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Preparation of Grignard reagents from magnesium metal under continuous flow conditions and on-line monitoring by NMR spectroscopy

Michel Goldbach^a, Ernesto Danieli^b, Juan Perlo^c, Bernard Kaptein^a, Victor M. Litvinov^d, Bernhard Blümich^b, Federico Casanova^c, Alexander L. L. Duchateau^{e,*}

^a DSM Ahead-Innovative Synthesis B.V., PO Box 18, 6160 MD Geleen, The Netherlands

^b Institut für Technische Chemie und Makromolekulare Chemie, RWTH Aachen University, Worringerweg 1, 52074 Aachen, Germany

^c Magritek GmbH, Philipstr. 8, 52068 Aachen, Germany

^d DSM Resolve, PO Box 18, 6160 MD Geleen, The Netherlands

^e DSM Biotechnology Center, PO Box 1, 2600 MA Delft, The Netherlands

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ABSTRACT

A convenient method for the classical preparation of Grignard reagents from aryl halides and magnesium using a fluidized bed reactor under continuous flow conditions was developed. The process was combined with quenching of the Grignard reagent by CO_2 as a model reaction performed using a second flow reactor. The formation and quenching of the reagent was monitored by on-line ¹H NMR spectroscopy. The combination of continuous flow operation for Grignard reagents with reaction monitoring by on-line NMR spectroscopy allows one to quickly optimize the working conditions.

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Grignard reagents are one of the most commonly used alkylation reagents to make C-C chemical bonds. Discovered in 1900 by Victor Grignard¹ and awarded with the Nobel Prize in Chemistry in 1912, Grignard reagents are still frequently used on an industrial scale for the production of fine chemicals and pharmaceuticals.² Although various trans-metallation reactions with alkyl magnesium halide solutions under continuous flow condition have been developed to prepare Grignard reagents,³ on an industrial scale Grignard reagents are still produced in stirred tank reactors from magnesium and alkyl or aryl halides which are used as such in further applications. With recent developments in continuous flow reaction processes and micro reactor technology the option of trans-metallation for preparing Grignard reagents has gained increasing interest, especially because of the homogeneous solution reaction conditions. On the other hand, the classical preparation of Grignard reagents is much more difficult to implement under process conditions due to the inhomogeneity of the reacting solid magnesium.

An important issue in the production process is the high sensitivity of the Grignard reagent to air and moisture. The literature describes methods for gas chromatography⁴ and colorimetric

* Corresponding author. Tel.: +31 15 279 3638. *E-mail address:* Lucien.duchateau@dsm.com (A.L.L. Duchateau).

http://dx.doi.org/10.1016/j.tetlet.2015.11.077 0040-4039/© 2015 Elsevier Ltd. All rights reserved. titration⁵ to quantify the amount of Grignard reagent formed. However, it is difficult to execute the analysis in an inert environment, to quantify the actual amount of Grignard reagent formed, and to quantify the amount of reagent oxidized during the reaction or analysis. Colorimetric titration experiences an extra level of difficulty due to the dark color of most Grignard reagents.

One of the analytical techniques suitable to monitor the progress of reactions is Nuclear Magnetic Resonance (NMR), which has largely been discarded because of the high cost required to acquire, maintain, and operate high performance superconducting magnets. However, during the last years compact NMR spectrometers with permanent magnets⁶ have become available commercially, with performance, in terms of sensitivity and resolution that is appropriate for chemical analysis.⁷ Moreover, the small size of these spectrometers makes them ideal candidates for operation in flow-through mode.

In this work we describe, for the first time, the preparation of a Grignard reagent from aryl halides and magnesium metal under continuous flow reaction conditions on a magnesium fluidized bed reactor combined with on-line flow analysis by ¹H NMR spectroscopy. A continuous Grignard process has been described in a US patent by Motta in 1978, but the use of a conventional packed bed of magnesium turnings makes it hard to control heat and mass transfer in the highly exothermic Grignard reactions.⁸ We

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 Table 1

 Settling velocities of spherical magnesium particles in THF and CPME

| 0 | 0 1 1 | |
|---------------------------|--|--|
| Particle diameter (µm) | Settling velocity (cm/s) in THF (0.89 g/mL) | Settling velocity (cm/s) in CPME (0.785 g/mL) |
| 100 | 0.010 | 0.010 |
| 200 | 0.038 | 0.043 |
| 250 | 0.059 | 0.067 |
| 400 | 0.15 | 0.17 |
| 1000 | 0.95 | 1.00 |

therefore focused on the use of a fluidized bed tube reactor with spherical magnesium particles ranging in size from 100 to 1000 μ m. In the vertically positioned tube reactor the magnesium particles are kept as a fluidized bed by the upward solvent flow. The settling velocities—the solvent flow velocity to prevent the magnesium particles from settling—in tetrahydrofuran (THF) or cyclopentyl methyl ether (CPME) differ with particle diameter, solvent density, and flow rate (Table 1).

As a model Grignard reaction for the continuous flow setup (Fig. 1) the preparation of phenyl magnesium bromide from bromobenzene in THF or CPME was chosen, followed by quenching with gaseous CO_2 to give benzoic acid (Scheme 1).

A stainless steel vertical tube reactor with 75 mL volume and a diameter of 1.1 cm together with a heating/cooling jacket was connected to a 1.2 mL flow cell by 1/8" Teflon tubing. The temperature of the reaction was controlled by a Lauda thermostat containing Marlotherm SH medium. The model substrate was fed to the reactor using a Gilson 307 HPLC pump. The nitrogen flushed tube reactor was loaded with 10 g (0.41 mol) of magnesium powder (250 μ m particles for fluidized bed conditions). To activate the magnesium particles, commercially available phenylmagnesium bromide (PhMgBr) solution in THF (1 M, 50 mL) was added by syringe via the top of the tube. Subsequently the column was sealed, connected to the in-line flow NMR spectrometer, heated to the reaction temperature (80 °C), and left for 30 min. A solution of bromobenzene in dry THF (1 M) was then pumped through the reactor at 5 mL/min. A mild exothermic effect of +3 °C was visible. The reaction mixture of the first 30 min was discarded before collecting the reaction data, by leading a fraction of the solution through the flow cell at 1 mL/min. Excess flow was collected under nitrogen for GC comparison and further reaction of the Grignard with gaseous CO₂.

For analysis of the continuous flow process, a Magritek Spinsolve[™] NMR spectrometer was connected to the output of



Scheme 1. The model Grignard reaction.

the reactor column and used for the low-field spectroscopy measurements. The permanent magnetic produced a magnetic field of 1 T (42 MHz ¹H Larmor frequency) with a homogeneity of about 0.01 ppm across the 5 mm diameter sample tube, which completely filled the solenoidal radio-frequency coil. The signal-to-noise ratio of a single-scan spectrum for a water sample was about 200,000. NMR spectra of the pure solution flowing through the magnet were measured every 10–15 s depending on the case.

Reference spectra of bromobenzene (1 M) and phenylmagnesium bromide (1 M) are depicted in Figure 2A while Figure 2B shows individual spectra of the Grignard solution aromatic region of a typical 2 h run monitored on-line at temperatures between 4 and 80 °C at a constant flow rate of 5 mL/min. From these spectra it was concluded that within 2 h the reaction to give the Grignard reagent was complete at T_{set} temperatures of 40 and 80 °C, but not at lower temperatures due to the absence of the bromobenzene signal in the frequency range between 7.2 ppm and 7.5 ppm. The small signal peak near 7.4 ppm was caused by the oxidation of the Grignard reagent. The amount of the oxidation side-product was much smaller for the reaction product generated under flow conditions than in a commercial sample of PhMgBr (spectra not shown). The evolution of the aromatic region in the NMR spectra as a function of reaction time for an incomplete run is depicted in Figure 2C. During the two-hour experiment at a fixed T_{set} of 25 °C (T_{actual} = 26–28 °C), different flow rates were used in order to determine in real time the influence on conversion. Under the chosen conditions it took approximately 30 min for the Grignard reaction to stabilize to constant conversion at a given flow rate. The reduced conversion to the Grignard reagent in this run from 76% to 39% upon increasing the flow rate from 2 to 6 mL/min can also be observed in Figure 2D and Table 2, entries 6-8.

The conversions of the Grignard reaction in flow experiments at different temperatures and flow rates are summarized in Table 2. NMR conversion rates were obtained by a weighted fit of the aromatic region of the measured spectra using as base functions the reference samples of bromobenzene (1 M) and Grignard reagent (1 M) in THF (Fig. 2A). In the run shown in Table 2, complete conversion to the Grignard reagent was observed at T_{set} of the reaction



Figure 1. Scheme (A) and photo (B) illustrating the experimental setup of the continuous flow reactor with the in-line bench-top NMR spectrometer (Spinsolve[®] by Magritek) under a fume hood.

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Figure 2. (A) Reference spectra of bromobenzene (1 M) and phenylmagnesium bromide (1 M). (B) Separate spectra of Grignard reagent produced at different temperatures (T_{set}) and a flow rate of 5 mL/min monitored on-line by NMR spectroscopy. (C) Aromatic region of the NMR spectra acquired during the (incomplete) production of the Grignard reagent production with different flow rates and T_{set} = 25 °C. Individual spectra were measured sequentially every 10 s. The red arrows in the figure indicate the instants of time at which the flow rate was changed. Flow instabilities or air bubbles are also evidenced at particular times. (D) Individual NMR spectra extracted from B after 40, 80, and 115 min.

| Table 2 | |
|---|--|
| Continuous flow results under various reaction conditions | |

| Experiment no. | $T_{\rm set} \left[{}^{\circ}{\rm C} \right]$ | $T_{\text{actual}} [^{\circ}\text{C}]$ | Flow rate [mL/min] | Conversion [%] |
|-------------------|--|--|--------------------|-------------------|
| 1 | 80 | 83 | 5 | 100 |
| 2 | 40 | 46 | 5 | 100 |
| 3 | 10 | 26 | 5 | 79 |
| 4 | 10 | >50 | 2 | 100 |
| 5 | 4 | 22 | 5 | 69 |
| 6 ^a | 25 | 27 | 2 | 76 |
| 7 ^a | 25 | 29 | 4 | 68 |
| 8 ^a | 25 | 26 | 6 | 39 |

^a After addition of new nonactivated magnesium (7 g).

column of 80 and 40 $^{\circ}$ C and a flow rate of 5 mL/min (entries 1 and 2). Due to the exothermic nature the actual temperature of the

reaction was slightly higher. In contrast to the results depicted in Figure 2 magnesium is insufficiently activated to undergo complete conversion at lower temperature. Entries 3 and 4 reveal, that at a T_{set} temperature of 10 °C, the flow rate had to be reduced for complete conversion, and that at 4 °C the flow rate of 5 mL/min was too high (entry 5). Incomplete conversion at 25 °C and different flow rates were also observed for regeneration of the flow column with nonactivated magnesium (entries 6–8).

Grignard reactions can occur within minutes or take up to several hours depending on the reactivity of the Grignard reagent and the substrate it reacts with. In this study the rapid exothermic Grignard reaction between phenylmagnesium bromide and gaseous carbon dioxide was followed in time with a compact NMR spectrometer by monitoring the decrease in Grignard reagent and the increase in the benzoate product. For this experiment gaseous CO_2 was bubbled through a solution of freshly prepared



Figure 3. (A) Stacked plot showing the NMR spectrum corresponding to the aromatic region of the PhMgBr (1 M) reacting with CO₂ recorded continuously. (B) 1D plots corresponding to particular times of the reaction.

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PhMgBr (1 M, 50 mL). Using a peristaltic pump, the reaction mixture was led through the flow NMR cell at 1 mL/min where conversion was measured (see Fig. 3). At zero time, the signals in the spectra can be associated to the Grignard reagent. As time proceeds, the signals corresponding to the benzoate start to appear at 7.55 and 8.20 ppm. After 70 min a conversion of about 80% was reached. The experiment was stopped at this time because the precipitated magnesium bromide clogged the tubing.

Various Grignard reagents have been prepared under similar continuous flow conditions using a fluidized magnesium bed, starting from iodobenzene, cyclopropyl bromide, methylchloride, 4-bromo-*tert*-butylbenzene, 4-bromobenzaldehyde dimethyl acetal, and others. In addition to gaseous CO₂ as described above, Grignard reactions have also been achieved by mixing PhMgI and benzaldehyde in a 1/8" stainless steel Swagelok T-piece. This resulted in over 90% conversion to benzhydryl alcohol after acidic work up. Details are published elsewhere.⁹

In conclusion, we have developed a continuous flow process for the preparation of Grignard reagents using a fluid bed magnesium column. The formation of the Grignard reagent and the further reaction with CO₂ could be followed by in-line measurements of NMR spectra. Depending on the set temperature of the column and the flow rate of the solution, complete conversion of bromobenzene to phenylmagnesium bromide was possible. Solutions of the Grignard reagents prepared in this way are suited for further reaction with various substrates under flow conditions. The NMR spectra acquired in-line showed that the amount of oxidized Grignard reagent was significantly less than that determined in off-line measurements with a standard NMR tube. This demonstrates the advantage of in-line measurement versus off-line measurement. The high analysis frequency of the NMR spectrometer and the extra qualitative information of the reaction progress make in-line NMR measurements a valuable complement to existing in-line analysis methods such as IR and Raman spectroscopy.

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