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Application of Dearomatization Strategy on the Synthesis of Furoquinolinone and Angelicin Derivatives

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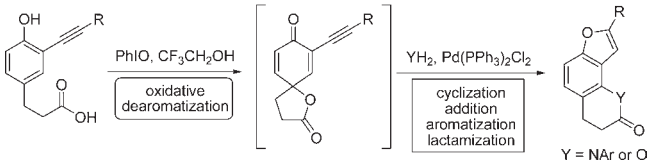
ABSTRACT



The oxidative dearomatization of 3-(3-alkynyl-4-hydroxyphenyl)propanoic acid is combined with a cascade transition-metal catalyzed cyclization/addition/aromatization/lactamization sequence, which provides a novel approach to prepare furoquinolinone and angelicin derivatives in a convergent and efficient manner.

Furoquinolinones (Figure 1), the bioisosters of angelicin,[1] are potential photochemotherapeutic agents.[2] For example, 1,4,6,8-tetramethylfuro[2,3-*h*]quinolin-2(1*H*)-one (FQ) shows strong antiproliferative activity against tumor cell lines upon UVA (Ultraviolet Radiation A) irradiation, without inducing interstrand cross-links (ISC).[3] The general synthetic route of furoquinolinones starts from *m*-phenylenediamines and involves multistep procedures and relatively harsh reaction conditions (Scheme 1).[4] With the aim to find more effective and less toxic antitumor compounds, the design and synthesis of new furoquinolinone derivatives with high efficiency is highly desirable.

Dearomatization of aromatic compounds is one of the most sustainable and straightforward methods for accessing complex molecules.[5] The fascination of such an approach has drawn significant attention in recent decades.[6,7] As part of an effort to extend the power of the dearomatization reaction,[8] we originally conceived that the scaffold of furoquinolinones could be readily constructed from (3-alkynyl-4-hydroxyphenyl)propanoic acids **1** with a dearomatization strategy. As shown in Scheme 2, compound **1** can be conveniently prepared from 3-(4-hydroxyphenyl)propanoic acid via an iodination and a Sonogashira coupling reaction. Under oxidizing conditions, dearomatization of compound **1** would provide

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2-alkynyl cyclohexadienone **2** as the intermediate. With a transition metal as the catalyst, intermediate **2** could react with an amine via a cascade cyclization/addition/aromatization/lactamization process[9] to afford 3,4-dihydrofuro-[2,3-*h*]quinolin-2(1*H*)-one **4**. After an oxidation, the scaffold of furoquinolinone could be formed.

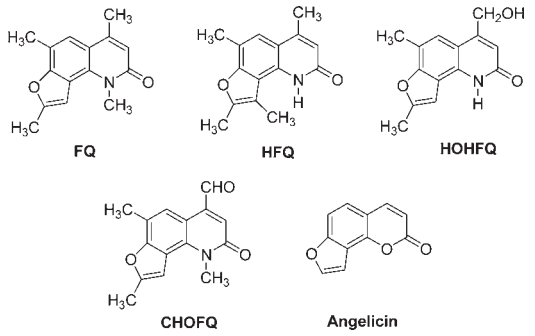
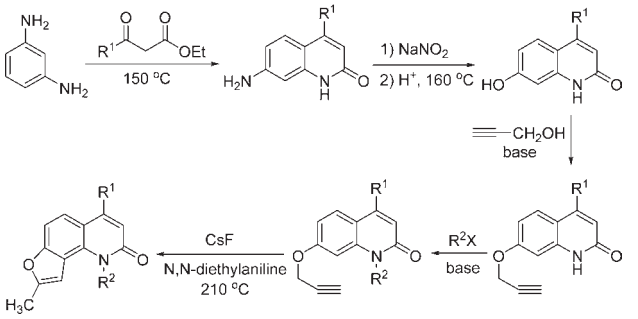


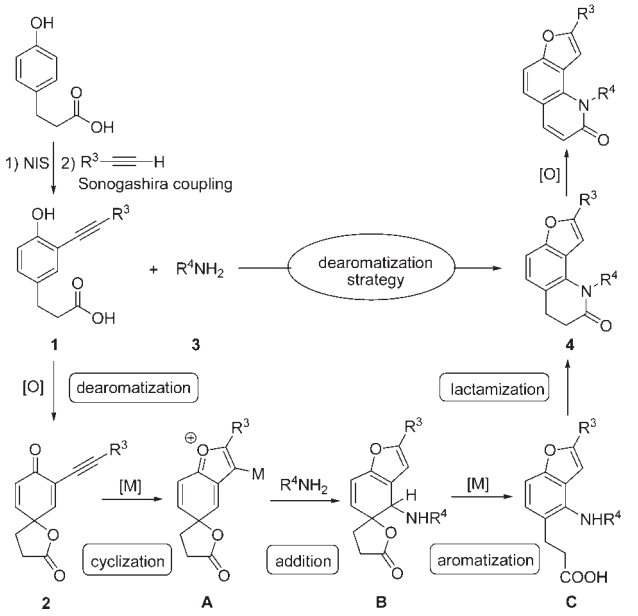
Figure 1. Structures of furoquinolinones and angelicin.

To implement this strategy, the first step was the realization of a rapid oxidative dearomatization of the phenol ring of compound **1** without affecting the sensitive alkynyl function.[10] The screening of oxidants and solvents revealed that PhIO was the best oxidant[11] and CF_3CH_2OH was the best solvent for the dearomatization. Treatment of compound **1a** with 1 equiv of PhIO in CF_3CH_2OH at 50 °C for

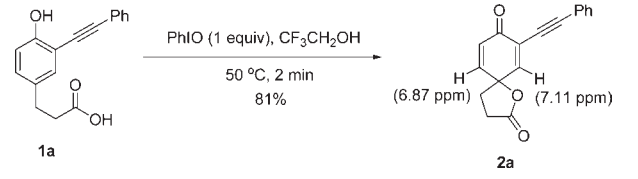
Scheme 1. General Synthetic Route of Furoquinolinones



Scheme 2. Synthesis of Furoquinolinones from 3-(4-Hydroxyphenyl)propanoic Acid with a Dearomatization Strategy



Scheme 3. Oxidative Dearomatization of 3-(4-Hydroxy-3-(2-phenylethynyl)phenyl)propanoic Acid **1a**



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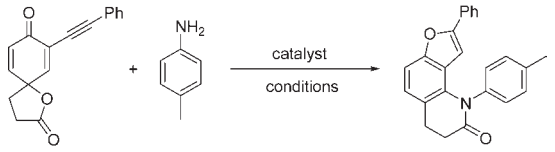
2 min provided 2-phenylethynyl cyclohexadienone **2a** in 81% isolated yield (Scheme 3). The ^{1}H NMR spectroscopy of compound **2a** showed that the hydrogen atom at the C-3 position has a higher chemical shift than that of the hydrogen atom at the C-5 position. It indicates that the nucleophilic addition might prefer to occur at the C-3 position.

Table 1. Evaluation of Catalyst and Conditions[a]



entry	catalyst	conditions	**4aa** (%)[b]
1	AuCl (0.1 equiv)	CH_3CN, reflux	48
2	$AuCl_3$ (0.1 equiv)	CH_3CN, reflux	37
3	CuBr (0.1 equiv)	CH_3CN, reflux	35
4	$PtCl_2$ (0.1 equiv)	CH_3CN, reflux	43
5	$Rh(PPh_3)_3Cl$ (0.1 equiv)	CH_3CN, reflux	0
6	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	CH_3CN, reflux	57
7	$Pd(OAc)_2$ (0.1 equiv)	CH_3CN, reflux	32
8	AgOTf (0.1 equiv)	CH_3CN, reflux	35
9	$Cu(OTf)_2$ (0.1 equiv)	CH_3CN, reflux	19
10	$Bi(OTf)_3$ (0.1 equiv)	CH_3CN, reflux	16
11	$In(OTf)_3$ (0.1 equiv)	CH_3CN, reflux	<5
12	$Ni(OTf)_2$ (0.1 equiv)	CH_3CN, reflux	<5
13	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	CF_3CH_2OH, reflux	23
14	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	DMF, 90 °C	59
15	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	toluene, 90 °C	56
16	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	1,4-dioxane, 90 °C	48
17	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	DMSO, 90 °C	<5
18	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	$ClCH_2CH_2Cl$, reflux	72
19	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	H_2O, 90 °C	16
20	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	$ClCH_2CH_2Cl$, 70 °C	69
21	$Pd(PPh_3)_2Cl_2$ (0.05 equiv)	$ClCH_2CH_2Cl$, reflux	68
22	$Pd(PPh_3)_2Cl_2$ (0.02 equiv)	$ClCH_2CH_2Cl$, reflux	63
23[c]	$Pd(PPh_3)_2Cl_2$ (0.1 equiv)	$ClCH_2CH_2Cl$, reflux	79

[a] Reaction conditions: substrate **1a** (0.1 mmol), 4-$CH_3C_6H_4NH_2$ (0.2 mmol), solvent (2 mL), unless noted. [b] Isolated yield based on substrate **1a**. [c] 1.5 equiv of 4-$CH_3C_6H_4NH_2$ was used.

Our further investigations were focused on examining the feasibility of the designed cascade reaction between compound **2a** with *p*-toluidine **3a**. We were pleased to observe that the reaction proceeded well in the presence of AuCl (10 mol %), and the desired product **4aa** was isolated in 48% yield (Table 1, entry 1). The structure of compound **4aa** was confirmed by its single-crystal diffraction analysis (Figure 2). Encouraged by this result, various metal salts were examined as catalysts (Table 1, entries 2−12). Pd-$(PPh_3)_2Cl_2$ proved to be the best catalyst for the generation of compound **4aa** (Table 1, entry 6). We then started to optimize the reaction conditions to improve the chemical yield. With $ClCH_2CH_2Cl$ as the reaction media, the yield of **4aa** was increased to 72% (Table 1, entry 18). The lower temperature or the reduced loading of $Pd(PPh_3)_2Cl_2$ resulted in the lower yield (Table 1, entries 20−22). The best ratio of substrate **1a**, *p*-toluidine **2a**, and $Pd(PPh_3)_2Cl_2$ for the reaction was 1:1.5:0.1, increasing the yield of **4aa** to 79% (Table 1, entry 23). Although *p*-toluidine **3a** is an electron-rich aromatic compound, the C-addition of the aryl ring of *p*-toluidine to compound **2a** was not observed in all cases.

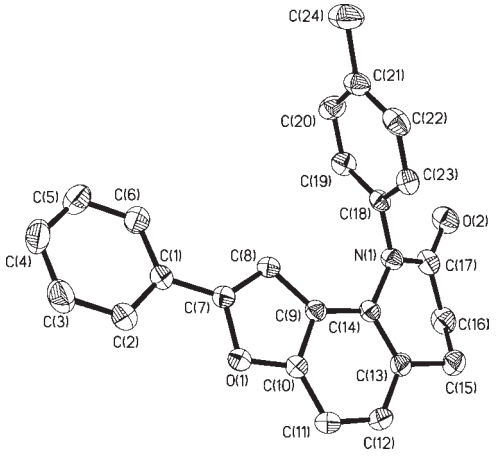


Figure 2. X-ray diffraction structure of compound **4aa**.

To simplify the reaction procedure, the crude oxidative dearomatization product was treated with *p*-toluidine **3a** without purification. Under the optimized conditions, this two-step reaction provided compound **4aa** in 62% yield based on substrate **1a** (Table 2, entry 1). As shown in Table 2, a variety of aromatic amines were suitable reaction partners (Table 2, entries 2−10). Reactions of amines bearing an electron-donating substituent delivered the corresponding products in higher yields compared with those bearing an electron-withdrawing substituent. Two kinds of heteroaromatic amines were also examined (Table 2, entries 22 and 23). The reaction of 5-amino-1,3-dimethyl-1*H*-pyrazole gave rise to product **4ep** in 61% yield, but the reaction of 4-amino-pyridine was very complex. When benzylamine, butylamine, benzyl carbamate, *tert*-butyl carbamate, or 4-methylbenzenesulfonamide was employed, the formation of the desired product was not observed (Table 2, entries 11−15). For the reaction with *tert*-butyl carbamate as the reaction partner, all metal salts listed in Table 1 were examined as catalysts, but all failed.

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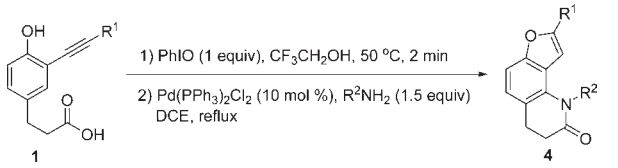
Table 2. Reaction Scope Investigation



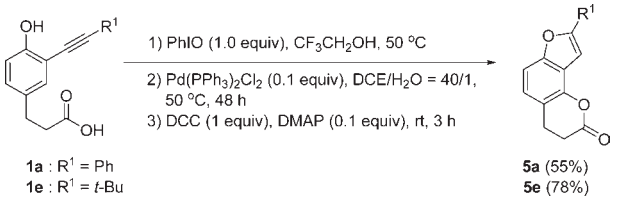
entry	R^1	R^2	**4** (%)[a]
1	C_6H_5	4-$CH_3C_6H_4$	**4aa** (62)
2	C_6H_5	C_6H_5	**4ab** (63)
3	C_6H_5	4-$CH_3OC_6H_4$	**4ac** (62)
4	C_6H_5	4-BrC_6H_4	**4ad** (61)
5	C_6H_5	4-ClC_6H_4	**4ae** (67)
6	C_6H_5	4-FC_6H_4	**4af** (64)
7	C_6H_5	4-$CF_3C_6H_4$	**4ag** (38)
8[b]	C_6H_5	1-naphthalen	**4ah** (59)
9[b]	C_6H_5	2,4,6-$(CH_3)_3C_6H_2$	**4ai** (53)
10	C_6H_5	3,5-$(CH_3)_2C_6H_3$	**4aj** (63)
11	C_6H_5	$C_6H_5CH_2$	**4ak** (0)
12	C_6H_5	$CH_3CH_2CH_2CH_2$	**4al** (0)
13	C_6H_5	$CbzNH_2$	**4am** (0)
14	C_6H_5	$BocNH_2$	**4an** (0)
15	C_6H_5	$TsNH_2$	**4ao** (0)
16	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	**4ba** (62)
17	4-ClC_6H_4	4-$CH_3C_6H_4$	**4ca** (36)
18	$CH_3CH_2CH_2CH_2$	4-$CH_3C_6H_4$	**4da** (82)
19	$(CH_3)_3C$	4-$CH_3C_6H_4$	**4ea** (91)
20	$(CH_3)_3C$	4-$CH_3OC_6H_4$	**4ec** (85)
21	$(CH_3)_3C$	4-ClC_6H_4	**4ee** (90)
22	$(CH_3)_3C$	1,3-$(CH_3)_2$-1*H*-pyrazol-5-yl	**4ep** (61)
23	$(CH_3)_3C$	4-pyridyl	**4eq** (00)
24	cyclopropyl	4-$CH_3C_6H_4$	**4fa** (63)
25	TMS	4-$CH_3C_6H_4$	**4ga** (0)
26	H	4-$CH_3C_6H_4$	**4ha** (0)
27[c]	$(CH_3)_3C$	4-$CH_3C_6H_4$	**4ea** (87)

[a] Isolated yield based on substrate **1**. [b] DCC (1 equiv) and DMAP (0.1 equiv) were added to promote the lactamization. [c] The reaction was conducted at a 2 mmol scale.

A substituent at the alkyne moiety of compound **1** also affected the reaction. For example, compound **1b** bearing a 4-methylphenyl group was a better substrate than compound **1c** bearing a 4-chlorophenyl group (Table 2, entries 16 and 17). When the R^1 group was an *n*-butyl or a *tert*-butyl group, the reactions gave rise to the corresponding products in good to excellent yields (Table 2, entries 18−21). When the R^1 group was a cyclopropyl group, a moderate yield was obtained (Table 2, entry 24). Complex reactions were observed when the R^1 group was a trimethylsilyl group or a hydrogen (Table 2, entries 25 and 26). When the reaction was conducted at a larger scale (2 mmol), a slightly low yield was obtained (Table 2, entry 27).

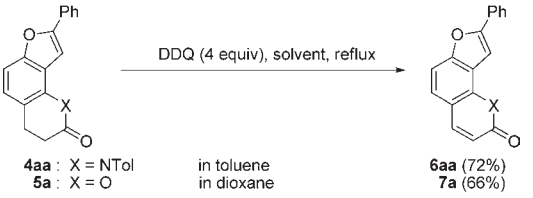
Moreover, the precursor of angelicin, 3,4-dihydrofuro[2,3-*h*]chromen-2-one **5** could also be prepared via a similar process with water as a nucleophile (Scheme 4). In these cases, *N*,*N*-dimethylpyridin-4-amine (DMAP) and dicyclohexylcarbodiimide (DCC) were added to promote the lactonization.

Scheme 4. Synthesis of 3,4-Dihydrofuro[2,3-*h*]chromen-2-one



Treatment of compound **4aa** or **5a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[12] led to the corresponding furoquinolinone derivative **6aa** or angelicin derivative **7a**, respectively (Scheme 5).

Scheme 5



In conclusion, we have developed a new strategy for accessing furoquinolinone and angelicin derivatives. This method involves the oxidative dearomatization of 3-(3-alkynyl-4-hydroxyphenyl)propanoic acids and the subsequential transition-metal catalyzed cascade cyclization/addition/aromatization/lactamization sequence. Current dedication has also been made to extend its scope, to explore its reaction mechanism and possible synthetic applications, and these results will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR of new compounds, and crystallographic data of compound **4aa** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.