

Phase Transfer Catalytic Synthesis of β -Lactams from β -Amino Acids

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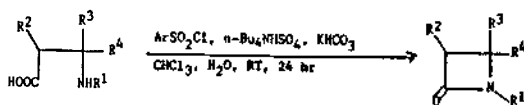
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Among a wide variety of coupling reagents developed for the construction of β -lactams from β -amino acids¹, phase transfer catalytic system utilizing methanesulfonyl chloride-quaternary ammonium salts² is unique in terms of the small quantity of the solvent employed. This catalytic system continuously maintains the concentration of the β -amino acids in a small quantity of organic solvent so low that it is practically equivalent to the usual high dilution system which requires large quantity of the solvent for the intramolecular cyclization reaction.

In connection with our research program directed toward the development of new synthetic methodologies for the formation of β -lactam derivatives from β -amino acids, we have examined several phase transfer catalytic systems by employing different arylsulfonyl chlorides such as benzenesulfonyl chloride, p-toluenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride and 4-methoxybenzenesulfonyl chloride in the presence of catalytic amounts (10 mol%) of tetrabutylammonium hydrogensulfate and compared the results.



The representative experimental procedure is as follows: To a mixture of 3-benzylamino-3-methylbutanoic acid (620 mg, 3 mmol), potassium hydrogencarbonate (1.20 g, 12 mmol) and tetrabutylammonium hydrogensulfate (34 mg, 10 mol%) were added successively water (5 ml) and a solution of 4-nitrobenzenesulfonyl chloride (1.33 g, 6 mmol) in chloroform (15 ml). After being stirred for 24 hr at room temperature, the reaction mixture was partitioned to organic and aqueous layers by addition of more water and chloroform, and the organic layer was washed with brine. Usual work-up and column chromatography on silica gel afforded 1-benzyl-4,4-dimethyl-2-azetidinone (533 mg, 94% yield) as an oil.

Some experimental results are summarized in Table. As can be realized, N-substituted β -amino acids were cyclized to

Table. Synthesis of β -Lactams from β -Amino Acids

Description	Isolated Yields (%)		
	PhSO ₂ Cl	4-CH ₃ -PhSO ₂ Cl	4-NO ₂ -PhSO ₂ Cl
R ¹ = CH ₂ Ph, R ² = H, R ³ = R ⁴ = CH ₃	94	91	94
R ¹ = CH ₂ Ph, R ² = R ⁴ = H, R ³ = CH ₃	86	94	90
R ¹ = CH ₂ Ph, R ² = CH ₃ , R ³ = R ⁴ = H	73	71	80
R ¹ = CH ₂ Ph, R ² = R ⁴ = H, R ³ = CO ₂ CH ₃	53	59	67
R ¹ = CH ₂ Ph, R ² = R ⁴ = H, R ³ = CO ₂ Ph	67	61	74
R ¹ = <i>c</i> -C ₆ H ₁₁ , R ² = R ⁴ = H, R ³ = CH ₃	68	64	78
R ¹ = <i>c</i> -C ₆ H ₁₁ , R ² = CH ₃ , R ³ = R ⁴ = H	65	62	72
R ¹ = R ² = H, R ³ = R ⁴ = CH ₃	33	30	35

the corresponding β -lactams in excellent yields but N-unsubstituted β -amino acids gave very poor results. Of the three arylsulfonyl chlorides, the most reactive 4-nitrobenzenesulfonyl chloride gave the best results, benzenesulfonyl chloride the next, and the least reactive p-toluenesulfonyl chloride relatively poor results. 4-Methoxybenzenesulfonyl chloride was also employed for the reaction but it was rapidly hydrolyzed under this reaction condition. Extension of the present study to include other coupling reagents for β -lactam formation is in progress.

Acknowledgement. The financial support of this research from Basic Science Research Institute administered by the Ministry of Education is gratefully acknowledged.

References

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