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A STABLE 1:1 LITHIUM ACYLCYANOCUPRATE. DEPENDENCE OF THE STABILITY OF ACYLCYANOCUPRATES ON THE NATURE OF THE ALKYL SUBSTITUENT.

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SUMMARY

Acylcuprates obtained by carbonylation of R(CN)CuLi cuprates (R = t-Bu, sec-Bu) at low temperature are effective in the direct nucleophilic 1,4-acylation of α,β-unsaturated ketones and aldehydes. The R = t-Bu reagent is sufficiently stable so that it can be used even at room temparature. The R = sec-Bu reagent is best used at -110°C.

In a previous communication[1] we reported a new procedure for the direct nucleophilic 1,4-acylation of α,β-unsaturated ketones and aldehydes. In these syntheses the carbonylation at atmospheric pressure of "higher order" cuprates of type "$R_2(CN)CuLi_2$"[2] was carried out at -110°C in a 4:4:1 (by volume) THF, diethyl ether, pentane mixture. A short time later, an equimolar (based on Cu) amount of the α, β-unsaturated substrate was added. The yields of 1,4-acylation products ranged from 65-85% for R = n-Bu, sec-Bu and t-Bu.

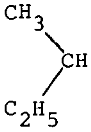
The 1:1 $R_2(CN)CuLi_2$/α,β-unsaturated substrate ratio used followed standard cuprate methodology,[2] but this, of course, wastes one-half of the organic groups charged. In exploratory reactions yields greater than 100% (based on Cu) were obtained when a 1:2 $R_2(CN)CuLi_2$/α,β-unsaturated substrate ratio was used. This led us to examine the carbonylation of 1:1 reagents, i.e., of "R(CN)CuLi".[3] The results of these experiments are reported here since they involve useful new preparative chemistry.

A typical reaction utilizing the $t\text{-}C_4H_9(CN)CuLi$ is described. A 300 mL three-necked flask was charged with 7.26 mmol of CuCN (nitrogen atmosphere). Degassed THF (20 mL) was added and the mixture was cooled to -78°C. t-Butyllithium (1.78N in hexane, 7.12 mmol) was added in portions. The resulting yellow suspension was allowed to warm to 0°C. The colorless solution which formed was cooled to -78°C again and another 180 mL of THF was added. Subsequently, CO was bubbled through a gas dispersion tube into the solution for 30 min. (Method I). While the CO stream was continued, the now yellow solution was allowed to warm to 0°C. Cyclohexen-2-one (7.02 mmol) then was added, slowly by syringe. The reaction mixture was maintained at 0°C for 90 min. under CO. Following warming to room temperature, the reaction mixture was treated with 75 mL of 1:10 NH_4OH/NH_4Cl. The blue aqueous layer was extracted with diethyl ether. The combined organic phases were dried, concentrated and analyzed by GC. The desired product, 3-pivaloylcyclohexanone, was present in 94% yield, based on cyclohexen-2-one. It was identified by comparison of its IR and NMR spectra with those of an authentic sample.[1] Table I gives the results of other experiments with the $t\text{-}C_4H_9(CN)CuLi/CO$ reagent. In some cases the addition of the α,β-unsaturated substrate and its subsequent reaction with the pivaloylcuprate solution were carried out at -20°C. However, it was found that good product yields could be obtained even when the pivaloylcuprate solution was warmed to room temperature immediately before the α,β-unsaturated substrate was added, even though the reagent mixture became grey and heterogeneous at this temperature. For example, addition of cyclohexen-2-one to the $t\text{-}C_4H_9(CN)CuLi/CO$ solution after it had been warmed to room temperature, followed by a reaction time of one hour at room temperature gave the expected 1,4-diketone in 88% yield. Thus the $t\text{-}C_4H_9(CN)CuLi/CO$ reagent is quite stable and gives in general, better yields, exclusively, of the 1,4 acylation product than does the $(t\text{-}C_4H_9)_2(CN)CuLi_2/CO$ system which was reported earlier.[1]

In an alternate procedure (Method II), the $t\text{-}C_4H_9(CN)CuLi$ reagent solution (cooled to -78°C) was cannulated into a 4:4:1 THF, Et_2O, pentane mixture at -110°C which was being kept saturated with a stream of CO. The CO stream was maintained for another 2 hours at -110°C after the addition was complete. The α,β-unsaturated substrate then was added and the reaction mixture stirred at -110°C for 90 min.; work-up as described above followed. This procedure was especially useful in the 1,4-acylation of the more reactive α,β-unsaturated electrophiles whose reactions in Method I gave 1,4-alkylated by-products, e.g. crotonaldehyde, methyl vinyl ketone and 5,6-dihydro-2<u>H</u>-pyran-2-one (Table 1).

The $sec\text{-}C_4H_9(CN)CuLi$ reagent is less stable. Best results were obtained using Method II, in which the cuprate reagent, prepared at -78°C, was carbonylated at -110°C for 30 min., with subsequent addition of the α,β-unsaturated substrate at -110°C. Excellent yields of 1,4-diketones were thus obtained (Table I) and the yield of the 1,4-ketoaldehyde prepared was good. In experiments in which the $sec\text{-}C_4H_9(CN)CuLi/CO$ reagent was allowed to warm to higher temperatures after its preparation at -110°C before the reaction with the α,β-unsaturated substrate was carried out (at the higher temperature for 90 min.) the 1,4-diketone yields were much lower: 44% in a reaction with cyclohexen-2-one at -20°C, 21% in a reaction at 0°C.

TABLE I. Direct Nucleophilic 1,4 Acylation of α,β-Unsaturated Substrates.

Reagent, R(CN)CuLi R=	α,β-Unsaturated Substrate	Method (see text)	Product (% Yield)
Me_3C	Cyclohexen-2-one	I[a]	3-Pivaloylcyclohexanone (94)
	$CH_2=CHC(O)CH_3$	I[b]	$Me_3CC(O)CH_2CH_2C(O)CH_3$ (68)[c]
	$CH_3CH=CHC(O)Et$	I[a]	$Me_3CC(O)CH(CH_3)CH_2C(O)Et$ (93)
	$PhCH=CHC(O)CH_3$	I[b]	$Me_3CC(O)CH(Ph)CH_2C(O)CH_3$ (88)
	$EtCH=CHCHO$	I[b]	$Me_3CC(O)CH(Et)CH_2CHO$ (72)
	$CH_3CH=CHCO_2CH_3$	I[d]	$Me_3CC(O)CH(CH_3)CH_2CO_2CH_3$ (72)
	5,6-Dihydro-2H-pyran-2-one	II[e]	4-Pivaloyl-δ-valerolactone (81)[f]
	$CH_3CH=CHCHO$	II[e]	$Me_3CC(O)CH(CH_3)CH_2CHO$ (71)
	$CH_2=CHC(O)CH_3$	II[e]	$Me_3CC(O)CH_2CH_2C(O)CH_3$ (86)
	Cyclohexen-2-one	I[g]	3-(2-Methylbutanoyl)cyclohexanone (80)
	Cyclohexen-2-one	II	3-(2-Methylbutanoyl)cyclohexanone (94)
	$CH_3CH=CHC(O)Et$	I[g]	$MeEtCHC(O)CH(CH_3)CH_2C(O)Et$ (75)
	$CH_3CH=CHC(O)Et$	II	$MeEtCHC(O)CH(CH_3)CH_2C(O)Et$ (99)
	$PhCH=CHC(O)CH_3$	II	$MeEtCHC(O)CH(Ph)CH_2C(O)CH_3$ (91)
	$EtCH=CHCHO$	II	$MeEtCHC(O)CH(Et)CH_2CHO$ (73)

[a] α,β Compound added at 0°C. [b] α,β Compound added at -20°C. [c] $Me_3CCH_2CH_2C(O)CH_3$ (14) by-product. [d] 4 molar equiv. of ester used; reaction at -20°C (1 hr) and room temp. (1 hr). [e] Carbonylation at -110°C for 2 hr. [f] 4-t-butyl-δ-valerolactone (11%) by-product. [g] α,β Compound added at -78°C.

Neither Method I nor II was successful in the case of n-$C_4H_9(CN)CuLi$. Even when the carbonylation and subsequent reaction with cyclohexen-2-one were carried out at -110°C, the only product (80% yield) was 3-n-butylcyclohexanone, the alkylation product. Addition of 2 molar equivalents of N,N,N',N'-tetramethylethylenediamine to the cuprate reagent prior to carbonylation did not change this result. In order to effect direct nucleophilic 1,4-acylation of α,β-unsaturated ketones and aldehydes with a primary acylcuprate, the less efficient n-$R_2(CN)CuLi_2$/CO procedure[1] must be used.

The apparent stability of the R(CN)CuLi/CO reagents which we have studied decreases in the order R = t-C_4H_9>sec-C_4H_9>n-C_4H_9. At one extreme, the pivaloylcuprate appears to be stable up to room temperature. At the other extreme, at first sight, the n-$C_4H_9(CN)CuLi$/CO reagent is not formed at all. A possible explanation of these observations is that the carbonylation is a reversible process (eq.1) and thus the α,β-unsaturated

$$\underset{\underline{1}}{R(CN)CuLi} + CO \rightleftharpoons \underset{\underline{2}}{RC(O)(CN)CuLi} \qquad (1)$$

substrate has the option of reacting with either 1 or 2. When R is a bulky secondary or tertiary alkyl group, reaction of the electrophile with 1 is hindered and reaction with the less bulky 2 is favored. When R is not bulky, as in the case of R = n-C_4H_9, then reaction with 1 is preferred. This is an explanation in terms of kinetic factors. We are seeking information on the position of the postulated equilibrium in eq. 1 by means of ^1H and ^{13}C NMR studies of these systems.

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