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Ring Transformation Mediated by Lewis Acids and Oxidizing Agents. Synthesis of 2-Methoxy-1*H*-imidazole from 5-Aminopyrimidin-4(3*H*)-one

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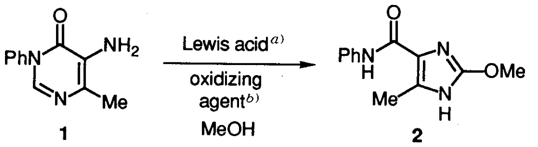
Treatment of 5-aminopyrimidin-4(3*H*)-one (1) with Lewis acidic metal salts such as zinc chloride, zinc bromide, zinc iodide, aluminum chloride, aluminum bromide, nickel chloride, copper(I) chloride, or copper(I) iodide in the presence of oxidizing agents such as ceric ammonium nitrate, ammonium persulfate, or phenyliodine(III) diacetate in methanol gave 2-methoxy-1*H*-imidazole (2).

Keywords ring transformation; pyrimidine; imidazole; Lewis acid; oxidizing agent

Various studies on the synthesis and reactions of pyrimidines, some of which have interesting biological activities, have been reported.[1] In the course of medicinal and chemical studies of pyrimidines in our laboratory,[2] we previously encountered the ring transformation of 5-aminopyrimidin-4(3*H*)-one (**1**) to 2-methoxy-1*H*-imidazole (**2**) in the presence of copper(II) chloride in methanol.[3] Since the reaction was presumed to be caused by Lewis acidity and oxidative ability of copper(II) chloride, we thought that if the chelated intermediate with a Lewis acid could be formed, the transformation of **1** to **2** might occur upon addition of an oxidizing agent. These considerations prompted us to examine the transformation of **1** into **2** by use of both a catalytic amount of Lewis acid and more than one equivalent of oxidizing agent to obtain more detailed information about the mechanism.

Compound **1**[4] was allowed to react with zinc chloride, which is a Lewis acid having no oxidative ability, in the presence of oxidizing agents such as ceric ammonium nitrate (CAN), ammonium persulfate, or phenyliodine(III) diacetate (PIDA)[5] in methanol. The reaction proceeded to give compound **2** (Table I). Among these oxidizing agents, PIDA gave the highest yield of **2**. Employment of zinc bromide or zinc iodide afforded similar results to those in the case of zinc chloride. We also examined other Lewis acids such as aluminum chloride, aluminum bromide, nickel chloride, copper(I) chloride, and copper(I) iodide. It was revealed that a catalytic amount of Lewis acid (0.2 molar eq) and more than one molar equivalent of oxidizing agent were required for the transformation.

Among various combinations of Lewis acids and oxidizing agents examined, zinc(II) salts and PIDA or Ni(II) salt and PIDA afforded **2** in moderate yields. Taking the reaction mechanism of the transformation into consideration, the reaction medium was expected to become acidic, and this might result in decomposition of reaction intermediates to reduce the yield of **2**. Thus, it was considered that the yield of **2** might be raised by facile elimination of the Lewis acid, which was chelated on the oxygen atom in the presence of base. We therefore examined the addition of base to the reaction medium (Table II), but



a) Zn(II), Ni(II), Al(III), Cu(I)

b) CAN, $(NH_4)_2S_2O_8$, PIDA

Chart 1

TABLE I. Transformation of **1** into **2** with Lewis Acidic Metal Salts and Oxidizing Agents

Run	Lewis acid (molar eq)	Oxidizing agent[a] (molar eq)	Condition	Reaction time (h)	Yield (%)
1	$ZnCl_2$ (0.2)	CAN (2.2)	r.t.	0.5	12
2	$ZnCl_2$ (0.2)	$(NH_4)_2S_2O_8$ (2.2)	Reflux	2.5	23
3	$ZnCl_2$ (0.2)	PIDA (1.2)	r.t.	1	57
4	$ZnCl_2$ (0.1)	PIDA (1.2)	r.t.	1.5	48
5	$ZnCl_2$ (0.5)	PIDA (1.2)	r.t.	1	55
6	$ZnCl_2$ (1.2)	PIDA (1.2)	r.t.	1	52
7	$ZnBr_2$ (0.2)	PIDA (1.2)	r.t.	1.5	52
8	ZnI_2 (0.2)	PIDA (1.2)	r.t.	0.5	59
9	$AlCl_3$ (0.2)	PIDA (1.2)	r.t.	3	12
10	$AlBr_3$ (0.2)	PIDA (1.2)	r.t.	2	Trace
11	$NiCl_2$ (0.2)	CAN (2.2)	r.t.	0.5	7
12	$NiCl_2$ (0.2)	$(NH_4)_2S_2O_8$ (2.2)	Reflux	1	23
13	$NiCl_2$ (0.2)	PIDA (1.2)	r.t.	0.5	61
14	CuCl (0.2)	PIDA (1.2)	r.t.	0.5	28
15	CuI (0.2)	PIDA (1.2)	r.t.	0.5	23

a) The necessary molar equivalent is based on the disappearance of **1**. r.t. = room temperature.

TABLE II. Transformation of **1** into **2** in the Presence of Base on the Lewis Acid-Oxidizing Agent System

Run	Oxidizing agent (molar eq)	Base (molar eq)	Condition	Reaction time (h)	Yield (%)
1[a]	CAN (2.2)	2.6-Lutidine (2.2)	r.t.	2	9
2[a]	CAN (2.2)	Et_3N (2.2)	r.t.	2.5	12
3[a]	CAN (2.2)	DBU (2.2)	r.t.	2.5	10
4[a]	$(NH_4)_2S_2O_8$ (2.2)	2.6-Lutidine (2.2)	Reflux	1.5	38
5[a]	$(NH_4)_2S_2O_8$ (2.2)	Et_3N (2.2)	Reflux	2	24
6[a]	$(NH_4)_2S_2O_8$ (2.2)	DBU (2.2)	Reflux	2	23
7[a]	PIDA (1.2)	2.6-Lutidine (2.2)	r.t.	0.5	56
8[a]	PIDA (1.2)	Et_3N (2.2)	r.t.	1	28
9[a]	PIDA (1.2)	DBU (2.2)	r.t.	0.5	35
10[b]	PIDA (1.2)	2.6-Lutidine (2.2)	r.t.	0.5	52
11[b]	PIDA (1.2)	Et_3N (2.2)	r.t.	0.75	23
12[b]	PIDA (1.2)	DBU (2.2)	r.t.	0.5	30

a) $ZnCl_2$ (0.2 molar eq). *b*) $NiCl_2$ (0.2 molar eq). r.t. = room temperature.

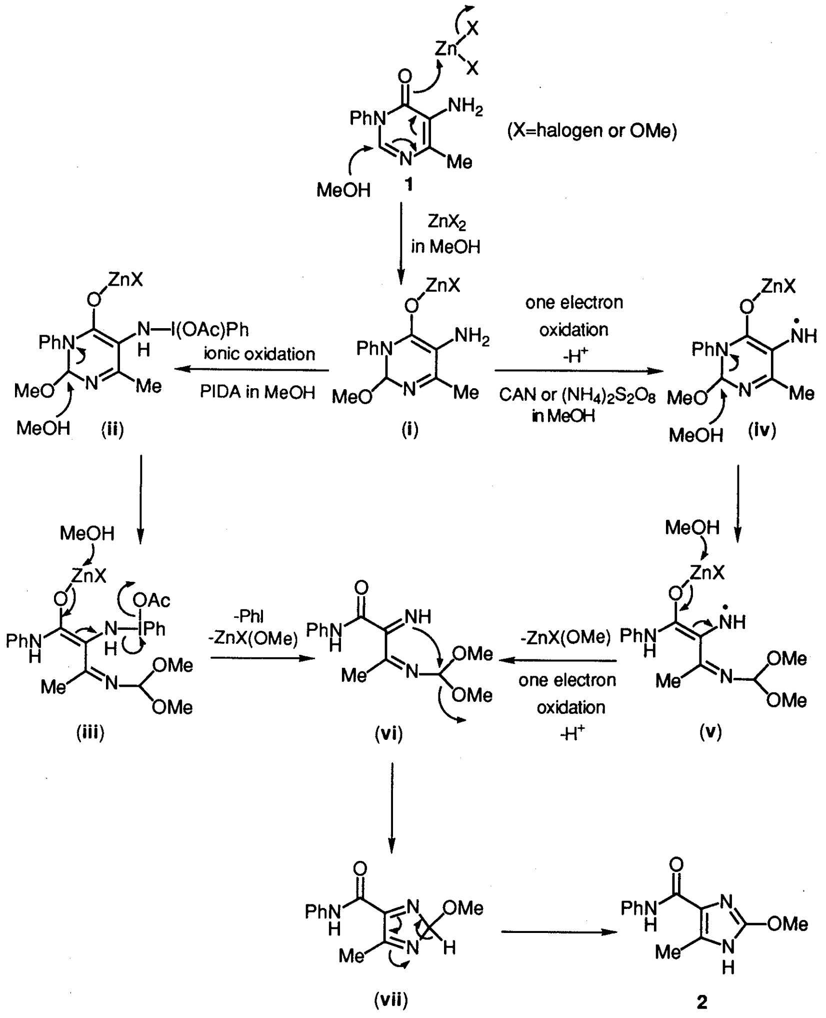


Chart 2

the yield was not markedly improved. Addition of triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) rather reduced the yield of **2**. In the case of 2,6-lutidine and ammonium persulfate, the yield of **2** was raised a little. The reaction never proceeded with only Lewis acid, base, or a combination of Lewis acid and base. The reaction required the combination of Lewis acid and oxidizing agent. Treatment of **1** with only oxidizing agent gave a complicated and partially decomposed mixture, which was difficult to separate. Moreover, thin layer chromatography showed no spot of **2**.

We previously reported the transformation of **1** into 2-alkoxy-1*H*-imidazoles by use of several oxidative metal salts.[3] In that reaction, we presumed that the metal salts acted as both Lewis acids and oxidative agents. However, Lewis acids have no oxidative ability in this reaction. Thus, a possible reaction mechanism of the ring transformation mediated by Lewis acid and oxidizing agent is presented in Chart 2. Lewis acids [ZnX_2] seem to work as circulatory catalysts, which might exist in the divalent state of ZnX(OMe) or $Zn(OMe)_2$. Initial nucleophilic attack of methanol on C(2) aided by chelation of the Lewis acidic metal salt to the C(4) carbonyl function would give intermediate **i**. The succeeding oxidation might take two pathways; ionic oxidation by PIDA and radical oxidation by CAN or $(NH_4)_2S_2O_8$. In the case of the ionic reaction, the amino group would be oxidized to imine **vi** *via* **ii** and **iii**, which was ring opened by cleavage of the C(2)–C(3) bond. On the other hand in the case of radical reaction, the amino group would be oxidized to give **iv** which would give **vi** by ring opening and oxidation. Intermediate **vi** would be recycled to furnish the imidazole **2** *via* **vii**. Similar reaction mechanisms seem to operate with other Lewis acids [Ni(II), Al(III), Cu(I)].

In conclusion, we have found that the ring transformation of **1** into **2** could be successfully carried out by using Lewis acidic metal salts and oxidizing agents in methanol. It is noteworthy that even nonoxidative Lewis acidic metal salts were effective for the transformation, if oxidizing agents were present in the reaction medium.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were measured with an IR-810 machine (Nihon Bunko Spectroscopic Co., Ltd.). ^1H-NMR spectra were recorded with a JEOL JNM-EX-270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL JMS-DX 300 spectrometer.

General Procedure for Preparation of 2-Methoxy-1*H*-imidazole (2) Lewis acid and oxidizing agent were added to a solution of 5-aminopyrimidin-4-(3*H*)-one (**1**) (100 mg, 0.5 mmol) in dry methanol (10 ml). Stirring was continued for 0.5—3 h at room temperature or under reflux. The reaction mixture was poured into water, and extracted with dichloromethane. The dichloromethane extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was purified by silica gel column chromatography (n-hexane : EtOAc = 2 : 1) to furnish 2-methoxy-5-methyl-4-phenylcarbamoyl-1H-imidazole (**2**), which was identical with an authentic sample obtained by the reported method[3] on the basis of IR, ^{1}H-NMR, and mass spectral comparisons.

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References

1) *a*) D. J. Brown, "The Pyrimidines," Interscience Publishers, New York, 1962; *b*) D. J. Brown, "The Chemistry of Heterocyclic Compounds. The Pyrimidines," Supplement I, ed. by A. Weissberger and E. C. Taylor, Wiley-Interscience Publishers, New York, 1970.
2) *a*) T. Ueda and J. Sakakibara, *Chem. Pharm. Bull.*, **32**, 2863 (1964); *b*) T. Ueda, I. Matsuura, N. Murakami, S. Nagai, J. Sakakibara, and M. Goto, *Tetrahedron Lett.*, **29**, 4607 (1988); *c*) I. Matsuura, T. Ueda, N. Murakami, S. Nagai, and J. Sakakibara, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2821.
3) I. Matusura, T. Ueda, N. Murakami, S. Nagai, and J. Sakakibara, *J. Chem. Soc., Chem. Commun.*, **1991**, 1688.
4) T. Ueda, N. Oda, and I. Ito, *Chem. Pharm. Bull.*, **28**, 2144 (1980).
5) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, John Wiley and Sons, Inc., New York, 1967, p. 508.