Dual Hypervalent Iodine(III) Reagents and Photoredox Catalysis Enable Decarboxylative Ynonylation under Mild Conditions

Hanchu Huang, Guojin Zhang, and Yiyun Chen*

Abstract: A combination of hypervalent iodine(III) reagents (HIR) and photoredox catalysis with visible light has enabled chemoselective decarboxylative ynonylation to construct ynone, ynamides, and ynoates. This ynonylation occurs effectively under mild reaction conditions at room temperature and on substrates with various sensitive and reactive functional groups. The reaction represents the first HIR/photoredox dual catalysis to form acyl radicals from α-ketoacids, followed by an unprecedented acyl radical addition to HIR-bound alkynes. Its efficient construction of an mGlu5 receptor inhibitor under neutral aqueous conditions suggests future visible-light-induced biological applications.

Organic carboxylates are readily available and stable, and a removable carboxylate acts as a latent activating group for organic synthesis.[1] Transition metals are widely used to activate carboxylates through formation of a transition-metal/carboxylate complex which facilitates extrusion of carbon dioxide.[2] Hypervalent iodine(III) reagents (HIR) demonstrate reactivity similar to transition metals, however, the analogous reactivity of HIR–carboxylate complexes has been less explored [Eq. (1)].[3] Our group recently discovered that HIR activated vinyl carboxylates similar to transition metals, which enabled radical addition followed by decarboxylation [Eq. (2)].[4] α-Ketoacids are important acyl synthons in organic synthesis; however, transition-metal-mediated decarboxylation requires activation by a transition metal followed by heating or strong oxidants.[5] We speculate that by forming the hypothetical HIR-ketoacid intermediate and subsequent photoredox catalysis, the decarboxylative acyl radical formation might be possible under mild reaction conditions [Eq. (3)].[6]

Ynones, ynamides, and ynoates are important structural motifs for the syntheses of natural products and heterocyclic molecules.[7] Although the transition-metal-catalyzed ynonylation by cross-coupling the acyl equivalent and the alkylene equivalent has been reported, such a ynonylation approach is limited and has poor functional-group tolerance because of the instability of the acyl halides used [Eq. (4)].[8,9] By using the readily available and stable α-ketoacids, we herein report the first decarboxylative ynonylation to construct ynone, ynamides, and ynoates by a HIR/photoredox dual catalysis [Eq. (4)].

We started our investigation with benzoylformic acid (1) by using the hypervalent iodine photoredox system[10] under irradiation with blue light-emitting diodes (LEDs, \( \lambda_{\text{max}} = 468 \pm 25 \text{ nm} \)). Although terminal alkynes gave no ynonylation adducts, alkynyl bromides and alkynyl sulfones with acetoxbenziodoxole (BI-OAc) as additives gave the desired ynone in low yields (Table 1, entries 1–3). To our delight, an alkynyl benziodoxole (BI-alkyne) gave ynone 3 in 81% yield. BI-alkyne was known as an electrophilic alkyne acceptor, but its tendency for acyl radical addition was unprecedented (entries 4).[10–12] Cyclic HIR reagents[13] including BI-OAc, hydroxybenziodoxole (BI-OH), and methoxynbenziodoxole (BI-OMe) were all effective, among which BI-OAc was the most efficient with a yield of 85% (77% yield of isolated product; entries 5–7). Photosensitizer, light, and BI-OAc were all critical for this reaction (see Table S3 in the Supporting Information).[14]

We evaluated the substrate scope of the reaction under the optimized reaction conditions (Table 1, entry 5). Benzoylformic acids bearing an electron-rich 4-methyl or 4-methoxyl group yielded ynones 4 and 5 smoothly, and
electron-deficient 3-ester, 4-trifluoromethyl, or 4-fluoro derivatives yielded ynones 6–8 in yields of 62–87% (Scheme 1). Functional groups sensitive to transition-metal catalysis remained intact in the reaction, including aryl bromides and aryl iodides, which could be readily used as synthetic handles for further derivatizations (9 and 10). Substrates with allyl esters, propargyl esters, alcohols, and azides (11–14), which were not tolerated in other transition-metal-catalyzed reactions,[9a] all performed uneventfully. Steric bulk did not affect the reaction, with ynones 15 and 16 obtained in yields of 75 and 81%, respectively. Heterocyclic thiophenes, furans, and indoles reacted smoothly to give ynones 17–19. Notably, alkyl-substituted ketoacids decarboxylated to give coupling adducts: Primary and secondary alkyl ketoacids gave ynones without decarbonylation in 66% and 82% yields, respectively (20, 21), while the tertiary alkyl ketoacid gave the dual decarboxylative-decarbonylative alkyne coupling product 22 in 73% yield.[15]

In addition to aryl- and alkyl-substituted α-ketoacids, carbamoyl ketoacids readily reacted to give ynamides: Primary carbamoyl ketoacids reacted to give, in yields of 61–69%, primary ynamide products, which could not be obtained by transition-metal-catalyzed aminocarbonylation because of the catalytic inhibition of primary amines by transition metals (23–28).[16] Secondary carbamoyl ketoacids including aliphatic amines and aniline substitutions all showed excellent reactivity (29–33). Alkoxycarbonyl ketoacids reacted to give ynoates: Primary and secondary alkoxycarbonyl ketoacids gave ynones 34 and 35 in yields of 75% and 63%, respectively, while tertiary alkoxycarbonyl ketoacid interestingly gave the dual-decarboxylative alkyne coupling product 22 in 53% yield.[16] We also investigated the reactivity of different BI-alkynes and found that aryl-, alkyl-, and silyl-substituted ynones were all obtained smoothly. Various aryl substituents were tolerated on the BI-alkynes including electron-rich methoxy and phenyl groups, as well as electron-deficient chlorides, ketones, aldehydes, and nitriles (36–41, 45–47). Alkyl-substituted BI-alkynes including bulky tert-butyl and linear hexyl groups resulted in slightly lower yields (43, 44, 49). The silyl-substituted BI-alkynes gave 42 and 48 in yields of 61 and 70%, respectively, which could be easily deprotected to give terminal ynones.

This observed broad substrate scope is unprecedented due to the mild reaction conditions for the dual HIR/photoredox catalysis, which prompted us to investigate the mechanism of the reaction. The radical quencher 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) was added to the reaction mixture, and no significant decrease in yield was observed, indicating that the reaction proceeds via a radical pathway.

Table 1: Optimization of the ynonylation reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>t [h]</th>
<th>Conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H, CH₂Cl₂/H₂O</td>
<td>10</td>
<td>91%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2</td>
<td>Br, CH₂Cl₂/H₂O</td>
<td>10</td>
<td>82%</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>Ts, CH₂Cl₂/H₂O</td>
<td>10</td>
<td>&gt;95%</td>
<td>39%</td>
</tr>
<tr>
<td>4</td>
<td>BI, CH₂Cl₂/H₂O</td>
<td>10</td>
<td>&gt;95%</td>
<td>81%</td>
</tr>
<tr>
<td>5</td>
<td>BI-OAc (1.0 equiv)</td>
<td>5</td>
<td>&gt;95%</td>
<td>59%</td>
</tr>
<tr>
<td>6</td>
<td>entry 5, BI-OH</td>
<td>5</td>
<td>87%</td>
<td>69%</td>
</tr>
<tr>
<td>7</td>
<td>entry 5, BI-OMe</td>
<td>5</td>
<td>&gt;95%</td>
<td>74%</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1 (0.15 mmol), 2 (0.10 mmol), BI-OAc (0.15 mmol), and [Ru(bpy)₃]PF₆ (0.002 mmol) in 2.0 mL CH₂Cl₂ under nitrogen gas with 4 W LED irradiation at 468 nm at 25°C, unless otherwise noted. [b] Conversions and yields were determined by ¹H NMR analysis, yields of isolated products are given in parentheses.

idinoyl (TEMPO) inhibited the ynonylation reaction and yielded the TEMPO addition adduct 51 in 81% yield (Scheme 2a). When benzoylformic acid (1) was injected into the reaction condition in the absence of BI-alkyne 50, the formation of the decarboxylative diketone adduct through dimerization further confirmed the acyl radical intermediate (see Scheme S3 in the Supporting Information).

We next mixed the ketoacid 52 (circles in Scheme 2c) with BI-OAc and observed a new set of signals (triangles in Scheme 2c) in the 1H NMR spectrum, thus indicating the formation of a new ketoacid/benziodoxole complex. We further developed methods to prepare the stable, but previously unknown, BI-ketoacid complex 53, and found the identical signals in the 1H NMR spectrum (labeled with triangles, see the Supporting Information for details). This BI-ketoacid complex 53 could substitute ketoacid 52 andBI-OAc in the ynonylation reaction to yield ynone 9 in 63% yield, which additionally confirmed the BI–ketoacid complex as the reaction intermediate (Scheme 2c). We also carried out 13C isotopic-labeling experiments to explore how the acyl radical added to the BI-alkyne. By using the 13C-labeled BI-alkyne 55, we found exclusive 13C retention in 56, which was formed in 70% yield. As the migration of the ester group was generally difficult,[21] a β-addition followed by an exclusive ester migration was unlikely (bottom equation in Scheme 2d), thus an α-addition[22] accompanied by benziodoxole radical elimination was suggested (top equation in Scheme 2d).

Based on the mechanistic investigations above, we propose that the ketoacid and BI-OAc generated a benziodoxole/ketoacid complex (BI–O2COR') in situ, which was subsequently oxidized by [Ru(bpy)3]3+ to the acyl radical after decarboxylation (Scheme 3). The resulting benziodoxole cation (BI+ or the BI-OAc) and [Ru(bpy)3]2+ were regenerated for new HIR catalysis and photoredox catalysis cycle.[13] The acyl radical undergoes α-addition to BI-alkyne to yield the ynone, and the eliminated benziodoxole radical oxidizes the photoexcited [Ru(bpy)3]2+* to complete the photoredox cycle[10].

We next aimed to construct ynamide 60, the structural motif of which represents an effective inhibitor for the metabotropic glutamate receptor 5 (mGlu5 receptor) and has therapeutic potential for disorders of both the peripheral and central nervous system.[24] Under the standard ynonylation conditions, ynamide 60 can be obtained in 75% yield on a gram scale (see the Supporting Information for details). As the hypervalent-iodine reagent/photoredox system was shown
to be compatible with biomolecules.\cite{10} we were curious if this ynone formation could be run under neutral aqueous reaction conditions. To our delight, the carbamoyl ketoacid 58 in pH 7.4 phosphate buffered saline (PBS) gave ynone 60 in 83% yield (Scheme 4). The addition of cell lysates as complex biomolecule mixtures did not inhibit the reaction\cite{23} and the ynone could be run at a 1 mM concentration in 75% yield within 15 min, with reaction kinetics sufficient for biomolecule studies.\cite{24} We envision this visible-light-induced construction of bioactive molecules under neutral aqueous conditions will be useful for biological studies.\cite{27}

In conclusion, we have developed the first decarboxylation/ynone formation by dual hypervalent iodine(III) reagents/photoreduct catalysis, where the HIR demonstrates reactivity similar to or even superior to transition metals. This novel ynone formation method constructs ynoones, ynamides, and ynoates with broad substrate scope, excellent chemoselectivity, and under mild reaction conditions at room temperature. The further reactivity and biological applications of this dual HIR/photoreduct system is under investigation in our laboratory.

**Keywords:** decarboxylation · homogenous catalysis · hypervalent compounds · photochemistry · ynone formation

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6. The HIR-ketoacid complex was reported before; however, only the oxidative reactivity of HIR was demonstrated, see H. Togo, M. Katohgi, Synlett 2001, 565–581.

**Scheme 4.** Construction of an mGlu5 receptor inhibitor under neutral aqueous reaction conditions.

