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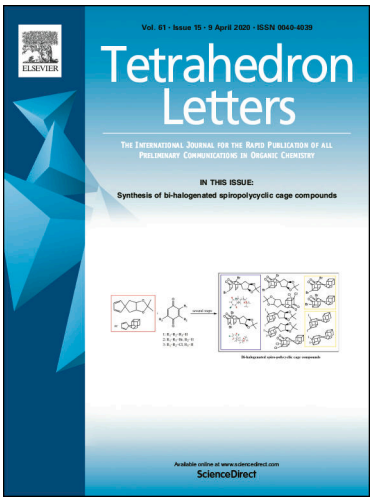

Facile Access to Fluoroalkylated 2-Aminopyridines by Cu-catalyzed [3+3] Couplings of Oxime Esters with β-CF_3 Acrylonitrile

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Graphical Abstract

A new and convenient method for the synthesis of trifluoromethylated 2-aminopyridines or difluoromethylated 2-aminopyridines through Cu-catalyzed [3+3] couplings of oxime esters with β-CF_3 acrylonitrile.

Facile Access to Fluoroalkylated 2-Aminopyridines by Cu-catalyzed [3+3] Couplings of Oxime Esters with β-CF_3 Acrylonitrile

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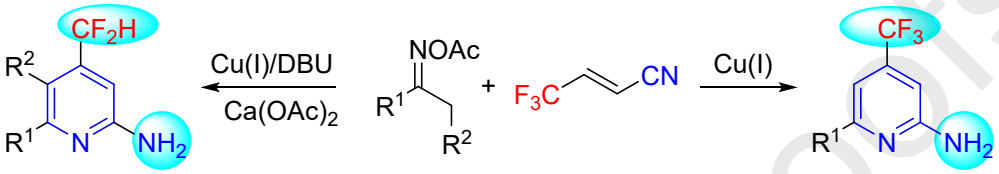

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Facile Access to Fluoroalkylated 2-Aminopyridines by Cu-catalyzed [3+3] Couplings of Oxime Esters with β-CF_3 Acrylonitrile

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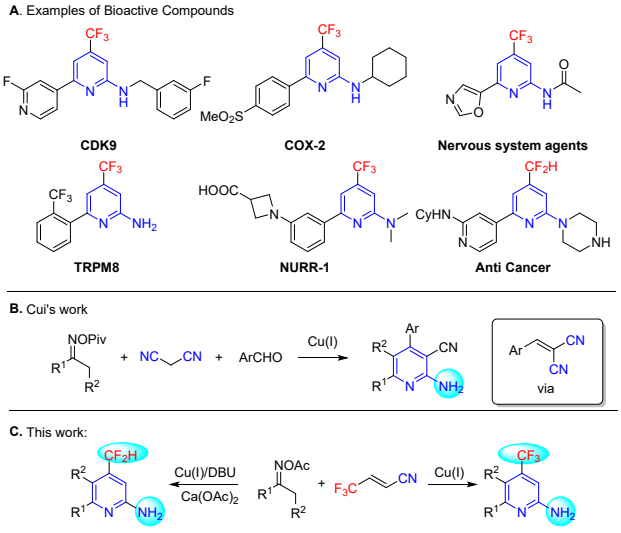
ABSTRACT

Copper catalyzed the [3+3] coupling of the oxime esters with β-CF_3-acrylonitrile toward divergent fluoroalkyl-substituted 2-aminopyridines was described. This redox-neutral coupling conditions with the acrylonitrile affording the trifluoromethylated 2-aminopyridines, respectively, under the reductive conditions, difluoromethylated 2-aminopyridines were obtained. The reactions occurred under mild conditions with high functional-group compatibility and excellent regioselectivity.

Naturally, fluorinated compounds synthesis are of great interest in the fields of biomedicine, agriculture, and material sciences.[1-7] The incorporation of the fluoroalkyl substituents into molecules is a powerful and widely employed strategy to improve the lipophilicity and metabolic stability of important leading compounds.[8-15] While the trifluoromethyl group(-CF_3) has been widely employed in medicinal chemistry,[16-21] the relatively underexplored difluoromethyl group (-CF_2H) has recently been realized as a lipophilic hydrogen bond donor and could act as a bioisostere of thiol or alcohol functional groups.[16-24] Traditional methods for the synthesis of difluoromethylated arenes include deoxyfluorination of arylaldehyde, transformation of CF_2H-containing building block or CF_2R- group. Recenetly, transition-metal catalyzed difluoromethylation of heteroarene was developed, and provided an efficient access to difluoromethylated heteroaromatic arenes and its derivatives.[25-40] On the other side, the 2-aminopyridines are widely used in heterocyclic synthesis, primarily because of their wide application in medicinally relevant structures, dyes, and luminescent materials.[41-45] While, traditional approaches need harsh reaction conditions, or *pre*-functional substrates.[41-46] Therefore, the development of a highly efficient method for the synthesis of fluoroalkylated 2-aminopyridine derivatives has significance value. As shown in Scheme 1A, the fluoroalkyl-substituted 2-aminopyridines are core structures in a large number of pharmacologically molecules.[47-49]

In recent decades, the oxime derivatives have emerged as readily available reagents to construct pyridine derivatives by transition-metal catalysis.[50-54] Notably, the Cu(I) catalyzed [3+3] annulations of oxime esters with α, β-unsaturated compounds have provided practical and simpler accesses to pyridines.[54-64] Recently, Cui and co-workers reported the synthesis of 2-aminopyridines *via* the copper-catalyzed cyclization using oxime esters and the *in situ* generated 2-benzylidenemalonitrile (Scheme 1B).[63]



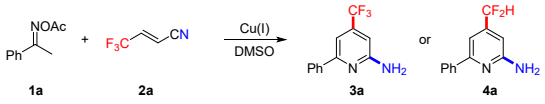
Scheme 1. Examples of Bioactive Compounds Containing 4-fluoroalkylated 2-Aminopyridine Skeleton and Previous Approaches for the Synthesis of 2-Aminopyridines through Copper-catalyzed Cyclization of Oxime Esters.

However, the methods for the synthesis of fluoroalkylated 2-aminopyridines have been rather limited. In 2018, we developed a facile protocol for the synthesis of fluoroalkylated pyridines/pyridones with β-CF_3 enones.[65] The β-CF_3 acrylonitrilewas applied in this system, while only one example

of difluoromethylated 2-aminopyridines was not explored. To further apply β-CF_3 acrylonitrile in this useful cyclization, we now report divergent synthesis of 4-CF_3-2-aminopyridine or 4-CF_2H-2-aminopyridine via copper catalyzed annulation of oxime esters with β-CF_3 acrylonitrile under operationally simple conditions (Scheme 1C).

Initially, we commenced our study by investigating the copper-catalyzed cyclization of oxime ester **1a** with **2a** (for details, see Table S1 in the Supporting Information). To our delight, the reaction delivered the desired product **3a** in 58% yield when CuCl was used at 100℃. Screening of the Cu(I) catalysts and temperature showed that the combination of CuCl and DMSO at 60℃ was optimal (Table 1, entries 1-5). Increasing the equivalent of **1a**, the product **3a** could be obtained in 71% yield at 80℃ (Table 1, entries 6 and 7). Interestingly, the addition of DBU switching the trifluoromethylated product **3a** to difluoromethylated product **4a** in 31% yield at 120℃. Different copper salts and F^- scavenges were examined, and further studies showed that when DBU and $Ca(OAc)_2$ were added, the yield of **4a** improved to 57% (Table 1, entries 8-12), more catalyst loading improved the yield to 65% (Table 1, entry 13). When $Ca(OAc)_2$ or LiOAc was used without DBU, only trifluoromethylated product **3a** was obtained (Table 1, entries 14 and 15). Based on our previous work, the DBU was probably served as a base as well as a reductant.[65]

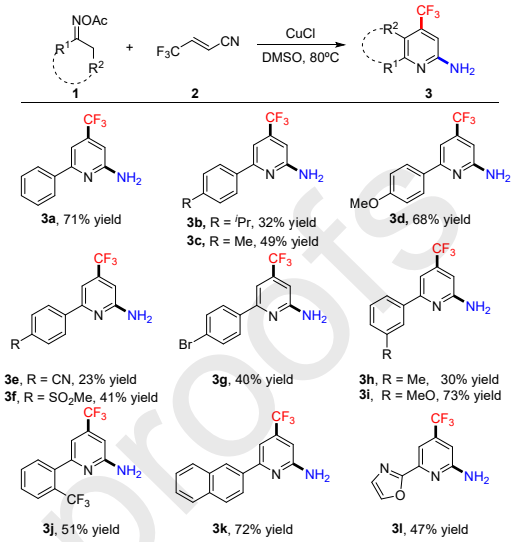
Table 1. Optimization Studies[a]



Entry	Catalyst (mol %)	1a: 2a	T(℃)	Additive	Yield 3a(%)	Yield 4a(%)
1	CuCl	1:1.5	100	--	58	--
2	CuCl	1:1.5	60	--	61	--
3	CuCl	1:1.5	40	--	14	--
4	CuBr	1:1.5	60	--	40	--
5	CuI	1:1.5	60	--	46	--
6	CuCl	1.5:1	60	--	62	--
7	CuCl	1.5:1	80	--	71	--
8	CuCl	1:1.5	120	DBU	--	31
9	CuCl	1:1.5	80	DBU	--	13
10	CuI	1:1.5	120	DBU	--	41
11	CuI	1.5:1	120	DBU	--	43
12	CuI	1.5:1	120	DBU/ $Ca(OAc)_2$	--	57
13[b]	CuI	1.5:1	120	DBU/ $Ca(OAc)_2$	--	65
14	CuI	1.5:1	120	$Ca(OAc)_2$	61	--
15	CuI	1.5:1	120	LiOAc	50	

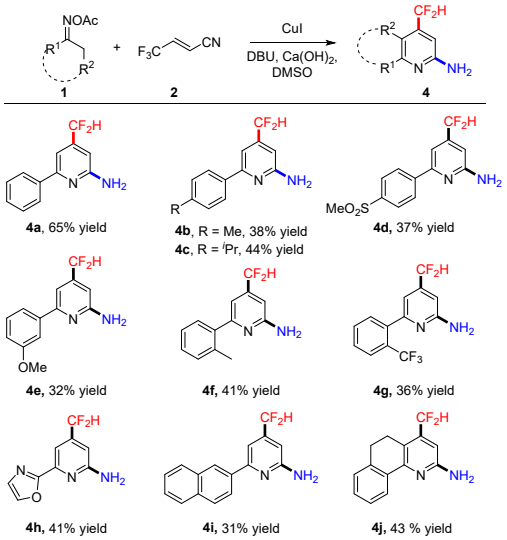
[a] Reaction Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), Cu^I (0.04 mmol), DMSO (2.0 mL), 24 h, DBU (0.4 mmol), $Ca(OAc)_2$ (0.2 mmol), LiOAc (0.2 mmol), isolated yields. [b]CuI (0.08 mmol)

On the basis of these optimized reaction conditions, we first investigated the scope and generality of the coupling systems for the preparation of 4-trifluoromethylated products (Scheme 2, **3a-3l**). Variation of the oxime esters with differential substitution on the aromatic ring, exhibited good functional group tolerance to afford the desired products with excellent chemoselectivity in halogens, EWGs and EDGs in the benzene ring, such as methyl, methoxyl, cyano, bromo, SO_2Me. The electron-rich arenes afforded the desired products with higher reactivity. Notably, this strategy was available for the construction of **3j** in reasonable yield, which could be used as therapeutic **TRPM8** receptor modulators. Heteroaryl-substituted oxime ester also performed well in this transformation (**3l**, 47% yield).



Scheme 2. Scope of oxime esters affording the 4-trifluoromethylated 2-aminopyridines. **Conditions A**: [a] Reaction Conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), CuCl (0.04 mmol), DMSO (2.0 mL), 24 h, isolated yields.

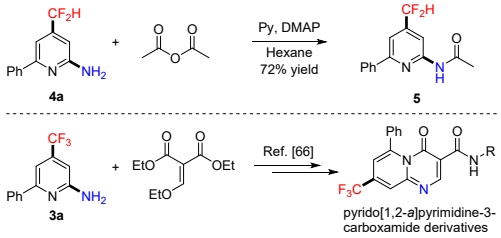
We next examined the scope of the transformation for the synthesis of 4-difluoromethyl-2-aminopyridines (Scheme 3, **4a-4j**). The coupling systems also tolerated oxime esters bearing *p*-Me, *p*-^{i}Pr, *p*-SO_2Me, *m*-MeO, *o*-Me, *o*-CF_3 substituents in the benzene ring (**4a-4g,** 31-65% yield), The coupling of oxazole and 2-Np substituted oxime esters also proceed smoothly to afford the corresponding products (**4h** and **4i,** 41% yield and 31% yield). *Tetra*-substituted difluoromethyl 2-aminopyridine **4j** was synthesized in 43% yield with the *α*-substituted oxime ester.



Scheme 3 Scope of oxime esters affording the 4-difluoromethylated 2-aminopyridines. **Conditions B**: [a] Reaction Conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), CuI (0.08 mmol),

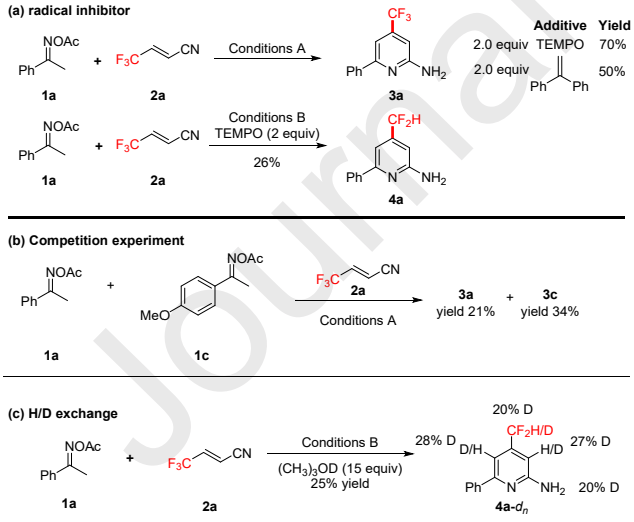
DBU by isolated yields.

The synthetic utility of the fluoroalkylated 2-aminopyridines was then briefly demonstrated (Scheme 4). The amino product **3a** could be easily transformed to *N*-acetyl derivative **5** in 72% yield. It has been reported that the pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives, which showed promising anticancer activity, could be synthetized from the 4-CF_3-2-aminopyridine **3a**.[66]



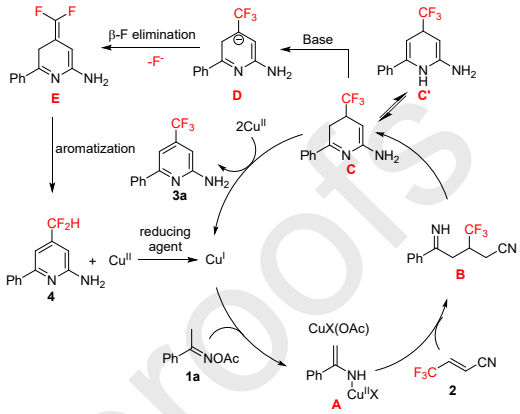
Scheme 4. Derivatization Reactions.

To gain the mechanism of the present 2-aminopyridine synthesis, several experiments were performed. [51,65] Addition of TEMPO or 1,1-diphenylethylene to the coupling of **1a** and **2a** did not inhibit the formation of the **3a**, and the addition of TEMPO also did not inhibit the formation of 4-CF_2H-2-NH_2-pyridine **4a**, these results indicated that this reaction did not proceed through a radical pathway. When an equimolar mixture of **1a** and **1c** was used to competitively couple with β-CF_3 acrylonitrile, products **3a** and **3c** were obtained in 21% and 34% yield, indicating that the electron-rich oxime ester reacted at a slightly higher rate (Scheme 5b). We also performed the H/D exchange experiment, with the ^{t}BuOD as deuterium source (modified conditions B), the isolated product **4a**-d_n revealed that both 3- and 5- positions were equally deuterated (27% D), and H/D exchanged was also detected at the difluoromethyl position (20% D), these results supports the tautomerization of intermediate E (see Scheme 6) in the system, which is consist with our previous studies.[65]



Scheme 5. Mechanistic studies.

On the basis of the above results and previous studies on the copper-catalyzed annulation of oxime derivatives, a plausible mechanism is given for the formation of fluoroalkylated 2-aminopyridines (Scheme 6). Oxidation of Cu(I) by oxime ester **1a** gives an intermediate **A** together with another Cu(II) species. Conjugate addition of **A** to β-CF_3 acrylonitrile and subsequent protolonysis leads to intermediate **B**. cyclization would produce a two copper(II) species furnishes 4-CF_3-2-aminopyridine **3a** with regeneration of the copper(I) catalyst. In presence of a suitable base and reductant, **C** would afford intermediate **E** through β-F elimination, which then isomerizes to the 4-CF_2H-2-amino-pyridine **4a**. Meanwhile, the Cu(I) catalyst is regenerated by further reduction of Cu(II). Following this mechanism, the dihydropyridone **C** species is either oxidized by Cu(II), or undergoes elimination of HF with DBU, which served as a stronger base and reductant.



Scheme 6. Proposed Mechanism.

In summary, we have developed Cu-catalyzed [3+3] cycloaddition of oxime acetates with β-CF_3 acrylonitrile for the synthesis of 4-CF_3-2-NH_2-pyridines and 4-CF_2H-2-NH_2-pyridines with high regioselectivity and redoxselectivity. Under redox-neutral conditions, the coupling afforded 4-CF_3-2-NH_2-pyridines smoothly. When DBU was used, 4-CF_2H-2-NH_2-pyridines were formed. The systems cover a particularly broad range of oxime acetates. The elegant control of reaction selectivity may provide insight for future studies of other Cu-catalyzed annulation reactions. Further studies and the application of this protocol are in progress.

Acknowledgments

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Conflicts of interest

There are no conflicts to declare

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1. Excellent regioselectivity
2. Broad substrate scope with good functional group tolerance
3. Trifluoromethylated or difluoromethylated 2-aminopyridines formation