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Visible Light Initiated Hantzsch Synthesis of 2,5-Diaryl-Substituted Pyrroles at Ambient Conditions

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Ⓢ *Supporting Information*

ABSTRACT: Irradiation of a mixture of enamines and α-bromo ketones, with a catalytic amount of $Ir(ppy)_3$ by visible light ($\lambda = 450$ nm), enables the production of various 2,5-diaryl-substituted pyrroles in good to excellent yields. The key intermediates in this reaction have been identified as alkyl radicals, generated from single-electron transfer from the photoexcited $Ir(ppy)_3$* to α-bromo ketones, which subsequently react with a broad range of enamines to undergo the Hantzsch reaction rapidly at ambient conditions.

Pyrrole, first isolated in 1857 from the products of bone pyrolysis, is found in a broad range of natural products and biologically active compounds.[1] The best known natural pyrroles are the heme derivatives and chlorophyll, which contain four pyrrole groups jointed by methyne bridges (Figure 1). As one of the most important simple heterocycles, pyrrole is also common structural fragment of marine origin, like lamellarin A. The architectural complexity and functional importance[2] of these compounds have rendered them popular synthetic targets. Developing methods for the fast and experimentally simple preparation of this typical five-membered ring structure has been of importance in the field of organic synthesis.[3]

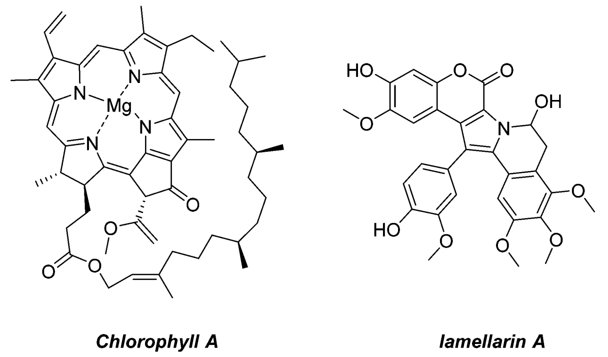
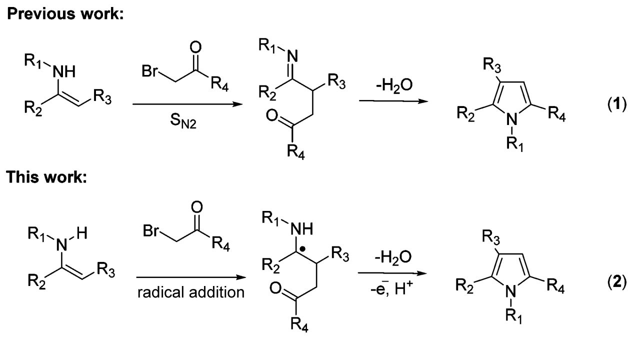

Chlorophyll A ***lamellarin A***

Figure 1. Natural products and biologically active compounds containing the pyrrole structure.

Early in 1890, Hantzsch reported the synthesis of pyrrole[4] by an equimolecular mixture of chloroacetone and acetoacetic ester under reflux in concentrated aqueous ammonia. However, further development of the so-called Hantzsch pyrrole synthesis has lagged far behind that of other classical name reactions[5] until recently.[3] Traditionally, the Hantzsch reactions involve an S_N2 nucleophilic substitution between enamine and α-bromo ketones, followed by dehydration condensation (Scheme 1). High temperature, strong organic base, or Lewis acid has always been required.

Scheme 1. Hantzsch Reaction



Here, a facile and efficient approach to polysubstituted pyrroles in a one-pot reaction is reported. This unique Hantzsch reaction is initiated by visible light. Owing to the inherent *green* and *mild* character of light, visible light catalysis has recently become an attractive strategy for organic synthesis.[6] By using Ru(II), Ir(III), and Pt(II) complexes and organic dyes as photosensitizers, a variety of organic transformations including reductive reaction,[7] oxidative addition,[8] and cross-coupling reaction[9] have been accomplished. Herein, we use $Ir(ppy)_3$ as a photosensitizer to initiate the Hantzsch reaction. In contrast to the conventional route reported in the literature, the α-bromo ketones are expected to be converted to alkyl radicals via single-electron transfer from the photosensitizer $Ir(ppy)_3$. Then the radical intermediates would react with the double bond of enamines to construct the five-

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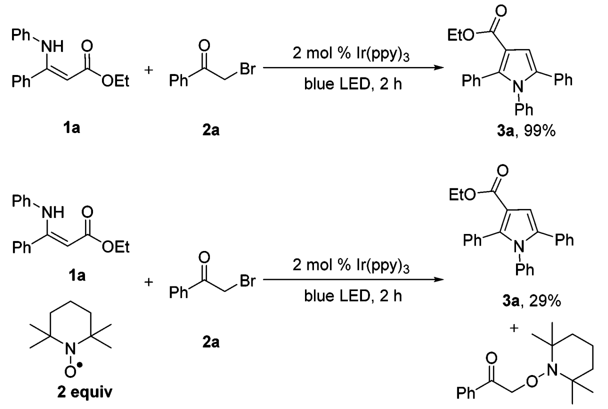
membered ring through dehydration condensation, as shown in Scheme 1. The successful application of this strategy for the Hantzsch synthesis of pyrrole derivatives is described as follows.

Initially, to explore the above transformation, we employed (*Z*)-ethyl 3-phenyl-3-(phenylamino)acrylate (**1a**) and 2-bromo-1-phenylethanone (**2a**) as substrates, with 2 mol % of Ir(ppy)$_3$ as the photosensitizer (Scheme 2). To our delight, the designed pyrrole **3a** was obtained in a yield of 92% after irradiation of the mixture containing **1a**, **2a**, and Ir(ppy)$_3$ in DMSO for 2 h (Table S1, entry 1). Moreover, when triethyamine (TEA) was added into the reaction solution, the yield of pyrrole **3a** was dramatically promoted to 99% (Table S1, entry 2). When 2 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the solution, the yield of pyrrole **3a** was decreased from 99% to 29%, implying some radicals were involved in the reaction system (Scheme 2). The selective removal of light, photosensitizer Ir(ppy)$_3$, enamines **1a**, or α-bromo ketone **2a** showed that each of them was necessary for the successful Hantzsch reaction between **1a** and **2a** (Table S1, entries 3−4).

Scheme 2. Visible Light Initiated Hantzsch Reaction



To understand the primary process of the reaction, we examined the interaction between photosensitizer Ir(ppy)$_3$ and the reaction substrates **1a** and **2a**, respectively. Figure 2 shows the absorption and luminescence spectra of Ir(ppy)$_3$ in the absence and presence of **1a** and **2a**. Ir(ppy)$_3$ displayed a broad visible light absorption ranging from 400 to 500 nm. Excitation of the absorption resulted in intense luminescence at 530 nm with a lifetime of 1340 ns in degassed DMSO solution at room temperature, which was readily quenched by **1a** and **2a** (Figure 2) following the Stern−Volmer kinetics (Figure S2). Under identical conditions, however, the absorption spectra of a mixture of Ir(ppy)$_3$ and **1a** or **2a** were simply the sum of the individual components (Figure S1), indicative of the interaction of the substrates with Ir(ppy)$_3$ in its excited state. The shortened lifetime of Ir(ppy)$_3$ from 1340 to 17 ns for **2a** and 454 ns for **1a** suggested further that the interaction of Ir(ppy)$_3$* with **1a** is much weaker than that of **2a**, as reflected in the luminescence quenching constant k_{et} of 7.07×10^7 s^{-1} M^{-1} for **1a** and 1.56×10^9 s^{-1} M^{-1} for **2a**, respectively. In addition, when triethylamine (TEA) was added into the system, little change could be detected in both luminescent intensity and lifetime of Ir(ppy)$_3$. Therefore, the interaction of photoexcited Ir(ppy)$_3$* with **2a** is the strongest among them with an order of association ability **2a** ≫ **1a** ≫ TEA.

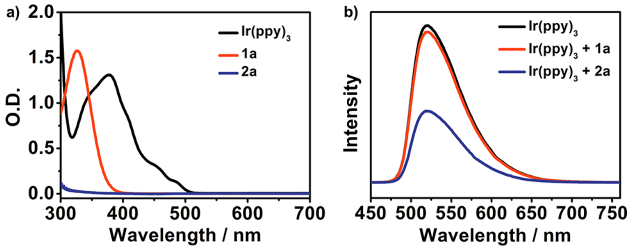
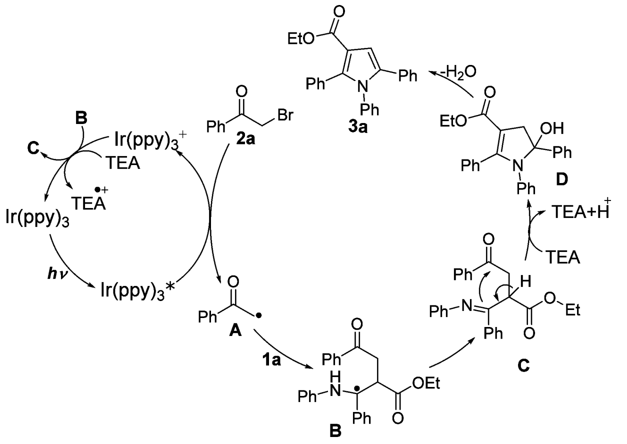


Figure 2. (a) Absorption spectra of Ir(ppy)$_3$, **1a**, **2a**: [Ir(ppy)$_3$] = 0.1 mM, [**1a**] = 0.1 mM, [**2a**] = 0.1 mM. (b) Luminescence spectra of Ir(ppy)$_3$ in the absence and presence of **1a** and **2a**: [Ir(ppy)$_3$] = 0.5 mM, [**1a**] = 0.5 mM, [**2a**] = 0.5 mM.

Combining the electrochemical and spectroscopic studies, we examined the possibility of the photoinduced electron transfer from Ir(ppy)$_3$ to **2a** initiating the Hantzsch reaction (Figure S3). The redox potentials $E^{IV/III}$ and $E^{III/II}$ of Ir(ppy)$_3$ were determined to be 0.72 V vs SCE and −2.3 V vs SCE, respectively. Together with the excited state energy E_{00} of Ir(ppy)$_3$ that was read from the cross point of the absorption and luminescence spectra at 485 nm being 2.56 eV, we obtained the redox potential of the excited Ir(ppy)$_3$* ($E^{IV/III*} = E^{IV/III} - E_{00} = -1.84$ V vs SCE, $E^{III*/II} = E^{III/II} + E_{00} = 0.26$ V vs SCE). According to the determined redox potentials of **1a** ($E_{ox} = 0.90$ V vs SCE, $E_{red} = -2.0$ V vs SCE), **2a** ($E_{ox} > 1.6$ V vs SCE, $E_{red} = -1.2$ V vs SCE), the free energy change (ΔG) calculated by using the Rehm−Weller equation[10] revealed that the electron transfer from Ir(ppy)$_3$* to **2a** is thermodynamically feasible but not for Ir(ppy)$_3$* to **1a**. In this situation, the luminescence quenching experiment of Ir(ppy)$_3$ by **1a** might be a result of energy transfer from the excited Ir(ppy)$_3$* to **1a** (Figure 2b). Indeed, **1a** prefers existing in *Z* form because of the hydrogen bond effect. Upon irradiation by blue LEDs for 5 min, the signal of **1a** in *E* form was detected by ^{1}H NMR (Figure S4), indicating the photoisomerization of **1a** taking place. Taken together, we believe the photoinduced electron transtfer from Ir(ppy)$_3$ to **2a** dominated the reaction pathway.

In view of the above experimental results, a possible mechanistic rationale of the transformation is outlined in Scheme 3. Upon excitation of Ir(ppy)$_3$ at 450 nm, single-electron-transfer oxidation of Ir(ppy)$_3$* by **2a** takes place to generate Ir(ppy)$_3^+$ and reduced **2a**, which is subsequently debrominated to yield alkyl radical **A**. The generated radical **A**

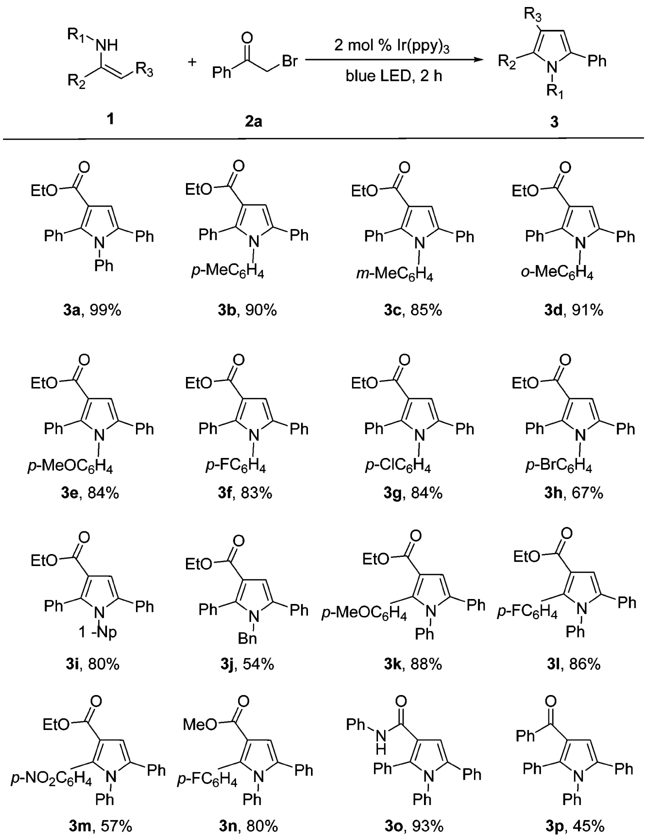
Scheme 3. Proposed Mechanism



reacts with enamine **1a** to form the intermediate **B**, and then **B** is further oxidized by Ir(ppy)$_3^+$ to afford imine **C** and simultaneously to regenerate Ir(ppy)$_3$. Dehydration of **C** leads to the formation of target product **3a**. Here, TEA helps with the regeneration of Ir(ppy)$_3$ photosensitezer and debromination of **2a**.

With an understanding of the mechanism in hand, we explored the generality of this visible light initiated reaction on the scope of enamines. When electron-donating and electron-withdrawing groups were introduced at different positions of the phenyl in enamines **1**, the desired 2,5-diaryl-substituted pyrrole products **3** could be obtained smoothly (Scheme 4, **3a**–**j**). For (*E*)-ethyl 3-phenyl-3-(phenylamino)acrylates, having methyl-substituted phenyl, the steric hindrance seemed not to affect the reaction, giving rise to **3b**–**d** in relative yields of 90%, 85%, and 91% (Scheme 4, **3b**–**d**). Other substrates bearing methoxyl, fluoro, and chloro also showed good performance (Scheme 4, **3e**–**g**), but irradiation of bromo-substituted enamine **1h** under identical conditions resulted in a relatively lower yield than that of fluoro- and chloro-substituted enamines (Scheme 4, **3h**). When the group on the nitrogen of **1** was α-naphthyl or benzyl, the reactions with **1a** afforded the products **3i** and **3j** in yields of 80% and 54%, respectively. The substituent R$_2$ next to nitrogen of **1** was then studied. The electron-donating groups were found to have a higher activity than electron-withdrawing groups (Scheme 4, **3k**–**m**). Even the nitro-substituted **1m** was tolerable for this conversion (Scheme 4, **3m**). Instead of the ethyl ester in enamines **1a**–**m**, methyl ester in **1n**, amide in **1o**, and carboxide in **1p** were also suitable for this transformation (**3n**–**p**). To our surprise, the species with an amide group in R$_3$ could convert into the desired product (**3o**) in 93% yield.

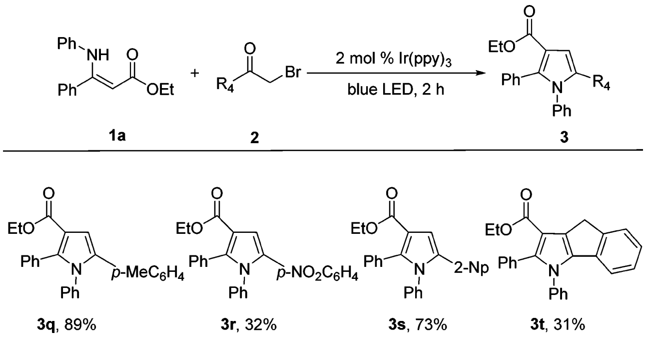
Scheme 4. Scope of Enamines[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), Ir(ppy)$_3$ (2 mol %), TEA (35 mol %), DMSO (2 mL), in the Ar under blue LED irradiation at room temperature for 2 h.

On the other hand, good to excellent yields for both 2-bromo-1-*p*-tolylethanone **2q** and 2-bromo-1-(naphthalen-2-yl)ethanone **2s** were achieved (Scheme 5, **3q**, **3s**), even for 2-bromo-1-(4-nitrophenyl)ethanone **2r**, which had a strong electron-withdrawing group and enabled production of **3r** in 32% yield. When 2-bromo-2,3-dihydro-1*H*-inden-1-one was used, a condensed ring could be obtained (Scheme 5, **3t**).

Scheme 5. Scope of α-Bromo Ketones[a]



[a]Reaction conditions: 1a (0.1 mmol), 2 (0.15 mmol), Ir(ppy)$_3$ (2 mol %), TEA (35 mol %), DMSO (2 mL), in Ar, under blue LED irradiation at room temperature for 2 h.

In conclusion, we have developed the Hantzsch reaction in a green and efficient manner for the synthesis of 2,5-diaryl-substituted pyrroles. Compared with the traditional Hantsch reaction, this system is initiated by visible light to yield alkyl radicals from Ir(ppy)$_3$ photosensitizer and α-bromo ketones, which subsequently react with enamine to realize radical addition over a short reaction time (2 h) at room temperature. This photocatalytic method is a practical tool for the synthesis of five-membered ring structure, pyrroles, in good to excellent yields. Such an approach enriches the Hantzsch reaction and represents a milder, greener, and more efficient process for the organic transformation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01059.

Experimental procedures, methods, and product characterization (PDF)

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Notes

The authors declare no competing financial interest.

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