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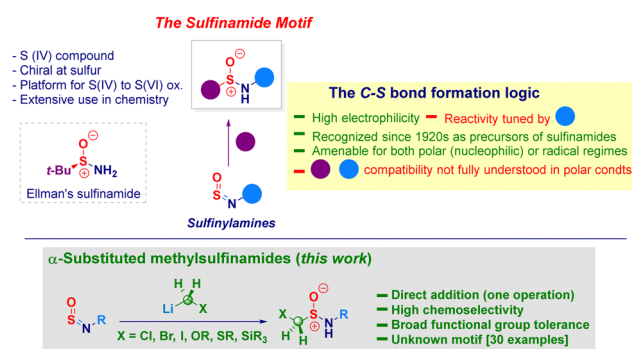
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Highly chemoselective homologative assembly of the α -substituted methylsulfinamide motif from *N*-sulfinylamines†

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α -Substituted methylsulfinamide are prepared through the homologation of electrophilic *N*-sulfinylamines with Li-CHXY reagents. The transformation takes place under full chemocontrol and exhibits good flexibility for preparing both *N*-aryl and *N*-alkyl analogues. Various sensitive functionalities can be accommodated on the starting materials, thus documenting a wide reaction scope.

The sulfinamide moiety constitutes an important organic framework of considerable interest across the chemical sciences,¹ also exhibited in natural products.² It is indeed a key representative example of sulfur(IV) entities featuring a unique reactivity profile imparted by the N–S delocalization. The constitutive chirality of the sulfur atom³ guided the development of enantiopure analogues – illustrated by the venerable Ellmann's *t*-butylsulfinamide⁴ (Scheme 1, box) – nowadays belonging to the synthetic chemist's toolbox.⁵ Moreover, they can be engaged in oxidative transformations *en route* to sulfonamides and aza-analogues, widely expressed in biologically active substances.⁶ The retrosynthetic analysis of the cluster enables individuating three main disconnections levered on: (i) N–S or, (ii) C–S bond forging events and, (iii) oxidation of low-valent sulfur species (sulfenamides).^{1,7} The notoriously not ideal manipulation of these latter reagents or, in general, sulfur(II) species (*e.g.* RSH),⁸ makes preferable adopting logics paved on the construction of C–S linkages.⁹ Inspired by his seminal work on heterocumulenes (carbon dioxide, isocyanates and isothiocyanates),¹⁰ Gilman in 1926 successfully prepared sulfinamides by treating readily accessible sulfinylamines (*i.e.* monoaza analogues of SO₂)¹¹ and Grignard reagents.¹² While considered intuitive, the



Scheme 1 General context of the presented work.

strategy may suffer from low chemocontrol due to the use of such hard nucleophiles and intrinsic high reactivity of the sp²-hybridized sulfur atom towards moisture.¹³ Notwithstanding, in recent years Willis uncovered the innate potential of both the tactic and the versatility of sulfinylamines, thus designing a plethora of elegant transformations conducting to versatile sulfur(vi) materials¹⁴ which complemented the well-studied application of sulfinylamines in cycloadditions and *ene* reactions.¹⁵ Among the fundamental achievements of Willis' work, it has to be emphasized the efficient transformations conducted on reluctant alkyl-type sulfinylamines through the judicious installation of sterically hindered substituents on nitrogen (*i.e.* *N*-trityl) thus, resulting in a remarkable extension of the scope of the methodology.^{14a,16} Analogous systems could also undergo Ni(II)-catalyzed (hetero)arylation – giving a series of sulfinamides analogues – when employing boroxines.¹⁷ Moreover, Bolm showed the metal-free addition of aryldiazoniums to *N*-tritylsulfinylamines for preparing sulfonimidamides.¹⁸ As a consequence of the challenging installation of C–sp³ hybridized elements under nucleophilic regime, Li and Zhao introduced in 2022 a photoredox protocol enabling the successful transfer of various functionalized alkyl elements released from 4-substituted-1,4-dihydropyridines.¹⁹ Intrigued by the lack of precedents in literature regarding substituted α -methylsulfinamides and

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4-Ethoxy-*N*-sulfinylbenzenamine (**1**) was selected as the model substrate for accomplishing the addition of LiCH_2Cl generated *in situ* from chloriodomethane and MeLi-LiBr (Table 1).²³ By running the reaction at $-78\text{ }^\circ\text{C}$ in diethyl ether, we were pleased to observe the formation of the homologated product (**2**) in 78% yield (Table 1, entry 1). The employment of less coordinating solvents (known to destabilize carbenoids)²⁴ – frequently used as alternative to classic ethereal solvents – such as *t*-butyl methyl ether (TBME), cyclopentyl methyl ether (CPME)²⁵ and 2-methyltetrahydrofuran (2-MeTHF),²⁶ resulted in lower yields (entries 2–4). By running the reaction in THF – a stronger coordinating solvent able to tame the degradative Kirmse’s α -elimination of carbenoids²⁴ – **2** was obtained in a very good 85% yield after 1 h (Table 1, entry 5); in agreement with the limited existing time of LiCH_2Cl ,²⁷ the increase of the reaction time up to 2 hours resulted in no further improvement (Table 1, entry 6). Conversely, the reaction did not reach

completion when kept for 30 min (53% yield, entry 7). The noticeable instability of compound **2** during the chromatographic purification [SiO₂ eventually deactivated with triethylamine (2% v/v) or TMSCl (1% v/v)] or neutral alumina (Brockmann degree III),²⁸ suggested us to maximize the rate of conversion, as judged by ¹H-NMR analysis. To this end, it was essential to use of 2.8 equiv. of carbenoids; in fact, lowering the loading to 1.8 equiv. [generated from ICH₂Cl (2.0 equiv.) and MeLi-LiBr (1.8 equiv.)], not only resulted in a less efficient process – 46% conversion – but, also the attack of the methyl carbanion to the sulfur atom of the sulfinylamine was observed thus, furnishing **2a** as a side product (entry 8). The same trend was also noticed when using 2.3 equiv. of carbenoid, though at a less extent (entry 9). Some additional aspects merit mention: (a) the less nucleophilic magnesium carbenoid - generated with *i*-PrMgCl-LiCl – did not promote the reaction regardless the adoption of Barbier or non-Barbier conditions (entry 10); (b) the use of the lithium carbenoid requires Barbier-type conditions, presumably because of the aforementioned intrinsic instability (entry 11); (c) at a higher temperature (–50 °C), reaction efficiency dropped significantly, as a consequence of the thermal sensitivity of the carbenoid (entry 12).

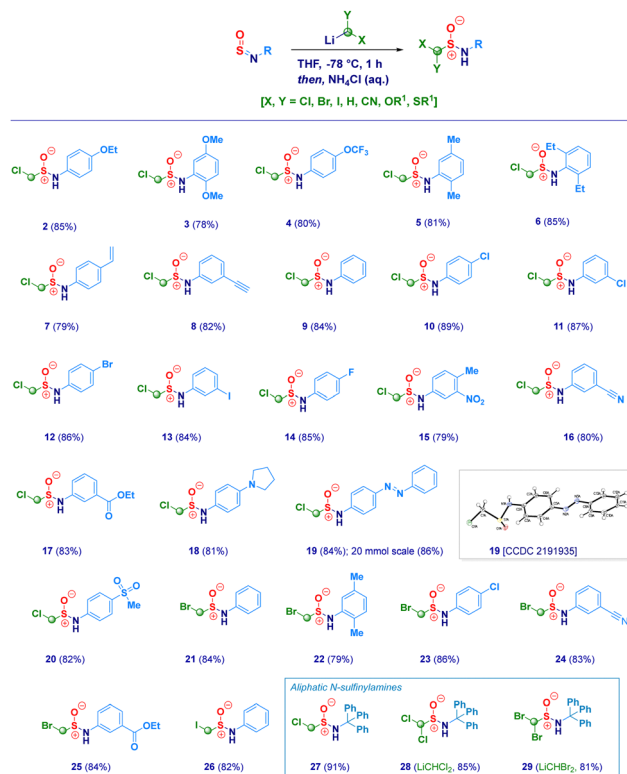
With the optimal conditions in hand, we then examined the scope of the method (Scheme 2). The protocol proved to be flexible, thus enabling the efficient transformation of a series of *N*-sulfinylanilines into the corresponding chloromethylated products. The high electrophilicity of the sulfur atom uniformly

Reaction scheme showing the synthesis of 2a from 1:

1 (4-ethoxy-1-nitrobenzene) reacts with MeLi-LiBr in THF, -78 °C, then, NH₄Cl (aq.) to form intermediate 2 (4-ethoxy-N-(chloromethyl)benzenesulfonamide).

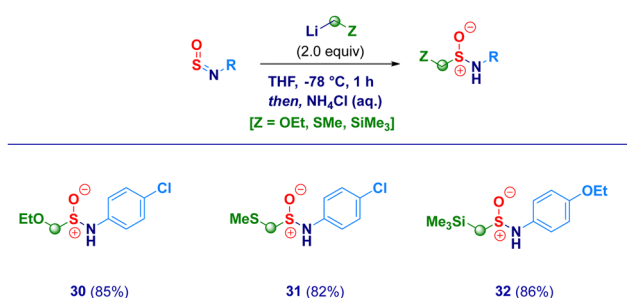
Intermediate 2 reacts with 2-mercaptoethanol to form 2a (4-ethoxy-N-(2-mercaptoethyl)benzenesulfonamide).

^a Unless otherwise stated, reactions were run with LiCH₂X. ^b Isolated yield. ^c The ¹H-NMR analysis of the reaction crude indicated 46% conversion – calculated as mol(2)/[mol(1) + mol(2)] × 100; 1,3,5-trimethylbenzene internal standard; by running chromatography on neutral Al₂O₃, **2** was recovered in 28% yield; Compound **2a** was formed as side product in 20% yield. ^d 62% conversion; 46% yield (purification on silica gel); 39% yield (purification on neutral Al₂O₃) for compound **2**, respectively; Compound **2a** was formed as side product in 17% yield. ^e Reactions run starting from ICH₂Cl and *i*-PrMgCl-LiCl under both Barbier and non-Barbier conditions. ^f Non-Barbier conditions.



Scheme 2 Homologation of *N*-sulfinylamines with halogenated α -methyl-lithiums.

allowed the nucleophilic attack of the carbenoid, thus making negligible the electronic and/or steric behavior of substituents on nitrogen. Electron-rich rings (2–3) were competent substrates regardless the position of the ethereal fragment, including the isosteric pharmaceutically relevant trifluoromethoxy- analogue (4).²⁹ Simple alkyl groups installed on the aromatic ring (5–6) were not detrimental for the process; remarkably, the protocol was further validated by embodying two ethyl moieties at the sterically demanding *ortho* positions (2,6-diethyl-), thus, obtaining **6** in an excellent 85% yield. Unsaturated – sp² and sp – carbon-centered functionalities (vinyl and ethynyl), susceptible of Simmons–Smith type cyclopropanation with carbenoids,³⁰ fully preserved the chemical integrity, furnishing exclusively the desired adducts **7** and **8**. It should be highlighted that the (basic) nucleophilic carbenoid did not deprotonate the acidic terminal alkyne. Besides the unsubstituted analogue **9**, the introduction of halogens was not detrimental for the genuine chemocontrol of the protocol. Thus, chloro-derivatives **10** and **11** could be easily prepared, as well as, the synthetically useful (see below) bromo-(**12**), iodo-(**13**) and fluoro-(**14**) analogues. No concomitant aromatic lithiation – potentially occurring on bromo- and iodo-derivatives³¹ – was noticed under the reaction conditions during the carbenoid generation event from the dihalomethane. The chemoselectivity of the protocol was further deduced by engaging *N*-sulfinylamines containing sensitive functionalities potentially reactive under the adopted conditions. Not only the challenging nitro group remained untouched (**15**) but, also when electrophilic cyano-(**16**) and ester (**17**, regioisomer of the common local anaesthetic drug benzocaine) were accommodated on the aromatic ring, the exclusive occurring process was the sulfur halomethylation. This outcome is particularly relevant in view of the established use of esters as placeholders for halomethylenic fragments under nucleophilic regime.³² Presumably, *N*-sulfinylanilines are stronger electrophiles than esters, thus enabling the selective attack at the sulfur atom instead of the carboxylic carbon. The presence of nitrogen-centered functionalities [*i.e.* pyrrolidine (**18**) or phenyldiazo (**19**)] further expanded the reaction scope: notably, the homologative process *en route* to **19** was scalable to 20 mmol in comparable efficiency, thus furnishing pure crystals suitable for X-ray analysis (see ESI†). Moreover, the methodology could be validated also in the case of the sulfonyl-substituted analogue (**20**). Not only chloromethylating agents could be employed for the homologation but, also the analogous bromo-derivative conveniently prepared from bromiodomethane:³³ accordingly, structures **21–25** were obtained under comparable chemocontrol, thus further highlighting the tolerance for strong electrophiles such as cyano (**24**) and ester (**25**) functionalities. The α -iodomethylation (with LiCH₂I generated from CH₂I₂) furnished analogue **26** featuring two exceptional high electrophilic vicinal sites (sulfur and methylene). The robust stabilizing effect imparted by the sterically hindered trityl group on the nitrogen,^{14a} enabled the extension of the protocol to aliphatic *N*-sulfinylamines suitable for homologation with both mono-halo (**27**) and di-halo carbenoids (**28–29**), being the latter generated through deprotonation of the corresponding dihalomethane.³⁴ With the aim to gain full insight into the potential of homologative transformations of

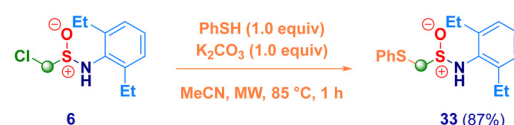


Scheme 3 Homologation of *N*-sulfinylamines with non-halogenated agents.

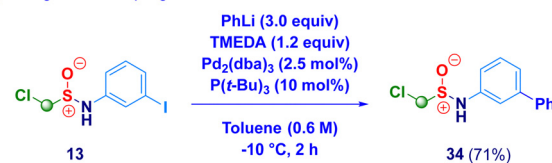
N-sulfinylanilines, we next turned our attention towards non-halogenated C1-lithiated agents. In this sense, LiCH₂OEt³⁵ (**30**) and LiCH₂SMe³⁶ (**31**) – both generated *via* Yus' reductive lithiation methodology in the presence of Li metal and DTBB³⁷ – could be efficiently added without altering the chemoselectivity profile. Though sceptical at the beginning as a consequence of the facile Cl–Li exchange under reductive conditions, we were delighted to observe exclusively the formation of the substituted α -methyl lithium species (from ClCH₂OEt or ClCH₂SMe) in the presence of potentially exchangeable chlorine atom on the aromatic nuclei. Finally, by running the reaction with the commercially available LiCH₂SiMe₃, the stable α -silylmethyl analogue **32** was prepared in high yield (Scheme 3).

Finally, we briefly screened the synthetic behavior of the newly introduced α -halomethyl sulfinamide motif through transformations realized on both the methylene unit and on the aromatic ring (Scheme 4). The treatment of derivative **6** with a thiol (PhSH) under basic conditions afforded the expected nucleophilic substitution product **33** (*path a*), thus remarking the electrophilic nature of the methylene introduced *via* homologation. Under Pd-catalytic conditions – halogenated arenes [iodo (**13**) and bromo (**12**)] – smoothly coupled with an

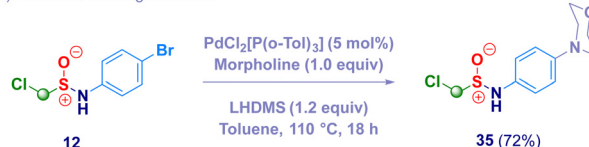
a) Nucleophilic substitution on the –CH₂Cl unit



b) Feringa cross-coupling with PhLi



c) Buchwald–Hartwig amination



Scheme 4 Derivatization of α -halomethylsulfinamides.



organolithium (Feringa – Fañanás-Mastral protocol,³⁸ **34**) or with an amine (morpholine, **35**) in Buchwald-Hartwig mode (*paths b* and *c*).³⁹ In summary, we have developed a straightforward synthesis of previously undisclosed α -substituted methylsulfinamides *via* a homologative tactic levered on the nucleophilic transfer of a formal $-\text{CH}_2\text{X}$ (or CHXY) reagent to the electrophilic sulfur atom of *N*-sulfinylamines. Upon tuning the nucleophiles genesis, a series of functionalized methyl fragments can be efficiently added, thus converting the starting materials into the homologues. Full chemocontrol is uniformly exhibited by the process, as showcased by challenging *N*-sulfinylamines embodying chemical moieties susceptible of nucleophilic attack such as ester, halogen, nitro, nitrile, olefin or alkynyl functionalities. This one-step, high yielding methodology is flexible for being applied to the synthesis of more elusive *N*-alkyl type analogues.

M. M. and R. S. performed the experiments and contributed equally. D. C. assisted and completed the experimental work. A. R.-P. realized X-ray analysis. V. P. directed the project and wrote the manuscript.

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Conflicts of interest

No conflict to declare.

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