http://dx.doi.org/10.5012/bkcs.2012.33.1.333

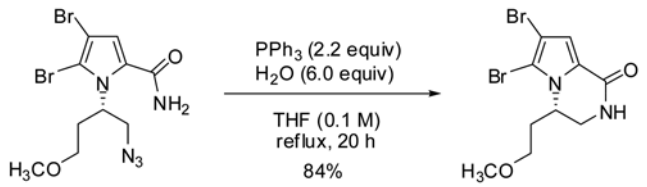
Direct Lactamization of Azido Amides *via* Staudinger-Type Reductive Cyclization

In-Jung Heo, Su-Jeong Lee, and Chang-Woo Cho*

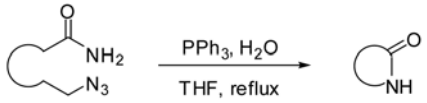
*Department of Chemistry, Kyungpook National University, Daegu 702-701, Korea. *E-mail: cwcho@knu.ac.kr*
Received November 11, 2011, Accepted November 18, 2011

Key Words : Lactamization, Azido amide, Staudinger reaction, Reductive cyclization, Lactam

The lactam ring system is one of the most ubiquitous structural motifs found in natural products and pharmaceuticals.[1] Owing to the prevalence of lactams, their synthesis has attracted considerable attention. Lactams are usually prepared by the coupling of activated carboxylic acid derivatives with amines.[2] Alternative routes include the Beckmann rearrangement of oximes,[3] the Schmidt reaction of cyclic ketones and hydrazoic acid,[4] the Kinugasa reaction of nitrones and terminal acetylenes,[5] the Diels-Alder reaction of cyclopentadiene and chlorosulfonyl isocyanate,[6] transition metal catalyzed lactamization of amino alcohols,[7] and iodolactamization of amides and alkenes.[8] In particular, the intramolecular Staudinger ligation of azides and activated carboxy acids, including esters, is well known as an environmentally friendly and mild protocol for lactam synthesis.[9] Recently, we discovered a direct lactamization of the azide group and the amide group *via* a Staudinger-type reductive cyclization while constructing the pyrrolopiperazinone skeleton in the formal synthesis of bromopyrrole alkaloids (Scheme 1).[10] Amides have been used with azides in the synthesis of cyclic imine compounds *via* the intramolecular aza-Wittig reaction.[11] However, interestingly, amides have never been used as electrophiles with azides in the synthesis of lactams *via* the Staudinger-type reductive cyclization, in spite of the widespread use of amides in organic, biological, and materials chemistry. Here, we report a generalized direct lactamization of 1,3- and 1,4-azido amides *via* the Staudinger-type reductive cyclization in order to develop a mild, functional group tolerant and efficient methodology for lactam synthesis (Scheme 2).



Scheme 1. Synthesis of a pyrrolopiperazinone skeleton by the direct lactamization of azido amide *via* a Staudinger-type reductive cyclization.



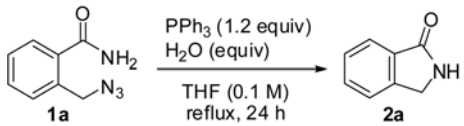
Scheme 2. Generalization of the direct lactamization of 1,3- and 1,4-azido amides.

On the basis of the previous result we obtained upon the direct lactamization of the azido amide during the synthesis of the pyrrolopiperazinone skeleton (Scheme 1), we undertook further optimization of the direct lactamization of the 1,3-azido amide **1a** in the presence of 1.2 equiv of triphenylphosphine. The amount of triphenylphosphine was reduced from that in the previous reaction condition in Scheme 1, and the optimization was carried out for various molar equiv of water in tetrahydrofuran (0.1 M) under reflux (Table 1). By comparing the yields of the lactamizations of **1a** using various molar equiv of water under the same conditions, 8.0 equiv was identified as the ideal amount that afforded the desired γ-lactam **2a** in 95% yield (Table 1, entry 5).

Next, we examined the scope of azido amides as substrates in the direct lactamization under the optimized conditions (Table 2). 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 2, entries 1-7). The aromatic and aliphatic azido amides afforded the desired γ- and δ-lactams in excellent yields (Table 2, entries 1-4). In addition, the aliphatic azido amides bearing functionalized alkyl and Cbz-protected amino substituents afforded the corresponding α-substituted γ- and δ-lactams in good to excellent yields (Table 2, entries 5-7).

Furthermore, the aliphatic 1,4-azido amides **1h** and **1i**

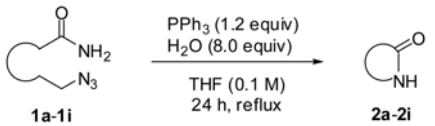
Table 1. Optimization of the direct lactamization of 1,3-azido amide **1a**[a]

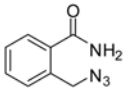
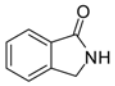
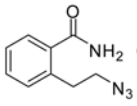
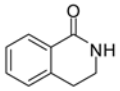
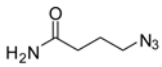
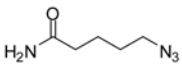
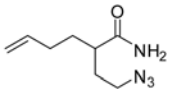
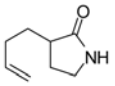
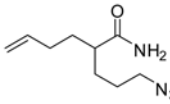
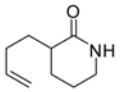
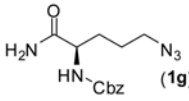
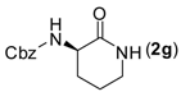
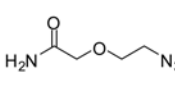
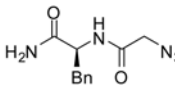
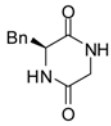


Entry	H_2O (equiv)	Yield (%)
1	1.2	65
2	2.0	77
3	4.0	87
4	6.0	90
5	**8.0**	**95**

[a]Procedure: Triphenyphosphine (120 mol %) was added to a solution of **1a** (100 mol %) in THF (0.1 M). The mixture was stirred at rt for 1 h, at which point water (120, 200, 400, 600, or 800 mol %) was added and the mixture was refluxed for 24 h. The solvent was removed and the residue was isolated by silica gel chromatography.

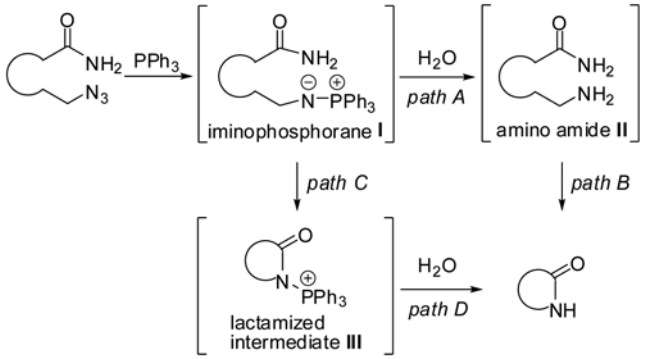
Table 2. Direct lactamizations of various azido amides **1a-1i**[a]



Entry	Substrate	Product	Yield (%)
1	 (**1a**)	 (**2a**)	95
2	 (**1b**)	 (**2b**)	96
3	 (**1c**)	 (**2c**)	94
4	 (**1d**)	 (**2d**)	91
5	 (**1e**)	 (**2e**)	86[b]
6	 (**1f**)	 (**2f**)	96
7	 (**1g**)	 (**2g**)	81[b]
8	 (**1h**)	 (**2h**)	88
9	 (**1i**)	 (**2i**)	78[b]

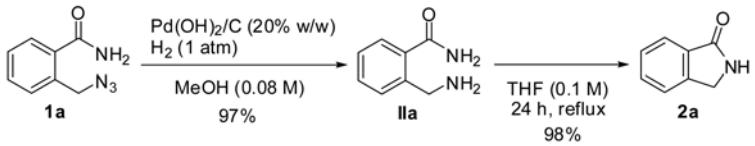
[a]Procedure: See the Experimental Section. [b]Reaction was carried out for 48 h.

bearing an oxygen and amide bond in the linear chains, respectively, were examined (Table 2, entries 8-9). In both cases, the direct lactamizations afforded the corresponding lactams, such as 3-morpholinone (**2h**) and 2,5-piperazinedione (**2i**), in good yields.

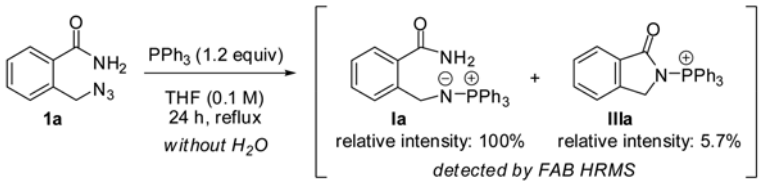


Scheme 3. Proposed mechanism of the lactamization of azido amides *via* Staudinger-type reductive cyclizations.

The proposed mechanism of the lactamization of the azido amides is presented in Scheme 3. It is supposed that the lactamization would proceed *via* the nucleophilic attack of the amine group to the amide group in the amino amide **II**, which is generated from the azido amide by the Staudinger reaction[12] (path A → path B, Scheme 3). Indeed, the plausibility of path B was confirmed by the lactamization of the amino amide **IIa**, which was obtained from **1a** under the hydrogenation condition,[13] in tetrahydrofuran under reflux for 24 h to afford the desired γ-lactam **2a** in 98% yield (Scheme 4).[14] However, the possibility that the lactamization would proceed *via* the nucleophilic attack of the nitrogen atom in the iminophosphorane **I**[9,11] (generated by the reaction between the azide group and triphenylphosphine) to the amide group and subsequent hydrolysis could not be ruled out (path C → path D, Scheme 3). This is because the molecular ion corresponding to the mass of the lactamized intermediate **IIIa** existed in low abundance, while the molecular ion corresponding to the mass of the iminophosphorane **Ia** was the most abundant ion in the spectrum, according to the results of FAB high-resolution mass spectrometric analysis of the intermediates **Ia** and **IIIa**, which were obtained by the reaction of the azido amide **1a** with triphenylphosphine in the absence of water in tetrahydrofuran under reflux for 24 h



Scheme 4. Lactamization of the amino amide **IIa**.



Scheme 5. Identification of the intermediates **Ia** and **IIIa** by FAB high-resolution mass spectrometric analysis.

(Scheme 5).[15]

In summary, the direct lactamization of 1,3- and 1,4-azido amides has been achieved using triphenylphosphine and water, affording various γ- and δ-lactams in good to excellent yields. The direct lactamization of the azido amides was performed *via* the Staudinger-type reductive cyclization in which the amide group acts as the electrophile for lactam synthesis. This lactamization provides a mild, functional group tolerant and efficient route for the synthesis of various γ- and δ-lactams found in natural products and pharmaceuticals. Further studies will be conducted to develop new synthetic routes for the synthesis of various lactams.

Experimental Section

General Procedure for the Direct Lactamization of Various Azido Amides. Triphenylphosphine (120 mol %) was added to a solution of azido amide **1** (100 mol %) in THF (0.1 M). The mixture was stirred at rt for 1 h, at which point water (800 mol %) was added and the mixture was refluxed for 24 h. The solvent was removed and the residue was isolated by silica gel chromatography to provide the desired lactam. Mass spectral data were obtained from the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer. The known compounds **2a**,[16a] **2b**,[16a] **2c**,[7a] **2d**,[7b] **2e**,[16b] **2f**,[16b] **2g**,[16c] **2h**,[16d] and **2i**[16e] were identified by comparison of their spectroscopic data with reported values in the literature. The spectroscopic data of unknown compounds **1a-1i** are as follows.

Compound 1a: white solid, mp 99-101 °C; IR (neat) 3369, 3181, 2095, 1651, 1622, 1389, 1238, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (m, 1H), 7.52-7.48 (m, 1H), 7.44-7.38 (m, 2H), 6.15 (br s, 1H), 5.96 (br s, 1H), 4.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 134.5, 134.1, 131.0, 130.1, 128.4, 128.0, 52.6; HRMS (FAB) calcd for $[M+H]^+$ $C_8H_9ON_4$ 177.0776, found 177.0775.

Compound 1b: white solid, mp 86-88 °C; IR (neat) 3371, 3188, 2112, 1650, 1620, 1399, 1259, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.50 (m, 1H), 7.44-7.40 (m, 1H), 7.32-7.29 (m, 2H), 6.03 (br s, 1H), 5.67 (br s, 1H), 3.63 (t, J = 6.8 Hz, 2H), 3.11 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 136.7, 135.3, 131.0, 130.6, 127.3, 126.9, 52.6, 32.9; HRMS (FAB) calcd for $[M+H]^+$ $C_8H_{11}ON_4$ 191.0933, found 191.0935.

Compound 1c: white solid, mp 71-73 °C; IR (neat) 3371, 3188, 2113, 1658, 1427, 1307, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (br s, 1H), 5.89 (br s, 1H), 3.37 (t, J = 6.4 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 1.95-1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 50.5, 32.2, 24.3; HRMS (FAB) calcd for $[M+H]^+$ $C_4H_9ON_4$ 129.0776, found 129.0779.

Compound 1d: white solid, mp 60-62 °C; IR (neat) 3389, 3194, 2098, 1651, 1423, 1251, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.16 (br s, 1H), 5.73 (br s, 1H), 3.31 (t, J = 6.4 Hz, 2H), 2.26 (t, J = 6.8 Hz, 2H), 1.76-1.61 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 50.8, 34.8, 28.0, 22.3; HRMS (FAB) calcd for $[M+H]^+$ $C_5H_{11}ON_4$ 143.0933, found 143.0932.

Compound 1e: white solid, mp 36-38 °C; IR (neat) 3390, 3193, 2933, 2099, 1654, 1455, 1259, 914, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83-5.73 (m, 1H), 5.50-5.46 (m, 2H), 5.07-4.99 (m, 2H), 3.45-3.39 (m, 1H), 3.31-3.24 (m, 1H), 2.38-2.31 (m, 1H), 2.21-2.02 (m, 2H), 1.96-1.87 (m, 1H), 1.82-1.66 (m, 2H), 1.57-1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 137.5, 115.4, 49.3, 42.7, 31.6, 31.6, 31.2; HRMS (FAB) calcd for $[M+H]^+$ $C_8H_{15}ON_4$ 183.1246, found 183.1249.

Compound 1f: white solid, mp 42-44 °C; IR (neat) 3390, 3195, 2939, 2100, 1652, 1456, 1282, 913, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82-5.72 (m, 1H), 5.45 (br s, 2H), 5.06-4.98 (m, 2H), 3.35-3.22 (m, 2H), 2.21-2.01 (m, 3H), 1.80-1.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 137.7, 115.1, 51.1, 45.5, 31.7, 31.2, 29.7, 26.6; HRMS (FAB) calcd for $[M+H]^+$ $C_9H_{17}ON_4$ 197.1402, found 197.1405.

Compound 1g: white solid, mp 110-112 °C; IR (neat) 3384, 3311, 2108, 1657, 1544, 1265, 1250, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 5.92 (br s, 1H), 5.36-5.31 (m, 2H), 5.12 (s, 2H), 4.24-4.22 (m, 1H), 3.36-3.33 (m, 2H), 1.99-1.93 (m, 1H), 1.76-1.63 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 156.2, 135.9, 128.5, 128.2, 127.9, 67.1, 53.7, 50.8, 29.8, 24.8; HRMS (FAB) calcd for $[M+H]^+$ $C_{13}H_{18}O_3N_5$ 292.1410, found 292.1413.

Compound 1h: white solid, mp 51-53 °C; IR (neat) 3400, 3181, 2099, 2058, 1665, 1341, 1282, 1133, 887, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (br s, 1H), 6.05 (br s, 1H), 4.02 (s, 2H), 3.72 (t, J = 4.8 Hz, 2H), 3.47 (t, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 70.1, 70.1, 50.5; HRMS (FAB) calcd for $[M+H]^+$ $C_4H_9O_2N_4$ 145.0726, found 145.0724.

Compound 1i: white solid, mp 122-124 °C; IR (neat) 3393, 3295, 2105, 1652, 1539, 1275, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 6.91 (d, J = 7.2 Hz, 1H), 5.51 (br s, 1H), 5.31 (br s, 1H), 4.67-4.62 (m, 1H), 3.97 (s, 2H), 3.17-3.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 167.0, 136.0, 129.2, 128.6, 127.1, 54.0, 52.2, 38.3; HRMS (FAB) calcd for $[M+H]^+$ $C_{11}H_{14}O_2N_5$ 248.1147, found 248.1149.

Acknowledgments. This work was supported by the R&D Program of MKE/KEIT [10035240, Development of new herbicides for resistant weeds with mutated genes].

References and Notes

1. (a) Pal, A. P. J.; Kadigachalam, P.; Mallick, A.; Doddi, V. R.; Vankar, Y. D. *Org. Biomol. Chem.* **2011**, *9*, 809. (b) Szostak, M.; Aubé, J. *Org. Biomol. Chem.* **2011**, *9*, 27. (c) Kim, M. H.; Choi, Y. L.; Heo, J.-N.; Min, Y. K.; Kim, S. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 2047. (d) Mehta, P. D.; Sengar, N. P. S.; Pathak, A. K. *Eur. J. Med. Chem.* **2010**, *45*, 5541. (e) Lim, S.-H.; Mahmood, K.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2008**, *71*, 1104. (f) Oshiro, Y.; Sakurai, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Miwa, T.; Nishi, T. *J. Med. Chem.* **2000**, *43*, 177. (g) Murakami, Y.; Hara, H.; Okada, T.; Hashizume, H.; Kii, M.; Ishihara, Y.; Ishikawa, M.; Shimamura, M.; Mihara, S.-I.; Kato, G.; Hanasaki, K.; Hagishita, S.; Fujimoto,

M. *J. Med. Chem.* **1999**, *42*, 2621.
2. Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999.
3. Hashimoto, M.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2008**, *73*, 2894.
4. Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146.
5. (a) Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M. *J. Org. Chem.* **2009**, *74*, 3094. (b) Marco-Contelles, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 2198.
6. Benedek, G.; Palkó, M.; Wéber, E.; Martinek, T. A.; Forró, E.; Fülöp, F. *Eur. J. Org. Chem.* **2008**, 3724.
7. (a) Dam, J. H.; Osztrovszky, G.; Nordstrøm, L. U.; Madsen, R. *Chem. Eur. J.* **2010**, *16*, 6820. (b) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643. (c) Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785.
8. Shen, M.; Li, C. *J. Org. Chem.* **2004**, *69*, 7906.
9. For a review on the Staudinger ligation, see: Köhn, M.; Breinbauer, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3106.
10. Lee, S.-J.; Youn, S.-H.; Cho, C.-W. *Org. Biomol. Chem.* **2011**, *9*, 7734.
11. For recent reviews on the aza-Wittig reaction for the construction of carbon-nitrogen double bonds, see: (a) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523. (b) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1.
12. Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
13. Yoshimitsu, T.; Ino, T.; Tanaka, T. *Org. Lett.* **2008**, *10*, 5457.
14. For examples of the intramolecular attack of amines to amides to form six-membered lactams, see: (a) Kopka, I. E.; Lin, L. S.; Jewell, J. P.; Lanza, T. J.; Fong, T. M.; Shen, C.-P.; Lao, Z. J.; Ha, S.; Castonguay, L. G.; der Ploeg, L. V.; Goulet, M. T.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4757. (b) Perrin, C. L.; Arrhenius, G. M. L. *J. Am. Chem. Soc.* **1982**, *104*, 2839.
15. Intermediate **Ia**: HRMS (FAB) calcd for $[M+H]^+$ $C_{26}H_{24}ON_2P$ 411.1626, found 411.1627; Intermediate **IIIa**: HRMS (FAB) calcd for $[M]^+$ $C_{26}H_{21}ONP^+$ 394.1361, found 394.1364.
16. (a) Ren, W.; Yamane, M. *J. Org. Chem.* **2009**, *74*, 8332. (b) Padwa, A.; Hertzog, D. L.; Nadler, W. R.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1994**, *59*, 1418. (c) Abe, M.; Akiyama, T.; Nakamura, H.; Kojima, F.; Harada, S.; Muraoka, Y. *J. Nat. Prod.* **2004**, *67*, 999. (d) Pfeil, E.; Harder, U. *Angew. Chem. Int. Ed.* **1967**, *6*, 178. (e) López-Cobeñas, A.; Cledera, P.; Sánchez, J. D.; López-Alvarado, P.; Ramos, M. T.; Avendaño, C.; Menéndez, J. C. *Synthesis* **2005**, 3412.