Cyclizations and cycloadditions of acetylenic sulfones on solid supports†

Thomas G. Back* and Huimin Zhai

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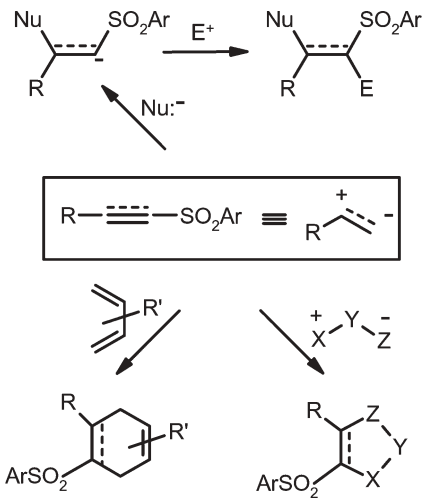
Acetylenic sulfones attached to solid supports by means of ester linkers were employed in a variety of cyclization and cycloaddition reactions, followed by cleavage of the products from the resin by ester hydrolysis or reductive desulfonylation.

The electron-withdrawing sulfone moiety[1] activates adjacent double and triple bonds[2] toward conjugate additions, and stabilizes the corresponding α-anions, which can then react with various electrophiles. Thus, when conjugate addition and intramolecular α-alkylation[3] or acylation[4] are employed in tandem, a sulfone-mediated cyclization protocol ensues. This approach has been employed in the synthesis of several alkaloids and related species.[5] Vinyl and acetylenic sulfones also undergo a variety of Diels–Alder and 1,3-dipolar cycloadditions.[1,2] Finally, the sulfone moiety can either be retained in the cyclized product, where it serves as a useful functional group for further transformations, or it can be cleaved by appropriate reductive desulfonylation methods.[6] These processes are illustrated in Scheme 1, where the unsaturated sulfone functions as the synthetic equivalent of hypothetical alkane and alkene dipole species.

The immobilization of reagents and starting materials on solid supports has become increasingly popular in organic synthesis.[7] Advantages typically include simplified work-ups, cleaner reactions and the possibility of conducting sequential transformations without the need to purify products at each stage. The preparation of libraries of biologically, or otherwise interesting compounds can be facilitated by conducting various combinations of reactions on solid-supported starting materials. To date, for example, β-benzoyloxyalkyl and γ-hydroxyalkyl sulfones anchored to solid supports have been employed in Julia–Lythgoe olefinations[8a] and in the preparation of trisubstituted 2-pyridones,[8b] while supported vinyl sulfones have been converted into libraries of tetrahydro-β-carbolines[9a] or tertiary amines,[9b] and into peptides used as probes of cysteine proteases.[10] We now report the preparation of the first acetylenic sulfones attached to solid supports, along with several types of subsequent transformation that illustrate their potential synthetic utility.

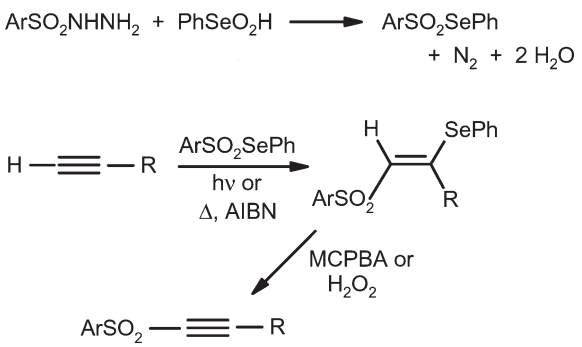


Scheme 1 Reactions of unsaturated sulfones.

Acetylenic sulfones can be easily prepared by the free radical selenosulfonation of acetylenes, followed by selenoxide *syn*-elimination (Scheme 2),[11] as well as by other methods.[2a]

Our first approach to attaching an acetylenic sulfone to a polymer support is shown in Scheme 3. The commercially available [4-(hydrazinosulfonyl)phenyl]propionyl resin **1** (Novabiochem Inc.) was converted to selenosulfonate **2**,[12] followed by free radical addition to 1-hexyne. Diphenyl diselenide was added to the mixture to facilitate the chain transfer step of the phenylseleno group to the intermediate β-sulfonylvinyl radical, thereby affording **3**. Selenoxide elimination then produced the desired acetylenic sulfone **4**, confirmed by a strong IR absorption at 2194 cm^{-1}.[13] Unfortunately, several efforts to perform cyclizations with **4** provided low yields of relatively impure products when attempts were made to cleave the latter from the support by reductive desulfonylation.

An alternative method was therefore developed, in which a series of acetylenic sulfones were attached to the solid support *via* an ester linker. Thus, the selenosulfonation of three representative acetylenes with **6**, which was in turn prepared from sulfonhydrazide **5**, afforded adducts **7a–7c**. Esterification of resin



Scheme 2 Preparation of acetylenic sulfones by selenosulfonation.

Department of Chemistry, University of Calgary, Calgary, AB, Canada T2N 1N4. E-mail: tgback@ucalgary.ca; Fax: (403) 289-9488; Tel: (403) 220-6256

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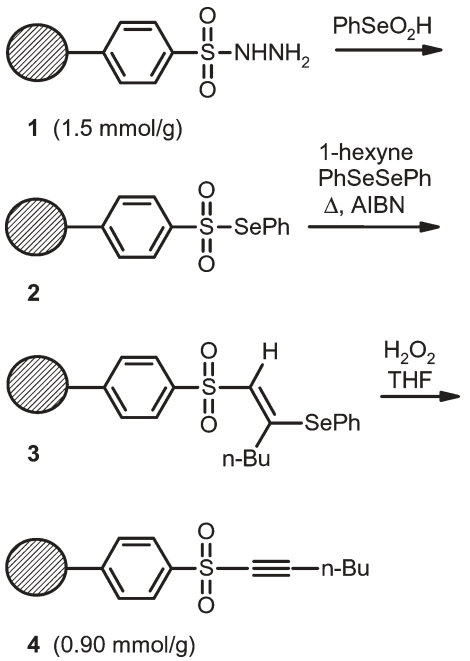
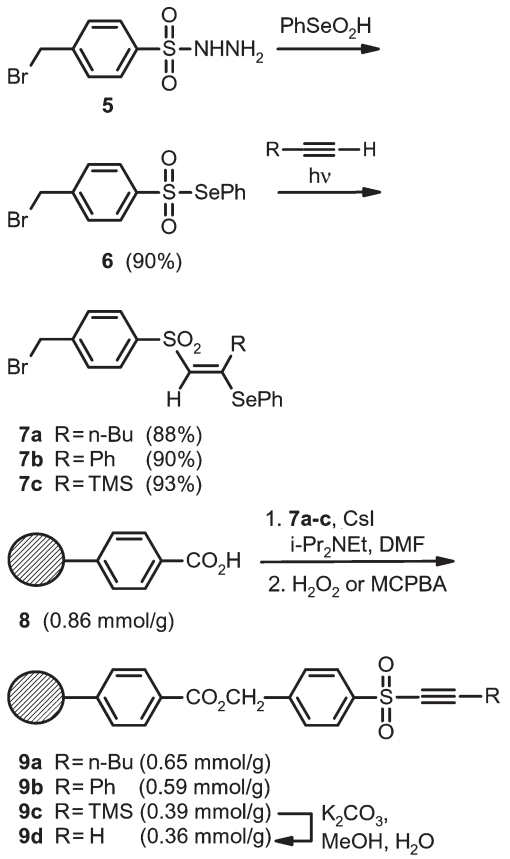
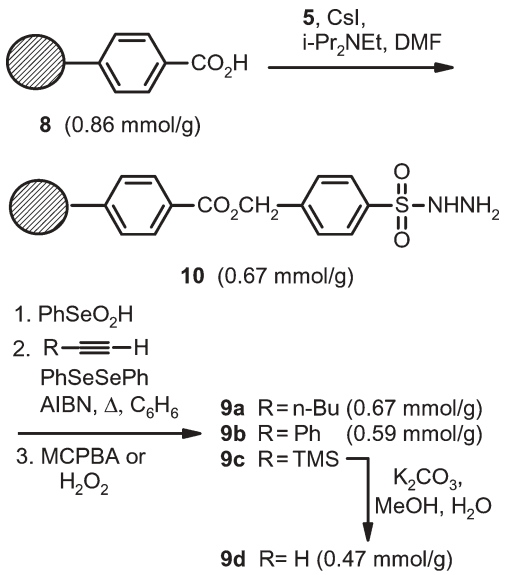


Scheme 3 Conversion of a sulfonhydrazide to an acetylenic sulfone on a solid support.

8[14] with **7a–7c** produced the desired products **9a–9c**, respectively. Desilylation of **9c** afforded the corresponding terminal acetylene **9d** (Scheme 4).[13]

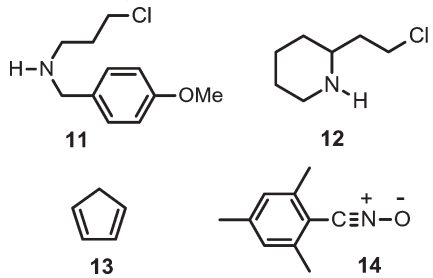


Scheme 4 Preparation of acetylenic sulfones on solid supports using an ester linker.



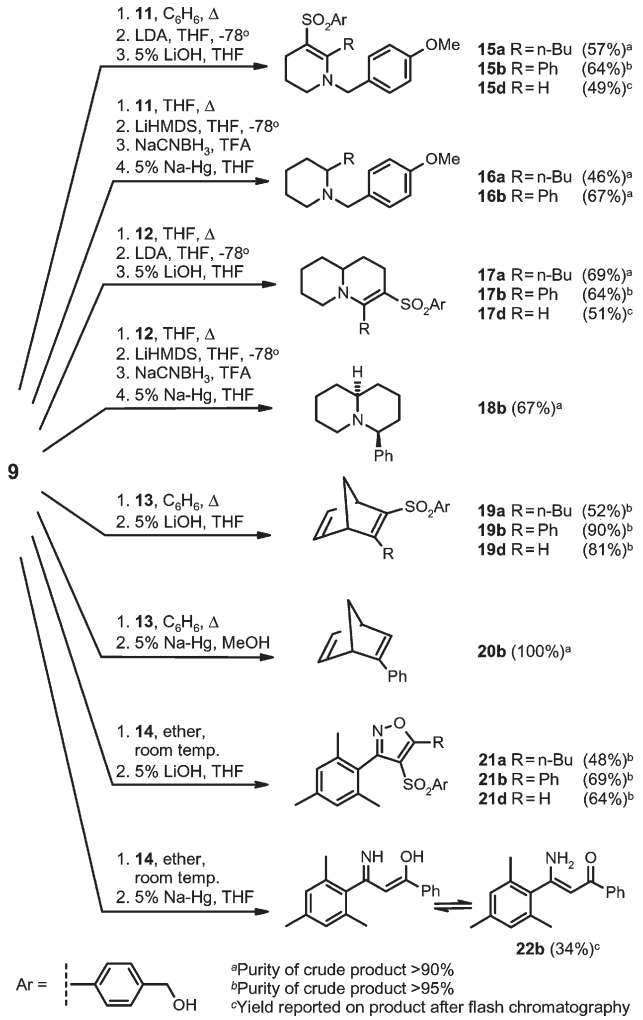
Scheme 5 Preparation of ester-linked acetylenic sulfones on solid supports from a sulfonhydrazide.

A third approach consisted of introducing the selenosulfonate moiety to the resin *via* the sulfonhydrazide **10**,[13] as shown in Scheme 5, followed by addition to the appropriate acetylene and selenoxide elimination. This method has the advantage that a single polymer-supported selenosulfonate can be used to generate an array of supported acetylenic sulfones **9**, making it more attractive for the eventual production of libraries of cyclization products when used in conjunction with subsequent transformations (*vide infra*).



Resins **9a**, **9b** and **9d** were then subjected to a variety of illustrative cyclization and cycloaddition reactions with chloroamines **11**[15] and **12**,[16] cyclopentadiene (**13**) and nitrile *N*-oxide **14**.[17] The results are summarized in Scheme 6.

Cyclization *via* conjugate addition of chloroamines **11** and **12**, followed by base-mediated intramolecular alkylation and cleavage from the resin with lithium hydroxide afforded **15** and **17**, respectively. The Diels–Alder reactions of the supported acetylenic sulfones with **13** and their dipolar cycloadditions with **14** were also successful, affording cycloadducts **19** and **21**, respectively, after similar cleavage from the support. Alternatively, enamine reduction with sodium cyanoborohydride, followed by reductive cleavage from the support with 5% sodium amalgam, afforded the corresponding desulfonylated products **16** and **18**. Similarly, reductive desulfonylation of the cycloadduct obtained from **13** and **9b** afforded **20b**, while that of the cycloadduct derived from nitrile oxide **14** and **9b** was accompanied by N–O cleavage to provide



Scheme 6 Cyclization and cycloadditions of acetylenic sulfones on solid supports.

22b. Products **21** and **22** were obtained as single regioisomers. The purities of the isolated products were typically >90%, and in many cases >95% (NMR analysis), without further purification. The exceptions were **15d**, **17d** and **22b**, where the purities of the crude products were <90%, and the corresponding yields are reported for products isolated by flash chromatography.

In conclusion, we have demonstrated that acetylenic sulfones can be anchored either directly, or *via* an ester linker, to appropriate solid supports. The latter species then undergo a variety of useful cyclization or cycloaddition reactions, and the resulting products can be isolated by cleavage from the resin *via* ester hydrolysis or reduction with sodium amalgam to afford the corresponding sulfone-functionalized or desulfonylated products, respectively.

We thank Merck Frosst (Canada) Ltd. and the Natural Sciences and Engineering Research Council of Canada for financial support.

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