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Triethylborane-Induced Intermolecular Radical Addition to Ketimines

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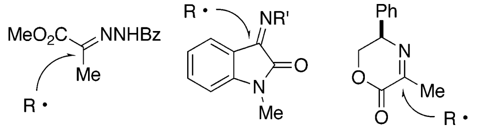
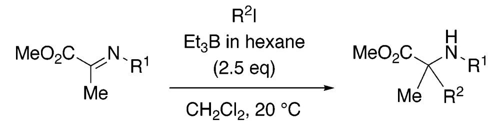


The intermolecular carbon radical addition to ketimines was investigated by using triethylborane as a radical initiator. The screening of reactive radical acceptors showed that pyruvic hydrazone **3** and isatin hydrazone **7** exhibit good reactivities toward nucleophilic alkyl radicals. The reaction of **3** and **7** proceeded effectively even under aqueous-medium reaction conditions. In the presence of $BF_3{\cdot}OEt_2$, the radical addition to chiral ketimine **11** proceeded with good diastereoselectivities.

Free radical reactions have developed as a powerful method for constructing the carbon−carbon bond.[1] The carbon−nitrogen double bond of imine derivatives has emerged as a radical acceptor.[2] Recently, the carbon−carbon bond formation based on intermolecular radical addition reactions of imines has been investigated.[3−9] However, the reaction of ketimines has not been widely studied;[10,11] thus, the screening of reactive ketimino acceptors is the new focus of our efforts.

SCHEME 1



1: R^1 = OBn
2: R^1 = NPh_2
3: R^1 = NHBz

4a: R^1 = NHBz, R^2 = Et
4b: R^1 = NHBz, R^2= *i*-Pr
4c: R^1 = NHBz, R^2 = c-Hexyl
4d: R^1 = NHBz, R^2 = *t*-Bu

Utimoto and Oshima were the first to apply the reaction of triethylborane with oxygen to initiate radical reactions.[12] Over other initiators, the triethylborane offers the great advantage of being efficient even under mild reaction conditions. Therefore, our laboratory is interested in developing the mild radical reaction of ketimines with triethylborane. Our recent studies showed that ketimines having a 2-phenolic hydroxyl group have excellent reactivities toward nucleophilic alkyl radicals.[13] In this paper, we now report the results of experiments to test the viability of several ketimines, having the *N*-heteroatom substituent stabilizing the intermediate aminyl radical or the *N*-alkyl group, in the intermolecular radical reactions.

As a preliminary study, the substrates of choice were ketimine derivatives **1**−**3** prepared from methyl pyruvate (Scheme 1), since an electron-deficient glyoxylic aldimine has shown an excellent reactivity toward nucleophilic carbon radicals in our previous work.[8] Among the different types of imino acceptors, the oxime ethers and hydrazones are well-known to be the excellent radical acceptors because of the stabilization of the intermediate aminyl radicals provided by the lone pair on the adjacent heteroatoms.[14] However, the triethylborane-induced radical addition to oxime ether **1** and *N*,*N*-diphenylhydrazone

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TABLE 1. Radical Addition to Ketimines 1−3[a]

entry	imine	R^2I (equiv)	time (min)	product	% yield (ratio)[b]
1	**1**	none	60		no reaction
2[c]	**1**	none	60		no reaction
3	**2**	none	60		no reaction
4	**3**	none	15	**4a**	82
5	**3**	*i*-PrI (15)	15	**4b**	75 (11:1)[d]
6	**3**	*i*-PrI (30)	15	**4b**	84 (20:1)[d]
7	**3**	c-Hexyl I (30)	15	**4c**	79 (15:1)[d]
8	**3**	*t*-BuI (15)	15	**4d**	89 (>30:1)[d]
9	**3**	*t*-BuI (30)	15	**4d**	90 (>30:1)[d]

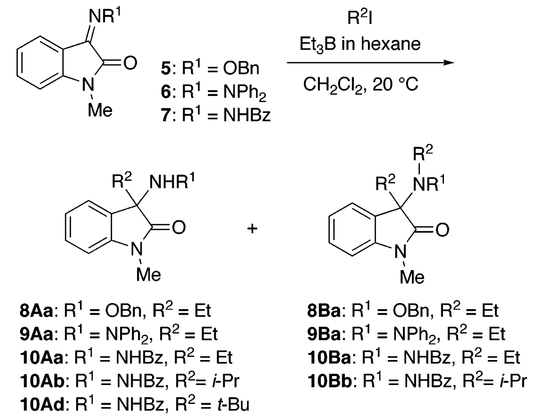
[a] Reactions were carried out using R^2I and 1.0 M Et_3B in hexane (2.5 equiv). [b] Isolated yields of the desired alkylated product. [c] The reaction was carried out in the presence of BF_3·OEt_2 (1 equiv). [d] Ratios for **4b**−**d**:**4a** determined by ^1H NMR analysis.

TABLE 2. Radical Addition to Ketimines 5−7

entry	imine	R^2I	Et_3B (equiv)	time (h)	product (% yield)[a]	ratio[b]
1[c]	**5**	none	2.5 equiv × 4	15	**8Aa** (50), **8Ba** (25)	
2[c]	**6**	none	2.5 equiv × 4	15	**9Aa** (21), **9Ba** (12)	
3[c]	**7**	none	2.5 equiv × 2	3	**10Aa** (41), **10Ba** (30)	
4[d]	**7**	*i*-PrI	2.5 equiv × 2	3	**10Ab** (53), **10Bb** (16)	>30:1
5[d]	**7**	*t*-BuI	2.5 equiv × 2	3	**10Ad** (72)	>30:1

[a] Isolated yields of the desired alkylated product. [b] Ratios for the desired alkylated products to ethylated products determined by ^1H NMR analysis. [c] Reactions were carried out using 1.0 M Et_3B in hexane. [d] Reactions were carried out using R^2I (30 equiv) and 1.0 M Et_3B in hexane.

SCHEME 2



2 did not proceed even in the presence of BF_3·OEt_2,[8b] probably due to the electron-donating property of the adjacent oxygen and nitrogen atoms (Table 1, entries 1−3). In marked contrast to **1** and **2**, the hydrazone **3** having an *N*-benzoyl group exhibited a good reactivity even in the absence of Lewis acids. All reactions were carried out in undegassed CH_2Cl_2 at 20 °C. The ethyl radical addition to hydrazone **3** with use of only 2.5 equiv of triethylborane proceeded effectively within 15 min to give an 82% yield of the desired product **4a** without the formation of significant byproducts (entry 4). In the case of the isopropyl radical addition reaction with isopropyl iodide (15 or 30 equiv), good yields of desired product **4b** were obtained, accompanied by a small amount of the ethylated product **4a** (entries 5 and 6). Under similar reaction conditions, cyclohexyl iodide worked well to give the desired product **4c** in 79% yield (entry 7). In comparison with secondary alkyl radicals, the reaction with more nucleophilic and stable *tert*-butyl radical afforded the desired product **4d** with excellent selectivities, due to the effective iodine atom transfer from *tert*-butyl iodide to ethyl radical (entries 8 and 9). These observations suggest that the electron-withdrawing property on the nitrogen atom of hydrazone increased the reactivity of the pyruvic C=N bond.

We next investigated the reaction of isatin imines **5**−**7** in CH_2Cl_2 at 20 °C (Scheme 2). Because of the lower reactivity of isatin imines **5**−**7**, triethylborane was added in portions as shown in Table 2 (2.5 equiv × 4 or × 2). In contrast to pyruvic oxime ether **1**, the isatin oxime ether **5** acted as a radical acceptor. The triethylborane-induced addition of an ethyl radical to oxime ether **5** proceeded slowly to afford the ethylated product **8Aa** in 50% yield and the *N*,*C*-diethylated product **8Ba** in 25% yield after the solution was stirred at 20 °C for 15 h (entry 1). However, the reaction of *N*,*N*-diphenylhydrazone **6** gave low yields of products **9Aa** and **9Ba**, along with a 30% yield of the recovered starting material **6** (entry 2). As expected, hydrazone **7** having an electron-withdrawing group exhibited good reactivity (entries 3−5). The reaction of **7** with an ethyl radical proceeded within 3 h to give the ethylated product **10Aa** in 41% yield and the *N*,*C*-diethylated product **10Ba** in 30% yield (entry 3). The radical precursors such as isopropyl iodide and *tert*-butyl iodide worked well without the formation of ethylated products **10Aa** and **10Ba** (entries 4 and 5). In the case of *tert*-butyl radical addition to **7**, the selective formation of monoalkylated product **10Ad** was observed (entry 5).

The reactions of a strictly neutral species such as uncharged free radicals are not affected by the presence of water.[15] In general, the reactions of water-sensitive imines have generally been performed in organic solvents under anhydrous reaction conditions. In connection with our program directed toward the development of the aqueous-medium radical reactions of aldimines,[16] the radical reaction of ketimines **3** and **7** has been investigated in aqueous media (Scheme 3). To a solution of hydrazone **3** in water/methanol (1:4, v/v) was added 1.0 M triethylborane in MeOH, and then the monophasic reaction mixture was stirred at 20 °C for 30 min. ^1H NMR measurement of the crude product showed almost quantitative conversion of **3** to the adduct **4a**, whereas the aqueous-medium reaction of pyruvic oxime ether **1** and

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SCHEME 3

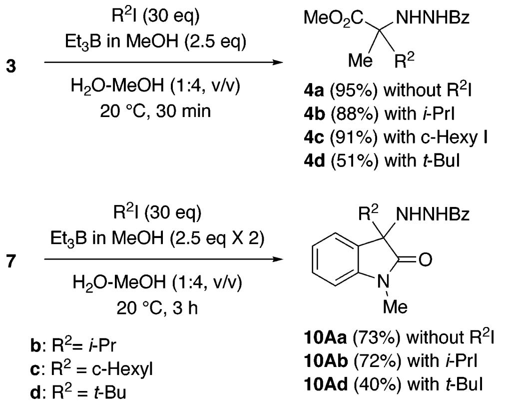
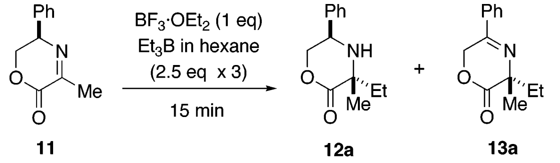


TABLE 3. Ethyl Radical Addition to Ketimine 11[a]

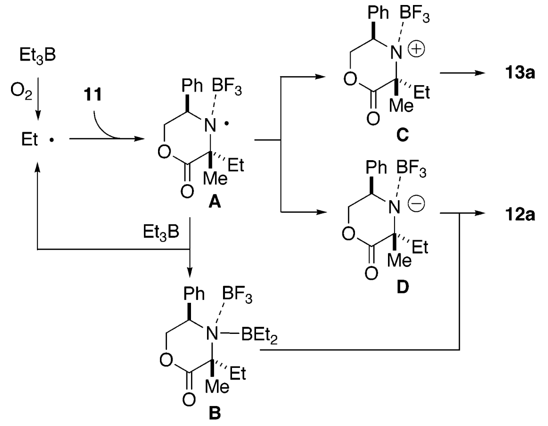
entry	solvent	*T* (°C)	yield (%)[b]	ratio[c] **12a**:**13a**	de (%)[d]
1	CH_2Cl_2	20	66 (6)	10:2	82
2	benzene	20	55 (16)	10:3	86
3	CH_2Cl_2	0	42 (22)	10:6	87
4	CH_2Cl_2	reflux	74	>10:1	81
5	benzene	40	55 (22)	>10:1	79

[a] Reactions were carried out using 1.0 M Et_3B in hexane (2.5 equiv × 3) under O_2 for 15 min. [b] Combined yields of **12a** and **13a**. Yields in parentheses are for the recovered starting material **11**. [c] Ratios for **12a**:**13a** determined by ^1H NMR analysis. [d] Diastereoselectivities were determined by ^1H NMR analysis.

SCHEME 4



SCHEME 5



pyruvic hydrazone **2** did not take place. The α,α-disubstituted amino acid derivative **4a** was obtained in 95% yield after purification by preparative TLC. In regard to the solvent effect, the replacement of $H_2O-MeOH$ by $H_2O-EtOH$ and H_2O-THF also gave good results. The aqueous-medium alkyl radical addition to **3** proceeded without any problem by using alkyl iodide (R^2I) and triethylborane. In contrast to the reaction of isatin hydrazone **7** in CH_2Cl_2 (Table 2, entries 3–5), the aqueous-medium reaction of **7** with an ethyl radical gave the monoethylated product **10Aa** with good chemical efficiency, along with a small amount of the diethylated product **10Ba**. The alkyl radical addition to **7** in water/methanol also gave the monoalkylated products **10Ab** and **10Ad** selectively.

Nothing has been known about the reactivity of simple ketimines having an *N*-alkyl group in the intermolecular radical reaction. To identify the reactivity of *N*-alkyl-substituted ketimines, we finally investigated the radical addition to cyclic ketimine **11** as a stable *N*-alkyl ketimine (Scheme 4). No reaction of **11** occurred in the absence of Lewis acids and 91% of the starting material **11** was recovered. In the presence of $BF_3 \cdot OEt_2$, the chiral ketimine **11** exhibited good reactivity toward the ethyl radical to give the desired ethylated product **12a** and the ethylated imine **13a**, along with a small amount of the recovered starting material **11** (Table 1, entries 1 and 2). The reaction of **11** under nitrogen gave the ethylated imine **13a** as the major product. Thus, the reactions were performed under oxygen, although the use of triethylborane under oxygen may induce fire and explosion. The absolute configuration at the newly formed stereocenter of the major isomer **12a** was determined to be *R* by direct comparison with (*R*)-**12a** prepared by the known reaction of **11** with Grignard reagent.[17] Although we studied the radical reaction of chiral imine having an isopropyl group instead of a phenyl group on **11**, the ethylated imine was still obtained. Therefore, the abstraction of an H-atom from the benzylic position of **11** by an ethyl radical is not the major reaction pathway addressing **13a**. The ethylated imine **13a** would be obtained from intermediate **C**, as a result of a disproportionation reaction of the intermediate radical **A** (Scheme 5). A similar disproportion reaction of intermediate aminyl radical is well-known in the reaction of nitrones.[8g] The ratio of the desired product **12a** to the ethylated imine **13a** was shown to be dependent on the reaction temperature (entries 3–5). Thus, the reaction in boiling CH_2Cl_2 afforded a good yield of **12a** with 81% de, accompanied by a trace of the ethylated imine **13a** (entry 4). A similar good ratio was observed in benzene at 40 °C (entry 5). After further investigations, the disproportionation reaction was found to be dependent on the amount of Et_3B; thus, the reaction with 1.0 equiv of triethylborane afforded a significant amount of **13a**, along with the recovered starting material **11**. These results indicate that triethylborane worked as not only a radical initiator but also a radical chain terminator to trap the intermediate radical **A** to give adduct **B** and a chain-propagating ethyl radical. Therefore, a large amount of triethylborane is required for suppressing the formation of the ethylated imine **13a**.

Finally, the reaction of **11** with an isopropyl radical was explored under iodine atom-transfer reaction conditions (Scheme 6). The isopropyl radical addition to **11** proceeded smoothly by using isopropyl iodide (30 equiv) in boiling CH_2Cl_2 to give the isopropylated product **12b** with 82% de, accompanied by a 15% yield of the isopropylated imine **13b**.

In conclusion, we have shown that pyruvic hydrazone **3**, isatin imines **5**–**7**, and chiral *N*-alkylated ketimine **11**

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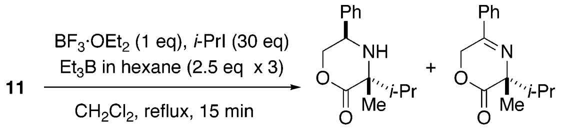
(17) Harwood: L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051.

SCHEME 6



12b (61%, 82% de) **13b** (15%)

exhibit good reactivities toward nucleophilic alkyl radicals to afford the corresponding alkylated products. In addition to the previously reported radical reaction of aldimines,[8,16] the reaction of ketimines disclosed a broader aspect of the utility of imine derivatives as a radical acceptor for the synthesis of amino compounds.

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Supporting Information Available: Experimental procedure and characterization data for all obtained compounds and ^{1}H and ^{13}C NMR spectra of all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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