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DIRECT DISPLACEMENT OF THE ACETOXY GROUP BY HALOGEN USING BORON TRIHALIDE IN THE CEPHALOSPORIN SERIES.

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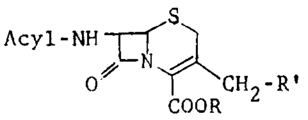
7-Acylamido-3-halomethyl-3-cephem-4-carboxylic acid ester (1) has been an useful intermediate for the syntheses of a variety of 3'-substituted cephem compounds[1], which are not accessible by the direct nucleophilic displacement of the 3-acetoxymethyl compound (3) prepared by the Glaxo group[2].

This intermediate (1) has been hitherto prepared from 7-acylamido-3-desacetoxy-3-cephem derivatives (2), derived from either 3 by hydrogenolysis[3] or penicillin derivatives by ring enlargement[4], and from 7-acylamido-3-desacetyl-cephalosporanic acid ester (4) derived from 3 by citrus esterase hydrolysis[5].

In this paper, we wish to report a new and simple method of synthesizing this compound (1) by the direct displacement of the acetoxy group of 3 by halogen with boron trihalide.

This simple chemical procedure was accomplished by adding boron trihalide to a solution of the ester (3) at -5°— 20°C, followed by stirring the solution within 1 hr.



(1): R =alkyl, R' =halogen
(2): R =alkyl, R'=H
(3): R =alkyl, R'=$OCOCH_3$
(4): R =alkyl, R'=OH

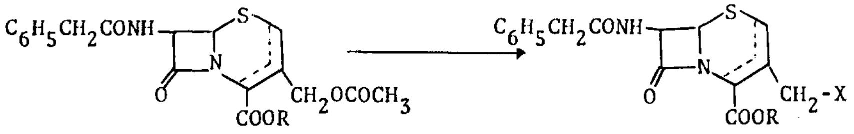
A typical reaction procedure is given below.

To a solution of 2.05g (0.005 mol) of methyl 7-phenylacetamido-3-acetoxymethyl-3-cephem-4-carboxylate in 50 ml of CH_2Cl_2 was added a solution of boron trichloride (0.015 mol) in benzene.

The reaction mixture was stirred at room temperature for 1 hr. The mixture was then evaporated, neutralized with an aqueous $NaHCO_3$ solution, and extracted with EtOAc. The solution was washed with water, dried, and evaporated to give crystalline materials, the recrystallization of which from $CHCl_3$-MeOH afforded methyl 3-chloromethyl-7-phenylacetamido-3-cephem-4-carboxylate (1.52g, 78.7% yield); mp 148-149°C (dec). IR(nujol)cm^{-1}; 3300, 1780, 1715, 1650, 1620. NMR($CDCl_3$)τ; 2.70(5H,s), 3.45(1H,d,J=7 Hz), 4.20(1H,dd, J=4.5, 7 Hz), 5.05(1H,d, J=4.5 Hz), 5.42, 5.65(2H,d, J=12 Hz), 6.14(3H,s), 6.38(2H,s), 6.48(2H,br,s). Calcd for $C_{17}H_{17}O_4N_2SCl$; C,53.59; H,4.50; N,7.35; S,8.42. Found: C,53.34; H,4.66; N,7.20; S,8.59.

The results of halogenation of 3-acetoxy cephem compounds are illustrated in Table 1.

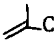
Table 1



starting material						product			
R	2 or 3 cephem	BX_3	mol	t	hr	R	X	yield	mp
-Me	3	BCl_3	3	rt	1	-Me	Cl	78.7	148-149(d)
$-CH_2CCl_3$	3	BCl_3	3	rt	1	$-CH_2CCl_3$	Cl	85.6	58- 61(d)
$-CH_2CCl_3$	3	BBr_3	3	-5°	0.5	$-CH_2CCl_3$	Br	56	powder
$-CH_2CCl_3$	2	BCl_3	1	-5°	0.5	$-CH_2CCl_3$	Cl	84	136-137(d)
-t Bu	2	BCl_3	1	-5°	0.5	-t Bu	Cl	64	55- 60(d)
-t Bu	2	BBr_3	1	-5°	0.5	-t Bu	Br	70.5	powder
-t Bu	2	BCl_3	3	rt	1	-H	OH	68	156-157(d)

Successful halogenation of the 2-cephem esters was also achieved using boron trihalide in the similar manner as in the 3-cephem esters. It is worthy of note that the former requires 1 equivalent of boron trihalide while the latter 3 equivalents of the reagent for the halogenation of the 3-acetoxymethyl group.

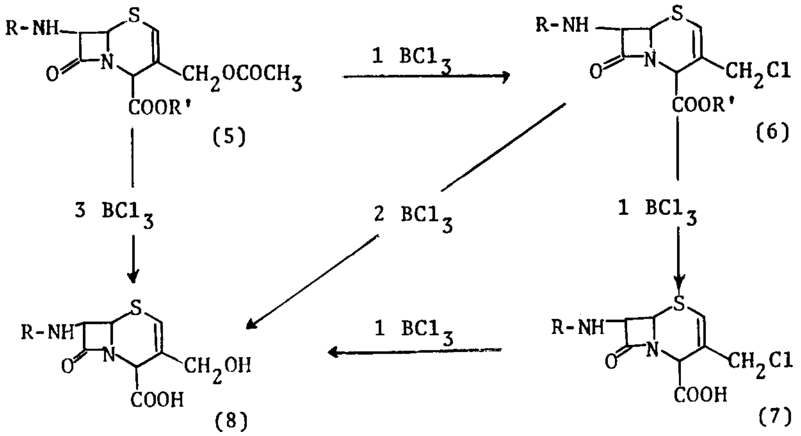
The products of the reaction of the 2-cephem esters (5) with boron trichloride depend on the amount of the reagent employed, which are illustrated in the Scheme. The product, which was obtained from 5 with 3 moles of boron trichloride, was indeed the hydroxy acid and was identified by direct comparison with the 3-hydroxymethyl cephalosporanic acid (8), prepared according to the direction of the Glaxo workers[6]. However, the reaction of one mole each of the 3-cephem esters with 1 or 2 moles of boron trichloride gave products with the β-lactam part decomposed and the yield of the corresponding halomethyl ester is poor even under prolonged reaction time. The course of the reaction of one mole of the 3-cephem methyl ester (3: R=Me) with 1 or 2 moles of boron trihalide was studied with NMR. This study indicated that the disappearance of the methoxycarbonyl group was accompanied by the production of methyl chloride, and the acetoxy group remained largely unchanged without formation of acetyl chloride.

Therefore, it can be concluded that the order of the reactivities of boron trihalide towards functional groups are as follows:
-COOR > CH_2OCOCH_3 for the 3-cephem ester and CH_2OCOCH_3 > -COOR
for 2-cephem ester. This difference of the order of the reactivities between 3-cephem and 2-cephem esters can be understood by the greater steric hindrance caused by the acetoxy-BX_3 complex in the 3-cephem series. Boron trichloride has been used for the fission of carboxylic esters[7] and the reaction of the esters of allylic alcohols with boron trichloride is reported to give polymeric products instead of affording the corresponding allylic chlorides.

The highly selective displacement of the acetoxy group in the presence of other potentially basic groups (-CONH-, -COOR) in 3-cephem derivatives in the present study is particularly interesting.

The same reaction could be performed with $AlCl_3$ or $TiCl_3$ although only in low yields.

Scheme



R = $C_6H_5CH_2CO$-, R'= t-Bu

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