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# Unusual Cu(I)-catalyzed 1,3-dipolar cycloaddition of acetylenic amides: formation of bistriazoles

Mihyun Kwon, Yujin Jang, Sunyoung Yoon, Dongsik Yang, Heung Bae Jeon *

*Department of Chemistry, Kwangwoon University, Seoul 139-701, Republic of Korea*

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ABSTRACT

*C*-carbamoyl-1,2,3-triazoles have recently attracted much interest due to their potent biological activity. While synthesizing *C*-carbamoyl-1,2,3-triazoles by the copper(I)-catalyzed 1,3-dipolar cycloaddition of organic azides **1** and acetylenic amides **2**, we found that the expected 1,2,3-triazole products **3** were obtained as the only products in excellent yields when $CuSO_4$ and sodium ascorbate were used as the Cu(I)-catalyst. Surprisingly, the unexpected bistriazole products **4** were one of the major products obtained along with the 1,2,3-triazoles **3** when using a direct Cu(I)-catalyst such as CuI or CuBr.

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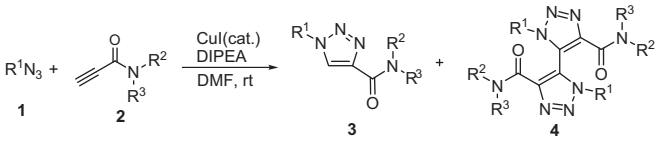
The copper(I)-catalyzed 1,3-dipolar cycloaddition of organic azides with alkynes, a click reaction, is one of the most attractive methods for ring formation because of its high efficiency.[1–4] The synthesis of 1,2,3-triazoles using this cycloaddition has become increasingly important due to the efficient bond formation between diverse building blocks for chemical synthesis,[5] bioconjugation,[6] materials and surface science,[7] combinatorial chemistry,[8] and medicinal chemistry.[9] In particular, a number of compounds containing *C*-carbamoyl-1,2,3-triazoles have recently been shown to possess a broad spectrum of biological activity.[10] Even simple *C*-carbamoyl-1,2,3-triazole compounds have shown antiaggregating and antithrombotic activities.[11]

Recently, we reported the convenient and efficient synthesis of *C*-carbamoyl-1,2,3-triazoles from alkyl bromides by a one-pot sequential addition using microwave irradiation.[12] In connection with other projects, we synthesized *C*-carbamoyl-1,2,3-triazoles using a 1,3-dipolar cycloaddition between alkyl azides **1** and acetylenic amides **2** with CuI as the catalyst and diisopropylethylamine (DIPEA) as the ligand at room temperature, which is one of the most popular Cu(I)-catalyst systems for this cycloaddition. Surprisingly, we obtained the expected 1,2,3-triazole **3** and the corresponding bistriazole **4** in an almost equal ratio. Sharpless and co-workers have previously observed minor amounts of bistriazole side products, but have not reported the characterization of these compounds.[3] However, we observed significant amounts of the bistriazoles **4**, often as one of the major products, when acetylenic amides **2** were reacted with alkyl azides **1** using direct Cu(I)-catalysts such as CuI or CuBr. As far as we know, only a few Letters have reported the synthesis and characterization of bistriazoles[13–17] since the initial report by Burgess and Angell.[18] Herein, we report that the direct Cu(I)-catalyzed 1,3-dipolar cycloaddition of acetylenic amides affords the corresponding bistriazoles **4** as one of the major products under the usual reaction conditions with catalytic CuI (Eq. 1).




(1)

Initially, we expected the 1,3-dipolar cycloaddition of benzyl azide (**1a**) and *N*-phenylacetylenic amide (**2a**) to provide the corresponding 1,2,3-triazole **3a** in a high yield when treated with CuI (0.1 equiv) and DIPEA (2 equiv) in *N*,*N*-dimethylformamide (DMF) at room temperature. Surprisingly, the reaction afforded the corresponding bistriazole **4a** in a 58% yield as the major product. The expected 1,2,3-triazole **3a** was obtained in only a 33% yield (Table 1, entry 1). Intrigued by this result, the reaction was carried out in different organic solvents. When solvents such as dimethylacetamide (DMA, entry 2), $CH_3CN$ (entry 3), MeOH (entry 4), methyl formamide (entry 5), dimethyl sulfoxide (DMSO, entry 6), and acetone (entry 7) were used, the 1,2,3-triazole **3a** was obtained as a major product with the bistriazole **4a** as a minor product.

* Corresponding author. Tel.: +82 2 940 5583; fax: +82 2 911 8584.
*E-mail address:* hbj@kw.ac.kr (H.B. Jeon).

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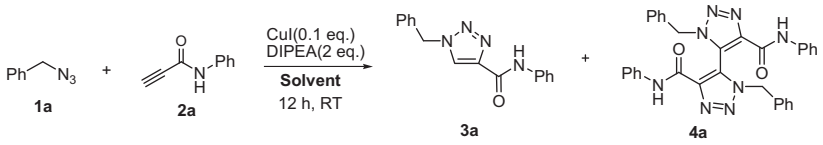
**Table 1**
Cycloaddition between azide **1a** and acetylenic amide **2a** using CuI in various solvents

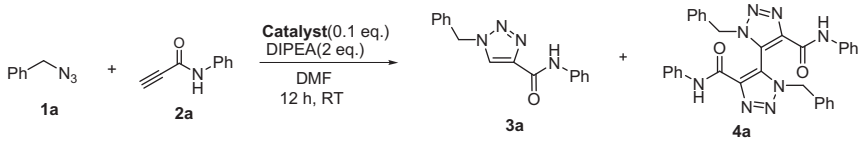



**1a** **2a** **3a** **4a**

| Entry | Solvent | Yield[a] (%) | |
|---|---|---|---|
| | | **3a** | **4a** |
| 1 | DMF | 33 | 58 |
| 2 | DMA | 54 | 37 |
| 3 | MeCN | 52 | 27 |
| 4 | MeOH | 64 | 28 |
| 5 | Methyl formate | 75 | 17 |
| 6 | DMSO | 58 | 31 |
| 7 | Acetone | 73 | 20 |
| 8 | THF | 95 | Trace |
| 9 | Toluene | 95 | Trace |

[a] Isolated yields.

**Table 2**
Cycloaddition between azide **1a** and acetylenic amide **2a** using various Cu(I)-catalysts




**1a** **2a** **3a** **4a**

| Entry | Catalyst | Yield[a] (%) | |
|---|---|---|---|
| | | **3a** | **4a** |
| 1 | CuI | 33 | 58 |
| 2 | CuBr | 42 | 49 |
| 3 | CuCl | 43 | 48 |
| 4 | CuCN | 43 | 46 |
| 5[b] | $CuSO_4$ | 95 | – |

[a] Isolated yields.
[b] Reaction was carried out with $CuSO_4$ (0.1 equiv) and Na ascorbate (0.25 equiv) in $H_2O$/*t*-BuOH (2/1) for 12 h.

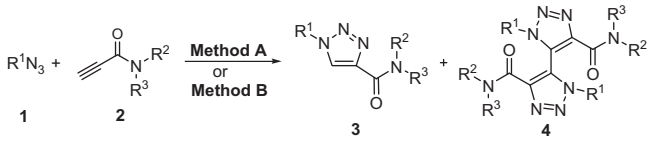
However, the use of THF (entry 8) and toluene (entry 9) as solvents gave the 1,2,3-triazole **3a** in a 95% yield with only a trace of the bistriazole **4a**.

Next, we carried out the experiments with different Cu(I) catalysts (0.1 equiv), such as CuBr (Table 2, entry 2), CuCl (entry 3), and CuCN (entry 4), in DMF. The reactions afforded the 1,2,3-triazole **3a** and bistriazole **4a** in an almost equal ratio. However, when the reaction was performed with $CuSO_4$ (0.1 equiv) and sodium ascorbate (0.25 equiv) in $H_2O$/*t*-BuOH (entry 5), which is one of the most common reaction conditions for Cu(I)-catalyzed 1,3-dipolar cycloadditions, 1,2,3-triazole **3a** was obtained as the major product in a 95% yield while no bistriazole **4a** was observed.

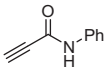
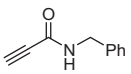
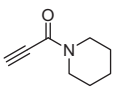
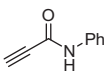
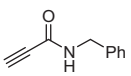
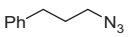
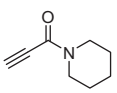
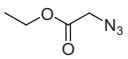
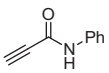
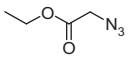
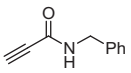
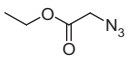
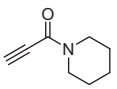
Based on these interesting results, we investigated the generality of this unusual Cu(I)-catalyzed 1,3-dipolar cycloaddition to form the bistriazole from acetylenic amides using a direct Cu(I)-catalyst, such as CuI (Table 3). A variety of organic azides and acetylenic amides were treated with CuI (0.1 equiv) and DIPEA (2 equiv) in DMF at room temperature (Method A).[19] To compare the results with a different copper catalyst, we also performed the Cu(I)-catalyzed 1,3-dipolar cycloaddition with $CuSO_4$ (0.1 equiv) and sodium ascorbate (0.25 equiv) in $H_2O$/*t*-BuOH (2/1) at room temperature with the same substrates (Method B). The reaction of benzyl azide (**1a**) and *N*-benzylacetylenic amide (**2b**) with CuI as the catalyst afforded a mixture of the corresponding 1,2,3-triazole **3b** and bistriazole **4b** in 54% and 42% yields, respectively. The same reaction with $CuSO_4$ as the catalyst gave 1,2,3-triazole **3b** exclusively in a 95% yield (entry 2). When acetylenic amide **2c** derived from a secondary amine, piperidine, was reacted with the azide **1a** in the presence of CuI, the reaction provided bistriazole **4c** as a major product in a 72% yield and 1,2,3-triazole **3c** as a minor product in a 22% yield. The same reaction in the presence of $CuSO_4$ furnished only 1,2,3-triazole **3c** in a 94% yield (entry 3). Further reactions with 3-phenylpropyl azide **1b** and ethyl azidoacetate **1c** with the acetylenic amides **2a**, **2b**, and **2c** using CuI (Method A) also afforded a mixture of the corresponding 1,2,3-triazoles **3d–3i** and bistriazoles **4d–4i** as major products in similar ratios. However, the same reactions using $CuSO_4$ (Method B) gave only the 1,2,3-triazoles **3d–3i** in excellent yields as expected (entries 4–9). Although the reason for different results between method A and B was not elucidated exactly, it is considered that direct Cu(I)-catalysts, in particular CuI, promote an oxidative coupling reaction to afford bistriazoles **4**, and the basic reaction condition is also important to produce bistriazoles **4**, which is supported by the experiments as shown in Scheme 1. According to the previously reported procedures,[13,18] benzyl azide (**1a**) and *N*-phenylacetylenic amide (**2a**) were treated with CuI in the presence of $Na_2CO_3$ or NaOH as the base. The reactions afforded the corresponding bistriazole **4a** in 73% and 21% yields, respectively.

As mentioned in a previous report,[18] we also observed that the core of the bistriazole molecule is chiral. Figure 1 shows a molecular representation from a single-crystal X-ray analysis of bistriaz-

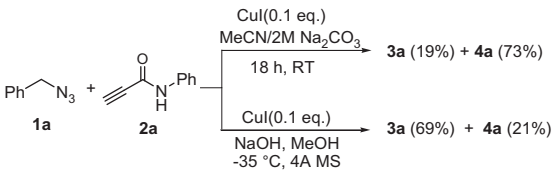
**Table 3**
Synthesis of 1,2,3-triazole **3** and bistriazole **4** using CuI or $CuSO_4$ on acetylenic amide **2**




**Method A**: CuI(0.1 eq.), DIPEA(2 eq.), DMF, 12 h, RT
**Method B**: $CuSO_4$(0.1 eq.), Na ascorbate(0.25 eq.), $H_2O$/*t*-BuOH(2/1), 12 h, RT

| Entry | Azide **1** | Acetylenic amide **2** | Method | Product yield (%)[a] | |
|---|---|---|---|---|---|
| | | | | **3** | **4** |
| 1 |  **1a** |  **2a** | A:<br>B: | **3a**<br>33<br>95 | **4a**<br>58<br>– |
| 2 |  **1a** |  **2b** | A:<br>B: | **3b**<br>54<br>95 | **4b**<br>42<br>– |
| 3 |  **1a** |  **2c** | A:<br>B: | **3c**<br>22<br>94 | **4c**<br>72<br>– |
| 4 |  **1b** |  **2a** | A:<br>B: | **3d**<br>37<br>96 | **4d**<br>52<br>– |
| 5 |  **1b** |  **2b** | A:<br>B: | **3e**<br>57<br>95 | **4e**<br>41<br>– |
| 6 |  **1b** |  **2c** | A:<br>B: | **3f**<br>47<br>94 | **4f**<br>46<br>– |
| 7 |  **1c** |  **2a** | A:<br>B: | **3g**<br>49<br>95 | **4g**<br>45<br>– |
| 8 |  **1c** |  **2b** | A:<br>B: | **3h**<br>64<br>96 | **4h**<br>34<br>– |
| 9 |  **1c** |  **2c** | A:<br>B: | **3i**<br>37<br>96 | **4i**<br>53<br>– |

[a] Isolated yields.




**Scheme 1.** Cu-catalyzed cycloaddition with other bases.

ole **4b**, which was performed to confirm the structure. When considering the AB-quartet pattern observed for the benzylic protons in the $^1$H NMR spectrum of compound **4b**,[20] it becomes clear that the rotation around the C–C bond connecting the two rings is restricted because it is extremely sterically hindered.

On the contrary, when methyl propiolate (**5**) and propiolic acid (**7**), which are derivatives of acetylenic amide, were reacted with benzyl azide (**1a**) using CuI as the catalyst under the same reaction conditions, only the corresponding 1,2,3-triazoles **6** and **8** were produced in excellent yields (Scheme 2). This result clearly indicates that the bistriazole can be obtained as one of the major products only when acetylenic amide is reacted with alkyl azide, although the reason remains unclear.

In conclusion, we have found that acetylenic amides **2** react with alkyl azide **1** using direct Cu(I)-catalyst, especially CuI, in Cu(I)-catalyzed 1,3-dipolar cycloaddition to form the corresponding bistriazoles **4** as one of the major products along with the expected 1,2,3-triazoles **3**. However, we also observed that the expected 1,2,3-triazoles **3** were provided as the only major product in excellent yields when the same substrates were treated with $CuSO_4$ as the catalyst with sodium ascorbate.

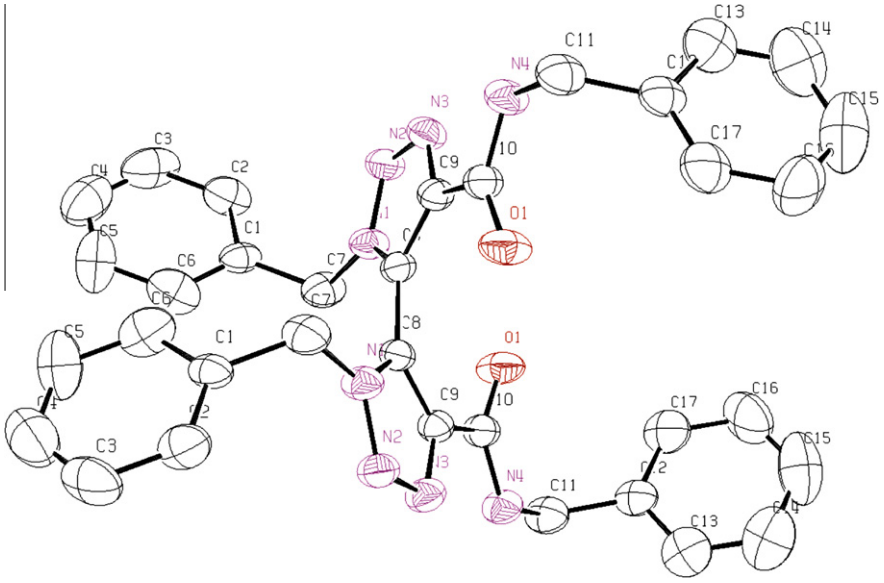
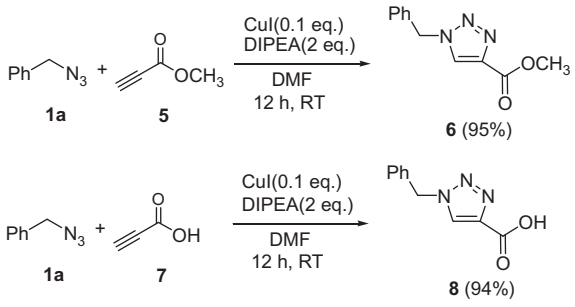



**Figure 1.** X-ray structure of bistriazole **4b**.




**Scheme 2.** Cu-catalyzed cycloaddition of methyl propiolate (**5**) and propiolic acid (**7**) using CuI.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.069.

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19. General Procedure for copper-catalyzed cycloaddition using CuI: To a solution of alkyl azide 1 (1.1 mmol) and acetylenic amide **2** (1.0 mmol) in DMF (3 mL) was added CuI (0.1 mmol) and DIPEA (2.0 mmol). The resulting solution was stirred for 12 h at room temperature and then concentrated in vacuo. The residue was subjected to column chromatography with EtOAc/$CH_2Cl_2$/hexanes (1:2:3) as eluent to afford bistriazole **4** and 1,2,3-triazole **3** as white solids.
20. See Supplementary data.