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Photo-induced formation of cyclopropanols from α-ketoamides via γ-C—H bond activation

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ABSTRACT

A novel type of photocyclization of α-ketoamides was developed, affording unique cyclopropanols bearing amide functionality. *N-tert*-Butyl, *N*-trityl, or *N*-non-substituted α-ketoamides with a bulky substituent at the β-position of the amide functionality were efficiently converted to corresponding cyclopropanols through the activation of the γ-C—H bond followed by C—C bond formation between the α- and γ-positions of the amide. Hydrogen abstraction from the γ-position of the amide was considered to be the rate-determining step of cyclopropanol formation, based on the kinetic isotope effect. Cyclopropanols could be converted to two different types of functionalized α-ketoamides depending on the method of ring-opening.

The photochemistry of α-dicarbonyls has been extensively investigated.[1] In particular, the photoreaction of α-ketoamides **1** to produce β-lactam derivatives **2** and/or oxazolidinone derivatives **3** as the main products (so-called Norrish type-II reaction) is well-known (Scheme 1-1)[2] in organic synthesis, because it enables direct C—C (Norrish–Yang cyclization to form **2**) or C—O bond formation (to form **3**) through selective cleavage of the C—H bond[3] at the α-position of the N-atom (Nα-proton). Moreover, the α-dicarbonyl system is conveniently activated by irradiation at relatively long wavelength compared to other standard functional groups in organic molecules. Various applications to the synthesis of biologically active molecules[4] or asymmetric reactions in chiral crystals[5] have also been reported.[6]

Based on the intensive experiments by Aoyama's group[7] and Whitten's group,[8] the mechanism of formation of **2** and **3** was proposed to be as follows (Scheme 1-1). Irradiation of **1** induces n–π^* transition and generates the singlet excited state. The amide functionality serves to quench the excitation state via an electron transfer process to generate the transient zwitterion species **4**. Since the acidity of the Nα-proton would be increased, abstraction of the H-atom followed by protonation of the carbonyl O-atom affords 1,4-biradical species **5** after electron reorganization. According to Whitten's report, β-lactam derivatives **2** are constructed via the intramolecular radical coupling reaction. In contrast, electron transfer can occur again to form another zwitterion species **6** as a precursor of the oxazolidinone derivatives **3**.

In many cases, *N*,*N*-disubstituted α-ketoamides **1** are expected to afford better results as substrates, since the keto-functionality and α-position of the N-atom are placed close to each other. Several examples of photolysis of *N*-monosubstituted α-ketoamides have been reported.[9] On the other hand, photo-induced cyclopropanol formation of ketones[10] has been reported only for a limited range of substrates, such as β-amino-,[11] β-oxy-,[13] or α-methylene-ketones,[12] in which the 1,4-hydrogen shift would be facilitated due to stabilization of the radical at the β-position by a heteroatom or double bond. However, as far as we know, no example of photo-induced cyclopropanol formation of α-ketoamides has been reported. We hypothesized that the formation of cyclopropanol **8** would be possible for *N*-monosubstituted α-ketoamides **7**, which favor *s*-trans conformation (Scheme 1-2). In contrast to the simple ketone, α-ketoamides **7** are expected to be activated by irradiation at a longer wavelength (longer than 300 nm) and to generate the transient zwitterion species **9**. We speculated that the amide functionality in **9** would facilitate abstraction of the unactivated γ-C—H bond to generate

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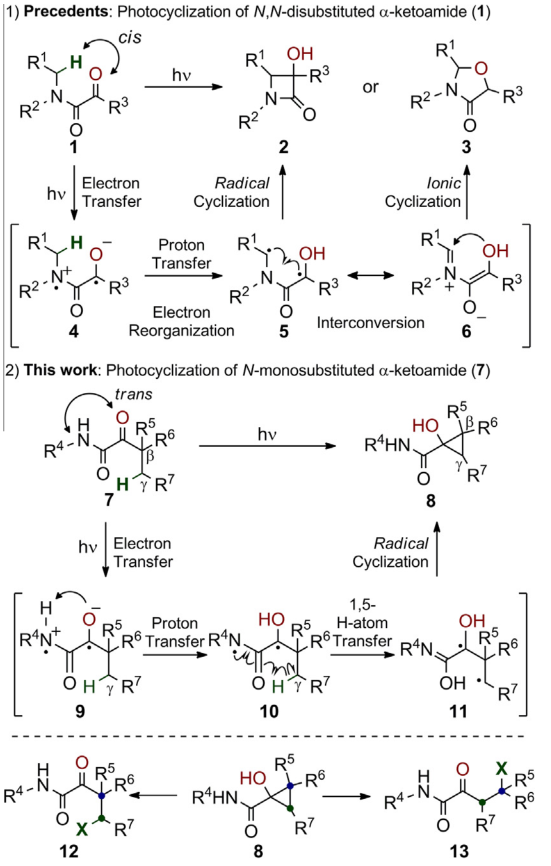
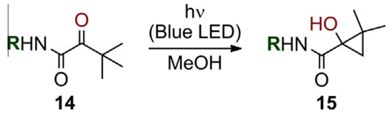


Scheme 1. (1) Photo-reaction of α-ketoamides; (2) working hypothesis for the formation of cyclopropanol derivatives.

1,3-biradical species **11**, which is then converted to the cyclopropanol product. Namely, the rapid proton transfer from the N-atom to the oxygen atom (from **9** to **10**, instead of transfer of the Nα-proton in the case of **1**) and the 1,5-hydrogen shift from the γ-position to the amide owing to its radical character (from **10** to **11**) result in γ-C—H bond activation.[14] The highly substituted cyclopropanol **8** bearing amide functionality is expected to be a unique synthetic building block for organic synthesis. Since various types of ring-opening reactions of cyclopropanol[15] are known, **8** could be converted to the γ-position-functionalized amides **12** or **13**. The overall transformation is regarded as functionalization of the γ-position, with or without rearrangement of the framework.

To test our working hypothesis, 3,3-dimethyl-2-oxobutyramides **14** having a substituent on the N-atom were selected as substrates for initial examination. Normally, functionalization of the C—H bond on the *t*-butyl group is challenging without a special directing group,[16] but we expected that 3 equivalent methyl groups at the γ-position would facilitate the desired reaction (Table 1). All reactions were conducted in glass tubes under a blue LED lamp (max. output 365 nm) under degassed conditions (see Fig. S1).[17] Preparation of α-ketoamides **14** is summarized in Schemes S1 and S2.[17] As we expected, photolysis of benzyl amide **14a** gave the isolable cyclopropanol **15a**, though in low yields (entry 1). Neither β-lactam **2** nor oxazolidinone **3** was detected. Instead, imide **14b** or its cyclized product **15b** was isolated. This observation suggested that H-atom abstraction from the Nα-proton competes with the desired reaction pathway. Hence, imide-type **14b** (phenyl) and **14c** (*n*-pentyl) without Nα-protons were investigated as substrates. As a result, cyclopropanol formation was slightly improved, but degradation of the substrates was still predominant (entries 2 and 3). Although no photoreaction of *t*-butyl hydroxamate **14d** occurred at all, to our delight, we found that the irradiation of *t*-butyl amide **14e** afforded the corresponding cyclopropanol **15e** in 71% yield (entries 4 and 5). In addition, the photo-reaction of the trityl-protected amide **14f** proceeded cleanly (entry 6), though with only moderate conversion. Since transient formation of the hemiacetal with methanol may disturb the reaction,[18] solvent screening was performed (see Table S1).[17] We found that the use of 2-butanol was effective, providing **14f** in almost quantitative yields (entry 7). Furthermore, it was found that the photo-reaction of the simple (*N*-non-substituted) 3,3-dimethyl-2-oxobutyramide (**14g**) was completed within 5 min, and 1-hydroxy-2,2-dimethylcyclopropanecarboxamide (**15g**) was obtained in 94% yield (entry 8).

Table 1
Effect of substituent on N-atom



Entry	Substrate	R	Time (h)	Product: yield (%)
1	**14a**	CH$_2$Ph	1.5	**15a**: 13[a]
2	**14b**	COPh	11	**15b**: 28
3	**14c**	CO(CH$_2$)$_4$CH$_3$	1	**15c**: 31
4	**14d**	O^{t}Bu	12	**15d**: 0[b]
5	**14e**	^{t}Bu	3	**15e**: 71
6	**14f**	CPh$_3$	12	**15f**: 50[c]
7[d]	**14f**	CPh$_3$	11	**15f**: 99
8	**14g**	H	5 min	**15g**: 94

[a] **14b** (31%) and **15b** (24%) were obtained.
[b] Starting material was recovered (98%).
[c] Starting material was recovered (49%).
[d] Reaction solvent: 2-BuOH.

With this knowledge of the effects of N-atom substituents and solvent in hand, we next investigated variations of the ketone. For easy monitoring of the proto-reaction by TLC, UV-active trityl-protected amides **16** were selected (Scheme 2). Preparation of **16** is shown in Schemes S3–S5.[17] Photo-reaction of **16a**–**16c** bearing a substituent Y (Me, OBn, or OTBS) proceeded smoothly to provide the corresponding cyclopropanols *syn*-**17a**–**17c** and their diastereomers *anti*-**17a**–**17c** in excellent yields. The stereochemistry of these products was mainly determined from their HMBC spectra. Namely, a stronger HMBC correlation from H^a to the C-atom of the amide carbonyl group was observed in the major isomers. We considered that this would be attributed to the *syn*-orientation (dihedral angle = ~0°) of these atoms, which should show a larger coupling constant (*J* value) than the corresponding *anti*-isomers (dihedral angle = ~135°). This consideration was supported by DFT calculations as well as by the different intensities of the HMBC correlations observed between H^a and the two methyl groups on cyclopropanols (Figs. S2–S6).[17]

It should be noted that no cyclized product at the methyl group **18a**–**18c** was detected in the photochemical reaction of **16a**–**16c**. In contrast, the reaction of **16d** with an acetoxy group provided regio-isomer **18d** as a major product (80%) along with a small amount of *syn*-**17d** (4%). The stereochemistry of these molecules was assigned in the same manner as described above (see also Figs. S7–S8).[17] These results indicated that the selective formation of cyclopropanols **17** and **18** can be achieved by the choice of a suitable substituent on the O-atom. On the other hand, photolysis of non-protected **16e** did not produce any cyclopropanol derivative. Instead, disproportionation occurred to give **19** in moderate yields.[19] In addition, **16f** with a bromine atom was converted to