

Desulfurization of Diaryl(heteroaryl) Sulfoxides with Benzyne

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S Supporting Information

ABSTRACT: Two benzyne-enabled desulfurization reactions have been demonstrated which convert diaryl sulfoxides and heteroaryl sulfoxides to biaryls and desulfurized heteroarenes, respectively. The reaction accessing biaryls tolerates a variety of functional groups, such as halides, pseudohalides, and carbonyls. Mechanistic studies reveal that both reactions proceed via a common assembly process but divergent disassemblies of the generated tetraaryl(heteroaryl) sulfuranes.



rynes are widely used in the synthesis of natural products 🖊 and bioactive compounds due to their versatile reactivities toward ionic and neutral nucleophiles.^{1,2} Among the numerous aryne reactions, the insertion of arynes into σ bonds³ or π bonds⁴ is particularly intriguing because this reaction mode allows the direct installation of multiple bonds on arynes to produce valuable polysubstituted arenes in one step.



In the past few years, aryne insertions into "S=O" bonds of sulfoxides have been validated and extensively studied.⁵⁻¹¹ In 2014. Chen and Xiao first demonstrated the feasibility of inserting arynes into the "S=O" bond of DMSO. As a result, 1,2-O,S-disubstituted arenes were assembled in a single step from three reaction partners including an aryne, DMSO, and an α -bromo carbonyl compound (eq 1).⁶ Afterward, aryl alkyl sulfoxides (eqs 2 and 3) and aryl vinyl and diaryl sulfoxides (eq 4) were all found to be suitable for the aryne insertion process by Wang,⁷ Li,⁸ Studer,⁹ and Yoshida and Hosoya.¹⁰ These reactions have produced a diverse range of 1,2-O,Sdisubstituted arenes.

In contrast, we have recently found that simply treating diaryl sulfoxides 1 with benzyne at room temperature could afford triarylsulfonium salts A1 in lieu of aryl thioethers (eq 5, Scheme 1).¹¹ As a continuation study of the aryne insertion chemistry, we report herein our discoveries of two new reactions between diaryl(heteroaryl) sulfoxides (2 and 3) and benzyne (eqs 6 and 7, Scheme 1). Unlike the reported cases (eqs 1-5), both reactions using benzyne as a reductant

Scheme 1. Reactions between Arynes and Sulfoxides

Our previous work: C CsF. MeCN Ar¹ (5) ŌTf rt 1 Ar¹ and/or Ar²: benzene Α1 or electron rich arenes This work ò rms CsF, MeCN (6) rt 2 B2 Ar³ and/or Ar⁴: naphthalene or electron poor arenes CsF, MeCN Het (7) Het rt СЗ 3 Initial discovery: TMS `OTf CI CsF (2.0 eq.) ŌTf MeCN (0.1 M) (8) °C. rt, 16 h ċι A2a 13% B2a 22%

proceed through the desulfurization of the diaryl(heteroaryl) sulfoxides and thus produce biaryls B2¹² or desulfurized heteroarenes $C3^{13}$ as the final products. The intriguing yet elusive differences among these two desulfurization reactions are also elucidated here by mechanistic studies.

Our research began with the attempted synthesis of triarylsulfonium salt A2a following our reported procedures

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(eq 8, Scheme 1). To our surprise, in addition to offering a low yield of A2a (13%), the reaction afforded a small amount of biaryl compound B2a (22%) (eq 8). This novel approach to biaryls via the desulfurization of diaryl sulfoxides is of great interest.^{12b} After optimization of the reaction conditions, we found the reaction proceeding with 4.0 equiv of benzyne precursor at rt for 36 h produced the best yield of biaryl B2a (81%) with only 5% of triarylsulfonium salt A2a.

Next, we examined the scope of the reaction with various diaryl sulfoxides 2. As shown in Scheme 2, a wide range of functionalized diaryl sulfoxides were found to be suitable for the reaction. Functional groups including aryl/alkyl halides (2a, 2b, 2u, etc.), pseudohalides (2d), esters (2f, 2t-2v), enolizable ketones (2g, 2s, 2z, etc.), nitriles (2h, 2n, 2q, etc.), and alkenes (2v) were all nicely tolerated. The functional groups tolerated in this reaction provide a versatile platform for further elaboration of the products. To our delight, naphthalenes (2w-2e') even without electron-withdrawing groups could also undergo the desulfurization process to afford biaryl species in synthetically useful yields. Nevertheless, diphenyl sulfoxide (1a) and diaryl sulfoxides (1b-1d) bearing an electron-donating group (Me) proved to be unsuitable for the reaction and exclusively furnished triarylsulfonium salts (Ala-Ale) in excellent yields, which is in line with the outcome of our reported reaction¹¹ (eq 5, Scheme 1).



To our surprise, when indole phenyl sulfoxide 3a was used as a substrate, the reaction afforded desulfurized indole C3a in 78% yield instead of expected biaryl product B3a (Table 1). After optimization of the reaction conditions, the best yield of C3a (82%) was obtained by carrying out the reaction using 3.0 equiv of benzyne precursor at rt for 12 h. As illustrated in entries 1 and 2, the electronic nature of the substrates was found to be critical to the reaction because the yields of desulfurized indoles C3 varied dramatically depending on the substituents on the phenyl rings (3a-3c) or indole nitrogens (3d and 3e). To our delight, this desulfurization protocol could be applied to other heteroaryl sulfoxides such as benzothiophene (3h), benzofuran (3i), and thiophene (3j)sulfoxides.

To gain more insight into both desulfurization reactions, we performed a few control experiments and deuterium-labeling studies (eqs 9-12). Under the optimum conditions, sulfoxide **2a** not only provided biaryl **B2a** but also gave a nearly equal





^aGeneral procedure: A mixture of diaryl sulfoxide 2 (0.25 mmol), benzyne precursor (2.0 equiv), and CsF (2.0 equiv) was stirred at rt for 36 h, during time which additional portions of benzyne precursor (1.0 equiv) and CsF (1.0 equiv) were added twice at 12 and 24 h. ^bTriarylsulfonium salts were obtained as the major products (A2c, 52%; A1a, 97%; A1b, 96%; A1c, 97%; A1d, 95%; and A1e, 93%). ^c47% of 2k, 56% of 2m, and 28% of 2f' were recovered, respectively.

amount of phenoxathiine 4 (eq 9). Submitting triarylsulfonium salt A2a to the optimum conditions did not furnish any biaryl B2a, and 95% of A2a was recovered (eq 10). This result clearly demonstrates that biaryls are not formed by the degradation of the triarylsulfonium salts. Interestingly, along with C3a, the reaction of indole sulfoxide 3a also provided 38% of triarylsulfonium salt 5 (eq 11). This result nicely explains the





^aReactions were performed with diaryl sulfoxide (0.25 mmol), benzyne precursor (3.0 equiv), and CsF (3.0 equiv) at rt for 12 h. ^bBenzyne precursor and CsF were added in three equal portions during the reaction at the beginning, 4 h, and 8 h.

outcome of the "S=O" moiety of **3a** in the desulfurization reaction. The isotope-labeling experiment was carried out by conducting the reaction of **3a** in CD₃CN (eq 12). As a result, C**3a** and *d*-C**3a** were obtained in a ratio of 35/65 (C**3a**/*d*-C**3a**). The deuterium atom was transferred from CD₃CN to the β -position of product C**3a**. The corresponding proton in unlabeled-C**3a** (35%) might be contributed by other proton sources, such as H₂O or CH₃CN (CD₃CN, Isotopic Enrichment, 99.8%).

To elucidate the versatility of the reactions between diaryl(heteroaryl) sulfoxides and benzyne, density functional theory (DFT) calculations were performed on both desulfurization processes (paths a and b, Figure 1) (see the Supporting Information for the computational details).¹⁴ Both reactions consist of two essential steps: (i) the assembly of tetraaryl-(heteroaryl) sulfuranes IM2 (IM2(2a) and IM2(3j)) from one molecule of sulfoxide and two molecules of benzyne¹⁵ and (ii) the disassemblies of sulfuranes IM2 into products B and C. For both reactions, sulfuranes IM2 are readily formed with large thermodynamic driven forces (>102.9 kcal mol⁻¹) overcoming small energy barriers (<4.7 kcal mol⁻¹). Compared to dication $[IM2]^{2+}$ with C_s symmetry, the neutral IM2 has a distorted structure with symmetry of C_1 due to a pseudo Jahn-Teller effect.¹⁶ Importantly, computations suggest that sulfuranes IM2 tend to interact with a Cs⁺ cation to form a strong π complex IM2·Cs⁺¹⁷ (see the Supporting Information for details). Furthermore, the four S-C bonds in IM2·Cs⁺ vary greatly depending on the substituents on sulfur, thus leading to two reaction pathways: (1) In path a, electron-deficient diaryl sulfoxide 2a readily undergoes the reductive elimination of IM2(2a)·Cs⁺ to B2a crossing the lowest barrier (12.1 kcal



Figure 1. Relative free energy profiles for the reactions of 2a (path a) and 3j (path b) with benzyne. Energies are reported in kcal/mol.

mol⁻¹), and internal reaction coordinate analysis is provided in Figure S4. Notably, the formation of B2a is also thermodynamically favored and is the most exothermic process (-91.8 kcal mol⁻¹). (2) In the case of 3j (path b), the release of thiophene C3j from IM2(3j)·Cs⁺ is kinetically more favored, as it has the lowest energy barrier of 10.2 kcal mol⁻¹.

In summary, we have developed two desulfurization reactions by simply treating diaryl or heteroaryl sulfoxides with benzyne, which produce biaryls or desulfurized heterarenes, respectively. The reaction to prepare biaryls B2 proceeded under mild conditions and exhibited excellent functional group compatibility. However, diphenyl sulfoxide 1a and diaryl sulfoxides 1b-1d bearing electron-donating groups are unsuitable for the reaction. Unlike diaryl sulfoxides 1 and 2, heteroaryl sulfoxides 3 including indoles, benzothiophenes, benzofurans, and thiophenes afford desulfurized heteroarenes C3. Control experiments and DFT studies proposed that tetraarvl(heteroarvl) sulfuranes IM2 were formed in both reactions. Due to their different electronic properties, the sulfurane intermediates (IM2) undergo distinct disassembly processes to deliver biaryls (B2) and desulfurized heterarenes (C3), respectively. Synthetic applications and further exploration of benzyne insertion reactions are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01144.

Experimental procedures, compound characterization, and copies of ¹H NMR and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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