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Synthesis of novel tetracyclo-isocoumarins via AcOH-catalyzed cascade reaction of heterocyclic ketene aminals with 2,2-dihydroxy-2*H*-indene-1,3-dione

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ABSTRACT

A facile synthesis of tetracyclo-isocoumarins based on the AcOH-catalyzed cyclocondensation and rearrangement reaction between heterocyclic ketene aminals and 2,2-dihydroxy-2*H*-indene-1,3-dione is described. This method provides direct access to tetacyclo-isocoumarins, a class of compounds with potential broad spectrum biological activities.

Isocoumarins are an important class of natural lactones that exhibit a broad range of biological activities[1] including antitumor[2] (e.g., Reticulol[2a]), anti-HIV-1 (Coriandrin),[3] anti-HSV-1 (6,8-dihydroxy-3-hydroxymethyliso-coumarin),[4] anti-allergic (such as Thunberginool A and B),[5] anticoagulants,[6] antifungal,[7] antimicrobial,[8] anti-inflammatory,[9] antimalarial,[10] herbicidal,[11] immunomodulatory,[12] cytotoxic activity,[13] DNA helicase inhibition (heliquinomycin),[14] β-amyloid eptide production inhibition[15] and protease inhibitory properties,[15,16] among others.[17] Due to their broad range of biological activities and their use as synthetic precursors in the synthesis of a variety of important pharmaceutical compounds, such as the anticancer agents nitidine[18] and (±)-*O*-methyl PD 116740,[19] the antibiotic heliquinomycin[20] and pretetramide,[21] isocoumarins have received increasing interest for many years.[1a,22–35] Recently, several methods have been reported for the synthesis of isocoumarins **1** (Fig. 1).[1a,22–35] The main synthetic routes are transition metal (Ag, AgI, CuCl, CuBr) or proton acid (TFA, PTSA) catalyzed reactions based on 2-ethynylbenzoic acid derivatives **2**[22] and the transition-catalyzed coupling and heterocyclization reaction of alkyl 2-iodobenzoates **3**[23] with alkynes or allenyltributyltins. In addition, there are many other procedures which have been used in the synthesis of isocoumarins[22–35] and among them, many substrates have been widely used, including substituted 3,4-dihydroisochromen-1-ones **4**,[24] enol ethers **5**,[25] enamines **6**,[26] isobenzofuran-1(3*H*)-one derivatives **7**,[27] phthalic acid or esters **8**,[28] α-(*o*-haloaryl)-substituted ketones **9**,[29] 2-formyl-benzoic acids **10**,[30] ketoaldehydes **11**,[31] aromatic keto acids **12**,[32] 2-iodobenzoic acids **13**,[33] and alkyl 2-ynyl-benzoates **14**,[34] and so on.[35] Although some of these methods are effective for the synthesis of simple isocoumarins, these methods have not been used in preparing the *cyclo*-fused isocoumarins. In a word, the synthesis of *cyclo*-fused isocoumarins is challenging work which often requires multistep reactions and complex experimental processes. The procedures available for preparing highly functional, diverse, cyclic fused isocoumarins are limited. Therefore, a general and concise approach for producing this class of *cyclo*-fused isocoumarins that tolerates a wide variety of functional groups is highly desirable.

In order to develop an isocoumarin synthesis method which avoids the use of substrates **2**–**14**, and in the process to expand

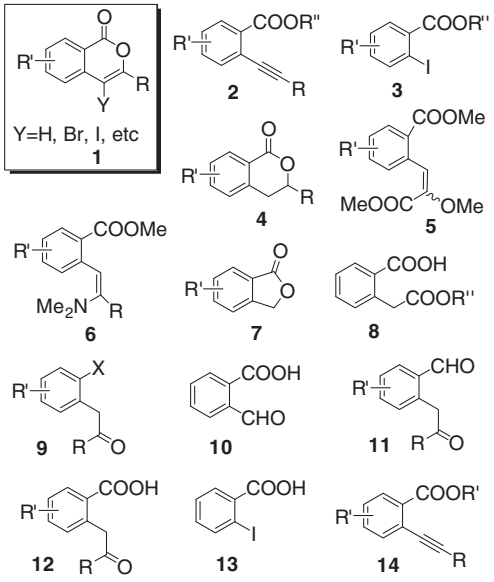

Figure 1. The substrates for synthesis of isocoumarins **1**.

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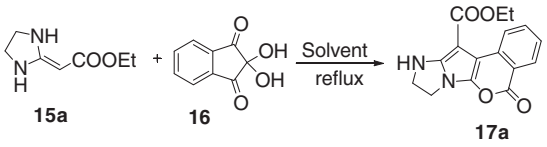
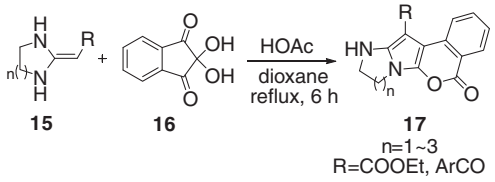


Scheme 1. Synthesis of tetracyclo-isocoumarine **17a**.

Table 1
Optimizing the reaction conditions for synthesis of **17a**

Entry	Solvent	Catalyst	*T* (°C)	Time (h)	Yield/%[a]
1	CH_3CN	—	Reflux	6	—
2	DMF	—	Reflux	6	—
3	DMSO	—	140	6	—
4	Dioxane	—	Reflux	6	—
5	CH_3CN	AcOH	Reflux	6	47
6	CH_3CN	TFA	Reflux	6	—
7	CH_3CN	$HClO_4{\cdot}SiO_2$	Reflux	6	50
8	CH_3CN	$H_3PW_{14}O_{40}$	Reflux	6	21
9	CH_3CN	$ZnCl_2$	Reflux	6	15
10	DMF	AcOH	Reflux	6	—
11	DMF	TFA	Reflux	6	—
12	DMF	$HClO_4{\cdot}SiO_2$	Reflux	6	—
14	DMF	$H_3PW_{14}O_{40}$	Reflux	6	—
15	DMF	$ZnCl_2$	Reflux	6	Trance
16	Dioxane	AcOH	Reflux	6	81
17	Dioxane	TFA	Reflux	6	23
18	Dioxane	$HClO_4{\cdot}SiO_2$	Reflux	6	35
19	Dioxane	$H_3PW_{14}O_{40}$	Reflux	6	Trance
20	Dioxane	$ZnCl_2$	Reflux	6	31

[a] Isolated yield.



Scheme 2. Synthesis of tetracyclo-isocoumarins **17**.

the pool of suitable starting materials which allow access to cyclic derivatives, we focused on the one-pot synthesis of tetracyclo-isocoumarin derivatives **17** based upon the cyclocondensation reaction of heterocyclic ketene aminals (HKAs) **15** and 2,2-dihydroxy-2*H*-indene-1,3-dione **16** catalyzed by acetic acid.

To explore the practicality of the projected synthetic route, we first evaluated the cascade reaction of ethyl 2-(imidazolidin-2-ylidene)acetate **15a** and 2,2-dihydroxy-2*H*-indene-1,3-dione **16**. The mixture, which was composed of a 1:1.1 ratio of **15a** to **16**, was treated under various conditions (Scheme 1) (Table 1, entries 1–11). We found that the reactions could not proceed in different solvents such as acetonitrile, DMF, DMSO, and 1,4-dioxane under catalyst-free conditions (Table 1, entries 1–4), while the catalysts AcOH, $H_3PW_{14}O_{40}$, $ZnCl_2$, and TFA promoted the reactions.

The results demonstrated that the best reaction conditions for the synthesis of tetracyclo-isocoumarins were dioxane as a solvent and acetic acid as a catalyst under reflux for 6 h with an isolated product of a good yield (81%) (Table 1, entry 16). The use of acetic acid as a catalyst can promote the cyclocondensation of HKAs **15a** with 2,2-dihydroxy-2*H*-indene-1,3-dione **16** and the rearrangement reaction of the intermediates (Table 1, entries 5 and 16). Removing the acids prevented the cyclocondensation of HKAs (Table 1, entries 1–4). This result indicated that this reaction is catalyzed by protic acids.

Table 2
Synthesis of tetracyclo-isocoumarins **17**

Entry	**15**	*n*	R	**17**	Yield[a] (%)
1	**15a**	1	COOEt	**17a**	81
2	**15b**	1	*p*-$MeOC_6H_4CO$	**17b**	73
3	**15c**	1	*p*-MeC_6H_4CO	**17c**	70
4	**15d**	2	*p*-$MeOC_6H_4CO$	**17d**	79
5	**15e**	2	*p*-MeC_6H_4CO	**17e**	75
6	**15f**	2	C_6H_4CO	**17f**	71
7	**15g**	2	*p*-ClC_6H_4CO	**17g**	74
8	**15h**	3	*p*-$MeOC_6H_4CO$	**17h**	89
9	**15i**	3	*p*-MeC_6H_4CO	**17i**	88
10	**15j**	3	C_6H_4CO	**17j**	84
11	**15k**	3	*p*-ClC_6H_4CO	**17k**	78

[a] Isolated yield by silica gel column chromatograph.

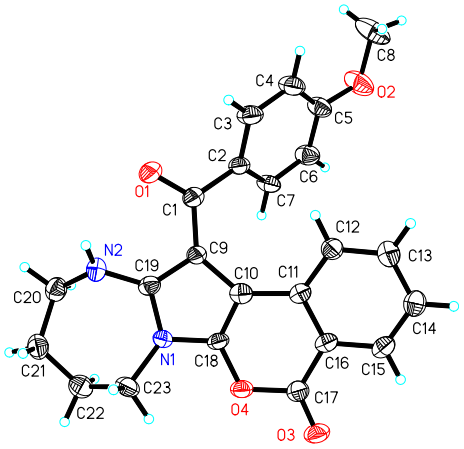
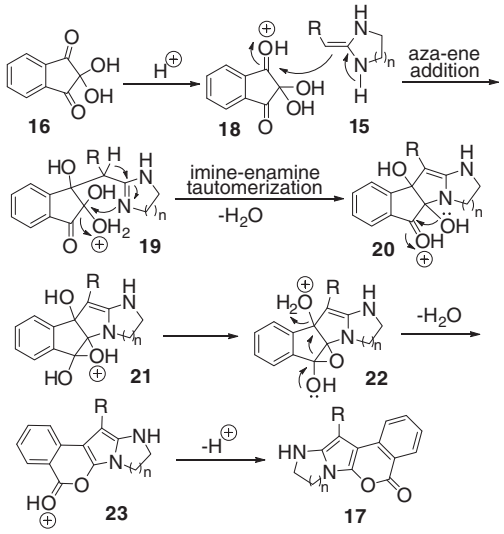


Figure 2. X-ray crystal structure of **17h**.



Scheme 3. The proposed mechanism for cascade reaction.

Encouraged by this result, we examined the scope and limitations of the cascade reactions involving various HKAs **15** with 2,2-dihydroxy-2*H*-indene-1,3-dione **16** (Scheme 2) (Table 2, entries 1–11). The results demonstrated that HKAs with various substituents were all good substrates for the cascade reaction (Table 2, entries 1–11). The reactions usually took ca. 6 h at reflux in 1,4-dioxane in the presence of AcOH and gave the target compounds with moderate to good yields.

The results in Table 2 demonstrate that HKAs, with various substituents (**15a–k**), were all good substrates for the reaction. The substituents of the HKAs **15** had slight influence on the reactivity and product yield. The yields of all substrates are all similar (Table 2, entries 1–11).

Additionally, in terms of the ring sizes of the HKAs **15**, the yields of the seven-membered HKAs was superior to that of the five-membered and the six-membered HKAs (entries 8–11 vs 1–3 and 4–7).

All new compounds **17** were fully characterized on the basis of their ^{1}H, ^{13}C NMR spectra, and high resolution mass spectra,[36] which indicated that the HKAs reacted with 2,2-dihydroxy-2*H*-indene-1,3-dione in a 1:1 ratio, affording novel kinds of tetracyclo-isocoumarins.

To verify the structure of the tetracyclo-isocoumarin products, **17h** was selected as a representative compound and characterized by X-ray crystallography, as shown in Figure 2 (CCDC 781822).[37]

A proposed mechanism of the acetic acid-catalyzed cascade reaction is depicted in Scheme 3. Firstly, carbonyl group of 2,2-dihydroxy-2*H*-indene-1,3-dione **16** accepted one proton of to form **18**. Then the reaction of HKAs **15**, due to the strongly electron-withdrawing groups at the α-position of the ketene *N*,*N*-acetals acted as heteroene components, with **18** proceeded via an aza-ene addition to afford **19**. The intermediate **19** was followed by imine–enamine tautomerization, intramolecular cyclization, and dehydration to get **20**. The adjacent OH undergoes intramolecular attack on the carbonyl group to obtain a hydroxy epoxide intermediate **21**, which through proton transfer is able to produce **22**. Subsequently ring-enlargement reaction occurs through opening of the epoxide ring with losing a molecule of H_2O to get **23**. Finally, **23** loses proton to result in the target product **17**.

In conclusion, we developed a procedure for the simple synthesis of a variety of potential, biologically active tetracyclo-isocoumarins. Using this method, a molecularly diverse tetracyclo-isocoumarin library was rapidly constructed with good yields by simply refluxing a reaction mixture of HKAs and 2,2-dihydroxy-2*H*-indene-1,3-dione, catalyzed by AcOH.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.100.

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36. General procedure for the synthesis of compounds **17**. HKAs **15** (2.5 mmol), 2,2-dihydroxy-2*H*-indene-1,3-dione **16** (2.75 mmol), and 1,4-dioxane (15 mL) were charged into a 50 mL round-bottomed flask, then acetic acid (3 mL) was added to the mixture and the mixture was refluxed. The resulting solution was stirred for 4–6 h until the HKAs **15** were completely consumed. The mixture was cooled to room temperature, neutralized with a saturated solution of Na_2CO_3 to pH 8–9, and then EtOAc (50 mL × 2) was added. The organic phase was washed with water (10 mL), dried over Na_2SO_4, concentrated, and purified by flash column chromatography to afford tetracyclo-isocoumarins **17** in a 71–89% yield. Compound **17a**: yellow solid; 81% mp: 140–144 °C. IR (KBr): 3437, 2979, 1723, 1678, 1600, 1455, 1320, 1130, 765 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.0 Hz, 3H, CH_3), 4.09 (t, J = 7.5 Hz, 2H, NCH_2), 4.21 (t, J = 7.5 Hz, 2H, NCH_2), 4.34 (t, J = 7.0 Hz, 2H, OCH_2), 4.94 (s, 1H, NH), 7.31 (t, J = 7.3 Hz, 1H, ArH), 7.70 (t, J = 7.3 Hz, 1H, ArH), 8.27 (d, J = 7.9 Hz, 1H, ArH), 9.01 (d, J = 7.9 Hz, 1H, ArH). ^{13}C HMR (125 MHz, $CDCl_3$): δ = 15.2, 43.8, 49.2, 60.0, 84.5, 99.6, 117.4, 125.3, 125.5, 131.3, 135.6, 137.0, 150.1, 161.6, 164.9, 196.2. HRMS (TOF ES$^+$): m/z calcd for $C_{16}H_{14}N_2NaO_4$ [(M+Na)$^+$], 321.0846; found, 321.0840.
37. CCDC 781822 contains the supplementary crystallographic data for compound **17h**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.