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Synthetic Utility of Dimethyl Formaminium Chloride Chlorosulphate in Preparation of Cephems

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Dimethyl formaminium chloride chlorosulphate, a stable complex formed from sulphuryl chloride/dimethyl formamide and its synthetic utility in the preparation of different cephem antibiotics described.

Key Words: Cephem, Silylation, Activation, Dimethyl formaminium chloride chlorosulphate.

INTRODUCTION

Synthesis of various cephalosporin antibiotics (**I**) mainly involves the acylation of 7-amino cephalosporanic acid (7-ACA) or 7-ADCA derivatives with corresponding carboxylic acid derivatives. Different methods for acylation reaction are reported in literature[1-4]. The activation of carboxylic acid is generally carried out by making acid chloride[5], which is then condensed with the corresponding 7-amino nucleus. Another method involves the condensation of silylated cephalosporin nucleus with corresponding acyloxy phosphonium chloride derivative which is prepared from triphenyl phosphine (TPP), hexachloro ethane or CCl_4 with corresponding carboxylic acid[6,7]. In the preparation of cefotaxime and ceftriaxone, $SOCl_2$/DMF complex is used to activate organic acid which is *in situ* condensed with 7-amino moiety[8]. The stability of this complex formed from $SOCl_2$/DMF is poor specially in solvent like toluene or benzene is the limitation of this process.

Dimethyl formaminium chloride chloro sulphate (DFCCS) (**II**) in stable complex formed by the reaction of SO_2Cl_2 with DMF[9-11]. It has been used as chlorinating reagent for aromatic and heterocyclic nucleus[12,13]. The present article describes the utility of DFCCS for preparation of various cephalosporin antibiotics.

EXPERIMENTAL

All the reagents and solvents were used as such without further purification. The progress of the reactions was monitored by TLC using silica gel plates (E. Merck). IR spectra were recorded on a ^{1}H NMR spectra on Bruker (300 MHz) spectrometer using TMS as an internal standard. The

structure of the isolated reaction products were confirmed by comparing IR, ^{1}H NMR spectra with that of authentic sample.

Synthesis

7-[(2-(2-Aminothiazol-4-yl)-2-syn-methoxyimino)acetamido]cephalosporanic acid (cefotaxime)

Activation of 2-(2-aminothiazol-4-yl)-2-syn-methoxyimino acetic acid: 11.9 g of sulfuryl chloride was added dropwise to 6.4 g of dimethlyformamide at -20ºC. The temperature was slowly raised to 0ºC at which the solid adduct crystallized out. This was stirred vigorously for 1 h and 50 mL of dichloromethane was added to the solid crystals. The temperature was again raised to 15-20ºC and at this temperature the crystallized adduct melted and formed an immiscible layer with dichloromethane. The lower portion (N,N-dimethyl formaminium chloride chlorosulphate) was added to a pre-cooled slurry of 16.02 g of 2-(2-aminothiazol-4-yl)-2-syn-methoxyimino acetic acid in 150 mL of dichloromethane at -20ºC to get a clear solution, which was kept for 1 h at this temperature.

7-Amino cephalosporanic acid: 20.0 g of 7-aminocephalosporanic acid was taken in 150 mL of CH_2Cl_2 and 12.42 g of hexamethyldisilazane was added to it, followed by refluxing for 2 h. The clear solution obtained was cooled to 10ºC and 12.1 mL of dimethylaniline was added, followed by further cooling to -55ºC.

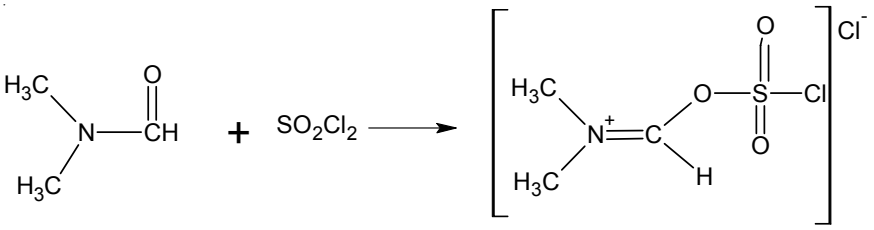
Acylation: The reaction mixture, 2-(2-aminothiazol-4-yl)-2-syn-methoxyimino acetic acid was cooled to -55ºC and 7-amino cephalosporanic acid was added to it to get a clear solution. The temperature was maintained at -55ºC for 10 min. The quantification of the condensed mass showed the formation of 90 % of cefotaxime acid.

Isolation of 7-[(2-(2-aminothiazol-4-yl)-2-syn-methoxyimino) acetamido]cephalosporanic acid: 200 mL of water was added to the above condensed mass and the temperature was brought to 25ºC in 20 min. At this temperature, the pH of the hydrolyzed mass was brought to 6.5 by using triethylamine. The aqueous layer was taken and 60 mL of isopropanol was added at 30ºC. The product was cooled to 5ºC and stirred for 1 h and finally filtered to yield 29 g (85 %).

Conversion of cefotaxime sodium from cefotaxime acid: 10.0 g of the above solvate was taken in 60 mL of methanol and 11 mL of water and the mixture was cooled to 5ºC. To this was slowly added 1.8 g of sodium acetate dissolved in 20 mL methanol to get a clear solution. Then, 400 mL of isopropyl alcohol was added within 1 h to get cefotaxime sodium (9.3 g) in the crystal form. NMR (DMSO-d_6) δ ppm: 2.00(s), 3.3(q) 3.8(s), 4.9(q) 4.97(q) 5.60(2d), 6.70(s), 7.2(bs), 9.47(d). IR: (KBr, cm^{-1}): 3420 ν(–NH_2), 3340 ν(–NH, –NH_2), 1760 ν(–C=O lactam), 1730 ν(–C =O, carboxylic, 1650 ν(–C=O–NH), 1385-1355 ν(–O–CO–CH_3).

RESULTS AND DISCUSSION

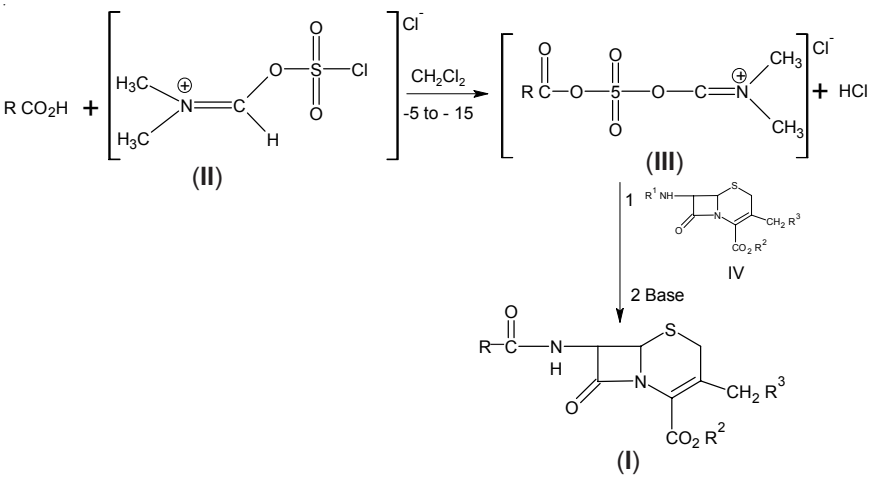
The reaction of SO_2Cl_2 with equimolar quantity of DMF with or without solvent *i.e.*, CH_2Cl_2 or $CHCl_3$, results dimethyl formaminium chloride chlorosulphate (DFCCS) (**II**).



(**II**)

DFCCS forms activated complex with carboxylic acid in this process to make reactive intermediate **III** *i.e.* activated carboxylic mixed sulphonic anhydride.

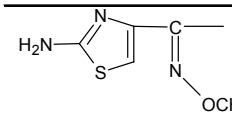
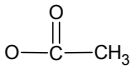
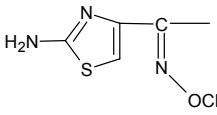
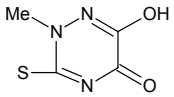
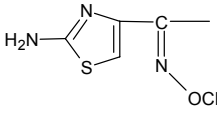
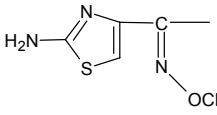
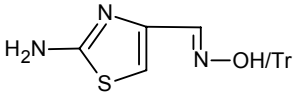
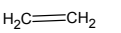
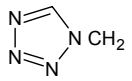
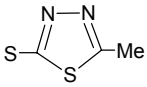
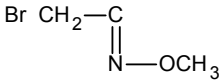
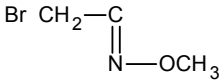
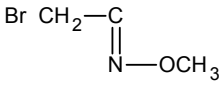
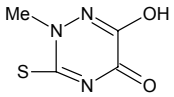
The activation of 2-(2-aminothiazol-4-yl)-2- syn-methoxyiminoacetic acid with DFCCS (**II**) in dichloromethane at -5 to -10ºC gives mixed carboxylic sulphonic anhydride (**III)** which on reaction with silylated 7-aminocephalosporanic acid (7-ACA) in presence of tertiary amine to yield cefotaxime acid (**I**) in 84-86 % yield (**Scheme-I**).



Scheme-I

Different cephem compounds are synthesized using this method and results are tabulated in Table-1.

TABLE-1

R	R_1	R_2	R_3	Yield (%)
	H / Si	H / Si		85
	H / Si	H / Si		75
	H / Si	H / Si	- OCH_3	80
	H / Si	H / Si	H	80
	H / Si	H / Si		70-75
	H / Si	H / Si		90-95
	H / Si	H / Si	- OCH_3	75
	H / Si	H / Si	- $OCOCH_3$	80
	H / Si	H / Si		70

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