INTRAMOLECULARLY ASSISTED ADDITION OF LiMe$_2$Cu TO METHYL CINNAMATES

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Some ortho-substituted methyl cinnamates have been prepared and their reaction with lithium dimethylcuprate investigated. A methoxymethyl group in the ortho-position caused a ten-fold enhancement of the reaction rate relative to methyl cinnamate, while the corresponding nitrogen and sulphur ligands had only minor effects on the reactivity. A model for the transition state of the reaction is suggested.

We have previously shown that a π-complex is formed between lithium dimethyl-cuprate, LiMe$_2$Cu, and methyl cinnamate and that it can be studied by NMR spectroscopy at temperatures below -40°C.[1] The formation of the alkene-copper(I) π-complex is likely to be the first step in the conjugate addition of the cuprate to the enoate[1,2] as has also been suggested by Corey and Boaz.[3] The fast formation of an initial complex in equilibrium with the reactants has been observed.[4]
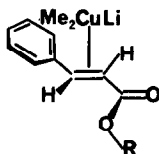
It has also been observed by us[5] and by others[6] that the success of the conjugate addition of lithium diorganocuprates is highly dependent on the choice of the solvent, diethyl ether being best. THF or solvents of higher Lewis basicity decrease the rate of the reaction and the yield of the desired product.

The observed deleterious effect of good donor solvents[5,6] on the rate of the conjugate additions can be correlated with the growing knowledge of the solid state as well solution structures of organic cuprates.[7] As shown by Lipshutz et al.[8] LiMe$_2$Cu is a well defined dimeric species in diethyl ether while equilibria between at least two cuprate clusters and methyllithium are obtained in THF. Good donor solvents thus seem to cause formation of other cuprate clusters[7] than those usually assumed[9] for LiMe$_2$Cu and used in Figure 1. Also, the presence of solvent-separated ion pairs, e.g. (LiL$_n$)$^+$ R$_2$Cu$^-$, can not be ruled out.
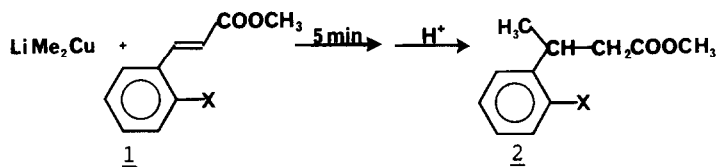
To gain further insight into the role of the solvent and the effect of the coordination to the cuprate during conjugate addition to enones and enoates we have now studied the reaction of LiMe$_2$Cu with methyl cinnamates having

built-in ligands. A series of methyl cinnamates carrying ortho-substituents, 1a-f, has been prepared and their reactions with $LiMe_2Cu$ have been studied. The methylthiomethyl, 1d, dimethylamino, 1e, and the methoxymethyl, 1f, groups were chosen to test S, N and O as coordinating atoms isolated from the delocalised π-electron system by a methylene group. A methoxy group, 1c, was included for comparison of electronic effects while the iso-propyl group, 1b, was studied to get a measure of the steric effect of an ortho-substituent on the rate of the conjugate addition.

When the reactions of 1a-f were carried out at $0^\circ C$ for 1 h the products 2a-f (characterized by NMR and MS) were obtained in >80 % isolated yield after distillation or chromatography.

The relative reactivities of 1a-f were determined by GC-MS measurement of the amount of products 2a-f formed after 5 min at $0^\circ C$ relative to an internal standard. The reactions of 1a and 1f were repeated at $-20^\circ C$ for 5 min to get a better measure of the relative reactivites. Since the reactions were quenched at an early stage the same rate expression should hold for each. The results are summarised in Table 1.

Table 1

$$LiMe_2Cu \; + \; \underset{1}{\overset{COOCH_3}{\bigcirc\!\!-\!X}} \xrightarrow{5\,min} \xrightarrow{H^+} \underset{2}{\overset{H_3C}{\bigcirc}\!\!\underset{}{CH\!-\!CH_2COOCH_3}\!-\!X}$$

X	yield, % of 2		$E_{\frac{1}{2}}$ V
	$0^\circ C$	$-20^\circ C$	
a, -H	18	2	-1.81 (ref. 11)
b, $-CH(CH_3)_2$	10		
c, $-OCH_3$	10		-1.83
d, $-CH_2SCH_3$	15		
e, $-CH_2N(CH_3)_2$	27		
f, $-CH_2OCH_3$	>98	20	-1.79

The methoxymethyl-substituted product, 2f, was formed in >98% yield while the yields of 2a-e varied from 10% to 27% after 5 min at $0^\circ C$. The formation of 2a and 2b was accompanied by the formation of small amounts (<2%) of heavier products. The mass balance is accounted for by remaining starting material. At $-20^\circ C$ ester 1f reacted roughly ten times faster than methyl cinnamate 1a.

As seen from the reactions of 1a and 1b in Table 1 a non-coordinating ortho-substituent does not exert a considerable steric effect. The methylthiomethyl substituted ester 1d reacts with $LiMe_2Cu$ at approximately the same rate as 1a, while substitution with the dimethylaminomethyl group, 1e, leads to a small increase in reaction rate.

The observed order of reactivity , $-CH_2OCH_3 > -H > -OCH_3$, is that expected from the limited electrochemical data available, Table 1, if a one-electron process[11] is the rate-limiting step. However, the differences in $E_{\frac{1}{2}}$ values are small and insignificant since the series $\underline{1b}$, $\underline{1d}$, $\underline{1e}$ and $\underline{1f}$ should be electro-chemically similar.

We suggest that the rate enhancement observed for the $-CH_2OCH_3$ group is the result of coordination of the methoxymethyl group to the cuprate in the transition state thus lowering the activation energy. The oxygen in the $-CH_2OCH_3$ should bind more strongly to metals than does the $-OCH_3$ oxygen in $\underline{1c}$. The "hard" oxygen is probably coordinated to lithium in the cuprate rather than to a "soft" copper(I) atom. Thus the methoxymethylcinnamate $\underline{1f}$ can be considered to be a tridentate ligand for a dimeric $LiMe_2Cu$ species[9]; in addition to bonding of copper(I) to the enoate C=C bond, coordination of the carbonyl oxygen and the methoxymethyl oxygen to two lithium atoms in the cuprate results in a three point interaction, $\underline{cf}$ Figure 1.
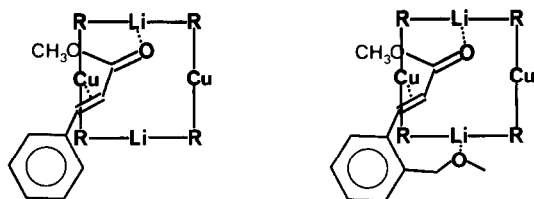

Figure 1

Structurally and electronically the methoxymethyl group of $\underline{1f}$ resembles diethyl ether, and can thus exchange diethyl ether from its coordination sites on dimeric $(LiMe_2Cu)_2$ without causing structural changes in the cuprate.

To further test the effect of coordination to the cuprate a methyl cinnamate carrying a crown ether like substituent in the ortho-position has been reacted with half an equivalent of $(LiMe_2Cu)_2$ (after removal of LiI) at 0°C for 2 h and was found to give the conjugate addition product in only 20% yield. The remaining starting material was present as a Li^+ complex. The triether side
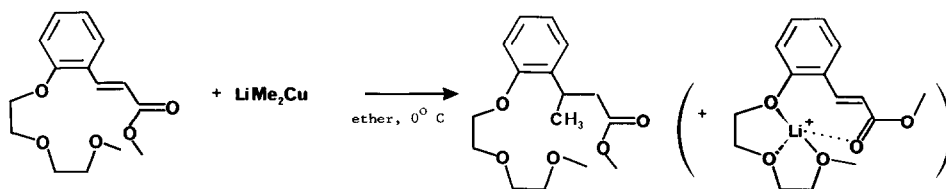
chain of the enoate forms a strong complex with lithium resembling a crown ether complex and thus breaks down the cuprate cluster structure ($\underline{cf}$ ref 6b). The result is in good agreement with our model and further work is in progress.

However, a model for the reaction has to be slightly more complex since the Gilman reagents as they are used in synthetic applications also contain lithium halides ($LiR_2Cu + LiX$). The reactions reported in Table 1 were all run with $LiMe_2Cu$ containing one equivalent of LiI from its preparation. When <u>1f</u> was reacted with $LiMe_2Cu$ after removal of LiI the product <u>2f</u> had formed in 6% yield after 5 min at $-20^{\circ}C$. We have previously shown that a lithium-enoate complex is present in equilibrium with the enoate.[2] Thus equilibria between several species have to be taken into account.

We propose that the dimeric cluster structure of the cuprate is essential for fast conjugate additions to take place. Accordingly, the structures shown in Figure 1 can be used as models for the transition state for the addition of $LiMe_2Cu$ to enoates. Other clusters or ion pair structures formed in good donor solvents or ligands would seem to be less reactive in this particular reaction.

EXPERIMENTAL

In a typical experiment 2 ml of a solution of $LiMe_2Cu$ (+LiI), 0.250 mmol, in diethyl ether was transfered to a three-necked flask. The solution was kept under argon at $0^{\circ}C$. The relevant methyl cinnamate, <u>1</u>, 0.125 mmol, and the internal standard, naphthalene, were dissolved in 2 ml of dry diethyl ether, cooled to $0^{\circ}C$ and added to the cuprate in one portion. The subsequent reaction was quenched after 5 min with NH_4Cl/NH_3 or in some cases with 2 M HCl. The crude product mixtures were analysed by GC-MS and the amount of conjugate addition products, <u>2</u>, determined after calibration with solutions of known concentrations.

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