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Synthesis of β-Lactams Using Dimethyl Formaminium Chloride Chlorosulphate Reagent

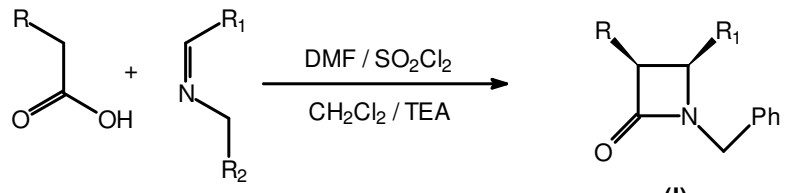
DAROGA SINGH*, BISHWA PRAKASH RAI and VANDANA SINGH
Department of Chemistry, Tilak Dhari College, Jaunpur-222 002, India
Tel: (91)(5452)261009; E-mail: daroga.singh@hotmail.com; bishwa.rai@hotmail.com

In this paper, dimethyl formaminium chloride chlorosulphate is formed by the reaction of sulphuryl chloride with dimethyl formamide and its utility is applied in the synthesis of β-lactam compounds.

Key Words: β-Lactam, Dimethyl formaminium chloride chlorosulphate, Cycloaddition.

INTRODUCTION

The construction of naturally occurring or unnatural β-lactam with attendant control of functional groups and stereochemistry has been the goal of the synthetic organic chemists for last four decades. Among a multitude of synthetic methods one of the most studied is the [2+2] cycloaddition reaction of imines and ketenes. Cycloaddition reactions of imines with acid chloride or with activated carboxylic acids in presence of base have been widely used for synthesis of β-lactam[1-6] (**Scheme-1**).



(I)

Scheme-I

The acid chloride from which ketene is generated is not always simple and easy to prepare and/is not commercially available. An alternative synthesis of β-lactam that circumvents the use of acid chlorides involves the use of carboxylic group activating agents. Various reagents have been reported for activating carboxylic group in the Staundinger reaction[7-13].

Dimethyl formaminium chloride chlorosulphate (DFCCS), a stable complex formed by the reaction of SO_2Cl_2 with DMF[14-16]. It has been used as chlorinating reagent for aromatic and heterocyclic nucleus[17-20]. The present article describes the utility of DFCCS for preparation of various β-lactam nucleus. This reagent was successfully used in β-lactam chemistry for acylation of various 7-aminocephem derivatives in the preparation of cephem antibiotics[21].

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

Synthesis of N,N-dimethyl formaminium chloride chlorosulphate (DFCCS): 21.47 g (0.294 mol) of dimethyl formamide was added to a mixture of 39.7 g (0. 294 mol) of sulfuryl chloride and 50 mL of methylene chloride slowly over 0.5 h, at a temperature of -10 to -20 °C. The mixture was stirred for 2 h at 20-22 °C. Further, 100 mL of methylene chloride was added and the mixture was allowed to settle down. N,N-dimethyl formiminium chloride chlorosulphate (DFCCS) that remains in the denser organic layer was separated.

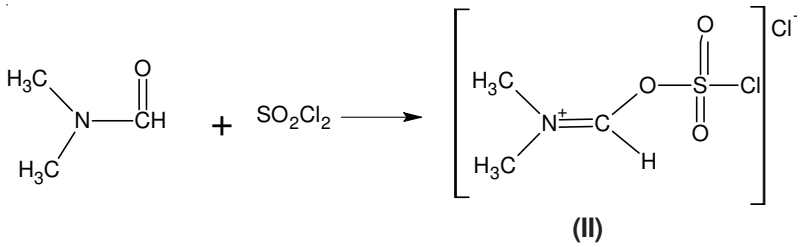
Synthesis of 1-benzyl-3β-[4-(S)-phenyloxazolidin-2-one-3-yl]-4β-[2-(2-furyl)ethenyl]azetidin-2-one (I): To a solution of (S)-4-phenyloxazolodin-2-one-3-yl-acetic acid (**III**) (50 g 0.226 mol) in dichloromethane (300 mL), cooled to -5 to -10 °C. To this solution added DFCCS (**II**), oily layered is formed in 10-15 min followed by stirring for 0.5 h at same temperature and cooled this reaction mixture to -50 °C. A solution of triethylamine (50.27 g, 0.497 mol) is added slowly by keeping temperature at -45 to -50 °C and stirred this reaction mixture for 0.5 h at -50 to -55 °C in order to get compound **V**.

To the above reaction mixture, slowly added the Schiff base (**VI**) solution [prepared from furyl acroline (30.5 g, 0.25 mol) and benzyl amine (26.75 g, 0.5 mol) in dichloromethane (300 mL)] at -50 to -55 °C in 15-20 min. The temperature of reaction mixture was allowed to raise -10 °C in ca 1 h and stirred for 0.5 h. Water (500 mL) is added and pH adjusted to 3.5 with 6 N HCl. The organic layer is separated and washed with 5 % aqueous $NaHCO_3$ (300 mL) and then with 5 % aqueous NaCl (300 mL).The resulting organic layer is concentrated under reduced pressure and added 2-propanol (500 mL). The slurry is cooled to 10 °C.The solid is filtered and washed with cold 2-propanol (100 mL) and dried. Yield 74 g (83 %). Chromatographic purity (By HPLC) > 99.0 %; m.p. 178-180 °C. (Reported in literature 181-182 °C); $[\alpha]_D$ 20 = + 13.1 ° (c = 1.6, $CHCl_3$), IR (KBr, ν_{max}, cm^{-1}) 3022, 1762, 1658, 1500, 1463, 1412; ^{1}H NMR ($CDCl_3$) δ: 7.45-7.07 (m, 11, ArH), 6.35 (dd, 1, *J* = 1.8, 3.3 Hz, OCH=CH), 6.26 (d, 1, *J* = 16 Hz, N-CH-CH=CH), 6.22 (d, 1, *J* = 3.3 Hz, O-C=CH), 5.76 (dd, 1, *J* = 16, 8.9 Hz, N-CH-CH=CH), 4.91 (dd, 1, *J* = 8.8, 7.4 Hz, OCH_2CH), 4.65 (t, 1H, *J* = 8.9 Hz, one of OCH_2 CH), 4.60 (d, 1H, J = 15 Hz, one of $ArCH_2$), 4.53 (d, 1H, *J* = 4.8 Hz, C-3 H), 4.20 (dd, 1H, J = 7.4, 8.8 Hz, one of OCH_2CH), 4.10 (dd, 1, *J* = 4.8, 8.9 Hz, C-4H), 4.01 (d, 1, *J* = 15 Hz, one of $ArCH_2$).

RESULTS AND DISCUSSION

DFCCS (**II**) remained stable and not converted to the normal Vielsmeir reagent. The complexes of $POCl_3$/DMF or $SOCl_2$/DMF are less stable and easily converted into normal Vielsmeir reagent. DFCCS can be prepared in any solvents such as benzene, toluene, CH_2Cl_2 and $CHCl_3$ or without solvent. This makes advantages over $SOCl_2$/DMF complex which cannot be synthesized in CH_2Cl_2 or $CHCl_3$. These solvents facilitate the formation of $SOCl_2$/DMF complex into normal Vielsmeir reagent[22].

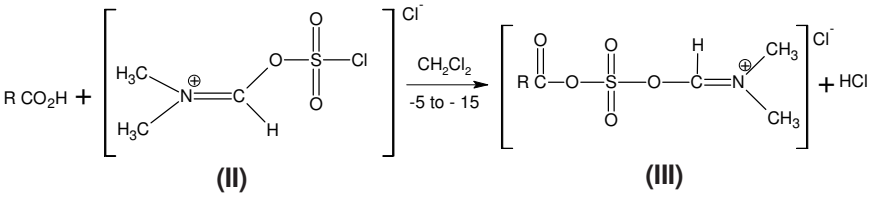
The reaction of SO_2Cl_2 with equimolar quantity of Dimethyl formamide with or without solvent *i.e.* CH_2Cl_2 or $CHCl_3$, results dimethyl formaminium chloride chlorosulphate (**II**) (**Scheme-II**).



(II)

Scheme-II

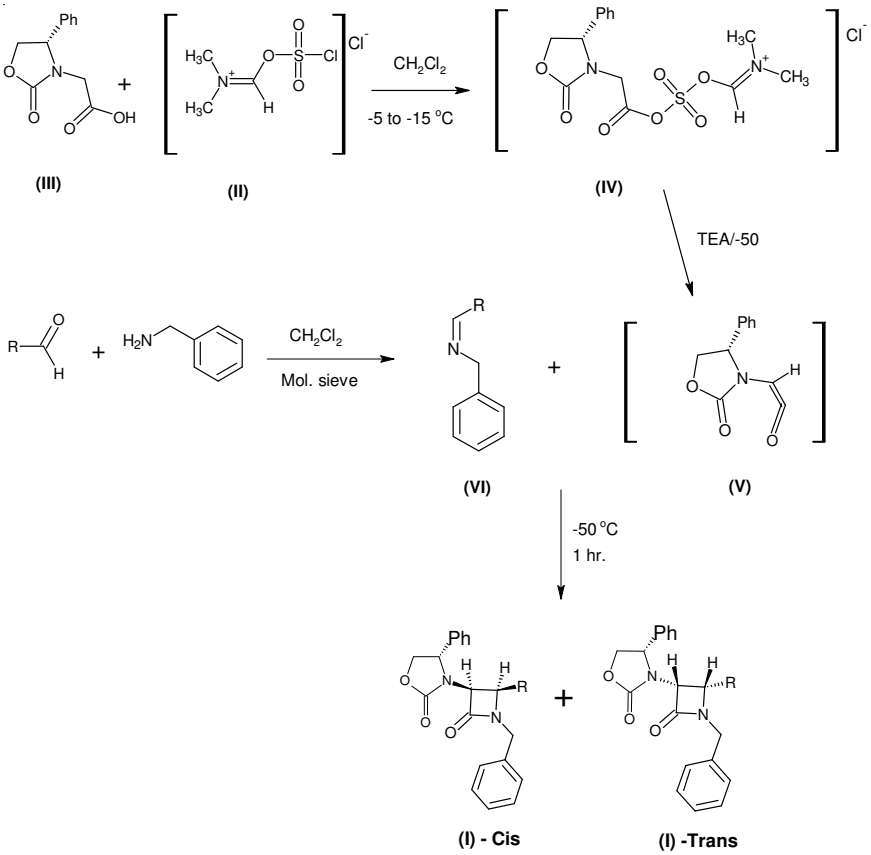
DFCCS (**II**) forms activated complex with carboxylic acid in this process to make reactive intermediate **III** (**Scheme-III**) *i.e.* activated carboxylic mixed sulphonic anhydride.



(II) **(III)**

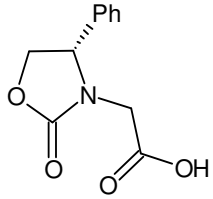
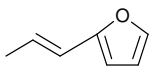
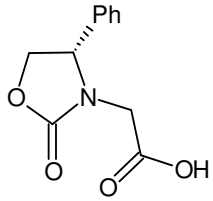
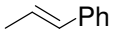
Scheme-III

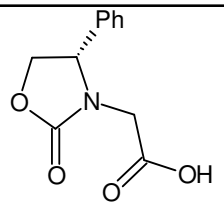
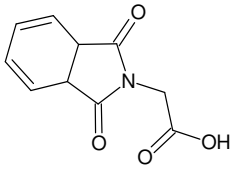
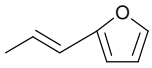
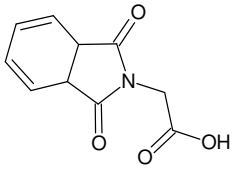
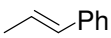
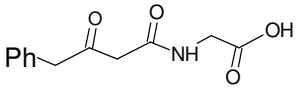
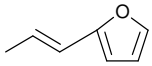
Activation of oxazolidinone acetic acid (**III**) with DFCCS in dichloromethane at - 5 to -15 °C gives mixed carboxylic sulphonic anhydride (**IV**). This activated carboxylic anhydride generates ketene (**V**) at -50 °C in presence of tertiary amine which is condensed with imine (**VI**) at -50 °C followed by usual work-up gives (**I**) in 80-85 % yields with > 90 % of *cis*-isomer. Different β-lactam compounds have been synthesized using this method and results are given in Table-1 (**Scheme-IV**).



Scheme-IV

TABLE-1

Acid	R	Yield (%)	*cis*:*trans* (reaction)	*cis*:*trans* (solid)
		83	92:8	≥98
		80	90:10	≥98

Acid	R	Yield (%)	*cis*:*trans* (reaction)	*cis*:*trans* (solid)
	Ph	78	92:8	≥98
		70	85:15	≥95
		75	88:12	≥95
		40	90:10	≥92

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REFERENCES

1. A.K. Mukerjee and R.C. Srivastava, *Synthesis*, 327 (1973).
2. J.C. Sheehan and E.J. Corey, Organic Reaction, Wiley, New York, Vol. 9, p. 388 (1957).
3. A.K. Mukerjee and A.K. Singh, *Synthesis*, 547 (1975).
4. M.S. Manhas, S.G. Amin and A.K. Bose, *Heterocycles*, **5**, 669 (1976).
5. C. Palomo, in eds.: G. Lukacs and M. Ohno, In Recent Progress in the Chemical Synthesis of Antibiotis, Springer-Verlag, Berlin, pp. 533-564 (1990).
6. D.A. Evans and E.B. Sjogren, *Tetrahedron Lett.*, **26**, 3783 (1985).
7. G.I. Georg, P.M. Mashava and X. Guan, *Tetrahedron Lett*., **32**, 581 (1991).
8. M.S. Manhas, H.P.S. Chawla, S.G. Amin and A.K. Bose, *Synthesis*, 407 (1977).
9. A. Arrieta, B. Lecea and C. Palomo, *J. Chem. Soc. Perkin Trans. I*, **28**, 845 (1987).
10. F.P. Cossío, I. Ganboa and C. Palomo, *Tetrahedron Lett.*, **26**, 3041 (1985).
11. F.P. Cossío, I. Ganboa, J.M. García, B. Lecea and C. Palomo, *Tetrahedron Lett.*, **28**, 1945 (1987).
12. G. Guanti, L. Banfi, E. Narisano and S. Thea, *J. Chem. Soc. Chem. Commun.*, 861 (1984).

13. A. Arrieta, B. Lecea, F.P. Cossio and C. Palomo, *J.Org. Chem.*, **53**, 3784 (1988).
14. U. Hasserodt, *Chem. Ber.*, **101**, 113 (1968).
15. E. Kuhle, *Angew. Chem. Int. Ed.*, **1**, 647 (1962).
16. H.H. Bosshard, R. Mory, M. Schmid and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).
17. A.F. Bramwell, I.M. Payne, G. Riezebos, P. Ward and R.D. Wells, *J. Chem. Soc. Perkin Trans. I*, 2004 (1972).
18. H.C. Kenneth and N.J. North Plainfield, 2,3- and 2,6-dichloropyrazines by Chlorination, US Patent, 3,291,802 (1966).
19. I.L. Finar, Organic Chemistry, The Fundamental Principles, Vol. 1, edn. 3, p. 519 (1959).
20. J.A. Alkins, Synthesis of Bicyclic Aromatic Sulfonyl Chlorides, Eur. Patent, 02,54,577 (1987).
21. D. Datta and B.P. Rai, Method for Manufacture of Cephalosporins and Intermediates, Eur. Patent, 0791596 A1 (1997).
22. J.D. Meseguer and A.E. Bianchini, Process for Preparing Cephalosporins and Intermediates, US Patent, 5,037,988 (1991).

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