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Ruthenium Catalyzed N-Methylation of Aminoarenes Using Methanol

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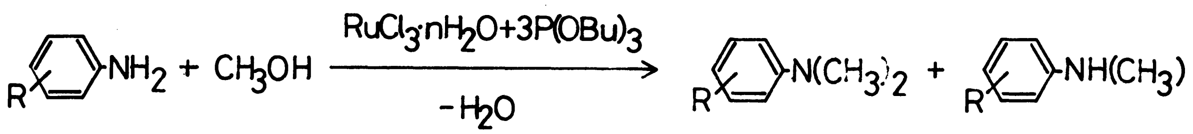
Methanol reacts with aminoarenes in the presence of a catalytic amount of ruthenium trichloride hydrate combined with tributylphosphite at 180 °C to give the corresponding N-methylaminoarenes in high yields.

We have recently developed ruthenium complex catalyzed N-alkylation[1,2] and N-heterocyclizations of amines,[3-5] where the ruthenium complex efficiently activates alcohol functionalities to give nitrogen compounds. With these catalyst systems, however, we could not utilize methanol as N-alkylating reagent.[1,2] Since methanol is one of the most promising chemical feedstocks[6,7] and N,N-dimethylaminoarenes are important class of amines,[8] we have been searching for an active catalyst system to utilize methanol.

N-Methylation of amines with methanol was performed over heterogeneous[9,10] catalysts under very severe reaction conditions (285-300 °C). As homogeneous catalyst, $RhH(PPh_3)_3$[11] and $RuCl_2(PPh_3)_3$[12] have been shown to be active for the N-methylation of aliphatic amines. However, no efficient catalyst has been reported for N-methylation of aminoarenes with methanol.[13] We now report here that a novel catalyst system, $RuCl_3 \cdot nH_2O\text{-}P(OBu)_3$, is highly active for the N,N-dimethylation of aminoarenes with methanol.

A general procedure is described as follows. A mixture of aminoarene (20 mmol), methanol (80 mmol, 3.2 cm^3), ruthenium trichloride hydrate (0.4 mmol, 105 mg, 2.0 mol% based on aminoarene), tributylphosphite (1.2 mmol, 0.32 cm^3) and 1,4-dioxane (10 cm^3) was stirred in a 50 cm^3 stainless reactor under argon atmosphere at 180 °C for 15 h.



(1)

1 2

Table 1. Influence of Ligands on the Reaction between Aniline and Methanol[a)]

Run	Catalyst	Conv./%[b)]	Product yield/%[c)]	
			1	2
1	$RuCl_3 \cdot nH_2O$ + $3P(OBu)_3$	99	80	6
2	$RuCl_3 \cdot nH_2O$ + $3P(OPr^i)_3$	76	46	30
3	$RuCl_3 \cdot nH_2O$ + $3P(OPh)_3$	87	40	22
4	$RuCl_3 \cdot nH_2O$ + $3P(OEt)_3$	85	44	23
5	$RuH_2(P(OEt)_3)_4$	79	30	34
6	$RuCl_3 \cdot nH_2O$	11	tr	11
7	$RuCl_2(PPh_3)_3$	68	3	23
8	$RuH_2(PPh_3)_4$	5	0	3
9	$RuCl_3 \cdot nH_2O$ + $3PBu_3$	9	0	8

a) Aniline (20 mmol), methanol (80 mmol), Ru-catalyst (0.4 mmol), 1,4-dioxane (10 cm^3), 180 °C, 15 h. b) Conversion of aniline. c) By GLC based on the amount of aniline used. See Eq. 1.

Activity of several catalyst systems was examined with aniline and methanol as the substrates (Table 1). Ruthenium trichloride hydrate with a tertiary phosphite was an effective catalyst precursor (runs 1-4). Particularly, ruthenium trichloride hydrate combined with tributylphosphite is the most effective to give N,N-dimethylaniline in high yield (run 1). However, $RuCl_2(PPh_3)_3$, which is an excellent catalyst for N-alkylation with higher primary alcohols such as ethanol and propanol,[1,2)] was not effective (run 7). More basic phosphorus ligand such as tributylphosphine was almost ineffective for this reaction (run 9). Ruthenium trichloride hydrate without phosphorus compound showed only low activity (run 6). Thus, the basicity of the added phosphorus ligand affects the catalytic activity drastically.

Table 2. N-Methylation of Various Aminoarenes with Methanol[a]

Run	Aminoarene	Catalyst[b]	Conv./%[c]	Product yield/%[d]	
				1	**2**
10	p-anisidine	A	100	(71)	
11	p-toluidine	A	100	(76)	
12	p-chloroaniline	A	100	(86)	
13[e]	N-methylaniline	A	88	60	-
14[e]	N-methylaniline	B	91	82	-
15[e]	N-ethylaniline	B	96	77[f]	-
16	cyclohexylamine	A	60	3	14

a) Aminoarene (20 mmol), methanol (80 mmol), catalyst (0.4 mmol), 1,4-dioxane (10 cm^3), 180 °C, 15 h. b) A: $RuCl_3 \cdot nH_2O + 3P(OBu)_3$, B: $RuCl_2(PPh_3)_3$.
c) Conversion of aminoarene. d) By GLC based on the amount of aminoarene charged. Figures in parentheses are isolated yields. See Eq. 1.
e) Methanol (40 mmol). f) N-Ethyl-N-methylaniline.

With the $RuCl_3 \cdot nH_2O$-$P(OBu)_3$ catalytic system, various primary aminoarenes were smoothly converted into N,N-dimethylated products in high yield, 70-90% (Table 2, runs 10-12). N-Methylaniline was also N-methylated by this procedure (run 13). $RuCl_2(PPh_3)_3$ was found to be active for N-methylation of N-alkylanilines (runs 13-14). Aliphatic amine such as cyclohexylamine afforded N-methylated products in only low yield (run 16).

These results indicated that a ruthenium catalyst combined with a phosphite ligand having lower basicity makes smooth N-methylation of primary aminoarenes with methanol. The mechanism of this reaction might be similar to that of N-alkylation of aminoarenes with higher alcohols, which includes a nucleophilic attack of the aminoarenes on formaldehyde intermediate generated by a hydrogen transfer from methanol.[2,3]

Thus, the novel catalyst system, $RuCl_3 \cdot nH_2O$-$P(OBu)_3$, activates methanol to provide the efficient method for N-methylation of aminoarenes.

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