Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 16 (2006) 6170–6172
Bioorganic & Medicinal Chemistry Letters

Allyl and benzyl iodides by the anomalous action of iodotrimethylsilane

Qing Zhu[a,*] and Matthew S. Tremblay[b]

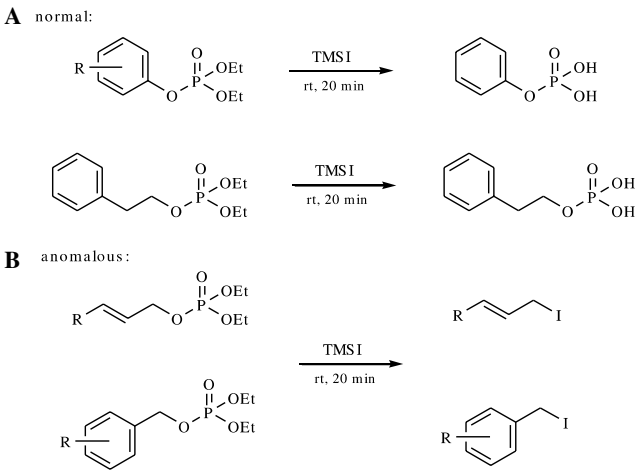
[a]*Institute of Bioengineering, Zhejiang University of Technology, Hangzhou, Zhejiang Province 310014, PR China*
[b]*Department of Chemistry, Columbia University, New York, NY 10027, USA*

Received 31 July 2006; revised 11 September 2006; accepted 14 September 2006
Available online 1 October 2006

Abstract—Iodotrimethylsilane (TMSI), routinely used for the dealkylation of ethers and esters, has been found to efficiently convert allyl and benzyl phosphotriesters into the corresponding iodides under mild, Brønsted-neutral conditions. In contrast, alkyl and aryl phosphotriesters were dealkylated to the corresponding phosphates under identical conditions.

Phosphate esters are ubiquitous in many classes of biomolecules[1] and natural products.[2] Accordingly, methods for the preparation and synthetic manipulation of phosphate esters are necessary for us to study and control the important biological processes in which they participate.[3] Typical synthetic routes to phosphate esters proceed through the unsymmmetrical phosphotriester, which can be selectively dealkylated to give the desired phosphate ester. Organosilicon reagents, such as iodotrimethylsilane (TMSI)[4], are often the reagent of choice, since they usually dealkylate phosphotriesters efficiently under mild, Brønsted-neutral conditions (Scheme 1A). The relatively high Lewis acidity of the silicon and the strong nucleophilicity of iodide make TMSI a competent reagent for cleaving oxygen containing groups, such as esters, lactones, ethers, ketals, and carbamates, as well as for the conversion of alcohols and sulfoxides to iodides and sulfides, respectively.[5] During the course of our research related to the synthesis of biologically relevant phosphate esters,[6] we observed the unexpected conversion of allyl and benzyl diethylphosphotriesters to the corresponding iodide in high yield and purity when exposed to standard cleavage conditions with TMSI (Scheme 1B).

Given the importance of phosphate esters and the seeming prevalence of TMSI as a key reagent in their synthesis, we thought it prudent to examine this anomalous iodination under a variety of conditions (Table 1). A typical procedure involved addition of TMSI (1–4 equiv) to a room temperature solution of the phosphotriester in CH_3CN. After 20 min, aqueous workup gave the corresponding iodide in 78–95% yield as assessed by GC, with isolated yields ranging from 45% to 89% (Table 1, entries 1–4). Four equivalents of TMSI gave the best yield. The reaction also proceeded in other solvents, although none proved to be better than CH_3CN (Table 1, entries 5–8).



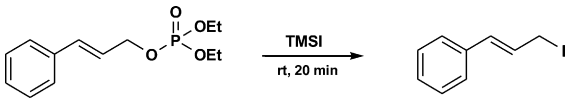
Scheme 1. The anomalous action of iodotrimethylsilane.

The substrate scope of this anomalous iodination was explored with a variety of allyl diethylphosphates under

Keywords: Phosphates; Protecting groups; Iodotrimethylsilane; Allyl iodides; Benzyl iodides.
* Corresponding author. Tel.: +86 571 88320781; fax: +86 579 8832 0781; e-mail: chmzhuq@hotmail.com

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.09.087

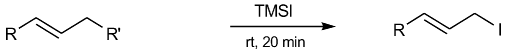
Table 1. Optimization of the reaction conditions



Entry	Solvent	TMSI (eqs)	Yield A[a] (Yield B)[b]
1	CH_3CN	1	45(78)
2	CH_3CN	2	79(90)
3	CH_3CN	3	87(95)
4	CH_3CN	4	89(95)
5	CH_2Cl_2	4	86(95)
6	DMSO	4	46(70)
7	Hexane	4	20(40)
8	Benzene	4	60(75)

[a] isolated yield.
[b] GC yield.

Table 2. Iodination of allylic phosphate esters[a]



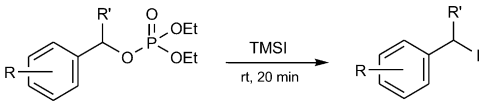
Entry	R	R′	Yield A[b] (yield B)[c]
1	Ph	$OP(O)(OEt)_2$	89(95)
2	2-$NO_2C_6H_4$	$OP(O)(OEt)_2$	78(95)
3	4-$CH_3OC_6H_4$	$OP(O)(OEt)_2$	82(90)
4	4-$CH_3C_6H_4$	$OP(O)(OEt)_2$	94(95)
5	2-$CH_3C_6H_4$	$OP(O)(OEt)_2$	92(95)
6	4-ClC_6H_4	$OP(O)(OEt)_2$	90(95)
7	4-CNC_6H_4	$OP(O)(OEt)_2$	94(95)
8	2,4-*di*-$MEOC_6H_3$	$OP(O)(OEt)_2$	n.p.[d]
9	CH_3	$OP(O)(OEt)_2$	68(95)
10	Ph	OMs	n.r.[e]

[a] All reactions were performed at room temperature with four equations TMSI for 20 min.
[b] Isolated yield.
[c] GC purity without purification.
[d] No desired product.
[e] No reaction.

the optimized conditions. Several cinnamyl diethylphosphates substituted with both electron-releasing and electron-withdrawing were efficiently converted to the iodide (Table 2, entries 1–7). A notable exception was 2,4-dimethoxycinnamyl diethylphosphate (Table 2, entry 8): no product was formed and decomposition of the substrate was observed, most likely due to instability of the electron-rich arene to TMSI.[7] Crotyl diethylphosphate also served as a competent substrate for the iodination, although in lower isolated yield (Table 2, entry 9). It should be noted that cinnamyl mesylate did not form the corresponding iodide, with no conversion of the starting material being observed after exposure to the reaction conditions (Table 2, entry 10).

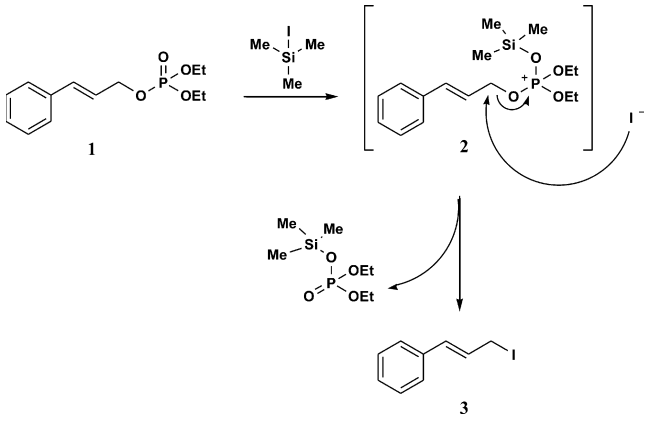
A number of substituted benzyl diethylphosphates were also converted to the corresponding iodides upon exposure to TMSI at room temperature in CH_3CN (Table 3)[8]. Electron-rich and electron-deficient benzyl diethyl phosphates were all converted to the iodides in excellent yield (Table 3, entries 1–5), and a methyl substituent in the Δ-position was tolerated (Table 3, entry 6).

Table 3. Iodination of benzylic phosphate esters[a]



Entry	R	R′	Yield A[b] (yield B)[c]
1	H	H	83(90)
2	4-NO_2	H	64(90)
3	4-Br	H	82(95)
4	3-CH_3	H	95(95)
5	4-Cl	H	93(95)
6	H	CH_3	81(90)

[a] All reactions were performed at room temperature with four equations TMSI for 20 min.
[b] Isolated yield.
[c] GC purity without purification.



Scheme 2. The proposed mechanism for the iodination.

A proposed mechanism for the iodination is shown in Scheme 2. Formation of a trimethylsiloxy species activates the phosphorus center for dealkylation. Iodide ion reacts with this intermediate at the allylic/benzylic carbon, resulting in dealkylation of the phosphotriester and formation of the allyl/benzyl iodide.

In conclusion, we found that the action of TMSI upon allyl/benzyl diethylphosphates was efficient iodination of the allyl/benzyl moiety, rather than dealkylative formation of the allyl/benzyl phosphates. Aside from being a notably high yielding 'side reaction,' this procedure may actually be useful for the preparation of allyl/benzyl iodides in certain contexts, since the conditions reported herein are milder than other known methods.[9]

Acknowledgments

This work was financially supported by the project sponsored by the Scientific Research Foundation for the Returned Overseas Chinese Scholars Fund, Zhejiang Province (No. Z01105002), and Scientific Research Foundation from Zhejiang University of Technology (No. 105002329).

References and notes

1. Weistheimer, F. H. *Science* **1987**, *235*, 1173.
2. (a) Kalidindi, R. S.; Yoshida, W. Y.; Palermo, J. A.; Scheuer, P. J. *Tetrahedron Lett.* **1994**, *35*, 5579; (b) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K. *J. Org. Chem.* **1988**, *55*, 3930; (c) DeRiccardis, F.; Iorizzi, M.; Minale, L.; Riccio, R.; Debitus, C. *Tetrahedron Lett.* **1992**, *33*, 1097.
3. Bunton, C. A. *Acc. Chem. Res.* **1970**, *3*, 257.
4. (a) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225; (b) Iwanami, K.; Oriyama, T. *Synlett* **2006**, 112; (c) Hartz, N.; Prakash, G. K. S.; Olah, G. A. . *Synlett* **1992**, 569.
5. (a) Voronkov, M. G.; Zgonnik, V. N. *Zh. Obshch. Khim.* **1957**, *27*, 1483; (b) Schwarz, R.; Schoeller, K. *Chem. Ber.* **1958**, *91*, 2103; (c) Rabinowitz, R. *J. Org. Chem.* **1963**, *28*, 2975.
6. Tremblay, M. S.; Zhu, Q.; Marti, A. A.; Dyer, J.; Halim, M.; Jockusch, S.; Turro, N. J.; Sames, D. *Org. Lett.* **2006**, *8*, 2723.
7. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.
8. TMSI was added dropwisely to the cinnamyl diethylphosphate in CH_3CN and the mixture was stirred at room temperature under argon atmosphere. After 20 min, the reaction was quenched with saturated NH_4Cl solution. The organic phase was extracted with ethyl acetate and washed with $NaHCO_3$ and 1 M HCl twice. The organic phase was dried over $MgSO_4$ and evaporated to obtain desired products which show satisfactory ^1H NMR, ^{13}C NMR and GC spectrum without purification.
9. (a) Kamal, A.; Ramesh, G.; Laxman, M. *Synth. Commun.* **2001**, *31*, 827; (b) Li, J.; Wang, X. X.; Zhang, Y. M. *Synlett* **2005**, 1039; (c) Das, B.; Majhi, A., et al. *Tetrahedron Lett.* **2005**, *46*, 7913.