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Three-Component Reactions of 2-Alkynylbenzaldoximes and α,β-Unsaturated Carbonyl Compounds with Bromine or Iodine Monochloride

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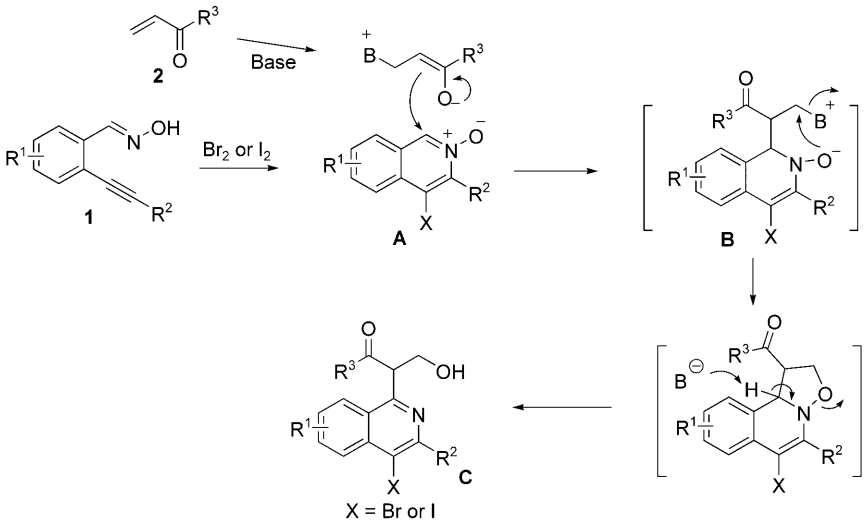
Abstract: The three-component reaction of 2-alkynylbenzaldoximes and α,β-unsaturated carbonyl compounds with bromine or iodine monochloride is described, which generates the unexpected 2-(4-haloisoquinolin-1-yl)ethanol derivatives in good to excellent yields.

Keywords: 2-alkynylbenzaldoximes; bromine; 2-(4-haloisoquinolin-1-yl)ethanols; iodine monochloride; α,β-unsaturated carbonyl compounds

Introduction

Diversity-oriented synthesis has been used as an engine to efficiently generate diverse small molecules in the field of chemical genetics.[1] Among the strategies utilized in diversity-oriented synthesis, multicomponent reactions have emerged as a powerful tool for delivering the molecular diversity needed in combinatorial approaches for the preparation of bioactive compounds.[2] As a "priviliged" scaffold, isoquinoline shows interesting biological properties[3,4] and the prominence of isoquinolines in natural products and biologically active molecules has promoted considerable efforts toward their synthesis.[5–7] For example, Larock and co-workers reported the synthesis of isoquinoline derivatives *via* transition metal-catalyzed cyclization of *ortho*-alkynylarylaldimines.[5] Recently, we are also interested in the methodology development for the construction of isoquinoline and related compounds.[7,8] In order to build up a diverse library of isoquinolines for our subsequent biological assays, the development of novel and efficient routes for a rapid access to functionalized isoquinolines under mild conditions is of high interest.

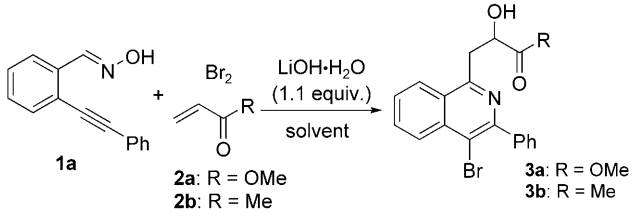
Recently, 2-alkynylbenzaldoxime has been recognized as a versatile building block for the construction of nitrogen-containg heterocycles.[7,9] For instance, Shin and co-workers reported the generation of complex molecules *via* Au-catalyzed internal redox/dipolar cycloaddition tandem reactions of 2-alkynylbenzaldoximes.[9c] We also developed several efficient methods for nitrogen-heterocycle formation starting from alkynylbenzaldoxime.[7] During the reaction process, isoquinoline *N*-oxide was identified as the key intermediate in the reaction of 2-alkynylbenzaldoxime in the presence of suitable Lewis acids or electrophiles. Meanwhile, we have described silver triflate and triphenylphosphine co-catalyzed reactions of 2-alkynylbenzaldehyde, amine, and α,β-unsaturated ketone.[10] In this transformation, an isoquinolinium intermediate was generated for further elaboration. Prompted by these results and the structural similarity between isoquinoline *N*-oxide and isoquinolinium salt, we conceived that 2-alkynylbenzaldoxime might be employed as substrate as well for a similar transformation. The synthetic plan is depicted in Scheme 1. In the pathway shown in Scheme 1, an enolate would be formed *via* reaction of α,β-unsaturated carbonyl compound **2** with Lewis base. Meanwhile, 2-alkynylbenzaldoxime **1** reacted with the electrophile leading to isoquinoline *N*-oxide **A**, which underwent nucleophilic addition to form intermediate **B**. After intramolecular rearrangement, the expected product **C** would be afforded.



Scheme 1. Propose route for the reaction of 2-alkynylbenzaldoxime and an α,β-unsaturated carbonyl compound with bromine or iodine.

Results and Discussion

To verify the practicability of the proposed route as shown in Scheme 1, we decided to pursue this three-component reaction. At the outset, the reaction of 2-alkynylbenzaldoxime **1a**, methyl acrylate **2a**, and bromine was performed in the presence of NaOAc (1.1 equiv.) and DABCO (20 mol%) in THF (Scheme 2). The addition of an inorganic base was essential as HBr scavenger in the reaction process. Fortunately, a product was observed with 10% isolated yield. Structural identification revealed that the compound obtained was the unexpected 2-(4-bromoisoquinolin-1-yl)ethanol **3a** instead of the compound **C** as proposed in Scheme 1. When triphenylphosphine was utilized as a replacement of DABCO as nucleophilic catalyst, the reaction was complicated. No better results were obtained when other Lewis bases were examined in the reaction. Blank experiments indicated that no reaction occurred without the addition of DABCO. Subsequently, but-3-en-2-one **2b** was tested in this reaction as well in the presence of DABCO and NaOAc in THF. Again, 2-(4-bromoisoquinolin-1-yl)ethanol **3b** was generated in 27% yield.

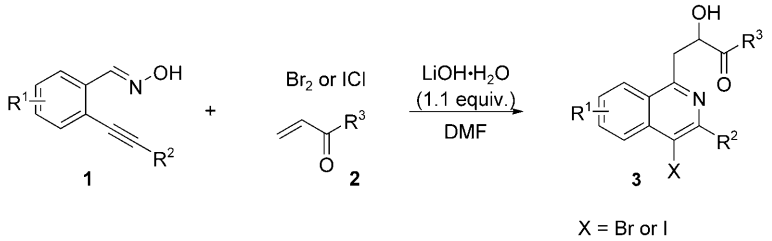


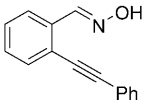
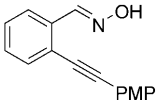
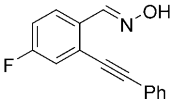
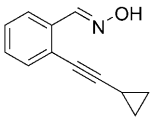
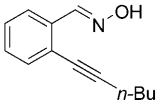
Scheme 2. Initial studies for the reaction of 2-alkynylbenzaldoxime **1a** and α,β-unsaturated carbonyl compound **2a** or **2b** with bromine.

The result could not be improved when 2.0 equiv. of DABCO were added. Since DMF has been well recognized as a Lewis base,[11] thus the reaction was carried out in DMF directly without the addition of DABCO in the presence of different inorganic bases. To our delight, the product **3b** was isolated in 65% yield when $LiOH·H_2O$ (1.1 equiv.) was employed in the reaction. Further screening of solvents displayed inferior results. With this result in hand, we re-surveyed the three-component reaction of 2-alkynylbenzaldoxime **1a**, methyl acrylate **2a**, and bromine in DMF in the presence of $LiOH·H_2O$. As expected, the corresponding product **3a** was furnished in 80% yield.

Using the mild conditions (1.1 equiv. of $LiOH·H_2O$, DMF), the scope of this three-component reaction was examined, and the results are shown in Table 1. For the reactions of 2-alkynylbenzaldoxime **1a**, not only acrylates were found to be workable with bromine or iodine monochloride, but also α,β-unsaturated ketones were good partners in the transformation. For instance, reaction of 2-alkynylbenzaldoxime **1a**, *n*-butyl acrylate **2d** with bromine afforded the corresponding isoquinoline **3e** in 76% yield (entry 5). When pent-1-en-3-one **2e** was utilized as a replacement in the reaction, the product **3f** was generated in 70% yield (entry 6). Besides bromine, iodine monochloride was a good substrate as well in this transformation, which furnished the product **3g** in 65% yield (entry 7). However, diminished reactivity was observed when iodine was used (data not shown in Table 1). Other 2-alkynylbenzaldoximes were tested meanwhile. Compound **1b** reacted with ethyl acrylate **2c** and bromine leading to the product **3h** in 70% yield (entry 8). A lower yield was observed when iodine monochloride was used in the reaction (entry 9). Three-component reactions of fluoro-substi-

Table 1. Three-component reactions of 2-alkynylbenzaldoxime **1** and α,β-unsaturated carbonyl compound **2** with bromine or iodine monochloride.



Entry	Compound **1**	R^3	X_2	Yield [%][a]
1	**1a** 	OMe (**2a**)	Br_2	80 (**3a**)
2	**1a**	Me (**2b**)	Br_2	65 (**3b**)
3	**1a**	OEt (**2c**)	Br_2	80 (**3c**)
4	**1a**	OEt (**2c**)	ICl	86 (**3d**)
5	**1a**	O-*n*-Bu (**2d**)	Br_2	76 (**3e**)
6	**1a**	Et (**2e**)	Br_2	70 (**3f**)
7	**1a**	Et (**2e**)	ICl	65 (**3g**)
8	**1b** 	OEt (**2c**)	Br_2	70 (**3h**)
9	**1b**	OEt (**2c**)	ICl	48 (**3i**)
10	**1b**	Et (**2e**)	Br_2	81 (**3j**)
11	**1c** 	OEt (**2c**)	Br_2	80 (**3k**)
12	**1c**	OEt (**2c**)	ICl	60 (**3l**)
13	**1c**	Et (**2e**)	Br_2	71 (**3m**)
14	**1d** 	OEt (**2c**)	Br_2	63 (**3n**)
15	**1d**	OEt (**2c**)	ICl	47 (**3o**)
16	**1d**	Et (**2e**)	Br_2	61 (**3p**)
17	**1e** 	OEt (**2c**)	Br_2	58 (**3q**)

[a] Isolated yield based on 2-alkynylbenzaldoxime **1**. PMP = *p*-methoxyphenyl.

tuted 2-alkynylbenzaldoxime **1c** proceeded smoothly as well, which generated the isoquinoline products in good yield (entries 11–13). In addition, the structure of **3m** was verified by X-ray diffraction analysis (Figure 1). Moreover, substrates **1** with alkyl groups (cyclopropyl, *n*-butyl) attached on the triple bond were examined, and all reactions worked well to give rise to the products in moderate yields (entries 14–17).

The possible mechanism is proposed in Scheme 3. We reasoned that 2-alkynylbenzaldoxime **1** would be cyclized to isoquinoline *N*-oxide **A** in the presence of electrophile (bromine or iodine monochloride). The subsequent nucleophilic addition of Lewis base to isoquinoline *N*-oxide **A** would afford intermediate **D**. Intramolecular removal of benzylic hydrogen resulted in a carbon anion, which then attacked the α,β-unsaturated carbonyl compound **2** to generate the intermediate **E**. Subsequently, an oxaziridine **F** would be formed with release of the Lewis base. After intramolecular rearrangement, the 2-(4-haloisoquinolin-1-yl)ethanol **3** would be obtained. In order to provide the evidence that base played an important role in this transformation, reaction of isoquinoline *N*-oxide

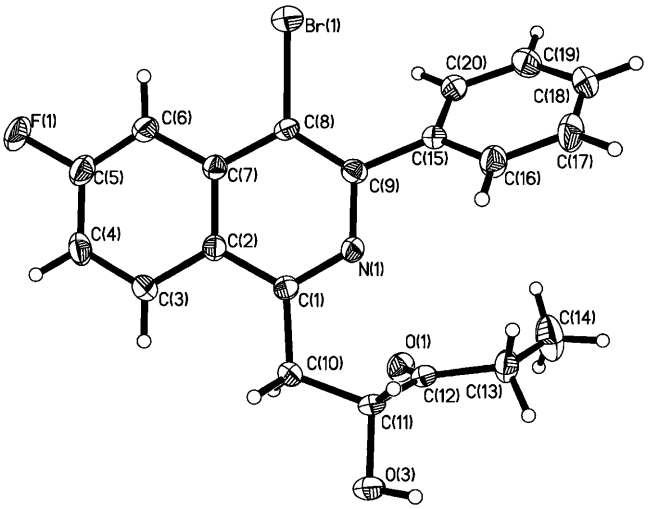


Figure 1. ORTEP Illustration of compound **3m** (30% probability ellipsoids).

A1 (R^1=H, R^2=Ph, X=Br) with but-3-en-2-one **2b** was tested (for details, please see Supporting Information). The corresponding product **3b** could be afforded when the solvent acted as a Lewis base in the reaction (DMF: 75%, DMA: 68%, NMP: 48%). In addition, inferior results were obtained when DABCO was added in the reaction as a base in different solvents.

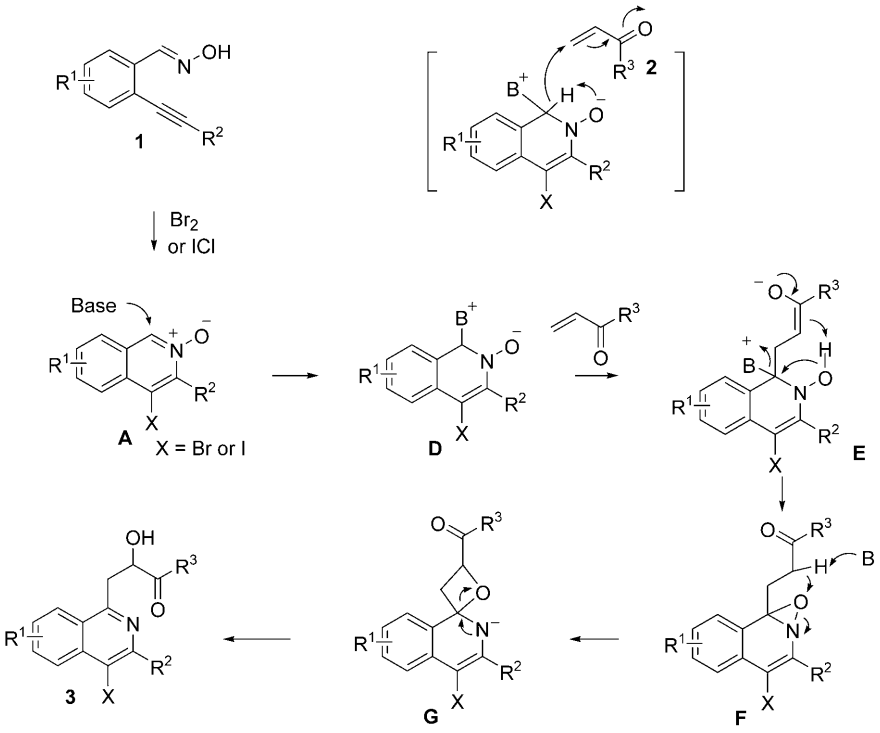
Conclusions

In conclusion, we have described an efficient three-component reaction of 2-alkynylbenzaldoxime and α,β-unsaturated carbonyl compound with bromine or iodine monochloride under mild conditions. This reaction proceeded smoothly to generate the unexpected 2-(4-haloisoquinolin-1-yl)ethanol derivatives in good to excellent yields. Further studies by adaptation of the methodology for isoquinoline alkaloids synthesis are currently in progress, and the results will be reported in due course.

Experimental Section

General Procedure for Three-Component Reactions of 2-Alkynylbenzaldoxime 1, α,β-Unsaturated Carbonyl Compound 2 with Br_2 or ICl

2-Alkynylbenzaldoxime **1** (0.2 mmol) was added to a solution of Br_2 or ICl in dichloromethane (0.4 mmol mL^{-1}, 0.5 mL). The solution was stirred at room temperature for 10 min, then LiOH·H_2O (1.1 equiv.) was added. Subsequently, DMF (1.5 mL) and α,β-unsaturated carbonyl compound **2** (4.0 equiv.) were added and the mixture was stirred at room temperature. After completion of reaction as indicated by TLC, the mixture was diluted with ethyl acetate (5.0 mL) and quenched with water (5.0 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified



Scheme 3. Possible mechanism for reaction of 2-alkynylbenzaldoxime **1** and α,β-unsaturated carbonyl compound **2** with electrophile.

by flash chromatography column on silica gel to provide the desired product **3**.

Data for methyl 3-(4-bromo-3-phenylisoquinolin-1-yl)-2-hydroxypropanoate (3a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.69 (s, 3H), 3.77 (dd, $J = 5.3$, 16.0 Hz, 1H), 3.83 (dd, $J = 5.3$, 16 Hz, 1H), 4.86 (dd, $J = 4.1$, 5.5 Hz, 1H), 5.07 (br, 1H), 7.43–7.50 (m, 3H), 7.66–7.72 (m, 3H), 7.83 (t, $J = 7.3$ Hz, 1H), 8.14 (d, $J = 8.3$ Hz, 1H), 8.37 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 36.4$, 52.2, 69.7, 117.2, 124.9, 127.3, 127.8, 127.9, 128.1, 128.4, 129.9, 131.8, 136.1, 140.2, 150.1, 156.7, 173.9; HR-MS: $m/z = 386.0416$, calcd. for $C_{19}H_{16}BrNO_3$ ($M+H^+$): 386.0392. (For details, please see Supporting Information)

Crystallographic data for the structure **3m** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 757863. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) (+44)-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

Supporting Information

Experimental procedures, characterization data, as well as ^{1}H and ^{13}C NMR spectra of compounds **3** are available as Supporting Information.

Acknowledgements

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