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DEVELOPMENT OF AN EFFICIENT AND SAFE PROCESS FOR A GRIGNARD REACTION VIA REACTION CALORIMETRY

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Abstract

A Grignard reaction of reactant *A* and phenyl magnesium chloride is used to make a pharmaceutical intermediate at the production scale. The elimination of protecting groups on *A* was proposed as a means to reduce synthesis costs. This new synthesis route, however, had process efficiency and safety issues associated with it: (1) build-up of unreacted *A* in the reactor, (2) influence of *A*'s particle size on the reaction rate, (3) the sensitivity of the reaction rate to the reaction temperature and to the (changing) solvent composition, and (4) the highly exothermic nature of the reaction.

The Mettler RC1 Reaction Calorimeter was used to quantify the influence of solvent composition, temperature, and particle size on the reaction rate. Results indicated a dramatic effect of solvent composition and reaction temperature on the reaction rate; for example, over a temperature range of just 30°C, the reaction time decreased from more than a day to just a few minutes. At such high reaction rates, the vessel jacket could not remove the reaction heat sufficiently and the internal temperature rose adiabatically.

These results were used to make process design and operation recommendations for safe and efficient plant operation with this modified Grignard reaction system.

Keywords: Grignard reaction, process development, process safety, reaction calorimetry

Introduction

Pharmaceutical intermediate *C* is formed upon the coupling of phenyl magnesium chloride (Grignard) with reactant *A* in a xylene/tetrahydrofuran (THF) solvent mixture (Fig. 1). THF is not only a solvent, but also binds to the Grignard. Increasing THF concentration is known to lower the minimum temperature at which reaction is detected; thus it accelerates the rate of reaction. It is believed that an increase in the THF complexation with the Grignard causes this increase in its reactivity. In previous studies of this reaction, increasing the THF:Mg ratio over 5.5 g:g was seen to decrease the yield [1].

The reaction takes place in two steps, first formation of a ketone, and second, via addition of a second phenyl group, the formation of the pharmaceutical intermediate product, *C* (Fig. 1). The current process uses protecting groups on *A* to avoid side reactions with the Grignard to form magnesium chloride salts and benzene.

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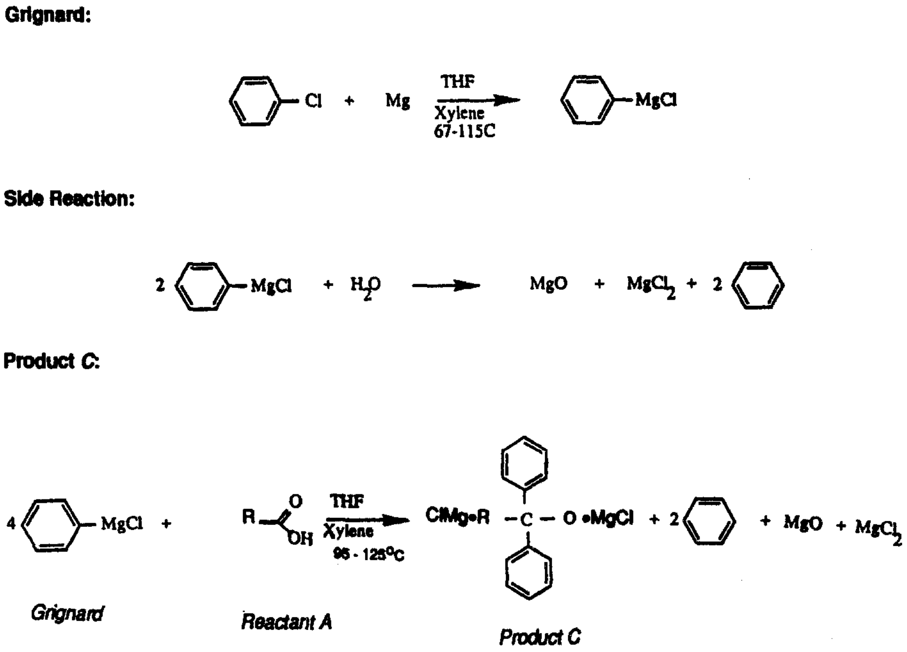

Fig. 1 Reaction scheme

However, it is estimated that about $1000000 per year could be saved via the elimination of the additional process steps and waste disposal issues associated with the protecting group chemistry.

In the proposed process route, in addition to the two moles of Grignard required to add two benzene rings on to *A*, two more moles of Grignard are required to react with the unprotected functional groups on *A* (producing magnesium chloride salts plus benzene as a byproduct). Additional amounts of benzene can be formed if water is present. Thus a minimum of four moles of Grignard are required per mole of reactant *A*. A further complication to the proposed process route is that while protected reactant *A* dissolves in the reaction mixture, unprotected *A* is only partially soluble and must be added to the pre-made Grignard in a slurry with xylene. In order to control the heat release rate from the reaction, a continuous addition of *A* is used.

This proposed process route was previously investigated at ambient pressure in the lab and in the pilot plant [2]. The system reached reflux soon after the addition of *A* was begun. The reaction temperature, which began at about 125°C, reduced to about 95°C as conversion progressed, owing to the release of THF from the Grignard. The addition of *A* was typically done over four hours, after which time some distillation was done to increase the reaction temperature back to about 115°C (to increase the reaction rate and finish off the reaction). Problems encountered in the pilot plant included: (1) build-up of unreacted *A*, (b) the inability to maintain adequate temperature control under some conditions, and (3) an apparent high degree of sensitivity of the reaction rate to THF concentration and to reaction temperature.

Maintaining good temperature control is critical since the operating temperature is close to the temperature at which decomposition reactions become unacceptably fast (135°C). However, since THF concentration and temperature could not be manipulated independently under reflux, their impact on the process was only understood qualitatively. The impact of the particle size of reactant *A* was unknown.

A reaction calorimeter is an automated laboratory reactor equipped with the necessary instrumentation to not only monitor and control system variables such as temperature, pressure, and addition rates; it is also equipped to measure the heat flow evolving from a given transformation (e.g. from a reaction). Reaction calorimetry is a powerful tool for use in process development, process optimization, and process safety [3–5]. For this particular application, the key advantages include: (1) the ability to follow reaction progress continuously via measurement of heat flow, (2) the ability to separate solvent composition from temperature by operating under pressure, and (3) the ability to simulate the current and the proposed plant production processes.

Experimental

The following variables were investigated (1) THF: Mg ratio, (2) temperature, and (3) particle size of *A*. To enable these variables to be studied independently, the experiments were run isothermally (and therefore under pressure). Experiments were made over the following ranges: THF:Mg ratio: 4:1 to 6:1 g:g; temperature: 95 to 125°C, and particle size: 20–60 mesh to >120 mesh (Table 1).

Experiments were performed in the Mettler RC1 Reaction Calorimeter, equipped with the 1.2 liter glass MP10 vessel. The Grignard reagents was premade and frozen, then an appropriate amount was thawed and transferred to the reaction vessel. After heating the Grignard up to reaction temperature, it was thermally equilibrated and calibrated (in order to quantify the heat flow from the reaction).

Table 1 Experiment summary. Small particle are >120 mesh, medium particles are 60–120 mesh and large particles are 20–60 mesh. The theoretical heat of reaction is 3.90 kJ g^{-1}. (1) No detectable reaction occurred at 80°C after adding the first shot of *A* and holding overnight; therefore the temperature was ramped up to 102°C for the remaining additions of *A*

Run #	THF:Mg/(g:g)	T/°C	Particle size of *A*	Heat/kJ (g $A)^{-1}$
5	4:1	125	large	3.93
4	6:1	125	large	3.70
1	6:1	80 to 102$^{(1)}$	large	3.31
6	4:1	125	small	3.70
2	6:1	125	small	4.32
3	6:1	110	small	2.22
9	5:1	95	medium	2.76
7	5:1	110	medium	3.54
8	5:1	125	medium	3.70

Aliquots of *A*, slurried in xylene, were then shot added into the reactor from a 50 ml slurry addition vessel. *A* was typically added in five aliquots, each comprising 20% of the total amount of *A* (1 mole *A* per 4.87 moles Mg) to be added. Following each addition, an aliquot of xylene was sprayed into the addition vessel and subsequently added to the reactor in order to flush out residual *A* from the slurry addition vessel. After a shot of *A* was added, it was allowed to react prior to addition of subsequent shots. Additional calibrations were performed in-between additions of *A* and at the end of the reaction as necessary. The reaction mixture was sampled via a 3/8 inch dip tube after each addition of *A* had reacted to completion (defined by no observable solids in the reactor and an unchanging system heat flow profile *vs.* time). Agitation was maintained during sampling in order to obtain a reasonably representative sample.

The analysis for ketone and product *C* was done using an external standard, gradient reverse phase HPLC procedure. Samples were first diluted in THF, then mixed either manually or via sonication prior to further dilution, acidification, and then filtration. Aliquots were then injected onto Spherisorb C-8, 5 micron, 250×4.6 mm, #0311 SP column. A gradient profile was used, beginning at 50/50 acetonitrile (ACN)/0.02 *M* KH_2PO_4 and ending at 25/75 ACN/0.02 *M* KH_2PO_4. Peak detection was done at 232 nm.

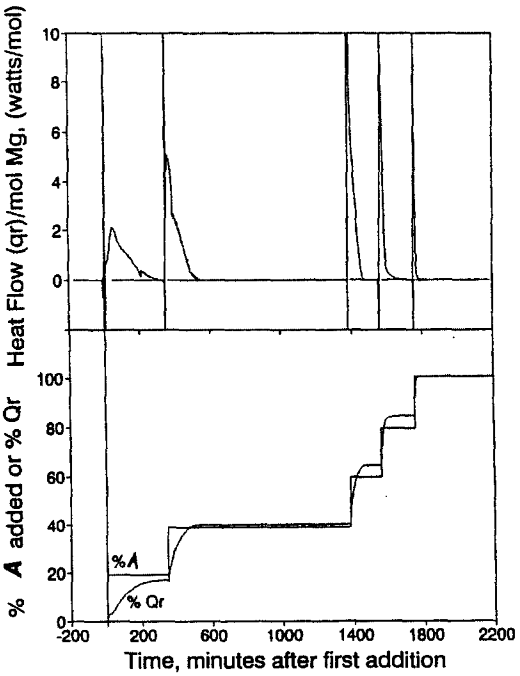

Fig. 2 A typical experiment. Heat flow (qr), percentage of integral heat observed (%Qr), and percentage of *A* added *vs.* reaction time for Run #6. Run #6 conditions: THF:Mg: 4:1; small particles of *A*, 534 g Grignard loaded (43 g Mg), a total of 49 g *A* added, and a reaction temperature of 125°C

Results and discussion

The calorimetric results for a typical experiment are shown in Fig. 2. Note that the reaction accelerates over time: for the first addition of *A*, the peak reaction heat flow is only about 2 W (mol Mg)$^{-1}$ and requires five hours to react whereas by the last (fifth) addition, the peak heat flow is about 10 W (mol Mg)$^{-1}$ and is complete in 15 min. It is believed that this acceleration is mainly due to the catalytic-like effect resulting from the release of THF complexed with the Grignard that occurs with reaction conversion for low to moderate THF loadings (4:1 to 5:1 g:g THF:Mg). In contrast, reactions that are initiated at high THF loadings (6:1 g:g THF:Mg) show little change in the reaction profile as a function of conversion. When the initial THF:Mg ratio is increased from 4:1 to 6:1, there is roughly an order of magnitude increase in the peak heat flow in conjunction with an order of magnitude decrease in the time for a shot to react (Fig. 3). This rapid release of

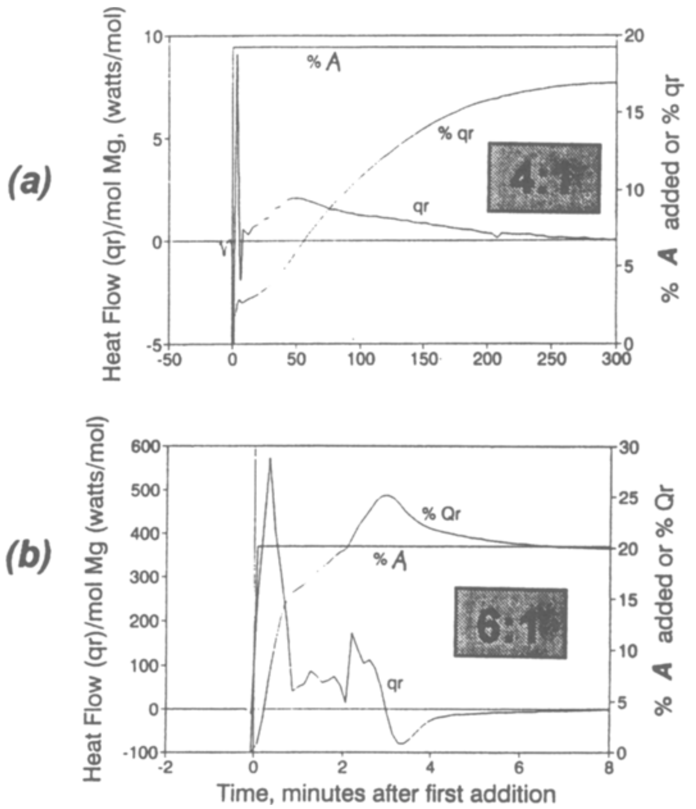

Fig. 3 Effect of THF concentration. 4:1 THF:Mg (a) is compared to 6:1 THF:Mg (b).
a: Run #6/Add #1–9.5 g *A* added, integral heat =3.2 kJ g^{-1} *A*.
b: Run #2/Add #1–9.6 g *A* added, integral heat =5.0 kJ g^{-1} *A*. Both runs shown have small particles of *A* and a reaction temperature of 125°C

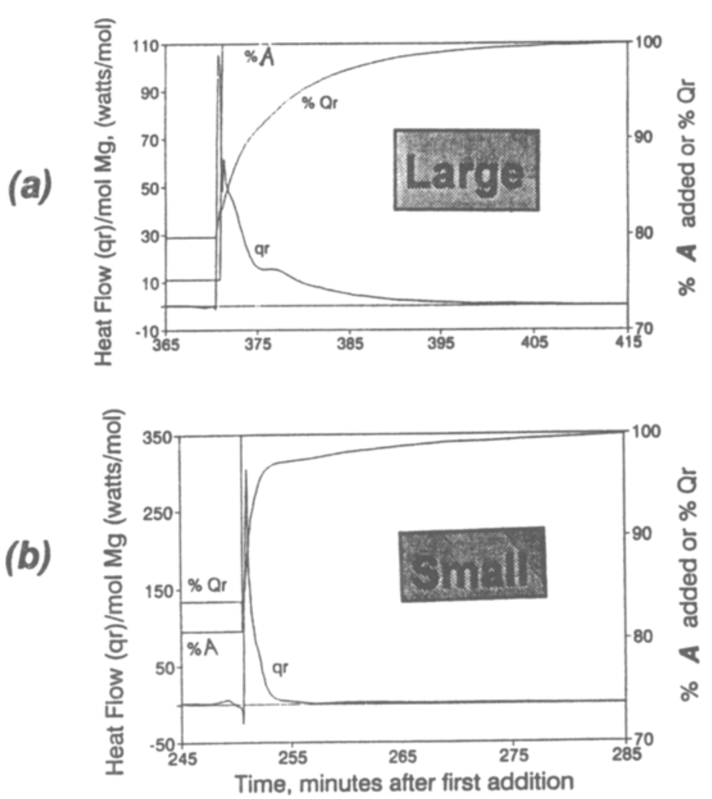

Fig. 4 Effect of *A* particle size. Large, 20–60 mesh, particles (a) are compared to small, > 120 mesh, particles (b). a: Run #4/Add #5–11.8 g *A* added, integral heat = 3.0 kJ g^{-1} *A*. b: Run #2/Add #5–9.1 g *A* added, integral heat =3.6 kJ g^{-1} *A*. Both runs shown have THF:Mg of 6:1 and a reaction temperature 125°C

heat caused the reactor contents to self-heat essentially adiabatically, the internal temperature rising 12°C above set-point in just one minute.

Increasing the particle size of *A* from > 120 mesh to 20–60 mesh significantly increases the "tailing out" of the heat flow peak, resulting in a lower maximum heat flow rate and about an order of magnitude increase in peak width (and thus in the time to react) (Fig. 4).

Experiments were run at three different temperatures, all with the medium particle size *A* and with the middle THF loading (5:1 THF:Mg) (Fig. 5). At 95°C, there was no detectable reaction upon addition of the first shot of *A* (Fig. 5a). The reaction temperature was brought up to 125°C to allow *A* to react out prior to adding the second shot. Only with the third shot of *A* did the reaction proceed at 95°C. In contrast, the time for the first shot of *A* to react at 110°C was six hours, while at 125°C, it was only about 20 min. Moreover, at a temperature of 110°C, the majority of the heat flow was removed at a steady rate of 1 W (mol Mg)$^{-1}$ spanning nearly the entire six hours of reaction time; at 125°C, 90% of the heat was removed

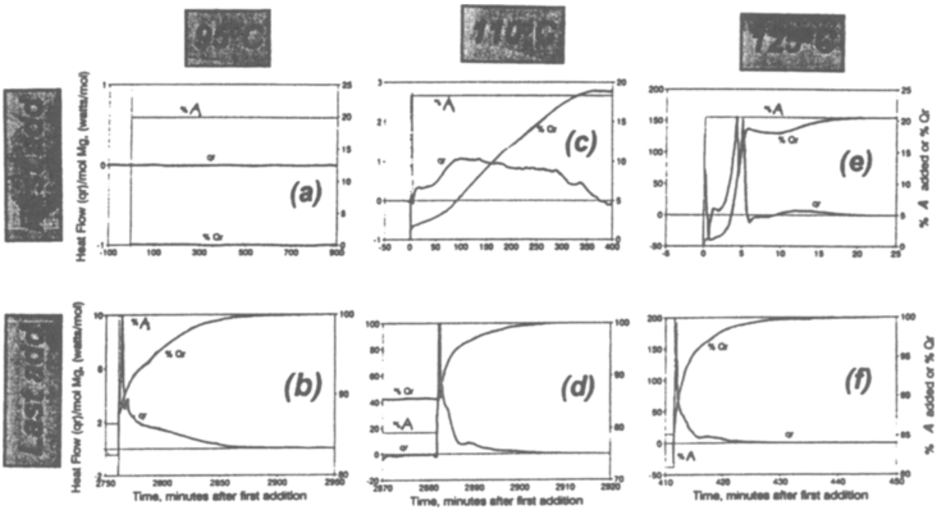

Fig. 5 Effect of temperature. The first and last additions for runs at 95°C (a and b), 110°C (c and d), and 125°C (e and f) are compared. For all plots, Y-axis is heat flow in watts/mole Mg and the X-axis is time in minutes after the first addition. a: Run #9/Add #1–8.8 g *A* added, integral heat =2.4 kJ g^{-1} *A* (obtained by temporarily increasing reaction temperature to 125°C). b: Run #9/Add #5–7.7 g *A* added, integral heat =2.1 kJ g^{-1} *A*. c: Run #7/Add #1–8.3 g *A* added, integral heat =3.6 kJ g^{-1} *A*.
d: Run #7/Add #6–9.5 g *A* added, integral heat =2.4 kJ g^{-1} *A*.
e: Run #8/Add #1–9.7 g *A* added, integral heat =3.7 kJ g^{-1} *A*.
f: Run #8/Add #5–9.0 g *A* added, integral heat =2.9 kJ g^{-1} *A*.
All runs shown have a THF:Mg of 5:1 g:g and medium-sized particles of *A*

in just the first five minutes. As was the case with 6:1 THF:Mg at 125°C (Fig. 3b), this high heat load exceeded the capability of the heat exchange system, again causing an internal temperature rise of about 12°C. (In this case, the effect was moderated by the longer time period (5 min) of the heat spike combined with a temporary 3°C reduction in the temperature set-point made just prior to the addition, in anticipation of this high heat load occurring).

Thus, at low conversion (less THF available) the time to react decreases by more than an order of magnitude upon a temperature increase of just 15°C (Figs 5a, 5c, 5e). This is several-fold more than would be expected if the system had a typical activation energy. However, as conversion increases (and more THF is released), the time to react decreases only two to four fold with a 15°C temperature increase, indicating a much more typical activation energy (Figs 5b, 5d, 5f). Consistent with this result, two experiments run with a high THF:Mg ratio (6:1), one at 110 and one at 125°C, gave a decrease of a factor of two with the 15°C rise in temperature (Run #3 at 110°C, Run #2 at 125°C, Table 1). Reaction rates for both these latter runs were very fast (just a few minutes) owing to the high loading of THF, combined with the small particle size of *A*.

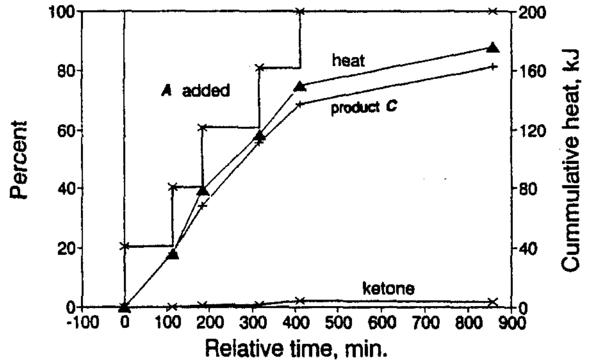

Fig. 6 A comparison of cumulative heat to HPLC analysis of samples. Data from Run #8: THF:Mg =5:1 g:g; reaction temperature =125°C; medium particles; 592 g Grignard added (44 g Mg); 47.5 g of *A* added in 5 shots

The heats of reaction measured ranged from 2.1 to 5.0 kJ g^{-1} *A* (Table 1, Figs 2–5), consistent with the theoretical heat of reaction of 3.9 kJ g^{-1} *A*. Variations are to be expected owing to incomplete conversion under some of the conditions run and to the reduced accuracy in the calorimetric measurements made for the additions having large, rapid heat flow spikes. Profiles of the amount of ketone intermediate and of product *C* *vs*. reaction time were in reasonable agreement with the cumulative (or integral) heat profiles *vs*. time observed via reaction calorimetry, authenticating the use of heat flow as a means to follow the reaction progress (Fig. 6).

Summary

THF concentration, reaction temperature, and reactant *A*'s particle size all had a significant effect on the reaction rate. The reaction time varied from just a few minutes to more than a day over the range of THF concentrations and temperatures studied. Under conditions in which the reaction rate was very fast, the jacket could not remove the heat produced sufficiently fast and the temperature increased essentially adiabatically.

Recommendations

Recommendations made to the process improvement team were:

1. Run the reaction (particularly in the early stages of conversion) such that reaction temperature can be set independently from the THF loading, for better process control. Two options to accomplish this are (a) to operate under pressure, rather than under reflux, and (b) to reflux with distillation.
2. Ensure that the proper amount of THF has been loaded, by measuring the THF concentration in the Grignard and/or by redundant THF addition monitoring devices.

3. Employ on-line monitoring of the reaction progress in the plant. Options to accomplish this include the use of (a) a reactor heat balance, (b) an in-situ FTIR, and (c) reactor sampling and subsequent HPLC analysis.

* * *

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