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A One-Pot Synthesis of β-Lactams by the Reaction of β-Haloacyl Chlorides with α-Amino Acids[1)]

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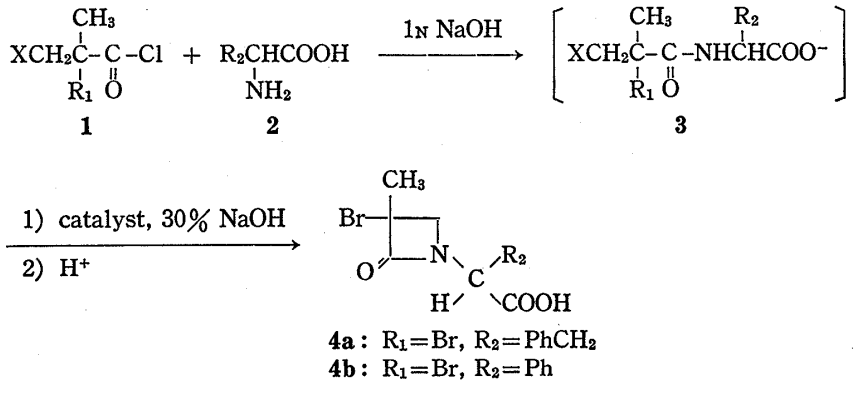
A one-pot synthesis of β-lactams (**4**) was successfully achieved by the reaction of β-haloacyl chlorides (**1**) with α-amino acids (**2**) in aqueous 5% sodium hydroxide solution in the absence of phase transfer catalyst in yields of 43—91%.

Keywords——β-lactam; one-pot synthesis; α-amino acid; β-haloacyl halide; intramolecular *N*-alkylation

The synthesis of β-lactams has been achieved by a variety of methods,[2)] in which anhydrous conditions were generally required. Kay[3)] reported the synthesis of α-methylene-β-lactam from 3-bromo-2-bromoethylpropionamide in a mixture of benzene and aqueous 40% sodium hydroxide solution with benzyltriethylammonium chloride (BTEAC) as a phase transfer catalyst. Recently, Yamazaki[4)] succeeded in the preparation of β-lactams from *N*-alkyl-β-halocarboxamides under anhydrous phase transfer conditions using powdered potassium hydroxide.

In the present study, we wish to report a one-pot synthesis of β-lactams from β-haloacyl chlorides and α-amino acids in aqueous sodium hydroxide solution and benzene or dichloromethane in the presence and absence of phase transfer catalysts. We found that α,β-dibromo-α-methylpropionyl chloride (**1**) reacted with (*S*)-phenylalanine (**2**, R_2=$PhCH_2$) and (*R*)-phenylglycine (**2**, R_2=Ph) in a mixture of aqueous 30% sodium hydroxide solution and dichloromethane in the presence of phase transfer catalysts to give the corresponding β-lactams (**4**) in one step in 45—65% yields, without isolation of the intermediate amides (**3**). The intermediates (**3**) were alternatively synthesized from **1** and **2**, by the Schotten-Bauman method, followed by intramolecular *N*-alkylation in a mixture of aqueous 30% sodium hydroxide solution and dichloromethane using BTEAC and a strongly basic ion exchange resin (Duolite A-109, Cl^- form, polystyrene quarternary type I, Diamond Shamrock Co.). The resulting β-lactams (**4**) were easily isolated by acidifying the solution with concentrated hydrochloric acid. The results are shown in Table I.



4a: R_1=Br, R_2=$PhCH_2$
4b: R_1=Br, R_2=Ph

Chart 1

Table I. The Preparation of β-Lactams (4)

	Catalyst	React. time (h)	Temp.	mp (°C)	Yield (%)
4a	BTEAC	24	r.t.	146	58
4a	Duolite A-109	24	r.t.	146	65
4b	BTEAC	24	r.t.	149	45
4b	Duolite A-109	24	r.t.	149	54

BTEAC: benzyltriethylammonium chloride
Duolite A-109: a strongly basic ion exchange resin

From the integration intensity in the ^{1}H-NMR spectra, crude **4a** was determined to contain almost equal amounts of the diastereoisomers, and upon recrystallization of crude **4a** from *n*-hexane-benzene the ratio changed to 95 : 5.

Next, we examined the influence of the concentration of aqueous sodium hydroxide on the yield of **4a**. In general, highly concentrated sodium hydroxide solution is used in the phase transfer reaction. When the reaction of **1** with **2** (R_2=$PhCH_2$) was carried out in three different concentrations of sodium hydroxide solution (30, 15, and 5%) in the presence of BTEAC, the yields of **4a** were 58, 61, and 91%, respectively, as shown in Table II.

Table II. Influence of the Concentration of NaOH on the Yield of **4a**

Concentration of NaOH	React. time (h)	Temp.	Yield (%)
30%	24	r.t.	58
15%	24	r.t.	61
5%	24	r.t.	91

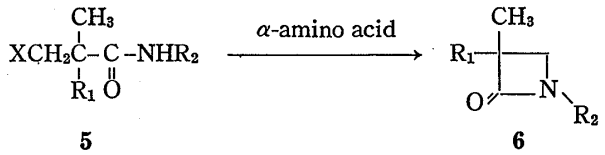
The yield of **4a** significantly increased at low concentration rather than high concentration. This result shows that highly concentrated sodium hydroxide solution is not necessary in this reaction.

To investigate the effect of the phase transfer catalyst, the reaction of **1** with **2** (R_2=$PhCH_2$) was carried out under the same conditions in the absence of the catalyst. Suprisingly, the reaction proceeded successfully to give **4** in 58% yield. This result suggests that the catalyst may not participate in the promotion of the reaction and α-amino acid may be effective for this. In order to test this assumption, we attempted the cyclization of *N*-α,β-dibromo-α-methylpropionyl (*S*)-phenylanine (**3**, X=R_1=Br, R_2=$PhCH_2$) to β-lactam (**4**, R_1=Br, R_2=$PhCH_2$) under the following three conditions: 1) in the absence of any catalyst, 2) in the presence of BTEAC, and 3) in the presence of phenylalanine. The results are shown in Table III.

Table III. The Cyclization of **3a** to **4a** in the Absence and Presence of Catalyst

Catalyst	React. time (h)	Temp.	Yield (%)
None	24	r.t.	0
BTEAC	24	r.t.	79
(*S*)-Phenylalanine	24	r.t.	66

The cyclization to **4a** did not occur in the absence of any catalyst. On the other hand, BTEAC and phenylalanine obviously exhibited a promoting effect. Subsequently, we examined the catalytic effect of several other α-amino acids in the cyclization of *N*-benzyl α,β-dibromo-α-methylpropionamide[5] (**5**, X=R_1=Br, R_2=$PhCH_2$) and *N*-phenyl β-chloro-



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X=Br, Cl R_1=Br, CH_3 R_2=$PhCH_2$, Ph

Chart 2

α,α-dimethylpropionamide[5] (**5**, X=Cl, R_1=CH_3, R_2=Ph) to the corresponding β-lactams (**6**). The reaction was performed by adding a catalytic amount of the α-amino acids.

The results are shown in Table IV.

Table IV. The Effect of α-Amino Acids as the Catalyst in the Cyclization of β-Halocarboxamides (**5**) to β-Lactams (**6**)

X	R_1	R_2	α-Amino acid	React. time (h)	Yield (%)
Br	Br	$PhCH_2$	Phenylalanine	100	89
Br	Br	$PhCH_2$	Alanine	100	34
Br	Br	$PhCH_2$	Isoleucine	100	91
Br	Br	$PhCH_2$	Serine	100	96
Br	Br	$PhCH_2$	Methionine	100	88
Br	Br	$PhCH_2$	Aspartic acid	100	45
Br	Br	$PhCH_2$	Ornithine	100	43
Cl	CH_3	Ph	Isoleucine	95	98
Cl	CH_3	Ph	Serine	95	92

From these results, it is clear that the α-amino acids effectively participate in the cyclization to the β-lactams (**6**), though the effect depended on the species of the α-amino acids. Quarternary ammonium halide derived from the α-amino acid and **3** in the course of the reaction may function as a phase transfer catalyst.

The one-pot synthesis of β-lactams (**4**) by the reaction of **1** with **2** was also carried out using a slight excess of **2**, and as expected, **4** was obtained with yields in the range of 31—76%. The results are shown in Table V.

Table V. The Preparation of β-Lactams (**4**)

4	X	R_1	R_2	React. time (h)	Temp.	mp (°C)	Yield (%)
a	Br	Br	$PhCH_2$	24	r.t.	146	76
b	Br	Br	Ph	24	r.t.	149	75
c	Br	Br	CH_3	24	r.t.	124—125	31
d	Br	Br	$(CH_3)_2CH$	24	r.t.	oil	75[a]
e	Cl	CH_3	$PhCH_2$	24	r.t.	103—104	66
f	Cl	CH_3	Ph	24	r.t.	104—105	57

a) Crude compound, which was identified by esterification with benzyl bromide.

This one-pot synthesis of β-lactams is noteworthy because of its simplicity. Further detailed studies are in progress.

Experimental

All the melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 grating infrared spectrometer. Nuclear magnetic resonance (^{1}H-NMR) spectra were determined with a JEOL C-60H high resolution NMR instrument. Mass spectra were measured with a JEOL-01 SG mass spectrometer.

α,β-Dibromo-α-methylpropionic Acid[5]——This compound was prepared from 2-methylpropenoic acid (43 g, 0.5 mol) and bromine (80 g, 0.5 mol) by Rhinesmith's method.[6] bp 106—109°C/3 mmHg, mp 43—46°C. Yield 95 g (77%).

α,β-Dibromo-α-methylpropionyl Chloride (1, X=R_1=Br)——This compound was obtained by refluxing α,β-dibromo-α-methylpropionic acid (73.5 g, 0.3 mol) in $SOCl_2$ (53.6 g, 0.45 mol) for 6 h. bp 83—85°C/25 mmHg. Yield 38.0 g (48%).

β-Chloro-α,α-dimethylpropionyl Chloride (1, X=Cl, R_1=CH_3)——This compound was obtained by refluxing β-chloropivalic acid (24.6 g, 0.18 mol) in $SOCl_2$ (32.1 g, 0.29 mol). bp 110—112°C. Yield 14.5 g (52%).

***N*-(α,β-Dibromo-α-methylpropionyl)-(*S*)-phenylalanine (3, X=R_1=Br, R_2=$PhCH_2$)**——α,β-Dibromo-α-methylpropionyl chloride (1, X=R_1=Br) (5.2 g, 20 mmol) and 5% NaOH (16 ml) were gradually added to a stirred solution of (*S*)-phenylalanine (2, R_2=$PhCH_2$) (4.0 g, 24 mmol) in 5% NaOH (20 ml) under cooling with ice and water. The reaction mixture was stirred for 3 h at room temperature and kept alkaline by addition of small amounts of 5% NaOH. Et_2O (20 ml) was added to the mixture with agitation. The alkaline solution was acidified with 6 N HCl and extracted with $CHCl_3$ (30 ml×2). The extract was washed with H_2O (30 ml×2), and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the residue was used for the following reaction. One-third of the residue was esterified with benzyl alcohol according to Bocchi's method[7] to give the benzyl ester, which was purified by silica-gel column chromatography (benzene: AcOEt=19: 1). Overall yield 2.7 g (28%). IR ν_{max}^{film} cm^{-1}: 3320 (NH), 1740 (C=O), 1660 (C=O). *m/e*: 483 (M^+). NMR (δ) ($CDCl_3$): 1.93 and 1.98 (s, CH_3, 3H), 3.14 (d, CH_2, 2H, *J*=3.0 Hz), 3.84 (s, CH_2, 2H), 4.86 (q, CH, 1H, *J*=3.0 Hz), 5.15 (s, CH_2, 2H), 7.25 (m, arom×2 and NH, 11H). *Anal.* Calcd for $C_{20}H_{21}NO_3Br_2$: C, 49.71; H, 4.38; N, 2.30. Found: C, 49.91; H, 4.28; N, 2.93.

General Procedure for Preparation of β-Lactams (4 and 6)

1) **β-Lactams (4) from 1 and 2 in 30% NaOH in the Presence of BTEAC**——Compound 1 (X=Br, R_1=CH_3, 5 mmol) was gradually added to a solution of α-amino acid (5 mmol) in 1 N NaOH (12 ml) under cooling with ice and water. After the addition was over, the reaction mixture was stirred for 3 h at room temperature, and 30% NaOH (5 ml) and BTEAC (1 mmol) or Duolite A-109 Cl^- form (1 g) were added. The mixture

Table VI. β-Lactams (4)

4	IR $\nu_{max}^{KBr\ (film)}$ (cm^{-1})	^{1}H-NMR (δ) in $CDCl_3$	*m/e* (M^+)	Analysis (%) Calcd (Found) C	H	N
a	1760 (CONH) 1720 (COOH)	1.55 and 1.92 (s, CH_3, 3H), 3.31 (m, CH_2×2, 4H), 4.75 (d, CH, 1H, *J*=2.6 Hz), 7.27 (s, arom, 5H), 9.36 (s, COOH, 1H)	313 311	50.02 (50.01	4.52 4.44	4.49 4.32)
b	1760 (CONH) 1740 (COOH)	1.80 and 1.97 (s, CH_3, 3H), 3.63 (q, CH_2, 2H, *J*=3.0 Hz), 5.67 (s, CH, 1H), 7.38 (s, arom, 5H), 9.09 (s, COOH, 1H)	299 297	48.34 (48.49	4.06 3.97	4.70 4.73)
c	1760 (CONH) 1740 (COOH)	1.47 and 1.53 (d, CH_3, 3H, *J*=3.6 Hz), 1.95 (s, CH_3, 3H), 3.75 (m, CH_2, 2H), 4.55 (m, CH, 1H), 10.58 (s, COOH, 1H)	237 235	35.62 (35.68	4.27 4.10	5.93 5.84)
d[a]	1760 (CONH) 1740 ($COOCH_2Ph$)	0.96 (d, CH_3×2, 6H, *J*=3.5 Hz), 1.84 and 1.91 (s, CH_3, 3H), 2.18 (m, CH, 1H), 3.79 (m, CH_2, 2H), 4.24 (m, CH, 1H), 5.17 (s, CH_2,2H), 7.35 (s, arom, 5H)	355 353	54.25 (54.20	5.69 5.68	3.95 3.92)
e	1740 (CONH) 1700 (COOH)	1.00 and 1.22 (s, CH_3×2, 6H), 3.11 (m, CH_2 and $C\underline{H}_2Ph$, 4H), 4.75 (q, CH, 1H, *J*=2.5 Hz), 7.25 (s, arom, 5H), 8.20 (s, COOH, 1H)	247	67.99 (67.80	6.93 6.54	5.66 6.05)
f	1740 (CONH) 1720 (COOH)	1.22 and 1.37 (s, CH_3×2, 6H), 3.17 (q, CH_2, 2H, *J*=2.6 Hz), 5.67 (s, CH, 1H), 7.37 (s, arom, 5H), 10.33 (s, COOH, 1H)	233	66.93 (66.74	6.48 6.40	6.01 5.99)

a) As the benzyl ester derivative.

was stirred for 24 h at room temperature, acidified with 6 N HCl, and extracted with $CHCl_3$ (20 ml × 2). The extract was dried over anhydrous Na_2SO_4. After removal of $CHCl_3$, the residue was recrystallized from *n*-hexane–$CHCl_3$. The IR, ^{1}H-NMR, and mass spectral data are listed in Table VI.

2) **β-Lactams (6) from N-Benzyl α,β-Dibromo-α-methylpropionamide (5a, R_1=X=Br, R_2=PhCH$_2$) and *N*-Phenyl β-Chloro-α,α-dimethylpropionamide (5b, X=Cl, R_1=CH$_3$, R_2=Ph)**——α-Amino acid (1 mmol) and 50% NaOH (10 ml) were added to a solution of **5** (5 mmol) in benzene (20 ml). The mixture was stirred for the period shown in Table IV at room temperature. The benzene layer was separated, washed with H_2O (15 ml × 2), and dried over anhydrous Na_2SO_4. After removal of the benzene, the residue was recrystallized from *n*-hexane–benzene to give **6**, which was identified by comparison of the IR spectra with those of authentic samples.[5]

3) **β-Lactams (4a) from 1 and 2 in 5% NaOH in the Absence of Catalyst**——The reaction was performed using **1** (5 mmol) and a slight excess of **2** (5.5 mmol) in 5% NaOH (17 ml) under the conditions described in Table V. The product was purified by recrystallization from *n*-hexane–$CHCl_3$ and by silica-gel column chromatography (benzene: AcOEt=9: 1). The resulting **4a** was identical with the authentic benzyl ester. The spectral data are listed in Table VI.

References and Notes

1) A part of this study was reported as a communication. T. Okawara, Y. Noguchi, T. Matsuda, and M. Furukawa, *Chem. Lett.*, **1981**, 185.
2) *a*) J.C. Sheehan and E.J. Corey, Organic Reactions, **9**, 388 (1957); *b*) M.S. Manhas and A.K. Bose, "β-Lactams: Natural and Synthetic," Wiley-Interscience, New York, 1969; *c*) A.K. Mukerjee and A.K. Singh, *Synthesis*, **1975**, 547; *d*) P.G. Sammes, *Chem. Rev.*, **76**, 1 (1976); *e*) H.H. Wasserman, D.J. Hlasta, A.W. Tremper, and J.C. Wu, *Tetrahedron Lett.*, **1979**, 549.
3) S R. Fletcher and I.T. Kay, *Chem. Commun.*, **1978**, 903.
4) *a*) H. Takahata, Y. Ohnishi, and T. Yamazaki, *Heterocycles*, **14**, 467 (1980); *b*) H. Takahata, Y. Ohnishi, Takehara, K. Tsurutani, and T. Yamazaki, *Chem. Pharm. Bull.*, **29**, 1063 (1981).
5) T. Okawara, T. Matsuda, and M. Furukawa, *Chem. Pharm. Bull.*, **30**, 1225 (1982).
6) H.S. Rhinesmith, *Organic Reactions*, **2**, 177 (1943).
7) V. Bocchi, G. Casnati, A. Dossena, and R. Marchelli, *Synthesis*, **1979**, 957.