Synthesis of Cephalosporin nucleus

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Abstract- Cephalosporins are readily used as antibiotics since ages. The synthesis of these molecules is a very arduous task. The article shows the synthetic scheme for Cephalosporin C nucleus.

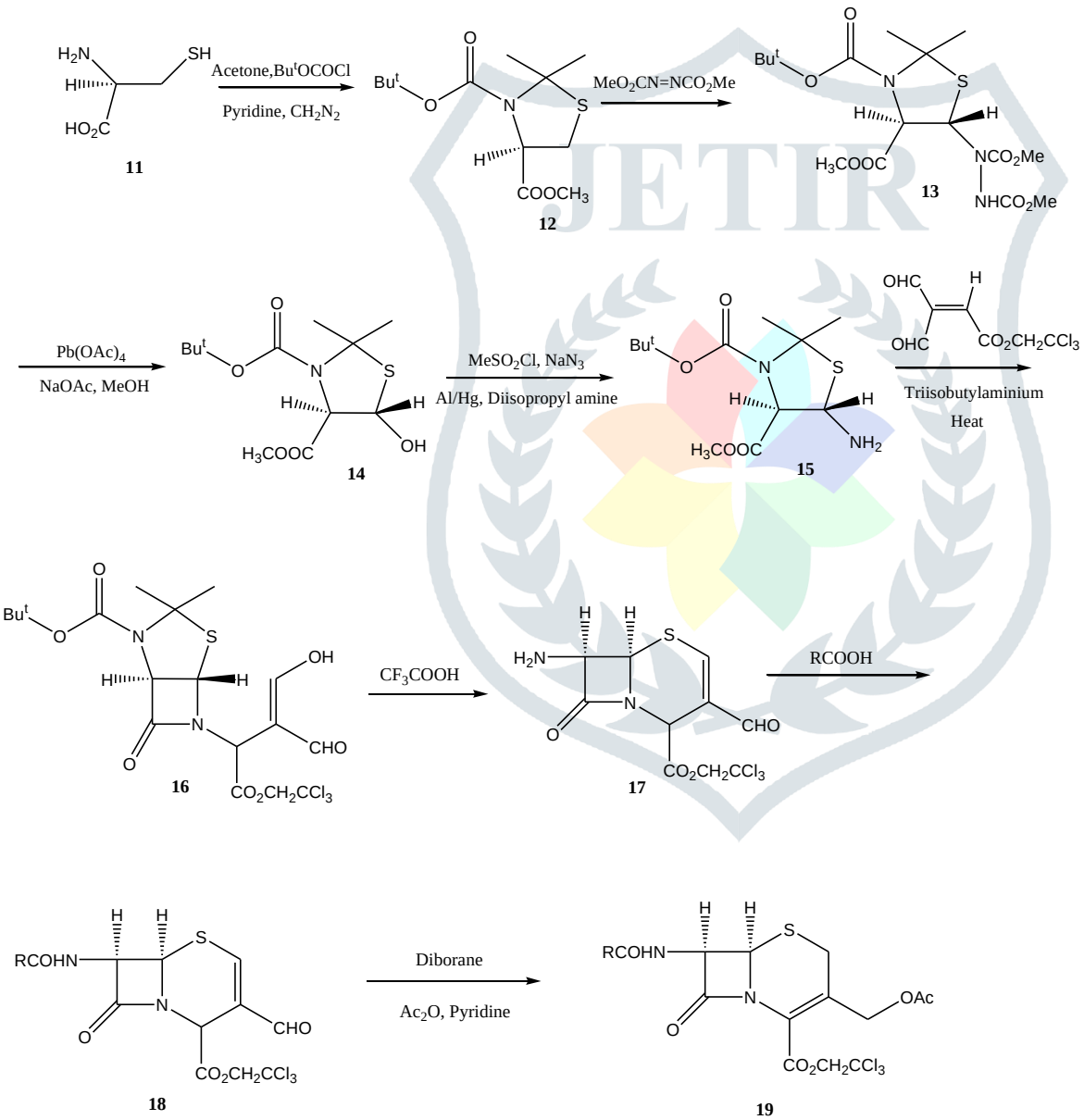
Keywords: Cephalosporin, synthesis, cephalosporin C

Introduction

The synthesis of Cephalosporin C nucleus is the main basis of synthesis of antibiotics. Cephalosporin C is the main precursor for the synthesis of almost all cephalosporins. The total synthesis of cephalosporin C nucleus has been reported in 1965 in nobel lecture and was published in 1966 by Woodward [1,2]. This route to cephalosporin C (Scheme 1.1) provides a classic example of any natural product synthesis. The β-lactam ring of the cephalosporin C was constructed first, starting from L-cysteine (11). In the first step, the protection of nitrogen, carboxylic acid and sulfur and groups followed by reaction with diazomethane afforded the cyclic intermediate 12. Introduction of the hydrazine group to give 13 was followed by oxidation and reaction with $Pb(OAc)_4$ yielding trans hydroxyl ester 14. Further steps involved the mesylation reaction followed by inversion in the stereochemistry due to displacement with azide. Further, the reduction step yielded the required the amino ester 15, which gave on cyclization the key β-lactam intermediate 16. The removal of the nitrogen and sulfur protecting groups were achieved by reaction with trifluoroacetic acid which resulted in cyclization to the cephalosporin precursor 17. The amino group of 17 was then acylated to form 18. Reduction, acetylation and equilibration in the presence of pyridine for three days provided the cephalosporin C ester 19.

Cephalosporin C ester formed by this synthetic route has been further converted to 7-aminodeacetoxycephalosporanic acid (7-ADCA) and to 7-amino-3-chlorocephalosporanicacid (7-ACCA) [3].

Morin et al has reported the process for the removal of the side chain of cephalosporin C to give 7-ACA [4]. 7-ACA, 7-ADCA and 7-ACCA have been used widely to synthesize various cephalosporin antibiotics. 7-ACA has been reported as a precursor for the synthesis of cefotaxime [5], cephalothin [6], cephapirin [7] and caphaloglycin [27]. Similarly, synthesis of cefadroxyl [8], ceftamet [9], cephalexin [10] and cephradine [11] have been reported from 7-ADCA intermediate. 7-ACCA has been used as an intermediate for the synthesis of cefaclor [12].



Scheme 1.1 Synthesis of cephalosporin C ester

1.5 Structure activity relationship (SAR)

Understanding of the structure activity relationship (SAR) of *β*-lactam antibiotics was once considered as an impossible dream [13]. Since the penicillin structure was first characterized, the structural features which were first believed to be necessary for imparting the antibacterial activity have been changed dramatically. By the 1980's the pharmacophore of the *β*-lactam antibiotics had been known to get reduced to sufficiently reactive azitidionone (**20**) unit which have the right molecular shape to bind with the target penicillin binding proteins (PBPS).

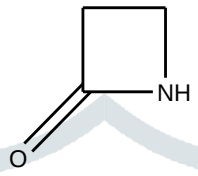


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Fig 1.6 Azitidionone structure

The molecular structure of cephalosporin can be altered by different substitutions on the cepham ring, at C-7 side chain and at C-3 position. The relative positions in cephalosporin are designated as in **21**.

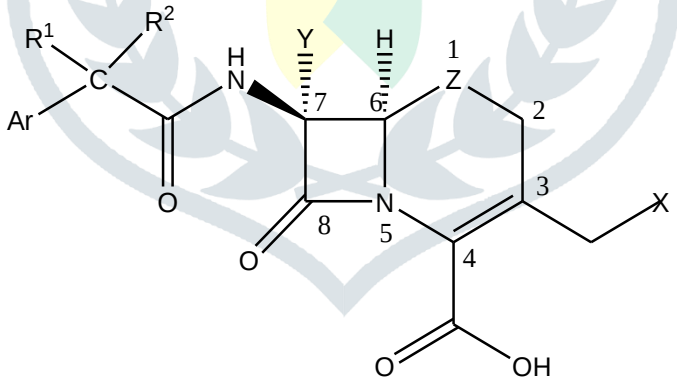

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Fig 1.7 Relative positions of cephalosporins

These substitutions at different positions have been reported to effect the *in vitro* stability, antibacterial activity and resistance against *β*-lactamases. The presence of amino and a hydrogen group at R^1 and R^2 positions increases *in vitro* stability in acidic conditions. Replacing Y with alkoxy group especially by methoxy group at 7-

position results in increase in the antibacterial activity due to increase in stability towards *β*-lactamases. The presence of amino group at 7-position is very necessary for the antibacterial activity. Z can be replaced by either sulfur or oxygen atom. Presence of sulfur increases the antibacterial activity, whereas the presence of oxygen increases the stability of the ring towards *β*-lactamases. Presence of hydrogen atom at 6-position is necessary for biological activity. Replacing X with five membered hetrocyclic ring instead of six membered ring increases the antibacterial activity. L-Isomer at positions R^1 and R^2 at C-7 side chain are 30-40 times more stable towards *β*-lactamases than D isomers. The stability is further increased to 100 folds by the presence of (Z) methoxyoxime at this position.

Conclusion:

The above mentioned scheme is the most widely used scheme in the pharma industry for the synthesis of cephalosprins.

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