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Synthesis of (3S)-(+) -diethyl-2-(1-oxoethyl)-5-phenyl-(3 N-p-Toluenesulfinamido) pentylphosphonate

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Synthesis of (3S)-(+-)-diethyl-2-(1-oxoethyl)-5-phenyl-(3-N-p-Toluenesulfinamido) pentylphosphonate

Submitted in Partial Fulfillment of the Requirements for Graduation with Honors to the Department of Natural Sciences for the Department of Chemistry at Carroll College, Helena, Montana.

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This thesis for honors recognition has been approved for the Department of Chemistry.

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Abstract

It has been found that reactions between pentacovalent oxaphospholenes (P(V)) and various electrophiles produced substituted phosphonates under mild conditions. Using an imine as an electrophile with the oxaphospholene would produce a γ-phosphonoamino acid. However, simple imines are not good enough electrophiles to react with a standard P(V) compound. Imines with attached electron withdrawing sulfoxide groups proved to be better electrophiles. The imine was prepared by the reaction of hydrocinnamaldehyde with p-toluenesulfinamide to produce (S)-(+)N-(3-phenyl)-propyl-p-toluenesulfinamide which was then treated with 2,2,2-triethoxy-2,2-dihydro-5-methyl-1,2λ5-oxaphospholene (P(V)) with MgBr₂ as a Lewis acid to produce the desired product, (3S)-(+)diethyl-2-(1-oxoethyl)-5-phenyl-(3-N-p-toluenesulfinamido) pentyolphophonate.
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Introduction

Organic phosphate compounds found in living systems are responsible for many important functions involving metabolic pathways, calcium regulation and cell proliferation. Unfortunately, it is difficult to study organic phosphates since so much of their exact functions are still not known. One way to study such biological functions is the use of phosphonates in which one of the labile phosphate C-O bonds is replaced with a nonhydrolyzable P-C bond. In addition to using these compounds to study metabolic pathways, phosphonate derivatives of biologically active phosphates have been found to be biologically active. For this reason, phosphonates are becoming of interest in pharmacology and drug design because methods to synthesize multiple derivatives need to be further developed. Derivatives of such research are also currently being tested for their antiviral capabilities, such as against HIV, and also for their antibiotic properties. Phosphonates have even been found to be active in the treatment of calcification diseases. Other phosphonates have been found to have insecticidal and herbicidal


properties. Because of their versatility and importance in the biological field, it is important to have an efficient and versatile way to synthesize such phosphonate compounds under mild conditions.

It has been found that pentacovalent oxaphospholenes (P(V)) when reacted with various electrophiles condense under mild conditions to yield highly substituted phosphonate compounds. \( \gamma \)-phosphono-amino acids produced when imines are electrophiles would make useful intermediates in the synthesis of amino sugars and their phosphonate derivatives. Simple imines do not make good electrophiles for reacting with P(V) compounds, but with an added electron withdrawing group their electrophilicity increases so \( \gamma \)-phosphono-amino acids can be created.

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Results and Discussion

Synthesis of (S)-(+-)N-(3-phenyl)-propyl-p-toluenesulfinamide (1)

The synthesis of compound 1 was relatively easy and successful. Figure 1 outlines the synthetic process taken to synthesize the compound.8 This reaction was performed twice. The first time was on a small scale using 0.25 g of p-toluenesulfinamide (starting material) and an excess of hydrocinnamaldehyde was used to make the reaction go to completion. Molecular sieves where used to absorb the water formed as a byproduct which kept the reaction moving in the forward direction. TLC (in 50% hexanes in ethyl acetate) was used to monitor the disappearance of p-toluenesulfinamide. TLC confirmed complete disappearance of p-toluenesulfinamidie after a 24 hour reflux at 40°C. The existence of compound 1 was confirmed by the presence of a triplet at 8.3 ppm in the NMR indicating the presence of the H on the carbon double bonded to the nitrogen. Different solvents were tested for separation purposes but 20% diethyl ether in hexanes proved to be the best. Flash chromatography was then used to separate the more polar product from the remaining hydrocinnamaldehyde.

The same reaction was scaled up and again an excess of aldehyde was used. After 48 hours, TLC showed complete disappearance of starting material. Again, the reaction was successful and the existence of the triplet at 8.3 ppm proved the presence of compound 1. Purification as before yielded a product (75% yield) which gave a proton NMR having a small peak at 9.2 ppm confirming the presence of a small amount of

aldehyde starting material (Appendix A). The aldehyde could be completely separated out using a more complete column technique such as high performance liquid chromatography (HPLC).

![Diagram of Scheme 1](image)

**Scheme 1**

**Synthesis of (S)-(+)-N-(3-phenyl)-propyl-p-toluenesulfinamide (1)**

*Synthesis of (3S)-(+)-diethyl-2-(1-oxoethyl)-5-phenyl-(3-N-p-Toluenesulfinamido) pentylphosphonate (2)*

The synthesis of compound 2 was more difficult and required experimentation of method and technique. Figure 2 outlines the first attempt to synthesize this compound. This reaction was done on a small scale using only heat and an excess of P(V). The reaction was started on ice at 0°C for a day, allowed to warm to room temperature overnight, followed by refluxing at 40°C for 4 days. TLC was used to monitor the disappearance of the imine (1). Even after five days there was still starting material left, illustration the poor electrophilicity of sulfoxoyimine under the reaction conditions.
First attempt to synthesize (3S)-(+) -diethyl-2-(1-oxoethyl)-5-phenyl-(3-N-p-Toluensulfinamido) pentylyphosphonate (2)

After the first attempt to synthesis compound 2 failed to produce a good yield, a Lewis Acid was added to help the reaction. Figure 3 outlines the second and successful attempt to synthesize compound 2. The reaction was done on a larger scale again with an excess of P(V). This time magnesium bromide was used to enhance the reaction. After 27 hours, all the starting material had disappeared according to TLC analysis. The phosphorus NMR showed several peaks at 32 ppm, which may indicate the presence of product 2 (Appendix B). This reaction yielded 1.0406 g of crude product.

Successful synthesis of (2)

The major byproduct of the reaction is shown in Figure 4(hydrolysis product). This was formed because excess P(V) was used in the reaction and this excess P(V)
reacts with the water. NMR confirmed the presence of the hydrolysis product with a peak in the phosphorus proton decoupled NMR at 27.116 ppm (Appendix B). For this reason, a good method of purification was needed. Several different methods were attempted to separate and purify compound 2. First, flash chromatography was tried using 2% methanol in CH$_2$Cl$_2$ but separation was not achieved. The second attempt was on a cromatatron again using 2% methanol in CH$_2$Cl$_2$. Though separation was better, some fractions eluded very close to each other and were not separated completely. Finally, HPLC using 1% methanol in CH$_2$Cl$_2$ achieved good separation. The ultra-violet detector showed when specific fraction where eluding which made it easy to completely separate out the components of the reaction mixture. Phosphorus NMR spectra showed to extraneous peaks suggesting complete separation of the product from all impurities (Appendix B).

![Scheme 4](image)

**Scheme 4**

**Formation of the Hydrolysis Product**

The desired product has four possible diastereomers shown in figure 5. Since the reaction was run at room temperature, three of the four are believed to be present. This is according to the phosphorus NMR that shows three different peaks around 32 ppm. A forth diastereomer may be present but just not in large enough concentrations for the phosphorus NMR to detect. The phosphorus NMR also indicates that one or two of the
diastereomers may be in larger amounts. This is probably due to certain diastereomers being less sterically hindered and therefore more thermally favorable. The three different diastereomers made the proton NMR hard to decipher and any further characteristic data difficult to obtain.

![Four Possible Diastereomers](image)

**Figure 1**
Four Possible Diastereomers
Conclusion

Pentacovalent oxaphopholene (P(V)s) can be reacted with electrophiles to produce highly substituted phosphonates. If an imine is used as an electrophile then γ-phosphono-amino acids are produced. However, simple imines are not good electrophiles. The addition of a sulfoxide group (electron withdrawing group) makes an imine a better electrophile. By reacting p-toluenesulfinamide with hydrocinnamaldehyde, (S)-(+)N-(3-phenyl)-butyl-p-toluenesulfinamide (1), a decent electrophile, was produced. With the aid of magnesium bromide, the imine was reacted with 2,2,2-triethoxy-2,2-dihydro-5-methyl-1,2λ5-oxaphospholene (P(V)) to make (3S)-(+)diethyl-2-(1-oxoethyl)-5-phenyl-(3-N-p-toluenesulfinamido) pentylyphosphonate(2). Since the reaction was run at room temperature, three of the four diastereomers resulted. To get stereoselectivity, the reaction should be run at 0°C.
Experimental

Preparation of (S)-(−)-N-(3-phenyl)-propyl-p-toluenesulfinamide (1). To 1.72 g (1.7 mL, 12.88 mmol, 2 eq) of hydrocinamaldehyde, 1 g (6.44 mmol, 1 eq) of p-toluenesulfinamide was added. To this reaction mixture, 12.0 g of molecular sieves were also added. The reaction was followed using TLC by looking for the disappearance of the starting material (p-toluenesulfinamide) using 50% hexanes in ethyl acetate as the solvent. In flash chromatography, 20% ether in hexanes was used as the solvent. The reaction yielded 1.26 g of pure product (75% yield).

Figure 2
Compound (1)

1: Rf (20% diethyl ether in hexanes)=.3; 1H NMR: 8.275 (1H, t, J=4.43, J=4.21, H on C1), 7.505 (2H, d, J=8.160, 1H on C11 and C15), 7.28 (2H, d, J=7.97, 1H on C12 and C14) 7.19 (5H, m, 1H on C5, C6, C7, C8, and C9), 2.93 (2H, m, H’s on C3), 2.80 (2H, m, H’s on C2), 2.40 (3H, s, H’s on C16)
Preparation of (3S)-(+)-diethyl-2-(1-oxoethyl)-5-phenyl-(3-N-p-Toluensulfinamido) pentylphosphonate. In a 50mL round bottom flask with a stir bar and fitted with an argon inlet was flushed with argon and allowed to cool. To this round bottom, 0.52g (2.32mmol, 1.14eq) of the standard P(V) was transferred via cannula. In a separate 15 mL round bottom flask flushed with argon, a solution of MgBr₂ was made by mixing 0.5264g (2.04mmol, 1eq) magnesium dibromide with 2 mL distilled diethyl ether and 1 mL distilled CH₂Cl₂. The MgBr₂ solution was added to the P(V) via cannula. The round bottom flask was washed with 1 mL diethyl ether and was added to the P(V) mixture. In a third 15 mL round bottom flask, 0.52g (2.04mmol, 1eq) of the amide was dissolved using 5 mL CH₂Cl₂. The amide solution was added to the P(V) via cannula. The round bottom was washed with 1 mL CH₂Cl₂ and the wash was added to the P(V) mixture. The mixture was allowed to stir in an ice bath at 0°C for 4 hours. It was then allowed to warm to room temperature overnight and stir at room temperature for 23 hours. The reaction was followed using TLC with 20% diethyl ether in hexanes as a solvent. This disappearance of the imine (1) was watched. To the reaction mixture, 5 mL of phosphate buffer (pH 7.2) was added and the mixture was allowed to stir at room temperature for 1 hour. The organic layer was extracted using CH₂Cl₂ (3 x 25 mL). The combined solution was dried over anhydrous Magnesium Sulfate. The solvent was removed under reduced pressure and the crude product was weighed (1.0406 g crude product). The crude mixture (only 300mg) was separated and purified using high performance liquid chromatography using 1% methanol in CH₂Cl₂. Like fractions were combined and the solvent was removed under reduced pressure.
Figure 3
Compound (2)
Appendix A

Figure 4
Proton NMR of product 1

Figure 5
Section of Proton NMR of product 1 (2.6-3.2 ppm)
Figure 6
Section of Proton NMR of product 1 (7.05-7.40 ppm)

Figure 7
Section of Proton NMR of product 1 (7.45-7.6 ppm)
Figure 8
Section of Proton NMR of product 1 (8.15-8.45 ppm)
Appendix B

Figure 9
Phosphorus 31-proton decoupled NMR of product 2 (Crude)

Figure 10
Phosphorus 31-proton decoupled NMR of product 2 (After HPLC)
Figure 11
Proton NMR of product 2 (Crude)
References


