Phototriggered Dehydration Condensation Using an Aminocyclopropenone

著者

表

著者別表示

表

表

表

表

doi: 10.1021/acs.orglett.7b02383
Phototrigged Dehydration Condensation Using an Aminocyclopropanone

Kenji Mishiro*,†, Yuki Yushima‡ and Munetaka Kunishima*†

1Institute for Frontier Science Initiative, Kanazawa University, Kakuma-machi, Kanazawa 920-1192 Japan
2Faculty of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192 Japan

Supporting Information Placeholder

![Diagram](image)

**ABSTRACT:** A phototrigged dehydration condensation using an aminocyclopropanone has been developed. The UV irradiation of an aminocyclopropanone generated a highly reactive ynamine *in situ*, and the dehydration condensation of a carboxylic acid and an amine coexisting in the reaction solution smoothly proceeded to afford an amide. This reaction is completely controllable by the ON/OFF states of a UV lamp.

Phototrigged chemical reactions have attracted considerable attention because of the following unique features: i) the reaction can be initiated and terminated whenever required, ii) the location of the reaction can be controlled by regulating the irradiation site, iii) the activation of a specific chromophore is possible by selecting an appropriate wavelength, and iv) highly reactive species can be generated *in situ* under mild conditions. These features are particularly useful for the fine control of the polymer synthesis and the chemical modification of biomolecules. In phototrigged chemical reactions, photoexcited species could form reversible active intermediates or photolytically generate active species, such as radicals, carbenes, nitrenes, and nitrile imines. These species have mostly been used for the insertion, addition, and abstraction reactions. To the best of our knowledge, there has been no report focusing on phototrigged dehydration condensation. Because dehydration condensation is abundantly observed in multiple situations, such as polymer synthesis, biomolecule synthesis, and biological processes, phototrigged dehydration condensation would be useful for the local control of these reactions with light.

Herein, we report the first phototrigged dehydration condensation using an aminocyclopropanone as a photolabile “caged” dehydrating agent. Cyclopropanone is a highly strained cyclic enone with 2π aromaticity, which was first reported by Breslow. Because of the strain, the ring-opening reaction occurs in the presence of an appropriate nucleophile. The ring strain is also released by thermal or photochemical decarboxylation to afford the corresponding alkyne. Cyclopropanones are normally stable under ambient conditions, and the thermal decarboxylation occurs at a high temperature. In contrast, photochemical decarboxylation efficiently occurs at ambient temperature with a quantum yield of 0.2–0.8. Popik demonstrated a broad range of applications of the phototriggered alkyne formation, such as phototriggered alkyne-azide click reaction and phototriggered en-diyne formation. Kresge reported photoexcitation of an aminocyclopropanone generates carbon monoxide and an aminoaalkyne (ynamine). An ynamine acts as a potent dehydrating agent, which converts a carboxylic acid to an acid anhydride, and a carboxylic acid and an amine to an amide. Despite the high reactivity, ynamines are rarely used in synthesis because of their low stability and complicated preparation procedure. Recently an ynamide was reported as a stable and racemization-free condensing agent. However, an ynamide is generally less reactive than an electron-rich ynamine as a compensation for its high stability.

We envisioned that if a highly reactive ynamine is photolytically generated from an aminocyclopropanone and used for the following reaction *in situ*, the high reactivity of the ynamine can be exploited without complicated handling and the generation of the ynamine would be controllable by the ON/OFF states of light irradiation (Scheme 1).

**Scheme 1. Design of a phototrigged dehydration condensation**

a) Phototrigged ynamine generation

b) Dehydration condensation with an ynamine

c) Phototrigged dehydration condensation (This work)

Aminocyclopropanones with various substituents 4a–f were readily prepared according to the procedures reported in the literature (Scheme 2). All of 4a–f was isolable using SiO2 column chromatography. These compounds are colorless or slightly yellow, and stable under household fluorescent light. The UV spectra were recorded for synthesized 4a–f in MeCN (Figure 1). All the aminocyclopropanones showed similar spectra pattern having absorption around the 200–350 nm region. The decomposition of the aminocyclopropanones during the UV measurement was negligibly small.
Scheme 2. Synthesis of aminocyclopropenones 4a–f.

Figure 1. The UV spectra of 4a–f in MeCN.

First, the phototriggered ynamine generation from 4 was examined (Table 1). Unexpectedly, a weak handheld UV lamp, which is generally used for TLC analysis, was sufficient for the photolysis reaction. The MeCN solutions of 4 were irradiated with a 6 W UVB lamp (280–350 nm) that was placed 4 cm from the reaction vessel. However, the yield was very low (entries 1–9), while alkyl-substituted aminocyclopropenones 4a–c resulted in unidentified complex mixtures (entries 1, 3, and 5). In general, electron-rich ynamines are more reactive than electron-poor ynamines.17 Thus, the decompositions observed for 4a–c were possibly related to the high reactivity of the produced ynamines. Consequently, for 4a–c, corresponding ynamines were indirectly detected as stable amides 6a–c that are formed by the hydration of the ynamines under the MeCN/H2O (1/1) condition (entries 2, 4, and 6).

Subsequently, the phototriggered dehydration condensation was examined (Table 2). A solution of 4, carboxylic acid 7a, and amine 8a in MeCN was irradiated under the same condition as that of the ynamine formation experiment until 4 disappeared. After the irradiation was stopped, the reaction was rapidly quenched by the acid/base workup and the yield of amide 9aa was determined via NMR analysis. The condensation of 7a and 8a satisfactorily proceeded to afford 9aa for most of 4. Ethyl- and isopropyl-substituted aminocyclopropenones resulted in a relatively high 9aa yield (entries 1–2) while benzyl-substituted one resulted in a low 9aa yield and a considerable number of byproducts were observed (entry 3). Aryl-substituted ones resulted in low 9aa yield probably because of the low reactivity of the generated ynamines (entry 4–5). For 4f, 9aa was not obtained and ynamine 5f was recovered in 70% yield (entry 6).

A plausible mechanism of the phototriggered reaction is shown in Scheme 3. The photoexcitation of an aminocyclopropenone 4 produces an ynamine 5. Subsequently, 5 reacts with a carboxylic acid 7 to form a carboxylic acid-ynamine adduct 10. Finally, 10 reacts with an amine 8 to afford a condensed product 9 and a hydrated ynamine 6.

Table 1. Ynamine generation from aminocyclopropenones.

Table 2. Phototriggered dehydration condensation using aminocyclopropenones.

For 4a and 4c, a small amount of 9aa was formed even under dark conditions (Table 2, entries 1 and 3). The background reaction in these conditions did not yield the hydrated ynamine 6, which should be observed if the ynamine 5 would be involved in 9aa formation. Therefore, the background reaction would occur with a mechanism different from that of the phototriggered dehydration condensation.18

Because 4b resulted in a good condensation yield without the background reactions, the reaction condition was further optimized with 4b (Table 3). For all the conditions, UV irradiation was performed until 4b disappeared. Solvent screening showed that chlorinated solvents were the best candidates for this reaction (entries 1–9). In the presence of water, the condensation yield was very low probably because the photogenerated ynamine was rapidly hydrated (entry 2). Higher concentration and longer irradiation distance resulted in higher 9aa yield but decreased the photodecarbonylation rate. The slower rate was probably due to a lower irradiation efficiency (entries 10–12). The UVC (240–260 nm) also initiated the reaction and resulted in a good yield (entry 13). The temperature difference did not affect the photodecarbonylation rate. However, low temperature conditions resulted in a slightly lower condensation yield (entries 14–15). Consistently, for low yielding conditions, multiple byproducts were observed. Although the byproducts have not been identified yet, they could have been formed by thermal
rearrangements or photoexcitation of the reaction intermediates competing with the dehydration condensation to afford 9aa. In general, photochemical reactions efficiently occur under intense light and low concentration conditions. However, for the phototriggered dehydration condensation using aminocyclopropenones, the light should not be too intense and the concentration should not be too low to avoid the undesired side reactions.

Table 3. Optimization of the conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>concn (mM)</th>
<th>temp (°C)</th>
<th>UV condition (lamp, distance)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>MeCN/H(O:1)</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>1,4-dioxane</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>AcOEt</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>CH2Cl2</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>CHCl3</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>1,2-dichloroethane</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>toluene</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>CH2Cl2</td>
<td>40</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>CH2Cl2</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>CH2Cl2</td>
<td>40</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>5</td>
<td>85</td>
</tr>
<tr>
<td>13</td>
<td>CH2Cl2</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>14</td>
<td>1,2-dichloroethane</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>3</td>
<td>87</td>
</tr>
<tr>
<td>15</td>
<td>CH2Cl2</td>
<td>20</td>
<td>20</td>
<td>UVB, 4 cm</td>
<td>3</td>
<td>77</td>
</tr>
</tbody>
</table>

* Distance between the lamp and the reaction vessel. ** NMR yield.

To investigate the details of the phototriggered dehydration condensation, the reaction progress was monitored by 1H NMR (Figure 2). A solution of 4b, 7a, 8a, and 1,3,5-trimethoxybenzene (as an internal standard) in CDCl3 was irradiated with the UVB in a glass NMR tube. The NMR spectrum was observed within 20 min after the irradiation was stopped.

**Figure 2. Monitoring of the phototriggered reaction by NMR.**

In the NMR study, intermediates such as an ynamine and an active ester were not observed, and the reaction did not progress under dark conditions. The results indicated that the condensation rapidly completed after the ynamine generation and that the reaction is completely controllable by ON/OFF states of the UV irradiation.

The phototriggered condensation with various substrates proceeded with approximately 70%–90% yield (Figure 3). For the secondary and tertiary carboxylic acids, 2.0 equiv of carboxylic acid was used to improve the yield. In general, less reactive bulky starting materials tended to afford multiple byproducts, which were probably generated by thermally or photochemically induced sidereactions of the intermediates.

**Figure 3. Phototriggered dehydration condensation of various substrates.** a 1.0 equiv carboxylic acid was used. b 2.0 equiv carboxylic acid was used. NMR yield. Isolated yield.

Finally, a naphthalene-conjugated aminocyclopropenone 4g was synthesized and employed for the phototriggered dehydration condensation. As shown in Figure 4, 4g absorbed longer wavelength than 4b. For the phototriggered reactions, UVA (330–400 nm), UVB (280–350 nm), or UVC (240–260 nm) were used as light sources (Table 4). The reactions with 4g proceeded with any of the UV sources. In the same manner as the reaction with 4b, 9aa and a hydrated ynamine were produced as 4g was consumed. It is worth noting that UVA which was not highly effective for 4b, efficiently worked for 4g (entries 3–4). Excitation with less harmful UVA would be particularly useful for the functionalization of biomolecules.

**Figure 4. UV spectra of 4b and 4g in CH2Cl2.**

**Table 4. Reactions with a naphthalene conjugated aminocyclopropenone.**
In conclusion, we demonstrated the first phototriggered dehydration condensation that is completely controllable by the ON/OFF states of UV irradiation. This method would be useful for a simple preparation of an extremely reactive ynamine and for the local control of a dehydration reaction. These studies are currently under investigation in our laboratory.

REFERENCES


ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures for the synthesis of aminocyclopropanones and photochemical reactions; 1H and 13C NMR spectra of all new compounds. (PDF)

AUTHOR INFORMATION

Corresponding Author

* mishiro@p.kanazawa-u.ac.jp
* kunisima@p.kanazawa-u.ac.jp

ACKNOWLEDGMENT

This research was supported by MEXT KAKENHI Grant No. 16H06824. KM appreciates the support from the Program to Disseminate Tenure Tracking System, MEXT. KM appreciates Prof. Tristan H. Lambert (Columbia University) for helpful discussion.

For more detailed information, see Supporting Information.