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Isomerization-Free Sulfonylation and Its Application in the Synthesis of PHA-565272A

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Abstract:

$FeCl_3$ catalyzed an isomerization-free Friedel−Crafts sulfonylation between 1-naphthalenesulfonyl chloride and halobenzenes. The coupled halide was then displaced using 35% hydrazine in DMSO to provide the Fischer indole precursor. Pure 5-chloro-2-pentanone was the key for a successful Grandberg modification of Fischer indole synthesis that effectively constructed both the indole core and side chain of the target molecule. The development of these methods enabled a rapid preparation of kilogram quantities of PHA-565272A.

Introduction

PHA-565272A (**8**) was a CNS drug candidate that required kilogram quantity for preclinical studies. The initial synthesis[1] of compound **8** had several potential scale-up problems (Scheme 1). The first three steps appeared straightforward and could be run on a large scale. The use of nitrite in step 4 would require extensive safety evaluation. The use of $SnCl_2$ could make it very difficult to remove tin byproducts from the reactors. Although the Grandberg modification of Fischer indole synthesis[2] was very efficient in constructing both the indole core and its side chain, poor yields suggested that significant development work would be needed. Furthermore, the cost and availability of 1-naphthalenethiol **1** presented a long-term cost of goods and sourcing issue.

Results and Discussions

The steps that led to the Fischer precursor **6** in the initial route (Scheme 1) were quite lengthy. The limited availability of 1-naphthalenethiol (**1**) further made this route unpractical. Thus, a Friedel−Crafts sulfonylation was proposed to react halobenzenes (**9**) and naphthalene-1-sulfonyl chloride (**10**) to produce a precursor that may lead to hydrazine **6** (Scheme 2). The bulky naphthalene ring is likely to preclude the formation of the undesired *meta* isomer of halobenzenes. It was decided to simultaneously test various Lewis acids with fluoro-, chloro- and bromobenzene (**9a**−**c**) (Scheme 3). If a direct displacement of halides was not successful, chloro- and bromobenzene (**9b&c**), especially bromide, would permit a Pd-mediated hydrazone formation developed by Buchwald and Hartwig.[3,4] Immediately, we were surprised to discover a significant amount of 1,2-isomerization of sulfonyl group on the naphthalene ring (Table 1). The 1,2-isomerization of naphthalene ketone is well-known and well studied.[5,6] Surprisingly, the 1,2-isomerization of naphthalene sulfone was reported only once in a case of bis-naphthalene sulfone.[7] Therefore, a number of conditions and Lewis acids were screened. Representative results are shown in Table 1.

Most Lewis acids efficiently mediated *para*-sulfonylation of halobenzenes. Interestingly, $FeCl_3$ produced a minimal amount of the naphthalene 2-isomer (**12a**−**c**) (Table 1, Entries 1, 3, 5 and 6), while $GaCl_3$ caused significant naphthalene isomerization (Table 1, Entries, 2, 4, 7 and 8). Other Lewis acids also caused isomerization with poor yields (Table 1, Entries 9, 10 and 12) or produced messy reaction mixtures (Table 1, Entries 11, 13 and 14). The dramatic difference between $FeCl_3$ and other Lewis acids led us to a further study of the isomerization.[8]

Entries 5−8 in Table 1 shows that the isomerization proceeds more extensively at higher temperatures. This suggested that the isomerization was a thermodynamic process. We tested this hypothesis via sulfonylating fluorobenzene with both 1- and 2-naphthalenesulfonyl chloride using 1 eq. of $FeCl_3$ at several temperatures (Table 2). Entries 1−3 of Table 2 confirmed the observation that high temperature caused more isomerization (Table 1, Entries 5−8). Entries 4−6 of Table 2 further demonstrated that compound **12a** is the thermodynamically more stable product. This result is similar to that of naphthaleneketones.[5]

Faster conversion and higher yields were achieved using fluorobenzene for this sulfonylation than chlorobenzene and bromobenzene, because fluorobenzene is the most active species for Friedel−Crafts reaction. Furthermore, the lower boiling point of fluorobenzene as solvent facilitated a convenient workup and isolation. The amount of fluorobenzene could be reduced to 2−2.5 eq. with no loss in yield, though the reaction time was slightly longer. The reaction could be performed in a combination of fluorobenzene and CH_2Cl_2; however, the yield is slightly lower, and the reaction requires a longer time. This reaction was readily scaled to

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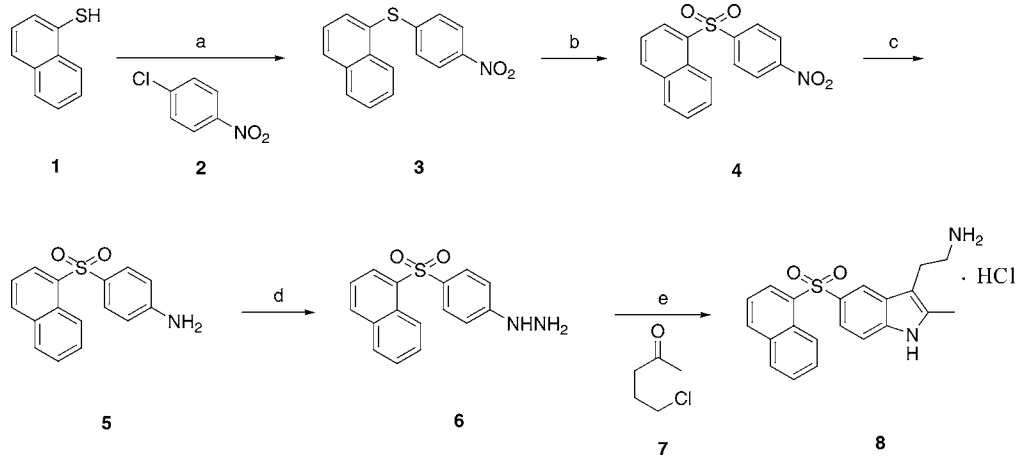
Scheme 1. **Initial synthesis**[a]



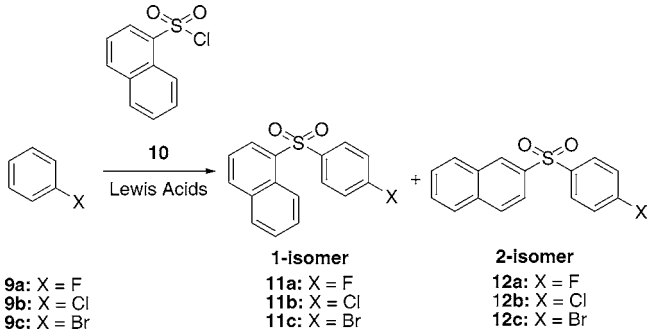
[a] Reagents and conditions: a) K_2CO_3, CH_3CN, rt, 66%; b) oxone, H_2O/MeOH/THF, 77%; c) H_2, 5% Rh/C, MeOH, 92%; d) i. $NaNO_2$/HCl, ii. $SnCl_2$, HCl; e) MeOH/H_2O, reflux, 6% crystal, 16% column.

Table 1. **Sulfonylation**[a] **with various Lewis acids**[b]

entry	Ar−X	Lewis acid	reaction temp (°C)	yield of 1-isomer (%)[c]	yield of 2-isomer (%)	entry	Ar−X	Lewis acid	reaction temp (°C)	yield of 1-isomer (%)[c]	yield of 2-isomer (%)
1	**9a**	$FeCl_3$	60	98	1	8	**9c**	$GaCl_3$	80	36	30
2	**9a**	$GaCl_3$	60	73	26	9	**9c**	TfOH	80	68	5
3	**9b**	$FeCl_3$	60	92	1	10	**9c**	TfOH	130	65	12
4	**9b**	$GaCl_3$	60	82	17	11	**9c**	cat. $Sn(OTf)_2$[d]	150	57	0
5	**9c**	$FeCl_3$	60	93	0	12	**9c**	cat. $Hf(OTf)_4$[d]	150	52	28
6	**9c**	$FeCl_3$	80	89	2	13	**9c**	$BiCl_3$	150	35	0
7	**9c**	$GaCl_3$	60	60	15	14	**9c**	$ZrCl_4$	60	30	0

[a] The reaction was run on 1 mmol scale using halobenzenes (**9a**−**c**) as solvent and 1 equiv of Lewis acid unless stated otherwise. The reaction was monitored using GC. Endpoint was determined based on the consumption of compound **10**, or was called complete after 24 h. [b] $AlCl_3$ caused an emulsion upon sampling and was messy. $ZnCl_2$ and $BF_3{\cdot}OEt_2$ did not induce sulfonylation. [c] GC yields. [d] Catalyst loading was 10 mol %.

Scheme 2. **Sulfonylation and isomerization**

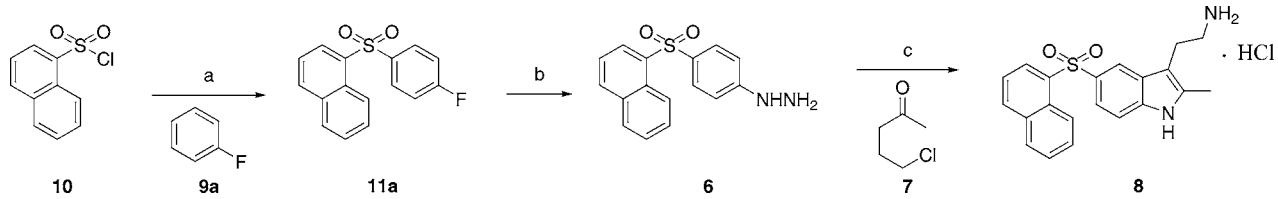


one kilogram. The product **11a** was isolated from 2-propanol as a white crystalline solid in a 93% yield.

The hydrazine displacements of compounds **11a**−**c** proceeded smoothly. Aqueous hydrazine (35%) was chosen for this displacement because of safety and availability. An organic solvent was needed for this reaction since compounds **11a**−**c** were not soluble in 35% aqueous hydrazine. A number of solvents were screened, but only a combination of DMSO/35% aqueous hydrazine gave a complete and clean conversion. Not surprisingly, the fluoro-substituted **11a** was converted at 60 °C in a day, while the bromo analogue **11c** required 3 days of heating at 100 °C. Product isolation involved a simple addition of water and a filtration to provide compound **6** as a white solid in 88% yield. This reaction was readily scaled to one-kilogram scale to provide **6** in a 92% yield (93% HPLC area purity). Attempts to purify compound **6** by crystallization resulted in fair yields and no apparent improvement in purity by HPLC. Since compound **6** could not be readily upgraded and conditions were found to effect high-yield formation of PHA-565272A (**8**) (vide infra), further crystallization studies were not pursued. Up to this point, compound **6**, the hydrazine penultimate, was prepared in only two steps from readily available starting materials (Scheme 3).

Although the Grandberg modification initially produced **8** in poor yields, the efficiency in constructing the indole ring and its side chain was incomparable. The Grandberg modification offered better opportunity for scale-up purpose. Due to the poor regioselectivity in the Grandberg modification, the purity of commercial 5-chloro-2-pentanone (**7**) was immediately called into question. The black liquid appeared to be very acidic. ^{1}H NMR spectrum of compound **7** showed a large impurity with a peak at 7 ppm. After aqueous K_2CO_3 treatment, CH_2Cl_2 extraction, and solvent removal, this unidentified impurity was removed. Based on the ^{1}H NMR integration and our isolated yield of compound **7**, *80-90% of the contents of the commercial material was this* impurity! Due to a lack of commercial pure compound **7**, it was prepared in-house starting from 2-acetylbutyrolactone (Scheme 4).[9] Unlike the "crude" commercial material, the distilled

Scheme 3. **Scale-up route**[a]



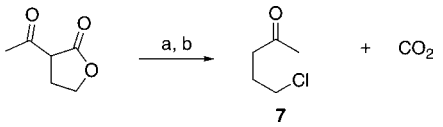
[a] Reagents and conditions: a) $FeCl_3$, 93%; b) 35% hydrazine/DMSO, 92%; c) EtOH/H_2O, reflux, then crystallization, 74%.

Table 2. **Sulfonylation of fluorobenzene (9a) using $FeCl_3$**[a]

entry	arylsulfony chloride used	temp (°C)	yield of **11a** (%)	yield of **12a** (%)
1	**10**	20	98.5	0.25
2	**10**	40	97.6	2
3	**10**	60	92	6[b]
4	2-Naph-SO_2Cl	20	0	98.9
5	2-Naph-SO_2Cl	40	0	98.9
6	2-Naph-SO_2Cl	60	0	98.9

[a] Reaction was run in fluorobenzene with 1 equiv of $FeCl_3$. [b] This is a result of a run >2 h.

Scheme 4. **Preparation of 7**[a]



[a] Reagents and conditions: a) 37% HCl, H_2O, NaCl, reflux; b) hexane extraction.

compound **7** prepared in-house was clear in color. With purer supplies of 5-chloro-2-pentanone (**7**) now available, the Grandberg modification was revisited. A recent review of Fischer indole synthesis noted an increased use of thermal conditions to effect this transformation, especially with heteroaromatic hydrazines that were difficult to cyclize under acidic conditions due to protonation of the heteroatom.[10] Several thermal conditions were therefore probed. Using only 1.2 eq. of this pure 5-chloro-2-pentanone **7** prepared in-house, reactions were performed in 9:1 MeOH:H_2O at 60 °C, 9:1 EtOH:H_2O at 80 °C, and 9:1 ethylene glycol:H_2O at 100 °C. For each reaction, compound **6** was converted almost immediately to an intermediate, probably the hydrazone. After 3 days, the reaction using MeOH/H_2O showed only 55.7% formation of PHA-565272A (**8**) with 26.1% of the intermediate still present. The reaction using EtOH/H_2O was much quicker with only 2.4% unreacted intermediate after 48 h. The reaction using ethylene glycol was not as clean, generating 12% of an unknown impurity and other impurities. Importantly, the yields from this quick screen all appeared to be >50%.

This reaction was then scaled to 20 g in EtOH/H_2O. When the reaction was near completion, product solids formed in the reaction. A distillation to a lower volume resulted in an 89% yield of the desired product. The ^{1}H NMR and elemental analysis for the product isolated confirmed the formation of the mono-HCl salt.

A material at 6.9 min (HPLC peak) with a similar retention time as the hydrazone intermediate was present at the 1.5%-2.4% level when the reactions were called complete. After distillation, cooling, and product filtration, this impurity level would generally drop to 1.2%-1.5%. This impurity was later confirmed by LC-MS not to be the hydrazone intermediate, but rather an impurity with a chlorine on the naphthalene. This impurity could derive from two possible sources. It could potentially arise from the 1-naphthalenesulfonyl chloride **10** or it could derive from chlorination during Step 1 $FeCl_3$-induced sulfonylation. A recent paper showed that aryl chlorination might occur in sulfonylation reactions in the presence of $AlCl_3$.[11] This suggested that a close monitoring of the Friedel−Crafts sulfonylation may be needed to reduce this impurity.

Several different conditions to recrystallize PHA-565272A (**8**) were probed. Acetone and EtOAc did not efficiently dissolve compound **8** at reflux. Recrystallization would not occur from neat *n*-BuOH; however, when H_2O was added, the solids dissolved. Improved yields were achieved with no loss in HPLC purity when partial distillation of the *n*-BuOH:H_2O solution occurred prior to cooling and filtration. An unfortunate side effect of this recrystallization procedure was the formation of greater color in the crystals. Prior to recrystallization the crystals were tan. However, after recrystallization there was a definite brownish tint. To remove the color, the solution of compound **8** in 20% H_2O:*n*-BuOH at 95 °C was treated with Ecosorb 793 carbon and then filtered hot over Celite 545. After product clarification, distillation, and filtration, crystals of light tan were achieved. The Grandberg modification and the subsequent recrystallization were performed on kilo-scale, which provided ∼1 kg of PHA-565272A (**8**) with an overall 74% yield in 98.8% HPLC area purity along with the 6.9 min (HPLC peak) impurity at <0.8%.

Conclusion

An isomerization-free sulfonylation was developed for 1-naphthalenesulfonyl chloride. This development allowed a much shorter route for the preparation of PHA-565272A. We discovered that the Grandberg modification of Fischer indole synthesis required pure 5-chloro-2-pentanone to achieve good yields. The new route was rapidly scaled to one kilogram of PHA-565272A uneventfully.

Experimental Section

General Procedures. All reagents were commercially obtained and used as received unless otherwise noted. All nonaqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. The drying of solids was

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performed in a vacuum oven. NMR spectra were measured on a Bruker AM-400 operated at 400 and 100 MHz for ^1H and ^{13}C, respectively, with data reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration and coupling constant (J, Hz). $^1H - ^{13}C$ Multiplicities are reported on the basis of DEPT data. Where ^{13}C -^{19}F coupling occurs, the coupling constant (J_{C-F}) is reported. UV, IR and HRMS and elemental analysis were conducted within Pfizer analytical support groups. High-Pressure Liquid Chromatography (HPLC) were performed on an Agilant 1100 Series HPLC System composed of a G1316A Column Compartment, G1315A Diode Array Detector, G1313A Automated Liquid Sampler, G1311A Quaternary Gradient Pump and a G1322A Vacuum Degasser. The conditions are as following: Solvent A; 2 L H_2O, 10 mL TEA, 5 mL AcOH, Solvent B; CH_3CN, $T_{init} = 0$ min, 35% A; $T_{fin} = 10$ min, 35% A, Zorbax RX-C8 Column, 4.6 mm × 25 mm, PN880967, UV = 254 nm, Flow rate = 1.0 mL/min, Col T = 40 °C. Gas Chromatography (GC) was performed on a system composed of a Hewlett-Packard 6890 Series GC System and Integrator with a Hewlett-Packard 7683 Series Injector. Conditions are: Inject 50μL of the resulting solution onto a 15 m capillary DB-1 column using the following run parameters: $T_{inj} = 200$ °C, $T_{init} = 50$ °C, $t_{init} = 5$ min, $T_{fin} = 300$ °C, $t_{fin} = 10$ min, Rate = 20 °C /min.

1-[4-(1-naphthalenylsulfonyl)phenyl]hydrazine (6). To a 22-L flask, compound **11a** (1170 g, 4.1 mol), 35% aqueous hydrazine (743 mL, 8.2 mol), and DMSO (5.1 L) were added. The resulting slurry was heated to 58 °C (The contents went into solution at 55 °C). After 24 h, the reaction was deemed complete with 2.3 area% starting material (GC) remaining. The solution was cooled to 16 °C. Water (28 L) was added to the 40 L wash tank followed by the reaction mixture. The reaction flask was rinsed with H_2O (5 L) and added to the wash tank. The resulting slurry was filtered onto the 9-L coarse fritted filter. The wash tank and filter were rinsed with H_2O (10 L). The solids were dried at 60 °C for 5 days to yield 1120 g (92%) of compound **6** with 93.2% HPLC area purity. The yield took into account the presence of 6.6% H_2O. mp. 129.2−131.4 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, 1H, $J = 8.7$ Hz), 8.31 (d, 1H, $J = 7.1$ Hz), 8.22 (d, 1H, $J = 8.2$ Hz), 8.05 (d, 1H, $J = 8.1$ Hz), 7.76 (s, 1H), 7.71−7.58 (m, 5H), 6.80 (d, 2H, $J = 8.6$ Hz), 4.22 (s, 2H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 155.88 (s), 137.51 (s) 134.30 (d), 133.8 (s), 129.12 (d), 128.41 (d), 128.05 (d), 127.30 (s), 126.82 (d), 125.35 (s), 124.80 (d), 124.04 (d), 110.03 (d). IR (diffuse reflectance) 3367, 1940 (w), 1902 (w), 1591 (s), 1288 (s), 1151 (s), 1145 (s), 1132 (s), 1082, 834, 822, 802, 768 (s), 718, 698, cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{14}N_2O_2S$ +H 299.0854, found 299.0847. Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.74. Found: C, 63.46; H, 4.92; N, 8.85; S, 10.52.

5-Chloro-2-pentanone (7). $NaHCO_3$ (200 g) was dissolved in H_2O (2 L) and set aside. To the 4 L separatory funnel was added H_2O (65 mL) and hexane (65 mL). To a 12-L flask, NaCl (230 g) and H_2O (1215 mL) were added. 37% HCl (1178 mL, 14.3 mol) was slowly added at 20 °C to 50 °C over 15 min from a 2 L addition funnel. The solution was heated to 101 °C with distillate sent into the 4 L separatory funnel. 2-acetylbutyrolactone (1000 g, 7.8 mol) was slowly added to the 12-L flask over 8 h. Distillation was continued for 2 h more while increasing the temperature to 110−115 °C. Hexane (1840 mL) was added to the 4-L separatory funnel, stirred, and the lower aqueous layer was separated. H_2O (800 mL) was added to the 4-L separatory funnel, and 10 mL of the $NaHCO_3$ solution was added to adjust the pH to 7.2. The lower aqueous phase was separated, and the hexane layer was washed again with H_2O (800 mL). The aqueous phases were combined and back extracted with hexane (500 mL). The hexane extractions were combined, washed with H_2O (400 mL), and distilled atmospherically to remove hexane. Vacuum distillation afforded a forerun of 100 mL followed by 655 g (70%) of 5-chloro-2-pentanone **7** of 99.9% GC area purity.

2-Methyl-5-(1-naphthalenylsulfonyl)-1H-indole-3-ethanamine monohydrochloride (8). To a 22-L flask, compound **6** (1090 g, 3.7 mol), 5-chloro-2-pentanone **7** (500 mL, 4.4 mol), EtOH (12 L) and H_2O (1.15 L) were added. The slurry was heated to reflux at which point all the solids dissolved. The solution was filtered through a 0.6 micron filter sending the filtrate into a second 22-L flask (GMP requirement to remove possible contaminated particles). The solution was stirred at reflux (78 °C) for 4 days at which point the reaction was deemed complete with 1.93% of an intermediate/impurity at 6.9 min (HPLC). Distillation was performed to a volume of 5−6 L. The resulting mixture was cooled to −35 °C to −27 °C, stirred 100 min, and filtered onto a 9 L coarse fritted filter. The solids were washed with cold EtOH (1 L) and then dried at 60 °C for 24 h to give 1296 g (88%) of PHA-565272A (**8**) with 95.7% HPLC area purity in beige color. This material (500 g) was added to a 22-L flask, followed with *n*-BuOH (12 L), and H_2O (3 L). The slurry was heated to 95 °C at which point all the solids dissolved. Ecosorb 793 (a type of carbon, 250 g) was added and the slurry was stirred for 1 h. The slurry was poured onto a 9 L coarse fritted filter containing Celite 545 (500 g). The filtrate was filtered through a 0.6 micron ultipore filter sending the filtrate into a second 22-L flask. Distillation was performed to a volume of 11−12 L. The resulting filtrate was cooled to −29 °C, stirred 3 h, and filtered onto a 9-L coarse fritted filter. The solids were rinsed with cold *n*-BuOH (1 L) and dried at 60 °C for 3 days to give 418 g (84%) of PHA-565272A (**8**) with 98.8% HPLC area purity. mp. 363−368 °C. ^1H NMR (400 MHz, DMSO- d_6) δ 11.65 (s, 1H), 8.73 (d, 1H, $J = 8.7$ Hz), 8.41 (d, 1H, $J = 7.6$ Hz), 8.36 (s, 1H), 8.24 (d, 1H, $J = 8.2$ Hz), 8.3−8.1 (br s, 3H), 8.03 (d, 1H, $J = 8.1$ Hz), 7.72 (t, 1H, $J = 7.6$ Hz), 7.69 (t, 1H, $J = 8.0$ Hz), 7.58 (t, 1H, $J = 7.3$ Hz), 7.47 (d, 1H, $J = 8.7$ Hz), 7.39 (d, 1H, $J = 8.1$ Hz), 3.07 (t, 2H, 7.6 Hz), 2.92 (t, 2H, $J = 7.6$ Hz), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 137.28 (s), 137.16 (s), 136.50 (s), 134.62 (d), 133.78 (s), 130.47 (s), 129.13 (d), 128.75 (d), 128.21 (d), 127.28 (s), 126.88 (d), 124.89 (d), 124.12 (d), 119.29 (d), 117.93 (d), 111.41 (d), 107.34 (s), 39.49 (t), 21.66 (t), 11.25 (q). IR (mull) 3050, 3012 (b), 1988 (w), 1951 (w), 1938 (w), 1506, 1300 (s), 1155 (s), 1136 (s), 1131 (s), 1104, 805, 768 (s), 638, 614, cm^{-1}; UV λ_{max} 232 (60200, 95% Ethanol); HRMS

(FAB) calcd for $C_{21}H_{20}N_2O_2S$ +H 365.1324, found 365.1315; Anal. Calcd for $C_{21}H_{21}N_2O_2SCl$: C, 62.91; H, 5.28; N, 6.99; Cl, 8.84; S, 8.00. Found: C, 62.57; H, 5.32; N, 6.93; Cl, 8.82; S, 7.92.

1-[(4-fluorophenyl)sulfonyl]naphthalene (11a). To a 22-L flask, 1-naphthalenesulfonyl chloride **10** (1004 g, 4.4 mol) and fluorobenzene **9a** (1061 g, 11 mol). The slurry was heated to 45 °C. $FeCl_3$ (856 g, 5.3 mol) was added to the 22-L flask over 30 min while maintaining the temperature around 40 °C. After 70 min, GC analysis showed the reaction was complete. The reaction mixture was cooled and quenched with 4 L of 1M HCl. The mixture was extracted with 5 L of CH_2Cl_2. The aqueous layer was back extracted with CH_2Cl_2 (2 × 2 L). The combined CH_2Cl_2 extractions were washed with 1M HCl (4 L). The aqueous layer was back extracted with CH_2Cl_2 (1 × 2 L). The combined organic layers were distilled and swapped to 2-propanol (7.2 L). The slurry was heated to reflux to dissolve the solids, cooled to −15 °C, stirred 30 min, and filtered onto a 9-L coarse fritted filter. The solids were washed with cold 2-propanol (2 L) and dried at 60 °C for 24 h to give 1172 g (93%) of compound **11a** with 98.7% GC and 94.9% HPLC area quality. mp 127.8−128.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, 1H, J = 8.1 Hz), 8.50 (d, 1H, J = 6.6 Hz), 8.10 (d, 1H, J = 7.6 Hz), 7.98 (br s, 2H), 7.90 (d, 1H, J = 7.7 Hz), 7.63−7.54 (m, 3H), 7.13 (t, 2H, J = 7.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.88 (s, J_{C-F} = 223.8 Hz), 134.38 (s), 132.83 (s), 130.94 (s), 128.47 (s) 135.7 (d), 130.37 (d), 130.27 (d), 130.11 (d), 129.28 (d), 129.61 (d), 127.11 (d), 124.40 (d, J_{C-F} = 26.1 Hz), 116.55 (d, J_{C-F} = 22.9 Hz). IR (diffuse reflectance) 2447 (w), 2413 (w), 2295 (w), 2215 (w), 2041 (w), 1312 (s), 1227 (s), 1161 (s), 1136 (s), 1131 (s), 1083 (s), 847 (s), 800 (s), 775 (s), 690 (s), cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{11}FO_2S$ +H 287.0542, found 287.0548; Anal. Calcd for $C_{16}H_{11}FO_2S$: C, 67.12; H, 3.87; S, 11.20; Found: C, 66.85; H, 3.91; N, 0.20; S, 11.09.

Synthesis of compounds 11b, 11c, 12a, 12b, and 12c: General procedure. To a solution of 1- naphthalenesulfonyl chloride (**10**) or 2-naphthalenesulfonyl chloride (1 eq. A g) in the corresponding halobenzene (B mL), $FeCl_3$ (1.2 eq.) was added in one portion at C °C. After D h, the dark solution was quenched with 2 × B mL of CH_2Cl_2 and 1 × B mL of 1M HCl. The aqueous layer was extracted with 1 × B mL of 1M HCl. The organic layers were concentrated to give a yellow solid, which was then re-recrystallized in IPA to give desired product.

1-[(4-chlorophenyl)sulfonyl]naphthalene (11b): A = 11.3, B = 50, C = 40, D = 5, 11.6 g (81%), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (m, 2H), 8.33 (d, 1H, J = 8.1 Hz), 8.08 (d, 1H, J = 8.1 Hz), 7.98 (d, 2H, J = 8.1 Hz), 7.77 (t, 1H, J = 7.6 Hz), 7.60−7.69 (m, 4H). Anal. Calcd for $C_{16}H_{11}ClO_2S$: C, 63.47; H, 3.66; N, 0.00. Found: C, 63.32; H, 3.63; N, 0.15.

1-[(4-bromophenyl)sulfonyl]naphthalene (11c): A = 11.3, B = 50, C = 50, D = 3, 12.4 g (72%), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, 2H, J = 8.6 Hz), 8.33 (d, 1H, J = 8.2 Hz), 8.09 (d, 1H, J = 7.5 Hz), 7.87−7.92 (m, 2H), 7.74−7.80 (m, 3H), 7.60−7.70 (m, 2H). Anal. Calcd for $C_{16}H_{11}BrO_2S$: C, 55.35; H, 3.19; N, 0.00. Found: C, 55.01; H, 3.11; N, 0.16.

2-[(4-fluorophenyl)sulfonyl]naphthalene (12a): A = 11.3, B = 30, C = 40, D = 1, 12.7 g (89%), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.21 (d, 1H, J = 7.6 Hz), 8.09−8.14 (m, 3H), 8.03(d, 1H, J = 8.2 Hz), 7.67−7.74 (m, 2H), 7.45 (t, 2H, J = 9.1 Hz). ^{19}F NMR (400 MHz, DMSO-d_6) δ 105.12. Anal. Calcd for $C_{16}H_{11}FO_2S$: C, 67.12; H, 3.87; N, 0.00. Found: C, 66.90; H, 3.91; N, 0.14.

2-[(4-chlorophenyl)sulfonyl]naphthalene (12b): A = 11.3, B = 50, C = 40, D = 2, 12.9 g (90%), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.21 (d, 1H, J = 7.6 Hz), 8.14 (d, 1H, J = 8.6 Hz), 8.01−8.05 (m, 3H), 7.90 (d, 1H, J = 8.7 Hz), 7.68−7.75 (m, 4H). Anal. Calcd for $C_{16}H_{11}ClO_2S$: C, 63.47; H, 3.66; N, 0.00. Found: C, 63.01; H, 3.61; N, 0.15.

2-[(4-bromophenyl)sulfonyl]naphthalene (12c): A = 11.3, B = 50, C = 40, D = 3, 12.1 g (70%), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.21 (d, 1H, J = 8.1 Hz), 8.13 (d, 1H, J = 8.6 Hz), 8.03 (d, 1H, J = 8.2 Hz), 7.93 (d, 2H, J = 8.7 Hz), 7.89 (d, 1H, J = 8.7 Hz), 7.82 (d, 2H, J = 8.6 Hz), 7.66−7.74 (m, 2H). Anal. Calcd for $C_{16}H_{11}BrO_2S$: C, 55.35; H, 3.19; Br, 23.01; N, 0.00. Found: C, 55.28; H, 3.23; N, 0.19.

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