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Ruthenium Complex-catalyzed Novel and Facile Synthesis of Imidazo[1,2-*a*]pyridines from 2-Aminopyridines and *vicinal*-Diols

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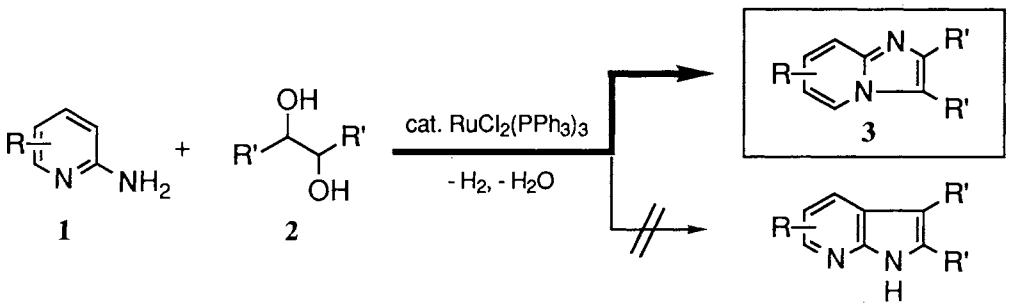
Ruthenium complex-catalyzed *N*-heterocyclization of 2-aminopyridines with *vicinal*-diols offers a novel synthetic method for various imidazo[1,2-*a*]pyridines. For example, the reaction of 2-amino-4-methylpyridine with 1,2-cyclohexanediol in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ under reflux in diglyme for 24 h afforded 2-methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazole in 74% yield.

Imidazo[1,2-*a*]pyridines belong to one of the most important classes of heterocyclic compounds[1a] and many kinds of biologically active imidazo[1,2-*a*]pyridines have been prepared as antiulcer drugs, calmodulin inhibitors and long-acting local anesthetics.[2] However, synthetic methods of them are strictly limited to (1) the reaction of imidazoles with 1,4-dicarbonyl compounds via the construction of a six-membered ring,[3] and (2) the reaction of 2-aminopyridines with α-halocarbonyl compounds by the formation of a five-membered ring.[4]

Recently, on the basis of our studies on ruthenium-catalyzed *N*-heterocyclization reactions,[5] we have been developing new catalytic syntheses of *N*-heterocycles containing two or more heteroatoms.[6] Herein, we report ruthenium-catalyzed reaction of 2-aminopyridines with *vicinal*-diols, which has two possibilities to give imidazo[1,2-*a*]pyridines (the upper equation in Eq. 1) and to give pyrrolo[2,3-*b*]pyridines (the lower equation in Eq. 1). Consequently, this reaction offers a novel and facile method for *catalytic* synthesis of imidazo[1,2-*a*]pyridines. The reaction mechanism is also discussed here.

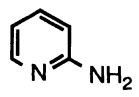
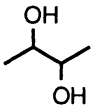
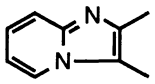
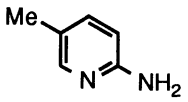
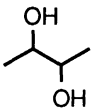
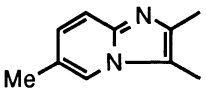
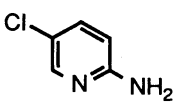
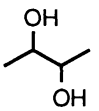
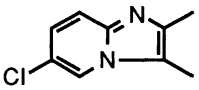
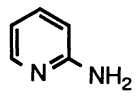
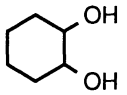
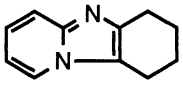
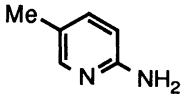
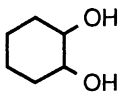
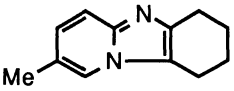


(1)

In a typical procedure, a mixture of 2-aminopyridine (**1**) (4.0-8.0 mmol), *vicinal*-diol (**2**) (4.0-6.0 mmol), $RuCl_2(PPh_3)_3$ (0.20 mmol) and diglyme (4.0 ml) was placed in a two-necked 50 ml Pyrex flask equipped with a magnetic stirring bar and a reflux condenser under an argon flow. The flask was immersed into a preheated silicone oil bath (*ca.* 170 °C) and the reaction was carried out under reflux with stirring for 24 h. The products were isolated by Kugelrohr distillation, recrystallization and/or preparative thin layer chromatography. The satisfactory spectroscopic and analytical data of all products were obtained.

Representative results under the optimized conditions for each substrate are shown in Table 1. When 2-aminopyridine (**1a**) was treated with 2,3-butanediol (**2a**) in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ under reflux in diglyme, 2,3-dimethylimidazo[1,2-*a*]pyridine (**3a**) was obtained in 50% yield (Run 1). This *N*-heterocyclization reaction proceeded with a spontaneous hydrogen evolution and after the reaction of Run 1, 2.40 mmol of hydrogen was detected in the gas phase. Therefore, the present reaction did not require any hydrogen acceptors. 2-Aminopyridines bearing some substituents on a pyridine ring such as 2-amino-5-methylpyridine (**1b**) and 2-amino-5-chloropyridine (**1c**) also reacted with 2,3-butanediol (**2a**) to afford the corresponding imidazo[1,2-*a*]pyridines (**3b** and **3c**) in moderate yields (Runs 2 and 3). 1,2-Cyclohexanediol (**2b**) (*cis*- and *trans*-mixture) smoothly reacted with 2-aminopyridines (**1a** and **1b**) to give the corresponding imidazo[1,2-*a*]pyridines, *i.e.*, 6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazoles (**3d** and **3e**), in moderate to good yields (Runs 4 and 5).

Table 1. $RuCl_2(PPh_3)_3$-catalyzed Synthesis of Imidazo[1,2-*a*]pyridines[a)]

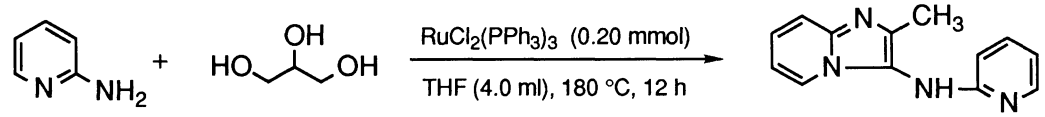
Run	2-Aminopyridine	/ mmol	*vicinal*-Diol	/ mmol	Product	Yield / %[b)]
1	 **1a**	4.0	 **2a**	5.0	 **3a**	50
2[c)]	 **1b**	8.0	 **2a**	4.0	 **3b**	49
3	 **1c**	4.0	 **2a**	4.0	 **3c**	32
4	 **1a**	4.0	 **2b**	6.0	 **3d**	46
5	 **1b**	4.0	 **2b**	6.0	 **3e**	74 (72)

a) A mixture of 2-aminopyridine (**1**), *vicinal*-diol (**2**), and $RuCl_2(PPh_3)_3$ (0.20 mmol) was treated under reflux in diglyme (4.0 ml) for 24 h. b) GLC yield (isolated yield). c) At 210 °C in THF (4.0 ml) using a 50 ml stainless steel autoclave.

As for the catalysts, the present reaction is characteristic of the $RuCl_2(PPh_3)_3$ catalyst. Other ruthenium catalysts ($RuH_2(PPh_3)_4$ and $RuCl_3 \cdot nH_2O$-PPh_3) and group VIII metal complexes ($PtCl_2(PPh_3)_2$, $PtCl_2(PhCN)_2$-$SnCl_2 \cdot 2H_2O$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, and $RhCl(PPh_3)_3$) were totally ineffective.

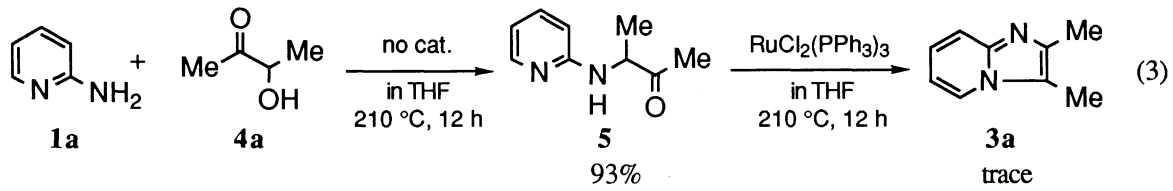
In addition, *vicinal*-diols such as ethylene glycol and propylene glycol bearing terminal hydroxy groups could not be employed in the present reaction. In these cases, only *vicinal*-diols were consumed, whereas 2-aminopyridines remained intact and the desired imidazo[1,2-*a*]pyridines were not obtained at all, probably due to

the comparative high reactivity of these diols. Among *vicinal*-diols containing terminal hydroxy groups, only glycerol (**2c**) reacted with 2-aminopyridine (**1a**) to give 2-methyl-3-(2-pyridylamino)imidazo[1,2-*a*]pyridine (**3f**) in 22% yield (Eq. 2).

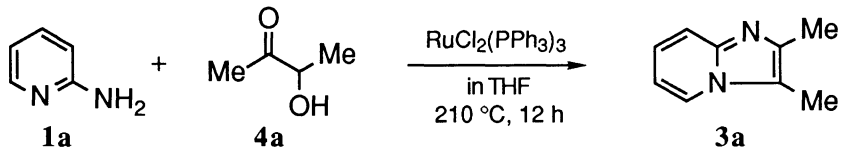


1a 3.9 mmol + **2c** 7.7 mmol → **3f** 22% (2)

In order to investigate the mechanism, when 2-aminopyridine (**1a**) was treated with acetoin (**4a**),[7] which would be an intermediate generated by ruthenium-catalyzed dehydrogenation of 2,3-butanediol (**2a**), in the absence of a catalyst, 3-(2-pyridylamino)butan-2-one (**5**) was obtained in 93% yield (Eq. 3). If ruthenium-catalyzed reaction of 2-aminopyridine (**1a**) with 2,3-butanediol (**2a**) proceeded via **5**, **5** should be transformed into 2,3-dimethylimidazo[1,2-*a*]pyridine (**3a**) by the ruthenium catalyst. However, treatment of **5** in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ at 210 °C for 12 h gave only a trace amount of 2,3-dimethylimidazo[1,2-*a*]pyridine (**3a**). On the contrary, the reaction of 2-aminopyridine (**1a**) with acetoin (**4a**) in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ afforded **3a** in 50% yield (Eq. 4). This result is consistent with the result of Run 1 in Table 1. So, we consider that the compound **5** is not the intermediate of the present reaction and ruthenium complex-catalyzed reaction of 2-aminopyridine (**1**) with an acyloin intermediate (**4**) initially occurs at the ring nitrogen,[4a] not at the exocyclic nitrogen.[4c]



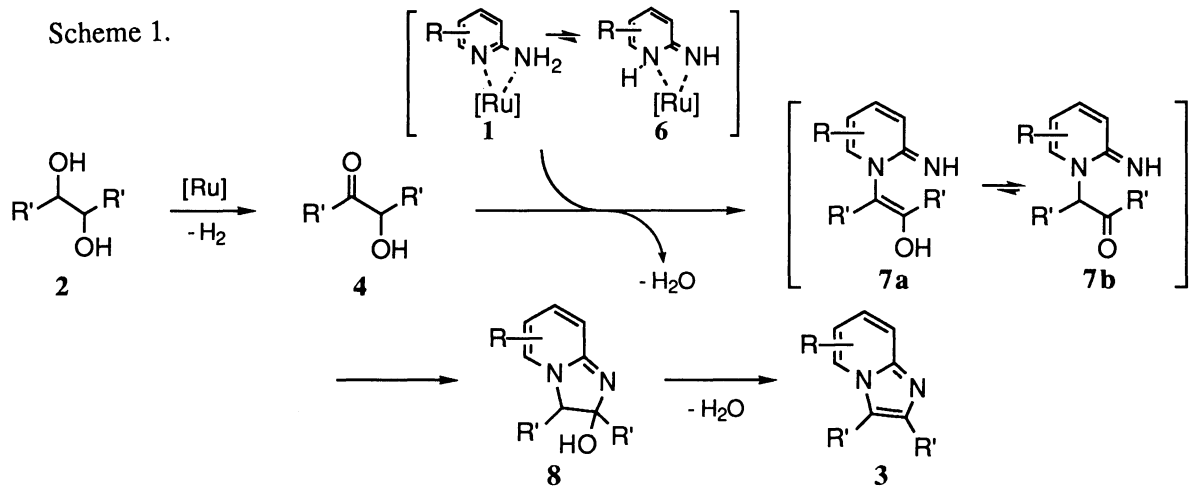
1a + **4a** → **5** 93% → **3a** trace (3)



1a + **4a** → **3a** 50% (4)

According to the above mentioned results, the most plausible reaction pathway is illustrated in Scheme 1. The reaction would start from ruthenium-catalyzed dehydrogenation of *vicinal*-diol (**2**) to an acyloin intermediate (**4**).[6b] In principle, an amino group α to a ring heteroatom can exist in the tautomeric forms, **1** and **6**.[1b] This tautomeric equilibration would lie well to **6** by its coordination to the ruthenium.[8,9] Thus, the nucleophilicity of the ring nitrogen increases and the first reaction with electrophiles, the acyloin (**4**) in this case, takes place at the ring nitrogen to afford **7a** which readily tautomerizes to **7b**. Finally, imidazo[1,2-*a*]pyridine (**3**) is obtained by the ring closure at the exocyclic nitrogen atom followed by the dehydration of the generated intermediate **8**. A similar ring closure mechanism was also proposed in the reaction of 2-aminopyridine with α-haloketones.[4a,b] The result that the present reaction did not afford pyrrolo[2,3-*b*]pyridines (the lower equation in Eq. 1) can be rationalized in consideration of the above mentioned mechanism as well as the formation mechanism of pyrrolo[2,3-*b*]pyridines involving electrophilic substitution at π-electron deficient pyridine ring.[5a]

Scheme 1.



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7) The reaction of 2-aminopyridine with α-hydroxyketones has been already reported, briefly. See, B. Alcaide, R. Pérez-Ossorio, J. Plumet, and M. A. Sierra, *Tetrahedron Lett.*, **27**, 1627 (1986); A. Mendel, *Res. Discl.*, **303**, 504 (1989); *Chem. Abstr.*, **112**, 138989s (1990).

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9) The simple *N*-alkylation of 2-aminopyridine with cyclohexanol catalyzed by $RuCl_2(PPh_3)_3$ at 180 °C for 12 h gave 2-(*N*-cyclohexyl)aminopyridine in 62% yield, whereas 3-aminopyridine and 4-aminopyridine did not react with cyclohexanol even at 200 °C. This result strongly suggests that only 2-aminopyridine can coordinate to the ruthenium, which extremely enhances its reactivity.

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