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Transition-Metal-Free N−O Reduction of Oximes: A Modular Synthesis of Fluorinated Pyridines

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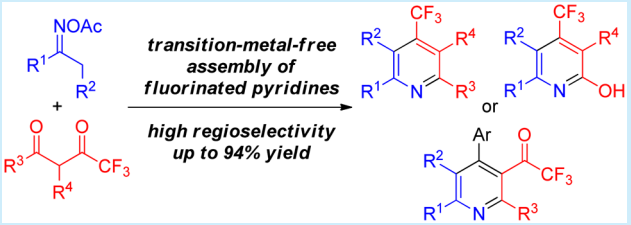
Supporting Information

ABSTRACT: An NH_4I-based reductive system has been explored to promote the oxime N−O bond cleavage and thereby enable a modular synthesis of a broad range of pharmacologically significant fluorinated pyridines. Compared with traditional condensation methods for pyridine assembly, this protocol was found to be highly regio- and chemoselective and presented broad functional group tolerance.



In recent decades, synthetic fluoro-organic chemistry has attracted intensive attention due to the successful introduction of fluorine for the development of small-molecule drugs.[1−4] Generally, fluorine functionalities are introduced to increase the basicity or to enhance the metabolic stability and binding affinity of a given molecule, which thereby results in an improved bioactivity.[2] For instance, 3,5-di(trifluoromethyl)-phenyl motif is currently introduced in organic molecules to enhance the binding affinity of NK1 antagonists in clinical development.[3] Among the fluorinated molecules with established pharmacological properties, fluorinated pyridines[4] represent the core structure of a large number of pharmacologically significant compounds, six of which are shown in Figure 1. Within our program on the development of facile methods for the synthesis of pyridines and other *N*-heterocycles,[5] we are now highly interested to develop a methodology for the construction of trifluoromethylated pyridines from readily available starting materials.

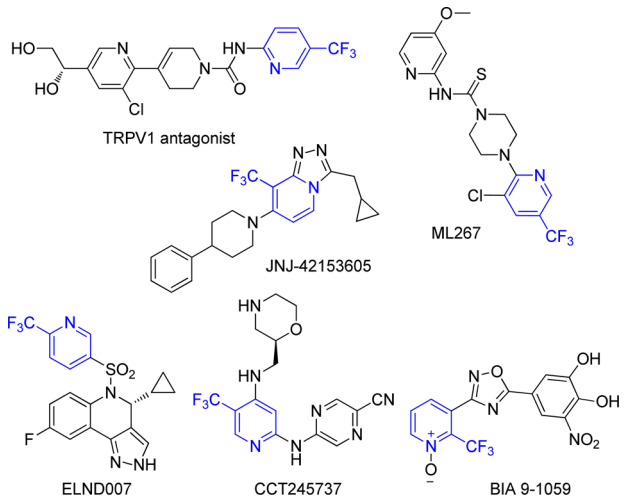
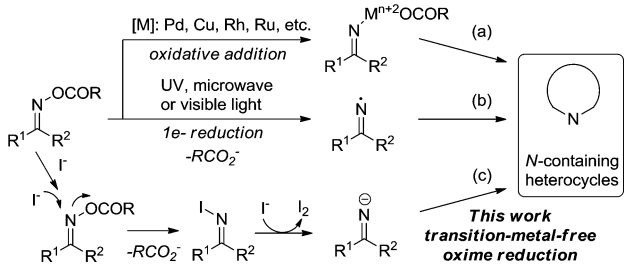


Figure 1. Fluorinated pyridines in drug molecules.

The strategy to use *O*-acyl oximes to construct heterocycles is generally facile and of easy handling because the *in situ* imine formation through the reduction of *O*-acyl oximes allows the reaction systems compatible to moisture and thereby obviating the need for anhydrous solvents.[6] Furthermore, the high regioselectivity achieved from the preassembled imine even with active carbonyl compounds highlights the flexibility of this strategy beyond the traditional condensation-based annulation such as Hantzsch pyridine synthesis.[7]

Generally, *O*-acyl oximes were used as versatile building blocks to form *N*-containing heterocycles through catalytic N−O bond reduction by transition-metal-mediated oxidative addition[8] (Pd, Cu, Rh, Ru, etc.) or light-triggered $1e^-$ reduction[9] such as UV, microwave, or visible light (Scheme 1a−b). Due to the development of sustainable chemistry and the pharmaceutical industry, the transition-metal-free conditions are highly desired to achieve the target chemical transformation.[10] Herein, we disclose an iodide-based system for the N−O bond reduction of oximes, which provides a

Scheme 1. Formation of *N*-Containing Heterocycles through Oxime N−O Reduction



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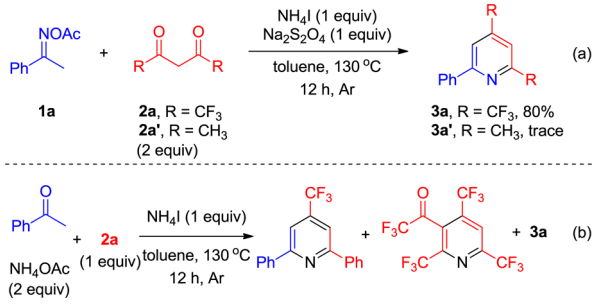
modular access to trifluoromethylated pyridines by using trifluoromethylated carbonyl compounds as the substrate to couple with *O*-acyl oximes. With the iodine reagents promoting the N−O bond reduction of oximes,[5a,11] our hypothesis is that the iodide is the direct one-electron donor for the N−O bond reduction (Scheme 1c), followed by the dehydration condensation with carbonyl compounds to afford pyridines. Mechanistically, we observed the formation of ketimine in the absence of carbonyl compounds. Moreover, the nitrogen-centered radical would not form in the present system.[12]

After systematic screening of a series of iodide salts and reductive reagents (see Supporting Information, Tables S1, S2), the annulation between oxime acetate **1a** and hexafluoroacetylacetonate (hfacac, **2a**) proceeded smoothly under an optimal $NH_4I/Na_2S_2O_4$-based system, giving the product 2-phenyl-4,6-bis(trifluoromethyl)pyridine (**3a**) in 80% yield (Scheme 2a).

Scheme 2. Transition-Metal-Free Reduction of Oximes for Fluorinated Pyridines

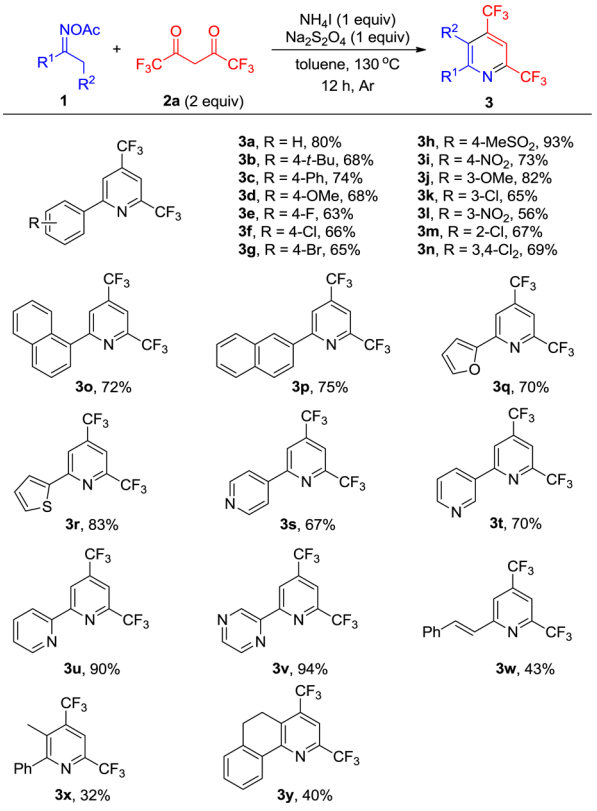


Notably, a copper-based reductive system was found to be much less efficient for this transformation. In contrast, acetylacetone (**2a′**) did not proceed through the annulation under the present system. When Hantzsch-type pyridine synthesis using acetophenone, hfacac **2a**, and NH_4OAc was performed under similar reaction conditions, we detected three pyridine products, the **3a** of which was generated in 31% GC yield (Scheme 2b).

The scope and generality of the annulation were probed first by using a broad range of ketoxime acetates to couple with hfacac **2a** (Scheme 3). Acetophenone oximes bearing a range of functionalities with different substitution patterns on the benzene ring afforded the target 2-phenyl-4,6-bis(trifluoromethyl)pyridine products (**3a**−**3n**) in moderate to excellent yields. Both electron-donating groups and -withdrawing functionalities were well compatible. Notably, oxime acetate with functional sulfone gave the highest yield (**3h**, 93%) among the substituted acetophenone oximes. The oxime acetates from naphthalenyl ketones gave good yields of the products (**3o** and **3p**). Heteroarenes such as furan, thiophene, pyridine, and pyrazine were all tolerated, giving the biheteroarenes in up to 94% yield (**3q**−**3v**). The use of styryl ketoxime afforded product **3w** in 43% yield. Notably, tetrasubstituted pyridines **3x** and **3y** were produced when using the oximes deriving from propiophenone and α-tetralone, albeit in lower yields, in which ketones were regenerated as the byproducts in significant amounts. Unfortunately, oximes from aliphatic ketones such as hexan-2-one afforded very low yield of product.

To explore the scope of the 1,3-diketones bearing one trifluoromethyl group, we initially employed thiophenyl ketoxime and thiophenyl 1,3-diketone (**2b**) to test the regioselectivity of the condensation reaction. To our delight,

Scheme 3. Scope of Oximes for Fluorinated Pyridines



symmetrical pyridine **4a** was exclusively obtained (Scheme 4). This observation encouraged us to subject a range of monotrifluoromethyl 1,3-diketones to the present system. Generally, those substrates gave moderate yields of the 4-trifluoromethylpyridine products (**4b**−**4s**). Notably, the oximes bearing an electron-deficient group such as pyridine (**4b**, **4d**, **4k**, and **4l**) and pyrazine (**4c**, **4m**) gave generally higher yields than those with an electron-rich group such as thiophene (**4a**, **4n**), benzene (**4e**−**4j**), and naphthalene (**4q**).

Unexpected results were observed when we utilized trifluoromethylethylacetoacetate as the coupling partner, which afforded pyridin-2-ols **4t** and **4u** as the sole product in moderated yields (Scheme 5). In this procedure, ethanol instead of H_2O was eliminated in the condensation step. Therefore, this protocol also provides a convenient entry to the 4-trifluoromethyl-pyridin-2-ol motif.

The pyridine product **3g** was obtained in 64% yield in a gram-scale reaction (Scheme 6). The incorporation of a bromo substituent in the product allows for further synthetic modification through Pd(0)-catalyzed Sonigashira coupling, Suzuki−Miyaura biaryl formation, and Buchwald−Hartwig aminations.[13] As shown in Scheme 6a−d, these reactions proceeded to give products **5a**−**5d** in moderate to excellent yield, offering rapid access to a broader range of functionalized molecules.

Finally, the three-component reaction of oximes, trifluoromethyldiketones, and aldehydes was found to proceed well by the combination of NH_4I and Et_3N, which generally afforded 2,3,4,6-tetrasubstituted pyridines in moderate yields (Scheme 7). In this case, hfacac **2a** and monotrifluoromethyl 1,3-diketone **2d** featured similar reactivity. Aromatic ketoximes and aromatic aldehydes with halogen and nitro functionalities were both tolerated (**7a**−**7c**, **7g**−**7h**). The oxime bearing the

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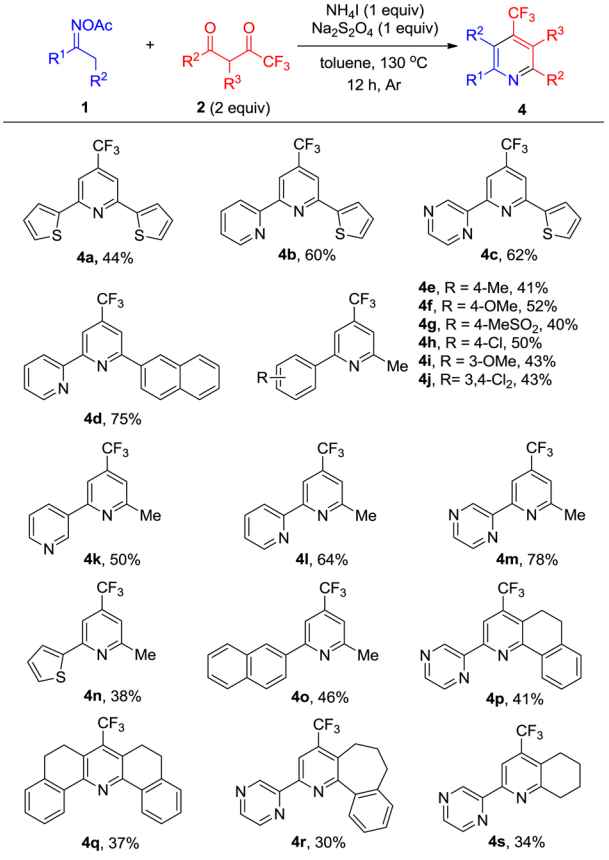
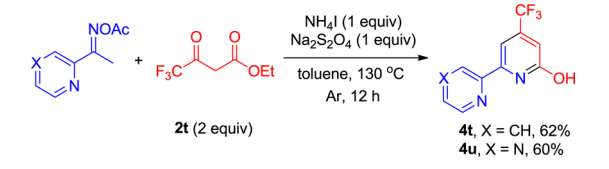
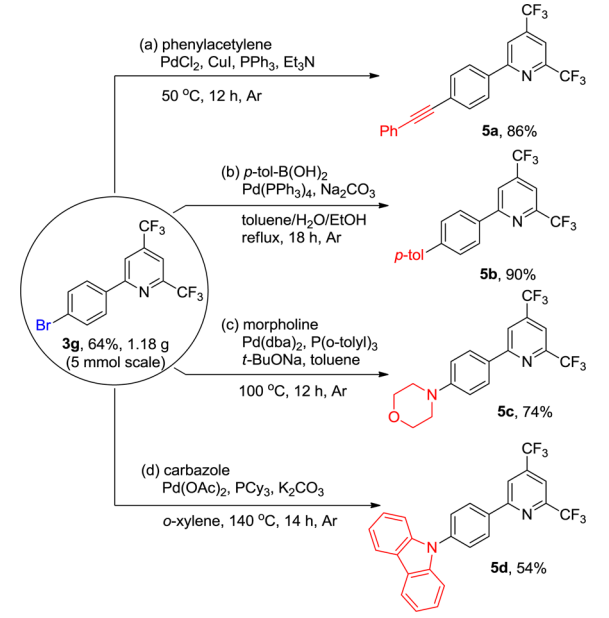
Scheme 4. Scope of Fluorinated Carbonyl Compounds



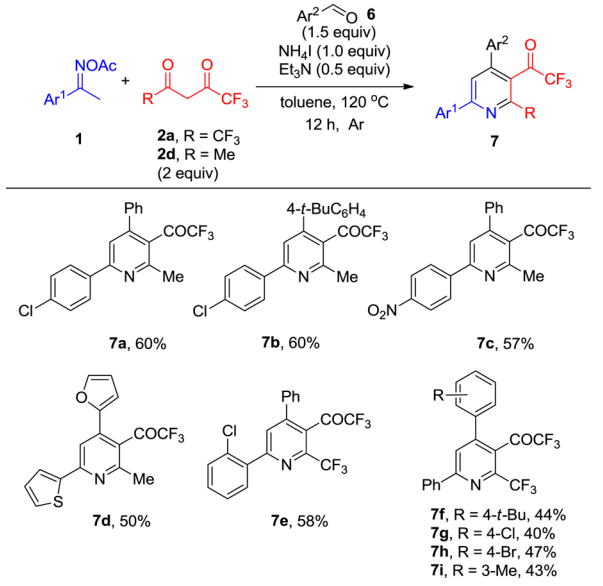
Scheme 5. Formation of Trifluoromethyl Pyridin-2-ols



Scheme 6. Derivation of Resultant Pyridines



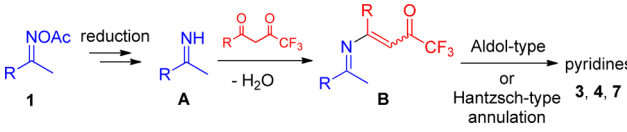
Scheme 7. 2,3,4,6-Tetrasubstituted Pyridine Synthesis through Three-Component Reaction



thiophen group coupled with furanyl aldehyde gave the corresponding 4-furanyl-6-thiophenylpyridine **7d** in 50% yield. Notably, the products **7** with the featured trifluoroacyl functionality could easily transfer into other functional molecules through simple treatments.[14]

Based on previous works and control experiments, a plausible reaction mechanism was proposed (Scheme 8). Ketimine **A** is

Scheme 8. Plausible Reaction Mechanism



initially formed by iodide-promoted reduction of oximes. Dehydration condensation of **A** and 1,3-diketone gives vinyl imine **B**, in which the regioselectivity is consistent with previously reported *N*-nucleophilic addition to trifolurometh-ylated 1,3-diketones.[15] Intermediate **B** undergoes intermolecular Aldol-type annulation to give pyridines **3** and **4**, or otherwise undergoes Hantzsch-type annulation with aldehydes to give products **7**.

In summary, we have developed an $NH_4I/Na_2S_2O_4$ reductive system which enabled the N−O bond cleavage of oximes and thereby the assembly of pharmacologically significant fluorinated pyridines. A number of fluorinated pyridines bearing diversified functionalities were prepared in satisfying yields. Compared with traditional condensation methods for pyridine assembly, this protocol was found to be highly regio- and chemoselective and functional group tolerant. The remarkable transition-metal-free N−O bond reduction of oximes is expected to inspire other cases of the *N*-heterocycle synthesis from oximes involving N−O bond cleavage.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01564.

Experimental procedures, characterization data, and ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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