COMMUNICATION

# Sonogashira Cross-Coupling Reaction of Bromocyanofluoro Pyridine Nuclei: Access to 5- and 6-Alkynylfluoropyridinamidoximes Scaffolds

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**Abstract:** We disclose a general two-step procedure to access hitherto unknown and under explored 5- and 6-alkynyl-3-fluoro-2-pyridinamidoximes from 5- and 6-bromo-3-fluoro-2-cyanopyridines and a wide range of easily available and bench-stable terminal alkynes, using Sonogashira cross-coupling, as the first step. The generation of the polar amidoxime group is realized at a late-stage upon treatment of the alkynylfluorocyanopyridine by hydroxylamine. This mild and operationally simple two-step room temperature process is compatible with enantiopure chiral substrates and various functionality including free alcohols, unprotected and CBz-protected amines, acetonides, benzyl ethers, amide, imide, di-subsituted alkynes and strained saturated heterocycles.

## Introduction

The amidoxime functional group is recognized as a priviledged fragment since it represents a unique binucleophilic group that possesses both the amino and the hydroxyimino functions at the same carbon.[1] These particular features have been advantageously exploited for the synthesis of relevant heterocycles of medicinal interest, such as imidazoles,[2] isoxazoles,[3] 1,2,4-oxadiazoles,[3] 1,2,4-oxadiazol-5-ones,[4] 1,2,4-thiadiazoles,[5] triazole,[6] and pyrimidines.[7] Amidoximes have also been reported to be powerful pharmacophores in the identification of lead compounds towards the discovery of new synthetic drugs and prodrugs, with significant biological activity.[8] In particular, the use of amidoximes as antioxidant,[9] antimycotic,[10] antibacterial,[11] antimicrobial,[12] antileishmanial,[13] antihypertensive,[14] and antithrombotic[15] agents has become widespread. On the other hand, amidoxime derivatives also exhibit promising histone deacetylase (HDACs) inhibitory activity for cancer therapy,[16] as well as anesthetic properties.[17] Besides this impressive spectrum of biological activities, amidoximes are of interest in materials and polymer chemistry for the preparation of adsorbents, such as fibers and resins for chelation and removal of heavy metal ions.[18]

In the course of our research towards original reactivators of organophosphorous (OP) inhibited human acetylcholinesterase (*h*AChE), we recently found that 3-hydroxy-2-pyridinamidoxime **1** as well as 3-hydroxy-2-pyridinaldoxime **2** (Figure 1) exhibited unprecedented efficacy for phenylphosphonothioate (PhX) hydrolysis, a less toxic analogue of the nerve agent VX.[19,20]

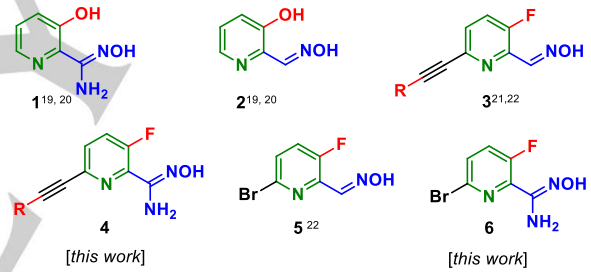
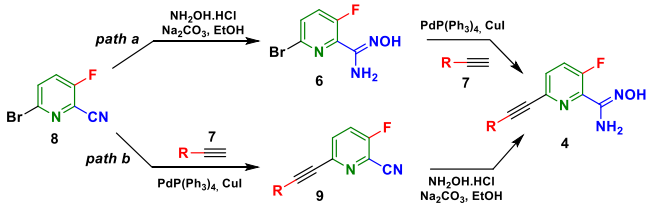



**Figure 1.** : Chemical structures of 3-hydroxy- and 3-fluoropyridin- amidoximes and -aldoximes **1**, **2**, **5** and **6**, and 6-alkynyl-3-fluoro-2-pyridin-aldoximes **3** and amidoximes **4**.

We also demonstrated that these oxime-containing scaffolds showed promise as reactivators of VX-inhibited *h*AChE *in vitro*.[20] More recently, further developments in that field led us, to discover and highlight the benefit of 6-alkynyl-3-fluoro-2-pyridinaldoximes **3** (Figure 1), as precursor of 6-alkanylfluoropyridinaldoximes, used for the efficient reactivation and resurrection of sarin-inhibited human acetylcholinesterase.[21] We then hypothesized that unknown alkynylfluoropyridinamidoximes such as **4**




**Scheme 1.** Two-step pathways syntheses of 6-alkynyl-3-fluoro-2-pyridin-amidoximes **4** from fluorocyanopyridine **8**.

could find novel applications as precursors of innovative reactivators of OP-inhibited *h*AChE. While halogenated aromatic amidoximes have been reported for use in medicinal chemistry,[4] it is noteworthy that molecules bearing fluoropyridinamidoxime scaffolds are rare and remain elusive intermediates in synthetic organic and in bioorganic chemistry. Such original structures are appealing for applications in medicinal chemistry projects.

Based on our recent reports on the late stage Sonogashira cross-coupling reactions of 6-bromo-3-fluoro-2-pyridinaldoxime **5** with various alkynes,[22] we envisaged that the analogous reaction performed with the unknown 6-bromo-3-fluoro-2-pyridinamidoxime **6**, and suitable alkynes **7** (Scheme 1, path a), could enable the synthesis of previously unexplored 6-alkynyl-3-fluoro-2-pyridinamidoximes **4** as potential reactivators or precursors of reactivators of OP-inhibited *h*AChE. Successful implementation of this methodology will also enlarge the molecular diversity of fluoropyridine libraries, known to be pharmaceutically valuable scaffolds for drug discovery.[23]

Herein, we disclose a simple two step protocol for the synthesis of new 6-alkynyl-3-fluoro-2-pyridinamidoximes **4**, using the Sonogashira cross-coupling of 6-bromo-3-fluoro-2-cyanopyridine **8** with alkyne **7**, followed by a late-stage selective amidoximation (Scheme 1, path b). This room temperature sequence is simple and provides underexplored highly versatile chemical scaffolds, with potential uses as reactivators of OP-inhibited *h*AChE.[24]

**Results and Discussion**

To investigate the direct Sonogashira reaction of bromofluoropyridinamidoxime **6** with alkynes **7** (Scheme 1, path a), we first required access to suitable starting pyridinamidoxime derivatives. Practically, our identified prototypical compound was commercially available 6-bromo-3-fluoro-2-pyridinecarbonitrile **8**. Initially, generation of the amidoxime **6** was achieved in high isolated yield (82%) upon treatment of the cyanopyridine **8** with hydroxylamine hydrochloride in EtOH at room temperature, in the presence of sodium carbonate.[25] Remarkably, Sonogashira cross-coupling reactions using either the starting cyanopyridine **8** (path b, Scheme 1) or the corresponding amidoxime **6** (path a, Figure 1) have not been reported previously, to the best of our knowledge. We therefore initiated our study by examining Sonogashira cross-coupling of **6** with 1-ethyl-4-ethynylbenzene **7a** as our model alkyne, using reported conditions for the C-C cross-coupling of bromopyridine derivatives.[26] Surprisingly, the reaction did not perform well, and provided the expected product **4a** in a low isolated yield of 25%, along with the alkyne homocoupling byproduct in about 10%. Unfortunately, these unsatisfactory results were invariably replicated during our attempts to optimize the process by screening different conditions, such as reaction temperature, solvent and catalyst loading (data not shown). A common trend was low conversion of the starting bromofluoroamidoxime **6**, suggesting that the efficiency of the Pd-catalysed pathway was impacted due to the known propensity of amidoximes to complex and sequester metals.[27] In particular, amidoximes are reported to form stable complexes with Pd, and Cu ions.[28,29] Subsequently, we hypotesized that a combination of electronic and steric factors may govern the overall properties of the palladium catalyst, and hence the overall chemical efficacy of the Sonogashira cross-coupling reaction.

Taking these considerations into account, we set out to overcome this obstacle and access our targeted alkynyl fluoroamidoximes **4** by reversal of the reaction steps as envisioned in path b (Scheme 1). To our delight the reaction of cyanopyridine **8** with 1-ethyl-4-ethynylbenzene **7a** performed well and yielded to the coupled product **9a** in excellent isolated yield of 92% (Table 1). The 6-alkynyl-3-fluoro-2-cyanopyridine **9a** was next subjected to the optimised reaction conditions for amidoxime formation,[25] using hydroxylamine hydrochloride in ethanol and in the presence of sodium carbonate. Gratifyingly, the desired 6-alkynyl-3-fluoro-2-pyridinamidoxime **4a** was formed and isolated in 91% yield (Table 2). No evidence was found for side reactions such as nucleophilic aromatic substitution[30] of the 3-fluoro group by hydroxylamine, or formation of undesired amide byproduct.[8] Having validated the synthetic efficiency of the two step procedure (path b, Scheme 1) to access of 6-alkynyl-3-fluoro-2-pyridinamidoxime **4a**, we investigated the scope for production of diversely functionalized fluoropyridinamidoximes. We first prepared the corresponding 6-alkynyl-3-fluoro-2-cyanopyridines **9b-9k** by Sonogashira C-C cross-coupling of **8** and alkynes **7b**-**7k** (Table 1). It is noteworthy that the reaction could be run with unfunctionalized alkynes such as **7b** and **7c** to afford the desired 6-alkynyl-3-fluoro-2-cyanopyridines **9b** and **9c** in high yields, 93% and 85%, respectively. A range of functionalized alkynes **7d**-**7k** also underwent coupling with **8**, with high efficiency. The reaction tolerated free alcohols and amines, and alkynes (**7d**, **7e**) bearing sterically demanding substitution, providing the respective products **9d** and **9e** in 90% yield each.

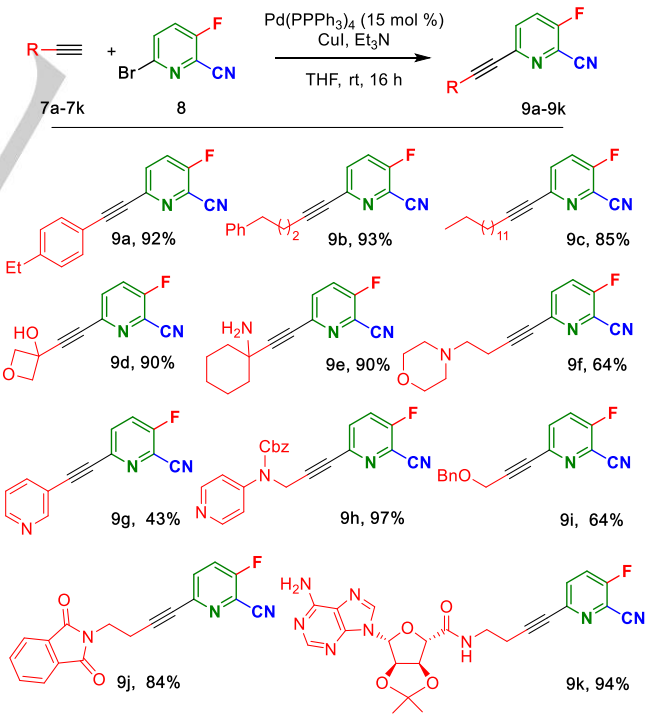



**Table 1.** Sonogashira cross-coupling of alkyne **7a**-**7j** with fluorocyanopyridine **8**

Pyridine and morpholine are common structural motifs found in numerous biologically active compounds. Under our conditions, alkynes **7f**, **7g**, and **7h** bearing these heterocycles also coupled readily with the fluorocyanopyridine **8** and afforded synthetically useful to excellent yields of the corresponding products **9f** (64%), **9g** (43%) and **9h** (97%). Functionalities such as O-benzyl protected alcohol **7i**, phthalimide **7j**, acetonide, amide and free aromatic amine of **7k** were well tolerated, under the cross-coupling conditions, and gave the expected alkynyl products **9i** (64%), **9j** (84%) and **9k** (94%) in high isolated yields. It is important to highlight that the chiral nucleoside alkyne **7k** provided the stereochemically pure coupling product **9k** without any sign of epimerization. Next we turned our attention to the conversion of alkynylfluorocyanopyridines **9b**-**9k** to the corresponding alkynylfluoropyridinamidoximes, by treatment with hydroxylamine at room temperature (Table 2). Pleasingly, the tested nitriles **9a**-**9k** smoothly provided the desired amidoximes **4a**-**4k** at room temperature, in high to excellent isolated yield, after purification by column chromatography. The sole exception was substrate **9g** that gave **4g** in low yield. The obtained results demonstrate that a wide array of functional groups, including imide, alcohol, aliphatic and aromatic amines, acetonides, aromatic and saturated heterocycles, as well as strained heterocycles such as oxetane, are well tolerated and compatible with the mild conditions of amidoximation, as shown in Table 2.

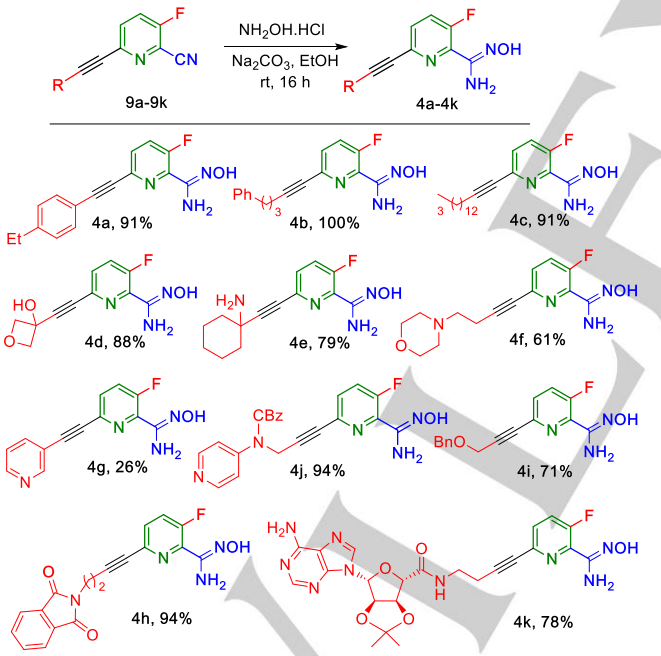
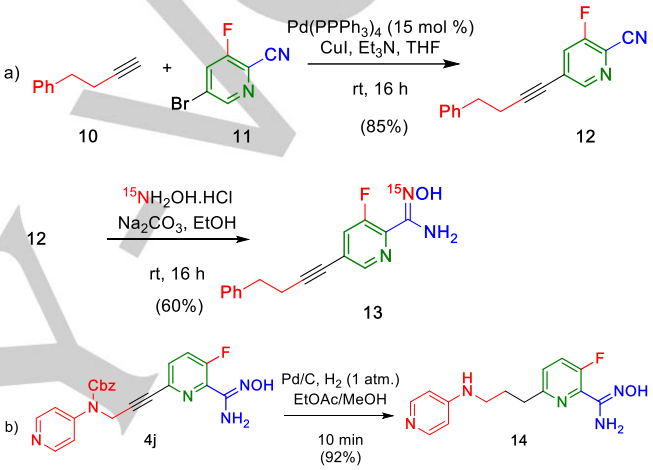



**Table 2.** Amidoximation of 6-alkynyl-3-fluoro-2-cyanopyridine **9a**-**9k** to produce 6-alkynyl-3-fluoro-2-pyridinamidoximes **4a**-**4k**.

We further illustrated the synthetic potential of this new two-step process for preparation of fluoropyridinamidoxime scaffolds, by application to an isomeric cyanofluoropyridine substrate. Commercially available 5-bromo-3-fluoro-2-cyanopyridine **11** was successfully converted in two-steps to the expected $^{15}N$ labelled 6-alkynyl-3-fluropyridinamidoxime **13** in 60% yield (Scheme 2), after Sonogashira reaction with alkyne **10**, and conversion of nitrile **12** upon treatment with $^{15}NH_2OH$ in ethanol, at 80°C.[22] $^{15}N$ labelled fluoropyridinamidoximes may be useful for non-radioactive isotopic metabolic labelling, $^{15}N$-tracing and for quantification purposes.[31] In addition, the value of alkynylfluoropyridinamidoximes as synthetic intermediates towards alkyl-linked hybrid reactivators was demonstrated by the one-pot selective hydrogenation/hydrogenolysis of the internal alkyne and CBz group present in **4j**. Exposure of **4j** to hydrogen (1 atm) over a Pd/C catalyst smoothly delivered the alkanylfluoropyridinamidoxime **14** in excellent 92% yield, without disturbing the potentially reducible amidoxime functionality, or the C-F bond.[21]




**Scheme 2.** Synthesis of 5-alkynyl-3-fluoro-2-pyridinamidoximes **13**, and selective hydrogenation of **4j** to produce 6-alkanyl-3-fluoro-2-pyridinamidoxime

In summary, an operationally simple two-step synthesis of alkynylfluoropyridinamidoximes is reported. The reaction conditions are compatible with a range of functional groups, giving efficient access to diverse amidoximes. Hydrogenation of the alkynyl linkage was effected in the presence of the amidoxime functionality, giving the alkyl-linked analogue **14**.

**Procedure for the Sonogashira cross-coupling reaction** for fluorocyanopyridine **8**, synthesis of 6-((4-ethylphenyl)ethynyl)-3-fluoropicolinonitrile (compound **9a**): To a degassed solution of picolinonitrile **8** (68 mg, 0.337 mmol, 1.1 equiv) in THF/$Et_3N$ (4 mL/ 2 mL), $Pd[PPh_3]_4$ (53 mg, 0.046 mmol, 0.15 equiv) and CuI (18 mg, 0.092 mmol, 0.3 equiv) were added. After degassing the reaction mixture for 5 min at room temperature, the alkyne **7a** (40 mg, 0.307 mmol, 1 equiv) was added dropwise and the reaction mixture was stirred at the room temperature for 16 h. After completion (TLC), the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/PE 1:9) to afford the desired coupled picolinonitrile **9a** as a white solid (71 mg, 92%).

**Procedure for amidoximation reaction** of 6-alkynyl-3-fluoro-2-cyanopyridine **9a**, synthesis of 6-((4-ethylphenyl)ethynyl)-3-fluoro-*N'*-hydroxypicolinimidamide (compound **4a**): A solution of picolinonitrile **9a** (50 mg, 0.20 mmol, 1 equiv), hydroxylamine hydrochloride (21 mg, 0.30 mmol, 1.5 equiv), and $Na_2CO_3$ (32 g, 0.30 mmol, 1.5 equiv) in dry ethanol (5 mL) was stirred at reflux over 16 h. After completion (TLC), the reaction mixture was filtered through a small celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/PE 1:3) to afford the amidoxime **4a** as a white solid (72 mg, 91%).

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**Keywords:** Fluorocyanopyridine • fluoroamidoxime •Sonogashira cross-coupling • alkynyl-fluoropyridinamidoxime • $^{15}N$ labelled amidoxime

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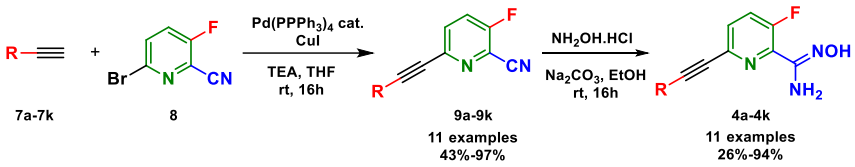


A practical and straightforward two-step protocol, to access highly valuable and unknown alkynyl-fluoro-pyridinamidoximes compounds.

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