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An Efficient One-Pot Synthesis of Unsymmetrical Ethers: A Directly Reductive Deoxygenation of Esters Using an $InBr_3/Et_3SiH$ Catalytic System

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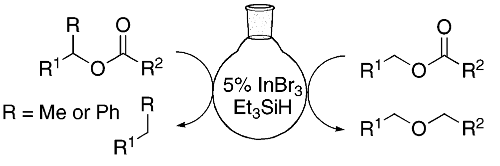

This study describes a novel one-pot procedure for a directly reductive conversion of the carbonyl function of esters to the corresponding ethers by Et_3SiH in the presence of a catalytic amount of $InBr_3$.

Previous methods for the preparation of ethers involved the reaction of an alkoxy anion with an alkyl halide/sulfonate under basic conditions (Williamson synthesis) and the acid-promoted dehydrogenate condensation of alcohols.[1] Since the 1960s, the representative preparation of ethers has been a direct reduction of a carbonyl function of esters and thioesters.[1] Although a number of protocols for the direct reduction of esters and thioesters have been developed, most were accomplished through treatment with stronger reducing agents, such as $LiAlH_4$[2] and DIBAL,[3] or a more toxic reagent, such as organotin hydride,[4] or by use of a complicated transition-metal complex.[5] In addition, these require γ-ray[6] or UV irradiation.[7] Thus, from the viewpoint of handling, workup, and environmental impact, development of a highly simple reductive procedure of esters, which proceeds under milder conditions, is needed. On the other hand, several groups have recently reported that a combination of a trivalent indium salt and a milder reducing reagent, a hydrosilane, is an effective reagent system for the reductive conversion of a functional group involving dehalogenation of organic halides, reduction of an alcohol, 1,4-reduction of enones, and reductive aldol reaction.[8] In this context, the reductive C−O bond cleavage of propargylic acetates using $InBr_3-Et_3SiH$ to produce an internal alkyne was demonstrated.[9] During ongoing investigations on the development of the selective deacetoxylation of several organic compounds using the $InBr_3-Et_3SiH$ system, remarkably it was found that, unlike our previous result,[9] the $InBr_3-Et_3SiH$ reducing system causes the reduction of the carbonyl function of esters under milder conditions, resulting in the preparation of unsymmetrical ethers.[10,11] Thus, we report herein on a further study of the present reductive procedure.

Initially, the reduction of phenethyl acetate (**1a**) with Et_3SiH in the presence of 0.05 equiv of $InBr_3$ as a model reaction was studied.[12] Table 1 shows the results of the search for optimized conditions. It was found that chloroform was the best solvent for this reaction (run 1). Benzene and toluene also showed a similar effect (runs 2 and 3). However, when the reaction was conducted in THF, the reaction did not proceed (run 4), and the use of acetonitrile also resulted in decreased yields (run 5). On the other hand, it was noted that when the similar reaction was carried out using $InCl_3$, $In(OAc)_3$, and $In(OTf)_3$, the desired ether product was not obtained, resulting in the recovery of the starting acetate (runs 6−8). Then, running this reaction with $(EtO)_3SiH$, instead of Et_3SiH, produced a low yield (run 9). In contrast, a reducing reagent, such as $PhMe_2SiH$, was effective for this reaction (run 10). Consequently, it was found that the combination of 0.05 equiv of $InBr_3$ and 4 equiv of Et_3SiH in chloroform gave the best results for the reaction.[13]

To generalize this reaction, the reduction of various esters **1** was carried out under optimized conditions with the reactions typically run at 60 °C in a $CHCl_3$ solution. The results are displayed in Table 2. In most cases, the reduction of esters with no relation to the length of the alkyl chain was completed in a

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[1] For selected reviews for the preparation of ethers, see: (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-VCH: New York, 1999. (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999.

[2] (a) Pettit, G. R.; Kasturi, T. R. *J. Org. Chem.* **1960**, *25*, 875. (b) Pettit, G. R.; Ghatak, U. R.; Green, B.; Kasturi, T. R.; Piatak, D. M. *J. Org. Chem.* **1961**, *26*, 1685. (c) Pettit, G. R.; Kasturi, T. R. *J. Org. Chem.* **1961**, *26*, 4553. (d) Pettit, G. R.; Piatak, D. M. *J. Org. Chem.* **1962**, *27*, 2127.

[3] Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.

[4] (a) Nicolaou, K. C.; Sato, M.; Theodorakis, E. A.; Miller, N. D. *J. Chem. Soc., Chem. Commun.* **1995**, 1583. (b) Jang, D. O.; Song, S. H.; Cho, D. H. *Tetrahedron* **1999**, *55*, 3479.

[5] (a) Raney-Ni: Baxter, S. L.; Bradshaw, J. S. *J. Org. Chem.* **1981**, *46*, 831. (b) Mn complex: Mao, Z.; Gregg, B. T.; Cutler, A. R. *J. Am. Chem. Soc.* **1995**, *117*, 10139. (c) Ti complex: Hansen, M. C.; Verdaguer, X.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 2360. (d) Ti−Si: Yato, M.; Homma, K.; Ishida, A. *Tetrahedron* **2001**, *57*, 5353. (e) Ru complex: Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem.* **2002**, *67*, 4985.

[6] Nakao, R.; Fukumoto, T.; Tsurugi, J. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 932 and references cited therein.

[7] (a) Baldwin, S. W.; Doll, R. J.; Haut, S. A. *J. Org. Chem.* **1974**, *39*, 2470. (b) Baldwin, S. W.; Haut, S. A. *J. Org. Chem.* **1975**, *40*, 3885.

[8] For selected papers of a reductive reaction using a combination of an indium(III) catalyst and a silane, see: (a) Miyai, T.; Ueba, M.; Baba, A. *Synlett* **1999**, 182. (b) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741. (c) Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 711. (d) Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985. (e) Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4981. (f) Miura, K.; Tomita, M.; Yamada, Y.; Hosomi, A. *J. Org. Chem.* **2007**, *72*, 787.

[9] Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2005**, *46*, 6407.

[10] Buchwald and Ohta groups reported titanocene- or rhodium-catalyzed reduction of esters with a silane producing the corresponding primary alcohols, respectively; see: (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751. (c) Barr, K. J.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 4323. (d) Ohta, T.; Kamiya, M.; Kusui, K.; Michibata, T.; Nobutomo, M.; Furukawa, I. *Tetrahedron Lett.* **1999**, *40*, 6963.

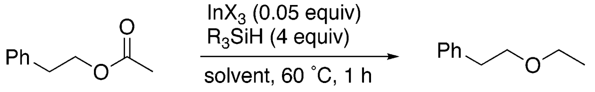
[11] Baba's group reported that an ester group is tolerant to the $InCl_3-Ph_2SiHCl$ system; see ref 8b.

[12] See details in Supporting Information.

[13] When the reaction was carried out using 2 and 3 equiv of Et_3SiH, the product **2a** was obtained in 67 and 91% yields, respectively. Using more than 3 equiv of Et_3SiH led to complete reduction.

10.1021/jo070814z CCC: \$37.00

TABLE 1. Examinations of Reaction Conditions



1a (1 equiv) **2a**

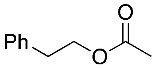
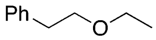
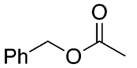
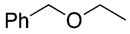
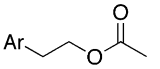
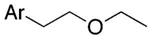
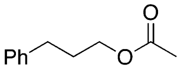
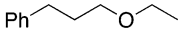
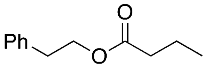
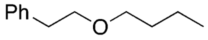
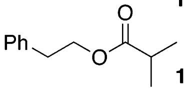
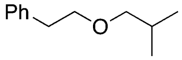
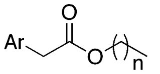
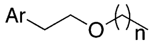
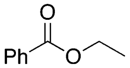
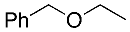
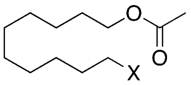
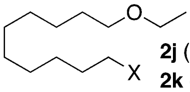
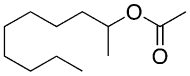
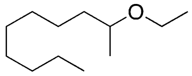
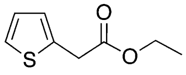
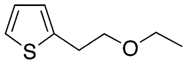
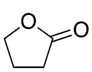
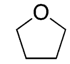
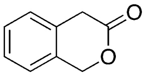
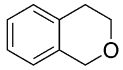
run	InX$_3$	R$_3$SiH	solvent	yield (%)[a]
1	InBr$_3$	Et$_3$SiH	CHCl$_3$	99
2	InBr$_3$	Et$_3$SiH	PhH	90
3	InBr$_3$	Et$_3$SiH	PhMe	85
4	InBr$_3$	Et$_3$SiH	THF	NR
5	InBr$_3$	Et$_3$SiH	MeCN	4
6	InCl$_3$	Et$_3$SiH	CHCl$_3$	NR[b]
7	In(OTf)$_3$	Et$_3$SiH	CHCl$_3$	trace[b]
8	In(OAc)$_3$	Et$_3$SiH	CHCl$_3$	NR[b]
9	InBr$_3$	(EtO)$_3$SiH	CHCl$_3$	10
10	InBr$_3$	PhMe$_2$SiH	CHCl$_3$	94

[a] GC yield based on an internal standard curve using isolated ether **2a**. [b] Average of two runs.

short time, producing the corresponding ethers **2** in good yields. Although more time was required for the reaction of the ester **1c** having a nitro group on the benzene ring to complete the reaction, it was found that the nitro group is tolerant toward the InBr$_3$–Et$_3$SiH system. A type of substituent next to the carbonyl group, other than the methyl group, could be extended to a linear carbon chain and to a branched carbon chain (entries 5 and 6). When the reaction with the ester **1g**, which reverses the location of the ester group, was carried out, the corresponding ether **2a** was also produced in excellent yield (entry 7). Moreover, a bromide substituent on a benzene ring was not affected by the reducing system (entry 8). By contrast, the reduction using the ester **1i** derived from benzoic acid was rather sluggish in the completion of the reaction (entry 9). On the other hand, the reduction using both the linear acetate **1j** derived from the primary alcohol and the branched acetate **1l** derived from the secondary alcohol gave the alkyl ethers **2j**,**l** in good yield, respectively (entries 10 and 12). Also, ester **1k** having a bromide substituent was chemoselectively converted to the corresponding ether **2k** in 73% yield, and it appeared that a halogen atom on a primary carbon is tolerant of the reducing reagent (entry 11). The reduction of a heteroaromatic ester containing a thiophene ring also reached 55% yield (entry 13). This method appeared to be a useful tool for the preparation of cyclic ethers **2n**,**o** under mild conditions (entries 14 and 15). This protocol appears to be a highly simple and practical method for preparation of a series of ether frameworks, the structure of which broadens in the central skeleton of fragrant compounds, such as perfumery and flavor.[14]

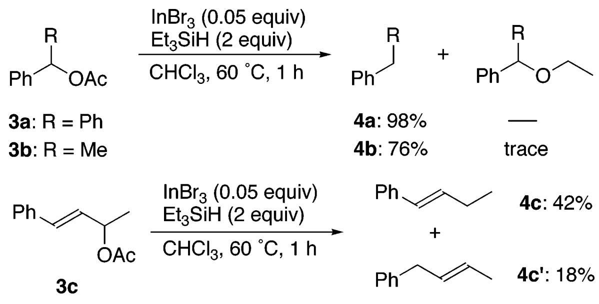
By contrast, when the reaction of the acetates **3a**,**b** derived from diphenylmethanol and α-methyl benzyl alcohol was carried out in the presence of 0.05 equiv of InBr$_3$ and 2 equiv of Et$_3$SiH at room temperature, the desired ether product did not form, but the deacetoxylation of the starting materials clearly occurred to produce diphenylmethane (**4a**) and ethylbenzene (**4b**) (Scheme 1). Similarly, the reaction using the ester having a conjugated olefin moiety produced β-ethylstyrene (**4c**) along with geometric isomer **4c′**. Thus, it was found that in the case of the acetoxy group on the secondary carbon bonding to a phenyl group or a conjugated double bond the deacetoxylation predominately proceeds.

TABLE 2. Reduction of Esters 1 Using the InBr$_3$–Et$_3$SiH System Leading to Ethers 2

entry	ester **1**		time (h)	ether **2**		yield (%)[a,b]
1		**1a**	< 1		**2a**	86 (99)
2		**1b**	< 1		**2b**	69
3		**1c**	3	 Ar = 4-NO$_2$-C$_6$H$_4$	**2c**	61
4		**1d**	4		**2d**	89
5		**1e**	2		**2e**	71
6		**1f**	1		**2f**	71
7	 **1g** (Ar = Ph, n = 1)		1		**2a**	89
8	**1h** (Ar = 4-Br-C$_6$H$_4$, n = 0)		6		**2h**	62
9		**1i**	6		**2b**	10
10		**1j**	1		**2j** (X = H)	77
11		**1k**	1		**2k** (X = Br)	73
12		**1l**	1		**2l**	69
13		**1m**	4		**2m**	55
14		**1n**	1		**2n**	53 (87)
15		**1o**	1		**2o**	84

[a] Isolated yield. [b] GC yield is in parenthesis.

SCHEME 1



Finally, to illustrate the utility of the present method, we examined the reduction of alternative types of carbonyl com-

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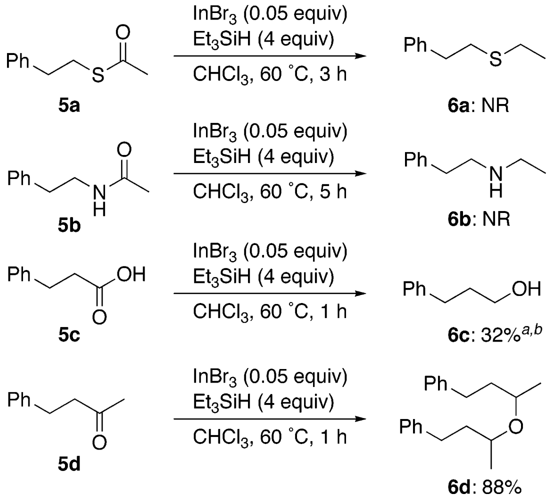
[14] Bokade, V. V. *Chem. Eng. Res. Des.* **2001**, *79*, 625.

SCHEME 2

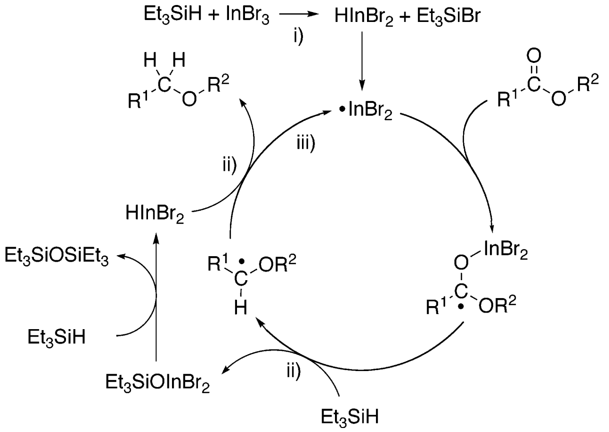


^{a} Average of two runs. ^{b}The silyl ether was also obtained in 36% yield.

pounds under optimal conditions, and the results are summarized in Scheme 2. For example, the reductive deoxygenation using thioacetate[15] **5a** and amide **5b** was examined. Unfortunately, the desired sulfide **6a** does not form nor does secondary amine **6b**. Although the $InBr_3-Et_3SiH$ system underwent the reduction of a carboxylic acid to produce the corresponding primary alcohol **6c** in 32% yield along with the silyl ether product,[16] treatment of ketone **5d** with the reducing system gave the corresponding symmetrical ether derivative **6d** in good yields.[17]

When 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO), a radical scavenger, was added to the reaction mixture containing ester **1a**, $InBr_3$, and Et_3SiH, the desired reduction was suppressed, and the starting ester was recovered. Thus, in situ generation of the indium radical species would play a key role in the promotion of this reductive process. A plausible mechanism for the reaction is shown in Scheme 3.[8f,18] The reaction path involves the following steps: (i) transmetalation between Et_3SiH and $InBr_3$ as an initial step, (ii) a consecutive abstraction of hydrogen by the radical intermediate and the formation of an ether product, and (iii) finally, the regeneration of an indium radical species. Accordingly, in case of the ester **1i** ($R^1 = Ph$), a resonance effect of the generated secondary (benzyl) radical with a benzene ring would hinder the hydrogen abstraction step, resulting in the sluggish reduction of the ester.

SCHEME 3



In conclusion, we demonstrated that the $InBr_3$ and Et_3SiH reagent system promotes direct and selective reduction of esters to produce corresponding unsymmetrical ethers. This simple catalytic system appeared to be remarkably tolerant to several functional groups and was applicable to the other functional groups, such as a carboxylic group. Further studies on the reduction of other types of functional groups are in progress.

Experimental Section

General Procedure for the Reduction of Esters Using the $InBr_3-Et_3SiH$ System. To a freshly distilled $CHCl_3$ solution (0.6 mL) in a screw-capped vial under N_2 atmosphere were added successively ester **1** (0.6 mmol), $InBr_3$ (10.6 mg, 0.0300 mmol), and Et_3SiH (380 μL, 2.40 mmol), and the vial was sealed with a cap containing a PTFE septum. During the stirring of the reaction mixture at 60 °C (bath temperature), the solution turned from colorless to yellow, then to orange. The reaction was monitored by GC analysis until consumption of the starting ester. After the reaction, H_2O (3 mL) was added, and the resulting orange suspension was stirred continuously until the disappearance of the color. The aqueous layer was extracted with CH_2Cl_2 (15 mL), the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and then evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2/hexane:AcOEt = 99:1) to give the corresponding ether **2**.

Ethyl Phenethyl Ether (2a): colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, 3H, $J = 7.5$ Hz), 2.90 (t, 2H, $J = 7.5$ Hz), 3.50 (q, 2H, $J = 7.5$ Hz), 3.63 (t, 2H, $J = 7.5$ Hz), 7.22 (m, 3H), 7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 36.4, 66.2, 71.6, 126.1, 128.3, 128.9, 139.0; MS (EI) *m/z* 150 (M^+), 105 (100%).

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Supporting Information Available: Detailed procedures and spectroscopic data for novel ether compounds, and copies of ^1H and ^{13}C NMR spectra for products prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070814Z

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