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Regiocontrolled Synthesis of *cis*-Enediynes via Intramolecular Trapping of Allylic Cations

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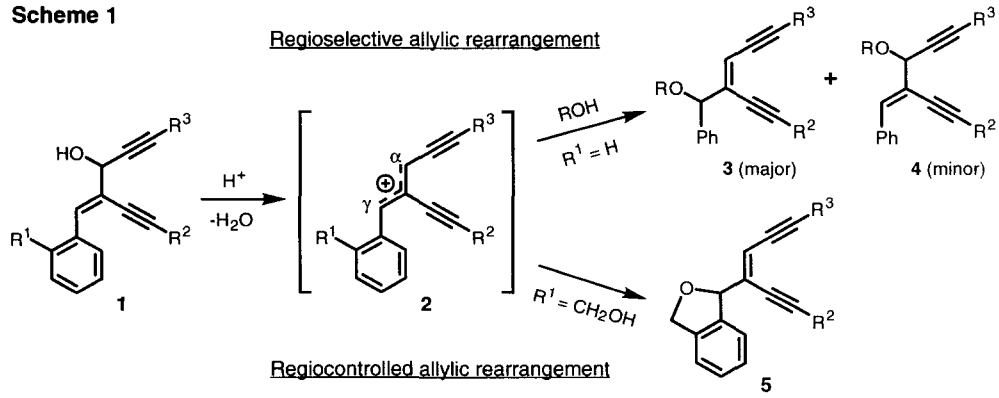
Abstract: Trapping of allylic cations possessing 1,2-dialkynyl groups by an external nucleophile such as ROH yields *cis*-enediynes in a regioselective manner; while similar allylic cations react with an internal nucleophilic group to afford exclusively *cis*-enediynes. This regiocontrolled allylic rearrangement has been used successfully in the synthesis of a number of 2,5-dihydro-2-benzofuryl *cis*-enediynes **5** and the sulfur analogs. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Allylic cations are reactive intermediates formed from 1,3-dienes by addition of an electrophile such as H^+ or from allylic substrates by dissociation of a leaving group such as a halide anion or an oxygen-containing moiety.[1] The resonance structures of allylic cations spread the positive charge over C1 (α) and C3 (γ) carbon atoms and make the charged species much more stable. On the other hand, a nucleophile can attack at either partially positively charged carbons to form a mixture of two regioisomeric products.[1] This disadvantage limits the use of allylic cations in organic synthesis and the most successful applications are found in the area of intramolecular cycloadditions.[2] In our recent work on the acid-catalyzed allylic rearrangement of **1** (R^1 = H), a mixture of two regioisomers **3** and **4** were formed in > 96:4 ratio as the result of reactions with ROH at α and γ positions of the "W-shaped" allylic cation **2** (R^1 = H) (Scheme 1).[3] For reactions of RSH with **1** (R^1 = H), the regioselectivity was quiet poor (ca. 70:30); this perhaps arose from a competing pathway where RSH attacks at

Scheme 1



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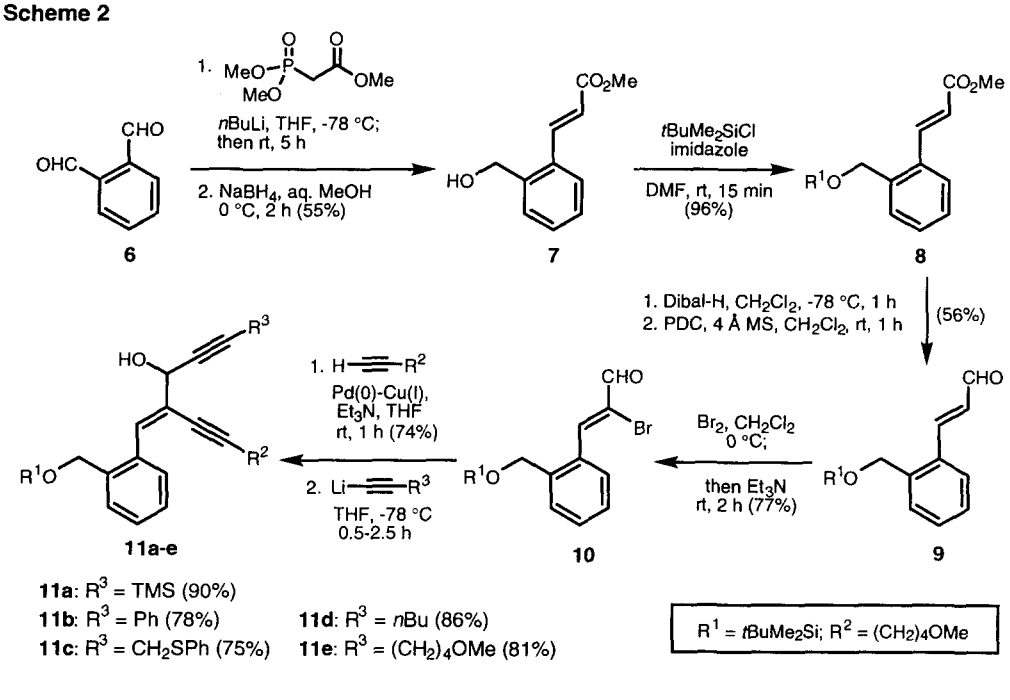
the protonated substrate in an S_N2 fashion.[3] We report here on the synthesis of a new class of allylic substrates **1** ($R^1 = CH_2OH$) possessing an internal nucleophilic site and the use of the acid-catalyzed rearrangement for the synthesis of 2,5-dihydro-2-benzofuryl *cis*-enediynes[4] **5** and the corresponding sulfur analogs **16**.

The kinetic and mechanistic studies by Pocker and Hill[5] showed that the acid-catalyzed rearrangement of both *trans*-1-phenyl-3-methylallyl alcohol and *cis*-1-methyl-3-phenylallyl alcohol gave the same product, *trans*-1-methyl-3-phenylallyl alcohol where conjugation with the phenyl group remained. These rearrangements involved a common "W-shaped" allylic cation in the product-forming step and the nucleophile (H_2O) preferred to attack the carbon atom *not bearing* the phenyl group. However, for the 1,2-dialkynyl substituted allylic cation **2** ($R^1 = H$) a different regioselectivity was noted in favor of enediyne formation.[3] We have successfully applied this methodology for synthesis of cyclic enediynes as well.[6] In order to control the regiochemistry, we designed the substrates **11a-e** whose synthesis was outlined in Scheme 2.[7] The Horner-Wadsworth-Emmons reaction of phthalic dicarboxaldehyde (**6**) with one mole equivalent of trimethyl phosphonoacetate gave the mono-olefination product whose formyl group was reduced by $NaBH_4$ to afford the alcohol **7**. After protection

Scheme 2

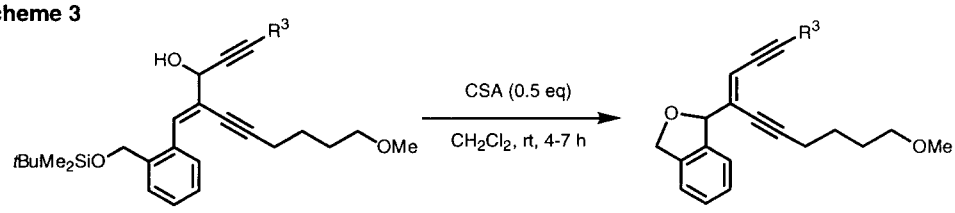


of the hydroxyl group in **7** as the silyl ether, the ester **8** was converted into the aldehyde **9** via reduction and oxidation. Bromination of **9** formed the α,β-dibromoaldehyde and base-promoted elimination of HBr gave the α-bromo-α,β-unsaturated aldehyde **10**. The Pd(0)-Cu(I)-catalyzed cross-coupling of **10** with the terminal alkyne, $HC{\equiv}C\text{-}R^2$ produced the eneyne aldehyde which reacted with the acetylides, $LiC{\equiv}C\text{-}R^3$ to furnish the target compounds **11a-e** in good yield, respectively (Scheme 2).

Treatment of the allyl alcohols **11a-e** with 0.5 mole equivalent of (±)-10-camphorsulfonic acid (CSA) in dry CH_2Cl_2 at room temperature gave the 2,5-dihydro-2-benzofuryl *cis*-enediynes **5a-e**[7] in 63-72% yield as the sole isolated product (Scheme 3). The transformation (**11** → **5**) is assumed to take place via cleavage of the

silyl ether and the allylic hydroxyl group in **11**, both catalyzed by CSA, to give the allylic cation **2** (R^1 = CH_2OH). Intramolecular attack by the benzylic hydroxyl group at the γ position of **2** concurrently forms the benzofuran ring and the *cis*-enediyne unit. The *cis* relationship of the two alkynyl groups in **5a-e** is controlled by the structure of allylic cation **2** and has been confirmed by the base-catalyzed cycloaromatization of the corresponding sulfone of the ene-yne-propargylic sulfide **5c**.[3b]

Scheme 3

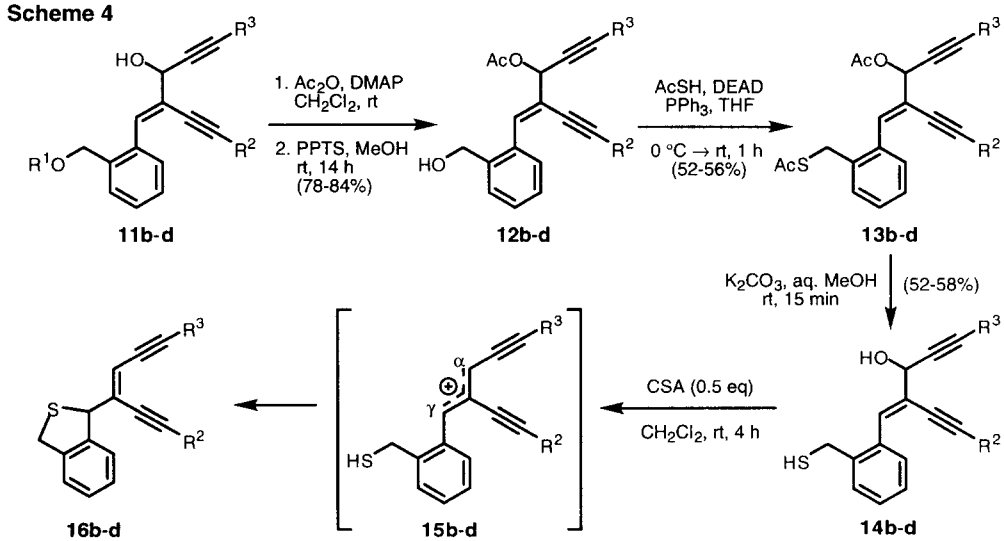


11a-e

5a: R^3 = TMS (70%); **5b**: R^3 = Ph (72%);
5c: R^3 = CH_2SPh (63%); **5d**: R^3 = *n*Bu (65%); **5e**: R^3 = $(CH_2)_4OMe$ (72%)

Encouraged by the successful rearrangement of **11a-e** given in Scheme 3, we turned to the reactions of the sulfur analogs **14b-d** (Scheme 4).[7] Treatment of the mono-protected diols **11b-d** with Ac_2O-DMAP formed the acetates and removal of the silyl group by pyridinium *p*-toluenesulfonate (PPTS) in MeOH afforded the benzyl alcohols **12b-d** in 78-84% yield, respectively. The Mitsunobu reaction of **12b-d** using 6 mole equivalents each of thiolacetic acid, diethyl azodicarboxylate (DEAD), and triphenylphosphine in THF provided **13b-d** in 52-56% yield. Cleavage of the acetyl groups in **13b-d** by K_2CO_3 in aqueous MeOH gave **14b-d** in good yield. Finally, exposure of the allyl alcohols **14b-d** to CSA (CH_2Cl_2, rt, 4 h) afforded exclusively the *cis*-enediynes **16b-d** possessing a 2,5-dihydro-2-benzothiophene moiety. Similar to the formation of **5**, it is proposed that the allylic cation **15b-d** may be formed from the acid-catalyzed dehydration of **14b-d**. Then, the

Scheme 4



11b-d **12b-d** **13b-d**

14b-d **15b-d** **16b-d**

16b: R^3 = Ph (58%)
16c: R^3 = CH_2SPh (55%) **16d**: R^3 = *n*Bu (53%)

R^1 = $tBuMe_2Si$; R^2 = $(CH_2)_4OMe$

intramolecular attack by the mercapto group at the γ position of **15b-d** furnishes the enediynes. Alternatively, if the mercapto group assists in the cleavage of H_2O from the protonated **14b-d** (in an S_N2' manner), the same enediyne products **16b-d** are expected since the mercapto group cannot reach the α position for an S_N2 reaction. The mechanistic detail needs further investigation.

In summary, we have demonstrated in the present work a good example of the control of regiochemistry associated with nucleophilic addition to allylic cations. By incorporating a nucleophilic group such as a hydroxyl or a mercapto group into a suitable position in the allylic substrates **11a-e** and **14b-d**, the desired *cis*-enediynes **5a-e** and **16b-d** can be obtained without contamination of regioisomers. The regiocontrolled allylic rearrangement catalyzed by acid is of synthetic value in the design and synthesis of novel anticancer agents based on the chemistry of enediynes.[8] Further work is in progress in our laboratory.

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