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Direct copper(II)-mediated regioselective α-halogenation of *N*-aryl enaminones

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ABSTRACT

A mild copper(II)-mediated α-halogenation of *N*-aryl enaminones was developed. α-Halogenated *N*-aryl enaminones were obtained in moderate to good yields using CuX_2 in EtOH at 40 °C.

Introduction

The sp^2 C–X units are one of the most important strategic tools in organic chemistry, which provide easy starting points for the preparation of functionalized building blocks and intermediates.[1] Conventionally, the synthetic methods for sp^2 C–X bond formation are mainly via electrophilic substitution using molecular halogen or *N*-X-based reagents.[2] However, these methods have some drawbacks, such as toxic reagents, harsh reaction conditions, low yields, and poor regioselectivity. Recently, transitional metal–catalyzed C–H functionalization–halogenation has been studied extensively,[3] which offers unique regioselectivities in high yields. But these methods require the assistance of nitrogen- or oxygen-containing directing groups, thus limiting their synthetic applications. Notably, for the direct halogenation of α,β-unsaturated carbonyl compounds, far fewer synthetic choices are available other than traditional methods.[4] Recent examples in this area include α-halogenation of cyclohexenones using oxidant/pyridine hydrohalides,[5a] one pot β-halogenation of cyclohexenones via a hydrazone intermediate,[5b] and α-halogenation of α,β-unsaturated amides by Rh (III)-catalyzed β-C–H activation.[5c]

Enaminones (Fig. 1, **1**) are well known for their versatile reactivity, and have been widely used in the synthesis of a variety of

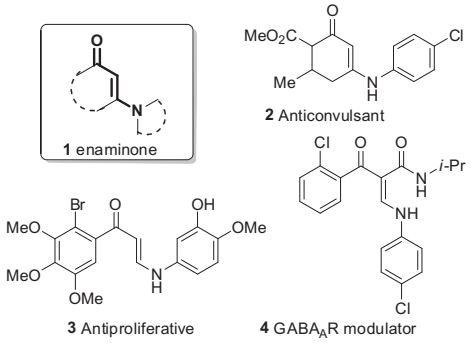
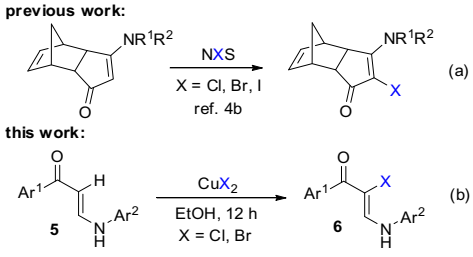


Figure 1. Representative bioactive enaminones.



Scheme 1. α-Halogenation of enaminones.

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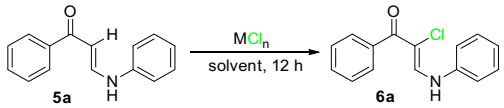
Table 1
Optimization of reaction conditions[a]



Entry	Solvent	Catalyst (equiv)	*T* (°C)	Yield[b] (%)
1	DCM	$FeCl_3$ (1.0)	80	n.r.
2	DCM	$CrCl_2$ (1.0)	80	n.r.
3	DCM	$BiCl_3$ (1.0)	80	n.r.
4	DCM	CuCl (1.0)	80	n.r.
5	DCM	$CuCl_2$ (1.0)	80	50
6	Xylene	$CuCl_2$ (1.0)	80	27
7	Toluene	$CuCl_2$ (1.0)	80	40
8	Hexane	$CuCl_2$ (1.0)	80	43
9	Cyclohexane	$CuCl_2$ (1.0)	80	45
10	Acetonitrile	$CuCl_2$ (1.0)	80	35
11	DMF	$CuCl_2$ (1.0)	80	n.d.[c]
12	DMSO	$CuCl_2$ (1.0)	80	n.d.[c]
13	Water	$CuCl_2$ (1.0)	80	n.r.[d]
14	Glycerol	$CuCl_2$ (1.0)	80	n.r.[d]
15	PEG-400	$CuCl_2$ (1.0)	80	n.r.[d]
16	MeOH	$CuCl_2$ (1.0)	80	36
17	EtOH	$CuCl_2$ (1.0)	60	62
18	EtOH	$CuCl_2$ (1.0)	40	67
19	EtOH	$CuCl_2$ (1.0)	rt	49
20	EtOH	$CuCl_2$ (2.0)	40	72
21	**EtOH**	**$CuCl_2$ (3.0)**	**40**	**74**

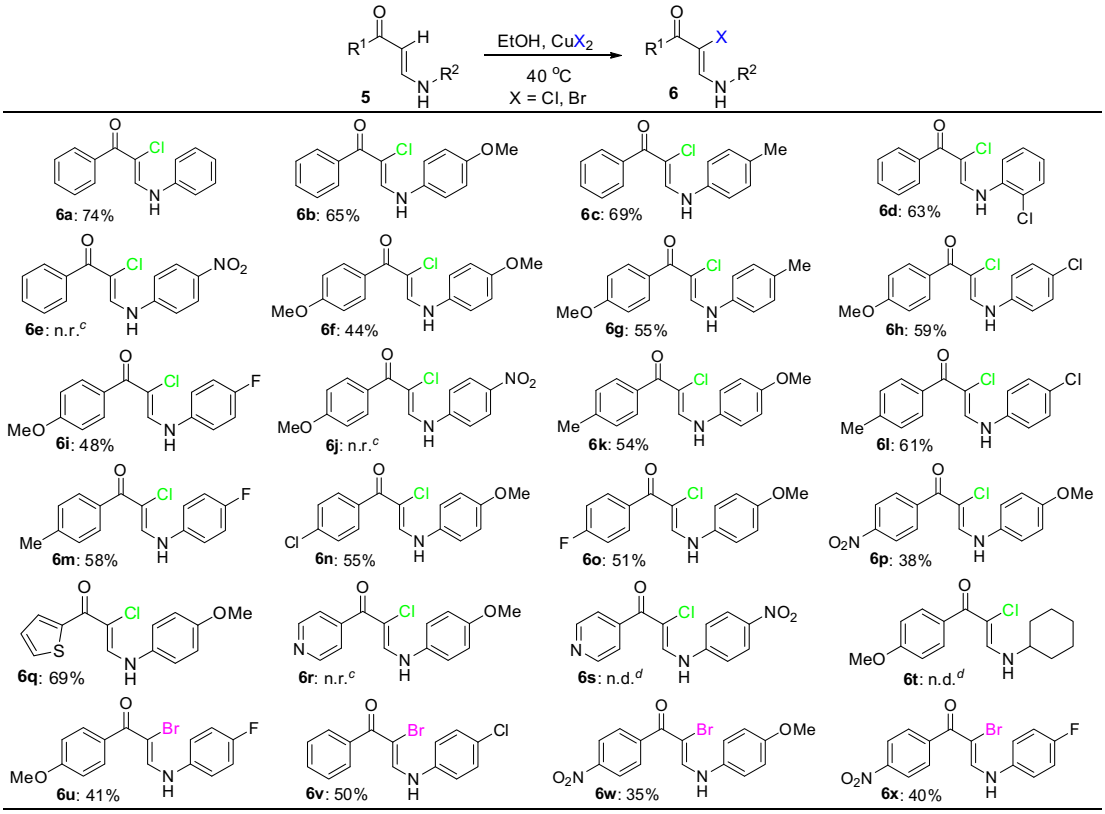
[a] Reagents and conditions: Enaminone **5a** (0.3 mmol), solvent (3.0 mL), 12 h.
[b] Isolated yield based on enaminone **5a**.
[c] n.d. = no detected.
[d] n.r. = no reaction.

heterocyclic[6] and fused heterocyclic compounds.[7] In addition, enaminone is also a common motif in some biologically active compounds and potential drug candidates[8] (Fig. 1, compounds **2**,[8a] **3**[8d] and **4**[8b]). As direct halogenation of enaminones could efficiently increase the structural diversity of target compounds and provide further chances of modification, developing selective methods is thus potentially valuable. However, to the best of our knowledge, although significant progress in halogenation has been achieved, the halogenation of enaminones is still surprisingly underdeveloped (Scheme 1a).[4b] Copper(II) salts has been demonstrated as effective reagents or catalysts for halogenation[9] as exemplified in the synthesis of aryl halides,[3h,10a] 2-/3-haloindoles,[10b,c] and halopyrrolones.[10d] Inspired by these studies, we herein report an efficient and highly regioselective method for the synthesis of α-halogenated *N*-aryl enaminones utilizing CuX_2 as the halogenation reagent (Scheme 1b).

Results and discussion

N-Aryl enaminone **5a** was first selected as a model substrate to define the optimal reaction conditions. As shown in Table 1, various transitional metal chlorides, solvents, and temperatures were screened. First, metal chlorides (1.0 equiv) were investigated; $FeCl_3$, $CrCl_2$, $BiCl_3$, and CuCl could not afford the desired product **6a** after reacting in DCM at 80 °C for 12 h (entries 1–4), while $CuCl_2$ delivered **6a** in 50% yield (entry 5). Next, the influence of solvents was studied using $CuCl_2$ as the halogenations reagent. DCM was found more efficient than non-polar solvent such as xylene, toluene, hexane, and cyclohexane (entries 6–9). Polar aprotic

Table 2
Scope of enaminones[a,b]



[a] Reagents and conditions: Enaminone **5** (0.3 mmol), CuX_2 (0.9 mmol), EtOH (3.0 mL), 40 °C, 12 h.
[b] Isolated yield based on enaminones.
[c] n.r. = no reaction.
[d] n.d. = no detected.

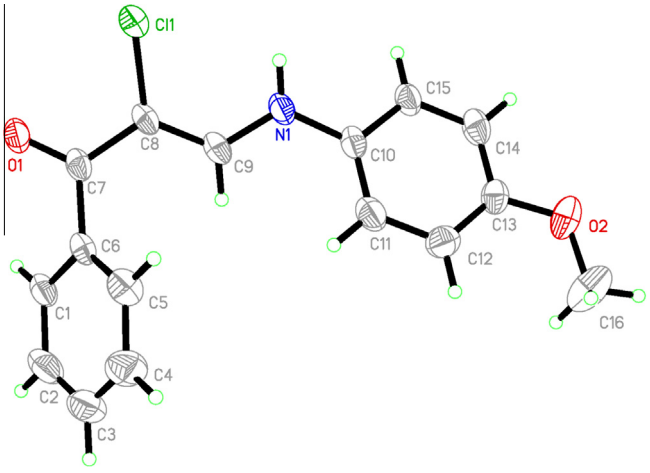


Figure 2. ORTEP diagram of **6b**; ellipsoids are drawn at the 30% probability level.

solvents, such as acetonitrile, DMF, and DMSO, failed to give any desired product (entries 10–12). To our delight, EtOH was found to be a better solvent than DCM (62% yield, entry 17). The reaction in MeOH gave a decreased yield of **6a** (entry 16), whereas water, glycerol, and PEG-400 were ineffective solvents (entries 13–15). In order to further improve the yield, the amount of $CuCl_2$, and temperature were evaluated. We found that the reaction using 3.0 equiv $CuCl_2$ in EtOH at 40 °C for 12 h provided the best results (74%, entry 21).[11]

With the optimal reaction conditions in hand, the scope of substrates was then explored. The results are summarized in Table 2. *N*-aryl enaminones **5** with various R^1 and R^2 substituents, including electron-withdrawing (4-NO_2, 4-F and 2/4-Cl phenyl), electron-neutral (phenyl) and electron-donating (4-OMe and 4-Me phenyl) groups, were tested. Most of the reactions proceeded smoothly and afforded the α-chlorinated enaminones in moderate to good yields utilizing $CuCl_2$ as the chlorinating reagent (**6a**–**6d**, **6f**–**6i** and **6k**–**6q**, 74–35%). However, the reactions failed for substrates containing a nitrated *N*-phenyl group or a pyridyl ketone moiety, presumably due to their highly electron deficient natures (**6e**, **6j**, **6r**, and **6s**). The substrate with *N*-cyclohexyl group was also unable to deliver the desired product (**6t**). In addition, the reactions of $CuBr_2$ were tested, and found able to give the corresponding α-brominated products **6u**–**6x** in 35–50% yields. At last, the structure of the product was further confirmed by the X-ray single-crystal diffraction studies on **6b** (Fig. 2, CCDC 1474342).[12]

In terms of the reaction mechanism, given that the C=C bond in enaminones is electron rich, and Cu(II) can be reduced to Cu(I), it is likely that the reaction experiences a single electron transfer (SET) mechanism. However, further evidences are necessary to disclose the details.

Conclusion

In summary, we have developed a novel method for the synthesis of α-halogenated *N*-aryl enaminones via a regioselective halogenation. Except substrates bearing extremely electron poor aryls, various *N*-aryl enaminones gave moderate to good yields in the presence of copper(II) halides in EtOH. Attempts toward further understanding of the reaction mechanism and synthetic applications are underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data and ^1H and ^{13}C NMR spectra of the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.09.076.

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Huang, F.; Wu, P.; Wang, L.; Chen, J.; Sun, C.; Yu, Z. *Chem. Commun.* **2014**, 12479.

11. *Procedure for the synthesis of compounds* **6a**: Enaminone **5a** (0.3 mmol), EtOH (3.0 mL) and $CuCl_2$ (0.9 mmol) were added into a 10mL Ace Glass pressure tubes, and the mixture was stirred at 40 °C for 12 h until enaminone **5a** were completely consumed. The mixture was cooled to room temperature, concentrated under reduced pressure, and then taken up in EtOAc (15 mL × 2). The solution was washed with water (10 mL), dried over Na_2SO_4, concentrated, and purified by flash column chromatography to afford α-halogenated enaminone **6a**. *2-chloro-1-phenyl-3-(phenylamino)prop-2-en-1-one* (**6a**): White solid; mp 163–165 °C; IR (KBr): 3344, 1644, 1507, 1311, 1246, 1102, 1028, 832, 796, 744, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.0 Hz, 2H, ArH), 7.06–7.10 (m, 1H, ArH), 7.23 (d, *J* = 13.0 Hz, 1H, NH), 7.29–7.33 (m, 2H, ArH), 7.45–7.48 (m, 2H, ArH), 7.51–7.54 (m, 1H, ArH), 7.61–7.62 (m, 2H, ArH), 7.85 (d, *J* = 13.0 Hz, 1H, C=CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 109.8, 116.4, 116.4, 124.1, 128.4, 128.4, 128.5, 128.5, 130.0, 130.0, 131.1, 138.8, 139.2, 141.2, 188.1; HRMS (TOF ES^+): *m/z* calcd for $C_{15}H_{12}ClNNaO$ [$(M+Na)^+$], 280.0500; found, 280.0503.
12. CCDC 1474342 contains the supplementary crystallographic data for compound **6b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.