Sulfondiimidamides unlocked as new S(VI) hubs for synthesis and drug discovery

Nicholas Ball

Follow this and additional works at: https://scholarship.claremont.edu/pomona_fac_pub

Part of the Organic Chemistry Commons

Recommended Citation
Ball, Nicholas, "Sulfondiimidamides unlocked as new S(VI) hubs for synthesis and drug discovery" (2022). Pomona Faculty Publications and Research. 490.
https://scholarship.claremont.edu/pomona_fac_pub/490

This Review is brought to you for free and open access by the Pomona Faculty Scholarship at Scholarship @ Claremont. It has been accepted for inclusion in Pomona Faculty Publications and Research by an authorized administrator of Scholarship @ Claremont. For more information, please contact scholarship@cuc.claremont.edu.
Sulfondiimidamides unlocked as new S(VI) hubs for synthesis and drug discovery

Nicholas D. Ball¹,*
¹Department of Chemistry, Pomona College, Claremont, CA, USA

Abstract

Despite their promise as drug targets, access to nitrogen-rich S(VI) compounds has been a significant synthetic challenge. In this issue of Chem, Zhang and Willis explore a new class of S(VI) compounds—sulfondiimidamides—providing robust strategies toward their synthesis, derivation, and promise as new sulfonamide bioisosteres.

Organosulfur compounds have served as powerful tools in various scientific applications ranging from agrochemicals to materials. Since the discovery of sulfonamides (RSO₂NR₂) in the early 20th century, S(VI)-based “sulfa” drugs have been pivotal in medicinal breakthroughs from antibiotics to anticonvulsants. Nitrogen-based S(VI) compounds represent nearly 25% of all sulfur-based FDA-approved drugs. Of this class of sulfur-based drugs, sulfonamides represent the vast majority. In contrast, more complex nitrogen-based S(VI) compounds that diverge from the sulfonamide manifold, such as sulfamates and sulfamides, represent only around 2% of sulfur-based FDA-approved drugs.¹ Together, their shared S=O and S–N bond architecture manifests in drug compounds with similar physicochemical profiles, metabolic and chemical stability, heteroatom-rich composition, and favorable bioactivity profiles.² The next frontier of S(VI) compounds is the exchange of the oxygen atoms in sulfonamides for nitrogen. Adding more nitrogen groups enables further functionalization of the S(VI) core, opening a new chemical space for bioisosteres of sulfonamides.³ Recent work by Arvidsson and co-workers³ and Stockman, Lückling, and colleagues⁴ showed promise for this strategy, where the replacement of a S=O bond in sulfonamides with a sulfonymidoyl S=NR bond resulted in sulfonimidamides incorporating new functionalizable N-imidic groups. However, further addition of nitrogen atoms toward more nitrogen-rich derivatives of sulfonamides has been hindered by the dearth of facile synthetic tools for accessing them.⁵

In this issue of Chem, Zhang and Willis⁶ have entered a novel chemical space in the synthesis and derivatization of a new class of nitrogenous S(VI) compounds: sulfondiimidamides.⁵ Their strategy centers on incorporating two different imidoyl groups, resulting in unsymmetrical sulfondiimidamides. This approach expands the number of nitrogen sites available for functionalization. As a result, it enables broader S(VI)
structural diversity, unlocking the potential of sulfoniimidamides as valuable hubs for
drug design and discovery. *En route* to sulfoniimidamides, Willis and co-workers’ strategy
centers around the synthesis of sulfoniimidoyl fluorides followed by sulfur-fluoride
exchange (SuFEx) with amines. Notably, applying S(VI) fluorides in organic synthesis has
experienced exponential growth. Pi donation from the fluorine atom to sulfur attenuates the
electrophilicity of the sulfur atom and renders the sulfur(VI) fluoride more stable than the
chlorinated analogs. As a result, the installation of fluorine in S(VI) organic compounds
introduces a functional group that is hydrolytically stable, is resistant to reduction and
oxidation chemistry, and reacts selectively at the sulfur atom. These properties are helpful
for the generation of bench-stable libraries of sulfur(VI) precursors that are readily available
for synthetic transformations.

Inspired by their previous work on synthesizing sulfoniimines, Zhang and Willis
employed N-trimethylsilyl-t-octyl sulfinylamine and Grignard or organolithium reagents
to first access *in situ* sulfinamide and then performed a N-nosyl (Ns) protection to form
the unsymmetrical N-Ns N-t-octyl sulfinamidines in good yield. Sulfinamidines in the
presence of NaH and electrophilic fluorinating reagent N-fluorobenzenesulfonimide (NFSI)
generated a broad set of alkyl, alkenyl, and aryl/heteroaryl sulfoniimidoyl fluorides (Figure
1A). There are essential items for consideration in this synthesis. First, sulfinylamines and
t-octyl-protected sulfinamidines could be susceptible to SO₂ formation via hydrolysis, so
the authors advised avoiding water and prolonged storage at room temperature. Similarly,
t-octyl protected primary sulfinamidines are sensitive to heat and moisture and are used
in their crude form after nosylation. Finally, converting sulfinamides to sulfoniimidoyl
fluorides involves allowing the crude material to sit for 1–8 days—depending on the
molecule—to allow for isomerization of the N-fluorinated product to the S-fluorinated
product. Nevertheless, the authors note that the sulfoniimidoyl fluorides are isolable and
stable.

With sulfoniimidoyl fluorides in hand, Zhang and Willis used Lewis acidic calcium
bistriflimide—Ca(NTf₂)₂—to affect SuFEx with a wide range of secondary amines to
make sulfoniimidamides. Demonstrating the utility of the chemistry in drug development,
they also synthesized sulfoniimidamide-based derivatives of amoxapine, clopidogrel,
risperidone, and others that have applications ranging from antipsychotics to treating
Parkinson’s disease (Figure 1B). SuFEx using Ca(NTf₂)₂ with primary amines proved
challenging because of the suspected catalyst deactivation. As a workaround, imidazole-
based sulfoniimidamides (5) were first synthesized with Ca(NTf₂)₂, sulfoniimidoyl
fluoride, and imidazole. Next, the imidazole moiety was converted to a better leaving group
via methylation with MeOTf to form a sulfoniimidamidium salt. Subsequent SuFEx with
primary amines resulted in sulfoniimidamides in good to excellent yields (Figure 1B). This
strategy was also successful in adding azoles and amino heterocycles to their corresponding
sulfoniimidamides.

The key feature of this work is the ability to utilize the unsymmetrical nature of the
sulfoniimidamides to incorporate structural diversity at the S(VI) core via selective
transformations at the nitrogen atoms. The first example demonstrated the derivatization
of the amino group (NH₂) of sulfoniimidamide 6. Under the appropriate conditions, the
addition of acyl chloride or isocyanate readily formed an amide or urea, respectively. Taking advantage of the unsymmetric nature of the differently protected imidic groups of sulfondiimidamide 7, trifluoroacetic acid (TFA) deprotection of the N-t-octyl imidic moiety allowed for the generation of a free NH imidic group. NH-imidic sulfondiimidamide could then undergo cyanation, sulfonylation, acylation, isocyanation, and subsequent deprotection of the N-nosyl imine, yielding functionalized unsymmetric sulfondiimidamides. Observing that imidic N-cyano moieties are found in several bioactive molecules, Zhang and Willis next utilized the free imido group of cyanated sulfondiimidamide 8 toward the addition of SCF₃, aryl, carbamate, propargyl, and benzyl groups (Figure 1C). These transformations exhibited the robustness of the sulfondiimidamide core to challenging reaction conditions, including metal catalysis, oxidation, and a strong base.

To exhibit the potential of sulfondiimidamides more directly in drug discovery, the authors next sought to build upon the demonstrated success of N–CN-substituted sulfoximines as COX-2 inhibitors by synthesizing N–CN sulfondiimidamide derivatives of celecoxib.¹⁰

Utilizing the chemistries above toward sulfondiimidamides, they synthesized both mono N–CN and bis(N–CN) sulfondiimidamides of celecoxib by using Ca(NTf₂)₂-mediated SuFEx, sequential deprotections, and cyanations. Calculations on the SwissADME platform demonstrated that, compared with the original compound, both sulfondiimidamide derivatives of celecoxib have promising physiological properties (Figure 1C).

In summary, this work by Zhang and Willis opens long-elusive avenues toward nitrogen-rich bioisosteres of sulfonamides. The three-stage approach—sulfonamide generation, transformation to sulfonimidoyl fluoride, and then SuFEx toward unsymmetrical sulfondiimidamides—introduces a new class of S(VI) compounds that are highly functionalizable and shows promise for drug discovery. Future applications could tap into the chiral nature of the sulfur center, which might have additional potential in catalysis, synthesis, chemical biology, and beyond.

References


Figure 1.
Synthesis and transformations of sulfondiimidamines