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Carbonylation of Dialkylcyanocuprates with Carbon Monoxide: Synthesis of α-Hydroxyketones

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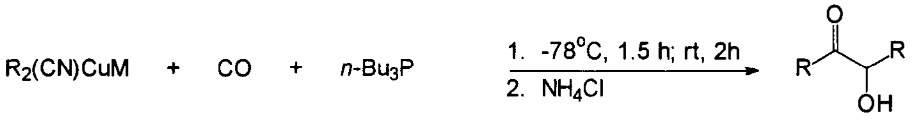
Abstract: Dialkylcyanocuprates, prepared from copper(I) cyanide and the corresponding alkyllithium or Gringard reagents, readily react with carbon monoxide in the presence of tri-*n*-butylphosphine at -78 °C in THF to give α-hydroxyketones in high yields (65-85%). © 1997 Elsevier Science Ltd.

The transformation of organometallic reagents into useful synthetic intermediates has played an important role in synthetic organic chemistry for many years. One such transformation involves the reaction of organometallic reagents with carbon monoxide.[1,2,3,4,5] For example, alkyllithium reagents react with carbon monoxide in the presence of electrophiles to give acylated products;[1,2] alkylmagnesium compounds react with carbon monoxide to produce alkenes;[3] and organoboranes react with carbon monoxide to generate alcohols, aldehydes, or ketones.[4] In addition, much attention has been paid to the carbonylation of transition metal reagents derived from palladium, thallium, copper, titanium, zirconium, etc.[3] These reactions generally afford the corresponding carbonyl compounds, i.e. aldehydes, ketones or esters. For example, Schwartz reported that lithium dialkylcuprates reacted with carbon monoxide to generate dialkylketones.[6] Seyferth reported the direct nucleophilic 1,4-acylation of α,β-unsaturated carbonyl compounds using acylcuprate reagents prepared via the carbonylation of alkylcyanocuprates with carbon monoxide.[7] However, it was reported that the reaction of primary and secondary alkyllithium reagents with carbon monoxide, in the absence of electrophiles, produced α-hydroxyketones in 21% and 27% yields respectively;[1] the reaction of primary and secondary dialkylzinc with carbon monoxide in the presence of potassium *t*-butoxide gave α-hydroxyketones in 42% and 35% yields respectively.[8] In a continuation of our studies focused on acyl anion chemistry,[5] we found that dialkylcyanocuprates react with carbon monoxide in the presence of tri-*n*-butylphosphine to afford α-hydroxyketones in very good yields (68-85%), **Scheme 1**.

Scheme 1



1 **2**

The dialkylcyanocuprate (**1**) was prepared *in situ* by adding 2 molar equivalents of the corresponding alkyllithium or Grignard reagent to copper(I) cyanide in degassed THF at -78 °C under an argon atmosphere. The resulting mixture was warmed until the solution cleared (by removing the dry ice bath) and then re-cooled to -78 °C while maintaining an argon atmosphere.[7a] The results of a study of the reaction of the lithium di-*n*-butylcyanocuprate complex with carbon monoxide under various conditions are summarized in **Table 1.**

As shown in **Table 1**, THF is the best reaction solvent (entries 1-5). The reaction can be carried out at -78 °C (entries 1 and 2). The reaction yields are not increased by refluxing the mixture after the initial reaction period (entries 3 and 6). The addition of Ph_3P, Et_3N, Me_2S, DBU, TMEDA and LDA has little effect on the reaction yields (entries 7-13). However, the reaction yields are dramatically increased in the presence of tri-*n*-butylphosphine and decreased in the presence of potassium *t*-butoxide (entries 14-16). The reactions of various dialkylcyanocuprate with carbon monoxide in the presence of tri-*n*-butylphosphine were then investigated and the results are presented in **Table 2**. As shown in **Table 2**, the reaction generally affords α-hydroxyketones in very good yields (68-85%).

Typical Procedure: To a 125 mL flask was added THF (75 mL) and *n*-Bu_3P (1.01 g, 1.25 mL, 5.0 mmol) at -78 °C while carbon monoxide was bubbled through it. After the solution was saturated with CO (30 min), a solution of dialkylcyanocuprate (5 mmol), which was prepared from an alkyllithium (10 mmol) or Grignard reagent (10 mmol) and copper (I) cyanide (5 mmol), was slowly added by cannula. The reaction mixture was stirred at -78 °C for 1.5 h and allowed to proceed at rt for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and the product α-hydroxyketone isolated via silica gel chromatography [hexane/ethyl acetate (v/v) = 9/1 as eluate].

Table 1. Preparation of 5-Hydroxyl-6-decanone (2a) Via the Carbonylation of *n*-$Bu_2(CN)CuLi_2$

Entry	Solvent	Additive	Reaction Conditions	Yield(%)[a]
1	THF:Et_2O:Pentane (4:4:1)[b]	-	-110 °C, 1.5h; rt, 2h	47
2	THF:Et_2O:Pentane (4:4:1)[b]	-	-78 °C, 1.5h; rt, 2h	46
3	THF	-	-78 °C, 1.5h; rt, 2h	53
4	Et_2O	-	-78 °C, 1.5h; rt, 2h	32
5	Toluene	-	-78 °C, 1.5h; rt, 2h	29
6	THF	-	-78 °C, 1.5h; reflux, 18h	51
7	THF	Ph_3P[C]	-78 °C, 1.5h; rt, 2h	48
8	THF	Et_3N[c]	-78 °C, 1.5h; rt, 2h	56
9	THF	Me_2S[c]	-78 °C, 1.5h; rt, 2h	61
10	THF	DBU[d]	-78 °C, 1.5h; rt, 2h	56
11	THF	TMEDA[c]	-78 °C, 1.5h; rt, 2h	58
12	THF	TMEDA[d]	-78 °C, 1.5h; rt, 2h	56
13	THF	LDA[d]	-78 °C, 1.5h; rt, 2h	50
14	THF	$KOC(CH_3)_3$[d]	-78 °C, 1.5h; rt, 2h	18
15	THF	*n*-Bu_3P[c]	-78 °C, 1.5h; rt, 2h	80
16	THF	*n*-Bu_3P[d]	-78 °C, 1.5h; rt, 2h	77

[a] Isolated yield

[b] A mixture of THF, diethyl ether, and pentane (4:4:1) by volume is used.

[c] One molar equivalent added to solvent prior to CO addition.

[d] One molar equivalent added to solution of lithium di-*n*-butylcyanocuprate prior to reaction.

Table 2. The Preparation of α-Hydroxyketones Via the Carbonylation of $R_2(CN)CuM$

Entry[a]	Product[b]	R	Cuprates	Yield(%)[c]
1[d]	**2a**	*n*-Bu	*n*-$Bu_2(CN)CuLi_2$	53
2	**2a**	*n*-Bu	*n*-$Bu_2(CN)CuLi_2$	80
3[d]	**2b**	*s*-Bu	*s*-$Bu_2(CN)CuLi_2$	52
4	**2b**	*s*-Bu	*s*-$Bu_2(CN)CuLi_2$	81
5[d]	**2c**	*t*-Bu	*t*-$Bu_2(CN)CuLi_2$	48
6	**2c**	*t*-Bu	*t*-$Bu_2(CN)CuLi_2$	70
7	**2d**	*n*-C_6H_{13}	(*n*-$C_6H_{13})_2(CN)CuLi_2$	79
8	**2e**	*n*-Pr	*n*-$Pr_2(CN)CuMg$	68
9	**2f**	*i*-Pr	*i*-$Pr_2(CN)CuMg$	70
10	**2c**	*t*-Bu	*t*-$Bu_2(CN)CuMg$	85

[a] All reactions were carried out in THF at -78 °C for 1.5 h, then at rt for 2 h in the presence of tri-*n*-butylphosphine except where noted. [b] All reaction products exhibited physical and spectral characteristics in accord with literature values.
[c] Isolated yield. [d] Experiment carried out in the absence of tri-*n*-butylphosphine.

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