Three-component Coupling Reaction for the Synthesis of Fully Substituted Triazoles: Reactivity Control of Cu-Acetylide toward Alkyl Azides and Diazo Compounds

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<td>Complete List of Authors:</td>
<td>Chen, Fa-Jie; University of Illinois at Chicago, Department of Chemistry Mamidipalli, Phani; University of Illinois at Chicago, Department of Chemistry Sabbasani, Venkatareddy; University of Illinois at Chicago, Department of Chemistry Liu, Huaqing; University of Illinois at Chicago, Department of Chemistry Lee, Daesung; University of Illinois at Chicago, Department of Chemistry Xia, Yuanzhi; Wenzhou University, Chemistry</td>
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Three-component Coupling Reaction for the Synthesis of Fully Substituted Triazoles: Reactivity Control of Cu-Acetylide toward Alkyl Azides and Diazo Compounds

Fa-Jie Chen, a,b Phani Mamidipalli, b Venkata Reddy Sabbasani, b Huqing Liu, b Yuanzhi Xia a* and Daesung Lee a**

Introduction

The copper(I)-catalyzed [3+2] cycloaddition between azide and alkyne known as the ‘azide-alkyne click reaction’ developed by Sharpless a and Meldal b independently has been drawn great interest because of its capacity to be applied to many fields including chemical biology, medicinal chemistry and material science (Scheme 1, eq 1). c While the thermal Huisgen cycloadditions generate a mixture of regioisomers under relatively harsh conditions, d the corresponding Cu-catalyzed click reactions generate single regioisomer product under much milder conditions. e, f In general, Cu-catalyzed azide-alkyne cycloaddition generates 1,4-disubstituted 1,2,3-triazoles 1, but switching the regioselectivity to form 1,5-disubstituted 1,2,3-triazoles was achieved by using a ruthenium catalyst. g Fu reported Cu-catalyzed reaction of alkyne with diazo compound, an isoelectronic structure of an azide, however, provided a formal C–H insertion product 2 rather than a [3+2] cycloaddition product (eq 2). h Because of the utility of a [3+2] cycloaddition of diazo compound with alkyne as a tool for copper-free bioconjugation, Raines explored the reactivity and selectivity between azide and diazo compound with alkynes under copper-free conditions. i While strained alkynes provided equal mixture of cycladducts of azide and diazo compound, unstrained electron-deficient alkyne generated D 2 -pyrazole 3 selectively along with unreacted azide (eq 3).

On the other hand, the reactivity difference between azide and diazo compounds toward electron-rich alkynes such as Cu-acetylide has not been explored despite the fact that the individual reactions were extensively studied. At this juncture, we envisage that the combined reaction of alkyl azide and diazo compound with copper catalyst (eq 4) would provide information about the relative reactivity of these isoelectronic functionalities toward Cu-acetylide. In addition, if the reaction rates of these two competing reactants could be controlled a new sequential reaction could be developed. The reactions to proceed through Path A, Path B and Path C would depend on multiple factors including the structure of azide and diazo compound, their stoichiometry, catalyst loading, and the.

Scheme 1. Reactions of Alkyne, Alkyl Azide, and Diazo Compound with Copper Catalyst.
ligand. We predict that in Path A, alkyl azide will outcompete diazo compound to form cycloadduct I-1 primarily due to its higher Cu-coordinating ability than diazo compound. Once generated, intermediate I-2 will be protonated to provide triazole 1 or react with diazo compound to generate I-2, which upon protonation will give three-component coupled product 4. However, the competing reaction of diazo compound in Path B will generate adduct I-3, which may cyclize to form I-4 or extrude N$_3$ to generate I-5. Because the Cu-catalyzed coupling of diazo compound with alkyne in eq 2 does not generate pyrazole, I-3 should disfavor to cyclized to generate I-4. Although I-5 can still undergo [3+2] cycloaddition to form I-2 the kinetically favored protonation is expected to generate 2 and unreacted azide. To maximize formation 4, the protonation of I-1 should be suppressed, which requires high concentration of diazo compound. However, the increased concentration of diazo compound would also increase the possibility of forming Cu-acetylide adduct I-3 in Path B and Cu-carbenoid I-6 in Path C as well, which ultimately increases the formation of product 2. We suspect that the ligand on the Cu-catalyst can modulate the relative rates of these competing pathways and ultimately can maximize the efficiency of forming three-component coupled 1,4,5-trisubstituted 4. Furthermore, tethering a pair of reactants, for example, alkyne and diazo compound would avoid the problem of undesired protonation at the intermediate stage (eq 5), which would constitute a new strategy for preparing ring-fused triazoles.9

Developing efficient methods for preparing 1,4,5-trisubstituted triazoles has drawn significant interest.6c,10 One-pot approaches employing a Cu-catalyzed click reaction followed by a C–H arylation sequence were effective,10 yet direct trapping of Cu-triazolide intermediate generated from the Cu(II)-catalyzed click reaction has gained popularity.11 In 2015, Wang reported an efficient direct trapping approach by employing N-tosylhydrazones as a precursor for diazo compounds under relatively harsh conditions.12 However, due to the high reactivity of diazo compounds in Cu-catalyzed reactions, controlling the sequence and timing of their incorporation at a particular stage of a catalytic cycle is difficult if preformed diazo compounds are employed. This is a general conundrum even when other reactive electrophiles are employed in the direct trapping. To achieve the selectivity for the desired reaction pathway, stoichiometric use of copper catalyst and less reactive trapping agents were needed,13 which in turn required harsh reaction conditions and long reaction time. Herein, we report sequential incorporation of alkyl azide and diazo compound in click reactions by modulating the reactivities of organocopper intermediates with the associated ligand under mild conditions. Also, relying on tethering of reactants to increase the effective molarity, high pathway-selectivity was achieved to efficiently generate ring-fused triazoles.

Results and Discussion

We commenced our investigation by comparing the reaction of phenyl acetylene and ethyl diazoacetate (EDA) in the presence and absence of benzyl azide (1:1:1) with CuI (10 mol %) in acetonitrile (Scheme 2). The reaction of phenyl acetylene, EDA and benzyl azide (1:1:1) generated triazole 1a (76%) and unreacted EDA along with only trace amount of phenylacetylene–EDA coupled product 2a and sequential coupling product 4a. On the other hand, the same reaction without benzyl azide under otherwise identical conditions generated product 2a in 74% yield. To prove the catalytic activity of copper remains the same in both the reactions, a sequential reaction was carried out (eq 8). After complete consumption of benzyl azide (phenyl acetylene: benzyl azide = 1:1), EDA and phenyl acetylene (1:1) was introduced to the reaction mixture. From this reaction, two major products 1a and 2a were obtained in 73% and 72% yields, respectively. This result indicates that the copper catalyst to promote the triazole formation in the first step remains to be an active catalyst for the coupling between an alkyne and EDA. At the same time, these results clearly show that EDA and copper catalyst react too slowly to generate a copper carbenoid under the conditions, which provides a solid basis to exclude the formation of Cu-carbenoid I-6 in Path C from the competing reactions.

Having seen that the expected product 4a was not produced efficiently in the reaction with equal amount of azide and diazo compound, we examined reaction conditions employing a bidentate ligand and increased stoichiometry of EDA (Table 1). While the reaction with CuI alone and 1:1 ratio of phenyl acetylene, benzyl azide, and EDA provided triazole 1a as the only isolable product (entry 1), adding 4,4’-di-tert-butyl-2,2’-bipyridine (dtbpy) to the reaction under otherwise identical conditions provided 1a, 2a, and 4a in a 4.9:0:1 ratio (entry 2). Increasing the catalyst loading to 20 mol% increased both the portions of 2a and 4a (entry 3) but base additive (K$_2$CO$_3$) increased the portion of 1a with decrement of 4a (entry 6). With the same stoichiometry, the dtbpy ligand was changed to 2,2’-bipyridine (bpy), which resulted in a decreased ratio of 4a (entry 7). Reaction with phenanthroline could achieve similar portion of 4a but the portion of 2a was significantly decreased (entry 8). Even though Box ligands L1 and L2 suppressed the formation of 2a the portion of protonated product 1a increased significantly (entries 9 and
Organic Chemistry Frontiers

### Table 1. Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>alkene : azide : EDA</th>
<th>Cu (mol%)</th>
<th>Ligand</th>
<th>Ratioa</th>
<th>Isolated yield of 4 (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
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<td>10</td>
<td>none</td>
<td>1:0:0</td>
<td>N.D.2</td>
</tr>
<tr>
<td>2</td>
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<td>10</td>
<td>dtbpy</td>
<td>4:0:1</td>
<td>N.D.1</td>
</tr>
<tr>
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<td>20</td>
<td>dtbpy</td>
<td>4:2:0</td>
<td>N.D.1</td>
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<tr>
<td>4</td>
<td>Ph</td>
<td>1:1:1</td>
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<td>dtbpy</td>
<td>7:1:1</td>
<td>N.D.1</td>
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<td>Ph</td>
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<td>20</td>
<td>dtbpy</td>
<td>1:3:1</td>
<td>N.D.1</td>
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<td>20</td>
<td>bpy</td>
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<td>Ph</td>
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<td>L2</td>
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<tr>
<td>11</td>
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<td>dtbpy</td>
<td>1:0:1</td>
<td>66a</td>
</tr>
<tr>
<td>12</td>
<td>n-Bu</td>
<td>1:2:3</td>
<td>20</td>
<td>bpy</td>
<td>1:9:1</td>
<td>N.D.1</td>
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<tr>
<td>13</td>
<td>n-Bu</td>
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<td>none</td>
<td>10:1:5</td>
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<td>14</td>
<td>n-Bu</td>
<td>1:2:3</td>
<td>10</td>
<td>none</td>
<td>14:1:5</td>
<td>N.D.1</td>
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aReaction conditions: alkene (0.2 mmol, 1.0 eq), azide, ethyl diazoacetate, CuI, ligand (30 mol %) in CH$_3$CN at rt under N$_2$ for 3 h.

bDetermined by $^1$H NMR of crude mixture. N.D. stands for not determined.

With 1 equivalent of K$_2$CO$_3$ as additive.

At this point, we suspected that the facile protonation in these reactions might be the consequence of the relatively high acidity of phenyl acetylene compared to alkyl acetylenes. Thus, we examined the same condition in entry 5 with 1-hexyne, which provided 4a as predominant product along with only a small portion of 1a and 2a was not observed (entry 11). The same reaction with bpy-ligand provided still provided 4a as the predominant product but with a compromised ratio (entry 12), and without ligand protonated product 1a became the major product (entries 13 and 14). These results indicate that the structure of alkene has a major impact on product distribution.

With these results in hand, we explored the reaction scope by employing a range of structurally different alkynes together with benzyl azide and EDA under the optimized conditions (Table 2). Many hydroxyl groups including free hydroxy group (4d, 4g, 4i), alkyl ether (4e), silyl ether (4f–4j) alkene (4j), 4k, 4n), lactone (4k), and sulfonamide and other nitrogen functionality (4n, 4p, 4q) are tolerant to the reaction conditions. While alkyl substituted alkynes provided 4ab and 4b in good yield and selectivity a bulky trimethylsilyl substituted alkyne also provided 4c with similar yield and ratio. Surprisingly, the free hydroxyl groups in 4d, 4g and 4g’ regardless of the distance from the reaction center did not compromise the yield and ratio of these products. Steric hindrance influences the yield, for example, 4h containing a silyl ether of a primary alcohol was obtained with higher yield than the secondary alcohol-derived congener 4j. The role of chelating nitrogen functionality was examined (4o–4r). It was found that chelating effect by 2-pyridyl group seems not involved at the intermediate stage. An N-Ts-containing ynamide provided 4n with slightly lower yield while triazole containing alkynyl afforded 4o in higher yield. Not unexpectedly, electron-withdrawing 2-alkynyl and alkynyl pyridines provided 4p (37%) and 4q (22%) in low yield with predominance of protonated products 1p and 1q. These results are not surprising because like phenyl acetylene, pyridyl-substituted alkynes are more prone to undergo proton transfer.

Having demonstrated the wide scope of alkynes and their structural effect on efficiency and selectivity, we turned our attention to the structural variation of azides (Table 3). In each reaction, 1-hexyne and EDA were employed while the structure of azides was varied. Although it was predicted that more electron-rich azide should be more favorable for increasing the selectivity for Path A over Path B no consistency of their behaviors was observed. For example, crotol and prenyl azide provided a relatively low yield of 5c (40%) and 5d (48%) while 2-butylnyl azide afforded 5e (77%) in much higher yield. For 5c and 5d, only a primary azide adduct was observed although the corresponding adducts of a secondary or a tertiary azide were possible.14 Benzyl azides with an electron-withdrawing or an electron-donating group at the para position did not show significant differences in forming 5f–5h. Even a strong electron-withdrawing ester- or a ketone functionality on the a-carbon of azides did not significantly

### Table 2. Impact of the Alkyne Structures on the Yield and Selectivity

<table>
<thead>
<tr>
<th>Reaction conditions: alkyne (0.2 mmol, 1.0 eq), azide (2.0 eq), ethyl diazoacetate (3.0 eq), CuI (20 mol %), dtbpy (30 mol %) in CH$_3$CN at rt under N$_2$ for 3 h.</th>
<th>Isolated yield of 4a (%)</th>
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<tbody>
<tr>
<td>4a: R = H, 71% (1:0.3)</td>
<td>66% (1:0.1:10)</td>
</tr>
<tr>
<td>4b: R = H, 79% (1:0.1:10)</td>
<td>66% (1:0.1:1)</td>
</tr>
<tr>
<td>4c: R = TBS, 65% (1:1:2:4)</td>
<td>75% (1:0:13)</td>
</tr>
<tr>
<td>4d: R = H, 64% (1:9.23)</td>
<td>80% (1:0:1)</td>
</tr>
<tr>
<td>4e: R = TBS, 80% (1:1:13)</td>
<td>75% (1:0:10)</td>
</tr>
<tr>
<td>4f: R = TBS, 80% (1:1:2:4)</td>
<td>70% (1:0:10)</td>
</tr>
<tr>
<td>4g: R = TBS, 65% (1:1:3)</td>
<td>80% (1:0:10)</td>
</tr>
<tr>
<td>4h: R = TBS, 65% (1:1:3)</td>
<td>75% (1:0:10)</td>
</tr>
</tbody>
</table>

aReaction conditions: alkyne (0.2 mmol, 1.0 eq), azide (2.0 eq), ethyl diazoacetate (3.0 eq), CuI (20 mol %), dtbpy (30 mol %) in CH$_3$CN at rt under N$_2$ for 3 h. bIsolated yield of 4. cRatios of 1a:2a:4 before purification are shown in the parenthesis. dCu$_2$H$_2$N$_3$ was used instead of N$_3$Bu. eN$_3$CH$_3$SiMe$_3$ was used instead of N$_3$Bu.
change the yield and selectivity in forming 5j–5m. The substrate scope of diazo compounds was also examined. Benzyl, and hexyl diazoacetate provided products 6a, and 6b in 62, and 60% yield, and even sterically more hindered adamantyl diazoacetate provided 6c in similar yield (55%).

These results indicate that controlling the reaction pathways by using a ligand has proven effective, however, the competing protonation of the organocopper triazole intermediate is yet to be further improved. We expected that by increasing the effective molarity of diazo compound the competing protonation event could be reduced. To test this hypothesis, alkyne-tethered diazo compounds 7a–7j were examined (Table 4). To our delight, the expected fused cyclic triazoles 8a–8j were produced without any protonated product. This suggests that once intermediate 1-I is generated, the copper moiety has a lesser chance to interact with alkyne 7 for proton exchange rather a more favorable intramolecular interaction of the diazo moiety at the copper center would generate 1-II. The less reactive diazo compound still can participate in the reaction to generate 8k in 27% along with a protonated product 8k′ in 18% yield. Surprisingly, diazo amide 7l did not provide 8l instead a furan derivative 8l′ was generated exclusively (52%). Under identical reaction conditions with dtbpy as a ligand, protonated product 8l′ was obtained as the major component (48%) along with 8l′′ (31%), which demonstrates the crucial role of a ligand for product distribution.

Shown in Scheme 3 is a mechanistic picture of all competing pathways leading to the observed products 1, 2, and 4. The initially formed Cu-acetylide A reacts mainly with azide to form adduct B, which undergoes [3+2] cycloaddition to generate intermediate C. At the same time, Cu-acetylide A competitively react with EDA to generate minor product 2. Subsequently, intermediate C reacts with EDA to generate Cu-carbenoid D, which will lead to intermediate E. Intermediate C also can interact with an alkyne followed by proton exchange to generate triazole 1 and Cu-acetylide A. Finally, alkyne coordination with E followed by proton exchange would generate 4 and regenerate Cu-acetylide A, which enters a new catalytic cycle.

Based on these mechanisms, we infer that the bidentate ligand provides increased steric hindrance with the bond-
forming event between A and EDA. However, the complexity of strongly coordinating azide at the metal center is not affected, which resulted in improved selectivity.

On the other hand, the interaction of a weakly coordinating alkyne with sterically congested C will be more severely affected by the ligand than the interaction of more polar EDA. Thus, the minor pathway leading to the formation of 1 is diminished.

Conclusions

We explored the reactivity difference between alkyl azide and diazo compound toward Cu-acetylide in the presence of a nitrogen-based bidentate ligand. Under this condition, alkyl azides are generally more reactive than diazo compounds toward Cu-acetylide to form organocopper triazole intermediate. This vinyl-Cu species is more reactive than Cu-acetylide toward diazo compound, thus selectivity between 3-alkynoate and diazo compound is significant. Under this condition, alkyl and diazo compound toward Cu-acetylide in the presence of a stoichiometry of azide and diazo compound, the sequence of reaction pathways could be orchestrated to maximize the selectivity of forming 4 over click reaction product 1 and alkyne-diazo coupling product 2. Besides, the use of aliphatic alkyynes could also improve the selectivity significantly for the three-component coupling reaction. In general, under the current reaction condition, the direct formation of Cu-carbenoids from diazo compound and the Cu-catalyst is not involved except for 7f, which provides 8f” via a carbened pathway. A variety of alkynes and azides could be employed and the electronic factors on these reactants were exploited to control the product distribution, providing fully substituted triazoles.

Experimental Section

I. General Information

All reactions were carried out under an inert nitrogen or argon atmosphere, unless otherwise indicated. Compounds were purchased from Aldrich unless otherwise noted. CH$_2$CN was purified based on standard procedures. Flash column chromatography was performed using silica gel 60 Å (32-63 mesh) purchased from SiliCycle. Analytical thin-layer chromatography (TLC) was performed on 0.25 mm Silicycle precoated silica gel 60 (particle size 0.040–0.063 mm). Iodide, KMnO$_4$, UV light (254 nm) and vanillin were used as the TLC stains. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AV-500 spectrometer. $^1$H and $^{13}$C chemical shifts were referenced to internal solvent resonances and reported relative to SiMe$_4$: multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, J, are reported in Hz (Hertz). Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT equipped with a time-of-flight analyzer on a Waters Micromass Q-ToF Ultima in the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra were obtained using a Micromass AutoSpecTM.

II. General Procedure for the Three-component Coupling Reaction

1-Hexyne (16 mg, 0.2 mmol), benzyl azide (53.3 mg, 0.4 mmol, 2.0 equiv.) and ethyl diazoacetate (68.7 mg, 0.6 mmol, 3.0 equiv.) were dissolved in dry CH$_2$CN (1.0 mL), then dtbpy (16.1 mg, 0.06 mmol, 0.3 equiv.) and CuI (7.6 mg, 0.04 mmol, 0.2 equiv.) were added and the reaction mixture was stirred under N$_2$ atmosphere for 3 h. On completion of the reaction, 1 mL ofaq. NH$_4$Cl and 1 mL of ethyl acetate were added to the reaction mixture and stirred for 5 min. Then reaction mixture was diluted with ETOAc (10 mL) and organic layer was separated and washed with brine. This organic layer dried over Na$_2$SO$_4$ filtered and concentrated under reduced pressure to afford the crude material. The crude material was purified by using flash column chromatography to afford product 4ab.

III. General Procedure for the Synthesis of Cyclic Triazoles

Diazooamide S7 (35.8 mg, 0.2 mmol), benzyl azide (53.3 mg, 0.4 mmol, 2.0 equiv.) were dissolved in dry CH$_2$CN (1.0 mL) and CuI (7.6 mg, 0.04 mmol, 0.2 equiv.) were added, and the reaction mixture was stirred under N$_2$ atmosphere for 3 h. On completion of the reaction, 1 mL ofaq. NH$_4$Cl and 1 mL of ethyl acetate were added to the reaction mixture and stirred for 5 min. Then reaction mixture was diluted with ETOAc (10 mL) and organic layer was separated and washed with brine. This organic layer dried over Na$_2$SO$_4$ filtered and concentrated under reduced pressure to afford the crude material. The crude material was purified by using flash column chromatography to afford product S8.

Characterization Data

Ethyl 2-(1-benzyl-4-butyl-1,2,3-triazol-5-yl)acetate (4ab)

The compound 4ab was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 5:1 to 1:1). 4ab was obtained as a yellow oil (40.0 mg, 66% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.31 (t, J = 7.8 Hz, 3H), 7.14 (d, J = 6.7 Hz, 2H), 5.57 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.44 (s, 2H), 2.61 (t, J = 7.7 Hz, 2H), 1.69–1.61 (m, 2H), 1.37–1.32 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.28, 147.35, 134.92, 129.09, 128.46, 127.41, 126.25, 61.75, 52.47, 31.69, 29.53, 29.09, 28.95, 25.19, 22.66, 14.16, 14.13; HRMS (ESI) calcld for C$_{17}$H$_{23}$N$_3$O$_2$ [M + H$^+$] 302.1869, found 302.1865.

Ethyl 2-(1-benzyl-4-hexyl-1H,1,2,3-triazol-5-yl)acetate (4b)

The compound 4b was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 2:1). 4b was obtained as a yellow oil (50.8 mg, 77%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.35–7.28 (m, 3H), 7.14 (d, J = 6.7 Hz, 2H), 5.56 (s, 2H), 4.03 (q, J = 6.9 Hz, 2H), 3.43 (s, 2H), 2.60 (t, J = 7.6 Hz, 2H), 1.70–1.62 (m, 2H), 1.35–1.24 (m, 8H), 1.18 (t, J = 7.0 Hz, 3H), 0.86 (t, J = 6.9 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.26, 147.37, 134.91, 134.92, 129.08, 124.69, 121.41, 126.01, 61.75, 52.47, 31.69, 28.96, 24.88, 22.50, 14.13, 13.96; HRMS (ESI) calcld for C$_{21}$H$_{29}$N$_3$O$_2$ [M + H$^+$] 320.2182, found 320.2179.

Ethyl 2-(1-benzyl-4-(trimethylsilyl)-1H,1,2,3-triazol-5-yl)acetate (4c)

The compound 4c was prepared according to the general procedure and was purified by flash column chromatography
(hexane: ethyl acetate = 2:1). 4c was obtained as a light-yellow oil (37.8 mg, 60% yield). 1H NMR (500 MHz, CD2Cl2) δ 7.36 (dd, J = 14.5, 7.8 Hz, 3H), 1.79 (d, J = 6.8 Hz, 2H), 5.64 (s, 2H), 4.05 (q, J = 7.1 Hz, 2H), 3.60 (s, 2H), 1.20 (t, J = 7.1 Hz, 3H), 0.36 (s, 9H); 13C NMR (126 MHz, CD2Cl2) δ 168.22, 146.85, 138.85, 134.85, 129.10, 128.64, 128.49, 128.47, 128.08, 127.82, 127.71, 127.62, 127.41, 126.66, 72.88, 69.32, 61.73, 52.52, 29.28, 28.78, 21.61, 14.13; HRMS (ESI) calcd for C21H20N2O3 [M + H]+ 394.2131, found 394.2131.

Ethyl 2-(1-benzyl-4-(3-hydroxypropyl)-1H-1,2,3-triazol-5-yl)acetate (4e)

The compound 4e was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1). 4e was obtained as a yellow oil (59.0 mg, 75% yield). 1H NMR (500 MHz, CD2Cl2) δ 7.35–7.24 (m, 8H), 7.14 (d, J = 6.3 Hz, 2H), 5.55 (s, 2H), 4.46 (s, 2H), 4.01 (q, J = 7.1 Hz, 2H), 3.50 (t, J = 6.1 Hz, 2H), 3.43 (s, 2H), 2.74 (t, J = 7.4 Hz, 2H), 2.06–1.96 (m, 1H), 1.17 (t, J = 7.1 Hz, 3H); 13C NMR (126 MHz, CD2Cl2) δ 168.27, 146.57, 138.67, 134.85, 129.10, 128.45, 127.31, 61.80, 61.43, 52.62, 31.40, 28.92, 21.30, 14.03; HRMS (ESI) calcd for C19H19N2O3 [M + H]+ 338.1638, found 318.1639.

Ethyl 2-(1-benzyl-4-(3-hydroxypropyl)-1H-1,2,3-triazol-5-yl)acetate (4d)

The compound 4d was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1 to acetone). 4d was obtained as a green oil (38.6 mg, 64% yield). 1H NMR (500 MHz, CD2Cl2) δ 7.36–7.29 (m, 3H), 7.14 (d, J = 6.8 Hz, 2H), 5.56 (s, 2H), 4.02 (q, J = 7.0 Hz, 2H), 3.81–3.58 (m, 2H), 3.51 (s, 2H), 2.80–2.72 (m, 2H), 2.00–1.91 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H), 1.12 (s, 1H); 13C NMR (126 MHz, CD2Cl2) δ 168.24, 146.51, 131.90, 129.02, 128.45, 127.31, 61.80, 61.43, 52.62, 31.40, 28.92, 21.30, 14.03; HRMS (ESI) calcd for C19H18N3O2Si [M + H]+ 304.1661, found 304.1663.

1-Benzyl-4-(3-benzoxoxy)propyl)-5-(2-(ethylperoxy)-2H-1)H-1,2,3-triazole (4e)

The compound 4e was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1). 4e was obtained as a yellow oil (59.0 mg, 75% yield). 1H NMR (500 MHz, CD2Cl2) δ 7.35–7.24 (m, 8H), 7.14 (d, J = 6.3 Hz, 2H), 5.55 (s, 2H), 4.46 (s, 2H), 4.01 (q, J = 7.1 Hz, 2H), 3.50 (t, J = 6.1 Hz, 2H), 3.43 (s, 2H), 2.74 (t, J = 7.4 Hz, 2H), 2.06–1.96 (m, 1H), 1.17 (t, J = 7.1 Hz, 3H); 13C NMR (126 MHz, CD2Cl2) δ 168.27, 146.57, 138.67, 134.85, 129.10, 128.64, 128.49, 128.47, 128.08, 127.82, 127.71, 127.62, 127.41, 126.66, 72.88, 69.32, 61.73, 52.52, 29.28, 28.78, 21.61, 14.13; HRMS (ESI) calcd for C25H20N3O2 [M + H]+ 394.2131, found 394.2131.
Ethyl 1-benzyl-5-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate (4m)

The compound 4m was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1 to 1:1). 4m was obtained as a mixture of triazole, yellow oil (80.0 mg, 30% yield of 4m).

Characteristic data for 4m: 1H NMR (500 MHz, CDCl₃) δ 7.31 (t, J = 7.9 Hz, 3H), 7.13 (d, J = 7.1 Hz, 2H), 5.56 (s, 2H), 4.02 (q, J = 7.1 Hz, 2H), 3.50 (s, 2H), 3.12 (t, J = 6.9 Hz, 2H), 3.04 (t, J = 7.5 Hz, 2H), 2.81 (s, 4H), 1.17 (t, J = 7.1 Hz, 3H); 13C NMR (126 MHz, CDCl₃) δ 168.99, 162.29, 167.98, 144.26, 134.62, 129.13, 128.52, 127.40, 127.23, 61.86, 52.58, 30.60, 28.83, 25.70, 20.15, 14.12; HRMS (ESI) calcd for C₁₄H₁₉NO₄ [M – O₆H⁺]⁺ 318.1454, found 318.1454.

Ethyl 1-benzyl-5-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate (4n)

The compound 4n was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1 to 1:1). 4n was obtained as a mixture of triazole, yellow oil (80.0 mg, 30% yield of 4n).

Characteristic data for 4n: 1H NMR (500 MHz, CDCl₃) δ 7.30 (t, J = 7.9 Hz, 3H), 7.12 (d, J = 7.1 Hz, 2H), 5.62 (s, 2H), 4.94–4.87 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.67 (t, J = 7.0 Hz, 2H), 3.61 (s, 2H), 2.41 (s, 3H), 2.15 (q, J = 6.6 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H); 13C NMR (126 MHz, CDCl₃) δ 168.19, 144.12, 144.01, 134.74, 134.50, 134.20, 129.75, 129.25, 128.76, 128.06, 127.44, 119.77, 116.98, 61.77, 53.63, 49.53, 32.62, 28.85, 21.74, 14.20; HRMS (ESI) calcd for C₁₄H₂₉NO₄ [M + H⁺]⁺ 469.1910, found 469.1900.
The compound 4q was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:5). 4q was obtained as a mixture of triazole, light-yellow solid (43.2 mg, 22% yield of 4q).

Characteristic data for 4q: 

\[ \text{IR (KBr):} \text{v} = 3036, 2995, 2925, 2853, 1734, 1497, 1450, 1200, 755 \text{ cm}^{-1}. \]

\[ \text{C NMR (126 MHz, CDCl}_3): \delta = 168.12, 146.95, 130.71, 129.37, 124.56, 123.69, 61.50, 38.80, 31.40, 29.00, 24.83, 22.23, 14.00, 13.83, 13.71, 12.64; \text{HRMS (ESI) calcd for C}_{28}H_{30}N_7O_2 [M + H]^+ 523.1658, found 523.1650.} \]

Ethyl 2-(4-butyl-1-octyl-1H-1,2,3-triazol-5-y)acetate (5a): The compound 5a was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 2:1). 5a was obtained as a light-yellow oil (40.0 mg, 62% yield).

\[ \text{IR (KBr):} \text{v} = 3037, 2928, 2853, 1732, 1490, 1450, 1200, 755 \text{ cm}^{-1}. \]

\[ \text{C NMR (126 MHz, CDCl}_3): \delta = 168.07, 146.90, 134.44, 124.60, 123.60, 61.89, 31.41, 29.09, 27.54, 13.73, 13.19; \text{HRMS (ESI) calcd for C}_{32}H_{33}N_2O [M + H]^+ 479.2561, found 479.2564.} \]

Ethyl 2-(4-butyl-1-(trimethylsilylmethyl)-1H-1,2,3-triazol-5-y)acetate (5b): The compound 5b was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 5:1 to 1:1). 5b was obtained as a light-yellow oil (41.0 mg, 69% yield).

\[ \text{IR (KBr):} \text{v} = 3037, 2928, 2853, 1732, 1490, 1450, 1200, 755 \text{ cm}^{-1}. \]

\[ \text{C NMR (126 MHz, CDCl}_3): \delta = 168.09, 146.90, 134.43, 124.60, 123.60, 61.89, 31.41, 29.09, 27.54, 13.73, 13.19; \text{HRMS (ESI) calcd for C}_{32}H_{33}N_2O [M + H]^+ 479.2561, found 479.2564.} \]

Ethyl 2-(1-(but-2-en-1-yl)-1H-1,2,3-triazol-5-y)acetate (5c): The compound 5c was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1 to 2:1). 5c was obtained as a light-yellow oil (21.5 mg, 40% yield).

\[ \text{IR (KBr):} \text{v} = 3037, 2928, 2853, 1732, 1490, 1450, 1200, 755 \text{ cm}^{-1}. \]

\[ \text{C NMR (126 MHz, CDCl}_3): \delta = 168.09, 146.90, 134.43, 124.60, 123.60, 61.89, 31.41, 29.09, 27.54, 13.73, 13.19; \text{HRMS (ESI) calcd for C}_{32}H_{33}N_2O [M + H]^+ 479.2561, found 479.2564.} \]

Ethyl 2-(1-(but-2-en-1-yl)-1H-1,2,3-triazol-5-y)acetate (5d): The compound 5d was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 2:1). 5d was obtained as a light-yellow oil (26.9 mg, 48% yield).

\[ \text{IR (KBr):} \text{v} = 3037, 2928, 2853, 1732, 1490, 1450, 1200, 755 \text{ cm}^{-1}. \]

\[ \text{C NMR (126 MHz, CDCl}_3): \delta = 168.12, 146.95, 130.71, 129.37, 124.56, 123.69, 61.50, 38.80, 31.40, 29.00, 24.83, 22.23, 14.00, 13.83, 13.71, 12.64; \text{HRMS (ESI) calcd for C}_{28}H_{30}N_7O_2 [M + H]^+ 523.1658, found 523.1650.} \]
Ethyl 2-(4-butyl-1-(3-cyanopropyl)-1H-1,2,3-triazol-5-yl)acetate (5i)

The compound 5i was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1 to 0:1). 5i was obtained as a light-yellow oil (36.7 mg, 66% yield). 1H NMR (500 MHz, CDCl3) δ 4.35 (t, J = 6.4 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.65 (s, 2H), 2.61 (t, J = 7.5 Hz, 2H), 2.47 (t, J = 6.9 Hz, 2H), 2.38–2.32 (m, 2H), 1.67–1.59 (m, 2H), 1.38–1.31 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 168.34, 146.70, 126.46, 118.70, 62.06, 46.25, 31.59, 28.80, 25.39, 24.76, 22.41, 14.82, 14.17, 13.89; HRMS (ESI) calcd for C14H13N2O3 [M + H]+ 279.1821, found 279.1824.

Diethyl 2,2′-(4-butyl-1H-1,2,3-triazole-1,5-diyl)diacetate (5j)

The compound 5j was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 5: 1 to 1:1). 5j was obtained as a mixture of triazole, light-yellow oil (45.0 mg, 76% yield of 5j).

Characteristic data for 5j: 1H NMR (500 MHz, CDCl3) δ 5.17 (s, 2H), 4.26–4.18 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.63 (s, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.67–1.59 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 168.33, 127.10; HRMS (ESI) calcd for C14H13N2O3 [M + H]+ 298.1767, found 298.1764.

Allyl 2-(4-butyl-5-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazol-1-yl)acetate (5k)

The compound 5k was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 3:1 to 1:1). 5k was obtained as a mixture of triazole, yellow oil (45.2 mg, 73% yield of 5k). 1H NMR (500 MHz, CDCl3) δ 5.91–5.83 (m, 2H), 5.33–5.25 (m, 2H), 5.23 (s, 2H), 4.65 (d, J = 5.4 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.64 (s, 2H), 2.64 (t, J = 7.5 Hz, 2H), 1.69–1.61 (m, 2H), 1.36–1.31 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 168.40, 166.49, 146.86, 131.04, 127.12, 122.03, 119.70, 119.61, 66.74, 61.95, 49.66, 31.65, 29.01, 24.81, 22.38, 14.14, 13.92; HRMS (ESI) calcd for C15H14N2O3 [M + H]+ 310.1766, found 310.1766.

Benzy1 2-(4-butyl-5-(2-ethoxy-2-oxoethyl)-1H-1,2,3-triazol-1-yl)acetate (5l)

The compound 5l was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1). 5l was obtained as a light-yellow oil (42.5 mg, 60% yield). 1H NMR (500 MHz, CDCl3) δ 7.34–7.28 (m, 3H), 7.14 (d, J = 7.0 Hz, 2H), 5.56 (s, 2H), 3.97 (t, J = 6.7 Hz, 2H), 3.44 (s, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.69–1.59 (m, 2H), 1.57–1.49 (m, 2H), 1.35–1.24 (m, 8H), 0.93–0.89 (m, 3H), 0.89–0.86 (m, 3H); 13C NMR (126 MHz, CDCl3) δ 168.36, 147.30, 134.91, 129.09, 128.45, 127.40, 126.25, 65.93, 52.45, 31.69, 31.44, 30.75, 28.95, 28.47, 25.56, 24.88, 22.61, 22.52, 14.08, 13.95; HRMS (ESI) calcd for C17H19N2O3 [M + H]+ 358.2495, found 358.2485.

Hexyl 2-(1-benzyl-4-butyl-1H-1,2,3-triazol-5-yl)acetate (6a)

The compound 6a was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 2:1). 6a was obtained as a light-yellow oil (45.0 mg, 62% yield). 1H NMR (500 MHz, CDCl3) δ 7.38–7.34 (m, 3H), 7.30–7.28 (m, 3H), 7.27–7.24 (m, 2H), 7.11–7.05 (m, 2H), 5.52 (s, 2H), 5.02 (s, 2H), 3.47 (s, 2H), 2.59 (t, J = 7.5 Hz, 2H), 1.65–1.57 (m, 2H), 1.35–1.26 (m, 2H), 0.87 (t, J = 7.2 Hz, 2H); 13C NMR (126 MHz, CDCl3) δ 168.10, 147.43, 135.14, 134.78, 129.10, 128.81, 128.53, 128.48, 127.42, 126.05, 67.49, 52.53, 31.66, 28.93, 24.86, 22.50, 13.93; HRMS (ESI) calcd for C19H21N2O3 [M + H]+ 364.2025, found 364.2019.

Benzyl 2-(1-benzyl-4-butyl-1H-1,2,3-triazol-5-yl)acetate (6b)

The compound 6b was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 3:1). 6b was obtained as a light-yellow oil (42.5 mg, 60% yield). 1H NMR (500 MHz, CDCl3) δ 7.34–7.28 (m, 3H), 7.14 (d, J = 7.0 Hz, 2H), 5.56 (s, 2H), 3.97 (t, J = 6.7 Hz, 2H), 3.44 (s, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.69–1.59 (m, 2H), 1.57–1.49 (m, 2H), 1.35–1.24 (m, 8H), 0.93–0.89 (m, 3H), 0.89–0.86 (m, 3H); 13C NMR (126 MHz, CDCl3) δ 168.36, 147.30, 134.91, 129.09, 128.45, 127.40, 126.25, 65.93, 52.45, 31.69, 31.44, 30.75, 28.95, 28.47, 25.56, 24.88, 22.61, 22.52, 14.08, 13.95; HRMS (ESI) calcd for C19H21N2O3 [M + H]+ 358.2495, found 358.2485.
1-Benzyl-5-buty1-1,4,5,7-tetrahydro-6H-[1,2,3]triazolo[4,5-c]pyridin-6-one (8a)

The compound 8a was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1). 8a was obtained as a light-yellow oil (43.2 mg, 76% yield). 1H NMR (500 MHz, CDCl3) δ 7.34 (m, 3H), 7.22 (m, 2H), 5.46 (s, 2H), 4.57 (t, J = 2.7 Hz, 2H), 3.47 (m, 2H), 3.37 (t, J = 2.6 Hz, 2H), 1.57 (m, 2H), 1.33 (m, 2H), 0.92 (t, J = 7.3 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ 163.9, 137.3, 133.7, 129.2, 128.9, 127.8, 110.2, 52.6, 48.0, 45.4, 28.9, 28.3, 20.1, 13.8; HRMS (ESI) calcd for C18H12N4O [M + H]+ 314.1868, found 314.1864.

5-Butyl-1-octyl-1,4,5,7-tetrahydro-6H-[1,2,3]triazolo[4,5-c]pyridin-6-one (8b)

The compound 8b was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1). 8b was obtained as a light-yellow oil (44.1 mg, 72% yield). 1H NMR (500 MHz, CDCl3) δ 4.60 (s, 2H), 4.22 (t, J = 7.1 Hz, 2H), 3.61 (s, 2H), 3.53 (m, 2H), 1.86 (m, 2H), 1.61 (m, 2H), 1.31 (m, 12H), 0.94 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 6.6 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 164.0, 136.6, 127.5, 48.4, 48.0, 45.4, 31.6, 29.8, 29.0, 28.9, 26.5, 22.5, 20.1, 14.0, 13.8; HRMS (ESI) calcd for C17H13N4O [M + H]+ 285.1710, found 285.1711.

Ethyl 2-(5-buty1-6-oxo-4,5,6,7-tetrahydro-1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl)acetate (8c)

The compound 8c was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1). 8c was obtained as a light-yellow oil (40.1 mg, 73% yield). 1H NMR (500 MHz, CDCl3) δ 5.06 (s, 2H), 4.61 (s, 2H), 4.26 (q, J = 7.0 Hz, 2H), 3.59 (s, 2H), 3.52 (m, 2H), 1.61 (m, 2H), 1.36 (td, J = 14.9, 7.4 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 165.8, 163.8, 137.2, 129.1, 62.6, 49.1, 48.0, 45.3, 28.9, 28.1, 20.1, 14.1, 13.8; HRMS (ESI) calcd for C17H13N4O [M + H]+ 281.1608, found 281.1609.

5-Allyl-1-benzyl-1,4,5,7-tetrahydro-6H-[1,2,3]triazolo[4,5-c]pyridin-6-one (8d)

The compound 8d was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1). 8d was obtained as a light-yellow oil (41.9 mg, 78% yield). 1H NMR (500 MHz, CDCl3) δ 7.35 (m, 3H), 7.22 (m, 2H), 5.77 (tdd, J = 16.6, 10.8, 6.1 Hz, 1H), 5.48 (s, 2H), 5.22 (m, 2H), 4.55 (t, J = 2.8 Hz, 2H), 4.12 (d, J = 6.1 Hz, 2H), 3.40 (t, J = 2.8 Hz, 2H); 13C NMR (125 MHz, CDCl3) δ 163.9, 137.3, 133.6, 131.6, 129.3, 128.9, 127.8, 127.7, 118.6, 52.6, 50.3, 44.8, 28.3; HRMS (ESI) calcd for C17H12N4O [M + H]+ 269.1397, found 269.1400.

Ethyl 2-(5-methoxybenzyl)-1,4,5,7-tetrahydro-6H-[1,2,3]triazolo[4,5-c]pyridin-1-yl)acetate (8i)

The compound 8i was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1). 8i was obtained as a light-yellow oil (55.1 mg, 80% yield). 1H NMR (500 MHz, CDCl3) δ 7.26 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.69 (s, 2H), 4.51 (s, 2H), 4.22 (t, J = 7.2 Hz, 2H), 3.79 (s, 3H), 3.67 (s, 2H), 1.85 (m, 2H), 0.92 (t, J = 11.5 Hz, 10H), 0.87 (t, J = 6.8 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 164.2, 158.7, 136.1, 129.9, 128.0, 127.1, 114.1, 55.3, 50.5, 48.8, 44.7, 31.7, 29.8, 28.5, 28.4, 26.5, 22.6, 14.0; HRMS (ESI) calcd for C17H13N4O [M + H]+ 349.1659, found 349.1662.
The compound 8j was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1). δH NMR (500 MHz, CDCl3) δ 7.57 (s, 1H), 7.36–7.31 (m, 3H), 7.24 (d, J = 6.1 Hz, 2H), 5.49 (s, 2H), 4.57 (s, 2H), 3.29 (t, J = 7.5 Hz, 2H), 2.27 (s, 3H), 1.60–1.52 (m, 2H), 1.29–1.20 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H); δ13C NMR (126 MHz, CDCl3) δ 161.22, 144.14, 141.28, 129.65, 52.7, 49.1, 28.8; HRMS (ESI) calcd for C18H17NO3+ [M + H]^+ 317.1137, found 317.1135.

N-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl-N-butyl-2-diazoo-oxobutamine (8l)

The compound 8k was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 1:1 to 1:3). δH NMR (500 MHz, CDCl3) δ 7.87 (d, J = 2.9 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 5.91 (s, 1H), 4.99 (s, 2H), 2.40 (s, 3H), 2.08 (s, 3H), 1.89 (s, 3H); δ13C NMR (126 MHz, CDCl3) δ 167.35, 159.49, 147.52, 144.65, 132.86, 120.45, 117.33, 48.49, 28.15, 27.66, 20.93; HRMS (ESI) calcd for C18H17NO3+ [M + H]^+ 317.1137, found 317.1135.

5-Butyl-3-methyl-5,6-dihydro-4H-furo[3,4-c]pyrrol-4-one (8l)

The compound 8l′ was prepared according to the general procedure and was purified by flash column chromatography (hexane: ethyl acetate = 2:1 to 1:1). δH NMR (500 MHz, CDCl3) δ 7.57 (s, 1H), 7.36–7.31 (m, 3H), 7.24 (d, J = 6.1 Hz, 2H), 5.49 (s, 2H), 4.57 (s, 2H), 3.29 (t, J = 7.5 Hz, 2H), 2.27 (s, 3H), 1.60–1.52 (m, 2H), 1.29–1.20 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H); δ13C NMR (126 MHz, CDCl3) δ 161.22, 144.14, 134.65, 129.20, 128.86, 128.08, 123.29, 54.30, 48.45, 42.42, 29.84, 27.29, 20.03, 13.75; HRMS (ESI) calcd for C16H16N2O3+ [M + H]^+ 355.1882, found 355.1874.

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References


2. C. W. Tornøe, C. Christensen and M. Meldal, Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides, J. Org. Chem., 2002, 67, 3057.


