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COMMUNICATION

A pseudopericyclic [3,5]-sigmatropic rearrangement of a coumarin trichloroacetimidate derivative

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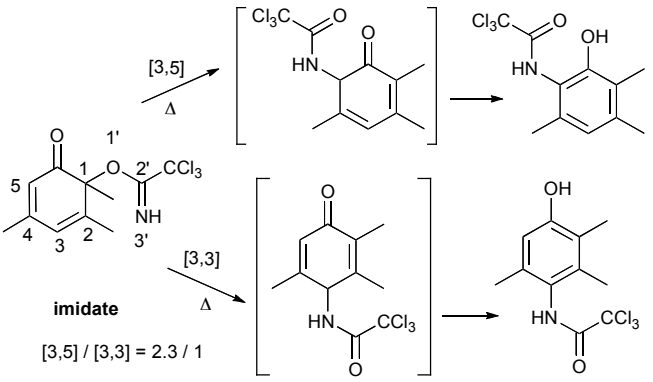
Thermolysis of a coumarin trichloroacetimidate yields a single rearrangement product. The proposed mechanism is a pseudopericyclic allowed (Woodward-Hoffman forbidden) [3,5]-sigmatropic rearrangement to form the corresponding amide followed by a sigmatropic [1,5]-hydrogen migration. Transition state calculations at the B3LYP/6-31G(d,p) level support this mechanism and suggest the selectivity is influenced by the stability of the intermediates.

Coumarins constitute a large family of heterocyclic compounds that are present in a variety of natural products and biologically active compounds.[1] Substituted coumarin derivatives are known for their medicinal and diverse physiological activities such as antibacterial, anticoagulant, antioxidant, anticancer, anti-TB and anti-inflammatory properties.[2-6] These scaffolds have also garnered attention as fluorescent cellular probes in medicinal applications.[7,8] A number of synthetic methods are known in the literature to access coumarin scaffolds.[9-11] Recently, our group also reported an efficient and functional group tolerant method to access a library of 4-substituted coumarins.[12]

As part of our continuing interest in pseudopericyclic reactions[13-16] we designed and synthesized a coumarin system that we anticipated would undergo preferentially a [3,5]-sigmatropic rearrangement. In recent years pseudopericyclic reactions have been of considerable interest among both the synthetic as well as the theoretical chemistry communities.[17-19] A planar (or nearly planar) transition state geometry owing to the participating orthogonal orbital overlap (disconnection) is one of the main characteristic features of pseudopericyclic reactions.[20] In contrast to pericyclic reactions that are governed by the Woodward-Hoffmann rules,[21] all pseudopericyclic reactions are allowed irrespective of the number of electrons involved. The [3,5]-sigmatropic rearrangement of 1,3,7-octatriene is predicted to be forbidden;[21A] if it were to occur, it is calculated to proceed through free-radical intermediates, but the allowed and concerted [3,3]-rearrangement has a much lower calculated barrier.[21B,C] In contrast, we have reported experimental evidence for a [3,5]-rearrangement of a cyclohexadienone ester that is allowed because it is pseudopericyclic; the [3,5]-rearrangement is experimentally favored over the more familiar [3,3]-rearrangement by a 3.2/1 ratio.[22]

Imidates are isoelectronic with acetate, and thus display similar reaction profiles. We have also found that [3,5]-rearrangements of trichloroacetimidates are competitive with, and indeed favored by a 2.3/1 ratio, over the well-known [3,3] Overman rearrangement.[23, 24] This was shown experimentally with cyclohexadienone trichloroacetimidate derivative, a molecular system where both [3,3]- and [3,5]-rearrangements are possible (Scheme 1).[23] The barriers for imidate rearrangements are generally lower than for acetates because of the stability of the product amide functionality.[22,23]



Scheme 1 Sigmatropic rearrangements of cyclohexadienone imidate.

Having successfully demonstrated that [3,5]-pseudopericyclic reactions were competitive in constrained

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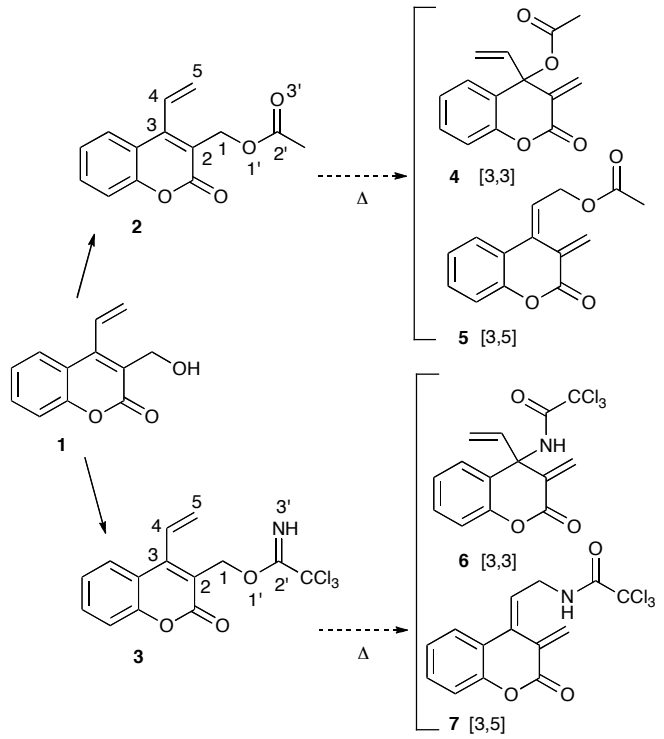
Electronic Supplementary Information (ESI) available: Experimental section for synthesis and pyrolysis of **2** and **3**; ^{1}H- and ^{13}C-NMR spectra for **3** and **8**; X-ray crystallographic details for **8**; Computational details and Cartesian coordinates for all calculated structures; full citation for reference 27 (PDF) See DOI: 10.1039/x0xx00000x

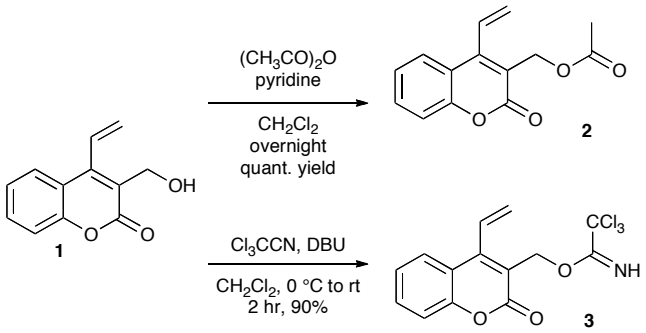
cyclohexadienone systems, we wanted to further explore the scope of this chemistry in other scaffolds and design a system where the [3,5]-rearrangement would be the favored or exclusive pathway. In our approach, we chose the coumarin system **1** for its synthetic as well as medicinal applications (Scheme 2). Compounds **2** and **3** are derivatives of a pentadienyl alcohol and are therefore predicted to be able to undergo thermal [3,3]- and [3,5]-sigmatropic rearrangements. The transition state geometry for a [3,5]-rearrangement is qualitatively predicted to be pseudopericyclic in nature, suggesting this barrier may be lower than a competing, pericyclic [3,3]-rearrangement. On the other hand, the thermal rearrangements might be endothermic, particularly for the acetate **2**, due to the loss of aromatic stabilization of the coumarin core in the products (**4** and **5**). We reasoned that the [3,5]-rearrangements of acetate **2** or trichloroacetimidate **3** to form **5** or **7** respectively, would be favored over the [3,3]-rearrangements to form **4** or **6** because the latter would disrupt the aromaticity of the coumarin more. Herein we report an experimental and computational study of this system, which demonstrates this anticipated selectivity.



Scheme 2 Proposed [3,3] and [3,5]-sigmatropic rearrangement of coumarin derivatives **2** and **3**.

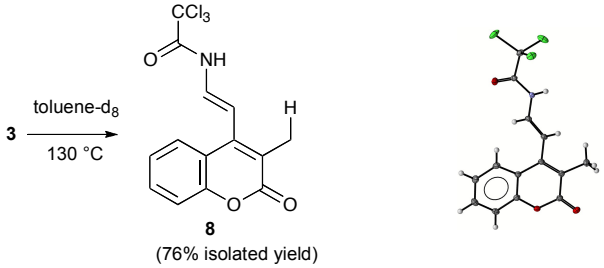
Coumarin acetate (**2**) and imidate (**3**) derivatives were synthesized from a common coumarin alcohol intermediate (**1**, Scheme 3) upon treatment with acetic anhydride/pyridine and trichloroacetonitrile/DBU[24] respectively, as reported earlier.[12] The key step in the multi-step synthesis, starting with commercially available 4-hydroxycoumarin, is the Suzuki cross-coupling reaction of 3-substituted 4-chlorocoumarins with potassium vinyl trifluoroborate using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5–10 mol%) as catalyst (Supporting Information).[12, 25]

Having successfully synthesized coumarin acetate **2** and imidate **3**, we then attempted thermal pyrolysis experiments to study the sigmatropic rearrangement reactions (Scheme 2). The ^{1}H-NMR of acetate **2** did not show any rearrangement upon heating in a thick-walled sealed tube at 250 °C for nearly 10 hours in deuterated benzene.



Scheme 3 Synthesis of coumarin acetate **2** and imidate **3**.

Recognizing that both of the rearrangements of **2** (Scheme 2) might be disfavored by enthalpy, we also attempted the pyrolysis of the trichloroacetimidate **3**, hoping that the stability of the amide functionality relative to the imidate might overcome the partial loss of aromaticity in the [3,5]-product. Indeed, the condensate from the initial flash vacuum pyrolysis (FVP) experiments at 300 °C and 350 °C showed no starting imidate present. However, the ^{1}H-NMR spectrum of the crude dark brown pyrolysate mixture showed no identifiable products. A lower temperature thermolysis was attempted. Heating of **3** in toluene-d_8 (dry, degassed) was carried out in J Young NMR tube and monitored by ^{1}H-NMR over time. After heating in a 110 °C oil bath for 8h, new signals appeared indicative of a slow reaction. The oil bath temperature was then increased to 130 °C and the solution was heated for another 8h. The ^{1}H-NMR showed new sets of signals (90% conversion) corresponding to **8** (Scheme 4) with traces of signals for unidentified products (SI). A larger scale reaction yielded sufficient **8** (76% isolated yield) for purification and recrystallization; this gave crystals suitable for X-ray diffraction which confirmed our NMR structural assignment. A plausible mechanism is proposed in Scheme 5; it would appear that imidate **3** selectively undergoes a pseudopericyclic [3,5]-rearrangement to **7** followed by a rapid pericyclic [1,5]-H shift[26] to form the observed product **8**.



Scheme 4 Thermolysis of coumarin imidate **3**. The X-ray crystal structure of **8** is shown at the right.

Concurrently, we undertook computational studies of the rearrangements of acetate **2** and imidate **3**, which offer an explanation of the results of thermolysis experiments. Calculations were performed using the Gaussian 09 suite of programs.[27] The geometries of the reactants **2** and **3**, transition states and products were optimized with the B3LYP

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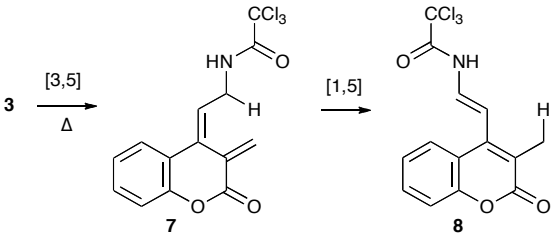
functional[28,29] using the 6-31G(d,p) basis set.[30] This level of theory was chosen so that direct comparisons could be made with previous calculations on closely related systems.[15,22,23] This level of theory reproduces the trends in relative energies and activation energies calculated at higher levels of theory for other rearrangements of esters and imidates.[15,22,23] Transition states and minima were verified by frequency calculations. Gibbs free energies were calculated based on these frequency calculations. The relative free energies (B3LYP/6-31G(d,p)) of the lowest energy conformations and transition states for acetate **2** and imidate **3** are presented graphically in Figures 1 and 3; transition state geometries are shown in Figures 2 and 4, respectively. Details of the calculations are presented in the Supporting Information (SI).



Scheme 5 Proposed mechanism for the formation of **8** in the thermolysis of coumarin imidate **3.**

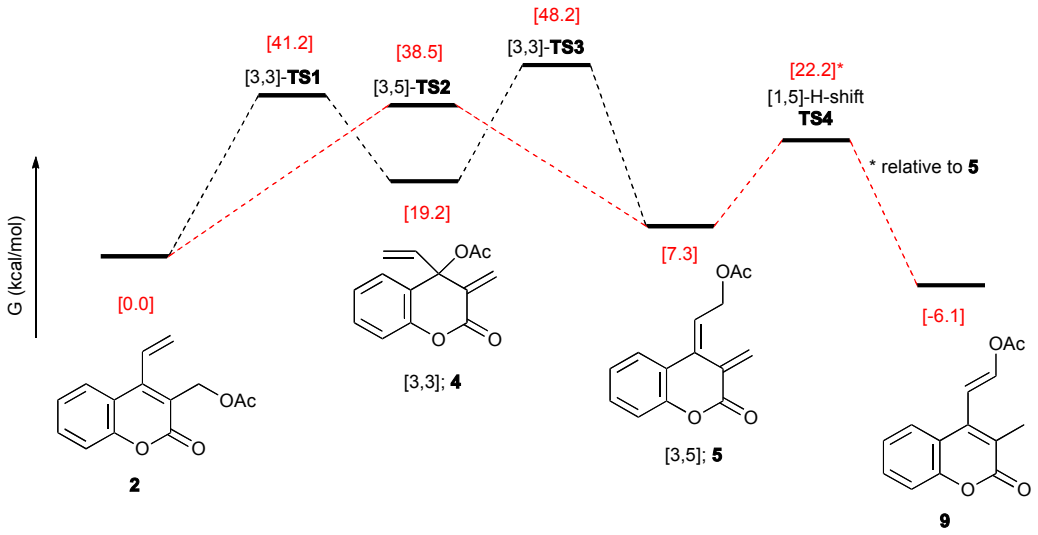


Fig. 1 Calculated Gibbs free energy profile for the sigmatropic rearrangements of acetate **2** at B3LYP/6-31G(d,p) level of theory; the vertical axis is approximately to scale.

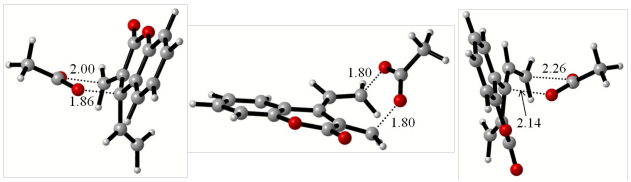


Fig. 2 B3LYP/6-31G(d,p) optimized geometries for the transition states of acetate **2**.

Based on both experimental and computational results, we have earlier shown that acetate and imidate derivatives of cyclohexadienones undergo competing thermal [3,3]- and [3,5]-sigmatropic rearrangements, with the [3,5]-rearrangements being favored[22,23] We designed the systems so that enthalpy might more strongly favor the [3,5]-rearrangements. The B3LYP/6-31G(d,p) free energy calculations (Figure 1) are consistent with these qualitative predictions for the reactions. Beginning with acetate **2**, the [3,5]-rearrangement ([3,5]-**TS2**) is calculated to be favored over the [3,3]-rearrangement ([3,3]-**TS1**) by 2.7 kcal/mol. The sequential pathway involving two [3,3]-sigmatropic rearrangements (via [3,3]-**TS1** and [3,3]-**TS3**) leading to the [3,5]-product (**5**) is higher in energy (9.7 kcal/mol above [3,5]-**TS2**), suggesting that the [3,5]-product would only arise from a single [3,5]-rearrangement step. However, both **4** and **5** are less stable than **2** (19.2 and 7.3 kcal/mol respectively); this is consistent with the observed lack of thermal reactivity of **2**. In analogy to the [1,5]-hydrogen shift from **7** to **8**, a rearrangement **5** to **9**, via **TS4** was calculated. The product **9** is calculated to be 6.1 kcal/mol lower in energy than **2**, but apparently the barrier heights and the instability of **5** contribute to the lack of an observed rearrangement.

The geometries of the optimized transition states (Figure 2) for the two sequential [3,3]-rearrangements ([3,3]-**TS1** and [3,3]-**TS3**) are both flattened boats. We have previously suggested that this transition state geometry at the acetate reflects a mixing of two orbital symmetry allowed possibilities: a pericyclic boat geometry as well as a planar pseudopericyclic geometry.[22] Consistent with previous calculations,[22] the eight-centered transition state [3,5]-**TS2** is planar at the acetate and therefore is purely pseudopericyclic.

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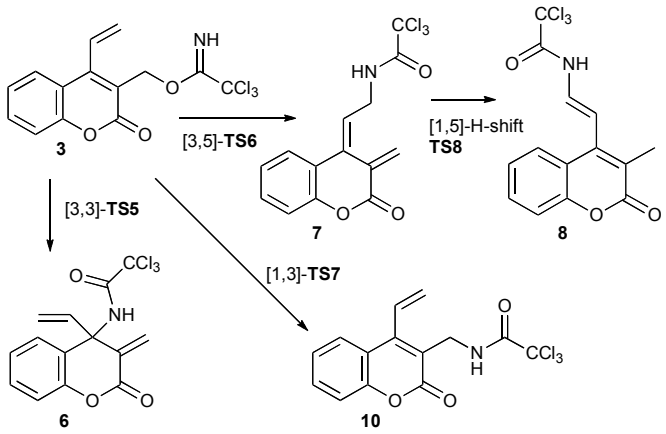

Scheme 6 Calculated sigmatropic rearrangements of **3**.

Qualitatively, the lower barrier for the [3,5]-**TS2** for the rearrangement of the ester **2**, and the modest endothermicity to the [3,5]-product (**5**), suggests that the [3,5]-rearrangement of the imidate **3** to the presumably more stable amide **7** might provide an energetically accessible route to the observed product. Therefore, we also undertook the computational studies of possible thermal rearrangements in this system (Scheme 6). We calculated transition state geometries for the [1,3]-, [3,3]- and [3,5]-rearrangements of **3** that would form the corresponding amides **10**, **6** and **7**, respectively. To support our proposed sequential pathway for the formation of **8**, we also calculated the [1,5]-H shift from intermediate [3,5]-product, **7.** The calculated relative energetics are summarized in Figure 3 and the transition state geometries are shown in Figure 4.

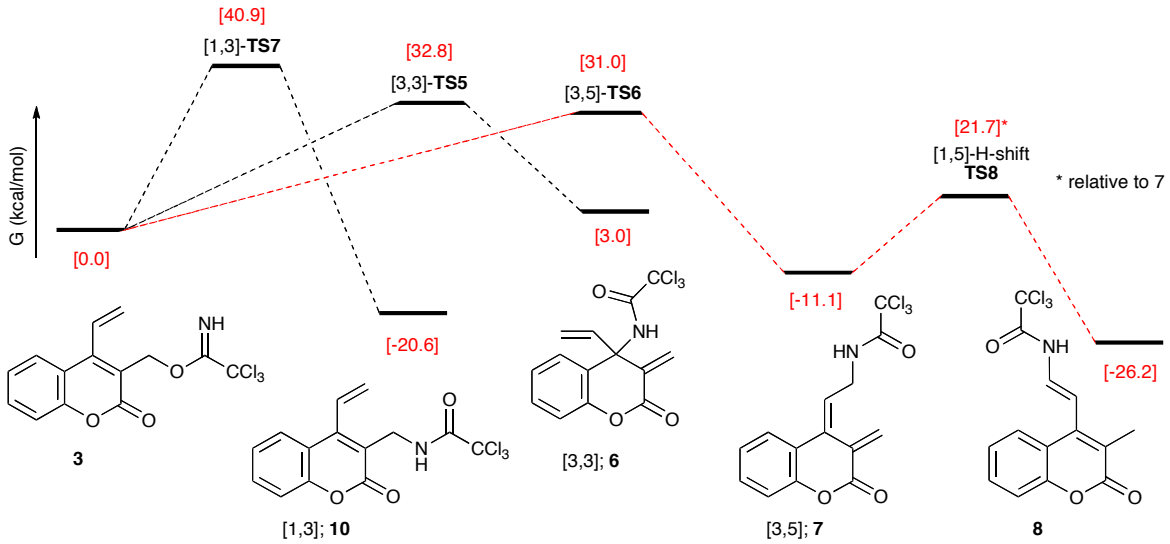

Fig. 3 Calculated Gibbs free energy profile for the sigmatropic rearrangements of imidate **3** at B3LYP/6-31G(d,p) level of theory; the vertical axis is approximately to scale.

In this case, formation of the [3,3]-product (**6**) from **3** is calculated to be modestly (3.0 kcal/mol) endothermic. This is likely due to dearomatization of the coumarin as well as steric crowding in **6**, offset to some extent by the stability of the amide as compared to the imidate functionality in **3**. The [3,5]-product (**7**) is calculated to be more stable than **3**, by 11.1 kcal/mol. The calculated barriers for [3,3]- and [3,5]-transition states suggest that the [3,5]-rearrangement ([3,5]-**TS6**) is favored over the [3,3]-**TS5** by 1.8 kcal/mol (Figure 3). The calculated barrier for the Woodward-Hoffmann forbidden four-centered [1,3]-**TS7** to the thermodynamically stable amide **10** is significantly higher in energy as compared to the [3,3]- and [3,5]-transition states (8.1 and 9.9 kcal/mol, respectively). Houk *et al.* have previously reported calculations on the 1,3-rearrangements of imidates.[31] We have argued that pseudopericyclic [1,3]-sigmatropic rearrangements (such as [1,3]-**TS7**) have higher barriers due to the unfavorable geometry of a four-centered transition state.[13]

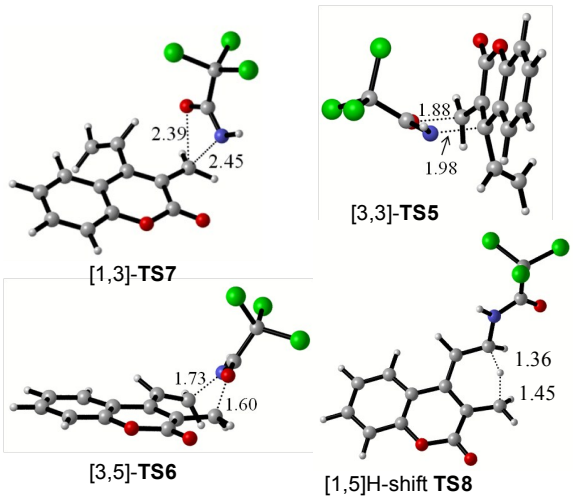

Fig. 4 B3LYP-optimized geometries for the transition states for imidate **3**.

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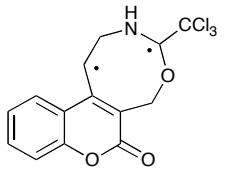
Only a modest barrier (21.7 kcal/mol, relative to the energy of **7**) was calculated for the [1,5]-hydrogen shift from **7** ([1,5]-H-shift **TS8**). Thus, both the lower barriers for the sequential pathway (i.e. [3,5]-rearrangement followed by [1,5]-H shift) and the thermodynamic stability of **8** are in agreement with our experimental observation of the selective formation of **8**.

Similar to the acetate ([3,3]-**TS1** and [3,3]-**TS3**), the transition state for [3,3]-rearrangement of imidate **3** ([3,3]-**TS5**) also has a flattened boat geometry. The [3,5]-**TS6** and [1,3]-**TS7** would be orbital symmetry-forbidden as pericyclic reactions. As expected both these transition state geometries are purely pseudopericyclic, i.e. planar on the imidate moiety (Figure 4).

In principle, a stepwise biradical mechanism via **11** is possible for the [3,5]-sigmatropic rearrangement from **3** to **7**. This is arguably unlikely for two reasons: first, the radical pathway for the [3,5]-rearrangement in 1,3,7-octatriene is calculated to have a much higher barrier than the pericyclic [3,3]-rearrangement.[21B,C] If the hypothetical [3,3]-rearrangement of **3** is assumed to be concerted, and the pseudopericyclic [3,5]-rearrangement of **3** is the only rearrangement observed, this argues that the latter does not involve radical intermediates. Second, it is possible to bias a hydrocarbon [3,3]-(Cope) rearrangement towards radical intermediates by stabilizing the radicals by conjugation.[21B,C] But the radical centers in **11** are not similarly stabilized. The calculations are consistent with a concerted pathway for the observed [3,5]-rearrangement of **3** via [3,5]-**TS6** with a lower barrier than via [3,3]-**TS5**.



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Conclusions

A substituted coumarin imidate (**3**) has been shown experimentally to selectively undergo a thermal [3,5]-sigmatropic rearrangement that would be forbidden by the Woodward-Hoffmann rules, yielding the rearrangement product **8**. Calculations suggest the energetically favorable pathway is a sequential one, in which a pseudopericyclic [3,5]-rearrangement gives the amide **7**, for which the modest decrease in the aromaticity of the coumarin system is offset by the increased stability of the amide functionality. This is followed by a facile [1,5]-hydrogen shift to yield the observed product **8**. The [3,3]-rearrangement of **3** is energetically disfavored because the stability of the amide is insufficient to overcome the loss of aromaticity in **6**. Attempted pyrolysis of the isoelectronic acetate **2** gave only unreacted **2**. DFT calculations (B3LYP/6-31G(d,p)) suggest that the [3,3]- and [3,5]-rearrangements of acetate **2** are not expected to occur because the expected products **4** and **5** are less stable. Moreover, the functionalized and structurally diverse coumarins reported herein are of potential biological interest to medicinal chemists.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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