B. Dihydrocodeinone (1f). Chromatography of the product mixture afforded 0.165 g (33%) of **3a** and 0.185 g (36.5%) of **4a**. A reaction time of 90 h was required to obtain exclusively **4a**.

C. 14-Hydroxydihydrocodeinone (1g). The reduction afforded 0.51 g (101%) of **2g** as a white foam. The IR and ^{1}H-NMR spectra of the product were identical to those of a reference sample supplied by Dr. Cone. Careful TLC analysis showed that the crude product was contaminated with a trace amount of **3b**. Crystallization of the foam from acetone/water (1:1) gave white needles, mp 167–168 °C (lit.[19] 166–167 °C).

D. 3-*O*-Methylnaltrexone (1h). When the reaction mixture was cooled, **2h** (0.41 g, 81.5%) precipitated as a white olid: mp 172–173 °C; IR ($CHCl_3$) no carbonyl; ^{1}H-NMR ($CDCl_3$) δ 3.46–3.72 (m, 1 H, 6α-**H**), 3.84 (s, 3 H), 4.47 (d, 1 H, 5β-**H**, J = 6 Hz), 6.63 ppm (ABq, 2 H). The ^{13}C-NMR of **2h** was very similar to that of 6β-naltrexol (**2a**).[17] Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.43; H, 7.84; N, 3.75.

Extraction of the filtrate afforded 0.08 g (16.5%) of a yellow foam. TLC analysis showed a major (**3c**) and a minor (**2h**) component. On repeat runs of this reaction the precipitated product was sometimes contaminated with **3c**.

Deuterium Experiments. A. Dihydrocodeinone (1f). Repetition of the heterogeneous reaction on a one-fifth scale using D_2O as the solvent afforded 58 mg of deuterated **3a** (mass spectrum: d_0, 9.6%; d_1, 26.5%; d_2, 36.3%; d_3, 21.4%; d_4, 6.2%) and 9 mg of deuterated **4a** (mass spectrum: d_0, 0.4%; d_1, 1.4%; d_2, 2.3%; d_3, 14.3%; d_4, 37.8%; d_5, 36.7%; d_6, 7.1%). In the ^{13}C-NMR spectrum of the major product the C-5 resonance was partially collapsed while the C-7 resonance was totally collapsed. Moreover, the C-6 resonance was extremely weak due to the removal of the nearby protons needed for efficient ^{13}C–^{1}H dipolar relaxation.[20] The lower deuterium content of **3a** was due in part to back-exchange during work-up and chromatography.

B. Naltrexone (1a). Reduction[1] of naltrexone (136 mg) using D_2O as the solvent afforded 128 mg of deuterated 6β-naltrexol (**2a**) (mass spectrum: d_1, 3.0%; d_2, 20.3%; d_3, 43.4%; d_4, 32.0%; d_5, 1.3%). In the ^{13}C-NMR spectrum of the product the C-5 resonance was partially collapsed while the C-6 and C-7 resonances were totally collapsed.

C. Dihydromorphinone (1e). The starting material (285 mg) was subjected to an exchange reaction using D_2O and potassium *tert*-butoxide to get 273.5 mg of deuterated **1e** (mass spectrum: d_0, 7.3%; d_1, 41.4%; d_2, 37.9%; d_3, 13.4%). A 200-mg sample of this material was subsequently reduced[2] using D_2O as the solvent. This reaction afforded 45 mg of deuterated dihydroisomorphine (**2e**) (mass spectrum: d_2, 6.3%; d_3, 34.2%; d_4, 56.4%; d_5, 3.1%). The C-5, C-6, and C-7 resonances were completely collapsed in the ^{13}C-NMR spectrum of the product.

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Registry No.—**2f,** 795-38-0; **2g,** 61949-73-3; **2h,** 65150-66-5; **3a,** 847-86-9; **3b,** 6199-38-8; **3c,** 65150,67-6; **4a,** 2447-32-7; formamidinesulfinic acid, 1758-73-2.

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(8) We have used "iso" to distinguish **4a** from the corresponding 6α isomer.
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Reactions of Magnesium Hydrides. 1. Reduction of Organic Functional Compounds by Magnesium Hydride and 2,6-Diisopropylphenoxymagnesium Hydride

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The reducing properties of magnesium hydride and tetrahydrofuran-soluble 2,6-diisopropylphenoxymagnesium hydride toward some representative organic functional compounds such as benzaldehyde, 4-*tert*-butylcyclohexanone, 1-iodo-, 1-bromo-, and 1-chlorodecanes, iodobenzene, nitrobenzene, ethyl benzoate, benzoyl chloride, 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one, octene, and phenylacetylene have been studied. For the first time it has been shown that MgH_2 (if prepared in an active form) and HMgOR compounds are very effective reducing agents in the reduction of certain organic functional groups. The fact that these hydrides reduce some functional groups at a much faster rate than others indicates their usefulness in functional group selectivity.

Introduction

Simple and complex metal hydrides of boron and aluminum have been known for over two decades for their reducing properties toward organic functional compounds.[1] Some of these hydrides have been found to be extremely reactive but have poor selectivity. For example, $LiAlH_4$ is a very powerful reducing reagent, capable of reducing most functional groups, but is of little value for selective reductions. On the other hand,

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Table I. Reactions of Magnesium Hydride (I)[a] and 2,6-Diisopropylphenoxymagnesium Hydride (II)[b] with Some Representative Functional Groups

Hydride reagent[c]	Organic substrate[c]	Registry no.	Reaction condition[f]	Product(s) (yield(s),[e] %)
I	1-Iododecane	2050-77-3	−40 °C, 1 h	*n*-Decane (10)
			0 °C, 1 h	*n*-Decane (40)
			RT, 24 h	*n*-Decane (100)
II	1-Iododecane		−40 °C, 1 h	*n*-Decane (5)
			0 °C, 1 h	*n*-Decane (20)
			RT, 24 h	*n*-Decane (100)
I	1-Bromodecane	112-29-8	RT, 24 h	*n*-Decane (5)
II	1-Bromodecane		RT, 24 h	*n*-Decane (5)
I	1-Chlorodecane	1002-69-3	RT, 24 h	*n*-Decane (0)
II	1-Chlorodecane		RT, 24 h	*n*-Decane (0)
I	Iodobenzene	591-50-4	RT, 24 h	Benzene (0)
II	Iodobenzene		RT, 24 h	Benzene (0)
I	Benzaldehyde	100-52-7	−40 °C, 1 h	Benzyl alcohol (100)
II	Benzaldehyde		−40 °C, 1 h	Benzyl alcohol (100)
I	Ethyl benzoate	93-89-0	−40 °C, 1 h	Benzyl alcohol (25)
			0 °C, 1 h	Benzyl alcohol (32)
			RT, 24 h	Benzyl alcohol (79)
II	Ethyl benzoate		−40 °C, 1 h	Benzyl alcohol (8)
			0 °C, 1 h	Benzyl alcohol (26)
			RT, 24 h	Benzyl alcohol (82)
I	Benzoyl chloride	98-88-4	−40 °C, 1 h	Benzyl alcohol (20)
			0 °C, 1 h	Benzyl alcohol (45)
			RT, 24 h	Benzyl alcohol (85)
II	Benzoyl chloride		−40 °C, 1 h	Benzyl alcohol (16)
			0 °C, 1 h	Benzyl alcohol (40)
			RT, 24 h	Benzyl alcohol (85)
I	2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one	20859-13-6	RT, 24 h	1,4 Product (4), 1,2 Product (92)
II	2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one		RT, 24 h	1,4 Product (7), 1,2 Product (80)
I	4-*tert*-Butylcyclohexanone[d]	98-53-3	RT, 1 h	4-*tert*-Butylcyclohexanol (100) (cis/trans alcohol = 24:76)
II	4-*tert*-Butylcyclohexanone[d]		RT, 1 h	4-*tert*-Butylcyclohexanol (100) (cis/trans alcohol = 83:17)
I	Benzonitrile	100-47-0	−40 °C, 1 h	Benzonitrile (50), Benzaldehyde (10), Benzyl alcohol (0)
			0 °C, 1 h	Benzonitrile (35), Benzaldehyde (15), Benzyl alcohol (5)
			RT, 24 h	Benzonitrile (0), Benzaldehyde (3), Benzyl alcohol (32)
II	Benzonitrile		−40 °C, 1 h	Benzonitrile (60), Benzaldehyde (7), Benzyl alcohol (0)
			0 °C, 1 h	Benzonitrile (40), Benzaldehyde (32), Benzyl alcohol (2)
			RT, 24 h	Benzonitrile (0), Benzaldehyde (8), Benzyl alcohol (0)
I	Nitrobenzene	98-95-3	RT, 24 h	Nitrobenzene (25)
II	Nitrobenzene		RT, 24 h	Nitrobenzene (20)
I	1-Octene	111-66-0	RT, 24 h	No reaction
I	Phenylacetylene	536-74-3	RT, 24 h	No reaction

[a] Registry no: 7693-27-8. [b] Registry no.: 65276-36-0. [c] Molar ratio of hydride reagent to substrate is 1:1 for MgH_2, 2:1 for II. [d] Molar ratio of hydride reagent to ketone is 4:1. [e] Yields were determined by GLC using suitable internal standard. [f] RT = room temperature.

sodium borohydride, which is a milder reducing agent, is much more useful as a selective reducing agent for compounds containing two or more reducible functional groups. However, because of certain deficiencies suffered by many complex metal hydrides (such as cost, difficulty of preparation, ease of oxidation, etc.), there has been considerable interest in finding new hydrides which can function as ideal reducing agents. In this connection, we have prepared a large number of complex metal hydrides, most of which suffer the same drawbacks as many of the earlier hydrides prepared by other workers.

It does seem rather surprising that although many boron and aluminum hydrides have been prepared and evaluated as selective reducing agents, we can find no mention in the literature of MgH_2 or any of its derivatives (e.g., HMgCl, HMgOR, $HMgNR_2$, and HMgR) undergoing evaluation as reducing agents except for a casual comment that MgH_2 is a very poor reducing agent toward organic functional compounds. Magnesium hydride has been neglected by organic chemists perhaps because of its insoluble nature in all solvents in which it does not react, a fact which might lead one to think that for this reason it would not be a good reducing agent. Recently, we have been able to prepare a very reactive form of magnesium hydride and have demonstrated its ready reactivity with MgX_2, MgR_2, $Mg(OR)_2$, and $Mg(NR_2)_2$ compounds to produce THF-soluble hydridomagnesium halides,[2] alkyl and aryl magnesium hydrides,[3] and alkoxy- and dialkylamino magnesium hydrides.[4] In this report we present the reactions of magnesium hydride and a THF-soluble HMgOR compound (2,6-diisopropylphenoxymagnesium hydride) with several organic functional compounds indicating the heretofore unreported utility of these compounds as selective reducing agents toward organic substrates.

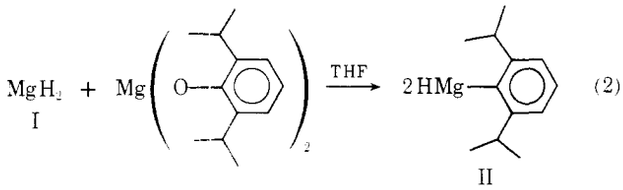
Results and Discussion

A THF slurry of an active form of MgH_2 was prepared by the reaction of diethyl- or diphenylmagnesium with $LiAlH_4$ in diethyl ether followed by separation of the insoluble MgH_2

from the ether soluble $LiAlR_2H_2$ compound and the addition of THF to the ether wet MgH_2 (eq 1).

$$LiAlH_4 + R_2Mg \xrightarrow{Et_2O} MgH_2\downarrow + LiAlH_2R_2 \quad (1)$$

Reaction of this magnesium hydride with bis(2,6-diisopropylphenoxy)magnesium in THF yielded 2,6-diisopropylphenoxymagnesium hydride which is soluble and stable in THF at room temperature (eq 2). Although MgH_2 is known to be



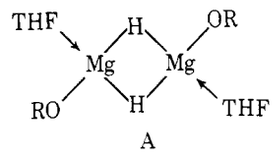
(2)

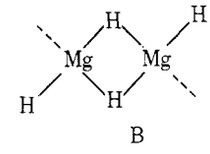
polymeric, we have found this new hydride (II) to be dimeric in refluxing THF.

Magnesium hydride and 2,6-diisopropylphenoxymagnesium hydride were allowed to react with some representative organic functional compounds. The results are reported in Table I. Both magnesium hydride and 2,6-diisopropylphenoxymagnesium hydride reduce 1-iododecane to *n*-decane in quantitative yield after a 24-h reaction period at room temperature. On the other hand, 1-bromodecane, 1-chlorodecane, and iodobenzene were found to be relatively inert to these hydrides. These results indicate better selectivity for C–I reduction to C–H in the presence of other halides since most of the other known hydride reagents that reduce alkyl iodides also reduce bromides and chlorides under the same conditions. For example, $LiAlH_4$, reduced 1-iododecane, 1-bromodecane, and 1-chlorodecane under similar conditions (24 h, room temperature) to give *n*-decane in yields of 100, 100, and 68%, respectively.

Benzaldehyde, ethyl benzoate, and benzoyl chloride were reduced to produce benzyl alcohol in 80–100% yield. In these reactions, magnesium hydride appears to have a slightly higher reactivity than the alkoxylmagnesium hydride although MgH_2 is insoluble in THF, whereas the HMgOR compound is soluble. 2,6-Diisopropylphenoxymagnesium hydride as well as MgH_2 reduce benzaldehyde to benzyl alcohol in 100% yield at −40 °C within 1 h. Under the same conditions, ethyl benzoate and benzoyl chloride are reduced to benzyl alcohol in only 8% and 16% yield, respectively. However, under more forcing conditions (0 °C for 1 h or room temperature for 24 h) it appears that both compounds are reduced at approximately the same rate although at a rate much slower than benzaldehyde. Thus it would appear that aldehydes can be reduced selectively in the presence of Cl, Br, C(=O)Cl and C(=O)OR groups as well as C=C, C≡C, CN, and NO_2 (to be discussed later).

Magnesium hydride and 2,6-diisopropylphenoxymagnesium hydride also react with the enone, 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one, to give predominantly 1,2-reduction (92–80%). Interestingly, 4-*tert*-butylcyclohexanone was reduced rapidly and quantitatively to 4-*tert*-butylcyclohexanol. The ratio of cis to trans alcohol was substantially different in both cases, e.g., 24:76 ratio for magnesium hydride and 83:17 for 2,6-diisopropylphenoxymagnesium hydride, indicating that the HMgOR compound is not reacting as MgH_2 as a result of disproportionation (eq 3). Formation of the cis alcohol in higher yield in the case of reagent II can be explained on steric grounds. The HMgOR compound is dimeric in THF, probably associated via double hydrogen bridge bonds (A), which provides for considerable steric hindrance by the bulky 2,6-diisopropylphenoxy groups. Although MgH_2, which is insoluble in THF, is also believed to be highly associated (linear polymer, B), the hydridic hydrogens are much





more accessible for reaction than the same hydrogens in II which are flanked by such bulky alkoxy groups.

$$2HMgOR \rightleftharpoons MgH_2 + Mg(OR)_2 \quad (3)$$

The high degree of association of 2,6-diisopropylphenoxymagnesium hydride causes this reagent to be much more selective than $LiAlH_4$ which reduces 4-*tert*-butylcyclohexanone to produce only 10% cis alcohol (equatorial attack of hydride) compared to 83% for the HMgOR compound. This high degree of selectivity warrants a more detailed study of the reaction of HMgOR compounds with various cyclohexanones in order to determine the selectivity for a wide range of hindered ketones.

As for the reactions of benzonitrile and nitobenzene, the expected reduction products were not isolated. Instead unidentified products were formed presumably as a result of free-radical polymerization. 1-Octene and phenylacetylene were found to be unreactive toward MgH_2 and 2,6-diisopropylphenoxymagnesium hydride, which is actually an advantageous result in terms of functional group selectivity. We have found that these hydrides add to olefins and alkynes in the presence of certain transition metal catalysts. We will report in more detail on these results later.

Experimental Section

Reactions were performed under nitrogen at the bench using Schlenk tube techniques.

Analytical. Active hydrogen analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line and collecting the gas with a Teopler pump.[5] Magnesium was analyzed by EDTA titration at pH 10 using Eriochrome Black T as indicator. GLPC was performed on an F & M Model 720 or 700 gas chromatograph using a 5% Carbowax 20M column.

Materials. Tetrahydrofuran (Fisher Certified Reagent Grade) was distilled under nitrogen over $NaAlH_4$ prior to use. All organic substrates and authentic samples of products were purchased from Eastman Organic Chemicals and used without further purification.

Diethyl- and diphenylmagnesium were prepared by the reaction of the corresponding organomercury compound with magnesium metal by a previously reported procedure.[6]

Preparation of MgH_2 Slurry in THF. To a well-stirred solution of diethylmagnesium (20.0 mmol) in diethyl ether (50 mL) was added dropwise a diethyl ether solution of $LiAlH_4$ (40 mL of 0.5 M solution, 20.0 mmol) at room temperature. An immediate precipitation of white insoluble solid took place. This reaction mixture was stirred further at room temperature for 1 h and was centrifuged. The supernatant solution was removed by syringe and the solid was washed for 3–4 times with fresh diethyl ether. Finally, the ether was removed by syringe and freshly distilled THF was added to the white solid to make a slurry. It was analyzed and stored in the refrigerator at about 0 °C. Anal. Calcd for MgH_2: Mg:H = 1.00:2.00. Found: 1.00:2.00.

Preparation of 2,6-Diisopropylphenoxymagnesium Hydride in THF by the Reaction of MgH_2 with Bis(2,6-diisopropylphenoxy)magnesium in 1:1 Ratio. Bis(2,6-diisopropylphenoxy)magnesium (10.0 mmol) was prepared by the reaction of 10.0 mmol of dimethylmagnesium in diethyl ether (15 mL) with 2,6-diisopropylphenol (3.6 g, 20.0 mmol) in 25 mL of THF. This reaction mixture was refluxed overnight, diethyl ether was removed under vacuum, and fresh THF was added. The THF solution of bis(2,6-diisopropylphenoxymagnesium (10.0 mmol) was added to a well-stirred solution of magnesium hydride (10.0 mmol) in THF (40 mL) at room temperature. The reaction mixture was further stirred for 2 h to give a clear solution. It was analyzed for magnesium, hydrogen, and alkoxy group. Anal. Calcd for HMgOR: MG:H:OR = 1.00:1.00:1.00. Found; 1.00: 0.97:1.04. 2,6-Diisopropylphenol was analyzed by GLPC analysis of the hydrolyzed sample.

General Reactions of Organic Substrates. A 10-mL Erlenmeyer flask with a Teflon-coated magnetic stirring bar was dried in an oven

and allowed to cool under nitrogen flush, then sealed with a rubber septum. The magnesium hydride slurry or 2,6-diisopropylphenoxymagnesium hydride was syringed into the flask. The low reaction temperature was controlled by a dry ice–acetone or ice–water bath, and then the calculated amount of organic substrate (with internal standard) was added to the stirred reagent. After the designated reaction time, the aliquot of the reaction was taken by syringe and quenched with H_2O. A 10-ft column of 5% Carbowax 20M on Chromosorb W was used to separate benzaldehyde, ethyl benzoate, benzonitrile, nitrobenzene, benzoyl chloride, 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one, phenylacetylene, and their products. A 6-ft 10% Apiezon L 60-805 column was used to separate 1-iododecane, 1-bromodecane, 1-chlorodecane, iodobenzene, 1-octene, and their products. Suitable hydrocarbons were used as internal standards.

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Registry No.—Diethylmagnesium, 557-18-6; $LiAlH_4$, 16853-85-3; bis(2,6-diisopropylphenoxy)magnesium, 65276-35-9; dimethylmagnesium, 2999-74-8; 2,6-diisopropylphenol, 2078-54-8.

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Reactions of Magnesium Hydrides. 2.[1] Stereoselective Reduction of Cyclic and Bicyclic Ketones by Hydridomagnesium Alkoxides

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The stereochemistry of reduction of 4-*tert*-butylcyclohexanone, 2-methylcyclohexanone, 3,3,5-trimethylcyclohexanone, and camphor with a series of alkoxymagnesium hydrides (ROMgH) has been determined. The hydrides employed in this study are MgH_2, CH_3OMgH, *i*-PrOMgH, *t*-BuOMgH, Ph_3COMgH, PhOMgH, 2,6-$Me_2C_6H_3OMgH$, 2,6-*i*-$Pr_2C_6H_3OMgH$, and 2,6-*t*-$Bu_2C_6H_3OMgH$. The yields are excellent and equatorial or endo attack is observed with unusual selectivity compared to most other hydride reagents.

Introduction

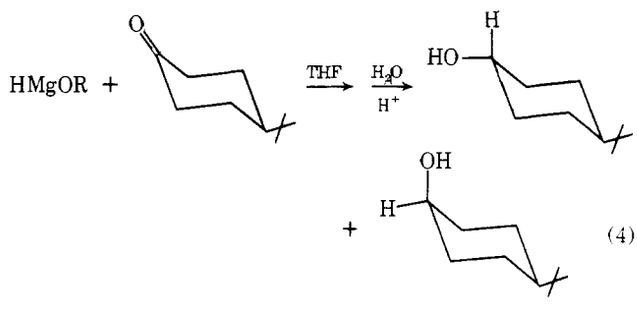
In recent years, the stereoselective reduction of cyclic ketones using hydrides of aluminum and boron has been an area of great interest.[2,3] "Steric approach control" has been considered one of the most important factors responsible for the stereochemical results in these kinds of reactions. For example, $LiAlH(OCH_3)_3$ results in a substantial increase in equatorial attack in the reduction of 4-*tert*-butylcyclohexanone compared to $LiAlH_4$.[3] Recently, lithium trialkylborohydrides have been reported as very selective reducing agents toward cyclic and bicylic ketones[4] presumably because of the increased steric requirement of these hydrides compared to other less sterically hindered metal hydrides. Unfortunately, magnesium hydride has been given little attention as a reducing agent because of its reportedly low reactivity and because of its low solubility in all solvents in which it does not react. However, we have recently found that the reactivity of MgH_2 depends on its method of preparation.[5] For example, MgH_2 prepared by the reaction of dialkylmagnesium compounds with $LiAlH_4$[6] or $MgBr_2$ with NaH[7] (eq 1 and 2) is much more reactive than MgH_2 prepared by other methods.

$$R_2Mg + LiAlH_4 \xrightarrow{Et_2O} MgH_2\downarrow + LiAlR_2H_2 \quad (1)$$

$$NaH + MgBr_2 \xrightarrow{THF} MgH_2 + NaBr \quad (2)$$

This form of MgH_2 reduced 4-*tert*-butylcyclohexanone to 4-*tert*-butylcyclohexanol in quantitative yield within 1 h at room temperature whereas the most reactive MgH_2 prepared previously by other methods performed the same reduction in 33% yield in 24 h. Furthermore, THF soluble hydridomagnesium alkoxides have recently been prepared for the first time in our laboratory and have exhibited a high degree of reactivity toward representative organic functional groups.[1] Because of the obvious advantages of economics and convenience in the preparation of MgH_2 and HMgOR compounds compared to complex metal hydrides of boron and aluminum, we decided to study the stereoselectivity of MgH_2 and HMgOR compounds toward cyclic and bicyclic ketones in some detail (eq 3 and 4).

$$MgH_2 + Mg(OR) \xrightarrow{THF} 2HMgOR \quad (3)$$



(4)

Results and Discussion

The MgH_2 used in these studies was prepared by the reaction of $(C_2H_5)_2Mg$ with $LiAlH_4$ in diethyl ether (eq 1). A slurry of the MgH_2 (prepared by this method) in THF was prepared by removing the supernatant solution containing the ether soluble $LiAl(C_2H_5)_2H_2$ by means of a syringe and then adding freshly distilled THF to the resulting insoluble ether-wet solid (MgH_2). Magnesium hydride prepared in this way was allowed to react with magnesium alkoxides in equal molar ratio in THF in order to prepare the desired alkoxymagnesium hydrides (eq 3, Table I).

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