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Facile Synthesis of Pyridines from Propargyl Amines: Concise Total Synthesis of Suaveoline Alkaloids

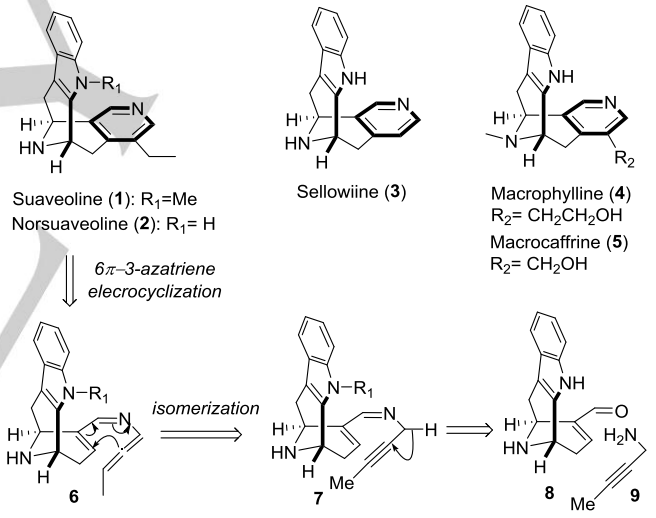
Zhiwen Zhao[+], Hongbo Wei[+], Ke Xiao, Bin Cheng, Hongbin Zhai and Yun Li*

Dedication ((optional))

Abstract: A general and efficient protocol was developed for the synthesis of polysubstituted pyridines from propargyl amines and unsaturated carbonyl compounds through a tandem condensation/ alkyne isomerization/ 6π-3-azatriene electrocyclization sequence. This process displays a wide scope of readily available substrates (30 examples, up to 95% yield) and could be easily performed at preparative scale (20 gram scale).Taken advantage of the late-stage pyridine incorporation protocol, the synthetic utility of this chemistry has been successfully applied to the collective total synthesis of suveoline, norsuveoline and macrophylline.

Pyridine is one of the privileged structural motifs present in a large number of biologically important natural products [1] and synthetic pharmaceuticals. [2] Some of the world's top selling drugs, such as Atazanavir [3] and Gleevec [4] undoubtedly render their medicinal importance of pyridine derivatives. In fact, pyridines also play pivotal role in coordination chemistry, catalysis and materials science. [5] Consequently, highly efficient methods for construction of pyridines will remain in high demand. Beside the conventional Hantzsch, [6] Chichibabin, [7] Bohlmann–Rahtz, [8] Bonnemann [9] and Diels-Alder [10] methods for the synthesis of pyridine derivatives, different approaches have been developed in recent years. [11] Given its important role recognized by multiple disciplines, the alternate methods to access highly functionalized pyridine derivatives under mild reaction conditions especially from steadily available materials are always highly desirable.

Suaveoline (**1**)[12] and its structurally related other four alkaloids (scheme 1) including norsuaveoline (**2**), [13] sellowiine (**3**),[14] macrophylline (**4**) [15] and macrocaffrine (**5**) [15b] were isolated from various botanical genus of *Rauwolfia*. The suaveoline series of indole alkaloids highlight such a case that their structures possess an interesting bicylic pyridine skeleton. Their synthetic access has been investigated by pioneers including Cook, [16] Bailey,[17] Ohba[18] and co-workers. In most case, pyridine motif incorporation requires multiple synthetic manipulations in their synthesis. Thus, more efficient strategy especially with new synthetic methodology involved divergent total synthesis is highly desirable. Based on our experience in the synthesis of polysubstituted pyridines from propargyl azides,[19] we sought to new synthetic possibility for quick access to suaveoline type alkaloids that enabled by new synthetic methodology. Herein, we report a facile synthesis of polysubstituted pyridines from propargyl amines and unsaturated carbonyl compounds through a tandem condensation/ alkyne isomerization/ 6π-3-azatriene electrocyclization sequence. The concise total synthesis of suaveoline, norsuaveoline and macrophylline were also achieved by using the present protocol.



Scheme 1. Structures of Suaveoline-type alkaloids and the designed synthetic strategy.

From a retrosynthetic perspective, for the suaveoline-type alkaloids, we envisioned an atom-economical approach (scheme 1) to access the substituted pyridine systems. The designed tandem process is expected to proceed through a condensation of aldehyde **8** with propargyl amine **9**, and the resulting imine would then isomerize to allenic imine **6**.[20] A thermal 6π-3-azatriene electrocyclization and a sequential aromatization would produce the suaveoline (**1**) as one of the represent *Rauwolfia* pyridine alkaloids.

Given that the success of above mentioned synthetic strategy of suaveoline-type alkaloids was highly depended on the proposed synthesis of pyridines from steadily available propargyl amines and unsaturated carbonyl compounds. As indicated in our previous work,[19] this proof of concept has been preliminarily evaluated by a single example. However, a more

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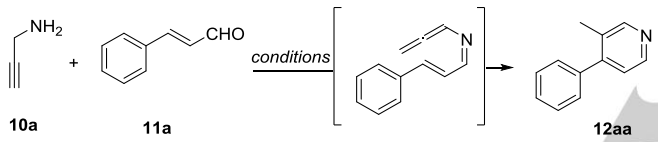
comprehensive profile for this reaction would insure its application in more complex structural context. Thus, propargyl amine **10a** and cinnamaldehyde **11a** were selected as the substrates to screen the reaction conditions for the desired transformation. As summarized in Table 1, treatment of **10a** and **11a** with DBU (1.2 equiv) in toluene at 50 ^{o}C only gave trace amount of desired pyridine **12aa** (Table 1, entry 1). Gratifyingly, it was found that the yield of pyridine could be improved to 51% by increasing reaction temperature to 70 ^{o}C (Table 1, entry 2). Further elevation of temperature did not give much improved result (entry 3). A survey of solvents including EtOH, THF, DMF and PhCl demonstrated that PhCl is the best choice (entry 7). Considering that one molecule of water is the only byproduct in this reaction, water scavengers might benefit to the reaction conversion. In this regard, molecular sieve (entry 9) and $MgSO_4$ (entry 10) was then added as the additives and the yield of the pyridine could be further improved to 82% (entry 10) when $MgSO_4$ was employed as dehydrating agent. A significant inhibition of this reaction was observed when Lewis acid such as $ZnCl_2$ was added (entry 11). Other base such as K_2CO_3, NaOH, Et_3N gave inferior results compared to DBU.

Table 1. Sceening of reaction conditions.[a]

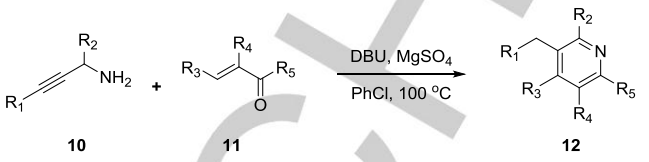


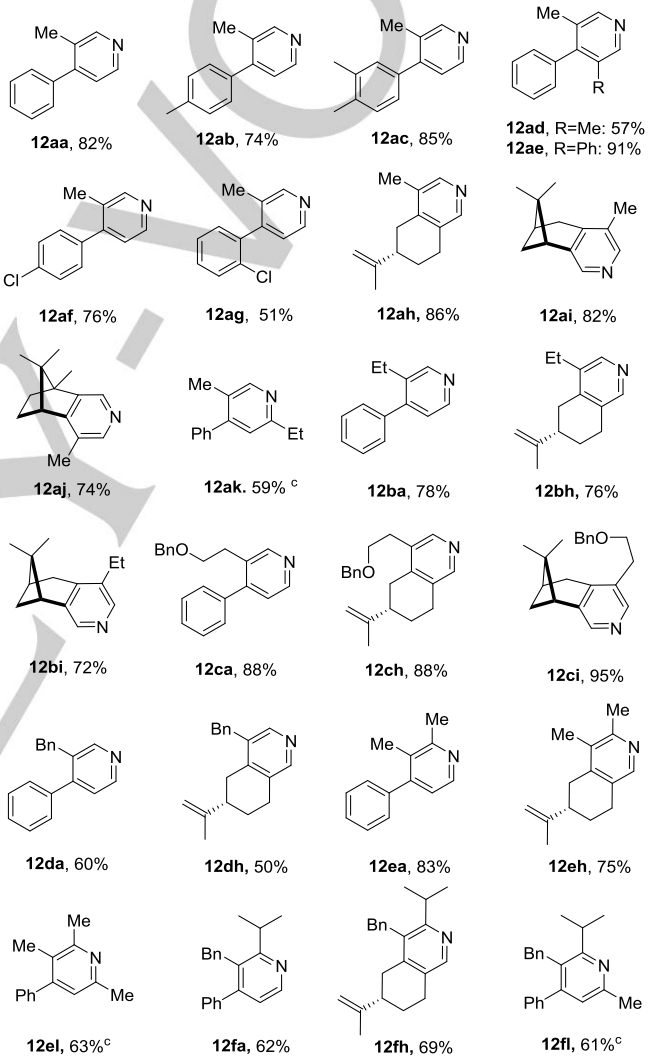
Entry	solvent	additive	*T* (^{o}C)	Yield [b] (%)
1	toluene	none	50	Trace
2	toluene	none	70	51
3	toluene	none	100	55
4	EtOH	none	100	50
5	THF	none	100	52
6	DMF	none	100	Trace
7	PhCl	none	100	70
8	PhCl	none	120	68
9[c]	PhCl	4Å MS	100	75
10[c]	PhCl	Mg_2SO_4	100	82
11[d]	PhCl	$ZnCl_2$	100	trace

[a] Reaction conditions: The reaction mixture of **11a** (0.8 mmol), **10a** (1.2 equiv), and **DBU** (1.2 equiv) in 4 mL of solvent were stirred under indicating temperature in sealed tube. [b] Isolated yield based on **11a**. [c] 100% weight of additive based on **11a** was added. [d] 0.1 equiv of ZnCl was added.

With optimized conditions in hand, we next sought to determine the scope of this reaction. As illustrated in table 2, with propargyl amine **10a,** an array of cinnamyl aldehyde derivatives (**11a** -**11g**) bearing various substituents were firstly evaluated in the cyclization reaciton. Both electronic rich and deficient aldehydes performed well and delivered the expected pyridine product (**12aa** – **12ag**) in 51- 91% yields. Moreover, the cyclic aliphatic aldehydes (**11h**, **11i**) and even sterically encumbered substrate (**11j**) also proceeded smoothly to give pyridine products **12ah**-**12aj** in good yield. Furthermore, the unsaturated ketone **11k** was also proved to be the suitable substrate. The desired pyridine (**12ak**) could be obtained in moderate yield under much elavated reaction temperature (150 ^{o}C). Next, we continued to investigate the substrate generality with a range of substituted propargyl amines (**10b**-**10f**).

Table 2. Reaction scope.[a][b]



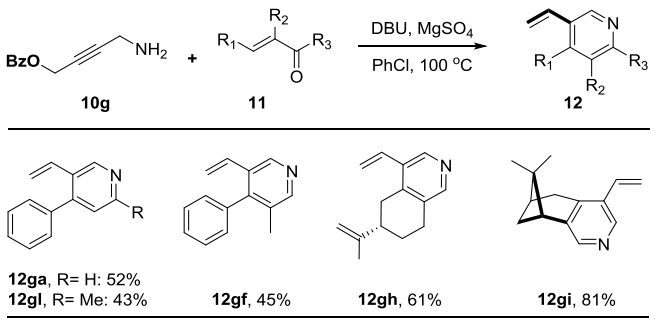


[a] Conditions: 1.2 equiv of **10**, 1.0 equiv of **11**, 1.2 equiv of DBU, 100% weight of $MgSO_4$ based on **11**, 0.2 M in PhCl. [b] Isolated yield. [c] Reaction was performed under 150 ^{o}C.

Generaly, the substitution patterns and electroic characteristics of propargyl amine showed only a negligible influence on the cyclization. Both aromatic, aliphatic aldehydes and ketones are suitable substrates and delivered the desired products (**12ba**-**12fl**) in good yields. Interestingly, when 4-aminobut-2-yn-1-yl benzoate (**10g**) was employed as the substrate, 3-vinylpyridines were isolated as the the main product instead of expected ethoxybenzoate pyridines with moderate to good yields (Table 2,

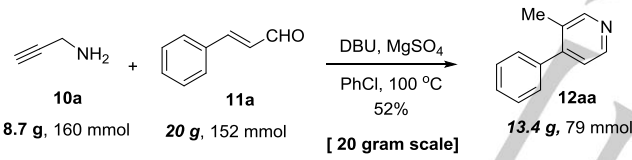
12ga-**12gi**). It is believed that the vinyl groups might come from the *in situ* elimination of initially generated benzoate in the presence of DBU.

Table 2. Reaction scope with 4-aminobut-2-yn-1-yl benzoate as substrate.[a][b]



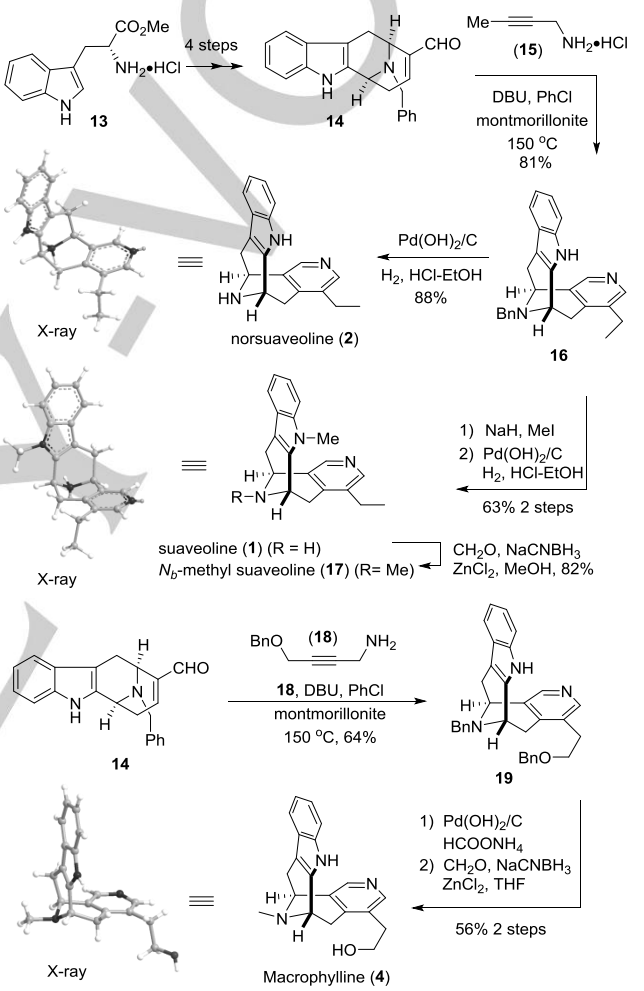
[a] Conditions: 1.2 equiv of **10g**, 1.0 equiv of **11**, 1.2 equiv of DBU, 100% weight of $MgSO_4$ based on **11**, 0.2 M in PhCl. [b] Isolated yield.

Thoes results undoubtedly great expand the structural diversity of resulted pyridine compounds and offer an extra synthetic manipulation site as well. To further test the practicality of our protocol, a 20-gram-scale (152 mmol) preparation of **12aa** was then executed (Schme 2). The reaction proceeded smoothly to give desired product in 52% yield (13.4 g), indicating the good scalability of present method.



Scheme 2. Preparative scale synthesis of **12aa.**

After establishment of the synthetic methodology, we then turned our attention to the total synthesis of pyridine-containing alkaloids suaveoline, norsuaveoline, and macrophylline (Scheme 3). To this end, the requisite tricyclic aldehyde **14** was prepared from methyl tryptophanate **13** according to the literature procedure.[16c] Under the slightly modified standard condition,[21] aldehyde **14** reacted smoothly with amine **15** and delivered the desired tricyclic pyridine **16** in 81% yield. In contrast, limited by the synthetic methodolgy in 1980s, Cook and coauthor took nine steps to incorporate the pyridine motiff from aldehyde **14**.[16a] Cleavage of benzyl protection of **16** by Pd-catalyzed hydrogenation gave norsuaveoline (**2**). Its structure was unambiguously confirmed by X-ray crystallographic analysis.[22] Total synthesis of suaveoline (**1**) was then achieved from pyridine **16** through methylation of indole N1 nitrogen and following benzyl deprotection in 63% combined yield. Its structure was also confirmed by X-ray crystallographic analysis.[22] Reductive amination of suaveoline with $NaCNBH_3$ in formalin led to a pseudonatural product N_b-methyl sueveoline (**17**) in 82% yield. The spectral data were identical to the literature that previously reported by Cook.[16c] To demonstrate the flexibility of our late-stage pyridine incorporation protocol, another natural product named marcrophylline was also synthesized from aldehyde **14** by quick switching the propargyl amine counterpart to **18**. The desired pyridine **19** was steadily obtained in 64% yield and was further converted to marcrophylline (**4**) through $Pd(OH)_2$ catalyzed N-benzyl deprotection and subsequential reductive amination. The full structure proof of marcrophylline was obtained by X-ray crystallographic analysis.[22] It should be noted, the ^1H NMR spectrum of our synthetic samples do not perfectly matched with the reported data by the isolation team for marcrophylline.[15a] While such kind of cases have been noted in many alkaloid syntheses. [23]



Scheme 3. Total synthesis of suaveoline, norsuaveoline, and macrophylline.

In summary, we have described a convergent and atom-economical method for the synthesis multisubstituted pyridines from steadily available propargyl amines and α,β-unsaturated carbonyl compounds. Incorporation of different substituents at various positions of pyridine moiety could be easily accessed by the present method. The practicality of this process is showcased by the collective total synthesis of three pyridine-containing natural products suaveoline, norsuaveoline, and macrophylline. With a scalable route established to this family of alkaloids, current efforts are underway to further explore the biological activities of the suaveoline-type alkaloids and their synthetic derivatives.

Acknowledgements

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Keywords: pyridine alkaloid • 6π-electrocyclization • heterocycles • total synthesis

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[21] Using montmorillonite-K10 as dehydrator instead of $MgSO_4$.

[22] CCDC 1872981, CCDC 1872982 and CCDC 1877473 contain the supplementary crystallographic data for norsuaveoline, suaveoline and marcrophylline respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

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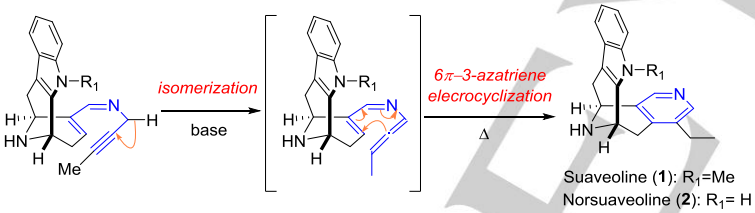

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