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PENICILLIN-CEPHALOSPORIN CONVERSION-XI.[1] SYNTHESIS OF 7-(α-SUBSTITUTED PHENYLACETOAMIDE)CEPHALOSPORINS BY UTILIZATION OF ALL THE FRAMEWORK ELEMENTS OF PENICILLIN G

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ABSTRACT: A successful synthesis of clinically significant cephalosporins 2a-c with use of all the framework elements of penicillin G is described.

Chemical conversion of natural penicillins into cephalosporins 2 has been a subject of intensive studies, and several significant conversions of the parent skeleton of penicillins to that of cephalosporins along with introduction of the required C(3')-substituents (Z) have been devised.[2] Subsequently, the cephalosporins have been converted into various antibiotics drugs by the acyl-exchange reaction of the C(7)-amide groups. In the hitherto disclosed synthesis, however, the C(6)-amide moieties of natural penicillins have not been substantially availed.

On the other hand, clinically useful cephalosporins 2a-c possess α-substituted phenylacetyl moieties as the C(7)-amide groups.[3] So, one normally expects that this class of amide substituents can be prepared from the phenylacetyl moiety of penicillin G (1), but any attempts along this line have not appeared yet, presumably due to lack of an appropriate procedure

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S-TZ = S-(N-N, N-N, CH3)

R = $PhCH_2$

2	X^1	X^2	Z
a	H	OH	S-TZ
b	H	OH	H
c	=N-OH		S-TZ
d	OH	H	S-TZ
e	OH	H	H
f	=O		S-TZ

for functionalization of the benzylic position of the phenylacetyl moiety.

We now found that thiazoline-azetidinone 3 derived from penicillin G[4] is a promising intermediate for the functionalization of both the phenylacetyl moiety and the C(3)-methyl group. This paper describes the first successful conversion of penicillin G (1) into beneficial cephalosporins 2a-c with complete utilization of all the framework elements.

In a preceding paper,[5] we reported the electrolytic ene-type chlorination of thiazoline-azetidinone 3 which can lead to benzylic gem-dichloride 5e (X^1= X^2= Cl; Z = H) and/or trichloride 5f (X^1= X^2= Z = Cl), depending on the electrolysis conditions. This fact suggested us that the benzylic position of 3 is susceptible enough to oxidation.[6] In fact, oxidation of 3 with $(NH_4)_2Ce(NO_3)_6$ in MeOH at 50-55 °C (15 min) proceeded in the manner as we expected, affording desired ketone 4a (Z = H) in 80% yield. Oxidation of 3 with I_2/AcONa/AcOH (60-70 °C, 6 h) or $K_3Fe(CN)_6$/AcOH/MeCN (40-60 °C, 8 h) also gave 4a in 80-86% yields.

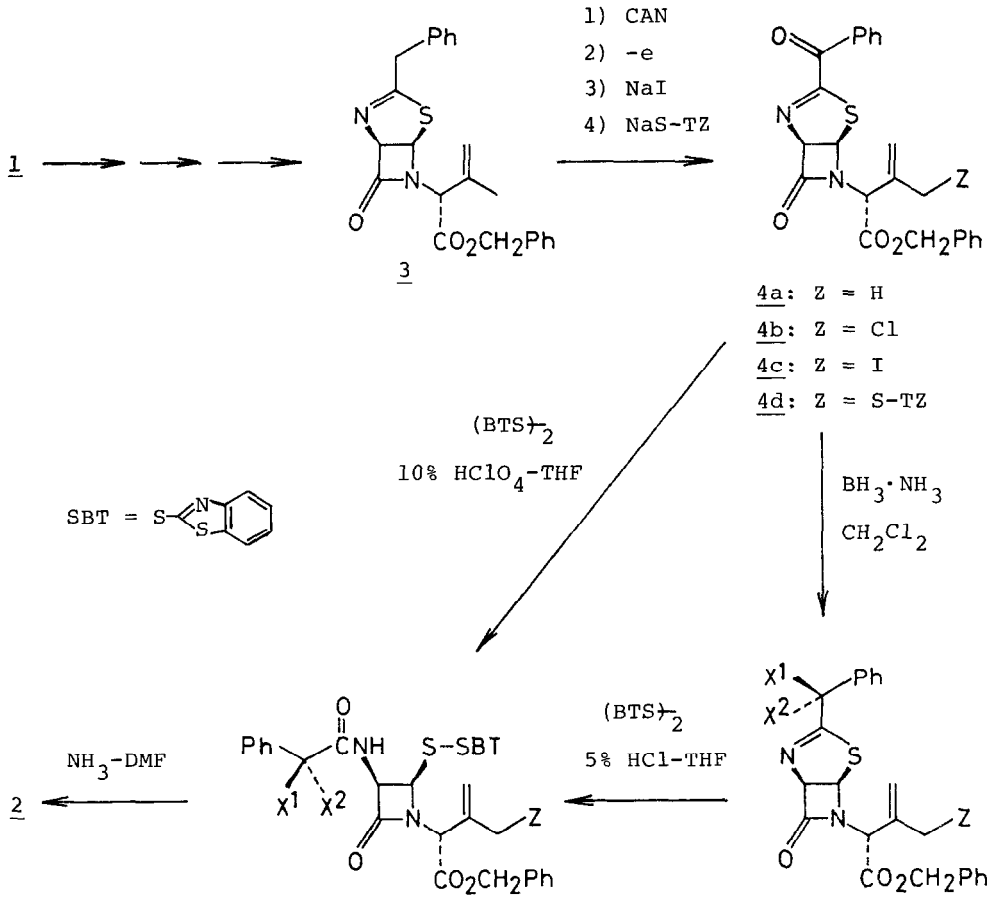
Introduction of the required functional group at the terminal methyl group of 4a was performed by the electrolytic ene-type chlorination in a $CHCl_3$-t-BuOH-aqueous NaCl (10/1/20)-cat. H_2SO_4-(Pt electrodes) system,[5] yielding 4b (Z = Cl) in 95% yield. Subsequent replacement of the allylic chlorine atom of 4b with thio-group (S-TZ) was accomplished by heating with NaI in acetone followed by treatment with thiolate (NaS-TZ) without isolating the iodide 4c (Z = I), yielding 4d (Z = S-TZ, 72%). The iodination was indispensable for avoiding migration of the C=C double bond to conjugation, when the S-TZ group was introduced.

The success prompted us to investigate further transformation of 4a and 4d into the target cephalosporins 2a-c. Cefamandole benzyl ester 2a[7] was obtained by the following three-step procedure starting from 4d. Reduction of 4d with $BH_3 \cdot NH_3$ in CH_2Cl_2 (-20 °C, 2 h) afforded a 55/33 mixture of diastereomeric alcohols 5a (R-isomer) and 5b (S-isomer) in 83% yield, which were separated by preparative tlc.[8] The stereochemistry of the alcohols 5a and 5b was confirmed by the following transformation into Cephamandole benzyl ester 2a and its diastereomer 2d, respectively. Thus, both isomers 5a and 5b were subjected to the hydrolytic ring-opening reaction with 2-benzothiazolyl disulfide (BT-SS-BT)[9] in aqueous 5% HCl-THF (1/5) at room temperature (40 min) to give the corresponding disulfides 6a (66%) and 6b (58%). Cyclization of 6a and 6b was performed by treatment with NH_3 in DMF at -35 °C, affording Cefamandole benzyl ester 2a ($[\alpha]_D^{16}$ -124.1, c = 0.54, $CHCl_3$)[10] in 93% yield and its isomer 2d ($[\alpha]_D^{16}$ -79.5, c = 0.82, $CHCl_3$) in 60% yield.

In a similar manner, 4a was transformed into Lafarquim AL-226 2b[11] ($[\alpha]_D^{25}$ +33.6, c = 0.22, $CHCl_3$)[10] through reduction with $BH_3 \cdot NH_3$ in CH_2Cl_2 (→ 5c/5d : 1/1, 75% yield), hydrolytic ring opening (5c → 6c, 85%), and cyclyzation (6c → 2b, 73%). Transformation of 4d into SFK-80000[12] was also achieved via a similar sequence of reaction (4d→ 6d→ 2f→ 2c). Thus,

hydrolytic ring-opening of 4d with BT-SS-BT in aqueous 10% $HClO_4$-THF (1/4) at room temperature (50 h) afforded disulfide 6d (78%), which was submitted to cyclization with NH_3/DMF at -30 °C (15 min) yielding the corresponding cephalosporin 2f (100%). Subsequent treatment of 2f with $NH_2OH \cdot HCl$ in EtOH (17 °C, 28 h) afforded desired 2c as a 1/1 mixture of syn/anti isomers.[10]

Manipulation of the α-functional groups (OH, C=O) of the phenylacetyl amide of 2a-f is expected to provide an efficient route to useful cephalosporins of newer generation from penicillin G. Details are discussed in the due course.



6a: X^1 = H, X^2 = OH, Z = S-TZ
6b: X^1 = OH, X^2 = H, Z = S-TZ
6c: X^1 = H, X^2 = OH, Z = H
6d: X^1, X^2 = O, Z = S-TZ

5a: X^1 = H, X^2 = OH, Z = S-TZ
5b: X^1 = OH, X^2 = H, Z = S-TZ
5c: X^1 = H, X^2 = OH, Z = H
5d: X^1 = OH, X^2 = H, Z = H
5e: X^1 = X^2 = Cl, Z = H
5f: X^1 = X^2 = Z = Cl

References and Notes

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8. The undesired S-isomer 5b was converted to the starting ketone 4d by oxidation with I_2/AcONa/AcOH in 92% yield.
9. Benzothiazolyl disulfide is an excellent reagent for this purpose, since the disulfide is quite stable in the acidic media and labile enough to trap the thiols generating from the hydrolytic ring-opening of the thiazoline moiety of 5a and 5b.
10. ^{1}H-NMR, IR, and Rt on HPLC were fully identical with those of the authentic samples, prepared independently from 7-aminocephalosporanic acid or 7-amino-3'-deacetoxycephalosporanic acid.
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