Reactions of partially solvated Grignard reagents with a ketone

Ants Tuulmets *, Meeri Sassian

Institute of Organic Chemistry, University of Tartu, Tartu 50090, Estonia

Received 3 March 1999; received in revised form 20 April 1999

Abstract

Ratios of the yields of addition and reduction products for the reactions of n-butylmagnesium chloride and bromide with diisopropyl ketone in toluene were determined at different THF, diethyl ether and methyl tertbutyl ether (MTBE) contents in the Grignard reagent. The reduction reaction yield is a maximum at the molar ratio 0.1 of THF or diethyl ether to the Grignard reagent. The addition reaction has a maximum in the region of 0.3–0.4 for the same ethers and about 1.5 for MTBE. The ratio Add/Red for conventional Grignard reagents is lower than that for partially solvated reagents. The results were discussed in terms of the solvation of the species in the reaction mixture. The decisive role of the steric requirements of the reagents over their intrinsic acid-base properties was demonstrated. Partially solvated Grignard reagents can serve as tools for the investigation of solvent effects in the Grignard reaction. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Grignard reaction; Grignard reagents; Solvation effects

1. Introduction

Organomagnesium compounds can be prepared not only in conventional ethers but also in hydrocarbon media with or even without additions of donor solvents [1,2].

Synthesis of unsolvated organomagnesium halides is limited to primary alkyl and aryl compounds, but in the presence of one molar equivalent of the complexing agents, e.g. ethers and tertiary amines, several organomagnesium compounds have been obtained in hydrocarbon media [1,2]. Primary, secondary and tertiary alkylmagnesium bromide and chloride reagents in toluene containing less than one equivalent of organic base have been prepared recently [3–6]. Whereas the Grignard reagents in donor solvents are solvated by at least two solvent molecules per atom of magnesium, those obtained in the presence of smaller amounts of donor substances are *partially solvated.*

Although partially solvated Grignard reagents have also been used in large-scale industrial processes [4,7], their properties have been little investigated. The rate of the reaction of the Grignard reagent with ethylethoxysilanes [8] and hydrazones [9] is greatly increased when

free ethers are replaced by toluene. The reactions of ketones with alkylmagnesium bromides solvated with one equivalent of diethyl ether or THF in benzene or toluene give higher yields of addition products in comparison with those in ethers [10]. In our previous work [11] we determined the ratios of the yields of reduction and addition products for the reaction of n-butylmagnesium chloride with diisopropyl ketone in toluene–diethyl ether mixtures, scanning the donor content in the Grignard reagent from zero addition up to the reagent bisolvated on the average. The obtained dependence appeared to be unexpectedly complicated having extreme points.

In this work the investigation was extended to ethers of different solvating ability and it also involved n-butylmagnesium bromide reagents. This enabled us to comprehend the observed dependences on the basis of solvation effects.

2. Experimental

Commercial reagents were carefully purified. The reagents and solutions were operated on under dry argon, and transferred by use of syringes. n-Butylmagnesium chloride and n-butylmagnesium bromide were

---

* Corresponding author. Fax: +372-7-465264.

prepared in toluene by using iodine-activated magnesium turnings and *n*-butylchloride or *n*-butylbromide in the presence of a small amount (about 0.01 mol of ether per mole of the halide) of diethyl ether, THF or methyl tertbutyl ether (MTBE). The obtained heterogeneous systems usually contained about 1.6 moles of the Grignard reagent per litre of toluene.

The basic magnesium content in the reagent was determined by quenching an aliquot with the standard sulphuric acid. The excess acid was back-titrated against aqueous sodium hydroxide. The chloride and bromide ion concentrations were determined in the same solution by the Mohr method after the acidimetric analysis. The ratio $Mg-X/R-Mg$ ($X = Cl$, Br) was calculated.

From the vigorously stirred reaction mixture 5 ml aliquots of the suspension were withdrawn and transferred to vials sealed with serum caps. Calculated amounts of the appropriate ether were added and the reagents were left for at least 6 h or overnight. Grignard reagents in pure ethers were prepared routinely and analyzed as described above.

Then diisopropyl ketone in the molar ratio 1:2 dissolved in toluene or in the appropriate ether was slowly added at 0°C to the reagents prepared as described above, and the mixtures were left overnight. The ketone solutions also contained *n*-nonane or *n*-decane, i.e. the internal standard for GLC analyses.

The reaction mixtures were slowly quenched at 0°C by the dropwise addition of 10 ml of the 20% aqueous solution of NH_4Cl. The organic layer was separated and analyzed on a Chrom-5 gas chromatograph with a flame ionization detector. The column was packed with 20% Carbowax 20 M on Chromosorb W AW-DMCS.

3. Results

We studied the compositions of products from the reaction of diisopropyl ketone with *n*-butylmagnesium chloride and bromide in toluene in the presence of diethyl ether, THF, or methyl tertbutyl ether (MTBE). Primary alkylmagnesium halides can be prepared in toluene in the absence of complexing agents. However, an easy initiation of the reaction and a small contribution of the Wurtz coupling were poorly reproducible, therefore, we preferred to initiate the reaction with a catalytic addition of the ether (about 0.01 mol per mole of the halide) that led to more consistent results.

By the addition of appropriate amounts of ethers to the obtained suspensions, Grignard reagents with different molar ratios of ethers were prepared. It is remarkable that the distribution of ether additions between the components of heterogeneous Grignard solutions arrived at completion within hours, since the reagents kept for 6 h or overnight (or for 1 week [11])

after the addition of the ether revealed the same reactivity. Furthermore, a seasoning of the mixtures for less than 4–6 h brought about irreproducible results in determining the product composition of the reaction with the ketone. Obviously, the fairly good solubility of the partially solvated Grignard reagents in toluene [3,5,6] favours the relatively rapid achievement of solvation equilibria. In this way, the Grignard reagents containing very small amounts of ethers were obtained that could not have been achieved by direct syntheses (see, e.g. Refs. [5,6]).

Grignard reagents with different molar ratios of ethers were further allowed to react with 0.5 molar equivalent of diisopropyl ketone. The reaction products were quantitatively determined by means of GLC. The enolization reaction occurred to a low extent, not exceeding 1–2%. No ketolization was observed. A precautionary quenching of the reaction mixture enabled us to avoid the dehydration of the addition product. Thus, we could directly use molar ratios 2-methyl-3-isopropylheptane-3-ol (addition product) to 2,4-dimethylpentane-3-ol (reduction product) from the GLC analysis as reactivity characteristics for the Grignard reagents with different molar contents of the ethers (Fig. 1). The use of internal standards in GLC analysis made feasible calculation of the material balance of the reaction. The sum of yields of addition and reduction products and of recovered ketone (the enolization product, never exceeding 2%) was always 96–102%.

All the experiments including the synthesis of *n*-butylmagnesium halide were repeated at least two to three times. In Fig. 1 the points indicate the mean values obtained from several experiments. The results of parallel experiments agreed within 10% or less.

The ratio $Mg-X/R-Mg$ indicates the extent of side reactions (mainly the Wurtz reaction) during the Grignard reagent formation. The ratio also indicates the excess of magnesium halide in the Grignard reagent. It is known that an increased content of magnesium halide in the Grignard reagent favours the addition reaction with ketones in case of alkylmagnesium bromides and iodides, whereas in case of chlorides the influence is the opposite (see Ref. [11] and references therein). In our experiments the ratio ranged from 1.10 to 1.15 for *n*-butylmagnesium chloride reagents and from 1.25 to 1.40 for *n*-butylmagnesium bromide Grignards.

Experimental results presented in Fig. 1 and in Table 1 are somewhat astonishing, since such complicated dependences of the ratio Add/Red on the ether molar content in the reagent could not be expected. At a very low ether content the reduction reaction is favoured, having a maximum in the region of 0.1 molar ratio of diethyl ether or THF to the organomagnesium compound. With an increasing ether content the addition

reaction prevails over reduction, but the ratio Add/Red passes a maximum (or even two in the case of THF), largely exceeding the value for the reagent in pure ether (Table 1), e.g. for the reagent nBuMgBr·0.4Et$_2$O the yield of the addition product was 79% while the same for n-butylmagnesium bromide in pure diethyl ether was about 53%. MTBE reveals a flat maximum only at greater additions of the ether.

4. Discussion

General features of the Grignard reaction with ketones are well understood now [1,2]. The coordination of ketone with magnesium is essential, and in donor solvents occurs by replacement of a solvent molecule at the magnesium atom. In partially solvated reagents the replacement is probably not necessary. Thus, a solvent molecule initially coordinated with magnesium is present in the complex influencing its further behaviour.

Synthetically desirable Grignard addition providing tertiary alcohols is frequently accompanied by the reduction and enolization of ketone. Although all three are competitive reactions, the resulting magnesium alcoholates favour reduction. For this reason the contribution of the reduction reaction increases during the process, particularly under preparative conditions, when a little or no excess of the Grignard reagent is used [12–14].

Grignard reagent solutions usually contain an equilibrium mixture of a variety of species. Apart from the association equilibria the Schlenk equilibrium (Eq. (1)) is essential.

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \qquad (1)$$
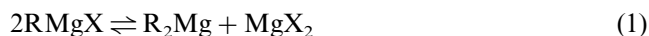
Both organomagnesium species are highly reactive toward ketones but diorganyl-magnesiums react at least ten times faster [15]. The primary reaction products, alcoholates R'OMgX and RMgOR', are able to complex with other species in the solution. Alkylmagnesium alcoxides are capable of alkyl addition to the carbonyl bond, but more by-products of enolization and reduction have been reported [16]. Alkylmagnesium alcoxides do not disproportionate with a recovery of dialkylmagnesiums in hydrocarbon solutions, however, magnesium bromide can catalyze the exchange reaction [17,18].

A decisive role of specific solvation in organomagnesium chemistry has been long recognized [1,2]. Later it was found that the steric effect of the donor solvent considerably controlled its solvating ability [19–22]. Moreover, it was shown quantitatively [23] that the effective basicity (solvating power) of a base in respect to a Lewis acid (to an organomagnesium compound) is greatly determined by the steric requirements of the base and by the effective (Lewis) acidity of the acid, the latter also being strongly dependent on the steric demands of the acid. In further discussion of experimental results the importance of both the specific solvation and the steric effects of the reagents will be stressed.
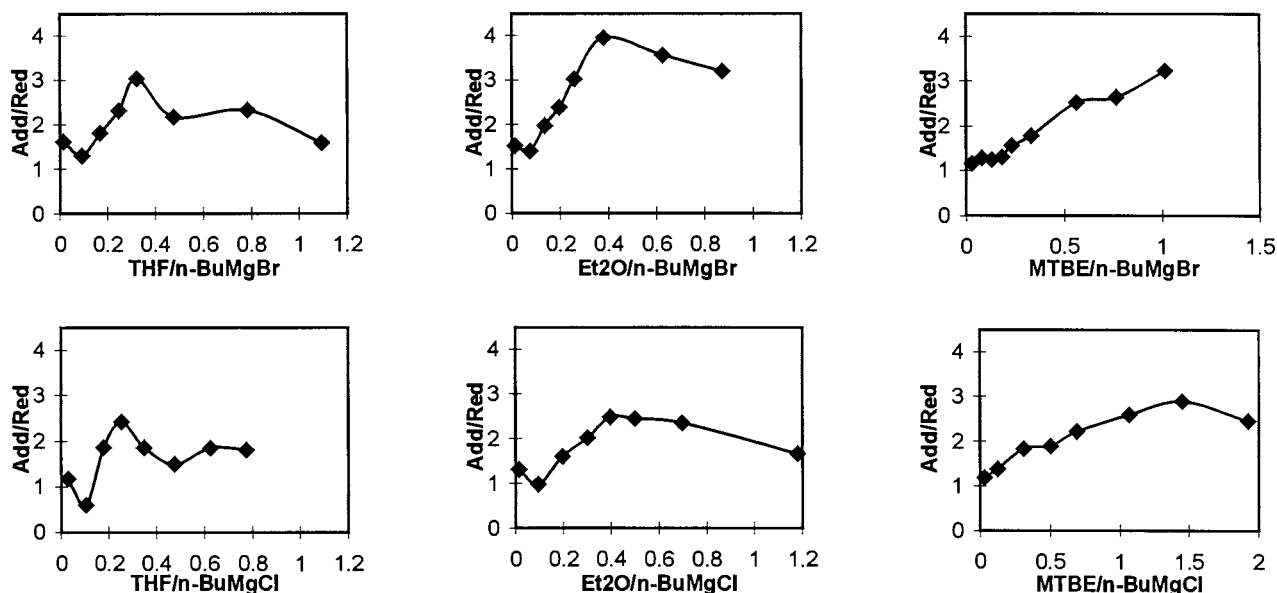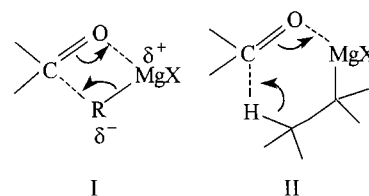

Fig. 1. The ratios of yields of addition and reduction products (Add/Red) vs. the molar ratio of ether to Grignard reagent in toluene.

Table 1
The ratios of yields of addition and reduction products for the reaction with diisopropyl ketone

Reagent	Base	Add/Red for the partially solvated reagent [a]	Add/Red in pure ether
n-BuMgBr	THF	3.1 (0.3)	0.80
	Et$_2$O	4.0 (0.4)	1.2
	MTBE	3.5	1.3
n-BuMgCl	THF	2.5 (0.25)	1.2
	Et$_2$O	2.5 (0.4)	1.3
	MTBE	2.8 (1.4)	1.1

[a] The maximum value. In parentheses the molar ratio of the ether to the Grignard reagent is given for the maximum point.

The heterolytic Grignard addition proceeds through a four-centre transition state (I), while a cyclic six-centre transition state (II) is necessary for the reduction reaction [2].

It is obvious that the nucleophilic solvation of the magnesium polarizes the carbon–magnesium bond increasing the nucleophilicity of the carbon and thus favouring the addition and enolization reactions. Reduction comprises a β-hydrogen transfer, less influenced by the donor at the magnesium centre. In addition to this, the nucleophilic solvation of magnesium can suppress the electrophilicity of the carbonyl group to some extent, thereby enhancing the selectivity of the reaction centre. Consequently, an increase in the solvating ability of the donor should bring about an increase in the addition reaction yield as well as in the extent of enolization. This conclusion is well supported by the experimental data (Ref. [24] and references therein). Although these have been considered in terms of the prevalence of enolization, an increase in the addition to the reduction ratio with an increasing effective basicity of the donors is evident.

It is also obvious that an increase in the steric hindrance causes a decrease in the solvating ability of the donor regardless of its Brønsted basicity. Likewise, the increasing bulkiness of the groups bound to the magnesium centre hinders complexing between the donor and the substrate. Consequently, the following sequence of effective acidity can be envisaged for species comprising a Grignard reaction mixture: $MgX_2 > RMgX > R'OMgX > R_2Mg > R'OMgR$.

On the basis of the above reasoning one can conclude that very bulky alkoxy groups in magnesium alcoholates resulting from Grignard addition reactions considerably hinder complexation with donors, thus suppressing the nucleophilicity of the organyl moiety. The consequence of this is the remarkable bias of R'OMgR species towards the reduction mentioned above.

The effectiveness of the solvation of the species is also important for the exchange reactions occurring in the reaction mixture. The R'OMgR species enter the dismutation equilibria (Eqs. (2) and (3)), thus recovering the more reactive species.

$$R'OMgR + RMgX \rightleftharpoons R_2Mg + R'OMgX \qquad (2)$$

$$R'OMgR + MgX_2 \rightleftharpoons RMgX + R'OMgX \qquad (3)$$
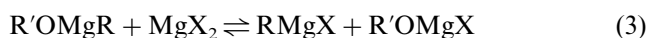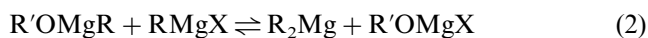
Note that the reverse reactions of the equilibria (Eqs. (2) and (3)) involve product alcoholates R'OMgX and produce less reactive species. It is obvious that stronger solvation shifts the equilibria to the left similarly with the Schlenk equilibrium (see, e.g. the discussion in Ref. [6]). On the other hand, all these dismutation reactions as well as the Schlenk equilibrium (Eq. (1)) evidently proceed through cyclic transition states, the formation of which is favoured by the electrophilicity of magnesium centers. Thus, an increase in the solvating power of the solvent increasingly retards the exchange reactions as it has been observed for the Schlenk equilibrium [2]. Consequently, a stronger solvation of the Grignard reagent suppresses the dismutation of R'OMgR species, ultimately favouring the reduction reaction.

Our experimental results, presented in the forms of curves in Fig. 1, can be interpreted now. The nature of the halogen in the Grignard reagent seems to be of minor importance since the shapes of the plots are rather similar for the chloride and bromide. However, the maximum Add/Red ratio is significantly higher in each case for the bromide (Table 1), and this may be of importance in synthetic application of the reagents. Variation of the donor reveals a strong effect of solvation. The ethers employed in this work are of very close Brønsted basicity, however, their effective basicities differ largely, decreasing in the order THF > Et$_2$O > MTBE as it was shown also in our previous paper [6].

The ratio Add/Red is a minimum at small additions of the ethers. In this region only a minor proportion of the species are solvated thus largely favouring the reduction of ketone. In addition, poor solvation shifts the Schlenk equilibrium to RMgX species which produce R'OMgX and via equilibrium (Eq. (3)) R'OMgR spe-

cies, in this way still enhancing the contribution of the reduction reaction.

An increase in nucleophilic solvation of the reagent raises the yield of the addition reaction at the expense of reduction as discussed above. This part of the curve is expectedly steeper for more effective donors. However, growing solvation involves shifts in all the equilibria as well as a slow down of the dismutation reaction, thus favouring again the reduction of the ketone. As a result, the ratio Add/Red passes a maximum, expectedly located at greater additions of weaker donors. A further increase in the molar ratio of base to the Grignard reagent leads to the diminishing of the Add/Red ratio down to the value for the conventional reagent (Table 1), this value being considerably lower than that for the 'monosolvated' or somewhat less solvated Grignard reagents.

The observed dependences undoubtedly reflect an integral effect of numerous interactions occurring in the systems. Therefore the assignment of minor details of a curve should be done cautiously. However, we suppose that the second, weaker maximum in the case of THF can be related to the Schlenk equilibrium, which unlike the other two ethers, is shifted further to the right both in pure THF and in the partially solvated primary alkyl reagents [2,6]. As to the short descending part of curves for extremely small additions of THF and diethyl ether, the first points of the curves correspond to reagents partially solvated with the ketone at the beginning of the reaction and complexed with magnesiumalcoholates by the completion of the reaction. Further donor additions are only sufficient for the solvating of some portion of the strongest acid, MgX_2, thus causing shifts of equilibria favourable for reduction. From a certain molar ratio of base to the Grignard reagent, effects fostering the addition reaction prevail and give rise to the curves discussed above.

Somewhat similar plots of the yields of reduction or enolization reactions of ketones versus the molar ratio of HMPT of Grignard reagents in diethyl ether have been published [25]. These curves can also be interpreted in the same way.

As a general conclusion, it can be inferred that specific solvation plays a crucial role in determining the structure and reactivity of the Grignard reagent. The decisive role of the steric requirements of the reagents over their intrinsic acid–base properties was also demonstrated. It becomes evident that partially solvated Grignard reagents can serve as tools for the investigation of the solvent effects in the Grignard reaction.

The practical implication of the results obtained in this work is that partially solvated Grignard reagents can be used to improve the yield of the Grignard addition reaction. Presumably MTBE Grignards may be the reagents for choice since they provide a good Add/Red ratio in an approximately 'monosolvated' form which is easily attainable by direct synthesis [6].

Acknowledgements

References

[1] B.J. Wakefield, Organomagnesium Methods in Organic Synthesis, New York: Academic Press, 1995.

[2] W.E. Lindsell, in: G. Wilkinson (Ed.), Comprehensive Organometallic Chemistry, vol. 1, Pergamon Press, 1982, Chap. 4; Comprehensive Organometallic Chemistry II, vol. 1, Pergamon Press, 1995, Chap. 3.

[3] (a) A. Tuulmets, P. Kullamaa, M. Mikk, Tartu Ülik. Toim. (Acta et Comment. Univ. Tartuensis. Publ. Chem. XXII) 975 (1994) 139. (b) Chem. Abstr. 124 (1996) 56009.

[4] B.A. Klokov, Zh. Prikl. Khim. (S-Peterburg) 68 (1995) 120.

[5] A. Tuulmets, M. Mikk, D. Panov, J. Organomet. Chem. 523 (1996) 133.

[6] A. Tuulmets, D. Panov, J. Organomet. Chem. 575 (1999) 182.

[7] M.V. Sobolevskii (Ed.), Oligoorganosiloksany: Svoistva, Poluchenie, Primenenie, Khimiya, Moscow, 1985.

[8] (a) A. Tuulmets, M. Hõrak, T. Kõopere, J. Ruotsi, Org. Reactivity (Tartu) 19 (1982) 102. (b) Chem. Abstr. 99 (1983) 53836.

[9] A. Alexakis, N. Lensen, J.P. Tranchier, P. Mangeney, J. Org. Chem. 57 (1992) 4563.

[10] P. Canonne, G. Foscolos, H. Caron, G. Lemay, Tetrahedron 38 (1982) 3563.

[11] A. Tuulmets, V. Pällin, Main Group Met. Chem. 20 (1997) 85.

[12] (a) A. Tuulmets, Reakts. Sposobn. Org. Soedin. 1 (1964) 196. (b) Chem. Abstr. 61 (1964) 13154.

[13] R. D'Hollander, M. Anteunis, Bull. Soc. Chim. Belg. 74 (1965) 71.

[14] M. Chastrette, R. Amouroux, Bull. Soc. Chim. Fr. (1970) 4348.

[15] E.C. Ashby, Pure Appl. Chem. 52 (1980) 545.

[16] H.O. House, W.L. Respess, J. Org. Chem. 30 (1965) 301.

[17] G.E. Parris, E.C. Ashby, J. Am. Chem. Soc. 93 (1971) 1206.

[18] G.E. Coates, J.A. Heslop, J. Chem. Soc. A (1968) 514.

[19] C. Agami, Bull. Soc. Chim. Fr. (1967) 4031.

[20] (a) J. Koppel, A. Tuulmets, Reakts. Sposobn. Org. Soedin. 9 (1972) 399. (b) Chem. Abstr. 79 (1973) 136278.

[21] J. Ducom, J. Organomet. Chem. 59 (1973) 83.

[22] P. Voorbergen, C. Blomberg, F. Bickelhaupt, J. Organomet. Chem. 40 (1972) 225.

[23] (a) A. Tuulmets, Reakts. Sposobn. Org. Soedin. 11 (1974) 81. (b) Chem. Abstr. 82 (1975) 42803.

[24] C. Blomberg, Bull. Soc. Chim. Fr. (1972) 2143.

[25] J. Fauvarque, J. Ducom. Compt. Rend. C 273 (1971) 268.