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PENICILLIN-CEPHALOSPORIN CONVERSION IV. DIRECT SYNTHESIS OF 3'-THIOSUBSTITUTED CEPHALOSPORINS FROM THIAZOLINE-AZETIDINONES

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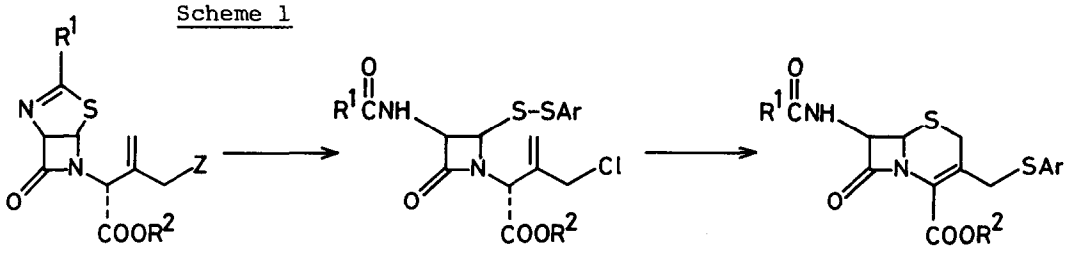
ABSTRACT: Direct transformation of thiazoline-azetidinones 2, derived from penicillin G and V, into 3'-thio-substituted cephalosporins 4 has been performed by ring opening of the thiazoline moiety with sulfenyl chlorides followed by ring closure with NH_3 in dimethylformamide and simultaneous displacement of the allylic chlorine atom with the leaving thiolates.

Since the pioneering work of Morin et al.[1] the transformation of penicillins into cephalosporins has been actively investigated in many laboratories.[2] Especially, the synthesis of 3'-substituted cephalosporins has attracted much attention of many investigators, but still only a few successful reports have appeared.[3] Recently, we disclosed chemoselective electrolytic chlorination of thiazoline-azetidinones 1 derived from penicillin G and V, providing potent intermediates 2.[4] We now wish to report a direct two-step conversion of 2 to 3'-thio-substituted cephalosporins 4.

Scheme 1



1: Z = H
2: Z = Cl

3

4

Most of clinically significant cephalosporin antibiotics possess a sulfenyl group at the C-3' position. They have been prepared by displacement of the acetoxy group of the corresponding 3'-acetoxycephalosporins.[5] We sought a direct route to 3'-thio-substituted cephalosporins 4 from 2. A possible approach for this goal must comprise the ring opening of 2 to disulfides 3 followed by a base catalyzed ring closure and simultaneous displacement of the allylic chlorine atom with the leaving thiolate (ArS^-).

The hydrolytic ring opening of the thiazoline moiety of 2 was accomplished by treatment with sulfenyl chloride in dioxane in the presence of water.[6] Namely, the treatment of 2a ($R^1 = R^2 = PhCH_2$, 0.15 mmol) with 2-benzothiazolesulfenyl chloride (0.59 mmol) in dioxane-H_2O (6 ml/0.1 ml) at room temperature for 30 min and the usual workup afforded disulfide 3a ($R^1 = R^2 = PhCH_2$, Ar = 2-benzothiazolyl (BT), 81%): IR (neat) 3280, 1775, 1740, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (s, 2H), 4.15, 4.39 (ABq, 2H, 11 Hz), 5.14 (s, 2H), 5.0-5.4 (m, 3H), 5.50 (s, 1H), 5.55 (d, 1H, 4 Hz), 6.92 (d, 1H, 8 Hz), 7.1-7.6 (m, 12 H), 7.6-8.0 (m, 2H). The presence of water in the media is indispensable, since absence of water brought about no ring opened products but considerable amounts of sulfenylated products 6a and/or 6b (~80% yields).

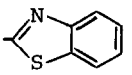
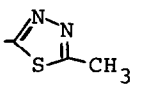
The ring closure of the disulfide 3a was widely examined by using acids, bases, halogens, and so on.[7] We finally found that a combination of gaseous ammonia (NH_3)[8] and dimethylformamide (DMF) achieved the task. Thus, the treatment of the disulfide 3a (0.07 mmol) with NH_3 (~0.14 mmol) in DMF (0.8 ml) at -30~-25 °C for 60 min afforded the desired 3'-benzothiazolylthiocephalosporin 4a ($R^1 = R^2 = PhCH_2$, Ar = BT, 74%): mp 156-158 °C; IR (nujol) 3315, 1765, 1715, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (s, 4H), 4.16, 4.83 (ABq, 2H, 13 Hz), 4.88 (d, 1H, 5 Hz), 5.30 (s, 2H), 5.78 (dd, 1H, 5 Hz, 9 Hz), 6.38 (d, 1H, 9 Hz), 7.1-7.6 (m, 12H), 7.6-8.0 (m, 2H).

Interestingly, the reaction of 3b ($R^1 = R^2 = PhCH_2$, Ar = C_6Cl_5) with ~1.5 equiv. of NH_3 in DMF (~-25 °C, 60 min) afforded a mixture of 4b (35%) and 3'-chlorocephalosporin 5b[9] ($R^1 = R^2 = PhCH_2$, 27%). The use of more than 2 equiv. of NH_3 resulted in an exclusive formation of 4b. This suggests that the ring closure and the thio-substitution proceed stepwise (Scheme 2) and 3'-chlorocephalosporin 5 is an intermediate.[10]

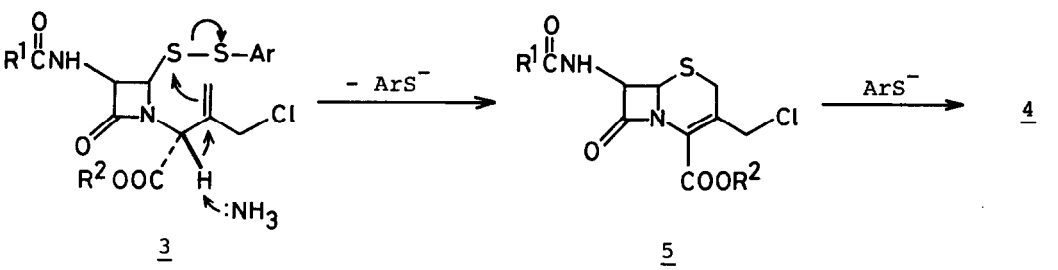
Some of 3'-thio-substituted cephalosporins similarly prepared along with yields are listed in the Table.[11] It is notable that the compound 4 (R^1 = 1H-tetrazol-1-ylmethyl, R^2 = H), bearing 2-methyl-1,3,4-thiadiazole-5-thio group (Ar = DZ), "Cefazoline", has been used as a theraputical antibiotics.

Table

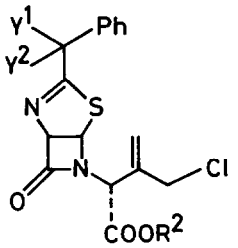
	R^1	R^2	Ar[a)]	yield, %[b)] 3	4
a	$PhCH_2$	$PhCH_2$	BT	81	74
b	$PhCH_2$	$PhCH_2$	DZ	70	83
c	$PhCH_2$	$PhCH_2$	C_6Cl_5	74	83
d	$PhCH_2$	CH_3	BT	61	64
e	$PhOCH_2$	$PhCH_2$	BT	84	83
f	$PhOCH_2$	$PhCH_2$	DZ	65	88
g	$PhOCH_2$	$PhCH_2$	C_6Cl_5	74	88

a) BT =  ; DZ =  b) Isolated yields.

Scheme 2



3 5



6a: Y^1 = ArS; Y^2 = H

6b: Y^1 = Y^2 = ArS

This direct two-step conversion of 2 to 4 provide us a new route to 3'-thio-substituted cephalosporins from natural penicillins. Application of this method to prepare various poter cephalosporin antibiotics is now under way.

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6) Reaction of 1 (R^1 = $PhCH_2$; R^2 = $p\text{-}NO_2PhCH_2$, Z = H) with $(CH_3)_2CHCH_2SCl$, yielding the corresponding ring-opened disulfide (65% yield), has been reported: W. G. E. Underwood, Ger. Offen., 2303889 (1973): Chem. Abstr., 79, 105249 (1973).

7) Reaction of 3 with Cl_2 and/or Br_2 gave 2,2-bis-(halomethyl)-penams: see ref. 3c).

8) In place of NH_3 (gas), aqueous NH_4OH (28%) could also be used, affording 5 in 35-70% yields.

9) (a) H. Yazawa, H. Nakamura, K. Tanaka, and K. Kariyone, Tetrahedron Lett;, 3991 (1974); (b) S. Torii, H. Tanaka, N. Saitoh, T. Siroi, M. Sasaoka, and J. Nokami, ibid., in press.

10) Conversion of 5 to 4 was achieved independently by treatment of 5 with thiol in NH_3-DMF.

11) When Ar group was butyl, no detectable amount of 4 was obtained.

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