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Synthesis of N-Sulfonyl Amidines and Acyl Sulfonyl Ureas from Sulfonyl Azides, Carbon Monoxide, and Amides

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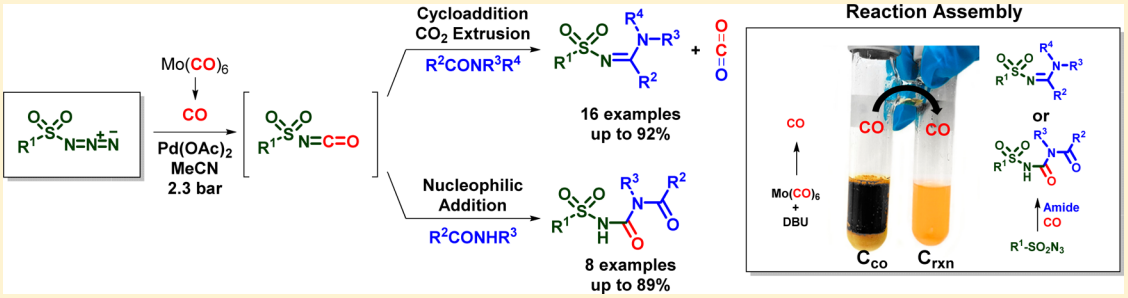
Supporting Information



ABSTRACT: A Pd-catalyzed and ligand-free carbonylation/cycloaddition/decarboxylation cascade synthesis of sulfonyl amidines from sulfonyl azides and substituted amides at low CO pressure is reported. The reaction proceeds via an initial Pd-catalyzed carbonylative generation of sulfonyl isocyanates from sulfonyl azides, followed by a [2 + 2] cycloaddition with amides and subsequent decarboxylation, which liberates the desired sulfonyl amidines, generating N_2 and CO_2 as the only reaction byproducts. Using this simple protocol, a diverse range of sulfonyl amidines was obtained in moderate to excellent yields. In addition, the reaction can also be directed through a more conventional amidocarbonylation pathway by employing N-monosubstituted amide nucleophiles to afford acyl sulfonyl ureas in good yields.

INTRODUCTION

Amidines are one of the most widely exploited moieties in medicinal and synthetic compounds. Notably, they serve as a highly conserved motif seen in both substrates and inhibitors of trypsin-like serine proteases due to their strong ionic interactions with the acidic S1 pockets.[1−4] In addition to being key intermediates in the synthesis of heterocyclic compounds, amidines are also chelators of transition metals (e.g., Zn^{II}) and have been successfully exploited as inhibitors of anthrax lethal factor, a zinc metalloenzyme.[5,6] The emergence of sulfonyl amidines as bioactive pharmacophores (Figure 1) with antiresorptive,[7] antitumor,[8] and antiproliferative[9] properties has led to numerous new synthetic developments to access this highly polar, structurally rigid, and hydrogen-bond-rich moiety (Scheme 1). These include (a) direct condensation of sulfonamide and formamide,[10] (b) three-component aerobic oxidative coupling of sulfonamides, terminal alkynes, and amines catalyzed by $Cu(OTf)_2$,[11] (c) the coupling of primary, secondary, or tertiary amines and sulfonyl azides with terminal alkynes,[12] (d) coupling of thioamides and sulfonyl azides,[13] and (e) dehydrogenation of tertiary amines coupled with a tandem reaction with sulfonyl azides[14] (Scheme 1).

In our previous work on sulfonyl-containing compounds, we reported a versatile Pd-mediated carbonylative preparation of sulfonyl carbamates and sulfonyl ureas by assembling sulfonyl azides, carbon monoxide, and alcohol or aromatic amine nucleophiles.[17] In contrast, aliphatic amines were found to form substituted sulfonamides under a direct substitution reaction with sulfonyl azides. In an effort to overcome this issue, we sought to develop a telescoped process involving the initial formation of a sulfonyl isocyanate intermediate followed by the addition of an amine nucleophile. During our initial studies, we observed the formation of an unexpected side product, identified herein as a sulfonyl amidine, formed from sulfonyl azides and the reaction solvent, *N*,*N*-dimethylacetamide (DMA). There are a few sparse literature reports on the ability of sulfonyl isocyanates to undergo cycloaddition/decarboxylation reactions with tertiary amides[18] (Scheme 1), and we postulated that a similar pathway was operating in this case. Here, the in situ generated sulfonyl isocyanate intermediate underwent cycloaddition with DMA to form a labile four-membered ring that subsequently collapsed to release the sulfonyl amidine product. Indeed, during the completion of this work, Huang et al. reported the synthesis of sulfonyl arylaldimines from sulfonyl isocyanates and aldehydes via a similar cycloaddition/cycloreversion process,[19] which further strengthened our mechanistic hypothesis. Due to the limited commercial availability of diverse sulfonyl isocyanates and their tendency to undergo hydrolysis to form sulfonyl amides,[20] we devised a one-pot synthesis of sulfonyl amidines from stable sulfonyl azide precursors and substituted amides via the in situ

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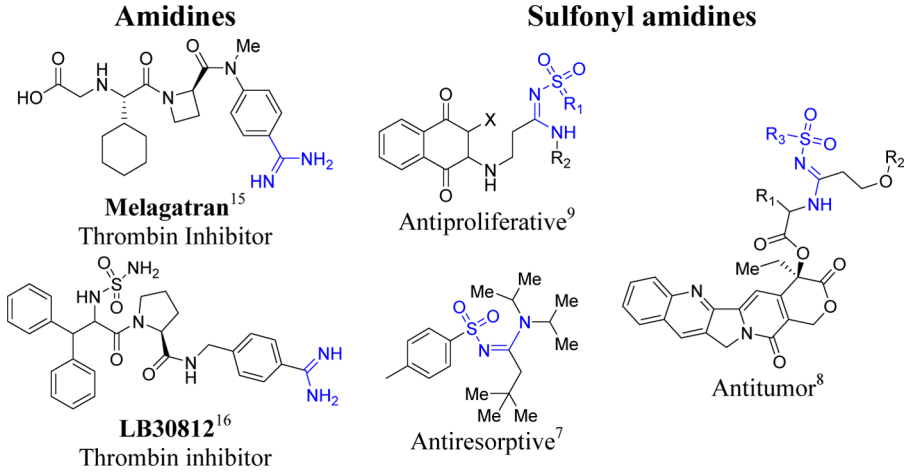
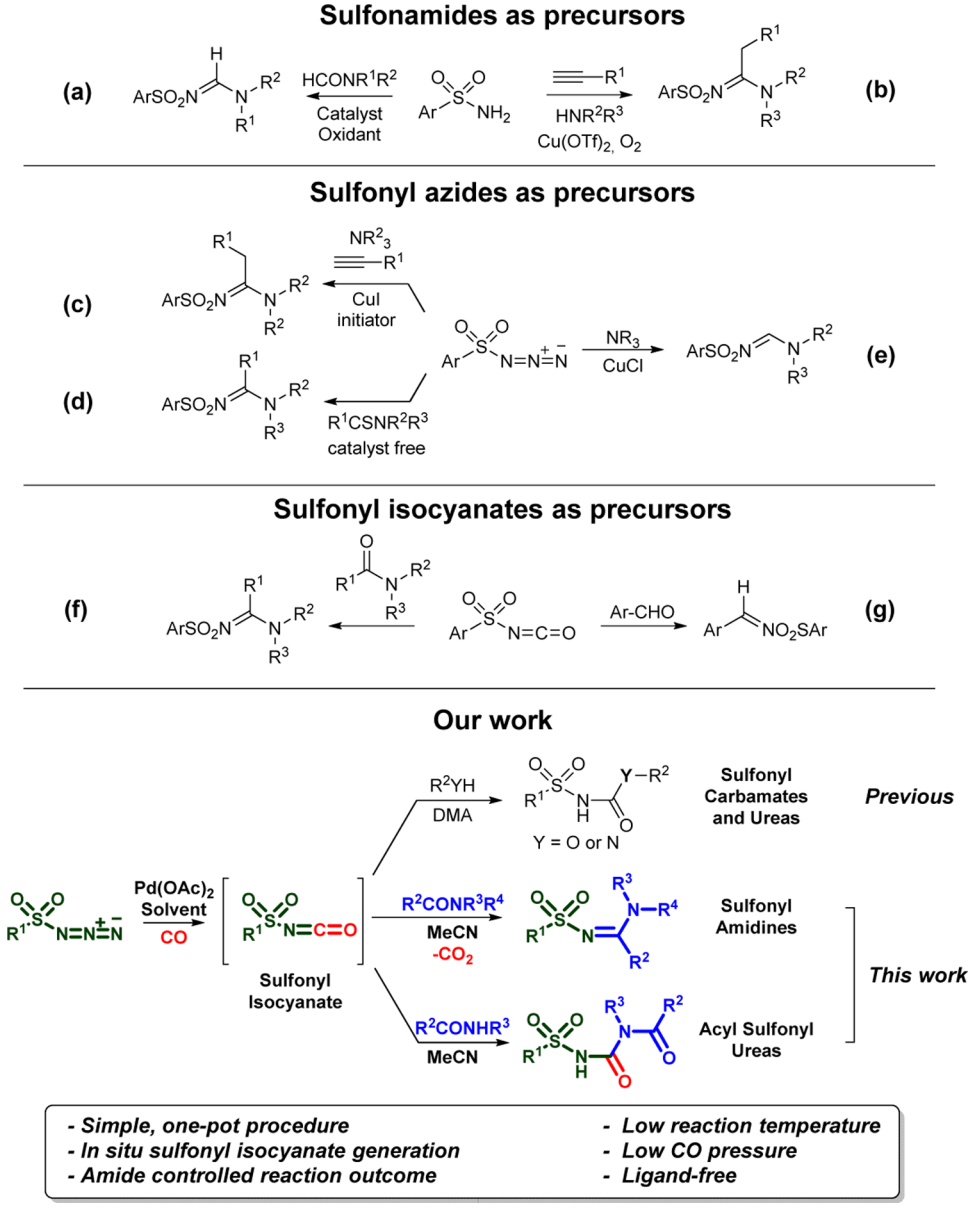


Figure 1. Biologically active amidines and sulfonyl amidines.

Scheme 1. Synthesis Routes To Access Sulfonyl Amidines and Derivatives



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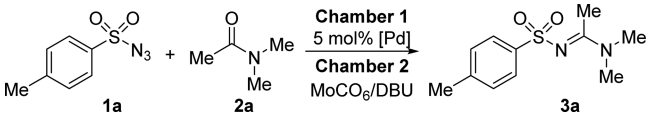
generation of sulfonyl isocyanate intermediates. In addition, this method would also complement the existing methods based on sulfonamide and sulfonyl azide chemistry, by allowing the introduction of small alkyl groups on the amidine carbon without requiring access to thioamide starting materials.

Herein, we report a simple carbonylation−cycloaddition protocol using a two-chamber reactor that involves (1) in situ carbonylative sulfonyl isocyanate formation from sulfonyl azides, followed by (2) [2 + 2] cycloaddition of the sulfonyl isocyanate intermediate with substituted amides, and finally (3) decarboxylation to produce the desired sulfonyl amidines concomitant with the release of CO_2. Furthermore, this protocol also allows access to acyl sulfonylureas by simply switching the nucleophile to an N-monosubstituted amide, providing an efficient and diverse strategy to two distinct product classes from a common intermediate.

RESULTS AND DISCUSSION

We began our investigation by using *p*-tolyl sulfonyl azide (**1a**) and DMA (**2a**) as model substrates in a modified two-chamber reaction vessel[17,21,22] originally developed by Skrydstrup et al. (Table 1).[23,24] Sulfonyl azide, $PdCl_2$ (5 mol %), and DMA (2

Table 1. Screening of Reaction Conditions[a]



entry	DMA	solvent	catalyst	yield (%)
1	excess	DMA	$PdCl_2$	56
2	excess	DMA	$Pd(OAc)_2$	96
3	excess	DMA	$Pd(TFA)_2$	91
4	excess	DMA	$Pd(cod)Cl_2$	94
5	excess	DMA	$Pd_2(dba)_3$	82
6	excess	DMA	$Pd(PPh_3)_4$	62
7	20 equiv	THF	$Pd(OAc)_2$	90
8	10 equiv	THF	$Pd(OAc)_2$	85
9	5 equiv	THF	$Pd(OAc)_2$	89
10	2 equiv	THF	$Pd(OAc)_2$	48

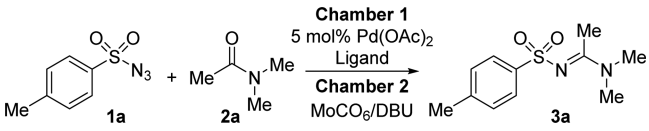
[a]Reaction conditions. Chamber 1: *p*-tolyl sulfonyl azide (0.25 mmol), Pd catalyst (5 mol %), DMA (2 equiv—excess), solvent (2 mL); Chamber 2: $Mo(CO)_6$ (0.6 equiv), DBU (1.5 equiv). Reaction was heated at 75 °C for 20 h. All yields are isolated yields.

mL) were added to chamber 1, and $Mo(CO)_6$ was added to chamber 2 as the ex situ CO generating source. Gratifyingly, formation of desired sulfonyl amidine **3a** was observed, and the product was isolated in 56% yield. The modest yield was attributed to the poor solubility of $PdCl_2$ in the reaction solvent, and a catalyst screen comprising a series of Pd(II) and Pd(0) catalysts was carried out.

In general, the use of Pd(II) salts was beneficial, and $Pd(OAc)_2$ was the most optimal, returning an excellent yield of 96%. In contrast, the use of $Pd(PPh_3)_4$ returned a significantly lower yield due to competing consumption of the starting material through a Staudinger reaction with the triphenylphosphine ligand. To assess the minimal stoichiometry of the amide, the amount of DMA was progressively decreased and THF was employed as the reaction solvent. It was observed that at least 5 equiv of DMA was required to maintain the optimal yield (>89%), and a drastic decrease in yield was observed with just 2 equiv of DMA. On the basis of the need for an excess of DMA, we reasoned that the amide reactant was also functioning as a chelating ligand of the Pd catalyst.

The requirement for a large excess of amide was considered a significant drawback due to potential waste, purification, and cost issues. In addition, we anticipated further issues when expanding the protocol beyond DMA, resulting from variation in the chelating efficiency of different amides. Thus, a ligand survey using $Pd(OAc)_2$ as the catalyst precursor was carried out in the presence of 2 equiv of DMA (Table 2). The use of

Table 2. Ligand and Temperature Optimization[a]



entry	solvent	Pd ligand	*T* (°C)	yield (%)
1	THF		75	48
2	THF	1,10-phenanthroline	75	69
3	THF	6-methyl-2,2′-pyridyl	75	64
4	THF	Xantphos	75	trace
5	MeCN		75	91
6	MeCN		55	90
7	**MeCN**		**40**	**92**
8	MeCN		RT	71

[a]Reaction conditions. Chamber 1: *p*-tolyl sulfonyl azide (0.25 mmol), Pd catalyst (5 mol %), DMA (2 equiv), ligand (7.5 mol %), solvent (3 mL); Chamber 2: $Mo(CO)_6$ (0.6 equiv), DBU (1.5 equiv). All yields are isolated yields.

bidentate N-based ligands, 1,10-phenanthroline and 6-methyl-2,2′-pyridyl, was moderately advantageous, leading to a slight improvement in yield, and xantphos returned only traces of the desired product. To further simplify the reaction conditions, we then employed acetonitrile as a dual reaction solvent and Pd ligand. Gratifyingly, the reaction proceeded smoothly to afford **3a** in an excellent yield of 91%. Moreover, the temperature could be reduced to 40 °C without affecting the yield (92%), whereas a slight decrease in efficiency was observed at room temperature (71%).

With the optimal conditions in hand, we proceeded to explore the reaction scope with an array of sulfonyl azides and amides (Table 3). Sulfonyl azides containing either an electron-withdrawing (**3b−c**) or electron-donating (**3d**) group underwent smooth conversion to the corresponding sulfonyl amidines, giving excellent yields of 81−94%. Similarly, electron-rich heterocyclic (**3e**) and benzylic (**3f**) sulfonyl azides performed well as substrates, returning high yields of the desired products (87−90%). Next, a range of di- and trisubstituted amides (**3g−p**) was employed as substrates to examine steric tolerance of the cycloaddition reaction. Similar to trisubstituted DMA (**3a**), disubstituted dimethylformamide (**3g**) performed well, affording an excellent yield of 91%. The introduction of bulkier isopropyl-N substituents resulted in lower conversion to **3h**, and no improvement was observed despite the addition of excess amide. Increasing the reaction temperature to 55 °C was beneficial, and a moderate yield of 43% was obtained. In contrast, a cyclic N-substituent was well-tolerated in which **3i** was isolated in a high yield of 86%, likely due to decreased steric interference by the constrained cyclohexyl ring.

Subsequently, a series of trisubstituted amides (**3j−m**) with various groups attached to the amide carbon was investigated,

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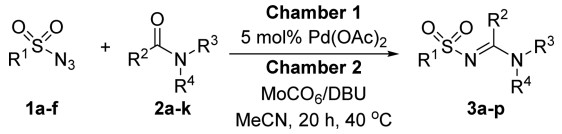
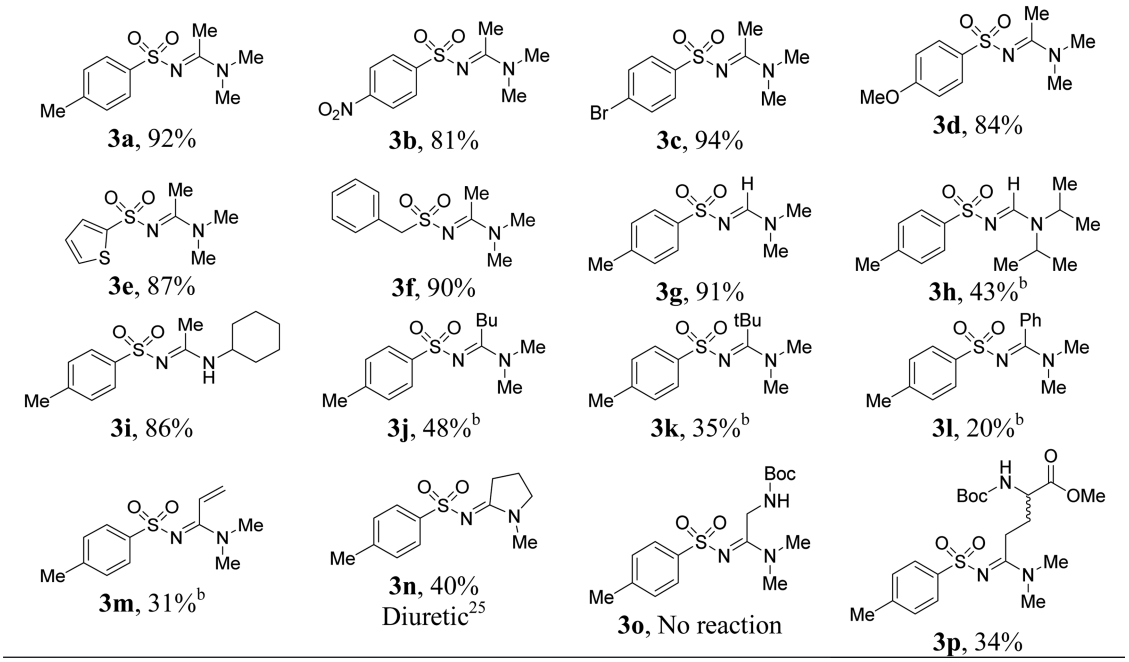
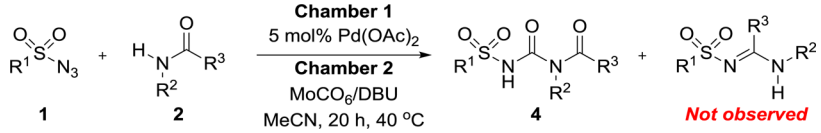
Table 3. Scope of the Carbonylative Sulfonyl Amidine Cascade Reaction[a]

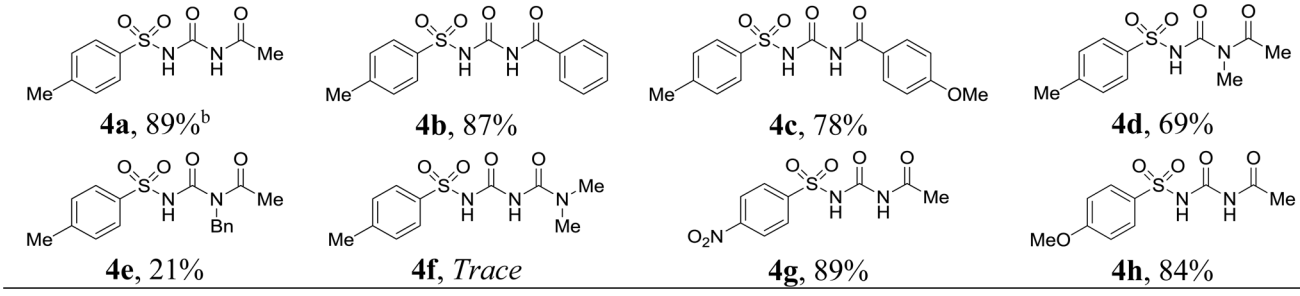




[a]Reaction conditions. Chamber 1: sulfonyl azide (0.25 mmol, 1 equiv), amide (1 mmol, 5 equiv), $Pd(OAc)_2$ (5 mol %); Chamber 2: $Mo(CO)_6$ (0.15 mmol, 0.6 equiv), DBU (0.35 mmol, 1.5 equiv). Reaction heated and stirred vigorously at 40 °C. [b]Reaction run at 55 °C.

Table 4. Acyl Sulfonyl Urea Reaction Scope[a]





[a]Reaction conditions: Chamber 1: sulfonyl azide (0.25 mmol, 1 equiv), amide (1 mmol, 2 equiv), $Pd(OAc)_2$ (5 mol %), MeCN (3 mL); Chamber 2: $Mo(CO)_6$ (0.15 mmol, 0.6 equiv), DBU (0.35 mmol, 1.5 equiv), MeCN (3 mL). Reaction heated and stirred vigorously at 40 °C.

in which elevated temperatures were used to overcome steric hindrance. Bulky groups (butyl, *t*-butyl, and phenyl) were indeed compatible and afforded modest, albeit decreased, yields (20–48%). Notably, the presence of a vinyl group was also compatible with the reaction conditions (**3m**), despite the potentially competing side reaction between the vinyl group and the sulfonyl isocyanate moiety. The cyclic substrate *N*-methyl-2-pyrrolidone was also tolerated and returned a moderate yield of the diuretic **3n**.[25] To investigate the functional group tolerance of the cycloaddition reaction, we also employed amino acids containing a N,N-dimethylated carboxyl group at either the α-position (Boc-Gly-CON(Me)$_2$, **3o**) or γ-position (Boc-*N,N*-dimethylGln-COOMe, **3p**). No product was observed in **3o**, likely due to steric interference by the bulky adjacent Boc-protected α-amino group, whereas a moderate yield was obtained for **3p** due to the distal position of the reacting γ-amide in relation to the α-carbon of the amino acid. Finally, we explored the use of other carbonyl derivatives (ester, ketone, and aldehyde) as the reacting partner, and no conversion was observed, indicating a possible preference for an electron-rich rather than electrophilic carbonyl derivative.

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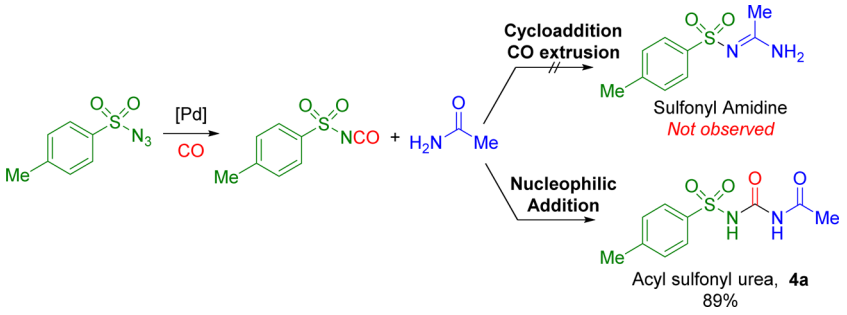
Scheme 2. Formation of Acyl Sulfonyl Urea from N-Monosubstituted Amide



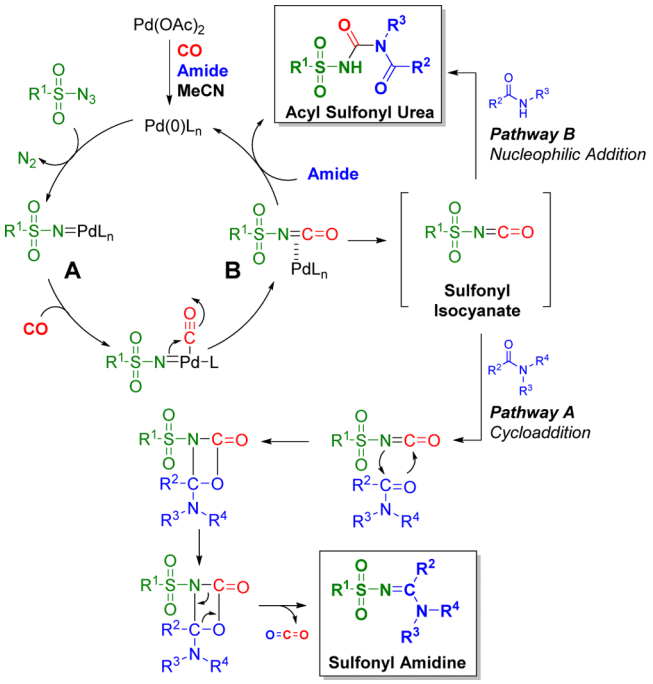
Next, we turned our attention to N-monosubstituted amides as substrates (Table 4). Surprisingly, when acetamide was employed as a substrate, the reaction led to the exclusive formation of an N-acyl sulfonyl urea (**4a**) and no trace of the expected sulfonyl amidine was observed (Scheme 2). In this case, the amide acted as an N-nucleophile with the sulfonyl isocyanate intermediate, leading to the formation of the acyl sulfonyl urea, analogous to the carbonylative preparation of sulfonyl ureas.[17] Due to self-catalyzed hydrolysis and stability issues, the compound was isolated as the triethylamine salt in an excellent yield of 89%.

We then proceeded to explore the use of N-monosubstituted amides with varying steric and electronic properties. Introduction of a bulkier aryl group at R^3 was well tolerated, returning **4b** and **4c** in excellent yields (78−87%). The presence of an N-methyl group led to a slight decrease in yield (**4d**), and *N*-benzylacetamide afforded **4e** in moderate yield due to sluggish conversion; increasing the reaction temperature to 55 °C led to no improvement as a result of thermal instability of the acyl sulfonylurea product (see Supporting Information for details). Unfortunately, the use of *N*,*N*-dimethylurea as nucleophile was unsuccessful, and only traces of the desired product (**4f**) were observed. Gratifyingly, the use of aryl sulfonyl azides containing either an electron-withdrawing or -donating group as substrate proceeded smoothly, and **4g** and **4h** were obtained in high yields of 89 and 84%, respectively.

A plausible mechanism for the cascade formation of sulfonyl amidines is depicted in Scheme 3. Analogous to the in situ generation of sulfonyl isocyanates that we reported in the alkoxy- and amino-carbonylation of sulfonyl azides,[17] the $Pd(OAc)_2$ precatalyst is first reduced by either CO, acetonitrile, and/or amide to an active Pd(0) species. Addition of the sulfonyl azide precursors to the Pd(0) species generates nitrene−palladium complex **A** via nitrogen extrusion and subsequent insertion of CO, followed by reductive elimination, which leads to the formation of complex **B**. The sulfonyl isocyanate intermediate then undergoes a [2 + 2] cycloaddition with a di- or trisubstituted amide, and finally, the four-membered ring intermediate collapses, releasing the final sulfonyl amidine product and CO_2. In contrast, when the reaction is conducted with a primary or secondary amide, addition to the sulfonyl isocyanate via the nucleophilic nitrogen center is favored and the competing amidocarbonylation pathway leads to the formation of the acyl sulfonyl urea products.

To further delineate the mechanism of the carbonylative formation of sulfonyl amidines, a series of control experiments was carried out (Scheme 4). Removal of either Pd catalyst or the CO source led to complete abolishment of conversion, and no product was observed, suggesting that the transformation is

Scheme 3. Plausible Mechanism of Carbonylation−Cycloaddition Synthesis of Sulfonyl Amidines and Formation of Acyl Sulfonyl Ureas



indeed palladium-catalyzed and that CO-mediated reduction of the Pd(II) precatalyst is required. The direct addition of DMA or acetamide to *p*-tolylsulfonyl isocyanate led to the formation of sulfonyl amidine **3a** and acyl sulfonyl urea **4a**, respectively, indicating that both reaction pathways proceed via the same sulfonyl isocyanate intermediate, generated in situ from a sulfonyl azide precursor in the present reaction (Scheme 4). This was further supported by the unsuccessful generation of **3a** and **4a** from *p*-tolylsulfonamide. Finally, we employed *p*-tolylsulfonyl chloride as the precursor in the presence of sodium azide for the in situ generation of the sulfonyl azide substrate;[26] however, no product was observed.

CONCLUSIONS

In conclusion, we have developed a simple, ligand-free, and versatile one-pot synthesis of sulfonyl amidines and acyl sulfonyl ureas from readily available sulfonyl azide precursors. Using acetonitrile as solvent in conjunction with ubiquitous $Pd(OAc)_2$, we have successfully identified a carbonylation−cycloaddition−decarboxylation cascade process to access a range of sulfonyl amidines from sulfonyl azides and amides without the requirement for additional ligands. Notably, aside

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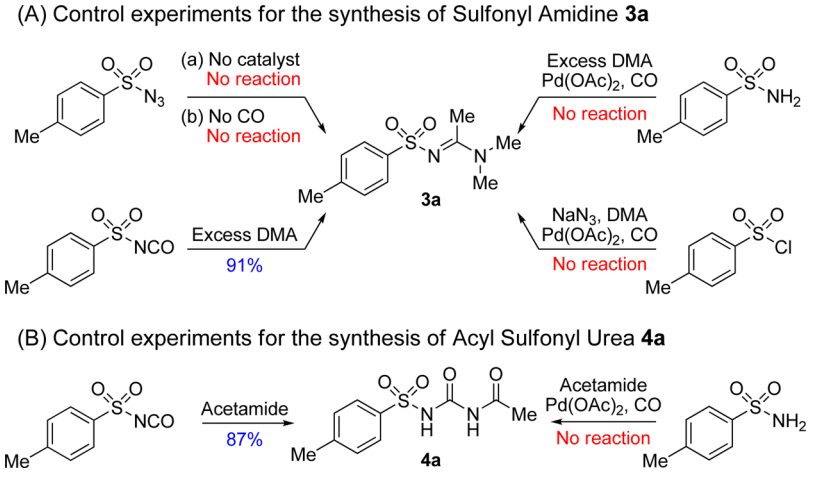
Scheme 4. Control Experiments for the Synthesis of 3a and 4a



from the Mo formed during the carbon monoxide releasing step, CO_2 and N_2 are the only byproducts formed in this reaction. This protocol can also be directed through an amidocarbonylation pathway by using primary and secondary amide nucleophiles to afford acyl sulfonyl ureas in moderate to excellent yields. These simple three-component carbonylative reactions represent a robust and divergent synthetic platform that provide access to two important classes of sulfonyl-containing compounds with immense pharmaceutical relevance, controlled only by the choice of amide nucleophile.

EXPERIMENTAL SECTION

General Methods. All reagents and solvents (anhydrous MeCN, EtOAc, hexane, *n*-pentane, acetone, methanol, and Et_3N) were of commercial quality and used without further purification. Yields are for isolated, homogeneous, and spectroscopically pure material. Silica gel chromatography was carried out on E. Merck silica gel (60 Å pore size, particle size 40−63 nm) columns. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz. The chemical shifts for ^{1}H and ^{13}C NMR were referenced to tetramethylsilane via residual solvent signals (^{1}H, $CDCl_3$ at 7.26 ppm; ^{13}C, $CDCl_3$ at 77.16 ppm; ^{1}H, $(CD_3)_2CO$ at 2.05 ppm; ^{13}C, $(CD_3)_2CO$ at 206.26 ppm). LC/MS was performed on an instrument equipped with a CP-Sil 8 CB capillary column (50 × 3.0 mm, particle size 2.6 μm, pore size 100 Å) running at an ionization potential of 70 eV with a CH_3CN/H_2O gradient (0.05% HCOOH). Accurate mass values were determined via electrospray ionization with a 7-T hybrid ion trap and a TOF detector running in positive mode.

General Procedure for the Preparation of Sulfonyl Azide Precursors. All sulfonyl azides were prepared from the corresponding sulfonyl chloride[26] following literature procedures. It should be noted that as sulfonyl azides are potentially explosive, all reactions should be carried out behind blast shields and the use of plastic spatulas for the handling of solid material is recommended.

General Procedure for the Synthesis of Sulfonyl Amidines, Exemplified by *N,N*-Dimethyl-*N*′-tosylacetimidamide[18] (CAS 93958-32-8) (3a). Chamber 1 of a two-vial reactor[17] was charged with toluene sulfonyl azide (50 mg, 0.25 mmol), *N,N*-dimethylacetamide (47 μL, 0.50 mmol, 2 equiv), and $Pd(OAc)_2$ (3 mg, 5 mol %), and chamber 2 was charged with $Mo(CO)_6$ (40 mg, 0.15 mmol, 0.6 equiv). Both chambers were capped, anhydrous MeCN (2 mL) was added through the septum to each chamber, and the reaction vessel was purged with N_2 for 5 min. DBU (57 μL, 0.38 mmol, 1.5 equiv) was added through the septum to chamber 2 to induce the release of CO, and the assembly was stirred vigorously for 20 h at 40 °C. The reaction mixture from chamber 1 was concentrated in vacuo and loaded directly onto a silica gel column. The sulfonyl amidine compound was obtained as a white solid (56 mg, 92%), eluting with 30% EtOAc in *n*-pentane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 3.07 (s, 3H), 3.05 (s, 3H), 2.47 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 141.9, 141.3, 129.2, 126.4, 38.9, 21.5, 18.1. MS *m/z*: $[M + H]^+$ calcd for $C_{11}H_{17}N_2O_2S$, 241.1; found, 241.3.

General Procedure for the Synthesis of Acyl Sulfonyl Ureas, Exemplified by *N*-(Tosylcarbamoyl)acetamide·TEA Salt[18] (CAS 34543-10-7) (4a). Chamber 1 of a two-vial reactor[17] was charged with toluene sulfonyl azide (50 mg, 0.25 mmol), acetamide (30 mg, 0.50 mmol, 2 equiv), and $Pd(OAc)_2$ (3 mg, 5 mol %), and chamber 2 was charged with $Mo(CO)_6$ (40 mg, 0.15 mmol, 0.6 equiv). Both chambers were capped, anhydrous MeCN (2 mL) was added through the septum to each chamber, and the reaction vessel was purged with N_2 for 5 min. DBU (57 μL, 0.38 mmol, 1.5 equiv) was added through the septum to chamber 2 to induce the release of CO, and the assembly was stirred vigorously for 20 h at 40 °C. The reaction mixture from chamber 1 was concentrated in vacuo and loaded directly onto a silica gel column, eluting with 1% MeOH and 2% TEA in acetone. The acyl sulfonyl urea compound was obtained as a colorless oil (76 mg, 89%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.33−7.16 (m, 2H), 3.09 (m, 6H), 2.35 (s, 3H), 2.03 (s, 3H), 1.89 (s, 1H), 1.18 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 173.1, 172.8, 157.2, 143.1, 141.7, 129.4, 127.7, 46.7, 24.5, 22.6, 21.3, 9.1. MS *m/z*: $[M + H]^+$ calcd for $C_{10}H_{13}N_2O_4S$, 257.1; found, 257.1.

3b, *N,N*-Dimethyl-*N*′-((4-nitrophenyl)sulfonyl)-acetimidamide. Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3b** as a white solid (55 mg, 81% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H), 3.23 (s, 3H), 3.08 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 166.3, 150.6, 149.3, 127.4, 123.9, 38.4, 38.1, 17.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{14}N_3O_4S$, 272.0700; found, 272.0696.

3c, *N*′-((4-Bromophenyl)sulfonyl)-*N,N*-dimethylacetimidamide. Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3c** as a white solid (72 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.76 (m, 2H), 7.60−7.52 (m, 2H), 3.09 (s, 3H), 3.05 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 143.1, 132.2, 131.8, 130.0, 128.0, 126.2, 39.1, 39.1, 18.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{14}BrN_2O_2S$, 304.9954; found, 304.9959

3d, *N*′-((4-Methoxyphenyl)sulfonyl)-*N,N*-dimethylacetimidamide. Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3d** as a white solid (64 mg, 84% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.79 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 3.17 (s, 3H), 3.02 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 165.8, 161.8, 137.4, 127.9, 113.5, 55.0, 38.1, 37.7, 16.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{17}N_2O_3S$, 257.0955; found, 257.0959.

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3e, *N,N*-Dimethyl-*N′*-(thiophen-2-ylsulfonyl)acetimidamide. Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3e** as a white solid (51 mg, 87% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.69 (dd, J = 5.0, 1.4 Hz, 1H), 7.51 (dd, J = 3.7, 1.3 Hz, 1H), 7.07 (dd, J = 5.0, 3.6 Hz, 1H), 3.21 (s, 3H), 3.09 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 166.1, 147.2, 129.9, 129.0, 126.6, 38.3, 37.9, 16.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_8H_{13}N_2O_2S_2$, 233.0413; found, 233.0419.

3f, *N′*-(Benzylsulfonyl)-*N,N*-dimethylacetimidamide. Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3f** as a white solid (54 mg, 90% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.44−7.42 (m, 2H), 7.35−7.28 (m, 3H), 4.17 (s, 2H), 3.10 (s, 3H), 2.98 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 165.7, 132.0, 131.1, 127.9, 127.5, 60.6, 37.9, 37.7, 17.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{17}N_2O_2S$, 241.1005; found, 241.1010.

3g, *N,N*-Dimethyl-*N′*-tosylformimidamide[18] (CAS 25770-53-0). Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3g** as a white solid (52 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, br, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.28−7.24 (m, 2H), 3.12 (s, 3H), 3.01 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $(CDCl_3)$ δ 159.2, 142.6, 139.7, 129.4, 126.7, 41.6, 35.6, 21.6. MS m/z: $[M + H]^+$ calcd for $C_{10}H_{15}N_2O_2S$, 227.1; found, 227.2.

3h, *N,N*-Diisopropyl-*N′*-tosylformimidamide[27] (CAS 1304779-03-0). Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3h** as a white solid (31 mg, 43% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.24 (s, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.34−7.27 (m, 2H), 4.36 (p, J = 6.8 Hz, 1H), 3.90 (p, J = 6.8 Hz, 1H), 2.38 (s, 3H), 1.34 (d, J = 6.8 Hz, 6H), 1.25 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 156.9, 141.8, 129.3, 129.1, 126.1, 49.8, 47.7, 22.3, 20.4, 18.7. MS m/z: $[M + H]^+$ calcd for $C_{14}H_{23}N_2O_2S$, 283.1; found, 283.2.

3i, *N*-Cyclohexyl-*N′*-tosylacetimidamide[28] (CAS 101354-34-1). Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3i** as a white solid (65 mg, 86% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.61−7.48 (s, br, 1H), 7.32 (d, J = 8.0 Hz, 2H), 3.78 (dq, J = 6.9, 3.6 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H), 1.97−1.83 (m, 2H), 1.70 (m, 2H), 1.61−1.51 (m, 1H), 1.45−1.04 (m, 5H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 165.6, 143.1, 142.5, 129.9, 127.1, 51.3, 32.5, 26.2, 25.5, 21.4, 20.8. MS m/z: $[M + H]^+$ calcd for $C_{15}H_{23}N_2O_2S$, 295.1; found, 295.2.

3j, *N,N*-Dimethyl-*N′*-tosylpentanimidamide. Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3j** as a white solid (33 mg, 48% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 3.20 (s, 2H), 3.00 (s, 3H), 2.38 (s, 3H), 1.70−1.58 (m, 2H), 1.29 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 168.5, 142.8, 141.3, 128.9, 126.0, 37.8, 32.4, 20.4, 19.8, 13.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{23}N_2O_2S$, 283.1475; found, 283.1484.

3k, *N,N*-Dimethyl-*N′*-tosylpivalimidamide. Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3k** as a white solid (25 mg, 35% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 3.39 (s, 6H), 2.38 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 172.9, 145.0, 141.5, 129.5, 126.3, 44.3 41.3, 29.1, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{23}N_2O_2S$, 283.1475; found, 283.1480.

3l, *N,N*-Dimethyl-*N′*-tosylbenzimidamide[29] (CAS 4115-23-5). Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3l** as a white solid (15 mg, 20% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.46−7.40 (m, 3H), 7.38−7.32 (m, 2H), 7.21−7.08 (m, 4H), 3.19 (s, 3H), 2.80 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 161.5, 143.1, 142.0, 130.2, 129.5, 128.7, 128.4, 127.1, 40.1, 38.1, 21.3. MS m/z: $[M + H]^+$ calcd for $C_{16}H19N_2O_2S$, 303.1; found, 303.2.

3m, *N,N*-Dimethyl-*N′*-tosylacrylimidamide. Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3m** as a white solid (20 mg, 31% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.71 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.60 (ddt, J = 18.1, 12.1, 0.4 Hz, 1H), 5.66 (dd, J = 12.1, 1.1 Hz, 1H), 5.47 (dd, J = 18.1, 1.1 Hz, 1H), 3.16 (s, 3H), 3.04 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 164.6, 142.5, 141.3, 129.2, 128.3, 126.3, 126.0, 123.7, 39.3, 37.2 20.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{17}N_2O_2S$, 253.1005; found, 253.1015.

3n, 4-Methyl-*N*-(1-methylpyrrolidin-2-ylidene)-benzenesulfonamide[18] (CAS 19734-35-1). Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3n** as a white solid (26 mg, 40% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 3.56−3.46 (m, 2H), 2.92 (m, 5H), 2.39 (s, 3H), 2.12−1.94 (m, 2H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 169.8, 141.9, 123.0, 128.1, 126.3, 51.2, 31.0, 30.5, 20.4, 18.8. MS m/z: $[M + H]^+$ calcd for $C_{12}H_{17}N_2O_2S$, 253.1; found, 253.2.

3p, Methyl 2-((*tert*-Butoxycarbonyl)amino)-5-(dimethylamino)-5-(tosylimino)pentanoate. Purification by column chromatography (30% EtOAc in *n*-pentane) afforded **3p** as a white solid (37 mg, 34% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.77 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.33 (br, 1h), 4.22 (m, 1H), 3.71 (s, 3H), 3.23 (s, 3H), 3.02 (m, 5H), 2.39 (s, 3H), 2.19 (m, 2H), 1.42 (s, 8H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 172.1, 167.6, 142.4, 141.6, 129.0, 126.0, 78.6, 53.4, 51.5, 38.0, 37.7, 28.0, 27.7, 27.2, 20,4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{32}N_3O_6S$, 442.2007; found, 442.2019.

4b, *N*-(Tosylcarbamoyl)benzamide·TEA Salt (CAS 100970-19-2).[30] Purification by column chromatography (1% MeOH and 2% TEA in acetone) afforded **4b** as a white solid (82 mg, 87% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.95 (d, J = 7.8 Hz, 2H), 7.82 (d, J = 7.9 Hz, 2H), 7.56 (d, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 2.95 (q, J = 7.2 Hz, 6H), 2.28 (s, 3H), 1.13 (t, J = 7.2 Hz, 9H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 167.6, 156.8, 143.3, 141.3, 134.6, 133.0, 129.1, 128.5, 127.7, 46.6, 21.1, 9.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_4S$, 319.0747; found, 319.0768.

4c, 4-Methoxy-*N*-(tosylcarbamoyl)benzamide·TEA Salt. Purification by column chromatography (1% MeOH and 2% TEA in acetone) afforded **4c** as a white solid (88 mg, 78% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.89 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.3 Hz, 1H), 7.60−7.50 (m, 2H), 7.40 (t, J = 7.9 Hz, 1H), 7.27 (dd, J = 14.8, 8.0 Hz, 2H), 7.19−7.14 (m, 1H), 3.84 (s, 3H), 2.35 (s, 3H), 1.19 (t, J = 7.2 Hz, 9H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 160.5, 135.3, 130.3, 129.4, 129.33, 128.1, 127.7, 120.9, 119.7, 113.2, 55.6, 46.6, 21.2, 9.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_5S$, 349.0853; found, 349.0849.

4d, *N*-Methyl-*N*-(tosylcarbamoyl)acetamide·TEA Salt. Purification by column chromatography (1% MeOH and 2% TEA in acetone) afforded **4d** as a white solid (64 mg, 69% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.35−7.22 (d, J = 8.2 Hz, 2H), 3.29 (q, J = 7.3 Hz, 6H), 3.13 (s, 3H), 2.39 (s, 3H), 2.34 (s, 3H), 1.32 (t, J = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 174.3, 142.0, 129.5, 129.0, 127.6, 126.3, 46.2, 31.4, 20.5, 8.1. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for $C_{11}H_{13}N_2O_4S$, 269.0591; found, 269.0606.

4e, *N*-Benzyl-*N*-(tosylcarbamoyl)acetamide. Purification by column chromatography (1% MeOH in acetone) afforded **4e** as a white solid (17 mg, 21% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.02−7.96 (m, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.39−7.28 (m, 3H), 7.18 (m, 2H), 5.06 (s, 2H), 2.49 (s, 3H), 2.35 (s, 2H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 178.0, 151.3, 146.0, 137.8, 137.3, 130.5, 129.8, 129.5, 128.4, 127.1, 48.5, 25.5, 21.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{19}N_2O_4S$, 347.1066; found, 347.1065

4g, *N*-(((4-Nitrophenyl)sulfonyl)carbamoyl)acetamide·TEA Salt. Purification by column chromatography (1% MeOH and 2% TEA in acetone) afforded **4g** as a white solid (86 mg, 89% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.24 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 8.8 Hz, 2H), 3.28 (q, J = 7.3 Hz, 6H), 2.00 (s, 3H), 1.30 (t, J = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 171.8, 157.5, 150.4, 149.0, 128.5, 128.1, 123.4, 46.4, 21.6. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for $C_9H_8N_3O_6S$, 286.0132; found, 286.0124.

4h, *N*-(((4-Methoxyphenyl)sulfonyl)carbamoyl)acetamide·TEA Salt.[31] (CAS 99069-29-1). Purification by column chromatography (1% MeOH and 2% TEA in acetone) afforded **4h** as a white solid (78 mg, 84% yield). ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.87 (d,

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J = 8.9 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 3.84 (s, 3H), 2.91 (t, J = 7.2 Hz, 6H), 2.08 (s, 3H), 1.15 (t, J = 7.2 Hz, 9H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 172.7, 162.1, 129.1, 128.6, 113.3, 55.0, 46.0, 23.4. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for $C_{10}H_{11}N_2O_5S$, 271.0387; found, 271.0380.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02894.

Reaction setup and ^{1}H and ^{13}C spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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