Heterocycles

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Synthesis of Highly Functionalized Polycyclic Quinoxaline Derivatives Using Visible-Light Photoredox Catalysis**

*Zhi He, Minwoo Bae, Jie Wu, and Timothy F. Jamison**

Abstract: *A mild and facile method for preparing highly functionalized pyrrolo[1,2-a]quinoxalines and other nitrogen-rich heterocycles, each containing a quinoxaline core or an analogue thereof, has been developed. The novel method features a visible-light-induced decarboxylative radical coupling of ortho-substituted arylisocyanides and radicals generated from phenyliodine(III) dicarboxylate reagents and exhibits excellent functional group compatibility. A wide range of quinoxaline heterocycles have been prepared. Finally, a telescoped preparation of these polycyclic compounds by integration of the in-line isocyanide formation and photochemical cyclization has been established in a three-step continuous-flow system.*

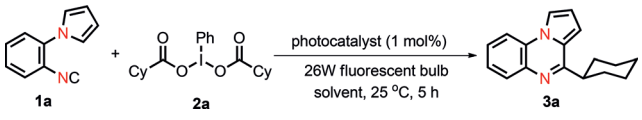
Among subclasses of quinoxaline derivatives, pyrrolo[1,2-*a*]quinoxalines or analogues with similar fusion of other nitrogen-rich five-membered heterocycles have been found in a variety of complex compounds displaying interesting biological activities, and have therefore received particular attention in the pharmaceutical industry.[1] However, only a few procedures for the preparation of pyrrolo[1,2-*a*]quinoxalines or other heterocycle-fused analogues thereof are described in the literature.[2] For instance, Kobayashi and coworkers recently reported the preparation of aminoalkyl or hydroxyalkyl pyrrolo[1,2-*a*]quinoxalines from iminium salts and aldehydes or ketones.[2f,g] Although conducted under ambient temperature, these methods are somewhat limited in functional-group compatibility because of the need for catalysis by strong and corrosive Lewis acids.

Herein, we describe a novel synthetic method in which 4-alkylated pyrrolo[1,2-*a*]quinoxaline derivatives and other nitrogen-rich heterocycle-fused analogues thereof are efficiently obtained from *ortho*-heterocycle-substituted arylisocyanides by employing visible-light induced decarboxylative radical cyclization under ambient conditions. The methodology demonstrates excellent functional-group tolerance, which enables preparation of a wide range of highly functionalized polycyclic quinoxalines. Further incorporation of the photochemical reaction in a three-step telescoping process involving the in-line isocyanide formation by using a continuous-flow microreactor system reveals its potential in sustainable pharmaceutical production.

Inspired by the recent development of constructing of phenanthridine derivatives through the use of biaryl isocyanides as radical acceptors which could undergo reaction cascades involving C-radical addition with subsequent homolytic aromatic substitution (HAS), oxidation, and deprotonation,[3] we were curious if a similar strategy could be employed to construct pyrrolo[1,2-*a*]quinoxalines or other heterocycle-fused quinoxaline derivatives. Given that visible-light-induced photoredox catalysis has proven to be a powerful approach to generate C radicals under mild reaction conditions,[4] we decided to investigate the synthesis of 4-alkylated heterocycle-fused quinoxalines from *ortho*-heterocycle-substituted arylisocyanides by a photoredox decarboxylative radical cyclization, using phenyliodine(III) dicarboxylates as an easily accessible and environmentally friendly source of alkyl radicals.[5]

We opted to investigate the photoredox transformation by using module substrates 1-(2-isocyanophenyl)-1*H*-pyrrole (**1a**) and phenyliodine(III) dicyclohexanecarboxylate (**2a**) (Table 1). The iridium complex [*fac*-Ir(ppy)$_3$] was chosen as the photocatalyst. When a solution of **1a** and **2a** in DMF was irradiated with a household 26 W compact fluorescent bulb in the presence of only 1 mol% of [*fac*-Ir(ppy)$_3$] for 5 hours, the desired pyrrolo[1,2-*a*]quinoxaline product **3a** was obtained smoothly in excellent yield (Table 1, entry 1). In contrast, negative results were observed in the absence of the metal

Table 1: Reaction conditions evaluation.[a]



Entry	Photocatalyst	Additives	Solvent	Yield [%][b]
1	[*fac*-Ir(ppy)$_3$]	–	DMF	73
2[c]	–	–	DMF	0
3[d]	[*fac*-Ir(ppy)$_3$]	–	DMF	0
4	[*fac*-Ir(ppy)$_3$]	–	MeCN	32
5	[Ir(dtbbpy)(ppy)$_2$]PF$_6$	–	MeCN	65
6	[*fac*-Ir(ppy)$_3$]	H_2O[e]	DMF	70
7	[*fac*-Ir(ppy)$_3$]	Et_3N[e]	DMF	71

[a] Unless stated otherwise, the reaction was carried out with **1a** (1.0 equiv), **2a** (1.5 equiv), and photocatalyst (1 mol%) in the indicated solvent and irradiated with 26 W compact fluorescent lamp for 5 h. [b] Yield of isolated product. [c] The reaction was irradiated in the absence of metal catalysts. [d] The reaction was carried out under dark. [e] 5.0 equiv of additives was added. DMF = *N*,*N*-dimethylformamide, ppy = phenyl pyridine.

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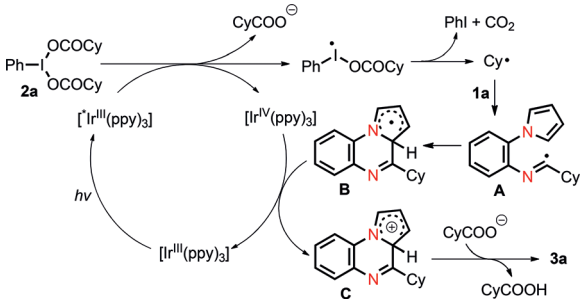
catalyst or visible light (entry 2 and 3). When MeCN was used instead of DMF in the reaction, the yield of **3a** decreased significantly because of the poor solubility of the catalyst (entry 4). In contrast, replacement of [*fac*-Ir(ppy)$_3$] with the soluable complex [Ir(dtbbpy)(ppy)$_2$]PF$_6$ led to a satisfactory yield of **3a** (entry 5). It is worth mentioning that despite the invovlement of a hypervalent iodine oxidant and plausible radical species, the photochemical process was found compatible with moisture and an amine base (entry 6 and 7).

A plausible catalytic cycle for the [*fac*-Ir(ppy)$_3$]-catalyzed visible-light-mediated cyclization process could thus be proposed (Scheme 1). The initial interaction of **2a** with the



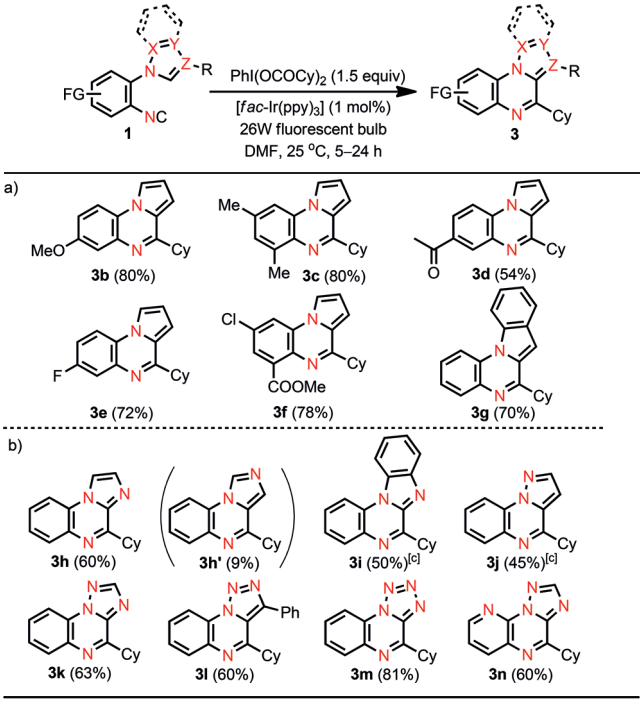
Scheme 1. Catalytic cycle for the formation of **3a**.

excited state of the catalyst, [*Ir^{III}(ppy)$_3$], which is formed under irradiation, triggers the generation of a cyclohexyl radical and the strong oxidant [Ir^{IV}(ppy)$_3$]. The resulting alkyl radical subsequently adds to **1a** to produce an imidoyl radical **A**, which undergoes intramolecular homolytic aromatic substitution with the nearby pyrrole ring to give the radical intermediate **B**. The radical **B** is then oxidized by [Ir^{IV}(ppy)$_3$] to generate the cation **C** and regenerate the catalyst [*fac*-Ir(ppy)$_3$] to complete the photoredox cycle. Ultimately, **C** could be easily deprotonated by the carboxylate anion to generate the final pyrrolo[1,2-*a*]quinoxaline product **3a**.

The robustness of the photoredox cyclization turned our attention to evaluating its scope in the construction of other pyrrolo[1,2-*a*]quinoxaline core structures. As shown in Table 2a, a range of substituted 1-(2-isocyanoaryl)-*1H*-pyrroles reacted smoothly with phenyliodine(III) dicyclohexanecarboxylate in the presence of [*fac*-Ir(ppy)$_3$] to give the corresponding pyrrolo[1,2-*a*]quinoxaline products in good to excellent yields. It is interesting that substrates equipped with the indole system (**3g**), which are vulnerable to oxidative conditions, were also tolerated in the transformation.

We envisioned that replacement of the pyrrole ring with other five-membered nitrogen-rich aromatic heterocycles in the starting arylisocyanides would supply opportunities to afford new classes of heterocycle-fused quinoxaline analogues through a similar cyclization process. A set of new functionalized isocyanides equipped with nitrogen-rich heterocyclic groups, including imidazole, benzoimidazole, pyrazole, 1,2,4-triazole, 1,2,3-triazole, and tetrazole, was subjected to the photoredox reaction (Table 2b). These new arylisocyanide reagents successfully afforded the corresponding nitrogen-rich polycyclic quinoxalines (**3h–n**) with satisfactory yields,

Table 2: Variation in the heterocycle-fused quinoxaline core structures.[a,b]

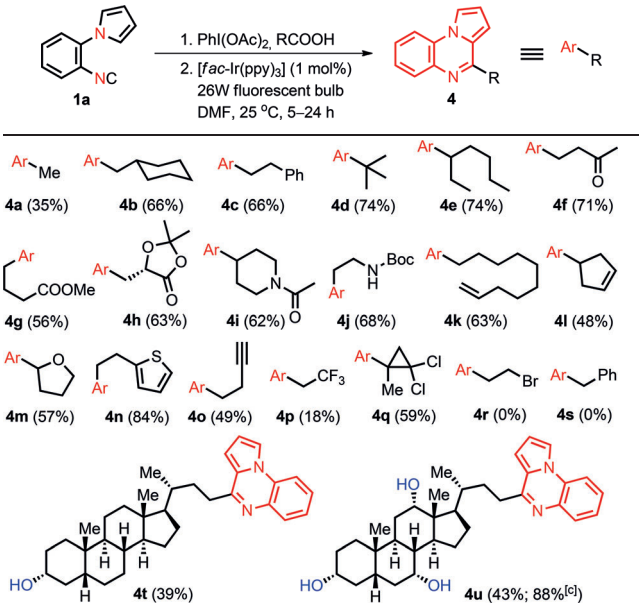


[a] Unless stated otherwise, the reactions were carried out using purified arylisocyanide **1** (1.0 mmol), PhI(OCOCy)$_2$ **2a** (1.5 mmol), and [*fac*-Ir(ppy)$_3$] (0.001 mmol, 1 mol%) in DMF (5 mL), and irradiated with 26 W compact fluorescent lamp for 5–24 h. [b] All yields within parentheses are yields of isolated product after silica gel chromatography. [c] The yields were based on aryl formamides, from which the crude arylisocyanide intermediates were obtained and directly subjected to the photochemical reaction without further purification (see the Supporting Information for details).

thus revealing excellent reactivity of five-membered nitrogen-rich aromatic heterocycles towards the intramolecular HAS process. It is noteworthy that the imidazole-substituted isocyanide afforded a mixture of regioisomeric products, **3h** and **3h′**, in a 6.7:1.0 ratio.

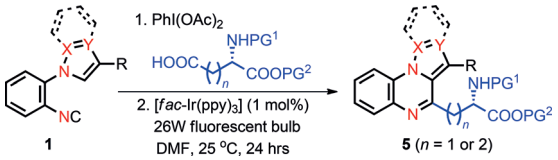
To further assess the functional-group tolerance of this transformation, we explored the reactivity of a wide range of phenyliodine(III) dicarboxylates (Table 3). These phenyliodine(III) dicarboxylate reagents can be easily prepared from the corresponding functionalized carboxylic acids by ligand exchange with phenyliodine(III) diacetate (DIB) and directly used in the visible-light photoredox reaction without further purification. As shown in Table 3, various primary, secondary, and tertiary aliphatic carboxylic acids equipped with different functional groups were employed and found to be effective in affording the desired cyclization products. Functional groups such as alkenes (**4k** and **4l**) or alkynes (**4o**) which are potentially susceptible to radical attacks were tolerated. While the chlorinated acid **4q** proceeded smoothly in the two-step tandem process, the trifluoropropanoic acid only afforded the desired product **4p** in 18% yield, presumably because of the strong electron-withdrawing inductive effect of the trifluoromethyl group which could obstruct the radical insertion. In addition, the phenyliodine(III) dicarbox-

Table 3: Preparation of 4-alkylated pyrrolo[1,2-*a*]quinoxalines.[a,b]



[a] Reaction conditions: 1) aliphatic carboxylic acid (2.0 equiv), PhI(OAc)$_2$ (1.0 equiv); 2) **1a** (1.0 mmol), PhI(OCOR)$_2$ **2** (1.5 mmol), [*fac*-Ir(ppy)$_3$] (0.001 mmol, 1 mol%) in DMF (5 mL) was irradiated with 26 W compact fluorescent lamp for 24 h. [b] All yields in parentheses are yields of isolated product after silica gel chromatography. [c] Yields based on recovered starting isocyanides.

Table 4: Preparation of unnatural α-amino acids.[a]



Entry	α-Amino acid	Product	Yield [%][b]
1	Boc-Asp-OBzl	**5a**	40
2	Boc-Glu-OBzl	**5b**	52
3	Fmoc-Glu-OAll	**5c**	38
4	Boc-Asp-OBzl	**5d**	34
5	Boc-Glu-OBzl	**5e**	30
6	Boc-Asp-OBzl	**5f**	25 (60%)[c]

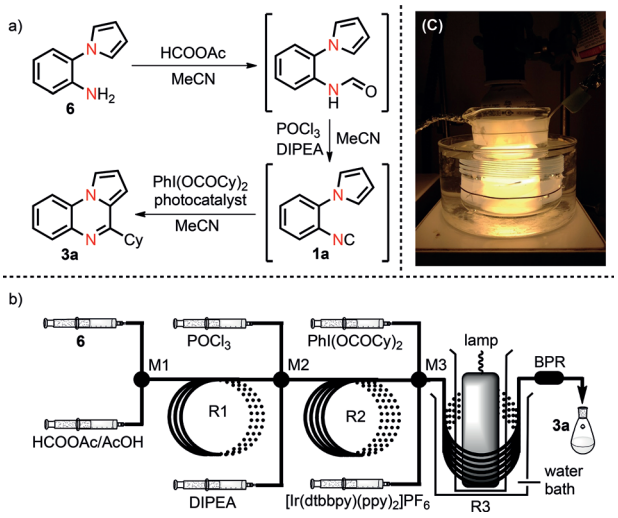
[a] Reaction conditions: 1) partially protected α-amino acid (2.0 equiv), PhI(OAc)$_2$ (1.0 equiv); 2) **1** (1.0 mmol), PhI(OCOR)$_2$ **2** (1.5 mmol), [*fac*-Ir(ppy)$_3$] (0.001 mmol, 1 mol%) in DMF (5 mL) was irradiated with 26 W compact fluorescent lamp for 24 h. [b] Yields of isolated product after silica gel chromatography. [c] Yields based on recovered starting isocyanides. All = allyl, Boc = *tert*-butoxycarbonyl, Bz = benzoyl, Fmoc = 9-fluorenylmethoxycarbonyl, PG = protecting group.

ylate derived from 3-bromopropanoic acid was found, unfortunately, to be incompatible with the photochemical process. The reaction resulted in an inseparable tar and the desired product **4r** was not observed. It is highly possible that the vulnerable carbon–bromine bond was destroyed by a radical atom transfer process during the photoredox reaction. Two steroid carboxylic acids, lithocholic acid and cholic acid, were also subjected to the isocyanide cyclization process. Both of these bile acid derivatives afforded the desired quinoxaline-modified steroid architecture (**4t** and **4u**) in moderate yields. Notably the free hydroxy groups in these naturally occurring carboxylic acids are compatible with the photoredox transformation. Phenylacetic-acid-derived reagents proved unsucessful, however, probably because of the nature of the benzylic radical which forms upon decarboxylation.

Encouraged by the excellent functionality tolerance of the photoredox reaction, we envisioned a strategy to access new classes of unnatural amino acids by incorporating the polycyclic quinoxaline core with an amino acid residue through a selective monodecarboxylation of partially protected α-amino diacids. A variety of phenyliodine(III) dicarboxylate reagents derived from partially protected aspartic acid (Asp) and glutamic acid (Glu) equipped with different protecting groups were subjected to the photoredox condition (Table 4). As expected, a series of unprecedented unnatural amino acid derivatives having an aromatic polycyclic tail, which is separated from the amino acid terminus by one or two rotatable bonds, was obtained. It is anticipated that the unique structures of these molecules will find utility in drug discovery and biological research.

Armed with the promise for the facile construction of highly functionalized heterocyle-fused quinoxaline derivatives by a photochemical isocyanide radical cyclization, we decided to integrate this transformation with the upstream isocyanide preparation in a multistep telescoping fashion by using continuous-flow techniques. The significance of the envisioned flow process is expected to be threefold: 1) As a result of its small dimensions, microreactor technology minimizes the exposure to toxic and foul smelling isocyanide intermediates;[6] 2) The high surface-to-volume ratios typical of flow reactors is particularly advantageous for photochemical synthesis since it allows more efficient irradiation of the reaction medium and a reduction in reaction time;[7,8] 3) The continuous telescoping protocol avoids unnecessary operations for each individual step and enhances the efficiency of the whole process, and would be better suited to the demands of industrial production.

Arylisocyanide reagents are usually generated by a two-step transformation involving formamide formation from



Scheme 2. Continuous-flow synthesis of the pyrrolo[1,2-*a*]quinoxaline **3a**.

substituted analines and its dehydration using phosphorus oxychloride ($POCl_3$) in the presence of amine base. A reaction sequence (Scheme 2a) targeting the preparation of **3a** was therefore chosen as the model transformation to test the feasibility of the three-step continuous-flow process. An integrated flow setup (Figure 2b) consisting of one polyetheretherketone (PEEK) T-mixer (M1), two PEEK Cross-mixers (M2 and M3), three perfluoroalkoxyalkane (PFA) tubing reactors (R1, R2, and R3), and a backpressure regulator (BPR) was assembled to carry out the reactions (see the Supporting Information for details). Reactor R3 is placed around a 26 W compact fluorescent bulb and immersed in a water-cooling bath (Scheme 2c). Considering solubility and compatibility of chemical intermediates or byproducts, we chose acetonitrile (MeCN) as a major solvent medium for the whole flow system. The complex $[Ir(dtbbpy)(ppy)_2]PF_6$ was used as the photocatalyst accordingly because of its excellent solubility in MeCN.

The first step of the flow synthesis was thus the fast formamide formation through the combination of a MeCN solution of the aniline **6** with a formic acetic mix anhydride in M1 and R1 (residence time: $t_R = 2.3$ min). The resulting mixture, containing the formamide intermediate and excess of acetic acid, was then merged with the stream of $POCl_3$ in MeCN and a dichloromethane solution of *N*,*N*-diisopropylethylamine (DIPEA) in M2 and R2 for the generation of the isocyanide intermediate by formamide dehydration ($t_R = 2.8$ min). It was found that a large excess of $POCl_3$ and DIPEA has to be applied to consume the remaining acetic acid from the previous step and to achieve a decent conversion of the formamide intermediate (see the Supporting Information for details).

The upstream reaction solution subsequently proceeds to merge with the MeCN solution of $[Ir(dtbbpy)(ppy)_2]PF_6$ and $PhI(OCOCy)_2$ simultaneously in mixer M3 and enters into the tubing reactor R3 for the visible-light photoredox cyclization. The reaction temperature was controlled at around 25 °C by the surrounding water-cooling bath. The photochemical transformation was compatible with all by-products or remaining reagents from previous steps and worked efficiently in the flow system. A residence time (t_R) of 9.5 minutes was enough to reach a full conversion of the isocyanide intermediate, while 5 to 24 hours of irradiation is usually required in batch setups. After the three-step one-flow telescoping process over a total linear residence time of 14.6 minutes, we successfully obtained the final pyrrolo[1,2-*a*]quinoxaline product **3a** in a moderate total yield of 47% (throughput: 6.3 μmol min^{-1}) from the aniline starting reagent (approx. 78% yield per step).

In summary, we have discovered a mild and efficient way of preparing highly functionalized 4-alkylated polycyclic quinoxalines by a visible-light-induced decarboxylative radical cyclization of arylisocyanides. The method utilizes phenyliodine(III) dicarboxylates as the easily accessible and environmentally friendly radical precursors, and demonstrates excellent functional-group compatibility. Telescoped preparation of pyrrolo[1,2-*a*]quinoxaline by integration of in-line isocyanide formation and photochemical cyclization have been achieved in a three-step continuous-flow system, thus revealing the potential of this chemistry in high-throughput production which would enable further exploration of such compounds in drug discovery.

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Communications

Heterocycles

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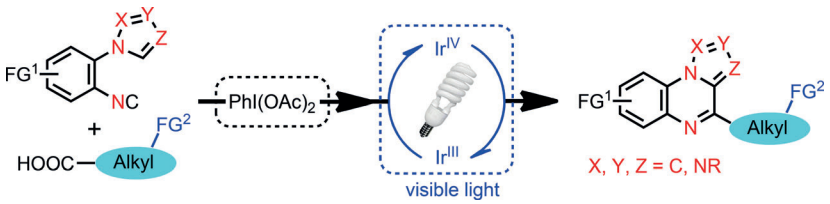
Synthesis of Highly Functionalized Polycyclic Quinoxaline Derivatives Using Visible-Light Photoredox Catalysis



Full of nitrogen: Highly functionalized pyrrolo[1,2-*a*]quinoxalines and other nitrogen-rich polycyclic quinoxaline analogues have been obtained by a visible-light-induced decarboxylative radical cyclization of arylisocyanides using phenyliodine(III) dicarboxylate reagents under mild reaction conditions. A telescoped preparation of these polycyclic compounds has been established by using a three-step continuous-flow system.

