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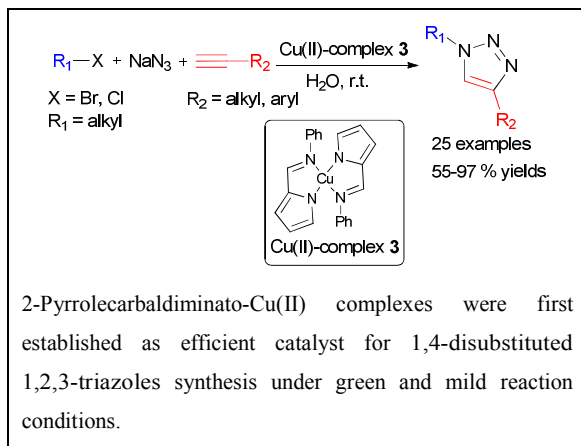


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ARTICLE

2-Pyrrolecarbaldiminato-Cu(II) complexes catalyzed three-component 1,3-dipolar cycloaddition for 1,4-disubstituted 1,2,3-triazoles synthesis in water at room temperature

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2-Pyrrolecarbaldiminato-Cu(II) complexes were established as efficient catalyst for three-component 1,3-dipolar cycloaddition reaction of benzyl halides, sodium azide with terminal alkynes in water at room temperature, and several of regioselective 1,4-disubstituted 1,2,3-triazoles have been synthesized under the reaction conditions in 55-97% yields.

Introduction

1,2,3-Triazoles are prevalent building blocks of several classes of nitrogen-containing heterocyclic compounds and are commonly employed as a powerful tool in many fields of chemistry such as pharmaceuticals, agrochemicals, dyes and materials.¹ Consequently, much attentions have been given to the development of efficient and practical methods for the synthesis of substituted 1,2,3-triazoles. Of these transformations, Cu(I)-catalyzed alkyne-azide cycloaddition reaction (CuAAC, better known as click chemistry) reported independently in 2002 by Sharpless² and Meldal³, was the most versatile protocol for 1,4-disubstituted 1,2,3-triazoles synthesis, which proceeds under mild conditions with high regioselectivity. Since then, CuAAC has been extensively studied and widely used. Traditionally, the standard catalytic system of this method usually consists of Cu(II) salts (such as CuSO₄·5H₂O) in conjunction with a reducing agent (such as sodium ascorbate), which generates the catalytically active Cu(I) species *in situ* in the reaction media for CuAAC reaction.^{2,4} Later, it was discovered that Cu(I) salts could be also used directly for this reaction, but bases and/or ligands were required to stabilize Cu(I) intermediates, protecting it from oxidation and disproportionation, and hamper undesired side-product formation.⁵ Recently, solid supported Cu(I)⁶ or Cu(II)⁷ species as heterogeneous catalytic systems have been prepared and applied for cycloaddition reaction, which have several advantages such as simpler isolation of the reaction products by filtration, as well as recovery and recycling of the catalysts. The protocols directly employed Cu(II) species without deliberate addition of a reducing agent for AAC reaction have been also discussed. The mechanism indicated that the catalytic Cu(I) species were generated in a short induction period via reducing

Cu(II) salts by alcoholic solvents⁸ or sodium azide^{7c,9} during this procedure.

Pyrrolide-imine Schiff base ligands are attractive ligands for coordination to various metal ions, and their metal complexes have been found a number of important applications to various processes.¹⁰ For example, 2-pyrrolecarbaldimine-based titanium^{10a} and hafnium^{10b} catalysts were reported for olefin polymerization, while its copper complexes have been used as CVD/ALD (chemical vapor deposition/atomic layer deposition) precursors^{10c} and as oxidation catalyst for benzylic alcohols in aqueous solutions^{10d}. Recently, we found that pyrrolecarbaldiminato-Cu complexes could efficiently catalyze C-N coupling reaction.¹¹ In order to further explore the scope of these complexes to other types of organic reactions, we report herein 2-pyrrolecarbaldiminato-Cu(II) complexes as novel and high active catalysts for alkyne-azide cycloaddition reaction.

Initially, the 1,3-dipolar cycloaddition reaction between benzyl bromide, sodium azide and phenylacetylene was selected as a model reaction to investigate the catalytic activity of four different 2-pyrrolecarbaldiminato-Cu (II) complexes, which synthesized by a simple condensation reaction between pyrrole-2-carbaldehyde and corresponding amines in the presence of Cu(OAc)₂ in a one-pot synthesis,¹¹ in neat water at room temperature. According to Table 1, the four Cu(II)-complexes with 10 mol% loading, as expected, all showed high catalytic activities to give the 1,4-disubstituted 1,2,3-triazoles in the yields of 78-95%, and Cu(II)-complexes **3** was found to be the best one (entries 1-4). When the amount of the catalyst **3** was reduced from 10 mol% to 5 mol%, excellent yield of triazole was also obtained only with prolonging the reaction time to 13 h (entry 5). To our surprise, the same results were observed when the catalyst loading decreased to 2.5 mol% and 1.0 mol% (entries 6 and 7). However, it was found that a further decrease of the loading of catalyst **3** to 0.5 mol% or 0.25 mol% led to

lower yield and longer reaction time (entries 8 and 9). Control experiment conducted in the absence of Cu(II)-complex from the reaction mixture resulted in no product (entry 10). Therefore, the optimal conditions for 1,4-disubstituted 1,2,3-triazoles synthesis involves the use of 1 mol% Cu(II)-complexes **3** as the catalyst, H₂O as the solvent at room temperature.

Table 1 Cu(II)-complex-catalyzed 1,3-dipolar cycloaddition reaction: optimization of the catalytic conditions^a

Entry	Catalyst (mol%)	Time	Yield ^b (%)
1	1 (10)	8	78
2	2 (10)	8	83
3	3 (10)	8	95
4	4 (10)	8	87
5	3 (5)	13	98
6	3 (2.5)	13	97
7	3 (1.0)	13	97
8	3 (0.5)	20	91
9	3 (0.25)	20	89
10	-	20	0

^a Reaction conditions: benzyl bromide (0.5 mmol), phenylacetylene (0.6 mmol), NaN₃ (0.6 mmol), catalyst, r.t. ^b Isolated yield.

With the optimal conditions in hand, the scope of the Cu(II)-complex **3** catalyzed one-pot cycloaddition reaction was explored for variety of benzyl halide and alkynes. The results are illustrated in Table 2. In general, most of electron-rich, electron-neutral and electron-poor aryl acetylenes reacted with benzyl bromide and NaN₃ smoothly to provide the target products in good to excellent yields within 24 h (entries 1 and 3-11). Conversely, the use of alkyl acetylenes gave relatively lower yields (entries 12-16). For benzyl halide, we found that the electron effect of substituents was more obvious than the aryl acetylenes. The substrates containing electron-withdrawing groups seemed to be less reactive than the ones containing electron-neutral and electron-donating groups (entries 17-21). Reaction of benzyl chloride needs longer reaction time due to the lower activity (entries 1 vs 2). Notably, the *o*-methylbenzyl bromide reacted also effectively under the standard conditions, which indicated that steric hindrance has no significant effect on the reaction (entry 22). To our delight, the reaction of benzyl bromide, NaN₃ and acetylene gas yield 1-benzyl-1*H*-1,2,3-triazole in 67 % yield, opening the possibility of using acetylene gas as an efficient source for 1,2,3-triazoles synthesis (entry 23). The Cu(II)-complexes **3** catalyzed three-component cycloaddition reaction was extended to di- and tri-halides in water at

60 °C, and the reactions proceeded without any difficult to give moderate to good yields of the corresponding products (Fig. 1).

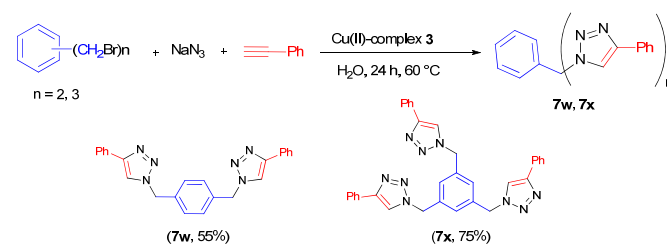


Fig. 1 Cu(II)-complex **3** catalyzed formation of di-/tri-triazoles.

Conclusions

In conclusion, we have established for the first time 2-pyrrole-carbaldiminato-Cu(II) complexes as novel and high efficient catalyst for one-pot three-component 1,3-dipolar cycloaddition for 1,4-disubstituted 1,2,3-triazoles synthesis in water at room temperature. A variety of benzyl halides and alkyl/aryl acetylenes even acetylene gas could be reacted well to afford the desired products in high yields under the optimal conditions. In addition, the low catalyst loading (1 mol%), ambient reaction conditions, high regioselectivity presented herein, are the salient features of this protocol, which made the operation much more practical.

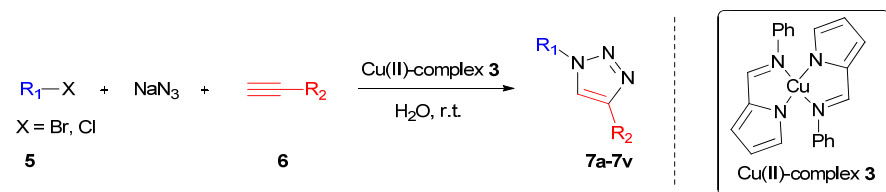
Experimental

General information

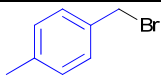
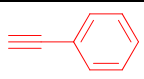
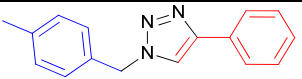
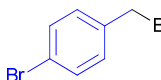
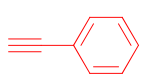
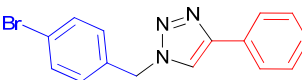
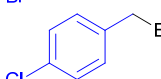
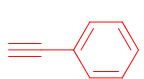
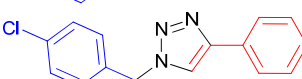
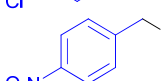
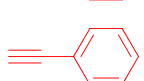
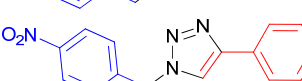
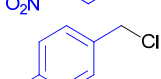
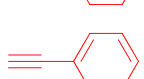
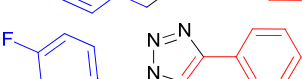
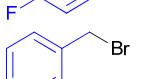
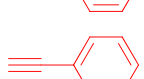
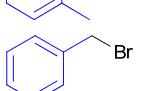
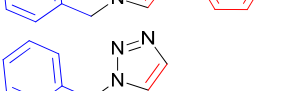
Unless otherwise stated, all reagents were purchased from Adamas-beta and used without further purification. Column chromatography was performed with silica gel (200-300 mesh), purchased from Qingdao Haiyang Chemical Co. Ltd. Thin-layer chromatography was carried out with Merck silica gel GF₂₅₄ plates and visualized by exposure to UV light (254 nm). All 1,4-disubstituted 1,2,3-triazoles are characterized by ¹H NMR and ¹³C NMR, which were compared with the previously reported data. ¹H NMR spectra and ¹³C NMR spectra were recorded at room temperature on a Varian Inova-400 instrument at 400 MHz and 100 MHz, respectively.

General procedure for the synthesis of 1,2,3-triazoles 7a-7v

A 25 mL Schlenk tube was charged with Cu(II)-complex **3** (0.005 mmol), benzyl halides (0.5 mmol), NaN₃ (0.6 mmol), alkynes (0.6 mmol) and water (1 mL). The mixture was stirred at room temperature and monitored by TLC until the benzyl halides being consumed. The reaction mixture was then extracted with ethyl acetate (3×10 mL). The combined organic phases was washed with water and brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether as the eluent) to provide the target products.

Table 2 Synthesis of 1,2,3-triazoles **7a-7v** catalyzed by Cu(II)-complex **3** in water at room temperature^a

Entry	Benzyl halide	Alkyne	Product		Time (h)	Yield ^b (%)
1				7a	13	97
2				7a	24	90
3				7b	10	97
4				7c	24	91
5				7d	12	91
6				7e	24	87
7				7f	12	91
8				7g	10	97
9				7h	12	87
10				7i	24	92
11				7j	24	89
12				7k	24	60
13				7l	24	77
14				7m	24	75
15				7n	12	96 ^c
16				7o	12	68 ^c

17				7p	14	80
18				7q	24	71
19				7r	30	74
20				7s	13	90 ^c
21				7t	30	79
22				7u	17	95
23		HC≡CH		7v	24	67 ^{c,d}

^a Reaction conditions: Cu(II)-complex **3** (0.005 mmol), benzyl halide (0.5 mmol), NaN₃ (0.6 mmol), alkyne (0.6 mmol), water (1 mL), r.t. ^b Isolated yield. ^c Reaction temperature: 60 °C. ^d Under C₂H₂ balloon.

General procedure for the synthesis of di-/tri-triazoles **7w** and **7x**

A 25 mL Schlenk tube was charged with Cu(II)-complex **3** (0.0025 mmol for dihalides and 0.00375 mmol for trihalides), benzyl halides (0.125 mmol), NaN₃ (0.30 mmol for dihalides and 0.45 mmol for trihalides), phenyl acetylene (0.6 mmol for dihalides and 0.9 mmol for trihalides) and water (1 mL). The mixture was stirred at 60 °C and monitored by TLC until the benzyl halides being consumed. The reaction mixture was then extracted with ethyl acetate (3×10 mL). The combined organic phases was washed with water and brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate / petroleum ether as the eluent) to provide the target products.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data for all products. See DOI: 10.1039/b000000x/

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