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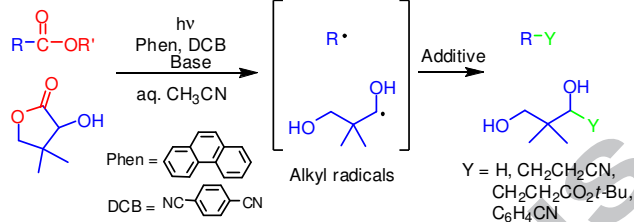


Graphical Abstract

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A strategy for generating alkyl radicals from aliphatic esters and lactones via sequential hydrolysis and photoinduced decarboxylation

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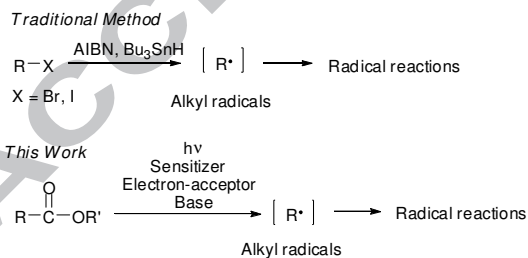
Generating alkyl radical
Aliphatic ester and lactone
Hydrolysis
Photoinduced decarboxylation
Radical reaction

ABSTRACT

Sequential hydrolysis and photoinduced decarboxylation of methyl aliphatic esters leads to efficient generation of alkyl radicals under mild conditions. The generated alkyl radicals react with a variety of reagents to produce addition, reduction, and substitution products. In addition, the new tin and halogen free process for alkyl radical generation is applicable to a variety of aliphatic esters including those of dipeptides, steroids, saccharides, and lactones.

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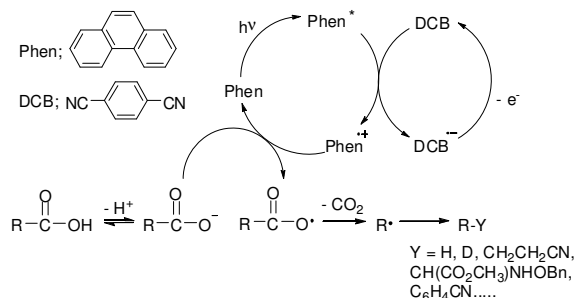
Radical reactions have become versatile and powerful tools in synthetic organic chemistry.¹ In these processes, alkyl radicals are usually generated by the reaction of organic halide (RX where X = Br or I) with AIBN as a radical initiator and Bu₃SnH as the halogen and/or hydrogen transfer agent (Scheme 1). However, the utility of this method is limited by the toxicity of the substrates and reagents, along with difficulties associated with the removal of tin containing byproducts (Bu₃SnX). As a result, several recent efforts have been carried out to develop new tin² and halogen free³ approaches for generating alkyl radicals.



Scheme 1. Generating alkyl radicals.

Recently, we described an interesting decarboxylation reaction of aliphatic carboxylic acids that produces alkyl radicals, which is promoted by the radical cation of phenanthrene (Phen) produced via single electron transfer (SET) from the excited state

of Phen to 1,4-dicyanobenzene (DCB) (Scheme 2).⁴ In the reaction, SET occurs from the carboxylate ion to the cation radical of Phen to form carboxy radicals that rapidly lose CO₂ to produce alkyl radicals. The formed alkyl radicals react with a variety of reagents such as an electron deficient alkenes,^{4c,d,g,i,j} oxime ethers,^{4c} thiols^{4a,f} and the radical anion of DCB^{4b} to provide the respective addition, reduction, and substitution products in high yields. Although similar photoinduced decarboxylative radical reactions of carboxylic acids by using phthalimides,⁵ cyanoarenes,⁶ TiO₂,⁷ Ir⁸ and the Fukuzumi⁹ catalyst have been widely explored, a related decarboxylative process starting with aliphatic esters has only been probed in a limited number of cases.¹⁰ Thus, a generic method for decarboxylative radical reactions from aliphatic ester under mild conditions is still in demand.



Scheme 2. Decarboxylative radical reactions of aliphatic carboxylic acids by photogenerated radical cation of Phen.

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In the effort described below, we investigated a route for photoinduced decarboxylative radical reactions using aliphatic esters as substrates, which are readily hydrolyzed under basic conditions. The new process for the alkyl radical generation, which utilizes sequential ester hydrolysis and photoinduced decarboxylation, does not require toxic and expensive organostannanes and alkyl halides. Moreover, in these reactions the ester moiety is directly converted under mild conditions into a variety of groups such as alkyl, hydrogen, and aryl.

Initial exploratory studies were carried out using the decarboxylative radical addition between *N*-Boc L-valine methyl ester **1a** and acrylonitrile **2a**.^{4c,d,g,i,j} Prior to irradiation, an aqueous CH₃CN solution (CH₃CN/H₂O = 9:1) containing **1a** (10 mM), **2a** (10 mM), Phen (10 mM), DCB (10 mM) and NaOH (50 mM) in a Pyrex vessel (15 x 180 mm) was heated at 40 °C for 2 h under an argon atmosphere. Irradiation of the resulting solution using a 100 W high-pressure mercury lamp for 3 h at room temperature led to formation of the adduct **3a** as a racemic mixture in 71% yield (Entry 1, Table 1). Prolonged irradiation (6 h) led to a slightly increased yield of **3a** (74%) and complete consumption of the hydrolyzed ester (Entry 2). A similar yield of **3a** was obtained when the original solution containing the ester was not preheated but rather directly irradiated for 6 h at 40 °C (Entry 3). Use of KOH and LiOH instead of NaOH led to slightly lower yields of **3a**, presumed consequences of the low basicity of KOH and low solubility of LiOH (Entries 4 and 5).

Table 1. Hydrolysis and photoinduced decarboxylative radical reaction of ester **1a** with acrylonitrile (**2a**).^a

Entry	Base	Irrad. time/h	Yield of 3a /%
1	NaOH	3	71
2	NaOH	6	74
3 ^c	NaOH	6	67
4	KOH	3	65
5	LiOH	3	55

^aAqueous acetonitrile solutions containing **1a** (10 mM), **2a** (10 mM), Phen (10 mM), DCB (10 mM), and base (50 mM) under an Ar atmosphere were heated at 40 °C for 2 h, and then photoreactions were carried out. ^bIsolated yield. ^cWithout preheating, photoreaction was carried out at 40 °C for 6 h.

The effects of sensitizer and electron acceptor employed in the photocatalytic system⁴ⁱ on the efficiencies of the photoinduced decarboxylative radical reaction between **1a** and **2a** were explored next (Table 2). Biphenyl (BP) and 1,4-dicyanonaphthalene (DCN) in place of Phen and DCB also serve as SET sensitizers the photoreaction step of the conversion of **1a** and **2a** to **3a** (Entries 1,2). In addition, photoreactions of **1a** using catalytic amounts of Phen (2 mM) and DCB (2 mM) or BP (2 mM) and DCN (2 mM) over longer irradiation times (10 h) also take place to produce **3a** in yields that are similar to those when 10 mM of these substances are used (Entries 3-5).

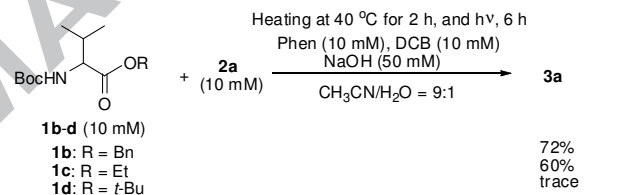
In the next phase of the study, the effect of the ester substituent on the efficiency of the process was investigated (Scheme 3). When benzyl ester **1b** and acrylonitrile **2a** were subjected to the sequential reaction involving preheating at 40 °C for 2 h followed by irradiation for 6 h, adduct **3a** was generated in a 72% yield. In reaction of ethyl ester **1c**, the yield of **3a** is slightly lower (60%) and **1c** is recovered in a 15% yield. Finally, in contrast to those of **1b** and **1c**, sequential reaction of *t*-butyl ester **1d** does not occur and the starting ester is almost recovered.

The results indicate that control of the hydrolysis conditions (concentration of base and temperature) and ester substituent is required in order to ensure efficient radical generation from the starting ester. This feature enables regioselective reactions of unsymmetric diesters. An example of this phenomenon is found in the sequential reaction of *N*-Boc Glu(*Or*-Bu)OCH₃ (**1e**), which selectively produces adduct **3b** (Scheme 4) arising by radical formation at the methyl α-aminocarboxylate center. In addition, the varying rates of ester hydrolysis also enable the use of unsaturated esters as radical traps. For example, reaction of *t*-butyl acrylate **2b** with methyl ester **1a** exclusively forms γ-amino acid ester **3c** (Scheme 4).

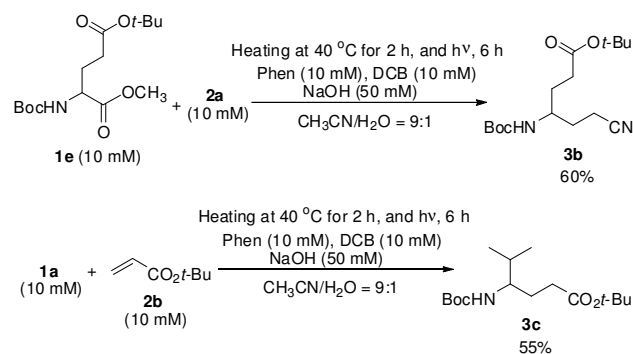
Table 2. Effects of sensitizer and electron acceptor in the catalytic system on the efficiency of photoreaction of **1a** and **2a**.

Entry	Sensitizer	Electron-acceptor	Irrad. time/h	Yield of 3a /%
1	Phen (10 mM)	DCN (10 mM)	6	64
2	BP (10 mM)	DCN (10 mM)	6	65
3	Phen (2 mM)	DCB (2 mM)	10	70
4	Phen (2 mM)	DCN (2 mM)	10	60
5	BP (2 mM)	DCN (2 mM)	10	62

^aIsolated yield.



Scheme 3. Effect of ester substituent on the photoreaction of **1** with **2a**.



Scheme 4. Selective photoinduced decarboxylation of esters.

In an effort aimed at elucidating the substrate scope of the new process, reactions of methyl esters of a peptide, steroid, saccharide and substituted arenes (**1f-1j**) with **2a** were carried out using the preheating protocol (Table 3). In reactions of the dipeptide methyl ester **1f** and phenoxyacetic acid methyl ester **1g**, modestly high yields of the corresponding adduct **3d** and **3e** were generated (Entries 1,2). Reactions of the methyl esters **1h-1j**, each containing a free OH group and a complex structure, also occur to form of **3f-3h**, respectively, but in lower yields (Entries 3-5).

Table 3. Photoinduced decarboxylative radical addition of **1f-1j** to **2a**.

Heating at 40 °C for 2 h, and hv, 6 h
Phen (10 mM), DCB (10 mM)
NaOH (50 mM)
 $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 9:1$

$\text{R}-\text{CO}_2\text{CH}_3 + \mathbf{2a} \rightarrow \text{R}-\text{CH}_2-\text{CH}_2-\text{CN}$

1f-j (10 mM) \rightarrow **3d-h**

Entry	Substrate 1	Yield of 3 / % ^a
1	1f:	3d: 70
2	1g:	3e: 71
3	1h:	3f: 49
4	1i:	3g: 29
5	1j:	3h: 26

^aIsolated yield.

A study was carried out to determine if the new radical process could be used to promote reduction^{7a,f} and substitution^{7b} reactions of *N*-Boc amino acid methyl esters (Table 4). We observed that reaction of ester **1a** (10 mM) in the presence of *t*-dodecanethiol (R-SH, 30 mM) as a hydrogen atom source under similar sequential heating and irradiation conditions leads to formation of reduction product **4a** (Entry 1).¹¹ Treatment of *N*-Boc phenylalanine and methionine methyl esters, **1k** and **1l**, under these conditions leads to formation of the respective reduction products **4b** and **4c** (Entries 2-3). Finally, reaction of **1a** conducted in the absence of a thiol and alkene leads to production of the cyanoarene adduct **5** (65%), formed by addition of the intermediate alkyl radical to the radical anion of DCB followed by loss of cyanide (Entry 4).^{4b}

Table 4. Photoinduced decarboxylative radical reduction and substitution of **1a**, **1k**, and **1l**.

Heating at 40 °C for 2 h, and hv
Phen (10 mM), DCB (10 mM)
NaOH (50 mM)
 $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 9:1$

$\text{BocHN}-\text{CH}(\text{R})-\text{C}(=\text{O})-\text{OCH}_3 + \text{Additive} \rightarrow \text{BocHN}-\text{CH}(\text{R})-\text{Y}$

1a, k, l (10 mM) \rightarrow **4** (Y = H)
1k: R = CH₂Ph \rightarrow **4b**
1l: R = CH₂CH₂SCH₃ \rightarrow **4c**

Entry	Substrate 1	Additive	Y	Irrad. time/h	Yield of 4 or 5 / % ^a
1	1a	R-SH (30 mM)	H	10	4a: 52
2	1k	R-SH (30 mM)	H	10	4b: 69
3	1l	R-SH (30 mM)	H	10	4c: 76
4 ^b	1a	none	C ₆ H ₄ CN	6	5: 65 ^c

^aIsolated yield. ^bConcentration of **1a** is 30 mM. ^cYield based on DCB.

In order to expand the scope of the new method, an investigation was carried out to explore the corresponding reaction of a lactone (Table 5). Lactones do not undergo hydrolysis under the conditions described above. However, ring opening hydrolysis of lactone **6** (10 mM) does take place upon treatment with KOH (50 mM) in CH₃CN/H₂O = 9:1 at reflux for 2 h. Addition of Phen, DCB, and additives such as **2a** and R-SH to the resulting solution followed by irradiation under an argon atmosphere at room temperature gives rise to production of the respective addition, reduction, and substitution products **7-9** (Entries 1-3).

Table 5. Photoinduced decarboxylative radical reactions of lactone **6**.

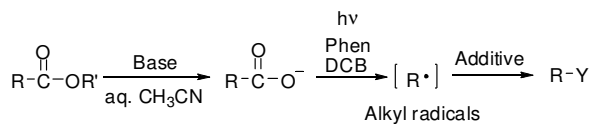
hv
Phen (10 mM)
DCB (10 mM)
+ Additive
 $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 9:1$

Reflux for 2 h
KOH (50 mM)

Entry	Additive	Irrad. time/h	Y	Yield of 7-9 / % ^a
1	2a (10 mM)	6	CH ₂ CH ₂ CN	7: 64
2	R-SH (30 mM)	10	H	8: 65
3 ^b	none	6	C ₆ H ₄ CN	9: 70 ^c

^aIsolated yield. ^bConcentration of **6** is 30 mM. ^cYield based on DCB.

In conclusion, the study described above led to the development of a new general method for the generation of interesting alkyl radical that involves sequential ester hydrolysis and SET promoted photodecarboxylation of esters and lactones (Scheme 5). This process can be used as part of radical addition, reduction, and substitution reactions. By selection of proper ester hydrolysis conditions, selective generation of alkyl radicals can be carried out. Further investigations of the applicability of this methodology to the modification of naturally occurring esters and polyesters are underway.

**Scheme 5.** Generating alkyl radicals from esters via sequential hydrolysis and photoinduced decarboxylation.**References and notes**

- (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. (b) Neumann, W. P. *Synthesis*, **1987**, 665-683. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286. (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177-194. (e) Yet, L. *Tetrahedron* **1999**, *55*, 9349-9403. (f) *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (g) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: New York, NY, 2003. (h) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563-1574. (i) Denes, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587-2693.
- (a) Boisvert, G.; Giasson, R. *Tetrahedron Lett.* **1992**, *33*, 6587-6590. (b) Kurono, N.; Honda, E.; Komatsu, F.; Orito, K.; Tokuda, M. *Tetrahedron* **2004**, *60*, 1791-1801. (c) Vaillard, S. E.; Postigo, A.; Rossi, R. A. *J. Org. Chem.* **2004**, *69*, 2037-2041. (d) Chatgililoglu, C.; Lalevee, J. *Molecules* **2012**, *17*, 527-555. (e) Pan, X.; Lacote, E.; Lalevee, J.; Curran, D. P. *J. Am. Chem. Soc.* **2012**, *134*, 5669-5674. (f) Yoshimi, Y.; Kanai, H.; Nishikawa, K.; Ohta, Y.; Okita, Y.; Maeda, K.; Morita, T. *Tetrahedron Lett.* **2013**, *54*, 2419-2422.
- (a) Akindede, T.; Yamada, K.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345-355. (b) Saraiva, M. F.; Couri, M. R. C.; Mireille, L. H.;

- Almeida, M. V. *Tetrahedron* **2009**, *65*, 3563–3572. (c) Rossi, B.; Prosperini, S.; Pastori, N.; Clerici, A.; Punta, C. *Molecules* **2012**, *17*, 14700–14732. (d) Gopalaiah, K.; Kagan, H. B. *Chem. Rec.* **2013**, *13*, 187–208.
- (a) Yoshimi, Y.; Itou, T.; Hatanaka, M. *Chem. Commun.* **2007**, 5244–5246. (b) Itou, T.; Yoshimi, Y.; Morita, T.; Tokunaga, Y.; Hatanaka, M. *Tetrahedron* **2009**, *65*, 263–269. (c) Yoshimi, Y.; Masuda, M.; Mizunashi, T.; Nishikawa, K.; Maeda, K.; Koshida, N.; Itou, T.; Morita, T.; Hatanaka, M. *Org. Lett.* **2009**, *11*, 4652–4655. (d) Yoshimi, Y.; Hayashi, S.; Nishikawa, K.; Haga, Y.; Maeda, K.; Morita, T.; Itou, T.; Okada, Y.; Ichinose, N.; Hatanaka, M. *Molecules* **2010**, *15*, 2623–2630. (e) Yoshimi, Y.; Kobayashi, K.; Kamakura, H.; Nishikawa, K.; Haga, Y.; Maeda, K.; Morita, T.; Itou, T.; Okada, Y.; Hatanaka, M. *Tetrahedron Lett.* **2010**, *51*, 2332–2334. (f) Itou, T.; Yoshimi, Y.; Nishikawa, K.; Morita, T.; Okada, Y.; Ichinose, N.; Hatanaka, M. *Chem. Commun.* **2010**, 6177–6179. (g) Nishikawa, K.; Yoshimi, Y.; Maeda, K.; Morita, T.; Takahashi, I.; Itou, T.; Inagaki, S.; Hatanaka, M. *J. Org. Chem.* **2013**, *78*, 582–589. (h) Nishikawa, K.; Ando, T.; Maeda, K.; Morita, T.; Yoshimi, Y. *Org. Lett.* **2013**, *15*, 636–638. (i) Yoshimi, Y.; Washida, S.; Okita, Y.; Nishikawa, K.; Maeda, K.; Hayashi, S.; Morita, T. *Tetrahedron Lett.* **2013**, *54*, 4324–4326. (j) Maeda, K.; Saito, H.; Osaka, K.; Nishikawa, K.; Sugie, M.; Morita, T.; Takahashi, I.; Yoshimi, Y. *Tetrahedron*, **2015**, *71*, 1117–1123.
 - (a) Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **2001**, *34*, 523–533. (b) Griesbeck, A. G.; Hoffmann, N.; Warzecha, K.-D. *Acc. Chem. Res.* **2007**, *40*, 128–140. (c) Gallagher, S.; Hatoum, F.; Zientek, N.; Olegemöller, M. *Tetrahedron Lett.* **2010**, *51*, 3639–3641. (d) Hatoum, F.; Engler, J.; Zelmar, C.; Wiben, J.; Motti, C. A.; Lex, J.; Olegemöller, M. *Tetrahedron Lett.* **2012**, *53*, 5573–5577.
 - (a) Libman, J. J. *Am. Chem. Soc.* **1975**, *97*, 4139–4141. (b) H. Yokoi, T. Nakano, W. Fujita, K. Ishiguro, Y. Sawai, *J. Am. Chem. Soc.* **1998**, *120*, 12453–12458. (c) Yoshimi, Y.; Hayashi, S.; Nishikawa, N.; Okita, Y.; Maeda, K.; Morita, T.; Itou, T. *Res. Chem. Intermed.* **2013**, *39*, 397–402.
 - (a) Manley, D. W.; McBurney, R. T.; Miller, P.; Walton, J. C. *J. Org. Chem.* **2014**, *79*, 1386–1398. (b) Shimaoka, K.; Kuwahara, S.; Yamashita, M.; Katayama, K. *Anal. Sci.* **2014**, *30*, 619–621.
 - (a) Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260. (b) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886–10889.
 - (a) Cassani, C.; Bergonzini, G.; Wallentin, C. *Org. Lett.* **2014**, *16*, 4228–4231.
 - (a) Photoinduced electron transfer reaction of aliphatic *t*-butyl ester with tetracyanobenzene, providing an alkyltricyanobenzene via decarboxylation, has been previously reported; Fasani, E.; Peverali, D.; Albini, A. *Tetrahedron Lett.* **1994**, *35*, 9275–9278. (b) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846–1913. (c) Recently, photoinduced decarboxylative allylation of amino alkanolic allyl esters by using both Ir and Pd catalysts has been reported; Lang, S. B.; O’Nele, K. M.; Tunge, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 13606–13609.
 - Isolated yield of **4a** is slightly lower owing to its high volatility of **4a**.

Supplementary Material

Experimental details including procedures, characterization, and spectra data.