Application Note 67: Generation of Grignard reagents on demand

Produced by Vapourtec

Abstract

This application note illustrates the capabilities of Vapourtec's new packed bed reactor for a fast, consistent generation of Grignard reagents in flow. Under continuous flow conditions, an organic bromide reacts with magnesium packed inside the Variable Bed Flow Reactor, adjusting its volume to keep a constant packing density. In a second inline reactor, an aldehyde is added to the Grignard reagent to form a secondary alcohol.

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Background

Since Victor Grignard published in 1900 his findings on the relationship between magnesium and organic compounds [1]; organomagnesium reagents have been a valuable synthetic tool for organic chemists.

Unfortunately, the initiation of formation of Grignard reagents from organohalides and magnesium can be capricious. A number of techniques are available to start the reaction effectively. Several publications have covered the best way to activate magnesium for Grignard reagents; from using Mg-Cu alloys in combination with I_2 [2], using DIBAH as drying and activating agent [3], to use 1,2-dibromoethane as activating agent [4].

In 2017, Alcázar et al. published a seminal paper on Grignard reagents in flow [5]. By packing a fixed bed reactor with magnesium, they made an array of Grignard reagents in flow. Unfortunately, this developed method still required two steps for magnesium activation prior to the generation a Grignard reagent.

With a fixed bed reactor, as reactions progress magnesium is consumed, altering the packing within the column and, ultimately creating a void which will be occupied by solvent. This becomes an issue as reactions progress, as channelling effects will take place, having severe, unpredictable effects on residence time. As the magnesium column depletes, the organohalide reagent will dilute when it reaches the column, as there will be more solvent in the column. The organohalide will simply pass through the column unreacted.

Vapourtec has recently developed a Variable Bed Flow Reactor (VBFR) which can be used to control Grignard reactions in continuous flow. The VBFR monitors in real time the differential pressure across the reactor. This differential pressure is generated by the restriction the packed bed opposes to flow through the reactor; the higher the packing density is, the bigger the differential pressure. The VBFR adjusts its internal volume to maintain a constant differential pressure, and therefore, a constant packed bed density. The level of accuracy of this reactor, with a resolution of 0.5 µl, allows the software to detect minor changes across the packed bed and react accordingly. This has proved to be a significant improvement for continuous flow synthesis where one of the reagents is in solid phase, especially in peptide synthesis [6]. Figure 1 shows the system layout of the VBFR, which fits, as any other Vapourtec reactor, into the R-Series.

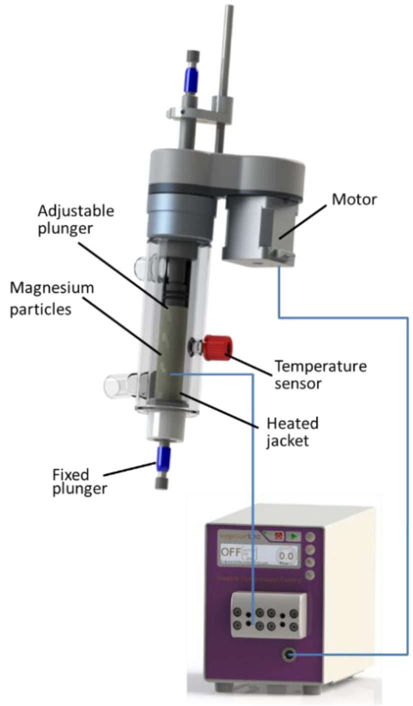

Figure 1 – Schematic diagram of the components of the VBFR

This application note demonstrates the use of the VBFR to consistently generate Grignard reagents without the need of any pre-activation step. The Grignard reagent is then reacted with benzaldehyde as Figure 2 shows.

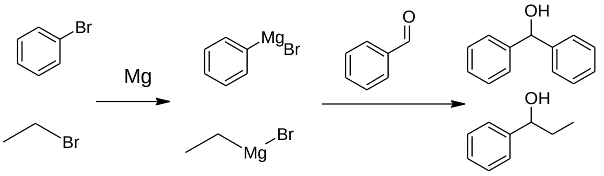

Figure 2 – Sequential Grignard formation and alkylation of benzaldehyde

By accurately controlling the temperature and packing density of magnesium particles, Grignard reagents can be made with ease. To test this hypothesis in this application note, two different types of organohalides were used as Grignard precursors; bromobenzene and bromoethane. The resulting Grignard reagent was coupled with benzaldehyde to generate a secondary alcohol.

Setup

The VBFR was setup using the R-Series flow chemistry system as shown in Figure 3.

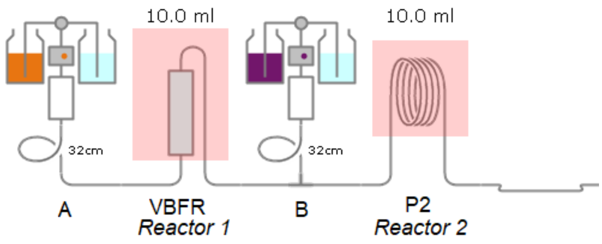

Figure 3 – Schematic of the R-Series used for this application

An R2C+ pump module was configured to pump both organohalide and benzaldehyde solutions.

Two reactors were set in the R4 reactor heater module; the VBFR (reactor 1) where Grignard reagents were made in flow and a 10 ml tubular reactor (reactor 2) for the coupling with a carbonyl derivative.

System pressure was maintained throughout the experiments using an SF-10 pump as back pressure regulator (BPR).

To ensure magnesium particles stay within the VBFR, a PTFE 30 µm frit was placed in the input port of the reactor. To prevent blocking of the frit from residual particulates, a stainless steel 325 mesh was placed in the output port of the moveable plunger of the reactor.

Crude product was collected under nitrogen in a 20 ml vial that contained an aqueous solution of ammonium chloride to quench any excess Grignard reagent.

Reagents

All materials were purchased from Sigma-Aldrich. Both reagent and solvent bottles were dried and kept under a nitrogen blanket throughout the experiment.

System Parameters

System solvent: Anhydrous THF

Magnesium: Reagent grade (98 % pure) Turnings (catalogue number 200905)

Solution A: 0.5 M and 1.0 M solution of bromobenzene or bromoethane in anhydrous THF

Flow rate A: 0.25 - 0.50 ml/min

Solution B: 0.5 M and 1.0 M solutions of benzaldehyde in anhydrous THF

Flow rate B: 0.25 - 0.50 ml/min

VBFR (*Reactor 1*): A 2.4 ml reactor was packed by hand with ~ 2.5 g (103 mmol) of magnesium turnings. The temperature was maintained at 80 °C throughout the experiments. The packing density was set to deliver 1 bar of differential pressure across the reactor.

Coil reactor (*Reactor 2*): 10 ml reactor, unless indicated otherwise, PFA was the reactor’s material. The temperature was maintained at 30 °C.

System pressure: 6 bar.

Results and Discussion

Work started with packing the VBFR with magnesium turnings. Once the reactor was online, solvent was pumped at the reaction's conditions (flow rate, temperature and system pressure) for 30 minutes, ensuring it was fully equilibrated.

All the products were collected in a vial with an aqueous saturated solution of ammonium chloride to quench unreacted Grignard product.

Formation of phenyl magnesium bromide

From preliminary work, it was found that working at 80 °C allowed the formation of the Grignard reagents to occur within minutes.

As this reaction is highly exothermic, the power required by the R4 to heat the reactor will theoretically decrease when Grignard reagents are formed, as the reaction reaches a self-heating state.

Experimentally this change could be correlated to the chemistry that happens on the outermost layer of magnesium particles. As the magnesium particles are consumed, the volume of the VBFR will decrease.

The first Grignard reagent that was prepared was 1.0 M phenyl magnesium bromide. Figure 4 shows the live data recorded on Flow Commander™, where heating power (W) and VBFR volume change (ml) are plotted over time.

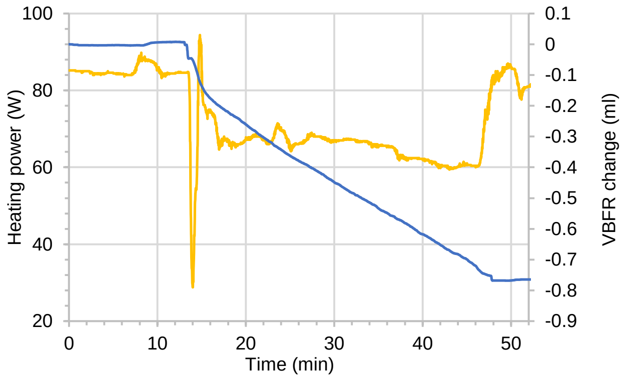

Figure 4 – Evolution of R4 heating power (yellow) and VBFR change in volume (blue) over time

At minute 6, solvent was switch for reagent, and at minute 13 a drop in power was recorded. This drop in power is a good indication that an exothermic reaction has started.

The volume of the VBFR started to decrease at the same time, although the rate of consumption did not stabilise until minute 15.

Reagent was pumped for 30 minutes and, during that period, there was a constant consumption of magnesium, requiring only 65 W to keep the reactor to 80 °C, a 21 W drop from 86 W.

To evaluate the "ease" of Grignard formation, at 80 °C, reagent solution was switched to solvent until the VBFR was full of solvent, and then switched back to reagent.

Figure 5 shows the effect on switching back to solvent (shown as white arrows on Figure 5) on the reactor's volume. Every time reagent bottle was selected using Flow Commander^{TM} (indicated with black arrows on Figure 5), Grignard started again.

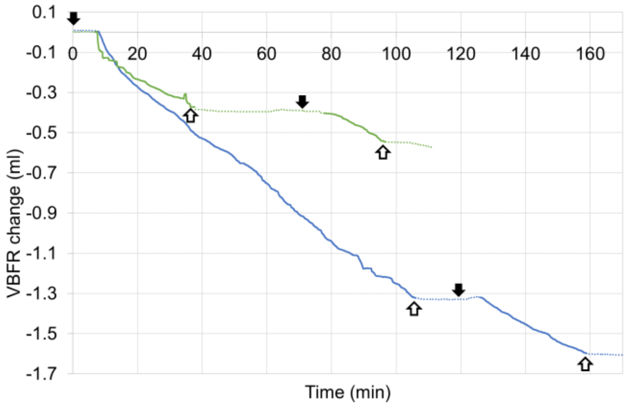

Figure 5 – Magnesium consumption (in ml) over time when pumping a solution of bromobenzene [1 M at 0.50 ml/min (blue); 0.5 M at 0.25 ml/min (green)]. Back arrow: switch to reagent. White arrow: switch to solvent

The reaction of benzaldehyde can be performed at a different temperature than the generation of Grignard. Table 1 compiles the results of the C-C coupling at 30 ºC.

Table 1 – Conversion rates of alkylation of benzaldehyde at 30 °C, at two different reagent loads

Reagent loading		NMR purity profile			
Bromobenzene (M)	**Benzaldehyde (M)**	**Bromobenzene (%)**	**Benzaldehyde (%)**	**Diphenylmethanol (%)**	**Benzophenone (%)**
0.25 ml/min (0.5 M)	**0.25 ml/min (0.5 M)**	0 %	1 %	95 %	4 %
0.5 ml/min (1.0 M)	**0.5 ml/min (1.0 M)**	0 %	1 %	93%	6 %

Working at different reagent loadings did not affect conversion, which indicates 10 ml reactor volume for the alkylation provided enough residence time for the reaction to reach completion.

Formation of ethyl magnesium bromide

To evaluate the effect of substrate on the formation of the Grignard species, bromobenzene was replaced by an alkyl bromide, bromoethane.

Under the same reaction conditions, 1 M solution of bromoethane was passed through the magnesium packed reactor.

Figure 6 shows the change in volume of the VBFR, when 1.0 M solution of bromoethane and 1.0 M solution of bromobenzene was passed at 80 ºC. The VBFR theoretical volume loss can be predicted. It can be calculated from the organohalide's loading (mol/min), magnesium's molecular weight and its density:

$$VBFR_{change}\left(\frac{ml}{min}\right) = Reagent\ loading x Mg_{M.W.} x Mg_{\rho}$$

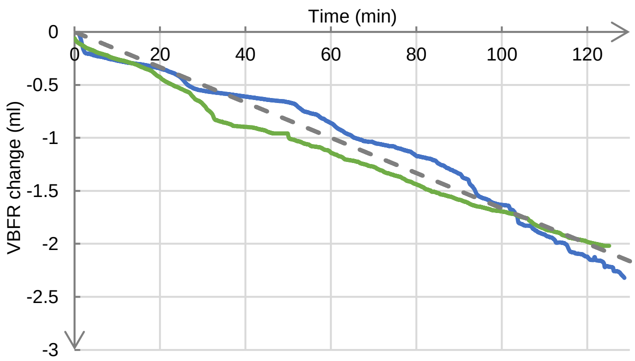

Figure 6 – Evolution of VBFR volume change over time when passing 1 M solution of bromobenzene (blue) and 1 M solution of bromoethane (green). Theoretical change in dotted line

The slight deviation from the theoretical slope can be attributed to the change in magnesium's packing and how the particles rearrange over time.

The alkylation of benzaldehyde with ethyl magnesium bromide was carried under the same experimental conditions as with phenyl magnesium bromide. VBFR was set at 80 ºC, the second reactor was set at 30 ºC and both reagents were pumped at 0.5 ml/min.

Results were comparable in terms of conversion, which are highlighted in Table 2.

Table 2 – Conversion rates of alkylation of benzaldehyde at 30 °C, with two different Grignard reagents. Both reagents were pumped at 0.5 ml/min

Reagent loading	**NMR purity profile**			
	Organohalide (%)	**Benzaldehyde (%)**	**Alcohol (%)**	**Ketone (%)**
Bromobenzene (1 M) ***Benzaldehyde (1 M)***	0 %	1 %	95 %	4 %
Bromoethane (1 M) ***Benzaldehyde (1 M)***	0 %	6 %	91 %	3 %

Evaluation of ketone formation

The presence of benzophenone and propiophenone indicated an undesired oxidation took place after the alcohol was formed

As the reactor was made of PFA, oxygen could permeate through the tube walls and oxidise the secondary alcohol into a ketone, reducing the overall conversion.

It was also noted the presence of 1 % benzaldehyde within the final product. Starting concentrations of both organohalide and benzaldehyde were the same. Any residual moisture with the reagents would quench organo magnesium bromide specie, making it the limiting reagent on the alkylation reaction.

In order to further increase the conversion on the final product, two changes were made on the reaction of phenyl magnesium bromide with benzaldehyde:

- PFA reactor was replaced for a stainless steel (SS) tubular reactor. This will prevent any oxygen diffusion into the reactor.
- Bromobenzene/benzaldehyde ratio was altered, from 1:1 to 1:0.8.

Flowrates for both reagents were kept at 0.5 ml/min and reactor temperatures were maintained at 80 ºC for the Grignard formation and 30 ºC for the alkylation of benzaldehyde.

Table 3 – Conversion rates of alcohol formation, with two different reactor materials and two different ratios bromobenzene/benzaldehyde.

Reagent loading	**Reactor 2 material**	**NMR purity profile**			
		Organohalide (%)	**Benzaldehyde (%)**	**Diphenylmethanol (%)**	**Benzophenone (%)**
Bromobenzene (1 M) at 0.5 ml/min ***Benzaldehyde (1 M)*** **at 0.5 ml/min**	PFA	0 %	1 %	95 %	4 %
Bromobenzene (1 M) at 0.5 ml/min ***Benzaldehyde (0.8 M)*** **at 0.5 ml/min**	SS	0 %	0 %	100 %	0 %

As table 3 shows, changing the reactor material from PFA to stainless steel had a positive effect, as benzophenone was not detected by NMR (see Figure 9 in supplementary information).

The addition of 25 % excess of bromobenzene proved beneficial to fully alkylate benzaldehyde to diphenylmethanol. Any excess phenyl magnesium bromide was quenched with water in the collection vial.

Conclusions

Making Grignard reagents in flow can be a challenging task to complete when using existing technologies; and will often require of an activation step for the reaction to happen.

We have successfully developed a new Variable Bed Flow Reactor which can control the packing density of magnesium particles, allowing generation of Grignard reagents in a fast, convenient, high yielding process.

We found that a stainless steel reactor was needed to prevent any oxidation of diphenyl methanol into benzophenone due to oxygen diffusion.

We have demonstrated by using the VBFR, the formation of phenyl and ethyl magnesium bromides occurred without the need of any pre-activating step

References

[1] V. Grignard, “Sur quelques nouvelles combinaisons organométaliques du magnésium et leur application à des synthèses d’alcools et d’hydrocarbures,” *Compt. Rend.*, vol. 130, p. 1322, 1900.

[2] H. Gilman and R. H. Kirby, “A simplified preparation of activated magnesium for grignard reagents,” *Recl. des Trav. Chim. des Pays-Bas*, vol. 54, no. 7, pp. 577–583, Jan. 1935.

[3] U. Tilstam and H. Weinmann, “Activation of Mg Metal for Safe Formation of Grignard Reagents on Plant Scale,” *Org. Process Res. Dev.*, vol. 6, no. 6, pp. 906–910, Nov. 2002.

[4] S. V Ley and C. M. R. Low, “Preparation of Activated Magnesium BT - Ultrasound in Synthesis,” S. V Ley and C. M. R. Low, Eds. Berlin, Heidelberg: Springer Berlin Heidelberg, 1989, pp. 33–38.

[5] L. Huck, A. de la Hoz, A. Díaz-Ortiz, and J. Alcázar, “Grignard Reagents on a Tab: Direct Magnesium Insertion under Flow Conditions,” *Org. Lett.*, vol. 19, no. 14, pp. 3747–3750, Jul. 2017.

[6] E. T. Sletten, M. Nuño, D. Guthrie, and P. H. Seeberger, “Real-time monitoring of solid-phase peptide synthesis using a variable bed flow reactor,” *Chem. Commun.*, 2019.

Supporting information

Figure 7 – NMR of diphenyl methanol obtained in flow with phenyl magnesium bromide with benzaldehyde at 30 ºC

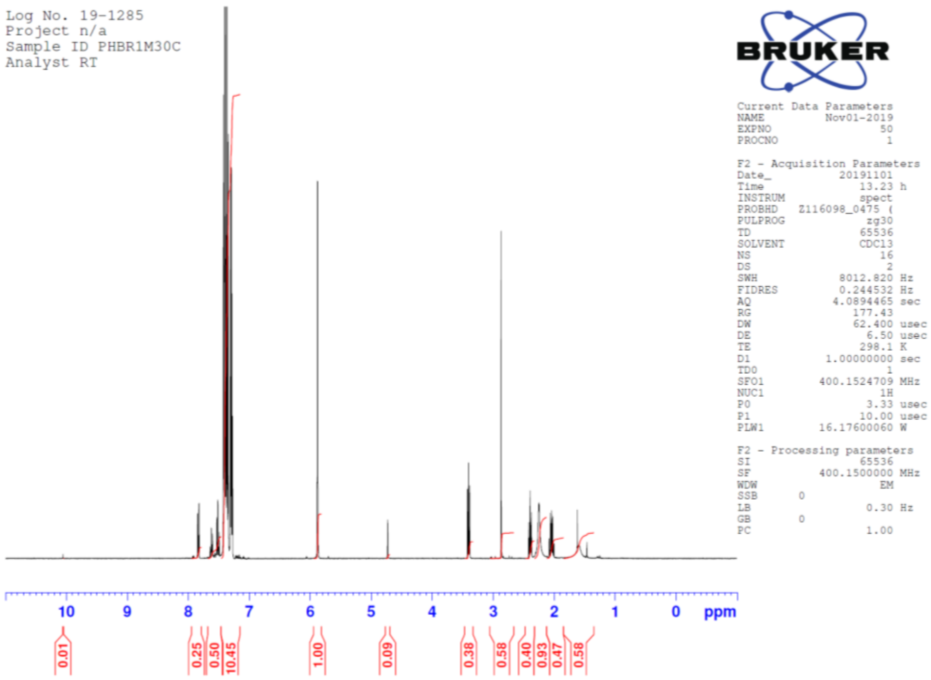

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Figure 8 – NMR of 1-Phenyl-1-propanol obtain from reacting ethyl magnesium bromide with benzaldehyde at 30 ºC

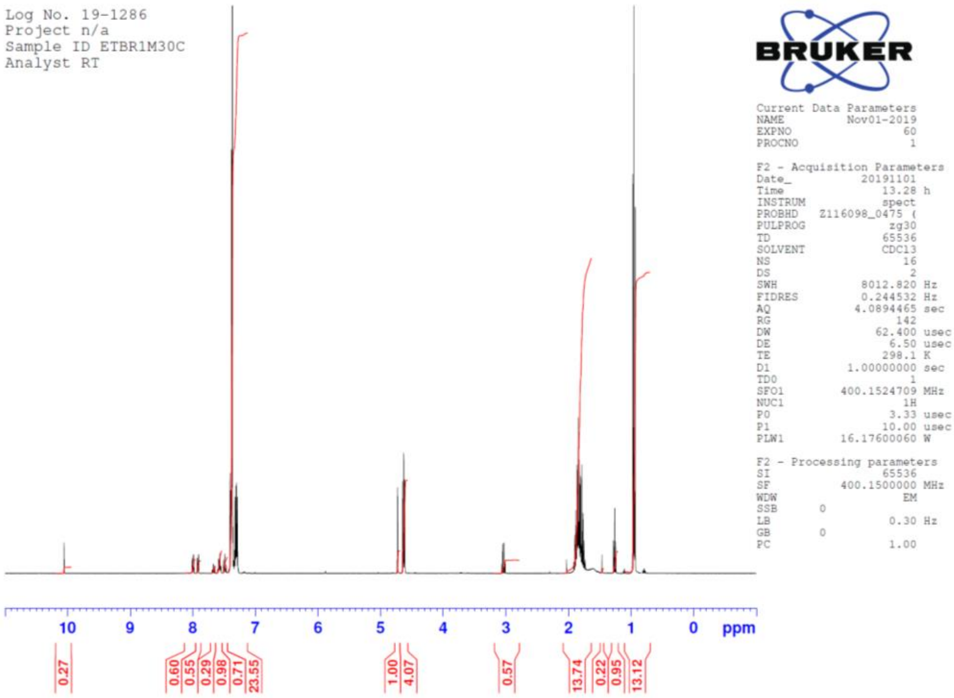

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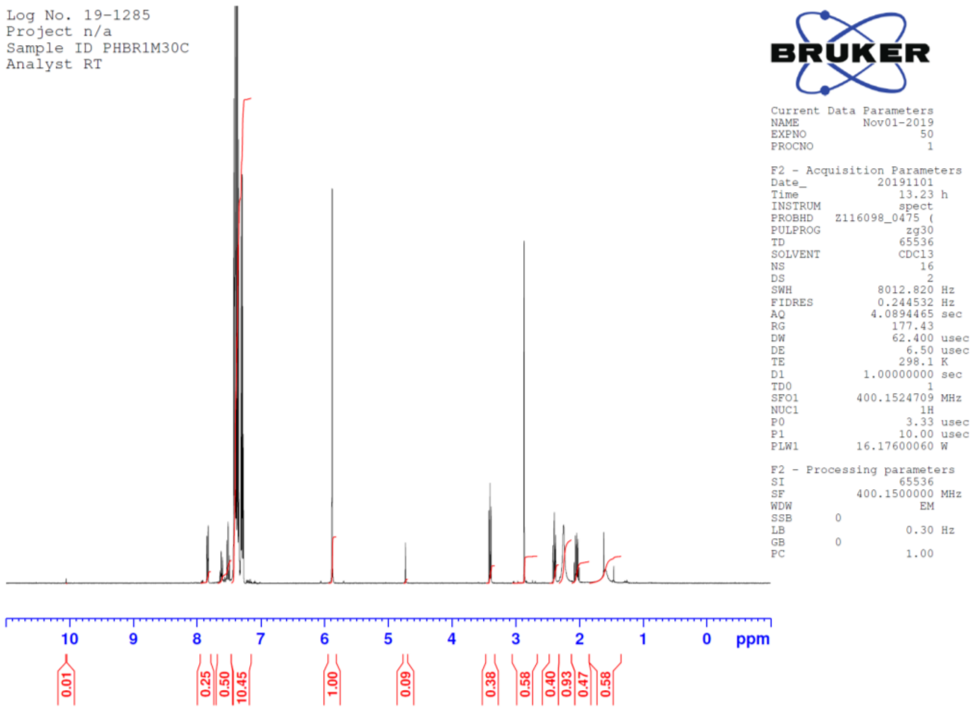
Figure 9 – NMR of diphenyl methanol obtained in flow with phenyl magnesium bromide with benzaldehyde at 30 ºC in a stainless steel tubular reactor



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