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Transition Metal-Catalyzed N-Alkylation of NH Groups of Azoles with Alcohols

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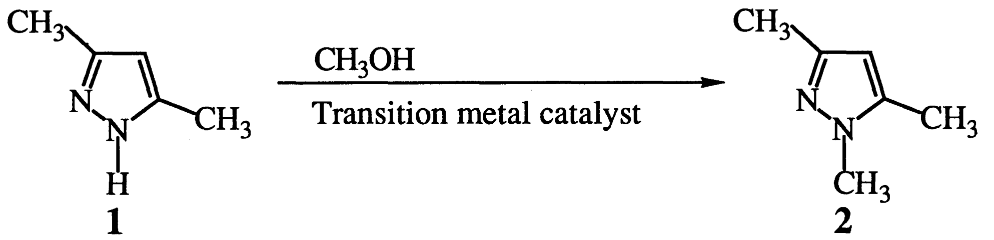
Azoles containing acidic NH-group react with various alcohols in the presence of catalytic amount of ruthenium-, rhodium-, and iridium-trialkylphosphite complexes to give the corresponding N-alkylated azoles in good to excellent yields.

Azoles, such as imidazole, pyrazole, and triazole, well-known as useful intermediates for fine chemicals, are prepared by various methods.[1)] The N-alkylation of NH groups is one of the important processes for synthesizing N-substituted azoles. However, because of weak basicities of azoles containing acidic NH groups, N-alkylation by alkyl halides or alkyl sulfonates under basic conditions is a general method. A large variety of methods are known for N-alkylation of amines.[2)] Recently, the N-alkylation of amines by using alcohols can be achieved by transition metal catalysts.[3)] In the course of our studies on the transition metal complex-catalyzed N-alkylation using alcohols, we found transition metal-trialkylphosphite complexes showed high catalytic activity for N-alkylation of acidic NH groups of azoles by alcohols. This reaction is unique because alkylation occurs under neutral conditions.

A typical procedure was as follows. A 40 ml stainless steel autoclave was charged azole (5 mmol), alcohol (20 mmol), transition metal catalyst (0.1 mmol, 2.0 mol% based on azole), trialkylphosphite (0.3 mmol), and 1,4-dioxane (20 ml). The mixture was heated at 200 °C for 15-20 h under 100 kg/cm^2 pressure of inert gas (nitrogen or argon). All products were identified by GLC and ^{1}H-NMR. The yields were determined by GLC analysis using internal standard methods .

Representative results of N-methylation of 3,5-dimethylpyrazole by methanol with various catalyst systems are listed in Table 1. Even with ruthenium trichloride alone as catalyst, the reaction proceeded moderately. Furthermore, the catalytic activity was large affected by the addition of ligands. Especially, ruthenium trichloride-trialkylphosphite systems showed very high catalytic activity (Runs 2,3, and 6). On the contrary, the addition of triphenylphosphine or triphenylphosphite suppressed the catalytic activity rather than ruthenium trichloride alone. Also, rhodium trichloride- and iridium trichloride-trialkylphosphite systems showed high catalytic activity close to ruthenium trichloride-

Table 1. N-Methylation of 3,5-dimethylpyrazole by methanol with various catalyst systems[a)]

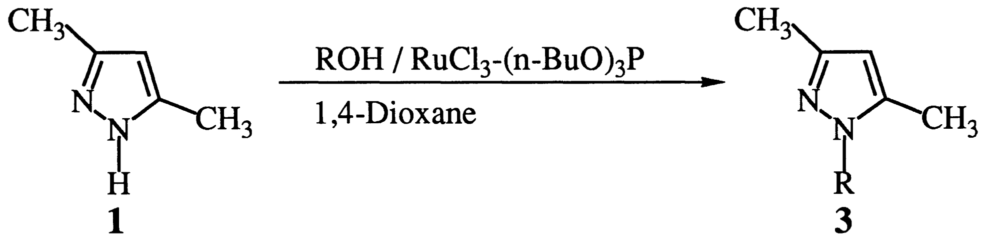


Run	Catalyst	Solvent	Conv. of **1** %	Select. of **2** %
1	$RuCl_3$	1,4-dioxane	49.0	26.4
2[b)]	$RuCl_3$-(n-BuO)$_3$P	1,4-dioxane	74.8	77.4
3	$RuCl_3$-(nBuO)$_3$P	1,4-dioxane	97.6	96.0
4[c)]	$RuCl_3$-(i-PrO)$_3$P	1,4-dioxane	10.1	98.5
5[d)]	$RuCl_3$-(i-PrO)$_3$P	1,4-dioxane	34.2	100.0
6	$RuCl_3$-(i-PrO)$_3$P	1,4-dioxane	99.0	100.0
7	$RuCl_3$-(i-PrO)$_3$P	methanol	96.1	100.0
8	$RuCl_3$-(nBuO)$_3$P	benzene	92.8	100.0
9	$RuCl_3$-(nBuO)$_3$P	acetonitrile	100.0	96.5
10	$RuCl_3$-(nBuO)$_3$P	N-methylpyrrolidone	87.9	100.0
11	$RuCl_3$-(i-PrO)$_3$P	hexane	92.8	100.0
12	$RuCl_3$-(i-PrO)$_3$P	H_2O	7.2	100.0
13[b)]	$RuCl_2(PPh_3)_3P$	1,4-dioxane	11.6	29.3
14[b)]	$RuCl_3$-(PhO)$_3$P	1,4-dioxane	12.8	23.0
15	$RuHCl(CO)(PPh_3)_3$	1,4-dioxane	14.0	87.3
16	$RuH_2(CO)(PPh_3)_3$	1,4-dioxane	3.4	48.5
17	$RuH_2(PPh_3)_4$	1,4-dioxane	4.3	88.8
18	$RhCl_3$-(n-BuO)$_3$P	1,4-dioxane	94.2	95.9
19	$RhCl(PPh_3)_3$	1,4-dioxane	26.1	100.0
20	$RhH(PPh_3)_4$	1,4-dioxane	22.5	94.0
21	$IrCl_3$-(n-BuO)$_3$P	1,4-dioxane	95.0	95.4

a) Reaction conditions; **1** 5 mmol, CH_3OH 20 mmol, catalyst 0.1 mmol, solvent 20 ml, N_2 100 kg/cm^2, temp 200 °C, time 15 h. b) N_2 10 kg/cm^2. c) Temp 150 °C. d) Temp 180 °C.

trialkylphosphite system (Runs 18 and 21). Other metal complexes shown in Table 1 showed poor catalytic activity. The conversions and selectivities could be enhanced by either elevating the pressure of inert gas or raising the reaction temperature (Runs 2-6). Except water, various solvents could be employed for this reaction, and no solvent effect was observed (Runs 6-12).

Table 2. N-Alkylation of 3,5-dimethylpyrazole by various alcohols with ruthenium trichloride-tributylphosphite system[a)]



Run	Alcohol	Conv. of **1**	Select. of **3**
		%	%
1	CH_3OH	97.6	96.0
2	C_2H_5OH	32.0	100.0
3	n-C_3H_7OH	71.7	99.3
4	i-C_3H_7OH	0	0
5	n-C_4H_9OH	28.7	90.9
6	t-C_4H_9OH	0	0
7	$C_6H_5CH_2OH$	100.0	100.0
8	$CH_2{=}CHCH_2OH$	81.3	38.6
9	$C_2H_5OC_2H_4OH$	25.1	45.8
10	CF_3CH_2OH	33.9	86.9
11	$C_2H_5OCOCH_2OH$	94.6	27.5

a) Reaction conditions; **1** 5 mmol, alcohol 20 mmol, $RuCl_3$ 0.1 mmol, tributylphosphite 0.3 mmol, 1,4-dioxane 20 ml, N_2 100 kg/cm^2, temp 200 °C, time 15 h.

The N-alkylation of 3,5-dimethylpyrazole by various alcohols with ruthenium trichloride-tributhylphosphite catalyst was examined (Table 2). Methanol and benzylalcohol showed high reactivity for this reaction to give the corresponding N-alkylated pyrazoles in excellent yields (Runs 1 and 7). Similarly, N-alkylation proceeded when other primary alcohols were employed to give N-alkylated products in moderate yields (Runs 2,3,5, and 8-11). The N-alkylation did not proceed when secondary and tertiary alcohols were employed (Runs 4,6).

Similarly, various azoles were reacted with methanol under the same conditions to give the corresponding N-methylazoles in moderate to excellent yields (Table 3). The reactivity appears to be correlated with basicity (proton gained pKa) of azoles rather than its acidity (proton losed pKa).

Since the ruthenium catalysts were reported as an effective catalyst for the hydrogen transfer reaction,[5)] one of the possible reaction routes including hydrogen transfer from alcohol, formation of Schiff base, and hydrogenation of it is proposed. Further studies on the reaction mechanism and optimization of the reaction are now in progress.

Table 3. N-Alkylation of various azoles by methanol with ruthenium trichloride-tributylphosphite system[a)]

Azole	Conv. of azole / %	Select. of N-methyl azole / %	Proton gained pKa[4)]	Proton losed pKa[4)]
Imidazole	99.5	98.6	7.2	14.5
Benzimidazole	100	91.9	5.6	12.9
3,5-Dimethylpyrazole	97.6	96.0	4.1	15.0
4-Methylpyrazole	92.1	92.5	3.0	14.7
Pyrazole	81.4	83.4	2.5	14.2
1,2,4-Triazole	57.2	83.3	2.5	10.0
Indazole	16.9	55.3	1.0	13.9
Pyrrole	40.0	62.7	-3.8	17.5

a) Reaction conditions; Azole 5 mmol, CH_3OH 20 mmol, $RuCl_3$ 0.1 mmol, tributylphosphite 0.3 mmol, 1,4-dioxane 20 ml, N_2 100 kg/cm^2, temp 200 °C, time 15 h.

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