strates or key intermediates for many synthetic applications. Further studies on the reactions are in progress.

Acknowledgment. This work is financially supported by the Organic Chemistry Research Center (sponsored by the Korea Science and Engineering Foundation) and the Ministry of Science and Technology, Korea.

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5. Typical procedure: Dimerization of 3-iodo-2-cyclohexenone (entry 3, Table 1). A solution of 3-iodo-2-cyclohexenone (222 mg, 1.00 mmol) in THF (10 mL) was added to a SmI_2 solution (0.1 M) in THF (22 mL, 2.2 equiv.)-HMPA (2.2 mL) under nitrogen atmosphere at -78 °C. After the reaction was completed (monitored by TLC and the color of the solution which changed to brown immediately after the addition), saturated NH_4Cl (5 mL) was added. After most of THF was removed *in vacuo*, water (10 mL) was added and, the products were extracted with benzene and ether mixture (4 : 1, 15 mL × 3). The organic layer was separated, washed with saturated NaCl, dried ($MgSO_4$), and concentrated. Flash chromatography (hexane : ethyl acetate=2 : 1) provided the desired dimerization product as a pale yellow solid (77 mg, 81%). ^1H NMR and ^{13}C NMR data of the product matched those reported in the literature.[6] IR (KBr) 1650 (C=O) cm^{-1}; MS (m/e, rel intensity) 190 (M^+, 100).
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Synthesis of Cephalosporin Derivatives Utilizing the Cephem Triflate. 2.[1] Introduction of 3-Position Substituents by the Reaction with Enamines†

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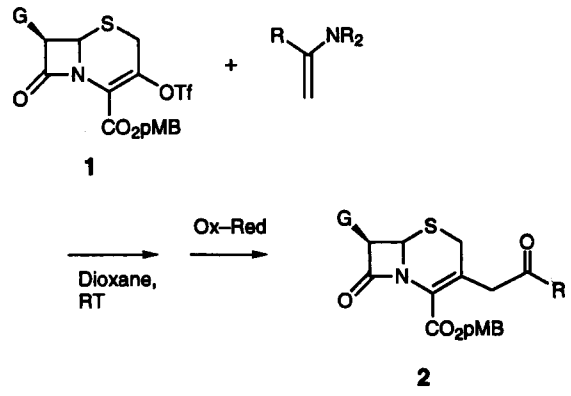
Received September 8, 1997

Cephalosporins have been a subject of synthetic efforts due to their antibacterial activities against many infectious diseases. For the synthesis of cephalosporin derivatives, introduction of substituents at the 3-position has attracted much attention.[2] Although 7-aminocephalosporanic acid (ACA) has been used extensively as a key starting material for preparing cephem derivatives *via* the bond formation at the 3'-position (*i.e.*, carbon adjacent to the 3-position), direct introduction of the substituent by a wide variety of ways has also been developed. The 3-cephem triflate has been a useful substrate for introducing substituents to the cephems. If the carbon atom of the 3-position of cephems is bonded to a heteroatom, such as oxygen, sulfur, or nitrogen, the cephalosporin derivatives are easily prepared by the reaction between the corresponding heteroatom nucleophiles (for example, thioheterocycles and *N*-heterocycles) and the cephem sulfonates.[3,4] The cephem triflate can be used extensively

†Dedicated to Professor Sang Chul Shim, KAIST, on the occasion of his 60th birthday.



Scheme 1.

for the introduction of 3-position substituents bonded to the carbon atom. Cuprates and stannes with a palladium catalyst are among the most popular organometallic reagents used for the introduction of side chains.[5] This method has attracted attention due to the advent of new types of cephalosporin antibiotics with olefinic side chains at C-3.[6]

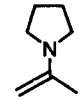
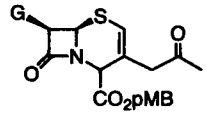
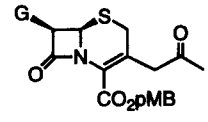
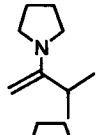
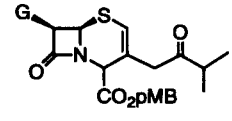
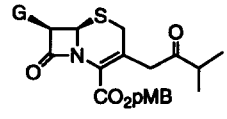
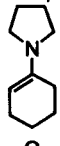
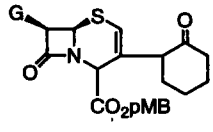
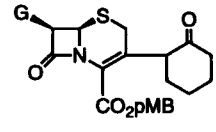
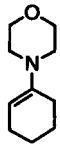
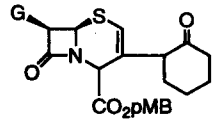
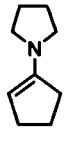
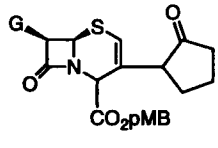
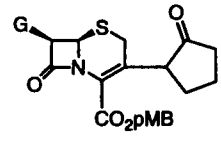
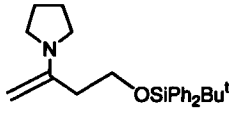
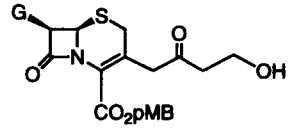
We have recently reported a route for synthesizing cephalosporin derivatives with substituents at the 3-position.[1] This involves cycloaddition with a silyl enol ethers or silylketene acetals followed by fragmentation which was based on the report by Elliot and coworkers who observed the [2+2] or [4+2] cycloadditions of the 3-cephem triflate **1** with olefins, acetylenes, and dienes in the presence of a base.[7]

As a natural extension of the previous investigation utilizing a silyl enol ether and silylketene acetals for the cycloaddition partners, we have studied the reaction of enamines and the cephem triflate. With regard to cephalosporin derivatives, despite many reports on addition of substituents to the cephem triflate **1** involving various heteroatoms as well as other carbon nucleophiles, enamines have never attracted attention as a nucleophilic partner. Here we report our investigation on employing enamines as a nucleophilic component to introduce the 3-position substituent for cephalosporin derivatives using the cephem triflate **1** (Scheme 1).

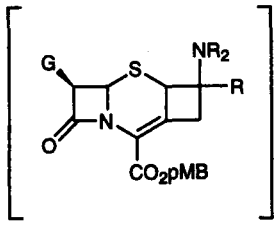
We intended to test enamines as candidates for introducing cephalosporin side chains *via* the previously developed cycloaddition-fragmentation route. We anticipated that the reactions would take place *via* [2+2] cycloadducts such as **3**.

In this case, however, reactions in dioxane at room temperature directly provided the cephem derivatives, and the expected [2+2] cycloadducts shown above were not isolated. Addition of the external base was not necessary. The results for the reaction of the cephem triflate **1** and various enamines are summarized in Table 1.[8] As a result, introduction

Table 1. Reactions of enamines with the cephem triflate **1**

Entry	Enamine	Product(2-/3-Cephems) (Yield)		After Ox-Red (Yield)	
1			33% ($\Delta^2 : \Delta^3$ = 2:3)		61%
2			40% (Δ^2)		58%
3			49% (Δ^2)[a] + 20% (Δ^3)[b]		66%[c]
4			22% (Δ^2)[d] + 6%(Δ^3)		—
5			47% (Δ^2)[e]		58%[e]
6			30%(Δ^3)[f]		—

[a] mixture of 2 kinds of 2-cephem isomers (1 : 1). [b] single 3-cephem isomer. [c] (1) yield obtained from reaction of 2-cephems (2) single 3-cephem isomer. [d] mixture of 2 kinds of 2-cephem isomers (1 : 1.7). [e] mixture of 2 isomers (1 : 1). [f] directly gave 3-cephem with TBDPS removed.



3

of the 3-position substituent was successfully achieved by this method. At this moment, we presume these products are formed *via* [2+2] cycloadduct followed by fragmentation as in the cases of the reaction of silyl enol ethers and silylketene acetals.

A simple enamine derived from acetone (entry 1) successfully provided the corresponding product with a 3-position substituent. We obtained the corresponding ketones, for all the case shown in Table 1, as the final isolated products, which indicated that hydrolysis occurred during the work-up. The 2-cephem product obtained was subjected to the usual oxidation-reduction sequence [(1)mCPBA (2)PBr_3] to provide the desired 3-cephem product (20% overall yield). Similarly, other enamines derived from 3-methyl-2-butanone and cyclohexanone provided the corresponding 3-cephems with the expected 3-position substituents (entry 2 and 3). When 1-morpholino-1-cyclohexene was used (entry 4), the yield was reduced compared to the case employing 1-pyrrolidino-1-cyclohexene as an enamine component (entry 3). The reactivity difference in the enamines could be responsible for the differences in yield. Introduction of a cyclopentanone moiety to the 3-position of cephem was also successfully achieved by this route (entry 5). An enamine with a protected hydroxyl group also can be used as an example for demonstrating further potential transformation of the resulting cephems (entry 6). In this case, after chromatographic separation, the corresponding 3-cephem product was directly obtained with the TBDPS protection removed. In the examples shown in Table 1 the enamine method exhibits an advantage over the previously reported silyl enol method in terms of yield and ease of the reaction.

In summary, we have shown that enamines can be used as more efficient and practical partners for the reaction of the cephem triflate **1** to introduce substituents at the 3-position of cephalosporin derivativs.

Acknowledgment. This work is supported by NON DIRECTED RESEARCH FUND, Korea Research Foundation and the Ministry of Science and Technology, Korea.

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8. Typical procedure (Entry 1): To a solution of 3-cephem triflate **1** (200 mg, 0.34 mmol) in dioxane (10 mL) was added 2-pyrrolidinopropene (57 mg, 0.51 mmol). After stirring for 10 min, the reaction mixture was quenched with water and the product was extracted with CH_2Cl_2. The organic layer was separated, washed with water and saturated NaCl solution. Drying ($MgSO_4$) followed by purification (silica gel chromatography, hexane : ether=2 : 1) provided 56 mg (33%) of the mixture of 2-cephem and 3-cephem product (*ca.* 2 : 3). This mixture was dissolved in dichloromethane (5 mL), cooled to 0 °C, mCPBA (30 mg, 0.17 mmol) was added and stirred for 30 min. After extracting with dichlomethane, the extract was washed with saturated $NaHCO_3$, water, and saturated NaCl solution. The product was dried ($MgSO_4$), concentrated and dissolved in DMF (10 mL). After the solution was cooled to −45 °C, PBr_3 (45 mg, 0.17 mmol) was added dropwise with stirring. After the reaction was completed, the product was extracted with ethyl acetate and the extract was washed with saturated $NaHCO_3$, water, and saturated NaCl solution. Drying ($MgSO_4$) followed by purification (silica gel chromatography, hexane : ether=2 : 1) provided the desired cephem **2** (34 mg, 61%).