Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202202066

Chemistry Europe
European Chemical Societies Publishing

www.chemeurj.org

Multistep Continuous Flow Synthesis of Isolable NH_2-Sulfinamidines via Nucleophilic Addition to Transient Sulfurdiimide

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Abstract: The growing interest in novel sulfur pharmacophores led to recent advances in the synthesis of some S(IV) and S(VI) motifs. However, preparation and isolation of uncommon primary sulfinamidines, the aza-analogues of sulfinamides, is highly desirable. Here we report a multistep continuous flow synthesis of poorly explored NH_2-sulfinamidines by nucleophilic attack of organometallic reagents to in situ prepared *N*-(trimethylsilyl)-*N*-trityl-λ^4-sulfanediimine (Tr–N=S=N–TMS). The transformation can additionally be realized under mild conditions, at room temperature, via a highly chemoselective halogen-lithium exchange of aryl bromides and iodides with *n*-butyllithium. Moreover, the synthetic potential of the methodology was assessed by exploring further manipulations of the products and accessing novel S(IV) analogues of celecoxib, tasisulam, and relevant sulfinimidoylureas.

Introduction

Sulfur-bearing functional groups play a leading role in the discovery of biologically relevant compounds for pharmaceutical and agrochemical applications.[1] While the use of sulfonamides, sulfones, and sulfoxides is widespread, very minor attention has been addressed to the exploitation of their aza-analogue.[2] In this scenario, sulfoximines, sulfonimidamides, and sulfondiimides are catching attention in modern drug discovery programs (Scheme 1, A).[3,4] The substitution of an oxygen atom with nitrogen can finely tune the physicochemical properties of the compounds and offers the possibility to explore a wider chemical space by varying the substituents on the nitrogen atom.[5] Hence, several efficient synthetic methods for the installation of these functional groups have been concurrently reported.[6,7,8] Interestingly, Willis and coworkers have recently prepared diverse electrophilic sulfinylamine reagents for the installation of Sulfur (IV and VI) functional groups to carbon nucleophiles.[9,10] In this context, while great efforts have been put in obtaining fashionable S(VI) functional groups, minor to no attention has been addressed to the synthesis of some S(IV) compounds (Scheme 1, A).

Sulfinamidines, the aza-analogues of sulfinamides, could be exploited as potential chiral sulfur pharmacophores, but their application is totally unexplored. This might be due to the lack of effective methods for their synthesis.[11] In this regard, we recently described the first general strategy for the preparation of *N*-alkyloxycarbonyl sulfinamidines and sulfinimidate esters by a nitrogen transfer to sulfenamides and explored their reactivity (Scheme 1, B).[12] In continuation of our interest in the development of synthetic tactics for accessing underexplored sulfur functional groups and being inspired by the recent literature concerning the use of electrophilic sulfur sources, we targeted the preparation of *N*-(trimethylsilyl)-*N*-trityl-λ^4-sulfanediimine (Tr–N=S=N–TMS) and documented its synthetic utility as a precursor of novel primary sulfinamidines by coupling with organometallic reagents.

While preparing this manuscript, Willis independently reported a six steps and two steps batch preparation of sulfondiimidamides starting from *N*-(triisopropylsilyl)- or *N*-(*t*-octly)- sulfinylamine and organometallic reagents (Scheme 1, C).[13,14] In these reports, the transient sulfurdiimide was prepared under cryogenic conditions (i.e. −30 to 0 °C) from sulfinylamine and $LiN(SiMe_3)_2$ in the presence of a stoichiometric amount of Me_3SiCl, and further reacted at low temperature with organometallic reagents. The *N*-functionalized sulfinami-

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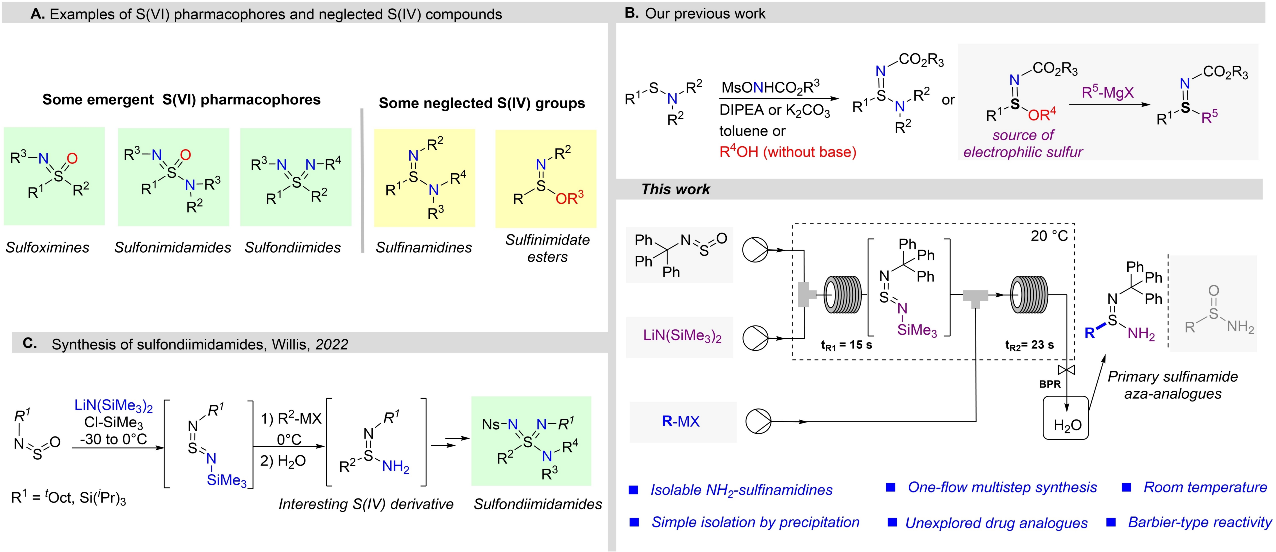
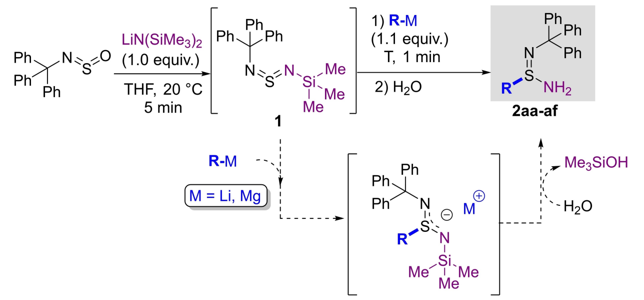
Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202202066



Scheme 1. [a] Examples of emergent S(VI) pharmacophores and neglected S(IV) motifs; [b] Preparation and reactivity of protected sulfinamidines and sulfinimidate esters; [c] Synthesis of sulfondiimidamides; Bottom: the multistep microfluidic approach to isolable NH_2-sulfinamidines reported in this work.

dines were then isolated by trapping with electrophilic reagents (i.e. NsCl, Br-CN, Ac2O, TsCl, Cbz-Cl), and further manipulated to afford valuable higher valence sulfur compounds. In the present work, we have been able to complement Willis' methodology under continuous flow conditions, at room temperature, and using an unsymmetrical sulfurdiimide, smoothly prepared from bench stable TrNSO and $LiN(SiMe_3)_2$. The use of the removable N-trityl group allows to easily isolate unprecedented primary sulfinamidines, which have been also characterized for the first time by X-ray analysis and further used in continuous flow reactions with organometallic reagents

Table 1. Synthesis of sulfinamidines **2 aa–af**.

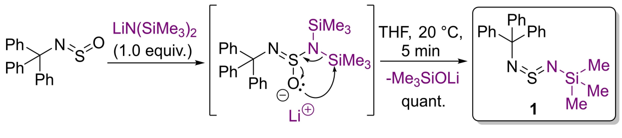


entry	R-MX	T (°C)	Yield (%)[a]
1	*n*BuLi	−78	**2 aa**, 88
2	PhLi	−78	**2 ab**, 93
3	PhLi	0	**2 ab**, 95
4	PhLi	20	**2 ab**, 94
5	BnMgCl	20	**2 ac**, 89
6	*i*PrMgBr	20	**2 ad**, 82
7	*i*PrMgCl·LiCl	20	**2 ad**, 80
8	$CH_2CHMgBr$	20	**2 ae**, 89
9	*t*BuMgCl	20	**2 af**, 75

[a] Yields for isolated products.

Results and Discussion

We started our investigation by preparing the *N*-(trimethylsilyl)-*N*-trityl-λ^4-sulfanediimine **1** by reaction of *N*-trityl sulfinylamine (Tr-NSO) with $LiN(SiMe_3)_2$ in THF at room temperature. The transformation occurred within only 5 minutes, and furnished sulfurdiimide **1** likely via an aza-Peterson-like elimination pathway (Scheme 2).



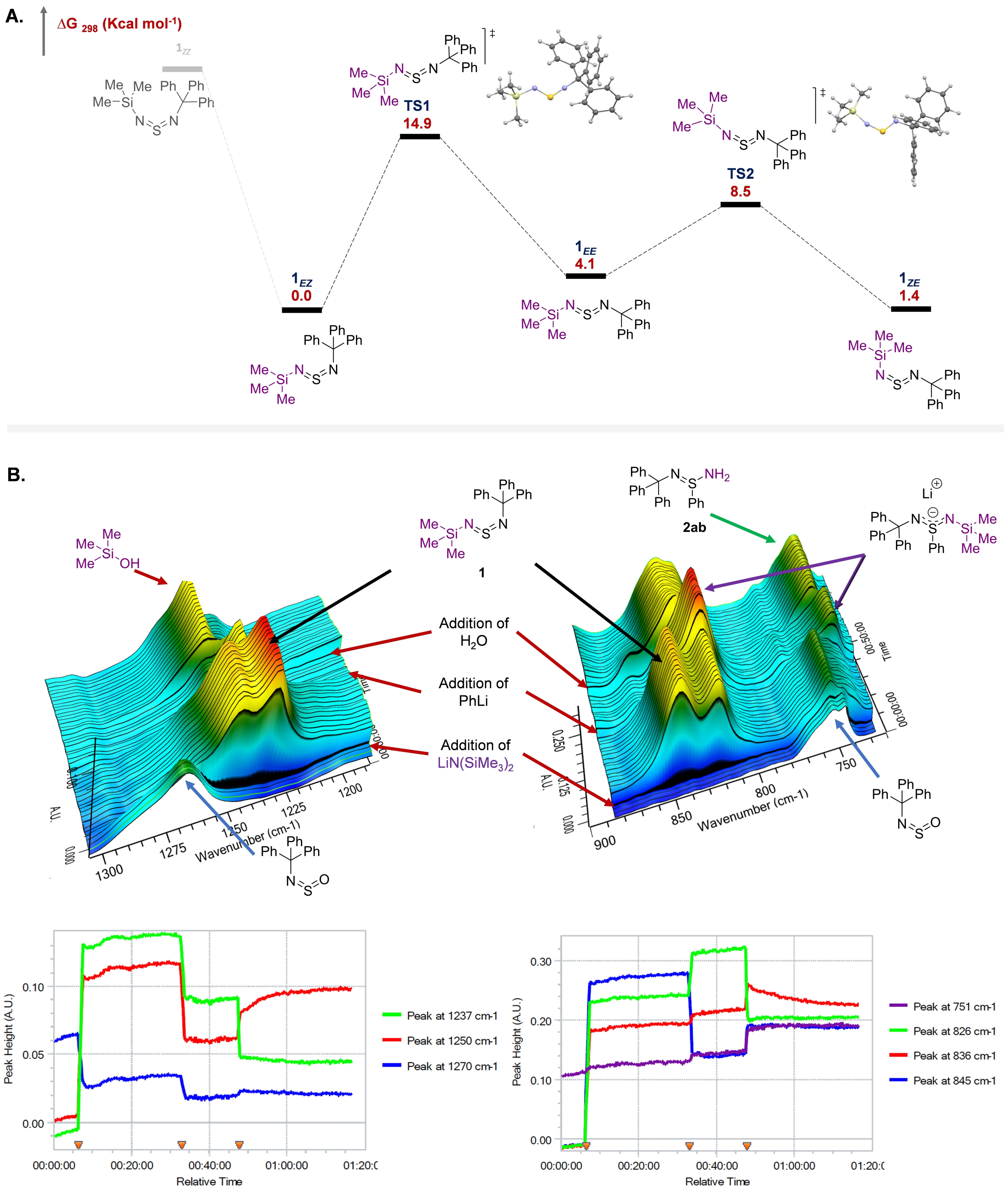
Scheme 2. Preparation of unsymmetrical sulfurdiimide **1**.

Although we were not able to isolate the product, we could directly react transient sulfurdiimide **1** with organometallic reagents en route to the corresponding primary sulfinamidines (Table 1). First, a solution of freshly prepared sulfurdiimide **1** was reacted with *n*BuLi and PhLi in THF at −78 °C, and the resulting mixture was stirred for 1 minute before quenching with water. To our delight, sulfinamidines **2 aa,ab** were easily isolated in very good yields from the crude mixture by simple precipitation from ethyl acetate/pentane after the aqueous work-up (see Supporting Information for further information) (Table 1, entries 1–2). As expected, the cleavage of the trimethylsilyl group occurred spontaneously during the addition of water.[10d] Performing the reaction with PhLi, at a higher temperature, we observed no reduction of yields (Table 1, entries 2–4), and we envisioned that diverse organometallics could be employed, avoiding cryogenic conditions. Therefore, different organomagnesium compounds were tested and delightfully afforded sulfinamidines **2ac**–**af** in good yields (Table 1, entries 5–9). It is worth pointing out that, differently from *N*-*t*-octyl and *N*-triisopropylsilyl protected primary sulfinamidines, *N*-trityl sulfinamidines showed good stability to heat and moisture, and the work-up did not require any particular precaution.[13,14] Encouraged by these promising results and relying on our expertise in the field of flow chemistry, we became interested in developing an easily automatable and multistep continuous flow method for accessing a variety of primary sulfinamidines exploiting this green technology.

In this context, flow technology offers several advantages allowing for the easy use of hazardous and toxic chemicals, such as organometallic reagents, and strong bases, in a confined space, and prevents the operator from direct handling.[15] Furthermore, the scalability of the process is ensured by long-runs and parallel approach, making the technology appealing for scale-up purposes.[16] Before starting the investigation under continuous flow conditions, we wanted to shed some light on mechanistic details for this transformation merging computational and spectroscopic information. In fact, spectroscopic data would provide details on the kinetic of the reaction justifying the use of flow technology for this expected fast transformation. Second, calculations would provide insights into the structure of unsymmetrical sulfurdiimides. The occurrence of unsymmetrical sulfurdiimides in the synthetic scenario is rather rare, and very little information can be found in the literature.[17]

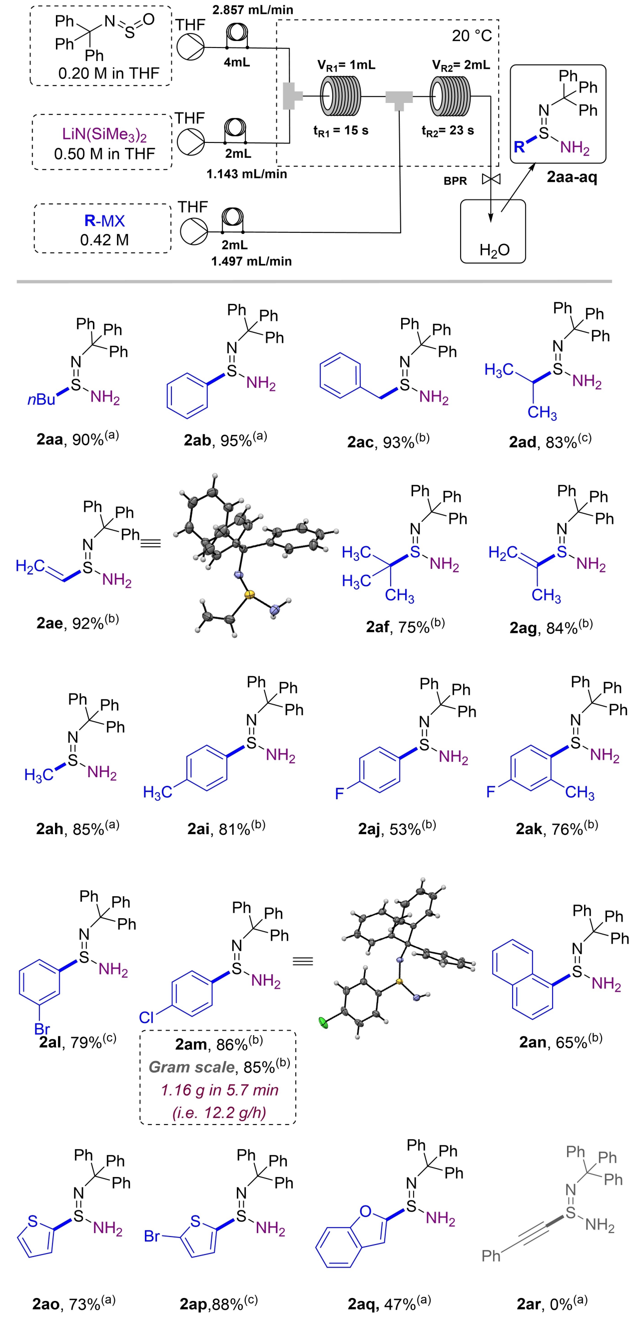
It is worth mentioning that stereoisomeric issues can be envisaged in sulfurdiimide **1**, depending on the orientation of the N-substituents with respect to the N=S=N backbone. We investigated in silico the isomerization at both nitrogen atoms via a rotation-like pathway on the C/Si-N-S-N dihedral angle, considering the solvent with a continuum solvation model (Scheme 3, A). The results suggested that the isomerization on both nitrogen atoms is expected to be very fast at room temperature in THF. The *E*(N–Si)*Z*(N–Tr) **1**$_{EZ}$ isomer was found to be the most stable, while a stable geometry for isomer **1**$_{ZZ}$ was computationally ruled out, likely because of the bulky nature of both N-substituents.[18] Interestingly, the inversion at the two different N-centers is characterized by significantly different activation energies (TS1, $\Delta G^{\ddagger}_{(EE\rightarrow EZ)}=10.8\ \mathrm{kcal\,mol^{-1}}$ and TS2, $\Delta G^{\ddagger}_{(EE\rightarrow ZE)}=4.4\ \mathrm{kcal\,mol^{-1}}$) and both TSs present S–N–Si/C angles approaching 180°. Taking into account the highest energetic barrier ($\Delta G^{\ddagger}_{(EZ\rightarrow EE)}=14.9\ \mathrm{kcal\,mol^{-1}}$), the equilibrium is assumed to be quickly reached, considering the limiting $k_{(EZ\rightarrow EE,\ 298.15K)}$ of 118 $\mathrm{s^{-1}}$. The solution is therefore populated mostly by stereoisomer **1**$_{EZ}$ (Boltzmann population at 298.15 K = 0.91) and **1**$_{ZE}$ (Boltzmann population at 298.15 K = 0.09), while the presence of **1**$_{EE}$ is negligible. Moreover, frequency analysis for **1**$_{EZ}$ in THF showed the presence of a characteristic N=S=N unsymmetrical stretching at slightly lower frequencies (about 40 $\mathrm{cm^{-1}}$) compared to the predicted N=S=O unsymmetrical stretching of the starting sulfinylamine (see Supporting material). With this information in hand and aiming to get more insights into the rate of the nucleophilic addition to sulfurdiimide **1**, we performed an in situ FTIR monitoring experiment. The results of this study are reported in Scheme 3 (B). According to computational data, we observed the complete disappearance of the characteristic vibration mode of TrNSO at 1270 $\mathrm{cm^{-1}}$ and the almost instantaneous formation of two intense signals at 1250 and 1237 $\mathrm{cm^{-1}}$ (see Supporting material). After the addition of phenyllithium, new signals were observed, reasonably related to the generation of the anionic intermediate (826 $\mathrm{cm^{-1}}$), which suddenly afford the final product **2ab** after the addition of water (see Supporting material). In fact, the cleavage of the N–Si bond seems to occur fast, and the signal of trimethylsilanol, deriving from the generation of the sulfurdiimide and the nitrogen deprotection, could be observed.[19] Merging computational and spectroscopic data, we postulate that one main stereoisomer (i.e. **1**$_{EZ}$) is involved in the nucleophilic addition of the organometallic reagent and that the formation of the sulfurdiimide, as well as the addition of the organometallic reagent, are very fast events. In addition, in situ FTIR analysis reveals that the silyl group remains attached to the nitrogen atom until the addition of water. With this picture in mind, we started to investigate the reaction under continuous flow conditions. It is widely recognized that the accurate heat transfer realized in flow microreactors makes this technology ideal for fast or very fast processes. For the optimization of the protocol, we employed a Vapourtec R2+ series equipped with two PTFE reactors ($\varnothing_{\mathrm{int}}=0.5$ mm) a passive back pressure regulator, and two stainless-steel T-shape micromixers ($\varnothing_{\mathrm{int}}{}^{1}=$ 250 μm and $\varnothing_{\mathrm{int}}{}^{2}=500$ μm). The reagent solutions were loaded in loops and then injected into the system using six-port valves and distilled THF as described in Scheme 4. Under optimized flow conditions (see Supporting Information for further details), the quantitative formation of sulfurdiimide **1** was observed at 20 °C using a residence time of 15 s. Subsequent reaction with *n*BuLi occurred in a second T-mixer, and after 23 s as residence time the outlet was quenched with water affording sulfinamidine **2aa** in 90 % yield (Scheme 4). Next, we explored the scope of the reaction by employing a selection of organometallic nucleophiles and collecting the outlet solution for 55 seconds under steady-state conditions (i.e. 0.53 mmol scale). Satisfyingly, all organometallic reagents reported in Table 1 led to the primary sulfinamidines **2aa**–**2af** in good to excellent yields under these flow conditions (Scheme 4).

Other organolithium compounds were next employed. For instance, the reaction of methyllithium gave sulfinamidine **2ah** in 85 % yield, and heteroaryl organolithium, with pharmaceutically relevant motifs (i.e. 2-thienyl and 2-benzofuranyl), afforded products **2ao** and **2aq** in 73 % and 47 % respectively. Surprisingly, we were not able to observe the formation of the expected product **2ar** with lithium phenylacetylide, likely because of a scarce reactivity of C_{sp} nucleophiles with the electrophilic sulfur, in line with previous observations.[12b] The reaction scope was further expanded employing diverse organomagnesium reagents. The transformation was compatible with methyl (**2ai**, 87 %), fluorine (**2aj**, 53 %), chlorine (**2am**, 86 %), and bromine (**2al**, 79 %) substituents on the aromatic rings as well as with an ortho-para disubstituted (**2ak**, 76 %) aromatic ring. Other arylmagnesium halides could be likewise employed, as for 1-naphthyl and 5-(2-bromothienyl) derivatives **2an** (65 %) and **2ap** (88 %). Moreover, the scalability of the



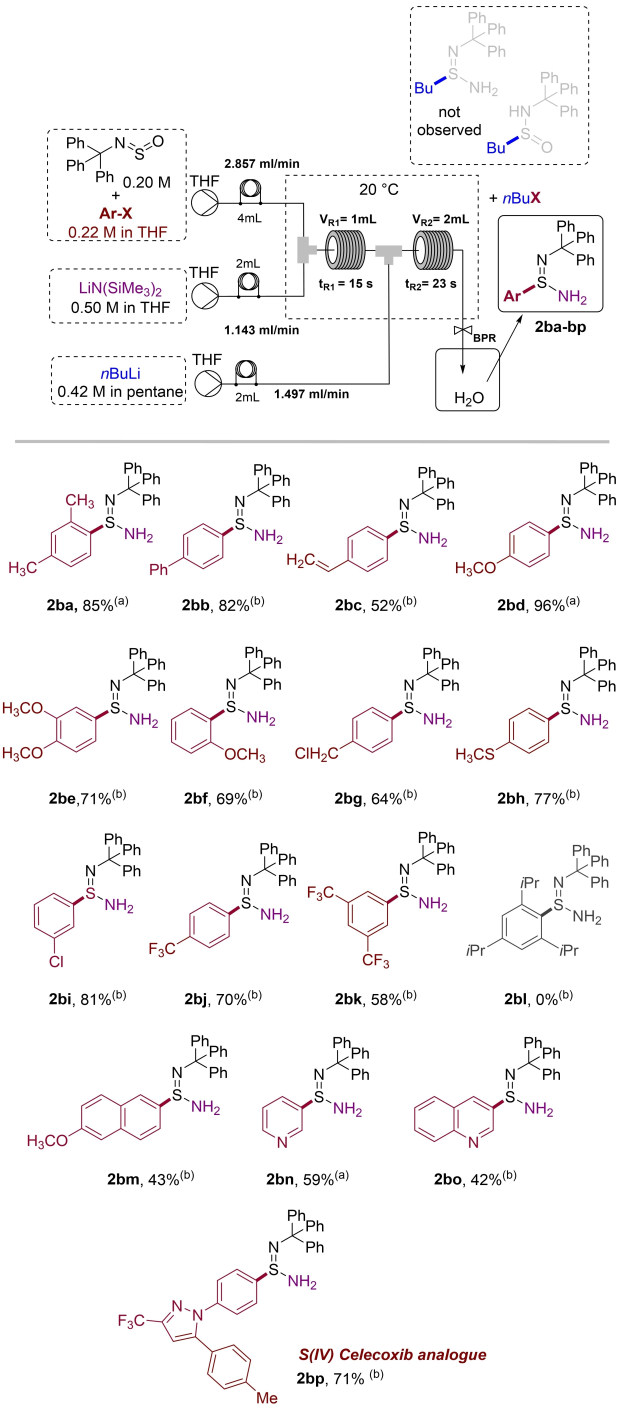
Scheme 3. [a] Computational study of sulfurdiimide isomers interconversion: dihedral angle scan operated with ORCA, B3LYP-def2-SVP, equilibrium geometries and transition states calculated at DSM(THF)-ωB97X–D3BJ-def2-TZVP. Relative Gibbs energies are reported in Kcal mol^{-1} considering ΔG_{298} (**1**$_{EZ}$) = 0.0. [b] In-situ IR monitoring experiment: synthesis of sulfinamidine **2ab** (see Supporting Information for further details).

process was assessed by performing a larger scale: collection of the outlet solution for 5.7 min afforded 1.16 g (i.e. 12.2 g/h) of the sulfinamidine **2am** (85 % yield). Due to the novelty of these sulfur-centered motifs, we were also interested in providing a structural unambiguous characterization for sulfinamidines **2**. Pleasingly, single crystal X-ray analysis of **2ae** and **2am** revealed the first crystal structure of a primary sulfinamidine. As expected, a pyramidal sulfur atom was observed, with bond angles ranging from 90.1° to 117.1° for **2ae** and from 95.5° to 105.2° for **2am**.[20] However, this efficient flow protocol is



Scheme 4. Continuous flow synthesis of NH$_2$-sulfinamidines. Yields are for isolated products. [a] Organolithiums used; [b] Grignard reagents used; [c] turbo-Grignard reagents used.

limited to the use of preformed solutions of organometallic reagents, which indeed could suffer from degradation at room temperature and depends on commercial availability. To overcome this limitation, and expand the scope of the flow methodology, we explored the possibility of selectively transforming sulfurdiimide **1** using organometallic reagents directly generated in flow. To this end, a solution of Tr-NSO (1.0 equiv.) and 4-iodo-*m*-xylene (1.1 equiv.) was first reacted at room temperature with LiN(SiMe$_3$)$_2$ (1.0 equiv.) and subsequently reacted with *n*BuLi (1.1 equiv.). To our delight, the ^{1}H NMR analysis of the crude showed the exclusive formation of 4-*m*-xylylsulfinamidine **2ba**, resulting from the selective addition of lithiated m-xylene to in-flow generated sulfurdiimide **1** (Scheme 5). Remarkably, under these conditions, two reactive events - i.e. the generation of sulfurdiimide **1** and the iodine-lithium exchange reaction on the iodoarene – occurred with excellent control of the selectivity (Scheme 5). In fact, the side products deriving from the attack of *n*BuLi to Tr-NSO or



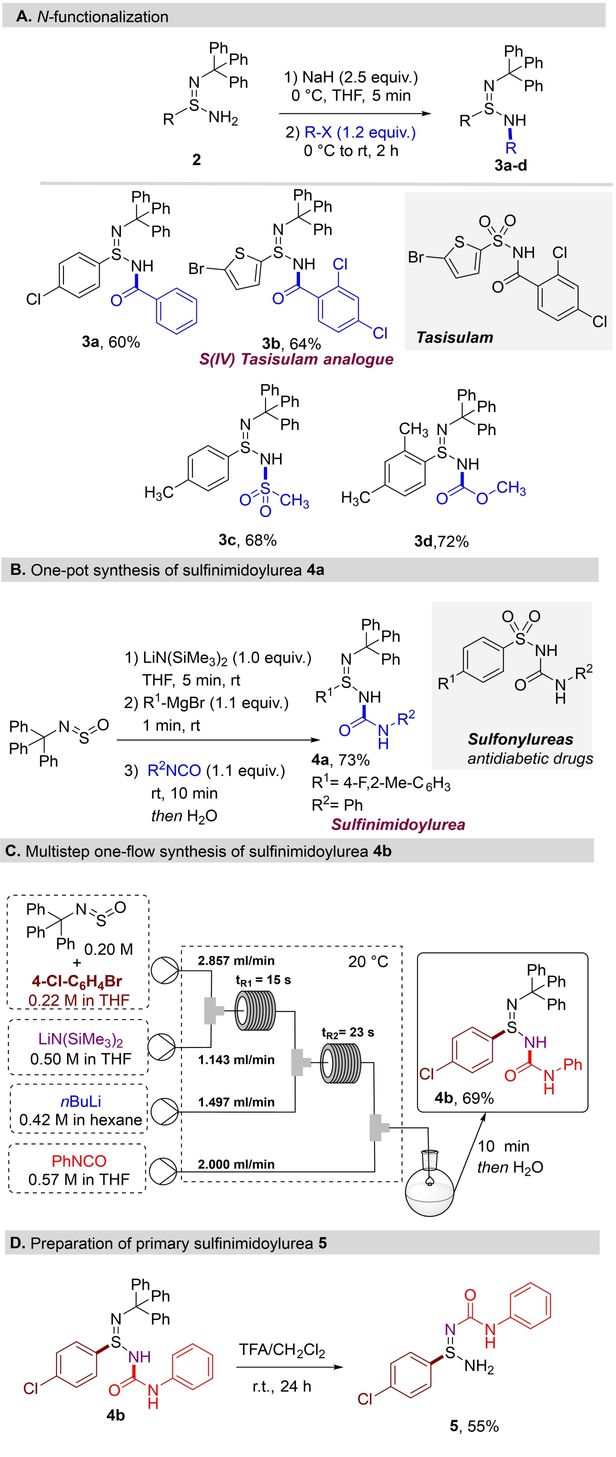
Scheme 5. Continuous flow synthesis of NH$_2$-sulfinamidines. Yields are for isolated products. [a] from iodoarenes; [b] from bromoarenes.

sulfurdiimide **1** were not observed (Scheme 5). By using the same protocol, 4-bromobiphenyl could be selectively lithiated and successfully reacted with **1** to furnish **2bb** in 82% yield, thus suggesting that even cheaper aryl bromides could be employed. Next, we explored the scope by employing a library of substituted aryl halides leading to *S*-aryl substituted sulfinamidines bearing a vinyl (**2bc**, 52%), chloromethyl (**2bg**, 64%), methylthio (**2bh**, 77%), and chlorine (**2bi**, 81%) as the substituents on the aromatic ring (Scheme 5). The flow protocol remained efficient using aryl bromides carrying either electro-donating (**2bd–bf**) or electron-withdrawing groups (**2bj–2bk**) and a variety of aryl substituents. Moreover, the presence of a methyl (**2ba**) or a methoxy group (**2bf**) at the *ortho* position of the aromatic ring was well tolerated. The reaction however met some steric limitations as sulfinamidine **2bl** could not be prepared from 1-bromo-2,4,6-triisopropylbenzene. Several aryl-lithiums were tested, allowing for the formation of primary sulfinamidines from 2-bromo-6-methoxynaphthalene (**2bm**), 3-iodopyridine (**2bn**) and 3-bromoquinoline (**2bo**) in good yields (Scheme 5).

The robustness of the method was further proved by targeting the installation of the sulfinamidine motif to the more complex 1-(4-bromophenyl)-5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazole, affording compounds **2bp** in 71% yield, a novel S(IV) analogue of the anti-inflammatory drug Celecoxib. Notably, this method allowed employing, at room temperature, a wide number of aryllithiums that usually require cryogenic conditions for their effective use (e.g. 3-pyridinyllithium, (3,5-bis(trifluoromethyl)phenyl)lithium).[21] Moreover, the Barbier-type method requires three pumps for the reagent solutions delivery, while the need of preforming the aryllithium in a separate reactor would have required an additional pump, complicating the flow set-up.

Finally, we tested the reactivity of the newly formed NH_2-sulfinamidines **2**, in particular with the functionalization with electrophiles of the primary NH_2 position.

Using NaH followed by benzoyl anhydride smoothly afforded *N*-benzoyl sulfinamidine **3a** (60%, Scheme 6, A). In turn, the reaction with 2,4-dichlorobenzoyl chloride led to *N*-acyl sulfinamidine **3b**, that represents a lower valence aza-analogue of the antitumor agent Tasisulam. In addition, methanesulfonyl chloride and methyl chloroformate could be employed, affording substituted sulfinamidines **3c** and **3d** in good yields (Scheme 6, A). In a complementary manner, starting from Tr-NSO, the anionic intermediate could also be in situ intercepted with phenyl isocyanate, providing the corresponding adduct **4a** (73%, Scheme 6, B). Notably, this sulfinimidoylurea represents a S(IV) analogue of pharmaceutically relevant sulfonylureas, an important class of antidiabetic drugs.[22] Due to the importance of such derivatives, we implemented a multi-step one-flow method for the preparation of sulfinimidoylurea **4b** (Scheme 6, C). Pleasingly, we were able to prepare compound **4b** executing three different synthetic steps in one-flow fashion. In detail, the flow set-up (see Supporting material) allowed for a (chemo)selective generation of sulfurdiimide **1**, followed by bromine-lithium exchange and nucleophilic addition of the resulting aryllithium, and the final reaction of the anionic intermediate with PhNCO, all in the same microfluidic system. Batch quenching of the outlet with water provided **4b** in 69% yield.



Scheme 6. [a] Transformation of NH_2-sulfinamidines with electrophiles. [b] One-pot synthesis of sulfinimidoylurea **4a**. [c] Multistep one-flow synthesis of sulfinimidoylurea **4b**.[d] N-trityl deprotection.

Finally, for further studies and applications, it was important to remove the trityl group from the S(IV) center. Treatment of the protected sulfinimidoylurea **4b** with TFA/CH_2Cl_2 (1:1) satisfyingly resulted into the cleavage of the N-trityl group, affording the unprecedented primary sulfinimidoylurea **5** (Scheme 6, D).

Conclusion

We have developed a scalable continuous flow strategy for the preparation of NH_2-sulfinamidines. We were able to provide a simple and automatable protocol for accessing new valuable compounds from readily available reagents, at room temperature, harnessing the installation of the trityl group en route to stable primary sulfinamidines, and addressing their manipulation to access underexploited sulfur functionalities. The method involves the generation of transient sulfurdiimide Tr-N=S=N-TMS, which could be directly reacted with organometallics, some selectively in situ generated from haloarenes and *n*BuLi. The products were easily purified by precipitation, and structural details were provided by single crystal X-ray analysis. The combination of computational studies and in situ FTIR monitoring helped to elucidate the reaction pathway, while further manipulations of the products gave some insights into the reactivity pattern of the NH_2-sulfinamidines. Moreover, the method allows for the preparation of unexplored S(IV) analogues of pharmaceutically relevant Celecoxib and Tasisulam, and interesting sulfinimidoylureas. Further investigation regarding the synthesis and reactivity of neglected S(IV) compounds is ongoing in our labs and will be reported in due course.

Experimental Section

Continuous flow synthesis of NH_2-sulfinamidines from organolithium and organomagnesium compounds: The process can be executed using Vapourtec R2+ series with two PTFE reactors ($Ø_{\mathrm{int}}=0.5$ mm) of 1 mL (R_1) and 2 mL (R_2) with a passive back pressure regulator. The solutions were prepared and loaded in PTFE loops as follows: loop A, 2 mL, $LiN(SiMe_3)_2$ 0.50 M in dry THF (1.00 mmol) [Solution A]; Loop B, 4 mL, Tr-NSO 0.20 M in dry THF (0.80 mmol, 244 mg) [Solution B]; Loop C, 2 mL, R-MX 0.42 M in the proper dry solvent, as described for each entry in the Supporting Information (0.84 mmol) [Solution C]. Solvent bottles containing freshly distilled THF under nitrogen atmosphere were employed for pushing solutions A, B and C in the system. The three solutions were pumped into the system using the following flow rates: Solution A [$LiN(SiMe_3)_2$] 1.143 mL/min; Solution B [Tr-NSO] 2.857 mL/min; Solution C [R-MX] 1.497 mL/min. The T-mixers and reactors were kept at 20 °C using a thermostated water bath. Solutions A and B were mixed using a stainless-steel T-shape micromixer ($Ø_{\mathrm{int}}=250$ μm). The resulting solution was passed through R_1 (1 mL, $t_{R1}=15$ s), mixed with solution C by a stainless-steel T-shape micromixer ($Ø_{\mathrm{int}}=500$ μm) and introduced in R_2 (2 mL, $t_{R2}=23$ s). The resulting solution was collected directly in a stirred flask with water (5 mL), after reaching the steady state (67 s) for 55 s (i.e., 0.53 mmol scale). The mixture was washed with brine and extracted with AcOEt (3× 15 mL). The organic phases were collected, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude was dissolved in the minimum quantity of AcOEt at 40 °C, then pentane (15 mL) was added, and the product was allowed to precipitate from the solution at −25 °C. Once the supernatant appeared clear, it was removed, and the products could be obtained as shown in the Supporting Information.

Continuous flow synthesis of NH_2-sulfinamidines via halogen-lithium exchange: The process can be executed using Vapourtec R2+ series with two PTFE reactors ($Ø_{\mathrm{int}}=0.5$ mm) of 1 mL (R_1) and 2 mL (R_2) with a passive back pressure regulator. The solutions were prepared and loaded in PTFE loops as follows: Loop A, 2 mL, $LiN(SiMe_3)_2$ 0.50 M in dry THF (1.00 mmol) [Solution A]; Loop B, 4 mL, Tr-NSO (0.80 mmol, 244 mg, 0.20 M) + Ar–X (0.88 mmol, 0.22 M) in dry THF [Solution B]; Loop C, 2 mL, *n*BuLi 0.42 M in pentane (0.84 mmol) [Solution C]. Solvent bottles containing freshly distilled THF under nitrogen atmosphere were employed for pushing solutions A, B and C into the system. The three solutions were pumped in the system using the following flow rates: Solution A [$LiN(SiMe_3)_2$] 1.143 mL/min; Solution B [Tr-NSO + Ar–X]: 2.857 mL/min; Solution C [*n*BuLi]: 1.497 mL/min. The T-mixers and reactors were kept at 20 °C using a thermostated water bath. Solutions A and B were mixed using a stainless-steel T-shape micromixer ($Ø_{\mathrm{int}}=250$ μm). The resulting solution was passed through R_1 (1 mL, $t_{R1}=15$ s), mixed with solution C by a stainless-steel T-shape micromixer ($Ø_{\mathrm{int}}=500$ μm) and introduced in R_2 (2 mL, $t_{R2}=23$ s). The resulting solution was collected directly in a stirred flask with water (5 mL), after reaching the steady state (67 s) for 55 s (i.e., 0.53 mmol scale). The mixture was washed with brine and extracted with AcOEt (3× 10 mL). The organic phases were collected, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude was dissolved in the minimum quantity of AcOEt at 40 °C, then pentane (15 mL) was slowly added, and the product was allowed to precipitate from the solution at −25 °C. Once the supernatant appeared clear, it was removed, and the products could be obtained as shown in the Supporting Information.

Acknowledgements

We gratefully acknowledge the ANR (project ketflo ANR-18-CE07-0035-01), and EUR-CBH (ANR-11-LABX-0003-01) for financial support. We thank the University of Bari (Ordinary Fund for the Research N. 25308-VIII/2) and Dompè spa (CT-2021 uniba) for financial support. We also thank the support from ICMG FR 2607, Grenoble, through which NMR, MS and X-ray analyses have been performed. Open Access funding provided by Università degli Studi di Bari Aldo Moro within the CRUI-CARE Agreement.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: flow chemistry · organolithiums · sulfinamidines · sustainable chemistry · synthetic methodologies

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Manuscript received: July 2, 2022
Accepted manuscript online: July 21, 2022
Version of record online: August 23, 2022