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A novel strategy for the synthesis of 2-arylpyridines using one-pot 6π-azaelectrocyclization

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ABSTRACT

A novel and useful method for the synthesis of 2-arylpyridines with a high efficiency and generality was achieved by utilizing the one-pot 6π-azaelectrocyclization followed by a base treatment. This is the first example of applying a sulfonamide to the azaelectrocyclization for efficient substituted pyridine synthesis.

Pyridine, a representative heteroaromatic ring compound, plays a significant role in various fields. For example, there are many bioactive pyridine compounds such as the prosthetic pyridine nucleotide (NADP),[1] pyridoxine (vitamin B6), and nicotine,[2] and there are also many pharmaceuticals[3,4] and agrochemicals[5] possessing a pyridine nucleus. Thus, new construction methods for multisubstituted pyridines are still intriguing studies.[6] 2-Arylpyridine compounds are used not only as medicinal chemicals[7] but also as functional materials in supramolecular and coordination chemistries.[8] The representative method for the synthesis of these molecules is to utilize the coupling reaction of 2-metallopyridine and an aryl halide (e.g., *Negishi*,[9] *Suzuki*,[10] *Stille*,[11] and *Kharash*[12] coupling). 2-Metallopyridine, however, is usually unstable and has a low compatibility with its substituents, because it needs to be prepared from pyridyl lithium which is highly polar and basic. Although some alternative methods for the synthesis of 2-arylpyridine have recently been reported by employing pyridine-*N*-oxide[13] and the C–H bond activation of pyridine,[14] they still need to be improved regarding the aspects of yield, efficiency, and generality. In this Letter, we describe a highly efficient and novel synthetic method of 2-arylpyridines using our own one-pot 6π-azaelectrocyclization. This strategy easily enabled us to obtain 2-arylpyridines by sequential three steps in one-pot; that is, the formation of azatriene, azaelectrocyclization, and aromatization.

In a previous study, we found the significant acceleration of 6π-azaelectrocyclization by the obvious substituent effect due to the presence of a pair of C4-electron-withdrawing and C6-conjugating substituents in azatrienes to quantitatively produce the corresponding dihydropyridines in 5 min at room temperature.[15,16] Moreover, we reported two types of one-pot pyridine syntheses from aldehyde **1** (Fig. 1A).[16b] The first one was achieved by the reaction of **1** with hydroxylamine hydrochloride in pyridine to produce the corresponding oxime, which continuously reacted with acetyl chloride in the same solvent to produce the corresponding pyridine derivative. The second method utilized the *Peterson* olefination. Thus, aldehyde **1** was treated with lithium hexamethyldisilazide to produce the unstable intermediate dihydropyridine derivative, which was continuously treated with DDQ. Although these are new methods of pyridine synthesis under mild conditions utilizing 6π-azaelectrocyclization, the generality of these methods had not been totally developed because of the relative instability of the corresponding aldehydes. We then tried to achieve the novel one-pot 2-arylpyridine synthesis including a sequence that involves the coupling of three components (amine, vinylstannane, and iodoolefin) in the presence of a palladium catalyst, generation of dihydropyridine by 6π-azaelectrocyclization, followed by aromatization by a treatment of base (Fig. 1B).

We first investigated the desirable amine derivative for the one-pot reaction possessing the appropriate leaving ability (Table 1). Acetamide and methylcarbamate did not produce the desired dihydropyridine derivative under the conditions which were previously established for our asymmetric one-pot azaelectrocyclization:[17] a mixture of amine derivative, vinylstannane, and iodoolefin in DMF was stirred at 80 °C in the presence of a Pd catalyst, trifurylphosphine, and lithium chloride (Table 1, entries 1 and 2). In the

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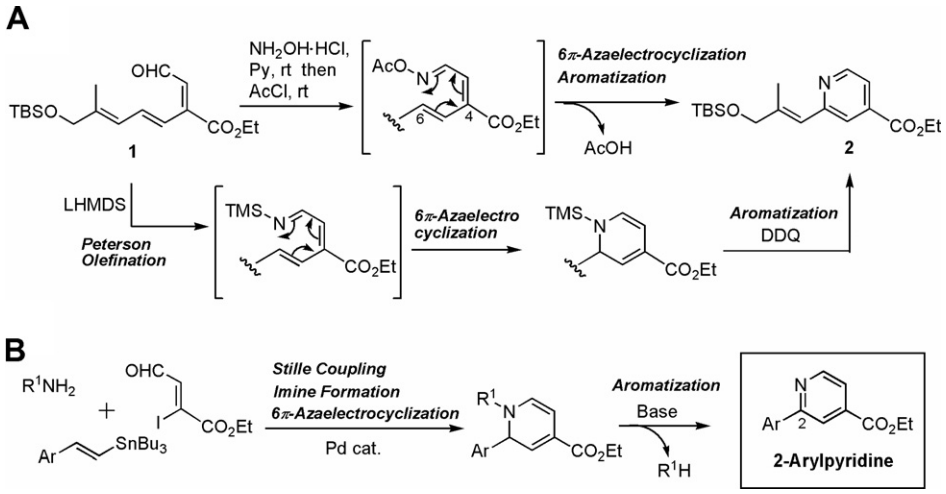
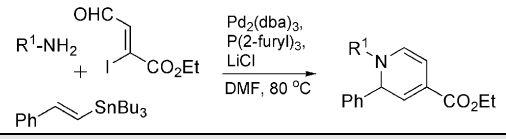


Figure 1. (A) Previous method for one-pot pyridine synthesis via 6π-azaelectrocyclization. (B) Novel one-pot pyridine synthesis from three components.

Table 1
Investigation of the desirable amine derivative

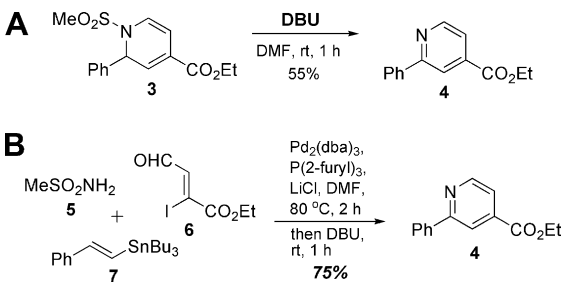


Entry	R^1-NH_2	Time (h)	Yield (%)
1	$MeCONH_2$	12	—
2	$MeOCONH_2$	12	—
3	*t*-$BuSONH_2$	1.5	18
4	$MeSO_2NH_2$	2	72

case of 2-methyl-2-propanesulfinamide, the desired product was obtained in low yield (Table 1, entry 3). When methanesulfonamide possessing a greater electron-withdrawing property was applied under the same condition, the reaction cleanly proceeded to afford the corresponding dihydropyridine in 72% yield.

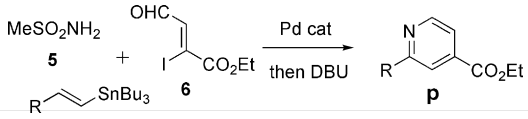
Next, the conversion of the obtained dihydropyridine derivatives into the desired pyridine compounds was examined (Scheme 1). After various trials, we obtained the required pyridine derivative **4** in 55% yield using DBU as a base in DMF.[18] The one-pot transformation from methanesulfonamide **5**, iodoolefin **6**,[16b] and vinylstannane **7**[19] into pyridine **4** was then examined. After the one-pot azaelectrocyclization of the three components, the resulting dihydropyridine was detected by TLC, and then DBU was added and the mixture was stirred at room temperature for another 1 h. As a result, the desired pyridine compound **4** was successfully obtained in 75% yield. Thus, we could rapidly construct the pyridine skeleton from the following three components: methanesulfonamide, iodoolefin, and vinylstannane, which were stable and easily synthesized.

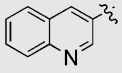
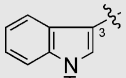
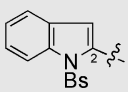
Next, we investigated the generality of our one-pot pyridine synthesis using various vinylstannanes[19] in order to make this method a practical synthetic strategy for 2-arylpyridines (Table 2). We applied two methods: Method A {$Pd_2(dba)_3$, P(2-furyl)$_3$, LiCl, DMF, 80 °C then DBU, rt} shown in Scheme 1 was normally used and method B {$Pd(PhCN)_2Cl_2$, LiCl, DMF, 50–70 °C then DBU,



Scheme 1. (A) Conversion of dihydropyridine **3** to pyridine **4**. (B) One-pot pyridine synthesis from three components (**5**, **6**, and **7**).

Table 2
One-pot pyridine synthesis using various vinyl stannanes



Entry	R	Condition	Product	Yield (%)
1		A	**4**	75
2	 **8**	A	**8p**	58
3	 **9**	B	**9p**	56
4	 **10**	B	**10p**	67
5	 **11**	B	**11p**	76
6	 **12**	B	**12p**	77
7	 **13**	B	**13p**	49

Method A: $Pd_2(dba)_3$, P(2-furyl)$_3$, LiCl, DMF, 80 °C then DBU, rt.
Method B: $Pd(PhCN)_2Cl_2$, LiCl, DMF, 50–70 °C then DBU, rt.

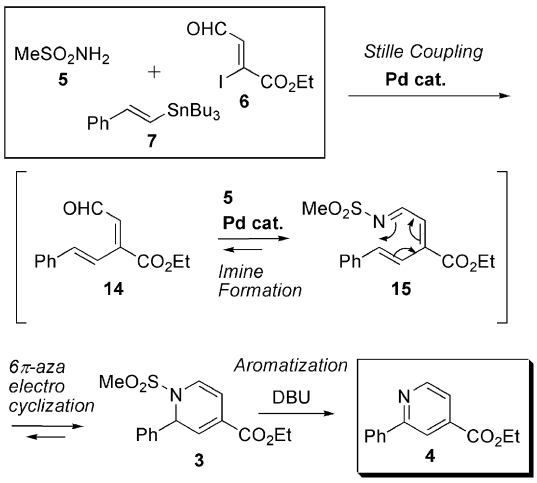


Figure 2. Plausible reaction mechanism leading to pyridine derivative **4** by one-pot azaelectrocyclization–aromatization.

rt} was often superior to method A.[20] When the pyridine derivatives of vinylstannane were used, the corresponding pyridylpyridine compounds **8p** and **9p** were obtained in good yield independent from their substitution pattern (Table 2, entries 2 and 3). The quinoline and thiophene derivatives also produced pyridine compounds **10p** and **11p** in 67% and 76% yield, respectively. Moreover, in the case of the indole derivatives, the C3-substituted indole **12p** was obtained in high yield and the C2-substituted one **13p** was formed in moderate yield.[21] Thus, we synthesized various types of 2-arylpyridines, and established a novel strategy for the simple and rapid synthesis of 2-arylpyridines with a high generality.

The plausible reaction mechanism is shown in Figure 2. When a mixture of **5**, **6**, and **7** was treated with a Pd catalyst, the *Stille* coupling of **6** and **7** firstly proceeded to form the dienal **14**.[22] Next, the resulting aldehyde reacted with methanesulfonamide **5** to give imine **15**, and then rapidly underwent 6π-azaelectrocyclization to afford the dihydropyridine **3**. A Pd catalyst would act as a Lewis acid during the imine formation, because aldehyde **14** did not react with methanesulfonamide **5** without a Pd catalyst. After the formation of **3** was ascertained by TLC, a DBU treatment facilitated the elimination of sulfinic acid to give the desired pyridine **4**. Thus, an efficient synthetic method of 2-arylpyridines was realized. By using a sulfonamide resin, a library synthesis of various substituted pyridines in the solid phase is now undertaken.

In conclusion, we established a novel synthetic method for 2-arylpyridines with a high efficiency and generality. This is based on the effective utilization of the one-pot 6π-azaelectrocyclization followed by aromatization. To the best of our knowledge, this is a first example of applying a sulfonamide to the azaeletrocyclization as a nitrogen source, whose reasonable leaving ability successfully led to the following simple conversion of the dihydropyridine into pyridine.

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18. Data for **4**: IR (KBr, cm^{-1}) 3409, 2984, 1728, 1310, 1246; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.83 (d, J = 5.1 Hz, 1H), 8.30 (s, 1H), 8.05 (m, 2H), 7.78 (dd, J = 5.1, 1.4 Hz, 1H), 7.48 (m, 3H), 4.45 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 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.
19. All vinylstannanes were prepared by the coupling between the corresponding aryl halides and *trans*-1,2-bis(tributylstannyl)-ethene.
20. Typical procedures of one-pot pyridine synthesis. *Method A*: To a solution of methanesulfonamide **5** (75 mg, 0.788 mmol), iodoolefin **6** (100 mg, 0.394 mmol) and vinylstannane (0.788 mmol) in DMF (5 mL/mmol) were added $Pd_2(dba)_3$ (7 mg, 0.008 mmol), P(2-furyl)$_3$ (7 mg, 0.032 mmol) and LiCl (34 mg, 0.788 mmol) at room temperature. After the reaction mixture was stirred at 80 °C for 2–3 h, it was cooled to room temperature, and DBU (0.071 ml, 0.472 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. The residue was purified by silica gel column chromatography to afford the desired pyridine compounds. *Method B*: To a solution of methanesulfonamide **5** (75 mg, 0.788 mmol), iodoolefin **6** (100 mg, 0.394 mmol) and vinylstannane (0.788 mmol) in DMF (5 mL/mmol) were added $Pd(PhCN)_2$ (15 mg, 0.039 mmol) and LiCl (34 mg, 0.788 mmol) at room temperature. After the reaction mixture was stirred at 50–70 °C for 2–4 h, it was cooled to room temperature, and DBU (0.071 ml, 0.472 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. The residue was purified by silica gel column chromatography to afford the desired pyridine compounds.
21. Data for **13p**: IR (KBr, cm^{-1}) 3434, 1721, 1372, 1175; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.83 (dd, J = 5.0, 0.7 Hz, 1H), 8.25 (dd, J = 1.4, 0.9 Hz, 1H), 8.20 (dd, J = 8.5, 0.7 Hz, 1H), 7.90 (dd, J = 5.0, 1.4 Hz, 1H), 7.66–7.69 (m, 2H), 7.49 (m, 1H), 7.44 (m, 1H), 7.31–7.41 (m, 3H), 7.26 (td, J = 7.6, 0.9 Hz, 1H), 6.91 (d, J = 0.7 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 152.4, 149.5, 140.2, 138.1, 137.4, 137.0, 133.6, 130.2, 128.7, 127.0, 125.7, 125.3, 124.5, 122.2, 121.5, 116.2, 115.7, 61.9, 14.2.
22. The generation of dienal **14** was confirmed by comparing with the one, which was obtained from the *Stille* coupling between vinylstannane **7** and the corresponding alcohol of **6** followed by oxidation, in a stepwise route. If the imine formation from **6** took place prior to the *Stille* coupling, the dienal **14** should not be observed.