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One-Pot Synthesis of Five-, Six-, and Seven-Membered Lactams *via* Bu_3SnH-Mediated Reductive Cyclization of Azido Amides

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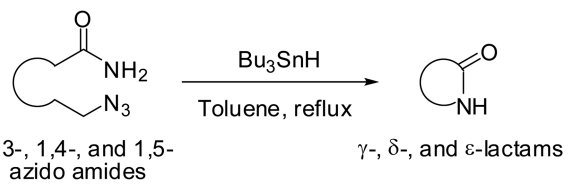
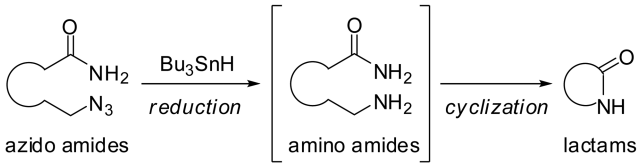
The lactam system ranks among the most ubiquitous skeletons found in naturally occurring organic molecules and pharmaceuticals.[1] Therefore, the synthesis of lactams has been the focus of intensive research effort. Lactams are usually prepared by the condensation of amines and activated carboxylic acids, including esters.[2] Alternative routes include the Beckmann rearrangement,[3] the Schmidt reaction,[4] the Kinugasa reaction,[5] the Diels-Alder reaction,[6] transition metal-catalyzed lactamization,[7] iodolactamization,[8] and the Staudinger ligation of azides and activated carboxy acid derivatives.[9] Recently, we reported the direct lactamization of 1,3- and 1,4-azido amides *via* the Staudinger-type reductive cyclization, in which the amide group acts as the electrophile for lactam synthesis.[10] Our lactamization process involves the use of triphenylphosphines and water to afford various γ- and δ-lactams in good to excellent yields. Owing to the importance of lactams in natural products and pharmaceuticals, the development of new and diverse routes for efficient, single-step lactam synthesis from azido amides with expanded substrate scope is highly desirable. Therefore, we planned to develop another methodology for the direct lactamization of various azido amides, including 1,5-azido amides to prepare ε-lactams. Here, we report a one-pot lactamization of 1,3-, 1,4-, and 1,5-azido amides *via* Bu_3SnH-mediated reductive cyclization to afford five-, six-, and seven-membered lactams (Scheme 1). Although Bu_3SnH has been used as the reducing agent for the conversion of azides into amines,[11] it has never been used for the direct lactamization of azido amides *via* reductive cyclization.

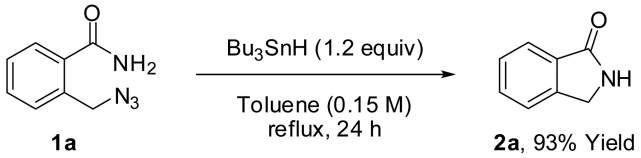
In general, in the absence of AIBN, Bu_3SnH converts azides into amines *via* thermally unstable stannyltriazene adducts.[12] Therefore, it is supposed that the lactamization will proceed *via* the nucleophilic attack of the amine group (generated by Bu_3SnH-mediated reduction of the azide group) to the amide group (Scheme 2).



Scheme 1. Bu_3SnH-mediated one-pot lactamizations of 1,3-, 1,4-, and 1,5-azido amides.



Scheme 2. Concept of Bu_3SnH-mediated one-pot lactamization of azido amides *via* reductive cyclization.



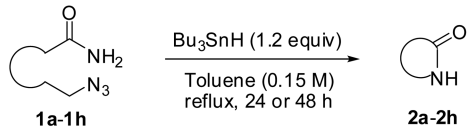
Scheme 3. Bu_3SnH-mediated one-pot lactamization of azido amide **1a**.

To realize the proposed transformation, the 1,3-azido amide **1a** was reacted with 1.2 equiv of Bu_3SnH in toluene (0.15 M) under reflux, affording the desired γ-lactam **2a** in 93% yield *via* the reductive cyclization (Scheme 3).

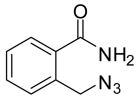
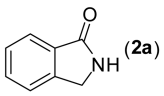
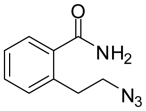
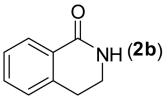
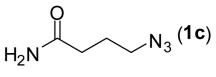
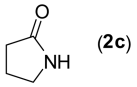
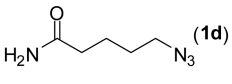
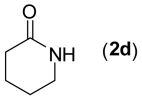
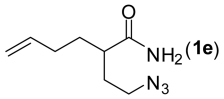
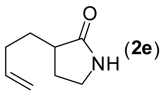
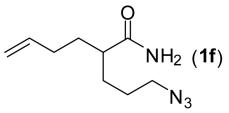
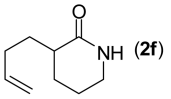
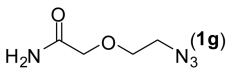
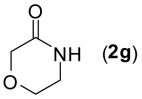
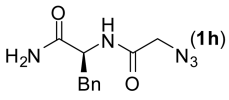
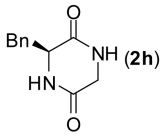
By adopting the optimized reaction conditions, we explored the feasibility of the Bu_3SnH-mediated one-pot lactamization of various azido amides (Tables 1-2). Firstly, we examined the scope of 1,3- and 1,4-azido amides as substrates in the lactamization under the optimized conditions (Table 1). A series of 1,3- and 1,4-azido amides bearing various backbones, such as aromatic, aliphatic, and substituted aliphatic azido amides, were examined (Table 1, entries 1-6). The aromatic and aliphatic 1,3- and 1,4-azido amides yielded the corresponding γ- and δ-lactams in good to excellent yields (Table 1, entries 1-4). In addition, the aliphatic 1,3- and 1,4-azido amides bearing functionalized alkyl substituents afforded the desired α-substituted γ- and δ-lactams in excellent yields (Table 1, entries 5-6). Furthermore, the lactamizations of the aliphatic 1,4-azido amides **1g** and **1h** bearing an oxygen and amide bond in the linear chain, respectively, afforded the desired lactams, such as 3-morpholinone (**2g**) and 2,5-piperazinedione (**2h**), in good to excellent yields (Table 1, entries 7-8).

Next, we carried out the one-pot synthesis of ε-lactams *via* the Bu_3SnH-mediated reductive cyclization of 1,5-azido amides under the optimized conditions (Table 2). A series of

Table 1. Bu_3SnH-mediated one-pot lactamizations of 1,3- and 1,4-azido amides **1a-1h**[a]



1a-1h **2a-2h**

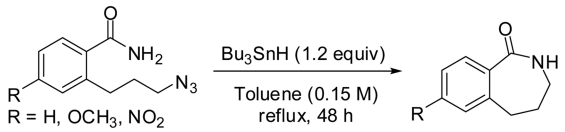
Entry	Substrate	Product	Time (h)	Yield (%)
1	 (**1a**)	 (**2a**)	24	93
2	 (**1b**)	 (**2b**)	24	92
3	 (**1c**)	 (**2c**)	48	94
4	 (**1d**)	 (**2d**)	24	84
5	 (**1e**)	 (**2e**)	48	93
6	 (**1f**)	 (**2f**)	48	98
7	 (**1g**)	 (**2g**)	48	94
8	 (**1h**)	 (**2h**)	24	88

[a]Procedure: Tributyltin hydride (1.2 equiv) was added to a solution of **1** (0.3 mmol) in toluene (0.15 M). The mixture was refluxed for 24 or 48 h. The solvent was removed and the residue was isolated by silica gel chromatography.

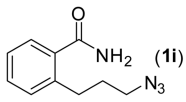
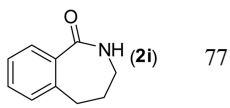
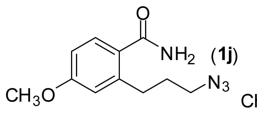
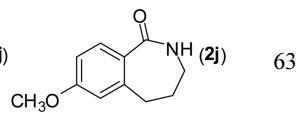
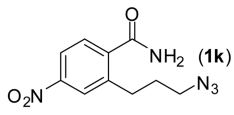
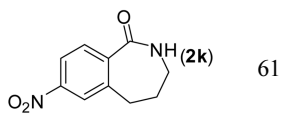
the aromatic 1,5-azido amides bearing various substituents were examined. In all cases, the ε-lactams **2i-2k** were obtained in moderate to good yields.

In summary, the one-pot lactamization of 1,3-, 1,4-, and 1,5-azido amides has been achieved using Bu_3SnH, affording various γ-, δ-, and ε-lactams in moderate to excellent yields. The one-pot lactamization of the azido amides, in which the amide group acts as the electrophile, was carried out *via* Bu_3SnH-mediated reductive cyclization. This lactamization provides a new and efficient route for the synthesis of five-, six-, and seven-membered lactams found in biologically and pharmacologically active compounds. Further studies on the development of new synthetic routes to prepare various lactams are underway.

Table 2. Bu_3SnH-mediated one-pot lactamizations of 1,5-azido amides **1i-1k**[a]



1i-1k **2i-2k**

Entry	Substrate	Product	Yield (%)
1	 (**1i**)	 (**2i**)	77
2	 (**1j**)	 (**2j**)	63
3	 (**1k**)	 (**2k**)	61

[a]Procedure: See the Experimental Section.

Experimental Section

General Procedure for the Bu_3SnH-mediated One-pot Lactamization of Various Azido Amides. Tributyltin hydride (105 mg, 0.36 mmol) was added to a solution of azido amide **1** (0.3 mmol) in toluene (0.15 M). The mixture was refluxed for 24 or 48 h. The solvent was removed and the residue was isolated by silica gel chromatography to afford the desired lactam **2**. Mass spectral data were obtained from the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer. The known compounds **1a-1h**,[10] **2a-2b**,[13a] **2c**,[7a] **2d**,[7b] **2e-2f**,[13b] **2g**,[13c] **2h**,[13d] **2i**,[14] and **2j**[15] were identified by comparison of their spectroscopic data with reported values in the literature. The spectroscopic data of unknown compounds **1i-1k** and **2k** are as follows.

Compound 1i: white solid, mp 93-95 °C; IR (neat) 3330, 3155, 2096, 1668, 1621, 1391, 1346, 1275, 1135, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 1H), 7.40-7.36 (m, 1H), 7.27-7.22 (m, 2H), 6.11 (br s, 1H), 5.87 (br s, 1H), 3.31 (t, J = 6.8 Hz, 2H), 2.93-2.89 (m, 2H), 1.98-1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 139.6, 135.0, 130.4, 130.4, 127.0, 126.2, 50.8, 30.5, 30.3; HRMS (FAB) calcd for $[M+H]^+$ $C_{10}H_{13}ON_4$ 205.1089, found 205.1087.

Compound 1j: white solid, mp 100-102 °C; IR (neat) 3379, 3192, 2097, 1644, 1616, 1396, 1255, 1131, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 1H), 6.77-6.72 (m, 2H), 6.08 (br s, 1H), 5.88 (br s, 1H), 3.82 (s, 3H), 3.31 (t, J = 6.8 Hz, 2H), 2.94-2.90 (m, 2H), 1.97-1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 161.0, 142.5, 129.0, 127.0, 116.1, 111.1, 55.2, 50.9, 30.6, 30.4; HRMS (FAB) calcd for $[M+H]^+$ $C_{11}H_{15}O_2N_4$ 235.1195, found 235.1197.

Compound 1k: white solid, mp 125-127 ºC; IR (neat) 3361, 3185, 2098, 1657, 1512, 1353, 815, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 2.0 Hz, 1H), 8.11 (dd, J = 8.4, 2.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 6.20 (br s, 1H), 5.93 (br s, 1H), 3.37 (t, J = 6.4 Hz, 2H), 3.01-2.97 (m, 2H), 2.03-1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 148.7, 141.7, 141.0, 128.0, 125.0, 121.4, 50.7, 30.3, 30.2; HRMS (FAB) calcd for $[M+H]^+$ $C_{10}H_{12}O_3N_5$ 250.0940, found 250.0938.

Compound 2k: yellow solid, mp 216-218 ºC; IR (neat) 3206, 3074, 2952, 1669, 1519, 1347, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 8.4, 2.0 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 6.84 (br s, 1H), 3.18-3.13 (m, 2H), 2.99 (t, J = 7.2 Hz, 2H), 2.14-2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 149.2, 140.8, 139.9, 130.0, 123.6, 122.0, 39.2, 30.1, 29.8; HRMS (FAB) calcd for $[M+H]^+$ $C_{10}H_{11}O_3N_2$ 207.0770, found 207.0771.

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