Efficient and Scalable Synthesis of Pyridine Sulfonamides

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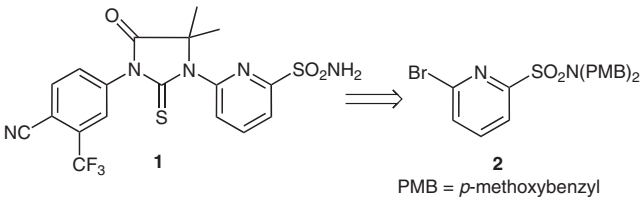
Received 13 January 2011

Abstract: Short-step and scalable transformations from 2,6-dibromopyridine to 6-bromopyridine-2-sulfonamide by means of halogen–metal exchange and subsequent reaction with sulfuryl chloride followed by amidation are established. Application of the method for the synthesis of various pyridine sulfonamides is also described.

Key words: sulfonyl chlorides, sulfonamides, pyridines, Grignard reaction, large-scale synthesis

Sulfonamide is an important functional group in medicinal chemistry as there are many pharmaceutical compounds possessing the functionality as a key structure.[1] Recently we found a promising drug candidate **1** for the treatment of prostate cancer carrying pyridine-2-sulfonamide in its molecule that necessitates 6-bromopyridine-2-sulfonamide **2** as a key building block (Scheme 1).[2]



Scheme 1

The known methods for such compounds require multiple steps including oxidation of corresponding mercaptanes using hazardous chlorine or its equivalent,[1a,3] after introducing a thio group to the pyridine ring. Addition of metalated pyridines to sulfur dioxide followed by oxidation with sulfuryl chloride is also a well-utilized way of synthesizing sulfonyl chlorides.[4] Recently Pandya et al. reported an efficient one-pot synthesis of heteroaromatic sulfonamides by this method.[5] But the handling of poisonous sulfur dioxide needs special care in the laboratory. Therefore the discovery of an efficient short-step synthesis of sulfonyl chlorides remains very desirable.

In 1968, Eaborn et al. reported the preparation of arenesulfonyl chlorides by the reaction of Grignard reagents with sulfuryl chloride.[6] But the application of the method has not been widely investigated and the synthesis of heteroarenesulfonyl chloride has not been reported.

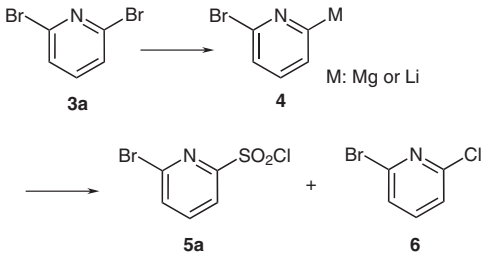
SYNLETT 2011, No. 8, pp 1117–1120
Advanced online publication: 18.04.2011
DOI: 10.1055/s-0030-1259953; Art ID: U00411ST

In response to this situation, we found that the reaction of metalated pyridine generated from halogen–metal exchange of 2,6-dibromopyridine (**3a**) with sulfuryl chloride efficiently afforded the corresponding 6-bromopyridine-2-sulfonyl chloride (**5a**). Here we wish to report the details of the results.

Our initial synthesis of the sulfonamide **2** started with 2,6-dibromopyridine (**3a**) involving sequential chlorosulfonylation by halogen–metal exchange with *i*-PrMgCl[7] and reaction with sulfuryl chloride, followed by amidation of the resulting monosulfonyl chloride **5a** with di(4-methoxybenzyl)amine. Although the halogen–metal exchange proceeded smoothly, we often encountered low yields of the product along with a fair amount of 2-bromo-6-chloropyridine (**6**) as a side product in the chlorosulfonylation step.

In order to find an optimum reagent system, various metallation conditions were tried.[8] Using the *i*-PrMgCl·LiCl developed by Knochel et al.,[9] the chlorosulfonylation reaction afforded irreproducible results in the product ra-

Table 1 Reagent and Reaction Conditions for 6-Bromo-2-pyridinesulfonyl Chloride Synthesis[a]

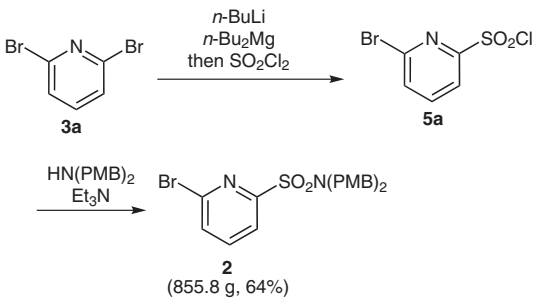


Entry	Metallation	Temp (°C)[b]	Ratio **5a/6**[c]	Yield of **5a** (%)[d]
1	*i*-PrMgCl	–10	21:79	16
2[e]	*i*-PrMgCl·LiCl	–10	87:13	–[f]
3	*i*-PrMgCl·LiCl	–10	31:69	–[f]
4	*n*-Bu_3MgLi	–10	83:17	74
5	*n*-Bu_3MgLi	10	83:17	59

[a] Reaction conditions: 2,6-dibromopyridine (0.8 mmol) and Grignard reagent (0.96 mmol) in THF (0.76 mL) then reacted with SO_2Cl_2 (1.2 mmol) at −10 °C.
[b] Reaction temperature for halogen–metal exchange.
[c] Molar ratio calculated by HPLC analysis.
[d] Yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as a standard compound.
[e] Reaction mixture was homogeneous on halogen–metal exchange.
[f] Not determined.

tio (Table 1, entries 2 and 3). The ratio likely depends on the appearance of the metallic species. Once the precipitation of the metalated pyridine came out, it gave 2-bromo-6-chloropyridine (**6**) selectively.[10] On the other hand when *n*-Bu_3MgLi generated by mixing *n*-Bu_2Mg with *n*-BuLi, developed independently by Oshima et al. and by Iida et al., was used for monoselective halogen–metal exchange,[11] sulfonyl chloride was obtained as a major product accompanied by 2-chloride **6** in a ratio of 83:17 reproductively in the reaction with sulfuryl chloride (Table 1, entry 4). When the chlorosulfonylation reaction was carried out at 10 °C, the yield decreased to 59% but the ratio of sulfonyl chloride **5a** to chloride **6** remained unchanged (Table 1, entry 5). The reason for the changeable result in the case of Grignard reagents is yet unclear, but chlorine generation caused by oxidation of the chloride ion, which itself had been generated by the Schlenk equilibrium of metallic species, and the subsequent reaction of the chlorine with insoluble metallic species would be one possibility of how the chloride side product **6** was formed.

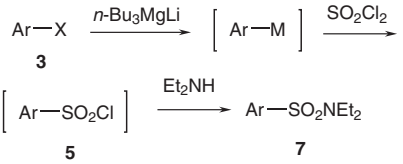
Having established acceptable conditions for the transformation of the dibromide **3a** into the monosulfonyl chloride **5a**, we next attempted its transformation into the amide **2** required for the synthesis of drug candidate **1** on a large scale. Thus, 700 grams of the dibromide **3a** was first treated with 0.4 equivalents of *n*-Bu_3MgLi in THF at –11 °C to carry out the halogen–metal exchange, and then the resulting metalated product was added to 1.5 equivalents of sulfuryl chloride in toluene at the same temperature to give the crude sulfonyl chloride **5a** accompanied by the side product **6**. Without further purification, the crude product was treated with 0.8 equivalents of di(4-methoxybenzyl)amine in EtOAc in the presence of 1 equivalent of triethylamine to give rise to the pure sulfonamide **2** in 64% overall yield after a single recrystallization of the crude product from aqueous EtOH (Scheme 2).[12]



Scheme 2

Very impressed by the established method allowing a facile introduction of chlorosulfonyl functionality on the pyridine ring, we next investigated the applicability of this method to other halogenated pyridine derivatives whose sulfonylation was presumed not to be an easy task. For convenience, we evaluated the reaction after conversion of the initially produced pyridinesulfonyl chloride **5** into the corresponding *N*,*N*-diethylsulfonamide **7** by treating the crude products with diethylamine to remove the unavoidable chloropyridine side products **6** in the chlorosulfonylation step.[13] *n*-Bu_3MgLi was used for halogen–metal exchange as a standard method but, if the halogen–metal exchange was unsuccessful with *n*-Bu_3MgLi, it was conducted with *i*-PrMgCl.

Table 2 Transformation of Halopyridines into Sulfonamides[a]



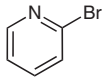
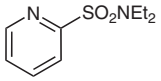
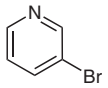
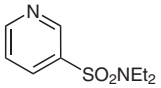
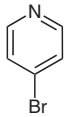
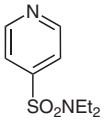
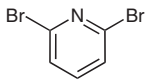
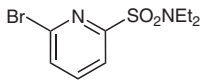
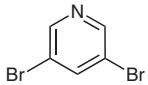
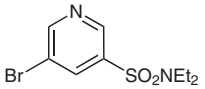
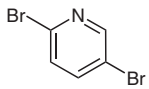
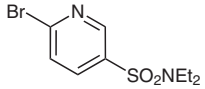
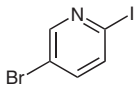
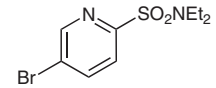
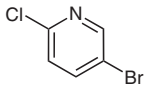
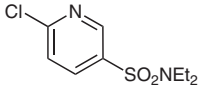
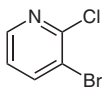
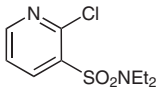
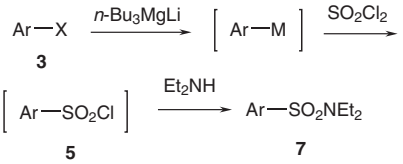
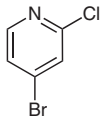
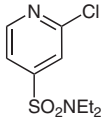
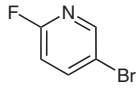
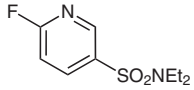
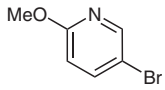
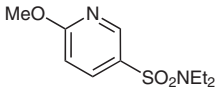
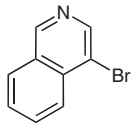
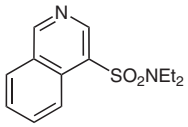
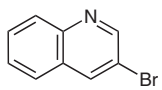
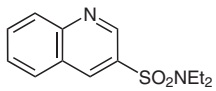
Entry	Halopyridine	Product	Yield (%)[b]
1	 **3b**	 **7b**	64
2[c]	 **3c**	 **7c**	60
3	 **3d**	 **7d**	71
4	 **3a**	 **7a**	72
5[c]	 **3e**	 **7e**	65
6	 **3f**	 **7f**	76
7[c]	 **3g**	 **7g**	67
8	 **3h**	 **7h**	76
9	 **3i**	 **7i**	78

Table 2 Transformation of Halopyridines into Sulfonamides[a] (continued)



3 5 7

Entry	Halopyridine	Product	Yield (%)[b]
10	 **3j**	 **7j**	63
11[d]	 **3k**	 **7k**	53[e]
12	 **3l**	 **7l**	80
13	 **3m**	 **7m**	52
14	 **3n**	 **7n**	46

[a] Reaction conditions: halopyridine (0.8 mmol), *n*-Bu_3MgLi (0.32 mmol), in THF (0.76 mL) at −10 °C, then SO_2Cl_2 (1.2 mmol) at −10 °C and Et_2NH (0.414 mL, 4.0 mmol) at 10 °C.
[b] Isolated yield.
[c] *i*-PrMgCl (0.96 mmol) was used for halogen–metal exchange at 10 °C.
[d] Et_2NH was added at −10 °C.
[e] 2-Diethylamino-5-pyridinesulfonamide was isolated in 5.3% yield.

In the reaction of monobromopyridines, each regioisomer afforded the pyridine sulfonamides in good yield (Table 2, entries 1–3). In the case of 3-bromopyridine (**3c**), since the use of *n*-Bu_3MgLi afforded non-transferable precipitate of the metalated pyridine, *i*-PrMgCl was used for halogen–metal exchange giving the sulfonamide **7c** as a major product by the usual chlorosulfonylation and amidation sequence (entry 2). Various dibromopyridines reacted in the same manner via monoselective halogen–metal exchange affording the bromo-substituted sulfonamides in good yield, which are versatile intermediates for further modification (entries 4–6).[8] In the case of 2,5-dibromopyridine (**3f**), halogen–metal exchange occurred regioselectively[8] giving the corresponding sulfonamide, whereas the regioisomer of **7f** was selectively synthesized by 2-iodo-5-bromopyridine (**3g**). Although chemoselective halogen–metal exchange of 2-iodo-5-bromopyridine (**3g**) with *n*-Bu_3MgLi was not performed, the use of *i*-PrMgCl selectively afforded the desired product by the same reaction sequence (entry 7).[14] Fluorine-substituted sulfonamide **7k** was also obtained in moderate yield because nucleophilic substitution of Et_2NH with a fluoro group in the amidation step proceeded to some extent (entry 11). We also examined the transformations with functionalized pyridine derivatives other than halogen-substituted pyridines. A methoxy group was tolerated affording the desired product (entry 12), but an ester group did not survive the standard conditions, as methyl 5-bromopyridine-2-carboxylate did not afford the desired product at all. Under the same reaction conditions bicyclic heteroaromatic compounds, 4-bromoisoquinoline (**3m**) and 3-bromoquinoline (**3n**) were also efficiently converted into the corresponding sulfonamide (entries 13 and 14).

In summary, we have developed an efficient synthetic procedure for large-scale preparation of 6-bromopyridine-2-sulfonyl chlorides. This method was proved to be applicable to the synthesis of functionalized sulfonyl chlorides and sulfonamides which are versatile intermediates for drug discovery.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank colleagues in process chemistry group (Masao Tsukazaki, Nobuaki Kimura, Sunao Takeda, Junichi Shiina, Minoru Yamawaki) for the support for large-scale synthesis and editing services of Chugai Pharmaceutical Co., Ltd for assistance with English usage.

References and Notes

(1) (a) Pu, Y.-M.; Christensen, A.; Ku, Y.-Y. *Tetrahedron Lett.* **2010**, *51*, 418. (b) Wang, C.; Hamilton, C.; Meister, P.; Menning, C. *Org. Process Res. Dev.* **2007**, *11*, 52. (c) Dudutiene, V.; Baranauskiene Matulis, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3335. (d) Allison, B. D.; Phuong, V. K.; McAtee, L. C.; Rosen, M.; Morton, M.; Prendergast, C.; Barrett, T.; Lagaud, G.; Freedman, J.; Li, L.; Wu, X.; Venkatesan, H.; Pippel, M.; Woods, C.; Rizzolio, M. C.; Hack, M.; Hoey, K.; Deng, X.; King, C.; Shanley, N. P.; Rabinowitz, M. H. *J. Med. Chem.* **2006**, *49*, 6371. (e) Hogan, P. J.; Cox, B. G. *Org. Process Res. Dev.* **2009**, *13*, 875.

(2) Yoshino, H.; Sato, H.; Shiraishi, T.; Tachibana, K.; Emura, T.; Honma, A.; Ishikura, N.; Tsunenari, T.; Watanabe, M.; Nishimoto, A.; Nakamura, R.; Nakagawa, T.; Ohta, M.; Takata, N.; Furumoto, K.; Kimura, K.; Kawata, H. *Bioorg. Med. Chem.* **2010**, *18*, 8150.

(3) (a) Park, Y. J.; Shin, H. H.; Kim, Y. H. *Chem. Lett.* **1992**, *21*, 1483. (b) Prakash, G. K. S.; Mathew, T.; Panja, C.; Olah, G. A. *J. Org. Chem.* **2007**, *72*, 5847. (c) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *J. Org. Chem.* **2009**, *74*, 9287.

(4) Hamada, T.; Yonemitsu, O. *Synthesis* **1986**, 852.

(5) Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. M. *J. Org. Chem.* **2003**, *68*, 8274.

(6) (a) Bhattacharya, S. N.; Eaborn, C.; Walton, D. R. M. *J. Chem. Soc. C* **1968**, 1265. (b) Gilbert, E. E. *Synthesis* **1969**, 3.

(7) (a) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett* **. 1999**, *40*, 4339. (b) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349.
(8) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Lett.* **2006**, *35*, 2.
(9) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
(10) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545.
(11) (a) Kitigawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2481. (b) Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4841.
(12) **Large-Scale Preparations of Sulfonamide 2**: *n*-BuLi (1.6 M, 737 mL), *n*-Bu_2Mg (2.0 M, 1176 mL), and THF (70 mL) were charged into a nitrogen-filled reaction vessel at r.t. After cooling at –11 °C, a solution of 2,6-dibromopyridine (700 g, 2.95 mol) in THF (2.7 L) was added dropwise over 1 h and 40 min and the mixture was stirred at –10 °C for 1 h. The resulting mixture was added to a solution of SO_2Cl_2 (364 mL, 4.53 mol) in toluene (2.8 L) at –12 °C over 1 h and 15 min and the mixture was stirred for 20 min. To the reaction mixture was added H_2O (2.8 L) over 40 min. After removal of the aqueous layer, the organic phase was dried over $MgSO_4$ (180 g). The mixture was filtered and concentrated affording the crude sulfonyl chloride **5a** (736.5 g). To a solution of the sulfonyl chloride (713 g) in EtOAc (2.1 L) at 0 °C was added a solution of $HN(PMB)_2$ (571.2 g, 2.22 mol) and Et_3N (385 mL, 2.76 mol) in EtOAc (2.1 L), and the mixture was stirred for 1 h and 10 min. The crude product obtained by extraction and concentration was purified by crystallization from EtOH and H_2O giving the sulfonamide **2** (855.8 g, 64%).
(13) **General Procedure**: *n*-BuLi (2.3 M, 0.139 mL) and *n*-Bu_2Mg (1.0 M, 0.321 mL) were charged into a nitrogen-filled reaction tube at r.t. A solution of halopyridine (0.8 mmol) in THF (0.76 mL) was added dropwise to the *n*-Bu_3MgLi solution at –10 °C and the mixture was stirred at –10 °C for 1 h. The resulting mixture was added to a solution of SO_2Cl_2 (0.096 mL, 1.2 mmol) in toluene (0.76 mL) at –10 °C and the mixture was stirred for 10 min. After allowing the temperature of the reaction mixture to rise to 10 °C, Et_2NH (0.414 mL, 4.0 mmol) was added and the mixture was stirred for 30 min. Extraction and purification by silica gel chromatography afforded the product.
(14) Song, J. J.; Yee, N. K.; Tan, Z.; Xu, J.; Kapadia, S. R.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4905.