An Efficient Method for Alkylation of Alcohols with Alkyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidates

Hidenori Aoki[†,††] and Teruaki Mukaiyama*[†,††]
[†]*Center for Basic Research, The Kitasato Institute, 6-15-5 (TCI), Toshima, Kita-ku, Tokyo 114-0003*
[††]*Kitasato Institute for Life Sciences, Kitasato University, 5-9-1, Shirokane, Minato-ku, Tokyo 108-8641*

(Received April 5, 2005; CL-050450)

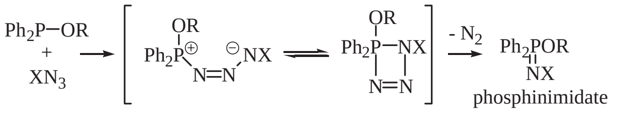
Alkyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidates, easily prepared from alkyl diphenylphosphinites and methanesulfonyl azide, are used as a useful reagent for O-alkylation of alcohols in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf).

Alkylation of alcohols is one of the most fundamental and frequently used important reactions in synthetic organic chemistry. A number of approaches to the preparation of ethers have been reported since the method of using alkyl halide and metal alkoxide was reported by Williamson in 1850.[1] Recently, various new methods for the ether synthesis using phosphorus compounds such as alkyl diphenylphosphinites[2] or alkyl diphenylphosphinates[3] were reported from our laboratory. Further, it is important to develop a useful method of alkylation of alcohols under even milder conditions for the preparation of ethers.

In the Staudinger reaction, phosphines (R_3P) were shown to react with azide compounds to form iminophosphoranes ($R_3P{=}NX$) along with a loss of nitrogen.[4] Likewise, alkyl diphenylphosphinites ($ROPPh_2$),[5] prepared from alcohols and chlorodiphenylphosphine, reacted with azide compounds to give phosphinimidates (Scheme 1).[6] Although there is an expectation for the phosphinimidates to work as good alkylating agents like alkyl diphenylphosphinates,[3] few reports have been introduced concerning alkylation of alcohols with phosphinimidates except for the glycosylation reaction in carbohydrate chemistry.[7] Here, we would like to show the high-yielding preparation of ethers by using alcohols and stable alkyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidates, prepared from alkyl diphenylphosphinites and methanesulfonyl azide, in the presence of Me_3SiOTf.

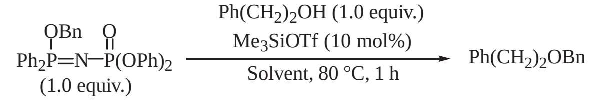
In the first place, the benzylation reaction of 1.0 equiv. of 2-phenylethyl alcohol was tried by using 1.0 equiv. of benzyl *P*,*P*-diphenyl-*N*-(diphenylphosphoryl)phosphinimidate, prepared from benzyl diphenylphosphinite and commercially available diphenylphosphoryl azide, in 1,2-dichloroethane. However, the expected product was not obtained and both the phosphinimidate and the alcohol were thus recovered quantitatively (Table 1, Entry 1). When 10 mol % of Me_3SiOTf was used as an activator, on the other hand, the corresponding ether was obtained in 16% yield (Entry 2). After screening several solvents, 1,2-dimethoxyethane was found to have the most suitable effect (Entries 3–7).

Next, the effect of the substituent of phosphinimidate was examined. When two phenyl groups on the phosphorus atom were replaced by two isopropyl groups, the yield decreased, whereas the yield increase up to 77% was observed when a diphenylphosphoryl group on the nitrogen atom was replaced by a benzoyl group (Table 2, Entris 1–3). In the case of the phosphinimidate having more an electron-withdrawing *p*-toluenesulfonyl or methanesulfonyl group[8] than a benzoyl group was used, the desired product was obtained in 89% and 93% yields, respectively (Entries 4 and 5).



Scheme 1.

Table 1. Effect of solvent on benzylation of 2-phenylethyl alcohol



$$\underset{(1.0\ \text{equiv.})}{Ph_2P(OBn){=}N{-}P(O)(OPh)_2} \xrightarrow[\text{Solvent, 80 °C, 1 h}]{\begin{array}{c}Ph(CH_2)_2OH\ (1.0\ \text{equiv.})\\ Me_3SiOTf\ (10\ \text{mol\%})\end{array}} Ph(CH_2)_2OBn$$

Entry	Solvent	Yield/%	Entry	Solvent	Yield/%
1[a]	EDC[b]	N.R.	5	1,4-Dioxane	54
2	EDC	16	6	DME[c]	55
3	Toluene	27	7	Acetonitrile	7
4	THF	33			

[a]The reaction was carried out without Me_3SiOTf. [b]1,2-Dichloroethane. [c]1,2-Dimethoxyethane.

Table 2. Effect of substituents of phosphinimidate on benzylation of 2-phenylethyl alcohol

$$\underset{(1.0\ \text{equiv.})}{R_2P({=}NX)OBn} \xrightarrow[\text{DME, 80 °C, 1 h}]{\begin{array}{c}Ph(CH_2)_2OH\ (1.0\ \text{equiv.})\\ Me_3SiOTf\ (10\ \text{mol\%})\end{array}} Ph(CH_2)_2OBn$$

Entry	R	X	Yield/%
1	Ph	$(PhO)_2P(O)$	55
2	*i*-Pr	$(PhO)_2P(O)$	38
3	Ph	Bz	77
4	Ph	Ts	89
5	Ph	Ms	93

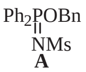
Alkylation of several alcohols with alkyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidates was tried next (Table 3). As a result, etherification of the alcohols having alkali- or acid-sensitive groups was found to proceed smoothly to afford the corresponding ethers in high yields in the presence of a catalytic amount of Me_3SiOTf, while the desired ether was not afforded when less reactive L-menthyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidate was used (Entry 11). In the case with ethyl (*S*)-(−)-lactate, the corresponding benzyl ether was exclusively obtained without accompanying any epimerization (Entry 3). Contrary to the above result, a racemic product was obtained when (*S*)-1-phenylethyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidate was reacted with 2-phenylethy alcohol or 2-methyl-4-phenyl-2-butanol, respectively (Entries 9 and 10).

Table 3. Alkylation of alcohols with alkyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidates and Me_3SiOTf

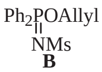
$$\underset{(1.0\ \text{equiv.})}{Ph_2P(=NMs)OR} + \underset{(1.0\ \text{equiv.})}{R^1OH} \xrightarrow[\text{DME, rt, Time}]{Me_3SiOTf} ROR^1$$

Entry	$Ph_2P(=NMs)OR$	R^1OH	Me_3SiOTf /mol %	Time /h	Yield /%
1[a]	**A**	**1**	10	1	95
2	**A**	**2**	10	3	94
3	**A**	**3**	10	3	88
4	**A**	**4**	10	3	77
5	**A**	**5**	10	3	73
6	**B**	**4**	10	24	72[b]
7	**C**	**1**	20	24	55
8	**D**	**1**	20	24	57
9	**E**	**1**	1	0.5	85[c]
10	**E**	**6**	1	0.5	83[c]
11	**F**	**1**	30	24	N.D.

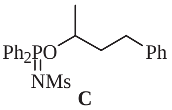
[a] The desired ether was obtained in 91% yield when TfOH was used instead of Me_3SiOTf. [b] 1.2 equivalent of the phosphinimidate was used. [c] Racemic product was obtained.



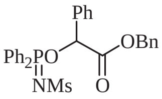
A



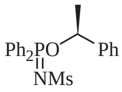
B



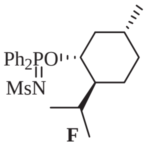
C



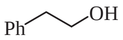
D



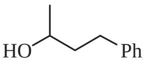
E



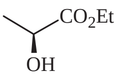
F



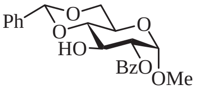
1



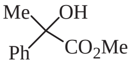
2



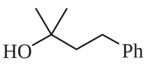
3



4



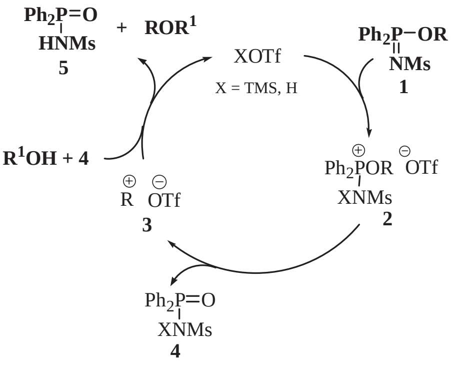
5



6

A proposed reaction mechanism is shown in Scheme 2: in the first step, alkyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidate **1** is silylated or protonated to yield the alkyl cation **3** which is a very reactive electrophile and reacts rapidly with alcohols to form ethers along with *N*-methanesulfonyl diphenylphosphinic amide **5**, which is separated easily by washing with sat. $NaHCO_3$ solution. The proton liberated in this step is subsequently involved in the catalytic cycle (Scheme 2).

The typical experimental procedure is as follows: to a stirred solution of benzyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidate (0.3 mmol) and 2-phenylethyl alcohol (0.3 mmol) in 1,2-dimethoxyethane (0.48 mL) under argon atmosphere was added a solution of Me_3SiOTf (10 mol %) in 1,2-dimethoxyethane (0.02 mL) at 0 °C. The reaction mixture was stirred for 1.0 h at room temperature. After completion of the reaction (detected by TLC), the mixture was quenched with saturated $NaHCO_3$ and was extracted with ethyl ether. Organic layers were dried over anhydrous sodium sulfate, then filtered and concentrated. The crude product thus obtained was purified by preparative TLC to give the corresponding benzyl 2-phenylethyl ether (0.0604 g, 95%) as colorless oil.



Scheme 2.

Thus, it is noted that a moisture- and air-resistant alkyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidates are easy to handle and are used as a useful O-alkylation reagent of alcohols. Further study on this type of reaction is now in progress.

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

1 a) J. March, in "March's Advanced Organic Chemistry, Reaction, Mechanism, and Structure," 5th ed., John Wiley & Sons, New York (2001), pp 477–478. b) F. M. Callahan, G. W. Anderson, R. Paul, and J. E. Zimmerman, *J. Am. Chem. Soc.*, **85**, 201 (1963). c) Y. Kashman, *J. Org. Chem.*, **37**, 912 (1972). d) S. Torii, S. Takagishi, T. Inokuchi, and H. Okumoto, *Bull. Chem. Soc. Jpn.*, **60**, 775 (1987). e) P. G. Sammers, D. Thetford, and M. Voyle, *J. Chem. Soc., Chem. Commun.*, **1987**, 1373. f) F. Toda, H. Takumi, and M. Akehi, *J. Chem. Soc., Chem. Commun.*, **1990**, 1270. g) N. Nakajima, M. Saito, and M. Ubukata, *Tetrahedron Lett.*, **39**, 5565 (1998), and references cited therein.
2 T. Shintou and T. Mukaiyama, *J. Am. Chem. Soc.*, **126**, 7359 (2004).
3 Y. Kobashi, T. Minowa, and T. Mukaiyama, *Chem. Lett.*, **33**, 1362 (2004).
4 For a review, see: Y. G. Gololobov, I. N. Zhmurova, and L. F. Kasukhin, *Tetrahedron*, **37**, 437 (1981).
5 Preparation of alkyl diphenylphosphinites, see: K. Ikegai, W. Pluempanupat, and T. Mukaiyama, *Chem. Lett.*, **34**, 638 (2005).
6 A. A. El-Kateb and F. M. Soliman, *Egypt. J. Chem.*, **24**, 465 (1981).
7 S. Hashimoto, H. Sakamoto, T. Honda, and S. Ikegami, *Tetrahedron Lett.*, **38**, 5181 (1997).
8 Synthetic procedure for benzyl *P*,*P*-diphenyl-*N*-(methanesulfonyl)phosphinimidate is as follows: methanesulfonyl chloride (10 mmol) was dissolved in DMF (10 mL) at 0 °C and was stirred for 1 h at 0 °C. Then, sodium azide (11 mmol) was added to the mixture at 0 °C to stir for 2 h at 0 °C. After warming up the reaction mixture to room temperature, a solution of benzyl diphenylphosphinite (10 mmol) in dichloromethane (10 mL) was added dropwise and the solution was kept stirring for 1 h at room temperature and chloroform was added. Then, the mixture was washed with water and brine and the organic layer was dried over anhydrous sodium sulfate. After filtration and evaporation, the resulted crude solid was washed by diethyl ether to afford the desired product (3.37 g, 87%) as a white solid.

Published on the web (Advance View) June 18, 2005; DOI 10.1246/cl.2005.1016