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Synthesis of Cephalosporin Derivatives Utilizing the Cephem Triflate. 1. Introduction of 3-Position Substituents via a Cycloaddition-Fragmentation Route

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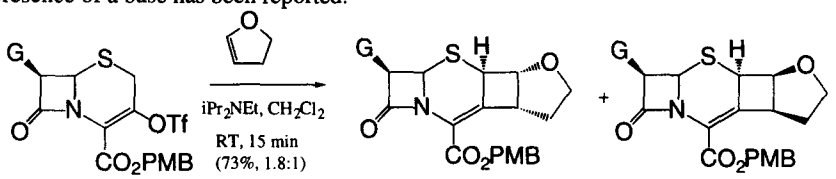
Abstract: *An efficient synthetic route for cephalosporin derivatives with various substituents at the 3-position has been developed. It involves cycloaddition with silyl enol ethers or silylketene acetals followed by fragmentation utilizing the 3-cephem triflate 1 as a starting material.*

Recently, an interesting observation on the reaction of 3-cephem triflate **1** with the unsaturated carbon-carbon bond in the presence of a base has been reported.[1,2]



1

PMB = p-methoxybenzyl G = $PhCH_2CONH$-

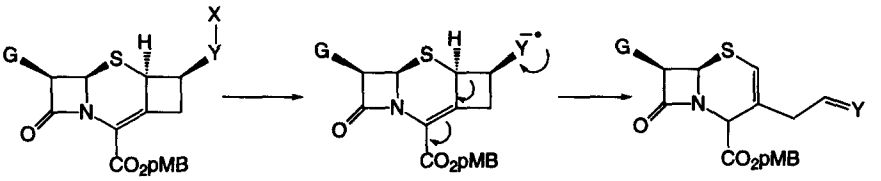
It has been suggested that the [2+2] cycloaddition reaction proceeds via a bicyclic allene intermediate. The reaction with a carbon-carbon triple bond also occurred when the cephem triflate **1** was treated with alkynes. This cycloaddition can also occur in a [4+2] fashion when a sulfoxide derivative of **1** was reacted with a 1,3-diene.

Cephalosporin derivatives have been a subject for synthetic efforts in view of their biological activities. In connection with our continuing research on the synthesis of cephalosporin derivatives,[3] it occured to us that the above cycloadducts, derived from the reaction between the 3-cephem triflate[4] and a C=C bond, could be utilized to prepare cephem derivatives with various substituents at the 3-position which are not easily accessible by other synthetic routes.

Our strategy, summarized in Scheme 1, is based on the assumption that a cycloadduct such as **2** would undergo a facile fragmentation to produce cephem derivatives with relief of ring strain. The X could be a functionality from which a radical or an anionic intermediate could be derived, followed by fragmentation of

the cyclobutane ring. The Y could be carbon or other heteroatoms. Related examples of the fragmentation of cyclobutane derivatives have been reported in the literature for other simpler systems.[5] Our initial atttempts to induce the desired fragmentation met with failure. We finally found that the cycloadducts from silyl enol ethers derived from ketones could be suitable for our synthetic strategy.

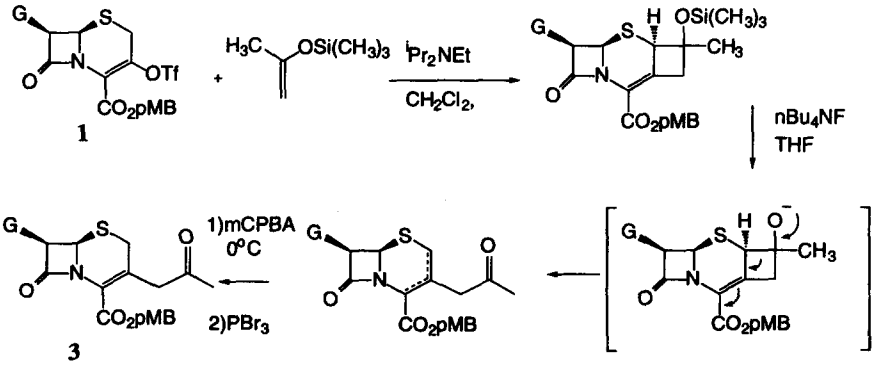
Scheme 1



2

The cycloaddition proceeded nicely to furnish the corresponding cycloadducts. The reaction of a trimethylsilyl enol ether derived from acetone was reacted with the cephem triflate **1** in the presence of triethyl amine as a base to furnish the cycloadduct in 37% yield along with 18% yield of the products which is presumed to be a mixture of ring-opened products although the precise structures were not identified. The desired cycloadducts were treated with tetrabutylammonium fluoride in THF to provide the desired ring-opened products with a substituent at the 3-position of the cephem nucleus. The products were a mixture of 2- and 3-cephem derivatives and, without isolation of the mixture, they were directly subjected to the well-known two-step sequence for converting 2-cephems to 3-cephems, that is, oxidation with mCPBA followed by reduction with PBr_3. The final 3-cephem product **3** was obtained in 55% yield (Scheme 2). Unambiguous identification of **3** was accomplished by an independent synthesis of the same compound by the procedure already reported in the literature.[6]

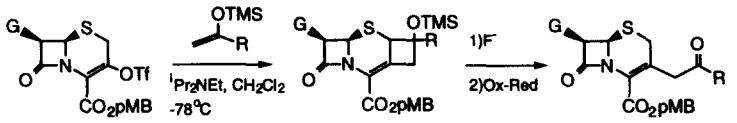
Scheme 2

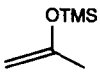
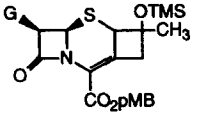
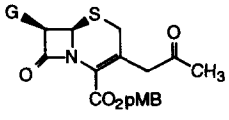
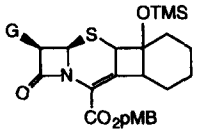
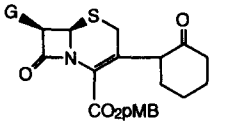
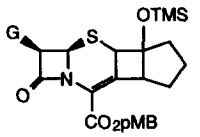
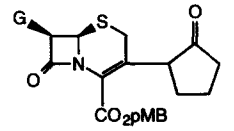
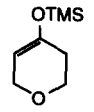
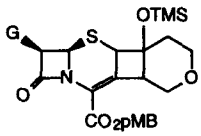
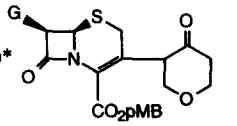


This reaction sequence which includes cycloaddition and fragmentation starting from the cephem triflate **1** was successfully applied to prepare cephalosporin derivatives with various 3-substituents. The results are summarized in Table 1. The cycloaddition of the silyl enol ether of cycloalkanones proceeded with the formation of some amount of unknown products. The yields for the cycloaddition steps were variable as shown in Table 1. The desired cycloadducts were separated and treated with fluoride (nBu_4NF in THF or HF,

CH_3CN) to produce the corresponding ring-opened products. After the two-step sequence the corresponding 3-cephem derivatives are efficiently obtained. Isomeric mixtures with respect to the 3'-position (position next to the 3-position) are obtained in various ratios when possible .

Table 1. Reactions with Silyl Enol Ethers and Silylketene Acetals



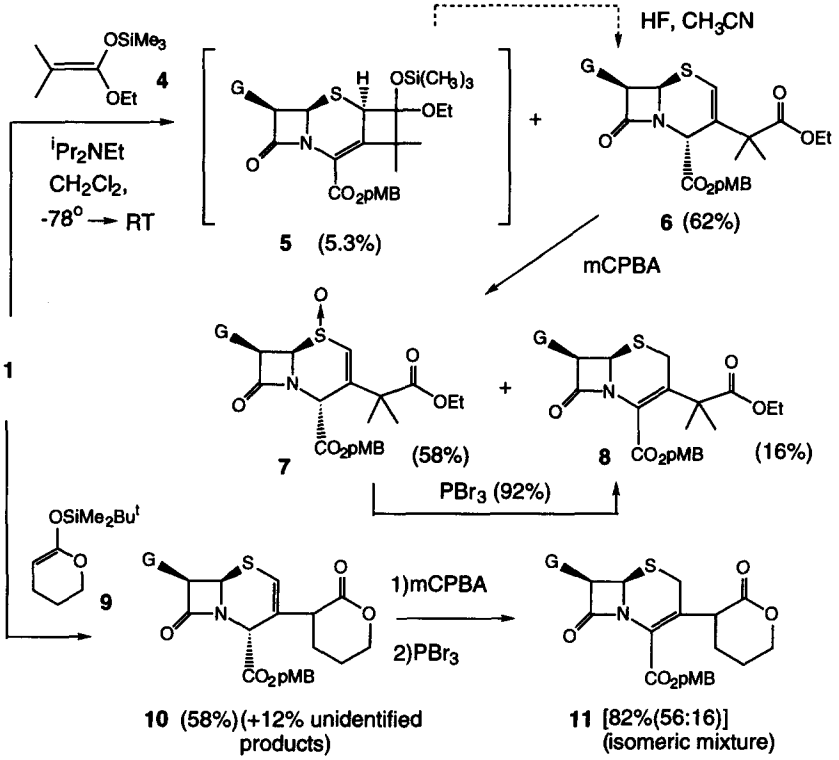
Silyl Enol Ether or Silyl Ketene Acetal	Cycloadducts		Ring-Opening Condition (2-cephem: 3-cephem)	Product(3-cephem) After Oxidation-Reduction Sequence	
		37% (+18% ring opened products)	87% nBu_4NF, THF (2:3)		(55%)
		73% (+10% unknown products)	80% HF, CH_3CN (3:2)		(67%) (~7:3 isomeric mixture)
		21% (+38% unknown products)	49% HF, CH_3CN		(50%) (~1:1 isomeric mixture)
		37% (+28% unknown products)	73% (3-cephem)* HF, CH_3CN		

* Separated directly from the mixture of ring-opened products.

To expand the utility of this cycloaddition-fragmentation methodology, silylketene acetals were also employed (Scheme 3). The reaction of ketene acetal **4** with the 3-cephem triflate **1** under the same conditions for the cycloaddition reaction provided a minor amount of the cycloadduct **5** along with the corresponding ring-opened 2-cephem **6** as the major product. The mixture of **5** and **6** was treated directly with HF in CH_3CN to afford **6** in 62% yield. The mCPBA oxidation, which provided the corresponding sulfoxide in most cases, generated a mixture of the expected sulfoxide **7** and the 3-cephem product **8** in 58 and 16% yield, respectively. Of course, the sulfoxide formed was easily converted to the same 3-cephem **8** in good yield. Other silyl ketene acetals such as **9** were also reacted with **1**. In this case, the expected cycloadduct was not isolated and without treatment of HF the 2-cephem derivative **10** was formed in 58%. After the oxidation-reduction step, the desired 3-cephalosporin derivative **11** was successfully obtained in 82% yield (a ratio of 56:16 isomeric

mixture).

Scheme 3



In conclusion, we have successfully developed an efficient synthetic route to synthesize 3-cephem derivatives with various substituents at the 3-position via cycloaddition followed by fragmentation starting from the 3-cephem triflate **1**.

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