Synthetic Methods

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Visible-Light-Mediated 1,2-Acyl Migration: The Reaction of Secondary Enamino Ketones with Singlet Oxygen**

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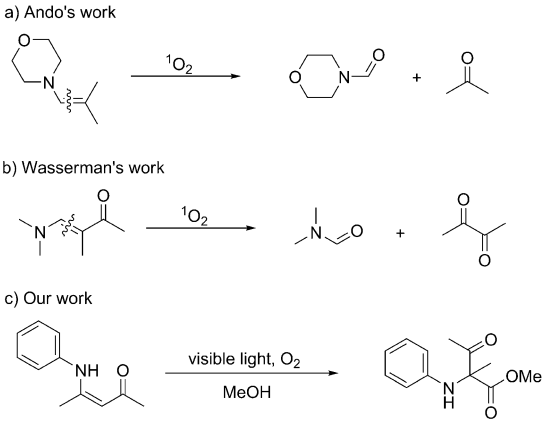
Abstract: *Secondary enaminones were oxidized by photochemically generated singlet oxygen, followed by nucleophilic addition of alcohol and an unexpected 1,2-acyl migration to afford quaternary amino acid derivatives. An ene-type reaction pathway is proposed. It is distinctively different from the typical [2+2] addition of singlet oxygen to a C=C bond pathway.*

Singlet oxygen is an electronically excited state of molecular oxygen and a reactive oxygen species. It has been applied in organic synthesis as a powerful reagent[1] since the seminal reports of Foote and Wexler[2] and Corey and Taylor[3] in the 1960s. There are several principal classes of reactions involving singlet oxygen, including oxidation of heteroatom compounds,[1c,4] [2+2] cycloaddition,[1c,5] Diels–Alder [4+2] reaction,[6] and Schenck ene reactions.[7] The reactions of singlet oxygen with enamines and enaminones were firstly disclosed by Ando et al.[8] and Wasserman and Ives[9] in the 1970s (Schemes 1a and b). In both cases, the C=C bonds of enamines were cleaved through [2+2] cycloaddition reaction to give two carbonyl compounds. For the past several years, addition of singlet oxygen to enecarbamates has been studied extensively.[10] Other oxidants, such as potassium permanganate[11] and H_2O_2,[12] were used to mediate the oxidation of enaminones to amides as well. Recently, the groups of Xia[13] and Wang[14] disclosed visible-light-promoted conversion of enamines into amides and ketones. Not surprisingly, all of the above-mentioned reactions afforded two carbonyl compounds by carbon–carbon double-bond cleavage.



Scheme 1. Selected examples involving oxidation of enamines or enaminones.

Herein, we report a visible-light-promoted transformation involving the ene-type reaction of secondary enamino ketones with singlet oxygen, followed by a 1,2-acyl migration to afford quaternary amino acid derivatives. The reaction pathway is distinctively different from the previous reports of C=C bond cleavage by singlet oxygen (Scheme 1c).

With our continuing interest in developing novel visible-light-mediated oxidation reactions using molecular oxygen as the terminal oxidant,[15] we investigated the aerobic oxidation of 4-(phenylamino)pent-3-en-2-one (**1a**) in the presence of 1 mol% $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ under the irradiation of a 14 W compact fluorescent lamp in MeOH. To our surprise, an unexpected product, **2a**, was obtained in 57% yield after 6 hours with a small amount of the compound **3a** (Table 1, entry 1). The structure of **2a** was confirmed by the X-ray analysis (see the Supporting Information).

Inspired by this result, we screened other reaction parameters. The reaction carried out under an O_2 balloon afforded **2a** in 62% yield, thus showing that a high concentration of O_2 promoted the reaction (Table 1, entry 2). Next, two iridium-based photocatalysts were examined. It was found that these sensitizers were not as effective for this transformation (entries 3 and 4). The reaction with higher loading of the photocatalyst did not provide better results and the reaction was sluggish with 0.5 mol% $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (entries 5 and 6). When other solvents, such as MeCN, CH_2Cl_2, DMF, DMSO, and THF, were used with 10 equivalents of MeOH, the yields fell significantly (entries 7–11). To improve the yield of the reaction, additives, such as ZnF_2, KH_2PO_4, and $LiBF_4$, were tested. Among them, KH_2PO_4 gave a slightly better yield (entry 13). It is notable that the photocatalyst, visible light, and dioxygen were all critical to this reaction. In the absence of any of these components, either none or only a trace amount of the product was detected (entries 15–17).

We next surveyed various secondary enamino ketone substrates to investigate the scope of the reaction. Enamino ketones containing different functional groups underwent the transformation smoothly. However, approximately 10% (by HPLC area) of the fragmentation product **3** was observed in most of the reactions. The results are summarized in Table 2.

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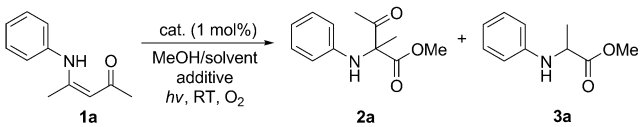
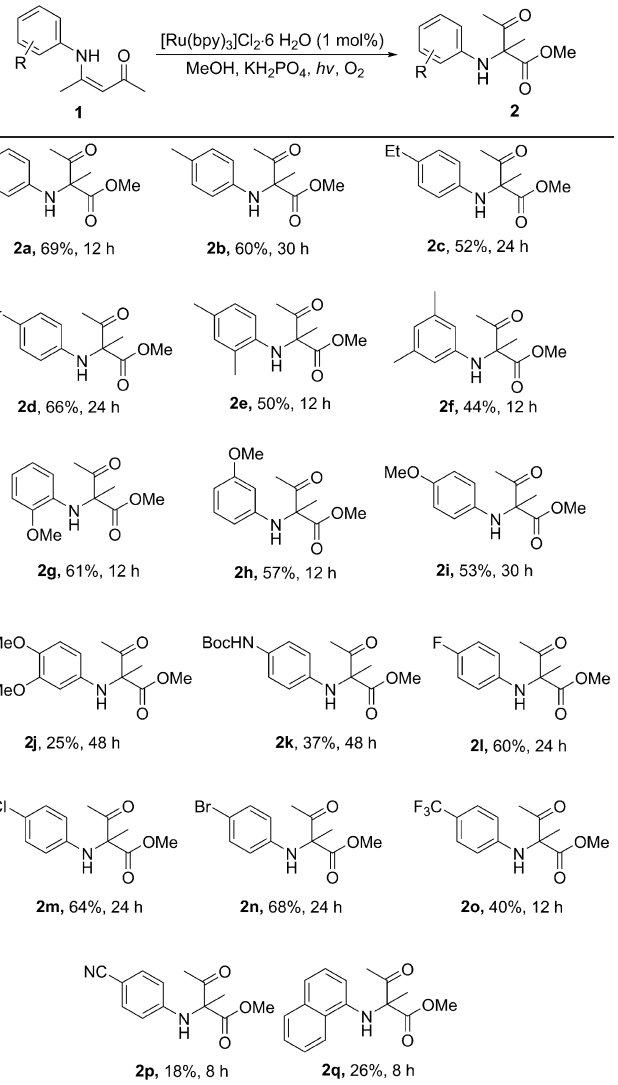
Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	Additive	**2a** Yield [%][b]
1[c]	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	MeOH	–	57
2	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	MeOH	–	62
3	$[Ir(ppy)_3]$	MeOH	–	trace
4	FIrpic	MeOH	–	n.r.
5	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (2 mol%)	MeOH	–	62
6	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (0.5 mol%)	MeOH	–	51
7[d]	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	MeCN	–	12
8[d]	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	CH_2Cl_2	–	23
9[d]	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	DMF	–	13
10[d]	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	DMSO	–	10
11[d]	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	THF	–	5
12	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	MeOH	ZnF_2	57
13	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	MeOH	KH_2PO_4	65
14	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	MeOH	$LiBF_4$	60
15	–	MeOH	KH_2PO_4	n.r.
16[e]	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	MeOH	KH_2PO_4	n.r.
17[f]	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	MeOH	KH_2PO_4	trace

[a] Reaction conditions: **1a** (0.5 mmol, 0.1 M in solvent), catalyst (1 mol%), additive (1 equiv), irradiation with a 14 W CFL under a O_2 balloon at room temperature for 6 h. [b] Determined by HPLC. [c] Open to the air. [d] MeOH (10 equiv) was used as reagent. [e] In the dark. [f] Under a N_2 balloon. bpy = 2,2′-bipyridine, DMF = *N*,*N*-dimethylformamide, FIrpic = iridium(III) bis(4,6-difluorophenylpyridinato)picolate, ppy = 2-phenylpyridine, n.r. = no reaction.

Table 2: Scope of enaminones.[a,b]

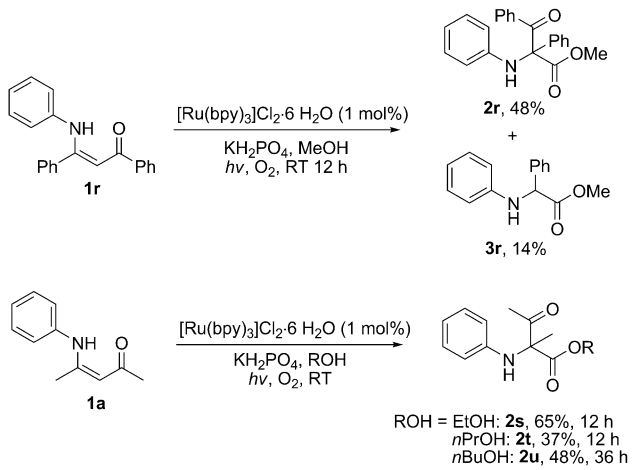


[a] Reaction conditions: **1** (0.5 mmol, 0.1 M in MeOH), $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (1 mol%), KH_2PO_4 (1 equiv), irradiation with a 14 W CFL under a O_2 balloon at room temperature. [b] Yield is that of the isolated product containing approximately 10% (HPLC area) of an inseparable impurity (**3**).

The *para*-methyl-, *para*-ethyl-, and *para*-isopropyl-substituted 4-(phenylamino)pent-3-en-2-ones afforded the corresponding products in 60, 52, and 66% yields, respectively (**2b–d**). Dimethyl-substituted enaminones gave the products in 50 and 44% yields (**2e** and **2f**). The electronics of the substitution groups on the phenyl ring have some impact on the reaction. An electron-donating methoxy group at the *ortho*-, *meta*-, or *para*- positions provided the products in 61, 57, and 53% yields, respectively (**2g–i**). The reaction of an enaminone bearing two methoxy groups became sluggish, and only 25% of the desired product was obtained after 48 h (**2j**). An enaminone with a *para*-NHBoc substituent gave 37% of the corresponding product **2k**. Weak electron-withdrawing groups, such as fluoro, chloro, bromo, at the *para* position of the phenyl ring afforded products in 60, 64, and 68% yields, respectively (**2l–n**). However, substrates with strong electron-withdrawing groups were easily hydrolyzed to anilines. And the desired products were formed in moderate yields (**2o** and **2p**). The naphthyl-substituted enaminone afforded the corresponding product in 26% yield upon isolation (**2q**).

To extend the scope of the reaction and gain insight into the reaction mechanism, a series of experiments were carried out. Firstly, the compound **1r** bearing a benzoyl group instead of an acyl group was studied (Scheme 2). The product **2r** was obtained in 48% yield upon isolation, together with 14% yield of **3r**. This result unambiguously indicated that the acyl/benzoyl group migrated to the adjacent carbon atom. Next several alcohols were used instead of methanol. It was found that ethanol afforded the corresponding ethyl ester in 65% yield (**2s**). Alcohols with longer chains, such as *n*-propanol and *n*-butanol, gave lower yields (**2t** and **2u**). These results clearly showed that the alkoxy groups of the esters in the final products were from the alcohols. The reaction carried out in isopropanol resulted in a complex mixture presumably because of the bulkiness of the secondary alcohol. And trifluoroethanol leaded to a bad reaction too probably because of its weak nucleophilicity.

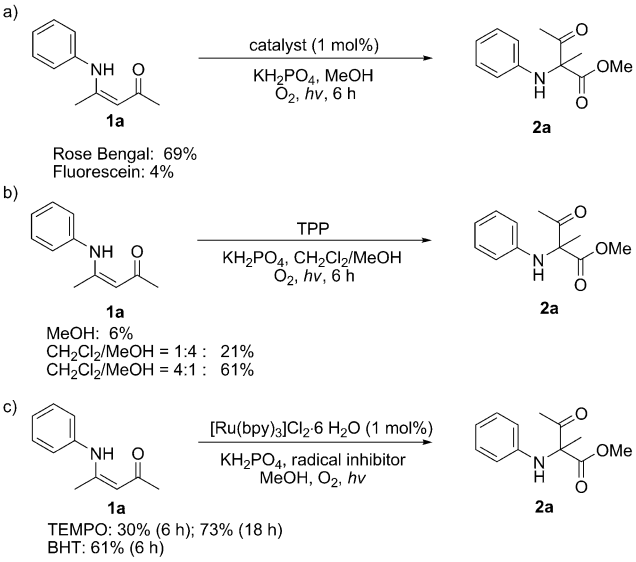
Typically, dioxygen can be activated through a single-electron transfer (SET) pathway to form $O_2^{\bullet-}$ or an energy-transfer (ET) pathway to form singlet oxygen under visible-light conditions. In recent visible-light-promoted reactions sensitized by ruthenium- or iridium-based polypyridyl com-



Scheme 2. Investigation of reactant scope.

plexes, energy-transfer processes are rare.[16] Furthermore, $^1O_2$ formed using photosensitizer under irradiation with an underpowered compact fluorescent lamp is scarce.[17]

To distinguish between the singlet-oxygen pathway or the radical pathway in our reaction, a serious of control experiments and analytical studies were carried out (Scheme 3). It is



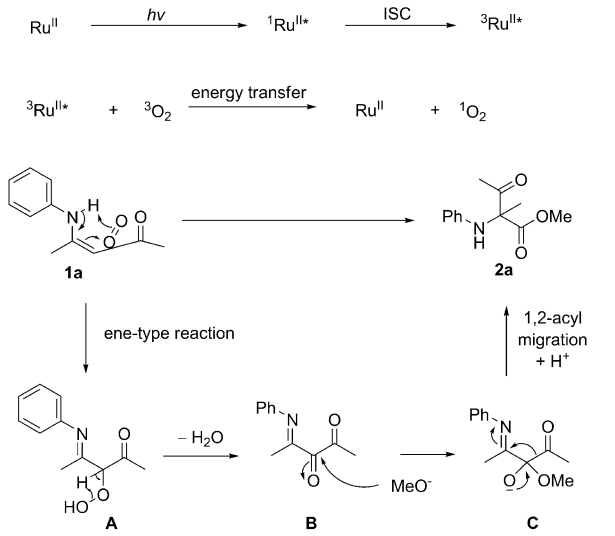
Scheme 3. Investigation of reaction mechanism. BHT = 3,5-di-*tert*-butyl-4-hydroxytoluene; TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl.

well known that Rose Bengal is a good photosensitizer for $^1O_2$ generation under visible-light irradiation. Therefore, we tested the reaction using Rose Bengal as the photocatalyst. The product **2a** was obtained in 69% yield after 6 hours (Scheme 3a). On the contrary, fluorescein afforded **2a** in only 4% yield under the otherwise same conditions. It is known that fluorescein is not capable of generating singlet oxygen.[18] These two reactions indicated that a singlet-oxygen pathway is probably operative. Moreover, because dichloromethane is a good solvent for tetraphenylporphine (TPP) to generate singlet oxygen, a series of TPP-sensitized reactions were performed in mixed solvent systems with different ratios of CH_2Cl_2 to MeOH (Scheme 3b). Clearly, the yields of the reactions were improved progressively with the increasing ratio of CH_2Cl_2 in the solvent mixture. It is another piece of good evidence that the reaction goes through a singlet-oxygen pathway. Moreover, addition of TEMPO or BHT as a radical inhibitor did not suppress the reaction (73% or 61% yield respectively, Scheme 3c), which indicated that the radical process was unlikely in this reaction. The only experimental result against the singlet-oxygen pathway is that the reaction proceeded smoothly and comparable yield was obtained when DABCO was added. However, it might be rationalized that the reaction rate of enaminone with singlet oxygen is faster than that of DABCO.

To investigate which reactant, either dioxygen or enaminone, interacts with the visible-light-excited photocatalyst, a fluorescence emission quenching study was carried out. The data showed that the emission intensity of excited catalyst was remarkably affected by O_2 (see the Supporting Information). The fluorescence emission was hardly changed in a deaerated solution of **1a** in MeOH. However, when the solution was bubbled with either air or oxygen gas, the emission intensity was dramatically suppressed. Therefore, dioxygen rather than **1a** reacted with the excited $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ directly, and triggered the reaction. Another result which could rule out the probability of an SET process is the redox potential of the substrate **1a** measured by cyclic voltammetry (CV) experiments. $E_{\mathbf{1a}^{+}/\mathbf{1a}}$ was measured at 1.24 V vs. SCE. It is higher than the potential of excited ruthenium(II) ($E_{Ru^{*2+}/Ru^{1+}} = 0.77$ V vs. SCE),[19] Rose Bengal ($E_{RB^*/RB^{\cdot-}} = 0.99$ V vs. SCE),[20] and TPP ($E_{TPP^*/TPP^{\cdot-}} = 0.81$ V vs. SCE).[21] Although the potential of **1a** ($E_{\mathbf{1a}^{+}/\mathbf{1a}}$) is lower than that of ruthenium(III) ($E_{Ru^{3+}/Ru^{2+}} = 1.29$ V vs. SCE)[19], it was believed that the generation of singlet O_2 by energy transfer is the dominant reaction pathway because it is not possible to go through oxidative quenching cycle with Rose Bengal ($E_{RB^{\cdot+}/RB} = 1.09$ V vs. SCE)[20] and TPP ($E_{TPP^{\cdot+}/TPP} = 0.95$ V vs. SCE).[21]

On the basis of our observations and the literature reports,[14,22] a plausible pathway for the reaction was proposed in Scheme 4. After the absorption of a photon, ruthenium(II) is converted into a high-energy excited singlet $^1Ru^{II}*$, which undergoes intersystem crossing (ISC) to triplet $^3Ru^{II}*$. Intermolecular energy transfer from $^3Ru^{II}*$ to $^3O_2$ regenerates the ground-state Ru^{II} and forms the reactive $^1O_2$ species. Next, an ene-type reaction between **1a** and $^1O_2$ occurs to form the intermediate **A**, which dehydrates to afford **B**. After that, a nucleophilic addition of alcohol to **B** followed by 1,2-acyl migration and protonation leads to the product **2a**.

During the study of the reaction mechanism, Rose Bengal was found to be as effective as the transition-metal-based $[Ru(bpy)_3]^{2+}$ catalyst. And the addition of 1 equivalent of TEMPO to the standard reaction conditions gave slightly better result (Schemes 3a and c). The two conditions were applied to the syntheses of **2a**, **2c**, **2m**, and **2n**. In the case of using Rose Bengal as the photocatalyst, the transition-metal-free conditions gave comparable results. The desired products were isolated in 64, 51, 62, and 63% yields, respectively. When 1 equivalent of TEMPO was added, the yields of the desired products were 73, 64, 69, and 72%, respectively. They were



Scheme 4. Proposed mechanism.

slightly better than those obtained without TEMPO. The yields of the reaction were not affected by the amount of the TEMPO added, but the reaction rate was slowed down with increasing addition of TEMPO.

In conclusion, we have discovered a visible-light-mediated aerobic oxidation of secondary enaminones by singlet oxygen. An unexpected 1,2-acyl migration afforded quaternary amino acid derivatives. Unlike the typically reported singlet-oxygen-promoted double-bond cleavage to form two carbonyl compounds, this reaction is proposed to go through an ene-type pathway. The investigation of developing an environmentally benign, metal-free reaction with better yields and the study of the role of TEMPO in the reaction are currently ongoing in our laboratory. The results will be reported in due course.

Experimental Section

Experimental details: $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ (1 mol%) and KH_2PO_4 (1 equiv) were added to a solution of the enaminone **1** (0.5 mmol) in alcohol (5 mL). The Schlenk tube was charged with O_2 using a balloon. The reaction mixture was stirred under a 14 W CFL irradiation at room temperature for an appropriate time. After reaction completion as monitored by TLC, the reaction mixture was quenched with water (20 mL), followed by extraction with ethyl acetate (3×20 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The mixture was filtered to remove drying agent. The filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography with petroleum ether/dichloromethane to give the desired product.

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