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Sulfonamide Trapping Reactions of Thermally Generated Benzynes

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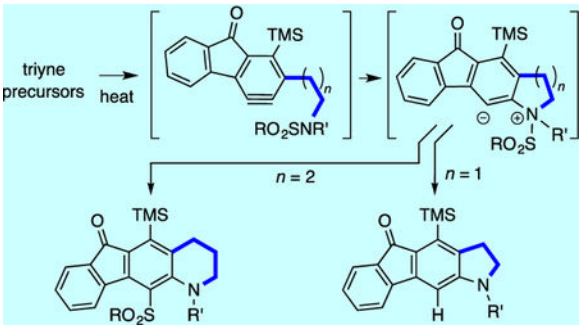
Abstract

Reactions of tethered, tertiary sulfonamides with thermally generated benzynes are reported. Typically, the N-S bonds in the substrates cleave and saturated heterocycles [tetrahydroquinolines (n = 2) and indolines (n = 1)] are formed. The process is accompanied by either sulfonyl transfer or desulfonylation from a zwitterionic intermediate, with the favored pathway being largely dependent upon the size (5- vs. 6-membered) of the *N*-containing ring in the zwitterion.

Graphical Abstract



Sulfonamides are known to react, in situ, with benzyne intermediates[1] made by the Kobayashi protocol[2] (fluoride ion + *o*-silylaryltriflate). Under these basic conditions, primary or secondary sulfonamides trap the benzyne intermediates (Figure 1a). Aryl-substituted sulfonamides are produced by this formal insertion reaction of the aryne triple bond into an N-H bond of the sulfonamide; the N-S bonds in the substrates remain intact in the product. We now disclose an alternative e mode of reaction that emerges when benzynes (cf. **I**) derived from thermal cyclization of triyne precursors[3] are trapped by fully substituted

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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; and spectroscopic data (including copies of ^{1}H and ^{13}C NMR spectra) for their characterization.

Notes

The authors have no competing financial interests to declare.

(i.e., tertiary) sulfonamides (Figure 1b). The evidence in hand suggests that (the intramolecular) reaction of various tertiary sulfonamides with HDDA-benzynes gives zwitterions II, from which different products are obtained via distinct reaction pathways. These mostly involve either sulfonyl transfer or desulfonylation. In these reactions, the sulfonyl group from the sulfonamide substrates are replaced by aryl groups, which, to our knowledge, is a unique feature of the reaction outcomes reported here.[4] The products contain either a tetrahydroquinoline (THQ) or indoline core structure depending on whether the diyne terminus of the triyne substrate and the sulfonamide nitrogen are connected by three or two atoms, respectively.[1]

Shown in Table 1 is a series of reactions of hexadehydro-Diels-Alder (HDDA) substrates that serve as precursors to products having a newly fused piperidine ring. That is, the amide (always a *p*-toluenesulfonamide) and alkyne are connected by a trimethylene linker. When each of the triynes **1a**–**f** was heated in a relatively inert[5] solvent, the corresponding THQs **2a**-**f** were isolated in excellent yield. We infer that within a THQ zwitterion such as **II** (*n* = 2) there is ample orbital overlap to permit 1,3-migration of the sulfonyl moiety (see further discussion below). It is worth mentioning that none of the product arising from a potential aza-Claisen rearrangement of the intermediate zwitterion arising from **1c** and leading to **2c** was observed.

We studied several related substrates that also contained a trimethylene linker between the terminal alkyne and trapping sulfonamide. The results are summarized in Table 2. Each substrate showed behavior different from those in Table 1. Substrate **1g** (entry 1) is an *N*-aryl sulfonamide; it gave rise to a complicated product array (tlc and ^{1}H NMR) with no clear evidence for the presence of any of **2g**. Triynes **1h** and **1i** (entries 2 and 3) are both methane- rather than toluenesulfonamides. They provided products (**2h** and **2i**, respectively) in which the sulfonyl group was absent. Elimination of sulfene (**IV**) from within the zwitterion **III** would account for these outcomes (see “mechanistic rationales,” at the bottom of Table 2). Finally, the nosylamide **1j** gave two products. Sulfone **2j** arises by the same path as that to the tosylamide products (Table 1), but its formation was accompanied by that of the *p*-nitrophenyl-substituted biaryl compound **2j’** in which SO_2 has been ejected. This variant of the Truce-Smiles rearrangement[6] can be viewed as proceeding by ipso-attack para to the nitro substituent in **V**. Loss of SO_2 from the delocalized zwitterion **VI** would lead to **2j’**. Similar transformations of classic benzynes have been demonstrated.[1c]

We also studied several lower homolog substrates (**1k-n**, Table 3) containing a dimethylene link between the diyne terminus and sulfonamide nitrogen atom. These led to the indoline derivatives **2k-n** (entries 1–4), each containing a newly formed 5-membered heterocycle. In this series we did not observe products of 1,3-sulfonyl migration analogous to those in reactions of the tosyl-sulfonamide leading to THQs (cf. Table 1). Rather, the isolated products were all devoid of the sulfonyl group. We attribute this (bottom of Table 3) to the higher activation energy (more strained transition state structure) that would be required for the conversion of the 5-membered zwitterion **VII**, which contains a retracted sulfonyl

[1]Throughout this manuscript we have used Roman numerals (**I**–**X**) to label structures of intermediate species that were not isolated and Arabic numerals to designate the structures of isolated (and newly characterized) compounds.

moiety, to the non-observed product **VIII**. Desulfonylation within **VII** could proceed by the sulfene ejection (cf. **III** to **IV**) for the Ms-substrates (entries 3 and 4) or by intervention of trace levels of a protic species such as water (**IX** to **X**, Table 3, bottom). Protonation of the carbon and desulfonylation by the resulting hydroxide would account for product formation. Given the relatively low concentration at which these experiments were performed (initial substrate concentration of 0.01 M), we cannot confidently judge which is the more likely scenario. The *N*-arylated, one methylene-lower homolog **1n** gave an interesting result in contrast to the behavior of substrate **1g** (Table 2, entry 1). The methanesulfonamide **1n** smoothly provided the *N*-phenylindoline **2n**, again by loss of sulfene.

Finally, we observed that each of these indoline products was susceptible to air autoxidation[7] to the corresponding indole. Performing the HDDA reaction under a nitrogen atmosphere substantially improved the cleanliness of the product mixture. In the case of **1m**, we heated the reaction mixture for an extended period of time (90 °C, 72 h) under a headspace of air and isolated the indole **3** as the main product; no indoline remained in the crude reaction mixture.

In conclusion, we have demonstrated that the nitrogen in tertiary sulfonamide groups can react with HDDA-generated benzynes to produce zwitterion intermediates. Various reaction pathways ensue from these species, depending on the size of the newly formed nitrogen heterocycle and the nature of the substituent (alkyl vs. aryl) present on the zwitterionic nitrogen atom. The processes include sulfonyl transfer to the vicinal, benzyne-derived carbon atom or desulfonylation events. Each results in the formation of a new, saturated, benzo-fused piperidine (i.e., a tetrahydroquinoline) or pyrrolidine (i.e., an indoline) ring. Among other things, each of these transformations results in the replacement of a robust N-SO_2R bond[8] by a N-C bond, potentiated by the high energy of the reactive benzyne intermediate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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Lett 2016, 18, 3726–3729. [PubMed: 27409978] (f) Ikawa T; Sumil Y; Masuda S; Wang D; Emi Y; Takagi A; Akai S Synthesis of Optically Active 2,3-Disubstituted Indoline Derivatives through Cycloaddition Reactions between Benzynes and α,β-Unsaturated γ-Aminobutyronitriles. Synlett 2018, 29, 530–536.

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5. Although solvents like toluene have been observed to trap benzynes in Diels-Alder and or ene type reactions, those processes are sufficiently slow that they do not interfere with the more facile trapping by the nucleophilic (and internally linked) nitrogen atom of the sulfonamide.
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8. For a discussion that reflects an early appreciation of the robustness of sulfonamides and their stability, see: Searles S; Nukina S Cleavage and Rearrangement of Sulfonamides. Chem. Rev 1959, 59, 1077–1103.

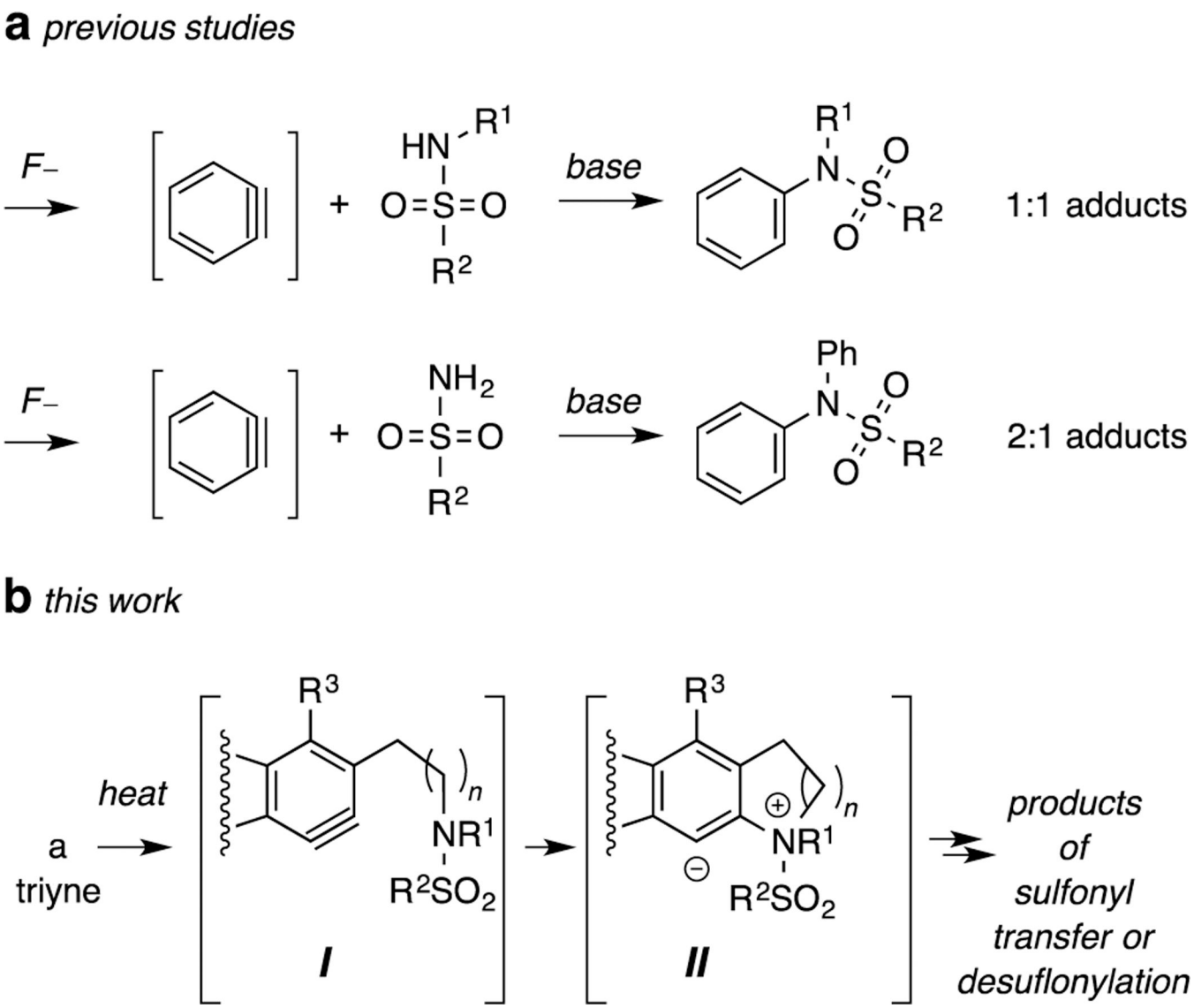
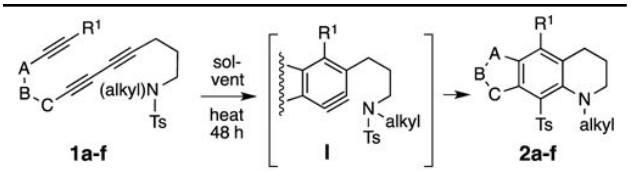


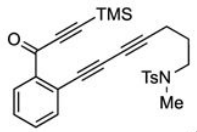
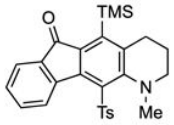
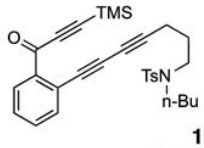
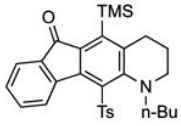
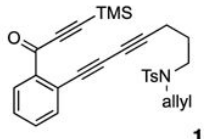
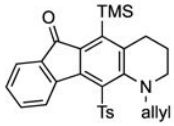
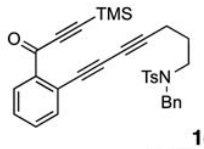
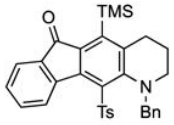
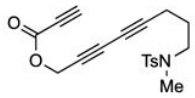
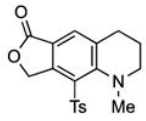
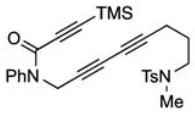
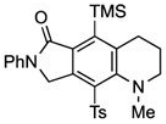
Figure 1.

a. Known modes of reaction of arynes with sulfonamides. **b**. Studies reported here show complementary reactions in which sulfonyl migration or desulfonylation occurs.

Table 1.

Reactions of Ts-amide-containing triynes 1a-f having various linkers (ABC) give sulfonyl-transfer product tetrahydroquinolines 2a-f via benzyne intermediates I.

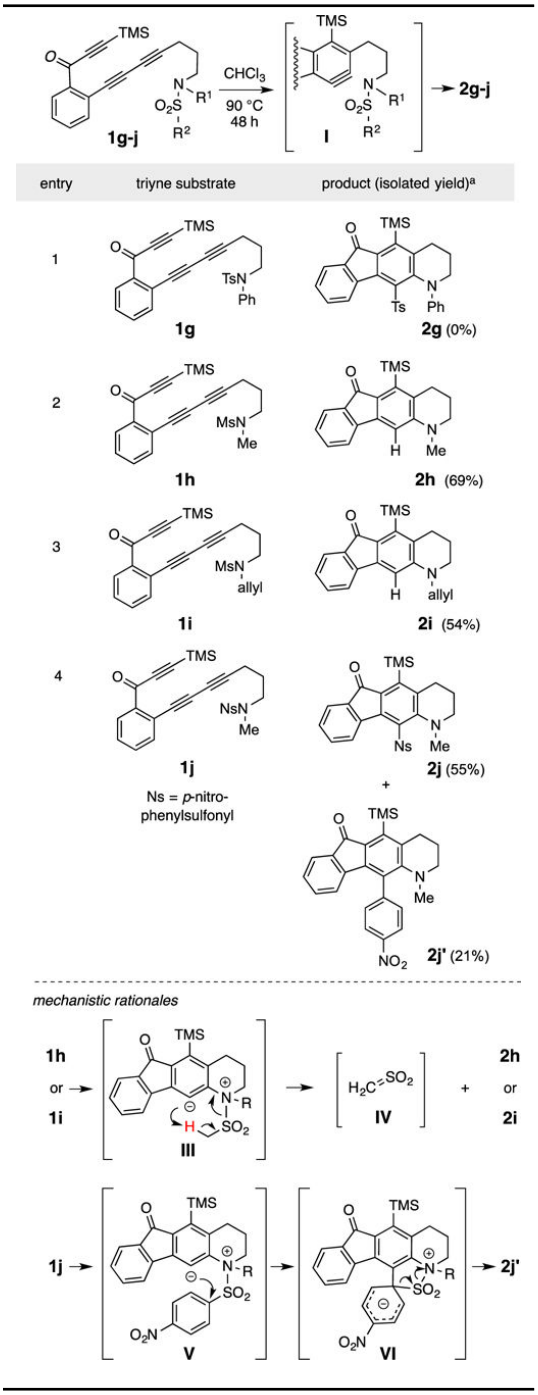


entry	triyne substrate	product (isolated yield)[a]
1	 **1a** ($CHCl_3$, 90 °C)	 **2a** (85%)
2	 **1b** ($CHCl_3$, 90 °C)	 **2b** (83%)
3	 **1c** ($CHCl_3$, 90 °C)	 **2c** (92%)
4	 **1d** ($CHCl_3$, 90 °C)	 **2d** (88%)
5	 **1e** (tol, 130 °C)	 **2e** (86%)
6	 **1f** (tol, 130 °C)	 **2f** (87%)

[a] % yield is of chromatographically purified material.

Table 2.

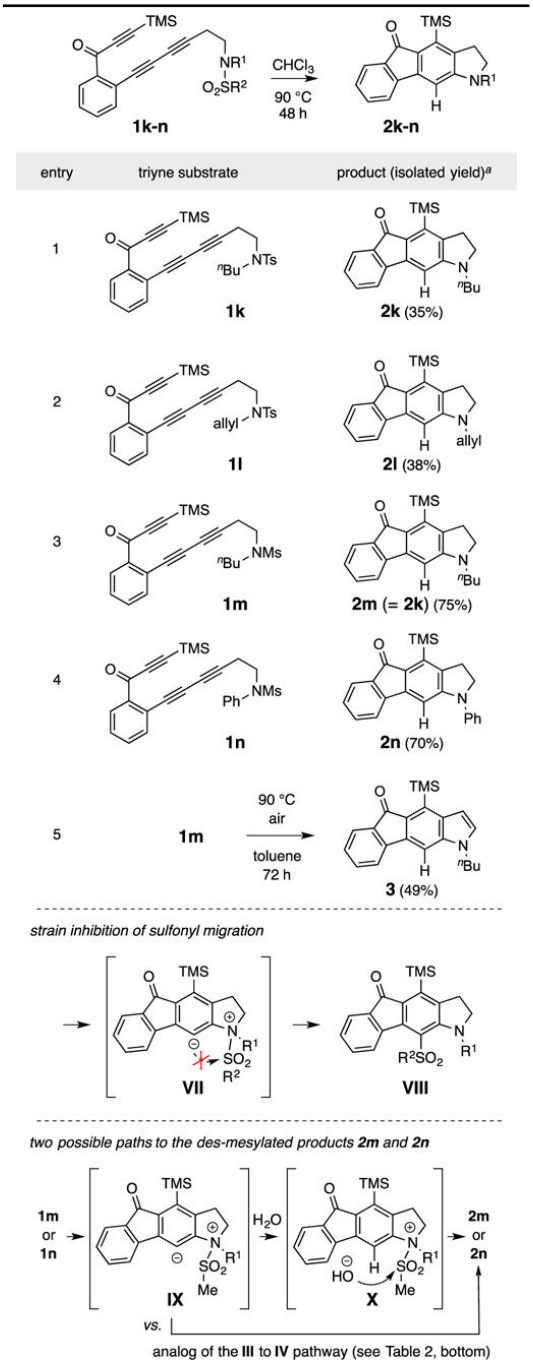
Reactions of triynes 1g-j, having various sulfonamide groups (R^2), leading to tetrahydroquinoline derivatives 2g-j via benzyne intermediates I.



[a] % yield is of chromatographically purified material.

Table 3.

Reactions of triynes 1k-n, having tosyl or mesyl sulfonamide groups (R^2), give desulfonylated indoline derivatives 2k-n.



[a] % yield is of chromatographically purified material.