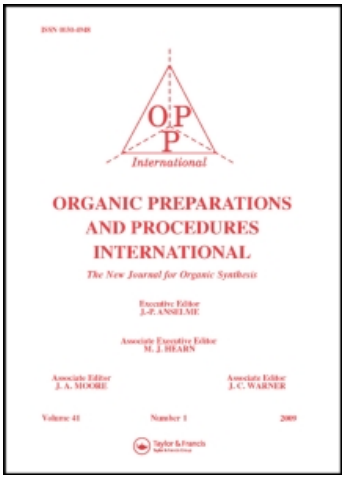

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SYNTHESIS OF t-BUTYL ESTER OF 7-AMINOCEPHALOSPORANIC ACID

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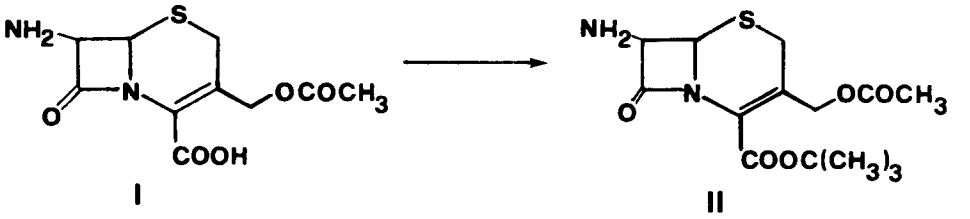
The t-butyl ester (II) of 7-amino-3-acetoxymethylceph-3-em-4-carboxylic acid (7-ACA)(I) is often used[1] in the synthesis of cephalosporins as a masking group of the carboxylic function, because this ester group can be easily removed by acids. Stedman[2] reported the preparation of II by the reaction of I with liquid isobutene in peroxide-free dioxane in presence of concentrated sulfuric acid according to the general procedure of Roeske.[3] To the best of our knowledge, this is the only method described in literature for the preparation of II.



I II

On a larger scale, this procedure is not so attractive because of the necessity of handling an inflammable gas under pressure and the use of an expensive solvent. A general method[4] for the esterification of free amino acids using t-butyl acetate as the reagent seemed much safer and more suited for application in scale up; however, dioxane and perchloric acid were used as solvent and catalyst.

After the first positive trials using the original procedure, the main goal was the proper replacement of the solvent and the acid for practical and economical reasons, as well as for safety. The esterification of I was easily achieved with t-butyl acetate both as solvent and a reagent in the presence of a mixture of p-toluenesulfonic and sulfuric acids. The choice of the first acid was made on the basis of the observation that the salt of I with it is much more soluble in the reaction medium and does not lead to the formation of tars which make it impossible to stir in large reactors, while sulfuric acid provides the high acidity necessary to the reaction.

Temperature, time and the molar ratio among reagents have been intensively studied and optimized. The critical point of this reaction is the instability of II in the process due to the high acidity required for the esterification; the degradation of II occurs mainly to give I, although the β-lactam moiety of I can be hydrolyzed further.

EXPERIMENTAL SECTION

t-Butyl 7-amino-3-acetoxymethylceph-3-em-4-carboxylate (II).- t-Butyl acetate (2 l) and 7-ACA (I) (120 g, 97% pure, 0.427 mole) were mixed in a 5 l four-necked flask, equipped with a dropping funnel, thermometer, stirrer and gas outlet and cooled to 10°. p-Toluenesulfonic acid monohydrate (84 g, 0.437 mole) was added to the mixture and the suspension was stirred again for 20 min., then 96% sulfuric acid (120 ml, 2.2 mole) was added dropwise over a 45 min. period while the temperature was carefully kept at 10°. The mixture was then stirred vigorously until complete dissolution of the salt (2 hrs after the end of addition of sulfuric acid). A mixture of sodium hydrogen carbonate (196 g), water (1 l) and ice (1 kg) was added as rapidly as the evolution of carbon dioxide allowed. The aqueous layer (pH 1.5-1.7) was separated immediately and transferred to a second flask containing a mixture of ethyl acetate (1 l), water (2 l) and potassium hydrogen

carbonate (1.1 kg) at -3° to 0°. At the end of neutralization, the pH was between 7.3-7.5. After separation, the aqueous layer was extracted with 500 ml of ethyl acetate (the aqueous layer from the second extraction was then discarded) and the two extracts were combined and concentrated (no drying with sodium sulphate was necessary) on a rotary evaporator below 40° to a volume of 400 ml. The solution was cooled (with stirring) to 0-5° and the ester crystallized. Dropwise addition of light petroleum (500 ml) resulted in a quantitative precipitation; after two hours of slow stirring, the solid was collected and dried in vacuo at a temperature lower than 30° to yield 98 g (65%) of II with an assay of 94% by HPLC, mp. 103-107°, lit.[2] 114-115°, sufficiently pure for the subsequent reactions. Pure material was obtained by recrystallization from ethyl acetate, mp. 114-115°; UV, IR and PMR data were identical to those described in literature.[2]

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