Coumarin (5,6-Benzo-2-pyrone) Trapping of an HDDA-Benzyne

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Coumarin (5,6-Benzo-2-pyrone) Trapping of an HDDA-Benzyne

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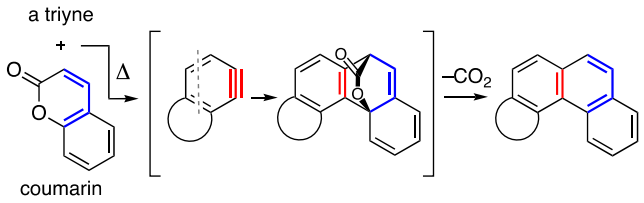
Supporting Information Placeholder

ABSTRACT: Although the parent 2-pyrone is known to react with simple *o*-benzynes to produce naphthalene derivatives, there appear to be no examples of the successful reaction of coumarin, a benzo-annulated 2-pyrone analog, with an aryne. We report such a process here using benzynes generated by the hexadehydro-Diels-Alder (HDDA) reaction to produce phenanthrene derivatives (i.e., benzo-annulated naphthalenes). DFT computations were used to help understand the difference in reactivity between 2-pyrone and the slower trapping agent, coumarin. Finally, the reaction of *o*-benzyne itself [from *o*-(trimethylsilyl)phenyl triflate and CsF] with coumarin was shown to be viable, although slow.



The reaction of pyrone (4) with *o*-benzyne (3) to produce naphthalene (6) was first described by Wittig and Hoffmann in 1962.[1] Heating the thiadiazole 1,1-dioxide 1 gave 6 in 36% yield, following ejection of CO_2 from the presumed Diels-Alder intermediate adduct 5. Over time, reactions of benzynes (or strained cycloalkynes) with a variety of pyrone-containing substructures have been reported.[2] Conspicuously absent from that body of work is a successful reaction or an aryne with coumarin [7a, 2H-chromen-2-one]. Indeed, in 1997, Guitián and coworkers reported reactions of substituted pyrones with 3, the latter produced from anthranilic acid (2).[2i] In that study, an attempt to effect an analogous reaction of 3 with coumarin (7a) to produce phenanthrene (8) was unsuccessful. This was attributed to the lower reactivity of 7a as a diene because a greater loss in aromatic resonance stabilization vis-à-vis the analogous reaction with 4 itself would attend the formation of potential intermediate 8.

Many triynes such as 10 will cycloisomerize to benzynes 11 in a process now commonly referred to as the hexadehydro-Diels-Alder (HDDA) reaction.[3] We describe here a variety of reactions between HDDA-benzynes 11 and coumarins. To our knowledge these are the first examples of trapping reactions of arynes using coumarin or coumarin derivatives.[2]

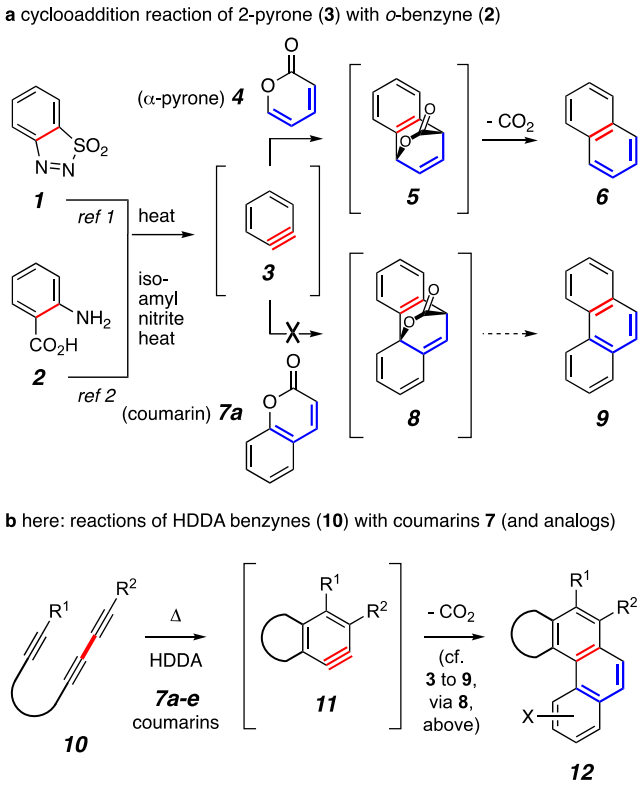


Figure 1. a) Reaction of *o*-benzyne (3) with pyrone (4) to produce naphthalene (6), following loss of CO_2 from initial

adduct **5**. **b**) Reactions of HDDA-benzynes **11** with coumarin derivatives **7a-e** to give phenanthrenes **12**.

As a prelude to introducing our experimental observations, we show in Figure 2 the results of DFT calculations of the reactions of the parent *o*-benzyne (**3**) with pyrone (**4**, panel a) as well as with coumarin (**7a**, panel b). As expected intuitively, the reaction to form the initial bicyclic adduct **5** is more exergonic than that leading to **8** because of the aforementioned increased loss of aromaticity that attends the addition to coumarin. Accordingly, the activation barrier through transition structure $\mathbf{TS}_{\mathbf{coumarin}}$ is also larger than that

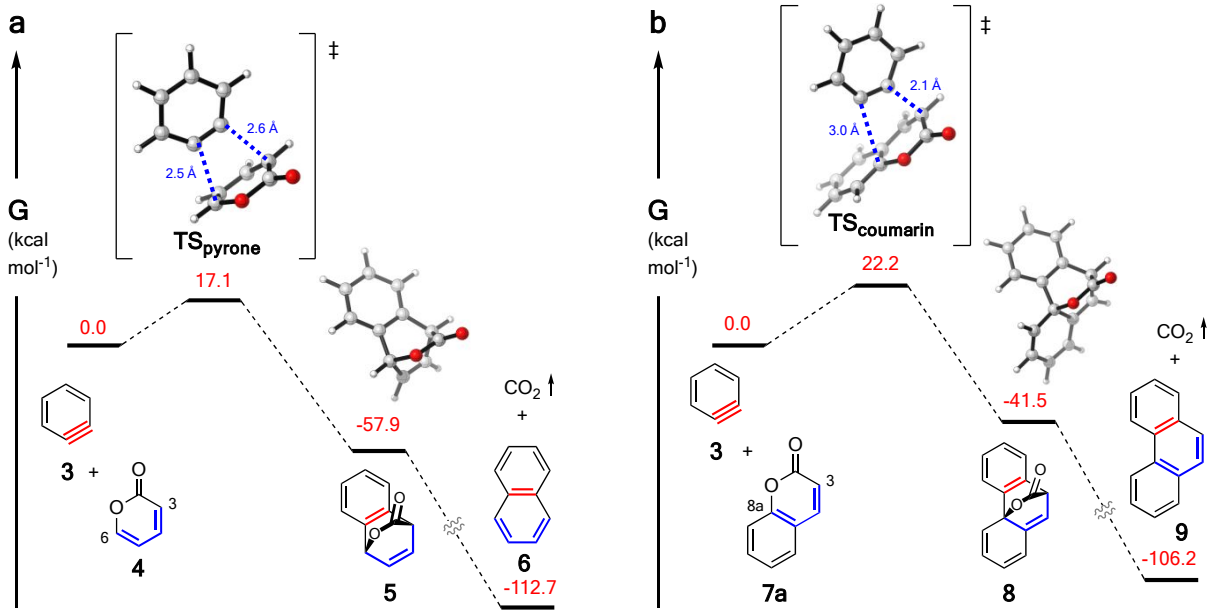
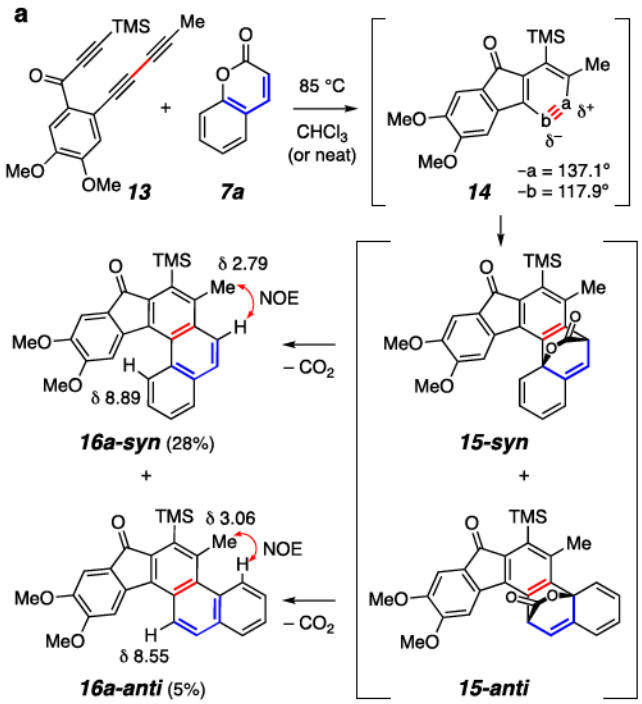
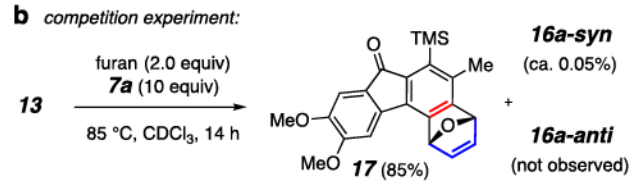


Figure 2. DFT calculations [SMD($CHCl_3$)/B3LYP/6-311G+(d,p) at 298 K] of the reaction of *o*-benzyne (**3**) with **a**) pyrone (**4**) and **b**) coumarin (**7a**). Gibbs energies in kcal mol^{-1}.

through TS_{pyrone}. These data support the earlier assessment[2i] that coumarin is a less reactive 4π-diene than pyrone toward benzyne. It is interesting to note the difference in the extent of asynchroneity in the two TSs. In TS_{pyrone} the bond lengths of the two forming C–C bonds (labeled in blue) are nearly the same as is the deformation of the two carbon atoms of the pyrone moiety (7.5° and 9.4° of puckering at C3 and C6, respectively). In contrast, in $TS_{coumarin}$ the extent of bond-formation is considerably different (blue), as is the degree of puckering at C3 (16.6°) vs. C8a (5°). The reduced amount of rehybridization at C8a is a computational validation of the reluctance of the coumarin diene to sacrifice its benzenoid aromatic resonance stabilization.

In our first experiment (Figure 3a), a solution containing the triyne **13** and coumarin (**7a**, 3 equiv) in chloroform was warmed to 85 °C. Rate-limiting HDDA cycloisomerization gave the benzyne **14**, which, following capture by **7a**, lost CO_2 to produce the (red-colored) naphthofluorenone **16a-syn** in 38% yield. Later scrutiny of the NMR spectrum of the crude product mixture, suggested the possible presence of a second isomeric product. When this reaction was then performed neat (1:10, **13**:**7a**), both **16a-syn** and **16a-anti** were isolated in 28% and 5% yields, respectively. The constitution of the major product was established by the clear NOEs indicated in structures **16a-syn** and **16a-anti**. In addition, the proton resonance for i) the aromatic methyl group was significantly deshielded in the anti-isomer and ii) the indicated aromatic protons showed diagnostic differences that reflected their relative extent of embeddedness in the bay region of the pentacycle [see Supporting Information (SI) for details].





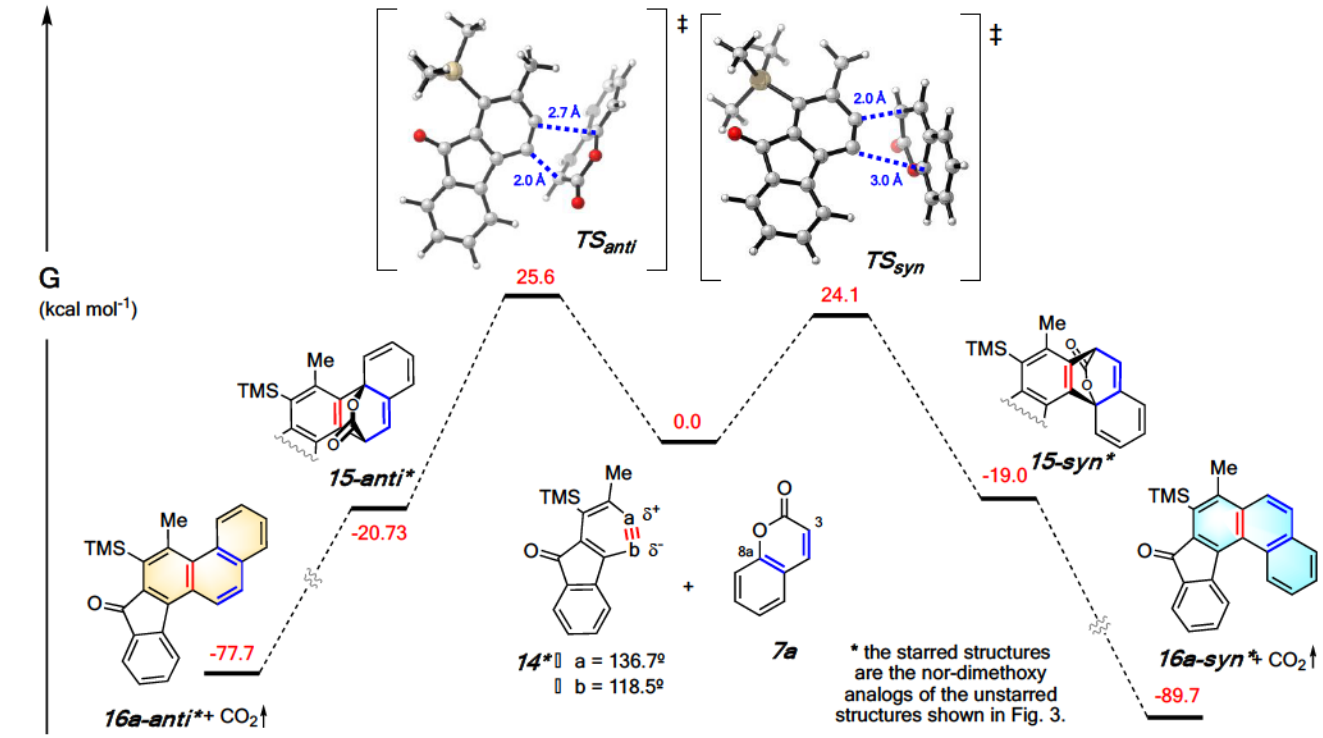


Figure 3. a) Reaction of triyne 13 with coumarin gives isomeric naphthofluorenones 16a-syn (minor) and 16a-anti (minor). b) Competition experiment showing that trapping by furan (2 equiv) is considerably faster than that by coumarin (7a, 10 equiv). (See SI for NMR spectrum of the crude product mixture in which 16-syn was detected.)

Figure 4. DFT calculations [SMD($CHCl_3$)/B3LYP/6-311G+(d,p) at 358 K] for the reaction of benzyne 14 (the truncated nor-methoxy analog of the benzyne from triyne 13) with coumarin (7a). The small difference in TS energies are consistent with, in fact, remarkably close to, that reflected by the product ratio of 16a-syn:16a-anti (6:1).

To gain understanding of the sense of regioselectivity shown by the reaction of the benzyne **14** with coumarin (**7a**), we identified the optimized transition structures of the species leading to TS_{syn} vs. TS_{anti} by DFT calculations. We used the same functional, basis set, and solvation model as those for the reactions with benzyne itself (Figure 2). The results are summarized in Figure 4. The computed activation barrier leading to adduct **15-syn*** is 1.5 kcal mol^{-1} lower than that proceeding to **15-anti*** in the competing pathway. This is remarkably consistent with the observed product ratio for the **16a-syn**:**16a-anti** (5:1, ^{1}H NMR of the crude product mixture for the neat reaction at 85 °C).

This preference for the regioselective addition of the unsymmetrical benzyne dienophile to coumarin can be explained by a careful examination of the two TS geometries. As with *o*-benzyne itself, there is a significantly advanced degree of bond formation at C3 vs. C8a for each of the transition structures TS_{syn} and TS_{anti}, indicating substantially asynchronous reactions. The shorter distance of 2.0 Å is identical in both; curiously, the second partial bond is shorter in TS_{anti} (2.7 Å vs. 3.0 Å in TS_{syn}) even though TS_{anti} is slightly higher in energy. Subtle remote steric compressions are likely responsible for this seeming anomaly. The difference in puckering angle at the benzenoid carbon C8a in each is, again, informative; the slightly larger deformation in TS_{anti} (8.1°) (and 17.2° at C3) vs. that in TS_{syn} = 5.5° (and 17.5° at C3) reflects a greater degree of sacrifice in aromaticity. Finally, we note that an FMO analysis of this cycloaddition is not a meaningful approach for rationalizing the sense of regioselectivity. That is, the π–type orbital coefficients at C3 vs. C8a in the HOMO of coumarin are computed to be virtually identical (see SI for details).

The imperfect yield of this transformation implied that the rate of the trapping by coumarin was slow (although serviceable), again consistent with the earlier conclusion of Guitián et al.[2i]**Error! Bookmark not defined.** To further evaluate that point, consider the computed activation barriers for the reactions of coumarin vs. pyrone with *o*-benzyne (Figure 2). A competition experiment (Figure 3b) was performed in which **13** was heated in $CDCl_3$ in the presence of the excellent trapping reagent furan (2 equiv) and coumarin (10 equiv). Direct NMR analysis of this reaction mixture after 14 h showed quite clean conversion to the furan adduct **17** and that ca. 0.05% of **16a-syn** was present (see SI for details). We conclude that coumarin reacts >1000 more slowly with the benzyne than does furan.

Having established the ability of a HDDA-benzyne to engage coumarin itself, we explored a) several coumarin derivatives (**7b-e**) as well as b) several aryl-substituted triyne substrates (**18a-e**) to establish some of the generality of the process. The results are shown in Figure 5. In each instance, only the major syn-isomer of products **16** or **19** was isolated and characterized (although when the crude product mixture was analyzed, a second minor isomer was present).

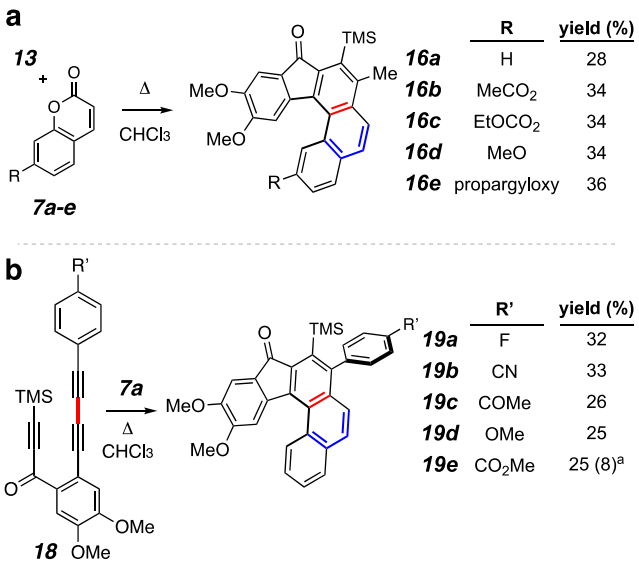


Figure 5. a) Reactions of triyne **13** with coumarin derivatives (**7a-e**) to produce products **16a-e**. b) Reactions of triynes **18** with coumarin (**7a**) to produce products **19a-e**.

[a] In the case of **19e**, the reaction was performed on a 1 mmol scale and the minor anti-isomer was also isolated and characterized (see SI for details).

We also examined the reaction of a tricyclic coumarin derivative, namely, the benzocoumarin **20a** and its brominated analog **20b**. These were reacted with the triyne **13** to give the chrysene derivatives **21a-b** by processes that closely paralleled those with coumarin itself. The bromo analog **21b** readily afforded the phenyl-substituted chrysene **21c**. The molecular skeleton of compounds **21** was established by a single crystal X-ray diffraction analysis, which also revealed the twisted[4] nature of the polycylic indenochrysenone skeleton.

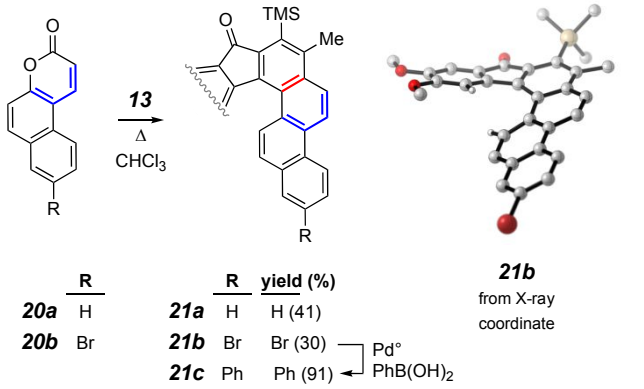


Figure 6. Reactions of triyne 13 with benzocoumarins 20a-b to produce the indenochrysenones 21a-b.

Finally, we briefly re-examined the reaction of coumarin with *o*-benzyne (3) itself,[2i] here generated via the Kobayashi method.[5] Most informative was an experiment performed in CD_3CN using the silylated phenyl triflate 22 and CsF in the presence of coumarin (7a, 3 equiv). Direct monitoring of the reaction by ^1H NMR spectroscopy (see SI for details) clearly showed the formation of, principally, phenanthrene (9) along

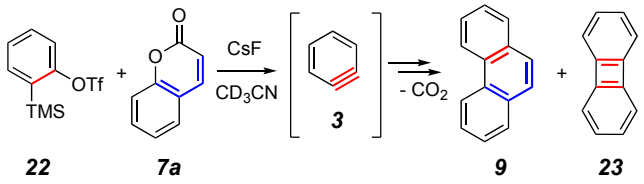


Figure 7. Reaction of coumarin (7a) and *o*-benzyne (3) affords phenanthrene (9) and biphenylene (23). The isolated yield of coeluting hydrocarbon products was 19%; analysis of the reaction mixture directly by ^1H NMR spectroscopy indicates that 9 and 23 were, by far, the major products produced (see SI).

with a lesser amount of the known benzyne dimer, biphenylene[6] (23), in a ratio of 4.8:1. Thus, 7a is capable of trapping *o*-benzyne (3) itself, but the reaction rate is relatively slow, because dimerization of two molecules of 3 is competitive, even though the steady-state concentration of 3 is, of course, quite small.[7]

In conclusion, we have described a new mode of aryne reactivity with coumarins. Namely, coumarins and *o*-benzynes undergo a [4+2] cycloaddition, albeit slowly, followed by a cheletropic ejection of CO_2 to afford conjugated polyaromatic scaffolds. DFT computations have provided additional mechanistic understanding of some of the elementary steps involved in this class of transformation.

■ ASSOCIATED CONTENT

The Supporting Information is available as one PDF and one .cif file free of charge at https://pubs.acs.org/doi/###.

Experimental procedures for preparation of and characterization data for all previously unknown compounds; computational details; copies of ^1H and ^{13}C NMR spectra; .cif file for 21b.

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Notes

The authors have no conflicting financial interests.

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