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Decarboxylative radical addition of *N*-Boc-amino acids to acrylonitrile via photoinduced electron transfer using 1,4-dicyanonaphthalene

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Abstract Decarboxylative radical addition of *N*-(*t*-butoxycarbonyl)amino acids to acrylonitrile was achieved by excitation of 1,4-dicyanonaphthalene. The photochemical decarboxylation was highly dependent on the dicyanoarenes used as electron acceptors and on addition of a base. The photoreaction proceeded smoothly to yield the decarboxylative adduct even in the presence of only a catalytic amount of 1,4-dicyanonaphthalene.

Keywords Decarboxylative radical addition · *N*-Boc-amino acids · Acrylonitrile · 1,4-Dicyanonaphthalene · Photoinduced electron transfer

Introduction

Decarboxylative radical addition of carboxylic acids to alkenes is one of the most important types of C–C bond formation in organic synthesis, because carboxylic acids occur widely in nature and are readily available commercially. This transformation is usually performed via Barton decarboxylation; however, this requires esterification of carboxylic acids to thiohydroxamic esters as precursors, and use of excess alkene [1–4]. A photochemical method involving intramolecular photoinduced electron

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This paper is dedicated to Professor Kazuhiko Mizuno of Osaka Prefecture University on the occasion of his retirement.

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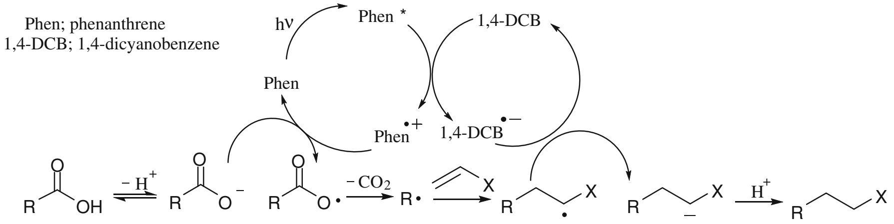


Scheme 1 Decarboxylative radical addition of carboxylic acids to alkenes via PET

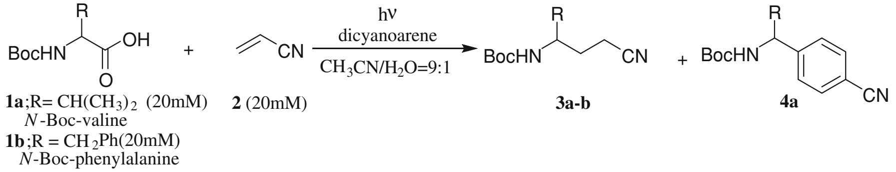
transfer (PET) of 3-(*N*-phthalimido)adamantane-1-carboxylic acids, which yields decarboxylative radical adducts with alkenes, can also be used [5].

We recently reported the decarboxylative radical addition of a variety of *N*-(*t*-butoxycarbonyl)amino acids (*N*-Boc-amino acids) to electron-deficient alkenes, for example acrylonitrile, ethyl acrylate, acrylic acid, and phenyl vinyl sulfone, in a redox-photosensitized reaction [6–8] (Scheme 1). Single-electron transfer (SET) from the carboxylate ion to the photogenerated radical cation of phenanthrene (Phen) proceeds to form an alkyl radical via decarboxylation of a carboxyl radical [9–14]. The alkyl radicals generated react with alkenes to produce adduct radicals. SET from the radical anion of 1,4-dicyanobenzene (1,4-DCB) and protonation lead to formation of the adduct in high yield, even in the presence of only one equivalent of alkene. Furthermore, this photodecarboxylation is applicable to intramolecular radical addition to alkenes, inducing cyclizations to macrocyclic lactones [9]. This discovery led us to investigate a more simple photochemical method that involves use of dicyanoarenes. Although the excited states of dicyanoarenes have been shown to decarboxylate carboxylate ions with generation of alkyl radicals [11, 15], decarboxylative radical addition to alkenes has not yet been investigated. In this study, we investigated decarboxylative radical addition of carboxylic acids, for example *N*-Boc-amino acids, to acrylonitrile **2** by use of dicyanoarenes.

Results and discussion

Initially, photodecarboxylative addition of *N*-Boc-valine **1a** to **2** in a variety of dicyanoarenes was examined, as shown in Table 1. Excitation of an aqueous acetonitrile solution (CH_3CN–H_2O 9:1) containing 1,4-dicyanonaphthalene (DCN, 20 mM), **1a** (20 mM), and **2** (20 mM) with a 400-W high-pressure mercury lamp through a Pyrex filter ($\lambda > 300$ nm) under an argon atmosphere for 6 h at room temperature afforded the adduct **3a** in 80 % yield (entry 1 in Table 1). By comparison, using only DCN produced **3a** via decarboxylation in a yield similar to that obtained from our photoreaction using Phen and 1,4-DCB [9]; however, prolonged irradiation or a more powerful light source was required. It is noteworthy that a catalytic amount of DCN (10, 5 mM) resulted in a similar product yield of **3a** by prolonged irradiation (entries 2 and 3). Use of 1,4-DCB, 1,3-DCB, and 1,2-DCB instead of DCN did not afford **3a** (entries 4–6). With 1,4-DCB, the substituted

Table 1 Decarboxylative radical addition of **1** to **2** using dicyanoarene



Entry	1	Dicyanoarene	Irradiation time (h)	Yield of **3** (%)[a]
1	**1a**	DCN (20 mM)	6	80
2	**1a**	DCN (10 mM)	18	72
3	**1a**	DCN (5 mM)	36	75
4	**1a**	1,4-DCB (20 mM)	18	0 (8)[b]
5	**1a**	1,3-DCB (20 mM)	18	0
6	**1a**	1,2-DCB (20 mM)	18	0
7[c]	**1a**	DCN (20 mM)	3	92
8[c]	**1a**	DCN (5 mM)	12	91
9[c]	**1b**	DCN (20 mM)	3	61

[a] Isolated yield

[b] The value in parentheses is the yield of **4a**

[c] Addition of 1 equiv NaOH

cyanobenzene **4a** was obtained in a low yield (8 %, entry 4). As previously reported by us [11], these results could be attributed to the lower absorption of these dicyanobenzenes at 313 nm than that of DCN, and to reaction of the generated alkyl radical with the radical anion of 1,4-DCB to produce **4a**. Addition of one equivalent of NaOH to this solution accelerated the photoreaction, and an improved yield of **3a** was obtained, even for a shorter irradiation time (entry 7), because decarboxylation of a carboxylate ion is more efficient than that of the corresponding carboxylic acid [9–11, 13, 14]. The photoreaction using a catalytic amount of DCN in the presence of one equivalent of NaOH also led to a high yield of **3a** (entry 8). Thus, DCN was proved to serve as a photocatalyst in the decarboxylative radical addition of carboxylic acids to alkenes. The decarboxylative adduct **3b** in the photoreaction of *N*-Boc-phenylalanine **1b** to **2** was obtained under the same conditions (entry 9); however, this resulted in a lower yield of **3b** and the formation of by-products. Further study of this photoreaction is now in progress and will be reported elsewhere.

The fluorescence of DCN in the aqueous acetonitrile solution was efficiently quenched by the sodium salt of **1a**, as shown in Fig. 1, and the rate constant for fluorescence quenching (k_q) was calculated as 3.95×10^9 $M^{-1}s^{-1}$ from the Stern–Volmer plot $I_0/I = 1 + k_q\tau[Q]$, where I_0 is the fluorescence intensity of DCN at 385 nm without the sodium salt of **1a**, I is the observed fluorescence intensity of DCN at 385 nm with the sodium salt of **1a**, τ, = 10.1 ns [16], is the fluorescence lifetime of DCN, and $[Q]$ is the concentration of the sodium salt of **1a**. This indicates that PET from the carboxylate ion of **1a** to the excited state of DCN

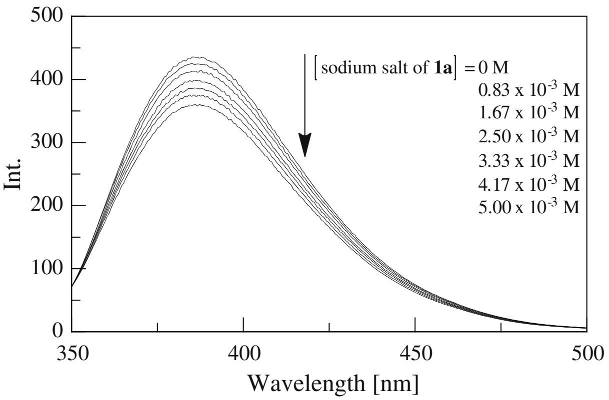
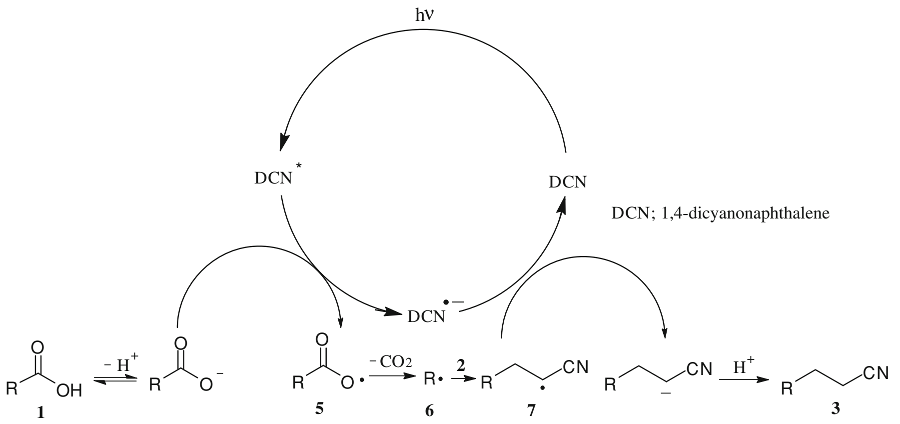


Fig. 1 Fluorescence quenching of DCN by the sodium salt of **1a** in aqueous acetonitrile (CH_3CN–H_2O 9:1, $\lambda_{EX} = 280$ nm)

occurred smoothly. The Rehm–Weller equation [17] confirms that the PET is an exothermic process, as indicated by the negative ΔG value (-97.4 kJ mol^{-1}; $\Delta G = 96.49\ [E(D^{\cdot+}/D) - E(A/A^{\cdot-})] - Es$) which was calculated using the reduction potential ($E(A/A^{\cdot-})$; -1.28 V vs. SCE in acetonitrile) [15], the excited singlet energy (*E*s; 333 kJ mol^{-1}) [15] of DCN, and the oxidation potential of the aliphatic carboxylate ion ($E(D^{\cdot+}/D)$; $+1.16$ V vs. SCE in acetonitrile) [18].

On the basis of these results, we propose a mechanism for this photoreaction (Scheme 2). PET from the carboxylate ion to the excited state of DCN leads to the formation of the radical anion of DCN and the carboxyl radical **5**. The alkyl radical **6** formed by decarboxylation of **5** reacts with **2** to produce the adduct radical **7**. SET from the radical anion of DCN, and protonation, yields the adduct **3**. The fact that a high yield of **3** was obtained, even in the presence of only one equivalent of **2**, can be explained as follows. The large rate constants for decarboxylation of the aliphatic



Scheme 2 Plausible mechanism for photochemical decarboxylation using DCN

carboxyl radical **5** [19] and for addition of the electron-rich alkyl radical **6** to the electron-deficient alkene **2** [4, 20] lead to the selective formation of **7**. SET from the radical anion of DCN to **7** occurs smoothly because **7** is highly electron-deficient and because of the relatively long lifetime of the radical anion of DCN [21–23].

Conclusion

In conclusion, we found that DCN can work as a photochemical catalyst in decarboxylative radical addition of *N*-Boc-amino acids to acrylonitrile. The highest yield of **3** was achieved by addition of one equivalent of NaOH. This is a simple method, because DCN is the only photosensitizer used in the photoreaction. Further investigation of the applications of this photoreaction is currently in progress.

Experimental

General

An IR spectrum was recorded on a Jasco FT/IR-620 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM-AL500 (500 and 125 MHz) spectrometer using solutions in $CDCl_3$ containing tetramethylsilane as internal standard. Chemical shifts (δ) are expressed in ppm. A high-resolution mass spectrum (HRMS) was obtained by use of a Jeol JMS-700T spectrometer. A Riko UV-400HA 400-W high-pressure mercury arc lamp was used as the light source. Dicyanoarenes were recrystallized from hexane and EtOAc. Column chromatography was conducted on a silica gel column (Wakogel C-200).

General procedure for photoreaction of *N*-Boc-valine **1a** to acrylonitrile **2**

An aqueous CH_3CN solution (CH_3CN 54 ml, H_2O 6 ml) of **1a** (1.2 mmol, 20 mM) and DCN (1.2 mmol, 20 mM) in four Pyrex vessels (18 × 180 mm) was purged with argon for 10 min, and to this was added **2** (1.2 mmol, 20 mM) under an argon atmosphere. The mixture was irradiated with the 400-W high-pressure mercury lamp for 6 h. The solvent was subsequently evaporated to yield the crude product. The adduct **3** was isolated by column chromatography on silica gel using hexane and EtOAc as eluents. A similar photoreaction of **1b** with **2** was performed under the same conditions.

3a: white solid; m.p. 76 °C; IR (KBr, cm^{-1}) ν 3383, 2964, 2249, 1680, 1512; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (brd, 0.75H, NH), 4.03 (brs, 0.10H, NH), 3.48–3.43 (m, 1H), 2.46–2.34 (m, 2H), 1.91 (m, 1H), 1.71 (m, 1H), 1.62 (m, 1H), 1.44 (s, 9H), 0.94–0.90 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 119.8, 79.6, 55.2, 32.3, 29.2, 28.3, 19.1, 17.8, 14.6; HRMS (FAB) calcd for $C_{12}H_{23}N_2O_2$: 227.1761, found: 227.1738 $[M + H]^+$.

3b: white solid; m.p. 100 °C; IR (KBr, cm^{-1}) ν 3373, 2977, 2242, 1687, 1504; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.15 (m, 5H), 4.44 (brs, 1H, NH), 3.88–3.82

(m, 1H), 2.84–2.70 (m, 2H), 2.44–2.31 (m, 2H), 1.91 (m, 1H), 1.69 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 137.0, 129.2, 128.6, 126.8, 119.5, 79.7, 51.1, 41.3, 30.5, 28.9, 14.1; HRMS (FAB) calcd for $C_{16}H_{23}N_2O_2$: 275.1760, found: 275.1712 $[M + H]^+$.

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