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Grignard reagents in toluene solutions[†]

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Grignard reagents were prepared from chloroalkanes and chlorobenzene in toluene in the presence of one or 0.5 equivalents of various organic bases (ethers and amines). Reagents with an average monosolvation can be obtained in high yields from primary or secondary alkyl chlorides and chlorobenzene. Diethyl ether is the most effective donor, in that it affords the reagents with a very small content of base. The kinetics of the reactions of *n*-butylmagnesium chloride in diethyl ether, and of this Grignard reagent monosolvated with the ether in toluene, with alkylalkoxysilanes were investigated. Reactivity of the partially solvated reagent greatly exceeds that of the conventional Grignard reagent. Yields of addition and reduction reactions of mono- and semi-solvated *n*-butylmagnesium chlorides in toluene with a ketone, an aldehyde, and two esters were determined. The partially solvated reagents afford the addition products (tertiary alcohols) in yields better than, or at least comparable to, those obtained with the conventional Grignard reagents. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: Grignard reagents; Grignard reaction; solvation effects; carbonyl compounds; alkylalkoxysilanes; kinetics

INTRODUCTION

The great scope and the versatility of the Grignard reaction has made it a frequent choice for laboratory synthesis, and increasingly for the industrial production of specialty chemicals used for intermediates in various industries. Since its discovery, a wide range of solvents have been used for Grignard reagent preparation. Organomagnesium compounds can be obtained not only in conventional ethers, but also in non-polar hydrocarbon media with or even without additions of donor solvents.[1–3]

The scope of synthesis of unsolvated organomagnesium halides, i.e. preparation in the absence of donor solvents, is limited to primary alkyl and aryl compounds. In the presence of complexing agents, e.g. ethers and tertiary amines, a greater variety of organomagnesium compounds can be obtained in hydrocarbon media.[4–9] Primary, secondary, and tertiary alkylmagnesium chlorides in toluene solutions containing less than one equivalent of organic base have been prepared recently.[7–9]

Whereas the Grignard reagents in donor solvents are solvated at least by two solvent molecules per atom of magnesium, those obtained in the presence of smaller molar amounts of donor substances are only partially solvated. As the solvating agent is firmly bound to the Grignard reagent, such solutions possess almost all the advantages of unsolvated organomagnesium halides in nonsolvating media.

Use of hydrocarbon solvents offers advantages, since they are cheap and non-hygroscopic. Employment of toluene as a solvent is, above all, environmentally important. Use of ethers in large-scale organomagnesium syntheses in industry is hazardous,[10] therefore, the replacement of readily flammable solvents by those of higher boiling points is desirable. The significance of those factors becomes apparent with the growing importance of organomagnesium compounds for the synthesis of silicone monomers and other chemicals. Obviously, this argument was one of the motives for setting up a toluene-based Grignard technology, in, for example, the Russian silicon industry.[1]

Toluene proved to be a particularly suitable solvent for partially solvated Grignard reagents. Whereas in alkanes their solubility is extremely low, one can obtain rather concentrated (1 M and higher) solutions in toluene.[2,3,6,8,9] A good solubility of the reagents is favourable for Grignard reagent preparation in toluene.

Although partially solvated Grignard reagents have also

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been used in large-scale industrial processes,[7,11] their properties have been little investigated. One can expect several features different from those of both conventional Grignard reagents and unsolvated organomagnesium compounds.

In this paper we report the results of a comparative investigation of partially solvated Grignard reagents aimed at an assessment of the prospects for their application in laboratory practice and in industry. Although some reagents can be obtained with a very low content of the donor, we focus our attention mainly on the stoichiometrically 'monosolvated' reagents as the most easily accessible ones.

PREPARATION OF PARTIALLY SOLVATED GRIGNARD REAGENTS IN TOLUENE

The synthesis of partially solvated organomagnesium compounds is principally similar to that of conventional Grignard reagents. Because the induction period of the reaction is longer in hydrocarbon solutions, the process has to be initiated with a little of the halide dissolved in the donor. Then the rest of the halide dissolved in toluene is added slowly. The overall rate of the reaction is lower than in common ethers; therefore, the reaction temperature should be maintained slightly below the boiling point of the halide or an ultrasound activation can be used while keeping the temperature below 40 °C. The application of ultrasound (20–50 kHz) is known to accelerate the formation of the Grignard reagent.[12] In our experiments, ultrasonic irradiation made the induction period practically negligible, and shortened the reaction time by a factor of two or more. Organic chlorides are preferable to the bromides because of lower price and a lesser tendency to form Wurtz reaction products.

The preparation of the reagents was carried out with different donor agents and for various initial amounts of the reagents. The ratios of the initial reagents were chosen to obtain approximately 1.0–1.2 M solutions. Lower concentrations were not used because these are less important for preparative-scale work, and the rate of the reaction decreases considerably with a decrease in the base concentration.

The reagents with an average monosolvation are homogeneous up to approximately 1 M concentration. More-concentrated or less-solvated systems are heterogeneous. The reagents undergo a dismutation reaction resembling the Schlenk equilibrium:

$$2RMgCl \rightleftharpoons R_2Mg + MgCl_2 \tag{1}$$

The formation of a precipitate rich in magnesium chloride occurs and the complexes in the solution contain more dialkyl- or diaryl-magnesium than those in the precipitate.[8,9] The concentration of the active Grignard reagent ([R–Mg]) in the supernatant solution is sensitively dependent on the amount of the organic base in the system (for details see Refs 8 and 9). Therefore, the solubility of a partially solvated Grignard reagent in toluene cannot be unequivocally defined.

Table 1. Yields of 'monosolvated' ($RMgCl\cdot B$) and 'semisolvated' ($2RMgCl\cdot B$) Grignard reagents in toluene

R	Organic base[a]	Yield (%)	
		$RMgCl\cdot B$	$2RMgCl\cdot B$
n-Bu	Et_2O	96	95
	THF	90	80
	MTBE	87	75
	Et_3N	92	70
	DME	95	90
i-Pr	Et_2O	90	88
	THF	92	53
	MTBE	83	40
	Et_3N	90	65
s-Bu	Et_2O	95	93
	THF	93	50
	MTBE	95	45
	Et_3N	90	63
t-Bu	Et_2O	40	30
	THF	43	27
	MTBE	no reaction	
	DME	50	37
Ph	Et_2O	no reaction	
	THF	90	
	DME	74	

[a] THF: tetrahydrofuran; MTBE: methyl tertiarybutyl ether; DME: 1,2-dimethoxyethane.

The results of the experiment are given in Table 1. For a more complete survey, some of the data are taken from Refs 8 and 9. Some are revised in this work. As can be seen in Table 1, Grignard reagents in toluene can be prepared from organic chlorides in the presence of various organic bases, at least with an average monosolvation or in less-solvated forms. Primary and secondary alkyl chlorides and chlorobenzene can be converted into 'monosolvated' Grignard reagents in high yields. Less solvated reagents, e.g. 'semisolvated' ($2RMgCl\cdot B$) ones, only form in good yields in the presence of diethyl ether; the exception chlorobenzene, which does not react at all under these conditions, or from primary, sterically encumbered alkyl chlorides. Diethyl ether proved to be an effective donor affording primary alkyl reagents with very little content of base (about 0.15 equivalents).[7,8] Actually, only the thickness of the reaction mixture sets limits to further progression of the reaction accompanied with an increase in Grignard to ether molar ratio. Moreover, the heterogeneous reagents can be used for synthetic purposes in the form of suspensions or slurries. In some cases, particularly when monosolvated reagents are suitable, diethyl ether can be replaced by less expensive and less volatile MTBE.

Table 2. Rate constants for reactions of silanes with 1 M *n*-BuMgCl in diethyl ether or with 1 M *n*-BuMgCl·Et$_2$O in toluene at 20 °C

Silane	Grignard reagent	$k \times 10^3$ (s^{-1})	Method
Si(OEt)$_4$	In the ether	4.7	GC
	Monosolvated	~1000	Thermography
n-BuSi(OEt)$_3$	In the ether	2.3	GC
	Monosolvated	70	Thermography
i-PrSi(OEt)$_3$	In the ether	0.03	GC
	Monosolvated	0.6	GC

REACTION RATES OF PARTIALLY SOLVATED GRIGNARD REAGENTS

In some long-established protocols for organomagnesium syntheses a portion of the ether has been replaced by benzene or toluene. Sometimes the same non-coordinating solvents are added to the reaction mixture at a certain stage of the process. A partial replacement of the solvent affords an elevated reaction temperature, thus promoting the process. However, kinetic investigations have revealed that an addition of toluene accelerates the reaction with substrates by itself.

The rate of the reaction of a Grignard reagent with hydrazones is greatly increased when free ether is replaced by toluene.[13] The same was observed for the reaction between ethyltriethoxysilane and ethylmagnesium chloride with increasing replacement of diethyl ether by toluene. At a molar ratio of 0.8 for toluene in the solution, the reaction proceeded 12 times faster than in pure ether.[14] Also, the reaction of phenylmagnesium bromide with hex-1-yne is markedly accelerated in binary mixtures of diethyl ether with non-solvating toluene, chlorobenzene, and dichloromethane.[15]

In Table 2 we present some examples from silane chemistry manifesting the enhanced reactivity of a partially solvated Grignard reagent.

A provisional explanation of these phenomena can be drawn from the necessity to substitute a donor molecule at the magnesium centre by the substrate for the Grignard reaction to proceed.[15,16] Replacement of the donor solvent by a non-complexing one shifts the solvation equilibrium towards a position more favourable for complexing the substrate with the Grignard reagent, thereby enhancing the reaction rate. However, a contribution by non-specific solvent effects cannot be excluded (e.g. cf., Refs 15 and 17).

REACTION YIELDS OF PARTIALLY SOLVATED GRIGNARD REAGENTS WITH CARBONYLS

The most important reactions of Grignard reagents are those with carbonyl compounds. Formation of a tertiary or secondary alcohol is frequently accompanied by the reduction and enolization reactions, lowering the yield of the target compound. It has been reported that reactions of ketones with alkylmagnesium bromides solvated with one equivalent of diethyl ether or THF in benzene or toluene afford higher yields of addition products in comparison with those in ethers.[18]

Recently, we determined the ratios of the yields of reduction and addition products for the reaction of *n*-butylmagnesium halides with diisopropyl ketone in various toluene–ether mixtures, scanning the donor content in the Grignard reagent from almost zero addition up to the reagents mono- or bi-solvated stoichiometrically.[19,20] The dependences obtained appeared to be unexpectedly complicated, including maximum and minimum points, the ratio Add/Red for conventional Grignard reagents being lower than that for partially solvated reagents. The results were discussed in terms of the solvation of the species in the reaction mixture.[20]

In this work, the investigation was extended to an aldehyde and some esters in view of possible application of partially solvated Grignard reagents in syntheses. In Table 3 the gas chromatography GC yields of addition and reduction products are presented for reactions of carbonyl compounds with 'semisolvated' and 'monosolvated' butylmagnesium chloride, i.e. with stoichiometric complexes 2BuMgCl·Et$_2$O and BuMgCl·Et$_2$O respectively, in toluene solutions. Data for complexes of such stoichiometry with respect to diisopropyl ketone were obtained in this work, and data for ether solutions were taken from previous work.[20] The enolization process recovering the ketone or yielding a ketone (in the case of esters) was a minor side-reaction. Other by-products could not be detected, either during the Grignard reaction or from the quenching of the reaction mixture. The use of internal standards in GC analysis made if feasible to calculate the material balance of the reaction. The sum of yields of addition, reduction, and enolization products was always 96–102%.

Data in Table 3 are the mean values obtained from several experiments. It is worth mentioning that the reagents prepared in the presence of the required amount of ether and those further supplemented by additions of the ether led to the same results within the experimental error (cf. also

Table 3. GC yields of addition and reduction products of the reaction between *n*-BuMgCl and carbonyl compounds in toluene[a] at −15 °C

Carbonyl compound	Molar ratio base to *n*-BuMgCl	Yield (%) Add/Red		
		THF	Et_2O	MTBE
Diisopropyl ketone[b]	0.5	59/39	70/28	63/35
	1.0	58/40	66/33	70/28
	Pure ether[c]	53/45	56/42	52/47
Benzaldehyde[d]	0.5	91/9	94/6	75/25
	1.0	89/11	95/5	81/19
	Pure ether	85/15	96/4	80/20
Methyl isobutyrate[e]	0.5	76/19	80/17	78/17
	1.0	80/16	79/16	81/15
	Pure ether	90/5	89/8	95/2
Methyl isobutyrate[e,f]	0.5	75/18	79/18	–
	1.0	78/16	78/18	–
Isopropyl isobutyrate[e]	0.5	92/7	94/4	92/6
	1.0	93/6	93/4	92/5
	Pure ether	90/5	94/5	90/6

[a] The molar ratio of Grignard reagent to ketone or aldehyde was 2:1 and to esters 3:1 unless indicated otherwise.
[b] Add: 2-methyl-3-isopropylheptane-3-ol; Red: 2,4-dimethylpentane-3-ol.
[c] Data from Ref. 19, temperature 0 °C.
[d] Add: 1-phenylpentane-1-ol; Red: benzylalcohol.
[e] Add: 5-isopropylnonane-5-ol; Red: 2-methylheptane-3-ol; enol: 2-methylheptane-3-one.
[f] The molar ratio of Grignard reagent to ester was 2:1.

Ref. 19). A detailed analysis of the data based on the solvation and dismutation equilibria in the reacting system will be published elsewhere. The practical implication of the results obtained so far is that partially solvated organomagnesium compounds can be used in the syntheses of alcohols tantamount to conventional Grignard reagents. In some cases, partially solvated reagents afford slightly better yields of the Grignard addition reaction.

CONCLUSIONS

Grignard reagents can be obtained in toluene in the presence of small amounts of organic bases. Diethyl ether proved to be the most effective donor, in that it affords Grignard reagents with a much smaller base content in comparison with other donors. Reagents with an average monosolvation can be prepared in good yields from primary and secondary chloroalkanes and chlorobenzene.

In the reactions investigated so far, the reactivity of partially solvated Grignard reagents in toluene considerably exceeds that of conventional Grignard reagents. The Grignard addition reaction with carbonyl compounds (ketones, aldehydes, esters) affords tertiary or secondary alcohols in comparable or even higher yields when partially solvated Grignard reagents are applied. When monosolvated Grignard reagents are suitable, diethyl ether, and THF can be replaced by the less expensive and less volatile MTBE.

Thus, difficulties associated with handling highly volatile and flammable solvents like THF and diethyl ether in large-scale organomagnesium synthesis can be mostly overcome by application of partially solvated Grignard reagents.

EXPERIMENTAL

Commercial reagents were carefully purified. The reagents and solutions were operated on under dry argon, and transferred by use of cannulas or syringes.

Preparation of Grignard reagents

The reagents were prepared in a flask equipped with a mechanical stirrer. The reaction vessel was charged with 3–4 g of magnesium turnings (Fluka, 99.8% Mg), 30 ml toluene, and the appropriate amounts of donor solvents. The magnesium metal was activated prior to use by dry heating with few milligrams of iodine. The reaction was initiated with a little of the halide dissolved in the donor and the rest was then added dropwise. The temperature was maintained slightly below the boiling point of the halide. The reaction was complete in 1–2 h.

When ultrasonic activation was applied, the mechanical stirrer was replaced by a titanium horn immersed in the reaction mixture. The ultrasound was generated by use of a probe disrupter UZDN-2T operating at 22 kHz. During sonication, the temperature of the reaction mixture was kept below 40 °C. Ultrasonic irradiation shortened the reaction time by a factor of two or more, but it did not influence the yields (the formation of Wurtz-coupling by-products).

Analyses of Grignard reagents

For analyses, approximately 2 ml samples were withdrawn from the vigorously stirred reaction mixture. For analysis of the supernatant solution the samples were centrifuged. The basic magnesium content was analysed acidimetrically, and the chloride ion concentration was by the Mohr method.

The yield of the Grignard reagent was estimated on the basis of the amount of unchanged halide (GC) and the extent of side reactions (from the R—Mg/Mg—Cl ratio). In control experiments, unreacted magnesium metal was separated, washed with dry ether, dried under reduced pressure, and weighed. All the results agreed satisfactorily (better than within 10%).

Kinetic measurements

Flasks equipped with magnetic stirrers and containing 15 ml of 1 M Grignard reagent were thermostatically controlled. To start the reaction, 0.1–0.2 ml of a silane was injected into each flask. At appropriate time points the reaction mixtures were quenched with iced water, the organic layer was separated, dried, and analysed by use of GC.

For investigation of a fast reaction the experiment was carried out in a thermostatic flask equipped with a magnetic stirrer and a thermistor. The thermistor was connected through a bridge circuit to a recording potentiometer. To a 20 ml sample of the Grignard reagent, 0.2 ml of silane was added and the temperature change of the reaction solution (about 3 °C by the end of the reaction) was recorded as a plot of temperature versus time. Use of a differential method for calculation of rate constants eliminated the contribution of heat exchange with the reaction vessel.

Determination of yields of reaction products

n-Butylmagnesium chloride was prepared in toluene using iodine-activated magnesium and *n*-butylchloride in the presence of a catalytic addition (about 0.01 mol of ether per mole of magnesium) of diethyl ether, THF, or MTBE and analysed. From the vigorously stirred reaction mixture, 5 ml aliquots of the suspension were withdrawn and transferred to 25 ml flasks sealed with serum caps. Calculated amounts of the ether were added and the reagents were left overnight or for at least 6 h. The samples were about 1.5 M in the Grignard reagent. Then, diisopropyl ketone or benzaldehyde in a molar ratio 1:2 (substrate to Grignard reagent), or an ester in a molar ratio 1:3, dissolved in toluene, was slowly added at −15 °C, and the mixtures were left overnight at room temperature. The solutions also contained *n*-nonane or *n*-decane, the internal standard for GC analyses.

The reaction mixtures were quenched at −15 °C by the dropwise addition of 10 ml of a 20% aqueous solution of NH_4Cl. The organic layer was separated and analysed on a Chrom-5 gas chromatograph (20% Carbowax 20 M on chromosorb W AW-DMCS), when the reactions with the ketone were investigated, and in other cases on a Varian 3700 gas chromatograph with a capillary column SGE BP 10 (0.3 mm × 24 m), with a flame ionization detector.

The reaction products were identified according to their spectra. The ^1H and ^{13}C NMR spectra were acquired on a Brucker AC 200 P spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. The mass spectra were recorded on a GC-MS Varian Star 3400 gas chromatograph with an Alltech ECONO-CAP EC-5 (SE-54) 0.25 mm × 30 m capillary column connected to a Finnigan MAT Magnum ion trap MS detector.

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