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Pyrrole-Based Scaffolds for Turn Mimics

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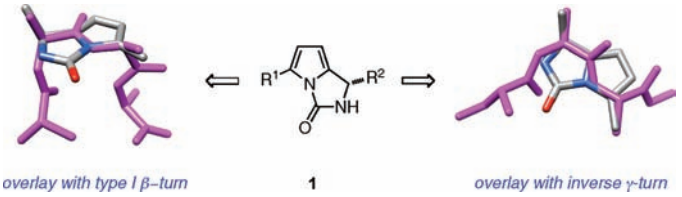
ABSTRACT



Two amino acid derived synthons were combined to give homopropargylic amines 2. Platinum dichloride was used to cyclize these intermediates into pyrroles 3 which collapsed to the target secondary structure mimics 1 on treatment with base. Side chains of these compounds overlay with an idealized type 1 β-turn *and* with an inverse γ-turn.

Placement of a carbonyl group at the 2- or 5-position of a pyrrole arranges the CO and heterocyclic *N*- in a 1,3-disposition, just like the main-chain CO and N of amino acids. Several groups have seen this as an opportunity to incorporate pyrrole 2-carboxylic acids into peptides as amino acid surrogates.[1] Simultaneously, others have used amino acid starting materials for syntheses of pyrroles with protein/peptide-like side chains.[2] However, to the best of our knowledge, none of these strategies have used *two* amino acids to give pyrrole derivatives with *two* amino acid derived side chains.

Our group is interested in molecules that resemble secondary structures by presenting pertinent amino acid side chains, *i.e.* minimalist secondary structure mimics.[3] We saw the opportunity to build on the insights of others outlined above, to produce analogs of β-turns, specifically compounds **1**, that project *two* amino acid side chains in orientations corresponding to $i + 1$ and $i + 2$ residues of a type I β-turn. Moreover, it was anticipated that syntheses of these molecules could be facilitated by numerous new methods that have emerged recently for intramolecular

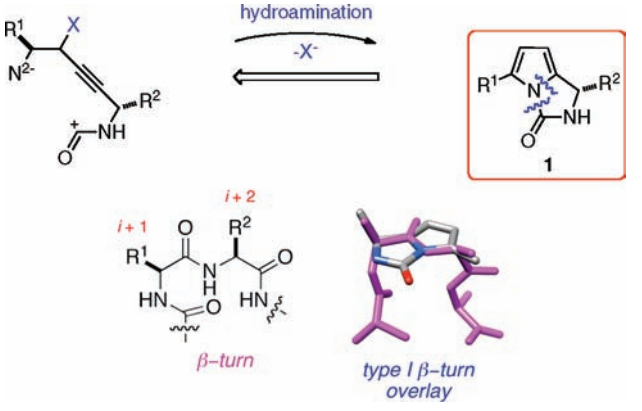


Figure 1. Conceptual basis of 1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-ones as β-turn mimics.

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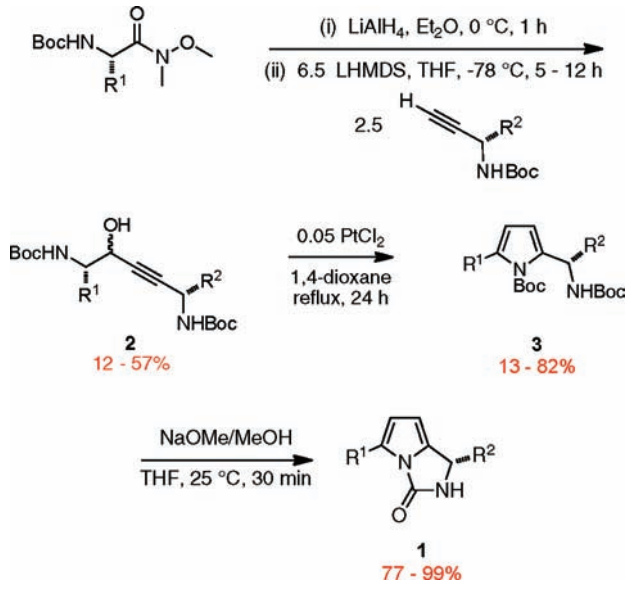
Scheme 1. Syntheses of the Target Compounds **1**



amination of alkynes to produce *N*-heterocycles via the disconnections shown (Figure 1).[4]

Syntheses of the target compounds **1** began with Weinreb amides[5] of Boc-protected amino acids (Scheme 1).[6] These were reduced to the corresponding aldehydes, which, without isolation, were immediately reacted with dianionic, Boc-protected alkynes derived from amino acids.[7] Several exploratory sets of conditions were employed to effect this transformation, and an alternative route involving formation of propargyl ketones was also investigated (see Supporting Information). The conditions outlined in Scheme 1 were the most effective overall. This is a difficult reaction, because it involves combination of an anionic electrophile with a nucleophile dianion.

Sarpong's platinum (2+) mediated cyclizations of propargylic (2-pyridyl)alcohols[8] were used as an initial paradigm for formation of pyrroles in this work (Scheme 2a). Scheme 2b reiterates the mechanistic hypothesis outlined by Sarpong et al. for their transformation. It soon became evident that elimination of the NHBoc group on the newly formed pyrrole side chain would be problematic. Consequently, a series of microwave-mediated trial reactions were run to optimize the conversion and **3**:**4** product ratio. Attempts to use other catalysts did not give better results. Similarly, acidic or basic additives, or phosphine ligands,

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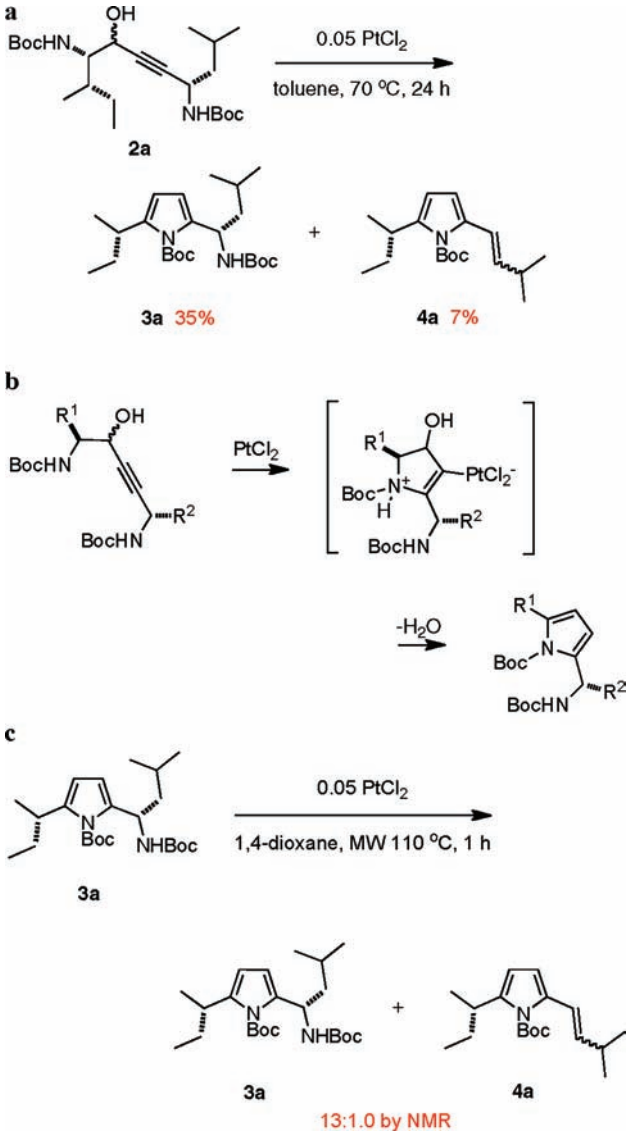
Scheme 2. Hydroamination/Cyclization



gave no benefits (see Supporting Information). However, changing the solvent from toluene to 1,4-dioxane markedly increased the conversion but gave approximately the same product selectivity (Table 1).

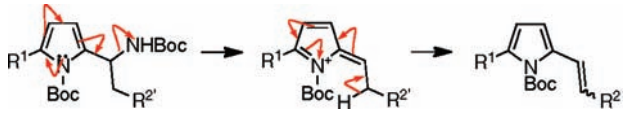
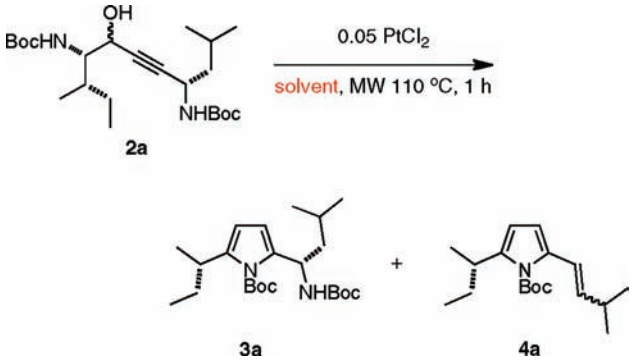


Figure 2. A possible mechanism for elimination of the NHBoc group.

Scheme 2c shows the result of subjecting the isolated, purified product **3** to the same reaction conditions used to make it in Table 1, entry 2. Alkenyl pyrrole **4a** was formed in this experiment, but the **3a**:**4a** product ratio favored **3a**

Table 1. Pt(II)-Catalyzed Pyrrole Formation through Hydroamination (Solvent Effect)



entry	solvent	**3a**:**4a**	conversion yield (%)
1	benzene	4.0:1.0	85
2	1,4-dioxane	4.3:1.0	80
3	THF	2.4:1.0	61
4	1,2-dichloroethane	2.1:1.0	50
5	toluene	4.8:1.0	46
6	EtOH	1.1:1.0	21

much more than in the synthesis of this material. This observation indicates some, but not all, of the elimination product **4** is derived from **3** via the process outlined in Figure 2. This competing mechanism could involve elimination of the NHBoc group to give an eneyne before pyrrole formation.

Table 2 shows data for a series of substrates **3** with the various amino acid side chains used. The methodology was therefore validated using Ile, Leu, Val, Tyr(Bn), Met, and Thr(Bn). An adjustment had to be made for the glycine-containing substrate **2f**, because very little product was formed in this situation. Product *was* formed when the *bis*-Boc protected substrate **2f'** was used instead, but still the product yield was low.

Scheme 3. Cyclization to the β-Turn Mimics

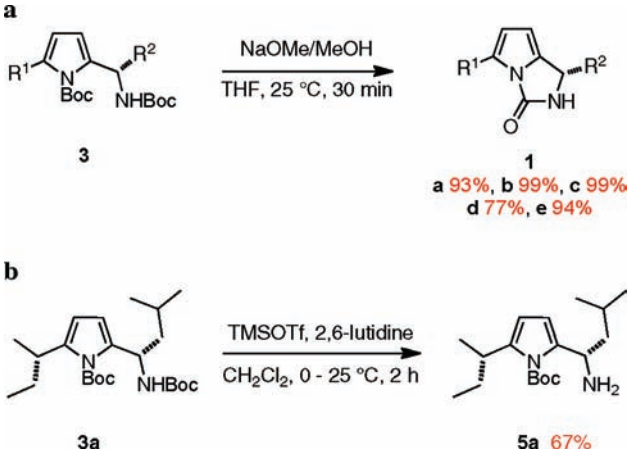
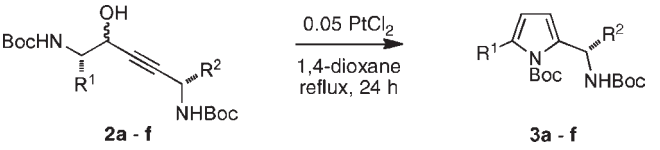
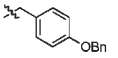
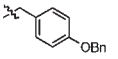
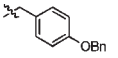
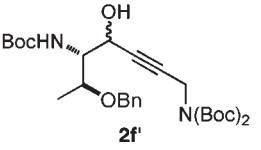


Table 2. Pt(II)-Catalyed Pyrrole Formation through Hydroamination



2	R^1	R^2	**3** (%)	**4** (%)
a			82	12
b			72	3
c			21	10
d			61	17
e			30	trace
f[a]		H	13	trace

[a] Substrate for **2f'** was used for this reaction.



Removal of the pyrrole-*N* protecting group under *basic* conditions led to simultaneous cyclization to the 1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one scaffolds **1** as in Scheme 3a. Removal of *both* Boc-protecting groups without cyclization was also of interest, because the diamines corresponding to **3** can be regarded as β-turn mimics, though less rigid than the target compounds **1**. It proved difficult to do this; in the event, we only succeeded in removing the Boc-protection from the side chain in **3a** under the buffered conditions indicated.[9] In fact, even this reaction was hard to control and reproduce.

1*H*-Pyrrolo[1,2-c]imidazol-3(2*H*)-ones of different kinds have been associated with various types of characteristics in medicinal chemistry. These include molluscicidal,[10] antidiabetic,[11] and $5HT_3$ antagonist[12] activities. This indicates the scaffold itself is amenable to interactions in biological systems.

As turn mimics, compounds **1** are compact and overlay well with the class of β-turns most frequently encountered

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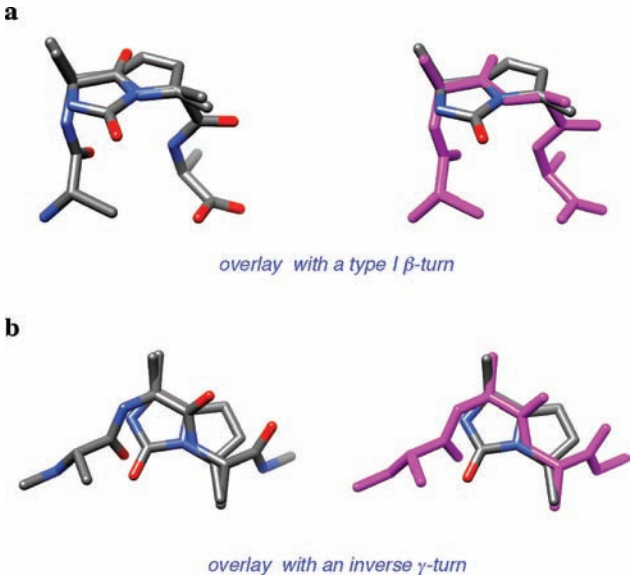

Figure 3. Overlay with the $i + 1$ and $i + 2$ side chains of an ideal type I β-turn (a) and with the $i + 1$ and $i + 2$ side chains of an inverse γ-turn (b).

in protein and peptide conformations, *i.e.* type I.[13] In our group, we refer to compounds like this, ones that achieve mimicry using *only* appropriately projected side chains, as *minimalist mimics*.[3a] Though they did not use this term, Hamilton[14] and Hirschmann/Smith,[15] for instance, employed a similar concept before us. However, we have recently noted[3b] that scaffolds described as *minimalist* tend to be superimposable on other elements of secondary structure; *i.e.* they tend to be promiscuous. In fact, this is true of compounds **1**. Figure 3 illustrates how scaffold **1** can be overlaid with the $i + 1$ and $i + 2$ side chains of an ideal type I β-turn *and* with $i + 1$ and $i + 2$ of an inverse γ-turn.

Peptidomimetic scaffolds that overlap more than one secondary structure may appear to be vulnerable to nonselective binding. This is not so, however, because proteins are targeted by proteins/peptides by choosing the corresponding side chains.[16] Thus duality, or even multiplicity, of fit *increases* the value of scaffolds for secondary structure mimics because they can be applied more widely, particularly in libraries designed for high throughput screening against many diverse targets.[3b] In our opinion, this is a concept that should become more widely applied in peptidomimetic design.

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

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