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C(2)-VINYLHALO-CEPHEMS

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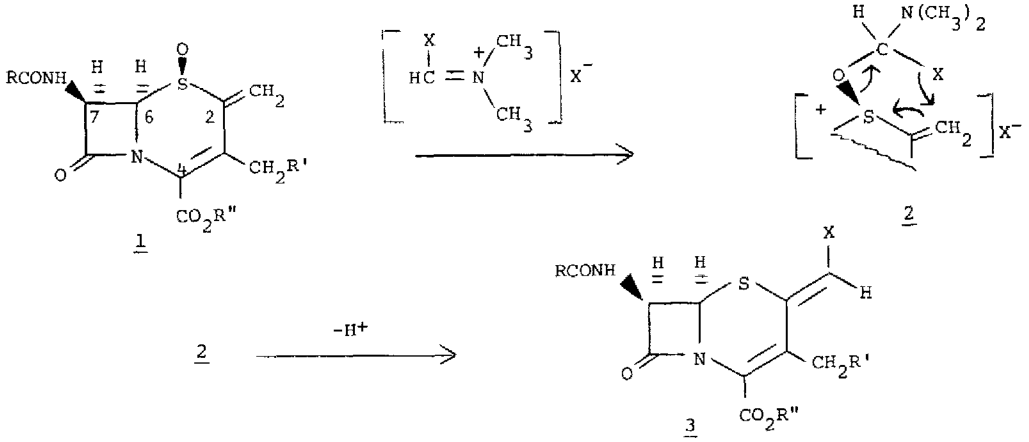
Abstract: C(2)-vinylhalo-cephems are prepared from a Pummerer type rearrangement of the corresponding sulfoxide with dimethyl immonium halide.

We recently reported the conversion of an α,β-unsaturated sulfoxide to a β-chloro-α,β-unsaturated sulfide via a vinylogous Pummerer rearrangement with dimethyl immonium chloride.[1]

We now wish to report the synthesis of various C(2)-vinylchloro and bromo cephems and their conversion into novel β-lactam derivatives. Thus the reaction of the diene sulfoxide[2] 1 with preformed[3] (PX_3 + DMF) Vilsmeier reagent gave 3 as the only product.

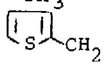


1

2

2

3

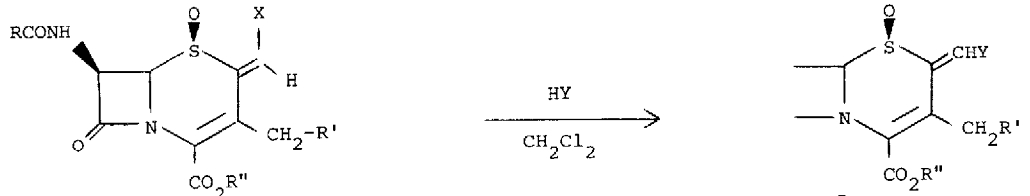
Where	R	R'	R''	X	%(3)	mp(3)	mp(4)
(a)	V	H	TCE	Cl	70-75	153-154	170-171
(b)	V	H	PNB	Cl	60-65	150-151	230
(c)	V	H	TCE	Br	82	145-146	177-178
(d)	V	H	PNB	Br	74	151-152	195
(e)	CH_3	H	TCE	Cl	70-80	176-177	
(f)	CH_3	H	TCE	Br	52		204
(g)		OAc	TCE	Cl	50		

PNB= p-nitrobenzyl, TCE= trichloroethyl, V=$C_6H_5OCH_2$

The structure of 3 was determined by elemental analysis, mass spec. and nmr. Thus 3(e) showed a mol. ion of m/e 434, a UV of 323 nm and an ir of 1783 cm^{-1}. Its nmr (100MC, CDCl$_3$, δ) showed: 2.10 (s,3,C(O)CH$_3$), 2.33 (s,3,C(3)Me), 4.81, 4.99 (AB J=12HZ,2,TCE) 5.15 (d J=4HZ,1,H$_6$), 5.86 (q J=4,9HZ,1,H$_7$), 6.52 (d J=9HZ,1,NH), 6.85 (s,1,C(2')vinyl H). NOE studies of the C(2)-vinyl proton and the C(3)-methyl [15-19% in CDCl$_3$, 18% for 3(e)] indicate that the reaction is stereospecific, presumably going through intermediate 2 followed by a cyclic rearrangement to give the halomethyl carbosulfonium ion and then loss of a proton to give 3.

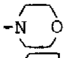
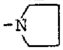
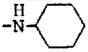
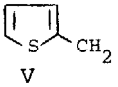
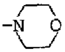
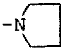
Meta-chloroperbenzoic acid oxidation of 3 then gave a high yield (75-90%) of crystalline sulfoxide 4, presumably of the β-configuration.

The vinylhalo sulfoxides 4 react with various primary and secondary amines to give crystalline enamines[4] 5 in high yield (See Scheme I). The enamines, however, failed to undergo the Stork acylation or alkylation reaction, being doubly stabililzed by the sulfoxide and the conjugated ester. Attempts to reduce the sulfoxide of the pyrrolidine enamine 5 with PCl$_3$/DMF followed by silica chromatography gave nonlactam products. Similar results were obtained by the reaction of pyrrolidine on the sulfide vinyl chloride 3(e).



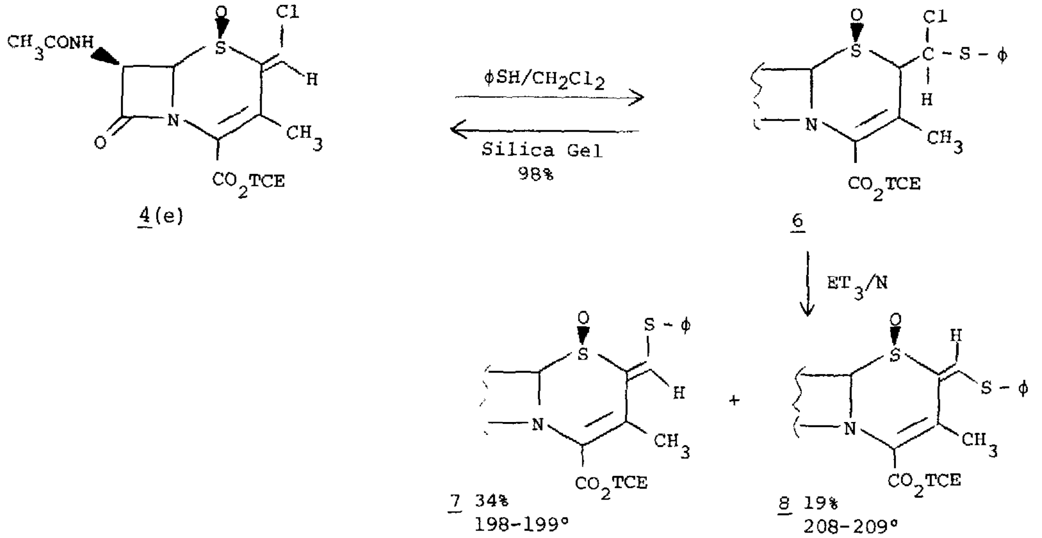
4

5

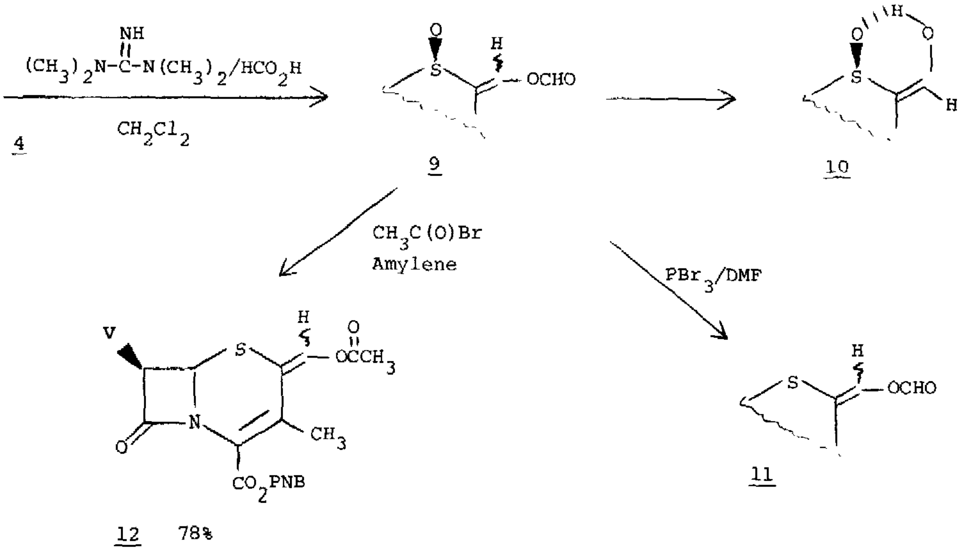
Where	R	R'	R''	X	Y	%5	mp 5
	CH_3	H	TCE	Cl		90	217-218
	CH_3	H	TCE	Cl		78	230
	CH_3	H	TCE	Cl		86	
		OAc	TCE	Cl		57	
	V	H	PNB	Br		90	231

SCHEME I

The vinylhalo sulfoxides also react with mercaptans to give addition products. Thus the reaction of thiophenol with 4(e) gave 6. Chromatography of 6 on silica gel resulted in elimination of thiophenol to give back the diene sulfoxide (98%). However, treatment of 6 with Et$_3$N gave a cis/trans mixture of the C(2)-vinyl sulfides[5] 7 and 8.



Reaction of 4 with tetramethylquanidinium formate[6] gave a high yield of the vinyl formate 9, which readily hydrolyzes on silica to give the hydrogen bonded enol 10. Sulfoxide reduction (PBr_3/DMF) of 9 gave 11. However, treatment of crude 9 with acetyl bromide-amylene[7] resulted in sulfoxide reduction, formate hydrolysis and enol acylation to give 12 in 78% overall yield from 4(d), as a cis/trans mixture.



The structure of 12 was evident from physical data. Thus: ir 1778 cm^{-1} UV 268, 313 nm, nmr (100 MC, $CDCl_3$, δ) 2.22, 2.25, 3.01, 4.44 (m,6,C(3)Me, $C(O)CH_3$), 4.59 (s,2,ϕOCH_2), 5.08 (d J=4HZ,1,H_6), 5.37

(s,2,PNB), 5.89 (q J=4,9HZ,1,H_7), 7.94 (s,1,C(2')vinyl H). The multiplicity of methyl peaks implies a cis/trans mixture.

Hydrogenolysis of the PNB group (79%) then gave the acid of 12.

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2. I. G. Wright, C. W. Ashbrook, T. Goodson, G. V. Kaiser, and E. M. Van Heyningen, J. Med. Chem., 14, 420 (1971).
3. If the Vilsmeier reagent is not preformed, PX_3/DMF results in sulfoxide reduction to give diene sulfide, particularly with PBr_3.
4. All crystalline compounds obtained in this work were crystallized from CH_2Cl_2/hexanes and gave satisfactory analyses.
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6. S. Wolfe, J. B. Ducep, K. C. Tin, and J. L. Lee, Can. J. Chem., 52, 3996 (1974).
7. L. D. Hatfield, U.S. Pat. 4044002.

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