Synthetic Methodology

Sonogashira Reaction of Bromofluoropyridinaldoxime Nuclei: Convergent Synthesis of Functionalized 2- and 3-Fluoropyridine Scaffolds

Jagadeesh Yerri[a] and Rachid Baati*[a]

Abstract: A chemoselective palladium catalyzed Sonogashira cross-coupling of bromofluoropyridinaldoxime with highly functionalized alkynes is presented. This reaction is fully compatible with unprotected sensitive aldoxime and affords representative underexplored new scaffolds. The process exhibits a broad scope of alkynes, dialkynes, and large functional group compatibility, including the use of non-radioactive isotopic reporter such as ^{15}N labeled oxime and chiral substrates.

Introduction

Chemoselective methodologies have the potential to fasten and shorten the chemical synthesis of pharmaceuticals, natural products and agrochemicals, resulting in the increase of the molecular diversity.[1] In this regard, methods for the incorporation of fluorinated nitrogen containing heteroaromatic scaffolds into drugs remains of considerable synthetic interest, by virtue of the physicochemical and biological properties of fluorine.[2] Fluorine substituents modulate the lipophilic and hydrophilic balance of the parent heteroaromatic sample resulting in increased bioavailability of drugs and enhanced metabolic and biological membranes permeability.[2–4] In recent years, significant progress has been made towards the synthesis of a variety of fluoropyridine building blocks.[5–8] However, methods devoted to the functionalization and derivation of fluoropyridines carrying sensitive heterosubstituents, such as unprotected aldoxime, remains elusive and essentially unexplored,[9,10] despite of the prevalence of this moiety in compounds of pharmaceutical value.[11,12] Besides this, only few examples of Sonogashira C–C cross-couplings using non fluorinated arylaldoxime or ketoxime have been reported.[13] To the best of our knowledge, the reactivity, the scope and the limitations of this transformation on fluoropyridinaldoximes have not been investigated so far.

In the course of our projects dedicated to the development of reactivators of organophosphorus (OP) inhibited acetylcholinesterase (AChE),[14–16] we hypothesized that the use of unprotected 6-bromo-3-fluoro-2-pyridinaldoxime nuclei would deliver new scaffold that could be used as reactivators, through the use of a late stage chemoselective palladium catalyzed cross-coupling Sonogashira reaction, with suitable alkynes.

Herein, we report for the first time, the development of a highly selective Pd-catalyzed Sonogashira cross-coupling reaction of unprotected 6-bromo-3-fluoro-2-pyridinaldoxime nuclei **2** with functionalized alkynes **1** (Scheme 1). This transformation yields a wide range of new and valuable 6-alkynyl-3-fluoro-2-pyridinaldoximes **3**.
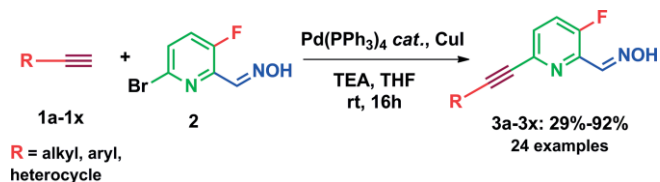
Scheme 1. Sonogashira reaction of 6-bromo-3-fluoro-2-pyridinaldoxime **2** with alkynes **1a**–**1x**.

The 6-alkynyl-3-fluoro-2-pyridinaldoximes may found numerous applications, such as reactivators of OP-inhibited AChE.[14–17]

Results and Discussion

Practically, we identified that readily available 6-bromo-3-fluoro-2-pyridincarboxaldehyde precursor represented a versatile heterocyclic building block that could be elaborated into an array of 6-alkynyl-3-fluoro-2-pyridinaldoximes. To initiate our work, we first prepared quantitatively the corresponding 6-bromo-3-fluoro-2-pyridinaldoxime **2** upon treatment with hydroxylamine hydrochloride in EtOH in the presence of CH_3CO_2Na under reflux conditions (See Supporting Information).[16,18a] In such conditions the proton NMR of **2** revealed that the (E)-aldoxime was obtained stereoselectively, no trace of the (Z)-oxime was observed.[18b] We then used conditions to promote the Sonogashira coupling of 6-bromo-3-fluoro-2-pyridinaldoxime **2** with 5-phenyl-1-pentyne **1a** as model substrate (Figure 1).[16] We were concerned whether the 3-fluoro group might inductively react under palladium catalysis, since electron-deficient fluoroarenes are known to participate in pal-

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ladium-catalyzed cross-coupling reactions,[9a,19,20] and whether the oxime would be compatible. We were first encouraged to observe that the reaction proceeded chemoselectively and the expected product **3a** was obtained with an excellent isolated yield of 92 % (Figure 1). The unprotected 2-pyridinaldoxime and the fluorine function of **2** were well tolerated under these mild conditions [THF/TEA, Pd(PPh$_3$)$_4$, CuI, room temp., 16 h] affording the desired corresponding new fluoroheterocycle **3a**. Notably, shorter reaction time (1 h) was observed with equal efficiency for substrate **1a**, under microwave conditions. These results demonstrated the robustness, and the chemo-compatibility of unprotected 3-fluoro-2-pyridinaldoxime moieties under basic Sonogashira cross-coupling conditions (**3a**, 92 %).
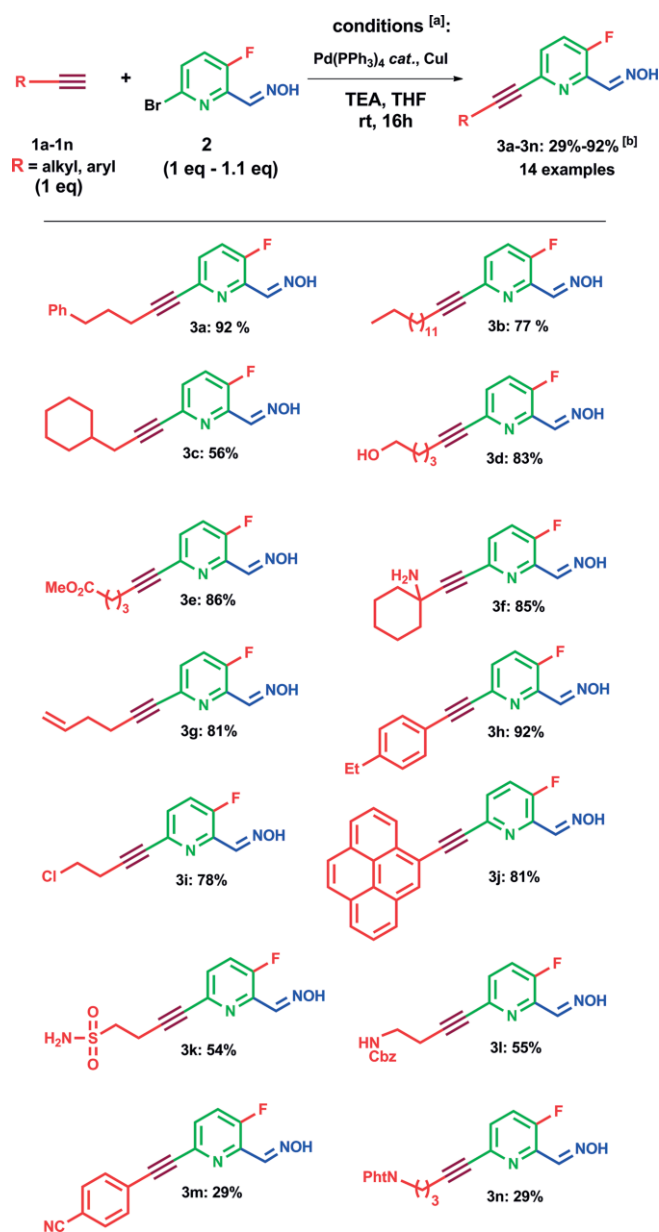

Figure 1. Scope of alkynes for Sonogashira cross-coupling reactions. (a) Reaction conditions: Pd[PPh$_3$]$_4$ (0.1–0.15 equiv.), CuI (0.2–0.3 equiv.), THF/Et$_3$N (2:1 v/v), room temp., 16 h. (b) Isolated yield.

Further experiments were conducted at room temperature for 16 h to demonstrate the alkyne scope of this reaction (Figure 1); for example, the Sonogashira coupling of 1-pentadecyne **1b** and 3-cyclohexyl-1-propyne **1c** worked well and gave **3b** and **3c** in high to good yields. Significantly, unprotected primary alcohols such as 5-hexyne-1-ol **1d**, and esters such as methyl 5-hexynoate **1e** had no obvious effect and were well tolerated. The corresponding products **3d** and **3e** were obtained in excellent 83–86 % yields.

To evaluate further the synthetic potential of this current methodology, alkynes bearing an unprotected amino group **1f**, a terminal alkene **1g**, a conjugated aromatic group **1h** and chlorinated substituent **1i** were tested. Pleasingly, the corresponding cross-coupled products **3f**–**3i** were obtained in all cases in high isolated 81–92 % yield. Polyaromatic hydrocarbon substrate such as 1-ethynylpyren **1j** underwent the cross-coupling reaction with equal efficiency to afford the expected fluorescent 3-fluoro-2-pyridinaldoxime **3j** in 81 % yield. For substrates bearing more polar groups such as unprotected sulfonamide **1k**, protected primary amine **1l** or an aromatic nitrile **1m**, the reaction proceeded, however, with moderate efficiency, the products **3k**–**3m** were obtained in acceptable yield 29–55 %. The observed decrease of yield is ascribed to the difficulty of isolation of pure products by usual column chromatography on silica, and some degradation was noticed when 4-ethynylbenzonitrile **1m** was used. The use of *N*-(4-pentynyl) phthalimide **1n** afforded identically the expected cross-coupled product in decreased 29 % isolated yield.

Inspired by these results, we next explored the reactivity of saturated and aromatic heterocyclic alkynes (Figure 2).

To our delight, unprotected and sterically hindered 4-ethynyltetrahydro-2*H*-pyran-4-ol **1o** and strained 3-ethynyloxetan-3-ol **1p** were also compatible with the reaction conditions and performed well into the desired products **3o** and **3p** in high yield 86–91 %.

When strained *N*-protected 3-ethynylazetidin **1q** was introduced the reaction proceeded efficiently resulting in good yield (76 %) of **3q**. Significantly, 4-ethynylpyridine **1r** and *N*-Boc-protected 4-aminopyridine **1s** have been proved to be suitable candidates, generating the corresponding desired products **3r** and **3s** in 79 and 62 % yield, respectively. Encouraged by the success of this methodology, we turned our attention to the reactivity of chiral reagents, such as amino-acid, and nucleoside analogue.[21]

We were pleased to see that the Sonogashira reaction of unnatural *N*-(Boc)-ʟ-propargylglycine methyl ester **1t** with 6-bromo-3-fluoro-2-pyridinaldoxime **2** afforded without complication the expected compound **3t** in good 76 % yield, without any alteration of the chiral center. In a similar fashion, initially prepared nucleosides **1u** provided the desired stereo pure coupling product **3u** in 61 % isolated yield. Any sign of epimerization of the chiral centers was observed for reactants **1t** and **1u**. Also, the late stage Sonogashira cross-coupling of alkyne **1v** with **2**, provided the expected 6-alkynyl-3-fluoro-2-pyridinaldoxime **3v** in excellent yield (87 %), which is an analog of a recently published hybrid reactivator of OP-inhibited AChE.[14b]
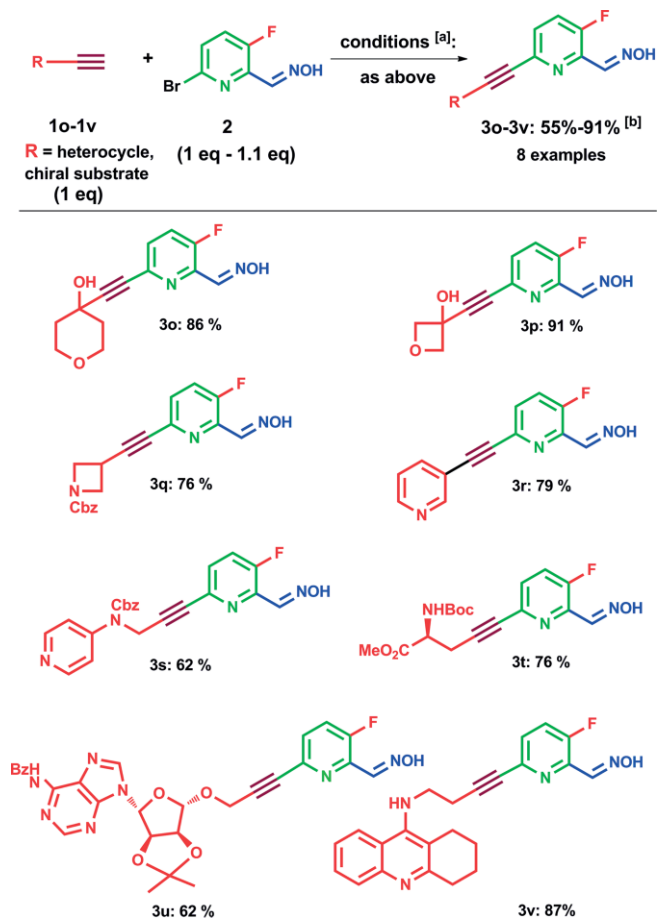
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Figure 2. Additional scope of alkynes for Sonogashira cross-coupling reactions. (a) Reaction conditions: Pd[PPh₃]₄ (0.1–0.15 equiv.), CuI (0.2–0.3 equiv.), THF/Et₃N (2:1 v/v), room temp., 16 h. (b) Isolated yield.

To further investigate the synthetic utility of this Sonogashira reaction and the versatility of corresponding products, we showed that (i) the use of non-radioactive isotopic reporter

such as ^{15}N labelled **2a** (See Supporting Information)[22] is compatible with the cross-coupling reaction (**3w**, 72 %) (Scheme 2a), (ii) terminal dialkynes such as **1x** are well tolerated substrates and deliver original symmetrical products **3x** (Scheme 2b), and (iii) alkyne (**3d**) and dialkyne (**3x**) products can be selectively reduced upon controlled hydrogenation under palladium catalysis, to generate selectively the corresponding *E*-alkene **5** or the fully saturated compounds **4** (Scheme 2b and Scheme 2c).

The scope and rationalization of the selective hydrogenation reaction are under investigation in our group and will be published in full in due course.

Finally to expand the scope of this reaction, the reactivity of isomeric unprotected 5-bromo-3-fluoro-2-pyridinaldoxime and 5-bromo-2-fluoro-3-pyridinaldoxime was briefly investigated, in Sonogashira reaction with alkyne **1a**, under the above same reaction conditions. The corresponding cross-coupled products **7** and **9** were isolated in 32 % and 45 % non-optimized yields, respectively, along with the isolation of starting oximes in both cases. In light of these promising results for **6** and **8**, the large scope of Sonogashira reaction for bromofluoropyridinaldoxime isomers is demonstrated contributing in the increase of molecular diversity for fluoropyridine derivatives (Scheme 3).
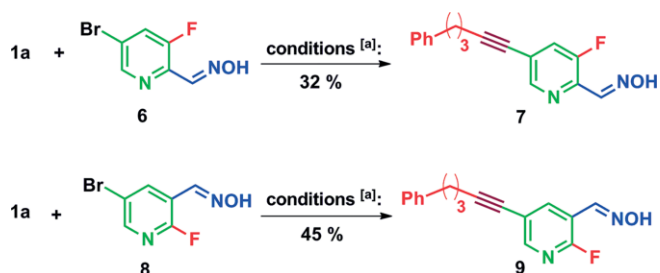
Scheme 3. Scope of isomeric fluorinated pyridinaldoxime for Sonogashira cross-coupling reactions. [a] Reaction conditions: Pd[PPh₃]₄ (0.1–0.15 equiv.), CuI (0.2–0.3 equiv.), THF/Et₃N (2:1 v/v), room temp., 16 h.
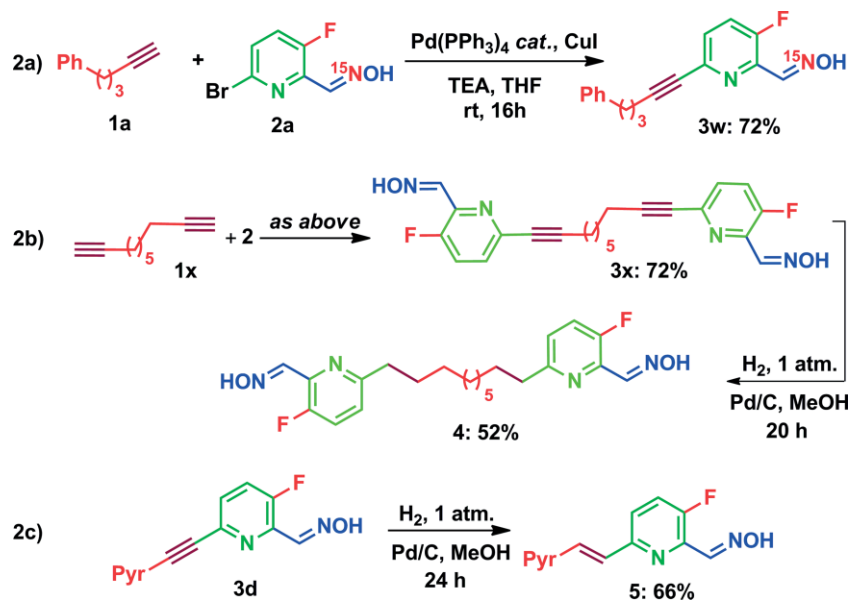
Scheme 2. Versatility of the Sonogashira cross-coupling and chemoselective hydrogenations of 6-alkynyl-3-fluoro-2-pyridinaldoximes **3x** and **3d**.

Conclusions

The results described herein establish the first examples of chemoselective Sonogashira cross-coupling reaction of 3 iso- mers of unprotected bromofluoropyridinaldoxime with func- tionalized alkynes, creating industrially and academically relevant new scaffolds for medicinal chemistry development. A variety of valuable functional groups, including unprotected alcohol, unprotected amine, ester, chloro, nitrile, sulfon- amide, *N*-protected amine, terminal alkene, acetonide, imide functions and strained heterocycles were well tolerated under the mild reaction conditions. Non-radioactive N^{15} labelled 5-alkynyl-3-fluoro-pyridinaldoxime scaffold are also ac- cessed in a straightforward manner for potential applications as biomolecular probes. Chiral amino-acid and nucleoside derivatives are fully compatible with the reaction. Owing to its unique scope, this late stage Sonogashira cross-coupling meth- odology proved to be an inestimable and indispensable tool for creating molecular diversity based on fluoropyridinaldoxime scaffold.

Experimental Section

General Procedure for the Late Stage Sonogashira Reaction Given for the Synthesis of 3a: To a degassed solution of oxime **2** (249 mg, 1.144 mmol, 1.1 equiv.) in THF/Et$_3$N (8 mL/ 3 mL) were added Pd[PPh$_3$]$_4$ (180 mg, 0.156 mmol, 0.15 equiv.) and CuI (60 mg, 0.312 mmol, 0.3 equiv.). After degassing the reaction mixture for 5 min at room temperature, alkyne **1a** (5-phenyl-1-pentyne, 150 mg, 1.04 mmol, 1 equiv.) was added dropwise, and the reaction mixture was stirred at the room temperature for 16 h. After completion (checked by TLC), the reaction mixture was concentrated under re- duced pressure, and the residue was purified by column chroma- tography (EtOAc/PE, 1:9) to afford the desired coupled fluoro oxime **3a** as a white solid in 92 % isolated yield.

Acknowledgments

Keywords: Fluoropyridines · Homogeneous catalysis · Cross-coupling · Reactivation · Oximes

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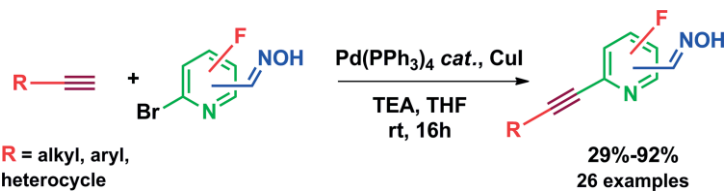[22] See the Supporting Information for the synthesis of **2a**.

Synthetic Methodology

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Sonogashira Reaction of Bromo-fluoropyridinaldoxime Nuclei: Convergent Synthesis of Functionalized 2- and 3-Fluoropyridine Scaffolds

The palladium catalyzed Sonogashira cross-coupling of bromofluoropyridin-aldoxime with highly functionalized alkynes investigated in this study is fully compatible with unprotected sensitive aldoxime and affords representative underexplored new scaffolds.