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N-Amino-imidazolin-2-one Peptide Mimic Synthesis and Conformational Analysis

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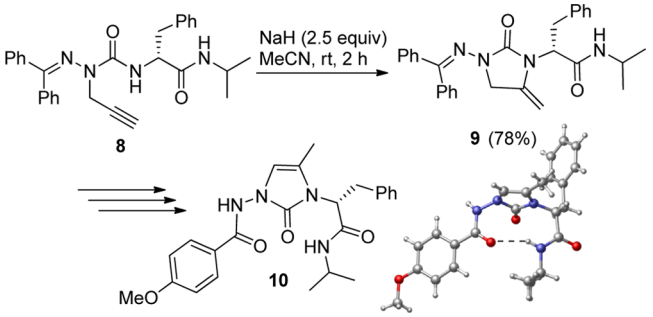
ABSTRACT



Base-promoted 5-*exo-dig* cyclizations of aza-propargylglycinamides provided *N*-amino-imidazolin-2-one peptide mimics, which exhibited turn geometry in X-ray crystallographic and NMR spectroscopic analyses. Sonogashira coupling prior to cyclization afforded *N*-amino-imidazolin-2-ones with diverse 4-position aromatic substituents with potential to serve as Phe and Trp mimics.

Identification of biologically active conformers is critical for developing therapeutics based on peptide structures, because precise folding is essential for function. Geometrically restricted analogs are thus valuable tools, because they may reduce energetic costs for folding into binding conformations and, thereby, improve potency, selectivity, and stability.[1]

To constrain backbone geometry and induce turn conformations, α-amino-γ-lactams,[2] so-called Freidinger–Veber lactams, have been commonly introduced into peptide sequences; however, their lack of side-chain functions may translate into loss of affinity and activity. Aza analogs of amino acids possess a nitrogen atom in place of the CHα. A variety of side chains have been installed onto these semicarbazide structures, which when introduced into azapeptides restrict the backbone ϕ and ψ dihedral angles, due to the lone pair–lone pair electronic repulsion of the adjacent nitrogen and urea planarity, respectively.[3] A strategy has now been devised to induce peptide turn geometry by combining the covalent constraints of α-amino-γ-lactams with the electronic restrictions and side-chain diversity of aza-amino acids through the synthesis of substituted *N*-amino-imidazolin-2-ones (Figure 1).

Imidazolin-2-ones have utility as antitumor agents,[4] antibacterial MurB inhibitors,[5] dopamine D_4 and CGRP

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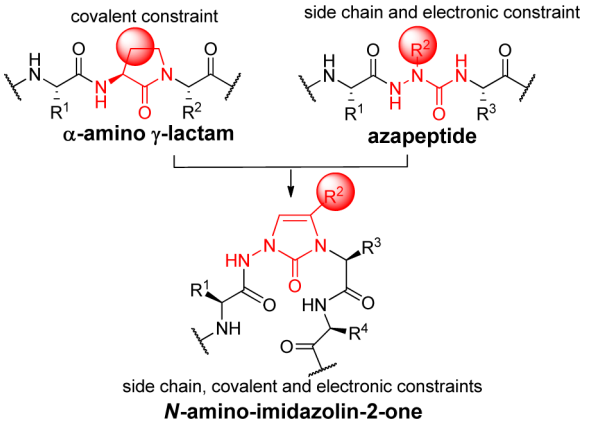


Figure 1. *N*-Amino-imidazolin-2-one turn mimic conception.

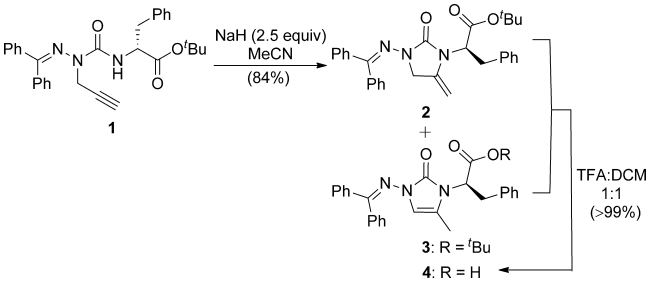
receptor antagonists,[6,7] antioxidants,[8] and unnatural base pairs.[9] To the best of our knowledge, however, the synthesis and biological evaluation of *N*-amino-imidazolin-2-ones had not been explored.

Previously, the submonomer approach for azapeptide synthesis surmounted issues of hydrazine chemistry to give access to side chains inaccessible by traditional methodology, including propargyl, allyl, and (hetero)aryl moieties.[10,11] The aza-propargylglycine side chain was later reacted in copper-catalyzed 1,3-dipolar cycloadditions to make aza-1,2,3-triazole-3-alaninyl peptide mimics.[12] Aza-propargylglycinamides have now been explored in 5-*exo-dig* cyclizations to access *N*-amino-imidazolin-2-one peptidomimetics, as well as in Sonogashira cross-coupling reactions prior to cyclization to provide their 4-arylmethyl analogues, which may mimic phenylalanine and tryptophan residues.

Imidazolin-2-ones and imidazolidin-2-ones have been respectively prepared from propargylic and allylic ureas by base-promoted 5-*exo-dig* cyclizations.[13] Annulation has typically necessitated an electron-deficient urea nitrogen and activation of the π-system using transition metal salts (i.e., silver,[14] palladium,[15] and gold complexes).[16] Moreover, cyclic amino acids, such as dehydroprolines, had been prepared respectively by Pd- and Ag-catalyzed 5-*endo-dig* cyclization of *N*-Ts- and Boc-protected propargylglycine analogs.[17,18]

To study the cyclization, aza-propargylglycinyl dipeptide **1** was used and prepared by chemoselective alkylation of benzhydrylidene aza-glycinyl-D-phenylalanine *tert*-butyl ester (**5**) with propargyl bromide (Schemes 1 and 2).[19] Attempted 5-*exo-dig* cyclization of azadipeptide **1** using homogeneous gold catalysis [$(t\text{-Bu})_2(o\text{-biphenyl})$PAuCl (5 mol %) and AgOTf (5 mol %)] failed, likely because the urea nitrogen was insufficiently electron-deficient.

Scheme 1. *N*-Amino-imidazolin-2-one synthesis



N-Amino-imidazolin-2-one **2** was, however, obtained in 81% yield, by adding 2.5 equiv of NaH to the mixture containing **1** and the cationic gold complex formed *in situ* in acetonitrile for 2 h. The impact of gold catalysis was later deemed negligible, because **2** was produced in 84% yield on reaction of **1** with 2.5 equiv of NaH in acetonitrile without a catalyst (Scheme 1). From the 5-*exo-dig* cyclization, an exocyclic double bond was first produced and migrated inside the ring to furnish the thermodynamically more stable *N*-amino-imidazolin-2-one **3**. Among the solvents studied, acetonitrile proved the best (see Supporting Information (SI)). Excess NaH was necessary for high yields.

To study the effect of *N*-amino-imidazolin-2-one on peptide conformation, model **10** was synthesized and examined by X-ray crystallography and NMR spectroscopy (Scheme 2). Benzhydrylidene aza-glycinyl-D-phenylalanine isopropyl amide **7** was made from **5** by *tert*-butyl ester cleavage in a 1:1 v/v mixture of TFA/DCM and coupling to isopropylamine by way of a mixed anhydride.[20] Alkylation of semicarbazone **7** with propargylbromide[19,20] gave aza-propargylglycinamide **8** in 71% yield without detectable racemization; however,

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(16) (a) Zhang, G.; Luo, Y.; Wang, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 1–6. (b) Verniest, G.; Padwa, A. *Org. Lett.* **2008**, *10*, 4379–4382.

(17) Wolf, L. B.; Tjen, K. C. M. F.; ten Brick, H. T.; Blaauw, R. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 70–83.

(18) Van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791–1795.

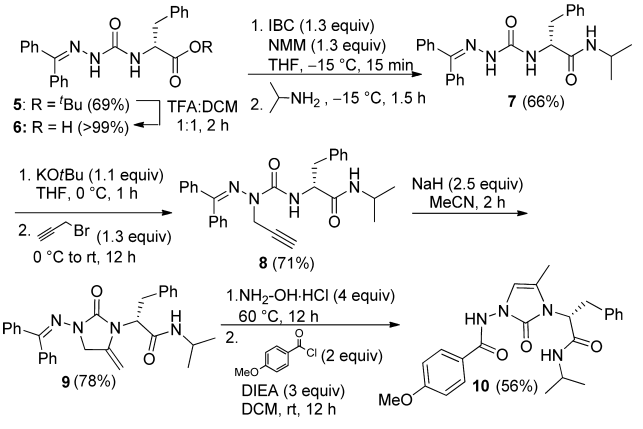
(19) García-Ramos, Y.; Proulx, C.; Lubell, W. D. *Can. J. Chem.* **2012**, *90*, in press.

(20) Bourguet, C. B.; Proulx, C.; Klocek, S.; Sabatino, D.; Lubell, W. D. *J. Pept. Sci.* **2010**, *16*, 284–296.

subsequent NaH-promoted 5-*exo*-*dig* cyclization gave imidazolin-2-one **9** in 78% yield with 10% racemization (see SI). Olefin migration occurred upon hydrazone removal, using hydroxylamine hydrochloride in pyridine,[9] to afford *N*-amino-imidazolone hydrochloride which, without further purification, was treated with 4-methoxybenzoyl chloride to provide *N*-acyl dipeptide amide **10** in 56% overall yield.

Crystals were grown by slow diffusion of hexanes into an ethyl acetate/chloroform solution of **10**. X-ray diffraction revealed two turn conformations in the solid state (Figure 2): **10a** exhibiting a type II′ β-turn with an intramolecular ten-membered hydrogen bond between residues i and $i+3$, and **10b** showing a seven-membered hydrogen bonded conformer in an inverse γ turn. The X-ray structures for **10** deviate primarily by rotation of the ψ_{i+2} dihedral angle, as shown by comparison of their φ and ψ dihedral angles with an ideal turn geometry and crystal structures of azapeptide and α-amino-γ-lactams, which adopted a turn geometry (Table 1).[21−23] In contrast to amino lactams, the planar geometry of the *N*-amino-imidazalone causes the ψ_{i+1} dihedral angle to deviate by 33°−46° from that of an ideal type II′ β-turn, the geometry of which is contingent on the stereochemistry of the *C*-terminal residue (i.e., Phe).

Scheme 2. Synthesis of *N*-(*p*-Methoxybenzamido)imidazolin-2-one Isopropyl Amide (**10**)



Measurement of the amide chemical shift values of **10** as a function of DMSO-d_6 % (1 to 100%) in $CDCl_3$ indicated relatively little variation (0.45 ppm) for the isopropylamide NH signal compared to the benzamide chemical shift (1.21 ppm; see SI), consistent with solvent-shielded

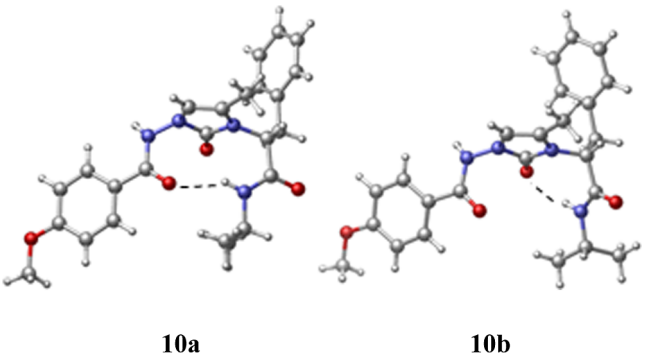
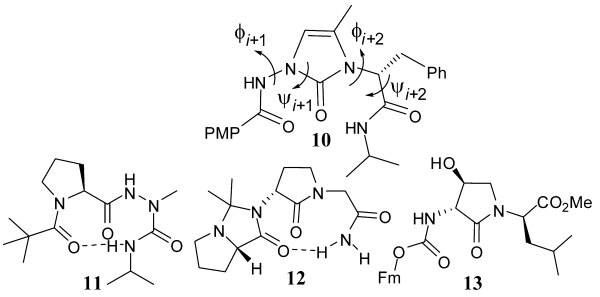


Figure 2. X-ray structures of *N*-(amido)imidazolin-2-one amide **10**. Broken lines represent inferred hydrogen bonds.

Table 1. Structures **10**−**13** and Their ϕ and ψ Dihedral Angles (in degrees) from Crystal Analyses Compared with Ideal Turns



type of turn	φ_{i+1}	ψ_{i+1}	φ_{i+2}	ψ_{i+2}
β-II′	60	−120	−80	0
inverse γ	n/a	n/a	−70	60
10a	58.9	−153.3	−69.1	−4.6
10b	62.1	−166.1	−71.7	65.7
β-II	−60	120	80	0
11	−55.4	120.9	89.3	17.8
12	−42	133	89	−6.9
13	−40	116	96	−97

(hydrogen-bonded) and exposed hydrogens,[24] as found in the X-ray structure.

To access constrained Phe, Trp, and His mimics, Sonogashira couplings were performed on dipeptide **1**, using various aryl iodides, $Pd(PPh_3)_2Cl_2$, and CuI in a 1:1 DMF/Et_2NH mixture (Scheme 3, Table 2). Electron-rich and -poor aryl iodides as well as *N*-protected indole and imidazole iodides all reacted in the coupling reaction to furnish aza-arylpropargylglycines **14** in 50−93% yields.

Exposure of **14** to the NaH-promoted 5-*exo*-*dig* cyclization produced mixtures possessing endo- and exocyclic double bonds. For example, imidazolin-2-ones **15a** and **16a** were isolated as isomeric mixtures in 69% yield. Although either *Z* or *E* geometry were possible for **15**, a

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Scheme 3. Sonogashira/Cyclization Reaction Sequence for the Synthesis of 4-Substituted *N*-Amino-imidazolin-2-ones

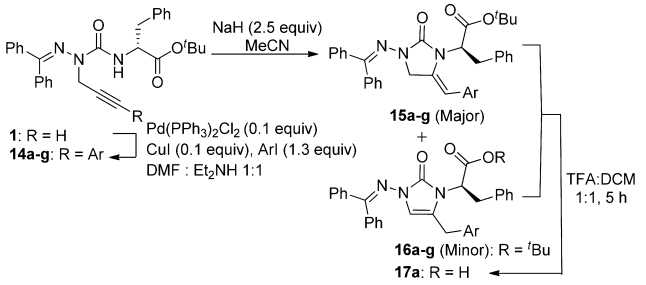
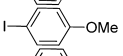
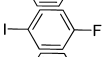
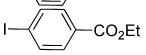


Table 2. Sonogashira/Cyclization Reaction Sequence Yields

entry	ArI	% yield (% recovered starting material)	
		14a-g	**15a-g + 16a-g**
a		87	69
b		85	10 (56)
c		90	64
d		93	42
e		80	34
f		65	40 (26)
g		50	0[a]

[a] Starting material was recovered.

through-space interaction between the vinyl proton and the methylene of imidazolidinone **15c** in a 2D NOESY experiment revealed an exclusive exocyclic *Z* double bond geometry. Acid cleavage of the *tert*-butyl ester promoted double bond migration inside the five-membered ring to furnish **17a** (Scheme 3).[25]

In the NaH-promoted 5-*exo-dig* cyclization, the fluorine *p*-substituent was well tolerated and gave **15c** in 64% yield (Table 2). Substrates **14** with electron-withdrawing substituents (i.e., trifluoromethyl) reacted rapidly giving complete consumption of the starting material, albeit with lower yields due to decomposition. In contrast, electron-rich aza-*p*-methoxyphenylpropargylglycinamide **14b** afforded *N*-amino-imidazolin-2-one **15b** in only 10% yield with recovered starting material. Imidazolyl alkyne **14g** failed to react and was exclusively recouped. In contrast, *N*-Boc-3-indolyl alkyne **14f** underwent base-promoted cyclization to afford constrained tryptophan mimic imidazolin-2-one **15f** in 40% yield with recovered starting material.

4-Substituted *N*-amino-imidazolin-2-ones have been prepared as hybrids of the covalent and electronic constraints of α-amino-γ-lactams and aza-amino acids. Opportunity for adding side-chain functionality was demonstrated by using a Sonogashira arylation prior to NaH-promoted 5-*exo-dig* cyclization of aza-propargylglycinamide to afford 4-substituted *N*-amino-imidazolin-2-one mimics. The propensity of the *N*-amino-imidazolin-2-one subunit to induce turn conformations was confirmed using X-ray crystallography and NMR spectroscopy of model peptide **10**. Considering their conformational preferences and potential for their diversification, *N*-amino-imidazolinones represent a promising class of geometrically restrained mimics for studying peptide structure. Incorporation of *N*-amino-imidazolinones into a biologically active peptide sequence is currently under investigation and will be reported in due time

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Note Added after ASAP Publication. The Table 1 graphic contained an error in the version published ASAP August 14, 2012. The correct version reposted August 22, 2012.

Supporting Information Available. Experimental procedures, compound characterization data, and NMR spectra for new compounds. Crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(25) Partial epimerization (er 74:26) was observed for **15a**, likely due to the alkaline cyclization conditions (see SI). The extent of racemization is consistent with that (er 88:12–85:15) observed during the NaH-promoted cyclization of phenylalanine-containing methionine-sulfonium dipeptides, to provide α-amino-γ-lactams in ref 1b.