Phototriggered Butenolide Formation from a Cyclobutenedione and an Acidic Nucleophile

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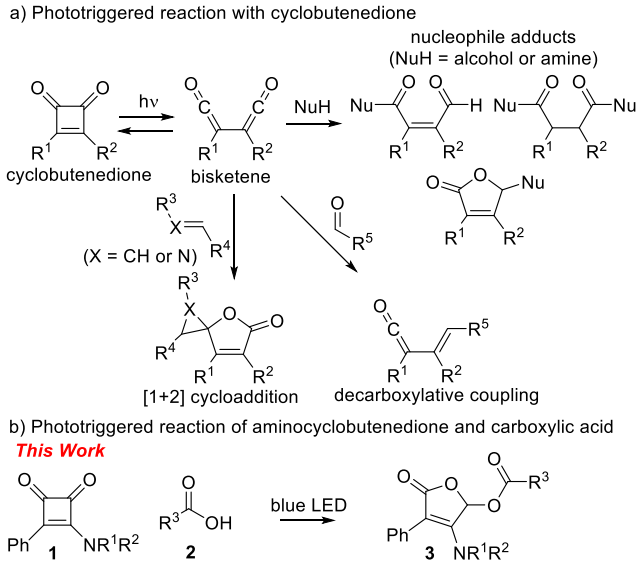
ABSTRACT: A phototriggered conjugation reaction of an aminocyclobutenedione and a nucleophile was discovered. Upon irradiation of the materials with a blue LED, a butenolide derivative with substituents derived from the aminocyclobutenedione and the nucleophile was produced. Acidic nucleophiles were favorable for the reaction, and the reaction proceeded efficiently under organic solvent or organic solvent/aqueous buffer (1/1) conditions. This reaction would be useful for synthesis of unique butenolide derivatives and derivatization of acidic functional groups.

Cyclobutenedione is a cyclic enone with a strained four-membered ring. By photoexcitation or high temperature heating, the ring opens to generate a bisketene.[1,2] The stability of bisketene highly depends on its substituents. Carbon and nitrogen substituted bisketenes are not stable and rapidly revert to cyclobutenedione,[1] while silyl substituted bisketenes are relatively stable and isolable at room temperature.[2] The produced bisketenes can react with various chemical species such as alcohol, [3,4,5]amine, [6] alkene, [7] imine, [8] and aldehyde[9] (**Scheme 1a**). In the reactions involving the bisketene, various products including butenolide derivatives can be produced. Because butenolides are seen in many bioactive natural product[10,11,12] and synthetic compounds[13,14], the butanolide synthesis from cyclobutenedione could be useful for the synthesis of bioactive butenolide libraries. Since the ring opening of cyclobutenedione does not proceed at room temperature without light, the location and timing of the bisketene generation is completely controllable by ON/OFF state of light irradiation. Because bisketene is a highly reactive species, the reaction involving bisketene should proceeds around the site where the bisketene is generated. Therefore, with the photochemical reaction of cyclobutenedione, the reaction involving bisketene can be performed with spatial and temporal controllability. These characteristics would be suitable for the study of temporal biological phenomenon and fine modification of polymer materials, as other photoreactive groups such as diazirine and benzophenone. [15,16,17,18] In the case of some cyclobutnediones, the bisketenes are generated reversibly. This property may allow the bisketenes to avoid unproductive decomposition, thereby reactions involving the bisketenes are expected to result in high yield. Despite these promising properties in the field of both chemistry and biology, the photochemical reactions of the cyclobutenediones have not gained widespread application.

Recently we reported photochemical reactions of aminocyclopropenones. Upon direct photoexcitation[19,20] or indirect photocatalytic excitation, [21,22] an aminocyclopropenone releases carbon monoxide and an ynamine, which can be used for modification of a carboxylic acid. In the course of the study of photochemical reactions using strained carbonyl compounds, we found an efficient photochemical conjugation reaction of an aminocyclobutenedione **1** and a carboxylic acid **2** to form an acyloxybutenolide **3** (**Scheme 1b**).



Scheme 1. Photochemical Reaction of Cyclobutenedione.

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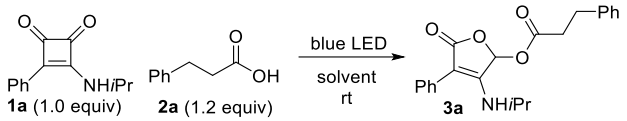
Although similar reactions of a cyclobutenedione and a nucleophile to form a butenolide have been reported, the reaction of a cyclobutnedione and a carboxylic acid has never been reported. Additionally, our reaction gave the butenolide as a major product while previous reactions could produce a mixture of a butenolide and noncyclic products. Moreover, this reaction proceeded under visible light conditions while most of previous reactions involving cyclobutenedione required UV light. Due to these properties, we expected that this reaction would be easier to handle than previous reactions with cyclobutenediones, and applicable in various field such as synthetic chemistry and biological study. This paper reports the unique characteristics of the phototriggered butenolide formation we have investigated.

First, the reaction conditions of the butenolide formation from cyclobutenedione **1a** and carboxylic acid **2a** were optimized (**Table 1**). The efficiency of the reaction depended significantly on the solvent polarity. Polar solvents, such as MeOH, acetone, 1,4-dioxane, and THF, resulted in low yield (entries 1–4). The reaction in MeCN resulted in a moderate yield (entry 5). The reaction in $CHCl_3$ was faster than that in MeCN, but the yield was moderate (entry 6). CH_2Cl_2 was the best of the solvents screened. Butenolide **3a** was obtained after 3 h irradiation in 76% yield (entry 7). The effect of the substrate concentration was investigated in CH_2Cl_2. In 5−100 mM, **1a** was consumed at a similar rate, but the butenolide yield increased slightly at higher concentrations (entry 8–11). Under dark in $CDCl_3$, the butenolide was not obtained, and **1a** was recovered quantitatively (entry 12).

Next the reaction was performed in 50% aqueous conditions to examine if the phototriggered reaction of the aminocyclobutnedione is applicable to the conjugation with aqueous substrates (**Table 2**). The reaction was performed in a 1:1 mixture of water and a water-miscible solvent, such as MeCN, THF, and 1,4-dioxane (entries 1–3). Among these conditions, the water/1,4-dioxane condition afforded the butenolide in the highest yield. As observed in the reaction in CH_2Cl_2, the yield increased as the substrate concentration was increased (entries 3–6). The reaction was then tried in HEPES buffer/dioxane solutions with different pH. The pH substantially affected the reaction efficiency. The pH 6.8 HEPES buffer resulted in a comparable yield with water/dioxane conditions, but the reaction rate was slower. By increasing the carboxylic acid to 3.0 equiv., the reaction was completed in 5.5 h, and the yield increased to 74 % (entries 7–10). Under pH 6.8 phosphate buffer (PB)/1,4-dioxane conditions, **1a** disappeared in 2 h, but multiple spots were observed by TLC, and **3a** was not obtained. Although the products were not characterized, phosphate ions would be involved in the side reaction (entry 11). **3a** contains diacyl acetal structure which may be prone to hydrolysis. However, **3a** was stable under the aqueous reaction conditions. After 24 h incubation in pH 6.8 HEPES buffer/1,4-dioxane at room temperature, >95% of **3a** remained intact. These results indicate this reaction is applicable to butenolide formation with aqueous carboxylic acids and functionalization of aqueous biomolecules.

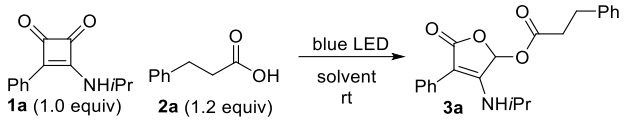
Table 1. Screening of the concentration and solvent.



entry	solvent	conc. of **1a** (mM)	time (h)	yield of **3a** (%)[a]
1	MeOH	10	12	6
2	Acetone	10	12	11
3	1,4-dioxane	10	24	18
4	THF	10	24	28
5	MeCN	10	7	53
6	$CHCl_3$	10	4	48
7	CH_2Cl_2	10	3	76
8	CH_2Cl_2	5	3	76
9	CH_2Cl_2	20	3	78
10	CH_2Cl_2	50	3	78
11	CH_2Cl_2	100	3	84
12[b]	$CDCl_3$	10	24	0

[a]NMR yield. [b]In dark.

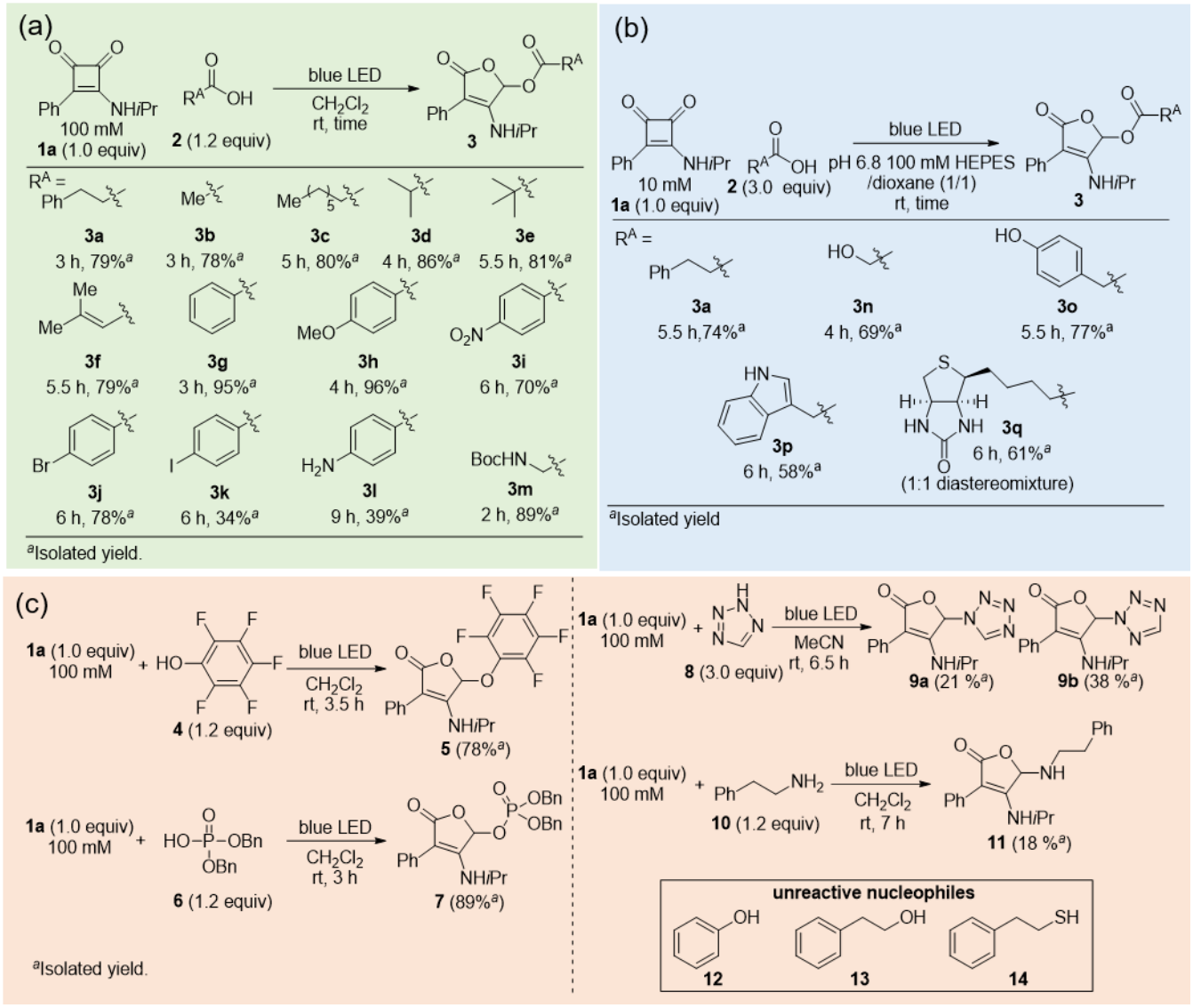
Table 2. Reaction under Aqueous Conditions



entry	solvent	conc. of **1a** (mM)	time (h)	yield of **3a** (%)[a]
1	H_2O/MeCN (1/1)	10	6	18
2	H_2O/THF (1/1)	10	7	40
3	H_2O/1,4-dioxane (1/1)	10	6.5	51
4	H_2O/1,4-dioxane (1/1)	5	6	42
5	H_2O/1,4-dioxane (1/1)	20	6.5	61
6	H_2O/1,4-dioxane (1/1)	50	7.5	66
7	pH 8 100 mM HEPES/ 1,4-dioxane (1/1)	10	24	<1
8	pH 7.4 100 mM HEPES/ 1,4-dioxane (1/1)	10	24	30
9	pH 6.8 100 mM HEPES/ 1,4-dioxane (1/1)	10	12	51
10[b]	pH 6.8 100 mM HEPES/ 1,4-dioxane (1/1)	10	5.5	74
11	pH 6.8 100 mM PB/ 1,4-dioxane (1/1)	10	2	0

[a]NMR yield. [b]3.0 equiv of carboxylic acid **3a** was used.

The substrate scope of the reaction was next investigated. In CH_2Cl_2, the reaction with a carboxylic acid, such as aliphatic, conjugated, aromatic carboxylic acids, and a protected glycine, were screened. Most carboxylic acids gave the corresponding butenolides in good yield, and no significant steric or electronic effect of the substituents on the carboxylic acids was observed. In the reaction with iodo- and amino-substituted benzoic acids that resulted in relatively low yields, the product decomposition, presumably via direct photolysis or electron transfer with excited cyclobutenedione during the reaction, was observed (**Scheme 2a**). Under the optimized aqueous conditions, carboxylic acids having functional groups, such as



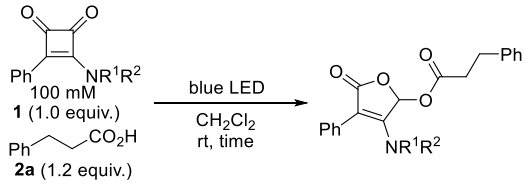
Scheme 2. Substrate Scope of Phototriggered Conjugation. (a) Reaction in CH_2Cl_2, (b) Reaction under Aqueous Conditions, (c) Reaction with Various Nucleophiles Other than Carboxylic Acids.

aliphatic and aromatic hydroxy groups, indole, and biotin, reacted with **1a** to afford a corresponding butenolide in 58–77% yield (**Scheme 2b**).

The phototriggered reaction was applicable to various nucleophiles other than the carboxylic acids. The acidity of the substrate was strongly related to the reactivity. Acidic nucleophiles with similar pK_a values to the carboxylic acid, such as pentafluorophenol (**4**), phosphoric acid dibenzyl ester (**6**), and tetrazole (**8**), reacted with aminocyclobutenedione **1a** to give the corresponding butenolide in moderate to high yield. The alkyl amine **10** also reacted with **1a** to give the butenolide **11**, but the reactivity was much lower than the acidic nucleophiles. Phenol (**12**), 2-phenethylalcohol (**13**), and 2-phenylethanethiol (**14**), which have much lower acidity than a carboxylic acid, were unreactive and did not give the corresponding butenolides (**Scheme 2c**).

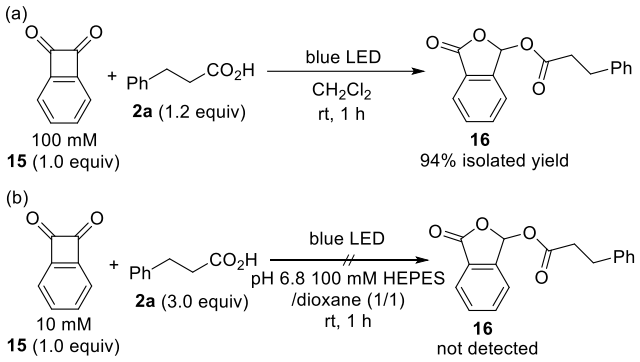
Next the effect of the amino group in the aminocyclobutenedione was investigated (**Table 3**). The primary alkylamino substituted cyclobutenedione **1b** gave the product in 62% yield (entry 2). The reaction with methylisopropylaminocyclobutenedione **1c** was significantly slower than that with **1a** and **1b**. Even after 24 h irradiation, the reaction was not complete, and the yield was 23% (entry 3). Diisopropylamino substituted cyclobutenedione **1d** did not give the product (entry 4). According to the results, aminocyclobutnediones with sterically less hindered amino groups tended to give a better yield. Because significant reactivity differences were observed between the monoalkylamino and dialkylamino substituted cyclobutenedione, the proton on the amino group might play important roles, such as hydrogen bonding with the substrate carboxylic acid for the efficient progress of the phototriggered butenolide formations.

Table 3. Substituent Effect of the Amino Group.



entry	-NR^{1}R^2 of **1**	time (h)	butenolide yield (%)[a]
1	-NH*i*Pr (**1a**)	3	79
2	-NHPr (**1b**)	4	62
3	-NMe*i*Pr (**1c**)	24	23
4	-N*i*Pr$_2$ (**1d**)	24	0

[a]Isolated yield.



Scheme 3. Acyloxybutenolide formation from benzocyclobutnedione. (a) Reaction in CH_2Cl_2, (b) Reaction under Aqueous Conditions.

As previously reported, benzocyclobutenedione (**15**) reacts with methanol under light irradiation to form an alkoxybutenolide.[3] To investigate if **15** also reacts with a carboxylic acid to form an acyloxybutenolide, **15** was irradiated in the presence of a carboxylic acid **2a**. In CH_2Cl_2, the reaction proceeded efficiently, and acyloxybutenolide **16** was obtained in 94% yield (**Scheme 3a**). In contrast, in pH 6.8 HEPES buffer/1,4-dioxane conditions, **15** disappeared after 1 h irradiation, but **16** was not obtained and resulted in multi-spot products, which could not be characterized (**Scheme 3b**). These results suggest that benzocyclobutenedione **15** could also react with a carboxylic acid to form an acyloxybutenolide, but the reaction does not tolerate aqueous conditions.

Figure 1 presents the proposed mechanism of the acyloxybutenolide formation and a DFT calculation of the intermediates and transition states starting from aminocyclobutenedione **1a** and carboxylic acid **2a**. First, cyclobutenedione **1a** is photoexcited to give a bisketene intermediate **17**. This bisketene formation would be reversible, according to previous reports.[1] Bisketene **17** then reacts with **2b** to give an enol intermediate **18**. Intramolecular cyclization of **18** gives a furane **19** followed by isomerization to more stable acyloxybutenolide **3b**, as suggested in some previously reported butenolide formation reactions.[3,23] The calculated ground state energy of the bisketene intermediate **17** was 29.3 kcal/mol higher than cyclobutenedione **1a**, and the activation energy of the reverse reaction was12.2 kcal/mol. Therefore, **1a** and **17** would be at equilibrium under the irradiation conditions.

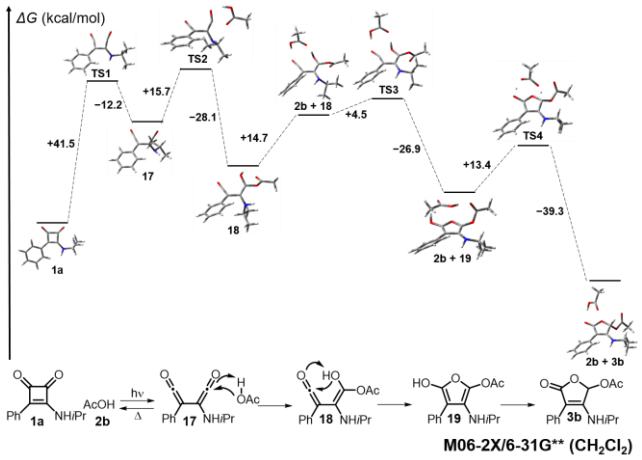


Figure 1. Computation Study of the Reaction Mechanisms. The geometries of the starting materials, the intermediates, the transition states, and the product were optimized using DFT calculations at the CPCM(DCM)-M06-2X/6-31G(d, p) level. [24]

The nucleophile adduct **18** was calculated to be 12.4 kcal/mol more stable than the sum of the ground state energies of **2b** and **17**, and the transition state energy from **2b** and **17** to **18** was 15.7 kcal/mol. The relevant transition states were not found for cyclization from **18** to **19** and isomerization from **19** to **3b** without additives. However, the relevant transition states were found for these steps when **2b** was added to support the proton transfer. The nucleophile adduct **18** formed an unstable complex with **2b** whose energy was 14.7 kcal/mol higher than the sum of the ground state energies of **2b** and **18**. From the complex, a transition state of the cyclization (**TS3**) was found, and the activation energy of **TS3** was 4.5 kcal/mol. The calculated activation energy of the transition state from furane **19** to **3b** with the support of **2b** was 13.4 kcal/mol. All the calculated activation energies from **17** to **3b** suggest that the reaction proceeds efficiently at room temperature. The activation energy of the reaction of **2b** and **17** at the phenyl group side of **17** was 4.1 kcal/mol higher than that at the amino group side. This is also consistent with the result that the adduct from the amino group side was solely obtained (The detailed result of the calculation is shown in the Supporting Information). In the proposed mechanism, multiple proton transfer steps are included. The energy barriers of these steps should be influenced by the nucleophile acidity, and the acidity of a carboxylic acid would be suitable for these steps.

In conclusion, an efficient phototriggered reaction of an aminocyclobutenedione and a nucleophile to give a butenolide derivative was discovered. When an acidic nucleophile with a pK_a value similar to that of a carboxylic acid was used, the butenolide was obtained in high yield. The synthesis of butenolide derivative conjugated with the acidic nucleophile has been rarely reported before. Therefore, this reaction holds promise for preparing unique butenolide libraries with potential unique bioactivities. Furthermore, since the reaction can modify a carboxy group under aqueous conditions at a specific timing by light irradiation, it would be applicable to specific labeling of biomolecules for the study of the biological phenomenon[15,16,17] and specific functionalization of biomolecules[25,26].

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