ORGANIC LETTERS

2002
Vol. 4, No. 1
131−134

Indium-Mediated Intermolecular Alkyl Radical Addition to Electron-Deficient C=N Bond and C=C Bond in Water

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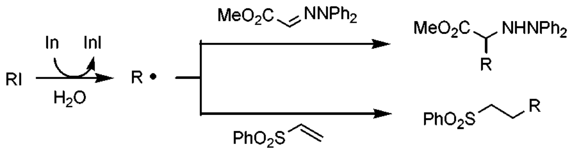
Received November 8, 2001

ABSTRACT



The intermolecular alkyl radical addition to imine derivatives was studied in aqueous media by using indium as a single-electron-transfer radical initiator. The one-pot reaction based on radical addition to glyoxylic hydrazone provided a convenient method for preparing the α-amino acids. The indium-mediated radical addition to an electron-deficient C=C bond also proceeded effectively to provide the new carbon–carbon bond-forming method in aqueous media.

Indium-mediated carbon−carbon bond-forming reactions in aqueous media have been of great importance from both economical and environmental points of view. Recently, numerous and useful indium-mediated allylation reactions of carbonyl compounds have been reported.[1] However, the corresponding reaction of imine derivatives has not been widely studied because of the lower electrophilicity of carbon−nitrogen double bond. Therefore, the development of indium-mediated reactions of imines in aqueous media has been a subject of current interest. Chan's group reported the first studies on the indium-mediated allylation of *N*-sulfonylimines in aqueous media.[2] These allylation reactions proceeded through an allylindium(I) intermediate, which reacts with the *N*-sulfonylimines, and thus, simple alkylation reactions were not investigated. As a part of our program directed toward the development of reactions of imines in aqueous media,[3,4] we now report the indium-mediated alkylation reactions of imine derivatives based on the alkyl radical addition to carbon−nitrogen double bond.

The carbon−nitrogen double bond has emerged as a radical acceptor, and thus several intermolecular radical addition reactions of imines were recently investigated in organic solvents.[5−7] Our recent studies show that imine derivatives such as oxime ethers, hydrazones, and nitrones are excellent water-resistant radical acceptors for the aqueous-medium reactions using triethylborane as a radical initiator.[3a]

On the basis of these results, we newly investigated the intermolecular radical addition to imine derivatives by using indium as a new radical initiator.[8,9] As a preliminary experi-

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(1) For a recent review, see: Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. For some examples of indium-mediated reaction, see: (a) Yang, Y.; Chan, T. H. *J. Am. Chem. Soc.* **2000**, *122*, 402. (b) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228. (c) Paquette, L. A.; Rothhaar, R. R. *J. Org. Chem.* **1999**, *64*, 217. (d) Woo, S.; Sqires, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573. (e) Engstrom, G.; Morelli, M.; Palomo, C.; Mitzel, T. *Tetrahedron Lett.* **1999**, *40*, 5967. (f) Loh, T.-P.; Zhou, J. R. *Tetrahedron Lett.* **1999**, *40*, 9115.

(2) (a) Lu, W.; Chan, T. H. *J. Org. Chem.* **2001**, *66*, 3467. (b) Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589. (c) Chan, T. H.; Lu, W. *Tetrahedron Lett.* **1998**, *39*, 8605. For examples of indium-mediated allylation of imines in organic solvents, see: (d) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronichi, A. *J. Org. Chem.* **1994**, *59*, 7766. (e) Beuchet, P.; Marrec, N. L.; Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959.

(3) (a) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043. (b) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071. We recently reported that *N*-sulfonylimines have shown the excellent reactivity toward nucleophilic carbon radical. See: (c) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059.

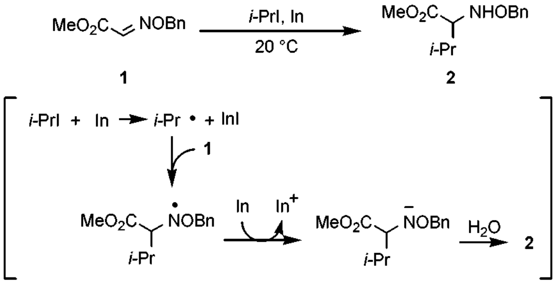
(4) For some selected examples, see: (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604. (b) Nakamura, T.; Yorimitsu, H.: Shinokubo, H.: Oshima, K. *Synlett* **1998**, 1351. (c) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anikumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157.

(5) For a recent review, see: Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461.

10.1021/ol017013h CCC: $22.00

ment, the substrates of choice were the glyoxylic oxime ether **1** and glyoxylic hydrazone **3** since they have shown excellent reactivity toward nucleophilic carbon radicals in our previous work on triethylborane-induced radical reactions.[3a] Additionally, we also expected that the direct comparison of indium-mediated reactions with triethylborane-induced reactions would lead to informative and instructive suggestions regarding indium as a single-electron-transfer radical initiator.

Scheme 1



We first investigated the reaction of glyoxylic oxime ether **1** under several reaction conditions (Scheme 1). To a biphasic solution of **1** and *i*-PrI (5 equiv) in $H_2O-CH_2Cl_2$ (4:1, v/v) was added indium (7 equiv), and then the reaction mixture was stirred at 20 °C for 22 h.[10] As expected, glyoxylic oxime ether **1** exhibits a good reactivity to give the desired isopropylated product **2** in 76% yield without formation of significant by-products such as a reduced product (Table 1, entry 1). It is important to note that practically no reaction of **1** occurred in the absence of water (entry 2). These results suggest that water would be important for the activation of indium and for the proton-donor to the resulting amide anion. In the case of monophasic reaction in $H_2O-MeOH$, the formation of isopropylated product **2** was observed after being stirred for only 0.5 h (entry 3).[11] In the presence of galvinoxyl free radical as a radical scavenger, the reaction did not proceed effectively (entry 4); thus, this reaction would proceed via the radical mechanism based on the single-electron transfer (SET) process from indium. However, an alternative mechanistic hypothesis involving addition of alkylindium species to the C═N bond would not be rigorously excluded, because it is possible that galvinoxyl free radical inhibited the non-radical reaction by scavenging radicals during the formation of the alkylindium species. In general, free radical synthetic methods largely rely on toxic organotin chemistry; therefore, the development of tin-free reactions including SET processes or atom-transfer and group-transfer processes has been of great importance in radical chemistry.[12] However, this indium-mediated reaction of **1** was slightly slower than the triethylborane-induced reaction of **1** in aqueous media shown in our recent report.[3a]

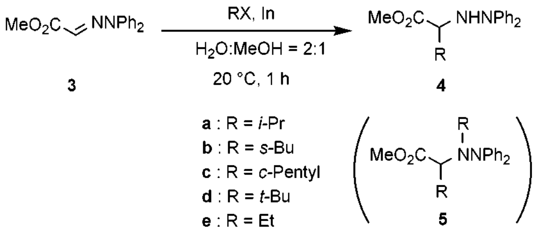
Table 1. Indium-Mediated Reaction of Glyoxylic Oxime Ether **1**

entry	solvent	time (h)	yield (%)
1[a]	$H_2O-CH_2Cl_2$ 4:1	22	76
2[a]	CH_2Cl_2	24	no reaction
3[b]	$H_2O-MeOH$ 2:1	0.5	74
4[c]	$H_2O-MeOH$ 2:1	0.5	no reaction

[a] Reactions were carried out with *i*-PrI (5 equiv) and indium (7 equiv). [b] Reaction was carried out with *i*-PrI (4 equiv × 2) and indium (7 equiv). [c] Reaction was carried out with galvinoxyl free radical (2 equiv), *i*-PrI (4 equiv × 2), and indium (7 equiv).

In our studies on the reactivity of several imine derivatives, we have found that the indium-mediated alkyl radical addition to glyoxylic hydrazone **3** is a highly promising approach to the synthesis of α-amino acids (Scheme 2 and Table 2). In the case of the aqueous-medium reactions of **3**

Scheme 2



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(6) For some examples, see: (a) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631. (b) Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138. (c) Kim, S.; Yoon, J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982. (d) Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190. (e) Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780. (f) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. (g) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. (h) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329. For some examples of our studies, see: (i) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922 (j) Miyabe, H.; Ushiro, C.; Naito, T. *Chem. Commun.* **1997**, 1789. (k) Miyabe, H.; Sibata, R.; Ushiro, C.; Naito, T. *Tetrahedron Lett.* **1998**, *39*, 631. (l) Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174. (m) Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569. (n) Miyabe, H.; Konishi C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443. (o) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176.

(7) For reviews on radical reactions, see: (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (b) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2563. (c) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301. (d) Curran, D. P.; Porter, N. A.; Giese, B. In *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996.

(8) Indium(I) iodide mediated radical cyclization was recently studied. See: (a) Cook, G. R.; Erickson, S.; Hvinden, M. *221th ACS National Meeting*, San Diego, April 1−5, 2001. Indium as a reducing agent, see: (b) Moody, C. J.; Pitts, M. R. *Synlett* **1998**, 1028. (c) Ranu, B. C.; Guchhait, S. K.; Sarkar, A. *Chem. Commun.* **1998**, 2113. (d) Ranu, B. C.; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1139. (e) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 3937. (f) Yadav, J. S.; Bandyopadhyay, A.; Reddy, B. V. S. *Tetrahedron Lett.* **2001**, *42*, 6385. Indium-mediated coupling reactions, see: (g) Araki, S.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 727. (h) Ranu, B. C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett.* **1998**, *39*, 9557. The use of indium trichloride, see: (i) Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2000**, *41*, 113. (j) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2001**, *42*, 4661.

(9) For the radical reaction using zinc as a radical initiator in water, see: (a) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149. (b) Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* **1992**, 441. (c) Erdmann, P.; Schäfer, J.; Springer, R.; Zeitz, H.-G.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 638.

Table 2. Alkyl Radical Addition to Glyoxylic Hydrazone **2**[a]

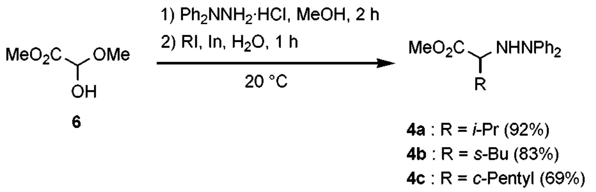
entry	RX	product	yield (%)
1	*i*-PrI	**4a**	98
2	*i*-PrBr	**4a**	no reaction
3	*s*-BuI	**4b**	90
4	*c*-pentyl I	**4c**	79
5	*t*-BuI	**4d**	48
6	EtI	**4e**	no reaction

[a] Reactions were carried out with RX (5 equiv × 2), indium (7 equiv), and H_2O in MeOH at 20 °C for 1 h.

using triethylborane, the undesired *C*- and *N*-dialkylated products **5** were only obtained as a result of the additional *N*-alkylation.[3a] In contrast, the indium-mediated alkyl radical addition to **3** gave selectively the desired *C*-monoalkylated products **4** with no detection of dialkylated products **5**. Not only a secondary alkyl but also the *tert*-butyl radical worked well to give **4a**−**d** in good yields after being stirred for 1 h (entries 1−5). However, the alkyl bromide such as *i*-PrBr and a less reactive primary ethyl iodide did not work (entries 2 and 6).

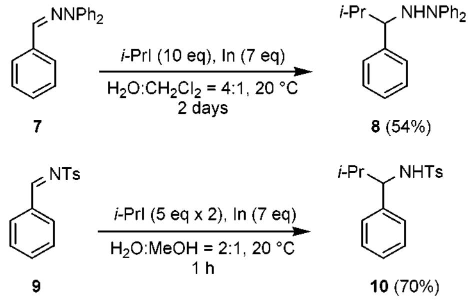
Integration of multi-step chemical reactions into one-pot reactions is of great significance as an environmentally benign method.[13] We next extended the indium-mediated reaction to the one-pot synthesis of α-amino acid derivatives (Scheme 3). Condensation of 2-hydroxy-2-methoxyacetic acid methyl ester **6** with *N*,*N*-diphenylhydrazine hydrochloride proceeded smoothly in MeOH to give **3** after being stirred at 20 °C for 2 h. Subsequently, alkyl iodide, In, and H_2O were added to the reaction vessel to afford good yields of α-amino acid derivatives **4a**−**c**.

Scheme 3



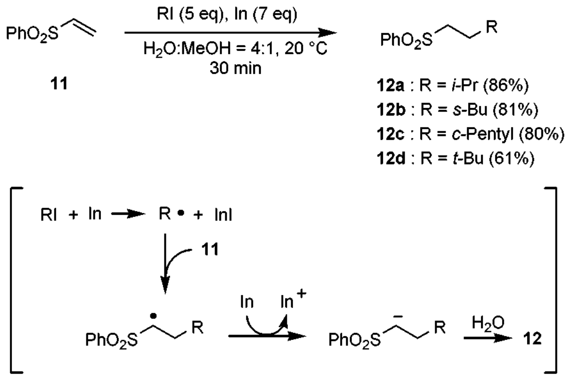
To survey the scope and limitations of the present method, we investigated the alkylation reaction of imines **7** and **9** prepared from benzaldehyde (Scheme 4). Although the reactivity of hydrazone **7** is not high, the biphasic reaction of **9** in $H_2O-CH_2Cl_2$ (4:1, v/v) proceeded to give **10** in 54% yield after being stirred for 2 days. The monophasic reaction of *N*-sulfonylimine **9** in H_2O−MeOH (2:1, v/v) proceeded effectively to give the desired isopropylated product **10** in 70% yield accompanied with 29% of $TsNH_2$ as a hydrolysis product after being stirred for only 1 h.[3c]

Scheme 4



To test the utility of indium as a single-electron transfer radical initiator, we next investigated the indium-mediated alkyl radical addition to electron-deficient C═C bond (Scheme 5). To a solution of phenyl vinyl sulfone **11** and RI (5 equiv) in MeOH were added indium (7 equiv) and H_2O, and then the reaction mixture was stirred at 20 °C for 30 min. As expected, **11** exhibits a good reactivity to give the desired alkylated products **12a**−**d** in good yields with no detection of by-products such as a reduced product. The reaction would proceed via the single-electron transfer process from indium as shown in Scheme 5.

Scheme 5



In conclusion, we have shown a new method for synthesis of α-amino acid derivatives based on the indium-mediated radical reaction of glyoxylic hydrazone. Since the known examples of indium-mediated carbon−carbon bond-forming reactions in aqueous media are mainly limited to allylation reactions, it is noteworthy that the newly found reaction involves the alkylation of imine derivatives. Additionally, the indium-mediated carbon−carbon bond-forming reactions

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(10) As a comparison, the triethylborane-induced reaction of **1** was usually run by using a large amount of alkyl iodides (more than 30 equiv) to suppress the competitive reaction with ethyl radical generated from triethylborane. See ref 3a.

(11) See Supporting Information for detail on the experimental procedures.

(12) We previously reported the radical reaction based on an iodine atom transfer process. See: Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465.

(13) We previously investigated the one-pot reactions via radical addition to oxime ethers. See: (a) Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* **2000**, *56*, 2413. (b) Miyabe, H.; Yamakawa, K.; Yoshioka, N.; Naito, T. *Tetrahedron* **1999**, *55*, 11209. (c) Miyabe, H.; Yoshioka, N.; Ueda, M.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3659.

based on the radical addition to electron-deficient C═C bond also proceeded smoothly in aqueous media.

Acknowledgment. We thank the Ministry of Education, Science, Sports and Culture of Japan and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants. H.M. gratefully acknowledges the financial support from Takeda Science Foundation and Fujisawa Foundation, Japan. This investigation was supported in part by The Mochida Memorial Foundation for Medical and Pharmaceutical Research (to H.M.).

Supporting Information Available: General experimental procedures and characterization data for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL017013H