Halogenation

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Importance of a Fluorine Substituent for the Preparation of *meta*- and *para*-Pentafluoro-λ^6-sulfanyl-Substituted Pyridines

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Abstract: *Although there are ways to synthesize ortho-pentafluoro-λ^6-sulfanyl (SF_5) pyridines, meta- and para-SF_5-substituted pyridines are rare. We disclose herein a general route for their synthesis. The fundamental synthetic approach is the same as reported methods for ortho-SF_5-substituted pyridines and SF_5-substituted arenes, that is, oxidative chlorotetrafluorination of the corresponding disulfides to give pyridylsulfur chlorotetrafluorides (SF_4Cl-pyridines), followed by chloride/fluoride exchange with fluorides. However, the trick in this case is the presence on the pyridine ring of at least one fluorine atom, which is essential for the successful transformation of the disulfides into m-and p-SF_5-pyridines. After enabling the synthesis of an SF_5-substituted pyridine, ortho-F groups can be efficiently substituted by C, N, S, and O nucleophiles through an S_NAr pathway. This methodology provides access to a variety of previously unavailable SF_5-substituted pyridine building blocks.*

Fluorinated aromatic heterocyclic compounds containing one or two nitrogen atom(s) in the aromatic ring have gained the attention of medicinal chemists owing to their distinctive physical, chemical, and biological properties arising from the reduced basicity of the nitrogen atom(s) as a result of the strongly electron withdrawing nature of fluorine and fluorinated substituent(s).[1] Fluorine substituents and fluorinated functional groups also modulate the lipophilicity/hydrophilicity balance of the parent heteroaromatic compounds to improve the bioavailability of drugs.[1g,2] Fluoropyridines[3] and trifluoromethylpyridines[4] are massively sought after building blocks for the preparation of pharmaceuticals and agrochemicals. In particular, CF_3-substituted pyridines occur widely in marketed drugs; the HIV protease inhibitor tipranavir (Aptivus)[5] is a representative example (see Figure SI-1 in the Supporting Information). Most widespread in biologically active compounds of this type is *meta*-CF_3 substitution of the pyridine ring (see Figure SI-1[5,6]), followed by *ortho*- and *para*-CF_3 substitution.[7]

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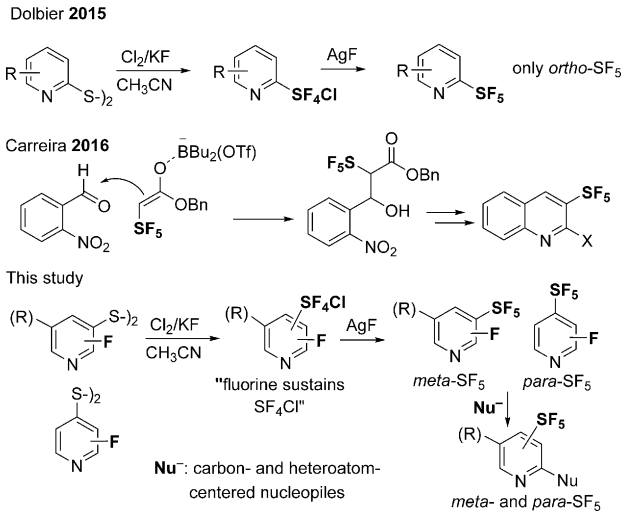
Owing to the success of trifluoromethylpyridines on the market[5,6] and the inherent recent difficulty in developing new small drugs by the current strategies, we became interested in pentafluoro-λ^6-sulfanyl (SF_5)-substituted pyridines as novel potential building blocks for pharmaceuticals.[8] The SF_5 group has garnered substantial attention in recent years for specialty materials, pharmaceuticals, and agrochemicals.[9] Owing to its extreme combination of lipophilicity, bulkiness, and electron-withdrawing properties, SF_5 has been named a "super CF_3 group".[9] Substantial efforts in synthetic SF_5 chemistry have made simple SF_5-substituted aromatic compounds readily available.[9] However, the preparation of SF_5-substituted pyridines remains a challenge.[10] SF_5-substituted benzenes can be prepared on an industrial scale by the direct fluorination[11] of aryl disulfides or by the procedure developed by Umemoto et al.[12] involving the oxidative chlorotetrafluorination of aryl disulfides to give arylsulfur chlorotetrafluorides (SF_4Cl-arenes), followed by a chloride/fluoride exchange reaction with fluoride; however, this approach has not been successful for heteroaromatic systems, for which different strategies are used.[13] In 2015, Kanishchev and Dolbier reported the first general method for the synthesis of *ortho*-SF_5-substituted pyridines on the basis of the method described by Umemoto et al.,[10b] in which 2,2′-dipyridyl disulfides interacted with the KF/Cl_2/MeCN system to afford SF_4Cl-pyridines. For the further transformation of these sulfur chlorotetrafluorides into SF_5-pyridines, silver fluoride (AgF) was found to be the most suitable reagent (Scheme 1).

However, *m*- and *p*-pyridine disulfides failed to form SF_4Cl-pyridines under the same conditions.[10b] Very recently, Carreira and co-workers reported the preparation of 3-SF_5-substituted quinolines, quinolones, and pyridones.[10a] The method involves an aldol reaction of an SF_5-substituted acetate enolate with aldehydes, followed by ring-formation steps. However, to the best of our knowledge, there is no straightforward route to *m*- and *p*-SF_5-pyridines.[10,14] Herein we disclose a general method for the preparation of *m*- and *p*-SF_5-pyridines. First, the presence of at least one fluorine atom in the pyridine ring effectively reduces the basicity of the nitrogen atom, thus inhibiting the major decomposition pathway. Second, this fluorine substituent induces greater stability of the SF_4Cl moiety. Moreover, a C–F bond at the *ortho* position of the pyridine ring can be readily activated towards nucleophilic aromatic substitution (S_NAr) under suitable conditions, thus providing straightforward access to various SF_5-pyridine building blocks (Scheme 1).

We first attempted to find the reasons for decomposition during the oxidative chlorotetrafluorination of *m*- and *p*-

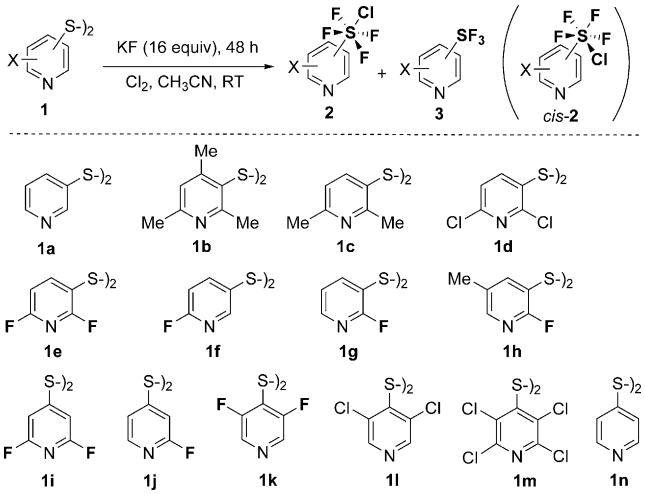


Scheme 1. Synthesis of SF_5-substituted pyridines and quinolines. Bn = benzyl, Tf = trifluoromethanesulfonyl.

pyridine disulfides **1** under Umemoto/Dolbier conditions.[10b,12] After stirring pyridine disulfides **1** with excess chlorine and dry potassium fluoride at room temperature for 48 h, we carefully examined the crude reaction mixture by ^{19}F NMR spectroscopy (Table 1). In most cases, degradation of the $C(sp^2)$–S bond to furnish SF_5Cl was detected (Table 1, entries 1–4).[15] We noticed that the distribution of decomposition products strongly depended on the original substituents on the pyridine ring. The reaction of unsubstituted 3,3′-pyridine disulfide **1a**, "*m*-pyridine", did not provide the desired pyridine-SF_4Cl **2a**; instead, the SF_3-containing compound **3a** (15%) was detected (Table 1, entry 1). The sterically demanding and electron-rich disulfide **1b** did not provide any detectable products (entry 2). When the reaction was examined using 2,6-dimethylpyridine **1c**, the desired SF_4Cl-pyridine product **2c** was detected in only 3% yield along with SF_3-pyridine product **3c** in 67% yield (entry 3). The yield of desired SF_4Cl-pyridine product **2d** was increased to 20% with the 2,6-dichlororopyridine derivative **1d**, although undesired SF_3-pyridine **3d** was the major compound obtained, in 70% yield. We next examined the reaction of 2,6-difluoropyridine **1e**. Gratifyingly, the desired SF_4Cl-pyridine product **2e** was obtained exclusively in 78% yield (Table 1, entry 5). Thus, *ortho*-fluorine substitution led to a large increase in the yield of **2** as compared to *ortho*-chlorine substitution (entries 4 and 5).

Encouraged by this result, we further attempted the reaction with fluorinated pyridine disulfides **1f–h**. As expected, the corresponding SF_4Cl products **2f–h** were produced in good yields (74–77%; Table 1, entries 6–8). Fluorine substitution was also effective for the reaction of *para*-substituted pyridine disulfides. Disulfides of 2,6-difluoropyridine, 2-fluoropyridine, and 3,5-difluoropyridine were very nicely converted into the corresponding *p*-SF_4Cl-pyridine products **2i–k** in 68–95% yield (Table 1, entries 9–11). On the other hand, the *para*-substituted chloropyridines **1l** and **1m** did not give the desired compounds, and SF_3-pyridines **3** were detected as by-products in low yields

Table 1: Preparation of SF_4Cl-pyridines **2**.



Entry	1	2, yield [%][a]		No. of F atoms on ring	3, yield [%][a]	
1	**1a**	**2a**	–	0	**3a**	15
2	**1b**	**2b**	–	0	**3b**	trace
3	**1c**	**2c**	3	0	**3c**	67
4	**1d**	**2d**	20	0	**3d**	70
5	**1e**	**2e**	78[b]	2	**3e**	–
6	**1f**	**2f**	77[b]	1	**3f**	–
7	**1g**	**2g**	76[b]	1	**3g**	–
8	**1h**	**2h**	74[b]	1	**3h**	–
9	**1i**	**2i**	90[b]	2	**3i**	–
10	**1j**	**2j**	68[b]	1	**3j**	–
11	**1k**	**2k**	95[c]	2	**3k**	–
12	**1l**	**2l**	–	0	**3l**	6
13	**1m**	**2m**	–	0	**3m**	23
14	**1n**	**2n**	–	0	**3n**	–

[a] Yield determined by ^{19}F NMR spectroscopy with HFB as an internal standard. [b] Yield of the isolated product. [c] Total yield for a mixture of **2k** and *cis*-**2k** isomers.

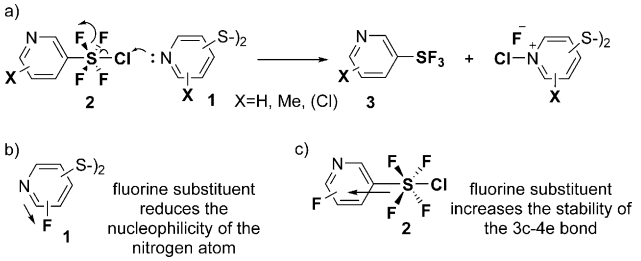
(Table 1, entries 12 and 13).[10b] The nonsubstituted *p*-pyridine disulfide **1n** decomposed entirely to release SF_5Cl (entry 14), a result similar to that observed with the *meta*-substituted analogue (entry 1). Comparison of the results of the reactions of *m*-sulfur-substituted pyridines **1a**, **1c**, **1d**, **1e**, **1f**, and **1g** and *p*-sulfur-substituted pyridines **1k**, **1l**, and **1n** with H, Me, Cl, and F substituents led to initial conclusions on the fluorine effect on the formation of SF_4Cl-pyridines.

The oxidative chlorotetrafluorination reaction of fluorinated pyridine disulfides proceeded very cleanly. ^{19}F NMR spectra showed only a single peak for SF_4Cl-pyridine products **2**. After filtration and evaporation of the solvent, compounds **2** were isolated. SF_4Cl-pyridines **2** are highly unstable under humidity. When they enter into contact with glass vessels, they slowly decompose and cause the perceptible erosion of glass within 1 h. However, if they are stored in Teflon vessels under an inert atmosphere, SF_4Cl-pyridines **2** are stable for at least 2 weeks at room temperature.

Among the SF_4Cl-pyridine compounds **2** prepared, the 3,5-difluoro compound **2k** existed as a mixture of isomeric tetrafluorosulfanyl chlorides in a 2:1 *trans*/*cis* ratio, whereas for the other SF_4Cl compounds **2**, no *cis* isomer was observed.

The compound *cis*-**2k** had a peculiar appearance in the ^{19}F NMR spectrum (see Figure SI-2). This result implies that the nearest two fluorine atoms even stabilize the unstable *cis* conformation of the SF_4Cl functionality (see discussion below and Figure SI-3). A similar phenomenon was reported for other SF_5-arene compounds.[12]

The effect of fluorine on the successful oxidative chlorotetrafluorination of *meta*- and *para*-substituted pyridine disulfides **1** can be explained as follows. First, a strong electron-withdrawing effect of fluorine effectively reduces the basicity of the nitrogen atom of pyridine, and thus inhibits intermolecular decomposition between the SF_4Cl-pyridine **2** and the starting materials **1** (and/or product **2**) to form SF_3-pyridine products **3** (Scheme 2 a,b).[16] The reported pK_a values of pyridine, 2-fluoropyridine, 2-chloropyridine, and 3-fluoropyridine are 5.23, −0.44, 0.49, and 2.97, respectively.[17] Hence, this effect is maximized by *ortho*-fluorine substitution. Furthermore, the electron-withdrawing effect of fluorine also stabilizes the hypervalent sulfur atom, which possesses a characteristic three-center–four-electron (3c-4e) bond (Scheme 2 c).[18,19] The formation of by-product SF_5Cl is not clear.

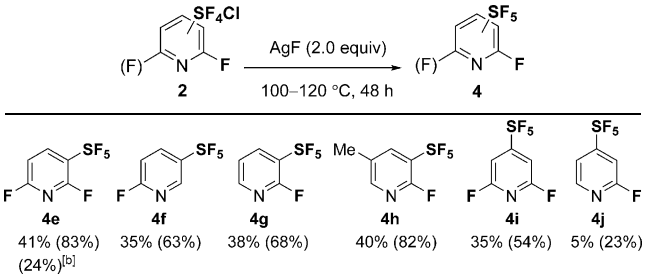


Scheme 2. a) Potential decomposition pathway of SF_4Cl-pyridines **2** to SF_3-pyridines **3** as promoted by **1**. b) A fluorine substituent in **1** reduces the nucleophilicity of the nitrogen atom. c) A fluorine substituent increases the stability of the SF_4Cl moiety.

DFT calculations were next attempted. The three compounds **2i**, **2k**, and **2n** were selected, and their bond lengths, charge distributions, and electrostatic potential maps were calculated (DFT/B3LYP/6-31G** level of theory; see Figure SI-3). The lengths of the S−Cl bonds of **2i**, **2k**, and **2n** are 2.135, 2.134 (shortest), and 2.142 Å. The lengths of the S–C(sp^2) bonds of **2i**, **2k**, and **2n** are 1.829, 1.822 (shortest), and 1.826 Å, respectively. The sulfur atomic charges (Mulliken) of **2i**, **2k**, and **2n** are 1.455, 1.474 (largest), and 1.449, respectively. These values suggest that fluorine substitution in the *meta* position most stabilizes the SF_4Cl moiety, in good agreement with the isolation of the unstable *cis* somer **2k** (see Figure SI-2). The mapping of the electrostatic potential on the surface of SF_4Cl shows color similarity of **2i** and **2k**, whereas the Cl group on **2n** is very different.

The *m*- and *p*-SF_4Cl-pyridines **2** were smoothly converted into the target SF_5-pyridine derivatives **4** by simple heating with anhydrous AgF without a solvent (Table 2). For the full conversion of *m*-SF_4Cl-pyridines, heating for 48 h at 100 °C was required. For *p*-SF_4Cl-pyridines, a temperature of 120 °C was needed for complete chloride–fluoride exchange. The

Table 2: Preparation of SF_5-pyridines.[a]



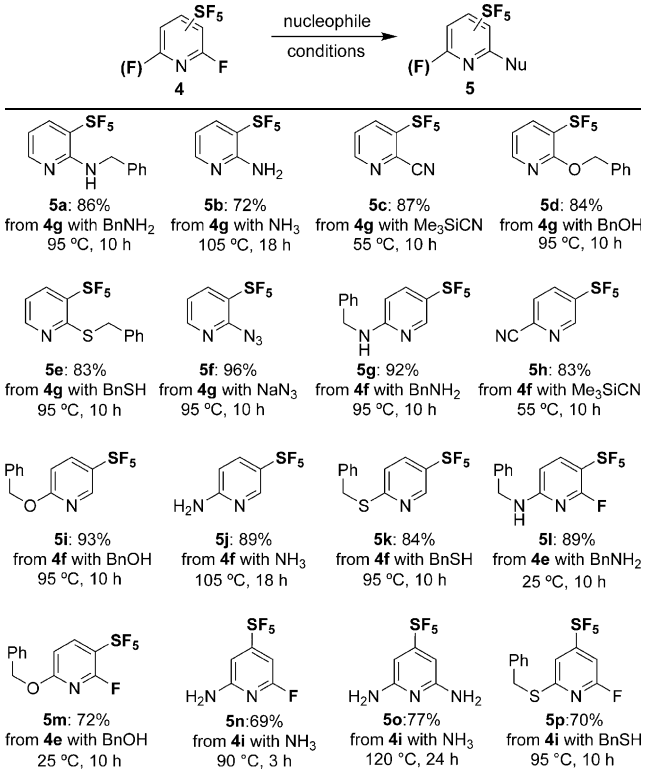
[a] Yields are for the isolated product after distillation. Yields determined by ^{19}F NMR spectroscopy are given in parentheses. [b] The reaction was examined with dichloride **2d** instead of fluoride **2e**.

SF_5-pyridines **4** were isolated as clear liquids in 35–41 % yield by distillation. The yields calculated by ^{19}F NMR spectroscopy for SF_5-pyridines **4** were quite high. The low yields of the isolated products can be explained by the rather small reaction scale (10 mmol) and the high volatility of the products. Product **4j** was formed in very low yield because the starting SF_4Cl-pyridine **2j** is unstable under these reaction conditions. The replacement of the SF_4Cl moiety of **2j** with fluoride provided 2,4-difluoropyridine and 2-chloro-4,6-difluoropyridine as by-products (detected by NMR spectroscopy and GC–MS). The SF_4Cl-pyridine dichloride **2d** (Table 1, entry 4) could be used for this transformation, but instead of corresponding SF_5-pyridine dichloride, difluoride **4e** was obtained in 24 % yield by additional chloride–fluoride exchange at the two *ortho* positions. This result also supports the use of fluoro-substituted pyridines rather than chlorides.

The chemistry of 2-fluorinated pyridines (*ortho*-fluorinated pyridines) has gained great attention in recent years. Even though the strong C−F bond stabilizes the structure, these compounds readily react with nucleophiles under suitable conditions through S_NAr substitution to provide 2-substituted pyridine derivatives.[3,20] The selective lithiation of 2-fluoropyridines has also been studied.[21] Thus, our fluorinated SF_5-pyridines **4** should be versatile building blocks. The electron-deficient SF_5 group in the pyridine ring should facilitate such transformations.[22] We demonstrated the further derivatization of 2-fluorinated SF_5-pyridines **4**. Parent SF_5-pyridines **4** were employed as substrates for nucleophilic substitution reactions with C-, S-, N-, and O-based nucleophiles. All reactions proceeded very smoothly to give S_NAr substitution products **5** in good to excellent yields (Table 3). A regioselective S_NAr reaction of the 2,6-difluorinated SF_5-pyridine **4e** furnished 6-substituted 2-fluoro-3-SF_5-pyridines **5** selectively in high yields of 72–89 %. This regioselectivity can be explained by steric hindrance by the SF_5 moiety; thus, nucleophiles react predominantly at the 6-position. X-ray crystallographic analysis of **5l** (CCDC 1481076) and **5n** (CCDC 1481241) provided not only the first 3D structures of *m*- and *p*-SF_5-substituted pyridines, but also confirmed the regioselective substitution of **4e** to give **5l** (see Figure SI-4).

In summary, a practical method to access *m*- and *p*-SF_5-substituted pyridines has been described. A two-step proce-

Table 3: S_NAr reaction of SF_5-pyridines with C-, S-, N-, and O-based nucleophiles.[a]



[a] Yields are for the isolated products. Details of the reaction conditions are shown in the Supporting Information.

dure involving SF_4Cl-pyridine synthesis by the oxidative chlorotetrafluorination of pyridine disulfides with a Cl_2/KF/CH_3CN system, followed by AgF-mediated chloride–fluoride exchange, was used. The important role of a fluorine atom in the pyridine ring for the implementation of this method has been shown. The key SF_5-pyridine products were converted into different SF_5-pyridine derivatives by nucleophilic aromatic substitution reactions of *ortho*-fluorine substituents. Further synthetic applications of the SF_5-pyridines would be possible on the basis of S–F bond activation by transition metals.[23]

Acknowledgments

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[14] In the study reported in Ref. [10c], 2,3,5,6-tetrachloro-4-pentafluorosulfanylpyridine was obtained from the reaction of 2,3,5,6-tetrachloro-4-pyridinethiol with IF_5, but no compound characterization or experimental procedures were specified. In our hands, the action of IF_5 on 2,3,5,6-tetrachloro-4-pyridinethiol at room temperature gave 2,3,5,6-tetrachloro-4-iodopyridine as the major product. We did not detect any trace of a SF_5 fragment by ^{19}F NMR spectroscopy of the reaction mixture.

[15] The formation of gaseous products, such as SOF_2 (*s*, +77 ppm), SO_2F_2 (*s*, +34 ppm), and SF_5Cl (*p*, +65 ppm, $J = 150$ Hz, 1F; *d*, +125 ppm, $J = 150$ Hz, 4F), was detected in ^{19}F NMR spectra of the reaction mixtures.

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