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FURTHER INSIGHT INTO LOWER ORDER CUPRATE CHEMISTRY; ON THE USE OF $CuBr \cdot Me_2S$ <u>VS</u> CuI <u>EN ROUTE</u> TO R_2CuLi‡

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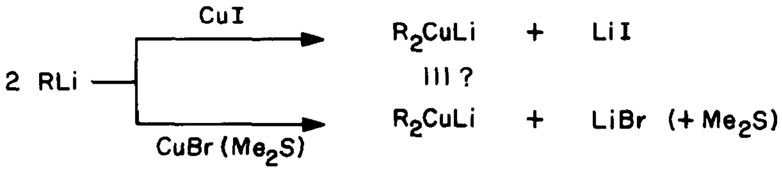
Abstract: **Both ^1H and ^7Li NMR experiments show that 2MeLi + either $CuBr \cdot Me_2S$ or CuI in THF afford the same species, Me_2CuLi (+ LiX). However, use of the former source of Cu(I), depending upon its purity and especially handling, can lead to significantly decreased chemical yields. The reasons behind these observations and the implications for cuprate couplings are discussed.**

Since the original report which presented $CuBr \cdot Me_2S$ as an attractive alternative source of Cu(I) for the preparation of lower order (L.O.) lithium organocuprates,[2] R_2CuLi, <u>1</u>, it has become widely accepted that treatment of this salt with two equivalents of an organolithium leads to the same reagent formed <u>via</u> CuI.[3] While by-product lithium salts (LiBr or LiI) which exist in solutions of <u>1</u> can occasionally play a pivotal role in determining a reaction's outcome,[4] the actual reagent involved is assumed to be <u>1</u>. Indeed, for over a decade one's choice of CuBr versus CuI as cuprate precursor has been and continues to be based usually on relative cost and convenience, and hence, both are routinely employed interchangeably.• As a natural outgrowth of our recent study on CuI derived lower (and higher) order cuprates[5] which, in essence, revealed considerable variations in composition as a function of reaction parameters (e.g., solvent(s), lithium salts, etc.), we decided to apply related chemical and spectroscopic techniques to L.O. systems prepared from $CuBr \cdot Me_2S$. In this Letter we describe experimental observations which point to some fundamental differences between the use of CuI and $CuBr \cdot Me_2S$ for cuprate generation, and their implications for organocopper mediated couplings.



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‡Dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.

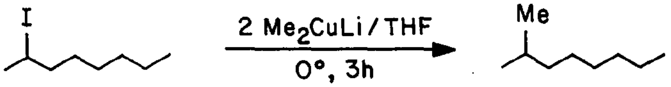
Our initial ^{7}Li NMR spectrum of Me_2CuLi, prepared utilizing freshly titrated, low halide MeLi (in Et_2O) with $CuBr{\cdot}Me_2S$, was rather startling. As with the cuprate derived from CuI + 2MeLi which has been freed of by-product LiI salts,[5] two singlets were present corresponding to methyl groups on copper and to free MeLi. This result was completely reproducible using the same sources of $CuBr{\cdot}Me_2S$ and MeLi. The implication here was that the $CuBr{\cdot}Me_2S$-derived reagent containing LiBr affords the same equilibrium mixture of $Me_3Cu_2Li/(Me_2CuLi_2)$ + MeLi seen for CuI based Me_2CuLi minus the LiI salts. Although this phenomenon seemed difficult to believe, it should be noted that inspection of the literature suggests that all ^{1}H data on Me_2CuLi[2,6] originates from treatment of CuI with MeLi. As best we can tell, no one has reported either the ^{1}H or ^{7}Li NMR spectrum of 2MeLi + $CuBr{\cdot}Me_2S$.

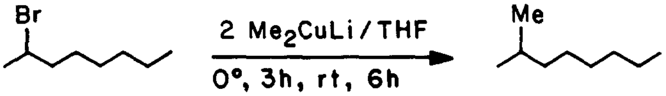
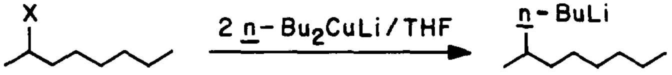
A closer look at the CuBr used, therefore, was in order. Firstly, it occurred to us that a critical feature associated with the use of $CuBr{\cdot}Me_2S$ may well be the manner in which it is handled. Unlike CuI,[7] which is usually soxhlet extracted or recrystallized and then placed under vacuum or oftentimes stored in a heated, evacuated Abderhalden,[8] $CuBr{\cdot}Me_2S$ is either used out of the bottle, or occasionally recrystallized.[9] Repeating our earlier experiment with a freshly opened commercial bottle of $CuBr{\cdot}Me_2S$ led to a ^{7}Li NMR spectrum containing but a single peak attributable to Me_2CuLi. A ^{1}H NMR experiment on this same cuprate using $CuBr{\cdot}Me_2S$ which had been dried azeotropically with toluene or *via* Abderhalden treatment at 56° overnight, revealed the presence of two species, Me_3Cu_2Li[6] and Me_2CuLi (which are indistinguishable by ^{7}Li NMR[5]) suggesting Cu(I):MeLi ratios > 1:2 (*vide infra*).

To corroborate these spectral observations, an array of chemical tests were performed on both 2-iodo and 2-bromooctane using Me_2CuLi prepared from CuBr (with and without Me_2S), the results from which were also compared with those obtained using CuI/2MeLi. Table I contains data which vividly attest to the significant impact which variations in quality and manipulation of CuBr can have on a reaction's outcome. Older bottles of $(CuBr)_2$ and $CuBr{\cdot}Me_2S$ which came "off the shelf" gave inferior yields of product. Recrystallizing these salts by known procedures prior to use increased yields considerably (compare column I: entries 1 *vs* 2, 6 *vs* 7). A relatively new bottle of $CuBr{\cdot}Me_2S$ gave similar results to those obtained from recrystallized CuBr (with or without Me_2S; see column I, entry 2; III, entries 1, 2). By contrast, however, prior drying under vacuum of "new" $CuBr{\cdot}Me_2S$ (Abderhalden, 56°, ≥ 8h) caused yields to drop *ca*. 25-60% (column III, entries 2 *vs* 3, 4 *vs* 5, 7 *vs* 8). The same trend appears for *n*-Bu_2CuLi (Table I), suggesting the generality of these results.

The explanation behind these observations, especially in light of our earlier studies,[5] is now readily apparent. The first scenario, where ^{7}Li NMR demonstrated the existence of free MeLi and chemical yields were low for this source of $CuBr{\cdot}Me_2S$ (column II) is attributed to the poor quality of the $CuBr{\cdot}Me_2S$. Less Cu(I) salt than anticipated implies less conversion of MeLi to Me_2CuLi, and hence free organolithium in solution, as seen by NMR, which increases products of reduction and elimination at the expense of substitution. With good quality $CuBr{\cdot}Me_2S$, as originally described by House,[2] or $(CuBr)_2$,[10] the desired Me_2CuLi is formed and clean spectroscopy and coupling occurs. Finally, handling of $CuBr{\cdot}Me_2S$ as done with CuI can be a costly mistake, as loss of any Me_2S increases the percentage of Cu(I) relative to MeLi. Ratios > 1:2 in THF give rise to incomplete generation of $(Me_2CuLi)_2$, and depending upon the amount of lost Me_2S, produce a quantity of the aggregate Me_3Cu_2Li, which is (relative to Me_2CuLi) chemically inert,[5] as summarized in Scheme I.

Table I. Reactions of R_2CuLi prepared from various sources of Cu(I) salts with 2° halides.



Entry[a]	I $(CuBr)_2$[b]	II CuBr·Me_2S (old)	III CuBr·Me_2S(new)	IV CuI[c]
	source of Cu(I), % yield			
1	73[d]	70[e]	89–92[f]	91–95
2	87[f]		85–92[g]	
3			60[f,h]	
4			31–39[g,i]	68[i]
5			17–21[h,i]	
				
6	59[d]		87[f]	80
7	74[f]		84[g]	
8			26[h]	
				
9			54[f] (X = I)[j]	
10			32[h] (X = I)[j]	
11			14[f] (X = Br)[k]	
12			2[h] (X = Br)[k]	

[a] Yields are based on quantitative VPC analysis. [b] Purified according to Ref. 10. [c] Purified according to Ref. 7. [d] From aged $(CuBr)_2$ from Fisher. [e] From aged CuBr·Me_2S (Aldrich). [f] Recrystallized according to Ref. 9. [g] From Aldrich. [h] After drying in an Abderhalden at 56°C under vacuum overnight. [i] Reaction was run in Et_2O. [j] Reaction conditions: -78°, 1h. [k] 0°, 3h.

Scheme 1

1. $\text{CuBr (with or without Me}_2\text{S)} \xrightarrow{\text{2 MeLi}} \text{Me}_2\text{CuLi} + \text{X MeLi}$

$\left[\text{aged} \Rightarrow \text{Cu(I)} \rightarrow \text{X Cu(II)}\right] \qquad \left[\text{gives side reactions}\right]$

2. $\text{CuBr (with or without Me}_2\text{S)} \xrightarrow{\text{2 MeLi}} \text{Me}_2\text{CuLi}$

$\left[\begin{array}{l}\text{fresh or well-stored,}\\ \text{no additional handling}\end{array}\right] \qquad \left[\text{only}\right]$

3. $\text{CuBr}\cdot\text{Me}_2\text{S} \xrightarrow{\text{2 MeLi}} \text{X Me}_3\text{Cu}_2\text{Li} + (1\text{-X})\text{Me}_2\text{CuLi}$

$\left[\text{dried} \Rightarrow -\text{X Me}_2\text{S}\uparrow\right] \qquad \left[\text{chemically inert}\right]$

In conclusion, the bottom line here is clear: if $(CuBr)_2$ or $CuBr\cdot Me_2S$ is to be used for the preparation of R_2CuLi (and hence, presumably other variations on Gilman reagents; i.e., mixed cuprates, heterocuprates, etc.), it is critical that salt of high quality be obtained, either via recrystallization or from commercial sources, and that no further handling be carried out. Improperly dried or partially oxidized material, wherein more or less than stoichiometric amounts of Cu(I) are present may lead to undesirable organometallic contaminants in solutions of R_2CuLi which affect reaction efficiency. With CuI, however, such issues are nonexistent.

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