Photochemistry

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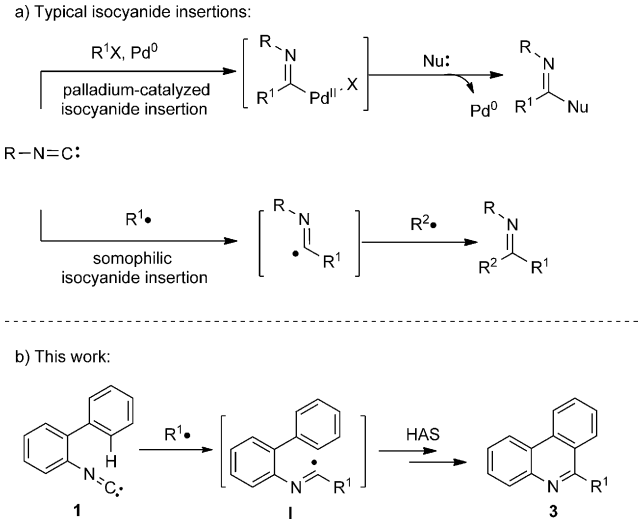
# Synthesis of 6-Alkylated Phenanthridine Derivatives Using Photoredox Neutral Somophilic Isocyanide Insertion**

*Heng Jiang, Yuanzheng Cheng, Ruzhi Wang, Mengmeng Zheng, Yan Zhang,* and Shouyun Yu**

*Dedicated to Professor Dawei Ma on the occasion of his 50th birthday*

Isocyanides have been important building blocks in synthetic chemistry since the discovery of the Ugi reaction and related multicomponent reactions.[1] Isocyanides are isoelectronic with carbon monoxide, and thus it is not surprising that isocyanides can undergo insertion reactions (also named imidoylative reactions)[2] to provide N-containing heterocycles which are ubiquitous in pharmaceuticals and biologically active molecules.[2–4] As depicted in Scheme 1a, palladium-catalyzed isocyanide insertion and somophilic isocyanide insertion represent two typical strategies currently reported for isocyanide insertion reactions. While the palladium-catalyzed isocyanide insertions often require high reaction temperatures and have the tendency to undergo multiple consecutive insertions,[5] the use of isocyanides as somophiles for insertion reactions holds promise for practical synthetic applications under mild reaction conditions.[6]




***Scheme 1.*** Typical isocyanide insertions and our design.

As a convenient approach to generate somophiles, photoredox catalysis,[7] which usually introduces alkenes,[8] alkynes,[9] and aromatic rings[10] as radical acceptors, has been widely used in the synthetic community to construct C–C bonds since 2008.[11] However, none of the reported work has employed photoredox catalysis to initiate isocyanide insertion. We consider photoredox-catalyzed isocyanide insertions to be a new synthetic protocol which circumvents the use of stoichiometric oxidants and harsh reaction conditions. As part of our ongoing work on photoredox neutral catalysis,[12] we report herein the first example of photoredox neutral, somophilic isocyanide insertions, which provide 6-alkylated phenanthridine derivatives under mild reaction conditions.[13]

Our design of photoredox netural isocyanide insertions is shown in Scheme 1b. The biphenyl isocyanide **1**,[6l] which incorporates an isocyanide group and a somophile (phenyl ring) into the same molecule, is selected to react with an alkyl radical $R^{1}$•. It is envisaged that the alkyl radical $R^{1}$• can be generated from an alkyl bromide (**2**) assisted by an excited-state photocatalyst. The radical $R^{1}$• adds to **1** to give the imidoyl radical **I**, which subsequently undergoes intramolecular homolytic aromatic substitution (HAS),[14] oxidation, and deprotonation to afford the phenanthridine **3**. Since the intramolecular HAS is faster than intermolecular radical couplings, multiple isocyanide insertions and double alkylation are avoided in this process. The stoichiometric amount of external oxidants can also be avoided because of the overall redox neutral process. It is noteworthy that the phenanthridine framework can be found in a variety of natural products possessing many important biological properties,[15] thus making this strategy more attractive.

This design was first examined using 2-isocyanobiphenyl (**1a**) and ethyl 2-bromopropanoate (**2a**) as model substrates (Table 1). The complex [*fac*-Ir(ppy)$_3$] (**A**) was chosen as the photocatalyst because of its superior oxidation capacity in the excited state.[7,8] When a solution of **1a** and **2a** in $CH_2Cl_2$ was irradiated with a 3 W blue LED in the presence of **A** and $Na_2HPO_4$ for 10 hours, the desired phenanthridine **3a** was isolated in 25% yield (Table 1, entry 1). Using $CH_3CN$,

[*] H. Jiang, Y. Cheng, R. Wang, M. Zheng, Prof. Dr. Y. Zhang, Prof. Dr. S. Yu
State Key Laboratory of Analytical Chemistry for Life Science
Institute of Chemical Biology and Drug Innovation
School of Chemistry and Chemical Engineering
Nanjing University, Nanjing 210093 (China)
E-mail: yushouyun@nju.edu.cn
njuzy@nju.edu.cn
Homepage: http://hysz.nju.edu.cn/yanzhang/
http://hysz.nju.edu.cn/yusy/

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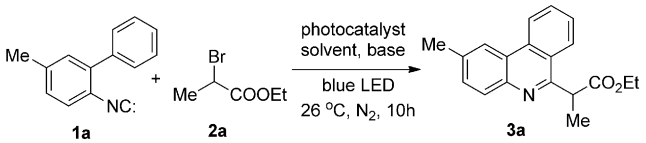
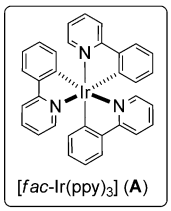
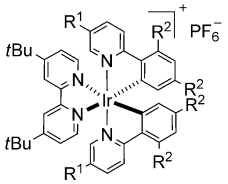
***Table 1:*** Reaction optimization.[a]

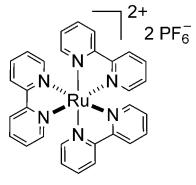



[Ir(ppy)$_2$(dtbbpy)PF$_6$] (**B**): $R^1 = R^2 = H$

[Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$] (**C**): $R^1 = CF_3$; $R^2 = F$

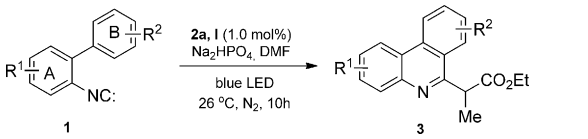


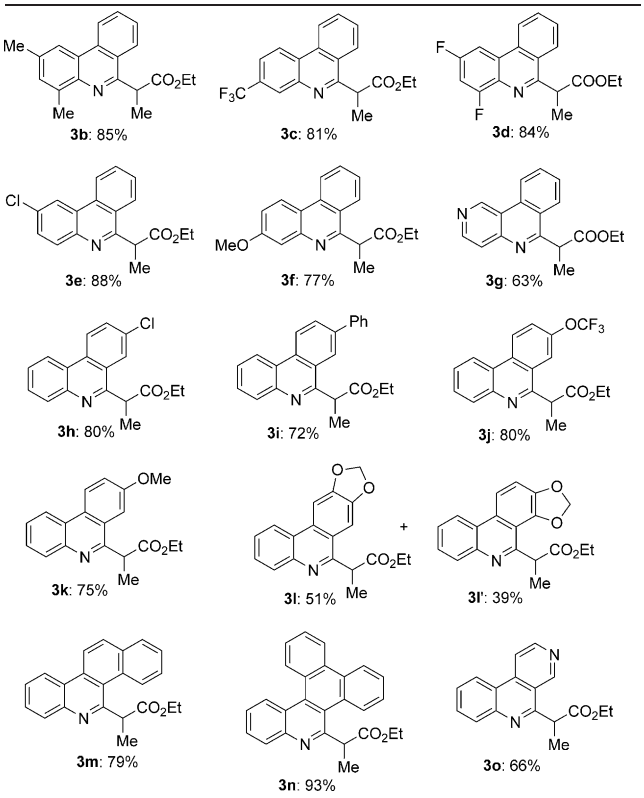

[Ru(bpy)$_3$(PF$_6$)$_2$] (**D**)

| Entry | Photo-catalyst | Base | Solvent | Yield [%][b] |
|---|---|---|---|---|
| 1 | **A** | $Na_2HPO_4$ | $CH_2Cl_2$ | 25 |
| 2 | **A** | $Na_2HPO_4$ | $CH_3CN$ | 17 |
| 3 | **A** | $Na_2HPO_4$ | DMSO | 69 |
| 4 | **A** | $Na_2HPO_4$ | MeOH | 45 |
| 5 | **A** | $Na_2HPO_4$ | DMF | 92 |
| 6 | **B** | $Na_2HPO_4$ | DMF | 5 |
| 7 | **C** | $Na_2HPO_4$ | DMF | 21 |
| 8 | **D** | $Na_2HPO_4$ | DMF | trace |
| 9 | **A** | $K_2CO_3$ | DMF | 83 |
| 10 | **A** | $NaHCO_3$ | DMF | 84 |
| 11 | **A** | $K_2HPO_4$ | DMF | 82 |
| 12 | **A** | none | DMF | 41 |
| 13 | none | $Na_2HPO_4$ | DMF | no reaction |
| 14[c] | **A** | $Na_2HPO_4$ | DMF | no reaction |

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), base (0.24 mmol, 1.2 equiv), and photocatalyst (0.002 mmol, 1.0 mol%) in indicated solvent (2.0 mL) was irradiated with a 3 W blue LED for 10 h. [b] Yield of isolated product. [c] No irradiation. DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide.

***Table 2:*** Scope of isocyanides.[a,b]



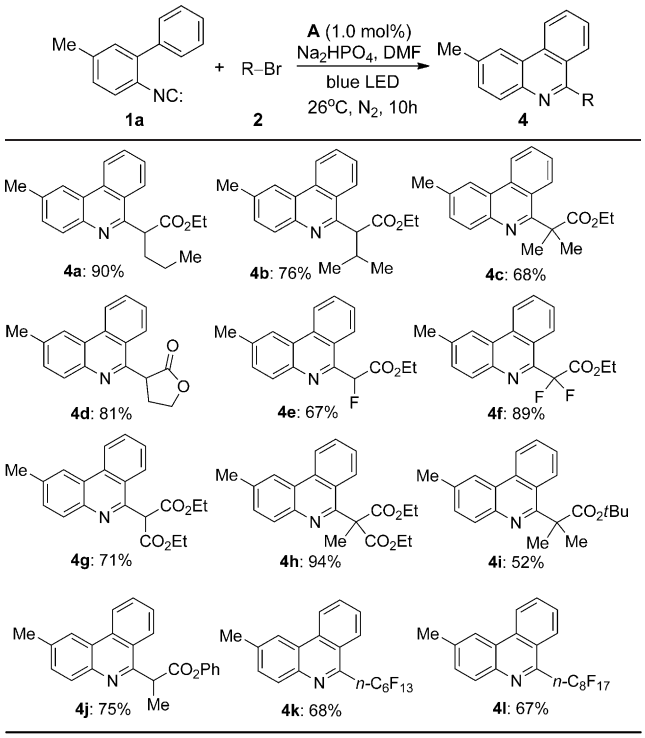

[a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), $Na_2HPO_4$ (0.24 mmol, 1.2 equiv) and **A** (0.002 mmol, 1.0 mol%) in anhydrous DMF (2.0 mL) was irradiated with a 3 W blue LED. [b] Yield of isolated product.

DMSO, and MeOH as solvents gave less than 70% yield (entries 2–4). To our delight, a 92% yield was achieved when DMF was used as the solvent (entry 5). The photocatalysts **B**–**D** were also tested, but none of them gave better results (entries 6–8). The base did not affect this transformation significantly and other bases, such as $K_2CO_3$, $NaHCO_3$, and $K_2HPO_4$ also gave good yields of the isolated products (entries 9–11). Control experiments verified the necessity of the base, irradiation, and photocatalyst (entries 12–14).

To assess the scope of this transformation, a variety of biphenyl isocyanides were employed to react with **2a** under the optimized reaction conditions. As shown in Table 2, a broad range of 2-isocyanobiphenyl compounds reacted smoothly with **2a** to give the corresponding phenanthridine derivatives in good to excellent yields. The 2-isocyanobiphenyl compounds with electron-withdrawing and electron-donating groups on the benzene ring A afforded **3b**–**f** with satisfactory yields. The isocyanide having a pyridine ring instead of the benzene ring A was also compatible in this reaction and the desired insertion product **3g** was isolated in 63% yield. The isocyanides having different functional groups on the benzene ring B were also convenient substrates and thus led to the products **3h**–**k** in good yield. When a disubstituted benzene ring B was employed, two regioisomers, **3l** and **3l′**, were generated in a 1.2:1 ratio. The isocyanides bearing naphthalene, anthracene, and pyridine rings instead of the benzene ring B were also successful in this transformation with good to excellent yields (**3m**–**o**).

We then turned our attention to explore the scope of alkylating reagents (**2**). A series of 6-alkylated phenanthridine derivatives were prepared as shown in Table 3. Long-chained, branched, saturated, and cyclic 2-bromide ethyl esters were suitable radical sources, thus producing the phenanthridines **4a**–**d** in yields of 68% to 90%. Ethyl 2-bromo-2-fluoroacetate (**2f**) and ethyl 2-bromo-2,2-difluoroacetate (**2g**) also reacted smoothly with **1a** to provide the phenanthridines **4e** (67%) and **4f** (89%), respectively. The malonate-derived bromides **2h** and **2i** reacted smoothly to afford **4g** and **4h**, respectively, with satisfactory yields. Little influence was observed when different esters were attached to bromides (**4i** and **4j**). It is worth mentioning that perfluoroalkyl bromides were favorable in this transformation and

***Table 3:*** Scope of bromides.[a,b]




[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), $Na_2HPO_4$ (0.24 mmol, 1.2 equiv) and **A** (0.002 mmol, 1.0 mol%) in anhydrous DMF (2.0 mL) was irradiated with a 3 W blue LED. [b] Yield of isolated product.

gave the 6-perfluoroalkylated phenanthridines **4k** and **4l** in acceptable yields.

A off/on light profile over time was generated to investigate the mechanistic details of this photoredox isocyanide insertion (Figure 1).[16] It was observed that the reaction progressed smoothly upon irradiation with light, but no further conversion was observed when the light source was removed. This experiment verified the necessity of light, and suggested that regeneration of the photocatalyst was necessary for the full consumption of the isocyanide. The quantum yield of the present reaction was also determined to be 0.18 (For the details, see the Supporting Information), and strongly suggests that the reaction proceeds through a photoredox pathway rather than radical propagation.

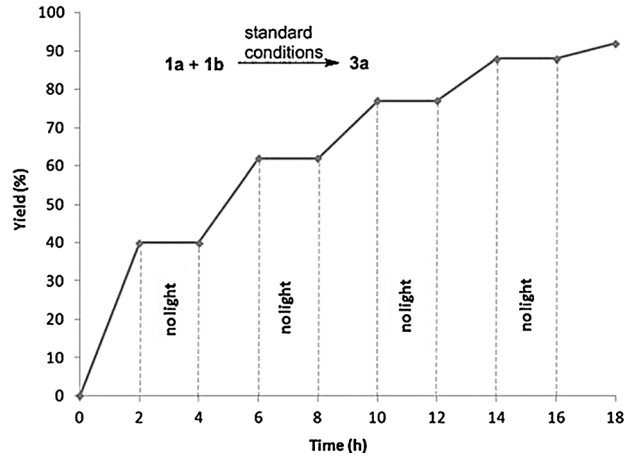
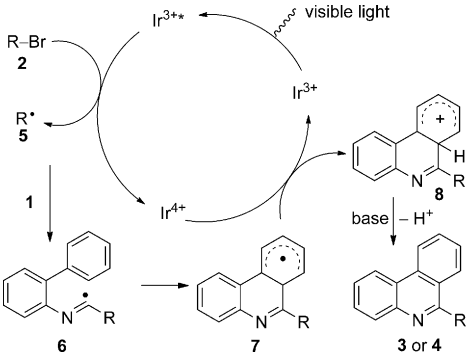



***Figure 1.*** Profile of the reaction with the light off/on over time. Yield was determined by HPLC analysis.

Based on our observations, a possible catalytic cycle is proposed for this transformation (Scheme 2). First, the




***Scheme 2.*** Proposed mechanism.

photocatalyst [*fac*-Ir(ppy)$_3$] is irradiated to the excited state [*fac*-Ir(ppy)$_3$*] which is oxidatively quenched by **2** with the generation of a [*fac*-Ir(ppy)$_3^{4+}$] complex and a radical species (**5**).[7–10] The radical **5** adds to **1** to produce the imidoyl radical intermediate **6**, which undergoes intramolecular homolytic aromatic substitution to give the radical intermediate **7**.[14] The intermediate **7** is then oxidized by [*fac*-Ir(ppy)$_3^{4+}$] to form the cationic intermediate **8** and regenerates [*fac*-Ir(ppy)$_3$]. Ultimately deprotonation assisted by base yields 6-alkylated phenanthridines. The quenching of this transformation in the presence of the radical inhibitor 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) also implies the involvement of a single-electron transfer (SET) process.

In summary, we have described the first visible-light-promoted somophilic isocyanide insertion. This efficient synthetic approach provides a rapid entry to 6-alkylated phenanthridine derivatives. These reactions proceeded at room temperature in good to excellent chemical yields with broad substrate scope and under environmentally friendly conditions. External stoichiometric oxidants were avoided because of the overall redox neutral process. In addition, isocyanides and electron-deficient bromides are both inexpensive and readily available compounds and the only by-product is hydrogen bromide, which is benign and can be easily removed. These advantages may open the possibility for using this method in synthetic applications. Exploration of the mechanistic details of this transformation and other somophilic isocyanide insertion reactions is underway.

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