Organic LETTERS

Copper-Catalyzed Aza-Diels−Alder Reaction and Halogenation: An Approach To Synthesize 7-Halogenated Chromenoquinolines

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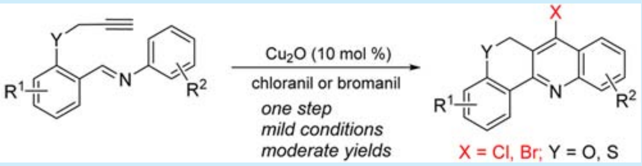
Supporting Information

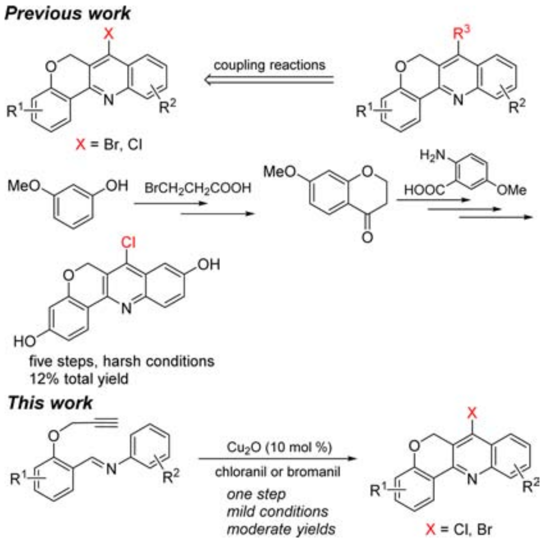
ABSTRACT: A new halogenation method to construct halogen-substituted quinoline moieties is described. The Cu-catalyzed intramolecular aza-Diels−Alder reaction and halogenation reaction proceeded smoothly under mild conditions to produce the corresponding 7-chloro-6*H*-chromeno[4,3-*b*]quinolines and 7-chloro-6*H*-thiochromeno[4,3-*b*]quinolines in satisfactory yields.



Chromenoquinoline structural motifs are frequently found in biologically active compounds.[1] As pharmaceuticals, substituted chromenoquinolines exhibit remarkable properties, such as anti-inflammatory activities and serotonin and estrogen receptor functions.[2] 7-Chloro-6*H*-chromenoquinolines and 7-bromo-6*H*-chromenoquinolines have attracted considerable attention because of their transcriptional activity in the human progesterone receptor, which plays an important role in medicine.[2c] Moreover, 7-chloro-6*H*-chromenoquinolines and 7-bromo-6*H*-chromenoquinolines are utilized as intermediates to synthesize various substituted chromenoquinolines through transition-metal-catalyzed cross-coupling reactions. Although chromenoquinolines can be easily synthesized through aza-Diels−Alder reaction,[3−8] the synthesis of 7-halogenated chromenoquinolines, such as 7-chloro-6*H*-chromeno[4,3-*b*]quinoline and 7-bromo-6*H*-chromeno[4,3-*b*]quinoline, is difficult. In 2007, Vu et al.[2c] synthesized 7-chloro-6*H*-chromeno[4,3-*b*]quinolines and 7-bromo-6*H*-chromeno[4,3-*b*]quinolines for the first time (Scheme 1). However, this process presents some limitations such as multiple steps (five steps), harsh reaction conditions (>200 °C), and low yields (12% total yield). Therefore, the development of a convenient and efficient method for the synthesis of 7-halogenated chromenoquinolines is an important requirement.

Conducting research on new strategies of Cu-catalyzed nitrogen-containing heterocycle synthesis and chlorination reaction,[9,10] we found that 7-chloro-6*H*-chromeno[4,3-*b*]quinolines and 7-bromo-6*H*-chromeno[4,3-*b*]quinolines can be directly obtained through Cu-catalyzed cascade reactions (aza-Diels−Alder reaction of Schiff base, followed by chlorination or bromination using chloranil and bromanil as halogen sources; Scheme 1).

Scheme 1. Synthesis of 7-Halogenated Chromenoquinolines



In our initial studies, the cascade reaction of Schiff base substrate **1a** was selected as a model reaction to optimize the reaction conditions. The results are summarized in Table 1. No reaction was observed when **1a** was treated with chloranil in 1,2-dimethoxyethane (DME) at 80 °C in the absence of a catalyst (entry 1). No reaction was also observed when $ZnCl_2$ and $FeCl_2$ were used as catalysts (entries 2 and 3). Several copper salts including CuCl, CuI, CuOTf, CuOAc, and Cu_2O were then tested as catalysts (entries 4−8). As expected, the desired product 7-chloro-6*H*-chromeno[4,3-*b*]quinoline (**2a**) was obtained as a major product along with the byproduct 6*H*-chromeno[4,3-*b*]quinoline (**3a**). Among the copper salts tested, Cu_2O proved to be the best catalyst; the chlorinated product **2a** was obtained with relatively high yield (entry 8 vs entries 4−7). To improve the yield of product **2a**, we examined 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and *N*-chlorosuccinimide (NCS) as chlorine sources instead of chloranil. Although the target reaction occurred in the presence of DDQ or NCS,

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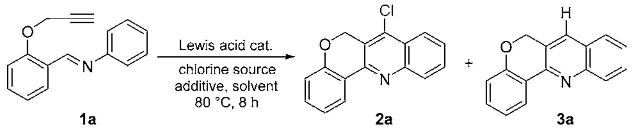
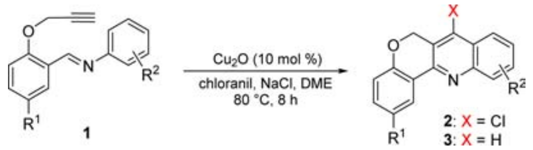
Table 1. Optimization of the Reaction Conditions[a]

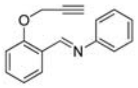
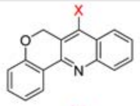
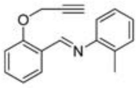
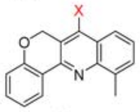
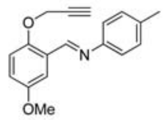
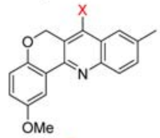
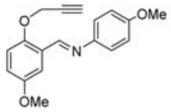
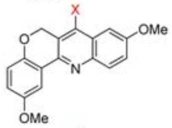
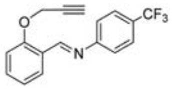
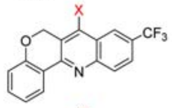
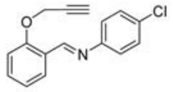
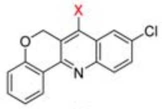
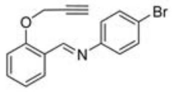
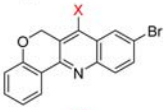
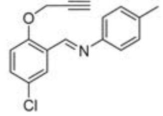
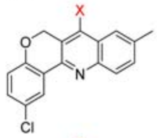
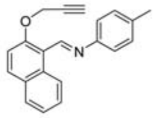
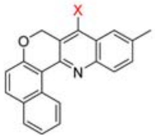


					yield[b,c] (%)	
entry	cat.	Cl source	additive	solvent	2a	3a
1	none	chloranil	none	DME	0	0
2	$ZnCl_2$	chloranil	none	DME	0	0
3	$FeCl_2$	chloranil	none	DME	0	0
4	CuCl	chloranil	none	DME	33	16
5	CuI	chloranil	none	DME	38	18
6	CuOTf	chloranil	none	DME	32	17
7	CuOAc	chloranil	none	DME	28	14
8	Cu_2O	chloranil	none	DME	43	17
9	Cu_2O	DDQ	none	DME	27	5
10	Cu_2O	NCS	none	DME	33	18
11	Cu_2O	chloranil	$CaCl_2$	DME	59	23
12	Cu_2O	chloranil	Na_2SO_4	DME	54	21
13	Cu_2O	chloranil	KCl	DME	54	22
14	Cu_2O	chloranil	NaCl	DME	63	21
15	Cu_2O	chloranil	NaCl	dioxane	48	29
16	Cu_2O	chloranil	NaCl	toluene	37	29
17	Cu_2O	chloranil	NaCl	DMF	0	0
18	Cu_2O	chloranil	NaCl	IPA	22	51

[a] Reaction conditions: *N*-(2-(prop-2-yn-1-yloxy)benzylidene) aniline (**3a**, 0.2 mmol, 47 mg), chlorine source (2.0 equiv), and additive (1.5 equiv) in 2.0 mL of solvent at 80 °C for 8 h. [b] Isolated yield. [c] Entries containing zeroes indicate no reaction.

Table 2. Synthesis of 7-Chloro-6*H*-chromeno[4,3-*b*]quinolines via Cu-Catalyzed Cascade Reaction[a]



entry	Schiff base 1		product 2 or 3		yield (%)[b]
1		**1a**		**2a** **3a**	63 21
2		**1b**		**2b** **3b**	54 21
3		**1c**		**2c** **3c**	65 16
4		**1d**		**2d** **3d**	62 0
5		**1e**		**2e** **3e**	38 26
6		**1f**		**2f** **3f**	57 18
7		**1g**		**2g** **3g**	52 17
8		**1h**		**2h** **3h**	64 18
9		**1i**		**2i** **3i**	42 16

[a] Reaction conditions: Schiff bases **1a**–**i** (0.2 mmol), Cu_2O (10 mol %, 3.0 mg), chloranil (2.0 equiv, 98 mg), and NaCl (1.5 equiv, 18 mg) in DME (2.0 mL) under a nitrogen atmosphere at 80 °C for 8 h. [b] Isolated yield.

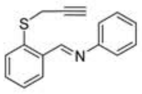
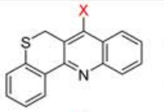
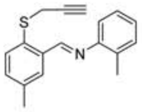
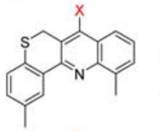
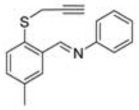
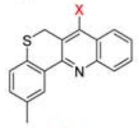
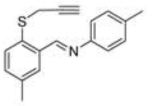
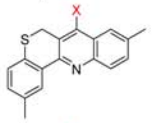
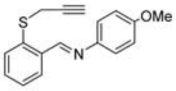
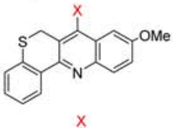
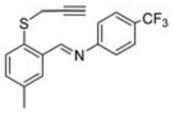
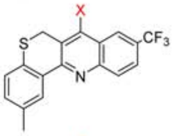
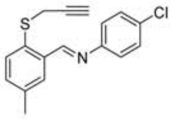
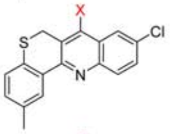
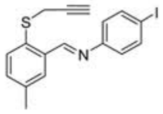
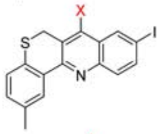
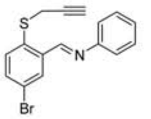
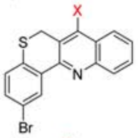
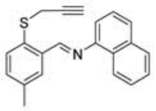
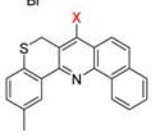
the yield of product **2a** remained low (entries 9 and 10). The yield of **2a** was remarkably increased when the inorganic salts $CaCl_2$, Na_2SO_4, KCl, and NaCl were individually added to the model reaction (59%–63%, entries 11–14). It was considered that NaCl might activate the aromatic ring by the cation–*π* interaction.[11]

The solvent was finally screened using NaCl as an additive (entries 14–18). Among DME, dioxane, toluene, *N*,*N*-dimethylformamide (DMF), and isopropyl alcohol (IPA), DME was identified as the best solvent. Therefore, the subsequent cascade reactions of Schiff base substrates **1** were performed using Cu_2O, chloranil, and NaCl as catalyst, chlorine source, and additive, respectively, in DME at 80 °C.

The reactions of the Schiff base substrates **1a**–**i** were allowed to proceed under optimized conditions; the results are summarized in Table 2. The 7-chloro-6*H*-chromeno[4,3-*b*]quinolines **2a**–**c**, along with the byproducts 6*H*-chromeno-[4,3-*b*]quinolines **3a**–**c** with approximately 20% yields, were obtained as major products in moderate yields (entries 1–3, 54–65%). The desired chlorination product **2d** was isolated as the sole product from the reaction of substrate **1d** (entry 4, 62%). The reaction of substrate **1e** containing a strong electron-withdrawing group (CF_3) on the benzene ring produced the desired product **2e** in low yield (entry 5). The Cl and Br atoms linked to the benzene ring were notably maintained in the structures of products **2f**–**h** under the specified reaction conditions. This observation suggests that further manipulation may produce more useful compounds. To further explore the reaction scope, we examined the fused aromatic ring-containing substrate **1i** under the optimized reaction conditions. The desired product **2i** was obtained in 42% yield (entry 9).

On the basis of our good preliminary results, we used the present method to synthesize 7-chloro-6*H*-thiochromeno[4,3-*b*]quinolines under the same reaction conditions. The results are summarized in Table 3. The reactions of Schiff base substrates **4a**–**e** proceeded smoothly to produce **5a**–**e** in satisfactory yields (entries 1–5, 51%–57%). By contrast, relatively low yields were observed in the reactions of **4f**–**i** containing an electron-withdrawing group on the benzene rings (CF_3, Cl, I, or Br). The desired chlorination products **5g**–**i** were separated in 39–53% yields (entries 6–9). Likewise, the

Table 3. Synthesis of 7-Chloro-6*H*-thiochromeno[4,3-*b*]quinolines via Cu-Catalyzed Cascade Reaction[a]

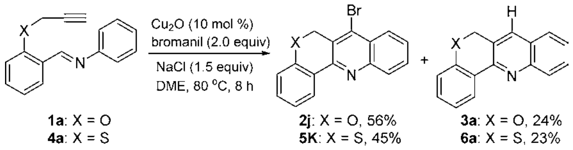
entry	Schiff base 4		product 5 or 6		yield (%)[b]
1		4a		5a 6a	54 25
2		4b		5b 6b	51 19
3		4c		5c 6c	55 27
4		4d		5d 6d	57 21
5		4e		5e 6e	57 0
6		4f		5f 6f	39 16
7		4g		5g 6g	42 23
8		4h		5h 6h	41 19
9		4i		5i 6i	53 0
10		4j		5j 6j	21 0

[a] Reaction conditions: Schiff base substrates **4a**–**j** (0.2 mmol), Cu_2O (10 mol %, 3.0 mg), chloranil (2.0 equiv, 98 mg), and NaCl (1.5 equiv, 18 mg) in DME (2.0 mL) under a nitrogen atmosphere at 80 °C for 8 h. [b] Isolated yield.

fused aromatic ring-containing substrate formed the desired product in low yield (entry 10, 21%).

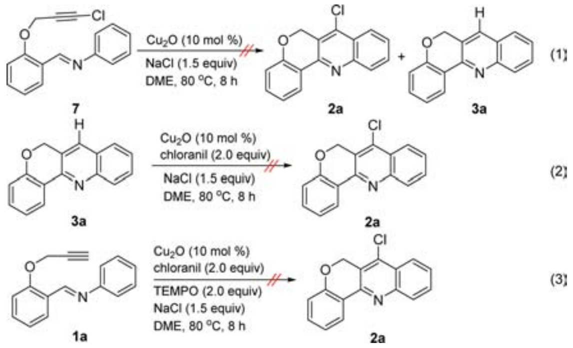
The Cu-catalyzed cascade reactions of the Schiff base substrates **1a** and **4a** with bromanil were also evaluated under the same reaction conditions. As expected, the bromination products 7-bromo-6*H*-chromeno[4,3-*b*]quinoline (**2j**) and 7-bromo-6*H*-thiochromeno[4,3-*b*]quinoline (**5k**) were obtained in 56% and 45% yields, respectively (Scheme 2).

Scheme 2. Synthesis of 7-Bromo-6*H*-chromeno[4,3-*b*]quinoline and 7-Bromo-6*H*-thiochromeno[4,3-*b*]quinoline



Control experiments were conducted to gain insights into the mechanism of this type of cascade reaction. No reaction was observed when chloroacetylene **7** was treated in the absence of chloranil (Scheme 3, eq 1). This result reveals that the chlorinated product **2a** was not formed via a chloroacetylene intermediate. No reaction was also observed when the byproduct **3a** was treated under the optimized reaction conditions (Scheme 3, eq 2). This phenomenon indicates that the chlorinated product **2a** was not formed through the chlorination reaction of the byproduct **3a**. The reaction of **1a** was conducted by adding 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the optimized reaction conditions (Scheme 3, eq 3). The target reaction was completely inhibited; this result suggests that the target reaction may involve radical intermediates.[12]

Scheme 3. Control Experiments



A plausible reaction mechanism is depicted in Scheme 4 on the basis of the mechanistic studies described above. The Schiff base substrate **1a** reacts with a Cu(I) species in the presence of chloranil to produce Cu(II) acetylide **A**,[13] which subsequently undergoes intramolecular aza-Diels–Alder reaction to form intermediate **B**. The Cl radical derived from chloranil[14] reacts with intermediate **B** to generate intermediate **C**. Intermediate **C** undergoes reductive elimination reaction to form a chlorinated intermediate **D** and regenerate Cu(I) species.[15] The dehydrogenation of intermediate **D** with chloranil occurs to produce the desired product **2a**. Byproduct **3a** is generated through the hydrolysis reaction of intermediate **B** with 2,3,5,6-tetrachlorobenzene-1,4-diol, followed by dehydrogenation reaction. 2,3,5,6-Tetrachlorobenzene-1,4-diol is generated in the dehydrogenation reaction step. Therefore, the side reaction can not be completely avoided.

In summary, a new method was developed to synthesize 7-halogenated chromenoquinolines and 7-halogenated thiochromenoquinolines. The Cu-catalyzed cascade reaction, namely,

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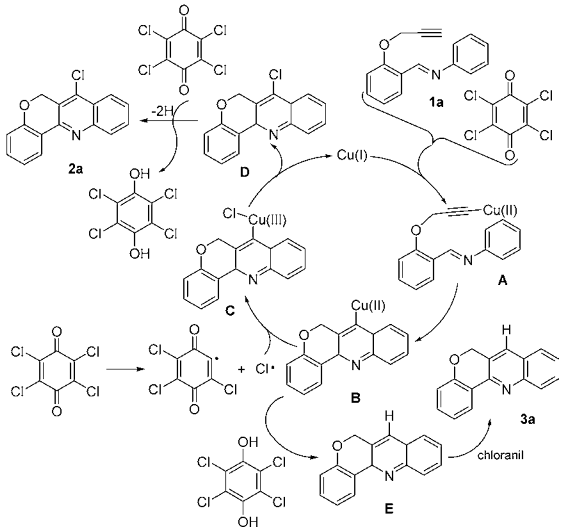
Scheme 4. Proposed Mechanism



aza-Diels–Alder reaction and halogenation (chlorination or bromination), proceeded smoothly in the presence of chloranil or bromanil to give the desired halogenated products in moderate yields. Cu$_2$O functioned as a Lewis acid catalyst and transition-metal catalyst in the aza-Diels–Alder reaction and halogenation reaction, respectively. Chloranil and bromanil also performed dual functions, that is, as a halogen source and oxidant. Although the halogenated products were obtained in moderate yields, the present method is highly useful in organic synthesis because of mild reaction conditions and experimental simplicity. Further studies on the extension of this method to synthesize 4-halogenated quinolines are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01065.

Experimental procedures, characterization, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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