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COMMUNICATION

A convenient synthetic route to sulfonimidamides from sulfonamides

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Sulfonimidamides were prepared in a one-pot transformation from sulfonamides, through nucleophilic substitution of sulfonimidoyl chlorides formed *in situ* with different amines. This methodology represents a convenient, safe, and easily accessible synthetic route to sulfonimidamides.

Sulfonamides (**SAs**) are a popular motif in drug discovery and development.[1] Sulfonimidamides (**SIAs**) as the isosteric replacements for **SAs** have received less attention from the scientific community than **SAs**, presumably due to the lack of commercial availability and synthetic accessibility. Chemistry of SIAs has focussed on three perspectives: 1) chemistry on the sp^2 N atom;[2] 2) chemistry on the sp^3 N atom;[3] 3) utilisation of the chirality in asymmetric hydrogenation,[4] metal-catalyzed C-H amination and aziridination,[5] and serving as chiral ligands in aldol reactions[6] and Henry reactions.[7]

Recently **SIAs** have been proposed as bioisosteres of **SAs** and carboxylic acids.[8] The replacement of **SAs** with **SIAs** can be a useful approach for the optimisation of lead compounds in drug discovery. However this replacement has been little-used, presumably due to the limitation of the synthesis of sulfonimidoyl chlorides (**SICs**) – the key intermediates to **SIAs**.

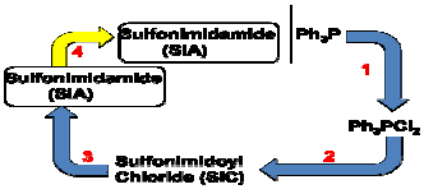
The first reported approaches to **SICs** were from Levchenko. (Scheme 1).[9]

Scheme 1 Literature precedent to make **SICs**

The oxidative route (approach 1) is based on the reaction of sulfinyl chlorides with *N*-halogen compounds.[10] Contemporary routes employ oxidative chlorinating reagents such as chlorine, *N*-chlorobenzotriazole,[11] *tert*-butyl hypochlorite,[12] anhydrous chloramine-T,[13] and *N*-chlorosuccinimide[2, 8b, 14a] to synthesise **SIAs** from sulfinamide substrates. However, this approach has limitations as the accessibility and ease of handling of sulfinyl chlorides or sulfinamides, is usually poor compared to the corresponding sulfur(VI) compounds. Oxidative chlorinating reagents, such as *tert*-butyl hypochlorite, are high-energy or unstable compounds that require special care.[14]

Levchenko also used phosphorus pentachloride (PCl_5) as direct chlorinating reagent.[15] In 1993, Roy synthesised sulfonimidates from **SICs**, which were directly synthesised from *trimethylsilyl* ***(TMS)*** group substituted **SAs** and triphenyldichlorophosphorane (Ph_3PCl_2) – a replacement of PCl_5.[14b]

To our knowledge, a *one-pot* methodology for the synthesis of **SIAs** from **SAs** has not been reported. We herein describe a one-pot procedure for the synthesis of **SIAs**: 1) synthesis of fresh Ph_3PCl_2; 2) *in situ* synthesis of **SICs** from **SAs**; 3) nucleophilic substitution with amines or anilines to afford **SIAs**; and 4) acidic workup on the *tert-butyl dimethylsilyl group* (***TBS***) protected intermediates to afford the products in moderate to excellent yields (Scheme 2).



Scheme 2 One-pot preparation of **SIAs** starting from Ph_3P (this work)

Because primary **SAs** will react with *in situ* formed **SICs**, sulfonamide-*N* protection is necessary. In this work we changed TMS, which was used by Roy, into the TBS group as it proved to be more stable (relevant experiments available in the supporting material). Additionally, the TBS protected **SIAs** can be isolated by column chromatography. Figure 1 shows the structure of substrates **1-3** that were used in this work and the relevant intermediates – **SICs 1a-3a**, and **2b**, which was only used for the stability study.

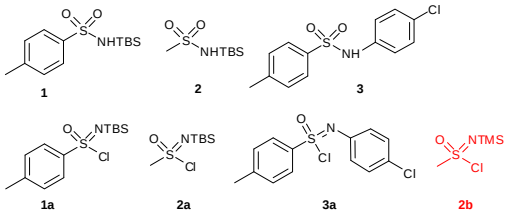
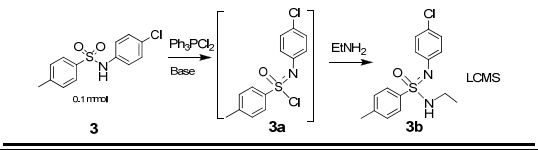


Figure 1 SAs (**1-3**) and key intermediates **SICs** (**1a-3a**)

Reaction conditions were screened using 0.1 mmol of substrate **3** (Table 1). The relevant **SIC 3a** was reported by Tillett through the reaction of 4-methylbenzene-1-sulfonyl chloride and *N*,4-dichlorobenzamide – an intermediate that was synthesised from 4-chlorobenzamide.[16] In our work, it was directly synthesised from **3**. In practice, few drops of the reaction mixture of **SIC 3a** were mixed with an excess of ethylamine to convert **3a** into *N*-ethyl sulfonimidamide **3b**, which could be detected by LCMS.

Table 1 Screening of reaction conditions

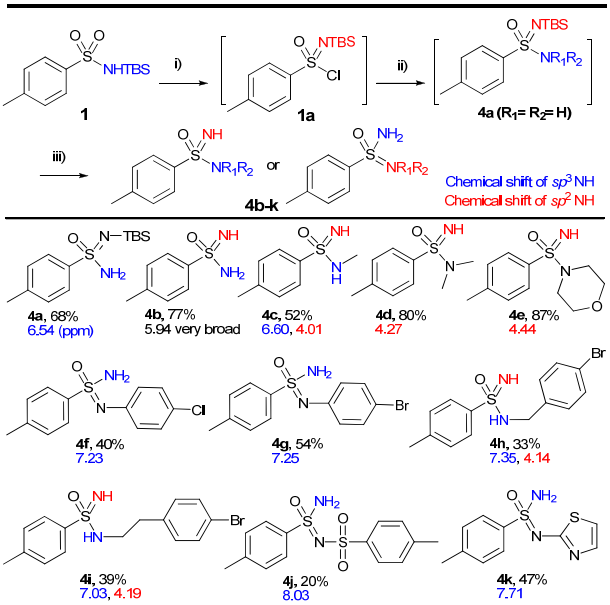


Entry[a]	Solvent	Time (hr)	Temp (°C)	Conversion to **3b** % [b]
1	$CHCl_3$	24	rt	57
2[c]	$CHCl_3$	24	rt	15
3	$CHCl_3$	4	35	90
4	**$CHCl_3$**	**6**	**35**	**95**
5	$CHCl_3$	6	45	61
6[d]	$CHCl_3$	4	35	16
7[e]	$CHCl_3$	4	35	10
8[c]	$CHCl_3$	4	35	25
9[f]	$CHCl_3$	4	35	21
10[g]	$CHCl_3$	4	35	45
11	THF	4	35	10

[a] 1.02 eq. Ph_3PCl2, 1.5 eq. base (DIPEA or TEA) were used. [b] As determined by LCMS. [c] Pyridine was used as base. [d] 4-Methylpyridine was used as base. [e] 2-Methoxypyridine was used as base. [f] acetonitrile (30% vol.) was used as co-solvent. [g] THF (30% vol.) was used as co-solvent.

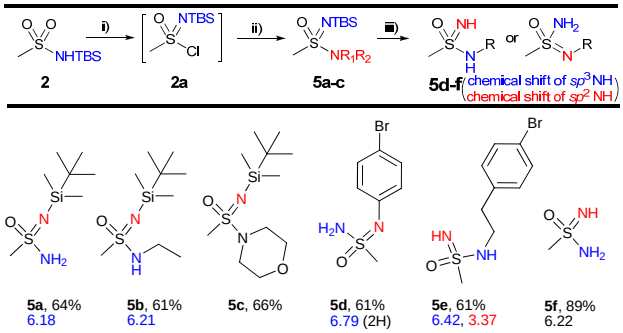
For substrate **3**, entry 4 showed the best results. For substrates **1** and **2**, we kept the same conditions as in entry 4, but optimised temperature and reaction time. The optimal conditions for these three substrates were shown in the tables below. When TBS protecting group was applied, some of the products were deprotected to give final products (Table 2-4).

Table 2 Substrate scope of **1**



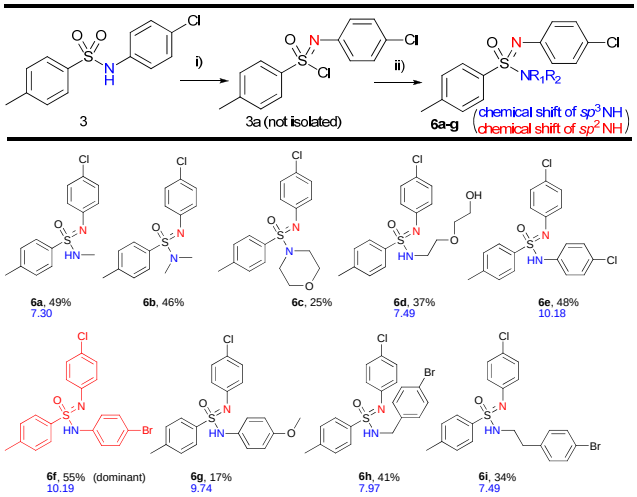
Reactions were usually conducted on a 1.0 mmol scale unless specifically stated. Conditions: i) **1** (1.0 mmol), Ph_3PCl_2 (1.1 mmol), triethylamine (TEA, 1.5 mmol), $CHCl_3$ (3.0 mL), 0 °C, 20 min; ii) amines/anilines (3.0 mmol), 0 °C for 30 min, and then rt for 30 min–2 d; iii) aqueous acid (HCl, HCOOH, or HOAc) or HCl/dioxane, 20-90 min.

Table 3 Substrate scope of **2**



Reactions were usually conducted on a 1.0 mmol scale unless specifically stated. Conditions: same as in Table 2, but **2** was used as starting material.

Table 4 Substrate scope of **3**



Conditions: i) **1** (1.0 mmol), Ph_3PCl_2 (1.1 mmol), triethylamine (TEA, 1.5 mmol), $CHCl_3$ (3.0 mL), 35 °C, 6 h; ii) amines/anilines (3.0 mmol), 30 min, room temperature.

Migration of a proton from one nitrogen atom to another in a **SIA** structure leads to tautomerisation. A recent report on tautomerism of **SIAs** by Arvidsson was based on theoretical calculations.[2] In our work ^{1}H NMR (DMSO-d_6 as solvent for all compounds) was used to determine the stable forms of tautomers. Compounds **4a**, **5a**, and **5b** are TBS-protected products. Therefore, protons on N can only sit on the sp^3 N atoms. The chemical shifts of these protons (S-NH_2) are > 6.10 ppm. Interestingly, the chemical shifts of the protons on the sp^2 N atoms (S=NH) in compounds **4d**, **4e** are generally below 4.5 ppm. This chemical shift difference of protons on sp^3 N and sp^2 N atoms was applied to facilitate the structure determination. For instance, two different NH peaks were found in compounds **4c**, **4h**, **4i**, and **5e**. This means that there is no tautomerism (*in NMR solvent*) after TBS deprotection. On the other hand, only one relevant peak is found in compounds **4f**, **4g**, **4j**, **4k**, and **5d**. One can conclude that tautomerism happens on those compounds to give the more stable forms (*in NMR solvent*). The similarity of 4-Br-phenyl and 4-Cl-phenyl groups in **6f** makes a clear structure determination difficult. The observed NH chemical shifts in compounds **6e**, **6f** are very similar, and they are different from the NH chemical shift in **6g**. We speculate that a rapid proton exchange exists in **6e** and **6f**, but

not in **6g**. From an electronegativity perspective, the structure of **6f** is empirically proposed as shown in Table 4. In general, all compounds in Table 4 keep the S=N double bonds connecting to the 4-Cl-phenyl groups without tautomerism.

Enantiomerically pure **SIA** (*S*)-**4j** and its analogues were used in the intermolecular nitrene C-H insertion.[5f] The corresponding **SICs** were obtained by action of anhydrous chloramine-T with sulfinyl chlorides, which were be prepared by treatment of the corresponding sulfinate salts with thionyl chloride. Then they reacted with (*R*)-(-)-α-methylbenzylamine, followed by diastereoisomer resolution and deprotection to give the pure enantiomer (*S*)-**4j**. In our work, we got **4j** in 20% yield in one-pot procedure from *p*-methylbenzenesulfonamide. Preparative separation on chiral HPLC afforded two enantiomers. The chirality was determined by comparing the observed optical rotation results with literature (see Supporting Information).

Sample of **SIA 6c** and analogues were reported few month ago by Arvidsson through Chan–Evans–Lam C–N cross coupling of aryl boronic acid and sulfonimidamides – key intermediates that were made from tosyl chloride in 6 steps.[17] In our work, compound **4e**, the key intermediate in Arvidsson's paper was obtained in 87% yield from **1**, and **6c** was obtained in 25% yield in one-pot procedure from **3**.

In conclusion, we have disclosed a multi-step, one-pot procedure to synthesise sulfonimidamides from the corresponding and readily available sulfonamides. The transformation can be performed under mild conditions. ^{1}H NMR was successfully applied in the tautomerism elucidation. Through the replacement of S=O in sulfonamides with S=NR, this remarkable functional group transformation affords a new modification opportunity for sulfonamides, an important functional group in drug discovery and development.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures and characterization data for compounds **1**, **2**, **4a-k**, **5a-f**, and **6a-i.**]. See DOI: 10.1039/b000000x/

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