

Forum

Crafting chemical space
with sulfur functional
groupsZe-Xin Zhang¹ and
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Two synthetic routes to sulfondiimidamides have recently been reported. The ability to prepare and manipulate sulfondiimidamides, which are the double aza-analogs of sulfonamides, in an efficient and predictable way, opens new possibilities for exploring chemical space.

A functional group is an arrangement of atoms that defines the key topology and reactivity of a molecule. The ability to modify these two parameters in useful and predictive ways is the foundation of synthetic organic chemistry and accounts for the wide-ranging applications enjoyed by organic molecules. New reactivity can lead to the development of unknown reactions and the making or breaking of new bonds. New topology can provide unique structures, which by definition will be novel molecules. Combining new structural motifs with reactions that allow the modification of these arrangements are key activities that allow medicinal- and agro-chemists to explore new areas of chemical space and, in doing so, search for unique bioactive molecules [1]. Crucially, new chemical space correlates with new, composition of matter derived, intellectual property. Defining a new functional group and establishing the intrinsic properties and reactivity profile of these, by definition, novel molecules, is a rare occurrence. In 2022, the Willis laboratory reported a general synthesis of sulfondiimidamides, which are the double-aza-derivatives of sulfonamides (Figure 1A) [2]. This report showed for the first time that molecules featuring this essentially unknown functional

group can be prepared in a convergent manner from readily available components, that they are chemically stable, and that they are amenable to synthetic manipulation. In reporting a practical synthetic method to sulfondiimidamides, together with the associated tools needed to allow appropriate modification, a new building block has been delivered to medicinal- and agro-chemists.

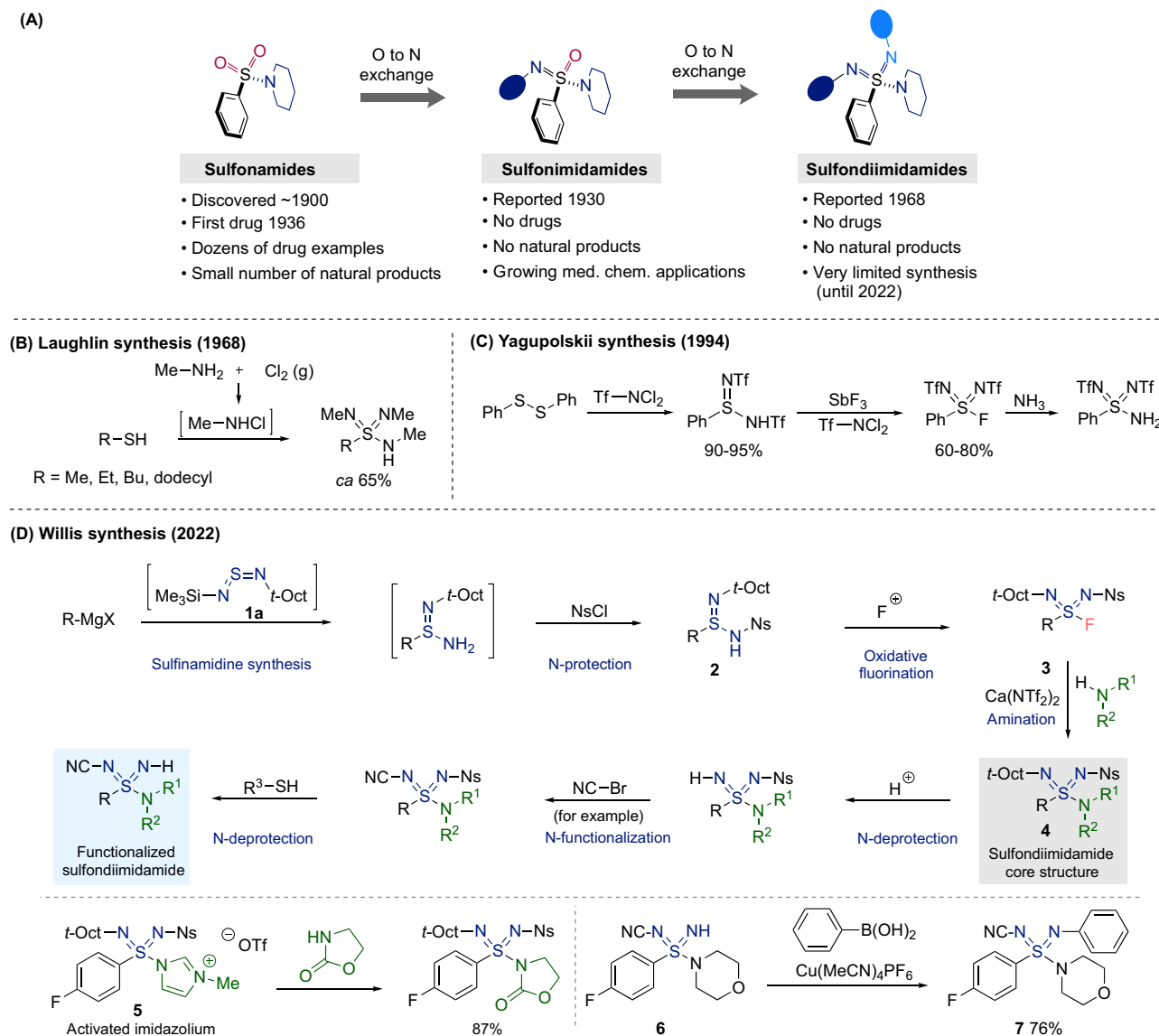
Sulfonamides have a long history in organic chemistry, dating back to the early 1900s, with the first biologically important examples, the ‘sulfa drugs’, being described in the 1930s. Since then, sulfonamide groups have featured on >100 marketed pharmaceuticals used to treat a broad range of indications [3]. It is interesting to note that despite the prevalence of sulfonamides in pharmaceuticals, and similarly in agrochemicals, there are only a handful of natural products that feature this motif [4]. The first example of a mono-aza analog of a sulfonamide, called a sulfonimidamide, can be traced back to the 1930s, although they have only emerged as common functional groups over the last 20 years. Although a sulfonimidamide is yet to appear in a marketed drug, this group is now common in the medicinal chemistry patent literature, covering a range of disease areas. This increase in the use of sulfonimidamides reflects the advances that have been made in synthetic methods towards these groups [5].

Now, 90 years since sulfonamides and sulfonimidamides were reported, sulfondiimidamides are established as viable functional groups for use in discovery chemistry. There are two existing methods to sulfondiimidamides, dating from 1968 and 1994 [6–8], but both of these approaches use unattractive reagents and prepare a small number of structurally limited examples. Laughlin reported the first synthesis of a sulfondiimidamide in 1968 [6]. The route starts with alkyl thiols, which are treated with an excess of the hazardous reagent methylchloramine,

itself generated from methylamine and chlorine gas, to provide fully N-methylated sulfondiimidamides (Figure 1B). The authors note the instability of these electron-rich examples. In 1994, the Yagupolskii group reported the preparation of four N,N-ditriflyl sulfondiimidamides [7]. Their multistep approach commenced by reacting disulfides with dichlorotrifluoromethanesulfonamide to provide sulfinamidine intermediates, via initially formed sulfondiimidoyl chlorides. The sulfinamidines were then again chlorinated, before antimony trifluoride generated the corresponding sulfondiimidoyl fluorides (Figure 1C). Finally, treatment with ammonia delivered the targeted sulfondiimidamides. List has recently shown that fluorination can also be achieved using Selectfluor [8]. Only N,N-ditriflyl derivatives were prepared using both sets of conditions. The unattractive reagents and limited structural diversity that can be achieved with these routes means that they are not attractive for use in discovery chemistry.

The initial 2022 route reported by the Willis laboratory is shown in Figure 1D and uses organometallic reagents, amines, and a sulfurdiimide reagent as the starting materials. The chemistry commences with the addition of organometallic reagents to unsymmetrical sulfurdiimide (**1a**), followed by N-nosyl-protection, providing sulfinamidines (**2**). Oxidative fluorination then delivers the key sulfondiimidoyl fluorides (**3**), which are converted to the sulfondiimidamide core (**4**) by treatment with an amine in the presence of calcium triflimide. An activated imidazolium intermediate (**5**) could also be prepared and allowed a more diverse range of N-nucleophiles to be used. With the key structure established, the authors were able to show that each imidic N-atom could be selectively manipulated, allowing the introduction of a selection of medicinal chemistry-relevant substituents; an example N-arylation (**6** → **7**) is shown.

Although this first synthesis from the Willis laboratory established the viability of



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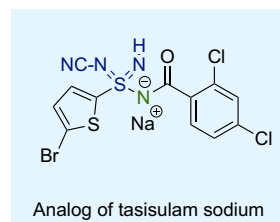
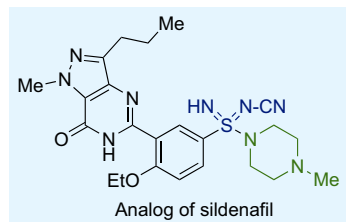
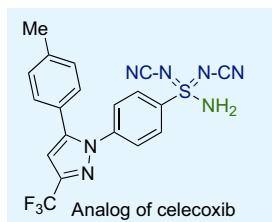
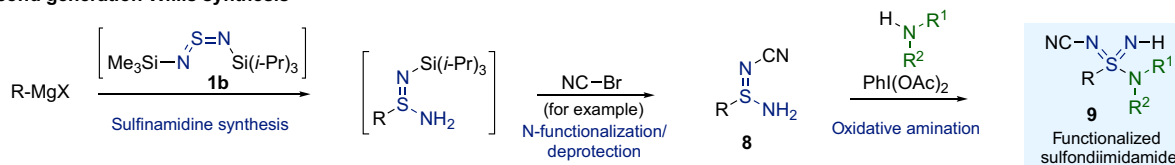
Figure 1. S(VI)-derivatives, and approaches to sulfondiimidamides. (A) Sulfonamides, sulfonimidamides, and sulfondiimidamides; (B) Laughlin synthetic route [6]; (C) Yagupolskii synthetic route [7]; (D) Willis synthetic route via sulfondiimidoyl fluorides **3** [2].

sulfondiimidamides as stable, readily prepared, and functionalizable groups, there were limitations with this route. In particular, the overall length of the sequence, requiring six steps to reach suitably functionalized target molecules, was unattractive for discovery applications, in which concise syntheses allowing the rapid preparation of compound libraries are often needed. The Willis laboratory has recently

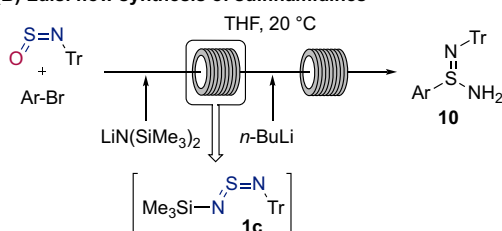
published a second generation synthesis of sulfondiimidamides [9], which addresses many of the limitations of the prior sequence. The preparation and reactivity of the sulfondiimidoyl fluoride intermediate was identified as a synthetic bottle-neck and the new route was developed with the aim of avoiding these species. In place of preparing sulfondiimidoyl fluorides, an iodine(III)-

mediated oxidative amination was used as the key step. Figure 2A details the route, which starts with the combination of organometallic reagents and an unsymmetrical sulfurdiimide (**1b**), this time featuring two different silyl substituents. The key oxidative amination was used to transform primary sulfonamidines directly into sulfondiimidamides (**8** → **9**) and was achieved by treatment of the requisite

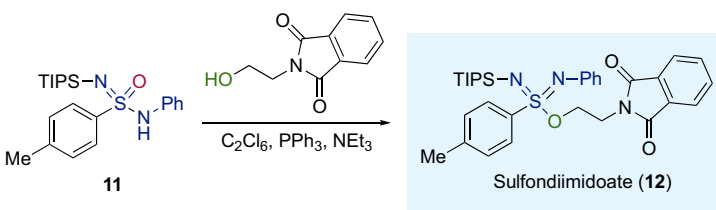
(A) Second generation Willis synthesis



(B) Luisi flow synthesis of sulfinamidines



(C) Reggeli sulfondiimidoate synthesis



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Figure 2. Recent advances in the synthesis of S(VI) derivatives. (A) Second generation Willis synthesis of sulfondiimidamides [9]; (B) Luisi flow synthesis of sulfinamidines [11]; (C) Reggeli synthesis of a sulfondiimidoate [12].

primary sulfinamidines with PhI(OAc)₂ and an amine. Importantly, this revised route allowed rapid access to sulfondiimidamides featuring diverse N-substituents. The new route replaced a six-step sequence with a two-step sequence. To demonstrate the utility of the developed chemistry, the authors were able to prepare sulfondiimidamide analogs of three medicinal agents: celecoxib, sildenafil, and tasisulam sodium.

The double oxygen to nitrogen substitution that is achieved on moving from a sulfonamide to a sulfondiimidamide is potentially attractive to medicinal chemists for several reasons; variation of the two N-substituents should allow control of the acid/base nature, as well as the H-bonding donor and acceptor capabilities, of these groups. Tuning of the physicochemical properties, such as solubility and polar surface area [10], will also be possible. The central sulfur atom of

sulfondiimidamides is tetrahedral and, with appropriate N-substituents, the molecules will be chiral. Collectively, these factors combine to provide a set of tools for medicinal chemists to deploy in their design of new bioactive molecules.

Very recently, Luisi and colleagues disclosed a streamlined approach to primary sulfinamidines exploiting flow chemistry (Figure 2B) [11]. Sulfinamidines are the key substrates used in the Willis route to sulfondiimidamides (see 8, Figure 2A) and so advances towards sulfinamidines will similarly impact sulfondiimidamides. Luisi and colleagues demonstrate that unsymmetrical sulfurdiimide reagent 1c can be generated *in situ*, in flow, before being directly combined, again in flow, with a range of *in situ* generated organometallic reagents, to provide N-Tr sulfinamidines (10) in good yields. Notably, all operations were performed at ambient temperature.

A second new S(VI)-based functional group has been reported in 2022. Reggeli and colleagues recently described the preparation of a sulfondiimidoate [12]. These molecules are the double-aza analogs of sulfonate esters. The Reggeli synthesis is shown in Figure 2C and the key step involves conversion of sulfonimide 11 into sulfondiimidoate 12 using a phosphine-mediated deoxygenation. Although only a single example of a sulfondiimidoate was reported, these are unique scaffolds and, similarly to sulfondiimidamides, they provide a new motif to explore in discovery chemistry.

With the development of efficient methods for the synthesis of sulfondiimidamides, it will be interesting to chart their use over the coming years. Similar advances in the synthetic methods associated with sulfoximines [13,14] and sulfonimides, both once neglected functional groups

[15], have led to dramatic increases in their use.

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Declaration of interests

No interests are declared.

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