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Divergent Syntheses of 2-Aminonicotinonitriles and Pyrazolines by Copper-Catalyzed Cyclization of Oxime Ester

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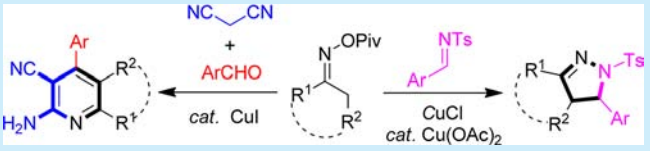
Supporting Information

ABSTRACT: Copper-catalyzed cyclization of an oxime ester toward divergent heterocycle synthesis is reported. Oxime ester serves as an enamine precursor to cyclize with malononitrile and aldehydes for access to 2-aminonicotinonitriles in a one-pot reaction, while cyclizing with *N*-sulfonylimines leads to synthesis of pyrazolines.

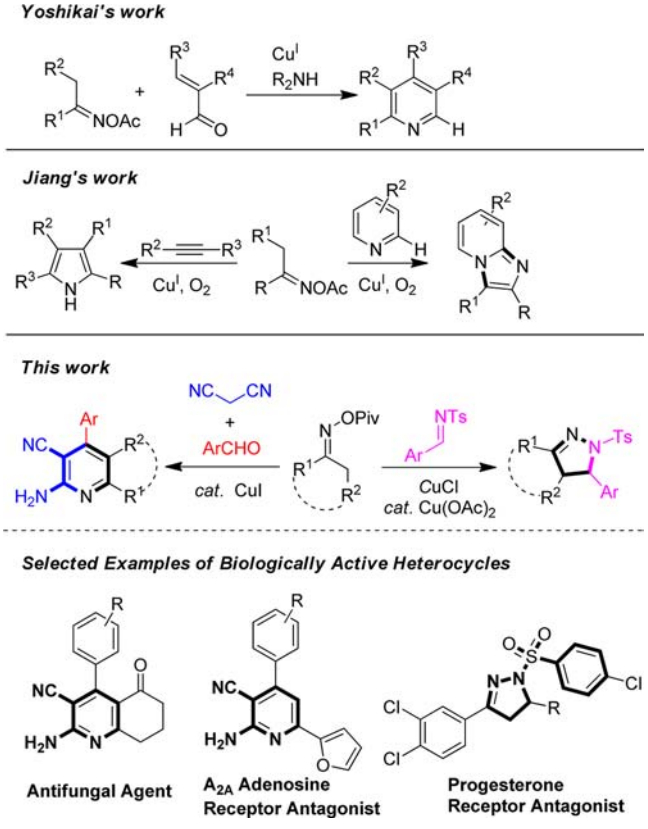


Divergent synthesis allows the rapid entry to structurally diverse compounds from the same starting material and therefore has been a popular and useful tool in the discovery of bioactive molecules and functional materials.[1] The success of divergent synthesis requires precise control of the chemo- and regioselectivity and a careful selection of the reaction conditions, guided by an understanding of the reactivity of intermediates and substrates.[2] So far, transition-metal-catalyzed cyclization has emerged as a powerful and distinct approach in the divergent synthesis of nitrogen-containing heterocycles.[3]

Recently, copper-catalyzed cyclization of oxime esters for heterocycle synthesis has been developed.[4] For example, Yoshikai reported pioneering work on the modular synthesis of pyridines using oxime esters and enals through synergistic copper/iminium catalysis (Scheme 1).[5] Jiang reported excellent work on the synthesis of pyrroles and imidazo[1,2-*a*]pyridines by copper-catalyzed cyclization of oxime esters with alkynes and pyridines (Scheme 1), respectively.[6] In those cases, the copper(I) catalyst presumably plays a role in reducing the oxime N−O bond to be an iminyl radical, which is further reduced by another copper(I) to an iminyl copper(II) which tautomerizes to the nucleophilic copper(II) enamide.[2−4] Therefore, oxime esters serve as enamine precursors in the presence of copper catalysts and definitely serve as an inspiration in heterocycle synthesis.

In the course of our research on metal-catalyzed cyclization for access to heterocyles,[7] we found that N−O bond cleavage would occur for *O*-pivaloyl hydroxylamine in the presence of a transition metal[7a,b] under conditions that were compatible with those in copper-catalyzed cyclization of oxime esters. Consequently, we envisioned that *O*-pivaloyl oxime esters would exhibit dramatically active reactivity under copper catalysis and give rise to enamine species. We also envisioned that further cyclization with electrophilic 2-benzylidenemalononitrile and *N*-sulfonylimine would deliver interesting heterocycles. Herein, we report divergent syntheses of 2-aminonicotinonitriles and pyrazolines via copper-catalyzed cyclization of oxime esters (Scheme 1).

Scheme 1



We initially commenced our study by investigating the multicomponent reaction of *O*-pivaloyl acetophenone oxime **1a**, benzaldehyde **2a**, and malonitrile **3**, since 2-benzylidenemalonitrile could easily be formed from benzaldehyde and malonitrile in one-pot.[8] To our delight, the reaction delivered

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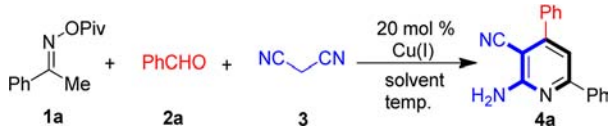
the desired 2-aminonicotinonitrile product **4a** in 25% yield when CuCl was used as a catalyst (Table 1, entry 1). A

Table 1. Reaction Condition Optimization.[a]



1a 2a 3 4a

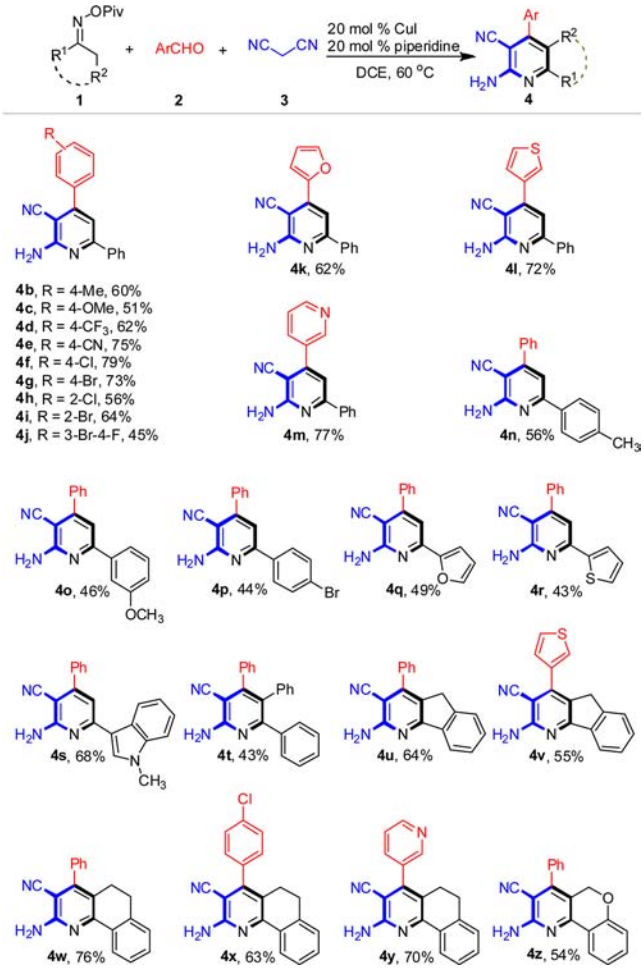
entry	catalyst	solvent	temp	additive	yield (%)[b]
1	CuCl	DCE	60 °C	-	25
2	CuBr	DCE	60 °C	-	32
3	CuI	DCE	60 °C	-	37
4	CuI	DCE	60 °C	piperidine/ 0.2 equiv	69
5	CuI	CH_3CN	60 °C	piperidine/ 0.2 equiv	52
6	CuI	DMSO	60 °C	piperidine/ 0.2 equiv	48
7	CuI	DCE	80 °C	piperidine/ 0.2 equiv	55

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3** (0.4 mmol), additive, solvent (2 mL), argon, 6–8 h. [b]Yields of isolated products.

screening of Cu(I) catalysts showed that CuI was optimal (Table 1, entries 2 and 3). Interestingly, the addition of piperidine dramatically increased the yield to 69% (Table 1, entry 4), and a survey of solvents revealed that CH_3CN and DMSO were inferior (Table 1, entries 5 and 6), while increasing the temperature to 80 °C led to a slightly lower yield (Table 1, entry 7).

With the data in hand, we next investigated the scope of this reaction involving various oxime esters and aldehydes. As shown in Scheme 2, various benzaldehydes, regardless of the electron-donating or electron-withdrawing group on the aromatic ring, were broadly tolerated, giving the products in moderate-to-good yield (**4b–j**, 45–79%). Valuable functional groups such as methyl, methoxy, trifluoromethyl, cyano, bromo, and chloro were also present in the products. Heterocyclic aldehydes like furan-2-aldehyde, thiophene-3-aldehyde, and pyridine-3-aldehyde also performed well in this transformation to produce the products in good yield (**4k–m**, 62–77%). Variation of the oxime esters, with differential substitution on the aromatic ring, showed that they reacted smoothly to afford the 2-aminonicotinonitriles in moderate yield (**4n–p**, 44–56%), while heterocyclic oxime esters with furan, thiophene, and indole skeletons also were applicable in this transformation, affording the products in moderate yield (**4q–s**, 43–68%). Interestingly, when polysubstituted oxime esters including a cyclic scaffold were used, this transformation proceeded smoothly to generate polycyclic products in moderate-to-good yield (**4t–z**, 43–76%). 2-Aminonicotinonitriles are important components of pharmaceuticals, with antifungal,[9] A_{2A} adenosine receptor antagonist[10] and prion protein inhibitory activity.[11] The classical synthesis of 2-amino nicotinonitriles relies on amination of 2-unsubstituted pyridines with sodium amide (Chichibabin reaction), which suffers from the limitation of low yield and narrow scope.[12,13] Therefore,

Scheme 2. Synthesis of 2-Aminonicotinonitriles[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.4 mmol), CuI (20 mol %), piperidine (20 mol %), DCE (2 mL), argon, 6–8 h.

this method represents an expedient approach toward the construction of 2-aminonicotinonitriles.

Since oxime esters successfully acted as enamine precursors, we next established the copper-catalyzed cyclization scope of oxime esters with *N*-sulfonylimines to gain access to *N*-sulfonylpyrazolines, through integration of enamine formation and oxidative cyclization.[14–16] By changing the reaction conditions, using 2 equiv of CuCl and 20 mol % $Cu(OAc)_2$ as additives, the reaction of oxime esters and *N*-sulfonylimines performed in DMSO at 100 °C could deliver the *N*-sulfonylpyrazoline product **6** successfully (for detailed reaction optimization, see the Supporting Information). As depicted in Scheme 3, various *N*-sulfonylimines, regardless of electron-donating or electron-withdrawing groups on the aromatic ring, were applicable in this cyclization generating *N*-sulfonylpyrazoline products in moderate-to-excellent yield (**6a–e**, 42–97%), with functional groups like methyl, methoxy, chloro, and nitro. The naphthyl- and dihydrocinnamyl-tethered *N*-sulfonylimines also performed well in this transformation producing the corresponding products in moderate-to-good yield (**6f,g**, 46–78%). Variation of the oxime esters showed that differential substitution on the aromatic ring of the oxime ester proceeded well to produce the products in moderate-to-good yield (**6h–l**, 53–82%). Interestingly, when the saccharin-derived cyclic *N*-sulfonylimine was used, this cyclization produced the fused

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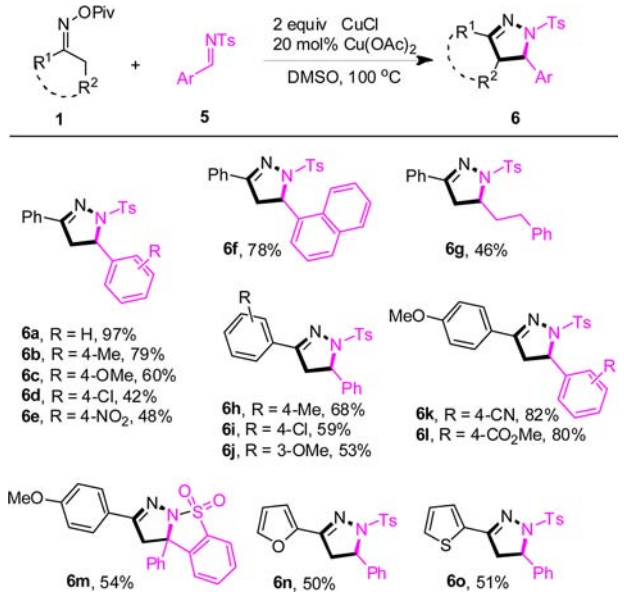
Scheme 3. Synthesis of *N*-Sulfonylpyrazolines[a]

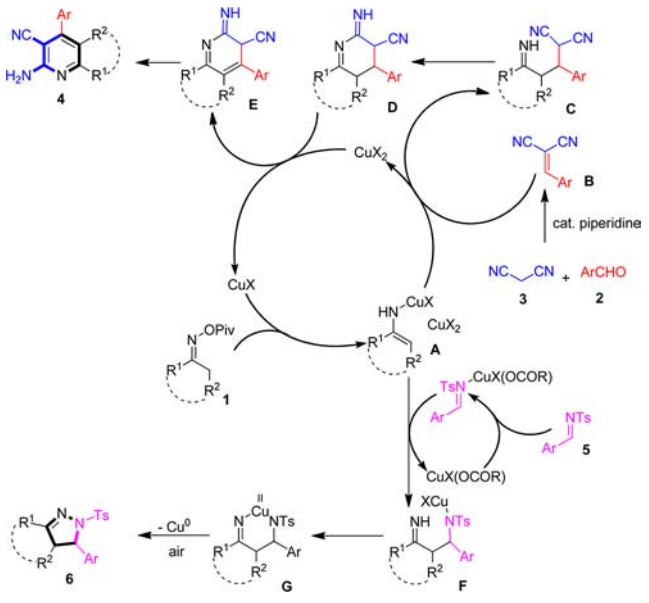


[a]Reaction conditions: **1** (0.2 mmol), **5** (0.4 mmol), CuCl (0.4 mmol), $Cu(OAc)_2$ (20 mol %), DMSO (2 mL), under air for 8 h.

pyrazoline product **6m** in 54% yield. The scope was also extended to heterocyclic oxime esters, thus providing access to functionalized pyrazolines (**6n** and **6o**). *N*-Sulfonylpyrazolines represent a core structure in many biologically active compounds, with progesterone receptor antagonist,[17] antimicrobial agent,[18] and monoamine oxidase inhibitory activities.[19] Therefore, this method provides a simple and expedient approach for the straightforward assembly of these compounds.

Based on these results and literature precedents, a plausible mechanism for this cyclization toward divergent heterocycles is proposed in Scheme 4. For 2-aminonicotinonitrile synthesis, the pivaloyl oxime ester **1** is converted to a copper(II) enamide **A**, in the presence of copper(I) catalyst. Michael addition then occurs between **A** and the in situ generated 2-benzylidenemalonitrile **B** to give **C**. Then an intramolecular addition takes place to form **D**, and a further oxidation of **D** with copper(II) furnishes **E** and regenerates the copper(I). Lastly, the isomerization of **E** leads to aromatic 2-aminonicotinonitrile **4**.

Scheme 4. Proposed Mechanism



With respect to *N*-sulfonylpyrazoline formation, copper(II) enamide **A** undergoes Michael addition to the activated *N*-sulfonylimine **5** to form **F**, which is converted to the copper–chelate complex **G**. The following oxidative cyclization of **G** under air provides the *N*-sulfonyl pyrazoline **6**.[15,16] This cyclization excludes the regeneration of copper(I) and therefore demands the stoichiometric use of CuCl.

In conclusion, we have documented the divergent syntheses of 2-amino nicotinonitriles and pyrazolines via the copper-catalyzed cyclization of oxime esters. Our results disclose that pivaloyl oxime esters convert to copper enamides in the presence of copper(I), which can undergo either Michael addition to 2-benzylidenemalonitrile or oxidative cyclization with *N*-sulfonylimines. Further studies and extensions of this protocol are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, and spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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