Ultrafast Grignard addition reactions in the presence of water

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Received 25th May 2010, Accepted 9th June 2010
First published as an Advance Article on the web 25th June 2010
DOI: 10.1039/c0ob00170h

The addition of allylmagnesium bromide and benzylmagnesium chloride to carbonyl compounds was investigated in the presence of protic reagents such as water and the rate of carbonyl addition was found to be comparable to the rate of protonation by the reagent.

The Grignard addition reaction is one of the most important organometallic transformations for forming a carbon–carbon bond.[1] The reaction between an organomagnesium halide and a carbonyl compound is performed under strictly anhydrous conditions in an ethereal solution (usually diethyl ether or THF). The exclusion of water is crucial since the protonation of the Grignard reagent is believed to be almost instantaneous. Therefore it is surprising that quantum mechanics calculations for the reaction of allylmagnesium bromide with water and acetone have suggested similar activation energies towards protonation and addition.[2] In these calculations, however, the addition is based on a polar mechanism and allyl Grignard is believed to add by a single electron transfer mechanism.[3] One of us have measured the rate for the reaction between allylmagnesium bromide and acetone by competition kinetics and found that allyl Grignard adds 1.5×10^5 times faster than the corresponding butyl reagent.[4] In fact, allylmagnesium bromide reacts with acetone at a rate which is near the diffusion controlled maximum. Since the addition reaction is extremely fast it may be able to compete with the protonation by a protic (co)solvent such as water. It should also be noted that the one-pot reaction between allyl bromide, magnesium metal and benzaldehyde in aqueous media gives rise to the addition product in moderate to good yields (Barbier conditions).[5] The mechanism is believed to involve a rate-determining single electron transfer reaction to the aldehyde,[5,6] but it is not known whether an allylmagnesium halide is actually formed under these conditions. Based on these observations we decided to compare the rate of addition to the rate of protonation by several Grignard reagents especially allyl Grignard.

The first experiments were carried out with allylmagnesium bromide in diethyl ether (containing octane as an internal standard) which was mixed with an equimolar mixture of acetone and water in diethyl ether.† Remarkably, the yield of the addition product was found to be around 90% (Table 1, entry 1 and 2) indicating that the addition reaction should be much faster than the protonation of the reagent. Since the result was unexpected the investigation was widened to include a number of Grignard reagents reacting with a number of protic reagents.

When allylmagnesium bromide was reacted with acetone in the presence of alcohols or benzoic acid yields of the addition products were in the 52–63% range indicating a higher degree of protonation (entries 3–5). Similar results were obtained when benzaldehyde was used as the carbonyl compound. The best result was obtained with water as the proton source giving 75% yield of the addition product (entry 6) while methanol, phenol and benzoic acid gave yields around 42–63% (entries 7–10). Methyl benzoate, acetophenone and *p*-methoxybenzaldehyde furnished moderate yield of the addition product in competition with water, methanol and phenol (entries 11–15). With methyl benzoate only double addition to afford the tertiary alcohol was observed and the intermediate ketone was not detected. Besides allylmagnesium bromide, benzylmagnesium chloride also reacted sufficiently fast with acetone and benzaldehyde to compete to a certain degree with protonation by water and alcohols (entries 16–22). Butylmagnesium bromide, on the other hand, yielded only trace amounts of the addition products in similar reactions (entry 23 and 24).

From these experiments it is clear that for allylmagnesium bromide the addition to acetone is faster than the protonation by water. The addition to other types of carbonyl compounds such as benzaldehyde, methyl benzoate and acetophenone seem to be slower. Surprisingly, a reversal in reactivity is observed with benzylmagnesium chloride which adds effectively to benzaldehyde in competition with protonation by water while the reaction with acetone is slower. Butylmagnesium bromide, as anticipated, undergoes complete protonation in competition with carbonyl addition.

The reactivities in acetone–water mixtures can be rationalized by the different reactivities of the three Grignard reagents. For allylmagnesium bromide the halftime for addition to acetone has been established to be around one µs.[4] There is no similar value available for benzylmagnesium chloride, but from the known rate constant for benzylmagnesium bromide[7] and an estimated 10 fold increase on going from the bromide to the chloride[8] it must be assumed that the halftime for the addition is about one ms. For butylmagnesium bromide the halftime for addition to acetone is almost one s.[7] Thus for the extremely reactive allyl Grignard reagent addition competes effectively with protonation while with the less reactive reagents protonation becomes the predominant reaction. However, there are still some inconsistencies in Table 1 which needs to be further addressed particularly why alcohols are better proton sources than water and why protonation seems to be more favoured at higher dilution.

In this regard, it has been shown that in the case of Grignard reagents, competition kinetics do not always give the correct ratio between two reacting reagents competing for a single substrate or when two substrates compete for a single reagent.[4] When a highly reactive reagent is tested in competition with a less reactive reagent the ratios found tend to be statistically controlled (by the relative concentrations) rather than kinetically controlled

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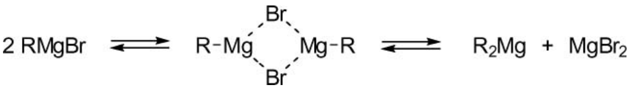
Table 1 Yield of addition product in the reaction of Grignard reagents with carbonyl compounds in the competition with protic compounds†

Entry	Grignard Reagent (0.1 M)	Carbonyl Compd (0.6 M)	Protic Compd (0.6 M)	Yield [a](%)
1	$CH_2=CHCH_2MgBr$	CH_3COCH_3	H_2O	91
2	$CH_2=CHCH_2MgBr^b$	CH_3COCH_3	H_2O	90
3	$CH_2=CHCH_2MgBr$	CH_3COCH_3	CH_3OH	56
4	$CH_2=CHCH_2MgBr$	CH_3COCH_3	C_2H_5OH	63
5	$CH_2=CHCH_2MgBr$	$CH_3COCH_3{}^c$	$C_6H_5COOH^c$	52
6	$CH_2=CHCH_2MgBr$	C_6H_5CHO	H_2O	75
7	$CH_2=CHCH_2MgBr^d$	C_6H_5CHO	CH_3OH	53
8	$CH_2=CHCH_2MgBr$	$C_6H_5CHO^e$	CH_3OH^e	42
9	$CH_2=CHCH_2MgBr^f$	$C_6H_5CHO^g$	$C_6H_5OH^g$	43
10	$CH_2=CHCH_2MgBr$	C_6H_5CHO	C_6H_5COOH	63
11	$CH_2=CHCH_2MgBr^f$	$C_6H_5COOCH_3$	H_2O	56
12	$CH_2=CHCH_2MgBr^f$	$C_6H_5COOCH_3$	CH_3OH^h	40
13	$CH_2=CHCH_2MgBr^f$	$C_6H_5COOCH_3$	C_6H_5OH	47
14	$CH_2=CHCH_2MgBr^f$	$C_6H_5COCH_3$	C_6H_5OH	31
15	$CH_2=CHCH_2MgBr$	p-$CH_3OC_6H_4CHO$	C_6H_5OH	35
16	$C_6H_5CH_2MgCl$	CH_3COCH_3	H_2O	30
17	$C_6H_5CH_2MgCl^b$	CH_3COCH_3	H_2O	14
18	$C_6H_5CH_2MgCl$	C_6H_5CHO	H_2O	89
19	$C_6H_5CH_2MgCl$	C_6H_5CHO	CH_3OH	63
20	$C_6H_5CH_2MgCl$	C_6H_5CHO	C_2H_5OH	46
21	$C_6H_5CH_2MgCl$	C_6H_5CHO	C_6H_5OH	29
22	$C_6H_5CH_2MgCl$	p-$CH_3OC_6H_4CHO^i$	$C_6H_5OH^i$	18
23	$CH_3(CH_2)_3MgBr$	CH_3COCH_3	H_2O	2
24	$CH_3(CH_2)_3MgBr$	C_6H_5CHO	CH_3OH	0

[a] GC yield. [b] 0.01 M. [c] 0.34 M. [d] 0.25 M. [e] 0.5 M. [f] 0.16 M. [g] 0.3 M. [h] 1.2 M. [i] 0.2 M.

(by the reactivities). As originally explained by Francis[9] the cause is that in "the meeting zone" when the solutions get in contact, the highly reactive reagent gets depleted locally. This gives the less reactive reagent a chance to get more than its fair share of the substrate. In the case of a water–acetone mixture meeting a Grignard reagent the possibility exists of water being removed by the Grignard reagent leaving acetone in dry diethyl ether ready to be attacked by unreacted Grignard reagent. It is impossible to predict the importance of this "depletion" or "scavenging" effect since it depends both on the concentrations used, on the method of mixing, and on the nature of reaction products. The effect tends to be smaller with higher dilution and could explain the higher degree of protonation in more dilute mixtures.

It should also be noted that a Grignard reagent is a combination of alkylmagnesium halide and dialkylmagnesium (and more complex oligomeric species) in a Lewis donor solvent. The ligands around magnesium exchange rapidly and the Schlenk equilibrium (Scheme 1) is positioned differently in weakly or strongly donating solvents, *e.g.* it is shifted from left to right by adding THF to an ethereal solution of an alkylmagnesium halide.[1a] The shift in the position of the Schlenk equilibrium is a result of small differences in the Lewis acidity of the various components which decrease in the order: $MgBr_2 > RMgBr \gg R_2Mg$. The complexation energy of one water molecule to allylmagnesium bromide has been calculated to -23.1 kcal mol^{-1} which reflects the strong Lewis acidity of the metal in the Grignard reagent.[2] While the overall Schlenk equilibrium is fast but measurable, the rate of ligand exchange around the individual magnesium atoms must be assumed to be diffusion controlled.



Scheme 1 The Schlenk equilibrium.

In all the experiments reported in this work the Grignard reagents are added to an excess of the two competing substrates (inverse addition). When the competition is between a carbonyl compound and water, it seems indicated that water will coordinate to magnesium. If coordinated water is less reactive in the protonation reaction, addition to the carbonyl group will be more favoured. Since alcohols coordinate less effectively to magnesium it will also explain the higher degree of protonation when Grignard reagents are competing with alcohols than with water.

The deactivation should be caused by coordination of water to any electrophilic magnesium compound, magnesium bromide inclusive. It was therefore decided to repeat the addition to acetone with extra magnesium bromide added. In fact, when allylmagnesium bromide was mixed with one equivalent of magnesium bromide and then added to an equimolar mixture of acetone and water, the yield of the addition product was quantitative. This is a pronounced increase compared to the 91% yield in Table 1, entry 1 and confirms that magnesium compounds may serve as water scavengers to some extent in fast Grignard addition reactions. The same was observed when allylmagnesium bromide with one equivalent of magnesium bromide was added to an equimolar mixture of benzaldehyde and water. In this case, 85% yield of the addition product was obtained which should be compared to 75% in the absence of added magnesium bromide (Table 1, entry 6)

A method to avoid the scavenging effect is to include the two competing groups in the same molecule giving them identical chances for meeting a reactive R–Mg entity in an intramolecular competition. We therefore made a series of experiments in which we reacted a Grignard reagent with bifunctional substrates containing both a hydroxy group and a carbonyl group. The results are shown in Table 2.

Table 2 Yield of addition product in the reaction of Grignard reagents with carbonyl compounds containing a hydroxyl group†

Entry	Grignard Reagent	Bifunctional Compd	Yield[a] (%)
1	0.16 M $CH_2{=}CHCH_2MgBr$	0.3 M p-HOC_6H_4CHO	5
2	0.16 M $CH_2{=}CHCH_2MgBr$	0.3 M m-HOC_6H_4CHO	30
3	0.16 M $CH_2{=}CHCH_2MgBr$	0.3 M o-HOC_6H_4CHO	0
4	0.16 M $CH_2{=}CHCH_2MgBr$	0.3 M p-$HOC_6H_4COCH_3$	13
5	0.16 M $CH_2{=}CHCH_2MgBr$	0.3 M p-$HOC_6H_4COOCH_3$	2
6	0.1 M $C_6H_5CH_2MgCl$	0.4 M p-HOC_6H_4CHO	0
7	0.1 M $C_6H_5CH_2MgCl$	0.4 M m-HOC_6H_4CHO	0
8	0.1 M $C_6H_5CH_2MgCl$	0.4 M p-$HOC_6H_4COCH_3$	0
9	0.2 M $CH_2{=}CHCH_2MgBr$	0.4 M C_6H_5COOH	18
10	0.1 M $CH_2{=}CHCH_2MgBr$	0.25 M $CH_3(CH_2)_6COOH$	9
11	0.1 M $C_6H_5CH_2MgCl$	0.2 M C_6H_5COOH	0

[a] GC yield.

From the table it is clear that the intramolecular competition gives results that are different from the results in the intermolecular competition. With both allylmagnesium bromide and benzylmagnesium chloride a higher degree of protonation is observed in the intramolecular competition. When allylmagnesium bromide was reacted with a mixture of *p*-methoxybenzaldehyde and phenol, the addition/protonation ratio was 35 : 65 (Table 1, entry 15). However, when the same reagent was added to *p*-hydroxybenzaldehyde the ratio was 5 : 95 (Table 2, entry 1). Similar allyl Grignard reactions with other hydroxy carbonyl compounds (entries 2–5) also gave lower yields of the addition product than in Table 1. When benzylmagnesium chloride was reacted with a mixture of *p*-methoxybenzaldehyde and phenol, the addition/protonation ratio was 18 : 82 (Table 1, entry 22). With *p*-hydroxybenzaldehyde as the substrate the ratio was zero (Table 2, entry 6) indicating that the rate of protonation of benzylmagnesium chloride by the hydroxy group is more than hundred times faster than the addition to the aldehyde. The higher degree of protonation in these intramolecular competition experiments confirm that the protic reagent in the intermolecular competition experiments is scavenged to some degree by the magnesium salts.

Similar results are obtained with benzoic acid and octanoic acid, which can also be considered as bifunctional substrates with both a hydroxy group and a carbonyl group (entries 9–11). With allylmagnesium bromide only double addition was observed to afford the tertiary alcohol and the intermediate ketone was not detected. Since the oxygen–hydrogen bond is broken in the protonation reaction a primary deuterium isotope effect might be expected. Experiments with the reaction between allylmagnesium bromide and deuterated benzoic and octanoic acid, however, showed no significant changes in the product distributions from those obtained with the non-deuterated acids. The ultrafast reactions most likely have early transition states in which case the k_H/k_D will be close to 1.0.

In conclusion, we have shown that the rate of carbonyl addition may compare with the rate of protonation for two highly reactive Grignard reagents. When the Grignard reagents are added to an excess of two competing substrates of which one has a carbonyl group and the other a hydroxy group rather high yields of the addition products may be obtained (intermolecular competition). This is seen especially with allylmagnesium bromide, but also to some extent with benzylmagnesium chloride while butylmagnesium bromide does not undergo carbonyl addition in the presence of protic reagents. The phenomenon is caused to some degree by a scavenging effect from electrophilic magnesium compounds which remove water or other hydroxy compounds by complexation and leave the carbonyl compound free to react with the alkylmagnesium reagent. When the competition is carried out in an intramolecular fashion with substrates containing both a carbonyl group and a hydroxy group the scavenging effect is absent and only allylmagnesium bromide is able to form the addition product in low to moderate yield.

Notes and references

† **General procedure for competition experiments:** Allylmagnesium bromide and benzylmagnesium chloride were prepared under argon in diethyl ether (distilled from benzophenone ketyl) from reagent grade magnesium by slow addition (6 h) of distilled allyl bromide and benzyl chloride. Solutions of the Grignard reagent (10 mL) and the substrates (10 mL) were prepared separately in 20 mL syringes which were connected with a polyethylene capillary tube. The Grignard solution contained 1 mol of octane per mol of Grignard reagent as an internal standard. The Grignard reagent was pressed into the syringe with the substrate solution within 2–3 s. The heterogeneous reaction mixture was shaken with saturated ammonium chloride solution and the organic layer isolated. The solution was analysed by quantitative GC and the peaks for the products were measured relative to the peak for octane. To obtain complete conversion the Grignard solution was reacted with an excess of the substrate mixture. Each experiment was repeated twice and the average yield reported in Tables 1 and 2.

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