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Chemoselective *N*- and *O*-Difluoromethylation of 2-Pyridones, Isoquinolinones, and Quinolinones with $TMSCF_2Br$

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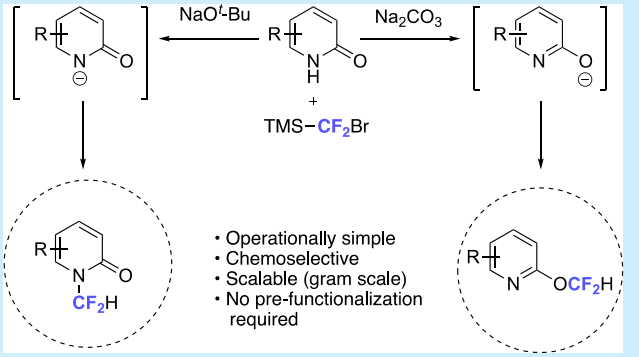
ABSTRACT: An operationally simple protocol for direct *N*- and *O*-difluoromethylation of 2-pyridones, quinolinones, and isoquinolinones using commercially available $TMSCF_2Br$ is disclosed. The chemoselectivity is modulated by simple variations in temperature, solvent, and strength of the base. Diverse, synthetically relevant functional groups are tolerated, including functional groups that have reported reactivity with $TMSCF_2Br$. Gram-scale reactions to prepare both *N*- and *O*-difluoromethyl compounds are included.



Fluorofunctionalization to enhance the physical and chemical properties of organic molecules is a successful strategy in pharmaceutical,[1−3] biochemical,[4] and material science[5,6] applications. Particularly, difluoromethylation has emerged as an important reaction paradigm due to the lipophilicity and hydrogen bond donor ability of $-CF_2H$,[7−9] enabling bioisosteric replacement of commonly encountered functional groups including −OH and −SH.[8] Consequently, nucleophilic,[10−12] electrophilic,[13−15] and radical[16−18] difluoromethylations have been developed. Electrophilic difluoromethylation using difluorocarbene is a popular method for insertion of $-CF_2-$ into alkenes/alkynes,[19,20] as well as C−H,[21,22] O−H,[23] S−H,[24] N−H,[25] and P−H[26] bonds. Numerous reagents have been developed to generate difluorocarbene. $ClCF_2COONa$ and its derivatives, despite widespread utility,[27−29] are limited by high activation temperatures. Freons and halons like HCF_2Cl and CF_3Br are used as difluorocarbene precursors despite their inherent toxicity, commercial inaccessibility, and environmental impact (ozone-depleting greenhouse gases).[30] Difluorocarbene can also be efficiently generated from (per)fluoroalkylsilanes like $TMSCF_3$[19] or $TMSCF_2Br$.[31] The latter compound, first synthesized by our group,[32] is defining a new trend in difluoromethylation methodology due in part to its versatility and ease of activation.[20,21,33]

2-Pyridones are important structures prevalent in pharmaceuticals and biomolecules.[34−36] For example, leporin A is known to possess antifungal properties.[37] In 2021, Forrestall and co-workers reported leporin A and 12 other analogues as potential treatments for the novel coronavirus, SARS-CoV-2.[38] 2-Pyridone moieties are also studied as selective inhibitors of HIV-1 RT.[35] Additionally, 2-pyridones have found increasing value in anticancer research in the past decade.[36]

In 2009, Ando and co-workers found that *N*-difluoromethyl-2-pyridones are important substructures which improve binding affinity with target receptors.[34] Despite the relevance of 2-pyridones, methods for their selective *N*- and *O*-difluoromethylation are scarce (Figure 1).[39,40] A two-step synthesis of *N*-difluoromethyl-2-pyridones using $ClCF_2COONa$ is reported. Initial attempts at selective *N*-difluoromethylation of 2-pyridones were unsuccessful, resulting

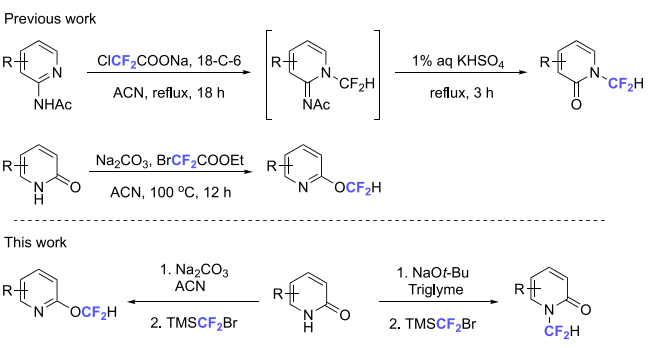


Figure 1. Prior art on the difluoromethylation of 2-pyridones.

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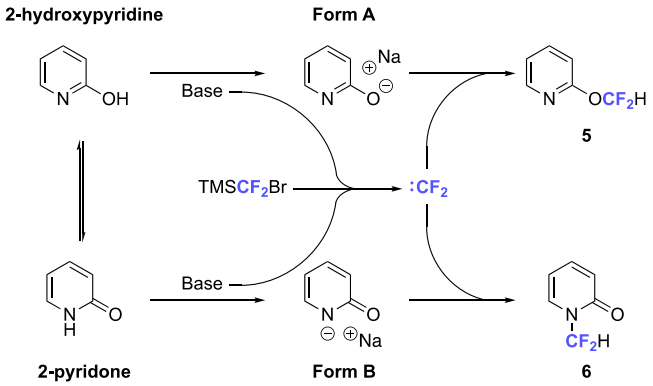
in mixtures of compounds favoring the O−CF_2H products. The pyridone substrates were prefunctionalized into (2-pyridyl)acetamides, thereby negating the possibility of forming *O*-difluoromethyl products and selectively furnishing the N−CF_2H compounds. The products could then be deprotected to yield *N*-(difluoromethyl)pyridones. The requisite protection and deprotection steps and long reaction times leave room for improvement. Furthermore, only 4- and 5-substituted substrates could be converted into the desired *N*-difluoromethyl-2-pyridone products.[39] In 2018, Ma and co-workers performed an *O*-difluoromethylation of 2-pyridones using $BrCF_2COOEt$, which suffers from long reaction times (12 h). Also, *N*-difluoromethylation was not explored.[40] Herein, we describe a fast, effective, and tunable approach to selectively obtain *N*- and *O*-difluoromethylated 2-pyridones in one pot.

The facile tautomerism of 2-pyridones, wherein the pyridone form is in equilibrium with the hydroxypyridine form, has been well-described in the literature.[41−43] Evidence has shown that temperature plays a role in the relative populations of the tautomers.[42] As shown by Forlani and co-workers, at 45 °C in a polar solvent system, the hydroxypyridine form is favored, and at 20 °C the pyridone form is favored.[44] On the basis of these considerations, we reasoned that elevated temperatures would favor the hydroxypyridine form, allowing for selective *O*-difluoromethylation. Likewise, lower temperatures would favor the pyridone form, allowing for selective *N*-difluoromethylation. Thus, our optimization was based on the following mechanistic hypothesis (Scheme 1). The deprotonation of

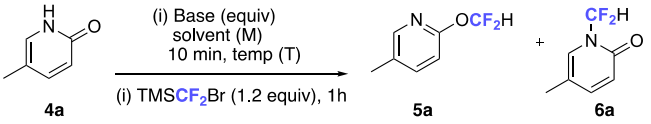
Scheme 1. Mechanistic Hypothesis



these structures produces form A (aryloxy form) and form B (amide form), respectively. It can be expected that the −OH form (hydroxypyridine) would have a lower pK_a than the −NH form (pyridone). This may warrant the need of a stronger base for the formation of form B, and a milder base for form A. Given that forms A and B are in equilibrium, strict temperature control would be necessary to limit the interconversion. Subsequent reaction with difluorocarbene affords the corresponding O−CF_2H and N−CF_2H products.

Initial trials with $TMSCF_3$ were unsuccessful, so $TMSCF_2Br$ was employed as the $:CF_2$ source. Over the course of our optimization (see SI for a detailed discussion), we found that **5a** could be produced selectively in near-quantitative yield from **4a** when reacted with 1.2 equiv of $TMSCF_2Br$ in acetonitrile at 60 °C using Na_2CO_3 as the base and activator. Subsequent changes to the reaction conditions flipped the chemoselectivity of the reaction. Compound **6a** was obtained in 84% yield from the reaction of **4a** with 1.2 equiv of $TMSCF_2Br$ in triglyme at −15 °C using NaO^tBu as the base and activator (Table 1). It is important to note that dropwise addition of $TMSCF_2Br$ is required for the efficient synthesis of **6a**.

Table 1. Optimization Experiments for 5a and 6a[a]



4a 5a 6a

	base (equiv)	Solvent	T (°C)	5a/6a (%)[b]
1[c]	KOH (2.2)	ACN	60	68/6
2[c]	K_2CO_3 (1.1)	ACN	60	44/54
3[c]	Na_2CO_3 (1.1)	ACN	60	99/1
4[d]	Na_2CO_3 (1.1)	ACN	0	68/2
5[d]	KO^tBu (2.2)	ACN	0	46/13
6[d]	NaO^tBu (2.2)	ACN	0	2/57
7[d]	NaO^tBu (2.2)	ACN	−15	2/63
8[d]	NaO^tBu (2.2)	triglyme	−15	5/84

[a]Reactions performed at 0.5 mmol scale. [b]Yields determined by ^{19}F NMR using fluorobenzene as internal standard. [c]0.4 M concentration. [d]0.25 M concentration.

The model substrate **4a** gave 88% of **5a** and 71% of **6a** under methods A and B, respectively (Scheme 2). Alkoxy-substituted substrates **4b** and **4c** afforded **5b** and **5c** in excellent yields. Methyl-2-pyridones **4d** and **4e** were isolated in 55% and 46% yields, respectively. Compounds **6d** and **6e** were also synthesized by method B in 42% and 39% yields, respectively. Volatility of these compounds is likely responsible for the reduced isolated yields. 6-Methyl-2-pyridone (**4f**) only generated **5f** under method A and was unable to produce **6f** (see Scheme 3). The brominated 2-pyridones **4g** and **4h** furnished **5g** and **5h** in good yields. Compound **4h** afforded **6h** in 38% isolated yield under method B. The strongly electron-withdrawing $-CF_3$ group was also compatible with both methods (**5i** and **6i**). Pyridones with electron-donating substituents (**4a**−**4f**) gave higher yields than those with electron-withdrawing groups (**4g**−**4i**) with both methods. Large-scale reactions (gram scale, 5 mmol) were performed on substrate **4b** with methods A and B (87% and 47% isolated yields, respectively). A disubstituted pyridone **4j** was also explored. Related isoquinolinones **4k**, **4l**, and **4m** were converted to **5k**, **5l**, and **5m** in good to excellent yields, while **6k**, **6l**, and **6m** were afforded in moderate yields. Similarly, difluoromethylated quinolinones **5n** and **5o** were obtained in good yields. However, both **4n** and **4o** gave very low yields of the N−CF_2H products likely due to the sterics of the benzo-fused system, which may deter nucleophilic attack. Similarly, **4s** furnished **5s** in 75% yield (method A), whereas only a trace amount of N−CF_2H product was formed under method B. Quinoline-2-thiol **4p** produced **5p** as the major product under both methods due to the enhanced nucleophilicity of S^-. Method A tolerated important functional groups, providing ester (**5q**) and amide (**5r**) (albeit in modest yield). Neither **6q** nor **6r** was obtained from method B. Heteroaryl-2-pyridones **4t**−**4x** afforded **5t**−**5x** in good to excellent yields, and **6t**−**6x** in moderate to good yields. Notably, the vinyl group on substrate **4t** was unreactive toward the difluorocarbene generated under our conditions, despite their known [2 + 1] cycloaddition.[19,20]

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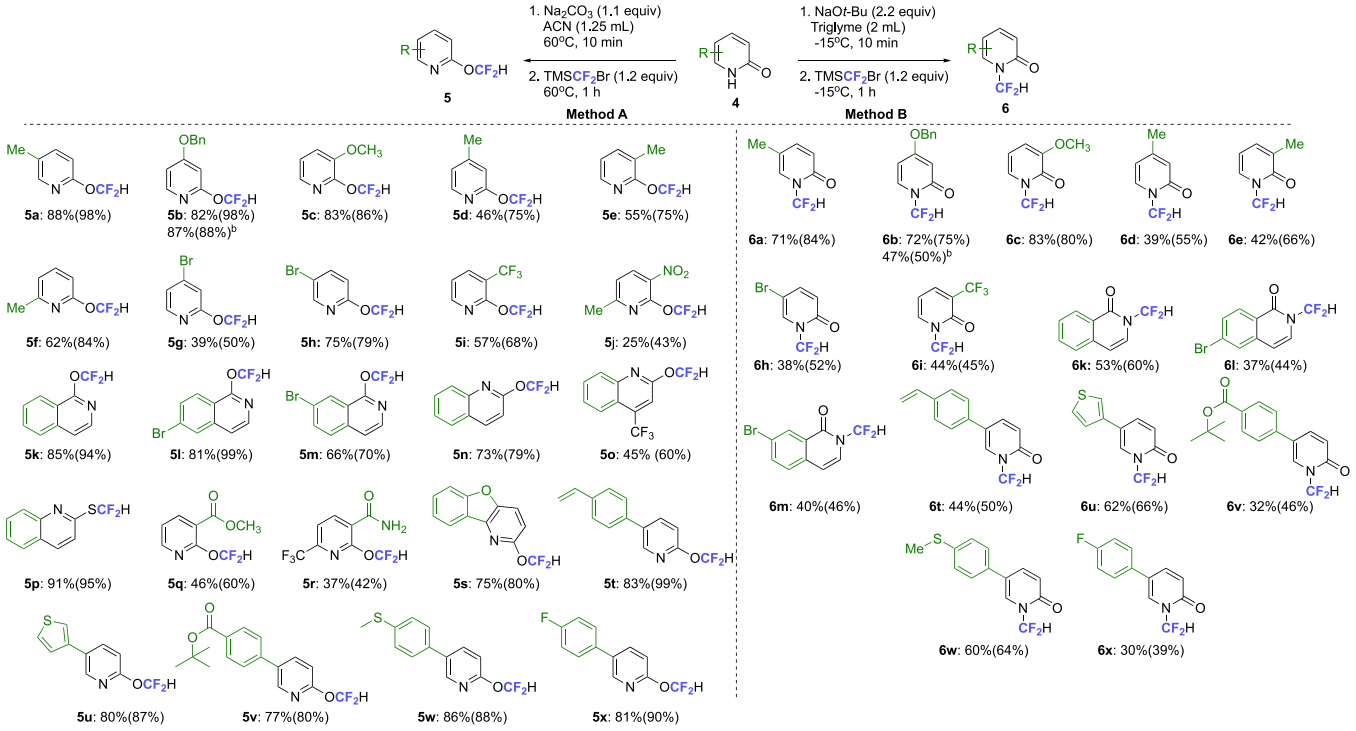
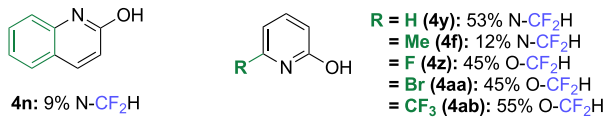
Scheme 2. Condition-Dependent *O*- and *N*-Difluoromethylation of 2-Pyridones, Isoquinolinones, and Quinolinones[a]



[a]Reactions performed at 0.5 mmol scale for isolated yield with standard conditions. Yields within parentheses determined by ^{19}F NMR using fluorobenzene as internal standard. [b]Reaction performed at 5 mmol scale. See Supporting Information.

Scheme 3. ^{19}F NMR yield of 6-Substituted 2-Pyridones under Method B



6-Subsituted 2-pyridones, **4f**, **4j**, and **4r**, were unreactive under method B. To further probe this interesting result, more 6-substituted 2-pyridones were tested. For the electron-withdrawing groups −Br and $-CF_3$, the major products were *O*-difluoromethylated pyridones even under method B (Scheme 3). Considering the small size of the F atom and its strong withdrawing effect, **4z** was subjected to method B to isolate the steric effects on the 6-position from the electronic effects. The reaction furnished 45% O−CF_2H product.

Accordingly, we propose that the electronics of the substituents influence the interconversion between form A and form B (Scheme 1) by inductive effects. The reversed selectivity when difluoromethylating **4z**, **4aa**, and **4ab** was due to the strong inductive effects of substituents *ortho* to the nitrogen. In contrast, the methyl group in **4f** did not completely inhibit the reaction and yielded 12% of N−CF_2H, which is lower than the analogous 3-, 4-, 5-methylated 2-pyridones (**3e**, **3d**, **3a**). These data suggest that steric effects can significantly inhibit the reaction despite favorable electronics rendering the N atom more nucleophilic. Finally, **4y** afforded 53% of the N−CF_2H product. These results demonstrate dependence of reaction outcomes on electronic and steric parameters.

In summary, this paper presents direct *O*- and *N*-difluoromethylations of 2-pyridones, isoquinolinones, and quinolinones. The chemoselective protocol employs commercially available reagents and mild conditions. Tolerance to important functional groups including esters, amides, and alkenes demonstrates potential for late-stage functionalization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02305.

Detailed procedures, characterization data, and images of ^1H, ^{19}F, and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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