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Synthesis of *N*-Substituted Sulfamate Esters from Sulfamic Acid Salts by Activation with Triphenylphosphine Ditriflate

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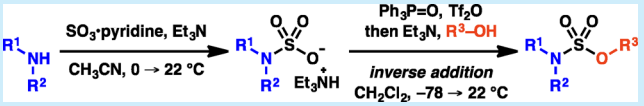
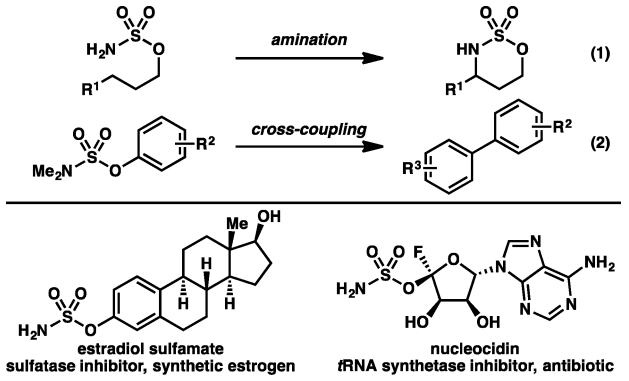
Supporting Information

ABSTRACT: A general approach to access sulfamate esters through preparation of sulfamic acid salts, subsequent activation with triphenylphosphine ditriflate, and nucleophilic trapping is disclosed. The method proceeds in modest to excellent yields to incorporate nucleophiles derived from aliphatic alcohols and phenols. This approach can be employed to furnish differentially substituted sulfamides.



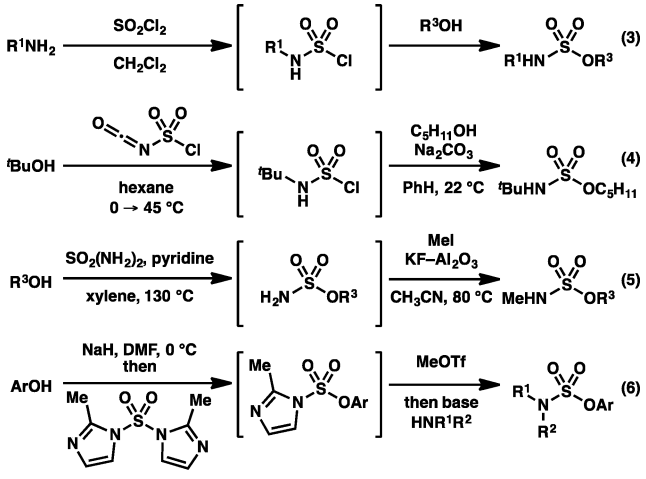
The sulfamate ester functional group has found broad utility, including use as nitrogen sources for amination and aziridination reactions,[1] as electrophiles in cross-coupling reactions,[2] and as an alcohol-masking moiety to modulate the bioactivity and bioavailability of pharmacologically relevant compounds (Scheme 1).[3] One classical approach to access

Scheme 1. Utility of Sulfamate Esters



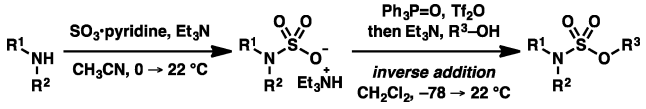
sulfamate esters relies on the use of sulfuryl chloride to furnish sulfamoyl or sulfonyl chloride intermediates. These procedures are inefficient or ineffective when the involved nucleophiles are sterically hindered or electron-deficient (Scheme 2, eq 3).[4,5] Although several alternative methods to access sulfamate esters have been reported (Scheme 2, eqs 4–6),[6−8] there are no operationally straightforward, efficient, general methods to prepare acyclic *O*-alkyl sulfamate esters incorporating primary or secondary alkyl substituents on the nitrogen. To identify a protocol that would provide access to these types of sulfamate esters with varied electronic and steric properties, we anticipated that initial sulfamation[9] of an amine with a sulfur trioxide complex would furnish a sulfamic acid salt. We hypothesized that the use of sulfamic acid salts would allow us to investigate an array of esterification strategies to install the sulfamate ester S−O bond. Described herein is a broadly

Scheme 2. Methods To Prepare Sulfamate Esters



effective protocol to prepare sulfamate esters based on this approach (Scheme 3).

Scheme 3. Disclosed Strategy



As anticipated, the reaction of amines with sulfur trioxide sources provided facile access to diverse sulfamic acid salts (Table 1). Initially, treatment of 2,2,2-trifluoroethylamine with sulfur trioxide·pyridine complex and triethylamine in acetonitrile furnished sulfamic acid salt **2a** in quantitative yield as an oil without need for purification. Solid trimethylammonium salt **2b** could be prepared through the reaction of 2,2,2-trifluoroethyl-

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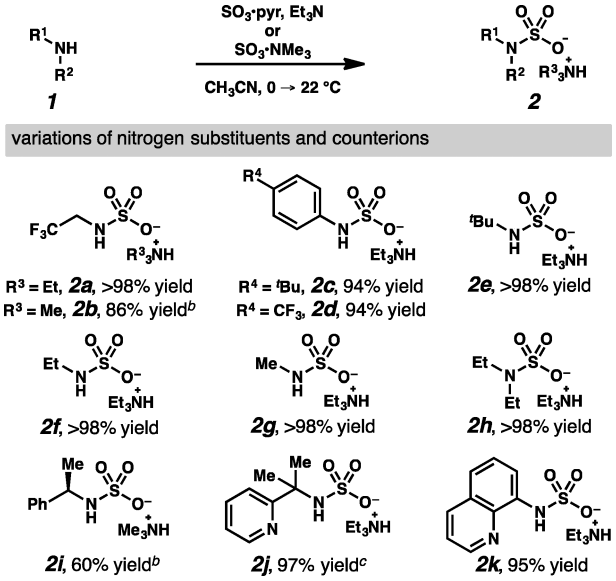
Table 1. Preparation of Sulfamic Acid Salts[a]



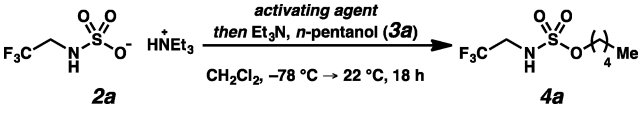
[a]General reaction conditions: 1.0 equiv of amine **1**, 1.0 equiv of sulfur trioxide·pyridine complex (SO_3·pyr), 0.33 M acetonitrile, 1.5 equiv of Et_3N, 30 min, 0 → 22 °C. [b]1 equiv of SO_3·NMe_3 in place of SO_3·pyr and Et_3N. [c]>90% purity.

amine with sulfur trioxide·trimethylamine complex and then recrystallized to purity. While the analogous sodium salt could be prepared from chlorosulfonic acid, incorporation of the ammonium cation simplified the isolation and offered a better solubility profile in subsequent reactions. By this strategy, sulfamic acid salts have been prepared efficiently from anilines, primary and secondary amines, enantioenriched amines, and amines with pendant heteroaromatic functionality.

These readily accessible salts enabled us to interrogate a variety of tactics for esterification of 2,2,2-trifluoroethylsulfamic acid salt **2a** with *n*-pentanol (**3a**) to install a sulfamate ester S−O bond. While sulfamoyl chlorides have been used for efficient access of unsubstituted sulfamate esters,[1,2] activation by in situ generation of a sulfamoyl chloride furnished, at best, *modest* yields of *N*-(2,2,2-trifluoroethyl)sulfamate ester **4a** (Table 2, entries 1−5). Anticipating that the reaction might be driven forward by the formation of a strong phosphorus−oxygen double bond, DIAD and PPh_3 were used to activate the salt and furnish the desired sulfamate ester **4a** in moderate yield (entry 6). As an extension of this approach, the Hendrickson reagent[10] furnished the desired sulfamate ester **4a** in slightly increased yield (entry 7). Under the optimal conditions, 1.5 equiv of triethylammonium sulfamate **2a** was activated by addition to a solution of triphenylphosphine ditriflate, which was generated in situ from 1.5 equiv of Tf_2O and 1.65 equiv of Ph_3PO (entry 10). Subsequent treatment with 3 equiv of triethylamine and 1 equiv of **3a** at −78 °C furnished sulfamate ester **4a** in 95% isolated yield. Trimethylammonium sulfamate salt **2b** reacted with similar efficiency under the optimal conditions (entry 11).

Under the optimized conditions, a range of *N*-substituted salts **2** can be converted to sulfamate esters **4** in modest to excellent yields (Table 3). While aryl and electron-deficient *N*-alkyl substituents are well-tolerated in the transformation (**4a**−**d**), more electron-rich *N*-alkyl substituents result in modest yields of sulfamate esters **4e**−**g**. Of these, *N*-*tert*-butylsulfamate esters can be prepared in similar yield using *tert*-butanol and chlorosulfonyl isocyanate to generate *N*-*tert*-butylsulfamoyl

Table 2. Optimization of Sulfamate Ester Preparation



entry[a]	activating agent	yield of **4a** (%)[b]
1	PCl_5 (2.0 equiv)	41
2	$POCl_3$ (2.0 equiv)	44
3	$SOCl_2$ (2.0 equiv)	<5
4	$(COCl)_2$ (10.0 equiv)	nd[c]
5	trichlorotriazine (1.0 equiv)	<5
6[d]	DIAD, PPh_3	50
7	Tf_2O (1.0 equiv), Ph_3PO (2.1 equiv)	56
8[e]	Tf_2O (1.5 equiv), Ph_3PO (3.15 equiv)	71
9[e]	Tf_2O (1.5 equiv), Ph_3PO (1.65 equiv)	78
10[e,f]	**Tf_2O (1.5 equiv), Ph_3PO (1.65 equiv)**	**95**
11[f,g]	**Tf_2O (1.5 equiv), Ph_3PO (1.65 equiv)**	**94**

[a]General reaction conditions: 1.0 equiv of *n*-pentanol (**3a**), 1.0 equiv of sulfamate **2a**, CH_2Cl_2, 2.0 equiv of Et_3N, Tf_2O (1.5 equiv), Ph_3PO (1.65 equiv), 18 h, −78 → 22 °C. [b]Isolated yields. [c]Not detected. [d]No Et_3N. [e]1.5 equiv of **2a**. [f]3.0 equiv of Et_3N. [g]1.5 equiv of **2b**.

chloride (Scheme 2, eq 4);[6] however, *N*-methyl- and *N*-ethylsulfamate esters cannot be accessed via a similar strategy. In principle, these *N*-alkyl sulfamates could be prepared in a two-step approach featuring monoalkylation of *O*-pentyl sulfamate (Scheme 2, eq 5).[7] Neither of these methods would be appropriate to access enantioenriched sulfamate ester **4i**, which is generated without any stereochemical erosion using the disclosed approach.

The optimized protocol is less effective at transforming salts that have been generated from secondary amines or that incorporate heteroaromatic substituents. When triethylammonium *N*,*N*-diethyl sulfamate (**2h**) is employed, diethylsulfamate ester **4h** forms in 17% yield (see the Supporting Information). Fortunately, this reaction proceeds in 68% yield when sulfamate **2h** is treated with 1 equiv of sodium pentoxide as the nucleophile. Notably, sulfamic acid salts incorporating nitrogen-containing heterocycle substituents were converted to sulfamate esters **4j** and **4k**. These products were not detected when PCl_5 was utilized to activate the sulfamic acid salt via sulfamoyl chloride intermediates.

Under the optimized conditions, a variety of alcohols serve as effective nucleophiles to generate sulfamate esters in modest to excellent yields (Table 3, **4l**−**w**). Primary and secondary aliphatic alcohols and phenols, including electron-deficient *p*-hydroxybenzonitrile (**3o**), are converted to sulfamate esters in high yield. In principle, phenol-derived **4p** could be generated from an activated sulfonyl imidazolium species (Scheme 2, eq 6).[8] However, when sulfonyl imidazolium reagents are used for the synthesis of sulfamate esters, the alcohol portion must be installed first, and the approach does not tolerate electron-rich or -neutral aliphatic alcohols. The disclosed reaction tolerates the benzyl and silyl ether groups in alcohols **3r** and **3s**, respectively, and the phthalimide moiety in alcohol **3t**, providing potential strategies for site-specific sulfamoylation of polylols and amino alcohols. As expected, these conditions efficiently incorporate more elaborate hydrocarbon scaffolds, such as those of tetrahydrogeraniol and 5α-cholestan-3β-ol, into sulfamate esters **4u**−**w**.

In addition to alcohols, nitrogen nucleophiles can be incorporated into sulfamides under the reaction conditions to

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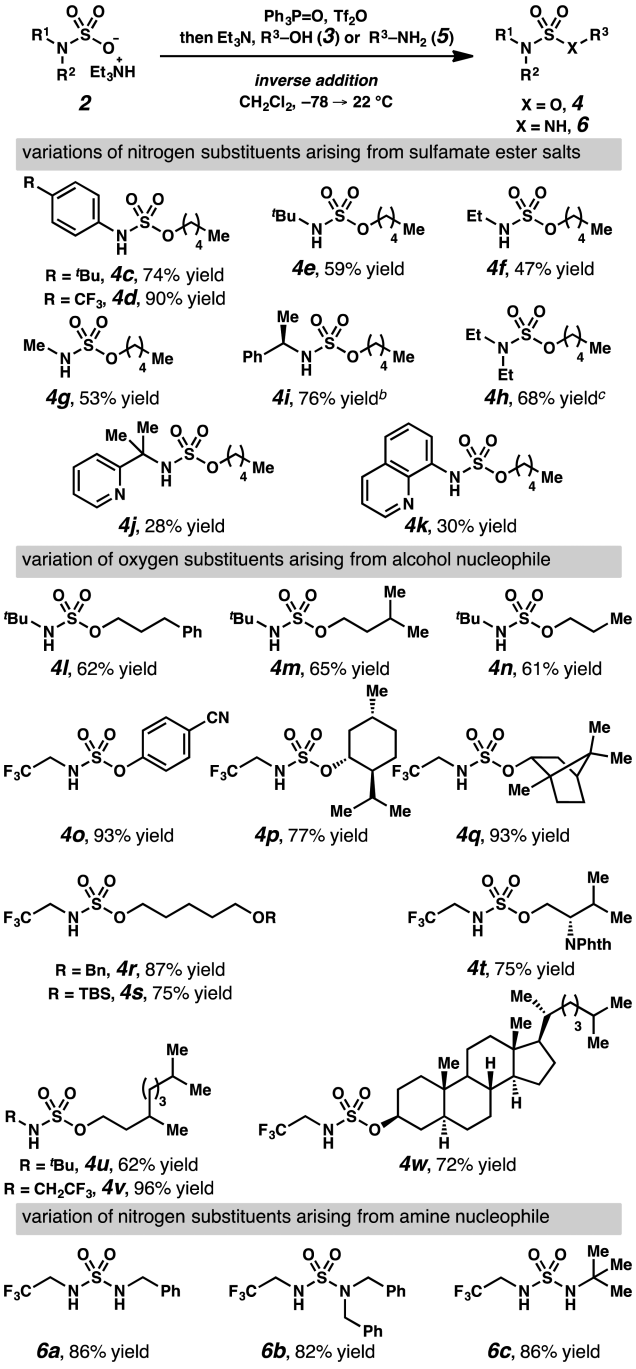
Table 3. *N*- and *O*-Substitutent Variations[a]



[a]General reaction conditions: 1.0 equiv of alcohol **3** or amine **5**, 1.5 equiv of sulfamic acid salt **2**, CH_2Cl_2, 3.0 equiv of Et_3N, Tf_2O (1.5 equiv), Ph_3PO (1.65 equiv), 18 h, −78 → 22 °C. [b]Sulfamic acid salt **2i** incorporates Me_3NH^+ as a counterion. [c]1.0 equiv of sodium pentoxide, 0 → 22 °C. The alcohol and Et_3N were omitted.

furnish unsymmetrically substituted sulfamides **6a**−**c**. Sulfamides are valuable components of some bioactive small molecules, with some nonsymmetrically substituted sulfamides demonstrating higher bioactivity than symmetrically substituted analogues.[11] Nevertheless, few methods[12] enable the efficient preparation of unsymmetrically substituted sulfamides. By the present approach, differentially substituted sulfamides are accessible from primary, secondary, or tertiary amines, including sterically encumbered *tert*-butylamine (i.e, **5c** → **6c**).

To conclude, the disclosed method employs inexpensive and readily available sulfur trioxide sources, primary and secondary alkyl amines, and aliphatic or aromatic alcohols to prepare sulfamate esters, many of which are not efficiently accessible through other known methods. Furthermore, the intermediate salts can be employed to generate differentially substituted sulfamides. This new approach provides ready access to a powerful, pharmacologically relevant, and synthetically versatile motif.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03059.

Full experimental details and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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