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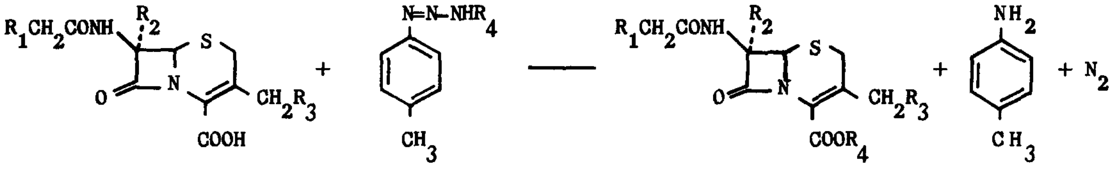
A SIMPLE METHOD FOR THE PREPARATION OF Δ^3-CEPHALOSPORANIC ESTERS

Alberto Mangia and Angelo Scandroglio

Department of Chemical Synthesis, Research Laboratories, Pierrel Spa, Via
degli Artigianelli 10, 20151 Milan, Italy

Δ^3-Cephalosporanic esters have been synthesized with the aim of obtaining orally active derivatives[1,2] or as a means for protecting the carboxylic function[3] with easily removable blocking groups. This esterification is usually associated with double bond isomerization resulting in a mixture of Δ^3- and Δ^2-ester with consequent low yields of the former. Up to date only one general method of preparing pure Δ^3-esters, free of the respective Δ^2-isomers, that is reaction of Δ^3-cephalosporanic acids with activated alkyl halides in a solution of liquid sulphur dioxide, is known.[4] Another method[2] of limited application is the esterification with 1-oxo-(3H)-isobenzofuran-3-yl iodide in DMSO.

In this communication we wish to report a simpler method for preparing Δ^3-esters in high yields without isomerization by reaction of Δ^3-cephalosporanic acids with 3-alkyl-1-p-tolyltriazenes, which are commercial reagents or which can be easily prepared.[5]

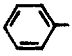
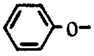


(I)

3-Alkyl-1-p-tolyltriazene in diethylether (2.1-2.5 eq.) was added to a solution of cephalosporanic acid in THF, which was stirred under nitrogen at room temperature for 6 hrs (R_4= CH_3) or overnight (R_4= CH_2-C_6H_5). The usual work up[5] gave the desired ester in a crude state, which was probed to be Δ^2-ester free[6] by NMR (no peak in the region of 6.4 δ was observed,[7] due to the vynilic proton of Δ^2-isomer). Recrystallization or column chromatography afforded analytically pure samples. The results are summarized in the Table.

Methyl and benzyl esters, among the possible alkyl groups, were chosen as models with the goal of substituting diazomethane as alkylating agent and of protecting the cephalosporanic acids as esters susceptible to a ready reconversion to the carboxylic function. Cleavage of the protecting benzyl group from 7 and 8 was indeed achieved using trimethylsilyl iodide according to the method of Jung and Lyster[8], while usual hydrogenolysis[9] (Pd/C, Hydrogen under 3 atm of pressure) was uneffective.

Table Δ^3-Cephalosporanic Esters (I)[10]

No	R_1	R_2	R_3	R_4	Yield%*	m.p.°C	[α]**	UV	
								ε	nm
1		H	$OCOCH_3$	CH_3	100(72r)	163-165	+101	13240	237
2	"	H	$OCOCH_3$	$CH_2C_6H_5$	91(70r)	134-136	+ 67	13060	236
3	"	OCH_3	$OCOCH_3$	CH_3	92(44c)	56	+197	13130	236
4	"	OCH_3	$OCOCH_3$	$CH_2C_6H_5$	-(33c)	oil	-	-	-
5	"	H	$OCONH_2$	$CH_2C_6H_5$	100(45c)	165-167	+ 81	12070	237
6		H	H	CH_3	-(96r)	180-182	+166	7200	262
7	"	H	H	$CH_2C_6H_5$	80(74r)	138-140	+115	7042	257
8		H	H	$CH_2C_6H_5$	62(43r)	132-135	+ 83	7865	262

* Values in brackets are referred to products recrystallized (r) or purified by column chromatography (c) on silica gel. ** c= 0.5% in methanol.

References and Notes

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6 The absence of enough basic species in the reaction mixture well accounts[2,4] for the lack of double bond isomerization; p-toluidine in fact does not isomerize pure Δ^3-ester in the above reported conditions

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10 All compounds had satisfactory analytical and spectroscopic data

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