.11 (t, *J* = 8.8 Hz, 2H), 8.18 (d, *J* = 8.8 Hz, 2H), 9.30 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 55.51, 114.66, 129.04, 129.13, 129.45, 130.25, 141.27, 142.38, 143.15, 151.51, 161.52; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2O$: 237.1029; found: 237.1033.

2-(4-Nitrophenyl)quinoxaline (3ha). Yellow solid; MP 188-190 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.83 (t, *J* = 3.6, 3.2 Hz, 2H), 8.17 (t, *J* = 7.6 Hz, 2H), 8.40 (s, 4H), 9.38 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 124.38, 128.42, 129.35, 129.92, 130.78, 130.97, 142.17, 142.27, 142.62, 142.88, 148.87, 149.30; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}N_3O_2$: 252.0774; found: 252.0778.

2-(Naphthalen-1-yl)quinoxaline (3ia). Off white solid; MP 134-136 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.51-7.58 (q, *J* = 6.8, 6.4 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.81-7.86 (distorted q, *J* = 6.8, 4.0 Hz, 2H), 7.96 (d, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.20-8.24 (m, 2H), 9.17 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 125.08, 125.41, 126.35, 127.18, 128.54, 128.64, 129.31, 129.69, 129.91, 130.13, 130.39, 131.18, 134.05, 135.15, 141.40, 142.24, 146.63, 154.28; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{13}N_2$: 257.1079; found: 257.1081.

2-(Naphthalen-2-yl)quinoxaline (3ja). Yellow solid; MP 138-140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.57 (s, 2H), 7.76-7.83 (distorted q, *J* = 8.8, 7.6 Hz, 2H), 7.92 (s, 1H), 8.03 (distorted d, *J* = 8.4 Hz, 2H), 8.14-8.22 (dd, *J* = 7.6 Hz, 2H), 8.37 (d, *J* = 7.6 Hz, 1H), 8.66 (s, 1H), 9.49 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 124.57, 126.79, 127.40, 127.59, 127.90,

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128.99, 129.14, 129.24, 129.68, 129.71, 130.45, 134.22, 141.64, 143.61, 151.81; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{13}N_2$: 257.1079; found: 257.1083.

2-(Furan-2-yl)quinoxaline (3ka). Light brown solid; MP 98-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.63 (s, 1H), 7.32 (d, *J* = 2.8 Hz, 1H), 7.68-7.77 (m, 3H), 8.05-8.10 (q, *J* = 8.4, 4.4 Hz, 2H), 9.24 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 111.91, 112.58, 129.28, 129.42, 130.57, 141.35, 142.11, 142.17, 143.92, 145.19, 151.64; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_9N_2O$: 197.0716; found: 197.0720.

2-(Thiophen-2-yl)quinoxaline (3la). Pale yellow solid; MP 120-122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 4.4 Hz, 1H), 7.55 (d, *J* = 4.8 Hz, 1H), 7.69-7.76 (q, *J* = 7.6, 6.8 Hz, 2H), 7.86 (d, *J* = 3.2 Hz, 1H), 8.05-8.08 (distorted q, *J* = 3.6, 2.4 Hz, 2H), 9.24 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 127.05, 128.55, 129.19, 129.28, 129.91, 130.51, 141.40, 142.12, 142.20, 142.30, 147.45; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_9N_2S$: 213.0487; found: 213.0491.

3-(Quinoxalin-2-yl)-2*H*-chromen-2-one (3ma). Yellow solid; MP 198-200 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 7.47 (t, *J* = 7.6, 7.2 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 7.6, 7.2 Hz, 1H), 7.90-7.96 (m, 2H), 8.03 (d, *J* = 7.6 Hz, 1H), 8.16-8.21 (distorted q, *J* = 7.2, 2.4 Hz, 2H), 8.94 (s, 1H), 9.60 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 116.14, 119.10, 123.62, 125.00, 128.86, 129.07, 129.76, 130.65, 130.77, 133.26, 141.24, 141.42, 144.59, 145.38, 147.84, 153.83, 159.61; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{11}N_2O_2$: 275.0821; found: 275.0823.

6-Chloro-2-phenylquinoxaline (3ab). White solid; MP 146-148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.52-7.59 (m, 3H), 7.71-7.74 (dd, *J* = 2.4, 2.0 Hz, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 8.11 (d, *J* = 2.0 Hz, 1H), 8.19 (d, *J* = 6.8 Hz, 2H), 9.33 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 127.54, 128.11, 129.24, 130.45, 130.86, 131.34, 135.28, 136.41, 140.88, 141.86, 144.17, 151.98; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0533; found: 241.0535.

7-Chloro-2-phenylquinoxaline (3ac). White solid; MP 126-128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.52-7.60 (m, 3H), 7.67-7.69 (dd, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 8.15 (d,

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J = 2.4 Hz, 1H), 8.18-8.20 (dd, *J* = 1.2 Hz, 2H), 9.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 127.62, 128.51, 129.22, 130.37, 130.51, 130.56, 136.11, 136.33, 140.12, 142.67, 143.43, 152.56; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0533; found: 241.0537.

6-Methyl-2-phenylquinoxaline (3ad) and **7-Methyl-2-phenylquinoxaline (3ae) 3ad:3ae = 1:4**. Pale yellow solid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 2.61 (s, 3H), 7.46-7.62 (m, 4H), 7.89 and 7.94 (s, 1H), 8.01 and 8.05 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 7.0 Hz, 2H), 9.26 and 9.28 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 151.78, 151.08, 143.28, 143.13, 142.49, 142.37, 141.58, 140.76, 140.13, 136.93, 132.71, 132.50, 130.06, 129.80, 129.21, 129.16, 128.61, 128.50, 127.99, 127.42, 127.39; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2$: 221.1079; found: 221.1083.

6-Methoxy-2-phenylquinoxaline (3af). Pale yellow solid; MP 94-96 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.99 (s, 3H), 7.38-7.40 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.51 (t, *J* = 7.5, 7.0 Hz, 1H), 7.56 (t, *J* = 8.0, 7.0 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 1H), 8.16 (d, *J* = 7.5 Hz, 2H), 9.16 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 55.90, 106.99, 122.99, 127.51, 128.97, 129.21, 130.07, 136.99, 137.76, 140.82, 143.95, 151.93, 161.05; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2O$: 237.1029; found: 237.1031.

7-Methoxy-2-phenylquinoxaline (3ag). Pale yellow solid; MP 92-94 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.99 (s, 3H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.42-7.45 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.49 (t, *J* = 7.5, 7.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 8.03 (d, *J* = 9.5 Hz, 1H), 8.15 (d, *J* = 7.5 Hz, 2H), 9.24 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 55.88, 106.41, 123.41, 127.20, 129.19, 129.80, 130.50, 136.99, 138.40, 143.10, 143.26, 149.62, 160.54; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2O$: 237.1029; found: 237.1033.

6-Nitro-2-phenylquinoxaline (3ah). Yellow solid; MP 210-212 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.60-7.63 (m, 3H), 8.25-8.29 (m, 3H), 8.54-8.56 (dd, *J* = 9.0, 2.5 Hz, 1H), 9.02 (d, *J* = 2.5 Hz, 1H), 9.49 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 123.82, 125.72, 127.92, 129.27, 129.51, 131.14, 135.60, 140.31, 144.89, 145.40, 147.43, 154.29; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}N_3O_2$: 252.0774; found: 252.0776.

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7-Nitro-2-phenylquinoxaline (3ai). Yellow solid; MP 208-210 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.60-7.63 (m, 3H), 8.24-8.29 (m, 3H), 8.49-8.51 (dd, *J* = 9.5, 2.5 Hz, 1H), 9.05 (d, *J* = 2.0 Hz, 1H), 9.47 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ = 122.83, 125.81, 127.71, 129.26, 129.49, 130.82, 135.52, 141.32, 143.88, 146.05, 148.26, 153.69; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}N_3O_2$: 252.0774; found: 252.0778.

2-(3-Chlorophenyl)quinoxaline (3na). Yellow solid; MP 130-132 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 4.4 Hz, 2H), 7.75-7.82 (q, *J* = 7.6, 6.8 Hz, 2H), 8.06 (s, 1H), 8.14 (t, *J* = 8.8 Hz, 2H), 8.22 (s, 1H), 9.29 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 125.59, 127.74, 129.24, 129.74, 130.06, 130.27, 130.44, 130.62, 135.42, 138.58, 141.87, 142.26, 143.01, 150.40; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0533; found: 241.0535.

2-(4-Bromophenyl)quinoxaline (3oa). Yellow solid; MP 128-130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.69-7.82 (m, 4H), 8.08-8.16 (m, 4H), 9.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 125.01, 129.03, 129.20, 129.64, 129.83, 130.50, 132.38, 135.68, 141.73, 142.27, 142.83, 150.69; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}BrN_2$: 285.0028; found: 285.0032.

2-(2,6-Dimethoxyphenyl)quinoxaline (3pa). Yellow solid; MP 68-70 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H), 3.87 (s, 3H), 7.01 (s, 2H), 7.48 (s, 1H), 7.75 (t, *J* = 3.6 Hz, 2H), 8.11-8.16 (q, *J* = 6.8, 6.4 Hz, 2H), 9.35 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 55.98, 56.37, 113.09, 116.11, 117.30, 127.08, 129.09, 129.52, 129.57, 129.86, 141.11, 142.67, 147.28, 151.79, 152.01, 154.30; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{15}N_2O_2$: 267.1134; found: 267.1136.

2-(4-Chlorophenyl)quinoxaline (3qa). White solid; MP 136-138 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.53-7.59 (distorted q, *J* = 8.0, 7.2 Hz, 2H), 7.75-7.82 (q, *J* = 7.6, 6.4 Hz, 2H), 8.12-8.17 (m, 4H), 9.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 128.80, 129.18, 129.42, 129.63, 129.81, 130.50, 135.23, 136.62, 140.64, 142.89, 143.98, 150.64; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$: 241.0533; found: 241.0537.

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2-(*m*-Tolyl)quinoxaline (3ra). White solid; MP 84-86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.50 (s, 3H), 7.33-7.46 (distorted dd, *J* = 7.2, 6.0 Hz, 2H), 7.76 (t, *J* = 8.4, 8.0 Hz, 2H), 7.96 (d, *J* = 6.8 Hz, 1H), 8.02 (s, 1H), 8.11-8.17 (q, *J* = 8.4, 7.6 Hz, 2H), 9.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.65, 124.76, 128.28, 129.12, 129.19, 129.54, 129.65, 130.33, 131.08, 136.81, 139.03, 141.62, 142.36, 143.61, 152.14; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2$: 221.1079; found: 221.1081.

Conclusion:

In conclusion, we have developed a direct and efficient method to prepare quinoxaline derivatives from easily available multiform substrates. Use of simple unactivated ethylarenes, ethylenearenes and ethynearenes, tolerance to broad range of functional groups and use of inexpensive catalyst are some striking features of this protocol. We anticipate that this operationally simple tandem process will be widely adopted for construction of quinoxaline moieties needed for the synthesis of complex molecules.

Acknowledgements

This work was supported by CSIR-New Delhi (sanction no. 01(2427)/10/EMR-II dated 28/12/2010, pool scheme no. 8644-A). K.S.V. and H.P.K. thank UGC-SAP and CSIR-New Delhi respectively for award of Senior Research Fellowships. The authors thank Prof. Prakash M. Bhate for his generous support.

[†]Author contributions

The authors contributed equally to this work.

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