Reactions of Magnesium Hydrides. 3. Stereoselective Reduction of Cyclic and Bicyclic Ketones by Dialkylaminomagnesium Hydrides[1]

Eugene C. Ashby,* J. J. Lin, and A. B. Goel

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Received July 26, 1977

Reactions of tetrahydrofuran-soluble dialkylaminomagnesium hydrides, R_2NMgH (where R_2N = *n*-Pr_2N, *i*-Pr_2N, Me(*i*-Pr)N, *s*-Bu_2N, c-$C_5H_{11}N$, 2,6-Me_2-c-C_5H_9N, and Me_3Si(*t*-Bu)N), with cyclic and bicyclic ketones such as 2-methylcyclohexanone, 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and camphor have been studied. These new hydride reagents exhibit unusual stereoselectivity in the reduction of these compounds. The selectivity of the hydride reagent has been shown to depend on the steric requirement of the dialkylamino group as well as on the solution aggregation of the hydride reagent.

Introduction

In recent years, the use of metal hydrides as stereoselective reducing agents in organic chemistry has received considerable attention.[2,3] Although numerous reports have appeared in the literature concerning the reduction of cyclohexanones by hydrides of boron and aluminum, nothing is known about reductions with magnesium hydride presumably because of its reported lack of reactivity and also because of its insolubility in all solvents studied.[4] Recently, we reported the first examples of soluble magnesium hydride compounds of empirical formula HMgX (where X = Cl and Br,[5] alkyl and aryl,[6] and alkoxy and aryloxy[7]). In spite of their solubility in THF and their potent reactivity toward cyclic and bicyclic ketones, HMgCl, HMgBr, and HMgR compounds (where R = alkyl and aryl) do not exhibit any unusual selectivity as reducing agents. Interestingly, in an earlier report[8] we showed that MgH_2 (which is insoluble in THF) prepared by the reaction of $(C_2H_5)_2Mg$ with $LiAlH_4$ reduces organic functional groups rapidly in THF solvent. More recently, we have shown that insoluble MgH_2 reacts with $Mg(OR)_2$ compounds to form HMgOR compounds which are soluble in THF and which exhibit considerable stereoselectivity toward cyclic and bicyclic ketones.[9] We have reasoned that if HMgOR compounds are such good stereoselective reducing agents by virtue of their bulky alkoxy group, then similar bulkiness in other groups such as NR_2 groups should produce the same effect.

We would now like to report, for the first time, the reactions of THF soluble dialkylaminomagnesium hydrides with cyclic and bicyclic ketones, showing their unusual stereoselective behavior as reducing agents.

Results and Discussion

Dialkylaminomagnesium hydrides[10] R_2NMgH (where R_2N = *n*-Pr_2N, *i*-Pr_2N, *i*-Pr(Me)N, Ph_2N, c-$C_5H_{11}N$, 2,6-Me_2-c-C_5H_9N, and Me_3Si(*t*-Bu)N) used in these studies were prepared conveniently and quantitatively by the reaction of bis(dialkylamino)magnesium compounds, $(R_2N)_2Mg$, with an active form of MgH_2 in equimolar ratio in THF at room temperature (eq 1). Although MgH_2 is insoluble in THF, a clear solution results when the bis(dialkylamino)magnesium compound is allowed to react with the MgH_2 slurry. The bis(dialkylamino)magnesium compounds in turn were prepared by the reaction of the corresponding dialkylamine with dimethylmagnesium (eq 2). The active form of MgH_2 used in these studies was prepared by the reaction of $LiAlH_4$ with $(C_2H_5)_2Mg$ in diethyl ether at room temperature (eq 3).

$$(R_2N)_2Mg + MgH_2 \xrightarrow{THF} 2HMgNR_2 \quad (1)$$

$$2R_2NH + Me_2Mg \rightarrow (R_2N)_2Mg + 2MeH\uparrow \quad (2)$$

$$Et_2Mg + LiAlH_4 \xrightarrow{Et_2O} MgH_2 + LiAlH_2Et_2 \quad (3)$$

Dialkylaminomagnesium hydrides were also prepared by the reaction of MgH_2 with an equimolar amount of the appropriate amine in THF as exemplified by the preparation of diisopropylaminomagnesium hydride (eq 4). This reation was slower than the redistribution reaction (eq 1); however, it did produce a satisfactory product.

$$i\text{-}Pr_2NH + MgH_2 \xrightarrow{THF} HMgN\text{-}i\text{-}Pr_2 + H_2 \quad (4)$$

The R_2NMgH compounds prepared by the methods just described were allowed to react with four representative ketones, i.e., 4-*tert*-butylcyclohexanone (I), 3,3,5-trimethylcyclohexanone (II), 2-methylcyclohexanone (III), and camphor (IV). The results of these reactions are summarized in Tables II–IV.

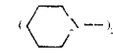
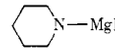
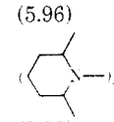
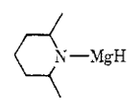
$LiAlH_4$ is considered to be the least sterically hindered hydride that reduces cyclic and bicyclic ketones. For example, $LiAlH_4$ produces 10, 80, 24, and 9% equatorial or exo attack, respectively, in ketones I, II, III, and IV. On the other hand, MgH_2 reduced ketones I, II, III, and IV in 23, 85, 35, and 8% equatorial or exo attack, respectively. The increased attack from the least hindered side of the ketone by MgH_2 can be explained by the increased steric requirement of MgH_2 due to its polymeric nature. Each dialkylaminomagnesium hydride reduced the cyclic and bicyclic ketones studied to give significantly more equatorial (or exo) attack than MgH_2 itself. Presumably $HMgNR_2$ compounds are sterically bulkier than MgH_2. The stereoselectivity depends on the combination of the steric bulk of the dialkylamino group plus the aggregation of the hydride reagent although the results are complicated by the fact that it is at least possible that some of these reductions by $HMgNR_2$ compounds take place through a small equilibrium amount of MgH_2 formed by disproportionation.

$$HMgNR_2 \rightarrow MgH_2 + Mg(NR_2)_2$$

The most selective reagent among those studied is trimethylsilyl-*tert*-butylaminomagnesium hydride, which reduced ketones I, II, III, and IV to give the less thermally stable alcohol produced in 73, 99, 98, and 95% yields, respectively. However, the least selective hydrides appear to be 2,6-dimethylpiperidinomagnesium hydride and isopropylmethylaminomagnesium hydride. The latter compound is less stereoselective than the other hydrides presumably because the R_2N group is less bulky. On the other hand, it is hard to explain the lack of selectivity of the 2,6-dimethylpiperidinomagnesium hydride unless a considerable amount of the reduction takes place through MgH_2. This suggestion is not unreasonable since 2,6-dimethylpiperidinomagnesium hy-

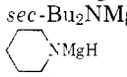
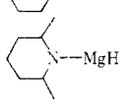
0022-3263/78/1943-1564$01.00/0

Table I. Preparation of Dialkylaminomagnesium Hydrides in THF[a]

Reactants, mmol		Registry	Reaction	Analysis (ratio)		
MgH_2	$Mg(NR_2)_2$	no.	time, h	Mg:H	Product	Solubility in THF
6.0	$[(n\text{-Pr})_2N]_2Mg$ (6.00)	23293-22-3	1	1.00:0.97	$n\text{-Pr}_2NMgH$	Very soluble
5.85	$[(i\text{-Pr})_2N]_2Mg$ (5.90)	23293-23-4	1	1.00:0.96	$i\text{-Pr}_2NMgH$	Very soluble
5.90	$[i\text{-Pr(Me)N}]_2Mg$ (5.90)	65277-26-1	3	1.00:0.96	$i\text{-Pr(Me)NMgH}$	Sparingly soluble, crystallized from THF
6.00	$[(sec\text{-Bu})_2N]_2Mg$ (5.95)	65277-27-2	2	1.00:0.97	$sec\text{-Bu}_2NMgH$	Moderately soluble, could be crystallized from THF
5.75	$(Ph_2N)_2Mg$ (5.70)	65277-28-3	1	1.00:0.97	Ph_2NMgH	Soluble, could be crystallized from THF
6.00	 (5.96)	65277-29-4	3	1.00:0.95		Moderately soluble, crystallized from THF
5.50	 (5.50)	65277-30-7	2	1.00:0.96		Moderately soluble, crystallized from THF
6.05	$(t\text{-Bu(SiMe}_3)N)_2Mg$	65277-31-8	1.5	1.00:0.97	$t\text{-Bu(SiMe}_3)NMgH$	Very soluble

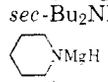
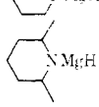
[a] All reactions were carried out at room temperature in THF (50–60 mL).

Table II. Reactions of 4-*tert*-Butycyclohexanone with Aminomagnesium Hydrides in THF[a]

			Relative yield, %		
Expt	Hydride	Registry no.	Axial-OH	Equatorial-OH	Yield, %
1	MgH_2	7693-27-8	24	76	100
2	$n\text{-Pr}_2NMgH$	65277-32-9	60	40	65
3	(i-Pr)(Me)NMgH	65392-10-1	38	62	50
4	$i\text{-Pr}_2NMgH$	33036-48-5	57	43	60
5	$sec\text{-Bu}_2NMgH$	65277-33-0	59	41	55
6		65277-34-1	63	37	39
7		65277-35-2	45	55	70
8	$t\text{-Bu(SiMe}_3)NMgH$	65277-36-3	73	27	75

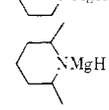
[a] All reactions were carried out in 4:1 molar ratio (hydride/ketone) for 24 h at room temperature.

Table III. Reactions of 3,3,5-Trimethylcyclohexanone with Aminomagnesium Hydrides in THF[a]

		Relative yield, %		
Expt	Hydride	Axial-OH	Equatorial-OH	Yield, %
9	MgH_2	85	15	92
10	$n\text{-Pr}_2NMgH$	98	2	46
11	(i-Pr)(Me)-NMgH	95	5	29
12	$i\text{-Pr}_2NMgH$	95	1	75
13	$sec\text{-Bu}_2NMgH$	99.5	0.5	70
14		98	2	35
15		94	6	52
16	$t\text{-Bu(SiMe}_3)$-NMgH	99	1	82

[a] All reactions were carried out in 4:1 molar ratio (hydride/ketone) for 24 h at room temperature.

Table IV. Reactions of 2-Methylcyclohexanone with Aminomagnesium Hydrides in THF[a]

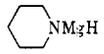
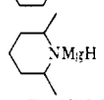
		Relative yield, %		
Expt	Hydride	Axial-OH	Equatorial-OH	Yield, %
17	MgH_2	35	65	100
18	$n\text{-Pr}_2NMgH$	90	10	28
19	(i-Pr)(Me)-NMgH	80	20	40
20	$i\text{-Pr}_2NMgH$	98.5	1.5	85
21	$sec\text{-Bu}_2NMgH$	98	2	62
22		92	8	40
23		82	18	58
24	$t\text{-Bu(SiMe}_3)$-NMgH	98	2	95

[a] All reactions were carried out in 4:1 molar ratio (hydride/ketone) for 24 h at room temperature.

dride, because of its large steric requirement, would be expected to react very slowly with the ketones studied compared to the other hydrides thereby giving a small equilibrium amount of MgH_2 sufficient time to react. The fact that 2,6-dimethylpiperidinomagnesium hydride reduces all ketones in significantly higher yield than the less sterically hindered piperidinomagnesium hydride indicates either (1) that indeed MgH_2 is a major reacting species since it produces the highest yield in all cases or (2) the hydride of greatest steric requirement would be expected to function as the weakest base in terms of producing enolization product.

Indeed we have found that the modest yields of reduction

Table V. Reactions of Camphor with Aminomagnesium Hydrides in THF[a]

Expt	Hydride	Relative yield, % Endo-OH	Exo-OH	Yield, %
25	MgH_2	8	92	100
26	n-Pr_2NMgH	13	87	92
27	(i-Pr)(Me)MgH	10	90	15
28	i-Pr_2NMgH	7	93	45
29	sec-Bu_2NMgH	6	94	55
30		12	88	10
31		7	93	42
32	t-Bu($SiMe_3$)-NMgH	5	95	100

[a] All reactions were carried out in 4:1 molar ratio (hydride/ketone) for 24 h at room temperature.

product are due to enolization of the ketones studied by the R_2NMgH compounds. Although MgH_2 gives quantitative yields in the reduction of ketones in nearly every case studied, its stereoselectivity toward cyclic and bicyclic ketones does not compare with that of the new R_2NMgH compounds, particularly $Me_3Si(t\text{-Bu})NMgH$.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques. 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 at pH 10 using Eriochrome Black T as an indicator.

Materials. Di-n-propylamine (Eastman), isopropylmethylamine (Eastman), di-sec-butylamine (Pfaltz I. Bauer), piperidine (Fisher), and 2,6-dimethylpiperidine (Aldrich) were dried over molecular sieve 4A and distilled prior to use.

Diethyl ether and THF were distilled over $LiAlH_4$ and $NaAlH_4$, respectively. Diethylmagnesium was prepared by the reaction of diethylmercury with excess magnesium metal at 60–80 °C and a solution in diethyl ether was standardized by magnesium analysis.[9] $LiAlH_4$ solution in diethyl ether was prepared by stirring $LiAlH_4$ in ether (1 M) for 24 h followed by filtration and standardization of the resulting clear solution by aluminum analysis.

Preparation of Trimethylsilyl($tert$-butyl)amine. To a magnetically stirred mixture of $tert$-butylamine (7.3 g, 100 mmol) and triethylamine (10.1 g, 100 mmol) in n-hexane (150 mL) was added dropwise, 10.9 g (100 mmol) of Me_3SiCl. The reaction mixture was stirred for ~2 h and the insoluble white solid (Et_3NHCl) was removed by filtration. The filtrate was concentrated and the residue was distilled at 124 °C. The ^1H NMR spectrum of this liquid showed signals at 9.67 (due to Me_3Si) and 8.57 (due to $tert$-butyl group) in the ratio of 1:1.

Preparation of Bis(dialkylamino)magnesium Compounds by the Reaction of $(CH_3)_2Mg$ with Dialkylamines in 1:2 Molar Ratio. Dialkylamines in THF were added dropwise to a well stirred solution of $(CH_3)_2Mg$ in diethyl ether in 2:1 molar ratio at room temperature. The reaction mixture was refluxed overnight and its completion was checked by the absence of any hydrolyzable gas. The solution was then standardized by magnesium analysis.

Preparation of MgH_2 slurry in THF was performed according to the procedure described in paper 1 of this series.

Preparation of Dialkylaminomagnesium Hydrides by the Reaction of Bis(dialkylamino)magnesium Compounds with MgH_2 Slurry in THF. A solution of bis(dialkylamino)magnesium compounds in THF was added dropwise to a well-stirred slurry of MgH_2 in THF at room temperature. The reaction mixture was further stirred to give a clear solution. The resulting solution was analyzed for magnesium (EDTA) and hydrolyzable gas (Table I).

Preparation of Diisoproplylaminomagnesium Hydride by the Reaction of Diisopropylamine with MgH_2 in 1:1 Molar Ratio in THF. Diisopropylamine (6.06 g, 6.0 mmol) in THF (15 mL) was added dropwise to a slurry of MgH_2 (6.0 mmol) in THF (50 mL) at room temperature. The reaction mixture was stirred for 15 h to give a clear solution. Anal. Calcd for $HMgN(i\text{-Pr})_2$: Mg:H = 1.00:1.00. Found: 1.00:0.96.

Acknowledgment. We are indebted to the National Science Foundation (Grant No. MPS 7504127) and the Office of Naval Research (Grant No. N00014-67-A-0419-005AD) for financial support of this work.

Registry No.—4-$tert$-Butylcyclohexanone, 98-53-3; 3,3,5-trimethylcyclohexanone, 873-94-9; 2-methylcyclohexanone, 583-60-8; camphor, 76-22-2; trimethylsilyl($tert$-butyl)amine, 5577-67-3; $tert$-butylamine, 75-64-9; Me_3SiCl, 75-77-4; diisopropylamine, 108-18-9.

References and Notes

(1) Parts 1 and 2: E. C. Ashby, J. J. Lin, and A. B. Goel, *J. Org. Chem.*, preceding articles in this issue.
(2) S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, **98**, 3383 (1976).
(3) For recent review, see H. O. House, "Modern Synthetic Organic Reactions", W. A. Benjamin, New York, N.Y., 1972, p 45.
(4) E. C. Ashby and J. R. Boone, *J. Org. Chem.*, **41**, 2890 (1976).
(5) E. C. Ashby and A. B. Goel, *J. Am. Chem. Soc.*, **99**, 310 (1977).
(6) E. C. Ashby and A. B. Goel, *J. Chem. Soc., Chem. Commun.*, 169 (1977).
(7) E. C. Ashby, J. J. Lin, and A. B. Goel, *Tetrahedron Lett.*, in press.
(8) E. C. Ashby, J. J. Lin, and A. B. Goel, *J. Org. Chem.*, submitted for publication.
(9) D. F. Shriver, "The Manipulation of Air Sensitive Compounds", McGraw-Hill, New York, N.Y., 1969.
(10) E. C. Ashby and A. B. Goel, *Inorg. Chem.*, submitted for publication.