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β-LACTAMS *via* CYCLOADDITION TO IMINOMALONATES[1]

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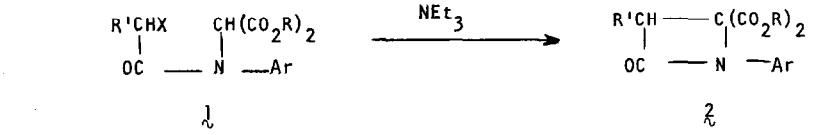
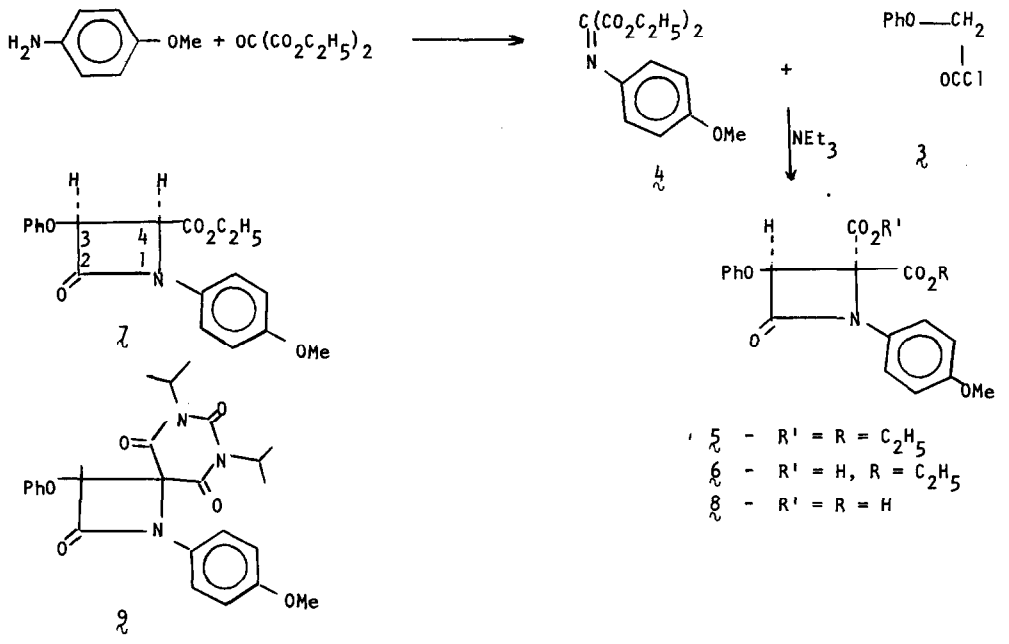
In 1950 Sheehan and Bose[2] reported a convenient synthesis of 4,4-dicarboxy-2-azetidinone 2 by the cyclization of α-haloamidomalonates 1. The intermediate 1 is readily available by the acylation of aminomalonates with a suitable α-halo acid but since this method cannot be extended to the preparation of α-amido or α-alkoxy β-lactams (2,R' = NHCOR" or OR"), we have devised an alternative approach which we describe here.

Condensation of ketomalonic acid esters proceeds smoothly with primary amines to give the imine 4 in high yield. In recent years we have used the reaction of a variety of acid chlorides with imines in presence of triethylamine to prepara β-lactams α-substituted[3] with functional groups such as N_3, OR, OCR, Br, etc. This acid chloride-triethylamine reaction proved equally applicable to the imine 4; thus, phenoxyacetyl chloride, triethylamine and 4 gave the desired β-lactam 5. The ester groups of 5 can be utilized for modifying the β-lactam: mild saponification of the diester β-lactam 5 produced the crystalline mono ester β-lactam 6 of "E" configuration because saponification of the carboethoxy group which is *trans* to the phenoxy group in 5 (and therefore less hindered) can be expected to proceed faster than that of the *cis* ester group. Decarboxylation of 6 in refluxing pyridine generated the *cis*-β-lactam 7 (J_{3H-4H}=5 Hz) suggesting thereby that decarboxylation had proceeded with retention of configuration. Since no epimerization could be expected under these mild conditions, the method reported here provides a facile pathway for the stereoselective synthesis of *cis*-3,4-disubstituted-2-azetidinones[4].

Treatment of 5 with two equivalents of sodium hydroxide in dioxane led to 4,4-dicarboxy azetidinone 8 in 35% yield, a versatile intermediate in the synthesis of N-substituted aspartic acid derivatives[2,5]. β,β-Dicarboxy-β-lactam 8 was also utilized for the synthesis of the spiro-β-lactam barbiturate 9 through condensation with diisopropyl carbodiimide in 17% yield. Substituted barbituric acids are of course of considerable current interest in medicinal chemistry. In the light of our earlier work it can be expected that various analogs of 5 will

be available through the use of different acid chlorides in the annelation step.





References

1. Part XXXVIII "Studies on Lactams". For part XXXVII see A.K. Bose, J.C. Kapur, S.G. Amin, and M.S. Manhas, *Tetrahedron Lett.*, 1917 (1974).
2. J.C. Sheehan and A.K. Bose, *J. Amer. Chem. Soc.*, 72, 5158 (1950).
3. A.K. Bose, Y.H. Chiang, and M.S. Manhas, *Tetrahedron Lett.*, 4091 (1972).
4. The hydrolysis step gave low yield of 6, no effort was made at this time to determine the optimum conditions.
5. T. Okawara and K. Harada, *J. Org. Chem.*, 37, 3286 (1972).

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