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Isobutyl Nitrite-Mediated Synthesis of Quinoxalines through Double C−H Bond Amination of *N*-Aryl Enamines

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Abstract. An efficient and metal-free double C−H bond amination of *N*-aryl enamines using isobutyl nitrite (IBN) has been developed. This method enables the preparation of functionalized quinoxalines in good to excellent yields and tolerates a variety of *N*-aryl enamines with diverse functional substituents. Mechanistic studies revealed the presence of a key *β*-imino oxime ester intermediate. A quinoxaline derivative could be prepared from *β*-carbonyl ester in one-pot sequence on a gram scale. Finally, two important quinoxaline scaffolds were easily prepared in moderate yields over two steps.

Keywords: Amination; *N*-Aryl enamine; C−N Bond formation; C−H Functionalization; Quinoxaline

Quinoxaline is one of the most important nitrogen heterocyclic scaffolds. It plays an important role in medicinal chemistry, and commonly occurs in pharmaceuticals, because of its good biological activity.[1] Examples of bioactive quinoxaline-containing compounds include the PDGF receptor inhibitor, Topo-II poison, and antitumor antibiotics, such as AG1295, XK469, PAQ, and CQS, which are shown in Figure 1.[2] Strategies for the efficient preparation of quinoxalines using simple conditions and readily available starting materials are highly desirable.

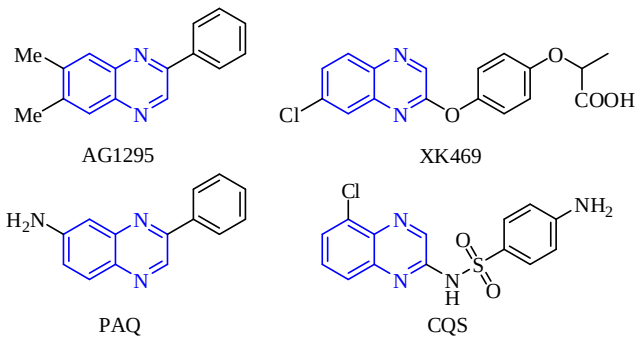


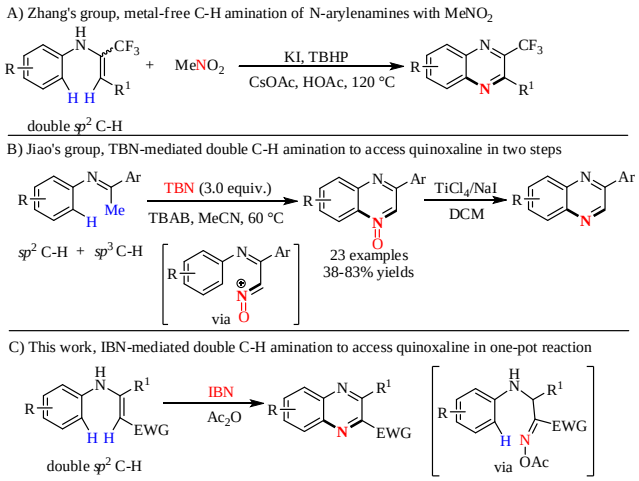
Figure 1. Some Bioactive Quinoxaline-contianing Compounds

Many elegant strategies have been developed to prepare quinoxaline scaffolds. However, these strategies typically use *ortho*-phenylenediamines or *ortho*-functionalized anilines as starting materials.[3] C−H amination is an efficient and direct strategy for the preparation of nitrogen containing compounds, because it avoids pre-functionalized starting materials.[4] Many transition metal-catalyzed strategies for the construction of C−N bonds *via* direct C−H functionalization have been developed.[5] However, metal-free C−H functionalization approaches are also desirable; these approaches meet the purity requirements of biological and medicinal chemistry research, and thereby complement metal-catalyzed methods.[6]

Transition metal-catalyzed synthesis of quinoxalines *via* C−H amination using diverse nitrogen reagents has received considerable attention.[7] However, only a few metal-free strategies have been reported.[8] For example, a 2014 report by Zhang and co-workers detailed the metal-free synthesis of 3-trifluoromethylquinoxalines from *N*-aryl enamines and nitromethane in a one-pot reaction (Scheme 1-A).[8a] However, this approach suffered from complicated additives such as KI, CsOAc and *tert*-butyl hydroperoxide, and is run in HOAc at 120 °C.

As demonstrated in recent reports, nitrous esters, such as *tert*-butyl nitrite (TBN) and *iso*-butyl nitrite (IBN), are a new type of nitrogen reagent for the construction of C−N bonds.[9] In 2014, Jiao's group developed a novel metal-free amination of C(sp^3)–H and C(sp^2)–H bonds. This approach was used to prepare 2-quinoxaline *N*-oxides from *N*-aryl ketimines using TBN (3.0 equiv.) in MeCN (Scheme 1-B).[10] Although this is a simple and efficient method to construct the quinoxaline *N*-oxide skeleton,

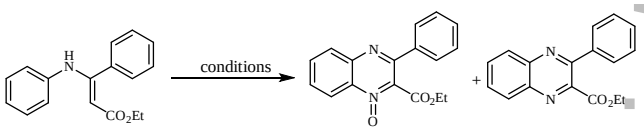
it required the use of $TiCl_4$/NaI reductive reagents. During the course of our research,[11] we found that quinoxaline could be obtained *via* consecutive condensation and *N*-arylation reactions under Lewis acid conditions. However, an oxime starting material and stoichiometric quantities of Lewis acid were required. Inspired by Jiao's work, and based on our group's nitrosation studies using TBN,[12] we surmised that quinoxalines could be synthesized directly from *N*-aryl enamines through nitrosation, to afford a *β*-imino oxime ester, and subsequent cyclization. Here, we describe an efficient and metal-free method to synthesize quinoxalines in a one-pot reaction *via* the double C(sp^2)–H bond amination of *N*-aryl enamines using IBN (Scheme 1-C).



Scheme 1. Metal-Free C–H Aminations to Access Quinoxalines.

Initially, *N*-aryl enamine **1aa** was chosen as a model substrate and the efficiency of formation of quinoxaline **3aa** was examined. The substrate was treated with TBN and the additive tetra-*n*-butylammonium bromide (TBAB) in MeCN at 60 °C. The desired quinoxaline **3aa** was obtained in 46% yield, but quinoxaline *N*-oxide **2a** was also produced in 52% yield (Table 1, entry 1). Lowering the temperature to 25 °C, decreased the total yield of both **2a** and **3aa** (Table 1, entry 2). To our surprise, when TBN was replaced with IBN, quinoxaline **3aa** was obtained as the major product, in 42% yield, while quinoxaline *N*-oxide **2a** was only afforded in 20% yield (Table 1, entry 3). Using tetra-*n*-butylammonium fluoride (TBAF) as an additive did not affect the yield significantly (Table 1, entry 4). The total yield of **2a** and **3aa** was improved slightly when TBAB was removed or when the reaction was increased to reflux (Table 1, entries 5-6). Solvent screening revealed that **2a** was afforded as the major product in DCE and THF, while **3aa** was obtained as the major product in toluene, DMF and HOAc (Table 1, entries 8-11). Pleasingly, in Ac_2O, quinoxaline **3aa** was obtained in 94% yield and quinoxaline *N*-oxide **2a** was not observed (Table 1, entry 12). The addition of TBAB in Ac_2O did not improve the yield of **3aa** (Table 1, entry 13). The yield of **3aa** decreased at lower temperatures, and at room temperature the reaction did not occur. Enamine **1a** was recovered from the room temperature reaction (Table 1, entries 14-16). To our delight, when 2.0 equiv. of Ac_2O was used as an additive, **3aa** was produced in 78% in MeCN and 73% yield in toluene. **2a** was observing as a minor product in both of these conditions (Table 1, entries 17-18). These results indicated that Ac_2O promoted the formation of **3aa**. Therefore, the optimal conditions for the formation of **3aa** was IBN in Ac_2O at reflux (Table 1, entry 12).

Table 1. Optimization of the Reaction Conditions.[a]



entry	"N" / additive / solvent / temp	**2a**%[b]	**3aa**%[b]
1	TBN / TBAB / MeCN / 60 °C	52	46
2	TBN / TBAB/ MeCN / 25 °C	41	37
3	IBN / TBAB / MeCN / 60 °C	20	42
4	IBN / TBAF / MeCN / 60 °C	21	40
5	IBN / TBAB / MeCN / reflux	27	46
6	IBN / - / MeCN / reflux	27	38
7	IBN / - / DCE / reflux	41	25
8	IBN / - / THF / reflux	47	22
9	IBN / - / toluene / reflux	13	31
10	IBN / - / DMF / reflux	16	29
11	IBN / - / HOAc / reflux	11	51
12	IBN / - / Ac_2O / reflux	-	94
13	IBN / TBAB / Ac_2O / reflux	-	93
14	IBN / - / Ac_2O / 80 °C	-	90
15	IBN / - / Ac_2O / 60 °C	-	41
16	IBN / - / Ac_2O / 25 °C	-	-
17[c]	IBN / Ac_2O / MeCN / reflux	11	78
18[c]	IBN / Ac_2O / toluene / reflux	<5	73

[a] Reaction conditions: **1aa** (0.5 mmol), TBN or IBN (0.5 mmol, 1.0 equiv.), additive (0.025 mmol, 5 mol%), solvent (2.0 mL), 2–24 h; [b] isolated yield; [c] Ac_2O (2.0 equiv.).

With the optimized conditions in hand, the scope of *N*-aryl enamines **1** for preparing quinoxalines was explored. As shown in Table 2, various substituents on the aniline moiety of the enamine were investigated. Substrates with electron-donating and electron-withdrawing groups at the *ortho*-, *meta*-, and *para*-positions of the aniline afforded the corresponding quinoxalines **3aa-3ao** in good yields; however, the substrates with electron-withdrawing groups required longer reaction times (**3ac**, **3ae**, **3af**, **3ak** and **3am**). When enamines **1ad** and **1ae**, with a methoxy and trifluoromethyl groups at their aryl *meta*-position, respectively, were subjected to the optimal conditions, only the regioisomers **3ad** and **3ae** were obtained (87% and 84% yields, respectively). However, enamine **1af**, with a fluoro group at the *meta*-position of its aryl ring, produced a mixture of **3af-1** and **3af-2** in a 1.3:1 ratio. A 1:2 ratio

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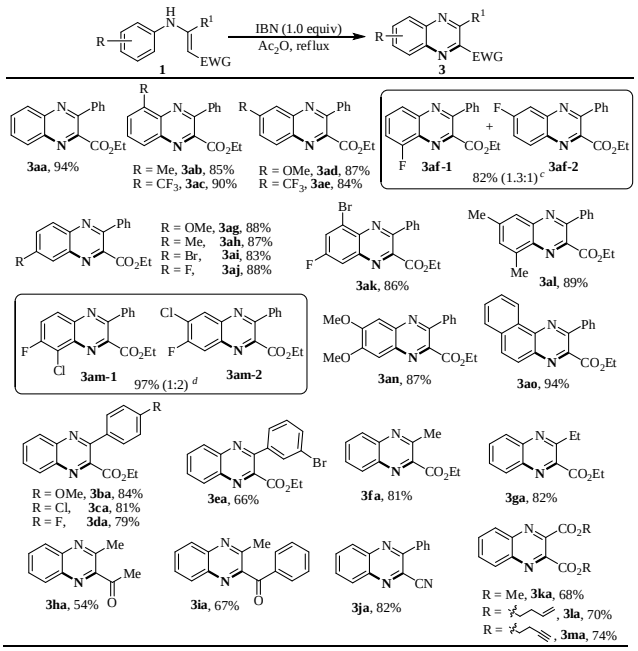
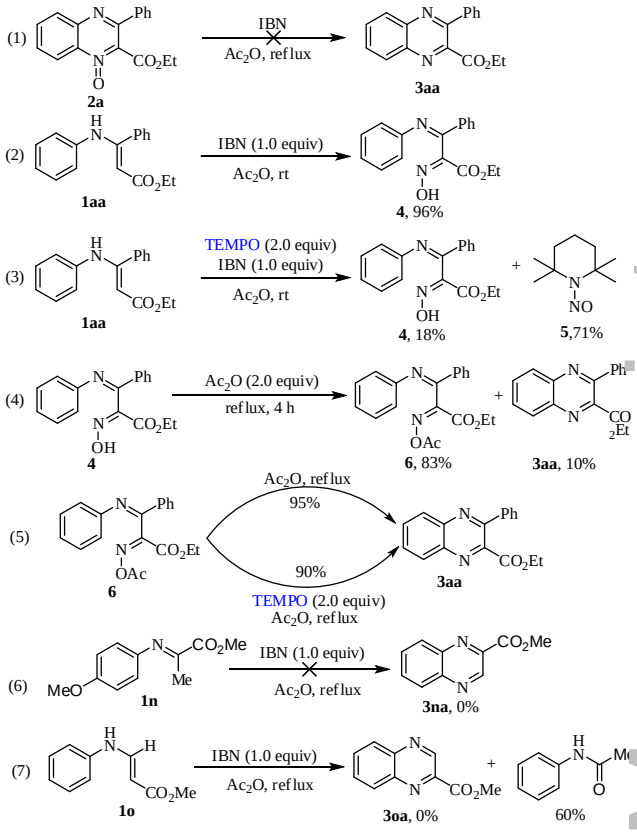
of quinoxaline **3am-1** and **3am-2** was also observed. Next, a variety of R^1 and electron-withdrawing groups (EWG) were evaluated. Aryl and alkyl groups were well tolerated at the R^1 position and afforded the desired products in good yields (**3ba-ga**). The EWG substituent could be an ester, a ketone, or a cyano group (**3ha-ja**). When acetylenedicarboxylates containing alkyl, alkene, and alkyne groups were used, the corresponding quinoxalines were also obtained in good yields (**3ka-ma**). The structure of quinoxaline **3** was further confirmed by X-ray diffraction analysis of compound **3ma**.[13]

Table 2. Scope of *N*-Aryl Enamines **1**.[a,b]



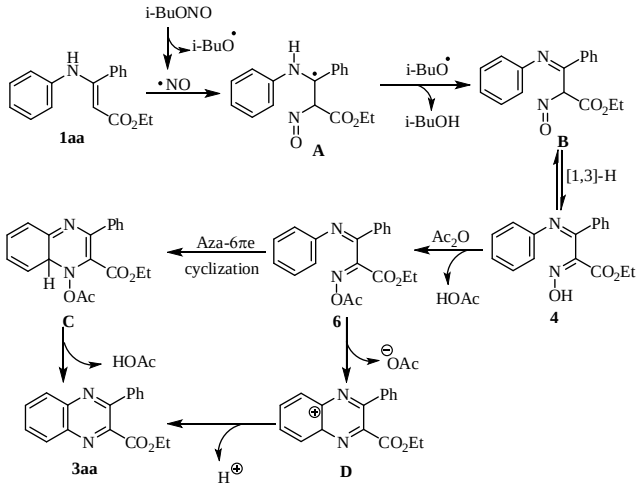
a) Reaction conditions: **1** (0.5 mmol), IBN (0.5 mmol, 1.0 equiv.), Ac_2O (2.0 mL), 2−18 h; b) isolated yield.

Control experiments were performed to study the mechanism of formation of quinoxaline **3aa** (Scheme 2). When quinoxaline *N*-oxide **2a** was subjected to the optimal conditions, quinoxaline **3aa** was not observed. This indicated that quinoxaline *N*-oxide **2a** was unlikely to be the intermediate in the formation of quinoxaline **3aa** (Scheme 2-1). When **1aa** was treated with IBN in Ac_2O at room temperature, oxime **4** was obtained in 96% yield and quinoxaline **3aa** was not observed (Scheme 2-2). The treatment of **1aa** with radical trapping reagent TEMPO afforded oxime **4** and the *N*-nitroso compound **5** in 18% and 71% yield, respectively (Scheme 2-3). These results suggested that the nitrosation of enamine **1aa** involved a radical process. When oxime **4** was treated with Ac_2O at reflux for 4 h, compound **6** was obtained in 88% yield and quinoxaline **3aa** was obtained in 10% yield (Scheme 2-4). Finally, when compound **6** was refluxed in Ac_2O, with and without the addition of TEMPO, quinoxaline **3aa** was afforded in 95% and 90% yield, respectively (Scheme 2-5). These results revealed that compound **6** was the key intermediate in the formation of quinoxaline **3aa**, and its conversion to **3aa** did not involve a radical process. No reaction took place using *N*-arylimine **1n** as substrate (Scheme 2-6). When enamine **1o** was subjected to the optimal conditions, product **3oa** was not observed while *N*-phenylacetamide was obtained in 60% yield (Scheme 2-7).



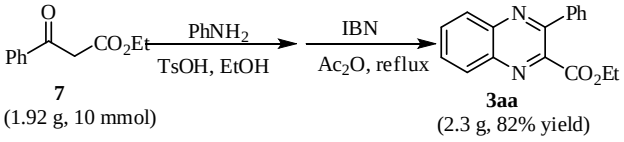
Scheme 2. Mechanistic Studies.

Based on the experimental results, a possible mechanism for the formation of quinoxaline **3aa** from *N*-aryl enamine **1aa** was proposed (Scheme 3). First, IBN is easily split into an •NO and an *i*-BuO• radical upon heating.[14] The addition of an •NO radical to enamine **1aa** gives intermediate **A**, which rapidly reacts with the *i*-BuO• radical to afford intermediate **B** and *i*-BuOH. Intermediate **B** then undergoes a [1,3]-H migration to yield oxime **4**.[9f,15] Esterification of oxime **4** with Ac_2O generates compound **6**, which undergoes a 6πe-azacyclization to yield intermediate **C**.[16] Finaly, elimination of HOAc affords product **3aa**. Alternatively, N−O bond cleavage of **6** and electrophilic cyclization under high reaction temperatures affords intermediate **D**.[17] Finally, **D** undergoes aromatization to yield product **3aa**. The key role of Ac_2O might be the production of ester **6**, thereby facilitating quinoxaline formation.



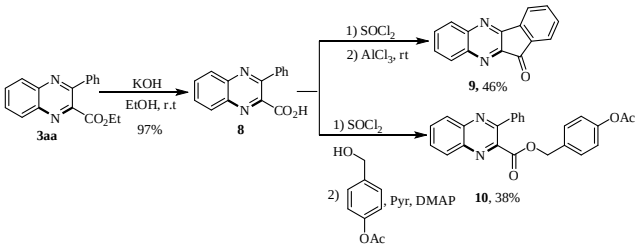
Scheme 3. Proposed Mechanism.

To further demonstrate the utility of this method, a one-pot preparation of quinoxaline **3aa** from *β*-carbonyl ester **7** was conducted on a gram scale. As shown in Scheme 4. 1.92 g of compound **7** could be condensed with $PhNH_2$ under heating, leading to *N*-phenyl enamine **1aa**. Then, IBN and Ac_2O was added to the mixture, yielding 2.3 g of quinoxaline **3aa** in 82% yield in a one-pot reaction. This protocol provides a facile approach to access quinoxalines.



Scheme 4. Gram Scale Preparation of Quinoxaline **3aa**.

Indeno[1,2-*b*]quinoxaline derivatives constitute a large number of potential bioactive agents.[18] Because our method proved to be efficient in the preparation of quinoxalines, the transformation of **3aa** to the indeno[1,2-*b*]quinoxaline scaffold was investigated. As shown in Scheme 5, hydrolysis of quinoxaline **3aa** with KOH afforded acid **8** in 97% yield. The reaction of **8** with $SOCl_2$, and followed by intramolecular acylation gave indeno[1,2-*b*]quinoxaline **9** in 46% yield. Meanwhile, treatment of **8** with $SOCl_2$ and sequential esterification with 4-(hydroxymethyl) phenyl acetate, afforded compound **10** in 38% yield. Analogues of compound **10** have been demonstrated that this group of quinoxalines possesses antimycobacterial activity against *M. tuberculosis* (Mtb).[19] The transformations reported here will allow access to these quinoxalines, furthering their potential use in pharmaceuticals.



Scheme 5. Applications of Quinoxaline **3aa**.

In summary, we have developed a IBN-mediated double C(sp^2)−H bond functionalization of *N*-aryl enamines to prepare various functionalized quinoxalines in good to excellent yields. Mechanistic studies revealed that the reaction proceeded through a *β*-imino oxime ester intermediate. Furthermore, a target quinoxaline was easily converted into two important quinoxaline scaffolds in two steps and in moderate yields.

Experimental Section

General procedure for the synthesis of quinoxaline 3aa. To a 10 mL round-bottom flask equipped with a magnetic stirring bar were added *N*-aryl enamine **1aa** (0.5 mmol), IBN (0.5 mmol, 1.0 equiv.) and Ac_2O (2.0 mL). The reaction mixture was stirred at room temperature for 10 min, and then was refluxed until the reaction was completed as monitored by TLC (2–18 h). At this time, the reaction was quenched by H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). Then, the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel with eluents (EtOAc/petroleum) to give product **3aa** as a yellow solid (0.127 g, 94%), mp: 65−66 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26–8.20 (m, 2H), 7.91–7.83 (m, 2H), 7.80–7.72 (m, 2H), 7.58–7.48 (m, 3H), 4.36 (q, J = 7.1 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 152.3, 145.8, 142.3, 139.9, 137.8, 131.7, 130.6, 129.6, 129.4, 128.7, 128.6, 62.4, 13.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}N_2O_2Na$ $[M+Na]^+$ 301.0948; found 301.0968.

Acknowledgements

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[16] Example for 6πe-azacyclization, see: T. Kobayashi, S. Hatano, H. Tsuchikawa, and S. Katsumura, *Tetrahedron Lett.* **2008**, *49*, 4349.

[17] Based on the results in Scheme 2-4, we did not propose the mechanism involving a radical process, though a radical process was proposed by Maroulis group, which might be caused by the EWG group. See: N. P. Xekoukoulotakis, C. P. Hadjiantoniou-Maroulis, and A. J. Maroulis, *Tetrahedron Lett.* **2000**, *41*, 10299.

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UPDATE

Isobutyl Nitrite-Mediated Synthesis of Quinoxalines through Double C−H Bond Amination of *N*-Aryl Enamines

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