

**Table 1.** Transport of Amino Derivatives by Calix[6]arene Ester

Amino acid derivatives	Transport rate $\times 10^5$ (mol/h/cm <sup>2</sup> )				
	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Cs <sup>+</sup>	(CH <sub>3</sub> ) <sub>4</sub> N <sup>+</sup>
Bz-Gly	—	—	1.2	1.5	1.2
Bz-Ala	—	1.7	1.4	7.0	1.3
Bz-Val	—	1.1	4.1	10.9	1.7
Bz-Trp	1.0	1.0	4.2	9.9	2.4
Bz-Phe	1.9	5.4	23.0	38.6	9.0

Transport condition: Source phase; N-Bz amino acid (0.25 mmol), cation chloride (1.0 mmol) in 0.1 N LiOH (10 ml). Membrane; carrier (0.05 mmol) in CHCl<sub>3</sub> (15 ml). Receiving phase; deionized water (10 ml). The amount of transported amino acid was determined by UV spectrophotometry. (—): Not measurable.

For a given amino acid, the transport rate increases with increasing size of the metal cation employed (Li<sup>+</sup> < Na<sup>+</sup> < K<sup>+</sup> < Cs<sup>+</sup>) besides tetramethylammonium (TMA) cation, which is known to act as a specific blocker for potassium channel in plasma membrane.<sup>7</sup> Although transport efficiency of amino acids with TMA cation is lower than those with K<sup>+</sup> and Cs<sup>+</sup>, it is still significant. The preliminary extraction efficiency of N-Bz amino acids in dichloromethane containing the carrier, modelling partition of guests between the aqueous feed phase and the liquid membrane, demonstrated a similar trend with the transport rate obtained. Thus, the high transport efficiency for TMA cation is seemingly due to the specific interaction between TMA and the carrier.

The possible interaction between TMA and the carrier was confirmed by following observations. First, the CPK model demonstrates that TMA fits well to the pseudocavity of the carrier surrounded by oxygen atoms of phenyl ether and ester carbonyls. Secondly, in <sup>1</sup>H NMR titration of the picrate salt of TMA with the carrier in CDCl<sub>3</sub>, methyl proton resonance of TMA was shifted upfield from 3.54 to 2.18 ppm with sharp break indicating 1:1 stoichiometry. Thirdly, in UV titration of TMA-picric acid salt with carrier in THF, a large bathochromic shift from 368 to 382 nm was also observed. The  $\lambda_{max}$  of 368 nm of the uncomplexed picric acid suggests the relative looseness of TMA-picric acid ion pair in THF compared to those of the metal picric acid salts (cf 357 nm for K<sup>+</sup> picric acid<sup>3</sup> and 362 nm for Cs<sup>+</sup> picric acid<sup>8</sup>). On the other hand, the  $\lambda_{max}$  of 382 nm denotes a typical solvent separated ion-pair state<sup>8</sup> of TMA-picric acid salt, which manifests the complete encapsulation of TMA cation by carrier. All these observations cited above demonstrate the specific interaction between the carrier and TMA cation, which results in the significant transport behavior.

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## Cyclization of $\beta$ -Amino Acids to $\beta$ -Lactams by Using Diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl)phosphonate

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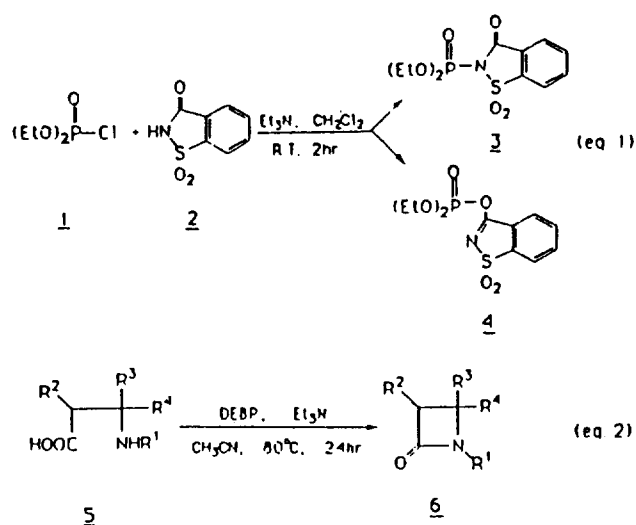
A great deal of synthetic work has been already carried out in the formation of  $\beta$ -lactams from  $\beta$ -amino acids. One of the popular synthetic method for the  $\beta$ -lactam formation is based on the intramolecular cyclization of  $\beta$ -amino acids using coupling reagents.<sup>1</sup> Among various organophosphorus coupling reagents currently available, triphenylphosphone-tetrahalomethane<sup>2</sup>, triphenylphosphine/2,2'-dipyridyl disulfide<sup>3</sup>, bis[5'-nitro-2'-pyridyl]-2,2,2-trichloroethylphosphate<sup>4</sup>, N,N'-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride<sup>5</sup>, tris[2-oxo-3-oxazolinyl]phosphine oxide<sup>6</sup>, and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate<sup>7</sup> are the most effective and reliable.

In connection with our on going research program directed toward the development of new synthetic methodologies for the formation of  $\beta$ -lactam derivatives from  $\beta$ -amino acids, we have examined the  $\beta$ -lactam formation from  $\beta$ -amino acids using diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl) phosphonate (DEBP reagent, **3**). It has been reported that DEBP reagent in the effective coupling reagent for the synthesis of amides, esters, and thioesters.<sup>8</sup> On the other hand, there are no reports on the application DEBP reagent for  $\beta$ -lactam formation from  $\beta$ -amino acids. In this paper, we wish to report a new method for the preparation of  $\beta$ -lactam derivatives (**6**) from  $\beta$ -amino acids (**5**) by using DEBP reagent.

DEBP reagent was conveniently obtained by the reaction of diethyl chlorophosphate (**1**) with 3-oxo-2,3-dihydro-1,2-benzisosulfonazole (Saccharin, **2**), and triethylamine in dichloromethane at room temperature for 2 hr (eq. 1). Phosphorylation of **2** might be expected to give either the O- or N-phosphoryl product, because of its well-known tautomerism. The reaction of **1** with **2** in dichloromethane at 25 °C gave preferentially N-phosphoryl product **3**. The struc-

**Table 1.** Synthesis of  $\beta$ -Lactams from  $\beta$ -Amino Acids

Description	Isolated yield (%)
$R^1 = \text{CH}_2\text{Ph}$ , $R^2 = \text{H}$ , $R^3 = R^4 = \text{CH}_3$	98
$R^1 = \text{CH}_2\text{Ph}$ , $R^2 = R^3 = \text{H}$ , $R^4 = \text{CH}_3$	68
$R^1 = \text{CH}_2\text{Ph}$ , $R^2 = \text{CH}_3$ , $R^3 = R^4 = \text{H}$	62
$R^1 = \text{CH}_2\text{Ph}$ , $R^2 = R^3 = \text{H}$ , $R^4 = \text{CH}_2\text{CH}_3$	72
$R^1 = \text{CH}_2\text{Ph}$ , $R^2 = R^3 = \text{H}$ , $R^4 = \text{CH}_2\text{CH}_2\text{CH}_3$	84
$R^1 = \text{CH}_2\text{Ph}$ , $R^2 = R^3 = \text{H}$ , $R^4 = \text{CO}_2\text{CH}_2\text{Ph}$	60
$R^1 = \text{CH}_2\text{Ph}$ , $R^2 = R^3 = \text{H}$ , $R^4 = \text{CO}_2\text{CH}_3$	57
$R^1 = \text{CH}_2\text{Ph}$ , $R^2 = R^3 = R^4 = \text{H}$	20
$R^1 = \text{CH}_2\text{Ph}$ , $R^2 = R^3 = \text{H}$ , $R^4 = \text{Ph}$	82
$R^1 = \text{CH}_2\text{CH}_2\text{Ph}$ , $R^2 = R^3 = \text{H}$ , $R^4 = \text{CH}_3$	53
$R^1 = \text{CH}_2\text{CH}_2\text{Ph}$ , $R^2 = \text{H}$ , $R^3 = R^4 = \text{CH}_3$	83



ture of DEBP(3) was assigned on the basis of Infrared spectroscopy. The IR spectrum showed the carbonyl absorption band at  $1740\text{ cm}^{-1}$ . The reagent 3 is a white crystalline solid melting at  $108\text{--}109^\circ\text{C}$  and can be stored in a refrigerator for several weeks without any decomposition, and is generally used without further purification.

The representative experimental procedure is as follows (eq. 2); To a mixture of 3-benzylamino-3-methylbutanoic acid (310 mg, 1.5 mmol) and DEBP reagent (585 mg, 1.8

mmol) in acetonitrile (150 mL) was added triethylamine (360 mg, 3.6 mmol) at room temperature. After being stirred for 24 hr at  $80^\circ\text{C}$ , the reaction mixture was concentrated under reduced pressure and the residue was passed through silica gel column using ether-chloroform (2:1) as an eluent to yield 1-benzyl-4,4-dimethyl-2-azetidinone (278 mg, 98% yield) as an oil.

We have briefly studied solvent effects using 3-benzyl-amino butanoic acid, 1.2 equivalent of DEBP reagent and triethylamine at  $80^\circ\text{C}$  for 24 hr. Among various solvents employed in this study, acetonitrile gave the best results, yielding 68 of 1-benzyl-4-methyl-2-azetidinone. Dichloromethane and tetrahydrofuran were much less effective, yielding the corresponding  $\beta$ -lactam in 56% and 64% yield, respectively.

Some experimental results are summarized in Table 1. As can be realized, N-substituted  $\beta$ -amino acids were cyclized to the corresponding  $\beta$ -lactams in good yields but N-unsubstituted  $\beta$ -amino acids gave very poor results. Extension of the present study to include other coupling reagents for  $\beta$ -lactam formation is in progress.

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