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 \(^\circ\)C by treatment with bromotrichloromethane in the presence of Ru(bpy)\(_3\)Cl\(_2\)·6H\(_2\)O 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 alkenylhydrazine 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 \(^\circ\)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 anhydride\(^4\) with which trifluoroacetylation of sp\(^2\) 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. Hydrazone 10 was reacted with arrays of oxidants (1.5 equiv) under the irradiating conditions (450 nm) in the presence of Ru(bpy)$_3$Cl$_2$·6H$_2$O (14, 1.0 mol%) in DMF. Bromotrichloromethane (BrCCl$_3$) 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 CH$_2$Cl$_2$. By contrast, the treatment of 10 in methanol improved the reaction efficiency, providing in-

<table>
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<th>Entry</th>
<th>Oxidant</th>
<th>Photocatalyst</th>
<th>Solvent</th>
<th>Conv. (%)$^b$</th>
<th>Yield (%)$^b$</th>
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$a$ The reactions were carried out using hydrazone 10 (0.1 mmol) and oxidant (1.5 equiv) in the presence of photocatalyst (1.0 mol%) in solvent (0.05 M) at 30 °C with irradiation of blue LED (450 nm) under an argon atmosphere for 2 h.

$b$ 1H NMR yields.

c Isolated yield.

$^d$ Reaction time was 8 h.
doke 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 \([\text{Ir(dF(CF_3)ppy)_2(dtbbpy)}]PF_6\) (15) (entry 11), showed comparable reactivity, while \([\text{Ru(bpy)_2}]PF_6\) (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), BrCCl\(_3\) (1.5 equiv), THF (1.0 mol%), irradiation (450 nm), 2-propanol] 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 indoline 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 is 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 photocatalyst 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 \([\text{Ru(bpy)}]^2\) is oxidized by the oxidant (BrCCl\(_3\) is reduced first), and the other, cycle B, involves the reductive quenching where the photogenerated activated 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
determine the reaction mechanism in the current photo-
redox Fischer indole synthesis.

First, luminescent quenching experiment was conduct-
ed to determine the plausible mechanistic cycles A and B. As shown in the data in Supporting Information, similar lu-
minescent quenching of photoactivated Ru(bpy)$_3$Cl$_2$ was observed with low solution concentration. This result indi-
cated the possibility of electron transfer between the pho-
tocatalyst and both of the substrates. However, it is still dif-
ficult to exclude the possibility of back-electron transfer. To
clarify the working mechanism of the reaction, electro-
chemical 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 re-
duction potential of [Ru(bpy)$_3$]$^{2+*}$ ($E_{1/2}^{III/II} = +0.76$ 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 re-
quires BrCCl$_3$ as oxidant. Photo-excitation of Ru(bpy)$_3$ initi-
ates the catalytic reaction cycle. If Ru(bpy)$_3$ initiates the re-
ductive quenching cycle, some intermediates from hydra-
zone 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 con-
sidered to involve the oxidative quenching cycle (cycle A) that
mediates the well-known reduction of BrCCl$_3$ ($E_{1/2,\text{red}}^{III/II}$ = −0.19 V [vs Fc$^*$/$Fc^{*+}$]) at the oxidation potential of the pho-
tocatalyst. This was further confirmed by the cyclic voltam-
mograms in the presence of BrCCl$_3$ (blue line) in Figure 2,
that indicate the cathodic current at the excited state oxidation
potential of [Ru(bpy)$_3$]$^{2+*}$ ($E_{1/2}^{II/II}^{III/II} = −0.82$ V [vs Fc$^*$/$Fc^{*+}$]) at the green line. The reported reduction potentials
($E_{1/2,\text{red}}$) of CCl$_4$ and BrCH(CO$_2$Et)$_2$ are −1.94 V [vs Fc$^*$/$Fc^{*+}$] and −0.63 V [vs Fc$^*$/$Fc^{*+}$], respectively. These
values support that the single-electron reduction of BrCCl$_3$
($E_{1/2,\text{red}}^{II/II} = −0.19$ V [vs Fc$^*$/$Fc^{*+}$]) by the excited state
[Ru(bpy)$_3$]$^{2+*}$ ($E_{1/2}^{III/II} = −0.82$ V [vs Fc$^*$/$Fc^{*+}$]) is kinetically
preferred than those of CCl$_4$ and BrCH(CO$_2$Et)$_2$. These dis-
tinctions are consistent with the results of entries 10–12 in
Table 1. With [Ir(dpF(CF$_3$)ppy)$_2$(dtbbppy)]PF$_6$ ($E_{1/2}^{IV/III} = −0.90$ V [vs Fc$^*$/$Fc^{*+}$]) as the photocatalyst, almost the same
redox characteristics indicate the same oxidative quenching
mechanism. The ground state reduction potential of Ir$^{4+}$
intermediate ($E_{1/2}^{IV/III} = +1.68$ V [vs Fc$^*$/$Fc^{*+}$]) is similar to
that of Ru$^{3+}$ ($E_{1/2}^{III/II} = +1.28$ V [vs Fc$^*$/$Fc^{*+}$]), which also sup-
ports the subsequent oxidation step (Table 1, entry 11). In
turn, the excited species [Ru(bpz)$_3$]$^{2+*}$ ($E_{1/2}^{III/II} = −0.27$ V [vs
Fc$^*$/$Fc^{*+}$])$_{12}$ has weaker oxidation potential for the reduction of
BrCCl$_3$. 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 BrCCl$_3$
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 rad-
icals such as acyl radicals are known to favor the attack at

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**Figure 1** Cyclic voltammograms (100 mV/s scan rate) of blank (black) and hydrazone 10 (5.0 mM, blue) recorded in 0.1 M tetrabutylammonium hexafluorophosphate 2-propanol electrolyte. Electrochemical potential was referenced to Fc$^*$/$Fc^{*+}$.

**Figure 2** Cyclic voltammograms (100 mV/s scan rate) of blank (black) and BrCCl$_3$ (5.0 mM, blue) recorded in 0.1 M tetrabutylammonium hexafluorophosphate 2-propanol electrolyte. Electrochemical potential was referenced to Fc$^*$/$Fc^{*+}$.
Deprotonation affords alkenyl-hydrazine 26 that is then susceptible to [3,3]-sigmatropic rearrangement to form a C–C bond to give 27. The following cyclization forms indoline 28. 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 29, formed by expelling the chloride. Final removal of iminophosgene and isomerization gives indole 13. Slow formation of indole 13 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 24. This mechanism could account for the typical induction period of the reaction before following the similar transformations to give the same alkenylhydrazine 26 possibly through 30.

Uncatalyzed Path

Oxidative Quenching Cycle

\[ \text{Oxidative Quenching Cycle} \]

\[ [\text{Ru(bpy)}_3]^{2+*} \rightarrow [\text{Ru(bpy)}_3]^{3+} \]

\[ h\nu \text{BrCCl}_3 \]

\[ \text{Br}^- + \text{CCl}_3 \]

\[ \text{A} \]

\[ [\text{Ru(bpy)}_3]^{2+*} \]

\[ \text{h}\nu \text{BrCCl}_3 \]

\[ \text{Br}^- + \text{CCl}_3 \]

\[ \text{N} \]

\[ \text{Ph} \]

\[ \text{t}-\text{Bu} \]

\[ \text{H} \]

\[ \text{H} \]

\[ \text{Cl}^- \]

\[ \text{H}_2\text{O} \]

\[ \text{N} \]

\[ \text{Ph} \]

\[ \text{t}-\text{Bu} \]

\[ \text{CCl}_3 \]

\[ \text{N} \]

\[ \text{Ph} \]

\[ \text{t}-\text{Bu} \]

\[ \text{CCl}_3 \]

\[ 10 \]

\[ 24 \]

\[ 25 \]

\[ 26 \]

\[ 27 \]

\[ 28 \]

\[ 29 \]

\[ 30 \]

Scheme 5 Proposed reaction mechanism for the photoredox Fischer indole synthesis

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 hydrazene 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 in ppm relative to the central line of the triplet for CDCl3 (7.26 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.
Typical Procedure for the Synthesis of N,N-Diphenylhydrazones

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 EtO (2 ×). The combined organic extracts were washed with brine and dried over anhyd Na2SO4, filtered; and concentrated in vacuo. The residue was purified by column chromatography on silica gel (n-hexane/EtOAc 100:1 to 40:1) to afford hydrazone 10 (7.8 g, 24 mmol, 70%) as a pale brown solid, mp 58.0–59.0 °C; [a]D = −15.1 (c 1, CHCl3); 1H and 13C NMR spectra were identical with the literature data.17


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Supporting Information
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