Modular Two-Step Route to Sulfondiimidamides

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ABSTRACT: Sulfur functional groups are common motifs in bioactive molecules. Sulfonamides are most prevalent but related aza-derivatives, in which oxygen atoms are replaced by imidic nitrogens, such as sulfoximines and sulfonimidamides, are gaining attraction. Despite this activity, the double aza-variants of sulfonamides, termed sulfondiimidamides, are almost completely absent from the literature. The reason for this is poor synthetic accessibility. Although a recent synthesis has established sulfondiimidamides as viable motifs, the length of the route and the capricious nature of the key sulfondiimidoyl fluoride intermediates mean that direct application to discovery chemistry is challenging. Herein, we describe a two-step synthesis of sulfondiimidamides, exploiting a hypervalent iodine-mediated amination as the key step. The starting materials are organometallic reagents, an unsymmetrical sulfurdiimide, and amines. The method allowed >40 examples to be prepared, including derivatives of three sulfonamide-based drugs. The operational simplicity, broad scope, and concise nature make this route attractive for discovery chemistry applications.

1. INTRODUCTION

Sulfur functional groups, most prominently sulfonamides, have made a tremendous impact on pharmaceuticals, with the first “sulfa-drugs”, the sulfonamide-based antibiotics that preceded the penicillins, being developed 90 years ago. Nearly a century later, almost 10% of FDA-approved drugs feature a sulfur functional group. The last decade has seen the emergence of sulfondiimidamides as viable motifs, the length of the route and the capricious nature of the key sulfondiimidoyl fluoride intermediates mean that direct application to discovery chemistry is challenging. Herein, we describe a two-step synthesis of sulfondiimidamides, exploiting a hypervalent iodine-mediated amination as the key step. The starting materials are organometallic reagents, an unsymmetrical sulfurdiimide, and amines. The method allowed >40 examples to be prepared, including derivatives of three sulfonamide-based drugs. The operational simplicity, broad scope, and concise nature make this route attractive for discovery chemistry applications.

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manipulated, commencing with removal of the N-t-octyl substituent to allow for installation of a range of terminal functional groups.14 An N-CN example is shown (5 → 6 → 7).15 Removal of the imidic Ns-substituent delivers the final sulfondiimidamide 8. Using this approach we were able to prepare a diverse range of sulfondiimidamides with reasonable variation at all positions. We also established the general viability of sulfondiimidamides as a useful functional group in synthesis as we were able to achieve a variety of synthetic manipulations around the core structure, obtaining stable, isolable products.

Despite these successes, there remain some limitations that will limit the uptake of this chemistry. Most significant among these is the overall length of the sequence, with six steps needed before sulfondiimidamides substituted with attractive medicinal chemistry-like groups are achieved. In addition, the oxidative fluorination transformation was not compatible with many heterocyclic carbon-substituents, thus limiting the scope with regard to the range of C-nucleophiles that could be used. The same fluorination step is slow and can take several days to reach completion. In addition, conversion of the sulfondiimidoyl fluorides into the protected sulfondiimidamides is mediated by stoichiometric quantities of the costly Lewis acid Ca(NTf2)2 and is inefficient with electron-rich examples. Finally, strong acidic conditions are needed to remove the imidic t-octyl-protecting group. To deliver a synthesis of sulfondiimidamides that would be attractive to discovery chemists, we targeted a route that would deliver final products, that is, molecules already substituted with desirable terminal groups, in far fewer steps than our prior chemistry. We also wanted to expand the scope of carbon-substituents that could be employed and to avoid the use of strong acids and bases and high temperatures. In this article, we describe the successful realization of these goals and validate these claims by the preparation of diverse sulfondiimidamides, as well as sulfondiimidamide derivatives of three medicinal agents.

Figure 1. (a) Sulfonamides, sulfonimidamides, and sulfondiimidamides as functional groups in medicinal chemistry. (b) Synthesis of sulfondiimidamides from Laughlin and Yagupolski. (c) Synthesis of sulfondiimidamides via sulfondiimidoyl fluorides 4. (d) This work: the synthesis of sulfondiimidamides exploiting I(III)-mediated amination.
2. RESULTS AND DISCUSSION

The preparation and onward reactivity of sulfondiimidoyl fluorides (4) were responsible for many of the challenges associated with our prior route to sulfondiimidamides. To avoid the issues associated with these intermediates, and to achieve a shorter overall sequence, we planned to generate and exploit a reactive sulfur(VI)-intermediate in situ. Taking inspiration from a recent synthesis of sulfonimidamides,16 we proposed an I(III)-mediated oxidative amination of suitably protected primary sulfinamidines as the key step in our new route (Figure 1d). Related I(III) chemistry has been described using tertiary sulfinamides and tertiary sulfinamides as substrates, leading to sulfonimidamides17 and sulfonimidates18 as products, depending on the reaction conditions employed. The use of sulfinamidines with I(III) reagents is unknown. To avoid steps associated with protecting group manipulations, we proposed installing the terminal N-substituents early in the reaction sequence and using the resultant N-functionalized sulfinamidines in the key I(III)-transformation. Finally, in order to achieve maximum functional group tolerance, we would exclude the 1-octyl-decorated sulfardiimide reagent in favor of an unsymmetrical bis(silyl)sulfuriimide (1b).16,19 Together, these innovations should provide a shorter route that is amenable to greater diversification than the earlier chemistry. The concise nature of this proposed route is clear if we consider the preparation of functionalized sulfondiimidamide 8, in which the imidic CN-substituent has been selected as a representative terminal functional group. Using our earlier synthetic route, six steps are needed to prepare sulfondiimidamide 8; the proposed route would provide the same molecule in only two steps (compare Figure 1c,d).

2.1. Primary Sulfinamide Synthesis. The substrates for the key I(III)-mediated amination are primary sulfinamidines 10. These were readily prepared from the addition of organometallic reagents to sulfuriimide reagent 1b, which was generated in situ from the commercially available sulfinylamine TIPS-NSO;20 N-functionalization and cleavage of the N-Si(i-Pr)3 substituent followed. The latter two transformations were carried out directly on the initial adducts 9 after an aqueous work-up, and the desired primary sulfinamidines (10) are the first intermediates that are isolated and purified (Table 1). A N-nosyl substituent was selected for initial investigation, which

Table 1. Synthesis of Primary Sulfinamidines 10 Using Sulfuriimide Reagent 1b

| Variation of Carbon Fragment | Variation of Imidic N-substituent |
|------------------------------|----------------------------------|
| ![Chemical Structures](image) | ![Chemical Structures](image) |

"Reaction conditions: tri-isopropylsilyl sulfinylamine (1.0 equiv), LiHMDS (1.0 equiv), THF (0.5 M), −30 °C, 5 min, then 0 °C, 5 min, then TMSCl (1.0 equiv), 0 °C, 10 min, then RMgBr (1.2 equiv), 0 °C, 10 min. Aqueous work-up. Then Et3N (1.2 equiv), NsCl (1.0 equiv), CH2Cl2 (0.2 M), 0 °C, 20 min, then TBAF (1.1 equiv), 0 °C, 10 min. Isolated yields. Organolithium reagent employed. "Turbo Grignard" reagent (R-MgCl·LiCl) employed. 4-Br-CN used. 4-CF3-BzCl used. Cbz-Cl used. NOS-Cl used. "Ts-Cl used. Ses-Cl used."
allowed for the scope of the carbon fragment to be explored; substituted aryl (10a–c), heteroaryl (10d–h), primary, secondary, and tertiary alkyl (10i–l), benzylic (10m), and alkynyl (10n) groups were all introduced. The aryl fragment of the COX-2 inhibitor celecoxib was also used, providing the corresponding sulfonimidamide in good yield (10o). Alternatives to the nosyl group were readily incorporated, with cyano (10p), acyl (10q, r), carbamate (10s), and sulfonyl (10t, u) imidic N-substituents all smoothly prepared.

2.2. Iodine(III)-Mediated Sulfondiimidamide Synthesis. Reaction conditions for the key oxidative amination were based on a related transformation to access sulfonimidamides. The optimized reaction conditions involved treating sulfonimidamide 10a with a slight excess of amine and using 1.5 equiv of commercial PhI(OAc)2 in the presence of NEt3, with toluene as the solvent. The reactions were performed at ambient temperature. Application of these conditions delivered N–H sulfonimidamide 8a in an excellent 93% yield (Table 2). This

| entry | variation from above | yield of 8a |
|-------|----------------------|------------|
| 1     | none                 | 93%        |
| 2     | no PhI(OAc)2         | 0%         |
| 3     | 1.0 equiv PhI(OAc)2  | 75%        |
| 4     | no Et3N              | 76%        |
| 5     | 1.5 equiv Et3N       | 81%        |
| 6     | 1.0 equiv morpholine | 65%        |
| 7     | 3.0 equiv morpholine | 97%        |
| 8     | DBU instead of Et3N  | 69%4       |
| 9     | CH3CN instead of toluene | 62%4     |
| 10    | CH2Cl2 instead of toluene | 88%4     |

“Reaction conditions: 10a (1.0 equiv), PhI(OAc)2, base, morpholine, solvent (0.1 M), 30 min. Isolated yields. 4Reaction complete after 10 min.

is the first report of hypervalent iodine oxidants being used with sulfonimidamines, which confirms the compatibility of these useful oxidants with this aza-S(IV) functional group. Variations from these conditions are summarized in Table 2; notable is the tolerance for the alternative solvents CH3CN and CH2Cl2 (entries 9 and 10).

We next applied these optimized conditions to the sulfonimidamines prepared in Table 1. Morpholine was used as the amine component in this scoping study (Table 3). All of the sulfonimidamines were smoothly converted to the corresponding N–H sulfonimidamides in good to excellent yields. The range of alkyl (8j, 8l, 8m) and heteroaryl (8e–8h) derivatives prepared using this method surpasses what was possible using the previous route via sulfonimidoyl fluorides. Amoxapine was used as the amine for the synthesis of alkynyl sulfonimidamide 8n due to purificational issues with the morpholine derivative; 8n is the first example of an alkynyl sulfonimidamide to be reported. Sulfonimidamides with varied N-substituents were then evaluated, and as can be seen, N-cyano (8p), acyl (8q, r), carbamate (8s), and sulfonyl (8t, u) derivatives were all converted into the corresponding N-functionalized sulfonimidamides in excellent yields. N-cyano derivative 8p was also prepared in our earlier report, which then required six steps; in the present study, the synthesis of sulfonimidamide 8p is achieved in only two steps from the starting Grignard reagent. The scope of the amine partners used in the reaction was then investigated. A wide range of cyclic secondary amines could be employed to give the corresponding sulfonimidamides in high yields. For example, piperidines (8v), including examples featuring ketal (8w) and cyano-substituents (8x), were incorporated efficiently. Piperazine fragments are common in medicinal agents, and we include examples present in the pharmaceuticals buspirone (8y), amoxapine (8z), and piperazine and ziprasidone (8aa). Pyrrolidine (8ab, ac) and azepane (8ad) examples were also obtained with high yields. Sulfonimidamide 8ac was formed as a 1:1 mixture of diastereomers at sulfur; N-acylation allowed separation of the diastereomers and isolation of enantiomerically pure examples. Acyclic secondary amines such as N-benzylmethylamine (8ae), diethyl amine (8af), and diallyl amine (8ag) could also be included.

The I(III)-mediated amination was poorly effective for primary amines and for electron-poor nitrogen nucleophiles such as amides and anilines. Accordingly, we have developed a modified procedure that allows sulfonimidamides derived from these types of nucleophiles to be prepared. Di-allyl N–Nsulfonimidamide 8ag was reacted with benzyl bromide and DBU to form the N–Bn derivative 11a (Figure 2). Then, removal of the two allyl groups from 11a using catalytic Pd(0) in combination with barbituric acid provided the primary sulfonimidamide 12a. Sulfonimidamide 12a is the formal product of the I(III)-mediated amination using benzylamine. Using this approach, we prepared sulfonimidamides formally derived from the addition of methyamine (12b), cyanamide (12c), a benzamide (12d), and a sulfonamide (12e); these are all nucleophiles incompatible with the I(III)-mediated amination. The derivatives with two strong electron-withdrawing substituents (12c–e) were isolated as their sodium salts following a basic work-up procedure.

2.3. Applications. To highlight the key advantages of the newly developed method, in particular the short reaction sequences and excellent functional group tolerance of the
chemistry, we have prepared sulfondiimidamide derivatives of three pharmaceuticals (Figure 3). In all three derivatives, we have chosen to install imidic N-cyano substituents. These are common imidic N-substituents in various aza-sulfur functional groups, with their popularity stemming from their good metabolic stability, small size, and the presence of such a group in the marketed agrochemical Sulfoxaflor. Using our earlier sulfondiimidoyl fluoride chemistry, we had previously prepared the bis(N-CN)-celecoxib derivative 16 in an eight-step sequence. Here, we prepare sulfondiimidamide 16 using a four-step route starting from the aryl halide 13. The key oxidative amination, employing primary sulfamidine 14 and di-allylamine, delivers sulfondiimidamide 15 in 81% yield. Cyanation of the free imidic N-H followed by de-allylation (as reported previously) delivers the target structure (16) in an overall yield of 59%. The yield exploiting the earlier method, from the same starting material, was 24%. The second target structure prepared was the N-CN sulfondiimidamide derivative of sildenafl 19. Addition of in situ generated sulfurdiimide 1b into the aryl lithium reagent derived from aryl halide 17,

Table 3. Synthesis of Sulfondiimidamides 8 Using Oxidative Amination

|a| Reaction conditions: sulfamidine (1.0 equiv), PhI(OAc)₂ (1.5 equiv), Et₃N (3.0 equiv), amine (1.5 equiv), toluene (0.1 M). Isolated yields.
|b| CH₂Cl₂ (0.1 M) used in place of toluene.
|c| Followed by Ac₂O (1.5 equiv), Et₃N (2.0 equiv), DMAP (0.2 equiv), CH₂Cl₂ (0.2 M).
|d| Amine (3.0 equiv), toluene (0.2 M).

![Chemical structures](https://doi.org/10.1021/jacs.2c04404)
followed by installation of a \( \text{N}−\text{CN} \) group and silyl deprotection, provided primary sulfonimidamide 18 in 51% yield. Oxidative amination using \( \text{N} \)-methyl piperazine provided the target sulfonimidamide 19 in 62% yield. The final example is a sulfonimidamide derivative of the investigational melanoma treatment, tasisulam sodium. Starting from 2-bromothiophene, the primary sulfonimidamide 20 was obtained in 60% yield. Oxidative amination using diallylamine, followed by \( \text{N} \)-benzoylation, delivered sulfonimidamide 22. \( \text{Pd}(0) \)-catalyzed de-allylation provided the target molecule, sulfonimidamide sodium salt 23.

An observation regarding the stability of sulfonimidamides is that at least one electron-withdrawing \( \text{N} \)-substituent is needed to deliver stable products. In addition, we have measured the stability of sulfonimidamides 8a, 8p, 11b, and 16 in DMSO/buffer solutions at pH 1, 7, and 10; \( \text{N}−\text{H} \) derivatives 8a and 8p show slow degradation under all conditions, while fully substituted derivative 11b and di-CN example 16 both showed excellent stability (see Supporting Information for more details).
3. CONCLUSIONS

In conclusion, we have demonstrated that sulfondiimidamides can be prepared in two steps, with pre-formed organometallic reagents, a sulffurdiimidamide reagent, and amines being the starting materials. An iodine(III)-mediated oxidative amination is the key operation and transforms primary sulfonamides into N-H sulfonamidamates in good yields. The reactions are broad in scope and encompass a variety of aryl, heteroaryl, alkenyl, and alkyl carbon fragments and a wide range of amines. Additionally, we demonstrate the suitability of the chemistry for the preparation of bioactive molecules by the synthesis of three sulfonamidamid-derivatives of known medicinal agents. Taken together, we anticipate that these attributes will lend the developed method to applications in discovery chemistry.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c04404.

Experimental procedures, spectral characterization, and additional data (PDF)

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Notes
The authors declare the following competing financial interest(s): Two of the authors (MW and ZZ) have submitted a patent application related to this work.

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