Investigation of a Grignard Reaction at Small Scale

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1. Introduction
A Grignard reaction is always difficult to scale up. Safety has to be the concern for Grignard reactions. Since it is obvious that a hazardous incident can occur with Grignard reactions, it is necessary to have a good understanding of the process.

The safety engineer must be able to answer two questions:
• Under normal operating conditions, can the cooling system remove the heat produced by the reaction? This question can easily be answered by calorimetric measurements of the process. The heat generated must be compared with the maximum heat the industrial reactor can remove.
• What will happen if a cooling or power failure occurs? In this case, the heat generated by the reaction is kept in the reactor and increases the reaction temperature. The boiling point may be reached, an over-pressure could arise or the reactor may burst! Finally, the safety engineer must design the process in a way that a failure will not result in a critical incident.

2. Reaction

The studied reaction is the first step in an industrial process. 0.84 part of tetrahydrofuran and 0.27 part of toluene are added to a calorimeter at room temperature. The mixture is heated up to 40°C. After mixing, 0.14 part of magnesium is added. 2.08 parts of p-bromotoluene solution is added within about 2 hours. Stirring the reaction mass is then continued for about 1 hour at 40°C. Some physical properties are also needed:

<table>
<thead>
<tr>
<th>Name</th>
<th>m in g/mol</th>
<th>( \rho ) in g/cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Bromotoluene</td>
<td>170</td>
<td>1.41</td>
</tr>
<tr>
<td>Toluene</td>
<td>92</td>
<td>0.87</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>72</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Table 1
Physical properties
3. Apparatus
Technology reducing the time required for screening, optimization, characterization, and scale-up of target compounds holds significant time-to-market value for chemical and pharmaceutical companies and contract manufacturing services. Automated laboratory reactors (ALR) are essential tools for these purposes. Companies are turning to this new technology offered by METTLER TOLEDO to decrease time to market while increasing their knowledge base of chemical processes at earlier stages of the development cycle. The information gained, directly impacts the areas of process research, organic synthesis, process development, and manufacturing.

The Automated Laboratory reactors (ALR) deliver precise and repeatable control of critical reaction variables (temperature, stirrer speed, etc.) and automation of routine experimental procedures (dosing, pH control, etc.), allowing the rapid optimization of critical reaction variables (catalyst, solvent, pressure, dosing rate, etc.). Experiments can be run on scales from as little as 25 mL during the characterization phase. In addition, calorimetric information can be obtained for use in scale-up and safety determinations.

The METTLER TOLEDO Reactor Box 04-50, part of the MultiMax™ family, is used here. MultiMax™ is an automated parallel reactor system designed for process screening and optimization. MultiMax™ increases productivity while benefiting from precise, reproducible and documented experiments. MultiMax™ is versatile, so that a wide range of experiments can be performed. MultiMax™ features simultaneous temperature control of the reaction mixture and jacket, as well as multiple dosing, magnetic or mechanical stirring, pH and dosing controls. Reactors are independent from each other, offering enhanced flexibility.

The high quality of temperature control and measurement allows getting valuable information such as reaction initiation, reaction end point and relative thermal data.

The METTLER TOLEDO MultiMax™ intuitive software interface has been designed for easy experiment definitions, data visualization, and data export. For in-depth reaction characterization, the MultiMax™ system can be combined with real-time analytics – ReactIR probes for FTIR and FBRM probes for particle size measurement – and with the MultiMax™ ART dedicated robot platform for sampling, quenching, dilution and chromatography injection. Four different versions of MultiMax™ are available in terms of number of reactors in parallel and volumes: 16 x 10 ml, 16 x 20 ml, 4 x 50 ml and 2 x 250 ml.

4. Heat flow theory
The following equation represents a heat balance over the reactor.

$$\sum m_i c_i \frac{dT}{dt} = q_{\text{in}} + q_{\text{loss}} - q_{\text{rx}} - q_{\text{ex}}$$  \hspace{1cm} Eq 1

where $m(i)$ and $c_p(i)$ are the mass and the specific heat capacity of the $i$th component in the reaction mixture, $q_{\text{rx}}$ and $q_{\text{loss}}$ are the power terms corresponding to (i) feeding at a temperature different from $T_r$, and (ii) the heat lost to the surroundings. $q_e$ is the heating power resulting from the calibration. The terms $q_{\text{ex}}$, $q_{\text{in}}$, and $q_{\text{loss}}$ represent inflow terms, while $q_{\text{ex}}$ and $q_{\text{loss}}$ are outflow terms.

In theory, $q_{\text{ex}}$ can be calculated from Eq 1 if the other terms can be evaluated or measured with sufficient accuracy. The various terms in Eq 1 are described next.

4.1 Accumulation of heat
The reaction is performed isothermally. Therefore, the heat accumulation is negligible.

$$\sum m_i c_i \frac{dT}{dt} = 0$$  \hspace{1cm} Eq 2
4.2 Heat effect of the feed stream
The heating effect due to the difference in temperature between the feed temperature $T_{\text{in}}$ and the temperature of the reactor contents $T_{\text{r}}$ is given by:

$$q_{\text{dos}} = \dot{V} \rho_{\text{in}} c_{\text{p, in}} (T_{\text{in}} - T_{\text{r}}) \quad \text{Eq 3}$$

where $\rho_{\text{in}}$ and $c_{\text{p, in}}$ are the density and the specific heat capacity of the feed stream. The MultiMax™ software allows correcting $q_{\text{dos}}$.

4.3 Calibration power
In order to evaluate the heat transfer coefficient $U$, a calibration is performed before and after the reaction, i.e., $q_c$ is zero during the reaction.

4.4 Heat exchange
Assuming steady-state conditions, $q_{\text{ex}}$ can be calculated from a heat balance over the jacket:

$$q_{\text{ex}} = F_{\text{cool}} c_{\text{p, cool}} (T_{\text{j, out}} - T_{\text{j, in}}) \quad \text{Eq 4}$$

where $F_{\text{cool}}$ and $c_{\text{p, cool}}$ are the mass flow rate and the specific heat capacity of the cooling medium, $T_{\text{j, out}}$ and $T_{\text{j, in}}$ the outlet and inlet temperatures of the cooling medium, respectively.

If the flow rate of the cooling medium is high, the temperature variation in the jacket is negligible and $T_{\text{j, out}} \approx T_{\text{j, in}}$. As this is the case with the MultiMax™, the heat exchanged through the reactor wall can be expressed as:

$$q_{\text{ex}} = U A (T_{\text{r}} - T_{\text{j}}) \quad \text{Eq 5}$$

where $T_{\text{j}}$ is the temperature of the jacket.

4.5 Heat losses
In every experiment, there are some losses (through the cover for example). The heat losses are integrated in the base line.

4.6 Measurement
For the isothermal reaction, Eq 1 becomes

$$q_{\text{ex}} = q_{\text{flow}} + q_{\text{dos}}$$

where all parameters are known, except the heat transfer coefficient. The heat transfer coefficient will be evaluated before and after the reaction. The calibration heater is switched on for 10 minutes and delivers a known amount of heat into the system.

At the same time, the software imposes the reaction temperature to stay constant, so Eq 1 becomes

$$O = U A (T_{\text{r}} - T_{\text{j}}) + Q_c$$

UA can then be evaluated by integration of the $T_{\text{j}} - T_{\text{j}}$ signal:

5. Heat measurements
22 g of tetrahydrofuran are mixed with 4 g of toluene. 2.4 g of magnesium are also added to the reactor (“first fill”). The reaction mass is heated to 40°C. After stabilization of the signal, a UA calibration is performed.

The p-bromotoluene solution is prepared and 20 ml of the solution dosed to the reaction mass. Two reactors (reactors “R11” and “R14”) are used in parallel to improve the speed of the project.

5.1 Calibration
After adding the first fill to the reactor, a calibration is performed at 40°C to determine the UA value before the experiment.

The calibrations are performed for the two reactors at the same time. At the end of the experiment, the same calibration is performed in order to determine the UA value after the reaction.

![UA calibration](image1)

![Calibration of UA](image2)

5.2 Calibration
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The calibrations for the two reactors are not performed at the same time. This has no impact on the results as the reactors are completely independent. The results are displayed in Figure 4.

Table 2
<table>
<thead>
<tr>
<th>Reactor</th>
<th>UA before reaction</th>
<th>UA after reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1 (reactor &quot;R11&quot;)</td>
<td>0.93 W/K</td>
<td>1.02 W/K</td>
</tr>
<tr>
<td>R2 (reactor &quot;R14&quot;)</td>
<td>0.98 W/K</td>
<td>1.04 W/K</td>
</tr>
</tbody>
</table>

UA results
The results correspond to our expectations. They are similar for both reactors and increase after the reaction. Indeed, the viscosity of the reaction mass does not change too much, but the exchange area does due to the dosing of p-bromotoluene.

Figure 5
Heat generated in reactor "R11"

Figure 6
Heat generated in reactor "R14"

5.2 Reaction
After the first calibration, the p-bromotoluene is dosed to the reaction mass step by step to both reactors. Integration limits are then drawn for the reaction (T_r – T_j curve), and the heat generation rate is calculated and integrated.

5.3 Heat generation results
The heat generated by the chemical reaction has been evaluated as

\[ Q_r = Q_{flow} + Q_{accu} + Q_{dos} \]

where
- the specific heat capacity of the reaction mass has been approximated to 2 J/(g K)
- the specific heat capacity of the dosed compound has been approximated to be 2 J/(g K) and the temperature of addition was approx. 25°C.
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6. Investigation of the reaction

6.1 Induction time

Figure 7 – At the beginning of the reaction, we noticed an induction time. This is an important message for the scale-up engineer: The reaction does not start right away.

6.2 Iodine effect

Figure 8 – As the reaction did not really start at the beginning of the dosing (no effect in the $T_r - T_j$ signal) and dosing was still going on, some accumulation generated. In order to verify this point, we added some Iodine to the reaction mass. The reaction started right away. We can see the effect in the $T_r - T_j$ curve:

6.3 Stirrer speed effect

We switched off the stirrer during the run to see the effect of mixing. At the same time we kept the addition running.

Figure 9 displays the evolution of $T_r - T_j$. It appears that the reaction stops when the stirrer speed is zero.

This is useful safety information: In case of a failure one can stop the reaction by stopping the agitation. However, if the dosing is not interrupted at the same time, some accumulation will occur. As a result, as soon as stirring is started again the heat generated will be higher than before. Again, this is a very important safety consideration.

6.4 Dosing accumulation

Figure 10 – At the end of the dosing, the reaction is almost done. There is not much accumulation.

<table>
<thead>
<tr>
<th>Curve</th>
<th>Index</th>
<th>Start time hh:mm:ss</th>
<th>End time hh:mm:ss</th>
<th>Baseline type</th>
<th>Integral kJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_{r11}$</td>
<td>1</td>
<td>00:58:56</td>
<td>03:24:50</td>
<td>Proportional to conversion</td>
<td>19.5</td>
</tr>
<tr>
<td>$Q_{r14}$</td>
<td>2</td>
<td>00:58:08</td>
<td>03:30:10</td>
<td>Proportional to conversion</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Enthalpy

In theory, the enthalpy should be the same for both reactors. Here, we have a difference of 7%. The system is therefore reliable and within the limits that can be expected for such a system.
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7. Conclusion
The reaction has been successfully carried out in METTLER TOLEDO MultiMax™ reactors. The engineers are given some interesting information about the process. The information is used for scale-up purposes. A Grignard reaction is always challenging. With this type of reaction, a good understanding of the behavior of the process is always necessary.

In the studied process, we noticed that:

- The $T_r - T_j$ measurement revealed an induction time.
  In practice, the induction time could go up to 24 hours. As it is not reasonable to wait that long, a lot of "tricks" have been proposed to start the reaction. For example, adding a part of a previous reaction could help. In our case, iodine has been added. The effect was immediate and led to the initiation of the reaction.

- If the stirrer is switched off as shown during the experiment, the reaction stops as well.
  Since the Grignard reaction is a heterogeneous reaction (solid/liquid), the mass transfer between the magnesium and the solution plays an important role. Therefore, the agitation is important and must be efficient enough to ensure a good mass transfer. As a rule, one can say that if the stirrer is not working properly, the addition must be stopped. From a safety point of view, switching off the stirrer will lower the heat exchange capacity of the reactor and create inhomogeneity in the reaction mass, particularly at the bottom of the reactor with an accumulation of magnesium.
  As shown with stability measurements (for example DSC), magnesium destabilizes the reaction mass and leads to high-energy decompositions.

- The accumulation is low.
  A cooling failure scenario can be considered with an accumulation of 20%. Not all Grignard reactions are identical of course and this assumption must be verified case by case.

For the scale-up of this type of reaction, it is necessary to take into account the moderate cooling capacities of industrial reactors; around 30 W/kg and 140 W/kg with a condenser. Dosing time or working under reflux may be the solution to investigate. At all times, the cooling capacity must be higher than the heat produced by the reaction.