An Example of a Novel Formation of an Oxepin

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A novel formation of an oxepin, namely 9,10,11,12-tetrafluoro-5,6-dihydrobenzo[*b*]naphth[2,1-*f*]oxepin (**5**), starting from pentafluoroacetophenone and 1-tetralone is described. Also, the same synthesis using 1-indanone affords a very different ring system namely 1,2,3,4-tetrafluoro-5,11b-dihydro-7*H*-benzo[*c*]fluoren-7-one (**10**). Both synthesis undergo an intramolecular nucleophilic substitution of an *ortho*-fluorine. In one case, the oxygen displaces the fluorine to afford the oxepin **5** and the other a carbon is used as the nucleophile to give the polycyclic ring system **10**.

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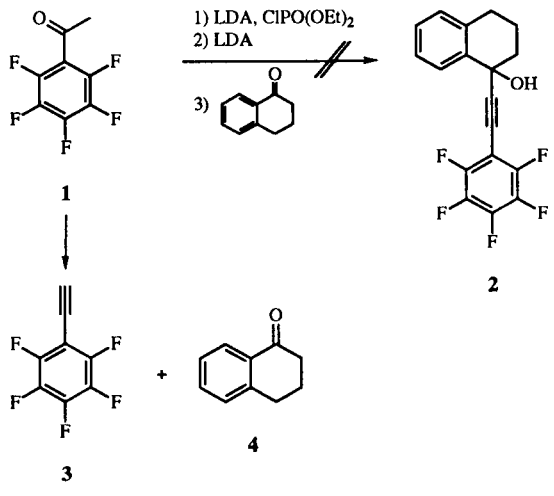
We have recently reported [1] the synthesis of a series of phenylproparginols and the related herbicidal activity. In the course of this work a novel synthesis of oxepins was discovered.

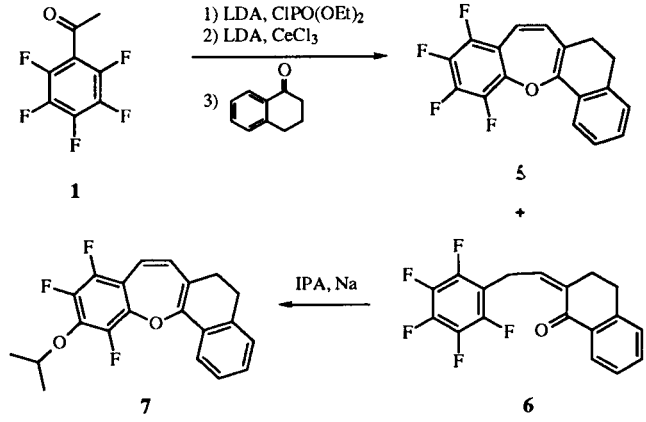
Previously, the synthesis of compound **2** was attempted using a sequential but "one-pot" enol phosphate procedure [2] as shown in Scheme 1. The enolate of pentafluoroacetophenone was formed using lithium diisopropylamide followed by the addition of diethyl chlorophosphate to afford the enol phosphate. The enol phosphate was treated with two equivalents of lithium diisopropylamide to form the acetylide anion followed by quenching with 1-tetralone only to yield the starting material **4** (1-tetralone) and 1-ethynyl-2,3,4,5,6-pentafluorobenzene **3**. No evidence of the desired product was observed in the mass spectrum. It is proposed that instead of addition of the acetylide anion to the carbonyl group of **4**, enolization occurred.

Scheme 1



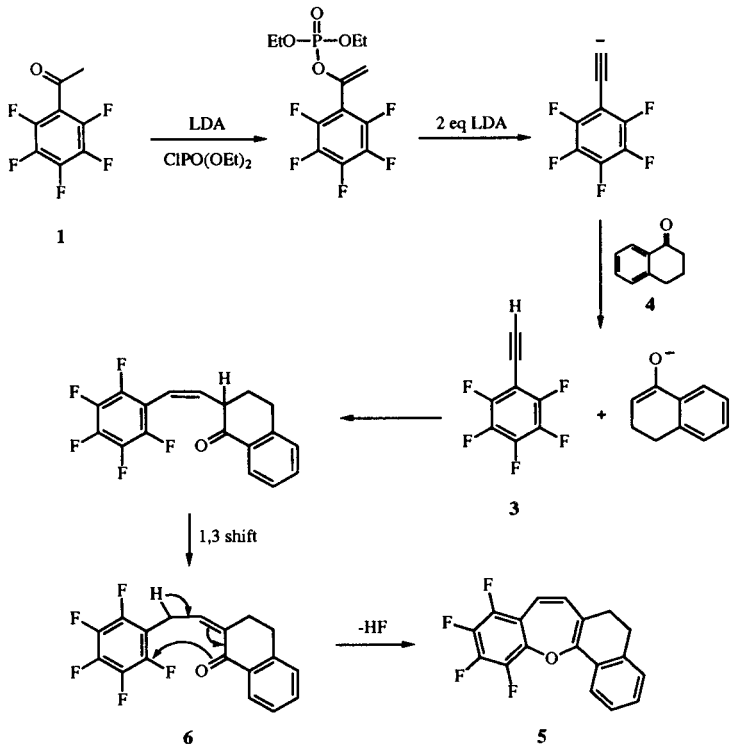
The issue of the acetylide anion not adding easily to enolizable carbonyl compounds has been overcome by the use of the organocerium reagent [3]. Thus in an effort to prepare the desired product **2**, the same reaction was run as shown in Scheme 1 using anhydrous cerium(III) chloride. After formation of the lithium acetylide salt, anhydrous cerium(III) chloride was added to form the cerium acetylide reagent. This was quenched with 1-tetralone to afford a mixture of two products (Scheme 2). The novel heterocycle **5** along with the uncyclized compound **6**. None of the desired product **2** was seen by ms. It was to our surprise to discover that this reaction would afford the heterocycle **5**. To our knowledge this is the first preparation of an oxepin starting from pentafluoroacetophenone using an intramolecular nucleophilic substitution of an *ortho*-fluorine. Both compounds **5** and **6** were identified through an exhaustive list of nmr studies [4]. Treatment of the uncyclized compound **6** with excess isopropoxide resulted in cyclization and displacement of an additional fluorine with isopropoxy group to afford the substituted oxepin **7**.

Scheme 2



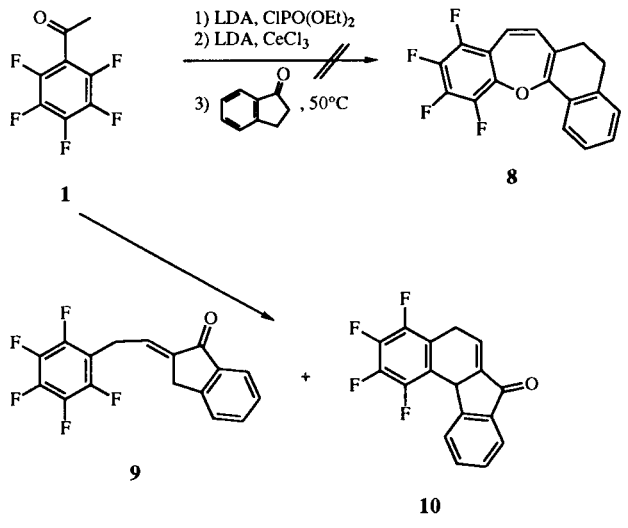
It appears that the α-carbon of the enol of 1-tetralone added to the terminal end of 1-ethynyl-2,3,4,5,6-pentafluorobenzene **3** resulting in the intermediate product shown in Scheme 3. The less stable intermediate compound underwent a 1,3-proton shift to afford the more stable compound **6**. Treatment of **6** with remaining excess base caused intramolecular cyclization with the oxygen displacing the fluorine atom to afford the oxepin **5**. This was facilitated by the cerium salt, as the prior reaction run

Scheme 3



without the cerium(III) chloride afforded only starting material. The reaction of intramolecular nucleophilic substitution of an *ortho*-fluorine atom is known as a specific method for the preparation of polyfluorinated 5- and 6-membered benzoheterocycles [5,6]. However, we could find only three examples of the formation of 7-membered heterocycles in this way [7,8,9], none of which included the formation of an oxepin.

Scheme 4



The same synthesis as in Scheme 2 was performed except 1-indanone was added to the acetylide anion followed by heating at 50° to help facilitate ring closure. The expected non-cyclized intermediate **9** was isolated along with an unexpected cyclized product **10**. Cyclization of **9** occurred, however, instead of the oxygen displacing the fluorine atom to form the oxepin **8**, the benzylic carbon displaced the fluorine atom to yield **10** (Scheme 4).

In summary, a sequential but "one-pot" synthesis starting from pentafluoroacetophenone was used to prepare two very different ring systems. The addition of anhydrous cerium(III) chloride is essential for the reaction to take place to afford these ring systems. The generality of this synthesis to prepare benz[*b*]oxepins is under investigation and will be described in future publications.

EXPERIMENTAL

Melting points were determined with a Mettler PF62 capillary melting point apparatus and are uncorrected. The ^{1}H, ^{13}C, ^{19}F nuclear magnetic resonance spectra were recorded using Bruker WM-360 and Varian XL-400 NMR spectrometers. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. Sample purity was determined by glc analysis on a Varian 3400 gas chromatograph utilizing a capillary column (0.53 mm internal diameter, DB-1 bonded phase, 1.5 micron film thickness, 30 meters). Normally, a temperature program from 100° to 300° at 15°/minute was employed. Column chromatography was performed on a Waters preparative liquid chromatography Model 500 using silica gel columns. Reported yields are not optimized with emphasis on purity of products rather than quantity.

9,10,11,12-Tetrafluoro-5,6-dihydrobenzo[*b*]naphth[2,1-*f*]oxepin (**5**).

At -78°, 3.0 g (0.014 mole) of pentafluoroacetophenone (**1**) dissolved in 30 ml of anhydrous tetrahydrofuran was treated with 7.7 ml of a 2.0 *M* solution of lithium diisopropylamide in heptane-tetrahydrofuran. After the addition was complete, the solution stirred an additional 15 minutes at -78°. A solution of 2.6 g (0.015 mole) of diethyl chlorophosphate in 5 ml of anhydrous tetrahydrofuran was added dropwise. After the addition was complete, the solution was allowed to warm to room temperature. The enol phosphate solution was added dropwise to a solution 16.9 ml of a 2.0 *M* lithium diisopropylamide in 20 ml of anhydrous tetrahydrofuran at -78°. After the addition was complete, the solution stirred an additional one hour at -78°. To the solution, 3.8 g (0.015 mole) of anhydrous cerium(III) chloride was added and the solution stirred an additional one hour at -78°. A solution 2.2 g (0.015 mole) of the 1-tetralone in 5 ml of anhydrous tetrahydrofuran was added dropwise. After the addition was complete, the solution was allowed to warm to room temperature overnight. The solution was then treated with 2*N* hydrochloric acid until acidic. The solution was extracted with ether and the ether layer was washed with water and brine. The solution was dried over magnesium sulfate, filtered and the solvent was removed to afford a mixture of two products. Fraction one of column chromatography (10% ethyl acetate-hexane) afforded 0.24 g (5.4%) of a yellow solid of **5**, mp 84-85°; ^{1}H nmr

(deuteriochloroform): ppm 2.48 (t, 2H, J = 8.1 Hz, CH_2), 2.85 (t, 2H, J = 8.1 Hz, CH_2), 6.30 (d, 1H, J = 11.4 Hz, =CH), 6.75 (d, 1H, J = 11.4 Hz, =CH), 7.14 (d, 1H, J = 7.3 Hz, ArH), 7.24 (t, 1H, J = 7.4, 7.4 Hz, ArH), 7.30 (t, 1H, J = 7.4, 7.4 Hz, ArH), 7.96 (d, 1H, J = 7.6 Hz, ArH); ^{13}C nmr (deuteriochloroform): ppm 26.8 (CH_2), 27.6 (CH_2), 118.1, 120.7 (=CH), 121.4, 122.9 (Ar-CH), 127.0 (Ar-CH), 127.3 (Ar-CH), 128.7 (Ar-CH), 130.8, 133.9 (=CH), 136.6, 137.9 (Ar-CF), 140.1, 140.3 (Ar-CF), 141.6 (Ar-CF), 143.0 (Ar-CF), 150.5; ^{19}F nmr (deuteriochloroform): ppm -145.2 (dd, 1F, J = 9, 22 Hz), -155.9 (t, 1F, J = 21, 20 Hz), -156.2 (dd, 1F, J = 9, 21 Hz), -162.7 (t, 1F, J = 20, 22 Hz).

Anal. Calcd. for $C_{18}H_{10}OF_4$: C, 67.93; H, 3.17. Found: C, 67.83; H, 3.17.

3,4-Dihydro-2-[2-(pentafluorophenyl)ethylidene]-1(2*H*)-naphthelenone (**6**).

Following the same procedure described for **5**, fraction two of column chromatography (10% ethyl acetate-hexane) afforded 0.76 g (16%) of a yellow solid of **6**, mp 72-73°; ^1H nmr (deuteriochloroform): ppm 2.95 (m, 2H, CH_2), 3.05 (m, 2H, CH_2), 3.64 (d, 2H, J = 8.0 Hz, CH_2), 6.78 (t, 1H, J = 8.0 Hz, =CH), 7.25 (d, 1H, J = 7.6 Hz, ArH), 7.32 (t, 1H, J = 7.6 Hz, ArH), 7.47 (t, 1H, J = 7.6 Hz, ArH), 8.06 (d, 1H, J = 7.6 Hz, ArH); ^{13}C nmr (deuteriochloroform): ppm 21.2 (CH_2), 25.7 (CH_2), 28.8 (CH_2), 112.3, 127.0 (Ar-CH), 128.2 (Ar-CH), 128.4 (Ar-CH), 132.2 (=CH), 133.1, 133.4 (Ar-CH), 136.2 (Ar-CF), 137.0 (=C), 138.8 (Ar-CF), 141.4 (Ar-CF), 143.6, 143.9 (Ar-CF), 146.4 (Ar-CF), 187.1 (C=O); ^{19}F nmr (deuteriochloroform): ppm -143.9 (dd, 2F, J = 8, 21 Hz), -157.1 (d, 1F, J = 217 Hz), -162.7 (dt, 2F, J = 8, 21 Hz).

Anal. Calcd. for $C_{18}H_{11}OF_5$: C, 63.91; H, 3.28. Found: C, 63.65; H, 3.26.

9,10,12-Trifluoro-5,6-dihydro-11-(1-methylethoxy)benzo[*b*]-naphth[2,1-*f*]oxepin (**7**).

To 15 ml of isopropyl alcohol at room temperature was added 0.5 g (0.021 mole) of sodium metal. The solution stirred until all of the sodium metal had reacted. To the solution was added 0.50 g (0.0014 mole) of **6** and the solution was heated at 50° overnight. The solution was diluted with ether and water. The ether layer was washed with water and brine. The solution was dried over magnesium sulfate, filtered and the solvent was removed to afford the crude product. The product was purified by column chromatography (3% ethyl acetate-hexane) to afford 0.30 g (57%) of a yellow oil of **7**; ^1H nmr (deuteriochloroform): ppm 1.88 (d, 6H, J = 6.0 Hz, CH_3), 3.00 (t, 2H, CH_2), 3.37 (t, 2H, CH_2), 5.04 (septet, 1H, J = 6.0 Hz, OCH), 6.75 (d, 1H, J = 11.1 Hz, =CH), 7.29 (d, 1H, J = 11.1 Hz, =CH), 7.65 (dd, 1H, J = 1.2, 7.5 Hz, ArH), 7.74 (dt, 1H, J = 1.5, 7.5 Hz, ArH), 7.81 (t, 1H, J = 1.2, 7.5 Hz, ArH), 8.51 (dd, 1H, J = 1.5, 7.5 Hz, ArH); ^{13}C nmr (deuteriochloroform): ppm 22.5 (2 CH_3), 27.0 (CH_2), 27.7 (CH_2), 78.1 (CH), 117.1 (J = 13.1 Hz, CH_2), 121.4 (=CH), 121.4, 123.0 (J = 6.2 Hz, Ar-CH), 126.9 (Ar-CH), 127.2 (Ar-CH), 128.4 (Ar-CH), 131.2, 132.9 (=CH), 136.6, 150.4, and the fluorinated benzene carbons; ^{19}F nmr (deuteriochloroform): ppm -148.1 (dd, 1F, J = 10, 21 Hz), -151.0 (d, 1F, J = 10 Hz), -158.0 (d, 1F, J = 21 Hz).

Anal. Calcd. for $C_{21}H_{17}O_2F_3$: C, 70.38; H, 4.78. Found: C, 70.26; H, 4.81.

2,3-Dihydro-2-[2-(pentafluorophenyl)ethylidene]-1*H*-inden-1-one (**9**).

At -78°, 3.0 g (0.014 mole) of pentafluoroacetophenone (**1**) dissolved in 30 ml of anhydrous tetrahydrofuran was treated with 7.7 ml of a 2.0 *M* solution of lithium diisopropylamide in heptane-tetrahydrofuran. After the addition was complete, the solution stirred an additional 15 minutes at -78°. A solution of 2.6 g (0.015 mole) of diethyl chlorophosphate in 5 ml of anhydrous tetrahydrofuran was added dropwise. After the addition was complete, the solution was allowed to warm to room temperature. The enol phosphate solution was added dropwise to a solution 16.9 ml of a 2.0 *M* lithium diisopropylamide in 20 ml of anhydrous tetrahydrofuran at -78°. After the addition was complete, the solution stirred an additional one hour at -78°. To the solution, 3.8 g (0.015 mole) of anhydrous cerium(III) chloride was added and the solution stirrred an additional one hour at -78°. A solution 2.0 g (0.015 mole) of the 1-indanone in 5 ml of anhydrous tetrahydrofuran was added dropwise. After the addition was complete, the solution was allowed to warm to room temperature overnight. The solution was then heated at 50° for five hours. The solution was treated with 2*N* hydrochloric acid until acidic. The solution was extracted with ether and the ether layer was washed with water and brine. The solution was dried over magnesium sulfate, filtered and the solvent was removed to afford a mixture of two products. Fraction two of column chromatography (5% ethyl acetate-hexane) afforded 0.90 g (20%) of a white solid of **9**, mp 142-143°; ^1H nmr (deuteriochloroform): ppm 3.61 (d, 1H, J = 7.5 Hz, CH_2), 3.72 (s, 2H, $ArCH_2$), 6.69 (t, 1H, J = 7.5 Hz, =CH), 7.33 (t, 1H, J = 7.4 Hz, ArH), 7.45 (d, 1H, J = 7.5 Hz, ArH), 7.54 (t, 1H, J = 7.4 Hz, ArH), 7.77 (d, 1H, J = 7.5 Hz, ArH); ^{13}C nmr (deuteriochloroform): ppm 22.5 (CH_2), 29.6 (CH_2), 112.0, 124.4 (Ar-CH), 126.3 (Ar-CH), 127.7 (Ar-CH), 130.2, 134.9 (Ar-CH), 138.2, 138.3, 149.0, 192.8 (C=O), and the fluorinated benzene carbons; ^{19}F nmr (deuteriochloroform): ppm -144.8 (dd, 2F, J = 8, 22 Hz), -157.6 (t, 1F, J = 22 Hz), -163.5 (dt, 2F, J = 8, 22 Hz).

Anal. Calcd. for $C_{17}H_9OF_5$: C, 62.97; H, 2.80. Found: C, 62.75; H, 2.87.

1,2,3,4-Tetrafluoro-5,11b-dihydro-7*H*-benzo[*c*]fluoren-7-one (**10**).

Following the same procedure described for **9**, fraction one of the column chromatography (5% ethyl acetate-hexane) afforded 0.43 g (10%) of a yellow solid of **10**, mp ~130-131°; ^1H nmr (deuteriochloroform): ppm 3.16 (dd, 1H, J = 5.4, 16.9 Hz, CH_2), 3.55 (s, 1H, CH), 3.61 (dd, 1H, J = 8.7, 16.9 Hz, CH_2), 4.18 (dd, 1H, J = 5.4, 8.7 Hz, =CH), 7.38 (t, 1H, J = 7.4 Hz, ArH), 7.44 (d, 1H, J = 7.7 Hz, ArH), 7.60 (t, 1H, J = 7.4 Hz, ArH), 7.77 (d, 1H, J = 7.7 Hz, ArH); ^{13}C nmr (deuteriochloroform): ppm 34.0 (CH_2), 43.2 (CH), 89.6 (=CH), 124.6 (Ar-CH), 126.5 (Ar-CH), 128.1 (Ar-CH), 135.5 (Ar-CH), 152.3 (C=O), and other non-hydrogen carbons; ^{19}F nmr (deuteriochloroform): ppm -138.8 (dd, 2F, J = 12, 21 Hz), -144.18 (unresolved m, 2F).

Anal. Calcd. for $C_{17}H_8OF_4$: C, 67.11; H, 2.65. Found: C, 67.36; H, 2.94.

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