Supporting Information

Simultaneous reaction- and analytical model building using dynamic flow experiments to accelerate process development

Peter Sagmeister,[a,b] Lukas Melnizky,[a,b] Jason D. Williams,*[,a,b] C. Oliver Kappe*[,a,b]

[a] Center for Continuous Flow Synthesis and Processing (CC FLOW), Research Center Pharmaceutical Engineering GmbH (RCPE), Inffeldgasse 13, 8010 Graz, Austria

[b] Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, 8010 Graz, Austria

* Email: jason.williams@rcpe.at, oliver.kappe@uni-graz.at

Contents

1. General Experimental Details

1.1. Materials and Methods

1.1.1. Chemicals

Methyl nicotinate (**1a**), Methyl butyrate (**1e**), piperidine (**2c**) triethylamine (TEA), ethyl bromoacetate **5**, were ordered from Sigma Aldrich. Methyl benzoate (**1b**), benzylamine (**2a**), *N*-methylbenzylamine (**2b**), butanoyl chloride and isopropyl benzoate (**1d**) were obtained from TCI. 2-Nitroimidazole (**4**) and 2,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidin (TBD) were purchased from BLD Pharmatech Ltd. Ethyl benzoate (**1c**) was ordered from Acros Organics. 2-methyltetrahydrofurane (MeTHF) was ordered from Merck-Millipore. Benzoyl chloride, DMSO, HPLC-grade methanol (MeOH) and HPLC grade acetonitrile (MeCN) were purchased from VWR Chemicals. NMR solvents ($CDCl_3$ and DMSO-d_6) were obtained from Eurisotop.

1.1.2. Analytics

High field NMR

High field NMR analysis was carried out on a Bruker 300 MHz spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz, ^{19}F: 282 MHz). The chemical shifts of ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvent. Coupling constants are given in Hertz (Hz). Multiplicity is indicated with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

LC-MS

LC-MS analysis was carried out on a Shimadzu instrument using a C18 reversed-phase (RP) analytical column (150 mm × 4.6 mm, particle size 5 µm using mobile phases A (H_2O/MeCN 90:10 (v/v) + 0.1% HCOOH) and B (MeCN + 0.1% HCOOH) at a flow rate of 0.6 mL/min. The following gradient was applied: hold at 5% B for 2 min, increase to 20% solvent B over 6 min, increase to 100% solvent B over 10 min and hold at 100% B for 6 min. Low resolution mass spectra were obtained on a Shimadzu LCMS-QP2020 instrument using electrospray ionization (ESI) in positive or negative mode.

Fluidic equipment

Equipment for the flow setup (PFA or PTFE tubing, PEEK connectors etc.) was purchased from Kinesis (Idex distributor).

1.2. Inline FTIR Analysis

1.2.1. General Details and Process Integration

Inline FTIR spectra were recorded on a ReactIR 15 instrument (Mettler Toledo, ReactIR 15) equipped with either a flow cell (Mettler Toledo, Micro Flow Cell DS SiComp) or a probe (Mettler Toledo, AgX 9.5 mm fiber, DiComp) mounted in an in-house made flow cell made out of a T-connector (Bola, PTFE, 6.5 mm bore, **Figure S1**). The acquisition time was 15 s per data point and the spectra were recorded between 600 and 4000 cm^{-1} using a resolution of 4 cm^{-1}. It was ensured that the MCT detector had stabilized after cooling with liquid N_2, the peak height was between 21000 and 23000 and the signal to noise ratio was above 9000.

The process stream was directly connected either to the micro flow cell or the in-house made flow cell.

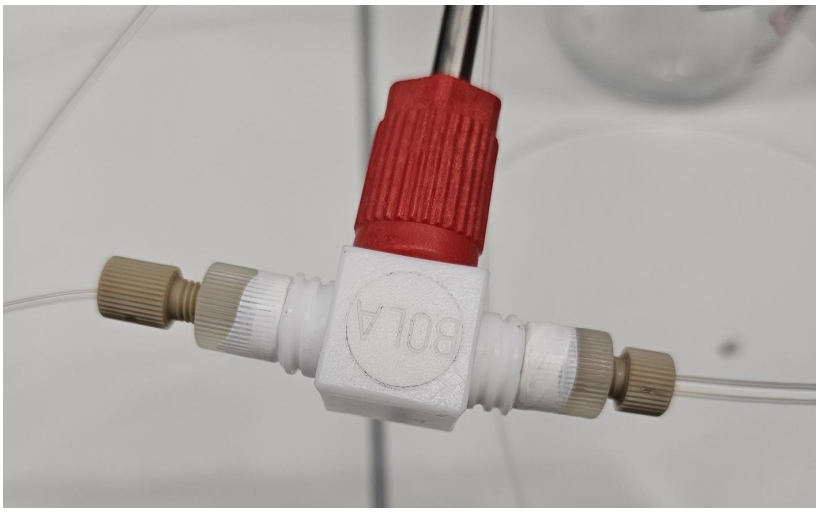


Figure S1. In-house designed flow cell made out of a Bola T-connector.

2. Process Control

2.1. Automation

The HPLC pumps, coil heater and the 6-port valves were connected via RS232 to the LabManager (HiTec Zang). The standard addition and the ramps for the concentration of ester, equivalents of amine, equivalents of TBD, residence time, temperature, product equivalents and the valve positions were programmed in HiText (HiTec Zang). The setpoints for the HPLC pumps, coil heater and the valves were automatically set in the LabVision software (HiTec Zang).

2.1.1. HiText Script and Experimental Plan

The set points for the flow rate, the temperature, the valve positions throughout the experiments were controlled by the following scripts. Each variable (concentration of ester, equivalents of amine, equivalents of TBD, residence time, temperature, product equivalents, and valve positions) was changed over time and the setpoints automatically adapted for the standard addition and the dynamic experiments (Figure S2).

Script for Pump 1

```
variable
      c_sub:Float = 2.5 {mol/L} {stock solution ester}
      c_reag:Float = 2.5 {mol/L} {stock solution amine}
      c_base:Float = 0.5 {mol/L} {stock solution TBD}
      flowrate_tot:Float
      flowrate_init_sub:Float
      reactor_volume = 5.67 {mL}
      VARIABLE_1 = equivalent amine
      VARIABLE_2 = Residence time {s}
      VARIABLE_3 = concentration_ester {mol/L}

end variable

begin
      flowrate_tot = reactor_volume /(!VARIABLE_2/60)
      flowrate_init_sub     =     (flowrate_tot     *     !VARIABLE_1     *
      (c_sub/c_reag))/(1+(!VARIABLE_1*(c_sub/c_reag)))
      !HPLC_PUMP_1.F_W = flowrate_init_sub / (((flowrate_init_sub * c_sub) /
      flowrate_tot) / !VARIABLE_3)
goto begin
```

Script for Pump 2

```
variable
      c_sub:Float = 2.5 {mol/L} {stock solution ester}
      c_reag:Float = 2.5 {mol/L} {stock solution amine}
      c_prod:Float = 1.5 {mol/L} {stock solution product}
      VARIABLE_1 = equivalent amine
end variable

begin
      !HPLC_PUMP_2.F_W = (!HPLC_PUMP_1.F_W * !VARIABLE_1 *c_sub ) / c_reag
goto begin
```

Script for Pump 3

```
variable
      c_sub:Float = 2.5 {mol/L} {stock solution triazole}
      c_reag:Float = 2.5 {mol/L} {stock solution acrylonitrile}
      c_base:Float = 0.5 {mol/L} {stock solution TBD}
      VARIABLE_4 = equivalent TBD
end variable

begin
      !HPLC_PUMP_3.F_W = (!HPLC_PUMP_1.F_W * !VARIABLE_4 *c_sub) / c_base
goto begin
```

Script for Pump 4

```
variable
      c_sub:Float = 2.5 {mol/L} {stock solution ester}
      c_reag:Float = 2.5 {mol/L} {stock solution amine}
      c_prod:Float = 1.5 {mol/L} {stock solution product}
      VARIABLE_5 = equivalents amide product
end variable

begin
      !HPLC_PUMP_4.F_W = (!HPLC_PUMP_1.F_W * !VARIABLE_5 *c_sub ) / c_prod
goto begin
```

Script for Pump 5

```
variable
      flowrate_tot:Float
      VARIABLE_2 = Residence time {s}
      reactor_volume = 5.67 {mL}
end variable


begin
      flowrate_tot = reactor_volume /(!VARIABLE_2/60)
      !HPLC_PUMP_5.F_W = flowrate_tot - !HPLC_PUMP_1.F_W - !HPLC_PUMP_4.F_W -
!HPLC_PUMP_3.F_W - !HPLC_PUMP_2.F_W


goto begin
```

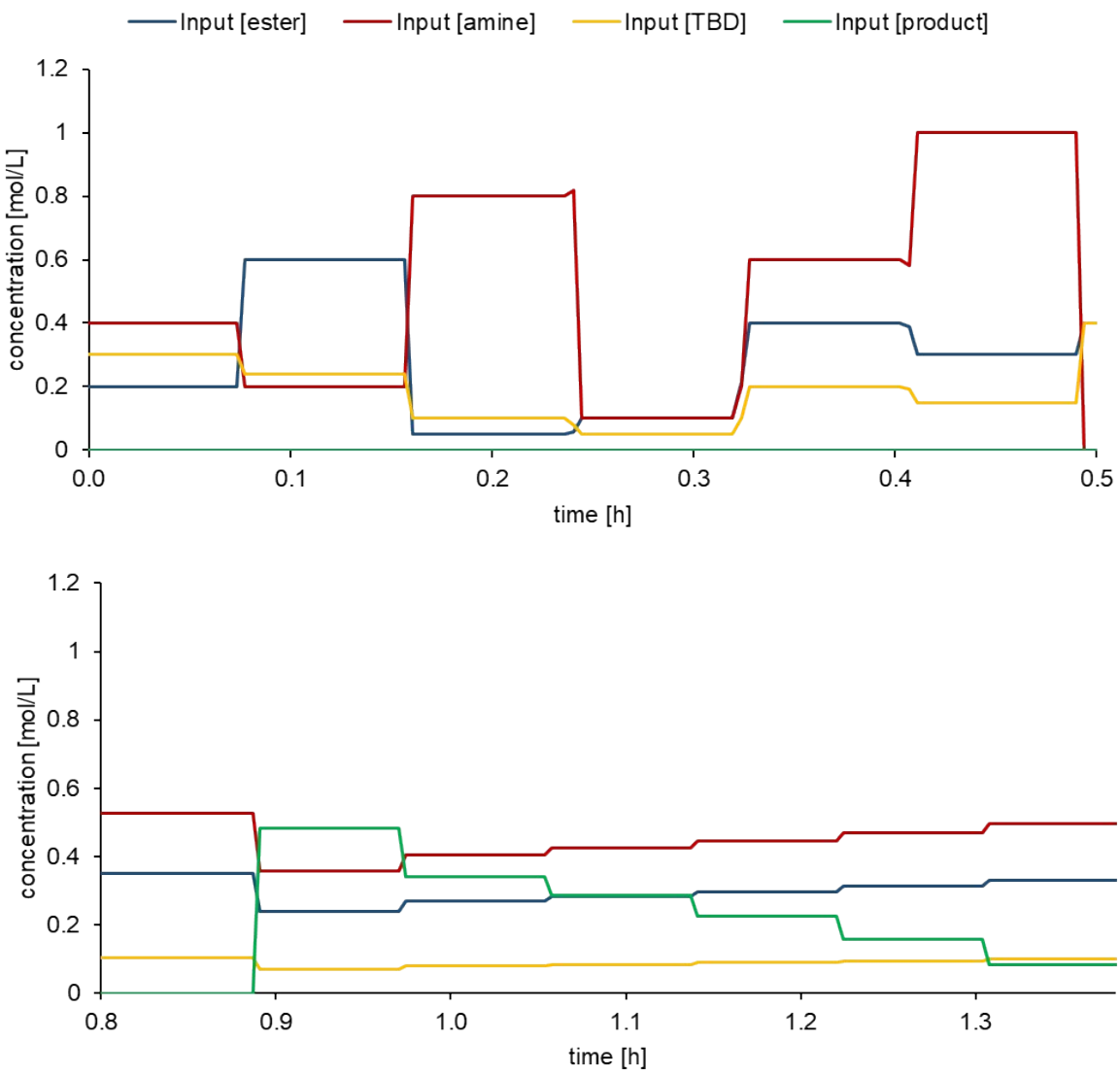


Figure S2. Input concentrations of ester (VARIABLE_3), amine (VARIABLE_1), TBD (VARIABLE_4) and product (VARIABLE_5) for the calibration levels 1-6 and levels 7-13, respectively.

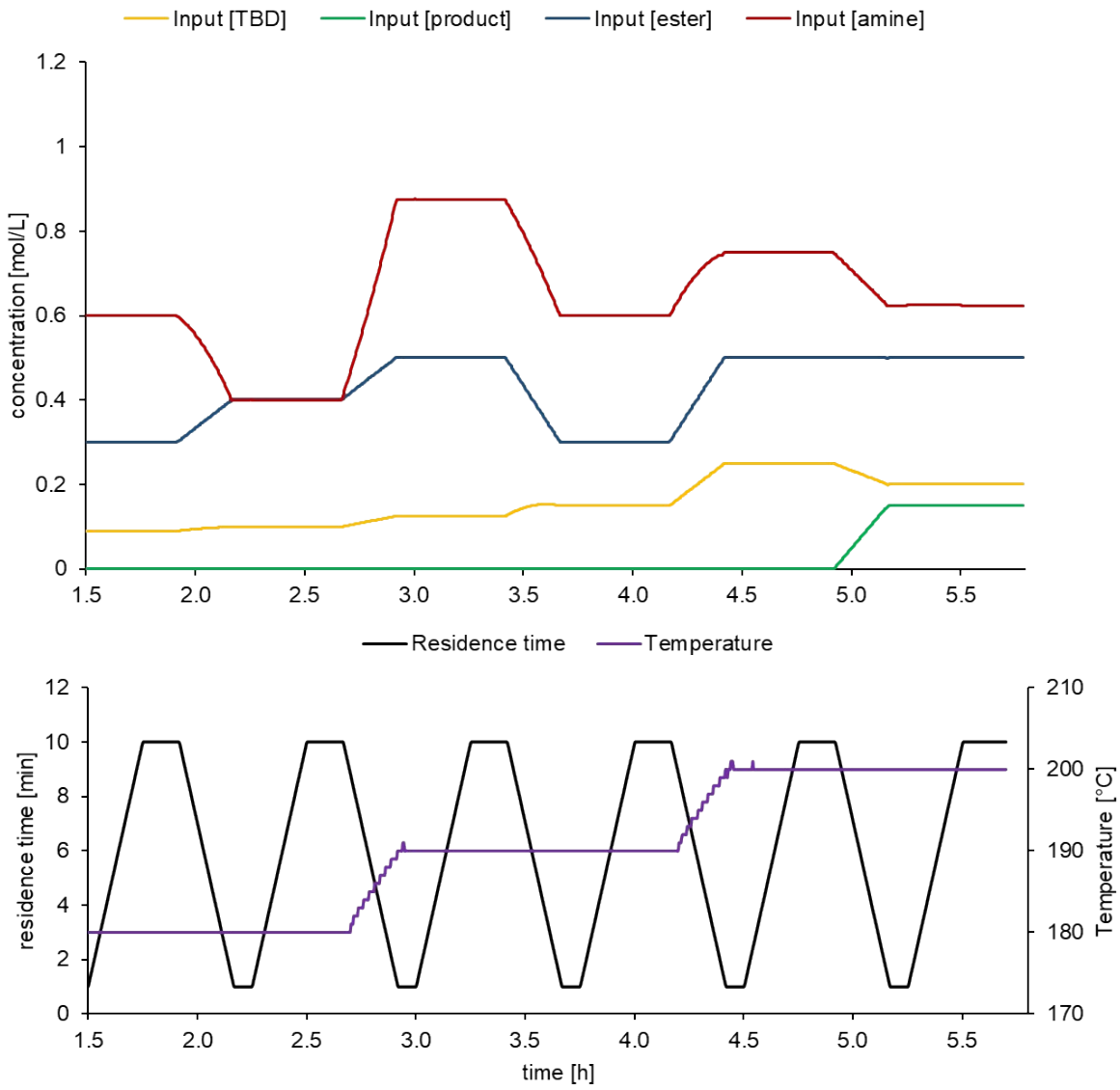


Figure S3. Input concentrations of ester (VARIABLE_3), amine (VARIABLE_1), TBD (VARIABLE_4) and product (VARIABLE_5) during the dynamic experiments and set values of residence time and temperature.

3. Data Management (Standard Addition)

3.1. Manual Approach

For manual data management, the commercial software (S-PACT, PEAXACT 5.8) was used for performing a product standard addition from the IR spectra files, grouping the resulting concentrations into the calibration levels, and performing an PLS model prediction with the grouped concentrations and IR spectra as inputs.

For the determination of suitable ester, amine, base and amide product peaks, the FTIR software (Mettler Toledo, iCiR 7.1) was used. With the signals of these components, the visualization of the calibration level grouping and a first estimation of the amide product formation during the kinetic runs was possible. The spectra files of the 13 calibration levels were exported to individual directories.

An Excel File with the corresponding time points, pump flow rates and heat coil temperatures was exported from the LabVision software.

In PEAXACT, the input concentrations of each component were grouped into the calibration levels and the rubberband-corrected area of integration for the product signal was calculated. With the exported Excel sheet, the concentration of product, which was formed in the reactor, was estimated by plotting the added concentration of product against the product peak integral (Figure S4).

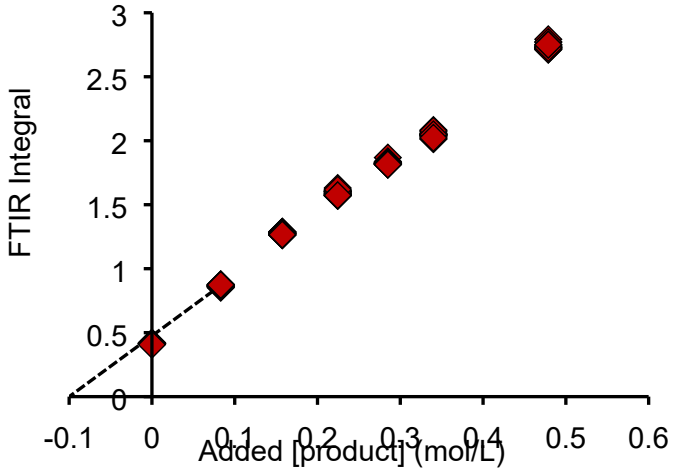


Figure S4. Example calibration used to estimate the amount of product formed in the reactor. In this case, at y = 0, x = -0.09995, therefore 0.09995 M product was formed in the reactor during the product standard addition measurements.

The corrected concentrations of all components were imported into PEAXACT again. With this calibration data, the PLS model was created. PLS ranks with low root-mean-square errors (RMSEs) of calibration and grouped cross-validation, as well as high R^2 values, were chosen for each compound. With this refined prediction model, the concentrations of each component in the kinetic run were calculated.

3.2. Automated approach

For automated data management, a Python script was developed. This script was executed at the same directory path level as the input excel file and the level-grouped FTIR spectra directories. The flow chart, subdivided into three parts for reading in the spectra and precalculated concentrations, PLS model prediction and cross validation, is shown below (**Figure S5**). The python script was executed twice. In a first run-through, all possible ranks from 1 to 10 for each reactant and product in all calibration levels

were iterated and the corresponding RMSE and R^2 values were then plotted for each rank and compound, as shown in **Figure S6**.

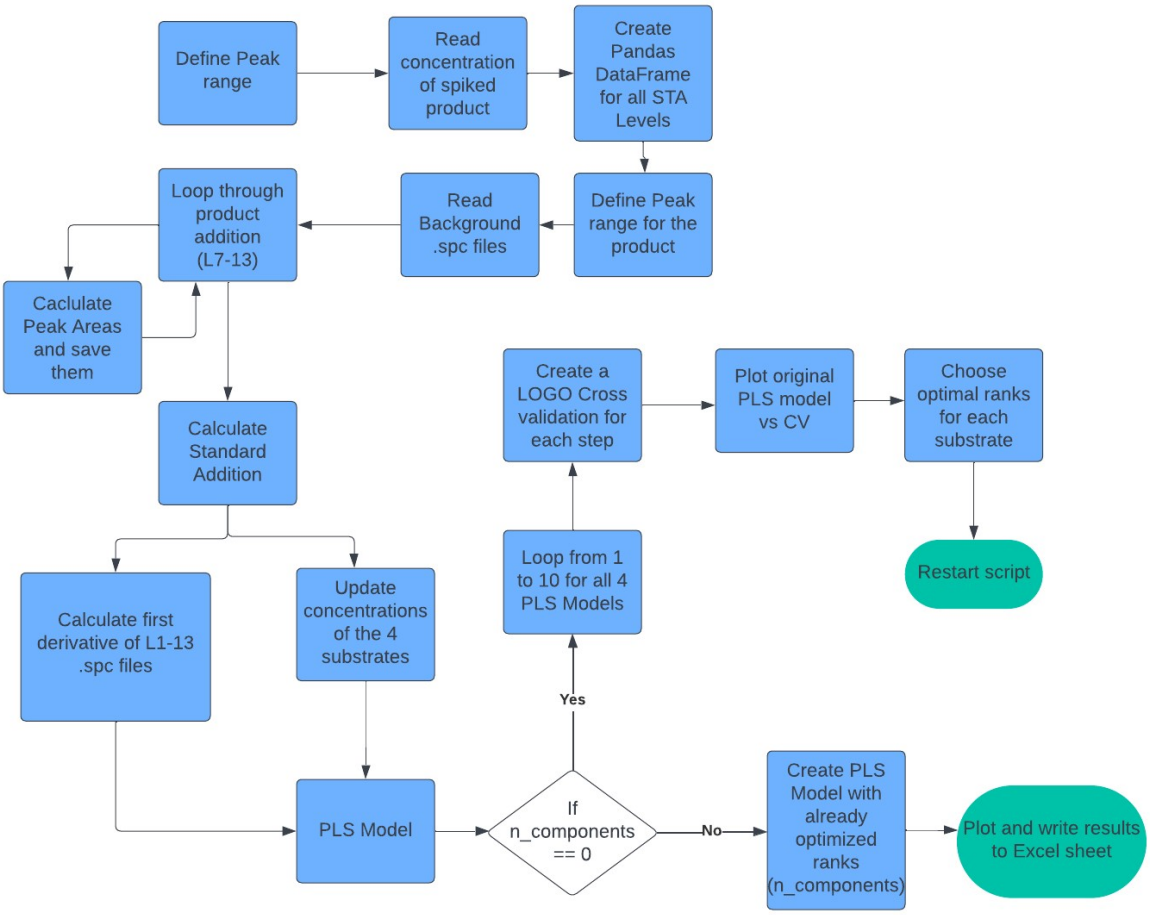


Figure S5. Flow chart of the python script for automated data evaluation and PLS prediction.

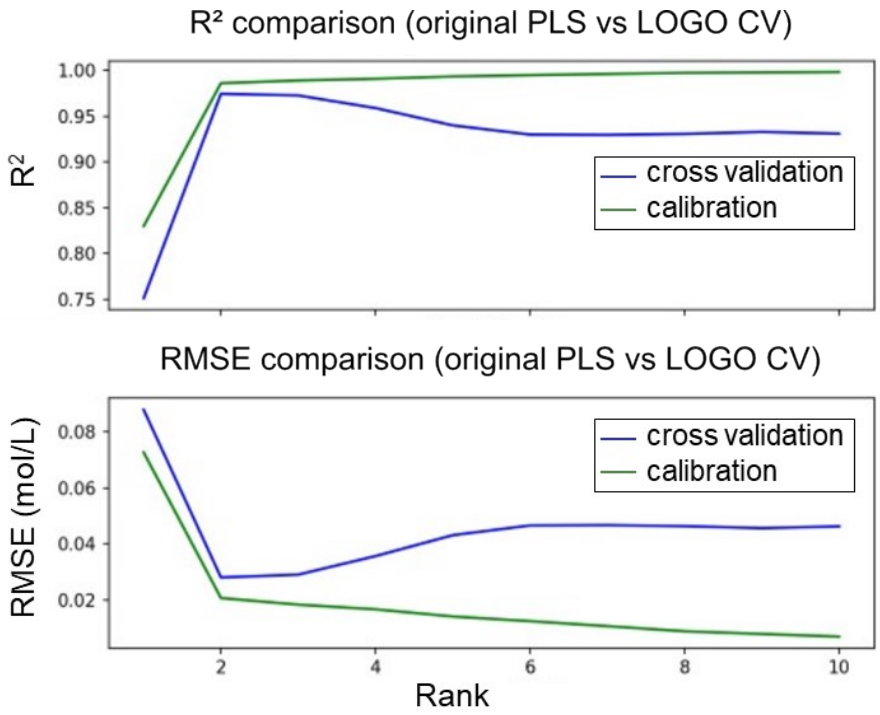


Figure S6. Pyplot graph for the comparison of R^2 and RMSE values for different PLS ranks (calibration error and cross validation error).

4. Fitting Kinetics – Julia Software

The software to fit kinetic parameters is available on GitHub and is written in Julia 1.85 using several freely available Julia libraries. The main task of the program is to fit kinetic parameters and provide a process model. Additionally, the software can perform *in-silico* optimization with the parameterized process model.

4.1. Program Design

The main program is split into several subparts, all of which are interconnected. The main task of the program can be summarized in three different modules (1) handling the experimental data, (2) identifying the process model, and (3) using the process model to optimize for the best conditions (**Figure S7**).

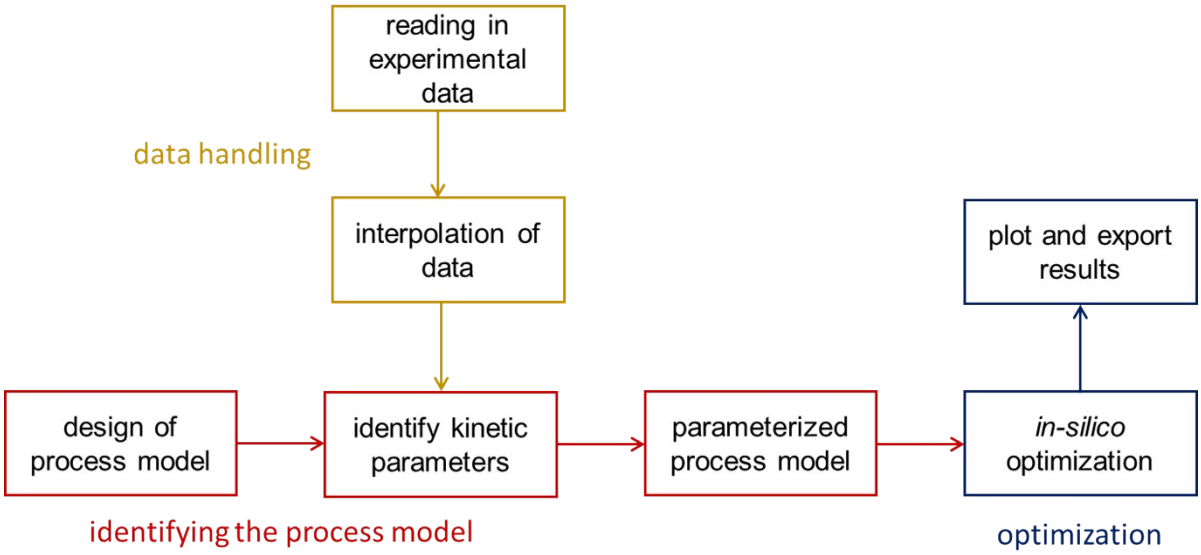


Figure S7. Flow chart showing the main subparts of the developed Julia software.

4.1.1. Data Handling

Excel spreadsheets with the experimental data (pump flow rates, temperature values, measured concentration values from PAT) are read into the program. The input concentrations (after mixing all streams) are calculated with the flow rates and stock solution concentrations. The measured concentration values from the PAT are saved in another variable. Using the DataInterpolations.jl library, the process input data is adjusted to a uniform timeseries.

4.1.2. Identifying the Process Model

The developed software currently has four different possible reaction networks. The preset settings include: one-step, two-step or three-step reaction network. It has the possibility to fit the reaction orders, preexponential factor and activation energy or to use predefined reaction orders and fit the preexponential factor and activation energy. The reaction network can be altered with minimal coding effort. The reactor parameters (heated parts, reactor volumes, and discretization steps) must be predefined within the code. The Julia library MethodofLines.jl is used to generate differential equations, which can describe the transport (by a “tanks in series” model) and the kinetics within the reactor. The boundary and interface conditions can be defined within the code. A global optimization algorithm (NLopt-BOBYQA) is used to fit kinetic parameters. The cost function for fitting the kinetic parameters returns the squared error between the prediction, using the current kinetic parameter set, and the measurement of the PAT. Additionally, different weights for each chemical species can be applied. During the development of the software several other global optimization algorithms have been tested

from the Metaheuristics.jl library. The NLopt-BOBYQA performed the best in terms of speed and loss of the cost function compared to the Evolutionary Centers Algorithm (ECA), Differential Evolution (DE), Particle Swarm Optimization (PSO), Artificial Bee Colony (ABC), Gravitational Search Algorithm (CGSA), Whale Optimization Algorithm (WOA), Machine-coded Compact Genetic Algorithm (MCCGA). The kinetic parameters are typically fitted within approximately 280 s. Additionally, refinement using a Nelder-Mead simplex algorithm can be activated to refine the global optimum within a reduced range of the boundaries (±5% from the values found by BOBYQA). The model can include the fitted kinetic parameters and can be solved at any position in space (along the reactor) with any given input parameters.

4.1.3. Optimization

The obtained process model can be used to perform *in-silico* optimization campaigns and provide the optimal operating point. Single or multiple objectives (e.g., yield, conversion, productivity, space-time yield, etc.) can be selected for the optimization. The NSGA-II algorithm from the Metaheuristics.jl library is used to find the pareto values for the objectives. To confirm that the pareto values cannot be surpassed, the process space can also be populated with random experimental points. The results from the optimization can be saved in Excel spreadsheets, or plotted in the Julia environment.

5. General Flow Configuration

In the flow setup, different PFA or PTFE tubing with an inner diameter of 0.8 mm and 0.3 mm were used, fittings, T-pieces manufactured from PTFE or PEEK were used as connectors. The back pressure regulators (BPRs) were obtained from Upchurch Scientific and Zaiput Flow Technologies (BPR-10, used for reaction stream).

5.1. Amidation Reactions

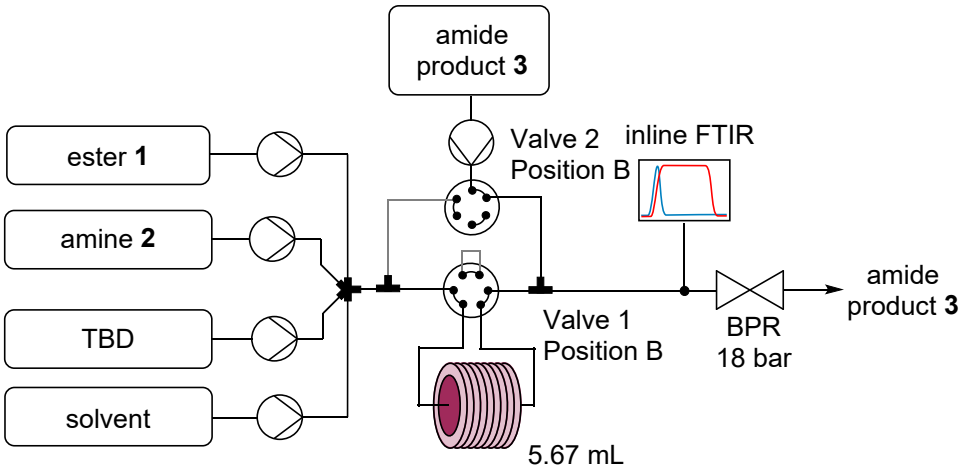


Figure S8. Detailed flow setup for the amidation reactions.

The reaction was performed in a stainless steel coil, placed on a coil heater from Uniqsis and the reaction stream was analyzed by a ReactIR instrument from Mettler Toledo. All five feeds were pumped with Knauer AZURA P 4.1S HPLC pumps (10 mL pump head with an integrated pressure sensor, made of Hastelloy C, stainless steel, or ceramic). The ester, amine, TBD, solvent, and product stock solutions were pumped with Hastelloy C, stainless steel, Hastelloy C, ceramic, ceramic pump heads, respectively. A back pressure regulator (BPR, Upchurch cartridge holder, P-465) equipped with a 34 bar (tan/green, P-765) cartridge was connected directly after each HPLC pump, except the pump which delivered the TBD feed (preliminary experiments showed incompatibility between the cartridge and TBD). A detailed flow setup scheme is depicted in **Figure S8** and a photograph from the laboratory in **Figure S9**.

The feeds containing ester, amine, TBD, and solvent were mixed in a 7-way mixing unit (IDEX P-151, 83 µL inner volume) with two of the ports blocked with a PEEK stopper. The combined streams entered a 6-port valve (valve 1, VICI C2V-2346EUHA) via PTFE tubing (0.055 mL, 0.8 mm i.d.). The valve guided the flow either directly via PTFE tubing (0.22 mL, 0.3 mm i.d.) to a BPR (Zaiput, BPR-10) or through a stainless steel coil (5.67 mL, 0.8 mm i.d.) placed on a Uniqsis coil heater, followed by PTFE tubing (0.33 mL, 0.8 mm i.d.) placed in a cooling bath (23 °C) prior to the BPR. Additionally, the product stream entered another 6-port valve (valve 2, VICI C2V-2346EUHA), which allowed product to be added (through a T-piece) to the reaction stream before or after the stainless steel reactor coil. The BPR was connected via PTFE tubing to the flow through cell for FTIR (Mettler Toledo, ReactIR 15) measurement (see section 1.2). After FTIR analysis, the reaction stream was collected in a 1 L Duran bottle.

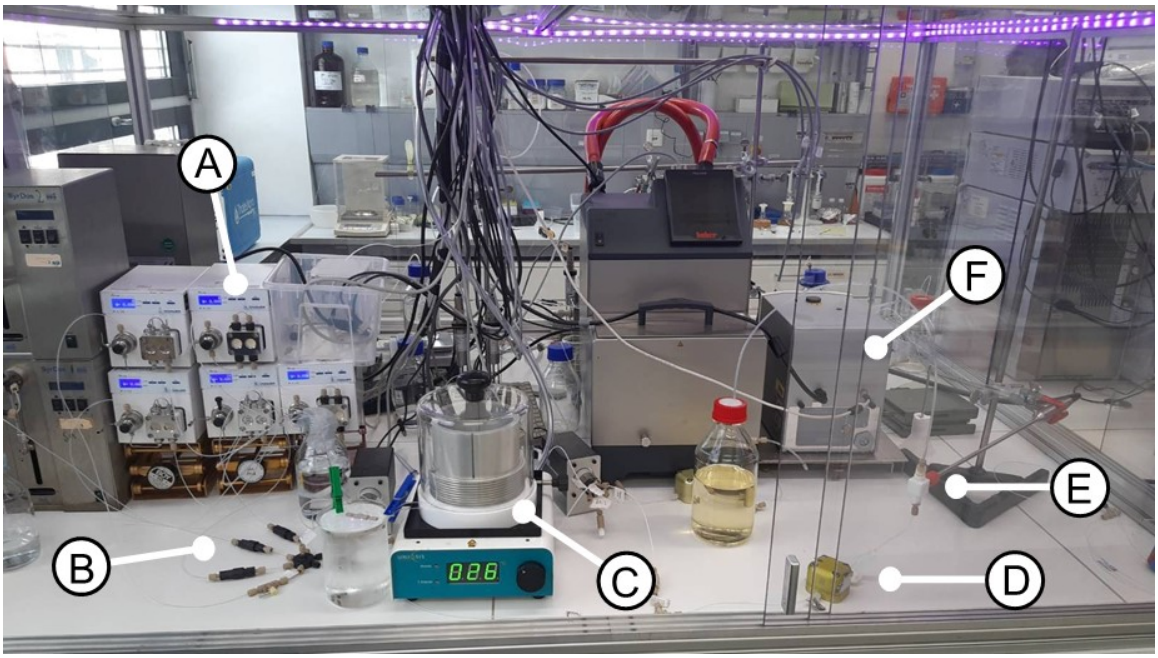


Figure S9. Photograph of the experimental setup in the laboratory. A: HPLC pumps, B: cartridge BPRs and mixing unit (7-port connector), C: Uniqsis coil heater, D: reactor BPR, E: FTIR probe inside in-house built flow cell, F: FTIR instrument.

5.2. Changes for API step 1 (alkylation)

The described process setup in section 5.1 was utilized with minor modifications. The stock solutions of **4**, **5**, TBD, EtOH and **6** were pumped with HPLC pumps equipped with a Hastelloy C, stainless steel, Hastelloy C, ceramic, ceramic pump head, respectively. Additionally, a shorter reaction coil was placed on the coil heater (2.79 mL, PFA).

5.3. Changes for API step 2 (amidation)

The described process setup in section 5.1 was utilized with minor modifications. The stock solutions of **6**, **2a**, TBD, EtOH and **7** were pumped with HPLC pumps equipped with a Hastelloy C, stainless steel, Hastelloy C, ceramic, ceramic pump head, respectively. Additionally, a shorter reaction coil was placed on the coil heater (2.79 mL, PFA).

6. Amidation Reactions

6.1. General

In the following sections, the preparation of the stock solutions is described, as well as the chosen PLS model parameters, the mass balance, and the kinetic values for each amidation experiment.

The tables with the PLS model parameters show the chosen PLS model ranks as well as the RMSE and R^2 values of the optimal PLS model for calibration and cross validation, respectively. Leave-One-Group-Out (LOGO) was selected as cross-validator, using the 13 calibration levels as groups. The mean value of the 13 different LOGO sub-predictions is given as R^2 (CV) for each rank. Ranks were chosen according to the procedure described in section 3.2.

The mass balances show the sum of the predicted concentrations of the amide product and the respective starting material versus the calculated input concentrations of each amine and ester. In the last kinetic step, the calculated concentration of the additional product stream was subtracted from the respective predicted concentrations.

6.2. Reaction of 1a and 2a Yielding 3aa

6.2.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M methyl nicotinate (**1a**) stock solution: In a 100 mL volumetric flask 34.3 g of **1a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M benzylamine (**2a**) stock solution: In a 100 mL volumetric flask 26.8 g of **2a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of TBD was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added, and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.5 M *N*-benzylnicotinamide (**3aa**) stock solution: In a 25 mL volumetric flask 7.99 g of **3aa** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.2.2. PLS Model

Table S1 lists the PLS model parameters and cross-validation scores. The mass balance of **1a** and **2a** is shown in the range of the kinetic runs (**Figure S10**).

Table S1. PLS model parameters for the reaction of **1a** with **2a**.

	Ester	Amine	TBD	Product
rank (n_components)	1	3	7	5
RMSE (cal)	0.0181 M	0.0208 M	0.00118 M	0.00685 M
RMSE (CV)	0.0293 M	0.0364 M	0.0183 M	0.0208 M
R^2 (cal)	0.98	0.992	1	0.999
R^2 (CV)	0.948	0.975	0.923	0.988

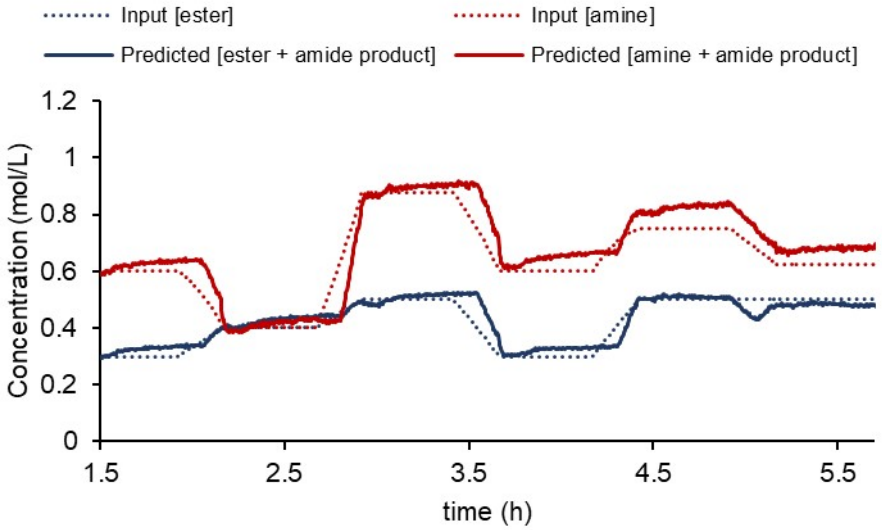


Figure S10. Mass balance for the reaction of **1a** with **2a**.

6.2.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 0, 1, and 0 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in **Table S2**. Additionally, the RMSE between the simulated results from the kinetic model (lowest loss) and the measured values from the FTIR for ester, amine, TBD, and product can be found in **Table S2**. The measured and predicted concentrations of each reaction species over the entire dynamic experiment are depicted in **Figure S11**. Parity plots for ester, amine, TBD and the amide product can be found in **Figure S12**.

Table S2. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	6.739588455	6.617348987	ester (**1a**)	34 mM
A_2 (L/mol)	7.336543711	6.760250321	amine (**2a**)	48 mM
E_a1 (kJ/mol)	21.05992369	21.02015619	TBD	27 mM
E_a2 (kJ/mol)	15.68567523	15.24409019	amide product (**3aa**)	40 mM
loss	5.334505942	5.333115053		

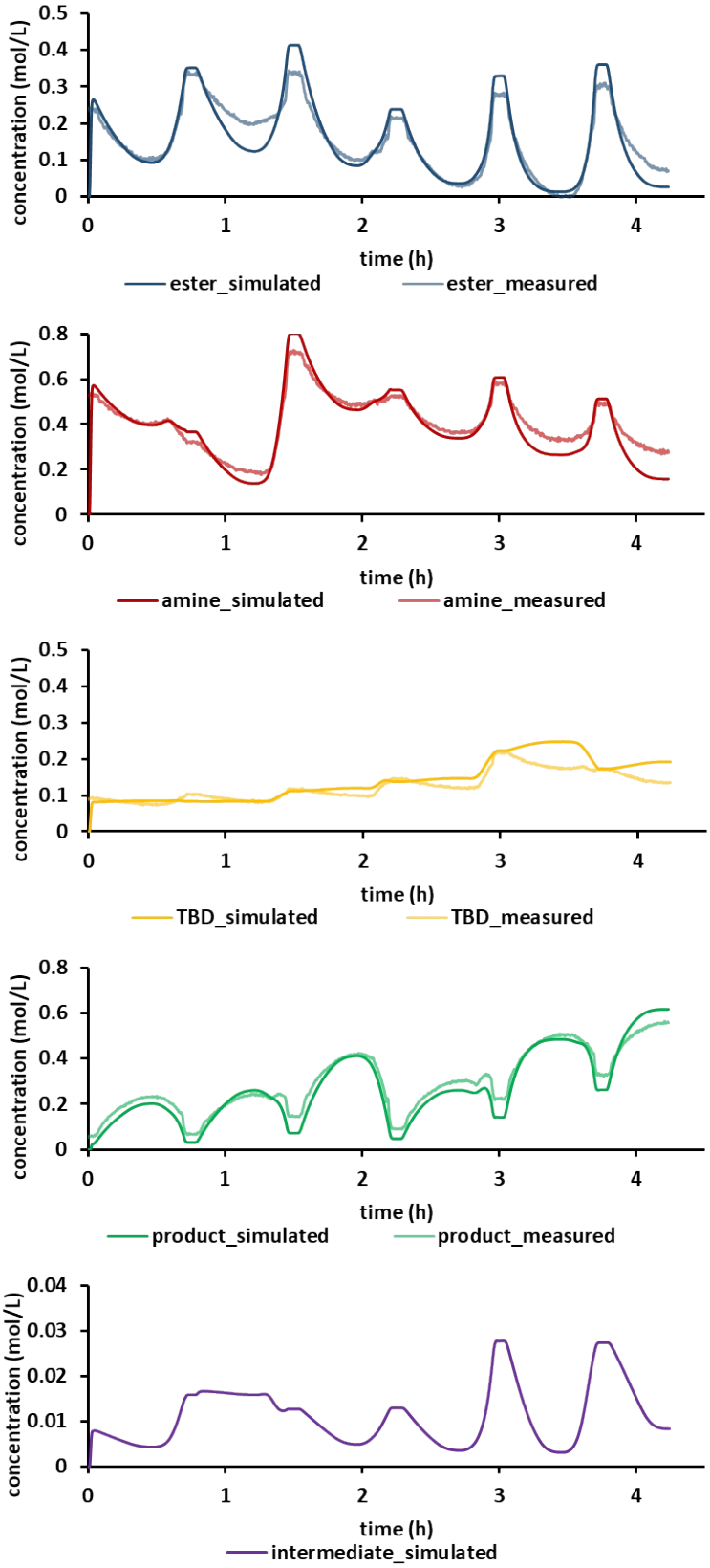


Figure S11. Concentrations of reaction species measured over the experiment duration (lighter solid lines) and their corresponding predicted values (darker solid lines) using the kinetic model.

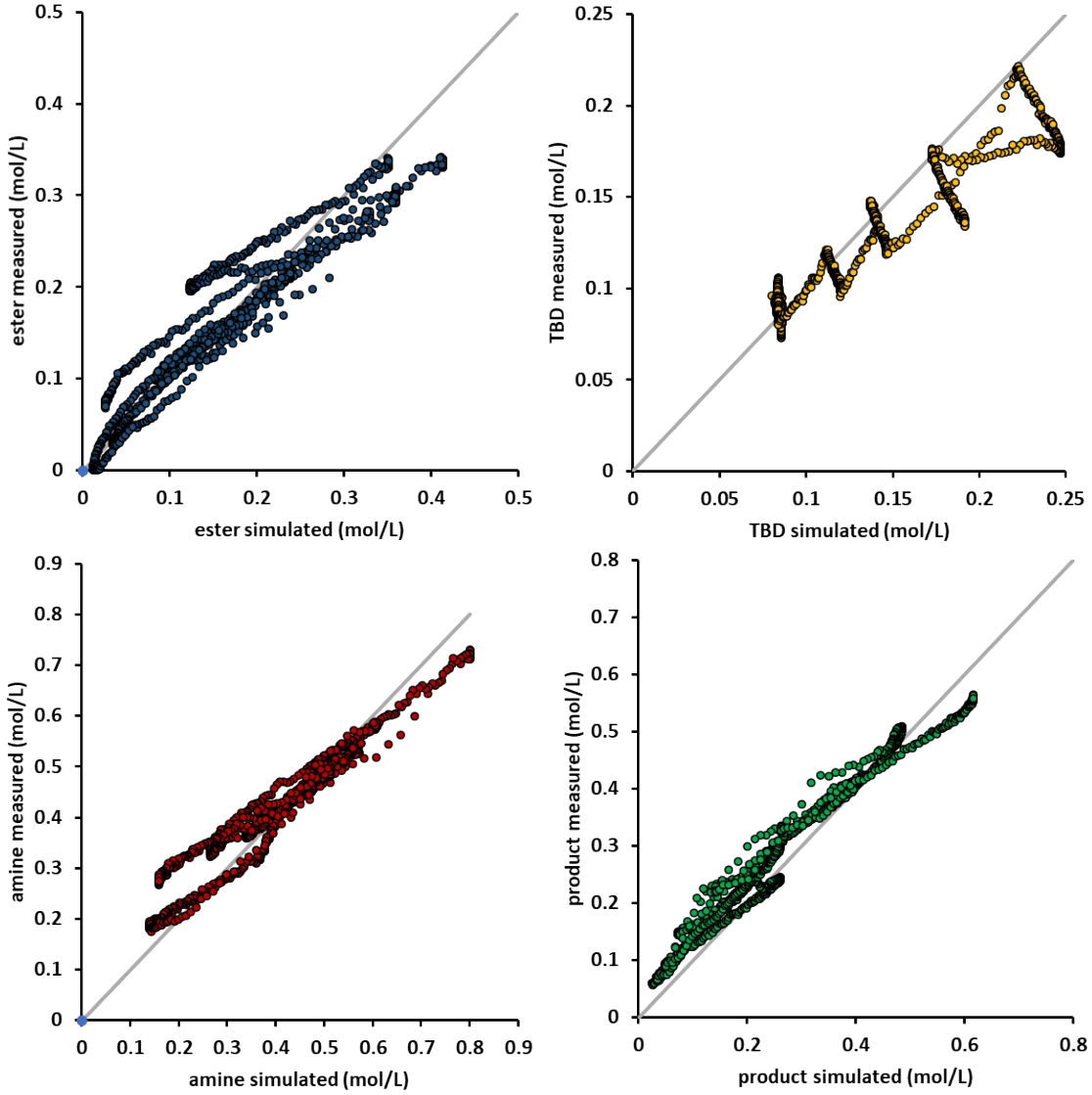


Figure S12. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.3. Reaction of 1a and 2b Yielding 3ab

6.3.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M methyl nicotinate (**1a**) stock solution: In a 100 mL volumetric flask 34.3 g of **1a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M *N*-methylbenzylamine (**2b**) stock solution: In a 100 mL volumetric flask 30.3 g of **2b** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of **TBD** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to

the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.5 M *N*-benzyl-*N*-methylnicotinamide (**3ab**) stock solution: In a 25 mL volumetric flask 9.07 g of **3ab** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.3.2. PLS Model

Table S3 lists the PLS model parameters and cross-validation scores. The mass balance of **1a** and **2a** is shown in the range of the kinetic runs (**Figure S13**).

Table S3. PLS model parameters for the reaction of **1a** with **2b**.

	Ester	Amine	TBD	Product
rank (n_components)	2	3	7	3
RMSE (PLS)	0.0149 M	0.0212 M	0.00173 M	0.0164 M
RMSE (CV)	0.0238 M	0.0377 M	0.0255 M	0.0246 M
R^2 (PLS)	0.988	0.993	0.999	0.995
R^2 (CV)	0.969	0.978	0.834	0.988

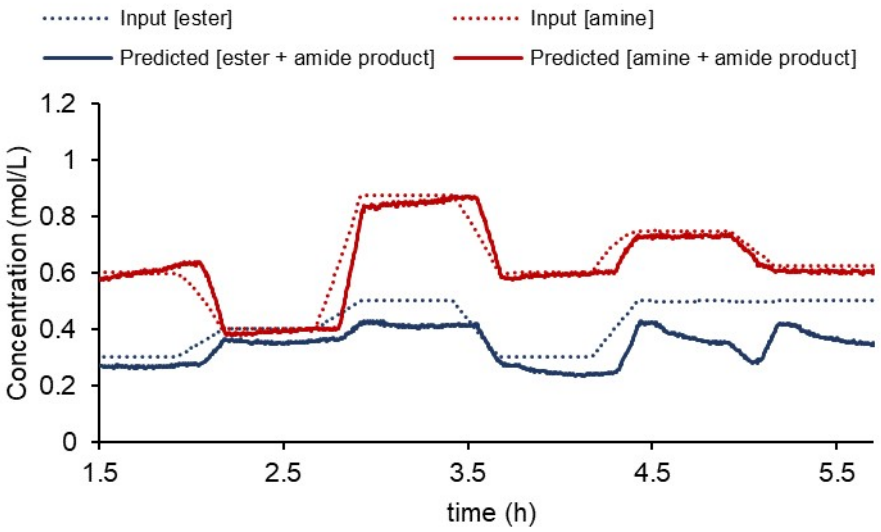


Figure S13. Mass balance for the reaction of **1a** with **2b**.

6.3.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 1, 1, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in **Table S4**. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found

in **Table S4**. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in **Figure S14**. Parity plots for ester, amine, TBD and the amide product can be found in **Figure S15**.

Table S4. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	10.07191867	9.933243114	ester (**1a**)	63 mM
A_2 (L/mol)	13.9086245	13.77325724	amine (**2b**)	38 mM
E_a1 (kJ/mol)	29.20335276	29.13482341	TBD	30 mM
E_a2 (kJ/mol)	5.889805023	6.03954779	amide product (**3ab**)	39 mM
loss	8.167009143	8.165357036		

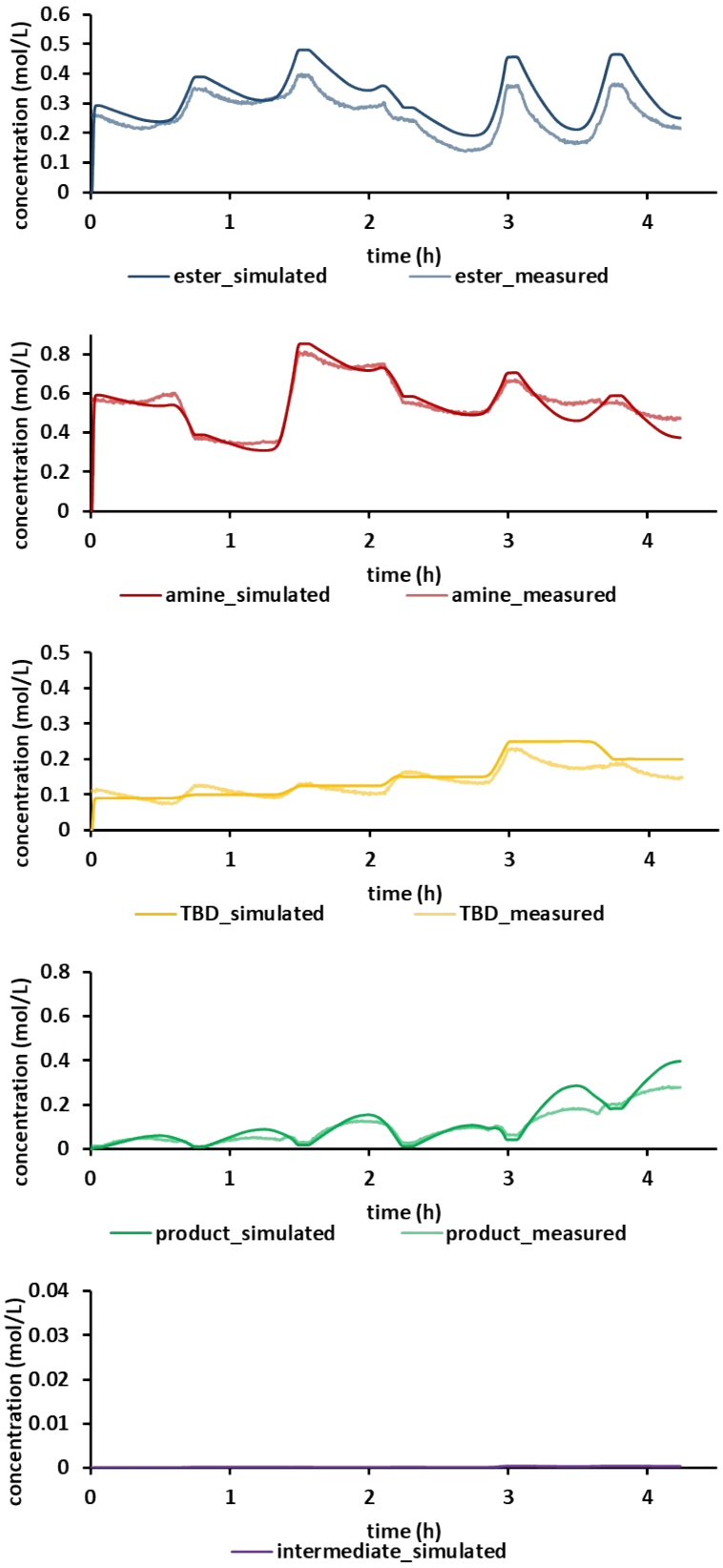


Figure S14. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

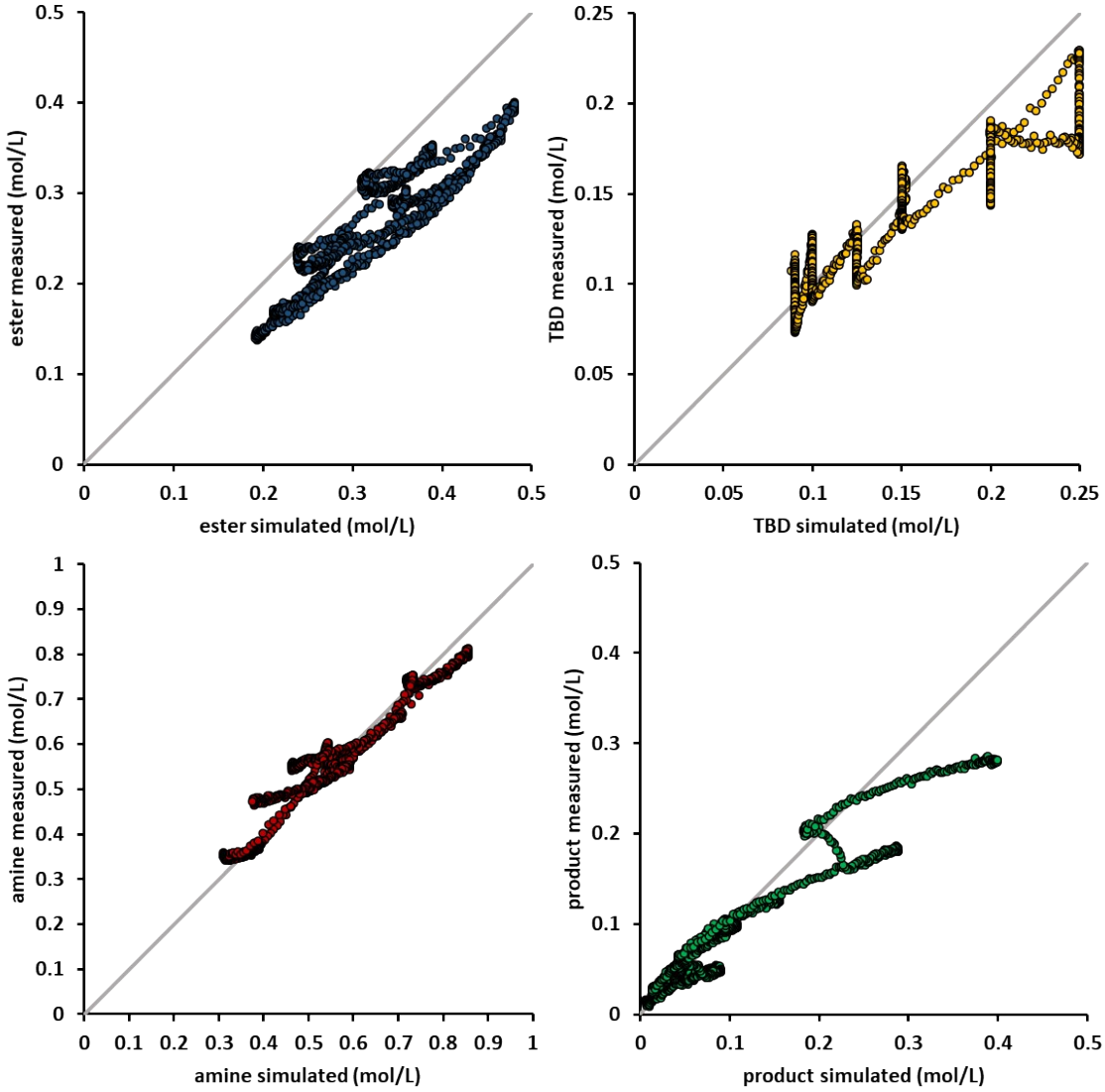


Figure S15. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.4. Reaction of 1a and 2c Yielding 3ac

6.4.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M methyl nicotinate (**1a**) stock solution: In a 100 mL volumetric flask 34.3 g of **1a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M piperidine (**2c**) stock solution: In a 100 mL volumetric flask 21.3 g of **2c** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of **TBD** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to

the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.5 M piperidin-1-yl(pyridin-3-yl)methanone (**3ac**) stock solution: In a 25 mL volumetric flask 7.46 g of **3ac** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.4.2. PLS Model

Table S5 lists the PLS model parameters and cross-validation scores. The mass balance of **1a** and **2c** is shown in the range of the kinetic runs (**Figure S16**).

Table S5. PLS model parameters for the reaction of **1a** with **2c**.

	Ester	Amine	TBD	Product
rank (n_components)	2	4	7	2
RMSE (PLS)	0.0152 M	0.0115 M	0.000953 M	0.0165 M
RMSE (CV)	0.02 M	0.0497 M	0.00974 M	0.021 M
R^2 (PLS)	0.988	0.998	1	0.994
R^2 (CV)	0.978	0.963	0.977	0.991

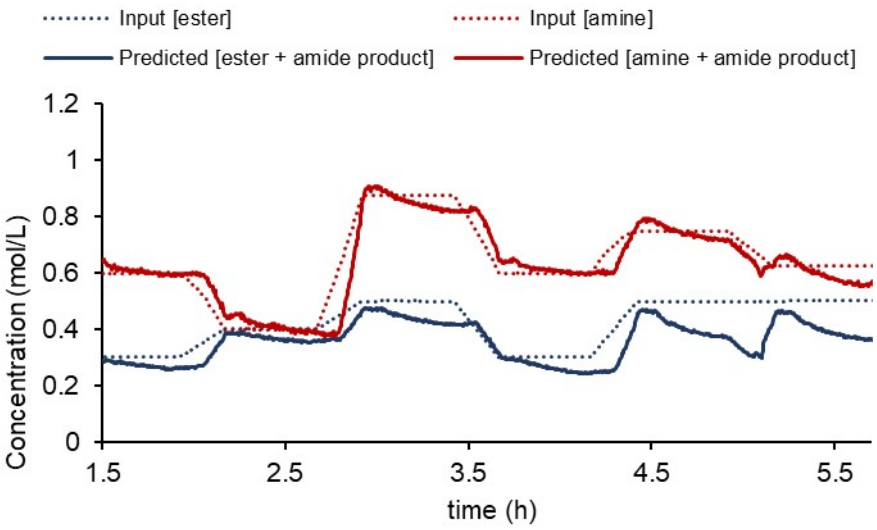


Figure S16. Mass balance for the reaction of **1a** with **2c**.

6.4.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 0, 1, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in **Table S6**. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found

in **Table S6**. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in **Figure S17**. Parity plots for ester, amine, TBD and the amide product can be found in **Figure S18**.

Table S6. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	7.475887774	7.46206464	ester (**1a**)	39 mM
A_2 (L/mol)	7.411710334	7.41532085	amine (**2c**)	34 mM
E_a1 (kJ/mol)	24.6073991	24.60162982	TBD	22 mM
E_a2 (kJ/mol)	20.70063674	20.70030725	amide product (**3ac**)	49 mM
loss	6.096515286	6.095943251		

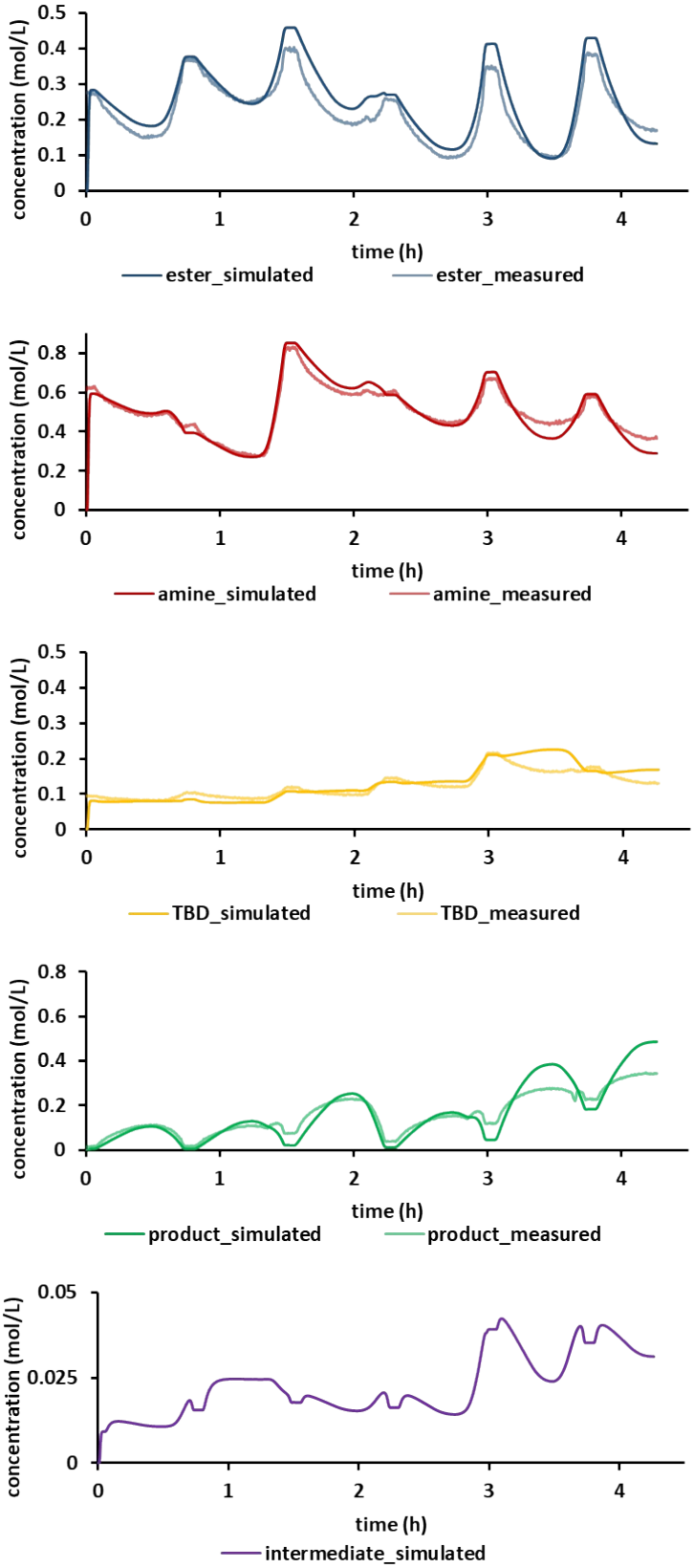


Figure S17. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

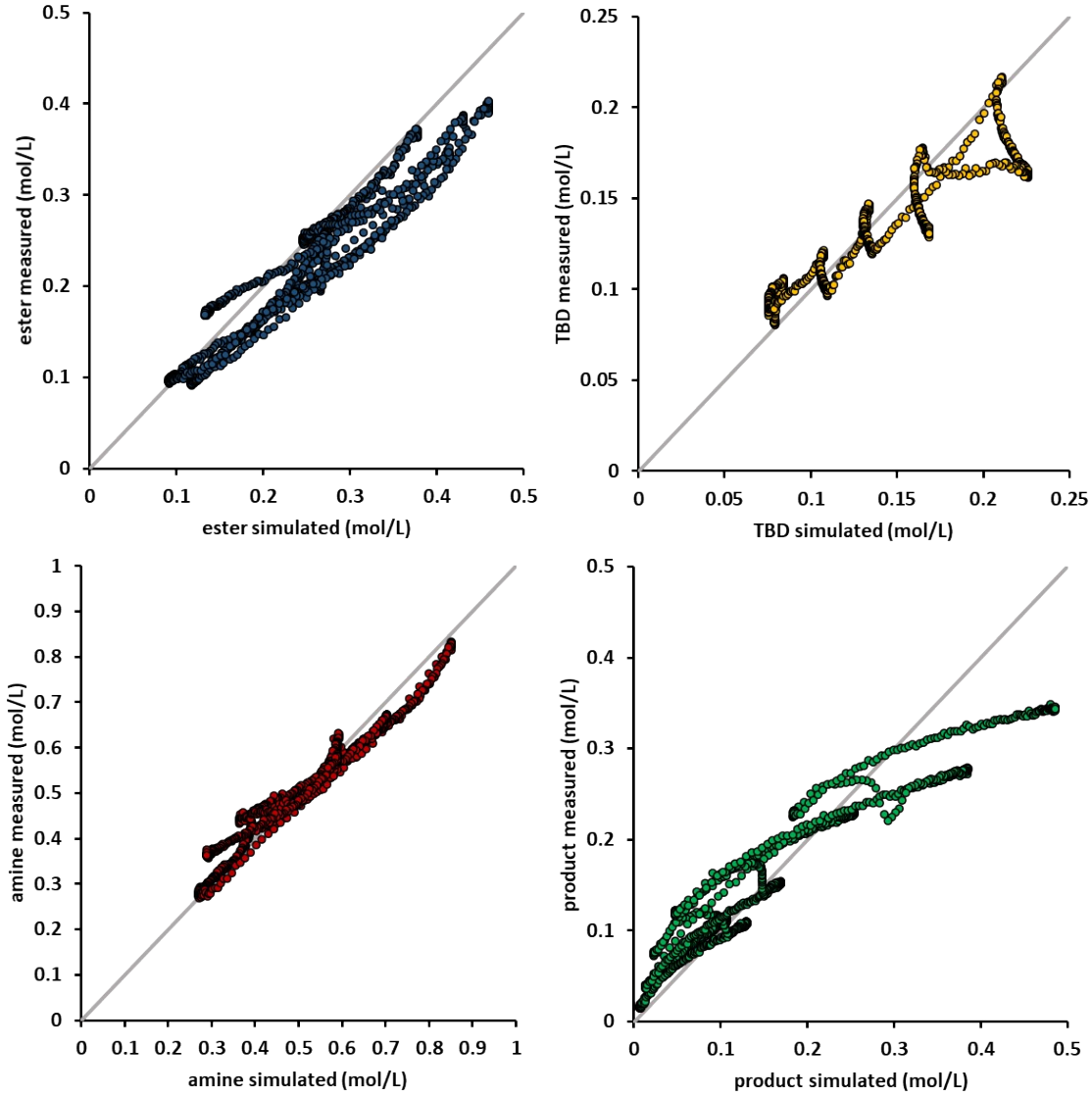


Figure S18. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.5. Reaction of 1b and 2a Yielding 3ba

6.5.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M methyl benzoate (**1b**) stock solution: In a 100 mL volumetric flask 33.9 g of **1b** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M benzylamine (**2a**) stock solution: In a 100mL volumetric flask 26.6 g of **2a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of TBD was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to

the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.1 M *N*-benzylbenzamide (**3ba**) stock solution: In a 25 mL volumetric flask 5.63 g of **3ba** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.5.2. PLS Model

Table S7 lists the PLS model parameters and cross-validation scores. The mass balance of **1b** and **2a** is shown in the range of the kinetic runs (**Figure S19**).

Table S7. PLS model parameters for the reaction of **1b** with **2a**.

	Ester	Amine	TBD	Product
rank (n_components)	2	6	6	4
RMSE (PLS)	0.0405 M	0.0167 M	0.00277 M	0.0186 M
RMSE (CV)	0.0621 M	0.046 M	0.0221 M	0.0265 M
R^2 (PLS)	0.889	0.995	0.998	0.987
R^2 (CV)	0.74	0.962	0.885	0.973

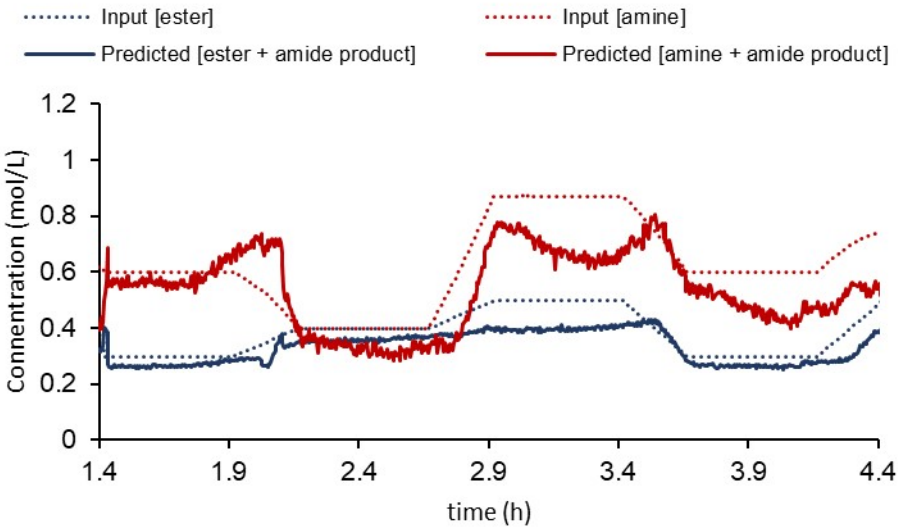


Figure S19. Mass balance for the reaction of **1b** with **2a**.

6.5.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 0, 1, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in **Table S8**. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found in **Table S8**. The measured and predicted concentration of each reaction species over the entire

dynamic experiments are depicted in **Figure S20**. Parity plots for ester, amine, TBD and the amide product can be found in **Figure S21**.

Table S8. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	7.650823971	7.668180455	ester (**1b**)	43 mM
A_2 (L/mol)	8.499185677	8.447499247	amine (**2a**)	96 mM
E_a1 (kJ/mol)	26.72918526	26.73834453	TBD	43 mM
E_a2 (kJ/mol)			amide product	
	8.983578721	9.035844428	(**3ba**)	50 mM
loss	9.047916036	9.047473527		

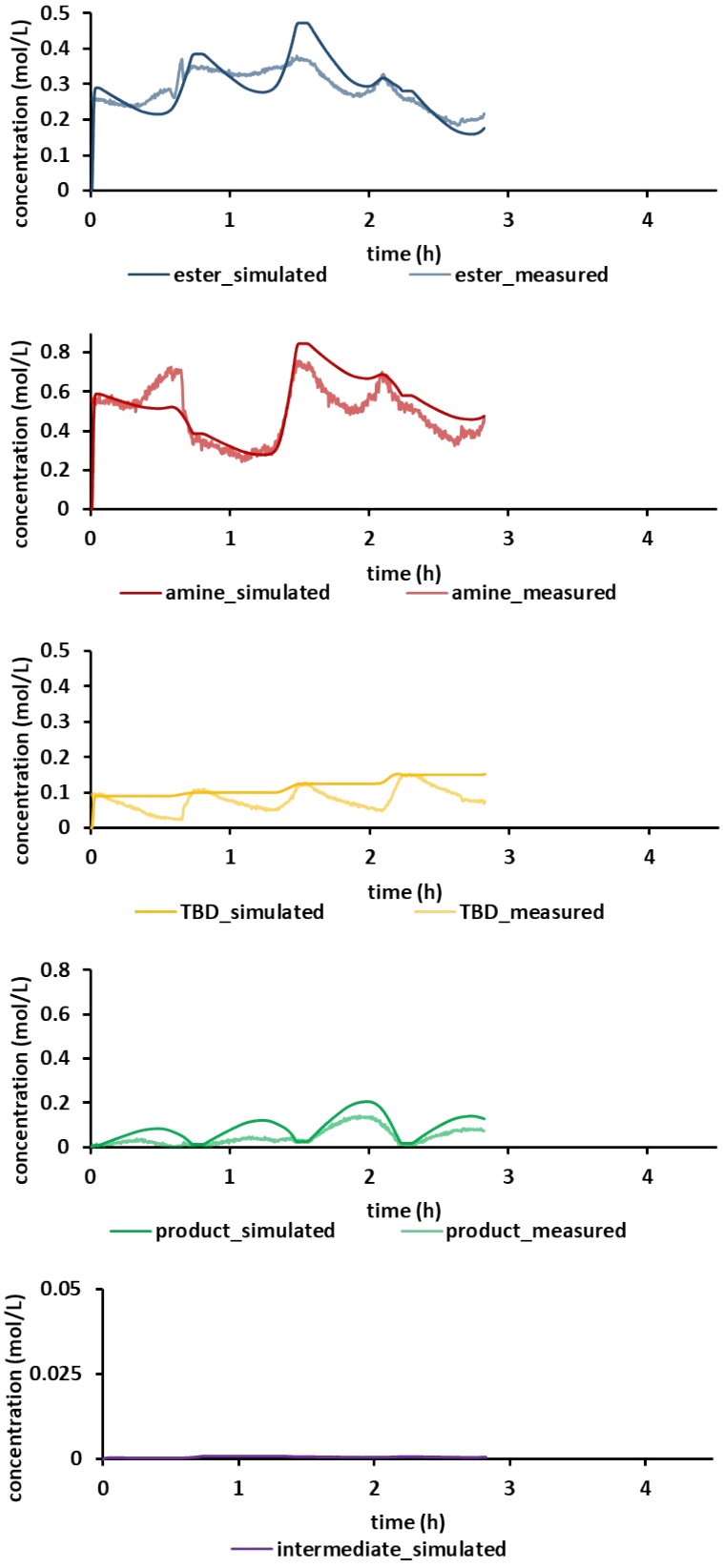


Figure S20. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

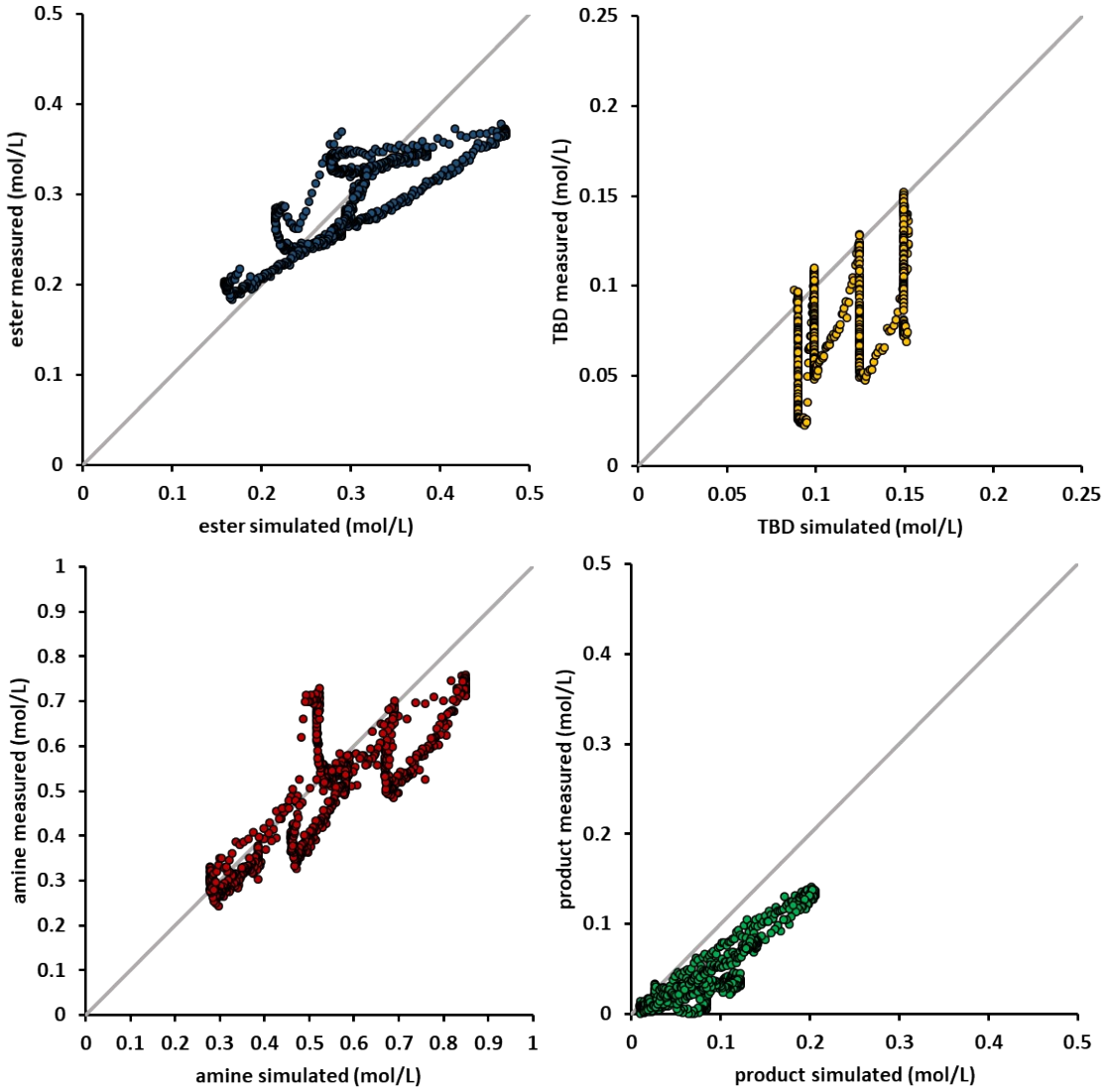


Figure S21. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.6. Reaction of 1b and 2b Yielding 3bb

6.6.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M methyl benzoate (**1b**) stock solution: In a 100 mL volumetric flask 34.0 g of **1b** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M *N*-methylbenzylamine (**2b**) stock solution: In a 100 mL volumetric flask 30.3 g of **2b** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of **TBD** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to

the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.5 M *N*-benzyl-*N*-methylbenzamide (**3bb**) stock solution: In a 25 mL volumetric flask 8.45 g of **3bb** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.6.2. PLS Model

Table S9 lists the PLS model parameters and cross-validation scores. The mass balance of **1b** and **2b** is shown in the range of the kinetic runs (Figure S22).

Table S9. PLS model parameters for the reaction of **1b** with **2b**.

	Ester	Amine	TBD	Product
rank (n_components)	2	3	6	4
RMSE (PLS)	0.0421 M	0.0816 M	0.00417 M	0.028 M
RMSE (CV)	0.0667 M	0.144 M	0.0184 M	0.0425 M
R^2 (PLS)	0.897	0.884	0.996	0.981
R^2 (CV)	0.743	0.637	0.922	0.956

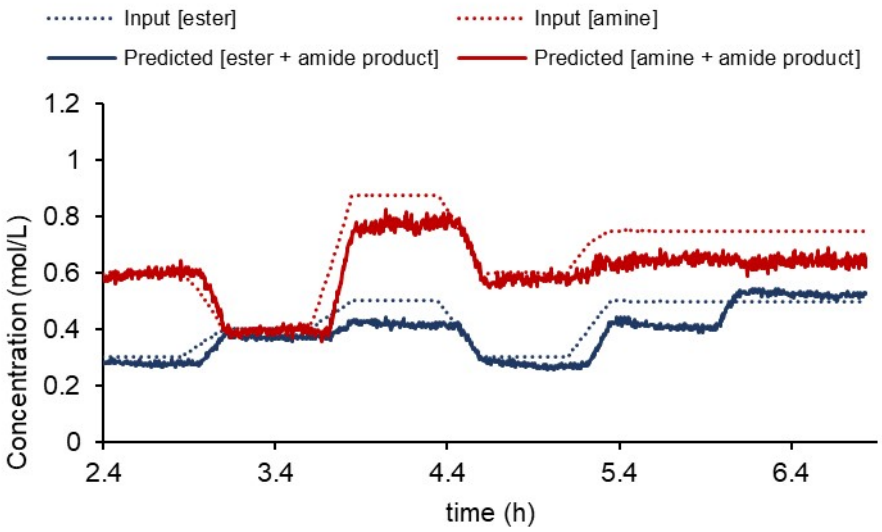


Figure S22. Mass balance for the reaction of **1b** with **2b**.

6.6.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 0.5, 0, 0, 1, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in **Table S10**. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found

in **Table S10**. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in **Figure S23**. Parity plots for ester, amine, TBD and the amide product can be found in **Figure S24**.

Table S10. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	14.21195828	14.22756244	ester (**1b**)	49 mM
A_2 (L/mol)	7.323201679	7.334791928	amine (**2b**)	62 mM
E_a1 (kJ/mol)	33.96228343	33.97596655	TBD	93 mM
E_a2 (kJ/mol)	0.100029069	0.100187319	amide product (**3bb**)	39 mM
loss	5.001588977	5.000945049		

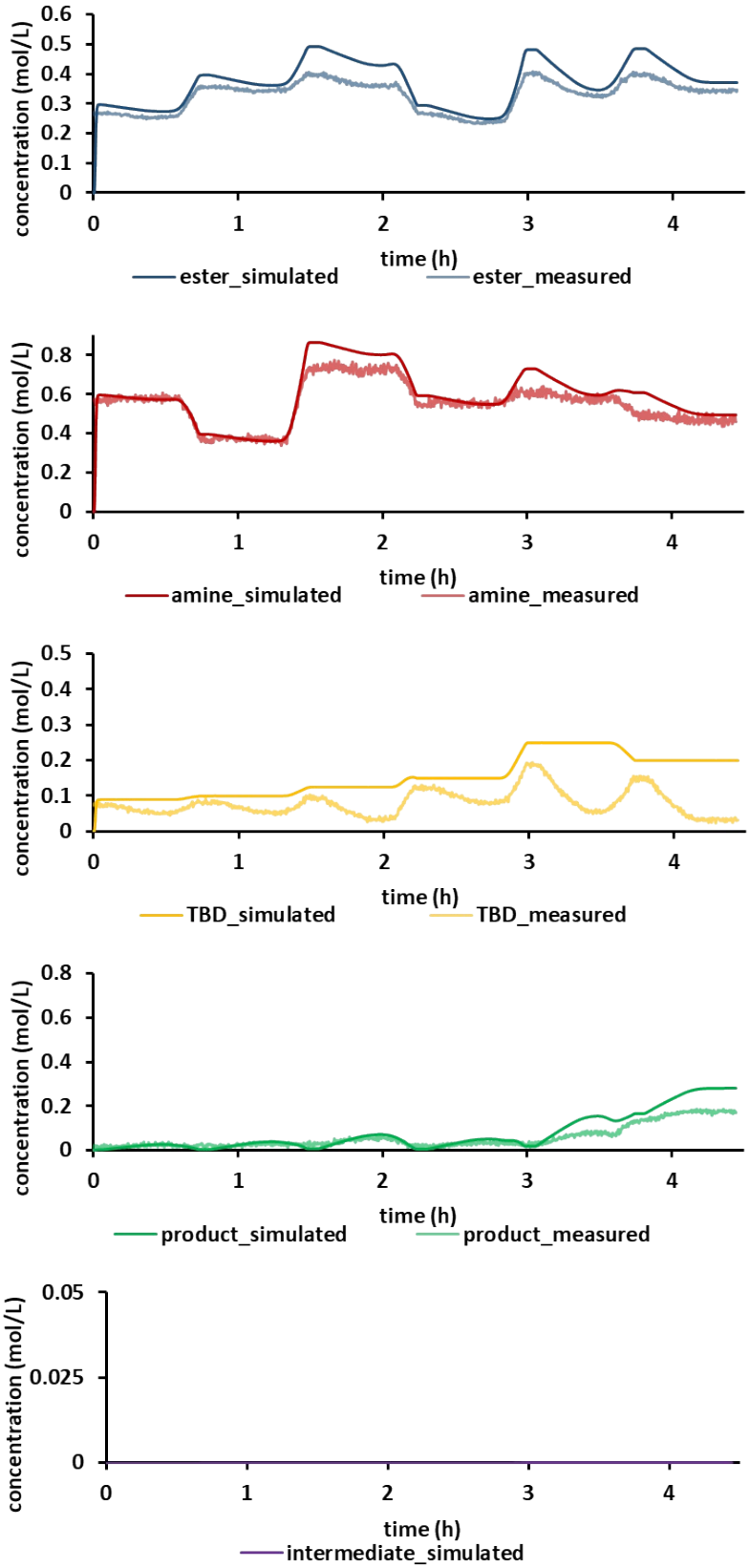


Figure S23. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

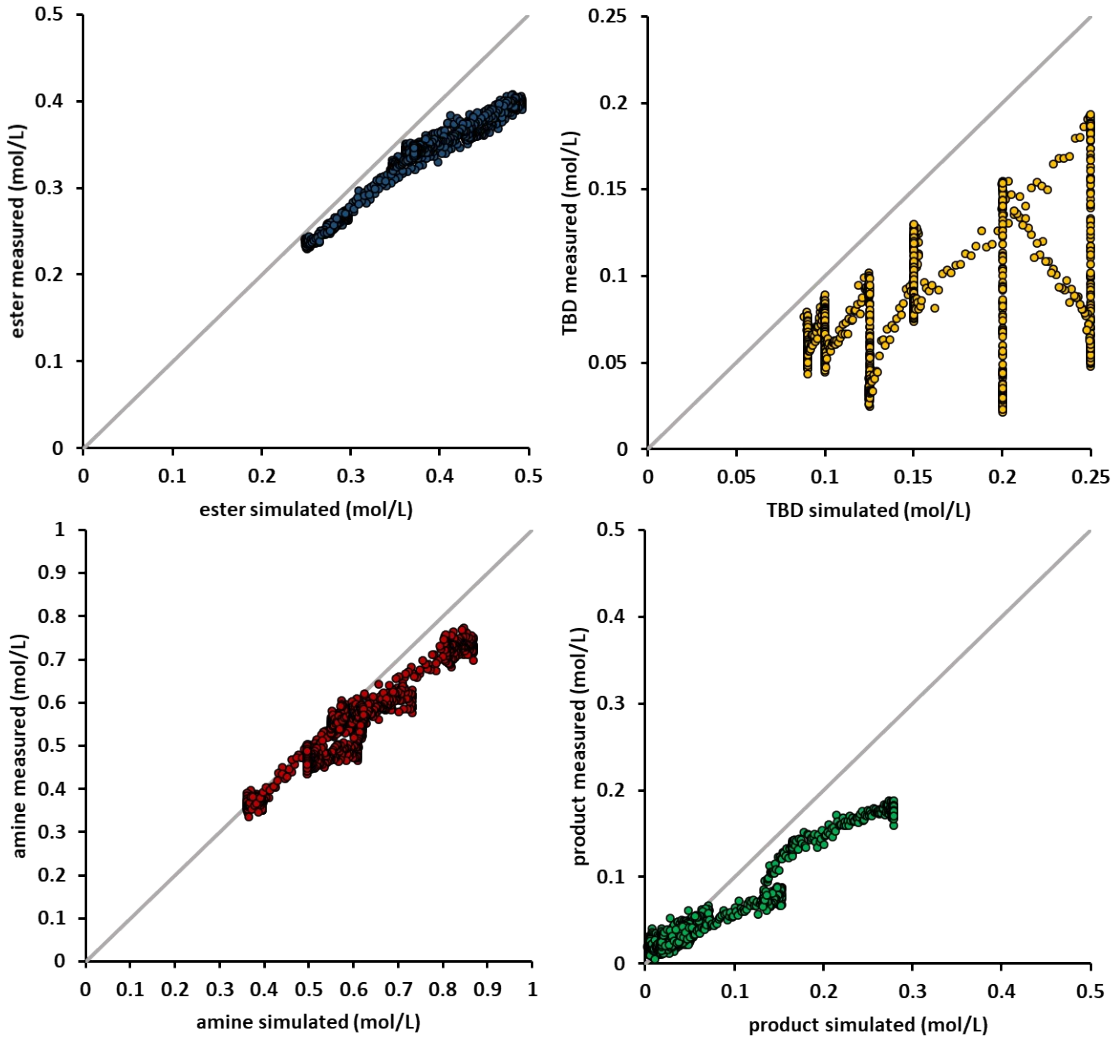


Figure S24. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.7. Reaction of 1b and 2c Yielding 3bc

6.7.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M methyl benzoate (**1b**) stock solution: In a 100 mL volumetric flask 34.1 g of **1b** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M piperidine (**2c**) stock solution: In a 100mL volumetric flask 21.3 g of **2c** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of **TBD** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.5 M phenyl(pyridin-1n-yl)methanone (**3bc**) stock solution: In a 25 mL volumetric flask 7.14 g of **3bc** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.7.2. PLS Model

Table S11 lists the PLS model parameters and cross-validation scores. The mass balance of **1b** and **2c** is shown in the range of the kinetic runs (Figure S25).

Table S11. PLS model parameters for the reaction of **1b** with **2c**.

	Ester	Amine	TBD	Product
rank (n_components)	2	4	6	2
RMSE (PLS)	0.0103 M	0.00483 M	0.00153 M	0.00812 M
RMSE (CV)	0.0186 M	0.0337 M	0.0116 M	0.0122 M
R^2 (PLS)	0.994	1	0.999	0.999
R^2 (CV)	0.98	0.98	0.97	0.997

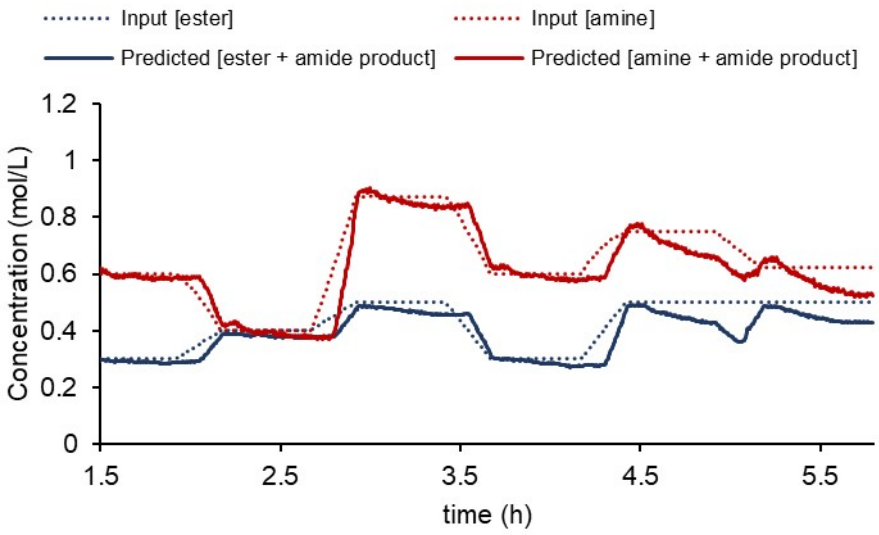


Figure S25. Mass balance for the reaction of **1b** with **2c**.

6.7.3. Identifying Kinetic Parameter and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 0, 1, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in Table S12. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found in Table S12. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in **Figure S26**. Parity plots for ester, amine, TBD and the amide product can be found in Figure S27.

Table S12. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	9.40991746	9.426122894	ester (**1b**)	17 mM
A_2 (L/mol)	5.493775198	5.431591576	amine (**2c**)	17 mM
E_a1 (kJ/mol)	31.87049839	31.90487092	TBD	44 mM
E_a2 (kJ/mol)	5.319038674	5.396567049	amide product (**3bc**)	24 mM
loss	1.364348243	1.363704201		

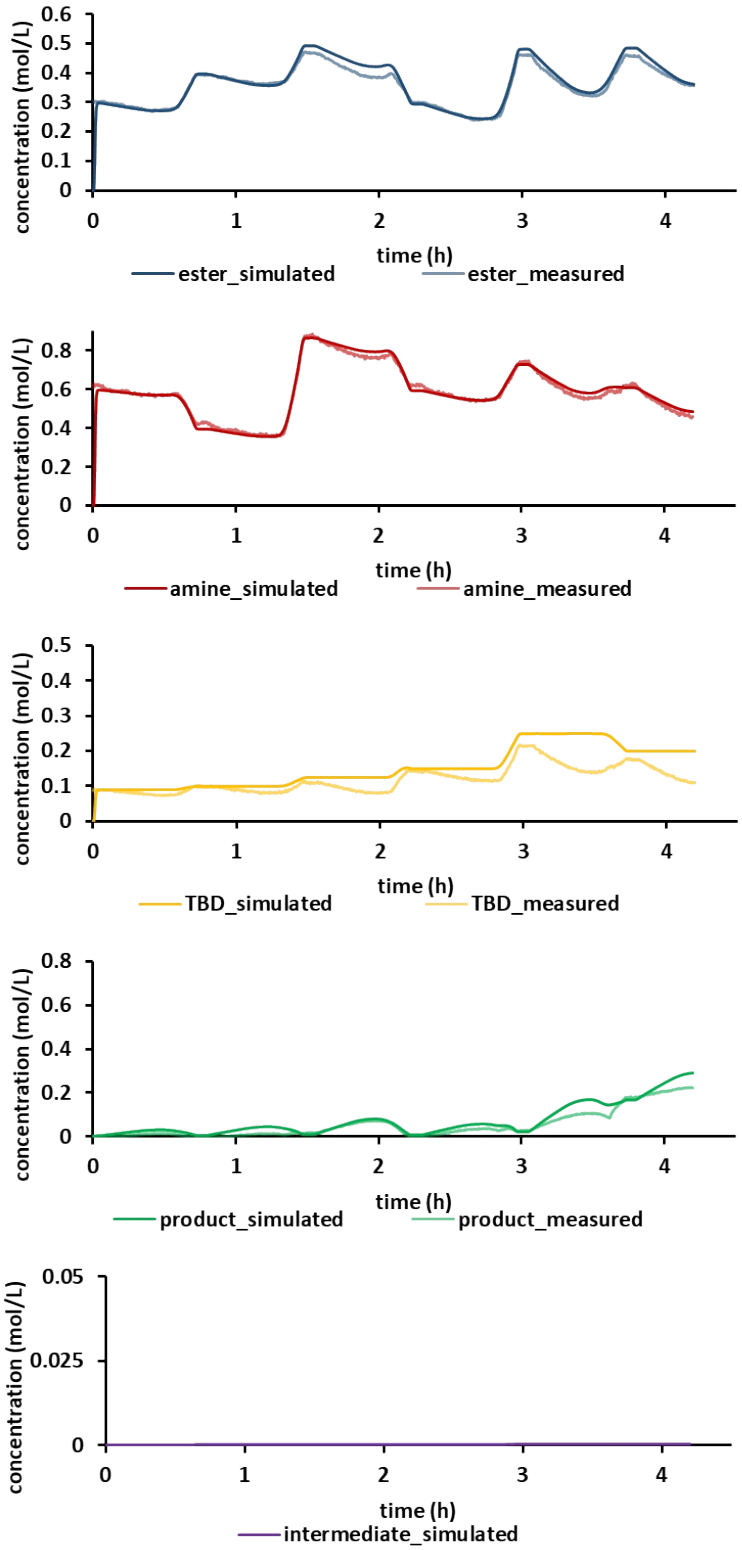


Figure S26. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

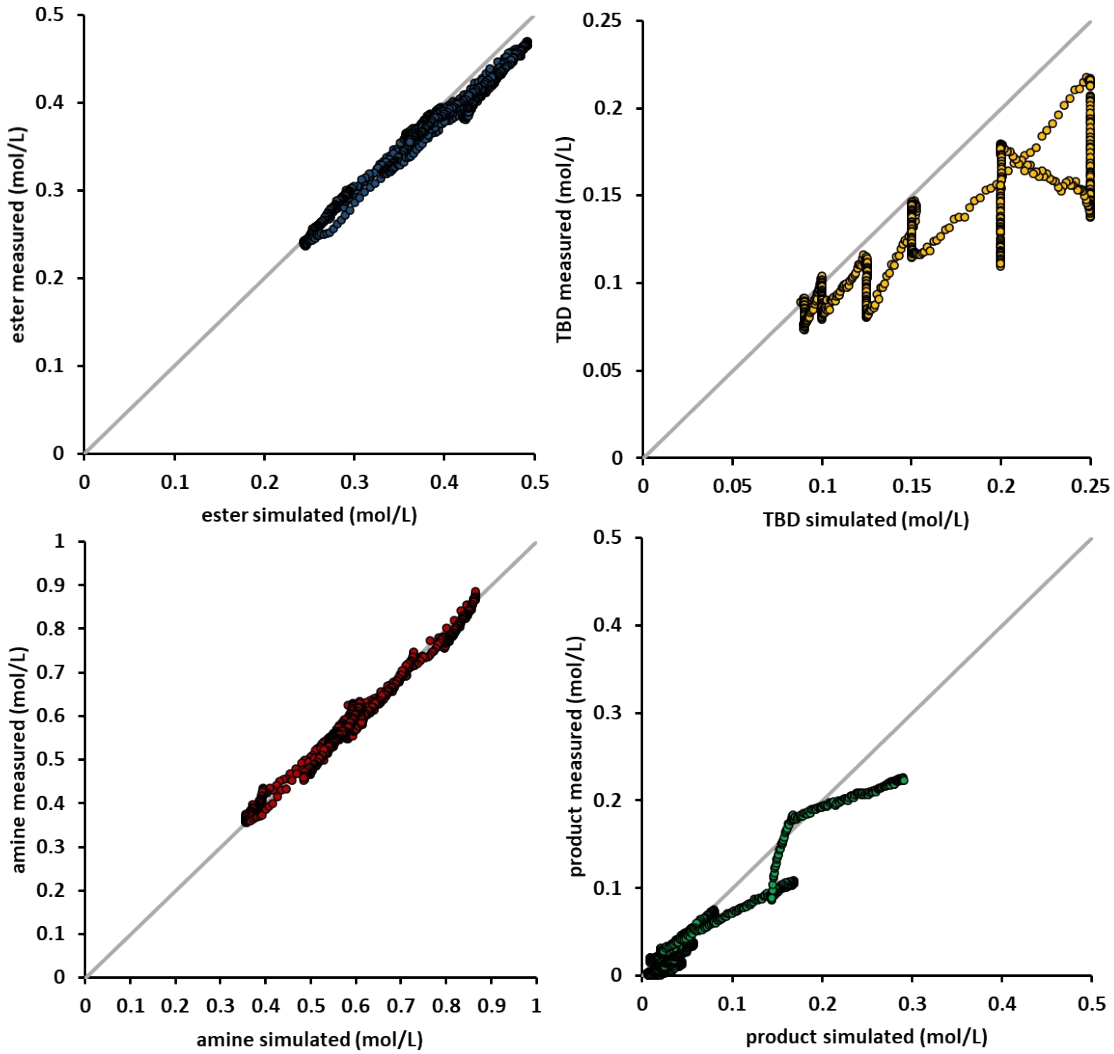


Figure S27. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.8. Reaction of 1c and 2a Yielding 3ba

6.8.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M ethyl benzoate (**1c**) stock solution: In a 100 mL volumetric flask 37.6 g of **1c** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M benzylamine (**2a**) stock solution: In a 100 mL volumetric flask 26.8 g of **2a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of TBD was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.0 M *N*-benzylbenzamide (**3ba**) stock solution: In a 25 mL volumetric flask 5.28 g of **3ba** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.8.2. PLS Model

Table S13 lists the PLS model parameters and cross-validation scores. The mass balance of **1a** and **2a** is shown in the range of the kinetic runs (Figure S28).

Table S13. PLS model parameters for the reaction of **1c** with **2a**.

	Ester	Amine	TBD	Product
rank (n_components)	2	3	6	5
RMSE (PLS)	0.0138 M	0.019 M	0.00169 M	0.00773 M
RMSE (CV)	0.023 M	0.0303 M	0.0184 M	0.0233 M
R^2 (PLS)	0.989	0.994	0.999	0.996
R^2 (CV)	0.97	0.985	0.923	0.968

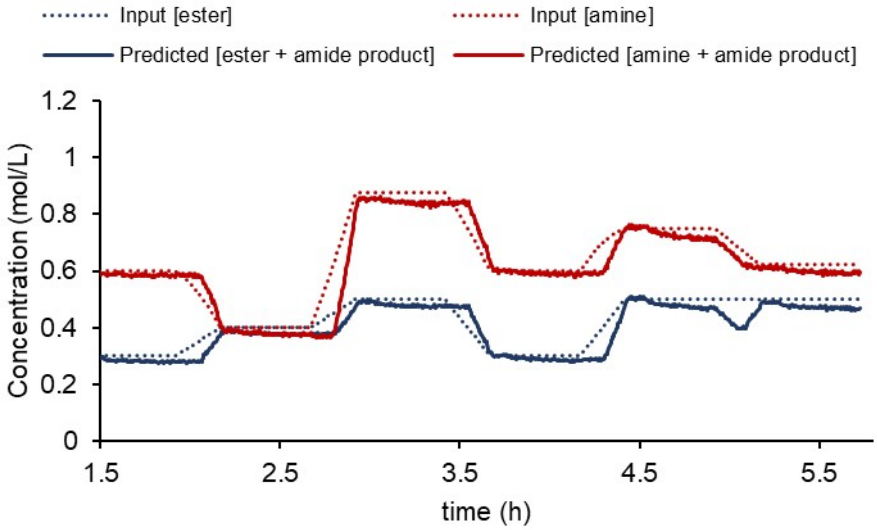


Figure S28. Mass balance for the reaction of **1c** with **2a**.

6.8.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 0, 1, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in Table S14. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found in **Table S14**. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in Figure S29. Parity plots for ester, amine, TBD and the amide product can be found in Figure S30.

Table S14. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	13.219677	13.24989494	ester (**1c**)	21 mM
A_2 (L/mol)	3.904571719	3.91914125	amine (**2a**)	28 mM
E_a1	34.56782799	34.55455533	TBD	15 mM
E_a2	5.557079277	5.575185506	amide product (**3ba**)	30 mM
loss	2.625108779	2.624676542		

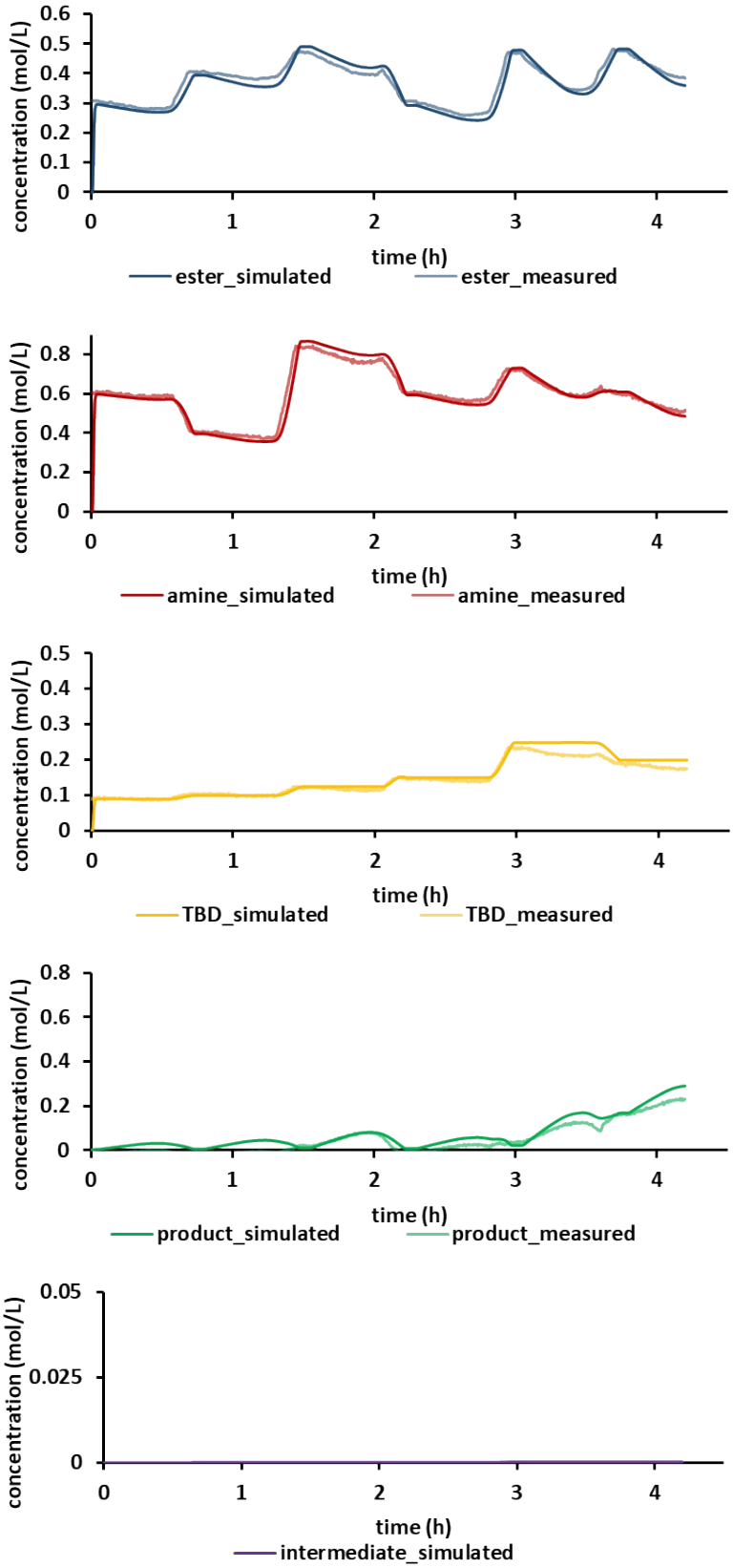


Figure S29. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

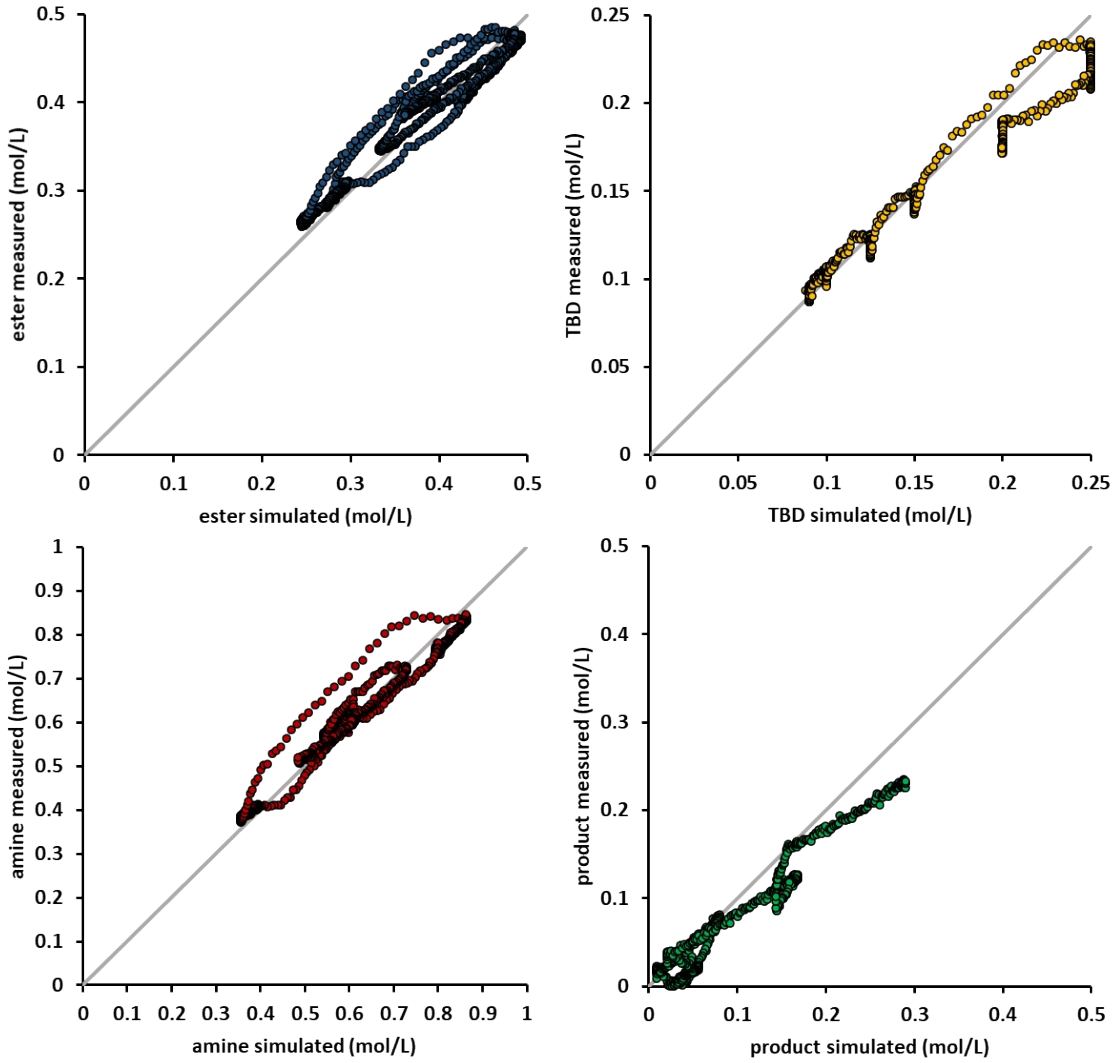


Figure S30. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.9. Reaction of 1d and 2a Yielding 3ba

6.9.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M isopropyl benzoate (**1d**) stock solution: In a 100 mL volumetric flask 41.1 g of **1d** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M benzylamine (**2a**) stock solution: In a 100mL volumetric flask 26.8 g of **2a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of TBD was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.0 M *N*-benzylbenzamide (**3ba**) stock solution: In a 25 mL volumetric flask 5.28 g of **3ba** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.9.2. PLS Model

Table S15 lists the PLS model parameters and cross-validation scores. The mass balance of **1a** and **2a** is shown in the range of the kinetic runs (Figure S31).

Table S15. PLS model parameters for the reaction of **1d** with **2a**.

	Ester	Amine	TBD	Product
rank (n_components)	1	3	4	3
RMSE (PLS)	0.0283 M	0.0496 M	0.0133 M	0.0256 M
RMSE (CV)	0.0452 M	0.0837 M	0.042 M	0.0395 M
R^2 (PLS)	0.953	0.953	0.958	0.958
R^2 (CV)	0.88	0.866	0.582	0.901

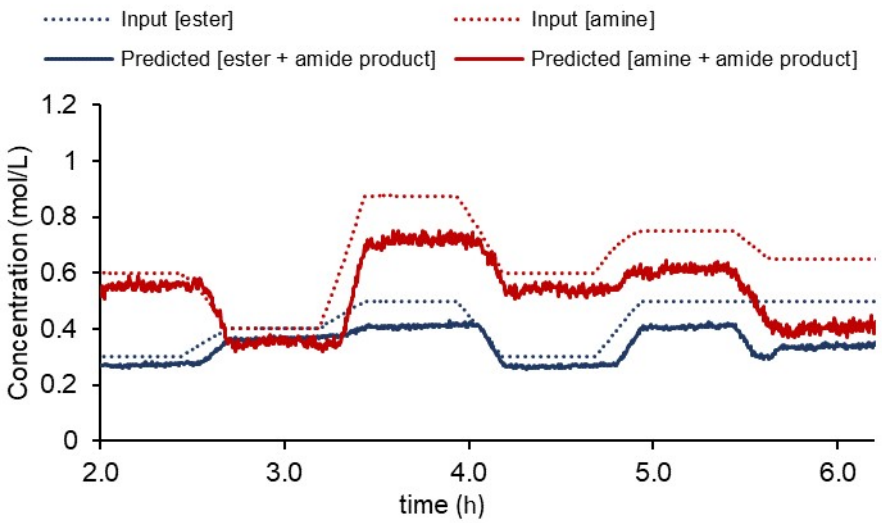


Figure S31. Mass balance for the reaction of **1d** with **2a**.

6.9.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 0, 1, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in Table S16. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found in Table S16. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in **Figure S32**. Parity plots for ester, amine, TBD and the amide product can be found in Figure S33.

Table S16. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	23.65293061	23.61974727	ester (**1d**)	34 mM
A_2 (L/mol)	6.921437596	6.936523833	amine (**2a**)	75 mM
E_a1	35.52621191	35.52407048	TBD	39 mM
E_a2	1.049068892	1.049697884	amide product (**3ba**)	55 mM
loss	10.09688095	10.09610741		

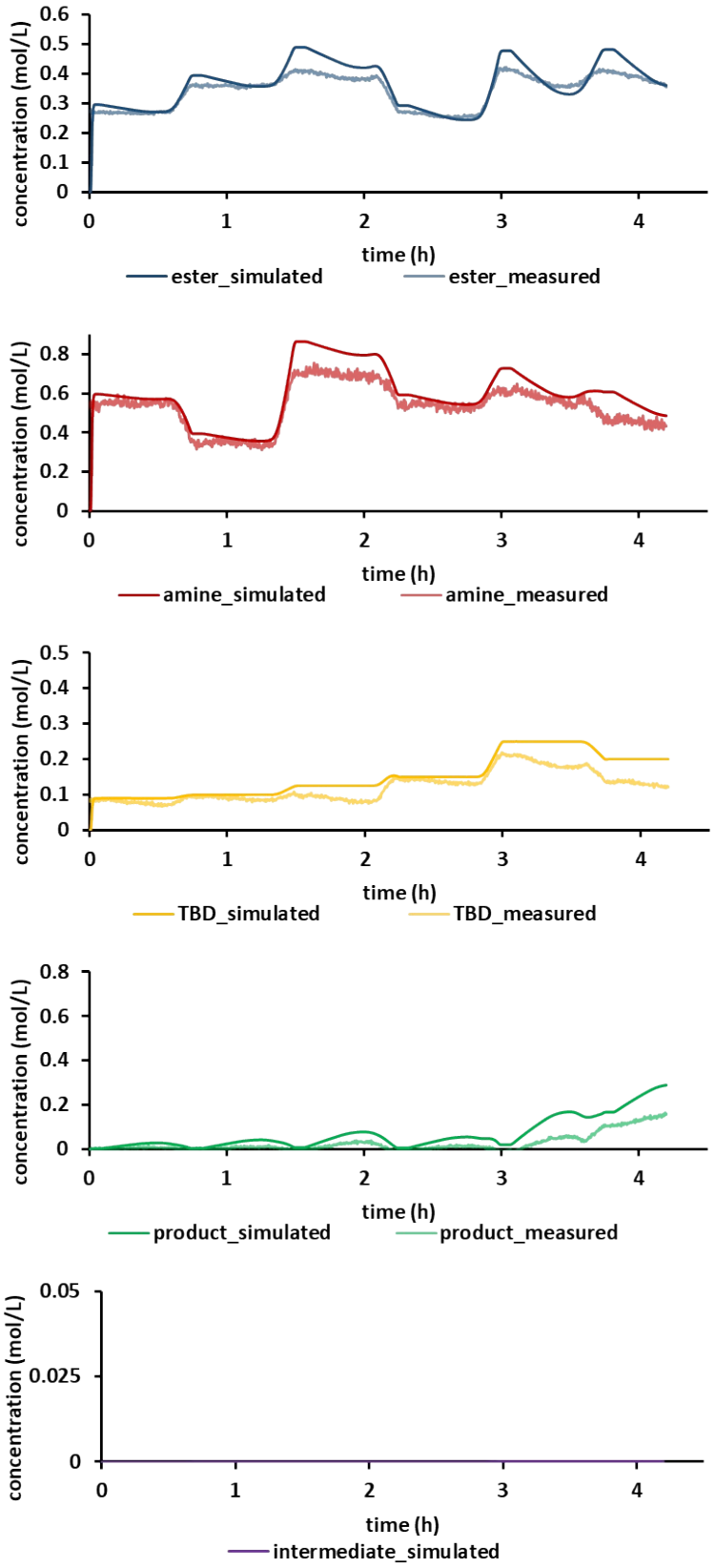


Figure S32. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

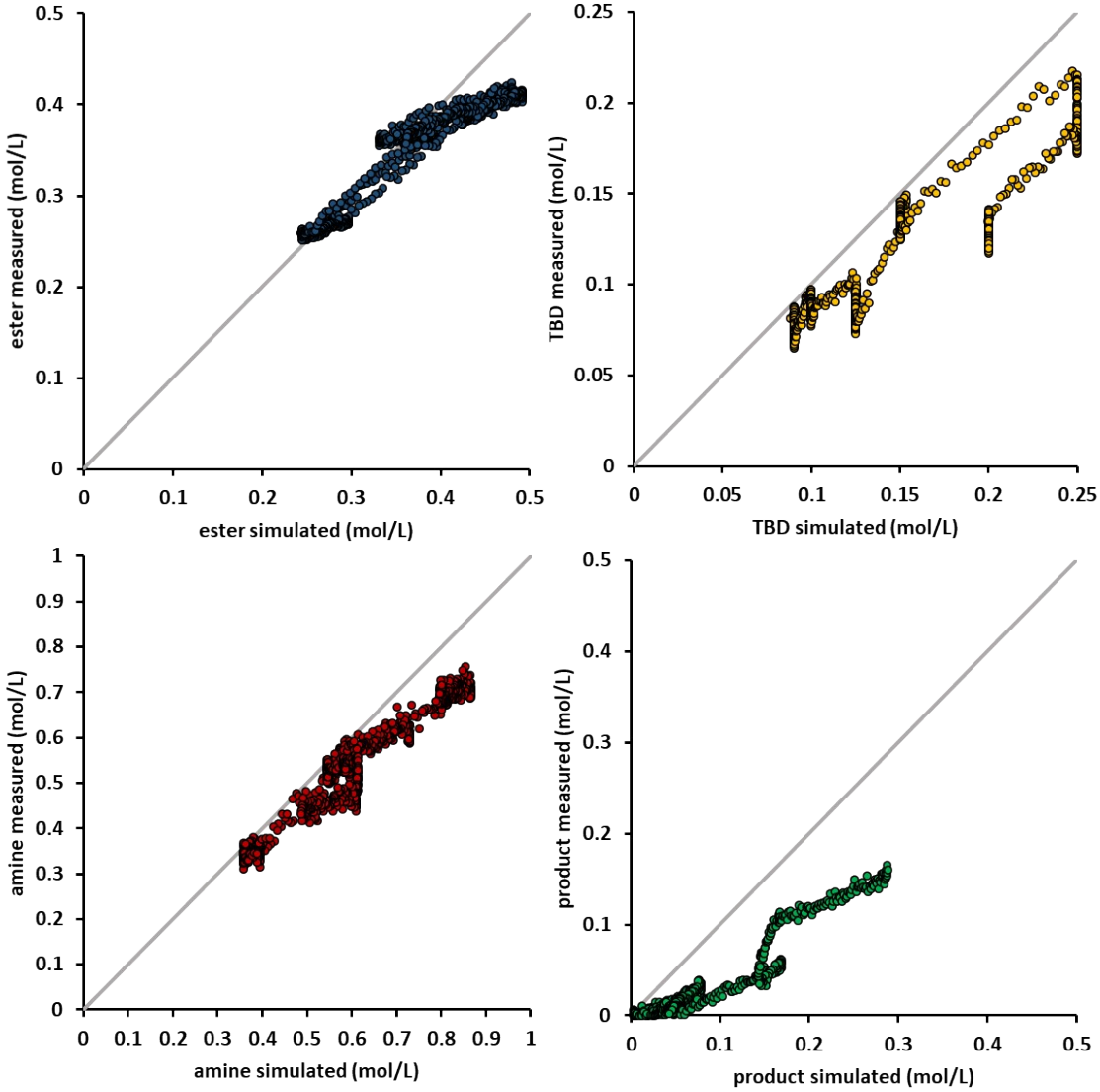


Figure S33. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.10. Reaction of 1d and 2b Yielding 3bb

6.10.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M isopropyl benzoate (**1d**) stock solution: In a 100mL volumetric flask 41.1 g of **1d** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M *N*-methylbenzylamine (**2b**) stock solution: In a 100mL volumetric flask 30.3 g of **2b** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of **TBD** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to

the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.5 M *N*-benzyl-*N*-methylbenzamide (**3bb**) stock solution: In a 25 mL volumetric flask 8.45 g of **3bb** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.10.2. PLS Model

Table S17 lists the PLS model parameters and cross-validation scores. The mass balance of **1d** and **2b** is shown in the range of the kinetic runs (Figure S34).

Table S17. PLS model parameters for the reaction of **1d** with **2b**.

	Ester	Amine	TBD	Product
rank (n_components)	1	2	4	4
RMSE (PLS)	0.0402 M	0.0754 M	0.0203 M	0.0227 M
RMSE (CV)	0.0611 M	0.214 M	0.0509 M	0.0316 M
R^2 (PLS)	0.906	0.893	0.907	0.987
R^2 (CV)	0.782	0.138	0.411	0.974

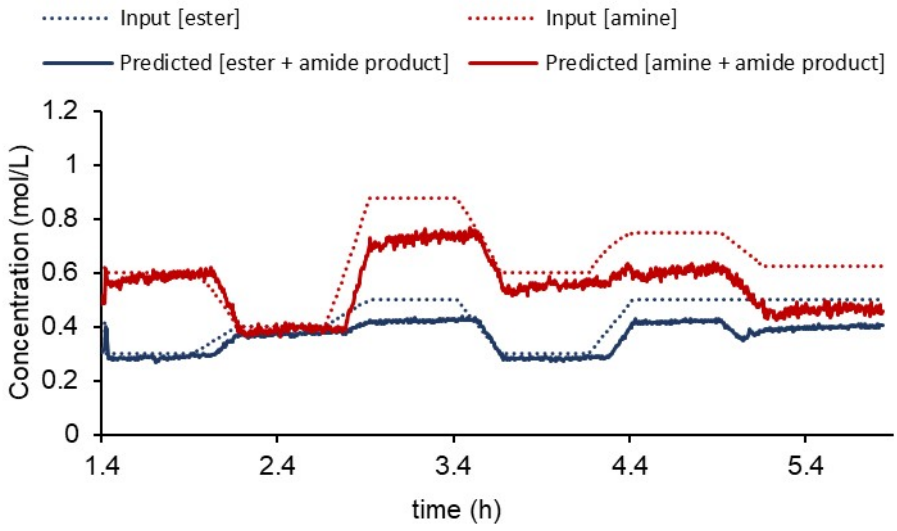


Figure S34. Mass balance for the reaction of **1d** with **2b**.

6.10.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the 0kinetic model and FTIR measurements) was 1, 1, 0, 10, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in **Table S18**. Additionally, the RMSE between the simulated result from the kinetic model

(lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found in Table S18. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in Figure S35. Parity plots for ester, amine, TBD and the amide product can be found in Figure S36.

Table S18. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	14.29101824	14.29101778	ester (**1d**)	51 mM
A_2 (L/mol)	6.637011118	6.637011268	amine (**2b**)	92 mM
E_a1 (kJ/mol)	38.6026085	38.60260837	TBD	34 mM
E_a2 (kJ/mol)	1.000000005	1.000000085	amide product (**3bb**)	10 mM
loss	16.12326398	16.12326398		

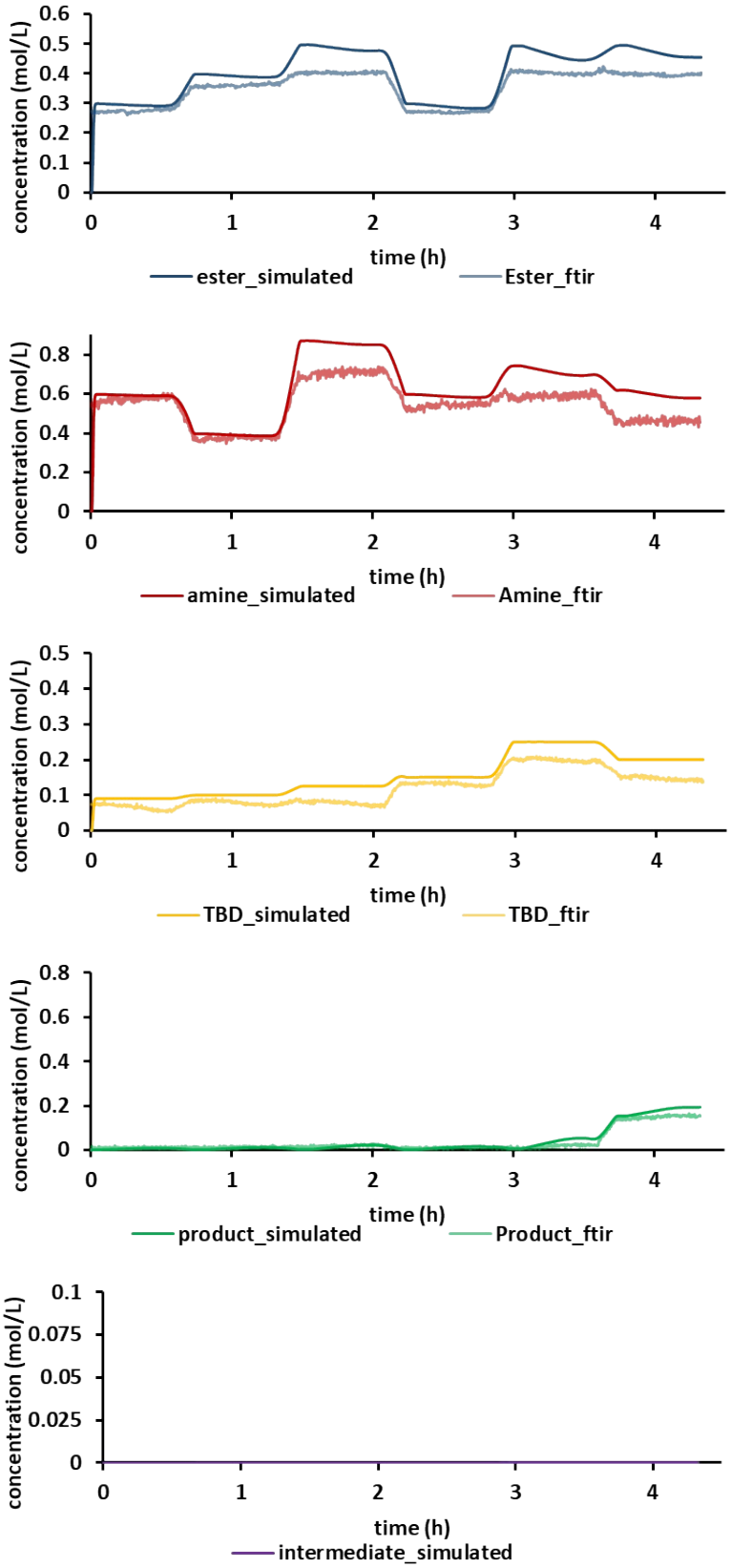


Figure S35. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

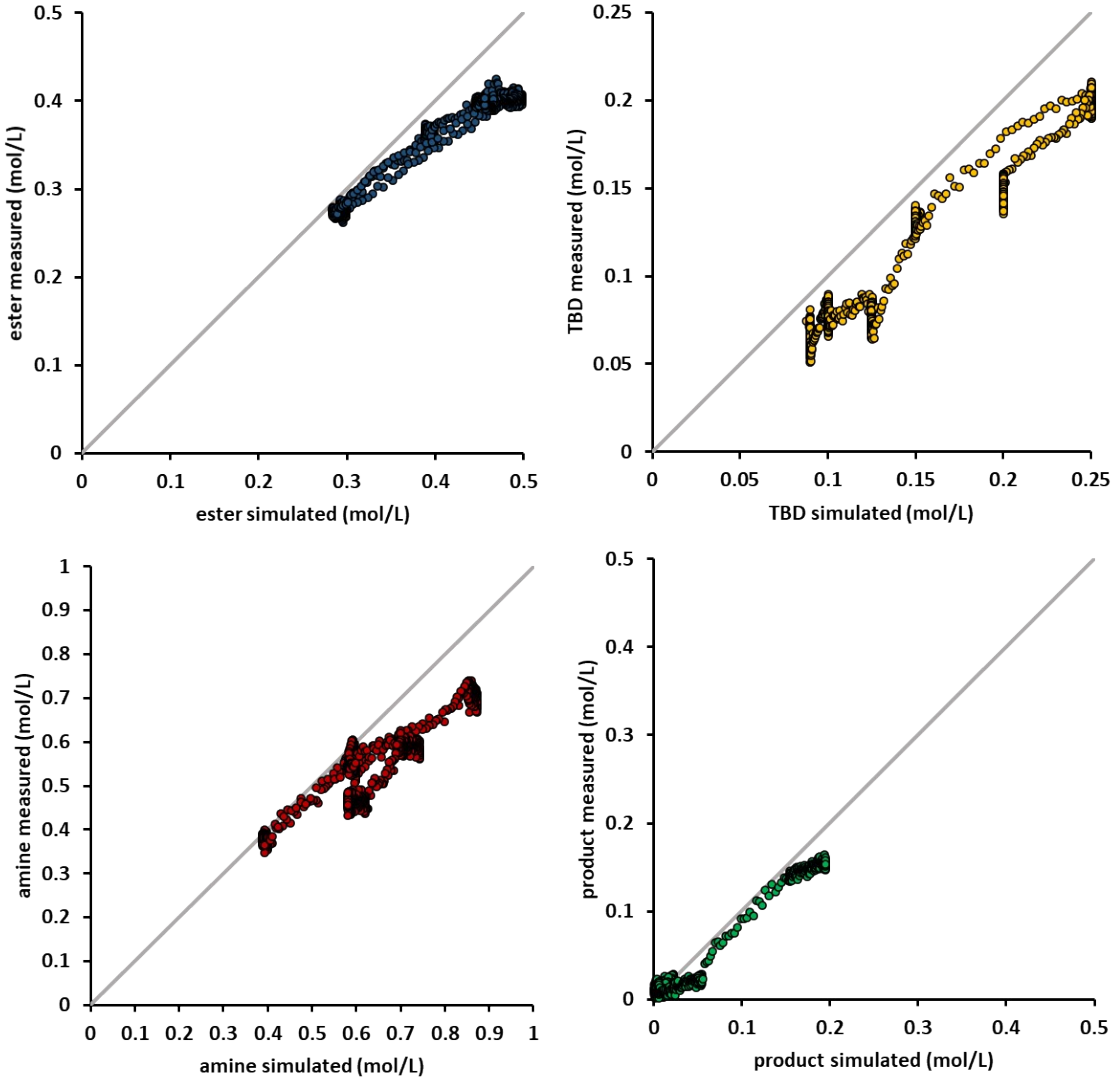


Figure S36. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.11. Reaction of 1e and 2a Yielding 3ea

6.11.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.5 M isopropyl benzoate (**1e**) stock solution: In a 100 mL volumetric flask 25.5 g of **1e** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.5 M benzylamine (**2a**) stock solution: In a 100 mL volumetric flask 26.8 g of **2a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 250 mL volumetric flask 17.4 g of TBD was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to the 250 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.0 M *N*-benzylbutyramide (**3ea**) stock solution: In a 25 mL volumetric flask 6.65 g of **3ea** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.11.2. PLS Model

Table S19 lists the PLS model parameters and cross-validation scores. The mass balance of **1e** and **2a** is shown in the range of the kinetic runs (Figure S37).

Table S19. PLS model parameters for the reaction of **1e** with **2a**.

	Ester	Amine	TBD	Product
rank (n_components)	3	2	6	4
RMSE (PLS)	0.0323 M	0.0344 M	0.00198 M	0.0235 M
RMSE (CV)	0.0621 M	0.0473 M	0.0143 M	0.0416 M
R^2 (PLS)	0.953	0.981	0.999	0.99
R^2 (CV)	0.825	0.963	0.956	0.969

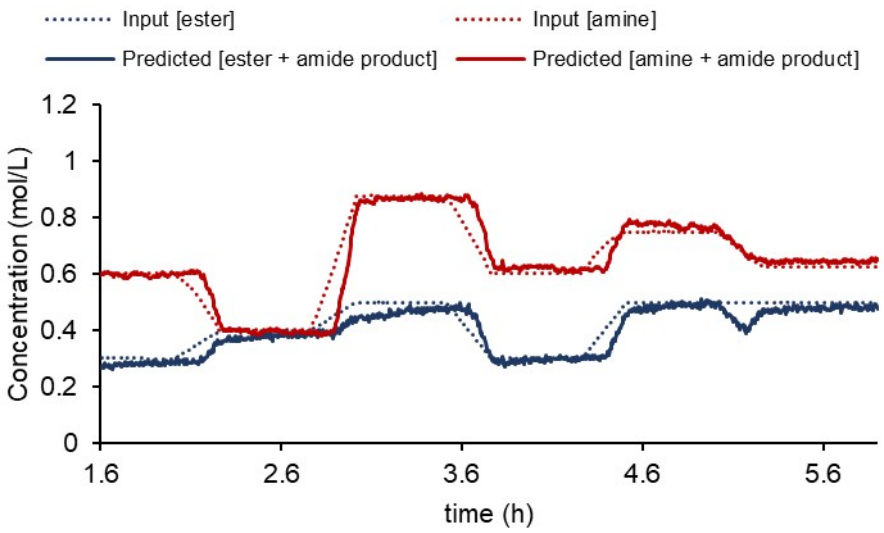


Figure S37. Mass balance for the reaction of **1e** with **2a**.

6.11.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 0, 1, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in Table S20. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found in Table S20. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in **Figure S38**. Parity plots for ester, amine, TBD and the amide product can be found in Figure S39.

Table S20. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	8.538333577	8.471611736	ester (**1e**)	40 mM
A_2 (L/mol)	6.416777756	6.318360517	amine (**2a**)	30 mM
E_a1 (kJ/mol)	29.65064961	29.63474464	TBD	22 mM
E_a2 (kJ/mol)	1.48274928	1.496103988	amide product (**3ea**)	23 mM
loss	3.330513361	3.329350661		

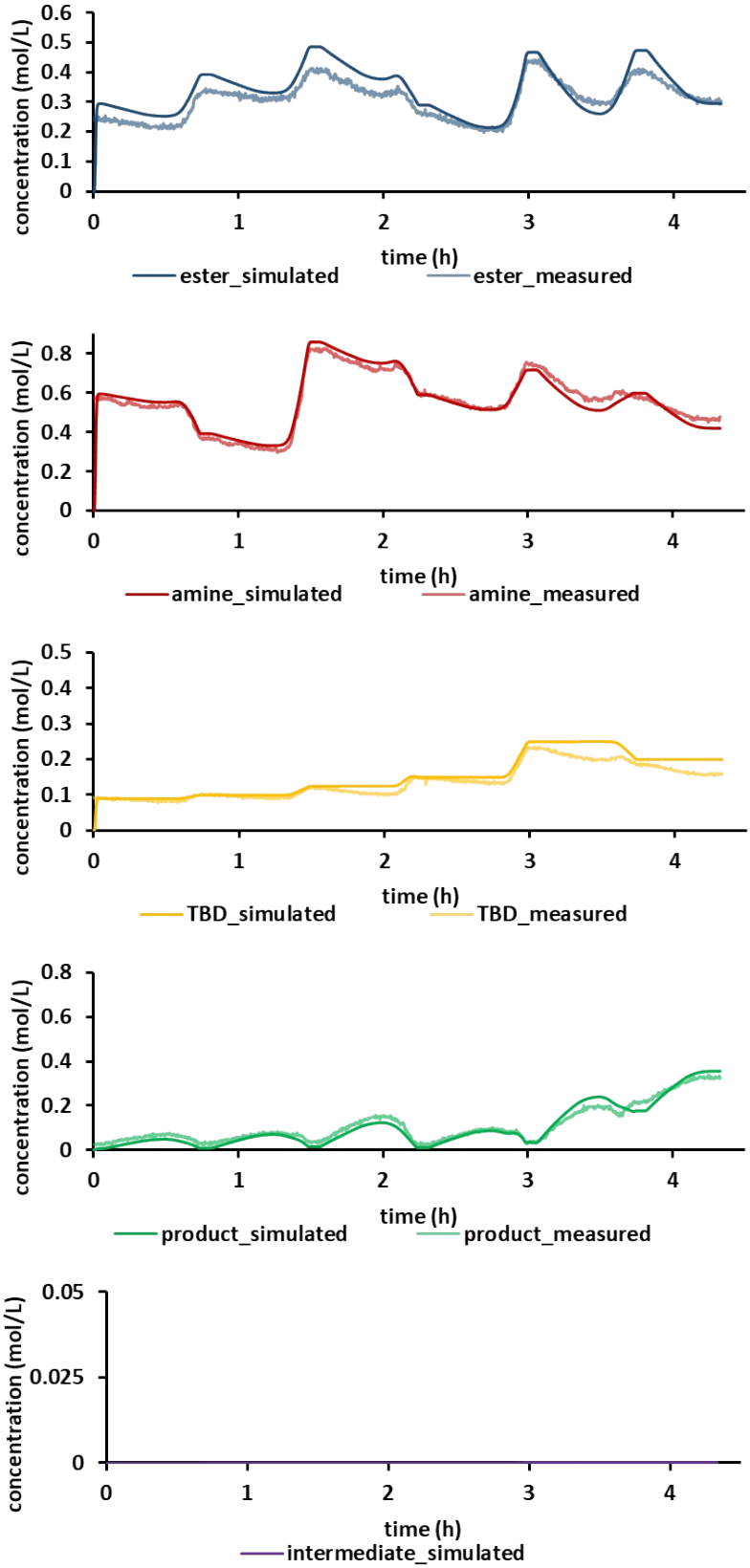


Figure S38. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

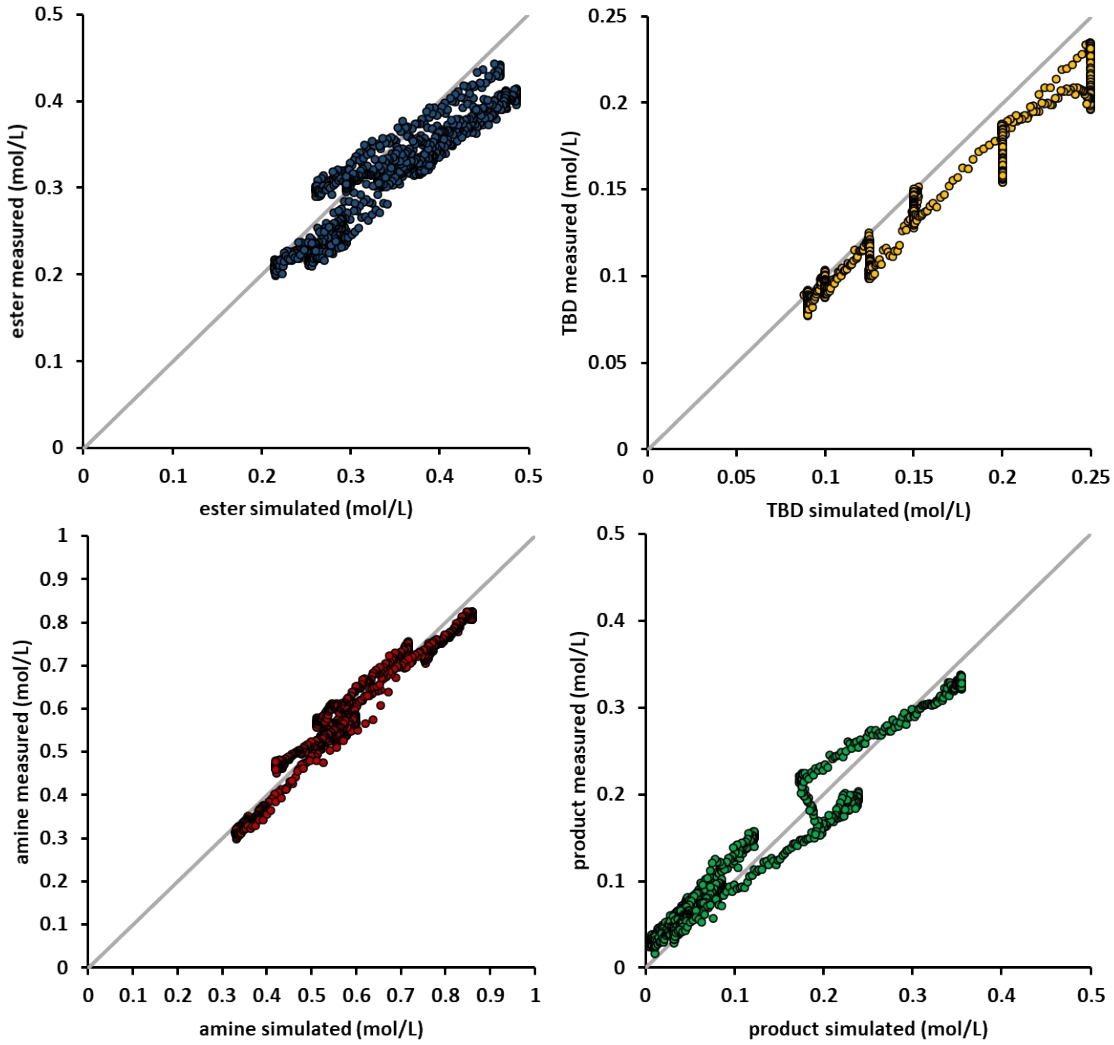


Figure S39. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

6.12. Reaction of 1a and 2a Yielding 3aa

6.12.1. Experimental and Stock Solutions

The process setup is described in section 5.1 and was used without any modifications. Input solutions were prepared with the following procedure:

2.0 M methyl nicotinate (**1a**) stock solution: In a 100 mL volumetric flask 27.4 g of **1a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

2.0 M benzylamine (**2a**) stock solution: In a 100 mL volumetric flask 21.4 g of **2a** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 100 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

0.5 M TBD stock solution: In a 200 mL volumetric flask 13.9 g of TBD was dissolved in a mixture of MeTHF and MeCN (9+1 v/v). The stock solution was sonicated (approximately 15 min) and filled up to the 200 mL mark with a mixture of MeTHF and MeCN (9+1 v/v). A stirring bar was added and the stock solution was constantly stirred during the experiment.

The solvent feed of mixture of MeTHF and MeCN (9+1 v/v) was prepared by mixing 900 mL of MeTHF and 100 mL of MeCN.

1.5 M *N*-benzylnicorinamide (**3aa**) stock solution: In a 25 mL volumetric flask 7.9 g of **3aa** was dissolved in a mixture of MeTHF and MeCN (9+1 v/v) and filled up to the 25 mL mark with a mixture of MeTHF and MeCN (9+1 v/v).

6.12.2. PLS Model

Table S21 lists the PLS model parameters and cross-validation scores. The mass balance of **1a** and **2a** is shown in the range of the kinetic runs (**Figure S40**).

Table S21. PLS model parameters for the reaction of **1a** with **2a**.

	Ester	Amine	TBD	Product
rank (n_components)	3	3	7	4
RMSE (PLS)	0.00967 M	0.0237 M	0.00162 M	0.00788 M
RMSE (CV)	0.0225 M	0.0398 M	0.0226 M	0.0119 M
R^2 (PLS)	0.995	0.99	0.999	0.998
R^2 (CV)	0.971	0.971	0.899	0.996

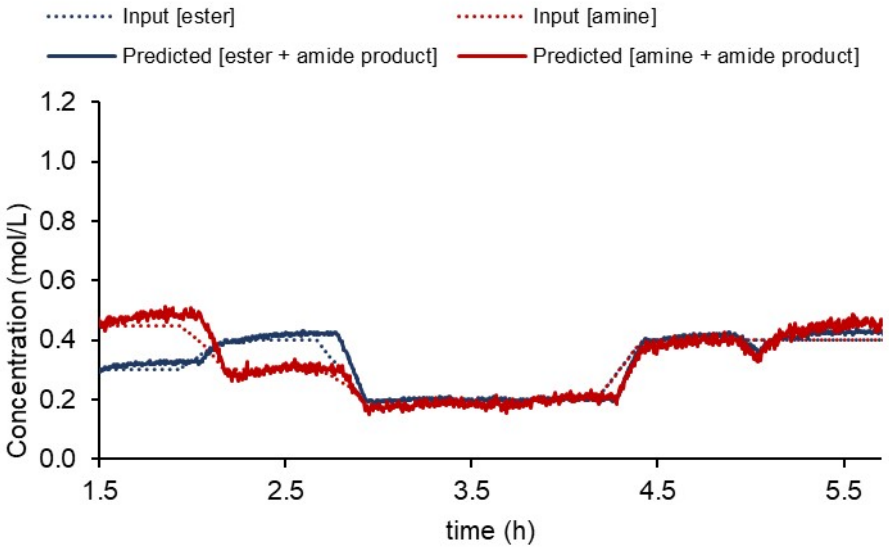


Figure S40. Mass balance for the reaction of **1a** with **2a**.

6.12.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 0, 1, and 0 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in Table S22. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found in **Table S22**. The measured and predicted concentration of each reaction species over the entire

dynamic experiments are depicted in Figure S41. Parity plots for ester, amine, TBD and the amide product can be found in Figure S42.

Table S22. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	8.763862211	8.330922359	ester (**1a**)	21 mM
A_2 (L/mol)	9.157393247	9.60625631	amine (**2a**)	25 mM
E_a1 (kJ/mol)	23.63142317	23.6021675	TBD	15 mM
E_a2 (kJ/mol)	17.25551695	16.71577197	amide product (**3aa**)	26 mM
loss	1.9335195	1.925178186		

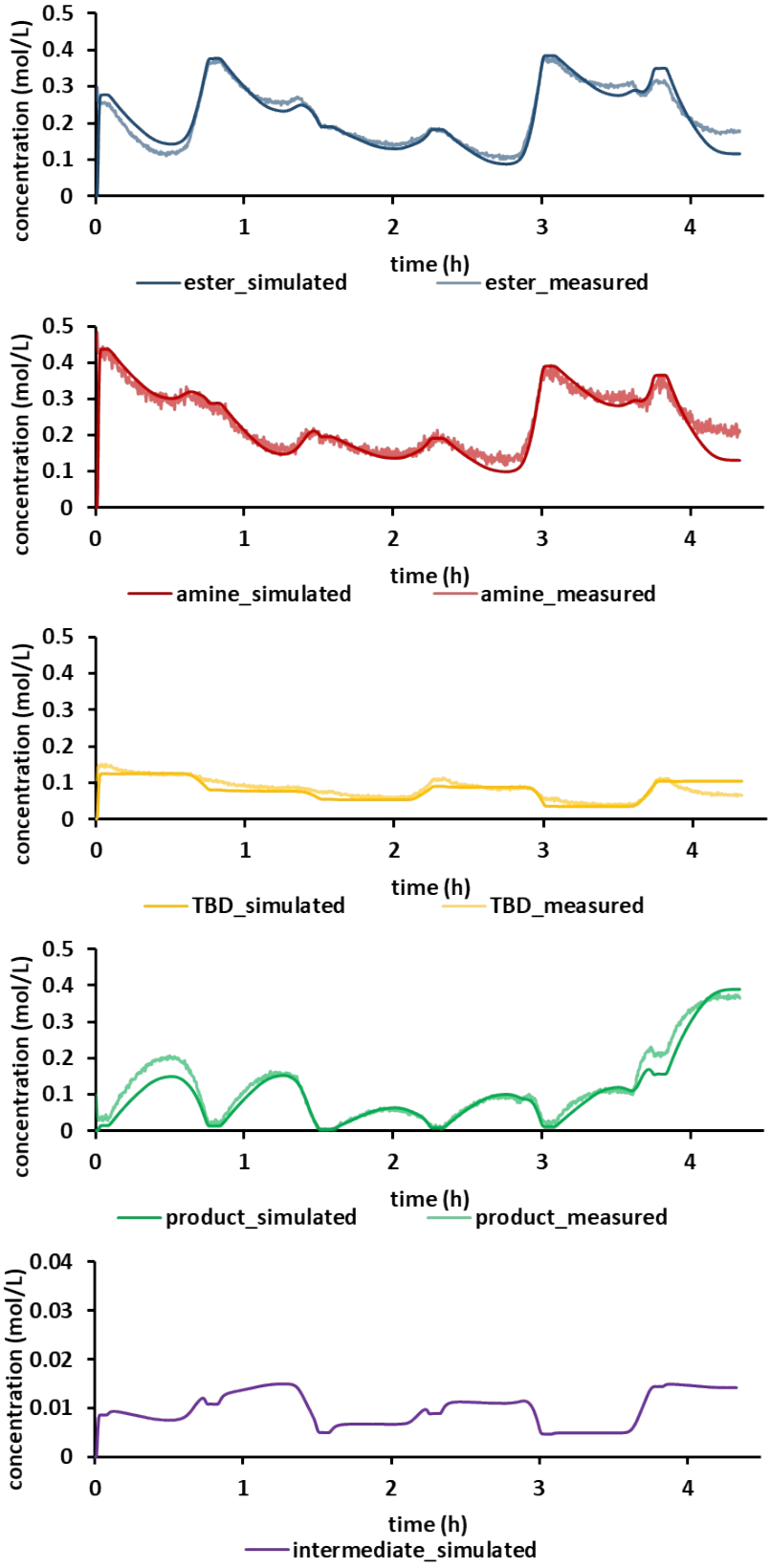


Figure S41. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

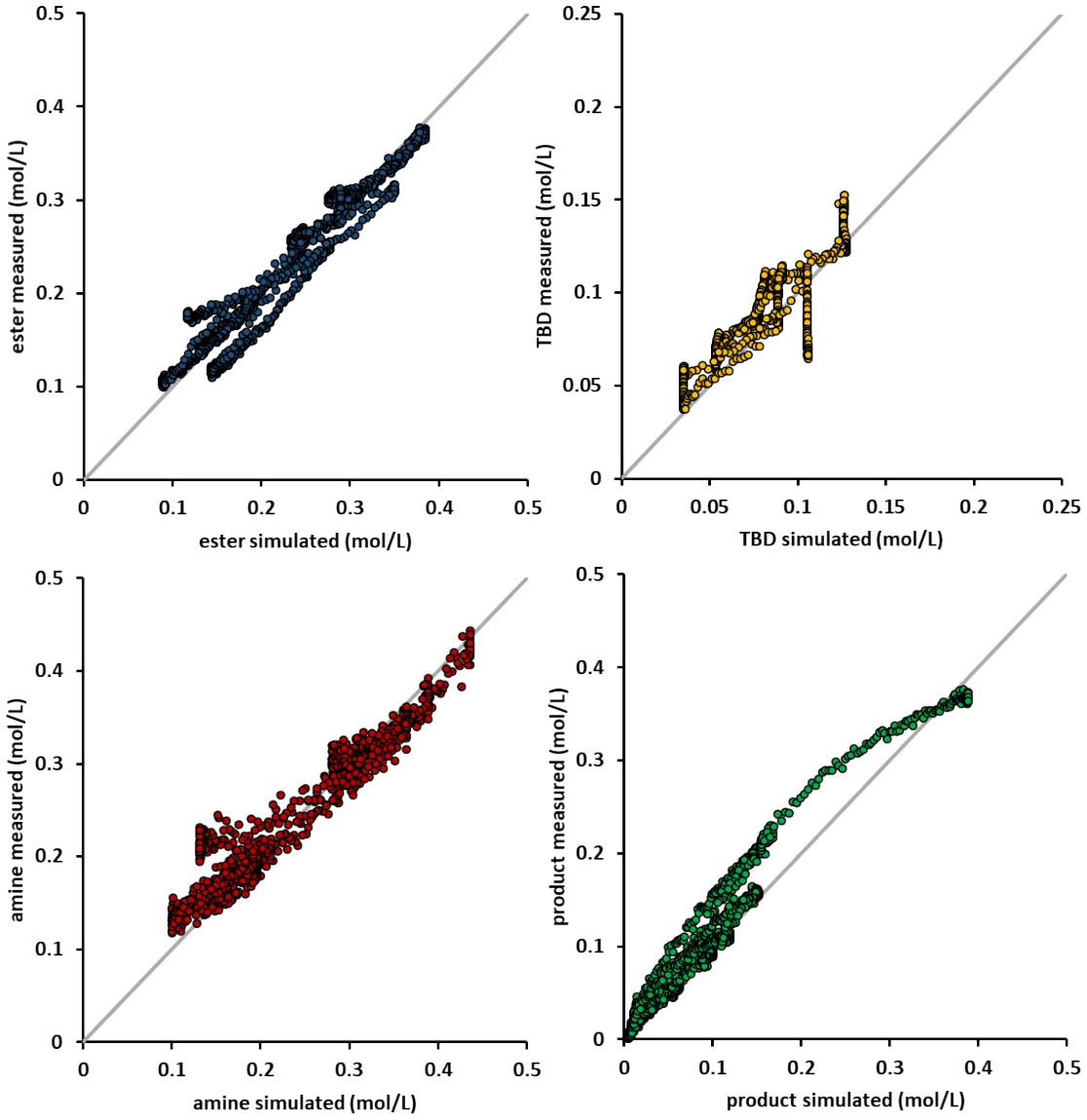


Figure S42. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

7. API Synthesis

7.1. Step 1 Alkylation

7.1.1. Experimental and Stock Solutions

The process setup is described in section 5.2 and was used without any modifications. Input solutions were prepared with the following procedure:

2.0 M 2-nitro-1*H*-imidazole (**4**) + 1.1 equivalent (2.2 M) triethylamine (TEA) stock solution: In a 100 mL volumetric flask 22.6 g of **1a** and 22.3 g of TEA were dissolved in MeOH and filled up to the 100 mL mark with MeOH.

2.5 M ethyl 2-bromoacetate (**5**) stock solution: In a 100 mL volumetric flask 41.8 g of **5** was dissolved in MeOH and filled up to the 100 mL mark with MeOH.

0.5 M TEA stock solution: In a 100 mL volumetric flask 5.06 g of TBD was dissolved in MeOH and filled up to the 100 mL mark with MeOH.

500 mL of MeOH were filled in a glass bottle as the solvent feed.

1.5 M ethyl 2-(2-nitro-1*H*-imidazol-1-yl)acetate (**6**) stock solution: In a 25 mL volumetric flask 7.47 g of **6** was dissolved in MeOH and filled up to the 25 mL mark with MeOH.

7.1.2. PLS Model

Table S23 lists the PLS model parameters and cross-validation scores. The mass balance of **1a** and **2a** is shown in the range of the kinetic runs (Figure S43).

Table S23. PLS model parameters for the reaction of **4** with **5**.

	Ester	Amine	TBD	Product
rank (n_components)	2	3	8	2
RMSE (PLS)	0.0303 M	0.0261 M	0.00436 M	0.0357 M
RMSE (CV)	0.0435 M	0.0423 M	0.0498 M	0.046 M
R^2 (PLS)	0.954	0.99	0.994	0.984
R^2 (CV)	0.905	0.973	0.278	0.973

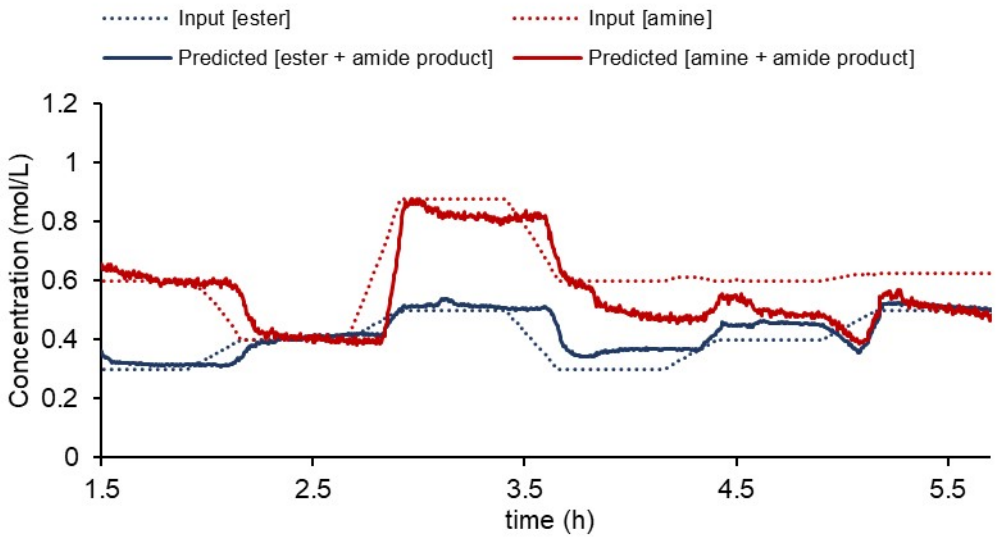


Figure S43. Mass balance for the reaction of **4** with **5**.

7.1.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with a one-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 1, 1, 0, and 1 for **4**, 5, TEA, and **6**, respectively. The optimized values for the kinetic parameter (A and E_a), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in **Table S24**. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found in Table S24. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in Figure S44. Parity plots for **4**, 5, TEA, and **6**, can be found in Figure S45.

Table S24. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A (L^2 mol^{-2})	196633.8355	198595.7951	**4**	44 mM
E_a (kJ/mol)	49.4421566	49.49918931	**5**	103 mM
loss	17.53684031	17.5335822	TEA	502 mM
			6	73 mM

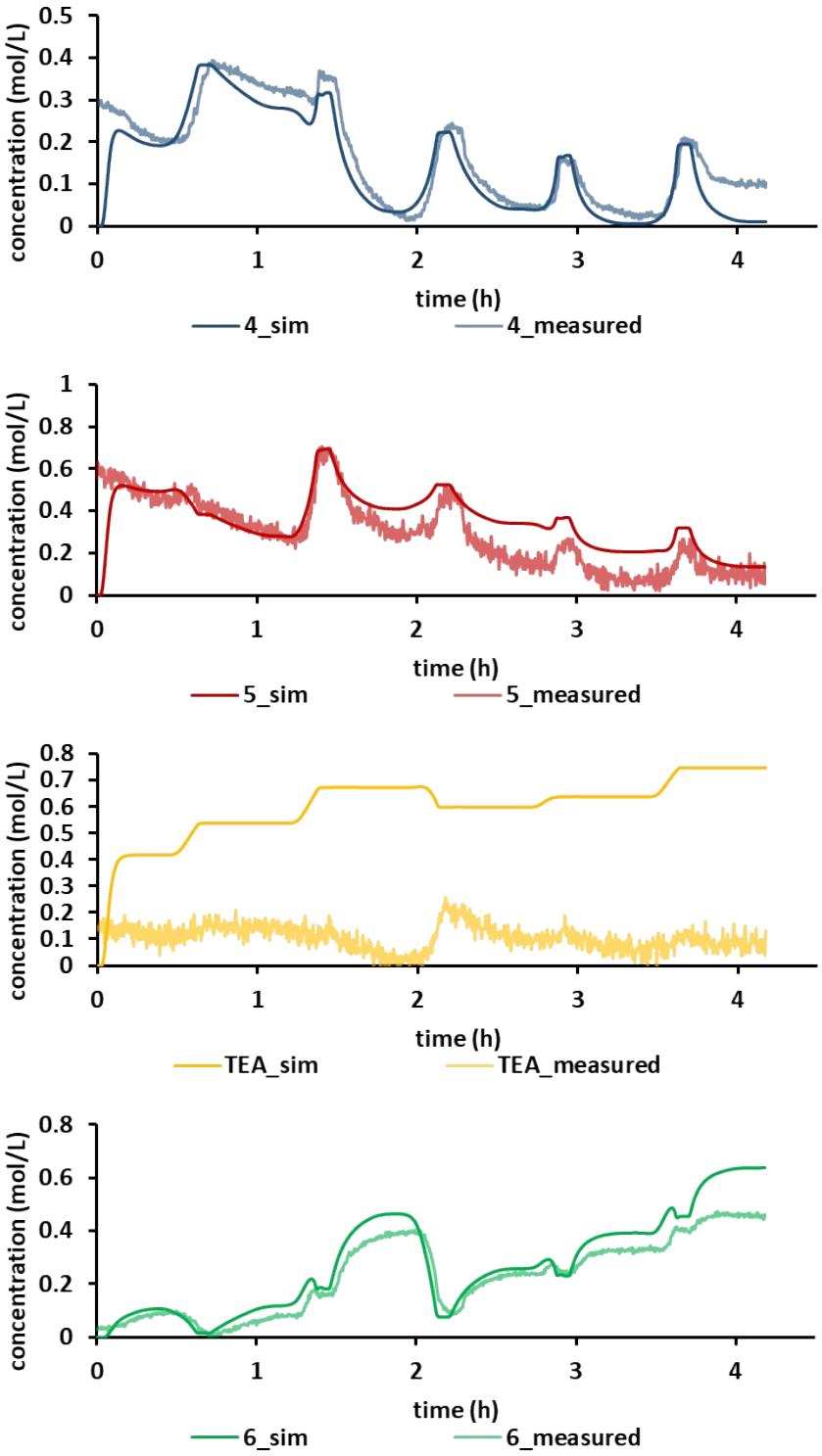


Figure S44. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

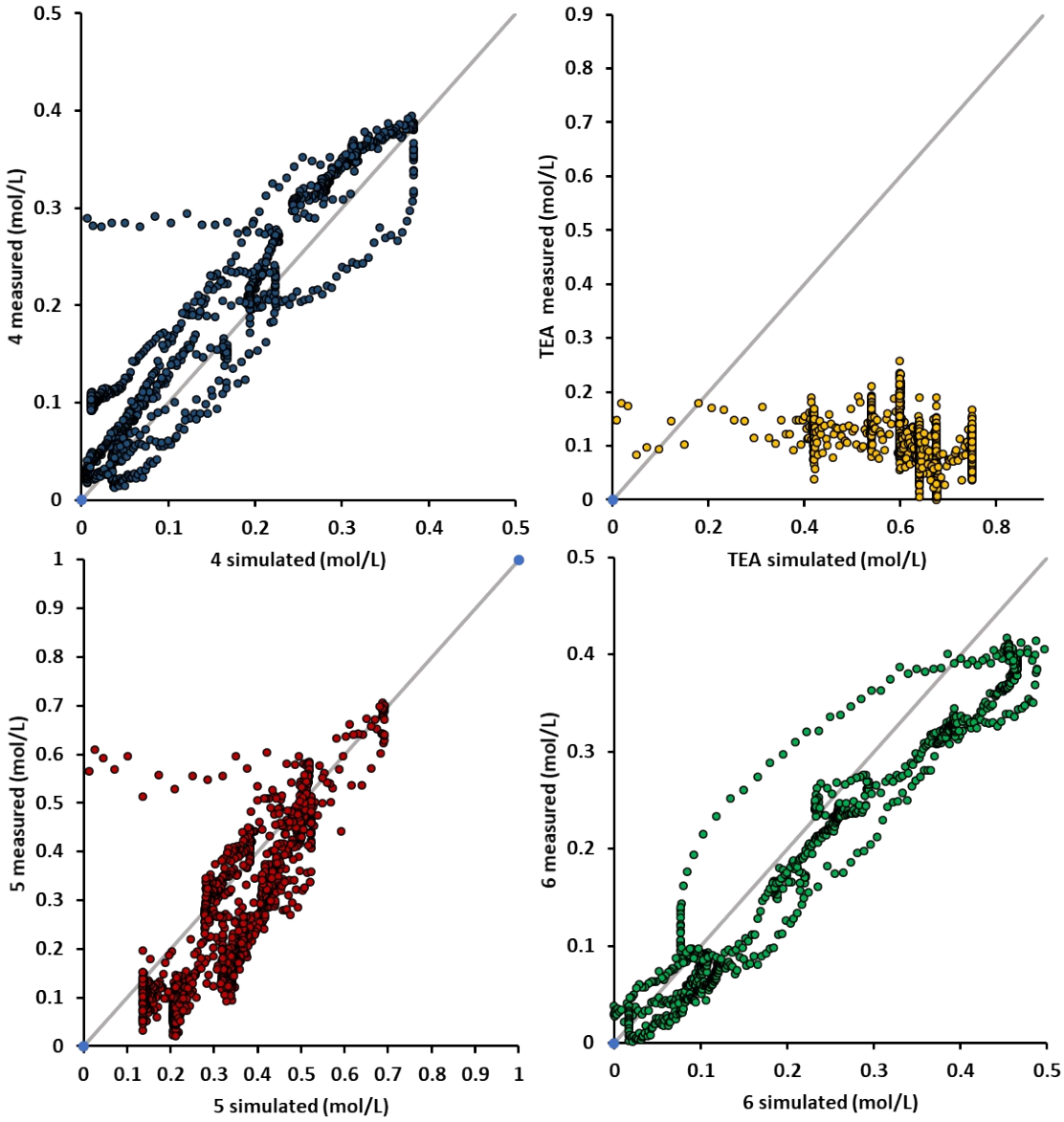


Figure S45. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

7.1.4. *In-Silico* Optimization

An in-silico optimization campaign was performed with the obtained process model for the alkylation step. The pareto front was identified for the two objectives conversion and space-time yield. Additionally, 30000 random points in the chemical space were simulated. The relations between residence time and conversion, and residence time and space-time yield are depicted in **Figure S46** and **Figure S47**.

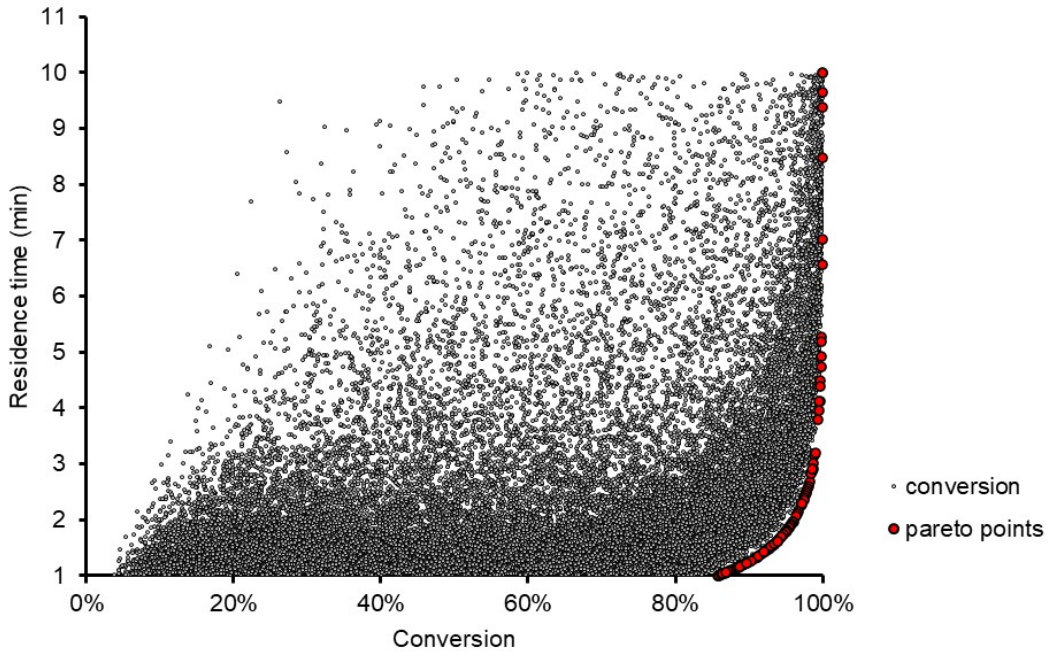


Figure S46. Visualization of residence time vs. conversion. The red points indicate the Pareto optimal points for the trade-off between conversion and space-time yield, whilst grey points are the result of random input parameters.

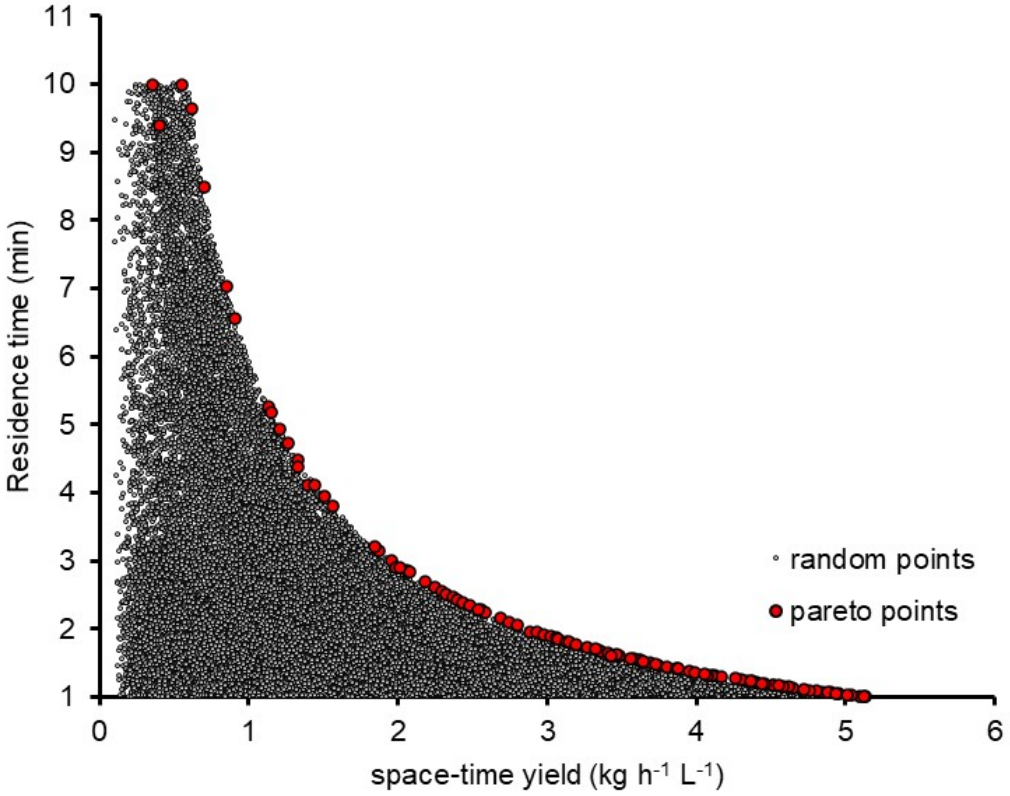


Figure S47. Visualization of residence time vs. space-time yield. The red points indicate the Pareto optimal points for the trade-off between conversion and space-time yield, whilst grey points are the result of random input parameters

7.2. Step 2 Amidation

7.2.1. Experimental and Stock Solutions

The process setup is described in section 5.3 and was used without any modifications.

Input solutions were prepared with the following procedure.

2.0 M ethyl 2-(2-nitro-1*H*-imidazol-1-yl)acetate (**6**) stock solution: In a 50 mL volumetric flask 20.0 g of **6** was dissolved in DMSO and filled up to the 100 mL mark with DMSO.

2.5 M benzylamine (**2a**) stock solution: In a 100 mL volumetric flask 26.8 g of **2a** was dissolved in DMSO and filled up to the 100 mL mark with DMSO.

0.5 M TBD stock solution: In a 100 mL volumetric flask 6.96 g of TBD was dissolved in DMSO. The stock solution was sonicated (approximately 15 min) and filled up to the 100 mL mark with DMSO. A stirring bar was added, and the stock solution was constantly stirred during the experiment.

500 mL of DMSO were filled in a glass bottle as the solvent feed.

1.0 M stock solution: In a 25 mL volumetric flask 6.8 g of benznidazole (**7**) was dissolved in DMSO and filled up to the 25 mL mark with DMSO.

7.2.2. PLS Model

Table S25 lists the PLS model parameters and cross-validation scores. The mass balance of **1a** and **2a** is shown in the range of the kinetic runs (**Figure S48**).

Table S25. PLS model parameters for the reaction of **6** with **2a**.

	Ester	Amine	TBD	Product
rank (n_components)	3	4	6	2
RMSE (PLS)	0.0158 M	0.013 M	0.0025 M	0.0207 M
RMSE (CV)	0.0235 M	0.031 M	0.0118 M	0.028 M
R^2 (PLS)	0.981	0.998	0.999	0.986
R^2 (CV)	0.959	0.986	0.977	0.975

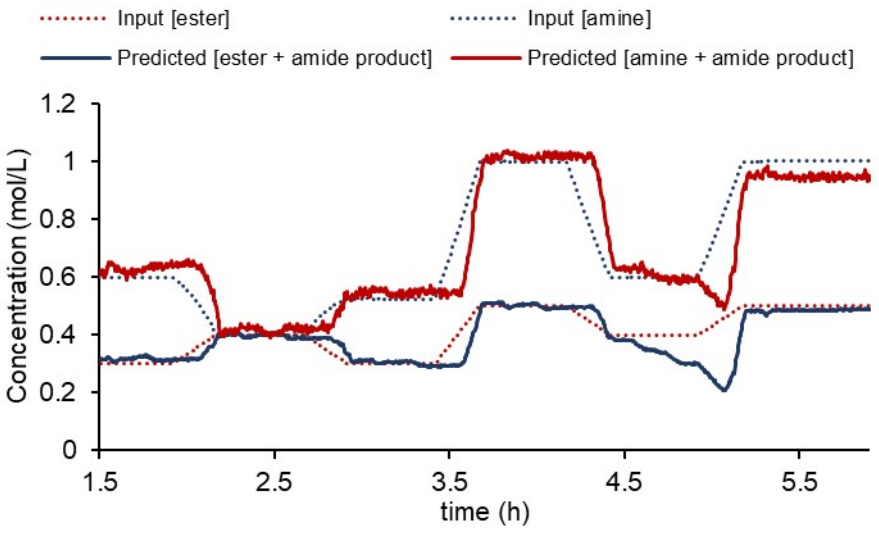


Figure S48. Mass balance for the reaction of **6** with **2a**.

7.2.3. Identifying Kinetic Parameters and Simulation

The kinetic parameters were fitted with the two-step reaction mechanism as described in the main manuscript. The weighting in the cost function (RMSE between the predicted concentrations from the kinetic model and FTIR measurements) was 0, 0, 0, 1, and 1 for ester, amine, TBD, amide product and intermediate, respectively. The optimized values for the kinetic parameter (A_1, A_2, E_a1, and E_a2), the loss of the cost function for the NLopt-BOBYQA and the refinement with the Nelder-Mead algorithm can be found in **Table S26**. Additionally, the RMSE between the simulated result from the kinetic model (lowest loss) and the measured value from the FTIR for ester, amine, TBD, and product can be found in Table S26. The measured and predicted concentration of each reaction species over the entire dynamic experiments are depicted in Figure S49. Parity plots for ester, amine, TBD and the amide product can be found in Figure S50.

Table S26. Results of the kinetic parameter optimization and RMSE values for ester, amine, TBD, and amide product for the simulated result using the kinetic model and the measured concentration by FTIR.

	NLopt-BOBYQA	Nelder-Mead	compound	RMSE
A_1 (L/mol)	7.524393058	7.524393049	ester (**6**)	43 mM
A_2 (L/mol)	6.658980213	6.658980251	amine (**2a**)	72 mM
E_a1 (kJ/mol)	14.19052903	14.19052903	TBD	62 mM
E_a2 (kJ/mol)	11.50382138	11.50382138	amide product (**7**)	49 mM
loss	10.51219704	10.51205084		

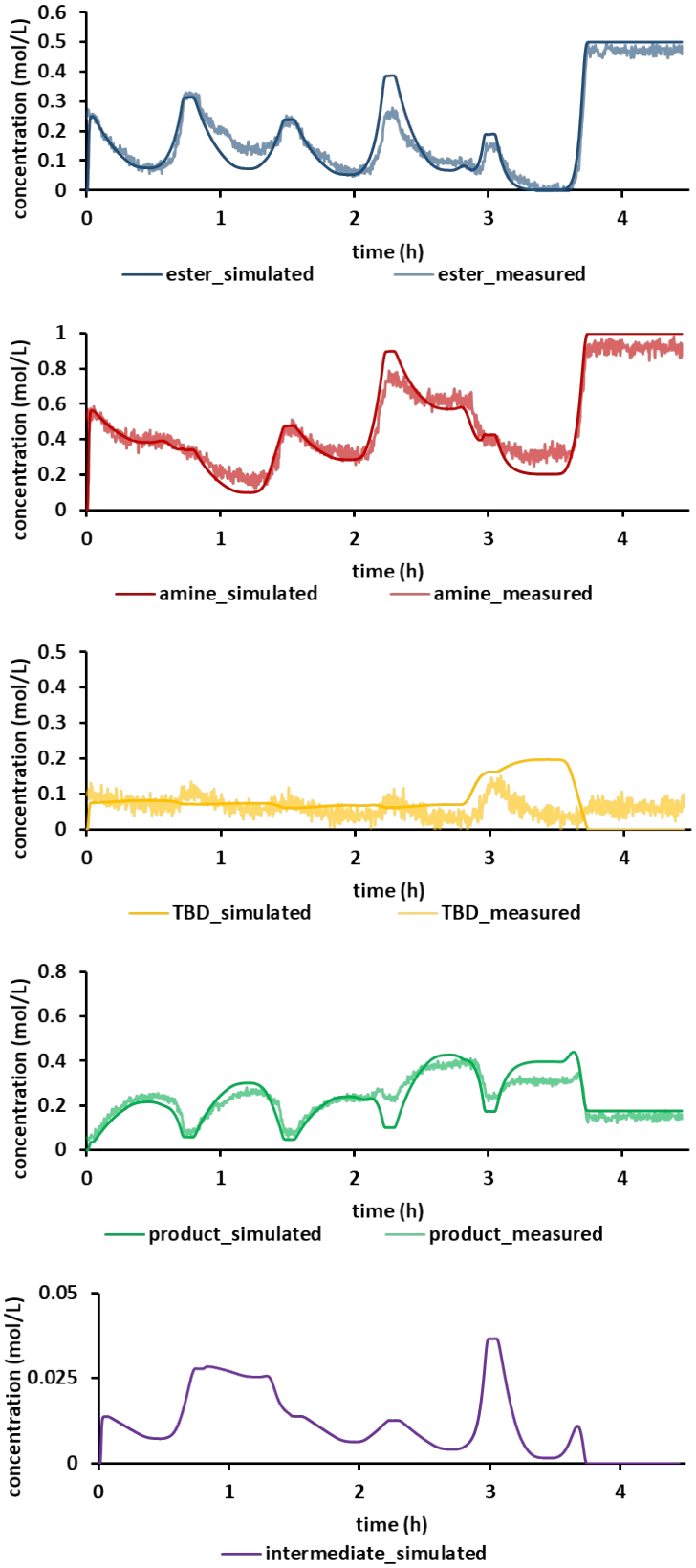


Figure S49. Concentration of reaction species measured over the experiment duration (lighter solid lines) and their corresponding prediction values (darker solid lines) using the kinetic model.

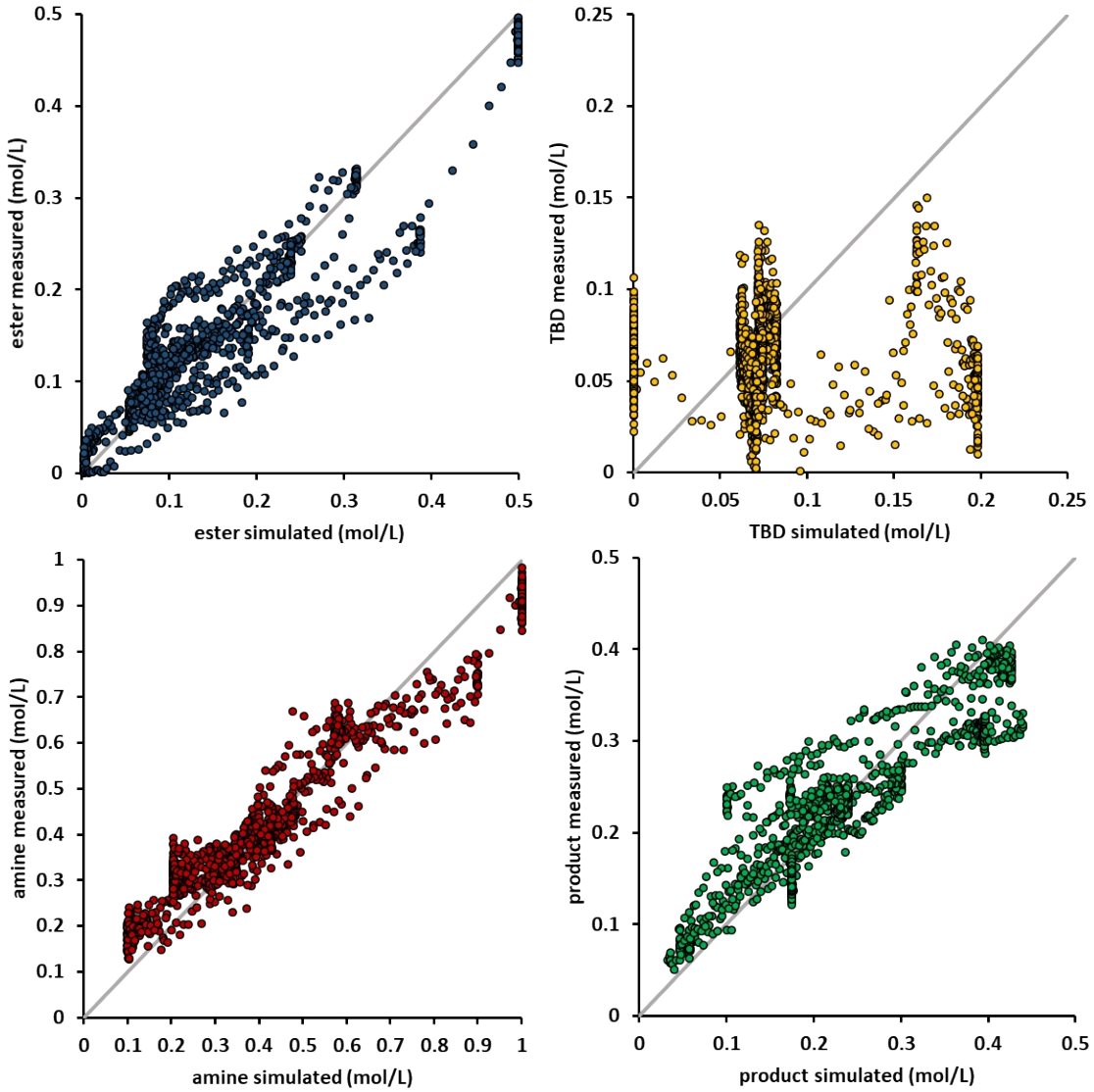


Figure S50. Parity plots describing the prediction from the kinetic model to the measured values of the FTIR.

7.2.4. *In-Silico* Optimization

An in-silico optimization campaign was performed with the obtained process model for the amidation step. The pareto front was identified for the two objectives conversion and space-time yield. Additionally, 30000 random points in the chemical space were simulated. The relations between conversion and space-time yield, and residence time and space-time yield are depicted in **Figure S51** and **Figure S52**.

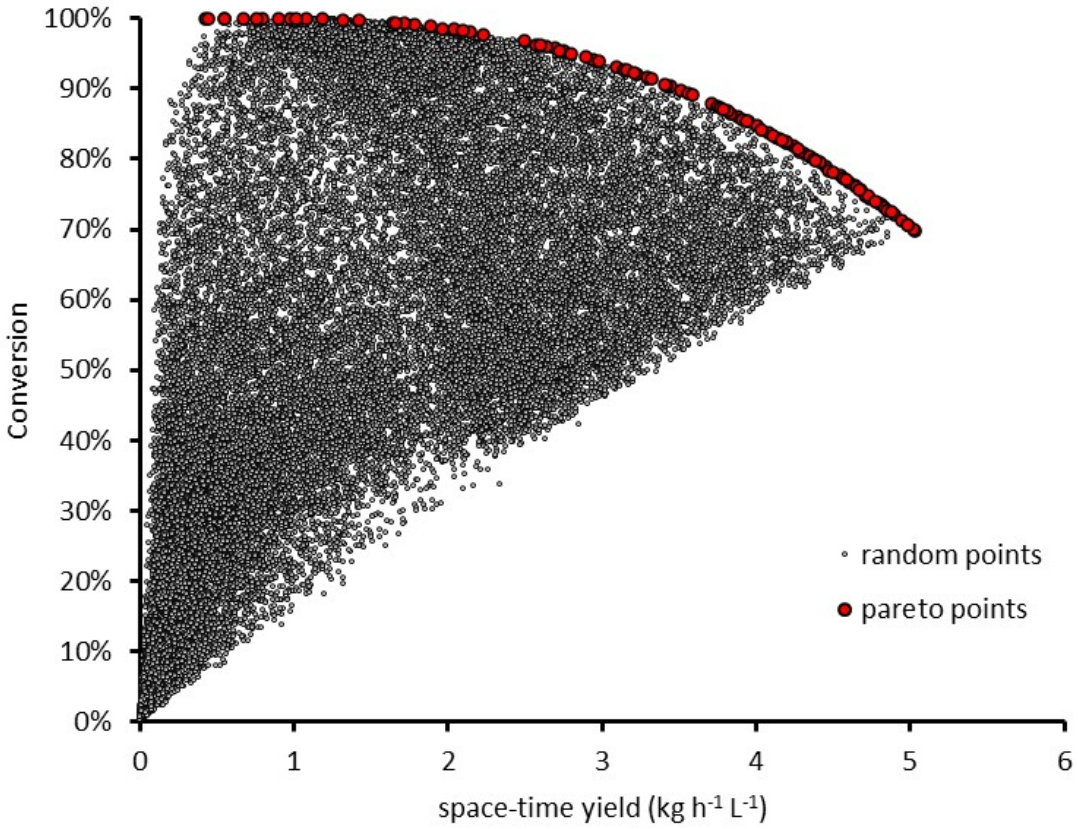


Figure S51. Visualization of conversion vs. space-time yield. Pareto optimal front is depicted by red points, contrasting with gray points that represent outcomes from random inputs.

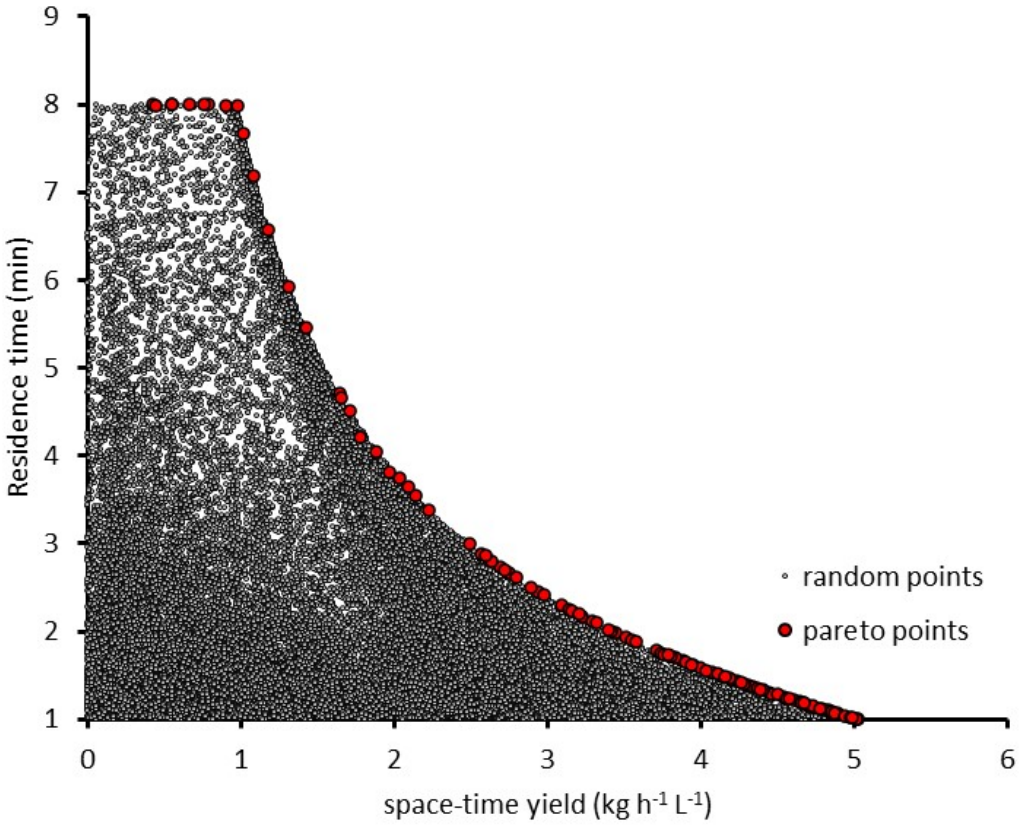
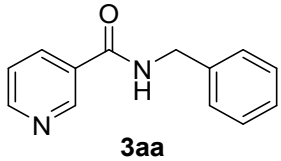


Figure S52. Visualization of residence time vs. space-time yield. The red points indicate the Pareto optimal points for the trade-off between conversion and space-time yield, whilst grey points are the result of random input parameters.

8. Synthetic Procedure for the Individual Products

Product purities were assessed by ^{1}H NMR analysis against an internal standard (1,3,5-trimethoxybenzene).

8.1. Amidation Products



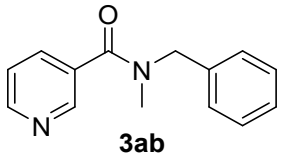
3aa

***N*-benzylnicotinamide**, **3aa**: A 250 mL round bottom flask was equipped with a reflux condenser and a stirring bar. The flask was charged with methyl nicotinate (14.1 g, 102 mmol), TBD (4.3 g, 31 mmol, 0.3 equiv) and diluted with 150 mL MeTHF. Benzylamine (17.1 g, 159 mol, 1.55 equiv) was added and the reaction mixture was heated to 75 °C for 5.5 h. The reaction mixture was concentrated under reduced pressure to approximately one third of its original volume. Then EtOAc (100 mL) was added and washed with NH_4Cl (4 x 30 mL) and brine (1 x 30mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The organic residuals were recrystallized with toluene (25 mL, reflux → 0°C). The formed solids were filtered off and washed with petroleum ether (3 x 30 mL) and dried under reduced pressure. After drying, the desired product was isolated as an off-white solid (15.2 g, 70% yield, 97% purity).

^{1}H NMR (300 MHz, DMSO D_6) δ 9.25 (t, *J* = 6.0 Hz, 1H) 9.06 (dd, J = 2.3, 0.9 Hz, 1H) 8.71 (dd, *J* = 4.8, 1.7 Hz, 1H) 8.23 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H) 7.51 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H) 7.37 – 7.19 (m, 5H) 4.51 (d, *J* = 6.0 Hz, 2H)

^{13}C NMR (75 MHz, DMSO D_6) δ 164.8, 151.9, 148.5, 139.3, 135.0, 129.8, 128.4, 128.3, 127.3, 126.9, 123.5, 42.6.

Characterization data is in accordance with previous literature reports.[1]



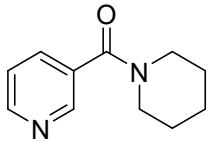
3ab

***N*-benzyl-*N*-methylnicotinamide**, **3ab**: A 250 mL round bottom flask was equipped with a reflux condenser and a stirring bar. The flask was charged with methyl nicotinate (20 g, 145 mmol), TBD (6.1 g, 43 mmol, 0.3 equiv) and diluted with 150 mL MeTHF. *N*-methylbenzylamine (26.5 g, 218 mol, 1.5 equiv) was added and the reaction mixture was heated to 70 °C for 2.5 h. The reaction mixture was concentrated under reduced pressure to approximately one third of its original volume. Then EtOAc (150 mL) was added and washed with NH_4Cl (4 x 40 mL) and brine (1 x 40mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a yellow oil (32.0 g, 97% yield, 94% purity).

^{1}H NMR (300 MHz, DMSO D_6) δ 8.76 – 8.55 (m, 2H) 7.88 (dd, *J* = 22.4, 7.9 Hz, 1H) 7.54 – 7.10 (m, 6H) 4.58 (d, *J* = 65.5 Hz, 2H) 2.89 (d, *J* = 23.3 Hz, 3H)

^{13}C NMR (75 MHz, DMSO D_6) δ 168.2, 150.4, 147.6, 147.2, 137.1, 134.8, 134.4, 132.1, 128.8, 128.7, 128.1, 128.0, 127.7, 127.3, 126.7, 126.6, 123.5, 55.0, 54.1, 49.9, 36.8, 35.5, 32.9.

Characterization data is in accordance with previous literature reports.[2]



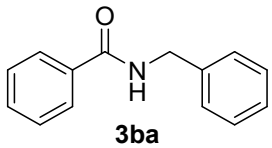
3ac

piperidin-1-yl(pyridin-3-yl)methanone, **3ac**: A 250 mL round bottom flask was equipped with a reflux condenser and a stirring bar. The flask was charged with methyl nicotinate (20 g, 145 mmol), TBD (6.1 g, 43 mmol, 0.3 equiv) and diluted with 150 mL MeTHF. Piperidine (18.6 g, 218 mol, 1.5 equiv) was added and the reaction mixture was heated to 70 °C for 2.5 h. The reaction mixture was concentrated under reduced pressure to approximately one third of its original volume. Then EtOAc (150 mL) was added and washed with NH_4Cl (4 x 40 mL) and brine (1 x 40mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a yellow oil (20.4 g, 74% yield, 96% purity).

^{1}H NMR (300 MHz, DMSO D_6) δ 8.69 – 8.53 (m, 2H) 7.80 (dt, *J* = 7.8, 2.0 Hz, 1H) 7.47 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H) 3.59 (s, 2H) 3.30 (s, *J* = 22.3 Hz, 2H) 1.69 – 1.38 (m, 6H)

^{13}C NMR (75 MHz, DMSO D_6) δ 166.6, 150.2, 147.3, 134.5, 132.3, 123.5, 48.1, 42.3, 25.9, 25.2, 24.0.

Characterization data is in accordance with previous literature reports.[3]



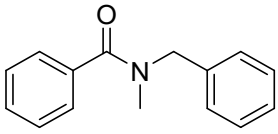
3ba

***N*-benzylbenzamide**, **3ba**: A 500 mL round bottom flask was equipped with a stirring bar, charged with benzoyl chloride (20.1 g, 143 mmol), diluted with DCM (200 mL) and cooled to 0 °C (ice batch). Benzylamine (31.4 g, 293.1 mmol, 2.05 equiv) was diluted with DCM (25 mL) in a dropping funnel and slowly added to the benzoyl chloride solution over 1 h. The reaction mixture was filtered and the filtrate was washed with 1 M HCl (3 x 50mL) and brine (2 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as an off-white solid (30.8 g, 99% yield, 99% purity).

^{1}H NMR (300 MHz, DMSO D_6) δ 9.06 (t, *J* = 6.1 Hz, 1H) 7.95 – 7.86 (m, 2H) 7.57 – 7.43 (m, 3H) 7.32 (d, *J* = 4.4 Hz, 4H) 7.28 – 7.19 (m, 1H) 4.49 (d, *J* = 6.0 Hz, 2H)

^{13}C NMR (75 MHz, DMSO D_6) δ 166.2, 139.7, 134.3, 131.3, 128.3, 128.3, 127.3, 127.2, 126.7, 42.6.

Characterization data is in accordance with previous literature reports.[4]



3bb

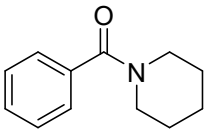
***N*-benzyl-*N*-methylbenzamide**, **3bb**: A 250 mL round bottom flask was equipped with a stirring bar, charged with benzoyl chloride (14.06 g, 100 mmol), diluted with DCM (75 mL) and cooled to 0 °C (ice batch). *N*-Methylbenzylamine (24.24 g, 200 mmol, 2.0 equiv) was diluted with DCM (25 mL) in a dropping funnel and slowly added to the benzoyl chloride solution over 1 h. After the addition, further DCM (25 mL) was added, then the reaction mixture was filtered. The filtrate was washed with 1 M HCl (3 x 50mL) and brine (2 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced

pressure. The pale-yellow oil started to crystallize, affording the desired product as an off-white solid (21.9 g, 97% yield, 99% purity).

^{1}H NMR (300 MHz, DMSO D_6) δ 7.56 – 7.04 (m, 10H) 4.57 (d, *J* = 63.7 Hz, 2H) 2.85 (d, *J* = 20.7 Hz, 3H)

^{13}C NMR (75 MHz, DMSO D_6) δ 170.3, 136.4, 129.4, 128.7, 128.4, 127.6, 127.2, 126.8, 54.1, 49.8, 36.8, 32.7.

Characterization data is in accordance with previous literature reports.[5]



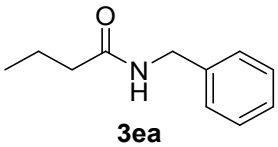
3bc

phenyl(pyridin-1n-yl)methanone, **3bc**: A 1 L round bottom flask was equipped with a stirring bar, charged with benzoyl chloride (56.2 g, 400 mmol), diluted with DCM (350 mL) and cooled to 0 °C. Piperidine (68.1 g, 800 mmol, 2.0 equiv) was diluted with DCM (100 mL) in a dropping funnel and slowly added to the benzoyl chloride solution over 2 h. The reaction solution was filtered and the filtrate was washed with 1 M HCl (3 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a pale-yellow oil (74.7 g, 98% yield, 99% purity).

^{1}H NMR (300 MHz, DMSO D_6) δ 7.47 – 7.31 (m, 5H) 3.57 (s, 2H) 3.26 (s, 2H) 1.68 – 1.32 (m, 6H)

^{13}C NMR (75 MHz, DMSO D_6) δ 168.8, 136.6, 129.2, 128.4, 126.6, 48.0, 42.2, 26.0, 25.3, 24.1.

Characterization data is in accordance with previous literature reports.[6]



3ea

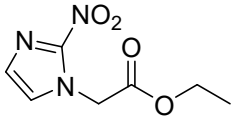
***N*-benzylbutyramide**, **3ea**: A 500 mL round bottom flask was equipped with a stirring bar, charged with butanoyl chloride (20.6 g, 193 mmol), diluted with DCM (180 mL) and cooled to 0 °C (ice batch). Benzylamine (48 g, 396 mmol, 2.05 equiv) was diluted with DCM (50 mL) in a dropping funnel and slowly added to the butanoyl chloride solution over 1 h. The reaction mixture was filtered, and the filtrate was washed with 1 M HCl (3 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a pale-yellow oil (28.8 g, 78% yield, 99% purity).

^{1}H NMR (300 MHz, DMSO D_6) δ 8.31 (d, *J* = 6.7 Hz, 1H) 7.35 – 7.27 (m, 2H) 7.27 – 7.18 (m, 3H) 4.26 (d, *J* = 6.0 Hz, 2H) 2.11 (t, *J* = 7.3 Hz, 2H) 1.54 (h, *J* = 7.4 Hz, 2H) 0.86 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (75 MHz, DMSO D_6) δ 172.0, 139.8, 128.3, 127.2, 126.7, 41.9, 37.3, 18.7, 13.7.

Characterization data is in accordance with previous literature reports.[7]

8.2. Products for the Alkylation and Amidation Step for the API Synthesis



6

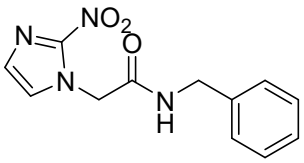
ethyl 2-(2-nitro-1H-imidazol-1-yl)acetate, **6**: A 250 mL round bottom flask was equipped with a stirring bar and charged with 2-nitroimidazole (21.4 g, 189 mmol) and diluted with 115 mL EtOH. Ethyl bromo acetate (36.9 g, 1.3 equiv) and TEA (22.4 g, 1.3 equiv) were added under stirring. The reaction mixture was transferred into eight 30 mL microwave glass vials. The reactions were performed at 130 °C at a temperature holding time of 10 min, each. The collected mixtures were combined, concentrated under reduced pressure, and diluted with EtOAc. The solution was washed with 1 M HCl (2 x 30 mL) and $NaHCO_3$ (4 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, to afford the desired product as an oily orange liquid (28.16 g, 89 % yield, 99 % purity).

^{1}H NMR (300 MHz, DMSO D6) δ 7.65 (d, *J* = 1.1 Hz, 1H) 7.24 (d, *J* = 1.1 Hz, 1H) 5.32 (s, 2H) 4.19 (q, *J* = 7.1 Hz, 2H) 1.21 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (75 MHz, DMSO D6) δ 167.3, 128.6, 127.9, 61.6, 50.6, 14.0.

LC-MS: $[M+H]^+$ = 200 $[M+MeCN+H]^+$ = 241

NMR characterization data is in accordance with previous literature reports.[8]



7

***N*-benzyl-2-(2-nitro-1H-imidazol-1-yl)acetamide**, **7**: The collected product stream of the flow experiment yielding the alkylated product **6** (20.0 g, 100 mmol, mixture of methyl and ethyl ester) was diluted with 140 mL of a mixture of MeTHF and MeCN (9+1 v/v). Benzylamine (11.9 g, 1.1 equiv) and TBD (7.10 g, 0.5 equiv) were added under stirring. The reaction mixture was stirred for 10 min at room temperature and reduced under reduced pressure to ca. two thirds of the original volume. 100 mL 1 M HCl was added, and the suspension was stirred for 1 h, then filtered. The filtered product was washed with cold H_2O, then dried under reduced pressure to afford the desired product as an off-white solid (23.6 g, 88% yield, 96 % purity).

^{1}H NMR (300 MHz, DMSO D6) δ 8.85 (t, *J* = 5.9 Hz, 1H, NH) 7.65 (d, *J* = 1.1 Hz, 1H) 7.38 - 7.22 (m, 5H) 7.20 (d, *J* = 1.1 Hz, 1H) 5.18 (s, 2H) 4.33 (d, *J* = 5.9 Hz, 2H)

^{13}C NMR (75 MHz, DMSO D6) δ 165.7, 138.9, 128.9, 128.4, 127.5, 127.3, 127.0, 51.6, 42.3.

LC-MS: $[M+H]^+$ = 261 $[M+MeCN+H]^+$ = 302

NMR characterization data is in accordance with previous literature reports.[8]

9. References

(1) J. Wu, Y. Wu, J. Dai and H. Xu, *Adv. Synth. Catal.*, 2014, **356**, 2429–2436.

(2) C. G. McPherson, N. Caldwell, C. Jamieson, I. Simpson and A. J. B. Watson, *Org. Biomol. Chem.*, 2017, **15**, 3507–3518.

(3) B. Nammalwar, N. P. Muddala, F. M. Watts and R. A. Bunce, *Tetrahedron*, 2015, **71**, 9101–9111.

(4) J. K. Laha, U. Gulati, and A. Gupta, *Org. Lett.*, 2023, **25**, 3402–3406.

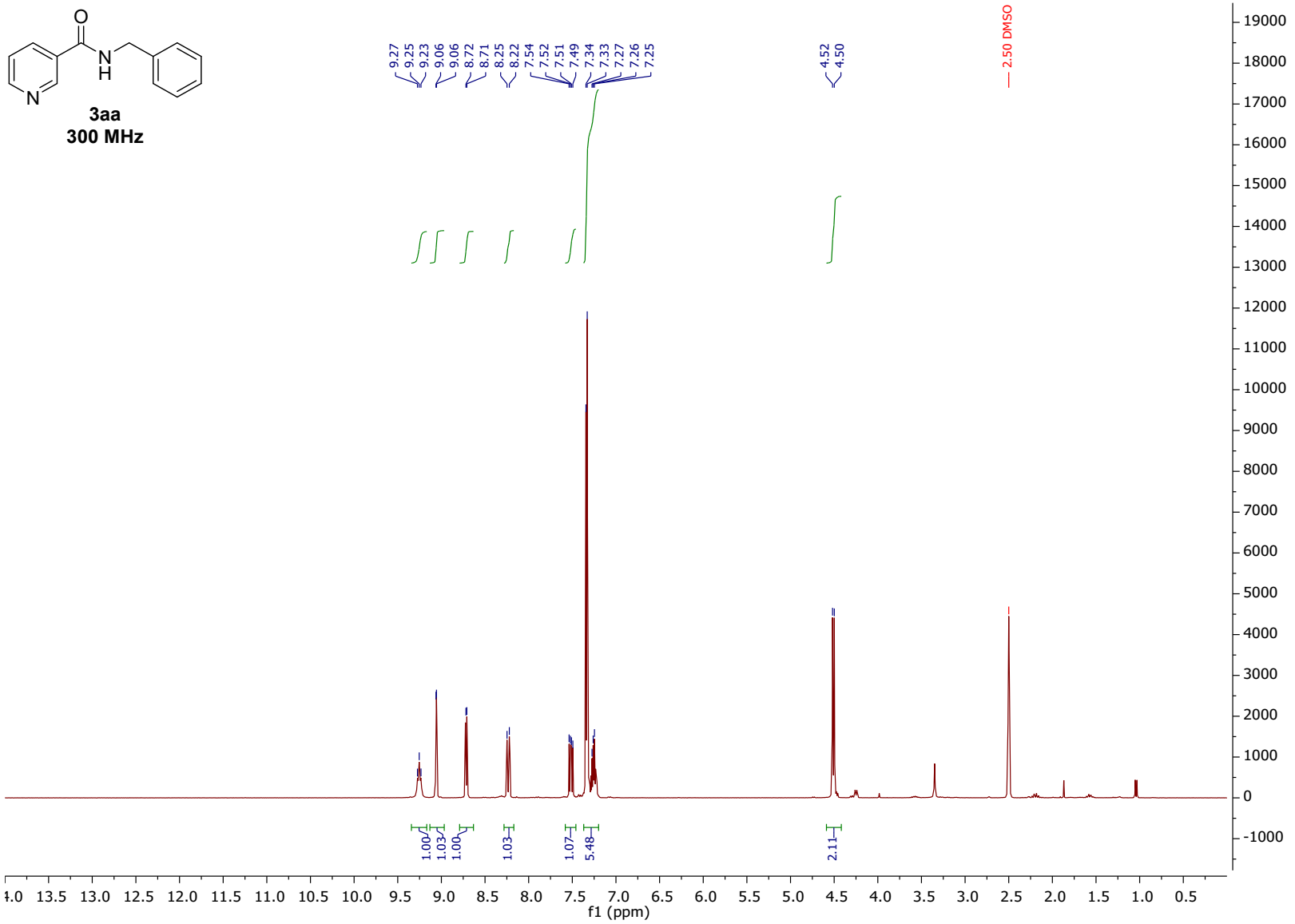
(5) V. Vinayagam, S. K. Sadhukhan, S. K. Karre, R. Srinath, R. K. Maroju, P. R. Karra, H. S. N. B. Bathula, S. Kundrapu and S. R. Surukonti, *Org. Lett.* 2023, **25**, 4610–4614.

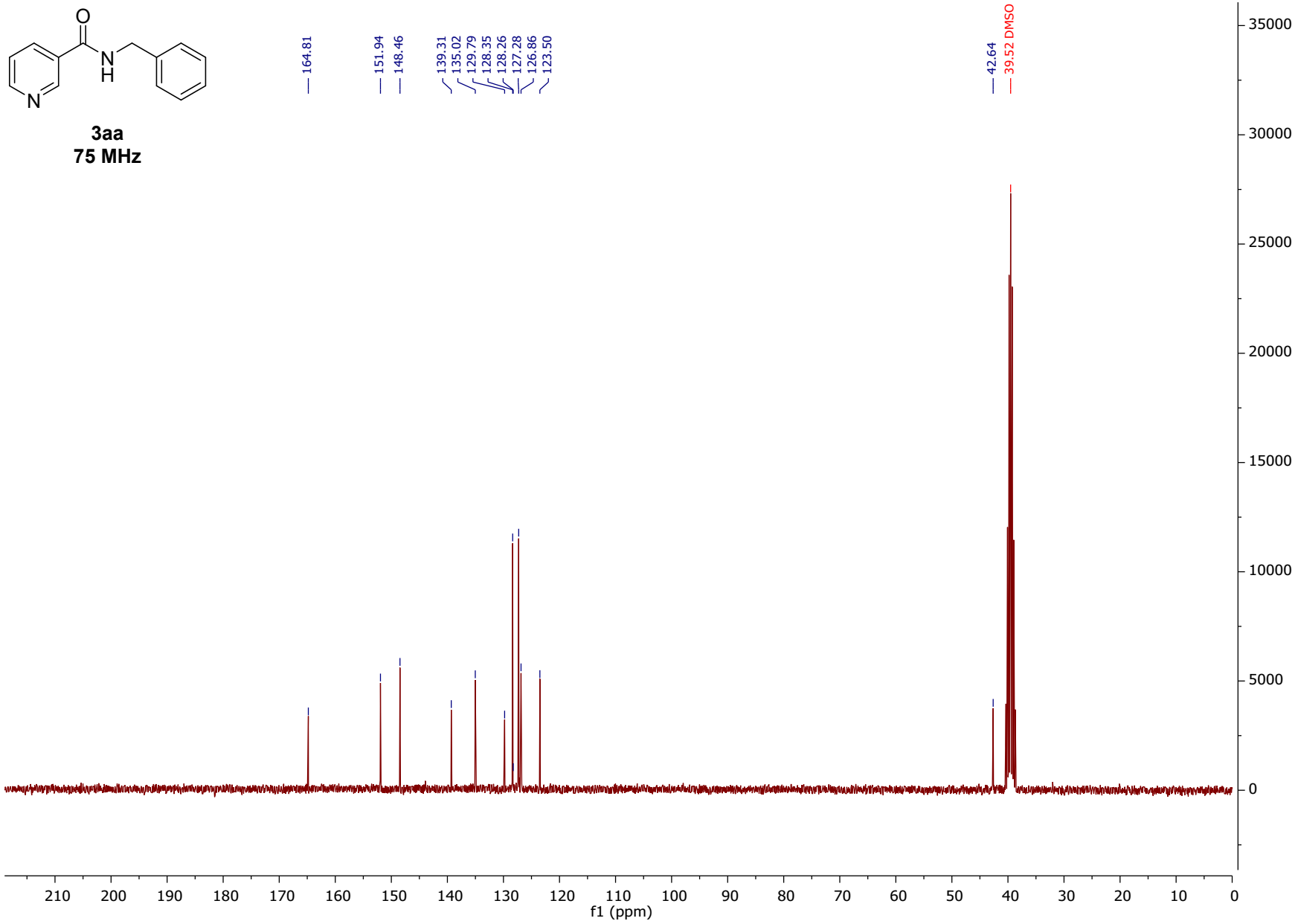
(6) A. Joshi, S. Kumari and S. Kundu, *Adv. Synth. Catal.*, 2022, **364**, 4371–4383.

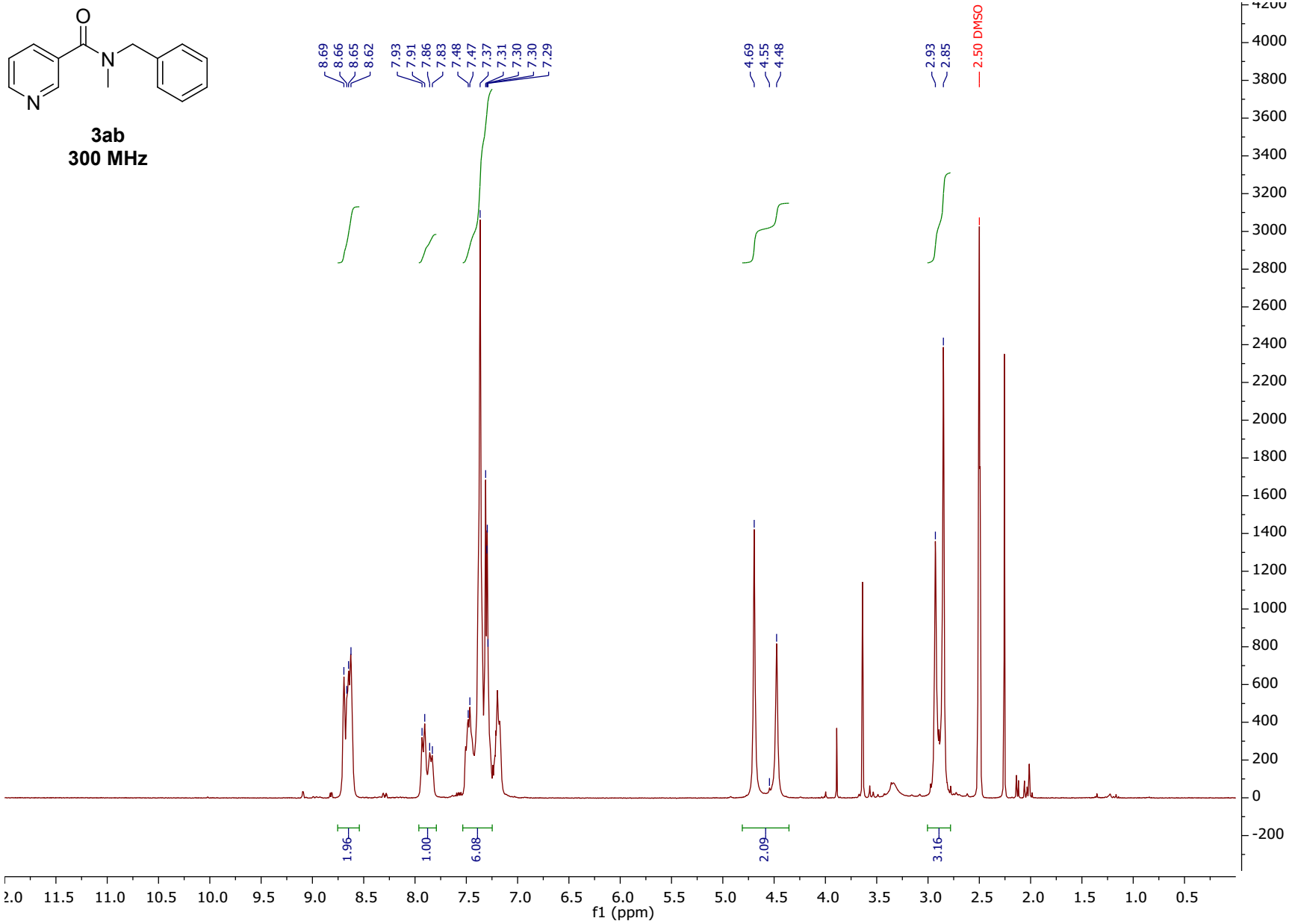
(7) M. Boyle, K. Livingstone, M. C. Henry, J. M. L. Elwood, J. D. Lopez-Fernandez and C. Jamieson, *Org. Lett.*, 2022, **24**, 334–338.

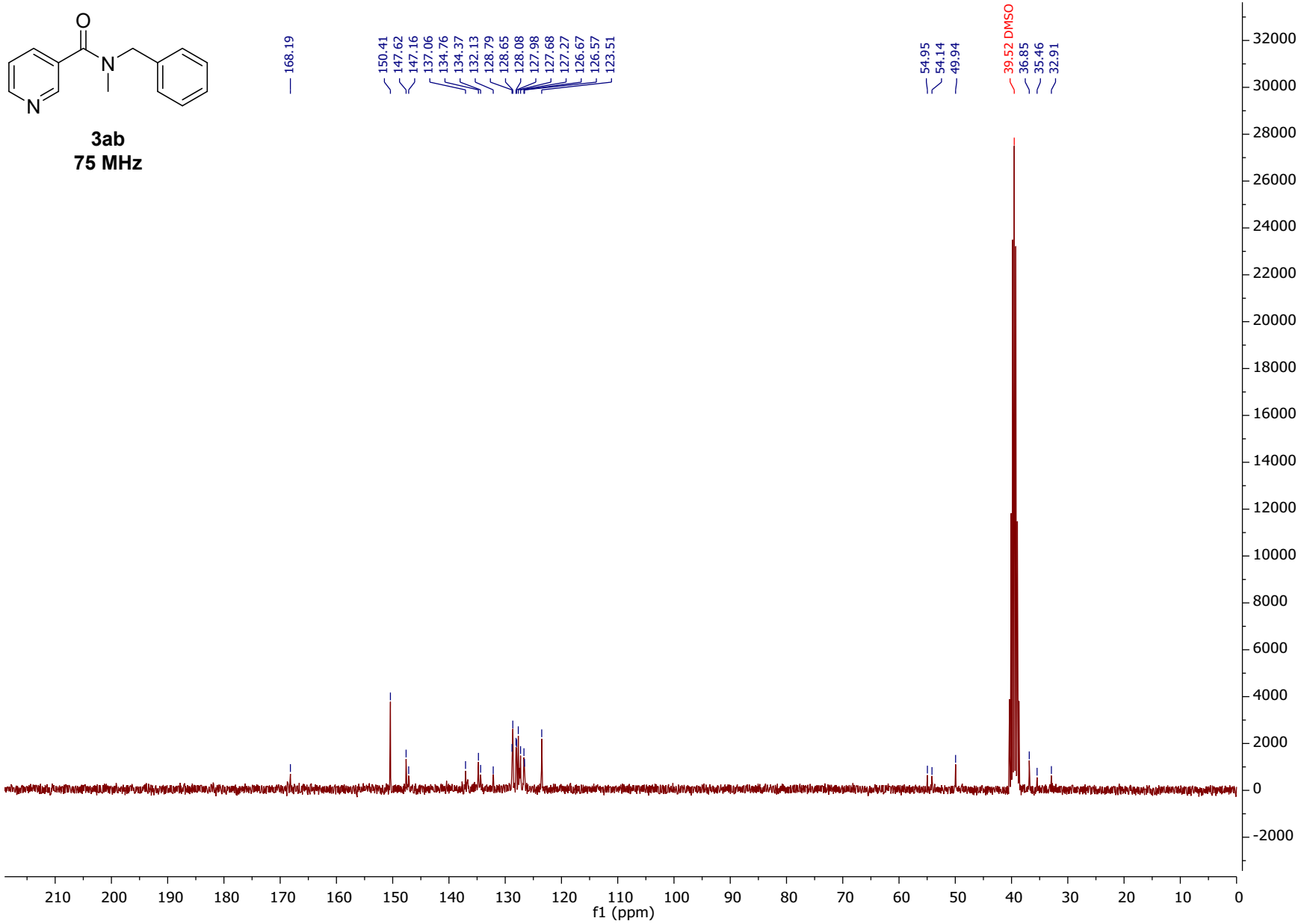
(8) Deuterated Benznidazole. CN108863943A, 2018.

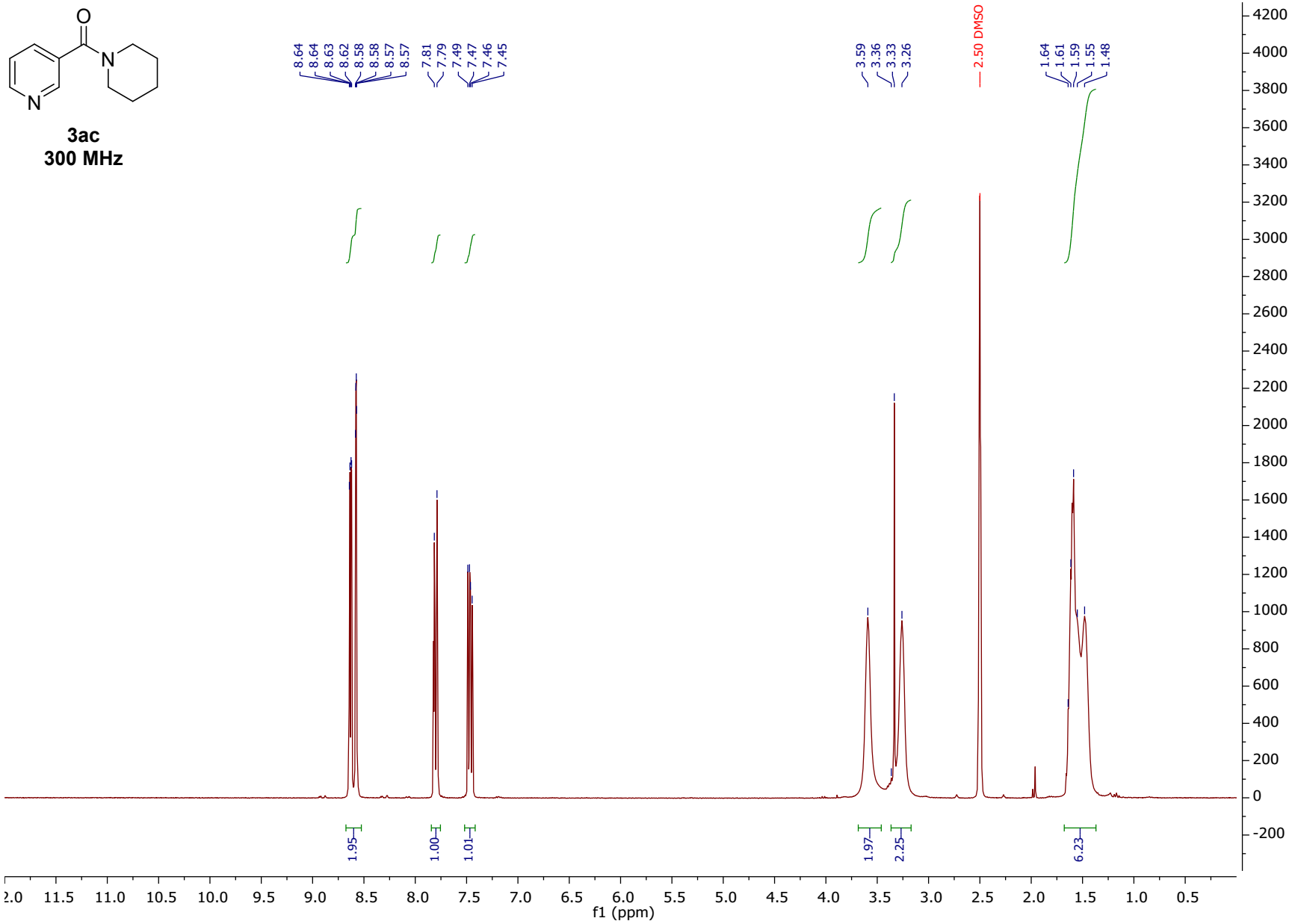
10. NMR Spectra

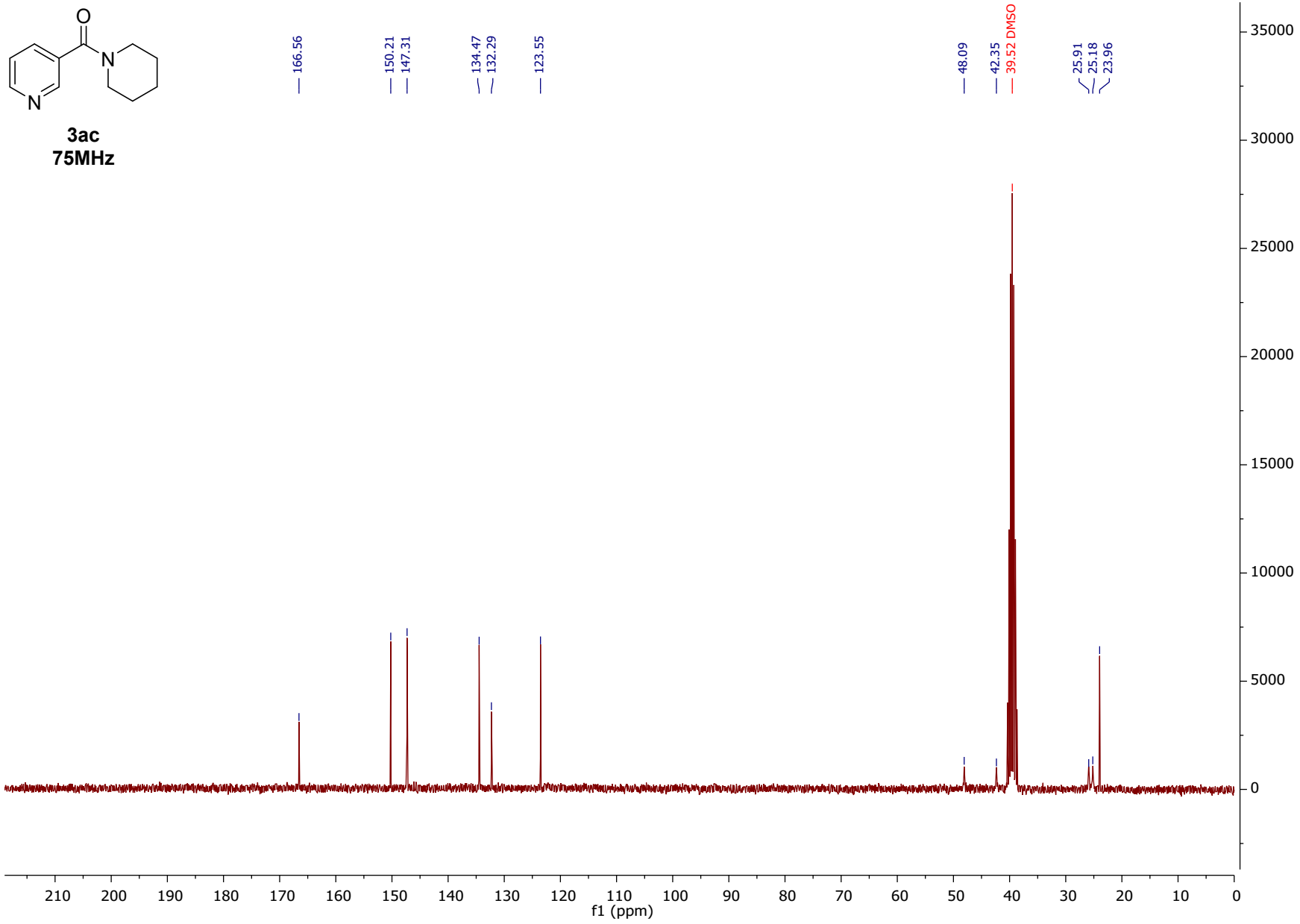


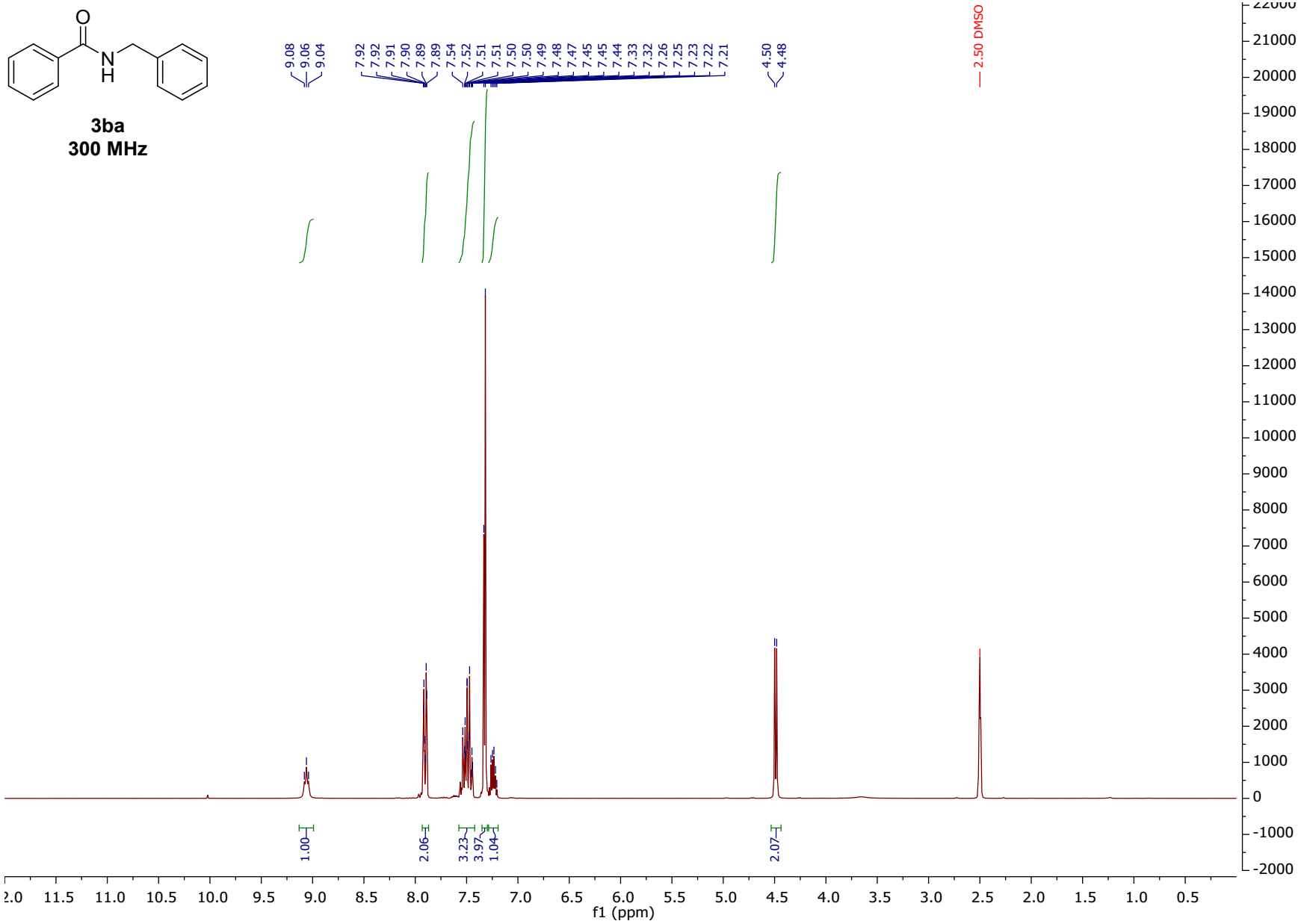

O
N
H
N
3aa
75 MHz
164.81
151.94
148.46
139.31
135.02
129.79
128.35
128.26
127.28
126.86
123.50
42.64
39.52 DMSO
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

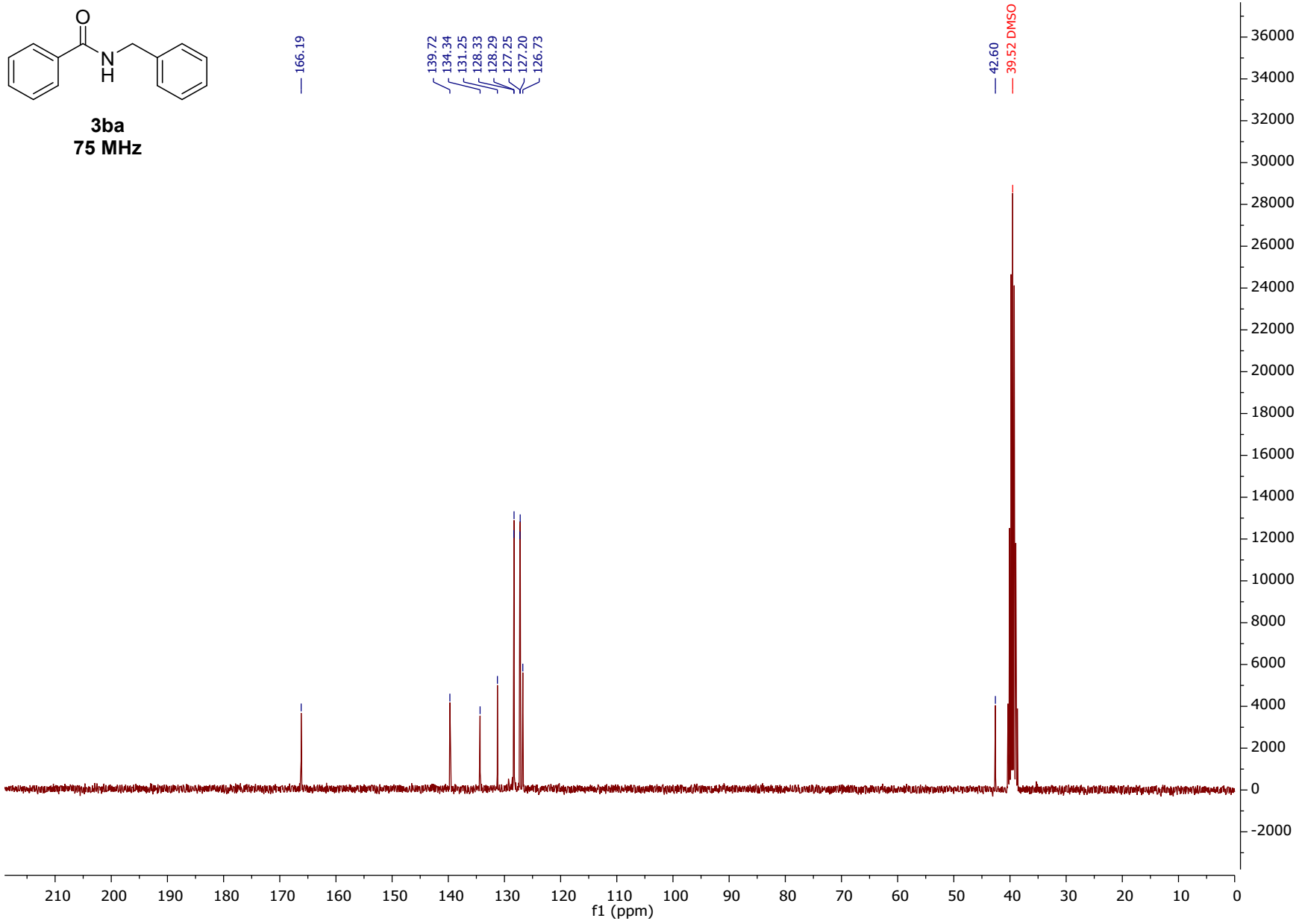

3ab
300 MHz
8.69
8.66
8.65
8.62
7.93
7.91
7.86
7.83
7.48
7.47
7.37
7.31
7.30
7.30
7.29
4.69
4.55
4.48
2.93
2.85
2.50 DMSO
1.96
1.00
6.08
2.09
3.16
f1 (ppm)

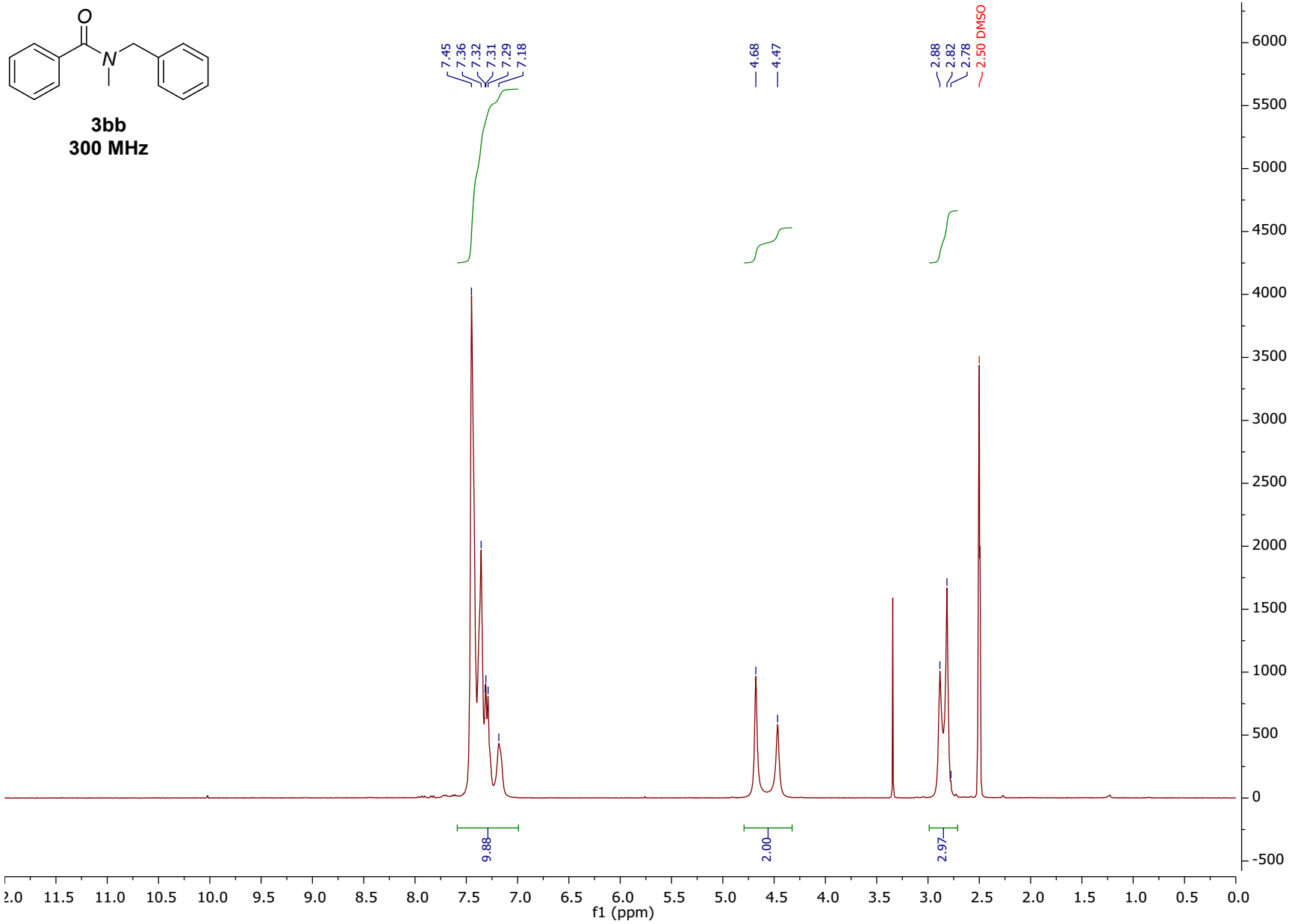

3ab
75 MHz
168.19
150.41
147.62
147.16
137.06
134.76
134.37
132.13
128.79
128.65
128.08
127.98
127.68
127.27
126.67
126.57
123.51
54.95
54.14
49.94
39.52 DMSO
36.85
35.46
32.91
f1 (ppm)

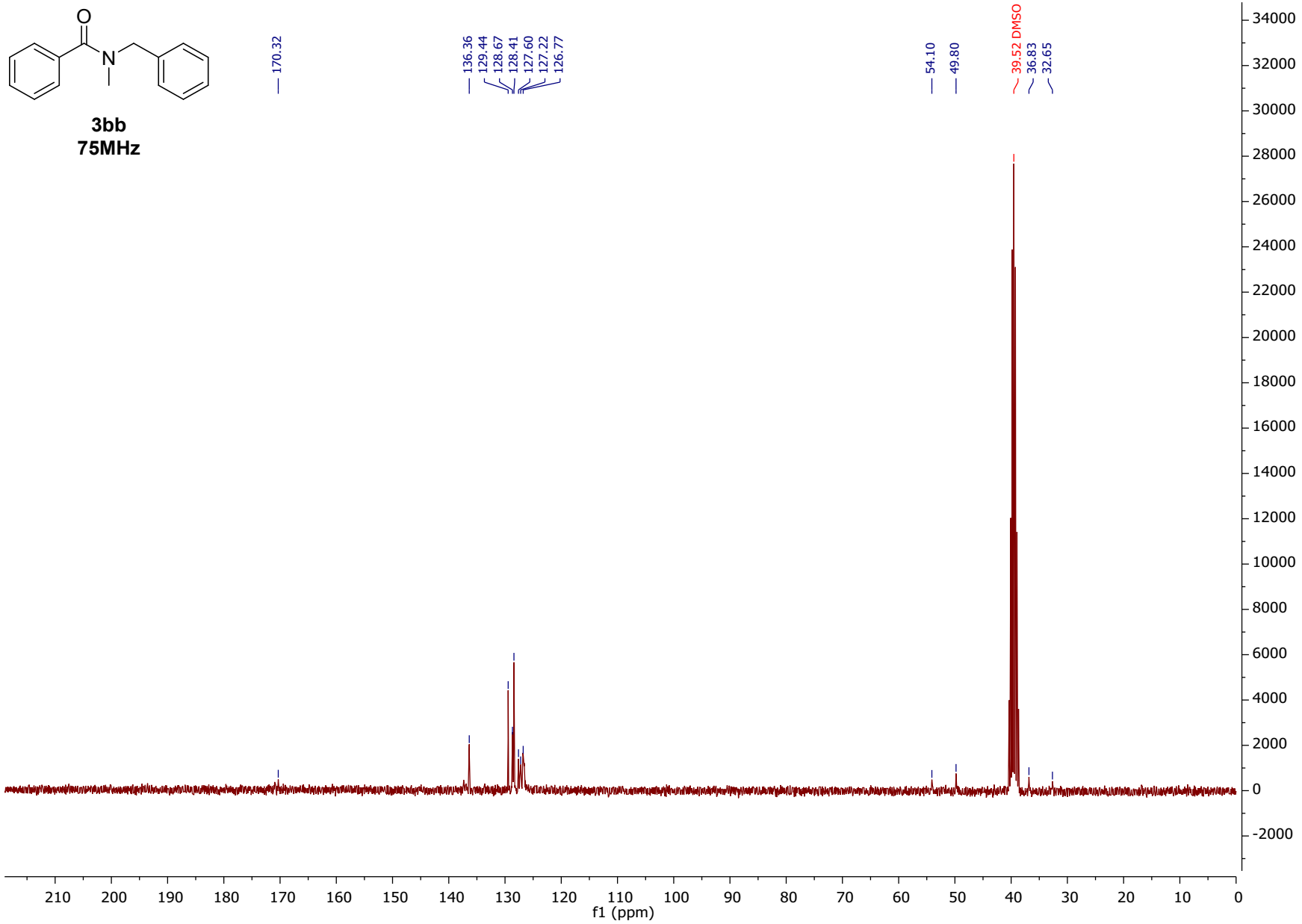

3ac
300 MHz
8.64
8.64
8.63
8.62
8.58
8.58
8.57
8.57
7.81
7.79
7.49
7.47
7.46
7.45
3.59
3.36
3.33
3.26
2.50 DMSO
1.64
1.61
1.59
1.55
1.48
1.95
1.00
1.01
1.97
2.25
6.23
f1 (ppm)

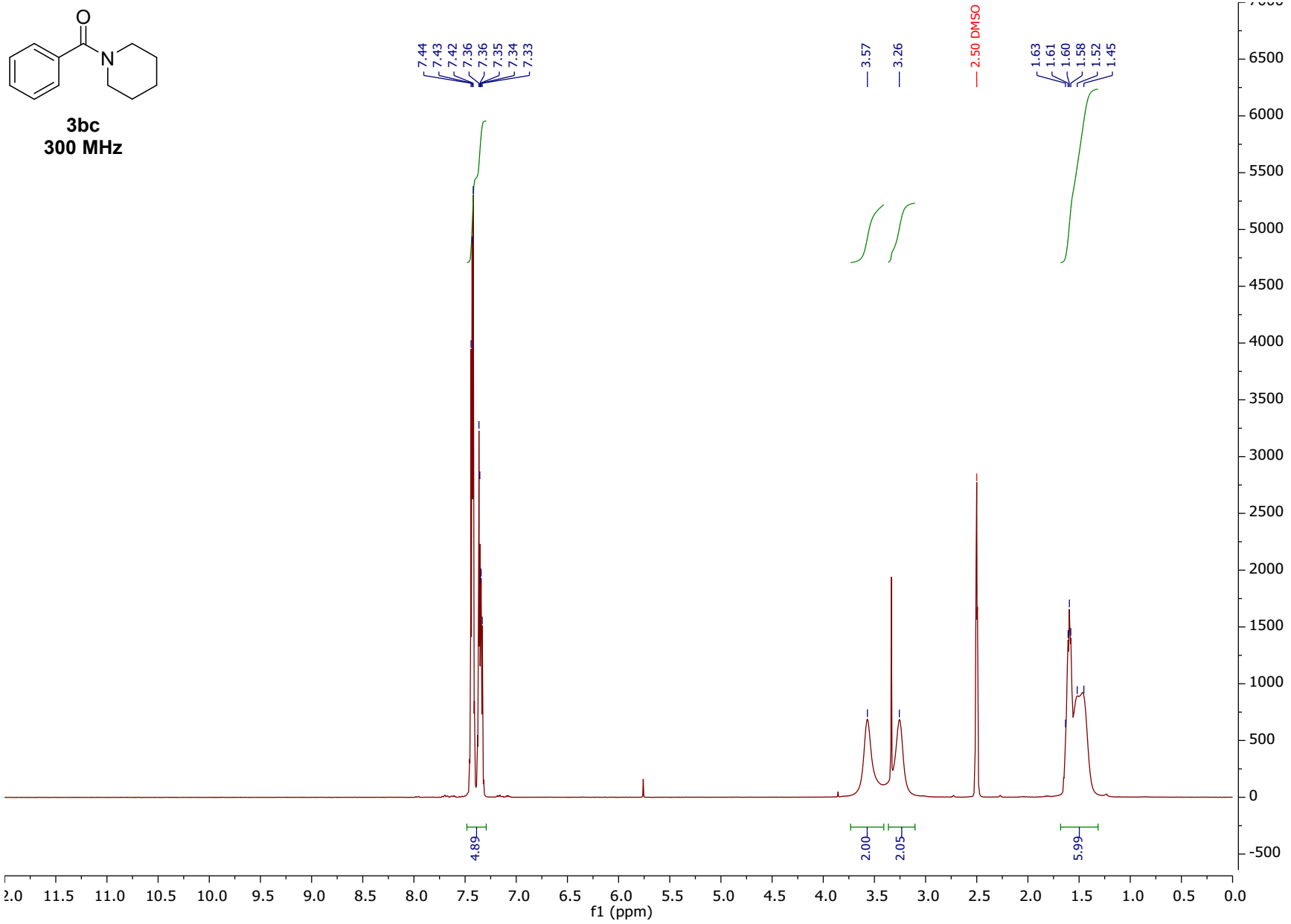

O
N
N
3ac
75MHz
166.56
150.21
147.31
134.47
132.29
123.55
48.09
42.35
39.52 DMSO
25.91
25.18
23.96
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

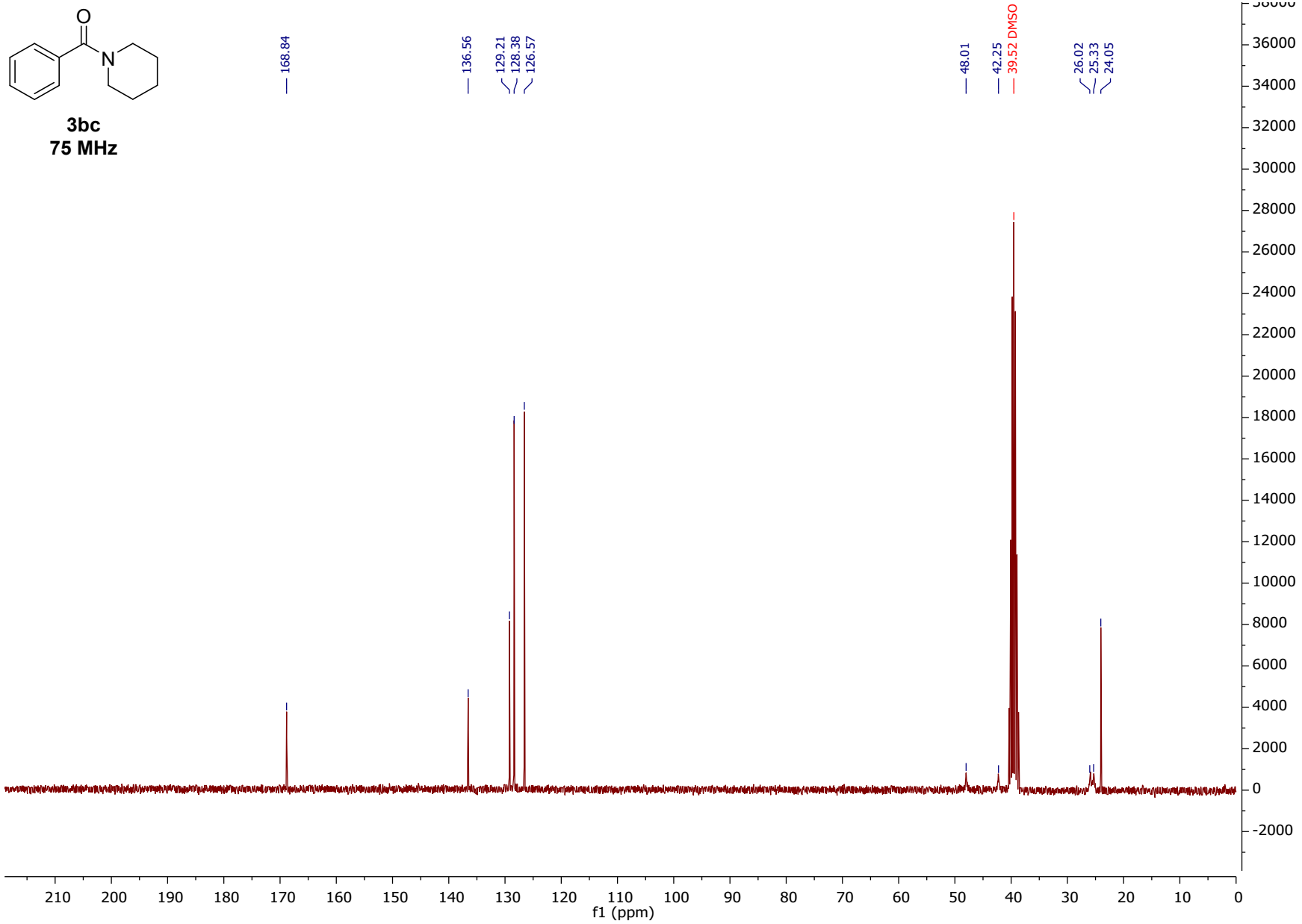

3ba
300 MHz
9.08
9.06
9.04
7.92
7.92
7.91
7.90
7.89
7.89
7.54
7.52
7.51
7.51
7.50
7.50
7.49
7.48
7.47
7.45
7.45
7.44
7.33
7.32
7.26
7.25
7.23
7.22
7.21
4.50
4.48
2.50 DMSO
1.00
2.06
3.23
3.97
1.04
2.07
f1 (ppm)

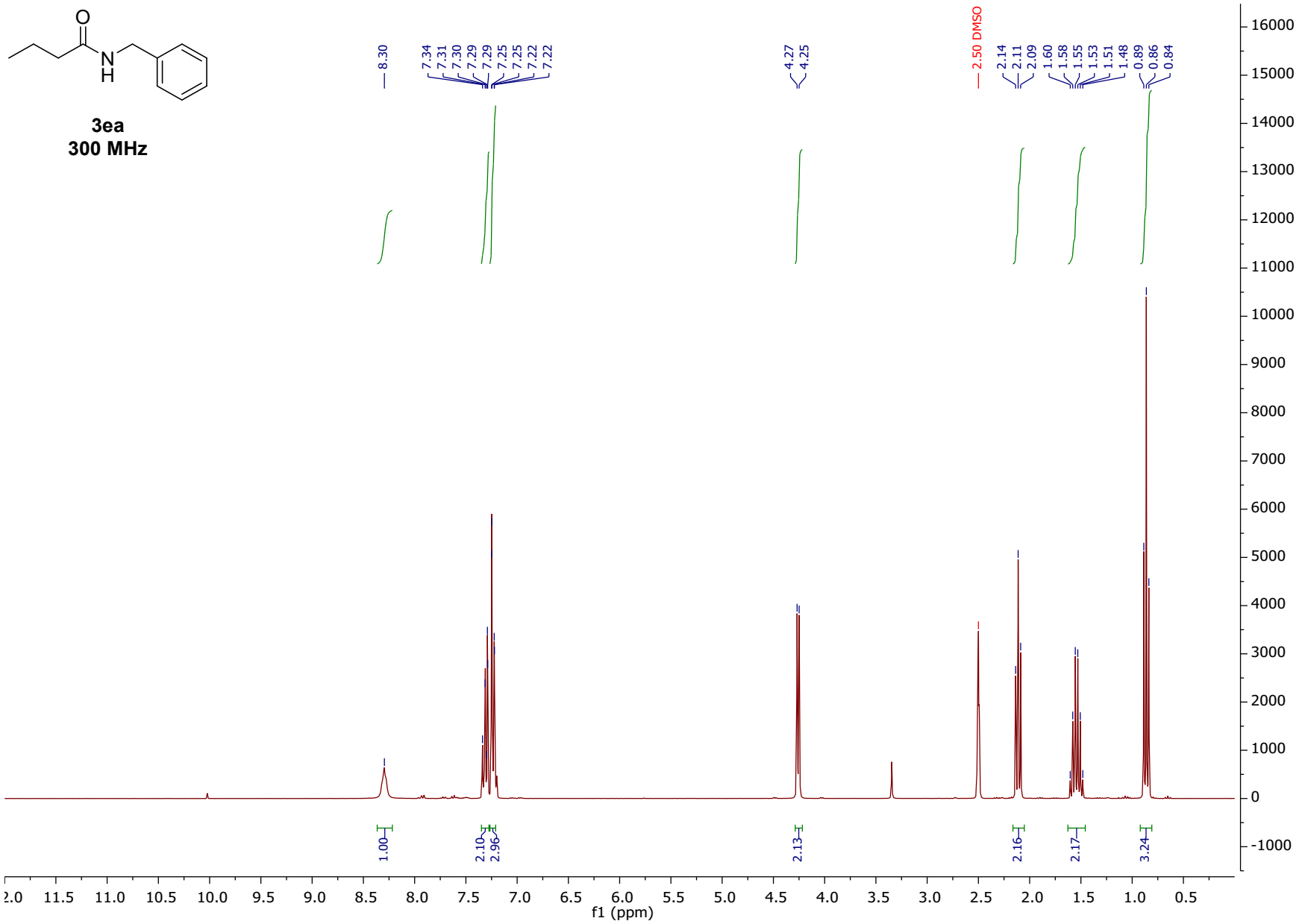

O
N
H
3ba
75 MHz
166.19
139.72
134.34
131.25
128.33
128.29
127.25
127.20
126.73
42.60
39.52 DMSO
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

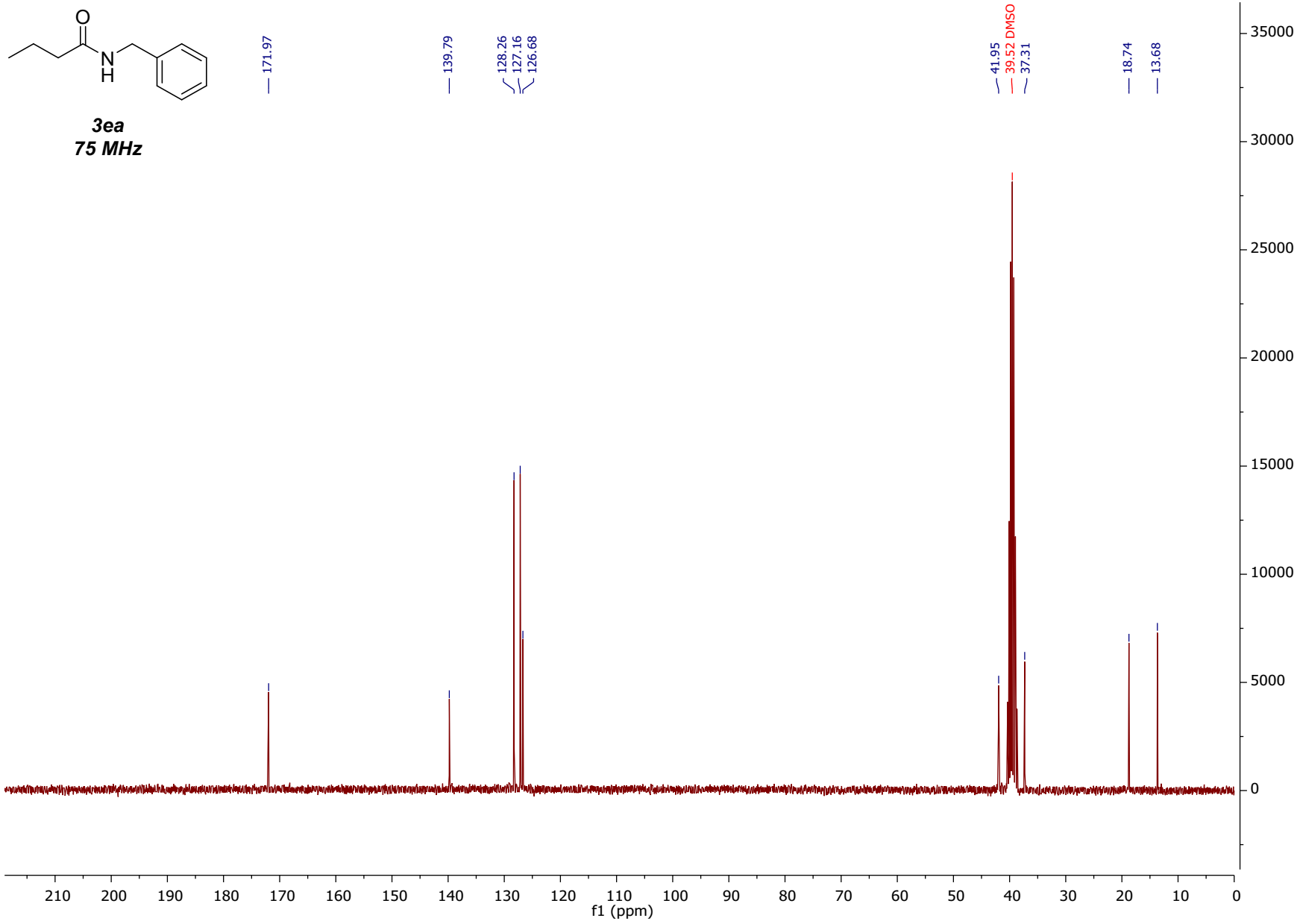

3bb
300 MHz
7.45
7.36
7.32
7.31
7.29
7.18
4.68
4.47
2.88
2.82
2.78
2.50 DMSO
9.88
2.00
2.97
f1 (ppm)

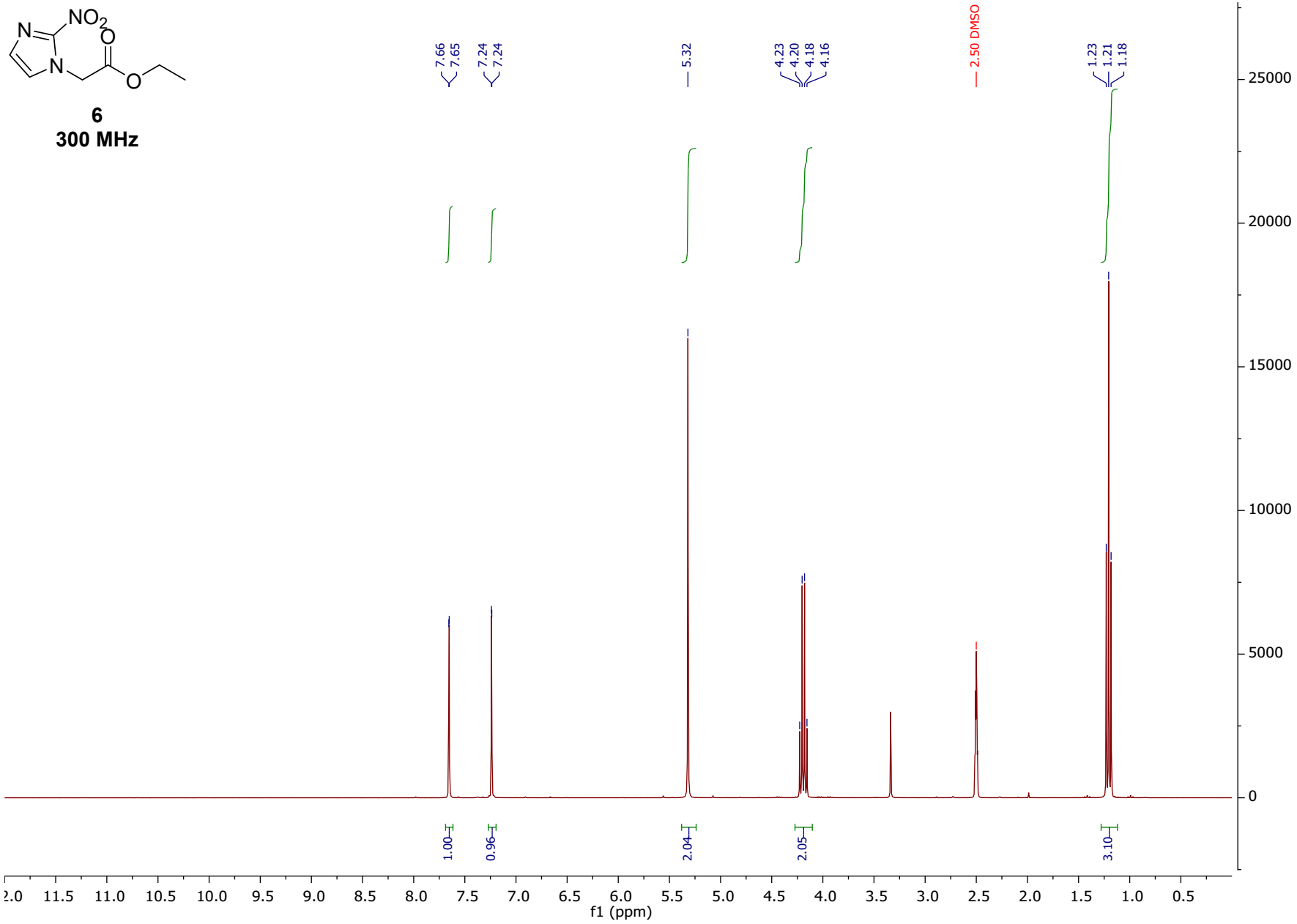

O
N
3bb
75MHz
170.32
136.36
129.44
128.67
128.41
127.60
127.22
126.77
54.10
49.80
39.52 DMSO
36.83
32.65
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

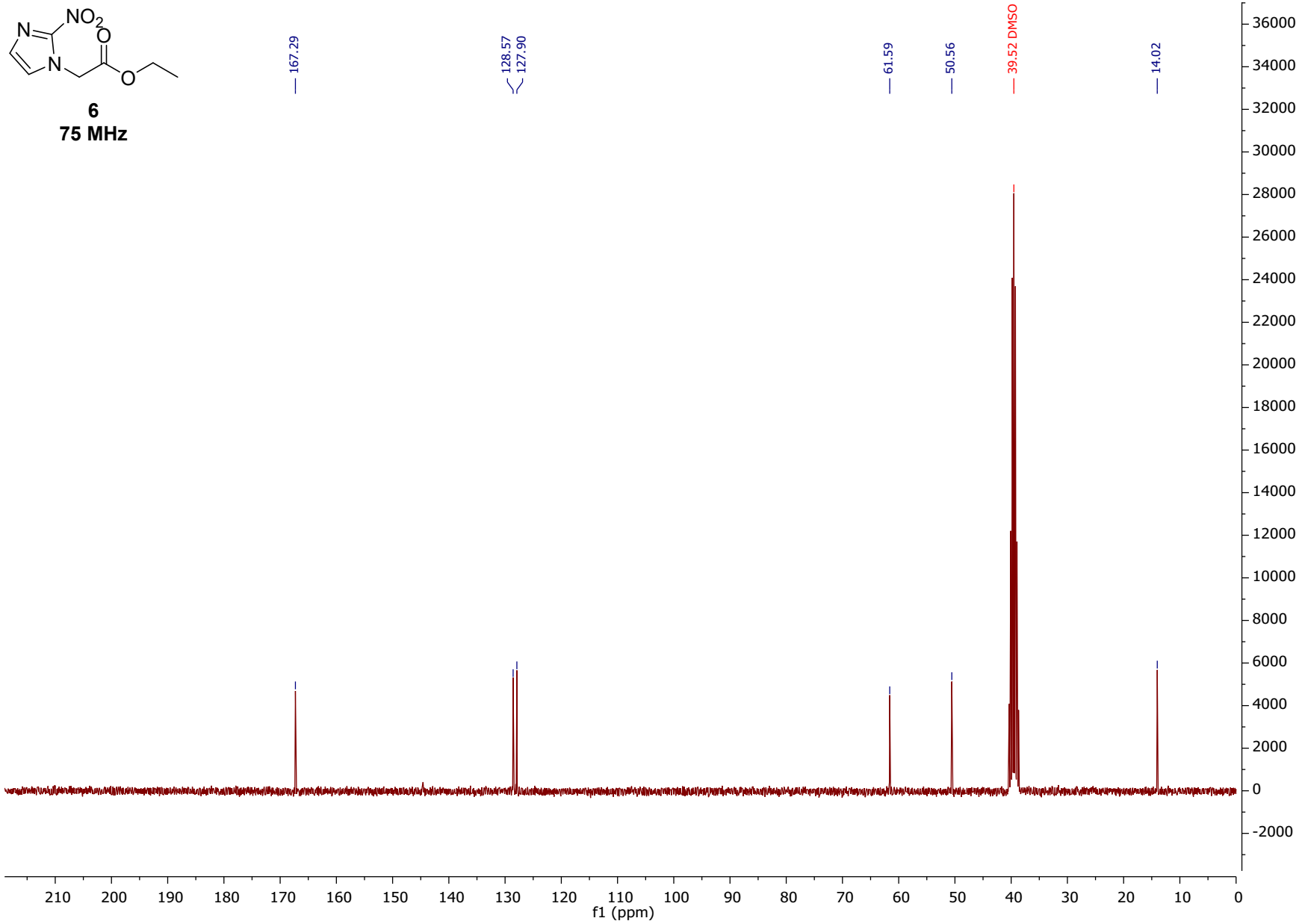

O
N
3bc
300 MHz
7.44
7.43
7.42
7.36
7.36
7.35
7.34
7.33
3.57
3.26
2.50 DMSO
1.63
1.61
1.60
1.58
1.52
1.45
4.89
2.00
2.05
5.99
f1 (ppm)

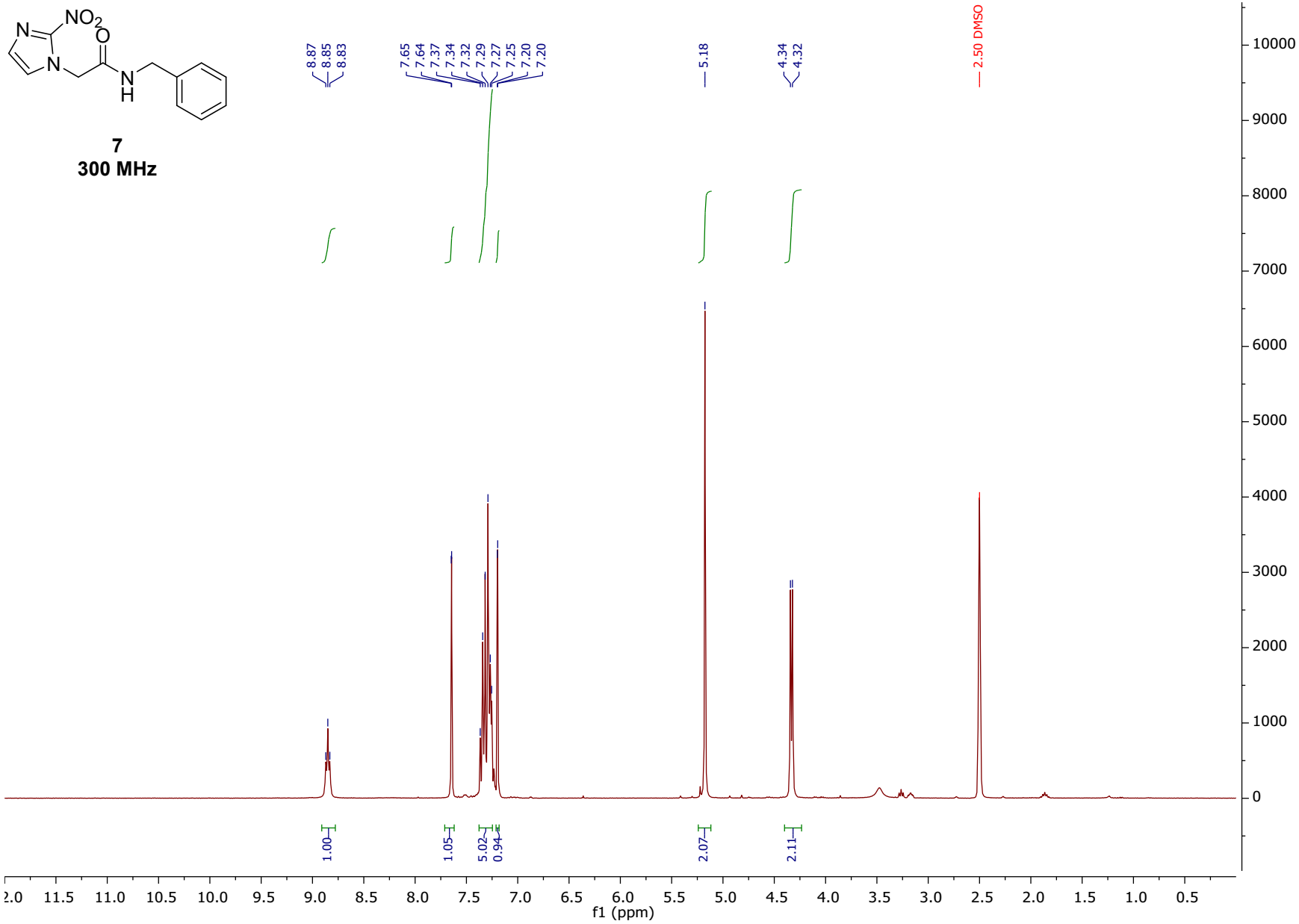

O
N
3bc
75 MHz
168.84
136.56
129.21
128.38
126.57
48.01
42.25
39.52 DMSO
26.02
25.33
24.05
f1 (ppm)

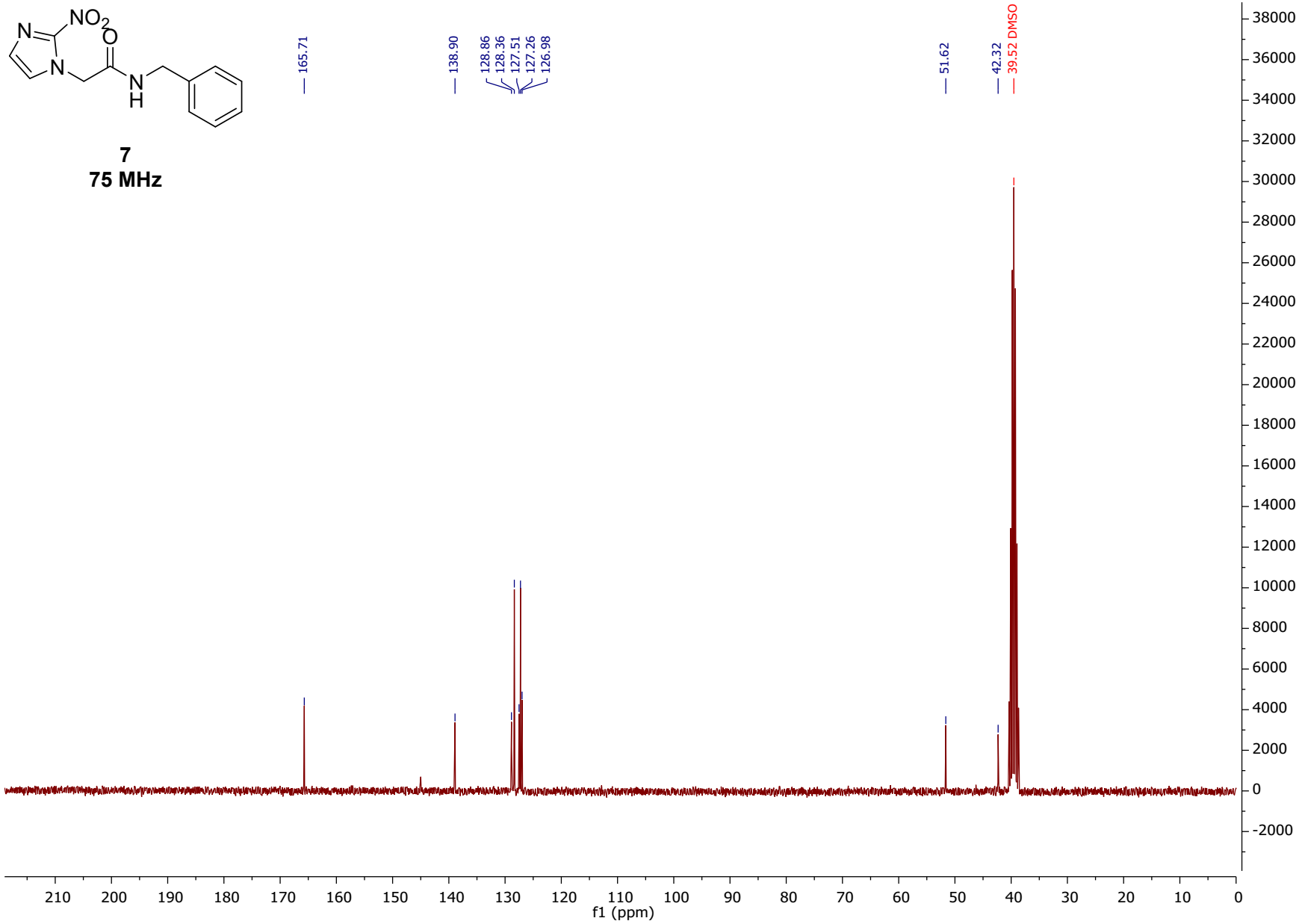

3ea
300 MHz
8.30
7.34
7.31
7.30
7.29
7.29
7.25
7.25
7.22
7.22
4.27
4.25
2.50 DMSO
2.14
2.11
2.09
1.60
1.58
1.55
1.53
1.51
1.48
0.89
0.86
0.84
1.00
2.10
2.96
2.13
2.16
2.17
3.24
f1 (ppm)


O
N
H
3ea
75 MHz
171.97
139.79
128.26
127.16
126.68
41.95
39.52 DMSO
37.31
18.74
13.68
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


NO2
N
O
N
O
6
300 MHz
7.66
7.65
7.24
7.24
5.32
4.23
4.20
4.18
4.16
2.50 DMSO
1.23
1.21
1.18
25000
20000
15000
10000
5000
0
1.00
0.96
2.04
2.05
3.10
f1 (ppm)


NO2
N
O
N
O
6
75 MHz
167.29
128.57
127.90
61.59
50.56
39.52 DMSO
14.02
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


NO2
N
O
N
N
H
7
300 MHz
8.87
8.85
8.83
7.65
7.64
7.37
7.34
7.32
7.29
7.27
7.25
7.20
7.20
5.18
4.34
4.32
2.50 DMSO
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.00
1.05
5.02
0.94
2.07
2.11
f1 (ppm)


NO2
N
O
N
N
H
7
75 MHz
165.71
138.90
128.86
128.36
127.51
127.26
126.98
51.62
42.32
39.52 DMSO
38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)