Synthesis of Phosphonate and Thiophosphonate Esters and Amides from Hydrogen-Phosphinates by a Novel One-Pot Activation–Coupling–Oxidation Procedure

Maria de Fatima Fernandez, Cornelis P. Vlaar, Hong Fan, Yen-Hsiang Liu, Frank R. Fronczek, and Robert P. Hammer*

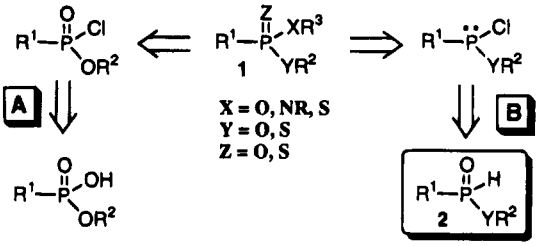
Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

Received May 1, 1995 (Revised Manuscript Received October 3, 1995)

Phosphonates and their derivatives are important analogs of nucleic acids,[1] peptides,[2] lipids,[3] other biologically important phosphates,[4] and as haptens for preparation of catalytic antibodies.[5] Currently, phosphonate esters (**1**, X = O, Y = O, Z = O) and phosphonamidates (**1**, X = NR, Y = O, Z = O) are generally formed by first activating a phosphonate monoester to the phosphonochloridate with thionyl chloride[2] or oxalyl chloride,[6] followed by coupling of the activated species with an alcohol or amine in the presence of base (Scheme 1, path A).[7] This method usually provides moderate yields of the desired products, in part due to the inherently slow nucleophilic displacement at P(V) centers by heteroatom nucleophiles.[8] An alternative approach to phosphonate diesters uses a modified Mitsunobu coupling of a phosphonate monoester with an alcohol (inversion of configuration at the alcohol-bearing carbon).[9] Also, dithiophosphonate esters have recently become available by addition of alcohol nucleophiles to 2-alkyl-2-thioxo-1,3,2-dithiaphospholanes.[10]

We report herein a new method to prepare phosphonates whereby P(III) compounds **2** are used in the key coupling step (Scheme 1, path B). In addition to potentially increasing the yield of **1**,[11] this approach also allows for easy design and preparation of phosphonates with a wide variety of heteroatoms around the phosphorus

Scheme 1



center (e.g., X = NR, Y = O, Z = S or X = O, Y = S, Z = S), many of which are difficult or impossible to prepare by current methodologies.

The success of the P(III) methods for oligonucleotide synthesis[12] is in large part due to the commercial availability of mononucleoside derivatives that can be manipulated under ambient conditions by the nonexpert. In this light, we envisioned H-phosphinate esters **2** as the ideal precursors for a P(III)-based phosphonate synthesis because of their air stability.[13] To be practical for phosphonate synthesis, however, the H-phosphinates must readily be converted to an activated species (e.g., RP(OR')(Cl), phosphonochloridites; Scheme 1, path B). Hata and co-workers reported that nucleoside H-phosphonate diesters [$(RO)_2PHO$] could be nonoxidatively converted to the phosphorochloridites [$(RO)_2PCl$] with dichlorotris(2,4,6-tribromophenoxy)phosphorane.[14] We used a crude preparation of dichlorotris(2,4,6-tribromophenoxy)phosphorane (^{31}P, −64.9 ppm) [contaminated with approximately 50 mol % of trichlorobis(2,4,6-tribromophenoxy)phosphorane (^{31}P, −72.1 ppm)] to activate menthyl phenylphosphinate (**2a**)[15] in pyridine. The corresponding phosphonochloridite **3a** was produced in high yield (as shown by ^{31}P-NMR) and then was readily coupled to a variety of alcohols to provide phosphonites **4a** (XR^3 = OCH_3, OEt, O*i*Pr, OCH_2Ph), which after sulfurization gave thiophosphonates **1a** (XR^3 = OCH_3, OEt, O*i*Pr, OCH_2Ph) in good isolated yields (data not shown).

Commercially available dichlorotriphenylphosphorane (95% purity, Aldrich) was used under the same conditions to activate isopropyl phenylphosphonate (**2b**) to produce almost exclusively phosphonochloridite **3b** (^{31}P-NMR, see Figure 1 in the supporting information). Subsequent addition of methanol gave the phosphonite **4d**, which was sulfurized to provide the thiophosphonate **1d**.

Table 1 describes the preparative experiments performed with H-phosphinates **2b–d**. All of the experiments used equimolar **2** and nucleophile (R^3XH), except when amines were used as the nucleophiles.[16] The isolated yields for all the various phosphonate derivatives were excellent to moderate. For reactions with **2b**, the

(1) Miller, P. S. *Biotechnology* **1991**, *9*, 358–362.

(2) (a) Kaplan, A. P.; Bartlett, P. A. *Biochemistry* **1991**, *30*, 8165–8170. (b) Morgan, B. P.; Scholtz, J. M.; Ballinger, M. D.; Zipkin, I. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 297–307. (c) Barelli, H.; Dive, V.; Yiotakis, A.; Vincent, J.-P.; Checler, F. *Biochem. J.* **1992**, *287*, 621–625. (d) Bertenshaw, S. R.; Rogers, R. S.; Stern, M. K.; Norman, B. H. *J. Med. Chem.* **1993**, *36*, 173–176.

(3) Martin, S. F.; Wong, Y.-L.; Wagman, A. S. *J. Am. Chem. Soc.* **1994**, *59*, 4821–4831.

(4) Engel, R. In *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; pp 559–600.

(5) Smith, A. B., III; Taylor, C. M.; Benkovic, S. J.; Hirschmann, R. *Tetrahedron Lett.* **1994**, *35*, 6853–6856.

(6) (a) Biller, S. A.; Forster, C.; Gordon, E. M.; Harrity, T.; Scott, W. A.; Ciosek, C. P. *J. Med. Chem.* **1988**, *31*, 1869–1871. (b) Stowell, M. H. B.; Ueland, J. M.; McClard, R. W. *Tetrahedron Lett.* **1990**, *31*, 3261–3262. (c) Musiol, H.-J.; Grams, F.; Rudolph-Böhner, S.; Moroder, L. *J. Org. Chem.* **1994**, *59*, 6144–6146. (d) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7616–7624.

(7) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Moore, W.; Sprengler, P. A.; Witherington, J.; Phillips, B. W.; Smith, A. B., III *J. Am. Chem. Soc.* **1995**, *117*, 6370–6371. These workers have shown that activation of phosphonate monoesters as the phosphonochloridates in the presence of triethylamine produces the phosphonyltriethylammonium salts, which are the most reactive species in the coupling with both alcohols and amines.

(8) For examples of the relative rates of nucleophile substitution at P(V) and P(III) intermediates see: Letsinger, R. L.; Lunsford, W. B. *J. Am. Chem. Soc.* **1976**, *98*, 3655–3661 and references therein.

(9) (a) Campbell, D. A. *J. Org. Chem.* **1992**, *57*, 6331–6335. (b) Campbell, D. A.; Bermak, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 6039–6040.

(10) Martin, S. F.; Wagman, A. S.; Zipp, G. G.; Gratchev, M. K. *J. Org. Chem.* **1994**, *59*, 7957–7958.

(11) As nucleophilic displacement is much faster at P(III) than at P(V) centers,[8] we hope this new phosphonate synthesis will increase the yield and efficacy of production of **1**. For oligonucleotide synthesis, the phosphotriester approach [P(V)] has been almost entirely supplanted by the phosphoramidite and H-phosphonate methods, both of which rely on P(III) chemistry.[12]

(12) (a) Phosphoramidite: Caruthers, M. H. *Acc. Chem. Res.* **1991**, *24*, 278–284. (b) H-Phosphonate: Froehler, B. C., In *Protocols for Oligonucleotides and Analogs*; Agrawal, S., Ed., Humana Press: Totowa, NJ, 1993; pp 63–80.

(13) H-Phosphinates are tautomeric with phosphonites [RP(OR)(OH)], but reside almost exclusively in the P=O form. Without a free lone pair of electrons, the H-phosphinate tautomers are kinetically and thermodynamically much more difficult to oxidize than is expected for a 3-coordinate P(III) compound.

(14) Wada, T.; Kato, R.; Hata, T. *J. Org. Chem.* **1991**, *56*, 1243–1250.

(15) Emmick, T. L.; Letsinger, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 3459–3465.

0022-3263/95/1960-7390$09.00/0

Scheme 2

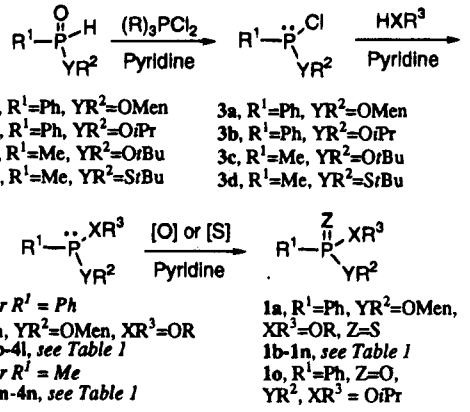


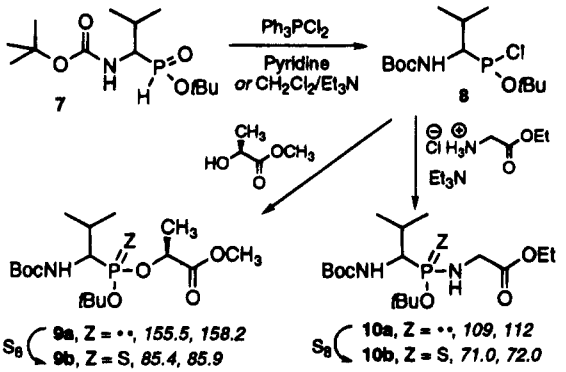
Table 1. Preparation of Phosphonates and Phosphonamides from H-Phosphinates[a]

entry	R^1	YR^2	XR^3	Z	% yield of **1**	^{31}P (**4**)[b]	^{31}P (**1**)[c]
b	Ph	O*i*Pr	OBn	O	71	153.2[g]	15.9
c	Ph	O*i*Pr	NEt_2	O	61[d,f]	125.9[h]	18.9
d	Ph	O*i*Pr	OMe	S	85	153.8	85.3
e	Ph	O*i*Pr	OEt	S	70	152.3	83.2
f	Ph	O*i*Pr	O*i*Pr	S	71	151.6	81.4
g	Ph	O*i*Pr	OBn	S	66	153.2[g]	83.8
h	Ph	O*i*Pr	O*t*Bu	S	70	141.4	74.5
i	Ph	O*i*Pr	NHBn	S	75[d]	111.2	72.3
j	Ph	O*i*Pr	NEt_2	S	75[d,f]	125.9[h]	74.6
k	Ph	O*i*Pr	NH*t*Bu	S	75[d]	102.2	68.2
l	Ph	O*i*Pr	SPh	S	83	144.8	88.7
m	CH_3	O*t*Bu	NH*t*Bu	S	61[e]	96.4	69.4
n	CH_3	S*t*Bu	OCH_3	S	47	136.0	98.8

[a] General procedure: At room temperature, a solution of dichlorotriphenylphosphorane (95% purity, Aldrich, 1.36 g, 3.9 mmol) in pyridine (15 mL) was added dropwise to a solution of the H-phosphinate (**2**) (2.6 mmol) in pyridine (5 mL). After 30 min, the nucleophile (R^3XH) (2.6 mmol for alcohols and thiols, 7.8 or 10.4 mmol for amines, see notes *d* and *e* below) was added dropwise with stirring, and after an additional 30 min sulfur (83 mg, 2.6 mmol) or anhydrous *tert*-butyl peroxide (3 M in toluene, 3.5 mL, 10.4 mmol) was added. The reaction mixture was stirred for 1 h. Then the pyridine was evaporated, and the residue was triturated with hexane (3 × 10 mL). The hexane phase was washed three times with saturated aqueous $NaHCO_3$ and dried with Na_2SO_4. The compounds were purified using flash chromatography on silica gel except where noted and were identified by ^{31}P, ^1H NMR, and GC/MS (data provided in the supporting information). [b] δ of crude reaction mixture (pyridine). [c] δ of purified **1** in $CDCl_3$. [d] For **1c**, **1i–k**, **1m**, 4 equiv (10.4 mmol) of amine nucleophile were added. [e] 3 equiv (7.8 mmol) of amine nucleophile were added. [f] Pressure alumina chromatography was used for purification. [g] **4b** = **4g**, PhP(OBn)(O*i*Pr). [h] **4c** = **4j**, PhP(O*i*Pr)(NEt_2).

major contaminant (3–10%, GC) was the diisopropyl phosphonate **1o** or diisopropyl thiophosphonate **1f**. These products are formed by oxidation or sulfurization of diisopropyl phenylphosphonite (**4f**), which is apparently formed by disproportionation of **2b** and phosphonochloridite **3b**. Particularly noteworthy are the good yields for compounds **1h** (71%), **1k** (75%),[17] and **1m** (61%), all which incorporate a very hindered *t*-Bu group in the alcohol or amine nucleophile. Such compounds are difficult to prepare by P(V) approaches because of the sensitivity of these reactions to steric factors (see refs 5 and 9a for examples).

Scheme 3



The relevance of this method for the preparation of biologically important molecules and its compatability with sensitive functionality was demonstrated by the synthesis of two phosphonopeptides (Scheme 3). Under the standard conditons (Table 1), N^{α}-Boc-protected phosphinate amino acid ester **7** was activated with dichlorotriphenylphosphorane in pyridine to produce phosphonochloridite **8** (^{31}P, 173.1 ppm). Reaction of **8** with methyl (*S*)-lactate or glycine ethyl ester (in the presence of 3.5 equiv of Et_3N), followed by sulfurization, produced the novel thiophosphonate and thiophosphonamide dipeptides, **9b** (^{31}P, 85.4, 85.9 ppm) and **10b** (^{31}P, 71.0, 72.0 ppm) in 30% and 40% yields, respectively, after column chromatographic purification. This same reaction sequence using dichloromethane in place of pyridine as solvent (with Et_3N added to scavenge HCl) gave similar results for the production of **9b** and **10b**.

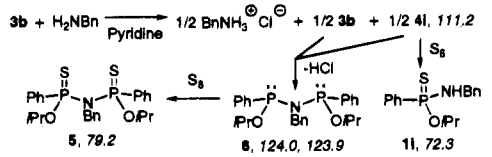
In summary, we have demonstrated that phosphonates, phosphonamides, thiophosphonates, and the previously unaccessible thiophosphonamides and dithiophosphonates can all be readily prepared from H-phosphinates using a one-pot activation–coupling–oxidation protocol. The key step in this process is the use of dichlorotriphenylphosphorane as activation reagent to generate the highly reactive phosphonochloridites (i.e, **3** and **8**). The first two thiophosphophosphonopeptide (P=S) analogs **9b** and **10b** have been prepared by this method. Currently, we are investigating the mechanism and stereochemistry of this reaction sequence, optimizing conditions such as phosphorane, solvent, and sulfurization/oxidation reagent, and applying this method to the preparation of biologically important phosphonate derivatives by both solution and solid-phase protocols.

Acknowledgment. We thank the Louisiana State University, the Louisiana Education Quality Support Fund (LEQSF), and the National Science Foundation (CHE-9500992) for financial support. The LSU NMR facilities were supported by grants from LEQSF and NSF. We are particularly grateful to Mr. Rolly Singh and Dr. Tracy McCarley for mass spectrometry analysis and to Mr. Marcus Nauman and Dr. David Vargas for assistance with NMR measurements.

Supporting Information Available: Detailed experimental procedures for **2a–d**, **7**, **9b**, and **10b**, full characterization data for **1b–n** and **5**, **7**, **9b**, and **10b**, X-ray data for **1k** and **5**, and Figure 1 (^{31}P-NMR of activation–coupling–oxidation procedure) (13 pages).

JO950802Q

(16) Reaction of equivalent amounts of benzylamine and phosphonochloridite **3b** produced, after sulfurization, >50% of the thiophosphonimide **5**[17] in addition to desired thiophosphonamide **1i**. Use of excess amine (3–4 equiv) significantly reduced this side reaction and allowed preparation of phosphonamides in good yield.



(17) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.