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Two Efficient Cascade Reactions to Synthesize Substituted Furocoumarins

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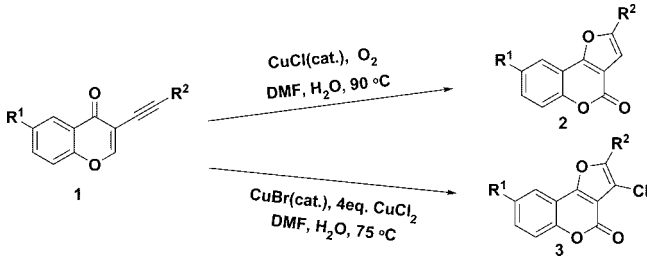
Received February 24, 2008

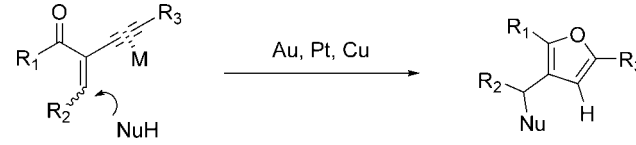


We have developed two efficient one-pot reactions to generate furo[3,2-*c*]coumarins and chlorofuro[3,2-*c*]coumarins through addition/cyclization/oxidation and chlorination. One cascade addition/cyclization/oxidation sequence of **1** with H_2O in the presence of 20% CuCl as Lewis acid under an air atmosphere generated the 2-substituted-4*H*-furo[3,2-*c*]chromen-4-one **2.** Another sequence in the presence of 10% CuBr and excess $CuCl_2$ as the oxidant afforded the 3-chloro-2-substituted-4*H*-furo[3,2-*c*]chromen-4-one **3**.

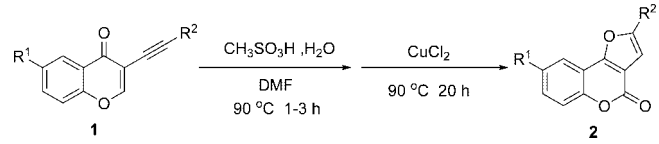
2-(1-Alkynyl)-2-alken-1-ones, which have three special functional groups, are very attractive units because a C−O bond and a remote carbon−nucleophile bond can be formed simultaneously. The groups of Larock, Oh, and Yamamoto have independently reported Au-, Pt-, and Cu-catalyzed approaches for the synthesis of highly substituted furans from this type of universal intermediate.[1] It has been suggested that a metal salt can facilitate the reaction by its dual function as both a Lewis acid to activate the carbonyl group and a coordination reagent with alkynes (Scheme 1).

In our recent paper, we demonstrated that using CH_3SO_3H as acid, water as nucleophile, and $CuCl_2$ as oxidant, a sequential one-pot reaction of **1** through addition/cyclization/oxidation (Scheme 2),[2] formed furocoumarins **2**, which can be found in many natural products and exhibits potent biological activity.[3] On the basis of these results, we commenced our program to develop a more convenient one-pot cascade process to construct

SCHEME 1. Reported Addition and Cyclization of 2-(1-Alkynyl)-2-alken-1-ones



SCHEME 2. Acid-Promoted Sequential One-Pot Reaction to Synthesize Furocoumarins



diversified furocoumarins. Herein, we report two approaches, namely catalytic CuCl-promoted addition and cyclization of **1** together with oxygen as oxidant to form 4*H*-furo[3,2-*c*]chromen-4-ones **2**, and catalytic CuBr with $CuCl_2$ as oxidant and chlorinated reagent to produce 3-chloro-4*H*-furo[3,2-*c*]chromen-4-ones **3** in a one-pot process.

The initial experiment was conducted by heating a mixture of 3-alkynylchromone (**1a**), H_2O (10 equiv), and CuCl (0.1 equiv) in DMF at 90 °C in an open flask. Furocoumarin (**2a**) was successfully obtained in 71% yield (Table 1, entry 1). When CuBr (0.1 equiv) was used instead of CuCl, the reaction gave a similar result in 69% yield (Table 1, entry 2). By shortening the reaction time to 2.5 h and lowering the reaction temperature to 70−80 °C, the yield of **2a** decreased (Table 1, entries 3−5). By increasing the loading rate of the catalyst (CuCl used in 0.2, 0.5, and 1.0 equiv), the reaction was accelerated and the yield of **2a** was improved to 86%, 80%, and 96%, respectively (Table 1, entries 6−8). However, there was no difference performing the reaction in a pure oxygen atmosphere (Table 1, entry 9). The use of other solvents such as dioxane, DMSO, CH_3CN, and toluene led to lower yields of the desired product (Table 1, entries 10−13). The chloride product **3a** was not obtained in any of the investigations.

We examined the scope and limitations of this newly developed domino approach under the optimized conditions (Table 2). With electronic and steric variation ($-R^2$) on the acetylene moiety, the corresponding products were obtained in good to moderate yields (Table 2, entries 1−5). Alkynes bearing functional groups such as a cyanide or a tertiary alcohol (Table 2, entries 6−8) also gave the desired product in reasonable yields. The alkyne with a TMS group only afforded desilylated product **2j** in 48% yield (Table 2, entry 9). However, electronic effects on aromatic substitution of the chromone showed equivocal results in the reaction. Substrate **1m** with an electron-

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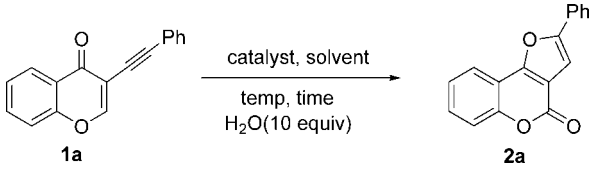
10.1021/jo800439y CCC: $40.75
Published on Web 05/28/2008

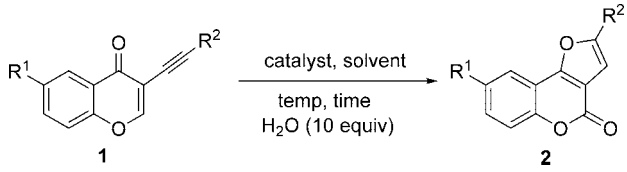
TABLE 1. Optimization of the CuCl-Catalyzed Cascade Reaction of 1a with H_2O and O_2[a]



entry	solvent	catalyst	temp, time	yield ([%)
1	DMF	10% CuCl	90 °C, 20 h	71
2	DMF	10% CuBr	90 °C, 20 h	69
3	DMF	10% CuCl	90 °C, 2.5 h	53
4	DMF	10% CuBr	90 °C, 2.5 h	41
5	DMF	10% CuCl	70−80 °C, 20 h	44
6	DMF	20% CuCl	90 °C, 10 h	86
7	DMF	50% CuCl	90 °C, 10 h	80
8	DMF	100% CuCl	90 °C, 10 h	96
9	DMF	10% CuCl	90 °C, 20 h	71[b]
10	CH_3CN	10% CuCl	reflux, 10 h	46
11	THF	10% CuCl	reflux, 10 h	8
12	toluene	10% CuCl	reflux, 10 h	low
13	dioxane	10% CuCl	reflux, 10 h	low

[a] Reaction was carried out on a 0.2 mmol scale and 0.04 mL of H_2O in 1 mL of solvent in an open flask and heated for the specified time. [b] The reaction was performed under an oxygen atmosphere.

TABLE 2. Scope of the Cu(I)-Catalyzed Reaction of 1 with H_2O and O_2 To Construct Furocoumarins[a]



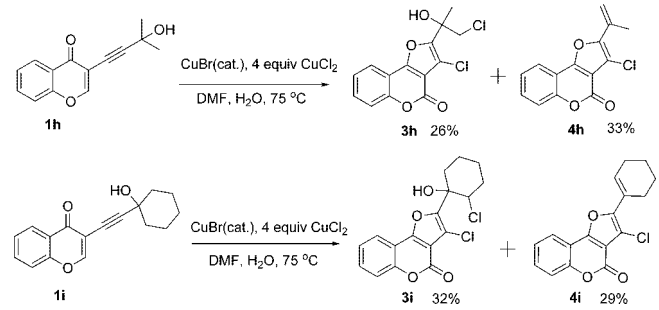
entry	R^1	R^2	product	yield (%)
1	H	4-CH_3-C_6H_4	**2b**	81
2	H	4-CH_3O-C_6H_4	**2c**	73
3	H	4-CF_3-C_6H_4	**2d**	73
4	H	$-(CH_2)_4CH_3$	**2e**	78
5	H	$-C(CH_3)_3$	**2f**	77
6	H	$-(CH_2)_3CN$	**2g**	69
7	H	$-C(CH_3)_2OH$	**2h**	55
8	H	$-C(CH_2)_5OH$	**2i**	56
9	H	$-Si(CH_3)_3$	**2j**	48[b]
10	CH_3	$-C_6H_5$	**2k**	74
11	Cl	$-C_6H_5$	***2l***	72
12	CH_3O	$-C_6H_5$	**2m**	45
13	NO_2	$-C_6H_5$	**2n**	46[c]

[a] Conditions: A mixture of 0.2 mmol of 3-alkynylchromone, H_2O (11.0 equiv) and 20 mol % of CuCl in 1 mL of DMF was heated at 90 °C. [b] R^2 = H. [c] The reaction was heated to 90 °C for 10 h, and then to 120 °C for 10 h.

donating group (R^1 = OMe) at the 6-position of the chromone gave the desired product **2m** in 45% yield (Table 2, entry 12), and substrate **1n** with an electron-withdrawing group (R^1 = NO_2) at the 6-position of the chromone afforded the corresponding product **2n** in 46% yield at 120 °C (Table 2, entry 13).

Our recent paper[2] reported that a mixture of **1a**, CH_3SO_3H (1.5 equiv), $CuCl_2$ (2.1 equiv), and 0.02 mL of H_2O in DMF at 90 °C in a one-pot process gave 3-chloro-2-phenyl-4*H*-furo[3,2-*c*]chromen-4-one **3a** (40%) and **2a** (35%), respectively (Table 3, entry 1). To improve the yield of **3a** for developing a coupling reaction to produce the diversified furocoumarins scaffold, optimization of this cascade addition−cyclization−chlorination−oxidation was further investigated. By increasing the amount

SCHEME 3. The Cascade Reaction with Subsequent Chlorination or Elimination



of $CuCl_2$ to 4.2 equiv, the yield of **3a** was improved with less directly cyclized product **2a** (Table 3, entry 2). Without the acid, the desired product **3a** was also obtained in low yield (Table 3, entry 3). Comparing the different catalysts (CH_3SO_3H, CuCl, and CuBr), CuBr is the most efficient, giving **3a** in 70% yield (Table 3, entry 6). The reason for the varying efficiencies of CuCl and CuBr is not clear at present.[1c] Reducing the reaction temperature to 75 °C was more beneficial, generating **3a** in 84% yield (Table 3, entry 7). However, with $CuBr_2$ as the brominating reagent and oxidant, the reaction gave complicated products (Table 3, entry 8). After testing other solvents, DMF was judged the best in the cascade addition−cyclization−oxidation−chlorination.

We applied the optimized conditions to synthesize a series of substituted 3-chloro-4*H*-furo[3,2-*c*]chromen-4-ones **3** (Table 4). With electronic and steric variation ($-R^2$) on the acetylene moiety, 3-alkynyl-4*H*-chromen-4-ones smoothly underwent reaction to give the corresponding products in good to moderate yields (Table 4, entries 1−6). Only an electron-withdrawing group on the aromatic ring of alkyne **1d** gave the corresponding product **3d** in 57% yield (Table 4, entry 3). When R^2 is TMS, the reaction only afforded the dichloride product **3j** in 40% yield (Table 4, entry 7). Substrates with a substituent of CH_3 or Cl at the 6-position of the chromone (R^1) reacted well to give **3k** and ***3l***. With an electron-donating group (R^1 = OMe), the reaction gave the desired product **3m** in 47% yield along with the chlorinated product of **3m** at the 8-position in 20% yield (Table 4, entry 10). The substrate with an electron-withdrawing group (R^1 = NO_2) afforded the desired product **3n** in 35% yield at a higher temperature (Table 4, entry 11).

Interestingly, substrates **1h** and **1i** bearing an α-hydroxyl group on the acetylene moiety generated products **3h** and **3i**, which were chlorinated at the carbon adjacent to the hydroxy group, together with elimination products **4h** and **4i** (Scheme 3. It is clear that the further chlorination in this cascade reaction is connected with the hydroxy group. This process may involve C−H activation by the SET transformation.[4] A mechanistic study of this reaction is under way.

On the basis of the above results, the mechanisms of the two cascade reactions are proposed (Figure 1). In the two processes, Cu(I) acting as a Lewis acid activates the carbonyl group and promotes a 1,4-addition of H_2O to the carbon−carbon double bond. In path A, Cu(I) could be coordinated with the alkynyl moiety of **B** to induce the cyclization, which is followed by the protonation of the resulting organocopper intermediate **C** to

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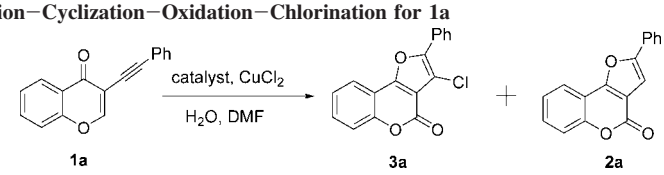
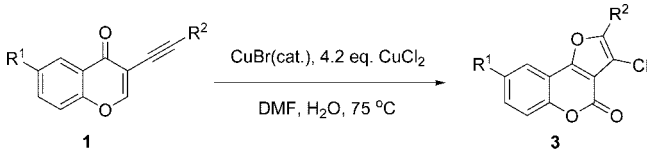
TABLE 3. Optimization of Addition−Cyclization−Oxidation−Chlorination for 1a



entry	solvent	catalyst	cupric salt	temp (°C)	yield (%) 3a	yield (%) 2a
1	DMF	CH_3SO_3H (1.5 equiv)	$CuCl_2$ (2.1 equiv)	90	40	35
2	DMF	CH_3SO_3H (1.5 equiv)	$CuCl_2$ (4.2 equiv)	90	59	19
3	DMF		$CuCl_2$ (4.2 equiv)	90	54	14
4	DMF	CH_3SO_3H (0.1 equiv)	$CuCl_2$ (4.2 equiv)	90	62	18
5	DMF	CuCl (0.1 equiv)	$CuCl_2$ (4.2 equiv)	90	48	17
6	DMF	CuBr (0.1 equiv)	$CuCl_2$ (4.2 equiv)	90	70	9
7	DMF	CuBr (0.1 equiv	$CuCl_2$ (4.2 equiv)	75	84	4
8	DMF	CuBr (0.1 equiv)	$CuBr_2$ (4.2 equiv)	75	complex	
9	CH_3CN	CuBr (0.1 equiv)	$CuCl_2$ (4.2 equiv)	reflux	15	0
10	acetone	CuBr (0.1 equiv)	$CuCl_2$ (4.2 equiv)	reflux	0	0

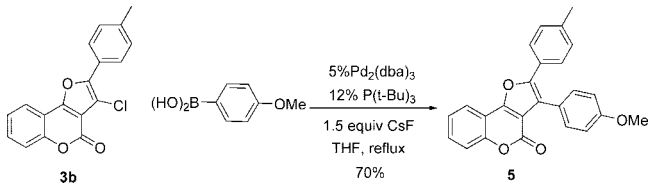
TABLE 4. Domino Addition−Cyclization−Oxidation−Chlorination To Construct Substituted 3-Chloro-4*H*-furo[3,2-*c*]chromen-4-ones 3[a]



entry	R^1	R^2	product	yield (%)
1	H	4-CH_3-C_6H_4	**3b**	77
2	H	4-CH_3O-C_6H_4	**3c**	86
3	H	4-CF_3-C_6H_4	**3d**	57
4	H	$-(CH_2)_4CH_3$	**3e**	75
5	H	$-C(CH_3)_3$	**3f**	76
6	H	$-(CH_2)_3CN$	**3g**	73
7	H	$-Si(CH_3)_3$	**3j**	40[b]
8	CH_3	$-C_6H_5$	**3k**	70
9	Cl	$-C_6H_5$	**3l**	65
10	CH_3O	$-C_6H_5$	**3m**	47
11	NO_2	$-C_6H_5$	**3n**	35[c]

[a] Conditions: 0.1 equiv of CuBr, 4.2 equiv of $CuCl_2$, and 10 equiv of H_2O, 75 °C, 10 h. [b] R^2 = Cl. [c] A mixture of **1n** (0.20 mmol), CuBr (0.02 mmol), $CuCl_2$ (0.84 mmol), and H_2O (2.2 mmol) in DMF (1 mL) was heated at 90 °C for 10 h, then heated to 110 °C for an additional 20 h.

SCHEME 4. Suzuki Coupling Reaction of 3b



afford lactol **D** with simultaneous regeneration of the Cu(I) catalyst.[1c] Lactol **D** is oxidized to lactone **E** by O_2 in an open-flask reaction. In this process, Cu(I) was not transformed to Cu(II) as oxidant because chlorofurocoumarins were not observed as byproduct. In path B, $CuCl_2$ could be employed as the chlorination reagent and oxidant as well because alkenes and alkynes can be halogenated by $CuCl_2$.[5] Compared with path A, $CuCl_2$ has a stronger association with the triple bond of **B** and promotes the cyclization to release CuCl even though Cu(I) exists in the reaction.

A further application for chlorofurochromenones was initially tested by a Suzuki reaction (Scheme 4). After testing several reaction conditions, only P(*t*-Bu)$_3$ as ligand gave a satisfactory result because **3b** is an inactive substrate.

In summary, we have developed two efficient one-pot cascade reactions to generate substituted furocoumarins. One cascade addition/cyclization/oxidation of **1** with H_2O in the presence of 20% CuCl as Lewis acid under an air atmosphere generated 2-substituted 4*H*-furo[3,2-*c*]chromen-4-one. Another reaction in the presence of 10% CuBr and excess $CuCl_2$ as the oxidant afforded 3-chloro-2-substituted-4*H*-furo[3,2-*c*]chromen-4-one. Comparing the two tandem processes, Cu(I) did not transform to Cu(II) as oxidant under the first reaction conditions because the chloride product was not obtained. $CuCl_2$ could be a stronger coordination reagent with the triple bond of 2-(1-alkynyl)-2-

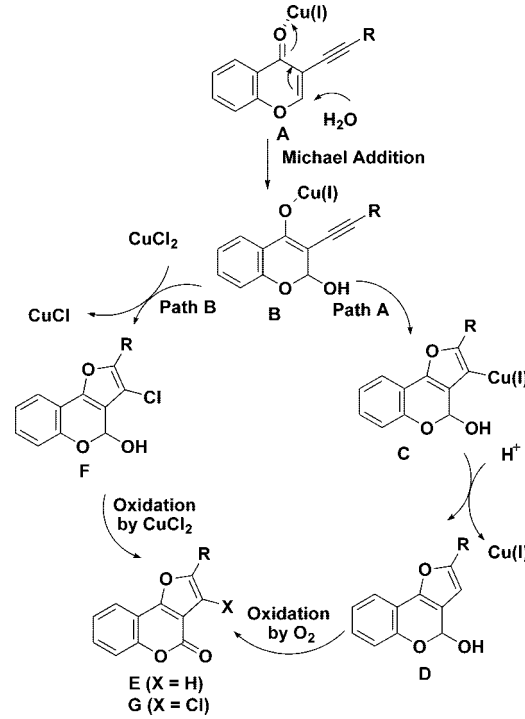


FIGURE 1. The proposed mechanisms of the two cascade processes.

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alken-1-one than CuCl because the major product was the chloride at the 3-position under the second reaction conditions. Further applications of these methods and the biological activities of these compounds are currently being investigated in our laboratory.

Experimental Section

Procedure A: Synthesis of 4*H*-Furo[3,2-*c*]chromen-4-ones by CuCl-Catalyzed Cascade Reaction of 1 with H_2O and O_2. A solution of substrate **1** (3-alkynyl-chromone, 0.2 mmol), CuCl (4.0 mg, 0.04 mmol), and H_2O (0.04 mL, 2.2 mmol) in DMF (1 mL) was heated at 90 °C for 10−20 h. Then the reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The organic layer was washed with water (3 × 30 mL) and brine (10 mL) and then dried over Na_2SO_4. Upon removal of the solvent, the residue was purified by column chromatography to afford corresponding 4*H*-furo[3,2-*c*]chromen-4-ones.

2-*p*-Tolyl-4*H*-furo[3,2-*c*]chromen-4-one (2b)[4]. With **1b** as substrate, procedure A was followed then the product was purified by flash chromatography (silica gel, 6:1 petroleum ether/ethyl acetate) to afford 45 mg of **2b** (81%) as a white solid: mp 205−206 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (dd, J = 7.8, 1.4 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.52 (td, J = 7.7, 1.4 Hz, 1H), 7.45 (dd, J = 7.7, 1.4 Hz, 1H), 7.37 (td, J = 7.7, 1.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.11 (s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 158.22, 156.83, 156.51, 152.47, 139.28, 130.38, 129.63, 126.16, 124.47, 124.43, 120.68, 117.28, 112.75, 112.47, 101.81, 21.36; MS (EI) m/z 276 (M^+, 100). Anal. Calcd for $C_{18}H_{12}O_3$: C 78.25, H 4.38. Found: C 77.92, H 4.38.

Procedure B: Synthesis of 3-Chloro-4*H*-furo[3,2-*c*]chromen-4-ones by the CuBr-Cascade Reaction of 1 with H_2O and $CuCl_2$. A solution of substrate **1** (3-alkynyl-chromone, 0.2 mmol), CuBr (2.9 mg, 0.02 mmol), $CuCl_2$ (113.4 mg, 0.84 mmol), and H_2O (0.04 mL, 2.2 mmol) in DMF (1 mL) was heated at 90 °C for 10−20 h. Next the reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The organic layer was washed with water (3 × 30 mL) and brine (10 mL) and then dried over Na_2SO_4. Upon removal of the solvent, the residue was purified by column chromatography to afford the corresponding 3-chloro-4*H*-furo[3,2-*c*]chromen-4-ones.

3-Chloro-2-*p*-tolyl-4*H*-furo[3,2-*c*]chromen-4-one (3b). With **1b** as substrate, procedure B was followed and the product was purified by flash chromatography (silica gel, 2:1 petroleum ether/CH_2Cl_2) to afford 48 mg of **3b** (77%) as a white solid: mp 169−171 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 3H), 7.53 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.28 (t, J = 8.4 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.17, 155.02, 152.41, 149.94, 139.57, 131.06, 129.38, 125.37, 124.83, 124.62, 120.64, 117.16, 112.04, 110.01, 109.27, 21.37; MS (EI) m/z 310 (M^+ (^{35}Cl), 100), 312 (33); HRMS calcd for $C_{18}H_{11}ClO_3$ (^{35}Cl) 310.0397, found 310.0389.

Acknowledgment. The Hundred Talent Project of the Chinese Academy of Sciences supported this work.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800439Y