Tetrahedron Letters,Vol.25,No.35,pp 3905-3908,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A CONVENIENT SYNTHETIC APPROACH TO alpha-AMINO-beta-LACTAM SYNTHESIS PROMOTED BY PHENYL DICHLOROPHOSPHATE REAGENT

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Summary : The ready and economical phenyl dichlorophosphate, in contrast to many reagents developed for activating carboxyl groups for the beta-lactam synthesis, is shown to be very efficient for the synthesis of alpha-vinylamino-beta-lactams from Dane salts and Schiff bases. Some observations toward the scope of the method are also briefly described. The interaction of acetic acids with ethanolimines afforded beta-lactams and/or oxazolidines according to the synthetic methodology used.

With the advent of the third generation of beta-lactam antibiotics, cephalosporins, nocardicin and aztreonam, the synthesis of alpha-amino-beta-lactams have received much atteintion in the past few years. The most commonly used methods for the alpha-amino-beta-lactam synthesis involve as a first step the annelation of imino compounds with activated phthalimidoacetic acid[1], azidoacetic acid[2] and more recently with the Dane salt of aminoacetic acid[3]. The alpha-phthalimido approach gives alpha--amino-beta-lactam having a trans configuration and the alpha-azido-beta-lactam approach is not convenient because of the potential explosive descomposition of azidoacetic acid and its active species[3a]. However, the synthesis of alpha-vinylamino-beta-lactam as cryptoamino function from Dane salts and imino compounds has been of great value in the beta-lactam chemistry and constitutes a hazard-free, economical method for the sterospecific synthesis of alpha-amino-beta-lactams on a large scale. Only three reported reagents, haloformate esters[3a], cyanuric chloride[3b] and phosphorus oxychloride[3c] are suitable for actvating Dane salts. Bose and coworkers[3a] have shown that the trifluoroacetic anhydride and chloroacetonitrile are ineffective for this alpha-vinylamino-beta-lactam approach, similarly diethyl chlorophosphate give very low yields in the expected beta-lactams[3a] and diphenylphosphoryl azide, diethylcyanophosphate and diphenyl phosphite pyridine did not lead to the formation of beta-lactams[4]. This aroused our interest to explore the behaviour of other several activating reagents of carboxyl group for this alpha-vinylamino-beta-lactam approach. Our finding is that among other tested reagents, only the available phenyl dichlorophosphate[5] has shown to be very efficient for the alpha-amino-beta--lactam synthesis.

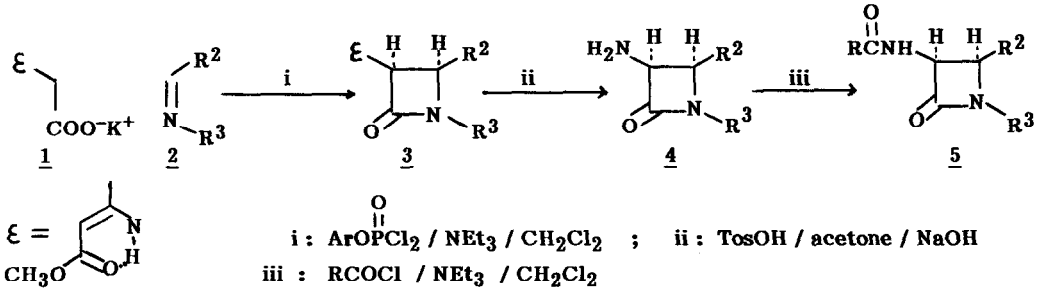


Table 1. Preparation of beta-lactams.

Compound	R^2	R^3	Yield[a] (%)	m.p. (ºC)
3a	4-CH_3OØ	4-CH_3Ø	62	177-178
3b	4-CH_3OØ	Ø	50	182-183
3c	Ø	Ø	50	161-162
3d	Ø-CH=CH	Ø	55	139-142
4a	4-CH_3OØ	4-CH_3Ø	43	125
4d	Ø-CH=CH	Ø	57	143-144
5e[b]	Ø	-$(CH_2)_2$Cl	63[d]	141-143
5f[c]	Ø	-$(CH_2)_2$Cl	61[d]	190

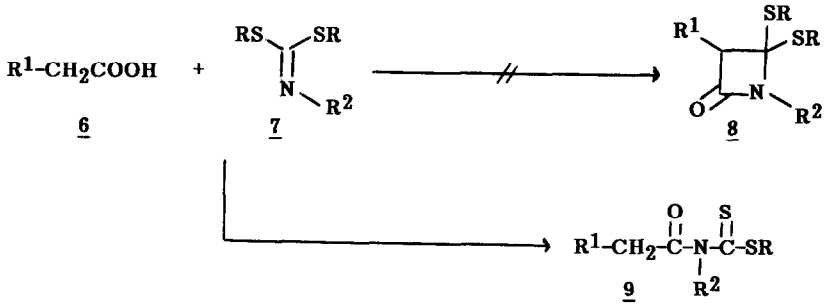
a) Yield of isolated pure product by crystallization from ethyl alcohol. b) R: ØCH_2 c) R : Ø
d) overall yield.

Formation of 1-(4'-methylphenyl)-3-(1'-methyl-2'-carbomethoxyvinylamino)-4-(4'-methoxyphenyl) azetidin-2-one 3a is illustrative for this approach: N-(1-methyl-2-methoxycarbonyl-vinyl)glicine potassium salt (21.2 gr, 0.1 mol) was suspended in anhydrous dichloromethane (250 ml) to which was added triethylamine (42 ml, 0.3 mol) and the imine (22.5 gr, 0.1 mol) derived from 4-methoxybenzaldehyde and 4-methylaniline. The reaction mixture was cooled (0ºC) and phenyl dichlorophosphate (15 ml, 0.1 mol) was then dropwisse added. The mixture was stirred overnight at room temperature, washed with water (2 x 200ml), 5% sodium hydrogen carbonate solution (200 ml), and dried with sodium suphate. Evaporation of the solvent gives the crude title compound which was cristallized from ethyl alcohol to give a pure product (23.6 gr, 62%) m.p. 177-178ºC N.M.R.($CDCl_3$)δppm: 8.50-8.13(s_b,1H,NH); 7.26--6.55(m,8H,arom.); 5.12(m,1H,CH-N); 4.89(d,1H,J= 5Hz); 4.27(s,1H,-CH=); 3.69(s,3H,CH_3); 3.38(s,3H,CH_3); 2.20 (s,3H,CH_3); 1.78(s,3H,CH_3). Under the same reaction conditions, we have tested other activating reagents, for example diethylbromophosphate, which is an efficient coupling agent for peptide bond formation[6a] and N,N--bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (BOPDC) recently used in the beta-lactam synthesis[6b] give 3a in 20% and 10% yield respectively. Phosphorus trichloride which also has been used in the peptide synthesis [6c] did not lead to the formation of beta-lactams from Dane salt 1 and the Schiff base 2a, neither tosyl chloride[6d], nor saccharyl chloride[6e] . Phenyl N-phenylphosphoramidochloridate recently used for activating carboxyl groups[6f] also was found inadequate for this beta-lactam approach. All these results clearly shows the importance of the introduction of the phenyl dichlorophosphate reagent in the synthetic methodology of the beta-lactam chemistry. The configuration of C-3 and C-4 protons in all these monocyclic beta--lactams was observed to be cis (J≈5Hz). These results assume added significance in view of the fact that the beta-lactam protons in active penicillins, cephalosporins, and other beta-lactam antibiotics for clinical use have cis stereochemistry.

In an attempt to extend our method to other acetic acids, we have found that phthalimidoacetic acid and the imine formed from anisaldehyde and 4-methylaniline afforded the corresponding trans beta-lactam in 70% yield. Similarly phenoxyacetic acid with the same imine give cis-3-phenoxy-4-(4-methoxyphenyl)-1-(4-methylphenyl)-azetidin-2-one in 65% isolated yield. The scope of the method is limited by the reactivity of N-acylaminoacids to produce oxazolones.

We next examined the use of N-arylthiocarbonimidates 7 as starting imines for the synthesis of beta-lactam 8 which would be used as precursors of 4-unsubstituted beta-lactam synthesis. However we have found that acylamino dithiocarbamic esters 9 were formed instead of the expected beta-lactam 8. Scheme 1.

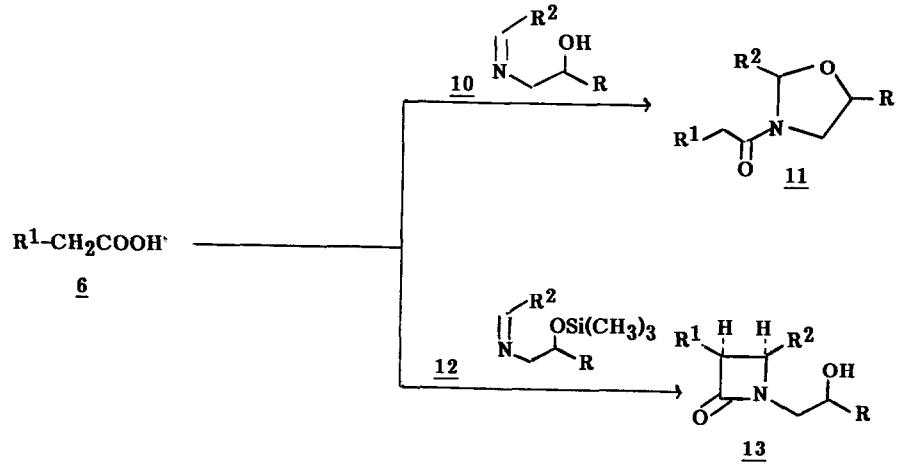
Another interesting finding of this preliminary investigation is that reaction of phenoxyacetic acid 6 (R^1 : ArO) with imines 10 derived from anisaldehyde and ethanolamine derivatives afforded oxazolidines 11 (R : H, C_6H_5) instead of the expected beta-lactam 13. However, protection of the hydroxy group as trimethylsilyl



R^1: C_6H_5O 9a R : C_2H_5 ; R^2 : C_6H_5

9b R : C_2H_5 ; R^2 : p-$CH_3C_6H_4$

- Scheme 1 -



R : H, C_6H_5 ; R^1 : C_6H_5O ; R^2 : 4-$CH_3OC_6H_4$

- Scheme 2 -

Table 2

Compound	R	Yield[a] (%)	m.p. (ºC)
9a	—	84	122-124
9b	—	60	119-120
11	Ø	90	99-100
13	Ø	91	167-169
13	H	70	146-148

a) Yield of isolated pure product by crystallization from ethyl alcohol. A single spot was detected by tlc analysis.

ether in the starting imines 12 provide a convenient route to the corresponding beta-lactams 13 avoiding the formation of competitive products. Therefore, by this method the reaction between acetic acids and ethanolimines can be directed to the formation of oxazolidines and/or beta-lactams according to the desired synthetic purposes. Scheme 2.

Although this investigations is still in its preliminary stages, the results obtained suggest that the procedure herein described and the use of selected Schiff bases provide and economical route for preparing beta-lactams of biological interest on a large preparative scale. A full paper is in preparation in which we disclose the reactivity of phenyl dichlorophosphate reagent and the formation of reaction products from mechanistic points of view[7].

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7. Considered as Reagents and Synthetic Methods 42. This work was financially supported by GEMA S.A. (Spanish) and LONZA A.G. (Swiss). Patent applications submited by GEMA S.A. A grant from Ministerio de Educación y Ciencia to F.P. Cossío is gratefully acknowledged.

(Received in UK 24 May 1984)