An Oxidant-Free Single-Step Synthesis of Tetra- or Disubstituted Symmetrical Pyridine Derivatives by a $Hf(OTf)_4$-Catalyzed Annulation

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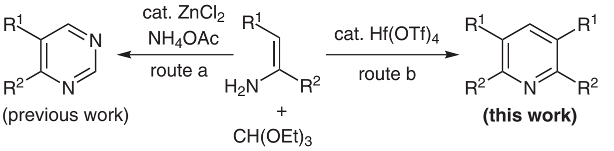
Abstract: The $Hf(OTf)_4$-catalyzed unprecedented annulation of an enamine with triethyl orthoformate leading to the preparation of tetrasubstituted symmetrical pyridine derivatives without an oxidant is described. This method accommodated the single-step synthesis of a disubstituted symmetrical pyridine using an acetophenone derivative, triethyl orthoformate, and ammonium acetate (NH_4OAc).

Key words: heterocycles, pyridines, hafnium triflate, enamines, orthoesters

Symmetrical pyridine nuclei are widely found in a variety of natural products and biologically active substances.[1] Although a number of approaches to the synthesis of a pyridine derivative have been reported by a number of organic and pharmaceutical chemists,[1–5] the general procedure for the preparation of a symmetrical pyridine skeleton has been restricted to a two-step synthetic route via the Hantzsch-type synthesis[6,7] of symmetrical 1,4-dihydropyridine derivatives,[8,9] followed by the aromatization of 1,4-dihydropyridines using increased stoichiometric amounts of an oxidant.[10] In addition, this synthetic process often requires stoichiometric additives such as a strong base and acid, a prolonged time-frame, and harsh reaction conditions that result in a decline in the desired product yield. Hence, the development of an efficient acid-catalyzed single-step synthesis of symmetrical pyridine derivatives using no oxidants, and with a shortened time-frame, is highly desirable.

We previously reported that Lewis acid mediated annulation of an enamine derivative[11,12] with an orthoester leads to the synthesis of a variety of nitrogen-containing heterocyclic compounds.[13] In a previous paper,[14] we found that the $ZnCl_2$-catalyzed reaction of an enamine with an orthoester leads to the synthesis of pyrimidine derivatives (route a in Scheme 1). During our ongoing studies of a practical synthetic process for nitrogen-containing heterocycles using a functionalized enamine and an orthoester, we found that $Hf(OTf)_4$[15] catalyzes the annulation of an enamine with triethyl orthoformate leading to the highly selective synthesis of tetrasubstituted symmetrical pyridine derivatives (route b). To our knowledge, a single-step synthesis of the pyridine derivative through annulation of an enamine with an orthoester as a C1 unit is yet to have been reported.[16] In this letter, we report on the preliminary results of the unprecedented synthesis of the pyridine. Moreover, we disclose the use of acetophenone derivatives and ammonium acetate, instead of the enamine, to produce disubstituted symmetrical pyridines.



Scheme 1 Previous and current synthesis methods

Initially, the starting materials, enamines **3a**–**d**, were easily prepared by the reaction of an α-acidic compound **1** with a nitrile **2** in THF at –70 °C for one hour in the presence of LDA, as reported previously.[14,17,18]

Annulation of the prepared enamine **3a** with orthoester **4** was then examined, and the results are listed in Table 1. When the reaction of enamine **3a** (0.50 mmol) with orthoester **4** (1.5 mL, 20 equiv for **3a**) was performed with neither a solvent nor a catalyst at room temperature for 16 hours, the annulation did not occur (entry 1). Addition of a typical Lewis acid, such as $ZnBr_2$, $MgBr_2{\cdot}OEt_2$, $InCl_3$, $BF_3{\cdot}OEt_2$, or $AlCl_3$, was also ineffective for the reaction (entries 2–6). On the other hand, use of $Yb(OTf)_3$ and $Cu(OTf)_2$ was effective for an improvement in the yield of pyridine **5a** to moderate, but the undesirable product **6** was formed in 28% and 40% yields, respectively (entries 7 and 8). Employment of $Hf(OTf)_4$ also gave the desired product **5a** and the undesired product **6** in 74% and 24% yields, respectively (entry 10). It was noteworthy that use of $CHCl_3$ as a solvent and reduction of the equivalent of orthoester **4** to one equivalent for **3a** decreased the formation of by-product **6** to a trace amount (entry 13). Moreover, when the reaction temperature was raised to 60 °C, the product **5a** was selectively obtained as a sole product in 76% yield (entry 16).

To explore the scope of the method, the reaction was examined using several enamines. The results are summarized in Table 2. When enamines **3b** and **3c**, having an electron-donating group on the benzene ring, were employed, the desired symmetrical pyridine derivatives **5b** and **5c** were obtained in good yields (entries 2 and 3). In contrast, use of enamine **3d**, which contains a chloro substituent, produced the corresponding product **5d** in mod-

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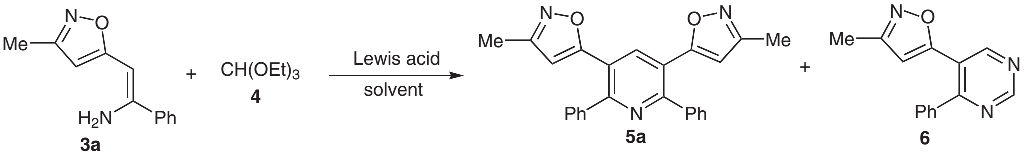
Table 1 Examination of the Synthesis of Pyridine Derivative **5a**



Entry	**4** (equiv)	Lewis acid (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]	
						5a	**6**
1	20	none	none	r.t.	16	NR	
2	20	$ZnBr_2$ (0.1)	none	r.t.	16	ND	ND
3	20	$MgBr\cdot OEt_2$ (0.1)	none	r.t.	16	ND	ND
4	20	$InCl_3$ (0.1)	none	r.t.	16	11	7
5	20	$BF_3\cdot OEt_2$ (0.1)	none	r.t.	16	14	trace
6	20	$AlCl_3$ (0.1)	none	r.t.	16	26	trace
7	20	$Yb(OTf)_3$ (0.1)	none	r.t.	16	44	28
8	20	$Cu(OTf)_2$ (0.1)	none	r.t.	16	45	40
9	20	$HfCl_4$ (0.1)	none	r.t.	16	36	trace
10	20	$Hf(OTf)_4$ (0.1)	none	r.t.	8	(74)	24
11	20	$Hf(OTf)_4$ (0.3)	none	r.t.	8	62	11
12	20	$Hf(OTf)_4$ (0.05)	none	r.t.	8	48	30
13	1	$Hf(OTf)_4$ (0.1)	$CHCl_3$	r.t.	8	61[b]	trace
14	1	$Hf(OTf)_4$ (0.1)	THF	r.t.	8	48[b]	trace
15	1	$Hf(OTf)_4$ (0.1)	toluene	r.t.	8	51[b]	trace
16	1	$Hf(OTf)_4$ (0.1)	$CHCl_3$	60	1.5	(76)	trace

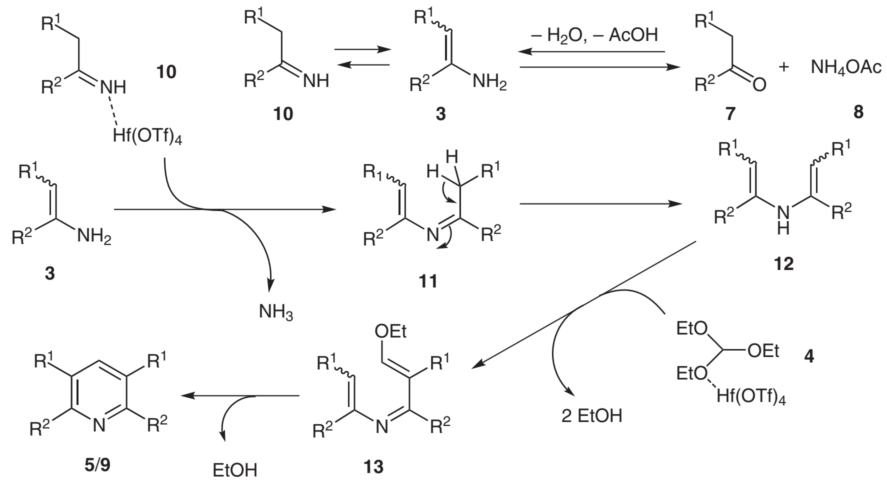
[a] NMR yield (isolated yield); NR = no reaction; ND = not determined.
[b] Average of two runs.

erate yield (entry 4). Similarly, use of enamines **3e** and **3f** gave the desired products **5e** and **5f** in 83% and 60% yields, respectively (entries 5 and 6), as they have a methyl group instead of a phenyl group, and they have an electron-withdrawing group, either an ester or a nitrile.

Moreover, as shown in Table 3, we applied the present method to the direct synthesis of disubstituted symmetrical pyridine derivatives **9** from acetophenone derivative **7** with NH_4OAc as a nitrogen source. Unfortunately, the reaction conditions shown in Table 2 were ineffective for the preparation of the desired pyridine derivative **9a** (entry 1). However, changing the solvent to toluene, increasing the amount of the catalyst to an equivalent of 0.5, and raising the reaction temperature to 100 °C dramatically improved the product yield to 85% (entry 3). With these reaction conditions, we examined the preparation of disubstituted pyridine derivatives using several acetophenone derivatives. All reactions successfully proceeded to produce the corresponding symmetrical pyridine derivatives **9b–d** in moderate to good yields (entries 4–6).

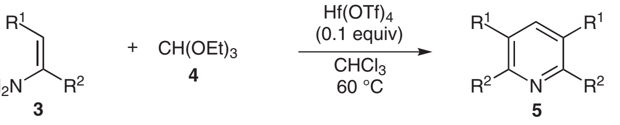
A plausible mechanism for this $Hf(OTf)_4$-catalyzed annulation is shown in Scheme 2. Previously, we have reported a $ZnCl_2$-catalyzed three-component synthesis of 4,5-disubstituted pyrimidines from an enamine, an orthoester, and ammonium acetate.[14] $Hf(OTf)_4$ is a Lewis acid harder than $ZnCl_2$,[19] and the imine **10** is a Lewis base harder than ketone **7** (or the orthoester **4**).[20] According to HASB principle, $Hf(OTf)_4$ binds strongly with **10** which is an tautomer of the enamine **3**, and $ZnCl_2$ has a tendency to bind with **4**. Firstly, $Hf(OTf)_4$ coordination with the imine **10** is followed by a reaction of the activated imine with the starting enamine **3** (or the enamine intermediate generated from an α-acidic ketone and NH_4OAc), which leads to the formation of intermediate **11** with liberation of ammonia (Scheme 2).

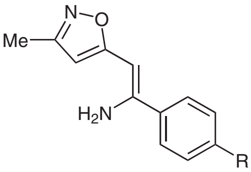
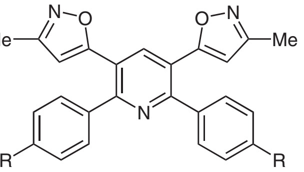
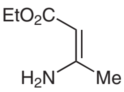
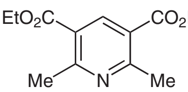
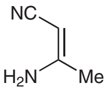
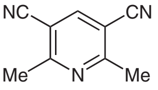
Finally, tautomeric bisenamine **12** reacts with the orthoester **4**, which is weakly activated by $Hf(OTf)_4$, to produce the corresponding tetra- or disubstituted symmetrical pyridine **5/9** through intramolecular cyclization of the 3-azatriene intermediate **13**.



Scheme 2 A plausible mechanism

Table 2 Synthesis of Tetrasubstituted Symmetrical Pyridines **5**



Entry	Enamine **3**	Time (h)	Pyridine **5**	Yield (%)[a]
				
1	**3a**	1.5	R = H **5a**	76
2	**3b**	1.5	R = MeO **5b**	65
3	**3c**	1.5	R = Me **5c**	73
4	**3d**	1.5	R = Cl **5d**	50
5	 **3e**	2	 **5e**	83
6[b]	 **3f**	3	 **5f**	60

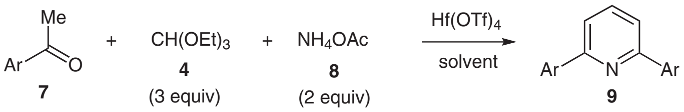
[a] Isolated yield.

[b] Two equivalents of **4** were used.

In conclusion, we have demonstrated that Hf(OTf)$_4$ catalyzes not only the annulation of an enamine with triethyl orthoformate leading to the single-step synthesis of tetrasubstituted symmetrical pyridine derivatives, but it also catalyzes the one-pot, three-component coupling reaction of an acetophenone derivative, an orthoester, and ammonium acetate to produce the disubstituted symmetrical pyridines.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 3 Synthesis of Disubstituted Symmetrical Pyridines **9**



Entry	Ketone 7		Solvent	$Hf(OTf)_4$ (equiv)	Temp (°C)	Time (h)	9	Yield (%)[a]
	Ar							
1	4-$MeOC_6H_4$	**7a**	$CHCl_3$	0.1	60	72	**9a**	8
2	4-$MeOC_6H_4$	**7a**	toluene	0.1	100	72	**9a**	51
3	4-$MeOC_6H_4$	**7a**	toluene	0.5	100	1	**9a**	(85)
4	4-MeC_6H_4	**7b**	toluene	0.5	100	1	**9b**	(72)
5	Ph	**7c**	toluene	0.5	100	1	**9c**	(54)
6	4-ClC_6H_4	**7d**	toluene	0.5	100	6	**9d**	(60)

[a] NMR yield (isolated yield).

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