Cycloadditions of Cephalosporins. The Formation of [4 + 2] Adducts with 5-Membered Heterocycles

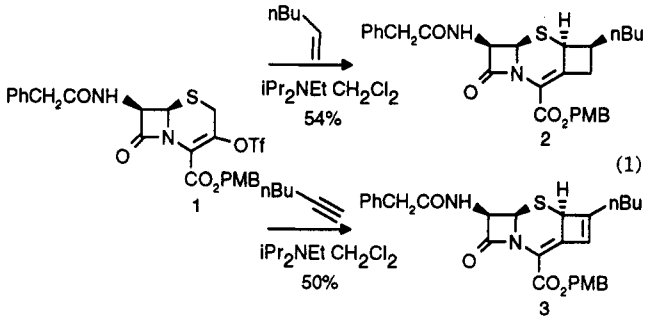
Richard L. Elliott,† Neville H. Nicholson,† Fiona E. Peaker,† Andrew K. Takle,*,† John W. Tyler,‡ and Janet White‡

SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ, U.K.

Received December 2, 1993•

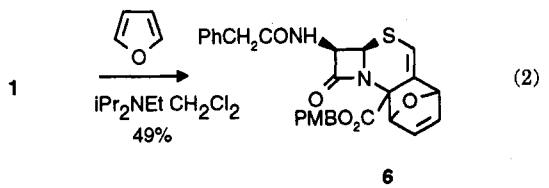
Summary: The cephalosporin triflate 1, and its sulfoxides 4 and 5, react with furan in the presence of a base to give [4 + 2] cycloadducts; the regiochemistry of the addition is determined by the oxidation state of the cephalosporin.

We have previously reported the unexpected reaction of the cephalosporin triflate (1) with olefins and acetylenes, leading to the formation of novel cephalosporins containing a 2,3-fused cyclobutane (2) or cyclobutene (3) ring[1] (eq 1).



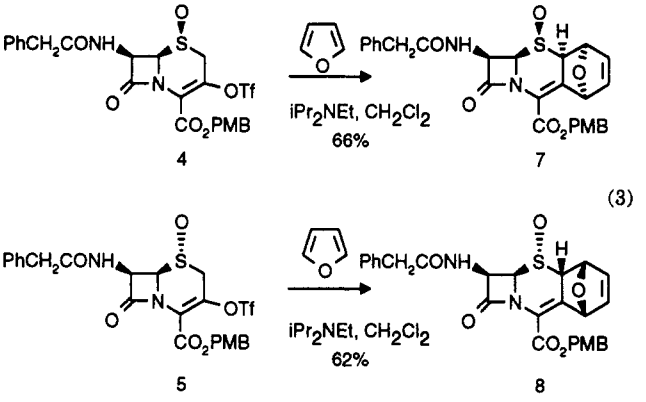
Here, we wish to report further reactions of this readily available triflate 1[2] and its sulfoxides 4 and 5.[3]

Treatment of a solution of 1 (1 equiv) and furan (5 equiv) in dichloromethane at room temperature with diisopropylethylamine (1 equiv) gave rise to the adduct 6, in 49% yield, where the addition had occurred across the 3,4 position of the cephalosporin nucleus (eq 2). The structure



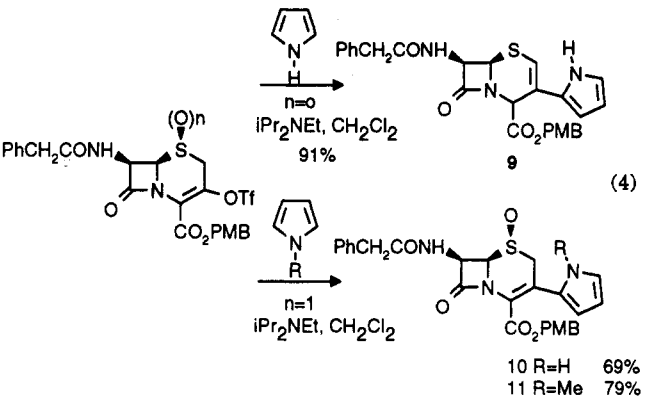
of 6 was determined by extensive NMR spectroscopy, although the stereochemistry at positions 4, 9, and 12 could not be determined.[4]

When the (*S*)- and (*R*)-sulfoxides 4 and 5 were treated with furan under the same conditions, the cycloadducts 7 and 8 were obtained in 66% and 62% yields, respectively (eq 3). In the case of the sulfoxides, however, the regiochemistry was different: namely, the addition had occurred across the 2,3 position of the cephalosporin nucleus as opposed to the 3,4 position with the sulfide. In addition to this, the two sulfoxide isomers gave rise to the opposite stereochemistry at the three new chiral centers.



The stereochemistry of the adducts 7 and 8 was unambiguously determined by NOE difference spectroscopy.

Intrigued by these findings, we next investigated the reaction of pyrrole with the triflates 1 and 4 with the intention of forming aza analogues of 6 and 7. However, the products obtained were the C3-substituted Δ2- and Δ3-cephems 9 and 10 in 91% and 69% yields, respectively (eq 4). Substitution on the pyrrole nitrogen was more



fruitful. Although *N*-methylpyrrole led to the C3-substituted cephem 11 (79%), *N*-(*tert*-butoxycarbonyl)-pyrrole[5] reacted with the (*S*)-sulfoxide triflate 4 to give the cycloadduct 12 in 29% yield (eq 5).

Our studies have shown that 1 equiv of base is required for complete consumption of the starting triflate. In the

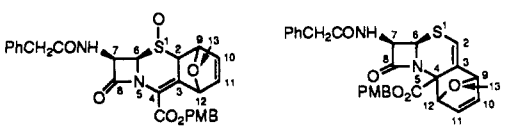
† Department of Medicinal Chemistry.
‡ Department of Analytical Sciences.
• Abstract published in *Advance ACS Abstracts,* March 15, 1994.

(1) Elliott, R. L.; Takle, A. K.; Tyler, J. W.; White, J. *J. Org. Chem.* **1993**, *58*, 6954. World patent no. WO 9318044-A.

(2) Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem.* **1989**, *54*, 4962.

(3) The (*S*)-sulfoxide 4 was prepared by oxidation of 1 with *m*-chloroperoxybenzoic acid. The (*R*)-sulfoxide 5 was prepared by oxidation with *N,N*-dichlorourethane based on the following method: Ochiai, M.; Aki, O.; Morimoto, A.; Okada, T. *Tetrahedron Lett.* **1972**, 3241.

(4) The numbering used in the text to describe the cycloadducts is based upon conventional cephalosporin numbering as follows: Systematic nomenclature is used in the experimental section of the supplementary material.



(5) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296.

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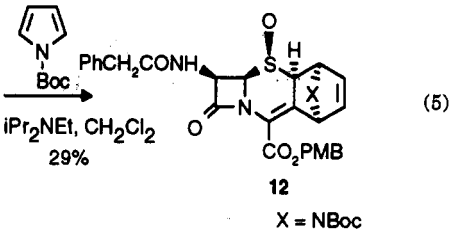
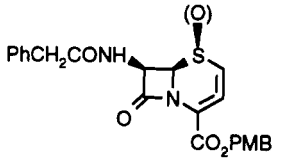


(5)

reaction we have described, a formal elimination of trifluoromethanesulfonic acid and a [4 + 2] cycloaddition have occurred. It is well known, in cephalosporin chemistry, that double-bond isomerization can occur to form mixtures of Δ2- and Δ3-isomers[6] on treatment of cephalosporins with base. Oxidation of such mixtures to the sulfoxide invariably reforms the Δ3-isomer. If the cycloaddition were to occur first, followed by the elimination, reaction with the sulfoxides **4** and **5** would occur across positions 3 and 4 of the cephalosporin, and in the case of the sulfide **1**, addition could occur across positions 2 and 3 or positions 3 and 4. This suggests that in the reaction that we have described, the first step is an elimination of trifluoromethanesulfonic acid to form a reactive intermediate, possibly the allene **13**. Furan then traps the



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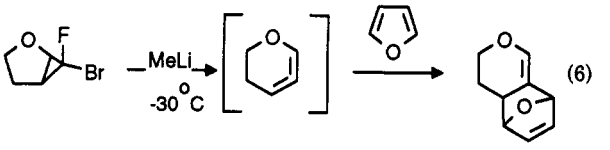
intermediate by undergoing a cycloaddition reaction. The regiochemistry of the cycloaddition is determined by the oxidation state of the sulfur atom of the cephalosporin. Presumably, the cycloaddition of the electron-rich furan occurs to the more electron-deficient π-system.

There has been much discussion in the literature concerning the existence and structure of small-ring cyclic allenes.[7] Christl and Braun have reported the existence of 1-oxa-2,3-cyclohexadiene (**15**) which has been trapped as a [4 + 2] adduct with furan **16**.[8] Again, the addition was to the least electron-rich π-system (eq 6).



(6)

14 **15** **16**

Further studies on the scope and mechanism of the reaction we have reported are ongoing and will be reported at a later date.[9]

Acknowledgment. We wish to thank Dr. M. J. Pearson and Professor P. Kocienski for their enthusiastic support of this work.

Supplementary Material Available: Typical experimental procedures and data for all new compounds (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(6) (a) Cocker, J. D.; Eardley, S.; Gregory, G. I.; Hall, M. E.; Long, A. G. *J. Chem. Soc. C* **1966**, 1142. (b) Kaiser, G. V.; Cooper, R. D. G.; Koehler, R. E.; Murphy, C. F.; Webber, J. A.; Wright, I. G.; Van Heyningen, E. M. *J. Org. Chem.* **1970**, *35*, 2430.

(7) Christl, M.; Schreck, M. *Chem. Ber.* **1987**, *120*, 915 and references cited therein.

(8) Christl, M.; Braun, M. *Chem. Ber.* **1989**, *122*, 1939.

(9) In common with other cephalosporins bearing a phenylacetamido group at C7, the antibacterial activity of these novel polycyclic cephems is mainly confined to Gram-positive organisms. Selected data of the sodium salts derived from **6** (by deesterification) and **7** (by sulfoxide reduction and deesterification), respectively, are as follows: *Moraxella catarrhalis* 1502, 8 and 0.5; *Bacillus subtilis* ATCC 6633, 2 and 0.125; *Staphylococcus aureus* Oxford, 4 and 0.5; *Streptococcus pyogenes* CN10, 0.5 and 0.125 μg/mL.