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Graphite catalyzed green synthesis of quinoxalines

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ABSTRACT

A new simple approach using environmentally benign, cheap, and easily recyclable graphite as a heterogeneous catalyst for the synthesis of quinoxalines is described. A library of pharmacologically interesting diphenylquinoxalines is prepared by the double condensation of substituted benzils, phenanthrene-9,10-dione, and benzoin with aromatic diamines in 71–93% yields at room temperature in ethanol. Aliphatic diamines gave corresponding dihydropyrazines from substituted benzils in 72–92% yields.

Quinoxalines are an important class of nitrogen containing heterocycles exhibiting diverse biological properties. They exhibit antibacterial, antiviral, anthelmintic, anti-inflammatory, kinase inhibitory, and anticancer activity.[1] For example, NCG555879-01[2a] acts as BRCA1 inhibitor. Quinoxaline moiety is also present in biologically active natural products like Izumiphenazine C[2b] and Echinomycin[2c] (Fig. 1). In addition to their medicinal properties, they are also used in dyes and semiconductors.[1]

Over the years several catalysts and reagents are reported for the synthesis of quinoxalines like CAN,[3a] sulfamic acid,[3b] IBX,[3c] $CuSO_4{\cdot}5H_2O$,[3d] polyaniline sulfate,[3e] amidosulfonic acid,[3f] PTSA,[3g] Mn octahedral molecular sieves,[3h] ionic liquid $(Hbim)BF_4$,[3i] $Ga(OTf)_3$,[3j] $SnCl_2$,[3k] montmorillonite K-10,[3l] DMSO-PdI_2,[3m] oxalic acid,[3n] Bi(III),[3o] $Zr(DS)_4$,[3p] ZrO_2 mixed metal oxide,[3q] silica bonded S-sulfonic acid,[3r] ZnI_2,[3s] silica supported $SbCl_3$,[3t] $NbCl_5$,[3u] amberlyte-15,[3v] I_2,[3w] Ru/C,[3x] etc.

Recently, many new methods are also reported like clayzic,[4a] silica gel,[4b] Zr(IV) modified silica gel,[4c] alumina,[4d] DABCO,[4e] $Sm(OTf)_2$,[4f] PEG-400 in MW,[4g] PEG–water,[4h] glycerol,[4i] silica sulfuric acid in PEG,[4j] $CeCl_3{\cdot}7H_2O$ in glycerin,[4k] $FeCl_3$ with morpholine,[4l] triethylamine/O_2,[4m] $Ga(ClO_4)_3$,[4n] and PTSA/H_2O.[4o] Catalyst-free process like reactions using MW[5a] and grinding[5b] are also reported. Many of these methods have disadvantages like using strong acidic condition; require heating condition, or use of transition metals to obtain good yields. Presently, appreciated synthetic methods are those using environmentally harmless reagents, recyclable catalysts, and energy efficient processes.

Continuing our interest in the synthesis of heterocycles using tandem reaction,[6a,b] green catalyst,[6c,d] and solvent-free synthesis,[6e] we herein report a highly efficient graphite catalyzed double condensation method for the synthesis of quinoxalines. The method

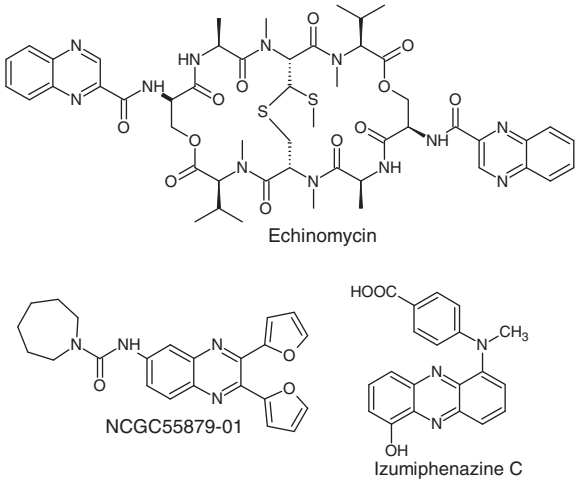
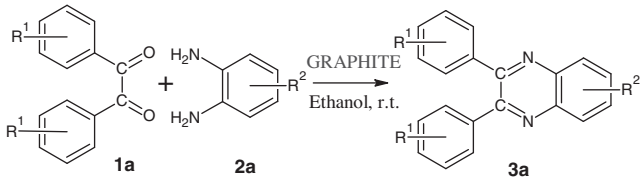


Figure 1. Biologically important quinoxalines.



Scheme 1. Graphite catalyzed synthesis of quinoxalines.

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Table 1
Optimization of graphite concentration

Entry	Graphite (equiv)	Time (min)	Yield[a] (%)
1	20	30	86
2	10	60	89
3	5	60	90
4	2	60	92
5	0.5	300	42
6	0	900	Trace
7	20	24 h	51[b]

[a] Benzil (1 mmol), *o*-phenylenediamine (1 mmol), graphite, ethanol (10 mL), stir, rt.
[b] Water (10 mL) was used as solvent.

has advantages of ambient reaction condition, environmentally acceptable solvent, high yields, simple work-up, and easy catalyst recovery and reusability.

Graphite a form of carbon, though abundantly and cheaply available benign chemical, has found very few applications in organic synthesis, for example, in Friedel–Crafts acylation,[7a] alkylation,[7b] and for conversion of aldehyde to nitriles.[7c] The benign nature and abundant availability of it prompted us to explore its potential use in organic synthesis. We visualized that it could be used for the rapid double condensation of *o*-phenylenediamine with 1,2-diketones to form quinoxalines.

As quinoxalines are medicinally important compounds, ethyl alcohol was chosen as a solvent due to its lower toxicity. For initial

Table 2
Synthesis of quinoxalines via Scheme 1[a]

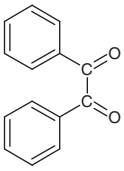
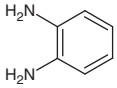
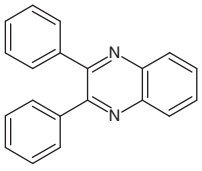
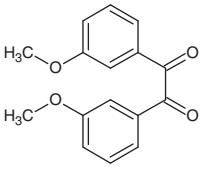
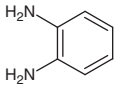
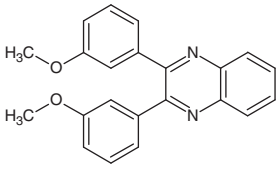
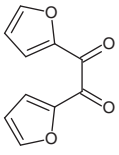
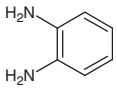
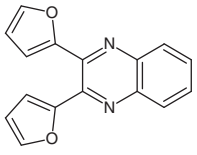
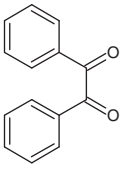
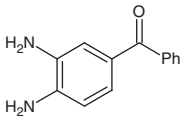
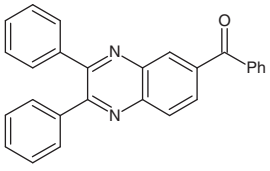
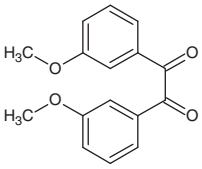
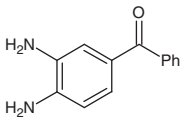
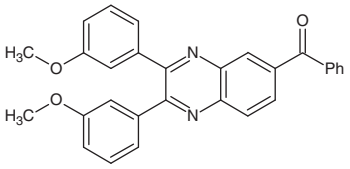
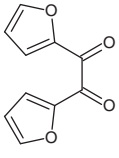
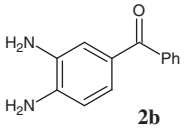
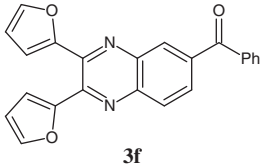
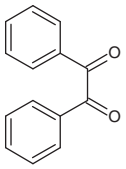
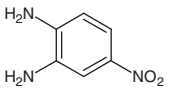
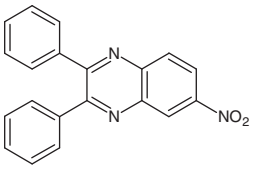
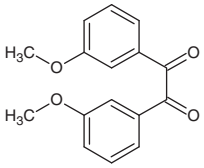
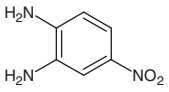
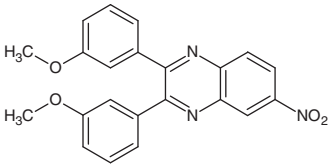
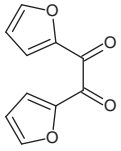
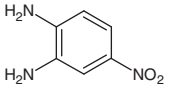
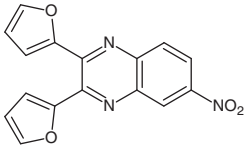
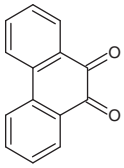
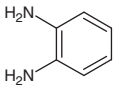
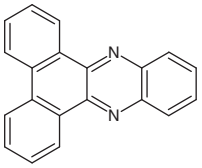
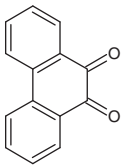
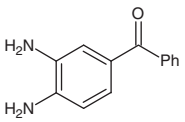
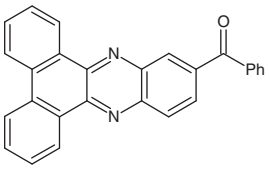
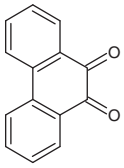
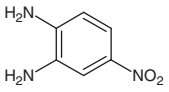
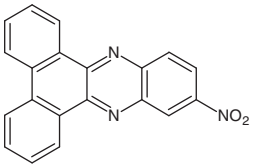
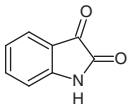
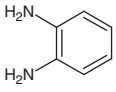
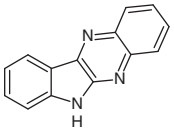
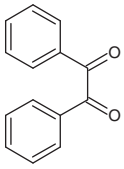
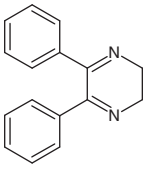
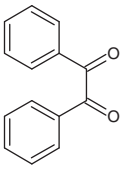
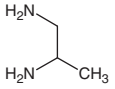
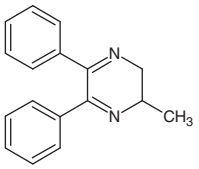
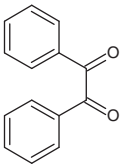
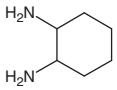
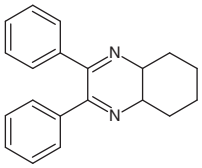
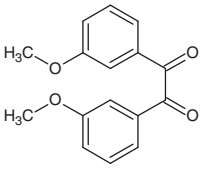
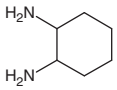
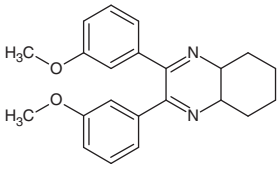
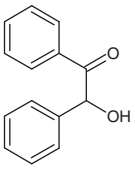
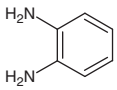
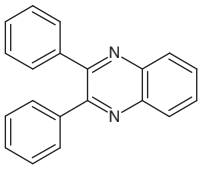
Entry	Diketone 1	Diamine 2	product[c] 3	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	1	92
2	 **1b**	 **2a**	 **3b**	2.5	79
3	 **1c**	 **2a**	 **3c**	3	86
4	 **1a**	 **2b**	 **3d**	3.5	77
5	 **1b**	 **2b**	 **3e**	18	77
6	 **1c**	 **2b**	 **3f**	24	80

Table 2 (*continued*)

Entry	Diketone 1	Diamine 2	product[c] 3	Time (h)	Yield[b] (%)
7	 **1a**	 **2c**	 **3g**	8	86
8	 **1b**	 **2c**	 **3h**	12	81
9	 **1c**	 **2c**	 **3i**	10	87
10	 **1d**	 **2a**	 **3j**	0.5	93
11	 **1d**	 **2b**	 **3k**	1	88
12	 **1d**	 **2c**	 **3l**	12	71
13	 **1e**	 **2a**	 **3m**	24 45	0[d] 12[d]
14	 **1a**	 **2d**	 **3n**	1	92

(*continued on next page*)

Table 2 (*continued*)

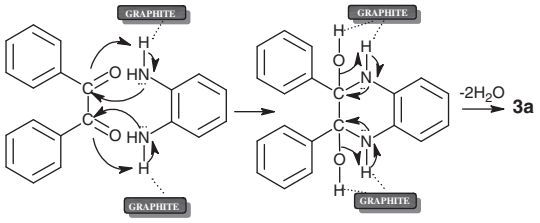
Entry	Diketone 1	Diamine 2	product[c] 3	Time (h)	Yield[b] (%)
15	 **1a**	 **2e**	 **3o**	1	81
16	 **1a**	 **2f**	 **3p**	2.5	72
17	 **1b**	 **2f**	 **3q**	3	86
18	 **1f**	 **2a**	 **3a**	12 45	64[d] (21[e]) 64[d] (21[e])

[a] Reaction condition: diketone (1 mmol), diamine (1 mmol), graphite (2 mmol), ethanol (10 mL), stir rt.
[b] Isolate yield.
[c] Products confirmed based on their ^{1}H NMR, ^{13}C NMR, DEPT, and elemental analysis/LCMS (Supplementary data).
[d] Graphite (5 mmol), diamine (1.2 mmol), 80 °C.
[e] 2-(2-aminophenylimino)-1,2-diphenylethanol **3r.**

Table 3
Reusability of catalyst[a]

Cycle	Time (min)	Yield[b] (%)
0	60	92
1	60	92
2	90	90
3	120	89
4	150	88
5	150	88
6	150	88

[a] Benzil (1 mmol), *o*-phenylenediamine (1 mmol), graphite (2 mmol), ethanol (10 mL), stir, rt.
[b] Isolated yield.



Scheme 2. Probable mechanism illustrating role of graphite in reaction.

condensation studies between benzil **1a** and *o*-phenylenediamine **2a** (Scheme 1), excess of graphite (20 equiv) was used. This gave quinoxaline **3a** in 86% yield in 30 min. at room temperature. Having observed the catalytic acceleration effect of graphite, we slowly reduced the amount of graphite for optimization studies (Table 1). It was observed that 2 equiv of graphite (entry 4) gave maximum yield (92%) after 1 h. Hence, this condition was chosen for further studies. Further decrease in graphite concentration resulted in decreasing its efficacy.

Using this protocol,[8] a library of quinoxalines (Table 2) was synthesized. It was observed that electron rich diketones (**1b**–**c**) and electron deficient diamines (**2b**–**c**) took a longer time to react due to +I effect and −I effect, respectively. The method could also be successfully extended to phenanthrene-9,10-dione **1d** for synthesizing corresponding dibenzophenazines (entry 10–12).

When isatin **1e** was used as dicarbonyl compound, after prolonged heating (entry 13), only 12% of product formation was observed. This may be due to the less reactive amide carbonyl group in isatin. When aliphatic amines were used corresponding dihydropyrazines were obtained (entries 14–17) in good yields. Further scope of this graphite catalyzed condensation process was tested with 2-hydroxyketone, benzoin (entry 18). Reasonable formation of product **3a** was observed along with 2-(2-aminophenylimino)-1,2-diphenylethanol **3r**, only under reflux condition using 5 equiv of graphite.

The separation of catalyst was very easy as mere filtration through an ordinary filter paper and drying (100 °C) was sufficient enough to quantitatively recover the catalyst in active form. Reusability of recovered catalyst was studied for a fresh reaction cycle and fairly reproducible yields were obtained up to 7 consecutive cycles as summarized in Table 3.

Though the role of graphite has not been clearly understood, a speculative mechanism for product formation is proposed (Scheme 2).

In conclusion, an efficiently recoverable, environment friendly, and cheap graphite catalyst is demonstrated for the condensation of diketones with *o*-phenylenediamine to give quinoxalines in excellent yield at ambient condition.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H NMR, ^{13}C NMR and DEPT spectra of all the products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.041.

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8. *General procedure*: Diketone (1 mmol), diamine (1 mmol), and graphite (2 mmol) were mixed in a 50 mL round bottom flask and ethanol (10 mL) was added. The reaction mixture was stirred vigorously at room temperature (monitored by TLC). On completion, the mixture was filtered through an ordinary filter paper and catalyst was washed with ethanol (10 mL). Organic layer was concentrated to give crude solid product which on recrystallization with ethanol/water (8:2) afforded analytically pure product. Structures of new compounds were confirmed based on their ^{1}H NMR, ^{13}C NMR, DEPT data, and elemental analysis.
(2,3-Bis(3-methoxyphenyl)quinoxalin-6-yl)(phenyl)methanone ***3e***: Pale yellow solid; mp 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$,δ ppm): 3.71 (3H, s), 3.73 (3H, s), 6.94 (2H, t, J = 8.0 Hz), 7.07–7.14 (4H, m), 7.26 (2H, q, J = 8.0 Hz), 7.53 (2H, t, J = 8.0 Hz), 7.64 (1H, t, J = 8.4 Hz), 7.91 (2H, d, J = 8.0 Hz), 8.28 (2H, s), 8.54 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$,δ ppm): 55.30 (CH_3), 55.31 (CH_3), 114.66 (CH), 114.77 (CH), 115.52 (CH), 115.66 (CH), 122.25 (CH), 122.38 (CH), 128.55 (2 × CH), 129.46 (2 × CH), 129.75 (CH), 129.94 (CH), 130.17 (2 × CH), 132.48 (CH), 132.88 (CH), 137.15 (Cq), 138.34 (Cq), 139.81 (Cq), 139.85 (Cq), 140.15 (Cq), 142.95 (Cq), 154.42 (Cq), 154.96 (Cq), 159.50 (2 × Cq), 195.83 (Cq); elemental analysis (calcd C = 78.01, H = 4.97, N = 6.27%) observed C = 77.65, H = 4.75, N = 5.90%.
2,3-Bis(3-methoxyphenyl)-4a,5,6,7,8,8a-hexahydroquinoxaline ***3q***: White solid; mp 136–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$,δ ppm): 1.42 (2H, t, J = 10.0 Hz), 1.62–1.64 (2H, m), 1.90 (2H, d, J = 8.0 Hz), 2.50 (2H, d, J = 14.0 Hz), 2.83 (2H, t, J = 4.0 Hz), 3.69 (6H, s), 6.83 (2H, d, J = 8.0 Hz), 6.91 (2H, d, J = 8.0 Hz), 6.99 (2H, s), 7.12 (2H, t, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$,δ ppm): 25.43 (CH_2), 33.49 (CH_2), 55.24 (CH_3), 59.55 (CH), 112.59 (CH), 115.91 (CH), 120.64 (CH), 129.15 (CH), 139.13 (Cq), 159.34 (Cq), 159.56 (Cq); elemental analysis (calcd C = 75.83, H = 6.94, N = 8.04%) observed C = 75.57, H = 7.10, N = 7.81%.