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Hypervalent iodine(III)-induced oxidative [4+2] annulation of *o*-phenylenediamines and electron-deficient alkynes: direct synthesis of quinoxalines from alkyne substrates under metal-free conditions†

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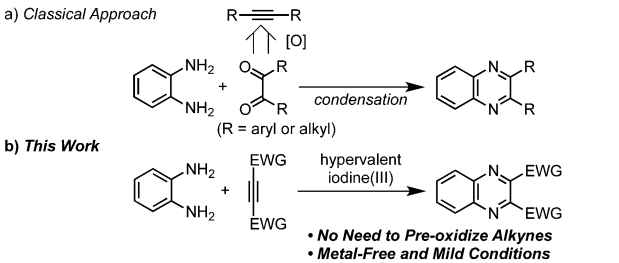
Hypervalent iodine(III)-induced oxidative [4+2] annulation of *o*-phenylenediamines and electron-deficient alkynes under metal-free conditions has been developed. The reaction allows for direct access to quinoxalines bearing two electron-withdrawing groups in an efficient manner.

Quinoxaline derivatives not only constitute an important class of biologically active agents,[1] but also find tremendous applications in materials science such as luminescent materials[2] and low-band-gap polymers.[3] Of the reported methods,[4] the most widely used approach involves condensation of *o*-phenylenediamines with 1,2-dicarbonyl compounds bearing electron-rich or neutral substituents, which are generally prepared by oxidation of upstream alkynes (Scheme 1a). On the other hand, the synthetic methods of the quinoxalines bearing electron-withdrawing groups (EWGs, *e.g.*, –COR, $-CO_2R$, $-SO_2R$) have been poorly explored,[5] although such compounds can serve as promising candidates for (opto)electronic materials[5a,6] and as versatile synthetic intermediates. Herein we present a hypervalent iodine(III) reagent-induced oxidative [4+2] annulation of *o*-phenylenediamines and electron-deficient alkynes (Scheme 1b), which allows for direct access to electron-deficient quinoxalines from alkynes instead of diketo substrates in an efficient manner.

Recently, we have reported an oxidative dimerization of anilines through the agency of a unique and powerful iodinating reagent, *tert*-butyl hypoiodite (*t*-BuOI), leading to aromatic azo compounds in an efficient and selective manner.[7] The key to the success is an efficient two-fold iodination of nitrogen-center, forming $ArNI_2$ species which then serves as an electrophile to form N–N bonds. Based on the findings, we envisioned that a tandem process consisting of (i) the Michael-addition of *o*-phenylenediamine to an electron-deficient alkyne and (ii) a subsequent nucleophilic attack on the highly



Scheme 1 Synthetic approaches to quinoxalines.

electrophilic N-center (NI_2) by the resulting enamine could form a dihydro-quinoxaline skeleton. The subsequent elimination of HI would produce quinoxalines. At the outset, we attempted the oxidative annulation of *o*-phenylenediamine (**1a**) and DMAD (**2a**) as a model reaction (Table 1). However, contrary to our preliminary expectation, the results were disappointing: the treatment of an equimolar mixture of **1a** and **2a** with *t*-BuOI (4 equiv.) at −20 °C gave *cis*,*cis*-muconononitrile (**5**) as a major product, which should be formed through oxidative dearomatization and the following C–C bond cleavage of the benzene core (entries 1 and 2).[8] These results clearly suggested that *t*-BuOI is not an appropriate oxidant for the aimed transformation, probably due to the rapid H–I exchange and dearomatization processes of **1a** prior to Michael-addition. After extensive screening of iodine-containing reagents, we were delighted to find that the employment of phenyliodine diacetate (PIDA) was highly effective for the progression of the desired annulation (entries 3–6). It should be noted that protecting group-free phenylenediamines, which are usually labile to oxidation reactions, were applicable to the annulation. Hypervalent iodine(III) compounds have been emerging as powerful reagents in organic synthesis due to their diverse reactivity as well as to high-availability and environmentally-benign character.[9] Specifically, PIDA and its derivatives have been utilized to develop privileged oxidative C–N bond forming reactions.[10,11] Nonetheless, to the best of our knowledge, hypervalent iodine(III)-mediated oxidative annulation reaction that leads to quinoxaline, has not been reported to date.[12] Intriguingly, a significant solvent effect was observed (entries 3–6): as the polarity of solvent increased, the yield of **3a** was enhanced while that of the by-product **4a**[13] was decreased.[14] Other representative

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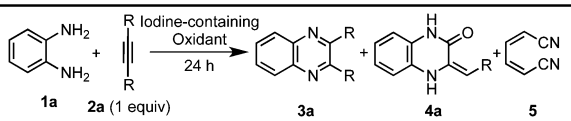
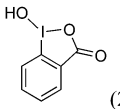
† Electronic supplementary information (ESI) available: Procedure for the synthesis and experimental data for quinoxalines and NMR spectra. See DOI: 10.1039/c3cc45469j

Table 1 Summary of the screening of the reaction conditions[a]



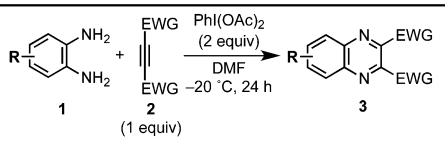
Entry	Oxidant (equiv.)	Solvent	T [°C]	Yield[b] [%] 3a	4a	5
1	*t*-BuOI (4)	THF	−20	12	0	64
2	*t*-BuOI (4)	DME	−20	2	0	33
3	$PhI(OAc)_2$ (2)	CH_2Cl_2	−20	5	40	0
4	$PhI(OAc)_2$ (2)	THF	−20	63	18	0
5	$PhI(OAc)_2$ (2)	DME	−20	60[c]	4[c]	0
6	$PhI(OAc)_2$ (2)	DMF	−20	92[c]	4[c]	0
7	$PhI(OCOCF_3)_2$ (2)	DMF	−20	3	—	0
8	PhI=O (2)	DMF	−20	0	—	0
9	 (2)	DMF	−20	0	—	0
10	PhI(OH)OTs (2)	DMF	−20	0	—	0
11	—	DMF	−20	0	21	0

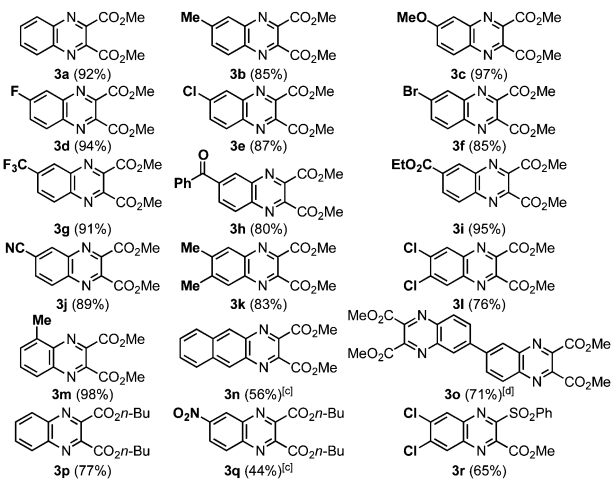
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), and iodine-containing oxidant (0.50–1.0 mmol) were mixed in a solvent (3 mL) at the temperature in the column and stirred for 24 h. [b] ^{1}H NMR yields. [c] Isolated yield.

hypervalent iodine(III) reagents were found ineffective for the annulation (entries 7–10), and PIDA was indispensable for the annulation reaction (entry 11).

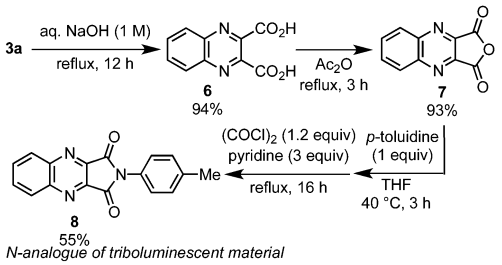
Having optimized the reaction conditions, the scope of the annulation was investigated (Table 2). A wide variety of diamines bearing an electron-rich, -neutral, and -deficient substituent reacted

Table 2 Scope of the oxidative [4+2] annulation[a,b]





[a] Reaction conditions: **1** (0.25 mmol), **2** (0.25 mmol), and $PhI(OAc)_2$ (0.50 mmol) were mixed in DMF (3 mL) at 20 °C and stirred for 24 h. [b] The values in parentheses indicate the yields of quinoxaline products. [c] Reaction time: 48 h. [d] [1,1′-biphenyl]-3,3′,4,4′-tetraamine (**1o**) (0.25 mmol), **2a** (0.50 mmol), $PhI(OAc)_2$ (1.0 mmol) were employed.



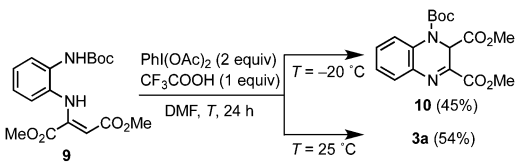
Scheme 2 Derivatization of **3a**.

with DMAD to give corresponding quinoxalines **3b–3j** in high yields. Multiple-substituted diamines afforded **3k** and **3l**. Furthermore, sterically demanding diamines gave the corresponding product **3m** in excellent yield. Although the reaction of naphthalene-2,3-diamine with DMAD required prolonged time, N-heteroacene **3n**, which constitutes a family of electron-transporting materials,[15] was obtained in 56% yield. Using the method, biquinoxaline **3o** was prepared in good yield. In respect to alkyne substrates, dibutyl acetylenedicarboxylate was successfully applied to the reaction conditions to afford **3p** and **3q** in 77% and 44% yield, respectively. In addition, an unsymmetrical alkyne having an ester and a sulfonyl group also successfully underwent the annulation to give **3r** in good yield.

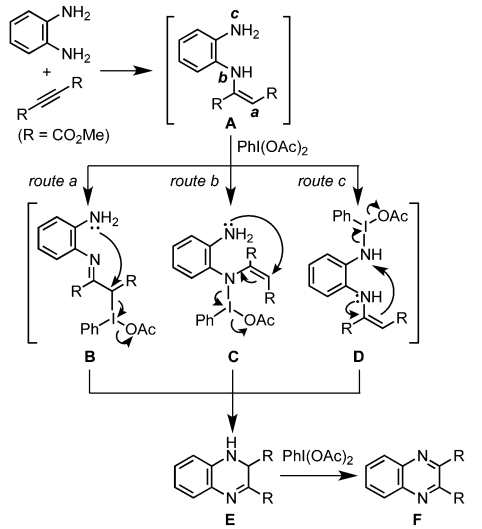
Taking advantage of the ester functionality, **3a** was diversely derivatized into functionalized quinoxalines (Scheme 2). For example, diester of **3a** easily underwent hydrolysis to give dicarboxylic acid **6** in high yield, which was further efficiently converted to **7** by dehydration. Moreover, anhydride **7** was successfully transformed into imide-fused quinoxaline **8** by condensation with *p*-toluidine, which is an N-analogue of triboluminescent material.[16] It is noted that such compounds are quite difficult to prepare by traditional condensation methods.[17]

To investigate the reaction pathways, several experiments were conducted as follows: enamine **9**, which was readily prepared by the Michael-addition of *N*-Boc-protected *o*-phenylenediamine to DMAD,[13] was treated with PIDA in the presence of trifluoroacetic acid (Scheme 3).[18] At −20 °C, **9** underwent oxidative cyclization to give *N*-Boc dihydroquinoxaline **10** in 45% yield,[19] while **9** was quantitatively recovered in the absence of PIDA. In contrast, at room temperature, quinoxaline **3a** was obtained in 54% yield. In conjunction with the fact that DMAD does not react with PIDA in the absence of *o*-phenylenediamine, the most likely intermediate of the annulation would be the deprotected counterpart of the Michael-adduct **9** as preliminary assumed.

On the basis of the experimental results and knowledge accumulated from the literature about hypervalent iodine(III)-mediated oxidative C–N bond forming reactions using enamine substrates,[20–22] conceivable reaction pathways are illustrated in Scheme 4. The reaction would start with Michael addition



Scheme 3 Oxidative cyclization of enamine **9**.



Scheme 4 Conceivable reaction pathways.

of *o*-phenylenediamine to DMAD, forming the enamine intermediate **A**, which has three possible reactive points when reacting with PIDA, namely, β-carbon of enamine (**a**),[20] enamine nitrogen (**b**),[21] and nitrogen on the benzene moiety (**c**).[22] Accordingly, three species should be extrapolated as intermediates prior to cyclization: (i) α-iodo(III) imine **B** (route a); (ii), (iii) enamines **C** and **D** (routes b and c, respectively). Successive cyclizative nucleophilic substitution on the iodine-attached sp^3-carbon (from **B**), on the enamine carbon in a pseudo-S_N2' manner (from **C**), or on the electrophilic N-center (from **D**) would provide a common intermediate **E**. Oxidative aromatization of **E** with another equivalent of PIDA should lead to quinoxaline **F**. Ma and Lei reported an oxidative dimerization of aromatic amines using PIDA to give azobenzenes.[22] No azo compounds were detected in our system, suggesting that the pathway *via* intermediacy of **D** (route c) might be excluded. On the one hand, according to the reactivity of carbonyl-conjugated enamines (*i.e.*, enaminones),[23] electrophilic reagents, including iodine electrophiles such as BTMA·ICl_2,[24a] $I(Py)_2BF_4$,[24b] and $CF_3CH_2I(OH)(OTs)$,[24c] react exclusively at the enamine β-carbon. Taken together, we believe that the most likely reaction pathway is route a, although routes b, c, and other possible pathways cannot be excluded completely.[25]

In summary, a simple, efficient and metal-free synthesis of electron-deficient quinoxalines through oxidative annulation of *o*-phenylenediamines and alkynes has been developed. Further investigations into the mechanism and application to the construction of functional materials are currently underway in our laboratory.

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