



One-pot synthesis of 1-monosubstituted-1, 2, 3-triazoles from 2-methyl-3-butyn-2-ol

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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.

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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 additives⁵ and biological science,⁶ especially in medicinal chemistry field such as anti-HIV,⁷ anticancer⁸ and antifungal⁹ activities, although the structures were not found in natural products (Fig. 1).

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, Sharpless¹² 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, Fokin¹³ 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 Carboni¹⁵ 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 decarboxylation of triazoles bearing a carboxylic acid substituent, which requires long reaction times and extreme temperatures.¹⁶ Another protocol is the cycloaddition of azides to acetylene¹⁷ and its analogs such as acetylides¹⁸ and vinyl compounds.¹⁹ Afterwards, Spagnolo, Zanirato²⁰ and Liang²¹ 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, Jensen²² group reported 1-monosubstituted-1, 2, 3-triazole was successfully constructed under microwave irradiation by ethylene acetate as alkyne source. Kuang²³ group reported a novel and useful protocol for the synthesis of 1-monosubstituted 1, 2, 3-triazoles by click reaction/decarboxylation under mild conditions. In 2011, the group²⁴ achieved metal-free synthesis of 1-monosubstituted-1,

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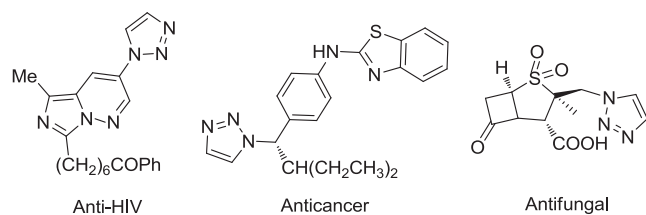


Fig. 1. 1-Monosubstituted-1, 2, 3-triazoles pharmaceutical activities.

2, 3-triazoles from acetylene sodium. During 2013, the same group²⁵ developed an easy one-pot synthesis of 1-monosubstituted aliphatic 1, 2, 3-triazoles from aliphatic halides (C1 and Br), sodium azide and propionic acid by a click cycloaddition/decarboxylation process. Another method has also been developed for the synthesis of monosubstituted 1-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.

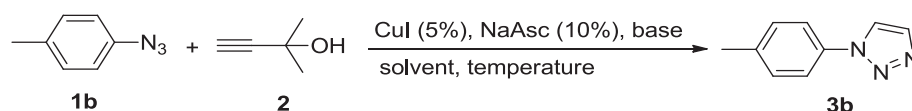
Results and discussion

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-monosubstituted-1, 2, 3-triazole **3b** in 79% yield (Table 1, entry 15).

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

Table 1
Selected optimization of the reaction conditions.^a



Entry	Base (eq.)	Solvent	Temp (°C)	Yield (%) ^b
1	K_3PO_4 (5.0)	Toluene/ CH_3OH = 1/1	120	0
2	<i>t</i> -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.

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