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Reductive Cleavage of Secondary Sulfonamides: Converting Terminal Functional Groups into Versatile Synthetic Handles

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Supporting Information Placeholder

ABSTRACT: Sulfonamides are pervasive in pharmaceuticals and agrochemicals, yet are typically considered as terminal functional groups rather than synthetic handles. To enable the general late-stage functionalization of secondary sulfonamides, we have developed a mild and general method to reductively cleave the N-S bonds of sulfonamides to generate sulfinates and amines, components which can further react *in-situ* to access a variety of other medicinally relevant functional groups. The utility of this platform is highlighted by the selective manipulation of several complex bioactive molecules.

The ability to selectively modify single sites of complex molecules is a powerful and efficient tool in drug discovery, as single-point modifications can have profound impacts on biological and physicochemical properties.[1] Given that sulfonamides and related bioisosteres are prevalent in medicines across all therapeutic areas,[2] the development of methods for their selective manipulation could accelerate drug discovery. Yet, beyond simple C-N bond forming reactions, secondary sulfonamides have been treated as terminal functional groups *as there are no other methods for their late-stage modification.*[3]

Sulfonamides are ubiquitous in drug design, in part because they are metabolically stable[4] and easy to prepare from sulfonyl chlorides and amines.[5] However, given that sulfonyl chlorides are highly reactive and not stable within typical complex molecules, sulfonamides are often formed early in a synthetic sequence and carried through with the sulfonamide moiety fixed. For example, the synthesis of a sulfonamide-containing drug candidate (Figure 1A) relied on a 6-step sequence following the installation of the aniline group.[6] While such a sequence could be satisfactory to prepare a single target, it is not practical for typical structure-activity relationship studies in drug discovery. In addition, early installation of sulfonamides could restrict the types of functional groups present on the substituents of the sulfonamide, as the downstream chemistry could present incompatibilities. Thus, a general platform that enables late-stage functionalization of complex secondary sulfonamides under mild reaction conditions in a single reaction vessel would be particularly powerful in drug discovery programs (Fig. 1B).[7]

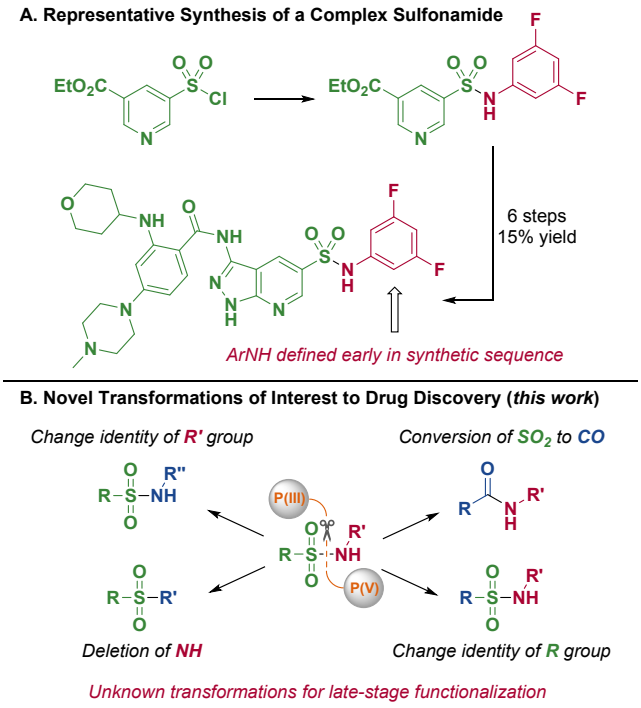


Figure 1. Secondary Sulfonamides in Drug-Like Molecules

As part of a program to realize sulfonamides as points of diversification, we recently reported a general platform for the conversion of primary sulfonamides to a variety of other bioactive motifs through the *in-situ* generation of sulfinates (Figure 2A).[8,9] While this method has already been adopted for late-stage functionalization, the reaction mechanism limits this chemistry to the diversification of primary sulfonamides. As primary and secondary sulfonamides are equally common across pharmaceuticals,[2] we sought to develop a method that could enable a similar reductive cleavage of the N-S bonds in secondary sulfonamides. However, secondary sulfonamides present additional challenges, most notably that across existing secondary sulfonamide-containing drugs there is a similar number of compounds in which the amine-containing piece is complex (Figure 2B)[10] and compounds in which the sulfonyl piece is complex (Figure 2C).[11] Thus, we aimed to develop a method that enables the functionalization of either component of a secondary sulfonamide under mild conditions while tolerating functionality commonly found in drug-like molecules.

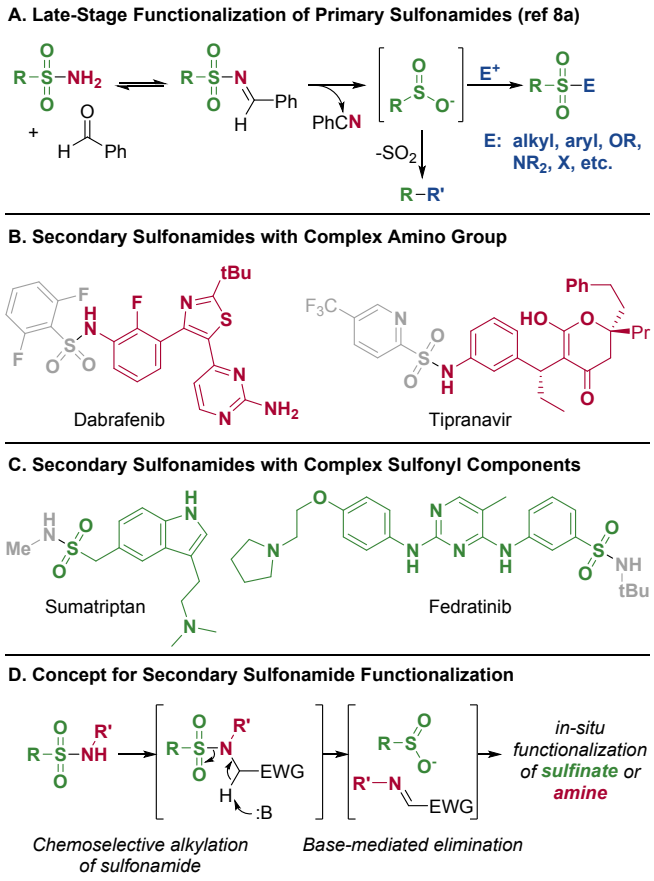


Figure 2. Late-Stage Functionalization of Sulfonamides: Inspiration and Strategy

In designing a method for the late-stage functionalization of secondary sulfonamides, we envisioned a reaction that would selectively functionalize secondary sulfonamides to generate an intermediate containing an acidic C-H bond adjacent to nitrogen. This intermediate would then react under basic conditions to liberate a sulfinate anion while at the same time generating an imine (Figure 2D). Such a reaction manifold would enable subsequent functionalization of the sulfinate using well-established chemistry, or functionalization of the amine after imine cleavage.

Initially, we investigated reactions for the chemo-selective alkylation of secondary sulfonamides with alkyl halides containing electron-withdrawing groups that would promote the subsequent elimination step. However, the use of such alkyl halides resulted in complex mixtures when we tried to apply this approach to complex, drug-like molecules (Figure 3A). Next, approaches based on the Petasis reaction were explored as a chemoselective entry to access *N*-sulfonyl phenylglycine ester intermediates.[12] While the Petasis reaction worked on simple substrates, the reaction was not general enough for a broadly useful platform in late-stage functionalization. Finally, we investigated reactions that would be chemoselective based on the acidity of the N-H bond of secondary sulfonamides. We found that Mitsunobu reactions of secondary sulfonamides with ethyl mandelate proceeded smoothly to form *N*-sulfonyl phenylglycine ester intermediates.[13] Unfortunately, the subsequent elimination was complicated due to the byproducts of the Mitsunobu Reaction. Therefore, to simplify the C-N bond forming step and avoid the hydrazine byproducts of the Mitsunobu reaction, the activated phosphonium intermediate was generated from ethyl benzoylformate and tris(dimethylamino)phosphine (Figure 3B).[14]

We found that secondary sulfonamides react rapidly and chemoselectively with the combination of ethyl benzoylformate and tris(dimethylamino)phosphine in THF at ambient temperature over 15-30 minutes to form *N*-sulfonyl phenylglycine ester interemediates. Although the phosphine reagent is moderately air and moisture sensitive, we carried out all reactions on the benchtop without any special precautions. For cleavage of the adducts, an exhaustive screen of bases revealed that reactions with *t*-butyl tetramethylguanidine (BTMG, Barton's base)[15] resulted in clean fragmentation and concomitant generation of the desired sulfinate and imine products, both of which can be re-functionalized *in-situ*. The net transformation in this cleavage process is a two-electron reduction of the N-S bond driven by the oxidation of P(III) to P(V). The ethyl benzoylformate in these reactions acts as a redox shuttle, initially undergoing reduction followed by base-mediated oxidation.

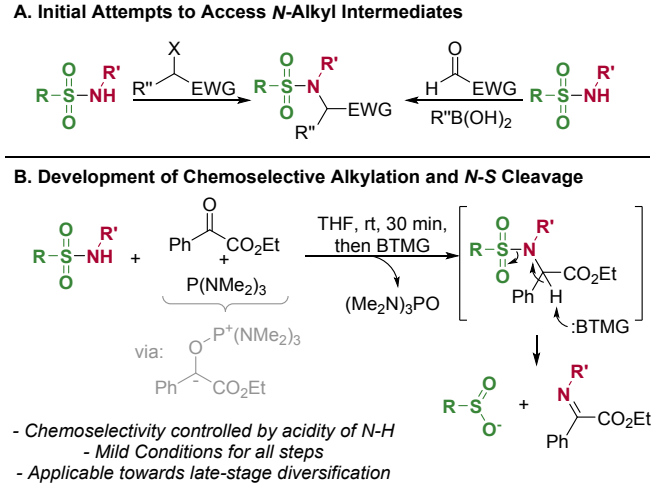
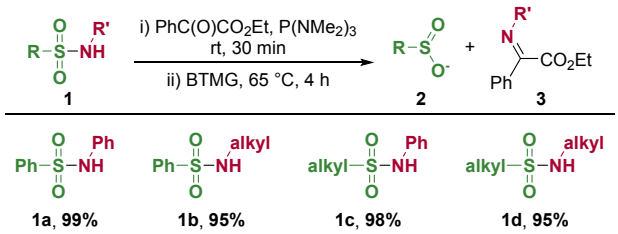


Figure 3. The development of a general platform for N-alkylation and base-mediated N-S cleavage

With conditions in hand for the chemoselective N-S cleavage of secondary sulfonamides, we carried out an initial survey of the scope with respect to the electronic properties of the sulfonamide. Four sulfonamide substrates comprising the combinations of alkyl and aryl groups on S and N were subjected to the standard reaction conditions and the conversion was analyzed on an HPLC instrument (Scheme 1). Across the four sulfonamides, high conversion to the sulfinate and imine were observed. The imines generated in the reaction were stable to HPLC analysis, and the free amine could be revealed in quantitative yield within minutes through the addition of aqueous hydroxylamine to the crude reaction mixture.

Scheme 1. Initial survey of scope for N-S cleavage with simple secondary sulfonamides

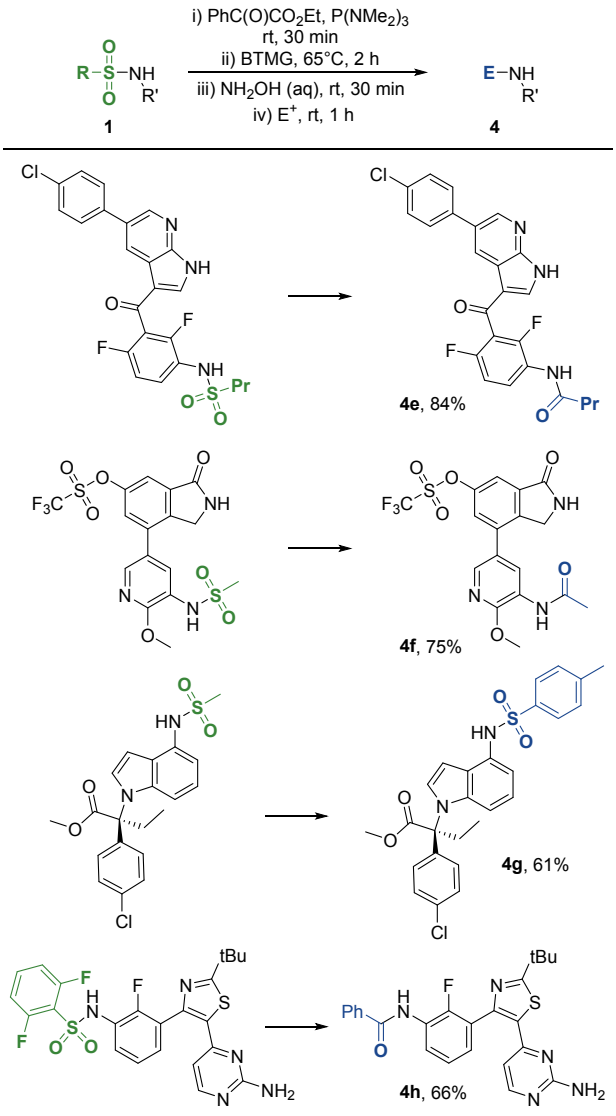


[a]Percent conversion of **1** to **2** + **3** based on HPLC area percent at 210 nm for reactions carried out on 1.0 mmol scale. Alkyl = CH_2CH_2Ph. For experimental details, see the Supporting Information.

Having validated the methodology on simple substrates, we then applied this N-S cleavage concept towards late-stage diversification. First, we carried out reactions on drug-like

compounds containing secondary sulfonamides in which the nitrogen component is complex. The standard conditions were applied to sulfonamides containing ketone, ester, triflate, halide, indole N-H, unprotected aminopyrimidine, secondary amide, and various heterocyclic functional groups. In all cases, the reductive cleavage process was chemoselective for reactions at secondary sulfonamides due to the acidity of the N-H bonds. Despite the broad generality, it should be noted that the acidity-controlled alkylation did present issues with substrates containing acidic functionality, namely carboxylic acids and electron-poor phenols. The imine generated in the reductive process was readily cleaved with aqueous hydroxylamine and the amine could be functionalized *in-situ*. As shown in Scheme 2, this sequence allows for the facile interconversion of sulfonamides and the transformation of sulfonamides to amides.

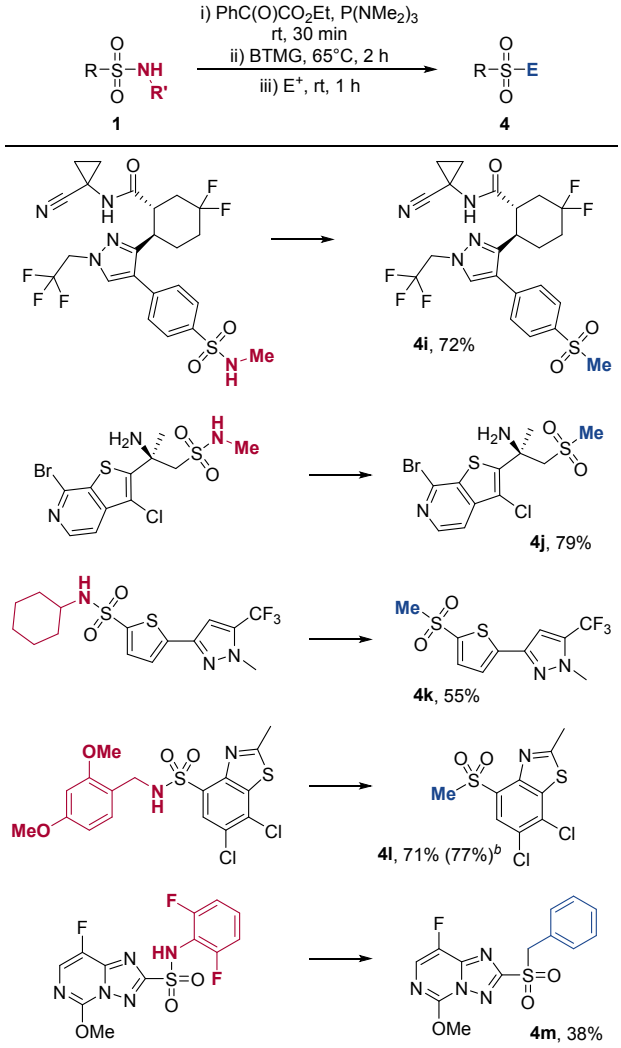
Scheme 2. Late-Stage Modification of Secondary Sulfonamides Containing Complex Nitrogen Fragments



[a]Isolated yields shown for reactions carried out with 0.5 mmol of sulfonamide substrate. For experimental details, see the Supporting Information.

Similar to the modification of the nitrogen component of secondary sulfonamides, this methodology was successfully applied to the late-stage functionalization of several secondary sulfonamides containing complex sulfonyl pieces. The resultant sulfinate species generated *in-situ* from the reductive cleavage process react with exogenous electrophiles to form a variety of S(VI) functional groups, such as sulfones, as shown in Scheme 3. The mild conditions are highlighted by the site-selective modification of sulfonamides in the presence of free amines, secondary amides, cyano groups, halides, and diverse heterocyclic functional groups.

Scheme 3. Late-Stage Modification of Secondary Sulfonamides Containing Complex Sulfonyl Fragments

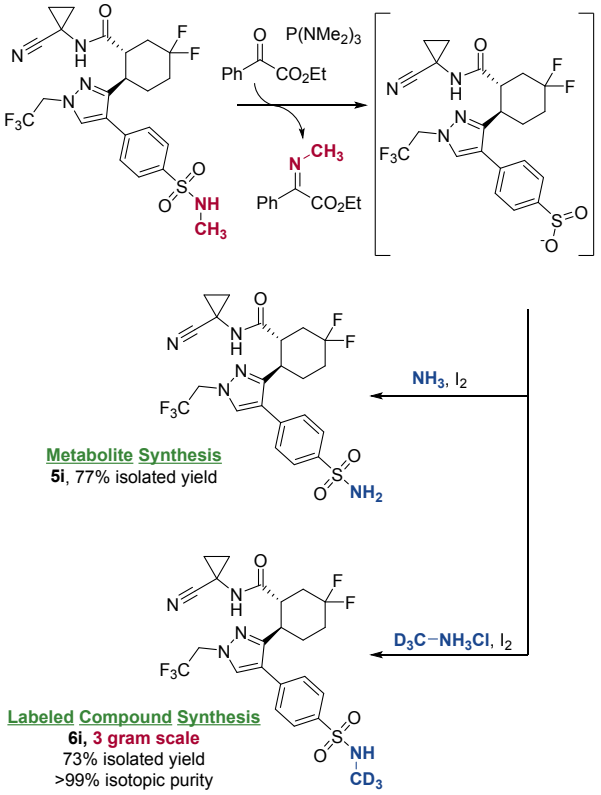


[a]Isolated yields shown for reactions carried out with 0.5 mmol of sulfonamide substrate. For experimental details, see the Supporting Information.[b]Yield in parentheses is for a separate reaction in which step iii was not carried out, and the sulfinic acid intermediate was isolated in pure form.

Lastly, we demonstrated the application of this method towards metabolite and labeled compound synthesis, both integral facets of drug discovery and development.[16] In the synthesis of metabolites or labeled compounds, the direct use of the drug molecule is generally preferred, as it is usually available and avoids long synthetic sequences. As depicted in Scheme 4, the complex *N*-methylsulfonamide was subjected to the reductive N-S cleavage, followed by treatment of the crude sulfinate mixture with either NH_4OH and iodine to preapre the des-methylated metabolite, or CD_3NH_3Cl and iodine to prepare the CD_3-labeled compound. The labeled compound was prepared in a one-pot process on 3-gram scale and led to net conversion of the CH_3 group to a CD_3 group. Notably, the methylamino group cleaved in the first step remained

sequestered as an imine and did not interfere in the reactions to reform sulfonamides.

Scheme 4. Late-Stage Metabolite Synthesis and Isotopic Labeling through N-S Cleavage and Reconstitution



[a]Isolated yields shown. For experimental details, see the Supporting Information

In summary, we have developed a general platform for the late-stage functionalization of secondary sulfonamides as part of our program on upgrading sulfonamides from terminal functional groups to synthetic handles. The exceptional functional group tolerance, use of simple reagents in air, and the ability to carry out unprecedented transformations on prevalent sulfonamide functional groups makes this a powerful tool for complex molecule functionalization.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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