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Ynol Ethers from Dichloroenol Ethers: Mechanistic Elucidation Through ^{35}Cl Labeling

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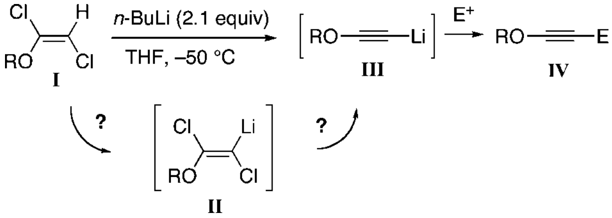
ABSTRACT

The mechanism of ynol ether formation from dichloroenol ethers, a decades-old transformation, has been studied by experimental and theoretical techniques to determine the relative importance of the Fritsch−Buttenberg−Wichell rearrangement (α-elimination) and *β*-elimination in the evolution of the intermediate carbenoid.

Ynol ethers are a useful and well-studied class of compounds that have often been employed in synthesis, in particular for the preparation of enol ethers.[1] The most convenient and frequently used method for their preparation employs the corresponding dichloroenol ethers **I** (Scheme 1).[2] These ethers are easily obtained through the addition of alkoxides to dichloroacetylene, a transformation applicable to a wide variety of alcohols. The ynol ethers are readily synthesized by reaction of the dichloroenol ethers with 2 equiv of *n*-butyllithium, leading to the intermediate lithioacetylide **III**, which is subsequently trapped with an electrophile.[2] Despite the use of this effective procedure for decades by numerous practitioners,[3] its mechanism, surprisingly, is still debated.

A probable, but still hypothetical, lithio-chloro carbenoid **II**, formed through vinylic proton abstraction by *n*-butyllithium, would be expected to evolve by one, if not competitively two, mechanistic pathways: Fritsch−Buttenberg−Wischell (FBW) rearrangement (formally α-elimination−migration)[4] and/or *cis* *β*-elimination (Scheme 1). Herein, we present the first experimental proof, as well

Scheme 1. Ynol Ether Formation from Dichloroenol Ethers



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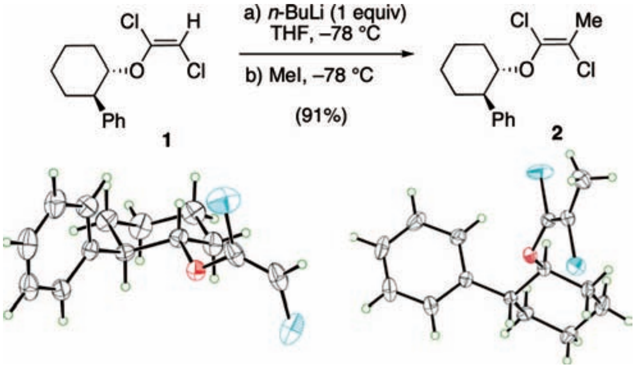
as a metadynamics study, of the mechanism of ynol ether formation from dichloroenol ethers.

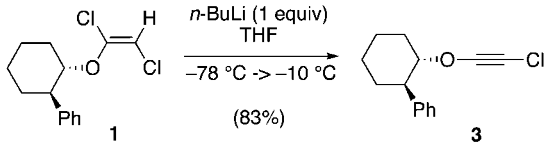
Since the configuration of enol ethers formed through the addition of metal alkoxides to dichloroacetylene was not on firm ground,[5] but relevant, it was first addressed. Fortunately, dichloroenol ether **1** could be crystallized and its structure determined by X-ray crystallography, which established the previously assumed *E* configuration (Scheme 2).[6] Deprotonation, as opposed to implausible chlorine−lithium exchange,[7] was next confirmed: treatment of **1** at −78 °C with a single equivalent of *n*-butyllithium, followed by the addition of methyl iodide, led to the methyl-substituted derivative **2** in excellent yield. The low-temperature configurational stability of the intermediate lithium carbenoid was evidenced by X-ray structure analysis of this product (Scheme 2), a finding in accord with the reported high energy required for isomerization of simple vinylic carbenoids.[8]

Scheme 2. X-ray Structures of *E*-Enol Ethers **1** and **2**



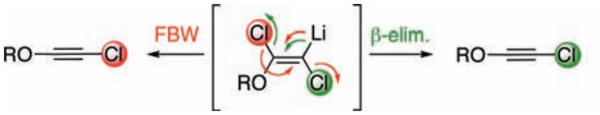
When the above solution containing the lithium carbenoid was allowed to warm, however, the corresponding chloroynol ether **3** could be isolated in high yield (Scheme 3).[9] The formation of the acetylene begins at −65 °C (6.6:1 **1**:**3** after 5 min) and the transformation is complete after 10 min at −50 °C. Thus, the second equivalent of *n*-butyllithium plays no role in acetylene formation but serves to generate the lithioacetylide by chlorine−lithium exchange.[7]

Scheme 3. Formation of Chloroynol Ether **3**



Armed with the knowledge that dichloroenol ether **1** undergoes conversion to the chloroynol ether **3** through an *E*-lithium carbenoid that is stereostable at low temperature, complete elucidation of the mechanism was reduced to determining the evolution of carbenoid:FBW rearrangement and/or *cis* β-elimination. The FBW rearrangement is commonly advanced to explain alkyne formation from alkenyl halides (e.g., the Corey−Fuchs reaction[10]), and furthermore, chlorine migration is known to be a facile process;[11] *cis* β-elimination, albeit less energetically favorable than *trans*, is also precedented.[12] A novel approach allowed us to resolve this dichotomy of possible pathways.

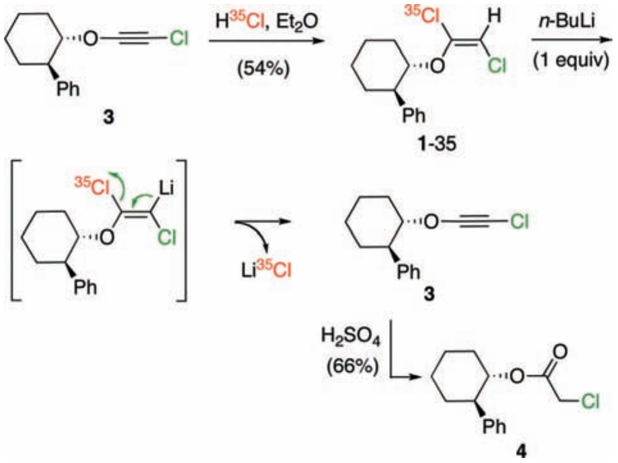
It was recognized that in a β-elimination process, the remaining chlorine atom would be the carbenoid one (in green, eq 1), but in the case of a FBW rearrangement, the other chlorine (in red) would be that found in the final product.



(1)

To determine which process (if not both) was operative, the ideal solution would therefore be to replace selectively one of the chlorines with an isotopically enriched one, either 35 or 37. Mass spectrometry of chloroynol ether **3** could then be used to identify the chlorine isotope(s) and thereby the mechanism. For the synthesis of such a labeled molecule, chloroynol ether **3** was chosen in the hope that it might cleanly and selectively undergo hydrochlorination,[13] in spite of the acid sensitivity of both the ynol and dichloroenol ethers. In the event, hydrochlorination of compound **3** with a 1 M solution of $H^{35}Cl$ in ether (from $Na^{35}Cl$, 99 atom %) could be cleanly achieved with careful temperature control to give the corresponding dichloroenol ether, *uniquely E*, in 54% yield (Scheme 4). The mass spectrum of **1**-35 displayed the expected 3:1 ratio of molecular ions at 293 and 295 $(M + Na)^+$, confirming the introduction of a single chlorine-35 into the molecule. Exposure of **1**-35 to 1 equiv of *n*-butyllithium (−78 → −10 °C) led to the chloroynol ether **3**. The CI mass spectrum of **3** revealed a 3:1 ratio of low-intensity molecular ions at 235 and 237 $(MH)^+$, respectively,

Scheme 4. ^{35}Cl-Labeling Experiment



indicative of predominant loss of the ^{35}Cl atom and proof that β-elimination is the major pathway. However, since the chlorine isotope ratio in chloroynol ether **3** reflects the extent of participation of the two mechanistic pathways, greater precision in the isotope ratio measurement was required. To this end, chloroynol ether **3** was hydrolyzed with sulfuric acid in THF to yield the α-chloro acetate **4**. ESI mass spectrometry (triple quadrupole analyzer) of **4** indicated with high precision an isotopic ratio that corresponded exactly to the theoretical ratio (100:33.6) for the nonlabeled product, *clear proof that cis β-elimination, and uniquely cis β-elimination, is operative in this transformation.*[14]

Metadynamics ab initio calculations[15] have also been carried out to gain a better appreciation of the free-energy requirements for the elimination pathways. While few theoretical studies have been realized to date on α- and β-eliminations in carbenoids, and none using metadynamics, this recently developed calculation method has already been used successfully for solving other problems in organometallic chemistry.[16] The calculated trajectory, interestingly, reveals a shortening of the $^{\alpha}$Cl−Li distance, close to values relevant for bond formation in a FBW event, twice during the evolution (1000 and 1700 fs, Figure 1). However, the final lowest energy pathway involves, as now expected, $^{\beta}$Cl−Li bond formation. The calculated total free energy of activation for the pathway is 6 kcal/mol, consistent with the fast reaction that is experimentally observed at low temperature. The meta-trajectory of the FBW pathway was also simulated and indicated a total free energy of activation of 11 kcal/mol. The 5 kcal/mol difference between the two mechanisms is fully concordant with the experimentally determined single pathway.

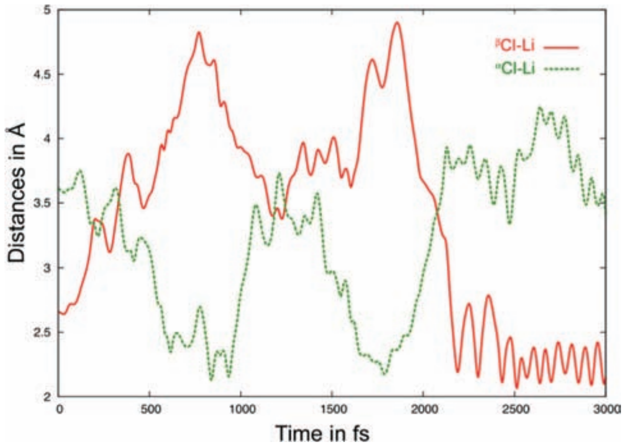


Figure 1. Metadynamics calculation results: evolution of Cl−Li distances.

In conclusion, after nearly half a century and considerable application, it has unambiguously been shown through chlorine-35 labeling that the formation of ynol ethers from dichloroenol ethers does not proceed by FBW rearrangement, but exclusively through *cis* β-elimination. Metadynamics calculations, furthermore, have confirmed the substantial energy difference between these two mechanisms.

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Supporting Information Available: Complete experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for compounds **1**-35 and **2**−**4**, metadynamics calculation details (including a videoclip of the trajectory), and a crystallographic information file for X-ray analysis of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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