

FORMATION OF KETONES IN THE REACTION OF ALDEHYDES WITH UNSOLVATED DIBUTYLMAGNESIUM IN HYDROCARBON SOLVENTS UNDER HOMOGENEOUS CONDITIONS, AND ITS IMPLICATIONS

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Summary

Unsolvated dibutylmagnesium reacts with aldehydes in the presence of lithium alkoxide in methylcyclohexane to give not only the expected secondary alcohol but also the ketone formed by oxidation of the alcohol. The amount of ketone produced depends on the reactant ratios, which can be chosen so that the ketone is the major product. The relevance of these observations to the reactions of aldehydes with organomagnesium and organolithium reagents in general is discussed.

The reaction of organolithium and dialkylmagnesium reagents with aldehydes, ketones, and carboxylic acid esters inevitably results in the presence of metal alkoxides in the reaction mixture. The questions then arise of whether there is any interaction between the organometallic reactant and the alkoxide produced and to what extent the alkoxide affects the reactivity of the organometallic reactant and the course of the reaction.

These questions are timely for a number of reasons. Diaryl- and dialkylmagnesiums have been shown to form hydrocarbon-soluble complexes with metal alkoxides; for example, unsolvated diphenylmagnesium has recently been shown to form an aromatic hydrocarbon-soluble complex with sodium 2-ethoxyethoxide, and the same complex can in fact also be obtained by reaction of phenylsodium with magnesium 2-ethoxyethoxide [1,2]. Complexation between organolithium compounds and lithium alkoxides has been known for many years [3,4]. The effect of the product alkoxide on the reactivity of solvated organomagnesium reagents has been considered by Ashby and coworkers [5]. Recently, McGarrity et al. have shown by rapid injection NMR spectrometry that mixed butyllithium-lithium alkoxide oligomers exhibit a reactivity markedly different from that of the butyllithium oligomer itself [6].

An additional reason for examining alkylmetal-metal alkoxide systems is the interest which has been shown in recent years in the possibility of using such

systems in asymmetric synthesis. Various chiral ligands such as amines [7a], amides [7b], aminoethers [7c,d] and alkoxides [8,9], have been examined, the most useful being the amino-alkoxide used by Mukaiyama [9]. The disadvantages of these systems are the need for low reaction temperatures and a large excess of alkylating agent. Thus it can be more profitable to induce asymmetry by other means at some other stage in a particular synthesis [10].

In view of our current interest in the solubilization of unsolvated dialkylmagnesium reagents in hydrocarbons (i.e. non-donor) solvents by means of alkali metal alkoxides [1,2,11], and in their reactivities compared with those of analogous reagents in donor solvents, we initiated a study aimed at exploring the possibility of asymmetric induction with these systems and also the complications arising from the presence of alkoxide. It soon became apparent that a variety of competing and consecutive reactions can take place in these systems, and these can be broadly classified into three categories:

- (1) Alkation reactions,
- (2) Meerwein-Ponndorf-Verley-Oppenauer (MVPO) reduction-oxidation reactions and the related Tishchenko reaction,
- (3) Aldol condensations or the Knoevenagel reaction.

(To these could be added, of course, other well known side-reactions characteristic of dialkylmagnesium reagents, such as reduction, enolization, and pinacol formation, but these will not be dealt with here.) We have examined the conditions under which these reactions are important, and have investigated the possibility of enhancing the MVPO reaction with a view to achieving a one-pot conversion of an aldehyde to the ketone corresponding to the replacement of the aldehydic hydrogen by an alkyl group.

Results and discussion

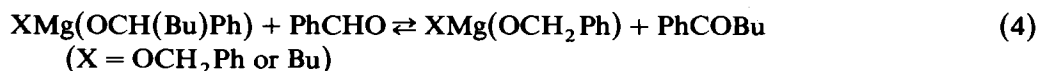
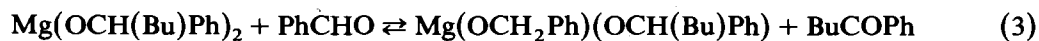
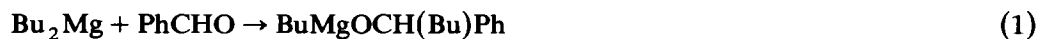
We have chosen as a model reaction that between unsolvated $(n\text{-Bu})_2\text{Mg}$, a reagent which is completely insoluble in hydrocarbon media [12], and benzaldehyde. We initially examined the system lithium(-)-menthoxide- unsolvated dibutylmag-

TABLE 1
REACTION OF DESOLVATED $n\text{-Bu}_2\text{Mg}$ WITH PhCHO IN THE PRESENCE OF LITHIUM MENTHOXIDE IN METHYLCYCLOHEXANE

Entry	Molar ratio			Yield (%) ^b			
	LiOR ^a	Bu ₂ Mg	PhCHO	Menthone	Menthol	Ph(Bu)-CHOH	PhCOBu
1	1	2.5	0.67	trace	ca. 100	84	1
2	1	2	2	1	99	84	1
3	1	1	1	trace	96	86	4
4	1	2	1	0	ca. 100	85	0
5	1	1	2	trace	ca. 100	45	7
6	2	1	2	1	92	61	11
7	2	1	4	17	83	25	44
8	4	1	4	5	95	52	21

^a ROH = (-)-menthol. ^b By GLC.

nesium-benzaldehyde with methylcyclohexane as solvent. The dibutylmagnesium was desolvated by heating in vacuo for 4 h at 80°C. (GLC examination of the reaction mixture obtained after treatment with amyl alcohol indicated that removal of ether was complete under these conditions.) The Bu₂Mg was suspended in methylcyclohexane and an appropriate quantity of the alkoxide was added to solubilize the Bu₂Mg; benzaldehyde was subsequently added at -60°C, and the mixture was allowed to warm to 0°C then worked up in a conventional manner. The results are presented in Table 1. It can be seen that the alcohol, Ph(Bu)CHOH, is formed in good yield when the ratio of Bu₂Mg to PhCHO is ≥ 1/1, and that the proportion of alkoxide appears to have little effect (entries 1-4). As the proportion of PhCHO is increased, however, appreciable amounts of PhCOBu are formed, with a maximum at a ratio of alkoxide to Bu₂Mg of between 1/1 and 2/1 (entries 5-8). In these cases, together with the ketone, equivalent quantities of benzyl alcohol were also produced. We can rationalize the formation of ketone on the basis of an Oppenauer oxidation of the alcoholate by hydrogen transfer to benzaldehyde:



We note that reactions 2 and 4 (X = Bu) are in competition, and thus it is to be expected, and is indeed found, that when more than one equivalent of PhCHO per Bu₂Mg is used, ketone formation will take place. The optical yields of alcohol were of the order of 7-9%. While these may be low purely by virtue of low induction by the alkoxide, they will also be adversely affected by the reversible oxidation steps 3 and 4. It is known that racemisation of chiral alcohols can occur under MVPO conditions [13].

The equations given above ignore the role of the alkoxide. Since we do not know the nature of the complex formed between lithium alkoxides and dialkylmagnesiums, we can only speculate that coordination of the alkoxide to magnesium increases the alkylating reactivity of BuMgOR. We have shown in previous work that alkoxides of alkali metals solubilize dialkyl- and diaryl-magnesium reagents in hydrocarbon solvents, and that the resulting systems show characteristics of alkyl- or arylalkali metal compounds [1,2]. Other workers have also provided evidence for the existence of mixed oligomers of alkyllithiums and lithium alkoxides [3,4] and for changes in reactivity upon complexation [6]. It therefore seems reasonable to suggest that similar oligomers, with similarly modified reactivity, can be formed between dialkylmagnesiums and lithium alkoxides. It is also noteworthy that Me₂Mg has been shown to react about 10 times faster than MeMgOR with 4-methylbenzophenone [5].

In order to study the Oppenauer oxidation step in isolation, further reactions were carried out between metal alkoxide mixtures and benzaldehyde. The appropriate proportions of lithium and magnesium alkoxides in methylcyclohexane were treated with benzaldehyde at -60°C and the mixture was allowed to warm to room temperature and stirring for 1.5 h then worked up in the usual way. The

TABLE 2

REACTION OF MIXED ALKOXIDES OF MAGNESIUM AND LITHIUM WITH BENZALDEHYDE IN METHYLCYCLOHEXANE

Entry	Molar ratio			Yield (%) ^b			
	LiOR ^a	Mg(OR) ₂ ^a	PhCHO	Menthone	Menthol	Ph(Bu)-CHOH	PhCOBu
1	1	0	1	1	50	—	—
2	0	1	2	23	75	—	—
3	2	1	2	26	74	—	—
4	2	1	4	46	46	—	—
5	1	1	3	35	64	—	—
6	2	1 ^c	2	13	74	44	47
7	0	1 ^c	2	—	—	25	58
8	2 ^c	1 ^c	4	—	—	27	52

^a ROH = (–)-menthol. ^b By GLC. ^c ROH = Ph(Bu)CHOH.

products were examined by GLC and the results are presented in Table 2. With lithium menthoxide alone, no significant amount of ketone is observed (entry 1). The less than 100% recovery of menthol plus menthone may be due to aldol condensation of the ketone, to a Knoevenagel reaction of the ketone with benzaldehyde, or to a Tishchenko reaction of benzaldehyde in the presence of menthoxide to give menthyl benzoate. As a strong base lithium menthoxide is capable of promoting any of these reactions.

Magnesium alkoxides are also strong bases, it can be seen that virtually no menthol remains unaccounted for, implying that the three reactions just mentioned do not take place in this case (entry 2). Comparison of the two alkoxides is complicated, however, by the ready solubility of lithium menthoxide in methylcyclohexane compared with the low solubility of magnesium menthoxide. The mixed alkoxide systems were more efficient in the Oppenauer oxidation of menthol, with the highest conversion being observed with a ratio of LiOR/Mg(OR)₂ of 2/1 (entries 3–6). Stoichiometric amounts of PhCHO were used in these reactions, and no attempt was made to optimize the yield of ketone by using a large excess of aldehyde. The species involved in these reactions are, we suspect, oligomers similar to those known for lithium alkoxides and enolates [14], rather than polymers based on magnesium alkoxides [15]. It can be envisaged that soluble clusters, with magnesium occupying at least one of the sites normally occupied by lithium, will be less efficient than lithium alkoxide alone in the aldol condensation or Knoevenagel reaction, whereas the overall solubility enhances the oxidation reaction regardless of whether this is promoted by the lithium alkoxide, the magnesium alkoxide, or both [16]. In the case of the mixed alkoxides the menthol used can be accounted for as recovered menthol plus menthone, which indicates that the three possible competing reactions, i.e. aldol, Knoevenagel, and Tishchenko, are unimportant. This is in contrast to the results in reactions with lithium alkoxide alone, in which a good percentage of menthol remains unaccounted for. The mixed alkoxide system derived from Ph(Bu)CHOH gave a yield of ketone comparable to that obtained by use of magnesium alkoxide alone (entries 7 and 8). In this case, however, the mixed alkoxide had only limited solubility in methylcyclohexane.

TABLE 3

ALKYLATION-OXIDATION REACTIONS OF ALDEHYDES WITH METAL ALKYLs IN THE PRESENCE OF METAL ALKOXIDE IN HYDROCARBON SOLVENTS

Entry	Molar ratio			R	Yield (%) ^a		Solvent
	Bu ₂ Mg	LiOCH(Bu)R	RCHO		RBuCHOH	RCOBu	
1	1	0	4	Ph	2	25	MCH ^b
2	1 ^c	2	6	Ph	15	39	MCH
3	1	2 ^d	6	Ph	15	35	MCH
4	1 ^c	2 ^d	6	Ph	24	67	MCH/toluene
5	1 ^c	2 ^d	2 ^e	Bu	35	12	MCH/toluene
6	1 ^c	2 ^d	2 ^f	Bu	10	32	MCH/toluene

^a By GLC. ^b Methylcyclohexane. ^c Bu₂Mg(Et₂O)₂ used in this experiment. ^d Formed in situ from BuLi and RCHO. ^e +4 eq. Ph₂CO. ^f +4 eq. PhCHO.

We are now in a better position to consider the alkylation of benzaldehyde. It is apparent that by a combination of the alkylation and oxidation reactions an overall conversion of aldehyde to ketone is possible:



In order to investigate the feasibility of this we carried out a further series of reactions, the results of which are presented in Table 3. Using a Li/Mg ratio of 2/1 and a Bu/PhCHO ratio of 1/2 we were able to prepare PhCOBu in 67% yield (entry 4). The mixed alkoxide in this case was formed in situ by reaction of two equivalents of BuLi and one equivalent of solvated Bu₂Mg with four equivalents of benzaldehyde in methylcyclohexane/toluene. A further four equivalents of benzaldehyde were added to effect the oxidation. With n-butanal as the substrate and PhCHO as the oxidizing reagent, we obtained a 32% yield of Bu₂CO (entry 6). Here enolization and base-catalyzed condensation reactions are probably more significant than with the aromatic aldehyde. The yields were not optimized, however.

Concluding remarks

Apart from the synthetic possibilities arising from this work, it is pertinent to emphasize a further point valid for reactions of organometallic reagents with carbonyl compounds in general. This is that the alkoxide produced in such reactions can, and probably will, have an important, and in some cases decisive, effect on the outcome of the reaction. For this reason, it should always be taken into account when considering such reactions, from either a mechanistic or synthetic viewpoint. In synthesis, particularly, the present study shows that, in order to avoid undesirable side-reactions in reactions of an alkylmetal compound with aldehydes, it is necessary to control the proportion of the carbonyl compound used. Use of a large excess of the carbonyl compound or of unnecessarily long reaction times and high reaction temperatures can lead to secondary carbinols contaminated with considerable amounts of the relevant ketone in addition to other products derived by an aldol, Knoevenagel, or Tishchenko reaction. Even when an overall excess of aldehyde is not used it may happen that at some stage in the reaction an excess is present, as in the inverse addition of organometallic reagent to the aldehyde, for example, in which case the above remarks are still applicable.

Experimental

All operations involving metal alkoxides and metal alkyls were performed under argon. Solvents were dried over 4 Å molecular sieves, degassed, and saturated with argon before use. Benzaldehyde was distilled before use. Other materials were obtained commercially and used as received. GLC analysis was carried out with a Pye Unicam GCV chromatograph fitted with an Apiezon L column. All product alcohols and ketones had retention times identical with those of authentic samples. They were further characterised by preparative GLC and by NMR spectroscopy. Optical rotations (at the sodium-D line) were determined on a Perkin-Elmer 241 polarimeter with toluene solutions (c 5 to 7).

Lithium menthoxide. To a solution of 7.81 g (50 mmol) of (–)-menthol in 10 ml methylcyclohexane were added 27.5 ml (50 mmol) of a 1.83 M solution of n-BuLi in toluene in the presence of a trace of *o*-phenanthroline to indicate the end-point [17]. After stirring for 30 min the solvents were taken off under reduced pressure and replaced by 60 ml of methylcyclohexane. The resulting solution was titrated against 0.100 M HCl. The concentration of lithium menthoxide was found to be 0.85 M. In subsequent reactions, appropriate amounts of solution were withdrawn with a syringe.

Dibutylmagnesium. Dibutylmagnesium was prepared by the addition of one equivalent of n-BuLi in toluene to one equivalent of n-BuMgCl in ether [18]. After stirring overnight, the suspension was allowed to settle and the supernatant solution was titrated against 0.100 M HCl to determine total alkalinity and against 0.050 M EDTA solution to determine the magnesium concentration [19]. Desolvation was achieved by withdrawing the required amount of solution, evaporating to dryness under reduced pressure, and then heating the residue in vacuo at 80°C for 4 h. Alcoholysis with amyl alcohol of Bu₂Mg which had been treated in this way followed by GLC examination of the resulting mixture indicated that complete desolvation had occurred.

Alkylation reactions

(1) Reaction of Bu₂Mg with PhCHO in the presence of lithium menthoxide (Table 1, all entries; Table 3, entry 1)

In a typical experiment, to 68 mmol of Bu₂Mg desolvated by the above procedure were added 40 ml of methylcyclohexane and 34 mmol of lithium menthoxide in methylcyclohexane solution. After overnight stirring, the resulting suspension was cooled in a dry ice/acetone bath and 3.5 ml (34 mmol) of benzaldehyde were added at –60°C. The mixture was followed to warm slowly to 0°C, hydrolyzed with ice, acidified with dilute sulfuric acid, and extracted twice with toluene. The combined toluene extracts were washed once with water and dried over anhydrous magnesium sulphate. Solvents were removed on a rotary evaporator and the residue was vacuum distilled and analyzed by GLC. Yield of Ph(Bu)CHOH 85%; PhCOBu 0% (by GLC).

Other reactions were carried out similarly.

(2) Reaction of Bu₂Mg with PhCHO in the presence of LiOCH(Bu)Ph (Table 3, entry 2)

To a mixture of 20 mmol n-BuLi in toluene and 25 ml methylcyclohexane cooled

in a dry ice/acetone bath were added 2.1 ml (20 mmol) PhCHO. The mixture was allowed to warm to room temperature then added to a suspension of 10 mmol Bu_2Mg (not desolvated) in 30 ml methylcyclohexane cooled to -40°C . The mixture was allowed to warm to room temperature then re-cooled to -40°C , and 6.1 ml (60 mmol) of PhCHO were added. The mixture was again allowed to warm to room temperature and worked up and analyzed as before. Yield Ph(Bu)CHOH 15%; PhCOBu 39%.

(3) Reaction of Bu_2Mg -BuLi with PhCHO (Table 3, entry 3)

A suspension of 10 mmol Bu_2Mg (desolvated) in 25 ml methylcyclohexane was cooled in ice, and 20 mmol BuLi in toluene were added. The mixture was allowed to warm to room temperature, then the solvents were removed under reduced pressure and 40 ml methylcyclohexane were added. The mixture was cooled in a dry ice/acetone bath and 8.2 ml (80 mmol) PhCHO were added, and the mixture was allowed to warm to room temperature. After 1 h stirring the mixture was worked up as before. Yield Ph(Bu)CHOH 15%; PhCOBu 35%.

(4) Reaction of Bu_2Mg -BuLi with PhCHO (Table 3, entries 4–6)

To a suspension of 20 mmol $\text{Bu}_2\text{Mg}(\text{Et}_2\text{O})_2$ in 20 ml methylcyclohexane were added 40 mmol BuLi in toluene. After overnight stirring the almost clear solution was cooled in a dry ice/acetone bath and 16.3 ml (160 mmol) PhCHO were added. The mixture was allowed to warm to room temperature and worked up as before. Yield Ph(Bu)CHOH 24%; PhCOBu 67%.

The reactions with butanal were carried out similarly except that after the addition of the appropriate quantity of BuCHO and warming to room temperature, the mixture was re-cooled to -50°C , the appropriate amount of Ph_2CO or PhCHO was added, and the mixture was allowed to warm to room temperature. Work-up was as before.

Oxidation reactions

Reaction of magnesium alkoxide/lithium alkoxide with PhCHO, (Table 2, all entries)

In a typical experiment, the mixed alkoxide was prepared by successive addition of 10 mmol BuLi in toluene and 5 mmol Bu_2Mg in toluene/ether to a solution of 3.1 g (–)-menthol in 20 ml ether cooled in a dry ice/acetone bath. The mixture was allowed to warm to room temperature then stirred for 1.5 h. The solvents were removed under reduced pressure and the residue kept in vacuo at 80°C for 2 h, then allowed to cool to room temperature, and 20 ml of methylcyclohexane were added. The almost clear solution was cooled in a dry ice/acetone bath and 2.05 ml (20 mmol) PhCHO were added. The mixture allowed to warm to room temperature, stirred for 1.5 h, then worked up as described above. Yield menthol 46%; menthone 46%.

The other reactions entered in Table 2 were carried out similarly.

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