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Article

Modified and Scalable Synthesis of *N*-Tosyl-4-Chlorobenzenesulfonimidoyl Fluoride (SulfoxFluor): Direct Imidation of Sulfinyl Chlorides with Chloramine-T Trihydrate

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ABSTRACT: *N*-Tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor) has emerged as a new fluorination reagent that can be used in the rapid deoxyfluorination of various alcohols. We disclose in this article a general and practical method for the preparation of SulfoxFluor and its adaption to a large scale. Starting from readily available 4-chlorobenzenesulfonyl chloride, chloramine-T trihydrate, and potassium fluoride, SulfoxFluor was prepared on a hectogram scale in 63% overall yield with simple purification techniques. The use of chloramine-T trihydrate (instead of anhydrous chloramine-T) is a significant improvement over previous work, which streamlines the process and avoids the risk of explosion during drying or heating. This research not only establishes a reliable method for the scale-up synthesis of SulfoxFluor but also provides an insight into the imidation of sulfinyl chlorides with chloramine-T in the presence of water.

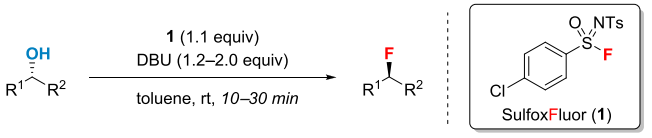
KEYWORDS: *fluorine, deoxyfluorination, sulfonimidoyl fluoride, alcohol*

INTRODUCTION

The incorporation of one or more fluorine atoms into organic compounds often deeply alters their physical and chemical properties.[1] Deoxyfluorination of alcohols, phenols, aldehydes, and ketones is an attractive means for the synthesis of fluorinated organic molecules owing to the easy availability of the raw materials;[2] therefore, the design and preparation of new deoxyfluorination reagents are of great significance. Over the past decades, a variety of new reagents have been developed for the deoxyfluorination of alcohols,[3] but there still lacks a general reagent that combines effectiveness and practicability.

In 2019, Hu's group reported a bench-stable, operationally simple, and highly efficient deoxyfluorination reagent,[4] *N*-tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor, **1**) (Scheme 1). In the presence of DBU, SulfoxFluor can rapidly react with various alcohols in toluene at room temperature to afford alkyl fluorides in good yields with high fluorination/elimination selectivity. The unique features of SulfoxFluor endow it great potential in the deoxyfluorination of complex alcohols. Recently, Wang and co-workers discovered a fluorinated analogue of azetidin-2-one,[5] a tubulin polymerization inhibitor that shows much higher bioactivities than the lead compound azetidin-2-one, by using SulfoxFluor as a deoxyfluorination reagent.

Scheme 1. Deoxyfluorination of Alcohols with SulfoxFluor (1)



In the original report, SulfoxFluor was prepared from inexpensive 4-chlorobenzenesulfonyl chloride, anhydrous chloramine-T, and potassium fluoride on a multigram scale (Scheme 2).[4] However, there still exist several problems such as tedious operation and poor repeatability, which limit the large-scale synthesis and application of SulfoxFluor. To promote the future applications of SulfoxFluor, we explored the whole synthetic process in terms of efficiency, cost, and operational simplicity. Herein, we report our effort toward the development of a reliable and streamlined route for the preparation of SulfoxFluor on a hectogram scale from readily available materials.

RESULTS AND DISCUSSION

Existing Route and Modified Route. Our reported method for the synthesis of SulfoxFluor (**1**) is shown in Scheme 2.[4] While all the starting materials are inexpensive and readily available in our original synthesis, this approach still has several downsides, among them being that the reduction of sulfonyl chloride **2** needs a large amount of water as the solvent (15 mL of water per gram of **2**), and the complete removal of

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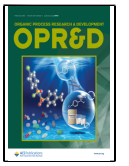
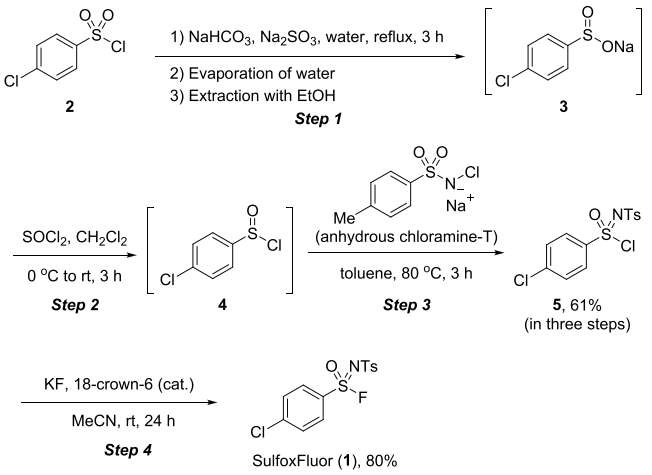


Scheme 2. Reported Synthesis of SulfoxFluor (1)

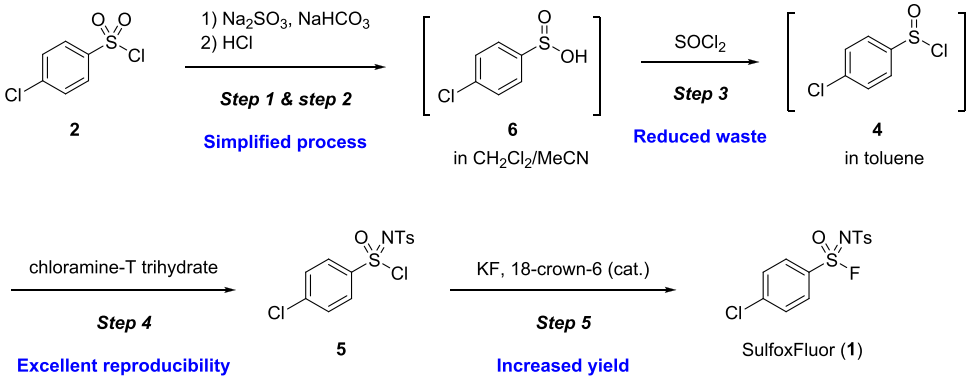


water by evaporation is difficult due to the formation of hydrate of sulfinate salt **3** (step 1); the heterogeneous reaction between **3** and thionyl chloride ($SOCl_2$) is inconvenient for both monitoring the reaction process and purification of sulfinyl chloride **4**, and the corrosive $SOCl_2$ is used in a large excess amount (step 2); the high temperature used in the imidation of **4** could increase potential safety risks as chloramine-T is a strong oxidant, and this step usually suffers from reproducibility problems, although chloramine-T has been dried prior to use (step 3); the yield of the fluoro/chloro-exchange reaction between sulfonimidoyl chloride **5** and KF is relatively low, and the incomplete conversion of compound **5** can complicate the separation and purification of SulfoxFluor (**1**) (step 4). Moreover, in step 3, the use of anhydrous chloramine-T requires pre-drying chloramine-T trihydrate, which not only complicates the procedures but also increases the risk of explosion.

After a thorough evaluation of our previous procedures, we envisioned that the modified synthetic route should fulfill the following requirements, namely, (i) the synthesis of sulfinyl chloride **4** should be operationally simple and avoid the evaporation of water, (ii) the reaction between **4** and chloramine-T should be reproducible and suitable for scale-up, and (iii) the yield of fluoro/chloro-exchange should be nearly quantitative to simplify the purification of the final product SulfoxFluor (**1**). Sulfinyl chloride **4** is a key intermediate, and thus, its easy availability is crucial to the whole synthesis. In the past decades, several methods have been developed for the preparation of sulfinyl chlorides,[6] including Lewis acid-catalyzed chlorosulfinylation of arenes with thionyl chloride ($SOCl_2$),[7] reaction of diaryl disulfide or thiophenols with Cl_2 or SO_2Cl_2 in the presence of acetic acid or acetic anhydride,[8,9] and deoxychlorination of arenesulfinate sodium or arenesulfinic acid with $SOCl_2$.[10,11] Considering both the operational simplicity and the cost-effectiveness, the use of sulfinate salt **3** would be more suitable for the synthesis of **4**. In this case, to avoid the heterogeneous reaction, we decide to convert sulfinate salt **3** to its acid form **6** first before its reaction with $SOCl_2$. Therefore, in the modified route, the acidification of the sulfinate **3** is introduced as an additional step (Scheme 3). It has been reported that both acidification of arenesulfinate sodium to arenesulfinic acid and the conversion of arenesulfinic acid to arenesulfinyl chloride could proceed with high efficacy.[11]

Synthesis of 4-Chlorobenzenesulfinic Acid (6) from 4-Chlorobenzenesulfonyl Chloride (2) (Steps 1 and 2 in Scheme 3). We first optimized the synthesis of 4-chlorobenzenesulfinic acid **6** from the commercially available and inexpensive starting material 4-chlorobenzenesulfonyl chloride **2**, which is industrially prepared from chlorobenzene and chlorosulfonic acid in large quantities.[12] Because sulfonyl chloride **2** is of poor solubility in water, THF was used as a co-solvent to make the reaction homogeneous, which can not only avoid side reactions such as hydrolysis of the sulfonyl chloride but also facilitate the monitoring of the process with thin layer chromatography (TLC). The reaction was conducted by gradually adding a THF solution of **2** into the water solution of the inorganic reactants Na_2SO_3 and $NaHCO_3$ at 75−80 °C. Normally, sulfinate **3** is isolated and purified by evaporation of water, which is not applicable for scale-up synthesis. Since the sulfinic acid is soluble in organic solvents such as dichloromethane (DCM) and methyl *tert*-butyl ether (MTBE) but of low solubility in water, we modified the route by first acidifying the sulfinate **3** with aqueous HCl followed by the extraction of the corresponding sulfinic acid **6** with MTBE. After evaporation of MTBE, sulfinic acid **6** was isolated in high yield with good purity. An optimization of the conditions showed that reducing the volume of water used has little influence on the yield of sulfinic acid **6** (Table 1, entries 1−3). Under the optimized conditions, the reaction can be conducted on a larger scale without loss of the efficiency (Table 1, entry 4). Starting from 178 g of 4-chlorobenzenesulfonyl chloride (**2**), we can get 137 g of 4-chlorobenzenesulfinyl acid (**6**).

Scheme 3. Modified Synthesis of SulfoxFluor (1)



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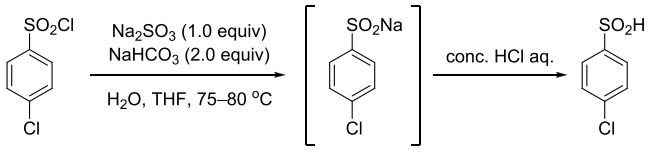
Org. Process Res. Dev. 2022, 26, 380−386

Table 1. Optimization of the Reaction Conditions for the Synthesis of Sulfinic Acid 6



2 3 6

entry	2, batch size	H_2O (mL)	THF (mL)	6, yield (%)[a]
1	59.2 g (0.28 mol)	600	60	92
2	59.2 g (0.28 mol)	450	60	90
3	59.2 g (0.28 mol)	300	60	91
4	177.6 g (0.84 mol)	900	180	92 (137.0 g)[b]

[a]Acidified with 2.0 equiv of HCl. [b]The isolated amount of **6** is given in the parentheses.

Synthesis of 4-Chloro-*N*-tosylbenzenesulfonimidoyl Chloride (5) from 4-Chlorobenzenesulfinic Acid (6) (Steps 3 and 4 in Scheme 3). Having developed a reliable method for the large-scale synthesis of sulfinic acid **6**, we next investigated the reaction of **6** with $SOCl_2$ and the subsequent reaction with chloramine-T to synthesize 4-chloro-*N*-tosylbenzenesulfonimidoyl chloride (**5**). In the presence of 1.5 equiv of $SOCl_2$, sulfinic acid **6** was consumed completely to afford sulfinyl chloride **4** in quantitative yield as determined by ^{1}H NMR analysis of the crude product (Table 2). Compared with

Table 2. Optimization of the Reaction Conditions for the Synthesis of Sulfinyl Chloride 4 from Sulfinic Acid 6

6 4

entry	$SOCl_2$ (equiv)	6, conversion (%)[a]
1	3.0	>99
2	1.5	>99

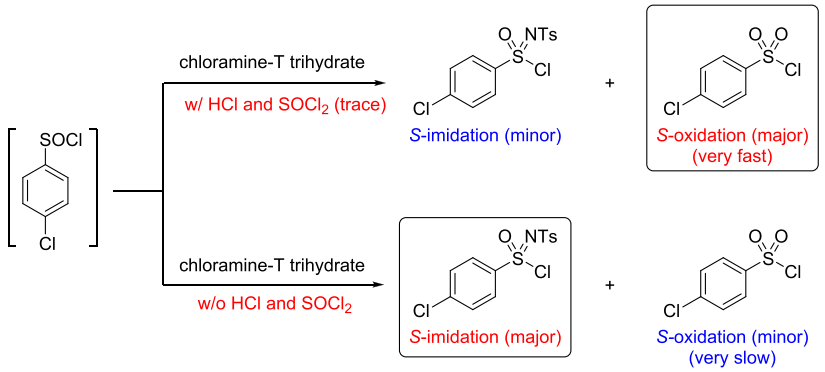
[a]Determined by ^{1}H NMR analysis of the crude product.

the direct transformation of sulfinate salt **3**, the amount of $SOCl_2$ required is significantly decreased.[4] After the removal of the volatile materials under reduced pressure, the crude product was used for the next step without distillation, which not only can simplify the operation but also can avoid its thermal decomposition.[8c] However, our initial attempts showed that, sometimes, the yield of the imidation with chloramine-T trihydrate is not reproducible due to the side effect of residual HCl and $SOCl_2$, which can promote the oxidation of sulfinyl chloride to sulfonyl chloride in nearly quantitative yield by chloramine-T in the presence of water (Scheme 4).[13] To our knowledge, the influence of HCl and $SOCl_2$ on the imidation of sulfinyl chlorides with chloramine-T in the presence of water has never been mentioned and there has been no report on the efficient imidation of sulfinyl chlorides with chloramine-T trihydrate.[10a,14] To address this problem, we tried to remove trace HCl and $SOCl_2$ from the crude product by co-distillation with toluene or hexane. In such a way, the reaction between sulfinyl chloride **4** and chloramine-T trihydrate proceeded smoothly in steady and acceptable yields (ranging from 69 to 79% based on chloramine-T). Note that chloramine-T can be used as received without the need of drying. Thus, starting from 4-chlorobenzenesulfinic acid (**6**), we prepared compound **5** on a 100 gram scale in 69% overall yield and on a 10 gram scale in 79% yield (Scheme 5). Previously, scale-up synthesis had been particularly challenging due to the difficulties in removing trace $SOCl_2$ from the mixture of fine NaCl powder and sulfinyl chloride **4** and acquiring anhydrous chloramine-T.

Scale-Up Synthesis of 4-Chloro-*N*-tosylbenzenesulfonimidoyl Chloride (5) from 4-Chlorobenzenesulfonyl Chloride (2) (Steps 1−4 in Scheme 3). With the optimized conditions for each step in hand, the feasibility of the whole process was investigated on a large scale. 4-Chloro-*N*-tosylbenzenesulfonimidoyl chloride (**5**) was prepared through sequential reduction of 4-chlorobenzenesulfonyl chloride (**1**), acidification of sulfinate salt **3**, chlorination of sulfinic acid **6**, and *S*-imidation of sulfinyl chloride **4** in a continuous operation without isolation and purification of the intermediates. Crystalline **5** was obtained after crystallization from the reaction solvent toluene by the addition of acetonitrile. In such a way, starting from 177.6 g of 4-chlorobenzenesulfonyl chloride (**1**), 198.0 g of compound **5** was prepared with an overall yield of 65%.

Scale-Up Synthesis of SulfoxFluor (1) from 4-Chloro-*N*-tosylbenzenesulfonimidoyl Chloride (5) via Fluoro/Chloro-Exchange (Step 5 in Scheme 3). Previously, the fluoro/chloro-exchange reaction was conducted at room temperature, and the full conversion of sulfonimidoyl chloride **5** usually needed 1 day. We found that the temperature is important for this transformation (Table 3). By heating the mixture at 45 °C, the reaction on a 10 mmol scale was completed in 3 h, affording SulfoxFluor (**1**) in 94% isolated

Scheme 4. Competitive *S*-Imidation and *S*-Oxidation Influenced by the Trace Amount of HCl and $SOCl_2$



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Org. Process Res. Dev. 2022, 26, 380−386

Scheme 5. Optimized Conditions for the Synthesis of Sulfonimidoyl Chloride 5 from Sulfinic Acid 6

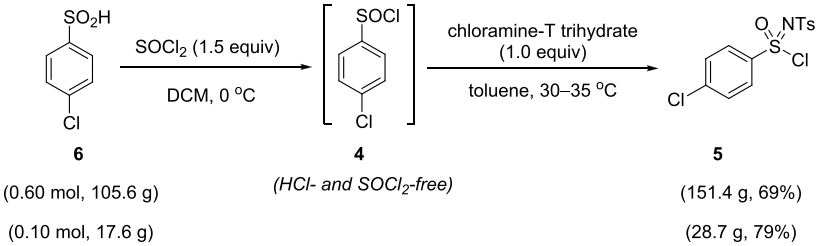
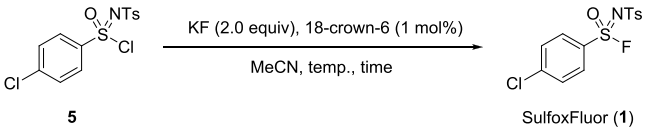


Table 3. Condition Optimization for the Synthesis of SulfoxFluor



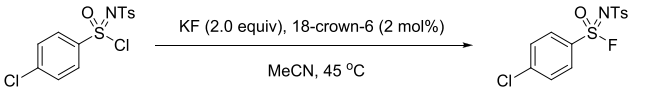
5 SulfoxFluor (1)

entry	5, batch size	MeCN (mL)	temp (°C)	time (h)	1, yield (%)[a]
1	3.63 g (0.01 mol)	25	25	23	90 (>99)
2	3.63 g (0.01 mol)	25	25	5	(90)
3	3.63 g (0.01 mol)	25	45	3	94 (>99)
4	18.15 g (0.05 mol)	125	45	3	(98.5)
5	18.15 g (0.05 mol)	125	45	4	99 (>99)
6	109.0 g (0.30 mol)	750	45	4.5	(87)
7[b]	177.6 g (0.49 mol)	1200	45	3	97.5 (>99)

[a]Conversion of **5** determined by ^{1}H NMR spectroscopy analysis of the crude product in DMSO-d_6 is given in the parentheses. [b]18-crown-6 (2 mol%) was used.

yield (Table 1, entry 3). When running the reaction on a larger scale, SulfoxFluor (**1**) was obtained in higher isolated yield in a slightly prolonged time (Table 1, entry 5). However, the rate of fluoro/chloro-exchange decreased as the scale of the reaction increased (Table 1, entry 6). Enhancing the catalyst loading to 2 mol % could recover the reaction rate (Table 1, entry 7). Thus, a hectogram scale fluoro/chloro-exchange reaction of **5** with KF under the catalysis of 2 mol % of 18-crown-6 in acetonitrile followed by crystallization from acetonitrile in the presence of water afforded SulfoxFluor (**1**) in 97.5% isolated yield (Scheme 6). For a hectogram scale synthesis starting from **2**, the overall yield of SulfoxFluor (**1**) is around 63%.

Scheme 6. Hectogram Scale Synthesis of SulfoxFluor (1) from Compound 5



5 (177.6 g) SulfoxFluor (1) (164.0 g, 97.5% yield)

CONCLUSIONS

We have developed an effective and scalable process to synthesize SulfoxFluor (**1**), which avoids the use of anhydrous chloramine-T by preparing the key intermediate 4-chlorobenzenesulfinyl chloride from the corresponding sulfinic acid instead of the corresponding sulfinate salt as previously described. This five-step procedure has been demonstrated in hectogram scale production to afford **1** in 63% overall yield from readily available 4-chlorobenzenesulfonyl chloride with two simple purifications. It is expected to be applied in large-scale production of **1** to meet the increasing need for cost-effective and highly efficient deoxyfluorination reagents. Moreover, our finding on the improvement of the imidation of 4-chlorobenzenesulfinyl chloride with chloramine-T trihydrate by avoiding any acids such as HCl is expected to find application in the imidation of other sulfinyl chlorides.

EXPERIMENTAL SECTION

General Methods. All reagents and solvents were purchased from suppliers and used as received unless otherwise mentioned. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured on 400, 100, and 376 MHz NMR spectrometers, respectively. ^{1}H NMR chemical shifts were determined relative to internal standard Me_4Si (TMS) at δ 0.0 ppm or used residual nondeuterated solvent signals as internal chemical shift references. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0 ppm or $CDCl_3$ at δ 77.16 ppm. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at δ 0.0 ppm.

4-Chloro-*N*-tosylbenzenesulfonimidoyl Chloride (5). *Steps 1 and 2.* Into a 2 L round-bottomed flask equipped with a mechanical stirrer were added Na_2SO_3 (105.9 g, 0.84 mol), $NaHCO_3$ (141.1 g, 1.68 mol), and H_2O (900 mL). The mixture was stirred at 80 °C until the solids were fully dissolved. Then, 4-chlorobenzenesulfonyl chloride (**2**) (177.6 g, 0.84 mol) in THF (180 mL) was slowly added. The mixture was heated in an oil bath at 80 °C with vigorous stirring for 0.5 h and then cooled to room temperature. After washing the mixture with methyl *tert*-butyl ether (MTBE) (300 mL), the aqueous phase was collected, acidified by adding concentrated aqueous HCl (144 mL, 36−38 wt %, ∼1.68 mol), and extracted with dichloromethane (DCM) (1.2 L). The organic phase was collected, dried over anhydrous $MgSO_4$ (100 g), and filtered to give a clear solution. The solid was washed with acetonitrile (100 mL). The organic solutions were combined and directly used for the next step.

Step 3. Under a N_2 atmosphere, to the above combined solution in a 2 L round-bottomed flask cooled in an ice-NaCl cooling bath was slowly added $SOCl_2$ (134.9 g, 1.13 mol) in 45 min (the temperatures inside the flask range from −1 to 2 °C). Thereafter, the reaction mixture was stirred at 0−5 °C for 0.5 h and then at room temperature for 1 h. The mixture was concentrated by vacuum distillation in an oil bath at 30−55 °C to remove the volatile materials, then was added toluene (500 mL), and concentrated again at 60 °C to yield a yellow solution (∼500 mL).

Step 4. Under a N_2 atmosphere, the above-obtained yellow solution was slowly added to the mixture of chloramine-T trihydrate (224.1 g, 24.02% available chlorine, calcd 95.4 wt % purity, 0.76 mol) and toluene (1.12 L) at 30−35 °C (the

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Org. Process Res. Dev. 2022, 26, 380−386

inside temperature) in 20 min. After stirring at the same temperature for another 25 min, the mixture was cooled to room temperature and filtered through a short pad of celite (50 g). The filtrate was transferred to a separatory funnel to remove the lower phase. The upper organic phase was collected and concentrated by vacuum distillation to about 500 mL. The so-obtained solution was diluted with acetonitrile (300 mL × 3) and concentrated three times. Finally, the solution (~500 mL) was cooled in an ice-cold bath for 1 h, and a lot of solids were formed. The solids were collected by filtration, washed with cold acetonitrile (5 °C, 150 mL), and dried under vacuum to give compound **5** (198.0 g, 71% yield from chloramine-T trihydrate) (65% overall yield from **2**).

HPLC purity: 98.7% (area %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.9 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 142.9, 141.0, 138.3, 130.3, 129.9, 128.4, 127.6, 21.8. The NMR data are consistent with a previous report.[4]

4-Chloro-*N*-tosylbenzenesulfonimidoyl Fluoride (SulfoxFluor) (1). Under a N_2 atmosphere, to a 2 L round-bottomed flask equipped with a mechanical stirrer were added compound **5** (177.6 g, 0.49 mol), anhydrous potassium fluorine (56.4 g, 0.97 mol), 18-crown-6 (2.58 g, 0.0098 mol), and acetonitrile (1.2 L). The mixture was stirred in an oil bath at 45 °C for 3 h (the inside temperature rose from 20 to 41 °C in 0.5 h and then kept between 41 and 42 °C). After the completion of the reaction as monitored by ^{1}H NMR spectroscopy analysis (with DMSO-d_6 as the solvent), the mixture was concentrated to 250−300 mL by vacuum distillation in an oil bath at 35 °C. After the addition of water (1.0 L), the mixture was stirred at room temperature for 0.5 h and then filtered under reduced pressure. The white solid was washed with a mixture of acetonitrile/water (200 mL, 1:5, v/v) three times and water (200 mL) once to remove any 18-crown-6 and salt and dried at 45 °C under reduced pressure for 20 h to afford SulfoxFluor (**1**) (164.0 g, 97.5% yield).

HPLC purity: 98.94% (area %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 143.4, 138.7, 131.5 (d, J = 21.7 Hz), 130.2, 129.7, 129.5, 127.1, 21.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ 74.0 (s). The NMR data are consistent with a previous report.[4]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00431.

Commercial sources of the reagents used; experimental procedures for the separate synthesis of intermediates **4** and **6**; experimental procedures for the synthesis of intermediate **5** from intermediate **6**; a demonstration for the monitoring of the fluoro/chloro-exchange process by ^{1}H NMR analysis; ^{1}H NMR spectra of intermediates **4** and **6**; ^{1}H and ^{13}C NMR spectra of intermediate **5**; and ^{1}H, ^{19}F, and ^{13}C NMR spectra of SulfoxFluor (**1**) (PDF)

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Author Contributions

#R.L. and X.-C.Z. contributed equally to this work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): A patent application on this work has been filed with the China National Intellectual Property Administration, application no. 202010453566.5.

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