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Reactions of Hexadehydro-Diels–Alder (HDDA)-Derived Benzynes with Thioamides: Synthesis of Dihydrobenzothiazino-Heterocyclics

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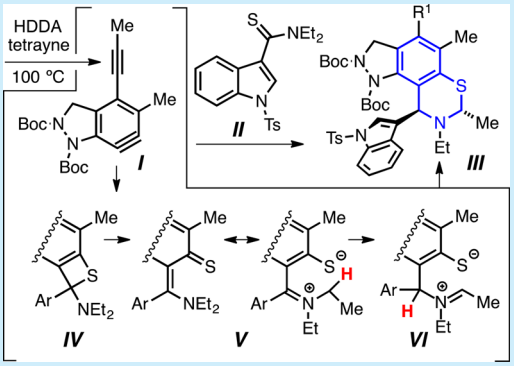
Supporting Information

ABSTRACT: Reaction of thioamides (e.g., **II**) with benzynes generated by the hexadehydro-Diels–Alder (HDDA) cycloisomerization (e.g., **I**) produces dihydrobenzothiazines (e.g., **III**). It is postulated that the reaction proceeds via benzothietene (cf. **IV**) and *o*-thiolatoaryliminium (cf. **V**) intermediates and that the latter undergoes intramolecular 1,3-hydrogen atom migration to produce the penultimate isomeric iminium zwitterions **VI**.



Benzynes are versatile reactive intermediates, capable of being captured by many classes of nucleophiles. We recently reported some new modes of reaction between sulfides and benzynes produced by the hexadehydro-Diels–Alder (HDDA) reaction.[1] For example, heating tetrayne **1** in the presence of 2-ethenyltetrahydrothiophene (2.3 equiv) and acetic acid (4.3 equiv) produced the arylsulfide **3** in a three-component reaction (Figure 1a). It is notable that acetic acid itself is a good trap of HDDA benzynes.[2] However, none of the aryl acetate expected from AcOH addition was observed in the presence of the (more nucleophilic) sulfide. This underscores the reactivity pairing of the polarizable electrophilic alkyne in **2** with the soft sulfur-based nucleophile compared to an oxygen atom in the carboxylic acid. This multistep reaction cascade—passing through a zwitterion, ylide,[3] and ion pair—exemplifies the type of complex reaction manifold that can be fueled by the substantial amount of potential energy afforded by the three alkynes that engage to produce the initial benzyne **2**. We have also explored compounds containing other functional groups that possess a softly nucleophilic sulfur atom. We report here our results using various thioamides as the trapping agents.

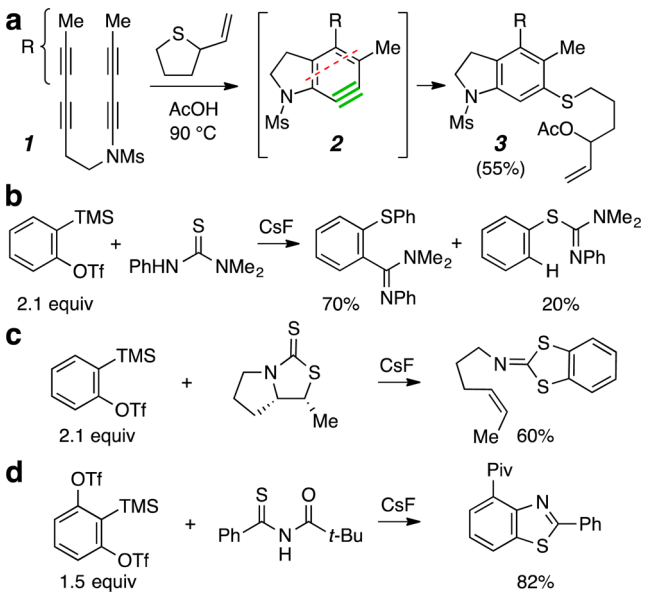


Figure 1. Examples of known reactions of benzyne with sulfur-containing nucleophiles.

Among the family of the common nitrogen-substituted thiono-containing functional groups—namely thioamide, thionocarbamate, dithiocarbamate, thiourea, and thioimide—we can locate examples of each of the last three having been reacted with an aryne. Greaney and co-workers have reported a unique thio-amidination reaction of Kobayashi-generated benzyne (i.e., *o*-$TMSC_6H_4OTf$ + CsF) when trapped by a variety of thioureas (Figure 1b).[4] Hwu et al. described an interesting addition–fragmentation reaction of a cyclic dithiocarbamate upon engaging *o*-benzyne (Figure 1c).[5] Li et al. have reported an intriguing bis-benzyne reaction in which the sulfur atom in a thioimide initiated the process by attacking the benzyne (Figure 1d).[6] We are unaware of previous reports of reactions of arynes with thioamides.

We initiated our study by attempting to trap the benzyne **5** with $PhC(=S)NMe_2$ (**6a**, Figure 2). Heating **4** with **6a** in benzene at 90 °C in a sealed vial for 12 h led to formation of an unexpected product, isolated in 42% yield following chromatographic

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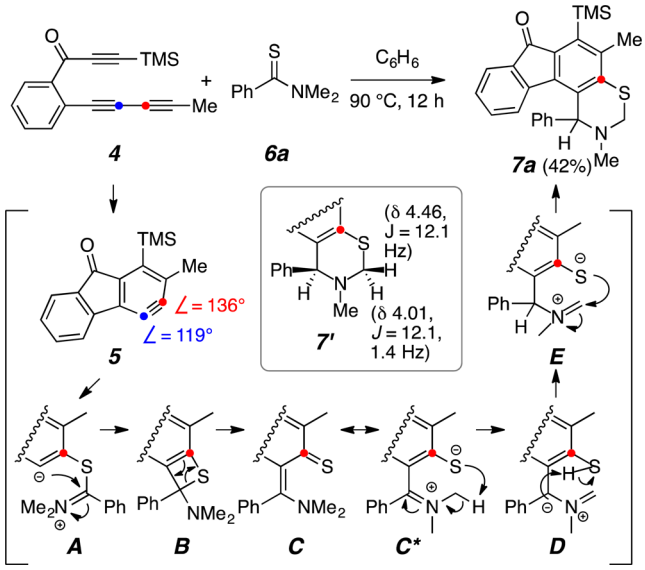
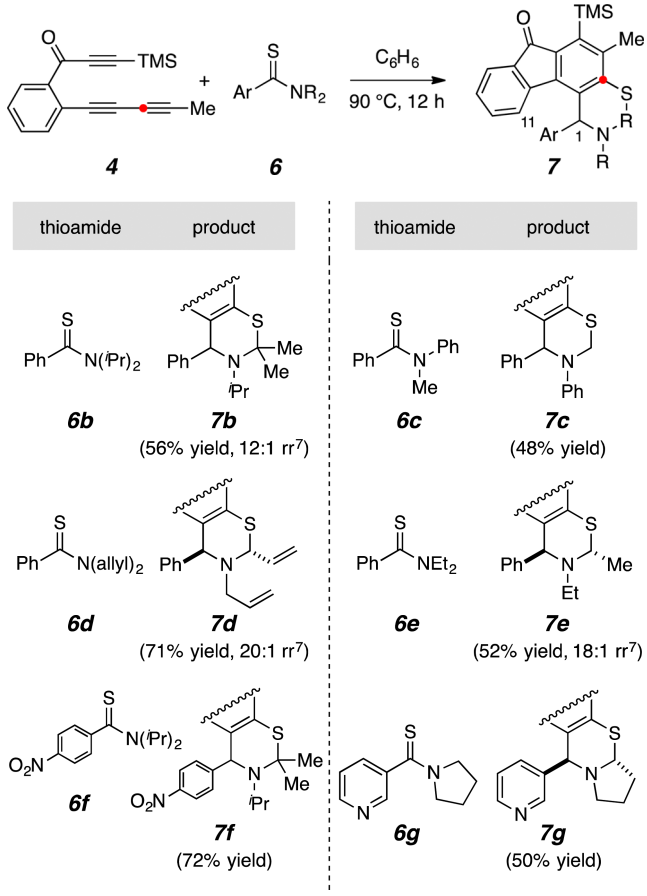


Figure 2. Trapping of HDDA-generated benzyne **5** by *N,N*-dimethylthiobenzamide (**6a**) gives the dihydrobenzothiazine **7a**.

purification. The mass of the major product clearly indicated it to be a 1:1 adduct of the two reactants, but, surprisingly, the ^{1}H NMR spectrum gave evidence of only one *N*-methyl group, a methine (at δ 5.4 ppm), and an AB pattern indicative of an isolated methylene moiety (at δ 4.0 and 4.5 ppm), seemingly bearing a nitrogen substituent and having diastereotopic protons. Through analysis of 2D correlation spectra, we deduced the structure to be that of the dihydrobenzothiazine **7a**. Although two regioisomeric modes of reaction are possible[7] with respect to addition of the thioamide to the unsymmetrical benzyne **5**, nucleophiles are known to undergo preferential addition to the carbon atom labeled with the red dot.[1,8] This is consistent with the computed structure of **5**,[1] which shows a significantly larger internal bond angle at the red carbon atom vis-à-vis the one denoted with the blue dot; a larger internal angle correlates well with greater electrophilic character in arynes.[9] This orientation of the attack was further supported by a nuclear Overhauser experiment with the analog **7b** (Table 1). Species **A**–**E** represent a logical progression of intermediates that could carry reactants to product. The hydrogen atom migration leading from **C**/**C*** to **E** is both interesting and unusual, a point revisited computationally below (Figure 3).

We proceeded to study the reactions of **4** (and **5**) with a series of thiobenzoic acid amide analogs. The results are shown in Table 1. The reaction has considerable generality, as demonstrated by this series. An isopropyl group (**6b** to **7b**) with a hindered methine proton will still undergo the **C** to **D** event. An *N*-aryl group (**6c** to **7c**) is tolerated. Amides with two primary alkyl substituents (**6d** and **6e**) give rise to a dihydrobenzothiazine with two stereocenters (**7d** and **7e**). In these reactions we have seen no evidence for the formation of a second diastereomer. This highly preferential formation of the isomer with a trans relationship between the vinyl and phenyl groups in **7d** was established from a single crystal X-ray analysis.[10] In the solid state, the 1,3-thiazine ring adopts a half-chair conformation in which the vinyl group is disposed to be equatorial and the phenyl pseudoaxial. Presumably, maintaining minimal interaction between the large phenyl substituent on C1 and H11 along the reaction coordinate for the cyclization favors the transition state leading to diastereomer **7d**.

Table 1. Reactions of Triyne 4 with Thioamides 6b–6g,[a] Leading to Fluorenone Derivatives 7



[a]All reactions were carried out under the same reaction conditions (starting $[4]_o$ = 0.1 M, 1.5 equiv of **6**); % yield is of chromatographically purified material.

The thioamide **6f**, containing the electron withdrawing nitro-group, proceeded efficiently. On the other hand, the analogous amide with a donor 4-methoxy substituent instead gave rise to a much less clean crude product mixture that we judged to contain a small amount of the methoxy version of product 7 (not shown) but was not otherwise further pursued. Finally, the nicotinic acid derived thioamide **6g** proceeded well to give the pyridine-containing bicyclic compound **7g**. The diastereomeric nature of **7e** and **7g** was assigned on the basis of similarities in ^{1}H chemical shifts of several analogous protons in comparison to those in **7d**. Moreover, since *none* of the second diastereomer was detected for any of these reaction products, a full reversal in the dr (>99:1 to <1:99) would be highly unlikely for any of these reactions that give products of such similar topology.

To establish that this transformation is not limited to some unidentified (and unanticipated) reactivity property of the benzyne **5**, we explored the reactivity of five additional benzyne precursors (**1** and **8a**–**8d**, Table 2). Similarly, to demonstrate an expanded scope of thioamides that function in this reaction, we studied reactions using thioamides **6h**–**6o**. There was no particular reason (nor, therefore, bias) for pairing the partners that are shown here. In a handful of instances, additional pairings were preliminarily explored, always with a very similar outcome in product type and reaction cleanliness.[11] In other words, we know of no reason to think that any one of these benzynes (and myriad

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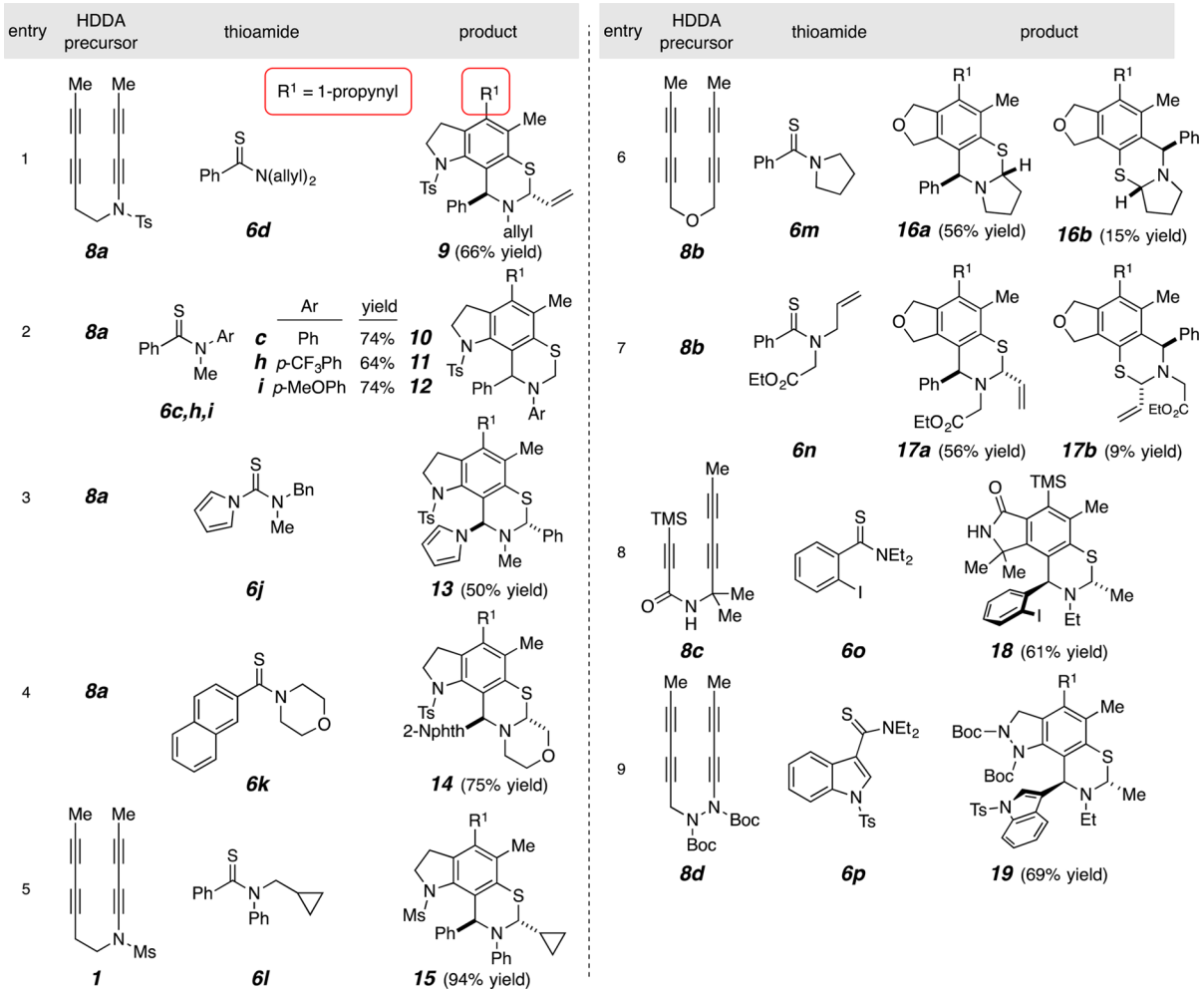
Table 2. Reactions of Five Other HDDA Substrates (1 and 8a–d) with Eight Other Thioamides[a]



[a]Reactions all performed between 75 and 95 °C for 12–24 h [see Supporting Information (SI) for details].

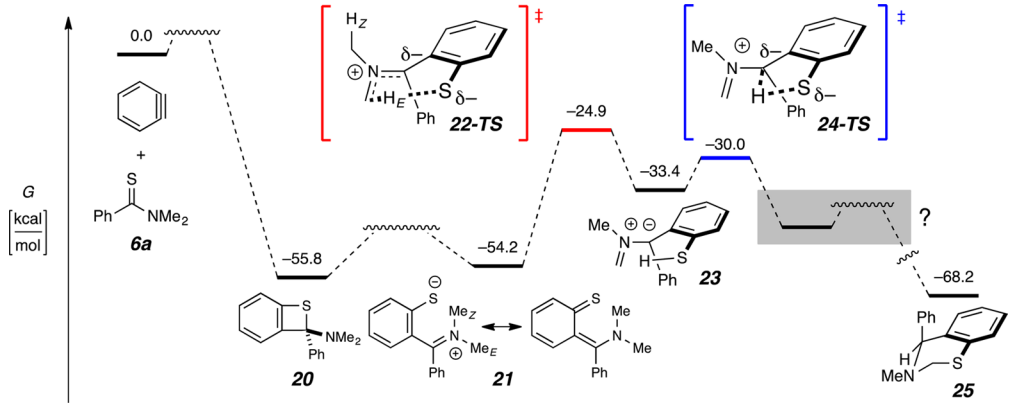


Figure 3. Computed [SMD(benzene)//M06-2X/6-31+G(d,p)] reaction profile for the transformation of *o*-benzyne and *N*,*N*-dimethyl thiobenzamide (**6a**) to the parent dihydrobenzothiazine **25**.

others) would be incompatible with any one of these aromatic[12] thioamides.

Notable aspects of this set of results include the following: (a) Sterically congested relationships in the products can be established (Ts and Ar in entries 1–4; gem-dimethyl and Boc with Ar in entries 8 and 9); (b) the electronic character of an *N*-aryl substituent makes little difference (entry 2); (c) a thiourea proceeded to give an analogous product (entry 3); (d) heterocyclic substituents are accommodated [entries 3, 4, and 9 and product **7g** (Table 1)]; (e) a cyclopropane ring survives the reaction (entry 5), suggesting the absence of a radical intermediate at the carbon from which hydrogen has been transferred; (f) benzo-fused bicyclic structures can arise (entries 4 and 6); and (g) functional groups capable of easy further transformation can be incorporated (allyl and vinyl in entries 1 and 7, ester in entry 7, and iodoarene in entry 8).

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We have also used DFT calculations to probe aspects of the mechanism (cf. Figure 2) of this unusual transformation (Figure 3). The benzothietene **20** is the [2 + 2] adduct between benzyne and the thiocarbonyl group in **6a**. This was observed to be similar in free energy to the isomeric, ring-opened, polarized thioquinone methide **21**, and both were considerably more stable than the reactant pair. We did not attempt to locate transition structures for any processes interconverting benzyne and **6a** with **20** or of **20** with **21**. We explored possible pathways for the unimolecular isomerization of **21** to the product **25**. This was fruitful once we allowed for the nonintuitive possibility of hydrogen atom removal by the basic sulfur atom from the iminium ion methyl group trans to the thiolated arene (cf. Me_E in **21** and H_E in **22-TS**). This produces the azomethine ylide **23**; **22-TS** was the only transition structure that we could identify for this step. This TS lies ca. 30 kcal·mol^{-1} higher in energy than **21**, which places that step in the category of being "feasible." A very rapid (and highly exergonic) progression from **23** is computed to ensue. We could not identify an iminium thiolate like **E** (Figure 1) as a stable entity. Instead, the TS **24-TS** collapsed directly to **25**. A related, thiolate-mediated proton shift via an azomethine ylide like **23** was described both experimentally and computationally by Seidel, Houk, and co-workers.[13]

We then carried out a deuterium labeling experiment to probe the mechanism experimentally (Figure 4). Triyne **4** was heated

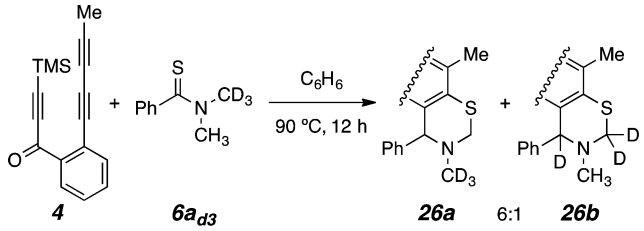

Figure 4. Mono-CD_3-labeled thioamide $\mathbf{6a}_{d_3}$ shows preference for 1,3-migration of the H- over D-atom.

with the trideuterated thiobenzamide $\mathbf{6a}_{d_3}$ to give a mixture of the products **26a** and **26b** in a ratio of 6:1. This clearly shows that a net, intramolecular 1,3-hydrogen migration is involved in this transformation and that it is most likely the rate-determining step (protium is preferentially transferred over deuterium) of the trapping sequence that converts **5** into **26**. We did not observe any appreciable amount of the di- or the tetradeuterated analog of **16**, which supports the view of the proton transfer as an intramolecular event, not requiring an external proton shuttle.

In conclusion, aromatic thioamides react with (thermally generated) benzynes to form dihydrobenzothiazine derivatives that we propose arise by an unusual, thiolate-assisted, 1,3-hydrogen atom migration. These mechanistic views are supported by a deuterium labeling experiment and DFT calculations. A wide range of thioamides participate in such a transformation to produce structurally diverse dihydrobenzothiazines in a regio- and diastereoselective manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03199.

Experimental details for the preparation of new compounds; spectroscopic data for their characterization, including copies of ^{1}H and ^{13}C NMR spectra; and computed (DFT) geometries and energies of benzyne intermediates and transition states (PDF)

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Notes

The authors declare no competing financial interest.

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(7) Indeed, **7a** was formed along with a coeluting constitutional isomer in a regioisomeric ratio (rr) of 21:1 (see Supporting Information); similar results were seen for **7b**, **7d**, and **7e**.

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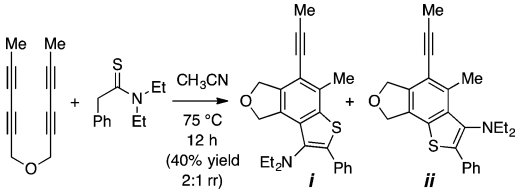
(10) Details can be found at the Cambridge Crystallographic Data Centre (CCDC deposition number 1508652).

(11) These reactions were typically not further explored (and, therefore, are not shown in Table 2) largely for pragmatic reasons. In some instances the product(s) coeluted with unreacted thioamide; in others, mixtures of products from regioisomeric modes of trapping (cf. entries 6 and 7) of the benzyne complicated the purification.

(12) We studied several aliphatic thioamides; the presence of an acidic α-proton diverted the reaction course to provide a benzothiophene, a process involving spontaneous (air?) oxidation. For example:



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