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ORGANOCOPPER CHEMISTRY. REACTION OF BENZAL AND OTHER BENZYLIC CHLORIDES WITH LITHIUM DIMETHYLCOPPER

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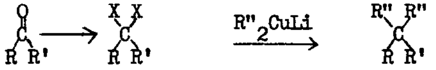
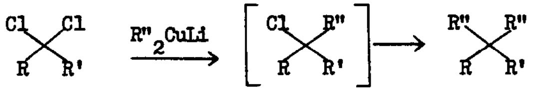
Organocopper reagents have recently been shown to be widely useful for selective replacement of halogen by alkyl, vinyl, and aryl groups in many types of organic monohalides[2] and have been applied to stereospecific synthesis of several natural products.[3] A general method for transformation of a ketone or aldehyde carbonyl group to a quaternary or tertiary alkyl carbon atom would be of broad utility in organic synthesis.[4] One possible sequence of steps for such a conversion involves replacing carbonyl oxygen by the *gem*-dihalide functionality followed by replacing each halogen by a carbon unit[5] (eq. 1, R = carbon or hydrogen). Our preliminary results indicate that lithium dimethylcopper reacts with benzal chloride with substitution of both chlorine atoms by methyl groups in fair yields, that (1-chloroethyl)benzene is not an intermediate in this methylation, and furthermore that this organocopper reaction with benzal chloride proceeds approximately five times faster than the analogous reaction with benzyl chloride.



(eq. 1)

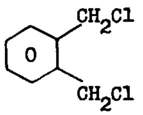
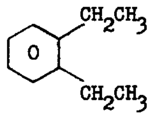
Benzal and other benzylic chlorides were studied first for the following reasons. Initially it was anticipated that lithium dimethylcopper replacement of both chlorine atoms in a primary or secondary alkyl *gem*-dichloride might proceed stepwise and thus might produce an intermediate secondary or tertiary alkyl chloride (eq. 2). Because organocopper reagents do not couple effectively with unactivated secondary or tertiary chlorides, a system was chosen in which the chlorines are benzylic and therefore activated toward substitution.[2] Furthermore to avoid formation of a vinylic chloride during conversion of carbonyl to *gem*-dichloride[6] this initial study was limited mainly to systems of the form $C_6H_5C(Cl_2)R'$ in which R' = H,Cl,C_6H_5.



(eq. 2)

Each benzylic chloride (1-3 mmol) examined was dissolved in several ml of anhydrous diethyl ether. This solution was added by syringe to a cold (either 0° or -78°) well-stirred solution containing per equiv of chlorine 5 equiv of lithium dimethylcopper[7] (ca. 0.25 M) which had been prepared in ether at 0° from 5 equiv of cuprous iodide and 10 equiv of methyllithium.[8] Product isolation involved quenching the reaction mixture by adding approximately 1.0 ml of absolute methanol, warming to room temperature, pouring the reaction mixture into twice its volume of an aqueous ammonium chloride solution, and finally separating and drying ($MgSO_4$) the ether extracts. After removal of an aliquot for gas chromatographic analysis, the remaining ether extracts were concentrated, giving products which were identified by comparing their physical and spectral properties with those recorded in the literature. The results are summarized in Table I.

Table I. Reaction of Lithium Dimethylcopper with Benzylic Chlorides in Diethyl Ether

Benzylic Chloride	Temp (°C)[a]	Product (Yield)[b]
$C_6H_5CHCl_2$	-78	No Reaction
	0	$C_6H_5CH(CH_3)_2$ (40%)
		$C_6H_5CH(CH_3)CH(CH_3)C_6H_5$ (40%, 1:1 dl:meso)[c]
$C_6H_5CH(CH_3)Cl$	0	No Reaction
	23[d]	$C_6H_5CH(CH_3)_2$ (40%)
		$C_6H_5CH(CH_3)CH(CH_3)C_6H_5$ (40%, 1:1 dl:meso)[c]
$C_6H_5CH_2Cl$	0	$C_6H_5CH_2CH_3$ (80%)
$(C_6H_5)_2CCl_2$	0	$(C_6H_5)_2C{=}C(C_6H_5)_2$ (81%)
	0	 (77%)

[a] Reactions were run for 1 hr unless otherwise noted. [b] Yields were determined gas chromatographically, using an internal standard. [c] meso and dl-2,3-Diphenylbutane were separated by preparative gas chromatography and had spectra identical with those recorded in the literature. [d] Reaction time was 22 hr.

Benzal chloride reacts with lithium dimethylcopper at 0° for 1 hour to form isopropylbenzene (40% yield) and 2,3-diphenylbutane (40% yield, 1:1 dl:meso). No stilbene is formed in this reaction, and no 7-phenylnorcarane is formed in an analogous reaction using 1:1 ether:cyclohexene as solvent. Thus, in contrast to lithium metal[9] and organolithium reagents[10,11] which convert benzal chloride into stilbene and 7-phenylnorcarane (when cyclohexene is present in the reaction mixture), lithium dimethylcopper replaces both chlorine atoms of benzal chloride by methyl groups in fair yield apparently without generating intermediate phenylcarbene species. Because formation of isopropylbenzene could have occurred through the intermediacy of (1-chloroethyl)benzene this chloride was examined next.

(1-Chloroethyl)benzene reacts with lithium dimethylcopper to form isopropylbenzene and 2,3-diphenylbutane in the same yields and in the same relative amounts as benzal chloride, *but substantially more severe reaction conditions are needed for complete organocopper consumption of (1-chloroethyl)benzene (22 hours at 23°) than for complete organocopper consumption of benzal chloride (1 hour at 0°).* Furthermore, when equivalent amounts of both benzal chloride and (1-chloroethyl)benzene are mixed together and then treated with excess lithium dimethylcopper at 0° for 1 hour, only benzal chloride is consumed and (1-chloroethyl)benzene is recovered in 99% yield. Therefore (1-chloroethyl)benzene is not an intermediate in lithium dimethylcopper reaction with benzal chloride, and furthermore loss of the second chlorine atom from this *gem*-dichloride must precede or occur simultaneously with introduction of the first methyl group. Although the mechanistic details of this double alkylation remain to be clarified by further experimentation, it is interesting to note that lithium dimethylcopper reacts with 1,2-bis(chloromethyl)benzene to give *o*-diethylbenzene and not benzocyclobutene (Table I).

The reactivity of benzylic chlorides toward lithium dimethylcopper increases as the number of chlorine atoms increases.[12] Benzotrichloride is consumed by lithium dimethylcopper even at -78° for 1 hour,[13] whereas both benzal and benzyl chlorides are stable to lithium dimethylcopper under these conditions. Competing for a limited amount of lithium dimethylcopper, benzal chloride is found to be consumed somewhat faster (*ca.* 5 times) than benzyl chloride.

We are currently exploring organocopper interaction with non-benzylic *gem*-dihalides[14] with the aim of developing a practical method for converting the oxo to the *gem*-dialkyl functionality (eq. 1).

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13. This reaction leads to a mixture of products whose structures have not yet been established.
14. Interaction of only one *gem*-dihalide with organocopper reagents has been reported previously (ref 2a); 7,7-dibromonorcarane reacts with lithium dimethyl- and diethylcopper to give 7,7-dimethyl- and 7,7-diethylnorcaranes in 65% and 60% yields, respectively.