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

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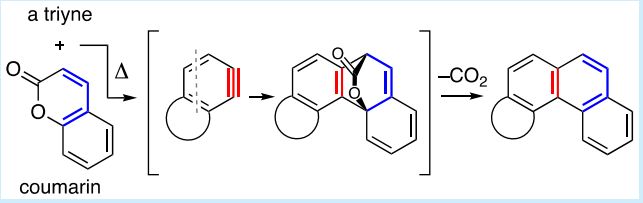
ABSTRACT: Although the parent 2-pyrone is known to react with simple *o*-benzynes to produce naphthalene derivatives, there appear to be no examples of the successful reaction of coumarin, a benzo-annulated 2-pyrone analogue, with an aryne. We report such a process here using benzynes generated by the hexadehydro-Diels–Alder reaction to produce phenanthrene derivatives (i.e., benzo-annulated naphthalenes). Density functional theory 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.



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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**, 2*H*-chromen-2-one). Indeed, in 1997, Guitián and co-workers 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 of 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 called the hexadehydro-Diels–Alder (HDDA) reaction.[3] We describe here a variety of reactions between HDDA-benzynes **11** and coumarins. To the best of our knowledge, these are the first examples of trapping reactions of arynes using coumarin or substituted coumarins (Figure 1).[2]

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 through $\mathbf{TS}_{\mathbf{pyrone}}$. 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 asynchronicity in the two **TS**s. In $\mathbf{TS}_{\mathbf{pyrone}}$, 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 $\mathbf{TS}_{\mathbf{coumarin}}$, the extent of bond formation is considerably different (blue), as is the degree of puckering at C3 (16.6°) versus 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 triyne **13** and coumarin (**7a**, 3 equiv) in chloroform was warmed to 85 °C. Rate-limiting HDDA cycloisomerization gave benzyne **14**, which, following capture by **7a**, lost CO_2 to produce the (red-colored) naphthofluorenone **16a-syn** in 38% yield. Further 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, (i) the proton resonance for the aromatic methyl group was significantly deshielded in the anti isomer and (ii) the indicated aromatic protons showed diagnostic differences that reflected their

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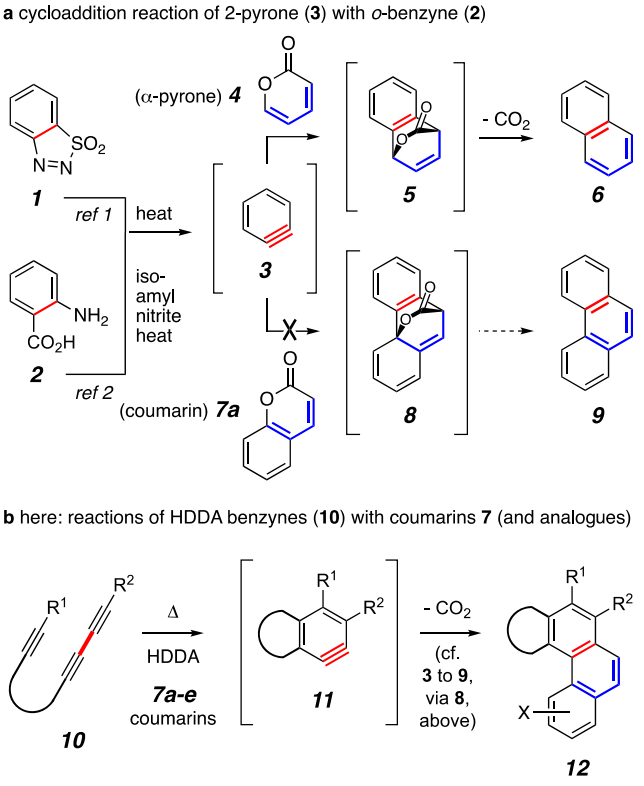

Figure 1. (a) Reaction of *o*-benzyne (**3**) with pyrone (**4**) to produce naphthalene (**6**), following loss of CO_2 from initial adduct **5**. (b) Reactions of HDDA-benzynes **11** with coumarin derivatives **7a**−**e** to give phenanthrenes **12**.

relative extent of embeddedness in the bay region of the pentacycle (see the Supporting Information for details).

To gain an understanding of the sense of regioselectivity shown by the reaction of benzyne **14** with coumarin (**7a**), we identified the optimized transition structures of the species leading to TS_{syn} versus TS_{anti} by DFT calculations. We used

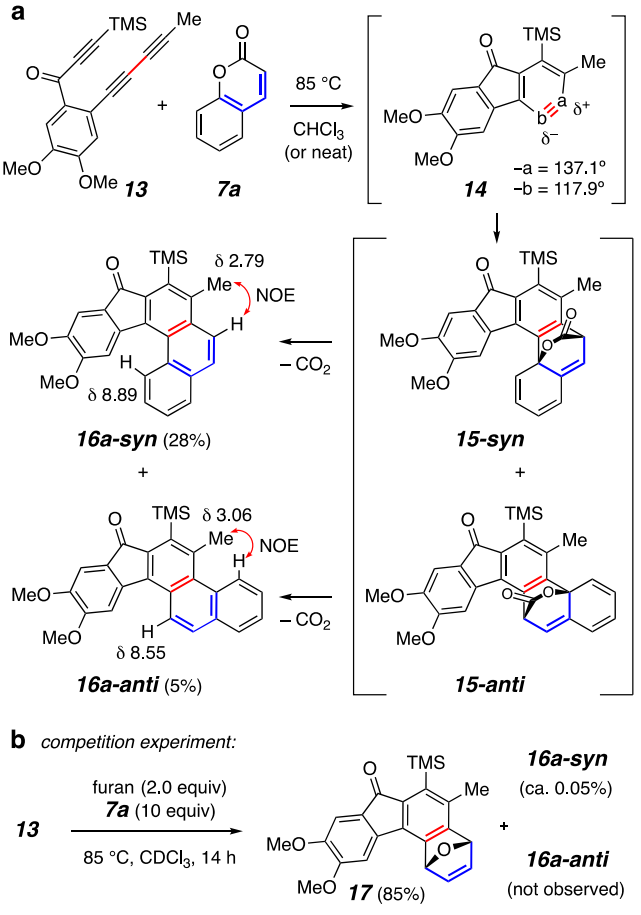

Figure 3. (a) Reaction of triyne **13** with coumarin gives isomeric naphthofluorenones **16a-syn** (major) and **16a-anti** (minor). (b) Competition experiment showing that trapping by furan (2 equiv) is considerably faster than that by coumarin (**7a**, 10 equiv) (see the Supporting Information for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

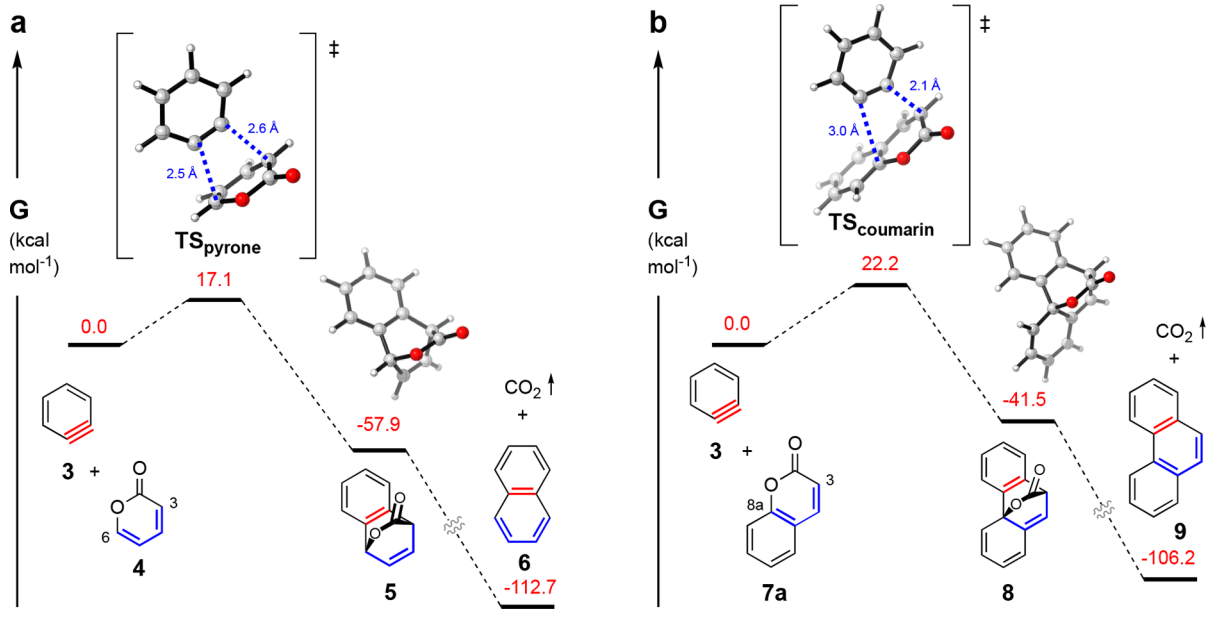

Figure 2. DFT calculations [SMD($CHCl_3$)/B3LYP/6-311G+(d,p) at 298 K] of the reaction of *o*-benzyne (**3**) with (a) pyrone (**4**) and (b) coumarin (**7a**). Gibbs energies in kilocalories per mole.

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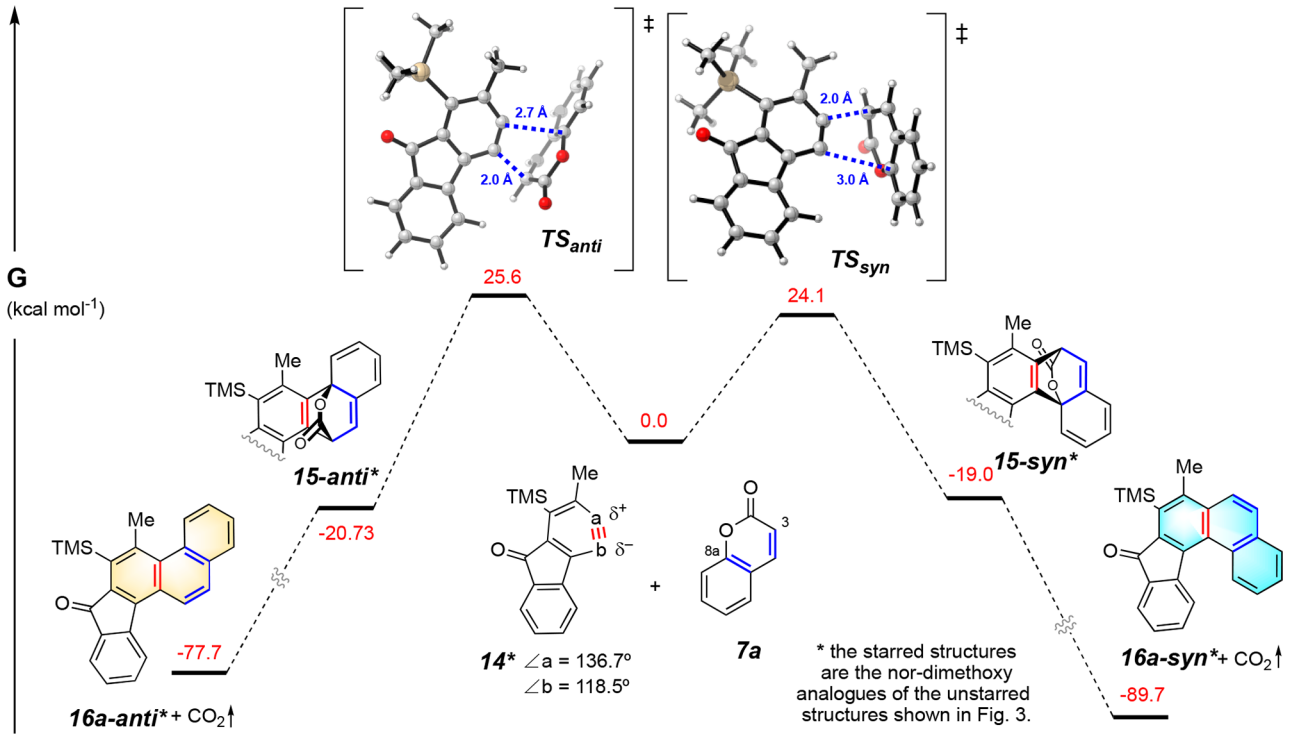

Figure 4. DFT calculations [SMD($CHCl_3$)/B3LYP/6-311G+(d,p) at 358 K] for the reaction of benzyne **14** (the truncated nor-methoxy analogue of the benzyne from triyne **13**) with coumarin (**7a**). The small differences in TS energies are consistent with, in fact, remarkably close to, that reflected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

the same functional, basis set, and solvation model that were used 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 **16a-syn**:**16a-anti** product ratio (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 versus C8a for each of the transition structures $\mathbf{TS}_{syn}$ and $\mathbf{TS}_{anti}$, indicating substantially asynchronous reactions. The shorter distance of 2.0 Å is identical in both; curiously, the second partial bond is shorter in $\mathbf{TS}_{anti}$ (2.7 Å vs 3.0 Å in $\mathbf{TS}_{syn}$) even though $\mathbf{TS}_{anti}$ is slightly higher in energy. Subtle remote steric compressions are likely responsible for this seeming anomaly. The difference in puckering angle at the benzenoid C8a in each is, again, informative; the slightly larger deformation in $\mathbf{TS}_{anti}$ (8.1°) (and 17.2° at C3) versus that in $\mathbf{TS}_{syn}$ (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 versus C8a in the HOMO of coumarin are computed to be virtually identical (see the Supporting Information 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] To further evaluate that point, consider the computed activation barriers for the reactions of coumarin versus 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 furan adduct **17** and that ~0.05% of **16a-syn** was present (see the Supporting Information for details). We conclude that coumarin reacts >1000 times 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).

We also examined the reaction of a tricyclic coumarin derivative, namely, benzocoumarin **20a** and its brominated analogue, **20b**. These were reacted with triyne **13** to give chrysene derivatives **21a** and **21b**, respectively, by processes that closely paralleled those with coumarin itself. Bromo analogue **21b** readily afforded phenyl-substituted chrysene **21c**. The molecular skeleton of compound **21b** was established by a single-crystal X-ray diffraction analysis, which also revealed the twisted[4] nature of the polycyclic indenochrysenone skeleton (Figure 6).

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 silylated phenyl triflate **22** and CsF in the presence of coumarin (**7a**, 3 equiv). Direct monitoring of the reaction by ^{1}H NMR spectroscopy (see the Supporting

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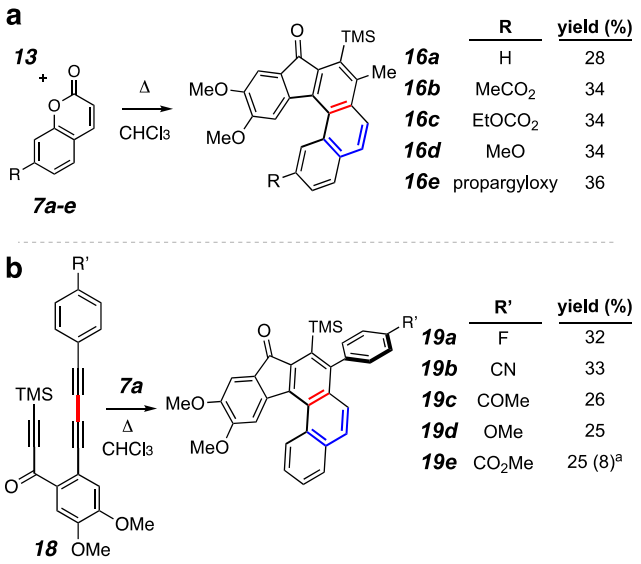

Figure 5. (a) Reactions of triyne **13** with coumarin derivatives (**7a**–**e**) to produce products **16a**–**e**, respectively. (b) Reactions of triynes **18** with coumarin (**7a**) to produce products **19a**–**e**. [a]In the case of **19e**, the reaction was performed on a 1 mmol scale and the minor anti isomer was also isolated and characterized (see the Supporting Information for details).

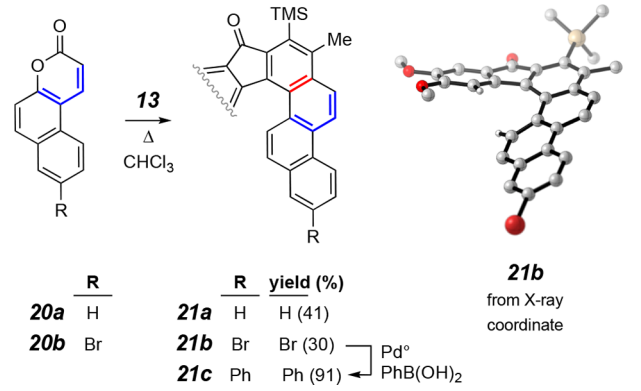

Figure 6. Reactions of triyne **13** with benzocoumarins **20a** and **20b** to produce indenochrysenones **21a** and **21b**, respectively.

Information for details) clearly showed the formation of, principally, phenanthrene (**9**) along with a smaller amount of the known benzyne dimer, biphenylene[6] (**23**), in a ratio of 4.8:1 (Figure 7). 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

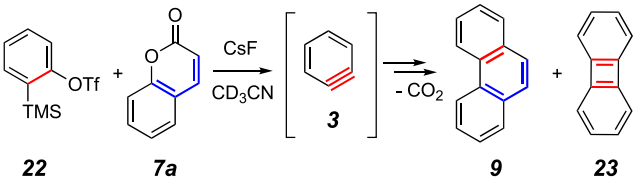

Figure 7. Reaction of coumarin (**7a**) and *o*-benzyne (**3**) affords phenanthrene (**9**) and biphenylene (**23**). The isolated yield of co-eluting hydrocarbon products was 19%; analysis of the reaction mixture directly by ^{1}H NMR spectroscopy indicates that **9** and **23** were, by far, the major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

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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00342.

Experimental procedures for the preparation of and characterization data for all previously unknown compounds, computational details, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2057879 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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