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High Yield Acyl Anion Trapping Reactions: Direct Nucleophilic Acylation of Isocyanates and Isothiocyanates.

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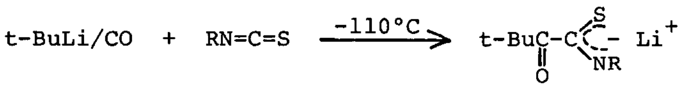
Summary. The reactions of t-BuLi, sec-BuLi and n-BuLi with CO in the presence of isothiocyanates and isocyanates gives, after hydrolytic work-up, α-oxothioamides, RC(O)C(S)NHR', and α-oxoamides, RC(O)C(O)NHR', respectively, in good yield. Competition from the direct reaction of RLi with the substrate is encountered only in the case of reactions of the n-BuLi/CO system with isocyanates.

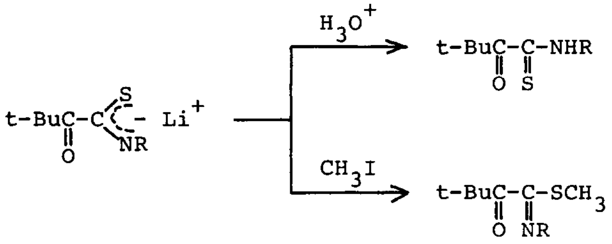
The additions of organolithium reagents to the heterocumulene systems of organic isocyanates and isothiocyanates are known reactions.[1,2] They are, however, not standard practice in organic synthesis since there are more practical routes to secondary amides and thioamides. The addition of acyl anions to isocyanates and isothiocyanates would be expected to produce, after hydrolysis, α-oxoamides, RC(O)C(O)NHR', and α-oxothioamides, RC(O)C(S)NHR', and it might be useful to have such a new route to α-dicarbonyl and α-carbonylthiocarbonyl derivatives of this type.

In recent papers we have reported that when acyllithium reagents, RC(O)Li, are generated by the addition of alkyllithium reagents to carbon monoxide at very low temperature in the presence of a suitable electrophile, nucleophilic acylation of the latter may, in many cases, be effected in good yield. Among the electrophiles successfully employed in this procedure were aldehydes and ketones,[3,4] esters,[3,4] lactones,[5] organic disulfides,[6] carbon disulfide and carbonyl sulfide,[7] and trialkylchlorosilanes.[8] We report here that such nucleophilic acylation of isocyanates and isothiocyanates can be carried out, often in high yield, using our low temperature, in situ procedure.

We describe as a typical experiment the acylation of methyl isothiocyanate with the t-BuLi/CO reagent. A solution of 9.06 mmol of CH_3NCS in 300 ml of 4:4:1 THF/Et_2O/pentane was prepared (under nitrogen) in a 500 ml three-necked Morton flask equipped with an overhead stirrer, a Claisen adapter (fitted with a pentane thermometer and a gas outlet tube), and a no-air stopper which held a gas dispersion tube (which was connected to a CO cylinder)and was cooled to -110°C. Gaseous carbon monoxide was bubbled through this solution for 30 min, and then, while the low temperature and the carbon monoxide stream were maintained, 4.20 ml of 2.16N t-butyllithium (9.07 mmol) in pentane was added at a rate of 0.24 ml per min. by means of an Orion syringe pump. The resulting orange-brown solution was stirred for 2h at -110° ± 5°C while the CO stream was continued. Subsequently, it was allowed to warm to room temperature, still under CO. A color change to orange was noted. The reaction mixture then was hydrolyzed with saturated NH_4Cl solution. The now yellow organic phase was dried and concentrated at reduced pressure. Examination of the residue by GLC showed the presence of a single product, $(CH_3)_3CC(O)C(S)NHCH_3$, mp 42-43°C, in 72% yield. In the solid state this compound is light yellow; molten it is orange-red. Its analysis was correct (C,H,N) and its mass spectrum showed the molecular ion at m/z = 159.1. Its ^1H and ^{13}C NMR spectra were in agreement with the indicated structure. Similar reactions of the t-BuLi/CO system with C_2H_5NCS, $n-C_4H_9NCS$ and $(CH_3)_2CHNCS$, followed by hydrolytic work-up, gave the expected t-BuC(O)C(S)NHR products in high yield (Table 1), but phenyl isothiocyanate did not appear to react with *in situ*-generated t-BuC(O)Li, at least under these conditions. In other experiments the reaction mixture was treated with methyl iodide at -50°C rather than with aqueous ammonium chloride solution. In these cases, S-methylation occurred (eq.1,2). The α-oxothioimidates thus formed were produced in good yield (Table 1). *n*-Butyllithium and sec-butyllithium reacted with CO in the presence of alkyl (but not phenyl) isothiocyanates equally well in the sense of eq.1, giving high yields of the expected products (Table 1). In the case of *n*-butyllithium it was found necessary to carry out the reactions at -135°C (in a $3Me_2O$:1THF solvent system).

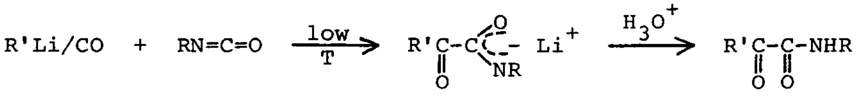


$$\text{t-BuLi/CO} + \text{RN=C=S} \xrightarrow{-110°C} \text{t-Bu}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-C}(\text{S})(\text{NR})^{-}\ \text{Li}^{+} \quad (1)$$



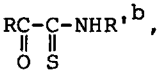
$$\text{t-Bu}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-C}(\text{S})(\text{NR})^{-}\ \text{Li}^{+} \begin{cases} \xrightarrow{H_3O^+} \text{t-Bu}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-}\underset{\underset{\text{S}}{\|}}{\text{C}}\text{-NHR} \\ \xrightarrow{CH_3I} \text{t-Bu}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-}\underset{\underset{\text{NR}}{\|}}{\text{C}}\text{-SCH}_3 \end{cases} \quad (2)$$

The same procedure worked well in effecting nucleophilic acylation of alkyl isocyanates with the RLi/CO *in situ* reagent at low temperature (eq.3) The



$$\text{R'Li/CO} + \text{RN=C=O} \xrightarrow[T]{low} \text{R'}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-C}(\text{O})(\text{NR})^{-}\ \text{Li}^{+} \xrightarrow{H_3O^+} \text{R'}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{-NHR} \quad (3)$$

TABLE 1. Nucleophilic Acylation of Alkyl Isothiocyanates.[a]

R in RLi	R' in R'NCS	Reaction Temp., °C	 $\underset{O}{\underset{\|}{RC}}-\underset{S}{\underset{\|}{C}}-NHR'$[b], % yield[c]
t-Bu	Me	-110°	72
t-Bu	Et	-110°	71[d]
t-Bu	i-Pr	-110°	70
t-Bu	n-Bu	-110°	80[e]
sec-Bu	Et	-110°	73
sec-Bu	n-Bu	-110°	85
n-Bu	Me	-135°	70
n-Bu	Et	-135°	84
n-Bu	i-Pr	-135°	71
n-Bu	n-Bu	-135°	68

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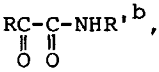
[a] 1:1 Reactant stoichiometry. Work-up by hydrolysis with saturated NH_4Cl solution. [b] All products were characterized by C,H, sometimes N analysis (± 0.4%), and IR and ^1H and, sometimes, ^{13}C NMR spectroscopy. [c] Determined by GLC using the internal standard procedure. [d] Quench with MeI at -50°C gave t-BuC(O)C-(SMe)=NEt (74%). [e] Quench with MeI at -50°C gave t-BuC(O)C(SMe)=NBu-n (69%).

TABLE 2. Nucleophilic Acylation of Isocyanates.[a]

R in RLi	R' in R'NCO	Reaction Temp., °C	 $\underset{O}{\underset{\|}{RC}}-\underset{O}{\underset{\|}{C}}-NHR'$[b], % yield[c]
t-Bu	Me	-110°	84
t-Bu	Et	-110°	84[d]
t-Bu	i-Pr	-110°	86
t-Bu	n-Bu	-110°	76
t-Bu	t-Bu	-110°	52[e]
t-Bu	Ph	-110°	78
sec-Bu	n-Bu	-110°	75
sec-Bu	Ph	-110°	70
n-Bu	Et	-135°	41[f]
n-Bu	n-Bu	-135°	43[g]
n-Bu	i-Pr	-135°	61[h]
n-Bu	t-Bu	-135°	58

[a,b,c] cf. footnotes a,b,c in Table 1. [d] Quench with Me_3SiCl gave t-BuC(O)C(OSi-Me_3)=NEt (60%). [e] Also t-BuC(O)C(t-Bu)(OH)C(O)NHBu-t in 31% yield. [f] Also n-BuC(O)NHEt (42%). [g] Also n-BuC(O)NHBu-n (36%). [h] Also n-Bu(C)NHPr-i (26%).

α-oxoamide yields were high in the case of t-BuLi and sec-BuLi when the reactions were carried out at -110°C (Table 2). In contrast to the result with PhNCS, phenyl isocyanate reacted readily and t-BuC(O)C(O)NHPh was produced in 78% yield upon hydrolysis of the reaction mixture. As expected, treatment of the t-BuLi/CO/C_2H_5NCO reaction mixture with Me_3SiCl resulted in O-silylation: t-BuC(O)C($OSiMe_3$)=NC_2H_5 was produced in 60% yield.

The *n*-BuLi/CO/RNCO reactions were less satisfactory. The isocyanates are quite reactive toward the less hindered *n*-butyllithium reagent even at -135°C. Although the expected α-oxoamides were produced, substantial quantities of the amides resulting from *n*-BuLi attack at RNCO were formed as well. Only in the case of the hindered t-butyl isocyanate was the α-oxoamide, *n*-BuC(O)C(O)NHBu-*t*, formed as the sole product.

This work has provided more examples of the high yield, *direct* nucleophilic acylation of organic electrophiles by the *in situ*, low temperature RLi/CO system. While this methodology does not provide the solution to all problems of nucleophilic acylation, it is now clear that it can be applied with good advantage to the nucleophilic acylation of diverse organic carbonyl and thiocarbonyl compounds.

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