

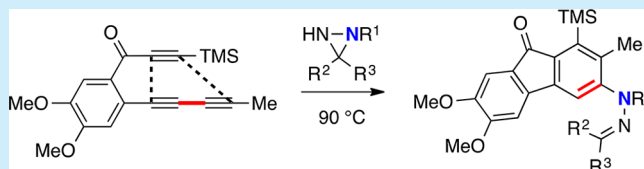
Reactions of Diaziridines with Benzynes Give *N*-Arylhydrazones

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S Supporting Information

ABSTRACT: Reactions of thermally generated benzynes with diaziridines are reported. These trapping reactions follow the same pathway as reported earlier by Heine and co-workers with electron-deficient alkynes. The resulting *N*-arylhydrazones were obtained efficiently in a single step. The preference for the mode of addition of the nucleophilic diaziridine nitrogen atom to the more electrophilic benzyne carbon was consistent with what is predicted on the basis of distortion analysis. The feasibility of converting the hydrazone into a Fisher-indole adduct was demonstrated.



Forty-five years ago, Heine and co-workers reported on the reactions of nucleophilic diaziridines with electrophilic alkynes (e.g., **1** + **2** to **3** in Figure 1).¹ Largely as a result of a ¹⁵N-labeling experiment (red atoms), the mechanism of the reaction was deemed to involve initial addition of the alkylated (*R*¹) nitrogen atom to provide the intermediate zwitterion **4**.³ Ring-opening was then invoked to give the iminium ion **5**, within which proton transfer would then lead to the adduct **3**.

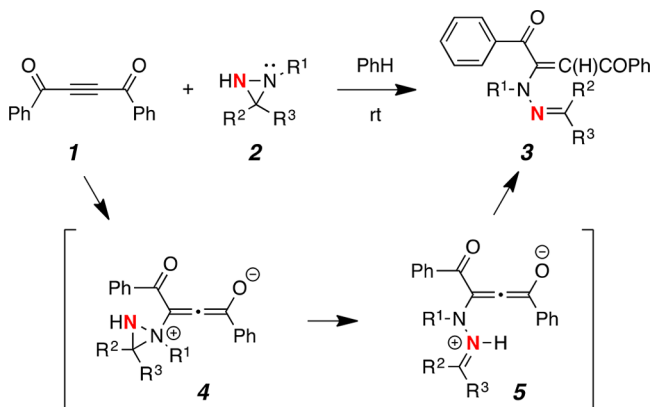


Figure 1. Reaction of nucleophilic diaziridines with electrophilic alkynes.¹

Arynes, another class of “electrophilic acetylene”,¹ have been trapped with myriad nucleophilic trapping agents.⁴ Benzyne derivatives can be formed by simple thermal activation of appropriately tethered triyne substrates⁵ via a process we have called the hexadehydro-Diels–Alder (HDDA) reaction.⁶ We report here reactions of various diaziridines with a number of electrophilic HDDA-generated benzynes. Gratifyingly, these transformations follow the same reaction course as uncovered in 1973. Namely (and as generically shown in Figure 2), when a substrate **6** is heated in the presence of a diaziridine **2**, a hydrazone **7** is formed efficiently. We suggest that this is best rationalized, again, by initial attack of the *N*-alkylated nitrogen in

2 to the benzyne **8** to produce the zwitterion **9**. Secondary amines readily add to electron poor alkynes, so the preferential attack by the more substituted and hindered (albeit also more electron rich) nitrogen atom in **2** to either of the “acetylenes” **1** or **8** may be attainable because of the highly unhindered nature of the electrophilic alkynes, all the more so because of the bent geometry of the *sp*-carbons in **8**. Also, the trapping of an aryne by a nucleophile (here, the diaziridine nitrogen) is often significantly exothermic. Accordingly, the transition state should be reached early on the reaction coordinate and have a relatively long distance between the nitrogen and benzyne carbon atoms.

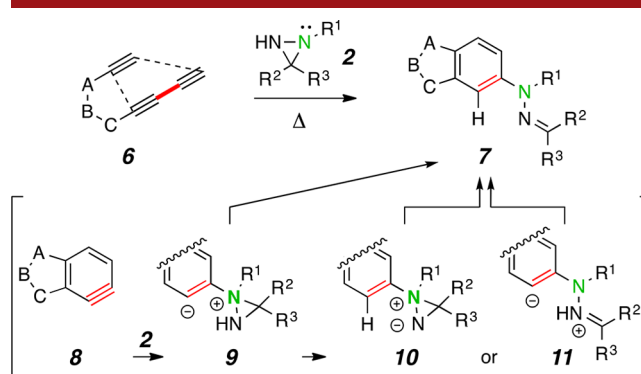


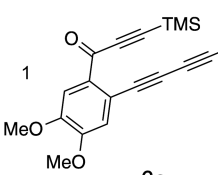
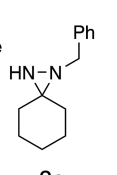
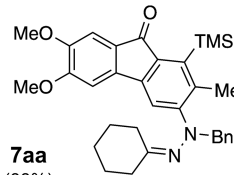
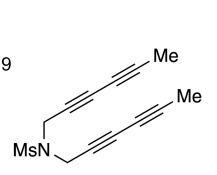
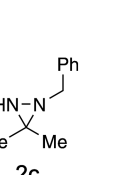
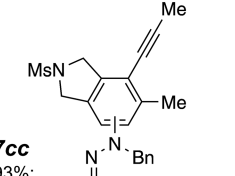
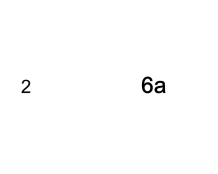
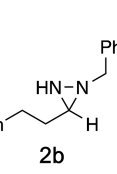
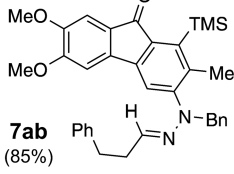

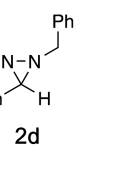
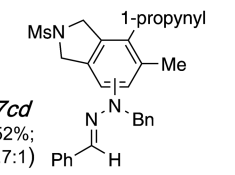
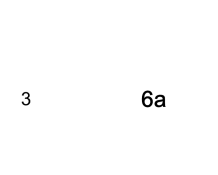
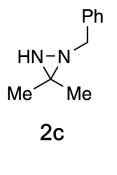
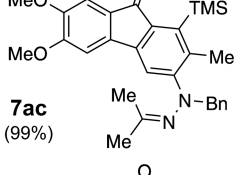
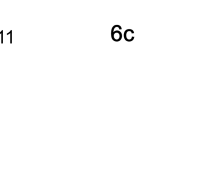
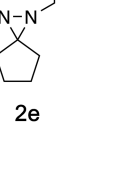
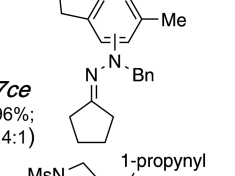
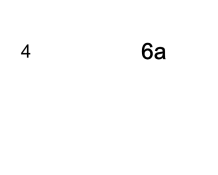
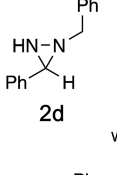
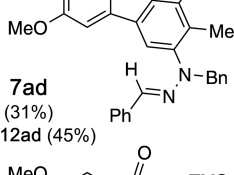
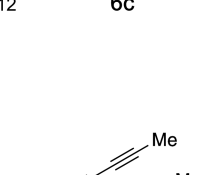
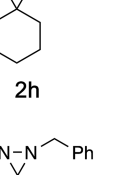
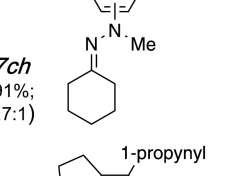
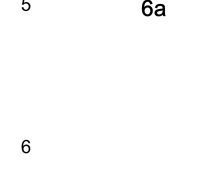
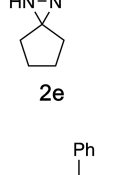
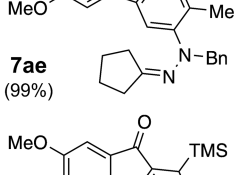
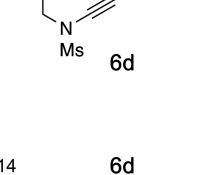
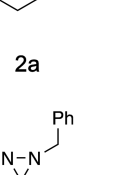
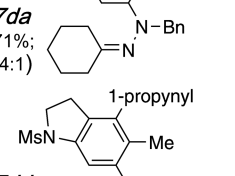
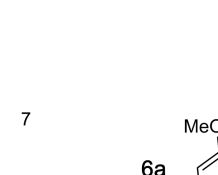
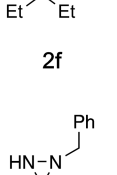
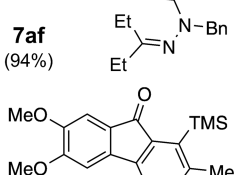
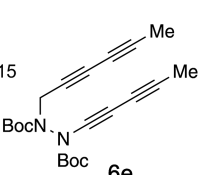
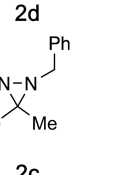
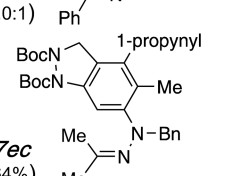
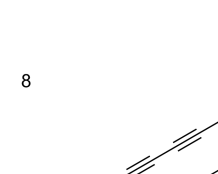
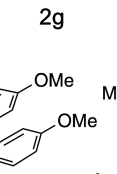
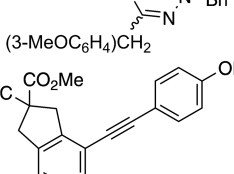
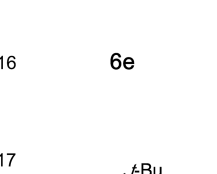
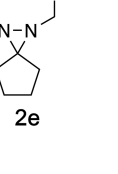
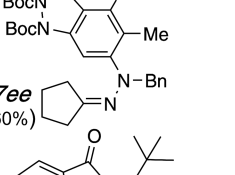
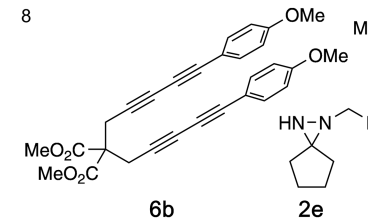
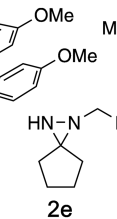
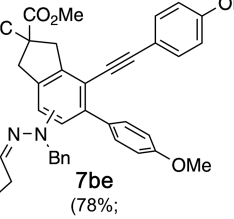
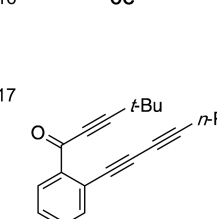
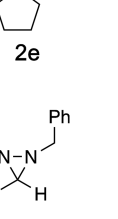
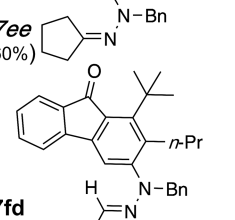
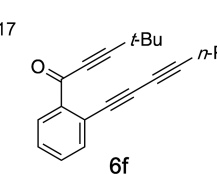
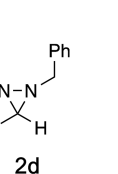
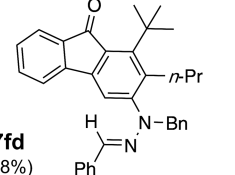
Figure 2. Reaction of a generic HDDA-generated benzyne and a monoalkylated diaziridine (this work).

This would further reduce the importance of steric interactions in the initial adduct formation. Further transformation of **9** to **7** requires both a proton transfer and ring-opening event of the strained ring. This could conceivably be a concerted process or occur in either order via intermediate 1,2- or 1,4-zwitterions **10** or **11**, respectively.

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Table 1. Products **7^a** from Reactions **b** between Benzyne Precursors **6a–f** and Diaziridines **2a–h**

entry	poly-yne substrate	diaziridine	product (yield)	entry	poly-yne substrate	diaziridine	product (yield; maj:min)
1			 7aa (88%)	9			 7cc (93%; 1.8:1)
2			 7ab (85%)	10			 7cd (52%; 3.7:1)
3			 7ac (99%)	11			 7ce (96%; 2.4:1)
4			 7ad (31%) with 12ad (45%)	12			 7ch (91%; 2.7:1)
5			 7ae (99%)	13			 7da (71%; 14:1)
6			 7af (94%)	14			 7dd (31%; 5.0:1)
7			 7ag (69%) (3-MeOC ₆ H ₄)CH ₂	15			 7ec (64%)
8			 7be (78%; 4.4:1)	16			 7ee (60%)
				17			 7fd (38%)

^aThe structure number of each product contains two letters, the first indicating the poly-yne **6** and the second the diaziridine **2** of origin. ^bAll reactions were performed in benzene having an initial [6] = 0.02 M and [2] = 0.04 M. Solutions were heated at 85–90 °C (external bath temperature) for 18–19 h, except for the case of the less reactive **6e**, where the reaction time was 48 h.

We first examined the reaction of triyne **6a** with seven different diaziridines (**2a–g**, entries 1–7, Table 1). These trapping agents differed in the nature of alkyl/aryl substitution at the 3-position of the diaziridine ring. All bear one *N*-alkyl group (benzyl), which differentiates the nucleophilicity of the two nitrogen atoms. The products from these seven experiments (**7aa–ag**) indicated that the benzyne trapping reactions with diaziridines had followed the same course of reaction as precedented (Figure 1) and projected on mechanistic grounds (Figure 2). They all can be rationalized as resulting from attack by the hindered, N1 nitrogen atom at the more electrophilic sp-hybridized carbon atom in the distorted benzyne intermediate **8a** (Figure 3).

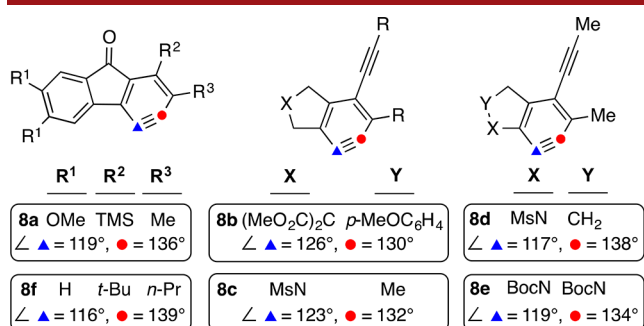


Figure 3. Internal bond angles (\angle) at the two benzyne carbons, reflecting the computed ring distortion of the benzynes **8a–f** derived from each of the polyynes **6a–f** {DFT: [SMD(benzene)//M06-2X/6-311+G(d,p)]}.

We proceeded to explore the reactions of other HDDA benzyne substrates, namely **6b–f** (entries 8–17). These reacted in similar fashion, demonstrating generality within the benzyne component, leading to various *N*-arylated hydrazone products. The matching of which two reactants were used in the examples in entries 8–17 of Table 1 (i.e., which benzyne precursor **6** with which diaziridine **2**) was arbitrarily chosen. Nonetheless, this representative subset demonstrates the generality of the reaction.

Each of the benzyne species **8a–f** derived from the set of polyyne substrates **6a–f** is shown in Figure 3. Their reactions with diaziridines were observed to proceed with exclusive regioselectivity for the cases of **8a**, **8e**, and **8f**; mixtures of constitutional isomers were formed in each of the cases of **8b–d**. These selectivities for nucleophilic addition to these benzynes are consistent with those expected either from (i) reported reactions with nucleophiles⁷ or (ii) the extent and direction of the computed distortion [DFT, Figure 3: **8a–c,f** (see SI), **8d**,^{7a} and **8e**].⁷¹ Distortion analysis has been used quite successfully to account for the strong preference for addition by a nucleophile at the more electrophilic, obtuse sp-center, which has a greater proportion of *p*-character.⁸ As the magnitude of the difference in the two internal angles diminishes, subtle differences in steric effects for the two potential modes of addition begin to play a more important role (cf. differences in the isomer ratios among entries 9–12 or of 13 vs 14).

The reactions using the 3-phenyl-substituted diaziridine **2d** gave less efficient formation of the hydrazone products (entries 4, 10, 14, and 17). In one instance (entry 4), we separated and identified the product of the major competing pathway, namely,

the (polar and chromatographically poorly behaved) amidine **12ad** (Figure 4). Presumably, in this reaction, the benzyne **8a** undergoes initial attack by the NH rather than the N_{Bn} nitrogen atom of the diaziridine leading to the zwitterion **13**. This species, now containing a benzylic C–H proton, can undergo internal proton transfer to produce **14** followed by a ring-opening event to give the amidine **12ad**.

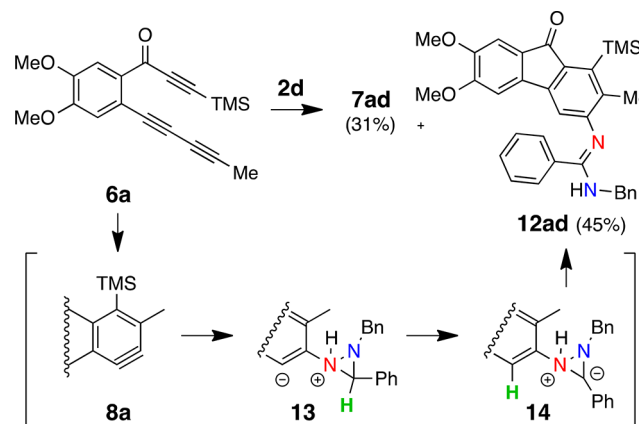


Figure 4. Rationale for formation of amidine **12ad** via initial attack of the secondary amine in **2d** to the benzyne **8a**.

Finally, we have also demonstrated two examples in which these hydrazone products can be converted into fused indole derivatives. Specifically, we were inspired by the report of Greaney et al. in which benzyne-derived hydrazones underwent Fischer indole cyclization using Lewis acid catalysis to produce indole adducts.⁹ When exposed to ZnCl₂ at elevated temperature in *tert*-amyl alcohol, the hydrazones **7ae** and **7aa** produced the corresponding cyclized products **9ae** and **9aa**, respectively (Figure 5). In both cases, Lewis acid mediated desilylation was observed under the reaction conditions.

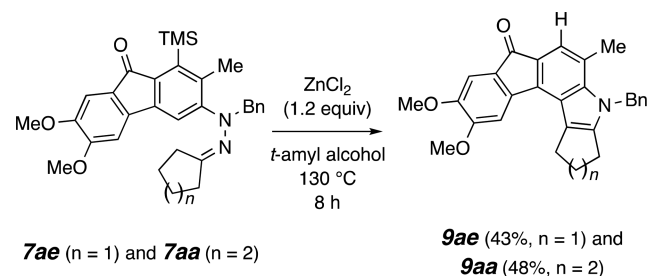


Figure 5. Fischer indole adducts **9ae** and **9aa** derived from hydrazones **7ae** and **7aa**, respectively.

In conclusion, the results presented here demonstrate the generality of trapping thermally generated, polycyclic benzyne species with heteroatom-rich diaziridines. These trapping reactions lead to *N*-arylated hydrazones in a single step. In some instances, these products can be converted to fused-ring indole derivatives. The mechanism of this trapping reaction with benzynes is consistent with one established previously with electron-deficient acetylenes. The preferred mode of addition was consistent with that suggested by DFT-derived structures of the intermediate benzynes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03439.

Experimental details for the preparation of all new compounds; and spectroscopic characterization data (including copies of ^1H and ^{13}C NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This manuscript is dedicated in memory of Professor Harold W. Heine (HWH), formerly of Bucknell University, and in recognition of his considerable scientific and mentoring legacy, which has so positively impacted so many (including the outgoing Editor-in-Chief of this journal).³

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