A Facile Ring Transformation of 5-Aminopyrimidin-4(3*H*)-one into 2-Alkoxy-1*H*-imidazoles in the Presence of Oxidative Metal Salts and Alkyl Alcohols

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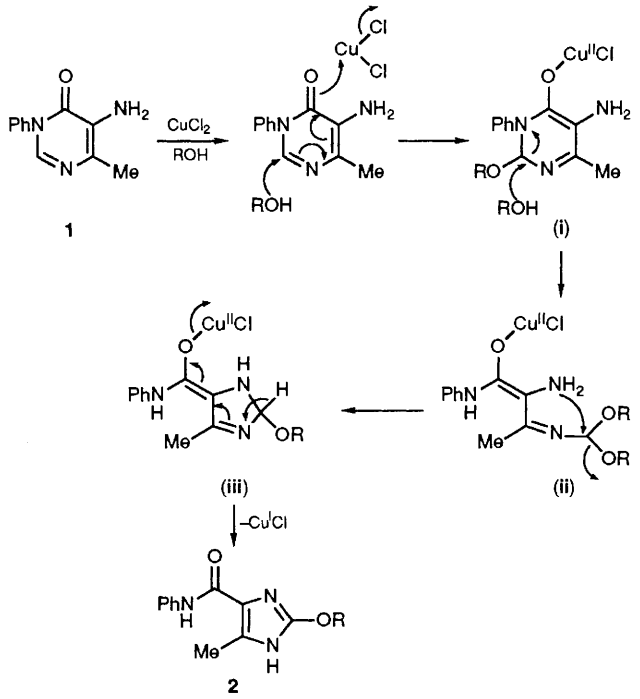
5-Amino-6-methyl-3-phenylpyrimidin-4(3*H*)-one **1** was transformed into 2-alkoxy-1*H*-imidazoles **2a–f** by treatment with various oxidative metal salts such as $CuCl_2$, $CuBr_2$, $Cu(NO_3)_2$, $CuSO_4$, $Tl(NO_3)_3$, $FeCl_3$ and $Pb(OAc)_4$ in alkyl alcohols.

Pyrimidines or pyrimidinones are important materials in view of their potential biological activities, and various studies on their syntheses and reactions have been reported.[1] In the course of medicinal and chemical studies of pyrimidones in our laboratory,[2] we previously found an interesting ring transformation of 5-acylaminouracils or 5-acylaminopyrimidinones into imidazoles.[3] The reaction involves the ring opening of pyrimidinones by aqueous sodium hydroxide and recyclization to give imidazoles. During continuing investigations of this ring transformation, we found another transformation of pyrimidinones into 2-alkoxy-1*H*-imidazoles using metal salts such as $CuCl_2$, $CuBr_2$, $Cu(NO_3)_3$, $CuSO_4$, $Tl(NO_3)_3$, $FeCl_3$ and $Pb(OAc)_4$ in various alkyl alcohols, which we report in this paper.

It was reported that treatment of enamines with $CuCl_2$ and oxygen gave rise to C–N bond cleavage,[4] and Tamaru[5]



a; R = Me **d**; R = Bu^n
b; R = Et **e**; R = Pr^i
c; R = Pr^n **f**; R = Bu^s

Scheme 1

Table 1 Transformation of **1** into **2a–f** in alkyl alcohols under reflux

Product[a]	M.p., *T*/°C	Metal salt (2.0 mol equiv.)	Solvent	Reaction time/h	Yield (%)
2a	193–194	$CuCl_2$	MeOH	3	59
2b	162–163	$CuCl_2$	EtOH	2.5	74
2c	189–190	$CuCl_2$	Pr^{n}OH	2	77
2d	112–113	$CuCl_2$	Bu^{n}OH	2	82
2e	170–172	$CuCl_2$	Pr^{i}OH	4	48
2f	138–139	$CuCl_2$	Bu^{s}OH	4	22

[a] All products gave satisfactory spectra and elemental analyses.

reported cleavage of cyclic urea derivatives with $CuCl_2$ and CuCl in methanol. We thought that the reaction of 5-amino-pyrimidin-4(3*H*)-one with $CuCl_2$ in methanol might bring about ring opening by cleavage of the C(2)–N(3) bond and recyclization might occur by nucleophilic attack of the 5-amino group on C(2) to give imidazoles. Thus, the reaction of 5-amino-6-methylpyrimidin-4(3*H*)-one **1**[6] with $CuCl_2$ (1.0 mol. equiv.) in refluxing methanol for 4 h gave 2-methoxy-5-methyl-4-phenylcarbamoyl-1*H*-imidazole **2a** in 54% yield. The structure of **2a**† was established on the basis of ^1H and ^{13}C NMR, IR, UV and mass spectroscopy. Its UV spectrum was similar to that of 2,5-dimethyl-4-phenylcarbamoyl-1*H*-imidazole (λ_{max} 269 nm, ε 23 800), which was obtained by treatment of 5-acetamido-6-methyl-3-phenylpyrimidin-4(3*H*)-one with 5% aqueous sodium hydroxide in ethanol.[3]

Since the methoxy group of **2a** seemed to originate from methanol, the reaction of **1** with $CuCl_2$ was examined in various alkyl alcohols: ethyl, n-propyl, n-butyl, isopropyl, and *sec*-butyl (Table 1). In the case of primary alcohols, the yields were 74–82%, while the yields were reduced when secondary alcohols were used as solvent. With *tert*-butyl alcohol as solvent, no reaction was observed.

Table 2 Transformation of **1** and **2a** in the presence of metal salts in MeOH under reflux unless noted otherwise

Product	Metal salt (mol equiv.)	Reaction time/h	Yield (%)
2a	$CuCl_2$ (1.0)	4	54
2a	$CuCl_2$ (2.0)	3	59
2a	$CuCl_3$ (3.0)	1.5	62
2a	$CuBr_2$ (2.0)	1	54
2a	$Cu(NO_3)_2$ (2.0)	15	51
2a	$CuSO_4$ (10)	24	71
2a[a]	$Tl(NO_3)_3 \cdot 3H_2O$ (1.0)	3	51
2a	$FeCl_3$ (10)	10	47
2a[a]	$Pb(OAc)_4$ (1.0)	1.5	31

[a] At room temperature.

In order to improve the yield of **2a**, we examined the reaction of **1** with different amounts of $CuCl_2$, but the amount had little effect on the yield. Next, we examined other metal salts such as $CuBr_2$, $Cu(NO_3)_2$, $CuSO_4$, $Tl(NO_3)_3$, $FeCl_3$ and $Pb(OAc)_4$ (Table 2); $CuSO_4$ gave the best yield. No reaction was observed when CuCl was used. Consequently, it appears that the oxidative activity of Cu^{II} is essential.‡ Other oxidative metal salts such as Tl^{III}, Fe^{III} and Pb^{IV} were also effective.

It therefore seems that the reaction of **1** with metal salts involves an oxidation process. A possible mechanism is shown in Scheme 1. Initial nucleophilic attack by the alcohol on C(2) aided by chelation of copper(II) to the C(4) carbonyl function would form intermediate (**i**). Ring opening and rotation (**ii**) followed by recyclization would give (**iii**), which would form **2** because of the oxidative activity of Cu^{II}. There are some reports on oxidative reactions with copper(II) halides.[7]

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† *Spectral data* of **2a**: Columnar crystals (from Pr^i_2O–hexane), m.p. 193–194 °C; ν_{max}/cm^{-1} (KBr) 3360, 1640 and 1520; λ_{max} 267 nm (ε 23 900); δ_H (100 MHz, $CDCl_3$) 2.54 (3H, s, 5-Me), 4.01 (3H, s, OMe), 7.06–7.68 (5H, m, Ph), 8.31 (1H, s, NH) and 8.82 (1H, s, NH); δ_C (67.5 MHz, $CDCl_3$) 162.6 (C=O), 151.4 (C-2), 138.1 (C-1′), 129.3 (C-4), 128.9 (C-3′, -5′), 125.1 (C-5), 123.8 (C-4′), 119.9 (C-2′, -6′), 56.5 (OMe) and 10.8 (5-Me); *m/z* (%): 231 (M^+, 75) and 139 (M^+, 100).

‡ This transformation was observed only when oxidative high-valent metal salts were used. Metal salts such as CuCl, CuBr, CuI and $FeCl_2$ were ineffective.