

## PREPARATION AND SOME REACTIONS OF HALOMAGNESIUM DIORGANOCUPRATES

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### Summary

Bromomagnesium diphenylcuprate and iodomagnesium dimethylcuprate have been prepared, and their thermal stability and some of their reactions investigated. In diethyl ether, 50% of the  $\text{BrMgPh}_2\text{Cu}$  decomposes in 12 h at room temperature and 50% of the  $\text{IMgMe}_2\text{Cu}$  decomposes at  $0^\circ\text{C}$  in 14 h but the cuprates are more stable in THF at or below  $0^\circ\text{C}$ . They react with acid chlorides to give 16–76% yields of the corresponding ketones. With bromine and iodine,  $\text{BrMgPh}_2\text{Cu}$  gives bromobenzene and iodobenzene in 56 and 48% yield, respectively. Oxidation of  $\text{BrMgPh}_2\text{Cu}$  with nitrobenzene or copper(II) chloride gives, respectively, 61 and 34% of biphenyl. Reaction of  $\text{BrMgPh}_2\text{Cu}$  with acetic or benzoic anhydride yields 46–55% of the corresponding ketone and 34–37% of the corresponding carboxylic acids.

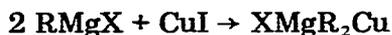
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### Introduction

Lithium diorganocuprates, the Gilman reagents, are now recognized as versatile and extremely useful reagents in organic synthesis, and have been a subject of numerous reviews [1–7]. The corresponding magnesium cuprates have been studied less extensively, although various types of organomagnesium copper compounds have been known for some time [8–10]. Since halomagnesium diorganocuprates should be less expensive than the corresponding lithium reagents, and are now beginning to be used as reagents in organic synthesis [11–24], a more detailed examination of their properties seemed appropriate and we describe below a study of bromomagnesium diphenylcuprate and its methyl analogue.

### Results and discussion

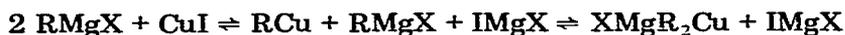
The halomagnesium diorganocuprates were prepared by the following metathetical reactions:



or,

R = C<sub>6</sub>H<sub>5</sub>, CH<sub>3</sub>.

The reaction is complete within 5–6 h at –10 to –15°C in either diethyl ether or THF. There is little doubt that a cuprate reagent is formed in the above reaction, since the reagents prepared in this way do not give a positive response to Gilman Test I, [25] indicating the absence of any significant amount of free Grignard reagent. Furthermore, when ethyl acetate is added no reaction occurs and the ester is recovered almost quantitatively. These observations indicated that the following equilibrium (if it exists at all under the conditions used) lies far over to the right.



That a cuprate reagent is formed in the system is further supported by the fact that when these reagents are treated with acid chlorides they give the corre-

TABLE 1  
STABILITY OF HALOMAGNESIUM DIORGANOCUPRATES IN VARIOUS SOLVENTS

Cuprate reagent	Solvent (100 ml)	Temp at which the reagent kept (°C)	Time for which the reagent kept (h)	Product Yields subsequent to derivatisation <sup>a</sup> (%)		
				PhCOCH <sub>3</sub>	Ph–Ph	
BrMgPh <sub>2</sub> Cu	Ether	~27	0	53	39	
		~27	2	31	53	
		~27	12	19	64	
		~27	24	12	68	
	THF	~27	0	57	31	
		~27	12	39	49	
		27	24	27	58	
	Ether-THF <sup>b</sup>	~27	24	21	56	
		Ether-Toluene <sup>b</sup>	~27	24	20	59
			Ether-benzene <sup>b</sup>	~27	24	18
IMgMe <sub>2</sub> Cu	Ether	0	0	60		
		0	2	55		
		0	14	31		
	Ether-THF <sup>b</sup>	0	0	63		
		0	14	50		
		0	24	41		
		0	36	20		
		~27	14	18		
		35	14	8		
	THF	0	4	65		

<sup>a</sup> Derivatisation was carried out with acetyl chloride (0.015 mol) in the case of BrMgPh<sub>2</sub>Cu (0.015 mol), and with benzoyl chloride (0.015 mol) in the case of IMgMe<sub>2</sub>Cu (0.03 mol). The derivatives were obtained after hydrolytic work-up. The yield of acetophenone is somewhat low in the case of BrMgPh<sub>2</sub>Cu, presumably because the cuprate and acid halide were used in 1 : 1 molar ratio, see Table 3. <sup>b</sup> A 1 : 1 (v/v) mixture.

sponding ketones in good yield (vide infra). This behaviour is very similar to that of lithium diorganocuprates [1].

Bromomagnesium diphenylcuprate, prepared as above, is not very stable. About 50% of it decomposes in 24 h in ether at room temperature ( $\sim 27^\circ\text{C}$ ), to give mainly biphenyl. The stability in various solvent systems decreases in the series (Table 1):

THF > THF-Ether > Ether-Toluene  $\geq$  Ether-benzene > Ether  
 (1 : 1)                      (1 : 1)                      (1 : 1)

If it is assumed that the stability increases with the co-ordinating power of the solvent, then the somewhat increased stability of the cuprate in ether-toluene or in ether-benzene as compared with that in ether alone suggests that it co-ordinates with the arene  $\pi$ -electron systems.

Iodomagnesium dimethylcuprate is less stable than bromomagnesium diphenylcuprate. About 50% of the former decomposes at  $0^\circ\text{C}$  in diethyl ether in 14 h, whereas the latter decomposes to the extent of 36% in the same solvent in 12 h but at a higher temperature ( $\sim 27^\circ\text{C}$ ). As before, the stability of the methylcuprate decreases in the following solvent series:

THF > THF-Ether > Ether  
 (1 : 1)

Both bromomagnesium diphenylcuprate and iodomagnesium dimethylcuprate are more stable in THF at or below  $0^\circ\text{C}$ , and this allows their reactions to be studied. However, both cuprates are less stable than their lithium counterparts [1,2].

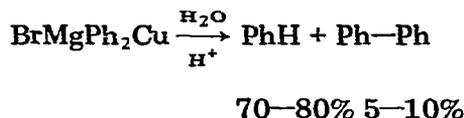
The magnesium-based cuprates, like [1,2] their lithium analogues, are very

TABLE 2  
SOME REACTIONS OF BROMOMAGNESIUM DIPHENYLCUPRATE <sup>a</sup>

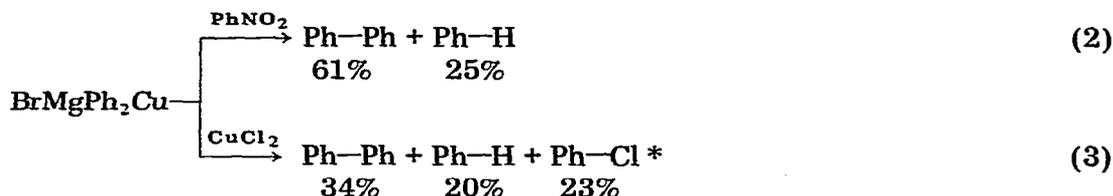
Reactn. medium (50 ml)	Reagent	Period of addn. (min)	Reactn. temp. ( $^\circ\text{C}$ )	Reactn. time (h)	Products (% yield) <sup>c</sup>				
					Ph-Ph	PhCl	PhBr	PhI	PhH
Ether	H <sup>+</sup> , H <sub>2</sub> O <sup>d</sup>	30	-8	1	5-10				70-80
THF	PhNO <sub>2</sub>	30	-5	1	61				25
	0.015 mol in 15 ml THF								
THF	CuCl <sub>2</sub>	all in	-5	1	34	23			20
	0.015 mol one lot								
Ether	Br <sub>2</sub>	30	0	1	39		56		-
	0.033 mol in 15 ml THF								
Ether	I <sub>2</sub>	all in	0	1	50			48	-
	0.033 one lot								

<sup>a</sup> The cuprate (0.015 mol) was prepared at  $-15^\circ\text{C}$  either in ether or THF. The molar amount has been calculated on the basis of the monomeric formula, BrMgPh<sub>2</sub>Cu. <sup>b</sup> After this period the reaction mixtures were allowed to attain room temperature and then stirred for 1 h before hydrolytic work-up. <sup>c</sup> Based on starting bromobenzene. <sup>d</sup> Deoxygenated in HCl (50 ml).

sensitive to moisture and air. Bromomagnesium diphenylcuprate reacts with deoxygenated dilute hydrochloric acid to give benzene and biphenyl.



Bromomagnesium diphenylcuprate is oxidized by nitrobenzene or copper(II) chloride. Biphenyl is the main product, but some benzene is often formed. Nitrobenzene is a better oxidizing agent than copper(II) chloride (Table 2), as in the oxidative coupling reactions of lithium diorganocuprates [26].



Since reaction 2 gives fair yields of biphenyl this method may have some potential as an alternative procedure for the synthesis of symmetric biaryls.

Halogenation [24] of bromomagnesium diphenylcuprate gives the corresponding halogenobenzenes (Table 2), but the low yields preclude use of the reaction in synthesis:



The biphenyl in reactions 4 and 5 is probably formed by oxidative coupling of the cuprate in the presence of the halogen. Bromomagnesium diphenylcuprate does not couple with either iodo- or bromo-benzene to give biphenyl under these conditions [27].

As mentioned above, the halomagnesium diphenylcuprate reacts with acid chlorides to give good yields of the corresponding ketones (Table 3). The best yields are obtained in THF at a molar ratio of cuprate to acid chloride of 2 to 1. The need to use this high molar ratio is possibly because of the thermal instability of the cuprates but it is also possible that the cuprates are reacting as cluster compounds.

In the case of iodomagnesium dimethylcuprate the yield of acetophenone decreases when the molar ratio of the cuprate to benzoyl chloride is 4 to 1 (eighteenth entry in Table 3). This is probably because acetophenone reacts further with the excess of cuprate. A similar reaction between lithium dimethylcuprate and acetophenone is known to occur, but slowly [28].

\* Chlorobenzene might have been formed by an exchange reaction, but there could be other explanations.

TABLE 3

 REACTIONS <sup>a</sup> OF HALOMAGNESIUM DIORGANOCUPRATES WITH ACID HALIDES AND CARBOXYLIC ACID ANHYDRIDES  $\text{XMgR}_2\text{Cu} + \text{R}'\text{COY} \rightarrow \text{RCOR}' + \text{YMgX}$ 

R	R'	Y	Molar ratio <sup>b</sup> $\text{XMgR}_2\text{Cu}/\text{R}'\text{COY}$	Solvent (100 ml)	Products <sup>c</sup> (% yield) <sup>d</sup> RCOR'		
C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	Cl	1 : 1	Ether	51		
			1 : 2	Ether	54		
			1 : 4	Ether	35		
			1 : 1	THF	61		
	C <sub>6</sub> H <sub>5</sub>	Cl	Cl	2 : 1	THF	68 <sup>e</sup>	
				1 : 1	THF	67	
		p-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	Cl	Cl	2 : 1	THF	72
					1 : 1	THF	76
					2 : 1	Ether	52 <sup>f</sup>
		CH <sub>3</sub>	OCOR'	Cl	2.5 : 1	Ether	46 <sup>f</sup>
					2 : 1	Ether	55 <sup>f</sup>
		CH <sub>3</sub> <sup>e</sup>	C <sub>6</sub> H <sub>5</sub>	Cl	2 : 1	THF	65
					2 : 1	Ether	60
p-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	Cl		Cl	1.5 : 1	Ether	30	
				1 : 1	Ether-THF <sup>g</sup>	18	
				1.5 : 1	Ether-THF <sup>g</sup>	40	
				2 : 1	Ether-THF <sup>g</sup>	63	
				4 : 1	Ether-THF <sup>g</sup>	44	
				2 : 1	Ether-THF <sup>g</sup>	18	
				2 : 1	Ether-THF <sup>g</sup>	16 <sup>h</sup>	

<sup>a</sup> All reactions were carried out at  $-8^\circ\text{C}$  for 2 h and then at  $0^\circ\text{C}$  for 0.5 h except where otherwise stated.

<sup>b</sup> Calculated on the basis of the monomeric formula,  $\text{XMgR}_2\text{Cu}$ . <sup>c</sup> Subsequent to hydrolytic work-up. Small quantities of R-R and RH were always formed. <sup>d</sup> Based on R'COY; in the case of second and third entries the yield is calculated on the assumption that only one equivalent of the substrate had reacted. <sup>e</sup> The reaction was carried out at  $0^\circ\text{C}$  for 2 h. <sup>f</sup> Additionally, 34–37% of R'COOH and up to 9% of R'R<sub>2</sub>COH were formed particularly when R' = CH<sub>3</sub>. <sup>g</sup> A 1 : 1 mixture. <sup>h</sup> The cuprate suspension was added to the substrate. In all other cases the substrate was added directly to the cuprate reagent.

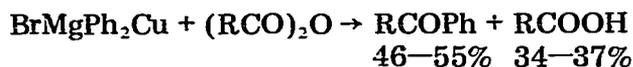
Table 3 indicates that the yield of the ketone increases as the electron-withdrawing character of R' increases (particularly in the reactions of bromomagnesium diphenylcuprate with acid halides). The yield also increases with increasing polarity of the medium. These facts indicate the involvement of a nucleophilic attack by the cuprate molecule at the carbonyl carbon of the acyl chloride.

The lower yield of the ketone when iodomagnesium dimethylcuprate reacts with 4-nitrobenzoyl chloride may mean that this cuprate is more sensitive [15,26] to oxidation by a nitro compound than its phenyl counterpart.

It is noteworthy that the highest yields of acetophenone and benzophenone obtained from  $\text{BrMgPh}_2\text{Cu}$  are 68 and 72%, respectively, whereas, when  $\text{LiPh}_2\text{Cu}$  is used the yields are 55 and 55–59% [28,29]. The yield (76%) of 4-nitrobenzophenone obtained by use of the organomagnesium copper reagent is also very high. Since Grignard reagents are more commonly available and relatively cheaper, and since the yields of the ketones are some 13–15% higher when a magnesium based diphenylcuprate is used instead of the lithium analogue, bromomagnesium diphenylcuprate may be better than the corresponding lithium cuprate for the synthesis of ketones of the type PhCOR.

Bromomagnesium diphenylcuprate reacts with carboxylic acid anhydrides

giving, after hydrolysis, the corresponding ketones and carboxylic acids (Table 3):



R = CH<sub>3</sub> or C<sub>6</sub>H<sub>5</sub>

When R = CH<sub>3</sub>, 1,1-diphenylethan-1-ol was also formed in 9% yield.

In view of the much higher yields of the ketones via the acid chlorides, this method does not offer much synthetic utility.

## Experimental

### General

The reactions were carried out under a positive pressure of dry, oxygen-free nitrogen. Diethyl ether and tetrahydrofuran (THF) were dried over sodium and distilled from sodium-benzophenone ketyl before use. Copper(I) iodide was obtained commercially (E. Merck) and used without further purification. The IR spectra were recorded on a Pye Unicam SP1025 Infrared Spectrophotometer.

### Preparation of bromomagnesium diphenylcuprate [20]

Copper(I) iodide (*x* mol) was added to a cooled (–10°C to –15°C) solution of phenylmagnesium bromide, (prepared from magnesium (2*x* g-atoms) and bromobenzene (2*x* mol) in dry diethyl ether (100 ml)) and the mixture stirred magnetically at that temperature until Gilman Test I [25] was negative. This generally took 5–6 h. The bromomagnesium diphenylcuprate thus prepared was in the form of a brown solid suspension. The reagent can be prepared in THF in the same way, but then appears as a white suspension.

### Preparation of iodomagnesium dimethylcuprate

This reagent was prepared as described above except that methylmagnesium iodide was used in place of phenylmagnesium iodide. To obtain the reagent in THF-ether, methylmagnesium iodide was first prepared in 50 ml ether, THF (50 ml) was added, the mixture was cooled to –10 to –15°C, and then the required amount of copper(I) iodide was added. The mixture was stirred for 5–6 h or until Gilman Test I [25] was negative.

Iodomagnesium dimethylcuprate was formed as dirty yellow solid in either ether or ether-THF.

Both cuprate reagents were used immediately after preparation without isolation.

### Reaction of bromomagnesium diphenylcuprate with ethyl acetate

To bromomagnesium diphenylcuprate (0.015 mol) prepared from phenylmagnesium bromide (0.03 mol) and copper(I) iodide (0.015 mol) in diethyl ether, was added slowly, with constant stirring, a solution of ethyl acetate (0.015 mol) in ether (30 ml). The mixture was stirred for 2 h at –8°C after the addition and then for 0.5 h at 0°C. After hydrolysis with aqueous ammonia, saturated with ammonium chloride (pH = ~8), the organic material was

extracted with ether (3 × 30 ml), and the ether extract dried over anhydrous sodium sulphate. Fractional distillation gave ethyl acetate (96%), b.p. 77–78°C (reported [31] b.p. 77°C), identical (IR) with the starting material.

*General procedure for the reaction of halomagnesium diorganocuprates with acid halides (Table 3)*

The acid chloride (0.01 mol) was added dropwise to halomagnesium diorganocuprate (prepared as described above from 0.04 mol of a selected Grignard reagent and 0.02 mol of copper(I) iodide at –15°C in THF or ether) over a period of 30 min with constant stirring. The mixture was stirred for 2 h at 0°C after the addition and then allowed to attain room temperature. The mixture was hydrolysed with aqueous ammonia/ammonium chloride solution (1 : 1, v/v), the organic matter extracted with ether (3 × 30 ml), and the ether extract washed three times with aq. NH<sub>3</sub>/NH<sub>4</sub>Cl solution or until the blue colour of the copper complex disappeared. The ether solution was dried over anhydrous sodium sulphate and filtered, and the solvents removed by distillation. Fractional distillation of the residue gave the corresponding ketones. Further details of this type of reaction are given in Table 3. The products were identified by comparing m.p. and/or b.p., IR spectra, TLC-R<sub>f</sub> values with those of authentic samples obtained commercially, and, where possible by mixed m.p.

*Stability of halomagnesium diorganocuprates in various solvents (Table 1)*

Halomagnesium diorganocuprates were prepared at –15°C from 0.03 mol of the appropriate Grignard reagent and 0.015 mol of copper(I) iodide in diethyl ether as described above. Most of the ether was then removed by bubbling nitrogen through the suspension. The solvent (100 ml) in which the thermal stability was to be studied was added slowly. The mixture was then allowed to attain room temperature (~27°C) by removing the cooling bath and kept at this temperature for varying lengths of time. If the stability of a cuprate was to be determined at 0°C, it was then cooled in ice. The undecomposed cuprate was treated with 0.015 mol of acetyl chloride in the case of bromomagnesium diphenylcuprate or with 0.015 mol of benzoyl chloride in the case of iodomagnesium dimethylcuprate, as described above. The yields of the acetophenone formed after hydrolytic work-up were taken as a measure of the amount of cuprate reagent remaining. Table 1 shows the results of these experiments.

*General procedure for reactions of bromomagnesium diphenylcuprate with various substrates (Table 2).*

Bromomagnesium diphenylcuprate was prepared on a 0.015 molar scale from 0.03 mol of phenylmagnesium bromide and 0.015 mol of copper(I) iodide in either diethyl ether or THF at –15°C, as described above. The cuprate suspension was brought to the desired temperature and the substrate 0.015 mol (in the cases of Br<sub>2</sub> and I<sub>2</sub>, 0.03 mol) was added either as an ether solution over a period of 30 min or all at once, as specified in Table 2. The mixture was stirred at the selected temperature for 1 h, and was then allowed to warm to room temperature and stirred for another hour. Hydrolysis with aqueous ammonia saturated with ammonium chloride was followed by the usual work-up. Table 2 gives the details.

The products were identified, where possible, by mixed m.p. with authentic samples and/or comparing the IR spectra, TLC- $R_f$  values and b.p with those of authentic samples.

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