Bismuth Trichloride Catalyzed Efficient Reductive Etherification of Carbonyl Compounds with Alcohols: A Novel Method for Preparation of Symmetrical and Unsymmetrical Ethers

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The reductive homocoupling of a carbonyl compound and heterocoupling of a carbonyl compound with a non-protected alcohol were both effected smoothly at room temperature with triethylsilane in the presence of a catalytic amount of bismuth trichloride to afford the corresponding ethers in good yields.

The preparation of ethers is limited in practical sense to Williamson's etherification involving alkylation of an alkoxy anion with an alkyl halide under basic conditions. However, olefin formation sometimes occurs under these basic conditions, thus it is desired to develop a useful method for the synthesis of symmetrical and unsymmetrical ethers under non-basic conditions.

Suzuki and we have shown that bismuth bromide can efficiently catalyze the cyanation of carbonyl compounds and acetals.[1] Komatsu and Suzuki described the catalytic utility of this salt for the reductive homocoupling of carbonyl compounds and heterocoupling of a carbonyl compound with an alkoxysilane by using triethylsilane to afford the corresponding symmetrical and unsymmetrical ethers, respectively.[2] Although similar etherifications of carbonyl compounds with alkoxysilanes[3,4] or alcohol THP ethers[5] via trialkylsilane reduction have already been developed, there are few methods which involve a simple process using non-protected alcohols.[6]

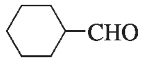
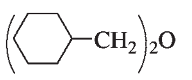
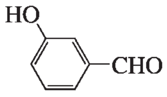
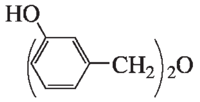
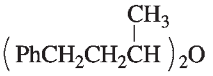
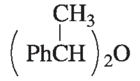
We now wish to report a convenient method for preparation of symmetrical and unsymmetrical ethers from aldehydes and aldehydes—non-protected alcohols, respectively, by the promotion of triethylsilane (Et_3SiH) and bismuth trichloride ($BiCl_3$).

$$R^1COR^2 + Et_3SiH \xrightarrow[CH_2Cl_2,\ r.t.]{cat.\ BiCl_3} R^1R^2CHOCHR^1R^2 \quad (1)$$

$$R^1COR^2 + R^3OH + Et_3SiH \xrightarrow[CH_2Cl_2,\ r.t.]{cat.\ BiCl_3} R^1R^2CHOR^3 \quad (2)$$

Similarly to the results obtained by Suzuki,[2] various symmetrical ethers are synthesized under mild reaction conditions as shown in the eq 1. Some of the results are summarized in Table 1. Benzaldehyde (Entry 1) and aliphatic aldehydes (Entries 2 and 3) reacted smoothly to afford the corresponding symmetrical ethers in good yields. As for ketones, sterically hindered one (Entry 7) afforded only a trace of the expected ether, and the starting ketone was recovered. It is noteworthy that the corresponding symmetrical ether was obtained from 3-hydroxybenzaldehyde without the protection of the hydroxyl group. As shown in Table 2, various aldehydes coupled smoothly with primary and secondary alcohols in good yields (Entries 1–12), while ketones gave the coupling products in low yields as the ketones were recovered (Entries 13–15).[7] The benzaldehyde–phenol reaction gave no product and *tert*-butyl alcohol could not be used at all as a substrate.

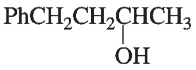
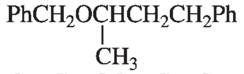
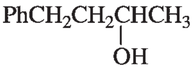
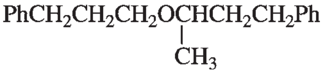
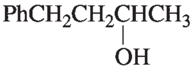
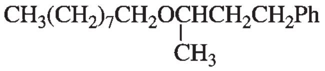
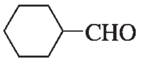
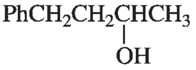
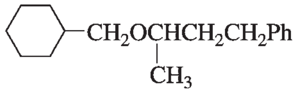
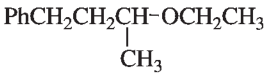
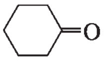
Table 1. Ether synthesis using carbonyl compounds and Et_3SiH in the presence of $BiCl_3$[a]

Entry	Carbonyl compound	Product[b]	Yield / %[c]
1	PhCHO	$(PhCH_2)_2O$	87
2	$PhCH_2CH_2CHO$	$(PhCH_2CH_2CH_2)_2O$	90
3			85
4			90
5	$PhCH_2CH_2COCH_3$	 $(PhCH_2CH_2CH(CH_3))_2O$	50
6	$CH_3CH_2CH_2CH_2COCH_3$	 $(CH_3CH_2CH_2CH_2CH(CH_3))_2O$	29
7	$PhCOCH_3$	 $(PhCH(CH_3))_2O$	Trace

[a] The reaction was carried out at room temperature using a carbonyl compound (2.0 mmol), Et_3SiH (2.6 mmol), and $BiCl_3$ (0.22 mmol) in CH_2Cl_2 (5 ml). [b] All the products gave satisfactory IR and ^1H NMR spectra, and some products were also identified by comparison with authentic samples. [c] Isolated yields are given.

Our results indicate several synthetic utilities of the present reaction: 1) It is noteworthy that equimolar amount of aldehydes and non-protected alcohols give the high yields of the corresponding ethers with Et_3SiH and $BiCl_3$ under mild conditions. 2) This is a convenient method for the preparation of various alcohols protected by synthetic useful protecting group. a) By the use of benzyl alcohol, benzaldehyde is reductively converted to dibenzyl ether (Table 2, Entry 3). b) When benzaldehyde is employed as a carbonyl component, alcohols are directly transformed to the corresponding benzyl ethers (Table 2, Entries 1–5 and Entry 16). 3) Reductive etherification of benzaldehyde proceeds chemoselectively with 3-phenyl-1-propanol (80% yield) even if acetophenone is present in the reaction mixture, and acetophenone is recovered intact. 4) An aldehyde containing a hydroxyl group (Table 1, Entry 4) and an alcohol containing a carboxyl group (Table 2, Entry 16) are usable as a substrate without a protection of their functional groups, which contribute to the overall synthetic efficiency because the tedious protection–deprotection process can be

Table 2. Ether synthesis using carbonyl compounds and alcohols by $BiCl_3$ and Et_3SiH[a]

Entry	Carbonyl compound	Alcohol	Product[b]	Yield / %[c]
1	PhCHO	CH_3CH_2OH	$PhCH_2OCH_2CH_3$	74
2	"	$CH_3(CH_2)_8OH$	$PhCH_2O(CH_2)_8CH_3$	95
3	"	$PhCH_2OH$	$(PhCH_2)_2O$	80
4	"	$PhCH_2CH_2CH_2OH$	$PhCH_2OCH_2CH_2CH_2Ph$	93
5	"	 $PhCH_2CH_2\underset{OH}{\underset{\mid}{C}}HCH_3$	 $PhCH_2O\underset{CH_3}{\underset{\mid}{C}}HCH_2CH_2Ph$	82
6	$PhCH_2CHO$	$PhCH_2CH_2CH_2OH$	$PhCH_2CH_2OCH_2CH_2CH_2Ph$	61
7	$PhCH_2CH_2CHO$	"	$(PhCH_2CH_2CH_2)_2O$	73
8	"	 $PhCH_2CH_2\underset{OH}{\underset{\mid}{C}}HCH_3$	 $PhCH_2CH_2CH_2O\underset{CH_3}{\underset{\mid}{C}}HCH_2CH_2Ph$	69
9	$CH_3(CH_2)_7CHO$	$PhCH_2CH_2CH_2OH$	$CH_3(CH_2)_7CH_2OCH_2CH_2CH_2Ph$	63
10	"	 $PhCH_2CH_2\underset{OH}{\underset{\mid}{C}}HCH_3$	 $CH_3(CH_2)_7CH_2O\underset{CH_3}{\underset{\mid}{C}}HCH_2CH_2Ph$	64
11		$PhCH_2CH_2CH_2OH$		77
12	"	 $PhCH_2CH_2\underset{OH}{\underset{\mid}{C}}HCH_3$		70
13	$PhCH_2CH_2COCH_3$	CH_3CH_2OH	 $PhCH_2CH_2\underset{CH_3}{\underset{\mid}{C}}H\text{-}OCH_2CH_3$	24
14	$PhCOCH_3$	$PhCH_2CH_2CH_2OH$	 $Ph\underset{CH_3}{\underset{\mid}{C}}H\text{-}OCH_2CH_2CH_2Ph$	29
15		$PhCH_2CH_2CH_2OH$		38
16	PhCHO	$HOOC(CH_2)_{11}OH$	$HOOC(CH_2)_{11}OCH_2Ph$	75

[a] The reaction was carried out as described in the text. [b] All the products gave satisfactory IR and ^1H NMR spectra, and some products were also identified by comparison with authentic samples. [c] Isolated yields are given.

simplified.

The mechanism of the present reaction is considered *via* hemiacetal[6] or hemiacetal-type[3] compound as described in the literature. In conclusion, we have developed a new convenient method for the preparation of ethers from carbonyl compounds and non-protected alcohols under non-basic conditions.

References and Notes

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6 a) Synthesis of ethers by the reduction of aldehydes and ketones by triethylsilane in alcoholic acidic media has been reported. However, a molar excess of sulfuric acid or trifluoroacetic acid to aldehydes and ketones is used in an excess of alcohols. M. P. Doyle, D. J. Debruyn, and D. A. Kooistra, *J. Am. Chem. Soc.*, **94**, 3659 (1972). b) It was reported that exposure of hydroxy ketones to excess Et_3SiH and TMSOTf resulted in the formation of oxepane. K. C. Nicolaou, C. K. Hwang, and D. A. Nugiel, *J. Am. Chem. Soc.*, **111**, 4136 (1989).

7 A typical procedure for the synthesis of benzyl 3-phenylpropyl ether by the benzaldehyde—3-phenyl-1-propanol reaction is described as follows: Bismuth trichloride (73.0 mg, 0.23 mmol) was placed in a 50 ml two-necked flask and dried in vacuo by heating. CH_2Cl_2 (5 ml) was added under nitrogen and to the resulting suspension were added benzaldehyde (104.7 mg, 0.99 mmol) and 3-phenyl-1-propanol (162.3 mg, 1.20 mmol) using a syringe. Then Et_3SiH (163.0 mg, 1.4 mmol) was added and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution, and the organic materials were extracted with Et_2O (20 ml × 3). After drying the ether layer over anhydrous Na_2SO_4, the solvent was evaporated in vacuo. The residue was purified by thin layer chromatography on silica gel (hexane:ethyl acetate = 10 : 1) to give benzyl 3-phenylpropyl ether (195.7 mg, 93%).