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A Copper Halide Promoted Regioselective Halogenation of Coumarins Using N-Halosuccinimide as Halide Source

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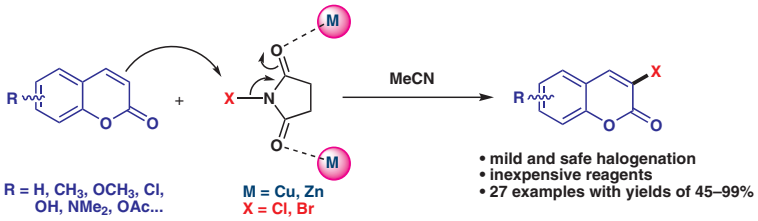

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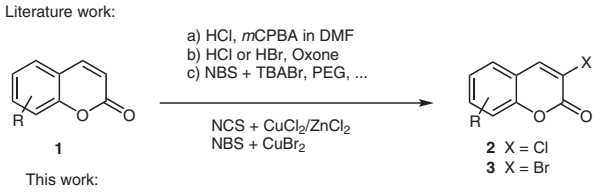
Abstract A safe, convenient, and regioselective synthesis of 3-halo coumarins using a metal halide (CuX_2 alone or with ZnX_2) promoted halogenation with *N*-halosuccinimide (NXS) as halide source is reported. The synthesis involved the steady in situ generation of highly reactive positive halogen (X^+) by the coordination of copper or zinc with the *N*-halosuccinimide and subsequent electrophilic aromatic substitution of the electron-deficient coumarins. This procedure works well also for the halogenation of less electron-rich naphthoquinones, flavones, and methoxypsoralen in moderate to quantitative yields. This protocol features simple experimental conditions using readily available inexpensive reagents and provides a convenient approach to the chlorination or bromination of some useful heteroaromatic compounds.

Key words coumarin, halogenation, aryl halide, electrophilic aromatic substitution, *N*-halosuccinimide

The halogenation of aromatic and heteroaromatic compounds is one of the most valuable synthetic transformations. The halogenated derivatives can be used as bioactive compounds and lead to new pharmaceuticals entities.[1] They also serve as important synthetic precursors for transition-metal-catalyzed cross-couplings.[2] Traditional halogenation protocols rely on the usage of toxic halogen X_2(Cl_2, Br_2) which could cause serious environmental problems. The replacement of X_2 by other safe reagents is ubiquitous to solve this problem,[3] among which, *N*-halosuccinimide (NXS, X = Cl, Br, I) is quite popular and practical, which, depending on the reaction conditions, can steadily release the halide 'cation' (X^+) or radical ($X^•$) for the halogenation reaction. The *N*-bromosuccinimide (NBS) works well with some electron-rich arenes.[4] However, it is difficult to brominate the electron-poor arenes, and the chlorination with the less reactive *N*-chlorosuccinimide (NCS) is even more difficult. Therefore, the halogenations of rather electron-deficient heteroaromatics remain a formidable synthetic task. Herein, we wish to report the copper activation of NXS for both chlorination and bromination of coumarin derivatives.

Coumarin (2*H*-chromen-2-one) can act as a privileged medicinal scaffold, which exhibits a broad spectrum of biological activities[5] such as anticancer,[6] antioxidant,[7] anti-inflammatory,[8] and so on. Besides these pharmaceutical applications, some coumarin derivatives can be used as fluorescent labels for bioimaging[9] and solar cell sensitizers.[10] These useful chemicals can often be synthesized via the transformations of halogenated coumarins. Although halogenated coumarins can be accessed through the cyclization from halogen-containing starting materials,[11] the direct halogenation of coumarin itself is evidently a more straightforward and economic pathway that benefits from the abundance of commercial availability of the starting materials.

However, it is known that coumarins are usually difficult to be halogenated for their electron-deficient character. In the literature, halogenation of coumarins is often accomplished by some highly reactive reagents (Scheme 1, path a, b). For example, the chlorination of coumarins usually needs to use such reagents as HCl/*m*CPBA in DMF (path a)[12] or HCl with oxone (path b).[13] The bromination can also be accomplished using HBr/Oxone (path b).[8,13] However, large excess of oxidant is needed to generate reactive X^+ from HX, which limited the reaction scope to substrates carrying oxidant-tolerable functional groups, and multichlorinated side products are often formed under the reaction conditions.



Scheme 1 The halogenation of coumarins from the literature and this work

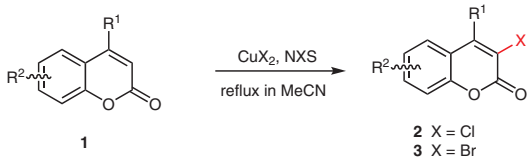
There are some reports on the bromination of coumarins with electron-donating groups such as OH or NH_2, using NBS together with Brønsted acid activators or in a highly polar solvent, such as NBS in the presence of sulfonic acid functionalized silica gel,[14] NH_4OAc,[15] in molten TBABr,[16] or in polyethylene glycol (Scheme 1, path c),[17] etc. The successful bromination can be attributed to both the activation of NBS and the electron-rich nature of the substrates. The lack of more efficient activation method excluded the further application of these reactions to inactive coumarins, not to mention the chlorination by the less active NCS.

Recently, there are a few reports on the Lewis acid activation of *N*-iodosuccinimide (NIS) for the iodination of electron-rich arenes. Sutherland and coworkers[18] reported a silver ($AgNTf_2$) catalyzed iodination; Romo's group[19] and Frontier's group[20] used indium(III) and gold(I) complexes, respectively, for the activation of NIS. However, the Lewis acid activation of NCS and chlorination of electron-deficient arenes is seldom reported to our knowledge. Inspired by this strategy, we set out to search for an inexpensive Lewis acid promoter to activate NCS or NBS for the halogenation of the less electron-rich coumarins.[21] Herein, we report a safe, convenient, and regioselective 3-halogenation protocol of coumarins promoted by CuX_2/ZnX_2 with the corresponding NXS as halide source.

In the beginning, control experiment for the chlorination reaction was conducted by heating coumarin (**1a**) with 5 equiv NCS in acetonitrile, but no reaction took place even after prolonged refluxing,[22] which indicated the NCS needed to be activated. Several Lewis acid promoters were evaluated for the chlorination of **1a** using the standard protocol (Table S1 in the Supporting Information). To our delight, the chlorination of **1a** could be successfully promoted by the Lewis acid catalysts investigated. Among them, the $CuCl_2{\cdot}2H_2O$ is the most efficient and affords the 3-chloro coumarin (**2a**) with 81% yield (entry 6, Table S1) based on consumed **1a** with no other regioisomers or multichlorinated side products found. Other Lewis acid catalysts such as $ZnCl_2$, $CdCl_2$, or $AlCl_3$, etc. exhibited relatively lower catalytic activities for this chlorination. $FeCl_3$ showed a poor regioselectivity for this reaction, which promotes the chlorination of **1a** at both 3- and 4- positions with a ratio of 70:30. The reaction solvent also influenced the reaction: The yield of the desired product decreased when the chlorination was carried out in acetic acid, 1,4-dioxane, or DMF. We further optimized the dosage of NCS and $CuCl_2{\cdot}2H_2O$ promoter (Table S2) to guarantee a complete conversion of **1a**. The conversion increased when more NCS was used, and the $CuCl_2{\cdot}2H_2O$ amount should be maintained at 1.6–2.4 times (molar ratio) that of NCS for better yields (entries 1–5, Table S2). Finally, when a molar ratio of 1:7:14 (coumarin/NCS/$CuCl_2$) was used, **2a** was obtained in 62% yield with full conversion of **1a** (entry 7, Table S2). The $CuCl_2{\cdot}2H_2O$ can be half replaced with $ZnCl_2$ to complete the chlorination with similar yield of the **2a** (entry 9, Table S2). Anhydrous $CuCl_2$ can promote chlorination with the same yield as the $CuCl_2{\cdot}2H_2O$, but more than 99 hours reaction time is needed. The addition of extra water can accelerate the halogenation, however, the yield decreased to 46% (entries 12–14, Table S2).

With the optimized chlorination conditions in hand, we extended this reaction to a series of coumarins substituted by methyl, methoxy, hydroxyl, chlorine, bromine, acetoxy, and dimethylamino groups. This method can also be applied to the bromination of these substrates using NBS, which is promoted by $CuBr_2$. The results of these halogenation reactions are summarized in Table 1. For detailed reaction conditions including the ratios of reactants, reaction temperature and time, see Tables S3 and S4 in the Supporting Information.

Table 1 The 3-Halogenation of Substituted Coumarins[a]



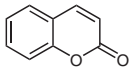
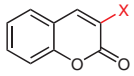
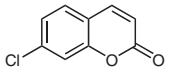
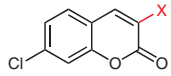
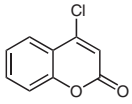
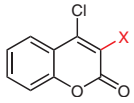
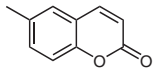
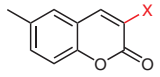
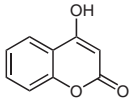
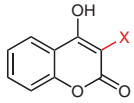
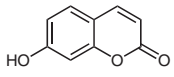
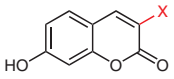
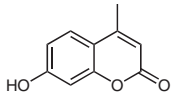
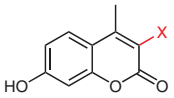
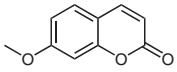
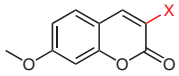
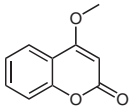
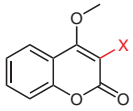
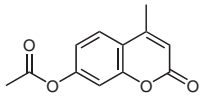
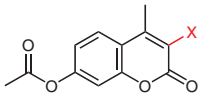
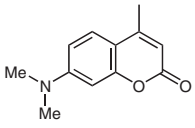
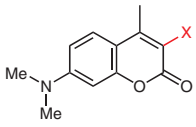
Entry	Substrate	Product	Yield (%)
1 2			**2a**, X = Cl, 62[b] **3a**, X = Br, 61[c]
3 4			**2b**, X = Cl, 45[b] **3b**, X = Br, 49[c]
5 6			**2c**, X = Cl, 84[b] **3c**, X = Br, NR[c]
7 8			**2d**, X = Cl, 71[b] **3d**, X = Br, 77[c]
9 10			**2e**, X = Cl, NR[b] **3e**, X = Br, NR[c]

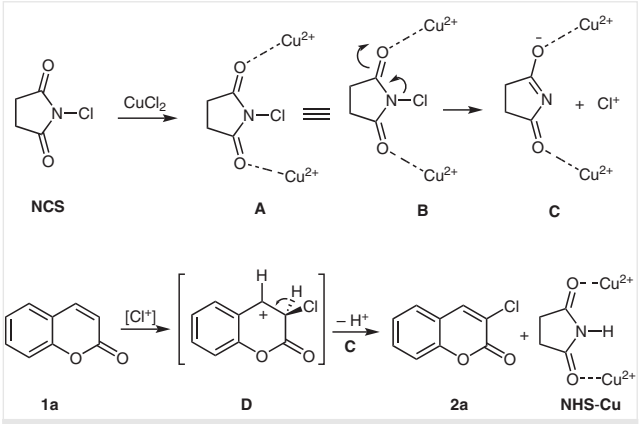
Table 1 (continued)

Entry	Substrate	Product	Yield (%)
11 12			**2f**, X = Cl, 74[b] **3f**, X = Br, 77[c]
13 14			**2g**, X = Cl, 84[b] **3g**, X = Br, 66[c]
15 16			**2h**, X = Cl, 95[b] **3h**, X = Br, 99[c]
17 18			**2i**, X = Cl, 68[b] **3i**, X = Br, 73[c]
19 20			**2j**, X = Cl, 76[b] **3j**, X = Br, 85[c]
21 22			**2k**, X = Cl, 58[b] **3k**, X = Br, 61[c]

[a] Isolated yield. NR = no reaction.
[b] Chlorination conditions: The materials were refluxing in 20 mL MeCN (ca. 82 ℃) until the coumarin is consumed. For **2a–e**: A mixture of coumarin (1.0 mmol), NCS (7.0 mmol), $CuCl_2·2H_2O$ (7.0 mmol), and $ZnCl_2$(7.0 mmol) is used; for **2f–j**: coumarin (1.0 mmol), NCS (1.0 mmol), $CuCl_2·2H_2O$ (2.0 mmol), and $ZnCl_2$(2.0 mmol) is used; for **2k**: coumarin (1.0 mmol), NCS (1.0 mmol), and $CuCl_2·2H_2O$ (1.6 mmol) are used and reacts at RT (room temperature).
[c] Bromination conditions: The starting materials were refluxed in 20 mL MeCN (ca. 82 ℃) until the coumarin is consumed. For **3a–c**: A mixture of coumarin (1.0 mmol), NBS (5.0 mmol), and $CuBr_2$ (10 mmol) is used; for **3d**,**e**,**h–j**: Coumarin (1.0 mmol), NBS (2.0 mmol), and $CuBr_2$ (3.2 mmol) is used; for **3f**,**g**: coumarin (1.0 mmol), NBS (1.5 mmol), and $CuBr_2$ (2.4 mmol) are used and reacts at RT, for **3k**: coumarin (1.0 mmol), NBS (1.0 mmol), and $CuBr_2$ (1.6 mmol) are used and reacts at RT.

As illustrated in Table 1, the amount of NCS is varied from 1 to 7 equiv, depending on the electronic properties of the substituents: it costs only one or two equivalents of NCS to chlorinate the activated coumarins (**2f–k**), but 7 equiv of NCS are needed to complete the chlorination of the substrates with electron-withdrawing or weakly electron-donating groups (**2a–d**). Less amount of NBS (1–5 equiv) was needed to complete the bromination reaction. Some halogenation reactions can be achieved at room temperature (**2k**, **3f**,**g**,**k**). Notably, the complete bromination of **1k** to afford **3k** can be achieved in less than one minute at room temperature, which otherwise would take 72 hours to complete when NH_4OAc was used as the activation reagent.[15] In regard to the halogenation yield, the halogenation of the active substrates gives good to excellent yields (**2f–k**, **3f–k**), and even the less active coumarins gives the 3-halo coumarins (**2a–d**; **3a–d**) in moderate to good yields (49–84%). In the case of 4-hydroxyl coumarin, no anticipated 3-halo products (**2e**, **3e**) were found, possibly owing to the lower reactivity of the C=C double bond, caused by chelating of copper with 4-hydroxyl group, which decreases the electron density. The bromination of 4-chloro coumarin (**1c**) and the halogenation of 4-bromo coumarin gives no anticipated products, obviously due to the steric hindrance of the 4-halogen atom.

According to previous reports,[23] Lewis acid catalyzed halogenation reactions might proceed through either copper(III) mechanism or electrophilic aromatic substitution (EAS) mechanism. As described above, the reaction conditions and yields are greatly affected by the substituents: electron-donating substituents favor the halogenation, while electron-withdrawing substituents impede the halogenation, which is in agreement with an EAS mechanism. A control experiment shows the chlorination reaction under O_2 atmosphere or argon protection gave similar results, this further supports the EAS mechanism.[23c] A plausible mechanism is illustrated in Scheme 2 with the chlorination of coumarin (**1a**) by NCS/$CuCl_2$ as an example.



Scheme 2 The proposed halogenation mechanism

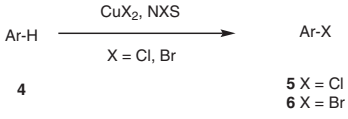
The chlorination proceeds via the highly reactive chlorine 'cation' (Cl^+) generated in situ. Firstly, copper chlorides coordinate with the carbonyls of NCS (**A**). This complexation in **A** substantially increased the electron-withdrawing power of the carbonyls, leading to the heterolytic cleavage of the N–Cl bond to expel a chlorine cation (Cl^+) as shown in **B** and **C**. The highly electrophilic Cl^+ regioselectively added to the 3-position of the coumarin ring to give a more stable benzyl carbocation **D**. Subsequent proton transfer from **D** to the N atom in **C** yields 3-chloro coumarin **2a** as the chlorinated product and succinimide, which is still coordinating with copper (**NHS-Cu**). This mechanism necessitates the use of two equivalents of copper chloride relative to NCS. Electron-donating substituents increase the electron density of the coumarin to facilitate the electrophilic attack of the positive halogen and render a higher stability of the carbocation intermediate **D**, thus leading to higher haloge-

nation efficiency. As a result, the halogenation of 7-methoxy coumarin gave the 3-halocoumarins (Table 1, **2h**, **3h**) quantitively, while the coumarins with chlorine groups (**2b**,**c**, **3c**) gave relative lower yields.

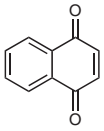
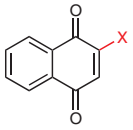
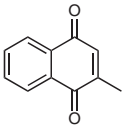
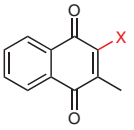
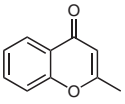
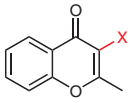
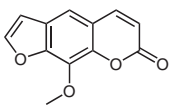
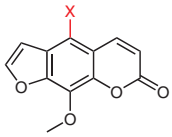
We also tested the halogenation of other heteroarenes using this copper activation strategy (Table 2) to access their valuable halo derivatives. For example, the selective halogenation of the naphthoquinones would provide an important platform for further derivatization of this important quinone.[24] The halogenation of naphthoquinones (**4a**,**b**) can regioselectively afford the monohalogenated products (**5a**, **6a**,**b**) in quantitative yields, except the chlorination of 2-methyl-1,4-naphthoquinone (**5b**, 69%). There was an early report of the bromination of 2-methyl flavone (**4c**) using NBS alone gave the methyl brominated product.[25] Interestingly, upon using copper activation, a selective 3-bromination takes place on the heteroaromatic ring (**5c**, **6c**), which also supports the EAS mechanism. The halogenation of 8-methoxypsoralen (**4d**) also affords quantitative yields of monohalogenated products (**5d**, **6d**).

In conclusion, we developed a CuX_2/ZnX_2 promoted regioselective halogenation of coumarins by NCS or NBS with moderate to excellent yields.[26] The NXS dosage depends on the electronic properties of the substituent groups and varies from 1–7 equiv of the substrates, and the metal halide needs to be used in an amount 1.6–2 times that of NXS. Due to the usage of inexpensive reagents, the reaction can be scaled up although excess NXS, and metal halides are often needed to complete the conversion for some relatively electron-deficient coumarins without electron-donating substituents or even with electron-withdrawing substituents. This methodology can be applied to other less electron-rich or rather electron-deficient heterocyclic compounds such as 1,4-naphthoquinones, flavone, and methoxypsoralen to give monohalogenated derivatives. Therefore, this protocol provides an alternative approach to the halogenation of heteroaromatic compounds using copper activation of NXS with safe workup. We believe this concise procedure may also be applied to the halogenation of other aromatic compounds.

Table 2 The Halogenation of Heteroarenes[a]



4 **5** X = Cl, **6** X = Br

Entry	Substrate	Product	Yield (%)
1 2			**5a** X = Cl, 99[b] **6a** X = Br, 98[c]
3 4			**5b** X = Cl, 69[b] **6b** X = Br, 96[c]
5 6			**5c** X = Cl, 72[b] **6c** X = Br, 86[c]
7 8			**5d** X = Cl, 98[b] **6d** X = Br, 98[c]

[a] Isolated yield.
[b] Chlorination conditions: The materials were refluxing in 20 mL MeCN (ca. 82 ℃) until the heteroarene was consumed. For **5a**,**c**: Heteroarene (1.0 mmol), NCS (7.0 mmol), and $CuCl_2{\cdot}2H_2O$ (14.0 mmol) are used. For **5b**: Naphthoquinone (1.0 mmol), NCS (10.0 mmol), and $CuCl_2{\cdot}2H_2O$ (20.0 mmol) are used. For **5d**: Methoxysalen (1.0 mmol), NCS (2.0 mmol), and $CuCl_2{\cdot}2H2O$ (4.0 mmol) are used and reacts at RT.
[c] Bromination conditions: For **6a**,**b**: Naphthoquinone (1.0 mmol), NBS (5.0 mmol), and $CuBr_2$ (10 mmol) are used. For **6c**,**d**: Heteroarene (1.0 mmol), NBS (1 mmol) and $CuBr_2$ (1.6 mmol) are used, and **6d** is prepared at RT.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612080.

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(21) We have applied for a Chinese patent CN 105541772 to protect the rough findings of this idea before the optimization. In the patent, the activation of NCS using $CuCl_2·2H_2O$, $AlCl_3$, $ZnCl_2$ or $FeCl_3$ (1–5 equiv) and the chlorination reactions to afford **2a**, **2c**, and **2d** are described, however, optimized reaction conditions for full conversion of the starting materials are not specified.
(22) In the control experiment, no reaction happened by mixing coumarin with either NCS or $CuCl_2$ alone in refluxing acetonitrile even after 36 h.
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(26) **3,7-Dichloro-2*H*-chromen-2-one (2b) – Typical Procedure**
To a 50 mL round-bottom flask, 7-chloro coumarin (180.6 mg, 1 mmol), NCS (935.2 mg, 7 mmol), $CuCl_2·2H_2O$ (2387 mg, 14 mmol), and 20 mL anhydrous MeCN were added and refluxed until the reaction completed. The cooled mixture was concentrated in vacuum, dispensed in 25 mL 5% $NaHSO_3$ aqueous solution and extracted with 25 mL EtOAc for three times. The organic layer was combined, washed with 10 mL water and dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was purified by silica gel column chromatography to afford 96.2 mg **2b** (44.9%).
3,7-Dichloro-2*H*-chromen-2-one (2b)
White solid, mp 123–124 ℃ (acetone/PE, 2:1, V/V). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.40 (d, *J* = 8.3 Hz, 1 H), 7.38 (d, *J* = 1.9 Hz, 1 H), 7.30 (dd, *J* = 8.3, 1.9 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.6, 152.9, 139.3, 137.9, 128.0, 125.7, 122.5, 117.4, 117.2, 100.0. IR (KBr): ν_{max} = 3103, 3061, 3040, 1736, 1720, 1702, 1604, 1484, 1403, 1348, 1318, 1245, 1206, 1144, 1123, 1077, 998, 969, 939, 916, 865, 825, 752, 681, 617, 595, 462 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_9H_5Cl_2O_2$ [M + H] (^{35}Cl): 214.9661; found: 214.9661.