

# Photoinduced Electron Transfer Promoted Radical Ring Expansion and Cyclization Reactions of $\alpha$ -( $\omega$ -Carboxyalkyl) $\beta$ -Keto Esters

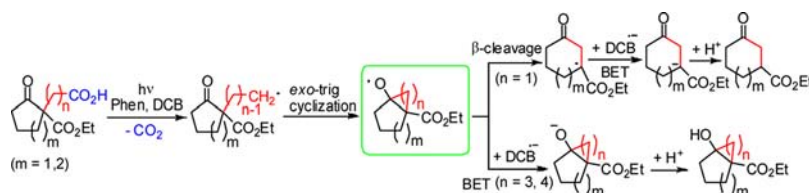
Keisuke Nishikawa, Tomoki Ando, Kousuke Maeda, Toshio Morita, and Yasuharu Yoshimi\*

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

y.yoshimi@u-fukui.ac.jp

Received December 18, 2012

## ABSTRACT



Photoinduced electron transfer (PET) promoted decarboxylation of  $\alpha$ -( $\omega$ -carboxyalkyl)  $\beta$ -keto esters undergoes radical ring expansion and cyclization reactions. This mild and environmentally friendly method can provide one-carbon expanded  $\gamma$ -keto esters and bicyclic alcohols, and the product distribution is strongly dependent on the length of the alkyl chain containing the terminal carboxylate group.

Owing to difficulties associated with the use of traditional methods,<sup>1</sup> radical ring expansion reactions are important processes for the preparation of medium-sized ring systems. For example, the Beckwith–Dowd ring expansion reaction is a well-known and efficient method for generating medium-sized ring cyclic ketones (Scheme 1).<sup>2–4</sup> However, this process requires the use of high temperatures, toxic reagents such as AIBN and  $\text{Bu}_3\text{SnH}$ , and environmentally unfriendly haloketone substrates. Thus, the development of reactions of this type that can be carried out under milder conditions using more benign substrates is a significant goal in organic synthesis.

Photoinduced electron transfer (PET) reactions that generate radical intermediates represent attractive alternative approaches for promoting Beckwith–Dowd ring expansion processes under mild and eco-friendly conditions.

Although methods involving PET-promoted Beckwith–Dowd ring expansion reactions of halomethyl substituted benzocyclic ketones with amines<sup>5</sup> and of  $\alpha$ -bromomethyl  $\beta$ -keto esters by using a  $\text{B}_{12}$ – $\text{TiO}_2$  hybrid catalyst<sup>6</sup> have been described, both approaches require the use of haloketones as reactants and generate environmentally unfriendly hydrogen halides.

Earlier, we observed interesting decarboxylation reactions of aliphatic carboxylic acids, which are promoted by PET to arene radical cations and produce alkyl free

(1) (a) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991. (b) Yet, L. *Tetrahedron* **1999**, *55*, 9349–9403. (c) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007. (d) Srikrishna, A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 163–187.

(2) (a) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3494–3494. (b) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 6548–6549. (c) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091–2115.

(3) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565–2572.

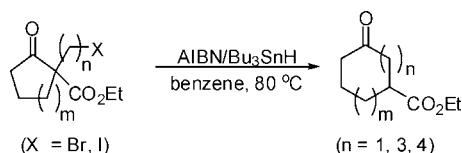
(4) Wang, C.; Gu, X.; Yu, M. S.; Curan, D. P. *Tetrahedron* **1998**, *54*, 8355–8370.

(5) (a) Hasegawa, E.; Tamura, Y.; Tosaka, E. *Chem. Commun.* **1997**, 1895–1896. (b) Hasegawa, E.; Takizawa, S.; Iwaya, K.; Kurokawa, M.; Chiba, N.; Yamamichi, K. *Chem. Commun.* **2002**, 1966–1967.

(6) (a) Shimakoshi, H.; Abiru, M.; Izumi, S.; Hiseada, Y. *Chem. Commun.* **2009**, 6427–6429. (b) Izumi, S.; Shimakoshi, H.; Abe, M.; Hiseada, Y. *Dalton Trans.* **2010**, 39, 3302–3307.

(7) (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.; 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) Yoshimi, Y.; Hayashi, S.; Nishikawa, K.; Okita, Y.; Maeda, K.; Morita, T.; Itou, T. *Res. Chem. Intermed.* **2013**, *39*, 397–402. (h) Nishikawa, K.; Yoshimi, Y.; Maeda, K.; Morita, T.; Takahashi, I.; Itou, T.; Inagaki, S.; Hatanaka, M. *J. Org. Chem.* **2013**, *78*, 582–589.

**Scheme 1.** Beckwith–Dowd Ring Expansion



radicals.<sup>7</sup> Alkyl radicals generated in this manner react efficiently with a variety of substances, such as thiols and alkenes, to yield the respective reduction<sup>7a,f</sup> and addition products.<sup>7c,d,g,h</sup> In a recent effort, we observed that PET-promoted decarboxylations can be applied to Beckwith–Dowd ring expansion reactions of  $\alpha$ -( $\omega$ -carboxyalkyl)  $\beta$ -keto esters. The studies described below have led to the development of a new process that serves as mild and environmentally friendly method for the preparation of seven-membered  $\gamma$ -keto esters.

In an initial phase of the studies exploring the Beckwith–Dowd ring expansion reaction of  $\alpha$ -carboxymethyl  $\beta$ -keto ester **1a**, we observed that irradiation of an aqueous acetonitrile solution ( $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 9:1$ ), containing phenanthrene (Phen, 20 mM), 1,4-dicyanobenzene (DCB, 20 mM), and racemic **1a** (1 mM), with a 400 W high-pressure mercury lamp through a Pyrex filter ( $> 280$  nm) under an argon atmosphere for 6 h at room temperature, leads to formation of the seven-membered  $\gamma$ -keto-ester **2a** in 83% yield as a racemic mixture (entry 1, Table 1) along with near-quantitative recovery of Phen and DCB. In the absence of Phen or DCB or both Phen and DCB, a photoreaction does not take place to recover **1a** in a quantitative yield. The photoreaction using a slightly higher concentration of **1a** (2 mM) also produces **2a** in high yield (entry 2), but when the concentration of **1a** is raised to 3–5 mM, **2a** is formed in lower yields (67–52%, respectively) (entries 3–5). We also observed that the addition of 1 equiv of NaOH to the reaction mixture leads to a more efficient photoreaction, which enables production of **2a** in a similar yield but with a shorter irradiation time (3 h) (entry 6). The decreased yield of **2a** (58%) along with the formation of byproduct occurred in the photoreaction using low concentrations of Phen and DCB (2 mM) (entry 7). Finally, photoreactions in which other arenes such as biphenyl and other electron acceptors such as 1,4-dicyanonaphthalene (DCN) are utilized also give **2a** in similar or slightly decreased yields (entries 8–10).

In an effort to elucidate the substrate scope of the process, photoreactions of  $\alpha$ -( $\omega$ -carboxyalkyl)  $\beta$ -keto esters **1b–j**, which contain different numbers of methylene groups in the ring and carboxylic acid side chain, were carried out using the conditions described above (Table 2). The results of the study show that irradiation of a solution containing  $\alpha$ -( $\beta$ -carboxyethyl)  $\beta$ -keto ester **1b** ( $n = 2$ ,  $m = 2$ , entry 1), Phen, and DCB does not give rise to formation of a ring expansion product, but instead products arising from decarboxylative reduction (**4b**) and substitution (**5b**) are produced. Interestingly, irradiation of a solution containing  $\alpha$ -( $\gamma$ -carboxypropyl)  $\beta$ -keto ester **1c** ( $n = 3$ ,  $m = 2$ , entry 2),

**Table 1.** PET-Promoted Radical Ring Expansion of  $\alpha$ -Carboxymethyl  $\beta$ -Keto Ester **1a**<sup>a</sup>

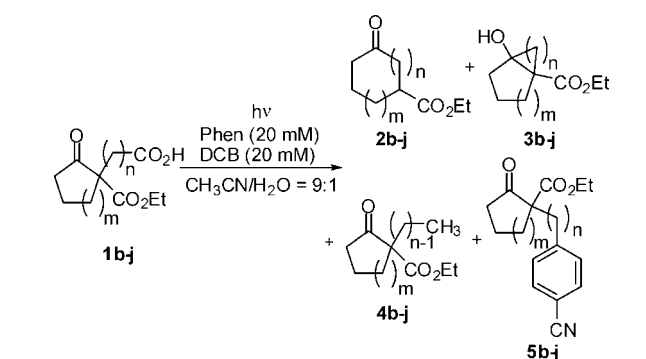
entry	<b>1a</b> (mM)	arene	electron acceptor	yield of <b>2a</b> (%) <sup>b</sup>
1	1	Phen	DCB	83
2	2	Phen	DCB	84
3	3	Phen	DCB	67
4	4	Phen	DCB	60
5	5	Phen	DCB	52
6 <sup>c</sup>	2	Phen	DCB	81
7 <sup>d</sup>	2	Phen	DCB	58
8	2	biphenyl	DCB	70
9	2	Phen	DCN	68
10	2	biphenyl	DCN	78

<sup>a</sup> The photoreaction of **1a** was carried out in the presence of an arene (20 mM) and electron acceptor (20 mM) using a 400-W high-pressure mercury lamp under an argon atmosphere for 6 h. <sup>b</sup> Isolated yield. <sup>c</sup> In the presence of 2 mM of NaOH, and irradiation time was 3 h. <sup>d</sup> Concentrations of Phen and DCB were 2 mM.

Phen, and DCB results in exclusive formation of a diastereomeric mixture of bicyclic alcohol **3c**. In contrast, bicyclic alcohol **3d**, reduction product **4d**, and substitution product **5d** are generated in nearly equal yields when a solution of  $\alpha$ -( $\delta$ -carboxybutyl)  $\beta$ -keto ester **1d** ( $n = 4$ ,  $m = 2$ , entry 3), Phen, and DCB is irradiated. Also, photoreactions of  $\alpha$ -( $\omega$ -carboxyalkyl)  $\beta$ -keto ester **1e,g–j** (entries 4, 6–9) under these conditions yield mixtures containing varying amounts of the corresponding fused cycloalkanols **3**, reduction products **4**, and substitution product **5**. Interestingly, unlike the other substrates except **1a**,  $\alpha$ -carboxymethyl  $\beta$ -keto ester **1f** ( $n = 1$ ,  $m = 1$ , entry 5) undergoes a PET promoted reaction to produce the ring expanded product exclusively. These results show that only Beckwith–Dowd one-carbon ring expansion reactions are efficient, as exemplified by transformations of **1a** and **1f** to the respective seven- or six-membered  $\gamma$ -keto esters.

On the basis of the above results, plausible mechanisms for the PET-promoted decarboxylative ring expansion and other reactions can be proposed (Scheme 2). In each route, initial decarboxylation of the carboxy radical of the substrate **1**, formed by single-electron transfer from the carboxylate to the radical cation of Phen, occurs to generate the corresponding alkyl radical **6**.<sup>7a</sup> In the cases of radicals **6**, containing one, three, and four methylene side chains, *exo*-trig cyclization by addition to the ketone takes place to form bicyclic radical intermediates **7**. In contrast, radicals possessing two and five methylene containing side chains cyclize slowly and, as a result, they are reduced by the radical anion of DCB or add to the radical anion of DCB more rapidly in the pathways for formation of the reduction or substitution products. The cyclopropyl-oxy radicals **7** ( $n = 1$ ), in which ring strain exists, undergo  $\beta$ -cleavage to yield the ring

**Table 2.** PET-Promoted Reactions of  $\alpha$ -( $\omega$ -Carboxyalkyl)  $\beta$ -Keto Ester **1b–j**<sup>a</sup>



entry	carboxylic acid <b>1</b>	product yields <sup>b</sup> (%)			
		<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
1	<b>1b</b> ( $n = 2, m = 2$ )	—	—	37	35
2	<b>1c</b> ( $n = 3, m = 2$ )	—	81	—	—
3	<b>1d</b> ( $n = 4, m = 2$ )	—	30	21	38
4	<b>1e</b> ( $n = 5, m = 2$ )	—	—	43	27
5	<b>1f</b> ( $n = 1, m = 1$ )	76	—	—	—
6	<b>1g</b> ( $n = 2, m = 1$ )	—	—	14	71
7	<b>1h</b> ( $n = 3, m = 1$ )	—	84	—	—
8	<b>1i</b> ( $n = 4, m = 1$ )	—	20	22	38
9	<b>1j</b> ( $n = 5, m = 1$ )	—	—	43	29

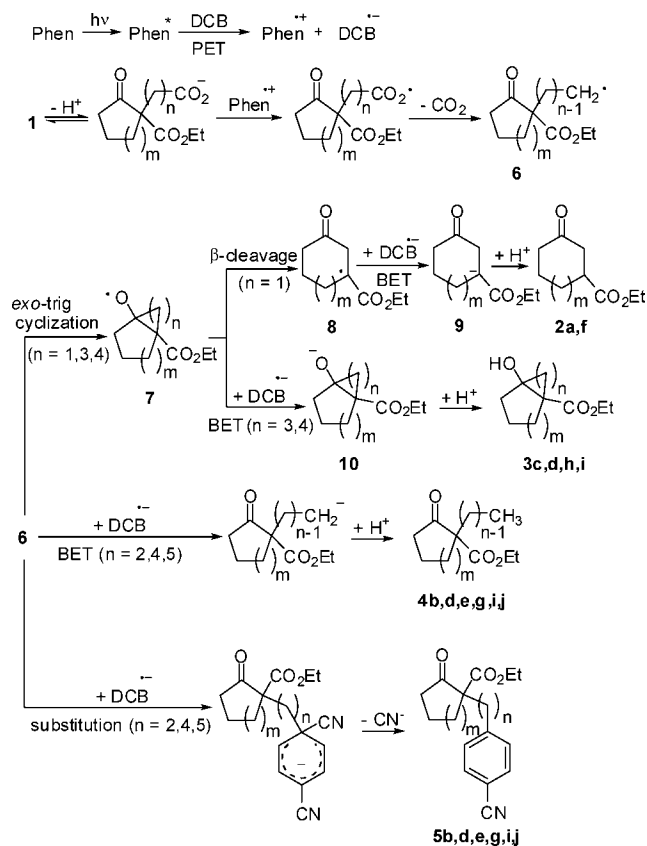
<sup>a</sup>The photoreaction was carried out in the presence of 2 mM of **1**.  
<sup>b</sup>Isolated yields.

expanded radicals **8**, which is then followed by back electron transfer (BET) from the radical anion of DCB to form anions **9** that undergo protonation to yield the ring expanded products **2a,f**. The low efficiency of BET in **8** when the photoreaction is carried out with low concentrations of Phn and DCB leads to the formation of byproduct and decreases the yield of **2**. In contrast, the relatively more stable five- and six-membered alkoxy radicals **7** ( $n = 3$  and  $4$ ) do not ring open rapidly but instead are captured by BET from the radical anion of DCB to produce alkoxy anions **10** that serve as precursors of the bicyclic alcohols **3c,d,h,i**.

As described earlier,<sup>8</sup> electrochemical reactions of the bromo derivatives of **1** also generate bicyclic alcohols that are similar to the ones formed in the above PET reactions. Although the Beckwith–Dowd reaction induced by using AIBN and Bu<sub>3</sub>SnH contains the reducing agent Bu<sub>3</sub>SnH, it appears that reductants present in reactions promoted by using both PET (DCB radical anion) and electrochemical (cathode) oxidations are capable of reducing those intermediate alkoxy radicals **7** that undergo ring opening slowly. In addition, the results arising from the current effort show that radicals **6**, possessing two and five carbon alkyl side chains, do not cyclize but rather participate in BET with or coupling to radical anions of DCB,<sup>7b</sup> which is similar to the typical Beckwith–Dowd reaction using AIBN and Bu<sub>3</sub>SnH. Finally, in the case of radical **6d.i** with a four methylene side

(8) Shono, T.; Kise, N.; Uematsu, N.; Morimoto, S.; Okazaki, E. *J. Org. Chem.* **1990**, *55*, 5037–5041.

### Scheme 2. Plausible Mechanism



chain, similar rates of cyclization, BET, and substitution cause formation of a mixture of products containing the bicyclic alkanol **3d,i**, reduction product **4d,i**, and substitution product **5d,i**.

In the investigation described above, we have developed a new method for promoting Beckwith–Dowd ring expansion reactions of  $\alpha$ -carboxymethyl  $\beta$ -keto esters. The process takes place under mild conditions via a PET-promoted decarboxylation reaction pathway and leads to formation of one-carbon expanded  $\gamma$ -keto esters. The efficiencies of the reactions are strongly dependent on the length of the alkyl chain containing the terminal carboxylate group. In addition, the process can be utilized to prepare bicyclic five- or six-membered cycloalkanols. Further investigations of the scope and applications of this new methodology are underway.

**Acknowledgment.** We are grateful to Prof. Minoru Hatanaka and Mr. Sho Inagaki at Iwate Medical University, for assistance with HR-MS measurements.

**Note Added after ASAP Publication.** Table 2 contained errors in the version Published ASAP on January 23, 2013, the correct version reposted February 1, 2013.

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

The authors declare no competing financial interest.