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Graphical Abstract

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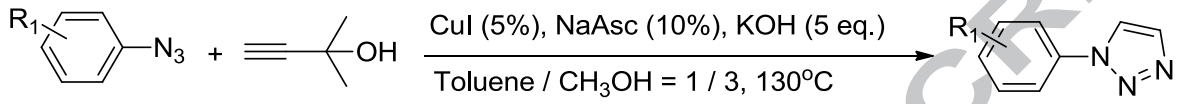
Yaowen Liu [a], Chunmei Han [a], Xinyuan Ma [a], Jianhua Yang [a], Xuepu, Feng [a], Yubo Jiang [a,*]



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Yaowen Liu [a], Chunmei Han [a], Xinyuan Ma [a], Jianhua Yang [a], Xuepu Feng [a], Yubo Jiang [a,*]

[a] *Faculty of Science, Kunming University of Science and Technology, Kunming 650500, China.*

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ABSTRACT

An efficient method for the synthesis of 1-monosubstituted-1, 2, 3-triazoles from 2-methyl-3-butyn-2-ol under copper catalyst conditions has been developed through a one-step one-pot sequence. This method provides a concise and efficient pathway to synthesize 1-monosubstituted-1, 2, 3-triazole derivatives in good to excellent yields.

Introduction

The class of heterocyclic compounds containing five-membered ring with three nitrogen atoms are known as triazoles; among triazole family, the 1, 2, 3-triazoles possess the diverse applications as potential bioactive compound and frequently used for the preparation of new drugs with diverse biological activities.[1] Recently, 1, 2, 3-triazoles were widely applied in various fields such as organic synthesis,[2] materials,[3] medicinal chemistry,[4] food additives[5] and biological science,[6] especially in medicinal chemistry field such as anti-HIV,[7] anticancer[8] and antifungal[9] activities, although the structures were not found in natural products (Fig. 1).

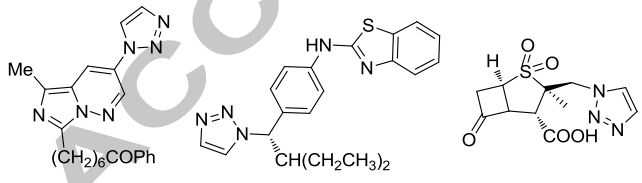

Fig. 1. 1-Monosubstituted-1, 2, 3-triazoles pharmaceutical activities.

As the 1, 2, 3-triazole derivatives were used in many expanding areas,[10] its preparation has attracted much attention and obtained encouraging progress in recent years. Thus, it is significant to develop general and efficient methods for their fabrication. The first method to form 1, 2, 3-triazole was the Huisgen dipolar cycloaddition, giving 1,4- and 1,5-disubstituted regioisomers.[11] In 2002, Sharpless[12] group found a copper-catalyzed 1,3-dipolar cycloaddition reaction (CuAAC) between alkynes and azides, allowing the regioselective formation of the 1, 4-disubstituted 1, 2, 3-triazoles. Ruthenium catalyzed cycloaddition of organic azide and alkyne is an important complement to copper catalyzed 1, 3-dipolar cycloaddition reactions, which are the essence of click chemistry. In 2007, Fokin[13] group found that ruthenium complexes can effectively catalyze organic azide and alkyne cycloaddition reaction, and specifically to generate 1, 5-disubstituted 1, 2, 3-triazoles. From then on these compounds come to the limelight, bringing researchers to explore more effective methods using different approaches to respectively obtain 1, 4-disubstituted 1, 2, 3-triazoles and 1, 5-disubstituted 1, 2, 3-triazoles.[14] However, The construction of the ring of monosubstituted 1, 2, 3-triazoles is more difficult than that of the other kinds of these heterocycles, owing to the special request for the structure of "alkyne source" and the relatively rigorous reaction conditions required in the system. As early as 1966, Kauer and Carboni[15] were the first to synthesize 1-(2-nitro phenyl)-1, 2, 3-triazole derivatives by using acetylene and *ortho* nitro azide, achieving the construction of 1-monosubstituted-1, 2, 3-triazole. One strategy is the decarboxvlation of triazoles bearing a carboxylic acid substituent, which requires long reaction times and extreme temperatures.[16] Another protocol is the cycloaddition of azides to acetylene[17] and its analogs such as acetylides[18] and vinyl compounds.[19] Afterwards, Spagnolo, Zanirato[20] and Liang[21] groups optimized the above method but are mainly limited to the acetylene gas. Thus, the synthesis of 1-monosubstituted-1, 2, 3-triazoles by using other alkyne sources attracts much attention continuously. During 2009, Jensen[22] group reported 1-monosubstituted-1, 2, 3-triazole was successfully constructed under microwave irradiation by ethylene acetate as alkyne source. Kuang[23] group reported a novel and usefu1 protocol for the synthesis of 1-monosubstitued 1, 2, 3-triazoles by click reaction / decarboxylationl under mild conditions. In 2011, the group[24] achieved metal-free synthesis of 1-monosubstituted-1, 2, 3-

* Corresponding author.

e-mail: ybjiang@kmust.edu.cn

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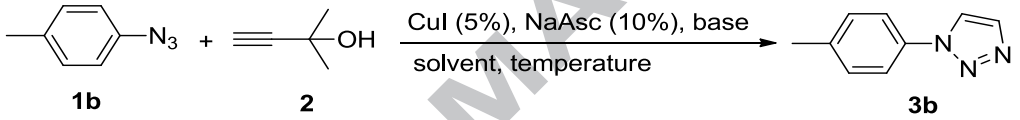
triazoles from acetylene sodium. During 2013, the same group[25] developed an easy one-pot synthesis of l-monosubstituted aliphatic 1, 2, 3-triazoles from aliphatic halides (C1 and Br), sodium azide and propiolic acid by a click cycloaddition / decarboxylation process. Another method has also been developed for the synthesis of monosubstitued1-aryl 1-*H*-1, 2, 3-triazoles from arylboronic acids and prop-2-ynoic acid or CaC_2.[26] Owing to the development of facile synthesis and modification of 1, 2, 3-triazole compounds, therefore these widely applications strongly attracted enormous interests.[27]

Herein, we would like to describe a convenient and efficient one-pot method for the preparation of 1-monosubstituted-1, 2, 3-triazoles. In this method, the aryl azides and 2-methyl-3-butyn-2-ol were involved directly as the starting materials under copper-catalyst in the presence of KOH by a one-step one-pot sequence.

Results and Discussion

An initial investigation of the reaction conditions was conducted using 1-azido-4-methylbenzene **1b** and 2-methyl-3-butyn-2-ol **2** as the starting materials. We respectively investigated the effects of base, solvent and temperature respectively, as summarized in Table 1. No target molecule of 1-(*p*-tolyl)-1*H*-1, 2, 3-triazole **3b** was detected when the reaction was conducted at 120°C in solvent of PhMe-MeOH (1:1 in volume) under the base of K_3PO_4 (Table 1, entry 1). To our delight, addition of other base to the reaction leads to significantly improved efficiencies (Table 1, entries 2−7). Among the bases screened, KOH (5 eq.) was observed to be the most effective, producing **3b** in 61% yield (Table 1, entry 7). Then, other solvents including single toluene or CH_3OH seemed ineffective for the system (Table 1, entries 8−9). Further screening of the volume ratios of the mixture solvent showed that 1:3 for Toluene-CH_3OH was the best choice (Table 1, entries 10−13). Subsequently, we investigated the effects of temperature and found that the yield could not be improved when the reaction temperature was adjusted to a lower temperature of 110°C (Table 1, entry 14). To gain the ideal yield, the reaction temperature was raised and it turned out that the 130°C could bring a highest yield of 79% than others including 140°C and 150°C (Table 1, entries 15-17). Additionally, the amount of KOH was also examined and reducing the amount of KOH to 3.0 equiv and 4.0 equiv or increasing it to 6.0 equiv and 7.0 equiv could not raise the yield evidently. After further optimization, the best results were obtained using a treatment of 5 mol% CuI, 10 mol% NaAsc and 5 equiv of KOH in Toluene-CH_3OH (1:3, v:v) at 130°C for 48 h, affording the desired 1-monosustituted-1, 2, 3-triazole **3b** in 79% yield (Table1, entry 15).

Table 1. Selected Optimization of the Reaction Conditions.[a]



1b **2** **3b**

Entry	Base (eq.)	Solvent	Temp (°C)	Yield (%)[b]
1	K_3PO_4 (5.0)	Toluene / CH_3OH = 1 / 1	120	0
2	t-BuOK (5.0)	Toluene / CH_3OH = 1 / 1	120	25
3	CH_3ONa (5.0)	Toluene / CH_3OH = 1 / 1	120	32
4	NaH (5.0)	Toluene / CH_3OH = 1 / 1	120	28
5	CsOH (5.0)	Toluene / CH_3OH = 1 / 1	120	45
6	NaOH (5.0)	Toluene / CH_3OH = 1 / 1	120	47
7	KOH (5.0)	Toluene / CH_3OH = 1 / 1	120	61
8	KOH (5.0)	Toluene	120	0
9	KOH (5.0)	CH_3OH	120	0
10	KOH (5.0)	Toluene / CH_3OH = 3 / 1	120	51
11	KOH (5.0)	Toluene / CH_3OH = 2 / 1	120	54
12	KOH (5.0)	Toluene / CH_3OH = 1 / 2	120	55
13	KOH (5.0)	Toluene / CH_3OH = 1 / 3	120	65
14	KOH (5.0)	Toluene / CH_3OH = 1 / 3	110	32
15	KOH (5.0)	Toluene / CH_3OH = 1 / 3	130	**79**
16	KOH (5.0)	Toluene / CH_3OH = 1 / 3	140	74
17	KOH (5.0)	Toluene / CH_3OH = 1 / 3	150	72
18	KOH (3.0)	Toluene / CH_3OH = 1 / 3	130	50
19	KOH (4.0)	Toluene / CH_3OH = 1 / 3	130	61
20	KOH (6.0)	Toluene / CH_3OH = 1 / 3	130	77
21	KOH (7.0)	Toluene / CH_3OH = 1 / 3	130	78

[a] Reaction conditions unless noted: 1-azido-4-methylbenzene **1b** (0.3 mmol), 2-methyl-3-butyn-2-ol **2** (0.3 mmol), CuI (0.015 mmol), NaAsc (0.03 mmol) and base (1.5 mmol) were added to 2 mL of solvent and stirred at 130 °C for 48 h.
[b] Isolated yield

With the optimized reaction conditions in hand, a series of aryl azides **1** and 2-methyl-3-butyn-2-ol **2** were then subjected to the reaction, affording the corresponding 1-monosubstituted-1, 2, 3-triazole **3**. The results summarized in Table 2 showed that aryl azides carrying either an electron donating substituent or an electron withdrawing group could proceed well and generated the desired products **3** in good to excellent yields (Table 2, **3a-3o**). The substrates with electron-donating groups (-CH_3, -OMe) could react well and afford good yields (Table 2, **3b-3f**), and those with an electron-withdrawing groups (-NO_2, -F, -Br, -Cl,) could also produce the desired compounds in moderate to good yields (Table 2, **3h-3q**). Azides with electron-donating groups or electron-withdrawing groups at *meta*- or *ortho*-position could only produce the corresponding products in lower yields

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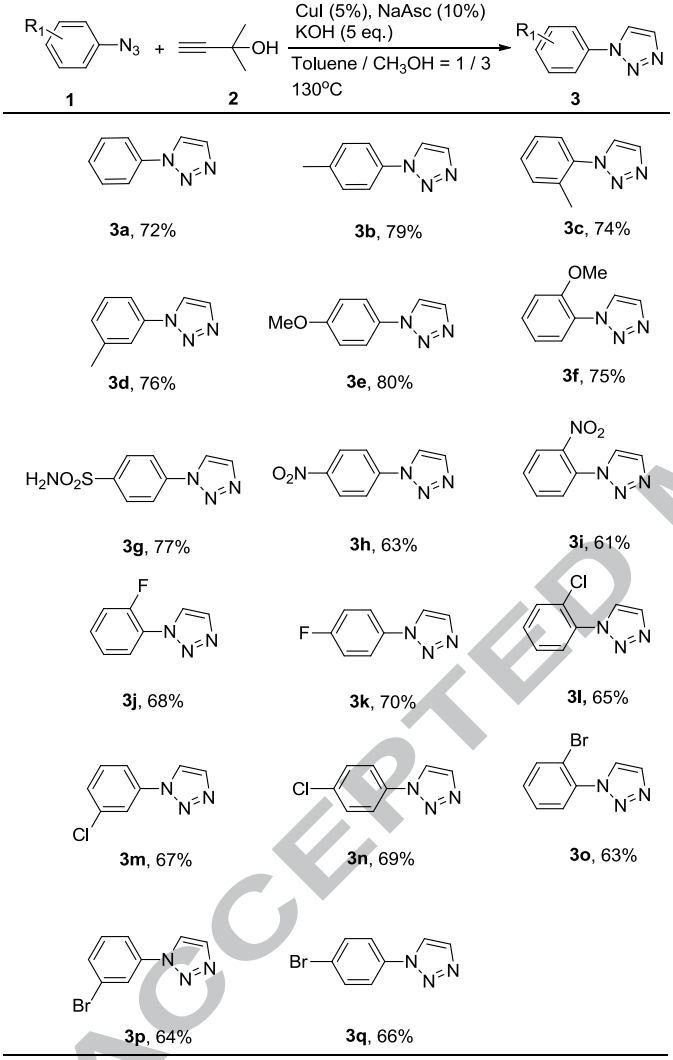
compared with those from substrates bearing a group at *para*-position, probably owning to the steric effect (Table 2, **3c** and **3d** *vs.* **3b, 3f** *vs.* **3e**, **3i** *vs*. **3h**, **3j** *vs*. **3k**, **3l** and **3m** *vs*. **3n**, **3o** and **3p** *vs*. **3q**). Moreover, the substrates with electron-donating group (-OMe) are superior to those with CH_3 on the same position (*para* or *ortho*) of *N*-1 aryl (Table 2, **3e** and **3f** *vs*. **3b** and **3c**). And, the substrates with electron-withdrawing group (-NO_2) on the same position produced only lower yields in comparison with those bearing halogens (-F, -Br, -Cl), probably owning to the electronic effects (**3h** *vs*. **3k**, **3n** and **3q**, **3i** *vs*. **3j**, **3l** and **3o**). It should be noted that the substrate possessing sulfonamido was also tolerated in the system and good yield was also obtained (**3g**).

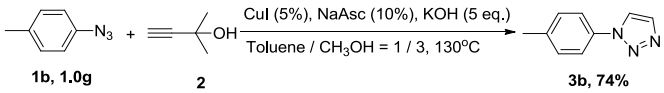
Table 2. Substrates Scope [a, b]



[a] Reaction conditions unless noted: aryl azides **1** (0.3 mmol), 2-methyl-3-butyn-2-ol **2** (0.3 mmol), CuI (0.015 mmol), NaAsc (0.03 mmol) and KOH (1.5 mmol) were added to 2 mL of solvent and stirred at 130 °C for 48 h.

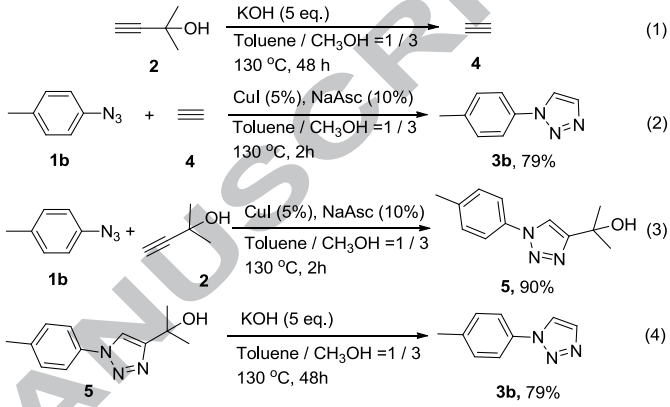
[b] Yield of isolated product after column chromatography.

To test the scalability of the current method, the reaction of 1-azido-4-methylbenzene **1b** (7.45 mmol, 1.0 g) and 2-methyl-3-butyn-2-ol **2**(7.45 mmol, 0.6 g) as the starting materials was carried out on a gram scale, and the product **3b** was isolated in 74% yield (Scheme 1).



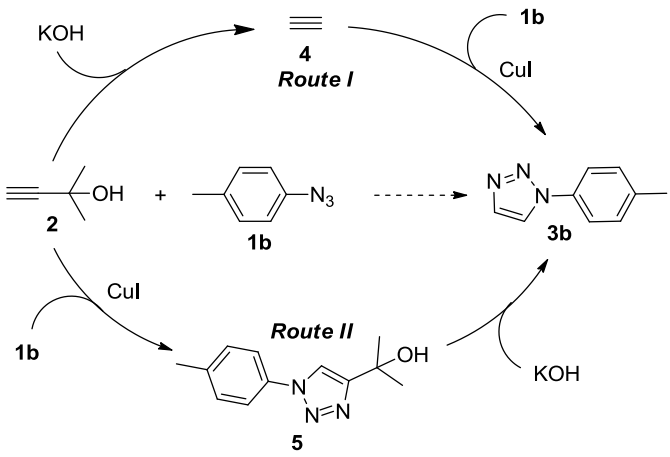
Scheme 1. Gram-Scale Synthesis of Product (**3b**)

To gain mechanistic insight into the reactions, several control experiments were carried out (Scheme 2). Firstly, the 2-methyl-3-butyn-2-ol **2** was consumed completely when heated to 130 °C for 48 hours at the existence of KOH in the solvent of PhMe-MeOH (1:3) (eq. 1). And the generated acetylene **4** could smoothly combine with 1-azido-4-methylbenzene **1b** to form the target molecules **3b** in 73% yield under the standard conditions without KOH (eq. 2). Meanwhile, the intermediate 2-(1-(*p*-tolyl)-1*H*-1, 2, 3-triazol-4-yl)propan-2-ol **5** could be obtained from the cycloaddition of 1-azido-4-methylbenzene **1b** and 2-methyl-3-butyn-2-ol **2** in 90% yield (eq. 3), which could also be converted to the target molecule **3b** in 79% yield mediated by KOH in the same solvent (eq. 4).



Scheme 2. Controlled Experiments.

On the basis of above results, two plausible routes may be involved in the construction of 1, 2, 3-triazoles (Scheme 3). In route I, elimination of 2-methyl-3-butyn-2-ol **2** firstly happened mediated by KOH, generating acetylene **4**, which underwent the Cu-catalyzed alkyne-azide cycloaddition to form the product **3b**. In route II, the starting material **2** experienced the Cu-catalyzed cycloaddition for the first step to form 2-(1-(*p*-tolyl)-1*H*-1, 2, 3-triazol-4-yl)propan-2-ol **5**, which transformed to the final product through an elimination process in the action of KOH.



Scheme 3. Plausible Routes.

Conclusions

In summary, we have developed a highly efficient protocol for the synthesis of 1-monosustituted-1, 2, 3-triazoles using aryl azides and 2-methyl-3-butyn-2-ol as the starting materials, in which a one-step one-pot sequence was involved under the optimization reaction. It is a facile method for the preparation of

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1, 2, 3-triazole derivatives, which are widely applied in many fields.

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Highlights

- 2-Methyl-3-butyn-2-ol as the alkyne source
- Synthesis of 1-monosubstituted-1, 2, 3-triazoles.
- One-step one-pot sequence.

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