Herein, we disclose a direct photolysis approach for the generation of tertiary alkyl radicals from 4-tert-alkyl-1,4-dihydropyridines (DHPs) under blue LED irradiation, as exemplified in a photochemical Giese reaction. Radical generation occurs under mild conditions, does not require the use of exogenous photocatalysts or oxidants, and the Giese reaction is compatible with a range of 4-tert-alkyl-DHPs and Michael acceptors (23 examples, up to 86% yield). Mechanistic investigations reveal that the presence of base is crucial for radical generation.

Carbon-centered radicals have become a key tool in the construction of complex molecules which has been driven by the development of many elegant methods for mild radical generation.1–3 In this light, significant progress has also been made in the development of new carbon-radical precursors.4 Among these, 4-alkyl-1,4-dihydropyridines (DHPs), which can be synthesized in a single step from aldehyde feedstocks, have been widely employed as precursors to alkyl radicals in photoredox transformations.5–15 Inspired by seminal work from Fukuwumi on 4-alkyl substituted NADH analogues,16 oxidation of 4-alkyl-1,4-DHP triggers a homolysis event to generate the corresponding alkyl radical which can then engage in a variety of C–C bond forming reactions.

As part of our ongoing studies of catalytic charge-transfer complex (CTC) photochemistry, we examined the Giese reaction of alkyl radicals generated from 4-alkyl-DHPs mediated by titanium dioxide (TiO2). While TiO2 photochemistry generally requires UV-A irradiation,17 we hypothesized that 4-alkyl-DHPs could associate to the surface of TiO2, resulting in a CTC that could be leveraged for the photogeneration of alkyl radicals using visible-light.18, 19 During our optimization studies of the radical Giese addition20 to benzyl acrylate using 4-tert-butyldihydropyridine 1 as the radical precursor, we discovered that the reaction proceeded efficiently even in the absence of TiO2 under blue LED (456 nm) irradiation (Scheme 1A, see ESI for experimental conditions and full reaction optimization). This reactivity initially came as a surprise, as none of the individual reaction components absorb at this wavelength (vide infra). However, we were excited by this observation as it provides a potential route for alkyl radical generation from 4-alkyl-DHPs under visible-light irradiation without the need for an exogeneous photocatalyst, which is generally a precious metal complex, or an oxidant. Highlighting the unusual nature of this reactivity at 456 nm, a comparable example from Melchiorre and co-workers is highlighted in Scheme 1B. Using the same 4-tert-butyl-DHP (1), the authors reported no reactivity when irradiating at 405 nm.11 However, when irradiating at 365 nm, the reaction proceeds efficiently, giving 80% yield of the desired Giese adduct. Melchiorre and co-workers noted that 365 nm was needed to directly sensitize 1 to the excited state, which is then oxidatively quenched by Ni(bpy)2(BF4)2 to generate a radical cation that ultimately homolyzes to yield a tert-butyl radical.

Scheme 1. (A) Initial observations for the direct photolysis of 4-tert-alkyl-DHPs using 456 nm irradiation. (B) Prior work from Melchiorre and co-workers for the photolysis of 4-tert-alkyl-DHPs using Ni(bpy)2(BF4)2 as a redox mediator.

A common theme in the various methodologies employing 4-alkyl-DHPs as radical precursors is that the reactions require some chemical entity to oxidize the DHP to the radical cation to furnish the alkyl radical. This is typically achieved using either a photocatalyst or through direct excitation of the DHP in the presence of an oxidant. Furthermore, reactions which proceed through direct sensitization require higher energy wavelengths (365 or 405 nm) to excite the 4-alkyl-DHP.10, 11 In this work, we present an approach for the direct photolysis of 4-tert-alkyl-DHPs under 456 nm irradiation. Our method represents a rare example of alkyl radical generation from DHPs in the absence of any exogenous photocatalyst or oxidant, and which does not require the use of higher energy UV-A wavelengths for direct sensitization. Furthermore, this example is mechanistically distinct in that the homolysis event does not occur through the
radical cation, but through the direct photolysis of the DHP anion, which absorbs strongly in the visible region.

After an extensive screening of reaction conditions (see ESI), we found that the Giese addition to benzyl acrylate proceeded efficiently using 1.2 equiv of 1 as the radical precursor in the presence of Cs$_2$CO$_3$ (1.0 equiv) and H$_2$O (10 equiv) in MeCN under irradiation from two 30 W 456 nm LEDs for 4 h, generating the desired Giese adduct 2 in 73% NMR yield (Table 1, entry 1). Performing the reaction in dry MeCN resulted in a slight decrease in the yield (entry 2). The reaction concentration could be increased up to 0.1 M, albeit resulting in a slight reduction in the yield of 2 (see ESI). Performing the reaction under air, in the dark, and in the absence of Cs$_2$CO$_3$ all lead to only trace amounts of 2 being formed, indicating that each of these components is crucial for reactivity (entries 3-5). Addition of TEMPO to the reaction also suppressed formation of 2 and 44% of the tert-butyl-TEMPO adduct was observed, supporting the formation of radical intermediates.

Table 1. Optimization and control reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Modifications from Standard Conditions</th>
<th>Product Yield$^{[a]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>No H$_2$O</td>
<td>52%</td>
</tr>
<tr>
<td>3</td>
<td>Under Air</td>
<td>5%</td>
</tr>
<tr>
<td>4</td>
<td>In the Dark</td>
<td>Trace</td>
</tr>
<tr>
<td>5</td>
<td>No Cs$_2$CO$_3$</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>1.0 equiv TEMPO Added</td>
<td>N.D.$^{[b]}$</td>
</tr>
</tbody>
</table>

$^{[a]}$ Yields determined by $^1$H NMR analysis using methyl 4-chlorobenzoate as an external standard. $^{[b]}$ 44% yield of the tert-butyl-TEMPO adduct was observed by $^1$H NMR. N.D.: not detected.

With the optimized conditions identified, we examined the scope of the Giese addition reaction using 4-tert-alkyl-DHPs as radical precursors (Scheme 2). A series of acrylates (2-5), phenyl vinyl sulfone (6), acrylamides (7,8) and other Michael acceptors bearing ester groups (9-12) were all well tolerated using this method. Dehydroalanines were also found to be suitable Michael acceptors under our reaction conditions (13-15), highlighting the potential utility of this method for the preparation of unnatural amino acid derivatives.$^{22}$ Other 4-tert-alkyl-DHPs, such as adamantyl (16), methylcyclohexyl (17-21), methyl isobutyrate (22), and DHPs derived from gemfibrozil (23) and clofibric acid (24) could also be employed as tert-alkyl radical precursors. DHPs bearing benzylic substituents at C4 could also be photolyzed efficiently under our reaction conditions, however, the corresponding benzylic radicals did not participate in the Giese addition reaction (see ESI).

Scheme 2. Reaction scope.$^{[a]}$

![Scheme 2 Reaction Scope](image)

$^{[a]}$ Yields of isolated, purified products after irradiation for 4 h using the optimized conditions (see ESI).

We postulated that the base, Cs$_2$CO$_3$, played a crucial role in generating the light-absorbing species in the reaction. During our reactions, we observed that upon the addition of Cs$_2$CO$_3$, the reaction mixture changed from colourless to yellow. This change was also detected by UV-vis spectroscopy, where a large redshift in the absorption spectrum of 1 was observed after the addition of Cs$_2$CO$_3$ (Scheme 3A). This large redshift is likely from the formation of the DHP anion, which has previously been shown to absorb strongly in the visible region.$^{23}$ To determine if Cs$_2$CO$_3$ was crucial for the direct photolysis of 1, we performed control experiments in the absence of a Michael acceptor (Scheme 3B). Under standard conditions (with Cs$_2$CO$_3$), only 10% of 1 was recovered, and 26% of the pyridine by-product (22) was detected. In contrast, the majority of 1 was recovered and 22 not detected in the absence of Cs$_2$CO$_3$. UV-vis studies also demonstrated that an electron donor-acceptor (EDA) complex between the DHP anion and the Michael acceptor was unlikely under our reaction conditions (see ESI).$^{24}$
Since our control experiments indicate that the DHP anion is the photoactive species under our reaction conditions, we hypothesized that the reactivity could be significantly impacted by the NH acidity of the DHP. Prior work by Dubur and co-workers demonstrated that the NH acidity of DHPs is heavily influenced by the substituents at the C3 and C5 positions (Table 2). If CN groups are located at C3 and C5 (1), the $pK_a$ of the DHP was determined to be 16.7, whereas the $pK_a$ increases to 20.1 if the DHP contains CO₂Et groups (23). By comparing the initial rates of both corresponding 4-tert-butyl-DHPs, we see an eleven-fold faster rate for 1. After 4 h, only 8% of the desired product is observed when 23 is employed. The slow rates for the reaction with 23 likely stems from a reduced concentration of the corresponding DHP anion, which is also supported by the UV-vis data (see ESI). These results further suggest that the generation and photolysis of the DHP anion is key for initiating the photochemical Giese reaction.

Scheme 3. (A) Absorption spectra of 1 and 1 + Cs₂CO₃. [1] = 45 mM, [Cs₂CO₃] = 37.5 mM in MeCN. (B) Control experiments in the absence of a Michael acceptor (See ESI for experimental conditions, N.D: not detected).

<table>
<thead>
<tr>
<th>R Group</th>
<th>0.15 mmol</th>
<th>t = 2 h</th>
<th>t = 4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN (1)</td>
<td>DHP pKₐ [2]</td>
<td>16.7</td>
<td>33%</td>
</tr>
<tr>
<td>CO₂Et (23)</td>
<td>20.1</td>
<td>3%</td>
<td>8%</td>
</tr>
</tbody>
</table>

[a] Yields determined by ³H NMR analysis using methyl 4-chlorobenzoate as an external standard. [b] pKₐ values correspond to DHPs bearing no substituents at C4 (ref 23).

The proposed mechanism of this transformation is outlined in Scheme 4. The 4-tert-alkyl-DHP is deprotonated by Cs₂CO₃, yielding the corresponding anion (I) which is capable of absorbing at 456 nm. Excitation of the DHP anion is followed by homolysis to generate a tert-alkyl radical and a DHP radical anion (II). Giese addition to a Michael acceptor (See ESI) by the observed low quantum yield (b) for the Giese reaction ($4.1 \times 10^{-4}$) indicates that chain propagation is unlikely (see ESI), we ultimately cannot rule out that III could also be reduced by 1, 1 or 1⁺. Protonation of IV by H₂O gives the final Giese adduct (2), and deuterium incorporation studies support that either H₂O or 1 can serve as the proton source for this final step (see ESI).

Scheme 4. Proposed mechanism.

Conclusions

In the presence of a suitable base, 4-tert-alkyl-DHPs can be directly photolyzed using blue (456 nm) LED irradiation. This unique reactivity allows for 4-tert-alkyl-DHPs to be used as radical precursors in photochemical Giese reactions in the absence of a photocatalyst or external oxidant. The reaction is suggested to proceed via excitation of the DHP anion, owing to its significantly redshifted absorption compared to the corresponding neutral DHP. Our work demonstrates a unique reactivity pathway for DHPs, in which the homolysis event leading to alkyl radicals does not proceed through the DHP radical cation but through a direct photolysis mechanism.
Conflicts of interest
There are no conflicts to declare.

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Notes and references