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Library-directed Solution- and Solid-phase Synthesis of 2,4-Disubstituted Pyridines: One-pot Approach through 6π-Azaelectrocyclization

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Abstract: An efficient one-pot synthetic procedure for the synthesis of 2,4-disubstituted pyridines has been successfully established. The method proceeds through a 6π-azaelectrocyclization-aromatization sequence. Using this method, a wide variety of pyridine structures substituted at the 2-position have been rapidly constructed from vinyl stannanes, vinyl iodide, sulfonamide, and a palladium catalyst. The method was further applied to the solid-phase synthesis wherein the use of a "traceless" sulfonamide linker enabled the rapid preparation of a small library of pyridines with high purity, without any chromatographic separation.

Keywords: cross-coupling · electrocyclic reactions · nitrogen heterocycles · solid-phase synthesis · sulfonamides

Introduction

Substituted pyridines play a significant role in various fields such as biology, pharmacology, and medicinal chemistry. There are many bioactive pyridines such as the prosthetic pyridine nucleotide (NADP)[1] and nicotine.[2] A pyridine nucleus can also be found in many pharmaceuticals[3,4] as well as agrochemicals.[5] Pyridine derivatives are applied to synthetic organic chemistry as well. For example, dimethylaminopyridine (DMAP) is a powerful nucleophilic base, often used for carboxylic acid activation and acylation. Considering the importance of pyridines, especially the substituted pyridines, a large number of synthetic methods have been developed, and they are still one of the most intriguing topics in the synthetic community.[6] Traditionally, 2-arylpyridines have been synthesized by coupling 2-metallopyridine with an aryl halide or alkylation with the pyridine *N*-oxides.[7] Improved methods for the substitution at the 2-position of the pyridine ring have recently been reported, which uses transition metal-catalyzed variants, such as C–H bond activation of the C1-hydrogen of pyridines through the coordination of the nitrogen to ruthenium,[8a–d] rhodium,[8e] or a nickel/Lewis acid complex.[8f] Alternatively, the ring-closing metathesis (RCM)-aromatization sequence,[9a] the three-component coupling between alkoxyallene, nitrile, and carboxylic acid,[9b] the condensation of *N*-vinyl and *N*-aryl amides to π-nucleophiles,[9c] and the ring expansion of isoxasoles[9d] have also been used to construct 2-substituted pyridines. Although these methods have proved to be quite useful for the preparation of these important heterocycles, they still need to be further improved in terms of efficiency, generality, and simplicity of the procedure.

The heteroatom-substituted electrocyclic reaction is widely utilized in organic synthesis, such as pentannulation,[10a] 2*H*-pyran synthesis,[10b] and dihydropyridine synthesis.[10c] Especially, 6π-azaelectrocyclization of 1-azatrienes is quite an attractive candidate for the construction of substituted pyridine skeletons, because the dihydropyridine, as a cyclized product, can easily be transformed to the corresponding pyridine, either by oxidative or eliminative aromatization. Nevertheless, the application of electrocyclization protocol to the substituted pyridine synthesis has been limited because of the difficulty in handling the unstable precursor, 1-azatrienes, under the vigorous reaction conditions required for electrocyclization. The tedious synthesis of the

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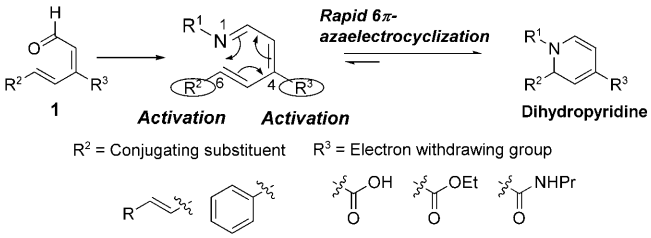
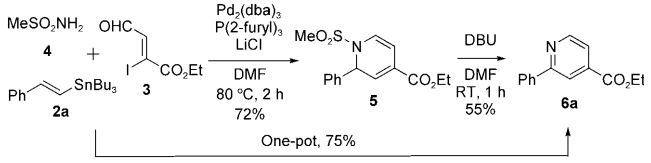
variously substituted 1-azatrienes, for diversification of the pyridine substituents, also limits the general application. Recently, the application of metal-catalyzed protocols and/or the in situ generation of 1-azatrienes has overcome the instability problem of the azatriene precursor; thus, the electrocyclization strategy in the substituted pyridine synthesis has now been refocused. For instance, Trost and co-workers prepared the 1-azatriene from diynols using a ruthenium catalyst.[11a] Rhodium catalysts were also applied to synthesize the 1-azatrienes, either from α,β-unsaturated benzyl imines and alkynes[11b] or from α,β-unsaturated ketoximes and alkynes.[11c] Liebeskind and co-workers have reported the Cu-catalyzed cross coupling of alkenyl boronic acids with oximes to yield the 3-azatrienes.[11d] Now, useful azaelectrocyclization has been developed for the synthesis of natural products. Weinreb and co-workers achieved the total synthesis of Ageladine A and its analogues using 6π-azaelectrocyclization.[12]

We have recently achieved a significant acceleration of the 6π-azaelectrocyclization by the substituent effects because of the presence of a pair of C4-electron withdrawing and C6-conjugating groups in azatriene systems (Scheme 1). The reaction quantitatively produces the corresponding 1,2-dihydropyridines in 5 min at room temperature.[13–16] Based on these findings, we have reported two types of one-pot procedures for the synthesis of 2,4-substituted pyridines from the unsaturated aldehydes **1**.[14b] The first method involves the azaelectrocyclization of the oxime derivative (R^1=OAc) followed by dehydrative aromatization. The second method makes use of the aza-Peterson olefination of **1** with lithium bis(trimethylsilyl)amide (R^1=TMS) and the oxidative aromatization of the resulting *N*-TMS-substituted dihydropyridine. Although our azaelectrocyclization strategy can be performed under extremely mild conditions in comparison with the previously reported protocols, the generality of the methods has not been totally realized in terms of the substituent diversity at the 2-position on the pyridines; it is rather difficult to synthesize the unsaturated (*E,E*)-ester aldehyde **1** by the introduction of a variety of substituents at the 5-position (Scheme 1).

We herein report an efficient one-pot procedure for the synthesis of substituted pyridines through a 6π-azaelectrocyclization-aromatization sequence in detail.[17] The method is quite general for the substituents at the 2-position of the pyridines, and a variety of aromatic- and olefin-containing pyridines were rapidly constructed using the substituted vinyl stannanes, vinyl iodide, sulfonamides, and a palladium catalyst (see Scheme 2 and Table 1). In pursuit of the library-directed synthesis of the substituted pyridines, the re-

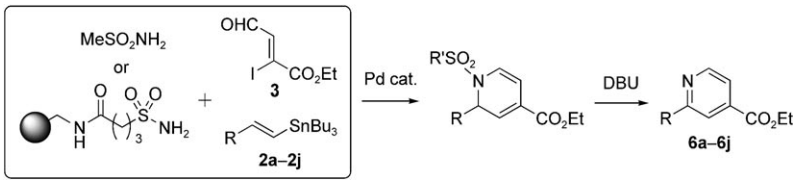


Scheme 1. Rapid 6π-azaelectrocyclization by substituent effects.



Scheme 2. One-pot pyridine synthesis by azaelectrocyclization.

Table 1. Solution- and solid-phase synthesis of substituted pyridines.



entry	R	product	solution-phase yield [%][a]	solid-phase yield [%][c]	entry	R	product	solution-phase yield [%][a]	solid-phase yield [%][c]
1	**2a**	**6a**	90	76	6	**2f**	**6f**	77	69
2	**2b**	**6b**	58[b]	40[d]	7	**2g**	**6g**	49	31
3	**2c**	**6c**	56	76	8	**2h**	**6h**	54	75
4	**2d**	**6d**	67	52[d]	9	**2i**	**6i**	13	22[d]
5	**2e**	**6e**	76	78	10	**2j**	**6j**	60[b]	31

[a] $Pd(PhCN)_2Cl_2$ (10 mol%), LiCl, DMF, 50–70°C, 1–4 h then DBU (1.0 eq), RT, 1 h. [b] $Pd_2(dba)_3$ (20 mol%), P(2-furyl)$_3$, LiCl, DMF, 80°C, 1–4 h then DBU (1.0 eq), RT, 1 h. [c] $Pd(PhCN)_2Cl_2$ (20 mol%), LiCl, DMF, 80°C 2 h, then DBU (1.0 eq), THF, RT, 1 h. [d] $Pd(PhCN)_2Cl_2$ (20 mol%), LiCl, DMF, 60°C 5 h, then DBU (1.0 eq), THF, RT, 1 h.

action was also performed on solid-supports in which the use of a "traceless" sulfonamide linker enabled the rapid preparation of the small library of pyridines with high purity.

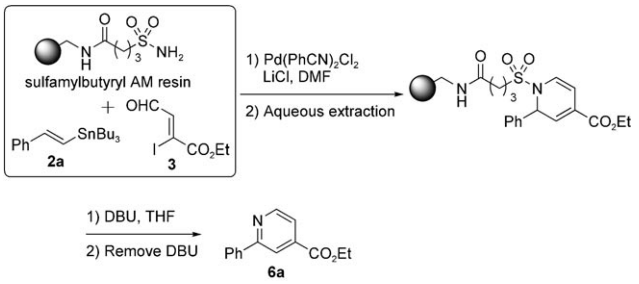
Results and Discussion

We have already achieved one-pot chiral piperidine synthesis[18] using aryl substituted vinyl stannanes such as **2a**, vinyl iodide **3** (Scheme 2), chiral substituted *cis*-1,2-aminoindanols[19] and a palladium catalyst, and the same method was directly applied to the current pyridine synthesis. The application of an amine with an appropriate leaving group such as methanesulfonamide ($MeSO_2NH_2$) **4** might achieve the efficient elimination of $H-SO_2Me$ from the 1,2-dihydropyridines such as **5** in the base treatments (Scheme 2). We initially examined amides suitable for the one-pot dihydropyridine formation; a DMF solution of styryl stannane **2a**, vinyl iodide **3**, and amides were heated to 80 °C in the presence of a $Pd_2(dba)_3/P(2\text{-furyl})_3$ catalyst, according to the already established protocol for piperidine synthesis (Scheme 2).[18] Although acetamide and methylcarbamide did not provide any detectable dihydropyridine for 12 h, methanesulfonamide **4** gave the corresponding *N*-sulfonyl dihydropyridine in 72% within 2 h. As we expected, when the dihydropyridine **5** was subsequently treated with DBU in DMF at room temperature, the desired pyridine **6a** was obtained in 55% yield (Scheme 2).

Having proved the concept of the pyridine synthesis through a multiple sequence of reactions, namely, the Stille coupling–Schiff base formation–azaelectrocyclization–elimination pathway (vide infra), the whole procedure was optimized to be realized in the same flask (one-pot procedure). After the dihydropyridine formation was detected by TLC, DBU was directly added to the same flask. Gratifyingly, by this simplified procedure, the pyridine **6a** was obtained in 75% yield.

The most prominent feature of the one-pot procedure is that differently substituted pyridines at the C2-position can easily be accessed by various vinyl stannanes (Table 1). The vinyl stannanes **2a–2j** with various aromatics or olefins, which can be easily prepared by the hydrostannylation of the corresponding acetylenes, were applied to the current one-pot synthesis. Most of the entries in Table 1 were examined using $Pd(PhCN)_2Cl_2$ as the palladium catalyst, which was found to show a reactivity superior to that of $Pd_2(dba)_3/P(2\text{-furyl})_3$, previously utilized as shown in Scheme 2. Under the optimized conditions, the simple styryl stannane **2a** provided the C2-phenyl substituted pyridine **6a** in 90% yield (entry 1). The pyridine-substituted stannanes **2b** and **2c** also gave the corresponding pyridines **6b** and **6c** in good yields, independent of their substitution positions (58% and 56%, entries 2 and 3). The quinoline- and the thiophene-substituted stannanes **2d** and **2e** similarly produced **6d** and **6e** in 67% and 76% yields, respectively (entries 4 and 5). A slight difference in reactivity was observed for the indolyl stannyl derivatives **2f** and **2g**, because of the stannyl substitution at the 2- and 3-positions of the indole. Although the 2-(3-indolyl)pyridine **6f** was obtained in 77% (entry 6), the 2-(2-indolyl)pyridine **6g** was produced in moderate yield (49%, entry 7). Similarly, 2-(2-naphthyl)pyridine (**6h**) was produced in 54% (entry 8), but the furyl derivative **6i** was obtained in only 13% yield by the current one-pot synthesis (entry 9). Not only the aromatic-substituted pyridines, but also the alkenyl substituted congener **6j** could also be prepared in 60% yield by applying the stannane **2j** (entry 10). An efficient and general one-pot protocol for the C2-substituted pyridine derivatives was thus established.

The method was further applied to the library-directed synthesis of the substituted pyridines on solid-supports. The application of the solid-supported technology will significantly simplify the purification procedures and will provide the desired products after cleavage from the resin.[20] We envisioned that the pyridines could efficiently be prepared on the solid-supports by the application of the sulfonamide linker as the traceless linker (Scheme 3). The multi-component synthesis of dihydropyridine on the solid-supports followed by DBU treatment would provide the desired pyridines with the concomitant release from the solid-supports. The product could then be separated from the DBU, simply by an extraction operation.



Scheme 3. Substituted pyridine synthesis on solid-supports.

Thus, following the procedure established for the solution-phase reaction, a DMF solution of styryl stannane **2a**, vinyl iodide **3**, $Pd(PhCN)_2Cl_2$, and LiCl was shaken with the sulfamylbutyryl AM resin (Novabiochem) at 80 °C for 2 h. After the excess reagents were removed by washing sequentially with DMF, diethyl ether, and THF, the resulting dihydropyridine-bound resin was treated with DBU in THF at room temperature for 1 h. After the resulting solution was washed with a saturated ammonium chloride solution, the product was extracted to an ethyl acetate phase. By such a simple operation, the desired pyridine **6a** was obtained in 76% yield with high purity as judged from the ^1H NMR spectrum (Figure 1).

Based on the solid-phase procedure established above, a variety of the 2,4-disubstituted pyridines **6a–6j** could be efficiently and rapidly accessed as shown in Table 1. Except for a few cases, such as entries 7 and 10, the solid-supported protocol provided the corresponding pyridines in the com-

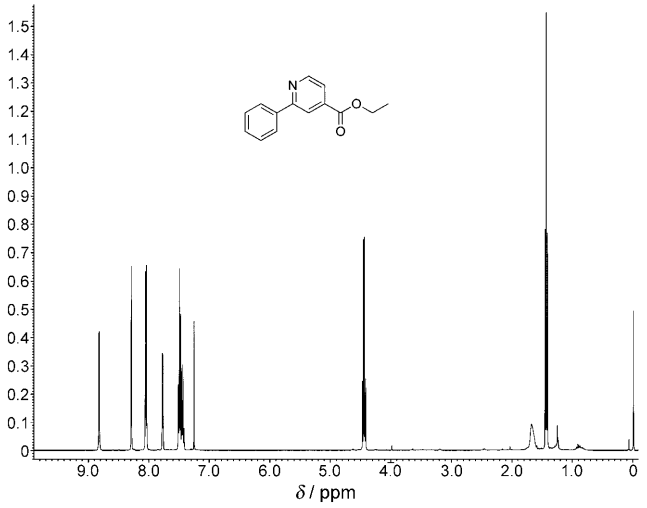
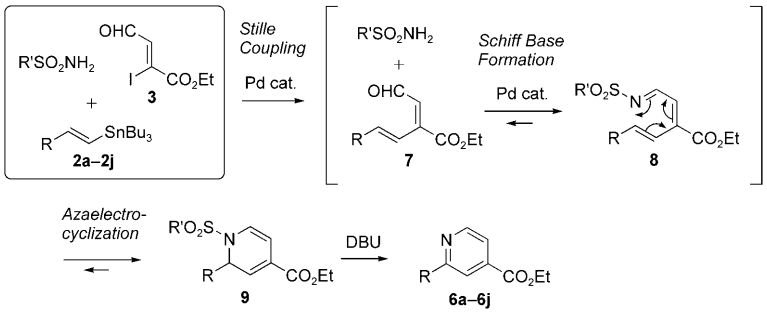


Figure 1. ^{1}H NMR spectrum of **6a** after extraction operation.

parable yields to those obtained by the solution-phase procedure. Notably these substituted pyridines were obtained in their pure forms without any chromatographic separation, thus expanding the methods to the library-directed combinatorial synthesis of the substituted pyridines.

The plausible mechanism for this one-pot pyridine synthesis is shown in Scheme 4. Initially, the dienal **7** was obtained as the Stille coupling product, which was detected in the reaction mixture. The aldehyde **7** subsequently reacts with the sulfonamide to produce the corresponding 1-azatriene **8**, which underwent smooth 6π-azaelectrocyclization to provide the dihydropyridine **9**. Because the cyclization of **8** is a very fast process, the success of the whole process depends on the Schiff base formation of **7** with a weak nucleophilic sulfonamide. Interestingly, in this reaction, the palladium catalyst might facilitate such a process, because the aldehyde **7**, which was independently prepared from **2a** and **3** by the Stille coupling, did not react with methanesulfonamide **4** without a Pd catalyst. Furthermore, we found that iodotributylstannane, a byproduct of the Stille coupling, is essential for the success of the Schiff base formation/electrocyclization process in Scheme 4, which is currently under investigation in this laboratory. Finally, the DBU treatment then promotes the elimination of sulfinic acid from the dihydropyridine **9** to provide the pyridine derivatives.



Scheme 4. Plausible mechanism of the one-pot pyridine synthesis.

Conclusions

In summary, we have established a one-pot synthesis of 2,4-disubstituted pyridines from easily available materials through the multi-step sequences of the reactions, namely, Stille coupling, Schiff base formation, azaelectrocyclization, and aromatization. Because variously substituted vinyl stannanes as one component of the reacting materials can easily be accessed from the corresponding acetylenes, the present method offers a quite general strategy for the synthesis of 2,4-disubstituted pyridines. Moreover, the protocol was applied to solid-supported synthesis by using the sulfonamide linker as a "traceless linker", which further expanded the applicability of the method, that is, to the library-directed combinatorial synthesis. To the best of our knowledge, this is the first example in which the azaelectrocyclic reaction was applied to solid-phase synthesis. Further application of the methods to the highly substituted pyridines, as well as the combinatorial synthesis/screening of the substituted pyridines with the promising biological activity, is now in progress in these laboratories.

Experimental Section

Representative procedure of *method a* (solution-phase, $Pd(PhCN)_2Cl_2$) for the synthesis of 2-phenyl-4-ethoxycarbonylpyridine (6a). Reagents of $Pd(PhCN)_2Cl_2$ (15 mg, 0.039 mmol) and LiCl (34 mg, 0.79 mmol) were added to a solution of methane sulfonamide (75 mg, 0.79 mmol), vinyl iodide **3** (100 mg, 0.39 mmol), and vinyl stannane **2a** (310 mg, 0.788 mmol) in DMF at room temperature. The mixture was then stirred at 50 °C for 20 min. After the mixture was cooled to room temperature, DBU (0.071 mL, 0.47 mmol) was added. The resulting mixture was stirred at this temperature for 1 h, quenched with H_2O, and extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel (from 9% to 17% ethyl acetate in hexane) gave the pyridine product **6a** (81 mg, 90%) as yellow crystals: m.p.: 40.5–42.0 °C; IR (KBr disk): $\tilde{\nu}$ = 3409, 2984, 1728, 1310, 1246 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (d, J = 5.1 Hz, 1H), 8.30 (s, 1H), 8.05 (m, 2H, J = 7.1 Hz), 7.78 (dd, 1H, J = 5.1, 1.4 Hz), 7.48 (m, 3H), 4.45 (q, 2H, J = 7.1 Hz), 1.44 ppm (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 158.4, 150.4, 138.6, 138.5, 129.4, 128.8, 127.0, 121.1, 119.7, 61.8, 14.2 ppm; ESI HRMS: *m/z* (%) calcd for $C_{14}H_{13}NO_2$: 228.1025 $[M+H]^+$; found: 228.1030.

Representative procedure of *method b* (solution-phase, $Pd_2(dba)_3$, P(2-furyl)$_3$) for the synthesis of 6a. To a solution of methane sulfonamide (75 mg, 0.79 mmol), vinyl iodide **3** (100 mg, 0.39 mmol), and vinyl stannane **2a** (310 mg, 0.79 mmol) in DMF were added $Pd_2(dba)_3$ (7 mg, 0.008 mmol), P(2-furyl)$_3$ (7 mg, 0.032 mmol), and LiCl (34 mg,

0.79 mmol) at room temperature. The mixture was then stirred at 80 °C for 2 h. After the mixture was cooled to room temperature, DBU (0.071 mL, 0.47 mmol) was added. The resulting mixture was stirred at this temperature for 1 h, quenched with H_2O, and extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel (from 9% to 17% ethyl acetate in hexane) gave the pyridine product **6a** (90 mg, 75%) as yellow crystals.

Representative procedure of the solid-phase synthesis of 6a. Sulfamylbutyryl AM resin (100 mg, 0.11 mmol) was washed with DMF twice. To the washed resin, a DMF solution of vinyl iodide **3** (56 mg, 0.22 mmol), vinyl stannane **2a** (173 mg, 0.44 mmol), $Pd(PhCN)_2Cl_2$ (8 mg, 0.022 mmol), and LiCl (11 mg, 0.26 mmol) was added at room temperature, and the resulting mixture was shaken at 80 °C for 2 h. The solution was then washed off, and the resin was washed sequentially with DMF, ether (each 2 mL, 5 sets), and then THF. To the obtained resin, a THF solution of DBU (0.05 mL, 0.33 mmol) was added, and the resulting mixture was shaken at room temperature for 1 h. The solution was washed off, and the resin was washed with THF and ether (each 2 mL, 5 sets). The resulting THF and ether solutions were combined, washed with sat. NH_4Cl aq. and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the pyridine product **6a** (19 mg, 76%) as yellow crystals.

Acknowledgements

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