Tetrahedron Letters 50 (2009) 57–59

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient stereoselective synthesis of benzoxazines via copper-catalyzed three-component coupling reactions

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ARTICLE INFO

Article history:
Received 7 August 2008
Revised 15 October 2008
Accepted 17 October 2008
Available online 22 October 2008

Keywords:
Copper catalyst
Benzoxazines
Three-component couplings
One-pot synthesis

ABSTRACT

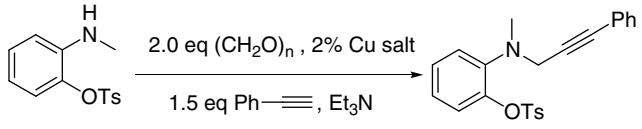
A convenient one-pot synthesis of 1,4-benzoxazines via three-component coupling and subsequent *O*-cyclization is reported. The present reaction provides an efficient protocol to functionalized 1,4-benzoxazine derivatives in good to high yields from aldehydes, amines and alkynes. Furthermore, the *O*-annulation process is completely regio- and stereoselective, only the six-membered rings and its *Z*-isomers were obtained.

Benzoxazines are important scaffolds of natural products and therapeutic agents. Various benzoxazine derivatives have been shown to be biologically active or have pharmacological properties.[1] As a consequence, several methods for the synthesis of benzoxazine derivatives have been reported.[2] However, most of the methods reported were multi-step procedures and lacked generality, and rather complex workup and purification procedure have limited a wider application. Thus, there is a need to develop a general and efficient route for its synthesis. On the other hand, multi-component coupling reactions have attracted much attention in recent years.[3] This strategy allows quick access to structurally diverse compounds from simple starting materials in an environmentally benign fashion. Especially, the three-component coupling of aldehydes, amines and alkynes (A^3 coupling) towards propargylamines mediated or catalyzed by Cu,[4] Ag,[5] Au,[6] Ru/Cu[7] and Ir[8] was disclosed. Other procedures assisted by ionic liquid,[9] supported catalysts,[10] microwave[11] and ultrasound[12] were also reported. Inspired by these developments, we have envisioned that if the arylamines bearing *ortho*-oxygen nucleophile were employed in the A^3 coupling reaction, a sequential intramolecular nucleophilic attack of the oxygen to the triple bond might occur to furnish the benzoxazine derivatives. Herein, we report for the first time the one-pot preparation of the benzoxazine derivatives through A^3 coupling reactions catalyzed by copper.

Initially, we examined the three-component coupling reaction using 2-(methylamino)phenyl-4-methylbenzenesulfonate (**1a**), paraformaldehyde (2.0 equiv) and phenylacetylene (**2a**) (1.5 equiv) with CuCl (2 mol %) as catalyst in dioxane at 110 °C. The reaction afforded the corresponding propargylamine, 2-(methyl(3-phenylprop-2-ynyl)amino)phenyl 4-methylbenzenesulfonate (**4**)[2a] in only 20% yield after 18 h, and no cyclized product could be detected (Table 1, entry 1). When the solvent was changed to DMF, **4** was produced in 43% yield (Table 1, entry 2).

Increasing the reaction temperature, the desired product could be isolated in nearly quantitative yield after 8 h (Table 1, entry 3). Without the addition of triethylamine, the yield was decreased considerably (Table 1, entry 4). The role of Et_3N may be the

Table 1
Screening of reaction conditions for A^3 coupling reactions



1a **4**

Entry	Cu salt	Solvent	Triethylamine (equiv)	Temperature (°C)	Time (h)	Yield[a] (%)
1	CuCl	Dioxane	3.0	110	18	20
2	CuCl	DMF	3.0	110	24	43
3	CuCl	DMF	3.0	130	8	98
4	CuCl	DMF	None	130	8	76
5	None	DMF	3.0	130	8	0
6	CuBr	DMF	3.0	130	8	96
7	CuI	DMF	3.0	130	8	84
8	CuCN	DMF	3.0	130	8	68

[a] Isolated yield.

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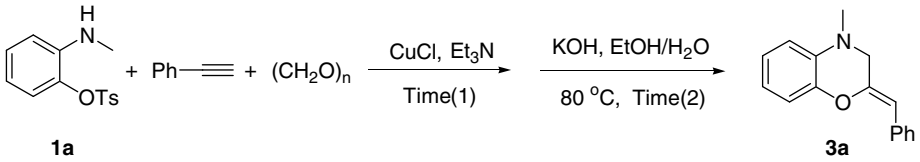
doi:10.1016/j.tetlet.2008.10.080

Table 2
Screening of reaction conditions for the one-pot formation of benzoxazines



1a **3a**

Entry	CuCl (mol %)	Solvent	Temperature (°C)	Time (1) (h)	KOH (equiv)	Time (2) (h)	Yield[a] (%)
1	2	DMF	130	8	10	10	—[b]
2	10	Dioxane	110	20	5	12	34
3	10	Dioxane	110	20	10	12	37
4	10	Dioxane	110	20	19	12	40
5	20	Dioxane	110	20	5	12	36
6	20	Dioxane	110	20	10	12	63
7	20	Dioxane	110	20	19	12	57
8	20	Dioxane	110	20	10	9	85[c]
9	20	Ph_2O	130	20	10	9	68[c]
10	20	DMSO	130	18	10	9	63[c]

[a] Isolated yield, the ratio of amine: phenylacetylene:paraformaldehyde is 1.0:1.5:2.0.
[b] A complex mixture was obtained.
[c] Phenylacetylene (2.0 equiv) and paraformaldehyde (3.0 equiv) were used.

Table 3
Preparation of 1,4-benzoxazine derivatives

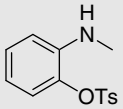
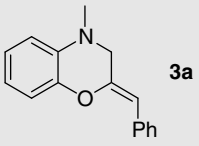
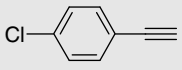
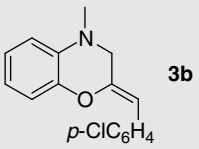
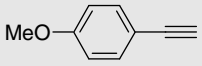
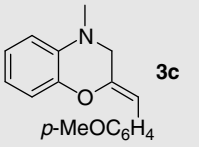
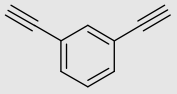
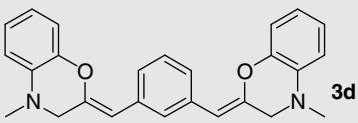
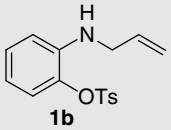
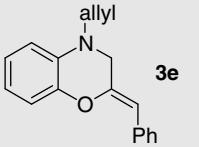
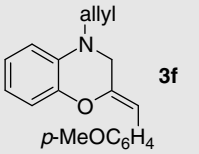
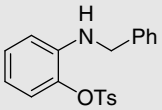
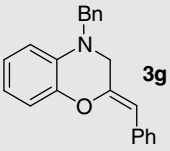
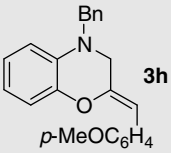
Entry	Amine	Acetylene	Product	Yield[a] (%)
1	 **1a**	 **2a**	 **3a**	85
2	**1a**	 **2b**	 **3b**	71
3	**1a**	 **2c**	 **3c**	73
4	**1a**	 **2d**	 **3d**	30[b]
5	 **1b**	**2a**	 **3e**	74[b]
6	**1b**	**2c**	 **3f**	66[b]

Table 3 (*continued*)

Entry	Amine	Acetylene	Product	Yield[a] (%)
7	 **1c**	**2a**	 **3g**	63[b]
8	**1c**	**2c**	 **3h**	70[b]

[a] Isolated yields.
[b] Reactions were carried out in DMSO at 130 °C.

neutralization of the in situ generated HCl. No reaction occurred in the absence of a copper catalyst (Table 1, entry 5). Other copper(I) salts were less effective as the yields decreased from CuBr to CuI and CuCN (Table 1, entries 6–8). It was clear that the optimized reaction condition for A^3 coupling to propargylamine was to use 2 mol % of CuCl, 3.0 equiv of Et_3N in DMF at 130 °C.

In order to achieve the intramolecular O-cyclization, KOH was then added to the reaction mixture since detosylation usually occurred easily through alkaline hydrolysis. However, only trace of the cyclized product could be detected after 10 h, and a complex mixture was obtained (Table 2, entry 1). Various reaction conditions were examined by changing the amount of catalyst, KOH, reaction temperature and solvents (Table 2, entries 2–10). After a survey of reaction conditions, it was observed that the reaction was best performed using 20 mol % CuCl as the catalyst, dioxane as the solvent at 110 °C followed by the addition of EtOH/H_2O and 10 equiv of KOH at 80 °C, and the desired 1,4-benzoxazine derivative (**3a**) was obtained in 85% isolated yield (Table 2, entry 8). The O-annulation proceeded in a completely regio- and stereoselective manner. In the ^1H NMR spectrum, the chemical shift of the vinylic hydrogen could be seen at 5.34 ppm, this indicates a *Z*-stereochemistry of compound **3a**.[2a] And no seven-membered ring compound was isolated.

Having established an effective three-component coupling reactions and the subsequent intramolecular O-cyclization system, we then synthesized a variety of aminophenyl tosylate (**1**) to explore the scope of the one-pot 1,4-benzoxazine forming reaction. The representative results are shown in Table 3. When *N*-methyl substituted aminophenyl tosylate (**1a**) was used, it reacted with both terminal alkynes bearing an electron-withdrawing group (*p*-ClC_6H_4) and electron-donating substituent (*p*-$MeOC_6H_4$) to give the corresponding 1,4-benzoxines in 71% and 73% yields, respectively (Table 3, entries 2 and 3). However, when *N*-allyl substituted aminophenyl tosylate (**1b**) was employed under the same reaction conditions, the yield of the desired product was rather low. Switching the solvent to DMSO, the *N*-allyl substituted 1,4-benzoxazine (**3e**) was produced in 74% yield (Table 3, entry 5). *N*-Benzyl substituted aminophenyl tosylate (**1c**) is also suitable for this reaction, it reacts with phenylacetylene and *p*-methoxyphenylacetylene to give the corresponding 1,4-benzoxazines **3g** and **3h** in 63% and 70% yields, respectively (Table 3, entries 7 and 8). It was a *Z*-isomer as the chemical shift of the vinylic hydrogen of **3h** was at 5.34 ppm. To our delight, the crystal of **3h** was suitable for single crystal analysis, and its structure was fully characterized by X-ray diffraction study which supported its structure and the *Z*-stereochemisty. Interestingly, the treatment of **1a** with 1,3-diethynylbenzene (**2d**) in DMSO resulted in the bis(benzoxazinyl) derivative **3d** in 30% yield (Table 3, entry 4).

In summary, we have developed an efficient one-pot procedure for the preparation of 1,4-benzoxazine derivatives in good to high yields through copper-catalyzed three-component couplings. This novel process constitutes a straightforward protocol to functionalized 1,4-benzoxazines from simple precursors. Further studies of its scope and efficiency are currently under investigation in our group.

Acknowledgement

We are grateful to the National Natural Science Foundation of China (20572025) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.080.

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