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ARTICLE TYPE

Visible Light-Induced Intermolecular Radical Addition: Facile Access to γ-Ketoesters from Alkyl-Bromocarboxylates and Enamines

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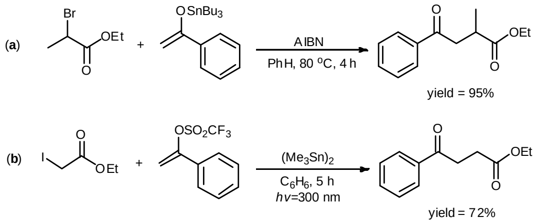
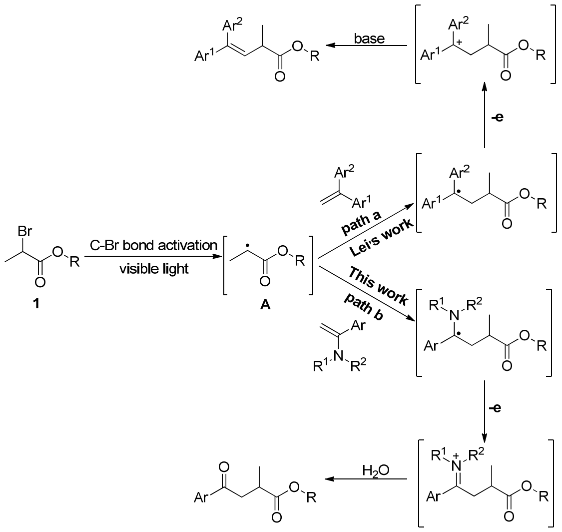
A highly efficient addition of alkyl α-bromocarboxylates to enamines by means of visible light-induced photoredox catalysis is reported. Comparing with the traditional methods, the reaction described herein provided an alternative route to the construction of valuable γ-ketoesters in generally good yields.

Traditional photo-initiated radical reaction was considered as an alternative method in the field of synthetic chemistry. However, the poor selectivity and the need of specialized UV reactors greatly limited its application. Visible-light serves as a new energy source of photo-induced radical reactions and photoredox reaction is showing the power of radical-involving reaction in organic synthesis. It has attracted much attention of many researchers ever since and emerged as a growing field because of the C-X bond formation continues to be a demand in organic synthesis.[1] The free radicals, which are generated by photoredox catalysis can react to construct the bond of C-X (X=C, S, N, O) and so on. For C-C bond formation has been documented by the groups of Stephenson,[2] Gagné,[3] Reiser[4] and Masson.[5] Xiao *et al*. have also reported the formation of C-O.[6] In spite of these significant advances, it remains a highly appealing objective to exploit novel and efficient organic radical precursors and extend their application to more reactions.[7]

γ-Ketoesters are important synthetic intermediates in organic synthesis. The traditional radical synthetic methods are the radicals were irradiated by AIBN or organotin reagent. Hosomi *et al* have reported the reaction of ethyl 2-bromopropanoate with tributylstannyl enolate to give γ-ketoesters initiated by AIBN in benzene at 80 °C (**Scheme 1a**).[8] Kim *et al* have also shown that the photo-stimulated reaction of ethyl α-iodoacetate with vinyl-triflate and hexamethylditin in benzene under irradiation at 300 nm for five hours afforded the target product (**Scheme 1b**).[9] It is still quite limited because organotin compounds were used as either starting material, or a radical initiator, which were not benign to the environment in the reaction.



Scheme 1. The addition of radical to the unsaturated compounds



Scheme 2. The addition of radical to the unsaturated compounds under visible light catalyzed reaction

A carbon-centered radical adds to an unsaturated carbon atom in an appropriate acceptor, followed by fragmentation of the adduct radical, is the key chain extension method for the construction of carbon–carbon bonds. Generation carbonyl alkyl radical is well known from an alkyl α-bromocarboxylates under visible light catalyzed reactions.[10] Lei *et al* have succeeded in the addition of carbonyl alkyl radical and alkene to obtain unsaturated ester compounds **(Scheme 2, path a).** We attempted to find an appropriate acceptor to trap the carbon-centered electron

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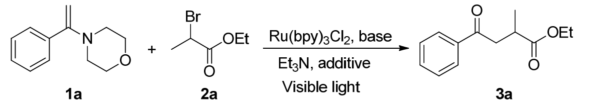
deficient radical, followed by the transformation of one electron, to form iminium cation, and eventually, γ-ketoesters was achieved (**Scheme 2, path b**). Considering that the α-carbonyl alkyl radical is relatively electrophilic, electron-rich alkenes may be beneficial to the reaction,[11] and therefore, enamines were preferentially chosen to test the reaction.

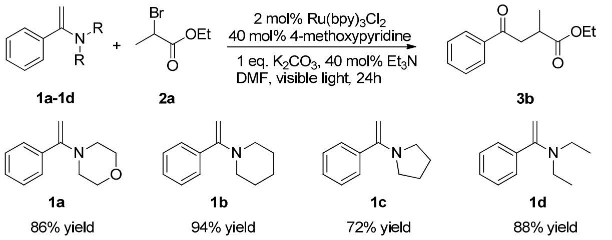
We initiated our investigation by examining the reaction of *N*-(1-styryl)morpholine and ethyl 2-bromopropanoate with $Ru(bpy)_3Cl_2$ (2 mol%) by employing Et_3N (40 mol%) in DMF under a 23W household fluorescent lamp irradiation (Table 1, entry 1). Fortunately, the reaction occurred in 16% yield. When $NaHCO_3$ (1eq.) was added, the reaction gave a slightly higher yield (Table 1, entry 2). The base Na_2CO_3 also was examined and a slightly better result was obtained (Table 1, entry 3). When we changed the base to K_2CO_3, still higher yield was achieved (Table 1, entry 4). However, poor result was obtained when K_3PO_4 or ^{t}BuOK was added to the reaction (Table 1, entries 5 and 6). We knew that Et_3N not only played a role as a reductant but also as a base in the reactions, however, when Et_3N (1.5 eq.) was used as the base, an even worse result was obtained (Table 1, entry 7). We then screened the solvents in the presence of K_2CO_3 as the base for the reaction. Among the solvents tested, DMF was proved to be the best for this transformation (Table 1, entries 8-13). The reaction proceeded with the formation of acetophenone as a by-product during the reactions. Thus, we tried to add some pyridine derivatives (Table 1, entries 14-19) which was claimed to be benefit to improve the reactivity in similar reactions.[1m, 10] When we applied pyridine into the reaction, the yield was slightly improved (Table 1, entry 14). When 40 mol% of 4-methoxypyridine relative to enamine was added to the reaction, an 86% isolated yield was obtained with significantly less by-product (Table 1, entry 15). There is no obvious influence with slightly less or more 4-methoxypyridine in the reaction (Table 1, entries 16 and 17). Other pyridine derivative, such as DMAP, did not give a satisfactory yield (Table 1, entry 18). Control experiments showed that both $Ru(bpy)_3Cl_2$ and visible light are essential for this reaction. When the reactions were conducted without catalyst or in the dark, essentially no products were formed regardless of background reaction (Table 1, entries 19 and 20). When the molar ratio of **1a** and **2a** was exchanged from 1:2 to 2:1, only a 47% yield was obtained (Table 1, entry 21). Besides that, we also conduct the reaction with an O_2 balloon, and only 35% yield was obtained, which indicate the cage effect existing in the reaction (Table 1, entry 22).[12] In the following experiments, different enamines (**1a-1d**) of acetophenone have been prepared[13] to test their reaction with **2a (Scheme 3)**. When **1b** was employed as the substrate, the best result (94% yield) was obtained. Other enamines, such as **1c** and **1d**, also gave good results.

Table 1. Optimization of the reaction conditions[a]



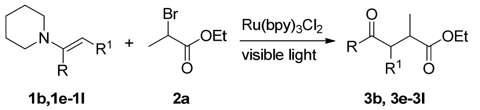
Entry	Base	Solvent	Additive	Yield[b] (%)
1		DMF		16
2	$NaHCO_3$	DMF		31
3	Na_2CO_3	DMF		55
4	K_2CO_3	DMF		64
5	K_3PO_4	DMF		12
6	^{t}BuOK	DMF		4
7[c]	Et_3N	DMF		11
8	K_2CO_3	CH_3CN		40
9	K_2CO_3	DMA		37
10	K_2CO_3	DCM		8
11	K_2CO_3	Toluene		5
12	K_2CO_3	NMP		35
13	K_2CO_3	DMSO		16
14	K_2CO_3	DMF	Pyridine	74
15	K_2CO_3	DMF	4-Methoxypyridine	90 (86[d])
16[e]	K_2CO_3	DMF	4-Methoxypyridine	87
17[f]	K_2CO_3	DMF	4-Methoxypyridine	89
18	K_2CO_3	DMF	DMAP	33
19[g]	K_2CO_3	DMF	4-Methoxypyridine	0
20[h]	K_2CO_3	DMF	4-Methoxypyridine	10
21[i]	K_2CO_3	DMF	4-Methoxypyridine	47
22[j]	K_2CO_3	DMF	4-Methoxypyridine	35

[a] Conditions: **1a** (0.5 mmol), **2a** (1 mmol), $Ru(bpy)_3Cl_2$ (0.01 mmol), Et_3N (0.2 mmol), 4-methoxypyridine (0.2 mmol), base (0.5 mmol), solvent (2 mL), irradiation with a 23 W household light bulb at about 35 °C for 24 h. [b] GC yields based on dibenzyl ether as an internal standard. [c] Et_3N (0.75 mmol). [d] Isolated yield. [e] 4-methoxypyridine (0.1 mmol) was used. [f] 4-methoxypyridine (0.4 mmol) [g] Without light. [h] Without catalyst. [i] **1a** (1 mmol), **2a** (0.5 mmol), GC yield based on dibenzyl ether as an internal standard. [j] O_2 balloon.



Scheme 3. Reactions of different enamines (**1a-1d**) with **2a**

Table 2. Reactions of enamines with **2a**[a]



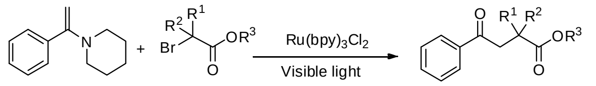
Entry	R	R^1	Yield[b] (%)
1	C_6H_5 (**1b**)	H	94
2	4-Me- C_6H_4 (**1e**)	H	92
3	4-F- C_6H_4 (**1f**)	H	92
4	4-Cl- C_6H_4 (**1g**)	H	91
5	4-CF_3- C_6H_4 (**1h**)	H	78
6	4-MeO- C_6H_4 (**1i**)	H	96
7	2-Me- C_6H_4 (**1j**)	H	97
8	C_6H_5 (**1k**)	Me	66[c]

[a] Conditions: **1b**, **1e-1l** (0.5 mmol), **2a** (1 mmol), $Ru(bpy)_3Cl_2$ (0.01 mmol), Et_3N (0.2 mmol), 4-methoxypyridine (0.2 mmol), base (0.5 mmol), DMF (2 mL), irradiation with 23 W household light bulb at about 35 °C for 24 h. [b] Isolated yields. [c] dr=11:1.

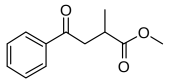
With this promising result in hand, we evaluated the substrate scope of this reaction with enamines prepared from piperidine and different ketones. The results are listed in Table 2. Enamines **1b, 1e-1l** derived from aryl methyl ketone provided good yields of keto esters. A significant electronic effect was observed in the reaction of **1h** and **1i**. The presence of an electron-withdrawing group decreased the reactivity of the enamine, while an electron-donating group increased the reactivity of enamine. As a result, reaction of **1h** gave **3h** in moderate yield in contrast to that the reaction of **1i** gave **3i** in excellent yield. It seemed that steric hindrance did not have a remarkable effect on the reaction when **1j** was used as substrate; **3j** was obtained in 97% yield. Enamine **1k** (***E***) prepared from propiophenone can react smoothly to give the desired product in 66% yield. Besides that, reaction of enamine of tetralone **1l** was also conducted which gave desired product in poor yield (**3l**, 33% yield).

In addition, we have extended this radical addition reaction to other α-carbonyl alkyl or benzyl bromides as well; similar results were obtained (Table 3). Substrates bearing more than one substituent at α-position of α-brominated carboxylates and ethyl bromoacetate resulted in relatively poor yields (**3n-3p**) with the formation of acetophenone which comes from hydrolysis of enamine. When cinnamyl or allyl α-brominated carboxylates were employed as substrates, moderate yields were obtained without intramolecular cyclization product.

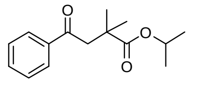
Table 3. Scope of secondary and tertiary α-carbonyl alkyl or aryl bromides reaction with **1b**[a]



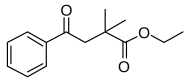
1b **2m-2r** **3m-3r**



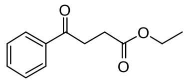
3m[b]
90% yield



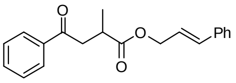
3n[b]
78% yield



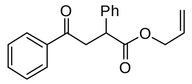
3o[b]
62% yield



3p[b]
66% yield



3q[b]
68% yield



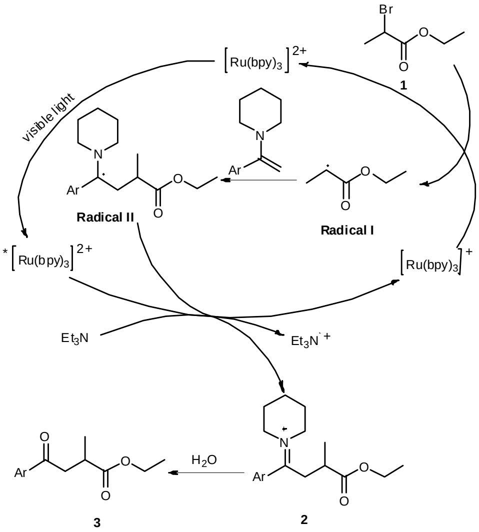
3r[b]
77% yield

[a] Conditions: **1b** (0.5 mmol), **2m-2r** (1 mmol), Ru(bpy)$_3$Cl$_2$ (0.01 mmol), Et$_3$N (0.2 mmol), 4-methoxypyridine (0.2 mmol), base (0.5 mmol), DMF (2 mL), irradiation with 23 W household light bulb at 35 ^{o}C for 24 h. [b] Isolated yields.

To make sure whether the reaction occurred via a radical addition reaction irradiated by visible light or a direct substitution reaction under thermal conditions, control experiments were conducted. We conducted the reaction in dark under different temperature ranging from 40 ^{o}C to 100 ^{o}C, only a little of desired products were isolated. Meanwhile, we ruled out the radical-chain propagation mechanism based on the experiments of turn on/off the light (see supporting information).

On the basis of the above experiments, a plausible mechanism for the reaction is shown in **Scheme 4**. Excitation of the metal catalyst under the visible light generates the excited $[Ru(bpy)_3]^{2+*}$ species,[14] which oxidizes Et$_3$N to give the active single electron transfer species, $[Ru(bpy)_3]^+$, along with the radical cation of the amine. The electron-rich metal complex $[Ru(bpy)_3]^+$ then reduces the activated C–Br bond[1m, 10] to furnish the electron-deficient radical **I** and regenerates $[Ru(bpy)_3]^{2+}$. The rapid addition of radical **I** to the electron-rich enamine forms radical **II**, which can be rapidly oxidized to iminium cation **2** and undergoes single-electron transfer to give $[Ru(bpy)_3]^{2+*}$,[3] and form the metal complex $[Ru(bpy)_3]^+$ to complete the photoredox catalytic cycle. Finally, the γ-keto ester **3** can be obtained by the hydrolysis of the iminium cation **2**.[15]

In summary, we have developed an efficient visible light mediated photoredox reaction of α-brominated carboxylates with enamines via an intermolecular radical addition reactions. The method provided a novel access to various synthetically important γ–ketoesters in good yields under very mild conditions. Further work towards expanding the use of photoredox catalysis in the context of radical chemistry is underway.



Scheme 4. Proposed mechanism

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