ORGANIC
LETTERS

2009
Vol. 11, No. 20
4652−4655

# Inter- and Intramolecular Addition Reactions of Electron-Deficient Alkenes with Alkyl Radicals, Generated by SET-Photochemical Decarboxylation of Carboxylic Acids, Serve as a Mild and Efficient Method for the Preparation of γ-Amino Acids and Macrocyclic Lactones

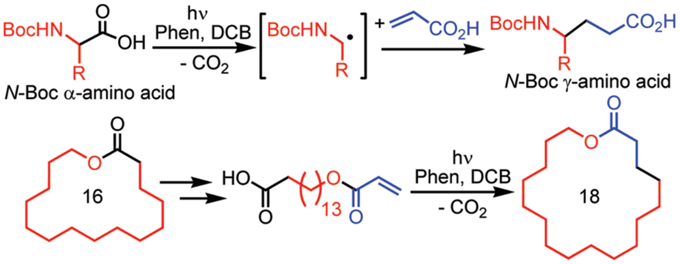
**Yasuharu Yoshimi,* Miho Masuda, Tomoyuki Mizunashi, Keisuke Nishikawa, Kousuke Maeda, Nobumasa Koshida, Tatsuya Itou, Toshio Morita, and Minoru Hatanaka***

*Department of Applied Chemistry and Biotechnology, Graduate School of Engineering, University of Fukui, 3-9-1 Bunkyo, Fukui 910-8507, Japan*

*yyoshimi@u-fukui.ac.jp; mhatanak@iwate-med.ac.jp*

**Received August 19, 2009**

## ABSTRACT



**Inter- and intramolecular additions of alkyl radicals, generated by SET photochemical decarboxylation reactions of free carboxylic acids, to electron-deficient alkenes take place under mild conditions as part of efficient routes for the formation of *N*-Boc γ-amino acids and macrocyclic lactones.**

Inter- and intramolecular radical additions to alkenes serve as the basis for useful methods for C−C bond formation.[1] The use of decarboxylation reactions of carboxylic acid groups in amino acids and peptides as sources for key radical intermediates has also attracted great interest.[2] Transformations involving both of these processes typically employ the

---

[1] (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. (b) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: Chichester, UK, 1995. (c) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (d) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: New York, 2003. (e) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377.

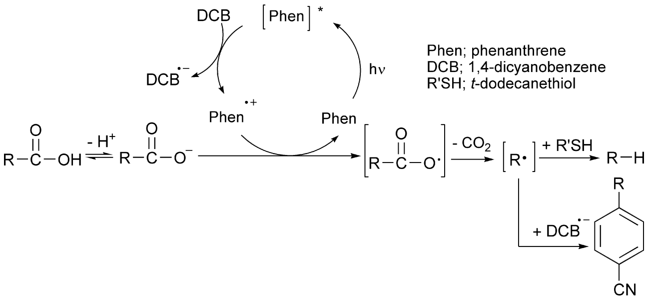
[2] (a) Barton, D. H. R.; Herve, Y.; Potier, P.; Thierry, J. *J. Chem. Soc., Chem. Commun.* **1984**, 1298. (b) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913. (c) Griesbeck, A. G.; Heinrich, T.; Oelgemoller, M.; Lex, J.; Molis, A. *J. Am. Chem. Soc.* **2002**, *124*, 10972. (d) Yoon, U. C.; Jin, Y. X.; Oh, S. W.; Park, C. H.; Park, J. H.; Campana, C. F.; Cai, X.; Duesler, E. N.; Mariano, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 10664. (e) Saavedra, C.; Hernandez, R.; Boto, A.; Alvarez, E. *J. Org. Chem.* **2009**, *74*, 4655.

10.1021/ol9019277 CCC: $40.75

Barton decarboxylation procedure to form alkyl radicals by homolysis of thiohydroxamic esters under either thermal or photochemical conditions.[3] One limitation of this approach stems from the fact that esterification of carboxylic acids is required in order to produce the thiohydroxamic ester precursors. Consequently, a technique that involves direct generation of alkyl radicals from free carboxylic acids under mild conditions would make the approach more efficient.

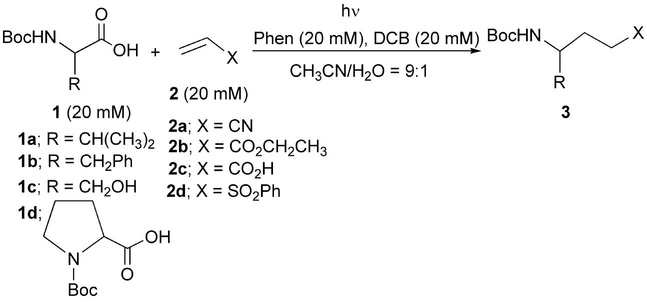
In a recent report,[4] we described results which show that aliphatic carboxylic acids undergo decarboxylation to form alkyl free radicals when subjected to redox-photosensitized reaction conditions[5] employing phenanthrene (Phen) and 1,4-dicyanobenzene (DCB) (Scheme 1). This process is promoted by single-electron transfer (SET) from the carboxylate ion to the cation radical, formed by SET from the singlet excited state of Phen to DCB. This process leads to the formation of carboxyl radicals that rapidly lose carbon dioxide to produce alkyl free radicals.[6] Alkyl radicals, formed in this manner, react by hydrogen atom transfer with a thiol or by addition to the cogenerated anion radical of DCB to yield the respective reduction or substitution products. These findings, which demonstrate that the SET photochemical route can be used to efficiently generate alkyl radicals from free aliphatic carboxylic acids under mild conditions, led us to investigate a novel approach to inter- and intramolecular radical additions to alkenes.

### Scheme 1



Decarboxylative addition reactions between *N*-Boc-α-amino acids and a variety of electron-deficient alkenes were examined (Table 1) initially to determine the scope of the process.

**Table 1.** Intermolecular Radical Addition of **1** to **2** via SET-Photochemical Decarboxylation[a]



| entry | amino acid | alkene | adduct (yield,[b] %) |
|---|---|---|---|
| 1 | **1a** | **2a** | **3aa** (85) |
| 2 | **1a** | **2b** | **3ab** (41) |
| 3[c] | **1a** | **2c** | **3ac** (57) |
| 4[d] | **1a** | **2d** | **3ad** (60) |
| 5 | **1b** | **2a** | **3ba** (83) |
| 6 | **1b** | **2b** | **3bb** (48) |
| 7[c] | **1b** | **2c** | **3bc** (43) |
| 8 | **1c** | **2a** | **3ca** (74) |
| 9 | **1c** | **2b** | **3cb** (36) |
| 10[c] | **1c** | **2c** | **3cc** (60) |
| 11 | **1d** | **2a** | **3da** (88) |
| 12 | **1d** | **2b** | **3db** (57) |
| 13[c] | **1d** | **2c** | **3dc** (52) |

[a] The photoreaction was carried out with Phen (1.2 mmol), DCB (1.2 mmol), **1** (1.2 mmol), and **2** (1.2 mmol) in aqueous $CH_3CN$ solution ($CH_3CN$, 54 mL; $H_2O$, 6 mL) using a 100-W high-pressure mercury lamp under argon atmosphere for 6 h. [b] Isolated yield. [c] Irradiation time is 8 h. [d] In the presence of 1 equiv of NaOH.

Irradiation of an aqueous acetonitrile solution ($CH_3CN/H_2O$ = 9:1) containing Phen (20 mM), DCB (20 mM), *N*-Boc-L-valine **1a** (20 mM), and acrylonitrile **2a** (20 mM) with a 100-W high-pressure mercury lamp through a Pyrex filter ($\lambda > 280$ nm) under an argon atmosphere for 6 h at room temperature was found to promote formation of the adduct **3aa** as a racemic mixture in 85% yield along with near-quantitative recovery (>90%) of Phen and DCB (entry 1, Table 1). This reaction proceeds smoothly, and only 1 equiv of **2a** is required. The presence of 1 equiv of NaOH in the photoreaction mixture accelerates the reaction. In this case, a similar yield of **3aa** is obtained even when a shorter irradiation time (3 h) is employed. Other electron-deficient alkenes, such as ethyl acrylate **2b**, acrylic acid **2c**, and phenyl vinyl sulfone **2d**, participate in this process to yield the corresponding adducts **3ab**, **3ac**, and **3ad** in moderate yields (entries 2−4). However, no adducts are formed when electron-rich alkenes, such as ethyl vinyl ether and allyl alcohol, are used. Importantly, moderate to good yields of adducts are obtained when other amino acids, including *N*-Boc-L-phenylalanine **1b**, *N*-Boc-L-serine **1c**, and *N*-Boc-L-proline **1d**, are subjected to the photoreaction conditions in the presence of the electron-deficient alkenes **2a**−**c** (entries 5−13). It is important to point out that the adduct formation takes place

---

(3) (a) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39. (b) Barton, D. H. R.; Herve, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1987**, *43*, 4297. (c) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413. (d) Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K. *J. Org. Chem.* **1998**, *63*, 5732.

(4) (a) Yoshimi, Y.; Itou, T.; Hatanaka, M. *Chem. Commun.* **2007**, 5244. (b) Itou, T.; Yoshimi, Y.; Morita, T.; Tokunaga, Y.; Hatanaka, M. *Tetrahedron* **2009**, *65*, 263.

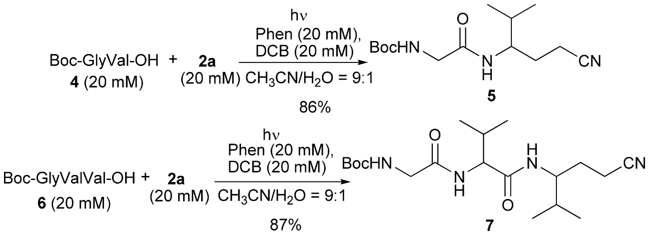
(5) (a) Pac, C.; Nakasone, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 5806. (b) Majima, T.; Pac, C.; Nakasone, A.; Sakurai, H. *J. Am. Chem. Soc.* **1981**, *103*, 4499. (c) Ohashi, M.; Nakatani, K.; Maeda, H.; Mizuno, K. *Org. Lett.* **2008**, *10*, 2741. (d) Ohashi, M.; Nakatani, K.; Maeda, H.; Mizuno, K. *J. Org. Chem.* **2008**, *73*, 8348.

(6) For SET-photochemical decarboxylation of carboxylic acids, see: (a) Libman, J. *J. Am. Chem. Soc.* **1975**, *97*, 4139. (b) Mariano, P. S. *Acc. Chem. Res.* **1983**, *16*, 130. (c) Chiu, F. T.; Ullrich, J. W.; Mariano, P. S. *J. Org. Chem.* **1984**, *49*, 228. (d) Karauchi, Y.; Nobuhara, N.; Ohga, K. *Bull. Chem. Soc. Jpn.* **1987**, *59*, 897. (e) Tsujimoto, K.; Nakao, N.; Ohashi, M. *J. Chem. Soc., Chem. Commun.* **1992**, 366. (f) Griesbeck, A. G.; Henz, A.; Peters, K.; Peters, E. M.; Schnering, H. G. *Angew. Chem., Int. Ed.* **1995**, *34*, 474. (g) Yokoi, H.; Nakano, T.; Fujita, W.; Ishiguro, K.; Sawai, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12453. (h) Griesbeck, A. G.; Hoffmann, N.; Warzecha, K. D. *Acc. Chem. Res.* **2007**, *40*, 128.

smoothly even with the unprotected hydroxyl group containing serine derivative **1c** (entries 8−10). Also noteworthy is the fact that the photoreactions of **1a**−**d** with acrylic acid **2c** for 8 h give the corresponding *N*-Boc-$\gamma$-amino acids (entries 3, 7, 10, and 13). This finding suggests that the difference between the p$K_a$ values of the starting *N*-Boc-α-amino acids **1a**−**c** and the product $\gamma$-amino acids **3ac**, **3bc**, **3cc**, and **3dc** is sufficiently large to prevent yield diminishing decarboxylation reactions of the products. Overall, the results show that a variety of *N*-Boc-$\gamma$-amino acids can be prepared directly by reactions between *N*-Boc-α-amino acids and acrylic acid.

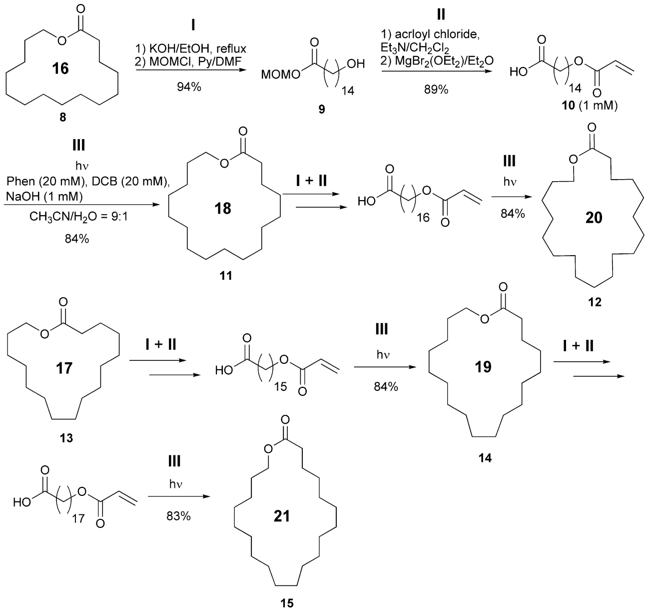
The synthetic utility of the process described above was demonstrated by its application to radical addition reactions of the *N*-protected peptides (Scheme 2). Photoreactions of the *N*-Boc-GlyVal-OH dipeptide **4** and *N*-Boc-GlyValVal-OH tripeptide **6** with acrylonitrile **2a**, promoted by using the conditions described above, take place smoothly to produce the respective adducts **5** and **7**.

**Scheme 2**



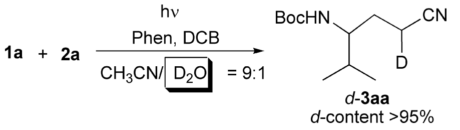
Intramolecular radical addition reactions of carboxylic acid, bearing tethered electron-deficient alkenes, were investigated next (Scheme 3). The first substrate explored was acid **10**, prepared in a 84% yield starting from the macrocyclic lactone **8** and using a four-step route (**I** + **II**). Ring-opening of **8** promoted by treatment with KOH followed by MOM protection of the carboxylic acid group leads to formation of the alcohol **9**. Esterification of **9** with acryloyl chloride followed by MOM deprotection gives the alkene-tethered carboxylic acid **10**. Photocyclization reaction of **10** (1 mM) in the presence of NaOH (1 mM), Phen, and DCB, occurs smoothly to form the macrocyclic lactone **11** in 84% yield (step **III**). The efficiency of this process decreases (73, 61, 51, 29% yields of **11**) when higher concentrations of **10** (2, 3, 4, 5 mM) are used. Repetition of a similar reaction sequence (**I** + **II** + **III**) starting with **11** produces the two-carbon elongated macrocyclic lactone **12** in good yield. Similarly, the 21 membered macrocyclic lactone **15** is generated when the 17 membered lactone **13** is subjected to the ring-opening−radical cyclization sequence. The results of this investigation show that macrocyclic lactones with desired ring sizes can be obtained by employing this novel radical cyclization method.

**Scheme 3**

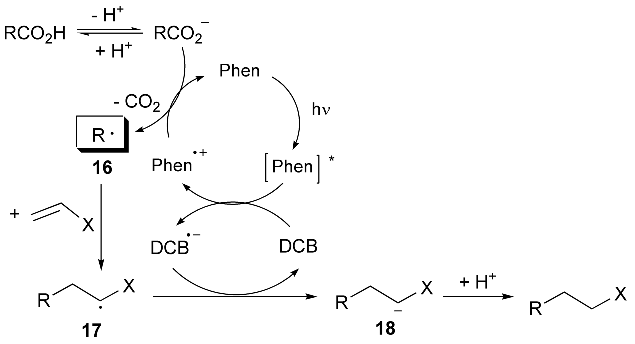


In order to gain information about the mechanism of the radical addition process, a deuterium incorporation experiment was carried out (Scheme 4). Irradiation of a mixture of *N*-Boc-amino acid **1a**, acrylonitrile **2a**, Phen, and DCB in a 1:9 mixture of $D_2O$ and acetonitrile was found to generate adduct ***d*-3aa** which contains a deuterium atom at the position α to the cyano group. This finding shows that the α-cyano anion serves as the ultimate intermediate in the pathway for adduct formation (Scheme 5). Thus, decarboxylation of carboxylate ions, induced by the photogenerated cation radical of Phen, produces alkyl radicals **16** that react with electron-deficient alkenes to produce adduct radicals

**Scheme 4.** Deuterium Incorporation Experiment Using $D_2O$



**Scheme 5.** Plausible Mechanism



**17**. The processes are terminated by SET from the anion radical of DCB, formed in the initial SET event, to the adduct radicals **17** to produce anions **18** that undergo protonation to yield the adducts.

In conclusion, the results of this effort demonstrate that alkyl free radicals, generated from free carboxylic acids via a photochemically promoted SET-decarboxylation pathway, undergo inter- and intramolecular additions to electron-deficient alkenes. The photoreactions proceed under mild conditions to generate *N*-Boc-$\gamma$-amino acids starting from *N*-Boc-$\alpha$-amino acids. In addition, macrocyclic lactones of various ring sizes can be obtained by using a stepwise ring enlargement pathway that is based upon the radical cyclization methodology. Further investigations of the scope, limitations, and applications of this methodology are currently in progress.

**Acknowledgment.** This work was supported by a Mitsubishi Gas Chemical Company Award in Synthetic Organic Chemistry, Japan.

**Supporting Information Available:** Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9019277