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N-Acryloyl amino acid esters and peptides as radical acceptors in photoinduced decarboxylative radical reaction

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This paper is dedicated to Prof. Yoshihisa Inoue of Osaka University on his retirement.

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ABSTRACT

The photoinduced electron transfer (PET) promoted decarboxylative radical additions of carboxylic acids using *N*-acryloyl amino acid esters and peptides as radical acceptors smoothly afforded the corresponding modified amino acids and peptides under mild reaction conditions. The radical additions of α-amino acids led to the formation of γ- and α-dipeptide, and peptides underwent peptide coupling via decarboxylation.

1. Introduction

The modifications of amino acids and peptides are one of the current attractive challenges in organic synthesis [1,2], because they play an important role not only in biochemistry [3–5], but also in nanomaterials such as nanotubes [6,7]. Although diverse methods have been used for the modification of amino acids and peptides, a radical method is interesting for directly introducing functional group into amino acids and peptides [8], because it is often difficult to use ionic reactions to form new C—C bonds in amino acids and peptides.

Recently, we reported a decarboxylative radical reaction of aliphatic carboxylic acids that is promoted by the radical cation of phenanthrene (Phen) via photoinduced electron transfer (PET) between Phen and 1,4-dicyanobenzene (1,4-DCB) (Scheme 1) [9–17]. The alkyl radicals, produced by a single electron transfer from carboxylates to the Phen radical cation followed by the decarboxylation of the intermediate carboxy radicals, reacted with a variety of reagents such as electron-deficient alkenes, oxime ethers, and thiols, to produce addition [11,13–17], reduction [9,12], and substitution [10] products in high yields. Particularly, an efficient intermolecular radical addition was achieved by this methodology, even with only 1 equiv of electron-deficient alkenes in the presence of catalytic amounts of Phen and 1,4-DCB [16]. The results of this early effort demonstrated that this photochemical process is an efficient method for forming new C—C bonds from aliphatic carboxylic acids under mild reaction conditions.

This finding encouraged us to investigate the intermolecular radical addition of carboxylic acids to *N*-acryloyl amino acid esters and peptides as radical acceptors in PET promoted decarboxylative radical reactions, because the *N*-alkylcarbonyl amino acids and peptides obtained by the photoreaction are potential pharmaceutical agonists and inhibitors [18,19]. The results of this effort that led to the development of a new method for the modification of amino acids and peptides using *N*-acryloyl amino acid esters and peptides are described below.

2. Experimental

2.1. General

All the reagents and solvents were used as received without further purification. The ^{1}H NMR spectra were recorded in $CDCl_3$ containing tetramethylsilane as the internal standard using either a 300 or 500 MHz spectrometer. The ^{13}C NMR spectra were recorded using either a 75 or 125 MHz spectrometer. The high resolution mass spectra were obtained using a time-to-flight mass spectrometer with a Fourier transform ion cyclotron resonance mass spectrometer with ESI positive mode. The light source was high-pressure mercury arc lamp. The spectra data of compounds **2 a**,**b** [20,21] and **4** [22] have been reported previously.

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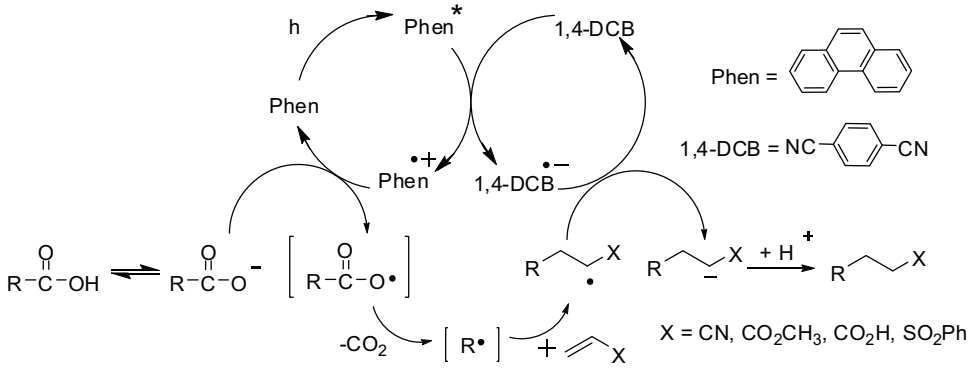


Scheme 1. PET promoted decarboxylative radical addition of carboxylic acids to electron-deficient alkenes.

2.2. Synthesis of N-acryloyl amino acid esters **2**

Acryloyl chloride (1.5 equiv) was added to a solution of amino acid methyl ester hydrochloride (1.0 equiv) and *i*-Pr_2NEt (2.0 equiv) in $CHCl_3$ at 0 °C. The resulting suspension was stirred at room temperature for 3 h, and then the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc, and sequentially washed with 4% $NaHCO_3$, 1 M HCl, and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography using hexane/EtOAc as the eluent to give the desired *N*-acryloyl amino acid methyl esters **2** as colorless liquids (83–90%).

2.3. Synthesis of N-*BocValValOH* **6**

EDC hydrochloride (1.2 equiv, 0.53 g) and HOBt (1.4 equiv, 0.49 g) were added to a solution of *N*-BocValOH (2.3 mmol, 0.50 g), valine methyl ester hydrochloride (2.3 mmol, 0.69 g), and *i*-Pr_2NEt (1.2 equiv, 0.48 mL) in DMF (15 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and then at room temperature for overnight. Then, the mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, and sequentially washed with 1 M HCl, 4% $NaHCO_3$, and water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography using hexane/EtOAc as the eluent to give *N*-BocValValOMe as a white solid (71%).

A MeOH solution (10 mL) of *N*-BocValValOMe (5.1 mmol, 1.69 g) was added to 1 M NaOH (5.1 mL). The solution was stirred at room temperature for 3 h. The pH of the mixture was decreased to 7 by adding 1 M H_2SO_4 and the resulting solution was concentrated *in vacuo*. The residue was dissolved in 5% $NaHCO_3$ and washed with EtOAc. The pH of the aqueous layer decreased to 2–3 with 1 M H_2SO_4. The solution was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography using hexane/EtOAc as the eluent to give the desired *N*-BocValValOH **6** as a white solid (77%).

2.4. Photoreaction of **1** with **2**

An aqueous CH_3CN solution (CH_3CN 90 mL, H_2O 10 mL) of *N*-Boc amino acid **1** (5 mM), *N*-acryloyl amino acid ester **2** (5 mM), Phen (89.1 mg, 5 mM), and 1,3-DCB (64.0 mg, 5 mM) in Pyrex vessels (18 mm × 180 mm) was purged with Ar for 10 min. The mixture was irradiated with 100 W high-pressure mercury lamp for 6 h. The crude product was purified by silica-gel column chromatography using hexane/EtOAc or $CHCl_3$/acetone as the eluents to give adduct **3**. The photoreaction of compound **6** was also performed similarly.

2.5. Characterization data

2c. Colorless liquid, IR (KBr, cm^{-1}) 3333, 2964, 1732, 1668; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.17–0.21 (m, 6H), 1.21 (s, 3 H), 1.38–1.49 (m, 1H), 2.98 (s, 3H), 3.79–3.83 (m, 1H), 4.60 (s, 1H), 4.99 (s, 1H), 5.99–6.02 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 17.1, 17.2, 17.3, 30.5, 51.2, 57.0, 119.4, 139.1, 167.9, 171.8; HRMS (FAB) calcd for $(M+H)^+$ $C_{10}H_{18}NO_3$: 200.1287, found 200.1291.

2d. White solid, mp 170 °C; IR (KBr, cm^{-1}) 3284, 3079, 2966, 1739, 1647, 1622; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.86–1.01 (m, 12H), 2.02–2.20 (m, 2H), 3.73 (s, 3H), 4.46–4.50 (m, 1H), 4.72–4.77 (m, 1H), 5.59 (dd, *J* = 9.4, 2.5 Hz, 1H), 6.19–6.39 (m, 2H), 7.55–7.58 (br, 1H), 7.81 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 18.0, 18.3, 18.7, 19.0, 30.6, 31.4, 51.8, 57.5, 58.4, 126.5, 130. 8, 165.6, 172.0, 172.5; HRMS (FAB) calcd for $(M+H)^+$ $C_{14}H_{25}N_2O_4$: 285.1805, found 285.1810.

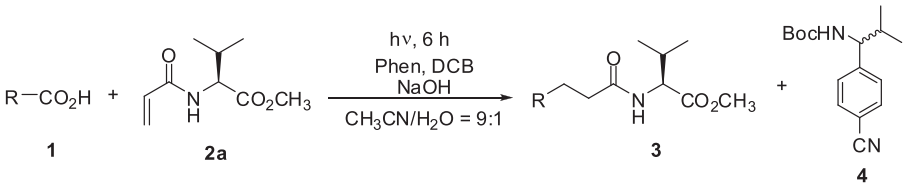
3a (mixture of diastereomers). White solid, mp 110–111 °C; IR (KBr, cm^{-1}) 3341, 2970, 1747, 1679; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.87–0.98 (m, 12H), 1.44 (s, 9H), 1.52–1.92 (m, 4H), 2.25–2.35 (m, 2H), 3.39–3.64 (m, 1H), 3.72–3.73 (m, 3H), 4.48–4.57 (m, 1H), 6.52–6.62 (br, 1H), 6.99–7.02 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 17.6, 17.7, 17.8, 18.9, 19.0, 28.3, 28.9, 29.0, 30,5, 30.9, 32.4, 33.2, 33.4, 51.9, 54.8, 55.1, 57. 1, 57.4, 79.1, 79.2, 156.4, 156.7, 172.5, 172.8, 173.3; HRMS (FAB) calcd for $(M+H)^+$ $C_{18}H_{35}N_2O_5$: 359.2547, found 359.2545.

3b. Colorless liquid, IR (KBr, cm^{-1}) 3326, 2969, 1742, 1694; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.94 (t, *J* = 7.1 Hz, 6H), 1.44 (s, 9H), 1.77–1.86 (m, 2H), 2.13–2.24 (m, 1H), 2.26–2.31 (m, 2H), 3.12–3.27 (m, 2H), 3.73 (s, 3H), 4.51–4.59 (m, 1H), 4.79 (br, 1H), 6.60 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.2, 17.7, 19.0, 26.5, 28.3, 31.0, 33.5, 39.6, 57.2, 61.1, 79.3, 156.4, 172.1, 172.7; HRMS (FAB) calcd for $(M+H)^+$ $C_{15}H_{298}N_2O_5$: 317.2077, found 317.2083.

3c (mixture of diastereomers). White solid, mp 115–116 °C; IR (KBr, cm^{-1}) 3335, 2966, 1740, 1681; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.91–0.96 (m, 6H), 1.43 (s, 9H), 1.64–1.86 (m, 3H), 2.10–2.34 (m, 6H), 3.73 (m, 3H), 4.46–4.55 (m, 1H), 4.91–5.03 (br, 1H), 5.81 (br, 1H), 6.41 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 17.7, 18.8, 19.0, 19.2, 28.2, 30.6, 30.9, 31.4, 31.5, 31.6, 31.7, 32.5, 32.6, 32.9, 49.9, 52.0, 57.1, 57.3, 79.3, 79.4, 156.5, 156.7, 172.7, 172.8, 172.9, 173.1, 175.5, 175.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{18}H_{34}N_3O_6$: 388.2448, found 388.2473.

3d (mixture of diastereomers). White solid, mp 94 °C; IR (KBr, cm^{-1}) 3338, 2958, 1745, 1680; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.92–0.97 (m, 6H), 1.44 (s, 9H), 1.56–1.98 (m, 5H), 2.06–2.17 (m, 3H), 2.24–2.36 (m, 2H), 2.44–2.69 (m, 2H), 3.58–3.90 (m, 4H), 4.48–4.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 15.6, 17.8, 19.0, 19.1, 28.3, 30.6, 30.7, 31.1, 31.8, 31.9, 33.0, 33.1, 35.5, 35.6, 49.7, 49.8, 52.0, 57.2, 57.4, 79.5, 156.1, 156.3, 172.5, 172.6, 173.0; HRMS (FAB) calcd for $(M+H)^+$ $C_{18}H_{35}N_2O_5S$: 391.2267, found 391.2260.

Table 1
Decarboxylative radical addition of **1** to **2a** by photoirradiation.[a]



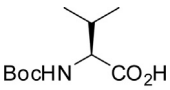
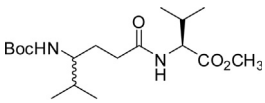
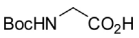
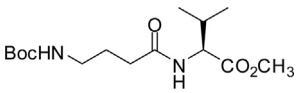
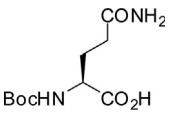
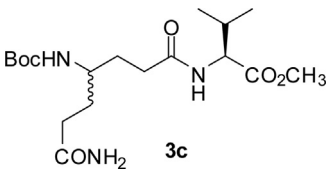
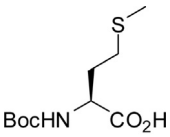
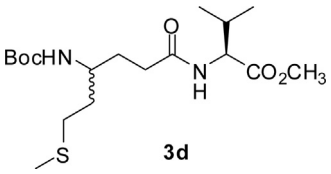
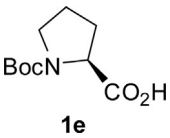
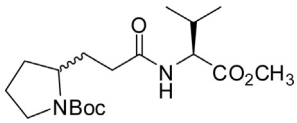
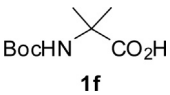
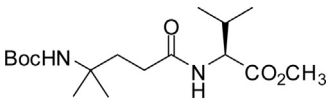
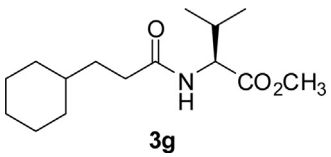
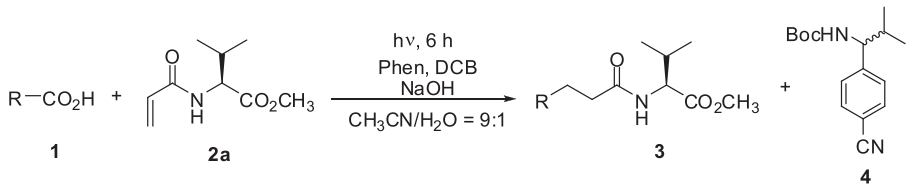
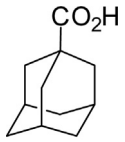
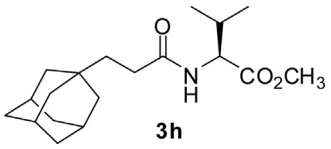
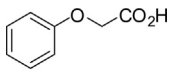
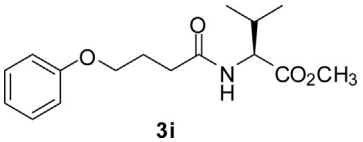
Entry	1	3	Yield of **3** (%)[b]
1[c]	 **1a**	 **3a**	47
2	**1a**	**3a**	58
3[d]	**1a**	**3a**	43
4	 **1b**	 **3b**	39
5	 **1c**	 **3c**	61
6	 **1d**	 **3d**	26
7	 **1e**	 **3e**	48
8	 **1f**	 **3f**	34
9	 **1g**	 **3g**	35
10			25

Table 1 (*Continued*)



Entry	1	3	Yield of **3** (%)[b]
	 **1h**	 **3h**	
11	 **1i**	 **3i**	23

[a] Aqueous acetonitrile solution containing **1** (5 mM), **2a** (5 mM), Phen (5 mM), 1,3-DCB (5 mM), and NaOH (5 mM) under an Ar atmosphere was irradiated for 6 h.
[b] Isolated yield.
[c] **1** (20 mM), **2** (20 mM), Phen (20 mM), 1,4-DCB (20 mM), and NaOH (20 mM).
[d] **1** (5 mM), **2** (5 mM), Phen (3 mM), 1,3-DCB (3 mM), and NaOH (5 mM).

3e (mixture of diastereomers). Colorless liquid, IR (KBr, cm^{-1}) 3301, 2969, 1744, 1683; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.96–0.98 (m, 6H), 1.46 (s, 9H), 1.62–2.52 (m, 9H), 3.30–3.34 (m, 2H), 3.75 (m, 3H), 3.88–4.20 (m, 1H), 4.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 17.8, 17.9, 18.9, 19.1, 19.2, 23.1, 23.6, 28.5, 30.7, 33.6, 46.2, 46.5, 52.0, 56.0, 57.6, 57.7, 79.4, 79.5, 154.7, 155.5, 155.8, 172.5, 172.7, 172.9, 173.3, 173.8; HRMS (FAB) calcd for $(M+H)^+$ $C_{18}H_{33}N_2O_5$: 357.2390, found 357.2373.

3f. Colorless liquid, IR (KBr, cm^{-1}) 3326, 2970, 1743, 1653; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.94 (t, J = 7.1 Hz, 6H), 1.26 (s, 6H), 1.43 (s, 9H), 1.92–2.16 (m, 3H), 2.27 (t, J = 8.1 Hz, 2H), 3.73 (s, 3H), 4.53–4.57 (m, 1H), 4.73 (br, 1H), 6.36 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.0, 18.7, 20.8, 28.2, 31.0, 31.4, 35.9, 51.8, 51.9, 56.8, 60.2, 78.6, 154.5, 172.4, 173.1; HRMS (FAB) calcd for $(M+H)^+$ $C_{17}H_{33}N_2O_5$: 345.2390, found 345.2401.

3g. White solid, mp 53–54 °C; IR (KBr, cm^{-1}) 3298, 2924, 1746, 1647; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.88–0.92 (m, 6H), 1.07–1.30 (m, 5H), 1.50–1.78 (m, 8H), 2.09–2.27 (m, 3H), 3.74 (s, 3H), 4.56–4.60 (m, 1H), 5.93 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 17.9, 19.0, 26.3, 26.6, 31.4, 33.0, 33.1, 34.3, 37.3, 52.2, 56.8, 172.8, 173.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{15}H_{28}NO_3$: 270.2070, found 270.2058.

3h. Colorless liquid, IR (KBr, cm^{-1}) 3299, 2901, 1746, 1647; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.89–0.94 (m, 6H), 1.415–1.49 (m, 7H), 1.59–1.74 (m, 7H), 1.95 (m, 3H), 2.06–2.27 (m, 3H), 3.74 (s, 3H), 4.55–4.59 (m, 1H), 5.92–5.95 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 17.9, 19.0, 28.6, 30.4, 31.4, 32.0, 37.1, 39.8, 41.3, 42.1, 52.2, 56.8, 172.9, 173.9; HRMS (FAB) calcd for $(M+H)^+$ $C_{19}H_{32}NO_3$: 322.2383, found 322.2386.

3i. Colorless liquid, IR (KBr, cm^{-1}) 3309, 3040, 2964, 1743, 1652; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.86–0.92 (m, 6H), 2.08–2.18 (m, 3H), 2.47 (t, J = 7.4 Hz, 2H), 3.71 (s, 3H), 4.02 (t, J = 5.6 Hz, 2H), 4.55–4.59 (m, 1H), 6.03–6.06 (br, 1H), 6.84–6.97 (m, 3H), 7.21–7.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 17.8, 19.0, 25.2, 31.3, 33.0, 52.2, 57.0, 66.7, 114.5, 114.9, 120.8, 129.5, 129.7, 158.8, 172.4, 172.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{16}H_{24}NO_4$: 294.1726, found 294.1715.

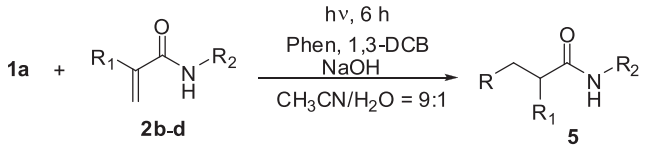
4. [22] White solid, mp 135–136 °C; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.84–0.93 (m, 6H), 1.40 (s, 9H), 1.93–1.97 (m, 1H), 4.46 (br, 1H), 4.93 (m, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 18.2, 19.7, 28.4, 33.5, 60.4, 79.9, 110.8, 118.9, 127.6, 132.2, 147.9, 155.4.

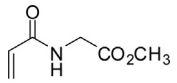
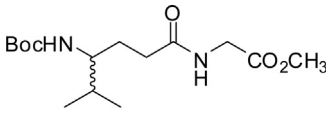
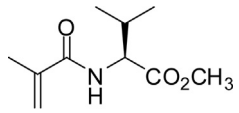
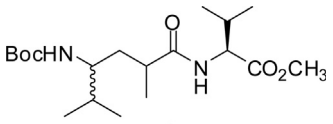
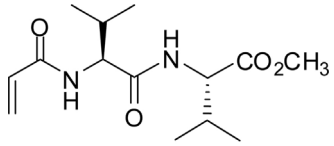
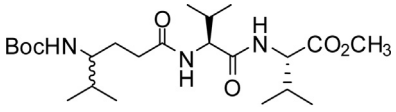
5a. White solid, mp 89–90 °C; IR (KBr, cm^{-1}) 3317, 2976, 1744, 1646; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.88–0.97 (m, 6H), 1.44 (s, 9H), 1.53–1.76 (m, 2H), 1.81–1.92 (m, 1H), 2.21–2.34 (m, 2H), 3.47–3.58 (m, 1H), 3.75 (s, 3H), 3.97–4.13 (m, 2H), 4.42–4.45 (m, 1H), 6.83 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 17.7, 19.1, 28.4, 29.1, 32.6, 33.3, 41.3, 52.2, 55.0, 79.3, 156.7, 170.4, 173.4; HRMS (FAB) calcd for $(M+H)^+$ $C_{15}H_{29}N_2O_5$: 317.2077, found 317.2086.

5b (mixture of diastereomers). White solid, mp 59–61 °C; IR (KBr, cm^{-1}) 3285, 2970, 1750, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.85–1.02 (m, 12H), 1.12–1.21 (m, 3H), 1.46 (s, 9H), 1.52-2.42 (m, 5H), 3.45-3.53 (m, 1H), 3.72 (m, 3H), 4.39–4.46 (m, 1H), 4.52–4.58 (m, 1H), 6.02–6.09 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 17.6, 17.8, 17.9, 18.0, 18.6, 18.7, 18.8, 19.0, 19.1, 19.2, 28.3, 30.8, 31.2, 31.4, 32.5, 32.9, 33.1, 35.4, 37.6, 38.4, 38.6, 39.5, 51.8, 52.1, 53.7, 54.0, 54.2, 56.8, 56.9, 57.5, 60.3, 78.9, 79.0, 79.5, 156.0, 156.9, 172.6, 172.7, 172.7, 176.0, 176.7, 176.8; HRMS (FAB) calcd for $(M+H)^+$ $C_{19}H_{37}N_2O_5$: 373.2703, found 373.2675.

5c (mixture of diastereomers). White solid, mp 142–144 °C; IR (KBr, cm^{-1}) 3292, 2964, 1747, 1639; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.87–0.98 (m, 18H), 1.44 (s, 9H), 1.55–1.77 (m, 2H), 2.08–2.21 (m, 2H), 2.23–2.38 (m, 2H), 3.39–3.53 (m, 1H), 3.73 (s, 3H), 4.38–4.67 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 17.7, 17.8, 17.9, 18.1, 18.3, 18.8, 18.9, 19.0, 19.1, 19.2, 28.3, 29.0, 29.1, 30.5, 30.9, 32.4, 32.6, 33.5, 51.9, 52.0, 54.9, 55.0, 57.0, 57.1, 58.4, 58.6, 79.0, 79.2, 156.4, 156.7, 171.4,

Table 2
Decarboxylative radical addition of **1a** to **2b–d** by photoirradiation.[a]



Entry	2	5	Yield of **5** (%)[b]
1	 **2b**	 **5a**	39
2	 **2c**	 **5b**	36
3	 **2d**	 **5c**	45

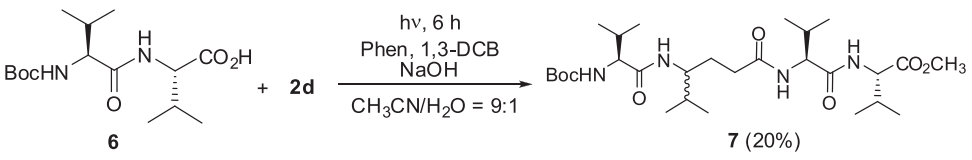
[a] Aqueous acetonitrile solution containing **1a** (5 mM), **2** (5 mM), Phen (5 mM), 1,3-DCB (5 mM), and NaOH (5 mM) under an Ar atmosphere was irradiated for 6 h.
[b] Isolated yield.

171.5, 172.1, 173.1, 173.2; HRMS (FAB) calcd for $(M+H)^+$ $C_{23}H_{44}N_3O_6$: 458.3231, found 458.3205.

7 (mixture of diastereomers). White solid, mp 110–111 °C; IR (KBr, cm^{-1}) 3297, 2964, 1747, 1646; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.87–1.01 (m, 24H), 1.44 (s, 9H), 1.91–2.21 (m, 6H), 3.31–3.75 (m, 4H), 3.76–4.58 (m, 3H), 6.35–6.60 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 17.9, 18.0, 18.1, 18.2, 18.4, 18.6, 18.7, 18.9, 19.0, 19.1, 19.3, 19.4, 19.5, 27.6, 28.3, 30.1, 30.5, 30.7, 30.8, 30.9, 31.1, 31.7, 32.3, 32.9, 52.0, 52.1, 54.0, 57.2, 57.3, 59.2, 59.3, 60.3, 79.8, 156.4, 171.9, 172.2, 172.5, 172.6, 172.7, 173.3, 173.6; HRMS (FAB) calcd for $(M+H)^+$ $C_{28}H_{53}N_4O_7$: 557.3915, found 557.3914.

3. Results and discussion

Initially, the photoinduced decarboxylative radical addition of *N*-Boc L-valine **1a** (Boc = *tert*-butoxycarbonyl) to *N*-acryloyl L-valine methyl ester **2a** was examined because γ- and α-dipeptide **3a** was obtained by the photoreaction (Table 1). Photoreaction of **1a** (20 mM) was carried out by irradiating (100 W high-pressure mercury lamp through a Pyrex glass filter; γ > 280 nm) aqueous acetonitrile solutions (CH_3CN/H_2O = 9:1, v/v) containing Phen (20 mM), 1,4-DCB (20 mM) and **2a** (20 mM) under argon for 6 h at room temperature to produce the decarboxylative radical adduct **3a** in a moderate yield (47%) as a 1:1 mixture of diastereomers along with the formation of substituted product **4** (17%) and polymeric materials. In contrast to the previous results obtained when acrylonitrile was used as a radical acceptor [11,16], the use of the relatively poorly electron-deficient alkenes such as **2a** instead of acrylonitrile led to significantly low rate of radical addition of the generated radical to **2a**. This promoted radical addition to the radical anion of 1,4-DCB, affording **4** via decyanation as reported by us [10]. In order to avoid this photosubstitution, the use of 1,3-dicyanobenzene (1,3-DCB) instead of 1,4-DCB led to no formation of the corresponding substitution product. Moreover, a low concentration of **2a** (5 mM) suppressed the polymerization and slightly increased the yield of **3a** (58%, Entry 2). In this photoreaction, catalytic amounts of Phen (3 mM) and 1,3-DCB (3 mM) also worked (Entry 3). When other *N*-Boc α-amino acids **1b–f** were subjected to photoreaction, the similar decarboxylative radical addition with **2a** successfully underwent to produce γ- and α-dipeptides **3b–f** (Entries 4–8). In addition, the use of other simple carboxylic acids such as cyclohexanecarboxylic acid **1g**, 1-adamantanecarboxylic acid **1h**, and phenoxyacetic acid **1i** also yielded the corresponding



Scheme 2. Formation of tetrapeptide **7** by the photoreaction of **6** and **2d**.

decarboxylative radical adducts **3g–i** (Entries 9–11). Thus, a variety of unique *N*-alkylcarbonyl amino acid derivatives **3** could be directly synthesized from carboxylic acids **1** and **2a** under mild reaction conditions, and, in particular, the photoreaction of α-amino acids afforded the corresponding γ- and α-dipeptides.

To demonstrate the utility of this methodology, the photoreactions of other *N*-acryloyl amino acid methyl esters **2b–d** such as glycine **2b**,*N*-methacrylic valine **2c**, and dipeptide derivatives **2d** were investigated (Table 2). Dipeptides **5a**,**b** and tripeptide **5c** were also obtained in moderate yields. Finally, tetrapeptide **7** was obtained from the photoreaction of dipeptides **6** and **2d** under the same photochemical conditions, even though the low solubility of adduct **7** in this solution decreased the yield of **7** (20%, Scheme 2). Notably, the photoreactions of peptides and *N*-acryloyl peptides can provide the decarboxylated coupling peptides with γ-amino acid as the connected part, even though the chirality at the generated radical carbon was not retained.

4. Conclusion

The *N*-acryloyl amino acid esters and peptides were used as radical acceptors in the PET promoted decarboxylation reactions to yield directly modified amino acids and peptides under mild reaction conditions. The yield of radical adducts **3** increased slightly when 1,3-DCB was used as the electron-acceptor with a low concentration of *N*-acryloyl amino acid esters **2**. This methodology can provide coupling peptides **3**, **5**, **7** containing γ-amino acids via decarboxylation when **2** was used with *N*-Boc amino acids **1** and peptides **6**. The applications of this photoreaction to the modification and coupling of peptide are underway.

Supplementary material

The ^{1}H and ^{13}C NMR spectra of 2c–d, 3, 4, 5, and 7 are provided in Supplementary material.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jphotochem.2015.11.001.

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