Carbon–Carbon Bond Formation through the Carbonylation of Lithium Dialkylamides. One-Pot Synthesis of *N*-Alkyl-Substituted Formamides, Glyoxylamides, and Hydroxymalonamides

Daniel G. Pêrez and N. Sbarbati Nudelman*

Depto. Química Orgânica, Facultad de Ciencias Exactas, Universidad de Buenos Aires, Pab. II, P.3 Ciudad Universitaria, 1428 Buenos Aires, Argentina

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The reaction of lithium dialkylamides 1 (dialkyl = dibutyl, dipentyl, dicyclohexyl, 3-oxapentamethylene, and isopropyl cyclohexyl) with carbon monoxide was examined under several reaction conditions. It is shown that the corresponding lithium carbamoyl is the first intermediate and its further reactions can lead to dialkylformamides 2, dialkylglyoxylamides 3, or tetraalkylhydroxymalonamides 4. Dialkylamides were previously assumed to come from hydrolysis of lithium carbamoyls, and these represent an unexplained "island of stability" among the area of acyl anions. Evidence is given that casts doubts on this assumption and suggests that 2 comes from the cleavage of lithium tetraalkylurea dianion. The yields of 2, 3, or 4 obtained by this one-step, rapid procedure are much higher than those afforded by the usual several steps methods of preparation, especially for compounds 3 and 4. Tetraalkylureas, tetraalkyloxalamines, or tetraalkylketomalonamides can be obtained in good yield by the same general procedure, followed by treatment of the reaction mixture with oxygen after the carbon monoxide absorption has ceased and before the regular workup.

Introduction

Carbonylation of metal amides to produce mainly alkylformamides has been of interest of many scientists in the last decade,[1-5] and a renewed interest in the subject is observed at present.[6-10] In the reaction of lithium dialkylamides with carbon monoxide[1-4,11] dialkylformamides have been isolated in variable yields, and this has been considered a good evidence of the stability of the "carbamoyl anions" formed and said to "represent an unexplained 'island of stability' in the area of acyl anion".[3] We have recently reported[12] that in the reaction of lithium dicyclohexylamide with carbon monoxide, conditions could be achieved to produce dicyclohexyl glyoxylamide (a double carbonylation product) in good yield instead of the usual dicyclohexylformamide. To examine the scope of this new method we studied the behavior of other lithium dialkylamides and we now report that results obtained in the reactions of lithium dibutyl-, dipentyl-, dicyclohexyl-, isopropylcyclohexyl-, and (3-oxapentamethylene)amides (morpholinolithium) with carbon monoxide under several reaction conditions. We also present some experimental facts that could cast some doubt on the existence of free carbamoyllithium in the reaction flask once the carbon monoxide absorption has ceased.

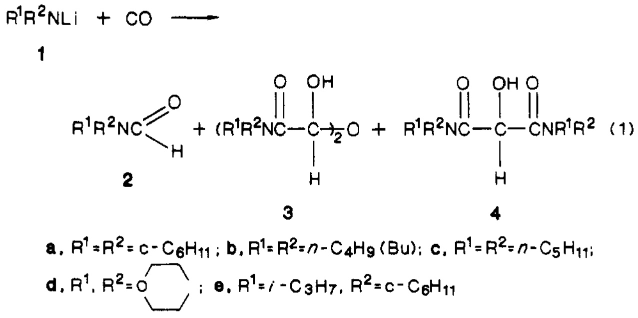
Table I. Reaction of Lithium Dibutylamide with Carbon Monoxide in THF at 0 °C. Effect of the [Amine]/[Amide] Ratio[a]

amine	[amine]/[$LiNBu_2$]	yield 2b	3b	4b
Bu_2NH	0.17		14.7	85.3
	0.21	3.8	14.6	81.6
	0.25	5.3	25.6	69.1
	0.29	3.9	22.7	73.4
	0.42	5.6	41.4	53.0
	0.47	5.1	52.4	42.5
	0.76	14.8	85.2	
	0.78	6.0	94.0	
	0.97	6.8	78.4	14.8
	1.10	9.4	83.2	7.4
Bu_3N[b]	0.30	10.9	14.4	74.8
	1.15	13.7	14.0	72.2
	1.24	9.9	16.3	73.8

[a] Yields represent percent conversion to the three major products. [b] [$LiNBu_2$] = 1 M; [$HNBu_2$]/[$LiNBu_2$] = 0.2.

Results

In our previous paper[12] on this subject we reported that the reaction of lithium dicyclohexylamide (**1a**) with carbon monoxide produces three main products: dicyclohexylformamide (**2a**), dicyclohexylglyoxylamide (**3a**), and tetracyclohexyltartronamide (**4a**) (eq 1).



I. Factors Influencing the Carbonylation Reactions. Yields of products **2–4** are influenced by various factors including the presence of free amine, the nature of the solvent and cosolvents, CO pressure, the speed of stirring the reaction mixture, the temperature of the re-

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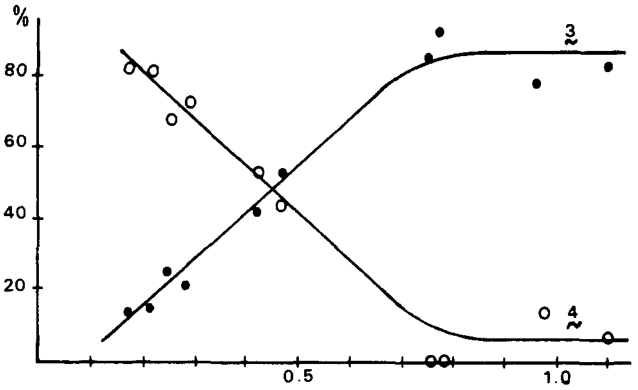

Figure 1. Reaction of lithium dibutylamide and carbon monoxide in THF at 0 °C at different [Bu_2NH]/[$LiNBu_2$]. Yields (%) are of **3** and **4** in the reaction mixture of **2**, **3**, and **4**.

Table II. Reaction of Lithium Dibutylamide with Carbon Monoxide in THF at 0 °C. Effect of the Initial Concentration of Lithium Dibutylamide[a]

		yield		
[$LiNBu_2$], M	[$HNBu_2$]/ [$LiNBu_2$]	**2b**	**3b**	**4b**
0.15	0.30		37.7	62.2
0.37	0.32	2.1	30.0	67.9
0.85	0.29	5.1	24.5	68.6
1.50	0.30	9.2	22.4	64.1

[a] Yields represent percent conversion.

action, the presence of added salts, etc. We have examined each of these factors.

(a) Free Amine. Since some equilibria involving free amine have been reported[13] (see Discussion below) a careful survey of its influence have been carried out, and the results are gathered in Table I for the reaction of lithium dibutylamide with carbon monoxide in THF at 0 °C. As can be observed the yield of compound **2** is almost insensitive to the amount of amine present in the reaction mixture, while the production of compounds **3** and **4** is strongly influenced. A higher yield of tetrabutyltartronamide, (**4b**), is obtained working at very low amine concentration, while yields higher than 80% of dibutylglyoxylamide (**3b**) are obtained at relatively high [amine]/[amide] ratios. Figure 1 shows that the yield of **3b** increases at the expense of **4b**. That the effect of the free amine is not due to a basicity effect is shown by the nul effect observed by addition of a tertiary amine (Table I).

(b) Influence of the Initial Lithium Amide Concentration. In some other studies with carbonyl anion equivalents[14-16] we have noticed that the initial concentration of the lithium reagent affects the product composition and/or the rate of the reaction. It was therefore of interest to find out the influence of the initial lithium amide concentration on this reaction. Table II shows that as long as the [free amine]/[lithium amide] ratio is kept constant the reaction is almost insensitive to the initial concentration of the lithium reagent in the range 0.15–1.5 M.

(c) Effect of the Reaction Temperature. In our previous paper on this reaction[12] we reported an irregular temperature effect in the carbonylation of lithium dicyclohexylamide. Table III shows that the reaction is extremely sensitive: the rate decreases steadily as the temperature is decreased, and the production of **2** and **3** is strongly dependent on it. A very good yield of dibutylformamide (**2b**) can be obtained by working at very low temperature (−95 °C), while, also, a very good yield of dibutylglyoxylamide (**3b**) is isolated from the reaction carried out at 50 °C.

Table III. Reaction of Lithium Dibutylamide with Carbon Monoxide in THF. Effect of the Reaction Temperature and Stirring[a]

	yield			reactn half-time, min
variable	**2b**	**3b**	**4b**	
temp, °C				
50[b]	3.1	83.3		1.90
25[b]	7.4	72.4		1.92
−40	8.0	63.8	23.0	3.38
−78	32.5	47.8	17.3	6.84
−95	82.7	17.3		11.00
stirring[c]				
vigorous	17.2	71.6		
feeble	32.5	64.2	0.3	
nil	38.7	45.0	0.6	

[a] Yields represent percent conversion. [b] In the reactions at 25 and 50 °C dibutylglycolamide and tetrabutylurea (5–10%) were also obtained. [c] At 0 °C.

Table IV. Reaction of Lithium Dibutylamide and Carbon Monoxide at 0 °C. Solvent Effects[a]

	yield		
solvent	**2b**	**3b**	**4b**
hexane	5.6	46.8	45.0
hexane–THF (3.5:0.5)	7.8	42.5	45.0
Et_2O	16.9	67.0	12.7
hexane–THF (1:1)	14.8	78.9	
THF	12.4	79.4	
THF–DABCO (12:1)	1.9	45.3	48.3
THF–HMPT (5:1)		89.6	7.5
THF–HMPT (4:0.8)		89.6	7.0
THF–HMPT (4:1.2)		90.0	5.3
THF–HMPT (4:2.0)		97.0	<2.0
THF–HMPT (4:4.0)		100.0	

[a] Yields represent percent conversion.

(d) Influence of the Speed of Stirring. Since this is a two-phase system it was of interest to determine how the rate of carbon monoxide dilution is related to the global rate of the carbonylation. Although it was not possible to normalize all the variables involved, some simple gross determinations were considered enough to the purpose of this study. A "blank reaction" was carried out by working with pure THF in the reaction pot at 0 °C.

Measurements of the CO absorption as a function of time indicate that the CO saturation of THF is over in 20 s, and it reaches ca. 90% in nearly 6–7 s. With these data, the results of CO absorption vs time found in the reaction of lithium dibutylamide with CO in THF at 0 °C, and assuming simple kinetic of the type $d[CO]/dt = k([CO]^{\circ} - [CO])$ where $[CO]^{\circ}$ is the CO concentration in saturated THF and [CO] is the actual CO concentration at time t, the results indicate that under the standard conditions the CO concentration in the first 30–60 s of reaction is ca. 85–90% of the saturation value. This means that although the reaction solution is not completely saturated by carbon monoxide, the rate of the reaction is mainly controlled by the reaction rates and not by CO diffusion into the solution. Kinetic determinations were beyond the scope of this work, but some average reaction half-times were measured and are shown in Table III.

Straightforwardly related to the amount of diluted CO is the influence of the viscosity of the media and the speed of stirring of the reaction mixture. Table III shows the

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Table V. Reaction of Lithium Dibutylamide in THF at 0 °C. Effects of Amine, Lithium Salts, and Alkyl Halides[a]

	yield		
reactn media	2b	3b	4b
THF	13.2	79.1	
THF–Bu_2NH (3:1)	27.7	69.1	
THF–LiCl[b]	32.3	12.2	28.3
THF–LiBr[b]	5.7	43.4	33.0
THF–BuOLi[c]	36.4	35.6	3.5
THF–BuCl[d]	5.9	57.8	26.9
THF–BuCl[e]	56.9	41.8	
THF–BuBr[f]	4.4	15.8	
THF–BuBr[g]	15.0	39.4	6.4

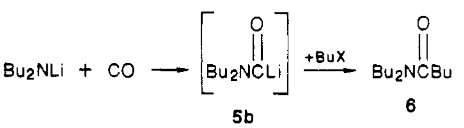
[a] Yields represent percent conversion. [b] 500 mg of Li salt. LiBr is completely dissolved, LiCl remains partially solid. [c] 200 mg of LiBuO. [d] Dibutylvaleramide (DBVA), 5.3%, also obtained. [e] Tributylamine (TBA), 1.4%, also obtained; reaction at −60 °C. [f] TBA, 69.4% also obtained. [g] TBA, 23.6%, and DBVA, 15.0% also obtained reaction at −60 °C.

gross effect of stirring, under conditions that favor production of compounds **2** and **3**. It can be observed that the amount of **3b** increases at high speed at expense of **2b**.

(e) Solvent Effects. Preliminary results on the effects of the solvent and mixed solvents as well as on the effect of added salts on the carbonylation of lithium dicyclohexylamide were reported in our previous paper.[12] Table IV gathers a more systematic study carried out with the reaction of lithium dibutylamide at 0 °C. It can be observed that formation of **3b** increases with the dielectric constant of the reaction media. The effect of HMPT, a good anion solvent, on the yield of **3b** is easily noticed. Quantitative production of dibutylglyoxylamide is achieved in a 1:1 THF–HMPT mixture. By the contrary, addition of a good donor base such as DABCO produces a strong decrease in the yield of **3** when compared with the results in pure THF. The yields obtained in THF–DABCO (12:1) are fairly similar to the product composition observed in the reaction carried out in pure hexane, in spite of the differences in the dielectric constants. The carbonylation of lithium dialkylamides in THF–HMPT at 0 °C constitutes an excellent method for the synthesis of compounds **3**.

(f) Effect of Added Lithium Salts. Since traces of lithium salts can be found in the reagent because of the method of preparation, it was of interest to determine whether there was any influence of the ionic strength of the reaction media or any other complexing effect of added salts. Table V shows the results obtained with the addition of lithium chloride, lithium bromide, and lithium butoxide. The amount of lithium chloride added to the reaction mixture is not completely dissolved; the rate of the reaction is slowed down probably because of the difficulties in achieving an efficient mixing of the reagents. The amount of dibutylformamide obtained is similar to that formed when the reaction mixture is not stirred. A similar effect occurs on addition of lithium butoxide. In these reactions variable amounts of dibutylglycolamide and tetrabutylurea are also formed. No synthetic utility was found for the effect of added salts, and, according with the results of Table V, no significant effect would have the presence of diluted lithium salts coming from the way of preparation of the butyllithium reagent.

(g) Effect of Added Alkyl Halides. With the double purpose of recognizing the effect that traces of butyl halide might have on the product composition and to find out if reaction with an electrophile present in the reaction media could be used for the synthesis of asymmetric amides, the effect of the addition of butyl chloride and bromide was studied at 0 and −60 °C. It can be observed in the second half of Table V that addition of butyl chloride diminishes the amount of product **3b** and increases the amount of **4b**, as it corresponds to a decrease in the dielectric constant of the solvent. But more meaningful is the formation of a small amount (5.3%) of dibutyl valeramide (**6**), which can be assumed to come from the reaction of **5b** with the butyl chloride (eq 2), which might be considered an evidence of the existence of the carbamoyl **5b**.[17]


$$Bu_2NLi + CO \longrightarrow \left[Bu_2N\overset{O}{\overset{\|}{C}}Li \right]_{\mathbf{5b}} \xrightarrow{+BuX} \underset{\mathbf{6}}{Bu_2N\overset{O}{\overset{\|}{C}}Bu} \quad (2)$$

When the reaction is carried out at lower temperature (−60 °C) **3b** formed and the yield of **2b** increased as expected. Addition of butyl bromide has a larger influence on the reaction product composition: in the reaction carried out at 0 °C tributylamine is formed as the main product (69.4%). Tributylamine is undoubtedly coming from the substitution reaction of **1b** with butyl bromide as demonstrated by an independent reaction carried out in the absence of CO. At low temperature the rate of this reaction slows down, and trapping of **5** by the electrophile (eq 2) occurs to a greater extent (15%). Since parallel reactions of **5b** with CO and also with **1b** compete with this reaction, conditions could not be attained yet to make it of synthetic utility.

II. Scope of the Reaction. To examine the extent of this reaction the carbonylation of lithium dipentyl-, diisopropyl-, isopropylcyclohexyl-, and (3-oxapentamethylene)amides was carried out under several reaction conditions, and some results are shown in Table VI. It can be observed again that the higher yields of compounds **3** are obtained in THF–HMPT. For the case of (3-oxapentamethylene)amide, good yields of **2** are obtained in pure THF. It can be observed that the reaction times are longer for reaction media of low dielectric constants.

Discussion

It has been usually assumed[3,11] that the alkylformamides arise from hydrolysis of the carbamoyl anion **5**, which would be the first intermediate in the carbonylation of **1** (eq 2). It has been also reported[2,13] that an equilibrium exists between lithium diisopropylamide and diisopropylformamide (eq 3).

$$i\text{-}Pr_2NLi + HCON\text{-}i\text{-}Pr_2 \rightleftarrows i\text{-}Pr_2NH + LiCON\text{-}i\text{-}Pr_2 \quad (3)$$

It is therefore not unreasonable to assume that an equilibrium could exist between **5** and any free amine present in the system (eq 4) and that this equilibrium could affect the reaction product composition.

$$\underset{\mathbf{5}}{R_2NC({=}O)Li} + R^1R^2NH \rightleftarrows \underset{\mathbf{2}}{HCONR^1R^2} + R^1R^2NLi \quad (4)$$

Nevertheless, the yield of **2b** is almost insensitive to the amount of amine present, suggesting that under the present conditions equilibrium 4 is well on the left, or that it is overwhelmed by the other reactions. In fact, although **2** has always been[1,3,4,9,13] assumed to come from hydrolysis of **5**, which has been considered "an unexplained island of stability in the area of acyl anions",[3] the present results

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[17] Although the carbamoyl anion is usually written as shown by **5b** we have evidence that could suggest some carbenoid character. X-ray diffraction studies of dihaptocarbamoyls of U and Th are also consistent with oxycarbenoid structures.[18]

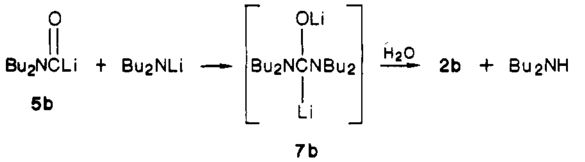
[18] Fagan, P. J.; Manriquez, J. M.; Vollmer, S. H.; Day, C. S.; Day, V. N.; Marks, T. J. *J. Am. Chem. Soc.* 1981, *103*, 2206.

Table VI. Reaction of Lithium Alkylamides with Carbon Monoxide at 0 °C[a]

amide	solvent	yield R^1R^2NCOH	yield $(R^1R^2NC(=O)C(OH)H)_2O$	yield $(R^1R^2NC(=O))_2CHOH$	$t_{1/2}$, min
$LiN(n\text{-}C_5H_{11})_2$	ligroin–THF (1:2)	19.0	68.5		5.0
	THF	7.7	79.2		2.3
	THF–HMPT (1:2)	3.7	89.9		1.0
$Li\overline{N(CH_2)_2OCH_2C}H_2$	THF	80.0	18.9		1.0
	THF–HMPT (1:1)	16.3	81.1		0.4
$LiN\text{-}i\text{-}Pr(c\text{-}C_6H_{11})$	ligroine	38.5	27.5	29.0	15.5
$LiN(n\text{-}C_4H_9)_2$	hexane	5.6	46.8	45.0	6.0
	THF–HMPT (1:1)		100.0		1.5
$LiN(c\text{-}C_6H_{11})_2$	hexane	24.5	10.0	45.0	19.5
	THF–HMPT (1:1)	7.0	85.5	1.0	4.7

[a] Yields represent percent conversion.

show that **5** is not stable under these reaction conditions. Some additional experiments carried out to test this assumption suggest another pathway which is shown in eq 5.

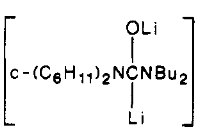


$$\underset{\mathbf{5b}}{\mathrm{Bu_2N\overset{O}{\overset{\|}{C}}Li}} + \mathrm{Bu_2NLi} \longrightarrow \underset{\mathbf{7b}}{\left[\mathrm{Bu_2N\overset{OLi}{\underset{Li}{C}}NBu_2}\right]} \xrightarrow{H_2O} \mathbf{2b} + \mathrm{Bu_2NH} \qquad (5)$$

First of all, when the reaction mixture was allowed to stand overnight in a CO atmosphere before quenching, the reaction product composition was the same (within experimental error) as that obtained when the reaction mixture was quenched immediately after that the CO absorption had ceased. Second, if **5** were present in the reaction mixture before quenching, addition of an electrophile such as butyl bromide should result in the formation of an adduct in an amount similar to the amount of alkylformamide found in the absence of the electrophile, but this is not the case.

Pathway 5 requires that an amount of dibutylamine similar to the amount of **2b** found in the reaction mixture should be formed. A careful determination of dibutylamine in the reagent and in the reaction mixture indicates that this is true within experimental error. Finally, when the reaction was quenched with deuteriomethanol, labeled dibutylamine and labeled dibutylformamide were found in similar amounts. If **5** were stable, some unlabeled **2b** should be found coming from eq 4. Control experiments with alkylformamides-d_1 show that no D/H exchange takes place during the isolation.[3]

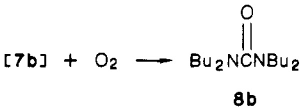
It could be expected, in principle, that intermediate **5** could be obtained by deprotonation of the corresponding amide as is shown in eq 3 for the diisopropylformamide. Notwithstanding, for the case of the amides studied in this work, the carbamoyllithium is not stable in the presence of formamide and several reversible proton transfer and addition reactions occur, which precludes its further use to check eq 5. Nevertheless, indirect experiments were carried out which prove the formation of the intermediate **5** and its further reaction as suggested by eq 5: dicyclohexylformamide was treated with lithium dibutylamine and the formation of a mixed intermediate of structure



$$\left[\mathrm{c\text{-}(C_6H_{11})_2N\overset{OLi}{\underset{Li}{C}}NBu_2}\right]$$

was detected.[19] Similar results were obtained when dibutylformamide was treated with lithium dicyclohexylamide.[19]

Further an unequivocal evidence for the existence of intermediate **7** is provided by oxidation studies. Reaction mixture of several runs carried out under conditions to produce mainly compounds **2** were treated with oxygen prior to the regular workup. Alkylformamides were not found; rather tetraalkylureas **8** (eq 6) are obtained instead, in the same yield expected for compound **2**.



$$[\mathbf{7b}] + O_2 \longrightarrow \underset{\mathbf{8b}}{\mathrm{Bu_2N\overset{O}{\overset{\|}{C}}NBu_2}} \qquad (6)$$

The formation of compound **8b** is good evidence for the existence of intermediate **7b** and a suitable method of preparation of this type of compounds. Similarly, tetrabutylketomalonamide can be obtained in excellent yield by oxygen quenching of the lithium dibutylamide carbonylation carried out under conditions to get **3** or **4** in good yields.[19]

Conclusions

The present paper reports experimental details that show how the carbonylation of lithium amides can be constructively used to prepare dialkylformamides, dialkylglyoxylamides, and tetraalkyltartronamides in good yields. It also reports workup conditions that allow the use of the reaction for the preparation of tetraalkylureas or tetraalkylketomalonamides. The yields of compounds obtained by this short and rapid procedure are much higher than those afforded by the less direct methods of preparation, particularly for the polycarbonyl compounds.

Although carbamoyl anion is the first intermediate formed in the present reaction, this study shows that it is not stable under the reaction conditions and gives evidence that alkylformamides are transformed by hydrolysis of a second precursor, the dilithium tetraalkylurea dianion.

Experimental Section

All reactions involving organolithium reagents were carried out by using standard techniques for the manipulation of air- and water-sensitive compounds.[20] All compounds reported here are fully characterized by mass spectrometry (using a Varian Mat CH 7A spectrometer), infrared spectroscopy (recorded on a Perkin-Elmer IR 121 spectrophotometer), and nuclear magnetic resonance spectroscopy (determined on a Varian 100 spectrometer) and showed spectral characteristics consistent with the spectra of authentic samples. The GLC analyses were carried out on a 5830 Hewlett-Packard gas chromatograph; GC–MS analyses were performed on a Varian 1440 gas chromatograph coupled to the Varian Mat CH 7A mass spectrometer equipped with a Varian

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[19] Pérez, D.; Lewkowicz, E.; Nudelman, N. S., to be submitted.

[20] Shriver, D. F. *The Manipulation of Air-Sensitive Compounds*; McGraw-Hill: New York, 1969; Chapter 7.

Mat Data System 166 computer. Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Hexane and THF were purified as previously described[21] and were distilled from dark blue solutions of benzophenone ketyl under nitrogen immediately before using. Carbon monoxide was generated by standard procedures[22] and was purified by passing through a column of potassium hydroxide and then bubbling through a solution of benzophenone ketyl in toluene. *n*-Butyllithium,[23] *N*,*N*-dibutylformamide,[24] and *N*,*N*,*N'*,*N'*-tetrabutylhydroxymalonamide[24] were prepared as previously described. Commercial dialkylamines were left overnight over sodium strings, refluxed, and distilled over fresh sodium strings.

Lithium Dialkylamides 1. The corresponding dialkylamine (7.4 mmol) was added dropwise by canula to 7.0 mL of a stirred solution of ca. 0.7 N butyllithium in hexane cooled in an ice bath. The precipitated lithium amide was centrifugated, the solution was removed, and the white crystals were washed thrice with 5 mL of hexane followed by centrifugation each time. The resulting solid was dried under vacuum at room temperature; ca. 500 mg of lithium dibutylamide was obtained as a white powder. Atmospheric pressure was restored by flushing with dry, oxygen-free nitrogen.

For the case of lithium isopropylcyclohexyl- and diisopropylamides, which are soluble in hexane, the preparation was similar, but, since no solid is formed, the solvent was distilled at reduced pressure through a canula until the total volume left was nearly 1.5–2 times the volume of the added amine. The resulting syrup was dissolved in the desired solvent and used immediately.

N,*N*-Dicyclohexylformamide (**2a**): mp 60.2–61.0 °C (lit.[24] mp 62.5–63.5 °C). *N*,*N*-Cyclohexylisopropylformamide (**2e**): bp 212 °C; IR (film) 2880, 1665, 1440, 1200 cm^{-1}; ^{1}H NMR (DCCl$_3$) δ 8.16 (s, 1 H), 8.14 (s, 1 H), 4.26 (m, 1 H), 3.75 (m, 2 H), 3.0 (m, 1 H), 1.7 (m), 1.27 (d), and 1.23 (d) [these three signals integrate for 32 H]. (3-Oxapentamethylene) formamide (**2d**): bp 232–234 °C (lit.[25] bp 234 °C). *N*,*N*-Dipentylformamide (**2c**): mp 20–21 °C; IR (film) 2850, 1650, 1460, 1420, 1120 cm^{-1}; ^{1}H NMR (DCCl$_3$) δ 8.05 (s, 14 H), 3.25 (m, 4 H), 1.35 (m, 12 H), 0.95 (t, 6 H). *N*,*N*-Diisopropylformamide (**2f**): bp 185–187 °C (lit.[26] bp 187–190 °C). **2a**,**c**–**f** were prepared by essentially the same procedure as that used for *N*,*N*-dibutylformamide.[23] A general description of the reactions used for the preparation of some standards follow. Full details of the methods used in each case as well as for other related compounds are given as supplementary material.

***N*,*N*-Dialkylglyoxylamides 3** were prepared by reductive ozonolysis of the diethyl tartrate in methanol, followed by amidation and hydrolysis. They are stable as the hemihydrates. *N*,*N*-Dicyclohexylglyoxylamide (**3a**): mp 115–117 °C (hexane); the structure was confirmed by X-ray analysis.[28] *N*,*N*-Dibutylglyoxylamide (**3b**): IR 3250, 2880, 1650, 1460, 1380, 1300, 1100, 1020 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 5.54 (d, 1 H), 5.26 (d, 1 H), 3.32 (m, 8 H), 1.40 (m, 16 H), 0.92 (m, 12 H); MS (70 eV), *m*/*e* (relative intensity) 186 (3.6), 185 (2.8), 156 (26.6), 114 (37.5) 100 (16.4), 57 (100). *N*,*N*-Dipentylglyoxylamide (**3c**): IR (film) 3300, 2850, 1645, 1450, 1400, 1360, 1260, 1095, 1020, 950, 760 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 5.50 (m, 4 H), 3.33 (m, 8 H), 1.35 (m, 24 H), 0.9 (m, 12 H).

***N*,*N*,*N'*,*N'*-Tetraalkylhydroxymalonamides (4).** Several procedures were examined but the best results were obtained by aminolysis of the malonic acid diethyl ester, followed by acetoxylation with lead tetraacetate and hydrolysis. The overall yield was below 10%. *N*,*N*,*N'*,*N'*-Tetracyclohexylhydroxymalonamide (**4a**): mp 194–197 °C; IR (KBr) 3300, 1640, 1300, 1270, 1220, 1180, 1090, 990, 890 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.92 (d, 1 H), 4.78 (d, 1 H), 3.62 (m, 2 H), 2.96 (m, 2 H), 2.5 (m, 4 H), 2.0–1.0 (m, 36 H); MS (70 eV), *m*/*e* (relative intensity) 446 (M$^+$, 0.5), 283 (31.1), 180 (35.9), 156 (18.0), 138 (34.9), 126 (52.5), 98 (29.0), 83 (100), 55 (70.1). *N*,*N*,*N'*,*N'*-Tetrabutylhydroxymalonamide (**4b**): IR (film) 3300, 2880, 1650, 1460, 1440, 1380, 1200, 1080 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.85 (d) and 4.75 (d) [2 H], 3.3 (m, 8 H), 1.45 (m, 16 H), 0.95 (t, 12 H); MS (70 eV), *m*/*e* (relative intensity) 342 (M$^+$, 7), 299 (3), 186 (100), 183 (13), 156 (34), 128 (45), 129 (6), 129 (6), 114 (10), 86 (33). *N*,*N*,*N'*,*N'*-Tetrapentylhydroxymalonamide (**4c**): IR (film) 3300, 2850, 1650, 1460, 1210 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.8 (m, 2 H), 3.3 (m, 8 H), 1.8–1.1 (m, 2 H), 0.9 (m, 12 H); MS (70 eV), *m*/*e* (relative intensity) 398 (M$^+$, 11.7), 341 (68.0), 214 (100), 184 (49.6), 156 (54.4). Bis(3-oxapentamethylene)hydroxymalonamide (**4d**): mp 170–174 °C; IR (KBr) 3300, 2850, 1635, 1100 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.73 (m, 2 H), 3.95 (m, 8 H), 3.72 (m, 8 H); MS (70 eV), *m*/*e* (relative intensity) 258 (M$^+$, 4.4), 144 (34), 114 (100), 87 (39.3), 86 (31.4), 70 (81.4). *N*,*N'*-dicyclohexyl-*N*,*N'*-diisopropylhydroxymalonamide (**4e**): IR (film) 3300, 2870, 1640, 1460, 1370, 1100, 1000, 900 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.84 (d, 1 H), 4.72 (d, 1 H), 4.1 (m, 2 H), 3.5 (m), 2.85 (m), 2.0-1.0 (m), 1.42 (d), 1.39 (d), 1.18 (d) [35 H].

N,*N*-Dibutylvaleramide,[29,30] dicyclohexylmethylamine,[31] and dibutylmethylamine were prepared by standard procedures.

Reaction of Lithium Dialkylamide with Carbon Monoxide. (a) General Procedure. A round-bottomed flask 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. Ligroin (3–4 mL) was added and heated to boiling until almost complete evaporation. With the remaining ligroin still boiling, the flask was capped with a no-air stopper, it was left to cool at room temperature and then put into an ice bath over vigorous magnetic stirring. A 10% lithium amide solution (7–8 mL) in THF was added by a cannula, and the stirred solution was exposed to carbon monoxide (ca. 900 mmHg). The major amount of carbon monoxide was absorbed within the first 3–4 min, and the gas absorption was over in 10–15 min. To assure there were no further steps involving slower absorption of carbon monoxide some experiments were run allowing the reaction mixture to remain several hours in the CO atmosphere, but no variations in the gas volume were observed. Once the reaction was complete, it was quenched with 1–2 mL of distilled water, which had been previously boiled to eliminate any dissolved oxygen and cooled under nitrogen. (This procedure is necessary since some of the intermediates are easily oxidized). The remaining carbon monoxide was evacuated, and 10 mL of THF was added and then 500 mg of NaHCO$_3$ added; after careful mixing the organic phase was quantitatively analyzed by GLC.

(b) Variation in the [Free Amine]/[Lithium Amide] Ratio. The lithium amide prepared according to the procedure described above contains a [free amine]/[lithium amide] = 0.6–0.7, i.e., in the first part of the plateau of Figure 1. For reactions at higher ratios, the desired amounts of free amine were added to the reaction flask before carbon monoxide exposure. For reactions at lower ratios the lithium amide was prepared as described above, but after drying it at room temperature it was vacuum-dried in a 50–60 °C bath for 30 min. In this way most of the remaining amine is eliminated. For reactions carried out in the presence of tributylamine, the reagent was prepared under conditions to get a low [amine]/[lithium amide] ratio, and then the tributylamine was added to the reaction flask before the CO exposure.

(c) Variation in the [Lithium Amide]. A stock solution of 1 was prepared and titrated. Further dilutions of the stock solution were made by weighing. A potentially important source of error is hydrolysis of the reagent due to unavoidable traces of water in the solvent, especially in the more diluted solutions, but careful determinations of the concentration of the reagent in the diluted solutions showed that, if any, hydrolysis of the reagent by added solvent was negligible.

(d) Variation in the Temperature. For reactions carried at temperatures above 0 °C, thermostated baths were used, at −78 °C a dry ice–acetone bath was used, and at −40 or −95 °C baths

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of liquid air in chlorobenzene or in chloromethane, respectively, were used.

(e) Variation in Solvent, Cosolvent, and Added Salts. For reactions carried out in hexane, the reagent was prepared directly into the reaction flask by the usual procedure until the white crystals were obtained. Hexane was added, and the suspension was exposed to CO. After quenching of the reaction a double amount of THF was added to assure complete dissolution of the organic products. For reactions carried out in hexane–THF mixed solvents, concentrated solutions of **1** in THF were added to the desired amount of hexane contained in the reaction flask. In the reactions carried out in hexane–THF (3.5:0.5) a double amount of THF was added after the reaction was quenched. In the reactions carried out in HMPT, HMPT (Aldrich) without purification was added in the desired amount into the reaction containing the THF solution of **1**. For reactions in the presence of DABCO, bisublimated DABCO was added to THF, and this solution was added to **1**.

LiCl and LiBr were dried at 350 °C for several hours and cooled in a desiccator. Lithium *tert*-butoxide: in a test tube was put 2.5 mL of 1 M BuLi in ligroin, the solvent was distilled at reduced pressure, the residue was diluted with 1.5 mL of THF, and 185 mg (2.5 mmol) of *tert*-butyl alcohol was added at 0 °C. This solution was transferred into a reagent solution of a concentration of **1** higher than usual.

(f) In the Presence of Alkyl Halide. A 1.5 M solution of **1** in THF was prepared by the standard procedure. Butyl chloride or bromide (2 mL) was added to a reaction flask provided with a stirring bar in a reduced pressure of hexane. The pressure was made ca. 900 mmHg with CO, and 2 mL of the 1.5 M solution of **1** was added at once under vigorous stirring. The general procedure was then followed.

Isolation and Purified of the Reaction Products. For preparative purposes the organic layer after quenching of the reaction was diluted with five volumes of ethyl ether. The ether extract was washed twice with 10% HCl, then with $NaHCO_3$ saturated solution, and with water. The organic phase was dried; distillation of the solvent at reduced pressure afforded a sweet-smelling yellow oil. The product mixture (2 g) of the reaction of **1b** was chromatographed in a 150 g silica column. Elution with dichloromethane, followed by ethyl acetate afforded pure tetrabutylhydroxymalonamide and then a mixture of dibutylformamide and dibutylglyoxylamide hemihydrate. The mixture was chromatographed in 20 g of neutral alumina. Elution with ethyl acetate and then with methanol afforded pure **2b** and then part of **3b**. (The behavior of **3b** in alumina is very different from that in silica. **2b** and **3b** have an almost identical interaction with silica: they exhibit identical R_f in all the solvents tested: going from 0 in hexane to 1 in methanol. But **3** strongly interacts with alumina and the R_f on alumina TLC is 0 for all the solvents tested. While recovery of **2b** and **4b** from the columns is almost quantitative, only 50% of **3b** could be recovered from alumina columns in the best case. The fraction of **3b** remaining in the alumina could not be eluted even with solvents such as methanol–5% ammonia or methanol–5% acetic acid or even by boiling the alumina with methanol.) The best results were obtained by keeping the sample weight/alumina weight ratio as low as possible, which was ca. 1:10. Under these conditions the recovery of **3b** was slightly higher than 50%. When the purpose of the reaction was synthesis of compounds **3** the following workup was used: After dilution of the reaction mixture with ether, the solution was treated twice with 5% H_3PO_4 and extracted with $NaHCO_3$ and with water. The organic layer was dried, and distillation of the solvent rendered with vitreous mass. Treatment of this residue with hexane and a small amount of boiling dichloromethane gave a clear solution, which afforded white crystals of pure **3** on cooling; isolated yields > 90%.

When the reaction is carried out under conditions to get high yields of compounds **4**, the reaction mixture is washed in the usual way and the solid crystallized from hexane. The slight contamination with compound **3** can be avoided by running the general procedure in hexane with a very low content of THF, e.g., the reaction mixture of **1a** under these conditions rendered white crystals of crude **4a**: mp 194–197 °C.

When compounds **2** are desired the best procedure is column chromatography of the reaction mixture. Ethyl acetate elution of the reaction mixture of **1a** rendered pure **2a**: mp 58–60 °C.

Quantitative Determinations of the Reagent Concentration and the Product Composition. The concentration of **1** was routinely determined by the double titration method[23] and by weighing the solid, but when more precise determinations were needed another method was devised. It was observed that alkylation of **1** with alkyl bromide is very fast even at very low temperature while secondary amines treated with alkyl bromides (3–4 times molar excess) in THF at 30 °C for 2 days do not show any reaction. A parallel undesirable elimination occurs at a small extent in the alkyl bromide, and for this reason it is better to use methyl iodide; although the undesired reaction of secondary amines is faster with methyl iodide than with alkyl bromide. Anyway, very accurate and reproducible results were obtained with the following procedure: the reagents were cooled at −40 °C and the lithium amide solution was added dropwise to 3 volumes of a hexane solution of methyl iodide. Under these conditions the secondary reactions are negligible, and the reaction mixture can be kept unchanged for at least 30 min at −20 °C; but within the first 10 min after mixing of the reagents, the reaction mixture was treated with alkaline aqueous solution and gas chromatographed, using *n*-decane as internal standard. Determinations were done by quenching the reaction mixture 1, 2, and 5 min after mixing of the reagents, and the results are identical within the experimental error, showing that the reaction is completed in the first minute. This method allows simultaneous determination of the amount of free amine and lithium amide in the reagent. It was also observed that 1:20 dilutions of **1** do not introduce any hydrolysis of the reagent.

GLC quantitative determination of the product composition was done by two methods: using the integer recorder and by weights of each peak cut from a double Xerox copy of the chromatogram. The difference between duplicate determinations by both methods was smaller than 2%. Since the relationship between the weight of the sample and the area of the signal is related to the amount of compound present in the reaction mixture for compounmds **2** and **4**, it was necessary to determine the "response" of these compounds as a function of the concentration by using decalin as internal standard. The variation is important for low values of sample mass. A wide set of reference chromatograms from several standard mixtures of different relative compositions was prepared in order to use, in each case, the "response" of standard samples of composition very similar to the unknown mixture to get a precise analysis.

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Registry No. **1a**, 4111-55-1; **1b**, 25440-26-0; **1c**, 111635-26-8; **1d**, 37828-58-3; **1e**, 32400-20-7; **1f**, 4111-54-0; **2a**, 22699-63-4; **2b**, 761-65-9; **2c**, 26598-27-6; **2d**, 4394-85-8; **2e**, 1195-42-2; **2f**, 2700-30-3; **3a**, 83862-72-0; **3b**, 83862-73-1; **3c**, 111689-11-3; **3d**, 111635-30-4; **3e**, 111689-12-4; **4a**, 82024-47-3; **4b**, 79251-71-1; **4b** (acetate), 79251-69-7; **4c**, 111635-27-9; **4d**, 111635-28-0; **4e**, 111635-29-1; **6**, 14313-88-3; **12**, 19757-96-1; **13**, 14287-98-0; **16**, 10256-01-6; **16** (acetate), 111635-32-6; **17**, 111635-33-7; **17** (acetate), 111635-34-8; Bu_2NH, 111-92-2; $EtO_2CCH{=}CHCO_2Et$, 623-91-6; $EtO_2CCH_2CO_2Et$, 105-53-3; $H_3C(CH_2)_3CO_2H$, 109-52-4; $H_3C(CH_2)_3COCl$, 638-29-9; Bu_2NMe, 3405-45-6.

Supplementary Material Available: Methods of preparation, physical constants, IR, ^1H NMR and mass spectra for formamides **2**; glyoxylamides **3**; hydroxymalonamides **4** and for the following compounds: *N,N*-diisopropylformamide (**2f**); ethyl ester of the hemiacetal of the glyoxylic acid (**12**); *N,N,N′,N′*-tetrabutylmalonamide (**13**); *N,N*-dibutylvaleramide (**18**); dicyclohexylmethylamine (**19**) and dibutylmethylamine (**20**) (6 pages). Ordering information is given on any current masthead page.