CARBONYLATION OF CYCLIC LITHIUM AMIDES IN THE PRESENCE OF TRANSITION METAL SALTS

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ABSTRACT

The effect of several transition metal halides on the rates and product distribution of the carbonylation of lithium-3-oxatetramethylenamide and lithium-pentamethylenamide in THF at 0°C was examined: it was found that whereas Ni(II) has almost no effect, Cu(I), Co(II) and Cr(III) produce a noticeable inhibition, presumably due to the formation of hetero transition metal-lithium complexes.

INTRODUCTION

Carbonylation of amines is an attractive process, useful not only for the generation of small molecules of industrial interest,[1-3] but also for the synthesis of fine chemicals,[3-7] and natural products.[8-9] Since the direct insertion of carbon monoxide into carbon-nitrogen bond of amine compounds is very difficult, active research is being developed mainly using transition metal complex catalysts. Most of the previous studies use platinum or palladium complexes,[1,3,10-13] but other later transition metal complex catalysts are being examined.[14-15]

We have recently shown the usefulness of the carbonylation of lithium amides for the synthesis of substituted amides,[16] ureas,[17] glyoxylamides and tartronamides;[16] and the reaction have been recently used also for the preparation of sulfur compounds,[18] and carbamoyl silanes.[19] Since it has been previously reported that organolithium compounds form complexes with some transition metal salts,[20] it was then of interest to examine their effect on the product distribution and reaction rates of the carbonylation of lithium amides. The present work describes the results obtained in the reactions of cyclic lithium amides with carbon monoxide, in the presence of Ni(II), Co(II), Cu(I) and Cr(III) halides, carried out in THF at atmospheric pressure, at 0°C.

MATERIALS AND METHODS

All reactions involving organolithium reagents were carried out by using standard techniques for the manipulation of air- and water-sensitive compounds.[21] All compounds reported here are fully characterized by mass spectrometry (using a BG Trio-2 mass spectrometer), infrared spectroscopy (taken of neat liquids and recorded on a Perkin- Elmer IR 121 spectrophotometer), and nuclear magnetic resonance spectroscopy (determined on a Brucker 200 spectrometer) and showed spectral characteristics consistent with the spectra of authentic samples. The GLC analyses were carried out on a 5830 Hewlett Packard (using a HP-17 column), or a 2000C Konik (SE-54 column) gas chromatographs, at 70-180°C programmed temperature. GC-MS analyses were performed on a gas chromatograph coupled to the BG Trio-2 mass spectrometer.

Solvents and Reagents.- Tetrahydrofuran (THF) was purified as previously described.[22] It was redistilled from dark blue solutions of benzophenone ketyl under nitrogen immediately prior to use. Amines were left over sodium strings for several days and then refluxed and distilled over sodium immediately prior tu use. *n-Butyllithium* was prepared by cutting lithium wire (4.6 g, 0.66 mol) in small pieces into a flask containing boiling hexane (250 mL), the flask was capped with a non-air stopper, and kept at 54-58°C. Butyl chloride (31.3 mL, 0.33 mol) was syringed in small aliquots into the flask during 3 h and the mixture left to react for 1 h at 50°C. *Lithium Amides*: cooled (0 °C) *n*-BuLi (2.5 mL, 0.8 M in hexane) was syringed into a non-air stopper capped tube under nitrogen atmosphere, and the freshly distilled amine (2 mmol) was added. The white lithium amide precipitate was worked up as previously described.[23] To obtain "pure" *amine-free* lithium (3-oxapentamethylene)amide, **2a**, and lithium pentamethyleneamide, **2b**, an excess of *n*-BuLi in hexane (5-8 mmol) was syringed into the tube and the solvent vacuum pumped. The resulting syrup was dissolved in THF and the amine (2 mmol) added. After vigorous shaking the resulting solution was used immediately.[24]

$CoCl_2$, $NiCl_2$, and $CrCl_3$. The hydrated salts ($MCl_n.x\ H_2O$) were made anhydrous by refluxing them over thionyl chloride for 5 h. The thionyl chloride was distilled, and the residue was dryed into a vacuum oven.[25] The salts were stored in a dry atmosphere under nitrogen. *CuCl* was prepared by reduction of a solution of copper sulfate and sodium chloride, using $NaHSO_3$ in NaOH soln.[26] The white precipitate of CuCl was washed several times with the $NaHSO_3$ solution, then with anhydrous acetic acid, and dried in a vacuum oven.

Reaction of Lithium Dialkylamide with CO. *General procedure*: A vial containing a Teflon-coated stirring bar was heated in a vacuum oven at 130-150 °C for at least 30 min and then cooled in a dried nitrogen atmosphere. The vial was capped with a non-air stopper, it was evacuated and filled with dry nitrogen alternatively, several times, and then put into an ice bath with vigorous magnetic stirring. A lithium amide solution (0.5 M) in THF (7-8 mL) containing free amine in a ratio [amine]: [lithium amide] = 0.8 was added by cannula (when necessary the cosolvent and/or the metal salt was then added), and the stirred solution was exposed to carbon monoxide at ca. 1013 mbar. The bulk of the carbon monoxide was absorpted within the first 3-4 min, and the gas absorption was over in nearly 30 min for the reaction in the absence of any salt. Once the reaction was completed, H_2O (O_2 free) was added; the remaining carbon monoxide evacuated, and THF (10 mL) and then $NaHCO_3$ (500mg, 6mmol) were added; after careful mixing, the organic phase was quantitatively analyzed by GLC.

Reactions in the Presence of Transition Metal Salts.- Three different procedures were examined. *Method I* : The salt (around 0.4-0.5 mmol of MCl_n) and the THF (2 mL) were added to the reaction flask, the solution (or suspension) was stirred; then ca. 0.8 mmol of a solution of **2** in THF (carefully measured) was syringed and the carbonylation was started as described in the general procedure.

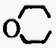
Method II: The salt and the THF (2 mL) were added to the reaction flask; the solution (or suspension) was exposed to CO at ca. 1013 mbar, until the gas absorption ceased. Then, 0.8 mmol of a solution of **2** in THF (carefully measured) was syringed and the carbonylation followed as described in the general procedure.

Method III: To the reaction flask, containing crystalls of the salt (around 0.4-0.5 mmol of MCl_n), capped with a non-air stopper and cooled at 0°C, freshly distilled amine (0.8 mmol) was syringed under nitrogen atmosphere and then n-BuLi (1 mL, 0.8 M in hexane) was added dropwise. The suspension was vigorously shaken, and left to sediment; then the supernatant solvent was syringed out, 2 mL of THF were added, and the stirred solution, cooled at 0°C, was exposed to CO as described in the general procedure.

RESULTS AND DISCUSSION

Dialkyl lithium amides were easily prepared by direct lithiation of the corresponding amines, **1** (eq. 1) as described in the experimental section.

$$\underset{\mathbf{1}}{R^1R^2NH} + BuLi \rightleftharpoons \underset{\mathbf{2}}{R^1R^2NLi} + BuH \qquad (1)$$

a) $R^1R^2=O$ **b)** $R^1R^2=$ **c)** $R^1=R^2=Bu$
d) $R^1=c\text{-}C_6H_{11}$, $R^2={}^iPr$ **e)** $R^1=R^2=c\text{-}C_6H_{11}$

Although lithium dialkylamides are usually written as monomers (and so will be used hitherto) it is known that they exist as dimers,[27a] trimers[27b] and even tetramers.[27c] They also form mixed aggregates with donor bases as well as di- or tri-solvated aggregates.[27,28] We have recently reported the X-ray structure of the first 1:1 amine:amide aggregate: lithium pentamethyleneamide, **2b**, crystallizes as a $[(\mathbf{1a})_4:(\mathbf{2a})_4]$.[29] In the case of lithium-3-oxatetramethyleneamide, **2a**, we have recently afforded experimental evidence that **2a** likely also crystallizes as a 1:1 amine:amide **mixed aggregate.**[24]

Table 1. Carbonylation of Lithium dialkylamides, 2, in THF at 0° C.

Amide	Solvent	[1]/[2]	% conversion		
			3	**4**	**5**
a	THF	b	100		
b	THF	b	100		
c	THF[a]	0.8	15	79	6
	THF	0.15		15	85
	HMPT	0.8		100	
d	Hexane	0.2	12	8	80
	THF - Hexane	0.8	66	30	4
e	THF - LiBr	0.8	91	8	1
	THF	0.2		10	90
	THF- HMPT	0.8	7	88	5

[a] At -78 °C

[b] The yield is independent of the [1] / [2] ratio

The carbonylation of **2** usually renders three main products, formamides, **3**, glyoxylamides, **4**, and tartronamides, **5** (eq. 2).

$$R^1R^2NLi + CO \rightarrow \underset{\mathbf{3}}{R^1R^2NCOH} + \underset{\mathbf{4}}{R^1R^2NCOCOH} + \underset{\mathbf{5}}{R^1R^2NCOCHOHCONR^1R^2} \qquad (2)$$

The fact that the cyclic lithium amides form mixed aggregates that remain even in THF solution,[24] has significant consequences of synthetic usefulnes. Thus, it is shown in Table 1 that while the other lithium amides are very sensitive to the [**1**]:[**2**] ratio in the reaction mixture, those reactants afford only the corresponding substituted alkyl formamides, **3a** or **3b**, respectively, regardless the amount of **1a** or **1b**, present in the reaction mixture. For the other cases, the effect of different reaction conditions was studied, and some results are gathered in Table 1 that afford products **3, 4** or **5**, in satisfactory yields. For the case of **2e** an interesting effect of lithium bromide as a complexing agent was observed: in effect, under these conditions, complexation prevents further reaction of the first intermediate and the reaction provides a satisfactory method for the synthesis of the corresponding formamide in a very good yield. The complexing effect of lithium bromide was recently described for the case of lithium 2,2,6,6-tetramethylpiperidide (LiTMP), which forms a 1:1 LiTMP/LiBr mixed aggregate;[30] nevertheless, in the carbonylations of the other dialkylamides studied no significant effect was observed.[16]

The reaction of **2a**, which render only one product, was then selected to study the effect of the addition of transition metal salts, MCl_n, **6**. Three alternatives were examined for the study of complexation effects, namely:

a) complexation of **6** with the THF (forming a complex $[(MCl_n).x\mathrm{THF}]$), and further reaction of **2a** with CO in the presence of the complex.

b) complexation of **6** with CO (forming a complex $[(MCl_n).(CO)_m]$, and further reaction of **2a** with the complex (transfer of CO ligands) in the presence of CO.

c) complexation of **6** with **2a** (forming a mixed aggregate $[[(MCl_n).(\mathbf{2a})_m]$, and further reaction of the mixed aggregate with CO.

Allowance for the formation of the three complexation alternatives was done by performing the overall reactions under the conditions described as Methods I-III in the **Materials and Methods Section.** Table 2 gathers the observed results. All the reactions were carried out at atmospheric pressure. Since this heterogeneous reaction is very sensitive to small variations in reaction conditions, such as: speed of stirring, reaction flask geometry, etc., the reported data are average of at least 3-5 determinations. The % variation in the product distribution is within ± 5%. The first line called "blank" means the reaction carried out in the absence of any salt. Although only one result is stated, the "blank" reaction was carried out every time in parallel to any reaction in the presence of salt, to be sure that any undesirable spurious effect such as: humidity, slight variations in reagent and/or solvent, stirring speed, etc. was avoided.

As it had been observed before,[24] the "blank" reaction showed almost equal amounts of morpholine and N-(3-oxatetramethylene)-formamide, **1a** and **3a**, in Table 2, respectively. This is interpreted as an evidence that the lithium-3-oxatetramethyleneamide, **2a**, crystallizes as a 1:1 amine:lithium amide mixed aggregate. Then, although 0.8 mmoles of BuLi is added to the same amount of morpholine, the real concentration of **2a** is half of the added BuLi, because only half of the amine is converted into **2a**. Only when **2a** is prepared under special conditions and with a great excess of BuLi, most of the initial morpholine can be converted into **2a.** Nevertheless, for the present study, the usual lithium amide preparation was chosen throughout the work. It can be observed in Table 2 that the half-reaction time ($t_{1/2}$) is very short, most of the carbon monoxide absorption occurs within the first 2-3 min. and the reaction was complete in nearly 30 min.(t_T).

When the reaction was carried out in the presence of Ni(II) chloride, it can be observed in Table 2 that no significant effects were found in the product distribution. The half-reaction time increased (possibly due to poorer mixing of the reactants due to residues of undissolved salt) but the overall reaction time as well as the volume of absorpted CO was the same than in the "blank" reaction.

Table 2. Carbonylation of Lithium-morpholide, 2a, in THF at 0° C. Effect of transition Metal Salts[a]

Salt	Method	10^4[salt] mol	$t_{1/2}$ min.	t_T[b] min.	10^4[CO] mol	10^4[**1a**][c] mol	10^4[**3a**][c] mol
-	Blank	-	1.5	30	7.0	3.5	3.4
$NiCl_2$	1	3.9	6.0	30	7.2	3.5	3.5
	2	3.9	15.0	30	3.7	3.2	3.5
	3	3.6	6.0	30	2.5	4.0	2.2
CuCl	1	3.7	8.0	40	6.3	5.6	0.6
	2	3.9	45	80	4.3	6.0	1.5
	3[d]	3.8	20	80	5.0	6.0	0.8
$CoCl_2$	1	3.9	0.5	15	0.4	6.5	-
	2	4.2	0	15	0	7.0	-
	3[d]	3.9	0	15	0	7.0	-
$CrCl_3$[e]	1	5.2	2	30	0.4	1.6	-
	2	4.6	1	15	0.4	2.0	-
	3	5.0	10	40	1.0	1.3	0.4

[a][**2a**] = $4.0.10^{-4}$ mol, unless otherwise stated. [b]t_T: Total reaction time. [c][**1a**]=morpholine; [**3a**]= morpholylformamide. [d][**2a**]= $3.5.10^{-4}$ mol. [e][**2a**]= $1.6.10^{-4}$ mol.

On the contrary, for the other three salts, a strong inhibition of the carbonylation was observed. Thus, for the case of CuCl, the kinetics of the reaction and the overall CO absorption have slown down. Although CO absorption occurs in some extent, only small amounts of **3a** were observed, and most of the reagent was recovered as **1a.** Presumably, a complex is formed between CuCl and the reagent (likely through the lithium atom), which prevents the CO activation which is needed for the carbonylation to occur (presumably by coordination of CO to the lithium atom). Heterocuprates are very well known reagents of high synthetic interest,[20] and they are likely formed in these reactions: it can be observed that under the conditions described as Method I, were formation of the heterocuprate is more probable, the smallest amount of **3a** is obtained. When the reaction was carried out under the conditions described as Method II , most of the CO absorption occurred before **2a** was added. This could indicate that a complex between CuCl and CO would be previously formed: transfer of the ligand to the reagent would occur at some extent and **2a** results partially carbonylated.

On the other hand, the reactions of **2a** in the presence of $CoCl_2$ or $CrCl_3$, showed almost no CO absorption. For the case of $CoCl_2$, the reagent is recovered unchanged as **1a**. This result is interpreted as due to a complexation of the reagent with the salt, likely through a hetero metal-metal coordination, which prevents its further carbonylation. Some hetero-metal amides forming polycycles and clusters have been recently characterized,[30] as well as mixed-alkali-metal amide complexes.[31] Structural studies of the crystalls of **2a** prepared in the presence of $CoCl_2$ are intended.

Finally, a reaction is suspected to occur between $CrCl_3$ and the reagent. In fact, no CO absorption was observed in any case (Table 2). To increase the reaction, major amounts of salts were used and the results with $CrCl_3$ are showed at the bottom of Table 2. It can be observed that no **3a** was formed by any of the three methods, only relatively small amounts of **1a** were found and most of the reagent was converted into other products as shown by the GC analysis. Similar results were found for the reaction of **2a** with $CrCl_3$ *in the absence* of CO. The study of this reaction is under progress, to find conditions that could lead the reaction toward the production of a majoritary compound, to make it synthetically appealing.

Although the reactions of lithium pentamethyleneamide, **2b,** were not so thoroughly studied, it was found that they showed a similar behaviour. $NiCl_2$ has almost no effect on the carbonylation, while the other salts have an inhibitory effect. It was considered unrelevant for the purposes of this work repeating the reactions several times to assure the data; for this reason no Table for the reactions of this lithium amide is given.

Conclusions. The carbonylation of cyclic lithium amides which crystallizes as a 1:1 amine:amide mixed aggregate, that seems to remain in THF solution, was chosen to study the effect of the addition of transition metal salts, since the reaction afforded only one product. It was found that whereas Ni(II) has a slight effect on the reaction rate, Cu(I) and Co(II) showed an inhibitory effect and almost all the reagent was recovered: this result was interpreted as an evidence of the formation of a hetero metal-lithium complex in THF solution that prevents the reaction of the reagent with CO. On the other hand, $CrCl_3$ reacted with the lithium amide even in the absence of CO: the study of this reaction in under progress.

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