Photochemistry

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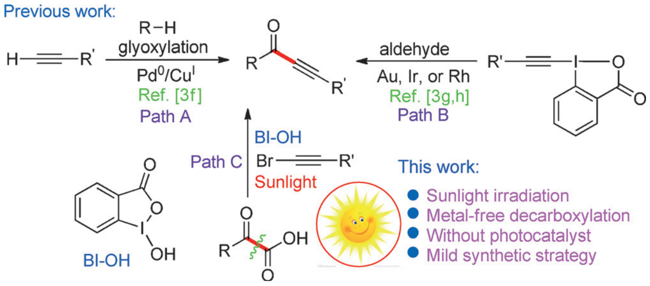
Sunlight-Driven Decarboxylative Alkynylation of α-Keto Acids with Bromoacetylenes by Hypervalent Iodine Reagent Catalysis: A Facile Approach to Ynones[**]

Hui Tan, Hongji Li, Wangqin Ji, and Lei Wang**

***Abstract:** A novel and practical decarboxylative alkynylation of α-keto acids with bromoacetylenes is catalyzed by hypervalent iodine(III) reagents when irradiation by sunlight at room temperature. The product ynones are generated in good yields. Experiments show that results obtained with blue light (λ = 450–455 nm) are comparable to those obtained when using sunlight. Mechanistic studies demonstrate that the sunlight-driven decarboxylation undergoes a radical process.*

The prevalence of carbonyl compounds as structural motifs[1] in natural products[1c–e] and pharmaceutical compounds[1f] has been recognized in organic synthesis. Especially ynones, which are often used as building blocks for the construction of target molecules with unique properties.[2] In the literature, ynones are used as attractive precursors to a number of heterocycles, such as furans,[2e] pyrazoles,[2f,g] flavones,[2h] and others.[2i–l] Because of these facts, a variety of strategies have been developed for the synthesis of ynones.[3] For examples, Muller and co-workers employed a Pd/Cu bimetallic catalyst to realize the one-pot coupling of acyl chlorides with terminal alkynes, and this method was also extended to ynediones (Scheme 1, Path A).[3f] More recently, Huang and co-workers developed an alternative approach to ynones from aldehydes and hypervalent alkynyl iodides through gold-catalyzed aerobic oxidation (Scheme 1, Path B).[3g] Very recently, Li and co-workers reported an iridium- and rhodium-catalyzed chelation-assisted formyl C−H alkynylation (Scheme 1, Path B).[3h] Despite the successful synthesis of ynones, current methods always suffer from significant limitations, including the requirement of high temperature, excessive additives, and toxic metals.[3] Therefore, developing a mild and green method for the synthesis of ynones is highly desirable.



Scheme 1. Synthetic strategies for ynones.

A photocatalysis strategy may provide a better alternative in organic synthesis because it avoids additional ligands, bases, and elevated temperatures.[4] Recent studies in photochemistry have reported the formation of C−C and C–heteroatom bonds by using visible-light and either ruthenium or iridium complexes, or organic dyes as photoredox catalysts.[5] It is well known that among renewable energy sources, sunlight is the largest energy source.[6] Using sunlight would solve the energy crisis and the drawbacks of traditional photochemical reactions which require UV-light.[7] Recently, α-keto acids were used as acylating reagents, through a decarboxylative process to form an acyl free radical along with extrusion of CO_2, in ketone synthesis owing to their high reactivity.[8] Meanwhile, the application of hypervalent iodine reagents (HIRs) has been been used in organic synthesis,[9] and HIRs were effective reagents for organic transformations through visible-light photoredox catalysis in the presence of $[Ru(bpy)_3](PF_6)_2$.[9c,d] Based on this understanding and our work,[8d,e,10] we herein report a novel sunlight-driven decarboxylative alkynylation of α-keto acids with bromoacetylenes[11] using an HIR catalyst under photolysis but in the absence of a visible-light photoredox catalyst, thus representing an energy-efficient approach to ynones (Scheme 1, Path C).

Our initial investigation focused on the model reaction of 2-oxo-2-phenylacetic acid (**1a**) with (bromoethynyl)benzene (**2a**) at room temperature (Table 1). Inspired by the common photoredox catalysts,[4,5] the model reaction was performed with $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (1.0 mol%) as photocatalyst and a catalytic amount of an HIR as an additive under irradiation from a fluorescent bulb (18 W) for 8 hours in toluene. Fortunately, addition of $PhI(OAc)_2$ (30 mol%) gave the desired product **3a** in 12% yield (entry 1). Subsequently, a series of HIRs, such as BI-OAc, BI-OTf, BI-OH, and BI-alkyne, were examined, and an improved yield of **3a** was observed in the presence of BI-OH (entries 2–5). Eosin Y and Na_2-Eosin Y gave lower yields of **3a** (entries 6 and 7). Furthermore, 40% yield of **3a** was achieved when this transformation was performed without the photoredox catalyst (entry 8). To our delight, the reaction exposed to sunlight irradiation underwent the decarboxylative coupling to give **3a**

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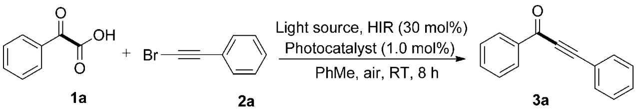
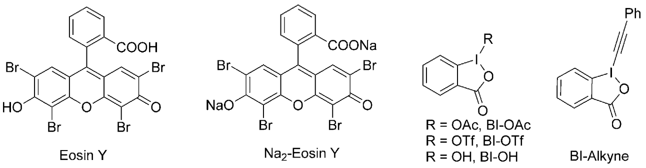
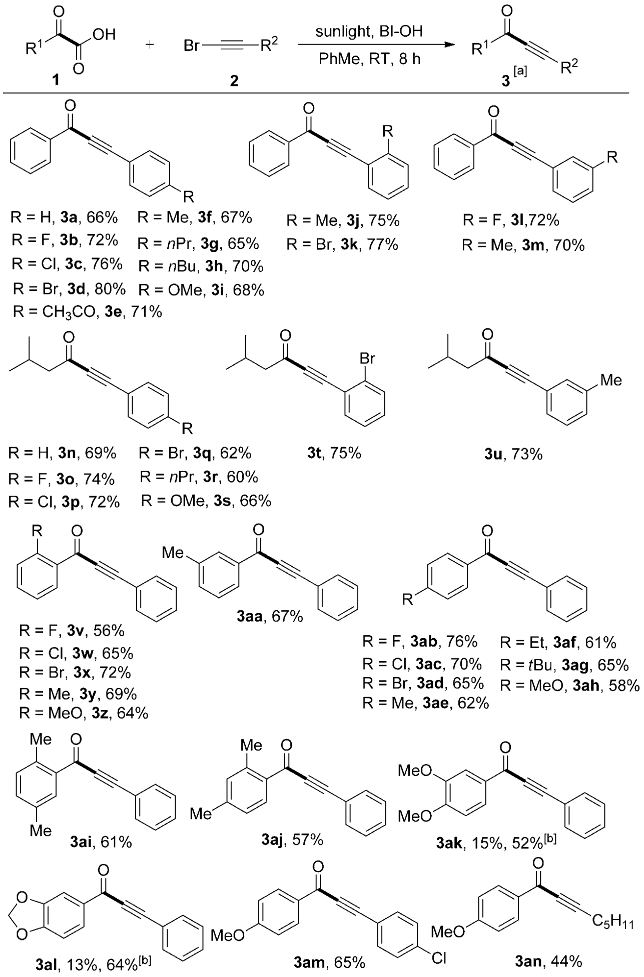
Table 1: Optimization of the reaction conditions.[a]



Entry	Light source	Photocatalyst	HIR	Yield [%][b]
1	light[c]	$[Ru(bpy)_3]Cl_2{\cdot}6\,H_2O$	$PhI(OAc)_2$	12
2	light[c]	$[Ru(bpy)_3]Cl_2{\cdot}6\,H_2O$	BI-OAc	17
3	light[c]	$[Ru(bpy)_3]Cl_2{\cdot}6\,H_2O$	BI-OTf	8
4	light[c]	$[Ru(bpy)_3]Cl_2{\cdot}6\,H_2O$	BI-OH	30
5	light[c]	$[Ru(bpy)_3]Cl_2{\cdot}6\,H_2O$	BI-Alkyne	16
6	light[c]	Eosin Y	BI-OH	23
7	light[c]	Na_2-Eosin Y	BI-OH	25
8	light[c]	–	BI-OH	40
9	sunlight	–	BI-OH	66
10	red LED	–	BI-OH	trace
11	green LED	–	BI-OH	21
12	blue LED	–	BI-OH	63
13	purple LED	–	BI-OH	38
14	UV (226 nm)	–	BI-OH	15
15	sunlight	–	BI-OH	49[d]
16	sunlight	–	BI-OH	67[e]
17	sunlight	–	–	n.r.
18	–	–	BI-OH	n.r.
19	–	–	BI-OH	n.r.[f]
20	–	–	BI-OH	19[g]



[a] Reaction conditions: 2-oxo-2-phenylacetic acid (**1a**, 0.60 mmol), (bromoethynyl)benzene (**2a**, 0.20 mmol), photocatalyst (1.0 mol%), HIR (30 mol%), PhMe (1.0 mL) at room temperature in air for 8 h. [b] Yield of isolated product. [c] Fluorescent bulb (18 W). [d] BI-OH (20 mol%). [e] BI-OH (40 mol%). [f] 60 °C. [g] 90 °C. bpy = 2,2′-bipyridine, n.r. = no reaction.



Scheme 2. The scope of α-keto acids and bromoacetylenes. Reaction conditions: **1** (0.60 mmol), **2** (0.20 mmol), BI-OH (30 mol%), PhMe (1.0 mL), sunlight irradiation at room temperature for 8 h. [a] Yield of isolated product. [b] 2 equiv of $PhI(OAc)_2$.

in 66% yield (entry 9). Further screening of light sources demonstrated that blue LED (450–455 nm) plays an important role in this alkynylation, thus providing **3a** in a yield comparable to that obtained under sunlight irradiation (entries 10–14). Changing the amount of BI-OH up to 40 mol% did not enhance the transformation (entries 15 and 16). The addition of BI-OH is essential in the reaction (entry 17). Specifically, no **3a** was formed when the reaction was performed at either room temperature or 60 °C, and 19% yield of **3a** was obtained at 90 °C in the dark (entries 18–20). It was found that decomposition of BI-OH produces 2-iodobenzoic acid and accounted for 30 mol% of BI-OH (a higher catalytic amount) used in this reaction.[12] In addition, solvent screening indicated that toluene is the best reaction medium (see Table S1 in the Supporting Information).

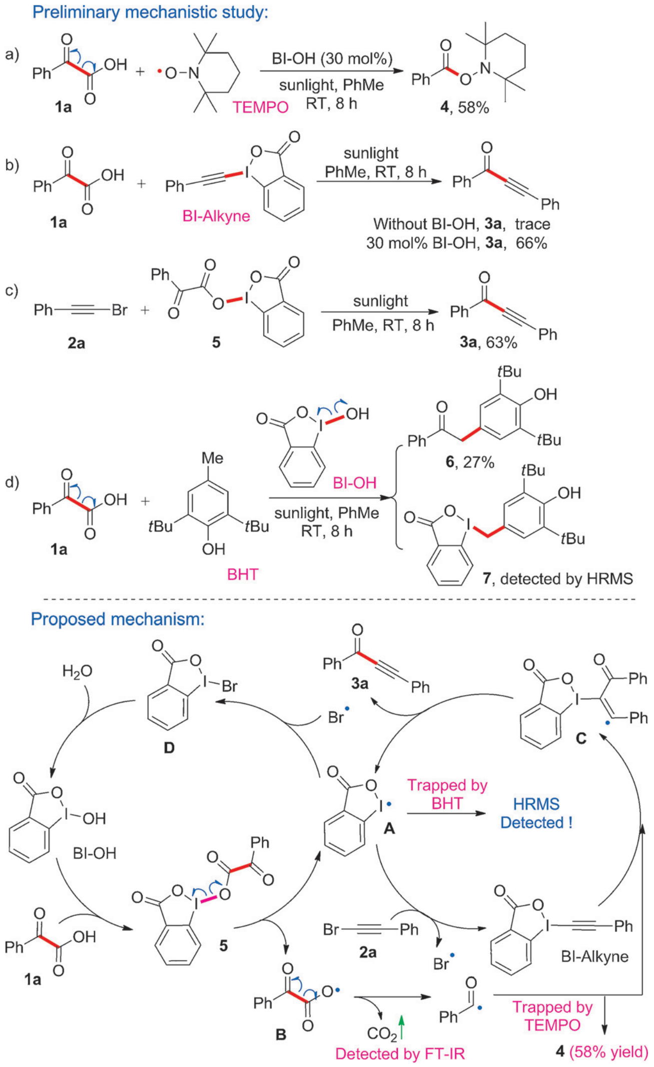
To our knowledge, this sunlight-driven reaction is novel and represents a successful example of photochemistry. The optimized reaction conditions were applied to the decarboxylative alkynylation of a variety of α-keto acids (**1**) with bromoacetylenes (**2**), as described in Scheme 2. Firstly, bromoacetylenes with F, Cl, Br, MeCO, Me, *n*Pr, *n*Bu, and MeO groups, at *para*-positions of the benzene rings in 2-aryl-1-bromoethynes, reacted with **1a** to afford the products **3b–i** in 62–80% yields. The results indicated that bromoacetylenes with attached electron-withdrawing groups on the benzene rings seemed to accelerate the transformation, and bromoacetylenes with electron-donating groups gave the inferior yields (**3b–e** veresus **3f–i**). In contrast, 2-aryl-1-bromoethynes bearing Br and Me at the *ortho*-positions, and F and Me at the *meta*-positions of the benzene rings demonstrated comparable reactivity in the reaction, with the formation of the corresponding ynones in good yields (**3j–m**). 4-Methyl-2-oxopentanoic acid (**1b**) reacted with a series of *ortho*-, *meta*-, and *para*-substituted 2-aryl-1-bromoethynes, and the desired products **3n–u** were obtained in 60–74% yields. In contrast, a variety of 2-oxo-2-arylacetic acids were used to extend the substrate scope. When 2-oxo-2-arylacetic acids, with *ortho*-substitutes, such as F, Cl, Br, Me, and MeO on the benzene rings, reacted with (bromoethynyl)benzene (**2a**), the corresponding ynones (**3v–z**) were isolated in acceptable yields (of the the *ortho*-position effect is ignored). When the reactions of 2-oxo-2-(*meta*- or *para*-substituted)-phenylacetic acids with **2a** were performed under the optimized reaction conditions, there was no noticeable influence on the formation of ynones (**3aa–ah**). It should be noted that dimethyl-substituted 2-oxo-2-arylacetic acids in the reaction with **2a** generated the anticipated ynones (**3ai** and **3aj**) in 57 and 61 % yields. The introduction of two strong electron-donating groups (RO) on the aromatic ring of 2-oxo-2-arylacetic acid obviously hindered the decarboxylative process. For example, 2-(3,4-dimethoxyphenyl)-2-oxoacetic acid and 2-(benzo[d][1,3]dioxol-5-yl)-2-oxoacetic acid reacted with **2a** to provide **3ak** (15 %) and **3al** (13 %), respectively. Fortunately, replacing BI-OH with a stoichiometric amount of $PhI(OAc)_2$ gave moderate yields of **3ak** and **3al**. It is important to note that the reaction of aliphatic bromoacetylene (1-bromohept-1-yne) with 2-(4-methoxyphenyl)-2-oxoacetic acid produced **3an** in 44 % yield.

We next attempted to explore the more challenging alkynylation using a terminal alkyne, instead of bromoacetylene, with an α-keto acid. When the reaction of phenylacetylene with **1a** was performed in PhMe with BI-OH as additive and irradiated by sunlight at room temperature for 8 hours, **3a** was isolated in 23 % yield. To improve the yield of **3a**, the formation of (bromoethynyl)benzene in situ was considered to accelerate this process. When NBS, $AgNO_3$, and phenylacetylene were added into the reaction, **3a** was obtained in 36 % yield (see the Supporting Information for full details).

To understand this decarboxylative process, we conducted intermediate-trapping experiments as shown in Scheme 3. In the presence of BI-OH and sunlight irradiation, the benzoyl radical derived from **1a** was in situ trapped by TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), thus affording **4** in 58 % yield (Scheme 3 a).[13] Next, an equivalent of BI-Alkyne was directly used for the alkynylation of **1a**, and only trace amounts of **3a** were observed. Interestingly, when employing 30 mol % BI-OH as the catalyst **3a** was formed in 66 % yield (Scheme 3 b). The prepared hypervalent iodine reagent **5** was used to react with **2a**, thus affording **3a** in 63 % yield (Scheme 3 c). These results imply that BI-Alkyne and **5** may be important intermediates involved in the reaction. Moreover, BHT (2,6-di-*tert*-butyl-4-methylphenol)[14] could trap both the iodanyl radical and benzoyl radical to generate **6** and **7** (Scheme 3 d).

Based on the preliminary study, a possible mechanism for the reaction is proposed in Scheme 3. Firstly, BI-OH reacts with 2-oxo-2-phenylacetic acid (**1a**) to form the intermediate **5**,[15] and is initiated by sunlight irradiation to generate the iodanyl radical **A**[9e,16] and acyl radical **B**. Next, **A** reacts with **2a** to give BI-Alkyne and a Br radical. Then an addition[9b–d] of the benzoyl radical, from decarboxylation of **B** (FT-IR analysis of the resulting CO_2 gas; see the Supporting Information),[10] to BI-Alkyne occurs to form **C**, followed by releasing **3a** and **A**. Additionally, a radical coupling reaction between Br radical and **A** produces **D**, which finally undergoes hydrolysis to generate BI-OH.

In conclusion, a sunlight-driven radical alkynylation of α-keto acids with bromoacetylenes catalyzed by BI-OH has been developed. This alkynylation tolerates a series of substituted groups and affords ynones in good yields. Considering the precedent in ynone synthesis, the rare example of sunlight-driven radical alkynylation has an advantage over the reported methods. Our ongoing studies are focused on gaining detailed insights into the reaction mechanism and applying this strategy to other organic transformations.



Scheme 3. Preliminary mechanistic study and proposed mechanism.

Experimental Section

General procedure for sunlight-driven decarboxylative alkynylation: A 5 mL oven-dried reaction vessel equipped with a magnetic stirrer bar was charged with α-oxocarboxylic acid (**1**; 0.60 mmol), alkynyl bromide (**2**; 0.20 mmol), BI-OH (0.06 mmol), and toluene (1.0 mL) in air. The reaction vessel was exposed to sunlight at room temperature for 8 h. After completion of the reaction, the reaction mixture was concentrated to yield the crude mixture, which was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 15:1 to 30:1) to give the desired product **3**.

Keywords: acylation · alkynes · hypervalent compounds · photochemistry · radicals

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