

## Novel Radical Alkylation of Carboxylic Imides

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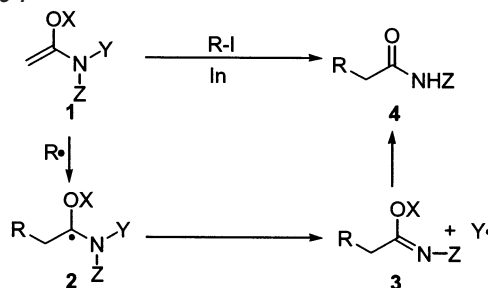
Alkylation is one of the most important and fundamental organic reactions for the formation of carbon–carbon bonds and is routinely performed with metal enolates and alkylating agents.<sup>1</sup> Despite extensive studies of radical reactions during the last two decades,<sup>2</sup> radical-mediated alkylations of carboxylic acid derivatives have not been well studied.<sup>3,4</sup>

To develop a novel approach for the alkylation of carboxylic acid derivatives, we designed a new type of carboxylic amide derivatives. Our approach is outlined in Scheme 1 and is based on the homolytic cleavage of the N–Y bond rather than that of the O–X bond, generating imino ether **3** to provide amide derivative **4**. Among several candidates for group Y, an alkoxy group seems to be the most attractive because of a facile cleavage of N–O bond along with the stability of ketene *O,N*-acetal **1**.<sup>5</sup> Furthermore, 1,2-phenyl transfer from silyl to oxygen was previously reported, but its synthetic application has not been examined to date.<sup>6</sup> Thus, we intended to utilize the *tert*-butyldiphenylsilyloxy group (TBDPS)<sup>7</sup> for group Y to investigate the possibility of achieving the radical alkylation under tin-free conditions. For group Z, we have chosen a benzyloxy carbonyl group (Cbz) not only to increase the stability of **1** but also to reduce the electron density of the carbon–carbon double bond in **1** to some extent. Herein we report that *this strategy is indeed promising and permits the radical alkylation of carboxylic imides with alkyl halides bearing an electron-withdrawing group under tin-free conditions for the first time.*<sup>8,9</sup>

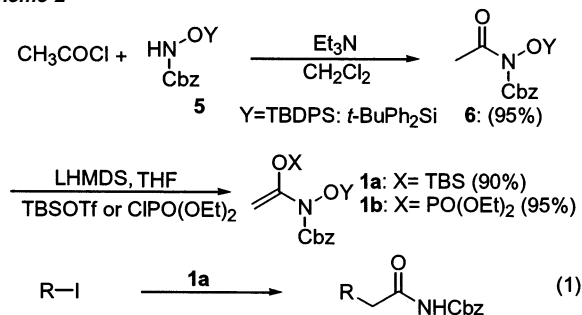
With these ideas in mind, we prepared two ketene *O,N*-acetals, **1a** and **1b** (Scheme 2).<sup>10</sup> Coupling of acetyl chloride with **5** and triethylamine in dichloromethane at room temperature gave imide **6** in 95% yield. The imide **6** was treated with LHMDS in THF at –78 °C in the presence of TBSOTf to afford **1a** in 90% yield.<sup>11</sup> **1b** was similarly prepared in 95% yield. As we expected, **1a** and **1b** were stable compounds and could be kept in a refrigerator for one week without any noticeable decomposition.

We began with our study with 4-phenoxybutyl iodide (**7a**) using **1a** and **1b** (eq 1). Irradiation of a solution of **7a**, **1a** (1.5 equiv), and hexamethylditin (1.0 equiv) in benzene at 300 nm for 6 h afforded alkylated product **8a** in 76% yield, while the use of **1b** gave a low yield (50%). Although a nucleophilic alkyl radical was known to be reluctant to add to an electron-rich alkene,<sup>12</sup> **1a** turned out to be a relatively good acceptor for both electrophilic and nucleophilic alkyl radicals. Irradiation of **7b** with **1a** (1.5 equiv) and hexamethylditin (1.0 equiv) in benzene for 3 h at 300 nm gave **8b** in 86% yield. To confirm the generation of a silyl radical by 1,2-phenyl transfer,<sup>6</sup> the reaction was carried out with **7b** and hexamethylditin (0.1 equiv), and **8b** was obtained in 67% yield. In the case of **7a**, 0.3 equiv of hexamethylditin was required for completion.

Scheme 1



Scheme 2



<b>7a</b> : R=PhO(CH <sub>2</sub> ) <sub>4</sub>	1 eq (Me <sub>3</sub> Sn) <sub>2</sub> , hv	<b>8a</b> : (76%)
	0.3 eq (Me <sub>3</sub> Sn) <sub>2</sub> , hv	(67%)
<b>7b</b> : R=EtOOCCH <sub>2</sub>	1 eq (Me <sub>3</sub> Sn) <sub>2</sub> , hv	<b>8b</b> : (86%)
	0.1 eq (Me <sub>3</sub> Sn) <sub>2</sub> , hv	(67%)
	0.1 eq AIBN, 80 °C	(64%)

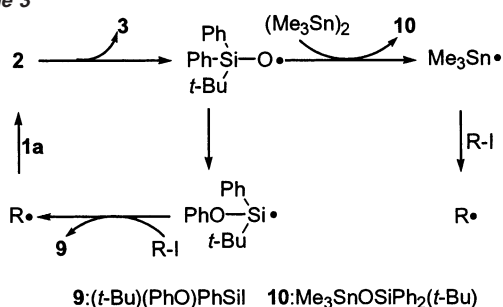
Encouraged by these results, we studied the feasibility of tin-free radical alkylation. Reaction of **7b** with **1a** using AIBN (0.1 equiv) as the initiator in benzene at 80 °C for 6 h afforded **8b** in 64% yield. However, somewhat disappointingly, reaction of **7a** using AIBN as the initiator under the same conditions did not proceed.<sup>13</sup>

From the results obtained here, it is clear that tin-free radical alkylation of **7b** occurred due to conversion of a silyloxy radical into a silyl radical (Scheme 3). In the tin-mediated radical reaction, trimethyltin radical could be generated not only by photochemical cleavage of hexamethylditin but also by the reaction of *tert*-butyldiphenylsilyloxy radical with hexamethylditin.<sup>14</sup> In the tin-catalyzed radical chain reaction, an alkyl radical could be generated by the reaction of an alkyl iodide with silyl radical mainly or with trimethyltin radical to some extent.

Table 1 summarizes the experimental results and illustrates the efficiency and scope of the present method. Alkyl iodides and bromides bearing an  $\alpha$ -electron-withdrawing group underwent alkylation under tin-free conditions (method A). Tin-mediated radical reactions (method B and C) worked well with simple alkyl

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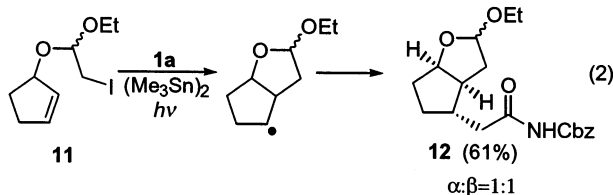
Scheme 3

Table 1. Radical Alkylation of Alkyl Halides with 1a<sup>a</sup>

RX	Yield (8)	RX	Yield (8)
	A: 71% B: 71%		B: 78% C: 62%
	A: 60% B: 64%		B: 64% C: 55%
	A: 84% B: 95%		B: 70% C: 56%
	A: 72% B: 76%		B: 64% C: 48%
	A: 74% B: 92%		B: 68% <sup>b</sup> C: 54%
	A: 63% B: 70%		B: 62% C: 47%

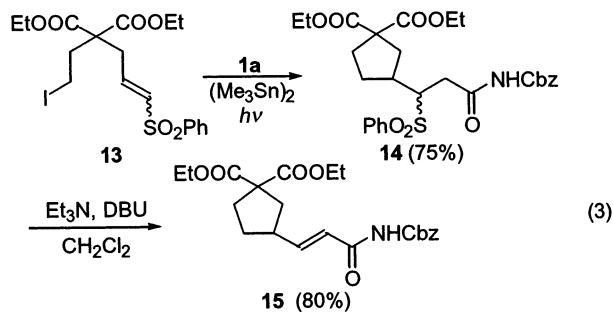
<sup>a</sup> Method A: AIBN/C<sub>6</sub>H<sub>6</sub>, 80 °C, 6 h, method B: 1 equiv (Me<sub>3</sub>Sn)<sub>2</sub>/C<sub>6</sub>H<sub>6</sub>, 300 nm, 8 h, method C: 0.3 equiv (Me<sub>3</sub>Sn)<sub>2</sub>/C<sub>6</sub>H<sub>6</sub>, 300 nm, 8 h. <sup>b</sup> *exo:endo* = 10:1.

iodides as well as those activated with an electron-withdrawing group. For most of the cases observed, method B gave the best results out of the three methods. The sterically hindered iodoadamantane underwent alkylation. However, a benzylic iodide gave the dimerized product without the formation of the desired alkylation product due to the low reactivity of the benzylic radical.<sup>15</sup>



We examined sequential radical reactions involving the cyclization and alkylation sequence, which cannot be achieved with conventional methods (eq 2 and 3). Treatment of **11** with **1a** (1.5 equiv), Me<sub>3</sub>SnSnMe<sub>3</sub> (1.0 equiv) in benzene at 300 nm for 5 h afforded **12** in 61% yield. Similarly, the radical reaction of **13** gave **14** in 75% yield under similar conditions, and **14** was further converted into **15** by treatment with DBU and triethylamine.

In conclusion, we have discovered the first successful radical alkylation of carboxylic imides, in which alkyl halides activated with an electron-withdrawing group underwent alkylations under tin-free conditions. Further detailed studies on the radical alkylation of carboxylic derivatives are in progress.



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**Supporting Information Available:** Typical experimental procedures and spectral data for products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) We also prepared benzyloxy ketene *O,N*-acetals **1** (Y = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, X = TBS, PO(OEt)<sub>2</sub>) which were somewhat less stable than **1a** and **1b**.
- (11) When lithium enolate of **6** was quenched with TBSOTf at –78 °C, **5** was isolated in 40% yield. Thus, it is essential to generate lithium enolate of **6** in the presence of TBSOTf and diethyl chlorophosphate to yield **1a** and **1b**. (a) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gartner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467. (b) Jiang, J.; DeVita, R. J.; Doss, G. A.; Goulet, M. T.; Wyrvt, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593.
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- (13) Since the rate of addition of a nucleophilic alkyl radical onto **1** would be relatively slow, the alkyl radical might react with a silyloxy radical, thereby stopping the radical chain reaction.
- (14) (Me<sub>3</sub>Sn)<sub>2</sub> (1.0 equiv) was almost completely consumed during the reaction. The structures of **9** and **10** are tentatively assigned.
- (15) Reaction of *p*-bromobenzyl iodide with **1a** and (Me<sub>3</sub>Sn)<sub>2</sub> in benzene at 300 nm for 6 h gave 4,4'-bromodibenzyl in 80% yield.

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