General Route to Phosphonodithioic Acid Derivatives

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Summary: A general procedure for the synthesis of esters of phosphonodithioic acids has been developed. The method involves the reaction of the Grignard reagents **2a–h** with 2-chloro-1,3,2-dithiaphospholane (**1**) to give **3a–h** that were sulfurized using elemental sulfur to furnish the intermediate phosphonotrithioates **4a–h**, reaction of which with a variety of alcohols in the presence of DBU furnished the desired phosphonodithioates **5a–h** and **6–9**.

Phosphonate derivatives are frequently used as replacements of the phosphate moiety of biologically active molecules.[1] Substitution of a methylene or difluoromethylene group for one of the bridging oxygen atoms of a phosphate provides a nonhydrolyzable analogue of a phosphoester linkage.[2] Phosphonate derivatives have recently been exploited as inhibitors of proteases and esterases,[3] mechanistic probes of PLA_2,[4] and haptens for the production of catalytic antibodies.[5] Although many methods exist to prepare simple phosphonic acids and their derivatives,[1a,6] there are few techniques available for the synthesis of highly functionalized phosphonates in which a sulfur is substituted for one or more of the oxygen atoms.[7] In the context of a project directed toward the design of novel inhibitors of phosphodiesterases, we required a series of phosphonodithioates, and we now wish to report a general procedure for their synthesis.

Scheme 1

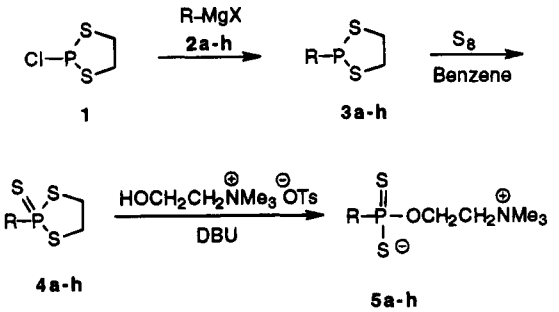

Table 1. Preparation of Choline-Derived Phosphonodithioates 5a–h

entry	R	% yield of **4**	% yield of **5**
a	$CH_3(CH_2)_8$–	71	78
b	*c*-$(C_6H_{11})CH_2$–	71	72
c	$C_6H_5CH_2$–	73	82
d	C_6H_5–	82	67
e	CH_2=$CHCH_2$–	73	73
f	(1,3-dioxolan-2-yl)$(CH_2)_3$–	72	77
g	[2,2-dimethyl-1,3-dioxolan-4(*S*)-yl]$(CH_2)_2$–	72	76
h	TBDMSO$(CH_2)_4$–	71	74

We recently discovered a novel tactic for the preparation of phosphorodithioate analogues of phospholipids that exploited 2-chloro-1,3,2-dithiaphospholane (**1**) as a reagent to couple two alcohols.[8] We reasoned that a modification of this method in which an organometallic reagent was used as one of the reaction partners should lead to the desired phosphonodithioates according to Scheme 1.[9] In preliminary experiments we discovered that simple alkyllithium reagents did not react with **1** to produce the desired dithiophosphinates **3**, whereas the corresponding organocerium reagents, which were generated *in situ* by adding cerium trichloride, gave **3** in yields of only 30%. On the other hand, **1** underwent facile reaction with a variety of unfunctionalized and functionalized Grignard reagents **2a–h** (1.1 equiv) to give the intermediate dithiophosphinates **3a–h**, which were sulfurized by exposure to elemental sulfur to provide the 2-alkyl-2-thio-1,3,2-dithiaphospholanes **4a–h** in 70–82% yields (Scheme 1). The subsequent reactions of **4a–h** with choline tosylate in the presence of 1,8-diazo[5.4.0]-bicycloundec-7-ene (DBU) followed by an aqueous acid workup then led to the series of choline-derived phosphonodithioates **5a–h** in 67–82% yields (Table 1).[10]

It now remained to establish whether other oxygen nucleophiles could be used to open the intermediate 2-alkyl-2-thio-1,3,2-dithiaphospholanes **4a–h** to provide access to a greater diversity of phosphonodithioate

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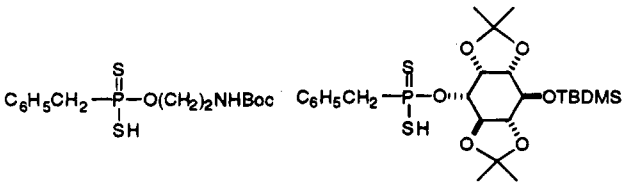
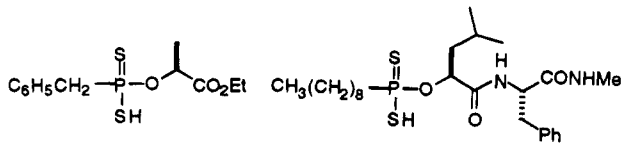
analogues. Toward this end, 2-benzyl-1,3,2-dithiaphospholane (**4c**) was treated with a protected ethanolamine derivative, a protected inositol derivative, and ethyl lactate to give the corresponding phosphonodithioates **6** (75%), **7** (73%), **8** (89%), and **9** (72%). The DBU salts of the products **6**–**9** were initially isolated from which the free acid could be liberated using an Amberlyst-15 column (basic form) followed by acidification.



6 **7**



8 **9**

We have now convincingly demonstrated that a number of novel phosphonodithioates may be readily prepared by the sequential reactions of the 1,3,2-dithiaphospholane **1** with Grignard reagents and a variety of polyfunctional oxygen nucleophiles. The products are formed in very good overall yields, and a number of functional groups are compatible with the method. Since **9** exhibited modest inhibitory activity (K_i = 25 μM) against the matrix metalloproteinase stromelysin,[11,12] the incorporation of a phosphonodithioate group as a replacement for a phosphate or related moiety appears to be a reasonable strategy for the design of novel enzyme inhibitors.

General Experimental Procedure. To a stirred solution of 2-chloro-1,3,2-dithiaphospholane (**1**) (0.174 g, 1.1 mmol) in anhydrous, deoxygenated THF (10–15 mL) at −78 °C was added dropwise a solution of the appropriate Grignard reagent **2a**–**h** (1.0 mmol) in anhydrous THF (0.2 M solution) over a period of 10 min.[13] After 1 h, the reaction mixture was warmed to room temperature. The reaction mixture was concentrated *in vacuo* to furnish the crude **3a**–**h**, which could be purified by flash chromatography eluting with 20–50% EtOAc/hexanes. After the **3a**–**h** thus obtained was dissolved in benzene (10 mL), elemental sulfur (0.15 g) was added, and the reaction was stirred for either 10 h at room temperature or 3 h at reflux. The solvent was then removed, and EtOAc (8 mL) was added. The resultant yellow flocculant solid was removed by filtration through a plug of glass wool. The filtrate was concentrated under reduced pressure and purified by flash chromatography eluting with EtOAc/hexanes (20–50%) to deliver **4a**–**h** in 70–82% yields. The 2-alkyl-2-thio-1,3,2-dithiaphospholanes **4a**–**h** (1.0 mmol) were then dissolved in MeCN, THF, or CH_2Cl_2 (10 mL) containing the appropriate alcohol reactant (1.0 mmol) and DBU (0.15 mL, 1.0 mmol), and the resulting solution was stirred for 1 h at room temperature. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography using either $CHCl_3$/MeOH/H_2O (66:30:4) or $CHCl_3$/Me_2CO/MeOH/H_2O (49:33.5:15:2.5) as the eluent to yield **5a**–**h** and **6**-**9**.

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of all new compounds (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) The structure assigned to each compound was in full accord with its spectral (^1H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of all new compounds were obtained by recrystallization, flash chromatography, or preparative HPLC and gave satisfactory identification by high-resolution mass spectrometry. All yields are based on isolated, purified materials.

(11) For a recent review of matrix metalloproteinases, see: Schwartz, M. A.; Van Wart, H. E. in *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Science Publishers, B. V., New York, 1992; Vol. 29, pp 271–331.

(12) We thank Dr. John E. Marlin and Ms. Melanie B. Anastasio (The Procter & Gamble Co.), respectively, for preparing the HO-Leu-Phe-NHMe starting material required for the synthesis of **9** and for performing the stromelysin inhibition assay.

(13) The magnesium metal was obtained from Timminco Metals, Division of Timminco Limited (Haley Station, Haley, Ontario KOJ 1Y0). We thank Mr. G. Andruszczenko for a generous gift of high purity magnesium turnings and filings.