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Articles

Preparation of Grignard Reagents: FTIR and Calorimetric Investigation for Safe Scale-Up

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Abstract:

Preparation of Grignard reagents from organic halides and magnesium pose potential safety hazards on scale-up due to their high exothermic potential which can lead to overpressurization, discharge of contents, or explosion. One of the main challenges arises in ensuring the reaction has initiated before excessive accumulation of organic halide occurs or that the reaction does not stall and then reinitiate. Specifically, in production-scale equipment, it is sometimes difficult to ascertain whether initiation has occurred at all and whether it is safe to proceed. By using in situ infrared technology (FTIR), we have developed a method for safer scale-up of Grignard chemistry that can definitively identify that initiation has occurred. The process would involve adding approximately 5% of the organic halide charge and waiting for the initiation to occur using an in situ FTIR probe. FTIR spectroscopy can be used to monitor the accumulation of the halide and reveal when initiation occurs by the resulting decrease in the infrared absorbance. Once it has been determined that the organic halide has reacted as a result of the initiation, it is safe to proceed with the remaining halide charge. The organic halide concentration can then be continuously monitored after initiation to ensure the reaction does not stall or to halt the feed if it does stall. Further, it was shown that IR can be used to quantify the amount of water that is present in THF which is needed to confirm that the THF is dry. The IR results along with reaction calorimetry and vent-sizing data are discussed.

Introduction

Grignard reagents are extremely important in organic synthesis because they provide the chemist a relatively easy route to carbon−carbon bond formation. On production-scale, engineers are faced with significant safety challenges. For example, an incident taken from the literature illustrates the consequence of excessive accumulation of the alkyl halide.[2] An impurity in one of the feed drums caused the Grignard reaction to stall at the midpoint of the process. Alkyl halide continued to be added, at which point the batch reinitiated and a runaway reaction ensued resulting in the release of approximately 30% of the batch through the open vent lines and emergency relief system.

This paper is intended to provide feasibility for the general application of IR technology to safely monitor large-scale Grignard reactions in addition to providing thermodynamic and kinetic results for the preparation of a Grignard reagent.

Background Chemistry

Grignard reagents are usually prepared by introducing an organic halide into a stirred suspension of magnesium turnings in ether (diethyl ether or THF). The reaction occurs at the surface of the magnesium and for this reason is considered to be hetereogeneous and has been shown to involve radical intermediates.[3,4] After the Grignard reagent forms on the reactive magnesium site it dissolves away from the metal surface into the ether, exposing another fresh site for reaction. Following the initiation period, mass transfer of the alkyl halide to the reactive magnesium sites is considered to be the rate-limiting step.[2] The magnesium of the Grignard reagent is two electron pairs short of an octet but the oxygen of the ether can donate these electron pairs to the magnesium of R−Mg−X. This coordination explains the fact that ether solvents are generally required for the formation of Grignard reagents because of their ability to solubilize the Grignard reagent as it is formed. If this did not occur, the metal would eventually be covered and the reaction would cease.[3] The actual mechanism and specifically how the magnesium is inserted into the substrate is still not completely understood.[4]

Example: Droloxifene

An example of Grignard chemistry being used on scale within Pfizer is in the production of droloxifene.[5] Droloxifene is a phase II candidate for the treatment of osteoporosis being co-developed by Pfizer and Klinge-Pharma. Step 1 of Scheme 1 refers to the preparation of the Grignard reagent from a slurry of magnesium chips, THF, and the aryl halide

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[2] Yue, Sharkey, Leung, Relief vent-sizing for a Grignard reaction, *J. Loss Prev. Process Ind.* **1994**, *7*, 413−418.

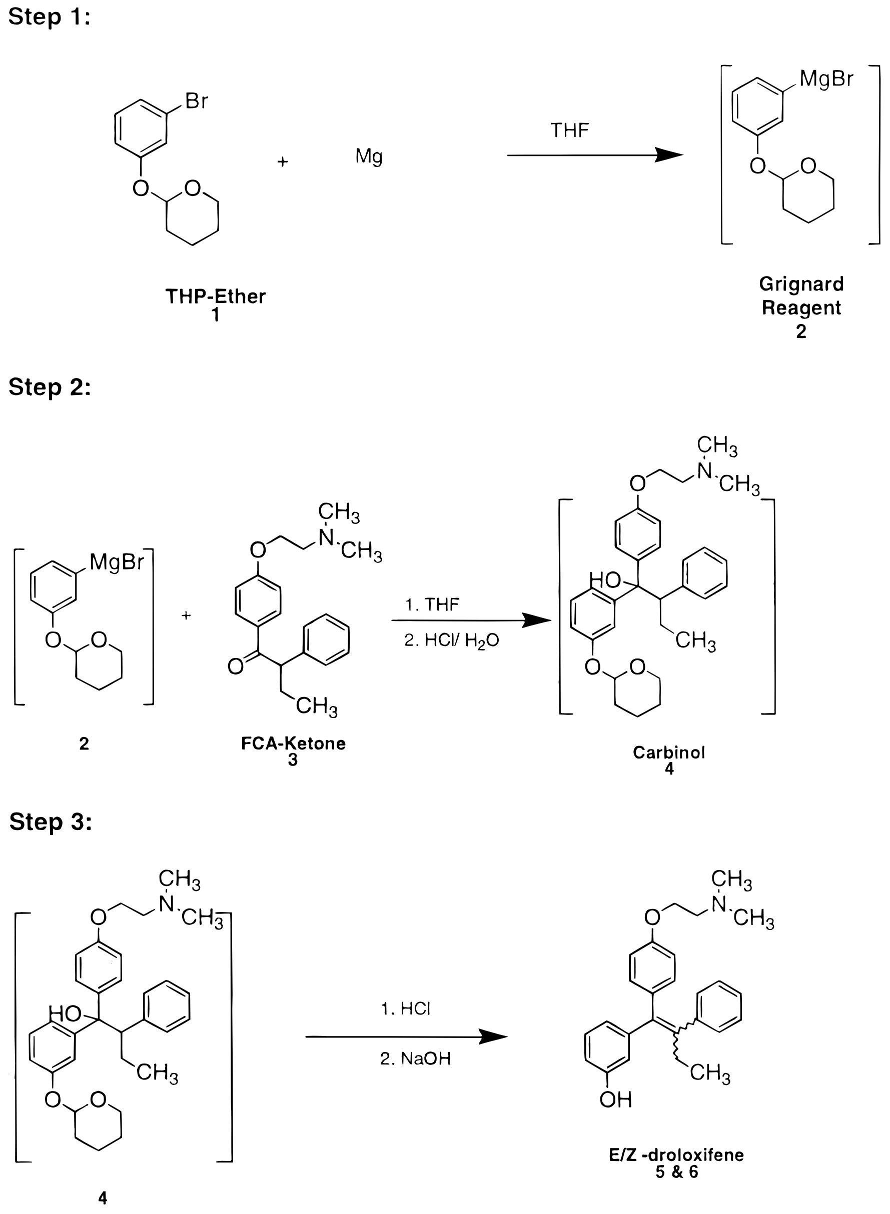
[3] Louden, G. M. *Organic Chemistry*; Addison-Wesley: Reading, MA, 1984.

[4] *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P., Eds.; Marcel Dekker: New York, 1996.

[5] Schickaneder, H.; Loser, R.; Grill, H. U.S. Patent 5,047,431, assigned to Klinge Pharma GmbH & Co., September 10, 1991.

10.1021/op9901801 CCC: $18.00

Scheme 1. **Droloxifene synthesis**



referred to as THP−ether.[6] Once the Grignard reagent is formed it is later reacted or condensed with a substrate FCA−ketone, **3**, shown in step 2, to form a carbinol **4**. Finally, the reaction is quenched to eliminate the magnesium complex to form aqueous salts of magnesium. Further treatment with acid leads to elimination and removal of the THP-protecting group. The desired isomer is isolated with further work up.

Process Safety

Preparation of Grignard reagents are generally accompanied by an initiation period which is the chief hazard associated with their manufacture. In addition, the reaction is sensitive to water and impurities which can result in delayed initiation periods. If the organic halide concentration reaches critical levels and then initiates, a serious potential runaway reaction can result which could lead to a release or an explosion due to overpressurization. Before this chemistry can be scaled up for production, many safety issues need to be addressed. For example the following are a few primary concerns:

- Accurate detection of initation is necessary to (1) signal the operators that it is safe to proceed and (2) prevent excessive accumulation of organic halide prior to initiation.
- Relief vent sizing for the scale-up equipment must be adequate to cope with runaway scenarios for the particular process.
- The condenser must be adequately sized to handle the maximum reflux rate.
- Adequate safety interlocks must be in place to prevent overcharging of either the organic halide or the substrate.

Water intrusion from all sources (solvents and condenser etc.) must be avoided for two reasons: (1) the reaction will fail to initiate if the system has too much moisture and (2)

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(6) THP−ether is 2-(3-bromophenoxy)tetrahydro-2H-pyran and is prepared from 3-bromophenol and 3,4-dihydro-2H−pyran. Chauez, F.; Godinez, R. *Synth. Commun.* **1992**, *22*, 159−164.

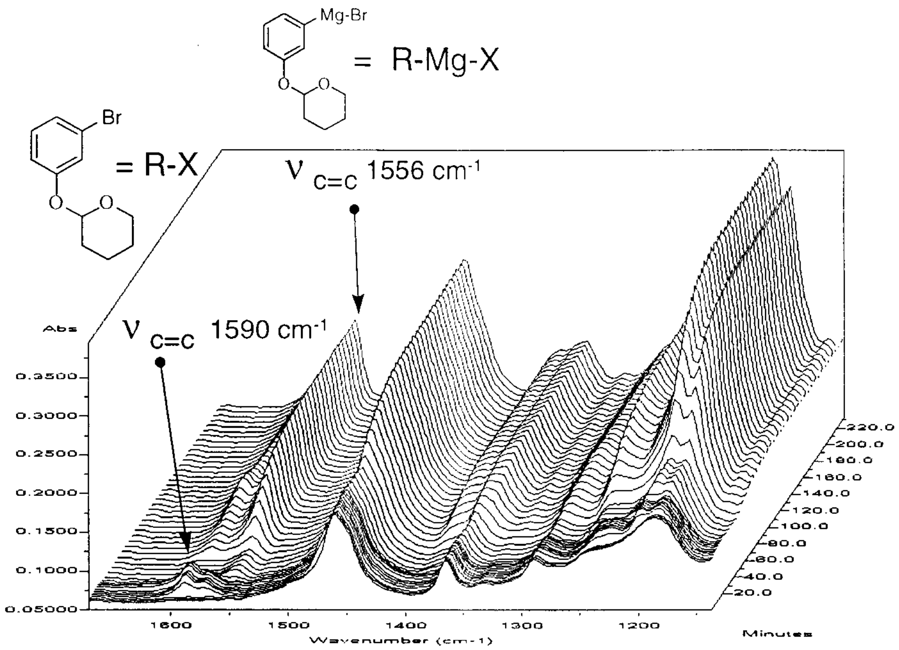


Figure 1. **Infrared spectra obtained during the preparation of Grignard reagent, a precursor in the synthesis of droloxifene shown in Scheme 1, step 1.**

water leaks after initation can result in a violent hydrolysis reaction with exothermic energy in the range of 20−40 kcal/mol.

Application of in Situ FTIR

Regarding safe process control for Grignard chemistry, we needed an online method to monitor the concentration of organic halide to prevent excessive accumulation of starting material **1**. We applied in situ FTIR to the droloxifene Grignard chemistry shown in Scheme 1 with particular emphasis on Step 1.

Detection of the Initiation

The Grignard reaction (Scheme 1, Step 1) for droloxifene was performed in a 1-L reaction calorimeter equipped with an in situ FTIR probe. Figure 1 shows an IR spectra “waterfall” plot obtained over the course of the reaction. At the beginning of the experiment only 5 wt % of the aryl halide (R−X) in THF solution was charged into the reaction vessel over 3 min. In this experiment we wanted to monitor the initiation period in situ after rapidly dosing in a fraction of the alkyl halide. Typically, Grignard reactions take several minutes or longer to initiate depending on the water content of the solvent and other factors such as the condition of the magnesium surface, impurities in the feed, and agitation rate. Before discussing the temporal profiles, it is necessary to review the infrared frequency assignments for the main reaction components.

The aryl halide referred to as THP−ether, **1** of Scheme 1, is distinguishable by IR from THF due to the ν(C═C) aromatic stretching absorbance peak which occurs at 1590 cm^{-1} as seen in Figure 2. THF has a strong absorbing asymmetric ether ν(C−O) stretch near 1069 cm^{-1} and a symmetric ν(C−O) stretch near 913 cm^{-1}. The insertion of magnesium to form **2** influences the aromatic ν(C═C) stretching vibration in the IR as a shift of about 34 wavenumbers from 1590 cm^{-1} down to 1556 cm^{-1} as seen in Figure 3. The formation of Grignard reagent, **2**, is observed without interference of solvent IR bands and can be seen “growing in” as a peak in Figure 1 at 1556 cm^{-1}. For online monitoring purposes the starting material and product are clearly resolved by IR.

The time-dependent IR profiles measured during and after initiation are discussed next. During the initial dosing of **1**, wavenumbers 1590 and 1556 cm^{-1} corresponding to R−X and R−Mg-X, respectively, were monitored and profiled in Figure 4. The mass of the aryl halide−THF solution charged to the reactor is shown on the left axis, while the IR absorbance for R−X and R−Mg−X is shown on the right axis. Absorbance for R−X increases immediately with the actual reactor charge as observed by the parallel profiles. Initiation occurred after about 15 min as seen by the decrease in absorbance of R−X at (1590 cm^{-1}) at 0.25 h and the corresponding increase in Grignard reagent, **2**, (1556 cm^{-1}). Figure 4 is precisely the type of profile that is needed by the plant engineer to confirm initiation has occurred.

The in situ IR data for R−X and RMgX are profiled for the entire experiment as shown in Figure 5. After initiation which occurred near 0.25 h, the remainder of the alkyl halide was dosed in linearly over 1 h. During this time, the R−X levels continue to rise as the magnesium is being consumed and the reaction rate diminishes. Eventually there is no reactive magnesium left because the alkyl halide was added in excess. From Figure 5, the absorbance for R−X reached a maximum near 0.045 relative absorbance at the end of the addition before leveling off which signified the completion of the reaction. This also indicated that the dose rate of R−X was slightly faster than the reaction rate. Because R−X was added in excess, relative to magnesium, the concentration of R−X did not return to zero but rather leveled off near

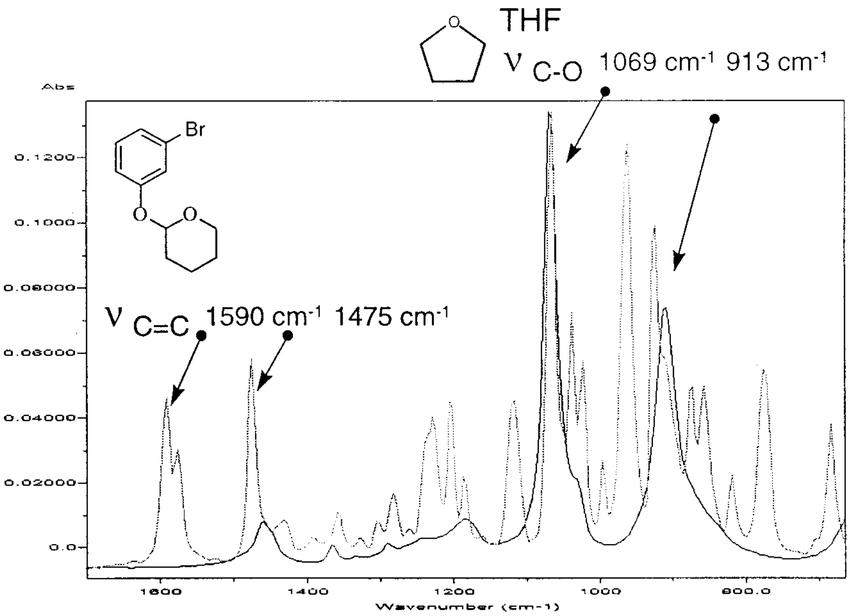


Figure 2. **IR spectra for R−X (THP−ether) and THF. The aromatic ring of R−X provides distinguishing absorbances due to the C=C stretch at 1590 and 1475 cm^{-1}. THF has asymmetric and symmetric C−O stretch frequencies at 1069 and 913 cm^{-1}, respectively. The R−X spectrum is autoscaled for comparison with the THF spectrum.**

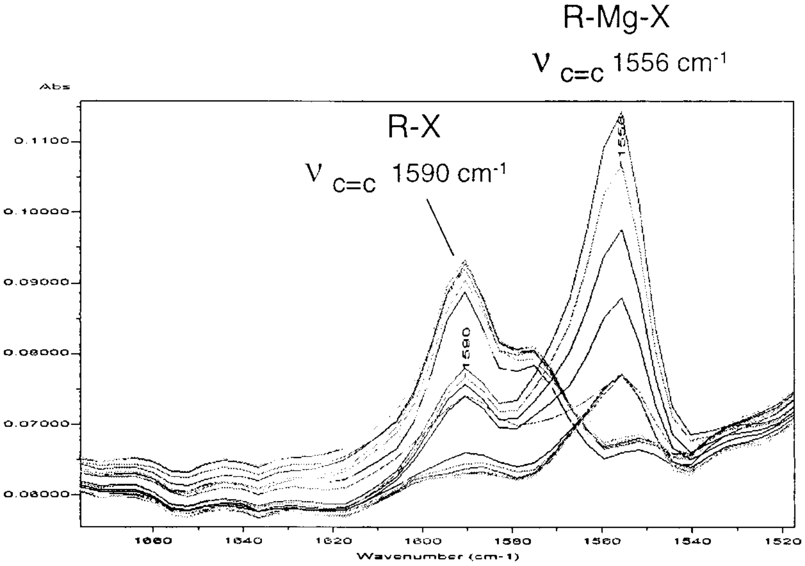


Figure 3. **Aryl halide, R−X, is easily distinguishable from the Grignard reagent R−Mg−X via of shift of 34 wavenumbers due to the insertion of magnesium and its influence on the aromatic carbon−carbon stretch frequency.**

0.035 relative absorbance. On production scale, the dose rate would be reduced to keep pace with the Grignard formation and maintain a concentration slightly lower than the 5% accumulation level (near 0.03 relative absorbance). On line monitoring by IR also provides confidence that the Grignard reagent was successfully generated by the increase in absorbance of wavenumber 1556 cm^{-1}, clearly seen in Figure 5.

The ether, or in the present work THF, plays a role in the mechanism mentioned above. Namely, the oxygen of the ether coordinates with magnesium in R−Mg−X and essentially solubilizes the species away from the magnesium surface. By IR it was evident that THF was involved "chemically" as the Grignard reagent was being formed due to the marked decrease in absorbance for the THF band as seen in Figure 6. The absorbance for the strong asymmetric C−O stretch at 1069 cm^{-1} of the THF decreased as a result of its "consumption" or coordination with the Mg in the R−Mg−X. This is consistent with the simplified stoichiometry shown in Scheme 2.

As we saw for R−X to R−Mg−X in Figure 3 which has an IR shift of 34 cm^{-1} from 1590 to 1556 cm^{-1} due to the insertion of magnesium, it appears that a similar shift occurred for the uncoordinated to the coordinated THF from 1069 to 1034, a shift of 35 cm^{-1}. Recall that wavenumber 1069 cm^{-1} was assigned the asymmetric C−O stretch for THF. Similarly, the symmetric C−O stretch of THF is visible at 911 cm^{-1} with an analagous shift of 35 cm^{-1} to 876 cm^{-1} as seen in Figure 6. The shifts are visible as shoulder peaks growing as seen in Figure 6. The shoulder peaks at 1034

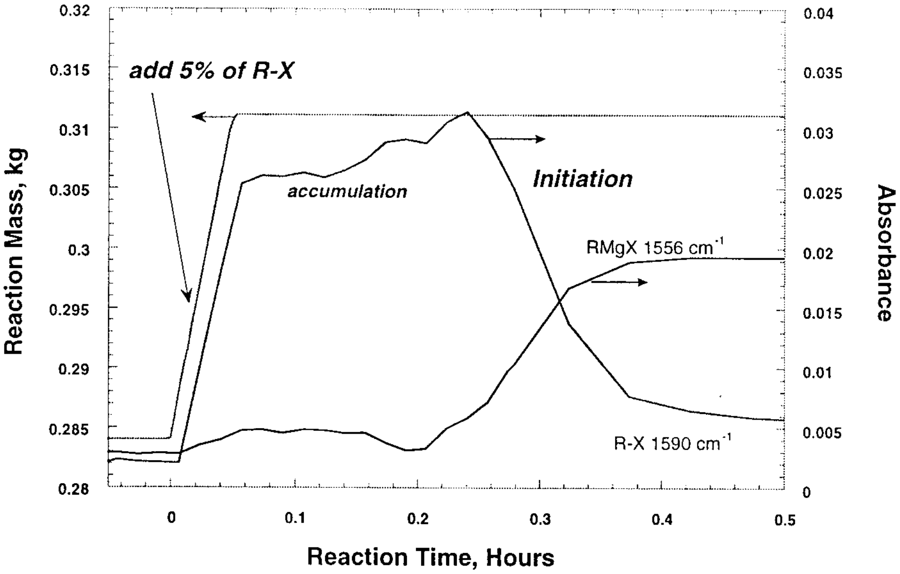


Figure 4. **IR monitoring during the initial phase of the reaction. Left axis is the reaction mass during the addition of the R−X/THF feed solution into the reactor. R−X solution (5 wt %) was added over 3 min to monitor the accumulation and initiation by IR. The relative IR absorbance values are shown on the right axis for R−X and R−Mg−X at 1590 and 1556 cm^{-1}, respectively.**

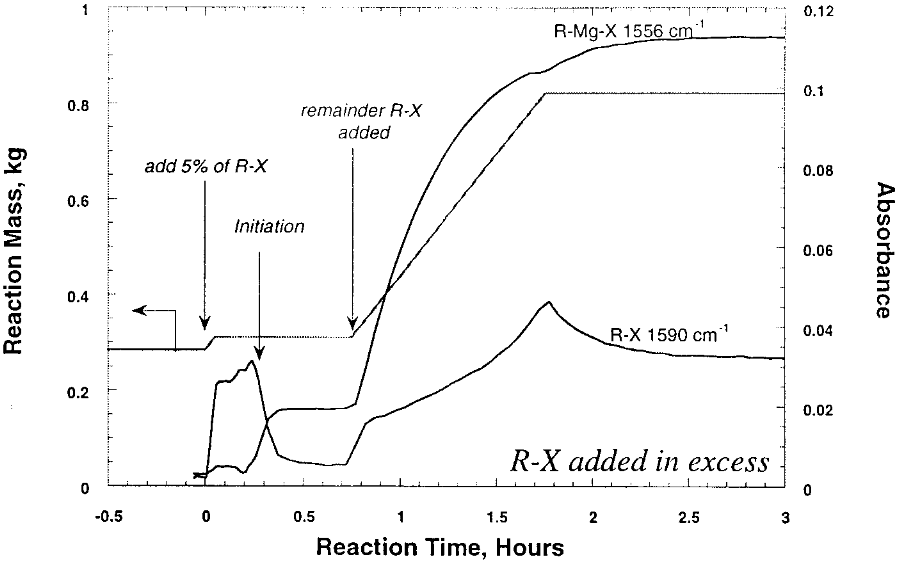


Figure 5. **IR and reaction mass flow profiles for the duration of the Grignard preparation experiment. R−X was added in excess and reaches a maximum at the end of the dose. Because the magnesium is completely reacted, some R−X remains at the end of the experiment.**

and 876 cm^{-1} are the new C−O stretch frequencies for the bound THF whose oxygen is coordinated with the Mg of the R−Mg−X.

As clarification, the FTIR probe used in our study "sees" only what is in solution. Solid magnesium turnings stirred in THF are not visible by IR until the Mg becomes dissolved and incorporated as Grignard reagent. Thus, initially, before any organic halide is added, the IR sees 100% THF. As the organic halide−THF solution is charged to the reactor, the concentration of the THF decreases, and thus the IR absorbance decreases. If no reaction was occurring, a linear decrease in the THF absorbance would be expected. Figure 7 shows IR profiles for the bound and unbound THF. Unbound THF is seen to decrease in IR absorbance at 1069 cm^{-1} in a nonlinear fashion as it coordinates with magnesium and becomes bound. The bound THF is seen to form at 1034 cm^{-1} with the same kinetic profile as seen with the formation of Grignard reagent. Figure 7 provides further evidence that THF is chemically involved in the formation of the Grignard reagent and that this in situ IR method is able to distinguish and monitor its kinetics.

Water in THF

The induction time for initiation of the Grignard reagent is profoundly affected by water present in the solvent. Excessive water levels, can tremendously increase time of initiation or prevent it completely. For this reason careful control of water content is essential prior to start of the reaction. Calibration standards of THF with different levels of water were prepared and tested by IR. We sought a method that could be used as in situ technique in place of the current method of pulling samples and performing Karl Fischer

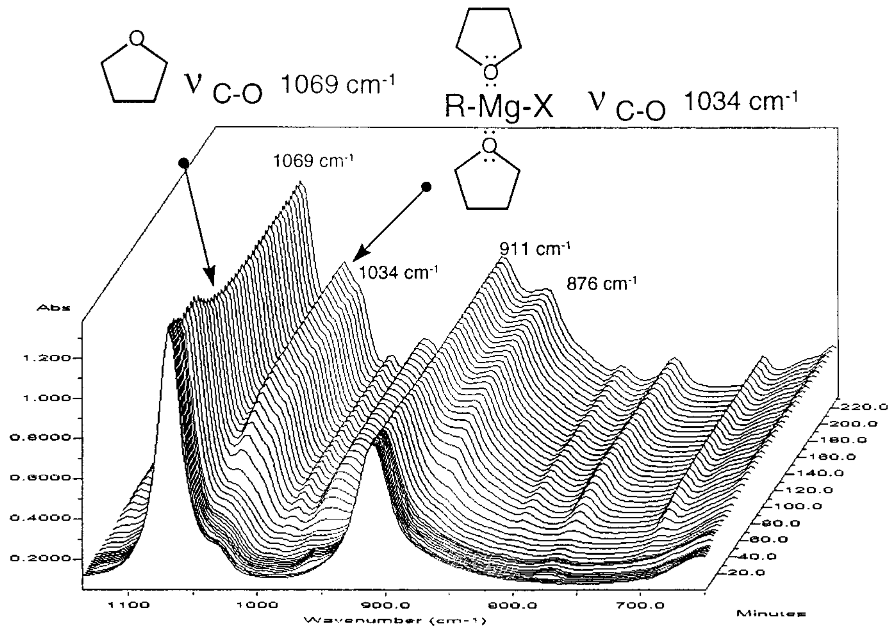
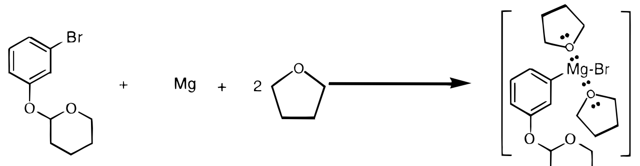


Figure 6. **THF plays a role in the mechanism by coordinating with the magnesium of R−Mg−X. This coordination enables the R−Mg−X to be solubilized by the THF and removed from the magnesium surface. The IR spectra is consistent with uncoordinated THF having a C−O stretch at 1069 cm^{-1} being shifted downward by 35 cm^{-1} as THF becomes coordinated to the Grignard reagent. Evidently the influence of magnesium on the C−O stretch causes this shift in absorbance.**

Scheme 2. **THF coordinates with the magnesium of the Grignard reagent[a]**



[a] The coordinated THF is distinguishable by IR from the unbound THF due to the effect of Mg on the C−O stretch frequency of the ether.

testing. Figure 8 shows overlayed spectra of varying water concentrations in THF. Water is distinguishable from THF at wavenumbers 3500 and 1648 cm^{-1}. The sensitivity of this initial testing was good enough to accurately measure below 0.05% water which is typically the dryness specification we use for scale-ups of Grignard reactions. A quantitative method which resulted in a linear calibration curve was generated on the basis of the spectral data between 0 and 2% water which provided accurate quantitation to within ±0.015 absolute error. Higher sensitivities with the IR probe can be obtained by increasing the number of scans taken per spectrum and thus a further reduction in the absolute error is feasible. The spectra shown in Figure 8 were acquired using 256 scans with a resolution of 8 cm^{-1} per spectrum. Scan numbers as high as 1024 are not unreasonable to increase the signal-to-noise by a factor of 2.

For process control purposes, concentration of **1** would be monitored during the entire step 1 process and not just for the initiation period. Further, IR technology has reached a stage where it could be used as part of a process control strategy.[7] For instance, in the early stage of the reaction this technology would clearly identify that initiation has occurred and that it is safe to proceed with further charging of organic halide. In the middle and latter stage of reaction IR monitoring could be used to provide an output signal for an alarm or to automatically deactivate a feed valve in the event the reaction began to stall and the concentration of R−X began to rise unexpectedly. Had this technology been available as an online monitoring strategy, it would have likely prevented the release incident reported by Yue et al.[2]

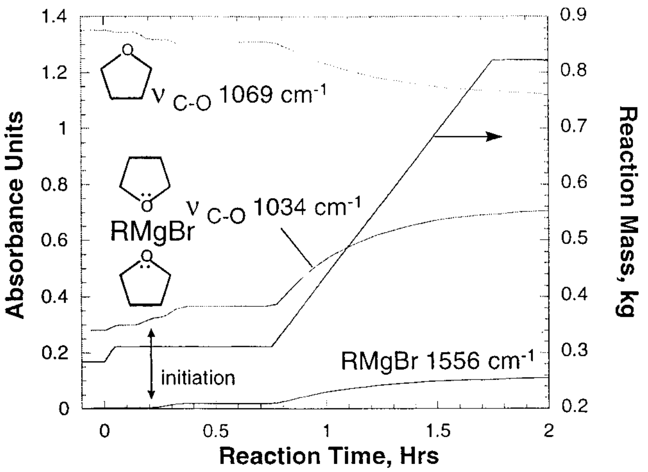


Figure 7. **Bound vs unbound THF. THF coordinated to Mg has C−O stretch frequency at 1034 cm^{-1}, while unbound or free THF has a C−O stretch frequency at 1069 cm^{-1}. The relative IR absorbance for the THF during the formation of the Grignard reagent is shown on the left axis. The reaction mass profile is shown on the right axis. After the initiation period, the aryl bromide was added to the reactor linearly over a period of 1 h.**

In general, the IR technology is a valuable tool for chemical process development and we have recently installed a process unit into a plant environment. Several issues that

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[7] Mettler-Toledo, Inc, Millersville, MD 21108, manufactures the RC-1 reaction calorimeter.

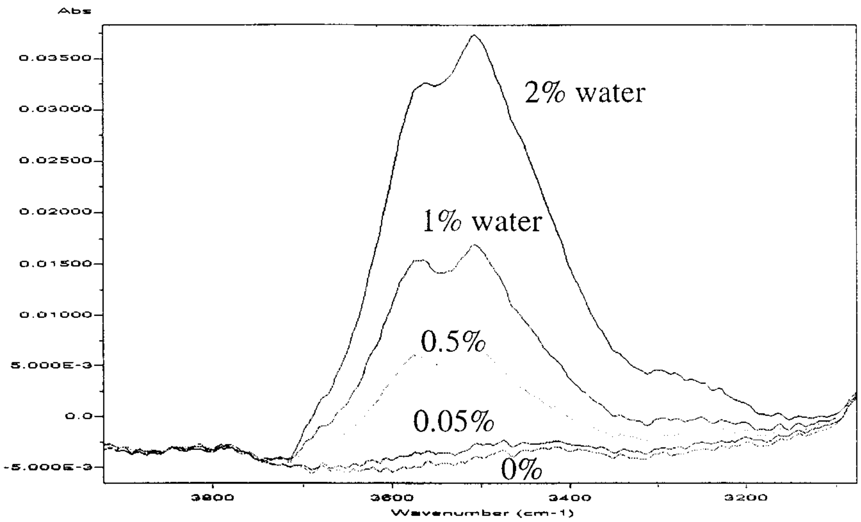

Figure 8. **Water content in THF as measured by IR. Water is distinguishable from THF at wavenumbers 500 and 1648 cm^{-1}. A linear quantitative method is obtained by using peak height to single point baseline method. The method produced an absolute error of 0.015.**

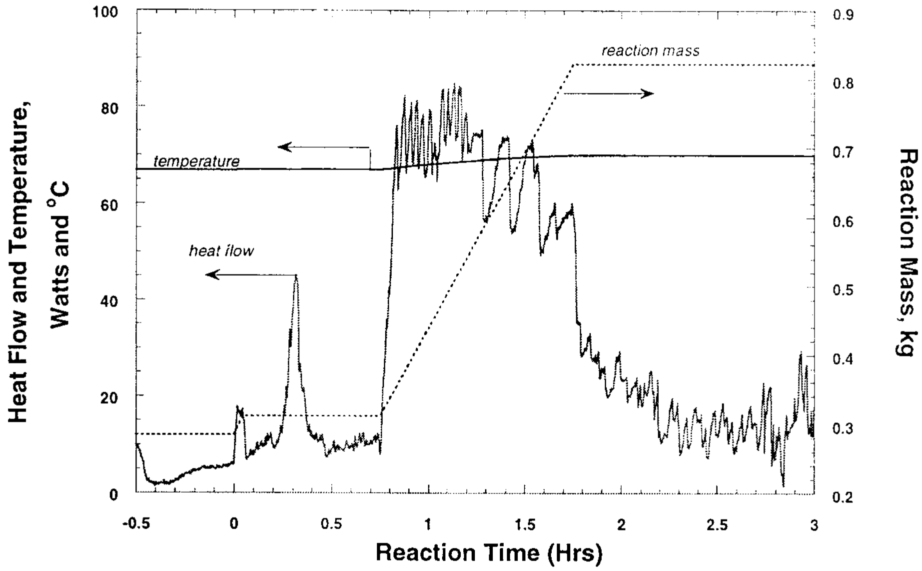

Figure 9. **Heat flow calorimetry data. Left axis refers to the temperature and heat flow associated with the Grignard reaction. The right axis refers to the dose of the R−X/THF feed solution. The heat flow due to initiation is visible at 0.3 h.**

we considered for implementing this technology into the plant are the following:

(1) A "light pipe" is required for transmission of the IR signal from the source to the detector. The length of the light pipe is currently limited to about 4 feet which constrains the location of the IR detector assembly to be placed in close proximity to the sampling probe.

(2) Since moisture within the light pipe can interfere with the signal, the light pipe should be continuously purged with a dry source of nitrogen or air.

(3) Other utilities needed for plant operation are liquid nitrogen for the high sensitivity (MCT) detector, cooling water to maintain constant temperature of the IR processor, and, of course, electrical utilities.

In general, the potential benefits of this in situ IR technology in terms of safety and productivity, in our view, clearly outweigh the initial challenges of implementing these units into the production facility.

Experimental Section

Instrumentation. Experiments were performed using a Mettler Toledo RC-1 reaction calorimeter[7] consisting of a 1-L conical shaped reactor (SV01) with a glass agitator and Brinkmann-style reflux condenser. The reactor cover and condenser were insulated with glass wool. FTIR data were collected in situ using Applied Systems ReactIR 1000 system[8] with DiComp probe during the calorimetry experiments. A VSP[9] vent-sizing package was used for the vent-sizing experiment.

Procedure. A weighed amount of magnesium was stirred into a known volume of THF. THF was used new as supplied by JT Baker. Karl Fischer analyses were performed to determine moisture content in the THF. The magnesium−

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(8) ASI Applied Systems, a Mettler-Toledo Company, Millersville, MD, 21108 (manufactures the ReactIR and Dicomp probe).

(9) Fauske and Associates of Burr Ridge, IL. The VSP2 is based on DIERS (Design Institute for Emergency Relief Systems) research results.

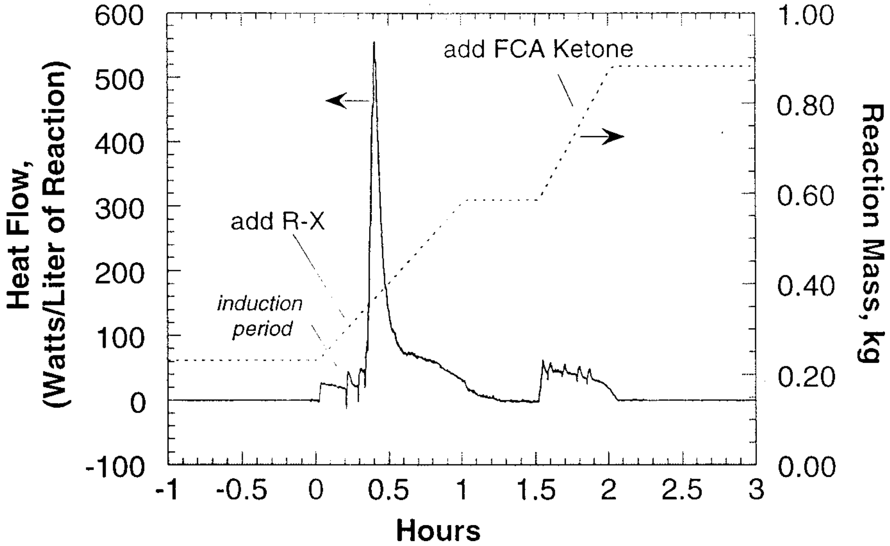

Figure 10. **Heatflow calorimetry obtained for the preparation of Grignard reagent and subsequent coupling with FCA−ketone of Scheme 1. The dose of R−X/THF was uninterrupted. The reaction initiated after 0.33 h (20 mins) with 30 wt % of the R−X added. An extremely high heat flow (550 W/L) was generated due to this excessive accumulation of R−X. The coupling with FCA−ketone was much less exothermic with heat never near 50 °C.**

THF slurry was brought to reflux (about 67 °C) in a 1-L reactor. A weighed amount of the alkyl halide (THP-ether) was dissolved in THF and placed into a dosing bottle which was positioned on a balance. After calibrations and heat capacity measurements were performed for calorimetry, the first 5 wt % of the alkyl halide−THF solution was dosed in linearly from a balance over a 3-min time interval via a control loop from the RC-1. IR scans were acquired every minute for the first 27 scans and then every 3 min thereafter. IR spectra were collected using 64 scans with a resolution of 8 cm^{-1}. The remainder of the alkyl halide solution was added over 1 h.

Heat Flow Calorimetry Theory

Heat flow calorimetry was performed under reflux conditions using an energy balance around the reactor and reflux condenser. The energy balance is made up of the following terms:

$$Q_r = Q_{\text{flow}} + Q_{\text{accum}} + Q_{\text{dose}} + Q_{\text{reflux}}$$

where:

$\mathbf{Q}_r$ = heat of reaction or other thermal event with units of Watts or J/s

$\mathbf{Q}_{\text{flow}}$ = heat flow through the vessel jacket = $U_oA(T_r - T_a)$ where T_a is the average jacket temperature, U_o is the overall heat transfer coefficient, W/m^2-K, and A is the wetted heat transfer area of the vessel.

$\mathbf{Q}_{\text{accum}}$ = heat flow accumulation of the reaction mass and the inserts = $(m_r\text{Cp}_r + M_i\text{Cp}_i)\text{d}T_r/\text{d}t$ where mCp refer to the mass and heat capacity of the reaction mass and inserts, respectively.

$\mathbf{Q}_{\text{dose}}$ = heat flow due to sensible heat of the feed = $\text{d}m/\text{d}t\ \text{Cp}_d\ (T_r - T_{\text{dose}})$ where dm/dt and Cp$_d$ refer to the mass flow rate and heat capacity of the material being dosed to the reactor, respectively.

$\mathbf{Q}_{\text{reflux}}$ = heat removed by the reflux condenser = $(\text{d}m/\text{d}t\ \text{Cp})_{\text{reflux}}\ \Delta T_{\text{reflux}} = (M\text{Cp})_{\text{reflux}}\ \Delta T_{\text{reflux}}$ for condenser flow rate and where $\Delta T_{\text{reflux}} = T_{\text{out}} - T_{\text{in}}$. T_{out} and T_{in} refer to the temperature of the condenser coolant outlet and inlet, respectively. $(M\text{Cp})_{\text{reflux}}$ is the mass and heat capacity of the condenser cooling fluid.

Ethylene glycol was used as the coolant through the reflux condenser and ΔT_{reflux} was measured by the calorimeter via inlet and outlet coolant thermocouples. To compute $(M\text{Cp})_{\text{reflux}}$ we used a 20-W calibration heater at reflux to measure the condenser response i.e., ΔT_{reflux}. By integrating the ΔT_{reflux} curve in response to the 20-W calibration heater, we were able to calculate $(M\text{Cp})_{\text{reflux}}$.[10] Because the mass flow rate of the coolant fluid was steady through the condenser, dm/dt is a constant flow rate designated as M, thus:

$$(M\text{Cp})_{\text{reflux}} = \int Q_c\,dt / \int (\Delta T_c - \Delta T_{\text{BL}})\,dt \equiv \text{J/s-K} \equiv \text{W/K} \quad (2)$$

where Q_c is the known calibration heater wattage, ΔT_c is the condenser temperature response, and ΔT_{BL} is the baseline condenser response when the calibration heater is off. Alternatively, one could use an accurate measure of the flow rate and the condenser coolants heat capacity to calculate $(M\text{Cp})_{\text{reflux}}$.

Given the collective terms of the energy balance, the heat of reaction can be computed by integrating over the time interval of the thermal event, namely:

$$\Delta H_{\text{reaction}} = \int Q_r\,dt \equiv \text{J} \quad (3)$$

Heat Flow Calorimetry Results and Discussion

The heat flow profile for step 1 Scheme 1 is illustrated in Figure 9 and was obtained in the same experiment that produced the IR data shown in Figure 5. The dosing of R−X was carried out in two stages with the first being the initial

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(10) Lerena, P., Reaction Calorimetry at Reflux, 8th RC-1 users forum, Lugano, Switzerland, 1997.

Table 1. **Summary of reaction calorimetry data**

operation	heat capacity of reaction mass (J/kg-K)	maximum heat flow	heat released (kcal/mol)	$\Delta T_{\mathrm{adiabatic}}$ (°C)
preparation of Grignard				
1. dose in 5% THP−ether	1987	140 @ reflux	89 (of R−X)	22
2. dose in remaining THP−ether	1836	240 @ reflux	87 (of Mg)	154
preparation of Grignard (uninterrupted feed)	1635	550 @ reflux	83 (of Mg)	150
coupling with FCA−Ketone	1490	50 @ reflux	41 (of FCA)	43
quench	1700−2500	600 (of short duration)	30 (of FCA)	15−20

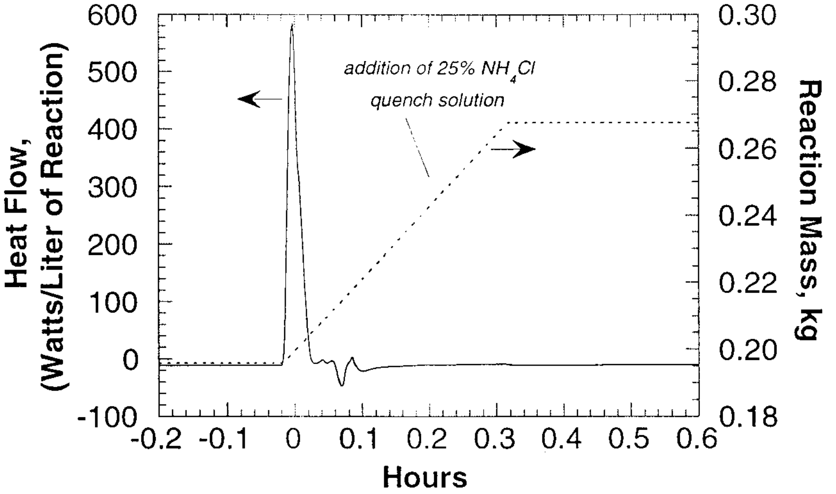

Figure 11. **Heat flow calorimetry for the quenching of the Grignard reaction with a 25% solution of ammonium chloride. The quench occurred after coupling with the FCA−ketone andthe temperature was lowered to 25 °C. The adiabatic temperature rise for the initial part of the dose was approximately 20 °C above the process temperature.**

5 wt % to induce initiation followed by the second stage to add the remaining 95 wt %.

Stage 1. The reactor contained 16.51 g (0.679 mols) of magnesium turnings and 267.8 g of THF. After calibrations were made, the temperature was raised to reflux. THP−ether (5%) in THF (27 g) was fed to the reactor over a period of 3 min. The resulting heat liberated as measured by the energy balance was −373 kJ/mol or −89 kcal/mol of R−X.[11] The maximum heat flow during this stage as seen in the graph was about 45 W or 140 W/L removed by the reflux condenser.

Stage 2. Once initiation was confirmed, the remainder of the R−X was added (510.7 g of solution) over 1 h. R−X was added in stoichiometric excess of the magnesium. The heat measured for stage 2 was −363 kJ/mol or −87 kcal/mol of magnesium.[12] The adiabatic temperature rise for the combined events was computed to be 167 °C based on a total of −246.8 kJ, a reaction mass of 1.133 kg, and a heat capacity of 1836 J/kgK, and using the relation:

$$\Delta T_{\mathrm{adiabatic}} = \Delta H / m\mathrm{Cp} \qquad (4)$$

Because $\Delta T_{\mathrm{adiabatic}}$ depends on the mass, the value will be correspondingly higher if less THF is used in the magnesium slurry or the feed solution. For the purpose of this experiment, 18 volumes of THF were used per gram of magnesium in the initial fill. For instance, if half the volume of THF were used in the initial fill, the new $\Delta T_{\mathrm{adiabatic}} =$ 199 °C which is about 30 °C higher than the more dilute case. During stage 2 the maximum heat flow was measured to be about 80 W or 240 W/L of reaction being removed through the condenser.

Table 2. **Vent-sizing parameters**

vessel parameters	
set pressure, Ps	60 psig
vessel rating, MAWP	100 psig maximum allowable working pressure
vessel volume, V	500 gal (67 ft^3)
charge, mo	3155 lb
specific heat, Cp	0.5 BTU/lb °F
vapor density, ρg	0.7 lb/ft^3
liquid density, ρf	50 lb/ft^3

In a separate experiment[13] the Grignard preparation was performed with constant dosing, without pausing for the initiation to occur. The heat flow profile is shown in Figure 10. In this case the R−X/THF solution was continuously dosed over a 1-h period. The initiation occurred after about 20 min and approximately 30% accumulation of THP−ether. The heat flow due to initiation at this point is extremely high, measured at reflux at 550 W/L as seen in Figure 9. Clearly, this is not the recommended approach to take on scale-up due to the potential for overpressurization from rapid

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(11) At this point, 0.037 mol of THP−ether had been added, and the heat measured was −13.8 kJ.

(12) During stage 2, there was 0.679 − 0.037 = 0.642 mol of magnesium left to react, and the heat measured was −233 kJ.

(13) Magnesium (10 g, 0.41 mol) was used in 25 volumes of THF. 383 g of R−X/THF (0.48 mol THP−ether) solution was added. FCA−ketone (100 g, 0.32 mol) dissolved in 220 mL of THF was used for coupling.

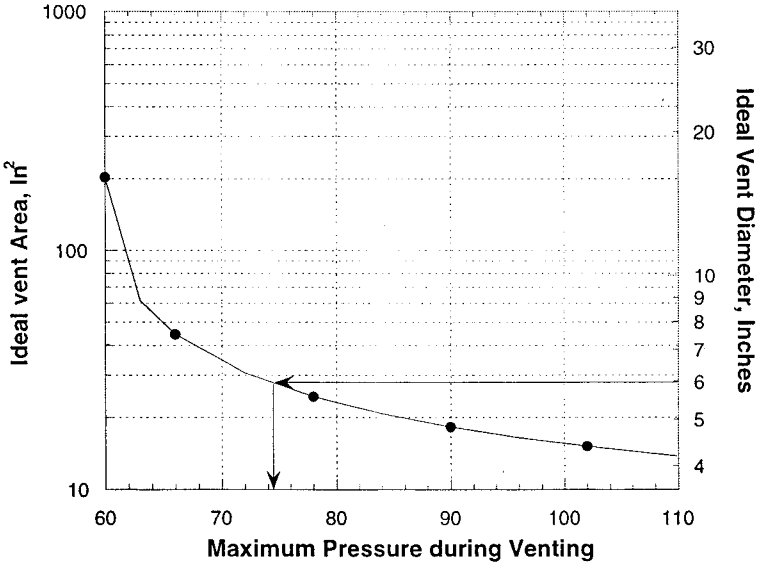

Figure 12. **VSP results for 500-gal vessel with rupture disk setting of 60 psig. These data represent the worst case scenario of an all-at-once addition of R−X/THF solution to a slurry of magnesium chips in THF with homogeneous vessel venting. The existing 6-in. vent will result in a slight but acceptable increase in pressure to about 74 psig for this scenario. The maximum allowable working pressure for the vessel is 100 psig.**

vaporization of solvent. The total heat of reaction for this experiment was −83 kcal/mol of Mg with an adiabatic temperature rise, $\Delta T_{\text{adiabatic}}$, of 150 °C. The heat measured during the coupling reaction with FCA−ketone was shown to be −41 kcal/mol of FCA ketone (Figure 10). Following the coupling, the reaction temperature was reduced to 25 °C, and a 25 wt % solution of ammonium chloride was added as a quench (shown in Figure 11). The quench resulted in an extremely high heat flow for the first fraction of the quench with values in excess of 500 W/L. This heat is no longer being removed by vaporization of solvent but rather by the cooling jacket of the vessel. Because, the RC-1 is not able to remove that rate of heat production, the temperature in the reactor increased about 13 °C. The high exotherm was short-lived. The calculated adiabatic temperature rise for the quench was 15−20 °C depending on how much of the quench solution was dosed. The calorimetry data are summarized in Table 1 for all the experiments described.

Vent-Sizing

Prior to scale-up to the plant, vent-sizing experiments were performed to assess the consequences of worst case scenarios in order to adequately design the relief system for the plant vessels.

Two vent-sizing experiments were performed using a VSP2 Vent Sizing Package: one for the preparation of the Grignard reagent and the second for the coupling of the Grignard reagent with FCA−ketone. The first experiment was for a worst case scenario of an all-at-once addition of the alkyl halide to the magnesium−THF slurry, and the second experiment was for all at once addition of the FCA−ketone. These tests were undertaken to indicate whether existing rupture disks were adequate to cope with these scenarios.

Test 1. The stainless steel test cell containing a large stir bar was filled with 1.47 g (0.06 mol) of magnesium turnings and 12.02 g of THF (8 volumes). The cell was equipped with a standard thermocouple whose tip was $^1/_2$ in. from the base of the cell and with dual $^1/_{16}$ in. o.d. fill lines. The sample was heated to 64 °C. At 21.3 min the THP−ether/THF solution was charged to the test cell via the auxiliary fill line. The test cell was closed. The dosed solution was made up of 16.48 g of THP−ether and 30.57 g of THF solvent. After the solution was added to the test cell, the temperature dropped to 38.6 °C, but the temperature then immediately rose due to the exotherm to 172 °C. Thus, the pseudo-adiabatic temperature rise for this experiment was (172 °C − 38.6 °C) = 133 °C. The pressure rose to 145 psig by 28.96 min and then slowly continued to rise to 170 psig.

DIERS calculations were performed for the scenario in a 500-gal reactor used to prepare the Grignard reagent. The DIERS two-phase venting technology was used which assumes a homogeneous-vessel venting behavior. The calculations were performed by Fauske and Associates using the input data shown in Table 2.

The output for the DIERS homogeneous-vessel venting prediction is graphically illustrated in Figure 12. The graph shows the accumulated pressure for a 500-gal plant vessel under the worst case scenario of a 100% accumulation of R−X. In this worst case scenario a sudden and complete charging of the THP−ether solution is made to the slurry of magnesium turnings. The existing vent on this vessel is 6-in. i.d. with a rupture disk pressure of 60 psig. The calculations presented in Figure 12 show that if a runaway occurred, the rupture disk would release at 60 psig but the pressure would continue to rise another 14 psig to 74 psig which is acceptable and well below the maximum allowable working pressure of 100 psig. The data shows that a 4.4 in. diameter vent-size vent would be the minimum vent-size to cope with this worst case scenario that would not exceed the 100 psig MAWP of the reactor. Thus the 6-in. vent currently in place would be more than acceptable to cope with this runaway scenario without exceeding the 100 psig allowable pressure in the tank. In summary, the vent-sizing experiments and calculations are essential for the scale-up engineers to ensure proper mitigation in the event of a process upset or overpressurization due to a runaway reaction.

Test 2. Test 2 involved the coupling reaction between FCA−ketone and the Grignard reagent. Grignard reagent was prepared from a solution containing 1.07 g of magnesium, 11.87 g of THP−ether, and 30.44 g of THF. The Grignard reagent (40.2 g) was introduced to a stainless steel closed test cell with dual $^{1}/_{16}$ in. o.d. fill lines and 1-in. stir bar and thermocouple. The sample cell was heated to 66 °C. Then at 15.67 min 27.46 g of the ambient solution of 34% FCA−ketone/THF was added which resulted in an immediate exotherm up to 84 °C with an accompanied pressure rise of 14.5 psig. Unlike test 1, the consequence of this scenario is not considered a significant hazard because of the relatively low resulting pressure rise.

Conclusions

Because of the runaway reaction and release potential of Grignard reactions we sought a general method to monitor the concentration of organic halide for scale-up considerations to increase safety and reduce the risk of incident. Online monitoring by IR can be used not only to ensure that initiation has been achieved but also to identify an accumulation of organic halide in the event the reaction stalled as was cited in the events that led to the incident reported by Yue et al.[2] Infrared technology currently being used in our Process Safety and Reaction Engineering Laboratory was utilized for the initial feasibility studies. As part of this work, it was also identified that this technology could be employed to quantify water levels for these water-sensitive reactions which could further reduce time and costs of current sampling and analytical testing via K−F methods. The infrared monitoring results described here were obtained at the R&D stage and have not been employed on scale to date. However, an FTIR unit was recently installed in our pilot plant facilities, in part, on the basis of the success of this work.

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