PHARMA

Towards advanced continuous manufacturing with Bruker's Fourier PAT

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Innovation with Integrity

Nuclear magnetic resonance (NMR) spectroscopy's powerful insights can be leveraged to improve advanced (bio) pharmaceutical manufacturing operations, such as continuous flow chemistry. This is now easier, thanks to the latest benchtop solutions. To maximize the effectiveness and benefits of data-driven, real-time control, on-line NMR analysis is coupled with process analytical technology (PAT). Bruker's Fourier PAT solution was used to showcase the advantages of this approach, enabling effective real-time monitoring and control of a continuous Hantzsch thiazole synthesis process.

NMR spectroscopy is a highly valuable characterization technique for organic products and in-process materials. It supports effective qualitative and quantitative non-destructive as well as non-invasive analysis while providing structural information on the chemicals being tested. Furthermore, NMR spectroscopy offers high selectivity and resolution.

NMR is a key asset in developing a detailed process understanding within R&D departments. Organic chemists and other subject matter experts (SMEs) can rely on high-quality, unambiguous data to monitor reactions in real-time, determine reaction kinetics as well as optimize process conditions. Ultimately, companies can transfer these comprehensive insights to the shop floor and downstream to drive highly effective manufacturing processes that can deliver competitive products in a timely and cost-effective matter.

While NMR instruments are common in R&D facilities, they have historically been difficult to implement in the late development and manufacturing stages to support PAT-driven operations. The equipment generally involves high upfront costs while requiring substantial space, specialized facilities and operating conditions that may not be available within pilot-scale or commercial-scale manufacturing plants. Furthermore, conventional NMR investigations involve at-line analysis. These limitations have been hindering the scale of conversion of NMR-based laboratory-based knowledge into industrial applications, impeding a rapid scale up of key processes. Also, this has required SMEs to define comparison tools in order to draw approximate parallels between NMR and shop floor analysis to drive efficiencies.

A benchtop NMR solution, with its compact footprint, cryogen-free, limited costs, minimal infrastructure requirements and ability to support on-line quality control, can help overcome these challenges, bridging the gap between R&D and manufacturing. It can also support more efficient and productive, advanced manufacturing strategies, such as continuous processing.[1] As a result, companies can benefit from more effective, streamlined applied research and scale up as well as enhanced production operations.

To further expand process and product understanding within R&D and commercial setups, it is advisable to adopt a PAT framework.[2,3] By leveraging the relation between a product's critical quality attributes (CQAs) and critical process parameters (CPPs), this provides a comprehensive system to understand, monitor and control reactions. When integrated with automation devices and machines, it can also support fully autonomous operations.[4]

As the correlation between CQAs and CPPs can be complex, it can be necessary to apply chemometrics, i.e. mechanistic and statistical methods, to the NMR data being collected.[5] Once relevant, high-quality measurement data are collected, a PAT knowledge management software can ease the building of data sets, analytical results, predictive models and higher-level control systems. This platform connects in real-time to physical systems, such as NMR instruments, and unit operations, as well as control and software systems. The software can run complex orchestrations, where multiple PAT instruments are harmonized into a PAT environment and their corresponding data streams visualized in the same interface to deliver comprehensive knowledge that translate into key process insights.

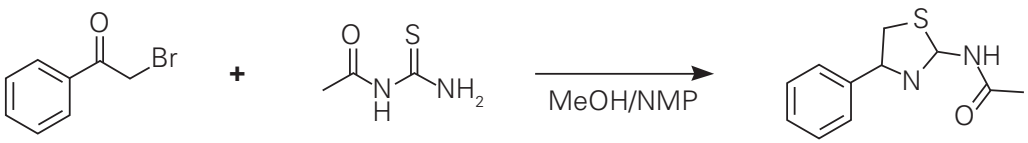
By combining a state-of-the-art benchtop NMR solution, a software platform for spectral analysis, a chemometric modeling system and PAT knowledge management platform, it is therefore possible to collect measurements and make quality predictions in real time. Based on these insights, it is possible to deliver products that will consistently meet set quality targets. On the shop floor, all these tasks can happen while the continuous process is taking place, ultimately enabling advanced manufacturing. It is also possible to check that the data are within specified parameters, and manually or automatically adjust the process on the fly, if needed, to deliver high-quality products with high efficiency. Finally, cutting-edge PAT software solutions are also starting to offer automated continuous improvement functions that enable users to continuously refine their models and, consequently, improve operations to drive product quality, efficiency and productivity.

A comprehensive setup as described above is offered by Bruker through its Fourier PAT solution. This whitepaper discusses the application of this solution to effectively control and optimize a popular flow chemistry process, the Hantzsch thiazole synthesis, in real-time. This reaction is one of the most common, reliable and high-yield routes for thiazole production.

Methodology

Reaction

The Hantzsch reaction was performed by flowing a solution of N-acetyl thiourea (1.0 M in 50% protonated solvents, methanol and N-methyl-pyrrolidone MeOH/NMP) at 0.5 mL/min in a reactor (Scheme 1).



Scheme 1. Hantzsch reaction between N-acetyl thiourea and N-methyl-pyrrolidone

After 20 minutes, the second reagent, 2-bromoacetophenone (1.0 M in MeOH), was added at a flow rate of 0.5 mL/min. The reactor was initially set at a temperature of 20°C and, every 18 minutes (to account for stabilization and residence time), the temperature was increased by 10°C until reaching 80°C.

Different reagent ratios and temperatures were tested to identify the most suitable conditions, as described in Table 1.

Temperature	N-acetyl thiourea:2-bromoacetophenone
20-80°C (in 10°C steps) for 2 hours	1:1
80°C	3:2
80°C	7:3
80°C	2:3
80°C	3:7

Table 1. Reaction conditions used for the synthesis of thiazole

Analytical equipment and methods

The Hantzsch thiazole synthesis was monitored with Bruker's Fourier RxnLab NMR technology. The system was used in combination with a Knauer double-piston pump. With this setting, the reaction mixture is pumped out of the reactor and flown into the NMR detector through active temperature-controlled lines. The temperature within the flow lines was controlled using an external thermostat working in combination with insulation lines to ensure that the reaction mixture could be maintained at the desired values.

400 MHz and 80 MHz ^{1}H NMR spectra were processed with Bruker's InsightMR 2.0 software, which includes the Mnova reaction monitoring platform.

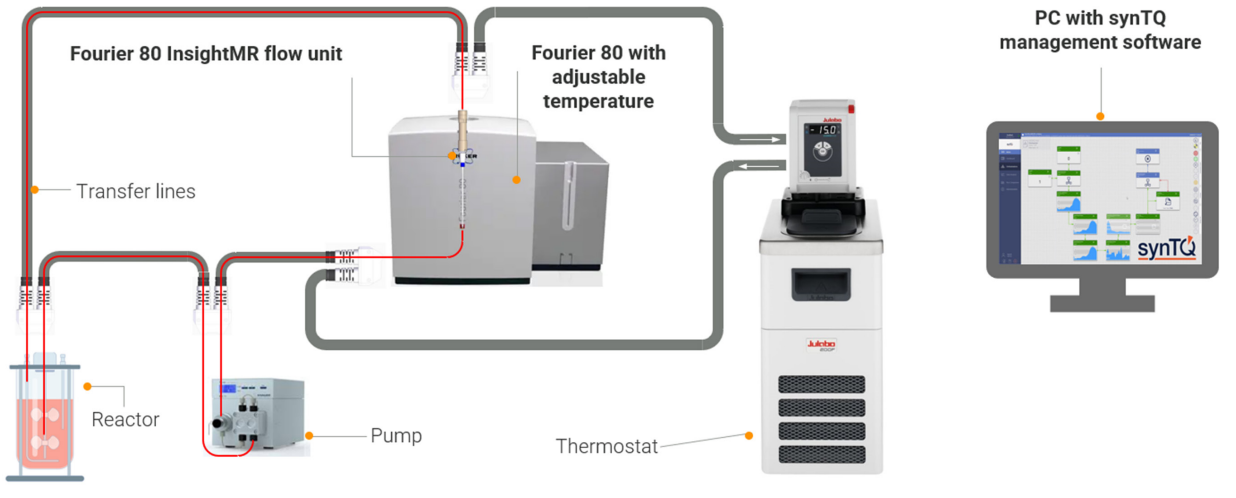


Figure 1. Fourier PAT setup

The data analysis methods were developed using PEAXACT software. Spectral Hard Modelling was implemented to analyze the NMR signals, especially those overlapping and accounting for nonlinear effects, such as peak broadening and shifts. A suitable model was developed using the aromatic and aliphatic signals from reactants and solvents. For comparison, high-field NMR signals were analyzed via peak integration method.

The different software components are integrated into synTQ knowledge management platform, which will enable to perform automated on-the-fly process optimization.

Results and discussion

The ^{1}H NMR 80 MHz as well as 400 MHz spectra, analyzed with PEAXACT models and supported by synTQ, could effectively detect the peaks for raw materials, i.e. acetyl thiourea, and products of the Hantzsch reaction.

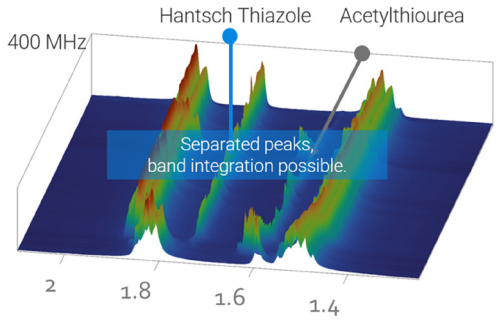


Figure 2. Aliphatic region of ^{1}H 400 MHz online NMR spectra

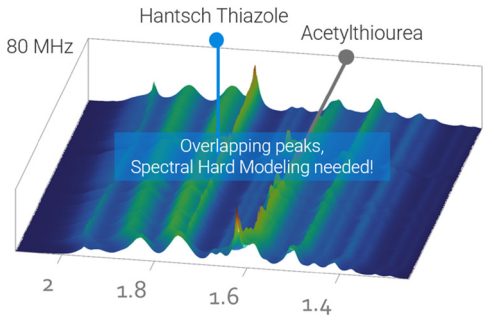
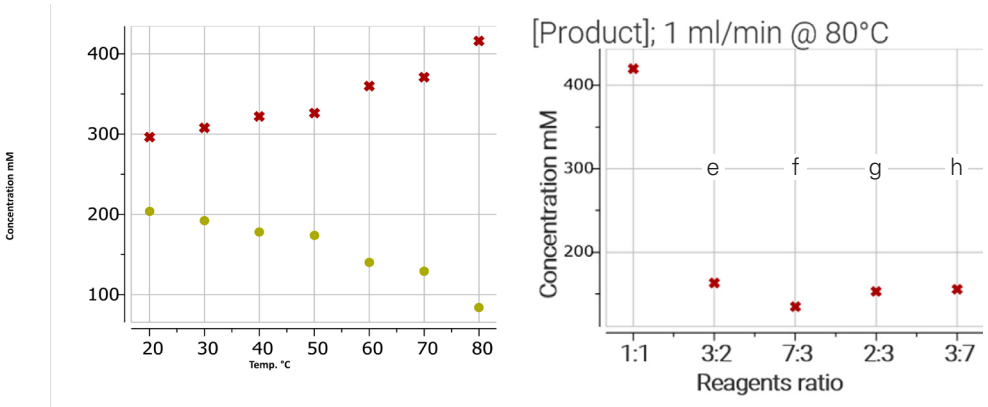


Figure 3. Aliphatic region of ^{1}H 80 MHz online NMR spectra

The setup could also detect and characterize the variations in molar ratios over time. The following figures show the evolution of the peak of the product (left figure, in red) compared to the decrease of the peak of one of the starting materials (left figure, in green) over changes of temperature. In the figure on the right, the comparison is between the concentration of product and the ratio of reagents (e.g. thiourea 3 to acetophenone 2 and so on).



Figures 4 (left) and 5 (right) showing starting material (in green) consumption and product formation (in red) over time (left figure); on the figure in the right, the comparison is between a different reagents ratio (x-axis) and product formation (in red, concentration on y-axis)

The chemometric model (Spectral Hard Modeling) was able to automatically deliver information on different peak areas to monitor the reaction.

Based on the NMR data, investigations on the effects of temperature and reagent ratios highlighted that optimum conditions could be achieved at 80°C and when the concentrations of N-acetyl thiourea and 2-bromoacetophenone were 1:1. Under such conditions, the concentration of the products (yield) was maximized. Moreover, 400 MHz and 80 MHz NMR Spectra from a whole optimization run were analyzed via peak integration as well as Spectral Hard Modelling. Oscillations in the molar ratios over time stem from fluctuations of the substrate feed and are clearly detected by both methods.
In particular, the data points a to c are related to reactions at different temperatures, e to h to the change of molar ratio (e to h are also depicted in the figure 5 above). The fluctuation at data point d was a single event when there was an error in the feed of reagents. The consistency between both instruments is clearly highlighted in figure 6, giving proof of the added value of a low field instrument.

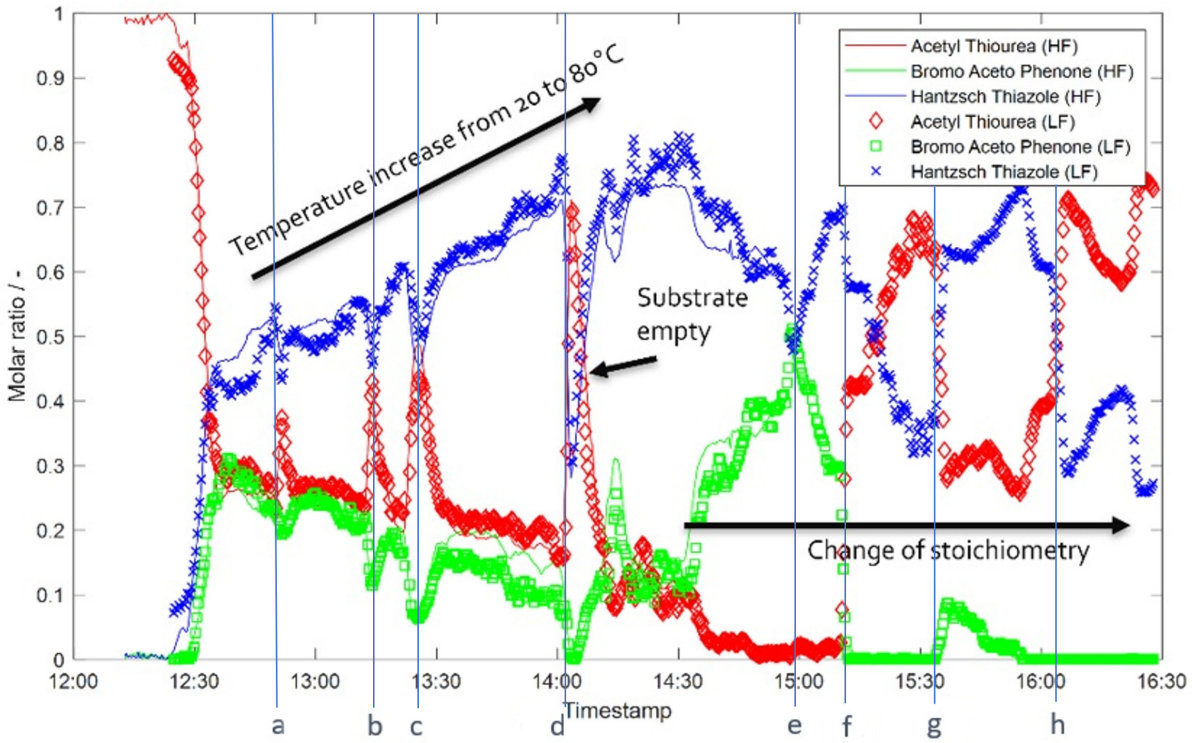


Figure 6. Quantitative comparison of 80 MHz and 400 MHz results (symbols are used for 80 MHz results, lines for 400 MHz ones)

Based on these insights, it was therefore possible to maximize productivity and maintain optimum conditions via continuous monitoring of the reaction mixture using the Bruker benchtop NMR solution.

Conclusions

The current study clearly showcased how on-line benchtop NMR spectroscopy within a PAT frame can support the monitoring, control and, ultimately, the optimization of the Hantzsch thiazole syntheses and, more in general, chemical processes. Spectral Hard Modeling methods were applied with PEAXACT to analyze complex overlapping signals. In addition to providing a tool for improving process understanding, the solution has the potential to support consistency and efficiency, driving optimal product quality and yield while reducing cycle time and waste. The Fourier PAT benchtop NMR reduces tedious calibrations and increase (bio)process understanding and control, hence further reducing risks and cost, bringing a wealth of structural information and direct quantification to the lab and/or plant.

By leveraging Bruker's Fourier PAT solution, users can enhance knowledge transfer from R&D to advanced manufacturing as well as drive standardization across multiple production lines within one or multiple facilities. In addition, thanks to synTQ, it can be possible to implement automated control strategies to adjust CPPs as well as notify operators when a process is deemed complete, optimizing, and accelerating the (bio)production of key chemicals and (bio)therapeutics.

References and additional resources

1. Schotten, C. et al. (2018). A continuous flow-batch hybrid reactor for commodity chemical synthesis enabled by inline NMR and temperature monitoring. Tetrahedron, 74(38), 5503-5509.
2. Chanda, A. et al. (2015). Industry perspectives on process analytical technology: tools and applications in API development. Organic Process Research & Development 19(1), 63–83
3. Simon, L. L. et al. (2015). Assessment of recent process analytical technology (PAT) trends: a multiauthor review. Organic Process Research & Development, 19(1), 3–62.
4. Rodriguez-Zubiri, M., Felpin, F. (2022). Analytical tools integrated in continuous-flow reactors: which one for what? Organic Process Research & Development, 26(6), 1766–1793
5. Gerzon, G., Sheng, Y., Kirkitadze, M. (2022) Process analytical technologies – advances in bioprocess integration and future perspectives. Journal of Pharmaceutical and Biomedical Analysis, 207, 114379.

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