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

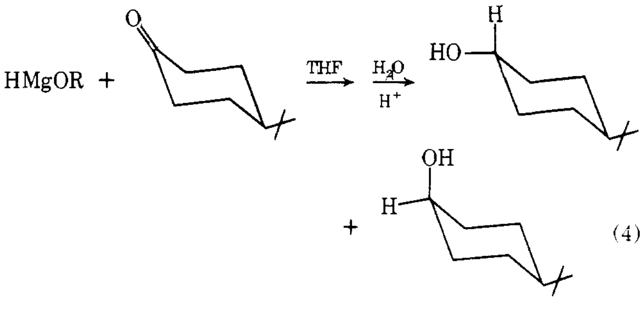
In recent years, the stereoselective reduction of cyclic ketones using hydrides of aluminum and boron has been an area of great interest.[2,3] "Steric approach control" has been considered one of the most important factors responsible for the stereochemical results in these kinds of reactions. For example, $LiAlH(OCH_3)_3$ 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.

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

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

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).

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



(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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Table I. Preparation of Alkoxymagnesium Hydrides

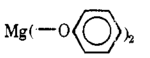
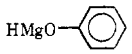
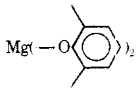
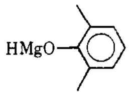
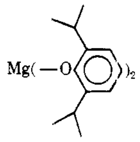
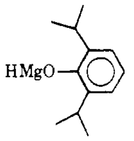
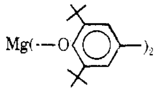
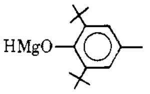
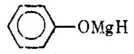
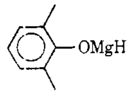
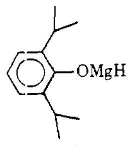
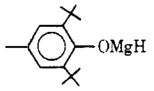
Reactants, mmol		Registry	Reaction	Solubility	Analysis (ratio)	
MgH_2	$Mg(OR)_2$	no.	time, h	in THF	Mg:H:ROH	Product
5.5	$Mg(OCH_3)_2$ (5.5)	109-88-6	40	Insoluble solid	1.00:0.94:-	$HMgOCH_3$
5.4	$Mg(OPr^i)_2$ (5.35)	15571-48-9	24	Insoluble solid	1.00:0.95:-	$HMgOPr^i$
5.1	$Mg(OBu^t)_2$ (5.0)	32149-57-8	24	Insoluble, gelatinous precipitate	1.00:0.95:1.05	$HMgOBu^t$
5.0		7721-07-5	48	Sparingly soluble crystallized from THF	1.00:0.96:1.03	
4.5		65277-19-2	2	Highly soluble	1.00:0.98:1.03	 (dimer)
4.0		65277-20-5	3	Highly soluble	1.00:0.97:1.02	 (dimer)
4.2		65277-21-6	2	Highly soluble	1.00:0.98:1.03	 (dimer)
4.5	$Mg(-OCPh_3)_2$	65277-22-7	2	Highly soluble	1.00:0.97:1.04	$HMg(O-CPh_3)$ (dimer)
	MgH_2		—	Insoluble	1.00:2.02:-	High associated

Table II. Reactions of 4-*tert*-Butylcyclohexanone with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent

					Relative yield, %		
Expt	Hydrides	Registry no.	Molar ratio reagent:ketone	Reaction time, h	Axial-OH	Equatorial-OH	Yield, %
1	MgH_2	7693-27-8	4:1	24	24	76	100
2	MgH_2		2:1	1	53	47	100
				24	53	47	100
3	MgH_2		1:1	1	56	44	90
				24	57	43	92
4	MgH_2		1:2	1	61	39	75
				5	62	38	77
				24	45	55	77
5	CH_3OMgH	32149-52-3	4:1	24	76	24	100
6	*i*-PrOMgH	32149-53-4	2:1	24	9	91	45
			4:1	24	15	85	55
7	*t*-BuOMgH	32149-54-5	4:1	24	69	31	90
8	Ph_3COMgH	65277-23-8	4:1	24	71	29	100
9		32149-55-6	4:1	24	76	24	100
10		65277-24-9	4:1	24	68	32	100
			1:1	24	60	40	92
			0.5:1	24	12.5	87.5	55
11		65276-36-0	4:1	24	83	17	100
12		65277-25-0	4:1	24	82	18	100
			1:1	24	80	20	100
			0.5:1	24	56	44	55

Some time ago during early attempts to prepare alkoxymagnesium hydrides,[8] we reported that these compounds probably dissociate to MgH_2 and $Mg(OR)_2$ since all attempts to prepare HMgOR compounds resulted only in the isolation of physical mixtures of MgH_2 and $Mg(OR)_2$. Unfortunately, previous studies had been carried out in diethyl ether. However, more recently, we have been able to prepare alkoxymagnesium hydrides by the reaction of MgH_2 and $Mg(OR)_2$ in THF[5] and have characterized these compounds by IR, NMR, and x-ray powder diffraction studies. The magnesium alkoxides used in this study (eq 3) for the preparation of the hydridomagnesium alkoxides were prepared by the reaction of 2 molar equiv of the appropriate alcohol with $(CH_3)_2Mg$ in ether/THF solvent under refluxing conditions.

Table III. Reactions of 3,3,5-Trimethylcyclohexanone with Alkoxymagnesium Hydrides at Room Temperature in the THF Solvent and 4:1 Molar Ratio of Reagent/Ketone

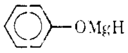
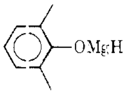
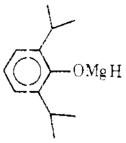
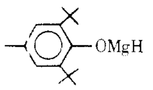
		Relative yield, %		
Expt	Hydride	Axial-OH	Equatorial-OH	Yield, %
13	MgH_2	85	15	92
14	CH_3OMgH	99	1	70
15	*i*-PrOMgH	65	35	40
16	*t*-BuOMgH	99	1	65
17	Ph_3COMgH	99	1	98
18		<99.5	<0.5	100
19		94	6	52
20		99.5	0.5	100
21		>99.5	<0.5	100

Table IV. Reactions of 2-Methylcyclohexanone with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent and 4:1 Molar Ratio of Reagent/Ketone

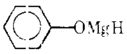
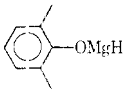
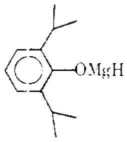
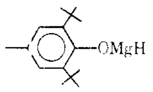
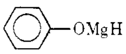
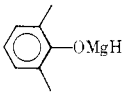
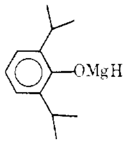
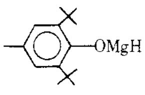
		Relative yield, %		
Expt	Hydride	Axial-OH	Equatorial-OH	Yield, %
22	MgH_2	35	65	100
23	CH_3OMgH	98	2	97
24	*i*-PrOMgH	68	32	30
25	*t*-BuOMgH	98	2	96
26	Ph_3COMgH	73	27	100
27		99	1	100
28		90	20	100
29		99	1	100
30		99	1	100

Table V. Reactions of Camphor with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent and 4:1 Molar Ratio of Reagent/Ketone

		Relative yield, %		
Expt	Hydride	*endo*-OH	*exo*-OH	Yield, %
31	MgH_2	8	92	100
32	CH_3OMgH	5	95	40
33	*i*-PrOMgH	8	92	15
34	*t*-BuOMgH	8	92	20
35	Ph_3COMgH	5	95	100
36		1	99	100
37		1	99	100
38		2	98	100
39		2	98	100

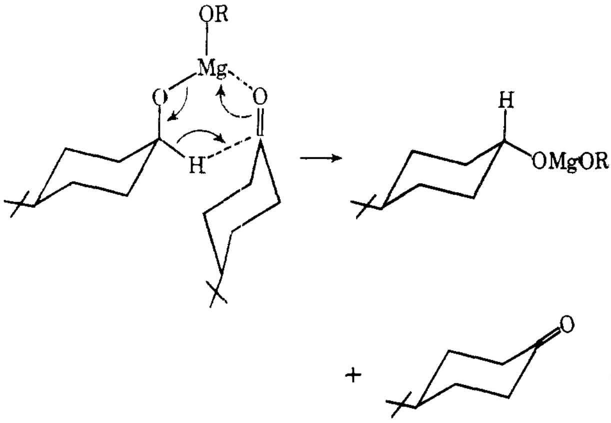
The completion of the reaction was determined by the absence of any gas (methane) during hydrolysis of the product. Interestingly, the alkoxymagnesium hydrides could also be prepared by the addition of equal molar amounts of alcohol to a well-stirred slurry of MgH_2 at −78 °C followed by warming the reaction mixture to room temperature.[9]

$$(CH_3)_2Mg + 2ROH \rightarrow Mg(OR)_2 + 2CH_4 \quad (5)$$

$$ROH + MgH_2 \xrightarrow{THF} HMgOR + H_2 \quad (6)$$

By the reaction of MgH_2 with $Mg(OR)_2$ several HMgOR compounds (where R = Me-, *i*-Pr-, *t*-Bu-, Ph_3C-, Ph, 2,6-dimethylphenyl, and 2,6-di-*tert*-butyl-4-methylphenyl) were prepared (Table I) and allowed to react with four representative ketones, 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, 2-methylcyclohexanone, and camphor in THF at room temperature. The results are summarized in Tables II–V. Lithium aluminum hydride is considered to be the least sterically hindered hydride that reduces 4-*tert*-butylcyclohexanone (I), 3,3,5-trimethylcyclohexanone (II), 2-methylcyclohexanone (III), and camphor (IV) (10, 80, 24, and 9% equatorial or exo attack, respectively). In comparison, MgH_2 reduced ketones I, II, III, and IV in 24, 85, 35, and 8% equatorial or exo attack, respectively, indicating that MgH_2 has a larger steric requirement than $LiAlH_4$. The larger steric requirement is probably due to the highly polymeric nature of MgH_2. An additional important observation is that MgH_2 exhibits a highly different stereoselectivity toward 4-*tert*-butylcyclohexanone depending on the hydride:ketone ratio. For example, more equatorial attack, 24 → 61%, was observed when the MgH_2:ketone ratio was changed from 4:1 to 1:2. Obviously, the intermediate alkoxymagnesium hydride formed during the reaction in 1:2 ratio is a bulkier reducing species than MgH_2 itself. It would appear then that the stereoselectivity expected in the reactions of cyclic ketones with ROMgH compounds should depend on the steric requirement of the alkoxy group and the aggregation in solution of the resulting hydride reagent. According to the steric bulkiness of the alkoxy group, the degree of stereoselectivity should follow in the order: Ph_3COMgH > *t*-BuOMgH > *i*-PrOMgH > MeOMgH. However, because of the degree of molecular association of the ROMgH compound in solution, we have found the stereoselectivity to be in the reverse order: CH_3OMgH > *t*-BuOMgH > Ph_3COMgH > *i*-PrOMgH. For example, in the reduction of 4-*tert*-butylcyclohexanone 76, 69, 71, and 15% equatorial attack, respectively, was observed. In a similar way 3,3,5-trimethylcyclohexanone showed 99, 99, 99, and 65% equatorial attack, respectively, 2-methylcyclohexanone showed 98, 98, 73, and 68% equatorial attack, respectively, and camphor showed 95, 92, 95, and 92% endo attack, respectively. A similar demonstration of the importance of the association of the reagent in solution is given by the fact that phenoxymagnesium hydride is more selective than 2,6-dimethylphenoxymagnesium hydride because of the higher degree of association of the phenoxy compound in solution. We have found the stereoselectivity of aromatic ROMgH compounds to be in the order: 2,6-t-$Bu_2C_6H_3OMgH$ > 2,6-i-$Pr_2C_6H_3OMgH$ > C_6H_5OMgH > 2,6-$Me_2C_6H_3OMgH$ for 4-*tert*-butylcyclohexanone (82, 83, 76, and 67% equatorial attack), for 3,3,5-trimethylcyclohexanone (99.5, 99.5, 99.5, and 94% equatorial attack), for 2-methylcyclohexanone (99, 99, 99, and 80% equatorial attack) and for camphor 98, 98, 99, and 99% endo attack, respectively).

Reactions of MgH_2 and 2,6-di-*tert*-butyl-4-methylphenoxymagnesium hydride with excess 4-*tert*-butylcyclohexanone shows that an equilibrium exists between the alkoxymagnesium intermediate and excess ketone according to eq 7, thus providing a pathway of converting kinetic to thermodynamic product.



(7)

In conclusion, active MgH_2 and alkoxymagnesium hydrides have been shown to reduce cyclic and bicyclic ketones to the corresponding alcohols in excellent yield under mild conditions in a reasonable period of time. The stereoselectivity of the reagents is excellent and is controlled by the steric requirement of the alkoxy group and the degree of molecular association of the hydride in solution.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques.[10] GLPC analyses were performed on an F&M Model 720 gas chromatograph.

Analyses. Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump. Magnesium was determined by EDTA titration. Alcohol analysis was carried out by GLC.

Materials. Methanol was distilled after treating with magnesium metal. Isopropyl alcohol was distilled over $Al(OPr^i)_3$ and *tert*-butyl alcohol was fractionally crystallized under nitrogen. 2,6-Dimethyl- and 2,6-diisopropylphenol were distilled prior to use. Triphenylmethanol and 2,6-di-*tert*-butylcresol were used without further purification.

Diethyl ether and THF were distilled over $LiAlH_4$ and $NaAlH_4$, respectively. Diethylmagnesium was prepared by the reaction of diethylmercury with magnesium metal at 60–80 °C and a standard solution in diethyl ether was calibrated by magnesium analysis. Lithium aluminum hydride solution in diethyl ether was prepared by the standard method and standardized by aluminum analysis.

Preparation of MgH_2 Slurry in THF. The slurry was prepared according to the procedure described in the previous paper in this series.

Preparation of Alkoxymagnesium Hydrides. A known amount of magnesium alkoxide in THF was made by the reaction of $(CH_3)_2Mg$ in diethyl ether/THF, with 2 molar equiv of the appropriate alcohol followed by reflux of the reaction mixture overnight. The diethyl ether was removed under vacuum and fresh THF was added. This magnesium alkoxide was allowed to react with MgH_2 slurry in THF at room temperature and analyzed (Table I).

Reaction of 2,6-Diisopropylphenol with MgH_2 in THF in 1:1 Molar Ratio. To a well-stirred slurry of MgH_2 (4.0 mmol) in THF (30 mL) at −78 °C was added dropwise a THF (10 mL) solution of 2,6-diisopropylphenol (4.0 mmol). This reaction mixture was allowed to warm to room temperature and stirred for 1 h to give a clear solution. Anal. Calcd for HMgOR: Mg:H: 2,6-i-$Pr_2C_6H_3OH$ = 1.00:1.00:1.00. Found, 1.00:0.97:1.04.

General Reaction of Ketones. A 10-mL Erlenmeyer flask with a Teflon-coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen. The flask was then sealed with a rubber septum, connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil-filled bubbler. The ketone solutions with internal standard (tetradecane for 4-*tert*-butylcyclohexanone and camphor, hexadecane for 3,3,5-trimethylcyclohexanone, and dodecane for 2-methylcyclohexanone) was syringed into the flask and the known concentration of hydride reagent (solution or slurry) was added to the flask at room temperature. After the designated reaction time, the reaction was quenched with H_2O slowly and dried over $MgSO_4$. A 10-ft 5% Carbowax 20M on Chromosorb W column (150 °C column temperature) was used to separate the products of 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and camphor. A 15-ft 10% diglycerol on Chromosorb W column (80 °C) was used to separate the products of 2-methylcyclohexanone. The order of elution for each ketone is the same: the ketone first, the axial or exo alcohol second, and equatorial or endo alcohol last.

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Registry No.—2,6-Diisopropylphenol, 2078-54-8; 4-*tert*-butylcyclohexanone, 98-53-3; 3,3,5-trimethylcyclohexanone, 873-94-9; 2-methylcyclohexanone, 583-60-8; camphor, 76-22-2.

References and Notes

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