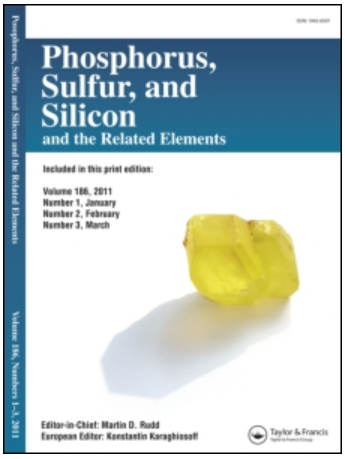

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Synthesis of Benzyl Diisopropyl 5-Phosphonopentanoate and 5-Phosphonopentanoic Acid: An Analog of Succinyl Phosphate

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Benzyl 5-(diisopropoxyphosphoryl)pentanoate (benzyl diisopropyl 5-phosphonopentanoate) was synthesized from 5-bromopentanoic acid in three steps. The first step esterified 5-bromopentanoic acid with benzyl alcohol, the second step was a Finkelstein halogen exchange with sodium iodide, and the third step was a Michaelis–Arbuzov reaction. This compound was characterized by NMR and high-resolution mass spectrometry. This compound was hydrolyzed to produce 5-phosphonopentanoic acid, which is an analog of succinyl phosphate and a possible enzyme inhibitor.

Keywords Dimethylaminopyridine (DMAP); esterification; Finkelstein reaction; Michealis–Arbuzov reaction; phosphonic acid; succinyl phosphate

INTRODUCTION

Phosphonates are commonly employed as substrate or reaction-coordinate analogs to study enzymes catalyzing phosphoryl-group transfer reactions. The P—C bond of the phosphonate replaces the reactive P—O bond of the substrate. The goal of this study was to produce 5-phosphonopentanoic acid, which is an analog of succinyl phosphate. Succinyl phosphate, which is a labile mixed anhydride, is thought to

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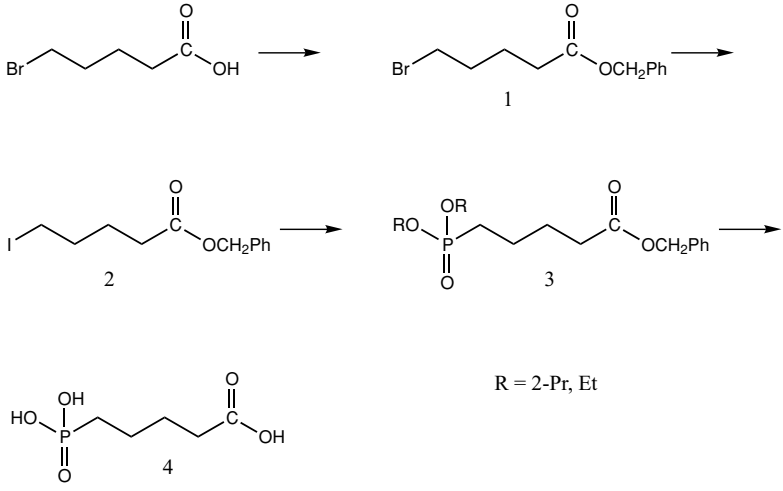
be an intermediate in the reactions of succinyl CoA synthetase and beta-oxoacyl-CoA transferase. Analogs of intermediates may bind more tightly than analogs of substrates or products.[1] This report is the first synthesis of benzyl 5-(diisopropoxyphosphoryl)pentanoate of which we are aware. 5-phosphonopentanoic acid has been synthesized previously by a different route.[2]

RESULTS AND DISCUSSION

Our strategy of synthesizing 5-phosphonopentanoic acid was patterned after the synthesis of 4-phosphonobutanoic acid (Scheme 1).[3] The synthesis of 5-phosphonopentanoic acid begins with the esterification of 5-bromopentanoic acid with benzyl alcohol catalyzed by dimethylaminopyridine (DMAP).[4] The next step is a Finkelstein halogen exchange reaction to produce benzyl 5-iodopentanoate.[5] The key step is the Michaelis–Arbuzov reaction with triisopropyl phosphite to produce benzyl diisopropyl 5-phosphonopentanoate.[6] This triester is hydrolyzed to 5-phosphonopentanoic acid in 6 M HCl.

Table I contains high-resolution mass spectrometry data on **3**. The difference between the calculated mass of 356.1752 and the experimentally observed mass of 356.1742 is −2.75 ppm. All of the chemical shifts and coupling constants collected by ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy are consistent with the identities of **3** and **4**. A ^{31}P NMR spectrum of **4** revealed a single peak at 32.1 ppm, which is consistent with a



SCHEME 1

TABLE I High-Resolution Mass Spectrometry Data for Benzyl Diisopropyl 5-phosphonopentanoate

Calculated mass (g/mol)	Observed mass (m/z)	Error (ppm)
356.1752	356.1748	−1.2
356.1752	356.1744	−2.4
356.1752	356.1744	−2.4
356.1752	356.1735	−4.9

phosphonic acid group. Heteronuclear $^{31}P/^{13}C$ coupling constants indicated that phosphorus must be coupled to the organic portion of the product and permit assignment of the carbon nuclei. In earlier work on the synthesis of **3**, we employed triethyl phosphite, rather than triisopropyl phosphite, in the Arbuzov reaction. We observed a lower concentration of side products when we used the latter nucleophile.

CONCLUSIONS

This work describes a synthesis of benzyl diisopropyl 5-phosphonopentanoate **3**, a compound that has not previously been described. It also describes a new synthesis and more extensive characterization of 5-phosphonopentanoic acid **4**. Experiments are underway to test the efficacy of **4** as an inhibitor of enzymes that utilize succinyl phosphate as an intermediate, such as succinyl CoA synthetase and beta-oxoacyl-CoA transferase. Experiments are also underway to test this compound as an inhibitor of aspartate semialdehyde dehydrogenase.

EXPERIMENTAL

Reactions were performed under nitrogen with oven-dried glassware. All chemicals were reagent-grade or better and were used without further purification unless specified. NMR spectra were recorded on a Bruker ARX-400 spectrometer. ^{31}P NMR spectra are referenced to phosphoric acid, downfield positive. ^{1}H and ^{13}C NMR spectra are referenced to $(CH_3)_4Si$. Coupling constants are given in Hertz. TLC plates with a fluorescent indicator were visualized with UV light and phosphomolybdate/sulfuric acid with heating. The melting point is uncorrected.

Benzyl 5-Bromopentanoate (1)

5-bromopentanoic acid (1.00 g, 5.49 mmol) and benzyl alcohol (0.572 mL, 5.527 mmol) in 6 mL of diethyl ether were stirred at 0°C

in a 50-mL round-bottom flask. A solution of dicyclohexylcarbodiimide (1.25 g, 6.07 mmol) and DMAP (0.0338 g, 0.277 mmol) in diethyl ether (6 mL) was added to a solution of acid and alcohol. The resulting mixture was left to stir overnight and reach r.t. as the ice bath melted. The mixture was filtered through Celite, and the filter cake was rinsed with ether. The solution was washed with water and then 5% acetic acid. The solution was dried with $MgSO_4$, and the solvent was removed using rotary evaporation. Proton NMR was used to identify the crude product. Silica-gel chromatography with 2:8 ethyl acetate:hexane as the solvent can be done to purify at this step, but this was found to be unnecessary. Yield: 73.8%; ^{1}H NMR ($CDCl_3$) δ 1.78–1.92 (m, 4H, $CH_2C\ \underline{H_2}C\ \underline{H_2}CH_2$), 2.40 (t, J = 7.2 Hz, 2H, $C(O)C\ \underline{H_2}CH_2$), 3.40 (t, J = 6.5 Hz, 2H, $C\underline{H_2}Br$), 5.12 (s, 2H, $PhC\underline{H_2}O$), 7.35 (m, 5H, Ph).

Benzyl 5-Iodopentanoate (2)

NaI (0.723 g, 4.82 mmol) was dissolved in about 4 mL of distilled, dry acetone with stirring, and then the ester **1** (1.007 g, 3.72 mmol) was added, causing immediate white precipitation. The reaction was stirred overnight with minimal exposure to light. The mixture was filtered through Celite and washed with dry acetone. The solvent was removed with rotary evaporation. The product was purified by silica-gel chromatography using 15:85 ethyl acetate:hexane. The yield was 77%; ^{1}H NMR ($CDCl_3$) δ 1.76–1.85 (m, 4H, $CH_2C\ \underline{H_2}C\ \underline{H_2}CH_2$), 2.39 (t, J = 7.2 Hz, 2H, $C(O)C\ H_2\underline{CH_2}$), 3.18 (t, J = 6.8 Hz, 2H, $C\ \underline{H_2}I$), 5.12 (s, 2H, $PhC\ \underline{H_2}O$), 7.34 (m, 5H, Ph).

Benzyl Diisopropyl 5-Phosphonopentanoate (3)

Triisopropyl phosphite was distilled under reduced pressure. Triisopropyl phosphite (0.719 g, 3.43 mmol) and benzyl 5-iodopentanoate **2** (1.218 g, 3.77 mmol) were combined in a round-bottom flask with a distillation setup attached to a collection flask in dry ice. Alternatively, a stream of nitrogen was flowed across the reaction in order to remove 2-iodopropane (5). The reaction flask was placed in a sand bath at ~115°C. After 4 hours and 15 minutes, the reaction was complete by ^{31}P NMR. Silica-column chromatography with a step gradient typically of 40:60 ethyl acetate:hexane to 60:40 ethyl acetate:hexane was used to purify the product. Acetone/hexane solvent systems were also used for some preparations. High-resolution mass spectrometry (Table I), proton NMR, and phosphorus NMR were used to identify the product. Yield: 77.05%; ^{31}P NMR ($CDCl_3$) δ 30.1; ^{1}H NMR ($CDCl_3$) δ 1.29 (multiplet, 12H, $C\ \underline{H_3}$), 1.63–1.69 (m, 6H, $CH_2C\ \underline{H_2}C\ \underline{H_2}CH_2$), 2.38 (t, J = 7.3 Hz,

2H, C(O)C $\underline{H}_2$), 4.66 (m, 2H, C$\underline{H}$), 5.11 (s, 2H, PhC$\underline{H}_2$O), 7.35 m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 22.2 (d, $^2J_{CP} = 5.2$ Hz, PCH_2 $\underline{C}H_2$), 24.0 (s, $\underline{C}H_3$), 25.2 (d, $^3J_{PC} = 18.1$ Hz, PCH_2CH_2 $\underline{C}H_2$), 26.7 (d, $^1J_{PC} = 144.0$ Hz, P $\underline{C}H_2$), 33.7 (s, HOC(O) $\underline{C}H_2$), 66.2 (s, O $\underline{C}H_2$Ph), 69.9 (d, $^2J_{CP} = 6.7$ Hz, PO $\underline{C}$H), 128.2–135.5 (Ph), 173.1 (s, $\underline{C}$(O)OCH_2).

5-Phosphonopentanoic Acid

The triester **3** (0.52 g, 1.46 mmol) was added to 2 mL of constant boiling HCl and refluxed for 72 h at 107°C. The sample was dissolved twice in deionized water, and the solvent was removed by rotary evaporation each time. The off-white solid was then dried in a stream of nitrogen to remove traces of HCl and dried overnight in vacuo over P_2O_5. It appeared to be pure by TLC on silica using 3:1:1 1-propanol:water:ammonia. The ^{1}H NMR chemical shifts were in broad agreement with a previous report, once differences in NMR solvents (d_6-DMSO versus D_2O) were considered.[2] Yield: 77%; m.p. 124–126.5°C; ^{31}P NMR (D_2O) δ 32.1; ^{1}H NMR (D_2O) δ 1.3–1.6 (m, 6H, PC$\underline{H}_2$C$\underline{H}_2$C $\underline{H}_2$), 2.15 (t, J = 7.4 Hz, 2H, HOC(O)C$\underline{H}_2$); ^{13}C NMR (D_2O) δ 21.3 (d, $^2J_{PC} = 4.7$ Hz, $PCH_2\underline{C}H_2$), 24.9 (d, $^3J_{PC} = 17.6$ Hz, $PCH_2CH_2\underline{C}H_2$), 25.6 (d, $^1J_{PC} = 132.6$ Hz, P $\underline{C}H_2$), 33.0 (HOC(O) $\underline{C}H_2$), 178.4 (HO$\underline{C}$(O)).

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