ARTICLE

Overlooked Aza-S(IV) Motifs: Sulfinamidines and Sulfinimidate Esters

Michael Andresini,[a] Marco Colella,[a] Leonardo Degennaro[a] and Renzo Luisi *[a]

Significant advancements have been made in the synthesis of overlooked aza-S(IV) motifs. The accessibility of sulfinamidines and sulfinimidate esters has greatly improved through the recent development of efficient and complementary synthetic strategies. Intriguingly, new discoveries have emerged regarding the reactivity of these substances, highlighting the electrophilic nature of sulfinimidate esters and the nucleophilic character of sulfinamidines. Moreover, sulfinamidines have been found to be prone to oxidation, leading to the formation of important aza-S(VI) derivatives. In this review, our aim is to present an almost comprehensive overview of the most relevant achievements in the preparation and structural characterization of these overlooked compounds.

1. Introduction

Traditional sulfur functionalities such as sulfones and sulfonamides have been widely disclosed as pharmacophores in drug discovery, leading to the development of several marketed drugs. [1] However, there has been notable advancement in the utilization of various sulfur-based pharmacophores, which were previously overlooked, resulting in the exploration of a new chemical space for medicinal chemists and offering prospects for patenting.[2] For example, sulfoximines, sulfondiimides, and sulfonimidamides, which are aza-S(VI) analogues of sulfones and sulfonamides, have captured the interest of researchers. This attention has resulted in the development of effective synthetic approaches for their synthesis, leading to the preparation of novel clinical candidates.[3-8] The success of these emerging aza-S(VI) functionalities largely depends on the ability to finely tune the physicochemical properties of molecules through the formal substitution of an oxygen atom with nitrogen. Moreover, this substitution enables addressing molecular complexity through the installation of additional functionalities due to the trivalent nature of the nitrogen. These considerations are expected to apply to other aza-analogues of sulfur motifs with lower valence, as demonstrated by bio-relevant sulfilimines, which are the aza-analogues of sulfoxides.[9,10] However, unlike aza-S(VI) derivatives, the preparation of aza-S(IV) compounds has been overlooked for long time. Within this framework, the S(IV) motif landscape consists mainly of sulfoxides, sulfinate esters, and sulfinamides, with significantly lesser focus given to sulfinimidate esters and sulfinamidines (Figure 1).[11-13] Nevertheless, delving into these aza-S(IV) motifs may expand the chemical landscape accessible to medicinal chemists and offer valuable reagents for organic synthesis. Given the potential utility of these compounds in various synthetic and biological scenarios, recent efforts have been directed towards developing synthetic strategies to obtain sulfinamidines and sulfinimidates and assessing their reactivity. It is important to note that, as of our current knowledge, no drug candidates containing an aza-S(IV) motif have been identified, likely due to the absence of efficient synthetic methodologies. Since the publication of our initial study in 2020, there has been a surge of interest in accessing these compounds, as evidenced by numerous subsequent reports detailing complementary strategies. This renewed enthusiasm reflects the growing importance and potential applications of these compounds in various fields.[14] The objective of this review is to draw the attention of organic and medicinal chemists to underappreciated functionalities, namely sulfinamidines and sulfinimidate esters, by referencing the latest and most effective methodologies that facilitate their synthesis, transformation, as well as oxidation into higher-valence aza-S(VI) compounds.
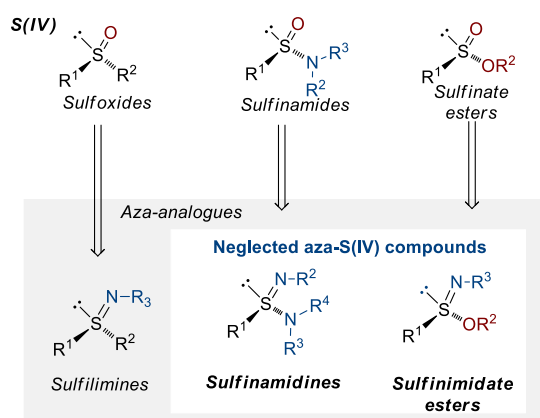

Figure 1. Overview of common S(IV) functionalities and their ana-analogues.
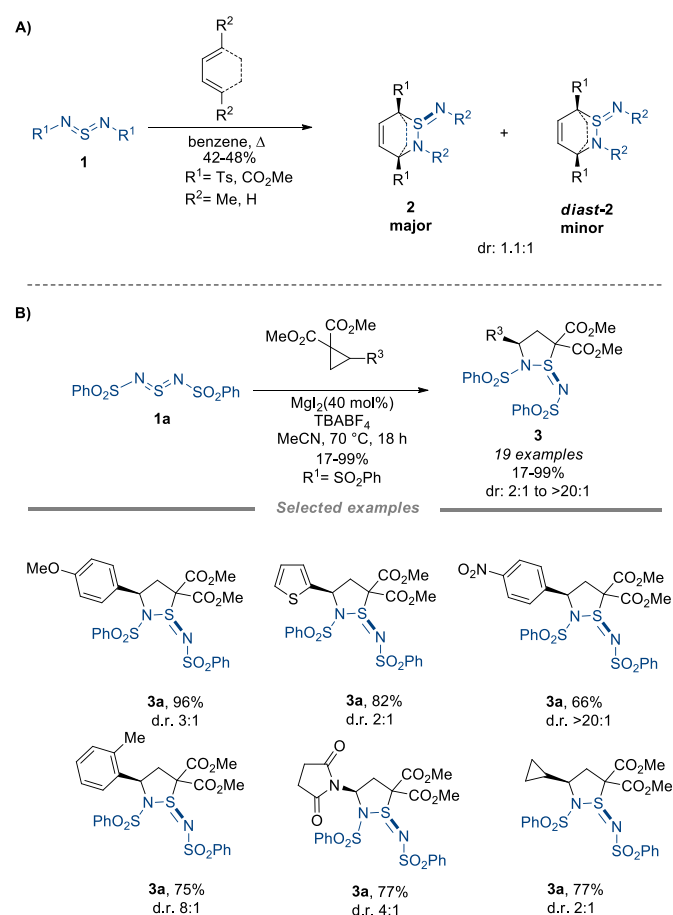
2. Sulfinamidines

Sulfinamidines are a class of tetravalent sulfur compounds that are distinguished by the presence of one carbon atom and two nitrogen atoms bonded to the central sulfur. The preparation of sulfinamidines has been recently achieved by exploiting the following

a. FLAME-Lab, Flow Chemistry and Microreactor Technology Laboratory
Department of Pharmacy– Drug Sciences University of Bari "A. Moro" Via E. Orabona 4 – 70125 Bari, Italy.

strategies: *i*) cycloaddition or *ene* reaction of sulfurdiimides; *ii*) imidation of sulfenamides; *iii*) nucleophilic addition of organometallics to sulfurdiimides

2.1 Synthesis of sulfinamidines through cycloaddition and ene-reaction reactions of sulfurdiimides

One of the earlier methods for synthesizing sulfinamidines involved the Diels-Alder cycloaddition reaction of 1,3-dienes with sulfurdiimides **1**, which generated 3,6-dihydrothiazinimine adducts **2** having preferential *cis* configuration between the exocyclic nitrogen linked to the sulfur, and the substituent at the C6 position (Scheme 1, A).[15,16] Although furnishing the products in moderate yields, this approach is limited to the use of symmetric sulfurdiimides bearing electron-withdrawing groups, and proceeds with poor diastereoselectivity. As a recent advance, in 2021 Werz and co-workers reported the formal 3+2 cycloaddition of dimethyl 2-arylcyclopropane-1,1-dicarboxylates with bis-sulfonyl sulfurdiimide **1a** furnishing five-membered cyclic sulfinamidines **3** in poor to excellent yields (Scheme 1, B).[17]

Scheme 1. Synthesis of sulfinamidines by cycloaddition reactions of sulfurdiimides.

As best conditions to achieve good reaction yields, an excess of sulfurdiimide (2.5 equiv.), a high load of catalyst (MgI$_2$, 40 mol%) and TBABF$_4$ were needed. Notably, this method furnished varied 1-λ^4-isothiazolidines that contained an aryl, heteroaryl, alkyl, or cycloalkyl substituent at the C3 position, with great variability in terms of yield and diastereoselectivity. The

reaction affords products that preferentially have a *syn* relationship between the C3 substituents and the exocyclic *N*-substituent linked to the sulfur atom. Beyond their efficient reactivity in cycloaddition reactions, sulfurdiimides showed to be prone to participate in Alder-ene-type transformations. At the beginning of the past decade, acyclic sulfinamidines were prepared by the ene-reaction of symmetric sulfurdiimide **1a** with olefins (Scheme 2).[18,19] This method furnished the corresponding *ene* adducts **4** within 12 hours at 4 °C. However, the products were found to be stable for several days below 0 °C, as these species undergo at higher temperatures to a spontaneous 1,3-sigmatropic rearrangement that releases compounds **5**. Hence, diverse approaches must be exploited for accessing acyclic sulfinamidines, as described in the following sections.
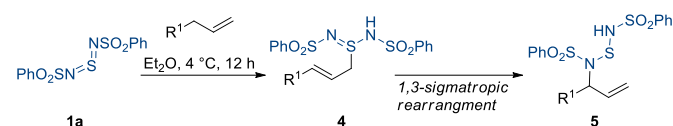

Scheme 2. *Ene* reaction of sulfurdiimdies.

2.2 Synthesis of sulfinamidines by sulfur imidation

Sulfinamidines can be prepared through imidation of the sulfur atom by employing N-donor reagents such as *N*-chloro-*p*-toluenesulfonamide sodium salt (chloramine-T). In this way, a very narrow selection of disulfides, thiophenolates and sulfenamides released the corresponding *N*-sulfonyl sulfinamidines when treated with chloramine-T.[20-22] In 2020, we reported the first imidation reaction of sulfenamides with *N*-mesyloxycarbamates to furnish *N*-carboalkyloxy sulfinamidines. The optimized protocol uses *N,N*-bisalkyl sulfenamides **6**, an excess of *N*-mesyloxycarbamate and a base (Scheme 3).[14] The reaction showed compatibility with electron-donating and electron-withdrawing groups, naphthyl group, and alkyl S-substituents. In the case of the alkyl S-substituents, the reaction required longer reaction times but ultimately provided excellent yields (Scheme 3). Remarkably, under the optimized reaction conditions, cyclic benzisothiazolinone was found as a suitable substrate furnishing *N*-carboalkyloxy sulfinamidines **7d** and **7h** in good yields (Scheme 3). These compounds are the aza-S(IV) analogues of saccharine and represented the first example of the sulfinamidine motif to be installed on a biologically-relevant scaffold. The reaction mechanism of this strategy was deeply investigated proposing the protonated intermediate **I** also supported by spectroscopic evidence. The generation of such an intermediate might arise from a nucleophilic substitution reaction involving the sulfenamide as the S-donor and the sulfonyloxycarbamate as the N-donor (Scheme 3, path a). An alternative reaction mechanism involves the generation of a nitrene from the *N*-mesyloxycarbamate through a deprotonation-alpha elimination sequence (Scheme 3, path b). The subsequent deprotonation of intermediate **II**, obtained from **I** after proton shift, releases the final product **7** (Scheme 3).
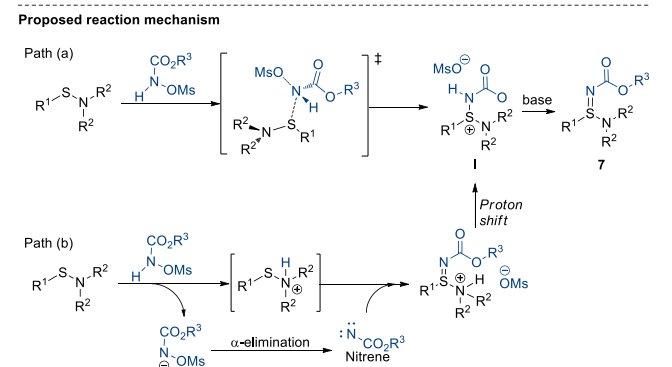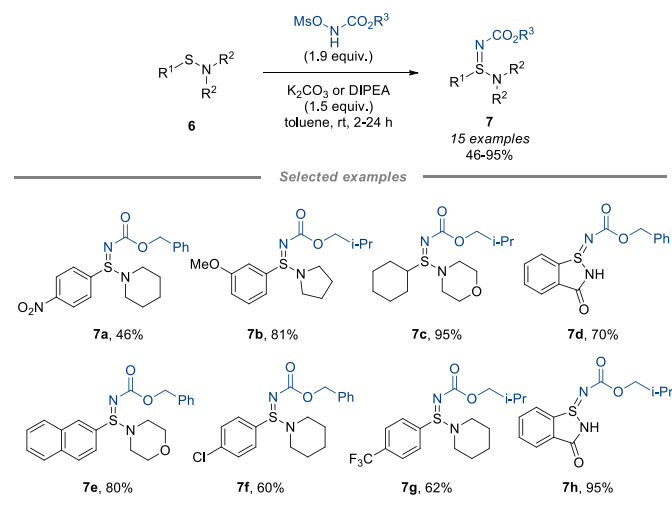
Scheme 3. Synthesis of sulfinamidines by imidation of sulfenamides with *N*-mesyloxycarbamates.
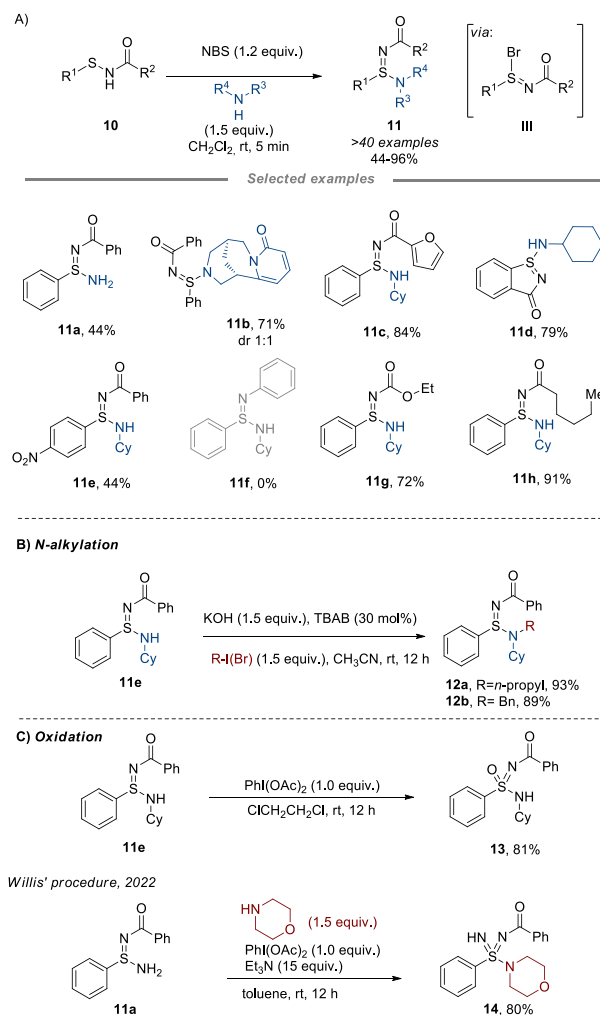
The preparation of sulfinamidines through a tandem oxidation-amination reaction has been also reported. In this context, the synthesis of sulfinamidines using sulfenamides and *N*-halo succinimide as the oxidant was disclosed in the late 70s.[23] The strategy involves first the preparation of azasulfonium tetrafluoroborates from *N,N*-bisalkylsulfenamides **8** in the presence of AgBF₄. The reaction of such sulfenamides with *N*-chloro succinimide proceeds smoothly in acetonitrile, and the corresponding salts could be isolated in very good yields. Treatment of **8** with primary or secondary amines led to the cleavage of the succinimide ring and furnished sulfinamidines **9** in moderate to good yields (Scheme 4).
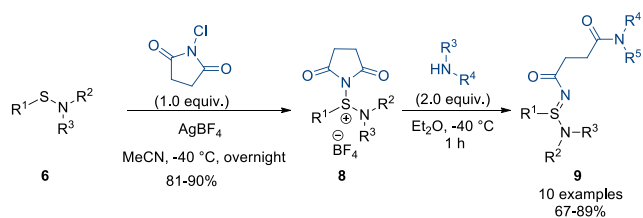
Scheme 4. Synthesis of sulfinamidines through tandem oxidative amination of sulfenamides.

In 2023, Li and coworkers re-examined the synthesis of *N*-acyl and *N*-aroyl sulfinamidines exploiting the formal oxidative amination of *N*-acyl sulfenamides.[24] The process entails utilizing commercially accessible NBS (*N*-bromo succinimide) as the oxidizing agent, alongside a range of primary and secondary amines, including motifs that are of pharmaceutical significance. This allows for the synthesis of a diverse array of products. (Scheme 5, A). The reaction was found to be tolerant to the presence of electron-withdrawing and electron-donating groups linked to the acylic and *S*-arylic portions. The reaction did not proceed when an *N*-aryl sulfenamide was used. Further experiments helped the authors to propose a reaction mechanism involving halogenated S(IV) intermediate **III**, which subsequently reacts with the nucleophilic amine partner. Interestingly, the reaction could be successfully conducted with ammonia, and sulfinamidine **11e** could be efficiently further alkylated at nitrogen with alkyl halides upon treatment with KOH and in the presence of TBAB (Scheme 5, B). It is worth mentioning that sulfinamidines **11a** and **11e** could be further oxidated releasing the corresponding aza-S(VI) sulfonimidamide **13** and sulfondiimidamide **14**, in the latter case employing Willis' procedure (Scheme 5, C).[25]


Scheme 5. Synthesis of sulfinamidines through oxidative amination of sulfenamides with NBS.

Similarly, in 2023 Waldvogel and co-workers described the electrochemical dehydrogenative imination of sulfenamide **6a** towards sulfinamidine **15** (Scheme 6).[26] Although the scope of the method is limited to a single example, it is reasonable to envision that such protocol might proceed with other *N,N*-bisalkyl sulfenamides *en route* to *N*-tosyl sulfinamidines. In this case, the reaction is supposed to involve the oxidation of the starting sulfenamide and the consequent generation of a brominated S(IV) intermediate **IV** enabled by the in-situ formation of molecular bromide (Scheme 6).
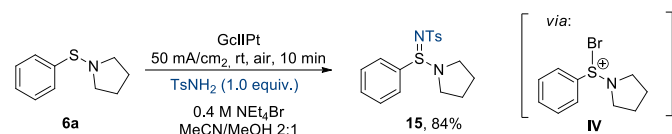

Scheme 6. Electrochemical dehydrogenative imination of sulfenamide **6a**.

Recently, Bull and Armstrong disclosed the preparation of sulfinamidine **7i** via the Rh$_2$(esp)$_2$-catalyzed nitrogen transfer to sulfenamide **6b** with *t*-butyl carbamate (Scheme 7). The reaction proceeds in toluene and requires 1.7 equiv. of carbamate and PhI(OAc)$_2$, and MgO (4.0 equiv.) as the base, with a catalyst loading of 2.0 mol%, furnishing the product in 38% yield.[27]
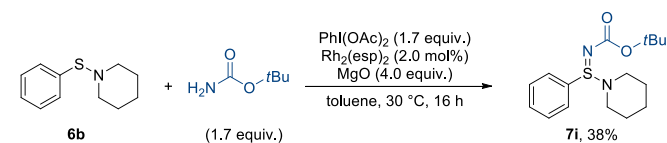
Scheme 7. Rhodium-catalyzed imination of sulfenamide **6b**.

In a recent work, Lu and colleagues reported the the efficient imination of *N*-acylsulfenamides **10** using PhI(OAc)$_2$ to obtain *N*-acyl sulfinamidines **11** (Scheme 8).[28] The optimized protocol employed an excess of oxidant (PhI(OAc)$_2$, 1.5 equiv.), a slight excess of amine (1.2 equiv.), and Na$_2$CO$_3$ as the base, in toluene at room temperature for 2 hours. Two different mechanistic pathways have been proposed by the authors. A ligand exchange on the hypervalent iodine reagent with the sulfenamide is likely to produce two possible intermediates with the coordination of the iodine to the sulfur (intermediate **V**) or the nitrogen atoms (intermediate **VI**), respectively, with the concurrent loss of acetic acid. Such intermediates are supposed to undergo a second ligand exchange sequence with the coordination of the amine to the iodine atom *en route* to intermediate **VII** and **VIII**. The reductive elimination step of **VII** eventually releases the target product **11**. Alternatively, the authors proposed that the product may arise from the reductive elimination step towards **IX** followed by its rearrangement (Scheme 8). In a recent preprint, Lu and colleagues preliminarily disclosed the imination of *N*-acylsulfenamides using air oxygen as the oxidant upon Cu(II) catalysis.[29]
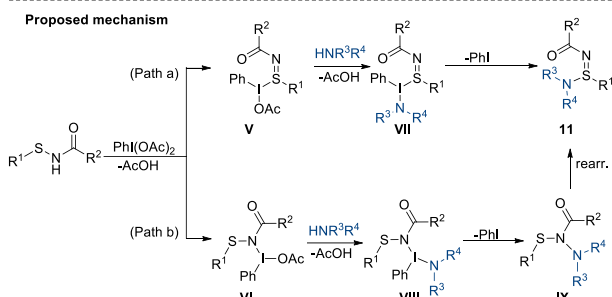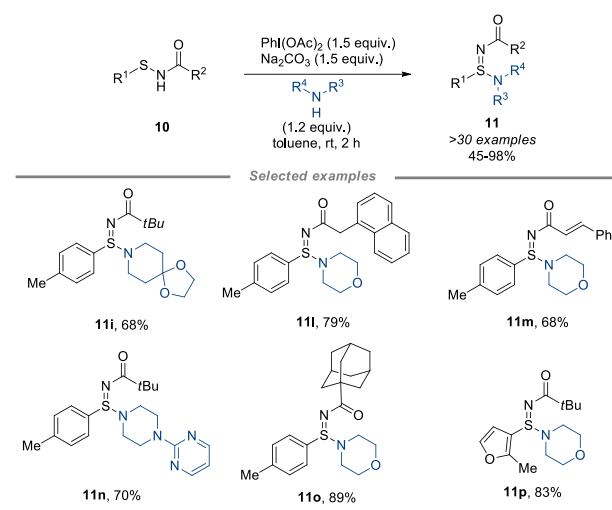
**Scheme 8.** PhI(OAc)$_2$-promoted oxidative amination of *N*-acyl and *N*-aroyl sulfenamides.

## 2.3 Synthesis of sulfinamidines by organometallics addition to sulfurdiimides

The nucleophilic addition of organometallic reagents to symmetrical sulfurdiimides was reported for the first time a long time ago.[30] However, the corresponding sulfinamidine intermediates were never isolated, but directly used and characterized as metal ligands.[31] Over the past few years, there has been a renewed focus on this traditional reaction, bringing it to the forefront and presenting a fresh and effective approach to obtaining sulfinamidines. This approach, recently published by Willis, involves the synthesis of a non-symmetrical sulfurdiimide bearing two orthogonal protecting groups on the nitrogen atoms, and its transformation with carbon nucleophiles. The transient sulfurdiimides, which could not be isolated, were efficiently prepared from *N*-sulfinyl amines and lithium bis(trimethylsilyl)amide in THF. In detail, in 2022 Willis reported the preparation, at low temperature, of *N-t*-octyl-*N'*-trimethylsilyl sulfurdiimide **17** and the subsequent reaction with organolithiums and organomagnesium compounds followed by the N-protection step with the nosyl group *en route* to isolable sulfinamidines **18** (Scheme 9, A).[32] Interestingly, the authors disclosed that sulfinamidines **18** are a valuable synthetic platform to access sulfondiimidoyl fluorides **19** by a deprotonation-oxidative fluorination sequence by using NFSI as the fluorine source (Scheme 9, B). The preliminary formation of a *N*-fluorinated sulfinamidine intermediate was documented, followed by a slow rearrangement toward the final sulfondiimidoyl fluoride. The further reaction of sulfondiimidoyl fluorides with amines in the presence of Ca(NTf$_2$)$_2$ gave access

to hardly accessible sulfondiimidamides **20** through a formal nucleophilic substitution reaction (Scheme 9, B).
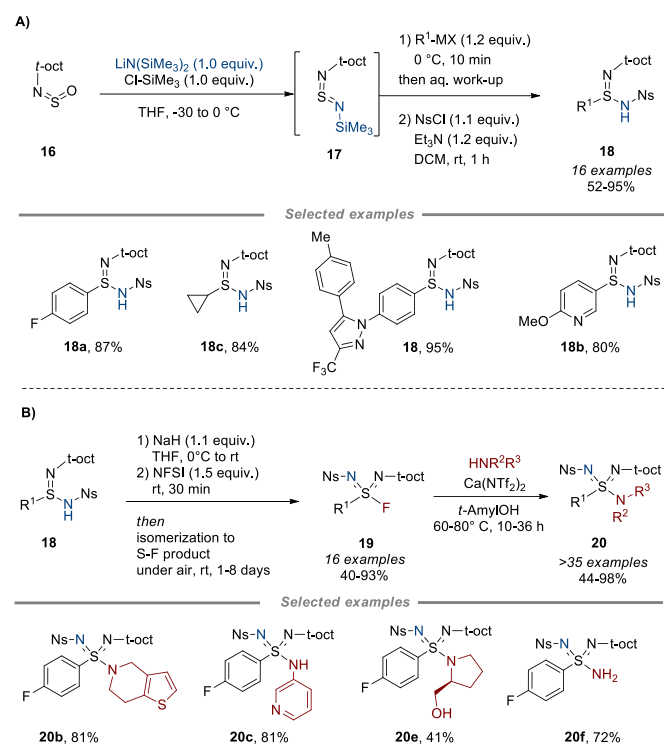
Scheme 9. A) Synthesis of *N*-nosyl sulfinamides via nucleophilic addition to sulfurdiimide **17**. B) Synthesis of sulfondiimidoyl fluorides and their transformation to sulfondiimidamides.

The same research group subsequently disclosed a step-economical preparation of sulfondiimidamides that involved the generation of primary sulfinamidines, followed by an oxidative amination towards higher-valence S(VI) products.[25] In this case, the authors harnessed the reaction of *N*-trimethylsilyl-*N'*-triisopropylsilyl sulfurdiimide **22** with organometallic reagents accessing to not isolable *N*-triisopropylsilyl primary sulfinamidine **23**. Remarkably, a variety of functionalities could be installed on the sulfinamidine motif **23** including sulfonyl, cyano, acyl, aroyl and carboalkyloxy terminations. The transformation takes place in dichloromethane and in the presence of triethylamine. Further deprotection of the silyl group operated by TBAF yielded *N*-functionalized primary sulfinamidines **24** in good yields (Scheme 10). The oxidative amination step with secondary amines involves the use of PhI(OAc)$_2$ as the oxidant and proceeds in the presence of triethylamine. In this way, a wide library of rare aza-S(VI) derivatives could be obtained in useful yields through the exploitation of sulfinamidines as key intermediates.
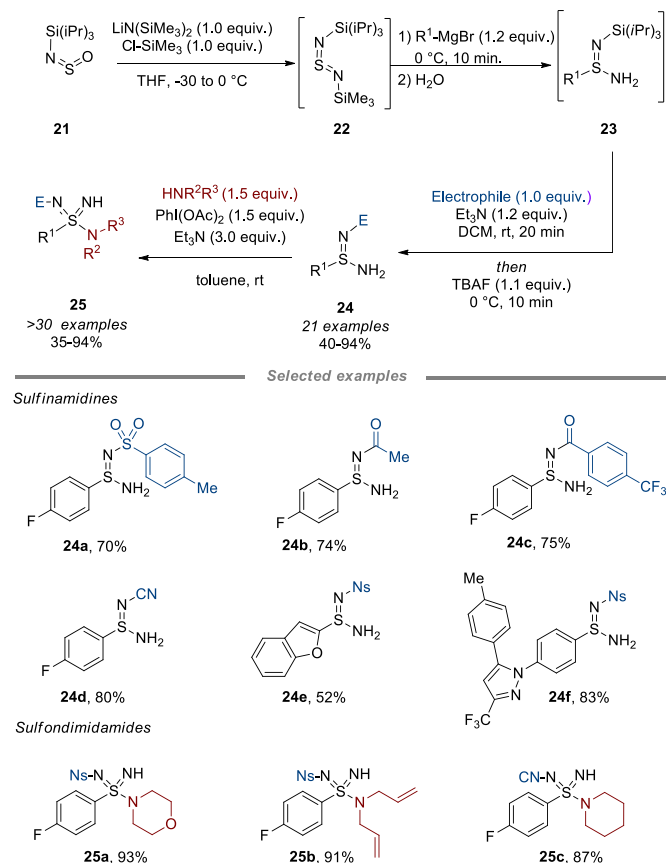

**Scheme 10.** Synthesis of primary sulfinamidines and their oxidative amination towards sulfondiimidamides.

Inspired by Willis' reports, we developed a continuous flow preparation of primary sulfinamidines from *N*-tritylsulfinyl amine.[33] By implementing the flow arrangement, the requirement for low temperature in the synthesis of non-symmetric sulfurdiimide **26** was circumvented. The sulfurdiimide was prepared at room temperature by combining a solution of *N*-tritylsulfinyl amine with lithium bis(trimethylsilyl)amide in THF, with a residence time of 15 seconds. The nucleophilic addition of carbon nucleophiles could be accomplished in a telescoped approach by fluxing an organometallic solution that was mixed with a solution of sulfurdiimide in a second T-shaped micromixer at room temperature (Scheme 11, Method A). The flow process enabled the preparation of NH$_2$-free *N*-trityl sulfinamidines **27** which were found to be very stable at room temperature. Notably, remarkable chemoselectivity was witnessed in the halogen-lithium exchange reaction when iodo- or bromoarenes were treated with *n*-buthyllithium in the presence of sulfurdiimide **26** (Scheme 11, Method B). Through this process, a collection of highly reactive aryllithiums could be generated in a continuous flow system and subsequently reacted with sulfurdiimide **26** under Barbier-type conditions, exhibiting exceptional selectivity at ambient temperature. Moreover, a selection of NH$_2$-sulfinamidines reacted with electrophiles upon deprotonation operated by sodium hydride allowing for the installation of varied functionalities on the nitrogen atom, including the aroyl, sulfonyl and carboalkyloxy groups. The synthesis of

sulfinimidoyl urea **29** was achieved starting from *N*-tritylsulfinyl amine and isocyanate, employing a continuous flow/batch approach as shown in Scheme 12. Additionally, the *N*-trityl deprotection reaction afforded primary sulfinimidoyl urea **30** as

an example of aza-S(IV) analogue of biologically relevant sulfonylureas.
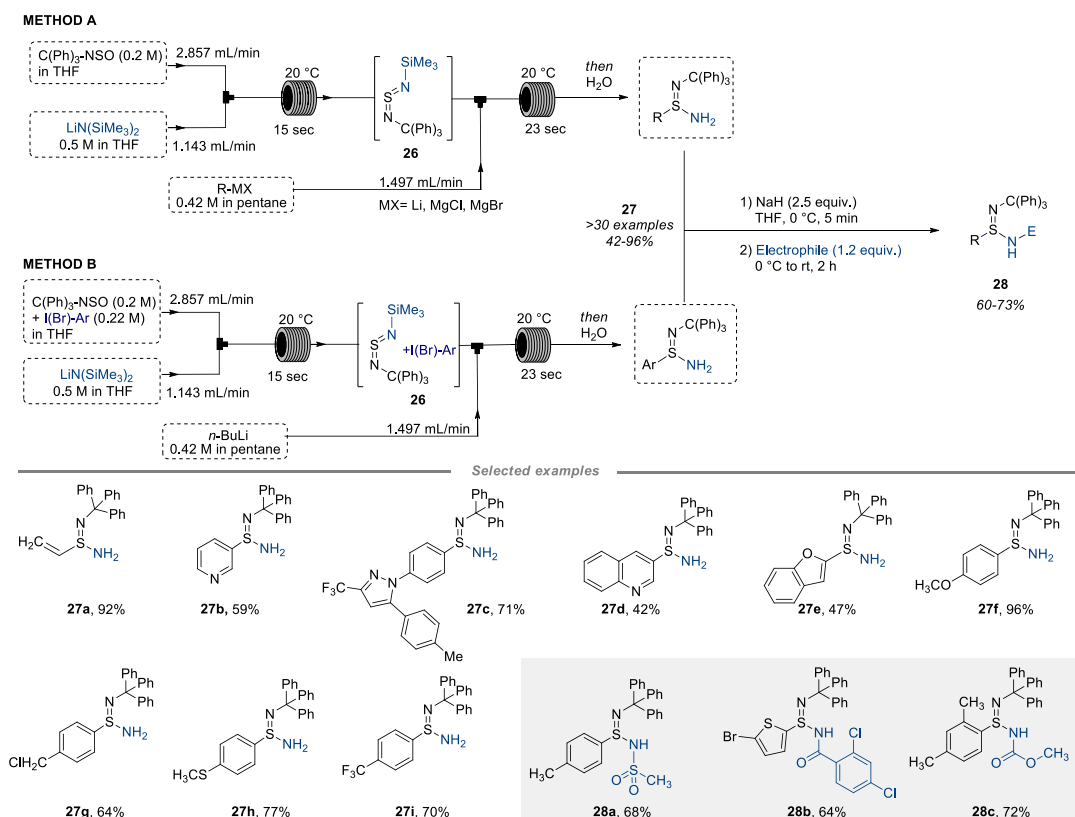
Scheme 11. Continuous-flow preparation of N-trityl sulfinamidines and their functionalization with electrophiles.
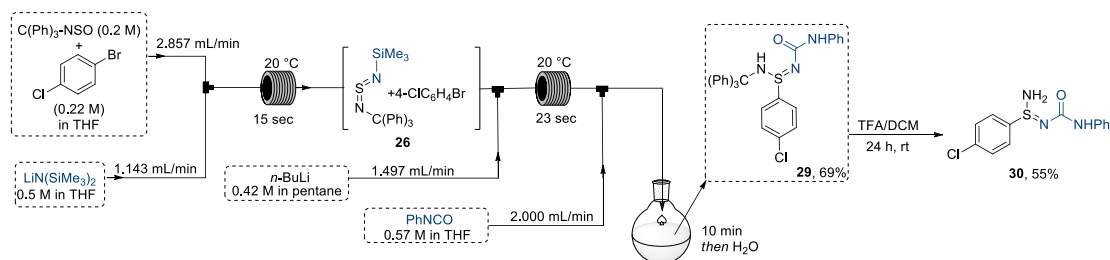
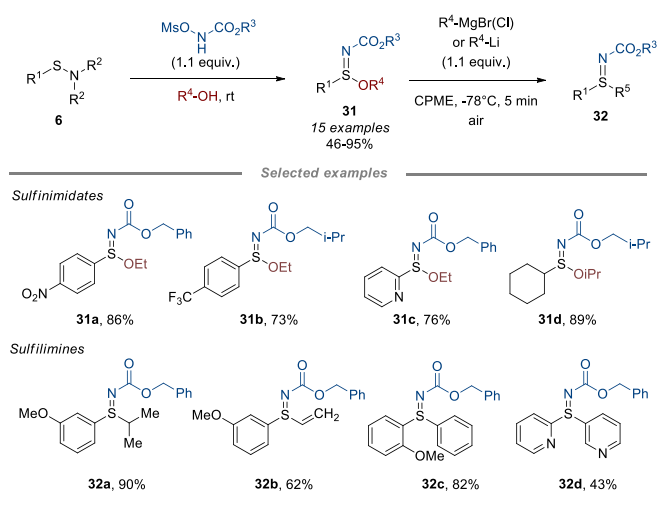**Scheme 12.** Mixed continuous-flow/batch preparation of sulfinimidoyl urea **29** and its deprotection.

3. Sulfinamidate Esters

Sulfinimidates are tetravalent sulfur compounds, where the sulfur atom forms covalent bonds with a carbon, a nitrogen, and an oxygen atom. Sulfinimidate esters have received relatively little attention compared to sulfinamidines, as evidenced by the scarcity of examples documented in the literature. In fact, until 2020 the synthesis of this functional group was limited to harsh and unselective synthetic methods. A very early approach involved the reaction of alcohols or alkoxylates with *N*-sulfonyl sulfinimidoyl chlorides.[34] Alternatively, a single example of imidation of a sulfenate ester with chloramine-B was reported.[21] In 1985 Kresze disclosed the alkylation reaction of

N-tosyl-*S*-allylsulfinamides with diazomethane that gave access to sulfinimidate esters.[35] Moreover, sulfinimidate esters have also been reported as byproducts or as sulfonium salts.[36,37]

As highlighted in this summary, the synthesis of sulfinimidate esters has presented considerable limitations for quite some time. However, we have recently made a noteworthy contribution to advancing the field of sulfinimidate chemistry by uncovering a simple method. Our research has revealed that the amidation reaction between sulfenamides and *N*-mesyloxycarbamates, using alcohols as the reaction medium without the need for a base, selectively yields *N*-carboalkyloxy sulfinimidate esters **35**. (Scheme 13).[14] Under

these conditions, the reaction affords the products arising from the formal substitution of the amine portion by the alcoholic solvent. The optimized conditions used a slight excess of *N*-mesyloxycarbamate (1.1 equivalents) and a primary or secondary alcoholic solvent. This method allowed to obtain S-aryl and S-alkyl sulfinimidates with yields ranging from good to excellent. Further mechanistic studies suggested two possible pathways for this transformation, involving the imidation reaction of the in-situ formed sulfenate esters (Scheme 13, path a), or alternatively the solvolysis of the cationic intermediate **I** (Scheme 13, path b). Notably, *N*-alkyloxycarbonyl sulfinimidates **31** exhibited a marked electrophilic character when treated with strong nucleophiles such as Grignard reagents, furnishing N-protected sulfilimines **32** by substitution of the alkoxy group.[38] This transformation was optimized using CPME as an environmentally responsible solvent and run under air, enabling access to a wide library of sulfilimines with remarkable structural variability The use of organolithium reagents furnished the desired sulfilimines in lower yields.
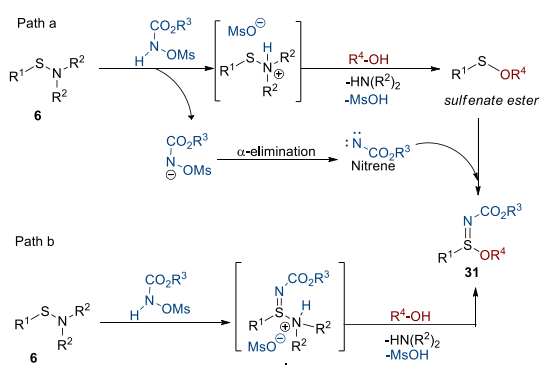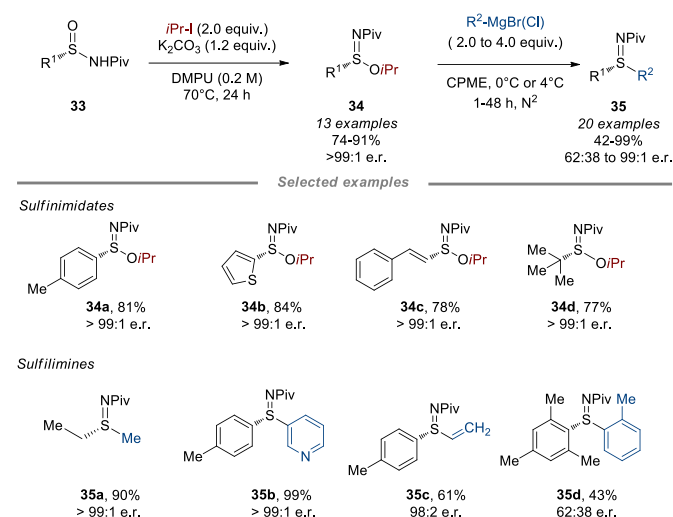

Scheme 13. Synthesis of sulfinimidate esters by imidation of sulfenamides in alcoholic solvents and their reaction with organometallic compounds.

Based on the previous results, Kano and coworkers reported the preparation of chiral optically active sulfinimidate esters by alkylation of chiral sulfinamides **33** (Scheme 14).[39] In detail, they disclosed a stereospecific O-alkylation of enantioenriched *N*-pivaloyl sulfinamides using isopropyl iodide in the presence of

K$_2$CO$_3$ and DMPU. The reaction afforded the corresponding sulfinimidates in good yields and excellent enantiomeric ratios. Further reaction with Grignard reagents furnished the corresponding optically active sulfilimines highly enantioenriched. A reduced stereoselectivity was observed when sterically demanding reagents were employed, as reported for compound **35d** (Scheme 14). Moreover, the transformation was found to be stereospecific, proceeding with inversion of configuration at sulfur via S$_N$2-modality.

Scheme 14. Synthesis of enantiopure sulfinimidate esters by alkylation of optically active sulfinamides and their reaction with Grignard reagents.

In 2023, Lu and coworkers reported the preparation of sulfinimidates from secondary *N*-acyl and *N*-aroyl sulfenamides.[40] A wide library of substrates could be efficiently transformed, including functionalized *S*-alkyl, *S*-aryl and *S*-heteroaryl sulfenamides **10** (Scheme 15). The protocol yielded the desired compounds **36** by reacting sulfenamides with primary or secondary alcohols in the presence of PhI(OAc)$_2$ as the oxidant. Interestingly, the developed method has been successfully applied to gram-scale production without a significant loss in yield. Furthermore, the use of bio-relevant alcohols such as (±)-citronellole and ospemifene was successful resulting in the release of corresponding sulfinimidate esters in good yields (Scheme 15, **36e,f**). Mechanistic investigations suggested that the reaction likely proceeds through the generation of a labile oxidative complex **X**, in which the sulfur is coordinated to the iodine atom, which subsequently undergoes a ligand exchange reaction with the solvent. The reductive elimination step affords the final compound with the formation of an S-O bond (Scheme 15, path a). Alternatively, an intermediate **XI** could be formed, involving the coordination of nitrogen to iodine, which then progresses towards intermediates **XIII** and **XIV** through a ligand exchange and a reductive elimination step, respectively. Finally, the suggested pathway leads to the formation of the target compound **36** after the rearrangement of **XIV** (Scheme 15, path b).
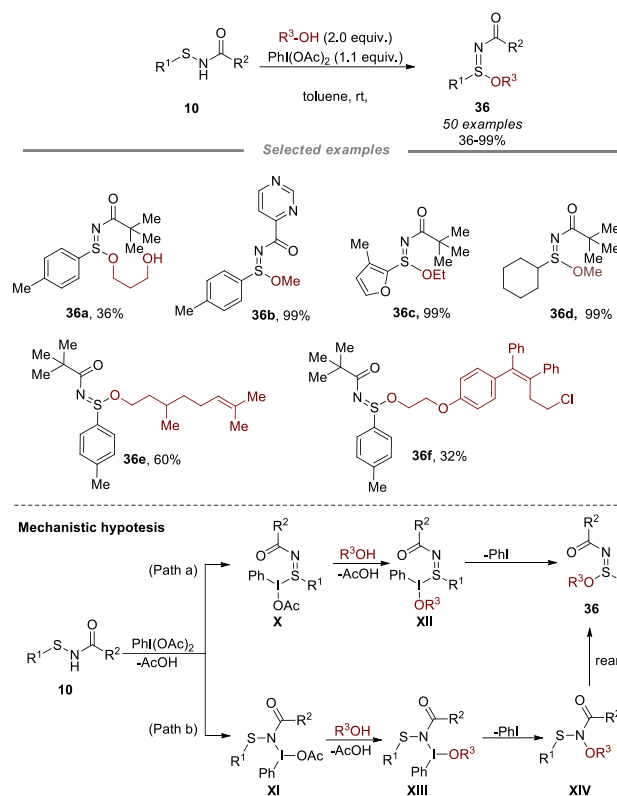
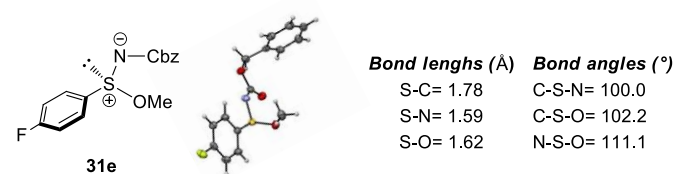**Scheme 15.** Synthesis of sulfinimidate esters **36** from *N*-acyl and *N*-aroyl sulfenamides **10**.

4. Structural features of sulfinamidines and sulfinimidate esters.

Single-crystal X-ray analysis has recently provided valuable insights into the structural features of these overlooked aza-S(IV) motifs. Specifically, in 2020, we obtained the X-ray structure of *N*,*N*-bis-alkyl-*N'*-carbobenzyloxy sulfinamidine **7j**.[14] It was disclosed that the sulfur atom in this compound adopts a pyramidal configuration, with bond angles ranging from 99° to 111° (Figure 2).
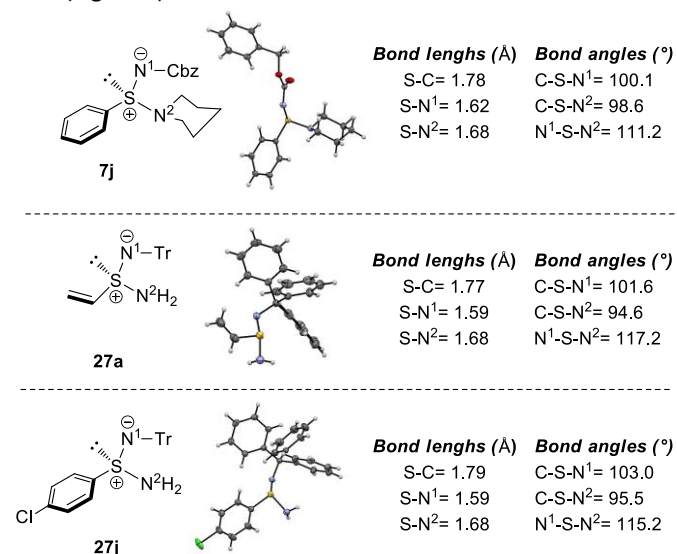
Figure 2. X-ray analysis and structural features of sulfinamidines **7j**, **27a**, **27j**.

The bond lengths were revealed to be 1.62 Å and 1.68 Å for the S-N bonds, and 1.78 Å for the C-S bond. Following this significant result, in 2022, we successfully carried out the first structural characterization of NH₂-sulfinamidines.[33] Once again, a pyramidal sulfur atom was observed (Figure 2). For compound **27a**, the bond angles ranged from 90.1° to 117.1°, while for compound **27j**, they varied from 95.5° to 105.2°. As for the bond lengths, the S-N bonds were assessed to be 1.68 Å (S-NH2), and 1.59 Å (S-NTr) for both the compounds (**27a,j**). Differently, the S-C bond lengths were found to be 1.77 Å (**27a**) and 1.79 Å (**27j**) Å. In 2020, we additionally obtained a single-crystal X-ray structure for sulfinimidate ester **31e** providing, to the best of our knowledge, the first structural elucidation of this aza-S(IV) motif (Figure 3).[14] The crystallographic analysis of sulfinimidate ester **31e** unveiled a pyramidal sulfur, characterized by bond angles ranging from 99° to 111° and bond lengths of 1.78 Å (C–S), 1.62 Å (S–O), and 1.59 Å (S-N) respectively.

Figure 3. X-ray analysis of sulfinimidate ester **31e**.

Conclusions

Organic chemists have recently witnessed significant advancements and a revived interest in the synthesis of overlooked aza-S(IV) motifs. To date, the accessibility of both sulfinamidines and sulfinimidate esters has significantly improved with the introduction of complementary and efficient synthetic methodologies. To the best of our knowledge, there is currently no available information regarding the configurational stability of these chiral functionalities, and no methods for stereocontrolled synthesis have been documented to date. Remarkably, have been introduced new findings on the reactivity of these compounds, highlighting the electrophilic nature of sulfinimidate esters and the potential of sulfinamidines to serve as viable nucleophiles for subsequent transformations. Most interestingly, the oxidation of sulfinamidines to higher valence aza-S(VI) compounds such as sulfonimidamides and sulfondiimidamides represents a key aspect of the synthetic utility of these tetravalent sulfur motifs. Despite this, the realm of organic synthesis continues to find great potential in the chemistry of sulfinimidates and sulfinamidines. Remarkably, there have been no documented instances of lead compounds or bioactive molecules incorporating these intriguing S(IV) aza-functional groups into their structures, as far as we know. This suggests that the absence of effective approaches for crafting such structural motifs has impeded the progress of drug discovery and the creation of synthetic entities with biological significance. Consequently, we remain optimistic that the field of S(IV) aza-functional groups holds even greater promise for the future.

Michael Andresini *is postdoctoral researcher in organic chemistry. He obtained his M.Sci. degree (summa cum laude) in Chemical Sciences from the University of Bari in 2018. In 2023, he obtained his Ph.D. in Chemical and Pharmaceutical Sciences working under the supervision of Prof. Renzo Luisi. In 2021, he was visiting Ph.D. student at the Département de Chimie Moléculaire, Grenoble (France), working in the group of Prof. J.-F. Poisson. His research activity is focused on the development of synthetic strategies for the preparation of sulfur-based functional groups and heterocycles, and continuous flow methods.*

Marco Colella *is researcher of Organic Chemistry at the University of Bari (Italy). He received his M.Sci. (summa cum laude) in Chemistry and Pharmaceutical Technology at the University of Bari (Italy) in 2016. In 2020, he obtained the Ph.D. in Chemical and Molecular Sciences under the supervision of Prof. Renzo Luisi. His research activity is focused on the use of flow microreactor technology applied to organometallic chemistry. In 2019, he was a visiting scholar in the group of Prof. Aiichiro Nagaki (Kyoto). He is the recipient of the 2020 CINMPIS award for the best Ph.D. thesis.*

Leonardo Degennaro *is associate professor of Organic Chemistry at the University of Bari (Italy). He obtained his Ph.D. in Applied Chemical and Enzymatic Synthesis in 2003. In 2002 he was "visiting scholar" at the University of Groningen under the supervision of Prof. B. L. Feringa. In 2006 he was appointed assistant professor in Organic Chemistry at the Department of Pharmacy of University of Bari. In 2011 he was "visiting assistant professor" in the group of Prof. J.-i. Yoshida (Kyoto). The research activity is aimed at developing new stereocontrolled synthesis by using small heterocycles and organometallic species, and microreactor technology.*

Renzo Luisi *is full professor of Organic Chemistry at the University of Bari (Italy). The research activity focuses on the chemistry of hetero-substituted organolithiums, the development of new synthetic methodologies, and the use of flow technology. He obtained the Ph.D. in 2000 under the guidance of Professor Saverio Florio. He was visiting student at the Roger Adams Lab at Urbana Champaign in the group of Prof. Peter Beak, and visiting professor at the University of Manchester in the group of Jonathan Clayden. He is RSC fellow and recipient of the 2022 "Organic Chemistry Research Award in Methodological Aspects in Organic Chemistry" awarded by the Organic Chemistry Division of the Italian Chemical Society. The research activity revolves around sustainable technologies (i.e. Flow technologies), the chemistry of strained heterocycles, and the chemistry of Sulfur, Fluorine and Lithium.*

Author Contributions

R.L., M.A. Conceptualize and Draft Manuscript; M.C., L.D. Review the manuscript.

## Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1   K. A. Scott, J. T. Njardarson, *Top. Curr. Chem.* **2018**, *376*, 5.
2   M. J. Tilby, M. C. Willis, *Expert Opin. Drug Discov.* **2021**, *16*, 1227–1231.
3   U. Lücking, *Org. Chem. Front.* **2019**, *6*, 1319–1324.
4   M. Frings, C. Bolm, A. Blum, C. Gnamm, *Eur. J. Med. Chem.* **2017**, *126*, 225–245.
5   S. Wiezorek, P. Lamers, C. Bolm*, Chem. Soc. Rev.* **2019**, *48*, 5408–5423.
6   B. Altenburg, M. Frings, J.-H. Schöbel, J. Goßen, K. Pannen, K. Vanderliek, G. Rossetti, S. Koschmieder, N. Chatain, C. Bolm, *ACS Med. Chem. Lett.* **2020**, *11*, 1928–1934.
7   M. Andresini, A. Tota, L. Degennaro, J. A. Bull and R. Luisi, *Chem. Eur. J.*, **2021**, *27*, 17293–17321.
8   G. C. Nandi and P. I. Arvidsson, *Adv. Synth. Catal.*, **2018**, *360*, 2976–3001.

9   G. Bhave, C. F. Cummings, R. M. Vanacore, C. Kumagai-Cresse, I. A. Ero-Tolliver, M. Rafi, J.-S. Kang, V. Pedchenko, L. I. Fessler, J. H. Fessler and B. G. Hudson, *Nat. Chem. Biol.*, **2012**, *8*, 784–790.

10 A.-D. Steinkamp, N. Seling, S. Lee, E. Boedtkjer and C. Bolm, *Med. Chem. Commun.*, **2015**, *6*, 2163–2169.

11 E. Wojaczyńska and J. Wojaczyński, *Chem. Rev.*, **2020**, *120*, 4578–4611.

12 Z. Qingle, Q. Zhang, J. Xi and H. Ze, *Synthesis*, **2021**, *53*, 2570–2582.

13 D. Kaiser, I. Klose, R. Oost, J. Neuhaus and N. Maulide, *Chem. Rev.*, **2019**, *119*, 8701–8780.

14 M. Andresini, M. Spennacchio, G. Romanazzi, F. Ciriaco, G. Clarkson, L. Degennaro and R. Luisi, *Org. Lett.*, **2020**, *22*, 7129–7134.

15 W. L. Mock, R. M. Nugent, *J. Am. Chem. Soc.,* **1975**, *97*, 6521–6526.

16 H. Natsugari, R. R. Whittle, S. M. Weinreb*, J. Am. Chem. Soc.,* **1984**, *106*, 7867–7872.

17 G. A. Oliver, M. N. Loch, A. U. Augustin, P. Steinbach, M. Sharique, U. K. Tambar, P. G. Jones, C. Bannwarth, D. B. Werz, *Angew. Chem. Int. Ed.,* **2021**, *60*, 25825–25831.

18 H. Bao, U. K. Tambar, *J. Am. Chem. Soc.,* **2012**, *134*, 18495–18498.

19 H. Bao, L. Bayeh, U. K. Tambar*, Angew. Chem. Int. Ed.*, **2014**, 53, 1664–1668.

20 I. V. Koval, *Rus. J. Org. Chem.,* **2002**, *38*, 232–234.

21 I. V. Koval, *Sulfur reports,* **1993**, *14*, 149–215.

22 G. Celentano, S. Colonna, *Chem. Commun.,* **1998**, 701–702.

23 M. Haake, H. Benack, *Synthesis,* **1976**, *1976*, 308–310.

24 G. Yang, H. Huang, X. Nie, S. Zhang, X. Cui, Z. Tang and G. Li, *J. Org. Chem.*, **2023**, *88*, 4581–4591.

25 Z.-X. Zhang, C. Bell, M. Ding and M. C. Willis, *J. Am. Chem. Soc.,* **2022**, *144*, 11851–11858.

26 M. Klein, D. L. Troglauer and S. R. Waldvogel, *JACS Au*, **2023**, *3*, 575–583.

27 Z. Zhong, J. Chesti, A. Armstrong and J. A. Bull, *J. Org. Chem.*, **2022**, *87*, 16115–16126.

28 G. Huang, J. Ye, M. A. Bashir, Y. Chen, W. Chen and X. Lu*, J. Org. Chem.*, **2023**, *88*, 11728–11734.

29 X. Lu, G. Huang, J. Ye, Y. Chen, M. Tan, *ChemRxiv.* Cambridge: Cambridge Open Engage; **2023**. DOI: 10.26434/chemrxiv-2023-31393-v2

30 G. Kresze and W. Wucherpfennig, *Angew. Chem. Int. Ed. Engl.*, **1967**, *6*, 149–167.

31 B. Walfort, R. Bertermann and D. Stalke, *Chem. Eur. J.*, **2001**, *7*, 1424–1430.

32 Z.-X. Zhang and M. C. Willis, *Chem*, **2022**, *8*, 1137–1146.

33 M. Andresini, S. Carret, L. Degennaro, F. Ciriaco, J. Poisson and R. Luisi, *Chem. Eur. J.*, **2022**, 28, doi: 10.1002/chem.202202066

34 E. S. Levchenko and L. V. Selesnenko, *Russ. J. Org. Chem.* **1966**, *2*, 890.

35 A. J. Ruminy, G. Kresze, *Phosphorus Sulfur Silicon Relat. Elem.* **1987**, *29*, 49–56.

36 Y. Maeda, S. Hamada, Y. Aota, K. Otsubo, T. Kano, K. Maruoka, *J. Org. Chem.* **2022**, *87*, 3652–3660.

37 H. Kitagawa, J. Matsuo, D. Iida, T. Mukaiyama, *Chem. Lett.* **2001**, *30*, 580–581.

38 M. Andresini, M. Spennacchio, M. Colella, G. Losito, A. Aramini, L. Degennaro and R. Luisi, *Org. Lett.*, **2021**, *23*, 6850–6854.

39 S. Tsuzuki and T. Kano, *Angew. Chem. Int. Ed.*, **2023**, 62, doi: 10.1002/anie.202300637.

40 X. Lu, G. Huang, J. Ye, M. A. Bashir, J. Su, K. Yang, F. Liang and X. Xu, *Org. Lett.*, **2023**, *25*, 2151–2156.

TOC
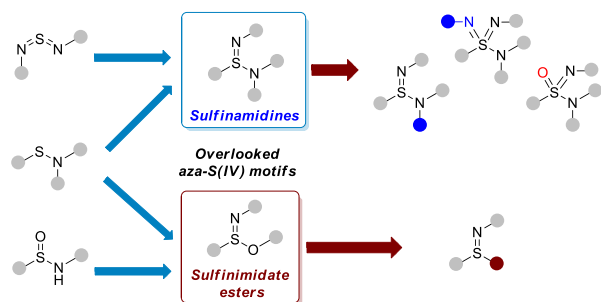
Significant advancements have recently been made in the chemistry of sulfinamidines and sulfinimidate esters. This review aims to provide an in-depth overview of the efficient methods for the preparation and transformation of these overlooked compounds.