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Activation of Mg Metal for Safe Formation of Grignard Reagents on Plant Scale

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Abstract:

A general and reliable method for the activation of magnesium metal for the formation of various kinds of Grignard reagents has been developed. Utilizing diisobutylaluminum hydride (DIBAH) for the activation of the surface and drying of the reaction mixture the initiation of the Grignard reagent formation can be performed at or below 20 °C for aryl Grignard reagents. For alkyl bromides it is possible to activate the magnesium turnings at even lower temperatures. As the temperature is well below the boiling point of THF, it is possible to detect the initiation of the reaction through the temperature rise. The initiation method was found to be reliable also under very diluted reaction conditions as long as the reaction mixture was stirred. We have also shown that with this method it is possible to manufacture Grignard reagents well below the boiling point of THF.

Introduction

The Grignard reaction is one of the most significant organometallic reactions, which can be determined from the following quotation; ”... every chemist has carried out the Grignard reaction at least once in his lifetime...”.[1,2] The Grignard reaction has, over the years, become extremely versatile. In the fine chemical and the pharmaceutical industry the use of the Grignard reaction has been state of the art for more than 40 years. Despite this long period of large-scale use of the reaction one part remains still unsatisfactory, at least in the pharmaceutical industry, and that is the activation of the magnesium metal for the formation of the Grignard reagent. The main hazard associated with the manufacture of Grignard reagents occurs at the initiation stage. If the addition of the halide is continued before the initiation takes place, the reaction will have the potential for a run-away situation after a later initiation of the reaction.[3] On production scale, engineers are faced with significant safety challenges. Recently, real-time online analytical analysis with FTIR has been shown to provide valuable information for a safe generation of a Grignard reagent on industrial scale.[3]

It is known that under completely dry conditions the formation of the Grignard reagent starts without an induction period. In commercial-scale equipment, drying is very difficult because the equipment is large and the piping is very complex.

Grignard reagents are normally prepared through addition of an organic halide into a stirred suspension of magnesium turnings in diethyl ether or THF. On large scale this can mean between 5 and 20 vols of ether with regard to magnesium, depending on the stirrer and reactor type, which actually means that more or less only the solvent is stirred and the turnings move around slightly. The reaction occurs on the surface of the turnings.[4] After the Grignard reagent forms on the reactive metal surface, it dissolves away from the site and sets the site free, exposing it to the organic halide. After the initiation stage of the reaction, mass transfer of the organic halide to the reactive site is considered to be the rate-limiting step.[5] The magnesium of the Grignard reagent is two electron pairs short of an octet, but the oxygen in the ether can donate these electrons. This explains why ether solvents are required at least partly for the formation of Grignard reagents. The stabilization of phenylmagnesium bromide by two diethyl ether molecules was proven by the crystallization of the complex.[6] On industrial scale diethyl ether is critical due to the low autoignition temperature and peroxide formation.

At Schering AG the standard method over decades has been the activation with iodine, which is one of the earliest catalysts for the formation of Grignard reagents.[7] As the activation has to be performed under reflux conditions, the temperature remains relatively constant and therefore cannot be used to determine initiation. In the laboratory initiation of a reaction run at reflux is often confirmed by observation of increased foaming or vigorous bubbles emanating from the magnesium chips, in addition to a darkening of the solution. These visual observations are often difficult to ascertain on large industrial scale. The method was replaced around 1990 with the entrainment method using 1,2-dibromoethane as activator, which was found to be more reliable than the activation with iodine (Scheme 1).

For the activation with 1,2-dibromoethane it was no longer necessary to reflux the reaction mixture to activate the metal surface, but the entrapment method is still rather unreliable. The activation is performed through addition of 5 mol % of 1,2-dibromoethane to magnesium in 2 vols of THF with regard to magnesium. This mixture is heated to 50−55 °C and 10% of the *p*-(dimethylamino)phenyl bromide dissolved in THF is added. The unstirred mixture is carefully con-

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(1) Silverman, G. S., Rakita, P., Eds. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996.

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(5) Yue, Sharkey; Leung *J. Loss Prev. Process Ind.* **1994**, *7*, 413.

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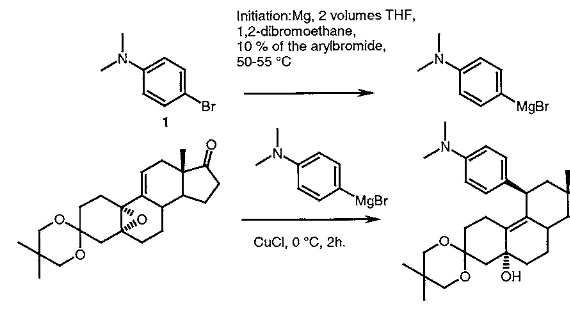
Scheme 1



trolled; when the reaction starts, 10 vols of THF is added, the stirring is turned on, and the cooling is started to keep the solvent from boiling off. The addition of the phenylbromide is thereafter continued. On several occasions problems occurred in the pilot plant with the initiation. Although more activator was added, the reaction did not initiate even with stirring at this high temperature for several hours.

Over the last 3 to 4 years the regulations established by the authorities have strengthened the protection of employees handling carcinogenic or suspected carcinogens such as 1,2-dibromoethane.

To overcome the requirement for this carcinogenic initiator and the hazardous initiation conditions involved in the activation with 1,2-dibromoethane it was decided to look for a new method which could be performed in a multipurpose reactor. The ideal method for the chemical initiation should be reliable, the initiation should not be performed with carcinogenic reagents, the initiation should preferably be performed below the boiling point of the etheral solvent, and it should be robust against a varying moisture content of the solvent.

Reported Methods for Magnesium Activation. The first step was to screen the literature for various methods for the initiation of the formation of the Grignard reagent especially those that have been reported for use in large scale.

Different Forms of Magnesium. Magnesium can take a variety of different physical forms: turnings, powder chips, and finely divided metal. Each form offers advantages and disadvantages. Turnings are easy to handle but can cause abrasiveness to glass-lined reaction vessels if stirred over a longer time. Powdered magnesium is more reactive but is more quickly oxidized on the surface and can be pyrophoric. Magnesium chips have a high purity, but the surface area is smaller than that for turnings, which results in less reactivity. In 1972 Rieke and associates[8] reported a general approach for preparing highly reactive metal powders by reducing metal salts with alkali metals. Rieke magnesium has been obtained from reduction of $MgCl_2$ in THF with potassium. The magnesium salt has to be anhydrous. Potassium metal is difficult to handle on large scale, and the prepared Rieke magnesium is also very pyrophoric.

Removal of Oxide Layers. Since Grignard reactions with organic bromides and iodides are diffusion-controlled after their initiation, the reaction rate is directly proportional to the available metal surface area.[9] The simplest "trick" for enforcing the initiation of magnesium-induced reaction by increasing the active metal surface is removal of the oxide layer through washing with a mineral acid. Although the removal of oxide layers by washing with a mineral acid will increase the active surface area, the removal of the acid and water is extremely difficult on industrial scale.

Dry Stirring of the Magnesium Turnings. Some reports have appeared in the literature on activation by stirring the magnesium turnings in an inert atmosphere. During stirring the oxide layer on the magnesium turnings is reduced, leaving the activated metal surface. For instance, the method was used for the synthesis of the Grignard reagent from *p*-(dimethylamino)phenyl bromide (**1**).[10] It was reported that this method gave a more reliable initiation of the reaction in comparison to standard techniques.

This method was never used at Schering for large-scale activation due to possible abrasiveness to the glass-lined reactor and because no reactor is fitted with a low stirrer.

Equipment Drying. On a laboratory scale, equipment drying does not present a significant challenge. Equipment drying is the largest impediment to the initiation of the reaction on large scale, given the large equipment and the complicated piping. In addition, it must be kept in mind that the surfaces of equipment, even if they appear to be completely dry, are often covered with a thin film of water. To ascertain a safe initiation, the equipment is usually dried through multiple solvent rinsings to a water content below 0.02%; afterwards the equipment is blown dry with inert gas and kept under a slightly positive pressure to ensure that it remains dry.

Prior to performing these drying operations, it is necessary that the ingoing solvent meet the final water specification. Dry THF can be purchased (water content <0.01%); however without special precautions, the solvent often picks up moisture to a level of 0.1%. To reduce the level back to 0.01%, recycling over molecular sieves has been reported to be necessary.[2]

Small Portion of the Grignard Reagent. An excellent method for initiation is the addition of a small portion of the Grignard reagent from a previous batch. The method immediately dries the system. This method has the advantage of being indigenous to the process; therefore, new chemical impurities are not a concern. A disadvantage is that the first batch in a campaign cannot be started using this method and if a previous batch has had an out-of-specification result it can affect the next one.[1]

Vitride. Vitride (sodium bis(2-methoxyethoxy)aluminum hydride) is a reducing agent which has been shown to activate magnesium.[11] It quantitatively removes moisture, alcohols, and peroxides, and it activates the metal surface. The activation is performed through addition of the hydride reagent (5−12 mol %) to magnesium metal in boiling ether prior to the addition of the organic halide, or through addition of the hydride to the etheral solvent which after the drying is distilled into the reactor with magnesium turnings. The

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(8) (a) Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94,* 7178. (b) Rieke, R. D.; Bales, S. E. *J. Chem. Soc., Chem. Commun.* **1973**, 879. (c) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96,* 1775.

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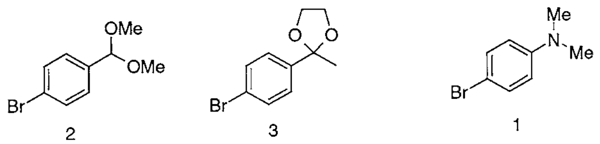
Scheme 2



method has also successfully been used for the activation of the zinc metal surface of zinc cubicles for a large-scale Simmons−Smith reaction.[12]

The Vitride method seemed to us to be the most interesting method for the initiation, and it was decided to adopt this method for our purposes.

Results and Discussion

In the report[11] also DIBAH diisobutylaluminum hydride was mentioned as being suitable. DIBAH reacts in the same way as Vitride with moisture, alcohols, and peroxides. The diluted 20% solution of DIBAH in toluene or hexane is easier to handle than the 65% sodium bis(2-methoxyethoxy)-aluminum hydride in toluene (Vitride). DIBAH does not have the limitation from Vitride where the 2 mol equiv of released methoxyethanol react with the formed Grignard reagent.

In our study we investigated the behavior of three different aryl bromides 4-bromobenzaldehyde dimethylacetal (**2**), 4-bromoacetophenone ethylene ketal (**3**), and 4-(dimethylamino)bromobenzene (**1**) from different projects (Scheme 2).

For the study the water content of THF was measured and found to be 0.05%. This water content is easily obtained through distillation of THF. In the first experiments the amount of DIBAH, which is necessary to initiate the reaction with normal water content of THF, was determined. It was found that at a level of 1 mol % of DIBAH per mol Mg a reliable initiation of the formation of the Grignard reagent takes place. In a series of experiments it was determined that after the addition of DIBAH to the mixture of magnesium and aryl bromide the initiation of the reaction had already taken place during warming to 50 °C. It was than decided to investigate if the reaction can also be initiated at 20 °C. This was then actually the case even with 4-bromo-*N*,*N*-dimethylaniline, previously reported as being notoriously difficult to initiate.[1] As this gives a possibility to activate the magnesium under safer conditions, it was decided to perform a series of experiments to determine the time it takes to initiate the reaction with magnesium turnings in various amounts of THF. The temperature rise of the reaction mixture when 5 mol % of the aryl bromide is added to the system prior to the addition of 1 mol % of DIBAH was also investigated. During the investigation no external cooling was used. The results of this investigation are summarized in Table 1. As these experiments were done using normal laboratory equipment, the obtained data are only indicative. For safety evaluation each formation of a new Grignard reagent should be investigated in a reaction calorimeter also when using this activation method, as the reaction calorimetry is independent of the activation method, and also when the formation is performed well below the boiling point of the solvent.

From the investigation it was found that the initiation time is dependent on the amount of THF. With 5 vols of THF with regard to magnesium the initiation was in all cases more or less spontaneous. In all studied cases the reaction started within 30 min except in the case with *p*-(dimethylamino)-phenyl bromide (**1**) with 30 vols of THF. In this case addition of a second mol % of DIBAH caused an immediate initiation of the reaction.

Furthermore the temperature rise is dependent on the amount of solvent. In every case also with 5 vols of THF with regard to magnesium the internal temperature in the reaction flask did not reach the boiling point of THF. The adiabatic temperature rise should be studied in a reaction calorimeter for each new Grignard reagent formation with different amounts of organic halide and solvent to ascertain a safe scale-up.

In every case also with 30 vols of THF it was possible to easily detect the increase in temperature. For 30 vols of THF the increase was 6 and 11 K.

From each aryl bromide the yield of the corresponding Grignard reagent was determined through hydrolysis and GC. The Grignard reagent 4-bromodimethylaniline (**1**) was obtained in 87% yield, from 4-bromobenzaldehyde dimethyl acetal (**2**) the yield was 92%, and from 4-bromoacetophenone ethyleneketal (**3**) the yield was 95%.

To ascertain that no accumulation of the aryl bromide occurs during the reaction, the addition of the remaining aryl bromide was started after the temperature from the initiation had reached its maximum.

For the reliability of the method one experiment with 4-bromobenzaldehyde dimethyl acetal (**2)** in 20 vols of THF was performed five times (see Table 1). In all cases the reaction started between 4 and 10 min after addition, and the maximum temperature was between 33 and 37 °C.

The effect of stirring the reaction mixture was also determined during the investigation. If the mixture is not stirred at all, the initiation takes much longer (up to more than 1 h), which indicates the oxide layer on the metal surface is not reduced with DIBAH. The same experiment was also done with Vitride with the same result. If stirring is turned on and the turnings are slightly moved, the reaction starts immediately. This makes the stirring of the mixture on large scale important, showing that a low stirrer is crucial for the initiation.

If the reaction does not initiate after 60 min at room temperature, the addition of another 1 mol % DIBAH normally causes the reaction to start within minutes.

The quality of the magnesium turnings was also studied. No difference of the activation was observed with magnesium turnings from different vendors, although it was found that a batch of magnesium turnings that was more than one year old needed more than 24 h to initiate with 2 mol % of DIBAH.

The addition of up to 10 mol % of DIBAH caused no change in the impurity profile or problems with the workup after the Grignard reaction.

The time in which the surface remains active after the initiation was determined through storing the reaction mixture

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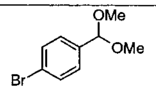
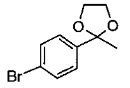
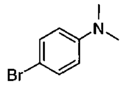
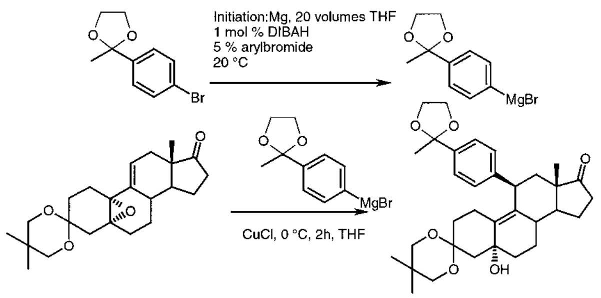
(12) Repic, O. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*; Wiley, New York, 1998.

Table 1.[a]

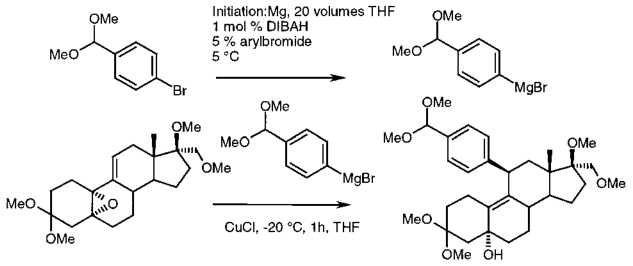
Dilution THF	 2	 3	 1
	Initiation time (max. temperature after initiation)	Initiation time (max. temperature after initiation)	Initiation time (max. temperature after initiation)
5	2 min. (55 °C)	5 min. (57 °C)	6 min. (54 °C)
10	3 min. (45 °C)*	5 min. (46 °C)*	10 min. (44 °C)*
20	4-10 min. (33-37 °C)**	8 min. (33 °C)	26 min. (32 °C)
30	15 min. (31 °C)	15 min. (28 °C)	2 min. (26 °C) ***
5	5 h (52 °C)***	24 h no initiation***	24 h no initiation***

[a] Conditions: 1 mol Mg in *x* vols of THF (with regard to weight of Mg) stirred with an overhead stirrer just enough to slightly move the turnings at an internal temperature of 20 °C. Addition of 0.05 mol aryl bromide dissolved in twice the amount of THF. Initiation of the reaction was performed through addition of 0.01 mol DIBAH (20% in toluene) at 20 °C. *The yield determined after complete addition. **This experiment was reproduced five times. **After addition of an extra mol % DIBAH. ***The initiation of the Grignard reagent formation without activator.

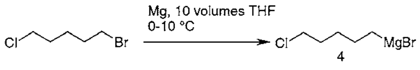
Scheme 3



Scheme 4



Scheme 5



overnight (16 h) prior to the addition of the rest of the bromide solution. This was found to function very well for all three studied aryl bromides.

After the success on laboratory scale the method was implemented on multikilogram plant scale.

Prior to the performance in the pilot plant the reaction was investigated in the RC1 reaction calorimeter. For 4.081 mol of magnesium and 4-bromoacetophenone ethyleneketal (**3**) in 4.8 dm^3 of THF the $\Delta T_{\mathrm{adiab}}$ was found to be 163 K, being independent of the activation method.

For the first reaction 4-bromoacetophenone ethyleneketal (**3**) was used. The initiation took 30 min in a 630-L glass-lined reactor fitted with an anchor with 20 vols of THF with regard to magnesium. The temperature rise of the internal temperature was 10 K without external cooling (Scheme 3).

Later, the method was also used for the manufacture of the Grignard reagent from 4-bromobenzaldehyde dimethyl acetal. The reaction was run in a 250-L glass-lined reactor fitted with an impeller. In this case the reaction started immediately after the addition of the DIBAH solution. In this case it is important to generate the Grignard reagent below 40 °C. To ascertain that the initiation was kept well below this temperature the initiation was performed at 5 °C. The temperature difference caused no difference in the initiation (Scheme 4).

The 5-chloropentylmagnesium bromide (**4**) is susceptible to Wurtz coupling and nucleophilic attack on the chlorine, giving cyclopentane. The manufacture of the Grignard reagent should be kept below 15 °C. Previously, the initiation with ethylene bromide was performed at 30−35 °C, and after initiation the reaction was cooled to 10 °C before the addition of the rest of the 5-chloropentyl bromide.

By utilizing the DIBAH method it was possible to initiate the reaction at 0 °C and to keep the formation of the Grignard reagent below 10 °C (Scheme 5).

Conclusions

By utilizing 1 mol % DIBAH as an activating reagent for the formation of various Grignard reagents we have shown that the initiation and the formation can be performed at or below 20 °C for aryl Grignard reagents. For alkyl bromides it is possible to activate the magnesium turnings at even lower temperatures. We have also shown that with this method it is possible to manufacture Grignard reagents well below the boiling point of THF. The method has been found to be general and reliable for the formation of various kinds of Grignard reagents.

Experimental Section

Dissolve in a 250-L glass-lined reactor 68.6 kg of 4-bromoacetophenone ethyleneketal (**3**) in 280 L of THF with water content below 0.1%. Add to a dry, clean 630-L glass-lined reactor 6.54 kg of magnesium turnings and 66 L of THF with a water content below 0.1%. Add to the stirred mixture at an internal temperature of 20 °C the 4-bromoacetophenone ethyleneketal solution (27 kg) and 20% DIBAH solution in toluene (2 kg). Observe the stirred mixture until the reaction initiates. After the exotherm of the initiation has faded, the addition of the bromide solution is continued under dose control. The so-obtained Grignard reagent is directly used in the 1,4-addition.

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