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Communication

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A Bifunctional Reagent Designed for the Mild, Nucleophilic Functionalization of Pyridines

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Supporting Information

ABSTRACT: Herein is reported the design and application of a reagent for the direct functionalization of pyridines. These reactions occur under mild conditions and exhibit broad functional group tolerance, enabling the late-stage functionalization of drug-like molecules. The reagent can be easily prepared on large scale from inexpensive reagents, and reacts in the title reaction with acetonitrile, sodium chloride, and sodium methanesulfonate as the sole byproducts. Although this Communication focuses primarily on reactions with cyanide as nucleophile, preliminary experiments with other nucleophiles foreshadow the broad reaching synthetic utility of this approach.

Pyridines are pervasive in synthetic chemistry as the most prevalent heteroarenes in pharmaceuticals, and as structural components of many natural products.[1] The majority of synthetic approaches to pyridine-containing targets largely rely on the manipulation of prefunctionalized building blocks.[2] However, methods that do not require prefunctionalization can result in more streamlined syntheses and can enable the late-stage diversification of complex molecules.[3]

Two classes of reactions for the direct functionalization of pyridines have become ingrained in organic synthesis. The first comprise Minisci-type reactions in which radicals add to pyridines under acidic and oxidizing conditions.[4] Although this approach has undergone extensive development, it remains primarily limited to alkyl and acyl radicals.[5]

A second approach for pyridine functionalization involves initial oxidation of pyridines to pyridine *N*-oxides, followed by *O*-activation and nucleophilic substitution (Figure 1A).[6] Although these reactions are useful in certain contexts, the pyridine *N*-oxides need to be prepared and isolated in a separate step.[7] Pyridine *N*-oxides are highly polar, hygroscopic, and generally water-soluble, which makes purification and handling difficult. More significantly, the oxidants used to prepare pyridine *N*-oxides can promote Baeyer–Villager oxidation of ketones, epoxidation of olefins, and the oxidation of 5-membered heterocycles, aldehydes, amines, and sulfides. Finally, the activating reagents used to promote the nucleophilic substitution step are highly reactive, and often exhibit modest functional group compatibility. All of these limitations are significant, and therefore the development of new reagents that enable similar transformations of pyridines under mild conditions would be of great synthetic value.[8]

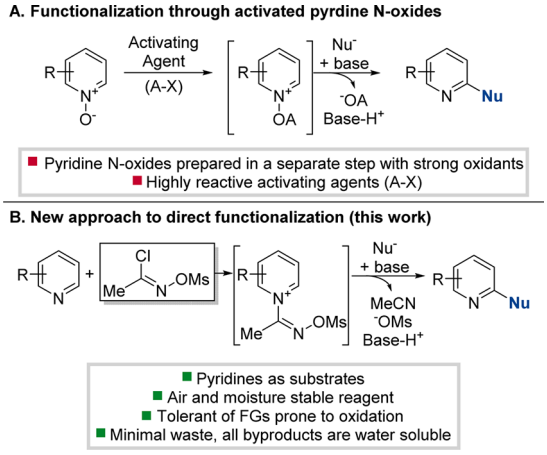
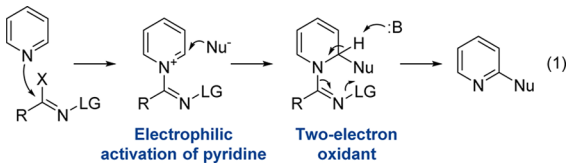


Figure 1. Nucleophilic functionalization of pyridines.

To develop a new approach to pyridine functionalization, a bifunctional reagent was conceptualized. First, the reagent would act as an electrophilic activator to facilitate nucleophilic addition to the pyridine ring (eq 1). Next, in the presence of a base, the



reagent would act as a two-electron oxidant to rearomatize the dihydropyridine intermediate (eq 1).[9] To be practical, the reagent would need to be readily available and easily handled, both steps would need to occur under mild conditions, and only innocuous byproducts would be formed. With these criteria in mind, a class of imine-based reagents containing a leaving group at both the α-carbon and nitrogen were envisioned to promote the direct functionalization of pyridines. More specifically, α-chloro *O*-sulfonyl aldehyde oximes were targeted due to their ease of synthesis from aldehyde oximes with inexpensive reagents.[10]

A small library of air- and moisture-stable α-chloro *O*-methanesulfonyl aldoximes were prepared (Scheme 1), and their reactivity toward pyridine was investigated. However, in all cases it was found that the formation of the intermediate pyridinium chloride salt was thermodynamically unfavorable, with the

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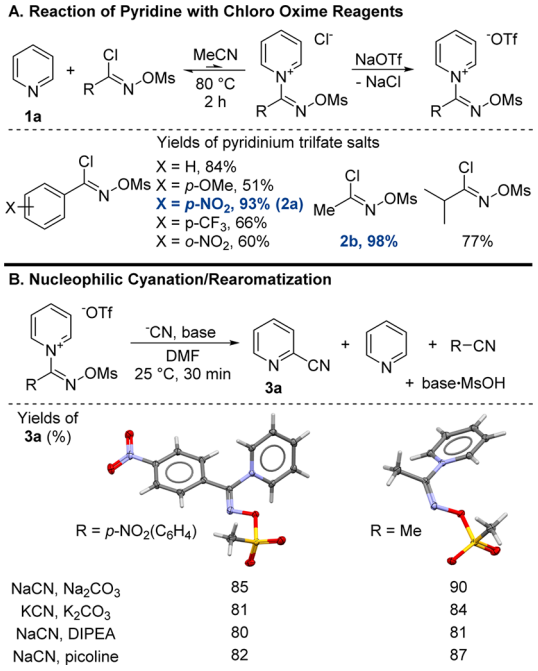
Scheme 1. Proof of Concept Studies[a]



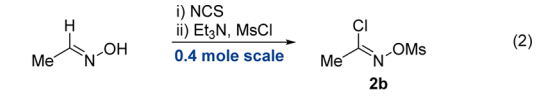
[a]For experimental details, see the Supporting Information. For clarity, the triflate counterions have been removed from the crystal structure images.

reaction equilibrium largely favoring the two starting materials. To overcome this, a stoichiometric amount of NaOTf was added to increase conversion to the pyridinium salt by the precipitation of NaCl.[11] Reagents **2a** and **2b** reacted with pyridine in nearly quantitative yields under mild conditions.

The pyridinium salts formed from **2a** and **2b** were analyzed by X-ray crystallography (Scheme 1B). Both contained a *cis* orientation of the OMs and pyridinium groups. The preferred orientation likely results from favorable orbital interactions of the lone pair on the oxime nitrogen and the σ^* orbital of the C—N (pyridinium) bond. In each case, the pyridinium ring was bent ~56° out of plane relative to the C=N bond of the oxime group.

For the nucleophilic substitution stage, reactions with cyanide nucleophiles were investigated.[12] Reactions with NaCN and KCN occurred rapidly and formed 2-cyanopyridine in comparable yields, with the identity of the auxiliary bases having minimal impact. In each case, <1% of isomeric 4-cyanopyridine was formed. The mass balance in each reaction was pyridine, resulting from cyanide attack at the oxime carbon. Overall, the novel reagent **2b** was identified as the bifunctional reagent that provided the highest yields, and is also the most atom-economic.

Reagent **2b** was prepared on 400 mmol scale from inexpensive, commercially available acetaldehyde oxime (eq 2).

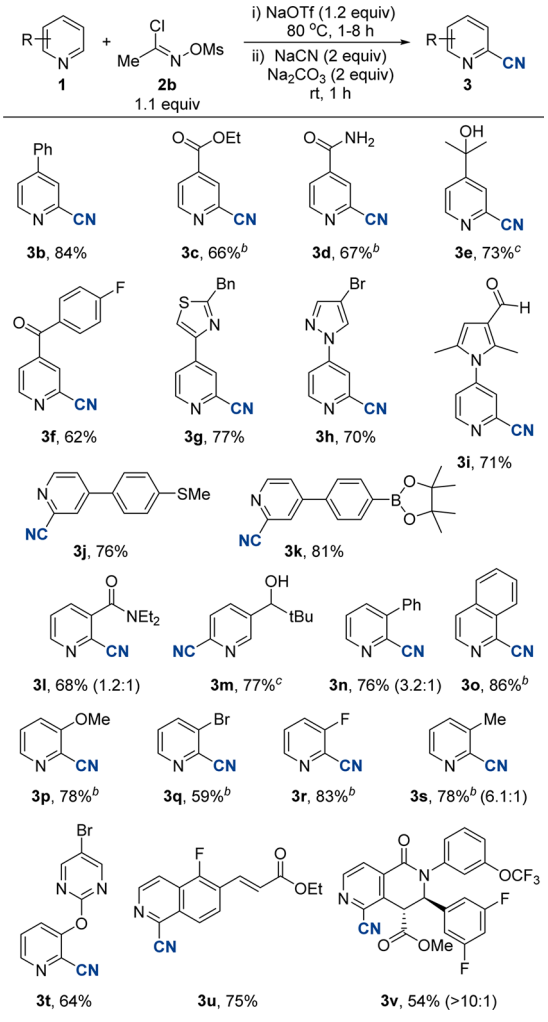


(2)

Acetaldehyde oxime was chlorinated with *N*-chlorosuccinimide (NCS), and the crude material was treated with triethylamine and MsCl to form reagent **2b** as an air- and moisture-stable crystalline solid in analytically pure form after an aqueous workup.[13]

With large quantities of reagent **2b** in hand, the direct cyanation reaction was demonstrated on a range of functionalized pyridines. In addition to being a simple protocol, the direct functionalization procedure reported here offers several advantages over related reactions with pyridine *N*-oxides. Functional groups prone to oxidation under the conditions used to oxidize pyridines to pyridine *N*-oxides were well tolerated, including electron-rich heterocycles, ketones, an electron-rich aldehyde, olefins, sulfide, and even an arylboronate ester. Amides and alcohols were well tolerated; this is noteworthy because these functional groups can react with typical activating agents used in pyridine *N*-oxide reactions (A-X, Figure 1). The mild conditions of the cyanation step enabled reactions to occur in the presence of an aryl fluoride susceptible toward S_NAr, an aldehyde prone to cyanide-catalyzed benzoin condensation, an α,β-unsaturated carbonyl compounds reactive

Scheme 2. Substrate Scope for the Cyanation of Pyridines[a,b,c]



[a]The reactions were performed by sequential addition of the reagents for the two stages, see the Supporting Information for details. Isolated yields shown for reactions performed on 0.5 mmol scale. [b]Assay yields of volatile products were determined by HPLC against authentic product standards. [c]Reagent **2a** was used in place of **2b**. Ratios in parentheses refer to isomeric 2,3- and 2,5-disubstituted pyridines formed in the reaction, with the major product shown.

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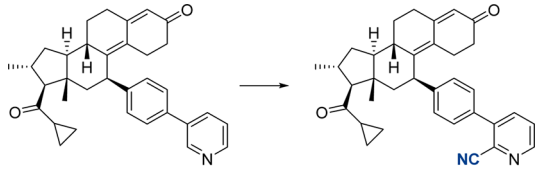
toward conjugate addition, and an epimerizable stereocenter. For every example shown in Scheme 2, the mass balance consisted of unreacted pyridine substrate, either from incomplete reaction with **2b**, or via competitive attack of cyanide at the oxime carbon of the intermediate pyridinium salt.

Reactions with 3-substituted pyridines were investigated in order to probe the site-selectivity of cyanation. Substrates containing halogen and oxygen substituents in the 3-position formed the 2-cyano-3-substituted pyridines with >95:5 selectivity. Isoquinoline substrates underwent cyanation exclusively at the 1-position. These observations are consistent with nucleophilic addition occurring at the most electrophilic carbon of the pyridinium intermediate, and is in-line with the selectivity observed with other reported nucleophilic addition reactions to activated pyridines.[6] Substrates containing bulkier or less-polar groups formed mixtures of two isomers. 4-cyanopyridine products were not observed in any case.

To demonstrate the application of this method in the context of late-stage functionalization, the direct cyanation was carried out on **1w**, a mixed progesterone agonist/antagonist (Scheme 3).[14] This compound contains two electrophilic ketones: one

Scheme 3. Gram-Scale Cyanation of a Mixed Progesterone Agonist/Antagonist



bearing an epimerizable stereocenter, the other conjugated to a diene. Of particular note, these functionalities are reactive toward the oxidants used to form pyridine *N*-oxides,[7] as well as typical radicals used in Minisci-type reactions.[4] The pyridine cyanation procedure was performed under the standard conditions with 1.0 g of **1w** to form a 2.5:1 mixture of 2-cyanopyridine products in 80% combined yield. The isomers were readily separated on silica gel, and the mass balance consisted of unreacted starting material.

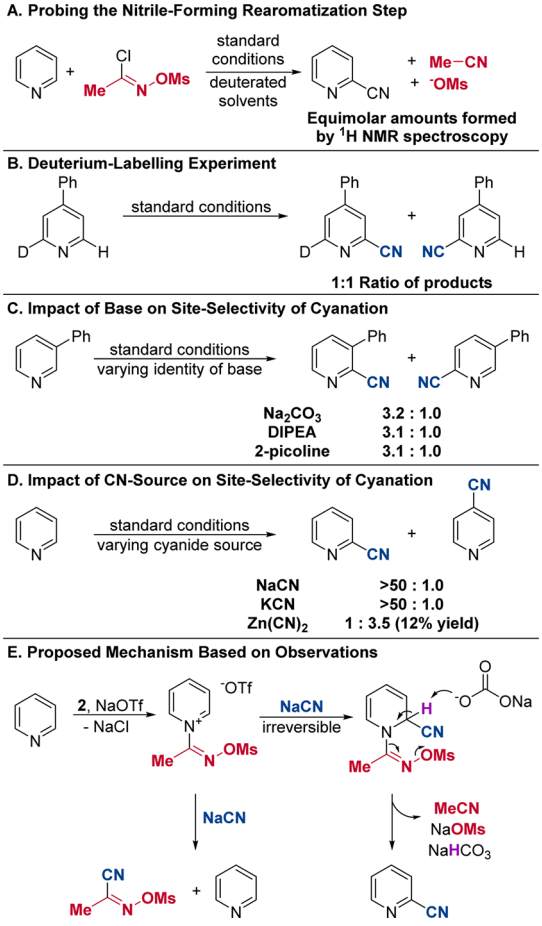
Although this method allows for the direct cyanation of a wide-range of functionalized pyridines, there are two limitations that need to be mentioned. First, because of the modest electrophilicity of reagent **2b**, diazines and 2-substituted pyridines exhibit poor reactivity in the current protocol. Second, although certain nucleophilic functional groups are tolerated, side-reactions were observed with substrates bearing unhindered alcohols and amines.

Having demonstrated the cyanation reaction on a broad range of substrates, experiments were designed in order to gain a deeper understanding of the reaction mechanism. First, a reaction with pyridine was carried out in deuterated solvents. At the end of the reaction, ^{1}H NMR spectroscopy of the crude mixture revealed an equimolar amount of CH_3CN, methanesulfonate anion, and 2-cyanopyridine (Scheme 4A), consistent with the nitrile-forming rearomatization step proposed above.

To probe the reversibility of nucleophilic addition of cyanide, 4-phenylpyridine containing a deuterium atom at the 2-position was subjected to the reaction conditions. If cyanide addition is reversible, a higher percentage of the deuterated product would be expected due to the slower rate of deprotonation of a C—D bond vs a C—H bond.[15] Under the standard cyanation conditions, a 1:1 ratio of deuterio- and protio-products was formed (Scheme 4B), consistent with irreversible cyanide addition occurring prior to deprotonation. Irreversible cyanide addition is also consistent with the observation that reactions of 3-phenylpyridine with various bases formed the isomeric cyanopyridine products in approximately the same ratio (Scheme 4C).[16] This is consistent with the product-determining step in the cyanation reaction of 3-substituted pyridines being controlled by the relative rates of cyanide attacking the pyridine ring at the isomeric 2-positions.

Finally, the impact of the cyanide source on site-selectivity was investigated with pyridine as the substrate (Scheme 4D).

Scheme 4. Investigating the Reaction Mechanism



Although both NaCN and KCN formed 2-cyanopyridine as the sole product, $Zn(CN)_2$ formed 4-cyanopyridine as the major product, albeit in modest yield. These observations are consistent with site-selectivity being controlled by the nucleophilic addition step.

Taken together, the results from the above-mentioned experiments are consistent with the mechanism illustrated in Scheme 4E. The intermediate pyridinium salt has been characterized by X-ray crystallography, the irreversibility of the cyanide addition step has been validated, and the byproducts from the elimination/rearomatization step have been observed.

Finally, to demonstrate that this concept for pyridine functionalization extends beyond cyanation, preliminary experiments with other nucleophiles were conducted (Scheme 5). With minimal screening, proof of concept was obtained showing

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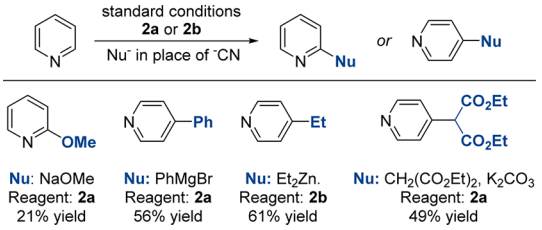
Scheme 5. Preliminary Results with Other Nucleophiles



that alkoxide, Grignard, organozinc, and malonate nucleophiles react to form a diverse set of functionalized pyridines. Furthermore, these results, along with those shown in Scheme 4D, reveal that changing the identity of the nucleophile leads to the selective functionalization at either the 2- or 4-position. Follow-up studies to investigate further reaction conditions with a wide array of nucleophiles are ongoing and will be reported in due course.

In summary, a novel bifunctional reagent has been designed for the direct functionalization of pyridines. The reagent acts to promote nucleophilic addition to pyridine, and as a mild two-electron oxidant in the presence of a weak base. The utility of the method is highlighted by the ability to carry out the cyanation of pyridines bearing functional groups sensitive toward acid, base, and oxidation. Preliminary results with other nucleophiles reveal that this approach to pyridine functionalization will be broad reaching. Work is ongoing to expand the scope to other nucleophiles, and to explore further the application of these bifunctional reagents in the development of new reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05414.

Data for pyridinium salts from **2a** (CIF)
Data for pyridinium salts from **2b** (CIF)
Experimental details and characterization data for new compounds (PDF)

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Notes

The author declares no competing financial interest.

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(16) An alternative explanation is that cyanide acts as the base to deprotonate the C-2 position of the dihydropyridine intermediate.

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