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Preparations and selectivities of magnesium-based mixed cuprates

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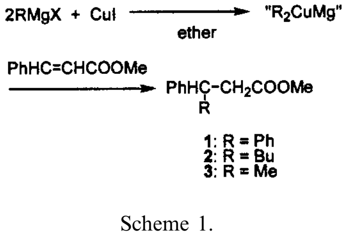
Abstract

The reactions of magnesium-based cuprates 'R_2CuMg' (prepared from $2RMgX + CuI$) with methyl cinnamate furnish conjugate addition products in 60–82% yields. The mixed cuprates 'PhBuCuMg', 'BuPhCuMg' or ['Ph_2CuMg' + 'Bu_2CuMg'], prepared in three different ways, conjugatively add to methyl cinnamate to produce butylated adduct selectively. Another set of mixed cuprates 'BuMeCuMg', 'MeBuCuMg' or ['Bu_2CuMg' + 'Me_2CuMg'] also selectively transfers butyl groups toward conjugate addition reactions. These results reflect to the fact that Cu–Bu bond is more reactive than Cu–Ph or Cu–Me bonds present in the mixed cuprates. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Mixed cuprates; Conjugate addition; Selectivity; Carbon–carbon bond formation; Carbon–copper bond

1. Introduction

Organocuprates $R_2CuLi{\cdot}LiX$ ($X = I$, Br, CN) [1], the Gilman reagents, have been proved as indispensable reagents for selective carbon-carbon bond formation [2]. Unfortunately, only one of the two R groups is utilized in synthetic applications [3]. A mixed cuprate $RR'CuLi{\cdot}LiX$ which is highly reactive yet selectively transfers only one group R. The best solutions of this problem appear to be $RCu(Th)Li{\cdot}LiI$ (Th = 2-thienyl), introduced by the Nilsson group [4] and $RCu(TMSM)Li{\cdot}LiI$ ($TMSM = CH_2SiMe_3$), introduced by Bertz et al. [5]. The corresponding magnesium-based cuprates are now emerging as an economical alternative [6–19] to lithium-based cuprates also transfer only one group R, when the auxiliary group R′ is essentially a nontransferred group. However, Sjoholm and Backlund [21] showed that in conjugate addition reaction the reagent [$RMgX + R'Cu{\cdot}LiI$] transferred R group with greater selectivity, i.e., the group originally attached to magnesium. Similar observations were also made by Bergbreiter et al. [9]. In this paper we wish to report that the totally magnesium-based mixed cuprates 'RR′CuMg', 'R′RCuMg' or ['R_2CuMg' + 'R'_2CuMg'] [where both R and R′ are transferable groups] transfer R group almost selectively toward the conjugate addition reactions with methyl cinnamate and this selectivity depends on the relative reactivities of C–M bonds present in the mixed cuprates rather than the method of preparation.



$$2RMgX + CuI \xrightarrow[\text{ether}]{} \text{"}R_2CuMg\text{"}$$

$$PhHC{=}CHCOOMe \longrightarrow PhH\underset{R}{C}{-}CH_2COOMe$$

1: R = Ph
2: R = Bu
3: R = Me

Scheme 1.

2. Results and discussion

Magnesium-based cuprates 'R_2CuMg' were prepared by treating one equivalent of CuI with two equivalents of respective Grignard reagents and the reactivity of each cuprate was determined how effectively it gave conjugate addition product with methyl cinnamate (Scheme 1). The best results were obtained when three equivalents of magnesium cuprates were employed against one equivalent of the substrate.

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Table 1
Reactions of magnesium-based unmixed and mixed cuprates with methyl cinnamate in 3:1 molar ratio

Entry	Magnesium-based cuprate	Reaction temperature (°C)	Yield (%)		
			1	**2**	**3**
1	‘Ph$_2$CuMg’	0	82		
2	‘Ph$_2$CuMg’	-40	25		
3	‘Bu$_2$CuMg’	-40		82	
4	‘Bu$_2$CuMg’	-40 to -20		87	
5	‘Me$_2$CuMg’	0			60
6	‘PhBuCuMg’	-40	4	73	
7	‘BuPhCuMg’	-40	3	74	
8	[‘Bu$_2$CuMg’ + ‘Ph$_2$CuMg’]	-40	4	60	
9	[‘Ph$_2$CuMg’ + ‘Bu$_2$CuLi’]	-40	29	51	
10	‘BuMeCuMg’	-40		55	1
11	‘MeBuCuMg’	-40		49	1
12	[‘Bu$_2$CuMg’ + ‘Me$_2$CuMg’]	-40		57	1

Thus, diphenylcoppermagnesium ‘Ph$_2$CuMg’ was treated with methyl cinnamate at 0 °C in ether and the conjugate addition product, methyl 3,3-diphenylpropanoate (**1**) was isolated in 82% yield (Table 1, entry 1). The same reaction, when conducted at −40°C to −20°C, gave compound **1** in 25% yield (entry 2). This result reflected the lower reactivity of phenylcoppermagnesium reagent at low temperature. Similarly, the dibutylcoppermagnesium was treated with methyl cinnamate at −40 to −20°C and the butylated adduct, methyl 3-phenylheptanoate (**2**) was obtained in 82% yield (entry 3). Interestingly, when the reaction mixture of ‘Bu$_2$CuMg’ with methyl cinnamate was hydrolyzed at −20°C, the butylated adduct was isolated in 87% yield (entry 4). This indicates that a few percent of the butylated adduct decomposes when the reaction mixture was brought up to room temperature. The reactivity of dimethylcoppermagnesium was also investigated. The treatment of dimethylcoppermagnesium ‘Me$_2$CuMg’ with methyl cinnamate at 0°C in ether gave methylated adduct, methyl 3-phenylbutanoate (**3**) in 60% yield (entry 5). These results indicate that the yields of the phenylated and butylated products are much higher than previously reported [22] under different reaction conditions and offer excellent possibilities in synthesis.

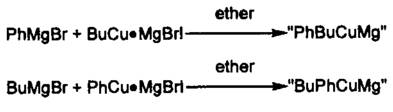
Magnesium-based mixed cuprates were prepared in three different ways and the selectivity of each cuprate was determined depending on the ratio of conjugate addition products with methyl cinnamate. The preparations and selectivities of mixed cuprates constituting phenyl and butyl groups were primarily investigated. The mixed cuprates ‘BuPhCuMg’ were prepared in two different ways, as shown in Scheme 2.

The reaction of ‘PhBuCuMg’ with methyl cinnamate at −40°C to room temperature gave phenylated adduct **1** and butylated adduct **2** in 4 and 73% yields, respectively (entry 6). This result indicates that the reagent ‘PhBuCuMg’ selectively transferred butyl group, although phenyl group was originally attached to magnesium (Scheme 3). The same reaction, when conducted at 0°C, gave a poorer yield of **2** (65%) and proportionately higher yield of **1** (11%). This reflects the temperature dependency of selectivity of mixed cuprates.

As shown in Scheme 4, the reagent ‘BuPhCuMg’ also selectively transferred butyl group and produced butylated adduct **2** and phenylated adduct **1** in 74 and 3% yields, respectively (entry 7). From these results it is clear that the selectivity for the formation of butylated adduct depends on the relative reactivities of Cu–Bu and Cu–Ph bonds at the temperatures used in our studies rather than on the methods of preparation.

This result is also clearly supported by the reaction of another mixed cuprate [‘Ph$_2$CuMg’ + ‘Bu$_2$CuMg’] with methyl cinnamate. Although this cuprate was prepared by mixing two unmixed cuprates, but the butylated adduct was formed selectively (Scheme 5).

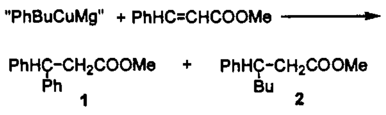
The compounds **1** and **2** were isolated in 4 and 60% yields, respectively (entry 8). Since the actual feature of the reacting species present in the mixed cuprates is not yet known, apart from the reactivities of C–M bonds, the halide ions may have some interesting effects on their selectivities. At this stage it was thought interesting to compare the results of the reaction of magnesium-based cuprates with those of lithium-based cuprates. The reagent [‘Ph$_2$CuMg’ + Bu$_2$CuLi] reacted with methyl cinnamate to give phenylated and butylated products in 29 and 51% yields, respectively (entry 9). The yield of the phenylated product is significantly



$$\text{PhMgBr} + \text{BuCu}\bullet\text{MgBrI} \xrightarrow{\text{ether}} \text{"PhBuCuMg"}$$

$$\text{BuMgBr} + \text{PhCu}\bullet\text{MgBrI} \xrightarrow{\text{ether}} \text{"BuPhCuMg"}$$

Scheme 2.



Scheme 3.

higher and that of the butylated product is noticeably lower than in other cases cited above. This could be taken to indicate that the reagent [‘Ph_2CuMg’ + Bu_2CuLi] is a different reagent system and an equilibrium is possible, as summarized in Eq. (1):

$$[\text{"}Ph_2CuMg\text{"} + Bu_2CuLi] \rightleftharpoons [\text{"}PhBuCuMg\text{"}] + [PhBuCuLi] \quad (1)$$

The reagent ‘PhBuCuMg’ would react with methyl cinnamate producing the normal product ratio but the reagent [BuPhCuLi], being a lithium based mixed cuprate, would be expected to give a different product ratio. The lower yield of the butylated product and the higher yield of the phenylated product would then reflect on the relative reactivities of Ph–Cu and Bu–Cu bonds in [BuPhCuLi] as compared to those in ‘PhBuCuMg’.

Since the mixed cuprates ‘PhBuCuMg’, ‘BuPhCuMg’ and [‘Ph_2CuMg’ + ‘Bu_2CuMg’] gave almost the same ratio of butylated and phenylated adducts, it may be assumed to produce an equilibrium mixture, as summarized in Eq. (2):

$$2[\text{"}PhBuCuMg\text{"}] \rightleftharpoons 2[\text{"}BuPhCuMg\text{"}] \rightleftharpoons [\text{"}Ph_2CuMg\text{"} + \text{"}Bu_2CuMg\text{"}] \quad (2)$$

In order to generalize the selectivities of magnesium-based mixed cuprates, another set of mixed cuprates were investigated constituting butyl and methyl groups. Again, the selectivity was determined depending on the ratio of conjugate addition products with methyl cinnamate. The mixed cuprates ‘BuMeCuMg’, ‘MeBuCuMg’ and [‘Bu_2CuMg’ + ‘Me_2CuMg’] were prepared in three different ways and the reactions of these cuprates with methyl cinnamate at −40°C to room temperature gave butylated adduct **2**, selectively (Scheme 6). The results are summarized in Table 1 (entries 10–12). These results indicate that Cu–Bu bond is more reactive than Cu–Me bond present in the mixed cuprates in our experimental conditions.

Since the mixed cuprates ‘BuMeCuMg’, ‘MeBuCuMg’ and [‘Bu_2CuMg’ + ‘Me_2CuMg’] gave almost the same ratios of butylated and methylated adducts, an equilibrium between these cuprates is conceivable (Eq. (3)).

$$2[\text{"}BuMeCuMg\text{"}] \rightleftharpoons 2[\text{"}MeBuCuMg\text{"}] \rightleftharpoons [\text{"}Me_2CuMg\text{"} + \text{"}Bu_2CuMg\text{"}] \quad (3)$$

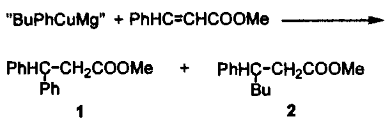
3. Experimental

3.1. General

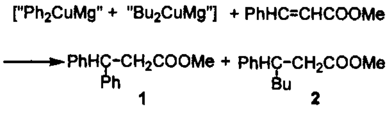
All reactions were carried out under an inert atmosphere. Diethyl ether was dried over sodium and distilled from sodiumbenzophenone ketyl before use. Copper(I) iodide was obtained commercially (E. Merck) and used without further purification. The IR spectra were recorded either as Nujol mull or as liquid film on a Shimadzu IR-470 Infrared spectrophotometer and NMR spectra were recorded on a Bruker 500 MHz spectrometer in $CDCl_3$ using TMS as an internal standard.

3.2. Preparations of diphenylcoppermagnesium ‘Ph_2CuMg’ and dimethylcoppermagnesium ‘Me_2CuMg’

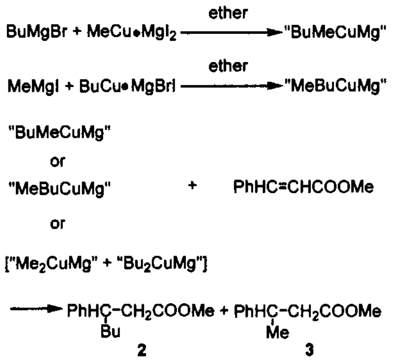
Diphenylcoppermagnesium reagent was prepared as described previously [15,20,22] by stirring phenylmagnesium bromide (2 × mol) with copper(I) iodide (× mol) in ether (100 ml) at 0°C for 3 h or until Gilman color test-I was negative.



Scheme 4.



Scheme 5.



Scheme 6.

Dimethylcoppermagnesium [20,22] was prepared as described above except that methylmagnesium iodide was used instead of phenylmagnesium bromide.

3.3. Preparation of dibutylcoppermagnesium 'Bu_2CuMg'

To a solution of butylmagnesium bromide prepared from 0.02 mol of 1-bromobutane and 0.025 mol of magnesium in 35 ml of ether was added copper(I) iodide (0.01 mol) with continuous stirring. The reaction was complete during 3.5 h at −40°C as evidenced by the negative response to Gilman color test-I. The butylcoppermagnesium reagent thus prepared was an orange suspension in ether and was employed for subsequent reactions immediately.

3.4. Preparations of mixed cuprates

3.4.1. ['PhBuCuMg']

To phenylcopper prepared from 0.012 mol of phenylmagnesium bromide and 0.012 mol of copper(I) iodide in 21 ml of ether at 0°C was added butylmagnesium bromide prepared from 0.012 mol of 1-bromobutane and 0.015 mol of magnesium in 21 ml of ether and the mixture was stirred for 2.5 h at −40°C. The Gilman color test-I was negative at this point. The phenylbutylcoppermagnesium reagent thus prepared was a black suspension in ether and was used immediately for subsequent reactions.

3.4.2. ['BuPhCuMg']

To butylcopper prepared from 0.012 mol of butylmagnesium bromide and 0.012 mol of copper(I) iodide in 21 ml of ether at −40°C was added phenylmagnesium bromide prepared from 0.012 mol of bromobenzene and 0.015 mol of magnesium in 21 ml of ether and the mixture was stirred for 2.5 h at −40°C. The Gilman color test-I was negative at this point. The butylphenylcoppermagnesium reagent thus prepared was a black suspension in ether and was used immediately for subsequent reactions.

3.4.3. ['Ph_2CuMg' + 'Bu_2CuMg']

This reagent was prepared by mixing diphenylcoppermagnesium and dibutylcoppermagnesium reagents at −40°C.

3.4.4. ['MeBuCuMg']

To methylcopper prepared from 0.012 mol of methylmagnesium iodide and 0.012 mol of copper(I) iodide in 21 ml of ether at 0°C was added butylmagnesium bromide prepared from 0.012 mol of 1-bromobutane and 0.015 mol of magnesium in 21 ml of ether and the mixture was stirred for 2.5 h at −40°C. The Gilman color test-I was negative at this point. The methylbutylcoppermagnesium reagent thus prepared was a black suspension in ether and was used immediately for subsequent reactions.

3.4.5. ['BuMeCuMg']

To butylcopper prepared from 0.012 mol of butylmagnesium bromide and 0.012 mol of copper(I) iodide in 21 ml of ether at −40°C was added methylmagnesium iodide prepared from 0.012 mol of methyl iodide and 0.015 mol of magnesium in 21 ml of ether and the mixture was stirred for 2.5 h at −40°C. The Gilman color test-I was negative at this point. The butylmethylcoppermagnesium reagent thus prepared was a black suspension in ether and was used immediately for subsequent reactions.

3.4.6. ['Me_2CuMg' + 'Bu_2CuMg']

This reagent was prepared by mixing dimethylcoppermagnesium and dibutylcoppermagnesium reagents at −40°C.

3.5. General procedure for the conjugate addition reactions with methyl cinnamate

Crystals of methyl cinnamate were added to cooled preparation of the diorganocoppermagnesium reagents. The mixture was stirred for 2 h and allowed to warm to room temperature. The reaction mixture was hydrolyzed with aqueous ammonia saturated with ammonium chloride in water (pH ~ 8). The organic layer was extracted in ether and the ether layer was washed several times with the hydrolyzing reagent until the blue color of the copper complex disappeared completely and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to leave a crude product, which was separated by silica gel column chromatography, followed by distillation or recrystallization.

4. Conclusion

Organocoppermagnesium reagents of the type 'R_2CuMg', prepared from $2RMgX + CuI$, undergo conjugative addition to methyl cinnamate to give 1,4-adducts in very high yields indicating strong potential in organic synthesis. In an appropriate reaction condition, the magnesium-based mixed cuprates '$RR'CuMg$', '$R'RCuMg$' or ['R_2CuMg' + 'R'_2CuMg'] selectively transfer one R group toward conjugate addition reaction with methyl cinnamate and this selectivity depends on the relative reactivities of Cu–C bonds present in the mixed cuprates.

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