SYNTHESIS OF 4-MERCAPTOAZETIDINONES AND THEIR APPLICATION TO PREPARATION OF β-LACTAM ANTIBIOTICS

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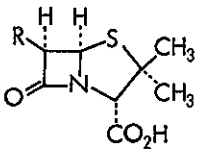
Penicillins 1 and cephalosporins 2 are currently useful β-lactam antibiotics and their nuclei have been obtained by fermentation. Since they have a common azetidinone moiety 3,[1] conversion of easily available 1 into 2 has been desired, as exemplified by production of the cephalexin nucleus (2, X = H) from 1 sulfoxide.[2] In this report, we describe syntheses of 4-mercaptoazetidinones 3a and their equivalents 3b and their application to the synthesis of β-lactam antibiotics.

The valuable intermediate 4, used in the ellegant synthesis of cephalosporin C by Woodward et al., has been employed effectively for syntheses of several new β-lactam antibiotics.[3]

Cooper[4] has found an interesting conversion. When thiazoline 5a was oxidized with m-chloroperbenzoic acid in the presence of a trace of trifluoroacetic acid, sulfoxides of 6a and 7a (R^5, CH_3) were obtained. By a similar oxidative cyclization of 5b and subsequent reduction with phosphor trichloride, Kishi et al.[5] isolated 6b and 7b (R^5, CH_3). They isolated[6] intermediate sulfoxides of 5, which were easily changed solely to 6 by a radical chain process. Also, Kishi et al. have succeeded in cyclization



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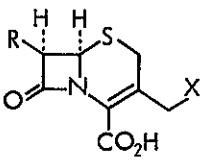

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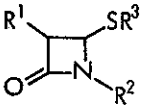
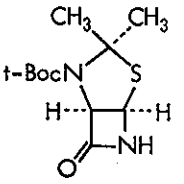


3a R^3, H

3b R^3, protecting group



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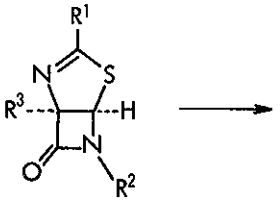

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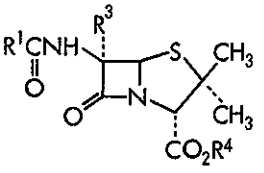

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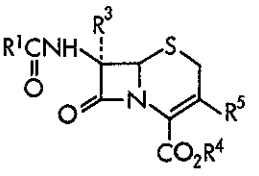

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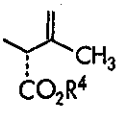
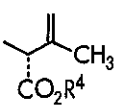
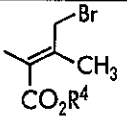
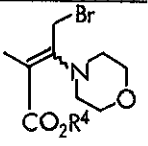
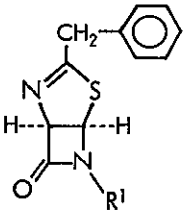
	a	b	c	d
R^2				
R^3	-H	$-OCH_3$	$-OCH_3$	-H



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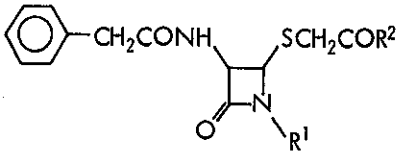


9

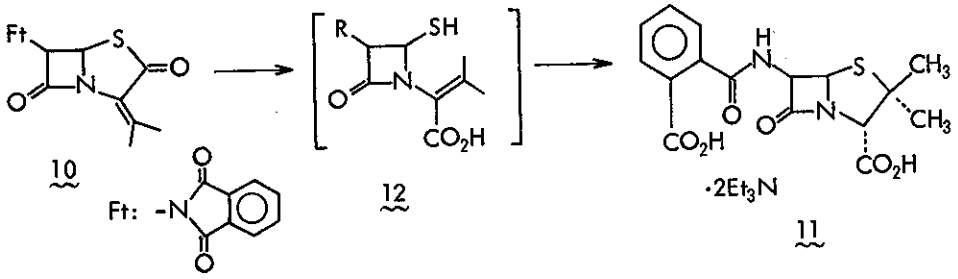
of 5c into 7b (R^5, CH_3). In our synthesis of 3-hydroxycephems,[7] 5d was treated with 10% hydrochloric acid to form 7d (R^5, OH).

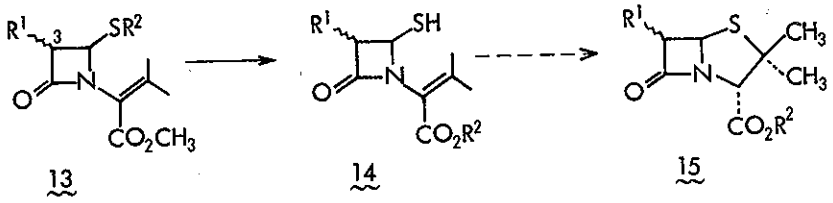
Glaxo research group has found that 8 can be alkylated to 9 with α-halocarbonyl compounds in dimethylformamide in the presence of urea.[8] Lattrell et al. also employed this reaction condition for preparation of α-carbonylmethylthio compounds 9.[9]

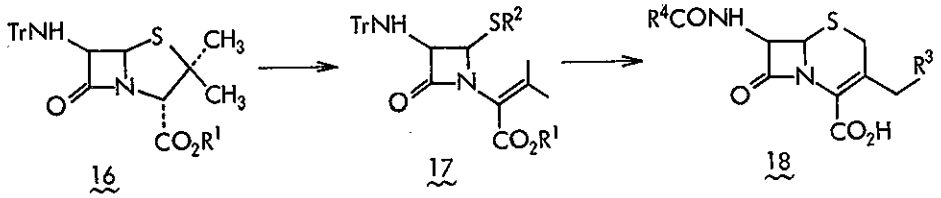
Wolfe et al.[10] obtained 11 by allowing anhydropenicillin 10 to stand in aqueous dimethyl sulfoxide at pH 7.4. An intramolecular Michael addition of 12 has been proposed. This interesting cyclization has been examined by several research groups using 12-type compounds 14. Compound 13a (R^1, 3α-Ft; R^2, p-methoxybenzyl), synthesized by Bachi et al.,[11] was converted into 14a by successive treatment with silver acetate and hydrogen sulfide. Attempts to cyclize 14a to 15a failed. Lattrell et al.[12] also synthesized 13b (R^1, 3β-phenoxyacetamido; R^2, trityl) which were deprotected similarly to 14b. However, no cyclization products were obtained by treatment of it under radical and ionic conditions including Wolfe's ones. Cyclization of a free acid 14c[13] (R^1, 3β-phenoxyacetamido; R^2, H) (vide infra) was also attempted in vain by allowing it to stand in buffer solutions of several pHs (3.4-8.5).

A retero-Michael reaction of penicillin 16 yielding 17a (R^2, ⊖) is the reverse path. Nayler et al.[14] trapped the intermediate as 17b (R^2, $CH_2C{\equiv}CR^3$) by treatment of 16 with potassium t-butoxide or sodium hydride in the presence of propargyl bromides ($BrCH_2C{\equiv}CR^3$). The compounds 17b were converted into new β-lactam antibiotics 18 (R^3, aromatic rings). Recently, Re et al.[15] obtained 17c (R^2, $CH_2COC_6H_5$) by alkylation of 16 with phenacyl bromide in the presence of potassium t-butoxide at -40°.

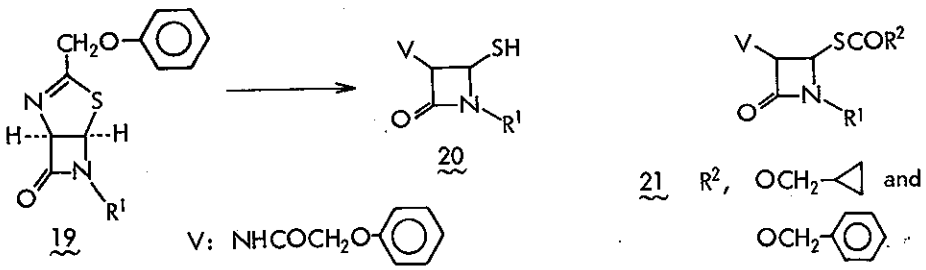
During the synthetic study of 3-hydroxycephem,[7] a method for preparation of 4-mercaptoazetidinone 20 from thiazoline 19 was found. The thiazoline was converted

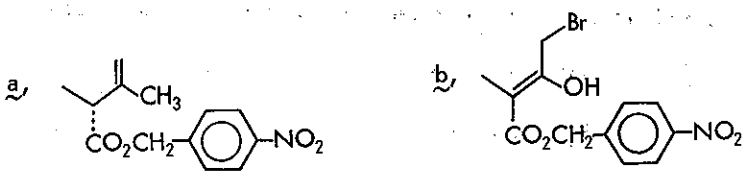

Ft
S
N
O
10
Ft: -N
R
SH
CO2H
12
H
N
S
CH3
CH3
CO2H
·2Et3N
11

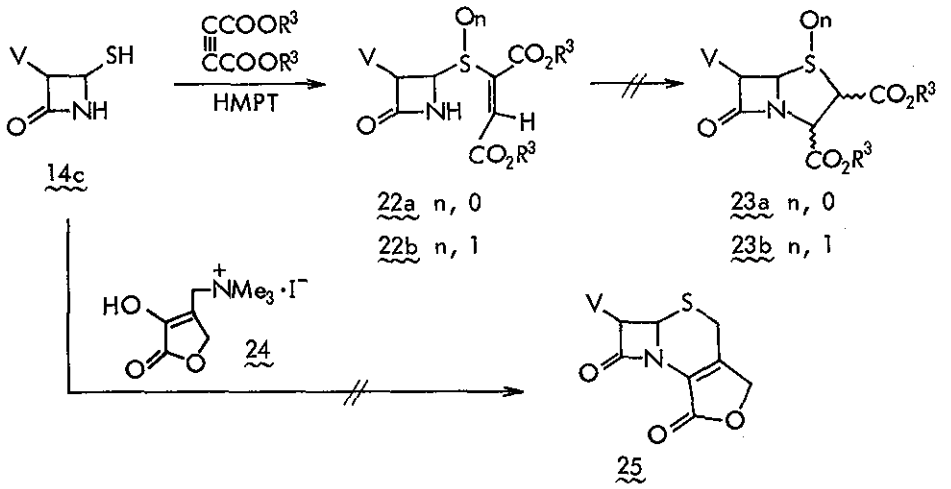

R1
3
SR2
CO2CH3
13
SH
CO2R2
14
S
CH3
CH3
15


TrNH
S
CH3
CH3
CO2R1
16
SR2
17
R4CONH
R3
CO2H
18

Tr: Trityl


CH2O
N
S
H
H
19
V
SH
20
SCOR2
21 R2, OCH2 and
OCH2
V: NHCOCH2O


a,
CH3
CO2CH2
NO2
b,
Br
OH
CO2CH2
NO2



into silver mercaptid with silver perchlorate or tetrafluoroborate under a mild condition. Treatment of the mercaptid with hydrogen sulfide gave a mercaptan.[7] Thus, 19a was converted into 20a. Acylation of 20a with acyl chloride gave acylthio compounds. Of these, 21a were changed to 21b by successive treatment with ozone, mesyl chloride, morpholine, bromine, and aqueous acid. Deprotection of 21b with aluminum chloride proceeded smoothly to give 20b, which was cyclized to 7d (R^5, OH) by treatment with silica gel.[7] By investigating the previously described cyclization of 5d to 7d more precisely, it was proved that the reaction proceeded successively from 5d, via 19b and 20b to 7d. The intermediates 19b and 20b were prepared by treatment of 5d with 60% perchloric acid at -40° and 30% perchloric acid at room temperature, respectively. The second procedure was found to be generally applicable for the thiazoline ring cleavage giving mercaptoazetidinones. Thus, several thiols including 14c were obtained.[13] Some attempts to prepare β-lactam antibiotics from 14c was carried out.[13] Michael addition of 14c to acetylenedicarboxylic acid esters proceeded smoothly, but

both of 22a and its sulfoxide 22b did not yield cyclize products 23a and 23b, respectively. Double addition reaction of 14c to 24[16] yielding 25 was tried without success.

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