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Preparation of Sulfamates and Sulfamides Using a Selective Sulfamoylation Agent

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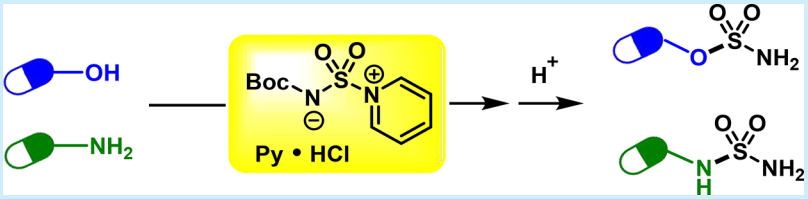


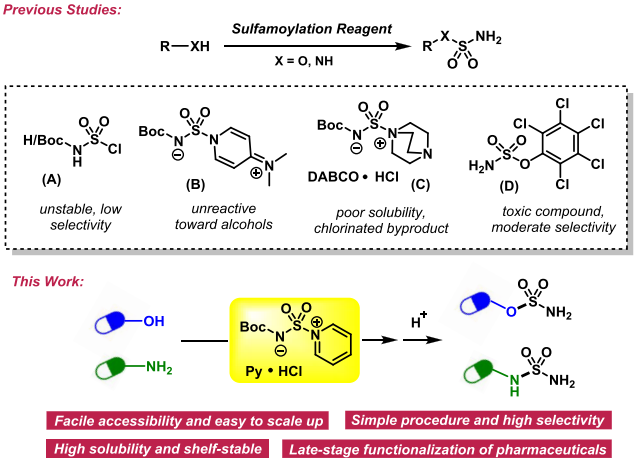
ABSTRACT: Sulfamates and sulfamides are prevalent in biological molecules, but their universal synthetic methods are limited. We herein report a sulfamoylation agent with high solubility and shelf stability. Various sulfamates and sulfamides can be synthesized directly from alcohols or amines by employing this agent with high selectivity and high yields. This protocol was also successfully used for late-stage sulfamoylation of pharmaceuticals containing a hydroxyl or amino group.

The sulfamate[1] and sulfamide[2] moieties are important structural elements in numerous biological molecules with a wide range of activities, including anticonvulsant, antiepileptic, antibiotic, and antitumor features. They are usually considered as isosteric replacements for sulfonamide, urea, carbamate, sulfate, and phosphate functionalities.

Until now, strategies for the preparation of primary sulfamates or sulfamides from alcohols or amines have been limited (Scheme 1). The most common method involves the sulfamoylation with unstable chlorosulfonamide or *N*-(*tert*-butoxycarbonyl)sulfamoyl chloride (**A**). The instability and overly strong reactivity of **A** limited their applications for sulfamoylation on polyfunctional compounds. In 2001, Winum et al. developed a novel Burgess-type reagent (**B**) that could react with various compounds containing an NH_2 group.[3] However, this sulfamoylation reagent has no reactivity toward alcohols. In 2012, Zhu and co-workers reported another solid Burgess-type reagent (**C**), used for selective sulfamoylation of alcohols as well as phenols.[4] Unfortunately, this reagent showed poor solubility in the solvent MeCN. In our control experiment, its saturated solubility in acetonitrile-d_3 is 0.06 mol/L (for details, see the Supporting Information). In their procedure, the mixture was too thick to stir efficiently, so larger volumes of solvent and heat were necessary.[5,6] In addition, the process of sulfamoylation required anhydrous HCl (≤0.4 equiv) to accelerate the nucleophilic reaction, leading to a chlorinated byproduct. Recently, Miller et al. reported a catalytic sulfamoylation of alcohols with pentachlorophenyl sulfamate.[7] However, this reagent exhibits toxicity that derives from pentachlorophenol, and the sulfamoylation selectivity toward polyols is not obvious.

Due to different deficiencies, the previous sulfamoylation agents were not efficiently used in the selective late-stage functionalization of pharmaceuticals containing an OH or NH_2 group. Developing a sulfamoylation agent that can balance reactivity and selectivity and exhibit satisfactory physical properties is in demand. Although few works have reported an *N*-(*tert*-butoxycarbonyl)aminosulfonylpyridinium salt as a

Scheme 1. Strategies for Sulfamoylation of Alcohols and Amines



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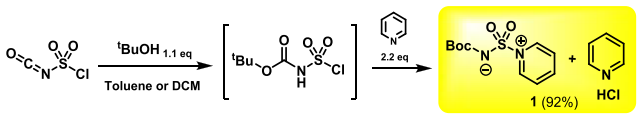
Burgess-type intermediate[8] for the synthesis of limited sulfamides, the separation, characterization, and further application of this useful reagent have been largely neglected. This is most likely due to the development of other methods[9] for the preparation of sulfamides. Pyridine (pK_a = 5.23) is a better leaving group than DMAP (pK_a = 9.70) in the substitution reaction due to its weaker nucleophilicity.[10] We guess a pyridine Burgess-type complex should be more reactive toward a relatively weak nucleophile alcohol in the sulfamoylation reaction.

On the basis of our previous experience with substitution reactions,[11] we herein report an efficient and easy-handling method for the selective conversion of ROH or RNH_2 into sulfamate or sulfamide through a reaction of sulfamoylation agent **1** at room temperature. This protocol could be successfully used for a late-stage sulfamoylation of biological molecules.

First, according to the preparation of sulfamoylation agent **C**,[4] *N*-(*tert*-butoxycarbonyl)sulfamoyl chloride was synthesized with chlorosulfonyl isocyanate and *tert*-butyl alcohol (1.1 equiv) in dichloromethane or toluene (Scheme 2). Then, 2.2

Scheme 2. Preparation of Sulfamoylation Reagent 1

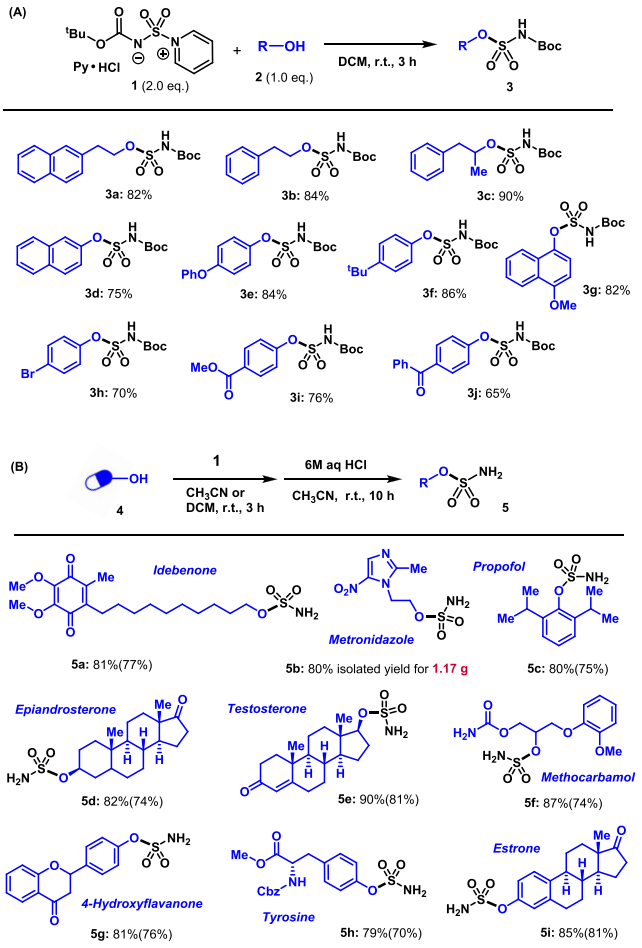


equiv of pyridine was added *in situ* to afford *N*-(*tert*-butoxycarbonyl)-aminosulfonylpyridinium salt and pyridine hydrochloride as a 1:1 mixture (**1**) in 92% yield. Our attempts to separate this mixture with different recrystallization solvents were unsuccessful. This sulfamoylation agent **1** is a white solid, can be prepared on 100 g scale, and has been stored at room temperature for 7 months without a decrease in activity. Reagent **1** also exhibited good solubility in the organic solvent. The saturated solubility in acetonitrile-d_3 is 0.40 mol/L (for details, see the Supporting Information), which is evidently better than that of reagent **C**.

Next, we examined the reaction of 2-(naphthalen-2-yl)-ethan-1-ol (**2a**) with reagent **1** as the model reaction to establish the optimum reaction conditions (for details, see the Supporting Information). It was found that sulfamate product **3a** could be obtained in the best yield with 2.0 equiv of reagent **1** in dichloromethane (0.2M) without any base or additive at room temperature (20−25 °C) in 3 h. The chlorinated side product was not detected.

Under the optimized conditions, we started to investigate the functional group compatibility and substrate scope of this transformation. Sulfamoylation with primary (**2a** and **2b**) and secondary (**2c**) alcohols proceeded smoothly to afford corresponding products **3a**−**3c** in 80−90% yields. Unfortunately, we could hardly obtain the products from tertiary alcohols due to the sluggish sulfamoylation of bulky tertiary alcohols as well as the chlorinated and eliminated byproducts. It was found that the reaction of 2-naphthol (**2d**) and phenols with an electron-donating substituent, including a phenoxy group (**2e**), a *tert*-butyl group (**2f**), or a methoxy group (**2g**), proceeded very well, giving the corresponding products **3e**−**3g** in 75−86% yields (Scheme 3A). Phenols with an electron-deficient group such as bromo (**2h**), ester (**2i**), or benzoyl (**2j**) reacted slightly slower but still gave 65−76% yields.

Scheme 3. Substrate Scope of Sulfamoylation of ROH Including Various Pharmaceuticals and Bioactive Molecules[a]



[a]Yields were obtained on the basis of ^1H NMR with mesitylene as an internal standard and purification (in parentheses).

To investigate the applicability of this sulfamoylation agent, various pharmaceuticals and bioactive molecules containing an OH moiety were subjected to the sulfamoylation conditions followed by the removal of a Boc group by HCl to provide the targeted sulfamate (Scheme 3B). Not only primary alcohols (**4a** and **4b**) but also secondary alcohols (**4d**−**4f**) reacted with **1** smoothly and provided the corresponding products **5a** and **5d**−**5f**, respectively, in moderate to high yields. The weak nucleophilic phenol (**4g**−**4i**) underwent the same reaction, giving **5g**−**5i**, respectively, with high efficiency (79−85% yields). It is noteworthy that the yield was not significantly reduced when sterically bulky phenol (**4c**) was used.

Considering the successful sulfamoylation of alcohol and phenol, we continued to explore the potential of the reaction with aniline or amine from reagent **1** under similar conditions. As shown in Scheme 4A, 2-naphthylamine (**6a**) and anilines bearing a dimethylamino (**6b**), acetyl (**6c**), or trifluoromethyl (**6d**) substituent reacted smoothly with only 1.5 equiv of reagent **1** to give **7a**−**7d** in 75−85% yields. Secondary amines, including *N*-methylaniline (**6e**), diphenylamine (**6f**), and tetrahydroquinoline (**6g**), were also converted in high yields (80−88%) to sulfamides **7e**−**7g**, respectively. Aliphatic amines (**6h**−**6j**) were found to react smoothly with **1** to provide products **7h**−**7j**, respectively, in moderate to high yields.

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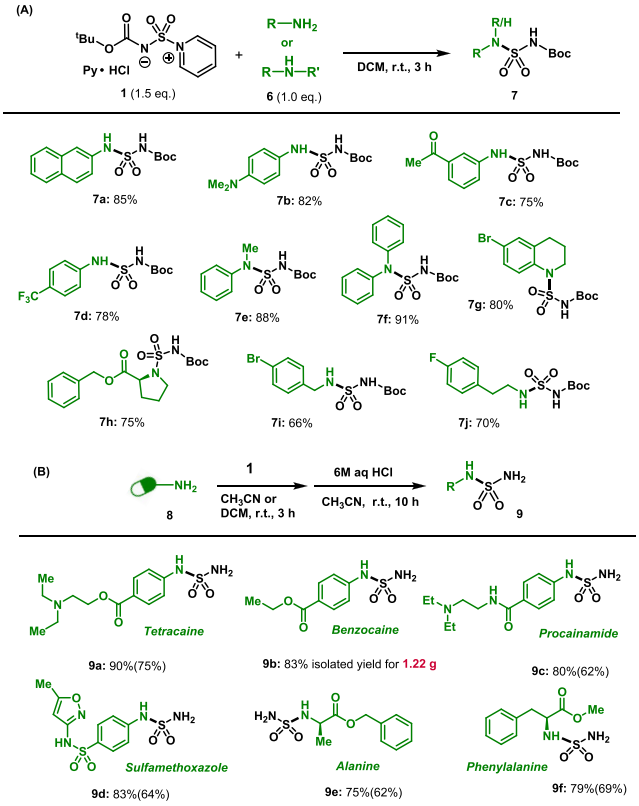
Scheme 4. Substrate Scope of Sulfamoylation of RNHR′(H) Including Various Pharmaceuticals and Bioactive Molecules[a]

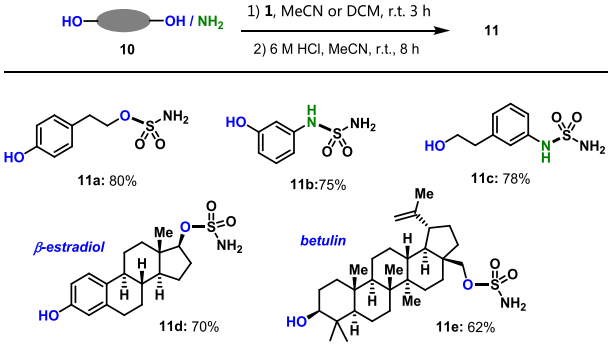


[a]Yields were obtained on the basis of ^{1}H NMR with mesitylene as an internal standard and purification (in parentheses).

Pharmaceutical anilines also afforded the sulfamoyl derivatives (**9a**–**9d**) without difficulty. Aliphatic amines easily proceeded through the sulfamoylation process, providing the amino acid derivatives (**9e** and **9f**) in 75–79% yields. To illustrate the scalability and robustness of this procedure, sulfamoylations of metronidazole (**4b**) and benzocaine (**6b**) were treated with **1** on a gram scale under standard conditions. The corresponding products **5b** (1.17 g) and **9b** (1.22 g) were obtained in 80% and 83% yields, respectively.

Substitution selectivity toward complex pharmaceuticals with multiple nucleophilic groups usually denotes significance as well as a considerable challenge. Recently, our group reported several selective substitutions of different heteroatom nucleophiles.[10] To investigate the selectivity of this method, sulfamoylation toward multiple nucleophilic groups was examined (Scheme 5). Diol with a phenolic -OH group and a primary alcoholic -OH group reacted smoothly with **1** at the primary alcoholic -OH position to give **11a** in 80% yield as the sole sulfamoylation products. Compounds **10b** and **10c** bearing both -OH and -NH_2 groups were also found to react with **1** selectively. The relative reactivity decreased in the following order: anilino NH_2 > primary alcoholic -OH > phenolic -OH. It is noteworthy that agent **1** could be applied to the selective sulfamoylation of biological diols. The sex hormone drug *β*-estradiol (**10d**) and pentacyclic triterpene natural product botulin (**10e**) were tested to react with **1**, and we found that the substitution reactions occurred exclusively on the secondary alcoholic -OH and primary alcoholic -OH,

Scheme 5. Selective Sulfamoylation of Compounds with Different Nucleophilic Groups

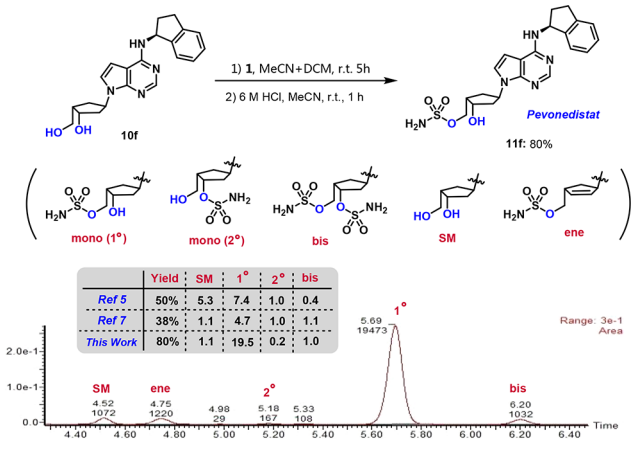


respectively, to give **11d** and **11e** in 70% and 62% yields, respectively.

Finally, we attempted to apply this method to the efficient preparation of first-in-class NAE inhibitor pevonedistat (MLN4924).[12] Pevonedistat, a structural analogue of AMP, was developed by Takeda Pharmaceutical Co. Ltd. as a clinical cancer treatment.[13] It was granted Breakthrough Therapy Designation by the U.S. Food and Drug Administration in July 2020 for the treatment of patients with higher-risk myelodysplastic syndromes (HR-MDS). For a practical and scalable synthesis, the late-stage selective sulfamoylation on the primary OH group (**10f**) presented a considerable challenge. In the current cGMP process, sulfamoylation of **10f** by reagent **C** (Scheme 1) afforded **11f** in only 50% yield.[5] The reaction mixtures contained starting material (SM), the primary sulfamate product, the secondary byproduct, and the bis byproduct in a 5.3:7.4:1.0:0.4 ratio, as well as a trace of the olefin byproduct. In Miller's procedure with PCPS as a sulfamoylation agent,[7] the corresponding ratio was 1.1:4.7:1.0:1.1, and pevonedistat was obtained in only 38% yield.

In contrast, by employing our sulfamoylation agent **1**, MLN4924 could be synthesized in high yield (80%) and selectivity (Scheme 6). According to a LCMS analysis, the ratio of the reaction mixture (SM:ene:secondary:primary:bis) was 1.1:1.2:0.2:19.5:1.0. We believe this method could be used in the GMP production of pevonedistat and other similar diol pharmaceuticals.

Scheme 6. Selective Sulfamoylation of Diols for the Preparation of Pevonedistat



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In summary, we re-examined *N*-(*tert*-butoxycarbonyl)-aminosulfonylpyridinium salt and developed a sulfamoylation agent **1** with the advantages of high solubility, shelf stability, and a large scale. Various sulfamates and sulfamides can be synthesized by employing this agent in high yields. These transformations performed efficiently at room temperature within a few hours and provided a good selectivity toward substrates with multiple nucleophilic groups. A wide range of pharmaceuticals and bioactive molecules containing an OH or NH_2 moiety were highly compatible with this protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00504.

Experimental information, detailed experimental procedures, and full spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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