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NHC-Catalyzed Deamination of Primary Sulfonamides: A Platform for Late-Stage Functionalization

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Supporting Information Placeholder

ABSTRACT: Herein we describe the development and application of a method for the mild, late-stage conversion of primary sulfonamides to several other other functional groups. These reactions occur via initial reductive deamination of sulfonamides to sulfinates via an NHC-catalyzed reaction of transiently formed *N*-sulfonylimines. The method described here is tolerant of nearly all common functional groups, as exemplified by the late-stage derivatization of several complex pharmaceutical compounds. Based on the prevalence of sulfonamide-containing drugs and building blocks, we have developed a method to enable sulfonamides to be applied as versatile synthetic handles for synthetic chemsitry.

Sulfonamides and related sulfur-based functional groups are of paramount importance in drug discovery and development. Since the first sulfa antibiotic, Prontosil, was introduced to the market in the 1930's, sulfonamides and other sulfur-containing drugs have become pervasive in medicines spanning all therapeutic areas (Figure 1).[1] In fact, a recent analysis revealed that sulfur is the 5th most common element in FDA-approved drugs, just behind the mainstays of organic chemistry: C, H, N, and O.[1] Based on the prevalence of *S*-containing drugs, methods that enable the late-stage interconversion of common sulfur functional groups will have a meaningful impact in drug discovery.[2]

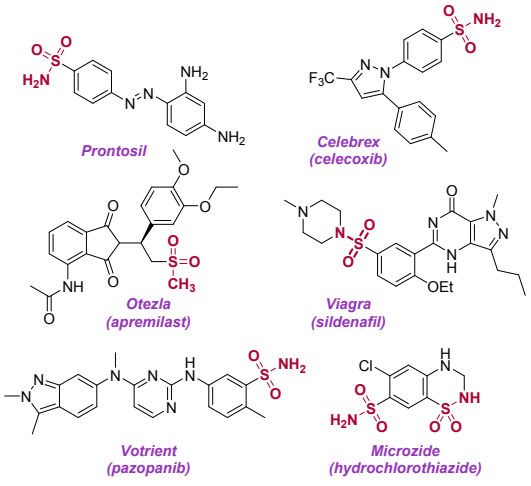
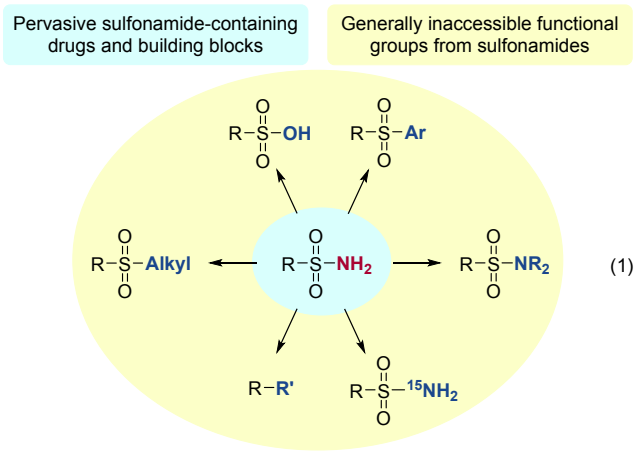


Figure 1. Representative sulfur-containing drugs

Of the many sulfur-containing drugs, nearly 30% contain a sulfonamide moiety (Figure 1).[1] As such, numerous methods have been developed to prepare sulfonamides from a wide-array of starting materials.[3] Yet, analogous methods for the conversion of sulfonamides into other functional groups, specifically in the context of complex molecule diversification, are essentially unknown. Such general methods, as exemplified in eq. 1, could have an immediate impact in the discovery of new biologically active compounds through late-stage functionalization,[4] given the prevalence of sulfonamide-containing molecules in compound libraries across pharmaceutical and agrochemical companies. *For instance, Merck's building block library contains similar numbers of sulfonamides and arylboronic acids, yet sulfonamides are almost exclusively considered to be terminal functional groups rather than synthetic handles*. To address the lack of late-stage functionalization methods for sulfonamides, we report here a general method to readily convert complex drug-like sulfonamides to a variety of common functional groups.



(1)

For the conversion of sulfonamides to other functional groups, we proposed that the most versatile method would occur via initial formation of a sulfinate salt. This proposal was based on the ease of functionalization of sulfinates via electrophilic trapping or through loss of SO_2, classes of reactions which typically occur under mild conditions.[5] To achieve this goal, we proposed that primary sulfonamides could be converted to sulfinate salts via the intermediacy of *N*-sulfonylimines that would form via condensation with aldehydes, ultimately liberating a nitrile as the stoichiometric byproduct (Figure 2).

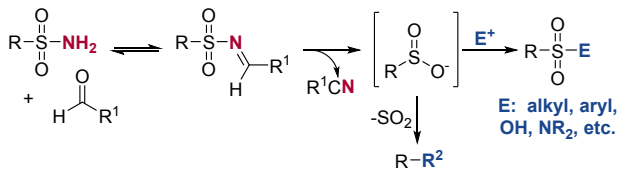


Figure 2. Strategy for the late-stage functionalization of sulfonamides

This hypothesis was tested with benzenesulfonamide as a model substrate under a multitude of reaction conditions, comprising a wide array of aldehydes, bases, and solvents (see Supporting Information). Yet, across this diverse set of reaction conditions, only trace amounts of the sulfinate product was observed (Figure 3A). In considering the elimination of the sulfinate leaving group, we hypothesized that an NHC catalyst could lower the energy barrier and facilitate the reaction (Figure 3B).[6] This proposal was largely inspired by pioneering work involving NHC-catalyzed reactions of α-reducible aldehydes that form acylazolium species (Figure 3C).[7] In the presence of benzaldehyde, a mild base (K_2CO_3), and 3 mol % of triazole-based NHC precatalyst **1,** benzenesulfonamide was converted to benzenesulfinate in quantitative yield, along with the formation of benzonitrile as the byproduct (see Supporting Information for additional details).

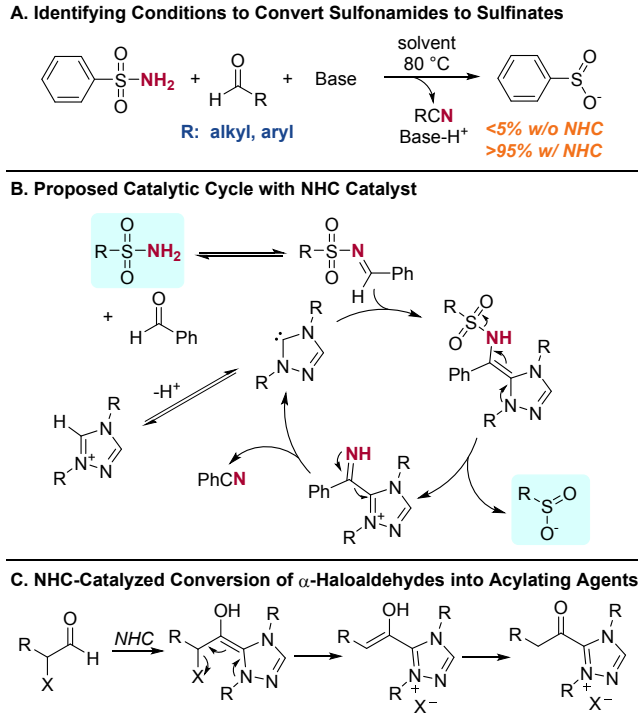
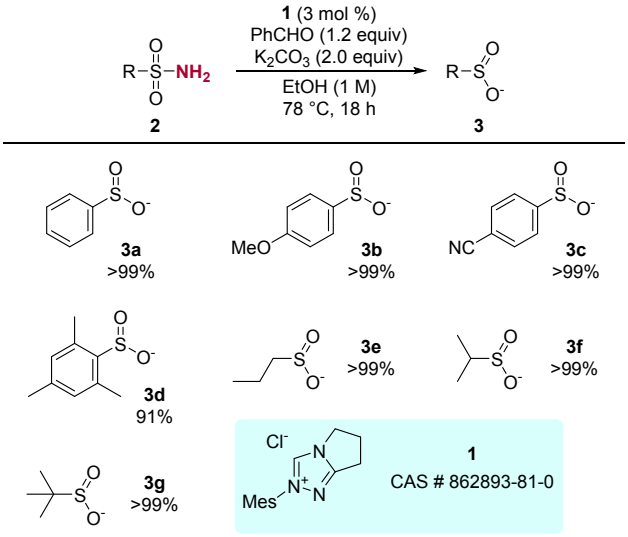


Figure 3. Discovery of a method for the functionalization of sulfonamides via NHC-catalyzed reductive N-S bond cleavage

The NHC-catalyzed deamination was investigated further, and a general set of reaction conditions were identified that could be applied to all classes of primary sulfonamides (Scheme 1). The reaction conditions involve heating a mixture of the sulfonamide substrate in the presence of a slight excess of benzaldehyde and potassium carbonate with 3 mol % of **1** in ethanol. During the course of the reaction, a portion of the benzaldehyde undergoes benzoin condensation.[8] However, as the benzoin reaction is reversible, this side process is of little consequence. Of particular practical importance is that the reactions can be set up on the benchtop without the exclusion of air or moisture, are run at high concentrations (1 M in EtOH), use only simple reagents, and form innocuous byproducts.

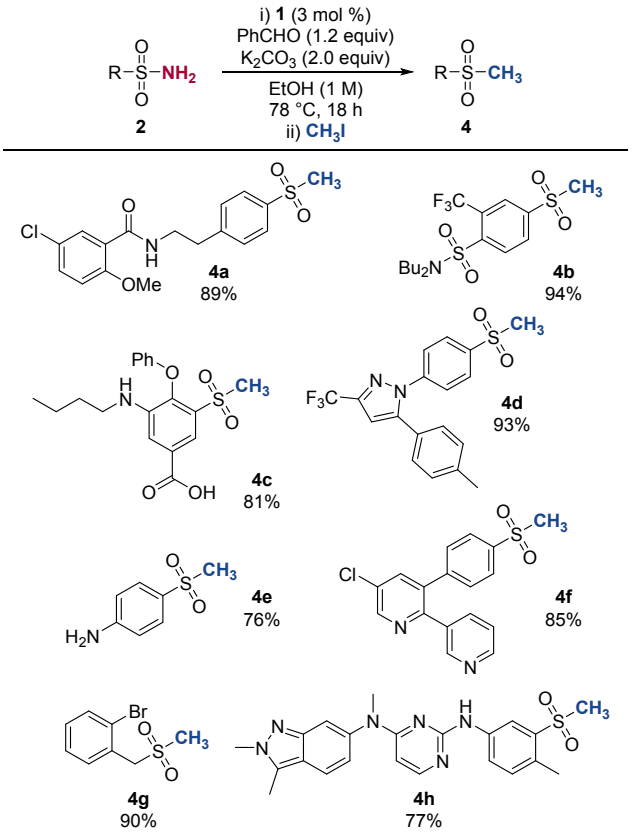
Scheme 1. Establishing substrate scope with respect to steric and electronic properties of sulfonamide **2**



[a]Conversion of sulfonamide to sulfinate based on UPLC area percent at 210 nm or ^{1}H NMR spectroscopy. Percent conversion compared within 2% of the assay yields of benzonitrile with a calibrated UPLC instrument.

Having validated the deamination reaction on aromatic and aliphatic sulfonamides with varying electronic and steric properties, we turned our attention to the functionalization of drug-like molecules, along with enabling the *in situ* functionalization of the sulfinate salts. Conditions were identified that enable the crude mixtures from the deamination reactions to be directly converted to methyl sulfones by treatment with methyl iodide (Scheme 2), or to sulfonic acids via oxidation with H_2O_2 (Scheme 3). The deamination step tolerates carboxylic acids, free amines, basic heterocycles, halides, non-primary sulfonamides, and several other common functional groups. While primary and secondary amino groups can reversibly condense with benzaldehyde, such imines do not react further, ultimately resulting in exclusive selectivity for the functionalization of primary sulfonamides in the presence of other amino functionality. Thus, the high selectivity for functionalizing primary sulfonamides underscores the value of this approach for predictable, high-yielding late-stage diversification.[4]

Scheme 2. Conversion of complex sulfonamides to methyl sulfones[a]

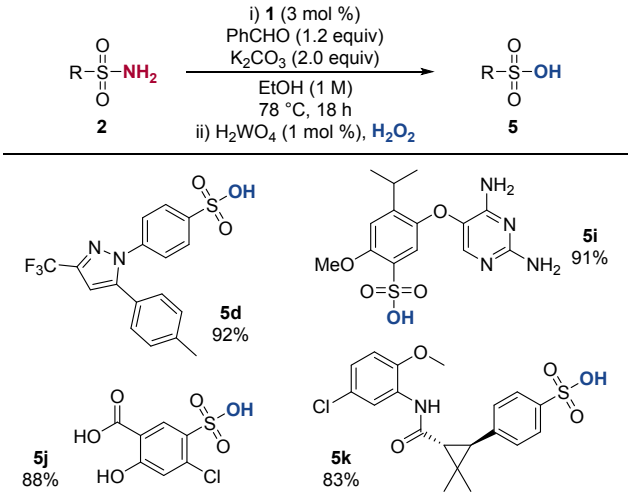


[a]Yields shown for reactions performed on 1.0 mmol scale, sulfinate intermediate not isolated. For experimental details, see the Supporting Information.

High selectivity was also observed during the conversion of the sulfinate intermediates to methyl sulfones. This observation is due to the fact that methyl iodide reacts more rapidly with sulfinate salts than with other nucleophilic groups.[9] Similarly, selective oxidation of the sulfinates to sulfonic acids could be carried out with excellent functional group tolerance (Scheme 3). In these cases, the pure sulfonic acid product could be isolated via crystallization by simply adding water and aqueous HCl.

While most of the sulfonamide substrates used throughout this work are widely studied drugs, many of the sulfone and sulfonic acid products prepared are novel. This is significant, as it serves to highlight the fact that sulfonamides have traditionally been synthetic dead-ends, and calls attention to the difficulty and lack of structure-activity relationship (SAR) studies at S(VI).

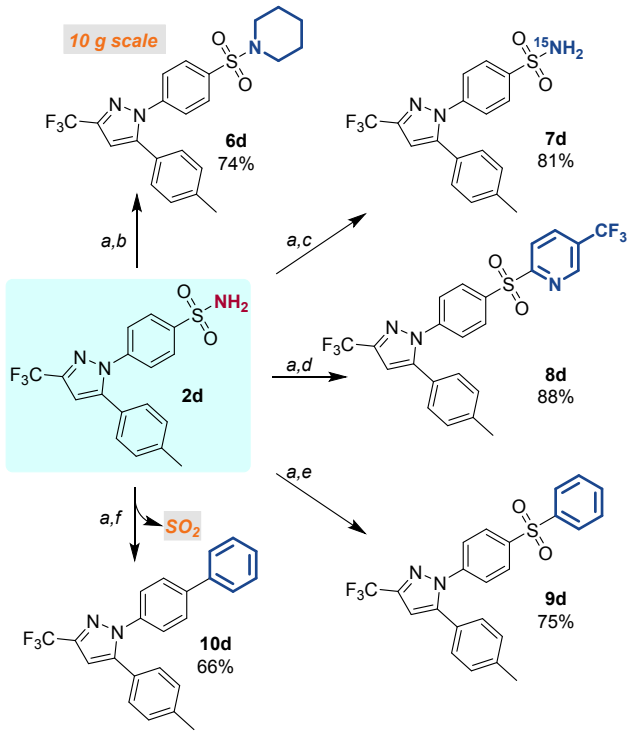
Scheme 3. Conversion of complex sulfonamides to sulfonic acids[a]



[a]Yields shown for reactions performed on 1.0 mmol scale, sulfinate intermediate not isolated. For experimental details, see the Supporting Information.

To further validate the utility of this late-stage functionalization method, we demonstrated that the crude sulfinate salts generated *in situ* could be diverted to several different functional groups (Scheme 4). Sulfonamide deamination followed by treatment of the sulfinate with I_2 in the presence of an amine offers a convenient method to interconvert sulfonamides.[10a,b] Beyond being a useful approach to SAR studies on small scale, this deamination/amination sequence was readily scaled to prepare decagram quantities of compound **6d**. Similarly, using $^{15}NH_4OH$ as the amine source enables rapid access to ^{15}N-labeled sulfonamide drugs directly from the ^{14}N parent molecule. The ability to selectively and completely exchange ^{14}N for ^{15}N on a drug-like molecule without resorting to multi-step syntheses is valuable for labeled compound synthesis to support pharmacological studies in drug discovery.[11]

Scheme 4. Late-stage diversification of Celebrex (celecoxib)[a]



[a]For experimental details, see the Supporting Information. Reaction conditions: (a) standard deamination conditions; (b) piperidine, I_2; (c) $^{15}NH_4OH$, I_2; (d) 2-chloro-5-trifluoromethylpyridine; (e) Xantphos/Pd, PhI; (f) XPhos/Pd, PhOTf.

The sulfinates generated *in situ*, as soft, anionic nucleophiles, can react with various alkyl electrophiles beyond methyl iodide, as well as electron deficient aryl halides in S_NAr reactions (Scheme 4).[9,10c] Furthermore, the crude sulfinate salts can engage in cross-couplings with aryl electrophiles to provide aryl sulfones.[10d] Finally, the sulfinates can act as aryl nucleophiles, analogous to arylboronic acids, in cross-coupling reactions to form biaryl compounds through loss of SO_2.[12] The latter reaction is particularly intriguing, as primary sulfonamides can now be thought of as precursors to aryl nucleophiles for cross-coupling. Overall, this diverse set of reactions showcases the remarkable breadth and utility of the deamination/sulfinate functionalization strategy reported here.

In conclusion, we have developed a general, reliable, and user-friendly approach to the late-stage functionalization of sulfonamides. These reactions occur with exceptional scope in regards to the steric and electronic properties of the sulfonamide, as well as the functionality contained within the molecule. The methods outlined here have been exemplified on several complex drug and drug-like sulfonamides and have been used to prepare novel derivatives that would otherwise require lengthy, *de novo* syntheses. Moreover, the value of this approach will continue to grow with the development of new methods for sulfinate functionalization. Having already witnessed a rapid uptake of this chemistry amongst our colleagues across drug discovery and development, we are confident that the work described here will have an immediate and tangible impact across synthetic chemistry, as primary sulfonamides can now be applied as versatile synthetic handles.

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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