



Concise synthesis of 3,4-dihydro-1,4-benzoxazines by three-component reactions of acyl chlorides, *o*-aminophenols and 1,2-dichloroethane

Yunyun Liu*, Xuwen Chen

College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, PR China



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ABSTRACT

The Cu(OAc)₂-catalyzed three-component reactions of *o*-aminophenols, acyl chlorides and 1,2-dichloroethane (DCE) have been established for the efficient synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines (3,4-dihydro-1,4-benzoxazines). This method features advantages of the one-pot operation enabling *N*-acylation, C–Cl bond amidation and etherification, as well as the structural divergence of the synthesized products.

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1. Introduction

3,4-Dihydro-1,4-benzoxazine is a motif with prevalent presence in natural products and biologically functional molecules.¹ For instance, levofloxacin (**1**) is a clinical anti-inflammatory drug for various symptoms,² and obscurinervidine (**2**) is an important natural aspidosperma alkaloid found in *A. obscurinervium* Azambuja and *A. neblinae* Monachino. (Fig. 1).³ Potential utilization of 3,4-dihydro-1,4-benzoxazines in the treatment of heart disease,⁴ diabetes,⁵ and divergent other biological profiles have also been reported.⁶

Owing to their known and potential merits, 3,4-dihydro-1,4-benzoxazines have received long lasting research interest as target molecules in organic synthesis. Thus, a range of synthetic tactics toward these heterocyclic scaffolds have been developed over the past decade.⁷ For example, the [5 + 1] type of annulation using 2-halo-1,3-dicarbonyl compounds and imines,⁸ the palladium-catalyzed intramolecular etherification,⁹ the stepwise reactions of epoxides with *o*-haloanilines,¹⁰ and the reduction of 2*H*-benzo[*b*][1,4]oxazines¹¹ are typical methods of the category. Regardless these important advances, however, the most

frequently used methods in 3,4-dihydro-1,4-benzoxazine ring construction are the annulation using *o*-aminophenol or its derivatives to incorporate different electrophilic partners such as vicinal dihaloalkanes,¹² imines,¹³ vinyl selenones,¹⁴ α -halo ketones,¹⁵ α -haloesters¹⁶ and vinyl bromides.¹⁷ In most of these known methods, the problems of multi-step operation, prior elaboration on the substrates, utility of noble metal catalyst and/or harsh reaction conditions remain as challenges. Therefore, it is yet highly demanding to develop more alternative synthetic methods which are able to overcome one or more of the present restrictions to afford 3,4-dihydro-1,4-benzoxazines. Herein, we report a three-component approach to synthesize *N*-acyl 3,4-dihydro-1,4-benzoxazines by the copper-catalyzed reactions of *o*-aminophenols, acyl chlorides and 1,2-dichloroethane (DCE). To our best knowledge, the known method for *N*-acyl 3,4-dihydro-1,4-benzoxazine synthesis is the *N*-acylation of prior prepared *NH*-3,4-dihydro-1,4-benzoxazines,¹⁸ this is the first example enabling the synthesis of such products via one-step, three-component operation, which benefits the advantages of the step economy and rapid generation of expanded product diversity of multicomponent reactions.¹⁹

* Corresponding author.

E-mail address: chemliuyunyun@jxnu.edu.cn (Y. Liu).

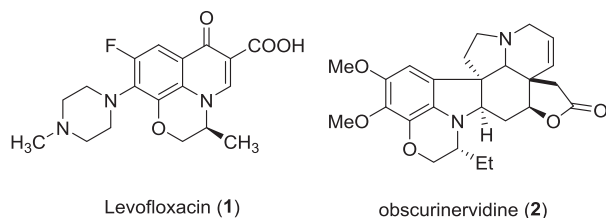


Fig. 1. Valuable 3,4-Dihydro-1,4-benzoxazine derivatives.

2. Results and discussion

To start the investigation, the reaction of *o*-aminophenol **3a**, benzoyl chloride **4a** and DCE (as solvent) **5** was carried out in the presence of $\text{Cu}(\text{OAc})_2$ and Cs_2CO_3 , which provided the 3,4-dihydro-1,4-benzoxazine **6a** with 43% yield (entry 1, Table 1). The target product was not practically provided in the absence of either $\text{Cu}(\text{OAc})_2$ or Cs_2CO_3 (entries 2–3, Table 1), suggesting the crucial importance of both reagents. Utilization of different copper salts, such as CuSO_4 , CuCl_2 , Cu_2O and CuI etc led to no identification of better catalyst (entries 4–8, Table 1). Subsequently, the impact of catalyst loading (entries 9 and 10, Table 1), base species (entries 11–14, Table 1) were screened, but no further improvement on the product yield was achieved. The higher loading of base additive, on the other hand, turned out to be helpful in enhancing the yield of **6a** (entries 15–16, Table 1). The reactions conducted at varied external

Table 1
Optimization of the reaction conditions^a.

Entry	Catalyst	Base	Yield (%) ^b
1	$\text{Cu}(\text{OAc})_2$	Cs_2CO_3	43
2	$\text{Cu}(\text{OAc})_2$	no	0
3 ^c	no	Cs_2CO_3	trace
4	CuSO_4	Cs_2CO_3	35
5	CuCl_2	Cs_2CO_3	31
6	Cu_2O	Cs_2CO_3	0
7	CuI	Cs_2CO_3	12
8	CuCl	Cs_2CO_3	39
9 ^d	$\text{Cu}(\text{OAc})_2$	Cs_2CO_3	25
10 ^e	$\text{Cu}(\text{OAc})_2$	Cs_2CO_3	42
11	$\text{Cu}(\text{OAc})_2$	K_2CO_3	31
12	$\text{Cu}(\text{OAc})_2$	Na_2CO_3	15
13	$\text{Cu}(\text{OAc})_2$	CH_3ONa	27
14	$\text{Cu}(\text{OAc})_2$	Et_3N	32
15 ^f	$\text{Cu}(\text{OAc})_2$	Cs_2CO_3	79
16 ^g	$\text{Cu}(\text{OAc})_2$	Cs_2CO_3	52
17 ^h	$\text{Cu}(\text{OAc})_2$	Cs_2CO_3	61
18 ⁱ	$\text{Cu}(\text{OAc})_2$	Cs_2CO_3	50
19 ^j	no	Cs_2CO_3	79

^a The reactions conditions: **3a** (0.2 mmol), **4a** (0.24 mmol), **5a** (2 mL), catalyst (0.04 mmol), base (0.4 mmol), external heating at 110 °C (reflux) for 12 h; nr = no reaction.

^b Yield of isolated product based on **3**.

^c The product of type **7** was produced in 70% yield (see Table 3).

^d 0.02 mmol $\text{Cu}(\text{OAc})_2$ was used.

^e 0.06 mmol $\text{Cu}(\text{OAc})_2$ was used.

^f 3 equiv. Base was used.

^g 4 equiv. Base was used.

^h The external heating temperature was 100 °C.

ⁱ The external heating temperature was 120 °C.

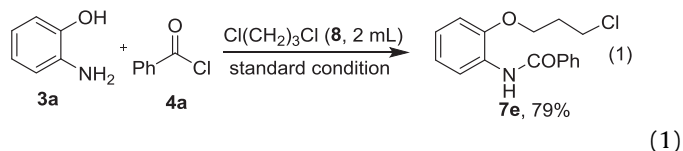
^j The reaction time was 24 h.

temperature confirmed that 110 °C external heating was proper for the reaction (entries 17–18, Table 1). It should be noted that prolonging the reaction to 24 h provided **6a** with high yield even without employing copper catalyst, indicating the major role of the $\text{Cu}(\text{OAc})_2$ was accelerating the reaction rate (entry 19, Table 1).

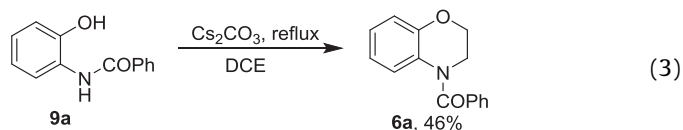
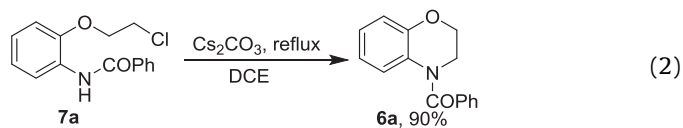
To demonstrate the substrate scope, the reactions employing various acyl halides **4** as well as different *o*-aminophenols **3** were carried out in DCE under the optimized conditions. Generally, the reactions employing all these different substrates gave corresponding products with good to excellent yields (Table 2). The tolerance to functional groups with both electron donating and withdrawing effect in the acyl chloride component was indicated. More notably, heteroaryl functionalized acyl chlorides such as thiophenyl and furyl carbonyl chlorides could also smoothly take part in the reaction (**6g**, **6h**, **6m** and **6n**, Table 2). In addition, the alkenyl-based carbonyl chloride underwent the three-component process to give enamide **6i** with moderate yield. On the other hand, alkyl functionalized carbonyl chlorides such as acetyl chloride was not applicable in such synthesis by the present operation. In addition, when the 1,2-dichloropropane was used to react with **3a** and **4a**, complex mixture was observed and the expect product of type **6** was not obtained.

In further study, we observed that simply lowering the reaction temperature switched the reaction selectivity to provide acyclic amides **7** by using identical substrates. These reactions involving simple acyl chloride amidation and the hydroxyl Williamson etherification also tolerated well to aryl, vinyl and alkyl functionalized acyl chlorides (Table 3).

Additionally, to examine the potential reactivity of the dichloroalkane with longer alkyl chain, the 1,3-dichloropropane **8** was utilized to react with benzoyl chloride and *o*-aminophenol under the standard conditions employed in Table 2, but only the acyclic product **7e** was obtained (Eq (1)).



Successively, to probe the possible intermediate of the reaction, the compound **7a** was heated in the presence of only Cs_2CO_3 , which provided the annulated product **6a** with excellent yield (Eq (2)), supporting that the formation of products **6** involved in the generation of **7** as intermediate. Moreover, the *N*-acyl *o*-aminophenol **9a** was found to provide product **6a** with much lower yield in the absence of copper catalyst, suggesting the $\text{Cu}(\text{OAc})_2$ plays crucial role in accelerating the subsequent transformation after the formation of **9** (Eq (3)).



According to all the reaction results acquired in the experiments, the reaction mechanism in providing products **6** and **7** is proposed as Scheme 1. The original transformation is the base promoted *N*-acylation of *o*-aminophenol **3** providing amide **9**.²⁰

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