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$CuBr_2$-promoted intramolecular bromocyclization of N-allylamides and aryl allyl ketone oximes

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ABSTRACT

A new and easy-to-perform route to 2-oxazolines amd isoxazolines was reported. Using $CuBr_2$ as both the bromide source and the reaction promoter, bromocyclization of N-allylamides and allyl ketone oximes proceeded readily, leading to oxazolines and isoxazolines in good to excellent yields.

1. Introduction

Oxazoline and isoxazoline moieties[1] are important subunits in natural products[2] and synthetic bioactive compounds.[3] They are also frequently found as key structures in important pharmaceuticals.[4] In addition, oxazoline moieties have been found widespread application as important chiral ligands and chiral auxiliaries in asymmetric synthesis.[5] For these reasons, significant efforts have been made to develop new and efficient methods for the formation of oxazolines.[6] Traditionally, oxazolines were prepared from carboxylic acids and β-amino alcohols under water removal or other dehydrative conditions.[7] However, application of such methods was limited due to the harsh reaction conditions. The breakthrough was made when Vorbrüggen et al. developed the cyclization of carboxylic acids with amino alcohols, amino mercaptans or diamines in the presence of triphenylphosphine, CCl_4 and tertiary bases.[8] Slow addition of either triphenylphosphine or CCl_4 to the reaction mixture led to the formation of oxazolines in high yields under mild conditions.[9] Reactions of β-amino alcohols with other carboxylic acid derivatives such as carboxylic esters,[10] nitriles,[11] or trimethylorthobenzoate[12] also provided the oxazolines in good yields.

Recently, electrophile-induced halocyclization of unsaturated amides also emerged as important methods for the formation of different 2-oxazolines. Using N-chlorosulfonamide salts such as chloramine-T as the electrophilic chlorine precursor, chlorocyclization of unsaturated amides gave the corresponding oxazolines in high yields.[13] In the presence of a suitable chlorine source, $(DHQD)_2PHAL$-catalyzed asymmetric chlorocyclization of unsaturated amides furnished chiral oxazolines in high yields and high ee's.[14] Using NBS as bromine source, chiral phosphine-catalyzed bromocyclization of allylic amides provided the chiral oxazolines in high ee's.[15] Iodine,[16] NIS,[17] I(III),[18] or (diacetoxyiodo)benzene[19]-promoted iodocyclization of unsaturated carboxamides also gave the functionalized oxazolines in high yields. In the presence of a suitable oxidant, iodoarene could be in situ oxidized to hypervalent I(III), and I(III)-catalyzed cyclization of unsaturated amides also provided oxazolines in high yields.[20]

It is our purpose to prepare biologically interesting heterocycles with easily accessible starting materials. Herein, we wish to report a new method for the preparation of oxazolines and isoxazolines under mild conditions.

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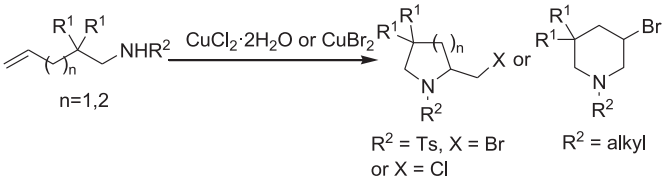
2. Results and discussion

Recently, we have shown that copper(II) could promote intramolecular bromo- and chloroamination[21] of unfunctionalized olefins under mild conditions, leading to 2-halomethylpyrrolidines or 3-halopiperidines in good to excellent isolated yields (Scheme 1). Preliminary study of the mechanism indicated that the reaction generally followed an intramolecular amination mechanism with the formation of Cu–N intermediate and the subsequent C=C double bond activation upon copper coordination.[22]

Intramolecular bromoxygenation of N-allyl benzamide **1a** was then trialed to extend the application scope of this Cu(II)-promoted halocyclization reaction.[23] Compound **1a** was chosen based on the assumption that successful intramolecular bromoxygenation of the substrate would lead to oxazolines that could be used as important structures in both organic chemistry and medicinal chemistry. The model reaction was carried out in acetonitrile with 1 equiv of $CuBr_2$ as both the reaction promoter and the bromide source. To our delight, 40% of substrate **1a** was converted to the desired 5-bromomethyl-2-phenyl-4,5-dihydrooxazole **2a** after reacting for 24 h at room temperature. The reaction was then studied in details to get further information. The reactions were carried out in the presence of different amount of $CuBr_2$ at different temperatures. The results are summarized in Table 1.

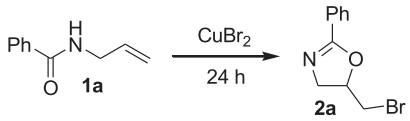
As shown in Table 1, the reaction did not take place in the absence of $CuBr_2$ (Table 1, entry 2), and the amount of $CuBr_2$ was very crucial for the reaction. The use 1 equiv of $CuBr_2$ was not successful, and only 40% of the substrate was converted at room temperature (Table 1, entry 1). Further increasing the amount of $CuBr_2$ led to significant increase of the substrate conversion (Table 1, entries 5–8). However, elevating the reaction temperature could not significantly increase the conversion of the substrate (Table 1, entries 3–4). Acetonitrile was the most suitable solvent among the reaction media tested (entry 6 vs. entries 9–16), and the reaction proceeded readily at room temperature in the presence of 3 equiv of $CuBr_2$.

After the validation of the Cu(II)-promoted reaction, development of a catalytic version of the reaction was tested. Based on our understanding of Cu(II) promoted halocyclization reaction, an oxidant would be applied to regenerate Cu(II) from Cu(I) formed during the reaction,[21,24] and *tert*-butyl peroxybenzoate was found to be the most suitable oxidant for the reaction. Different bromide sources were tested,[25] and TMSBr gave the most promising result (Table 2). In the absence of $CuBr_2$, only small amount of substrate was converted (Table 2, entries 1 and 2). This background reaction may be caused by Br_2 which was formed via oxidation of Br^- in the presence of oxidant. When 10 mol% of $CuBr_2$ was used, the substrate **1a** was completely converted (Table 2, entry 4). However, considerable amount of dibrominated product **2a'** was also obtained irrespective of whatever bromine source was used. When NaBr or KBr was used as the bromide source, only 20% of the substrate was converted to product **2a** (Table 2, entries 6 and 7). Pyridine hydrobromide salt was also tested as the bromide source, but increased formation of dibromation product **2a'** was observed (Table 2, entry 8) possibly due to the increase of background



Scheme 1. Cu(II)-promoted haloamination of unfunctionalized olefins.

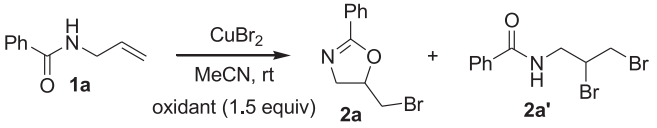
Table 1
$CuBr_2$-promoted intramolecular bromoxygenation reaction of N-allylbenzamide **1a** under different conditions.[a]



Entry	$CuBr_2$ (equiv)	Temp. (°C)	Solvent	Conversion[b]
1	1	rt	MeCN	40%
2	–	rt	MeCN	NR[c]
3	1	40	MeCN	46%
4	1	80	MeCN	50%
5	1.5	rt	MeCN	65%
6	2	rt	MeCN	88%
7	2.5	rt	MeCN	92%
8	3	rt	MeCN	>95%
9	2	rt	acetone	NR[c]
10	2	rt	toluene	NR[c]
11	2	rt	THF	trace
12	2	rt	DMF	trace
13	2	rt	dioxane	trace
14	2	rt	$CHCl_3$	42%
15	2	rt	DCM	76%
16	2	rt	DCE	87%

[a] The reactions were carried out with 1 mmol of **1a** and 50 mL of solvent.
[b] Determined by crude ^1H NMR analysis.
[c] NR = no reaction.

Table 2
$CuBr_2$-catalyzed intramolecular bromoxygenation reaction of N-allylbenzamide **1a** under different conditions.[a]



Entry	$CuBr_2$ (equiv)	Bromide source (1.5 equiv)	Conversion[b] (**2a**:**2a'**)
1	NO	TMSBr	NR[c,d]
2	NO	TMSBr	11%
3	10%	TMSBr	10%[d]
4	10%	TMSBr	>99% (7:1)
5	10%	LiBr	87% (4:3)
6	10%	NaBr	20%
7	10%	KBr	21%
8	10%	PyHBr	95% (2:1)
9	5%	TMSBr	>99% (7:1)
10	2.5%	TMSBr	>99% (5:1)

[a] Reaction conditions: substrate: 1 mmol, reaction time = 12 h, solvent = CH_3CN (50 mL), oxidant = *tert*-butyl peroxybenzoate (1.5 equiv).
[b] Determined by crude ^1H NMR analysis.
[c] NR = no reaction.
[d] In the absence of oxidant.

reaction. Similarly, further decreasing the amount of catalyst also led to the background formation of **2a'** (Table 2, entries 9 and 10). Considering the ease of operation and product separation of stoichiometric amount of $CuBr_2$-promoted reaction, development of Cu(II)-catalyzed reaction was not further pursued at this stage, and the reactions were finally carried out at room temperature in the presence of 3 equiv of $CuBr_2$.

Next, different aryl carboxamides **1b**-**1q** were subjected to the reaction to extend the scope of the substrates. The results are summerized in Table 3. As these results showed, 5-bromomethyl-2-aryloxazolines could be obtained in good to excellent isolated yields. Electronic effects of the substituents on the aryl groups