Published in final edited form as:

Org Lett. 2019 April 19; 21(8): 2615–2619. doi:10.1021/acs.orglett.9b00595.

Divergent reactivity during the trapping of benzyne by glycidol analogs: Ring cleavage via pinacol-like rearrangements vs. oxirane fragmentations

Juntian Zhang, Thomas R. Hoyer*

Department of Chemistry, 207 Pleasant St. SE, University of Minnesota, Minneapolis, MN 55455

Abstract

Hydroxyl-containing cyclic ethers react with thermally generated benzyne to produce aryl ethers. Diverse reactivity was observed. Cleavage of the cyclic ether was involved in most of the pathways. The transformations are rationalized via initial formation of oxonium ion-containing 1,3-zwitterions arising from preferential nucleophilic attack on the benzyne by the ether oxygen. Pinacol-like rearrangements, including ring expansion, to yield aldehydes or ketones and oxirane fragmentations to generate aryl enol ethers were main competing events.

Graphical Abstract

Many oxygen-containing nucleophiles are known to function as nucleophilic reagents that effectively engage classically generated arynes to give aryl ether or ester products (Figure 1a). These trapping agents include alcohols,¹ carboxylic acids,² and phenols [Figure 1a–(i)].² A previous report has also shown that styrene oxide reacts with *o*-benzyne to yield aryl enol ethers [Figure 1a–(ii)].³ Selective multi-component reactions in which the benzyne engages, first, a cyclic ether and, then, an alcohol have also been demonstrated [Figure 1a – (iii)].¹

*Corresponding Author hoye@umn.edu.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Experimental details for the preparation of new compounds; spectroscopic data for their characterization, including copies of ¹H and ¹³C NMR spectra (PDF).

The authors declare no competing financial interests.

We have reported a number of details of the reactions between thermally generated benzyne [by the hexadehydro-Diels-Alder (HDDA) reaction⁴] and alcohols⁵ or phenols.⁶ We now present results of studies in which we have used various hydroxy-containing cyclic ethers (e.g., glycidol derivatives, Figure 1b) to trap HDDA-benzyne. These characteristically tend to give rearranged products by way of a pinacol-like rearrangement process in which the cyclic ether ring is cleaved (cf. curved arrows in Figure 1b, which indicate the overall bond reorganization). The only related rearrangement reactions of glycidol derivatives that we can find are those induced by silyl triflate reagents, a reaction motif first reported by Jung and coworkers.⁷

In an early experiment (Figure 2), we explored the simple competition between epoxide and alcohol moieties within the same trapping molecule by generating the HDDA-benzyne **3a** (from heating triyne **1a**) in the presence of glycidol (**2a**). Three products were identified: aldehyde **4**, epoxide **5**, and the H₂-addition product **6**. Each can be rationalized by the events indicated in the bracketed structures labeled **IV**, **V**, and **VI**, respectively. Throughout this manuscript, we have used Roman numerals to label structures in which the overall bond/atom reorganizations are identified by a set of curved arrows. The Roman numeral corresponds to the cardinal number of the product (e.g., **IV** pertains to **4**, etc.). Also, these bracketed depictions are not intended to represent full mechanistic details. For example, the rearrangements could either be concerted or, arguably more likely for stereoelectronic reasons, stepwise, the latter involving an initial proton transfer to produce an intermediate alkoxide-oxonium zwitterion.

For all of the reactions reported in this manuscript, we only observed a single regioisomer. This outcome is consistent with the extent and direction of the distortion of the benzyne intermediates (cf. Figure 1, panel b)⁸ as well as the selectivities seen for numerous previously reported examples of nucleophilic trapping reactions of the HDDA polyene substrates used in this study (i.e., **1a** and **1b**). The structure of that sole regioisomer was confirmed by a nuclear Overhauser experiment (NOE) for a product from each of **1a** and **1b** (i.e., **8** and **15**, see Supporting Information).

The ratio of products **4-6** (Figure 2, bottom) was shown to depend on the amount of glycidol that was used. In the case of the highest concentration of that trapping agent (entry 1, 2.0 M, 100 equiv), the aryl ether **5**, arising from addition of the alcohol hydroxyl in **2a** to the benzyne, predominated slightly over the amount of rearranged aldehyde **4**. A trace of the dihydrogen transfer product **6** was formed.⁹ On the other hand, the use of only 3 equiv of **2a** (entry 3, 0.06 M) resulted in a good yield of the aldehyde, again a small amount of **6**, and just 6% of the aryl ether **5**. The varying amount of **5** is consistent with our understanding⁵ that the addition of primary alcohols to an HDDA-benzyne likely proceeds by way of the dimer of the alcohol (cf. **V**), the concentration of which is reduced significantly across this range of initial concentrations of **2a**. The formation of the aldehyde **4** can be rationalized by initial 1,3-zwitterion formation from attack of the ether oxygen atom at the more electrophilic benzyne atom (cf. **IV**). Intramolecular proton transfer would generate an alkoxide-oxonium ion species within which 1,2-hydride migration ensues. Finally, arene **6** is the result of dihydrogen transfer to the benzyne from the primary hydroxymethyl substituent

in **2a**, a process that we have shown to be a concerted event for simple primary alcohols (cf. **VI**).^{5,9}

To explore the question of whether the strained oxirane ring was necessary to promote this kind of ring-opening/rearrangement reaction, we carried out experiments using 2-(hydroxymethyl)tetrahydrofuran (**7**, Figure 3a) to trap the benzyne derived from triyne **1b**. The major product, **8**, was a linear homolog of the glycidol-derived aldehyde **4**. A small amount of the dihydrogen-trapped product **9** was observed as well.¹⁰

We used a deuterium labeling experiment (Figure 3b) to seek support for the 1,2-hydride shift proposed to account for formation of each of **4** and **8**. Indeed, when **1b** was heated in the presence of **7-d₂**, in which the carbinol carbon is a CD₂ group, the aldehyde product was primarily labeled at both the aldehyde hydrogen and at one of the hydrogen atoms alpha to the aldehyde (cf. **8-d₂**). Because the sample of the trapping agent **7**, produced by LiAlD₄ reduction of methyl 2-tetrahydrofuroate, also contained ca. 4% of **7-d₁**, small amounts of the isomeric monodeuterated products **8-d₁** and **8-d₁'** (Figure 3c) were also detected in the ¹H NMR spectrum of the sample of aldehyde **8-d₂** produced in this experiment. Qualitatively there was a greater amount of **8-d₁** than **8-d₁'** formed, as would be expected from a normal kinetic isotope effect associated with the product-determining, 1,2-hydride shift.¹¹ Partial overlap of key resonances in the ¹H NMR spectrum (see SI) precluded an accurate, quantitative determination of the actual **8-d₁** : **8-d₁'** product ratio.

We then probed the reactivity of the additional epoxide-containing substrates **2b-g** (Figures 4 and 5). Those shown in Figure 4 (**2b-d**) proceeded with 1,2-pinacol-like migration of an alkyl group or a hydride. In the case of **2c**, these two pathways were in competition (cf. **XI** vs. **XII**). However, stereoelectronic factors are in play, as suggested by the fact that the more constrained *cis*-epoxycyclohexanol **2d** rearranged (to **13**) only with hydride migration, presumably because the endocyclic C–C bond is not well-oriented for overlap with the activated epoxide C–O bond. (cf. **XIII**).

Different reactivity patterns were revealed using the tri-substituted epoxides **2e-g** (Figure 5), each of which gave rise to epoxide-fragmentation products. One mode of fragmentation involves C–C bond cleavage to liberate either formaldehyde (from **2e**) or acetaldehyde (from **2f**) (**XVI**, R' = H or Me, respectively). The acetaldehyde byproduct formed in the reaction of **2f** was observed in nearly equimolar amount to that of **16** when the reaction of **1a** and **2f** was performed in CDCl₃ and assayed directly by ¹H NMR spectroscopy. However, the diastereomer **2g** gave neither a pinacol-like product nor the fragmentation product **16**. Instead, it followed a new reaction course, yielding the enol ether **18** as the only isolated product.

These differing fates of diastereomers **2f** and **2g** are instructive and serve to reinforce the importance of stereoelectronic factors in the reactivity of these benzyne-derived internal ion pairs (zwitterions). The dominant conformation for each of these tri-substituted epoxyalcohols (and the initial zwitterions derived therefrom) can be expected to have the carbinol methine proton oriented toward the *cis*-methyl group. Consequentially, the blue hydroxyl proton is more readily accessible to the aryl carbanion in **XVII** than in **XVIII**. In

the case of **2f**, fragmentation (to **16**) and 1,2-methyl migration (to **17**, magenta arrows in **XVII**) compete. Alternatively, the blue hydroxyl proton in diastereomer **XVIII** is remote from the carbanion center, allowing abstraction of the epoxide methine proton to intervene, leading to the enol ether **18** (red arrows).

To complement the experiments already described, we have carried out several “one-off” experiments, which are portrayed in Figure 6. As mentioned, the reaction of styrene oxide with 1,2-dehydrobenzene³ has been previously studied as one of only a few reports we have found describing oxirane-aryne reactivity.¹² Similar to those previous reports, the reaction of **1b** with styrene oxide yielded two isomeric aryl enol ethers—namely, **19** and **20**, along with the dihydrobenzofuran derivative **21** (Figure 6a). The formation of these three products can be rationalized via the events depicted in **XIX–XXI**. Alternatively, the reaction of **1a** with cyclohexene oxide gave **22–24** (Figure 6b). The first and last proceeded by processes (**XXII** and **XXIV**) analogous to the styrene oxide reaction and the third, **23**, by an eliminative opening¹³ via **XXIII**. The *cis*–ring-fusion in **24** was assigned on the basis of a modest 6.5 Hz coupling constant between H_{6a} and H_{10a}.¹⁴ This outcome requires net retention of configuration at the site of epoxide cleavage, which suggests the intermediacy of a zwitterion like that in **XXIV**. Finally, to further explore the reactivity of the pinacol-like rearrangement, we designed a substrate that contains a cyclopropane ring, namely, 1-(tetrahydrofuran-2-yl)cyclopropan-1-ol (**25**). The reaction between **25** and benzyne **3a** cleanly yielded the ring-expanded cyclobutanone derivative **26**.

In conclusion, we have described here a variety of reactions between benzyne and cyclic ethers that bear adjacent hydroxyalkyl substituents. Because the benzyne is produced thermally, these reactions take place in the absence of other reagents or byproducts of the benzyne-producing event. Many of the reactions can be rationalized as proceeding through preferential attack of the cyclic ether oxygen to form a 1,3-zwitterion, followed by internal proton transfer and subsequent opening of the cyclic oxonium ion. An isotopic labeling experiment established that 1,2-hydride migration within the oxyanionic-oxonium intermediate is most likely operative. Studies of a number of substituted glycidol derivatives, including a diastereomeric pair, reveal a variety of different reaction pathways that are rationalized on stereoelectronic grounds. Reaction outcomes using the simple epoxides styrene oxide and cyclohexene oxide demonstrate the viability of some of the elementary steps used to rationalize the reaction outcomes with the hydroxyalkyl epoxides. A cyclopropane ring expansion reaction results in the formation of a novel cyclobutanone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Support for this research was provided by the National Institutes of General Medical Sciences of the U.S. Department of Health and Human Services (R35 GM127097). Some of the NMR data were obtained with an instrument acquired with funds from the NIH Shared Instrumentation Grant program (S10OD011952).

REFERENCES

1. Thangaraj M; Bhojgude SS; Mane MV; Biju AT From Insertion to Multicomponent Coupling: Temperature Dependent Reactions of Arynes with Aliphatic Alcohols. *Chem. Commun.* 2016, 52, 1665–1668.
2. Liu Z; Larock RC Facile O -Arylation of Phenols and Carboxylic Acids. *Org. Lett.* 2004, 6, 99–102. [PubMed: 14703360]
3. Beltran-Rodil S; Peña D; Guitián E Reaction of Benzyne with Styrene Oxide: Insertion of Arynes into a C-O Bond of Epoxides. *Synlett* 2007, 8, 1308–1310.
4. Hoye TR; Baire B; Niu D; Willoughby PH; Woods BP The Hexadehydro-Diels-Alder Reaction. *Nature* 2012, 490, 208–212. [PubMed: 23060191]
5. Willoughby PH; Niu D; Wang T; Haj MK; Cramer CJ; Hoye TR Mechanism of the Reactions of Alcohols with o -Benzynes. *J. Am. Chem. Soc.* 2014, 136, 13657–13665. [PubMed: 25232890]
6. Zhang J; Niu D; Brinker VA; Hoye TR The Phenol–Ene Reaction: Biaryl Synthesis via Trapping Reactions between HDDA-Generated Benzyne and Phenolics. *Org. Lett.* 2016, 18, 5596–5599. [PubMed: 27767316]
7. Jung ME; D'amico DC Enantiospecific Synthesis of All Four Diastereomers of 2-Methyl-3-((trialkylsilyl)oxy)alkanal: Facile Preparation of Aldols by Non-Aldol Chemistry. *J. Am. Chem. Soc.* 1993, 115, 12208–12209.
- 8 (a). Garg NK; Houk KN Indolyne and aryne distortions and nucleophilic regioselectivities. *J. Am. Chem. Soc.* 2010, 132, 1267–1269. [PubMed: 20058924] (b) Medina JM; Mackey JL; Garg NK; Houk KN The Role of Aryne Distortions, Steric Effects, and Charges in Regioselectivities of Aryne Reactions. *J. Am. Chem. Soc.* 2014, 136, 15798–15805. [PubMed: 25303232]
9. Niu D; Willoughby PH; Woods BP; Baire B; Hoye TR Alkane Desaturation by Concerted Double Hydrogen Atom Transfer to Benzyne. *Nature* 2013, 501, 531–534. [PubMed: 24067712]
10. Trapping with 2-(tetrahydropyranyl)methanol was briefly examined. Similar product mixtures composed of four principle products were observed (alcohol addition, dihydrogen addition, an unidentified aldehyde, and the aldehyde homolog of 8.
- 11 (a). Smith WB; Bowman RE; Kmet T The Role of Hydrogen in the Pinacol Rearrangement of 2-Methyl-2,3-butanediol. *J. Am. Chem. Soc.* 1959, 81, 997–1003. (b) Smith WB Hydrogen as a Migrating Group in Some Pinacol Rearrangements: a DFT study. *J. Phys. Org. Chem.* 1999, 12, 741–746.
- 12 (a). Okuma K; Hino H; Sou A; Nagahora N; Shioji K Cascade Approach to Trichloroalkyl Phenyl Ethers from Benzyne, Epoxides, and Chloroform. *Chem. Lett.* 2009, 38, 1030–1031. (b) Okuma K; Fukuzaki Y; Nojima A; Sou A; Hino H; Matsunaga N; Nagahora N; Shioji K; Yokomori Y Three Component Reaction of Arynes with Cyclic Ethers and Active Methines: Synthesis of ω -Trichloroalkyl Phenyl Ethers. *Bull. Chem. Soc. Jpn.* 2010, 83, 1238–1247.
13. Sdergren MJ; Andersson PG New and Highly Enantioselective Catalysts for the Rearrangement of meso-Epoxides into Chiral Allylic Alcohols. *J. Am. Chem. Soc.* 1998, 120, 10760–10761.
- 14 (a). A similar trans-fused tetrahydrodibenzofuran derivative showed an 11.6 or 12.8 Hz coupling: Zhao G; Wang B; Yang W; Ren H Lewis-Acid-Promoted Arylation Reaction: Synthesis of Dihydrobenzofuran Derivatives from Aryltriazenes. *Eur. J. Org. Chem.* 2012, 6236–6247. (b) A somewhat similar cis-fused tetrahydrodibenzofuran derivative showed an 8.4 Hz coupling: Yamashita M; Yadav ND; Sawaki T; Takao I; Kawasaki I; Sugimoto Y; Miyatake A; Murai K; Takahara A; Kurume A; Ohta S Asymmetric Total Synthesis of (–)-Linderol A. *J. Org. Chem.* 2007, 72, 5697–5703. [PubMed: 17579456]

a known reactions of *o*-benzynes with ordinary, *O*-containing functional groups **b** this work **Figure 1.**

- (a) Previous studies of reactions of benzynes with various oxygen-containing nucleophiles.
 (b) In this report we disclose reactions of hydroxyalkyl substituted cyclic ethers.

Figure 2.

Competition between epoxide and alcohol moieties using various concentrations.

Figure 3.

(a) Trapping reactions using a 5-membered cyclic ether. (b) A deuterium-labeling experiment that supports a pinacol-like mechanism. (c) The greater amount of isomeric monodeuterated product **8-d₁** compared to **8-d₁'** is consistent with preferential migration of protide vs. deuteride.¹¹

Figure 4.
 Trapping of HDDA-derived benzyne from **1b** or **1a** by epoxide-containing substrates **2b-d**:
 Pinacol-like rearrangements.

Figure 5.
Trapping (85 °C) of HDDA-derived benzynes from **1a** by epoxide substrates **2e-g**:
Rearrangement vs. fragmentation.

Figure 6. Reactions between HDBA-derived benzynes and: **a**) styrene oxide, **b**) cyclohexene oxide, and **c**) the cyclopropanol **25**.