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Boron Trifluoride Catalyzed Rearrangement And Dehydration Of Epoxyalkynols

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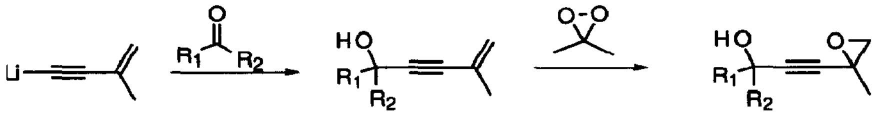
Abstract: Epoxyalkynols undergo a rerrangement/dehydration when reacted with boron trifluoride to provide [3]cumulenals and α-hydroxy allenes.

The emergence of enediyne anti tumor agents[1] such as Neocarzinostatin chromophore and dynemycin has sparked considerable interest in the synthesis and study of epoxyalkynes capable of undergoing cycloaromatization processes.[2] In the case of Neocarzinostatin chromophore, the onset of biological activity is triggered via a nucleophilic addition of a thiol to an epoxyenediyne. This reaction generates a cyclic [3]cumulene intermediate which undergoes Meyers cyclization[2] and results in the production of a DNA damaging diradical. Cumulene intermediates have also been postulated in the conversion of epoxyalkynols to furans upon treatment with base.[3] In this context we now describe the formation of [3]cumulenes from the boron trifluroide catalyzed rearrangement/dehydration of epoxyalkynols.

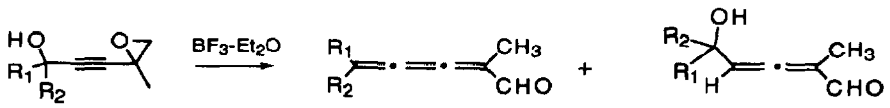
The boron trifluoride rearrangement of epoxides has met with moderate acceptance for the synthesis of ketones and aldehydes.[4] Similarly, the acid-catalyzed rearrangement of propargylic alcohols provides a facile entry to α,β-unsaturated ketones via the Rupe or Meyer-Schuster rearrangement.[5] Since there were no previous reports on the Lewis acid catalyzed reactions of epoxyalkynols, we set out to investigate the outcome of this reaction with the expectation of observing pinacol-type rearrangements products.[6] Epoxyalkynols used in this study were prepared via the addition of the lithio anion of 2-methyl-1-buten-3-yne to ketones or aldehydes to give enynol **1**. Epoxidation of enynol **1** with dimethyldioxirane rendered the required pure epoxyalkynol **2** in excellent yields.[7]



1 **2**

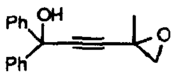
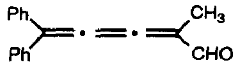
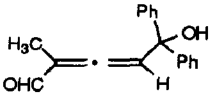
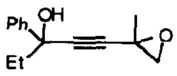
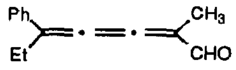
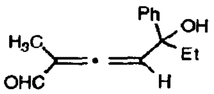
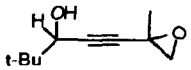
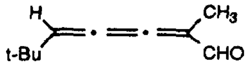
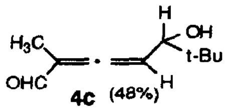
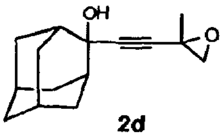
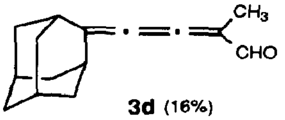
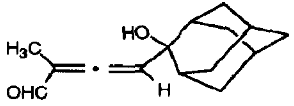
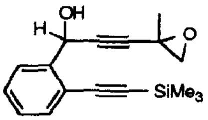
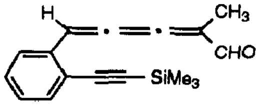
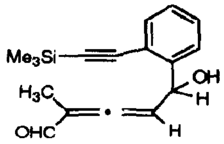
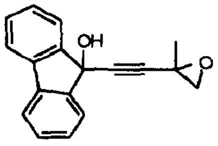
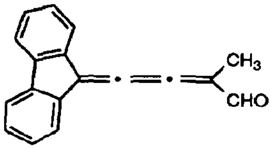
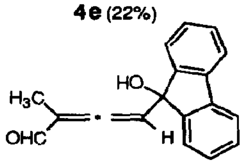
With these compounds on hand, Lewis acid-catalyzed rearrangement reactions were investigated. A typical experimental procedure consisted of reacting a tetrahydrofuran solution of **2** with 0.1 equivalent of boron trifluoride etherate at -78°C. This solution was allowed to warm to room temperature, and, after an aqueous workup, a mixture of cumulenal **3** and hydroxy allene **4** was isolated.

Although cumulenal **3** was air sensitive, it could be purified by flash silica gel chromatography and characterized spectroscopically.[8] The experimental results are provided in Table I. It was observed that cumulenal **3** is susceptible to polymerization initiated by oxygen or mild acidic conditions.[9]



2 **3** **4**

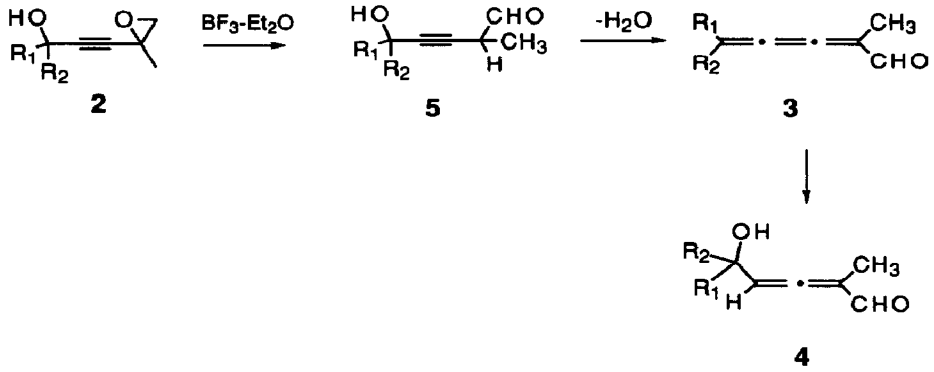
TABLE I: BF_3-Et_2O REARRANGEMENT/DEHYDRATION OF EPOXY ALKYNOLS

Epoxy alkynol	Yields of Cumulenal 3 and hydroxyallene 4	
 **2a**	 **3a** (58%)	 **4a** (28%)
 **2b**	 **3b** (16%)	 **4b** (38%)
 **2c**	 **3c** (3%)	 **4c** (48%)
 **2d**	 **3d** (16%)	 **4d** (31%)
 **2e**	 **3e** (unstable)	 **4e** (22%)
 **2f**	 **3f** (46%)	 **4f** (unstable)

The structures of cumulenal **3** and hydroxyallene **4** were confirmed with the aid of infrared spectroscopy. The cumulenals showed the characteristic [3]cumulene stretching frequencies at ca. 2030-2060 cm^{-1}, the allenes showed the expected stretching bands at 1940-1950 cm^{-1}. Although the isolated yields of cumulenals **3b-e** are low, these products were identified as the major components in the crude reaction mixtures prior to aqueous work up. Cumulenals **3 b-e** decomposed upon chromatographic purification and were observed to readily polymerize when exposed to air. This was not the case with cumulenals **3a** and **3f** both of which contain diaryl substituents. This observation suggests that the rearrangement/dehydration reaction of epoxy alkynols can be employed as an effective route for the synthesis of diaryl [3]cumulenals. The α-hydroxy allenes **4b** and **4c** were obtained as 1:1 mixture of diastereomers which could not be separated by chromatography.[10]

The formation of the reaction products can be rationalized via the mechanism shown in Scheme I. Epoxide **2** rearranges to aldehyde **5** upon treatment with BF_3-etherate. Lewis acid-induced dehydration of **5** leads to cumulenal **3**, which reacts with water to produce hydroxyallene **4**. This mechanism is consistent with the Lewis acid catalyzed rearrangement of epoxides and with our experimental observations. For example, when the reaction is followed by TLC, a polar intermediate is initially formed (presumably, hydroxyaldehyde **5**) and subsequently disappears producing a nonpolar product (cumulenal **3**).

SCHEME I



Additional support for the proposed mechanism comes from a related reaction in which the acid catalyzed hydrolysis of propargylic enol ethers also produces [3]cumulenes and hydroxyallenes.[11]

The reaction presented represents a simple method for the synthesis of functionalized diaryl[3]cumulenals[12] and hydroxyallenic aldehydes.[13] All of the epoxyalkynols studied to date contain a 1,1 substitution pattern on the epoxide functionality. This is by design because the rearrangement/dehydration of epoxyalkynols containing a 1,2-disubstituted epoxides, in our hands, is quite complex and does not afford cumulenals as the major products. This is not entirely unexpected because the regiochemical outcome of the boron trifluoride rearrangement of 1,2 substituted epoxides is not straightforward and often leads to a mixture of products. Ongoing experiments seek to improve the yields and further explore the scope of the reaction.

Acknowledgments

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8. **3a**: IR (neat) 3040, 2030, 1648 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 2.09 (s, 3H), 7.4 (m, 6H), 7.6 (m, 4H) and 9.63 (s, 1H), ^{13}C- NMR (CDCl$_3$, 63 MHz) δ14.3, 116.7, 128.5, 129.7, 132.5, 137.5, 151.8, 170.2 and 189.0; HRMS for $C_{18}H_{14}O$: 246.3113, found 246.3112.

   4a: isolated as a 1:1mixture of diastereomers: IR (neat) 3426, 3054, 1946, 1674 cm^{-1}, ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 1.58/1.59 (s, 3H), 6.27/6.28 (s, 1H), 7.1-7.4 (m, 10H) and 9.30/9.31 (s, 1H), HRMS for $C_{18}H_{16}O_2$: 264.3265 found 264.3265.
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10. **4c**: Isolated as a 1:1 mixture of two diasteromers:IR neat: 3458, 2959, 2870,1947, 1681 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 250 MHz) δ 0.91/0.92 (s, 9H),1.70/1.72 (d,3H), 2.8 (s, 1H), 3.90/3.93 (s, 1H), 5.70/5.73 (m, 1H) and9.44/9.47 ppm (d,1H). ^{13}C- NMR (CDCl$_3$, 63 MHz) δ 10.5/10.6, 25.3,35.3, 77.3, 97.0, 107.2/107.3, 192.2/192.4, 217.1/217.4.
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