Tetrahedron Letters 49 (2008) 6300–6303

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Convenient synthesis of primary sulfonamides

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ARTICLE INFO

Article history:
Received 15 July 2008
Revised 13 August 2008
Accepted 14 August 2008
Available online 22 August 2008

ABSTRACT

An efficient protocol for a one-pot synthesis of mono-sulfonamides has been developed. It features utilization of excess of sulfonylating agent followed by base mediated recovery of the primary sulfonamide.

1. Introduction

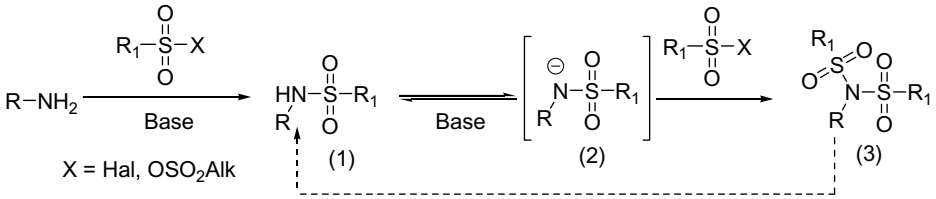
Methane- and trifluoromethanesulfonamides are often used in medicinal chemistry as bioisosteres of alcohol and phenol functions present in many bioactive molecules. The introduction of sulfonamides into clinical medicine in the 1930s marked the beginning of microbial chemotherapy.[1] The very simple drug sulfanilamide (*p*-aminobenzenesulfonamide) ushered the development of new and important classes of medicines with a wide variety of biological actions. Their commercial success is exemplified by *nimesulide* (*N*-(4-nitro-2-phenoxyphenyl) methanesulfonamide)—a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties.[2] Nimesulide is among the top five non-steroidal anti-inflammatory drugs used worldwide by ~0.5 billion people.

The synthesis of sulfonamides is usually performed by reacting an amine with a substituted sulfonyl chloride or anhydride often in the presence of a buffering base in an aprotic solvent. The yields are variable, but can be improved by optimization. While satisfactory in a laboratory environment, most of the current protocols suffer on a larger scale when reaction efficiency is important or when applied in a parallel synthesis format when simplicity and generality are more valuable.

We initiated this study to devise a simple, universal, and high yielding synthetic methodology, applicable to a wide range of amines and both methane- and trifluoromethanesulfonyl functions. Based on both literature data and our preliminary results, the traditional synthetic scheme can be mechanistically described as in Scheme 1.

The scheme details that a known non-productive pathway, leading to bis-sulfonamides (3), occurs via the formation of anion (2) even in transient amounts. The concentration of (2), as well as its nucleophilicity and reactivity, depends on the nature of R and R_1 making it difficult to find a universal approach to prevent formation of bis-sulfonamide (3). In our hands, variations of amine and sulfonyl components, buffering bases, and reactant ratios regularly led to reaction mixtures containing starting material and mixtures of both mono- and bis-sulfonamides in varying amounts. Thus, mono-desulfonylation of (3), depicted by dashed lines, might seem like a plausible way to furnish exclusively (1).

It is known that bis-sulfonamides easily lose one of the sulfonyl groups under nucleophilic attack. *N*-Phenyl-trifluoromethanesulfonimide is a commercial reagent for mild triflation of amines, phenoxides, and enolates.[3–5] Since the reagent itself converts into primary *N*-phenyltriflyl amide, we felt this served as good precedent for an efficient conversion of bis-trifluoromethanesulfonamide into the desired mono-sulfonamide derivative. Furthermore, mono-desulfonylation of bis-methanesulfonamides can be induced by treatment with alkali, quaternary ammonium fluoride, and even highly basic amines,[6–10] often leading to improved



Scheme 1.

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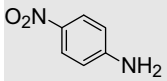
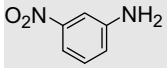
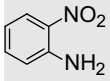
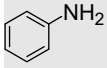
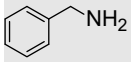
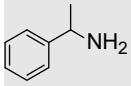
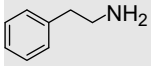
doi:10.1016/j.tetlet.2008.08.054

Table 1
Effect of anhydride/amine stoichiometry on conversion of amines

Amine	Conversion into methanesulonamides		Conversion into trifluoromethanesulfonamides	
	1.1 equiv Ms_2O	2.2 equiv Ms_2O	1.1 equiv Tf_2O	2.2 equiv Tf_2O
	70% Mono 30% SM	50% Mono 50% Bis	45% Mono 21% Bis 32% SM	100% Bis
	80% Mono 20% SM	16% Mono 81% Bis	18% Mono 26% Bis 55% SM	100% Bis
	53% Mono 45% SM	50% Mono 40% SM	52% Mono 46% SM	62% Mono 36% SM
	70% Mono 30% SM	30% Mono 70% Bis	60% Mono 40% SM	35% Mono 65% Bis
	80% Mono 20% SM	10% Mono 90% Bis	60% Mono 20% Bis 20% SM	10% Mono 90% Bis
	40% Mono 20% Bis 40% SM	100% Bis	50% Mono 10% Bis 40% SM	100% Bis
	40% Mono 10% Bis 50% SM	100% Bis	40% Mono 10% Bis 50% SM	100% Bis

Legend: Ms_2O and Tf_2O—methane and trifluoromethanesulfonic anhydrides, respectively, mono—mono-sulfonamide, bis—bis-sulfonamide, SM—starting material. Percentages are approximate (~5% error), based on LC area normalization @ 254 nm.

recoveries and overall yields. To the best of our knowledge, however, there was no systematic study designed to utilize these results to build a robust (high yielding) and widely applicable protocol for the synthesis of mono-sulfonamides.

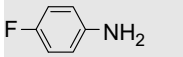
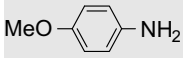
We hypothesized that combining conditions for complete consumption of primary amine substrate (leading to formation of mono- and bis-adducts) with base-induced hydrolysis of the bis-product into the mono-product, and incorporation of this two-step process in 'one-pot' would satisfy our requirements for efficiency and simplicity. We quickly identified methylene chloride as the solvent of choice, an organic amine (triethylamine or diisopropylethylamine) as a buffering base, and anhydrides as sulfonylating agents.

Our initial round of optimization was carried out on isomeric nitroanilines and a few representative amines (Table 1). Our initial efforts showed that, depending on the nature of the amine substrate and the amount of residual water in solvents, reagents, and equipment, up to 2.2–2.5 equiv of sulfonylating agents is required for full consumption of the starting amine. Correspondingly, the amount of base also needed to be increased to 3 equiv or more, particularly when utilizing triflic anhydride as a reagent or for substrates bearing sensitive functionalities. In the later cases it was also important to use low temperatures (−10 to −40 °C) during the anhydride addition.

In our investigation, sequential addition of an anhydride (Table 1) showed, as a rule, that addition of the 1st equiv led to ~50% conversion (partly because of the residual water), and the formation of the bis-adduct preceded full conversion of the amine substrate.

We found experimentally that 1.5–2.2 equiv of the sulfonylating agent (buffered with 2–4 equiv of base) was adequate for the vast majority of cases to achieve complete conversion without causing excessive decomposition (particularly important for parallel synthesis). Interestingly, unlike *m*- and *p*-nitroanilines that delivered nearly quantitative conversion of starting materials (Table 1), the case of *o*-nitroaniline afforded formation of up to ~60% of mono-sulfonamides, as well as unreacted starting material. We attributed this to the stereo-electronic properties of the *ortho*-functionality. However, reactions that did not proceed to completion still afforded high yields of products based on consumed starting material.

Table 2
Applicability of the procedure in parallel synthesis

Amine	Methane sulfonamides		Trifluoromethanesulfonamides	
	Sequential yield (%)	Parallel yield (%)	Sequential yield (%)	Parallel yield (%)
	96[a]	82	>95	84
	97	80	>95	80

[a] Isolated yields. All products were fully characterized.

Furthermore, we explored the in situ hydrolysis of bis-sulfonamides and found that 2.5 N sodium hydroxide with methanol, as a co-solvent, is the most convenient reagent to complete the hydrolytic recovery of mono-sulfonamides in 0.5–24 h at room temperature. When applied to the amines shown in Table 1, it delivered nearly quantitative isolated yields of mono-sulfonamides.

2. General procedure

To a solution of 1.0 mmol of amine and 1.5–2.5 mmol of buffering amine in methylene chloride is added 1.5 mmol of anhydride in methylene chloride solution dropwise at room temperature or

Table 3
Synthesis of methanesulfonamides and trifluoromethanesulfonamides

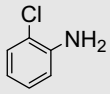
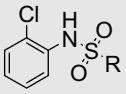
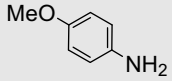
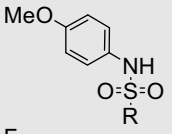
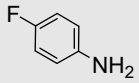
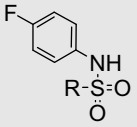
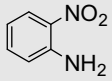
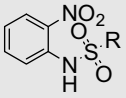
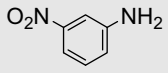
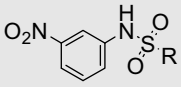
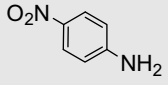
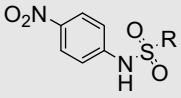
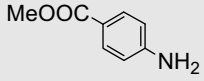
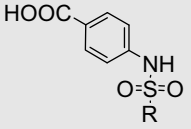
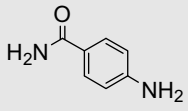
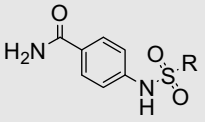
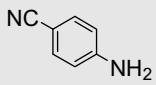
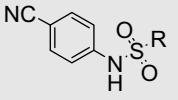
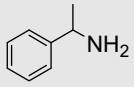
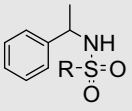
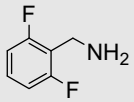
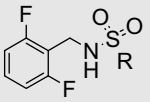
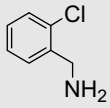
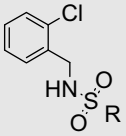
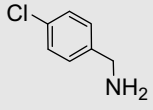
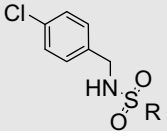
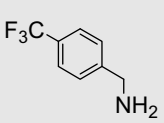
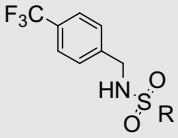
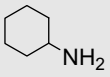
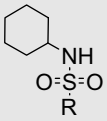
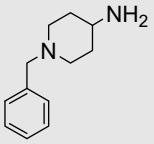
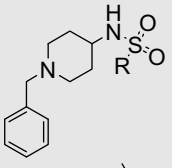
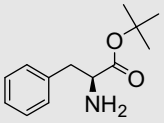
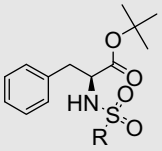
	Amine	Sulfonamide	Yield[a] (%)	
		R = CH_3, CF_3	Methanesulfonamides	Trifluoromethanesulfonamides
1			92	>95
2			97	>95
3			96	>95
4			49	45
5			96	>95
6			95	>95
7			95	>95
8			84	85
9			91	92
10			>95	100
11			>95	>95
12			>95	>95
13			>95	>95

Table 3 (*continued*)

	Amine	Sulfonamide R = CH_3, CF_3	Yield[a] (%) Methanesulfonamides	Trifluoromethanesulfonamides
14			>95	>95
15			>95	>95
16			>95	>95
17			>95	>90

[a] Isolated yields. All products were fully characterized. Reaction were run in a sequential manner.

below. If TLC analysis shows starting material remaining, additional amount of anhydride can be added. The reaction mixture is stirred for half an hour allowing the temperature to reach ambient if needed, followed by the addition of 2–10 times excess of 2.5 N NaOH/methanol (1:2–3). The resulting mixture is stirred at room temperature until conversion to the target mono-sulfonamide is complete (0.5–24 h). Weakly acidic work-up (pH 3–6) followed by conventional isolation affords the desired materials with yields greater than 90% (purity of crude material 90% or higher).

Note: When carrying out reactions in a parallel format, in order to avoid reaction monitoring, an excess of anhydride up to 2–2.2 equiv and, correspondingly, base should be added, and the initial temperature lowered to prevent local overheating. Typical yields are >80%.

To evaluate the applicability of the procedure in a parallel synthesis format, we compared sequential versus parallel setup on selected examples (Table 2). The results presented in Table 2 suggest this approach to be high yielding in a parallel syntheses setup despite the large excess (~2.2 equiv) of sulfonylating agent used.

Application of the protocol to a diverse set of amines is shown in Table 3. A wide range of primary amines such as anilines, benzylamines, aliphatic, and non-chromophoric amines, and aminoacids were investigated.

Additionally, we explored various substitution patterns on both anilines and benzylamines, and showed that the nature of the substituent has little or no influence on the yield of the target monosulfonamide. In the case of non- and weakly chromophoric amines (Ex. 15 and 16), we modified the protocol and used 2.5 equiv of the anhydride and 3 equiv of base in order to provide complete conversion without monitoring. For a vast majority of amines, the yields of corresponding sulfonamides were nearly quantitative. The hydrolytically unstable methyl ester (Ex. 7) afforded the corresponding acid, while 4-aminobenzamide (Ex. 8) produced the sulfonamide in slightly lower yield presumably due to its low solubility. Less successful sulfamidation of *o*-nitroaniline (Ex. 4) was accompanied by low conversion rather than selectivity. However, even in this case, the yields of products based on consumed starting material were ~90%.

In summary, we developed a general and highly efficient one-pot protocol for the synthesis of primary methane- and trifluoromethanesulfonamides that includes a simple reaction setup, offers high product yields, facile isolation, and is applicable to a wide range of amine substrates.

Acknowledgments

We would like to thank Drs. D. Rotella, A. Robichaud, and R. Magolda for their support and encouragement.

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