

# Novel sulfur containing 1,4-disubstituted-1,2,3-triazoles catalyzed by CuI in water

Mozhgan Navidi and Barahman Movassagh\*

*Department of Chemistry, K.N. Toosi University of Technology, P. O. Box 16315-1618, Tehran, Iran; Fax: +98(21)22853650; E-mail: [bmovass1178@yahoo.com](mailto:bmovass1178@yahoo.com)*

## Abstract:

A new one-pot three component reaction of thiols, propargyl bromide and organic azide for the synthesis of novel sulfur containing 1,4-disubstituted-1,2,3-triazoles was demonstrated. The protocol is simple, mild and green. The reactions are performed under aerial condition and at room temperature using CuI as a cheap and available catalyst.

## Keywords:

Terminal alkyne; thiol; 1,2,3-triazole; CuI; Huisgen reaction

## 1. Introduction

1,2,3-Triazoles are important heterocycles with a wide range of biological applications [1-4] such as anti-cancer [5], anti-HIV [6] and anti-allergic [7]. The most common method for the synthesis of 1,4-disubstituted-1,2,3-triazoles is through Huisgen 1,3-dipolar cycloaddition reaction of terminal alkynes with azides. Many of the reported procedures favor simple copper salts of Cu(I) [8-13] or Cu(II)/reductant [14-17] as the catalyst. However, owing to the advantages of the heterogeneous catalysts, different support materials are employed: Cu/porous glass [18], Cu/zeolites [19], Cu/chitosan [20], Cu/chelate resins [21], Cu/magnetic silica [22], and Cu/Al<sub>2</sub>O<sub>3</sub> [23], to name only a few. The application of Cu-nanoparticles has been also described [24].

Although the number of reports on this topic are numerous, to the best of our knowledge, protocols for the synthesis of heteroatom containing 1,4-disubstituted-1,2,3-triazoles are not many. Nitrogen and oxygen containing 1,4-disubstituted-1,2,3-triazoles are reported by Rostovtsev et al. [25] and Yan et al. [26] respectively, and sulfur containing triazoles are

relatively rare [27-30]. Herein, we describe the synthesis of novel sulfur containing 1,4-disubstituted-1,2,3-triazoles via a one-pot CuI-catalyzed three component reaction of thiols, organic azides and terminal alkynes.

## 2. Results and discussion

Initially, we investigated the effect of solvent on the model reaction of thiophenol, propargyl bromide and benzyl azide using CuI and Et<sub>3</sub>N for 24 h in air and at ambient temperature (Table 1). As can be seen from Table 1, the best result was obtained when water was used as solvent. Moreover, in comparison with Et<sub>3</sub>N and DIPEA, Et<sub>3</sub>N performed the reaction better. Our further attempts to improve the yield by increasing temperature or adding sodium dodecylsulfate (SDS) additive to the reaction mixture, proved to be unsuccessful. In addition, the

**Table 1.** Optimization reactions <sup>a</sup>

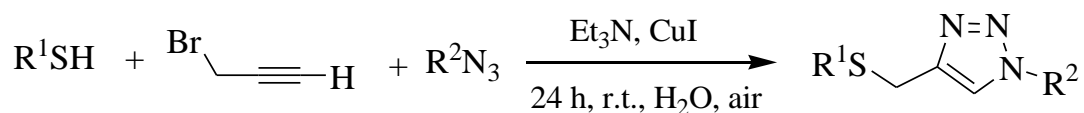
En.	Base	T (°C)	CuI (mol %)	Additive (mol %)	Solvent	Yield (%)
1	Et <sub>3</sub> N	r.t.	10	-	H <sub>2</sub> O	86
2	Et <sub>3</sub> N	r.t.	10	-	THF:H <sub>2</sub> O	69
3	Et <sub>3</sub> N	r.t.	10	-	CH <sub>3</sub> CN:H <sub>2</sub> O	57
4	Et <sub>3</sub> N	r.t.	10	-	Neat	62
5	DIPEA	r.t.	10	-	H <sub>2</sub> O	82
6	Et <sub>3</sub> N	50	10	-	H <sub>2</sub> O	83 <sup>b</sup>
7	Et <sub>3</sub> N	r.t.	10	SDS (3.5)	H <sub>2</sub> O	74
8	Et <sub>3</sub> N	r.t.	20	-	H <sub>2</sub> O	88
9	Et <sub>3</sub> N	r.t.	5	-	H <sub>2</sub> O	87
10	Et <sub>3</sub> N	r.t.	3	-	H <sub>2</sub> O	67

<sup>a</sup> Reaction conditions: thiophenol (1.2 mmol), propargylbromide (1 mmol), benzylazid (1 mmol), base (2 mmol), solvent (1 mL), 24 h; <sup>b</sup> The reaction was performed for 6 h

influence of different amounts of the catalyst on the course of the reaction was studied and 5 mol % of CuI gave the highest yield. Later, in order to examine the possibility of substituting benzyl azide with sodium azide, an experiment was performed using propargyl bromide (1 mmol), NaN<sub>3</sub> (1 mmol), benzyl bromide (1 mmol), thiophenol (1.2 mmol) and Et<sub>3</sub>N (2 mmol) in H<sub>2</sub>O (1 mL)

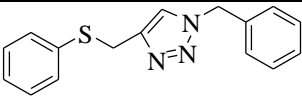
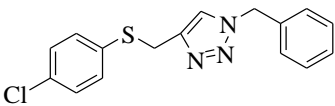
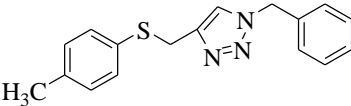
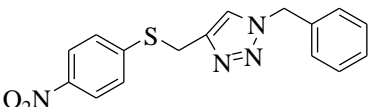
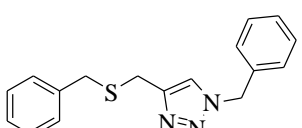
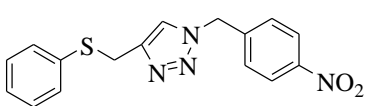
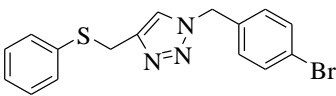
for 24 h at room temperature. Unfortunately, very weak result (20%) was obtained for this reaction.

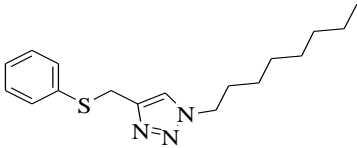
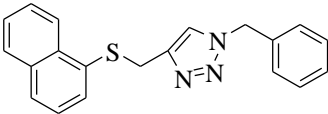
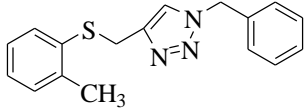
With optimized conditions in hand (Scheme 1), we then explored the scope of the reaction using various thiols and azides to afford novel sulfur containing-1,4-disubstituted-1,2,3-triazoles.



**Scheme 1**

**Table 2.** Sulfur containing-1,4-disubstituted-1,2,3-triazole derivatives

Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield <sup>a</sup> (%)
1	Ph	PhCH <sub>2</sub>		<b>3a</b> 87
2	4-Cl-C <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>		<b>3b</b> 85
3	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>		<b>3c</b> 80
4	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>		<b>3d</b> 80
5	PhCH <sub>2</sub>	PhCH <sub>2</sub>		<b>3e</b> 42
6	Ph	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		<b>3f</b> 73
7	Ph	4-Br-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		<b>3g</b> 68

8	Ph	<i>n</i> -C <sub>8</sub> H <sub>17</sub>		<b>3h</b>	40
9	1-Naphthyl	PhCH <sub>2</sub>		<b>3i</b>	87
10	2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>		<b>3j</b>	72
11	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	PhCH <sub>2</sub>	-		N.R.

<sup>a</sup> Isolated yields

As clear from Table 2, the reaction was performed smoothly with thiols bearing both electron-donating and electron-withdrawing groups (**3b-d**, **3j**, Table 2). However, due to their hydrogen's lower acidity, aliphatic thiol gave weak result (Table 2, **3e**) and even in the case of *n*-octanethiol, no product was isolated (Table 2, entry 11). It was also indicated that the presence of electron-withdrawing groups on the azides used, could decrease the yield (Table 2, **3f** and **3g**). Finally, steric effect was observed comparing the results obtained for 2- and 4-methyl thiophenol reactions (Table 2, entries 3 and 10).

### 3. Conclusion

In summary, we have demonstrated a new one-pot three component reaction of thiols, propargyl bromide and organic azides for the synthesis of novel sulfur containing-1,4-disubstituted-1,2,3-triazoles. The protocol is simple, green and mild using a cheap and available CuI. Moreover, the reactions could be performed in air without further considerations.

### 4. Experimental

#### *Synthesis of organic azides*

Azides were synthesized according to the procedure reported by Campbell-Verduyn et al. [31]. To a stirred solution of the corresponding benzyl bromide (1 eq.) in a 50 mL water/acetone mixture (1:4) was added NaN<sub>3</sub> (1.5 eq). The resulting suspension was stirred at room temperature

for 24 h. Dichloromethane was added to the mixture and the organic layer was separated. The aqueous layer was extracted with  $3 \times 10$  mL aliquots of dichloromethane and the combined organic layers were dried over  $\text{MgSO}_4$ . Solvent was removed under reduced pressure, and the azide was sufficiently pure to use without further work up.

*General procedure for the synthesis of sulfur containing-1,4-disubstituted-1,2,3-triazoles*

A mixture of water (1 mL), thiol (1.2 mmol),  $\text{Et}_3\text{N}$  (2 mmol) and propargyl bromide (1 mmol) was stirred for 2 h at room temperature. Then, 1 mmol of azide and 5 mol % of  $\text{CuI}$  was added and the reaction was continued for 24 h. After this time, the reaction mixture was extracted with ethylacetate ( $3 \times 5$  mL) and the organic layer was dried using  $\text{MgSO}_4$ . After removal of the solvent under reduced pressure, the residue was purified on silica gel with *n*-hexane-ethylacetate (2:1). The products were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy. **(3a)**: White crystals; mp = 77.9-79.1 °C; IR (KBr):  $\nu = 3062, 1582 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.14\text{-}7.36$  (m, 11H), 5.46 (s, 2H), 4.21 (s, 2H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 145.3, 135.3, 134.7, 129.8, 129.1, 128.9, 128.7, 127.9, 126.5, 122.1, 54.1, 29.0$  ppm; **(3c)**: White crystals; mp = 80.7-81.3 °C; IR (KBr):  $\nu = 2921, 1604 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.33\text{-}7.35$  (m, 3H), 7.18 (d,  $J = 6.4$  Hz, 5H), 7.02 (d,  $J = 7.9$  Hz, 2H), 5.43 (s, 2H), 4.14 (s, 2H), 2.28 (s, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 145.4, 136.8, 134.7, 131.5, 130.7, 129.7, 129.0, 128.6, 128.1, 122.1, 54.0, 29.7, 21.1$  ppm; **(3e)**: White crystals; mp = 72.4-72.8 °C; IR (KBr):  $\nu = 3059, 2908, 1604 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.36$  (s, 3H), 7.27 (s, 8H), 5.47 (s, 2H), 3.69 (d,  $J = 7.2$  Hz, 4H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 146.1, 138.1, 134.7, 129.1, 129.0, 128.8, 128.5, 128.1, 127.0, 121.8, 54.1, 36.0, 25.6$  ppm; **(3h)**: White crystals; mp = 59.7-60.5 °C; IR (KBr):  $\nu = 3065, 2921, 1590 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.14\text{-}7.33$  (m, 6H), 4.25 (m, 4H), 1.81 (quin,  $J = 6.8$  Hz, 2H), 1.24 (s, 10H), 0.87 (t,  $J = 6.9$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 144.8, 135.6, 129.4, 128.9, 126.4, 121.8, 50.3, 31.7, 30.2, 29.0, 28.9, 28.8, 26.4, 22.6, 14.1$  ppm.

## Acknowledgement

We are pleased to acknowledge financial support from the K. N. Toosi University of Technology Research Council.

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