

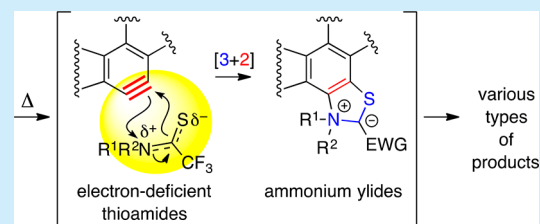
# Atypical Mode of [3 + 2]-Cycloaddition: Pseudo-1,3-dipole Behavior in Reactions of Electron-Deficient Thioamides with Benzynes

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**S** Supporting Information

**ABSTRACT:** Thioamides bearing electron-withdrawing groups on the thiocarbonyl carbon atom react with benzynes [generated by the hexadehydro-Diels–Alder cycloisomerization] in an unprecedented fashion. Namely, the dihydrobenzothiazole products are consistent with a pathway involving initial formation of a stabilized ammonium ylide by a rare type of [3 + 2]-cycloaddition reaction. The fate of this species depends upon the nature of the R group(s) attached to the ylide nitrogen atom. The demonstration of new modes of reactivity represents the major advance arising from this study.



We recently reported reactions between benzynes such as **II** (thermally generated from **I**) and aromatic thioamides such as **III** to produce dihydrobenzothiazines such as **V** (Figure 1a, structures designated by **I–V** refer to species that appeared in our previous report).<sup>1</sup> We rationalized this process as proceeding through the series of intermediates **IVa–IVc**. With this in mind, we have been surprised to now see an alternative type of product (and mode of reaction) to arise upon heating **1a** in the presence of electron-deficient thioamides such as **3a**. This produced, instead, the dihydrobenzothiazole **5aa**.<sup>2</sup> We propose that this transformation proceeds by a rare type of net [3 + 2]-cycloaddition (yellow highlight) to produce the ammonium ylide<sup>3,4</sup> **4aa**, followed by ethylene elimination. We are unaware of any similar reactions between a thioamide and a 2 $\pi$  (alkene or alkyne) component, although related transformations of trithiocarbonate and dithiocarbamate<sup>5</sup> functional groups have been reported.<sup>6</sup>

Although the reaction between **2a** and **3a** may evoke the notion of a 1,3-dipolar cycloaddition,<sup>7</sup> it differs in important ways. More specifically, each of the nonsacrificial resonance contributors of classical 1,3-dipoles has the same overall bond order, regardless of whether it is of the allyl or propargyl type (Figure 1b). Each is a zwitterionic species with a formal positive charge on the central atom and negative charge on one of its terminal atoms.<sup>8</sup> The [3 + 2]-cycloaddition products that arise from engagement of a 1,3-dipole with the  $\pi$ -bond of a dipolarophile are, formally, uncharged at all atoms in the principal resonance contributor of the newly created five-membered ring. The nature of **3a** as well as its conversion to the ylide **4aa** are just the opposite; that is, **3a** does not meet the definition of a 1,3-dipole, and now, the resulting adduct **4aa** is zwitterionic.

We turned to DFT calculations to help further assess this novel type of [3 + 2]-cycloaddition (Figure 2). The computed reaction profile (with minima represented by **6–8** and transition structures by **TS1** and **TS2**) for the model addition

of *N,N*-diethyltrifluoroacetamide (**3a**) to *o*-benzyne (**6**) is shown in Figure 2. The computed exergonicity for the formation of the ammonium ylide **7** as well as for its further conversion to **8** and ethylene (ca. 20 and 50 kcal·mol<sup>-1</sup>, respectively) are notable. We identified a transition structure (**TS1**) corresponding to a low barrier process for a concerted cycloaddition of **3a** to **6**. The geometry of that TS suggests that the addition proceeds with the nucleophilic portion of the thioamide leading the way; that is, the carbon–sulfur bond formation is more advanced than that of the carbon–nitrogen (cf. indicated bond lengths in **TS1** vis-à-vis those in **7**). The 1,2-zwitterion character in **7** sets up a facile intramolecular elimination reaction via **TS2** to produce **8**, the simplified analogue of **5aa**, and ethylene. The low activation barrier for this step (ca. 15 kcal·mol<sup>-1</sup>) is also notable.<sup>9</sup>

To gain direct experimental evidence for the ejection of an alkene from an ylide such as **4aa** (or **7**), we studied the reaction of triyne **1a** and *N,N*-dioctyltrifluoroacetamide (**3b**, Figure 3). A 2.2:1 ratio of the isomeric *N*-octylbenzothiazolines **5ab** and **5ab'** was formed.<sup>10</sup> In addition, a very nearly equimolar ratio of 1-octene was observed in the crude reaction mixture (<sup>1</sup>H NMR and GC–MS). This result is consistent with the eliminative fragmentation shown in species **4ab**.

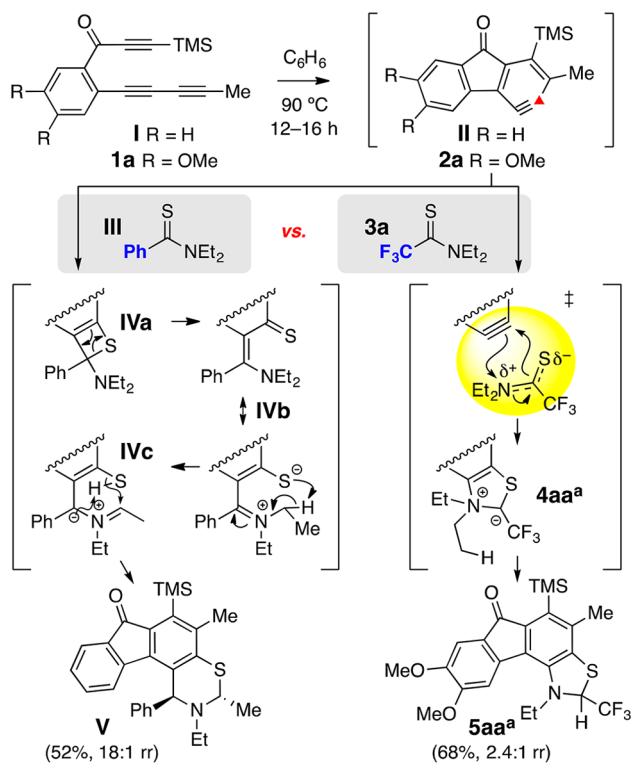
Another example of this new type of cycloaddition (Figure 4) was revealed when the *N*-allyltrifluoroacetamide **3c** (3 equiv) was heated (85 °C) with triyne **1a** (Figure 1a). The dihydrobenzothiazole **5ac**<sup>10b</sup> results from a [3,2]-sigmatropic migration of the allyl group, which again implicates the intermediacy of the ammonium ylide **4ac**, formed through capture of **2a** by the polarized thioamide **3c**.

We then explored a series of reactions (Table 1) to probe additional aspects of the reaction. First, would other electron-

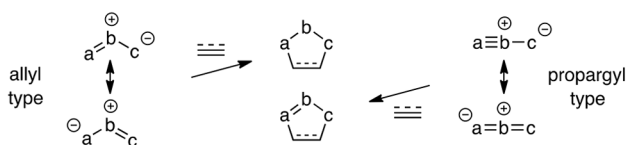
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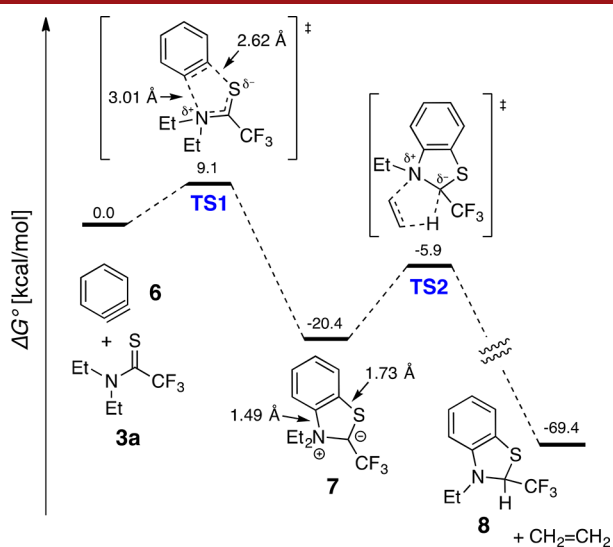
**a** previous (III to V) vs. these (3a to 5aa) reactions of benzyne + thioamides



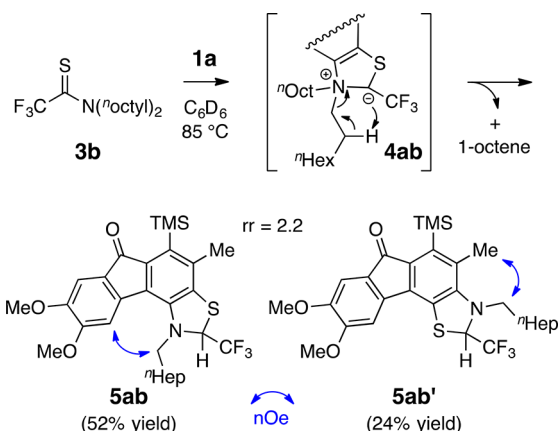
**b** classical 1,3-dipolar cycloadditions



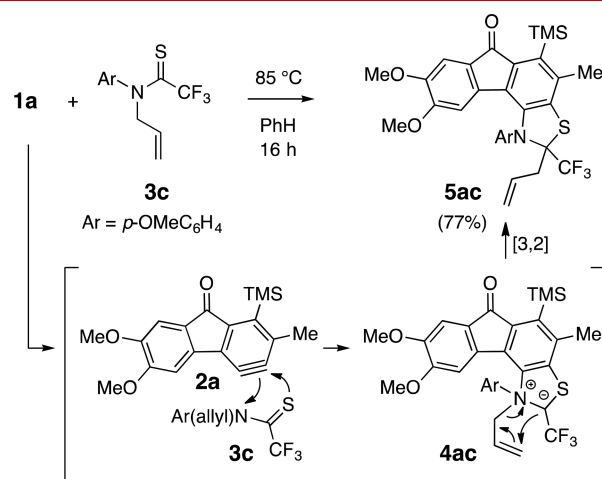
**Figure 1.** Background. (a) Previous and current work reporting divergent (left vs right, respectively) behavior in the trapping reactions of benzyne with thioamides. (b) Classical 1,3-dipolar cycloaddition reactions. <sup>a</sup>See ref 2 for a description of the two-letter structure designations.



**Figure 2.** DFT [SMD(benzene)//M06-2X/6-311+G(d,p)] calculations for the [3 + 2]-cycloaddition and subsequent ethylene elimination for the hypothetical reaction between *o*-benzyne (6) and the *N,N*-diethylthioamide 3a.



**Figure 3.** Use of the *N,N*-dioctylthioamide 3b allowed identification of 1-octene, the elimination product from 4ab, and led to the structural assignment of the major and minor products 5ab and 5ab', respectively, by the indicated NOEs.



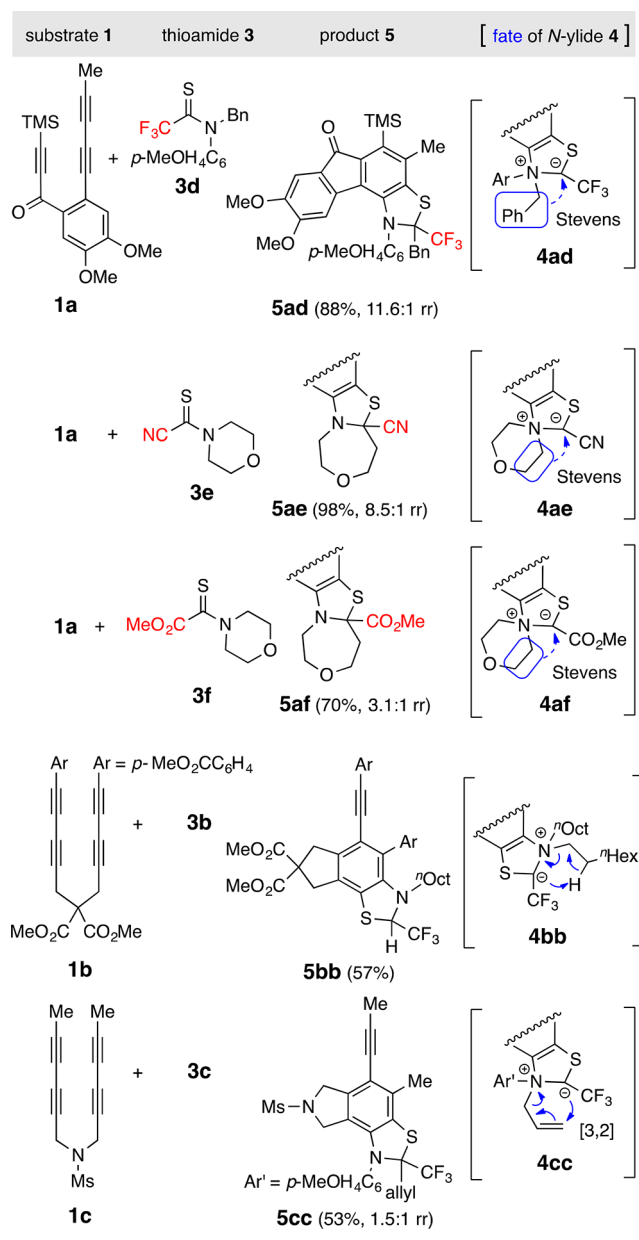
**Figure 4.** Product 5ac from [3,2]-sigmatropic rearrangement also supports the intermediacy of ylide 4ac.

withdrawing groups in the thioamide also promote this new type of cycloaddition reaction? The reactions using thioamides 3d–f, containing  $-\text{CF}_3$ ,  $-\text{CN}$ , and  $-\text{CO}_2\text{Me}$  groups, respectively, all gave rise to products (5ad,<sup>10b</sup> 5ae,<sup>10b</sup> and 5af,<sup>10b</sup> respectively) that demonstrate just that. Second, is the reaction unique to benzyne 2a? No, as evidenced by the conversions of 1b and 1c to products 5bb<sup>10b</sup> and 5cc,<sup>10b</sup> respectively, via eliminative or [3,2]-sigmatropic processes within the ammonium ylides 4bb or 4cc, respectively.

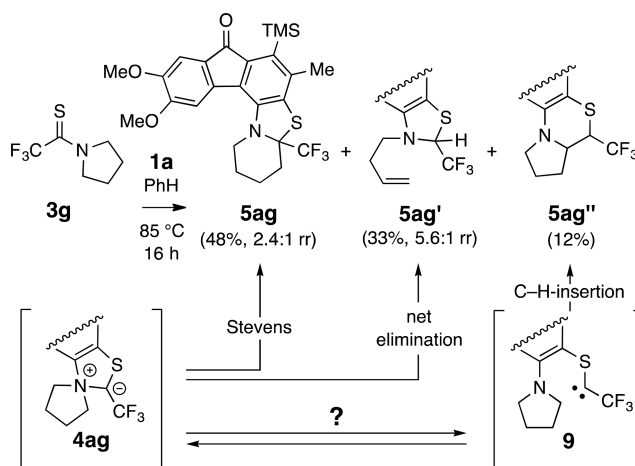
Trapping with the pyrrolidine-containing thioamide 3g revealed an additional new mode of reaction (Figure 5) beyond the products of Stevens rearrangement (5ag) and elimination (5ag').<sup>11</sup> Here, we also isolated the novel dihydrobenzo-1,4-thiazine derivative 5ag'.<sup>10b,12</sup> We suggest that this formally ring-expanded compound arises from a C–H insertion event within the intermediate, isomeric carbene 9, arising from dissociation of the nitrogen atom from the ammonium ylide carbon. This overall process reveals yet another facet of the reactivity of the ammonium ylides encountered in this study. The reverse reaction, generation of an ammonium ylide from a carbene, is known.<sup>13</sup>

A comment about the observed regioselectivities leading to the major constitutional isomer in these reactions is warranted.

**Table 1. Products 5 Arising from Several Different Electron-Deficient Thioamides 3 and Several Different Benzyne Precursors 1 via the Mechanistic Events Suggested in the Intermediates Ammonium Ylides 4**



In most cases, the major product is consistent with the well-established preference for benzyne **2a** to add nucleophilic species<sup>14</sup> at the *sp*-hybridized carbon with the larger internal bond angle<sup>15,16</sup> (see red triangle in **2a** in Figure 1a). In contrast, the benzynes derived from **1b** and **1c** generally show a lower degree of regioselectivity for the addition of nucleophiles.<sup>14</sup> The rr for the product **5cc** and its isomer is only 1.5:1. However, **5bb** was formed as the sole dihydrobenzothiazole. This substrate (and intermediate benzyne), uniquely among all studied here, contains a bulky aryl substituent adjacent to one of the benzyne carbons and thus sterically guides the nucleophilic sulfur atom to add to the distal benzyne carbon. This demonstrates that steric differences encountered during benzyne trapping reactions can override (at least small) inherent electronic preferences.<sup>17</sup>



**Figure 5.** Pyrrolidino thioamide **3g** gave rise to three distinct types of products.

In conclusion, this study of reactions of thioamides bearing an electron-withdrawing substituent on the thiocarbonyl carbon (cf. **3**) with benzynes generated by the HDDA reaction of tri- and tetrayne precursors (cf. **2**) has led to the identification of a new type of [3 + 2]-cycloaddition reaction. The sulfur and nitrogen atoms of the thioamide engage the benzyne *sp*-carbon atoms to produce an intermediate ammonium ylide structure (cf. **4**). This species shows a variety of different paths for reaction, including several heretofore unseen, as deduced from the products that are produced. This adds to the overall body of understanding of these relatively rarely encountered species. Overall, this work represents another instance<sup>14</sup> in which the HDDA cycloisomerization reaction has allowed a fundamentally new type of transformation to be discovered.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02133.

Experimental details for the preparation of new compounds; spectroscopic data for their characterization, including copies of <sup>1</sup>H and <sup>13</sup>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.

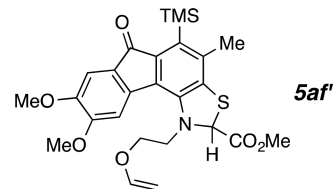
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GM127097). A.C.S.P. and V.P. appreciate the support of a Gleysteen–Heisig fellowship for undergraduate students. Some of the NMR data were obtained with an instrument acquired with funds from the NIH Shared Instrumentation Grant program (S10OD011952).

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- (2) The structures of products **5** (and intermediate ammonium ylides **4**) presented in this manuscript carry two letter descriptors that reflect, first, the HDDA substrate (**1a–c**) and, second, the electron-deficient thioamide (**3a–f**) from which they were generated. Also, see ref **10** for a discussion of the fact that isomers arising from two regioisomeric modes of addition, indicated by “rr”, are typically observed and for the basis of assignment of the constitution of **5aa**.
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- (9) We also computed the reaction energy for the transformation of the analogue of **3a** in which the CF<sub>3</sub> substituent was replaced with a CH<sub>3</sub> group to give the CH<sub>3</sub> analogue of **7**. That step is less exergonic (5 kcal·mol<sup>-1</sup>, see the Supporting Information) than that of **3a** to **7**. Whereas it was a trivial matter to locate **TS1**, we have been unable to identify a bound TS for the case of the methyl analogue. The presence of the electron-withdrawing substituent in the model thioamide **3a** appears to play an important role.
- (10) (a) In many of the reactions reported here, two constitutional isomers were formed, arising from competitive modes of addition of the thioamide to the various unsymmetrical benzyne. The assignment of constitution to the major and minor isomers **5ab** and **5ab'** rests on the NOEs shown in blue in Figure 3. (b) For many of the additional isomeric pairs (ratios indicated as rr), only the major isomer is shown in the manuscript [see the Supporting Information for additional details]. The constitution of the major product is assigned on the basis of the very high field chemical shift of the aromatic H10 proton for the *N*-arylated products (**5ac**, **5ad**, and **5cc**), an NOE analogous to that for **5ab** for the *N*-alkylated products (**5aa**, **5ae**, **5af**, **5ag''**, and **5bb**), and an abnormally high-field resonance for the *N*-CH<sub>2</sub> because of shielding by the nearby *p*-carbomethoxyphenyl group in **5bb**.
- (11) We also observed a small amount (6% yield) of what we judged to be the analogous elimination product, the vinyl ether **5af'**, accompanying product **5af** (Table 1).



(12) This compound was obtained as a single diastereomer, but the NCHCHS vicinal coupling constant (4.0 Hz) did not allow for a confident assignment of its relative configuration.

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