

Phosphonyltriethylammonium Salts: Novel Reactive Species for the Synthesis of Phosphonate Esters and Phosphonamides

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Received February 14, 1995

Phosphonate esters and amides find great utility as stable mimetics of tetrahedral transition states. Transition state analogs incorporating these functionalities have been exploited *inter alia* as enzyme inhibitors¹ and as haptens for catalytic antibody research,² including the recently reported formation of dipeptides.³ Phosphonate esters and phosphonamides are generally prepared by the reaction of phosphonochloridates or phosphonodichloridates⁴ with alcohols or amines. Use of monochloridates is the more common practice. Phosphonochloridates in turn are prepared by reaction of phosphonate diesters with 1 equiv of phosphorus pentachloride,⁵ by treatment of monoesters with thionyl chloride or oxalyl chloride,⁶ or by oxidative chlorination of phosphinate esters with carbon tetrachloride.⁷ The phosphonochloridate strategy has also been extended to the solid phase.⁸ In addition, the syntheses of phosphonopeptides from hydroxybenzotriazole esters and phosphonochloridates with silver ion catalysis have been reported,⁹ as have methods for preparing complex phosphonate esters using mixed BOP–phosphonate ester¹⁰ and modified Mitsunobu¹¹ strategies.

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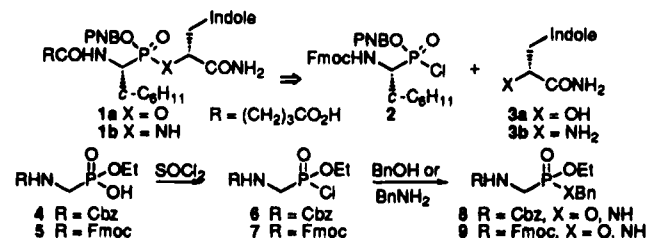
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In our recently reported¹² synthesis of hapten **1a**, we encountered considerable difficulty in coupling phosphonochloridate **2** with (*R*)- β -indolylactamide **3a**.¹³ Moreover, we were unable to prepare the corresponding phosphonamide **1b** from D-tryptophanamide, **3b**. To gain mechanistic insight into these problematic transformations, we studied the model reactions outlined in Scheme 1 via ³¹P-NMR spectroscopy.

Scheme 1



Model substrates **4** and **5** were prepared by treatment of diethyl (phthalimidomethyl)phosphonate^{5a,b} with hydrazine, followed by N-carbamoylation with either Cbz-Cl or Fmoc-Cl and subsequent generation of the monoesters via treatment with aqueous base^{5b} (**4**) or sodium iodide¹⁴ (**5**). The ³¹P-NMR spectra of the resultant monoesters **4** and **5** displayed major resonances at 24.8 and 24.9 ppm, respectively (relative to 85% H₃PO₄). Minor (ca. 3%) upfield signals at 24.2 or 23.9 ppm were assigned to carbamate rotamers on the basis of temperature-dependent ³¹P-NMR studies. Similar minor rotamers were observed in the spectra of all of our carbamate-protected phosphorus-containing compounds.

Treatment of **4** or **5** (0.05 M, CDCl₃) with the theoretical amount of thionyl chloride led within 30 min to their complete consumption, as revealed by ³¹P-NMR. Significantly, in addition to the expected phosphonochloridates **6** and **7** (35.6 ppm, R = Cbz; 35.7 ppm, R = Fmoc), a pair of upfield singlets (byproducts) at 16.4 and 16.1 ppm (R = Cbz) or 16.5 and 16.2 ppm (R = Fmoc) were also observed. When these reaction mixtures were treated with 5 equiv of benzyl alcohol, both the phosphonochloridates and the new upfield intermediates were consumed, affording the expected mixed diesters **8** and **9** (X = O, 23.6 ppm for both compounds) as the sole products.¹⁵ In contrast, treatment with 5 equiv of benzylamine led to selective reaction of the phosphonochloridates, furnishing the benzyl phosphonamides **8** and **9** (X = NH, 27.2 ppm for both compounds), leaving the upfield signals unchanged. We speculated that the appearance of two upfield phosphorus resonances for each byproduct was indicative of diastereomeric phosphorus atoms; this in turn strongly suggested the formation of pyrophosphonate anhydride diastereomers **10** and **11** (Scheme 2). These structures were confirmed as follows: addition of the Cbz-protected monoester **4** to thionyl chloride (3 equiv, 1 h, evaporation \leq 1 mmHg) provided primarily the phosphonochloridate **6**, accompanied by little (or no) symmetrical anhydrides **10**. Upon addition of 1 equiv of the Fmoc-protected monoester **5**, **6** was converted to the diastereomeric unsymmetrical anhydrides **12** (16.5 and 16.2 ppm). In the reciprocal experiment, treatment of the Fmoc-protected phosphonochlo-

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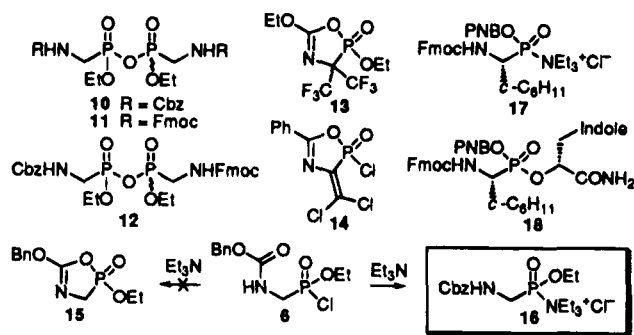
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(15) Presumably monoesters **4** and **5** produced when benzyl alcohol reacts with anhydrides **10** and **11** are converted to ester products by reaction with residual thionyl chloride. When excess thionyl chloride is removed prior to coupling, **4** and **5** are observed.

Scheme 2



ridate 7 with 4 led to an analogous mixture of the three pyrophosphonate anhydrides. The elemental compositions of the anhydrides 10–12 were confirmed by electrospray mass spectrometry.

Although phosphonic acid anhydrides have been described in the literature,^{16,17} they had not been recognized as side products of phosphonochloridate preparation. The alcoholysis and aminolysis experiments outlined above demonstrate that anhydrides 10 and 11 are less reactive than phosphonochloridates 6 and 7 and that all four compounds couple less readily with benzylamine than with benzyl alcohol. This latter observation, in marked contrast to the well-known greater reactivity of amines toward activated carboxylic acids compared to alcohols, demonstrates that relative nucleophilicity depends on the electrophile.¹⁸ Our results are consistent with the findings of Greenhalgh *et al.*,¹⁶ who studied couplings of activated phosphonic and phosphinic acids and observed that increasing charge transfer in the transition state resulted in enhanced reactivity toward alcohols relative to amines.

It is well-known that activated, acyl- or urethane-protected amino acids are readily cyclized by tertiary amines to form oxazolones,¹⁹ which are themselves reactive acylating agents. We therefore studied the reaction of the phosphonochloridates with tertiary amines. The substituted oxazaphospholines 13 and 14 had been prepared previously by alternate routes.^{20,21} When a mixture of 6 and 10 was allowed to react with triethylamine (1 equiv, Scheme 2), phosphonochloridate 6 was converted to a new species displaying a dramatic downfield shift of the ³¹P-NMR resonance (44.7 ppm); anhydride 10 again did not react. We propose that the product is not the oxazaphospholine 15, but rather the novel phosphonyltriethylammonium salt 16, on the basis of the following considerations:²² (1) The IR spectrum of 14 displays a characteristic absorption at 1625 cm⁻¹ (C=N), which is absent in the spectrum of 16. (2) The reported ³¹P-NMR chemical shifts of 13 and 14 (23 and 24.6 ppm, respectively) are considerably upfield of the observed 44.7 ppm resonance. (3) Intermediate 16 reacted more rapidly than 6 with benzyl alcohol, although both afforded the desired diester in

high yield (~86%). (4) Importantly, this difference in reactivity between 16 and 6 is even more pronounced in the coupling with amines. When a 1:1 mixture of 6 and 16 was treated with a limiting amount of benzylamine, the amine reacted exclusively with 16 to give 8 (X = NH), with no detectable consumption of the phosphonochloridate as indicated by ³¹P-NMR. The efficiency of the benzylamine coupling was also enhanced: the triethylammonium salt 16 gave the desired phosphonamide 8 (X = NH) in 85% yield after purification, compared with the 69% yield from phosphonochloridate 6. (5) Finally, the highly reactive nature of 16 is manifested also by our inability to observe a molecular ion via the electrospray ionization technique successfully employed with the anhydrides.

In our initial route to hapten precursor 18, the silver-assisted²³ coupling of phosphonochloridate 2 did produce the requisite diester, but the yields varied unpredictably from 0 to 32%, whereas conversion to the phosphonyltriethylammonium intermediate 17 prior to the addition of silver cyanide now reproducibly furnishes diester 18 in ca. 40% yield. Despite the increased reactivity of 16 toward both alcohols and amines, the α-carbon of the phosphonylammonium species is not prone to racemization, as evidenced by the formation of only two diastereomers at phosphorus in the coupling of 17 with 3a, and by the retention of enantiomeric purity upon aqueous quench of 17.²⁴ Additional support derives from the absence of deuterium incorporation (²H-NMR, HRMS) at the α center in coupling of 16 with excess *N*-d₂-benzylamine.

In summary, we have shown that (1) pyrophosphonate anhydrides are readily formed in the preparation of phosphonochloridates from phosphonate monoesters;²⁵ (2) the anhydrides are less reactive toward nucleophiles than the corresponding phosphonochloridates; (3) unlike their carboxylic acid counterparts, the phosphonochloridates do not cyclize to oxazaphospholines upon treatment with triethylamine, but instead afford the hitherto unrecognized phosphonyltriethylammonium salts; (4) importantly, the phosphonyltriethylammonium salts are highly reactive phosphorylating agents, superior to phosphonochloridates as precursors to phosphonate esters and amides.

Acknowledgment. Support was provided by the National Institutes of Health (Institute of General Medical Sciences) through Grant GM-45611, by Bachem, Inc. (Torrance, CA), and by the Merck Research Laboratories.

Supplementary Material Available: Analytical data and procedures for the preparation of 8 (X = O, NH) and 18 and representative ³¹P-NMR spectroscopy experiment illustrating the conversion of 4 to 8 (X = O) via 16 (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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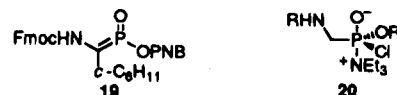
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(22) The "P-ketene" 19 and trigonal bipyramidal (TBP) species 20 have been considered as potentially representing the new reactive intermediate. The former possibility has been eliminated (*vide infra*)²⁴ while the TBP structure 20, although not excluded on rigorous chemical grounds, seems unlikely in light of the known lability of phosphorus derivatives with this coordination number (phosphorus pentahalides excluded) and their proclivity toward reorganization to the more stable tetrahedral coordination environment. See: Van Wazer, J. R. *Phosphorus and its Compounds*; Interscience Publishers: New York, 1964; Vol. 1, Chapter 3, pp 74–75.



(23) Subsequent to our synthesis¹² of 1a, Moroder *et al.* also reported the beneficial effects of silver ion on phosphonate diester formation.⁹

(24) This experiment also rules out the "P-ketene" structure 19 (see footnote 22) as an alternative to 17.

(25) Anhydride formation may involve competition between 6 or 7 and thionyl (oxalyl) chloride for unreacted monoester. A referee suggested that the mixed anhydride with thionyl chloride converts 4 or 5 into 10 or 11. That pyrophosphonate anhydrides are observed during chloridation in the presence of 10-fold excess chloride ion (*t*-Bu₄NCl) supports the former.