CHEMISTRY LETTERS, pp. 1465 - 1466, 1984.

A CONVENIENT METHOD FOR THE CONSTRUCTION OF β-LACTAM COMPOUNDS FROM β-AMINO ACIDS USING 2-CHLORO-1-METHYLPYRIDINIUM IODIDE AS CONDENSING REAGENT

Huamin HUANG, Nobuharu IWASAWA, and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

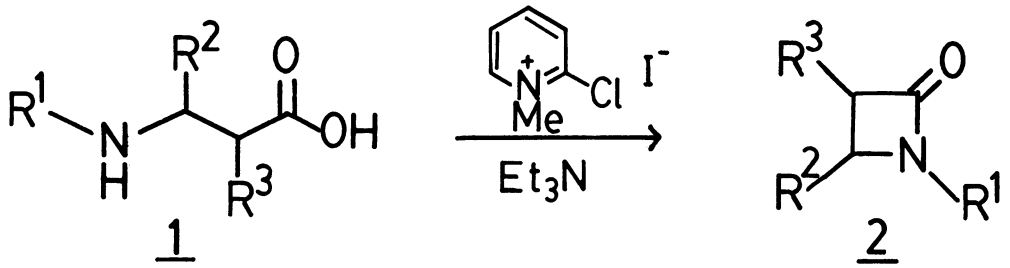
Various β-lactams are prepared from the corresponding β-amino acids under mild reaction conditions in high yields by employing 2-chloro-1-methylpyridinium iodide as a condensing reagent.

β-Lactam compounds have long been attracting much interest as a synthetic target for the organic chemists because of their biological activity and unique four-membered cyclic structure. One of the most fundamental approaches to the construction of β-lactams is the dehydration of β-amino acids.[1] However, β-lactam ring is rather sensitive to acidic or basic reaction conditions, and the usefulness of known methods for this purpose is limited because the yields are widely dependent on the structural features of a substrate, and furthermore β-elimination reaction proceeds simultaneously when drastic reaction conditions are employed.[1] Thus, a general method for the preparation of β-lactams from β-amino acids under mild reaction conditions is required, and a variety of condensing reagents and reaction conditions are examined during recent years.

The most commonly employed method is the DCC method, but the yields are not necessarily high.[2] More recently the Ph_3P-$(PyS)_2$ method is employed, but according to this reaction, rather high reaction temperature and tedious purification of the product are necessary.[3]

In this communication, we wish to report a new and convenient method for the construction of β-lactam skeleton, under mild reaction conditions, starting from β-amino acid by using 2-chloro-1-methylpyridinium iodide as a condensing reagent.[4]

Thus, according to the previously mentioned procedure,[5] to a dichloromethane suspension (48 ml) of 3-benzylaminopropanoic acid (1 mmol) and 2-chloro-1-methylpyridinium iodide (1.1 mmol) was added, in one portion, a dichloromethane solution (2 ml) of Et_3N (2.2 mmol), and the reaction mixture was stirred for 2 h at room temperature. Evaporation of the solvent, followed by purification of the residue by silica-gel thin layer chromatography, afforded the corresponding β-lactam in 95% yield. We next examined the reactions of various β-amino acids and the results are summarized in Table 1.



1

a. R^1=$PhCH_2$, R^2=Me, R^3=H, d. R^1=$PhCH_2$, R^2=R^3=H,
b. R^1=$PhCH_2$, R^2=n-C_3H_7, R^3=H, e. R^1=R^3=H, R^2=Ph,
c. R^1=$PhCH_2$, R^2=H, R^3=Me, f. R^1=R^3=H, R^2=Me.

Table 1.

Substrate	Solvent	Reaction conditions	Concentration/M	Yield/%
1a	CH_2Cl_2	room temp, 2 h	0.02	95
1b	CH_2Cl_2	room temp, 2 h	0.01	94
1c	CH_2Cl_2	room temp, 2 h	0.01	83
1c	CH_2Cl_2	room temp, inverse addition[a)]	0.01	90
1d	CH_2Cl_2	room temp, 1 h	0.01	60
1d	CH_2Cl_2	room temp, inverse addition[a)]	0.01	86
1e	CH_3CN	reflux, 3 h	0.01	89
1f	CH_3CN	reflux, 2.5 h	0.01	87

a) β-Amino acid is added to a suspension of 2-chloro-1-methylpyridinium iodide and triethylamine over 1 h and further stirred for another 1 h at room temperature.

It is noted that, in every case examined, β-lactams are obtained in good yields compared to the conventional methods.

The noteworthy features of this method are as follows:

1) the reaction proceeds under mild reaction conditions,

2) β-lactams and 1-methyl-2-pyridone are the only detectable products and purification of the products is quite easy.

We are currently examining the reaction of functionalized β-amino acid and its application to the synthesis of natural β-lactam antibiotics.

References

1) J. C. Sheehan and E. J. Corey, Org. React., 9, 388 (1957).

2) D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger, Tetrahedron Lett., 1980, 2783; T. Kametani, S. Huang, S. Yokohama, Y. Suzuki, and M. Ihara, J. Am. Chem. Soc., 102, 2060 (1980).

3) S. Kobayashi, T. Iiomri, T. Izawa, and M. Ohno, J. Am. Chem. Soc., 103, 2406 (1981).

4) T. Mukaiyama, Angew. Chem., Int. Ed. Engl., 18, 707 (1979).

5) E. Bald, K. Saigo, and T. Mukaiyama, Chem. Lett., 1975, 1163.

(Received June 12, 1984)