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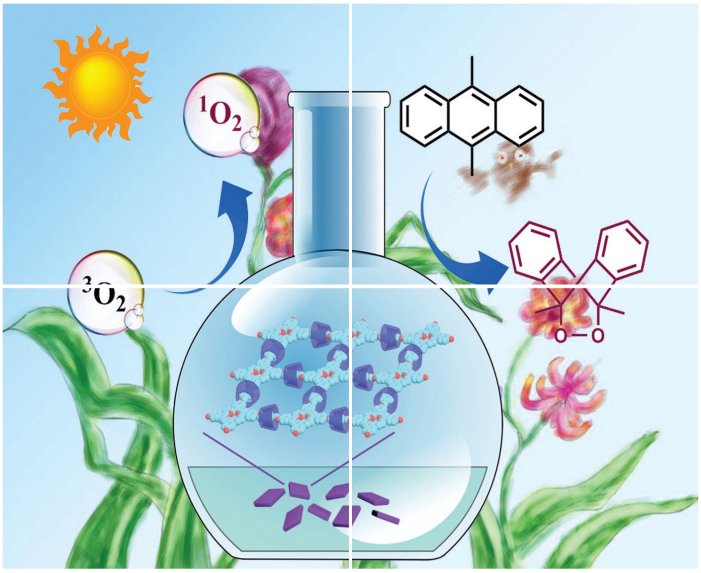

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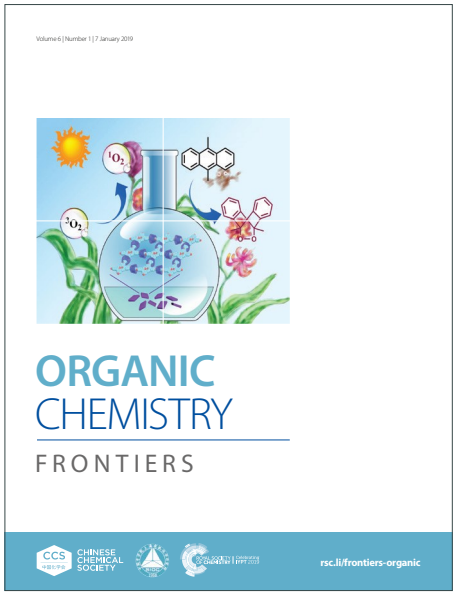

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ARTICLE

meta-Selective thiofluoroalkylation of substituted pyridines *via* Zincke imines†

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Zincke imines enable the regioselective thiofluoroalkylation of substituted pyridines, grating access to thioalkylated pyridines bearing a range of fluorination patterns. Crucial to success of this strategy was the use of saccharine-derived thiofluoroalkylating reagents, which, upon reaction with TMSCl, generate electrophilic sulfenyl chlorides.

Introduction

During the last 25 years, more than half of new agrochemicals[1] and 1 in 3 new pharmaceuticals are fluorinated.[2] A powerful structural mimic for hydrogen, fluorine can drastically alter the properties of biologically relevant molecules, such as conformation, p*K*a, membrane permeability, and metabolic pathways.[3] Beyond the widely studied trifluoromethyl group, the SCF_3 motif has attracted attention due to its lipophilic[4] yet strongly electron-withdrawing properties.[5] The installation of such motifs generally rely on either preinstalled functional handles with metal SCF_3 salts,[6] or reaction of thiols with electrophilic fluoroalkyl sources (*e.g.*, hypervalent iodine, Fig. 1A, left).[7] Alternatively, the thiol can be activated and used in umpolung reactivity (*e.g.*, as a disulfide or thiocyanate) to react with radical or anionic R_F species (Fig. 1A, right). Longer chain thiofluoroalkyl groups are underdeveloped, yet their greater range of possible fluorination topologies renders them a useful tool to tweak the overall molecular lipophilicity and polarity with great precision.[8]

The functionalisation of pyridines, which are the most common heteroarene in new FDA-approved drugs,[9] mostly relies on the electron-poor nature of pyridine's C2 and C4 positions.[10] Direct C3-selective C–H functionalisation is difficult and can require harsh conditions,[11] directing groups, or electrochemical apparatus.[12] Recently, elegant dearomative strategies have revealed electron-rich enamine-type intermediates, converting pyridine's C3-position into a competent nucleophile for halogenation,[13] transition-metal-catalysed arylation,[14] fluoromethylation,[15] silylation[16] or amidation.[17] Crucially, this strategy has proven useful for the *meta*-selective introduction of SCF_3 and SCF_2H motifs, in this case with a Lewis-acid-catalysed *N*-borylation system (Fig. 1B).[18] We wondered whether the use of Zincke imines would enable the formal C–H thiopolyfluoroalkylation of pyridines (Fig. 1C).

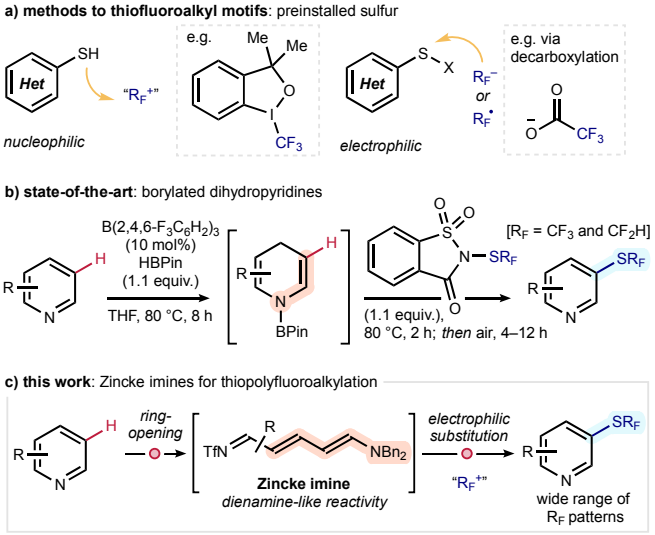

Fig. 1. a) General strategies to access thiofluoroalkyl motifs on heteroaromatic rings. b) Wang *et al.*'s borane-mediated *N*-borylated dihydropyridine strategy for C3-thiotrifluoromethylation of pyridines. c) Ring-opening of pyridines to Zincke imines and their reaction with an electrophilic source of thiofluoroalkyl chain. LG = leaving group; Pin = pinacol; Tf = trifluoromethylsulfonyl; R_F = polyfluoroalkyl.

This approach avoids the S–R_F disconnection that requires a preinstalled sulfur functionality and ensures regioselectivity for the *meta*-position of the pyridine. We envisaged the use of our recently reported bench-stable electrophilic thiofluoroethylating reagents as appropriate reaction partners.[19] These simple reagents permit the installation of SR_F motifs to simple carbon or nitrogen nucleophiles with a wide array of fluorination patterns. During the preparation of this manuscript, Chen and Fu *et al.* reported a related Zincke imine-type strategy for the thioarylation of *N*-aryl pyridinium salts, which included one example of the installation of the SCF_3 motif.[13d]

Results and Discussion

To test our hypothesis, we prepared Zincke imine **1** from 3-phenylpyridine based on the seminal report of McNally,[13b] in

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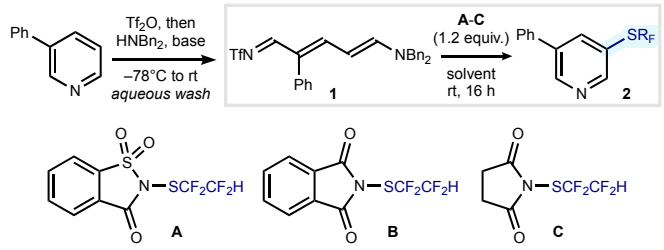
which addition of dibenzylamine promotes the ring-opening of an intermediate *N*-trifluoromethylsulfonyl pyridinium salt. We then focussed on the single reaction step of Zincke imine **1** with *N*-thio(1,1,2,2-tetrafluoroethyl) saccharine **A**, aiming to achieve maximum yield of functionalised pyridine **2**. Firstly, reaction at room temperature in anhydrous ethyl acetate overnight (Table 1, entry 1) lead to only moderate conversion of the Zincke imine **1** (up to 40%), while changing solvent to dichloromethane was unproductive (entry 2). Increased reaction temperature led to the formation of various unidentified side-products. Addition of trifluoroacetic acid (TFA) led to rapid cyclisation of **1** to the unfunctionalized pyridine and low quantities of desired product (entry 3, <10%). However, chlorotrimethylsilane (TMSCl) was identified as an excellent additive,[19] promoting the formation of *meta*-functionalised thiofluoroalkyl pyridine **2** in good isolated yield (entry 4, 63%). Reaction of Zincke imine **1** with other *N*-thio(1,1,2,2-tetrafluoroethyl) reagents **B** or **C** resulted in lower isolated yields of **2** (entries 5 and 6, <50%). After a brief optimisation of stoichiometry, an excess of TMSCl (1.5 equiv.) was found to be beneficial, giving product **1** in 90% isolated yield (entry 7). Pleasingly, a one-pot protocol demonstrated that isolation of the intermediate **1** was not necessary (entry 9, 70%).

To investigate the reaction scope, two optimal conditions from Table 1 were selected: i) the two-step procedure of entry 7; and ii) the one-pot procedure of entry 9. For the transformation of both 3-phenylpyridine and 2-phenylpyridine, the one-pot procedure was found to be effective. Firstly, a range of saccharine-based thiofluoroalkyl reagents bearing different fluorination patterns were tested as electrophilic partners (Fig. 2). Alongside the model product **2** (70%), a thioethyl group bearing terminal difluorination was installed in good yield (**3**, 72%), granting access to pyridines with a weak hydrogen-bond donor motif (CF_2H).[8e,20] A thioethyl group bearing internal difluorination[17] was installed, granting access to pyridine **4** in good yield (67%). Highly lipophilic thioperfluoroethyl (**5**) and thioperfluorobutyl (**6**) chains were introduced in excellent yields (80% and 84%, respectively). Terminal trifluorinated thioethyl pyridine **7** was synthesised in good yield, while use of a monofluorinated thiomethyl saccharine reagent gave the functionalised pyridine **8** in slightly reduced but good yield (62%).

In reactions of 2-phenylpyridine, addition of NH_4OAc and heating in ethanol was required to close the pyridine ring after functionalisation. In this case, a 1:1 regioisomeric mixture of 3- and 5-(thiofluoroalkyl) pyridines (**9a** and **9b**) was obtained with an overall yield of 80%, alongside low amounts of bis-functionalised pyridine **9c** (<5%). Reducing the amount of the thiofluoroalkyl reagent from 1.2 equivalents to 1.0 equivalent resulted in suppression of **9c**. The regioisomeric outcome appears to be unaffected by the nature of the thiofluoroalkyl group under these conditions, as installation of the terminal trifluorothioethyl group gave the same ratio of products (**10a** and **10b**, 1:1). In contrast, McNally found that halogenation of Zincke imine occurs with high regioselectivity at the C3-position,[13b] while Wang's borylated dihydropyridine intermediates mostly underwent double functionalisation.[18c] In our protocol, moderate yields of both C3- and C5-functionalised

Table 1. Optimisation of the reaction conditions.[a]



Entry	Reagent	Solvent	Additive (equiv.)	Yield (%)[b]
1	**A**	EtOAc	–	n.d
2	**A**	CH_2Cl_2	–	n.d
3	**A**	EtOAc	TFA (1.0)	<10[c]
4	**A**	EtOAc	TMSCl (1.0)	63
5	**B**	EtOAc	TMSCl (1.0)	43
6	**C**	EtOAc	TMSCl (1.0)	50
7	**A**	EtOAc	TMSCl (1.5)	90
8	**A**	CH_2Cl_2	TMSCl (1.5)	61
9[d]	**A**	EtOAc	TMSCl (1.5)	70

[a] *Reaction conditions*: Zincke imine **1** (0.2 mmol, 1 equiv.), reagent **A–C** (1.2 equiv.), TMSCl (1.5 equiv.), EtOAc (2 mL), room temperature, 16 h. [b] Isolated yield. [c] Yield determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3-bis(trifluoromethyl)benzene as internal standard. [d] *One-pot procedure*: 3-phenylpyridine (0.2 mmol, 1 equiv.), Tf_2O (1 equiv.), EtOAc (2 mL), – 78 °C, 30 min; then $HNBn_2$ (1 equiv.), 2,4,6-collidine (1 equiv.), –78 °C to rt, 1 h; then reagent **A** (1.2 equiv.), TMSCl (1.5 equiv.), rt, 16 h. N.d. = not detected.

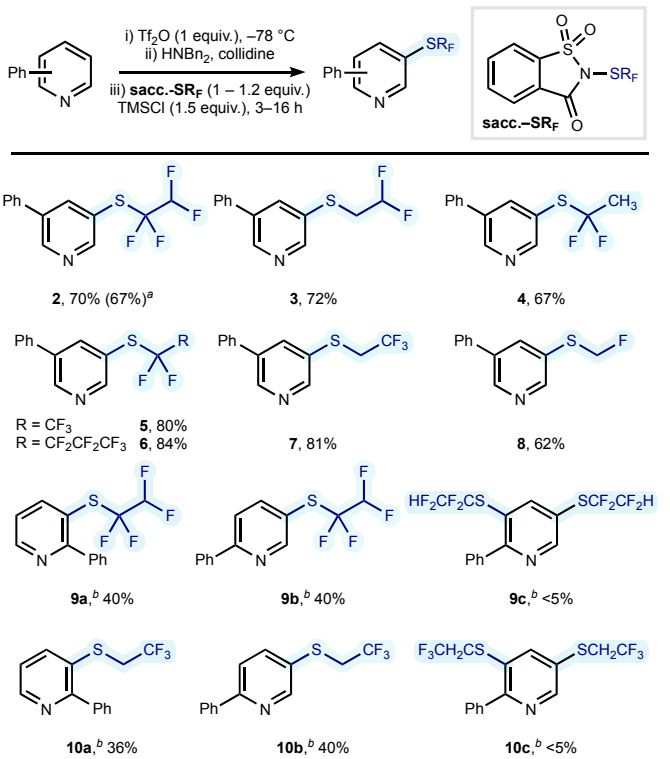


Fig. 2. Scope of the one-pot protocol with respect to the thiofluoroalkylating reagent. *Reaction conditions*: see Table 1, entry 9. [a] Reaction carried out on 5 mmol scale. [b] After full conversion of the starting material, NH_4OAc (10 equiv.) and EtOH (2 mL) was added followed by heating at 60 °C for 1 h. For **9** and **10**, ^{1}H NMR analysis of the crude reaction mixture reveals a regioisomeric ratio of 1:1 (C3:C5).

products could be obtained after chromatographic separation of the regioisomers. Furthermore, the scalability of our protocol was confirmed by carrying out the model reaction on a 5 mmol scale, obtaining tetrafluoroethylated pyridine **2** in 67% isolated yield. Next the reaction was tested with a range of substituted pyridines (Fig. 3). Preliminary experiments showed that washing of the intermediate Zincke imine with water generally improved the yield of functionalized pyridine and led to fewer side-products, even if the Zincke imines were used without further purification (see Electronic Supporting Information (ESI†) for details). In this way, a range of substituted 3-aryl pyridines were converted to their corresponding Zincke imines. Substrates bearing *para*-alkyl, methoxy, ester and CF_3 groups underwent efficient thiofluoroalkylation in good to excellent yields (65–91%), yielding pyridines **11–14**. In addition, *meta*-substituted 3-aryl pyridines **15–17** were furnished in excellent yields (68–91%), while the highly fluorinated bis-3,5-CF_3 product **18** (68%) and naphthalene-containing pyridine **19** (77%) were obtained in good yield. The dialkyl substituted pyridine 5,6,7,8-tetrahydroquioline gave the desired thiofluoroalkylated product **20** in good yield (75%) after addition of ammonium acetate and heating in ethanol. When 2-aryl pyridines bearing different *para*-methyl or *para*-fluoro substituents were used, a regioisomeric mixture (1:1) of products **21** and **22** was obtained, alongside small amounts of doubly functionalised products. Finally, the thiofluoroalkylation procedure was tested on loratadine, a commercial antihistamine drug bearing a 2,3-annulated pyridine. Gratifyingly, the thiofluoroalkylated pharmaceutical **23** was obtained in good yield (67%), demonstrating the potential of this methodology for late-stage incorporation of fluorinated thioalkyl motifs. In general, the reaction is less efficient or irreproducible in pyridines bearing non-carbon substituents (see ESI† for a summary of incompatible and moderately tolerated pyridines). To better understand the reaction, a series of control experiments were conducted (Fig. 4).

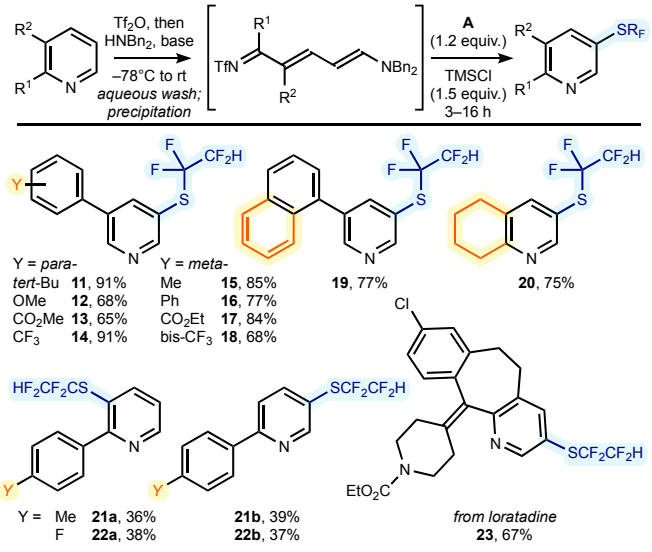


Fig. 3. Scope of the two-step protocol with respect to different Zincke imines formed from their corresponding pyridines. *Reaction conditions*: see Table 1, entry 7. NB: For the synthesis of products **21** and **22**, 1.0 equivalent of **A** was used.

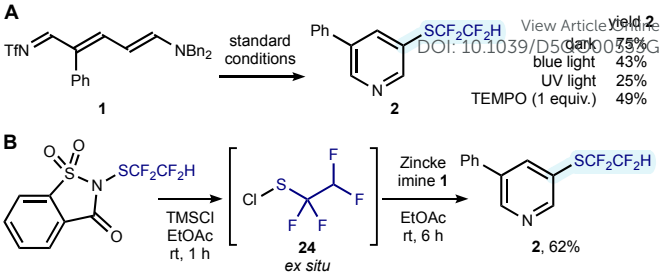


Fig. 4. Control reactions, carried out on 0.1 mmol scale.

It was reasoned that both reactant partners may be sensitive to photonic activation: i) the extended π-system of the Zincke imine **1** is responsible for its strong red-orange coloration, therefore photoactivation is plausible; ii) the saccharine reagent contains a weak N–S σ-bond that may prone to homolysis.[13d] Zincke imine **1** was subjected to the standard reaction conditions with strict exclusion of light, with pyridine **2** formed in excellent yield (75%) (Fig. 4A). When the reaction was carried out under irradiation with blue light (λ_{max} = 440 nm) or UV-light (λ_{max} = 370 nm), the functionalised pyridine was formed in reduced yields of 44% and 25%, respectively, allowing us to conclude that photoactivation is not operative in the dominant reaction mechanism. Inclusion of TEMPO, a commonly employed kinetically stable radical that can inhibit radical reactions, led to formation of product **2** in slightly reduced yield (49%), although no radical coupling products were detected. Treatment of a solution of saccharine reagent **A** with TMSCl for 1 hour in EtOAc, lead to the formation of the corresponding sulfenyl chloride **24**, as confirmed by ^{19}F NMR.[19] To this solution was added Zincke imine, and within 6 h the thiofluoroalkylated pyridine **2** was formed in 62% yield. These experiments suggest that a radical mechanism is highly unlikely, and that a polar addition of Zincke imine **1** to sulfenyl chloride **24** *via* S_N2-type substitution is most probable.

Conclusions

To conclude, a simple method for the *meta*-selective introduction of thiopolyfluoroalkyl motifs onto substituted pyridines is described. Substituted pyridines are converted to nucleophilic Zincke imines through triflation and ring-opening with the addition of dibenzylamine. These intermediates undergo simple addition-elimination with a proposed sulfenyl chloride, which is formed in situ through the reaction of TMSCl with a bench-stable saccharine-based thiofluoroalkyl precursor. This method permits the introduction of a wide range of thiopolyfluoroalkyl motifs, granting access to libraries of pyridines with modulable physicochemical profile. Through the thiofluoroalkylation of loratadine, a commercial antihistamine drug, the potential usefulness of the method to the drug discovery community has been demonstrated.

Conflicts of interest

O.B. is co-inventor on a patent application (PCT/EP2021/067690) that describes some of the electrophilic thiopolyfluoroalkyl reagents used in this manuscript.

Acknowledgements

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Data availability

The data supporting this article have been included as part of the Electronic Supplementary Information (ESI)†.

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The data supporting this article have been included as part of the Electronic Supplementary Information (ESI).†