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A NOVEL METHOD FOR THE SYNTHESIS OF β-LACTAMS BY MEANS OF PHASE TRANSFER SYSTEM

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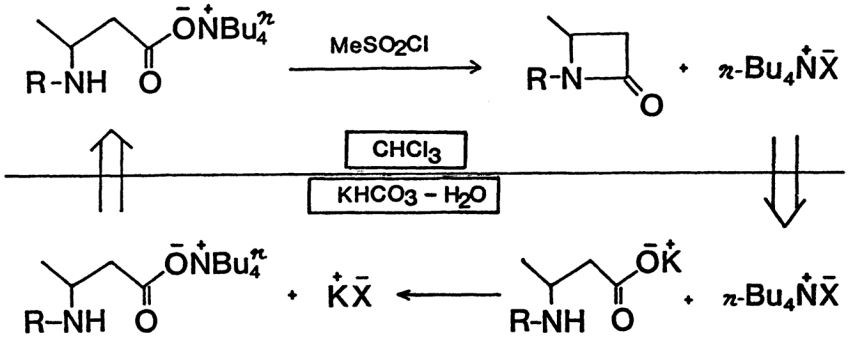
The reaction of β-amino acids with methanesulfonyl chloride in a chloroform-water bilayer system in the presence of 15 mol% of tetrabutylammonium hydrogen sulfate gives the corresponding β-lactams in good yields.

In our previous papers,[1] we have reported an efficient method for the synthesis of peptides using carboxyl components as their quaternary ammonium salts. Recently, we also described a convenient synthetic method of carboxamides and peptides employing phase transfer technique.[2]

In this communication, we wish to describe a new and convenient synthetic method of β-lactams starting from β-amino acids. In this kind of reaction, intramolecular dehydration of β-amino acids is generally accompanied with intermolecular side reactions leading to straight chain and cyclic oligomers, even though such a reaction is usually carried out under diluted condition.[3] In order to resolve this problem our effort was devoted to introduce the concept of phase transfer system. This basis is that quantity of β-amino acid staying in an organic



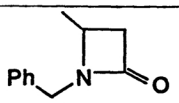
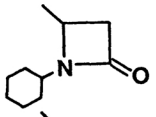
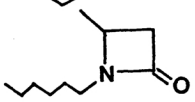
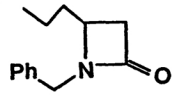
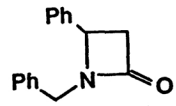
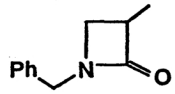
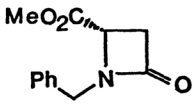
(reaction phase) and water (innert phase) phases is controlled by a phase transfer catalyst, resulting in realization of a system equivalent to a high dilution technique. Thus, β-lactams were obtained in good yields when the reaction of β-amino acids with methanesulfonyl chloride was carried out in chloroform-water bilayer system containing a quaternary ammonium salt and potassium hydrogencarbonate.

General experimental procedure is as follows: To a mixture of a β-amino acid (1 mmol), $KHCO_3$ (4 mmol), and a quaternary ammonium salt (15 mol%) were added water (1~1.5 ml) and a chloroform (4~5 ml) solution of methanesulfonyl chloride (2 mmol).

After being stirred for about 24 h, the reaction mixture was partitioned to organic and aqueous layers by addition of ethyl ether and water, and the organic layer was washed with saturated brine and dried. The β-lactam thus formed was isolated by silica gel chromatography or distillation.

The results are summarized in Table. Of several ammonium salts, tetrabutylammonium hydrogensulfate (5-30 mol%) gave good results as a phase transfer catalyst. However, use of 50 mol% of the sulfate decreased dramatically the yield of 1-cyclohexyl-4-methyl-2-azetidinone. Moreover, treatment of tetrabutylammonium 3-benzylaminobutyrate, prepared prior to the reaction,[1b] with methanesulfonyl chloride in the presence of $KHCO_3$ in chloroform (5 ml / 1 mmol acid) resulted in the formation of only 28% of the corresponding β-lactam along with intermolecular reaction products.

Table. Synthesis of β-lactams from β-amino acids

β-Lactam	Quaternary salt (mol%)	Yield, %
	$n\text{-}Bu_4\overset{+}{N}\overset{-}{Br}$ (15)	68
	$n\text{-}Bu_4\overset{+}{N}H\overset{-}{SO_4}$ (15)	87
	$n\text{-}Bu_4\overset{+}{N}\overset{-}{Br}$ (30)	48
	$n\text{-}Bu_4\overset{+}{N}H\overset{-}{SO_4}$ (15)	81
	$n\text{-}Bu_4\overset{+}{N}H\overset{-}{SO_4}$ (50)	59
	$n\text{-}Bu_4\overset{+}{N}H\overset{-}{SO_4}$ (15)	80
	$n\text{-}Bu_4\overset{+}{N}H\overset{-}{SO_4}$ (15)	84
	$n\text{-}Bu_4\overset{+}{N}H\overset{-}{SO_4}$ (15)	82
	$(n\text{-}C_8H_{17})_3\overset{+}{N}Me\overset{-}{Cl}$ (15)	79
	$n\text{-}Bu_4\overset{+}{N}H\overset{-}{SO_4}$ (15)	60

These results suggest that the present phase transfer technique for the intramolecular cyclization replaces a commonly employed high dilution technique. Consequently, the present procedure would provide a convenient method for the synthesis of β-lactams staring from β-amino acids.[4] This system may be also applicable to the preparation of macrocyclic compounds. Investigation along this line are now in progress.

References and Note

1) (a) T. Mukaiyama, N. Morito, and Y. Watanabe, Chem. Lett., 1979, 1305;
(b) Y. Watanabe, N. Morito, K. Kamekawa, and T. Mukaiyama, ibid., 1981, 65.
2) Y. Watanabe and T. Mukaiyama, Chem. Lett., 1981, 285.
3) F. Moll, Arch. Pharm. (Weinhein, Ger.), 301, 230 (1968).
4) Recently, Takahata et al. reported the transformation of β-bromopropionamides to the β-lactams utilizing a phase transfer system. In the reaction, a dilution technique is required because all of the reacting substrate exist in the reaction phase irrespective of the quantity of the catalyst: H. Takahata, Y. Ohnishi, and T. Yamazaki, Heterocycles, 14, 467 (1980).

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