Tetrahedron Letters,Vol.25,No.19,pp 2017-2020,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

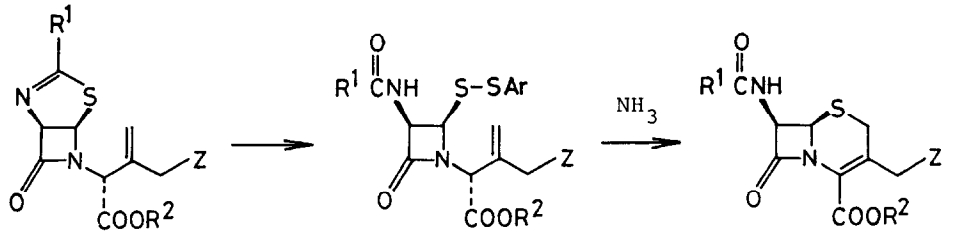
PENICILLIN-CEPHALOSPORIN CONVERSION X.[1] NEW SYNTHESIS OF DITHIOAZETIDINONES FROM THIAZOLINE-AZETIDINONES

Sigeru Torii,* Hideo Tanaka, Takashi Siroi, and Michio Sasaoka
Department of Industrial Chemistry, School of Engineering,
Okayama University, Okayama 700, Japan

ABSTRACT: New ring-opening reaction of thiazoline-azetidinones 1 to dithioazetidinones 2 was achieved with 2-benzothiazolyl disulfide in aqueous acidic media and its potentiality for the preparation of a variety of cephalosporins 3 from various thiazoline-azetidinones 1 is demonstrated.

Recently, we have reported the hydrolytic ring-opening of thiazoline-azetidinones 1 derived from penicillins to dithioazetidinones 2 (R^1 = $PhCH_2$ and $PhOCH_2$; Z = Cl) by the reaction with sulfenyl chlorides (ArSCl: Ar = aryl and hetero-aromatic groups) in dioxane-H_2O.[2] These disulfides 2 were subsequently cyclized to 3'-thiosubstituted cephalosporins 3 (Z = SAr) by treatment with NH_3 in N,N-dimethylformamide (DMF). This sequence is one of the most efficient and short-cut route among the penicillin-cephalosporin conversions hitherto disclosed in obtaining 3'-substituted cephalosporins.[3] However, the procedure can not be operated on the thiazoline derivatives 1 which resist hydrolysis and/or possess functional groups sensitive toward sulfenyl chlorides.

We wish to report here a successful transformation of thiazoline-azetidinones 1 to dithioazetidinones 2 by using 2-benzothiazolyl disulfide (6) as a new thiol-trapping agent of 4-mercaptoazetidinones 4 which are formed under acid-hydrolysis conditions. We also proved the wide applicability of this method by synthesizing cephalosporins 3 from various thiazoline-azetidinones 1.[4]



1 2 3

The sulfenyl chloride promoted ring-opening of 1 into 2 seems to proceed stepwise, first hydrolysis of the thiazoline ring to thiol 4 and trapping the thiol by the sulfenyl chloride.[2b] The reaction of thiazoline 1o (R^1 = $PhCCl_2$; R^2 = $PhCH_2$; Z = Cl) with 2-benzothiazolesulfenyl chloride (BTS-Cl) in dioxane-H_2O failed and 1o was completely recovered intact. The similar results were obtained with other thiazoline derivatives 1p-t bearing PhCH(OAc), PhOCH(SPh), PhCO, and Ph as R^1 under the same conditions.[5] It seems that the decomposition of sulfenyl chloride (BTS-Cl) in the aqueous media proceeds before suitable amounts of thiol 4 are accumulated. Actually, these thiazoline derivatives 1o-t were stable in the aqueous media and underwent hydrolysis slowly.[6]

In order to achieve this transformation (1 → 2) we needed a new thiol trapping agent, which must be stable under the acid hydrolysis conditions as well as labile enough to react with thiols 4 successively as they are formed, so as to suppress ring-opening reaction to thiazoles 5[4] (Scheme 2). Beside these two requirements which seem to contradict each other, the sulfenyl moieties (ArS in 2) must act as a good leaving group at the cyclization step later (2 → 3). We have found that 2-benzothiazolyl disulfide 6 is an excellent reagent for this purpose and many sort of thiazoline-azetidinones 1 reacted successfully with the disulfide 6 under acid-hydrolysis conditions to afford the corresponding unsymmetrical disulfides 2 (Table 1).[7]

The experimental procedure is very simple as one mixes 1a with 1.3 equiv. of disulfide 6 in aqueous 5% HCl-THF (1/5) at room temperature for 40 min, affording 2a in 90% yield after a short column chromatography (SiO_2, benzene-AcOEt, 8/1) (entry 1). It was a pleasant surprise that any detectable amounts of symmetrical disulfide 7 were not formed under above reaction conditions.[7] The various type of the substituents on the β-lactam nitrogen atom were not affected under these conditions. It is especially noteworthy that carboxylic acid and hydroxyl groups are not required to be protected (entries 3 and 6). Further more, this method was applicable to the hydrolysis resistant thiazoline-azetidinones 1o-t,[8] *vide supra*, by

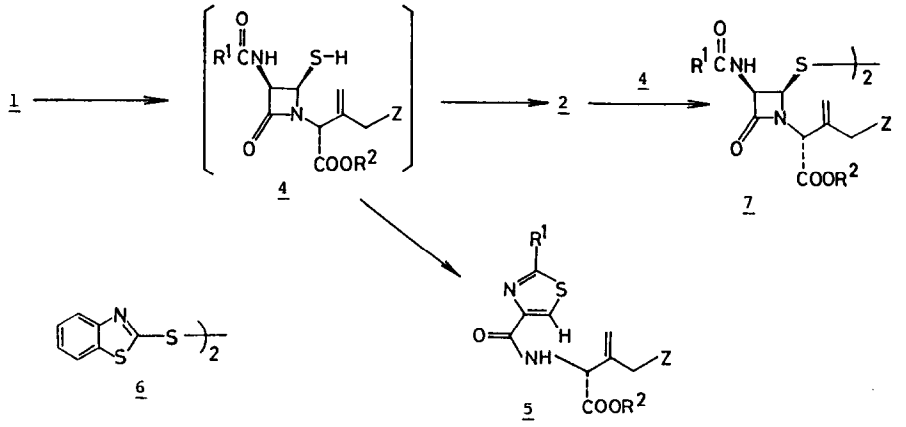
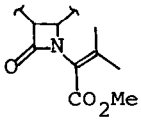
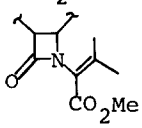
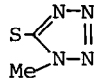
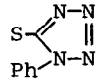
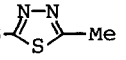


Table 1. Ring-opening of Thiazoline-Azetidinones with BTS-SBT

entry	Thiazoline-Azetidinone 1			Conditions[a]	Yield, %[b]	
	R^1	R^2	Z[c]	aq. Acid/ h	1→2	2→3
1 a	$PhCH_2$	$PhCH_2$	H	5% HCl	90	
2 b	$PhCH_2$			5% HCl	100	
				27% p-TsOH	98	
3 c	$PhCH_2$	H	H	5% HCl	100	
4 d	$PhCH_2$	$PhCH_2$	Cl	5% HCl	89	74[2]
5 e	$PhCH_2$			5% HCl	90	
6 f	$PhCH_2$	$PhCH_2$	OH	5% HCl	65	80
7 g	$PhCH_2$	$PhCH_2$	OAc	5% HCl	69	84
8 h	$PhCH_2$	$PhCH_2$	ONO_2	5% HCl	51	73
9 i	$PhCH_2$	$PhCH_2$	S-TZ-Me	5% HCl	88	90
10 j	$PhCH_2$	$PhCH_2$	S-TZ-Ph	5% HCl	89	89
11 k	$PhCH_2$	$PhCH_2$	S-DZ	5% HCl	92	86
12 l	$PhCH_2$	$PhCH_2$	SCSOEt	5% HCl	90	82
13 m	$PhCH_2$	$PhCH_2$	$SCSNMe_2$	5% HCl	93	85
14 n	$PhOCH_2$	$PhCH_2$	H	10% $HClO_4$	94	
15 o	$PhCCl_2$	$PhCH_2$	Cl	20% $HClO_4$/24	64	
16 p	$PhCCl_2$	$PhCH_2$	S-TZ-Me	20% $HClO_4$/70	65	81
17 q	PhCH(OAc)	$PhCH_2$	H	5% HCl/2	65	
18 r	PhOCH(SPh)	$PhCH_2$	Cl	20% $HClO_4$/116	80	
19 s	PhCO	$PhCH_2$	Cl	5% HCl/120	83	
20 t	Ph			5% HCl/20	40	(52)[d]

a) Carried out in THF with 1.3 equiv. of disulfide 6 at room temperature for 40 min unless otherwise noted. b) Isolated yields.

c) S-TZ-Me:  ; S-TZ-Ph:  ; S-DZ: 

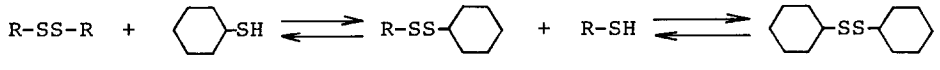
d) Recovered 1t

employing prolonged reaction time to give the corresponding dithioazetidinones 2 (entries 15-20).

The dithioazetidinones 2 obtained by this method were cyclized smoothly by treatment with NH_3 in DMF at -35 °C to give the desired 3'-substituted cephalosporins 3. These cephalosporins 3 can be converted into clinically important antibiotics by manipulation of the C(7)-amide groups as well as deprotection of the esters.

References

1. Part IX: submitted for publication; Part VIII: S. Torii, H. Tanaka, T. Siroi, and M. Sasaoka, J. Org. Chem., 48, 3551 (1983).
2. (a) S. Torii, H. Tanaka, M. Sasaoka, M. Saitoh, T. Siroi, and J. Nokami, Tetrahedron Lett., 23, 2495 (1982); (b) S. Torii, H. Tanaka, M. Sasaoka, N. Saitoh, T. Siroi, and J. Nokami, Bull. Soc. Chim. Belg., 91, 951 (1982).
3. For a review: F. A. Jung, W. R. Pilgrim, J. P. Poyser, and P. J. Siret, "Topics in Antibiotic Chemistry", Vol. 4, ed. P. G. Sammes, Ellis Harwood Limited, Chichester, 1980; Chapter 3.
4. The hydrolytic ring-opening of thiazoline-azetidinones to 4-mercapto-azetidinones in aqueous acidic media and subsequent trapping of the thiol group with alkyl halides, acetyl chloride, etc., have been reported. However, the latter has been operated in non-aqueous media and no attempts have been made to trap *in situ* the thiol moiety in the aqueous media: (a) M. Narisada, H. Onoue, M. Ohtani, F. Watanabe, T. Okada, and W. Nagata, Tetrahedron Lett., 1755 (1978); (b) J. E. Baldwin and M. A. Christie, J. C. S. Comm., 1978, 239; (c) N. F. Osbone, J. C. S. Perkin I, 1980, 150 and references cited therein.
5. Starting materials were recovered intact. It is not clear whether the stability of these thiazoline 1o-t is due to steric or electronic reasons.
6. We confirmed that it took 2 days to complete the hydrolytic ring-opening of the thiazoline moieties of 1o (R^1 = $PhCCl_2$) in 10% HCl-THF (1/5) at room temperature.
7. In a preliminary experiment, we examined the reaction of various kinds of disulfides (R-SS-R) with cyclohexanethiol, resulting in the formation of a mixture of symmetrical disulfides and unsymmetrical disulfides in a ratio: 2/91 (R = BT); 10/77 (2-pyridyl); 55/44 (p-NO_2-phenyl); 73/16 (C_6Cl_5); no reaction (Ph). Details will be reported elsewhere.



8. Compound 1t (R^1 = Ph) was reported not to undergo hydrolytic ring-opening reaction with dialkyl azodicarboxylates: G. Franceschi, M. Foglio, P. Masi, A. Suarato, G. Palamidessi, L. Bernardi, F. Arcamone, and G. Cainelli, J. Am. Chem. Soc., 99, 248 (1977).

(Received in Japan 21 January 1984)