An Efficient Method for the Ether Forming Reaction between Alkyl Diphenylphosphinate and Alkoxytrimethylsilane by the Promotion of Trimethylsilyl Triflate

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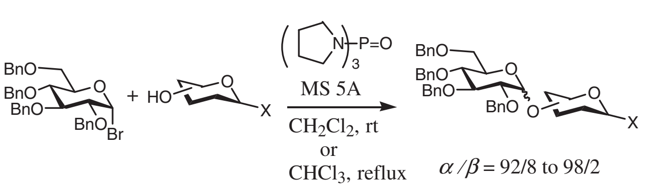
(Received August 6, 2004; CL-040929)

The trimethylsilyl triflate promoted reactions of alkyl diphenylphosphinates with alkoxytrimethylsilanes in chloroform, 1,2-dichloroethane or 1,2-dichloropropane, proceeded smoothly to give the corresponding ethers in good yields.

A number of methods have been reported for etherification of alcohols after the Williamson's method of using alkyl halide and metal alkoxide was reported.[1] In these methods, strong bases such as sodium hydride are used for generating alkoxy anions from alcohols except for the case of reactive substrates like benzyl alcohol.[2] Therefore, development of a new and efficient etherification reaction to be carried out under mild condition is one of the most challenging and important topics in organic synthesis.

Very recently, it was shown from our group that phosphine oxide effectively promoted stereoselective glycosylation reactions (Scheme 1).[3] It is noteworthy that phosphine oxide attacks glycosyl halide to form a reactive phosphonium salt intermediate that immediately reacts with glycosyl acceptors to afford the corresponding α-glycosides effectively. In order to apply this unique nucleophilic character of phosphine oxide to form the highly reactive phosphonium salt, a new carbon–oxygen bond forming reaction by using the phosphonium salt generated from alkyl diphenylphosphinate and Lewis acid was planned.

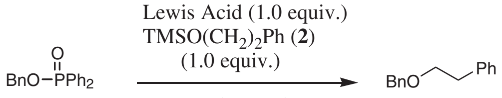


Scheme 1. Glycosylation of several acceptors with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl bromide promoted by tri(1-pyrrolidino)phosphine oxide.

In this communication, we would like to report an efficient method for carbon–oxygen bond forming reaction by using alkyl diphenylphosphinate and alkoxytrimethylsilane in the presence of trimethylsilyl triflate as a promoter.

In the first place, the reaction of benzyl diphenylphosphinate (**1**) and trimethyl(2-phenylethoxy)silane (**2**) by using various Lewis acids in dichloromethane at room temperature was tried (Table 1). The use of iodotrimethylsilane that is known to react readily with triphenylphosphine oxide[4] resulted in the formation of benzyl iodide in 45% yield (Table 1, Entry 1). On the other hand, no reaction took place when powerful Lewis acids such as $AlCl_3$ and $TiCl_4$, a mild one such as $MgBr_2OEt_2$ and transition metal triflates were used (Table 1, Entries 2–13). It was interesting to note that the desired benzyl 2-phenylethyl ethers (**3**) were obtained in moderate yields when trialkylsilyl triflates were used as Lewis acids (Table 1, Entries 14–17). Studies on solvent effects and ratios of substrates and trimethylsilyl triflate showed that the desired **3** was afforded in 70% yield when 1.2 equiv. of **2** and 1.0 equiv. of **1** were allowed to react in the presence of 1.0 equiv. of trimethylsilyl triflate in chloroform (Table 1, Entry 19) while the yield remained low when 2-phenylethyl alcohol instead of **2** was used in the presence of trimethylsilyl triflate (Table 1, Entry 20).

Table 1. Reactions of benzyl diphenylphosphinate (**1**) and trimethyl-(2-phenylethoxy)silane (**2**) in the presence of various Lewis acids



1 **3**

Entry	Lewis Acid	Yield/%	Entry	Lewis Acid	Yield/%
1	TMSI	N.D.[a]	11	$Sc(OTf)_3$	N.R.
2	BF_3OEt_2	N.R.	12	$Hf(OTf)_4$	N.R.
3	$AlCl_3$	N.R.	13	$Yb(OTf)_3$	N.R.
4	$TiCl_4$	N.R.	14	TMSOTf	51
5	$MgBr_2OEt_2$	N.R.	15	TIPSOTf	49
6	$ZnCl_2$	N.R.	16	TESOTf	52
7	$Zn(OTf)_2$	N.R.	17	TBSOTf	53
8	$Cu(OTf)_2$	N.R.	18[b]	TMSOTf	58
9	$SnCl_4$	N.R.	19[b,c]	TMSOTf	**70**
10	$Sn(OTf)_2$	N.R.	20[d]	TMSOTf	8

[a]45% of BnI was obtained. [b]The reaction was performed in chloroform. [c]1.2 equiv. of **2** was used. [d]2-Phenylethylalcohol was used in chloroform instead of **2**.

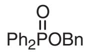
Next, etherifications of alkyl diphenylphosphinates and alkoxytrimethylsilanes were tried (Table 2). When trimethylsilyl triflate was treated with benzyl diphenylphosphinate and trimethyl(2-phenylethoxy)silane, benzyloxytrimethylsilane, or trimethyl(1-methyl-2-phenylethoxy)silane, the reactions proceeded smoothly at room temperature to afford the corresponding benzyl ether derivatives (Table 2, Entries 1–3). The etherification of using 3-phenylpropyl diphenylphosphinate or 2-phenoxyethyl diphenylphosphinate proceeded in 1,2-dichloroethane or 1,2-dichloropropane at refluxing temperature (Table 2, Entries 5–7). When (*S*)-1-phenyethyl diphenylphosphinate was used, the reaction proceeded more rapidly and completed at 0 °C to afford racemic products within several hours, indicating that this reaction proceeded by S_N1 mechanism (Table 2, Entries 8–10). The use of less reactive D-menthyl diphenylphosphinate, on the other hand, did not afford the desired ether product (Table 2, Entry 11).

Table 2. Reaction of alkyl diphenylphosphinate and alkoxyltrimethylsilane in the presence of TMSOTf

$$\underset{(1.0\text{ equiv.})}{\mathrm{Ph_2P(=O)OR}} + \underset{(1.2\text{ equiv.})}{\mathrm{R'OTMS}} \xrightarrow[\mathrm{CHCl_3}]{\text{TMSOTf (1.0 equiv.)}} \mathrm{ROR'}$$

Entry	$Ph_2P(=O)OR$	R′OTMS	Temp.	Time	Yield/%
1	**1**	**2**	rt	4 h	70
2	**1**	**8**	rt	4 h	74
3	**1**	**9**	rt	4 h	69
4	**1**	**10**	rt	4 h	63
5[a]	**4**	**2**	reflux	12 h	80
6[b]	**4**	**9**	reflux	12 h	68
7[a]	**5**	**2**	reflux	12 h	71
8	**6**	**2**	−60 °C → 0 °C	2 h	82[c]
9	**6**	**8**	−60 °C → 0 °C	3 h	90[c]
10	**6**	**10**	−60 °C → 0 °C	3 h	59[c]
11[1]	**7**	**2**	reflux	11 h	N.D.

[a] 1,2-Dichloropropane was used as a solvent. [b] 1,2-Dichroloethane was used as a solvent. [c] Racemic product was obtained.



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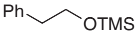

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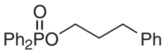

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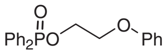

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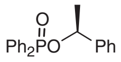

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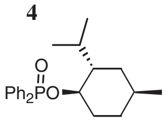

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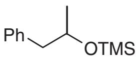
BnOTMS

8



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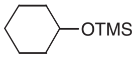

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The present reaction is assumed to proceed via the reactive phosphonium triflate intermediate generated by the activation of oxygen atom of alkyl diphenylphosphinate with TMSOTf. Then, the S_N1 attack of alkoxytrimethylsilane to the carbon atom of the alkoxy phosphonium triflate afforded the corresponding ether and a complex of diphenylphosphinic acid trimethylsilyl ester and TMSOTf, that is easily separated by washing with sat. $NaHCO_3$ solution.

The typical experimental procedure is described for the reaction of **1**[5] and **2** (Table 2, Entry 1): to a stirred mixture of **1** (0.0621 g, 0.201 mmol) and **2** (0.0469 g, 0.241 mmol) in chloroform (1 mL) was added trimethylsilyl triflate (36.2 μL, 0.196 mmol) at 0 °C. The mixture was stirred for 4 h at room temperature and then quenched with sat. $NaHCO_3$. After the resulting mixture was extracted with dichloromethane, dried over $MgSO_4$, filtered and evaporated, it was purified by preparative TLC (silica gel, THF/*n*-Hex = 25/1) to give the desired benzyl 2-phenylethyl ether (**3**) (0.0299 g, 70%) as a colorless oil.

Thus, etherification between alkyl diphenylphosphinate and alkoxytrimethylsilane proceeded successfully to afford the corresponding ether in good yield by promoting with trimethylsilyl triflate. This reaction is quite practical because alkyl diphenylphosphinates are prepared easily from the corresponding alcohols and diphenylchlorophosphinate often as white crystals in the presence of triethylamine. Moreover, diphenylphosphinic acid trimethylsilyl ester, a co-product, is easily separated by washing with saturated $NaHCO_3$ solution.

This study was supported in part by the Grant of the 21st Century COE Program, Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

References and Notes

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