Journal of Organometallic Chemistry, 330 (1987) 429–435
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

Solvent effect in the ruthenium catalyzed carbonylation of amines. Selective synthesis of dialkylformamides

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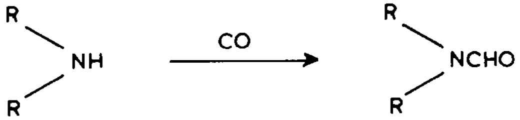
(Received February 19th, 1987)

Abstract

Formamides are selectively produced in the ruthenium-catalyzed carbonylation of amines in alcoholic solvents. The process is shown to occur sequentially via initial carbonylation of the alcohol to yield the corresponding formate, which then reacts with the amine to yield the formamide. The method is of interest for the carbonylation of unreactive amines (aniline, t-butylamine).

Introduction

The direct synthesis of formamides by the transition metal catalyzed reaction of the appropriate amine with carbon monoxide is a well documented synthetic procedure [1,2].



(1)

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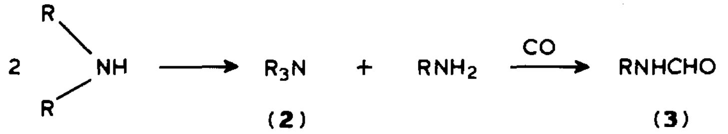
The formamidation reaction is generally easy with primary as well as with cyclic amines [3–5] provided that α-hydrogens are present. Selectivity for the desired formamide approaches 100% in all cases when the catalyst is a ruthenium compound [4,5]. Secondary acyclic amines, however, do not show such selectivity. and also undergo transalkylation and condensation to substituted ureas concurrent with the formamidation reaction [5].

In a previous study [5], we examined the effect of various parameters on the carbonylation reaction in order to improve the selectivity towards the dialkylformamide **1**. High pressure or use of a ruthenium–cobalt mixed catalytic system were effective in a limited way.

0022-328X/87/$03.50



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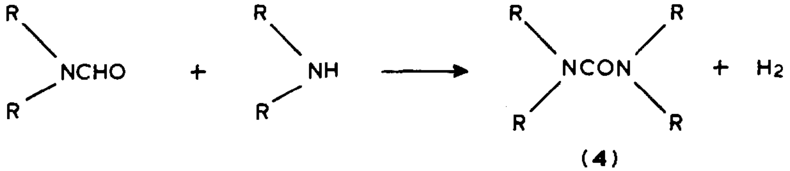


(3)

Laine has shown that in the ruthenium-promoted transalkylation of tertiary amines, the alcohols used as solvents enhance the formation and the stabilization of anionic catalytic species [6]. Solvent effects have been studied in catalyzed carbonylation and hydrocarbonylation reactions [7]; they can be important when they lead to a modified catalyst system enhancing the catalytic activity, as was the case in the hydrocarbonylation of methanol [8].

We describe here the results of a study of the effects of various solvents on the ruthenium-catalyzed carbonylation of secondary and unreactive primary amines. The experimental procedures and analytical methods were described previously [4,5] and are not presented again here.

Results

1. Solvent effect

A range of solvents of various polarities (based on the dielectric constant) were studied for formamide formation (Table 1). There is no evident correlation between

Table 1

Solvent effect in the carbonylation of di-n-butylamine [a]

Solvent	ϵ_{25}	Catalyst [b]	Conversion (%)	Selectivity (%) [c]	
				1	**2**
none	3 [d]	Ru	94	35	22
octane	1.9	Ru	52	38	15
dioxanne	2.2	Ru	77	43	26
isobutylether	4.2	Ru	79	42	25
hexametanol	30	Ru	94	15	23
water	78.5	Ru	50	1	0
methanol	32.6	Ru	96	61	15
ethanol	24.3	Ru	97	58	19
n-butanol	17.1	Ru	98	58	21
glycerol	42.5	Ru	100	55	18
methanol		Rh	79	35	27
methanol		Co	16	75	6
methanol		Ru	96	61	15
methanol		Ru/Co [e]	96	65	14

[a] Amine (2.5 ml), Ru (0.16 mmol), p(CO) (220 bar), T (200 °C), t (2 h), solvent (2.5 ml). [b] Ru = $RuCl_3,3H_2O$; Co = $Co(OAc)_2,4H_2O$; Rh = $RhCl_3,3H_2O$. [c] Other products include mainly RNHCHO (3) and tetraalkylurea (4). [d] Dielectric constant of the pure amine. [e] Ru (0.09 mmol); Co (0.07 mmol).

Table 2

Ru promoted carbonylation of di-n-butylamine (2.5 ml) in methanol. Optimization experiments.

Catalyst concentration (mmol)	p (bar)	T (°C)	t (h)	Conversion (%)	Selectivity (%)		Turnover [a] (a)
					1	2	
0.075	480	200	1	74	89	3	133
0.075	760	180	1	45	100	0	91
0.16	220	200	2	96	61	15	28
0.16	480	200	1	88	83	6	69
0.16	480	160	2	50	98	1	24
0.16	480	180	2	87	87	4	36
0.16	760	200	2	100	84	2	62

[a] mol **1**/at. g Ru/h.

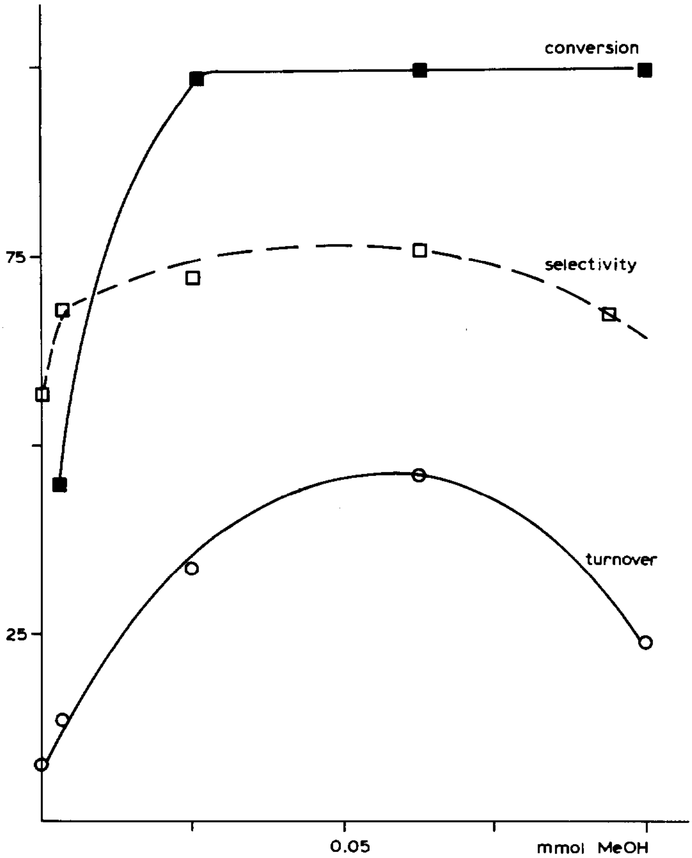


Fig. 1. Effect of the concentration of methanol in the carbonylation of di-n-butylamine (amine: 15 mmol, p: 480 bar, T: 200 °C, t: 2 h). Conversion and selectivity (in %), Turnover (in mol formamide/mol Ru/h).

the yield of formamide and the solvent dielectric constant. Introduction of an aprotic solvent lowers the conversion (dilution effect) and does not increase (or only barely increases) the formamide selectivity. In alcohols, however, the dialkylamine is almost totally converted, and selectivity towards the corresponding amide is clearly improved even for polyalcohols. In water, the behaviour is different and somewhat puzzling: depending on the amine, either more urea is produced or the rate of carbonylation is sharply decreased.

With methanol as solvent, ruthenium is the best carbonylation catalyst. There is no improvement if $RhCl_3$ is used, and cobalt acetate has a low catalytic activity as observed earlier [5]. Mixed Co/Ru catalytic systems, which were found to have a synergetic effect in the carbonylation of dialkylamines, do not show any special behaviour in the present case. Table 2 shows the formamide selectivities and turnovers as a function of various parameters (optimization experiments); the common solvent in all the runs was methanol (2.5 ml).

High pressures suppress the transalkylation reaction and greatly improve the selectivity. The best result is obtained in the reaction at 180 ° C and 760 bar with a short reaction time, and there is an acceptable turnover.

The volume of methanol has an effect, as illustrated in Fig. 1. Amine conversion, selectivity towards the formamide, and turnover number reach optimal values when equal volumes of amine and methanol are used. The result implies a process in which the alcohol is stoichiometrically involved.

2. *Extension to other dialkylamines*

Extension of the studies to the carbonylation of other dialkylamines was tried (Table 3). For secondary amines, the addition of methanol has a beneficial effect on conversion, selectivity, and turnover. The results for the carbonylation of diisoalkylamines are highly informative. These amines are almost unreactive or are reluctantly carbonylated in the absence of methanol [5], but reaction occurs upon

Table 3

Ru promoted carbonylation of dialkylamines in methanol [a]

Amine	Solvent	Conversion (%)	Selectivity to 1 (%)	Turnover
$(C_2H_5)_2NH$	none	39	54	16
	CH_3OH	80	89	54
$(C_3H_7)_2NH$	none	55	58	18
	CH_3OH	65	82	64
$(C_5H_{11})_2NH$	none	74	66	19
	CH_3OH	90	80	59
$(C_6H_{13})_2NH$	none	89	65	20
	CH_3OH	89	82	52
$(i\text{-}C_3H_7)_2NH$	none	0	–	0
	CH_3OH	5	85	5
$(i\text{-}C_4H_9)_2NH$	none	0	–	0
	CH_3OH	82	80	69

[a] Amine (2.5 ml), methanol (2.5 ml), $RuCl_3$ (0.16 mmol), P(CO) (450 bar), T (200 ° C), t (2 h).

addition of the alcohol, especially with diisobutylamine. These results, combined with those from the experiments involving various volumes of methanol suggest that methanol plays an integral part in the reaction sequence leading to the formamide.

3. Discussion and application to unreactive amines

Dialkylamines are organic bases with pK_a's in the range 10–11. It has been shown recently that methanol can be carbonylated to give methyl formate in the presence of alkali metals [9] or converted into the formate by catalyzed hydrogen transfer with unsaturated inorganic compounds, e.g. ketones [10]:

$$CH_3OH \xrightarrow{CO} HCOOCH_3 \qquad (4)$$

$$CH_3OH + 2RR'C{=}O \rightarrow HCOOCH_3 + 2\ RR'CHOH \qquad (5)$$

In the present case, we suggest that methyl formate is the initial product formed in the first step of the reactional sequence. Once the formate is formed, it reacts stoichiometrically with the dialkylamine to yield the formamide and to regenerate the alcohol:

$$HCOOCH_3 + RR'NH \rightarrow RR'NCHO + CH_3OH \qquad (6)$$

Conversion of esters to amides is a known reaction [11] and involves nucleophilic substitution with a mechanism (probably of B_{AC2} type [12]), which is still uncertain.

If the scheme is correct, it means that the formamide is mainly produced by reaction 6, CO serving principally to convert methanol into methyl formate, so that the calculated turnovers refer to this reaction. The process seems to be very general, since all alcohols give almost the same yields and selectivity towards the formamide, even glycerol.

To confirm this reaction sequence, we submitted dibutylamine to the standard carbonylation conditions, but diluted with an equimolar quantity of methyl formate instead of methanol. As shown in Table 4, the amine is converted into 100% of di-n-butyl formamide, and the methyl formate into methanol. Replacing the formate by methyl acetate gave a different result: the formamide is obtained in only 40% selectivity, implying that formates are the most reactive esters in the acylation of amines via equation 6. The reactions involving formates do not require a catalyst (Table 4); even those with diisopropylamine, which lead to 100% formamide, whereas in methanol as solvent the yield was only 5%.

The acyclic amine 2,6-dimethylpiperidine, which was found to be inert towards carbonylation [4], reacts in the presence of either methanol or methyl formate, but with difficulty. The successful use of alcohols in the carbonylation of secondary amines prompted us to contemplate use of primary amines, which are not carbonylated under standard conditions. In the presence of methanol, t-butylamine reacts to give the formamide in excellent yield, while aniline shows a special behaviour, described below.

Methyl formate reacts with aniline according to equation 6, giving the expected formamide in 76% yield. Minor by-products (15%) were identified as compounds **A**–**D** (see below) (Table 5).

Methanol reacts with aniline in different ways depending essentially on the CO pressure applied. High pressures promote the formamidation, while at lower pressures alkylation of the amino group, as well as of the aromatic ring occurs, according to Scheme 1.

Table 4

Formamidation of amines [a]

Amine	Solvent	Catalyst	Conversion (%)	Formamide selectivity (%)
$(C_4H_9)_2NH$	methanol	Ru	96	61
	methyl formate	Ru	99	100
	methyl formate	none	100	94
	methyl acetate	Ru	99	40
$(i\text{-}C_3H_7)_2NH$	none	Ru	0	–
	methanol	Ru	5	85
	methyl formate	none	100	100
2,5-dimethylpiperidine	none	Ru	0	–
	methanol	Ru	20	11
	methyl formate	Ru	55	18
$t\text{-}C_4H_9NH_2$	methanol	Ru	82	100

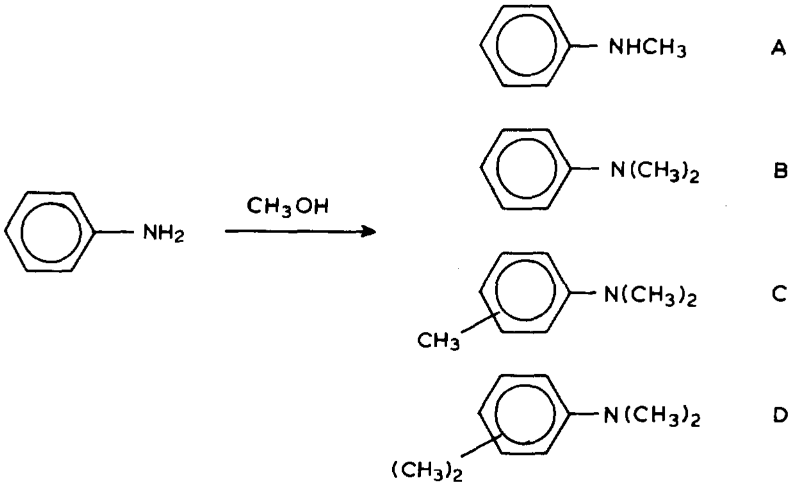
[a] Conditions as in Table 1.

Table 5

Carbonylation and alkylation of aniline [a]

Co-reactant	p(CO) (bar)	Conversion (%)	Yield (%)			
			formamide	A	B	C+D
none	480	5	0	3	0	0
methyl formate	510	95	76	2	2	11
methanol	500	59	21	15	3	9
methanol	110	44	2	29	9	3
methanol [b]	110	0	0	0	0	0
ethanol	100	3	0	2	0	0

[a] Aniline (2.5 ml), $RuCl_3$, $3H_2O$ (0.075 mmol), T (200 °C), t (2 h). [b] Triphenylphosphine was added (0.225 mmol).



Scheme 1

The reaction in the presence of $RuCl_2(PPh_3)_3$ at 180 °C and 1 bar has been investigated by Japanese authors [13]. Their results showed that the reaction involving methanol gave only poor yields of **A** and **B**, and neither **C** nor **D** was detected. When methanol was replaced by ethanol, with the same catalyst, the results were better, in contrast with our observations, implying that $RuCl_3$ is efficient only in the methanol reaction. **A** and **B** are probably formed via an acylruthenium intermediate (methanol would be dehydrogenated to formaldehyde complexed by the ruthenium catalyst) as suggested by Watanabe [13]. The ring alkylation products **C** and **D** would result from aromatic substitution, possibly catalyzed by the ruthenium complex.

We conclude that alcohols are the solvents of choice for the ruthenium-catalyzed carbonylation of amines to formamides, especially in the case of secondary amines. Even sterically congested amines, which in the absence of alcoholic solvents are unreactive, give the formamide in good yields (diisoalkylamines or t-butylamine). The enhanced selectivity and turnover are attributed to the transformation of the alcohol into the formate which subsequently acylates the amine. The carbonylation of alcohols to give formates is currently under investigation.

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