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Ruthenium Complex-Catalyzed Facile Synthesis of 2-Substituted Benzo-azoles

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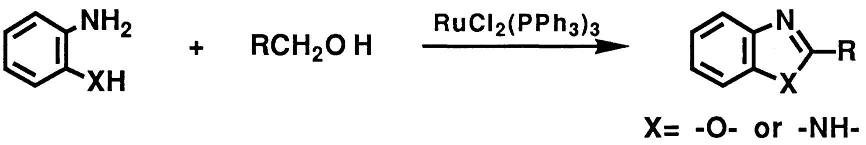
Ruthenium complex shows high catalytic activity for the reaction of 2-aminophenol with primary alcohols to give the corresponding 2-substituted benzoxazoles in high yields. Similarly, 2-substituted benzimidazoles are also synthesized readily by the ruthenium catalyzed reaction of 1,2-phenylenediamine with primary alcohols.

Since interest in many of oxazole and imidazole derivatives has been stimulated because of their application in industry and agriculture, and because of their biological and analytical importance,$^{1)}$ numerous methods have been reported for the preparation of these compounds.$^{2a,b)}$ However, little is known on transition-metal complex-catalyzed synthesis of them. In the course of our study on ruthenium complex catalysis,$^{3)}$ we disclose herein a first example of ruthenium-catalyzed facile synthesis of benzo-azoles by the condensation reaction of 2-aminophenol and 1,2-phenylenediamine with primary alcohols (Eq. 1).



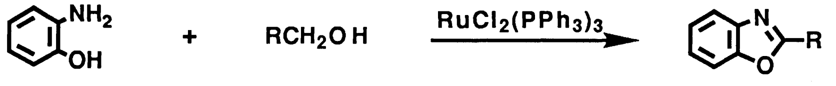
(1)

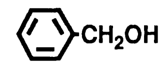
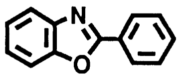
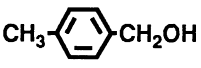
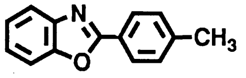
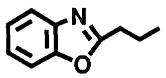
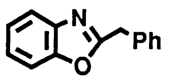
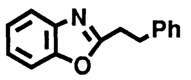
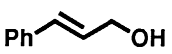
The reaction of 2-aminophenol with benzyl alcohol is typical. A mixture of 2-aminophenol (3.0 mmol), benzyl alcohol (9.0 mmol) and $RuCl_2(PPh_3)_3$ (0.10 mmol) in 10 ml toluene was placed in a 50 ml stainless steel autoclave under an argon atmosphere and stirred at 215 °C for 6 h. The product was isolated by a column chromatography (silica gel) and identified as 2-phenylbenzoxazole by means of ^1H NMR, ^{13}C NMR, elemental analysis and MS.

As shown in Table 1, 2-substituted benzoxazoles were generally obtained by the condensation reaction of 2-aminophenol with primary alcohols in moderate to high yields. Only when cinnamyl alcohol was employed in the reaction, the corresponding benzoxazole was not obtained at all (run 6), probably owing to Michael type condensation and/or polymerization of the generated benzoxazole with cinnamyl alcohol.[4] Furthermore, secondary alcohol such as 2-octanol did not react with 2-aminophenol and 2-aminophenol was quantitatively recovered after the reaction. Concerned with the reaction temperature, the present reaction could proceed at 200 °C but at 180 °C, only *N*-alkylation of 2-aminophenol with alcohol proceeded and 2-(*N*-alkylamino)phenol was obtained as a main product.

In addition, the present reaction is characteristic of ruthenium catalyst, but other group 8 metal complexes such as $RhCl(PPh_3)_3$ did not show the catalytic activity. Among the ruthenium complexes, $RuCl_2(PPh_3)_3$ is the most effective catalyst and the catalytic activities of $RuCl_3 \cdot nH_2O$, $RuCl_3 \cdot nH_2O\text{-}P(OBu)_3$ and $RuH_2(PPh_3)_4$ were low.

Table 1. Ruthenium-Catalyzed Synthesis of 2-Substituted Benzoxazoles[a]



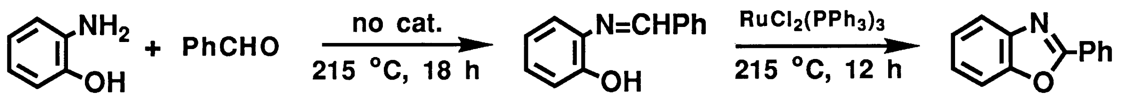
Run	Alcohol	Product	Yield/%[b]
1			80 (85)
2			62
3	n-BuOH		60
4			56
5			48
6		-	-

a) 2-Aminophenol (3.0 mmol), alcohol (9.0 mmol), $RuCl_2(PPh_3)_3$ (0.10 mmol), toluene (10 ml) at 215 °C for 5 h under an argon atmosphere. b) Isolated yields. Figure in parentheses is GLC yield.

Similarly, 2-substituted benzimidazoles were also synthesized readily in high yields by the reaction of 1,2-phenylenediamine with primary alcohols (Table 2). On the contrary to the case of synthesis of benzoxazoles, cinnamyl alcohol gave a product in which the double bond was hydrogenated (run 6).

In order to investigate the mechanism, we tried to examine the reaction of 2-aminophenol with benzaldehyde in the absence of $RuCl_2(PPh_3)_3$. After the reaction, only 2-(*N*-benzylideneamino)phenol was obtained in 72% yield and further cyclization could not proceed. In fact, 2-(*N*-benzylideneamino)phenol converted into

2-phenylbenzoxazole quantitatively by adding a catalytic amount of $RuCl_2(PPh_3)_3$ (Eq. 2).

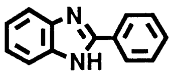
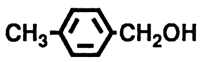
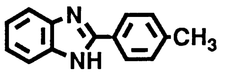
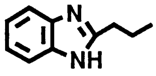
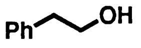
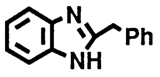
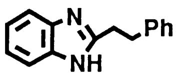
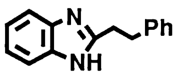


(2)

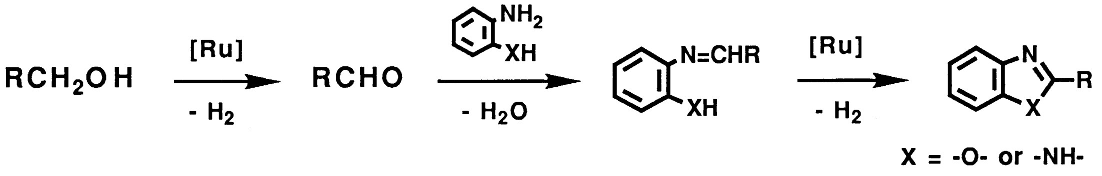
Thus, even though the detail mechanism of the present reaction is not clear at this stage, the ruthenium complex operates as a dual catalyst for the cyclization step of 2-iminophenols to the corresponding 2-substituted benzoxazoles,[5] as well as for the oxidation step of primary alcohols to aldehydes.[3,8] From these results, one of the possible reaction pathways is illustrated in Scheme 1.

Further mechanistic study and application of the present reaction to the synthesis of other azoles are now in progress.

Table 2. Ruthenium-Catalyzed Synthesis of 2-Substituted Benzimidazoles[a)]

Run	Alcohol	Time/h	Product	Yield/%[b)]
1		20		80
2		24		71
3	n-BuOH	8		51
4		8		79
5		8		72
6		8		75

a) 1,2-Phenylenediamine (3.0 mmol), alcohol (9.0 mmol), $RuCl_2(PPh_3)_3$ (0.10 mmol), toluene (10 ml) at 200 °C under an argon atmosphere. b) Isolated yields.



Scheme 1.

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5) It is essential to add the oxidant such as $H_2[Pb(H_2PO_4)_2(HPO_4)_2]$ or $Cu(OAc)_2$ for the cyclization of 2-iminophenols6) and amino Schiff bases.7)

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