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Synthesis of *N*-substituted sulfamate esters from sulfamic acid salts by activation with triphenylphosphine ditriflate

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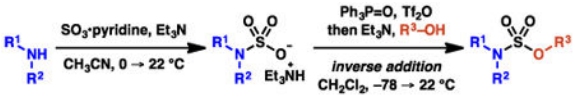
Abstract

A general approach to access sulfamate esters through preparation of sulfamic acid salts, subsequent activation with triphenylphosphonium 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.

Graphical abstract



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 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 have been reported to access sulfamate esters (eqs 4–6),[6, 7, 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 use of sulfamic acid salts would allow us to investigate an array of esterification strategies to install the sulfamate ester S–O bond. Based on this approach, described herein is a broadly effective protocol to prepare sulfamate esters (Scheme 3).

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As anticipated, 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-trifluoroethylamine with sulfur trioxide trimethylamine complex, and then recrystalized to purity. While the analogous sodium salt could be prepared from chlorosulfonic acid, incorporation of the ammonium cation simplified isolation and offered a better solubility profile in subsequent reactions. Using 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-trifluoroethyl sulfamic 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 formation of a strong phosphorous–oxygen double bond, DIAD and PPh_3 were used to activate the salt, and furnish desired sulfamate ester **4a** in moderate yield (entry 6). As an extension to this approach, the Hendrickson reagent[10] furnished desired sulfamate ester **4a** in slightly increased yield (entry 7). Under the optimal conditions, 1.5 equivalents of triethylammonium sulfamate **2a** were activated by addition to a solution of triphenylphosphine ditriflate, which was generated *in situ* from 1.5 equivalents of Tf_2O and 1.65 equivalents of Ph_3PO (entry 10). Subsequent treatment with 3 equivalents of triethylamine and 1 equivalent of *n*-pentanol (**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 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 the mono-alkylation 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 Supporting Information). Fortunately, this reaction proceeds in 68% yield if sulfamate **2h** is treated with 1 equivalent of sodium pentoxide as the nucleophile. Notably, sulfamic acid

salts incorporating nitrogen-containing heterocycle substituents are converted to sulfamate esters **4j–k**. These products are not detected when utilizing PCl_5 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–**4w**). 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 benzyl or silyl ether groups in alcohols **3r** and **3s**, respectively, and a 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**–**4w**.

In addition to alcohols, nitrogen nucleophiles can be incorporated into sulfamides under the reaction conditions to furnish unsymmetrically substituted sulfamides **6a**–**6c**. 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 efficient preparation of unsymmetrically substituted sulfamides. Using this 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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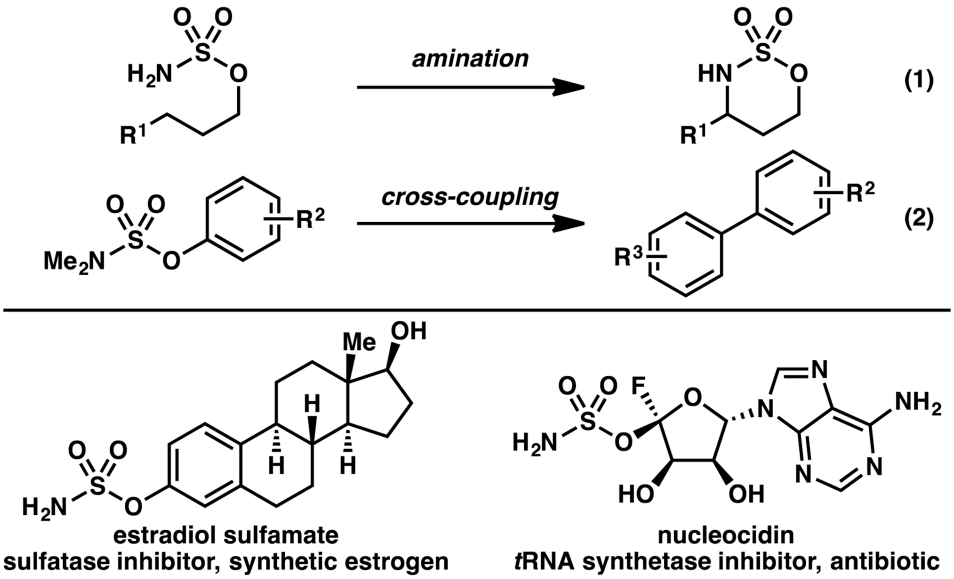
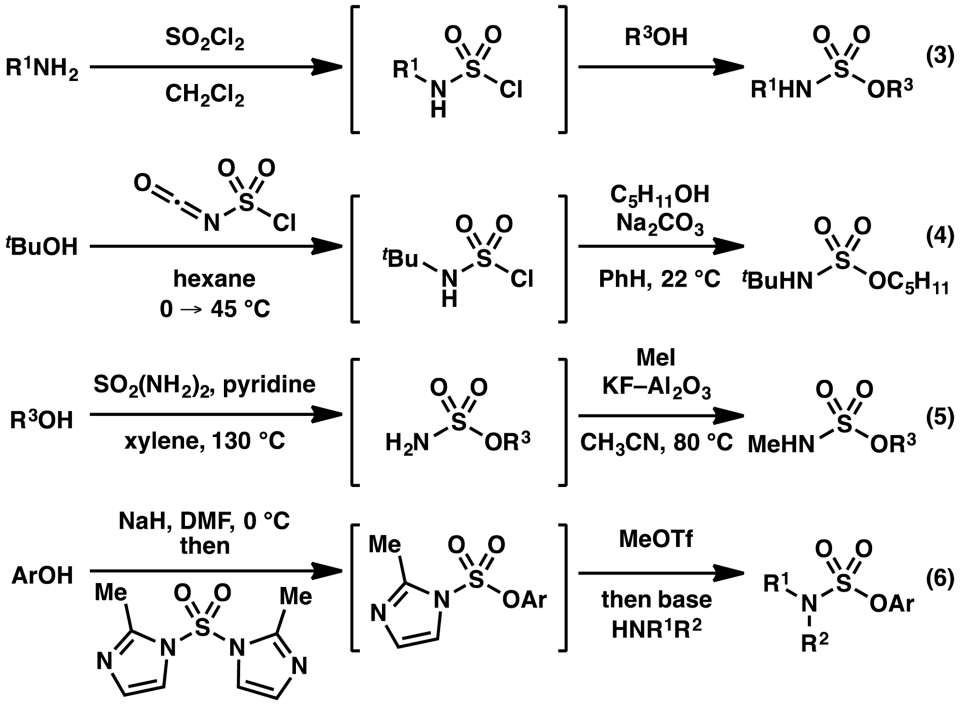
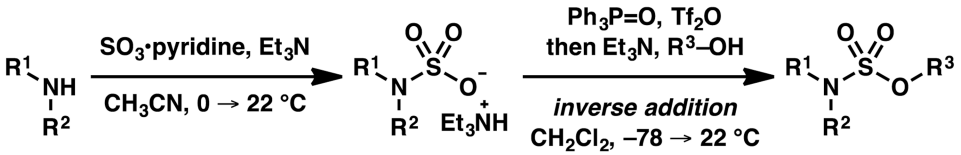


Scheme 1. Utility of sulfamate esters



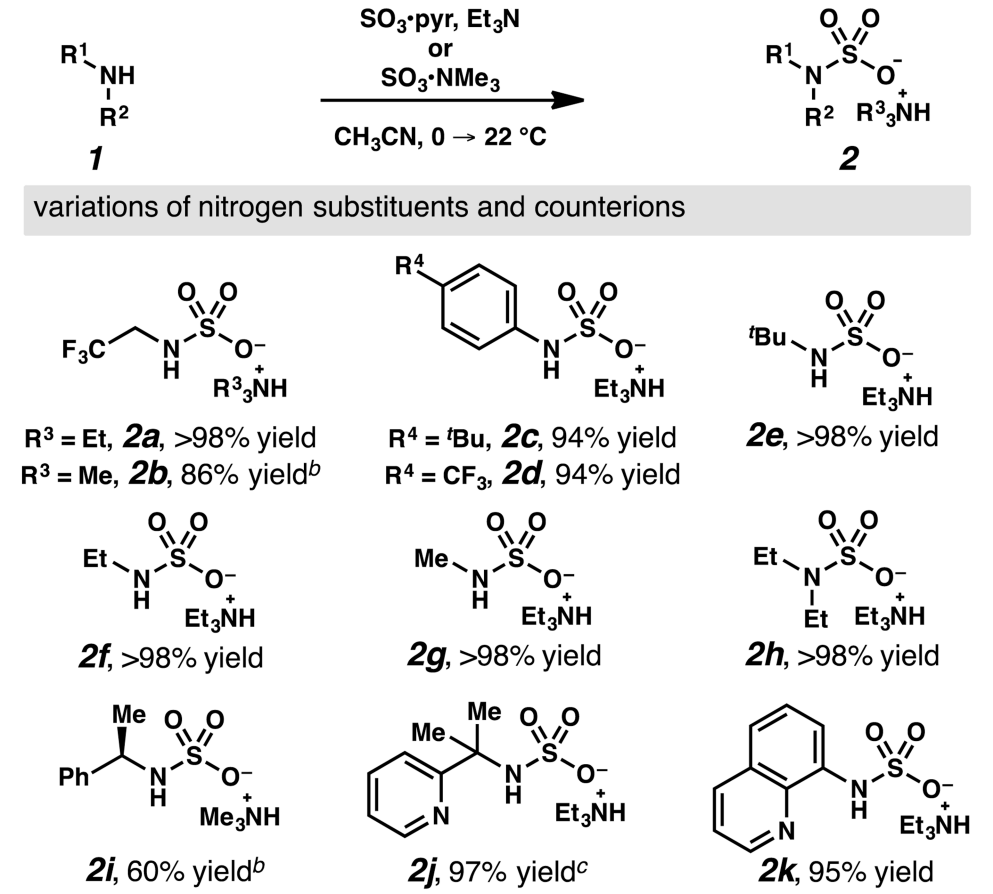
Scheme 2. Methods to prepare sulfamate esters



Scheme 3. Disclosed strategy

Table 1

Preparation of sulfamic acid salts[a]

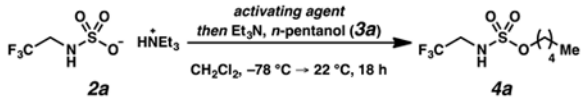


[a]General reaction conditions: 1.0 equiv amine **1**, 1.0 equiv sulfur trioxide pyridine complex (SO_3•pyr),0.33 M acetonitrile, 1.5 equiv Et_3N, 30 min, 0 → 22 °C.

[b]1 equiv SO_3•NMe_3 in place of SO_3•pyr and Et_3N.

[c]>90% purity.

Table 2
Optimization of Sulfamate Ester Preparation



entry[a]	activating agent	yield (%)[b] 4a
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 *n*-pentanol (**3a**), 1.0 equiv sulfamate **2a**, CH_2Cl_2, 2.0 equiv Et_3N, Tf_2O (1.5 equiv), Ph_3PO (1.65 equiv), 18 h, −78 → 22°C.

[b] Isolated yield.

[c] Not detected.

[d] No Et_3N.

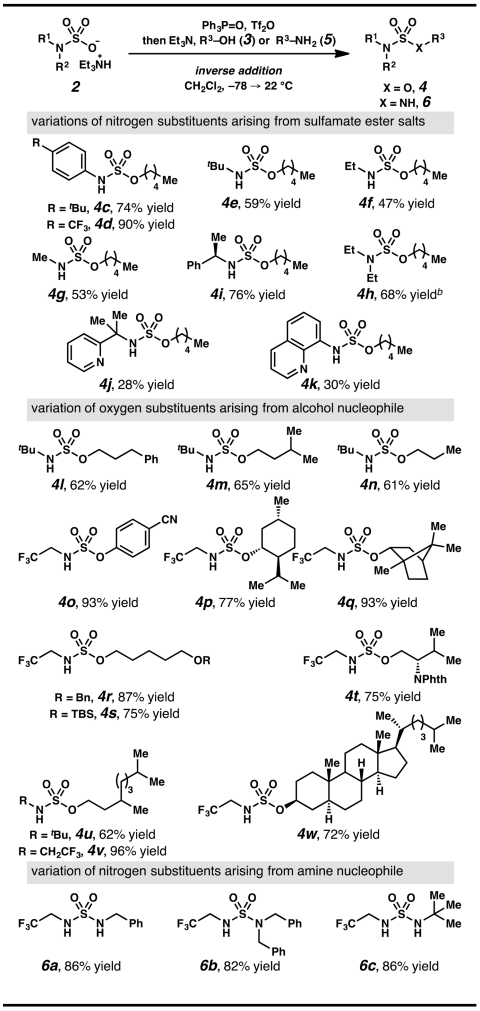
[e] 1.5 equiv triethylammonium sulfamate **2a**.

[f] 3.0 equiv Et_3N.

[g] 1.5 equiv trimethylammonium sulfamate **2b**.

Table 3

N- and *O*-substitutent variations[a]



[a]General reaction conditions: 1.0 equiv alcohol **3** or amine **5**, 1.5 equiv sulfamate **2**, CH_2Cl_2, 3.0 equiv Et_3N, Tf_2O (1.5 equiv), Ph_3PO (1.65 equiv), 18 h, −78→ 22°C.

[b]1.0 equiv sodium pentoxide, 0 → 22°C.Alcohol and Et_3N were omitted.