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HIGH YIELD ACYL ANION TRANSFER REACTIONS: NUCLEOPHILIC ACYLATION OF ALDEHYDES

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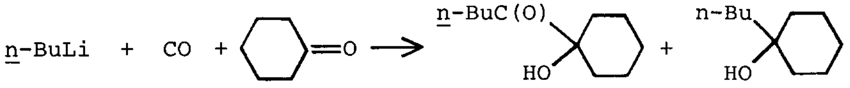
Summary. Aldehydes may be acylated to give R'CH(OH)C(O)R in good yield by the RLi/CO *in situ* procedure at very low temperatures. Examples are given of ketone acylations which demonstrate the advantages of 1:1 RLi/substrate stoichiometry and the use of lower (-135°C) temperature.

We have recently reported preliminary results of our studies of the nucleophilic acylation of ketones and esters using the low temperature *in situ* RLi/CO procedure.[1] In these reactions the alkyllithium reagent was added at a very slow rate to a solution of two molar equivalents of the organic electrophile which was being kept constantly saturated with carbon monoxide at -110°C at atmospheric pressure. In the case of the reactions of *in situ* generated RC(O)Li with ketones the product yields varied from 45 to 92%, and, in many cases, especially with *n*-butyllithium, the carbinol which resulted from the addition of the alkyllithium to the ketone was a by-product, obtained in yields of up to 30% when more reactive ketones were involved. Also, with a more acidic ketone, such as acetophenone, deprotonation by the RLi base was a competing process which resulted in low conversions to the desired product. Reactions of the *in situ* RLi/CO system with aldehydes gave only very low yields of the desired acyloin, RC(O)CH(OH)R'; the major product was that of RLi addition to the C=O bond of the aldehyde.

We have made a more detailed study of the nucleophilic acylation of aldehydes and have found the *in situ* RLi/CO procedure to be preparatively useful. Important reaction variables are the steric factors associated with the alkyllithium and the aldehyde, the reactant stoichiometry and the reaction temperature. Selected results are given in Table I. In the case of Me_3CCHO, a hindered aldehyde, acylation with the *n*-BuLi/CO reagent is a useful reaction when carried out using 1:1 stoichiometry at -135°C.[2] Similar reactions of *sec*-BuLi/CO and *t*-BuLi/CO with Me_3CCHO proceeded in almost quantitative yield. With unhindered aldehydes, the direct addition of *n*-butyllithium to the aldehyde C=O bond is the favored process and no nucleophilic acylation of the aldehydes was observed, even when 1:1 stoichiometry was used at -135°C. However, the *sec*-BuLi/CO and *t*-BuLi/CO systems served well in the nucleophilic acylation of unhindered aldehydes when 1:1 stoichiometry was used (Table I), with acyloin yields being quite satisfactory. The principal side reaction is the "dimerization" of the RC(O)Li reagent to give

LiO(R)C=C(R)OLi (or RC(O)C(Li)(OLi)R); upon hydrolysis or reaction with Me_3SiCl, RCH(OH)C(O)R or $RCH(OSiMe_3)C(O)R$, respectively, are obtained.

Improved acylation product yields were obtained with ketones as well when the improved reaction conditions were used. Cyclohexanone had been a problem when the 1:2 RLi/ketone stoichiometry was applied at -110°C: only a 54% yield of the acylation product had been obtained, and the undesired alkylation product had been obtained in 31% yield (eq.1). Using a 1:1 stoichiometry at -110°C increased the yield of the acylation product to 66% and decreased that of the alkylation product to 15%. Further improvement was realized when the 1:1 reaction was carried out at -135°C: the acylation product yield rose to 73%; that of the alkylation product dropped to 9%. Similar improvements were seen in the case of in situ generated $Me_3CC(O)Li$; at -135°C using 1:1 stoichiometry, a 96% GC yield (87% recrystallized yield) of 1-pivaloylcyclohexanol was obtained.



(1)

Acetophenone, as mentioned above, presented special problems because it underwent enolization to a large extent on reaction with the n-BuLi/CO system. When a 1:2 n-BuLi/$PhC(O)CH_3$ ratio was used at -110°C, and the mixture was quenched with Me_3SiCl, the enolization product, $Me_3SiO(Ph)C=CH_2$, was obtained in 50% yield, and the acylation product, n-BuC(O)C(Me)(Ph)$(OSiMe_3)$, in only 43% yield. The yield of the latter rose to 66% and to 77% while the yield of the former fell to 31% and to 15% as the reaction conditions were changed to 1:1 stoichiometry at -110°C and to 1:1 stoichiometry at -135°C, respectively.

More generally, we have found that for most organic carbonyl compounds the optimum conditions for nucleophilic acylation using in situ-generated acyllithium reagents involve 1:1 RLi/organic substrate stoichiometry. Side reactions such as RLi addition to the C=O function and enolization are minimized when an excess of the organic electrophile is avoided. Also, in many cases, lowering the reaction temperature to -135°C can be beneficial. Under these conditions the reactions are much cleaner and the acylation product yields are gratifyingly high.

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TABLE I. Nucleophilic Acylation of Aldehydes.

R'CH=O	RLi[a]	Reaction Temp., °C	Quenched with	Product, % Yield		
				Alkylation RC(OH)R'	Acylation RC(O)CH(R')OH or RC(O)CH(R')OSiMe$_3$	Dimer
Me$_3$CCHO	n-BuLi[b]	-110	aq.NH$_4$Cl	50	17	--
Me$_3$CCHO	n-BuLi	-110	aq.NH$_4$Cl	34	45	--
Me$_3$CCHO	n-BuLi	-135	aq.NH$_4$Cl	18	62	--
Me$_3$CCHO	sec-BuLi	-135	aq.NH$_4$Cl	--	86	--
Me$_3$CCHO	t-BuLi	-135	aq.NH$_4$Cl	--	90	--
PhCHO	n-BuLi	-135	aq.NH$_4$Cl	45	--	--
PhCHO	sec-BuLi	-135	Me$_3$SiCl	--	78	--
PhCHO	t-BuLi	-110	Me$_3$SiCl	--	95	--
Me$_2$CHCHO	n-BuLi	-135	aq.NH$_4$Cl	49	--	--
Me$_2$CHCHO	sec-BuLi	-110	Me$_3$SiCl	--	64	20
Me$_2$CHCHO	sec-BuLi	-135	Me$_3$SiCl	--	66	24
Me$_2$CHCHO	t-BuLi	-110	Me$_3$SiCl	--	59	19
n-C$_3$H$_7$CHO	n-BuLi	-135	aq.NH$_4$Cl	58	--	--
n-C$_3$H$_7$CHO	sec-BuLi	-110	Me$_3$SiCl	--	55	24
CH$_3$CHO	t-BuLi	-110	Me$_3$SiCl	--	70	trace
n-C$_6$H$_{13}$CHO	t-BuLi	-110	Me$_3$SiCl	--	68	18

[a] All reactions carried out using 1:1 stoichiometry unless otherwise noted.

[b] 2 Me$_3$CCHO/1 n-BuLi stoichiometry.

References and Notes.

1. D. Seyferth, R.M. Weinstein and W.-L. Wang, J. Org. Chem., 48, 1144 (1983).

2. The general procedure detailed in our previous communication[1] was used. In those reactions in which the reaction mixture was maintained at -135°C the solvent system used was THF/dimethyl ether.[3] For instance, in a 12 mmol Me_3CCHO/n-C_4H_9Li/CO reaction the flask was charged with 70 ml of THF and the aldehyde, cooled to -50°C, and then ca. 220 ml of Me_2O was condensed into the flask. Further cooling to -135°C followed and then the solution was saturated with CO.

3. D. Seyferth, D.C. Mueller and F.M. Armbrecht, Jr., Organometal. Chem. Synth. 1, 3 (1970).

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