study.

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1. In writing the formula for an aqueous ion, we will omit coordinated wate molecules except for Eq. (1).
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Ruthenium Complex Catalyzed Synthesis of 2-Substituted Benzoxazoles from *o*-Aminophenol and Alcohol with Spontaneous Hydrogen Evolution

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o-Aminophenols react with alcohols in the presense of a catalytic amount of ruthenium catalyst at 180℃ to give 2-substituted benzoxazole in good yield. The yields of 2-substituted benzoxazoles were affected by the yield of N-alkylation compound from *o*-aminophenol and alcohol as starting materials. During the reaction, a stoichiometric amount of hydrogen was spontaneously evolved into the gas phase.

Introduction

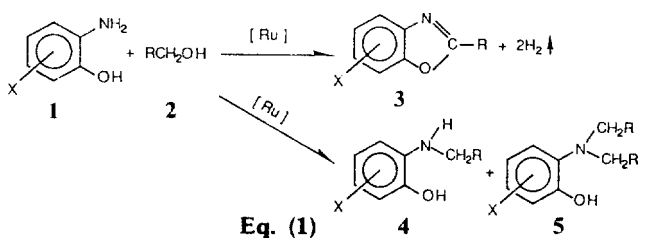
Synthesis of bezoxazole derivatives from readily available starting materials have recently received some attention[1]. The synthesis of benzoxazoles often carried out by heating the *o*-aminophenol with the carboxylic acid or its derivatives, such as the acid chloride, anhydride, an ester, amide or nitrile[2].

We have recently developed rutheium complex catalyzed N-methylation[3], N-alkylation[4,5], N-heterocyclization of amines[6-8], where the ruthenium complex efficiently activates alcohol functionalities to give nitrogen compounds.

Here we repot synthesis of 2-substituted benzoxazoles, using transition metal complexes as a catalyst. The ruthenium complex catalyzed reaction between *o*-aminophenol and alcohols to give the corresponding 2-substituted benzoxazoles.

Results and Discussion

o-Aminophenol (**1**) reacts with alcohol (**2**) in the presence of a catalytic amount of a ruthenium complex to give 2-substituted benzoxazoles (**3**) in good yield (Eq. 1).



Eq. (1)

Table 1. Effect of Molar Ratio and Temperature on the Synthesis of 2-Ethylbenzoxazole from *o*-Aminophenol and 1-Propanol[a]

Run	[Alcohol]/[Amine][b]	Temp., ℃	Product yield/%[c]
1	1.5	180	65 (58)[d]
2	2.0	180	52
3	2.5	180	41
4	3.0	180	27
5	4.0	180	13
6	1.5	200	65
7	1.5	150	59
8	1.5	120	21
9	1.0	180	49
10	0.5	180	26[e]

[a] *o*-Aminophenol (2.2 g, 20 mmol), $RuCl_2(PPh_3)_3$ (198 mg, 0.2 mmol), dioxane (10 mL), reaction time; 5 h. [b] Molar ratio of 1-propanol to *o*-aminophenol. [c] Determined by GLC based on the amount of *o*-aminophenol used. [d] Isolated yield. [e] Determined by GLC based on the amount of 1-propanol used.

Table 2. Solvent Effect of the Synthesis of 2-Ethylbenzoxazole from *o*-Aminophenol and 1-Propanol[a]

Run	Solvent	Product yield/%[b]
1	dioxane	65 (58)[c]
11	diglyme	61
12	1,3-dimethyl-2-imidazolinone	49
13	1-methyl-2-pyrrolidinone	37
14	N,N-dimethylformamide	10
15	acetonitrile	2
16	dimethylsulfoxide	0

[a] *o*-Aminophenol (2.2 g, 20 mmol), 1-propanol (2.2 mL, 30 mmol), $RuCl_2(PPh_3)_3$ (198 mg, 0.2 mmol), solvent (10 mL), at 180℃, 5 h. [b] Determined by GLC based on the amount of *o*-aminophenol used. [c] Isolated yield.

In order to optimize the reaction conditions effects of molar ratio and temperature were examined with *o*-aminophenol and 1-propanol as the substrate (Table 1). The yield of product, 2-ethylbenzoxazole, was considerably affected depending upon a molar ratio (runs 1-5, 9-10). The highest yield of 2-ethylbenzoxazole was realized at the molar ratio of 1.5 (run 1). As the molar ratio was changed from 1.5, the yield of 2-ethylbenzoxazole was significantly decreased. Instead, a large amount of N-alkylated products, N-propyl-*o*-aminophenol (**4**) and N,N-dipropyl-*o*-aminophenol (**5**) were isolated in 32% and 44% (run 5). The reaction temperature was to be higher than 160℃. At 120℃, the conversion rates were so low that the yield of 2-ethylbenzoxazole was considerably reduced (run 8).

The product yield was also affected by the solvent employed (Table 2). The highest yield was realized in dioxane (run 1). The reaction proceeded similar in diglyme. The reactions were considerably suppressed in N,N-dimethylformamide, acetonitrile, and dimethylsulfoxide which seemed to interact strongly with transition metal center (runs 14-16)[9].

Table 2. Effect of Catalyst on the Synthesis of 2-Ethylbenzoxazole from *o*-Aminophenol and 1-Propanol[a]

Run	Catalyst	Product yield/%[b]
1	$RuCl_2(PPh_3)_3$	66 (58)[c]
17	$RuCl_3 \cdot nH_2O + 3PPh_3$	65
18	$RuCl_3 \cdot nH_2O + 3PBu_3$	58
19	$RuCl_3 \cdot nH_2O + 3PPt_3$	56
20	$RuCl_3 \cdot nH_2O + 3P(OBu)_3$	17
21	$RuCl_3 \cdot nH_2O$ + 1.5dppe	0
22	$RuCl_3 \cdot nH_2O$	0
23	—	0

[a] *o*-Aminophenol (2.2 g, 20 mmol), 1-propanol (2.2 mL, 30 mmol), Catalyst (0.2 mmol), dioxane (10 mL), at 180℃, 5 h. [b] Determined by GLC based on the amount of *o*-aminophenol used. [c] Isolated yield.

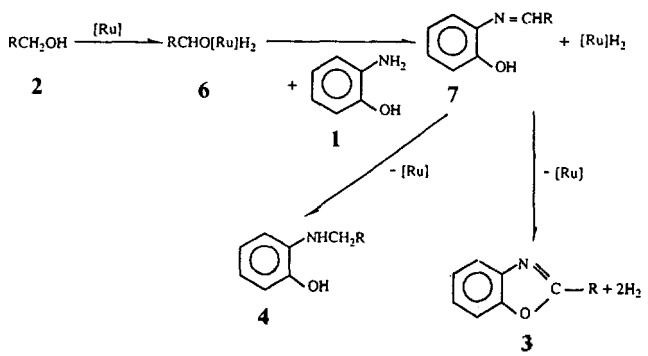
In this reaction, the catalyst precursor had a critical effect (Table 3). Dichlorotris(triphenylphosphine)ruthenium, $RuCl_2(PPh_3)_3$, exhibited the highest activity, giving 2-ethylbenzoxazole in 66% yield (run 1). $RuCl_3 \cdot nH_2O$ combined with PPh_3 showed the same catalytic activity as $RuCl_2(PPh_3)_3$ (run 17), suggesting that $RuCl_2(PPh_3)_3$ is formed in situ from $RuCl_3 \cdot nH_2O$ and PPh_3[10]. Ruthenium combined with PBu_3 or PEt_3 showed similar catalytic activity (runs 18, 19). Ruthenium combined with $P(OEt)_3$ or bis(1,2-diphenylphosphino)ethane, DPPE, as ligands exhibited little or no activitity (runs 20, 21). In the absence of either $RuCl_3 \cdot nH_2O$ or phosphine, the substrates were recovered quantitatively (runs 22-23).

It is well-known that phosphorus (III) ligands modify or improve activities of transition metal catalyst[11].

Under similar reaction conditions, rhodium and palladium complex such as $RhCl(PPh_3)_3$, $RhH(PPh_3)_4$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ showed low catalytic activities giving only trace of 2-substituted benzoxazoles with low conversion of the substrates.

Other representive *o*-aminophenols reacted with alcohols in the same manner (Table 4). Methyl and chloro substituents on the phenyl ring did not affect the reaaction and the corresponding 2-substituted bezoxazoles were obtained in good yields (runs 24-27). However, an attempted synthesis of benzoxazole itself from *o*-aminophenol and methanol was unsuccessful (run 28).

A possible reaction pathway for these reaction is postulated as follows (Eq. 2).



Eq. (2)

Table 4. Syntheses of 2-Substituted Benzoxazoles from *o*-Aminophenol and Alcohol[a]

Run	*o*-Aminophenol	Alcohol	Product	Yield/%[b]
24	2-amino-4-chlorophenol	propanol	5-chloro-2-ethylbenzoxazole	52 (38)
25	2-amino-4-methylphenol	propanol	2-ethyl-5-methylbenzoxazole	68 (61)
26	2-amino-5-methylphenol	propanol	2-ethyl-6-methylbenzoxazole	65
27	6-amino-2,4-dimethylphenol	propanol	5,7-dimethyl-2-ethylbenzoxazole	65 (62)
28	o-aminophenol	methanol	benzoxazole	0
29	o-aminophenol	ethanol	2-methylbenzoxazole	47
30	o-aminophenol	butanol	2-propylbenzoxazole	72
31	o-aminophenol	2-methyl-1-propanol	2-iso-propylbenzoxazole	62 (53)
32	o-aminophenol	3-methyl-1-butanol	2-(2-iso-butyl)-benzoxazole	57

[a] *o*-Aminophenol (20 mmol), alcohol (30 mmol), $RuCl_2(PPh_3)_3$ (198 mg, 0.2 mmol), dioxane (10 mL), at 180℃, 5 h. [b] Determined by GLC based on the amount of alcohol used. Figures in parentheses show isolated yields.

A hydroxy group of the alcohol (**2**) oxidatively coordinates to the active catalyst center. Oxidation pathways *via* alkoxohydrido complexes have been proposed by several authors[12]. Nucleophilic attack of the aminophenol (**1**) on the resulting aldehyde intermediate (**6**) yields the Schiff base complex (**7**). Benzoxazoles (**3**) are formed through intramolecular cyclization of Schiff base complex (**7**). A chelate intermediate of 7 should be a key species for the present N-heterocyclization. Otherwise N-alkyl-(**4**) or N,N-dialkyl-aminophenol (**5**) were obtained from hydrogenation of the Shiff base complex (**7**). In the present N-heterocyclization, the yield of the benzoxazole was appreciably affected by the molar ratio of *o*-aminophenol (**1**) to alcohol (**2**) (vide supra; Table 1, runs 1-5). 2-Ethylbenzoxazole was obtained in the highest yield at the molar ratio of 1.5 in the reaction of *o*-aminophenol and 1-propanol. Using excess of alcohol may be suppressive for formation of the chelate intermediate of 7.

Experimental

Commercially available *o*-aminophenols, alcohols, PPh_3, PBu_3, PEt_3, $P(OBu)_3$, and the solvent were purified by either distillation or by recrystallization before use. Diphenylphosphinoethane (dppe) was purchased from Alfa Division and used without further purification. $RuCl_3 \cdot nH_2O$ (mainly $n=3$) was purchased from Wako Pure Chemical Industries and used without further purification. $RuCl_2(PPh_3)_3$[13], $RhCl(PPh_3)_3$[14], $RhH(PPh_3)_4$[15], $Pd(PPh_3)_4$[16], $PdCl_2(PPh_3)_4$[17] were prepared according to literature procedures.

General Proceddure

A typical reaction of *o*-aminophenol with 1-propanol is described as a representative reaction procedure. A stainless steel reactor (50 mL, Taiatsu Glass Industry, TVS-1 type) containing a glass liner was used in the reaction. Under argon stream, dioxane (10 mL), *o*-aminophenol (2.2 g, 20 mmol), 1-propanol (2.2 mL, 30 mmol), and $RuCl_2(PPh_3)_3$ (192 mg, 0.20 mmol, 1.0 mol% based on *o*-aminophenol used) were added into the glass liner set in the reactor. After the reactor was sealed, an air purge was confirmed by three pressurization (10 atm)-depressurization sequences with argon. The reactor was heated to 180℃ ain 30 min in the mantle heater and thermostated at this temperature with stirring for 5 h. The reaction was terminated by rapid cooling and the reactor was discharged. Hydrogen evolution was measured by means of burett and the gaseous was product was analyses by GLC (active carbon). The product was isolated from clear dark brown solution by vacuum distillation and a flash column chromatography (hexane : ethyl acetate=9 : 1, aluminium-oxide 90, Merck, Art. 1076). 2-Ethylbenzoxazole was isolated in 58% yield.

Analytical Procedure

All boiling points and melting points were uncorrected. The products were identified by analysis of ^{1}H- and ^{13}C-NMR and mass spectra, which were all identical with those of authentic samples. The ^{1}H-NMR spectra were obtained with a JEOL GSX-270 and ^{13}C-NMR spectra at 25.05 MHz with a JEOL JNM FX-100 spectrometers. Samples were dissolved in $CDCl_3$, and chemical shifts were expressed relative to Me_4Si as an internal standard. Mass spectra were recorded with a VG 7070E. The GLC analysis was made by Varian Vista 6000 with a column (3 mm×3 m) packed aith OV-17 on Chromosorb W, 60-80 mesh. In some cases, the yields of product were determined by the internal standard method according to the calibration curve obtained for each product in a separate experiment.

2-ethylbenzoxazole. Colorless oil; bp. 77℃ (4.7 mmHg); ^{1}H-NMR 1.24 (t, 3H, CH_3), 2.75 (q, 2H, CH_2), 7.11-7.69 (m, 4H, Ar); ^{13}C-NMR 15.7 (q, CH_3), 30.1 (t, CH_2), 111.4 (d), 121.0 (d), 125.3 (d), 125.9 (d), 140.1 (s), 149.5 (s), 151.8 (s); MS: m/e 147 (M^+).

5-chloro-2-ethylbenzoxazole. Colorless oil; bp. 72℃ (1.1 mmHg); ^{1}H-NMR 1.28 (t, 3H, CH_3), 2.81 (q, 2H, CH_2), 7.31-8.12 (m, 3H, Ar); ^{13}C-NMR 16.1 (q, CH_3), 30.3 (t, CH_2), 114.4 (d), 124.3 (d), 127.8 (d), 137.6 (s), 141.1 (s), 154.7 (s), 151.8 (s); MS: m/e 181 (M^+).

2-ethyl-5-methylbenzoxazole. Colorless oil; bp. 69℃ (4.2 mmHg); ^{1}H-NMR 1.23 (t, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.76 (q, 2H, CH_2), 7.19-7.53 (m, 3H, Ar); ^{13}C-NMR 15.6 (q, CH_3), 22.4 (q, CH_3), 30.0 (t, CH_2), 112.3 (d), 121.9 (d), 128.4 (d), 140.1 (s), 140.9 (s), 150.7 (s), 152.6 (s); MS: m/e 161 (M^+).

2-ethyl-6-methylbenzoxazole. Colorless oil; bp. 79℃ (6.1 mmHg); ^{1}H-NMR 1.22 (t, 3H, CH_3), 2.41 (q, 3H, CH_3), 2.71 (q, 2H, CH_2), 7.03-7.51 (m, 3H, Ar); ^{13}C-NMR 15.3 (q, CH_3), 23.0 (q, CH_3), 30.4 (t, CH_2), 109.8 (d), 121.2 (d), 126.3 (d), 140.1 (s), 140.7 (s), 151.6 (s), 152.7 (s); MS: m/e 161 (M^+).

5,7-dimethyl-2-ethylbenzoxazole. Colorless oil; bp.

53℃ (0.9 mmHg); ^{1}H-NMR 1.20 (t, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.50 (q, 3H, CH_3), 2.74 (q, 2H, CH_2), 6.94-7.31 (m, 2H, Ar); ^{13}C-NMR 15.5 (q, CH_3), 22.6 (q, CH_3), 23.7 (q, CH_3), 30.2 (t, CH_2), 120.9 (d), 124.7 (d), 136.3 (s), 140.1 (s), 143.2 (s), 150.9 (s), 153.4 (s); MS: m/e 175 (M^+).

2-methylbenzoxazole. Colorless oil; bp. 65℃ (4.5 mmHg); ^{1}H-NMR 2.61 (t, 3H, CH_3), 7.13-7.76 (m, 4H, Ar); ^{13}C-NMR 22.3 (q, CH_3), 111.6 (d), 121.1 (d), 125.2 (d), 126.2 (d), 140.4 (s), 149.9 (s), 152.7 (s); MS: m/e 133 (M^+).

2-propylbenzoxazole. Colorless oil; bp. 63℃ (3.1 mmHg); ^{1}H-NMR 0.92 (t, 3H, CH_3), 1.69 (q, 2H, CH_2), 2.63 (t, 2H, CH_2), 7.10-7.63 (m, 4H, Ar); ^{13}C-NMR 13.9 (q, CH_3), 25.0 (t, CH_2), 37.4 (t, CH_2), 111.3 (d), 121.2 (d), 125.5 (d), 140.1 (s), 149.6 (s), 151.9 (s); MS: m/e 161 (M^+).

2-iso-propylbenzoxazole. Colorless oil; bp. 75℃ (4.4 mmHg); ^{1}H-NMR 1.26 (d, 6H, $2CH_3$), 2.94 (m, H, CH), 7.12-7.63 (m, 4H, Ar); ^{13}C-NMR 23.9 (q, $2CH_3$), 34.6 (d, CH), 111.5 (d), 121.1 (d), 125.3 (d), 125.8 (d), 140.3 (s), 150.1 (s), 152.3 (s); MS: m/e 161 (M^+).

2-(2-iso-butyl)-benzoxazole. Colorless oil; bp. 61℃ (1.8 mmHg); ^{1}H-NMR 0.93 (d, 6H, $2CH_3$), 1.89 (m, H, CH), 2.64 (d, 2H, CH_2), 7.14-7.67 (m, 4H, Ar); ^{13}C-NMR 22.2 (q, $2CH_3$), 30.1 (d, CH), 34.6 (t, CH_2), 111.5 (d), 121.0 (d), 125.4 (d), 126.3 (d), 141.3 (s), 150.6 (s), 152.1 (s); MS: m/e 175 (M^+).

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