Catalysis Letters 19 (1993) 339–344

Ruthenium complex-catalyzed synthesis of carbamates by dehydrogenative reaction of formamides with alcohols

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Received 27 January 1993; accepted 12 April 1993

In the presence of a catalytic amount of $RuCl_2(PPh_3)_3$, various alkyl N-arylcarbamates are obtained in 23–82% yields by dehydrogenative reaction of N-aryl substituted formamides with alcohols. The present reaction offers an alternative method for phosgene- and carbon monoxide-free synthesis of carbamates.

Keywords: Homogeneous catalyst; ruthenium complex; carbamate; formamide; alcohol

1. Introduction

N-aryl substituted carbamate is one of the most useful and important synthetic intermediates because of its applications in pharmacology, agriculture, and chemical industry [1]. Especially in chemical industry, alternative synthetic methods of carbamates have been recently studied in attempts to find a phosgene-free route to isocyanate, because carbamate can be transformed into isocyanate by thermal cracking [2]. Among them, reductive N-carbonylation of nitro compounds [3] and oxidative N-carbonylation of amines [4], both catalyzed by transition metals, represent interesting approaches to carbamate; the methods avoid the use of highly toxic and corrosive phosgene. However, these reactions require a poisonous carbon monoxide atmosphere. On the basis of our study on ruthenium complex-catalyzed activation of formyl C–H bonds [5,6], we directed our attention to the phosgene- and carbon monoxide-free synthesis of carbamate using formyl compounds, i.e., formamides, as a versatile carbonyl source [7]. In this paper, we wish to report ruthenium complex-catalyzed synthesis of alkyl N-arylcarbamates by dehydrogenative reaction of N-aryl substituted formamides with alcohols [8] [#1],

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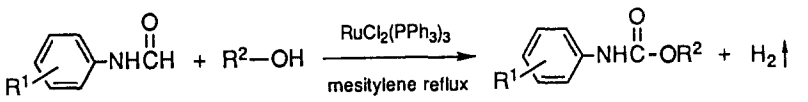
[#1] Electrochemical synthesis of carbamates from N-alkylformamides has been reported by BASF Co. Ltd.; see also ref. [8].



(1)

Noteworthy is that the reaction proceeds under an argon atmosphere, and neither carbon monoxide pressure nor atmosphere is required.

2. Experimental

Catalysts, $RuCl_2(PPh_3)_3$ [9], $RuHCl(CO)(PPh_3)_3$ [10], and $Ru(CO)_3(PPh_3)_2$ [11] were prepared according to the literature methods. $RuCl_3 \cdot nH_2O$ (mainly $n = 3$) was purchased from Mitsuwa Chemicals and used without further purification. Solvents, alcohols, PPh_3 (triphenylphosphine), PBu_3 (tributylphosphine), and $P(OPh)_3$ (triphenylphosphite) were purified by distillation or recrystallization before use. PCy_3(tricyclohexylphosphine) and 1,2-bis(diphenylphosphino)ethane were purchased from Strem Chemicals Inc. and used without further purification. N-aryl substituted formamides were prepared according to the literature method [12].

All experiments were carried out in a similar manner as described below. A 50 ml two-necked pyrex flask equipped with a reflux condenser and a magnetic stirring bar was charged under an argon flow with $RuCl_2(PPh_3)_3$ (0.20 mmol, 5 mol% based on formamides), N-aryl substituted formamide (4.0 mmol), mesitylene (5.0 ml), and alcohol (6.0 mmol). Then, the flask was immersed into a preheated silicone oil bath (ca. 170°C), and the reaction was performed under reflux for 12 h with stirring. The reaction was terminated by rapid cooling and the resulting brown solution was analyzed by GLC and FT-IR. The evolved gas was collected in a gas buret and was analyzed by GC. The products were isolated by Kugelrohr distillation and/or preparative thin-layer chromatography. Further purification was performed by recrystallization, if necessary and possible. The identification of the products was confirmed by ^1H (270 MHz) and ^{13}C (67.8 MHz) NMR, FT-IR, elemental analyses, and GC-MS.

3. Results and discussion

Table 1 summarizes the catalytic activity of several ruthenium complexes in the reaction of formanilide with 1-octanol. Among the catalysts employed, $RuCl_2(PPh_3)_3$ showed the highest catalytic activity and octyl N-phenylcarbamate was obtained in 48% yield (run 1). During the reaction, hydrogen was spontaneously evolved into a gas phase and after the reaction of run 1, hydrogen was detected in 86% yield based on the amount of formanilide charged. Thus, the present system does not require any hydrogen acceptors. The catalyst systems of $RuCl_3 \cdot nH_2O$ combined with trialkylphosphines such as tributylphosphine and tri-

Table 1
Catalytic activities of several ruthenium complexes in the synthesis of octyl N-phenylcarbamate from formanilide and 1-octanol [a]

Run	Catalyst	Conv. [b] (%)	Products (%) [b]			
			$PhNHCO_2C_8H_{17}$	$PhNH_2$	$PhNHC_8H_{17}$	$PhN(C_8H_{17})_2$
1	$RuCl_2(PPh_3)_3$	100	48	0	9	6
2	$RuCl_3 \cdot nH_2O + PBu_3$ [c]	82	12	35	8	10
3	$RuCl_3 \cdot nH_2O + PCy_3$ [d]	67	24	12	0	0
4	$RuHCl(CO)(PPh_3)_3$	100	7	10	69	6
5	$Ru(CO)_3(PPh_3)_2$	100	8	2	43	0

[a] Formanilide (4.0 mmol), 1-octanol (6.0 mmol), and catalyst (0.20 mmol) under reflux in mesitylene (5.0 ml) for 12 h.
[b] Determined by GLC based on the amount of formanilide charged.
[c] $RuCl_3 \cdot nH_2O$ (0.20 mmol) and tributylphosphine (0.90 mmol).
[d] $RuCl_3 \cdot nH_2O$ (0.20 mmol) and tricyclohexylphosphine (0.60 mmol).

cyclohexylphosphine gave less than quantitative conversion of formanilide (runs 2 and 3). Other ruthenium catalyst systems such as $RuCl_3 \cdot nH_2O$ alone, $RuCl_3 \cdot nH_2O$ +$P(OPh)_3$, and $RuCl_3 \cdot nH_2O$ + 1.2-bis(diphenylphosphino)ethane showed no catalytic activity. Although ruthenium complexes bearing carbonyl ligands gave low yields of carbamate, they showed high catalytic activity for both decarbonylation of formanilide to aniline and subsequent N-alkylation of aniline with 1-octanol (runs 4 and 5). For example, a mixture of aniline (10%), N-octylaniline (69%) and N,N-dioctylaniline (6%) was obtained by $RuHCl(CO)(PPh_3)_3$ catalyst, together with the generation of carbon monoxide in 93% yield based on formanilide (run 4). The formation of these products can be rationalized by our previous study on ruthenium-catalyzed decarbonylation of formyl compounds [5] and N-alkylation of amines with alcohols [13].

Among the solvents employed in the synthesis of cyclohexyl N-phenylcarbamate from formanilide and cyclohexanol (table 2), mesitylene (b.p. 167°C) was the most suitable solvent (run 1). The reaction also proceeded under reflux in decane (b.p. 174°C) (run 2), but in *o*-xylene (b.p. 144°C) or toluene (b.p. 111°C), the yields of the carbamate drastically decreased (runs 3 and 4). In addition, diglyme (b.p. 162°C) retarded the reaction, perhaps due to the coordination of the solvent to the ruthenium (run 5).

Various alkyl N-arylcarbamates can be synthesized by $RuCl_2(PPh_3)_3$-catalyzed dehydrogenative reaction of N-aryl substituted formamides with alcohols under the optimum reaction conditions (catalyst: $RuCl_2(PPh_3)_3$; solvent: mesitylene) (table 3). Formanilides containing substituents on the aromatic rings reacted with 1-octanol to afford the corresponding octyl N-arylcarbamates in yields of 35–82%

Table 2
Effect of solvents in the synthesis of cyclohexyl N-phenylcarbamate from formanilide and cyclohexanol [a]

Run	Solvent (b.p. (°C))	Yield (%) [b]
1 [c]	mesitylene (167)	56
2	decane (174)	40
3 [d]	*o*-xylene (144)	24
4 [d]	toluene (111)	trace
5	diglyme (162)	18

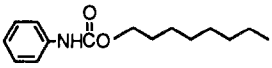
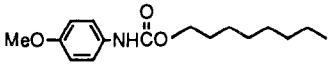
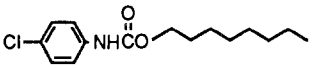
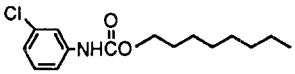
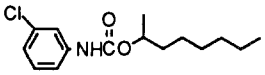
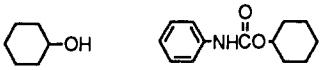
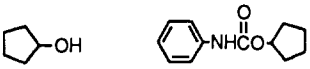
[a] Formanilide (5.0 mmol), cyclohexanol (5.0 mmol), and $RuCl_2(PPh_3)_3$ (0.10 mmol) under reflux in solvent (5.0 ml) for 12 h.
[b] Yield of cyclohexyl N-phenylcarbamate determined by GLC based on the amount of formanilide charged.
[c] Formanilide (4.0 mmol), cyclohexanol (6.0 mmol), and $RuCl_2(PPh_3)_3$(0.20 mmol).
[d] Formanilide (10 mmol), cyclohexanol (5.0 mmol), and $RuCl_2(PPh_3)_3$ (0.20 mmol). Yields were determined by GLC based on the amount of cyclohexanol charged.

(runs 1–4). Secondary alcohols such as 2-octanol, cyclohexanol and cyclopentanol as well as primary alcohols also reacted with formanilides to give the corresponding alkyl N-arylcarbamates (runs 5–7). In the reactions using 1-octanol and 2-octanol, an addition of a catalytic amount of suitable bases, tertiary amines such as 1,2-dimethylimidazole, increased the yields of the corresponding carbamates to some extent (compare run 1 in table 1 with run 1 in table 3) [14]. Nevertheless, tert-butyl alcohol did not react with formanilide, probably due to the steric hindrance (run 8) [15].

In order to examine the scope of the reaction, we investigated the reaction of N-octylformamide, *N-alkyl substituted formamide*, with 1-octanol. However, trioctylamine was obtained predominantly and the yield of octyl N-octylcarbamate was less than 10%.

Although the detailed mechanism is now under investigation, we believe that the ruthenium complex-catalyzed dehydrogenation of N-substituted formamide to the isocyanate intermediate would firstly occur. Subsequent nucleophilic attack of alcohol to the isocyanate intermediate gives the carbamate. It is reasonable that N,N-disubstituted formamide such as N-methylformanilide did not react with 1-octanol (run 9 in table 3), since N,N-disubstituted formamides cannot be converted into isocyanate intermediate. In addition, it is well known that tertiary alcohols and phenols hardly react with isocyanates under uncatalyzed conditions, i.e., in the absence of acids or bases, in carbamate synthesis [15]. Therefore, the fact that the reaction of formanilide with tert-butyl alcohol did not afford the corresponding carbamate (run 8 in table 3) also suggests that the reaction would proceed via the isocyanate intermediate.

Table 3
$RuCl_2(PPh_3)_3$-catalyzed synthesis of various alkyl N-arylcarbamates [a]

Run	Formamide	Alcohol	Product	Yield (%) [b]
1	formanilide	1-octanol		69
2	*p*-methoxyformanilide	1-octanol		(35)
3	*p*-chloroformanilide	1-octanol		78(42)
4	*m*-chloroformanilide	1-octanol		82
5	*m*-chloroformanilide	2-octanol		57(48)
6 [c]	formanilide			56
7 [d]	formanilide			(23)
8 [d]	formanilide	^{t}BuOH	–	0
9 [c]	N-methylformanilide	1-octanol	–	0

[a] Formamide (4.0 mmol), alcohol (6.0 mmol), $RuCl_2(PPh_3)_3$ (0.20 mmol), and 1,2-dimethylimidazole (0.5 mmol) under reflux in mesitylene (5.0 ml) for 12 h.
[b] Yields were determined by GLC based on the amount of formamide charged. Figures in parentheses are isolated yields.
[c] 1,2-dimethylimidazole was not added.
[d] Formamide (10 mmol), alcohol (5.0 mmol), and $RuCl_2(PPh_3)_3$ (0.10 mmol) without 1,2-dimethylimidazole. Yields were determined based on the amount of alcohol charged.

Acknowledgement

This work was partly supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Science and Culture.

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