Regio- and Stereocontrol in Allylic Rearrangement. Application to Enediyne Synthesis

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Enediynes [1] are a new class of antitumor antibiotics isolated from the fermentation broths of various microorganisms. These antitumor antibiotics possess a 9-/10-membered ring enediyne core which, after bioreductive activation, undergoes a cycloaromatization reaction (the Bergman cyclization) to generate the reactive radical intermediate. The latter species cause DNA strand cleavage via hydrogen atom abstraction from the deoxyribose moiety of DNA. Besides the natural products, synthetic enediynes also exhibit very promising DNA cleavage and cytotoxicity against cancer cell lines [2]. In this presentation, our progress in development of stereo- and regiocontrolled allylic rearrangement of 1,5-diyynes into cis-enediynes will be discussed.

1. Rearrangement via Allylic Mesylates [3]. 1,5-Diyne alcohols 1 were converted into cis-enediyne alcohols 3 via allylic mesylates 2 under very mild reaction conditions (Eq. 1). Formation of 2 should be carried out at -80 °C in order to suppress the attack of chloride anion. The mesylates could not be isolated but were readily converted into cis-enediynes 3 on quenching with water. The allylic rearrangement gave very high regioselectivity (100%) and cis/trans stereoselectivity (>95%); in most cases, only cis-enediynes 3 were isolated.

![Chemical Structure](attachment:structure1)

Reactions of 2 with ROH and RSH were examined and both Sn2 and Sn2 products were formed in the ratios of ~90:10 for ROH and ~70:30 for RSH, respectively, in favor of cis-enediynes (Sn2 products) [4]. trans-Enediynes were not detected in all reactions.

2. Acid-Catalyzed Rearrangement of Allylic Alcohols [5]. Conversion of 1 into cis-enediynes 5 could be achieved under acid catalysis (Eq. 2). Treatment of 1 with CSA gave the most stable W-type allylic cation 4 which was then trapped by NuH (H2O, ROH, RSH) to afford 5 in good yield together with its regioisomers. High ratios of >96:4 were obtained for 5

![Chemical Structure](attachment:structure2)

(Nu = RO) from the reaction with ROH. The 10-membered ring 6 and other cyclic enediynes 7 were prepared under the acid catalysis [4,5].

In order to control the regioselectivity in the acid-catalyzed rearrangement, a nucleophilic group was incorporated into substrates 8 which were synthesized from phthalic dicarboxaldehyde in 8 steps. Treatment of 8 with CSA in CH2Cl2 at rt afforded exclusively cis-enediynes 10 in good yield (Eq. 3) [6]. Acid-catalyzed dehydration of the allylic hydroxy group and deprotection of the silyl ether in 8 should form
allylic cation 9 which was trapped by the internal hydroxyl group to furnish the 2,5-dihydrobenzo-2-furyl enediyne 10 as the sole product. The trans-enediyne isomers were not detected in the rearrangement reaction.

3. Rearrangement of Allylic Methoxacetates Catalyzed by Eu(fod). [6]. Recently, an Eu(fod)-catalyzed rearrangement of allylic methoxacetates has been reported. The method is compatible with a substrate possessing an alkynyl group [7]. We found that methoxacetate 11 (R = Ph) underwent the rearrangement reaction in the presence of Eu(fod) at rt to provide cis-enediynne 12 (R = Ph) in good yield (Eq. 4). However, a similar substrate 11 (R = H) did not provide the corresponding product 12 (R = H) in refluxing CHCl₃. The effect of substituent on the rearrangement reaction will be examined.

4. Radical Formation and DNA Cleavage of cis-Enyne-propargylic Sulphones. Acyclic cis-ene-nyne-propargylic sulphones 13 are the precursors of reactive radical species 15 capable of cleaving DNA (Eq. 5). In the presence of a mild base such as Et₃N, isomerization of 13 took place to form cis-ene-nyne-allenic sulphones 14 which underwent cycloaromatization to give diradical species 15 [3,8]. Abstraction of hydrogen atoms from hydrogen donors or from deoxyribose of DNA converted 15 into the corresponding benzene derivatives. DNA cleavage by 13 (R = H) has been demonstrated by us [3]. An alternative pathway of DNA damage by 14 is the alkylation of nucleic base by the allenic sulphone moiety. This mode of DNA damage has been investigated in a series of propargylic sulphones by us [9].

References: