Simple sonochemical protocols for fast and reproducible Grignard reactions

Giancarlo Cravotto,*a Antonio Procopio,b Manuela Oliverio,b Laura Orio† and Diego Carnaroglio†

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The Grignard reaction is one of the most common synthetic pathways in organic chemistry and has widely been used in the preparation of fine chemicals and pharmaceutical intermediates. The reaction's reproducibility can be affected by several factors (metal purity, degree of association in solution, Schlenk equilibrium) and its activation with chemical, mechanical, sonochemical or electromagnetic treatments is practically essential. In this study we demonstrate that ultrasound-assisted Grignard reactions are safe, efficient and reproducible. The activation of the Mg surface, the single electron transfer (SET) from the metal to organic halide, and the subsequent nucleophilic addition of ArMgX to carbonyl substrates, fall into the larger domain of sonochemistry. As expected for a radical mechanism the best sonochemical conditions were observed at 300 kHz (cup horn). An efficient one-pot protocol with poorly-reactive aryl halides and the subsequent quenching with a hindered ketone are reported.

Introduction

The reaction discovered by Victor Grignard at the beginning of the XXth century still plays a relevant role in organic and organometallic synthetic chemistry. The activation of magnesium turnings for the preparation of organomagnesium halides (the Grignard reagent) and the subsequent initiation of the Grignard reaction still makes for a tricky procedure during which chemists moderately heat iodine, 1,2-dibromomethane or TMSCl in freshly distilled ethereal solvents or toluene under dry argon or nitrogen. Although several investigations have tried to replace tetrahydrofuran (THF), it remains the solvent of choice because of its high Mg2+ coordinating capacity and ability to stabilize the products. Practical limitations and safety concerns have emerged from its use in industrial applications due to the large amount of heat released during the initiation step in low-boiling point media. Traces of impurities can react strongly with the Grignard reagents, and process control under reflux conditions is difficult to maintain. Different metallic magnesium chip sizes and forms have been tested, under chemical, mechanical and sonochemical activation. Hulshof et al. have studied the influence of microwave (MW) irradiation on metallic magnesium, and showed that this method can produce a surface which is just as accessible as the one obtained via the use of an initiator. Mass-transport and kinetics are strongly favored by MW irradiation at these interfaces between solid and liquid, although this interaction generates violent electrostatic discharge phenomena between the Mg particles (arcing). More recently Kappe et al. have shown that the preparation of the same Grignard reagent in different professional MW instruments (mono- or multimodal) can lead to entirely different results, even at the same macroscopically determined reaction temperature. In other words, the authors have demonstrated that Grignard reagent formation under MW irradiation is either accelerated or slowed down as a result of field density conditions.

In the search for a simple and better reproducible general procedure, we have investigated both the reaction of magnesium with organic halides which leads, via oxidative addition, to the Grignard reagent and the alkylation of carbonyl derivatives, in a one-pot sonochemical protocol. High-intensity ultrasound (US) proved to be effective in metal surface activation. Sonochemical reactors, and even simple cleaning baths, facilitate the removal of the oxide film on the metal surface and counteract the depositing of Grignard reaction products onto the new surface. Despite the leading role of US in metal-assisted synthetic chemistry (i.e. Barbier reaction), this technique has so far only been considered as an alternative way to activate the magnesium metal. All the studies that have described the promoting effect of US on the Grignard reaction have only covered the initiation process and not the whole synthesis which is usually performed under conductive heating and stirring. The optimization of a Grignard reaction, from the preparation of organomagnesium halides to its scaling up for industrial purposes, is hampered by several factors and intrinsic dangers. The spontaneous heat release during the initiation step, the induction of very exothermic radical side reactions and the risk of explosive reactant accumulation are the main safety
problems associated with the reaction. Efficient MW-activation might unfortunately, on a larger scale, result in violent arcing and the danger of explosion. Simultaneous US/MW irradiation is a promising innovation in metal-assisted synthesis, although it is not much safer for this application and in fact cannot overcome the massive arcing risk.

Sonication is a milder technique for activating metal surfaces in organometallic chemistry and has been widely used for Mg activation in Grignard reagent formation.

Our aim was to design a safe and reproducible general procedure for Grignard synthesis which could be suited for scaling up processes.

Results and discussion

In this study, various conditions and US reactors have been used to prepare several Grignard reagents and to carry out the quenching of the corresponding adducts with a ketone. After a preliminary screening of the experimental conditions, we focused our investigation on four US instruments: a common cleaning bath (35 kHz), a high power US bath (19.6 kHz) and two cup horns (20 kHz and 300 kHz).

We started our experiments using 2-bromopyridine (1) as our model halide, magnesium chips in dry THF and an inert atmosphere.

The results of the three different non-conventional irradiation techniques, MW, US and MW/US (Scheme 1), have been compared.

At MW experiments, in our hands, substrate 1 showed exactly the same reaction rate, yield and arcing as had been reported in the literature under MW (path a, Scheme 1). The reaction under simultaneous MW/US irradiation increased the amount of electrical discharge caused by violent particle collisions. The best result was achieved under sonication in a common cleaning bath (50 kHz), a high power US bath (19.6 kHz) and two cup horns (20 kHz and 300 kHz).

The reaction conditions, times and yields for all the substrates and all the US equipment employed are shown in Table 1 together with the results obtained under MW irradiation for comparison.

In almost all US-assisted reactions, with the exception of chlorobenzene (4), complete conversion was observed when working with a 300 kHz cup horn at mild temperatures (entry 4, Table 1). The most reactive substrates, such as 2-bromopyridine (1) and bromobenzene (3), showed equivalent results for US and MW assisted irradiation and for the various US devices used (entries 1 to 5, Table 1), giving complete conversion in all cases. Substrates with moderate reactivity, such as 2-chloropyridine (2) and 3,5-dimethoxybromobenzene (5), gave a more interesting proof of the promoting effect of US on Grignard reagent formation. In these cases, only the instruments which generate more intensive cavitation energy gave good yields of Grignard reagents 2a and 5a (entries 3 and 4, Table 1). The experiments performed using the 20 kHz cup horn, which allows the reaction temperature to be strictly regulated, showed a direct yield/temperature dependence (entry 3, Table 1). In

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fact no conversion was observed at 45 °C, while 100% and 65% conversions were achieved at 80 °C for 2 and 5 respectively. Prolonged exposure to US did not improve the reaction yield and only served to increase the amount of Wurtz-type side products generated from radical coupling or from the reaction of the initially formed organometallic with more organic halide.

It was interesting to find that the optimal US frequency was 300 kHz which gave complete conversion for both substrates 2 and 5 (entry 4, Table 1) even at low temperature (45 °C). Only chlorobenzene (4) failed to react; no organomagnesium halides were detected while a significant amount of Wurz-type side products was formed (entries 1 to 5, Table 1). The low reactivity of chlorobenzene in the Grignard formation has been extensively described in the literature\(^\text{19-21}\). When comparing US- and MW-assisted reactions it can be seen that reaction times and yields were comparable. However, US provides the great advantage of working at milder and safer conditions and avoids the risk of arcing.

In the second step, a solution of 1.5 eq of benzophenone in dry THF was added to each of the Grignard reagent mixtures which had been formed in the previous step and the resulting system was irradiated in the 300 kHz cup horn. The reaction yields were determined by GC-MS analysis after work-up (step 2, Scheme 2). All the tertiary alcohols obtained were identified by chromatographic purification by \(^1\)H and \(^13\)C NMR and compared with the data reported in the literature\(^\text{19-21}\).

As shown in Table 2, all the Grignard reagents formed in the previous step efficiently reacted with benzophenone in a few minutes giving products 1b, 3b and 5b (entries 1–3, Table 2) in good-to-excellent yields. These results have confirmed that the 300 kHz cup horn is the best US device for a fast, safe and efficient one-pot US-assisted Grignard reaction over both steps.

### Table 1  Power US-assisted Grignard formation (step1, Scheme 1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 US cleaning bath (40 W, 35 kHz) (T = 35 ^\circ)C</th>
<th>2 Power US bath (200 W, 19.6 kHz) (T = 40 ^\circ)C</th>
<th>3 US Cup Horn (100 W, 20 kHz) (T = 45 ^\circ)C</th>
<th>4 US Cup Horn (200 W, 300 kHz) (T = 45 ^\circ)C</th>
<th>5 Multimode MW (165 W) (T = 65 ^\circ)C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (min) Conv (%) Yield (%)</td>
<td>Time (min) Conv (%) Yield (%)</td>
<td>Time (min) Conv (%) Yield (%)</td>
<td>Time (min) Conv (%) Yield (%)</td>
<td>Time (min) Conv (%) Yield (%)</td>
</tr>
<tr>
<td>1</td>
<td>20 (5) 100 100</td>
<td>20 (10) 100 100</td>
<td>20 (10) 100 100</td>
<td>20 (7) 100 100</td>
<td>10 (2) 100 100</td>
</tr>
<tr>
<td>2</td>
<td>240 (120) 2 2</td>
<td>285 (45) 1 1</td>
<td>240&lt;sup&gt;a&lt;/sup&gt; 90 (30)</td>
<td>30 (10)&lt;sup&gt;a&lt;/sup&gt; 100</td>
<td>60 (30) 100 100</td>
</tr>
<tr>
<td>3</td>
<td>25 (10) 100 100</td>
<td>25 (5) 100 100</td>
<td>20 (5) 100 100</td>
<td>20 (5) 100 100</td>
<td>10 (2) 30 (5) 100 80&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>180 — — 180 — — 120&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1&lt;sup&gt;c&lt;/sup&gt; &lt;1</td>
<td>180 — — 60 (5) 2 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>180 — — 180 — — 180&lt;sup&gt;e&lt;/sup&gt;</td>
<td>65 50</td>
<td>10 (5) 100 100</td>
<td>60 (30) 18 17</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Total reaction time. Activation time is reported in parentheses. \(^\text{b}\) Reaction carried out at 10 °C. \(^\text{c}\) A significant percentage of Wurtz-type side products were detected. \(^\text{d}\) Reaction carried out in standard conditions (reflux) without MW irradiation. \(^\text{e}\) Reaction carried out at 80 °C. \(^\text{f}\) Reaction carried out in solvent-free conditions and in the presence of 2.5 eq of Mg. \(^\text{g}\) Reaction carried out directly in the cup horn cavity.

### Table 2  Power US-assisted Grignard reaction with benzophenone (step 2, Scheme 2)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (min)</th>
<th>Conv (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td>98</td>
<td>94</td>
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<tr>
<td>2</td>
<td>3b</td>
<td>10</td>
<td>100</td>
<td>98</td>
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<tr>
<td>3</td>
<td>5b</td>
<td>10</td>
<td>92</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>a</sup> Product 1b is obtained under the same reaction conditions by both 2-pyridinyl magnesium chloride (2a) and bromide (1a).
Conclusions

In this work we have reported the first comparative study of Grignard reactions using several physical activation techniques; high-intensity US using different frequencies and reactors and MW irradiation.

The reactions were monitored following the formation of the organomagnesium halides and their subsequent addition to benzophenone. Under such sonochemical conditions we optimised yield, reaction times and process reproducibility. The milder, safer conditions and its ability to be scaled up were the main advantages of this efficient 300 kHz protocol over the MW-assisted procedure.

Experimental

Materials

All the chemicals were obtained from commercial sources and used without further purification. THF was freshly distilled before each experiment. Reactions were monitored by TLC, work up with NH4Cl/diethyl ether. For product purification, column chromatography and characterized according to literature procedures.

The high-power US-bath (19.6 kHz)22 and cup horns for irradiation at 20ºC and 300 kHz23 were made by Danacamerini (Torino) in collaboration with the corresponding author’s group and are commercially available. An Elma TS540 cleaner bath operating at 35 kHz was used to provide some comparison of sonochemical effects.

US 300 kHz general procedure

366 mg (15 mmol, 1.5 eq) of Mg chips, 3 mL of dry THF and 1 mmol (0.1 eq) of aryl halide were added to a dry, one neck, round bottom flask. The mixture was sonicated (water bath temperature: 55 ºC) under a nitrogen atmosphere until activation, then another 9 mmol (0.9 eq) of aryl halide were added and the mixture was sonicated until completion (reaction monitored by TLC, work up with NH4Cl/diethyl ether). For product 3a, bromobenzene was added dropwise to avoid the formation of Wurz-type side products. A sample of the solution was quenched with saturated NH4Cl solution, extracted with diethyl ether and analyzed by GC-MS. We calculated the ratio starting material/Grignard reagent on the base of the corresponding quenching product (i.e. benzene, pyridine, dimethoxybenzene).

A solution of benzophenone (2.73 g, 15 mmol, 1.5 eq) in 3 mL of dry THF was then added dropwise in 10 min under sonication (water bath temperature: 55 ºC). After cooling, 10 mL of a NH4Cl saturated solution was added and the product was extracted with 5 x 3 mL of EtOAc. The combined organic layers were dried over Na2SO4, and the solvent was removed under reduced pressure.

Yield and conversion were calculated using GC-MS. Products were purified using column chromatography and characterized according to literature procedures.

Acknowledgements

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References