4-23-2015

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Chem 360: Research Paper (Laboratory Project)
Spring 2015

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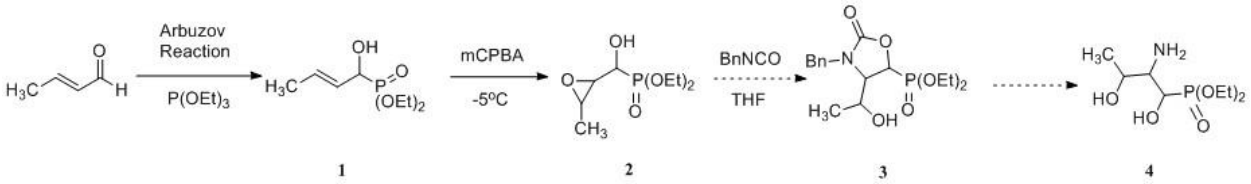

Figure 1. Reaction Scheme

ABSTRACT: This research involves the synthesis of one diethyl amino-dihydroxy butyl phosphonate which hold characteristics shown to serve as an anti-fungal and anti-microbial agent. The first step of this research involves epoxidation of the phosphonate-containing olefin made using the Arbuzov procedure with crotonaldehyde. The second step synthesizes an oxazolidone using benzyl isocyanate to open the epoxide and cyclize the compound. Hydrolysis of the oxazolidone is performed for the production of the 1, 2 amino-alcohols in the third stage. This step synthesizes the amino-phosphonates. The first and second steps have been completed. Upon successful retrieval of the oxazolidones, the alcohol can be synthesized. The oxazolidone will also be manipulated to produce phosphonosugars. Throughout the exploration of these compounds, stereo-chemical manipulation on the epoxides and their resulting products will also be investigated.

1. INTRODUCTION

Amino alcohols are widely studied for their use as anti-microbial and anti-bacterial agents. Because they are structurally similar to naturally occurring amino acids, these compounds have proven to be important for medicinal purposes.

One example of an amino alcohol used is ethambutol, used in the treatment of tuberculosis **1**.[9] Ethambutol stops the reproduction of bacteria from the tuberculosis bacilli. The hydroxyl and amino groups of the amino alcohol interact with mycolic acids which prevent the formation of the cell wall.

Amino alcohols are also useful in ring closure reactions, 1,2-additions and conjugate additions providing a demand for alternative methods of synthesis. These alcohols can be made via reaction of an

amine and an epoxide under acidic conditions however, this research uses the Arbuzov method to lead to phospho-amino alcohols. The intermediate phosphonate of this research can serve as an anti-fungal analogs and the cyclized product is biologically active, as it mimics several different cellular compounds. The resulting products of this technique are expected to hold characteristics similar to anti-microbial and anti-bacterial agents.

This technique provides one alternative method to the syntheses of this family of compounds.

2. RESULTS AND DISCUSSION

The initial procedure used for the formation of compound **1** involved triethylamine.

Figure 2. TEA vs. Solvent-free conditions (product)

Although compound **1** had been obtained, the triethylamine proved to be difficult to remove from the product. Step **1** was then performed under solvent-free conditions resulting in the desired product with a 94% yield. The phosphorus NMR spectra had shown two peaks possibly due to the presence of excess phosphite.

Compound **2** had been obtained within the crude product (43% yield). This step resulted in an abundance of mCPBA side product however, H^1NMR spectra served as evidence of the epoxide with the peaks appearing at 3.13 ppm and 3.21 ppm. The alkene peaks had disappeared from the spectra as well, compared to the starting olefin phosphonate. To retrieve the pure epoxide, Reversed-phase chromatography was performed to separate the epoxide from the mCPBA side product. This column provided a 5.21 % yield, i.e. for every 10 mg placed on a 10 g C18 column, only ~0.5 g of pure epoxide was received. Evidence of the pure epoxide was given by a peak in mass spectrometry data of the sample showing ~225 g (the molecular mass of compound **2**).

Step **3** had been performed, however the product obtained contained an excess of benzyl isocyanate making it difficult to interpret whether or not compound **3** had been achieved. After removing some benzyl isocyanate, one promising peak had been discovered in the P^{31}NMR at 22.86 ppm. The absence of epoxide peaks in the H^1NMR also hints that the cyclization step is promising with the epoxide resulting from the crotonaldehyde phosphonate. It is vital that freshly distilled or freshly opened benzyl isocyanate is used in this step to ensure that the amount of side reactions taking place is reduced.

3. CONCLUSION

Step **1** shows no issues that should be addressed other than ensuring the phosphonate is isolated before continuing to step **2**. Alternative methods of epoxidation should be explored to reduce the amount of time spent on purification. Apart from this, an economic alternative would be to find a more efficient method of separating the mCPBA side product from the epoxide as well as any starting material.

To further enhance the phospho-amino alcohol products, stereochemical methods of epoxidation will be explored. Once steps **2** & **3** have been improved to receive the best results, the oxazolidinone can be hydrolyzed to form the phosopho-amino alcohol.

4. EXPERIMENTAL SECTION

Spectral Measurements: Infrared spectra were recorded using Thermo Scientific iD5 ATR. Nuclear Magnetic Resonance spectra measured using JEOL instrument ECA-400 MHz. Gas Chromatography with Mass Spectrometry data collected using Varian 3800 Gas Chromatography and Varian 2000 GC/MS. Method used had inlet temperature of 250^{o}C. Ramp rate was 1 ml/min. Column oven started at 100^{o}C/ min and was held for 1 minute. Temperature in column oven moved to 250^{o}C/min and was held at 20 minutes for a total of 31 minutes.

Chemicals: Crotonaldehyde was purchased from Kodak Chemicals Company. Diethyl phosphite, calcium oxide and dihydrogen potassium phosphate purchased from Fisher Scientific. Solvents were provided by the stockroom.

Synthesis of Phosphonate of Crotonaldehyde: A solution 0.414 ml (0.005 mol) crotonaldehyde and 0.652 ml (0.0051 mol) diethyl phosphite was made at room temperature. 0.286 g (0.0051 mol) calcium oxide was added to this mixture and the reaction was ran for 15 minutes while being monitored via TLC with 50:50 hexanes/ethyl acetate. The product was extracted using dichloromethane (5 ml x 4). This solution was ran through a glass pipette packed with celite and a small layer of $MgSO_4$. The obtained filtrate was evaporated down to a yellow, transparent liquid. This compound was dissolved in dichloromethane (10 ml), ran through a silica gel plug and concentrated to a light yellow, transparent liquid. IR (ATR): 3300.53 (O-H) cm^{-1}, 1443.64 (C=C) cm^{-1}, 1230.21 (C-O) cm^{-1}; 1H-NMR ($CDCl_3$, 400 MHz): 1.34 (6H, dt, J= 8 Hz, 4 Hz, $CH_2C\mathbf{H}_3$), 1.75 (3H, t, J= 0.8 Hz, $CHC\mathbf{H}_3$), 4.16 (4H, dq, J= 8 Hz, 4 Hz, $C\mathbf{H}_2CH_3$), 4.38(1H, dd, J= 4 Hz, CHC**H**OH), 5.63(1H, dq, $CH_3\mathbf{H}C$), 5.86(1H, dq, CHOC**H**COH); 13C-NMR ($CDCl_3$, 400 MHz): 16.55(CH2**C**H3), 18.05(**C**H_3CHCHCOH), 63.10 (O**C**H2CH3), 68.74 (CHOH), 70.34 (CHOH), 125.48 (CH_3**C**HCHCOH), 130.50 (CH**C**HCOH).

Synthesis of Crude Epoxide: A solution of 5 ml dichloromethane and 0.42 g (2 mmol) previously synthesized phosphonate was made. 1.05 g (6 mmol) K_2HPO_4 was added to the mixture and combined mixture was kept at -5^{o}C using an ice and salt water bath. In 3 ml dichloromethane, 1.04 g (6 mmol) mCPBA was initially dissolved and quickly transferred to stirring mixture. The mixture was stirred for 2 hours at -5^{o}C. $NaHCO_3$ (6 ml) and TBME (30 ml) were added to the mixture while stirring. The aqueous layers were extracted using TBME (6 ml x 2). Combined organic layers were washed with $NaHCO_3$ (3 ml x 2) and brine (6 ml). Extracted layers were dried, filtered and evaporated to receive crude epoxide. White chunky solid was obtained. 1H-NMR ($CDCl_3$, 400 MHz): Epoxide peaks 3.13(1H, OC**H**CHOH), 3.21(1H, $CH_3C\mathbf{H}O$) NO ALKENE PEAKS. 13C-NMR ($CDCl_3$, 400 MHz): NO C=C PEAKS.

Purification of Epoxide: Crude epoxide was purified using C18 column and a Reversed-phase column chromatography method. Fractions were dried using lyophilizer and analyzed. 1H-NMR ($CDCl_3$, 400 MHz): 3.13(1H, t, J= 8 Hz, OC**H**CHOH), 3.21(1H, q, J= 16 Hz, $CH_3C\mathbf{H}O$); GC/MS: 8.483 min, 225 ($C_8H_{17}O_5P$)

Cyclization of Epoxide using Benzyl Isocyanate: A solution of 0.021 g (0.09 mmol) purified epoxide and 5 ml THF was prepared and treated with 0.0043 g (0.18 mmol) sodium hydride. This mixture was allowed to stir for 10 minutes at room temperature. Freshly opened benzyl isocyanate (0.018 g, 0.135 mmol) was added

and reaction was heated to reflux for 1.5 hours. The mixture was cooled to 0^{o}C and quenched with saturated NH_4Cl (0.5 ml). The solution was extracted using dichloromethane (0.5 ml x 4). Combined organic layers were dried over sodium sulfate, filtered and evaporated to receive crude product. An opaque orange solid was obtained.

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