ORGANIC LETTERS

2009
Vol. 11, No. 11
2257−2260

Accessing Skeletal Diversity Using Catalyst Control: Formation of *n* and *n* + 1 Macrocyclic Triazole Rings

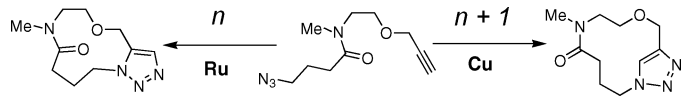
Ann Rowley Kelly, Jingqiang Wei, Sarathy Kesavan, Jean-Charles Marié, Nicole Windmon, Damian W. Young, and Lisa A. Marcaurelle*

Chemical Biology Platform, Broad Institute of MIT and Harvard, 7 Cambridge Center, Cambridge, Massachusetts 02142

lisa@broad.mit.edu

Received March 17, 2009

ABSTRACT



A regioselective intramolecular Huisgen cycloaddition was performed on various azido alkyne substrates giving rise to macrocyclic triazole rings. Using catalyst control, a common intermediate has been converted to two structurally unique macrocycles with either a 1,5- or a 1,4-triazole resulting in an *n* or *n* + 1 ring size. This is the first example of an intramolecular ruthenium-catalyzed Huisgen cycloaddition.

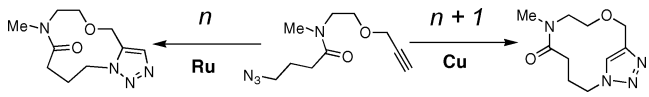
The preparation and screening of small molecules constitutes a powerful strategy for the discovery of biological probes and pharmaceutical agents.[1−3] Diversity of structure within a particular compound collection is key to the discovery of hits over a wide range of biological areas. It has recently been shown that even large screening collections that lack diversity are insufficient to provide lead compounds against a range of antibacterial targets.[4] A current strategy for achieving diverse compound collections through diversity-oriented synthesis (DOS) focuses on the use of functional group pairing.[5,6] By using scaffolds with multiple functional group "handles" and joining them in a pairwise, intramolecular, and chemoselective fashion, both skeletal diversity and rigidity are achieved. A complementary approach for generating structural diversity is known as "reagent-based" diversification.[7] This strategy involves the preparation of a singular scaffold that, when subjected to different reaction conditions, selectively yields different products.[1,8] To further develop this strategy, robust methodologies that allow for reagent-based differentiation must be developed.

The Huisgen 1,3-dipolar cycloaddition is a widely utilized reaction in DOS.[9,10] This "click" reaction results from the ligation of azides and alkynes to give a triazole moiety. This reaction has been shown to be effective in the formation of a variety of macrocyclic rings.[11] A key point of interest for us was the regioselectivity of the cycloaddition. We surmised that a reagent-based diversity approach could be applied to generate both possible regioisomers from a common substrate as shown in Scheme 1. While many advances have been made in the formation of 1,4-triazoles using copper(I) catalysis,[9] the formation of 1,5-triazole rings using ruthenium(II) catalysis has only recently been reported and has

(1) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5178.
(2) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613.
(3) Ortholand, J.; Ganesan, A. *Curr. Opin. Chem. Bio.* **2004**, *8*, 270.
(4) Payne, D. J.; Gwynn, M. N.; Holmes, D. J.; Pompliano, D. L. *Nature Rev. Drug Discovery* **2007**, *6*, 29.
(5) Comer, E.; Rohan, E.; Deng, L.; Porco, J. A. *Org. Lett.* **2007**, *9*, 2123–2126.
(6) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48.
(7) Brummond, K. M.; Chen, D. *Org. Lett.* **2008**, *10*, 705.
(8) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245.
(9) Wu, P.; Fokin, V. V. *Aldrichim. Acta* **2007**, *40*, 7.
(10) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.
(11) (a) Looper, R. E.; Pizzirani, D.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 2063. (b) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638. (c) Bock, V. D.; Perciaccante, R.; Jansen, T. P.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 919. (d) Turner, R. A.; Oliver, A. G.; Lokey, R. S. *Org. Lett.* **2007**, *9*, 5011.

10.1021/ol900562u CCC: $40.75
Published on Web 04/30/2009

Scheme 1. Use of Huisgen Cycloaddition for Divergent Pairing

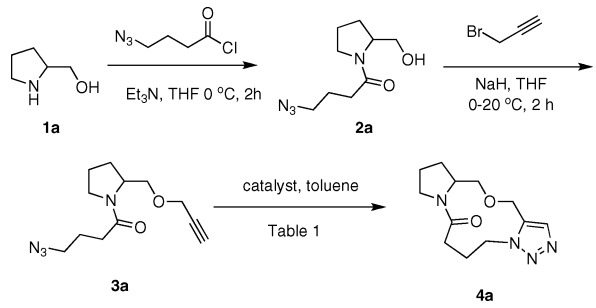


been demonstrated in an *intermolecular* fashion and in a much more limited scope.[10,12]

With this in mind, we sought to expand the existing Huisgen methodology to make macrocyclic triazole rings regioselectively. This method is ideally suited to the preparation of small-molecule libraries because one compound can be converted into two structurally unique macrocycles that have an n or $n + 1$ ring size (Scheme 1). Access to macrocyclic triazoles that are different yet structurally related could provide insight into antibacterial and cytotoxic biological activity, two areas in which triazole-containing small molecules have shown promise.[13,14]

To explore the substrate scope of this divergent pairing strategy, we synthesized various alkynyl azides embedded within different structural frameworks (Scheme 2). The first

Scheme 2. Substrate Synthesis and Intramolecular Ru-Catalyzed Cycloaddition



pairing partner was provided by coupling an amino alcohol (**1a**) to an azido acyl chloride, resulting in the amide (**2a**). The second requisite functional group, the alkyne, was added via propargylation of the alcohol (**3a**). This general synthesis was applied to all of our substrates except in the synthesis of the linear (**3e**−**g**) and cyclohexyl substrates (**3j**−**k**), in which we observed bisacylation. In this instance, protection of the alcohol as a silyl ether was necessary to avoid ester formation.[15]

Using the pyrrolidine azido alkyne substrate (**3a**), different conditions were screened for the macrocyclic triazole formation. First, we examined the ruthenium(II)-catalyzed formation of the 1,5-triazole. When Cp*RuCl(COD) (Table 1, entries 1 and 2) was employed as the catalyst,[9] the reaction yielded no product even at elevated temperatures, most likely due to catalyst thermal instability.[12] More encouraging results were achieved with Cp*RuCl(PPh_3) (Table 1, entry 3); however, 50% dimer formation was observed and purification of the desired product proved difficult due to the presence of phosphine oxide. Improved results were obtained with the $[Cp^*RuCl]_4$ catalyst (Table 1, entries 4−8) which yielded improved monomer to dimer ratios (entries 5 and 8) and a more straightforward purification. Using 5% $[Cp^*RuCl]_4$ (Table 1, entries 6−8), we found that higher temperatures (80 °C) and lower concentrations (0.002 M) (entry 8) led to optimal monomer to dimer ratios. With our optimized protocol in hand, we obtained the desired 1,5-macrocyclic triazole **4a** in 58% isolated yield and confirmed the structure as the 1,5-regioisomer via X-ray crystallography (Figure 1).[15]

Table 1. Optimization of Ru-Catalyzed Cycloaddition tTo Yield **4a**[a]

entry	catalyst	mol %	T (°C)	conc (M)	% conv[b]	monomer/dimer
1	Cp*RuCl(COD)	15	25	0.002	0	
2	Cp*RuCl(COD)	15	65	0.002	dec	
3	Cp*RuCl(PPh_3)	15	80	0.002	60	50:50
4	$[Cp^*RuCl]_4$	15	40	0.002	100	60:40
5	$[Cp^*RuCl]_4$	15	80	0.002	100	80:20
6	$[Cp^*RuCl]_4$	5	60	0.010	100	40:60
7	$[Cp^*RuCl]_4$	5	60	0.005	100	50:50
8	**$[Cp^*RuCl]_4$**	**5**	**80**	**0.002**	**100 (58)**[c]	**80:20**

[a] Reactions were run as a solution in toluene for 30 min at the indicated concentrations. [b] Conversion was determined by LCMS analysis. [c] Isolated yield of **4a** after silica gel chromatography.

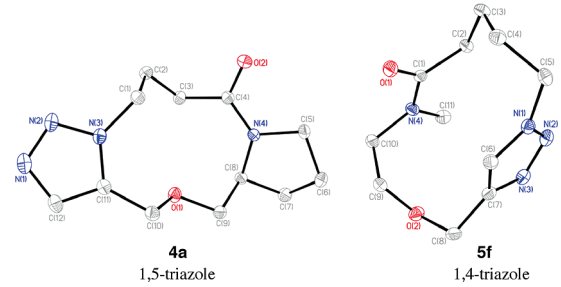


Figure 1. X-ray crystal structures of representative macrocyclic triazoles (**4a** and **5f**).

To the best of our knowledge, this is the first demonstration of a ruthenium-catalyzed intramolecular 1,5-triazole formation.

Using the same pyrrolidine substrate (**3a**), we attempted to find the best conditions for the formation of the 1,4-

(12) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923.

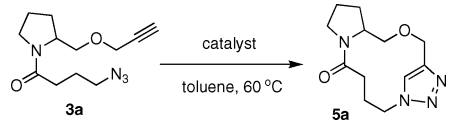
(13) (a) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem.* **2005**, *48*, 499. (b) Horne, W. S.; Olsen, C. A.; Beierle, J. M.; Montero, A.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2009**, *48*, ASAP.

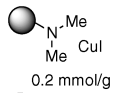
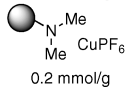
(14) Odlo, K.; Hentzen, J.; Chabert, J. F. d.; Ducki, S.; Gani, O. A. B. S. M.; Sylte, I.; Skrede, M.; Fløreneśd, V. A.; Hansena, T. V. *Bioorg. Med. Chem.* **2008**, *16*, 4829.

(15) See the Supporting Information.

triazole. Starting with $Cu(CN)_4PF_6$, we ran the reaction at 0.01 M in toluene at 60 °C and saw complete consumption of starting material but no desired product (Table 2, entry 1). It was determined this was due to the

Table 2. Optimization of Intramolecular Cu-Catalyzed Cycloaddition



entry	catalyst	conc (M)	% yield[a]
1	$Cu(CN)_4PF_6$	0.01	0
2	$Cu(CN)_4PF_6$	0.002	50
3	 0.2 mmol/g	0.01	Iodine incorporation
4	 0.2 mmol/g	0.01	55

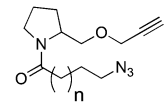
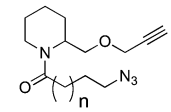
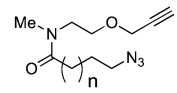
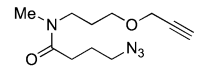
[a] Isolated yield of **5a** after silica gel chromatography.

intermolecular formation of dimers and oligomers; therefore, we decreased the concentration of the reaction to favor the intramolecular reaction. Gratifyingly, by changing the reaction concentration from 0.01 to 0.002 M we were able to obtain the 1,4-triazole **5a** in 50% yield (Table 2, entry 2). Although encouraged by these results, such dilute conditions were not suitable for the scalability of our protocol, so we sought to optimize the reaction further.

A recent publication by Girard and co-workers showcased the utility of CuI loaded on Amberlyst resin as a catalyst for an intermolecular Huisgen cycloaddition.[16] We envisioned utilizing this technology to facilitate pseudodilution and suppress dimer formation in the intramolecular Huisgen reaction.[17] First, we examined the exact conditions reported in the manuscript, Amberlyst-21 and CuI at 0.2 mmol/g loading (Table 2, entry 3). The monomeric 1,4-triazole was obtained; however, there was evidence of iodine incorporation.[15] While this observation is not uncommon in the use of solution phase CuI, it was not reported by Girard with the solid-phase catalyst. In light of this problem, we applied the Girard protocol to the generation of a $CuPF_6$ Amberlyst. We chose $CuPF_6$ (as opposed to CuBr) due to its high solubility in CH_3CN, the solvent used in the preparation of the solid-supported copper reagents. We were pleased to find that using this catalyst (0.2 mmol/g loading) we were able to achieve a 5-fold increase in reaction concentration along with a slight increase in yield for the desired product (Table 2, entry 4). These observations were consistent with pseudodilution.[17]

With these optimized conditions in hand, the effect of substrate specificity, conformation, and ring size on these metal-catalyzed macrocyclizations was investigated. The results of these experiments are shown in Table 3. The same

Table 3. Results for Intramolecular Cycloadditions with Linear and Carbocyclic Substrates[a]

entry	substrate	catalyst	ring size	% yield	ratio (1,5:1,4)[c]
					
1	**3a** n = 1	Ru	11	58 **4a**[b]	100:0
2	**3a** n = 1	Cu	12	55 **5a**	0:100
3	**3a** n = 1	Thermal		nd	97:3
4	**3b** n = 2	Ru	12	67 **4b**	100:0
5	**3b** n = 2	Cu	13	56 **5b**	0:100
6	**3b** n = 2	Thermal		nd	92:8
					
7	**3c** n = 1	Ru	11	45 **4c**	100:0
8	**3c** n = 1	Cu	12	38 **5c**	0:100
9	**3c** n = 1	Thermal		nd	98:2
10	**3d** n = 2	Ru	12	58 **4d**	100:0
11	**3d** n = 2	Cu	13	40 **5d**	0:100
12	**3d** n = 2	Thermal		nd	80:20
					
13	**3e** n = 1	Ru	11	60 **4e**	100:0
14	**3e** n = 1	Cu	12	37 **5e**	0:100
15	**3e** n = 1	Thermal		nd	80:20
16	**3f** n = 2	Ru	12	54 **4f**	100:0
17	**3f** n = 2	Cu	13	40 **5f**[b]	0:100
18	**3f** n = 2	Thermal		nd	80:20
					
19	**3g**	Ru	12	61 **4g**	100:0
20	**3g**	Cu	13	48 **5g**	0:100
21	**3g**	Thermal		nd	75:25

[a] Ru conditions: 5 mol % of $[Cp^*RuCl]_4$, 80 °C, toluene, 0.002 M, 10 min. Cu conditions: 0.2 mmol/g Amberlyst−$CuPF_6$, 60 °C, toluene, 0.01 M, 16 h.Thermal conditions: 110 °C, toluene, 0.01 M, 16 h (nd = not determined). [b] Structure confirmed by X-ray crystallography. [c] For the Ru- and Cu-catalyzed entries, only the major regioisomer was detected by LCMS.

pyrrolidine system was examined with an additional methylene group in the azido acid side chain (Table 3, entries 4−6). The isolated yields for the formation of the 12- and 13-membered rings were slightly higher than that of the 11- and 12-membered rings, a trend which is consistent with thermodynamic arguments.[18]

Since the pyrrolidine substrates (**3a**,**b**) assume a pseudoaxial position, the piperidine azido alkynes (**3c**,**d**) were

(16) Girard, C.; Onen, E.; Aufort, M.; Beauviere, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689.

(17) For an example of pseudodilution, see: Gonthier, E.; Breinbauer, R. *Mol. Diversity* **2005**, *9*, 51.

(18) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117.

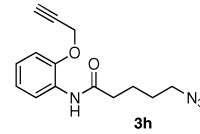
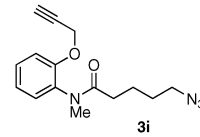
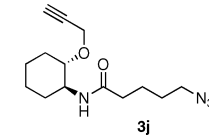
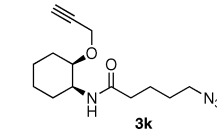
synthesized in order to examine the effect of a true axial substituent on ring closure. The resulting yields of the cycloaddition were slightly lower than that of their pyrrolidine counterparts (Table 3, entries 7−12). The drop in yield is most likely due to the difficulty of the cycloaddition. We hypothesize that the axial substituent places the alkyne and the azide further apart and leads to greater dimer and oligomer formation.

Three linear substrates (**3e**−**g**) were then tested to see if the rigidity imparted by the pyrrolidine ring was facilitating macrocyclization. The results of the metal-catalyzed cyclizations were very similar to that of the pyrrolidine substrate; however, the inherent bias in the system, determined by the thermal reaction, seemed to be less specific. When exposed to the thermal conditions the pyrrolidine substrates formed the 1,5-triazole products almost exclusively; whereas, the linear substrates gave a 4:1 ratio of the 1,5- to 1,4-triazoles (Table 3, entries 3 and 6 vs 15 and 18). We also compared substrates derived from 1,2-amino alcohols (**3e**,**f**) to substrates derived from 1,3-amino alcohols (**3g**) to determine if the position of the oxygen in the macrocyclic ring had any effect on the cycloaddition. The 1,3-amino alcohols (Table 3, entries 19 and 20) were only slightly higher in yield than their 1,2-amino alcohol counterparts (entries 16 and 17) and their thermal ratios were quite similar (entries 18 and 21). From these observations, it would not seem that the position of the alcohol has a dramatic effect on the macrocyclization. During the course of our work an X-ray crystal structure was obtained for one of the 1,4-triazoles (**5f**, Figure 1).

With the general reaction conditions established for the regioselective triazole pairing reactions, we chose to further explore conformational effects, as well as examine stereochemical effects on the macrocyclic triazole ring formation. Our results of these experiments are shown in Table 4. The first system that we examined was the planar 2-aminophenol derivatives (Table 4, entries 1−6). To better understand the system, we studied both the primary (Table 4, entries 1−3) and secondary amides (entries 4−6), however, no trend was observed. Both of these substrates gave moderate yields in all cases except for the copper-catalyzed primary amide (Table 4, entry 2). Next, we examined a saturated system of the *cis*- and *trans*-cyclohexyl amino alcohol compounds (Table 4, entries 7−12). Surprisingly, the *cis* or *trans* configuration had little effect for the ruthenium-catalyzed reaction (Table 4, entries 7 and 10); however, the *trans* system showed a remarkable loss in yield for the copper-catalyzed case (Table 4, entry 8). Optimization of this reaction for this substrate was effected by a 5-fold dilution, leading to a significant increase in yield, from 17% to 46% (Table 4, entry 8).

In conclusion, we have expanded on the existing Huisgen cycloaddition methodology, showing the utility of pseudodilution and performing the first example of a ruthenium-catalyzed intramolecular cyclization. Furthermore, as a result of this study, we have developed an understanding of which substrates and ring sizes provide the best yields. The performance of these regioisomeric triazoles in a wide variety of biological screens is currently under investigation. We are also following up these substrate examples with a more comprehensive library synthesis, the results of which will be reported in due course.

Table 4. Influence of Stereochemistry on Intramolecular Cycloadditions[a]

entry	substrate	catalyst	ring size	% yield		ratio (1,5:1,4)[c]
1	 **3h**	Ru	12	64	**4h**	100:0
2		Cu	13	31	**5h**	0:100
3		Thermal		nd		68:32
4	 **3i**	Ru	12	48	**4i**	100:0
5		Cu	13	65	**5i**	0:100
6		Thermal		nd		100:0
7	 **3j**	Ru	12	71	**4j**	100:0
8		Cu	13	17(46)[b]	**5j**	0:100
9		Thermal		nd		98:2
10	 **3k**	Ru	12	70	**4k**	100:0
11		Cu	13	62	**5k**	0:100
12		Thermal		nd		73:27

[a] Ru conditions: 5 mol % of $[Cp^*RuCl]_4$, 80 °C, toluene, 0.002 M, 10 min. Cu conditions: 0.2 mmol/g of Amberlyst-$CuPF_6$, 60 °C, toluene, 0.01 M, 16 h. Thermal conditions: 110 °C, toluene, 0.01 M, 16 h (nd = not determined). [b] Reaction was run at a concentration of 0.002 M. [c] For the Ru- and Cu-catalyzed entries, only the major regioisomer was detected by LCMS.

Acknowledgment. We gratefully acknowledge Marie Harton for help with characterization and Dr. Peter Mueller for X-ray analysis. This work was funded in part by the NIGMS-sponsored Center of Excellence in Chemical Methodology and Library Development (Broad Institute CMLD; P50 GM069721).

Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900562U