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Original article

Synthesis of hexacyclic fused isocoumarin framework through selective domino multicyclizations under catalyst and solvent free conditions

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ABSTRACT

A novel fused isocoumarin skeleton has been synthesized through selective domino multicyclizations by mixing homothallic acid and 2,3-diphenylacryloyl chloride at 200 °C under catalyst and solvent free reaction conditions. Six fused rings with two stereogenic centers were assembled in a convenient one-pot operation in good yield. The resulting hexacyclic fused isocoumarin skeleton and its stereochemistry was fully characterized and unambiguously confirmed by X-ray diffraction analysis.

1. Introduction

The assembly of complex polycyclic skeletons of chemical and biomedical interest has become an important, challenging and active area of research in modern organic chemistry [1]. Among these skeletons, isocoumarin based fused ring system present in many natural products (Fig. 1) shows a broad range of biological activities [2]. In recent years, a variety of methods have been developed to prepare these structurally complex fused skeletons [3]. However, synthetic chemists are continuously searching for the development of new, cleaner and efficient chemical transformation methodologies, or modifications in the established synthetic pathways to ensure eco-friendly and cost effective synthesis with minimal or no use of toxic chemicals.

Till date, excellent region-, chemo-, diastereo- and enantioselectivities are obtained for the preparation of complex molecules by developing several highly selective procedures [4]. The procedure usually used for the construction of such organic compounds involves a step-wise formation of individual bonds in the target molecule. However, it is much more desirable, if one could form several bonds in one go without isolating the intermediates and changing the reaction conditions. The waste produced in such synthetic procedures is very small as compared to step-wise pathways. Therefore, from the synthetic point of view, one-pot synthesis of fused-ring systems is an attractive procedure for searching bioactive compounds.

Coumarin derivatives [5] are important synthetic targets because of possessing diverse biological applications [6]. They are also known to have vasodilatory [7], anticoagulant [8], anti-HIV [9], antitumor [10] and anti-inflammatory [11] properties. The fluorescent properties of some isocoumarin derivatives are also reported [12]. Herein, we report one-pot synthesis of novel fused isocoumarin framework through highly selective domino multicyclizations under catalyst and solvent free reaction conditions. The resulting fused isocoumarin framework is an interesting scaffold for drug design and discovery and can play an important role in pharmaceutical research.

2. Experimental

2.1. Materials and methods

All reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as required. Thin layer

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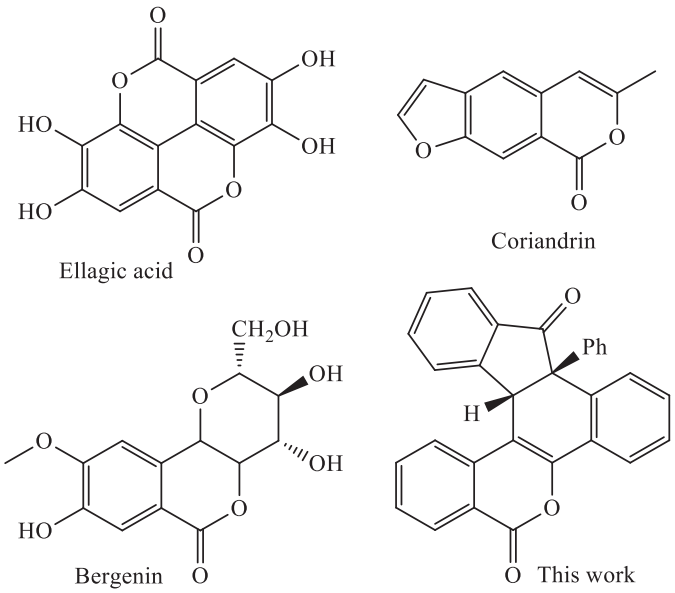


Fig. 1. Some representative natural products.

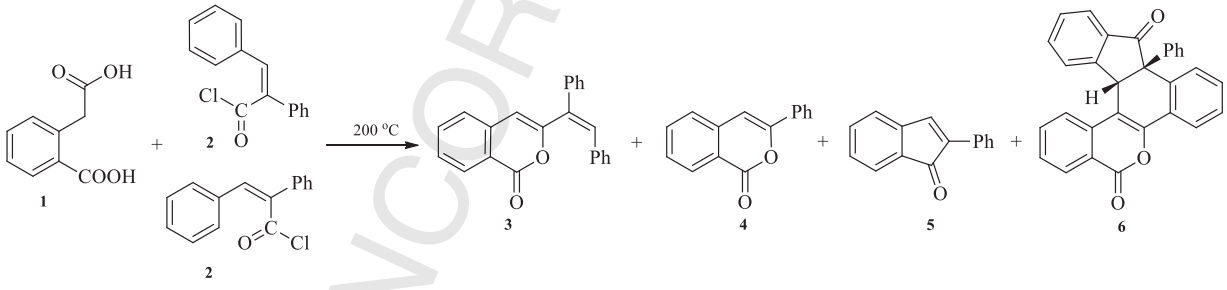
chromatography (TLC) was performed using aluminum sheets (Merck) coated with silica gel 60 F254. The melting points of compounds were determined using capillary tubes and an electrothermal melting point apparatus, model MP-D Mitamura Riken Kogyo, Japan. IR spectra of compounds were recorded on a Bio-Rad FTS 3000 MX spectrophotometer (400–4000 cm^{-1}). NMR spectra were recorded using a Bruker AM-300 spectrometer and chemical shifts are reported in ppm *versus* tetramethylsilane with either tetramethylsilane or the residual solvent resonance used as an internal standard. Mass spectra were acquired on a Bruker Omniflex MALDI-TOF instrument and elemental analyses were carried out with a LECO-183 CHNS model.

2.2. Procedure for the synthesis of hexacyclic fused isocoumarin (*6*)

A mixture of 2,3-diphenylacrylic acid (2.07 g, 9 mmol) and thionyl chloride (1 mL) was heated in the presence of a few drops of DMF for 30 min at 70 °C. Completion of reaction was indicated by the disappearance of gas evolution. Excess thionyl chloride was removed under reduced pressure to afford 2,3-diphenylacryloyl chloride. Homophthalic acid (0.54 g, 3 mmol) was then added to it and the mixture was heated first for 3.5 h at 200 °C and then cooled to room temperature. Addition of aqueous solution of sodium carbonate (5%, 200 mL), followed by filtration and washing thoroughly with water furnished the crude product, which was recrystallized in toluene to give compound **6** in pure form (68%). Mp: 135–136 °C; IR (KBr, cm^{-1}): ν 2918 (C–H), 1704 (C=O), 1569 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (dd, 1H, J = 1.2, 7.5 Hz), 7.91 (d, 1H, J = 7.5 Hz), 7.88–7.82 (m, 1H), 7.59–7.19 (m, 12H), 6.98 (dd, 2H, J = 1.2, 7.5 Hz), 4.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.6, 161.4, 151.1, 142.7, 137.5, 135.8, 135.7, 135.3, 133.1, 130.6, 128.8, 128.7, 128.6, 128.4, 128.2, 127.4, 124.9, 124.4, 123.6, 122.7, 107.8, 62.7, 48.2, 31.0; MS [MALDI-TOF] (m/z) 427.13 [M+H$^+$] (100), 428.13 (33), 429.13 (5). Anal. Calcd. for $C_{30}H_{18}O_3$: C, 84.49; H, 4.25; Found: C, 84.53; H, 4.23.

3. Results and discussion

We commenced our studies by reacting equimolar quantities of homophthalic acid **1** and 2,3-diphenylacryloyl chloride **2** at 200 °C with an aim of getting isocoumarin derivative, 3-(1,2-diphenylvinyl)-1*H*-isochromen-1-one **3** [13] (Scheme 1 and Fig. S1 in Supporting information). However, instead of obtaining the expected product **3**, compound **4**, *i.e.* 3-phenyl-1*H*-isochromen-1-one [14] and the novel fused hexacyclic isocoumarin framework **6**, formed by the domino multicylization reaction, were isolated in 75% and 1% yields, respectively (Table 1, entry 1). Structure of the novel fused ring system **6** was established through spectral (IR, ^{1}H NMR, ^{13}C NMR, COSY, NOESY, MS) and single crystal X-ray analyses (Fig. 2, Table 2). This unprecedented observation prompted us to pursue further the domino cyclization reaction from both the mechanistic as well as synthetic viewpoints. Accordingly, we retroanalyzed the fused isocoumarin skeleton **6** (Fig. S2 in Supporting information); it was hypothesized that some of the 2,3-diphenylacryloyl chloride **2** might be cyclized under the conditions to give 2-phenyl-1*H*-inden-1-one **5** [15], which reacted with the already observed 3-phenyl-1*H*-isochromen-1-one **4** through Michael addition reaction (Fig. 3). To check our hypothesis, the concentration of **2** was gradually increased under the same reaction conditions. To our delight, the yield of **6** significantly



Scheme 1. Novel domino multicyclization reaction with all possible byproducts.

Table 1
Optimization of reaction conditions for the synthesis of 6.

Entry	Reactants ratio (**1**:**2**)	Temp. (°C)	Time (h)	**3** (%)	**4** (%)[a]	**5** (%)[a]	**6** (%)[a]
1	1:1	200	2	0	75	0	1
2	1:2	200	2	0	45	0	20
3	1:3	200	2	0	28	0	30
4	1:3	200	3	0	7	0	46
5	1:3	200	4	0	0	3	67
6	1:3	200	3.5	0	0	Trace	68

[a] Isolated yield.

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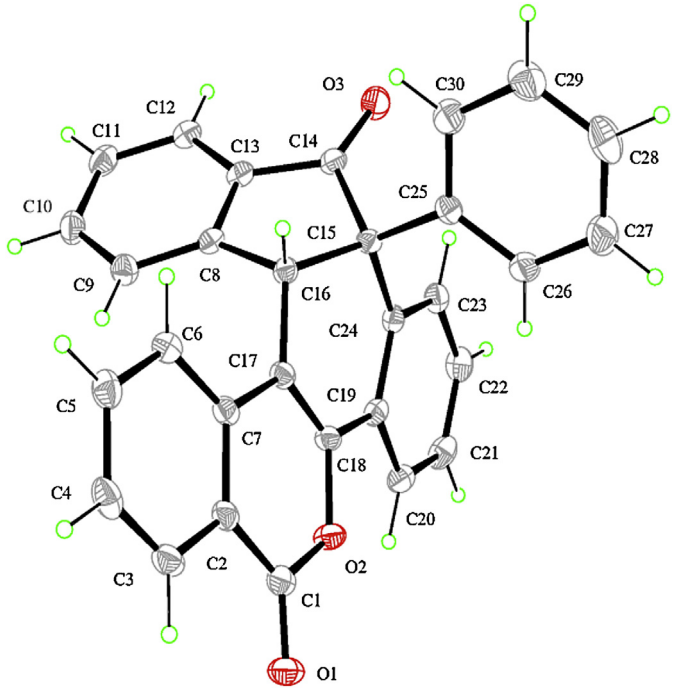

Fig. 2. ORTEP diagram of **6**.

Table 2
X-ray crystallographic data of **6**.

Crystal data	
Chemical formula	$C_{30}H_{18}O_3$
M_r	426.44
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	123
a, b, c (Å)	10.726 (5), 15.309 (7), 13.867 (7)
β (°)	113.005 (5)
V (Å^3)	2095.8 (17)
Z	4
Radiation type	Mo Kα
μ (mm^{-1})	0.09
Crystal size (mm)	0.50 × 0.42 × 0.35
Data collection	
Diffractometer	Rigaku/MSC Mercury CCD diffractometer
Absorption correction	–
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	16,708, 4757, 4470
R_{int}	0.031
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.649
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.060, 0.121, 1.23
No. of reflections	4757
No. of parameters	298
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	0.43, −0.18

increased (1% → 20%), while that of isocoumarin derivative **4** diminished (75% → 45%) (Table 1, entry 2). Interestingly, when the concentration of **2** was enhanced to 3 equivalents, the yield of **6** further increased (20% → 30%), while that of **4** decreased (45% → 28%) (Table 1, entry 3). At this stage, it was assumed that the formation of 2-phenyl-1*H*-inden-1-one **5** compared with 3-phenyl-1*H*-isochromen-1-one **4** was slow and it needed more time to cyclize. Thus, the reaction time was increased from 2 to 3 h. It was found that the yield of **4** pronouncedly decreased (28% → 7%), while that of **6** increased (30% → 46%) (Table 1, entry 4). Surprisingly, further increase in the time duration (3 → 4 h) led

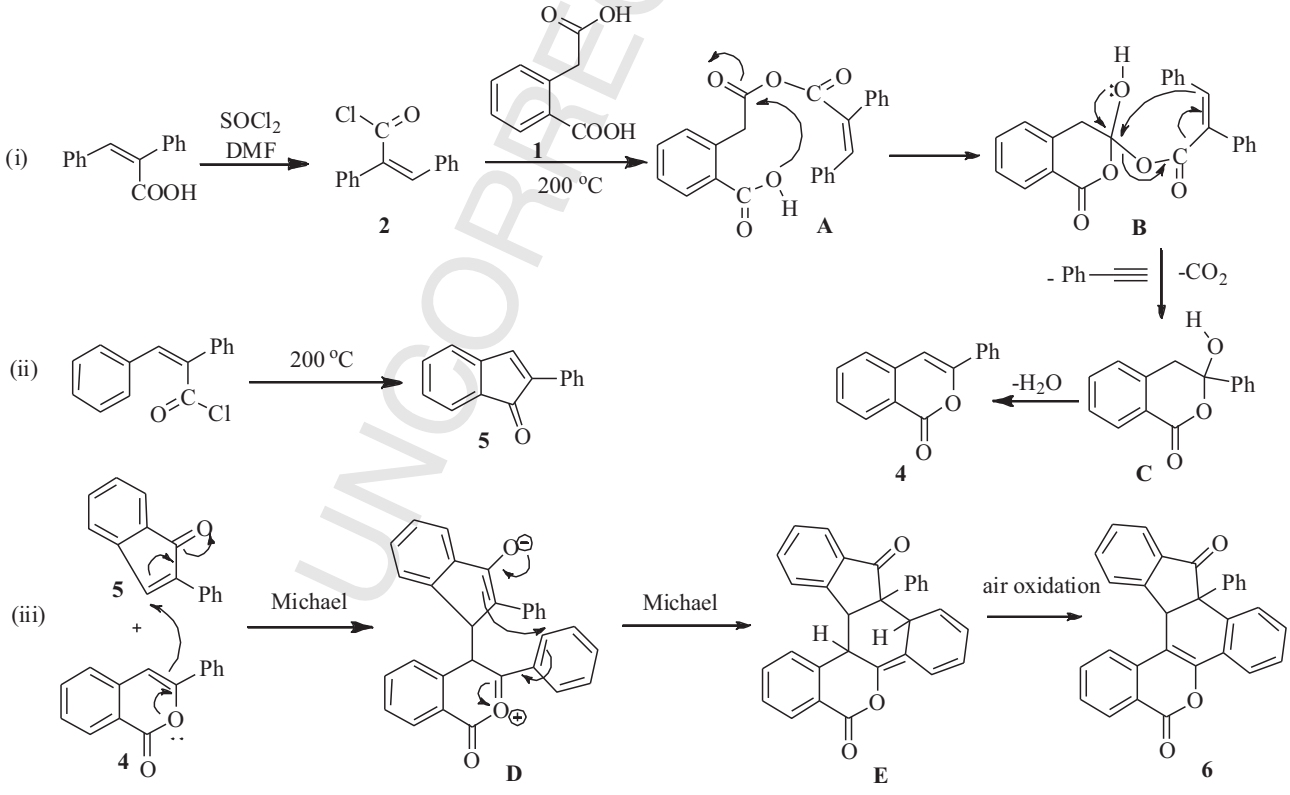

Fig. 3. Proposed mechanism for the synthesis of **6**.

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to the formation of compounds **5** and **6** in 3% and 67% yields, respectively (Table 1, entry 5). It is pertinent to mention that compound **4** was not isolated under the conditions, indicating that compound **5** reacts with it very quickly as soon as it forms. Interestingly, a slight decrease in the time duration (4 → 3.5 h) provided maximum yield (68%) of the fused compound **6** along with a trace amount of compound **5** as an impurity (Table 1, entry 6).

The attractive feature of this domino reaction is demonstrated by the fact that four new chemical bonds and three new rings were readily formed in domino fashion. In addition, work-up of the reaction is very simple. Water and phenylacetylene are the only byproducts, which may be evaporated under the reaction conditions/during the concentration of the reaction mixture, making the work-up very convenient simply by adding water/filtration/washing/recrystallization. Finally, it is important to address here that only a single diastereomer of **6** was detected first by spectroscopic and then by X-ray diffraction analysis (Fig. 2 and Table 2).

The mechanism for this domino multicyclization reaction is proposed and shown in Fig. 3. It can be divided into three steps. The first step involves ring closure cascade reaction, which consists of regioselective condensation of acyl chloride **2** with homophthalic acid **1** leading to A and HCl (**2** to **A**), intramolecular cyclization (**A** to **B**), removal of CO_2, phenyl acetylene and phenyl migration in a concerted fashion (**B** to **C**), and finally dehydration (**C** to **4**). The second step includes intramolecular cyclization of **2** to give intermediate **5**. In the third step, double Michael addition reaction between **4** and **5** leads to intermediate **E** through **D**, which after aerobic oxidation, provides thermodynamically stable hexacyclic fused isocoumatin framework **6**. This mechanism has been partially supported by an experiment in which the isolated intermediates **4** and **5** were reacted at 200 °C under solvent and catalyst free conditions; the hexacyclic product **6** was again generated in 66% yield (Scheme S1 in Supporting information). To the best of our knowledge, the synthetic strategy and mechanistic sequences described herein have not been reported so far.

4. Conclusion

Conclusively, a novel three component domino reaction was used for the construction of unprecedented hexacyclic fused isocoumarin framework. It is noteworthy for its cheap and readily available starting materials, eco-friendly procedure, easy work-up and potential biological applications of the resulting product. Our future efforts will be focused on using various computational and experimental methods for exploring the biological applications of this novel fused ring system. The facile one pot synthetic procedure may also be used to construct more useful and potential bioactive derivatives of this fused isocoumarin skeleton.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.03.022.

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