9102 *J. Am. Chem. Soc.* **1998,** *120,* 9102−9103

Unexpected Barbier−Grignard Allylation of Aldehydes with Magnesium in Water

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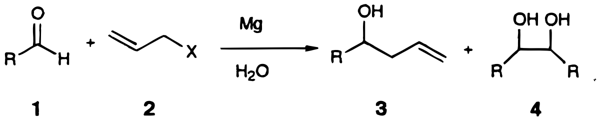
Received March 26, 1998

An important step in the history of modern chemistry was the introduction of magnesium for carbon−carbon bond formations[1] by Barbier and Grignard about a century ago,[2] through the addition of an organometallic reagent to a carbonyl group. The study of magnesium-based reactions since then has sparked the development of new reagents based on electronically more negative and more positive metals as well as semi-metallic elements for various synthetic purposes to tailor reactivities and selectivities (chemo, regio, and stereo).[3] For carbonyl additions based on organomagnesium reagents, it is generally accepted that strict anhydrous reaction conditions are required for a smooth reaction.[4] The presence of moisture inhibits the reaction. Various methods, such as using dibromoethane[5] or iodine initiators, mechanical activation[6] and ultrasonic irradiations,[7] have been developed to help initiate the reaction. More recently activated magnesium has also been developed.[8] Because of economical and environmental concerns, the use of water as a solvent for metal-mediated carbon−carbon bond formations has generated considerable interests. Within the last several years, various metals have been developed to mediate Barbier−Grignard-type reactions.[9] For a long time, we have been intrigued by the possibility of performing classical Barbier−Grignard reactions by using magnesium in water. The study would possibly extend the scope of aqueous metal reactions as well as increase the understanding of the mechanism of the classical Barbier−Grignard reaction. However, in view of the high reactivity of organomagnesium reagents toward water, it is doubtful that magnesium could be used for such a purpose. Nevertheless, this question has constantly haunted our minds and led us to test the magnesium-mediated allylation reaction of benzaldehyde in water. Historically, the allylation of carbonyl compounds with allylmagnesium reagents had not been well-established for decades until Gilman and McGlumphy developed a new procedure to prepare Grignard reagents from allyl halides.[10] Herein we report the observation that Barbier−Grignard allylation of aldehydes (**1**) with magnesium and allyl halides (**2**) proceeds smoothly in water (eq 1).



(1)

To start our investigation, we reacted allyl bromide with benzaldehyde and magnesium turnings in 0.1 N aqueous HCl for 3 h at room temperature. TLC analysis of the ether extract clearly showed a spot that corresponds to the desired allylation product. Subsequently, ^{1}H NMR measurement of the crude reaction mixture showed about 28% of the allylation product (**3**), together with 66% of the pinacol coupling product (**4**),[11] and 6% benzyl alcohol. This promising result prompted us to examine factors that influence the reaction. We then examined in greater detail the effect of the solvent system on the magnesium reaction by using various combinations of water and THF as the reaction solvent together with a small amount of iodine to initiate the reaction. Workup of the reactions involved extraction with diethyl ether, drying over magnesium sulfate, and careful removal of the low boiling solvent in vacuo. In the case where no organic cosolvent was involved, the reaction mixture was extracted with $CDCl_3$ and the extract was examined directly. ^{1}H NMR spectra of the reaction products under various solvent combinations revealed a very interesting phenomenon. The results are listed in Table 1. In freshly distilled THF dried over sodium/benzophenone, the reaction between benzaldehye, allyl bromide, and magnesium turnings together with a small amount of iodine occurred almost quantitatively, generating the expected allylation product. The addition of a small amount of water to the freshly dried THF did not affect the progress of the reaction. The expected reaction proceeded effectively until about 7% of water in THF was used, which suddenly blocked the reaction progress. After repeating several times, we identified a midpoint (entry 4) at which ca. 56% conversion of the starting benzaldehyde was oberved. However, when the composition of the solvent is changed to water alone, a smooth reaction started again, generating the allylation product albeit with a low conversion. The low conversion could be attributed to the formation of magnesium hydroxide on the metal surface which blocks further reactions. Additional reactions using 0.1 N HCl or NH_4Cl solutions as the reaction solvent gave a quantitative conversion, generating a mixture of the allylation and pinacol coupling products. Other aromatic aldehydes gave similar results; whereas reactions of aliphatic aldehydes gave more complicated mixtures. The use of 0.1 N NH_4Cl aqueous solution as the solvent was found to be superior to the use of 0.1 N HCl. The use of a catalytic amount of $InCl_3$ did not affect the reaction.[12] Changing the allyl bromide to allyl iodide further increased the formation of the allylation product (58%). Only a minute amount of the allylation product was observed with allyl chloride. In the absence of HCl, NH_4Cl, or iodine, virtually no reaction was observed with allyl bromide. Experiments revealed that, with iodine, the reaction of allyl bromide proceeded through an allyl iodide intermediate. The formation of such an allyl iodide intermediate, however, is not necessary in 0.1 N NH_4Cl or 0.1 N HCl.

To explain the unusual phenomenon of the solvent change, we postulate that in freshly dried THF, the normal reaction occurs between the organo halide and magnesium generating the

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S0002-7863(98)01020-8 CCC: $15.00

Table 1. Magnesium−Mediated Barbier−Grignard Allylation of Benzaldehyde in Various Solvents[a]

entry	allyl halide	solvent	mediator	**3**/**4**/benzyl alcohol	conversion (%) of aldehyde
1	allyl bromide	THF/H_2O (10:0.04)	Mg/I_2	100%/0/0	quantitative
2	allyl bromide	THF/H_2O (10:0.2)	Mg/I_2	100%/0/0	quantitative
3	allyl bromide	THF/H_2O (10:0.55)	Mg/I_2	98%/0/0	98
4	allyl bromide	THF/H_2O (10:0.67)	Mg/I_2	9%/43%/4%	56
5	allyl bromide	THF/H_2O (10:0.7)	Mg/I_2	0/0/0	0
6	allyl bromide	H_2O	Mg/I_2	13%/2%/1%	16
7	allyl bromide	0.1 N HCl	Mg/I_2	28%/66%/6%	quantitative
8	allyl bromide	0.1 N NH_4Cl	Mg	41%/52%/7%	quantitative
9	allyl iodide	0.1 N NH_4Cl	Mg	58%/34%/8%	quantitative

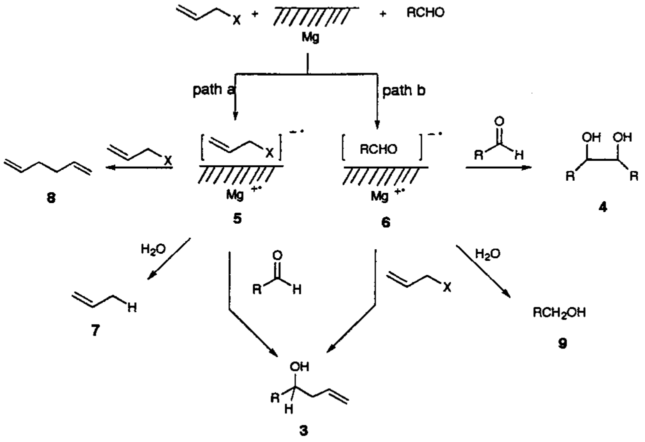
[a] Entries 1−6: benzaldehyde:allyl halide:magnesium = 1:3:20. Entries 7−9: benzaldehyde:allyl halide:magnesium = 1:3:10 (the use of a stoichiometric amount of magnesium resulted in a low conversion).

magnesium reagent. Subsequent reaction with carbonyl compounds generates the allylation product. However, in a homogeneous mixture of THF and water, the water molecule would be evenly distributed throughout the solution; hence the contact between water and the metal surface would prohibit the formation of the organomagnesium reagent. The solvent system with ca. 7% water may correspond to the point where the surface is completely covered by water molecules. With water alone, allyl bromide might be squeezed on to the metal surface due to hydrophobic effect;[13] locally and microscopically, magnesium would not be in direct contact with water. The formation of allylmagnesium can thus occur as in dry organic solvents, which leads to the generation of allylation products.

The mechanisms of magnesium mediated Barbier and Grignard reactions have been studied intensively by several groups.[14,15] It is generally believed that radicals on the metal surface are involved in the organomagnesium reagent formation reaction.[14] There is still no conclusion as to the freedom of these free radicals.[15] To gain mechanistic information of the present reaction, we quenched the allylation process in 0.1 N aqueous NH_4Cl. The reaction mixture was extracted with $CDCl_3$ and the ^1H NMR spectrum was taken directly. The measurement shows the formation of the three products (allylation, pinacol, and benzyl alcohol) reflecting our previous experiments. In addition, 1,5-hexadiene was clearly formed. However, no propene formation was detected with NMR.[16] To explain the experimental observations, we tentatively proposed Scheme 1. The transfer of electrons from magnesium to the allyl halide (path a), the aldehyde (path b), or both generates the corresponding radical anions **5** and **6**. Then, reaction of either **5** with the aldehyde or **6** with the allyl halide generates the corresponding allylation product **3**. Reaction of **5** with the allyl halide gives the Wurtz-coupling product **8**; reaction of **6** with the aldehyde gives pinacol product **4**. The reaction of these radical anions with water led to the corresponding reduced products **7** and **9**. Subsequent experiments show that in the absence of the allyl halide, the corresponding pinacol coupling product **4** was obtained.

Alternatively, the reaction of allyl bromide on the metal surface generates an organometallic intermediate that is in an equilibrium with the charge-separated form and the radical form as proposed by Alexander.[17] These two forms will also lead to either the protonation of the carbanion (overall reduction of the halide) or Wurtz-type coupling;[18] whereas the intermediate reacts with aldehydes through the usual six-membered-ring mechanism as proposed by Young and Roberts[19] (represented by the symbol S_E2').[20] The radical intermediate leads to the formation of 1,6-hexadiene, pinacol product, and benzyl alcohol.[21] A detailed exploration of the origin and synthetic utilities of this magnesium-mediated reaction are under investigation.

Scheme 1. Postulated rationale for magnesium mediated carbon-carbon bond formation in water



Acknowledgment. We are grateful to the support provided by the NSF-EPA joint program for a Sustainable Environment. Acknowledgment is also made to the donors of the Petroleum Research Fund (administered by the American Chemical Society), LEQSF, and the NSF CAREER Award program for partial support of this research. We also thank Prof. H. Ensley for discussions and the anonymous reviewers for their suggestions.

Supporting Information Available: Experimental procedures for the magnesium mediated allylation of benzaldehyde in water (1 page, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981020S

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