Crafting chemical space with sulfur functional groups

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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, 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. 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 and agro-chemicals, serving a range of disease areas. This increase in the use of sulfonimidamides 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 sulfurdime reagent as the starting material. The chemistry commences with the addition of organometallic reagents to unsymmetrical sulfurdime (1a), followed by N-nosyl-protection, providing sulfurdime intermediates, via fluoromethanesulfonamide to provide sulfurdime intermediates, via fluorination then delivers N-fluorination then delivers N-fluoride generated fluorination then delivers N-fluoride generated fluorination then delivers N-fluoride generated fluorination then delivers N-fluoride generated fluorination then delivers N-fluoride generated and 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 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 sulfarnimides directly into sulfondiimidamides (8 → 9) and was
achieved by treatment of the requisite primary sulfinamides 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 physiochemical 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 sulfinamides exploiting flow chemistry (Figure 2B) [11]. Sulfinamides are the key substrates used in the Willis route to sulfondiimidamides (see 8, Figure 2A) and so advances towards sulfinamides will similarly impact sulfondiimidamides. Luisi and colleagues demonstrate that unsymmetrical sulfurdimidide 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 sulfinamides (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. Reggelin and colleagues recently described the preparation of a sulfondiimidoate [12]. These molecules are the double-aza analogs of sulfonate esters. The Reggelin synthesis is shown in Figure 2C and the key step involves conversion of sulfinimidamide 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 sulfonimidamides, both once neglected functional groups [15], have led to dramatic increases in their use.

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No interests are declared.

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