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Copper-free Route to Triazole-Modified Peptidomimetic by the Combination of Two Multicomponent Reactions in One Pot

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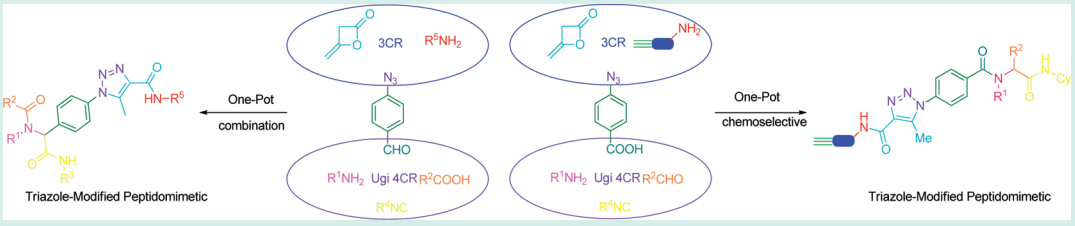
Supporting Information



ABSTRACT: An efficient copper-free protocol for the synthesis of 5-methyl-1*H*-1,2,3-triazole-modified peptidomimetics through the combination of Ugi four-component reaction with a three-component cycloaddition, has been developed. The copper-free straightforward process is suitable for drug discovery. The chemoselective preparation of 1,4-disubstituted, triazole-modified peptidomimetics by using alkynyl substituted amines may have potential biological and synthetic application. At last, a "Lapinski type" analysis of the physical properties was performed, which is expected to help drug discovery.

KEYWORDS: *peptidomimetic, triazole, multicomponent reaction, Ugi reaction, copper-free, chemoselective*

INTRODUCTION

1*H*-1,2,3-Triazole-modified peptidomimetics (Figure 1) are attractive nonnatural molecules for drug discovery because of their many biological activities.[1] It is reported that triazole-modified peptidomimetics can act as peptide surrogate[2] and be used as blood components,[3] anticancer medications,[4] cysteine protease[5] and HIV-1 protease inhibitors.[6] Moreover, they have been introduced into protein-like oligomers and nonpeptidic protein mimetic foldamers.[7] Consequently, they serve as a platform for developing pharmaceutical agents for diverse applications[8] and have gained considerable attention for the study of the associated biological processes and drug design.[9]

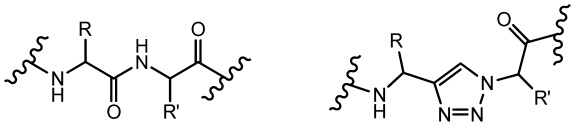


Figure 1. General structures of (a) a peptide and (b) a 1*H*-1,2,3-triazole-modified peptidomimetics.

Recently, many triazoles in peptide terminal, center, or side chain positions linked to sugars or other peptides have been reported.[10] The typical approach for the synthesis of such molecules is by a rather inefficient, step-by-step reaction sequence requiring many protecting groups. However, in modern therapeutic discovery, the rapid assembly of drug without protecting groups is gaining considerable interest which fully lives up to the principle of "Green Chemistry" and atom economy. Multicomponent reactions (MCRs) are one type of the approaches to address this challenge.[11] Owing to their atom economy, facile execution, and high efficiency, a wide range of components can be subjected to one-pot reactions.

The usefulness of MCRs is even greater if two or more MCRs can be combined in one pot to generate such "privileged medicinal scaffolds".[12] However, a one-pot multicomponent synthesis of triazole-modified peptidomimetics from readily accessible starting materials still remains elusive. The biggest challenge to such a combination lies in the incorporation of a functional group that is unreactive in the initial MCR but reactive in a subsequent MCR. The solvent for the subsequent reaction steps also should be compatible with the first step. In an ideal case, different reactions are run in a single pot to generate the target products without protecting groups. However, there are few reports about conjugating two MCRs to generate triazole-modified peptidomimetics in one pot.

In our initial experiment, triazoles are synthesized by copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction between acetylenes and azides (CuAAC), which are the common protocol for the click chemistry.[5,13] However, the residual copper catalyst could be toxic to both bacterial and mammalian cells.[14] Therefore from a biological perspective the CuAAC is not a preferred catalytic method for preparing triazole-modified peptidomimetics. A copper-free triazole synthesis protocol is highly desirable for drug discovery. To this end we were interested in developing a copper-free

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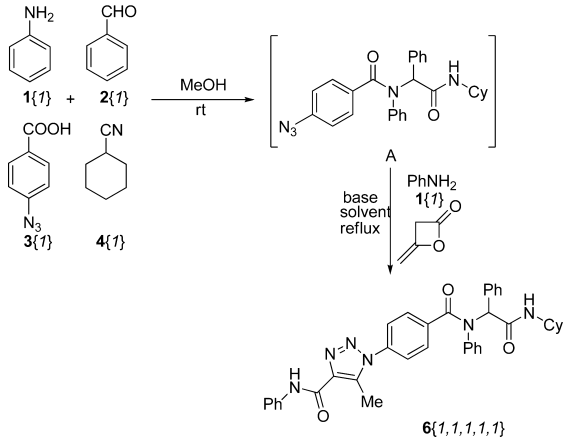
synthesis of triazole-modified peptidomimetics, in which two multicomponent reactions were conjugated in one pot.

RESULTS AND DISCUSSION

In an initial approach, we selected the Ugi reaction as an efficient method for the construction of peptide building blocks and peptoid molecules in one step (Scheme 1). With its wide

Scheme 1. One-Pot Synthesis of Triazole-Modified Peptidomimetics

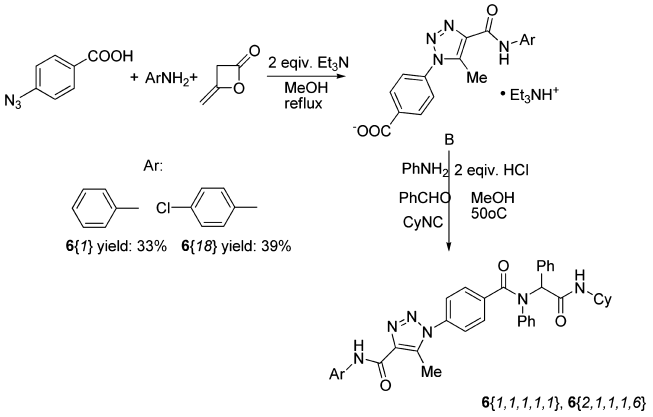


tolerance of functional groups, Ugi reaction has been extensively developed. Many research groups have utilized the Ugi reaction followed by another multicomponent reaction to assemble complex structures.[15] We focused on the synthesis of the triazole structure by a three-component cycloaddition utilizing azides, amines and diketene as the reactants under base catalysis.[16] Although many copper-free triazole syntheses have been reported[3,17] not all are viable in such a combination since the functional groups for the second MCR reaction should not be participants in the Ugi reaction. Initially, para-azido-benzoic acid **3**{*1*} (all components see Figure 2) was chosen as the "bridge molecule" to combine Ugi 4CR with 3CR triazole synthesis. The Ugi reactions were preferred as the first MCR. Based on classical reports on Ugi 4CR, **3**{*1*} was reacted with **1**{*1*}, **2**{*1*}, and **4**{*1*} in MeOH at room temperature to form intermediate **A**. Then without isolation of the intermediate, a one-pot combination with 1 equiv of **1**{*1*}, diketene, and 1 equiv of triethylamine in the second MCR at reflux, led to the isolation of 5-methyl-1*H*-1,2,3-triazole-modified peptidomimetics **6**{*1,1,1,1,1*}in 38% yield after 48 h.

To optimize the reaction, we screened a number of experimental conditions. For the second 3CR, it was discovered that both organic and inorganic bases could catalyze the formation of triazole-modified peptidomimetics. Although strong bases such as *t*-BuOK and NaOH resulted in short reaction time, Et_3N gave an excellent yield. The solvent effect in the second reaction was also examined by replacing MeOH with other solvents. Ugi 4CR was carried out in MeOH. After completion of the Ugi reaction, evaporation of the solvent in vacuo without separation of the intermediate, addition of **1**{*1*}, diketene and triethylamine in a different solvent was tested. Compared with DMF, THF, and 1,4-dioxane, the use of MeOH resulted in higher yields of the products within a shorter reaction period. Although MeCN system afforded a similar yield (as an example, **6**{*1,1,1,1,1*} can be obtained in 39% yield), the use of MeOH as solvent is more convenient for this one-pot process. The best result was obtained when 1.2 equiv of **1**{*1*}, diketene, and triethylamine were used in the second step (yield = 43%).

We subsequently investigated the possibility of the triazole synthesis as the first MCR. An alternative route for triazole-modified peptidomimetics was offer in Scheme 2. Diketene,

Scheme 2. Alternative Route for Triazole-Modified Peptidomimetics



3{*1*} and **1**{*1*} were reacted in the presence of 2 equivalents of triethylamine to form the intermediate **B**. After protonation of the intermediate by two equivalents of methanolic HCl, a one-pot combination with **1**{*1*}, **2**{*1*}, and **4**{*1*} in an Ugi 4CR led to the isolation of **6**{*1,1,1,1,1*} in 33% yield while 39% yield when **1**{*2*} was used instead of **1**{*1*}. Apparently, the chosen

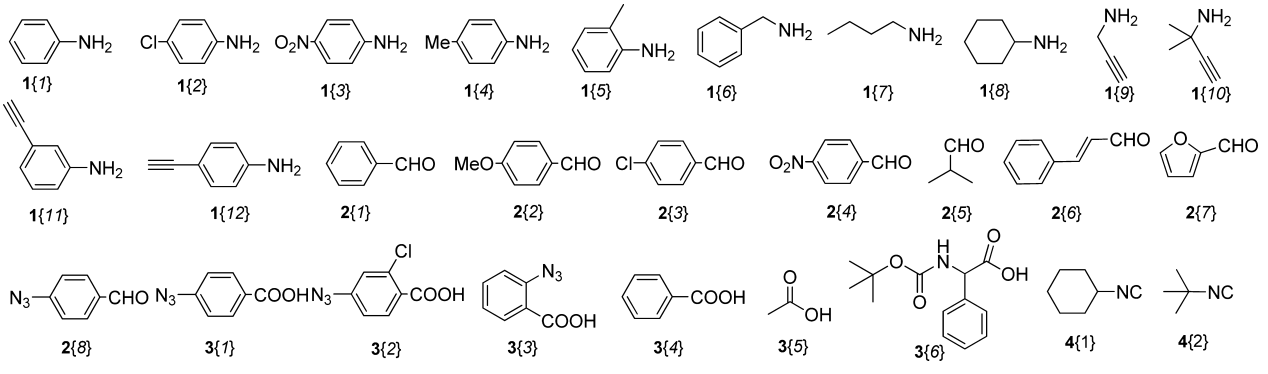


Figure 2. Components involved in the described six-component one-pot sequential reactions.

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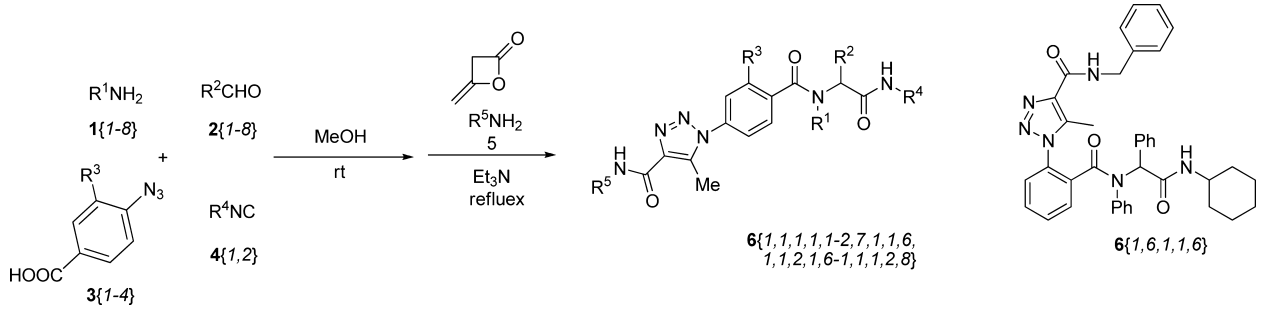
Table 1. Scope of Six-Component One-Pot Sequential Reaction for the Synthesis of 5-Methyl-1*H*-1,2,3-triazole-Modified Peptidomimetics



entry	1	2	3	4	5	product	yield [%][a]
1	1{1}	2{1}	3{1}	4{1}	1{1}	6{1,1,1,1,1}	43
2	1{1}	2{1}	3{1}	4{1}	1{6}	6{1,1,1,1,6}	47
3	1{2}	2{1}	3{1}	4{1}	1{6}	6{2,1,1,1,6}	51
4	1{3}	2{1}	3{1}	4{1}	1{6}	6{3,1,1,1,6}	0
5	1{4}	2{1}	3{1}	4{1}	1{6}	6{4,1,1,1,6}	53
6	1{6}	2{1}	3{1}	4{1}	1{2}	6{6,1,1,1,6}	50
7	1{7}	2{1}	3{1}	4{1}	1{6}	6{7,1,1,1,6}	52
8	1{8}	2{1}	3{1}	4{2}	1{6}	6{8,1,1,1,6}	48
9	1{2}	2{2}	3{1}	4{1}	1{6}	6{2,2,1,1,6}	55
10	1{1}	2{4}	3{1}	4{1}	1{6}	6{1,4,1,1,6}	53
11	1{2}	2{3}	3{1}	4{1}	1{6}	6{2,3,1,1,6}	50
12	1{2}	2{5}	3{1}	4{1}	1{6}	6{2,5,1,1,6}	47
13	1{2}	2{7}	3{1}	4{1}	1{6}	6{2,7,1,1,6}	45
14	1{1}	2{6}	3{1}	4{1}	1{6}	6{1,6,1,1,6}	42
15	1{1}	2{1}	3{2}	4{1}	1{6}	6{1,1,2,1,6}	41
16	1{1}	2{1}	3{3}	4{1}	1{6}	6{1,1,3,1,6}	34
17	1{1}	2{1}	3{1}	4{2}	1{6}	6{1,1,1,2,6}	53
18	1{1}	2{1}	3{1}	4{1}	1{2}	6{1,1,1,1,2}	47
19	1{1}	2{1}	3{1}	4{1}	1{3}	6{1,1,1,1,3}	31
20	1{1}	2{1}	3{1}	4{1}	1{4}	6{1,1,1,1,4}	51
21	1{1}	2{1}	3{1}	4{1}	1{5}	6{1,1,1,1,5}	45
22	1{1}	2{1}	3{1}	4{1}	1{7}	6{1,1,1,1,7}	61
23	1{1}	2{1}	3{1}	4{2}	1{8}	6{1,1,1,2,8}	43

[a]Isolated yield.

Ugi reaction as the first MCR was the best chose for this combination.

The scope of the one-pot combination reaction sequence is illustrated by the examples in Table 1. In most cases, the yields of the product **6**{*1.1.1,1.1−2,1,1,1,6, 4,1,1,1,6−1,1,1,2,8*} were good. For the Ugi reaction step, both aromatic and aliphatic amines gave satisfactory results (Table 1, entries 1−3, 5−8). However, the substituted 4-nitro-aniline **1**{*4*} was not tolerated (Table 1, entries 4); the intermediate Ugi product decompose in the second step and the desired product was not found. While the *α,β*-unsaturated aldehydes, such as furaldehyde and cinnamaldehyde, were found to be compatible affording into the products **6**{*2,7,1,1,6*} and **6**{*1,6,1,1,6*} in good yields (Table 1, entries 13, 14). Steric effects were also indicated by the slight reduction in yield of substrate **3**{*3*} be used as "bridge molecule" (Table 1, entry 16). Compound **3**{*2*} was incorporated with no difficulty as a bridge molecule (Table 1, entry 15).

However, the electronic properties of the substituted anilines for the second MCR had a significant influence on the yield of the reaction (Table 1, entries 19, 20). Electron-deficient 4-nitro-aniline **1**{*3*} produced in 31% yield of final product **6**{*1,1,1,1,3*}, while 4-methyl-aniline **1**{*4*} in 51% yield **6**{*1,1,1,1,4*}. And the steric effects of the substituted anilines also had a significant influence on the yield of the reaction (Table 1, entries 20, 21). The best result was given by the *n*-butyl amine **1**{*7*} (Table 1, entry 22). Unfortunately, secondary amines (piperidine, morpholine) failed to react under these conditions even DIPEA or DMAP was used as catalyst.

To explore the possible conformational preorganization effect of triazole-modified peptidomimetics, para-azido-benzaldehyde **2**{*8*} was chosen instead of para-azido-benzoic acid **3**{*1*} as "bridge molecule" to combined the two MCRs (Table 2). The corresponding 5-methyl-1*H*-1,2,3-triazole-modified peptidomimetics were obtained in good yields **7**{*1,8,4,1,6−1,8,6,2,6,*}.

To further expand the scope of this combination reaction, the alkynyl substituted amines **1**{*9−12*} were used in the second step (Table 3). We were pleased to find that the reaction was exclusively resulting 1,4-disubstituted-triazole-modified peptidomimetics **8**{*1,1,1,11, 1,1,1,9−1,8,5,2,11*}. There were non **9a** or **9b** as Husigen 1,3-dipolar cycloaddition products were found. That means in such condition, the 1,4-disubstituted-triazole-modified peptidomimetics could be chemoselectively prepared by alkynyl substituted amines. The type of the alkynyl substituted amines was found to be important.

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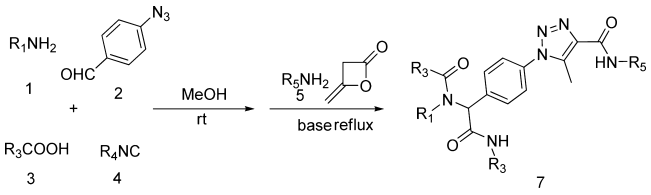
Table 2. One-Pot Synthesis of 5-Methyl-1*H*-1,2,3-triazole-Modified Peptidomimetics by Using Para-azido-benzaldehyde as a Bridge Molecule



entry	1	2	3	4	5	product	yield (%)[a]
1	1{*1*}	2{*8*}	3{*4*}	4{*1*}	1{*6*}	7{*1,8,4,1,6*}	29
2	1{*1*}	2{*8*}	3{*4*}	4{*1*}	1{*7*}	7{*1,8,4,1,7*}	39
3	1{*1*}	2{*8*}	3{*5*}	4{*2*}	1{*6*}	7{*1,8,5,2,6*}	52
4	1{*1*}	2{*8*}	3{*5*}	4{*2*}	1{*7*}	7{*1,8,4,2,7*}	56
5	1{*2*}	2{*8*}	3{*5*}	4{*2*}	1{*6*}	7{*2,8,5,2,6*}	63
6	1{*1*}	2{*8*}	3{*6*}	4{*2*}	1{*6*}	7{*1,8,6,2,6*}	46

[a]Isolated yield.

The meta-substituted ethynylaniline **1**{*11*} gave significantly higher yield than alkynylamines **1**{*9, 10*}, presumably because of electronic effects (Table 3, entries 1, 3, 4). However, para-substituted ethynylaniline **1**{*12*} was not tolerated; the desired product **8**{*1,1,1,1,12*} was not formed and only Ugi reaction was found (Table 3, entry 2).

Finally, to evaluate this synthetic method, a Lapinski type analysis of the physical properties was performed. It was found that most of the products adhered to Lapinski's Rule-of-5 for parameters NHD and NHA, only products **6**{*1,4,1,1,6*}, **6**{*1,1,1,1,3*}, and **7**{*1,8,6,2,6*} violating the rule. And the products **7** adhered the Rule in parameter log *P*. However, the MW of all the products are about 600, which do not adhered the Rule of Lapinski. So we believe that this method is potentially useful to discover new drug.

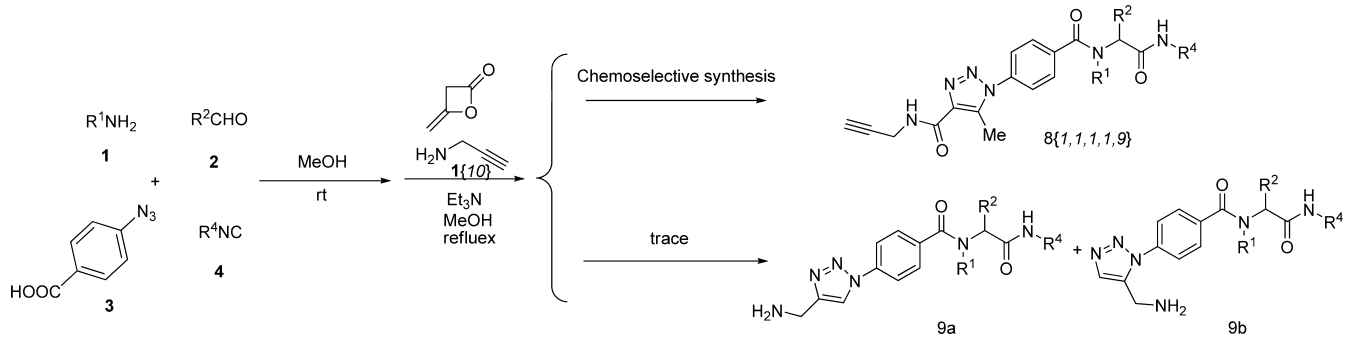
CONCLUSIONS

In conclusion, we have developed an efficient approach to synthesize 5-methyl-1*H*-1,2,3-triazole-modified peptidomimetics by using a sequential Ugi reaction and a copper-free cycloaddition from simple and commercially available materials and gave a Lapinski type analysis of the physical properties. The synthetic protocol embodies a combination of two multicomponent reactions in a one-pot process successfully. We anticipate that this method could have interesting applications in the construction of diversified 5-methyl-1*H*-1,2,3-triazole-modified peptidomimetics, and can be a useful protocol in biochemistry, and medicinal discovery. Moreover, the observed chemoselective preparation of 1,4-disubstituted-triazole-modified peptidomimetics by using alkynyl substituted amines may have potential biological and synthetic application and worth noticing.

EXPERIMENTAL PROCEDURES

General. Melting points were determined uncorrected. Analytical thin-layer chromatography were performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm). The plates were visualized by exposure to ultraviolet light. ^{1}H NMR spectra were recorded on Bruker DRX500 (500 MHz) and ^{13}C NMR spectra on Bruker DRX500 (125 MHz) spectrometer. Mass spectra were taken on a Finnigan TSQ Quantum−MS in strument in the electrospray ionization (ESI) mode. Elemental analyses were performed on a Yanagimoto MT3CHN recorder. The distribution of clog *P* was analyzed by high performance liquid chromatograph (HPLC) on Agilent 1120 (Eclipse XDB-C18,

Table 3. Chemoselective Preparation of 1,4-Disubstituted-triazole-Modified Peptidomimetics by Using Alkynyl Substituted Amines



entry	1	2	3	4	5	product	yield (%)[a]
1	1{*1*}	2{*1*}	3{*1*}	4{*1*}	1{*11*}	8{*1,1,1,1,11*}	48
2	1{*1*}	2{*1*}	3{*1*}	4{*1*}	1{*12*}	8{*1,1,1,1,12*}	0
3	1{*1*}	2{*1*}	3{*1*}	4{*1*}	1{*9*}	8{*1,1,1,1,9*}	36
4	1{*1*}	2{*1*}	3{*1*}	4{*1*}	1{*10*}	8{*1,1,1,1,10*}	44
5	1{*2*}	2{*1*}	3{*1*}	4{*1*}	1{*11*}	8{*2,1,1,1,11*}	52
6	1{*6*}	2{*1*}	3{*1*}	4{*1*}	1{*11*}	8{*6,1,1,1,11*}	58
7	1{*8*}	2{*1*}	3{*1*}	4{*1*}	1{*11*}	8{*8,1,1,1,11*}	46
8	1{*1*}	2{*3*}	3{*1*}	4{*1*}	1{*11*}	8{*1,3,1,1,11*}	50
9	1{*1*}	2{*5*}	3{*1*}	4{*1*}	1{*11*}	8{*1,5,1,1,11*}	46
10	1{*1*}	2{*7*}	3{*1*}	4{*1*}	1{*11*}	8{*1,7,1,1,11*}	42
11	1{*1*}	2{*8*}	3{*5*}	4{*2*}	1{*11*}	8{*1,8,5,2,11*}	55

[a]Isolated yield.

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Table 4. Lapinski Type Analysis of the Physical Properties

entry	product	molecular weight (MW)[a]	number of H-donors (NHD)	number of H-acceptors (NHA)	tPSA (polar surface area)[b]	partition coefficient (log P)[c]
1	**6**{*1,1,1,1,1*}	612	2	9	106.47	5.57
2	**6**{*1,1,1,1,6*}	626	2	9	106.47	5.57
3	**6**{*2,1,1,1,6*}	661	2	9	106.47	5.59
4	**6**{*4,1,1,1,6*}	640	2	9	106.47	5.56
5	**6**{*6,1,1,1,6*}	660	2	9	106.47	5.57
6	**6**{*7,1,1,1,6*}	606	2	9	106.47	6.58
7	**6**{*8,1,1,1,6*}	606	2	9	106.47	5.57
8	**6**{*2,2,1,1,6*}	690	2	10	115.76	5.57
9	**6**{*1,4,1,1,6*}	671	2	11	158.26	8.18
10	**6**{*2,3,1,1,6*}	694	2	9	106.47	5.67
11	**6**{*2,5,1,1,6*}	626	2	9	106.47	6.18
12	**6**{*2,7,1,1,6*}	650	2	10	115.70	5.51
13	**6**{*1,6,1,1,6*}	686	2	9	106.47	5.59
14	**6**{*1,1,2,1,6*}	660	2	9	106.47	5.31
15	**6**{*1,1,3,1,6*}	626	2	9	106.47	5.55
16	**6**{*1,1,1,2,6*}	600	2	9	106.47	6.27
17	**6**{*1,1,1,1,2*}	646	2	9	106.47	5.58
18	**6**{*1,1,1,1,3*}	657	2	11	106.47	8.27
19	**6**{*1,1,1,1,4*}	626	2	9	158.28	5.64
20	**6**{*1,1,1,1,5*}	626	2	9	106.47	5.79
21	**6**{*1,1,1,1,7*}	592	2	9	106.47	5.50
22	**6**{*1,1,1,2,8*}	592	2	9	106.47	5.57
23	**7**{*1,8,4,1,6*}	626	2	9	106.47	3.81
24	**7**{*1,8,4,1,7*}	592	2	9	106.47	3.30
25	**7**{*1,8,5,2,6*}	536	2	9	106.47	3.31
26	**7**{*1,8,4,2,7*}	504	2	9	106.47	4.10
27	**7**{*2,8,5,2,6*}	572	2	9	106.47	3.11
28	**7**{*1,8,6,2,6*}	749	2	12	132.49	3.27
29	**8**{*1,1,1,1,11*}	636	2	9	106.47	5.54
30	**8**{*1,1,1,1,9*}	574	2	9	106.47	5.41
31	**8**{*1,1,1,1,10*}	602	2	9	106.47	5.31
32	**8**{*2,1,1,1,11*}	670	2	9	106.47	5.81
33	**8**{*6,1,1,1,11*}	650	2	9	106.47	5.59
34	**8**{*8,1,1,1,11*}	642	2	9	106.47	5.70
35	**8**{*1,3,1,1,11*}	670	2	9	106.47	5.41
36	**8**{*1,5,1,1,11*}	602	2	9	106.47	5.82
37	**8**{*1,7,1,1,11*}	626	2	10	115.70	5.52
38	**8**{*1,8,5,2,11*}	548	2	9	106.47	3.69

[a]Mass spectra were taken on a Finnigan TSQ Quantum−MS in strument in the electrospray ionization (ESI) mode. [b]tPSA were given by ChemBioOffice 2008. [c]log *P* was tested in n-octyl alcohol−water system by HPLC analysis.

G1214B VWD). All other chemicals were commercially available and used without further purification.

Typical Experimental Procedure. Amine (2 mmol) and aldehyde (2 mmol) were dissolved in a sealed tube with 3 mL of MeOH and stirred at room temperature for 30 min. Then *para*-azido-benzoic acid (2 mmol) and isocyanide (2 mmol) were added. The mixture was stirred for 1−24 h. Then corresponding aniline (2.4 mmol), diketene (2.4 mmol) and triethylamine (2.4 mmol) were added in the seal tube and raised the reaction temperature to 80 °C for 24 h. Then, the mixture was cooled to room temperature, and the product precipitated. The product was filtered and washed with methanol. When the product was well soluble in MeOH, the solvent was removed in vacuo, and the residue was purified by column chromatography (hexanes/ethyl acetate 3/1).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The experimental details and the spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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