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Development of an Acyl Sulfonamide Anti-Proliferative Agent, LY573636 · Na†

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Abstract:

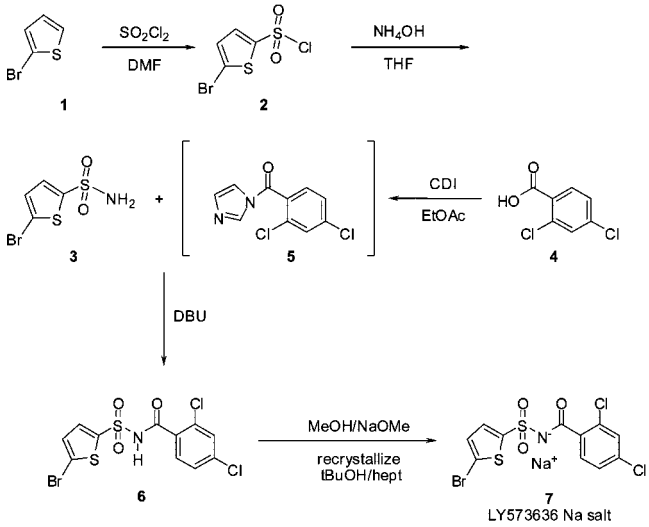
The synthesis of 5-bromo-thiophene-2-sulfonic acid 2,4-dichlorobenzoylamide sodium salt on multikilogram scale is described. The initial clinical supplies were made using carbonyl diimidazole to converge the two fragments. A more efficient acid chloride process has been developed, which also provides better control of impurities and color throughout the synthesis.

1. Introduction

The acyl sulfonamide LY573636·Na has been recently reported[1] as having potent antitumor activity against a variety of tumor xenografts in animal models including: colon, lung, breast, ovary and prostate. These encouraging results led to the need for more material for clinical trials. Initial supplies were met using the chemistry outlined in Scheme 1.

Handling concerns and cost of 1,1′-carbonyldiimidazole (CDI) were seen as a liability in such a simple coupling, especially since there was neither stereochemistry to preserve nor delicate functionality on the acid. In this case CDI is more expensive than the carboxylic acid being coupled. The development of this synthesis focused on minimization and control of impurities, and reduction in environmental impact.†

Scheme 1. **Initial synthesis of LY573636·Na**

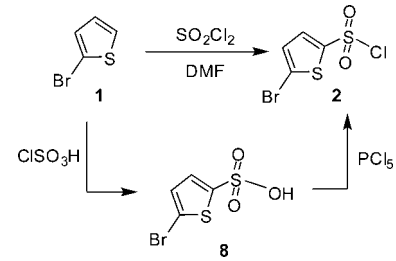


2. Results and Discussion

The initial synthesis of LY573636 as outlined in Scheme 1 is very straightforward but a requirement for tight impurity control led to further process optimization at each step. The short synthesis and simple structure of the API and related substances made it difficult to separate impurities during processing so minimization at their introduction/generation was essential. Below is described the development of each of the steps with special attention to impurity generation and fate.

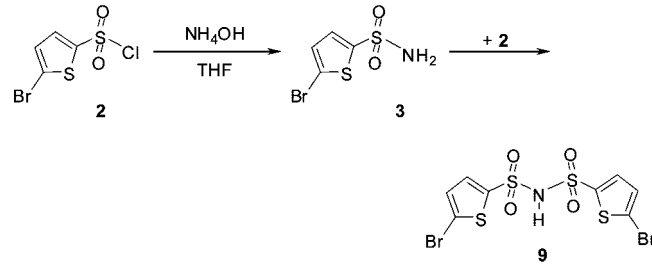
2.1. Preparation of Sulfonyl Chloride 2. 2-Bromothiophene **1** is a bulk commodity chemical which can be processed under well established conditions[2] to give the corresponding sulfonyl chloride **2**, as shown in Scheme 2. Impurities seen in **2** from either route included some that originated from the quality of the bromothiophene, as well as the bis-thiophene sulfone, and sulfonic acid. The sulfonylchloride **2** is a low-melting solid that can be distilled under reduced pressure or crystallized from alkanes.

Scheme 2. **Preparation of sulfonyl chloride 2**



2.2. Preparation of Sulfonamide 3. Initially the sulfonyl chloride was dissolved in 2 volumes of THF, and ammonium hydroxide was added to the solution. This resulted in ∼3−5% of the dimer impurity **9**, which is only partially rejected during the isolation and therefore carried through the synthesis (Scheme 3).

Scheme 3. **Preparation of sulfonamide 3**



Surprisingly, inverse addition (sulfonyl chloride into ammonium hydroxide) did not reduce the levels of **9**. At 2 volumes of THF, the reaction mixture is biphasic. The formation of this impurity is dependent on the solubility of the product and miscibility of the solvent in the aqueous ammonium hydroxide. As the reaction progressed, the sulfonamide quickly saturated the organic layer but could be easily deprotonated and taken into the aqueous phase, where it competed with the ammonia.

† This paper is dedicated to the memory of our friend and former colleague Dr. Christopher R. Schmid.

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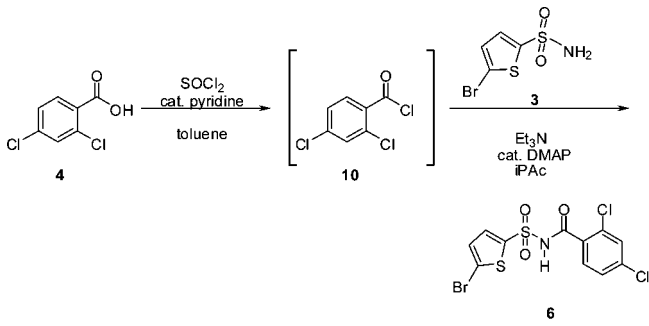
At 6 volumes of THF, the level of the dimer **9** was reduced from 4% to 2%. Switching solvents to an ester greatly reduced the level of dimer seen to <0.5% in EtOAc or iPAc. Unfortunately the degradation of both solvents was seen, which gave >1% of acetamide in reaction mixtures. Since residual acetamide needs to be controlled to the ppm level,[3] these solvents were considered undesirable. 2-Methyl tetrahydrofuran was stable to the ammonium hydroxide conditions and behaved like the ester solvents, thus minimizing the dimer **9** formation to <0.5%.

The initial isolation involved the addition of water followed by distillation to remove 2-methyltetrahydrofuran. Variability in the dimer levels was due to varying levels of ammonia remaining after the solvent distillation. To achieve more consistent ammonia removal, the aqueous layer was separated after neutralization of the excess ammonium hydroxide with HCl. The product was then crystallized by adding water to the final organic phase and distilling off the organic solvent. Since impurity **9** is sufficiently more acidic than the desired product **3**, it can be selectively removed by adding sodium bicarbonate to the slurry of product **3** in water. This process resulted in pure (>99.9%) sulfonamide in 96% yield.

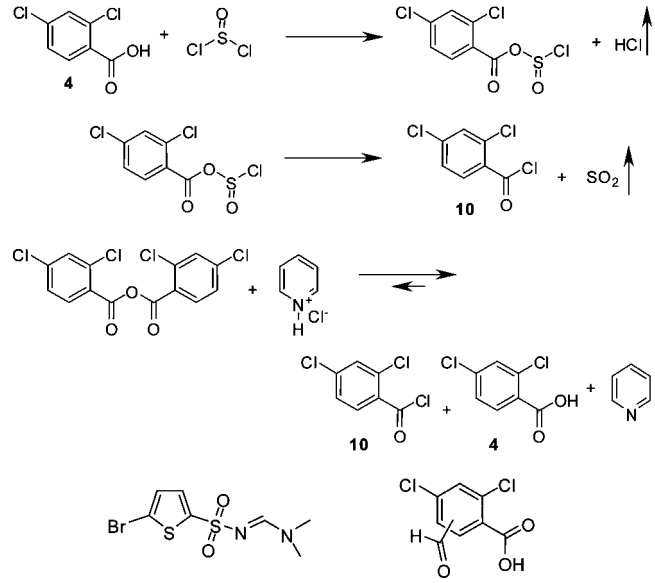
2.3. Preparation of Acyl Sulfonamide 6. An acid chloride process was developed to replace the CDI process for the activation of the benzoic acid, as a separate step *via* thionyl chloride in toluene. Using thionyl chloride is advantageous in comparison to using CDI on the basus if synthetic simplicity, cost,[4] and preferred liquid handling versus a hygroscopic solid (Scheme 4).

Scheme 4. **Preparation of acyl sulfonamide 6**



During the acid chloride formation, the symmetrical anhydride was formed in ~5% yield (Scheme 5). Pyridine was preferred as the catalyst to decompose the symmetrical anhydride as a soluble source of chloride,[5] since DMF formed new impurities (Figure 1). Toluene was selected as the solvent for the acid chloride formation, since it is compatible with the reagents and product **10** and because **6** could be easily isolated from toluene/heptane. After the reagents were combined and heated, the mixture was distilled to remove excess thionyl chloride, resulting in a toluene solution of the acid chloride in essentially quantitative yield.

Scheme 5. **Formation and decomposition of symmetrical anhydride**



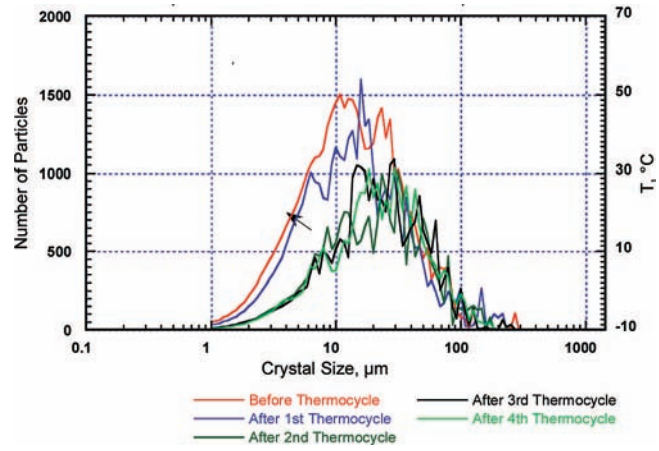


Figure 1. **New impurities formed when DMF was used as the catalyst.**

Online mass spectrometry data were acquired during the development and scale-up of the acid chloride using thionyl chloride. Gas evolution was found to be an indicator of reaction progress and degassing, as SO_2 and HCl are byproducts. Upon scale-up, gas removal rates were slower, even when N_2 was

(1) (a) De Dios, A.; Grossman, C. S.; Hipskind, P. A.; Lin, H. S.; Lobb, K. L.; Lopez De Uralde Garmendia, B.; Lopez, J. E.; Mader, M. M.; Richett, M. E.; Shih, C. WO Patent 2003/035629, 2003. (b) Lobb, K. L.; Hipskind, P. A.; Aikins, J. A.; Alvarez, E.; Cheung, Y.; Considine, E. L.; De Dios, A.; Durst, G. L.; Ferritto, R.; Grossman, C. S.; Giera, D. D.; Hollister, B. A.; Huang, Z.; Iversen, P. W.; Law, K. L.; Li, T.; Lin, H.-S.; Lopez, B.; Lopez, J. E.; Martin Cabrejas, L. M.; McCann, D. J.; Molero, V.; Reilly, J. E.; Richett, M. E.; Shih, C.; Teicher, B.; Wikel, J. H.; White, W. T.; Mader, M. *J. Med. Chem.* **2004**, *47*, 5367–5380. (c) Mader, M.; Shih, C.; Considine, E.; De Dios, A.; Grossman, C.; Hipskind, P.; Lin, H.; Lobb, K.; Lopez, B.; Lopez, J.; Cabrejas, L.; Richett, M.; White, W.; Cheung, Y.; Huang, Z.; Reilly, J.; Dinn, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 617–620.

(2) (a) Sone, T.; Abe, Y.; Sato, N.; Ebina, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1063–1064. (b) Igarashih, Y.; Nobeshima, H. Japanese Patent JP-143060, 2004. (c) Chan, M. F.; Kois, A.; Verner, E. J.; Raju, B. G.; Castillo, R. S.; Wu, C.; Okun, I.; Stavros, F. D.; Balaji, V. N. *Bioorg. Med. Chem.* **1998**, *6*, 2301–2316.

(3) Acetamide is listed by IARC as a Level IIb compound "sufficient evidence in experimental animals for the carcinogenicity of acetamide". *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* ; 1999; Vol. 71, p 1211.

(4) Aldrich prices for the largest standard package is $71/mol for CDI, $15/mol for oxalylchloride, and $14/mol for 2,4-dichlorobenzoic acid.

(5) (a) Cason, J.; Reist, E. *J. Org. Chem.* **1958**, *23*, 1492–1496. (b) Wirth, D. In *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; Vol. 7, pp 4873−4876.

purged through the reactor. The formation of an insoluble scum in the reactor was attributed to the poor removal of reactive byproducts such as SO_2.[6] Additionally, the acid chloride solutions were golden in color, unlike the colorless solutions prepared in the laboratory. Although the initial scale-up of this chemistry used thoinyl chloride, future preparations of the acid chloride **10** will use oxalyl chloride since the byproducts (CO and CO_2) are expected to be more innocuous.

With the acid chloride solution in hand, various base/solvent combinations were tried. Schötten−Baumann conditions with 1.3 equiv of acid chloride failed to go to completion, due to the relative rate of hydrolysis vs coupling at room temperature. More equivalents of acid chloride **10** would have overcome the hydrolysis issue, yet would have resulted in larger amounts of benzoic acid **4** to reject in the workup and isolation.

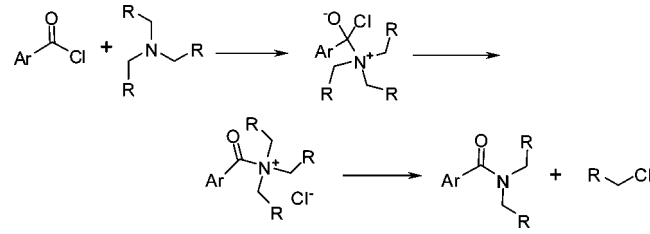
Initial results using solid sodium carbonate in refluxing iPAc appeared promising. This approach was later abandoned due to variability in reaction completeness. Careful analysis showed that water level in the reaction mixture was critical. For example, if the reaction was too dry (200 ppm water), no reaction occurred because no Na_2CO_3 was in solution; if the reaction mixture was too wet (0.4% water), hydrolysis of acid chloride competed with the desired coupling.

Alkyl tertiary amines resulted in complete consumption of **3** without the level of competing hydrolysis as seen in the other approaches. Therefore, a toluene solution of acid chloride **10** was added to an iPAc solution of sulfonamide **3** with 2.5 equiv of alkyl tertiary amine at 70−80 °C. Triethylamine (TEA) was preferred over Hünig's base for ease of workup. In both cases the initial product formed is the amine salt of **6**. With TEA, the amine salt of **6** is soluble in warm solvent, allowing removal of some of the benzoic acid **4** by an initial water wash.

With these conditions, a new amidine impurity **12** was seen, at 1−4%, which was not removed in the isolation. It is proposed that this impurity originates from diacylated product **11** (Scheme 6). The addition of catalytic pyridine minimized the formation of the amidine impurity **12**, presumably through decomposition of the diacylated product **11**.[7]

Color is an important attribute for a parenteral product; however, the sulfonamide **6** from the original process was consistently yellow to tan. Color could be removed in the crystallization at the expense of yield. Color was seen in the reaction mixtures at the end of the acid chloride addition, which was attributed to the reaction of the acid chloride with the tertiary amine.

Scheme 7. **Benzamide formation**



Combining just tertiary amines with the acid chloride showed that more color was seen with ethyl amines and much less color with methyl or aromatic amines. Therefore, dimethylbutylamine and pyridine were compared in the coupling reaction. Dimethylbutylamine resulted in improvement in color but contained large amounts (0.35%) of benzamides (Scheme 7). Pyridine, which is a weaker base, in place of triethylamine resulted in less color, no benzamides, but incomplete reactions.

Triethylamine with catalytic pyridine resulted in low benzamides and amidines and reaction completeness, but the products were colored. Alternative acylation catalysts were explored as a way to increase the rate of the reaction and minimize color formation (Table 1). To quantitate the level of color, the product was assayed at 400 nm. Catalytic 4-dimethylaminopyridine (DMAP)[8] resulted in the ability to perform the reaction at a lower temperature (55 °C, the temperature at which the amine salt of **6** was soluble), resulting in white to off-white products in higher yields.

The workup consisted of a water wash, two aqueous acid washes, and another water wash. The final organic phase was distilled to result in a toluene concentrate of the product. After seeding and cooling, heptane was added, resulting in a 91- 93% isolated yield and 99.8% purity.[9]

There is limited literature on the formation of acyl sulfonamides with acid chlorides;[10] we wanted to see if this chemistry could be generalized across the class. Several substrates were screened, and the results are shown in Table 2. This process provides consistently high yields

Scheme 6. **Formation of amidine impurity**

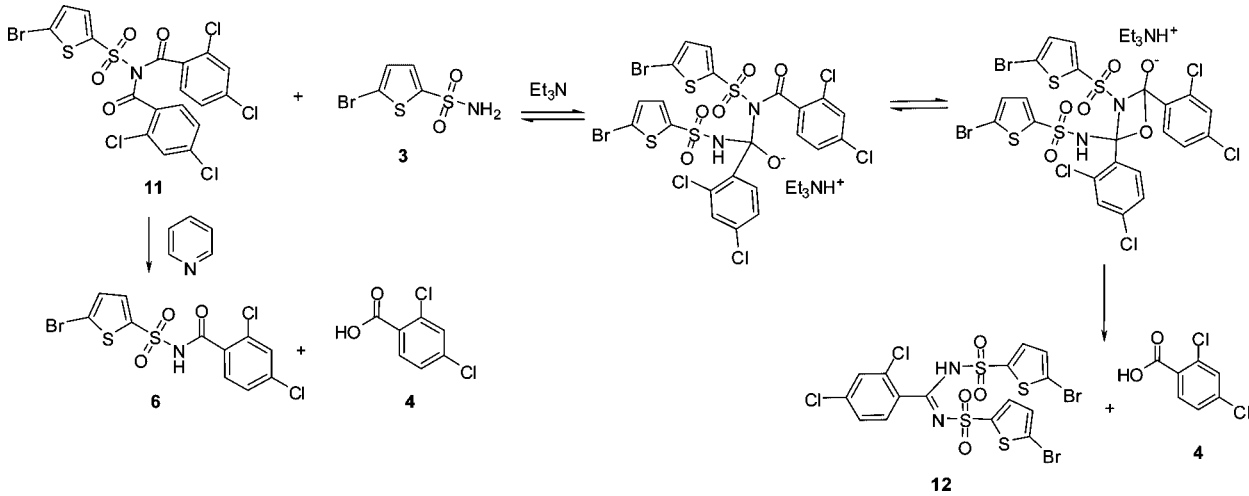
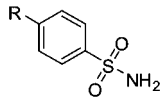
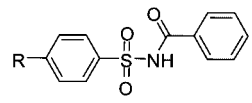
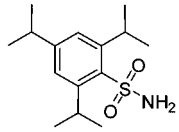
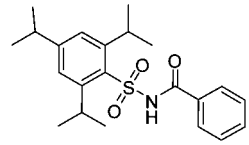
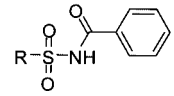
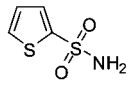
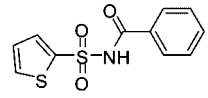
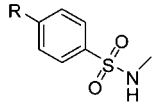
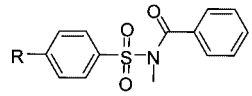
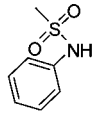
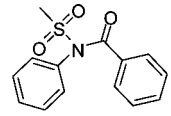
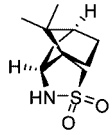
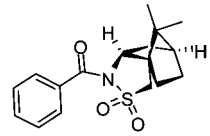
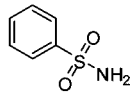
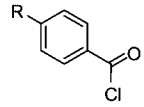
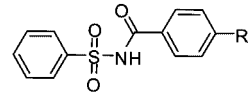
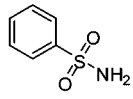
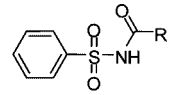
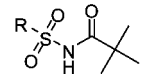


Table 1. **Use of acylation catalysts at 1 mol % in the formation of acylsulfonamide 6 at 55 °C**

catalyst	product color	area at 400 nm	% sulfonamide **3** remaining	area % amidine **12**
pyridine	light yellow	318.2	0.08	0.33
2-methoxypyridine	light yellow		1.87	4.39
N-methylimidazole	white	50.2	0.02	0.11
4-dimethylaminopyridine	white	22.5	0.03	0.04
4-methoxypyridine	light yellow	48.9	0.00	0.02

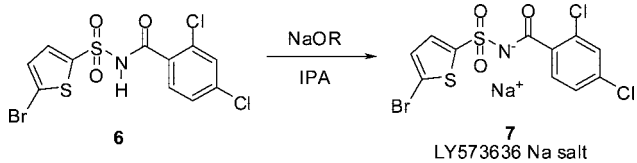
Table 2. **Preparation of acyl sulfonamides**

Entry	Sulfonamide	Acid Chloride	N-Acylsulfonamide	Isolated Yield (%)
1		PhCOCl		a) R=H, 90% b) R=Cl, 91% c) R=OMe, 85% d) R=NO_2, 93% e) R=Me, 96%
2		PhCOCl		97%
3		PhCOCl		a) R = Me, 96% b) R = t-Bu, 69%
4		PhCOCl		97%
5		PhCOCl		a) R = H, 100% b) R = Me, 100%
6		PhCOCl		94%
7		PhCOCl		97%
8				a) R = OMe, 83% b) R = Me, 83% c) R = Cl, 96% d) R = CF_3, 93%
9				a) R = Me, 89% b) R = t-Bu, 97% c) R = CCl_3, 79%
10				a) R = Me, 96% b) R = t-Bu, 69%

across a variety of functional groups on both coupling partners, proving to be a more general method than those in previous communications.[11]

2.4. Salt Formation. The final step to make the API is sodium salt formation (Scheme 8). Since impurity control has been maintained at each step, there was no need for a recrystallization if the correct form could be made directly. A screen of several conditions indicated that IPA/*n*-heptane would consistently give the desired stable form. As a parenteral oncolytic, there were several additional challenges to making

Scheme 8. **Preparation of sodium salt 7**



6 **7**
LY573636 Na salt

(6) SO_2 is very corrosive to Hastelloy and stainless steel. The insoluble scum and colored acid chloride solutions are thought to be related to the presence of SO_x byproducts. Trace levels of sulfuryl chloride in thionyl chloride will lead to the formation of SO_3. There are some spectroscopic data in support of the reaction of symmetrical anhydrides with SO_3 at low temperature. Montoneri, E.; Giuffre, L.; Cassago, M.; Tempesti, E.; Fornaroli, M. *Can. J. Chem.* **1977**, *55*, 355–359. Montoneri, E.; Tempesti, E.; Giuffre, L.; Cassago, M.; Castoldi, A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 662–667.

this API: control of trace levels of color and containment to limit exposure to the product. The sulfonamide proton is quite acidic,[12] and any number of sodium bases can make the salt.

However, sodium alkoxide solutions are colored due to unknown impurities, and the solids are hygroscopic. Sodium hydroxide is not only effective at making the salt but also brings in enough water to increase the solubility allowing for polish filtration. The water could then be removed by distillation with IPA, resulting in crystallization of the API.

Since the API is dissolved and then lyophilized in the drug product, particle size is not critical for clinical performance. Instead it was desirable to control particle size for processing performance: filtration rate, drying profile, and handling (static and dust). To this end, xonce the product crystallized from IPA, *n*-heptane was added to boost recovery. The slurry was ripened with a slow heating and cooling cycle, favoring crystal growth and a gradual increase in the average particle size (Figure 2).

These larger particles processed well with an estimated cake flux[13] of >3000 L/min per m^2 and a drying time of <20 h at ~15 kg scale. The material was free flowing without any need to delump or process further.

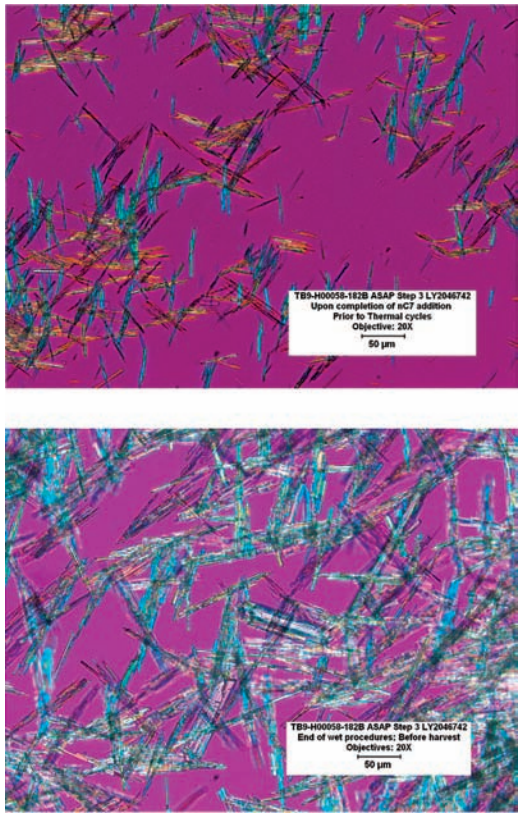


Figure 2. **Changes to particle size of acylsulfonamide sodium salt during thermocycles.**

3. Conclusion

A robust process that can produce high-quality API has been developed and demonstrated. A complete understanding of impurity generation and control was critical to improving the efficiency of the process while achieving an overall yield of 77%. A simple calculation of process mass intensity (kg in/kg out) shows a 45% reduction in environmental impact over the original process. We found our small-scale (~20 g) modeling of the reactions to be predictive of scale-up results, even for the crystallizations. The noticeable exception was the formation of the scum in the reactor during the acid chloride formation which was attributed to poor vapor−liquid mass transfer which is a common "scale-up effect" that is difficult to model. The final process is summarized in Scheme 9.

4. Experimental Section

Described below are the preferred conditions to make LY573636·Na; unfortunately, some of these developments took place after the pilot-plant scale-up, using slightly different conditions (pyridine as the coupling catalyst instead of DMAP and thionyl chloride for the preparation of the acid chloride). These alternative procedures, at multikilogram scale, can be found in the Supporting Information.

5-Bromothiophene-2-sulfonamide (3). Sulfonyl chloride **2** (200.36 g, 766.1 mmol) and 2-methyltetrahydrofuran (1.2 L) were combined under N_2, forming a light-yellow solution. The solution was chilled to 0−5 °C. Concentrated aq NH_4OH (384.29 g, 3.07 mol) was added dropwise to the reaction over 0.5 h. The reaction was allowed to warm to room temperature, and DI water (600 mL) was added. The pH of the reaction mixture was adjusted to pH ~2 using 37% conc. aq HCl (484.1 g, 4.85 mol). The phases were separated, the aqueous layer was back extracted with 2-methyltetrahydrofuran (200 mL), and the organic layers were combined. DI water (1 L) was added to the organic layer, and the mixture was distilled at atmospheric pressure until the reactor temperature reached 99 °C. A total of 1475 mL of distillate was collected. The mixture was allow to cool to room temperature, during which time a slurry of sulfonamide **3** formed. Once at room temperature, solid sodium bicarbonate (19.65 g, 233.9 mmol) was added, and the slurry was stirred for 90 min. The product was filtered, and the wetcake was washed with DI water (600 mL). The product was dried *in vacuo* at 45 °C overnight, resulting in 178.54 g (734.9 mmol, 95.9% yield) of off-white product, containing nonde-

(7) Diacylated product **11** has been prepared and isolated. When **11** was combined with sulfonamide **3** and Et_3N, amidine **12** was formed. When **11** was combined with pyridine, **6** and **4** were formed. In the coupling to form **6**, no **11** was seen in the isolated **6**.

(8) Hasegawa, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423–428.

(9) Most of the impurities that result are impurities derived from the quality of benzoic acid **4**.

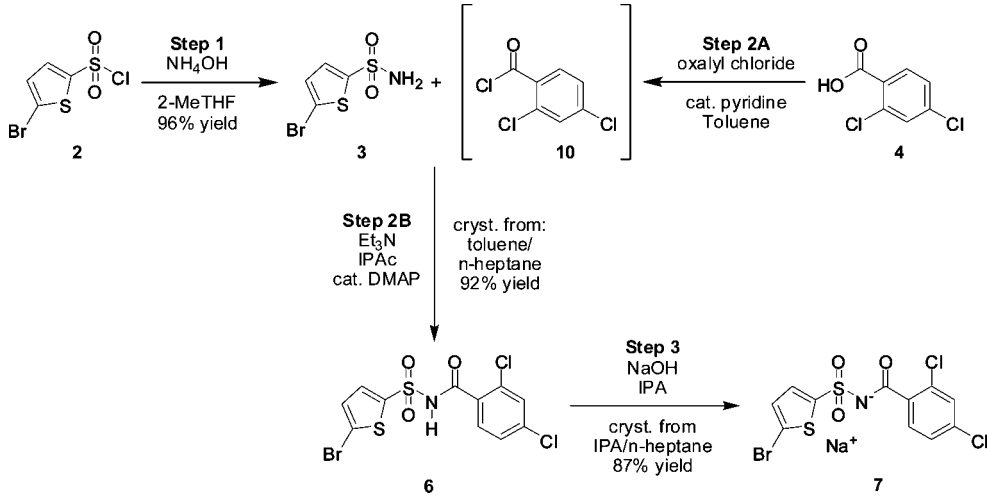
(10) (a) Cremlyn, R. J.; Swinbourne, F. J.; Yung, K.-M. *J. Heterocycl. Chem.* **1981**, *18*, 997–1006. (b) Kazhemekaite, M.; Stumbryavichyute, Z.; Astrauskas, V. *Khim.-Farm. Zh.* **1997**, *31*, 37–39. (c) Kondo, K.; Sekimoto, E.; Miki, K.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2973–2974. (d) Kondo, K.; Sekimoto, E.; Nakao, J.; Murakami, Y. *Tetrahedron* **2000**, *56*, 5843–5856. (e) Ishizuka, N.; Matsumura, K.; Hayashi, K.; Sakai, K.; Yamamori, T. *Synthesis* **2000**, 784–788.

(11) For methods using anhydrides see:(a) Kravchenya, N. A. *Khim.-Farm. Zh.* **1990**, *24*, 49–50. (b) Martin, M.; Roschangar, F.; Eaddy, J. *Tetrahedron. Lett.* **2003**, *44*, 5461–5463. (c) Singh, D.; Singh, P.; Samant, S. *Tetrahedron. Lett.* **2004**, *45*, 4805–4807. For a catalytic rhodium method see: (d) Chan, J.; Baucom, K. D.; Murry, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14106–14108. High yields have been reported using carbodiimides: (e) Matassa, V. G.; Brown, F. J.; Bernstein, P. R.; Shapiro, H. S.; Maduskuie, T. P.; Cronk, L. A.; Vacek, E. P.; Yee, Y. K.; Snyder, D. W.; Krell, R. D.; Lerman, C. L.; Maloney, J. J. *J. Med. Chem.* **1990**, *33*, 2621–2629. (f) Johnson, D. C., II.; Widlanski, T. S. *Tetrahedron Lett.* **2001**, *42*, 3677–3679.

(12) A pK_a of 2.2 was determined experimentally via titration.

(13) Flux is calculated by dividing the flow rate (L/min) by the filter area (π·(filter diameter/2))2.

Scheme 9. **Final acyl sulfonamide**



tectable levels of dimer **9**. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 7.79 (s, 2H); 7.38 (d, J = 4.0 Hz, 1H); 7.30 (d, J = 4.0 Hz, 1H). ^{13}C NMR (d_6-DMSO, 100 MHz): δ 146.6, 130.9, 130.6, 116.8.

2,4-Dichlorobenzoyl chloride (10). Benzoic acid **4** (17.41 g, 91.2 mmol) was combined with toluene (102.7 mL) and pyridine (0.225 g, 2.84 mmol), and heated to 60 °C. Oxalyl chloride (14.95 g, 117.8 mmol) was added over 15−30 min. The mixture was held at 60 °C for at least 1 h. The solution was distilled at atmospheric pressure; after 52 mL of distillate was collected, 68.0 mL of fresh toluene was added back, and an additional 65 mL was distilled. This resulted in 70.05 g of a solution of 26.02 wt % acid chloride **10** (87.02 mmol, 95.5% yield). Cooling below RT, the trace of pyridine-HCl that was present precipitated.

***N*-(5-Bromothiophen-2-ylsulfonyl)-2,4-dichlorobenzamide (6).** Sulfonamide **3** (5.02 g, 20.65 mmol) was combined with isopropylacetate (45 mL), triethylamine (5.24 g, 51.8 mmol), and DMAP (13.3 mg, 108.5 umol) under N_2, forming a light-yellow solution. The mixture was heated to 55 °C, before the toluene solution of acid chloride **10** (1.64 M, 13.59 g, 22.31 mmol) was added over 1 h, maintaining the temperature at 50−60 °C. During the addition, the amine salt precipitated, forming an off-white slurry. The container from which the acid chloride was added was rinsed with toluene (5 mL), and this rinse was added to the reaction mixture. After the addition was complete, the mixture was maintained at 50−60 °C for 1 h.

DI water (30.55 g) was added, and the mixture was heated to 45−55 °C, dissolving the salts and resulting in two phases. The lower aqueous phase was drawn off and discarded. While still at 45 −55 °C, the mixture was washed with 0.7 M HCl (35.91 g, 24.9 mmol). The layers were separated, and the aqueous phase was discarded. The organic phase was washed (at RT) with 0.7 M HCl (35.64 g, 24.7 mmol), followed by DI water (25.1 g).

The washed organic phase was transferred to a flask with iPAc (4.93 g, 5.66 mL) and atmospherically distilled, collecting 33.63 g of distillate, diluting with toluene (22.07 g, 25.3 mL), distilling to 18.7 g, diluting with toluene (21.43 g, 24.6 mL), and distilling to 23.5 g. This resulted in a mixture with low levels of iPAc and TEA. The mixture was cooled to 45−55 °C, seeded with acylsulfonamide **6** (5 mg), and held at this temperature for 1 h, before cooling to 20−25 °C over at least 1 h. After reaching 25 °C, *n*-heptane (60 mL) was added over 2 h. The white slurry was stirred at 20−25 °C for at least 1 h before the slurry was filtered. The wet cake was washed with 10 mL of 2:1 *n*-heptane/toluene, followed by 10 mL of *n*-heptane. The product was dried at 45 °C *in vacuo* with N_2 purge. This resulted in acyl sulfonamide product **6** (8.07 g, 19.39 mmol, 93.9% yield), <0.3% impurities, that is white in color. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 7.74 (d, J = 2.4 Hz, 1H); 7.71 (d, J = 4.8 Hz, 1H); 7.58 (d, J = 8.4 Hz, 1H); 7.51 (dd, J = 8.4, 2.0 Hz, 1H); 7.42 (d, J = 4.0 Hz, 1H). ^{13}C NMR (d_6-DMSO, 100 MHz): δ 164.5, 139.9, 136.2, 135.1, 132.4, 131.3, 131.2, 130.6, 129.5, 127.5, 121.1.

Sodium (5-Bromothiophen-2-ylsulfonyl)(2,4-dichlorobenzoyl)amide (7). Acyl sulfonamide **6** (18.335 kg, 44.17 mol), isopropyl alcohol (185 L), 51% aqueous NaOH solution (3.350 kg, 42.71 mol, 0.967 equiv), and DI water (2.215 kg) were combined under N_2. The slurry was stirred at 25 °C until it became a clear solution. This solution was passed through a carbon filter followed by filtering through a 0.45 μm filter, followed by a 0.22 μm filter, and was collected in the crystallization vessel, rinsing the initial vessel and filters with IPA (90 L).

The filtered solution was atmospherically distilled until 55 L of solution remained in the crystallization vessel. The concentrated solution was cooled to 25 °C, seeded with acyl sulfonamide sodium salt **7** (0.178 kg), and stirred for at least 30 min. *n*-Heptane (127.5 L) was added, causing the product to crystallize. The resulting slurry was stirred at 25 °C for at least 30 min. The diluted slurry was thermally cycled from 25 to 60 °C at a rate of 0.5 °C/min three times. After ripening, the slurry was cooled at 0.5 °C/min to −5 °C and stirred for at least 1 h before it was filtered. The wetcake was washed with a 95:5 *n*-heptane/IPA mixture (92.5 L of *n*-heptane, 5 L IPA) precooled to −5 °C. Finally, the wet cake was dried *in*

vacuo at 40 °C with N_2 purge. This resulted in acyl sulfonamide sodium salt product **7** (16.838 kg, 38.52 mol, 87.2% yield), that is white in color. ^{1}H NMR (d_6-DMSO, 400 MHz): δ 7.53 (d, J = 8.4 Hz, 1H); 7.49 (d, J = 1.6 Hz, 1H); 7.35 (dd, J = 8.4, 1.6 Hz, 1H); 7.31 (d, J = 4.0 Hz, 1H); 7.14 (dd, J = 4.0, 0.8 Hz, 1H). ^{13}C NMR (d_6-DMSO, 100 MHz): δ 169.9, 148.7, 138.7, 132.9, 131.4, 131.0, 129.3, 129.2, 129.0, 126.6, 114.6.

General Procedure for the Preparation of Acyl Sulfonamides. Into a 100 mL vessel containing a stir bar were added (under N_2) sulfonamide (5 mmol, limiting reagent), iPAc (10.90 mL), triethylamine (2.5 equiv for primary sulfonamides, 1.5 equiv for secondary sulfonamides), and DMAP (0.5 mol %), forming a clear solution. The solution was heated under a N_2 atmosphere.

In a vial was added acid chloride (1.10 equiv) and toluene (3.65 mL). This solution was drawn up into a 5 mL syringe and added to the sulfonamide/iPAc solution at 55 °C over 1 h via syringe pump, rinsing the syringe and vial with toluene (1.20 mL). After the addition was complete, the mixture was stirred for at least 1 h at 55 °C. In all cases the reaction was complete after 1 h, but additional time at 55 °C was not detrimental to the reaction.

After cooling to room temperature, the residual acid chloride was quenched with DI water (1.1 mL), and 0.7 M HCl (16.90 mL) was added, dissolving the amine salts. The aqueous phase was drawn off and assayed. If necessary, the aqueous phase was extracted with iPAc. The organic phases were combined and stripped to dryness, resulting in a solid (except 2 entry 5, which were oils). The product was dried at 50 °C *in vacuo* with N_2 purge.

In the case of 2 entries 1d, 4, and 8c, a solid resulted upon the addition of aq HCl. In those cases, the solid was filtered off, and the organic phase was separated and concentrated to dryness, resulting in two crops of product. In some cases, if residual reagents (i.e., TEA/HCl) were seen by ^{1}H NMR, the crude product was purified by passing through a plug of silica gel with EtOAc to obtain analytically pure material.

^{1}H and ^{13}C NMR and HRMS for 22 compounds in Table 2 are given below (copies of spectra are available in the Supporting Information).

***N*-(Phenylsulfonyl)benzamide (1a):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.55 (s, 1H); 8.02 (d, J = 8.0 Hz, 2H); 7.86 (d, J = 8.0 Hz, 2H); 7.75−7.58 (m, 4H); 7.49 (t, J = 6.8 Hz, 2H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 165.4, 139.4, 133.6, 133.2, 131.4, 129.1, 128.5, 128.3, 127.6. HRMS calcd for $C_{13}H_{11}NO_3S$ *m/z* 262.0532 (MH^+), Found: 262.05350.

***N*-(4-Chlorophenylsulfonyl)benzamide (1b):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.64 (s, 1H); 8.02 (dd, J = 8.4, 0.8 Hz, 2H); 7.87 (d, J = 8.0 Hz, 2H); 7.72 (dd, J = 8.4, 0.8 Hz, 2H); 7.64−7.60 (m, 1H); 7.49 (t, J = 7.2 Hz, 2H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 165.5, 138.6, 138.2, 133.3, 131.3, 129.6, 129.3, 128.6, 128.4. HRMS calcd for $C_{13}H_{10}ClNO_3S$ *m/z* 296.0413 (MH^+), Found: 296.04137.

***N*-(4-Methoxyphenylsulfonyl)benzamide (1c):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.38 (s, 1H); 7.95 (d, J = 8.4 Hz, 2H); 7.85 (d, J = 7.2 Hz, 2H); 7.61 (d, J = 6.4 Hz, 1H); 7.48 (d, J = 14.4 Hz, 1H); 7.48 (s, 1H); 7.16 (d, J = 7.6 Hz, 2H); 3.85 (s, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 165.2, 163.1, 133.1, 131.5, 130.8, 130.1, 128.5, 128.3, 114.2, 55.7. HRMS calcd for $C_{14}H_{13}NO_4S$ *m/z* 292.0638 (MH^+), Found: 292.06442.

***N*-(4-Nitrophenylsulfonyl)benzamide (1d):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 8.45 (dd, J = 8.8, 1.2 Hz, 2H); 8.25 (dd, J = 8.8, 1.6 Hz, 2H); 7.87 (d, J = 8.4 Hz, 2H); 7.66−7.62 (m, 1H); 7.50 (t, J = 7.2 Hz, 2H), 3.43 (s, 1H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 165.9, 150.1, 144.9, 133.4, 131.3, 129.3, 128.6, 128.5, 124.4. HRMS calcd for $C_{13}H_{10}N_2O_5S$ *m/z* 307.0383 (MH^+), Found: 307.03840.

***N*-(4-Methylphenylsulfonyl)benzamide (1e):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.46 (s, 1H); 7.89 (dd, J = 8.8, 7.2 Hz, 3H); 7.85 (s, 1H); 7.64−7.60 (m, 1H); 7.49 (d, J = 14.0 Hz, 1H); 7.46 (dd, J = 13.2, 8.4 Hz, 3H); 2.40 (s, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 165.3, 144.2, 136.5, 133.2, 131.4, 129.5, 128.5, 128.3, 127.7, 21.0. HRMS calcd for $C_{14}H_{13}NO_3S$ *m/z* 276.0689 (MH^+), Found: 276.06881.

***N*-(2,4,6-Triisopropylphenylsulfonyl)benzamide (2):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.66 (s, 1H); 7.90 (d, J = 8.0 Hz, 2H); 7.61 (t, J = 6.8 Hz, 1H); 7.49 (t, J = 7.6 Hz, 2H); 7.26 (s, 2H); 4.36 (dd, J = 13.2, 6.4 Hz, 2H); 2.94−2.90 (m, 1H); 1.20 (dd, J = 6.8, 2.8 Hz, 18H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 165.6, 153.0, 150.4, 133.0, 129.2, 128.5,128.5, 128.1, 123.6, 33.3, 28.3, 24.3, 23.3. HRMS calcd for $C_{22}H_{29}NO_3S$ *m/z* 388.1941 (MH^+), Found: 388.19438.

***N*-(Methylsulfonyl)benzamide (3a):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.13 (s, 1H); 7.94 (d, J = 7.6 Hz, 2H); 7.65−7.63 (m, 1H); 7.53 (d, J = 16.0 Hz, 1H); 7.52 (d, J = 6.8 Hz, 1H); 3.37 (d, J = 4.4 Hz, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 166.4, 133.2, 132.9, 131.7, 129.2, 128.6, 128.4, 41.4. HRMS calcd for $C_8H_9NO_3S$ *m/z* 200.0375 (MH^+), Found: 200.03810.

***N*-(*tert*-Butylsulfonyl)benzamide (3b):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.94 (s, 1H minor); 11.55 (s, 1H major); 7.95 (dd, J = 8.0, 1.6 Hz, 1H); 7.88 (d, J = 8.0 Hz, 1H); 7.62 (t, J = 7.6 Hz, 1H); 7.51 (s, 1H); 7.51 (d, J = 14.4 Hz, 1H); 1.41 (s, 9H major); 1.269 (s, 1H minor). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 167.3, 165.8,132.8, 132.7, 130.7, 129.2, 128.5, 128.5, 128.4, 128.4, 128.4, 61.1, 57.0, 24.1, 24.0. HRMS calcd for $C_{11}H_{15}NO_3S$ *m/z* 264.0664 (MNa^+), Found: 264.06660.

***N*-(Thiophen-2-ylsulfonyl)benzamide (4):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.68 (s, 1H); 8.07−8.05 (m, 1H); 7.89 (d, J = 6.4 Hz, 1H); 7.88 (d, J = 8.8 Hz, 1H); 7.87 (d, J = 2.4 Hz, 1H); 7.66−7.61 (m, 1H); 7.50 (d, J = 15.6 Hz, 1H); 7.49 (d, J = 6.8 Hz, 1H); 7.24−7.21 (m, 1H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 165.5, 139.7, 134.8, 134.4, 133.3, 131.5, 128.6, 128.4, 127.5. HRMS calcd for $C_{11}H_9NO_3S_2$ *m/z* 268.0096 (MH^+), Found: 268.01000.

***N*-Methyl-*N*-(phenylsulfonyl)benzamide (5a).** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 7.99 (dd, J = 6.8, 1.2 Hz, 2H); 7.79−7.75 (m, 1H); 7.69−7.60 (m, 2H); 7.58 (dd, J = 3.2, 1.2 Hz, 1H); 7.56 (d, J = 1.6 Hz, 1H); 7.50 (d, J = 1.6 Hz, 1H);

7.48 (d, J = 4.8 Hz, 1H); 7.46 (d, J = 2.0 Hz, 1H); 3.25 (s, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 170.6, 138.2, 134.1, 133.9, 132.0, 129.3, 128.5, 128.1, 127.9, 35.9. HRMS calcd for $C_{14}H_{13}NO_3S$ m/z 276.0688 (MH^+), Found: 276.06980.

***N*-Methyl-*N*-tosylbenzamide (5b):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 7.86 (d, J = 6.8 Hz, 1H); 7.85 (s, 1H); 7.57 (d, J = 6.0 Hz, 1H); 7.56 (t, J = 4.0 Hz, 1H); 7.49 (d, J = 1.2 Hz, 1H); 7.46 (d, J = 8.0 Hz, 4H); 3.24 (d, J = 2.0 Hz, 3H); 2.42 (s, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 170.6, 144.8, 135.2, 134.0, 132.0, 129.7, 128.4, 128.1, 128.0, 35. 9, 21.1. HRMS calcd for $C_{15}H_{15}NO_3S$ m/z 290.0845 (MH^+), Found: 290.08360.

***N*-(Methylsulfonyl)-*N*-phenylbenzamide (6):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 7.51 (d, J = 1.6 Hz, 1H); 7.49 (t, J = 1.6 Hz, 1H); 7.42−7.26 (m, 8H); 3.54 (dd, J = 10.4, 1.6 Hz, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 170.3, 136.6, 133.7, 131.6, 130.4, 129.1, 128.7, 128.1, 40.6. HRMS calcd for $C_{14}H_{13}NO_3S$ m/z 276.0688 (MH^+), Found: 276.06930.

***N*-[(1*S*)-(−)-2,10-Camphorsultam]benzamide (7):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 7.65 (d, J = 1.2 Hz, 1H); 7.61 (dd, J = 16.4, 1.2 Hz, 2H); 7.48 (s, 1H); 7.48 (d, J = 14.8 Hz, 1H); 4.13−4.10 (m, 1H); 3.84 (d, J = 14.0 Hz, 1H); 3.64 (d, J = 14.0 Hz, 1H); 1.89 (d, J = 7.2 Hz, 3H); 1.84 (d, J = 10.8 Hz, 2H); 1.54−1.48 (m, 1H); 1.31 (d, J = 8.4 Hz, 1H); 1.25 (d, J = 11.6 Hz, 3H); 0.98 (s, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 169.2, 133.9, 132.4, 128.94, 128.0, 65.0, 52.6, 48.0, 47.3, 44.6, 40.1, 37.9, 32.1, 25.9, 21.1, 19.5. HRMS calcd for $C_{17}H_{21}NO_3S$ m/z 320.1315 (MH^+), Found: 320.13192.

4-Methoxy-*N*-(phenylsulfonyl)benzamide (8a): ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.38 (s, 1H); 8.07 (d, J = 13.2 Hz, 1H); 8.05 (d, J = 12.4 Hz, 1H); 7.92 (d, J = 11.6 Hz, 1H); 7.88 (s, 1H); 7.66 (dd, J = 18.0, 6.8 Hz, 2H); 7.62 (d, J = 7.6 Hz, 1H); 7.00 (d, J = 8.4 Hz, 2H); 3.79 (s, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 164.7, 163.2, 139.7, 133.5, 130.6, 129.1, 127.7, 123.5, 113.9, 55.5. HRMS calcd for $C_{14}H_{13}NO_4S$ m/z 292.0638 (MH^+), Found: 292.06400.

4-Methyl-*N*-(phenylsulfonyl)benzamide (8b): ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.46 (s, 1H); 8.03 (d, J = 6.4 Hz, 1H); 8.01 (s, 1H); 7.78 (d, J = 8.8 Hz, 1H); 7.77 (s, 1H); 7.73−7.62 (m, 3H); 7.28 (d, J = 7.6 Hz, 2H); 2.34 (s, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 165.2, 143.7, 139.6, 133.6, 129.1, 129.1, 128.6, 128.5, 127.7, 21.1. HRMS calcd for $C_{14}H_{13}NO_3S$ m/z 276.0688 (MH^+), Found: 276.06830.

4-Chloro-*N*-(phenylsulfonyl)benzamide (8c): ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.65 (s, 1H); 8.00 (dd, J = 8.4, 0.8 Hz, 2H); 7.89 (t, J = 1.6 Hz, 1H); 7.87 (t, J = 2.0 Hz, 1H); 7.71−7.56 (m, 3H); 7.54 (d, J = 4.4 Hz, 1H); 7.53 (d, J = 2.8 Hz, 1H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 164.7, 139.7, 138.0, 133.502, 130.7, 130.3, 129.0, 128.6, 127.6. HRMS calcd for $C_{13}H_{10}ClNO_3S$ m/z 296.0143 (MH^+), Found: 296.01460.

***N*-(Phenylsulfonyl)-4-(trifluoromethyl)benzamide (8d):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.95 (s, 1H); 8.05 (dd, J = 9.6, 8.4 Hz, 4H); 7.85 (d, J = 8.0 Hz, 2H); 7.73 (t, J = 7.2 Hz, 1H); 7.69 (d, J = 17.2 Hz, 1H); 7.64 (dd, J = 7.2, 1.6 Hz, 2H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 166.2, 164.6, 139.3, 135.4, 133.8, 133.1, 132.8, 132.5, 132.2, 130.1, 129.4, 129.2, 128.1, 127.7, 125.6, 125.5, 125.5, 125.5, 124.9, 122.3, 119.6. HRMS calcd for $C_{14}H_{10}F_3NO_3S$ m/z 330.0406 (MH^+), Found: 330.04080.

***N*-(Phenylsulfonyl)acetamide (9a):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 12.09 (s, 1H); 7.92 (d, J = 9.6 Hz, 1H); 7.91 (d, J = 2.4 Hz, 1H); 7.71−7.69 (m, 1H); 7.63 (t, J = 7.2 Hz, 1H); 7.61 (d, J = 7.2 Hz, 1H); 1.92 (s, 3H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 169.2, 144.6, 139.8, 134.0, 132.2, 129.5, 129.3, 127.9, 126.0, 23.7. HRMS calcd for $C_8H_9NO_3S$ m/z 200.0375 (MH^+), Found: 200.03770.

***N*-(Phenylsulfonyl)pivalamide (9b):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 11.70 (s, 1H); 7.89 (d, J = 10.0 Hz, 1H); 7.88 (s, 1H); 7.71−7.59 (m, 3H); 1.05 (s, 9H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 176.7, 139.5, 133.4, 129.0, 127.3, 39.6, 25.9. HRMS calcd for $C_{11}H_{15}NO_3S$ m/z 242.0845 (MH^+), Found: 242.08481.

2,2,2-Trichloro-*N*-(phenylsulfonyl)acetamide (9c): ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 13.18 (s, 1H); 7.90−7.83 (m, 2H); 7.60 (dt, J = 7.2, 2.4 Hz, 1H); 7.57 (d, J = 1.2 Hz, 1H); 7.54 (dd, J = 6.8, 1.6 Hz, 1H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 162.008, 144.1, 141.2, 132.6, 131.9, 129.0, 128.7, 127.2, 125.6, 94.9. HRMS calcd for $C_8H_6Cl_3NO_3S$ m/z 301.9206 (MH^+), Found: 301.92110.

***N*-(Methylsulfonyl)pivalamide (10a):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 11.26 (s, 1H); 3.22 (s, 3H); 1.14 (s, 9H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 177.8, 40.9, 39.7, 26.1. HRMS calcd for $C_6H_{13}NO_3S$ m/z 180.0688 (MH^+), Found: 180.06890.

***N*-(*tert*-Butylsulfonyl)pivalamide (10b):** ^{1}H NMR (d_6-DMSO, 400.00 MHz): δ 10.63 (s, 1H); 1.32 (s, 9H); 1.15 (s, 9H). ^{13}C NMR (d_6-DMSO, 100.00 MHz): δ 176.4, 61.1, 56.9, 40.3, 26.1, 24.0, 24.0. HRMS calcd for $C_9H_{19}NO_3S$ m/z 222.1158 (MH^+), Found: 222.11590.

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Supporting Information Available

Pilot-plant procedures for compounds **3**, **6**, and **10**, experimental procedures and characterization of impurities **11**, **12**, and **13**, and spectra of the 22 compounds in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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