S-Trideuteromethylation of Sulfenamides: Redox-Neutral Synthesis of Trideuteromethyl Sulfilimines

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This study presents an innovative approach to the synthesis of trideuteriosulfilimines, a class of sulfur(IV)-derived compounds with significant potential in organic synthesis and medicinal chemistry. Our research focused on the modification of sulfenamides and the introduction of a deuterated methyl group, employing an electrophilic trideuteromethylating reagent in an anionic reaction. The method demonstrated broad applicability across various sulfenamides derived from different amides, alkyl amides, and aryl amides, as well as thiol-derived sulfenamides. The reactions generally resulted in excellent yields and high deuteration rates. The study also explored the reaction mechanism, confirming that the process does not proceed via a free radical pathway. This research contributes to the development of efficient and reliable methods for the synthesis of sulfilimines, which are valuable building blocks in organic synthesis and medicinal chemistry.

The field of pharmaceutical research has seen significant advancements with the introduction of deuterated reagents.[1] Deuterium, a heavier isotope of hydrogen, can form stronger bonds within a molecule, potentially leading to improved pharmacokinetics, enhanced stability, and reduced toxicity.[2] Austedo (deutetrabenazine) serves as a prime example of a deuterated drug that has capitalized on these properties. Austedo, a deuterated version of tetrabenazine, is used for the treatment of movement disorders. The introduction of deuterium has improved its metabolic stability and efficacy, leading to a more favorable safety and tolerability profile.[2a, 3] Another promising candidate is AVP-786, a combination of deudextromethorphan and an ultra-low dose of quinidine, which is currently being investigated in phase 3 clinical trials for multiple neurological and psychiatric disorders. The deuterium in AVP-786 enhances the bond strength, potentially leading to a longer duration of action and improved therapeutic efficacy.[4]

Building on these examples, the introduction of a deuterated methyl group into a molecule, a process known as trideuteromethylation, has become a focal point in deuterium

chemistry. This process can influence the behavior of a drug, including its activity, distribution, metabolism, and excretion.[5] Moreover, the use of deuterium can reduce the toxicity of certain drugs, as the stronger C-D bonds (carbon-deuterium) are less likely to undergo metabolic reactions that can lead to the formation of toxic metabolites.[6] Various reagents and methods for trideuteromethylation are being explored, each with their own advantages and limitations, contributing to the development of more effective and safer medications.[7]

Sulfilimines, are sulfur(IV) compounds that are integral to organic synthesis and medicinal chemistry due to their unique sulfur-to-nitrogen bond. They serve as versatile intermediates in a variety of chemical reactions and are key in the synthesis of diverse N-heterocycles from alkenes, a crucial component in many pharmaceutical compounds (Fig 1).[8] Their structural similarity to sulfoxides, coupled with an additional site for derivatization, has led to their use as functional groups in bioactive compounds. The biological significance of sulfilimine bonds was highlighted when they were found in collagen IV networks, a major component of basement membranes across various species[9]. Furthermore, sulfilimines have potential applications in the development of pesticides and as crosslinkers in polymer chemistry.[8]

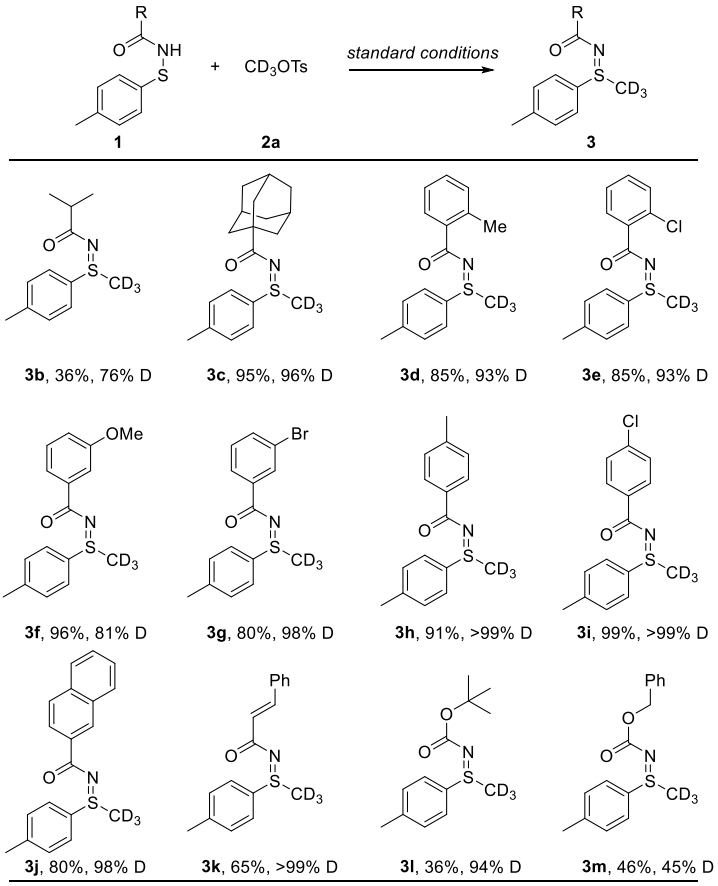
Cutting-edge synthetic strategies have been honed to focus on the modification of sulfenamides, thereby enabling the creation of sulfilimines with diverse backbones. This field has seen significant contributions from several research groups, including those led by Ehrman,[10] Li,[11] and myself,[12] among others.[13] Notably, our research group introduced the concept of 'sulfinimidoyl anion', which facilitated the realization of redox-neutral S-alkylation and S-arylation reactions of sulfenamides. In this context, we propose that S-trideuteromethylation of sulfenamides could be achieved using an appropriate electrophilic trideuteromethylating reagent in conjunction with an anionic reaction. This approach could potentially lead to the successful construction of trideuteriosulfilimines.

Initially, we used 1a as a model substrate and CD3OTs (2a), a cost-effective and easily prepared trideuteromethylation reagent (Table S1, see the Supporting Information for more details). From our previous studies, we knew that the choice of base significantly influences reactivity, so we focused our screening on this aspect. Unfortunately, the organic base NEt3 did not facilitate the reaction. We then tested slightly stronger inorganic bases, including KHCO3, NaHCO3, and K2CO3, but were disappointed to find no product formation after one hour of reaction. Surprisingly, even with the more basic Cs2CO3, only trace amounts of the product were observed.

We then opted for NaH, a stronger base, and were pleased to find 89% of the trideuteromethylated product 3a after one hour of reaction. However, reactions involving NaH often require more stringent conditions, such as anhydrous environments. For operational convenience, we chose tBuONa. The results were encouraging: after one hour of reaction, we obtained 96% of the product 3a, and extending the reaction time to 1.5 hours brought the yield close to equivalence. The deuteration rate remained above 99% without decay.

We then experimented with a different trideuteromethylation reagent, 2b, which is also easy

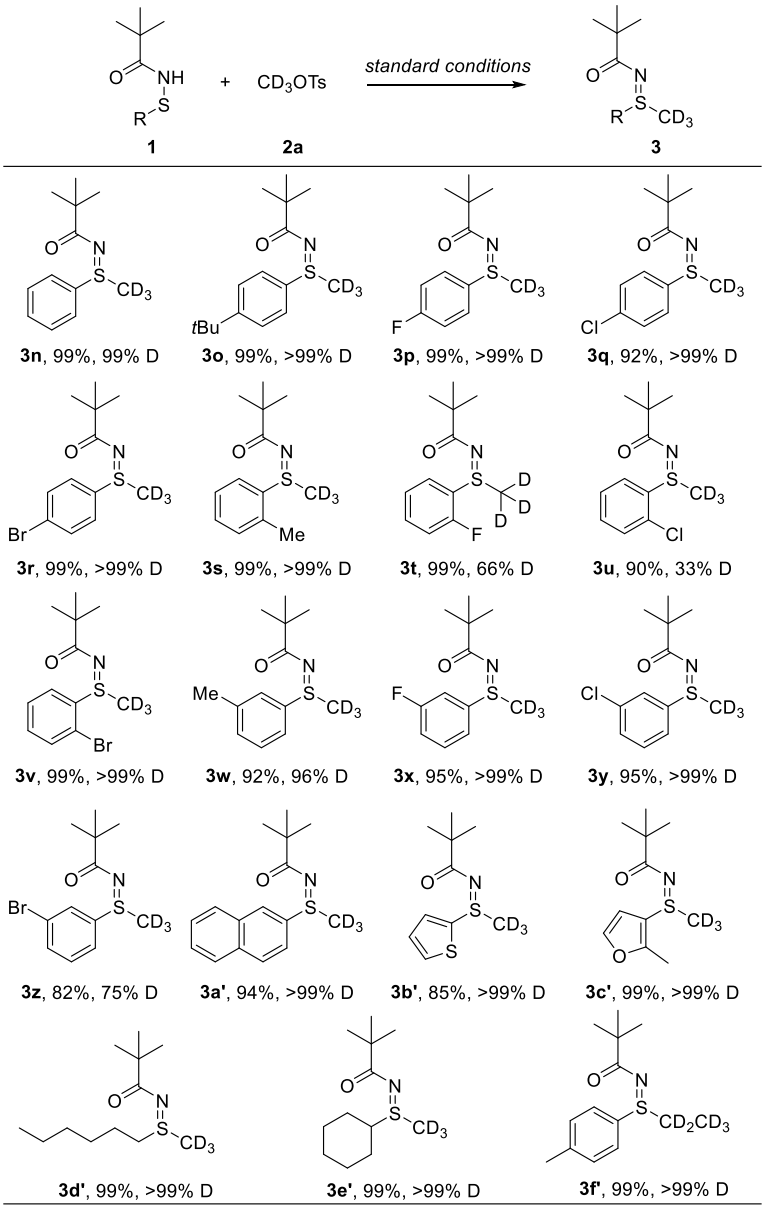
and inexpensive to prepare. However, only trace amounts of the product formed after 1.5 hours of reaction. Extending the reaction time to 12 hours yielded 88% of 3a, with a deuterium rate consistently above 99%.



Upon establishing the optimal reaction conditions, we proceeded to investigate the general applicability of various sulfenamides derived from different amides, including alkyl amides and aryl amides, under standard conditions. Among the substrates tested, the sulfenamide derived from isobutyramide yielded the corresponding target product with a 36% yield and a trideuterium incorporation rate of 79%. Meanwhile, the sulfenamide derived from adamantane carboxamide yielded the target product with a significantly higher yield of 95% and a trideuterium incorporation rate of 96%. We subsequently explored sulfenamides derived from arylamides. Generally, these sulfenamides yielded excellent results in terms of both yield and deuteration rates under standard conditions. However, when chlorine was introduced at the ortho position or bromine at the meta position on the amide benzene ring, the yields decreased to 85% and 80% respectively, with corresponding deuteration rates of 93% and 98%. Despite this, the introduction of methyl groups and electron-withdrawing chlorines at the para-position still resulted in excellent yields, with the deuteration rate consistently above 99%. When a naphthalene ring was used, the yield varied significantly, reaching 80%, but the deuterium substitution rate remained largely unaffected.

To our delight, cinnamamides, substrates containing alkenes, and carbamate-derived sulfenamides all smoothly produced the target products under standard conditions, albeit with moderate yields. The lower yield for the reaction generating 3k could be attributed to

poor reactivity, while the reactions generating 3l and 3m were likely impacted by the poor stability of the substrate under alkaline conditions.

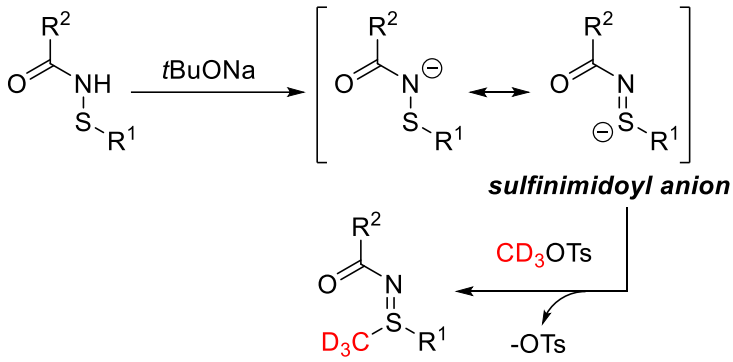


Buoyed by the aforementioned results, we proceeded to investigate the tolerance of various sulfenamides derived from thiols (specifically thiophenols) under standard conditions. Generally, sulfenamides derived from thiophenols with different substituents and positions successfully yielded the corresponding target products with excellent yields and deuteration rates above 96% under optimal reaction conditions. However, when fluorine and chlorine groups were at the ortho position, the deuteration rates dropped to 66% and 33% respectively. This could be attributed to a combination of ortho electron effects and steric hindrance, as no reduction in the deuteration rate was observed in reactions involving para-group substrates.

Interestingly, when bromine was at the meta position, the deuteration rate of the

corresponding product was only 75%. This was puzzling as no decrease in the deuteration rate was observed for F and Cl, which are stronger electron-withdrawing groups. The reaction system we developed was also applicable to naphthalene rings and aromatic heterocycles, yielding 85%-99% with a deuteration rate above 99%. To our delight, sulfenamides derived from aliphatic thiols successfully yielded the corresponding target products with excellent yield and deuteration rates under optimal reaction conditions. Lastly, we investigated the universality of the conditions using the selected deuterated ethylating reagent, and the results were very satisfactory, yielding deuterated ethyl substituted sulfilimines.

Finally, to demonstrate the scalability of our reaction, we conducted a scale-up experiment. When the reaction scale was increased to 3 mmol under standard conditions, we obtained 90% of the target product after 1.5 hours of reaction, with the deuteration rate remaining unaffected. We found that the resulting product 3a could be readily oxidized in the presence of an Ru(II) catalyst, yielding the hexavalent product 5 with a yield of 95%. However, the deuteration rate dropped to 76%. Furthermore, removal of the N-pivaloyl group using basic hydrolytic conditions produced an NH-free product 6 in a yield of 84%. This provides an easily modifiable group for the development of novel sulfilimines for drug discovery purposes. However, disappointingly, no deuteration was observed after hydrolysis. Therefore, it is necessary to continue research on this condition and develop a new deprotection group method that does not compromise the deuteration rate.



We embarked on a preliminary investigation of the reaction mechanism through meticulously controlled experiments. The incorporation of free radical scavengers, namely TEMPO and BHT, into the optimal reaction conditions did not precipitate a decrease in yield. This observation substantiates the assertion that the reaction does not transpire via a free radical pathway. Drawing from these control experiments and the wealth of knowledge accumulated from our group's prior research endeavors,[12] we proposed a plausible reaction mechanism. Initially, the sulfenamide undergoes deprotonation under basic conditions, engendering a divalent nitrogen-centered anion. This anion subsequently undergoes resonance to form the pivotal intermediate, the sulfinimidoyl anion, which serves as an exceptional nucleophile. This anion then orchestrates an attack on the trideuteromethylating reagent (CD3OTs), displacing the leaving group OTs-, and

successfully culminates in the synthesis of the target compound.

Our research has made significant strides in the synthesis of trideuteriosulfilimines, a unique class of sulfur(IV)-derived compounds with diverse applications in organic synthesis and medicinal chemistry. We focused on modifying sulfenamides and introducing a deuterated methyl group, using a suitable electrophilic trideuteromethylating reagent in an anionic reaction. The method proved to be widely applicable to various sulfenamides derived from different amides, alkyl amides, and aryl amides, as well as thiol-derived sulfenamides. The reactions typically yielded excellent results and high deuteration rates. We also delved into the reaction mechanism, confirming that it does not involve a free radical pathway. This work paves the way for more efficient and reliable methods for synthesizing sulfilimines, which are crucial in organic synthesis and medicinal chemistry.

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