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# Synthesis of 5-Iodo-1,2,3-triazole-Containing Macrocycles Using Copper Flow Reactor Technology

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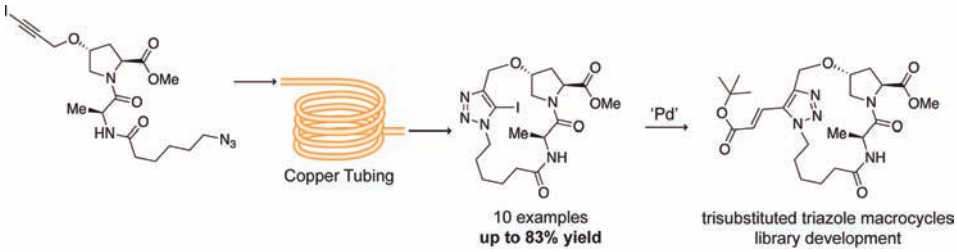
## ABSTRACT




**A new macrocyclization strategy to synthesize 12- to 31-membered 5-iodo-1,2,3-triazole-containing macrocycles is described. The macrocycles have been generated using a simple and efficient copper-catalyzed cycloaddition in flow under environmentally friendly conditions. This methodology also permits the facile, regioselective synthesis of 1,4,5-trisubstituted-1,2,3-triazole-containing macrocyles using palladium-catalyzed cross-coupling reactions.**

Macrocyclic systems offer a compelling new approach to modulating protein−protein interactions,[1] since their intrinsic conformational preorganization allows them to span noncontiguous binding sites on shallow protein surfaces, while retaining attractive drug properties.[2] Consequently, there is considerable interest in novel macrocyclization strategies that are applicable to drug discovery programs and amenable to library development.[3] In particular, there is a need for new macrocyclization protocols capable of generating diverse, drug-like structures, without resorting to high dilution conditions.[4]

Recently we reported the efficient construction of triazole-containing macrocycles in flow using copper tubing.[5] While this method proved to be effective for the synthesis of 1,4-disubstituted-1,2,3-triazole-containing macrocycles, a general procedure for the synthesis of 1,4,5-trisubstituted-1,2,3-triazole-containing macrocycles would be advantageous. While ruthenium-catalyzed azide−alkyne cycloadditions[6] and triazole functionalization[7] have proven to be effective methods to synthesize trisubstituted triazole rings, these methods can exhibit problematic regiocontrol and limited scope. Hein et al. recently described a copper-catalyzed, regiocontrolled synthesis of 5-iodo-1,2,3-triazoles that could be converted to 1,4,5-trisubstituted-1,2,3-triazoles.[8] Since the presence of such an iodotriazole moiety would permit facile library development via palladium-catalyzed cross-couplings, we have

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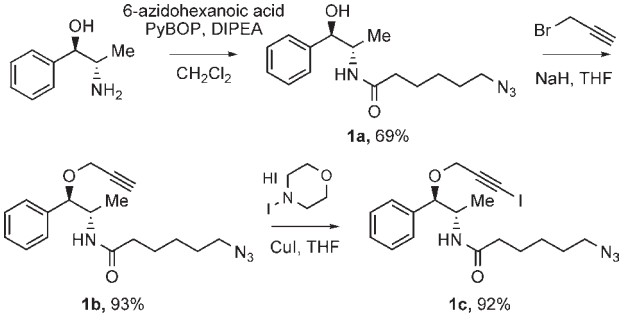
examined the use of this reaction in the construction of drug-like macrocycles. We report herein a novel and efficient methodology to synthesize drug-like 5-iodo-1,2,3-triazole-containing macrocycles through the implementation of copper-catalyzed cycloaddition chemistry in flow, together with examples of the elaboration of these systems via palladium-catalyzed cross-coupling reactions.

We were drawn to a flow methodology employing copper tubing because the copper(I)-catalyzed azide–acetylene cycloaddition (CuAAC) reaction[9] has already been reported using flow conditions to yield simple, linear triazoles.[10] It was anticipated that using 1-iodoalkynes instead of terminal alkynes would lead to similarly high yields for the cycloaddition, using the heterogeneous copper tube as the catalyst source.

Macrocycle precursors were synthesized in short synthetic sequences similar to Scheme 1. Chiral amino alcohol fragments were coupled to an organic azide using standard peptide coupling conditions, followed by an alkylation using propargyl bromide. The alkyne was subsequently iodinated using *N*-iodomorpholine hydrogeniodide[11] and

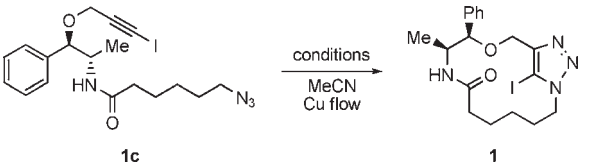
**Scheme 1.** Synthesis of Azido-Iodoalkyne Macrocycle Precursors




catalytic CuI. Notably, no CuAAC-derived macrocyclic or oligomeric products were detected by LC/MS analysis during the alkyne iodination, despite the presence of copper(I). Following column chromatography, azido-iodoalkyne **1c** could be isolated as a light-yellow oil.

Using azido-iodoalkyne **1c** as the model system, the macrocyclization was optimized in flow, using copper

**Table 1.** Optimization of Reaction Conditions[a]




| entry | time (min) | *T* (°C) | ligand | DIPEA equiv | **1c**[c] (%) | **1**[c] (%) |
|---|---|---|---|---|---|---|
| 1 | 5 | 75 | TTTA (0.1)[b] | – | 77 | 4 |
| 2 | 5 | 100 | TTTA (0.1) | – | 42 | 39 |
| 3 | 5 | 100 | TTTA (0.1) | 1.0 | 16 | 64 |
| 4 | 5 | 100 | TTTA (0.5) | 1.0 | 50 | 32 |
| 5 | 5 | 100 | TTTA (0.1) | 2.0 | 4 | 78 |
| 6 | 5 | 100 | TBTA (0.1) | 2.0 | 6 | 73 |
| 7 | 10 | 100 | TTTA (0.1) | 2.0 | 0 | 86 (80)[d] |
| 8 | 5 | 100 | – | – | 52 | 30 |
| 9 | 5 | 100 | – | 2.0 | 27 | 51 |

[a] Conditions: Accendo Conjure Flow Reactor, copper tubing (0.75 mm inner diamter, 1.6 mL internal volume), [**1c**] = 0.017 M. [b] Number in parentheses corresponds to equivalents of ligand. [c] Percent UV from LC/MS analysis. [d] Number in parentheses corresponds to isolated yield. TTTA, tris-((1-*tert*-butyl-1*H*-1,2,3-triazoyl)methyl)amine; TBTA, tris-((1-benzyl-1*H*-1,2,3-triazoyl)methyl)amine; DIPEA, diisopropylethylamine.

tubing as the copper source.[12] The conditions for the macrocyclization are outlined in Table 1. Optimization was performed using MeCN after initial screening indicated promising results. Furthermore, its low boiling point simplifies the workup, allowing convenient solvent removal *in vacuo* prior to column chromatography. As anticipated from our previous macrocyclization studies[5] and the seminal publication from Hein et al.,[8] the ligand tris-((1-*tert*-butyl-1*H*-1,2,3-triazoyl)methyl)amine (TTTA) was necessary to obtain high yields of macrocycle **1** (Table 1, entry 9 versus 5). It was also noted that addition of DIPEA to the reaction mixture increased the yield of **1** (Table 1, entries 3 and 5 versus entry 2). Increasing the temperature beyond 100 °C resulted in decomposition of the starting material and blocked the reactor. Optimal conditions for the macrocyclization were determined to be 10 min at 100 °C, with 10 mol % TTTA and 2.0 equiv of DIPEA (Table 1, entry 7). 5-Iodo-1,2,3-triazole-containing macrocycle **1** was characterized by X-ray crystallography (Figure 1). Additionally, it was determined that the reaction did not proceed to high yield when no additives were present (Table 1, entry 8) or when DIPEA was used alone (Table 1, entry 9).

In order to establish the scope of this procedure, a series of azido-iodoalkynes were synthesized and subjected to the optimized macrocyclization conditions described above. It was observed that macrocycles comprised of 12- to

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(12) For the flow reactions, an Accendo Conjure Flow reactor was used with copper tubing (0.75 mm inner diamter, 1.6 mL internal volume). http://www.accendocorporation.com.

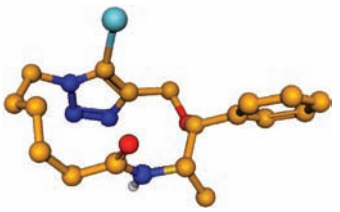

**Figure 1.** Crystal structure of iodotriazole macrocycle **1**. Hydrogens omitted for clarity.

31-membered rings could be synthesized in modest to excellent yields (Figure 2).

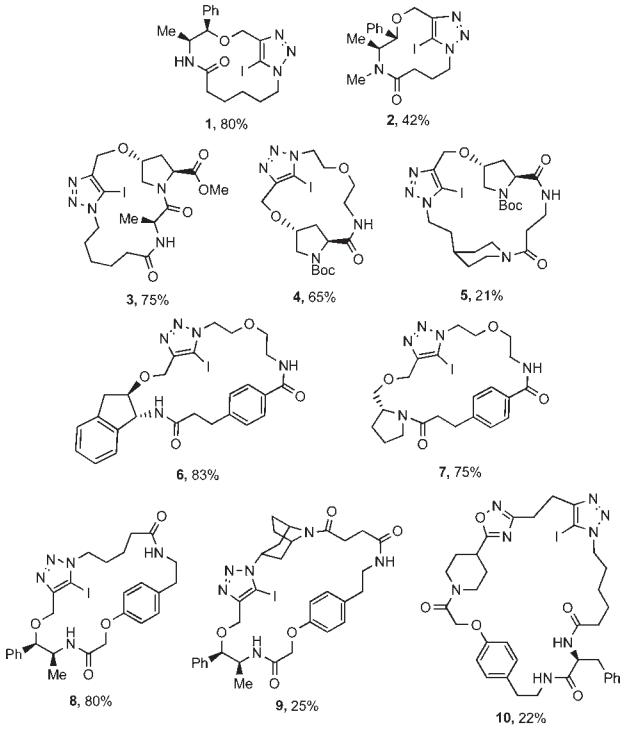


**Figure 2.** Substrate scope for the copper flow-mediated iodotriazole macrocyclization. Percentages correspond to isolated yields.

Smaller macrocyclic rings such as **2** were obtained in lower yields, as were systems that contained multiple bridged rings within the macrocycle (**5** and **9**). Furthermore, larger macrocyclic rings (**9** and **10**) also showed a significant amount of deiodination, yielding significant amounts of the corresponding proteo triazole. This may result from the rate of deiodination becoming competitive with a slower rate of macrocyclization for these larger rings. Since these isolated yields were obtained using conditions which had been optimized for a 14-membered macrocycle, it may be possible to increase the yields of 5-iodo-1,2,3-triazole in these cases through further optimization.

Macrocycles **2**, **4**, and **6** were characterized by X-ray crystallography (Figure 3). Depending on ring size and the inherent strain within the macrocycle, differing degrees of atropisomerism were observed as a result of restricted rotation of the iodotriazole. In the smaller, more strained macrocycle **2** (a 12-membered ring), only a single product was observed, representing one of two possible atropisomers arising due to the inability of the triazole ring to rotate freely through the interior of the macrocycle. Thus, the reaction is stereoselective, yielding the isomer where the iodine and amide carbonyl are *syn* to each other. In the slightly larger, but strained macrocycle **4** (a 15-membered system containing a bridged ring junction), a mixture of atropisomers was observed. Although the cycloaddition generated both iodotriazole conformers, their rate of interconversion is slow enough that the resultant atropisomers can be separated by chromatography at room temperature. And finally, in the larger macrocycle **6** (a 22-membered ring), there appears to be little conformational strain present. In this case therefore, both triazole conformers are formed and interconvert rapidly at room temperature. Consequently, atropisomers are not observed. This trend in conformational constraint is consistent with the noted increase in yield from the more strained to less strained macrocycles.

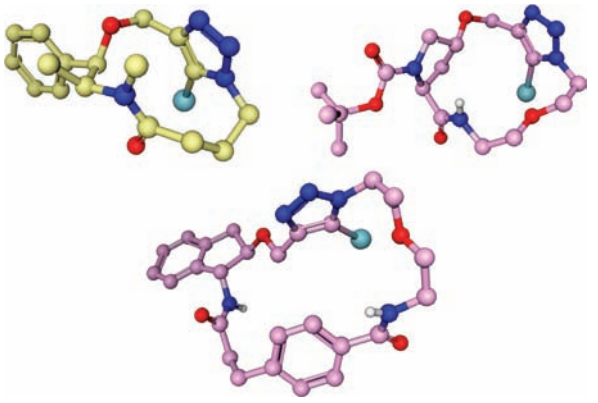

**Figure 3.** Crystal structures of iodotriazole macrocycles **2**, **4**, and **6** (clockwise from upper left). Hydrogens omitted for clarity.

To demonstrate the potential of the 5-iodo-1,2,3-triazole as a point of diversification in library synthesis, three macrocycles (**1**, **3**, and **7**) were subjected to palladium-catalyzed cross-coupling reactions (i.e., Suzuki, Heck, and Sonogashira, respectively).[13] High yields of the corresponding 1,4,5-trisubstituted-1,2,3-triazole macrocycles were obtained in all cases (Scheme 2). Interestingly, in the case of the 14-membered trisubstituted macrocycle **11**, a mixture of atropisomers (~1.2:1.0) was obtained.

In this case, it was possible to separate the atropisomers using chromatography and characterize them both using X-ray crystallography (Figure 4). The two atropisomers

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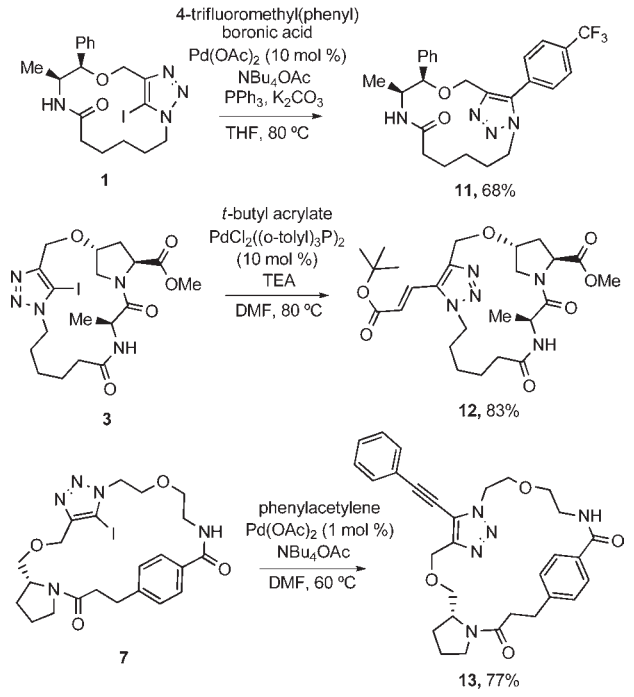
**Scheme 2.** Synthesis of 1,2,5-Trisubstituted-1,2,3-Triazole Macrocycles via Pd-Mediated Cross-Couplings




are diastereomeric by virtue of opposite chirality at the newly created axial stereocenter, which again arises through the inability of the trisubstituted triazole to rotate freely, and therefore differ in the orientation of the trifluoromethylphenyl ring relative to the other macrocycle substituents. In the case of the major atropisomer, the two phenyl rings attached to the macrocycle are *syn*, whereas the phenyl rings are *anti* in the minor atropisomer. Using variable temperature NMR, it was determined that macrocycle **11** begins to slowly atropisomerize when heated to elevated temperatures (~80 °C). In the larger macrocyclic systems (**12** and **13**), this atropisomerism was not observed, presumably due to the flexible nature of the larger ring allowing facile conversion between the triazole rotamers, as discussed above.

In conclusion, we have demonstrated an efficient method to synthesize 5-iodo-1,2,3-iodotriazole-containing macrocycles in a flow reactor using copper tubing as the catalyst source. Unlike typical macrocyclization strategies that generate no new reactive centers as a result of the ring

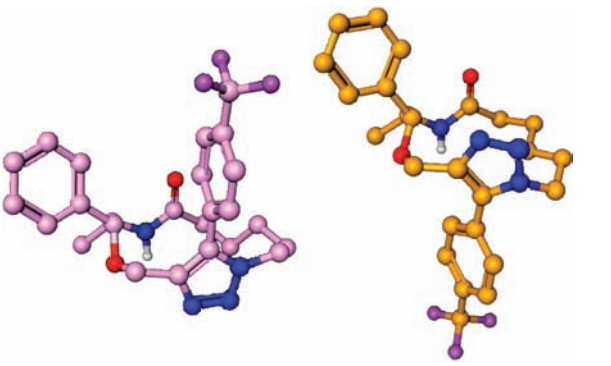


**Figure 4.** X-ray crystal structures of the atropisomers of 1,4,5-trisubstituted-1,2,3-triazole macrocycle **11**. The major *syn* atropisomer is on the left, and the minor *anti* atropisomer is on the right. Hydrogens omitted for clarity.

closure, the chemistry described herein creates a new, versatile functional group that can be used in further reactions. The resultant iodotriazoles can be converted into 1,4,5-trisubstituted-1,2,3-triazoles using palladium chemistry, thereby opening the way to their use in library development. This is also therefore the first example of a macrocyclization strategy that enables the efficient synthesis of a regiocontrolled, trisubstitued triazole ring. As a result, we have been able to observe and characterize an unusual atropisomerism resulting from restricted rotation of a trisubstituted heterocyclic ring embedded within a macrocyclic framework.

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**Supporting Information Available.** Experimental procedures and full characterization ($^1$H and $^{13}$C NMR data and spectra, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.