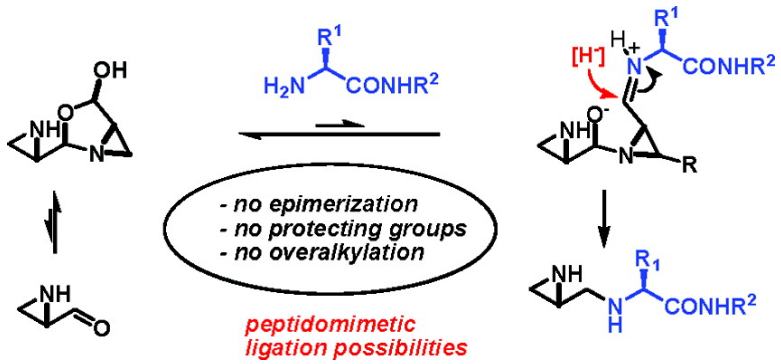
Communication

Epimerization- and Protecting-Group-Free Synthesis of Peptidomimetic Conjugates from Amphoteric Amino Aldehydes

Xinghan Li, and Andrei K. Yudin

J. Am. Chem. Soc., **2007**, 129 (46), 14152-14153• DOI: 10.1021/ja076155p • Publication Date (Web): 27 October 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 5 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 10/27/2007

Epimerization- and Protecting-Group-Free Synthesis of Peptidomimetic Conjugates from Amphoteric Amino Aldehydes

Xinghan Li and Andrei K. Yudin*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada, M5S 3H6

Received August 15, 2007; E-mail: ayudin@chem.utoronto.ca

Peptide bonds are ubiquitous components of numerous bioactive molecules that play important roles in regulating cellular function. Replacement of the peptide bonds by their isosteres can give rise to molecules with superior stability and specificity. For example, the so-called reduced amide bond isosteres contain aminomethylene functional groups in place of the selected amide linkages (Figure 1a).[1] This structural substitution is present in a wide range of aspartyl protease inhibitors.[2] The aminomethylene fragment is isosteric with the tetrahedral transition state formed during amide bond hydrolysis. This ensures that the peptidomimetic inhibitor binds to the protease target tighter than the substrate. At the same time, the reduced amide bond analogue is not cleaved by the protease and often displays better binding than its peptide prototype.[3] Many different modes of interaction between proteases and their inhibitors have been observed by X-ray crystallography.[4] The diversity of recognition mechanisms underscores the importance of modulating the target/peptidomimetic ligand interactions in the vicinity of the active site. Herein, we report a general strategy that addresses three critical issues in methodology directed toward peptidomimetic molecules: (1) the reaction sequence can be used in order to selectively attach an unprotected aziridine electrophile to an amino-acid-containing molecule; (2) it delivers a peptidomimetic connection without epimerization on either side of the reduced amide bond; and (3) it allows for a late-stage peptidomimetic ligation.

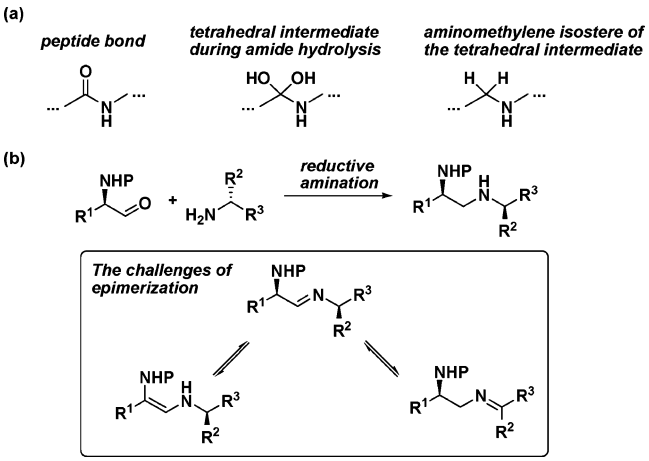
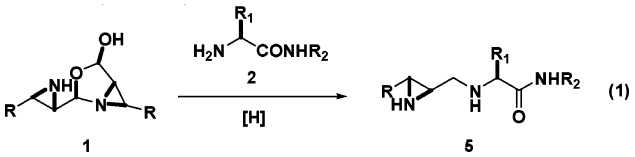


Figure 1. (a) Amide bond hydrolysis and its aminomethylene isostere; (b) the challenges of peptidomimetic construction.

The most widely employed strategy toward reduced amide bond isosteres is based on N-protected amino aldehydes (Figure 1b).[5] Typically, a peptide or a nitrogen-protected amino acid is converted into the corresponding aldehyde by first forming an ester or a Weinreb amide, which is subsequently reduced by a hydride transfer reagent. These steps are followed by reductive amination with an appropriate amine component. Although this valuable reaction sequence has been used in numerous academic and industrial applications, there are significant challenges that face this chemistry. The amino aldehydes as well as their immediate precursors are notoriously sensitive to epimerization.[6] In addition, the imine/enamine equilibrium triggered during the reductive amination can lead to further epimerization on both the amine and the aldehyde sides of the peptidomimetic fragment (Figure 1b).[7] Last but not least, reliance on protecting groups at nitrogen in amino aldehydes diminishes the synthetic efficiency of these operations.

We became interested in exploring the potential of the recently discovered unprotected amino aldehydes in constructing peptidomimetic conjugates.[8a] The *kinetic amphoterism* has been coined in order to describe the coexistence of an unprotected aziridine and aldehyde groups in such molecules.[8b] We reasoned that if one were to attach an unprotected aziridine unit to an amino acid residue via a non-peptide bond,[9] one would not only gain access to an electrophilic peptidomimetic conjugate but also facilitate synthesis of both natural and unnatural amino-acid-based peptidomimetics via aziridine ring-opening chemistry (eq 1). Standard reductive amination conditions ($NaBH_3CN$, MeOH, 1% HOAc) on aziridine aldehyde dimers and amino acid derivatives delivered poor conversions and yields. Further experiments revealed that $ZnCl_2/NaBH_3CN$ combination gives optimal selectivity. Most importantly, the reductive amination was not accompanied by overalkylation or epimerization on either side of the peptidomimetic connection. A mechanistic investigation uncovered the salient features of this process (Scheme 1). According to our data, the monomeric amino aldehyde-derived imine formation is not taking place during the reaction. Instead, the adduct **3**, formed upon condensation between the amino aldehyde dimer **1** and amine **2**, participates in an unfavorable equilibrium with its "half-opened" form **4**, which is rapidly reduced by the hydride transfer agent. The short lifetime of **4** ensures that tautomerization and, therefore, epimerization are negligible. Using this protocol, a variety of unprotected amino aldehydes can be cleanly conjugated with α-amino acid derivatives (Table 1).



The absence of epimerization on the aldehyde side of the aminomethylene linkage is secured through energetically uphill enolization of the strained aziridine aldehyde. Another key feature of this process is that the equilibrium concentration of the free aldehyde is unobservably low, resulting in no overalkylation.[10] A presently unexplained fidelity with regard to homochiral dimer reformation during the reaction must be responsible for the low concentration of the free aldehyde. A crossover between two

10.1021/ja076155p CCC: $37.00

Scheme 1. Mechanistic Underpinnings of Epimerization-Free Synthesis of Peptidomimetic Conjugates

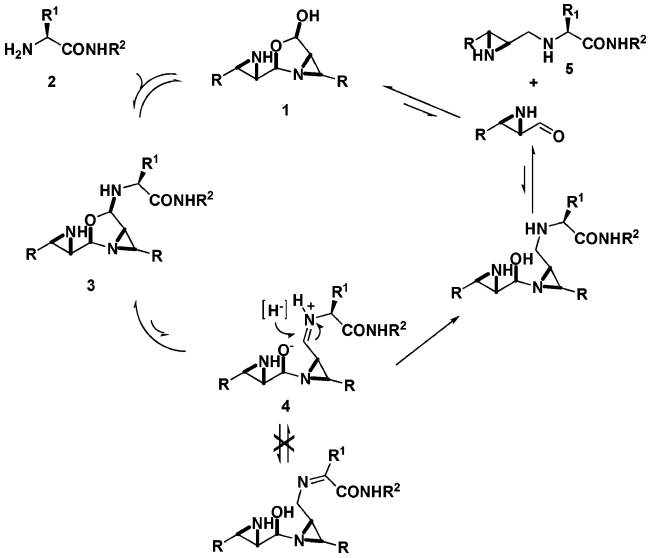
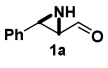
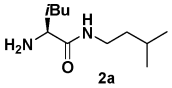
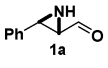
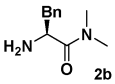
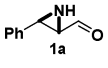
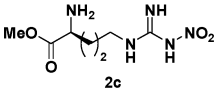
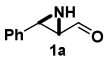
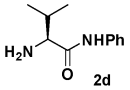
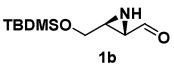
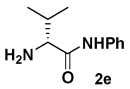
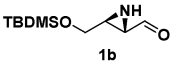
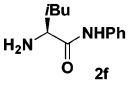
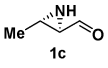
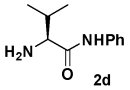
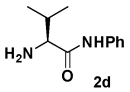
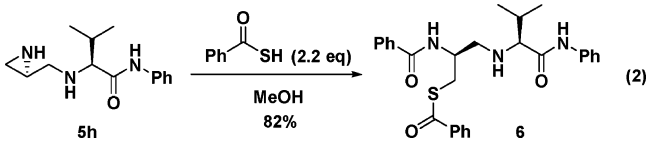


Table 1. The Scope of Peptidomimetic Conjugation Chemistry[a]

entry	aziridine aldehyde[b]	amino acid derivative	yield[c]
1	 1a	 2a	85%
2	 1a	 2b	75%
3	 1a	 2c	86%
4	 1a	 2d	81%
5	 1b	 2e	92%
6	 1b	 2f	84%
7	 1c	 2d	60%
8	 1d	 2d	51%

[a] Unless stated otherwise, the reactions were carried out using 0.5 equiv of the dimer (1 equiv of aldehyde), 1.2 equiv of amine, 1.5 equiv of $NaBH_3CN$, and 1 equiv of $ZnCl_2$ in THF and MeOH (1/1) at room temperature. [b] The corresponding monomer. [c] Isolated yield.

different amino aldehyde dimers has been detected by ESI MS only in trifluoroethanol ($pK_a = 12.4$), definitively suggesting appreciable concentration of the free aldehyde species in that solvent. Importantly, the reductive amination is not occurring in trifluoroethanol. Instead, the reaction leads to preferential aldehyde reduction, providing further evidence for the dimer-driven mechanism depicted in Scheme 1. The utility of amino acid conjugates is demonstrated by a thioacid-triggered process (eq 2). This sequence offers a possibility for a *peptidomimetic ligation* of two fragments such that a reduced amide bond isostere is specifically introduced at the cysteine residue with complete stereocontrol of the nearby chiral centers.[11]



In closing, we have developed a protecting-group-free strategy for replacing amide bonds with versatile aziridine-containing templates for the synthesis of peptidomimetic molecules. A high degree of stereocontrol achieved during reductive amination hinges upon unusual preferences of the amphoteric amino aldehydes. One can anticipate straightforward construction of structurally diverse affinity probes using this chemistry.[12] The resulting conjugates also offer a possibility for peptidomimetic ligation. Taken together, these findings should allow access to templates for introducing both natural and unnatural amino acid residues in close proximity to the reduced amide bond isosteres. Studies along these lines are being actively pursued in our laboratories.

Acknowledgment. We thank NSERC and CIHR for financial support of this work. Mr. Ryan Hili is thanked for helpful discussions.

Supporting Information Available: Experimental procedures and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359.
(2) (a) Maly, D. J.; Huang, L.; Ellman, J. A. *ChemBioChem* **2002**, *3*, 17. (b) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305.
(3) Szelke, M.; Leckie, B.; Hallett, A.; Jones, D. M.; Sueiras, J.; Atrash, B.; Lever, A. F. *Nature* **1982**, *299*, 555.
(4) Wlodawer, A.; Erickson, J. *Annu. Rev. Biochem.* **1993**, *62*, 543.
(5) Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514.
(6) Potetinova, J. V.; Milgotina, E. I.; Makarov, V. A.; Voyushina, T. L. *Russ. J. Bioorg. Chem.* **2001**, *27*, 141.
(7) Epimerizations on both the amine and the aldehyde sides during peptidomimetic synthesis have been documented: (a) Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Chem. Rev.* **2004**, *104*, 5823. (b) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, *23*, 465. (c) Jensen, K. J.; Alsina, J.; Songster, M. F.; Vagner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441. (d) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (e) Ho, P. T.; Chang, D.; Zhong, J. W. X.; Musso, G. F. *Peptide Res.* **1993**, *6*, 10.
(8) (a) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772. (b) Hili, R.; Yudin, A. K. *Chem.—Eur. J.* **2007**, *13*, 6538.
(9) For recent applications of aziridine carboxylic acids, see: (a) Vicik, R.; Busemann, M.; Baumann, K.; Schrimeister, T. *Curr. Top. Med. Chem.* **2006**, *6*, 331. (b) Galonić, D. P.; Ide, N. D.; van der Donk, W. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2005**, *127*, 7359.
(10) Overalkylation during reductive amination is a recognized problem: Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
(11) For *native* chemical ligation, see: Johnson, E. C. B.; Kent, S. B. H. *J. Am. Chem. Soc.* **2006**, *128*, 6640.
(12) (a) Evans, M. J.; Cravatt, B. F. *Chem. Rev.* **2006**, *106*, 3279. (b) Fonović, M.; Bogyo, M. *Curr. Pharm. Des.* **2007**, *13*, 253.

JA076155P