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FULL PAPER

Regioselective Access to Structurally Diverse Coumarin Analogues via Iron-catalyzed Annulation Reactions

Qiao Ren,*[b] Jie Kang,[c] Muyao Li,[b] Lujiang Yuan,[b] Ruoyun Chen,[c] and Lei Wang*[a]

[a] Prof. Dr. L. Wang
Department of Natural Medicine Chemistry Research Center
Institute of Medicinal Plant Development
Chinese Academy of Medical Science and Peking Union Medical College
Beijing 100193, P.R. China.
E-mail: siquanwl@gmail.com

[b] Dr. Q. Ren, M. Li, L. Yuan
College of Pharmaceutical Sciences
Southwest University
No.2 Tiansheng Road, BeiBei District, Chongqing 400715, P. R. China
Email: qren2014@swu.edu.cn

[c] J. Kang, R. Chen
State Key Laboratory of Bioactive Substance and Function of Natural Medicines
Institute of Materia Medica
Chinese Academy of Medical Sciences & Peking Union Medical College
No. 1 Xiannongtan Street, Beijing 100050, P.R. China.

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Abstract: A highly efficient iron-catalyzed propargylation-alkyne oxacyclization-isomerization strategy is disclosed to expeditiously assemble representative bioactive furo[3,2-*c*]coumarins and pyrano[3,2-*c*]coumarins with moderate to good yields and a broad substrate scope. The regioselective access to different coumarins is mainly dependent on the terminal group of the secondary propargylic alcohol.

Introduction

The coumarin ring, a privileged oxygen-containing heterocycle structural motif, is ubiquitous in a diverse range of natural products and pharmaceuticals. Among them, furo[3,2-*c*]coumarin, the well-known tricyclic compound in which a coumarin unit is angularly fused to the furan scaffold, has drawn considerable attention due to its broad spectrum biological activities on cell cycle, apoptosis and differentiation (Fig. 1).[1] For example, neo-tanshinlactone is a natural product isolated from *Salvia miltiorrhiza* and selectively inhibits the proliferation of estrogen receptor positive breast cancer cells through transcriptional down-regulation of *ESR1* mRNA.[1,2] Additionally, many naturally occurring coumestans demonstrate intriguing anti-inflammatory, estrogenic, antitumor, antioxidant and antihepatotoxic activities, such as glycyrol[3], coumestrol[4], medicagol[5], plicadin[6] and wedelolactone[7]. Therefore, the efficient construction of furo[3,2-*c*]coumarin skeleton is of great significance in chemical and biological community.

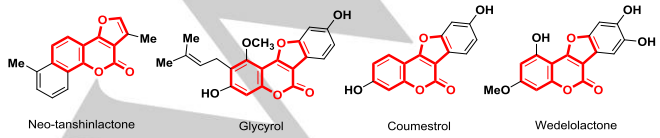
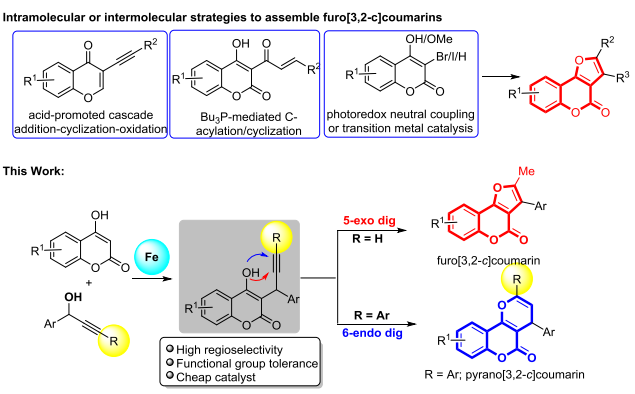


Figure 1. Representative bioactive natural products built on the furo[3,2-*c*]coumarin core scaffold.

Consequently, numerous elegant approaches have been developed to access the furo[3,2-*c*]coumarin derivatives, such as acid-promoted cascade addition-cyclization-oxidation, Bu_3P-mediated C-acylation/cyclization reaction, photoredox neutral coupling and transition metal catalysis (Scheme 1).[8] Notably, the readily accessible propargylic alcohols have been employed as the powerful substrates to construct the densely functionalized furans by the aid of transition metal (Ru, Ca, Yb, Al and Cu).[9] However, these typical methods always suffer from expensive transition metal catalysts, harsh conditions and limited functional group tolerance. In this regards, the development of novel approaches is still highly desirable to expeditiously assemble diverse coumarin derivatives from readily available starting materials. Recent studies indicated the iron catalysis could be employed as an important alternative to trigger the transformations in comparison with using expensive transition metals catalysts.[10] To the best of our knowledge, the iron-catalyzed synthesis of furo[3,2-*c*]coumarins and related coumarin analogues from the readily available starting materials is less explored.[11] Herein, we disclosed an expeditious assembly of valuable furo[3,2-*c*]coumarins and pyrano[3,2-*c*]coumarins with high regioselectivities *via* iron-catalyzed annulation reactions.

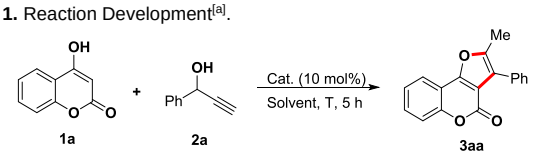


Scheme 1. Routes for the construction of the coumarin core scaffold.

Results and Discussion

Preliminary studies were conducted with 4-hydroxycoumarin **1a** and 1-phenylprop-2-yn-1-ol **2a** as the model substrates in the presence of $FeCl_3·6H_2O$ in $MeNO_2$ at 80 °C. Gratifyingly, $FeCl_3·6H_2O$ exhibited an excellent catalytic activity, resulting in the construction of the desired furo[3,2-*c*]coumarin product **3aa** in 80% yield (Table 1, entry 1). To seek a more efficient metal catalyst, we then examined some other Fe(III) and Fe(II) salts (entries 2—7). As a result, the iron(III) perchlorate monohydrate enabled the model reaction to give the best yield (entry 3, 87%). Some other transition metal catalysts , such as Cu, Ag and Zn salts, were also evaluated under identical reaction conditions, but no improvement was achieved (entries 8—10, <43%). Further exhaustive optimization was also performed by evaluating other parameters, such as solvent as well as temperature (entries 11—17). Results revealed that the best catalytic activity was obtained with $MeNO_2$ at 80 °C. It is notable that a slightly lower yield was achieved when the catalyst loading was reduced to 5 mol% (entry 18, 75%).

Table 1. Reaction Development[a].

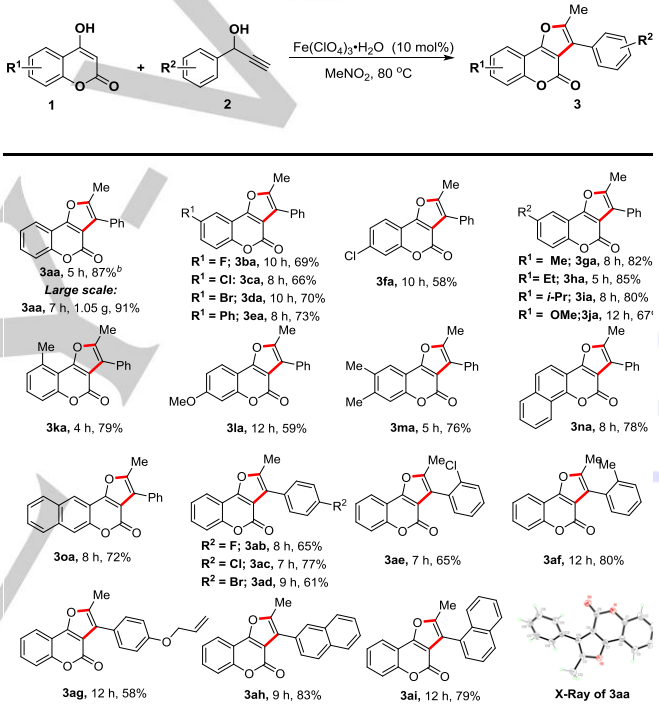


Entry	Solvent	Catalyst	Temp (°C)	Yield[b] (%) of **3aa**
1	$MeNO_2$	$FeCl_3·6H_2O$	80	80
2	$MeNO_2$	$FeBr_3$	80	60
3	$MeNO_2$	$Fe(ClO_4)_3·H_2O$	80	87
4	$MeNO_2$	$Fe(NO_3)_3·9H_2O$	80	56
5	$MeNO_2$	$FeCl_2·4H_2O$	80	26
6	$MeNO_2$	$Fe(BF_4)_2·4H_2O$	80	30
7	$MeNO_2$	$Fe(ClO_4)_2·6H_2O$	80	57
8	$MeNO_2$	CuI	80	NR
9	$MeNO_2$	AgOAc	80	NR
10	$MeNO_2$	$Zn(CF_3SO_3)_2$	80	43
11	DCE	$Fe(ClO_4)_3·H_2O$	80	65
12	DMF	$Fe(ClO_4)_3·H_2O$	80	NR
13	Toluene	$Fe(ClO_4)_3·H_2O$	80	37
14	$MeNO_2$	$Fe(ClO_4)_3·H_2O$	100	87
15	$MeNO_2$	$Fe(ClO_4)_3·H_2O$	60	57
16	$MeNO_2$	$Fe(ClO_4)_3·H_2O$	40	10
17	$MeNO_2$	$Fe(ClO_4)_3·H_2O$	RT	Trace
18[c]	$MeNO_2$	$Fe(ClO_4)_3·H_2O$	80	75

[a] Reaction conditions: 4-hydroxycoumarin **1a** (0.30 mmol, 1.5 equiv), 1-phenylprop-2-yn-1-ol **2a** (0.20 mmol, 1.0 equiv) and the indicated catalyst (10 mol%) in $MeNO_2$ (2.0 ml) was stirred at 80 °C for 5 h. [b] Isolated yield. [c] Catalyst (5 mol%).

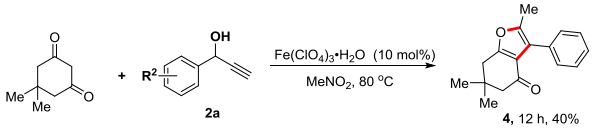
With the optimal conditions in hand, the generality of this methodology was investigated with various representative 4-hydroxycoumarins **1** (Table 2). A number of electron–withdrawing (F, Cl, Br and Ph) and electron–donating groups (Me, Et, *i*-Pr and OMe) in the 6-position of the 4-hydroxycoumarins were well tolerated to furnish the corresponding furo[3,2-*c*]coumarins in moderate to good yields (**3ba**—**3ea** and **3ga**—**3ja**, 66—85%). Additionally, the substituent in the 5-position had no impact on the yield (**3ka**, 79%). Conversely, the presence of either an electron–withdrawing group (Cl) or an electron–donating group (OMe) in the 7-position resulted in relatively lower yields of the desired products (**3fa** and **3la**, 58% and 59%, respectively), indicating that the steric hindrance of the substituents could reduce the reaction rate. It is noteworthy that 4-hydroxybenzo[*h*]coumarin and 4-hydroxybenzo[*g*]coumarin also gave the corresponding products **3na** and **3oa** in 78% and 72% yields respectively. Then, we examined the scope of this strategy with respect to the terminal propargylic alcohol **2**. Moderate to good yields were generally obtained with various terminal alkynols bearing one or two electron–withdrawing/donating groups (**2a**—**2g**, 52—87%). To our delight, this domino transformation smoothly accommodated diverse propargylic alcohols bearing 2-naphthyl and 1-naphthyl, affording the expected furo[3,2-*c*]coumarins **3ah** and **3ai** (83% and 79%, respectively).

Table 2. Substrate scope[a].



[a] Reaction conditions: 4-hydroxycoumarin **1** (0.30 mmol), 1-phenylprop-2-yn-1-ol **2** (0.20 mmol), $Fe(ClO_4)_3·H_2O$ (10 mol%), $MeNO_2$ (2.0 ml), 80 °C. [b] Isolated yield.

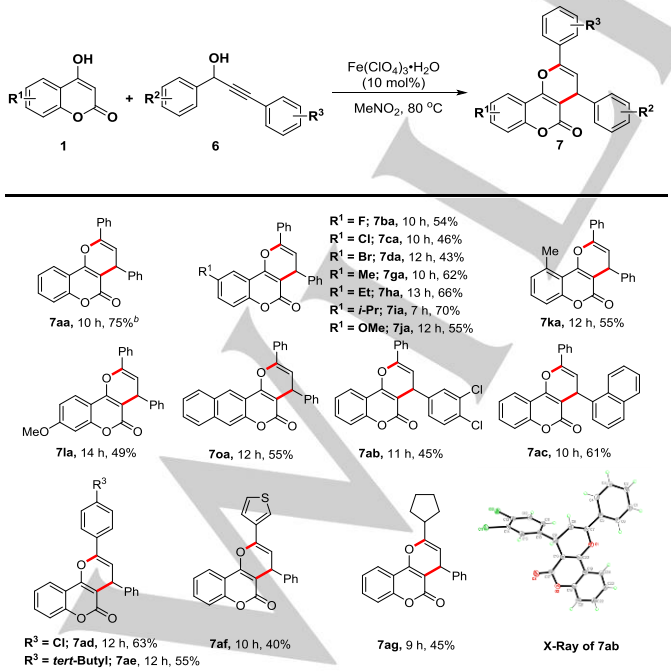
In addition, the gram-scale synthesis of **3aa** was also evaluated to investigate the practicability of this process. 0.92 g of **1a** reacted smoothly with 0.50 g of **2a** in 7 h to construct 1.05 g of the corresponding furo[3,2-*c*]coumarin **3aa** (91%). Meanwhile, we anticipated that this methodology could be extended to a more versatile substrate scope from coumarin derivatives. Therefore, the general cyclic 1,3-diketone was examined under identical reaction conditions. Gratifying, the fused furan derivative **4** was generated in 40% yield (Scheme 2). It is noteworthy that the less reactive β-keto ester could be well employed as the substrate to assemble the densely functionalized furan core structure **5** in 85% yield (Scheme 2).



Scheme 2. Synthesis of the densely functionalized furans **4** and **5**.

To emphasize the generality of our strategy, we next investigated the feasibility of utilizing internal propargylic alcohols as substrates in this iron-catalyzed propargylation-alkyne oxacyclization-isomerization strategy. The reaction of 4-hydroxycoumarin **1a** with 1,3-diphenylprop-2-yn-1-ol **6a** was performed in $MeNO_2$ at 80 °C in the presence of $Fe(ClO_4)_3{\cdot}H_2O$. Surprisingly, the novel functionalized 2,4-diphenyl-4*H*,5*H*-pyrano[3,2-*c*]coumarin **7aa** was obtained in 75% yield with high regioselectivity (Table 3), instead of the corresponding furo[3,2-*c*]coumarin complex. We next examined the generality of this domino catalytic process. Remarkably, the process not only allowed for diverse structural variations of 4-hydroxycoumarins **1**, but also tolerated a variety of the internal secondary propargylic alcohols. $Fe(ClO_4)_3{\cdot}H_2O$ smoothly promoted this domino reaction to afford diverse pyrano[3,2-*c*]coumarins with moderate to good yields (40—75%). This methodology accommodated a large number of 4-hydroxycoumarin substrates bearing neutral functional groups (**7oa**, 55%), electron–withdrawing groups (**7ba**—**7da**, 43—54%) and electron–donating groups (**7ga**—**7la**, 49—70%) on the benzene ring. Moreover, versatile 1,3-diphenylprop-2-yn-1-ols **6** incorporated with both electron–withdrawing groups and electron–donating groups afforded moderate to good yields (45—63%). Noticeably, when a heterocyclic thiophene or a cyclopentane moiety was introduced to the internal secondary alkynol backbone, the reaction still provided a moderate yield (40% and 45%, respectively). The molecular structures of **3aa** and **7ab** were unequivocally confirmed by means of single-crystal X-ray analysis.[12]

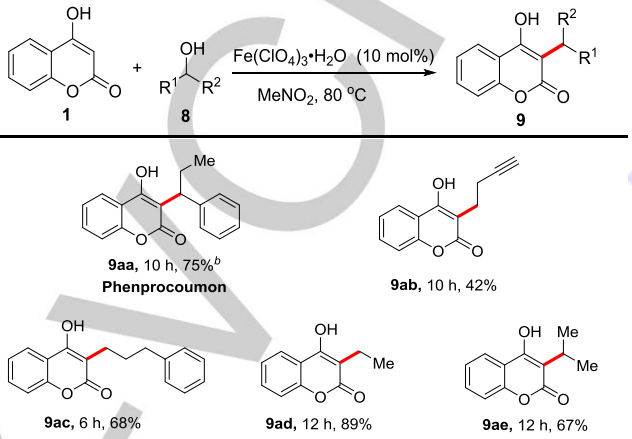
Table 3. Substrate scope[a].



[a] Reaction conditions: 4-hydroxycoumarin **1** (0.30 mmol), **6** (0.20 mmol), $Fe(ClO_4)_3{\cdot}H_2O$ (10 mol%), $MeNO_2$ (2.0 ml), 80 °C. [b] Isolated yield.

To confirm the reaction pathway of this protocol, we next attempted to synthesize and isolate the 3-substituted coumarins **9** (Table 4).[13] The efficiency of iron(III) perchlorate monohydrate allowed the reaction to tolerate a variety of secondary and primary alcohols in moderate to excellent yields (**9aa**—**9ae**, 42-89%). Noticeably, the 1-phenylpropan-1-ol afforded the effective long-acting oral anticoagulant drug phenprocoumon **9aa** in 75% yield.

Table 4. Substrate scope[a].

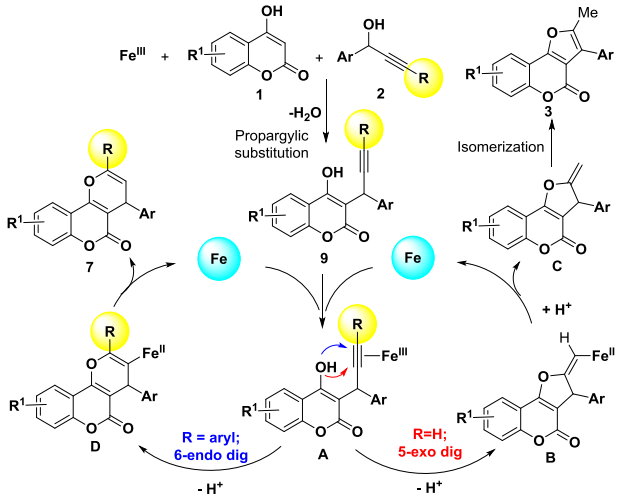


[a] Reaction conditions: 4-hydroxycoumarin **1** (0.20 mmol), alcohol **8** (0.30 mmol), $Fe(ClO_4)_3{\cdot}H_2O$ (10 mol%), $MeNO_2$ (2.0 ml), 80 °C. [b] Isolated yield.

Therefore, we postulate this one-pot domino process involves the initial propargylic substitution of the 4-hydroxycoumarins **1** by the secondary alkynols **2**, affording the resulting γ-ketoalkynes **9** in the presence of the iron(III) Lewis acid (Scheme 3).[8n, 9a-9c] The subsequent π-coordination and 5-*exo* dig cyclization occurs through the intramolecular regioselective nucleophilic attack of the 4-hydroxy group at the β-carbon position of the coordinated alkyne moiety with terminal propargylic alcohols as substrates. Eventually, the protonolysis of the alkenyl-iron intermediates **B** constructs the 2-methylene-2,3-dihydrofuro[3,2-*c*]coumarins **C** along with the regeneration of the iron salt. Additionally, these key intermediates **C** could be aromatized to the thermodynamically stable furo[3,2-*c*]coumarins **3** in the presence of the iron(III) salts. Remarkably, when the protocol is performed with internal alkynols, the 6-*endo* dig cyclization is preferred to generate the pyrano[3,2-*c*]coumarins **7** instead of the corresponding furans, probably due to the conjugation effect of the aryl group attached to the alkyne moiety.

Conclusions

In summary, we have developed an iron-catalyzed domino propargylation-alkyne oxacyclization-isomerization reaction of readily available 4-hydroxycoumarins to secondary propargylic alcohols. The densely functionalized furo[3,2-*c*]coumarins and pyrano[3,2-*c*]coumarins were generated in a one-pot and elegant manner in moderate to high yields (40—87%) with high regioselectivities. The different outcome of this catalytic protocol is ascribed to the terminal group attached to the alkyne moiety. Further application of this iron(III) catalytic system to novel reactions and elaboration of the final products are now ongoing in our laboratory.



Scheme 3. A plausible reaction pathway.

Experimental Section

General Procedure for the Synthesis of Furo[3,2-*c*]coumarins: To a solution of 4-hydroxy-2*H*-chromen-2-one **1a** (48.6 mg, 0.30 mmol, 1.5 equiv) and 1-phenylprop-2-yn-1-ol **2a** (26.4 mg, 0.20 mmol, 1.0 equiv) in 2.0 mL nitromethane, iron(III) perchlorate hydrate (7.4 mg, 0.02 mmol, 0.1 equiv) as a catalyst was added. The reaction mixture was stirred at 80 °C for 5 h. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc=15:1 then 10:1 to afford 47.6 mg (86 % yield) of the desired product **3aa** as white solid.

General Procedure for the Synthesis of Pyrano[3,2-*c*]coumarins: To a solution of 4-hydroxy-2*H*-chromen-2-one **1a** (48.6 mg, 0.30 mmol, 1.5 equiv) and 1,3-diphenylprop-2-yn-1-ol **6a** (41.7 mg, 0.20 mmol, 1.0 equiv) in 2.0 mL nitromethane, iron(III) perchlorate hydrate (7.4 mg, 0.02 mmol, 0.1 equiv) as a catalyst was added. The reaction mixture was stirred at 80 °C for 10 h. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc=20:1 then 8:1 to afford 53.1 mg (75 % yield) of the desired product **7aa** as white solid.

Acknowledgements

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Keywords: iron catalysis • regioselectivity • domino reaction • furo[3,2-*c*]coumarin synthesis • pyrano[3,2-*c*]coumarin sythesis

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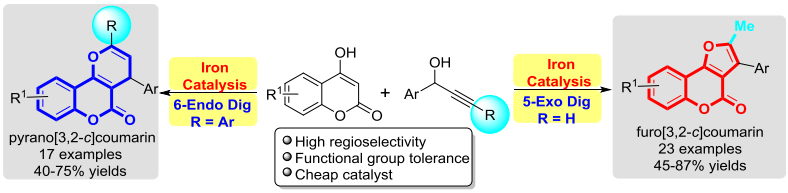

A highly efficient iron-catalyzed propargylation-alkyne oxacyclization-isomerization strategy is disclosed to expeditiously assemble representative bioactive furo[3,2-*c*]coumarins and pyrano[3,2-*c*]coumarins with high regioselectivities.