JOC*Note*

Ring Closure to β-Turn Mimics via Copper-Catalyzed Azide/Alkyne Cycloadditions

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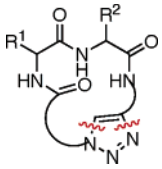

Copper-catalyzed azide alkyne cycloadditions of the linear substrates **1** were used to form the cyclic derivatives **2**. Computational, NMR, and CD analyses of these compounds indicate that their most favorable conformational states include type I and type II β-turn conformations. Selectivity for the dimeric products **6** in these cyclization reactions is discussed.

Many groups are interested in syntheses of β-turn peptidomimetics that have potential applications in medicinal chemistry.[1−4] Our focus in this area has been to constrain dipeptide fragments in appropriate conformations by using macrocyclizations, particularly to form 14-membered rings.[5−9] That ring size facilitates conformational arrangements of edge shared C^{10} systems, one featuring the dipeptide and the other comprising a nonpeptidic fragment (Figure 1).

Many nonpeptidic fragments can be used in the peptidomimetics featured above. This is a means to incorporate diversity and to use different chemical reactions in the ring-closure step. Our bias is to avoid reactions that make the macrocycles more peptidic (i.e., amide bond formation) and to favor ones that give the small heterocyclic fragments found in pharmaceuticals. Moreover, we are currently interested in scalable solution phase methods to do this. Solid-phase syntheses were used in all our previous syntheses of dipeptide-containing peptidomimetics. These have the advantage of *pseudo*-dilution caused by reactive site isolation on solid supports at moderate to low loading. Solution phase methods, on the other hand, require ring closure via efficient reactions. There have been at least two applications of cycloaddition reactions to ring-close β-turn peptidomimetics,[10,11] but none featuring the copper-catalyzed azide alkyne cycloadditions (i.e., "click reactions").[12] Consequently, this Note features application of those reactions as depicted in Figure 2.

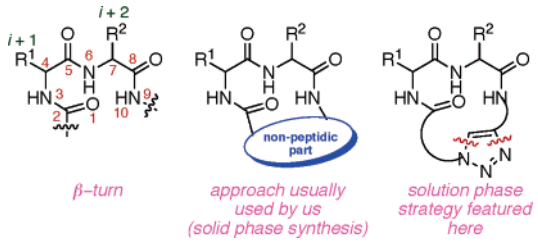

FIGURE 1. Some β-turn nomenclature, semipeptidic mimics usually prepared via solid-phase reactions, and the solution phase click strategy featured in this Note.

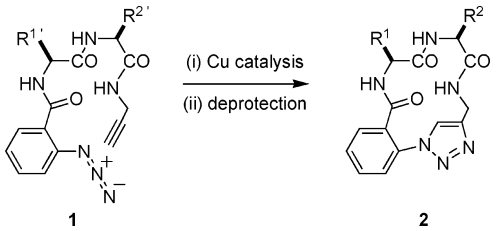

FIGURE 2. Substrate and product structures in this study. $R^{1\prime}$ and $R^{2\prime}$ denote protected side chains; R^1 and R^2 are deprotected ones.

Scheme 1 outlines the preparation of the starting materials **1**. Side chain protection was necessary for the Lys (Cbz), Glu (Bn), Thr (Bn), Ser (Bn), and Tyr (Bn) amino acids. These protecting groups render the intermediates relatively lipophilic, hence use of a water-soluble diimide reagent in the coupling steps facilitated separation of the products via aqueous extractions. Finally, the linear precursors **1** were recrystallized and isolated in an overall average yield of 70%. Thus the substrates **1** were conveniently accessible in gram amounts via syntheses that could be performed in parallel.[13]

Cyclization of the linear precursors gave the "monomeric" and "dimeric" products **5** and **6**. Two measures were taken to favor formation of the protected 14-membered ring products **5**: THF solutions of the azides **1** were added to the copper catalyst over 10−14 h via a syringe pump, and the final concentration was kept low (approximately 0.001 M). Nevertheless, dimeric products

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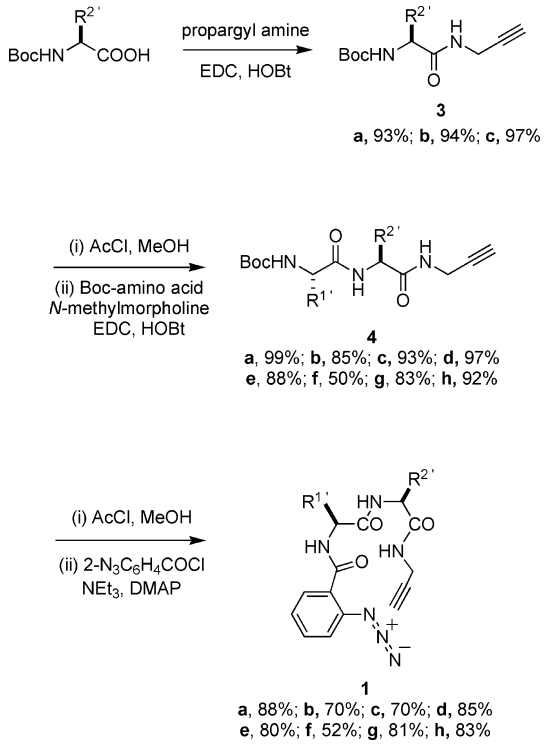
SCHEME 1. Preparation of the Linear Substrates 1[a]



[a] $R^{1\prime}$ and $R^{2\prime}$ denote protected side chains; R^1 and R^2 are deprotected ones (see Table 1 for **a**–**h** definitions).

tended to predominate; data for the cyclization reactions are shown in Table 1.

Even though the crude purities of the monomer/dimer mixtures were high after the cyclization described above, relatively low yields were isolated after purification via HPLC. This is mainly because of the limited solubility of the products in organic and in aqueous solvents. For example, the crude yield of compounds **5a** and **6a** together (39:61) was 92%, but the isolated yield of **5a** was only 12%.

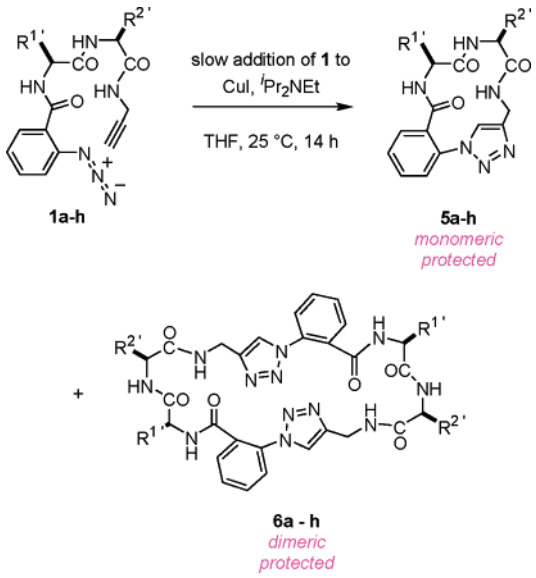
Deprotection of the products **5** (Pd/C, H_2, MeOH, or EtOH) proceeded cleanly to give the unmasked products **2**; any losses of material at this stage probably were attributable to these relatively insoluble materials sticking to the catalyst. Lysine side chains of the peptidomimetics **5d** and **5e** were converted entirely to *N*,*N*-dimethyl and *N*-ethyl derivatives, respectively, under these conditions. Alkylation of amino groups during hydrogenolysis in methanol and ethanol is well-known.[14,15] However, it is curious that this was only observed for the two peptidomimetics containing Gly/Lys amino acids.

Conformational analyses of **2a**–**c** were performed by simulating preferred conformations via the quenched molecular dynamics technique[16,17] without any physical constraints. Bond parameters for low energy conformations were then compared to those measured from ^{1}H NMR, ROESY, temperature coefficient studies, and coupling constants. For instance, interactions of the triazole C*H* proton with the N*H*(i + 1) and N*H*(i + 2) were informative. Circular dichroism (CD) spectra were also recorded. Details of this approach are given elsewhere[18,19] and in the Supporting Information.

Figure 3 shows the low energy conformers that were identified for compounds **2a**–**c** that best fit with the observed physical data. These conformations of compounds **2a** and **2b** resemble type I β-turns, and for **2c** a type II β-turn is most relevant. These data indicate the compounds can sample turn conformations. However, the CD data (Supporting Information) do not closely fit the shape spectra commonly associated with types I and II turn conformations,[20–22] indicating nonideal matches and/or other important contributions to the conformational ensemble.

The studies described above successfully generated monomeric β-turn mimics, the original goal of this work.

TABLE 1. Copper-Catalyzed Cyclization Reactions of Compounds 1



	amino acids			
5	$i+1$	$i+2$	**5/6** (monomer/dimer)[a]	isolated yield **5** (%)[b]
a	Ile	Lys	39:61	12
b	Glu	Lys	54:46	11
c	Thr	Gly	29:71	8
d	Gly	Lys	23:77	14
e	Lys	Gly	23:76	9
f	Gly	Ser	39:61	9
g	Ser	Gly	20:79	8
h	Tyr	Ser	18:82	12

[a] Monomer/dimer ratio was based on the UV peak area of HPLC traces at 254 nm. [b] Calculated on the basis of the mass after preparative HPLC separation.

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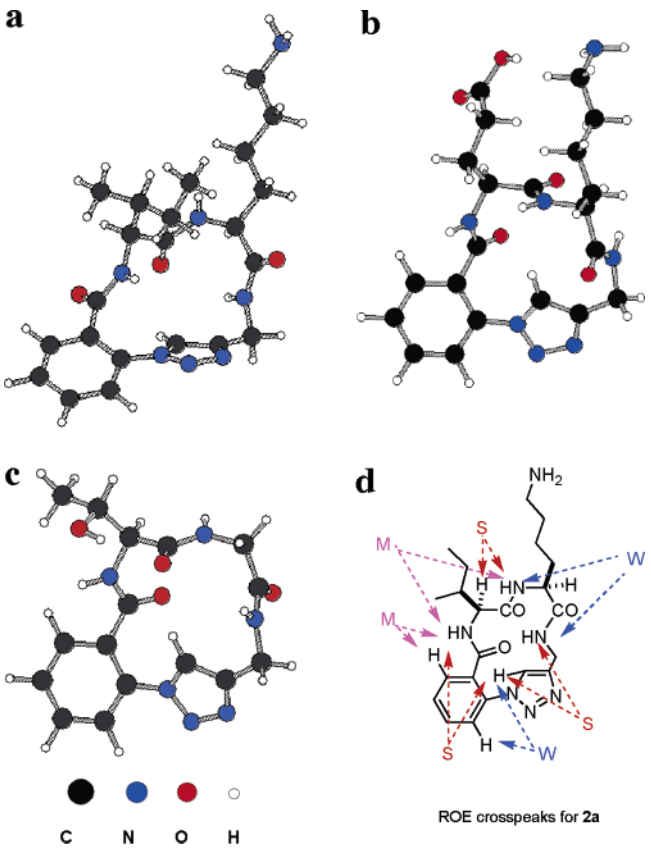

FIGURE 3. (a–c) Best fit low energy conformers for **2a**–**c**, respectively, and (d) illustrative ROE cross-peaks.

However, it was surprisingly difficult to do this. Dimers **6** were preferred for seven of the eight cases cited in Table 1. Further, azidoalkynes similar to the linear substrates **1** were also tested as cyclization precursors, but without success. For instance, when substrates **7** and **8** were subjected to the copper-catalyzed conditions described above there was no evidence of the monomeric cyclized product in the ESI-MS of the crude reaction material; instead, complex mixtures of compounds formed.

The literature reveals that at least four groups have attempted to use copper-mediated azide/alkyne cycloaddition reactions to form macrocyclic rings, but "dimers" were formed in each case.[23–26] Finn et al.[23] described dramatic examples in which 76- and 124-membered rings were formed in preference to the corresponding monomeric ones. This result was unexpected particularly since solid-phase syntheses were used (i.e., conditions in which there is an inherent dilution effect).

Finn and co-workers hypothesized that preferential formation of dimeric products could be due to coordination of two alkynes prior to the cycloaddition and/or to coordination of the catalyst to the peptidic part of the molecule. The immediate precursor to cycloaddition in the copper-mediated transformations is not known, but

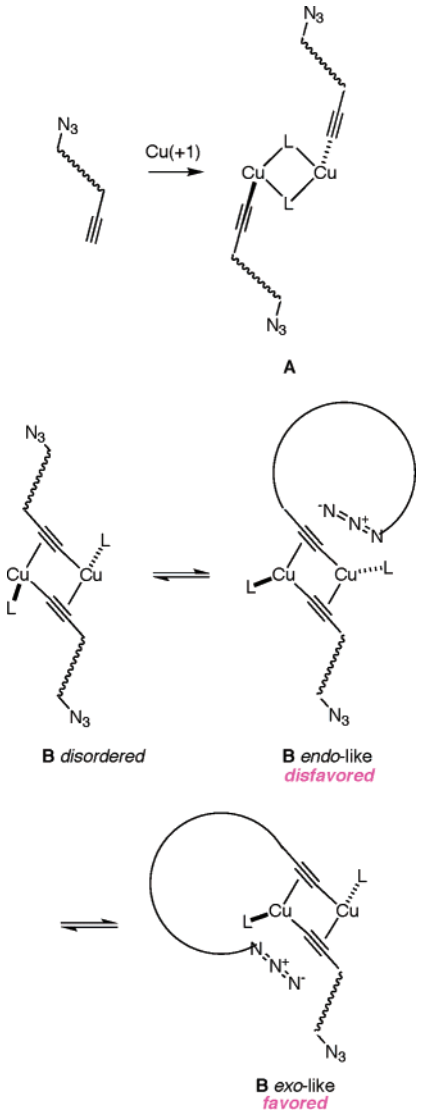

FIGURE 4. Formation of dimeric products in copper-mediated azide/alkyne cycloadditions may be associated with less populated "endo-like" conformations relative to less well-ordered, more populated, exo-like ones.

the kinetic studies[27] suggest it contains two copper atoms and possibly two alkynes. Intermediates **A** and **B** are possible candidates (Figure 4). For the following discussion, intermediate **B** is assumed to be the important one (though this is not critical).

In a simple elaboration of the hypothesis presented by Finn et al., we suggest that selectivity for dimers in these copper-mediated cyclizations may be explained as follows. The perfect regioselectivity of the copper-mediated cycloaddition processes for 1,4-disubstituted triazoles would require the azido alkyne coils in an endo-like conformation to form a monomeric cyclization product. In the absence of extenuating circumstances, this conformational state would be less populated than exo-like ones that are intrinsically less ordered. The effects in question are small, but so are the rate differences leading to mixtures of monomeric and dimeric products. We suggest

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that the preference for the exo-like orientation **B** prevails over the conformational biases of the peptide part, or secondary copper coordination effects, that might sometimes favor reactions via endo-like conformations.

Experimental Section

General Procedure for Cyclization. *N*,*N*-Diisopropylethylamine (4.0 mmol, 0.70 mL, 20 equiv) was added to a suspension of CuI (0.4 mmol, 76 mg, 2 equiv) in 200 mL of dry THF. A solution of **1a**−**h** (0.2 mmol, 1.0 equiv) in 20 mL of dry THF was added to the suspension slowly over 10 h and stirred for another 4 h under nitrogen. The suspension was filtered with a pad of Celite and concentrated. Flash chromatography on silica gel (3% MeOH in CH_2Cl_2) gave a mixture of monomeric and dimeric compounds. Preparative HPLC experiments were run using 20−90% B in 30 min (solvent A: H_2O with 0.1% TFA, solvent B: CH_3CN with 0.1% TFA) to provide **5a**−**h** as white powder. Data for cyclic isoleucine−lysine mimic **5a**: ^{1}H NMR (DMSO-d_6) 8.62 (d, 1H, J = 8.5 Hz), 8.32 (s, 1H), 8.01 (d, 1H, J = 8.5 Hz), 7.85 (s, 1H), 7.79 (d, 1H, J = 7.5 Hz), 7.69 (m, 1H), 7.61 (t, 1H, J = 7.5 Hz), 7.53 (d, 1H, J = 6.0 Hz), 7.38−7.31 (m, 5H), 7.24 (t, 1H, J = 6.0 Hz), 5.00 (s, 2H), 4.67 (dd, 1H, J = 15.5 Hz, 8.0 Hz), 4.06 (m, 3H), 2.97 (dd, 2H, J = 12.5 Hz, 6.0 Hz), 1.77 (m, 1H), 1.59 (m, 1H), 1.40 (m, 2H), 1.24 (m, 5H), 0.87 (m, 6H); MS (ESI, *m*/*z*) 576 $(M + H)^+$.

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Supporting Information Available: Procedures for the preparation of compounds **3a**−**c**, **4a**−**h**, **5a**−**h**, **1a**−**h**, **2a**−**h**, **7**, and **8**. Data for conformational analysis of compounds **2a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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