

A Practical, One-Pot Synthesis of
Sulfonylated Pyridines

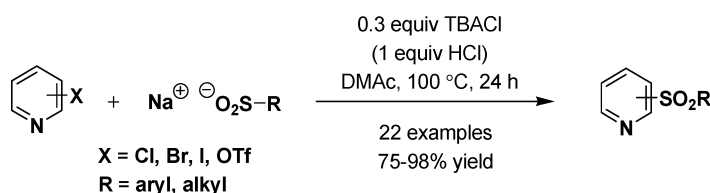
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ABSTRACT



A concise and efficient one-pot synthesis of functionalized sulfonylated pyridines via an $\text{S}_{\text{N}}\text{Ar}$ reaction of readily available pyridines and sodium sulfinate salts in the presence of tetrabutylammonium chloride is presented.

The pyridyl sulfone moiety has proven to be a valuable building block in both medicinal¹ and agricultural chemistry.² Sulfonylated pyridines have been shown to be anti-inflammatory,³ antihyperglycemic,⁴ and immunosuppressive⁵ agents as well as inhibitors of HIV-1 reverse transcriptase.⁶ In addition to their medicinal importance, sulfonylpyridines are useful intermediates in organic synthesis⁷ and exhibit

interesting chemical properties.⁸ Due to their unique physical properties and promising biological activities, sulfonylated pyridines have emerged in recent years as important synthetic targets and central pharmacophores in a large number of biologically active medicinal agents.

The most common approach for the preparation of sulfonylated pyridines has typically involved displacement of a halopyridine with a thiol followed by oxidation of the corresponding sulfide (eq 1).⁹ Limitations of this protocol include the use of odoriferous thiols and problematic oxidations that can generate large quantities of hazardous waste.¹⁰ In addition to the high environmental burden, the two-step protocol suffers from poor atom economy. Recently, metal-catalyzed cross-coupling of sulfinate salts with ha-

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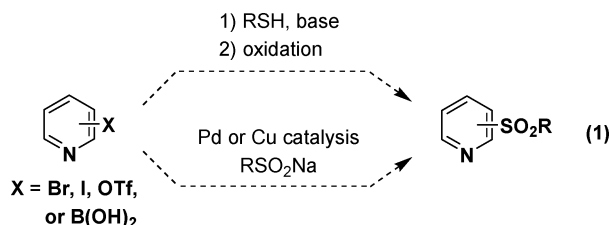
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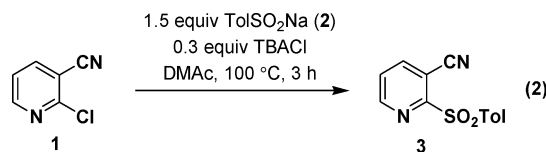
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lopyridines¹¹ and pyridyl boronic acids¹² have been reported; however, yields are generally low (<50%) for the preparation of sulfonylated pyridines. While the nucleophilic S_NAr reaction of activated aryl halides with sulfinic acid salts has been reported,¹³ application of this protocol for the preparation of sulfonylated pyridines has been limited to a single report which utilized microwave heating in refluxing DMSO behind a blast shield.¹⁴ In order to fully define biological profiles, strategies which provide rapid and efficient access to sulfonylated pyridines are important synthetic tools. In this paper, we describe the development of a practical, one-pot synthesis of sulfonylated pyridines via the direct S_NAr displacement of readily available chloropyridines with sulfinic acid salts.



Our investigations began by examining the preparation of sulfonylpyridine **3** (eq 2). After conducting a thorough catalysis screen exploring Pd sources, Cu sources, ligands, additives, and solvents, we observed that tetrabutylammonium chloride (TBACl) as an additive^{11a} and dimethylacetamide (DMAc) as solvent afforded moderate yields of **3** irrelevant of the metal source or ligand. Intrigued by these results, we decided to explore the feasibility of a simple phase-transfer-catalyzed (PTC) S_NAr approach to pyridine **3**. As shown in eq 2, simply heating chloropyridine **1** with sulfinate **2**¹⁵ in the presence of a catalytic amount TBACl in DMAc at 100 °C for 3 h afforded pyridine **3** in 93% isolated yield.¹⁶ In the absence of TBACl, conversion was <20% at the same time point.¹⁷ We speculated that the significant rate increase in the presence of TBACl could be explained by the formation of *n*-Bu₄NSO₂Tol from TBACl and NaSO₂Tol.^{18,19} In order to probe this possibility, we prepared *n*-Bu₄NSO₂Tol and subjected it to the reaction with **1**. This gave complete conversion to **3**. The fact that *n*-Bu₄NSO₂Tol is more soluble than NaSO₂Tol in DMAc nicely accounts for the increased reaction rates.²⁰ Isolation

of **3** in analytically pure form was achieved by addition of water at the end of the reaction and filtration of the resulting slurry to give analytically pure **3** avoiding the need for chromatography.



Having identified optimal conditions for the sulfonylation of chloropyridine **1**, we set out to explore the scope and generality of the procedure. As shown in Table 1, electron-

Table 1. Sulfonylation of Electron-Deficient Chloropyridines

General Procedure A:
1.5 equiv TolSO₂Na
0.3 equiv TBACl, DMAc, 100 °C

entry	substrate	product	conditions	yield (%) ^a
1			A	85%
2			A	96%
3			A	89%
4			A	98%
5			A	98%
6			A	90%

^a Isolated yields.

deficient chloropyridines afforded an array of highly functionalized sulfonylated pyridines in excellent yields. Of particular importance is entry 5, where the inherently less reactive 3-position of **12** underwent successful sulfonylation.

Attempts to apply our standard procedure (A) to electron-neutral chloropyridines proved unsuccessful as shown in

(20) *N*-Bu₄NSO₂Tol was completely soluble in DMAc at 100 °C.

(11) (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem.* **2004**, 69, 5608. (b) Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, 70, 2696.

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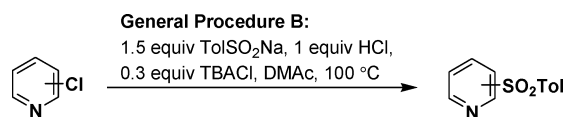
(15) Both commercially available sodium *p*-toluenesulfinate and sodium *p*-toluenesulfinate hydrate could be employed with equal success.

(16) DMAc was found to be the superior solvent for this reaction; nonpolar aprotic solvents resulted in no reaction.

(17) For a related transformation on a chloropyridine in the absence of TBACl, see: Caron, S.; Do, N. M.; Sieser, J. E.; Whritenour, D. C.; Hill, P. D. *Org. Process Res. Dev.* **2009**, 13, 324.

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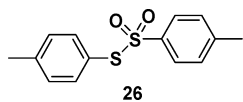
(19) The solubility of sodium *p*-toluenesulfinate in DMAc at rt was measured to be 1.0 mg/mL and at 100 °C was 1.5 mg/mL by HPLC analysis.

Table 2. Sulfonylation of Electron-Neutral or -Rich Chloropyridines

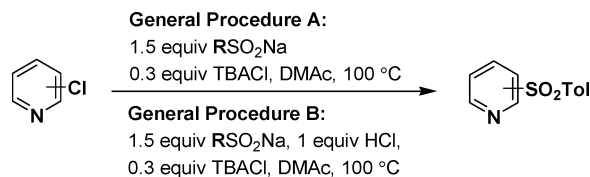
entry	substrate	product	conditions	yield (%) ^a
1			A B	<1% 89%
2			B	97%
3			B	95%
4			B	0%
5			B	88%

^a Isolated yields.

entry 1 (Table 2). Realizing we needed to activate the pyridine ring for S_NAr displacement, we explored the possibility of an acid-promoted sulfonylation. After screening several acids, we discovered that addition of 1 equiv of concd HCl to our standard reaction conditions facilitated the reaction of electron-neutral chloropyridines presumably via protonation of the pyridine nitrogen (entry 1).²¹ With a modified procedure in hand (procedure B), electron-neutral chloropyridines **18** and **20** were successfully sulfonylated to give **19** and **21** in excellent yields. In the case of 3-chloropyridine **22** (entry 4), no identifiable product was obtained and represents the only limitation to the present methodology.²² Even more exciting was the successful sulfonylation of the electron rich chloropyridine **24** to give **25** in 88% yield as shown in entry 5. It should be mentioned that under the acidic conditions of procedure B we identified small amounts of ester **26**²³ as a byproduct.



Having identified general conditions for the sulfonylation of a variety of chloropyridines, we investigated the scope of

Table 3. Sulfonylation of Nitrogen Heterocycles

entry	substrate	product	conditions	yield (%) ^a
1			A	91%
2			A	82%
3			A	75%
4			A	90%
5			B	90%
6			A	80%
7			A	86%

^a Isolated yields.

the sulfonylation with respect to other halopyridines, heterocycles, and sulfinate salts. As shown in entries 1–3 (Table 3), the sulfonylation worked equally as well with iodopyridines, bromopyridines, and pyridine triflates to afford the products in good to excellent yield. However, in the case of triflate **31**, we did observe ca. 15% hydrolysis to give the corresponding 2-hydroxypyridine by product. It should be mentioned that hydrolysis was not seen in any of the

(21) While protonation of sodium *p*-toluenesulfonate is a possibility in the presence of HCl, the fact that these reactions proceed to completion and in high yield suggest that protonation of the pyridine nitrogen is faster.

(22) 3-Bromopyridine, 3-fluoropyridine, and 3-iodopyridine also failed to react with sulfinate **2**.

(23) For the preparation of compound **26** under similar conditions, see: (a) Smiles, G. *J. Chem. Soc.* **1924**, 125, 181. (b) Freeman, F.; Bartosik, L. G.; Van Bui, N.; Keindl, M. C.; Nelson, E. L. *Phosphorus Sulfur* **1988**, 53, 375.

Table 4. Sufonylation of Dichloropyridines

entry	dichloropyridine	product	yield(%) ^a
1			92
2			91
3			93
4			81

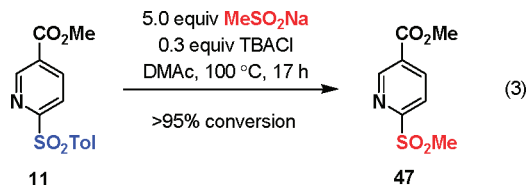
^a Isolated yields.

halopyridines cases. As shown in entries 4 and 5 (Table 3), we were able to extend the methodology to other nitrogen heterocycles. Chloropyrazine **33** afforded the desired sulfone **34** in 90% yield under our standard conditions. Interestingly, subjecting chloroquinoline **35** to general procedure B afforded predominantly the hydrolysis by product 2-hydroxyquinoline. However, switching to anhydrous HCl instead of concd HCl reduced the hydrolysis product from 70% to <8% and afforded the desired sulfone **36** in 90% isolated yield. Finally, we explored the sulfonation procedure utilizing other sodium sulfinate salts. As shown in entries 6 and 7, our sulfonation procedure afforded methyl sulfone **37** and *p*-chlorophenyl **38** in 80% and 90% yields, respectively.²⁴

Next, we set out to explore the reactivity of several dichloropyridines utilizing general procedure B. As shown in Table 4, treatment of dichloropyridine **39** with 3 equiv of sulfinate **2** afforded disulfonated pyridine **40** in 92% yield.

(24) Although not investigated in the present study, the methodology should be applicable to other types of alkyl and aryl sulfinate salts.

Alternatively, sulfonation of dichloropyridine **41** afforded exclusively the monosulfonated pyridine **42** in 91% yield (entry 2). Analysis of the crude reaction mixture by both HPLC and ¹H NMR analysis revealed no detectable sign of the expected disulfonated pyridine. In a similar fashion, reaction of dichloropyridines **43** and **45** also gave the monosulfonated pyridines **44** and **46** as the exclusive products in excellent yields. In stark contrast to entry 5 of Table 1 bearing similar activation products **42**, **44**, and **46**, this reaction remained resistant to further displacement of the second chlorine atom even upon prolonged heating. Mechanistically, this suggested that the sulfonyl group at C-2 (entries 2 and 3, Table 4) and C-4 (entry 4, Table 4) is more reactive toward S_NAr than the chloro substituent. Therefore, the monosulfonated products are continually reacting at C-2 and C-4 and never at the carbon bearing the second chlorine atom. To support this hypothesis, we subjected sulfonated pyridine **11** to our standard sulfonation conditions with a different sulfinate salt as shown in eq 3. As predicted, MeSO₂Na underwent addition at the C-2 sulfonyl group to give sulfonated pyridine **47** in >95% conversion.



In conclusion, a concise, one-pot protocol has been developed for the rapid preparation of highly functionalized sulfonated pyridines. This efficient and high-yielding procedure is operationally simple and generally requires no chromatographic purification. The use of TBACl imparts a significant rate acceleration through the in situ formation of *n*-Bu₄NSO₂Tol. From a mechanistic standpoint, displacement of the sulfonyl group is a continuous process and potentially allows for a switchable procedure to evaluate alternative sulfonyl moieties. Finally, the method is safe, scalable, and significantly greener than current alternatives.

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Supporting Information Available: Experimental details and characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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