Decarboxylative reduction of free aliphatic carboxylic acids by photogenerated cation radical†

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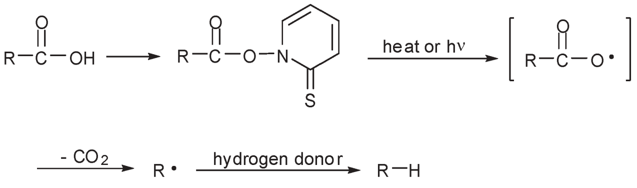
The decarboxylation of free carboxylic acids was effected by a photogenerated cation radical of phenanthrene to yield the reduction product in the presence of a thiol, which provides an alternative method to the Barton decarboxylation procedure for aliphatic acids such as *N*-Boc amino acids.

The decarboxylative reduction of carboxylic acid is a useful synthetic transformation. Although several methods have been reported,[1] this reduction has been most effectively performed by the Barton decarboxylation[2] involving the decomposition of the thiohydroxamic ester into radical fragments by either light or heat in the presence of a hydrogen donor such as a thiol or tributyltin hydride (Scheme 1). In addition to the Barton decarboxylation, carboxylic acids are also known to undergo decarboxylative reduction *via* photoinduced electron transfer in the presence of several electron acceptors such as cyanonaphthalene,[3] acridine[4] and benzophenone;[5] however, the carboxylic acids used in these cases were limited to aryl and aryloxy acetic acids.

In the course of our study, the photochemical reaction in water using a photosensitive surfactant yielded a decarboxylated product, probably *via* the electron transfer between the photogenerated cation radical and the carboxylate ion.[6] On the basis of this observation, we undertook to investigate the decarboxylative reduction of free carboxylic acid in a redox-photosensitized reaction system[7] (Scheme 2).

We now report that the decarboxylation of free carboxylic acids was effected by the reaction with a photogenerated cation radical of phenanthrene to yield the reduction product in the presence of a thiol. The reaction provides an effective method for the decarboxylative reduction of free aliphatic carboxylic acids, including *N*-Boc amino acids, and several naturally occurring substrates.

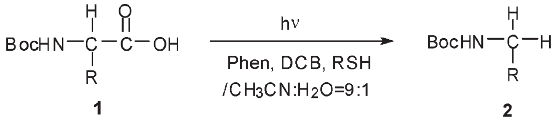


Scheme 1 Barton decarboxylation.

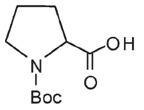
An aqueous acetonitrile solution ($CH_3CN–H_2O$ = 9 : 1)[8] containing phenanthrene (Phen, 10 mM),[9] 1,4-dicyanobenzene (DCB, 10 mM), *t*-dodecanethiol (RSH, 20 mM), and *N*-Boc-L-phenylalanine **1a** (10 mM) was irradiated with a 400 W high-pressure mercury lamp through a Pyrex filter (>300 nm) under an argon atmosphere for 6 h at room temperature. This resulted in a decarboxylated product **2a** in a 97% yield; further, this reaction recovered Phen and DCB (>95%) (Table 1, entry 1).

The addition of one equivalent of NaOH to this solution accelerated the photoreaction in the initial stage (2 h) (entry 2) and finally produced **2** in a similar or slightly higher yield (yields of **2** in the presence of 1 equiv. NaOH are given in the parentheses in Table 1). On the other hand, the addition of HCl (10 mM) resulted in the recovery of **1** without the formation of **2**. Thus, the

Table 1 Decarboxylative reduction of *N*-Boc amino acids **1a–i**[a,b]



1a; R = CH_2Ph *N*-Boc-L-phenylalanine
1b; R = $CH(CH_3)_2$ *N*-Boc-L-valine
1c; R = $CH_2CH(CH_3)_2$ *N*-Boc-L-leucine
1d; R = $CH_2CH_2SCH_3$ *N*-Boc-L-methionine
1e; R = CH_2indole *N*-Boc-L-tryptophan
1f; R = $CH_2CH_2CONH_2$ *N*-Boc-L-glutamine
1g; R = $CH_2CH_2CO_2H$ *N*-Boc-L-glutamic acid
1h; R = $CH_2CH_2CH_2CH_2NHBoc$ *N*,*N*′-bisBoc-L-lysine
1i;



N-Boc-L-proline

Entry	1	Yield of 2[c] (%)
1	a	97 (97)
2[d]	a	26 (51)
3	b	78 (74)
4	c	78 (86)
5	d	83 (87)
6	e	56 (44)
7	f	78 (82)
8	g	45 (64)[d]
9	h	82 (90)
10	i	62 (73)

[a] Photochemical reactions were carried out with 0.6 mmol (10 mM) of **1** for 6 h. **1**–Phen–DCB–RSH = 1 : 1 : 1 : 2. [b] The values in parentheses are for the reactions with 1 equiv. NaOH. **1**–NaOH–Phen–DCB–RSH = 1 : 1 : 1 : 1 : 2. [c] Isolated yield. [d] Irradiation time was 2 h.

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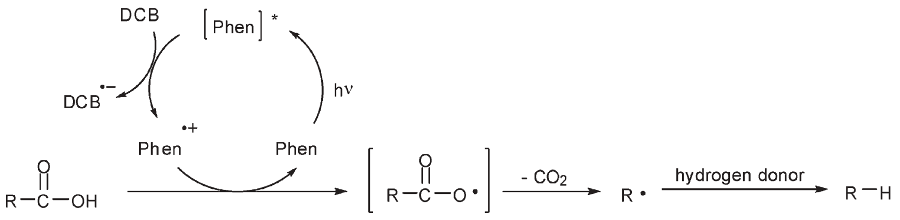
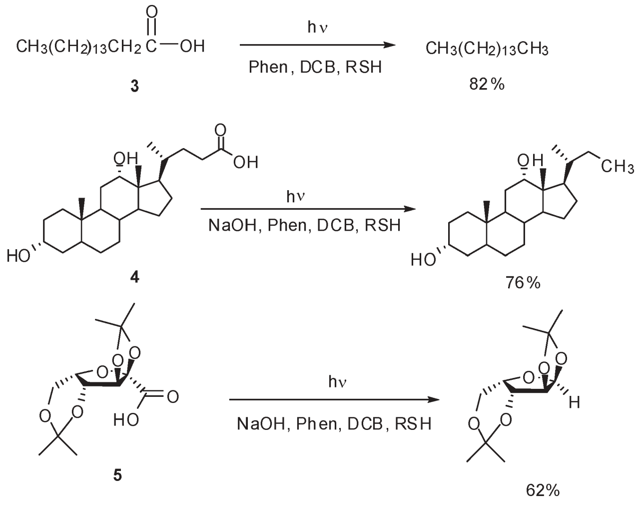


Scheme 2 Decarboxylative reduction of free carboxylic acid with the photogenerated cation radical of Phen.

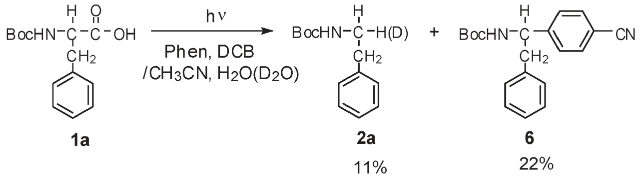
decarboxylation of the carboxylate ion was more efficient than that of the corresponding carboxylic acid. An examination of the results summarized in Table 1 indicates that most of the *N*-Boc amino acids successfully undergo the decarboxylative reduction in good to excellent yields. It should be noted that *N*-Boc-L-glutamic acid **1g** (entry 8) having two carboxyl groups selectively gave the decarboxylative reduction product of the α-carboxyl group, and an increased yield of **2g** was observed with 1 equiv. NaOH at 2 h, indicating that the decarboxylation of the α-carboxyl group of **1g** was faster than that of the side chain carboxyl group.

When other aliphatic acids such as fatty acid **3**, acids of steroid **4** and sugar **5** were subjected to this photoreaction, decarboxylative reduction products were also obtained in moderate yields (Scheme 3).



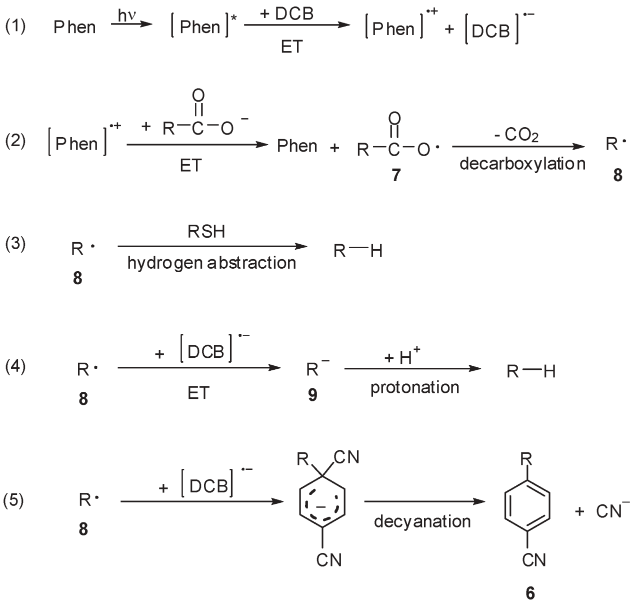
Scheme 3 Decarboxylative reduction of **3**, **4** and **5**.

Next, we examined the behaviour of this photoreaction in the absence of a hydrogen donor and found that a low yield of the decarboxylative reduction product **2a** was observed along with a decarboxylative substitution product **6** (Scheme 4). In addition, a deuterium incorporation experiment using D_2O showed that a deuterated product was obtained in a high *d*-content (100%). These results reveal that the minor process *via* the corresponding anion existed in the photoreaction.



Scheme 4 Decarboxylative reduction of **1a** in the absence of RSH.

Scheme 5 shows a plausible mechanism for this photoreaction. Initially, a cation radical of Phen and an anion radical of DCB are formed *via* electron transfer (ET) between the excited Phen and DCB (1). The secondary electron transfer from a carboxylate ion, which is generated by the dissociation of the carboxylic acid in aqueous solution, to the cation radical of Phen is an exothermic process; this fact is indicated by the negative ΔG values (−0.34 V)[10] calculated by using the oxidation potential of Phen (1.50 V *vs.* SCE in acetonitrile)[11] and an aliphatic carboxylate ion such as hexanoate ion (1.16 V *vs.* SCE in acetonitrile).[12] Thus, the cation radical of Phen can be reduced by carboxylate ions[13] to produce radical **7**, which is decarboxylated to form radical **8** (2). The generated alkyl radical **8** can abstract a hydrogen atom of the thiol to give the reduction product (3). In addition, the minor process *via* ET between the anion radical of DCB and radical **8** to form anion **9** also yielded the reduction product by protonation (4). In the absence of the thiol, radical **8** is coupled with the anion radical of DCB, which undergoes a successive decyanation to yield **6** and CN^- as reported earlier[14] (5).



Scheme 5 Plausible mechanism.

In conclusion, we found that the decarboxylation of free aliphatic carboxylic acids such as *N*-Boc amino acids proceeded by using the photogenerated cation radical to yield the reduction product in the presence of the thiol. This photoreaction can be useful for generating carbon-centered radicals derived from aliphatic carboxylic acids *via* decarboxylation, and the application of this photoreaction to intra- and inter-molecular addition to alkenes is in progress.

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8 When dry acetonitrile was used as a solvent a lower yield of **2** was observed.

9 The use of naphthalene or triphenylene instead of phenanthrene led to a lower yield of **2**.

10 Such calculations often include a Coulomb term, which accounts for the stabilization of the ion pair; however, this Coulombic stabilization gives a very low yield of acetonitrile. Thus, the Coulomb term is not considered in this calculation.

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