Intramolecular Staudinger Ligation

Intramolecular Staudinger Ligation: A Powerful Ring-Closure Method To Form Medium-Sized Lactams**

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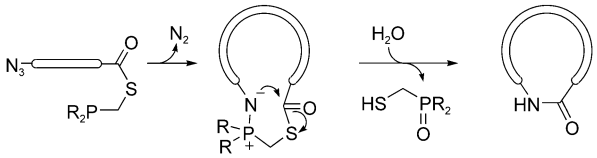
Medium-sized lactams constitute a very important class of compounds with high potential in drug,[1] materials,[2] and catalysis[3] research. Efficient ring closure to form many medium-sized (7–10-membered) lactams is still a significant synthetic problem.[4] Direct ring closure through the activation of the carboxy group of an ω-amino acid only gives high yields if structural elements that favor the facile approach of the mutually reactive end groups are present within the linear precursor. A class of compounds that are especially resistant to ring closure are dipeptides made up of a linear α- and a linear β-amino acid, which represent potential prescursors to the monocyclic seven-membered [1,4]diazepane-2,5-dione (or homodiketopiperazine) skeleton.[5] The main reason for the failure of these dipeptides to undergo cyclization is the predominant *trans* arrangement of the amide bond, which prevents the required spatial positioning of the terminal amine and activated carboxy groups for cyclization to occur.[6]

Recently, we developed a novel auxiliary-mediated combined tether–template strategy toward medium-sized lactams.[7] It occurred to us that the Staudinger ligation reaction, independently developed by the research groups of Bertozzi[8] and Raines[9], might also serve as a powerful method for the facilitation of difficult lactamization reactions. Herein we show the power of the intramolecular Staudinger ligation method (Scheme 1), which provides access to 7–9-membered lactams including the monocyclic homodiketopiperazine series.



Scheme 1. Intramolecular Staudinger ligation.

Ligation strategies have been developed to overcome the problems encountered in the coupling of large peptide fragments.[10] In the Staudinger ligation a carboxylic acid (or the C terminus of a peptide) is transformed into a phosphanyl thioester, which is then treated with an azide (or the N-terminal azide of a peptide).[11] The ensuing Staudinger reaction[12] produces an intermediate iminophosphorane, which undergoes an intramolecular S→N acyl-transfer reaction via a favored five-membered transition state. The auxiliary residue is removed in the presence of a small amount of water in the reaction mixture, which causes the in situ hydrolysis of the P–N bond of the final amido phosphonium salt. Thus, the intramolecular Staudinger ligation should be a powerful method for effecting difficult lactamizations, as the macrocycle that is initially formed collapses in a series of thermodynamically favored and proximity-driven ring-contraction reactions with expulsion of a total of five atoms of the original ring (Scheme 2).[13]

Direct application of the Bertozzi–Raines method in an intramolecular fashion, that is, thioesterification of a linear ω-azido acid with diphenylphosphanylmethanethiol, was expected to compete with undesired premature Staudinger reactions and thus lead to complex mixtures. We overcame this key problem by protecting the phosphane-containing auxiliary as the borane complex **3** (Scheme 3).

Model reactions revealed that borane-protected phosphanes were totally unreactive towards azides.[14] Thus, we

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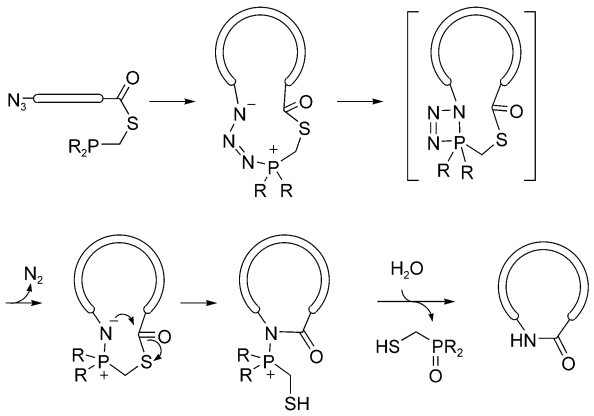
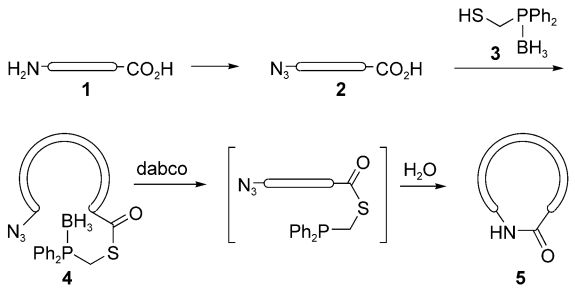


Scheme 2. Ring-contraction events in the intramolecular Staudinger ligation.

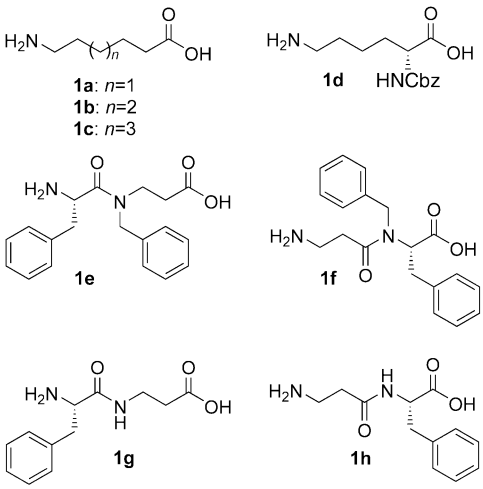


Scheme 3. Reaction sequence of the intramolecular Staudinger ligation.

could start directly from ω-amino acids **1**, which were conveniently transformed into ω-azido acids **2** by a diazo-transfer reaction, as described by Lundquist and Pelletier.[15] Thioesterification of the ω-azido acids **2** with the borane-protected auxiliary **3** provided the stable cyclization precursors **4**. Following liberation of the phosphane in **4** by decomplexation with dabco, the intramolecular Staudinger reaction and in situ hydrolysis of the resulting amidophosphonium salt should occur to give lactams **5**. The representative amino acids **1a–h** (Scheme 4) were chosen as substrates for the intramolecular Staudinger ligation.

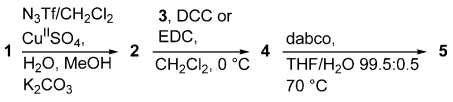
Cyclizations of the amino acids **1a–c** by using traditional carboxylic acid activating reagents are known to occur in low to moderate yields accompanied by cyclic-dimer formation.[16] In previous work the direct lactamization of **1e** and **1f** by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) activation gave homodiketopiperazines **5e** and **5f** in low yields of 30 and 11%, respectively.[7b] The same work showed the dipeptides **1g** and **1h** to be particularly challenging substrates, as all attempts at direct lactamization in the presence of the current state-of-the-art carboxy-group-activating reagents failed.

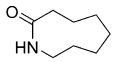
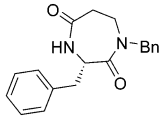
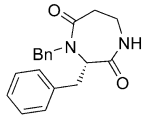
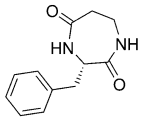
Amines **1a–h** were subjected to the diazo-transfer reaction by treatment with TfN_3 to furnish the corresponding azides **2** in excellent yields (Table 1). The borane-protected auxiliary **3** was synthesized in one step by saponification of the known corresponding thioacetate with sodium hydroxide in methanol.[9c] Subsequent coupling of the auxiliary **3** in the



Scheme 4. Amino acid substrates for the intramolecular Staudinger ligation. Cbz = benzyloxycarbonyl.

Table 1: Yields of the cyclization precursors and the intramolecular Staudinger ligation.



1	Yield [%][a] **2**	**4**	**5** (Yield [%])[a,b]	
a	95	100	**a** (84)	
b	99	96	**b** (59; *95*)	
c	99	98	**c** (80; *95*)	
d	95	97	**d** (80)	
e	91	61	**e** (80)	
f	76	95	**f** (60)	
g	89	88	**g** (35)	
h	85	84	**g** (29)	

[a] Yields of isolated products. The yields in italics were calculated from the ^{1}H NMR spectrum (400 MHz) of the crude reaction mixture. [b] The lactamization reactions were carried out at a concentration of 0.01 M. Tf = trifluoromethanesulfonyl.

presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) or EDC gave the cyclization precursors **4a–h** in high yields.

Compounds **4a–h** are exceptionally stabile and do not undergo undesired premature Staudinger reactions or oxidation by air. The final intramolecular Staudinger reaction was

effected after liberation of the phosphane by decomplexation with 1,4-diazabicyclo[2.2.2]octane (dabco; 2–5 equiv) at 70 °C. The unfunctionalized 7–9-membered lactams **5a–c** were isolated in yields of 84, 59, and 80 %, respectively. It was calculated by ^{1}H NMR spectroscopic analysis of the reaction mixtures that the cyclizations to **5b** and **5c** occurred essentially quantitatively. $^{\alpha}$Z-lysine (**1d**) also cyclized efficiently to give **5d** in 80 % yield. The cyclization of precursors **4e** and **4f**, which have a conformationally unbiased tertiary N–CO bond, gave bislactams **5e** and **5f** in yields of 80 and 60 %, respectively. Finally, we turned our attention to the highly challenging target 3-benzyl-[1,4]diazepane-2,5-dione (**5g**). Gratifyingly, both **4g** and **4h** reacted to give **5g** in isolated yields of 35 and 29 %, respectively, as **1g** and **1h** can not be lactamized directly by using traditional methodologies.[7b] The higher yields in the reactions of **4e** and **4g** in comparison to those of **4f** and **4h** suggests that the cyclization is sensitive to steric congestion in the C-terminal fragment. This is a phenomenon that has been observed in peptide cyclizations previously by us and others.[7b,17]

In conclusion, the results described herein show that medium-sized lactams that are inaccessible or can only be prepared with great difficulty by methods that rely on the direct carboxy activation of ω-amino acids can be prepared by using this intramolecular Staudinger ligation method. Work is currently in progress to expand the intramolecular Staudinger ligation approach to the synthesis of small cyclopeptides.

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Keywords: cyclization · lactams · medium-ring compounds · ring contraction · synthetic methods

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