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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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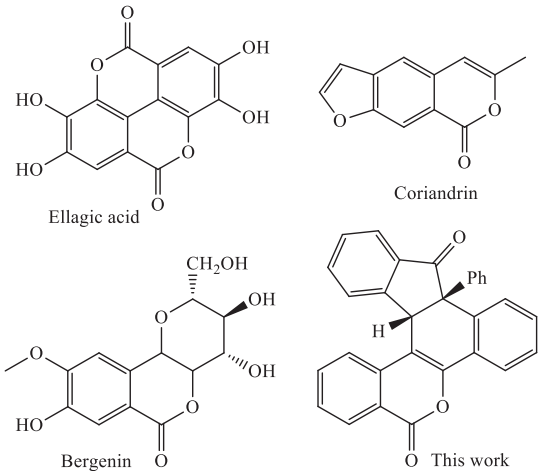


Fig. 1. Some representative natural products.

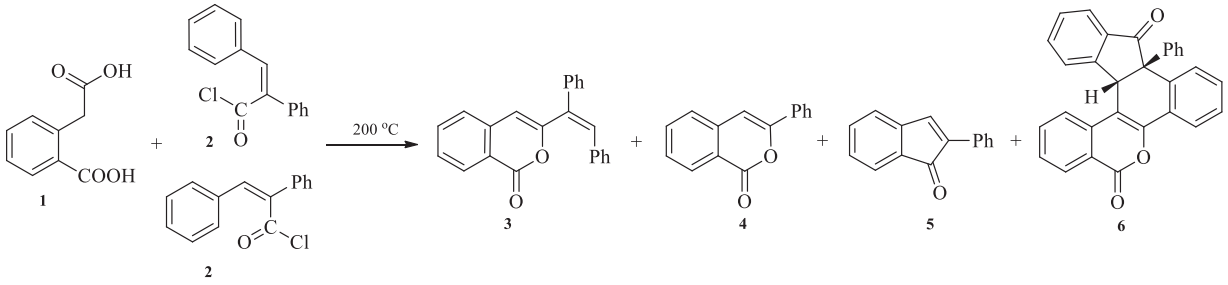
chromatography (TLC) was performed using aluminum sheets (Merck) coated with silica gel 60 F254. The melting points of compounds were determined using capillary tubes and an electrothermal melting point apparatus, model MP-D Mitamura Riken Kogyo, Japan. IR spectra of compounds were recorded on a Bio-Rad 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



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.