COMMUNICATIONS

LETTERS

Autoxidation of Organocuprates. The preparation of Esters from Acid Chlordes and Lithium Dialkylcuprates in the Presence of Oxygen

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Organocuprate reagents are extremely useful in organic synthesis because of the selectivity that they behave as good nucleophiles in conjugate addition to α, β-unsaturated carbonyl compounds and in displacement reaction of alkyl halides but as poor nucleophiles in addition to nonconjugated carbonyl compounds.[1] However, the oxidation of organocuprate reagents with oxygen has not extensively utilized in organic synthesis due largely to the fact that they give the symmetric coupling products as a major product.[2]

We have recently reported that the reaction of S-2-pyridyl thioates with lithium dialkylcuprates in the presence of oxygen results in the formation of carboxylic esters in high yields.[3] To the best of our knowledge, no oxygen-containing products have been exclusively obtained from the oxidation of organocuprate reagents.[4] Thus, further experimental work was undertaken to confirm our previous results and to ascertain the generality of this procedure by substituting acid chlorides for S-2-pyridyl thioates.

We now wish to report that the reaction of lithium dialkylcuprates with acid chlorides in the presence of oxygen gives carboxylic esters in high yields.

$$R'COCl + R_2CuLi \xrightarrow[Et_2O]{O_2} R'COOR$$

In a typical experiment, lithium dialkylcuprate, which is prepared in diethyl ether under nitrogen by the known procedure, is further stirred at −78°C for 5 min under a balloon-filled atmosphere of oxygen,[5] and the resulting organocuparte reagent is added to the acid chloride in diethyl ether containing oxygen at −78°C with stirring. The resulting mixture is allowed to attain room temperature gradually. Within 3 h the reaction is normally complete and the product is isolated in the usual manner.

Some experimental results are summarized in Table1. This procedure seems to be best applicable to primary cuprate reagents. Tertiary butyl cuprate gave poor yields of carboxylic esters. Of special synthetic significance is the stoichiometric requirement of only 1 equiv of R (0.5 equiv of R_2CuLi) for this conversion.

Thus, the reaction of benzoyl chloride in diethyl ether with either 0.6 or 1.0 equiv of lithium di-n-butylcuprate gave similar yields of n-butyl benzoate. Also, the fact that the ketone formation was completely suppressed under reaction conditions is of interest to note. Furthermore, this ester formation was successfully extended to acid chlorides substituted by bromo or conjugated double bond.

TABLE 1: Preparation of Esters from Acid Chlorides and Lithium Dialkylcupates in the presence of Oxygen.

$$R'COCl + R_2CuLi \xrightarrow[Et_2O]{O_2} R'COOR$$

R′COCl R′	R_2CuLi R	Molar equiv of R_2CuLi	% Yield, R′COOR
C_6H_5	Me	0.6	91
	Bu^n	0.6	85
	Bu^n	1.0	90
	Bu^t	0.6	40
$C_6H_5OCH_2$	Bu^n	0.6	66
	Bu^n	1.0	73
$CH_3(CH_2)_6$	Bu^n	1.0	91
	Bu^t	0.6	40
$(CH_3)_2CH$	Bu^n	1.0	81
$(CH_3)_3C$	Bu^n	0.6	77
	Bu^n	1.0	88
$Br(CH_2)_5$	Bu^n	1.0	71
$C_6H_5CH=CH$	Bu^n	1.0	89

Compared with our previous results,[3] the results presented here indicate that 2-pyridyl moiety, which is believed to stabilize the copper species by internal complexation, is not essential to the high-yield ester formation.

Since it is well known that the reaction of acid chlorides with organocuprate reagents under nitrogen gives ketones,[6] the ester formation is attributed to oxidation of organocuprate reagents with oxygen. However, the available data in our hands are not sufficient at the present time what species is responsible for the observed oxidation. Presumably the reaction proceeds via the intermediacy of copper alkoxide.[7]

Further studies towards detailed mechanistic insights of the oxidation of organocuprate reagents are in progress and will be the subject of future reports.

References and Notes

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Conjugate Addition of Benzyl Cyanide to a Quinone Monoacetal and Aromatization of the Adduct

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Much of Michael type addition to quinone moiety have been known, but synthetic utility of these 1, 4–addition may be limited by a lack of regioselectivity and further transformation.[1] Quinone monoacetal which has recently been synthesized would be a good substitute for a quinone in a Michael reaction. Recently, oxidation of quinone monomethyl ether with $Tl(NO_3)_3$, DDQ or $FeCl_3$ in dry methanol[2] or regioselective hydrolysis of bisacetals[3] have made quinone monoacetal readily available and attractive as synthetic intermediate.[4] A few example of 1,4–addition of active methylene compounds(p*Ka*; 8–13) to quinone monoacetals have recently appeared,[5] but no example of conjugate addition of benzyl cyanide (p*Ka*; –17) to quinone monoacetal has been reported, which would be a good synthetic reaction.

We thought that conjugate addition of benzyl cyanide to quinonemonoacetal would be a key step in a regiospecific approach to synthesis of anthracyclinone antibiotics, Adriamycin (**1**).[6]

We envisioned the conjugate addition of a masked acyl anion[7] to a quinone monoacetal (Figure 1). Nitrile enolates add conjugatively to enones.[8] In view of the numerous methods for the oxidative conversion of nitriles to ketones,[9] we felt that addition of nitrile enolate to quinone monoacetal followed by oxidation might provide a simple entry to the desired benzoylated methoxyphenol.

In a model study, We studied addition of benzyl cyanide to 3,4,4–trimethoxycyclohexa–2,5–diene–1–one (**2**) which was prepared from 3,4–dimethoxybenzaldehyde by Baeyer–Villiger oxidation and hydrolysis followed by $Tl(NO_3)_3$ oxidation in 65 % overall yield.[10] Addition of benzyl cyanide to the above quinone monoacetal (**2**) was effected with a catalytic amount (0.1 eq) of sodium ethoxide at room temperature to afford the Michael adduct(**3**) (Figure 2).

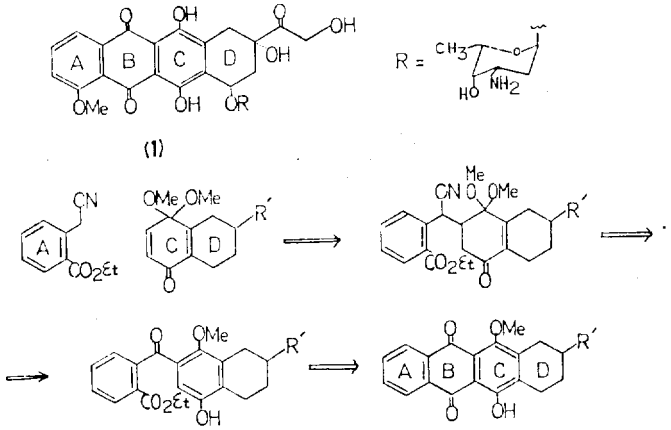

Figure 1.

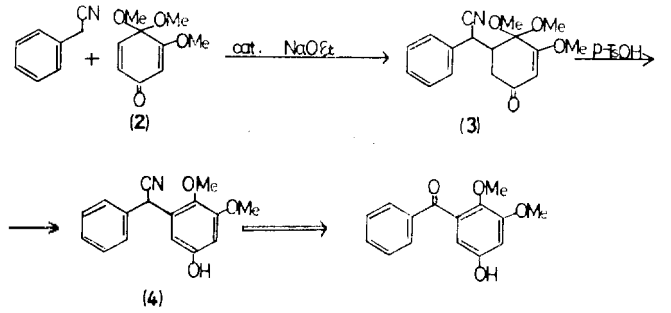

Figure 2.

In our hands, nitrile enolate prepared from benzyl cyanide by NaH in THF, or LDA in THF and HMPA did not add to quinone monoacetal (**2**). Stirring of the adduct (**3**) in refluxing benzene with *p*–TsOH gave the aromatized product (**4**).

A typical experimental procedure is as follows.

Benzyl cyanide (0.210g) was added to a solution of sodium ethoxide (0.012g, 0.1eq) in 1 m*l* EtOH, and 0.330g of quinone monoacetal (**2**) in 1 m*l* EtOH was added dropwise. The reaction mixture was stirred for 24 hrs at room temperature, and then EtOH was evaporated, and the residue was extracted