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Copper-Catalyzed Efficient Multicomponent Reaction: Synthesis of Benzoxazoline-Amidine Derivatives

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Abstract: We have developed an efficient copper-catalyzed method for the synthesis of the benzoxazoline-amidine derivatives. The protocol uses inexpensive copper(I) iodide as the catalyst, and furnished the expected product in good to excellent yields by a three-component reaction of sulfonyl azides, terminal alkynes and Schiffs' bases in terahydrofuran (THF) at room temperature for 8 h in the presence of triethylamine. This novel synthetic protocol is selective, efficient and general. A plausible mechanism for this process is proposed.

Keywords: alkynes; azides; benzoxazoline-amidine derivatives; copper catalysis; multicomponent reaction; phenolic Schiffs' bases

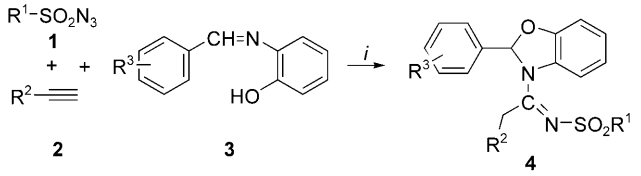
Introduction

Arylbenzoxazoline derivatives are an important class of compounds and provide a common heterocyclic scaffold. They exhibit a wide range of biological and medicinal activities including anticancer, Gram-positive antibacterial,[1] anti-HIV,[2] antibiotic,[3] antiparasitic,[4] anti-inflamatory,[5] H_2-antagonist, and elastase inhibitor[6] properties. They are also fluorescent whitening agents,[7] constituents of cyanine dyes,[8] heat resistant fibers,[9] fluorescent materials,[10] optical brighteners,[11] metal-coordinated ligands,[12] and medicinally significant compounds.[13]

It was previously demonstrated that arylbenzoxazoline derivatives can be obtained from 2-aminophenols *via* heterocyclization reactions catalyzed by strong acid.[14] Another method for the synthesis of arylbenzoxazoline derivatives is the oxidative cyclization of Schiffs' bases.[15] The oxidants could be $PhI(OAc)_2$,[16] NiO_2,[17] $Ba(MnO_4)_2$,[18] DDQ,[15b] $Mn(OAc)_2$,[19] $Pb(OAc)_2$,[20] and $ThClO_4$.[21] Other methods for synthesis of arylbenzoxazoline derivatives involving Ru-catalyzed hydroamination of diynes[22] and CuI-catalyzed[23] cyclization of *ortho*-haloanilides have been reported. However, most of these methodologies suffer from lengthy procedures that require excess amounts of reagents such as PPTS/PPA, *p*-TsOH, $SOCl_2$/HF, PPh_3-DEAD, metal catalyst/oxidizing agents, etc, and harsh reaction conditions such as strong acid, high temperature. As a result, a general, practical and efficient protocol for the synthesis of benzoxazoline derivatives is of interest and remains a challenging project.

Many MCRs (multicomponent reactions) show advantages in atomic economy, environmental friendness, simplified steps, and efficient use of resources.[24] The synthetic utility of the generated molecules from copper-catalyzed three-component reactions has been extensively investigated in various areas. Recently, CuI-catalyzed[25] MCRs concerning sulfonyl azides and alkynes have drawn special interest. Chang et al.[26] and Wang's group[27] have reported the efficient copper-catalyzed multicomponent reactions of sulfonyl azides, terminal alkynes and amines, water, alcohol, imines, salicylaldehyde or aziridine to afford *N*-sulfonylamidines, hydrated amides, *N*-sulfonylazetidin-2-imines, iminocoumarins, and 5-arylidene-2-imino-3-pyrrolines efficiently.

Amidines are prominent structural motifs in numerous bioactive natural products.[28] We accordingly envisioned that amidines containing benzoxazoline moieties may afford unique biological activities, which

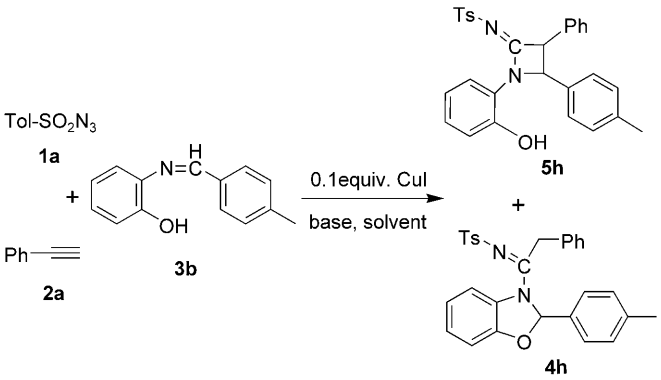


Scheme 1. Synthesis of benzoxazoline-amidine derivatives (**4**). *Conditions:* 1) CuI (0.1 equiv.), 2) TEA (2 equiv., slow addition), 3) THF (solvent), 0–5 °C, 8 h.

provided the impetus to synthesize these novel compounds.

Meanwhile the application of the copper-catalyzed three-component reactions as a tool for the synthesis of high utility compounds continues to expand. And copper-catalyzed azide-alkyne three-component reactions are an efficient way to produce the *N*-sulfonylamidines. Herein, we report a novel pathway for the synthesis of benzoxazoline-amidine derivatives *via* CuI-catalyzed multicomponent reactions of sulfonyl azides, alkynes and phenolic Schiffs' bases (Scheme 1). At the outset of our studies, we tried to optimize the reaction conditions and studied the effect of the substituents of the substrates, and then we also proposed a plausible mechanism for this three-component reaction.

Table 1. The optimal reaction conditions of CuI-catalyzed three-component reactions of sulfonyl azides, alkynes and phenolic Schiffs' bases.



Entry	Base	Solvent	Temp. [°C]	Yield [%][a]	
				4h	**5h**
1	TEA	THF	r.t.	70	5
2	TEA	DMF	r.t.	62	11
3	TEA	CH_3CN	r.t.	67	10
4	TEA	CH_2Cl_2	r.t.	63	9
5	Pyridine	THF	r.t.	47	7
6	K_3PO_4	THF	r.t.	69	6
7	K_3PO_4	CH_2Cl_2	r.t.	65	11
8	K_3PO_4	THF	0–5	71[b]	trace
9	K_2CO_3	THF	0–5	65	8
10	TEA	DMSO	0–5	53	9
11	TEA	THF	0–5	72	trace
12	TEA	THF	50	54	15

[a] *Reaction conditions:* **1a** (1.1 mmol), **2a** (1.0 mmol), **3a** (1.1 mmol), CuI (0.1 mmol), and TEA (2.0 mmol), 8 h, N_2, 0 ~ 5 °C.

[b] Reaction time: 12 h.

Results and Discussion

We began our investigation by performing the three-component reaction of *p*-tolylsulfonyl azide, phenylacetylene and 4-methylphenolic Schiffs' base in DMF in the presence of CuI and TEA at room temperature (Table 1, entry 2), the major isolated product was not the expected azetidinimine (11%) product **5h**,[25d] but instead benzoxazoline-amidine **4h** (62%) was isolated. The structure of product **4h** was unambiguously confirmed by X-ray diffraction analysis, which was in accordance with the observed ^{1}H NMR, ^{13}C NMR, and HR-MS results (Figure 1).[29]

In order to study the effect of various reaction conditions, we tested a wide range of reaction parameters, including catalyst, bases, temperatures and solvents. While no reaction took place in the absence of a copper catalyst, when the reaction of *p*-tolylsulfonyl azide (1**a**) with phenylacetylene (**2a**) and the phenolic Schiffs' base (3**b**) was tried with CuI in the absence of an external base, also no conversion was observed. We found that the use of alternative bases, such as

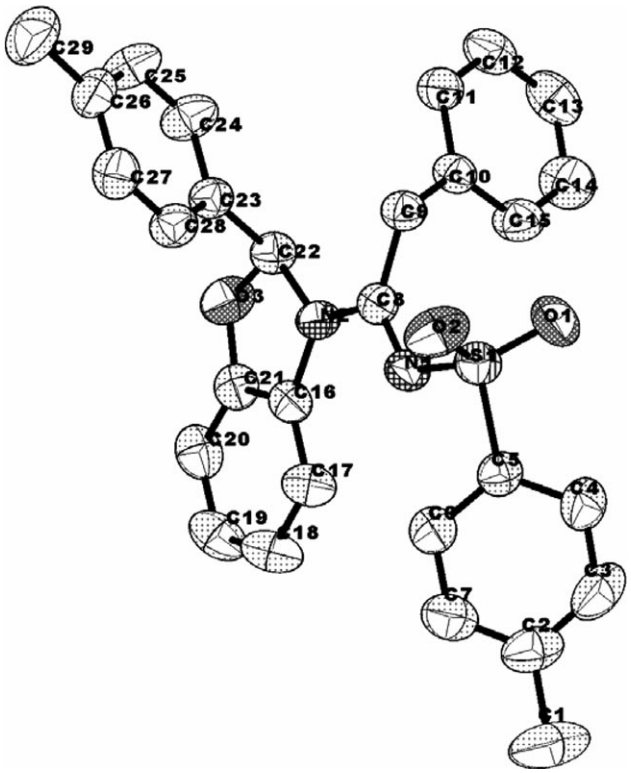
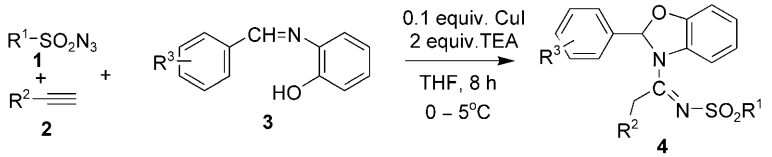


Figure 1. X-ray crystal structure of product **4h**.

Table 2. Cu-catalyzed tri-component coupling for the formation of arylbenzoxazolines.[a]



Entry	R^1	R^2	R^3	Product	Yield [%]
1	C_6H_5 (**1a**)	C_6H_5 (**2a**)	H (**3a**)	**4a**	70
2	4-MeC_6H_4 (**1b**)	**2a**	**3a**	**4b**	73
3	**1a**	CH_2CH_2OTBS (**2b**)	**3a**	**4c**	81
4	**1b**	**2b**	**3a**	**4d**	83
5	**1a**	*n*-C_5H_{11} (**2c**)	**3a**	**4e**	92
6	**1b**	**2c**	**3a**	**4f**	90
7	**1a**	**2a**	4-CH_3 (**3b**)	**4g**	75
8	**1b**	**2a**	**3b**	**4h**	72
9	**1a**	**2b**	**3b**	**4i**	79
10	**1b**	**2b**	**3b**	**4j**	83
11	**1a**	**2c**	**3b**	**4k**	92
12	**1b**	**2c**	**3b**	**4l**	91
13	**1b**	**2a**	4-Cl (**3c**)	**4m**	85
14	**1a**	**2b**	**3c**	**4n**	80
15	**1b**	**2b**	**3c**	**4o**	84
16	**1b**	**2c**	**3c**	**4p**	91
17	**1a**	**2a**	4-NO_2 (**3d**)	**4q**	65
18	**1b**	**2b**	**3d**	**4r**	86
19	**1a**	**2b**	**3d**	**4s**	83
20	**1b**	**2c**	4-OCH_3 (**3e**)	**4t**	90
21	**1a**	**2c**	**3e**	**4u**	91
22	4-ClC_6H_4 (**1c**)	4-$CH_3C_6H_4$ (**2d**)	**3a**	**4v**	83

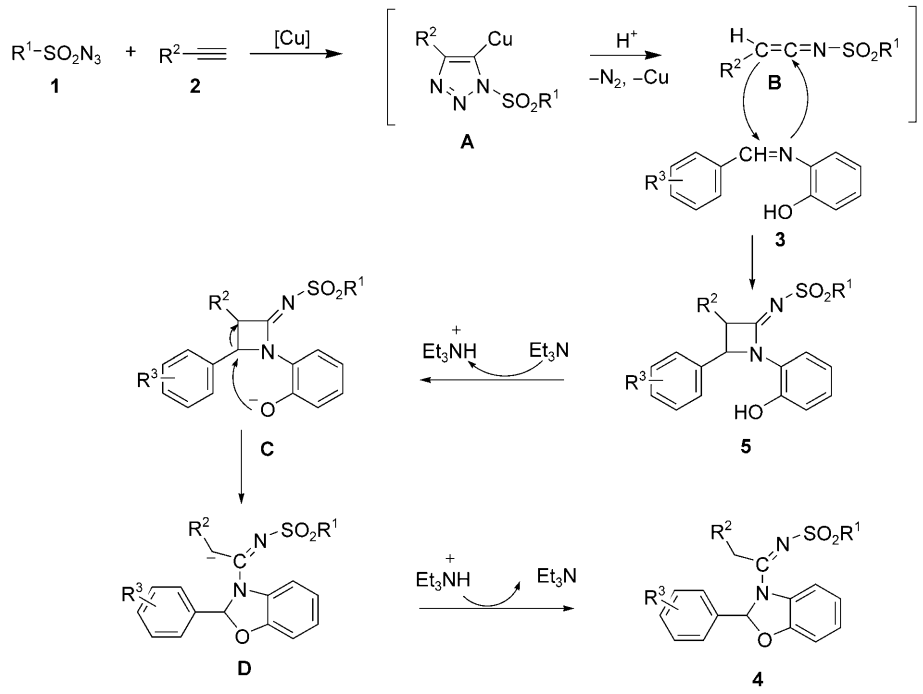
[a] *Reaction conditions:* sulfonyl azide (1.1 mmol), alkyne (1.0 mmol), phenolic Schiffs' bases (1.1 mmol), CuI (0.1 mmol), THF (5 mL), TEA (2.0 mmol), N_2, 0–5 °C, 8 h

Et_3N, and solvents, such as tetrahydrofuran (THF), in the reaction gave good chemoselectivity. Solvents other than terahydrofuran afforded low yields (Table 1, entries 2–4 and 10). As shown in Table 1, the optimal reaction conditions are those with THF as solvent, K_3PO_4 or TEA as base, at the temperature of 0–5 °C (Table 1, entries 8 and 11), which led to the formation of benzoxazoline-amidines in 71% or 72% yield with a trace amount of the corresponding azetidinimines. Other bases and solvents gave lower yields and chemoselectivities. We also found that increasing the reaction temperature to 50 °C (Table 1, entry 12), also led to lower yields and lower chemoselectivities.

Utilizing the optimal reaction conditions, we investigated the scope of the multicomponent reaction of various sulfonyl azides, phenolic Schiffs' bases, and terminal alkynes to produce arylbenzoxazoline derivatives.[28] The results of these reactions are given in Table 2.

We found that both alkyl- and arylalkynes gave the desired products, but the arylalkynes gave relatively lower yields of the products. Good to excellent yields of products were also obtained from substrates incorporating additional substituents on the phenolic Schiffs' bases. Electron-donating groups (Table 2, entries 7 and 20) on the phenolic Schiffs' bases gave higher yields compared to electron-withdrawing groups (Table 2, entry 17). Phenyl- and *p*-tolylsulfonyl azides appeared to have similar reactivity and equally high yields were obtained with these azides.

We propose a plausible mechanism for this three-component domino-like process (Scheme 2). First, in the presence of CuI, sulfonyl azide **1** reacts with the alkyne **2** to form the ketenimine species **B** proposed by Chang[26] and Wang.[27] Protonation of **A** gives rise to the highly reactive ketenimine **B**, and the imine nitrogen of **3** attacks the intermediate **B** to generate a [2+2] cycloaddition product **5**. And then the base (TEA) removes a proton of the hydroxy group of **5** to give a phenoxide ion **C**, which quickly attacks the carbon of the azetidinimine ring to generate the anionic benzoxazoline **D**, which receives a proton to generate the benzoxazoline-amidines derivatives **4**.



Scheme 2. Possible mechanistic pathways leading to the benzoxazoline-amidines derivatives 4.

Conclusions

In conclusion, a novel, selective and efficient general method for the synthesis of benzoxazoline-amidines *via* a three-component reaction of readily available sulfonyl azides, terminal alkynes and phenolic Schiffs' bases is presented. The resulting heterocycle products should have an important potential applications in the synthesis of the medicines, dyes, and pesticides etc. Further studies on related MCRs and their applications are in progress.

Experimental Section

General Comments

All reagents involved in the experiments were commercially available and used without further purification. Melting points were determined on XT4 A (uncorrected temperatures are given). IR spectra were obtained on a Perkin–Elmer FT-IR spectrometer spectrum-2000 using potassium bromide pellets or as liquid films between two sodium chloride pellets. Mass spectra were recorded in a TOF-mass spectrometer model no. Agilent 6460. ^{1}H NMR and ^{13}C NMR spectra (300 MHz) were recorded on a Bruker spectrospin 300 MHz. All NMR samples were run in $CDCl_3$ and chemical shifts are expressed as ppm relative to internal Me_4Si and the metallic nature of the particles was confirmed with a UV spectrophotometer (Shimadzu). Column chromatography was carried out with the use of silica gel (200–300 mesh), purchased from Qingdao Haiyang Chemical Plang, China.

General Procedure for the Synthesis of Benzoxazoline-Amidine Derivatives

To a stirred mixture of CuI (0.1 mmol), *p*-toluenesulfonyl azide (1.2 mmol), phenylacetylene (1 mmol), and phenolic Schiffs' base (1.2 mmol) in anhydrous tetrahydrofuran (5 mL) was slowly added triethylamine (2 mL) *via* syringe under an N_2 atmosphere at 0–5 °C. After stirring the reaction mixture for 8 h, it was evaporated, washed by water, and then extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (200–300 mesh) with ethyl acetate and petroleum ether (1:15) as eluting solvent to give the desired product **4**.

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[29] Crystallographic data for **4h**: space group *P*-1, $a=8.8304(7)$ Å, $b=11.8409(10)$ Å, $c=12.9085(11)$ Å, $\alpha=66.1610(10)°$, $\beta=84.2010(10)°$, $\gamma=83.5160(10)°$, $V=1224.38(18)$ Å^3, $T=293(2)$ K, $Z=2$. CCDC 670360 contains the supplementary crystallographic data for compound **4h** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cifon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK[fax.: (internat.) +44–1223–336–033; e-mail: deposit@ccdc.cam.ac.uk].

