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Development of the Large-Scale Preparation of 2-(Methanesulfonyl)benzenesulfonyl Chloride

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ABSTRACT: A practical and scalable process is described for the preparation of 2-(methansulfonyl)benzenesulfonyl chloride, a key building block used in the synthesis of several drug candidates. The material is prepared by an efficient four-step sequence from inexpensive 1,2-dichlorobenzene and methanethiol, and the process has been demonstrated on a multikilogram scale in 32% overall yield with a chemical purity of >98%.

INTRODUCTION

As part of a previous drug development program, we required multikilogram quantities of a key building block 2-(methanesulfonyl)benzenesulfonyl chloride (**8**). While the material is currently commercially available, it is expensive, available at times only in gram quantities, and at the time convenient processes for preparation on large scale were lacking. In order to meet an aggressive timeline, it was a high priority to rapidly develop a practical and scalable synthesis of **8**, which has more recently found use as an important raw material for the synthesis of several lead drug and candidate molecules.[1]

RESULTS AND DISCUSSION

At the time we began this research effort, we based our strategy for the preparation of 2-(methanesulfonyl)benzenesulfonyl chloride on a route described in the patent literature for the production of 2-substituted arylsulfonyl chlorides from ortho-dichloroaromatics and alkyl metal sulfides as depicted in Scheme 1.[2] Specified in this process was the nucleophilic substitution of 1,2-dichlorobenzene (**1**) with potassium alkyl mercaptides, requiring the use of polyethylene glycol (PEG) ether reagents as catalysts. Exemplified were the substitution reactions to provide the methyl aryl thioether **2** (147-g scale) and the *n*-propyl aryl thioether congener **3** (100-g scale). Oxidation of the resulting aryl alkyl sulfide **3** by various conditions (exemplified by the bleach conditions shown on a 9.3-g scale) afforded 2-chlorophenyl *n*-propyl sulfone (**5**) in good overall yields. In contrast, the transformation from **2** to **4** was simply referred to in the text as an example, but without yield or details. Aryl *n*-propyl sulfone **5** was subjected to a second nucleophilic aromatic substitution to generate the 2-substituted-aryl *n*-propyl sulfone product **7**, although a biphasic solvent system was used for the 2.2-g scale transformation. Again, the process was described as amenable for the thiolation of **4** to provide the adduct **6**, but without yield or details. Finally, oxidative chlorination of the alkylthio moiety to transform the final intermediates into the corresponding 2-substituted-arylsulfonyl chlorides was described, with both the conversion of methyl thioanisole **6** to **8** (13.2-g scale) and the conversion of *n*-propyl thioanisole **7** to **9** (18.7-g scale). The overall preparation of 2-(*n*-propylsulfonyl)benzenesulfonyl chloride (**9**) by this route was calculated at 59% yield for the four-step process, which was initiated with 100 g of 1,2-dichlorobenzene for the first step, but elaborated through the later stages below 20-g scale.

We elected to follow the guidelines of this route, with an eye toward modifications that allowed for multikilogram scale preparation, and our ultimate process is described in Scheme 2. For the first step, we were encouraged by literature that suggested the monodisplacement of 1,2-dichlorobenzene with alkali metal salts of alkanethiols could be achieved at high temperature without the need for catalysis.[3] Initially we set out to examine the reaction of **1** with commercially available sodium methanethiolate to produce 2-chlorophenylthioanisole (**2**), conducting the reaction in a variety of higher-boiling solvents at 100−120 °C, with and without phase-transfer catalysis. Eventually we settled our concerns of reagent cost and availability by using methanethiol gas (methyl mercaptan) and one equivalent of finely ground potassium hydroxide to generate the metal alkanethiol in situ. On scale-up (typically a 5-L batch of **1**), methyl mercaptan was introduced into the flask subsurface over 4 h through the gas inlet tube, operating with a gas outlet through a mechanically stirred aqueous sodium hypochlorite/sodium hydroxide scrubber. During the gas addition, exothermic heating of the reaction mixture increased the internal reaction temperature to 50 °C, which was maintained throughout the gas addition, after which the mixture was heated to 100 °C to stir for 30 min. Although the amount of potassium methanethiolate was controlled to one equivalent to avoid bis-substitution of 1,2-dichlorobenzene, experiments showed that excess amounts of the reagent generated at 100 °C did not generate significant amounts of the bis-substituted byproduct. While the amount of methyl mercaptan charged on large scale was not measured, we found on smaller-scale experiments that the charging of approximately three equivalents of the gas were necessary to ensure complete generation of the equivalent of potassium methanethiolate to consume substrate **1**. Upon completion, a quench with one volume of water at room temperature followed by extraction of the product with two volumes of hexanes produced **2** as an

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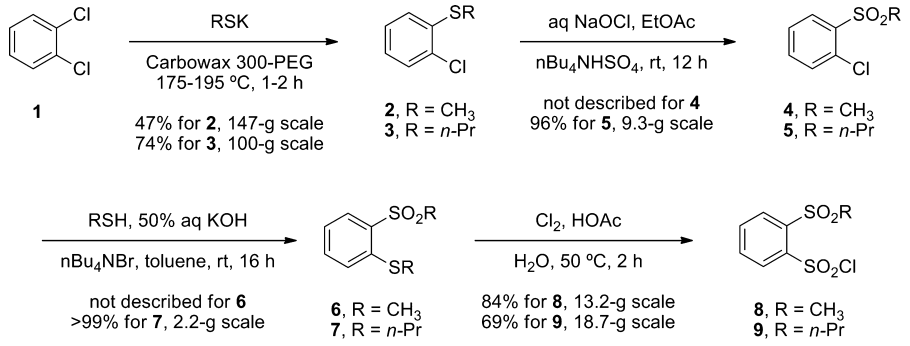
Scheme 1. Patent literature synthetic route to 2-substituted-arylsulfonyl chlorides 8 and 9



Scheme 2. Scale-up process for 2-(methanesulfonyl)benzenesulfonyl chloride synthesis

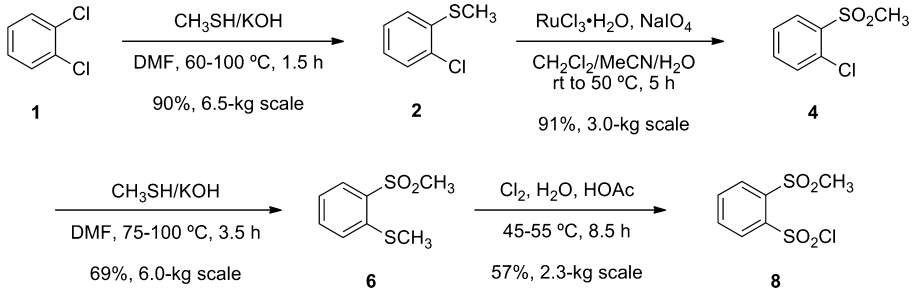
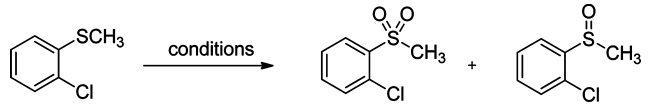


Table 1. Selected exploratory conditions for the oxidation of thioanisole 2 to sulfone 4



entry	conditions	outcome
1	5% aq NaOCl, nBu_4NHSO_4, EtOAc, rt, 24 h	incomplete, unclean conversion of **10** to **4**
2	5% aq NaOCl, DMF, rt, 24 h	incomplete, unclean conversion of **10** to **4**
3	35% aq H_2O_2, HOAc, reflux, 1 h	incomplete conversion of **10** to **4**
4	oxone, MeOH/H_2O, reflux, 18 h	incomplete, unclean conversion of **10** to **4**
5	oxone, H_2O, bentonite clay, CH_2Cl_2, rt, 16 h	incomplete conversion of **10** to **4**
6	$NaIO_4$, $RuCl_3$, 1:2:1 MeCN/H_2O/$CHCl_3$, rt, 17 h	complete, but unclean conversion of **2** to **4**
7	$NaIO_4$, $RuCl_3$, 1:4:1 MeCN/H_2O/$CHCl_3$, rt, 22 h	incomplete, unclean conversion of **10** to **4**
8	$NaIO_4$, $RuCl_3$, 1:2:1 MeCN/H_2O/DCE, rt, 3.5 h	complete, clean conversion of **2** to **4**
9	$NaIO_4$, $RuCl_3$, 1:2:1 MeCN/H_2O/CH_2Cl_2, rt, 4 h	complete, clean conversion of **2** to **4**

opaque, colorless oil that was suitable for further use in the next step without further purification. Typically the material was measured at >95% purity by ^{1}H NMR analysis, and this process functioned well at up to 7-kg scale. Although the product was isolated by evaporation to dryness, we anticipated that a simple solvent exchange in the subsequent step would avoid the stripping operation on further scale-up. In general, however, we were pleased to find that our first transformation was at least on par with the patent description (Scheme 1), and was amenable to the preparation of much larger quantities.

Discovering a suitable and reproducible method for the oxidation of thioether **2** to the aryl methyl sulfone **4** was more challenging (Scheme 2). Initial attempts to doubly oxidize **2** using the patent procedure (Scheme 1) failed to provide the requisite sulfone, as several experiments to optimize the conditions were inadequate to push the full conversion of the intermediate sulfoxide **10** to **4** (Table 1, entry 1). After examination of conditions with several reagents and reagent combinations (some shown in Table 1),[4] we eventually settled on an efficient oxidation system using 2 equiv of sodium periodate under catalysis by ruthenium trichloride.[5] Modifications demonstrated that a biphasic water/acetonitrile/methylene chloride mixture at 2:1:1 was critical for clean conversion (entry 9), and that portionwise addition of the ruthenium catalyst was necessary to control the mild but immediate exothermic reaction. Sodium periodate readily oxidizes **2** to the sulfoxide intermediate **10**, so the ruthenium reagent is only required to catalyze the second oxidation to the sulfone product **4**, and was optimized to 0.05 mol % loading on a typical 3-kg scale run.

Upon completion of the reaction, the product **4** was extracted with methylene chloride, washed with water to remove the sodium iodate byproduct, and subjected to charcoal treatment to remove the catalyst. The crude product solution was partially concentrated and triturated with hexanes to produce clean 2-chlorophenyl methyl sulfone (**4**) as a free-

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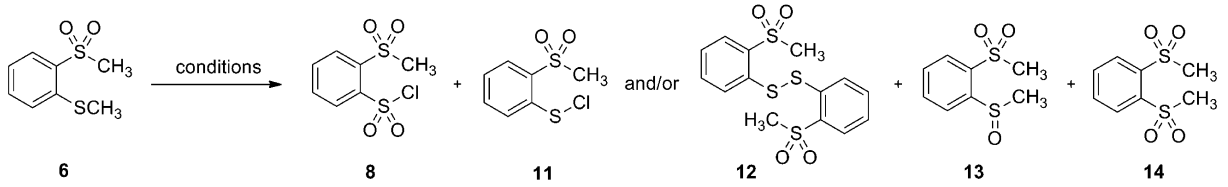
Table 2. Selected small-scale exploratory chloroxidation conditions



entry	conditions	outcome
1	NCS, H_2O/HOAc, rt to 50 °C, 4 h	incomplete, unclean conversion of **6** to **8**; formation of adduct **14**; inadequate extraction and isolation
2	SO_2Cl_2, CH_2Cl_2/H_2O/HOAc, 0 to 50 °C, 6 h	incomplete, unclean conversion of **6** to **8** and **14**; inadequate extraction and isolation
3	5% aq NaOCl, 4 N HCl/CH_2Cl_2, 0 °C to rt, 12 h	incomplete conversion of **6** to **8**; formation of adduct **14**; solubility problems; inadequate extraction and isolation
4	mCPBA, CH_2Cl_2, 0 °C, 1 h; SO_2Cl_2, reflux, 12 h	clean conversion of **6** to **14**, but no conversion of **14** to **8**
5	Cl_2, H_2O/dioxane, rt, 12 h	incomplete conversion of **6** to **8**; solubility problems; inadequate extraction and isolation
6	Cl_2, H_2O/HOAc/CH_2Cl_2, rt, 12 h	incomplete conversion of **6** to **8**; inadequate extraction and isolation
7	Cl_2, H_2O/HOAc, rt to 50 °C, 5 h	complete conversion of **6** to **8**

flowing powder. Typically the material was measured at >95% purity by ^{1}H NMR analysis, and we were pleased that our process was not only comparable to the patent procedure (Scheme 1) but also adaptable to the synthesis of much larger amounts of material.

We next investigated other methods for the second nucleophilic aromatic substitution step from **4** to 2-(thiomethyl)phenyl methyl sulfone (**6**), as the patent experimental procedure (Scheme 1) did not describe the actual setup or workup of the transformation, and only a GLC analysis was reported. Ultimately, however, we relied on the use of the same method that we defined in step one to achieve our step-three transformation (Scheme 2). One drawback, however, was that the use of multiple equivalents of potassium methanethiolate (reagent controlled by the amount of milled potassium hydroxide used), always led to the retention of 10−15% of the unreacted chloro substrate **4** that could not be pushed to product. Rather than resubject the incomplete precursor/product mixture to the reaction conditions, we eventually devised a method to remove most of the unreacted **4** through an aqueous wash, and the residual impurity was carried into the final step where the remainder was removed. Workup of this reaction on scale (typically 6-kg runs) was to dilute the mixture at room temperature with water followed by stirring for 2 h and vacuum filtration to provide the 2-(thiomethyl)-substituted product **6** as a white solid, contaminated only with 4−7% of the 2-chloro-substituted starting material **4**. Although this purification method significantly diminished the yield for this step, the material was typically measured at >90% purity by ^{1}H NMR analysis. Even with the lower throughput in comparison to the yield described for the analogous substrate exemplified in the patent procedure (Scheme 1), we demonstrated that our process was amenable to the production of kilogram quantities of our pure desired product.

We initially devoted a small amount of effort toward identifying an oxidative chlorination process different from the patent procedure (Scheme 1) for the conversion of thioanisole **6** to aryl sulfonyl chloride **8**, although we ultimately elected to utilize the chlorine gas oxidation method to complete our campaign. Small-scale exploratory experiments (some shown in Table 2)[6] were performed with conditions known to oxidatively chlorinate aryl alkyl sulfides, many of which in our hands led to incomplete conversion of **6** to desired sulfonyl chloride **8**. Formation of in-process intermediates were often observed at early stages in the progress of most reactions, but were not seen in significant amounts in the final product analyses. These fleeting adducts could never be completely identified as either sulfenyl chloride **11** or disulfide **12** and sulfoxide **13**, all of which are purported intermediates in the oxidative chlorination mechanism.[6] However, the sulfone adduct **14**, proposed as a nonproductive side product from an earlier step in the transformation, was also often isolated in significant amounts (entries, 1, 2, and 5) and could not be separated from the product mixture to a satisfactory degree. In one experiment (entry 6) we intentionally produced the sulfone compound **14**, but could not convert it to **8**, which is consistent with observations from the literature. Other experiments (entries 3 and 4) did produce the desired product **8** in relatively clean amounts, but required an extraction step for their purification, and therefore were deemed less efficient than the later experiments where product **8** was isolated more directly. In the case of entry 5, in which the biphasic conditions required a high volume of water, there was also the complication of precipitation of components from the mixture during the course of the reaction.

Upon examination of conditions to produce **8** from **6** using chlorine gas and water as reagents (entries 7−10), we ultimately found that the use of acetic acid as a solvent was preferable to mixed solvent systems in terms of workup, as the product could be isolated upon reaction completion by simple trituration with water followed by vacuum filtration. We also found that complete conversion to product could be achieved through heating the mixture for a defined time period after the exothermic portion of the reaction had subsided. Monitoring of the reaction during this heating period was critical, as prolonged reaction at 50 °C led to yield losses resulting from the hydrolysis of product **8** to the corresponding sulfonic acid.

Thus, to effect the transformation on scale (typically run with 2.3-kg lots), chlorine gas (about 5 equiv, measured by weight) was introduced subsurface to a slurry of the thioanisole **6** (contaminated at 4−7% with intermediate **4**) in glacial acetic acid and 2−3 equiv of water as the oxygen source, with the gas addition at a rate which maintained the exothermic heating below 60 °C, followed by heating at 50 °C for no more than 4 h (Scheme 2). Upon completion, the mixture was reverse quenched with ice water and stirred for 1 h, and the solids were collected by vacuum filtration to provide 2-(methanesulfonyl)benzenesulfonyl chloride (**8**) with near

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complete rejection of the contaminant **4**. Typically the material was measured at >98% purity by both HPLC and ^{1}H NMR analyses. Interestingly, the impurity **4** could subsequently be recovered for recycle by further dilution of the filtrate with water, stirring for 1 h and filtration. About 2−5% of 2-chlorophenyl intermediate **4** could be reclaimed in this manner in varying degrees of purity (typically 80−90%), and in one case several batches of the reclaimed material were combined and triturated from water to provide a single lot of **4** that was clean enough to carry forward.

The apparent disparity between the good yields reported for the patent procedure (Scheme 1) and lower throughput reported for our process (Scheme 2) seems to rest largely on the difference in scale. In our hands the patent procedure (reported at 84% on 13.2-g scale) worked very well on smaller-scale demonstration reactions, but returned lower yields upon successively large-scale preparations. This lowering of throughput from **6** to **8** directly correlated with the amount of sulfonyl chloride hydrolysis byproduct (sulfonic acid) observed in the aqueous filtrates from the product isolation step. Although the extent of sulfonic acid byproduct formation was difficult to quantitate precisely (both from the mother liquors and from in-process reaction samples), we concluded that amount of hydrolysis was related to the amount of water in the reaction required as a reagent (more than 3 equiv was sometimes used) as well as the necessity for prolonged heating at the reaction stage on larger scale. Additionally, the solubility of product **8** in the reaction solvent (acetic acid) required large volumes of water to precipitate it from the reaction mixture, but even so, this purification and isolation step was never optimized and in some runs significantly diminished the yield for this final step. Nevertheless, we were pleased to find that our oxidative chlorination procedure was sufficient for the preparation of the multikilogram lots of material we required to meet an aggressive timeline. We also noted that there was no significant hydrolysis of the isolated solid product observed, even in lots of solid retainer samples analyzed several years afterward.

In conclusion, we have devised a practical and scalable multikilogram-scale process for the preparation of 2-(methanesulfonyl)benzenesulfonyl chloride (**8**), a key building block used in the synthesis of several drug candidates.[7] The material can be prepared by an efficient four-step sequence using inexpensive precursors (1,2-dichlorobenzene, methanethiol, potassium hydroxide, water, and chlorine gas), demonstrating a throughput in 32% overall yield and with a product chemical purity of >98%.

EXPERIMENTAL PROCEDURES

2-Chlorothioanisole (2).[3b,8] A flask was equipped with a gas outlet bubbler leading to a mechanically stirred aqueous sodium hypochlorite scrubber. The flask was charged with *N*,*N*-dimethylformamide (30 L), 1,2-dichlorobenzene (**1**, 5.0 L, 6.5 kg, 44.4 mol), and finely ground potassium hydroxide (2.7 kg, 48.9 mol, 1.1 equiv). Methyl mercaptan (3 equiv estimated) was introduced into the flask over 3.5 h through the gas inlet tube, below the surface of the reaction mixture. During this time, the gas addition had caused an exothermic heating of the reaction mixture, increasing the internal reaction temperature to 60 °C, and this temperature was maintained throughout the gas addition. The methyl mercaptan flow was then terminated, and the reaction mixture was heated at 100 °C for 1.5 h. The reaction mixture was then cooled to room temperature over 12 h. Water (28 L) was added to the reaction mixture, and the resulting solution was extracted with hexanes (2 × 10 L). The combined organic layers were washed with water (12 L) and saturated aqueous sodium chloride solution (2 L). The solvent was removed under reduced pressure (30 mmHg vacuum, final bath temperature 45 °C) on a rotary evaporator to produce **2** as an opaque, light-yellow oil that was suitable for further use without purification (6.36 kg, 90% yield): TLC R_f (1:19 ethyl acetate/hexanes) = 0.72; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.08 (m, 4H), 2.48 (s, 3H); ESI MS m/z 158 $[M]^+$. The spectral data were also identical to those of a sample obtained commercially.

2-Chlorophenyl Methyl Sulfone (4).[8a,9] A flask was charged with methylene chloride (10 L), acetonitrile (10 L), and water (20 L). To this biphasic mixture was added 2-chlorothioanisole (**2**, 3.00 kg, 18.9 mol) and then sodium metaperiodate (8.49 kg, 39.7 mol, 2.1 equivalents). Ruthenium trichloride hydrate (2.0 g, 19 mmol, 0.05 mol %) was introduced in 500-mg portions at 15-min intervals to minimize the immediate exothermic heating of the reaction mixture, which increased the internal reaction temperature to 50 °C during the 1-h addition. The reaction mixture was stirred for an additional 4 h, during which time the mixture cooled to room temperature. Water (60 L) was added, the organic layer was collected, the aqueous layer was extracted with methylene chloride (2 × 10 L), and the combined organic layers were washed with water (20 L) and saturated aqueous sodium chloride solution (4 L). The solvent was removed under reduced pressure (25 mmHg vacuum, final bath temperature 50 °C) on a rotary evaporator to produce a dark-green oil which was triturated with hexanes (4 L) and stirred on a rotary evaporator (no heat or vacuum) for 14 h. The precipitates were collected by filtration and washed with hexanes (1 L) to produce **4** as a light-green powder (3.30 kg, 91% yield): TLC R_f (3:7 ethyl acetate/hexanes) = 0.41; mp 89−91 °C (lit.[8a] 93−94 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, J = 1.6, 8.5 Hz, 1H), 7.67−7.56 (m, 2H), 7.55−7.43 (m, 1H), 3.28 (s, 3H); ESI MS m/z 190 $[M]^+$. The spectral data were also identical to those of a sample obtained commercially.

2-Thiomethylphenyl Methyl Sulfone (6). A flask was equipped with a gas outlet bubbler leading to a mechanically stirred aqueous sodium hypochlorite scrubber. The flask was charged with *N*,*N*-dimethylformamide (20 L), 2-chlorophenyl methyl sulfone (**4**, 5.99 kg, 31.4 mol), and finely ground potassium hydroxide (1.94 kg, 34.6 mol, 1.1 equiv). Methyl mercaptan (3 equiv estimated) was introduced into the flask over 2.5 h through the gas inlet tube below the surface of the reaction mixture. During this time, the gas addition had caused an exothermic heating of the reaction mixture, increasing the internal reaction temperature to 75 °C, and this temperature was maintained throughout the gas addition. The methyl mercaptan flow was then terminated, and the reaction mixture was heated to 100 °C and stirred for 1 h, after which it was cooled to room temperature over 12 h. Water (40 L) was added to the mixture, and the resulting slurry was stirred at room temperature for 1 h. The precipitate was collected by filtration and washed with water (2 L). The solid product was dried over 12 h (30 mmHg vacuum, 60 °C) to provide **6** as a light-tan solid that was shown to contain unreacted starting material **4** as a 5% impurity, but was used in the next step without further purification (4.39 kg, 69% yield): TLC R_f (3:7 ethyl acetate/hexanes) = 0.34; mp 71−73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, J = 1.2, 8.0 Hz, 1H), 7.57 (dt, J = 1.3, 7.4 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H),

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3.24 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.80, 137.27, 133.78, 130.03, 126.72, 124.93, 41.66, 16.16; ESI MS m/z 202 $[M]^+$.

2-Methanesulfonylbenzenesulfonyl Chloride (8).[2,7,10] A flask was equipped with a coldfinger condenser operating at −78 °C as a gas outlet bubbler. The flask was charged with glacial acetic acid (7.5 L), water (640 mL, 35.4 mol), and 2-thiomethylphenyl methyl sulfone (**6**, 2.31 kg, 11.4 mol, contaminated at 5% with intermediate **4**). Chlorine gas (about 6 equiv) was introduced into the flask over 5 h through the gas inlet tube below the surface of the reaction mixture at a rate which kept the internal reaction temperature from exothermic heating in the 45−55 °C range. [Note: During this time, TLC analysis of the reaction mixture showed the formation of a more polar component (R_f = 0.16; 1:1 ethyl acetate/hexanes), which later converted to the less polar product component.] The chlorine flow was then terminated, and the reaction mixture was heated to 50 °C and stirred for 3.5 h, after which it was cooled to room temperature over 12 h. Ice and water (10 L) were added, and the resulting slurry was stirred for 1 h, after which the precipitate was collected by filtration. The solids were then dried overnight (30 mmHg vacuum, 50 °C) to produce **8** as a white solid (1.57 kg, 57% yield): TLC R_f (1:1 ethyl acetate/hexanes) = 0.54; mp (DSC) 136 °C (lit.[10] 136−137 °C); IR (KBr) 2108, 1570, 1426, 1372, 1323 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dt, J = 1.4, 7.5 Hz, 2H), 7.98−7.26 (m, 2H), 3.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.04, 134.66, 133.09, 131.61, 45.02; ESI MS m/z 255 $[M + H]^+$. Anal. Calcd. For $C_7H_7ClO_4S_2$: C, 33.01; H, 2.77. Found: C, 33.12; H, 2.67. HPLC analysis (Keystone Scientific Kromasil C18 column, 4.6 mm × 150 mm, 25 °C, 1:1 acetonitrile/water, 1.0 mL/min flow, retention time = 5.22 min) showed one peak, with a total purity of 99.1% (area %). The spectral data were also identical to those of a sample obtained commercially. The filtrate was further diluted with water (30 L), and the resulting slurry was stirred for 30 min, after which the precipitate was collected by filtration and washed with water (1 L). The solids were then dried overnight (30 mmHg vacuum, 50 °C) to produce 2-chlorophenyl methyl sulfone (**4**) as a light-yellow solid (47 g, 41% recovery from the second step).

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Notes

The authors declare no competing financial interest.

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