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USE OF A NOVEL REAGENT IN THE SYNTHESIS OF 3-EXOMETHYLENECEPHAMS

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ABSTRACT: An improved synthesis of 3-exomethylene cephams, employing the use of $ZnCl_2$-Et_2O complex has been described.

3-Exomethylene cepham serves as a versatile intermediate in the synthesis of novel cephem antibiotics including Cefaclor, Cefroxadine, etc. Kukolja[1] etal., first reported the synthesis of 3-exomethylene by ring expansion of penicillin derivative. This is a two step method which involves the intermediacy of 2-chlorosulfinyl azetidin-4-one and its intramolecular cyclization by a Friedel crafts catalyst. A variety of Friedel crafts catalysts[2] have been tried in literature but stannic chloride is found to be the most preferred one till date. Due to its high reactivity and hazardous nature, use of stannic chloride requires costly safety measures and strong environmental controls.

Zinc chloride as Lewis acid catalyst has been tried in the synthesis of 3 – exomethylene- cephams but the reported yields[2] are very poor.

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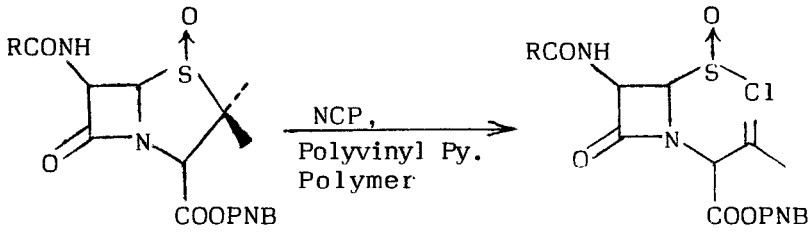
However, it did not work at all in our hands. The lower catalytic activity of $ZnCl_2$ compared to other lewis acids such as $SnCl_4$, $TiCl_4$ or BCl_3 is attributed primarily to its poor solubility in inert organic solvents. This disadvantage can be avoided by using zinc chloride-diethyl ether complex[3] in inert solvent. In an attempt to improve the synthesis of 3-exomethylene cephams we found $ZnCl_2$-Et_2O complex a better alternative which is easy to handle, cost effective and also less toxic.

We here report the successful utilization of zinc chloride-diethyl ether complex in inert solvents (e.g. CH_2Cl_2, Toluene) for the synthesis of 4'-p-Nitrobenzyl 7-phenoxyacetamido-3- methylenecepham -4-carboxylate-1-oxide (5) and 4'-p-Nitrobenzyl-7- phenylacetamido-3-methylenecepham-4-carboxylate-1-oxide (6) in 60-70% yield which is the unknown observation till date. Starting from penicillin V and penicillin G, via oxidation with peracetic acid[4] followed by esterification with p-nitro benzyl bromide (PNB)[5], 4-p-Nitrobenzyl -6-phenoxy-acetamido penicillinate-1- oxide (1) and 4-p-Nitrobenzyle -6-phenylacetamido penicillinate-1-oxide (2) were obtained respectively in quantitative yields.

Treatment of (1) and (2) with N-chlorophthalimide in presence of an acid scavanger (e.g. polyvinyl pyridine polymer) in toluene gave sulfinyl Chlorides (3) and (4) respectively. Cyclization of latter was effected (without isolation) by the treatment with $ZnCl_2$ - Et_2O complex in toluene and di-n-butyl ether (as oxoligand). An orange coloured intermediate complex thus obtained in both the cases, was found to be

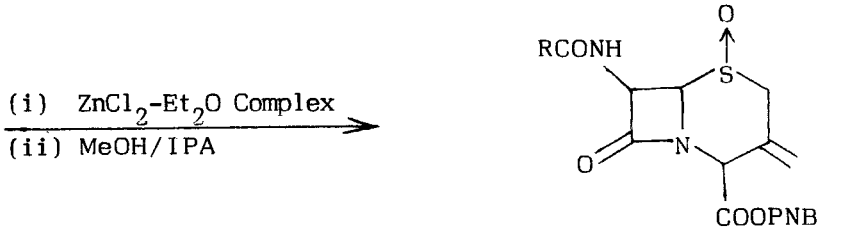


(1), R=$PhOCH_2$-

(2), R=$PhCH_2$-

(3), R=$PhOCH_2$-

(4), R=$PhCH_2$-



(5), R=$PhOCH_2$-

(6), R=$PhCH_2$-

SCHEME

stable at room temperature. It was filtered and dried to an orange powder which on decomposition with alcohol preferably a mixture of methanol and i-propyl alcohol afforded the corresponding exomethylene derivatives (5) and (6) in 60-70% yield.

The zinc chloride-ether complex prepared in dichloromethane was used in the earlier experiments. But later it was discovered that this catalyst

system if prepared in the mixture of dry toluene and dichloromethane gives better results.

EXPERIMENTAL:

All melting points were taken on Electrothermal 9300 and are uncorrected. Qualitative analysis were done on Hewlet-Packard model 1090 liquid chromatograph while ^{1}HNMR and IR spectra were recorded on Hitachi FT R-1500, and Perkin Elmer 16 PC FT. respectively.

Preparation of catalyst-system:

Commercial grade $ZnCl_2$ (35.4 gm), dried by fusion in furnace at 200-280°C followed by slow cooling under vacuum, was dissolved in diethylether (dry, 30.6 gm) by vigorous shaking for several hours to get a viscous solution. Latter was diluted with dichloromethane (40 ml) to get a pale yellow solution. In another case $ZnCl_2$-Et_2O complex was diluted with toluene (30 ml) and dichloromethane (30ml) to afford a homogenous solution.

Typical procedure:

Preparation of p-nitrobenzyl 7-phenoxyacetamido-3-exomethylene cepham-4-carboxylate-1-oxide (5)

Toluene (400 ml) was azeotroped to discard 30 ml. It was cooled to 70°C and copolymer (4.6 gm, moisture = 0.5%) was added and mixture

refluxed to azeotropically distill off 30 ml of the toluene. The toluene was again cooled to 50°C and penicillin V sulfoxide ester (10 gm, 0.02 mole) (1) and NCP (5.1 gm., 0.02 mole) were added. The mixture was stirred at 108-109°C for about 110 min. Contents were slowly cooled down and stirred at 0°C to 5°C for 30 min. Copolymer was filtered off and the sulphinyl chloride solution was added to a precooled mixture of $ZnCl_2$-Et_2O complex prepared in CH_2Cl_2/toluene (30 ml, 7 mole) and di-n-butyl ether (3.7 ml, 1 eqiv.) at -15°C. The orange coloured complex thus formed was initially stirred at 0-5°C for 30 min. and then at 20-25°C for 5 hrs. Filtration followed by washing with hexane (15x3 ml) gave a fluffy yellow powder of the intermediate complex which on decomposition with a mixture of Methanol and i-propyl alcohol (40 ml, 1:1) afforded an off-white crystalline powder after washing with methanol (15 ml) and oven drying at 40°C for 3 hrs.

Yield : 7 gm, 70%; M.pt. 190-190.5°, 'H NMR ($CDCl_3$): 83.82 and 4.13 (q, J=14Hz, C-2H), 4.89 (d,1, C-6H), 5.27 (S,1,C-4 H), 5.59 (m,z, Olefinic H), 5.98 (d,1,J=4.5 Hz, C-7H), 7.86 (m,4,Ar-H), 7.9-8.56 (dd,4,Ar-PNB)

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