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Synthesis of quinoxalines through iodine-catalyzed one-pot annulation of alkynes with *o*-phenylenediamines

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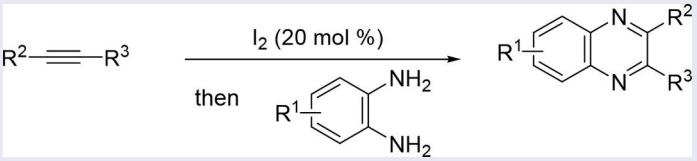
ABSTRACT

The synthesis of N-heterocycles of quinoxalines has been developed by an efficient protocol of one-pot annulation of alkynes with *o*-phenylenediamines. A variety of quinoxalines were prepared in good to high yields in the presence of catalytic amount of iodine as a catalyst.

GRAPHICAL ABSTRACT



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KEYWORDS
Alkynes; iodine-catalyzed; *o*-phenylenediamines; organic reaction; quinoxalines

Introduction

The development of efficient protocols for the synthesis of heterocycles has received much attention because of the great biological activity of heterocycles.[1] As one of the important *N*-heterocycles, quinoxalines show some significant biological activities. For example, quinoxalines are known to be antitumors,[2] antibacterials,[3] anti-inflammatories,[4] antivirals,[5] and kinase inhibitors.[6]

Several synthetic methods have been developed for the synthesis of quinoxalines.[7] The use of commercially available *o*-phenylenediamines and alkynes as starting materials should be one of the most efficient and economic strategies toward the formation of quinoxalines. Using this strategy, some examples of both transition metal-catalyzed[8] and metal-free mediated[9] reactions have been developed. However, most of them suffered the disadvantages of using expensive metal catalysts or equivalents of metal-free mediators. These results led us to focus on the development of a new catalyst system for the synthesis of quinoxalines owing to their diverse biological activities.

Recently, iodine, with the advantages of inexpensive, nontoxic, and readily available, has been used as a good mediator and a catalyst in organic synthesis.[10,11] Herein, we report an efficient method for the synthesis of quinoxalines through a one-pot reaction. Using this reaction protocol, the quinoxalines were obtained in good to high yields in the

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presence of a catalytic amount of iodine as a catalyst from easily available alkynes and *o*-phenylenediamine.

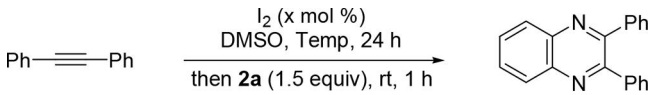
Results and discussion

Initially, we choose 1,2-diphenylethyne (**1a**) and *o*-phenylenediamine (**2a**) as the starting materials to investigate the formation of quinoxalines. The reaction was performed through one-pot procedure of iodine-catalyzed oxidation of **1a** followed by addition of **2a**. In preliminary experiments, we tested the effect of amount of iodine on this reaction. As shown in Table 1, when 1 equiv. of iodine was used, the one-pot reaction gave the corresponding quinoxaline **3aa** in 42% yield (Table 1, entry 1). The use of 50 mol% of iodine improved the yield of **3aa** to 72% (Table 1, entry 2). To our pleasure, employment of 20 mol% of iodine in the reaction afforded **3aa** in 92% yield (Table 1, entry 3). However, the reaction provided **3aa** in 52% yield when 10 mol% of iodine was used (Table 1, entry 4). We used 20 mol% of iodine as the optimal catalyst to test the reaction temperature. It was found that the desired **3aa** was formed in 90% yield when the reaction temperature was increased to 140 °C (Table 1, entry 5), while decreasing the reaction temperature afforded **3aa** in lower yields (Table 1, entries 6–7).

Under the optimal reaction conditions (Table 1, entry 3), we tested the scope of internal alkynes. As shown in Table 2, a variety of 1,2-disubstituted alkynes were suitable for the reaction to provide the corresponding quinoxalines in high yields. For example, the reaction of **1a** in the presence of 20 mol% of iodine as the catalyst in DMSO at 130 °C for 24 h followed by addition of 1.5 equiv. of **2a** at room temperature for 1 h afforded the product **3aa** in 92% yield (Table 2, entry 1). It was found that both electron-donating and electron-withdrawing substituted internal alkynes gave the corresponding products in high yields (Table 2, entries 2–9). Some functional groups, such as fluoro, ester, and nitrile groups, were tolerated in the reaction to provide the corresponding quinoxalines in high yields (Table 2, entries 4–6 and entry 9).

The scope of *o*-phenylenediamines was also examined. As shown in Table 3, several of *o*-phenylenediamines can be used for the reaction to afford the corresponding quinoxalines

Table 1. Iodine-catalyzed one-pot synthesis of quinoxaline (**3aa**): Optimization of the reaction conditions.[a]

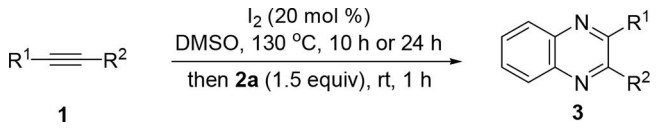


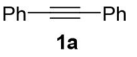
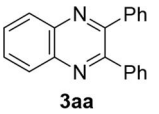
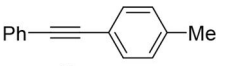
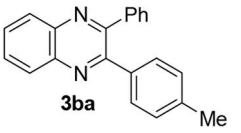
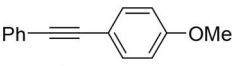
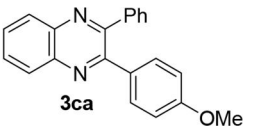
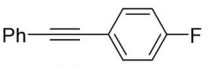
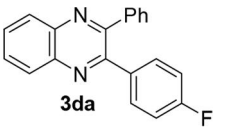
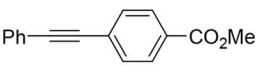
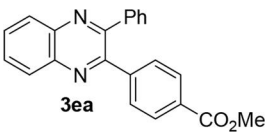
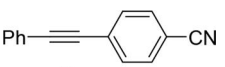
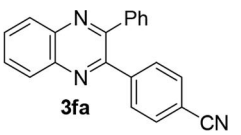
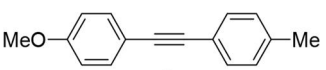
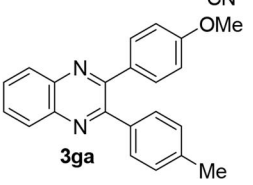
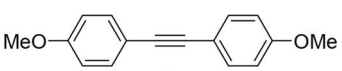
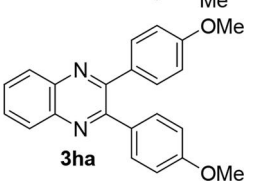
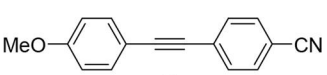
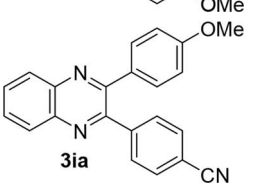
1a **3aa**

Entry	I_2 (x mol%)	Temperature (°C)	Yield (%)[b]
1	100	130	42
2	50	130	72
3	**20**	**130**	**92**
4	10	130	52
5	20	140	90
6	20	120	79
7	20	110	62

[a]The reactions were performed in a tube with 1,2-diphenylethyne **1a** (0.2 mmol), I_2 (× mol%) in DMSO (2.0 mL) at designated temperature for 24 h in air, then cooled to room temperature, *o*-phenylenediamine **2a** (0.3 mmol) was added to the solution and stirred at room temperature for 1 h.
[b]Isolated yield.

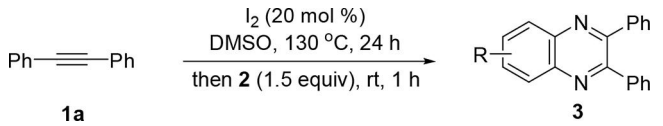
Table 2. Iodine-catalyzed one-pot synthesis of quinoxalines: Scope of alkynes **1**.[a]



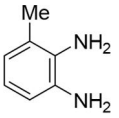
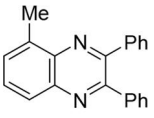
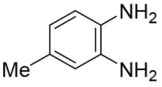
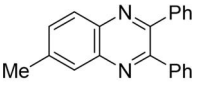
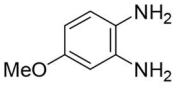
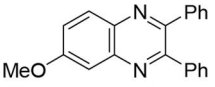
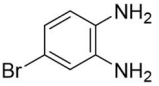
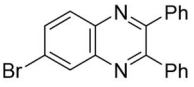
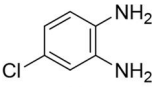
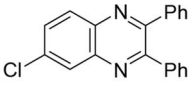
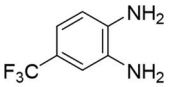
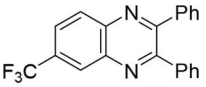
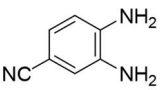
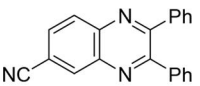
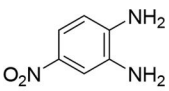
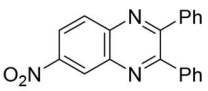
Entry	Alkyne **1**	Product **3**	Yield (%)[b]
1	 **1a**	 **3aa**	92
2	 **1b**	 **3ba**	78
3[c]	 **1c**	 **3ca**	92
4	 **1d**	 **3da**	92
5[c]	 **1e**	 **3ea**	71
6	 **1f**	 **3fa**	86
7[c]	 **1g**	 **3ga**	93
8[c]	 **1h**	 **3ha**	85
9[c]	 **1i**	 **3ia**	90

[a]The reactions were performed in a tube with alkyne **1** (0.2 mmol), I_2 (0.04 mmol) in DMSO (2.0 mL) at 130 °C for 24 h in air, then cooled to room temperature, *o*-phenylenediamine **2a** (0.3 mmol) was added to the solution and stirred at room temperature for 1 h.
[b]Isolated yield.
[c]The reaction time is 10 h in the first step.

Table 3. Iodine-catalyzed one-pot synthesis of quinoxalines: Scope of *o*-phenylenediamines **2**.[a]

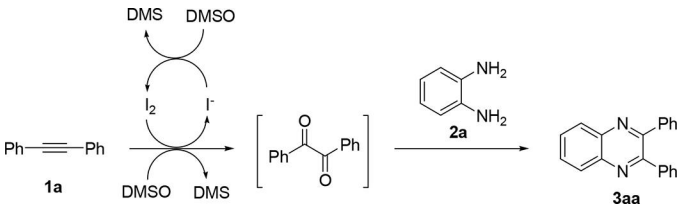


1a **3**

Entry	Amine **2**	Product **3**	Yield (%)[b]
1	 **2b**	 **3ab**	96
2	 **2c**	 **3ac**	93
3	 **2d**	 **3ad**	96
4[c]	 **2e**	 **3ae**	91
5[c]	 **2f**	 **3af**	93
6[d]	 **2g**	 **3ag**	86
7[e]	 **2h**	 **3ah**	88
8[f]	 **2i**	 **3ai**	66

[a]The reactions were performed in a tube with alkyne **1a** (0.2 mmol), I_2 (0.04 mmol) in DMSO (2.0 mL) at 130 °C for 24 h in air, then cooled to room temperature, *o*-phenylenediamines **2** (0.3 mmol) were added to the solution and stirred at room temperature for 1 h.
[b]Isolated yield.
[c]rt for 2 h in the second step.
[d]50 °C for 4 h in the second step.
[e]50 °C for 5 h in the second step.
[f]50 °C for 8 h in the second step.

in good to high yields. Although both electron-donating and electron-withdrawing substituted *o*-phenylenediamines are suitable for the reaction, the reactions of *o*-phenylenediamines with a bromo, chloro, trifluoromethyl, nitrile, or nitro group on



Scheme 1. Plausible mechanism.

the 4-position of benzene ring are much slower than those of electron-donating partners (Table 3, entries 4–8 vs entries 1–3).

A plausible mechanism for present reaction is outlined in Scheme 1. 1,2-Diphenylethyne (**1a**) is oxidized to benzil in the presence of I_2/DMSO.[9b,11a] Subsequently, the condensation reaction of benzil with *o*-phenylenediamine (**2a**) affords the desired quinoxaline (**3aa**).

Experimental

DMSO was distilled over CaH_2 under N_2. Compounds **1a** and **2a–2i** were purchased without further purification. Compounds **1b–1i** were prepared according to the reported procedure.[12] All commercial reagents were used without further purification. NMR spectra were recorded on a 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) with deuterated chloroform ($CDCl_3$) as a solvent at 298 K. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR, chloroform-d (δ 77.16) for ^{13}C NMR: the following abbreviations are used; s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. HRMS were obtained on an ESI-TOF mass spectrometer. Flash column chromatography was performed on silica gel (300–400 mesh).

General procedure for iodine-catalyzed one-pot annulation of alkynes and o-phenylenediamines

To a stirred solution of alkyne (0.2 mmol) in DMSO (2.0 mL) was added I_2 (10.1 mg, 0.04 mmol). The solution was stirred at 130 °C for 24 h in air. Then the mixture was cooled to room temperature, and *o*-phenylenediamine (0.3 mmol) was added. The solution was stirred at room temperature for 1 h. After completion, the solution was diluted with ethyl acetate, washed with H_2O, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by preparative thin-layer chromatography on silica gel with PE/EtOAc (15/1) as an eluent to give quinoxaline **3**.

Complete experimental details are available online in the Supplemental Material.

Conclusion

In conclusion, we developed an efficient iodine-catalyzed one-pot reaction for the synthesis of quinoxalines. Using of a catalytic amount of iodine as a catalyst, a variety of quinoxalines were prepared in good to high yields from easily available alkynes and *o*-phenylenediamines. This one-pot protocol provided an efficient synthetic method for the construction of six-membered *N*-heterocycles.

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