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Solution- and Solid-Phase Synthesis of Triazole Oligomers That Display Protein-Like Functionality

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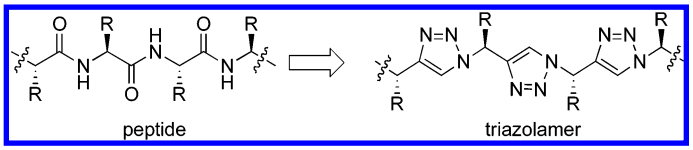

We recently developed a new class of oligomers that contain α-amino acid residues linked by 1,2,3-triazole groups [Angelo, N. G.; Arora, P. S. *J. Am. Chem. Soc.* **2005,** *127*, 17134−17135]. Synthesis of these oligomers involves an iterative sequence consisting of diazotransfer and Huisgen 1,3-dipolar cycloaddition steps. In this contribution, we describe an efficient one-pot, two-step sequence for the preparation of triazoles from the corresponding amino acid-derived amines and alkynes in solution. The one-pot sequence affords the desired products in significantly higher yields than our original method. We also outline a highly effective protocol for the synthesis of these triazole-based biomimetic oligomers on the solid phase. We find that amino acid derivatives and iterative formation of triazole rings require nontraditional reaction conditions for high yields.

Introduction

Peptidomimetics that display protein-like functionality yet do not contain the labile amide linkage have wide-ranging potential as modulators of protein−protein interactions.[1−5] Our efforts have focused on the design and synthesis of oligomers that contain amino acid residues linked via 1,2,3-triazole moieties rather than the amide bond (Figure 1). We have described NMR studies which indicate that short versions of these oligomers, dubbed "triazolamers", can adopt zigzag conformations reminiscent of β-strands.[6]

In our reported studies, we synthesized triazole oligomers from corresponding amines by an iterative procedure that relied on two key steps: (1) metal-catalyzed diazotransfer to form an azide intermediate[7,8] and (2) Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction with the suitable amino alkyne to obtain the triazole linkage.[9,10]

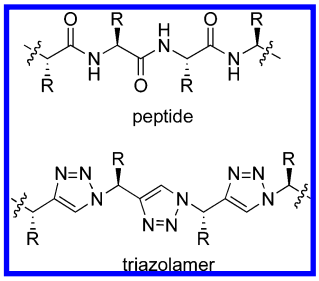

FIGURE 1. Structure of a triazolamer where amide bonds are replaced with triazole linkages. R = amino acid side chain.

We chose this synthetic strategy because mild and efficient conditions for both of these steps had been previously described.[10−16] Scheme 1 illustrates our original synthesis in

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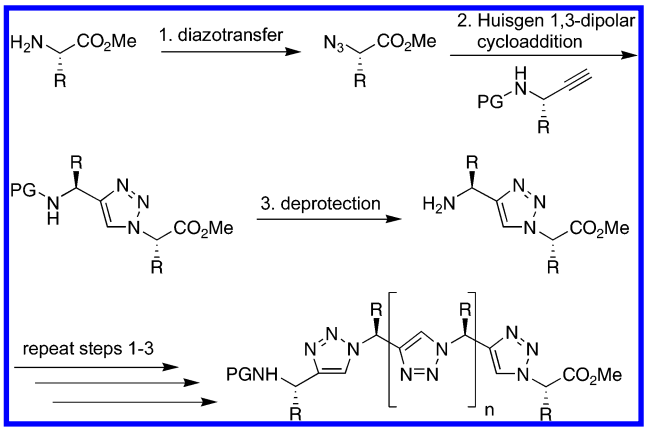
SCHEME 1. Iterative Synthesis of Triazolamers; R = Amino Acid Side Chain



which an amino acid methyl ester was converted to the corresponding azide via a Cu(II)-catalyzed diazotransfer reaction using triflic azide.[7,8] The isolated azido compound was then reacted with an amino acid-derived alkyne in the presence of Cu(I). The amine was deprotected, and the process was repeated to obtain triazolamers of the desired length. This method allowed for the synthesis of trimers in 6−12% overall yields.[6] Although these yields provided material for our initial studies, we required a more efficient methodology for the synthesis of longer oligomers and further analysis.

We postulated that the low overall yields for the synthesis of triazolamers primarily reflected a combination of the instability of the amino acid-derived azide to purification conditions and the inefficiency of the diazotransfer reaction to form this azide. On the basis of this hypothesis, we refrained from isolating, purifying, or handling the azide intermediate for prolonged periods during these optimization studies. This limitation meant that we could not ascertain the efficiency of the diazotransfer conditions until after the azide−alkyne cycloaddition step and that, essentially, we were optimizing two different reactions at one time. To improve our synthetic procedure, we explored various diazotransfer conditions including in situ azide formation.[17,18] We also tested various methods, including microwave irradiation, to further improve the cycloaddition step.[13−15] Although several improvements for the Huisgen [2+3] cycloaddition have been reported, most of these reports describe the synthesis of single triazole groups.[16,17] We discovered that oligomers of triazoles present special synthetic challenges and require a different set of optimized conditions.

Results and Discussion

Solution-Phase Synthesis of Triazolamers. Our initial studies suggested that the preparation of azides from the corresponding amino-triazolamers was difficult and low yielding. In agreement with previous reports, we found that amino acid azides may be purified by column chromatography and isolated in high yields,[19] but handling and purification of azides became difficult as the number of triazole rings in the oligomer increased. To limit the handling of the triazolamer-azides, we examined two approaches that involved (a) an in situ diazo generation procedure and (b) a sequential single-pot procedure (Figure 2). In the in situ method, all reagents for the diazotransfer and the cycloaddition steps were added simultaneously. The sequential procedure involved addition of the alkyne and cycloaddition catalyst to the flask containing freshly generated azide but without the isolation or purification of the azide. These optimization reactions were performed with phenylalanine methyl ester as the starting amine, and 4-phenyl-1-butyne **2** or Boc-Phe-alkyne **4** as the source of the alkyne. We obtained our

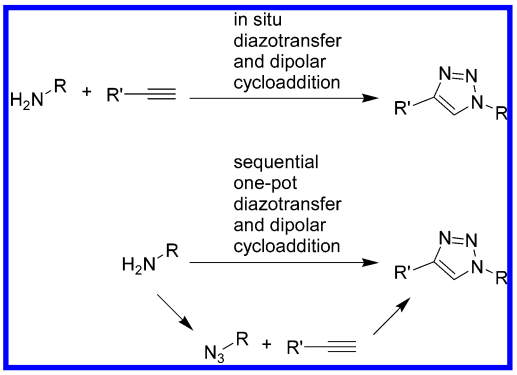
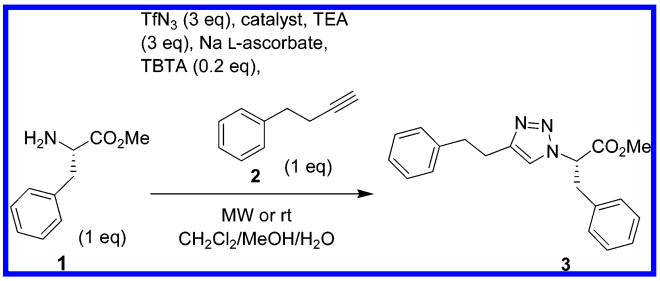


FIGURE 2. Synthesis of triazoles from amines via in situ azide formation and one-pot sequential diazotransfer and dipolar cycloaddition reactions.

TABLE 1. One-Pot Synthesis of Triazoles via in Situ Azide Formation: Representative Results



entry	catalyst[a]	sodium L-ascorbate (equiv)	T (°C)[b]	reaction time	yield (%)
1	$CuSO_4{\cdot}5H_2O$ (0.5 equiv)	0.4	25	18 h	28
2	$CuSO_4{\cdot}5H_2O$ (0.5 equiv)	0.4	80 MW	5 min	32
5	$CuSO_4{\cdot}5H_2O$ (0.5 equiv)	0.4	80 MW	15 min	27
6	$ZnCl_2$ (0.1 equiv) and $CuSO_4{\cdot}5H_2O$ (0.2 equiv)	0.4	80 MW	15 min	14
7	$ZnCl_2$ (0.1 equiv) and $CuSO_4{\cdot}5H_2O$ (0.2 equiv)	1	25	18 h	30
8	$ZnCl_2$ (0.1 equiv) and $CuSO_4{\cdot}5H_2O$ (0.2 equiv)	1	80 MW	15 min	16
9	$CuSO_4{\cdot}5H_2O$ (0.2 equiv)	1	80 MW	15 min	26

[a] Catalyst for both the diazotransfer and the dipolar cycloaddition reaction: In each entry, Cu(II) is included to catalyze the dipolar cycloaddition reaction after in situ reduction to Cu(I). [b] MW = microwave irradiation, TBTA = tris-(benzyltriazolylmethyl)amine

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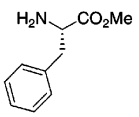
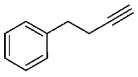
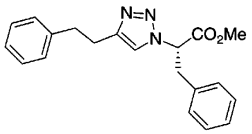
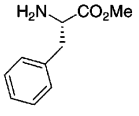
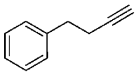
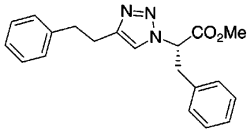
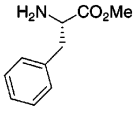
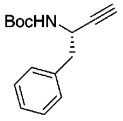
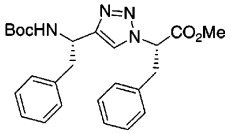
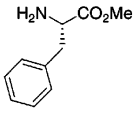
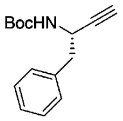
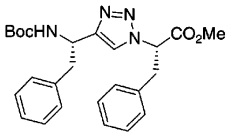
(18) Kacprzak, K. *Synlett* **2005**, 943−946.
(19) Lundquist, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781−783.

TABLE 2. One-Pot Synthesis Of Triazoles via Sequential Diazotransfer and Huisgen 1,3-Dipolar Cycloaddition: Representative Results

entry[a]	amine	alkyne	diazotransfer catalyst	diazotransfer reaction time at 25 °C	microwave irradiation	product	% yield
1	 **1**	 **2**	$ZnCl_2$ (0.1 eq)	1.5 h	80 °C, 5 min.	 **3**	93
2	 **1**	 **2**	$CuSO_4 \cdot 5H_2O$ (0.05 eq)	18 h	80 °C, 5 min.	 **3**	92
3	 **1**	 **4**	$ZnCl_2$ (0.1 eq)	2 h	100 °C, 5 min.	 **5**	51
4	 **1**	 **4**	$CuSO_4 \cdot 5H_2O$ (0.05 eq)	18 h	100 °C, 5 min.	 **5**	96

[a] Reaction conditions: TfN_3 3 equiv, diazotransfer catalyst, TEA 2−3 equiv, 25 °C then alkyne 1−1.2 equiv, $CuSO_4 \cdot 5H_2O$ 0.1−0.2 equiv, sodium L-ascorbate 0.2−0.4 equiv, TBTA 0.2−0.4 equiv, microwave irradiation.[20]

highest yields (>90% overall) for the triazole products with the sequential procedure.

Table 1 lists a sampling of in situ diazotransfer−cycloaddition reaction conditions analyzed. We performed a series of studies where we changed various reaction parameters, including the catalysts (Cu(II) or Zn(II)), reaction temperatures (microwave or oil bath heating) and times, and the amounts of additive (sodium ascorbate) for the cycloaddition step. Although microwave irradiation afforded higher yields than conventional heating, none of the in situ conditions tested provided the desired triazole product in sufficiently high yields to be synthetically useful (Table 1).

As part of these optimization studies, we next investigated the one-pot sequential diazotransfer−cycloaddition reaction procedure with the same substrates as used for the in situ test reactions (Table 2). The procedure for the sequential protocol consisted of allowing the diazotransfer reaction to reach completion, as indicated by thin layer chromatography, followed by the addition of the alkyne and other reagents for the dipolar cycloaddition step, and microwave irradiation of the reaction mixture. We discovered that this procedure provides high yields of the triazole product **3** from phenylalanine methyl ester and 4-phenyl-1-butyne when $ZnCl_2$ was employed as the catalyst in the diazotransfer step (Table 2, entry 1). However, similar reaction conditions with Boc-Phe-alkyne **4** as the substrate afforded much lower yields of the desired product **5**. Replacement of $ZnCl_2$ with $CuSO_4 \cdot 5H_2O$ increased the yield of **5** (Table 2, entry 3 vs entry 4). This disparity in yields may reflect the stability of the Boc group on alkyne **4** in the presence of $ZnCl_2$; indeed, $ZnCl_2$ has previously been used for removal of the Boc group.[21]

During the course of our studies, Beckmann, et al. reported the one-pot generation of triazoles from amines via one-step and sequential diazotransfer and cycloaddition reactions.[22] These workers principally investigated primary alkyl and aryl amines and a single sequence of azide generation and cycloaddition to obtain triazole monomers, whereas our studies have involved amino acid derivatives and iterative syntheses of triazole rings to obtain oligomers. We find that amino acid derivatives and triazole oligomers require modified conditions. Our optimized sequential one-pot methodology affords trimer **7** in 62% overall yield (Scheme 2), which corresponds to a significant improvement over our previously reported procedure.

Solid-Phase Synthesis of Triazolamers. The high yields obtained from these optimized conditions suggested that it might be possible to further improve our methodology and generate libraries of triazolamers by implementing solid-phase techniques (Scheme 3). We therefore embarked on a comprehensive study to determine efficient solid-phase conditions for the synthesis of triazolamers.

The conversion of amines to azides via Cu(II)-catalyzed diazotransfer on the solid phase has been reported;[23] Cu(II) also

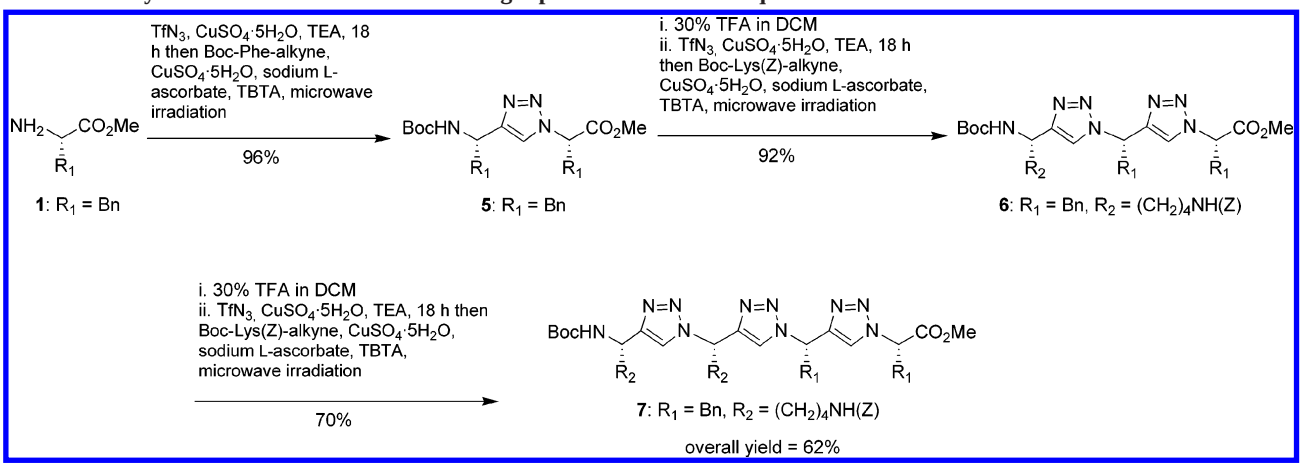
(20) The microwave reactions were performed in the CEM Discover single-mode reactor with controlled power, temperature, and time settings.

(21) Devasagayaraj, A.; Tour, J. M. *Macromolecules* **1999**, *32*, 6425−6430.

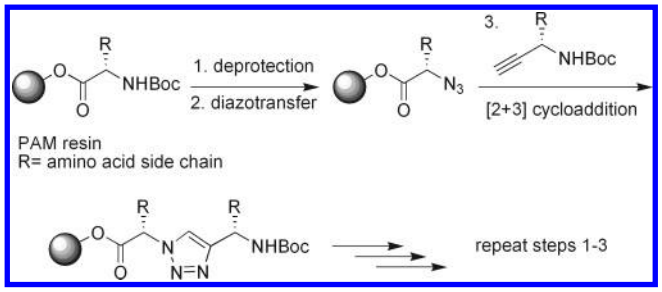
(22) Beckmann, H. S. G.; Wittmann, V. *Org. Lett.* **2007**, *9*, 1−4.

(23) Rijkers, D. T. S.; van Vugt, H. H. R.; Jacobs, H. J. F.; Liskamp, R. M. J. *Tetrahedron Lett.* **2002**, *43*, 3657−3660.

SCHEME 2. Synthesis of Triazole Trimer 7 using Optimized One-Pot Sequential Solution-Phase Conditions



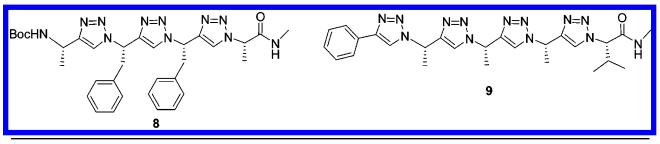
SCHEME 3. Solid-Phase Synthesis of Triazolamers



served as an efficient catalyst for our solution-phase studies. However, we discovered that the yields for peptido-triazoles were higher in the presence of Zn(II)[8] as the diazotransfer catalyst on solid phase. We ascribe these results to possible cleavage of the substrates from the PAM resin or to copper-mediated aggregation of triazole rings.[16,24,25] Use of Zn(II) was detrimental to the solution-phase synthesis with Boc-protected alkynes (Table 2) but is not a problem with the solid-phase methodology because the resin is washed extensively to remove Zn(II) prior to the introduction of the Boc-alkyne. Other reaction parameters, including the choice of TfN_3 solution,[26,27] did not have a significant effect on the yields. A multitude of solid-phase conditions for the azide−alkyne cycloaddition reaction exists in the literature.[10,28,29] While the protocols for this reaction differ considerably (choice of solvents, bases, equivalents of reagents), yields of over 90% are regularly reported. We tested a number of different conditions for the cycloaddition reaction to arrive at our optimized protocol (Table 3).

The solid-phase methodology affords excellent yields of triazolamers (up to tetramers) when two conditions are met: (1) Zn(II) is used as the catalyst for the diazotransfer reaction, and (2) a large excess of sodium L-ascorbate relative to Cu(I) is used for the cycloaddition reaction. During the course of the

TABLE 3. Solid-Phase Reaction Conditions and Results for Compounds 8 and 9[a]



entry	diazotransfer catalyst[b]	cmpd	number of triazoles in product	overall yield[c] (%)	average yield per step[d] (%)
1	$CuSO_4$·$5H_2O$ (0.1 equiv)	**8**	3	37	85
2	$CuSO_4$·$5H_2O$ (0.1 equiv)	**9**	4	33	87
3	$ZnCl_2$ (0.2 equiv)	**8**	3	57	91
4	$ZnCl_2$ (0.2 equiv)	**9**	4	78	97

[a] Reactions performed on PAM resin. Dipolar cycloaddition conditions: $CuSO_4$·$5H_2O$ (0.1 equiv), sodium L-ascorbate (3 equiv), TBTA (0.2 equiv), alkyne (2−3 equiv), 25 °C 18 h. [b] Diazotransfer conditions: TfN_3 (8 equiv), triethylamine (4 equiv), diazotransfer catalyst, 25 °C, reaction time: entries 1 and 2 = 18 h, entries 3 and 4 = 3−6 h. [c] Determined by chromatographic isolation of products after cleavage from the resin. [d] Calculated average yield of each diazotransfer and Huisgen 1,3-dipolar cycloaddition assuming all other steps (i.e., deprotection, cleavage) to be quantitative.

cycloaddition step, we often observed a color change from yellow to green which suggested that oxidation of the Cu(I) species to Cu(II) had occurred. Addition of a large excess of sodium L-ascorbate relative to Cu(I) was needed to prevent this color change and to achieve higher yields of the desired products (data not shown). We did not observe a significant effect of the amount of TBTA used on the yield when a large excess of sodium L-ascorbate was present.[16] The preference for Zn(II) over Cu(II) for the diazotransfer and the necessity for a large excess of sodium L-ascorbate during the cycloaddition reaction suggest that the presence of Cu(II) may be detrimental to the synthesis of triazolamers on the solid phase. We detected cleaved intermediates in the wash solutions after the diazotransfer steps. This cleavage appears to result from Lewis acid-catalyzed cleavage of the benzyl ester that tethers the compound to the PAM resin. Although these intermediates were detected in the wash solutions of both the Cu(II)- and Zn(II)-catalyzed reactions, the extended reaction time required for the Cu(II)-catalyzed diazotransfer likely leads to a greater degree of cleavage during this step. Likewise, the presence of Cu(II) during the Huisgen

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(25) Punna, S.; Kuzelka, J.; Wang, Q.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2215−20.
(26) Yan, R. B.; Yang, F.; Wu, Y. F.; Zhang, L. H.; Ye, X. S. *Tetrahedron Lett.* **2005**, *46*, 8993−8995.
(27) Titz, A.; Radic, Z.; Schwardt, O.; Ernst, B. *Tetrahedron Lett.* **2006**, *47*, 2383−2385.
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1,3-dipolar cycloaddition step may also lead to premature cleavage especially since this step is generally performed for 18 h. Using our optimized conditions, the average yields per step in the synthesis were high (Table 3, entries 3 and 4). We are using these optimized conditions to develop libraries of these oligomers to fully examine their biological potential.

In conclusion, we have reported efficient solid- and solution-phase syntheses of peptido-triazole oligomers in which each amide bond in a peptide has been replaced with a triazole ring. Although the methodology developed herein has been tuned specifically for the synthesis of triazolamers, it may find general application (e.g., for the synthesis of triazole-based dendrimers[30]) as the use of these reactions becomes more widespread.

Experimental Section

General Procedure for Triazole Formation from an Amine via in Situ Azide Generation (Synthesis of 3: Table 1, entry 7). To a solution of H-Phe-OMe·HCl (50 mg, 0.23 mmol) and $ZnCl_2$ (3 mg, 0.023 mmol) in H_2O, (5 mL) triethylamine (0.097 mL, 0.70 mmol), and methanol (16 mL) was added a solution of TfN_3 in dichloromethane (5 mL, 0.70 mmol) followed by 4-phenyl-1-butyne (30 mg, 0.23 mmol), $CuSO_4 \cdot 5H_2O$ (12 mg, 0.046 mmol), TBTA (25 mg, 0.046 mmol), and sodium L-ascorbate (46 mg, 0.23 mmol). The reaction mixture was stirred at room temperature for 18 h, and a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with dichloromethane (four times), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography (3:7 ethyl acetate/hexanes) to afford compound **3** as a light-yellow oil (23 mg, 30%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.91 (s, 1H), 7.27−7.22 (m, 2H), 7.21−7.16 (m, 6H), 7.12−7.08 (m, 2H), 5.77 (dd, J = 10.6, 5.2 Hz, 1H), 3.69 (s, 3H), 3.54 (dd, AB pattern, J = 14.3, 5.2 Hz, 1H), 3.45 (dd, AB pattern, J = 14.2, 10.7 Hz, 1H), 2.88 (app s, 4H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.8, 146.0, 141.0, 135.9, 128.8, 128.31, 128.26, 128.18, 126.8, 125.9, 122.2, 62.8, 52.8, 36.6, 34.7, 26.9; HRMS *m*/*z* for $C_{20}H_{22}N_3O_2$ $[M + H]^+$, calcd: 336.1712, found: 336.1713.

General Procedure for Triazole Formation from an Amine via One-Pot Sequential Diazotransfer and Huisgen 1,3-Dipolar Cycloaddition (Synthesis of 3: Table 2, entry 1). To a solution of H-Phe-OMe·HCl (23 mg, 0.11 mmol) and $ZnCl_2$ (1.5 mg, 0.011 mmol) in H_2O (1 mL) and triethylamine (0.045 mL, 0.32 mmol) was added a solution of TfN_3 in dichloromethane (1.7 mL, 0.32 mmol) and methanol (3.5 mL). The reaction mixture was stirred at room temperature for 1.5 h and monitored by thin layer chromatography. A solution of TBTA (11 mg, 0.021 mmol) in dichloromethane (0.5 mL) and a solution of sodium L-ascorbate (8.5 mg, 0.043 mmol) and $CuSO_4 \cdot 5H_2O$ (5 mg, 0.021 mmol) in H_2O (0.5 mL) were added to the mixture followed by 4-phenyl-1-butyne (14 mg, 0.11 mmol). The reaction mixture was subjected to microwave irradiation at 80 °C for 5 min. A saturated aqueous solution of sodium bicarbonate was added, and the mixture was extracted with dichloromethane (four times). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography (2:8 ethyl acetate/hexanes) to afford compound **3** as a white solid (33 mg, 93%).

Synthesis of Triazolamer 9 (Table 3, entry 4). PAM resin was swelled in dichloromethane (1 mL) for 15 min, and a solution of $ZnCl_2$ (4 mg, 0.029 mmol), methanol (0.5 mL), and triethylamine (0.081 mL, 0.58 mmol) was added, followed by a 0.4 mmol/mL solution of TfN_3 in toluene (2.92 mL, 1.17 mmol). The reaction mixture was shaken at room temperature for 5 h. Reaction progress was monitored by LC−MS or Kaiser Test.[31] The resin was filtered and washed sequentially with dichloromethane, NMP, 0.02 M sodium diethyldithiocarbamate trihydrate solution in NMP, NMP, methanol, NMP, and dichloromethane. The resin was resuspended in NMP (1 mL), and then Boc-Ala-alkyne (74 mg, 0.44 mmol) was added followed by a suspension of TBTA (15 mg, 0.029 mmol), $CuSO_4 \cdot 5H_2O$ (4 mg, 0.015 mmol), and sodium L-ascorbate (87 mg, 0.44 mmol) in NMP/H_2O (1 mL:0.1 mL). The reaction mixture was shaken at room temperature for 18 h, and the reaction was monitored by LC−MS. The resin was filtered and washed sequentially with dichloromethane, NMP, 0.02 M sodium diethyldithiocarbamate trihydrate solution in NMP, NMP, methanol, NMP, and dichloromethane. The resin was treated with 30% trifluoroacetic acid in dichloromethane for 1 h to remove the Boc group. The diazotransfer step, the Huisgen 1,3-dipolar cycloaddition step using the appropriate alkyne, deprotection step, and intermittent washing steps were repeated as needed to complete the synthesis. Cleavage of the final product from the resin was effected by suspending the resin with 40% methylamine in H_2O/THF, 1:1 solution for 2 h. The resin was filtered, and the filtrate was concentrated under vacuum. A saturated aqueous solution of sodium bicarbonate was added, and the mixture was extracted with dichloromethane (five times). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography (5:95 methanol/dichloromethane) to afford compound **9** as a white solid (62 mg, 78%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.66 (s, 1H), 8.53 (q, J = 4.6 Hz, 1H), 8.29 (s, 0.5H), 8.28 (s, 0.5H), 8.26 (s, 2H), 7.85 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 6.15−6.07 (m, 3H), 4.88 (d, J = 10.3 Hz, 1H), 2.66 (d, J = 4.9 Hz, 1H), 2.62 (d, J = 4.5 Hz, 2H), 2.42−2.32 (m, 1H), 1.93 (d, J = 7.1 Hz, 3H), 1.86 (d, J = 7.0 Hz, 6H), 0.92 (d, J = 6.7 Hz, 3H), 0.61 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.6, 146.4, 146.2, 130.7, 128.8, 127.8, 125.1, 121.8, 121.7, 121.6, 120.0, 69.1, 52.3, 31.0, 25.5, 20.4, 20.4, 18.8, 18.5; HRMS *m*/*z* for $C_{26}H_{33}N_{13}O$ $[M + H]^+$, calcd: 544.3010, found: 544.3013.

Synthesis of Triazolamer 8 (Table 3, entry 3). A procedure analogous to that used for the synthesis of **9** was used for the synthesis of **8**. ^{1}H NMR (400 MHz, d_4-methanol) δ 8.08 (m, 1H), 7.97 (m, 1H), 7.62 (s, 1H), 7.07−7.04 (m, 6H), 6.96−6.88 (m, 4H), 6.09−6.05 (m, 1H), 5.98 (t, J = 7.8 Hz, 1H), 5.27 (q, J = 6.7 Hz, 1H), 4.72−4.68 (m, 1H), 3.54 (d, J = 8.1 Hz, 2H), 3.49 (t, J = 7.2 Hz, 2H), 2.65 (d, J = 1.4 Hz, 3H), 1.65 (app dd, J = 7.2, 2.2 Hz, 3H), 1.33−1.30 (m, 12H); ^{13}C NMR (100 MHz, d_4-methanol) δ 210.4, 171.3, 146.5, 146.4, 137.5, 137.4, 130.2, 130.12, 130.09, 129.6, 129.57, 128.1, 128.0, 124.4, 124.0, 122.1, 80.3, 60.7, 60.5, 60.1, 42.0, 41.9, 29.9, 28.8, 26.6, 21.3, 18.4; HRMS *m*/*z* for $C_{33}H_{41}N_{11}O_3$ $[M + H]^+$, calcd: 640.3472, found: 640.3476.

Synthesis of Triazolamers 5, 6, and 7. Compounds **5, 6**, and **7** were synthesized as indicated in Scheme 2. Synthetic characterization of these compounds has been previously reported.[6]

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Supporting Information Available: Copies of spectra of compounds **3**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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