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Synthesis of Monocyclic β-Lactams via Cyclodehydration of β-Amino Acids Using $POCl_3$

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ABSTRACT

β-Lactams **2** have been synthesized through a convenient use of $POCl_3$ via cyclodehydration of β-amino acids **1**.

Key Words: β-Lactams; Cyclodehydration; β-Amino acids; Amide bond formation.

INTRODUCTION

Development of newer methods for the construction of appropriately substituted 2-azetidinones continues unawaited because of their therapeutic importance. There is resurgence of interest, because, this class of compounds

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can effectively inhibit proteases[1–4] and suppress induced inflammation in animal lungs.[5] They are also capable of offering protection against human leukemia, prostrate, and head and neck cancer by inducing DNA damage.[6]

Among many methods for the construction of β-lactam ring, one of the most useful ones involves dehydration of β-amino acids using various reagents. The chemistry began with the use of Grignard reagent[7] followed by thionyl chloride[8–11] in the presence of weak bases for alkyl and aryl substituted β-lactams. Later, acetic anhydride,[8] acetyl chloride-PCl_5,[12] and alanes[13] were proposed as cyclizing agents. More recently, β-amino acids have been converted to β-lactams using an array of reagents like ethylphosphorodichloridate,[14] phenylphosphorodichloridate,[15] methanesulfonyl chloride,[16] *N*-alkyl-2-benzothiazolylsulfenamide/Ph_3P,[17] phosphorodimorpholidic halides,[18] *N*,*N*-(diethoxyphosphinyl) benzo-1,2,5-thiazolidine-1, 1-dioxide,[19] and 3,3′-(phenylphosphoryl)-*bis*(1,3-thiazolidine-2-thione).[20]

In this paper, we report the synthesis of β-lactams from β-amino acids using the easily available and comparatively inexpensive reagent phosphorous oxychloride (Sch. 1). It is worth mentioning here that the use of $POCl_3$ has already been demonstrated in our laboratory[21–23] for the preparation of a wide variety of β-lactam compounds using the [2+2] cycloaddition reaction of imines and acetic acids in the presence of triethylamine. Besides this, the dehydrating properties of $POCl_3$ have also been amply demonstrated by us in a review article.[21] However, use of this reagent for cyclodehydration of β-amino acids to the corresponding 2-azetidinones seems to be so far unexplored and hence, we are pleased to report our successful attempts in this direction through this communication.

When β-amino acids **1** were treated with $POCl_3$ in dichloromethane in the presence of triethylamine at low temperature, cyclization proceeded smoothly to give high yields of β-lactams 2 (Sch. 1). The structures of the products were confirmed on the basis of IR and ^{1}H NMR spectral data. IR spectrum showed the characteristic β-lactam carbonyl absorption peaks in the range generally found for monocyclic β-lactams as reported under various references cited herein. It may also be emphasized that these frequencies come in the higher range for more strained bicyclic β-lactam compounds such as penicillins and cephalosporins. β-Amino acids **1** (entries **a–i**) used in this study were prepared[24] by direct addition of the corresponding amine to the appropriate α,β-unsaturated acid in basic solvent such as pyridine. The β-phenyl β-amino propionic acid (entry **1j**) was synthesized by interaction of benzaldehyde, malonic acid, and ammonium acetate.[25] This acid was converted into ethyl β-phenyl β-aminopropionate, which was benzylated and then hydrolyzed to yield β-phenyl β-(benzylamino) propionic acid[26] (entry **1k**).

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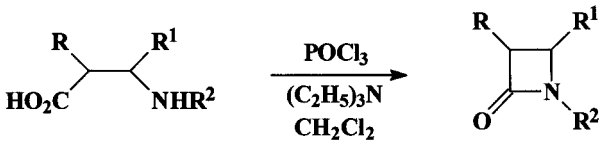

1 2

ENTRY 1,2	R	R^1	R^2
a	H	CH_3	$CH_2C_6H_5$
b	H	CH_3	$CH_2CH(CH_3)_2$
c	H	CH_3	CH_2CH_2OH
d	H	CH_3	$CH_2(CH_2)_2CH_3$
e	H	CH_3	$CH_2CH(OH)CH_3$
f	H	CH_3	$CH_2CH_2CH_2OH$
g	CH_3	H	$CH_2C_6H_5$
h	CH_3	H	$CH_2CH(CH_3)_2$
i	CH_3	H	CH_2CH_2OH
j	H	C_6H_5	H
k	H	C_6H_5	$CH_2C_6H_5$

Scheme 1.

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The $POCl_3$ mediated amide bond formation[27] proceeds via the activation of the carboxylic acid function as the mixed anhydride rather than via the activation of amino group, because, the amine intermediates of $POCl_3$ require drastic conditions for its initial formation and subsequent participation in coupling reaction. In view of this, the high yields of the β-lactam ring formation under the present conditions employed can probably be explained by the role of nitrogen electron pair to provide a six-membered transition state (**3**) which in the presence of triethylamine undergoes a facile intramolecular amide bond formation reaction as shown (Fig. 1).

In conclusion, we can say that the present method is a versatile procedure for the construction of β-lactam ring from β-amino acids in terms of its simplicity and high yields.

EXPERIMENTAL PROCEDURE

Typical Procedure for Cyclodehydration

To a cooled solution (0°C) of the β-amino acid (1 mmol), triethylamine (3 mmol) in methylene chloride (25 mL) was added $POCl_3$ (3 mmol) dropwise, and the reaction mixture was stirred overnight at room temperature. The resulting solution was washed with saturated $NaHCO_3$ (25 mL), brine (25 mL), and water (25 mL × 3). Drying over anhydrous Na_2SO_4 and evaporation of the solvent yielded the desired β-lactams. (Sch. 1)

1-Benzyl-4-methylazetidin-2-one[28] (2a). Oil (83%); IR: $\nu = 1747\,cm^{-1}$ (C═O); ^1H NMR ($CDCl_3$): 1.18 (d, $J = 6.1$ Hz, 3H, CH_3), 2.50 (dd, $J = 14.5$, 2.0 Hz, 1H, C_3–H), 3.35 (dd, $J = 14.6$, 5.0 Hz, 1H, C_3–H), 3.55 (m, 1H, C_4–H), 4.07 (d, $J = 15.3$ Hz, 1H, benzylic), 4.55 (d, $J = 15.3$ Hz, 1H, benzylic), 7.26 (m, 5H, C_6H_5). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.15; H, 7.29; N, 7.85.

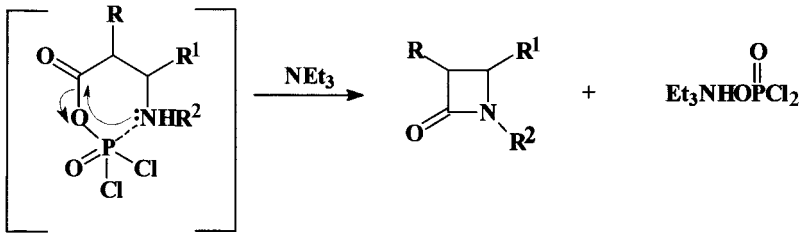

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Figure 1. Intramolecular amide bond formation reaction.

4-Methyl-1-(2-methylpropyl) azetidin-2-one (2b). Oil (77%); IR: $\nu = 1747\,cm^{-1}$ (C═O); ^1H NMR ($CDCl_3$): 0.85, 0.95 (2 × d, $J = 7.0$ Hz, 6H, 2 × CH_3), 1.18 (*d*, $J = 6.1$ Hz, 3H, CH_3), 2.0 (m, 1H, CH), 2.50 (dd, $J = 14.5$, 1.9 Hz, 1H, C_3–H), 3.1 (m, 2H, $-NCH_2$), 3.35 (dd, $J = 14.6$, 5.0 Hz, 1H, C_3–H), 3.54 (m, 1H, C–H). Anal. Calcd for $C_8H_{15}NO$: C, 68.09; H, 10.64; N, 9.93. Found: C, 67.89; H, 10.52; N, 9.82.

1-(2-Hydroxyethyl)-4-methylazetidin-2-one (2c). Oil (78%); IR: $\nu = 1740\,cm^{-1}$ (C═O); ^1H NMR ($CDCl_3$): 1.71 (bs, 1H, –OH, D_2O exchangeable), 1.18 (d, $J = 6.5$ Hz, 3H, CH_3), 2.50 (dd, $J = 14.3$, 1.9 Hz, 1 H, C_3–H), 3.25 (m, 1H, $-NCH_2$), 3.33 (m, 1H, $-NCH_2$), 3.35 (dd, $J = 14.6$, 5.0 Hz, 1H, C_3–H), 3.54 (m, 1H, C_4–H), 3.82 (m, 2H, $-OCH_2$). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.81; H, 8.53; N, 10.85. Found: C, 55.98; H, 8.16; N, 9.80.

1-Butyl-4-methylazetidin-2-one (2d). Oil (76%); IR: $\nu = 1740\,cm^{-1}$ (C═O); ^1H NMR ($CDCl_3$): 1.01 (t, 3H, $-CH_2CH_3$), 1.18 (d, $J = 6.5$ Hz, 3H, CH_3), 1.8 (m, 4H, $-(CH_2)_2CH_3$), 2.50 (dd, $J = 14.5$, 1.9 Hz, 1H, C_3–H), 3.35 (dd, $J = 14.6$, 5.0 Hz, 1H, C_3–H), 3.4 (m, 2H, $-NCH_2$), 3.54 (m, 1H, C_4–H). Anal. Calcd for $C_8H_{15}NO$: C, 68.09; H, 10.64; N, 9.93. Found: C, 67.88; H, 10.52; N, 9.53.

1-(2-Hydroxypropyl)-4-methylazetidin-2-one (2e). Oil (74%); IR: $\nu = 1740\,cm^{-1}$(C═O); ^1H NMR ($CDCl_3$): 1.15 (d, $J = 6.5$ Hz, 3H, $-CHCH_3$), 1.22 (d, $J = 6.6$ Hz, 3H, CH_3), 2.50 (dd, $J = 14.5$, 2.0 Hz, 1H, C_3–H), 3.18 (d, $J = 6.7$ Hz, 2H, NCH_2) 3.35 (dd, $J = 14.6$, 5.0 Hz, 1H, C_3–H), 3.54 (m, 1H, C_4–H), 4.14 (m, 1H, –CHOH). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.74; H, 9.09; N, 9.79. Found: C, 58.78; H, 9.19; N, 9.60.

1-(3-Hydroxypropyl)-4-methylazetidin-2-one (2f). Oil (74%); IR: $\nu = 1744\,cm^{-1}$(C═O); ^1H NMR ($CDCl_3$): 1.18 (d, $J = 6.4$ Hz, 3H, CH_3), 1.71 (m, 2H, $-CH_2$), 2.34 (bs, 1H, OH, D_2O exchangeable), 2.50 (dd, $J = 14.5$, 1.9 Hz, 1H, C_3–H), 3.35 (dd, $J = 14.5$, 5.0 Hz, 1H, C_3–H), 3.43 (m, 2H, $-NCH_2$), 3.54 (m, 1H, C_4–H), 3.68 (m, 2H, $-OCH_2$). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.74; H, 9.09; N, 9.79. Found: C, 58.70; H, 8.98; N, 9.95.

1-Benzyl-3-methylazetidin-2-one[29] (2g). Oil (82%); IR: $\nu = 1747\,cm^{-1}$(C═O); ^1H NMR ($CDCl_3$): 1.27 (d, $J = 7.2$ Hz, 3H, CH_3), 2.73 (dd, $J = 5.2$, 2.1 Hz, 1H, C_4–H), 3.15 (m, 1H, C_3–H), 3.26 (dd, $J = 6.0$, 5.2 Hz, 1H, C_4–H), 4.30 (d, $J = 15.1$ Hz, 1H, benzylic), 4.45 (d, $J = 15.1$ Hz, 1H, benzylic), 7.29 (m, 5H, C_6H_5). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00. Found: C, 76.00; H, 7.39; N, 7.82.

3-Methyl-1-(2-methylpropyl) azetidin-2-one (2h). Oil (78%); IR: $\nu = 1743\,cm^{-1}$(C═O); ^1H NMR ($CDCl_3$): 0.9, 0.99 (2 × d, $J = 7.0$ Hz, 6H, 2 × CH_3), 1.27 (d, $J = 7.4$ Hz, 3H, CH_3), 2.05 (m, 1H, CH), 2.73 (dd, $J = 5.2$, 2.2 Hz, 1H, C_4–H), 3.1 (m, 2H, $-NCH_2$), 3.25 (m, 1H, C_3–H), 3.36 (dd, $J = 6.0$, 5.2 Hz, 1H, C_4–H). Anal. Calcd for $C_8H_{15}NO$: C, 68.09; H, 10.64; N, 9.93. Found: C, 67.79; H, 10.58; N, 9.78.

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1-(2-Hydroxyethyl)-3-methylazetidin-2-one (2i). Oil (79%); IR: $\nu = 1747\,cm^{-1}$ (C═O); ^1H NMR ($CDCl_3$): 1.27 (d, $J = 7.3$ Hz, 3H, CH_3), 1.71 (bs, 1 H, −OH, D_2O exchangeable), 2.73 (dd, $J = 5.2$, 2.2 Hz, 1 H, C_4−H), 3.15 (m, 1H, C_3−H), 3.25 (m, 1H, $-NCH_2$), 3.36 (dd, $J = 6.0$, 5.2 Hz, 1H, C_4−H), 3.43 (m, 1H, $-NCH_2$), 3.82 (m, 2H, $-OCH_2$). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.81; H, 8.53; N, 10.85. Found: C, 55.35; H, 8.47; N, 10.88.

4-Phenylazetidin-2-one[30] (2j). Solid (73%), m.p. 114−116°C; IR: $\nu = 1778\,cm^{-1}$(C═O); 1H NMR ($CDCl_3$): 2.8 (ddd, $J = 1.5$, 2.7, 15 Hz, 1H, C_3−H), 3.42 (ddd, $J = 3.0$, 4.5, 15 Hz, 1H, C_3−H), 4.73 (dd, $J = 2.7$, 4.5 Hz, 1H, C_4−H), 6.6 (br, 1H, −NH), 7.38 (m, 5H, $-C_6H_5$). Anal. Calcd for C_9H_9NO: C, 73.47; H, 6.12; N, 9.52. Found: C, 73.05; H, 5.95; N, 9.23.

1-Benzyl-4-phenylazetidin-2-one (2k). Oil (79%); IR: $\nu = 1750\,cm^{-1}$(C = O); ^1H NMR ($CDCl_3$): 2.88 (dd, $J = 14.6$, 2.3 Hz, 1H, C_3−H), 3.35 (dd, $J = 14.7$, 5.1 Hz, 1H, C_3−H), 3.76 (d, $J = 15.1$ Hz, 1H, benzylic), 4.41 (dd, $J = 5.2$, 2.2 Hz, 1H, C_4−H), 4.81 (d, $J = 15.0$ Hz, 1H, benzylic), 7.35 (m, 10H, 2 × C_6H_5). Anal. Calcd for $C_{16}H_{15}NO$: C, 81.01; H, 6.32; N, 5.90. Found: C, 80.99; H, 6.19; N, 5.98.

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