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Investigation of New Methods for the Synthesis of Pyrrolidines and the Generation of Novel Heterocumulenes

Travis R. Taylor
Utah State University

SENIOR THESIS

INVESTIGATION OF NEW METHODS FOR THE SYNTHESIS OF PYRROLIDINES AND THE GENERATION OF NOVEL HETEROCUMULENES

TRAVIS R. TAYLOR

Utah State University

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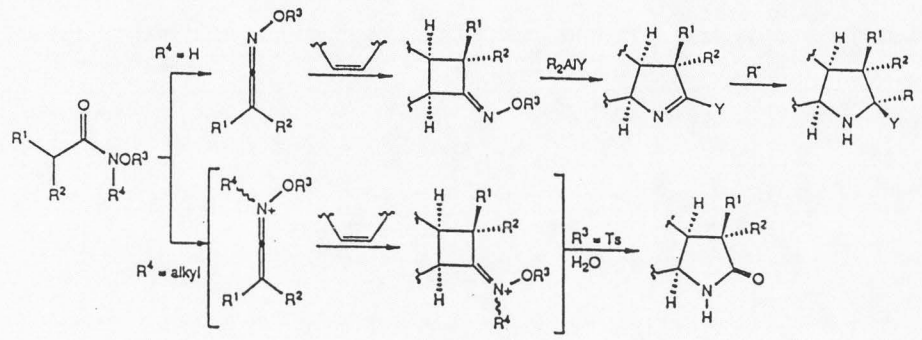
for
Dr. Eric Edstrom

INTRODUCTION

The following paper is a summary of the research completed from March to August of 1990. This research project proceeded through the guidance of Dr. Eric Edstrom incorporating a senior thesis in conjunction with the Honors Program.

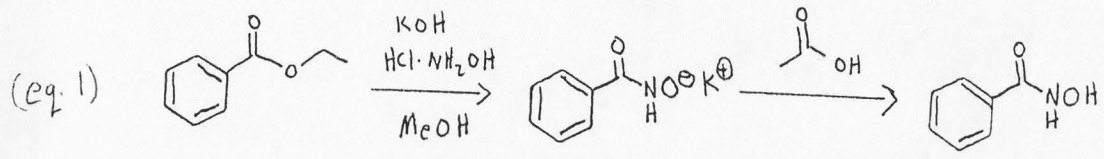
The long term research plan[1] is to investigate new synthetic methods for the generation of substituted pyrrolidines. The synthesis begins with the generation O-benzyl acetohydroxamate esters containing electron withdrawing groups on the alpha carbon. The top route shows O-alkylated hydroxamate esters being converted to their respective ketene oximes in the presence of electron rich alkenes to form the [2+2] cycloadduct. The cycloadduct, an oxime analog of cyclobutanone, would then be subjected to a literature presented ring expansion to give a cyclic imine which then would be reduced to give the substituted pyrrolidine. The bottom route shows the O-alkylated-N-alkylated hydroxamate esters being converted to their corresponding ketene iminium salt. These molecules would be more reactive than the ketene oximes and we would expect that they would undergo cycloadditions with a wider variety of alkenes. Literature shows that ring expansion to give the lactam is spontaneous upon the addition of water. The scheme is shown below.



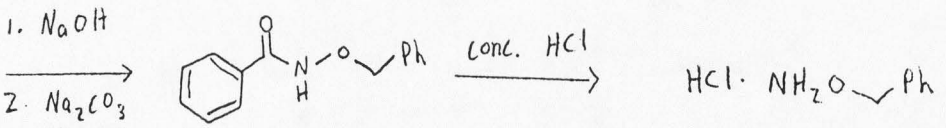
The top reaction scheme from the synthesis of the O-alkylated hydroxamate esters to the [2+2] cycloadduct was investigated. The synthesis of N-alkylated-O-alkylated hydroxamate esters was briefly explored.

DISCUSSION

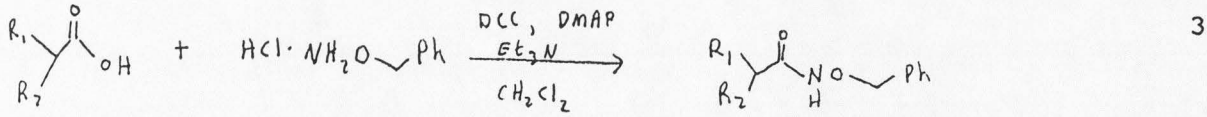
The first step in this project is the synthesis of the O-benzyl hydroxamate esters. A reasonable synthetic route was found incorporating several preparations. The route involves making potassium benzohydroxamate[2] **1**, alkylating it with benzyl bromide[3], and cleaving the amide bond with concentrated hydrochloric acid to form the O-benzyl hydroxylamine hydrogenchloride salt[4] **3** (eq 1). The substituted hydroxamates **4a,b,c** were prepared by deprotonating the hydroxylamine salt and subjecting it to a DCC coupling with the appropriate carboxylic acid[5](eq 2).



1 (62.8%)

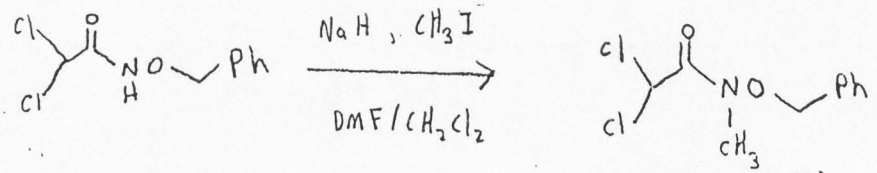


2 (73.0%) 3 (62.5%)

(eq 2) 

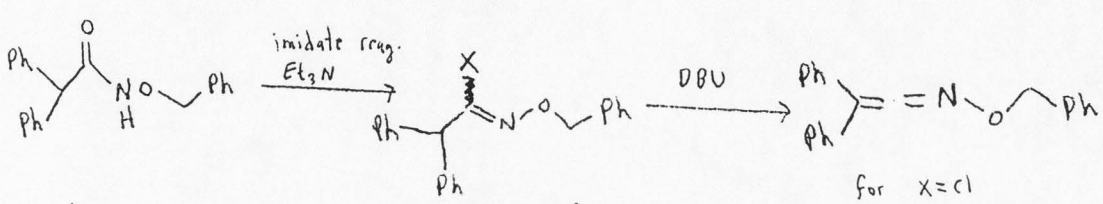
4a $R_1 = R_2 = Ph$ (88.9 %)
4b $R_1 = R_2 = Cl$ (92.3 %)
4c $R_1 = H$, $R_2 = SO_2Ph$ (69.5 %)

The generation of the N-methyl-O-benzyl hydroxamate esters was investigated[6]. The acetohydroxamate ester **4b** afforded the product **5** with a yield of 20% (eq 3).

(eq 3) 

5 (22.8 %)

The preparation of diphenyl-acetohydroxamate **4a** (eq. 4) was initially investigated because it should give the more stable cumulene which can be isolated. Several reagents were used to make the imidate. These reagents included triflic anhydride[7], triphenyl phosphine dibromide[8], phosphorus pentachloride[9], and oxalyl chloride. Most imidates formed were unstable and reliable isolated yields were difficult to obtain.

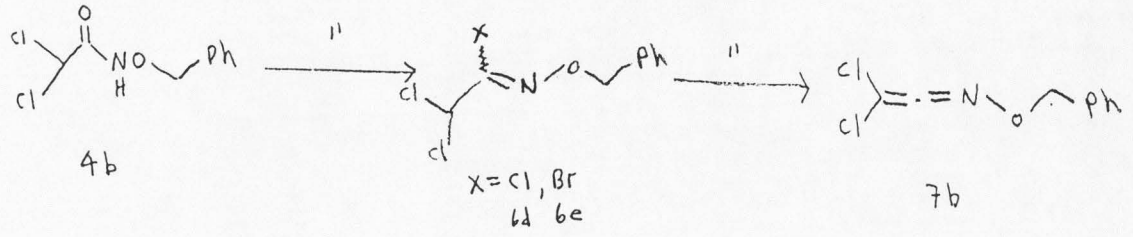
(eq 4) 

4a

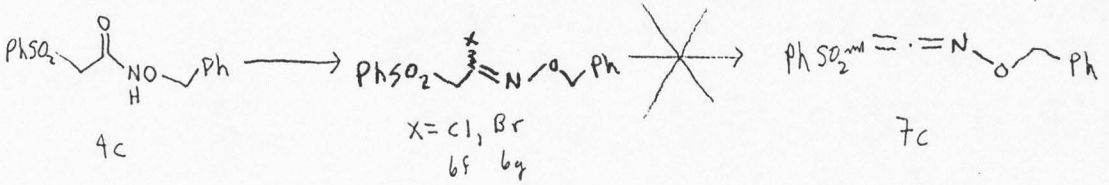
X = OTf, Cl, Br
6a 6b 6c

for X = Cl
7a (79.6 %)

(eq 5)



(eq 6)



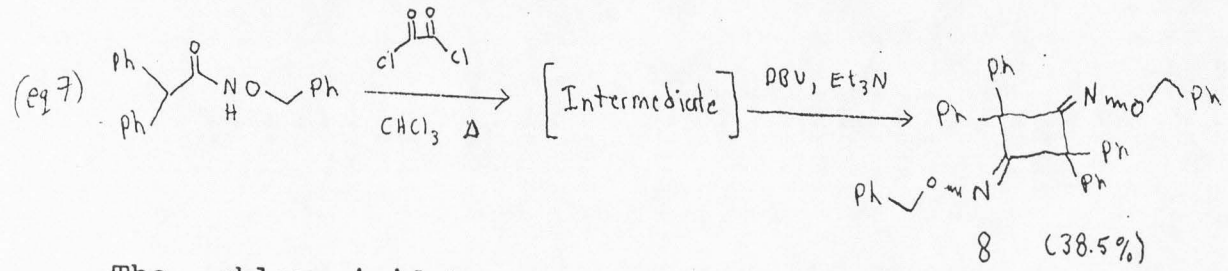
Triflic anhydride appeared to make the imidate **6a**, however the imidate did not chromatograph well and was hard to isolate. Attempts were made to form the cumulene by treatment with base however, no success was met. Treatment of **6a** with lithium diisopropyl amide under refluxing gave none of the desired cumulene as evidenced by inspection of the crude NMR data.

Triphenyl phosphine dibromide was utilized to make the bromo-imidate **6c,e,g**. The preparation of the bromo-imidate **6c** afforded product in 40.8% yield and a 15.2% recovery of starting material. Attempts were made to collapse the **4c** into the cumulene using DBU, but this failed(eq. 6).

Phosphorus pentachloride was used to make chloro-imidates **6b,d**. Phosphorus pentachloride sublimes and is very sensitive to the moisture in air, thus the use of this reagent was suspended. The chloro-imidate **6b** was made with a 49.2% crude yield (eq. 4).

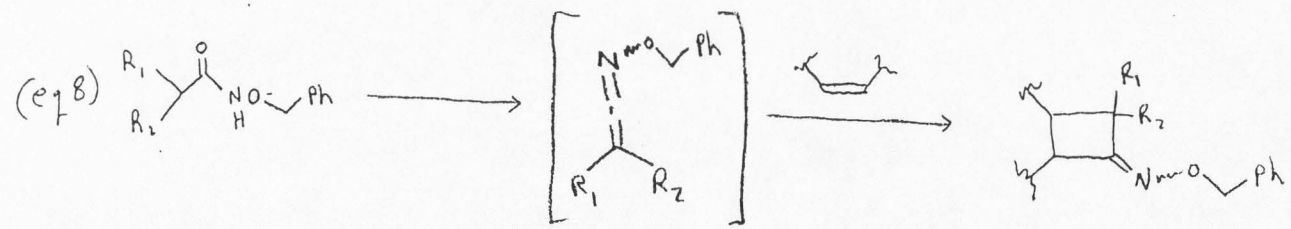
Oxalyl chloride appeared to be the most promising reagent because it gives no byproducts. It gave the chloro-imidate **6f** with moderate yields. The cumulene **7a** and the chloro-imidate **6b** were

also generated. The cumulene **7a** was isolated to afford a yield of 79.6% (eq. 4). Refluxing a solution of **4a** with oxalyl chloride and later adding the two equivalents of base, generated a possible dimer **8** of the cumulene (eq. 7).



8 (38.5%)

The chloro-imidate **6d** and the cumulene **7b** of the dicholoroacetohydroxamate were synthesized, but both compounds were extremely reactive and decomposed on silica (eq. 5). They were tentatively identified by inspection of their crude ^{1}H NMR spectra.



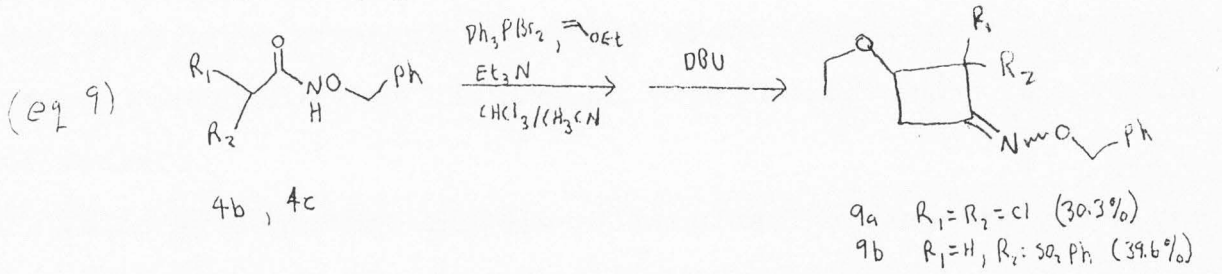
The generation of electron deficient ketene oximes in the presence of electron rich alkenes was carried out with the expectation that these transient species would be readily trapped as the [2+2] cycloadduct[10] (eq. 8).

Experiments were carried out using dihydropyran, norbornylene, 1-cyclohexenyloxytrimethylsilane[11], and ethyl vinyl ether as the traps. As expected, cycloadducts were only formed from the electron rich alkenes.

Several trapping experiments were tried using oxalyl chloride

and two equivalents of base. It appears that these experiments were the victim of severe polymerization of the trap and cumulene. In some cases it appeared that the dimer and trimer cycloadducts were formed, however, these products decomposed on silica gel. These experiments were also duplicated in a sonicator. The crude ^1H NMR suggested the presence of polymeric material which was further supported by streaky multiple spotted TLC runs.

The most promising cycloadditions utilized triphenyl phosphine dibromide. The cycloadduct **9a** of dichloroacetohydroxamate with ethyl vinyl ether was isolated to give a 30.3% yield. The cycloadduct **9b** of phenyl sulfonyl hydroxamate and ethyl vinyl ether gave a 39.6% yield (eq. 9).



Compounds **4c**, **7a**, **8**, **9a**, and **9b** were found to be consistent with their respective ^1H NMR, ^{13}C NMR, and FT-IR spectra. However the mass spectrometer data doesn't show molecular ion for any of the compounds and most of the spectra doesn't show expected fragments. More intense NMR data will need to be performed to determine absolute structure proof.

SUMMARY

The experiments performed showed a distinct pattern for the

instability of the triflate, chloro-, and bromo-imidates. They also showed the instability of the cumulenes containing EWGs. It appears that the cyclo-addition products are promising. However it may take some period of time to fully work out the reaction conditions to hinder polymerization and improve yield of currently working reactions.

It appears that the reaction doesn't follow a concerted pathway. It has been observed when dealing with the brominating reagent that if the trap and the second equivalent of base is added at the same time or if the base is added before the trap that the reaction doesn't proceed with any efficiency. However, if the trap is added to the bromoimidate and the second equivalent of base added hours later a reasonable amount of desired product is formed. It seems reasonable that the product goes through and a zwitter ion intermediate.

It is evident that the use of brominating reagents gives the desired product and chlorinating reagents give polymerizations. From this evidence brominating reagents should be the focus in future experiments. Oxalyl bromide, triphenyl phosphine dibromide, and thionyl bromide would be worth exploring. Thionyl bromide is relatively inexpensive and its byproduct is easily removed. Another method[13] involving phosphorus pentaoxide and aluminum oxide may also be useful.

The ketene iminium salts may prove to be much more reactive and give better yielding cycloadducts.

EXPERIMENTALS

The ^{1}H and ^{13}C NMR spectra were obtained from a Varian 300XL nuclear magnetic resonance spectrometer. ^{1}H chemical shifts were reported in ppm relative to chloroform-d_1 assigned at δ 7.26 ppm. ^{13}C chemical shifts are reported in ppm relative to chloroform-d_1 at δ 77.0 ppm.

Infrared spectra was taken using a Perkin-Elmer FT-IR spectrometer. All solvents used were distilled prior to use over calcium hydride.

O-benzyl hydroxylamine hydrogen chloride salt[2,3,4] A solution was prepared by adding 46.7 g (0.67 mole) of hydroxylamine hydrogen chloride to 240 mL methanol. A second solution was prepared by adding 56.1 g (1.00 mole) of potassium hydroxide to 140 mL of methanol. The solutions were prepared at the boiling point of methanol. The solutions were cooled slowly to 30-40 °C and the potassium hydroxide solution was added to the hydroxylamine hydrogen chloride solution. The reaction mixture was cooled in an ice bath to ensure the precipitation of potassium chloride. Next 50.0 g (0.33 mole) of ethyl benzoate was added to the reaction mixture. The resulting mixture was shaken momentarily and filtered by suction. The filtrate was washed with cold methanol and allowed to stand for two days. The crystals were collected from the filtrate and washed with cold absolute ethanol. The reaction yielded 36.6 g (62.8%) of potassium benzohydroxamate.

The potassium benzohydroxamate was converted to the corresponding hydroxamic acid by dissolving it in one equivalent

of 1.25 N acetic acid. The hydroxamic acid was recrystallized by dissolving it in 4.5 times its weight in hot ethyl acetate.

A solution of 20.0 g (0.146 mole) of benzohydroxamic acid was prepared in 45 mL of water. A solution of 5.84 g (0.146 mole) of sodium hydroxide in 45 mL of water was added to the benzohydroxamic acid solution. To the existing mixture 133 mL of methanol, 20.9 mL (0.175 mole) of benzyl bromide, and 7.74 g (0.073 mole) of sodium carbonate were added. The reaction was stirred at room temperature for 24 h. The reaction was tested for completion using the ferric chloride test.

After the reaction was complete the methanol was removed under reduced pressure and acidified with 12 N hydrochloric acid. The reaction mixture was extracted with four portions of chloroform. The chloroform extractions were washed with a 10% sodium bicarbonate solution. The chloroform layer was extracted with six 18 mL portions of a 6 N sodium hydroxide solution.
The aqueous layer was acidified with 12 N hydrochloric acid and extracted with two equal portions of chloroform. The chloroform layer was dried with sodium sulfate. The O-benzyl benzohydroxamate ester was recrystallize from a 50% ethyl acetate and hexanes mixture. The reaction gave a yield of 23.9 g (73.0%).

A solution of 23.0 g (0.102 mole) of O-benzyl benzohydroxamate was prepared in 191 mL of ethanol. The amount of 272 mL (32 eq) of 12 N hydrochloric acid was added to the solution and the mixture was refluxed for 30 min. The solution was cooled briefly and 200

mL of water was added. The solution was extracted with 332 mL of chloroform while the reaction mixture was still hot. The aqueous layer was evaporated to dryness. The crude product was recrystallized from 2.0 N hydrochloric acid. The crystals were washed with cold absolute ethanol and dry ether. The reaction yielded 10.2 g (62.5%) of O-benzyl hydroxylamine hydrogen chloride.

General synthesis for O-benzyl hydroxamate esters (4a,b,c) A solution of 2.26 g (14.2 mmol) of O-benzyl hydroxylamine hydrogen chloride and 1.97 mL (14.2 mmol) of triethylamine was prepared in 50 mL of dichloromethane. To the existing mixture 2.92 g (14.2 mmol) of DCC, 3.00 g (14.1 mmol) of diphenylacetic acid, and 0.173 g (1.41 mmol) of DMAP were added. The reaction was allowed to stir for 24-36 h at room temperature. The reaction mixture was filtered by suction to remove urea. (Note: The phenyl sulfonyl acetic acid by prepared by oxidation of the corresponding sulfide with 30% hydrogen peroxide.)[12]

O-benzyl diphenylacetohydroxamate (4a) This compound was purified by flash chromatography (20% ethyl acetate:hexanes) to give 3.98g (88.9%) of a white solid: FT-IR (neat) 3175, 3088, 3063, 3030, 2979, 1657, 1368, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.76 (1 H, bs), 4.90 (2 H, bs), 7.29 (15 H, m), 8.22 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 55.86, 78.10, 127.32, 128.52, 128.67, 129.36, 134.93, 138.35, 169.48; MS m/e 28.0, 91.2, 167.0, calcd for $C_{21}H_{19}N_1O_2$ 317.0, measured 317.0.

O-benzyl dichloroacetohydroxamate (4b) This compound was purified by flash chromatography (20% ethyl acetate:hexanes) to

give 0.838g (92.3%) of a white solid: FT-IR (neat) 3169, 3020, 2933, 2872, 1682, 1218, 1009, 838, 808 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.96 (2 H, s), 5.90 (1 H, s), 7.41 (5 H, bs), 8.94 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 64.30, 78.46, 128.70, 128.98, 129.16, 129.53, 134.12, 161.60; MS m/e 51.1, 65.2, 77.3, 91.2, calcd for $C_9H_9Cl_2N_1O_2$ 233.9, measured 233.0.

O-benzyl phenyl sulphonylacetohydroxamate (4c) This compound was purified by flash chromatography (40% ethyl acetate:hexanes) to give 0.55g (69.5%) of a white solid: FT-IR (neat) 3203, 3034, 1657, 977, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.55 (2 H, s), 4.84 (2 H, s), 7.30 (10 H, m), 8.93 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 35.26, 78.23, 126.89, 128.53, 128.67, 128.95, 129.15. 134.73, 165.47; MS m/e 28.0, 91.4, 273.6.

Diphenyl cumulene (7a) A solution of 150 mg (0.474 mmol) of O-benzyl diphenylacetohydroxamate in 1.0 mL of acetonitrile was prepared. Then 45.6 μL (0.522 mmol) of oxalyl chloride was added and the reaction was stirred at room temperature for 15 min. Next 69.3 μL (0.498 mmol) of triethylamine was added and the reaction mixture was stirred for 4-5 h at room temperature. An amount of 78.0 μL (0.522 mmol) of DBU was added to the reaction mixture and the reaction was stirred for 12-18 h at room temperature. The crude reaction mixture was passed through a silica plug with a 20% ethyl acetate and hexanes mixture. The reaction afforded 113 mg (79.6%) of a yellow solid: FT-IR (neat) 3063, 3033, 2926, 2855, 1778, 1584, 1496, 1235, 1186 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.31 (2 H, s), 6.98 (5 H, bs), 7.33 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 79.22, 128.20,

128.59, 128.72, 128.88, 129.06, 129.93, 130.36, 132.21, 134.27, 154.86, 168.20, 190.25; MS m/e 91.2, 165.5, 194.2, 237.1.

Diphenyl dimer (8) A solution of 150 mg (0.474 mmol) of O-benzyl diphenylacetohydroxamate in 1.0 mL of chloroform was prepared. Then 45.6 μL (0.522 mmol) of oxalyl chloride was added and the reaction allowed to stir at room temperature for 2 h. The solution was refluxed for 2 h. Then 69.3 μL (0.498 mmol) of triethylamine was added and the mixture was stirred for 15 min. after which 78.0 μL (0.522 mmol) of DBU was added. The reaction was allowed to stir for 30 min at room temperature. The crude reaction mixture was run through a pipet silica plug with a 30% ethyl acetate and hexanes mixture. The reaction gave a crude mass of 112 mg. The compound was purified by flash chromatography (30% ethyl acetate:hexanes) to afford an isolated yield of 54.5 mg (38.5%) of an oil: FT-IR (neat) 3061, 3032, 2366, 1713, 1497, 1452, 1149 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.55 (2 H, s), 6.00 (2 H, s), 7.10 (10 H, m), 7.33 (20 H, m); ^{13}C NMR ($CDCl_3$) δ 56.96, 77.93, 127.35, 128.63, 128.79, 129.16, 129.68, 133.58, 137.79, 172.39; MS m/e 319.0, 339.0, 381.0.

Dichloro-cumulene adduct w/ethyl vinyl ether (9a) A solution was prepared by dissolving 47.8 mg (0.182 mmol) of triphenyl phosphine in .350 mL of a 1:1 acetonitrile/chloroform mixture. This solution was cooled to 0 °C and 9.40 μL (0.182 mmol) of bromine was added. The reaction was stirred until a precipitate formed. Next 36.95 mg (0.158 mmol) of O-benzyl

dichloroacetohydroxamate, 0.150 mL of the solvent mixture, 23.6 μL (0.169 mmol) of triethylamine, and 39.9 μL (0.417 mmol) of ethyl vinyl ether were added to the reaction. The reaction mixture was stirred at room temperature for 30-45 min. Then 25.3 μL (0.169 mmol) of DBU was added to the reaction. The reaction was stirred for another 5-6 h at room temperature. Water was added to the reaction mixture and it was extracted with ether. The organic layer was dried with sodium sulfate. The compound was purified by flash chromatography (20% ethyl acetate:hexanes) to give 13.8 mg (30.3%) of an oil: FT-IR (neat) 3034, 2976, 1698, 1396, 1110, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (3 H, t), 1.54 (2 H, d), 3.62 (1 H, m), 3.80 (1 H, m), 5.03 (1 H, d), 5.31 (1 H, d), 5.78 (1 H, m), 7.44 (5 H, bs); ^{13}C NMR ($CDCl_3$) δ 14.98, 18.16, 63.34, 64.28, 80.5, 84.57, 129.00, 129.47, 133.65 (**note we are missing one carbon, the oxime carbon, from the proposed structure take another spectra and find it**); MS m/e 45.1, 73.4, 77.2, 91.2, 260.0, 304.9.

Phenyl sulfonyl adduct w/ethyl vinyl ether (9b) A solution was prepared by dissolving 41.4 mg (0.158 mmol) of triphenyl phosphine in 0.315 mL of dichloroethane. The solution was cooled to 0 °C and 8.14 μL (0.158 mmol) of bromine was added. The reaction was stirred until a precipitate formed. Next 48.2 mg (0.158 mmol) of O-benzyl phenyl sulfonylacetohydroxamate, 0.185 mL of dichloroethane, 23.6 μL (0.169 mmol) of triethylamine, and 39.9 μL (0.417 mmol) of ethyl vinyl ether were added to the reaction mixture. The reaction was stirred at 0 °C for 45 min. The solution was warmed to room temperature and stirred for 7 h. Last of all

25.3 μL (0.169 mmol) of DBU was added. The reaction mixture was stirred at room temperature for 12-16 h and refluxed for 6 h. The product was purified by flash chromatography (30% ethyl acetate:hexanes). The reaction afforded a yield of 22.5 mg (39.6%).

WORK CITED

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