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

Amino acid derivatives	Transport rate × 10^5 (mol/h/cm^2)				
	Li^+	Na^+	K^+	Cs^+	$(CH_3)_4N^+$
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 m*l*). Membrane; carrier (0.05 mmol) in $CHCl_3$ (15 m*l*). Receiving phase; deionized water (10 m*l*). 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 ($Li^+ < Na^+ < K^+ < Cs^+$) besides tetramethylammonium (TMA) cation, which is known to act as a specific blocker for potassium channel in plasma membrane.[7] Although transport efficiency of amino acids with TMA cation is lower than those with K^+ and Cs^+, 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 ^1H NMR titration of the picrate salt of TMA with the carrier in $CDCl_3$, 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-picrate salt with carrier in THF, a large bathochromic shift from 368 to 382 nm was also observed. The λ_{max} of 368 nm of the uncomplexed picrate suggests the relative looseness of TMA-picrate ion pair in THF compared to those of the metal picrate salts (cf 357 nm for K^+ picrate[3] and 362 nm for Cs^+ picrate–)[8]. On the other hand, the λ_{max} of 382 nm denotes a typical solvent separated ion-pair state[8] of TMA-picrate 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 β-Amino Acids to β-Lactams by Using Diethyl 2-(3-oxo-2,3,-dihydro-1,2-benzisosulfonazolyl)phosphonate

Young Haeng Lee*, Won Sik Choi*, and Dong-Seok Lho†

Department of Chemistry, Won Kwang University, Iri 570-749

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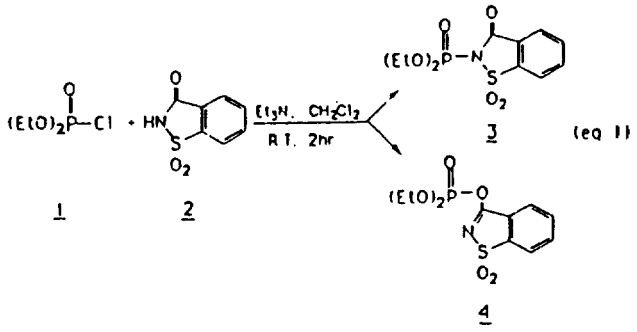
A great deal of synthetic work has been already carried out in the formation of β-lactams from β-amino acids. One of the popular synthetic method for the β-lactam formation is based on the intramolecular cyclization of β-amino acids using coupling reagents.[1] Among various organophonsphorus coupling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

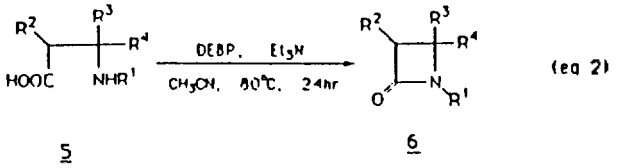
In connection with our on going research program directed toward the development of new synthetic methodoligies for the formation of β-lactam derivatives from β-amino acids, we have examined the β-lactam formation from β-amino acids using diethyl 2-(3-oxo-2,3-dihydro-1,2-benzisosulfonazolyl phosphonate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

Description	Isolated yield (%)
$R^1=CH_2Ph$, $R^2=H$, $R^3=R^4=CH_3$	98
$R^1=CH_2Ph$, $R^2=R^3=H$, $R^4=CH_3$	68
$R^1=CH_2Ph$, $R^2=CH_3$, $R^3=R^4=H$	62
$R^1=CH_2Ph$, $R^2=R^3=H$, $R^4=CH_2CH_3$	72
$R^1=CH_2Ph$, $R^2=R^3=H$, $R^4=CH_2CH_2CH_3$	84
$R^1=CH_2Ph$, $R^2=R^3=H$, $R^4=CO_2CH_2Ph$	60
$R^1=CH_2Ph$, $R^2=R^3=H$, $R^4=CO_2CH_3$	57
$R^1=CH_2Ph$, $R^2=R^3=R^4=H$	20
$R^1=CH_2Ph$, $R^2=R^3=H$, $R^4=Ph$	82
$R^1=CH_2CH_2Ph$, $R^2=R^3=H$, $R^4=CH_3$	53
$R^1=CH_2CH_2Ph$, $R^2=H$, $R^3=R^4=CH_3$	83





ture of DEBP(3) was assigned on the basis of Infrared spectroscopy. The IR spectrum showed the carbonyl absorption band at 1740 cm^{-1}. The reagent 3 is a white crystalline solid melting at 108–109 °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 a 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 m*l*) was added triethylamine (360 mg, 3.6 mmol) at room temperature. After being stirred for 24 hr at 80 °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-benzylamino butanoic acid, 1.2 equivalent of DEBP reagent and triethylamine at 80 °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 β-lactam in 56% and 64% yield, respectively.

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

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