

## Carbon-Carbon Bond Formation *via* Intermolecular Carbon Radical Addition to Aldoxime Ethers

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**Abstract:** The first example of intermolecular carbon radical addition to unactivated aldoxime ethers in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  has provided a new efficient carbon-carbon bond-forming method for the synthesis of a variety of amines. © 1998 Elsevier Science Ltd. All rights reserved.

The nucleophilic addition to the carbon-nitrogen double bond constitutes an extremely useful method for preparing a variety of amines. Typically, organometallic reagents can be utilized to achieve the carbon-carbon bond forming reaction.<sup>1</sup> However, this addition of organometallic reagents is frequently plagued by the enolization of substrates with acidic  $\alpha$ -hydrogens, the poor electrophilicity of the imino group and the formation of reductive coupling products.<sup>1</sup> We report here a new efficient carbon-carbon bond-forming reaction based on the intermolecular carbon radical addition to oxime ethers, providing a highly general solution to the fundamental problems that are associated with the strong basicity of organometallic reagents (Fig. 1).<sup>2</sup>

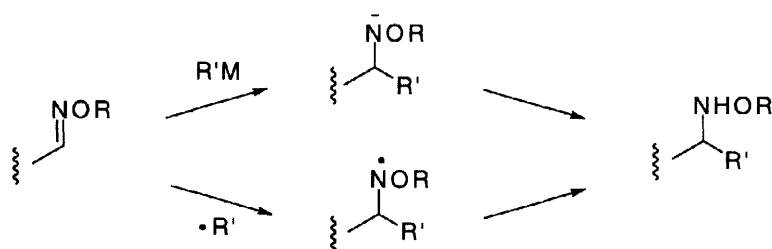
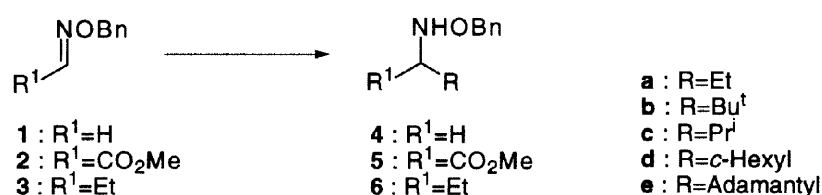


Fig. 1

Compared with numerous reports on the intramolecular radical reaction of oxime ethers, the intermolecular carbon radical addition, which is difficult to be achieved, has not been investigated except for formaldoxime ether **1**.<sup>3</sup> We have recently reported the diastereofacial control in intermolecular radical additions to the sultam derivative of glyoxylic oxime ether **2**.<sup>4</sup> Indeed, the intermolecular addition of an ethyl radical to either sterically less hindered formaldoxime ether **1** or glyoxylic oxime ether **2** which is activated by an electron-withdrawing substituent proceeded smoothly to give an excellent yield of ethylated product **4a** or **5a** (Table 1, entries 1, 2). It is important to note that practically no reaction of unactivated aldoxime ether **3** occurred under the same

reaction conditions (entry 3). In order to establish a general method for the radical additions to the oxime ether group, we explored in some detail the simple intermolecular addition of an ethyl radical to unactivated aldoxime ether **3**. The reactions were run in dichloromethane at 25 °C by using Et<sub>3</sub>B as a radical initiator. To enhance the reactivity of the oxime ether group as a radical acceptor toward nucleophilic alkyl radicals, we examined the effect of Lewis acids which would lower the LUMO energy of the radical acceptor and decrease the electron density at the iminyl carbon atom.<sup>5</sup> Among several Lewis acids evaluated,<sup>6</sup> a twofold excess of BF<sub>3</sub>·OEt<sub>2</sub> was found to be most effective for the successful radical addition to the aldoxime ether **3** which gave the ethylated products **6a** in 95% yield just after a 5-min reaction (entries 4-8). This newly-found radical reaction has a tremendous practical advantage over the conventional organometallic reactions which require rigorous reaction conditions such as carefully dried reagents, solvents and apparatus.

High chemical yield was also observed in the radical addition using different radical precursors such as *tert*-butyl, *iso*-propyl, cyclohexyl and adamantyl iodides in the presence of BF<sub>3</sub>·OEt<sub>2</sub> (entries 9-12). The reaction proceeded smoothly when secondary and tertiary alkyl iodides were employed to give the desired C-alkylated products though a small amount of ethylated product **6a** was formed as a result of the addition of an ethyl radical generated from Et<sub>3</sub>B and O<sub>2</sub>. During the course of our investigation, we have found that use of



**Scheme 1.** Reagents and conditions: Et<sub>3</sub>B, RI, EtOH or Bu<sub>3</sub>SnH, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 5-30 min.

**Table 1.** Carbon-carbon bond-forming radical addition to oxime ethers **1**, **2** and **3**

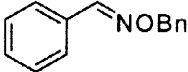
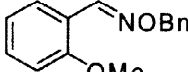
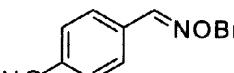
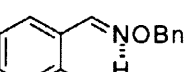
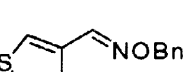
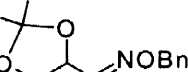
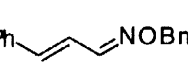
Entry	Oxime ether	R	Lewis acid <sup>a</sup>	Product	Yield (%) <sup>b</sup>
1 <sup>c</sup>	<b>1</b>	Et	none	<b>4a</b>	90
2 <sup>c</sup>	<b>2</b>	Et	none	<b>5a</b>	97
3 <sup>c</sup>	<b>3</b>	Et	none	<b>6a</b>	n.r. (94)
4 <sup>c</sup>	<b>3</b>	Et	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6a</b>	95
5 <sup>c</sup>	<b>3</b>	Et	TFA	<b>6a</b>	13 (83)
6 <sup>c</sup>	<b>3</b>	Et	Et <sub>2</sub> AlCl	<b>6a</b>	14 (78)
7 <sup>c</sup>	<b>3</b>	Et	Zn(OTf) <sub>2</sub>	<b>6a</b>	28 (70)
8 <sup>c</sup>	<b>3</b>	Et	Yb(OTf) <sub>3</sub>	<b>6a</b>	17 (68)
9 <sup>d</sup>	<b>3</b>	Bu <sup>t</sup>	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6b</b>	98
10 <sup>d</sup>	<b>3</b>	Pr <sup>i</sup>	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6c</b>	76
11 <sup>d</sup>	<b>3</b>	<i>c</i> -Hexyl	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6d</b>	58
12 <sup>d</sup>	<b>3</b>	Adamantyl	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6e</b>	41 (28)

<sup>a</sup>2 equiv. of the Lewis acid was used. <sup>b</sup>Yields of isolated product; Yields in parentheses are for the recovered starting material. <sup>c</sup>Reaction conditions: Under a nitrogen atmosphere, to a solution of oxime ether in CH<sub>2</sub>Cl<sub>2</sub> were successively added EtOH (2.5 equiv), Lewis acid (2 equiv), ethyl iodide (5 equiv) and Et<sub>3</sub>B (2.5 equiv, 1.0 M solution in hexane) at 25 °C. <sup>d</sup>Under the same reaction conditions, to a solution of oxime ether in CH<sub>2</sub>Cl<sub>2</sub> were successively added Bu<sub>3</sub>SnH (2.5 equiv), alkyl iodide (20 equiv), Et<sub>3</sub>B (2.5 equiv, 1.0 M solution in hexane) and then BF<sub>3</sub>·OEt (2 equiv) as a final reagent.

tributyltin hydride for the generation of an alkyl radical and the addition sequence of the reagents involving  $\text{BF}_3 \cdot \text{OEt}_2$  as the final reagent are responsible for the successful radical reaction.<sup>7</sup> Thus, the reaction conditions are crucial for the successful  $\text{Bu}_3\text{SnH}$ -mediated exchange of the unstabilized primary ethyl radical, which is generated from  $\text{Et}_3\text{B}$  and  $\text{O}_2$ , to the more stable secondary and tertiary alkyl radical.

To survey the scope and limitations of the present method, we investigated the reaction of the oxime ethers **7-13** bearing a variety of substituents as in Table 2. The aryl aldehyde derivatives **8** containing electron-donating substituents, which were expected to be less reactive than **7**, also produced excellent yields of ethylated products (entries 1-4). Though the reaction of the oxime ether **9** involving a 4-hydroxy group was successful, only a modest alkylation yield was observed in the reaction of intramolecularly hydrogen-bonded salicylaldehyde derivative **10** (entries 5-8).<sup>8</sup> In the case of  $\alpha,\beta$ -unsaturated aldoxime, a highly selective 1,2-addition of alkyl radical to the aldoxime ether **13** was observed with no detection of 1,4-adduct (entries 13, 14). It is known that the orientation of radical addition to  $\alpha,\beta$ -unsaturated carbonyl compounds is influenced by steric factors and addition takes place mainly at the  $\beta$ -carbon of the carbon-carbon double bond.<sup>9</sup> In agreement with the general advantages of the radical reactions over the anionic reaction using traditional organometallic reagents, the present radical method would be useful because of the exceptional tolerance of functional groups such as aromatic heterocycle, alcohol, acetal, ester and amide moieties.

**Table 2.** Intermolecular addition of ethyl radical to oxime ethers

Entry	Substrate	Lewis acid <sup>a</sup>	Yield (%) <sup>b</sup>
1	 <b>7</b>	none	19 (73)
2		$\text{BF}_3 \cdot \text{OEt}_2$	98
3	 <b>8</b>	none	15 (72)
4		$\text{BF}_3 \cdot \text{OEt}_2$	93
5	 <b>9</b>	none	n.r.
6		$\text{BF}_3 \cdot \text{OEt}_2$	96
7	 <b>10</b>	none	5 (89)
8		$\text{BF}_3 \cdot \text{OEt}_2$	41 (38)
9	 <b>11</b>	none	n.r.
10		$\text{BF}_3 \cdot \text{OEt}_2$	57 (25)
11	 <b>12</b>	none	n.r.
12		$\text{BF}_3 \cdot \text{OEt}_2$	70
13	 <b>13</b>	none	5 (81)
14		$\text{BF}_3 \cdot \text{OEt}_2$	62

<sup>a</sup>Reaction conditions c in Table 1. <sup>b</sup>Yields of isolated product; Yields in parentheses are for the recovered starting material.

In conclusion, we have shown the first example of the successful intermolecular radical addition to a wide range of aldoxime ethers which would provide a novel and general method for preparing not only alkoxyamines but also amines *via* the known route involving reductive cleavage of the N-O bond.<sup>4</sup>

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