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Technical Notes

Safety Improvement of a Grignard Reaction Using On-Line NIR Monitoring

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Abstract:

A quantitative on-line NIR (near-infrared) method for the monitoring of the formation of a Grignard reagent was developed on laboratory scale using chemometrics and tested in a 630 L pilot plant reactor. Good accuracy of the model was obtained, and feasibility of the on-line measurement was demonstrated. The concentrations of the added reagent (and thus its degree of accumulation) and of the formed Grignard reagent (indication of the reaction initiation) can be determined in real time. Therefore, the safety of the highly exothermic process and its robustness are significantly improved. Furthermore, the method is applicable to monitoring concentrations during the following cross-coupling reaction so that it can be used to determine in real time the reaction yield. By using on-line spectroscopy, the product quality and performance can be guaranteed on an industrial scale. Moreover, the cycle times are reduced due to the elimination of waiting times caused by traditional analysis.

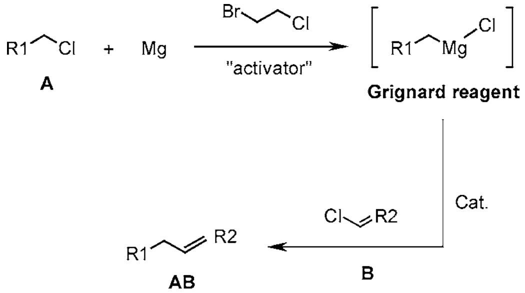
Introduction

Grignard reactions are important in organic synthesis because this kind of process is an easy way to form very various compounds. On the other hand, these reactions are often highly exothermic and are performed near or at the boiling point of the solvent. Therefore, the detection of the initiation of the reaction based on temperature measurements is in many cases difficult. In the case of reactant accumulation followed by a sudden initiation of the reaction, high heat release rates are produced, which can lead to vigorous boiling and to flooding in the vapor tube with risks of overpressure and explosion. Accumulation of reagents should be avoided by on-line monitoring of the involved components' concentrations. This paper is intended to demonstrate the feasibility of monitoring the safety of large scale Grignard reactions using NIR technology.

Chemistry

The Grignard reagent is an important class of extremely reactive chemical compounds used in the synthesis of hydrocarbons, alcohols, carboxylic acids, and other compounds.[1,2]

Scheme 1. **Synthesis of the Product AB**



The formation reaction occurs on the surface of the magnesium which is insoluble. The Grignard reagent formed at the reactive surface of the magnesium is solubilized in the (anhydrous) ether solvent.

Many cross-coupling reactions involving Grignard reagents are mentioned in the literature. This kind of chemistry emerged in 1972, when Corriu et al.[3] and Kumada et al.[4] independently described nickel-catalyzed reactions. This metal can be replaced by palladium[5] or iron salts.[6] Within a few decades, these cross-coupling reactions are now routine tools for the preparation of fine chemicals and pharmaceutically active compounds. The mechanism of these reactions includes an oxidative addition, a transmetalation, and a reductive elimination.[7]

Reaction Scheme

The investigated reaction is described in Scheme 1. The compound A reacts with bromochloroethane and magnesium to form a Grignard reagent (bromochloroethane is used as an activator). Then, this substance reacts with the reactant B to form the product AB (coupling reaction).

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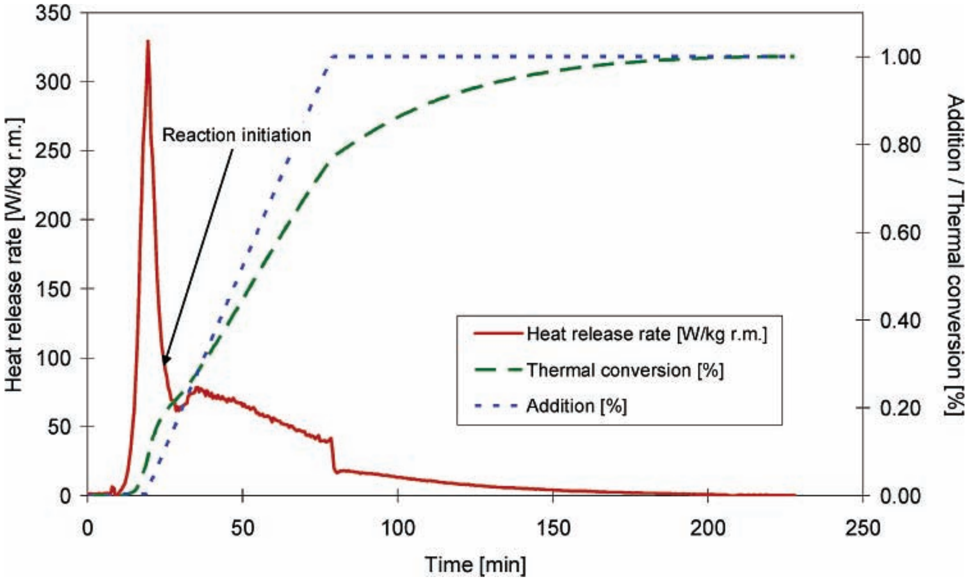

Figure 1. **Heat release rate during the addition of bromochloroethane and compound A.**

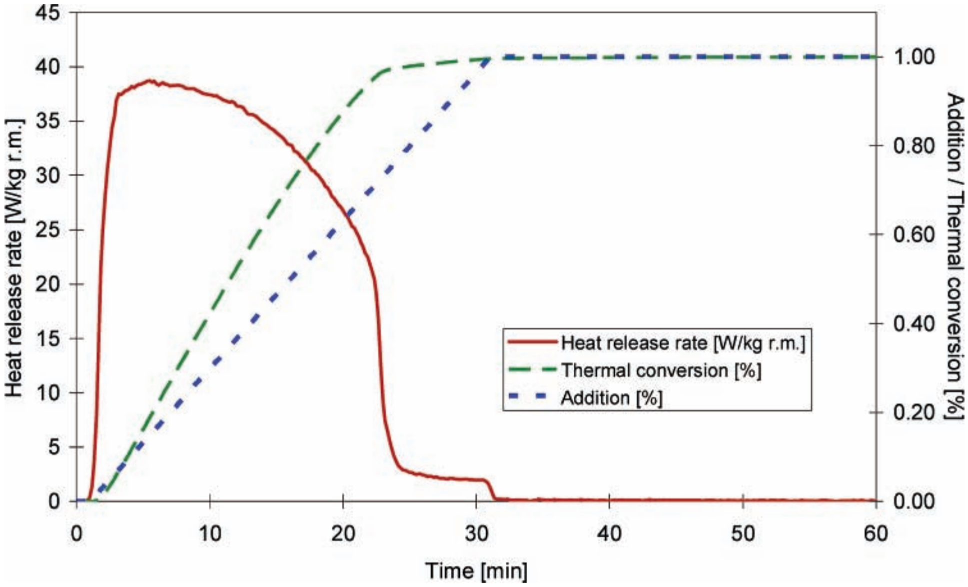

Figure 2. **Heat release rate during the addition of compound B.**

Safety Aspects of the Process/Reaction Calorimetry

Many Grignard reactions are fast and exothermic, carrying a risk of runaway if insufficiently controlled.[8] Therefore, experiments for the safety investigation were performed with a Mettler-Toledo RC1 reaction calorimeter equipped with a 0.9l glass reactor, a four-bladed glass anchor stirrer, a heated steel/Teflon-cover, glass inserts, and a condenser.

Formation of the Grignard Reagent. Magnesium turnings and THF were charged into a dry reactor, and the reaction mixture was heated to 66 °C (boiling temperature of the solvent). After a first calibration of the calorimeter, bromochloroethane was added in small portions in order to start the reaction. After the reaction initiation (detected by measuring the heat release rate), a solution containing the compound A, bromochloroethane, and THF was added within 2 h. A second calibration of the calorimeter was performed after a stirring period of 2.5 h.

Cross-Coupling Reaction. Afterwards, the reaction mixture was cooled to 25 °C, and another calibration was carried out. Then, a catalyst was added, and a solution containing the compound B and THF was added within 30 min. A last calibration was performed after a stirring time of 30 min.

The formation of the Grignard reagent is highly exothermal [ca. −227 kJ/kg of reaction mixture]. High heat release rates were measured during the starting phase of the reaction (up to 330 W/kg of reaction mixture). During the addition of the compound A solution, the heat production rate decreased from 75 to 50 W/kg of reaction mixture (see Figure 1). About 20% of the total heat of reaction is accumulated at the end of the addition. This accumulated energy is dissipated during the 2.5 h stirring period after the addition.

The following cross-coupling reaction is moderately exothermic [about −44 kJ/kg of reaction mixture] and is controlled by the feeding rate (no reagent accumulation; see Figure 2).

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Table 1. **Cross validation of the models used for the monitoring of the Grignard reagent formation (models based on laboratory and pilot plant experiments)**

	frequency range (cm^{-1})	data preprocessing	number of factors	RMSEE [mass %]	RMSECV [mass %]	R^2
compound A	4594−5581 and 6557−9018	first derivation and vector normalization	4	0.321	0.348	98.38
Grignard	8057−9504	first derivation and vector normalization	4	0.374	0.405	99.72

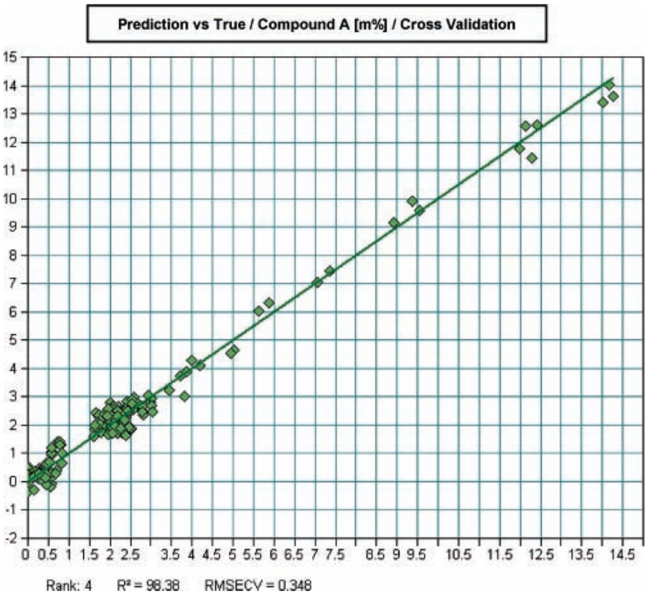

Figure 3. **Results of the cross validation for the determination of the concentration of the compound A (formation of Grignard reagent, model based on laboratory and pilot plant experiments).**

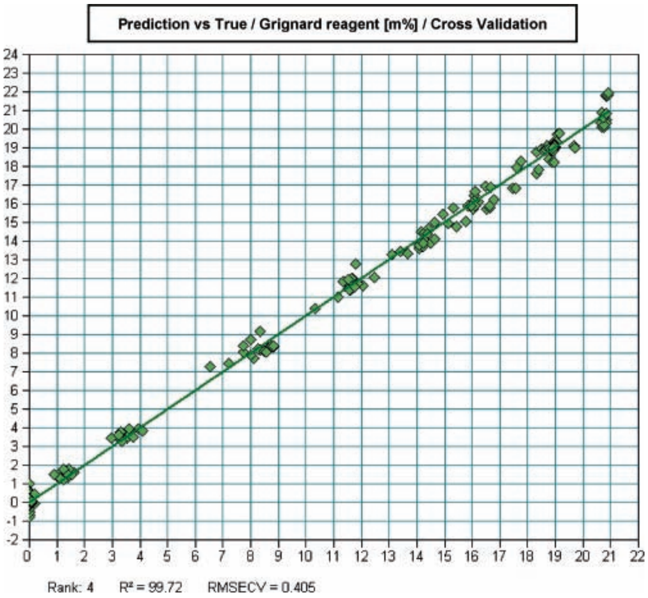

Figure 4. **Results of the cross validation for the determination of the concentration of the Grignard reagent (formation of Grignard reagent, model based on laboratory and pilot plant experiments).**

Additional thermal stability studies of the reaction mixtures during the process show that the synthesis of the product AB does not occur in the temperature range of a safety relevant exothermic decomposition reaction.

During the development of this process, the initiation of the reaction was not obvious (often delayed initiation). Moreover, this step of the process was not reproducible. In the case of a slow initiation of the formation of the Grignard reagent (or if the reaction drops off), the compound A could be accumulated. If this is followed by a sudden increase of the reaction rate, a significant solvent quantity could be evaporated within a short time period which can lead to a dangerous overpressure in the reactor or in the vapor tube.

To avoid this hazardous situation, the concentrations of the accumulated compound A and of the formed Grignard reagent must be monitored during the starting phase of the reaction. A thermal detection of the reaction initiation is difficult because the process is performed at reflux. Thus, only the increase of the solvent flow in the condenser can be measured, but the determination of the temperature difference of the cooling medium between the inlet and the outlet of the condenser is often not accurate enough to guarantee safe reaction conditions.

Off-line HPLC analyses can be performed to determine the concentrations of the compounds involved and, thus, the compound A accumulation. This kind of tests requires the presence of laboratory technicians and can lead to delays due to the time necessary to perform the analyses. These are serious disadvantages for a high volume production plant.

Therefore, on-line measurement of these concentrations is a promising alternative. It can lead to a significant saving of time and also guarantee a high level of safety in the process.

NIR Experiments

The spectroscopic experiments were performed with an NIR−spectrometer Matrix F (Bruker Optics). This spectrometer was equipped with a Zafiro Transmission immersion probe (Solvias) with an optical path length of 5 mm and a sapphire window (body in stainless steel). The experimental conditions were the following: resolution, 8 cm^{-1} and number of scans, 200 (duration: ca. 90 s.)

Calibration Model

To calibrate the NIR analysis system, many calibration samples are needed. They should contain each component of interest in various concentrations. These concentrations must be determined by a different analytical method and correlated with the corresponding NIR spectra to develop a chemometric model (PLS, partial least squares regression method[9]). This model is the calibration function used for

Table 2. **Cross validation of the models used for the monitoring of the formation of the AB product (models based on laboratory experiments)**

	frequency range (cm^{-1})	data preprocessing	number of factors	RMSEE [mass %]	RMSECV [mass %]	R^2
AB product	6098−7502	first derivation and vector normalization	4	0.397	0.474	99.4
Grignard	6098−10 001	first derivation and vector normalization	4	0.567	0.642	99.1

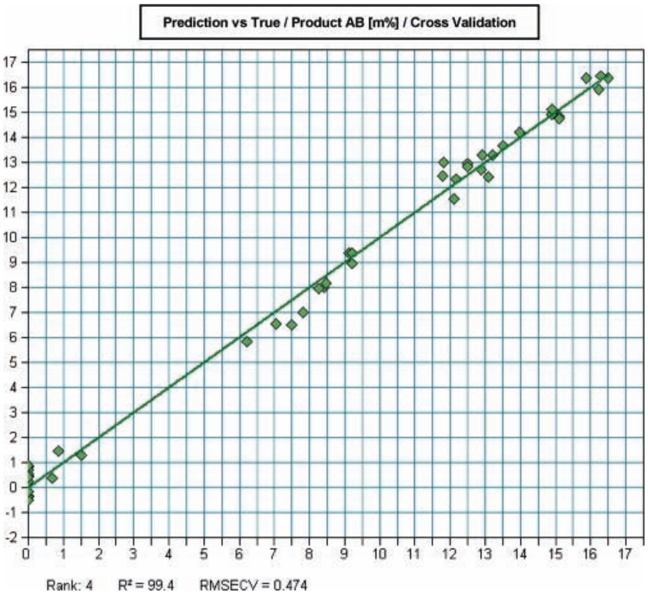

Figure 5. **Results of the cross validation for the determination of the concentration of the product AB (coupling reaction, model based on laboratory experiments).**

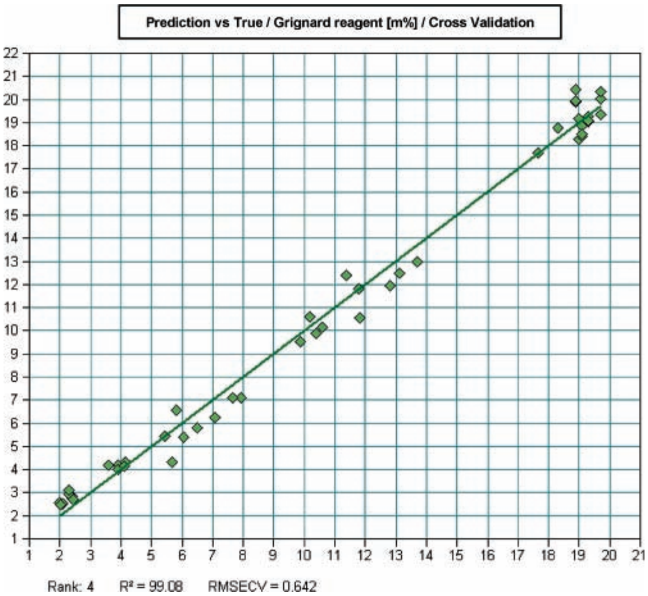

Figure 6. **Results of the cross validation for the determination of the concentration of the Grignard reagent (coupling reaction, model based on laboratory experiments).**

the analysis of unknown samples. Before using the model for routine application, its prediction capability must be tested (validation).

Models for the Monitoring of the Grignard Reagent Formation. Five reactions were performed on laboratory scale to build a quantitative calibration model. The NIR probe was immersed in the reaction mixture for the spectra acquisition. Slightly different experimental conditions were chosen for these experiments to introduce a certain variability of the experimental data (different concentrations and addition time of the reagents). Samples were taken every 15 min and analyzed with the traditional reference method (HPLC). The results of the HPLC analyses calculated as area percents were converted to absolute mass percents considering the added amount of reagents and assuming comparable response factors for all compounds of interest.

Quantitative calibration models were established with the OPUS software (Bruker Optics PLS algorithm) using the spectra obtained during the laboratory experiments.

The same NIR probe used on laboratory scale was installed in a 630 L reactor in the pilot plant for the first scale-up of the process (11 operations). During this phase of the development, the chemometric models were further optimized using the same procedure as before. Moreover, a fine Teflon grating was installed around the probe slot to reduce the spectral noise caused by the magnesium turnings agitating in the reactor (mesh 0.5 mm).

The models were optimized for the Grignard formation step of the reaction sequence. A total of 60 samples are contained in the model stemming from both laboratory scale and pilot plant experiments. The concentration ranges covered by the models are the following:

Compound A: 0.0−14.3 [mass %]
Grignard: 0.0−20.9 [mass %]

The frequency ranges used for the PLS regression, the used data preprocessing, the number of factors, RMSEE (root-mean-square error of estimation), RMSECV (root-mean-square error of cross validation), and R^2 (determination coefficient) are summarized in Table 1. RMSECV was plotted as a function of the rank to determine the optimum number of factors (the curve goes through a minimum for the optimal rank). The results of the cross validation are shown in Figure 3 for the compound A and in Figure 4 for the Grignard reagent.

Models for the Monitoring of the Formation of the AB Product. The models for the monitoring of the formation of the AB product were established in the same way. The

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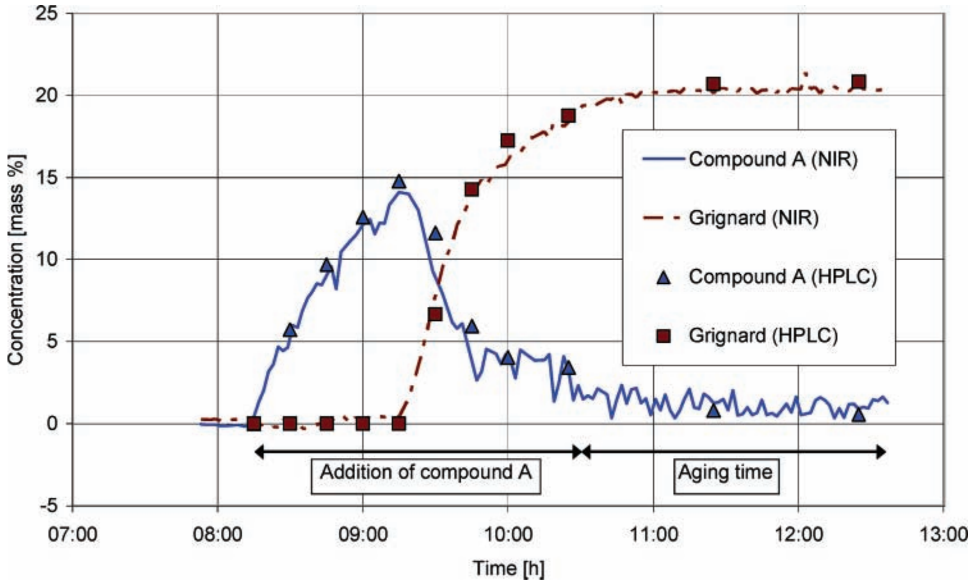

Figure 7. **Concentration profiles of the compound A and of the Grignard reagent (laboratory experiment).**

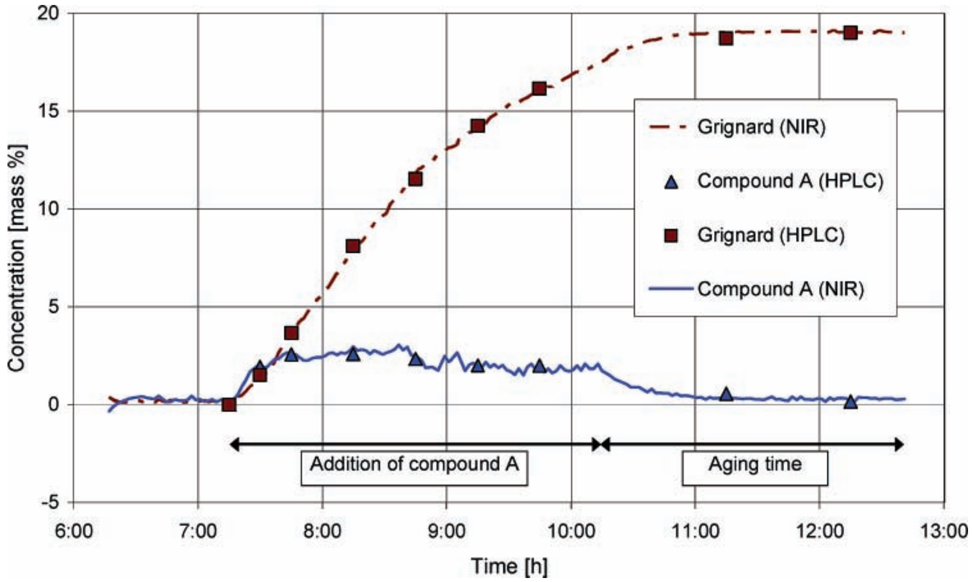

Figure 8. **Concentration profiles of the compound A and of the Grignard reagent (pilot plant operation).**

concentration ranges covered by the models are the following:

AB product: 0.0−16.5 [mass %]

Grignard: 2.0−19.7 [mass %]

A total of 16 laboratory samples are contained in the model. Due to technical reasons, no samples were taken during the pilot plant manufacturing period. The frequency ranges used for the PLS regressions, the data preprocessing used, the number of factors, RMSEE, RMSECV, and R^2 are summarized in Table 2.

The results of the cross validation are shown in Figure 5 for the AB product and in Figure 6 for the Grignard reagent.

Results and Discussion

Formation of the Grignard Reagent. The model developed with the laboratory and pilot plant experiments allows us to accurately determine the concentration of the major compounds involved in the formation of the Grignard reagent. The formation of the Grignard reagent as well as the compound A concentration (indicator of the accumulation) can be monitored in real time.

The concentration profiles of these compounds during the synthesis of the Grignard reagent are shown in Figure 7 (laboratory experiment) and Figure 8 (pilot plant operation). The laboratory experiment example displayed in Figure 7 shows a significant accumulation of the compound A that should absolutely be avoided in the large scale production plants.

A maximum admissible compound A concentration of 5% was determined during the risk analysis of the process. For the synthesis of the Grignard reagent, the mean deviation between NIR and reference analysis ($3\,\sigma$) is about 0.9−1.2% (abs) for the compound A, and about 1.2−1.5% (abs) for the Grignard reagent (probability of 99.5% that the deviation is below 3σ). This accuracy is sufficient for detecting the

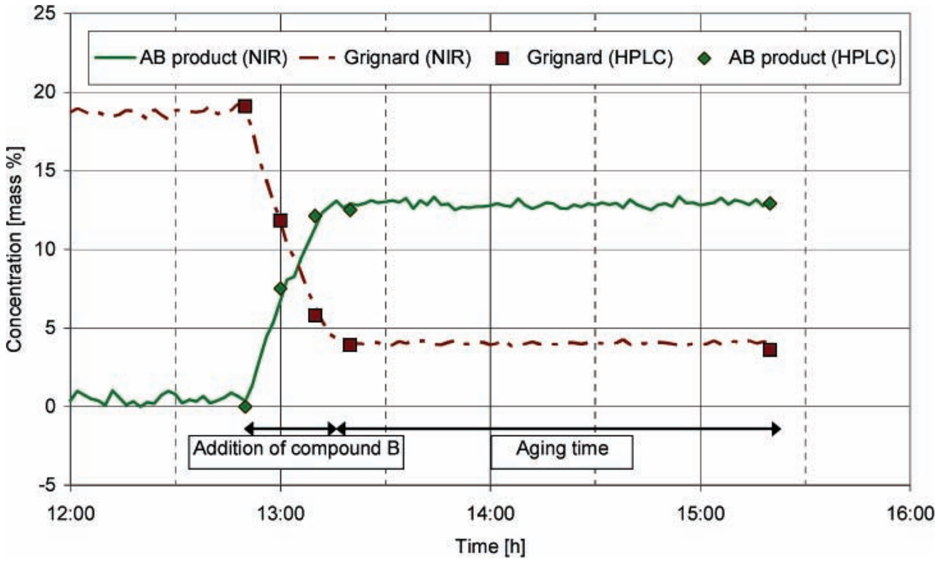

Figure 9. **Concentration profiles of the Grignard reagent and of the AB product during the coupling reaction (laboratory experiment).**

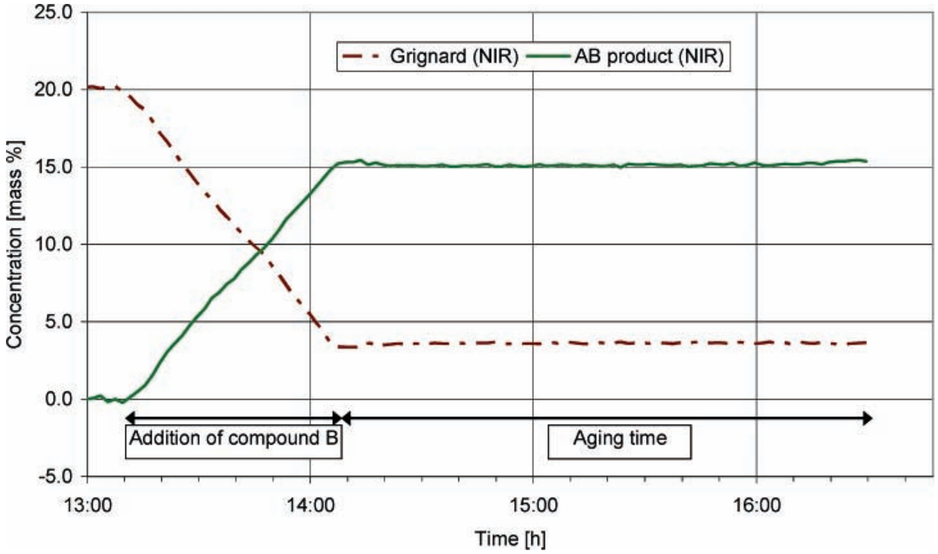

Figure 10. **Concentration profiles of the Grignard reagent and of the AB product during the coupling reaction (pilot plant experiment).**

initiation of the Grignard formation reaction by means of on-line NIR monitoring. The dangerous accumulation of compound A can thus be avoided. Moreover, the progress of the reaction can be followed in real time.

Coupling Reaction. During the coupling reaction, the concentrations of the Grignard reagent and of the AB product can be monitored. The concentration profiles of these compounds are shown in Figure 9 (laboratory experiment) and Figure 10 (pilot plant operation). Samples were only taken during the laboratory experiments (i.e., there is no HPLC comparative analysis available for the pilot plant experiments). The concentration profiles obtained in the pilot plant are similar to those of the laboratory experiments.

For the coupling reaction, the mean deviation between NIR and reference analysis (3 σ) is about 1.8−2.1% (abs) for the Grignard reagent, and about 1.2−1.5% (abs) for the AB product. The accuracy is lower for this process step than for the Grignard reagent formation step, because fewer samples are contained in the model.

Moreover, the observed discrepancy between the concentrations measured with the spectroscopic method and HPLC is mainly due to the limited accuracy of the available HPLC reference method (a deviation of 1−2% can occur). This analysis is carried out with a 100 mm Merck Chromolith Performance RP18e column (mobile phase A, 2 mL of phosphoric acid 85% in 1000 mL of water; mobile phase 2, acetonitrile; solvent, ethanol/water (1:1 v/v).

Conclusion

A quantitative on-line NIR method for the monitoring of the formation of a Grignard reagent was developed on laboratory scale using chemometrics and tested in a 630 L pilot plant reactor. Good accuracy of the model was obtained, and feasibility of the on-line measurement was demonstrated. The concentrations of the added reagent (i.e. its degree of accumulation) and of the formed Grignard reagent (indication of the reaction initiation) can be followed in real time. Thus, the safety of the highly exothermal process and its robustness are significantly improved. Moreover, the method is applicable to following the cross-coupling reaction so that it can be used to determine the reaction yield in real time.

An NIR spectrometer using the developed calibration method was also successfully installed in a 2500 L reactor in the production plant for the automated monitoring of the process.

This kind of innovative monitoring of the process is in accord with the PAT[10] (process analytical technology) concept. By using on-line spectroscopy, the product quality and performance can be ensured. Moreover, the cycle times are reduced due to the elimination of waiting times caused by traditional analytics.

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(10) Guidance for Industry, PAT a Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance, U.S. Department of Health and Human Services, Food and Drug Administration, September 2004.