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Technical Notes

Green Chemical Synthesis of 2-Benzenesulfonyl-pyridine and Related Derivatives

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Abstract:

A practical synthesis of 2-benzenesulfonylpyridine, 1, is described which is a key starting material for the manufacture of an investigational new drug candidate at Eli Lilly and Company. An optimized green chemical process was developed which features a novel tandem S_NAr/oxidation under mild conditions to produce the target sulfone, 1, in 86% yield and >99% purity. In addition, this novel, environmentally friendly methodology was found to be general for the synthesis of substituted aromatic pyridyl sulfides and sulfones.

Introduction

A recent program at Eli Lilly and Company required the synthesis of multi-kilogram quantities of key starting material 2-benzenesulfonylpyridine, **1**. In order to meet the aggressive clinical timeline, rapid development of a safe, robust, and scalable synthesis of **1** was of high priority. One-pot conditions have recently been described in the patent literature to produce 2-benzene sulfonyl pyridine derivatives including the target compound **1**.[1] Although the reported yields (85%) and purity (98%) are high for this synthetic approach, this methodology requires the use of stoichiometric benzenesulfonyl cyanide, which is not commercially available and is extremely hazardous. In addition, an excess of crotonaldehyde is employed, which is also a highly toxic reagent. A practical alternative to the aforementioned methodology that we envisioned for the synthesis of **1** was direct oxidation of 2-phenylthiopyridine, **2**. Methodologies for preparing functionalized pyridine derivatives are well known, and there are many natural products and pharmaceutical drug candidates that contain substituted pyridines. However, functionalization of the pyridine ring often requires long reaction times, use of a transition metal catalyst, or microwave irradiation to produce thioethers such as **2**.[2] In addition, these synthetic methodologies frequently require cumbersome workup conditions and operate for a relatively narrow range of substrates. Yet, it was anticipated that a scalable, environmentally friendly method of aryl sulfide synthesis could be developed to produce to the target 2-benzenethiopyridine, **2**, and related thiopyridines.

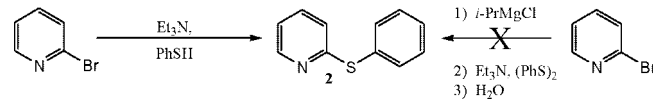

Figure 1. **Approaches to 2-benzenethiopyridine, 2.**

Although many methods are known for oxidizing sulfides to sulfones, very few are practical on a multi-kilogram scale. In addition, many methodologies exhibit poor functional group tolerance[3] or generate large quantities of hazardous waste.[4] By far, the most common oxidant cited in the chemical literature is hydrogen peroxide,[5] but known safety hazards exist because of the potential release of oxygen, and recently an incident has been reported where vapor ignition occurred in a reactor.[6] An attractive alternative to the aforementioned routes for the synthesis of sulfones is use of sodium hyopochlorite, which is inexpensive andrelatively non-toxic and which would eliminate much of the waste-stream issues. Herein we report development of a high-yielding, mild, green chemical tandem S_NAr/oxidation sequence to produce **1** and related sulfones.

Results and Discussion

2-Benzenethiopyridine, **2**, was initially prepared by modification of a known literature preparation that utilized an S_NAr reaction (Figure 1).[7] Although this procedure was effective and produced thiopyridine **2** in ~90% crude yield, the synthesis

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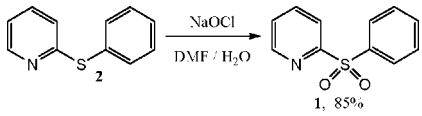

Figure 2. **Oxidation of 2 with concentrated sodium hypochlorite.**

was untenable for multi-kilogram scale production for the following reasons: (1) 2 equiv of thiophenol used for the reaction was undesirable because of its stench and acute toxicity;[8] (2) excess triethylamine was used to promote the reaction; (3) benzene was the workup solvent. In addition, an unsuccessful alternative we explored was preparation of thiopyridine **2** via Queguiner's thioether Grignard approach (Figure 1).[9]

The S_NAr approach was optimized using 1 equiv of thiophenol and potassium carbonate at 85 °C in DMSO. After an extractive workup with methyl-*tert*-butyl ether as a substitute for benzene, 2-phenylthiopyridine **2** was produced in 90% yield and contained only small amounts of 2-BrPy, PhSH, and $(PhS)_2$ impurities. Although issues remained surrounding the large volumes of solvent used in the workup, the S_NAr approach was sufficient for generating large quantities of **2** for evaluation of the oxidation step. Conversion of sulfide to the sulfone was initially successfully accomplished via the use of magnesium bis(monoperoxyphthalate)-hexahydrate (MMPP) in DMF, which produced clean sulfone in 65–72% yield. However, 5 min after charging MMPP, a severe safety hazard resulted in that the mixture exothermed from ambient temperature to ~150 °C. In addition, due to the higher molecular weight and low potency of commercial MMPP (which is sold as an 80 wt % solid), it was necessary to use four times as much by weight of MMPP as starting sulfide, which created a large waste disposal issue on top of the safety concerns. OXONE was also screened and resulted in incomplete conversion with similar difficulties with the waste profile. Sodium hypochlorite was the next oxidant screened, and rather than 5% household bleach, a concentrated solution of 10–13 wt % NaOCl was evaluated. It was anticipated that concentrated bleach would reduce the quantity of aqueous waste and minimize the risk of sulfoxide precipitation, which was problematic using OXONE. Addition of 2 equiv of concentrated hypochlorite to a DMF solution containing sulfide **2** resulted in the complete conversion of starting material to sulfoxide intermediate.[10] The resulting mixture was then heated to 85 °C, and two additional charges of bleach were added followed by a short stir time to complete conversion to product. Water was added to bring the total aqueous content to 12.5 volumes (L/kg starting material), the mixture was cooled to 23 °C, and sulfone **2** was collected via filtration in 85% yield (Figure 2).

With the individual steps worked out in a rough fashion for the preparation of 2-benzene sulfonyl pyridine, **1**, attention was directed toward telescoping both steps in order to avoid the troublesome workup and isolation of 2-benzenethiopyridine, **2**. Since the oxidation step was not compatible with DMSO, the S_NAr would have to be performed in a non-reactive aprotic solvent such as DMF. To this end, a trial S_NAr was carried out in DMF under the same conditions as employed with DMSO, and the crude reaction performance appeared comparable. While addition of 10.8% bleach to an unfiltered reaction mixture of sulfide **2** eventually consumed **2** fully, a mixture of sulfoxide and sulfone was produced in a 2:1 ratio, which did not improve even with added bleach. The obvious next step was to test the oxidation in the absence of carbonate salts. This was accomplished by performing the S_NAr in 5 volumes of DMF, cooling the reaction mixture to 23 °C after S_NAr completion, and then filtering off the waste salts. The filtrate was then treated with concentrated bleach in portions until the sulfide and resulting sulfoxide were fully consumed as per HPLC analysis. To facilitate complete conversion of sulfoxide to sulfone, it was necessary to heat the oxidation mixture to ~80 °C and maintain this temperature during the bleach addition. After completion of the bleach feed, water was added to increase the total aqueous content to 18 volumes,[11] the mixture was then cooled to 5 °C, and the resulting slurry was filtered and rinsed with water. These conditions produced pristine 2-phenylsulfonyl pyridine as a white crystalline solid in 78% over the two steps on a 10-g scale (Table 1, entry 1). When this procedure was scaled from 20 to 100 g, the yield of **1** improved to 85% and the results from multiple runs were consistent (Table 1, entries 2–5).

Despite the successes of the tandem S_NAr/oxidation sequence to produce **1**, the amount of concentrated NaOCl required for complete conversion to sulfone was inconsistent from run to run and generally required 3–4 equiv. The Chapman–Stevens oxidation is a well-known method for synthesis of aldehydes and ketones from primary or secondary alcohols,[12] and in this procedure bleach and acetic acid are combined to produce hypochlorous acid (vide infra), which serves as the active oxidizing agent. Most commonly, acetic acid is used as solvent then bleach is added and the product is obtained via an extractive workup or precipitation. We reasoned that it might be possible to extend this procedure to the synthesis of sulfones. In addition, it was reasoned that the acetic acid may impart additional solubility for the intermediate sulfoxide and further facilitate the conversion to sulfone. To assess the impact of acetic acid on the oxidation of **2** with bleach, a DMF solution of crude **2** prepared from the S_NAr was treated with 4 equiv of acetic acid, and then 2 equiv of 10.8% bleach was added over 45 min while maintaining the pot contents at <45 °C throughout the bleach feeds. Under these conditions complete conversion to sulfone was observed without any detectable sulfoxide intermediate. In a separate experiment the acetic acid charge was reduced to 1.5 equiv, and under these conditions the product crystallized at 40–45 °C and was isolated in 92% yield. With these results

(8) Thiophenol has been designated a P-code chemical as per 40CFR261.33 that specifies even unused thiophenol is hazardous waste.

(9) Bonnet, V.; Breton, G.; Marsais, F.; Mongin, F.; Quéguiner, G.; Trécourt, F. *Tetrahedron* **2000**, *56*, 1349.

(10) The temperature of the pot contents was raised from 23–60 °C; while the exotherm for the Trankopach reaction was sharp, it was addition-rate controlled, an important safety feature.

(11) This was an increase from the 12.5 vol of aqueous used in the original procedure due to the extra DMF and the much lower salt content in the bleach oxidation as compared to that with MMPP.

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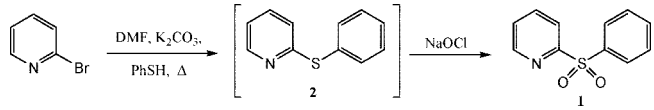
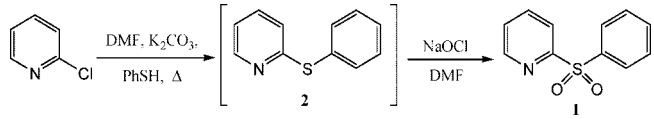
Table 1. **Tandem S_NAr/oxidation**



run	scale (g)[a]	NaOCl (equiv)[b]	yield (%)
1	10	3.0	78
2	100	3.6	86
3	25	3.7	84
4	20	2.4	86
5	50	4.0	85

[a] Amount of 2-BrPy used. [b] Adjusted for titrated strength.

Table 2. **Optimized oxidation/S_NAr synthesis of 2-phenylsulfonyl pyridine, 1**



entry	S_NAr temp (°C)	S_NAr time (h)	S_NAr conv (%)	bleach strength (w/w %)	isolated **1** (g)	yield (%)	purity (%)[a]
a[b]	110	12	100	10.6	24.7	85.0	99.6
b	110	17	98.2	8.3	99.7	87.3	100
c	110	16	97.4	10.8	99.0	86.7	99.5
d	110	20	98.4	12.6	148.6	86.0	99.8
e[c]	85	13	97.7	10.8	98.2	88.5	99.1
av						86.7	99.6

[a] Purity determined by HPLC relative to 2-phenylsulfonyl pyridine reference standard. [b] Reaction run with 0.96 equiv of 2-chloropyridine and spiked with 0.05 equiv of 3-chloropyridine. [c] 2-Bromopyridine comparator.

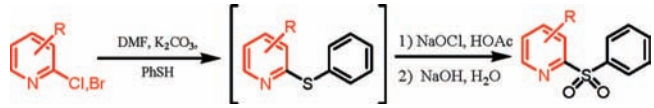
in hand we proceeded rapidly to scale up this chemistry, and all future experiments were run by the combined S_NAr/oxidation approach.

Despite the absence of literature reports of successful tandem S_NAr/oxidation chemistry for sulfone synthesis via aryl chlorides without activation, we investigated 2-chloropyridine as a substrate due to the potential large positive economic impact on the project.[13] As shown in Table 2, the results were exemplary using 2-chloropyridine; the only modification required in order to achieve equivalent conversion to the bromide system was to perform the chemistry at 110 °C rather than 80–90 °C. The standard conditions were rapidly scaled, several runs were performed on a 100-g scale or greater, and the process was found to work acceptably with bleach strength ranging from 8 to 13% (Table 2) to produce **1** in 85–88% yield, which allowed us to give the 2-bromopyridine approach the hard goodbye. Overall, the purity of isolated **1** was excellent in all cases, and potential positional isomers present in the 2-chloropyridine feedstocks that were evaluated in the synthesis did not appear to carry through in any significant amount, which was an important requirement. For example, an experiment was performed where the S_NAr was run with a slight subcess of 2-chloropyridine (0.96 equiv) while spiked with 5 mol % of 3-chloropyridine (Table 2, entry a). In this case, 100% conversion was observed in the S_NAr and only a trace amount of 3-benzenesulfonylpyridine, **3** (0.01%) was detected in the isolated product, **1**, as per HPLC analysis. To provide a consistent crystallization, the amount of water added to the workup was adjusted to provide a total aqueous content of 12 vol based on the bleach strength; typically after isolation approximately 6% of **1** is retained in the filtrate. In all cases tested, a clean conversion to sulfone was achieved with a maximum operating temperature of 50 °C. In a typical experiment, the bleach feed was commenced at ambient temperature, then the mixture was heated to 40 °C, and the exotherm of the reaction was controlled by adjusting the bleach dosing rate.

With the development of a commercial process for the syntheses of **1** completed, we now had the occasion to investigate the generality of the methodology to the synthesis of selected aryl sulfides and sulfones. The first set of sulfone syntheses evaluated were regioisomeric or disubstituted sulfones (Table 3, entries b–f) related to **1** that were potential starting material based process impurities. The S_NAr for the dihalopyridines were more facile than with the parent system **2** as a result of the favorable electronic influence of the additional electron-withdrawing group. In cases where bis-sulfones were possible (Table 3, entries d–f), high selectivity for the monosulfones were achieved. Predictably, electron-withdrawing groups on the pyridine ring resulted in dramatic acceleration in the S_NAr reaction rates. For example, the S_NAr reaction for pyridine substrates containing nitro groups went to completion within 1 h at 23 °C, and these systems produced the highest yielding sulfones (93%) of any evaluated via the standard conditions (Table 3, entries h and i). Similarly, the pyridine *N*-oxides saw a rapid increase in reaction rate in the S_NAr (Table 3, entries j and k). However, in these cases the yield of isolated

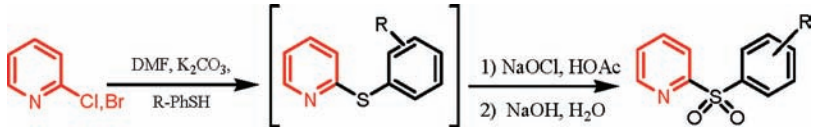
(13) Aldrich Pricing: 2-bromopyridine = $224/500 g or $70.80/mol; 2-chloropyridine = $73.30/500 g or $16.60/mol.

Table 3. **Tandem S_NAr/oxidation evaluation with alternative pyridine and aromatic substrates (HPLC purity data is reported for isolated solids)**



entry	R-pyridine	S_NAr time (h)	S_NAr temp (°C)	S_NAR conv (%)	bleach strength (%)	sulfone purity (%)	sulfone yield (%)	compound no.
a	2-chloro	16	110	97	10.8	>99	87	**1**
b	3-bromo	48	100–120	95	10.8	98	73	**3**
c	4-bromo	15	85	100	10.8	98	83	**4**
d	2,3-dichloro	3	60	99	8.9	92	85	**5**
e	2,3-dibromo	1	35	100	12.0	97	76	**6**
f	2,6-dichloro	1	50	100	8.9	92	85	**7**
g	2-chloro-4-methyl	17	110	94	8.9	95	82	**8**
h	2-chloro-5-nitro	1	23	100	8.9	95	93	**9**
i	2-chloro-3-nitro	0.2	23	100	8.9	>99	93	**10**
j	2-bromo- *N*-oxide	0.5	40	100	8.3	>99	66	**11**
k	2-chloro- *N*-oxide	1	105	99	11.7	>99	73	**11**
l	3-chloro-5-cyano	1	90	100	11.9	94	86	**12**
m	2-chloro-quinoxaline	1	110	100	12	>99	75	**13**
n	2-chloro-quinoline	1	110	100	12	95	65	**14**

Table 4. **Tandem S_NAr/oxidation with substituted thiophenols**



entry	thiophenol	Cl/Br	S_NAr time (h)	S_NAr temp/conv (%)	bleach strength (%)	sulfone purity (%)	sulfone yield (%)	compound no.
a	H	Cl	16	110/97	10.8	>99	87	**1**
b	3-Cl	Cl	20	110/96	8.9	>99	76	**15**
c	3-Cl	Br	4	80/100	8.9	>99	91	**15**
d	3-F	Br	20	80/100	11.9	95	87	**16**
e	3,5-bis(CF_3)	Br	20	95/97	12.0	97	72	**17**
f	2-Br	Br	16	120/100	11.0	98	75	**18**
g	4-NO_2	Br	20	115/100	11.7	89	82	**19**
h	4-Me	Cl	20	110/98	8.0	92	89	**20**
i	4-MeO	Cl	5	110/98	8.3	94	61	**21**
j	2-CF_3	Br	18	110/97	12.0	95	78	**22**

sulfone, **11** was lower as a result of the increased solubility of the *N*-oxide products in the filtrate. The most sluggish performance in the S_NAr was observed with the 3-bromopyridine substrate, which required 120 °C and 48 h reaction time and still did not go to completion (Table 3, entry b).

Another class of compounds evaluated under standard conditions were 2-chloroquinoxaline and 2-chloroquinoline (Table 3, entries m and n), and in both cases the S_NAr was efficient. Because of the extreme insolubility of their sulfoxide intermediates, it was not possible to isolate either of the target sulfones free of sulfoxide contamination under the standard processing conditions. However, in both cases the isolated sulfone/sulfoxide mixtures (containing 15–30% sulfoxide impurities) were resubjected to the oxidation reaction conditions to achieve conversion to product in overall 65% and 75% yield. Finally, we assessed the compatibility of the tandem S_NAr/oxidation sequence to nitrile functionality (Table 3, entry l) and the S_NAr was facile under the standard conditions without nitrile oxidative hydrolysis.

After completing the screening of substituted pyridines, we next assessed the generality of the tandem S_NAr/oxidation toward substitution on the thiophenol ring (Table 4). Predictably, electron-withdrawing substituents on the thiophenol ring retarded the S_NAr reaction rate, whereas electron-donating substituents resulted in a slight increase in reaction rate. In most cases, high quality sulfones were produced by the standard conditions.

Conclusion

An efficient, novel, green chemical synthesis for the production of 2-benzene-sulfonyl pyridine, **1**, has been demonstated, and we have shown this methodology to be general for the synthesis of aryl pyridylsulfones. To our knowledge this is an unprecedented application of a tandem S_NAr/oxidation sequence to produce sulfones, and this methodology potentially has broad applicability to the synthesis of this class of compounds.

Experimental Section

General. Unless otherwise noted, stated reagents were commercially available and used without purification. Solvents were not distilled prior to use, and NMR data were obtained using a Varian instrument at 300 or 500 mHz for ^{1}H and 125 Hz for ^{13}C. Products were isolated using polypropylene filters purchased from U.S. Filter, 100% Polypro; Egg-shell finish 20 μm nominal pore size.

Procedure for Preparation of 2-Benzenesulfonyl-pyridine (1). A 2-L flask is charged with 2-chloropyridine (75 mL, 790 mmol), thiophenol (90 mL, 852 mmol), and DMF (450 mL). K_2CO_3 (134.6 g, 962 mmol) is added, and then the mixture is heated to 110°C and stirred for 20 h. The mixture is filtered through polypropylene, the waste cake is rinsed with DMF (195 mL), and then the crude sulfide solution and rinsings are transferred to a 5-L flask. The oxidation is carried out by addition of glacial HOAc (57 mL, 995 mmol), heating to 40 °C, and addition of 13 wt % NaOCl solution (850 mL, 1.7 mol) slowly over 2 h. The conversion of the sulfide to sulfoxide and sulfone is monitored by HPLC. When the oxidation is complete, water (530 mL) is added, and the heating is discontinued. The pH of the mixture is raised to 9 with 20 % (w/v) NaOH solution (250 mL), and the resulting slurry is cooled to <5 °C. The mixture is stirred cold for 1.5 h and filtered through polypropylene, and then the wetcake rinsed with water (3 × 200 mL). The cake is dried in a 55 °C vacuum oven for at least 12 h to provide 2-benzenesulfonyl pyridine (149 g, 676 mmol) in 86 % yield and>99% purity. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 7.7 Hz, 1H), 8.05 (m, 2H), 7.92 (ddd, J = 9.3, 7.7, 1.6 Hz, 1H), 7.60 (m, 1H), 7.54 (m, 2H), 7.44 (m, 1H); IR (KBr) 788, 984, 1124, 1166, 1306, 1424, 1446, 1575, 3085 cm^{-1}; MS (TOF) m/z 220.0439 (220.0427 calcd for $C_{11}H_{10}NO_2S$, MH). Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39; S, 14.62. Found: C, 60.40; H, 4.02; N, 6.40; S, 14.76.

Acknowledgment

We thank Dr. Alfio Borghese and Mr. Luc Antoine for their contributions to this project at its early stages. We also acknowledge the contributions of Mr. Steven Bandy and Miss Amy Hargis who developed an HPLC purity method for compound **1**.

Supporting Information Available

General experimental procedures, synthetic details, ^{1}H and ^{13}C NMR spectra for key compounds shown in Tables 1–4. This material is available free of charge via the Internet at http://pubs.acs.org.

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