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CuX_2-mediated oxybromination/aminochlorination of unsaturated amides: synthesis of iminolactones and lactams†

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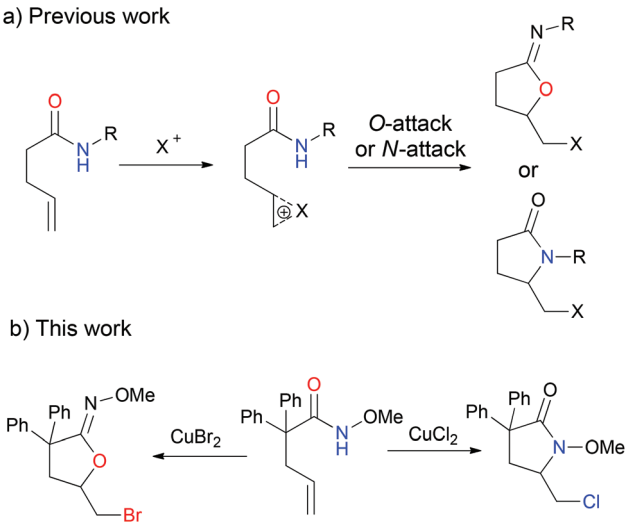
We report herein a CuX_2-mediated halocyclization of γ,δ-unsaturated amides for the synthesis of functionalized iminolactones and lactams respectively under mild reaction conditions. Mechanism studies indicated that *N*-attack cyclization was *via* a radical route while oxycyclization was *via* a nucleophilic attack on the activated C═C bond.

Intramolecular halo-heteroatom cyclization of unactivated olefins allows access to the synthesis of functionalized heterocyclic compounds (lactones, ethers, lactams, amines, *etc.*). Among the heterocycles, lactones and lactams are not only present in many biologically active natural products and pharmaceutical agents[1,2] but also serve as intermediates in organic synthesis. Classical methods for synthesis of vicinal halogenated iminolactones (or lactones) or lactams *via* halogenation of unsaturated amides usually involve activation of the C═C double bond with halonium ion sources such as Br_2, NBS, NCS or NIS, followed by nucleophilic *O*-attack or *N*-attack onto the halonium intermediates[3] (Scheme 1a). The *O*-attack or the *N*-attack ring closure of unsaturated amides is typically subjected to the structures of the amides and (or) the natures of the electrophiles.[3a]

Palladium-catalyzed intramolecular cyclization of unactivated olefins provides another powerful tool for the formation of functionalized heterocycles, frequently, using CuX_2 as the oxidant and/or halogen source.[4] Very recently, we have reported Pd-catalyzed synthesis of vicinal chlorinated and brominated isoxazolines from unsaturated oximes using CuX_2 as the oxidant and halogen source.[5] It seems that, in the Pd(II)–CuX_2 system, the Pd catalysis is requisite in such halocyclization reactions. However, in some cases, noble metals such as palladium are not required for activation of the double bond. Li and co-workers developed the CuX_2-mediated intramolecular haloamination of 4-penten-1-amines and 5-hexen-1-amines for preparation of pyrrolidines and piperidines.[6] As Pd(II), Cu(II) could play a similar role in activation of the C═C double bond through coordination.[6,7] Alternatively, as an oxidant, the copper(II) reagent could also initiate generation of nitrogen-centered radicals, followed by aminocyclization for synthesis of N-heterocycles.[8] Iron-catalyzed haloamination of olefins *via* an iron–nitrenoid intermediate represents another approach to construct heterocycles.[9]



Scheme 1 Halocyclization of unsaturated amides.

Numerous examples were reported to predominately give either iminolactones (or lactones) or lactams as final products from unsaturated amides *via* an electrophilic *O*-attack or *N*-attack pathway.[3] In fact, this dual reactivity is controllable by changing the reaction conditions and/or the structure of the amides.[3a] However, competitive *O*-attack and *N*-attack cyclization of the same substrate to afford iminolactone and lactam

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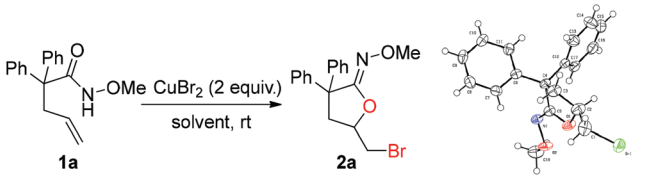
Table 1 Optimization of reaction conditions[a]



1a 2a

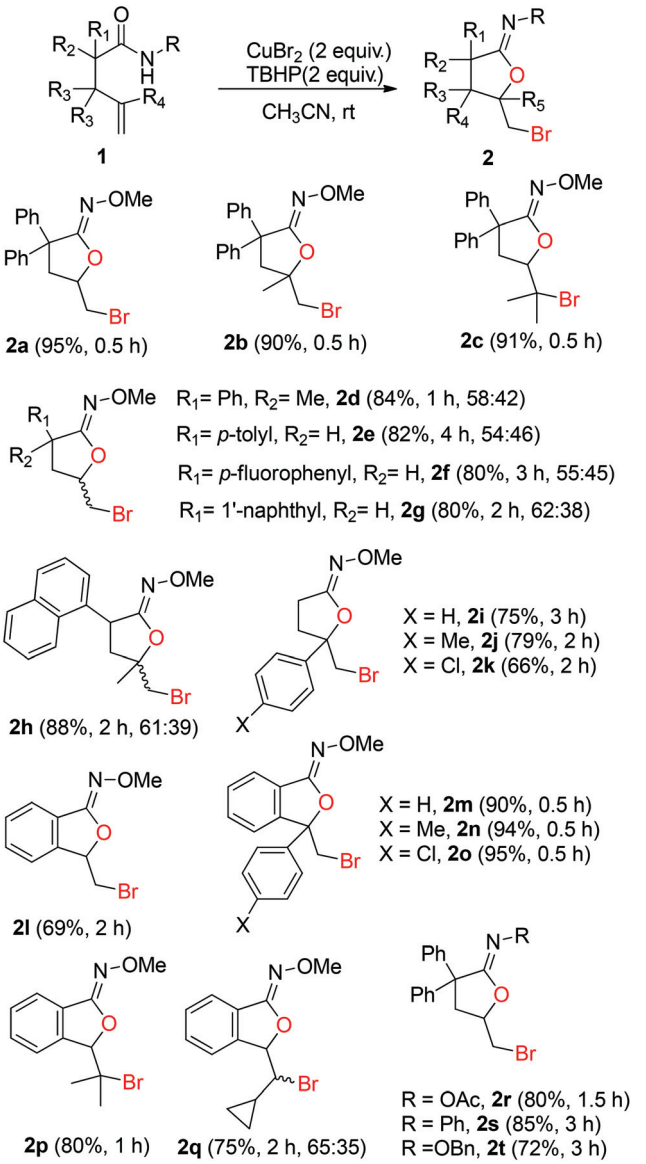
Entry	Oxidant	Solvent	Time[b]	Yield[c] (%)
1	—	CH_3CN	5	78
2	$K_2S_2O_8$	CH_3CN	2	90
3	$KHSO_5$	CH_3CN	2	86
4	H_2O_2	CH_3CN	1	78
5	TBHP	CH_3CN	0.5	95
6	$^tBuOOBu^t$	CH_3CN	1	79
7	CAN	CH_3CN	1	80
8	TBHP	CH_2Cl_2	2	81
9	TBHP	AcOEt	2	85
10	TBHP	Acetone	0.5	89
11	TBHP	THF	1	90
12	TBHP	Toluene	2	75
13[d]	TBHP	CH_3CN	1	84
14[e]	TBHP	CH_3CN	0.5	83

[a] **1a** (0.10 mmol), $CuBr_2$ (0.20 mmol) in 1 mL solvent; oxidant (0.20 mmol). [b] Based on entire conversion. [c] Isolated yield. [d] TBHP (1 equiv., 0.10 mmol). [e] $CuBr_2$ (1 equiv., 0.10 mmol).

respectively depending on reaction conditions has only been observed in few cases.[10] In this paper, we would like to report a CuX_2-mediated synthesis of vicinal brominated iminolactones or chlorinated lactams by halocyclization of unsaturated amides (Scheme 1b).

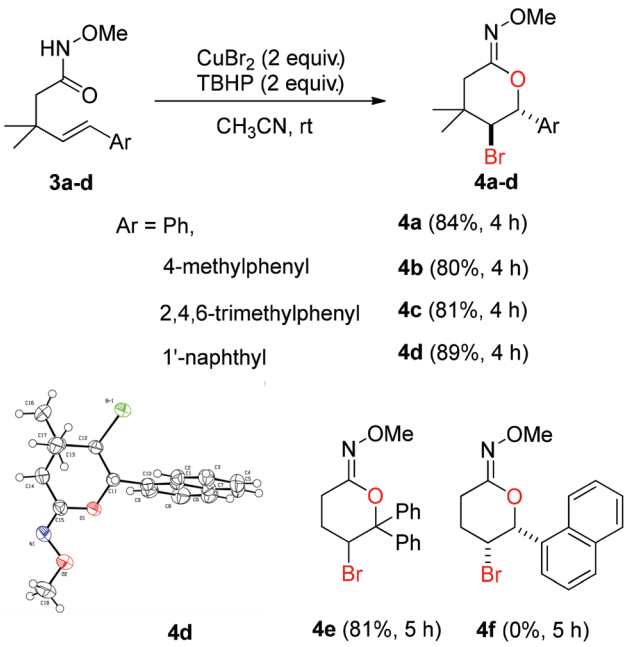
We carried out the optimization of this room-temperature $CuBr_2$-mediated bromocyclization of **1a** by screening an oxidant and an organic solvent (Table 1). Oxidant additives which could recycle the by-product CuBr back to $CuBr_2$ were first assessed in acetonitrile (entries 2–7). In terms of chemical yield and reaction rate, *tert*-butyl hydroperoxide (TBHP) was determined as the best one (entry 5).[11,12] The solvent screen showed that acetonitrile was better than other solvents (entries 8–12), probably due to the fact that $CuBr_2$ has best solubility in CH_3CN. Reducing either the amount of TBHP or $CuBr_2$ resulted in lower yields (entries 13 and 14).

With the optimized reaction conditions established, we first explored the substrate scope for 5-*exo* cyclization of γ,δ-unsaturated amides. As depicted in Scheme 2, a variety of vicinal brominated 5-membered iminolactones **2a–t** were readily obtained in good to excellent yields within 4 hours. With regard to stereochemistry of the cyclization, we studied the α-position substituent effect though the diastereoselectivities were poor (**2d–2h**). To exclude the possibility of the radical mechanism,[8] the reaction of **1q** (a mixture of *E*, *Z* isomers) which was designed as the radical probe[13] led to **2q** as the product with the cyclopropyl group intact. It should be noted that addition of TEMPO (2.0 equiv.) did not show a remarkable effect in the reaction of **1b**. The product **2b** was still isolated in 80% yield.



Scheme 2 Scope for 5-*exo* oxybromocyclization. Reaction conditions: amide **1** (0.10 mmol), $CuBr_2$ (0.20 mmol), TBHP (0.20 mmol), CH_3CN (1 mL), rt. Diastereomeric ratios determined by ^1H NMR of crude products. Isolated yields based on **1**.

We then moved on to study the cyclization of 5-arylpent-4-enamides **3a–3f** under the optimized reaction conditions (Scheme 3). As expected, Wacker-type 6-*endo* cyclization was observed and furnished the desired products (**4a–4e**) in satisfactory yields. In the examples of *E*-olefin substrates (**3a–3d**), they were readily converted to *anti*-form 6-membered iminolactones (**4a–4d**) as the products. It was confirmed by the crystal structure of **4d**.[12] These results also showed that bromocyclization was a nonradical process. However, the reaction of *Z*-olefin substrate **3f**, which was supposed to give *syn*-form 6-membered iminolactone, resulted in an undesired complex mixture, probably due to higher activation energy to form the *cis*-Cu adduct intermediate.



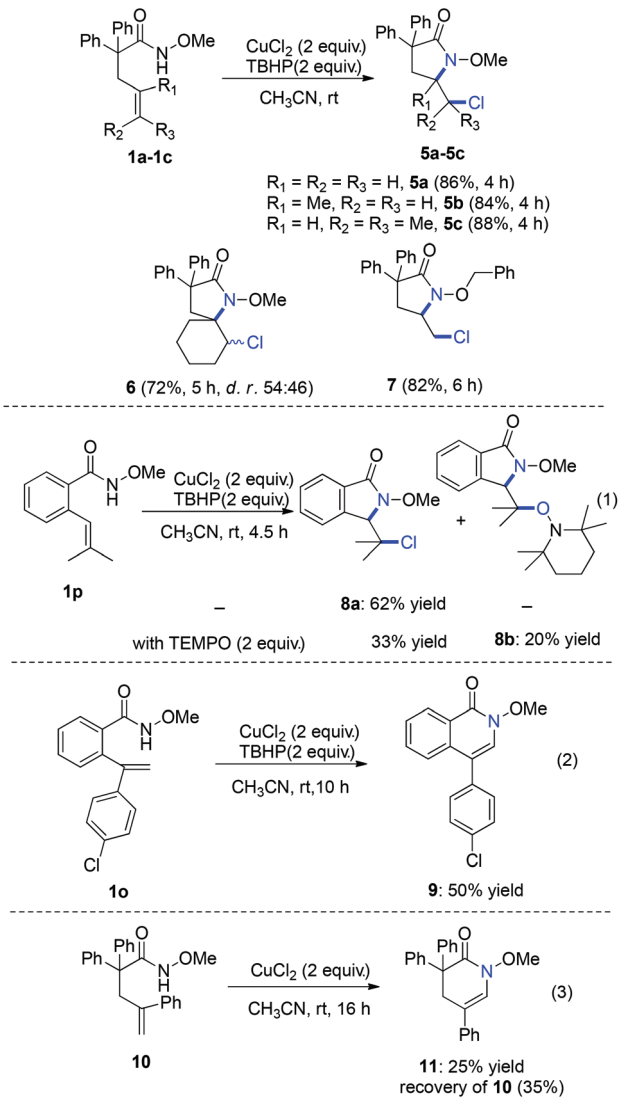
Scheme 3 6-*endo* cyclization of unsaturated amides.

We further carried out the reactions of the unsaturated amides **1** by simply replacing copper(II) bromide with copper(II) chloride (Scheme 4). In contrast to $CuBr_2$-mediated formation of vicinal brominated iminolactones, vicinal chlorinated lactams (**5a–5c** and **6–8a**) were readily provided in satisfactory yields. It should be noted that the diastereomeric ratio of **6** is nearly 1 : 1. To probe the mechanism of this $CuCl_2$-mediated aminocyclization, a classical carbon radical scavenger TEMPO was added into the reaction of **1p** (eqn (1)). It was found that the TEMPO adduct **8b** was isolated in 20% yield, and the yield of **8a** dropped. We did find that the transformation of **1o** gave isoquinolinone **9** which might be formed *via* 6-*endo* nitrogen-centered radical cyclization[14] followed by elimination of H^+ or HCl (eqn (2)). Similarly to the cyclization of **1o**, **10** was able to be converted to lactam **11** (eqn (3)).

Based on the above results, a proposed reaction mechanism is shown in Fig. 1. The Wacker-type pathway involves the activation of the C=C bond with $CuBr_2$, followed by nucleophilic *O*-attack and reductive elimination[15] to afford vicinal brominated iminolactones. On the other hand, a radical process takes place in $CuCl_2$-promoted aminocyclization in which an aminocupration intermediate may be involved.[8]

Conclusions

In conclusion, we have developed a $CuBr_2$-mediated oxybromination and a $CuCl_2$-mediated aminochlorination of γ,δ-unsaturated amides with the assistance of TBHP, and thus provided access to both iminolactones and lactams under mild reaction conditions. This competitive *O*-attack and *N*-attack cyclization



Scheme 4 Synthesis of lactams.

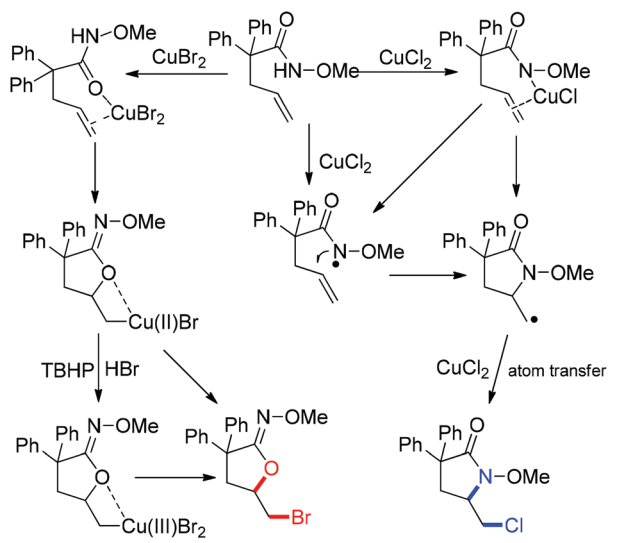


Fig. 1 Proposed mechanism.

depending on the reagent will show utility in organic synthesis.

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