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The Synthesis of Alkyl and (Hetero)aryl Sulfonamides From Sulfamoyl Inner Salts

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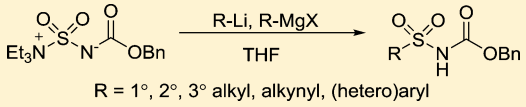
Supporting Information

ABSTRACT: An approach to the synthesis of sulfonamides from sulfamoyl inner salts and organometallic species is presented. A range of sulfamoyl carbamates, amines, and metals are explored. Primary, secondary, and tertiary alkyl-, aryl-, and heteroaryllitihium and magnesium nucleophiles were successful. This approach yields bench-stable intermediates and avoids many of the functional group incompatibilities, regioselectivity issues, and high-energy reagents generally associated with the synthesis of sulfonamides. Additionally, the products may be purified by basic extraction or salt formation, avoiding chromatography.



Sulfonamides are an important functional group found throughout the pharmacopeia in therapeutic agents as diverse as sulfadimidine[1] and tipranavir.[2] They impart several attributes to molecules that make them attractive in drug discovery, including a high topological surface area,[3] which has been associated with improved outcomes in toxicology studies,[4] a moderately high pK_a,[5] and a distinct conformation[6] that creates an approximately 90° turn in a molecule. Despite this utility and an increasing number of options for arylating and alkylating on the nitrogen,[7−9] syntheses of primary sulfonamides still rely almost entirely upon high-energy aminating reagents,[10] Friedel−Crafts sulfaminations of electron-rich benzene rings and olefins,[11,12] oxidations of sulfinamides, or the condensation of ammonia with sulfonyl halides, which themselves are synthesized using either strongly oxidizing or chlorinating reagents[13−15] and can be unstable.[14] Recent advances in sulfinate synthesis have given rise to a number of excellent publications addressing some of the liabilities of these approaches. For example, two recent publications by Shavnya[16] and Willis[17] provide efficient protocols for the coupling of an *in situ* generated sulfinate with an amine using a chlorinating or brominating agent, removing the need for isolation of the sulfinate or sulfonyl chloride by providing the sulfonamide directly from a multicomponent coupling. However, all of these advances still require a sulfur or nitrogen oxidation step, and we propose that an alternative method which improves tolerance for electron-rich (hetero)arenes, generates bench-stable products, and reduces safety hazards would be extremely attractive.

The use of a readily purchased or synthesized organometallic species[18,19] and a S(IV) or S(VI) source to directly form the C−S(O)$_2$(NR$_2$) bond would meet our desired criteria, but this disconnection is infrequently used for the synthesis of sulfonamides. There are several examples of the synthesis of sulfinamides from S(IV) sources, including *N*-aryl aminosulfones[20] or alkylsulfuramidous chlorides[21] and esters,[22] using a range of organometallics (Figure 1). These sulfinamides may then be converted to sulfonamides via a subsequent oxidation reaction, typically with *m*-CPBA.[23] While the yields of each step are generally excellent, this remains an underutilized method of sulfonamide synthesis, which is likely due to two reasons. The first two protocols (Figure 1, eqs 1 and 2) yield a limited set of secondary or tertiary sulfinamides with nitrogen substituents that can be difficult to further modify. Meanwhile, alkylsulfuramidous esters, generally generated *in situ* from thionyl chloride and an amino alcohol, have found widespread use for the synthesis of highly hindered sulfonamides such as *t*-butyl and mesityl, but are rarely used to functionalize more reactive nucleophiles due to the competing formation of symmetric sulfoxides (Figure 1, eq 3). Therefore, we sought a more general protocol involving a suitable S(VI) reagent which could afford more easily diversifiable reaction products as well as obviating the need for subsequent oxidative manipulations.

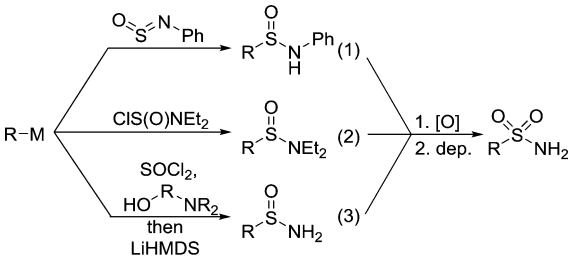


Figure 1. Literature examples of organometallic sulfinamidation.

Interestingly, to the best of our knowledge, only three examples of this transformation using an S(VI) source are reported in the literature (Figure 2). Nishimura and co-workers opened an *N*-alkyl thiadiazolidinone 1,1-dioxide with methyl magnesium bromide to form a methanesulfonamide (Figure 2, eq 4),[24] Lacôte and co-workers performed a radical-mediated coupling of chlorosulfonamides with allyl stannanes (Figure 2, eq 5),[25] and Arnswald and co-workers utilized aryl stannanes in a

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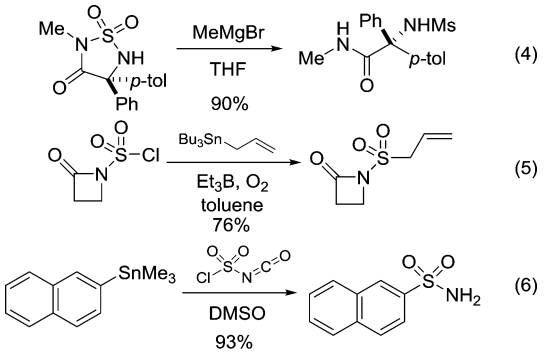
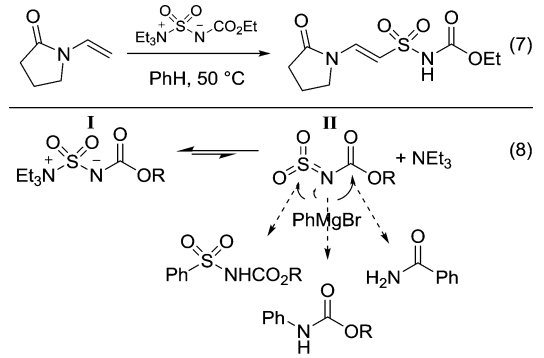


Figure 2. Examples of organometallic sulfonamidation.

Friedel–Crafts-like *ipso* substitution reaction with chlorosulfonyl isocyanate (Figure 2, eq 6).[26]

This last example is related to a large, but rarely utilized, subset of chemistry using *N*-carbamoyl sulfamide inner salts. Typically used for dehydration or amination chemistry,[27,28] these salts react with a range of soft carbon nucleophiles such as enamines (Scheme 1, eq 7), to yield *N*-carbamoyl sulfonamides.[29,30]

Scheme 1. Precedent (eq 7) and Proposed (eq 8) Reaction of C-Nucleophiles with Burgess Inner Salts



However, we could find no examples of a reaction between a sulfamide inner salt and a hard carbon nucleophile such as a Grignard reagent (Scheme 1, eq 8), and we were intrigued by this absence from the literature.

We envisioned three possible products could result from addition of a single equivalent of phenylmagnesium bromide to **I**. There was some concern that the Grignard reagent, a "hard" nucleophile, would preferentially add to the carbonyl of **I** or **II**, over the "soft" sulfur center, and that this accounted for the dearth of literature in this area. Gratifyingly, however, phenylmagnesium bromide added cleanly to commercial inner salt **1** (Table 1, entry 1), yielding the desired benzyl (phenylsulfonyl)-carbamate in 56% yield after chromatography. Similar reactivity was observed with readily prepared inner salts **2**[31] and **3**[27] (Table 1, entries 2–3).

Benzyl carbamoyl derivative **3** offered several advantages over **1** and **2**, including indefinite stability at 5 °C, and reaction products that were readily quantified by NMR (Figure 3, eq 9) and easily visualized during purification.[32,33] Using **3** as the limiting reagent, the balance of the material in the crude NMR spectrum from entry 3 was identified as *O*-benzyl carbamate **B**, arising from unreacted **3** (0–10%, based on integration of $PhCH_2OC(O)NH_2$ peak), and products arising from addition to the carbamate of the product, *N*-phenylsulfonyl benzamide **C** and phenylsulfonamide **D** (0–5% based on integration of $PhCH_2OH$ peak). Unsurprisingly, **C** and **D** increased with addition of extra equivalents of nucleophile and increasing reaction times and temperatures. Although unpurified mass recoveries ranged from 70 to 90% and >80% purity, the isolated yields were modest and reflect issues with chromatographically separating the desired material from side products on small scale in order to generate analytically pure material. The desired product could generally be isolated from the observed byproducts via extractive purification to improve isolated yields, *vide infra.*

Three additional inner salts were surveyed. The bench-stable DABCO (**5**)[34] and DMAP (**6**)[35] complexes did not yield the desired products (entries 4–5). Complex **5** was insoluble under the standard reaction conditions, even with addition of two extra equivalents of phenylmagnesium bromide, while **6** yielded only products arising from addition to the pyridine moiety.[36] The extremely stable trifluoroethylcarbamoyl inner salt **4**[37] also failed to react (entry 6). This result implies that the reaction likely proceeds through sulfonyl carbamate **II**. If the inner salt form **I** was the dominant electrophilic species, we expect **4** to be more reactive due to greater anion stabilization and thus greater partial positive charge on the sulfur center.

Two additional metals were explored. Organolithiums reacted similarly to Grignards (entries 7–8) with one notable exception. *t*-Butyllithium (entry 11) cleanly provides benzyl (*t*-butylsulfonyl) carbamate,[38] while *t*-butyl and adamantyl Grignards[13] (entries 9–10) yielded only *O*-benzyl carbamate.[39] Aryl zincates proved not to be competent nucleophiles, even with prolonged reaction times and warming (entry 12).[40]

A wide range of organometallics was successfully utilized. Simply substituted aryl Grignards added rapidly with only 1 equiv of nucleophile (entries 13–18), while more hindered *o*-substituted nucleophiles typically required longer reaction times and additional equivalents of nucleophile for full consumption of the inner salt (entries 19–21). The addition of Lewis acids in an attempt to accelerate the reaction either by capturing the NEt_3 or activating the electrophile resulted only in recovery of **A** (entries 22–23). Non-aryl nucleophiles were also viable. Primary alkyl Grignards added cleanly with only 1 equiv of nucleophile, (entry 24), while the more hindered secondary alkyl Grignards required additional time and reagent (entries 25–26). Heterocycles **7** and **8** both provided acceptable yields of pharmaceutically relevant sulfonamides (entries 27–28). Alkynes also proved to be successful, although not with **3**, (entries 29–31), yielding a primary ethynylsulfonamide precursor in four fewer steps than previous syntheses.[41] Finally, aryl Grignard reagents bearing electron-withdrawing groups did not efficiently add to inner salt **3** (entry 32).

One major concern with our established protocol was the lower-than-expected postpurification yields for many of the substrates. Prepurification mass-recovery was typically >80%, but poor resolution between **A** and the other reaction products on silica gel meant that large portions were lost during chromatographic isolation of analytically pure material. The difference in yields between entries 7 and 8 indicated that perhaps purification by salt formation would improve mass recovery. Although this did work in the case of the 3-methoxyphenyl (entry 16 vs 15), the wide range in pK_a's and solubility of our products precluded development of a standard protocol, and substrates such as entry 28 proved difficult to purify in this manner. Initial attempts with direct purification of the magnesium amides generated in the reaction by liquid–liquid extraction yielded poor results as well,

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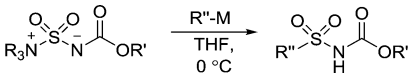
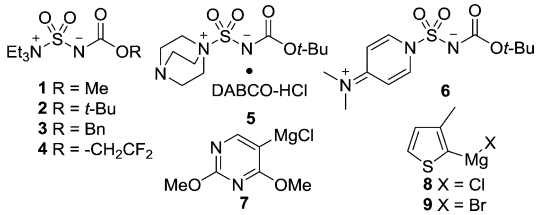
Table 1. Nucleophilic Additions to Sulfamoyl Inner Salts[a]



entry	R"-M	equiv of R"-M	inner salt	yield	entry	R"-M	equiv of R"-M	inner salt	yield
1	PhMgBr	1.1	1	56%	18	4-MeSC$_6$H$_4$MgBr	1.1	3	51%[c]
2	PhMgBr	1.1	2	60%	19	2-MeC$_6$H$_4$MgBr	3.0	3	47%
3	PhMgBr	1.1	3	57%	20	2-MeOC$_6$H$_4$MgBr	3.0	2	21%[c]
4	PhMgBr	4.0	5	NR	21	2-MeOC$_6$H$_4$MgBr	3.0	3	31%
5	PhMgBr	1.1	6	NR	22[e]	2-MeC$_6$H$_4$MgBr	1.2	3	NR
6	PhMgBr	1.1	4	NR	23[f]	2-MeC$_6$H$_4$MgBr	1.2	3	NR
7	PhLi	1.1	2	50%[a]	24	BnMgBr	1.0	3	31%
8	PhLi	1.1	3	28%	25	C$_6$H$_{11}$MgBr	3.0	3	33%
9	*t*-BuMgBr	3.0	3	NR	26	*i*-PrMgCl•LiCl	4.0	3	27%
10	AdMgBr	3.0	3	NR	27	7	2.0	3	34%
11	*t*-BuLi	1.0	3	20%	28	8	3.0	3	17%[c]
12[b]	PhZnBr	0.66	2	NR	29	Ph—≡—Li	1.0	1	49%
13	3-MeC$_6$H$_4$MgBr	1.5	2	39%[c]	30	Ph—≡—Li	1.0	3	NR
14	3-MeC$_6$H$_4$MgBr	2.0	3	57%	31	Ph—≡—MgBr	1.0	3	NR
15	3-MeOC$_6$H$_4$MgBr	1.0	3	53%	32	4-CO$_2$Me-C$_6$H$_4$MgCl	2.0	3	NR
16[d]	3-MeOC$_6$H$_4$MgBr	1.1	3	64%[c]					
17	4-MeOC$_6$H$_4$MgBr	4.0	3	50%					



[a]General conditions: 0 °C, 0.15 M final concentration, 60−90 min. (a) Purified by salt formation followed by acidification. (b) 0−55 °C. (c) Isolated as an ammonium salt. (d) 1 g scale. (e) 2.5 equiv BF_3·OEt_2. (f) 2.5 equiv $MgBr_2$·OEt_2. NR: no reaction.

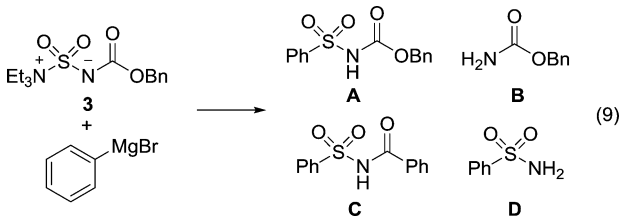
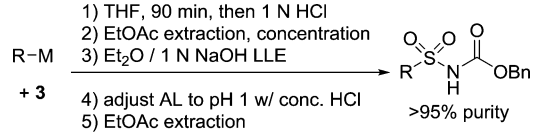


Figure 3. Products observed.

as these salts were too soluble in organic solvents in the presence of THF to efficiently extract. Fortuitously, however, a protocol consisting of isolation of the protonated acid, extraction from Et_2O with 1 N NaOH, acidification of the aqueous layer to pH 1 with concentrated HCl, and then re-extraction of the product with EtOAc yielded material >95% pure by NMR and in significantly better yields.

Table 2. Isolation of Products in High Purity via Extractive Purification



entry	R″-M	equiv of R″-M	yield from LLE (%)	previous yield (%)
1	*t*-BuLi	1.0	55	20
2	2-MeO C$_6$H$_4$MgBr	2.0	68	31
3	9	2.0	51	17

The sulfonyl carbamates generated with this method are useful in a range of chemistry. The *t*-butyl[42] and benzyl[43] carbamates

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can be smoothly removed under mild, orthogonal conditions to afford primary sulfonamides. The low pK_a[44] of the products permits smooth alkylation under Mitsunobu conditions[45] to provide both useful intermediates[46] and secondary sulfonamides after carbamate removal.

In conclusion, we have developed a broad method for the direct sulfonamidation of organolithium and organomagnesium nucleophiles that avoids unstable intermediates and highly energetic reagents. The *N*-carbamoyl products generated are benchstable, useful in a wide variety of *N*-alkylation and *N*-arylation chemistries, and can be readily deprotected.

EXPERIMENTAL SECTION

General Procedure A for the Addition of Alkyllithium and Grignard Reagents to Sulfamoyl Inner Salts. In an oven-dried, nitrogen-purged round-bottomed flask equipped with magnetic stirbar and rubber septum, the inner salt (1.0 equiv) was dissolved in THF sufficient to make the final concentration of the reaction 0.15 M. The mixture was cooled in an ice−water bath, and a solution of the nucleophile (1−3 equiv) was added dropwise. After 60−90 min, the reaction was quenched with sufficient acid such that the final pH was <5 (or <1 if the calculated pK_a <4). The mixture was extracted with EtOAc, dried, and concentrated. The material was then purified by flash-column chromatography, by formation of an ammonium salt, or both sequentially.

General Procedure B for the Addition of Alkyllithium and Grignard Reagents to Sulfamoyl Inner Salts. In an oven-dried, nitrogen-purged round-bottomed flask equipped with magnetic stirbar and rubber septum, the inner salt (1.0 equiv) was dissolved in THF sufficient to make the final concentration of the reaction 0.15 M. The mixture was cooled in an ice−water bath, and a solution of the nucleophile (1−2 equiv) was added dropwise. After 90 min, the reaction was quenched with 5 equiv 1 N HCl. The mixture was extracted with EtOAc, dried, and concentrated. The material was suspended in Et_2O and extracted thrice with 1 N NaOH. The combined aqueous layers were acidified to pH 1 with concentrated HCl and extracted with EtOAc. The combined EtOAc layers were dried over Na_2SO_4, filtered, and concentrated to provide the desired material.

Methyl(phenylsulfonyl)carbamate (Table 1, Entry 1).[47] Using the general procedure A, to **1** (213 mg, 0.894 mmol) in THF (5.0 mL) was added PhMgCl in THF (0.49 mL, 0.98 mmol, 2.0 M). The reaction was stirred for 60 min and quenched with 1 N HCl and worked-up as above. The material was loaded onto diatomaceous earth with DCM and purified on a 12 g silica ISCO Gold cartridge (0−100% EtOAc in heptanes, 25 column volumes) to provide the title compound as a white solid (108 mg, 56%), which was identical by ^{1}H- and ^{13}C NMR to the published material. Mp: 131−135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05−8.08 (m, 2H), 7.98 (bs, 1H), 7.67 (tt, J = 7.4, 1.6 Hz, 1H), 7.54−7.59 (m, 2H), 3.71 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 150.9, 138.3, 134.0, 129.0, 128.3, 53.7.

tert-Butyl(phenylsulfonyl)carbamate (Table 1, Entry 2).[48] Using the general procedure A, to **2** (200 mg, 0.713 mmol) and THF (3.2 mL) was added PhMgCl in THF (0.39 mL, 0.79 mmol, 2.0 M). The reaction was stirred for 60 min and quenched with 1 N HCl and worked-up as above. The crude mixture was treated with 500 μL THF, 70 uL conc. NH_4OH, and 2 mL of Et_2O, and the resulted slurry was stirred overnight. The ammonium salt of the desired material was collected by filtration the next day. These solids were redissolved in 10 mL of 0.1 N HCl and extracted 2 × 30 mL of DCM. The combined organic extract was dried over Na_2SO_4, filtered, and concentrated to isolate 110 mg (60% yield) of desired as white crystalline solids. Mp 116.4−120.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (bs, 1H), 8.01−8.03 (m, 2H), 7.61−7.66 (m, 1H), 7.51−7.56 (m, 2H), 1.36 (s, 9H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 149.7, 139.2, 133.9, 129.1, 128.4, 84.5, 28.3; HRMS (ESI) m/z calcd for $C_{11}H_{15}NNaO_4S$ [M + Na]$^+$, 280.0614; found, 280.0617.

Benzyl(phenylsulfonyl)carbamate (Table 1, Entry 3). Using the general procedure A, to **3** (203. mg, 0.646 mmol) and THF (3.9 mL) was added PhMgCl in THF (0.33 mL, 0.65 mmol, 2.0 M). The reaction was stirred for 60 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (0−100% EtOAc in heptanes, gradient over 25 CV, hold at 12% for 4 CV) to provide the title compound as a white solid (108 mg, 57.4%). Mp 102.7−106.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98−8.04 (m, 3 H), 7.64 (tt, J = 7.8, 1.2 Hz, 1H), 7.48−7.53 (m, 2H), 7.31−7.35 (m, 3H), 7.23−7.27 (m, 2H), 5.10 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 150.4, 134.3, 133.9, 128.9, 128.7, 128.6, 128.4, 128.3, 68.6; HRMS (ESI) m/z calcd for $C_{14}H_{13}NNaO_4S$ [M + Na]$^+$, 314.0457; found, 314.0456.

Benzyl(tert-butylsulfonyl)carbamate (Table 1, Entry 11). Using the general procedure A, to **3** (205 mg, 0.652 mmol) and THF (3.9 mL) was added *t*-BuLi in pentane (0.42 mL, 0.42 mmol, 1.7 M). The reaction was stirred for 90 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0−60% EtOAc in heptanes) to provide the title compound as a white solid. (36 mg, 20% yield). Mp: 64−73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.39 (m, 5H) 7.29 (bs, 1H), 5.20 (s, 2H), 1.48 (s, 9H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 151.0, 134.6, 128.72, 128.66, 128.5, 68.7, 63.3, 24.3; HRMS (ESI) m/z calcd for $C_{12}H_{17}NNaO_4S$ [M + Na]$^+$, 294.0770; found, 294.0768.

Benzyl(tert-butylsulfonyl)carbamate (Table 2, Entry 1). Using general procedure B, to **3** (672 mg, 2.14 mmol) and THF (12.6 mL) was added *t*-BuLi in pentane (1.4 mL, 2.4 mmol, 1.7 M). The reaction was stirred for 90 min and worked up as described to provide the product as a solid (339 mg, 58%).

Ammonium(tert-butoxycarbonyl)(m-tolylsulfonyl)amide (Table 1, Entry 13). Using the general procedure A, to **2** (1.69 mL, 0.713 mmol, 0.42M) in benzene and THF (2.0 mL) was added *m*-MePhMgCl in THF (1.1 mL, 1.1 mmol, 1.0 M). The reaction was stirred for 60 min and quenched with 1 N HCl and worked-up as above. The material was loaded onto diatomaceous earth with DCM and purified on a 12 g silica ISCO Gold cartridge (0−100% EtOAc in heptanes, 25 column volumes), and the peak at 10 column volumes was isolated to provide 135 mg of the free acid of the title compound as a white solid and containing a 5% *t*-butylcarbamate impurity. This solid was was treated with 500 μL THF, 70 μL conc NH_4OH, and 2 mL of Et_2O, and the resulted slurry was stirred overnight. The solids were collected via vacuum filtration, and the cake washed with Et_2O, to provide the title compound as a white solid (80 mg, 39%). Mp: 131−135 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.51−7.53 (m, 2H), 7.31 (t, J = 8.6 Hz, 1H), 7.26 (d, J = 6.8 Hz, 1H), 2.34 (s, 3H), 1.22 (s, 9H); ^{13}C{^{1}H}NMR (DMSO-d_6, 100 MHz) δ 150.9, 138.3, 134.0, 129.0, 128.3, 53.7; HRMS (ESI) m/z calcd for $C_{12}H_{17}NNaO_4S$ [M + Na]$^+$, 294.0770; found, 294.0769.

Benzyl(m-tolylsulfonyl)carbamate (Table 1, Entry 14). Using the general procedure A, to **3** (202 mg, 0.646 mmol) and THF (3.3 mL) was added *m*-MePhMgCl in THF (1.2 mL, 1.2 mmol, 1.0 M). The reaction was stirred for 60 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0−60% EtOAc in heptanes) to provide the title compound as a clear oil. (112 mg, 57% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (s, 1H), 7.80 (m, 2H), 7.43−7.45 (m, 1H), 7.36−7.40 (m, 1H), 7.32−7.34 (m, 3H), 7.24−7.27 (m, 2H), 5.10 (s, 2H), 2.39 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 150.4, 139.2, 138.2, 134.7, 134.3, 128.8, 128.7, 128.6, 128.5, 128.3, 125.4, 68.6, 21.2; HRMS (ESI) m/z calcd for $C_{15}H_{15}NNaO_4S$ [M + Na]$^+$, 328.0614; found, 328.0615.

Benzyl((3-methoxyphenyl)sulfonyl)carbamate (Table 1, Entry 15). Using the general procedure A, to **3** (199 mg, 0.633 mmol) and THF (3.6 mL) was added 3-MeOPhMgCl in THF (0.63 mL, 0.63 mmol, 1.0 M). The reaction was stirred for 60 min and quenched with AcOH and worked-up as above. The layers were separated, and the aqueous layer extracted twice with 10 mL EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated, followed by azeotroping thrice with heptanes to provide a clear oil. The crude material was dissolved in 10 mL DCM, charged with diatomaceous

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earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0−60% EtOAc in heptanes) to provide the title compound (108 mg, 53% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (bs, 1H), 7.59 (m, 1H), 7.51 (t, J = 1.95 Hz, 1H), 7.32−7.43 (m, 4H), 7.25−7.27 (m, 2H) 7.16 (ddd, J = 8.2, 2.7, 0.8 Hz, 1H), 5.11 (s, 2H), 3.80 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 159.67, 150.3, 139.5, 130.0, 128.7, 128.6, 128.3, 120.7, 120.4, 112.6, 68.7, 55.6; HRMS (ESI) m/z calcd for $C_{15}H_{15}NNaO_5S$ [M + Na]$^+$, 344.0563; found, 344.0565.

Gram-Scale Synthesis of Ammonium((benzyloxy)carbonyl)((3-methoxyphenyl)sulfonyl)amide (Table 1, Entry 16). An oven-dried round-bottomed flask was equipped with a dried stirbar, capped with a rubber septum, fitted with an electronic temperature probe, and purged with nitrogen gas. The flask was charged with **3** (1.05 g, 3.34 mmol) and THF (18.6 mL), and the solution was stirred until the inner salt had completely dissolved. The flask was placed in an ice-brine bath and then charged with 3-MeOPhMgCl in THF (3.7 mL, 3.7 mmol, 1.0 M), keeping the internal temperature < −5 °C. Upon completion of addition, the cooling bath was exchanged with an ice-water bath. At 60 min, the reaction had reached 0.5 °C and was quenched by addition of 3 mL 1 N HCl. The mixture was diluted with 10 mL of water, and the pH adjusted to 1 with concentrated HCl. The reaction was diluted with 20 mL EtOAc. The layers were separated, and the aqueous layer extracted twice with 20 mL EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to provide a clear oil. The crude material was dissolved in 5 mL of iPA and 2 mL 7 N NH_3 in MeOH. After 10 min, the volatiles were removed *in vacuo* to leave a gummy residue. The residue was stirred in 5 mL of EtOAc until a precipitate began to form, and then 10 mL heptanes was added. After 2 h, the solid was collected by vacuum filtration, and the cake washed with EtOAc and heptanes to afford the title compound as a tan solid (720 mg, 64%). Mp: 90−95 °C, then decomposition. Mp: 90−95 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.18−7.33 (m, 12H), 6.95−7.01 (m, 1H), 4.80 (s, 2H), 3.75 (s, 3H); ^{13}C{^{1}H}NMR (DMSO-d_6, 100 MHz) δ 158.5, 157.9, 147.2, 138.4, 128.9, 128.1, 127.3, 127.1, 118.9, 115.6, 112.0, 64.8, 55.2; HRMS (ESI) m/z calcd for $C_{15}H_{15}NNaO_5S$ [M + Na]$^+$, 344.0563; found, 344.0567.

Benzyl((4-methoxyphenyl)sulfonyl)carbamate (Table 1, Entry 17). Using the general procedure A, to **3** (200. mg, 0.636 mmol) and THF (1.7 mL) was added 4-MeOPhMgBr in 2-MeTHF (2.5 mL, 2.5 mmol, 2.0 M). The reaction was stirred for 90 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0−60% EtOAc in heptanes) to provide the title compound (102 mg, 49.9% yield) as a white solid. Mp: 100−105 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (m, 2H), 7.32−7.36 (m, 3H), 7.25−7.26 (m, 2H), 6.95 (m, 2H), 5.10 (s, 2H), 3.88 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 163.9, 150.4, 134.4, 130.7, 129.7, 128.7, 128.6, 128.4, 114.1, 68.5, 55.7; HRMS (ESI) m/z calcd for $C_{15}H_{15}NNaO_5S$ [M + Na]$^+$, 344.0563; found, 344.0559.

Ammonium((benzyloxy)carbonyl)((4-(methylthio)phenyl)-sulfonyl)amide (Table 1, Entry 18). Using the general procedure A, to **3** (206 mg, 0.655 mmol) and THF (3.0 mL) was added 4-MeSPhMgBr in THF (1.5 mL, 0.72 mmol, 0.5 M). The reaction was stirred for 60 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0−100% EtOAc in heptanes) to provide the free acid of the title compound a white solid containing *O*-benzyl carbamate. The material was dissolved in 500 μL THF and 70 μ 28% aqueous NH_4OH. After 10 min, 3 mL Et_2O was added, and the slurry stirred overnight. The solids were collected via vacuum filtration, and the cake washed with Et_2O to provide the title compound as a white solid (112 mg, 51%). Mp: 123−135 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.63−7.66 (m, 2H), 7.21−7.32 (m, 7H), 7.08 (bs, 4H), 4.78 (s, 2H) (S-Me is under solvent peak); ^{13}C{^{1}H}NMR (DMSO-d_6, 100 MHz) δ 167.07, 151.3, 150.6, 147.9, 137.8, 137.0,136.97, 136.8, 134.1, 74.6, 23.9; HRMS (ESI) m/z calcd for $C_{15}H_{15}NNaO_4S_2$ [M + Na]$^+$, 360.0335; found, 360.0335.

Benzyl(o-tolylsulfonyl)carbamate (Table 1, Entry 19). Using the general procedure A, to **3** (200 mg, 0.636 mmol) and THF (3.0 mL) was added *o*-MePhMgCl in THF (1.9 mL, 1.9 mmol, 1.0 M). The reaction was stirred for 90 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0−60% EtOAc in heptanes) to provide the title compound a clear oil containing an 8% *O*-Bn Carbamate impurity (95 mg, 47% yield adjusted for impurity). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (m, 1H), 7.52 (td, J = 7.4, 1.6 Hz, 1H), 7.45 (bs, 1H), 7.3−7.4 (m, 4H), 7.20−7.23 (m, 2H), 5.08 (s, 2H), 2.65 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 150.4, 137.7, 136.3, 134.3, 133.9, 132.5, 131.2, 128.6, 128.5, 128.3, 126.2, 68.6, 20.2; HRMS (ESI) m/z calcd for $C_{15}H_{15}NNaO_4S$ [M + Na]$^+$, 328.0614; found, 328.0616.

Ammonium(tert-butoxycarbonyl)((2-methoxyphenyl)sulfonyl)-amide (Table 1, Entry 20). Using the general procedure A, to **2** (1.2 mL, 0.71 mmol, 0.61M) in benzene and THF (0.9 mL) was added 2-MeOPhMgBr in THF (2.2 mL, 2.1 mmol, 1.0 M). The reaction was stirred for 90 min and quenched with 1 N HCl and worked-up as above. The material was dissolved in 0.5 mL THF, and 70 μL of 28% NH_4OH was added. After 10 min, the mixture was concentrated under streaming nitrogen to dryness. The resulting brown solid was pulped in 4 mL 3:1 heptane:EtOAc overnight. The solids were collected via vacuum filtration, and the cake washed with EtOAc to provide the title compound as a tan solid (46 mg, 21%). Mp: 105−113 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.88 (dd, J = 7.8, 1.6 Hz, 1H), 7.51 (m, 1H), 7.11 (d, J = 7.4 Hz, 1H), 7.02 (td, J = 7.8, 1.2 Hz, 1H), 3.91 (s, 3H), 1.29 (s, 9H); ^{13}C{^{1}H}NMR (CD_3OD, 100 MHz) δ 158.5, 134.9, 131.9, 131.8, 120.8, 113.5, 80.6, 56.6, 28.6 (carbamate RNC(O)OR below the noise); HRMS (ESI) m/z calcd for $C_{12}H_{17}NNaO_5S$ [M + Na]$^+$, 310.0720; found, 310.0718.

Benzyl((2-methoxyphenyl)sulfonyl)carbamate (Table 1, Entry 21). Using the general procedure A, to **3** (200 mg, 0.636 mmol) and THF (1.7 mL) was added 2-MeOPhMgBr in THF (1.9 mL, 1.9 mmol, 1.0 M). The reaction was stirred for 90 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0−100% EtOAc in heptanes). The fractions that absorbed most strongly at 280 nm were concentrated to provide the title compound as a clear oil that solidified upon standing (63 mg, 31% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, J = 7.8 Hz, 1H), 7.78 (bs, 1H), 7.60 (t, J = 8.20 Hz, 1H), 7.32 (m, 3H), 7.19 (m, 2H), 7.06 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 5.08 (s, 2H), 3.92 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 156.8, 150.47, 135.8, 134.6, 131.7, 128.5, 128.2, 125.8, 120.4, 112..2, 68.3, 56.3; HRMS (ESI) m/z calcd for $C_{15}H_{15}NNaO_5S$ [M + Na]$^+$, 344.0563; found, 344.0557.

Benzyl((2-methoxyphenyl)sulfonyl)carbamate (Table 2, Entry 2). Using general procedure B, to **3** (591 mg, 1.88 mmol) and THF (5.0 mL) was added 2-methoxyphenylmagnesium bromide in THF (3.8 mL, 3.8 mmol, 1.0 M). The reaction was stirred for 90 min and worked up as described to provide the product as a solid (408 mg, 68%).

Benzyl(benzylsulfonyl)carbamate (Table 1, Entry 24). Using the general procedure A, to **3** (200 mg, 0.636 mmol) and THF (4.0 mL) was added BnMgCl in THF (0.32 mL, 0.64 mmol, 2.0 M). The reaction was stirred for 60 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0−100% EtOAc in heptanes). The fractions containing only a single CAM-staining spot were collected and concentrated to provide the title compound as a white solid (60 mg, 31% yield). Mp: 106−109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.46 (m, 6H), 7.29−7.33 (m, 2H), 7.23−7.26 (m, 2H), 6.91 (bs, 1H), 5.25 (s, 2H), 4.61 (s, 2H);); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 150.8, 134.4, 130.6, 129.2, 129.01, 128.99, 128.8, 128.7, 127.7, 68.9. 58.4; HRMS (ESI) m/z calcd for $C_{15}H_{15}NNaO_4S$ [M + Na]$^+$, 328.0614; found, 328.0614.

Benzyl(cyclohexylsulfonyl)carbamate (Table 1, Entry 25). Using the general procedure A, to **3** (209 mg, 0.665 mmol) and THF (2.28 mL) was added $C_6H_{11}MgCl$ in THF/toluene (1.5 mL, 2.0 mmol, 1.3 M). The reaction was stirred for 90 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL

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DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0−60% EtOAc in heptanes) to provide the title compound (66 mg, 33% yield), containing a 5% *O*-benzyl carbamate impurity, as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (bs, 1H), 7.36−7.40 (m, 5H), 5.21 (s, 2H), 3.47 (tt, J = 12.1, 3.5 Hz, 1H), 2.14−2.19 (m, 2H), 1.87−1.92 (m, 2H), 1.68−1.73 (m, 1H), 1.58 (qd, J = 12.5, 3.1 Hz, 2H), 1.12−1.33 (m, 3H);); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 151.0, 134.5, 128.8, 128.7, 128.4, 68.7, 61.3, 25.8, 24.87, 24.85; HRMS (ESI) m/z calcd for $C_{14}H_{19}NNaO_4S$ [M + Na]$^+$, 320.0927; found, 320.0926.

Benzyl(isopropylsulfonyl)carbamate (Table 1, Entry 26). Using the general procedure A, to **3** (200.0 mg, 0.636 mmol) and THF (2.3 mL) was added *i*PrMgCl·LiCl in THF (2.0 mL, 2.5 mmol, 1.3 M). The reaction was stirred for 2.75 h and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (see attachment) to provide the title compound as a white solid (45 mg, 27%). Mp: 82−87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.45 (m, 5H), 7.18 (bs, 1H), 5.22 (s, 2H), 3.77 (sept, J = 7.0 Hz, 1H), 1.43 (d, J = 7.0 Hz, 6H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 150.8, 134.4, 128.9, 128.8, 128.5, 68.83, 53.91, 16.1; HRMS (ESI) m/z calcd for $C_{11}H_{15}NNaO_4S$ [M + Na]$^+$, 280.0614; found, 280.0612.

Benzyl((2,4-dimethoxypyrimidin-5-yl)sulfonyl)carbamate (Table 1, Entry 27). Using the general procedure A, to **3** (203.7 mg, 0.648 mmol) and THF (1.0 mL) was added **7** in THF (3.0 mL, 1.3 mmol, 0.65 M). The reaction was stirred for 90 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0% 2 CV, 0−30% 5 CV, 30% 5 CV, 30−100% 10 CV, EtOAc in heptanes) to provide the title compound a white solid, which was pulped in 1 mL EtOAc overnight to provide the title compound as a white solid containing a 5% 2,4-dimethoxypyrimidine impurity (80 mg, 34% yield adjusted for impurity). Mp: 145−157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (s, 1H), 7.65 (bs, 1H), 7.34−7.37 (m, 3H,), 7.25−7.28 (m, 2H), 5.13 (s, 2H), 4.09 (m, 6H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 167.7, 167.0, 150.0, 134.3, 128.9, 128.7, 128.5, 113.4, 68.9, 56.0, 55.4; HRMS (ESI) m/z calcd for $C_{14}H_{15}N_3NaO_6S$ [M + Na]$^+$, 376.0574; found, 376.0573.

Ammonium((benzyloxy)carbonyl)((3-methylthiophen-2-yl)-sulfonyl)amide (Table 1, Entry 28). Using the general procedure A, to **3** (207 mg, 0.658 mmol) and THF (2.8 mL) was added **8** in THF (1.5 mL, 2.0 mmol, 1.3 M). The reaction was stirred for 90 min and quenched with AcOH and worked-up as above. The crude material was dissolved in 10 mL DCM, charged with diatomaceous earth, concentrated, and then purified on a 12 g Redi-Sep Gold cartridge (gradient elution, 0% 2 CV, 0−30% 5 CV, 30% 5 CV, 30−100% 10 CV, EtOAc in heptanes). The fractions containing the peak at 10 CV were concentrated to provide the free acid of the title compound a white solid containing *O*-benzyl carbamate (63 mg, 85% pure). The material was dissolved in 2 mL 7 N NH_3 in MeOH. After 20 min, the volatiles were removed, and the oil slurred in 3 mL 2:1 heptanes:EtOAc overnight. The solids were collected via vacuum filtration and the cake washed with EtOAc to provide the title compound as a white solid (35 mg, 17%). Mp: 103.6−109.1 (decomposition); ^{1}H NMR (CD_3OD, 400 MHz) δ7.41 (d, J = 5.1 Hz, 1H), 7.21−7.30 (m, 5H), 6.86 (d, J = 4.7 Hz, 1H), 4.97 (s, 2H), 2.43 (s, 3H); ^{13}C{^{1}H}NMR (CD_3OD, 100 MHz) δ 160.2, 141.5, 139.9, 138.9, 132.0, 129.4, 128.7, 67.6, 15.0; HRMS (ESI) m/z calcd for $C_{13}H_{13}NNaO4S_2$ [M + Na]$^+$, 334.0178; found, 334.0176.

Benzyl((3-methylthiophen-2-yl)sulfonyl)carbamate (Table 2, Entry 3). Using general procedure B, to **3** (604 mg, 1.92 mmol) and THF (2.53 mL) was added (3-methylthiophen-2-yl)MgBr in THF (7.68 mL, 3.84 mmol, 0.5 M). The reaction was stirred for 90 min and worked up as described to provide the product as an oil (304 mg, 51%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (s, 1H), 7.50 (d, J = 4.7 Hz, 1H), 7.30−7.36 (m, 3H), 7.21−7.26 (m, 2H), 6.88 (d, J = 5.1 Hz, 1H), 5.12 (s, 2H), 2.48 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 150.4, 145.3, 134.2, 132.0, 131.9, 131.4, 128.6, 128.5. 128.3, 68.6, 14.9.

Methyl((phenylethynyl)sulfonyl)carbamate (Table 1, Entry 29). An oven-dried round-bottomed flask was equipped with a dried stir bar, capped with a rubber septum, and purged with nitrogen gas. The flask was charged with phenyl acetylene (540 mg, 5.20 mmol) and THF (2.59 mL). The mixture was cooled to 0 °C and treated with *n*-BuLi (2.5 M in hexane, 2.1 mL, 5.2 mmol). The mixture was allowed to warm to room temperature to afford a 1.1 M solution of (phenylethynyl)-lithium. Then using the general procedure A, to **1** (122 mg, 0.512 mmol) and THF (3.0 mL) was added the (phenylethynyl)lithium solution (0.44 mL, 0.51 mmol). The reaction was stirred for 60 min and quenched with 1 N HCl and worked-up as above. The material was loaded onto diatomaceous earth with DCM and purified on a 12 g silica ISCO Gold cartridge (0−100% EtOAc in heptanes, 20 column volumes) to provide the title compound as a white solid (60 mg, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, J = 8.0 Hz, 2H), 7.54 (t, J = 8.0 Hz, 1 H), 7.43 (t, J = 8.0 Hz, 2 H), 3.90 (s, 3 H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 150.2, 133.1, 132.0, 128.8, 117.3, 91.3, 82.1, 54.2; this compound proved too unstable to obtain an HRMS.

■ ASSOCIATED CONTENT

Supporting Information

Materials and instrumentation data with associated references and copies of ^{1}H- and ^{13}C{^{1}H}NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01287.

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Notes

The authors declare no competing financial interest.

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