

PHARMA

Introduction to ^{19}F NMR in Modern Drug Development

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Innovation with Integrity

Fluorine (^{19}F) is widely used in pharmaceuticals for its ability to enhance pharmacokinetic and pharmacodynamic properties. Its unique NMR characteristics include high sensitivity, a broad chemical shift range, and minimal background. These features make it ideal for real-time reaction monitoring. Here we demonstrate the use of benchtop NMR with Bruker Fourier RxnLab, integrating a Fourier80 spectrometer and InsightMR flow cell, to monitor nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) reactions under controlled conditions. Continuous in situ analysis enables direct observation of substrates, intermediates, and products, providing quantitative kinetic profiles without external standards. Combined with advanced software tools for automated data processing and modelling, this approach supports Process Analytical Technology (PAT) and Quality by Design (QbD) principles, offering a robust, scalable solution for efficient development of fluorinated pharmaceuticals.

Introduction

Fluorine (^{19}F) is present in about 20% of pharmaceuticals marketed globally, and about half of newly approved small-molecule drugs often bear fluorine substituents.¹

Incorporation of ^{19}F is used to control pharmacokinetic properties: improving metabolic stability, modulating lipophilicity and $\text{p}K_a$, increasing membrane permeability, and often reducing clearance. On pharmacodynamics, fluorine can sharpen binding specificity, influence conformation via stereo electronic effects, and improve target selectivity.^{2,3}

In NMR, ^{19}F offers high sensitivity, 100% natural abundance, large chemical shift range, and minimal background in biological matrices. These traits make fluorine ideal for reaction monitoring by NMR. ^{19}F NMR can easily be used to detect substrates and products, and to immediately track conversion, detect intermediates, and quantify yield without needing separate reference standards in very complex matrices.⁴

$\text{S}_{\text{N}}\text{Ar}$ Transformation Case Study: Regioselective Substitution of Difluoronitrobenzene with Morpholine and Piperidine

Nucleophilic Aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) reactions play a crucial role in pharmaceutical synthesis, enabling efficient formation of aromatic C–N and C–O bonds found in numerous drug molecules.⁵ They are widely used to construct heteroaryl frameworks in antivirals, kinase inhibitors, and central nervous system (CNS) active compounds. Their compatibility with continuous flow and green chemistry approaches makes them ideal for scalable, sustainable drug manufacturing.

The specific transformations studied include nucleophilic aromatic substitution of 3,4-difluoro-4-nitrobenzene and with piperidine to yield 1-(2-fluoro-4-nitrophenyl)piperidine (FNBPP) and 3,4-difluoro-4-nitrobenzene with morpholine to produce 4-(2-fluoro-4-nitrophenyl)morpholine (FNPM), both releasing hydrogen fluoride (HF) as a by-product, which is quenched *in situ* by the base (Figure 1). In these reactions, the nitro group strongly withdraws electron density, stabilizing the Meisenheimer intermediate and activating the para-fluorine for selective displacement. This electronic effect ensures regioselectivity and efficient synthesis under mild conditions.

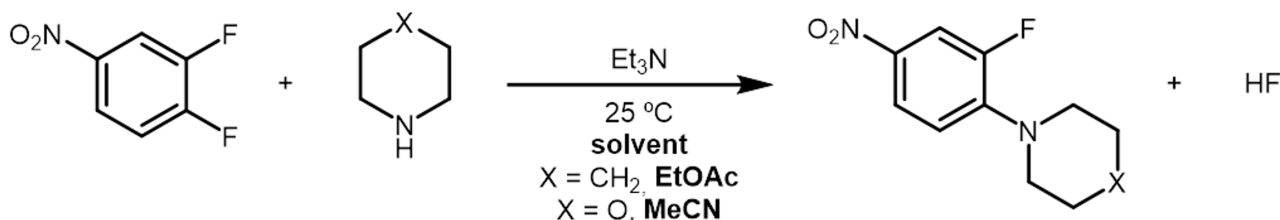


Figure 1: $\text{S}_{\text{N}}\text{Ar}$ reaction between 3,4-difluoro-4-nitrobenzene and piperidine or morpholine in the presence of Et_3N and EtOAc or MeCN as a solvent.

Integrated Hardware Solutions for NMR Reaction Monitoring

The reaction monitoring system features a Bruker Fourier RxnLab equipped with an adjustable-temperature probe ($25\text{--}60\text{ }^\circ\text{C}$) and a dedicated flow cell for real-time analysis. The RxnLab integrates a Bruker Fourier 80 NMR spectrometer with an InsightMR flow cell, enabling continuous, *in situ* monitoring and real-time analysis of chemical reactions. The process stream is circulated through actively temperature-controlled transfer lines connected to a thermostat, ensuring thermal stability during sampling. A precision pump enables continuous recirculation between the reactor and the flow cell, allowing seamless monitoring of both batch and flow reactions. This closed-loop configuration maintains consistent temperature throughout transfer, eliminating fluctuations that could impact reaction kinetics or spectral accuracy. Moreover, loss of temperature control can reduce solubility of intermediates or products, leading to precipitation and potential clogging of the lines, which would disrupt flow and compromise the process. The result is a robust, reliable solution for real-time process monitoring under fully controlled conditions (Figure 2).

The configuration can initially be simplified to the RxnLite setup, which excludes the Snadjustable-temperature option for the Fourier 80 and omits temperature-controlled transfer lines. This base configuration can later be upgraded to the RxnLab solution, adding an adjustable-temperature probe and actively controlled transfer lines for enhanced thermal management.

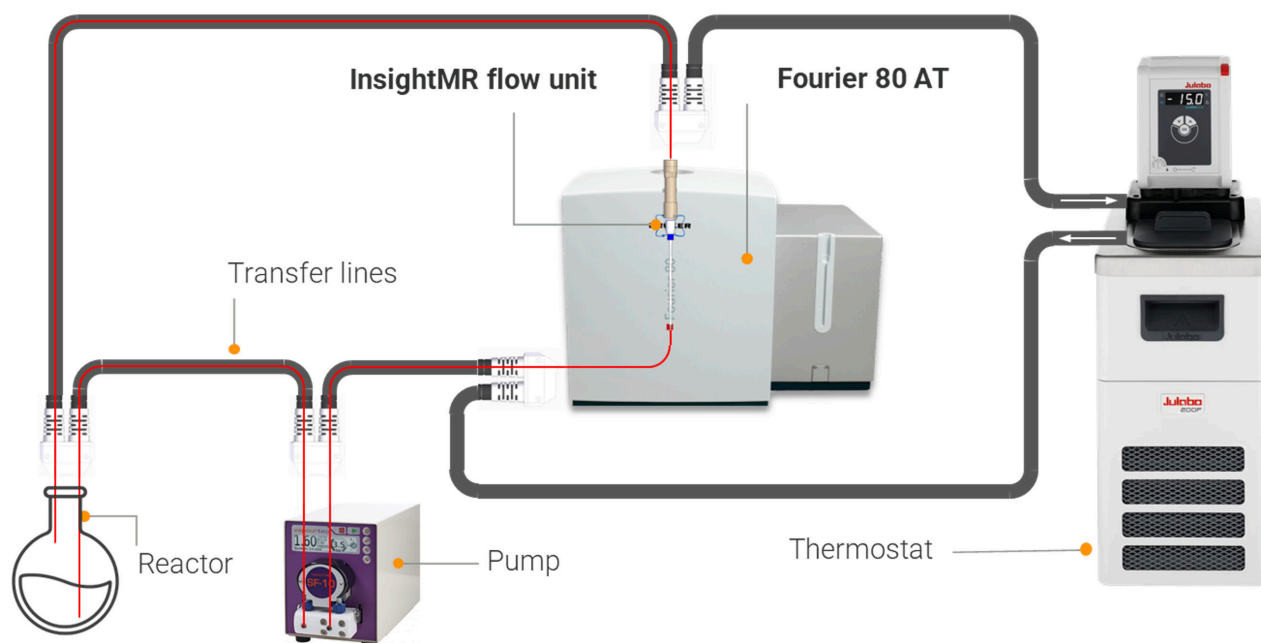


Figure 2: RxnLab configuration (Fourier 80 Adjustable Temperature, InsightMR flow cell, temperature controlled transfer line, thermostat, pump).

¹⁹F NMR as a Solution for Real-Time Reaction Monitoring

For detecting the ¹⁹F nucleus with the Bruker Fourier 80, two main configurations are available: Multi-Talent and TripleXpert, each offering distinct sensitivity and flexibility for heteronuclear detection. The Fourier 80 Multi-Talent ¹H/X system allows software selection among 15 X-nuclei (²H, ⁷Li, ¹¹B, ¹³C, ¹⁵N, ¹⁹F, ²³Na, ²⁷Al, ²⁹Si, ³¹P, ⁵¹V, ⁷⁷Se, ⁷⁹Br, ¹¹⁹Sn, ¹²⁹Xe), enabling versatile multinuclear experiments. The TripleXpert ¹H/¹³C/¹⁹F system is optimized for maximum X-channel sensitivity, ideal for demanding ¹⁹F applications.

Both systems support flow operation and adjustable sample temperature, essential for reaction monitoring. In ¹⁹F spectral acquisition, ¹H decoupling provides 5–8× higher signal-to-noise and resolves overlapping signals (Figure 3); similarly, ¹H spectra can be acquired with ¹⁹F decoupling, offering the same advantages in sensitivity and spectral clarity. When acquiring ¹H of fully protonated solvents, solvent suppression with carbon decoupling is available – particularly useful when organic solvents require suppression of ¹³C satellites that could overlap with analyte signals. The Fourier 80 supports both quantitative and qualitative ¹⁹F NMR, with robust and user-friendly workflows.

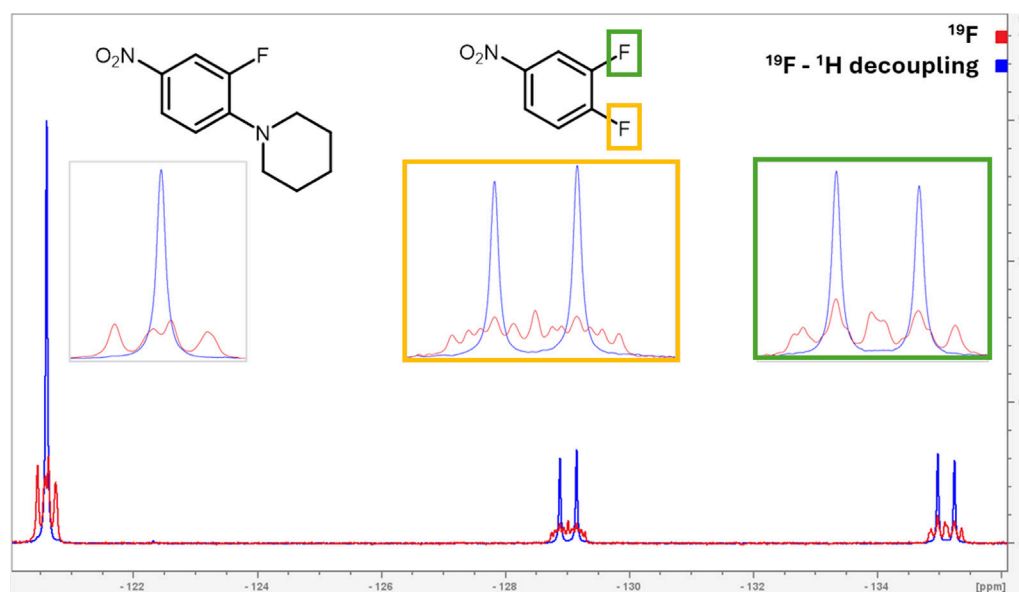


Figure 3: 1D-¹⁹F (in red) and 1D-¹⁹F with ¹H decoupling (in blue) comparison (results from Fourier 80 TripleXpert NMR system) during S_NAr piperidine reaction.

Integrated InsightMR Software Solutions for NMR Reaction Monitoring

InsightMR2.0 software is a dedicated real time monitoring solution to monitor (bio)chemical reaction in function of time for high field NMR and benchtop NMR systems (Figure 4).

It includes a dedicated acquisition graphical user interface (GUI) (Figure 5) compatible with both flow accessories and sample changer.

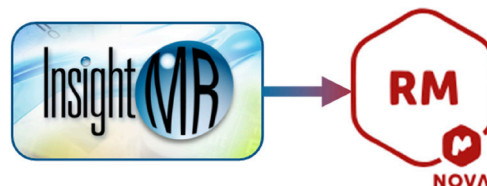


Figure 4: InsightMR allows MestReNova Reaction Monitoring package for automatic real time reaction monitoring.

Figure 5: InsightMR acquisition GUI for easy selection of experiments.

The software allows the user to easily select and combine automatic solvent suppression experiments, interleave experiments (sequential experiments on ^1H and ^{19}F nuclei) and also monitoring on multiple samples appearing on different documents tabs (Figure 6).

Within MestReNova software, the user can have access to a series of packages (previous license activation) for data analysis and reports. To mention some, they could include NMR Predict, Verify, qNMR, DB, Structure Elucidation, StereoFitter, IUPAC Name and Advanced Chemometrics that would improve the work for specific task like chemical mixture peak assignment, reaction mechanism understanding, reaction yield calculation and kinetic profile study of the specific reaction.

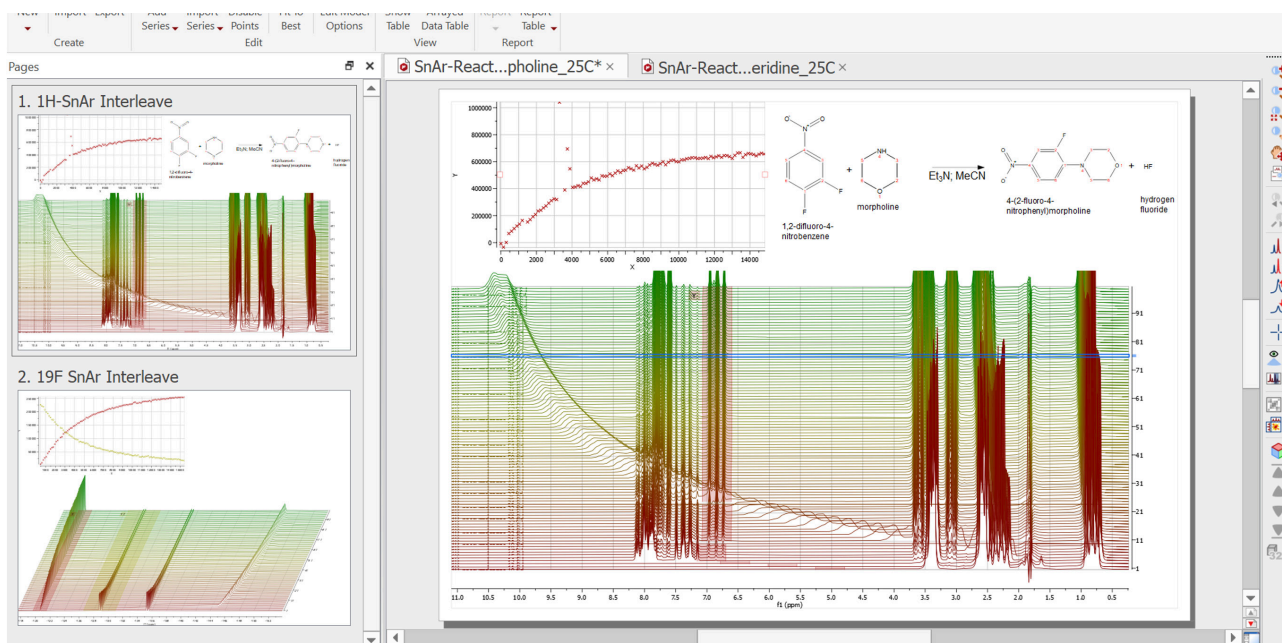


Figure 6: MestReNova workstation package. S_NAr reaction monitored by 1D ¹H and 1D ¹⁹F interleaved experiments acquired with Fourier RxnLab system.

¹⁹F NMR Data Analysis

After assigning all spectral components involved in the reaction, regions corresponding to each ¹⁹F nucleus can be integrated to generate concentration-versus-time profiles. Mnova RM workstation supports automated updating of these profiles as spectra are acquired. When peak positions drift during the reaction – such as the gradual chemical-shift migration of the HF signal formed *in situ* – the peak-tracking algorithm maintains correct feature identification and integration boundaries, preserving quantitative reliability (Figures 7, 8, 9 and 10).

Kinetic traces derived from these integrations can be fitted using user-defined mathematical models. The Fit to Best procedure evaluates multiple candidate functions and selects the model that provides the statistically optimal description of the dataset, while still allowing users to define or customize equations for nonstandard kinetic behavior. Interactive plotting tools enable refinement of integration limits, fitting intervals, and tracked peak regions to improve data quality. The interface supports high-complexity reactions, large datasets, and preprocessing operations such as automatic phase correction and peak alignment.

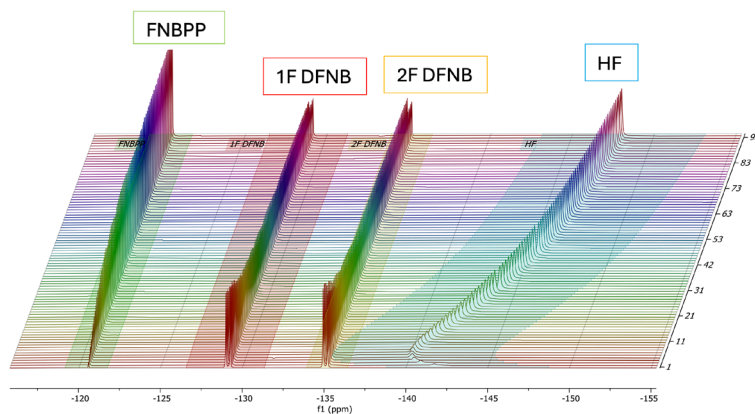


Figure 7: S_NAr piperidine reaction. Stack view of 1D ¹⁹F NMR spectra. Integration region respectively from left to right: 2-fluoro FNBP; 1-fluoro DFNB; 2-fluoro DFNB; HF.

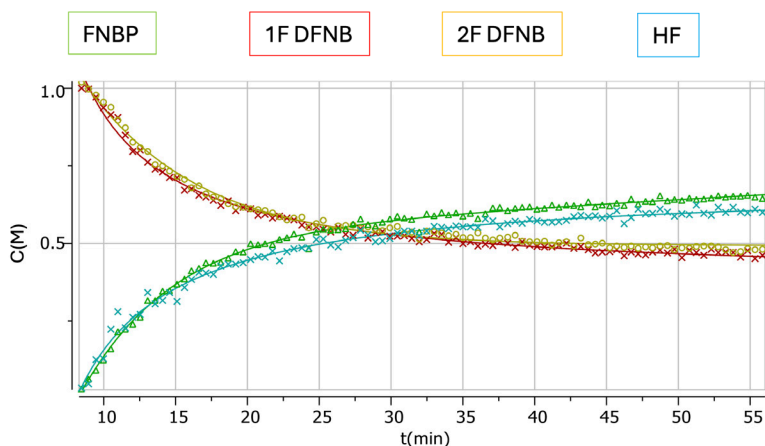


Figure 8: Kinetic curve of concentration vs. time generated automatically relative to the integration region defined on NMR data for S_NAr piperidine reaction (Figure 7). Automatic fitting procedure based on "Fit To Best" functionality.

Scalable, Modular NMR Integration for Advanced PAT Workflows

NMR spectroscopy, equipped with the synTQ NMR adapter, provides a powerful and automated PAT solution for real-time process understanding. The adaptor seamlessly controls sample changers and integrates with flow accessories, enabling off-line, at-line, and fully on-line monitoring. Expandable to Fourier PAT, the Fourier 80 benchtop NMR combined with synTQ supports IPC (In-Process Control) across multiple nuclei. ^{19}F and ^{31}P are especially valuable for rapid, unambiguous IPC in systems where spectral overlap can limit low-field performance, including applications such as fluorinated oligonucleotide synthesis. For high-field NMR, dedicated probes and flow cells minimize matrix background for enhanced sensitivity.

NMR can also be orchestrated with IR and Raman spectroscopy to provide orthogonal monitoring. IR and Raman data can be used to train robust vibrational spectroscopy chemometric models, while NMR adds structural accuracy and absolute quantification. Beyond reaction monitoring, NMR remains the best technique for mechanism elucidation and significantly strengthens PAT robustness by supporting and complementing other analytical technologies.

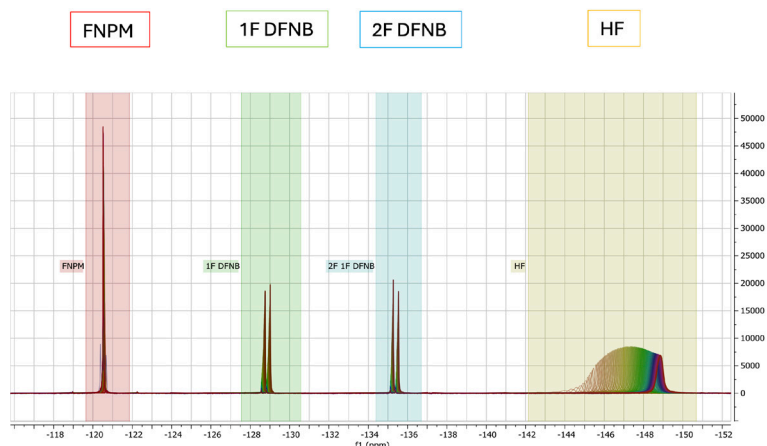


Figure 9: $\text{S}_{\text{N}}\text{Ar}$ morpholine reaction. Superimposed view of $1\text{D } ^{19}\text{F}$ NMR spectra. Integration region respectively from left to right: 2-Fluoro FNPM; 1-Fluoro DFNB; 2-Fluoro DFNB; HF.

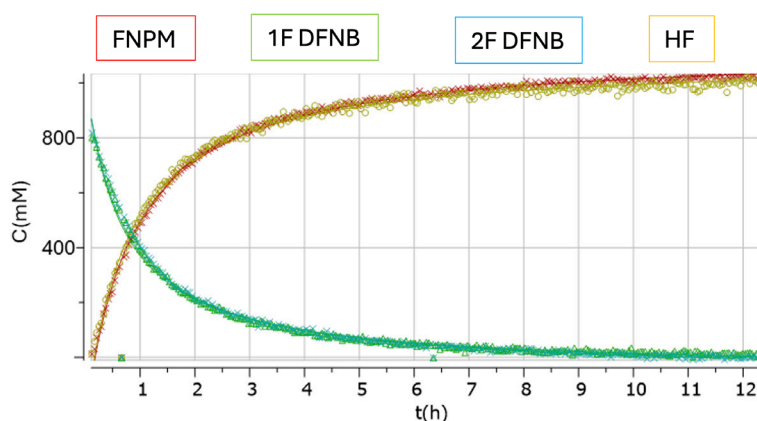


Figure 10: Kinetic curve of concentration vs. time generated automatically relative to the integration region defined on NMR data for $\text{S}_{\text{N}}\text{Ar}$ morpholine reaction (Figure 9). Automatic fitting procedure based on "Fit To Best" functionality.

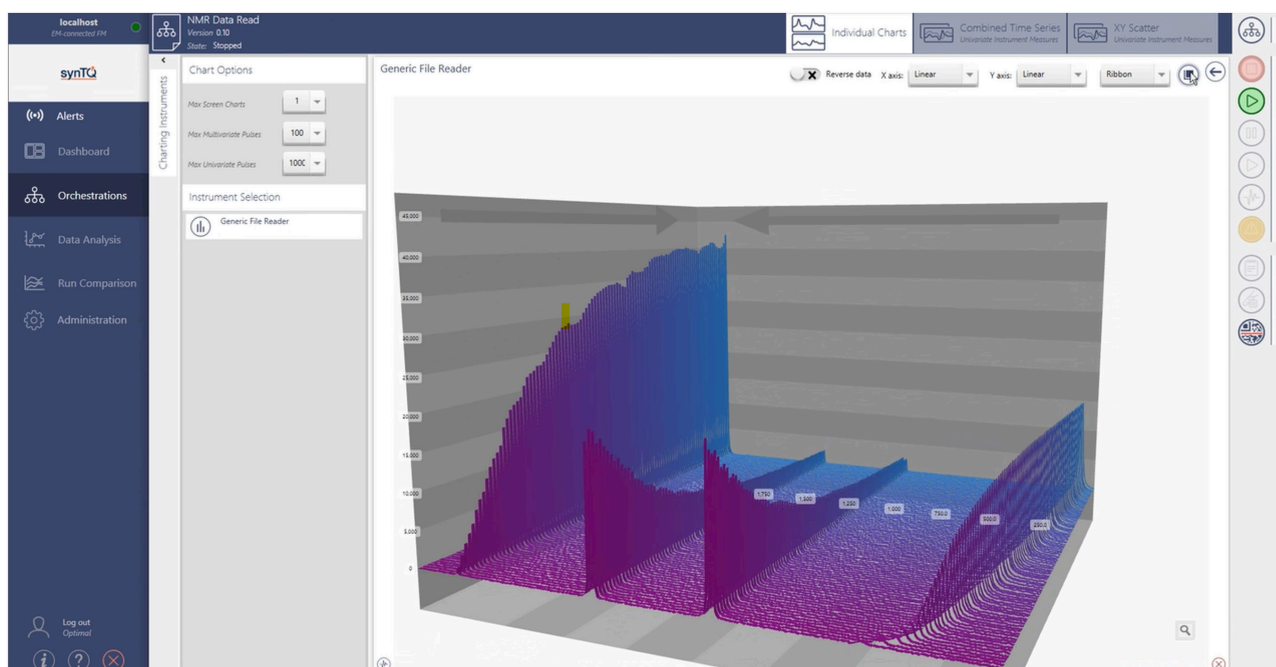


Figure 11: $1\text{D } ^{19}\text{F}$ monitoring using the NMR adapter in synTQ software as part of the Fourier PAT system.

Conclusion

The integration of ^{19}F NMR spectroscopy with real-time monitoring platforms such as Bruker Fourier RxnLab provides a powerful solution for understanding and optimizing $\text{S}_{\text{N}}\text{Ar}$ reactions in pharmaceutical synthesis. Fluorine's unique NMR properties – high sensitivity, wide chemical shift range, and minimal background – enable precise tracking of substrates, intermediates, and products without additional reference standards, even in complex matrices. Combined with InsightMR software and advanced data analysis tools, this approach delivers quantitative kinetic profiles and mechanistic insights under fully controlled conditions. The ability to monitor reactions continuously in situ supports process intensification, scalability, and compliance with modern PAT and QbD principles, making benchtop NMR a practical and robust technology for sustainable drug development.

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