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S(1)-C(2)-SECOCEPHEMS

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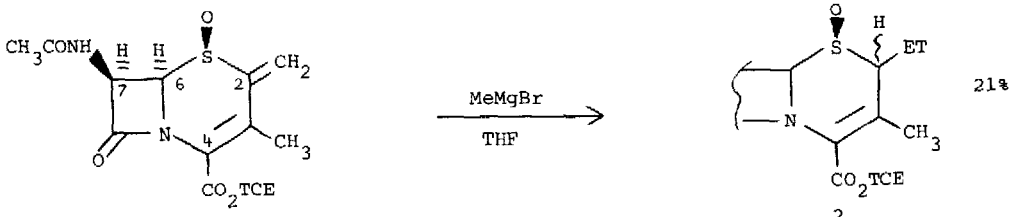
Abstract: Preparation of acetylenic-S(1)-C(2)-secocephems from the reaction of Grignard reagents on cis-α-vinylhalo sulfoxides.

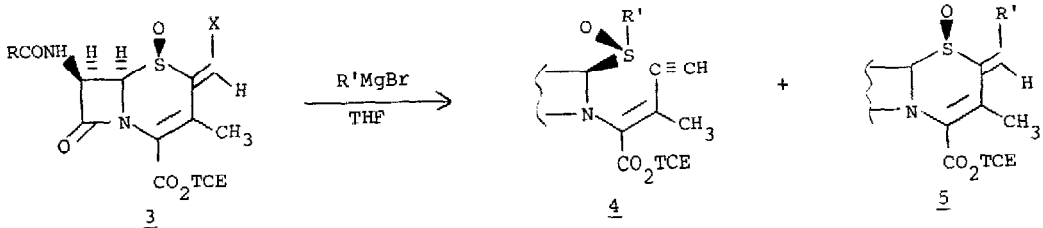
We recently reported the synthesis of various C(2)-vinylhalo cephems.[1] We now wish to report the use of these compounds to synthesize monocyclic β-lactam derivatives via an S(1)-C(2) bond cleavage[2] using Grignard reagents.

Treatment of the diene sulfoxide 1 with methyl Grignard results in Michael addition to give the C(2)-ethyl derivative 2.



1 2

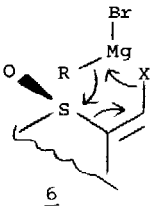
The C(2)-vinylhalo sulfoxides 3, however, react with Grignard reagents as vinylogous sulfinyl chlorides to give the acetylenic-S(1)-C(2)-secocephems 4, presumably via the transition state 6.



3 4 5

Where	R	R'	X	%4	%5
(a)	CH_3	CH_3	Cl	60-70	--
(b)	CH_3	Et	Cl	25	12
(c)	CH_3	n-pr	Cl	60	22
(d)	V	CH_3	Br	40-50	12

V = $C_6H_5OCH_2$, TCE = trichloroethyl



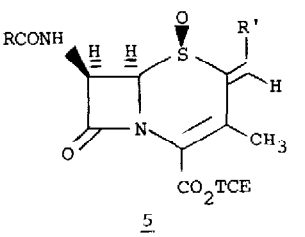
6

The reaction of 3 with methyl lithium failed to give 4.

The yield of 4 appears to be a function of the ester (p-nitrobenzyl failed), of the side chain, and of the Grignard reagent used. When N-acetyl-TCE [3(a)], in THF at -68°, was reacted with three equivalences of methyl Grignard for 2.0 min. and then acidified, 60-70% yields of the chromatographed acetylene could be realized. This constitutes a very mild method of forming the acetylene bond.[3] Using N-phenoxyacetyl side chain or ethyl and n-propyl Grignard on the N-acetyl derivative gave lower yields of the acetylene, and in addition 5, which apparently results from Michael addition to 3 and subsequent elimination of the halogen.

Compound 5 was identified from physical data. Thus 5(d) [180-181°][4] gave an ir spectrum ($CHCl_3$) of 1805 cm^{-1} for the β-lactam and the nmr spectrum showed: 2.23 (d J=8HZ,3,C(2) vinyl methyl), 2.29 (S,3,C(3)Me), 4.59 (d J=5HZ,1,H_6), 4.58 (S,2,ϕOCH_2), 4.84, 5.05 (AB J=12HZ,2,TCE), 6.13 (q J=5,10HZ,1,H_7), 6.73 (d J=8HZ,1,C(2) vinyl H), 7.94(d J=10HZ,1,NH).

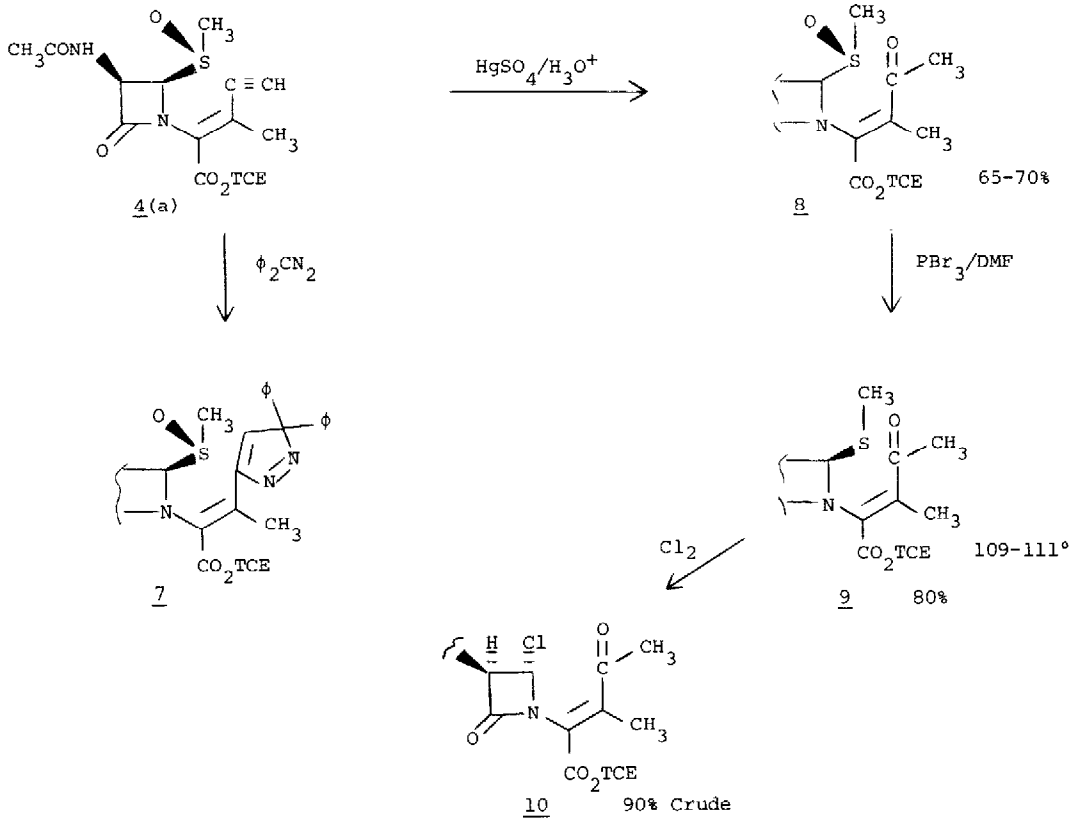
In addition, 5(d) was synthesized [80%] from 3(d) using lithium dimethylcuprate. Only one geometrical isomer of 5(d) was present and its stereochemistry was determined by NOE studies between the C(2) vinyl proton and the C(3) methyl [22% in $CDCl_3$] to be cis-methyl relative to the sulfoxide[5], i.e., retention of configuration[6]. Lithium di-n-butylcuprate also has been used to give 5(e) in somewhat lower yield (48%).



3 $\xrightarrow{R'_2LiCu}$ 5

Where	R	R'	X	%5	mp 5
(a)	CH_3	CH_3	Cl	65	224°
(d)	V	CH_3	Cl	80	180-181°
(e)	CH_3	n-Bu	Cl	48	--

Identification of 4 follows from the physical data. The ir spectrum ($CHCl_3$) of 4(a) showed a β-lactam stretch at 1790 cm^{-1}, the C≡C and ≡C-H stretch vibrations at 2108 cm^{-1} and 3300 cm^{-1}. The nmr spectrum (T-60, $CDCl_3$, δ) showed: 2.13 (s,3,$CH_3C[O]$), 2.47 (s,3,C(3)Me), 2.75 (s,3, $S[O]CH_3$), 4.13 (s,1,≡CH), 4.95 (AB 2,TCE), 5.10 (d J=5HZ,1,H_6), 6.01 (q J=5,10HZ,1,H_7), 7.98 (d J=10HZ,1,NH). Mass spectrum of 4(a) showed a small mol. ion m/e (429) and a large m/e M-63 (366) resulting from loss of $S(O)CH_3$. There also is chemical evidence to support structure 4. The sulfoxide can be oxidized to the sulfone (82%) or reduced to the sulfide (70%). The acetylene rapidly undergoes 1,3-dipolar cycloaddition with diazomethane (58%) or diphenyldiazomethane (78%) to give the corresponding pyrazole (See Scheme I). In addition the acetylene can be hydrated to give the sulfoxide methyl ketone 8 (65-70%) and then reduced to the crystalline sulfide methyl ketone 9 (80%, mp 109-111°). Chlorinolysis of 9 then gave the trans chloroazetidinone 10 (90% crude).



SCHEME I

Acknowledgement: We thank Mr. T. K. Elzey for running the NOE studies.

REFERENCES

1. D. O. Spry, Tetrahedron Lett., -------(1980).
2. For another example of cephem S(1)-C(2)-bond fission see: A. Yoshida, S. Oida, and E. Ohki, Chem. Pharm. Bull. Jap., 362 (1976).
3. The generality of this method of forming the acetylene bond has not been studied.
4. All crystalline compounds obtained in this work were crystallized from CH_2Cl_2/hexanes and gave satisfactory analysis.
5. For a synthesis of 2-alkylidene-3-hydro-cephalosporins with the same stereochemistry see: R. B. Woodward, K. Heusler, I. Ernest, K. Burri, R. J. Friary, F. Haviv, W. Oppolzer, R. Paioni, K. Syhora, R. Wenger, and J. K. Whitesell, Nouv. J. Chem., 1, 85 (1977).
6. C. V. Maffeo, G. Marchese, F. Naso, and L. Ronzini, J. Chem. Soc., Perkin I, 92 (1979).

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