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PRACTICAL PROCEDURE FOR EPIMERIZATION OF 7α-AMINO-1-OXACEPHEMS TO 7β-AMINO EPIMERS

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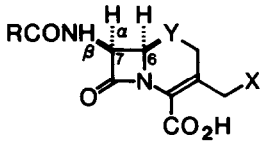
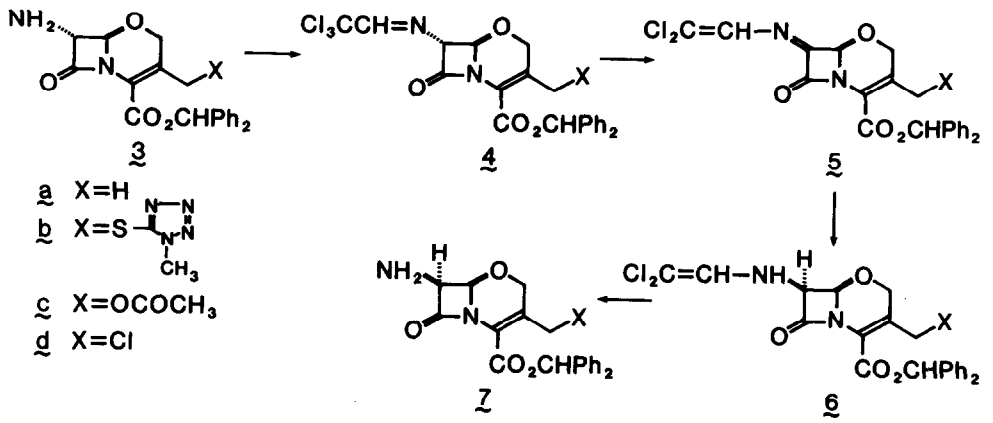
Abstract: 7α-Amino-1-oxacephems can be epimerized to their 7β-amino epimers by treatment with chloral to give Schiff bases, followed by dehydrochlorination with Hünig base, borohydride reduction, and hydrolysis.

An important stereochemical feature of cephalosporin antibiotics is the (6R,7R) configuration[1] in the bicyclic β-lactam ring; the β-lactam hydrogens are cis in the clinically useful antibiotics 1. The trans epimers are biologically inactive. This is also the case with 1-oxacephem antibiotics, and any active 1-oxacephem antibiotics 2 have the (cis) configuration. However, cis isomers are not always primary products in partial[2] or total syntheses[3] of 1-oxa and (1-thia)cephem antibiotics, and considerable effort has been directed to epimerization of the 7α-amino group to 7β. Since the reported procedures are not satisfactory in stereoselectivity[4,5] and practicability,[6] we have searched for a mild and efficient procedure for converting 7α-amino-1-oxacephems, the primary products in our practical syntheses of 7α-methoxy-1-oxacephem antibiotics,[7-9] to 7β-amino epimers. Here, we describe a practical four-step procedure for epimerization of 7α-amino-1-oxacephems, which consists of chloral Schiff base formation, dehydrochlorination, hydride reduction, and acid hydrolysis.



1 Y=S
2 Y=O

Reaction of 7α-amino-3-methyl-1-oxacephem 3a with an excess of chloral in refluxing benzene in the presence of molecular sieves 4A gave the Schiff base 4a (yellow crystals from diethyl ether, mp 140-142°C (decomp) 68% yield; NMR ($CDCl_3$) δ 2.16 (3H, s), 4.40 (2H, s), 4.83 (1H, d, J = 2 Hz), 5.15 (1H, d, J = 2 Hz), 7.0-7.8 (10H, m), 8.13 (1H, d, J = 2 Hz). Compound 4a is stable and can be purified by silica gel chromatography. Dehydrochlorination of 4a with 1 molar equivalent of diisopropylethylamine (Hünig base) in dichloromethane at -40°C proceeded in a 1,4-elimination manner and the conjugated imine 5a was obtained after short-path silica gel chromatography (yellow powder, 91% yield; NMR ($CDCl_3$) δ 1.93 (3H, s), 4.20 (2H, s), 5.27 (1H, s), 6.97 (1H, s), 7.1-7.7 (10H, m), 8.03 (1H, s)). On treatment of 5a with 1.5 molar equivalents of sodium borohydride (or potassium borohydride)



in 50% aqueous tetrahydrofuran at 0°C, a labile enamine 6a having the easily hydrolyzable β,β-dichlorovinylamino group as the 7β substituent was obtained, with hydride transfer occurring stereoselectively from the α-face of the β-lactam ring. The reaction mixture containing 6a was treated with a 2:1 mixture of 2 N hydrochloric acid and acetonitrile for 2.5 hr at 0°C to give 7β-aminooxacephem 7a (93% yield from 5a after silica gel chromatography). The thus-obtained product is identical with an authentic sample of 7a, prepared from a 7β-acylamino-1-oxacephem derivative,[10] and contains no 7α-amino isomer. The high stereoselectivity in the reduction is due to steric approach control of the hydride reagent to imine 5 substituted with the bulky dichlorovinyl group.[11] Analogously, 7α-amino-1-oxacephems, 3b, 3c, 3d, and 8 were epimerized at the 7 position to give 7β-amino isomers, 7b,[12] 7c,[12]

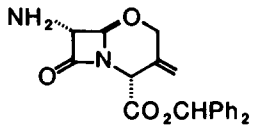
Table 1. Epimerization of 7α-amino-1-oxacephems to 7β-amino epimers via chloral Schiff bases

Starting material	Yields[a] of intermediates (%) Chloral Schiff base	Conjugated imine[f]	Product (yield, %)
3a	68[b]	91	7a (93)
3b	50	95[b]	7b (92)
3b	-[g]	one-pot process	7b (46 from 3b)
3c[c]	53	-[g]	7c[c] (32)
3d[c]	63	one-pot process	7d[d] (46 from 4d)
8	81	-[g]	9[e] (40)

[a] Isolated yield of pure product after chromatography unless otherwise indicated. [b] Yield of crude crystalline product. [c] HCl salt. [d] Yield of chloroacetylated product ($ClCH_2COCl$/Py) after chromatography. [e] Yield of phenylacetylated product ($PhCH_2COCl$/Py) after chromatography. [f] Conjugated imines were reduced with KBH_4 in all cases except for 5a. [g] Crude extract was used without purification.

7d, and 9, respectively (Table 1). In the epimerization of 3b, enamine 6b was stable enough to be isolated and its structure was confirmed by NMR spectroscopy (NMR ($CDCl_3$-CD_3OD) δ 3.83 (3H, s), 4.28 (2H, s), 4.50 (1H, d, J = 3 Hz), 4.68 (2H, s), 5.03 (1H, d, J = 3 Hz), 5.31 (1H, s), 6.93 (1H, s), 7.2-7.7 (10H, m)).

The present epimerization procedure is characterized by the use of inexpensive reagents such as chloral, Hünig base, borohydride, and hydrochloric acid and also by mild reaction conditions as exemplified by smooth conversion of 3d and 8 into 7d and 9, the versatile intermediates for preparation of 1-oxacephem antibiotics, with keeping intact the reactive 3-chloromethyl and base-sensitive 3-exomethylene groups. An additional advantage of this



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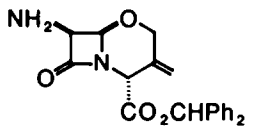

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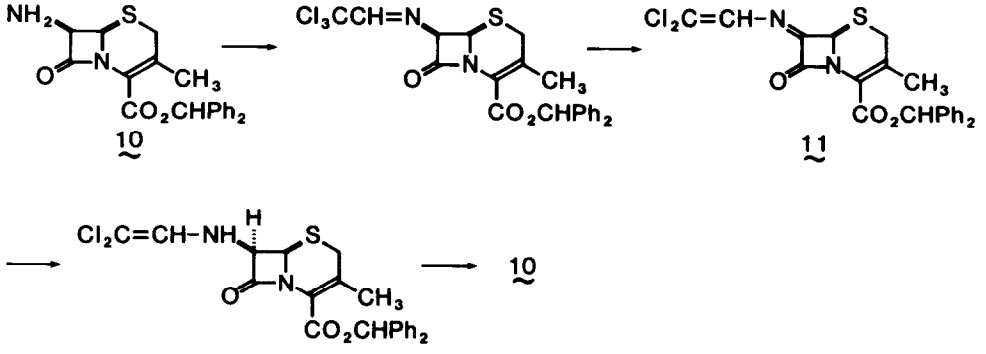
procedure is that the epimerization can be carried out in a one-pot process as shown by the following representative experiment. A mixture of 3b (205 mg), chloral (0.343 ml), molecular sieves (675 mg), and benzene (7 ml) was refluxed for 2.5 hr, cooled, and filtered. The filtrate was evaporated *in vacuo* and the residue (crude 4b) dissolved in tetrahydrofuran (2 ml) was treated with Hünig base (0.076 ml) at -40°C under nitrogen for 20 min. After the temperature was raised to 0°C, the reaction solution was successively treated with a solution of potassium borohydride (51 mg) in 50% aqueous tetrahydrofuran (3 ml) for 3 min and a mixture of 2 N hydrochloric acid (3 ml) and acetonitrile (1.5 ml) for 2 hr. The resulting mixture was poured into aqueous sodium bicarbonate and extracted with dichloromethane. Evaporation of the extract followed by crystallization from ether gave 7b (mp 138-140°C, 95 mg, 46% yield from 3b).

This method can be applied generally to other β-lactam derivatives. Thus, 7-aminodesacetoxycephalosporanic acid benzhydryl ester 10 was converted



into conjugated imine 11 (67% yield). Compound 11, in analogy the with the 1-oxacephem example, underwent reduction and subsequent hydrolysis to give 10 (50% yield from 11). Product 10 was free from its 7α-amino epimer. Since the imine 11 can be obtained from the 7α-amino derivative, the above result illustrates a feasible application of the present procedure to epimerization of the 7α-amino group to 7β in the (1-thia)cephem and other β-lactam compounds.

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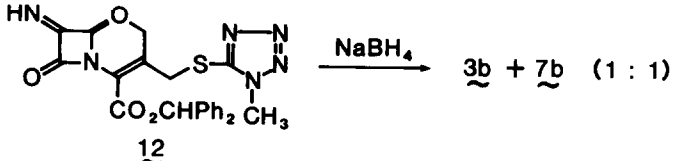

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