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ALKYLATION OF ORGANOMERCURIALS VIA ORGANOCOPPER REAGENTS

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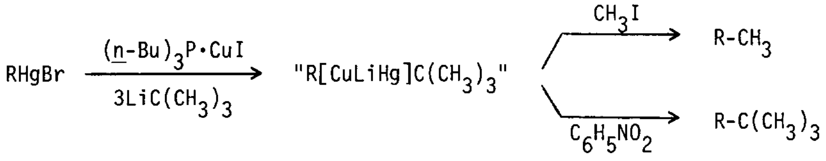
Summary: Aryl-, alkenyl-, and alkylmercurials readily cross-couple with primary and secondary alkyl- and alkenylcuprate reagents to provide the first truly general method for the alkylation of a wide variety of organomercurials.

Cross-coupling reactions of organometallic reagents have become an increasingly important tool in the formation of carbon-carbon bonds. The ability of organomercurials to accommodate essentially all important organic functional groups, and the ease with which they undergo a variety of mild carbon-carbon bond forming reactions have made organomercurials increasingly attractive as synthetic intermediates in organic synthesis.[1] Unfortunately, no general method for the alkylation of organomercurials presently exists. Alkyl halides react with organomercurials only under forcing conditions[2-5] or in the presence of aluminum bromide[6] to give low to modest yields of cross-coupled products. We recently reported a convenient method for the methylation of alkenyl- and arylmercurials using $CH_3RhI_2(PPh_3)_2$, but that approach does not work with alkylmercurials and does not appear applicable to other alkylrhodium compounds.[7] Bergbreiter and Whitesides have reported that the reaction of primary and secondary alkylmercurials, iodo(tri-n-butylphosphine)copper(I) and tert-butyl lithium gives an intermediate of unknown composition that may either be alkylated with methyl iodide or oxidatively coupled with nitrobenzene (eq.1).[8] It was concluded that the intermediate



$$\begin{tikzcd} & & R\text{-}CH_3 \\ RHgBr \arrow[r, "(\underline{n}\text{-}Bu)_3P\cdot CuI", "3LiC(CH_3)_3"'] & \text{"}R[CuLiHg]C(CH_3)_3\text{"} \arrow[ur, "CH_3I"] \arrow[dr, "C_6H_5NO_2"'] & \\ & & R\text{-}C(CH_3)_3 \end{tikzcd} \qquad (1)$$

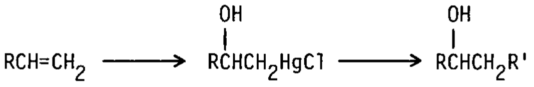
involved is a ternary ate complex containing all three metals and not a simple organocuprate reagent, since conjugate addition to mesityl oxide could not be effected. Unfortunately, using this procedure, arylmercurials could not be cross-coupled with alkyl halides, and alkenylmercurials were not studied. We have recently re-examined these reactions and wish now to report that under the right conditions, aryl-, alkenyl-, and alkylmercurials can be cross-coupled in modest to excellent yields with alkyl- and alkenylcuprate reagents to provide the first truly general method for the alkylation of a wide variety of organomercurials.

Our initial work was carried out using phenylmercuric chloride and methyl copper reagents, studying the effect on the yield of toluene of various oxidizing agents, solvents, temperatures, transition metal catalysts, ligands, stoichiometries, and the addition of methyl iodide. Best results were obtained using five equivalents of dilithium trimethylcuprate in diethyl ether at -78°C for 1 hour, followed by warming to 0°C for 1 hour, then quenching with excess methyl iodide and oxygen (92% yield). Lithium dimethylcuprate gave slightly lower yields, while methylcopper was almost completely unreactive. The addition of transition metal salts had relatively little effect, but quenching with oxygen and methyl iodide improved the yields substantially. Comparable results were obtained in ether and tetrahydrofuran (THF), or upon addition of dimethylsulfide. Substantially lower yields were obtained using a variety of heterocuprate reagents.

The methylation of a variety of other arylmercurials was also easily effected, including those bearing electron-donating and -withdrawing groups or steric hindrance. The results are summarized in the Table (entries 2-4). Unfortunately, organocuprate reagents derived from _n_-butyl and _sec_-butyl lithium were less successful (entries 5,6). Best results were obtained running these reactions in THF and maintaining the temperature at -78°C. The dialkylcuprate reagents seemed to be just as effective as the trialkylcuprate reagents in this case. With a vinylcopper reagent (entry 7), the best yield of styrene was obtained in THF with added dimethylsulfide, by allowing the reaction to warm to 0°C before quenching with oxygen. Unfortunately, no one procedure has proved best for all systems.

Alkenylmercurials can also be alkylated in moderate yield using procedures similar to those described above. The results are summarized in the Table (entries 8,9). It is noteworthy that the reaction is highly stereospecific (>99%) and can be applied to the synthesis of 1, 3- dienes as well.

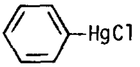
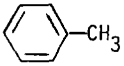
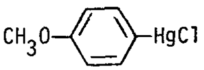
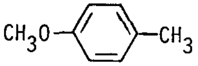
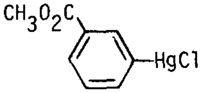
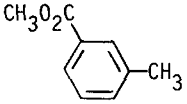
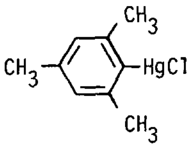
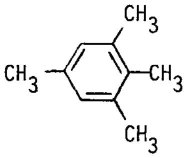
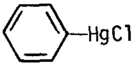
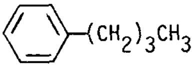
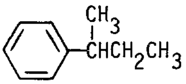
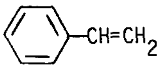
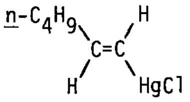
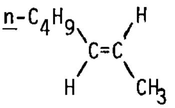
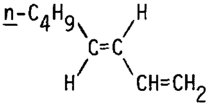
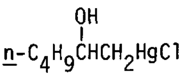
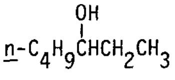
Unlike our earlier work on the rhodium promoted alkylation of organomercurials, by using organocopper reagents, we are able to effect the alkylation of alkylmercurials as well (entries 10,11). Primary alkylmercurials react to give fair yields of alkylated product, but secondary alkylmercurials give significantly lower yields. The ability to alkylate organomercurials prepared via oxymercuration of alkenes provides a novel method for the overall hydroxyalkylation of olefins (eq.2).[8]



$$RCH{=}CH_2 \longrightarrow R\overset{OH}{\overset{|}{C}}HCH_2HgCl \longrightarrow R\overset{OH}{\overset{|}{C}}HCH_2R' \qquad (2)$$

The mechanism of these cross-coupling reactions seems best represented by the following scheme, the important feature of which is the formation of a mixed diorganocopper intermediate LiCuRR' which can be either oxidatively or thermally cross-coupled to give the observed products. The high stereospecificity of the alkenylmercurial methylation reactions seems to rule out a radical anion chain mechanism[9] for this cross-coupling. It should also

Table. Alkylation of Organomercurials via Organocopper Reagents

Entry	Organo-mercurial	Organocopper Reagent (5 equivalents)	Reaction Procedure	Product	% Yield
1		$Li_2Cu(CH_3)_3$	Et_2O -78°→0° CH_3I/O_2		92
2					65
3					82
4					75
5		$LiCu(\underline{n}\text{-}C_4H_9)_2$	THF -78° O_2		42
6		$LiCu(\underline{sec}\text{-}C_4H_9)_2$			35
7		$Li_2Cu(CH{=}CH_2)_3$	$THF/(CH_3)_2S$ -78° ⟶ 0° O_2		59
8		$LiCu(CH_3)_2$	$Et_2O/(CH_3)_2S$ -78° ⟶ 0° CH_3I/O_2		57
9		$Li_2Cu(CH{=}CH_2)_3$	$Et_2O/(CH_3)_2S$ -78° ⟶ 0° O_2		66
10	$\underline{n}\text{-}C_6H_{13}HgCl$	$Li_2Cu(CH_3)_3$	Et_2O -78° ⟶ 0° CH_3I/O_2	$\underline{n}\text{-}C_7H_{16}$	62
11	 $\underline{n}\text{-}C_4H_9\overset{OH}{\overset{\mid}{C}}HCH_2HgCl$		Et_2O -78° CH_3I/O_2	 $\underline{n}\text{-}C_4H_9\overset{OH}{\overset{\mid}{C}}HCH_2CH_3$	51

Scheme

$$RHgCl + LiCuR'_2 \longrightarrow RHgR' + CuR' + LiCl$$

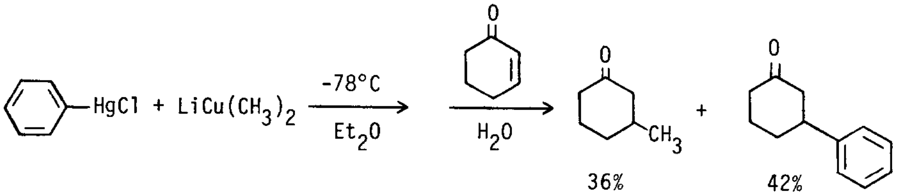
$$RHgR' + CuR' + LiCl \longrightarrow LiCuRR' + R'HgCl$$

$$RHgR' + LiCuR'_2 \longrightarrow LiCuRR' + HgR'_2$$

$$LiCuRR' \xrightarrow{O_2} R\text{-}R'$$

$$LiCuRR' + R'I \longrightarrow R\text{-}R'$$

be pointed out that our intermediates behave significantly different from the ternary complexes of lithium, copper, and mercury described by Bergbreiter and Whitesides.[8] Their intermediate fails to undergo conjugate addition to mesityl oxide, while ours adds readily to 2-cyclohexenone (eq.3). From our work, there appears to be no need to describe our intermediates as anything other than "simple" organocuprate reagents.



(3)

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