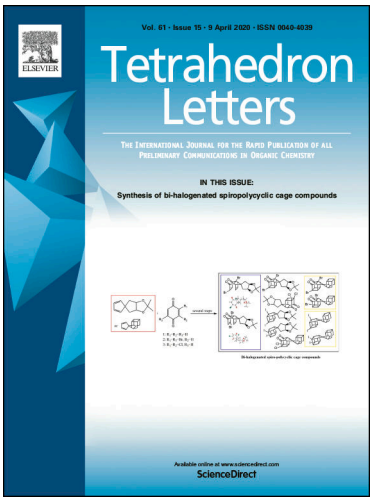

Facile synthesis and characterization of indene-fused 4-methylcoumarins and an unexpected skeletal rearrangement *via* Pechmann condensation

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Facile synthesis and characterization of indene-fused 4-methylcoumarins and an unexpected skeletal rearrangement *via* Pechmann condensation

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ABSTRACT

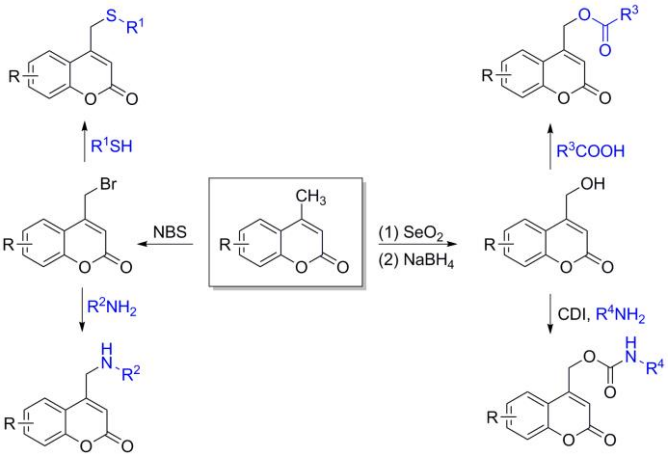
The Pechmann condensation of phenolic fluorenes with ethyl acetoacetate afforded indene-fused 4-methylcoumarins. In addition to the expected indeno[1,2-*g*]coumarin, a skeletal rearranged compound was obtained as a concomitant product when 9,9-dimethyl-9*H*-fluorene-2,7-diol was utilized as the substrate. X-ray crystallography was used to identify the structures of the isomers. Photochemical and photophysical studies indicated that compared with the non-rearranged products, the skeletal rearranged isomers have red shifted absorption maxima and much higher fluorescence quantum yields. A mechanism involving two competitive pathways for the simultaneous production of isomers was proposed.

Introduction

The Pechmann condensation is an efficient strategy to synthesize coumarins *via* the reaction of phenols with β-keto esters.[1] Coumarins are attractive molecules with versatile applicability. In addition to their widely studied pharmaceutical applications, such as anticoagulant,[2] antioxidant,[3] anticancer[4] and anti-Alzheimer,[5] coumarins are popular in photochemical studies due to their rigid planar skeleton and delocalized charge between the aromatic ring and the pyrone moiety. For example, they are used as fluorescent probes,[6] fluorescent chemosensors[7] and photoremovable caging groups for bioactive molecules.[8]

Photoremovable caging groups, also known as photoremovable protecting groups (PPGs), are photolabile compounds that can be covalently bonded to bioactive molecules to cage their activities. Once irradiated at a specific wavelength, the benign precursors can be triggered and instantaneously release active molecules at target sites. With this strategy, precise drug delivery is achieved in a spatiotemporal controlled manner.[9] Coumarin is one of the most commonly used PPGs. It was first reported by Givens as a photoactivatable phosphate-caging group[10] which led to the development of a new class of coumarinyl-4-methyl PPGs[11] (Scheme 1).

Although coumarin based PPGs have been widely applied in many areas, they are not suitable for biological applications. The absorption maxima of coumarin chromophores usually fall in the UV range; the intrinsic phototoxicity to living cells and poor penetration depth in organic tissues of UV light has greatly restricted their application in biological systems. To address this issue, structural modification of the coumarin core to red shift its absorption maximum has been applied. The introduction of electron-donating and electron-withdrawing groups onto the



Scheme 1. Coumarinyl-4-methyl PPGs for various functional groups.

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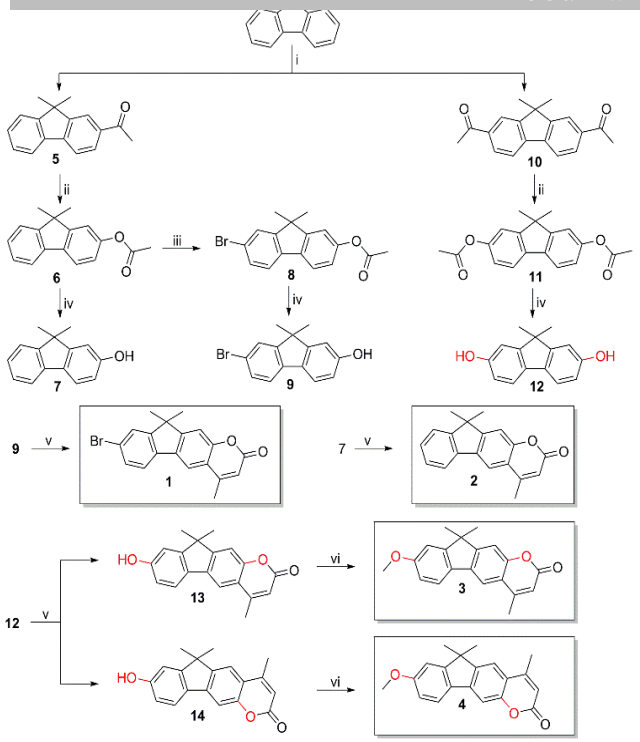


Scheme 2. Synthesis of indene-fused 4-methylcoumarins. *Reagents and conditions:* (i) CH_3COCl, $AlCl_3$, 1,2-dichloroethane, reflux, 88-91% yield; (ii) *m*CPBA, CF_3COOH, $CHCl_3$, r.t, 91-93% yield; (iii) NBS, DMF, 60 °C, 84% yield; (iv) 10% NaOH (aq), r.t, 81-88% yield; (v) ethyl acetoacetate, 70% H_2SO_4, r.t, 21-49% yield; (vi) CH_3I, K_2CO_3, DMF, rt, 90-92% yield

aromatic ring and extension of the molecular π-conjugation system are frequently adopted methods to make coumarin PPGs favourable for long wavelength stimuli.[12] Expanding the π-system of the coumarin scaffold by fusing it to aromatic or heterocyclic moieties typically results in altered chemical/physical properties, which offers an alternative to develop novel coumarinyl caging groups.[13] In addition to their use as PPGs, fused coumarins were also studied as possible anti-cancer[14] or anti-inflammatory agents,[15] as well as fluorescent probes for thiol,[16] hydrazine[17] and carbon monoxide.[18]

Due to the diverse applications of fused coumarins in various areas, efforts have been dedicated to the design and synthesis of novel π-expanded coumarins. In addition to the Pechmann reaction, strategies including the Knoevenagel condensation,[19] metal-catalyzed reactions[20] and microwave technology[21] have also been reported. To increase the diversity of fused coumarin derivatives as well as to expand the library of coumarinyl PPGs for potential applications, herein we report a facile approach to prepare indene- fused 4-methylcoumarins *via* the Pechmann

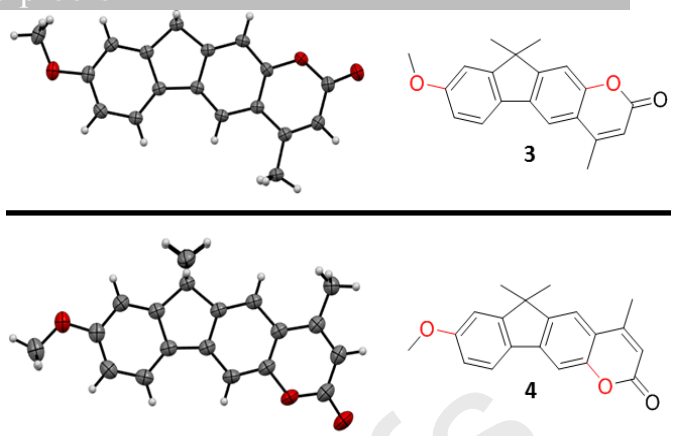


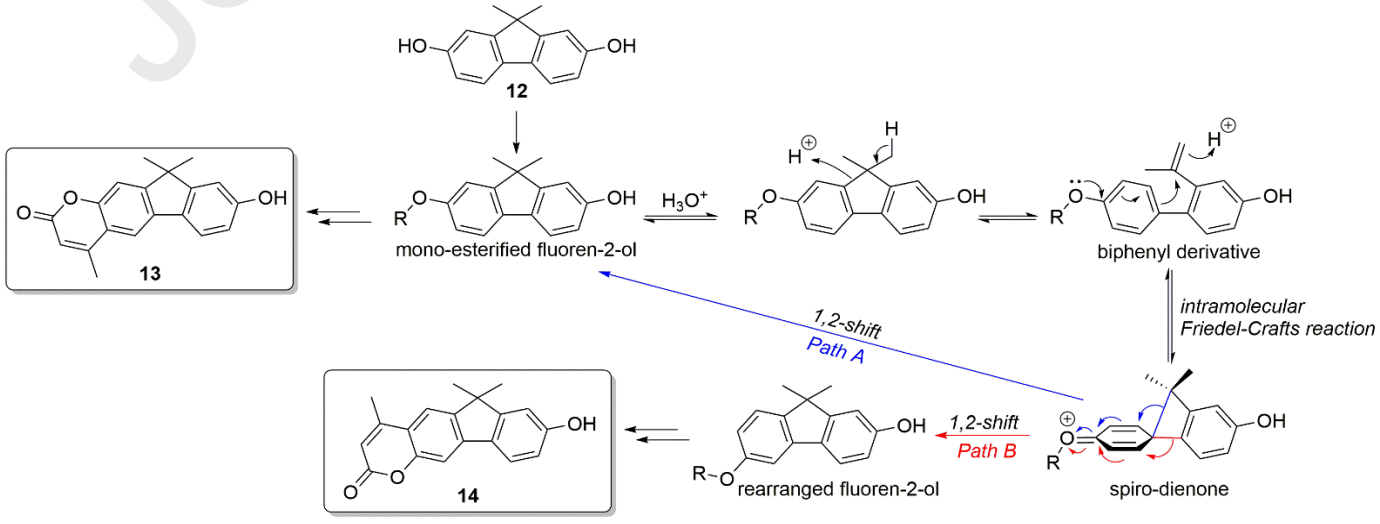
Figure 1. X-ray crystal structures of **3** (CCDC 1946838）and **4** (CCDC 1946839.

condensation. The rigid planar molecular structure of the introduced fluorene moiety provides an expanded π-conjugated scaffold to the fused coumarins. Meanwhile, the high fluorescent quantum yield of fluorene derivatives would be beneficial to improve the performance of PPGs.

Results and Discussion

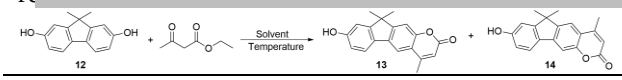
9,9-Dimethylfluorene was heated at reflux with 1.2 equiv. or 3.5 equiv. of acyl chloride in the presence of aluminum chloride in 1,2-dichloroethane to afford mono-acylated product **5** in 88% yield or di-acylated product **10** in 91% yield (Scheme 2). Following subsequent Baeyer-Villiger oxidation, esters **6** and **11** were obtained. Compound **8** was afforded by heating compound **6** with *N*-bromosuccinimide (NBS) in *N*,*N*-dimethylformamide (DMF) at 60 °C for 4 h. Esters **6**, **8** and **11** were hydrolyzed to phenolic fluorenes **7**, **9** and **12** using a 10% NaOH solution. Finally, the Pechmann reaction was applied by stirring the phenols with ethyl acetoacetate in the presence of 70% H_2SO_4 at room temperature to give coumarin **1** from compound **9** and **2** from compound **7**, respectively. Interestingly, the Pechmann condensation of compound **12** with ethyl acetoacetate produced not only the expected compound **13** but also an isomer **14** in which the oxygen atom at the C-7 position of the fluorene skeleton had transferred to the C-6 position. Methylation of **13** and **14** yielded compounds **3** and **4**, respectively.

The molecular structures of **1** and **2** were confirmed with NMR and HRMS analyses. However, we were unable to differentiate compounds **3** and **4** due to their structural similarity. The ^{1}H NMR spectra of their parent molecules **13** and **14** were similar (ESI, Fig. S1). Two-dimensional NMR spectroscopy gave detailed structural information about the individual compounds;



Scheme 3. Proposed mechanism for the competitive synthesis of compound **13** and isomer **14**.

Table 1. Relative amounts of **13** and **14** under different re



Entry	Temp. (℃)	Solvent (70% H_2SO_4 + EtOH)[b]		Solvent (70% H_2SO_4)	
		13 (%)	**14** (%)	**13** (%)	**14** (%)
1	25	83	17	70	30
2[a]	10	85	15	74	26
3[a]	0	81	19	68	32
4[a]	-10	60	40	34	66

[a] Data were determined by HPLC. Detection wavelength was set at 350 nm. [b] 70% H_2SO_4/EtOH = 4/1 (v:v)

however, it was still difficult to distinguish the isomers (ESI, Fig. S2-S7). Therefore, X-ray crystallography was used (Fig. 1).[22] As shown in Figure 1, compound **3** was verified as an indeno[1,2-*g*]coumarin derivative while compound **4** was proved to be an indeno[2,1-*g*]coumarin derivative.

We were puzzled by the formation of isomer **14** because, to the best of our knowledge, there are no reports of structural rearrangement during the Pechmann condensation. The C-O covalent bond of the phenolic hydroxyl group at the 7-position of the fluorene moiety is quite stable due to p-π conjugation between the aromatic ring and the oxygen atom. Theoretically, only compound **13** should be obtained. HPLC analysis showed that the molar ratio of intermediates **13** to **14** was 7:3 when the reaction was carried out at 25 °C. It could be slightly increased to 8:2 when 20% of ethanol (v/v) was added to the reaction mixture. We then conducted a series of reactions by varying the reaction conditions to investigate the relative amounts of the isomers; these results are summarized in Table 1.

As shown in Table 1, the reactions conducted in the presence of ethanol have larger **13** to **14** molar ratios compared with those without ethanol. Meanwhile, the percentage of compound **14** gradually increased with the decrease of the reaction temperature; it even became the major product when the reaction was performed at -10 °C under ethanol-free conditions. The various molar ratios of the isomers in response to the reaction conditions indicated that compound **13** and **14** were produced simultaneously in a competitive manner. Isomer **14** was preferentially formed at low temperatures, which indicated a kinetically controlled reaction behaviour. Non-rearranged product **13** was preferentially obtained in a protic solvent (ethanol) or at higher temperatures, which suggested that **13** was a thermodynamically controlled product. It is interesting that only compound **12** underwent the rearrangement reaction. There were no isomers found in the cases of compound **7** and **9**.

The classical Pechmann reaction involves transesterification of phenols with β-keto esters, intramolecular electrophilic aromatic substitution (EAS) and dehydration. To determine at which stage of the Pechmann reaction the rearrangement reaction occurs, we first studied the stability of compound **12** in 70% H_2SO_4 solution to see if isomers could be formed before esterification. We found that compound **12** remained intact after being stirred for several hours either at room temperature or at low temperature before the addition of ethyl acetoacetate (ESI, Fig. S8). We next studied the stability of compound **13** by stirring with ethyl acetoacetate in 70% H_2SO_4 to check if **14** could be obtained from **13** *via* isomerization; this showed that compound **13** was stable towards the acidic environment (ESI,

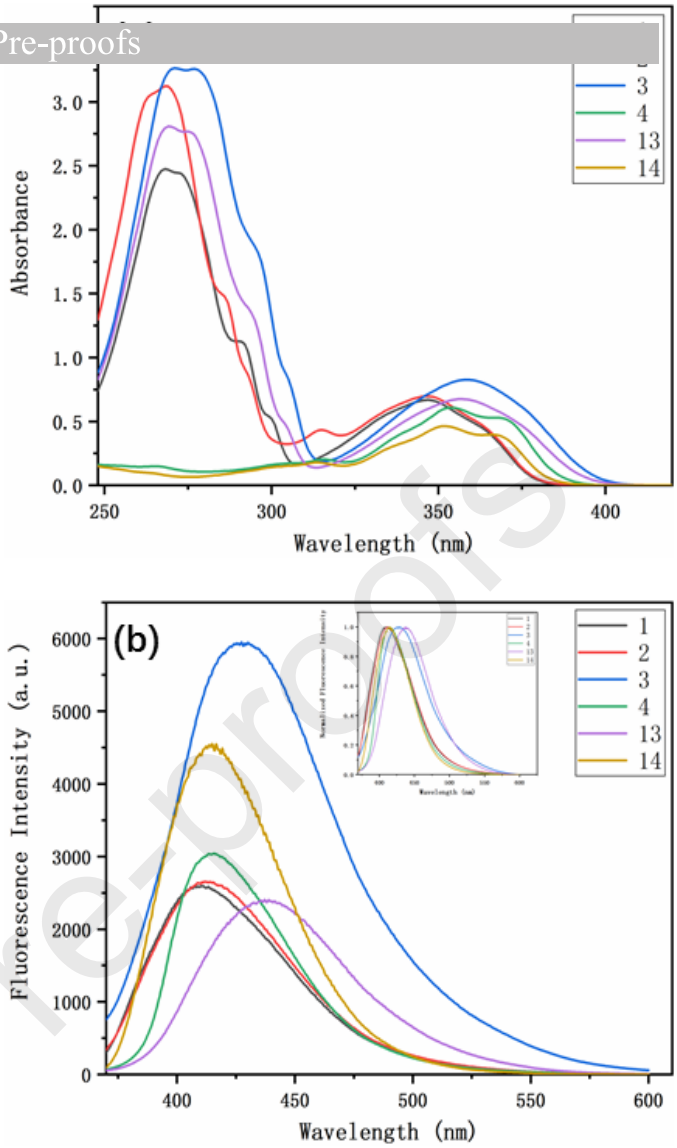


Figure 2. UV-vis absorption (a) and emission (b) spectra of indene-fused 4-methylcoumarins measured in dichloromethane (inset: the normalized fluorescence spectra).

Fig. S9). Therefore, the fluorene scaffold rearrangement should occur between the transesterification and the EAS stages of the Pechmann reaction. Based on the results obtained, a possible mechanism involving two competitive reactions was proposed in Scheme 3. As illustrated, 9,9-dimethylfluorene-2,7-diol **12** was mono-esterified to fluoren-2-ol by transesterification with ethyl acetoacetate. Following a ring opening reaction in the acidic medium, a multi-substituted biphenyl derivative was produced. Subsequent intramolecular Friedel-Crafts alkylation results in the formation of an unstable spiro-dienone intermediate, which immediately underwent a 1,2-alkyl shift to revert to the mono-esterified fluoren-2-ol (Path A), which was converted to coumarin **13** *via* the Pechmann reaction. Alternatively, the spiro-dienone might also undergo a competitive 1,2-phenyl shift to afford a skeletally rearranged fluoren-2-ol (Path B), which was finally converted to the rearranged isomer **14**.

The photophysical and photochemical properties of the

Table 2. Photophysical and photochemical properties of **1-4** and **13-14** measured in dichloromethane. Fluorescence quantum yields were determined using an integrating sphere method.

Compounds	λ_{abs} (nm)	λ_{em} (nm)	Stokes Shift (nm)	ε (10^4 M^{-1} cm^{-1})	Φ_F (%)
1	268, 347	411	143, 64	0.8	2.0[a]
2	268, 347	412	144, 65	1.3	3.3[a]
3	271, 359	427	156, 68	0.9	10.4[a]
4	354	421	67	3.3	59.3[a]
13	269, 357	437	168, 80	0.9	13.3[b]
14	352	415	63	2.9	81.9[b]

[a] Data were measured on an Edinburgh Instrument FLS900. [b] Data were measured on a Hamamatsu Photonics C9920-02.

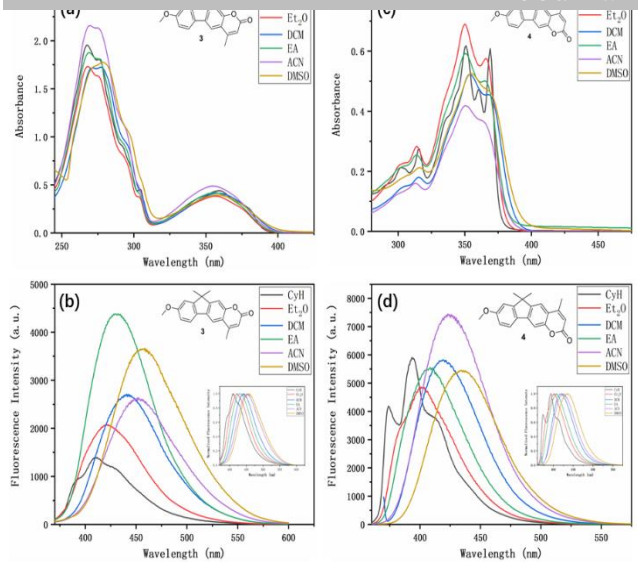


Figure 3. Photophysical and photochemical properties of **3** and **4** in different solvents: (a) Absorption spectra of **3**; (b) Emission spectra of **3**; (c) Absorption spectra of **4**; (d) Emission spectra of **4**. Insets: normalized emission spectra. CyH = cyclohexane, Et_2O = diethyl ether, DCM = dichloromethane, EA = ethyl acetate, ACN = acetonitrile, DMSO = dimethyl sulfoxide.

obtained coumarins were characterized (Fig. 2). Coumarins **1-3** and **13** showed similar absorption behaviours in dichloromethane. They have a strong absorption maximum at about 270 nm and a broad shoulder with a maximum around 350 nm. In terms of isomers **4** and **14**, the plotted spectra exhibited relatively broad absorption bands that cover from 300 nm to 400 nm with a maximum at about 354 nm, i.e. the absorption shoulders of non-rearranged coumarins are the absorption maxima of the isomers. Although the absorption properties of the isomers are quite different to the non-rearranged coumarins, their emission properties are similar. As shown in Figure 2b, the emission maxima of these fused coumarins are located between 400 nm and 440 nm. The solvent effects on the absorption and emission spectra of isomers **3** and **4** were studied (Fig. 3). Coumarin **3** has a maximum absorption at 268 nm and a small shoulder peak at 276 nm in cyclohexane (CyH). However, the maximum absorption red-shifted to 279 nm with a small shoulder peak at 273 nm when **3** was characterized in dimethyl sulfoxide (DMSO). It seems that the positions of the absorption peak and the shoulder peak have switched with each other. The absorption spectrum of isomer **4** measured in CyH exhibited two major peaks at 351 nm and 369 nm, respectively, as well as a minor peak at 360 nm. With the increase in solvent polarity, the minor peak diminished quickly; the shoulder peak at a longer wavelength also decreased and finally weakened into a small shoulder peak in DMSO (Fig. 3c). A bathochromic shift of the fluorescence emission spectra with increasing solvent polarity was observed in both compounds **3** (Fig. 3b) and **4** (Fig. 3d).

Fluorescence quantum yields (QYs) of the fused coumarins were measured, and the data are summarized in Table 2. Compound **1** and **2** have QYs of 2.0 and 3.3, respectively. The heavy atom effect of bromine might be responsible for the slight decrease of the QY of compound **1** in comparison to compound **2**. Compound **3** has a higher QY of 10.4 due to the presence of an electron-donating methoxy group. Isomer **13** has a similar QY to **3** because of their structural similarity. However, isomers **4** and **14** have much higher QYs. As shown in Table 2, the QY of compound **4** is 59.3, nearly five times larger than that of compound **3**. As for compound **14**, the highest QY of 81.9 was recorded. Since coumarins **3** and **4** (or **13** and **14**) are quite similar in their molecular structures, it is difficult to give a rational explanation for the vast differences in the QYs. Further studies are needed to explore the structure-property relationships of such compounds.

In summary, we have synthesized a series of indene-fused 4-methylcoumarin derivatives including four indeno[1,2-*g*]coumarins **1-3** and **13** together with two indeno[2,1-*g*]coumarins **4** and **14** *via* the Pechmann condensation. An unexpected rearrangement reaction that gave rise to the formation of a pair of isomers was observed. The competition between the thermodynamically and kinetically controlled reactions under different reaction conditions resulted in various molar ratios of the isomers. Structures of the fused coumarins were confirmed with NMR and HRMS. X-ray crystallography was used to identify the isomers. Photophysical and photochemical studies found that the structurally rearranged coumarins have red shifted absorption maxima and higher quantum yields in comparison to their counterparts. Further investigations regarding the application of these novel indene-fused 4-methylcoumarins as photoremovable protecting groups are underway in our group.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data (general procedures, copies of NMR, HRMS spectra, HPLC traces) to this article can be found online at:

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22. Methyl groups are disordered due to the rotational freedom.

► The facile synthesis of indene-fused 4-methylcoumarins
► The observation of a fluorene skeletal rearrangement during the Pechmann reaction.
► The differences between the photophysical properties of the indeno[1,2-*g*]coumarins and indeno[2,1-*g*]coumarins.

Graphical Abstract

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Facile synthesis and characterization of indene-fused 4-methylcoumarins and an unexpected skeletal rearrangement *via* Pechmann condensation

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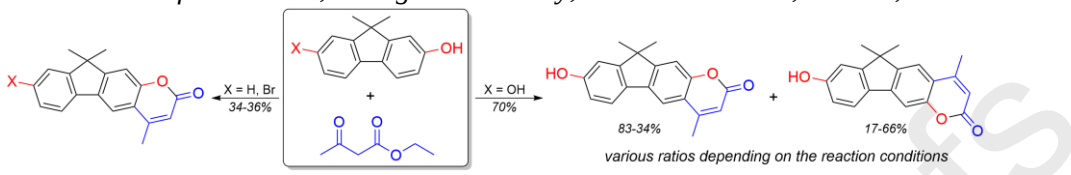
Jie Wu[a], Wei Liu[b], Li Liang [a], Ya Gan[b], Shuang Xia[c], Xiaojun Gou[a,*] and Xiaohua Sun[a,d,*]
Sichuan Industrial Institute of Antibiotics, Chengdu University, Sichuan Province, 610052, P. R. China



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