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# Addition of alkyl radicals, generated from carboxylic acids via photochemical decarboxylation, to glyoxylic oxime ether: a mild and efficient route to α-substituted α-aminoesters

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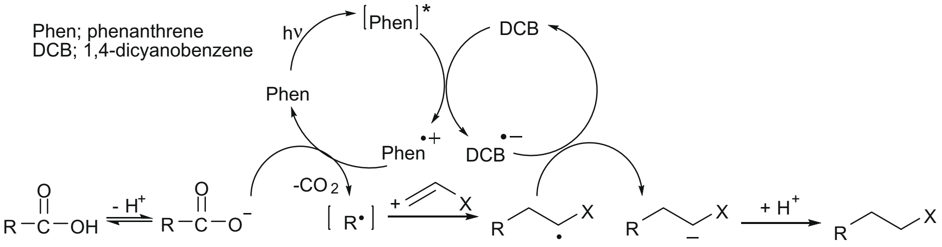
## ABSTRACT

Radical addition to a glyoxylic oxime ether was accomplished under mild conditions using an alkyl radical generated from a free carboxylic acid via photochemical decarboxylation. The photoreaction provided an efficient route to α-substituted α-aminoesters from carboxylic acids and oxime ether.

Radical addition to glyoxylic oximes is attracting increased attention as a synthetic method for the preparation of α-amino acid derivatives.[1] In this method, Lewis acids such as $Et_3B$, In, and Zn are used to increase the reactivity of oximes by the coordination of the C=N bond and radical generation from an alkyl iodide. However, less toxic and mild reaction conditions are still desired from an environmental point of view.

We have recently reported that the decarboxylation of free aliphatic carboxylic acids is effected by the photogenerated cation radical in a redox-photosensitized reaction[2] system, and inter- and intra-molecular additions of electron-deficient alkenes proceed via the generated radical (Scheme 1).[3] The finding provides an efficient generation method of alkyl radicals from free aliphatic carboxylic acids under mild conditions, and led us to investigate radical addition to a glyoxylic oxime ether by using the photoreaction. The use of a carboxylic acid both as a Brønsted acid for increasing the reactivity of the oxime ether and as a radical source is attracting interest because of its ready availability and less toxicity as compared to Lewis acid and alkyl iodides.

Initially, decarboxylative addition of carboxylic acid **1** to glyoxylic oxime ether **2** (Bn = benzyl) was examined, as shown in Table 1. Excitation of an aqueous acetonitrile solution ($CH_3CN/H_2O$ = 9:1) containing phenanthrene (Phen, 20 mM), 1,4-dicyanobenzene (DCB, 20 mM), cyclohexanoic acid **1a** (20 mM), and **2** (20 mM) with a 100-W high-pressure mercury lamp through a Pyrex filter (>300 nm) under an argon atmosphere for 6 h at room temperature afforded **3a** in 45% yield along with the recovery of Phen and DCB (>90%) (entry 1 in Table 1). In contrast to previous results obtained with alkenes,[3c] the addition of 1 equiv of NaOH to this solution prevented the photoreaction, and the formation of **3** was not observed at all. In addition, the use of the sodium salt of **1a** instead of **1a** did not provide the adduct **3a**. These results



**Scheme 1.** Radical addition to alkene via photochemical decarboxylation of free carboxylic acids.

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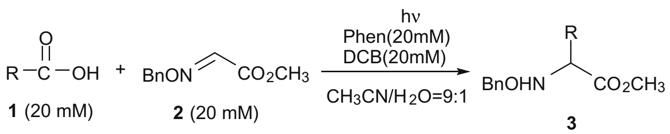
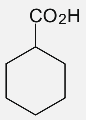
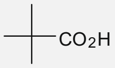
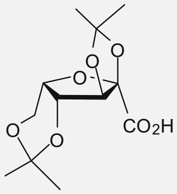
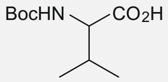
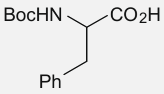
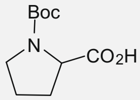
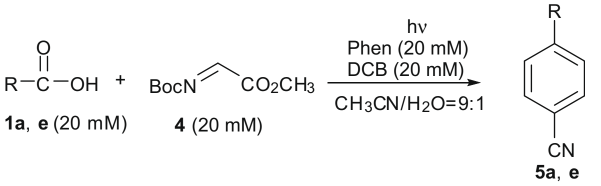
**Table 1**
Radical addition to glyoxylic oxime ether **2** from carboxylic acids **1** via photochemical decarboxylation[a]



| Entry | Carboxylic acid **1** | Yield of **3** (%) |
|---|---|---|
| 1 | **1a**;  | 45 |
| 2[b] | **1a** | 55 |
| 3 | **1b**:$CH_3(CH_2)_4CO_2H$ | 38 |
| 4 | **1c**;  | 37 |
| 5[b] | **1c** | 46 |
| 6 | **1d**;  | 32 |
| 7[b] | **1d** | 40 |
| 8 | **1e**;  | 55 |
| 9[b] | **1e** | 70 |
| 10 | **1f**;  | 57 |
| 11[b] | **1f** | 65 |
| 12 | **1g**;  | 45 |

[a] The photoreaction was carried out with Phen (0.8 mmol), DCB (0.8 mmol), **1** (0.8 mmol), and **2** (0.8 mmol) in aqueous $CH_3CN$ solution ($CH_3CN$, 36 mL; $H_2O$, 4 mL) using a 100-W high-pressure mercury lamp under argon atmosphere for 6 h.

[b] The photoreaction was carried out with Phen (0.8 mmol), DCB (0.8 mmol), **1** (1.6 mmol), and **2** (0.8 mmol) in aqueous $CH_3CN$ solution ($CH_3CN$, 36 mL; $H_2O$, 4 mL) using a 100-W high-pressure mercury lamp under argon atmosphere for 6 h.

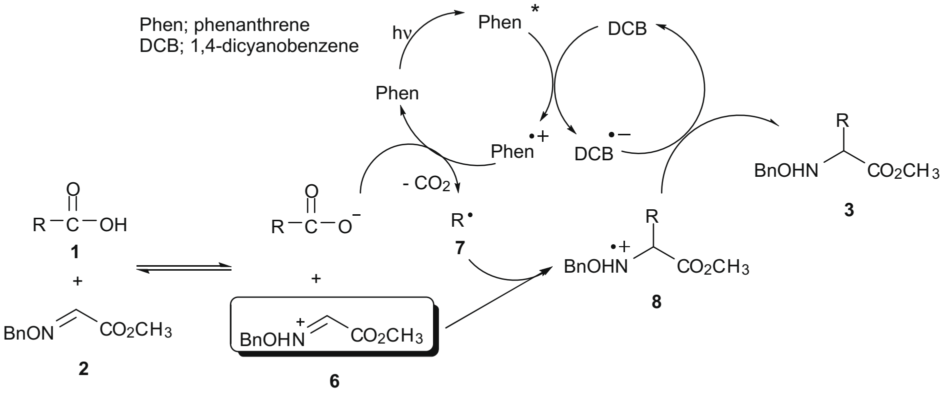


**Scheme 2.** Photoreaction of **1** with **4**.

indicate that the formation of iminium cation through the protonation of **2** by carboxylic acid **1** was essential for the successful completion of the reaction. An increase in the concentration of **1** (40 mM) slightly increased the yield of **3** (entries 2, 5, 7, 9, and 11); however, the addition of Brønsted acids such as $HClO_4$ and TsOH or Lewis acids such as $Sc(OSO_2CF_3)_3$ decreased the yield of **3**, since these acids prevented the deprotonation of **1**. Also, the higher concentration of **1** (>60 mM) decreased the yield of **3**. When the solution was irradiated in the absence of Phen or DCB, photochemical decarboxylation of **1** did not occur. Thus, the photoreaction required Phen to act as a photosensitizer and DCB to act as an electron-acceptor; oxime ether **2** acted as neither a photosensitizer nor an electron-acceptor.[4] The use of other carboxylic acids such as primary alkyl carboxylic acid **1b**, tertiary alkyl carboxylic acid **1c**, and protected gulonic acid **1d** instead of **1a** also yielded the corresponding adducts **3b–3d** in moderate yields (entries 3–7). It is noteworthy that the photoreaction provided the novel α-amino acid derivative **3d** having a sugar skeleton with a slight diastereoselectivity (3:2) under mild conditions (entries 6 and 7). On the other hand, cyanoacetic acid, which produces an electron-poor radical via photochemical decarboxylation, did not result in the formation of adducts. When amino acids such as *N*-Boc-L-valine **1e**, *N*-Boc-L-phenylalanine **1f**, and *N*-Boc-L-proline **1g** (Boc = *t*-butoxycarbonyl) were subjected to photoreaction, α,β-amino acid derivatives **3e–g** were also obtained in moderate yields as a diastereoisomer mixture (entries 8–12). Thus, a variety of unique α-amino acid derivatives could be directly prepared from carboxylic acid **1** and oxime ether **2**.

Next, we examined photodecarboxylative addition of *N*-Boc glyoxylic imine **4** (Scheme 2). Photoreaction of **1a** or **1e** with **4** under the same conditions provided 4-alkyl-1-cyanobenzene **5a,e** (30, 27%) via a substitution of DCB, respectively.[3b] No formation of the adduct with **4** indicates that the lower basicity of **4** than that of **2** prevented the formation of the iminium cation of **4**, and the generated radical via the photochemical decarboxylation could not add to **4**.

Scheme 3 shows a plausible mechanism for this photoreaction. First, protonation of **2** by **1** led to the formation of iminium cation **6** and a carboxylate ion. Decarboxylation of the carboxylate ion with the photogenerated cation radical of Phen produced the radical **7**. The addition of the radical **7** to **6** produced the cation radical **8**. Subsequently, electron transfer between **8** and the anion radical of DCB produced the adduct **3**.



**Scheme 3.** Plausible mechanism for the photoreaction.

In conclusion, we found that carboxylic acid **1** served both as a Brønsted acid and as a radical source in this photoreaction, and the generated radical underwent addition to iminium cation **6** through the protonation of **2**. The photoreaction proceeded smoothly under very mild conditions without any metal catalysts and allowed the direct preparation of α-substituted α-amino acid derivatives starting from **1** and **2**. Further investigation of the diastereoselectivity of this photoreaction is currently in progress.

## Acknowledgment

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## Supplementary data

Supplementary data (general procedure for photoreaction and characterization data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.112.

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