A Reagent for Introducing the Phosphinic Acid Isostere of Phosphodiesters

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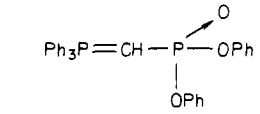
In the course of synthesis of a phosphonate–phosphinate analogue of the liponucleotide intermediates of phospholipid biosynthesis,[1] a reagent was developed that may be useful for the introduction of the $-CH_2P(\rightarrow O)CH_2-$ phosphate isostere into many other analogue types. Since details of the preparation and use of this compound have not as yet been presented, it seemed appropriate to describe separately this portion of the synthetic route.

In 1968, Jones et al.[2] described a synthetic stabilized Wittig reagent, diphenyl triphenylphosphoranylidenemethylphosphonate (I), which, after normal Wittig reaction



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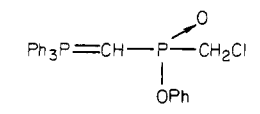

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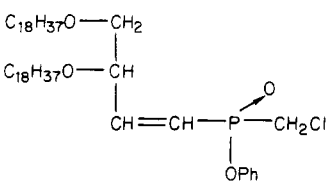

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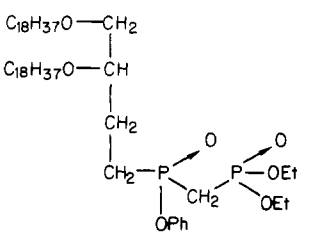

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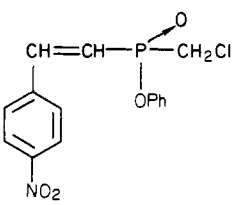

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followed by hydrogenation, allows the introduction of the methylphosphonate moiety when the appropriate aldehydes are available. The reagent was used for the synthesis of analogues of a number of nucleotides.[3]

For the synthesis of isosteric *phosphinic* acid analogues of the natural phosphoric acid diesters by the same general approach, it was clearly necessary to provide an additional functionalizable substituent attached to phosphoryl phosphorus. Therefore, the chloromethyl derivative II of the Jones–Moffatt reagent I was prepared as the desired phosphinate-forming compound. Due to the reactivity of its Wittig product, this new reagent can accommodate later Arbuzov or other reactions, depending upon the type of analogue desired.

Phenyl bis(chloromethyl)phosphinate[4] on reaction with triphenylphosphine in hot xylene precipitated the pure monophosphonium chloride. Reaction of the salt with aqueous potassium carbonate gave the ylide II as an uncrystallizable semisolid, which was used in situ to react with (*R*)-glyceraldehyde 2,3-dioctadecyl ether[5] to give the chloromethyl phosphinate III, which on reaction with triethyl phosphite followed by hydrogenation gave the desired phosphonate–phosphinate intermediate IV.

In a second unrelated illustration of the utility of the Wittig reagent, II was reacted with *p*-nitrobenzaldehyde. The expected Wittig product V was isolated by preparative reversed-phase HPLC as an almost equal cis–trans mixture and characterized by NMR, IR, and elemental analysis.

Experimental Section

Phenyl (Chloromethyl)[(triphenylphosphoranylidene)-methyl]phosphinate Chloride. To 1.2 g (5 mmol) of phenyl bis(chloromethyl)phosphinate in xylene (5 mL) was added a solution of 1.4 g (5.4 mmol) of triphenylphosphine in xylene (10 mL). The clear reaction mixture, under a static nitrogen atmosphere, was heated at 110 ± 3 °C overnight.

The crystalline product that had formed was filtered, washed twice with xylene and then with hexane, and dried in vacuo to give 1.1 g (44%) of white crystals, mp 236–238 °C. The yield can be improved by evaporation of the filtrate and washings, redissolving the residue in 8 mL of xylene, and continuing the reaction at 110 °C for several days. The second crop obtained was less pure and was purified by crystallization several times from ethanol: IR (KBr) 3050 (w), 2870 (w), 2750 (w), 2625 (w), 1575 (s), 1460 (s), 1420 (s), 1260 (s), 1210 (s), 1110 (s), 945 (s), 830 (s), 750 (s), 740 (s), 720 (s), 690 (s), 525 (s), 485 (s) cm^{-1}; ^1H NMR (D_2O, 60 MHz) δ 3.95 (d, 2 H, J = 8.8 Hz), 6.6–6.8 (m, 2 H), 7.1–7.2 (m, 2 H), 7.6–7.8 (m, 15 H). Anal. Calcd for $C_{26}H_{24}O_2Cl_2P_2$: C, 62.29; H, 4.82; Cl, 14.14; P, 12.35. Found: C, 62.27; H, 5.06; Cl, 13.94; P, 12.64.

(*R*)-Phenyl (3,4-Dioctadecoxybut-1-enyl)(chloromethyl)phosphinate[6] (III). The above phosphonium salt (4.8 g, 9.6 mmol) was dissolved in 150 mL of warm water; after cooling of the solution to room temperature, toluene (60 mL) was added, followed by 20% aqueous K_2CO_3 (15 mL) with vigorous stirring. The toluene phase was washed with water, dried (K_2CO_3), and filtered. The ylide I in 100 mL of toluene was added to (*R*)-glyceraldehyde 2,3-dioctadecyl ether[5] prepared in situ from 2.46 g (2.06 mmol) of D-mannitol 1,2,5,6-tetraoctadecyl ether,[7] and the solution was heated at 115 ± 3 °C for 40 h under nitrogen.

The reaction mixture was cooled, the solvent evaporated, and the Wittig product (2.8 g) precipitated by addition of cold acetonitrile. This material was applied to a 1.5-cm column containing 160 g of SilicAR CC-7 (Mallinkrodt) and eluted with hexane and then with 5–20% ethyl acetate in hexane. Analytically pure product was thus obtained (1.13 g, 35%). The relatively low recovery from the column is apparently due to a significant degree of irreversible adsorption to the silica. Crude product, however, can be used in the subsequent step provided that product is carefully purified. IR and NMR data accorded with that of III. Anal. Calcd for $C_{47}H_{86}O_4ClP$: C, 72.22; H, 11.09; Cl, 4.54; P, 3.96. Found: C, 71.86; H, 11.10; Cl, 4.70; P, 3.83.

(*S*)-Phenyl (3,4-Dioctadecoxybutyl)[(diethoxyphosphinyl)methyl]phosphinate[6] (IV). The (chloromethyl)-phosphinate (1.1 g, 1.4 mmol) was heated with 30 mL of triethyl phosphite under a slow stream of nitrogen for 48 h at 150 ± 2 °C. Excess phosphite was removed under reduced pressure and to the residue was added cold acetonitrile. The precipitate was washed thoroughly with cold acetonitrile and dried in vacuo.

The crude product (1.0 g) was dissolved in 20 mL of freshly distilled tetrahydrofuran stabilized with 1% ethanol. The solution

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was hydrogenated over 10% palladium on carbon (0.2 g) at 50 lb/in.^{2} at room temperature overnight. After filtration and washing of the catalyst, the crude product was obtained by precipitation with cold acetonitrile after removal of the solvent in vacuo.

The product (0.79 g) in chloroform was applied to a SilicAR CC-7 column (130 g, 2 in. i.d.), which was then eluted with chloroform and then 0.5% methanol in chloroform. The pure product obtained from the latter eluate weighed 0.67 g (53.8%); R_f 0.17 in chloroform–ethyl acetate–methanol (89:10:1). IR and NMR data agreed with the expected structure for IV. Anal. Calcd for $C_{51}H_{98}O_7P_2$: C, 69.19; H, 11.16; P, 7.00. Found: C, 68.82; H, 11.11; P, 7.07.

Phenyl [2-(4-Nitrophenyl)ethenyl](chloromethyl)phosphinate (Cis–Trans Mixture) (V). *p*-Nitrobenzaldehyde (0.1 g, 0.7 mmol) in acetonitrile (2 mL) was added dropwise to an acetonitrile solution (5 mL) of the ylide II prepared from 0.25 g (0.5 mmol) of the phosphonium salt. The reaction mixture was heated at 50 °C for 18 h under nitrogen. The solvent was evaporated and the product V was separated by HPLC, employing a spectrophotometric detector and a 10-μm RP-18 column (250 mm × 10 mm E. Merck semi-prep), using an isocratic 65:35 (v/v) MeOH–H_2O eluent with a flow rate of 2.0 mL/min; the retention times of the cis and trans olefins were 29.0 and 32.0 min, respectively. The analytically pure product, 53 mg (32%), a 1.0:1.12 cis–trans mixture, was collected. IR and NMR data agreed with the expected structure for V. Anal. Calcd for $C_{15}H_{13}NO_4PCl$: C, 53.35; H, 3.88; N, 4.15; P, 9.17. Found: C, 53.44; H, 4.03; N, 4.03; P, 9.27.

Registry No. III, 87517-94-0; IV, 80991-34-0; *cis*-V, 87517-95-1; *trans*-V, 87517-96-2; phenyl (chloromethyl)(triphenylphosphoniomethyl)phosphinate chloride, 87517-93-9; phenyl bis(chloromethyl)phosphinate, 14212-98-7; triphenylphosphine, 603-35-0; triethyl phosphite, 122-52-1; *p*-nitrobenzaldehyde, 555-16-8; (*R*)-glyceraldehyde 2,3-dioctadecyl ether, 80991-31-7.

Selenosulfonation of Disubstituted Acetylenes: Reactions of Corresponding Vinyl Selenoxides and Anomalous Formation of a Ketene Diselenoacetal[1a]

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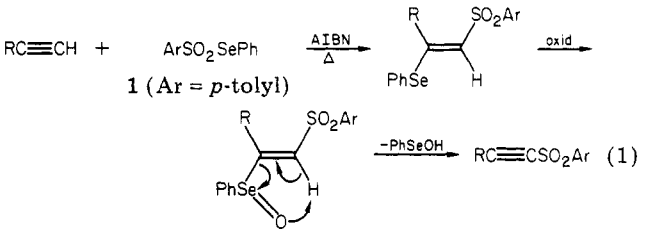
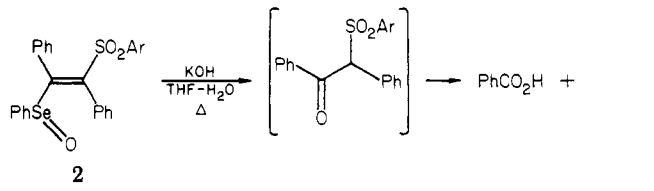
Se-Phenyl areneselenosulfonates ($ArSO_2SePh$) undergo 1,2-additions to olefins via electrophilic[2] or free-radical reactions,[2,3] which we have collectively named "selenosulfonations". The free-radical processes may be initiated thermally[2] or photochemically[3] and have also been performed with allenes[4] and diazomethane[5] as substrates. Several synthetic applications of olefin selenosulfonations have subsequently appeared.[6]

We,[7] and independently Miura and Kobayashi,[8] have recently extended these studies to acetylenes. *Se*-Phenyl *p*-tolueneselenosulfonate (1) adds regio- and stereoselectively to various acetylenes under thermal free-radical conditions, which can be initiated with azobis(isobutyronitrile) (AIBN).[7] The adducts can be oxidized to selenoxides which, when derived from terminal acetylenes, readily undergo syn-[7,8] or base-catalyzed[7a] elimination of benzeneselenenic acid[9] (PhSeOH) to afford high yields of acetylenic sulfones (eq 1; the symbol Ar will indicate the *p*-tolyl group throughout this work).



1,2-Adducts can also be prepared from disubstituted acetylenes, but the behavior of the corresponding selenoxides has only been investigated in one isolated case.[7a] Clearly, such compounds cannot react according to eq 1 as no vinylic hydrogen atom is available for elimination. Selenoxide **2** was found to be stable and isolable but fragmented under base-catalyzed conditions according to eq 2.[7a] In order to determine whether such behavior is



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general or atypical, we prepared three other selenoxides from disubstituted acetylenes and subjected them to pyrolytic or hydrolytic conditions. We now report that two other reaction modes have been identified and that the fate of such selenoxides is largely dependent on the nature of the substituents in the original acetylenes. We also describe an unexpected and anomalous selenosulfonation reaction observed when 1-(trimethylsilyl)propyne was treated with **1**.

Selenoxide **4**, derived from the known[7a] selenide **3** by oxidation with *m*-chloroperbenzoic acid (MCPBA) in THF, was treated with 3 M aqueous potassium hydroxide solution in the presence of 18-crown-6 at room temperature. Neither the β-keto sulfone **5** nor products derived from its further hydrolysis were isolated. Instead, the allylic alcohol **6** was formed in 65% yield. When deuterium oxide was used in place of water, the product was deuterated exclusively (within the limits of detection by ^1H NMR spectroscopy) at the vinylic position. These results indicate that a base-catalyzed isomerization of the double bond occurs to form an allylic selenoxide intermediate **8** (Scheme I). This species rapidly rearranges via a [2,3] sigmatropic shift[9] to provide, after hydrolysis of the initially formed

(1) (a) We thank the Natural Sciences and Engineering Research Council of Canada and the Research Corp. for financial support. (b) Recipient of an NSERC Postgraduate Scholarship and an Honorary Killam Scholarship.

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