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Synthesis of isoquinolines *via* visible light-promoted insertion of vinyl isocyanides with diaryliodonium salts†

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A synthetic strategy for multi-substituted isoquinoline derivatives has been developed using visible light-promoted vinyl isocyanide insertion with diaryliodonium salts at room temperature. The methodology presented here represents the first example of isoquinoline synthesis *via* somophilic isocyanide insertion.

Isoquinoline and its derivatives are widely present in numerous natural products, biologically active molecules and pharmaceutical drugs.[1] Traditional isoquinoline syntheses primarily rely on Friedel–Crafts type acylation, such as Bischler–Napieralski and Pomeranz–Fritsch reactions (Fig. 1A).[2] These methods are normally carried out under acidic conditions and are limited to electron-rich carbocycles. Therefore, the development of new routes to isoquinolines is of current research interest.[3,4] One of the most convenient strategies to construct isoquinoline frameworks is the transition metal-catalyzed C–H activation of aryl imines, oximes, amines or azides with alkynes (Fig. 1B).[3] Noble metal catalysts, such as palladium, rhodium and ruthenium, and elevated temperatures are necessary to promote these transformations.[4] To the best of our knowledge, no strategies based on homolytic aromatic substitution (HAS) have been reported to construct isoquinoline frameworks.[5]

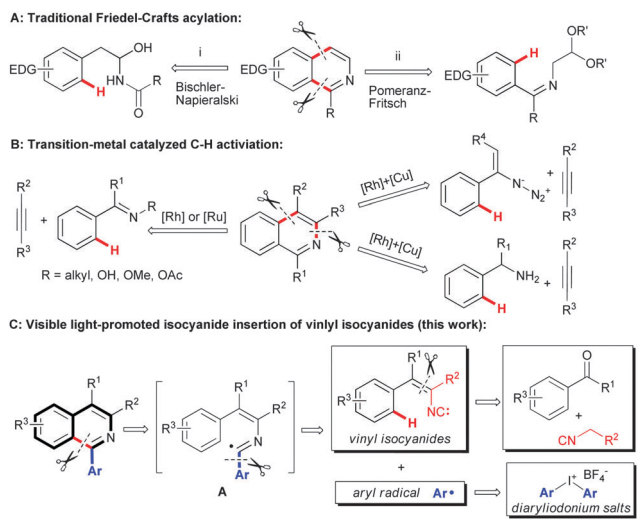

Fig. 1 Strategies for construction of isoquinolines.

With our recent research interests on visible light-promoted somophilic isocyanide insertion,[6,7] we speculated that isoquinoline synthesis from vinyl isocyanides *via* the HAS pathway could be accomplished using this strategy. Compared with enormous recent research interests in synthetic applications of aromatic isocyanides,[8] the chemistry of vinyl isocyanides remains largely unexplored,[9] which inspires us to investigate the reactivity and synthetic applications of vinyl isocyanides. It is envisaged that the somophilic addition of aryl radicals to the aryl-substituted vinyl isocyanides will lead to the imidoyl radical **A** (Fig. 1C), which upon an intramolecular HAS reaction will give the isoquinoline skeleton. While vinyl isocyanides can be prepared by the condensation of aryl ketones/aldehydes with isocyanides,[10] aryl radicals can be easily accessed from diaryliodonium salts[11] under photoredox catalysis.[12] Based on this blueprint and as a part of our ongoing efforts on *de novo* synthesis of aromatic heterocycles using triple bond insertions,[13] herein we report the first example of visible light-mediated vinyl isocyanide insertion as a modular approach to synthesize highly-substituted isoquinolines, which are potent non-benzodiazepine peripheral benzodiazepine receptor (PBR) ligands.[14]

We chose vinyl isocyanide **1a** and diphenyliodonium tertafluoroborate **2a** as model substrates to screen the optimal conditions for the visible light-mediated formation of the isoquinoline framework. $Ir(ppy)_2(dtbbpy)PF_6$ ($E_{1/2}^{IV/*III} = -0.96$ V *vs.* SCE), which has been proved to be an efficient reductant to produce phenyl radicals from **2a** under visible light irradiation,[11] was firstly tested as a photocatalyst. When a solution of **1a** and **2a** in CH_3CN was irradiated with 3 W white LED in the presence of $Ir(ppy)_2(dtbbpy)PF_6$ and Na_2CO_3 for 24 h, the desired isoquinoline **3a** was obtained in 47% isolated yield, structure of which was established ambiguously by the single crystal

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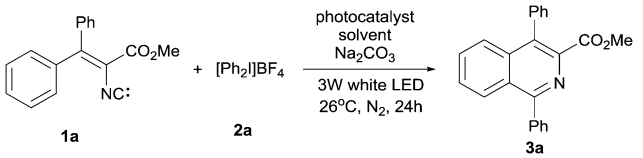
Table 1 Optimization of reaction conditions[a]



Entry	Photocatalyst	Solvent	Yield[b] (%)
1	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	47
2	$Ir(ppy)_2(dtbbpy)PF_6$	DMF	39
3	$Ir(ppy)_2(dtbbpy)PF_6$	DMSO	26
4	$Ir(ppy)_2(dtbbpy)PF_6$	CH_2Cl_2	0
5	$Ir(ppy)_2(dtbbpy)PF_6$	MeOH	74
6	***fac*-Ir(ppy)$_3$**	**MeOH**	**83**
7	$Ru(bpy)_3Cl_2$	MeOH	44
8	$Ru(Phen)_3Cl_2$	MeOH	41
9	None	MeOH	No reaction
10[c]	*fac*-Ir(ppy)$_3$	MeOH	No reaction

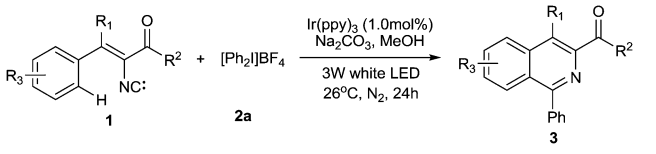
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Na_2CO_3 (0.2 mmol) and photocatalyst (0.002 mmol, 1.0 mol%) in indicated solvent (4.0 mL) was irradiated by 3 W white LED at 26 °C for 24 h. [b] Isolated yield. [c] No irradiation.

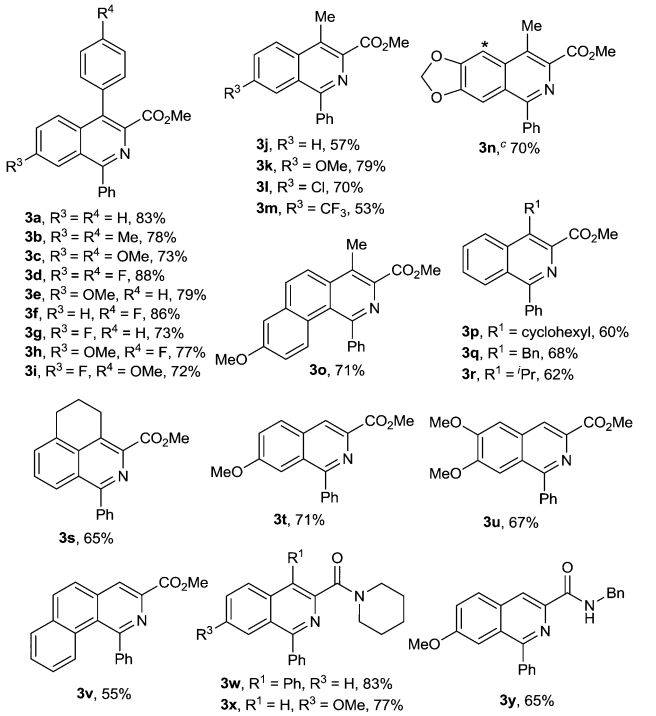
X-ray diffraction analysis[15] (Table 1, entry 1). With the screening of solvents, we found that DMF, DMSO and CH_2Cl_2 were inferior to CH_3CN with less than 40% yield (entries 2–4). To our delight, 74% yield was achieved when MeOH was used as the solvent (entry 5). Different photocatalysts were then investigated. The best chemical yield (83%) was obtained with the full consumption of **1a** when *fac*-Ir(ppy)$_3$ ($E_{1/2}^{IV/*III}$ = −1.73 V *vs.* SCE) was used because of its superior reductive potential at the excited state compared with $Ir(ppy)_2(dtbbpy)PF_6$ (entry 6). The ruthenium-based photocatalysts, such as $Ru(bpy)_3Cl_2$ ($E_{1/2}^{III/*II}$ = −0.81 V *vs.* SCE) and $Ru(Phen)_3Cl_2$ ($E_{1/2}^{III/*II}$ = −0.87 V *vs.* SCE), gave only less than 50% yields due to their lower reductive potential at excited states (entries 7 and 8). Control experiments verified the necessity of a photocatalyst and irradiation (entries 9 and 10).

To explore the scope of this transformation, we used a variety of vinyl isocyanides to react with **2a** under the established optimized conditions (Table 2). All reactions with diaryl ketone-derived vinyl isocyanides worked quite well and the desired isoquinolines **3a–i** were produced in satisfactory yields (72–88%). The substitutions on both benzene rings did not affect this transformation significantly. Aliphatic aryl ketone-derived vinyl isocyanides **1j–s** were also tested and the results showed a slightly lower reactivity. But acceptable yields (53–79%) of the corresponding isoquinolines **3j–s** could be obtained. When aryl aldehyde-derived vinyl isocyanides were employed, it was found that only electron-rich aryl aldehyde-derived vinyl isocyanides **1t–v** could go through this reaction to give the isoquinolines **3t–v** in 55–71% yields. Electron-deficient aryl aldehyde-derived vinyl isocyanides did not work at all. Amide-based vinyl isocyanides also worked quite well, the corresponding isoquinolines **3w–y** were generated in good yields (65–83%).

We then evaluated the diaryliodonium salts containing diverse substitutions in this visible light-promoted isoquinoline synthesis, as shown in Table 3. A variety of diaryliodonium salts were explored. All of them succeeded in providing the desired 1-aryl isoquinolines **4a–l** in 65–90% yields. The steric effect did not affect this transformation significantly. Hindered mesityl and *o*-Cl-phenyl-derived

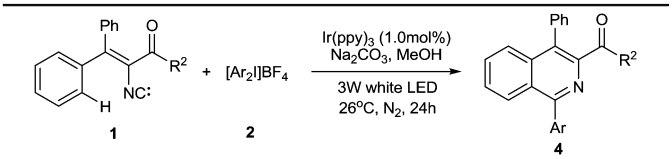
Table 2 Scope of vinyl isocyanides[a,b]

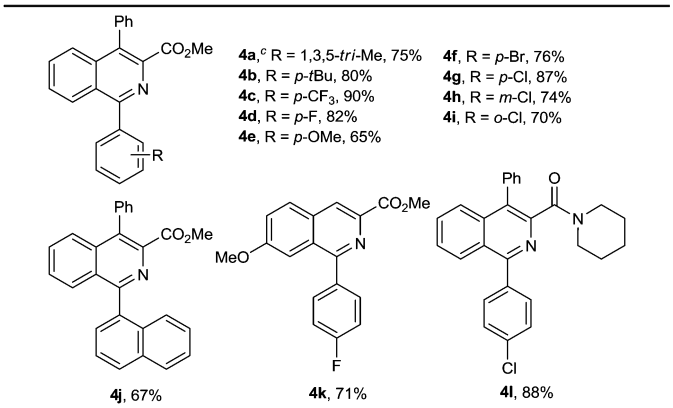




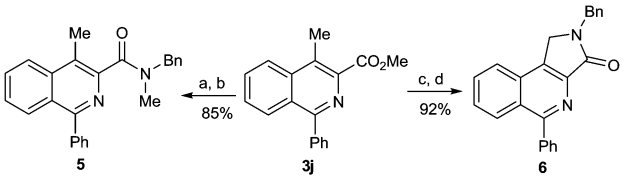
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), Na_2CO_3 (0.2 mmol) and *fac*-Ir(ppy)$_3$ (0.002 mmol, 1.0 mol%) in dry MeOH (4.0 mL) was irradiated by 3 W white LED for 24 h. [b] Isolated yield. [c] Regioisomer ratio: **3n** : **3n′** = 1.8 : 1.

Table 3 Scope of diaryliodonium salts[a,b]





[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Na_2CO_3 (0.2 mmol) and *fac*-Ir(ppy)$_3$ (0.002 mmol, 1.0 mol%) in dry MeOH (4.0 mL) was irradiated by 3 W white LED for 24 h. [b] Isolated yield. [c] Mes_2IOTf instead of Mes_2IBF_4.



a) NaOH, MeOH; b) $SOCl_2$, MeNHBn, CH_2Cl_2; c) NBS, BPO, CCl_4; d) $BnNH_2$, EtOH

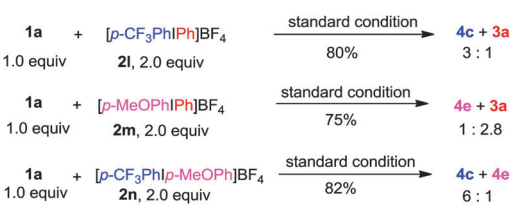
Scheme 1 Synthesis of non-benzodiazepine PBR ligands.

diaryliodonium salts could go through this reaction smoothly to give the isoquinolines **4a** and **4i** in 74% and 70% yields, respectively. Electronic properties of diaryliodonium salts had obvious influence on this transformation. The diaryliodonium salt with an electron-deficient substituent, such as CF_3, could give the corresponding isoquinoline **4c** in excellent yield (90%) while the diaryliodonium salt with an electron-rich substituent, such as OMe, gave the corresponding isoquinoline **4e** in much lower yield (65%).

1-Arylisoquinolinecarboxamides, such as PK 11195, are good non-benzodiazepine peripheral benzodiazepine receptor (PBR) ligands.[14] The method presented here provides a rapid access to this motif. As shown in Scheme 1, 1-phenylisoquinoline ester **3j** could be converted to 1-phenyisoquinolinecarboxamide **5** efficiently through a hydrolysis and amidation sequence in 85% overall yield. Similarly, isoquinolinecarboxamide **6** could be prepared from **3j** through bromination and intramolecular amination in 92% yield over 2 steps. Both isoquinolinecarboxamides **5** and **6** are excellent PBR ligands with nanomolar affinity.[14c]

In order to gain some insights into the mechanism of this reaction, a series of control experiments were carried out. Firstly, unsymmetrical diaryliodonium salts **2l–n** were used to react with isocyanide **1a**. As shown in Scheme 2, the electron-deficient phenyl group was transferred faster than the electron-rich one, which suggests that the radical pathway should be preferred over the carbon cation mechanism.[11b,16] Secondly, the quenching of the model reaction in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TMPEO) also implies a single electron transfer pathway. Thirdly, the reaction progressed smoothly under light irradiation, but no further conversion was observed when the light source was removed (for details, see ESI†). This light off/on and time profile experiment verifies the necessity of continuous irradiation, suggesting that regeneration of the photocatalyst is necessary for the full consumption of the vinyl isocyanide.

Based on these observations, a plausible catalytic cycle is proposed in Fig. 2. The first step is the formation of excited state *fac*-Ir(ppy)$_3$* from the irradiation of photocatalyst *fac*-Ir(ppy)$_3$.[12] *fac*-Ir(ppy)$_3$* is



Scheme 2 Reactivity of isocyanide **1a** with unsymmetrical diaryliodonium salts.

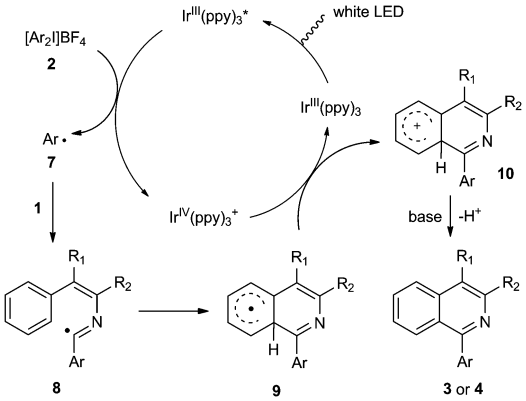


Fig. 2 Proposed mechanism.

then oxidatively quenched by diaryliodonium salts **2** with the generation of the *fac*-Ir(ppy)$_3^+$ complex and an aryl radical **7** respectively.[11] Addition of radical **7** to vinyl isocyanide **1** produces the imidoyl radical intermediate **8**. The imidoyl radical **8** goes through intramolecular HAS to give the radical intermediate **9**,[5] which is then oxidized by *fac*-Ir(ppy)$_3^+$ to form cation intermediate **10** and regenerate *fac*-Ir(ppy)$_3$. Ultimately deprotonation of **10** assisted by a base gives isoquinoline **3** or **4**.

In summary, we have described the first example of visible light-promoted vinyl isocyanide insertion, which can rapidly access highly substituted isoquinolines. The reactions proceed at room temperature in good to excellent chemical yields without the use of any external stoichiometric oxidant due to the overall redox neutral process. This modular synthesis method can introduce various functional groups to produce multi-substituted isoquinolines from readily available vinyl isocyanides and diaryliodonium salts. The resultant 1-arylisoquinoline carboxamides and esters are biologically intriguing motifs, which can be used as chemical probes, such as PBR ligands. Further explorations on the chemistry of vinyl isocyanides and biological evaluation of the resultant isoquinolines are underway in our laboratory.

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