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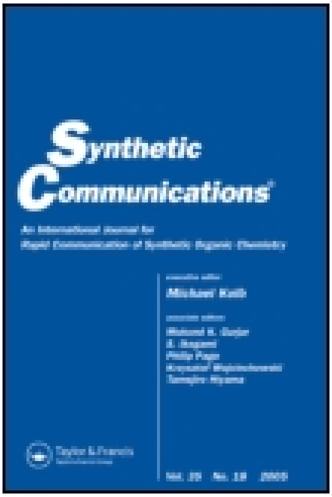

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Facile Synthesis of Oxamides by Efficient Trapping of Carbamoyl Lithiums with Isocyanates

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FACILE SYNTHESIS OF OXAMIDES BY EFFICIENT TRAPPING OF CARBAMOYL LITHIUMS WITH ISOCYANATES

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Abstract : Unsymmetrical oxamides are conveniently synthesized in good yields by a new trapping reaction of unstable carbamoyl lithiums with isocyanates.

Carbamoyl anoins **1**, readily prepared from lithium dialkylamides and carbon monoxide, are unstable under ordinary conditions because of having a negative charge on the carbonyl carbon of **1**. Therefore, the applications of **1** to organic syntheses are considerably limited. Only the syntheses of amides[1] and S-alkyl thiocarbamates[2] were found by

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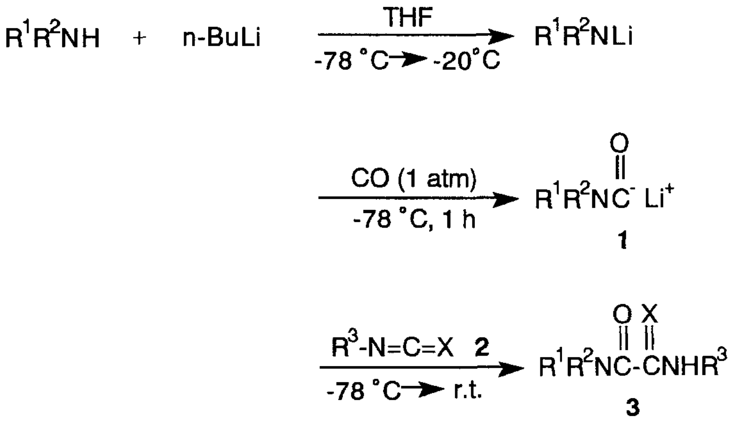
trapping of **1** with electrophiles such as aldehyde, ketone, and elemental sulfur at low temperature.

We herein wish to report a new trapping reaction of unstable carbamoyl lithiums **1** by isocyanates **2** to give oxamide derivatives **3** in good yields (Eq. 1). To our best knowledge, the reactivity of **1** toward heterocumulenes has not been hitherto known.[3]

At the outset, the trapping of carbamoyl lithiums **1** with isocyanates **2** was examined. For example, diethylcarbamoyl lithium (**1 a**) was prepared from the reaction of lithium diethylamide with carbon monoxide at -78 °C for 1 h. Then, the reaction of **1 a** with phenyl isocyanate (**2 a**) was performed at -78 °C followed by gradual warmed-up of the mixture to room temperature to give N,N-diethyl-N'-phenyloxamide (**3 a**) in a 83% yield.



$$R^1R^2NH \;+\; n\text{-BuLi} \xrightarrow[-78\,^\circ C \rightarrow -20^\circ C]{THF} R^1R^2NLi \xrightarrow[-78\,^\circ C,\ 1\ h]{CO\ (1\ atm)} \underset{\mathbf{1}}{R^1R^2N\overset{O}{\overset{\|}{C}}{}^-\ Li^+} \xrightarrow[-78\,^\circ C \rightarrow r.t.]{R^3\text{-}N{=}C{=}X\ \ \mathbf{2}} \underset{\mathbf{3}}{R^1R^2N\overset{O}{\overset{\|}{C}}\text{-}\overset{X}{\overset{\|}{C}}NHR^3} \quad (1)$$

A variety of unsymmetrical oxamides (**3a-h**) were obtained from the reaction of **1** with isocyanates **2** in a similar manner, as shown in Table 1. Most of oxamides **3** were successfully afforded in good yields,

Table 1. Synthesis of Oxamides (**3a-i**)

amine		heterocumulene		product
R^1	R^2	R^3	X	yield, %[a)]
Et	Et	Ph	O (**2 a**)	83 (**3 a**)
		c-Hex	O (**2 b**)	77 (**3 b**)
		t-Bu	O (**2 c**)	62 (**3 c**)
		1-Naphth	O (**2 d**)	39 (**3 d**)
n-Pr	n-Pr	Ph	O (**2 a**)	93 (**3 e**)
i-Pr	i-Pr	Ph	O (**2 a**)	84 (**3 f**)
		c-Hex	O (**2 b**)	72 (**3 g**)
$-(CH_2)_4-$		Ph	O (**2 a**)	56 (**3 h**)
Et	Et	Ph	S (**2 e**)	34 (**3 i**)
		$PhCH_2$	S (**2 f**)	mixture
n-Pr	n-Pr	Ph	S (**2 e**)	mixture
$-(CH_2)_2-O-(CH_2)_2-$		Ph	S (**2 e**)	0
Et	Et	c-Hex	c-Hex-N (**2 g**)	0
n-Pr	n-Pr	c-Hex	c-Hex-N (**2 g**)	0
i-Pr	i-Pr	c-Hex	c-Hex-N (**2 g**)	mixture

a) Isolated yields. All of the products were characterized by spectroscopic methods such as IR, ^{1}H-NMR, MS, and exact MS spectra.

even in the case of using bulky tert-butyl isocyanate as a trapping reagent.

Employment of isothiocyanates (**2e**, **f**) (X=S) or dicyclohexyl carbodiimide (**2g**) (R^3=c-Hex, X=c-Hex-N) instead of isocyanates (**2a-d**) (X=O) as a trapping electrophile of carbamoyl lithiums **1** resulted in the formation of a complex mixture of many products or almost no reaction except for the synthesis of N,N-diethyl-N'-phenyl-thiooxamide (**3i**) owing to low reactivities of those electrophiles (**2e-g**).

In summary, we examined the reactivity of carbamoyl lithiums **1** with heterocumulenes. In the case of the reaction with isocyanates **2**, **1** were readily trapped to give oxamide derivatives **3** in good yields. However, isothiocyanates and carbodiimide **2** were not suitable for trapping of **1**. The present reaction of **1** with isocyanates **2** is not only an effective method for trapping of unstable carbamoyl anions **1** but also a new convenient method for selective synthesis of unsymmetrical oxamides **3**.

EXPERIMENTAL

General Comments : Gas chromatography (GC) was measured using Shimadzu GC-7A. ^{1}H-NMR spectra were obtained through JEOL JNM-EX270 spectrometer. Chemical shifts were reported in ppm relative to tetra-methylsilane (δ-units). Infrared (IR) spectra were recorded using a JASCO A-3 spectrometer. Mass spectra were recorded using JEOL JMS-DX303HF spectrometer. THF was dried over sodium wire before use and purified freshly by distillation.

A Typical Procedure for Synthesis of N,N-Diethyl-N'-phenyloxamide (3a) :A solution of 10%w/v n-butyl lithium in hexane (6.4 mL, 10 mmol) was added slowly to a THF solution (20 mL) of diethylamine (1.03 mL, 10 mmol) at -78 °C, and the solution was gradually warmed to -20 °C with stirring. Then, the resulting colorless solution of lithium diethylamide was cooled to -78 °C and was vigorously stirred under carbon monoxide (1 atm) atmosphere for 1 h at -78 °C. After the absorption of carbon monoxide was completed, phenyl isocyanate (**2 a**) was added at -78 °C to the orange solution of N,N-diethylcarbamoyl lithium (**1 a**). This solution was gradually warmed-up to room temperature. The reaction mixture was then poured into aq. 1N HCl (100 mL), and extracted by Et_2O (100 mL, 2 X 50 mL). The extract was dried over anhydrous $MgSO_4$ and after removal of the drying agent by filtration, the solvent was evaporated. Purification by short-column chromatography (silica gel, ethyl acetate) gave 1.83 g (83%) of N,N-diethyl-N'-phenyloxamide (**3 a**).[4]

N,N-diethyl-N'-phenyloxamide (**3 a**). Oil; IR (neat) 3270 (N-H), 1690, 1630 (C=O), 1600 cm^{-1} (C=C) ; ^1H-NMR ($CDCl_3$) δ 1.06-1.19 (m, 6H, CH_3), 3.33-3.41 (m, 4H, CH_2), 6.96-7.75 (m, 5H, Ph), 8.11 (s, 0.11H, NH), 8.64 (s, 0.22H, NH), 10.67 (s, 0.64H, OH) ; MS, m/z (%), 220 (M^+, 100), 100 (80), 72 (89) ; exact MS calcd. 220.1212, found 220.1187.

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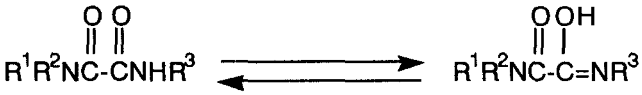
3. The reaction of acyl anions with heterocumulenes (isocyanates, isothiocyanates, and carbodiimides) was reported, see : Seyferth, D.; Hui, R. C. *Tetrahedron Lett.*, **1984**, *25*, 5251, Seyferth, D.; Hui, R. C. *J. Org. Chem.*, **1985**, *50*, 1985.

4. It was observed by ^{1}H-NMR analysis of oxamides **3** that **3** are in equilibrium with **5**.



$$\mathrm{R^1R^2N\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}NHR^3} \rightleftharpoons \mathrm{R^1R^2N\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{|}{C}}=NR^3}$$

3 **5**

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