One-pot synthesis of furocoumarins through cascade addition–cyclization–oxidation†

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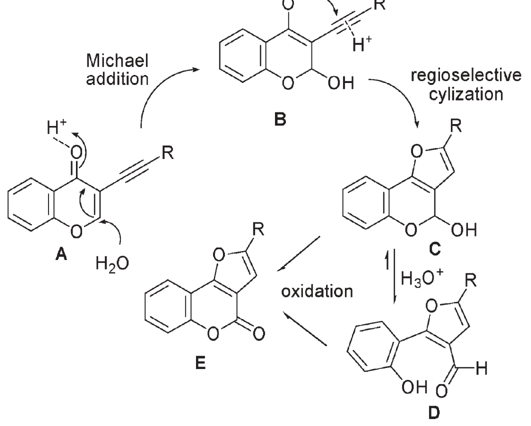
A novel one-pot cascade addition–cyclization–oxidation for the regioselective synthesis of furo[3,2-*c*]coumarins has been developed; the reaction is mild and easily handled without the necessity for dry solvents and inert atmosphere.

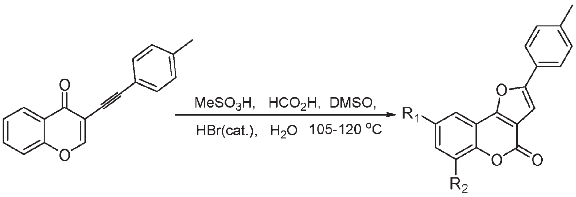
Furocoumarins can be found in many natural products and exhibit potent biological activity.[1] Most synthetic methods have focused on coumestrol which is the combination of the benzofuran and coumarin scaffold.[2] Only a few reports have described the synthesis of substituted furo[3,2-*c*]coumarins and furo[2,3-*b*]coumarins in poor regioselectivity by rhodium(II)-catalysed heterocyclization of 3-diazobenzopyran-2,4(3*H*)-dione[3] or CAN mediated [3 + 2] cyclization of 4-hydroxycoumarin[4] with terminal alkynes. Herein, we report a highly efficient, acid-promoted and regioselective one-pot reaction to construct furo[3,2-*c*]coumarins by addition–cyclization–oxidation.

Recently much attention has been paid to the synthesis of highly substituted furans from 2-(1-alkynyl)-2-alken-1-ones by transition metal-catalyzed (Au, Pt, Cu)[5] or electrophilic cyclization.[6] This unique cyclization is particularly attractive because it allows the formation of a C–O bond and a nucleophilic domino attack on a double and triple bond. Based on the current plausible reaction mechanism, we hypothesized the transformation from chromone **A** could be promoted by acid without transition metal[7] and water as nucleophile through cascade 1,4-addition and cyclization to afford the corresponding product **C** or **D**, which is followed by oxidation to give furocoumarin **E** (Scheme 1).



Scheme 1 Plausible reaction mechanism.

Initially, we investigated the reaction of **1** with CH_3SO_3H–HCO_2H as the acidic promoter and DMSO–H_2O–HBr[8] as the oxidant, three products **2a** (25%), **2b** (23%) and **2c** (5%) were obtained (eqn (1)). After a mixture of **1** with CH_3SO_3H and HCO_2H in DMSO was heated at 105 °C for 10 min, HBr was added and the reaction was stirred for 3 h to give only **2a** in 50% yield. When the excess amount of $CuCl_2$ was employed as the oxidant in this sequential one-pot reaction, the yield of **2a** was increased to 75%.



(1)

1

2a R_1=H, R_2=H 25%
2b R_1=Br, R_2=H 23%
2c R_1=Br, R_2=Br 5%

Based on the above results, a number of different oxidants, solvents, acids and operating procedures were tested to optimize this domino reaction condition. Substrate **3** was treated with 1.5 equiv. of CH_3SO_3H or CF_3COOH and an excess amount of H_2O in DMF at 90 °C without protection for 1 h, and then 2.1 equiv. of $CuCl_2$ was added to the reaction mixture. After the reaction mixture was stirred for 20 h at 90 °C, the desired product **4** was obtained in 89 or 85% yields (Table 1, entries 11, 13).‡ Among the selected oxidants, $CuCl_2$ is the most efficient one. Without acids or with only a catalytic amount of CH_3SO_3H in the sequential one-pot process, compound **4** was afforded in 30 or 41% yield, respectively (Table 1, entries 9, 10). The protonic acid facilitates the transformation of **A** to **C**, and might promote the process from **C** (or **D**) to **E** as well. When all reagents (CH_3SO_3H and $CuCl_2$) were mixed in this domino reaction, 35% yield of **4** and 40% yield of **4a** were obtained simultaneously (Table 1, entry 15). An excess of $CuCl_2$ (2.1 equiv.) could play the dual roles as Lewis acid and the oxidant in the absence of protonic acid in DMF at 90 °C, and reaction occurred to give **4** and **4a** in 39 and 40% yields, respectively (Table 1, entry 16). In the presence of a catalytic amount of $CuCl_2$, oxygen could be the oxidant in an open-flask operation, and reaction proceeded with the catalytic acid or without the acid to gave **4** in 63 and 55% yields, respectively (Table 1, entries 17, 18). The optimisation of the reaction under different conditions gave the best yield of **4** in entry 11.

In order to determine the regioselectivity of the cyclization from two different hydroxyl nucleophiles, the structure of **4** was verified by single-crystal X-ray diffraction analysis (Fig. 1).§

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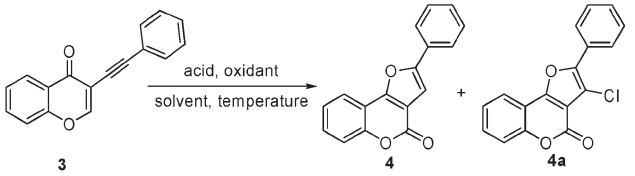
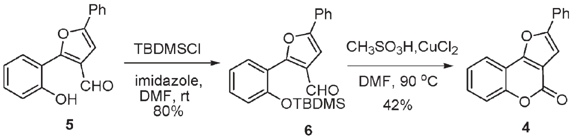
Table 1 Optimisation of the cascade one-pot reaction of **3**[a]



Entry	Solvent	Acid	Oxidant	*T*/°C	Yield (%)
1	DMSO	$CH_3SO_3H–HCO_2H$	$CuCl_2$	80–90	74
2	DMSO	CH_3SO_3H	$CuCl_2$	80–90	84
3	DMSO	CH_3SO_3H	$CuSO_4$	80–90	50
4	DMSO	CH_3SO_3H	$CuBr_2$	80–90	30
5	DMSO	CH_3SO_3H	$Cu(OAc)_2$	80–90	9
6	DMSO	CH_3SO_3H	$FeCl_3$	90	31
7	DMSO	CH_3SO_3H	$CuCl_2$	100–110	44
8	DMF	CH_3SO_3H	$CuCl_2$	100–110	69
9	DMF	—	$CuCl_2$	90	30[b]
10	DMF	cat. CH_3SO_3H	$CuCl_2$	90	41[c]
11	**DMF**	$\mathbf{CH_3SO_3H}$	$\mathbf{CuCl_2}$	**90**	**89**
12	DMF	CH_3SO_3H	cat. $CuCl_2$	90	38
13	DMF	CF_3CO_2H	$CuCl_2$	90	85
14	DMF	CH_3SO_3H	$FeCl_3$	90	31
15	DMF	CH_3SO_3H	$CuCl_2$	90	35[d]
16	DMF	—	$CuCl_2$	90	39[d]
17	DMF	cat. CH_3SO_3H	cat. $CuCl_2$	90	63[d]
18	DMF	—	cat. $CuCl_2$	90	55[d]

[a] *Reaction conditions*: a mixture of substrate **3** (60 mg, 0.24 mmol), acid (0.38 mmol) and H_2O (2.22 mmol) in solvent (2 mL) was heated at 80–110 °C for 1 h, and then the oxidant was added (0.50 mmol). [b] The mixture without the acid was heated at 90 °C for 2.5 h, and then $CuCl_2$ was added. [c] The mixture with the catalytic amount of CH_3SO_3H (0.024 mmol) was heated for 2.5 h, $CuCl_2$ was added. [d] All of the reagents were mixed and heated.

Since the intermediate **C** or **D** from the acid promoted cyclization of **3** is not stable, we successfully trapped it by the protection of the hydroxyl group with TBDMSCl (eqn (2)), which provided the stable species **6** in 80% yield. Compound **6** could be further oxidized to lactone **4** in 42% yield by addition of CH_3SO_3H and $CuCl_2$ at 90 °C in DMF.



(2)

When methanol was employed as the nucleophile instead of water in the acid promoted cascade reaction at 60 °C, 4-methoxy-2-phenyl-4*H*-furo[3,2-*c*]chromene **7** was generated in a high yield,

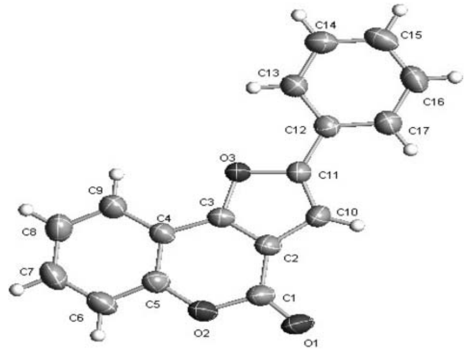
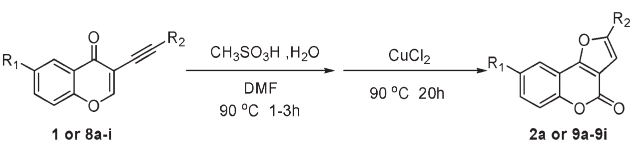
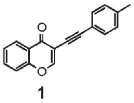
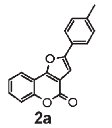
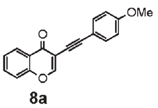
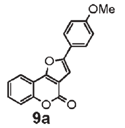
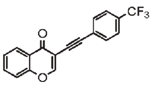
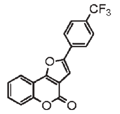
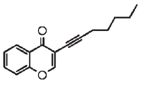
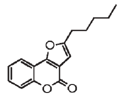
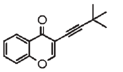
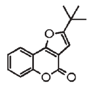
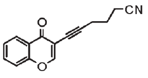
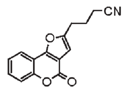
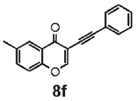
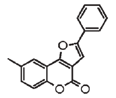
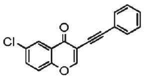
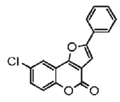
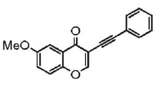
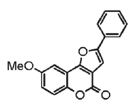
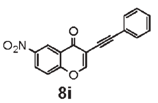
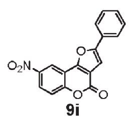


Fig. 1 X-Ray crystal structure of **4**. Ellipsoid probability: 50%.

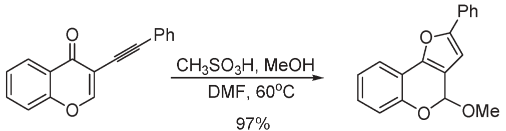
Table 2 One-pot synthesis of substituted furocoumarins[a]



Entry	Substrate	Product	Yield (%)
1	 **1**	 **2a**	89
2	 **8a**	 **9a**	74
3	 **8b**	 **9b**	72
6	 **8c**	 **9c**	60
5	 **8d**	 **9d**	77
6	 **8e**	 **9e**	64
7	 **8f**	 **9f**	72
8	 **8g**	 **9g**	70
9	 **8h**	 **9h**	37
10	 **8i**	 **9i**	51[b]

[a] *Reaction conditions*: a mixture of substrate (0.24 mmol), CH_3SO_3H (0.025 mL, 0.38 mmol) and H_2O (0.04 mL, 2.22 mmol) in the DMF (2 mL) was stirred at 90 °C for 1 h, $CuCl_2$ was added (67 mg, 0.50 mmol) and the reaction was stirred for 20 h. [b] After addition of $CuCl_2$, the reaction was heated at 120 °C for an additional 40 h.

which is superior to the reported transition-metal catalyzed results in the literature.[5a,5c] (eqn (3)).



3 **7** (3)

To delineate this approach, particularly in regard to library construction, this methodology was evaluated by using different substituted chromones and alkynes. The results are given in Table 2. With electronic and steric variation (–R_2) on the acetylene moiety the corresponding products were obtained in good to moderate yields. However, electronic effects on aromatic substitution of chromone showed the complicated results in the reaction. Substrate **8h** with electron-donating group (R_1 = OMe) at 6-position of chromone gave the desired product **9h** in 37% yield with a byproduct (chlorinated product of **9h** at 8-position) in 20% yield (Table 2, entry 9). Substrate **8i** with electron-withdrawing group (R_1 = NO_2) at 6-position of chromone gave the final product **9i** in 51% yield.

In conclusion, we have developed a novel one-pot cascade reaction for regioselective synthesis of furo[3,2-*c*]coumarins. Notably, this reaction is easily handled and mild, without the necessity for dry solvents and inert atmosphere. Further application of this method and biological activities of compounds are under investigation.

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Notes and references

‡ *Synthesis* of **4**: After the solution of **3** (60 mg, 0.24 mmol), CH_3SO_3H (0.025 mL, 0.38 mmol) and H_2O (0.04 mL, 2.2 mmol) in DMF (1.5 mL) was heated at 90 °C for 0.5 h, $CuCl_2$ (67 mg, 0.50 mmol) was added and the reaction mixture was stirred for 20 h. After complete consumption of the intermediate as determined by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The organic layer was washed with water (30 mL × 3) and brine (10 mL) and then dried over $MgSO_4$. Upon removal of the solvent, the residue was purified by column chromatography (silica gel, 2 : 1 petroleum ether–CH_2Cl_2) to afford 57 mg (89%) of compound **4**.

§ *Crystallographic data*: **4**; CCDC 622672. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b705315k

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