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Copper-Catalyzed Synthesis of Furo[3,2-*c*]coumarins and Dihydrofuro[3,2-*c*]coumarins through a Propargylation/Alkyne Oxacyclization/Isomerization Cascade under Microwave Irradiation

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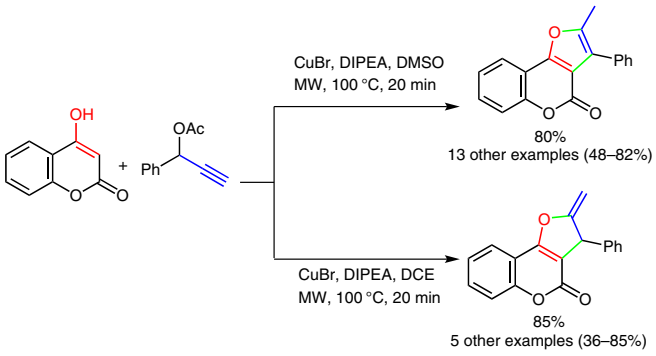

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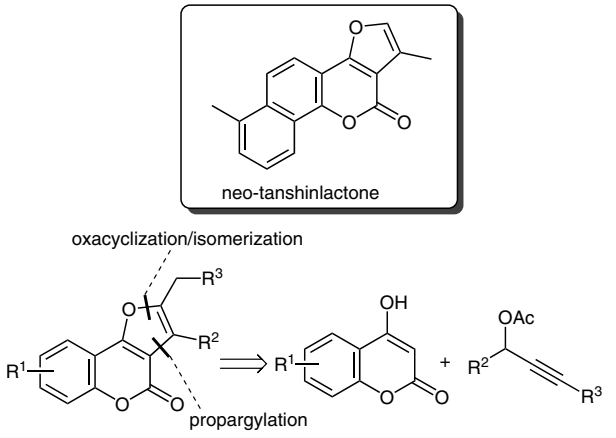
Abstract A novel copper-catalyzed microwave-promoted propargylation/alkyne oxacyclization/isomerization cascade for the synthesis of 2-methylfuro[3,2-*c*]coumarins has been developed. This reaction provides furo[3,2-*c*]coumarins in moderate to good yields (≤82%) from readily available 4-hydroxycoumarins and terminal propargyl acetates as starting materials. Interestingly, by changing the solvent from dimethyl sulfoxide to 1,2-dichloroethane, the isomeric series of 2-methylene-2,3-dihydrofuro[3,2-*c*]coumarins were obtained in good to acceptable yields (≤85%).

Key words cascade reactions, coumarins, propargyl acetates, furocoumarins, cyclization

The furo[3,2-*c*]coumarin (4*H*-furo[3,2-*c*]chromen-4-one) framework occurs frequently in many medicinally important compounds with a wide variety of biological activities.[1,2] For example, neo-tanshinlactone and its analogues, which contain a furo[3,2-*c*]coumarin moiety, show selective cytotoxicity against two estrogen receptor-positive breast cancer cell lines, MCF-7 and ZR-75-1 (Scheme 1).[1,2] Consequently, the efficient construction of furo[3,2-*c*]coumarins from readily available starting materials has attracted much attention. Although several approaches[3] have already been developed for the synthesis of furo[3,2-*c*]coumarin analogues, these protocols have the drawbacks of requiring multiple steps or expensive metal catalysts or of tolerating a limited range of substituents. Given the potential applications of these compounds in drug-discovery research, a rapid, simple and efficient construction of structurally diverse furo[3,2-*c*]coumarins is much desired.



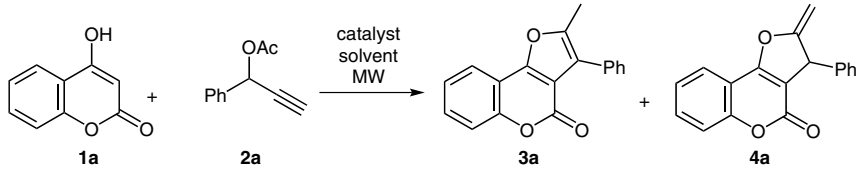
Scheme 1 Neo-tanshinlactone and a retrosynthetic analysis of its analogues containing a furo[3,2-*c*]coumarin moiety

Recently, a propargylation/alkyne oxacyclization/isomerization cascade,[4] based on the activation of propargylic alcohols and their derivatives by transition metals, has emerged as a powerful tool for the assembly of heterocycles that show potential applications in biomedical research.[5,6] Because the use of microwave irradiation frequently results in efficient processes, clean reactions, and high yields in synthetic chemistry,[7] we aimed to combine the efficiency of the cascade reaction with that of a microwave-assisted process to develop rapid, simple, and efficient protocols for

the synthesis of medicinally important molecules. Inspired by recent achievements,[5] we surmised that microwave irradiation might be introduced into the synthesis of furocoumarins by the propargylation/alkyne oxacyclization/isomerization cascade (Scheme 1). Here, we report a copper-catalyzed synthesis of furocoumarins and dihydrofurocoumarins from the corresponding 4-hydroxycoumarins and propargyl acetates under microwave irradiation.

We chose 4-hydroxycoumarin (**1a**) and the propargylic ester **2a** as model substrates with copper(I) bromide as catalyst in the presence of *N*,*N*-diisopropylethylamine in dimethyl sulfoxide at 100 °C with microwave irradiation for 20 minutes as our initial conditions (Table 1). To our delight, the desired product **3a** and the isomeric 2-methylene-2,3-dihydrofuro[3,2-*c*]coumarin **4a**, bearing an exocyclic C=C double bond, were detected by NMR spectroscopy in 74% and 11% yield, respectively (Table 1, entry 1). This initial experiment demonstrated that the transformation into a furocoumarin or a dihydrofurocoumarin is possible in principal; we therefore conducted a screening of copper salts and solvents. Other copper salts under the same conditions gave lower yields of the desired furo[3,2-*c*]coumarin **3a** (entries 2–5). No improvement in the yield was achieved by changing the solvent (entries 6–10). Interestingly, however, the use of 1,2-dichloroethane gave the dihydrofurocoumarin **4a** as the major product of the reaction. We reasoned that it is because of the absence of the proton-transforming enhancement observed in reactions with dimethyl sulfoxide as solvent (entry 1 versus entry 8). By using an excess of the 4-hydroxycoumarin **1a** and performing the reaction at a higher concentration, we obtained improved yields, whereas decreasing the catalyst loading had no significant influence on the yield (entries 11–13). An excess of the 4-hydroxycoumarin, a lower catalyst loading, and a higher concentration gave an improved yield (92%) of the dihydrofurocoumarin **3a** (entry 14). However, the yield of dihydrofurocoumarin **3a** was sensitive to both the reaction

Table 1 Reaction Development[a]



1a **2a** **3a** **4a**

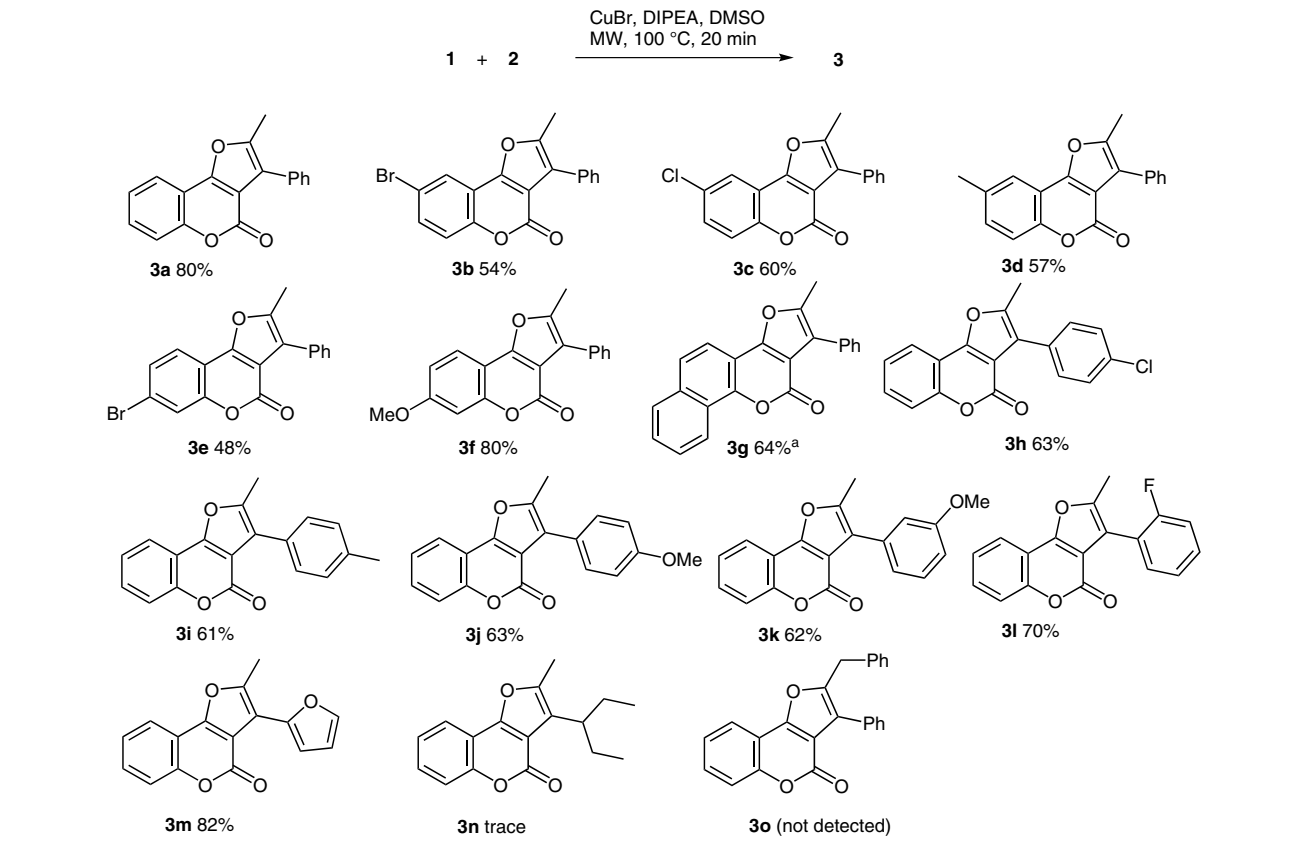
Entry	Catalyst	Solvent	Temp (°C)	Time (min)	Yield[b] (%) of **3a**	Yield[b] (%) of **4a**
1	CuBr	DMSO	100	20	74	11
2	CuI	DMSO	100	20	57	<5
3	CuCl	DMSO	100	20	52	<5
4	$Cu(OTf)_2$	DMSO	100	20	49	<5
5	$Cu(OAc)_2 \cdot H_2O$	DMSO	100	20	44	<5
6	CuBr	MeOH	100	20	15	60
7	CuBr	MeCN	100	20	51	30
8	CuBr	DCE	100	20	16	74
9	CuBr	1,4-dioxane	100	20	6	48
10	CuBr	toluene	100	20	12	73
11[c]	CuBr	DMSO	100	20	82	<5
12[c,d]	CuBr	DMSO	100	20	81	<5
13[c–e]	CuBr	DMSO	100	20	91 (80)[f]	<5
14[c–e]	CuBr	DCE	100	20	<5	92 (85)[f]
15[c–e]	CuBr	DCE	120	20	40	22
16[c–e]	CuBr	DCE	100	30	58	24

[a] Reaction conditions: (unless otherwise noted) **1a** (0.2 mmol), **2a** (0.2 mmol), DIPEA (1 equiv), catalyst (10 mol%), solvent (1.0 mL).
[b] Determined by ^1H NMR with CH_2Br_2 as internal standard.
[c] **1a** (1.2 equiv).
[d] CuBr (5 mol%).
[e] Concentration 0.4 M.
[f] Isolated yield.

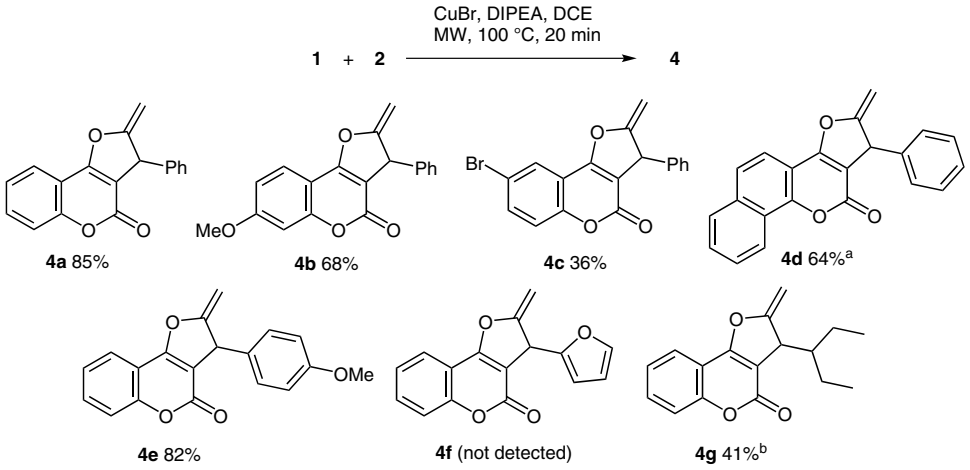
time and the temperature, partly as a result of its isomerization into the furocoumarin **4a** in the presence of a base (entries 15 and 16)

Having determined the optimized conditions (Table 1, entry 13), we subjected various 4-hydroxycoumarins **1** to the developed procedure. 4-Hydroxycoumarins **1** bearing either an electron-withdrawing group (Br or Cl) or an electron-donating group (Me) in the 6-position gave the corresponding furo[3,2-*c*]coumarins **3b**–**d** in fair yield (54–60%). 7-Bromo-4-hydroxycoumarin gave a lower yield of product **3e**, whereas 7-methoxy-4-hydroxycoumarin gave a good yield of **3f**, indicating that an electron-donating group is beneficial for the reaction. 4-Hydroxybenzo[*h*]coumarin also gave the expected product **3g** in 64% yield. We then examined the scope of the reaction with respect to the propargyl acetate **2** (Scheme 2). Reactions with aryl propargylic esters proceeded smoothly to give the desired products **3h**–**l** in moderate to good yields (61–70%). The substituents on the aryl ring had little effect on the yield. A hetaryl-substituted propargylic ester gave the corresponding furo[3,2-*c*]-coumarin **3m** in good yield. A trace of product **3n** was detected in the case of an alkylated propargylic ester, which showed poor reactivity.[8] The reaction did not seem to be amenable to the use of a propargylic ester with an internal alkyne group, as this type of substrate failed to give the product **3o** under the usual conditions. This suggests that the formation of a copper–allenylidene complex is essential for catalysis to occur.[9]

Because both dihydrofurans[10] and coumarins[11] are common moieties in natural products and act as important precursors in synthetic chemistry, we also attempted to synthesize dihydrofuro[3,2-*c*]coumarins, combining both moieties.[12,13] From our studies on the optimized conditions (Table 1, entry 14), we surmised that replacing dimethyl sulfoxide as a solvent with 1,2-dichloroethane might give the corresponding 2-methylenedihydrofuro[3,2-*c*]coumarin products. This hypothesis turned out to be correct, and product **4a**–**e** were obtained in moderate to good yields (Scheme 3). A 4-hydroxycoumarin bearing an electron-withdrawing group gave compound **4c** in a lower yield as a result of an isomerization side reaction. However, dihydrofuro[3,2-*c*]coumarin **4f** was not obtained under the current reaction conditions because of the formation of the isomerized product **3m**.[14] Compound **4g** was not obtained with 1,2-dichloroethane as solvent, but the use of dimethyl sulfoxide as the solvent did give the desired product.



Scheme 2 Scope of the copper-catalyzed microwaved-promoted process for the construction of furo[3,2-*c*]coumarins. *Reagents and conditions*: **1** (0.48 mmol), **2** (0.4 mmol), DIPEA (0.4 mmol), CuBr (5 mol%), DMSO (1.0 mL), microwave irradiation, 100 °C, 20 min. The reported yields are isolated yields.
[a] Irradiated for 30 minutes.



Scheme 3 Synthesis of dihydrofuro[3,2-*c*]coumarins. *Reagents and conditions*: **1** (0.48 mmol), **2** (0.4 mmol), DIPEA (0.4 mmol), CuBr (5 mol%), DCE (1.0 mL), microwave irradiation, 100 °C, 20 min. The reported yields are the isolated yields. [a] Irradiated for 40 min. [b] In DMSO at 150 °C with CuBr (20 mol%).

In conclusion, we have developed a novel copper-catalyzed microwaved-promoted process for the construction of furo[3,2-*c*]coumarins from 4-hydroxycoumarins and terminal propargyl acetates in moderate to good yields through a propargylation/alkyne oxacyclization/isomerization cascade.[15] By using 1,2-dichloromethane as the solvent instead of dimethyl sulfoxide, a range of 2-methylenedihydrofuro[3,2-*c*]coumarins could be obtained as the major products.[16] The extension of the strategy to the synthesis of other analogues and its application in biomedical research are currently ongoing in our laboratory.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560500.

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(14) In this case, the isomerized product **3m** was isolated in 91% yield.

(15) **Furo[3,2-*c*]coumarins 3; General Procedure**
A mixture of 4-hydroxycoumarin **1** (0.48 mmol, 1.2 equiv), propargyl acetate **2** (0.40 mmol, 1.0 equiv), DIPEA (0.40 mmol, 1.0 eq), CuBr (0.02 mmol, 5 mol%), and DMSO (1 mL) was stirred at r.t. for 30 s and then heated at 100 °C for 20 min by microwave irradiation. The mixture was then cooled to r.t., the reaction was quenched with sat. aq NH_4Cl, and the mixture was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by a flash chromatography (silica gel, hexane–EtOAc) gave the desired product **3**.

(16) **2-Methylene-2,3-dihydrofuro[3,2-*c*]coumarins 4; General Procedure**
A mixture of 4-hydroxycoumarin **1** (0.48 mmol, 1.2 equiv), propargyl acetate **2** (0.40 mmol, 1.0 equiv), DIPEA (0.40 mmol, 1.0 equiv), CuBr (0.02 mmol, 5 mol%), and DCE (1 mL) was stirred at r.t. for 30 s and then heated at 100 °C for 20 min by microwave irradiation. The mixture was cooled to r.t. and directly purified by flash chromatography (silica gel, hexane–EtOAc) to give the desired product **4**.