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# Preparation of sulfonamides from *N*-silylamines.

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ABSTRACT

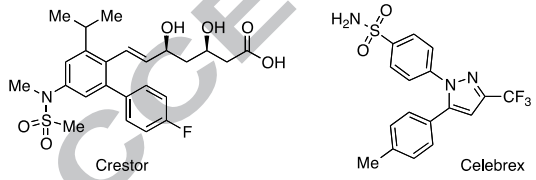
Sulfonamides have been prepared in high yields by the reactions of *N*-silylamines with sulfonyl chlorides and fluorides. In a competition experiment, the sulfonyl chlorides were found to be far more reactive than sulfonyl fluorides. The chemistry may be used to prepare aliphatic, aromatic, tertiary, secondary, and primary sulfonamides. It may also be done in the absence of solvent and the byproduct trimethylsilyl chloride recovered in good yield. Primary sulfonamides were synthesized from the sulfonyl chloride with aminotriphenyl silane ($Ph_3SiNH_2$), a conversion demonstrated with the synthesis of the carbonic anhydrase inhibitor, acetazolamide.

Keywords: Sulfonamides, sulfonyl transfer, *N*-silylamine, substitution



## Introduction

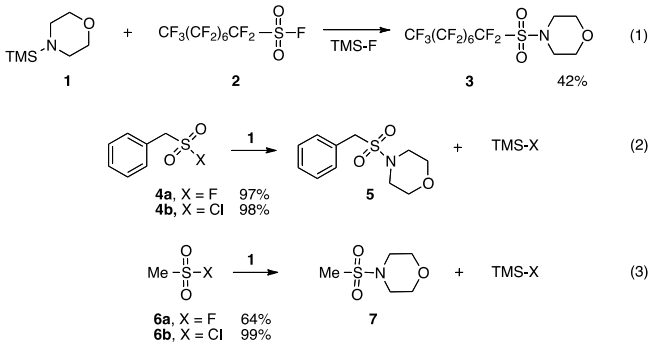
The sulfonamide functional group is a structure with broad importance, as it is found in numerous medicinal agents, dyes/pigments, polymers, and other structures.[1] For example, the anti-cholesterol drug *Crestor* and anti-arthritic drug *Celebrex* both contain the sulfonamide functional group. Sulfonamides are




often prepared by the reactions of sulfonyl chlorides with amines, accompanied by the release of HCl.[2] Given the importance of the sulfonamide functional group, convenient methods of preparing this structure are highly desirable. In this manuscript, we report the efficient preparation of sulfonamides from *N*-silylamines and sulfonyl halides. Our results indicate that sulfonyl chlorides are superior to sulfonyl fluorides in the reaction.

## Results and Discussion

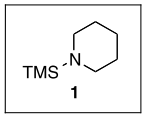
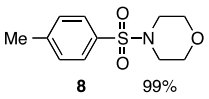
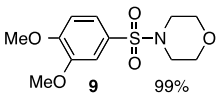
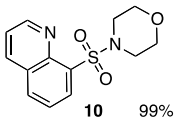
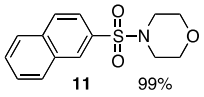
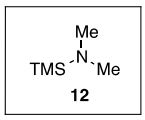
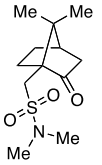
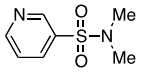
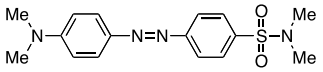
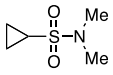
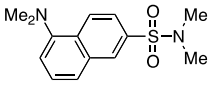
In our initial studies, we sought to react sulfonyl fluorides and *N*-silylamines. With formation of the sulfonamide, the byproduct of the reaction should be the silyl fluoride. We reasoned that the formation of the fluorine-silicon bond could be a good driving force for the conversion. Our initial experiment involved a reaction between *N*-(trimethylsilyl)morpholine (**1**) and the perfluorinated sulfonyl fluoride (**2**, eq 1). Although the expected sulfonamide (**3**) was isolated, the yield of the conversion was somewhat disappointing. Other sulfonyl fluorides (**4a**,**6a**) were




studied and the expected sulfonamide products (**5**,**7**) were obtained in fair to good yields (eqs 2-3). Even with added fluoride (20 mol %, $Bu_4NF$), the sulfonyl fluorides exhibited sluggish reactivities. However, the same reactions with analogous sulfonyl chlorides (**4b**,**6b**) provide the sulfonamides (**5**,**7**) in quantitative yields. The greater reactivity of the sulfonyl chlorides was also observed in a competition experiment. One equivalent of **4a** and **4b** were reacted with one equivalent of *N*-(trimethylsilyl)morpholine (**1**) and product **5** was formed exclusively by reaction of the sulfonyl chloride (**4b**). Unreacted sulfonyl fluoride (**4a**) could be recovered quantitatively. These results were somewhat surprising as the formation of the trimethylsilylfluoride – and the strong fluorine-silicon bond – is evidently not the most important factor in determining reaction rates or yields (*vide infra*).

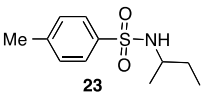
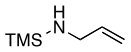
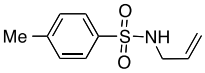
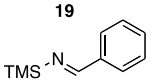
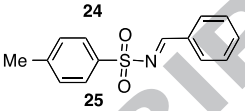
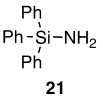
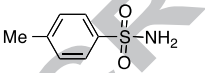
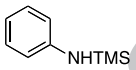
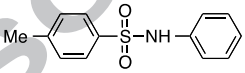
The *N*-silylamines **1** and **12** were shown to react with a variety of sulfonyl chlorides to give the respective sulfonamide products (**8-11**, **13-17**; Table 1). Heterocyclic, aromatic, and carbocyclic

**Table 1.** Sulfonamide products (**8-17**) and yields from *N*-silylamines **1** and **12**.

| *N*-Silylamine | Sulfonamide products and yields[a,b] |
|---|---|
|  **1** |  **8** 99%  **9** 99% |
| |  **10** 99%  **11** 99% |
|  **12** |  **13** 97%  **14** 99% |
| |  **15** 99% |
| |  **16** 99%  **17** 99% |

[a]Isolated yield of pure product. [b]1 mmol *N*-silylamine, 1 mmol tosyl chloride, and 15 mL $CH_3CN$, reflux 1 hr.

**Table 2.** Sulfonamide products (**23-27**) and yields from tosyl chloride and *N*-silylamines (**18-22**).

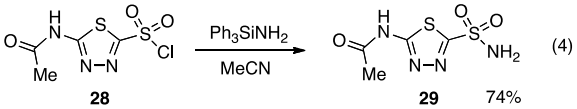
| *N*-SIlylamine | Product | Yield[a] |
|---|---|---|
|  **18** |  **23** | 96%[b] |
|  **19** |  **24** | 94%[b] |
|  **20** |  **25** | 91%[b] |
|  **21** |  **26** | 90%[b] |
|  **22** |  **27** | 94%[c] |

[a]Isolated yield of pure product. [b]1 mmol *N*-Silylamine, 1 mmol tosyl chloride, and 15 mL $CH_3CN$, reflux 1 hr. [c]Neat reaction.

sulfonamides have all been prepared in quantitative yields. In the optimized reaction conditions, equimolar quantities of *N*-silylamine and sulfonyl chloride are combined in acetonitrile and the mixture is stirred at reflux for one hour. Removal of the solvent and silyl chloride provides the sulfonamide.

Other *N*-silylamines were reacted with *p*-toluenesulfonyl chloride to provide varied sulfonamides (Table 2). The *N*-silylamines include those from a secondary alkyl amine (**18**), allyl amine (**19**), and the imine (**20**). Primary sulfonamides have found significant use in drug design. In order to prepare the primary sulfonamide (**26**), aminotriphenylsilane (**21**) was utilized. The silane **21** itself was prepared from triphenylsilyl chloride and ammonia.[3] In the case of sulfonamide **27**, this conversion was accomplished without the use of solvent. Thus, the byproduct trimethylsilyl chloride can be distilled off directly and recovered in greater then 75% yield.

As an application of the chemistry, aminotriphenylsilane ($Ph_3SiNH_2$, **21**) was also used in the synthesis of the carbonic anhydrase inhibitor, acetazolamide (**29**; eq 4). Starting from the




**28** **29** 74% (4)

commercially available 5-amino-1,3,4-thiadiazole-2-thiol, the sulfonyl chloride (**28**) is prepared in two steps by acetylation of the amino group and oxidation of the thiol group.[4] A subsequent reaction between the sulfonyl chloride **28** and $Ph_3SiNH_2$ provides acetazolamide (**29**) in 74% yield.

Regarding the relative reactivities of the sulfonyl fluorides and chlorides in the reactions above, it is known that sulfonyl transfer reactions are considerably faster with sulfonyl chlorides versus sulfonyl fluorides.[5] For nitrogen nucleophiles, $k_{Cl}/k_F$ has been measured to be around $10^3$ to $10^5$ in reactions with benzenesulfonyl halide (acetonitrile/water).[5] As noted by Maccarone, these results are clearly related to the relative sulfur-halogen bond strengths,[6] where the S-F and S-Cl bonds are respectively 82 and 66 kcal•mol$^{-1}$.[7,8] Previous studies with sulfonyl transfer reactions have suggested a two-step addition-elimination process, $S_AN$, for the substitution mechanism involving nitrogen nulceophiles and sulfonyl halides.[6] Other studies have also suggested a one-step, $S_N2$ mechanism for sulfonyl transfer reactions.[5]

Our own theoretical calculations[9] (B3LYP 6-311G(d, p) level) showed the sulfonyl fluoride reaction to be more highly exothermic compared to the same conversion with the sulfonyl chloride (Figure 1). This is likely due to the strong Si-F bond formed in the product mixture. This suggests that sulfonamide formation is a kinetically controlled process involving *N*-silylamine attack at the sulfur with subsequent elimination of the silyl halide. Assuming the $S_AN$ mechanism is operating, the sulfonyl halide (**4a,b**) reacts with the *N*-silylamine to give the adduct **30**. The reverse reaction is more important with X = F, while the forward reaction is favored with X = Cl. Elimination of the silyl halide gives the sulfonamide **5**. Rather than a concerted elimination process, the halide may also dissociate from the sulfur and directly attack the silyl group. This process could occur from the adduct **30**, or alternatively, by the $S_N2$-type mechanism where **30** would represent a transition state. Other mechanistic proposals are conceivable, for example a catalytic cycle with halide anion reacting directly with the *N*-silylamine. Such a pathway is not likely, given that added fluoride does not improve the reaction yields/rates for the conversions involving sulfonyl fluorides.

## Conclusions

In summary, we have found a convenient procedure for the synthesis of sulfonamides from *N*-silylamines and sulfonyl chlorides.[10] A "solvent-free" example of the conversion has been demonstrated. Our studies also show that the conversions to sulfonamides may be done with sulfonyl fluorides, although the chemistry is less efficient. A mechanism is proposed involving an addition-elimination process. The methodology compliments an earlier report describing the synthesis of amides with acid chlorides and *N*-silylamines.[11]

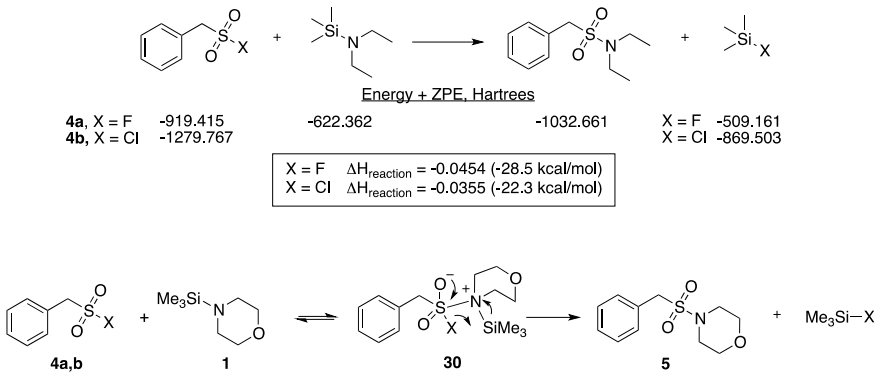



**Figure 1.** Calculated energies of reactants, products, and the conversion (B3LYP 6-311G (d,p) level), as well as the proposed mechanism of formation for sulfonamide **5**.

## Acknowledgments

We gratefully acknowledge the support of the NIH-National Institute of General Medical Sciences (GM085736-01A1) and the Northern Illinois University for Great Journeys Fellowship (R.R.N.). This manuscript is dedicated to Rachel A. Klumpp on the occasion of her tenth birthday.

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10. **Typical procedure:** The sulfonyl chloride (1 mmol) is dissolved in 15 ml acetonitrile and then silylamine (1 mmol) is slowly added. The reaction mixture is refluxed for 1 hour and concentrated with rotary evaporator. If necessary, the product may be further purified by silica gel chromatography (hexane: ethyl acetate).
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## Supplementary Material

Supplementary data (characterization data and NMR spectra) and computational methods associated with this article may be found in the online version, at doi:

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