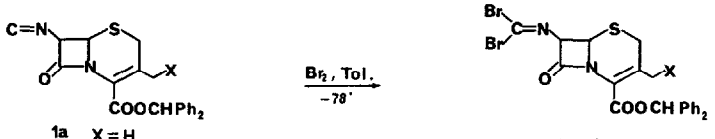
Tetrahedron Letters,Vol.30,No.18,pp 2375-2378,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CEPHALOSPORINS WITH C-7-ISOCYANIDE DIHALIDES : USEFUL SYNTHONS FOR THE INTRODUCTION OF AMINO HETEROCYCLES AT C-7 - NEW ROUTES TO THE SYNTHESIS OF AMINO IMIDAZOLES

F. JUNG*, C. DELVARE, D. BOUCHEROT, A. HAMON
I.C.I. Pharma, Centre de Recherches, Zone Industrielle La Pompelle
B.P. 401 - 51064 REIMS CEDEX (FRANCE)

Summary : Isocyanide dibromides 2 are new cephalosporin synthons, useful in the synthesis of a variety of compounds bearing amino heterocycles at C-7 (Scheme 1). In particular amino imidazoles 5 have been obtained from 2 via novel, mild approaches (Scheme 2).

The profound influence of the chemical structure of the C-6 and C-7 side chains of penicillins and cephalosporins on their biological properties is well known[1]. Mecillinam, for instance, is a commercial penicillin with an original mode of action and a novel type of C-6 side chain[2] (formamidine). In our search for cephalosporins with novel properties, we decided to synthesise compounds having amino heterocycles of various structures and basicities at C-7 of the cephalosporin nucleus. The isocyanide dihalides 2[10], easily obtainable by low temperature (-78°C) halogenation of the corresponding isonitrile 1[3] in toluene, were selected as the key intermediates in the synthesis of our target compounds.

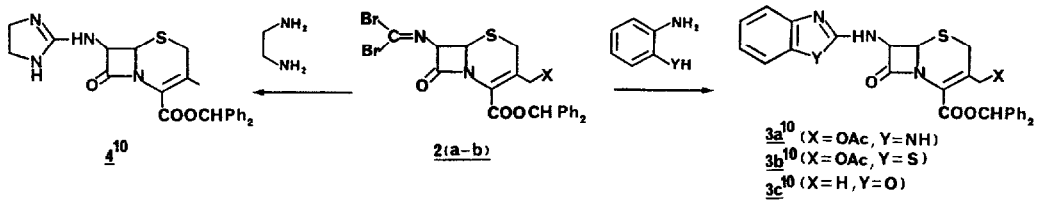


1a X=H
1b X=OAc

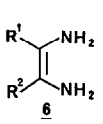
2(a-b)

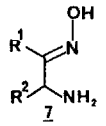
The high electrophilic reactivity of isocyanide dihalides is well known, and their utility in the synthesis of heterocyclic derivatives has also been described[4]. It is of interest that, even in the case of cephalosporins 2, the superior electrophilic reactivity of the isocyanide dihalide function over the β-lactam ring[5] allowed the regioselective attack of various dinucleophiles on the isocyanide dihalide group (Scheme 1).

SCHEME 1



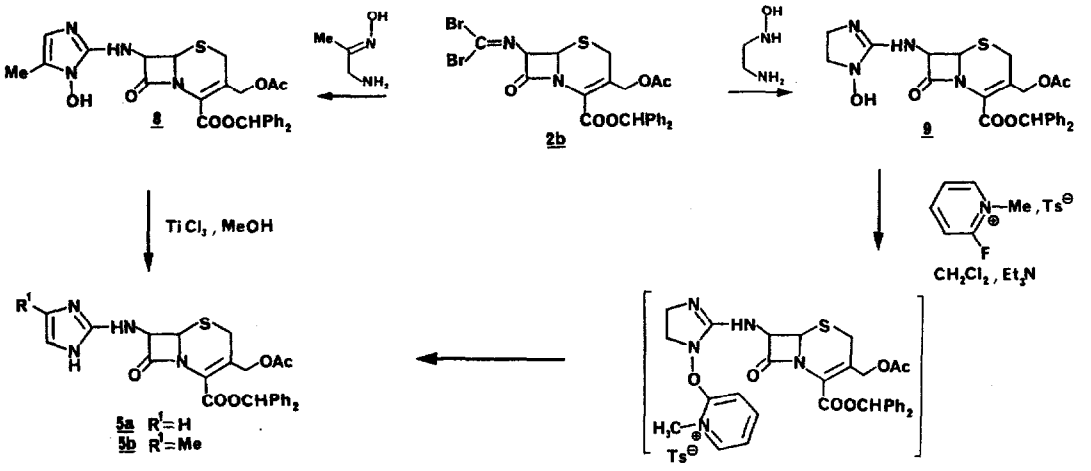
The synthesis of 7-imidazolylamino cephalosporins of general structure 5 (Scheme 2), using the same key isocyanide dihalide intermediate, hinges on the accessibility of dienamines of structure 6 which are, in general, unstable molecules. We turned our attention therefore towards anti α-amino oximes 7, a readily available class of compounds[7] which can be considered as masked stable dienamine equivalents. The utility of this class of compounds in the synthesis of a variety of heterocycles has been demonstrated[7].


6


7

We found that these molecules can be condensed with dibromoisonitriles in THF at -40°C/0°C to give, for instance, N-hydroxy imidazole 8[10], which can be reduced using mild reducing agents ($TiCl_3$, MeOH, R.T.[8] or $P(OMe)_3$ neat, R.T.) to the desired amino imidazole 5b[10] (Scheme 2). The overall sequence is thus equivalent to the reaction of an unstable dienamine 6 with the isocyanide dihalide 2b. An alternative oxidative version of the synthesis of cephalosporin 5a[10] consists in the condensation of α-amino hydroxylamine with the isocyanide dihalide 2b under our usual conditions to give the N-hydroxy imidazoline 9[6,10]. The elimination-aromatisation step can be carried out by treatment of N-hydroxy-imidazoline 9 with 2-fluoro-N-methyl-pyridinium tosylate in CH_2Cl_2 at -40°C with Et_3N as base[9] (Scheme 2).

SCHEME 2



In conclusion, the isocyanide dihalides 2 are easily accessible and versatile synthetic intermediates, which have been used successfully in the synthesis of a variety of cephalosporins with novel C-7 heterocyclic substituents. In particular, two new mild approaches to amino imidazoles using these intermediates have been applied to the cephalosporin series. The free acids of some of these compounds possess high antibacterial activity against both Gram-positive and Gram-negative organisms : MIC in µg/ml Jewell and Permain growth medium 10^5 cfu :

3a (free acid) Staph. aureus A6, 2 ; Strep. pyogenes A1, 2 ; E. coli A8, 2 ; P. mirabilis A18, 4 ; K. pneumoniae A24, 1.

5a (free acid) Staph. aureus A6, 32 ; Strep. pyogenes A1, 16 ; E. coli A8, 0.06 ; P. mirabilis A18, 0.06 ; K. pneumoniae A24, 0.06.

References

(1) - Structure-Activity Relationships Among Semisynthetic Antibiotics, D. PERLMAN ed., Academic Press 1977
- Chemistry and Biology of β-Lactam Antibiotics - Volume 1, R.B. MORIN and M. GORMAN, Academic Press 1982, p 371

(2) - F. LUND, L. TYBRING, Nature, New Biology, 1972, 236, 135

(3) - Ger. Offen. 2.337.105, 1974, GLAXO (Chem. Abstr. 80, 108550v)

(4) - E. KÜHLE, B. ANDERS, E. KLAUKE, H. TARNOW, G. ZUMACH, Angew. Chem. Int. Ed. Engl. 1969, 8, 20

(5) - A.F. MARTIN, J.J. MORRIS, M.I. PAGE, J. Chem. Soc. - Chem. Comm. 1976, 495

(6) - In a typical experiment, one equivalent of the isocyanide dihalide is dissolved in THF at temperatures varying between -78°C and R.T. depending on the reactivity of the amine (-78°C for ethylene diamine ; R.T. for orthophenylene diamine). Two equivalents of the diamine are added to the reaction mixture. The reaction is monitored by t.l.c., and is complete usually after 1-2 h. Two equivalents of TFA are added to the reaction mixture which is evaporated and the crude product is purified on silica gel at -20°C.

(7) - H. GNICHTEL, Chem. Ber. 1970, 103, 2411
- H. GNICHTEL, S. EXNER, H. BIERBÜSSE, M. ALTERDINGER, Chem. Ber. 1971, 104, 1512
- H. GNICHTEL, W. GRIEBENOW, W. LÖWE, Chem. Ber. 1972, 105, 1865

(8) - B.H. LIPSHUTZ, M.C. MOREY, Tetrahedron Lett. 1984, 1319

(9) - T. MUKAIYAMA, T. TSUJI, Y. WATANABE, Chem. Lett. 1978, 1057

(10) - 2a Anal. C, H, N. ^{1}H-NMR, 60 MHz, $CDCl_3$, δ ppm : 2.1, s, 3H ; 3.4, 3.7, AB (J = 18 Hz), 2H ; 4.92, 5.14, AB (J = 4.6 Hz), 2H ; 6.9, s, 1H ; 7.3, m, 10H. IR, film : 1795, 1730 cm^{-1}.
- 2b Anal. C, H, N. ^{1}H-NMR, 60 MHz, $CDCl_3$, δ ppm : 2.02, s, 3H ; 3.45, m, 2H ; 4.73, 5.07, AB (J = 13.9 Hz), 2H ; 4.97, 5.25, AB (J = 4.6 Hz), 2H ; 6.34, s, 1H ; 7.32, m, 10H. IR, film : 1795, 1745, 1730 cm^{-1}.
- 3a Anal. C, H, N, S. ^{1}H-NMR, 60 MHz, $CDCl_3$, δ ppm : 1.92, s, 3H ; 3.25, m, 2H ; 4.57, 4.97, AB (J = 16 Hz), 2H ; 5.15, 5.9, AB (J = 4.5 Hz), 2H ; 6.85, s, 1H ; 7.25, m, 14H. IR, film : 1790, 1745, 1730, 1665 cm^{-1}.
- 3b ^{1}H-NMR, 60 MHz, $CDCl_3$, δ ppm : 1.92, s, 3H ; 3.4, m, 2H ; 4.67, 5.03, AB (J = 13.5 Hz), 2H ; 5.35, 6.0, AB (J = 4.3 Hz), 2H ; 6.87, s, 1H ; 7.25, m, 14H. IR, film : 1790, 1745, 1730, 1615 cm^{-1}.
- 3c Anal. C, H, N, S. ^{1}H-NMR, 60 MHz, $CDCl_3$, δ ppm : 2.08, s, 3H ; 3.22, m, 2H ; 5.05, 5.75, AB (J = 4.4 Hz), 2H ; 6.88, s, 1H ; 7.3, m, 14H . IR, KBr : 1780, 1718, 1650 cm^{-1}.
- 4 Anal. C, H, N, Br. ^{1}H-NMR, 90 MHz, DMSO d_6, δ ppm : 2.05, s, 3H ; 3.55, m, 2H ; 3.65, s, 4H ; 5.15, 5.6, AB (J = 4.5 Hz), 2H ; 6.85, s, 1H ; 7.3, m, 10H. IR, KBr : 1790, 1720, 1655 cm^{-1}.
- 5a Anal. C, H, N. ^{1}H-NMR, 90 MHz, DMSO d_6, CD_3COOD, δ ppm : 2.0, s, 3H ; 3.7, m, 2H ; 4.7, 4.9, AB (J = 13 Hz), 2H ; 5.4, 5.7, AB (J = 4.5 Hz), 2H ; 6.9, s, 1H ; 7.0, s, 2H ; 7.3, s, 10H.
- 5b ^{1}H-NMR, 90 MHz, DMSO d_6, δ ppm : 2.1, s, 3H ; 2.2, s, 3H ; 3.7, s, 2H ; 4.8, 5.0, AB (J = 13 Hz), 2H ; 5.3, d, (J = 4.5 Hz), 1H ; 5.7, m, 1H ; 6.9, s, 1H ; 7.0, s, 1H ; 7.4, s, 10H. IR, KBr : 1785, 1740, 1720, 1665 cm^{-1}.
- 8 ^{1}H-NMR, 90 MHz, DMSO d_6, δ ppm : 2.0, s, 3H ; 3.6, m, 6H ; 4.7, 4.9, AB (J = 13 Hz), 2H ; 5.2, 5.6, AB (J 4.5 Hz), 2H ; 6.85, s, 1H ; 7.35, m, 10H. IR, KBr : 1785, 1740, 1725, 1665 cm^{-1}.
- 9 ^{1}H-NMR, 90 MHz, CD_3COD, δ ppm : 1.9, s, 3H ; 2.1, s, 3H ; 3.4, m, 2H ; 4.75, 4.95, AB (J = 13 HZ), 2H ; 5.2, 5.7, AB (J = 4.5 Hz), 2H ; 6.6, s, 1H ; 6.9, s, 1H ; 7.3, s, 10H. IR, KBr : 1875, 1740, 1720, 1670 cm^{-1}.

(Received in France 23 January 1989)