Application Note

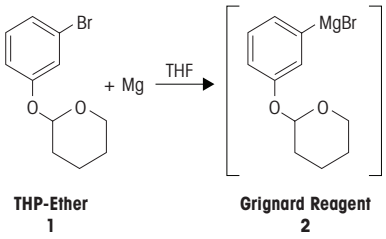
Progression of a Grignard Reaction

Inline Analysis Under Reflux

Am Ende, D. J., Clifford, P. J., DeAntonis, D. M., SantaMaria, C. and Brenek, S. J.
Preparation of Grignard Reagents. Org. Process Res. Dev. 3, 319–329 (1999)

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

The authors present a simple and safe method to form a Grignard reagent while tracking the reaction progression *in situ* (at all times), ensuring no accumulation of organic halide, and mitigating the risk of unsafe conditions associated with a stalled reaction and runaway conditions. Typically the strategy of a Grignard reaction is to charge the reactor with Mg and THF, add <10 % organic halide (R-X), raise temperature to reflux, and await initiation (by detecting an exothermic temperature rise). Upon initiation, the remainder of R-X is fed into the reactor. The challenge of this strategy is detecting the exothermic initiation while at reflux conditions, as well as, monitoring the reaction progression to avoid any potential stall conditions that can lead to an exothermic runaway.



Scheme 1. Step one of the synthesis.

In situ mid-infrared was implemented to monitor the R-X concentration and the Grignard product in real time. This new strategy allowed for instantaneous determination of initiation, reaction kinetics (during feed stage), as well as immediate detection of unsafe conditions.

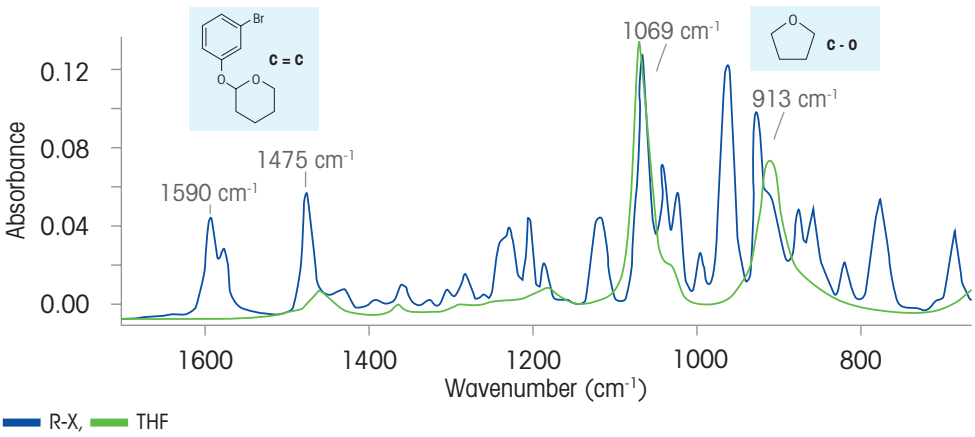


Figure 1. IR spectra for R-X (THP-ether) and THF. The aromatic ring of R-X provides distinguishing absorbances due to the C=C stretch at 1590 cm^{-1} and 1475 cm^{-1}. THF has asymmetric and symmetric C-O stretch frequencies at 1069 cm^{-1} and 913 cm^{-1}, respectively. The R-X spectrum is auto-scaled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

METTLER TOLEDO

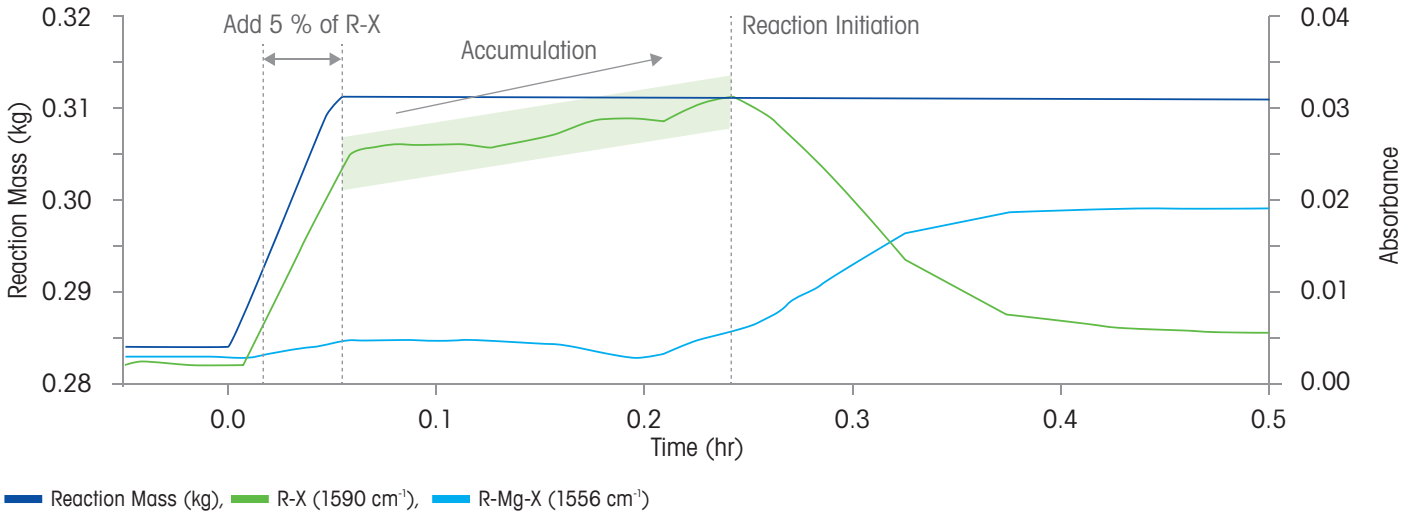


Figure 2. IR monitoring during the initial phase of the reaction. Left axis is the reaction mass during the addition of the R-X/ THF feed solution into the reactor. R-X solution (5 wt %) was added over 3 minutes prior to monitor the accumulation and initiation by IR. The relative IR absorbance values are shown on the right axis for R-X and R-Mg-X.

Results

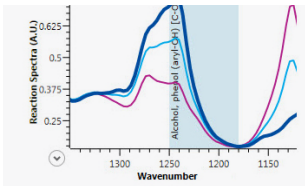
From a single experiment, an understanding of the complete reaction profile (or behavior) was achieved by collecting *in situ* mid-infrared data every one minute over a period of 30 minutes (Figure 2). Accumulation of the aryl halide was detected and watching for the subsequent reaction initiation point, allowed operators to safely dose the remainder of aryl halide into the reactor. Product formation and reaction endpoint were also measured in this study. This provided a full understanding of the behavior and mechanics of this reaction for safe scale up and control.

Conclusions

In situ mid-infrared demonstrated the ability to detect initiation, reaction progression, stall event(s), as well as avoid the exposure of hazardous substances to operators. Real-time monitoring insured continuous validation that the reaction was proceeding correctly.

ReactIR: Real-Time Reaction Mechanisms

In Situ Reaction Monitoring
Monitor chemistry under difficult conditions (reflux), and increase operator safety by reducing exposure to hazardous material.



Comprehensive Reaction Information in Real Time
Detect and monitor instantaneous changes (initiation, stall, intermediate, and endpoint) that are otherwise difficult or impossible to detect via offline methods.

Reaction Kinetics, Pathway and Mechanism
In-depth understanding of reaction mechanism for critical process parameters, efficiency, robustness, and safety progression.

Applications of ReactIR include:

- Reaction Kinetics
- Flow Chemistry
- High Pressure Reactions
- Polymer Synthesis
- Energetic Reactions

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