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COMMUNICATION

A Simple, Tandem Approach to the Construction of Pyridine Derivatives under Metal-free Conditions: A One-step Synthesis of the Monoterpene Natural Product, (–)-Actinidine†

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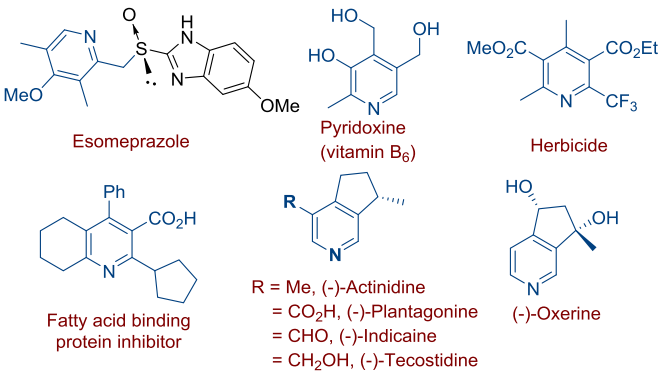
A simple and modular one-step synthesis of diversely substituted pyridines from readily available α, β–unsaturated carbonyl compounds and propargylic amines has been developed. The present protocol has a broad substrate scope and allows access to multi-substituted pyridines with select control of the substitution pattern under mild and metal-free conditions. The reaction involves imine formation followed by concomitant cyclization through an allenyl intermediate to afford pyridines in excellent yields, with water as the sole by-product. This mild strategy is also suitable for functionalization of natural products or other advanced intermediates having α, β–unsaturated carbonyl functionality. The utility of the present protocol was showcased with the synthesis of the monoterpene alkaloid, (–)-actinidine, an ant-associated iridoid.

Pyridines are privileged scaffolds found in numerous natural products and biologically active molecules (Figure 1).[1] Pyridines are also ubiquitous in pharmaceuticals, agrochemicals and in advanced organic materials such as OLEDs and fluorescent sensors.[2] Pyridine and its derivatives have significant applications as organic bases, ligands, catalysts and directing groups in C-H activation reactions.[3]

Figure 1: Representative pyridine-containing natural products and bioactive molecules.



Traditional methods of pyridine synthesis (Chichibabin and Hantzsch reactions) involve condensation of carbonyl compounds and amines.[4] More recently, transition metal-catalyzed cross couplings, ring-closing metathesis, cycloadditions, radical reactions and microwave-assisted reactions have been developed for the synthesis of pyridines.[5] Despite this progress, there is still opportunity to develop an efficient method for the construction of variously and diversely substituted pyridines under simple and metal-free conditions with high atom- and pot-economy and excellent functional group tolerance, which is applicable to the total synthesis of biologically important natural products.

Mild and metal-free reactions have a significant impact in organic synthesis due to their greener and environmentally benign properties, with the potential to reduce cost and waste generation.[6] The propargylic system is an excellent and common building block for the construction of aromatic and heteroaromatic compounds, along with various natural products. In particular, propargylamine is a common precursor in the formation of a number of heterocycles including pyrroles, pyridines, indoles, carbazoles and carbolines, etc.[7] Precursors derived from propargylic amine/amides and alkynes are widely used in the synthesis of pyridines.[8, 9] For example, Hua and co-workers described the silver-catalyzed [4+2] annulation reaction for the construction pyridine rings from propargylamine and electron-deficient alkynes (Scheme 1a).[8d] In 2015, Zhai and co-workers reported a metal-free cascade approach to the synthesis of substituted pyridines from α, β-unsaturated ketones and phosphazene derived from propargylazide (Scheme 1b).[8f] Recently, the Cui and Cheng groups independently reported the syntheses of pyridines using *N*-propargyl enaminones under metal-free reaction conditions (Scheme 1c).[8c, 8g] Most of the reported pyridine synthetic methods require metal catalysts or multi-step synthetic starting materials and lack diversity in the substitution pattern. There remains a need to develop a simple and metal-free synthetic route to provide access to diversely substituted pyridines, with varying substitution patterns, which are useful for the synthesis of natural products.

We have recently disclosed a unified strategy for the synthesis of β-carbolines, γ-carbolines, and fused aromatic aza heterocycles, with the goal of constructing various aza-heterocycles via a simple and efficient method from readily

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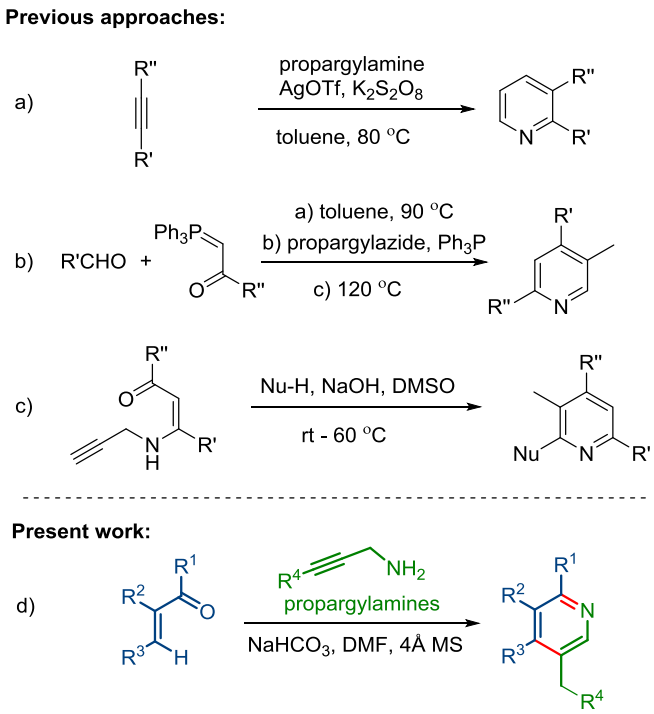
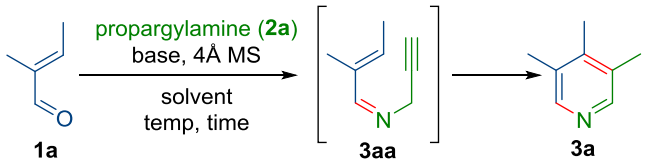


Scheme 1: Approaches to the synthesis of pyridines from propargylamine.

available starting materials.[10] In continuation of our efforts to develop efficient routes to the syntheses of heterocyclic compounds[10-11] and natural products,[12] herein, we report an atom- and pot-economical method for the synthesis of diversely-substituted pyridines under mild and metal-free reaction conditions with application to a one-step synthesis of the natural product, (–)-actinidine. The present protocol has a broad substrate scope and is applicable to late stage derivatizations of natural products and key intermediates.

Our preliminary investigation into the preparation of variously substituted pyridines began with tiglic aldehyde (**1a**) and propargylamine (**2a**) (Table 1). Initially, the reaction of **1a** and **2a** in DMF at room temperature was conducted. After 36 hours, the imine intermediate **3aa** was isolated in 85% yield (entry 1). Increasing the reaction temperature to 80 °C for 24 h provided the imine **3aa** in 74% yield, with no pyridine detected (entry 2). Interestingly, following addition of the mild base, K_2CO_3, and heating to 80 °C the pyridine derivative, 3,4,5-collidine (**3a**) was isolated in 67% yield (entry 3). Examination of additional inorganic bases including $CsCO_3$, $NaHCO_3$, NaOAc and K_2HPO_4 at 80 °C (entries 4-7) revealed that $NaHCO_3$ was the most efficient base for this transformation (**3a**, 83%, entry 4). The influence of solvent selection on the reaction yield was also investigated. Moderate yields of the desired pyridine were obtained with toluene and DCE (entries 8 and 9), while THF and DMSO resulted in a significant reduction in product yield (entries 10 and 11). Treatment of **1a** with DBU in chlorobenzene[13] gave only 47% of **3a**. Based on this investigation, pyridine construction occurs optimally using propargylamine and tiglic aldehyde in DMF in the presence of a simple base ($NaHCO_3$) at 80 °C over 15 h. We have previously demonstrated that cyclization reactions of this type occur via *in situ*-generated allene intermediates (see Supporting Information).[10]

Table 1. Optimization of reaction conditions for the synthesis of 3,4,5-collidine (3a).[a]

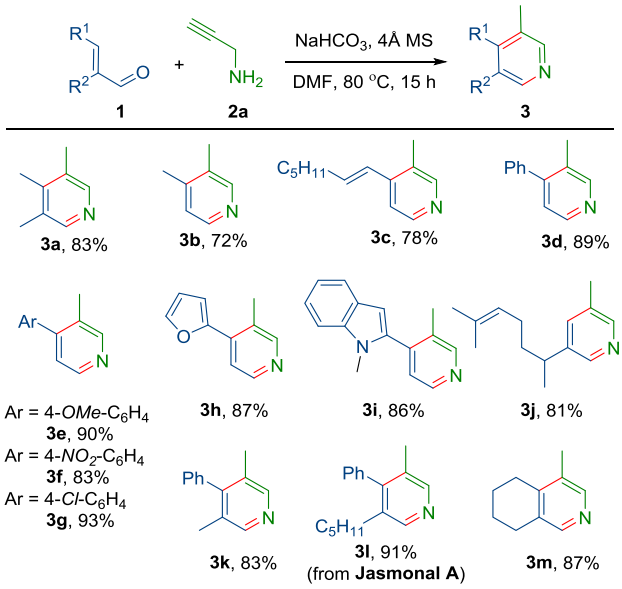


entry	base	solvent	temp (°C)	time (h)	yield (%)[b]
1[c]	-	DMF	rt	36	0
2[c]	-	DMF	80	24	0
3	K_2CO_3	DMF	80	15	67
4	**$NaHCO_3$**	**DMF**	**80**	**15**	**83**
5	NaOAc	DMF	80	24	50
6	$CsCO_3$	DMF	80	24	47
7	K_2HPO_4	DMF	80	24	25
8	$NaHCO_3$	toluene	100	24	71
9	$NaHCO_3$	DCE	80	24	63
10	$NaHCO_3$	THF	80	24	15
11	$NaHCO_3$	DMSO	100	24	23
12	DBU	C_6H_5Cl	80	24	47

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.9 mmol) and base (1.2 mmol); [b]isolated yield; [c]Imine **3aa** was isolated.

After optimizing the standard reaction conditions, the substrate scope for pyridine synthesis was then investigated. Various α, β-unsaturated aldehydes (**1**), with different substitution patterns, were tested with propargylamine (**2a**) (Scheme 2). Crotonaldehyde (**1b**), an α, β-unsaturated aldehyde with a β-methyl substitution, provided 3, 4-lutidine (**3b**) in 72% yield upon treatment with propargylamine (**2a**). Next, *trans*-decanal **1c** gave the pyridine **3c** in 78% yield. β-Aryl aldehydes (**1d** to **1g**) provided access to 4-aryl pyridines (**3d** to **3g**) in excellent yields. The electronic characteristics of substituents on the aryl ring (electron-donating or withdrawing) did not seem to influence the outcome of the reaction to any appreciable amount. β-Heteroaryl-substituted aldehydes (**1h** and **1i**) reacted with **2a** to give pyridines **3h** in 87% and **3i** in 86% yields, respectively. Moreover, aldehyde **1j**, a key intermediate derived from citronellal proceeded smoothly to afford the 3, 5-disubstituted pyridine **3j** in 81% yield. Fortunately, α, β-unsaturated aldehydes with substitutions at both the α– and β–positions (**1k**, α-methyl cinnamaldehyde and **1l**, jasmonal A–a natural product commonly used as an additive in the perfume and cosmetic industry) were also successful under the present reaction conditions and gave the appropriately tri-substituted pyridines, **3k** and **3l** in 83 and 91% yields, respectively. Extension of this strategy allowed for the efficient construction of 5,6,7,8-

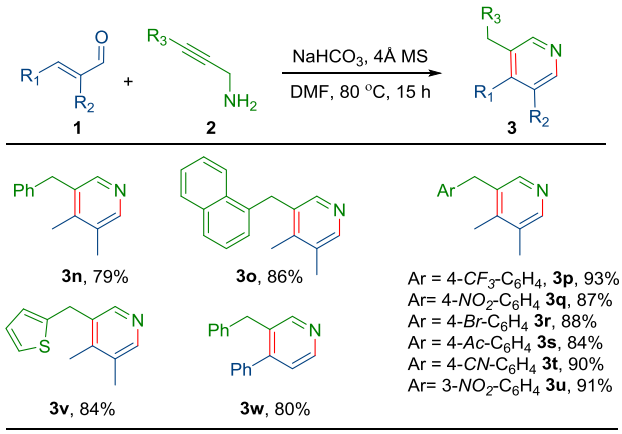
tetrahydroisoquinoline **3m** in 87% yield, starting from the commercially available 1-cyclohexenal (**1m**) and **2a**.



[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.9 mmol) and $NaHCO_3$ (1.2 mmol)

Scheme 2. Synthesis of substituted pyridines from various unsaturated aldehydes.[a]

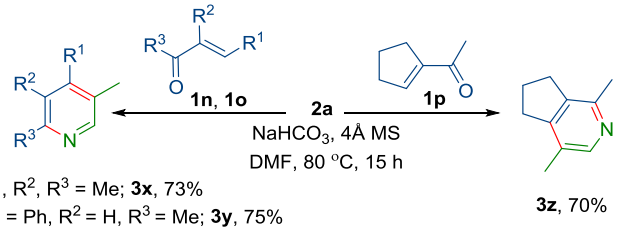
After successful utilization of α, β-unsaturated aldehydes for the synthesis of diversely substituted pyridines, we turned our attention to the effects of substitution on the propargylamine for the construction of further 3-substituted pyridines. Various 3-aryl- or 3-heteroaryl prop-2-yn-1-amines were studied with tiglic aldehyde (Scheme 3). 3-Phenylprop-2-yn-1-amine (**2b**) and 3-(naphthalen-1-yl) prop-2-yn-1-amine (**2c**) were successfully utilized for the synthesis of tri-substituted pyridines, **3n** and **3o**, in 79% and 86% yields, respectively. Furthermore, amines with different substitutions on the aryl ring (**2d** to **2i**) also afforded



Scheme 3. Substituted propargylamines (**2**) for the construction of pyridines (**3**).

the corresponding pyridines, **3p** to **3u**, in excellent yields. A 2-thienyl group (**2j**) allowed for the synthesis of pyridine **3v** (84%). Interestingly, cinnamaldehyde (**1d**) underwent the present cascade reaction with **2b** to give the tri-substituted pyridine **3w** in 80% yield.

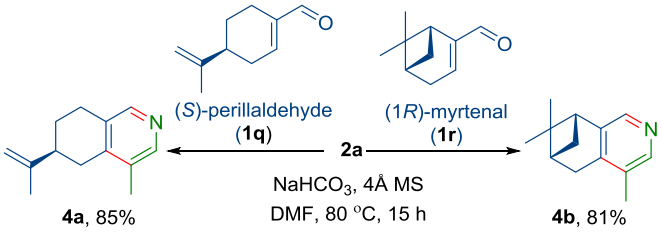
After successful application of various aldehydes and substituted propargylic amines to the construction of diversely substituted pyridines, we focused on extending this method to encompass α, β-unsaturated ketones as a means to introduce substitution at the C-2 position of the pyridine ring (Scheme 4). To our delight, 2, 3, 4, 5-tetramethyl pyridine **3x** was constructed in 73% yield from 3-methyl-3-penten-2-one (**1n**) and **2a** under standard reaction conditions. Encouraged by these results, we examined the reactivity of benzylidene acetone (**1o**) to afford pyridine **3y** in 75% yield. Gratifyingly, 1-acetylcyclopentene (**1p**) gave the bicyclic product, cyclopenta[*c*]pyridine (**3z**) in 70% yield.



Scheme 4: Pyridine formation from α,β-unsaturated ketones.

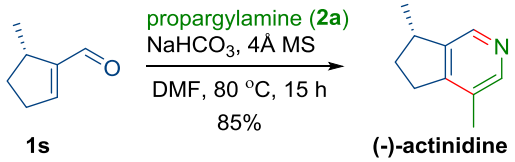
Inspired by these results, we sought to apply this new method to the construction of pyridines starting from natural product aldehydes (Scheme 5). The cosmetic, flavor and fragrance agent, (*S*)-(−)-perillaldehyde (**1q**) was condensed with **2a** followed by cyclization to provide the pyridine derivative **4a** in 85% yield. Similarly, the flavoring agent found in cardamom, (1*R*)-myrtenal (**1r**), was used to produce the fused pyridine **4b** in 81% yield.

Synthesis of products **3j**, **3l**, **4a** and **4b** demonstrate that the current mild and metal-free strategy is highly efficient for late-stage structural modifications of natural products and advanced intermediates.



Scheme 5: Construction of pyridine rings on natural products.

To further elaborate the synthetic utility of the present method, we prepared the cyclopenta[*c*]pyridine alkaloid, (−)-actinidine (**5**)[14] in synthetically useful yield (85%) starting from the easily accessible enal **1s**[15] and propargylamine **2a** (Scheme 6).



Scheme 6: Preparation of (−)-actinidine (**5**).

In conclusion, we have established a highly efficient method for the one-pot synthesis of variously and diversely substituted pyridines using commercially available α, β-unsaturated carbonyl compounds and propargylamines. This method is

simple and efficient and proceeds under mild and metal-free conditions via the condensation of the starting aldehyde and amine, followed by cyclization and concomitant aromatization. This method is environmentally benign, owing to the fact that it does not require harmful metals or reagents, and water is the sole by-product. The current strategy is excellent to incorporate pyridine rings onto a wide variety of α, β-unsubstituted aldehydes, including natural products and key intermediates. The utility and efficiency of this method was demonstrated through the synthesis of the iridoid natural product, (–)-actinidine (**5**).

Conflicts of interest

There are no conflicts to declare.

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(–)-Actinidine, along with various diversely substituted pyridines were synthesized from simple starting materials, including natural products, using a mild and metal-free method.