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# Synthesis of α-Substituted-α-Amido-β-Lactams[1]

Ajay K Bose, J C Kapur, B Dayal and M S Manhas

Department of Chemistry and Chemical Engineering
Stevens Institute of Technology
Hoboken, New Jersey 07030

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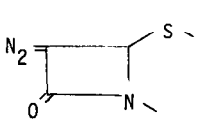
Stromınger's hypothesis that α-methyl substituted penicillins and cephalosporins should have enhanced antibacterial activity[2] and the isolation of 7-methoxycephalosporin antibiotics from *Streptomyces*[3] created considerable interest among synthetic organic chemists. Reactive intermediates such as α-diazo-β-lactam[4] 1, various Schiff bases[5] 2 and N-chloroamide[6] 3 have been utilized for introducing functionalities at the α-position to the β-lactam carbonyl starting from penicillins, cephalosporins and derivatives.



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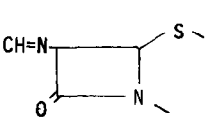

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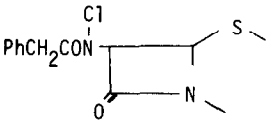

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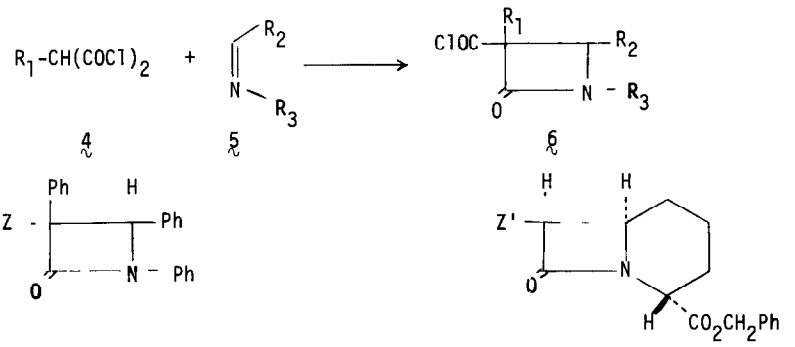
In the course of our investigations toward β-lactam antibiotics we have explored a cycloaddition approach to α-substituted-α-amido-β-lactams. In our scheme advantage has been taken of the high yield formation of a single isomer of α-substituted acid chloride β-lactam 6 from substituted malonyl chloride 4 and Schiff base 5 by the method of Ziegler and Kleinberg[7] Thus 1,3,4-triphenyl-2-azetidinone-3-carboxy-chloride 7 was converted into acid azide 9 by treatment with aqueous sodium azide in acetone at 0°. The isocyanate 10 was prepared *in situ* by heating the azide 9 in dry benzene until ir monitoring showed disappearance of absorption for the azido group. Thereafter, addition of p-anisyl alcohol and catalytic amount of aluminum chloride to the benzene solution of isocyanate 10 and further refluxing for 2 hrs (ir monitorin gave the anisyl carbamate β-lactam 11 after evaporation of solvent Other carbamates were also prepared in good yield



Z Z Z'

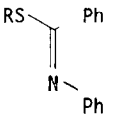
7. COCl 11. $NHCO_2C_6H_4OCH_3(p)$ 14. N = C = O
8. $CO_2H$ 12. $NHCOCH_2OPh$ 15. $NHCOCH_2Ph$
9. $CON_3$ 13 $NHCOCH_2Ph$
10. N=C=O

Lowe *et al*[8], encountered difficulties in trying to convert the isocyanate β-lactam 14 into the phenylacetamido derivative 15 by treatment with phenylacetic acid We have been more successful using somewhat different reaction conditions - the isocyanate 10 reacted with phenoxyacetic acid in presence of catalytic amounts of anhydrous pyridine in refluxing benzene solution to provide α-phenyl-α-phenoxyacetamido-β-lactam 12 [$\nu_{max}^{nujol}$ $cm^{-1}$ 3367 (-NH), 1754 (β-lactam CO), 1692(amide CO), NMR($CDCl_3$) τ 2 26-3.46 (m,21H), 4 38(s,1H), 5 9(s,2H)] in 65% yield 1,3,4-Triphenyl-3-phenylacetamido-2-azetidinone 13 was also prepared similarly.

Previously we have reported[9] the stereoselective synthesis of α-substituted-β-alkylthio-β-lactams from acid chlorides and thioimidates and their desulfurization to *cis*-β-lactams. We have now extended the malonyl chloride approach to substituted 4-alkylthio-2-azetidinones. Thus, condensation of phenylmalonyl chloride with the thioimidates 16 and 17 produced 4-alkylthio-3-chlorocarbonyl-2-azetidinones (18,19) each as a single isomer The corresponding crystalline methyl ester β-lactams (20,21) were prepared by reaction with methanol. The stereochemistry of these β-lactams were not obvious from their NMR spectra Desulfurization of 20 and 21 with Raney nickel in acetone gave the α-carbomethoxy-β-lactam 22 which proved to be identical with the methyl ester of 8

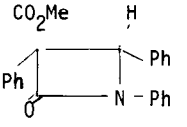
In an earlier publication[10] we have assigned the "E" configuration to 7 and 22 Raney nickel desulfurization has been shown to proceed with retention of configuration[9] The condensation of phenylmalonyl chloride with a thioimidate, therefore, produces a "Z"-β-lactam in which the alkylthio and the chlorocarbonyl groups are *cis* to each other.

It is well established that the Curtius rearrangement is characterized by retention of configuration. The α-amido β-lactams 12 and 13 must therefore have the "E" configuration placing the two phenyl groups *cis* to each other. The entire sequence for the formation of α-substituted-α-amido-β-lactams described here is thus stereospecific. On the basis of the available data it is difficult to make a broad generalization regarding the steric course of the substituted malonyl chloride-imines reaction, however, the COCl group of the acid chloride component does appear to induce stereoselectivity




16 Me

17 $CH_2Ph$

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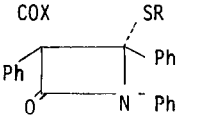


| | R | X |
|---|---|---|
| 18 | Me | Cl |
| 19 | $CH_2Ph$ | Cl |
| 20 | Me | OMe |
| 21. | $CH_2Ph$ | OMe |

Previously we have described several variations of the syntheses of β-lactams through the "acid chloride-imine" reaction[11] The present method in conjunction with the earlier ones should result in the stereospecific synthesis of a variety of new β-lactams with multiple functional groups.

All the new compounds reported in the communication have been characterized by satisfactory elemental and spectral analyses

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