Photoredox Fischer Indole Synthesis

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Abstract

Visible light photoredox conditions were applied to the traditional Fischer indole synthesis. N,N-Diarylhydrazones were efficiently converted into the corresponding indoles even at 30 °C by treatment with bromotrichloromethane in the presence of Ru(bpy)3Cl2·6H2O as the photocatalyst. Electrochemical study revealed the viability of oxidative quenching cycle for the photocatalysis, which set the basis for proposing the redox-based reaction mechanism.

Key words Fischer indole synthesis, [3,3]-sigmatropic rearrangement, photoredox, radicals, hydrazones, cyclic voltammetry

Fischer indole synthesis is a well-known reaction that has a long history and broad range of applications in organic synthesis.1 This traditional transformation is still often in use because of its ready availability of the starting materials and economical one-step experimental procedure. Various acids and activating methods have already been developed for this reaction (Scheme 1a). Typically, the reaction proceeds from hydrazone 1 via the formation of alkenylhydrazone 2 that then goes through [3,3]-sigmatropic rearrangement, cyclization to form indoline 4, and elimination of ammonia that lead to the core of indole 5. In addition to the use of typical Brønsted acids as reagents/catalysts that are occasionally associated with side reactions, thermal reaction conditions are sometimes employed to give better results even though high temperature is required for efficient transformation (180–250 °C).2 These potential drawbacks prompted chemists to develop alternative reaction conditions for the Fischer indole synthesis.3 One of the most interesting activating reagents that has been developed is trifluoroacetic anhydride4 with which trifluoroacetylation of sp² nitrogen atom of hydrazone 6, instead of protonation, mediates the activation of hydrazone moiety to form the

Scheme 1 Fischer indole synthesis and its mode of activation on hydrazone moiety
isolable trifluoroacetylated hydrazine 7 (Scheme 1b). Final removal of trifluoroacetamide from indoline intermediate 8 gives indole target 9. During our research campaign toward various application of photoredox reaction conditions, we envisioned to implement this concept to Fischer indole synthesis as an attempt to develop milder reaction conditions. Herein, we describe novel photoredox conditions for Fischer indole synthesis of certain diphenylhydrazones (Scheme 1c). This manuscript deals with the brief scope of the developed reaction, as well as the mechanistic reasoning of this novel transformation as a foundation to further researches.

For the optimization of the reaction conditions, 4-tert-butylcyclohexanone diphenylhydrazone 10 was selected as the standard substrate as the precursor to indole 13. Table 1 shows the details of our optimization of the conditions. The scope of oxidants was examined first. Hydrazine 10 was reacted with arrays of oxidants (1.5 equiv) under the irradiating conditions (450 nm) in the presence of Ru(bpy)3Cl2·6H2O (14, 1.0 mol%) in DMF. Bromotrichloromethane (BrCCl3) showed better reactivity than diethyl bromomalonate or carbon tetrachloride (Table 1, entries 1–3). With bromotrichloromethane as the best performing oxidant, the solvent effect was examined next. As can be seen from entries 4–6, lower conversion of 10 was observed in DMSO, THF, and CH2Cl2. By contrast, the treatment of 10 in methanol improved the reaction efficiency, providing in-
dole 13 in 64% yield (entry 7). Screening of other alcoholic solvents (entry 8–10) revealed that 2-propanol was the optimal solvent among examined (83% isolated yield, entry 10). Change of the photocatalyst to \([\text{Ir(dF(CF}_{3})ppy})_{2}(\text{dtbbppy})]PF_{6} \) (entry 11), showed comparable reactivity, while \([\text{Ru(bpz})_{2}]PF_{6}] \) (entry 16) mediated more sluggish reaction (entry 12). Interestingly, the conditions without any photocatalyst gave the same result under the prolonged reaction conditions (entries 13, 14). From the optimization above, the conditions of entry 10 [hydrazone (0.05 M), BrCCl3 (1.5 equiv), THF, 65 °C, 4 h] was determined to be the best conditions.

To briefly illustrate the scope of the reaction, several substrates were subjected to the present reaction conditions. Scheme 2 shows the results with 3-pentanone diphenylhydrazone 17. As previously reported, activation by TFAA gives the trifluoroacetate 18. Subsequent heating in THF at 65 °C mediates [3,3]-sigmatropic rearrangement and formation of indole moiety, followed by the ready elimination of trifluoroacetamide to give indole 19 (Scheme 2a). Our optimized reaction conditions to 17 gave the same indole 19 in good yield in one step even at 30 °C (Scheme 2b). Cyclopentanone diphenylhydrazone 20 was reported to give trifluoroacetyl adduct 21 when treated with TFAA and collidine (Scheme 3a). Interestingly, heating 21 in THF at 65 °C gives the cyclized indoline product 22. This indicated the ready [3,3]-sigmatropic rearrangement and the cyclization to form indoline moiety, while the elimination of trifluoroacetamide does not proceed readily. This fact could be ascribed to the formation of strained iminium cation intermediate and product that retarded the elimination. Under the refluxing conditions of xylene at 140 °C, this elimination proceeds to afford the indole product 23 in good yield. Our new photoredox conditions for the same substrate 20 gave the indole product 23 in 70% yield even at 30 °C, with the prolonged reaction time (Scheme 3b). The formation of indole 23 was not associated with the formation of any remaining intermediate, indicating the increased tendency toward the removal of the nitrogen functionality from the indoline intermediate. Our preliminary study indicated almost ignorable reactivity for the synthesis of NH, N-Me, N-Bn, and N-Boc indoles.

The mechanism of this photoredox Fischer indole synthesis has two possibilities (Scheme 4). Cycle A involves the oxidative quenching cycle where photoactivated ruthenium species \([\text{Ru(bpy})_{2}]^{2+} \) is oxidized by the oxidant (BrCCl3 is reduced first), and the other, cycle B, involves the reductive quenching where the photogenerated species is reduced by the hydrazone (hydrazone is oxidized first). Photophysical and electrochemical experiments were thus conducted to see the electrochemical reactivity of the reactants and to

\[ \begin{align*}
\text{hydrazone} & \rightarrow \text{hydrazone}^{**} \\
\text{Br}^{-} + \text{CCl}_{3} & \rightarrow \text{BrCCl}_{3} \\
\text{BrCCl}_{3} & \rightarrow \text{Br}^{-} + \text{CCl}_{3}
\end{align*} \]

\[ \begin{align*}
\text{Oxidative Quenching Cycle} & \\
\text{Reductive Quenching Cycle}
\end{align*} \]
determine the reaction mechanism in the current photoredox Fischer indole synthesis.

First, luminescent quenching experiment was conducted to determine the plausible mechanistic cycles A and B. As shown in the data in Supporting Information, similar luminescent quenching of photoactivated Ru(bpy)3Cl2 was observed with low solution concentration. This result indicated the possibility of electron transfer between the photocatalyst and both of the substrates. However, it is still difficult to exclude the possibility of back-electron transfer. To clarify the working mechanism of the reaction, electrochemical experiments were next examined. Figure 1 shows the cyclic voltammogram of hydrazone 10 (blue) referenced to redox couple of decamethylferrocene (Fc/Fc+) (black). In this manuscript, reported electrochemical potentials of known compounds versus SCE was converted to the values referenced to Fc+/Fc+ (in 2-propanol) according to the Lay’s report. Thus the redox potential of Fc+/Fc+ (55 mV in 2-propanol vs Ag/AgCl) was estimated to be 10 mV (vs SCE) through the known potential of Ag/AgCl (–45 mV vs SCE). Cyclic voltammogram of hydrazone 10 in Figure 1 indicates almost ignorable amount of current at the excited state reduction potential of [Ru(bpy)3]2+* (E1/2III/II = +0.76 V [vs Fc+/Fc+]) (orange). This indicates the inability of [Ru(bpy)3]12-- to oxidize hydrazone 10 within the reductive quenching cycle. Reductive quenching cycle (cycle B) is thus proposed unlikely for the current photoredox Fischer indole synthesis. This is because our Fischer indole synthesis requires BrCCl3 as oxidant. Photo-excitation of Ru(bpy)3 initiates the catalytic reaction cycle. If Ru(bpy)3 initiates the reductive quenching cycle, some intermediates from hydrazone should be observed. However, we did not observe the product effectively. These results suggest that oxidative quenching cycle with oxidant is plausible in terms of the mechanistic investigation. The reaction could be thus considered to involve the oxidative quenching cycle (cycle A) that mediates the well-known reduction of BrCCl3 (E1/2,red = –0.19 V [vs Fc+/Fc+]) at the oxidation potential of the photocatalyst. This was further confirmed by the cyclic voltammograms in the presence of BrCCl3 (blue line) in Figure 2, that indicate the cathodic current at the excited state oxidation potential of [Ru(bpy)3]3+ (E1/2III/II = –0.82 V [vs Fc+/Fc+]) at the green line. The reported reduction potentials (E1/2,red) of CCl4 and BrCH(CO2Et)2 are –1.94 V [vs Fc+/Fc+] and –0.63 V [vs Fc+/Fc+], respectively. These values support that the single-electron reduction of BrCCl3 (E1/2,red = –0.19 V [vs Fc+/Fc+]) by the excited state [Ru(bpy)3]2-- is kinetically preferred than those of CCl4 and BrCH(CO2Et)2. These discussions are consistent with the results of entries 10–12 in Table 1. With [Ir(dfCF3)ppy]2(dtbbppy)PF6 (E1/2IV/III = –0.90 V [vs Fc+/Fc+]) as the photocatalyst, the almost same reactivity characteristics indicate the same oxidative quenching mechanism. The ground state reduction potential of Ir4+ intermediate (E1/2IV/III = +1.68 V [vs Fc+/Fc+]) is similar to that of Ru32+ (E1/2III/II = +1.28 V [vs Fc+/Fc+]), which also supports the subsequent oxidation step (Table 1, entry 11). In turn, the excited species [Ru(bpz)3]2+* (E1/2III/II = –0.27 V [vs Fc+/Fc+])12 has weaker oxidation potential for the reduction of BrCCl3. This is consistent with the slower reaction (entry 12).

Collectively, the reaction mechanism is in accordance with the following proposal (Scheme 5). First, [Ru(bpy)3]2+ (14) is photoactivated to [Ru(bpy)3]2+* that reduces BrCCl3 to generate [Ru(bpy)3]3+, bromide anion, and trichloromethyl radical. The radical species attacks the nitrogen atom of C=N bond of hydrazone 10 leading to α-aminoalkyl radical 24, which would be oxidized to cation 25 by single-electron oxidation mediated by [Ru(bpy)3]3+. This regioselectivity may be associated with the fact that electron-deficient radicals such as acyl radicals are known to favor the attack at
nitrogen atom of imines. Deprotonation affords alkenylhydrazine that is then susceptible to [3,3]-sigmatropic rearrangement to form a C–C bond to give 27. The following cyclization forms indoline. The ease of elimination of nitrogen functionality under the current reaction conditions indicate the increased leaving ability, possibly exerted by the formation of iminium ion, formed by expelling the chloride. Final removal of iminophosgene and isomerization gives indole. Slow formation of indole without the addition of photocatalyst could be similarly reasoned by considering the uncatalyzed photoactivation of BrCCl₃ to give bromine radical and trichloromethyl radical, which would mediate a radical chain reaction to generate the active species. This mechanism could account for the typical induction period of the reaction before following the similar transformations to give the same alkenylhydrazine possibly through.

In conclusion, novel photoredox Fischer indole synthesis was developed employing the combination of photocatalyst and BrCCl₃. From the results on the selected substrates, the methodology thus developed suggests its usability for constructing N-aryl 2,3-disubstituted indoles. Mechanistic studies revealed that the oxidative quenching cycle is the plausible catalytic mechanism. Trichloromethyl radical is suggested to attack the nitrogen atom of hydrazone moiety and helps the formation of alkenylhydrazine as the efficient substrate of [3,3]-sigmatropic rearrangement, followed by the ready removal of nitrogen functionality for the facile formation of indole core even at 30 °C.

All nonaqueous reactions were carried out under an inert atmosphere of N₂ in oven-dried glassware, unless otherwise noted. DMF, DMSO, MeCN, and 2-propanol were distilled over CaH₂. All other reagents were commercially available and used without further purification, unless otherwise noted. Analytical TLC was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F₂54. Preparative flash chromatography was performed using Silica Gel (AP-300, irregular, 38–75 μm) purchased from Toyotakako Co., Ltd. ¹H and ¹³C NMR spectra were recorded on a JEOL JNM-ECA600 or JNM-ECZ600 spectrometer. All ¹H NMR spectra are reported on a JEOL JNM-ECA600 or JNM-ECZ600 spectrometer. All ¹H NMR spectra are reported in ppm relative to the central line of the triplet for CDCl₃ (77.0 ppm). High resolution mass spectra (HRMS) were obtained on a Bruker microTOF II spectrometer. Melting points, determined on a Stanford Research Systems MPA100 melting point apparatus, are uncorrected.
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2-[4-({tert-Butyl)cyclohexyliden]-1,1-diphenylhydrazine (10); Typical Procedure for the Synthesis of N,N-Diphenyldiazones

A 300 mL round-bottomed flask equipped with a magnetic stir bar was charged under argon gas with 1,1-diphenylhydrazine (6.8 g, 37 mmol), 4-tert-butylcyclohexanone (5.4 g, 35 mmol), AcOH (20 μL, 0.35 mmol), and EtOH (70 mL). The resulting mixture was stirred at 60 °C for 15 h and cooled to r.t. The mixture was partitioned between EtO and H2O. The organic phase was collected and the aqueous phase was extracted with Et2O (2 ×). The combined organic extracts were washed with brine and dried (anhyd Na2SO4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (n-hexane/EtOAc 1:0 to 40:1) to afford hydrazone 10 (7.8 g, 24 mmol, 70%) as a pale brown solid, mp 58.0–59.0 °C; Rf = 0.58 (n-hexane/EtOAc 5:1, UV, PMA (phosphomolybdic acid)).

1H NMR (CDCl3, 600 MHz): δ = 7.27 (t, J = 7.6 Hz, 4 H), 7.04 (d, J = 8.3 Hz, 4 H), 7.00 (d, J = 8.3, 7.6 Hz, 2 H), 3.10 (m, 1 H), 2.79 (m, 1 H), 2.25 (ddd, J = 14.5, 13.1, 4.8 Hz, 1 H), 2.03 (m, 1 H), 1.76 (m, 1 H), 1.53 (ddd, J = 14.5, 13.8, 5.5 Hz, 1 H), 1.33 (ddd, J = 13.1, 4.2, 1.4 Hz, 1 H), 1.23 (m, 1 H), 0.99 (ddd, J = 13.8, 13.1, 4.1 Hz, 1 H), 0.85 (s, 9 H)

13C NMR (CDCl3, 150 MHz): δ = 175.4, 148.6, 148.3, 128.9, 122.5, 120.9, 47.2, 35.1, 32.4, 30.1, 27.8, 27.5, 26.5.


2-(Pentan-3-ylidene)-1,1-diphenylhydrazine (17)

Reaction of 3-pentanone (1.26 g, 15 mmol), 1,1-diphenylhydrazine (2.2 g, 12 mmol), AcOH (50 μL, 0.88 mmol), and EtOH (10 mL) at 90 °C for 12 h gave hydrazone 17 (2.0 g, 7.9 mmol, 66%) as a pale yellow oil after purification by column chromatography on silica gel (n-hexane/EtOAc 20:1 to 10:1); mp 58.0–59.0 °C; Rf = 0.58 (n-hexane/EtOAc 5:1, UV, PMA).

1H NMR (CDCl3, 600 MHz): δ = 7.18 (d, J = 8.6, 7.4 Hz, 4 H), 7.08 (d, J = 8.6, 1.0 Hz, 4 H), 7.04 (t, J = 7.4 Hz, 2 H), 2.49 (d, J = 15.1, 7.6 Hz, 2 H), 2.31 (d, J = 15.3, 7.7 Hz, 2 H), 1.26 (d, J = 7.6 Hz, 3 H), 0.90 (d, J = 7.7 Hz, 3 H).

13C NMR (CDCl3, 150 MHz): δ = 179.0, 148.6, 128.9, 122.5, 120.8, 29.0, 25.0, 11.2, 9.8.

HRMS (APCI-MS, positive): m/z [M + H]+ calcd for C17H19N2: 251.1543; found: 251.1543.

2-Cyclopentylidene-1,1-diphenylhydrazine (20)

Reaction of cyclopentanone (1.26 g, 15 mmol), 1,1-diphenylhydrazine (2.2 g, 12 mmol), AcOH (50 μL, 0.88 mmol), and EtOH (10 mL) at 90 °C for 5 h gave hydrazone 20 (1.99 g, 7.95 mmol, 66%) as a pale yellow solid after purification by column chromatography on silica gel (n-hexane/EtOAc 20:1 to 10:1); mp 48.1–49.4 °C; Rf = 0.45 (n-hexane/EtOAc 5:1, UV, PMA).

1H NMR (CDCl3, 600 MHz): δ = 7.84 (d, J = 8.8, 7.38, 2.06 Hz, 4 H), 7.07 (dd, J = 8.58, 1.20 Hz, 4 H), 7.04 (t, J = 7.38 Hz, 2 H), 2.58 (t, J = 7.38 Hz, 2 H), 2.03 (t, J = 7.35 Hz, 2 H), 1.78–1.67 (m, 4 H).

13C NMR (CDCl3, 150 MHz): δ = 178.8, 148.2, 129.0, 128.8, 121.4, 33.8, 31.6, 24.9, 24.4.

HRMS (APCI-MS, positive): m/z [M + H]+ calcd for C13H13N2: 201.0911; found: 201.0914.

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