Organocatalysis

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One-Pot Synthesis of Tri- and Tetrasubstituted Pyridines by Sequential Ring-Opening/Cyclization/Oxidation of N-Arylmethyl 3-Aziridinylpropiolate Esters**

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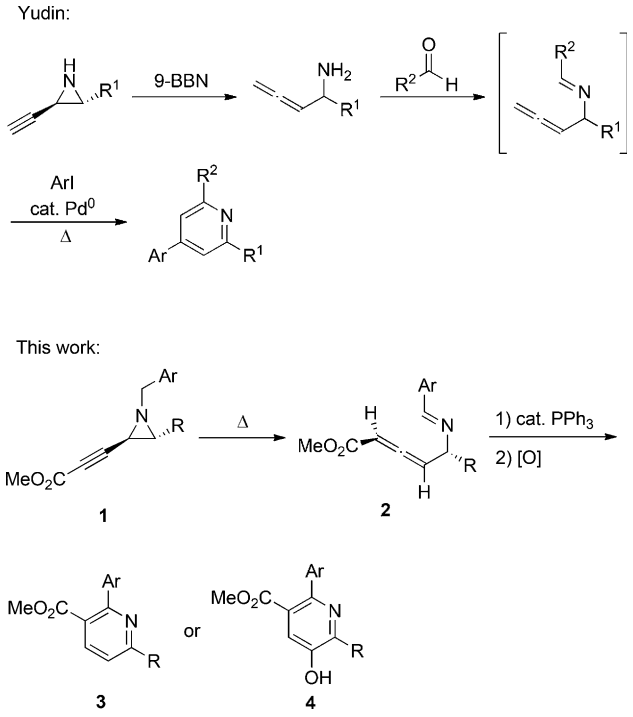
Abstract: *A novel strategy for the one-pot synthesis of substituted pyridines from N-arylmethyl 3-aziridinylpropiolate esters is described. The method employs a three-step procedure including the formation of allenyl imines, phosphine-catalyzed cyclization, and subsequent oxidation of the dihydropyridines. Depending on the reaction conditions of the final oxidation step, tri- and tetrasubstituted pyridines can be selectively produced.*

Pyridines are an important class of N-heterocyclic compounds with many uses as pharmaceutical compounds, natural products, functional materials, and building blocks of chiral ligands.[1] As a consequence, considerable effort has been devoted to the development of methods for the preparation of pyridines.[2,3] However, efficient a tailormade synthesis of substituted pyridines with high chemo- and regioselectivity remains a challenge.

Alkynylaziridines are useful synthetic building blocks in organic chemistry. By utilizing the strain of the three-membered aziridine ring and the adjacent carbon–carbon triple bond, a variety of reactions including the opening of the aziridine ring and construction of N-heterocyclic compounds have been reported.[4–8] As an example, Yudin recently reported a modular synthesis of pyridines by the sequential transformation from alkynylaziridines (Scheme 1).[8] In this process, substituted pyridines are regioselectively obtained in a three-step procedure by the formation of allenyl imines followed by palladium-catalyzed arylation/electrocyclization. During the course of our studies on the reaction of alkynylaziridines,[7f–i] we found that the substituted pyridines **3** and **4** are produced from the 3-aziridinylpropiolate esters[9] **1** by the formation of the allenyl imines **2** (Scheme 1). We describe herein a sequential ring-opening/cyclization/oxidation of 3-aziridinylpropiolate esters, a sequence in which tri- (**3**) and tetrasubstituted (**4**) pyridines can be selectively synthesized depending on the reaction conditions used in the final oxidation step.



Scheme 1. Synthesis of pyridines from alkynylaziridines.

The initial attempt began with the conversion of the N-arylmethyl 3-aziridinylpropiolate esters **1** into allenyl imines **2**. It is known that N-benzyl vinylaziridine causes a [1,5] hydrogen shift under heating to afford the allyl imines.[10] We expected that similar reactions could occur in the case of **1**. When N-benzyl 3-aziridinylpropiolate ester (**1a**), having a cyclohexyl group on the aziridine ring, was heated in toluene at 100 °C for 9 hours, the desired reaction formed the allenyl imine **2a** in quantitative yield (Table 1, entry 1). Other alkyl-substituted substrates (**1b–f**) had similar reactivities, thus providing the corresponding products **2b–f** (entries 2–6). The reactions using the N-arylmethyl-substituted substrates **1g–k** afforded the corresponding allenyl imines **2g–k** (entries 7–11). N-Naphthylmethyl- and N-thienylmethyl-substituted substrates, **1l** and **1m**, respectively, were also converted into the corresponding products **1l** and **1m** (entries 12 and 13). Since in all cases the resulting products **2a–m** had been obtained quantitatively as a single diastereomer, it was determined that the reaction proceeded in a highly efficient and selective manner.

We next investigated the one-pot synthesis of substituted pyridines from **1a** (Table 2). Since the allenyl imines **2** contain

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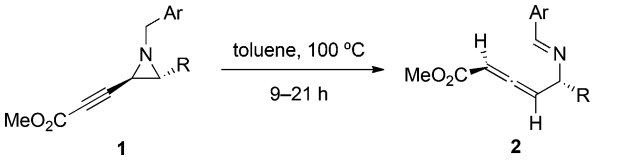
Table 1: Conversion of **1** into the allenyl imines **2**.[a]

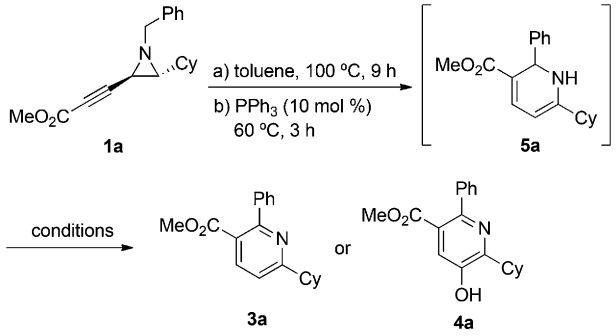


1 **2**

Entry	**1**	R	Ar	**2**
1	**1a**	Cy	Ph	**2a**
2	**1b**	*i*Pr	Ph	**2b**
3	**1c**	*t*Bu	Ph	**2c**
4	**1d**	*n*Bu	Ph	**2d**
5	**1e**	$Ph(CH_2)_2$-	Ph	**2e**
6	**1f**	$BnO(CH_2)_3$-	Ph	**2f**
7	**1g**	Cy	2-BrC_6H_4	**2g**
8	**1h**	Cy	4-BrC_6H_4	**2h**
9	**1i**	Cy	4-ClC_6H_4	**2i**
10	**1j**	Cy	4-FC_6H_4	**2j**
11	**1k**	Cy	4-$MeOC_6H_4$	**2k**
12	**1l**	Cy	2-naphthyl	**2l**
13	**1m**	Cy	2-thienyl	**2m**

[a] Quantitative yields for crude reaction mixtures in all cases (the purity of products were confirmed by ^1H and ^{13}C NMR spectroscopy).

Table 2: Reaction optimization for the synthesis of **3a** and **4a**.



1a **5a** **3a** **4a**

Entry	Reagent (equiv)	*T* [°C]	*t* [h]	Yield [%][a] **3a**	**4a**
1	MnO_2 (5.0)	60	0.3	33	–
2	DDQ (1.2)	RT	0.3	69	–
3	*m*CPBA (1.5)	60	8	38	37
4	CSA (2.0)	60	3	37	15
5	$PhCO_2H$ (2.0)	60	21	53	14
6	PPTS (2.0)	60	10	53	trace
7	AcOH (2.0)	60	6	71	trace
8	AcOH (1.5)	60	10	77	trace
9	O_2 (1 atm)	60	2	18	51
10	O_2 (1 atm)	0	4	8	80
11	O_2 (1 atm), AcOH (5.0)	60	2	67	7
12	open air	0	9	7	62

[a] Yield of isolated products.

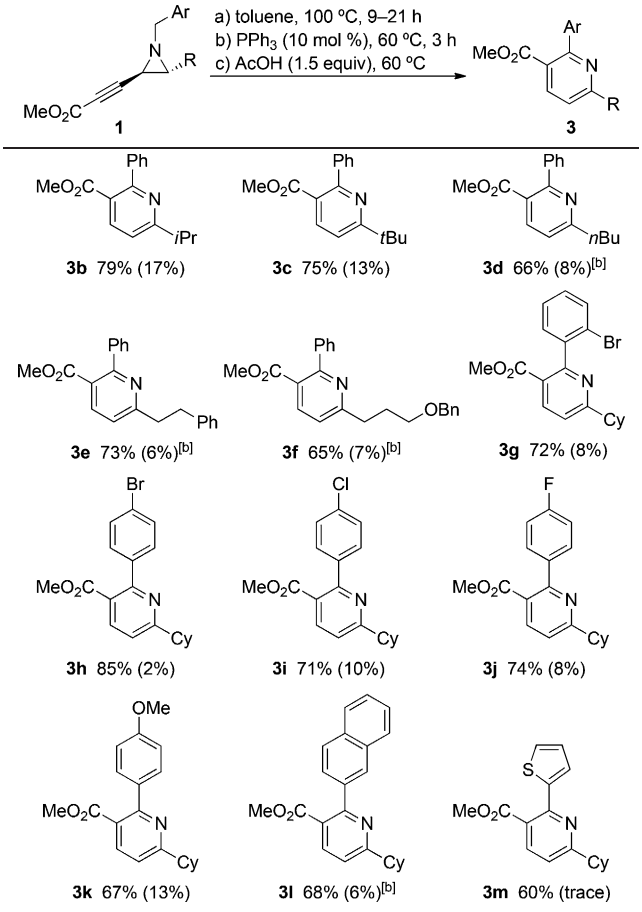
an imino group and an allenoate moiety, it is predicted that the corresponding cyclized product would be obtained by an intramolecular aza-Baylis–Hillman reaction.[11,12] After **1a** was converted into **2a** at 100 °C in toluene, the in situ generated allenyl imine **2a** was reacted with 0.1 equivalents PPh_3 at 60 °C. As a result, the desired reaction successfully proceeded to afford the dihydropyridine **5a** in 99 % yield as determined by NMR spectroscopy. Because the isolation of **5a** was difficult as a result of its instability,[13] the direct conversion into the pyridine under oxidizing conditions was attempted. When MnO_2 was added to the reaction mixture after the formation of **5a** in situ, the trisubstituted pyridine **3a** was produced in 33 % yield in three steps (entry 1). The yield was increased to 69 % in the case of DDQ (entry 2), and it was found that the tetrasubstituted hydroxypyridine **4a** was produced together with **3a** when *m*CPBA was used as the oxidant (entry 3). Addition of acid favored the selective formation of **3a** (entries 4–8), and the best results were obtained when 1.5 equivalents of AcOH were added at 60 °C to give **3a** in 77 % yield (entry 8). In this case, it is expected that the dissolved oxygen in the reaction mixture would act as the oxidant. Furthermore, it has been revealed that **4a** is selectively formed by using oxygen (entries 9 and 10). Thus, **4a** was obtained in 80 % yield when the in situ generated **5a** was subjected to the reaction under oxygen at 0 °C (entry 10). The reaction was also attempted in the presence of both AcOH and oxygen to reveal the effect of acid. As a result, **3a** was predominantly produced in 67 % yield (entry 11), and clearly demonstrates that the addition of AcOH affects the selective formation of **3a**. We also carried out the reactions under aerobic oxidation conditions. When the one-pot synthesis of pyridines from **1a** was attempted open to air at the final oxidation step, **4a** was selectively produced in 62 % yield (entry 12).[14] From this result, it was found that the reactions can also be carried out using air as an oxidant.

Having identified useful sets of reaction conditions, we next explored the one-pot synthesis of various trisubstituted pyridines (**3**) from 3-aziridinylpropiolate esters (**1**), and includes sequential ring-opening and cyclization reactions followed by acid-promoted oxidation (Table 3). As a result, the alkyl-substituted substrates **1b–f** were converted into the corresponding products **3b–f** in good yields. The reactions of **1g–m**, having N-arylmethyl and N-thienylmethyl groups, also afforded the corresponding trisubstituted pyridines **3g–m** with a tolerance for bromo, chloro, fluoro, methoxy, and thienyl groups.

The results of a one-pot synthesis of tetrasubstituted pyridines (**4**) from **1** by air- and oxygen-promoted oxidation in the final step are summarized in Table 4. The reactions using various substituted 3-aziridinylpropiolate esters (**1a–m**) successfully proceeded in all cases to give the corresponding products **4a–m**. While the yields of some products were not so high when running the reaction open to air (Method A), the tetrasubstituted pyridines were effectively produced in moderate to good yields under oxygen (Method B). From these results, broad generalities and good selectivities can be drawn about the production of both tri- and tetrasubstituted pyridines.

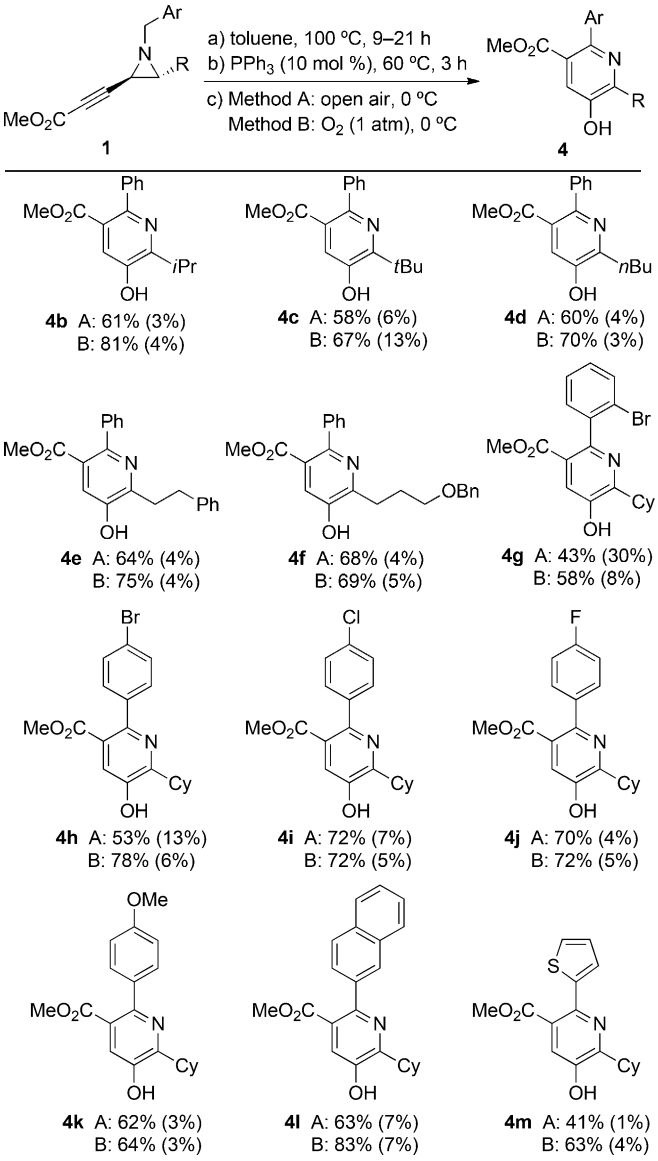
A plausible mechanism for the cyclization process is shown in Scheme 2. The 3-aziridinylpropiolate ester (**1**) initially causes a stereospecific [1,5] hydrogen shift under heating to afford the allenyl imine **2** as a single diastereomer. Formation of a preferred transition state such as **6** may account for this stereospecificity. By reacting with triphenylphosphine, **2** then undergoes an intramolecular aza-Baylis–

Table 3: Synthesis of various trisubstituted pyridines **3**.[a]



[a] The yields of the corresponding hydroxypyridines **4** are given within parentheses. [b] AcOH was added at 100 °C.

Table 4: Synthesis of various tetrasubstituted pyridines **4**.[a]



[a] The yields of the corresponding trisubstituted pyridines **3** are given within parentheses.

Hillman reaction to afford the cyclic betaine intermediate **7**. Finally, the intermediate **8**, formed by the sequential proton transfer of **7**, produces the dihydropyridine **5** along with a regeneration of the phosphine catalyst. In the synthesis of the trisubstituted pyridine **3** under acidic conditions, **5** undergoes protonation leading to the intermediate **9**, which gradually becomes oxidized to **3** by the dissolved oxygen in the reaction mixture. When the reaction was carried out in oxygen but without AcOH, hydroperoxylation at the electrophic C5 of **5** would selectively occur to give the intermediate **10**,[15] which when further subjected to dehydration and then aromatization afforded the tetrasubstituted pyridine **4**. The control experiments to clarify the effect of AcOH (entries 9 and 11 in Table 2) indicate that AcOH inhibits the hydroperoxylation of **5** by protonation to the enamino nitrogen atom, and consequently promotes the direct aromatization to the trisubstituted pyridine **3**.

To demonstrate the synthetic utility of our new methodology, transformations of the resulting substituted pyridines to the niacin derivatives[1] were carried out. The ester group of the trisubstituted pyridine **3a** was easily hydrolyzed under basic conditions to afford the carboxylic acid **11** in 96% yield (Scheme 3). Furthermore, conversion of **11** into the amide **12** successfully proceeded using NH_4Cl with EDCI/HOBt. Similar transformations of **4a** into the corresponding carboxylic acid **13** and amide **14** also occurred, uneventfully.

In conclusion, we have developed a new methodology for the synthesis of substituted pyridines involving sequential transformations of 3-aziridinylpropiolate esters. The sequence comprises [1,5] hydrogen shift of a 3-aziridinylpropiolate ester, an intramolecular aza-Baylis–Hillman reaction of the resulting allenyl imine, and a final oxidation to the pyridine. The versatility of this chemistry could provide a valuable protocol for the synthesis of highly substituted pyridines.

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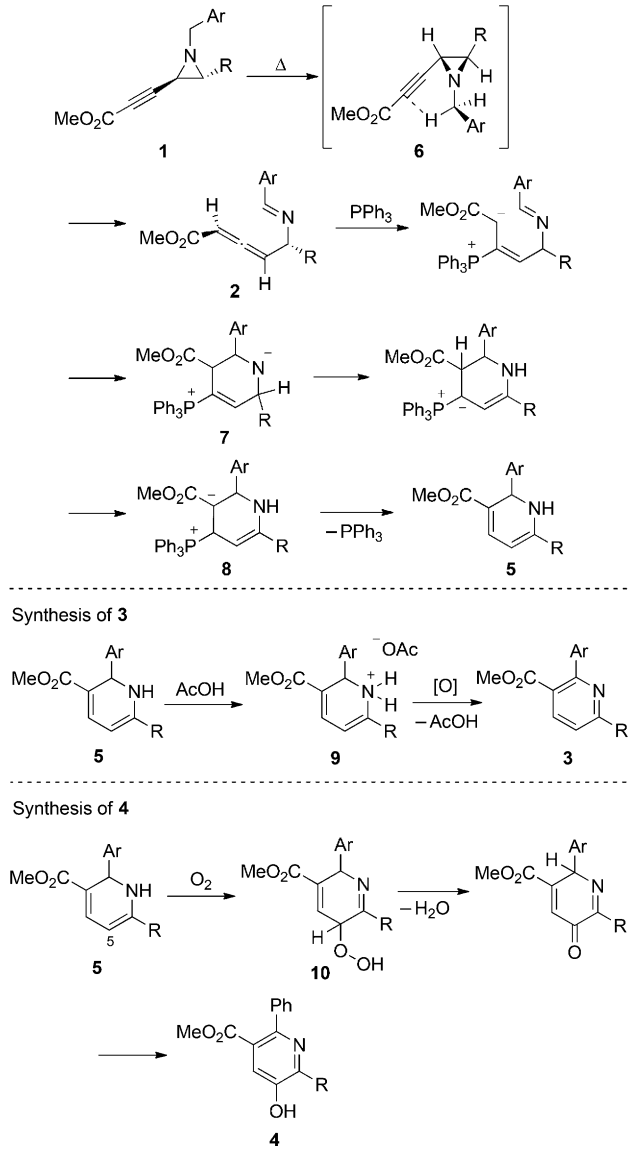
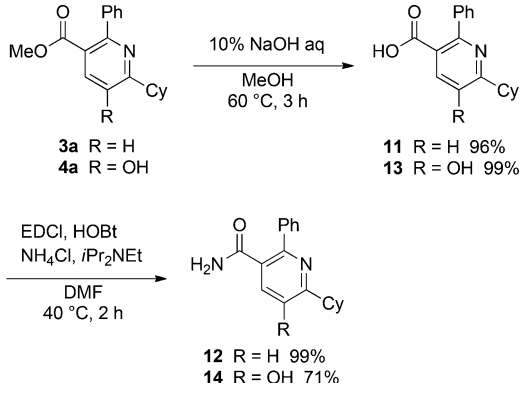


Scheme 2. Proposed reaction mechanism.



Scheme 3. Conversion into niacin derivatives.

Keywords: cyclization · heterocycles · organocatalysis · small ring compounds · synthetic methods

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[13] Only N-naphthylmethyl-substituted dihydropyridine **51** was relatively stable and can be isolated. See the Supporting Information.

[14] Although the reason for the decrease of the yield compared to that of the oxygen-promoted reaction conditions (entry 10) is not clear, it is expected that the concentration of the oxygen is essential for the efficient oxidation.

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