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Intramolecular Addition to an Unactivated Carbon-Carbon Triple Bond *via* an Apparent 6-Endo Digonal Pathway

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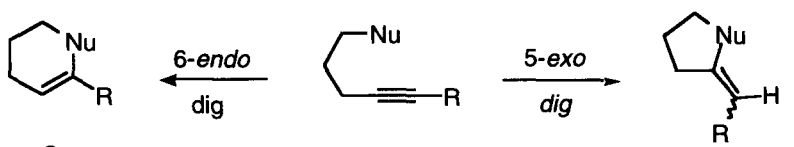
Abstract: Investigation of an apparent 6-*endo-dig* cyclization reveals an unusual acid-catalyzed rearrangement of the initially formed benzofuran derivative.

The construction of ring systems by intramolecular addition of an anionic center to a carbon-carbon π-bond has attracted considerable attention in recent years.[1-7] Various organometallic reagents have been used resulting in the formation of cycloalkenyl containing products. The synthetic utility of these anionic cyclizations is further enhanced by the ease with which the organometallic product may be functionalized by reaction with various electrophiles. The demonstration by Dunitz and Burgi[8] of favored trajectories for the approach of one reactant molecule toward another led to the formulation of rules governing the ease of intramolecular ring closure reactions.[9] Cyclization of the 5-hexenyl anion is predicted to occur by way of a 5-*exo-trig* closure since this pathway permits the optimum trajectory by the nucleophile of 109° to the double bond in the plane of its π-orbitals. For cyclizations involving nucleophilic attack at triple bonds, the situation remains less clear-cut than for the analogous ring closures in tetrahedral or trigonal systems. The original rules[9] postulated an acute approach angle of about 60° in *digonal* systems and stated that *endo-dig* ring closures are generally preferred for the formation of five- and six-membered rings. Since that time, there have been several theoretical studies which indicate that the favored path of approach of a nucleophile to a triple bond is at an obtuse angle of 120-127 degrees.[10-14] In the case of electronically unbiased acetylenes, *exo-dig* cyclizations are favored.[15] Thus, Bailey and co-workers have repeatedly shown that 5-alkyn-1-yllithiums prefer to undergo anionic cyclization *via* a highly regioselective 5-*exo-dig* process involving stereoselective *syn*-addition to the triple bond.[4] Indeed, a wide variety of compounds of type **1** undergo exclusive 5-*exo-dig* cyclization to give cyclopentenyl (**2**) rather than cyclohexenyl (**3**) products.[16-19]

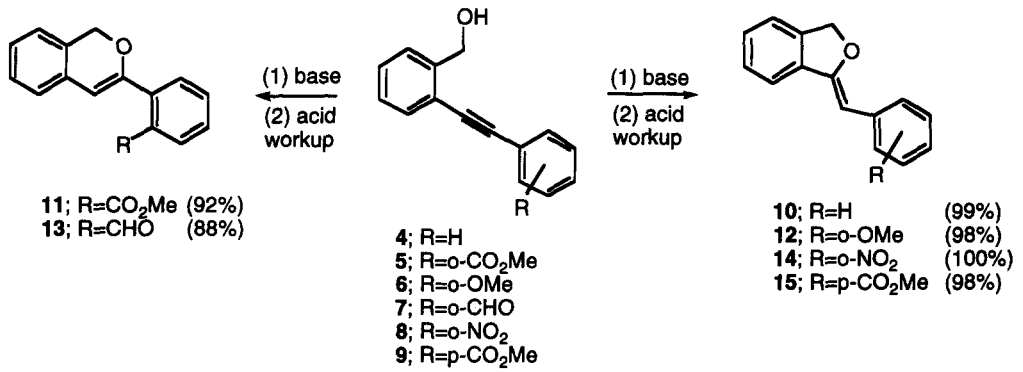


3 **1** **2**

Since questions of angle of approach of an internal nucleophile to the triple bond as well as the degree of involvement of a carbonyl group along the reaction pathway[20] are still of considerable interest, we decided to carry out an exploratory study on the base-induced cyclizations of *o*-ethynylaryl

benzylic alcohols of type **4-9**. As far as we know, this reaction has not yet been investigated in any detail, in spite of the ability of unactivated alkynes to undergo nucleophilic additions with alkoxide ions. Our results are relevant to the understanding of cyclizations involving nucleophilic attack at triple bonds.

Under basic conditions, the hydroxyl functionality of alkynes **4-9** underwent smooth cyclization with the unactivated acetylenic group. Much to our surprise, the mode of cyclization seemed to be greatly influenced by the nature of the substituent in the *ortho*-position of the aromatic ring. For example, treatment of alkynyl alcohol **5** (R=*o*-CO_2Me) with NaH in THF followed by an aqueous acid workup produced benzopyran **11** in 92% yield. The formation of **11** corresponds to a rare example of a 6-*endo-dig* cyclization. On the other hand, treatment of the related alkynyl alcohols **4** (R=H) and **6** (R=*o*-OMe) under the same conditions produced only the 5-*exo-dig* products **10** and **12** in quantitative yield. Since it appeared that the 6-*endo* cyclization of these benzylic alcohols was dependent on the presence of an electron- withdrawing group in the *ortho*-position, we prepared the corresponding alkynyl alcohols **7** (R=*o*-CHO), **8** (R=*o*-NO_2), and **9** (R=*p*-CO_2Me). The 6-*endo-dig* cyclization product **13** was exclusively formed with **7**, but only the 5-*exo-dig* process occurred with **8** and **9**.



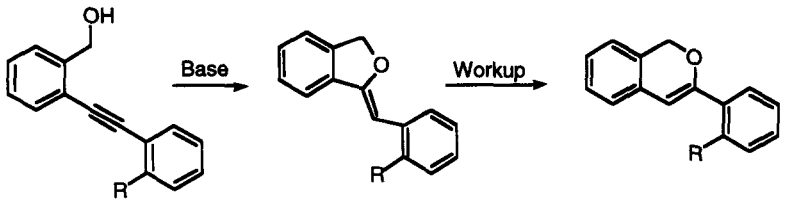
11; R=CO_2Me (92%)
13; R=CHO (88%)

4; R=H
5; R=o-CO_2Me
6; R=o-OMe
7; R=o-CHO
8; R=o-NO_2
9; R=p-CO_2Me

10; R=H (99%)
12; R=o-OMe (98%)
14; R=o-NO_2 (100%)
15; R=p-CO_2Me (98%)

The fact that the 6-*endo* cyclization mode only occurs when a carbonyl group is present in the *ortho*-position of the aromatic ring prompted us to examine the reaction in greater detail. Further study showed that the product distribution was found to be markedly dependent upon the reaction conditions. Careful monitoring of the crude mixture of **5** and **7** by NMR spectroscopy indicated that the reaction proceeded by initial formation of the 5-*exo-dig* product followed by a subsequent acid induced reorganization to the 6-*endo* product. Thus, these apparent 6-*endo* cyclizations are actually the consequence of a 5-*exo* cyclization followed by a rapid acid-catalyzed rearrangement. Although we were unable to isolate benzofurans **16** and **17** due to their facile conversion to benzopyrans **11** and **13**, their structures were confirmed by ozonolysis of the crude reaction mixture to phthalide and the corresponding aryl aldehydes.

A plausible mechanism for the acid-catalyzed rearrangment of **16** to **11** is outlined below. The

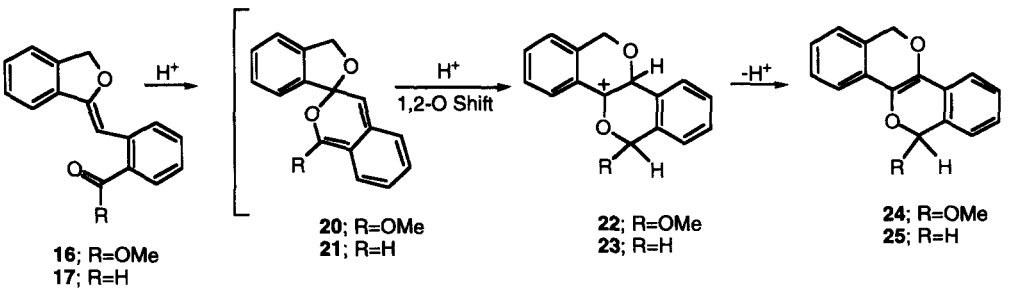


5; R=CO_2Me
7; R=CHO

16; R=CO_2Me
17; R=CHO

11; R=CO_2Me
13; R=CHO

first step involves an initial protonation of benzofuran **16** followed by intramolecular cyclization of the *ortho* carbonyl group to form spiro ketal **20** which then proceeds to benzopyran **11** *via* a series of reactions. Ring expansion by a 1,2-O shift results in the formation of cation **22** which undergoes proton loss to produce **24**. This intermediate proceeds to the final product by a 1,5-sigmatropic hydrogen shift and a subsequent cycloreversion.[21] Further reaction of **11** with dilute hydrochloric acid results in the formation of spiro lactone **18** (95%). Benzofuran **17** undergoes a related sequence ultimately affording lactol **28** which is converted to a 1:1-mixture of lactone **18** and spiro ketal **19** *via* an acid-catalyzed Cannizzaro reaction in 68% yield.[22]

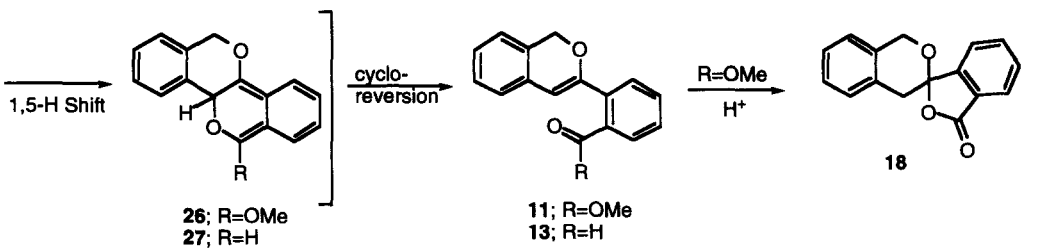


16; R=OMe
17; R=H

20; R=OMe
21; R=H

22; R=OMe
23; R=H

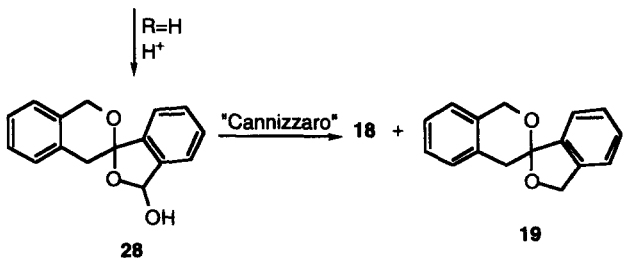
24; R=OMe
25; R=H



26; R=OMe
27; R=H

11; R=OMe
13; R=H

18



28

19

Further studies on the mechanistic details and synthetic potential of these cyclizations are in progress.

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