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A Practical, One-Pot Synthesis of Sulfonylated Pyridines

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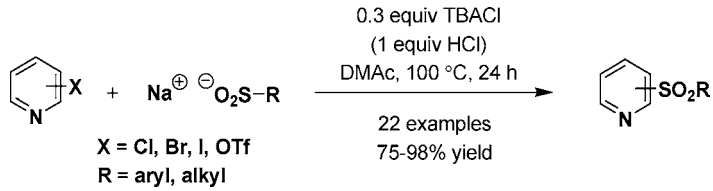
ABSTRACT



A concise and efficient one-pot synthesis of functionalized sulfonylated pyridines via an S_NAr 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 medicinal[1] and agricultural chemistry.[2] Sulfonylated pyridines have been shown to be anti-inflammatory,[3] antihyperglycemic,[4] and immunosuppressive[5] agents as well as inhibitors of HIV-1 reverse transcriptase.[6] In addition to their medicinal importance, sulfonylpyridines are useful intermediates in organic synthesis[7] 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-

(1) For leading references, see: (a) Furukawa, A.; Fukuzaki, T.; Onishi, Y.; Kobayashi, H.; Matsufuji, T.; Honda, T. WO 2010082601, July 22, 2010. (b) Harris, J. M.; Neustadt, B. R.; Stamford, A.; Liu, H. WO 2010075271, July 1, 2010. (c) Smith, N. D.; Bonnefous, C.; Kahraman, M.; Noble, S. A.; Payne, J. E.; Govek, S. P. WO 2010048149, April 29, 2010. (d) Hussain, I.; Yawer, M. A.; Lalk, M.; Lindequist, U.; Villinger, A.; Fischer, C.; Langer, P. *Bioorg. Med. Chem. Lett.* **2008**, *16*, 9898. (e) Galambos, J.; Keseru, G.; Gal, K.; Bobok, A. A.; Weber, C.; Prauda, L.; Wagner, G. A. WO 2008155588, December 24, 2008. (f) Harz, R. A.; Arvanitis, G.; Arnold, C.; Rescinito, J. P.; Hung, K. L.; Zhang, G.; Wong, H.; Langley, D. R.; Gilligan, P. J.; Trainor, G. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 934.

(2) For leading references, see: (a) Adams, J. B. US 4456469, 1984. (b) Taylor, J. B.; Wailes, J. S.; Jeanmart, S. A. M.; Govenkar, M. WO 2010069834, June, 24, 2010. (c) Selby, T. P.; Smith, B. T.; Stevenson, T. M. WO 2008100426, August 21, 2008. (d) Doweyko, A. M. P.; Regis, R. R.; Bell, A. R. US 4360677, November 23, 1982. (e) Nakagawa, T.; Tejima, I.; Okuma, N. JP 62181260, August 8, 1987.

(3) (a) Cheng, H.; Li, J.; Lundy, K. M.; Minich, M. L.; Sakya, S. M.; Uchida, C. WO 01/30216, June 7, 2001. (b) Reitz, D. B.; Manning, R. E.; Huang, H. C.; Li, J. US 5393790, February, 28, 1995.

(4) (a) Xia, Y.; Boyle, C. D.; Greenlee, W. J.; Chackalamannil, S.; Jayne, C. L.; Stamford, A. W.; Dai, X.; Harris, J. M.; Neustadt, B. R.; Neelamkavil, S. F.; Shah, U. G.; Lankin, C. M.; Liu, H. WO 2009055331, April, 30, 2009. (b) Asakawa, K. Sawada, N.; Tsuritani, T. Itoh, T.; Mase, T.; Takahashi, K. Xu, F. WO 2009041475, April 2, 2009.

(5) (a) Nicholas, B. ; Harcken, C.; Lee, T.; Liu, P.; Mao, C.; Lord, J.; Mao, W.; Denbush, B. C.; Razavi, H.; Sarko, C. R. WO 2009/137338, November 12, 2009. (b) Gilligan, M.; Humphries, A. C.; Ladduwahetty, T.; Merchant, K. J. WO 2006095205, September 14, 2006.

(6) Wassmundt, F. W. Preparation of aryl and heteroaryl compounds having anti-retrovirus activity. WO 9206683, 1992.

(7) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, 1993.

(8) For leading references, see: (a) Hama, F.; Kondo, F. JP 61271271, 1986. (b) Sato, F.; Ogoshi, T.; Shimizu, A. JP 04120050, 1992.

(9) For a leading reference, see: Trankle, W. G.; Kopach, M. E. *Org. Process Res. Dev* **2007**, *11*, 913.

(10) (a) Scalone, M.; Waldmeier, F. *Org. Process Res. Dev.* **2003**, *7*, 418. (b) Yang, D.; Yip, Y. C.; Jiao, G. S.; Wong, M. K. *J. Org. Chem.* **1998**, *63*, 8952.

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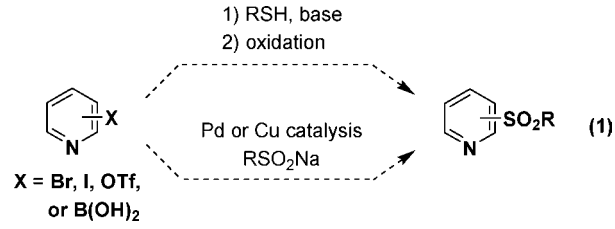
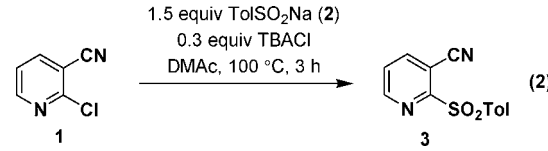
lopyridines[11] and pyridyl boronic acids[12] have been reported; however, yields are generally low (<50%) for the preparation of sulfonylated pyridines. While the nucleophilic S_NAr reaction of activated aryl halides with sulfinic acid salts has been reported,[13] application of this protocol for the 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.

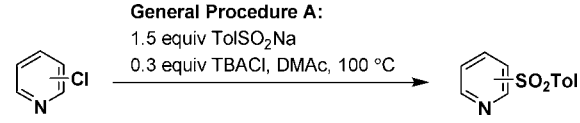


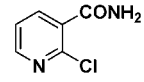
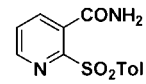
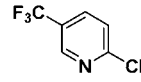
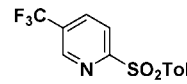
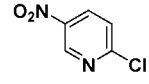
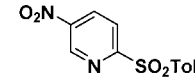
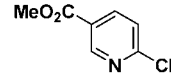
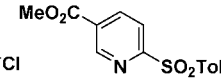
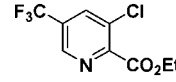
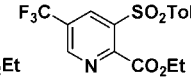
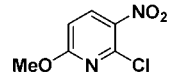
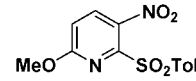
Our investigations began by examining the preparation of sulfonylpyridine **3** (eq 2). After conducting a thorough catalysis screen exploring Pd sources, Cu sources, ligands, additives, and solvents, we observed that tetrabutylammonium chloride (TBACl) as an additive[11a] and dimethylacetamide (DMAc) 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*-Bu_4NSO_2Tol from TBACl and $NaSO_2Tol$.[18,19] In order to probe this possibility, we prepared *n*-Bu_4NSO_2Tol and subjected it to the reaction with **1**. This gave complete conversion to **3**. The fact that *n*-Bu_4NSO_2Tol is more soluble than $NaSO_2Tol$ 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-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-postion of **12** underwent successful sulfonylation.

Table 1. Sulfonylation of Electron-Deficient Chloropyridines



entry	substrate	product	conditions	yield (%)[a]
1	 **4**	 **5**	A	85%
2	 **6**	 **7**	A	96%
3	 **8**	 **9**	A	89%
4	 **10**	 **11**	A	98%
5	 **12**	 **13**	A	98%
6	 **14**	 **15**	A	90%

[a] Isolated yields.

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

(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.

(12) (a) Kar, A.; Sayyed, I. A.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Org. Lett.* **2007**, *9*, 3405. (b) Huang, F.; Batey, R. A. *Tetrahedron* **2007**, *63*, 7667.

(13) Ulman, A.; Urankar, E. *J. Org. Chem.* **1989**, *54*, 4691.

(14) Zou, J.; Feng, L.; Feng, G. T. *Chin. J. Chem.* **2009**, *20*, 17.

(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.

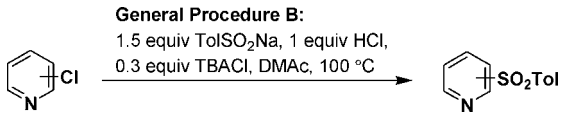
(17) For a related transformation on a chloropyridine in the absence of TBACl, see: Caron, S.; Do, N. M.; Sieser, J. E.; Whritenour, D. C.; Hill, P. D. *Org. Process Res. Dev* **2009**, *13*, 324.

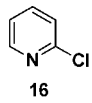
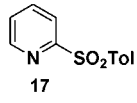
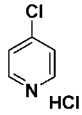
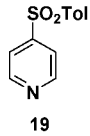
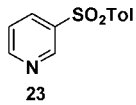
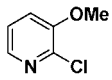
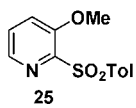
(18) Vennstra, G. E.; Zwaneburg, B. *Synthesis* **1975**, 519.

(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.

(20) *N*-Bu_4NSO_2Tol was completely soluble in DMAc at 100 °C.

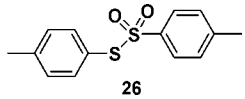
Table 2. Sulfonylation of Electron-Neutral or -Rich Chloropyridines



entry	substrate	product	conditions	yield (%)[a]
1	 **16**	 **17**	A B	<1% 89%
2	 **18**	 **19**	B	97%
3	 **20**	 **21**	B	95%
4	 **22**	 **23**	B	0%
5	 **24**	 **25**	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. In should be mentioned that under the acidic conditions of procedure B we identified small amounts of ester **26**[23] as a byproduct.



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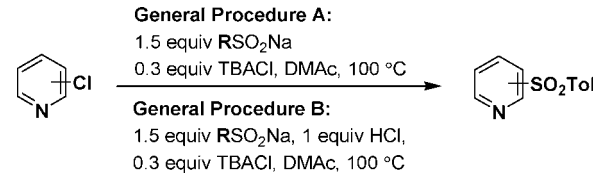
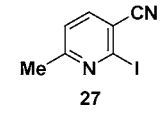
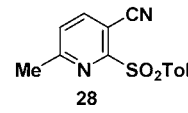
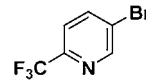
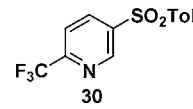
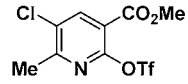
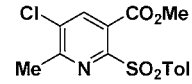
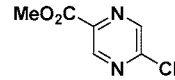
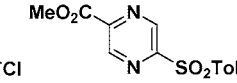
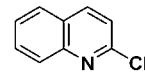
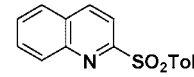
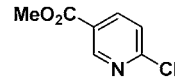
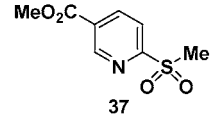
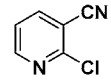
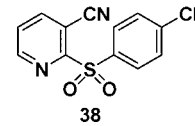
Having identified general conditions for the sulfonylation of a variety of chloropyridines, we investigated the scope of

Table 3. Sulfonylation of Nitrogen Heterocycles



entry	substrate	product	conditions	yield (%)[a]
1	 **27**	 **28**	A	91%
2	 **29**	 **30**	A	82%
3	 **31**	 **32**	A	75%
4	 **33**	 **34**	A	90%
5	 **35**	 **36**	B	90%
6	 **10**	 **37**	A	80%
7	 **1**	 **38**	A	86%

[a] Isolated yields.

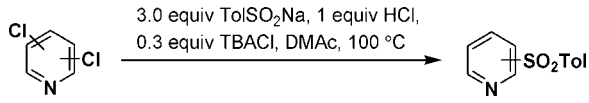
the sulfonylation with respect to other halopyridines, heterocycles, and sulfinate salts. As shown in entries 1−3 (Table 3), the sulfonylation worked equally as well with iodopyridines, bromopyridines, and pyridine triflates to afford the products in good to excellent yield. However, in the case of triflate **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

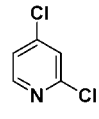
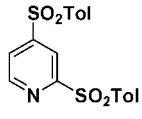
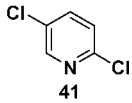
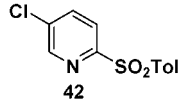
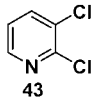
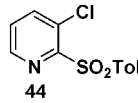
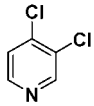
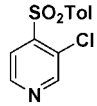
(21) While protonation of sodium *p*-toluenesulfinate is a possibility in the presence of HCl, the fact that these reactions proceed to completion and in high yield suggest that protonation of the pyridine nitrogen is faster.

(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	 **39**	 **40**	92
2	 **41**	 **42**	91
3	 **43**	 **44**	93
4	 **45**	 **46**	81

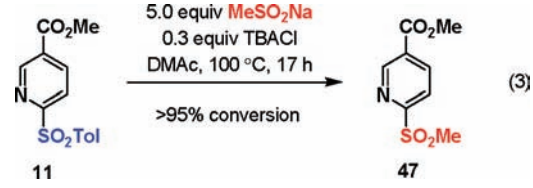
[a] Isolated yields.

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 sulfonylation 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 disulfonylated 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, sulfonylation of dichloropyridine **41** afforded exclusively the monosulfonylated pyridine **42** in 91% yield (entry 2). Analysis of the crude reaction mixture by both HPLC and ^{1}H NMR analysis revealed no detectable sign of the expected disulfonylated pyridine. In a similar fashion, reaction of dichloropyridines **43** and **45** also gave the monosulfonylated 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 monosulfonylated 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 sulfonylated pyridine **11** to our standard sulfonylation conditions with a different sulfinate salt as shown in eq 3. As predicted, $MeSO_2Na$ underwent addition at the C-2 sulfonyl group to give sulfonylated pyridine **47** in >95% conversion.



(3)

In conclusion, a concise, one-pot protocol has been developed for the rapid preparation of highly functionalized sulfonylated 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*-Bu_4NSO_2Tol. 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.

Acknowledgment. We thank Dr. Jingjun Yin (Merck & Co., Inc.) for valuable experimental assistance.

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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