

The reaction of the phenyl-copper-magnesium reagent, prepared from 2 PhMgBr and CuI, with some organic halides

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Abstract

The reagent prepared from 2 PhMgBr and CuI reacts with allyl and benzyl bromides to give allylbenzene and diphenylmethane, respectively, in 52 and 62% yields. The yields rise to 82–84% in the presence of nitrobenzene as an oxidant. During the reaction with allyl bromide some copper-bromine exchange takes place. Methyl iodide reacts with the copper reagent to give toluene in 65% yield. Iodoarenes react slowly and give poorer yields of the biaryls (18–46%); in these reactions some metal-iodine exchange is observed. Nitrobenzene seems to be better as an oxidant than copper(II) chloride, which brings about some metal-chlorine exchange in addition to acting as an oxidant.

Introduction

Two of the most important reactions undergone by lithium diorganocuprates, the Gilman reagents, are those with α,β -unsaturated carbonyl compounds to give the 1,4-addition products [1], and with organic halides to give the corresponding coupling products [2,3]. Both these reactions have been extensively employed in the synthesis of many natural products [4]. We have been interested in the study of the magnesium-based organocoppers, primarily because the Grignard reagents required for the preparation of the magnesium cuprates are more readily available than the corresponding lithium reagents, particularly in humid, tropical climates. We reported previously that the Grignard-based organocoppers are comparable to, and sometimes more advantageous than, the corresponding Gilman reagents in their reactions with acyl halides to give ketones [5], and with α,β -unsaturated carbonyl compounds to give the conjugate addition products [6]. We subsequently examined the effectiveness of these magnesium-based cuprate reagents in the Corey–Posner type of coupling reaction [7] for the formation of the carbon–carbon σ -bond, and this paper describes some of the results.

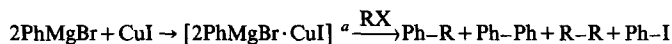
There is much less information on the constitution of a magnesium-based organocopper than on that of the corresponding lithium diorganocuprates; some of these have been shown to be dimeric in nature, with a cluster of four metal atoms with bridging organic groups [8]. Ashby et al. [9] have shown by NMR studies that when methylmagnesium halide reacts with one equivalent of copper(I) halide in THF at -78 to -30°C , several THF-soluble species, e.g., CuMgMe_3 , $\text{Cu}_3\text{Mg}_2\text{Me}_7$, Cu_2MgMe_4 , Cu_3MgMe_5 , Cu_4MgMe_6 and Cu_6MgMe_8 are formed. The reaction mixture also contains some insoluble copper(I) halide and/or MeCu . It thus seems inappropriate to name a copper reagent, generated by treating a Grignard reagent with copper(I) halide, 'magnesium organocopper' or 'organomagnesium copper' [9] since each of these names could be taken to refer to discrete chemical compounds which such a copper reagent is not. Likewise it may be incorrect to name these copper reagents 'halomagnesium diorganocuprates' or halomagnesium diorganocuprates, as was previously done [5,6], rather in line with the nomenclature for the lithium diorganocuprates reagents. A magnesium-based organocopper reagent, prepared from two equivalents of a Grignard reagent and one equivalent of copper(I) halide, will thus be represented by $[2\text{RMgX} \cdot \text{CuX}]$ and for simplicity referred to as the "organo-copper-magnesium reagent" without any structural implications.

Results and discussions

Table 1 shows that when the phenyl-copper-magnesium reagent, prepared from 2PhMgBr and CuI , reacts with allyl bromide in THF it gives allylbenzene in 62% yield. The yield increases to 82% if nitrobenzene is added to the reaction and the oxidation allowed to proceed for 2 h before hydrolytic work-up. Similar results are

Table 1

The reaction of the phenyl-copper-magnesium reagent with some organic halides



Entry no.	RX 0.01 mol	Additive 0.01 mol	Solvent 100 ml	Products ^b , % yield			
				Ph-R	Ph-Ph	Ph-I	Others
1	$\text{CH}_2=\text{CHCH}_2\text{Br}$	—	THF	62	trace	—	PhBr, —
2	$\text{CH}_2=\text{CHCH}_2\text{Br}$	PhNO_2	THF	82	7	—	PhBr, 18
3	PhCH_2Br	—	THF	52	22	—	PhBr, nil
4	PhCH_2Br	PhNO_2	THF	84	14	—	PhBr, nil
5	MeI	—	Et_2O	11	5	nil	—
6	MeI	—	THF	41	trace	nil	—
7	MeI	PhNO_2	Et_2O	20	35	—	—
8	MeI	PhNO_2	THF	65	trace	nil	—
9	MeBr	PhNO_2	THF	60	trace	—	PhH, 30
10	PhI	—	THF	—	5	83	PhH, > 30 ^c
11	PhI	PhNO_2	THF	—	78	62	—
12	—	PhNO_2	THF	—	60	—	—
13	PhI	CuCl_2	THF	—	32	93	PhCl, 24
14	—	CuCl_2	THF	—	32	—	PhCl, 22
15	4-I-Tol	PhNO_2	THF	46	23	41	4-I-Tol, 37

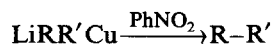
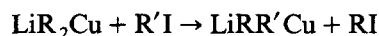
^a The copper reagent was prepared from 0.04 mol of PhMgBr and 0.02 mol of copper(I) iodide. ^b No R-R is observed to have formed. ^c Actual amount not determined.

obtained with benzyl bromide. The yield of diphenylmethane is 84% in the presence and 52% in the absence of nitrobenzene (entries 3 and 4). When the phenyl-copper-magnesium reagent reacts with methyl iodide in THF in the absence of nitrobenzene, the yield of the coupling product, toluene, is 41%. A lower yield of 11% is obtained in the less polar solvent, diethyl ether. The yield of toluene rises to 65% for reaction in the presence of nitrobenzene in THF. As expected methylbromide gives a somewhat lower yield of toluene (60%) than methyl iodide.

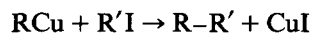
In the absence of any substrate, the phenyl-copper-magnesium reagent is oxidized by nitrobenzene to give biphenyl in 60% yield. Addition of iodobenzene to the magnesium-cuprate reagent followed by the addition of nitrobenzene increases the yield of biphenyl to 78%, and 62% of the iodobenzene is recovered. In the absence of nitrobenzene the cuprate reagent reacts sluggishly with iodobenzene to give a 5% yield of biphenyl and most (83%) of the iodobenzene is recovered. It thus appears that the phenyl-copper-magnesium reagent reacts with iodobenzene in the presence of nitrobenzene to give biphenyl only to the extent of 20%. In the absence of nitrobenzene this reaction is negligible. It is, however, difficult to say from these experiments whether or not some metal-iodine exchange reaction has taken place during this reaction.

The phenyl-copper-magnesium reagent reacts with 4-iodotoluene in THF in the presence of nitrobenzene to give 4-methylbiphenyl in 46% yield. Biphenyl is obtained in 23% yield, presumably by the oxidation of the copper reagent. Additionally a significant amount of metal-iodine exchange occurs during this reaction as is evidenced by the isolation of iodobenzene in 41% yield. Such an exchange reaction has previously been observed with lithium diorganocuprates and iodoarenes [10]. Thus replacing lithium with magnesium in the copper reagent does not make a significant difference to the extent of the metal-halogen exchange reaction.

Entries 12 and 14 of Table 1 show that nitrobenzene is perhaps a better oxidant than copper(II) chloride. This has precedent in the chemistry of lithium diorganocuprates [10]. It is not understood at this moment, however, how the oxidant improves the yields of the coupling products. Whitesides et al. [10] concluded from their work with lithium diorganocuprates that an organic iodide undergoes metal-iodine exchange of the following type to give a mixed cuprate reagent, the oxidation of which gives the unsymmetrical coupling product in an amount greater than that obtained by Corey-Posner coupling. This accounts for the fact that higher yields of the coupling products are obtained when lithium diorganocuprates react with organic iodides when an oxidant is present.



The contribution from the Nilsson type coupling reaction [11]:



to the yield of R-R' should be negligible, because this reaction is slow, and requires higher temperatures and longer times for completion [11,12].

However, the involvement of a mixed cuprate of the above type (LiRR'Cu) is not so important in the rate of the magnesium cuprate reagent since when the latter

reacts with methyl iodide no iodobenzene is formed even though the presence of nitrobenzene increases the yield of toluene significantly. Furthermore when a mixed cuprate reagent of the type $[(\text{PhMgBr} \cdot \text{CuI}) + \text{MeMgI}]$ (corresponding to say, LiPhMeCu) is prepared then oxidized with nitrobenzene, it gives toluene in only 4–5% yield, and the major isolable product is biphenyl [13]. The involvement of a mixed cuprate as intermediate in the reaction of the magnesium-based cuprate reagent with organic iodides thus appears to be less significant than that in the corresponding lithium-based cuprate chemistry, unless of course the major cuprate species [9] formed during the possible exchange reaction between the phenyl-copper-magnesium reagent and methyl iodide contains many more phenyl than methyl groups. In that case, during oxidation there might be a greater probability of two phenyl groups coupling with each other to give biphenyl than of one phenyl coupling with one methyl to give toluene.

Some of the nitrobenzene in the reaction of the phenyl-copper-magnesium reagent with organic halides is found to be converted into its reduction products, azoxybenzene, and azobenzene; the rest is recovered. Copper(II) chloride, in addition to acting as an oxidant, participates in a different type of exchange reaction to give chlorobenzene in 22–24% yield. We checked whether the chlorobenzene could have been formed from the action of iodobenzene on copper(II) chloride under our conditions, and no chlorobenzene was detected in the products. Thus chlorobenzene is probably formed by the reaction of copper(II) chloride with the magnesium cuprate reagent.

Entry number 2 in Table 1 shows that during the reaction of the magnesium cuprate reagent with allyl bromide some metal-bromine exchange takes place, as indicated by the isolation of bromobenzene. We have repeated this reaction several times with essentially the same results. (We are certain that the bromobenzene isolated from this reaction is not the unreacted residue of the bromobenzene employed in the preparation of the phenyl-copper-magnesium reagent via phenyl-magnesium bromide because the phenylmagnesium bromide employed for the preparation of the cuprate reagent did not contain any free bromobenzene (as shown by GLC).) The bromobenzene is probably formed by copper-bromine exchange between the copper reagent and allyl bromide. However, we did not observe any copper-bromine exchange between benzyl bromide and the phenyl-copper-magnesium reagent.

Our results indicate that the phenyl-copper-magnesium reagent reacts with alkyl, aryl, or allyl halides in the presence of nitrobenzene under mild conditions to give fair to good yields of the corresponding coupling products. For the synthesis of the C–Ph bond, the phenyl-copper-magnesium reagent can thus be employed, especially when lithium diphenylcuprate is not easily available.

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 wire and distilled from sodium benzophenone ketyl before use. Copper(I) iodide was a commercial product (Merck) and used without further purification.

Preparation of the phenyl-copper-magnesium reagent [5]. Copper(I) iodide (0.02 mol) was added to a cooled (-8°C) solution of phenylmagnesium bromide (pre-

pared from 0.04 g-atom of magnesium and 0.04 mol of bromobenzene in 100 ml of diethyl ether), and the mixture was stirred at that temperature until Gilman colour test I [14] was negative. This usually took 2–3 h. The phenyl-copper-magnesium reagent thus prepared in ether was in the form of a brown solid suspension. In THF most of the reagent appeared as white suspension.

General procedure for the reaction of the phenyl-copper-magnesium reagent with organic halides in the presence of an oxidant. The organic halide (0.01 mol) was added in one portion to the phenyl-copper-magnesium reagent (prepared from 0.04 mol of phenylmagnesium bromide and 0.02 mol of copper(I) iodide at -8°C in THF or diethyl ether) with constant stirring. The mixture was stirred for 1 h at -8°C , then nitrobenzene (0.01 mol) or copper(II) chloride (0.01 mol) was added and the mixture was stirred for a further 1 hour at that temperature, then for 30 min at room temperature, and finally refluxed for 30 min. The cooled mixture was treated with aqueous ammonia/ammonium chloride solution (1/1, v/v), the organic matter was extracted with diethyl ether (3×30 ml), and the ether extract was washed three times with aqueous $\text{NH}_3/\text{NH}_4\text{Cl}$ solution or until the blue colour of the copper complex disappeared. The extract was dried over anhydrous sodium sulphate and filtered, and the solvents were distilled off. Fractional distillation of the residue gave the corresponding coupling products which were identified by comparing their melting and/or boiling points, IR spectra, TLC and GLC with those of authentic samples and, where possible or necessary, by mixed melting points, these procedures were used to identify toluene, biphenyl, bromobenzene, chlorobenzene and iodobenzene. Allylbenzene, diphenylmethane and 4-methylbiphenyl in addition gave the expected NMR and mass spectra. Further details of these experiments are given in Table 1. When nitrobenzene was used as the oxidant, GLC analysis of the product mixture indicated the presence of azoxybenzene, azobenzene, and roughly 50% of the nitrobenzene. The yields of azoxybenzene and azobenzene were not determined.

The reaction of the phenyl-copper-magnesium reagent with organic halides in the absence of an oxidant. These reactions were carried out in the same way as described under "the reaction of the phenyl-copper-magnesium reagent with organic halides in the presence of an oxidant", except that no oxidant was added to the mixture obtained by the addition of an organic halide to the copper reagent. The mixture was thus stirred at -8°C for 1 h, then at room temperature for 30 min and finally at the refluxing temperature of the solvent media for 30 min. The cooled reaction mixture was worked up as described above.

The reaction of the phenyl-copper-magnesium reagent with nitrobenzene or copper(II) chloride. To the cuprate reagent (prepared in a 0.02 molar scale from 0.04 mol of phenylmagnesium bromide and 0.02 mol of copper(I) iodide in THF at -8°C) was added nitrobenzene (0.01 mol) or copper(II) chloride (0.01 mol) and the mixture was stirred at this temperature for 1 h then at room temperature for 1 h. The cooled mixture was hydrolysed and worked up as described above, to give biphenyl in 60% yield when nitrobenzene was used as the oxidant, and 32% yield when copper(II) chloride was used. From the reaction in the presence of copper(II) chloride chlorobenzene was also isolated by the conventional work-up procedure in 22% yield.

The reaction of iodobenzene with copper(II) chloride. Equimolar amounts of copper(II) chloride and iodobenzene were stirred in THF at -8°C for 1 h, then at

room temperature for 30 min and finally at the reflux temperature for 30 min. The mixture was cooled, hydrolysed, and worked up in the usual way. No chlorobenzene was detected.

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