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Graphical Abstract

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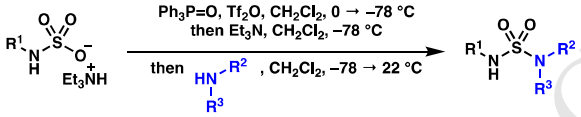

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Efficient synthesis of unsymmetrical sulfamides from sulfamic acid salts by activation with triphenylphosphine ditriflate

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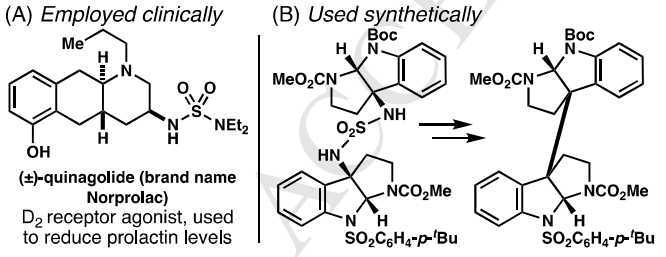
ABSTRACT

A general approach to prepare unsymmetrical sulfamides is described. This method relies on the activation of sulfamic acid salts with triphenylphosphine ditriflate, and subsequent trapping by a nucleophilic amine. This strategy improves access to *N*-octadecyl-*N*'-propylsulfamide, a feeding suppressant.

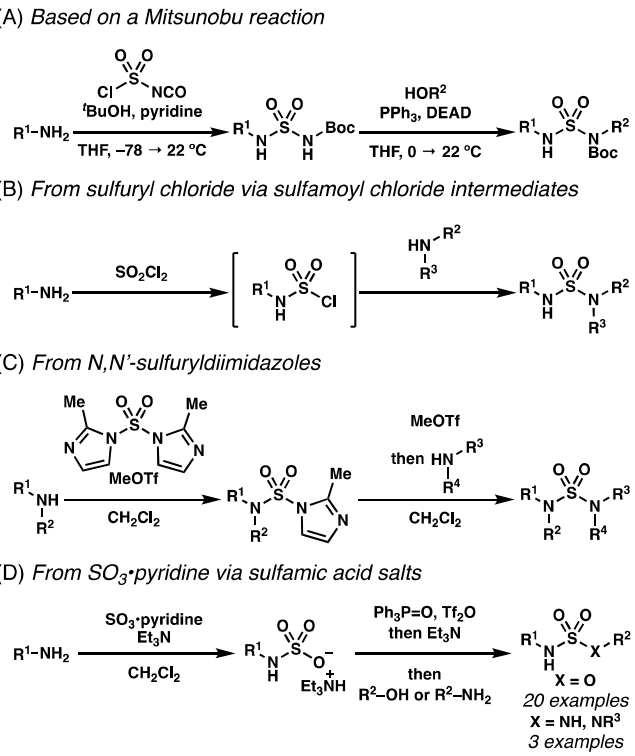
1. Introduction

Sulfamides are valuable synthetic targets.[1] They can be thought of as bioisosteres for amides, ureas, carbamates, and sulfonamides.[2] Unsymmetrical acyclic *N*,*N*'-dialkyl sulfamides are employed clinically (Scheme 1A) and serve as powerful synthetic intermediates as precursors to sterically encumbered carbon–carbon bonds (Scheme 1B).[3] Additionally, sulfamides incorporate hydrogen-bonding motifs that are critical to chiral auxiliaries[4] and organocatalysts.[5]



Scheme 1. Sulfamides are useful

Owing to these applications, chemists have developed a few methods to access sulfamides. An efficient and operationally straightforward Mitsunobu reaction sequence furnishes unsymmetrical dialkyl sulfamides from primary or secondary alcohol precursors (Scheme 2A);[6] however, access to dialkyl sulfamides from amines can be challenging. Some *N*,*N*'-dialkyl sulfamides can be prepared by sequential addition of two alkylamines to sulfuryl chloride (Scheme 2B),[7] a sulfuryldiimidazole analogue (Scheme 2C),[8] or catechol sulfate (not depicted).[9]



Scheme 2. Few tactics provide access to unsymmetrical *N*,*N*'-dialkyl sulfamides

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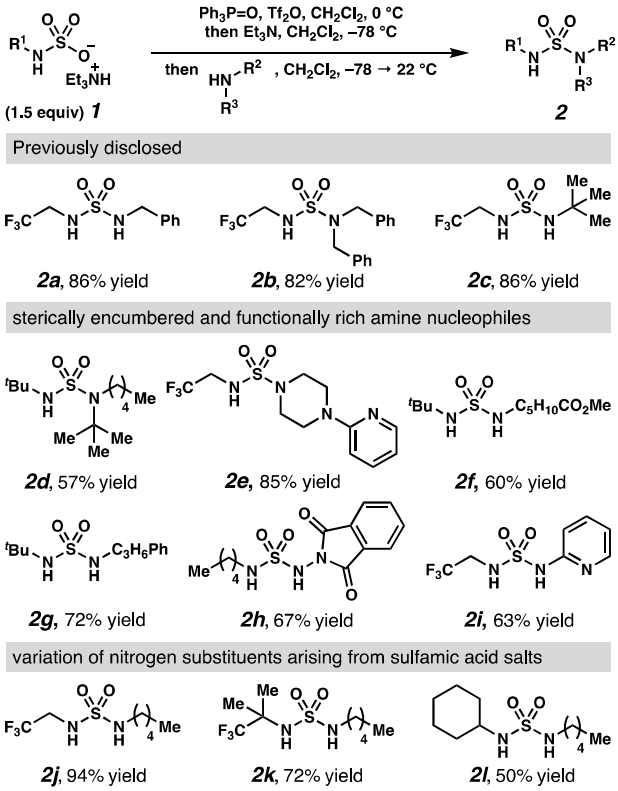
Unfortunately, these protocols do not provide synthetically useful yields of many dialkyl sulfamides, a challenge that is exacerbated when the involved nucleophiles are sterically hindered or electron deficient amines. We recently reported the preparation of sulfamate esters from the inexpensive and broadly available solid, SO_3•pyridine, by way of sulfamic acid salts based on activation with triphenylphosphine ditriflate (Scheme 2D).[10] Herein described is research to extend this reaction platform to be a broadly effective protocol to access unsymmetrical dialkyl sulfamides.

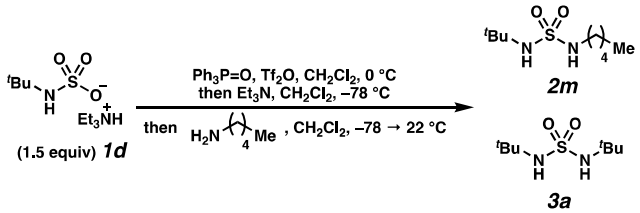
2. Results and discussion

Previously, the disclosed protocol had been applied to access three unsymmetrical sulfamides (i.e. **2a**–**2c**), demonstrating the ability of primary, secondary, and sterically encumbered primary amines to serve as nucleophiles in their preparation (Scheme 3).[10a] Without significant modifications, this technology also transforms sterically encumbered secondary amines (**2d**) and cyclic amines (**2e**). Amines react even when they are incorporated into scaffolds that present other functional groups, such as esters, arenes, heterocycles, and even *N*-aminophthalimide (**2f–2i)**. Given our interest in 2-functionalized pyridines,[11] we were delighted to find that 2-aminopyridine proved a competent nucleophile to furnish 2-pyridyl-sulfamide **2i**. Furthermore, the reaction conditions activate electronically and sterically varied sulfamic acid salts to access differentially substituted **2j**–**2l**.



Scheme 3. Application of sulfamate ester preparation protocol to access sulfamides

Unfortunately, this protocol proved fickle when sulfamides were constructed from two electronically similar amines. For example, application of the published procedure to access *N*-*tert*-butyl-*N'*-pentylsulfamide (**2m**), furnished *N*,*N'*-di(*tert*-butyl)sulfamide (**3a**) as a byproduct (Scheme 4). Sadly, symmetrical **3a** was not readily separable from desired unsymmetrical **2m**, presumably because both sulfamides incorporate amines of similar polarity.

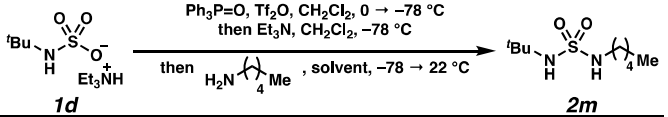


Scheme 4. Previously reported conditions generate mixture of desired sulfamide and *N*,*N'*-di(*tert*-butyl)sulfamide **3a**

To circumvent this challenge, the protocol was adjusted to employ sulfamic acid salt as limiting reagent, and to enable careful control of the reaction temperature. Specifically, the reaction of *tert*-butylsulfamic acid salt with triphenylphosphine ditriflate in dichloromethane was cooled to –78 °C prior to the addition to triethylamine. Additionally, while the ultimate reaction concentration was maintained, the salt was activated at a lower concentration in an effort to limit formation of symmetrical *N*,*N'*-di(*tert*-butyl)sulfamide (**3a**).

Owing to these operational changes, two electronically similar amines could be incorporated into unsymmetrical sulfamides cleanly (Table 1, entry 1). We anticipated that some amine nucleophiles would not be amenable to reaction in dichloromethane, owing to their insolubility. To surmount this foreseen challenge, we assessed a single solvent from each of seven solubility clusters for the addition of the amine nucleophile (Table 1, entries 2–8).[12] Within a given cluster, the evaluated solvent is more likely to be accepted at some production sites[13] based on safety, health, environmental, and legal constraints. To our delight, this range of solvents proved effective in sulfamide formation from pentylamine, though with diminished yields.

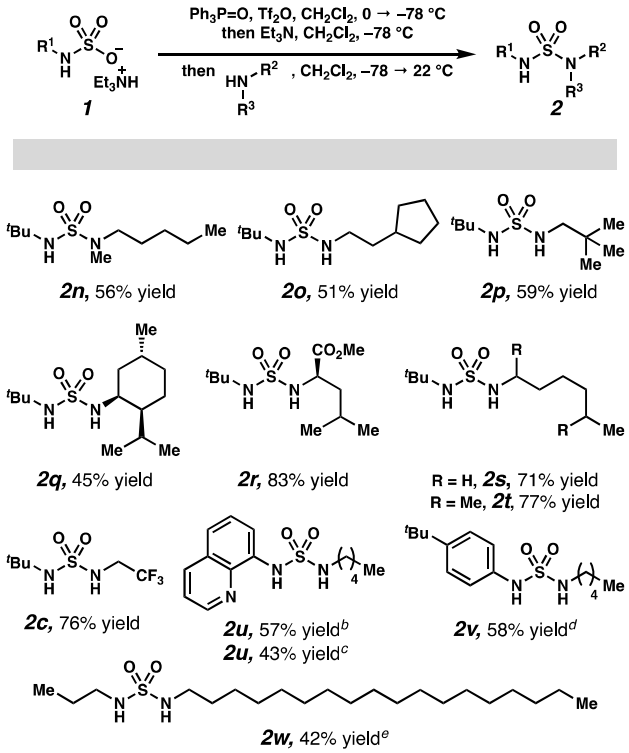
Table 1. Solvent variations are tolerated



Entry[a]	Solvent	Yield [%][b]
1	CH_2Cl_2	79
2	MeCN	47
3	heptane	48
4	PhMe	63
5	2-MeTHF	61
6	DMF	57
7	MTBE	52
8	DMSO	36

[a] General reaction conditions: 1.65 equiv of Ph_3PO, CH_2Cl_2 (0.15 M with respect to amine), 1.5 equiv of Tf_2O, 1.0 equiv of sulfamic acid salt (**1d**) in CH_2Cl_2 (1.25 M with respect to amine), 3.0 equiv of Et_3N in CH_2Cl_2 (0.36 M with respect to amine), 1.0 equiv of $H_2NC_5H_{11}$ in solvent (1.25 M), –78 → 22 °C. [b] Isolated yields.

As a testament to the synthetic utility of these operational changes, several sulfamides that could not be accessed in high purity under the original protocol can now be prepared. This improved protocol is effective with primary and secondary amines to yield sulfamides **2m** and **2n**. The reaction converts pendant acyclic, cyclic, and sterically encumbered alkyl amines to furnish **2o**–**2p** and **2s**. Furthermore, primary amines at secondary centers are readily incorporated into sulfamides **2q**– **2r** and **2t**, even tolerating a pendant methyl ester to furnish leucine-derived sulfamide **2r**. Additionally, electron deficient amines and 8-aminoquinoline are effective nucleophiles providing access to sulfamides **2c** and **2u**. This improved protocol is also successful when activating *N*-aryl sulfamic acid salts, yielding *N*-aryl sulfamides **2u** and **2v**.



Scheme 5. Modified conditions results in formation of only desired sulfamides. General conditions : 1.65 equiv of Ph_3PO, CH_2Cl_2 (0.15 M with respect to amine), 1.5 equiv of Tf_2O, 1.0 equiv of *tert*-butyl sulfamic acid salt (**1d**) in CH_2Cl_2 (1.25 M with respect to amine), 3.0 equiv of Et_3N in CH_2Cl_2 (0.36 M with respect to amine), 1.0 equiv of amine in CH_2Cl_2 (1.25 M), –78 → 22 °C. [a] Isolated yields. [b] Prepared from pentyl sulfamic acid salt and 8-aminoquinoline. [c] Prepared from quinolin-8-yl sulfamic acid salt and pentylamine. [d] Prepared from 4-(*tert*-butyl)phenyl sulfamic acid salt and pentylamine. [e] Prepared from crude propyl sulfamic acid salt and octadecylamine added as a solution in toluene.

We wanted to improve access to the potential hypolipidemic compound and feeding suppressant *N*-octadecyl-*N*'-propylsulfamide (**2w**; CAS 925892-74-3).[14] It has been generated previously in up to 31% yield through the patented reaction of octadecylamine and *N*-propylsulfamoyl chloride (CAS 10305-42-7).[15, 16] As *N*-octadecylamine is insoluble in CH_2Cl_2, an alternative solvent was required to affect the addition of this nucleophile. Through preparation of propyl sulfamic acid salt and addition of *N*-octadecylamine as a solution in toluene, *N*-octadecyl-*N*'-propylsulfamide (**2w**) was isolated in 42% yield over 2 steps. This constitutes a marked improvement over the previously reported routes to the desired compound from commodity chemicals following a single purification.

3. Conclusion

The disclosed reaction conditions enable preparation of a series of sulfamides. Importantly, these reaction conditions minimize the formation of *N,N'*-di(*tert*-butyl)sulfamide as a byproduct, and is robust across a range of solvents. These conditions improve access to the potential feeding suppressant *N*-octadecyl-*N*'-propylsulfamide.

4. Experimental section

4.1. General methods

Moisture-sensitive reactions were performed using flame-dried glassware under an atmosphere of dry nitrogen (N_2). Flame-dried equipment was stored in a 130 °C oven before use and either allowed to cool in a cabinet dessicator or assembled hot and allowed to cool under an inert atmosphere. Air- and moisture-sensitive liquids and solutions were transferred *via* plastic or glass syringe. Chromatographic purification of products was accomplished by flash column chromatography using Silicycle Silica flash F60 (particle size 40–63 μm, 230–400 mesh) or by Teledyne Isco CombiFlashRf system using 12–220 g Redi Sep Rf normal phase silica columns (particle size 40–63 μm irregular, 230–400 mesh). Thin layer chromatography was performed on EMD Millipore silica gel 60 F254 glass-backed plates (layer thickness 250 μm, particle size 10–12 μm, impregnated with a fluorescent indicator). Visualization of the developed chromatogram was accomplished by fluorescence quenching under shortwave UV light and/or by staining with *p*-anisaldehyde or $KMnO_4$ stains. Unless otherwise noted, room temperature is 22 ºC.

NMR spectra were obtained on Varian iNOVA spectrometers operating at 400 or 500 MHz for ^{1}H NMR, 101 or 126 MHz for ^{13}C NMR, and 376 MHz for ^{19}F NMR at 23–25 °C, or on a Bruker Neo spectrometer operating at 500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR at 23–25 °C, and are reported as chemical shifts (δ) in parts per million (ppm). Spectra were referenced internally according to residual solvent signals (^{1}H: $CDCl_3$, 7.26 ppm; ^{13}C: $CDCl_3$, 77.0 ppm; CD_3CN, 1.3, 118.3 ppm). Data for NMR spectra use the following abbreviations to describe multiplicity: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublet of doublets; qd, quartet of doublets; m, multiplet. Coupling constant (*J*) are reported in units of Hertz (Hz). IR spectra were obtained on a Nicolet 6700 FT-IR system. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T); w (weak, 67–100% T); and br (broad). High resolution mass spectra (HRMS, m/z) were recorded on an Agilent LCMS-TOF-DART spectrometer using electrospray ionization (ESI, Duke University Department of Chemistry Instrumentation Center).

All reagents and chemicals were obtained commercially and used without further purification or prepared according to previously reported procedures. Anhydrous dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were obtained from Sigma Aldrich and were purified, dried, and degassed by passage through two columns of neutral, activated alumina under N_2 using an Innovative Technologies solvent purification system. Anhydrous toluene was purified, dried, and degassed by passage through a column containing copper followed by a column of neutral, activated alumina under N_2 using an Innovative Technologies solvent purification system. Triethylamine (Et_3N) was distilled from CaH_2 and stored in a Schlenk flask for future use.

4.2. General Procedure A: Preparation of sulfamides using previously disclosed procedure (Schemes 3 and 4)

A flame-dried round bottom flask equipped with magnetic stir bar was charged with triphenylphosphine oxide (1.65 equiv) and fitted with a rubber septum. The flask was evacuated and backfilled with N_2. Anhydrous CH_2Cl_2 (0.22 M with respect to amine) was added and the flask was cooled at 0 °C in an ice water bath. Trifluoromethanesulfonic anhydride (1.5 equiv) that had been freshly removed from the glovebox was then added to the cooled solution dropwise via syringe. The reaction was allowed to stir at 0 °C in an ice water bath for 15 minutes. This suspension was treated with a solution of sulfamic acid salt (1.50 or 1.65 equiv as noted below) in CH_2Cl_2 (1.25 M with respect to amine) that had been cooled at 0 °C via cannula transfer. The flask containing sulfamate salt solution was rinsed with CH_2Cl_2 (ca. 5.0 M with respect to amine) to achieve quantitative transfer. The resulting yellow solution was stirred for 15 minutes at 0 °C. During this time, a clean, flame-dried round bottom flask equipped with stir bar was fitted with a rubber septum and subsequently evacuated and backfilled with N_2. This process was repeated two more times. The flask was then charged with Et_3N (3.0 equiv) and CH_2Cl_2 (0.22 M with respect to amine) and the mixture was cooled at –78 °C in an ^{i}PrOH/dry ice bath. The sulfamate salt solution was transferred dropwise to the Et_3N solution via cannula (during which time a yellow to intense red color often developed), rinsing the flask with CH_2Cl_2 (ca. 2.0 M with respect to amine) to achieve quantitative transfer. The resultant solution was stirred at –78 °C for 15 minutes. A solution of the amine ($(R^2)(R^3)$–NH, 1.0 equiv) in CH_2Cl_2 (1.25 M) that had been precooled at 0 °C was then added to the triethylamine solution via cannula. The amine-containing flask was rinsed with CH_2Cl_2 (ca. 5.0 M with respect to amine) to achieve quantitative transfer. Without removing the cooling bath, the reaction was then stirred overnight, during which time no additional dry ice was added to the bath and the mixture gradually warmed to room temperature.

After stirring overnight, the reaction was diluted with 1 M HCl (ca. 5 mL/mmol of sulfamide) and H_2O (ca. 5 mL/mmol of sulfamide). The biphasic mixture was transferred to a separatory funnel, rinsing the flask with CH_2Cl_2 to achieve quantitative transfer. The organic phase was separated and the aqueous phase was extracted twice more with CH_2Cl_2 (ca. ½ reaction volume). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reaction mixtures were then purified by silica gel flash chromatography by dry loading the samples and eluting with a hexanes:EtOAc solvent system as noted below.

*4.2.1. N-tert-Butyl-N'-tert-butyl-N-pentylsulfamide (**2d**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d**, 839 mg, 3.30 mmol, 1.65 equiv) and *N-tert*-butyl-*N*-pentylamine (**S2**, 286 mg, 2.00 mmol) according to general procedure A. The product was isolated as a white solid (317 mg, 57% yield) after purification on a Teledyne Isco CombiFlashR_f system using a Redi Sep R_f normal phase silica gel column (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (br s, 1H), 3.18 (dd, *J* = 8.1, 10.7 Hz, 2H), 1.71–1.63 (m, 2H), 1.43 (s, 9H), 1.34 (s, 9H), 1.25–1.17 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 58.6, 54.5, 47.3, 31.7, 30.1, 29.7, 29.3, 22.4, 14.1. IR (neat) ν 3276 (br), 2960 (m), 2931(w), 2872 (w), 1469 (w), 1391 (m), 1365 (m), 1308 (m), 1217 (m), 1189 (m), 1129 (s), 1040 (w), 992 (m), 916 (m), 864 (m), 836 (w), 797 (w), 766 (w), 726 (w), 680 (m), 588 (m) cm^{-1}. TLC R_f = 0.49 in 8:2 hexanes/EtOAc. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{23}N_2O_2S$ 279.2106; Found 279.2097.

*4.2.2. N-(4-(Pyridin-2-yl)piperazin-1-yl)-N'-(2,2,2-trifluoroethyl)sulfamide (**2e**)*

Prepared from triethylammonium *N*-(2,2,2-trifluoroethyl)sulfamate (2.31 g, 8.25 mmol, 1.65 equiv) and 1-(2-pyridyl)piperazine (0.76 mL, 5.00 mmol) according to general procedure A. The product was isolated as a white solid (1.37 g, 85% yield) after purification on a Teledyne Isco CombiFlashR_f system using a Redi Sep R_f normal phase silica gel column (65:35 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 5.0, 2.1 Hz, 1H), 7.54–7.50 (m, 1H), 6.71–6.66 (m, 2H), 4.56 (t, *J* = 6.8 Hz, 1H), 3.72 (qd, *J* = 8.8, 7.1 Hz, 2H), 3.64 (dd, *J* = 6.6, 4.9 Hz, 4H), 3.35 (dd, *J* = 6.6, 5.2 Hz, 4H). ^{13}C NMR (101 MHz, CD_3CN) δ 160.0, 148.7, 138.6, 125.1 (q, *J* = 277.6 Hz), 114.7, 108.3, 46.6, 45.3, 45.3 (q, *J* = 34.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –72.55 (t, *J* = 8.7 Hz). IR (neat) ν 3324 (br), 2975 (w), 2853 (w), 1597 (m), 1566 (w), 1477 (m), 1459 (m), 1436 (m), 1394 (m), 1365 (w), 1346 (m), 1333 (m), 1313 (m), 1291 (m), 1275 (m), 1242 (m), 1153 (s), 1119 (s), 1105 (s), 1068 (m), 983 (m), 946 (s), 918 (m), 828 (m), 778 (s), 751 (m), 729 (s), 659 (m), 622 (m), 553 (s), 529 (m) cm^{-1}. TLC R_f = 0.31 in 6:4 hexanes/EtOAc. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{16}F_3N_4O_2S$ 325.0946; Found 325.0950.

*4.2.3. N'-tert-Butyl-N-(methyl hexano-6-yl)sulfamide (**2f**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d**, 4.19 g, 16.5 mmol, 1.65 equiv) and methyl 6-aminohexanoate hydrochloride (1.82 g, 10.0 mmol) according to general procedure A. The product was isolated as a colorless oil (1.68 g, 60% yield) after purification on a Teledyne Isco CombiFlashR_f system using a Redi Sep R_f normal phase silica gel column (6:4 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (br s, 2H), 3.67 (s, 3H), 3.05 (dt, *J* = 6.8, 6.8 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.70–1.52 (m, 4H), 1.42–1.38 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 53.6, 51.3, 42.8, 33.6, 29.5, 28.8, 26.0, 24.2. IR (neat) ν 3283 (br), 2940 (w), 2868 (w), 1723 (m), 1434 (m), 1391 (m), 1366 (m), 1303 (m), 1205 (m), 1136 (s), 1094 (m), 1041 (w), 992 (m), 930 (w), 892 (m), 734 (w), 607 (m) cm^{-1}. TLC R_f = 0.28 in 8:2 hexanes/EtOAc. HRMS (ESI) m/z: $[M – H]^-$ Calcd for $C_{11}H_{23}N_2O_4S$ 279.1378; Found 279.1382.

*4.2.4. N-tert-Butyl-N'-(3-phenylprop-1-yl)sulfamide (**2g**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d**, 3.05 g, 12.0 mmol, 1.50 equiv) and 3-phenylpropylamine (1.1 mL, 8.00 mmol) according to general procedure A. The product was isolated as a white solid (1.56 g, 72% yield) after purification on a Teledyne Isco CombiFlashR_f system using a Redi Sep R_f normal phase silica gel column (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.4 Hz, 2H), 7.22–7.17 (m, 3H), 4.03 (br s, 2H), 3.07 (dt, *J* = 6.8, 6.8 Hz, 2H), 2.69 (m, 2H), 1.94–1.86 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0, 128.4, 128.3, 126.0, 53.9, 42.8, 33.0, 31.0, 29.7. IR (neat) ν 3282 (br), 3027 (w), 2975 (w), 1601 (w), 1494 (w), 1477 (w), 1453 (w), 1427 (w), 1390 (w), 1365 (w), 1339 (w), 1297 (m), 1230 (w), 1208 (w), 1137 (m), 1082 (m), 1062 (m), 1044 (m), 1031 (w), 1005 (m), 921 (m), 749 (m), 698 (m), 613 (m), 576 (m) cm^{-1}. TLC R_f = 0.17 in 8:2 hexanes/EtOAc. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{23}N_2O_2S$ 271.1480; Found 271.1480.

*4.2.5. N'-Pentyl-N-(phthalimid-2-yl)sulfamide (**2h**)*

A flame-dried round bottom flask equipped with magnetic stir bar was charged with triphenylphosphine oxide (2.755 g, 9.90 mmol, 1.65 equiv) and fitted with a rubber septum. The flask was evacuated and backfilled with N_2. Anhydrous CH_2Cl_2 (50 mL, 0.12 M with respect to amine) was added and the flask was cooled at 0 °C in an ice water bath. Trifluoromethanesulfonic anhydride (1.51 mL, 8.99 mmol, 1.5 equiv) that had been freshly removed from the glovebox was then added to the cooled solution dropwise via syringe. The reaction was allowed to stir at 0 °C in an ice water bath for 15 minutes. This suspension was treated with a solution of triethylammonium *N*-pentylsulfamate (2.42 g, 9.00 mmol, 1.50 equiv) in CH_2Cl_2 (9 mL, 0.67 M with respect to amine) via cannula transfer. The flask containing sulfamate salt solution was rinsed with CH_2Cl_2 (1.2 mL, ca. 5.0 M with respect to amine) to achieve quantitative transfer. The resulting yellow solution was stirred for 15 minutes at 0 °C. During this time, a clean, flame-dried round bottom flask equipped with stir bar was fitted with a rubber septum and subsequently evacuated and backfilled with N_2. This process was repeated two more times. The flask was then charged with Et_3N (2.5 mL, 18.0 mmol, 3.0 equiv) and CH_2Cl_2 (72 mL, 0.08 M with respect to amine) and the mixture was cooled at –78 °C in an ^{i}PrOH/dry ice bath. The sulfamate salt solution was transferred dropwise to the Et_3N solution via cannula (during which time a yellow to intense red color often developed), rinsing the flask with CH_2Cl_2 (0.33 mL, ca. 2.0 M with respect to amine) to achieve quantitative transfer. The resultant solution was stirred at –78 °C for 15 minutes. During this time, a flame-dried round bottom flask equipped with a stir bar was charged with *N*-aminophthalimide. (973 mg, 6.00 mmol, 1.00 equiv) and CH_2Cl_2 (6.0 mL, 1.0 M) and chilled to –78 ºC in a dry ice/ ^{i}PrOH bath. After 15 minutes, the Et_3N solution was cannula transferred to the solution of the amine. The triethylamine-containing flask was rinsed with CH_2Cl_2 (ca. 5.0 M with respect to amine) to achieve quantitative transfer. Without removing the cooling bath, the reaction was then stirred overnight, during which time no additional dry ice was added to the bath and the mixture gradually warmed to room temperature.

After stirring overnight, the reaction was diluted with 1 M HCl (ca. 10 mL/mmol of sulfamide) and H_2O (ca. 10 mL/mmol of sulfamide). The biphasic mixture was transferred to a separatory funnel, rinsing the flask with CH_2Cl_2 to achieve quantitative transfer. The organic phase was separated and the aqueous phase was extracted twice more with CH_2Cl_2 (ca. ½ reaction volume). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The product was isolated as a white solid (1.25 g, 67% yield) after purification on a Teledyne Isco CombiFlashR_f system using a Redi Sep R_f normal phase silica gel column (7:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.6, 3.0 Hz, 2H), 6.78 (br s, 1H), 4.45 (t, *J* = 5.8 Hz, 1H), 3.33 (dt, *J* = 6.8, 6.8 Hz, 2H), 1.66–1.58 (m, 2H), 1.38–1.34 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 134.8, 129.6, 124.0, 43.9, 29.1, 28.6, 22.1, 13.9. IR (neat) ν 3276 (br), 3165 (br), 2929 (m), 2865 (m), 1791 (m), 1726 (s), 1609 (m), 1426 (m), 1379 (m), 1341 (s), 1200 (m), 1153 (s), 1111 (m), 1080 (s), 1021 (m), 993 (m), 923 (m), 879 (s), 788 (m), 719 (s), 706 (s), 656 (s), 584 (s) cm^{-1}. TLC R_f = 0.28 in 6:4 hexanes/EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_{13}H_{16}N_3O_4S$ 310.0861; Found 310.0863.

*4.2.6. N-(2-Pyridyl)-N'-(2,2,2-trifluoroethyl)sulfamide (**2i**)*

A flame-dried round bottom flask equipped with magnetic stir bar was charged with triphenylphosphine oxide (2.29 g, 8.25 mmol, 1.65 equiv) and fitted with a rubber septum. The flask was evacuated and backfilled with N_2. Anhydrous CH_2Cl_2 (23 mL, 0.22 M with respect to amine) was added and the flask was cooled at 0 °C in an ice water bath. Trifluoromethanesulfonic anhydride (1.26 mL, 7.50 mmol, 1.5 equiv) that had been freshly removed from the glovebox was then added to the cooled solution dropwise via syringe. The reaction was allowed to stir at 0 °C in an ice water bath for 15 minutes. This suspension was treated with a solution of triethylammonium *N*-(2,2,2-trifluoroethyl)sulfamate (2.31 g, 8.25 mmol, 1.65 equiv) in CH_2Cl_2 (6.6 mL, 1.25 M with respect to amine) that had been cooled at 0 °C via cannula transfer. The flask containing sulfamate salt solution was rinsed with CH_2Cl_2 (1 mL, ca. 5.0 M with respect to amine) to achieve quantitative transfer. The resulting yellow solution was stirred for 15 minutes at 0 °C. During this time, a clean, flame-dried round bottom flask equipped with stir bar was fitted with a rubber septum and subsequently evacuated and backfilled with N_2. This process was repeated two more times. The flask was then charged with Et_3N (2.1 mL, 15.0 mmol, 3.0 equiv) and CH_2Cl_2 (23 mL, 0.22 M with respect to amine) and the mixture was cooled at –78 °C in an ^{i}PrOH/dry ice bath. The sulfamate salt solution was transferred dropwise to the Et_3N solution via cannula (during which time an intense red color developed), rinsing the flask with CH_2Cl_2 (2.5 mL, ca. 2.0 M with respect to amine) to achieve quantitative transfer. The resultant solution was stirred at –78 °C for 15 minutes. A solution of 2-aminopyridine (471 mg, 5.00 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL, 1.25 M) that had been precooled at 0 °C was then added to the triethylamine solution via cannula. The amine-containing flask was rinsed with CH_2Cl_2 (1 mL, ca. 5.0 M with respect to amine) to achieve quantitative transfer. Without removing the cooling bath, the reaction was then stirred overnight, during which time no additional dry ice was added to the bath and the mixture gradually warmed to room temperature.

After stirring overnight, the suspension was filtered. The solid was suspended in a 4:1 mixture of EtOAc/hexanes (50 mL) and the suspension was vigorously stirred in an oil bath held at 100 ºC for 15 minutes. After 15 minutes, the suspension was vacuum filtered hot and the white solid was rinsed with hexanes to afford the pure product as a white powder (804 mg, 63% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (dd, J = 5.4, 2.0 Hz, 1H), 7.74 (ddd, J = 8.4, 7.0, 2.0 Hz, 1H), 7.12 (dd, J = 8.4, 2.0 Hz, 1H), 6.97 (ddd, J = 7.0, 5.4, 2.0 Hz, 1H), 3.68 (q, J = 9.2 Hz, 2H).^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 152.7, 145.7, 139.0, 124.6 (q, *J* = 279.1 Hz), 116.6, 112.4, 44.0 (q, *J* = 33.8 Hz). ^{19}F NMR (376 MHz, $(CD_3)_2SO$) δ –71.01 (t, *J* = 9.7 Hz). IR (neat) ν 3274 (br), 2996 (w), 2736 (w), 1637 (m), 1615 (m), 1535 (m), 1468 (w), 1449 (w), 1426 (w), 1394 (m), 1357 (m), 1301 (m), 1291 (m), 1281 (m), 1257 (m), 1176 (w), 1135 (s), 1100 (m), 1040 (m), 1015 (m), 991 (m), 972 (m), 939 (m), 867 (w), 821 (m), 771 (s), 726 (m), 678 (m), 661 (m), 642 (m), 617 (m), 578 (m), 555 (s) cm^{-1}.

*4.2.7. N-(2,2,2-Trifluoroethyl)-N'-pentylsulfamide (**2j**)*

Prepared from triethylammonium *N*-(2,2,2-trifluoroethyl)sulfamate (947 mg, 3.40 mmol, 1.65 equiv) and pentylamine (0.24 mL, 2.00 mmol) according to general procedure A. The product was isolated as a white solid (484 mg, 94% yield) after purification on a Teledyne Isco CombiFlashR_f system using a Redi Sep R_f normal phase silica gel column (8:2 hexanes/EtOAc).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (br s, 1H), 4.30 (br s, 1H), 3.72–3.63 (m, 2H), 3.06 (q, *J* = 6.8 Hz, 2H), 1.60–1.53 (m, 2H), 1.35–1.30 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, CD_3CN) δ 125.3 (q, *J* = 277.4 Hz), 44.8 (q, *J* = 34.8 Hz), 43.7, 29.6, 29.5, 22.9, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ –72.57 (t, *J* = 8.9 Hz). IR (neat) ν 3273 (br), 2962 (w),

2938 (w), 2865 (w), 1466 (m), 1426 (m), 1394 (m), 1325 (s), 1291 (s), 1267 (s), 1160 (s), 1138 (s), 1124 (s), 1109 (s), 1058 (s), 1040 (m), 1015 (m), 964 (s), 910 (s), 890 (m), 856 (m), 835 (m), 731 (m), 657 (s), 573 (s), 545 (s) cm^{-1}. TLC R_f = 0.19 in 8:2 hexanes/EtOAc. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_7H_{16}F_3N_2O_2S$ 249.0884; Found 249.0882.

*4.2.8. N-(2-Methyl-1,1,1-trifluoroprop-2-yl)-N'-pentylsulfamide (**2k**)*

Prepared from triethylammonium *N*-pentylsulfamate (3.37 g, 12.5 mmol, 1.65 equiv) and 1,1-dimethyl-2,2,2-trifluoroethylamine hydrochloride (1.24 g, 7.60 mmol) according to general procedure A. The product was isolated as a white solid (1.51 g, 72% yield) after purification on a Teledyne Isco CombiFlashR_f system using a Redi Sep R_f normal phase silica gel column (Gradient: 100% hexanes → 7:3 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (br s, 1H), 4.12 (br s, 1H), 3.07 (q, *J* = 7.4 Hz, 2H), 1.60–1.53 (m, 2H), 1.56 (s, 6H), 1.36–1.30 (m, 4H), 0.91 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 126.0 (q, *J* = 284.3 Hz), 58.1 (q, *J* = 28.9 Hz), 43.0, 28.7, 28.7, 22.1, 20.7, 13.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ –82.30. IR (neat) ν 3303 (br), 2959 (w), 2933 (w), 2874 (w), 1442 (m), 1399 (w), 1378 (w), 1318 (m), 1233 (m), 1206 (m), 1151 (s), 1119 (s), 1078 (s), 1036 (m), 1012 (m), 933 (m), 842 (m), 728 (w), 654 (w), 589 (m), 556 (m) cm^{-1}. TLC R_f = 0.33 in 8:2 hexanes/EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_9H_{18}F_3N_2O_2S$ 275.1041; Found 275.1047.

*4.2.9. N-Cyclohexyl-N'-pentylsulfamide (**2l**)*

Prepared from triethylammonium *N*-cyclohexylsulfamate (3.05 g, 12.0 mmol, 1.5 equiv) and pentylamine (0.93 mL, 8.00 mmol) according to general procedure A. The product was isolated as a white solid (993.3 mg, 50% yield) after purification by silica gel column chromatography (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24–4.20 (m, 2H), 3.24–3.12 (m, 1H), 3.01 (dt, *J* = 6.8, 6.8 Hz, 2H), 2.01–1.95 (m, 2H), 1.75–1.68 (m, 2H), 1.60–1.52 (m, 3H), 1.37–1.12 (m, 9H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 52.6, 43.2, 34.0, 29.2, 28.9, 25.3, 24.8, 22.2, 13.9. IR (neat) ν 3291 (br), 2927 (m), 2855 (m), 1468 (w), 1454 (m), 1377 (w), 1321 (m), 1301 (m), 1257 (w), 1242 (w), 1192 (w), 1135 (s), 1080 (m), 1070 (s), 1032 (m), 1012 (w), 992 (m), 928 (m), 916 (m), 887 (m), 840 (m), 822 (m), 759 (m), 727 (w), 664 (m), 582 (m), 558 (m) cm^{-1}. TLC R_f = 0.17 in 8:2 hexanes/EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_{11}H_{23}N_2O_2S$ 247.1480; Found 247.1489.

4.3. General Procedure B: Preparation of sulfamides using modified conditions (Table 1 and Scheme 5)

A flame-dried round bottom flask equipped with magnetic stir bar was charged with triphenylphosphine oxide (1.65 equiv) and fitted with a rubber septum. The flask was evacuated and backfilled with N_2. CH_2Cl_2 (0.15 M with respect to amine) was added and the flask was cooled at 0 °C in an ice water bath. Trifluoromethanesulfonic anhydride (1.5 equiv) that had been freshly removed from the glovebox was then added to the cooled solution dropwise via syringe. The reaction was allowed to stir at 0 °C in an ice water bath for 15 minutes. This suspension was treated with a solution of sulfamic acid salt (1.0 equiv) in CH_2Cl_2 (1.25 M with respect to amine) via cannula transfer. The flask containing sulfamate salt solution was rinsed with CH_2Cl_2 (ca. 5.0 M with respect to amine) to achieve quantitative transfer. The resulting yellow solution was stirred for 5 minutes at 0 °C and was then cooled at –78 °C in an ^{i}PrOH/dry ice bath. During this time, a clean, flame-dried round bottom flask equipped with stir bar was fitted with a rubber septum and subsequently evacuated and backfilled with N_2. This process was repeated two more times. The flask was then charged with Et_3N (3.0 equiv) and CH_2Cl_2 (0.36 M with respect to amine) and the mixture was cooled at –78 °C in an ^{i}PrOH/dry ice bath. The sulfamate salt solution was transferred dropwise to the Et_3N solution via cannula (during which time a yellow to intense red color often developed), rinsing the flask with CH_2Cl_2 (ca. 2.0 M with respect to amine) to achieve quantitative transfer. The resultant solution was stirred at –78 °C for 15 minutes. The amine ($(R^2)(R^3)$–NH, 1.0 equiv) was then added as a solution in solvent 1 (1.25 M) to the triethylamine solution via cannula. The amine-containing flask was rinsed with solvent 1 (ca. 5.0 M with respect to amine) to achieve quantitative transfer. Without removing the cooling bath, the reaction was then stirred overnight, during which time no additional dry ice was added to the bath and the mixture gradually warmed to room temperature. Unless otherwise noted, solvent 1 = CH_2Cl_2.

After stirring overnight, the reaction was diluted with 1 M HCl (ca. 5 mL/mmol of sulfamide) and H_2O (ca. 5 mL/mmol of sulfamide). The biphasic mixture was transferred to a separatory funnel, rinsing the flask with CH_2Cl_2 to achieve quantitative transfer. The organic phase was separated and the aqueous phase was extracted twice more with CH_2Cl_2 (ca. ½ reaction volume). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reaction mixtures were then purified by silica gel flash chromatography by dry loading the samples and eluting with a hexanes:EtOAc solvent system as noted below.

*4.3.1. N-tert-Butyl-N'-pentylsulfamide (**2m**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d**, 5.09 g, 20.0 mmol) and pentylamine (2.4 mL, 20.0 mmol) according to general procedure B. The product was isolated as a white solid (3.54 g, 79% yield) after silica gel column chromatography (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (br s, 1H), 4.16 (br s, 1H), 3.02 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.59–1.52 (m, 2H), 1.33–1.30 (m, 4H), 1.34 (s, 9H), 0.90 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.9, 43.3, 29.8, 29.1, 28.9, 22.3, 13.9. IR (neat) ν 3278 (br), 2958 (w), 2931 (w), 2871 (w), 1427 (w), 1392 (m), 1367 (m), 1298 (m), 1230 (m), 1208 (w), 1136 (s), 1092 (m), 1041 (m), 996 (m), 930 (m), 907 (m), 808 (m), 719 (m) 607 (m), 568 (m) cm^{-1}. TLC R_f = 0.23 in 8:2 hexanes/EtOAc. HRMS (ESI) m/z: $[M + H]^+$ Calcd for *$C_9H_{23}N_2O_2S$ 223.1480; Found 223.1475.*

*4.3.2. N'-tert-Butyl-N-methyl-N-pentylsulfamide (**2n**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d**, 2.54 g, 10.0 mmol) and *N*-methylpentylamine (1.0 g, 10.0 mmol) according to general procedure B. The product was isolated as a colorless oil (1.33 g, 56% yield) after silica gel column chromatography (Gradient: 20:1 hexanes/EtOAc → 9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (br s, 1H), 3.09 (dd, *J* = 7.8, 9.5 Hz, 2H), 2.75 (s, 3H), 1.6–1.53 (m, 2H), 1.35–1.24 (m, 4H), 1.30 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.9, 50.2, 34.4, 29.8, 28.8, 27.2, 22.3, 13.9. IR (neat) ν 3277 (br), 2958 (w), 2931 (w), 2870 (w), 1466 (w), 1391 (w), 1366 (w), 1309 (m), 1229 (m), 1206 (m), 1135 (s), 1090 (w), 1039 (w), 996 (m), 948 (m), 893 (m), 866 (m), 766 (w), 719 (m), 606 (m), 566 (m) cm^{-1}. TLC R_f = 0.36 in 8:2 hexanes/EtOAc. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{25}N_2O_2S$ 237.1636; Found 237.1633.

4.3.3. N-tert-*Butyl*-N'-*(2-cyclopentylethyl)sulfamide (**2o**)*

A flame-dried flask with stir bar and fitted with a reflux condenser was charged with lithium aluminum hydride ($LiAlH_4$,

797 mg, 21.0 mmol, 2.1 equiv). The flask was fitted with a rubber septum and evacuated and back-filled with N_2. Anhydrous Et_2O (45 mL, 0.2 M) was added and the reaction flask was cooled at 0 °C in an ice/water bath. 2-Cyclopropylacetamide (**S1**, 1.27 g, 10.0 mmol, 1.0 equiv) was carefully added portion-wise as a solid (ca. 3 portions) by briefly removing the reflux condenser and then replacing it. Once all amide had been added, the ice/water bath was replaced with an oil bath and the reaction flask was heated at reflux and stirred overnight.

After refluxing overnight, the reaction was removed from the heat and allowed to cool to room temperature and then further cooled at 0 °C in an ice/water bath. The reaction was then carefully quenched by dropwise, sequential addition of deionized H_2O (0.8 mL), 15% w/v aq. NaOH (0.8 mL), and deionized H_2O (0.8 mL). The quenched reaction was left stirring at 0 °C for ca. 30 minutes to ensure complete quenching of remaining $LiAlH_4$. Once fully quenched, the reaction was filtered through a pad of celite in a glass-fritted funnel by vacuum filtration eluting with Et_2O (ca. ½ reaction volume). The filtrate was then concentrated under reduced pressure. The concentrated crude material used directly in the preparation of sulfamide **2o**. Sulfamide **2o** was prepared from triethylammonium *N-tert*-butylsulfamate (**1d**, 2.54 g, 10.0 mmol) and crude 2-cyclopentylethyl amine following general procedure B. The product was obtained as a white solid (1.27 g, 51% yield, 2 steps) after silica gel column chromatography (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (br s, 1H), 4.07 (br s, 1H), 3.04 (dt, *J* = 6.4, 6.4 Hz, 2H), 1.85–1.74 (m, 3H), 1.63–1.51 (m, 6H), 1.35 (s, 9H), 1.14–1.05 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.7, 42.6, 37.4, 35.6, 32.4, 29.6, 25.0. IR (neat) ν 2866 (m), 1470 (w), 1446 (m), 1430 (m), 1391 (m), 1364 (m), 1305 (s), 1211 (m), 1133 (s), 1068 (m), 1042 (m), 1004 (s), 946 (m), 898 (m), 618 (s), 580 (s)□ cm^{-1}. TLC R_f = 0.33 in 4:1 hexanes:EtOAc. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{24}N_2O_2S$ 249.1631; Found 249.1631.

*4.3.4. N-tert-Butyl-N'-neopentylsulfamide (**2p**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d**, 2.54 g, 10.0 mmol) and neopentylamine (872 mg, 10.0 mmol) following general procedure B. The product was obtained as a white solid (1.31 g, 59% yield) after silica gel column chromatography (9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (br s, 1H), 4.13 (t, *J* = 6.7 Hz, 1H), 2.78 (d, *J* = 6.7 Hz, 2H), 1.35 (s, 9H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 54.9, 53.8, 31.0, 29.7, 27.3. IR (neat) ν 3287 (br m), 2956 (m), 2912 (w), 2870 (w), 1475 (m), 1456 (m), 1431 (m), 1392 (m), 1367 (m), 1323 (s) 1296 (s), 1209 (m), 1147 (s), 1080 (s), 1055 (m), 1039 (m), 1029 (m), 990 (s), 947 (m), 930 (m), 863 (s), 817 (m), 613 (s), 568 (s) cm^{-1}. TLC R_f = 0.33 in 4:1 hexanes:EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_9H_{22}N_2O_2S$ 221.1329; Found 221.1323.

*4.3.5. N-tert-Butyl-N-((1S, 2S, 5R)-2-isopropyl-5-methylcylcohexyl)sulfamide (**2q**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d**, 1.20 g, 4.73 mmol) and (*1S, 2S, 5R*)-2-isopropyl-5-methylcyclohexan-1-amine (735 mg, 4.73 mmol) following general procedure B. The product was obtained as a white solid (617 mg, 45% yield) after silica gel column chromatography (Gradient: 20:1 hexanes/EtOAc → 9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (br s, 1H), 4.03 (br s, 1H), 3.81–3.79 (m, 1H), 2.21–2.17 (m, 1H), 1.79–1.71 (m, 2H), 1.60–1.47 (m, 4H), 1.42–1.26 (m, 2H), 1.36 (s, 9H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 54.3, 51.1, 47.7, 39.8, 34.6, 29.8, 28.5, 26.1, 24.6, 22.1, 21.0, 20.9. IR (neat) ν 3327 (br), 3275 (br), 2947 (m), 2867 (w), 2844 (w), 1452 (m), 1424 (m), 1391 (m), 1367 (m), 1323 (m), 1303 (m), 1292 (m), 1225 (w), 1209 (w), 1195 (m), 1125 (s), 1039 (m), 992 (s), 981 (s), 953 (m), 932 (m), 860 (m), 812 (w), 766 (w), 661 (m), 609 (s) cm^{-1}. TLC R_f = 0.50 in 4:1 hexanes:EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_{14}H_{30}N_2O_2S$ 289.1955; Found 289.1947.

*4.3.6. N'-tert-Butyl-N-((2R)-methyl 4-methylpentano-2-yl)sulfamide (**2r**)*

A flame-dried round bottom flask equipped with magnetic stir bar was charged with triphenylphosphine oxide (2.29 g, 8.25 mmol, 1.65 equiv) and fitted with a rubber septum. The flask was evacuated and backfilled with N_2. CH_2Cl_2 (33 mL, 0.15 M with respect to amine) was added and the flask was cooled at 0 °C in an ice water bath. Trifluoromethanesulfonic anhydride (1.25 mL, 7.5 mmol, 1.5 equiv) that had been freshly removed from the glovebox was then added to the cooled solution dropwise via syringe. The reaction was allowed to stir at 0 °C in an ice water bath for 15 minutes. This suspension was treated with a solution of triethylammonium *tert*-butylsulfamate (**1d,** 1.27 g, 5.00 mmol, 1.0 equiv) in CH_2Cl_2 (4.0 mL, 1.25 M with respect to amine) via cannula transfer. The flask containing sulfamate salt solution was rinsed with CH_2Cl_2 (1.0 mL, ca. 5.0 M with respect to amine) to achieve quantitative transfer. The resulting yellow solution was stirred for 5 minutes at 0 °C and was then cooled at –78 °C in an ^{i}PrOH/dry ice bath. During this time, a clean, flame-dried round bottom flask equipped with stir bar was fitted with a rubber septum and subsequently evacuated and backfilled with N_2. This process was repeated two more times. The flask was then charged with Et_3N (2.1 mL, 15.0 mmol, 3.0 equiv) and CH_2Cl_2 (13.6 mL, 0.36 M with respect to amine) and the mixture was cooled at –78 °C in an ^{i}PrOH/dry ice bath. The sulfamate salt solution was transferred dropwise to the Et_3N solution via cannula (during which time a yellow to intense red color often developed), rinsing the flask with CH_2Cl_2 (1.0 mL, ca. 2.0 M with respect to amine) to achieve quantitative transfer. The resultant solution was stirred at –78 °C for 15 minutes. (*2R*)-methyl-2-amino-4-methylpentanoate hydrochloride (908.3 mg, 5.00 mmol, 1.00 equiv) in CH_2Cl_2 (4.0 mL, 1.25 M) chilled at 0 ºC was treated with Et_3N (0.70 mL, 5.0 mmol, 1.0 equiv). The cooled solution of (*2R*)-methyl-2-amino-4-methylpentanoate hydrochloride and Et_3N was added to the solution of Et_3N and activated sulfamic acid salt via cannula. The flask was rinsed with CH_2Cl_2 (1.0 mL, ca. 5.0 M with respect to amine) to achieve quantitative transfer. Without removing the cooling bath, the reaction was then stirred overnight, during which time no additional dry ice was added to the bath and the mixture gradually warmed to room temperature.

After stirring overnight, the reaction was subjected to an aqueous workup as described in general procedure B. The product was isolated as a colorless oil (1.16 g, 83% yield) after purification on a Teledyne Isco CombiFlashR_f system using a Redi Sep R_f normal phase silica gel column (8:2 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (d, *J* = 9.9 Hz, 1H), 4.11 (br s, 1H), 3.99 (ddd, *J* = 9.9, 8.0, 6.6 Hz, 1H), 3.77 (s, 3H), 1.80 (septet, *J* = 6.7 Hz, 1H), 1.56–1.52 (m, 2H), 1.34 (s, 9H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 54.5, 52.3, 41.9, 29.7, 24.4, 22.6, 21.7. IR (neat) ν 3279 (br), 2958 (w), 2871 (w), 1732 (m), 1433 (w), 1392 (w), 1367 (w), 1310 (w), 1274 (w), 1232 (m), 1202 (m), 1136 (s), 1091 (w), 1042 (w), 993 (m), 908 (m), 861 (w), 817 (w), 731 (m), 614 (m) cm^{-1}. TLC R_f = 0.56 in 6:4 hexanes/EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_{11}H_{23}N_2O_4S$ 279.1378; Found 279.1377.

*4.3.7. N-tert-Butyl-N'-hexylsulfamide (**2s**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d,** 1.27 g, 5.0 mmol) and hexylamine (0.66 mL, 5.0 mmol) following general procedure B. The product was obtained as a white solid (1.68 g, 71% yield) after silica gel column chromatography (10:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (br s, 1H), 4.13 (t, *J* = 6.8 Hz, 1H), 3.02 (dt, *J* = 6.8, 6.8 Hz, 2H), 1.58–1.51 (m, 2H), 1.34 (s, 9H), 1.32–1.26 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 53.8, 43.3, 31.3, 29.7, 29.3, 26.4, 22.5, 13.9. IR (neat) ν 3275 (br m), 2968 (w), 2928 (m), 2853 (m), 1481 (w), 1467 (w), 1427 (m), 1391 (m), 1368 (m), 1341 (w), 1300 (s), 1233 (m), 1206 (m), 1240 (s), 1084 (m), 1041 (m), 997 (s), 918 (m), 762 (w), 728 (m), 609 (s) cm^{-1}. TLC R_f = 0.36 in 4:1 hexanes:EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_{10}H_{24}N_2O_2S$ 235.1486; Found 235.1482.

*4.3.8. N-tert-Butyl-N'-(6-methylhept-2-yl)sulfamide (**2t**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d,** 2.54 g, 10.0 mmol) and 2-amino-6-methylheptane (1.7 mL, 10.0 mmol) following general procedure B. The product was obtained as a white solid (2.04 g, 77% yield) after silica gel column chromatography (Gradient: 20:1 hexanes/EtOAc → 9:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (br s, 1H), 3.97 (d, *J* = 7.6 Hz, 1H), 3.46–3.36 (m, 1H), 1.57–1.50 (m, 2H), 1.42–1.38 (m, 2H), 1.35 (s, 9H), 1.33–1.29 (m, 2H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.19–1.16 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.8, 49.8, 38.6, 37.4, 29.7, 27.7, 23.3, 22.5, 22.4, 21.0. IR (neat) ν 3283 (m, br), 2953 (w), 1464 (w), 1430 (m), 1392 (w), 1365 (w), 1299 (m), 1208 (w), 1127 (s), 1085 (w), 1041 (m), 998 (m), 931 (w), 907 (m), 736 (w), 619 (m), 590 (m), 548 (m) cm^{-1}. TLC R_f = 0.32 in 4:1 hexanes:EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_{12}H_{28}N_2O_2S$ 263.1799; Found 263.1801.

*4.3.9. N-tert-Butyl-N'-(2,2,2-trifluoroethyl)sulfamide (**2c**)*

Prepared from triethylammonium *N-tert*-butylsulfamate (**1d,** 2.54 g, 10.0 mmol) and 2,2,2-trifluoroethylamine (1.7 mL, 10.0 mmol) following general procedure B. The product was obtained as a white solid (1.77 g, 76% yield) after silica gel column chromatography (Gradient: 9:1 hexanes/EtOAc → 4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (t, *J* = 6.3 Hz, 1H), 4.24 (br s, 1H), 3.71–3.62 (m, 2H), 1.37 (s, 9H). The characterization data for this compound were in agreement with previously published information.[10]

*4.3.10. N-Pentyl-N'-(quinolin-8-yl)sulfamide (**2u**)*

Prepared from triethylammonium *N*-pentylsulfamate (1.34 g, 5.0 mmol) and 8-aminoquinoline (721 mg, 5.0 mmol) following general procedure B. The product was obtained as a brown oil (838 mg, 57% yield) after silica gel column chromatography (Gradient: 20:1 hexanes/acetone → 4:1 hexanes/acetone).

Sulfamide **2u** was obtained in 43% yield (628 mg) from triethylammonium *N*-(quinolin-8-yl)sulfamate (1.63 g, 5.0 mmol) and pentylamine (0.58 mL, 5.0 mmol) following general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.77–7.75 (m, 1H), 7.52–7.51 (m, 2H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.63 (br s, 1H), 3.00 (dt, *J* = 6.7 Hz, 2H), 1.38–1.31 (m, 2H), 1.08–1.04 (m, 4H), 0.69 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 138.4, 136.3, 134.4, 128.2, 127.0, 122.0, 121.6, 114.2, 43.2, 28.8, 28.5, 21.9, 13.7. IR (neat) ν 3292 (br), 2955 (w), 2930 (w), 2859 (w), 1621 (w), 1579 (w), 1504 (s), 1471 (m), 1410 (m), 1363 (m), 1331 (m), 1308 (s), 1235 (w), 1153 (s), 1086 (s), 1058 (m), 1027 (m), 918 (s), 845 (m), 823 (s), 780 (s), 756 (s), 732 (s), 635 (m), 567 (s) cm^{-1}. TLC R_f = 0.36 in 2:1 hexanes:acetone. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_{14}H_{19}N_3O_2S$ 292.1125; Found 292.1117.

*4.3.11. N-((4-tert-Butyl)phenyl)-N'-pentylsulfamide (**2v**)*

Prepared from triethylammonium *N*-((4-*tert*-butyl)phenyl)sulfamate (1.65 g, 5.0 mmol) and pentylamine (0.58 mL, 5.0 mmol) following general procedure B. The product was obtained as an orange oil (857 mg, 58% yield) after silica gel column chromatography (Gradient: 9:1 hexanes/EtOAc → 4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.71 (br s, 1H), 4.55 (t, *J* = 5.8 Hz, 1H), 3.05 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.50–1.43 (m, 2H), 1.29 (s, 9H), 1.24–1.19 (m, 4H), 0.83 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 134.3, 126.3, 120.0, 43.3, 34.3, 31.3, 29.0, 28.6, 22.1, 13.9. IR (neat) ν 3273 (br), 2957 (m), 2865 (w), 1613 (w), 1515 (m), 1457 (m), 1394 (m), 1363 (m), 1323 (m), 1300 (m), 1268 (m), 1235 (w), 1202 (w), 1150 (s), 1083 (m), 1017 (m), 934 (m), 830 (m), 734 (m), 702 (m), 640 (m), 595 (s), 535 (s) cm^{-1}. TLC R_f = 0.42 in 4:1 hexanes:EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_{15}H_{26}N_2O_2S$ 297.1642; Found 297.1635.

*4.3.12. N-Octadecyl-N'-propylsulfamide (**2w**)*

A round bottom flask equipped with magnetic stir bar was charged with sulfur trioxide pyridine complex (SO_3•pyr, 318 mg, 2.0 mmol 1.0 equiv). Acetonitrile (6 mL, 0.33 M) was then added in a single portion without taking any precautions to exclude air or moisture. The suspension was stirred at 22 °C until all of the SO_3•pyr had dissolved. Upon complete dissolution, the reaction flask was cooled at 0 °C in an ice water bath and capped with a rubber septum containing a nitrogen inlet. Propylamine (0.164 mL, 2.0 mmol, 1.0 equiv) was then added dropwise via Hamilton syringe. Following complete addition of amine, Et_3N (0.31 mL, 2.2 mmol, 1.1 equiv) was added dropwise. The reaction was removed from the ice bath and stirred for 0.5 h. Upon completion, the solvent was removed under reduced pressure to give triethylammonium *N*-propylsulfamate, which was further dried on the high vacuum and used directly in the preaparation of sulfamide **2w**. Sulfamide **2w** was prepared from crude triethylammonium *N*-propylsulfamate and octadecylamine (539 mg, 2.0 mmol) added as a solution in PhMe (9 mL, 0.2 M) following general procedure B (solvent 1 = PhMe). The product was obtained as an off-white solid (330 mg, 42% yield, 2 steps) after silica gel column chromatography (Gradient: 9:1 hexanes/EtOAc → 4:1 hexanes/EtOAc). The characterization data for this compound were in agreement with previously published information.[15a]

*4.3.13. N,N'-Di(tert-butyl)sulfamide (**3a**)*

Isolated as a byproduct when attempting to prepare sulfamide **2n** following general procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (br s, 2H), 1.34 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 53.8, 29.7. IR (neat) ν 3304 (br), 2981 (w), 1476 (w), 1432 (w), 1417 (w), 1392 (m), 1369 (m), 1304 (m), 1227 (w), 1198 (m), 1130 (m), 1044 (m), 993 (s), 931 (m), 884 (m), 771 (w), 735 (w), 623 (m), 593 (m), 535 (m) cm^{-1}. TLC R_f = 0.33 in 4:1 hexanes:EtOAc. HRMS (ESI) m/z: $[M - H]^-$ Calcd for $C_8H_{19}N_2O_2S$ 207.1167; Found 207.1173.

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Conflicts of Interest

There are no conflicts to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at XX.

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