Supplementary Information (SI) for ChemComm.

Supporting Information

Water-Compatible Acylation Reactions with Acid Chlorides Using a Flow Microreactor

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1. General Remarks

1.1 Materials

Unless otherwise stated, commercially available chemicals were used as received.

1.2 Experimental equipment

1.2.1 NMR spectroscopy

^{1}H NMR (400 MHz) and ^{13}C {^{1}H} NMR (101 MHz) spectra were measured with JEOL JNM-ECZ400S. The ^{1}H NMR chemical shifts are reported relative to tetramethylsilane (0.00 ppm).

1.2.2 Gas chromatography (GC)

GC analysis was performed on a SHIMADZU GC-2025 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, Rtx-200; 0.25 mm x 30 m). GC yield was determined by calibration curve method (internal standard; dodecane).

1.2.3 Flow synthesis

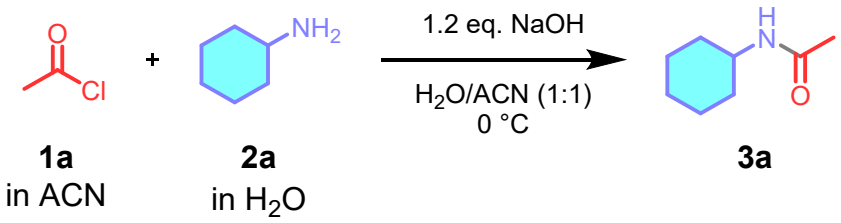
Stainless steel (SUS316) microtube reactors with inner diameter of 1000 μm or 250 μm were purchased from GL Science and were cut into appropriate lengths. Stainless steel (SUS304) T-shaped micromixers with inner diameter of 500 μm or 250 μm made by Sanko Seiki Co., Inc. were used in all experiments. The micromixer and microtube reactors were connected with stainless steel fittings (GL Science, 1/16” OUW). The flow microreactor system was immersed in a cooling water bath to control the temperature with ice. Solutions were introduced to the flow microreactor system using syringe pump, Harvard PHD 2000, equipped with 50 mL gastight syringes purchased from SGE (50MR-LL-GT).

1.2.4 High Resolution Mass Spectroscopy (HRMS)

Electrospray ionization (ESI) mass spectra were obtained using Thermo Scientific Orbitrap Elite at the Instrumental Analysis and Open Facility Unit, Global Research Facility Alliance Center, Office for Integrated Technical Core Hub, Hokkaido University. Field desorption (FD) mass spectra were obtained using JEOL JMS-T2000GCalpha at GC-MS & NMR Laboratory, Research Faculty of Agriculture, Hokkaido University.

2. Experimental procedures

2.1 Batch experiments



Scheme S1. Synthesis of **3a** with a batch-type reactor.

2.1.1 Method a: Adding 1 to 2

To solution of **2** (0.1 M in H_2O; 30.0 mL) and NaOH (3.6 mmol), **1** (0.1 M in ACN; 30.0 mL) was added dropwise at 0 °C and stirred for 3 min at this temperature. The crude mixture was extracted with dichloromethane (50 mL × 3), washed with brine, dried over Na_2SO_4. The crude was evaporated in vacuum and purified by column chromatography (eluent: AcOEt:MeOH = 10:1) to yield by product **3** as a white solid (324.0 mg, 76%).

2.1.2 Method b: Adding 2 to 1

To solution of **1** (0.1 M in ACN; 30.0 mL), **2** (0.1 M in H_2O; 30.0 mL) and NaOH (3.6 mmol) were added dropwise at 0 °C and stirred for 3 min at this temperature. The crude mixture was extracted with dichloromethane (50 mL × 3), washed with brine, dried over Na_2SO_4. The crude was evaporated in vacuum and purified by column chromatography (eluent: AcOEt:MeOH = 10:1) to yield by product **3** as a white solid (50.7 mg, 12%).

2.2 Flow rate screening experiments

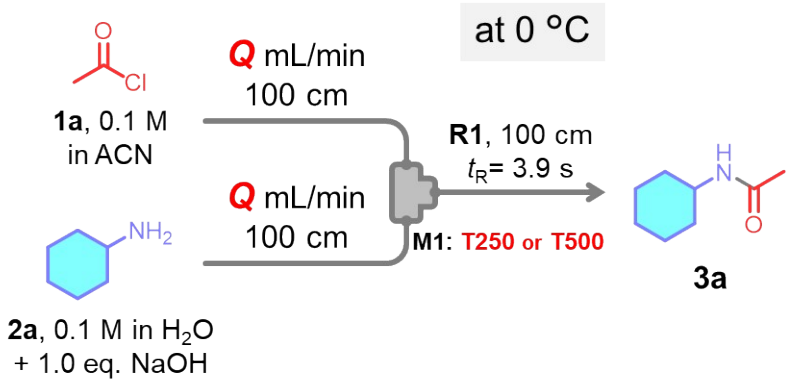


Figure S1. Experimental setup of flow rate screening.

A flow microreactor system consisting of one T-shaped micromixer (**M1**), one microtube reactor (**R1**) and two tube pre-temperature-retaining units ($\varnothing_{I.D.}$: 1000 μm, *L*: 100 cm) were used. The FMR system was immersed in a cooling bath (0 °C). A solution of acetyl chloride **1a** (0.1 M in ACN, *Q* mL/min) and a

solution of cyclohexylamine **2a** (0.1 M in H_2O and 1.0 eq. NaOH, *Q* mL/min) were introduced to **M1** ($\varnothing_{M1}$ 250 μm or 500 μm) by syringe pumps. The resulting solution flowed through **R1** ($\varnothing_{R1}$: 1000 μm, L_{R1} cm, t_{R1} = 3.9 s). After steady state was reached, the product solution was collected for 30 s in a vessel. The collected samples were analyzed by GC and quantified by calibration curve method (internal standard: dodecane).

Table S1. Flow conditions and results of the flow rate screening experiments.

T / °C	$\varnothing_{M1}$ / μm	R1		*Q* / mL min^{-1}	Yield of **3a** / %
		L_1 / cm	t_{R1} / s		
0	250	25	3.9	1.5	56
		50		3	82
		100		6	86
		150		9	85
		200		12	84
	500	25		1.5	61
		50		3	67
		100		6	81
		150		9	80
		200		12	84

2.3 Base screening experiments

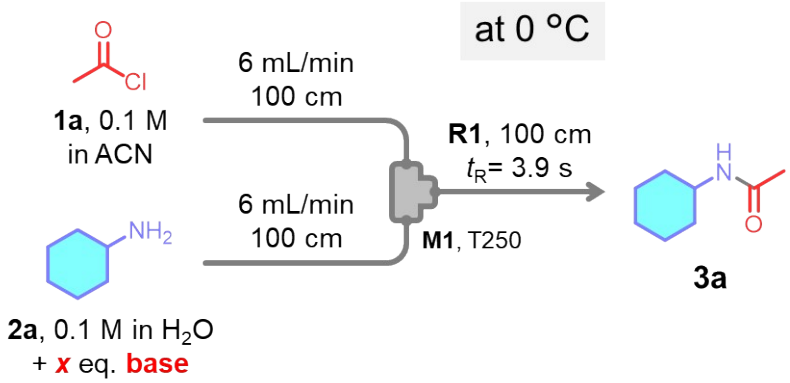


Figure S2. Experimental setup of base screening.

A flow microreactor system consisting of one T-shaped micromixer (**M1**), one microtube reactor (**R1**) and two tube pre-temperature-retaining units ($\varnothing_{I.D.}$: 1000 μm, *L*: 100 cm) were used. The FMR system was immersed in a cooling bath (0 °C). A solution of acetyl chloride **1a** (0.1 M in ACN, 6.0 mL/min) and a solution of cyclohexylamine **2a** (0.1 M in H_2O and *X* eq. base, 6.0 mL/min) were introduced to **M1** ($\varnothing_{M1}$ 250 μm or 500 μm) by syringe pumps. The resulting solution flowed through **R1** ($\varnothing_{R1}$: 1000 μm, 100 cm, t_{R1} = 3.9 s). After steady state was reached, the product solution was collected for 30 s in a vessel. The collected samples were analyzed by GC and quantified by calibration curve method (internal standard: dodecane).

Table S2. Flow conditions and results of the base screening experiments.

T / °C	$\varnothing_{M1}$ / µm	R1		Q / mL min^{-1}	Base	Base eq.	Yield of **3a** / %
		L_1 / cm	t_{R1} / s				
0	250	100	3.9	6	LiOH	1.0	87
					NaOH		86
					KOH		82
					Na_2CO_3		79
					K_2CO_3		80
					Cs_2CO_3		70
					NaOH	0	42
					NaOH	0.2	50
					NaOH	0.5	62
					NaOH	1.2	87
					NaOH	1.5	84
					NaOH	2	83
					NaOH	5	82

2.4 Quenched-flow experiments

2.4.1 Competitive quenching experiment

To verify the quenching step, a competitive quenching experiment was performed with cyclohexylamine **2a** as the target substrate and *n*-propylamine **4** as the quencher. As a result, the formation of **3a** was almost completely suppressed under neat n-propylamine conditions, demonstrating the effectiveness of the quenching process.

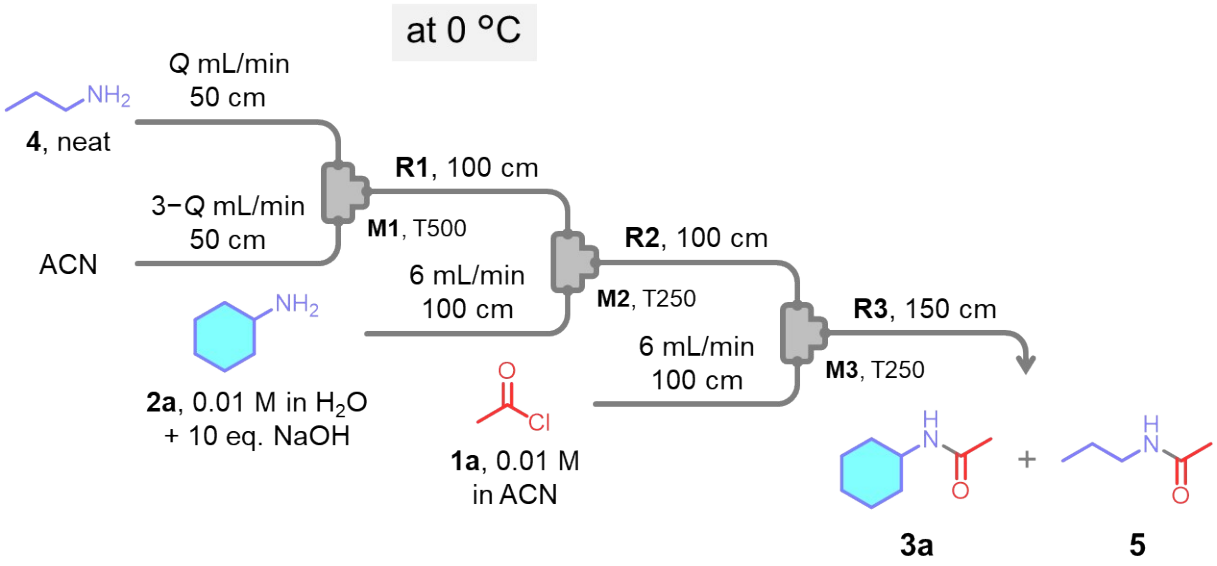
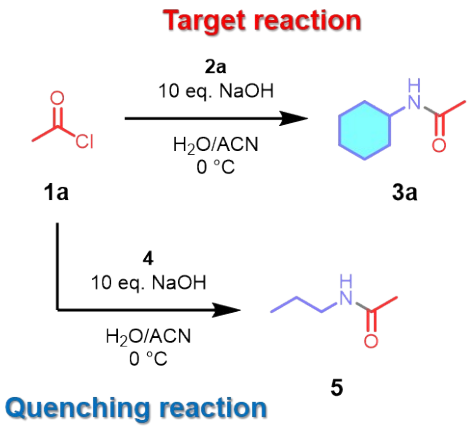


Figure S3. Experimental setup of competitive quenching experiment.



Scheme S2. Target reaction and competitive quenching reaction used for competitive quenching experiments.

A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2**, **M3**), three microtube reactors (**R1**, **R2**, **R3**) and four tube pre-temperature-retaining units ($\varnothing_{I.D.}$: 1000 μm, *L*: 50 or 100 cm) were used. The FMR system was immersed in a cooling bath (0 °C). *n*-Propylamine **4** (*Q* mL/min) and acetonitrile (3−*Q* mL/min) were introduced to **M1** ($\varnothing_{M1}$ 500 μm) by syringe pumps. The resulting solution flowed through **R1** ($\varnothing_{R1}$: 1000 μm, L_1 = 100 cm) and was mixed with a solution of cyclohexylamine **2a** (0.01 M in H_2O and 10 eq. NaOH, 6.0 mL min^{-1}) in **M2** ($\varnothing_{M2}$: 250 μm). The resulting solution flowed through **R2** ($\varnothing_{R2}$: 1000 μm, L_2 = 100 cm) and was mixed with a solution of acetyl chloride **1a** (0.01 M in ACN, 6.0 mL/min) in **M3** ($\varnothing_{M3}$: 250 μm). The resulting solution flowed through **R3** ($\varnothing_{R3}$: 1000 μm, L_3 = 150 cm). After steady state was reached, the product solution was collected for 30 s in a vessel. The collected samples were analyzed by GC and quantified by calibration curve method (internal standard: dodecane).

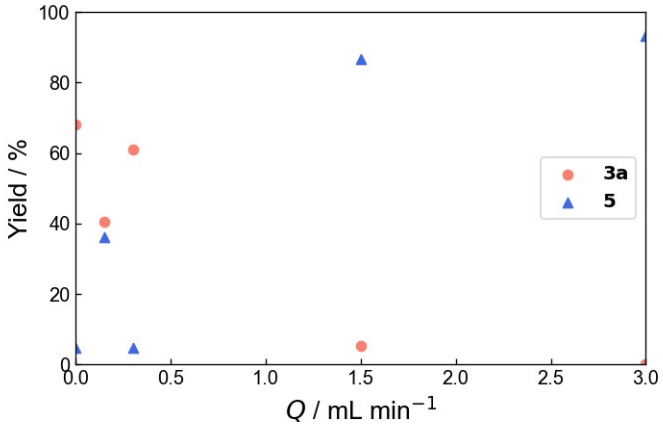


Figure S4. Yields of target product **3a** (red circles) and quenched product **5** (blue triangles) in the competitive quenching experiment at different flow rates (*Q*).

Table S3. Flow conditions and results of the competitive quenching experiments.

T / °C	$\varnothing_{M1}$ / μm	R1		$\varnothing_{M2}$ / μm	R2		$\varnothing_{M3}$ / μm	R3		Q / mL min^{-1}	3–Q / mL min^{-1}	Yield of **3a** / %	Yield of **5** / %
		L_1 / cm	t_{R1} / s		L_2 / cm	t_{R2} / s		L_3 / cm	t_{R3} / s				
0	500	100	15.7	250	100	5.2	250	100	3.1	0	3	68	5
										0.15	2.85	40	36
										0.3	2.7	61	5
										1.5	1.5	5	87
										3	0	0	93

2.4.2 Quenched-flow experiments

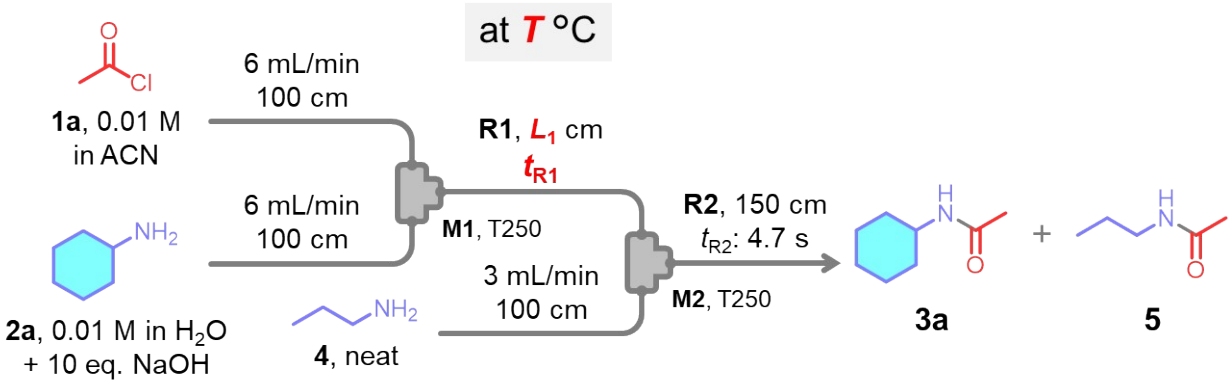


Figure S5. Experimental setup of quenched-flow experiment.

A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), two microtube reactors (**R1**, **R2**) and three tube pre-temperature-retaining units ($\varnothing_{I.D.}$: 1000 μm, *L*: 100 cm) were used. The FMR system was immersed in a cooling bath (*T* °C). A solution of acetyl chloride **1a** (0.01 M in ACN, 6.0 mL/min) and cyclohexylamine **2a** (0.01 M in H_2O and 10 eq. NaOH, 6.0 mL min^{-1}) were introduced to **M1** ($\varnothing_{M1}$ 250 μm) by syringe pumps. The resulting solution flowed through **R1** ($\varnothing_{R1}$, L_1) and was mixed with *n*-propylamine **4** (3.0 mL min^{-1}) in **M2** ($\varnothing_{M2}$: 250 μm). The resulting solution flowed through **R2** ($\varnothing_{R2}$: 1000 μm, L_3 = 150 cm). After steady state was reached, the product solution was collected for 30 s in a vessel. The collected samples were analyzed by GC and quantified by calibration curve method (internal standard: dodecane).

Table S4. Flow conditions and results of the quenched-flow experiment.

T / °C	$\varnothing_{M1}$ / µm	R1			$\varnothing_{M2}$ / µm	R2		Yield of **3a** / %
		$\varnothing_{R1}$ / µm	L_1 / cm	t_{R1} / s		L_2 / cm	t_{R2} / s	
0	250	250	5	0.0123	250	150	4.7	29
			10	0.0245				40
		500	5	0.0491				44
			10	0.0982				58
		1000	5	0.196				61
			10	0.393				62
			30	1.18				67
			50	1.96				66
5	250	250	5	0.0123	250	150	4.7	28
			10	0.0245				36
		500	5	0.0491				42
			10	0.0982				50
		1000	5	0.196				50
			10	0.393				56
			30	1.18				53
			50	1.96				54
10	250	250	5	0.0123	250	150	4.7	26
			10	0.0245				35
		500	5	0.0491				40
			10	0.0982				42
		1000	5	0.196				47
			10	0.393				45
			30	1.18				44
			50	1.96				43
15	250	250	5	0.0123	250	150	4.7	37
			10	0.0245				44
		500	5	0.0491				47
			10	0.0982				51
		1000	5	0.196				54
			10	0.393				50
			30	1.18				49
			50	1.96				48
20	250	250	5	0.0123	250	150	4.7	35
			10	0.0245				39
		500	5	0.0491				44
			10	0.0982				45
		1000	5	0.196				49
			10	0.393				42
			30	1.18				42
			50	1.96				46
25	250	250	5	0.0123	250	150	4.7	33
			10	0.0245				36
		500	5	0.0491				38
			10	0.0982				40
		1000	5	0.196				39
			10	0.393				38
			30	1.18				39
			50	1.96				38

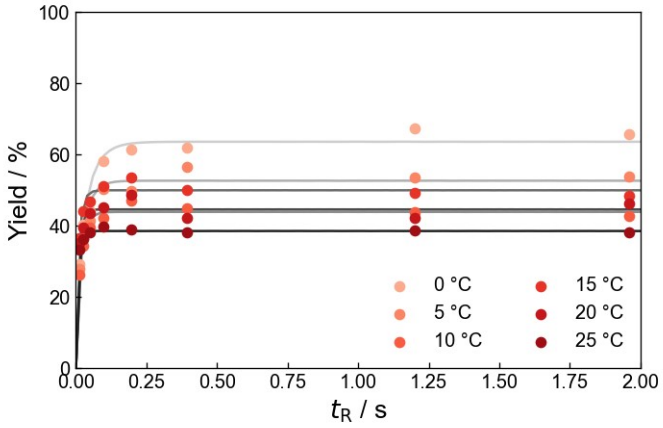


Figure S6. Experimental setup of quenched-flow experiment.

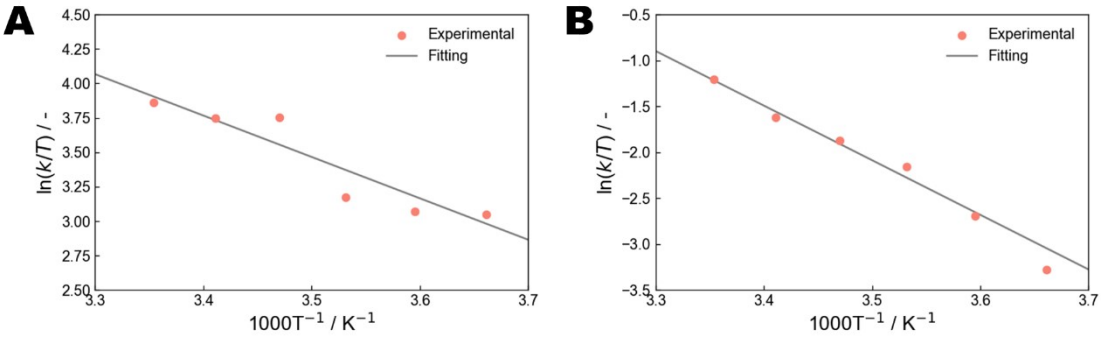


Figure S7. Experimental setup of quenched-flow experiment.

2.5 Synthesis of 3a-t

2.5.1 General methods

2.5.1.1 Method A

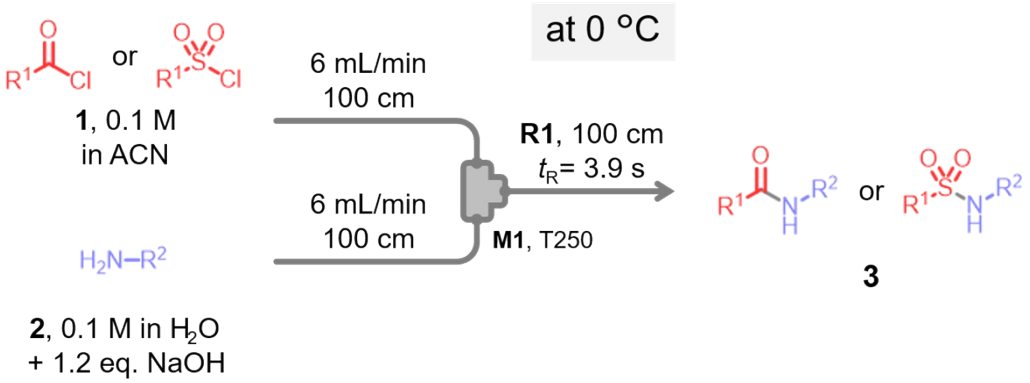


Figure S8. FMR setup of Method A.

A flow microreactor system consisting of one T-shaped micromixer (**M1**), one microtube reactor (**R1**) and two tube pre-temperature-retaining units ($\varnothing_{I.D.}$: 1000 μm, *L*: 100 cm) were used. The FMR system was

immersed in a cooling bath (0 °C). A solution of carboxylic acid chloride or sulfonyl chloride **1** (0.1 M in ACN, 6.0 mL/min) and a solution of amine **2** (0.1 M in H_2O and 1.2 eq. NaOH, 6.0 mL/min) were introduced to **M1** ($\varnothing_{M1}$ 250 μm) by syringe pumps. The resulting solution flowed through **R1** ($\varnothing_{R1}$: 1000 μm, 100 cm, t_{R1} = 3.9 s). After steady state was reached, the product solution was collected for 5 min in a vessel. The crude product was purified by each procedure.

2.5.1.2 Method B

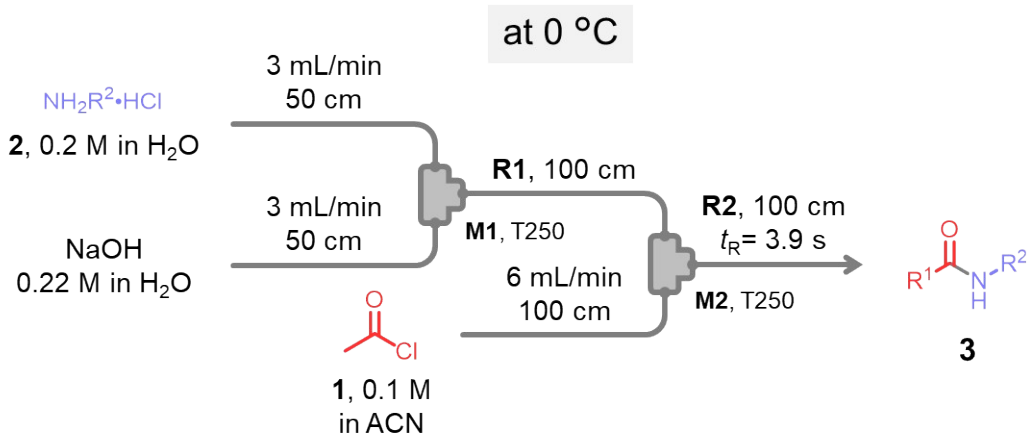


Figure S9. FMR setup of Method B.

A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), two microtube reactors (**R1**, **R2**) and three tube pre-temperature-retaining units ($\varnothing_{I.D.}$: 1000 μm, *L*: 50 or 100 cm) were used. The FMR system was immersed in a cooling bath (0 °C). A solution of amine hydrochloride **2** (0.2 M in H_2O, 3.0 mL/min) and NaOH (0.22 M in H_2O, 3.0 mL min^{-1}) were introduced to **M1** ($\varnothing_{M1}$ 250 μm) by syringe pumps. The resulting solution flowed through **R1** ($\varnothing_{R1}$: 1000 μm, L_1: 100 cm) and was mixed with carboxylic acid chloride **1** (0.1 M in ACN, 6.0 mL min^{-1}) in **M2** ($\varnothing_{M2}$: 250 μm). The resulting solution flowed through **R2** ($\varnothing_{R2}$: 1000 μm, L_3 = 100 cm). After steady state was reached, the product solution was collected for 5 min in a vessel. The crude product was purified by each procedure.

2.5.1.3 Method C

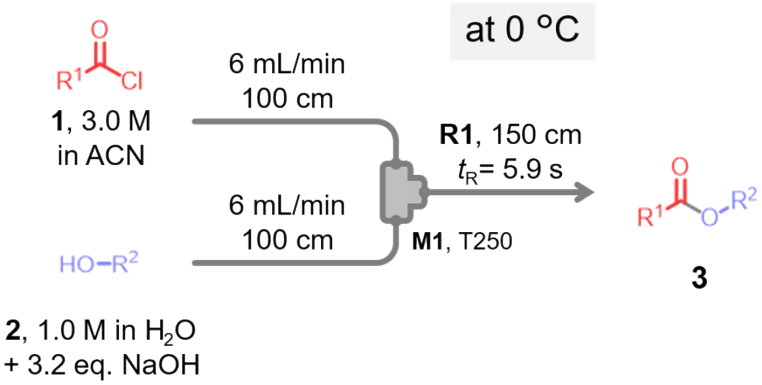
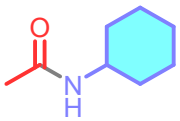


Figure S10. FMR setup of Method C.

A flow microreactor system consisting of one T-shaped micromixer (**M1**), one microtube reactor (**R1**) and two tube pre-temperature-retaining units ($\varnothing_{I.D.}$: 1000 μm, *L*: 100 cm) were used. The FMR system was immersed in a cooling bath (0 °C). A solution of carboxylic acid chloride **1** (3.0 M in ACN, 6.0 mL/min) and a solution of alcohol **2** (1.0 M in H_2O and 3.2 eq. NaOH, 6.0 mL/min) were introduced to **M1** ($\varnothing_{M1}$ 250 μm) by syringe pumps. The resulting solution flowed through **R1** ($\varnothing_{R1}$: 1000 μm, 100 cm, t_{R1} = 3.9 s). After steady state was reached, the product solution was collected for 30 s in a vessel. The crude product was purified by each procedure.

2.5.2 Compound Data

N-Cyclohexylacetamide (**3a**)

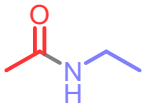


Compound **3a** was synthesized according to method a, b (batch method), and A (flow method). The yields of the flow experiments were determined by GC analysis of the crude reaction mixtures using dodecane as an internal standard.

^{1}H NMR (400 MHz; $CDCl_3$) δ 5.29 (br s, 1H), 3.80-3.71 (m, 1H), 1.95 (s, 3H), 1.94-1.89 (m, 2H), 1.74-1.66 (m, 2H), 1.64-1.62 (m, 1H), 1.41-1.30 (m, 2H), 1.20-1.05 (m, 3H).

The ^{1}H NMR spectrum was consistent with those previously reported.[1]

N-Ethylacetamide (**3b**)

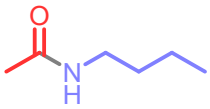


Compound **3b** was synthesized according to method B. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (AcOEt/MeOH = 10:1) to yield **3b** as a colorless oil (108 mg, 41%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 5.46 (s, 1H), 3.29 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.97 (s, 3H), 1.14 (t, *J* = 7.3 Hz, 3H).

The ^{1}H NMR spectrum was consistent with those previously reported.[2]

N-Butylacetamide (**3c**)

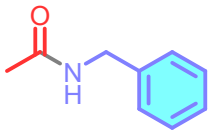


Compound **3c** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (AcOEt/MeOH = 10:1) to yield **3c** as a colorless oil (288 mg, 83%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 5.41 (br s, 1H), 3.25 (td, *J* = 7.2, 5.7 Hz, 2H), 1.98 (s, 3H), 1.50-1.45 (m, 2H), 1.40-1.32 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

The ^{1}H NMR spectrum was consistent with those previously reported.[3]

N-Benzylacetamide (**3d**)

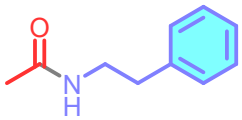


Compound **3d** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (100% AcOEt) to yield **3d** as a white solid (318 mg, 89%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.36-7.28 (m, 5H), 5.69 (br s, 1H), 4.44 (d, *J* = 5.6 Hz, 2H), 2.03 (s, 3H).

The ^{1}H NMR spectrum was consistent with those previously reported.[4]

N-Phenethylacetamide (**3e**)

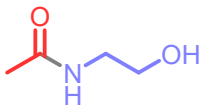


Compound **3e** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (AcOEt/MeOH = 10:1) to yield **3e** as a white solid (442 mg, 90%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.34-7.30 (m, 2H), 7.25-7.19 (m, 3H), 5.46-5.39 (br s, 1H), 3.52 (td, *J* = 6.9, 5.9 Hz, 2H), 2.82 (t, *J* = 6.9 Hz, 2H), 1.94 (s, 3H).

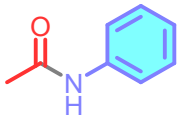
The ^{1}H NMR spectrum was consistent with those previously reported.[5]

N-(2-Hydroxyethyl)acetamide (**3f**)



Compound **3f** was synthesized according to method B. After evaporation of the crude reaction mixture under reduced pressure, $CHCl_3$ was added and the suspension was filtered. The filtrate was again concentrated under reduced pressure. The NMR yield of **3f** was determined by the ^{1}H NMR analysis of the residue in $CDCl_3$ using 1,3,5-trimethoxybenzene as an internal standard. The structure of **3f** was confirmed by comparison of its ^{1}H NMR spectrum with that of an authentic (commercially available) sample.

N-Phenylacetamide (**3g**)

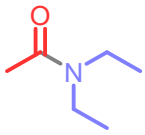


Compound **3g** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (hexane/AcOEt = 1:1) to yield **3g** as a white solid (229 mg, 70%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.23-7.05 (m, 2H), 2.19 (s, 3H).

The ^{1}H NMR spectrum was consistent with those previously reported.[6]

N,*N*-Diethylacetamide (**3h**)

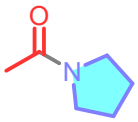


Compound **3h** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (100% AcOEt) to yield **3h** as a pale yellow oil (54.7 mg, 16%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 3.37 (q, *J* = 7.1 Hz, 2H), 3.30 (q, *J* = 7.2 Hz, 2H), 2.08 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H).

The ^{1}H NMR spectrum was consistent with those previously reported.[7]

1-(Pyrrolidin-1-yl)ethan-1-one (**3i**)

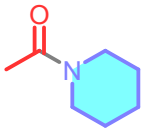


Compound **3i** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (100% AcOEt) to yield **3i** as a pale yellow oil (138 mg, 41%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 3.38-3.49 (m, 4H), 2.06 (s, 3H), 2.00-1.83 (m, 4H).

The ^{1}H NMR spectrum was consistent with those previously reported.[3]

1-(Piperidin-1-yl)ethan-1-one (**3j**)



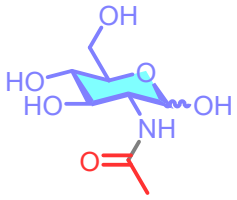
Compound **3j** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (100% AcOEt) to yield **3j** as a pale

yellow oil (259 mg, 68%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 3.54 (t, *J* = 5.5 Hz, 2H), 3.39 (t, *J* = 5.4 Hz, 2H), 2.08 (s, 3H), 1.66-1.62 (m, 2H), 1.59-1.51 (m, 4H, overlapped with the water signal).

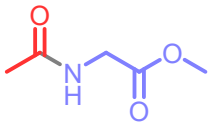
The ^{1}H NMR spectrum was consistent with those previously reported.[8]

N-((3*R*,4*R*,5*S*,6*R*)-2,4,5-Trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3-yl)acetamide (**3k**)



Compound **3k** was synthesized according to method B. The NMR yields were determined by ^{1}H NMR analysis after evaporation of the crude reaction mixtures, with the residue dissolved in D_2O/H_2O using maleic acid as an internal standard (WET solvent suppression). The structure of **3k** was confirmed by comparison of its ^{1}H NMR spectrum with that of an authentic (commercially available) sample.

Methyl acetylglycinate (**3l**)

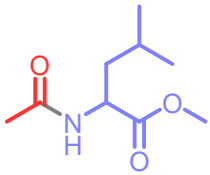


Compound **3l** was synthesized according to method B. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (AcOEt/MeOH = 10:1) to yield **3l** as a colorless oil (174 mg, 44%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 5.96 (br s, 1H), 4.05 (d, *J* = 5.0 Hz, 2H), 3.77 (s, 3H), 2.05 (s, 3H).

The ^{1}H NMR spectrum was consistent with those previously reported.[9]

Methyl acetylleucinate (**3m**)

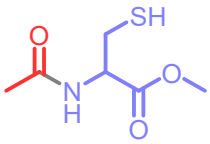


Compound **3m** was synthesized according to method B. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (100% AcOEt) to yield **3m** as a colorless oil (433 mg, 77%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 5.87 (br d, *J* = 7.8 Hz, 1H), 4.64 (td, *J* = 8.7, 5.0 Hz, 1H), 3.73 (s, 3H), 2.02 (s, 3H), 1.67-1.49 (m, 3H), 0.93 (dd, *J* = 6.3, 3.4 Hz, 6H).

The ^{1}H NMR spectrum was consistent with those previously reported.[10]

Methyl acetylcysteinate (**3n**)

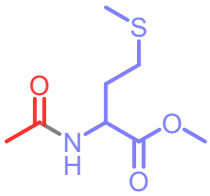


Compound **3n** was synthesized according to method B. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (AcOEt/MeOH = 19:1) to yield **3n** as a white solid (236 mg, 44%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.35 (br s, 1H), 4.90 (dt, *J* = 7.4, 4.0 Hz, 1H), 3.80 (s, 3H), 3.08-2.96 (m, 2H), 2.08 (s, 3H), 1.33 (t, *J* = 9.0 Hz, 1H).

The ^{1}H NMR spectrum was consistent with those previously reported.[11]

Methyl acetylmethioninate (**3o**)

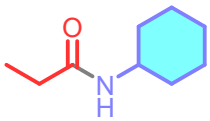


Compound **3o** was synthesized according to method B. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (100% AcOEt) to yield **3o** as a yellow solid (410 mg, 67%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.15-6.14 (br d, 1H), 4.72 (td, *J* = 7.4, 5.2 Hz, 1H), 3.76 (s, 3H), 2.51 (m, 2H), 2.21-2.13 (m, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 2.01-1.94 (m, 1H).

The ^{1}H NMR spectrum was consistent with those previously reported.[12]

N-Cyclohexylpropionamide (**3p**)

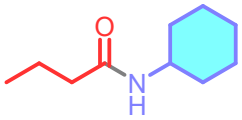


Compound **3p** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (100% AcOEt) to yield **3p** as a white solid (419 mg, 90%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 5.26 (br s, 1H), 3.81-3.72 (m, 1H), 2.17 (q, *J* = 7.6 Hz, 2H), 1.93-1.89 (m,

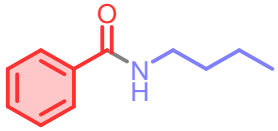
2H), 1.74-1.65 (m, 2H), 1.65-1.57 (m, 1H), 1.42-1.31 (m, 2H), 1.19-1.05 (m, 6H).
The ^{1}H NMR spectrum was consistent with those previously reported.[13]

N-Cyclohexylbutyramide (**3q**)



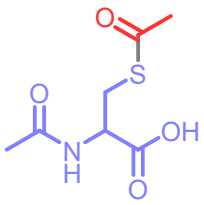
Compound **3q** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (100% AcOEt) to yield **3q** as a white solid (474 mg, 93%).
^{1}H NMR (400 MHz; $CDCl_3$) δ 5.26 (br s, 1H), 3.82-3.73 (m, 1H), 2.11 (t, *J* = 7.5 Hz, 2H), 1.96-1.86 (m, 2H), 1.71-1.60 (m, 5H), 1.42-1.32 (m, 2H), 1.20-1.05 (m, 3H), 0.94 (t, *J* = 7.4 Hz, 3H).
The ^{1}H NMR spectrum was consistent with those previously reported.[14]

N-Cutylbenzamide (**3r**)



Compound **3r** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography (100% AcOEt) to yield **3r** as a colorless oil (524 mg, 98%).
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.77-7.74 (m, 2H), 7.51-7.47 (m, 1H), 7.45-7.41 (m, 2H), 6.08 (br s, 1H), 3.47 (td, *J* = 7.2, 5.8 Hz, 2H), 1.64-1.58 (m, 2H), 1.47-1.38 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).
The ^{1}H NMR spectrum was consistent with those previously reported.[4]

N,*S*-Diacetylcysteine (**3s**)



Compound **3s** was synthesized according to method B. After evaporation of the crude reaction mixture under reduced pressure, MeOH was added and the suspension was filtered. The filtrate was again concentrated under reduced pressure. The NMR yield of **3s** was determined by the ^{1}H NMR analysis of the residue in CD_3OD using 1,3,5-trimethoxybenzene as an internal standard. The structure of **3s** was confirmed by comparison of its ^{1}H NMR spectrum with that of a sample prepared via an independent

route.

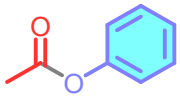
Synthesis of **3s** in batch reactor

N-Acetyl-L-cysteine (1.66 g, 10.2 mmol) was added to a solution of NaOH (0.863 g, 21.6 mmol) in H_2O (10 mL) at 0 °C, followed by the addition of Ac_2O (1.12 g, 10.9 mmol). The mixture was stirred for 30 min at 0 °C. The reaction mixture was acidified to pH 2 with 1M HCl aq. The mixture was extracted with ethyl acetate (4 × 30 mL). The organic layers were combined, dried over $NaSO_4$, filtered, and concentrated under reduced pressure to give **3s** as a white solid (1.36 g, 65%).

^{1}H NMR (400 MHz; CD_3OD) δ 4.58 (dd, *J* = 8.0, 4.6 Hz, 1H), 3.52 (dd, *J* = 13.9, 4.6 Hz, 1H), 3.12 (dd, *J* = 13.9, 8.0 Hz, 1H), 2.33 (s, 3H), 1.96 (s, 3H).

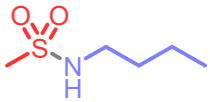
The ^{1}H NMR spectrum was consistent with those previously reported.[15]

Phenyl acetate (**3t**)



Compound **3t** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 4 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The GC yields (80%) were determined by GC analysis of the crude using dodecane as an internal standard.

N-Butylmethanesulfonamide (**3u**)

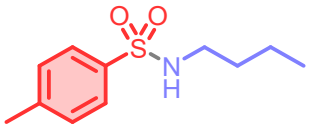


Compound **3u** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum to yield **3u** as a colorless oil (198 mg, 44%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 4.21 (br s, 1H), 3.14 (td, *J* = 7.1, 6.2 Hz, 2H), 2.96 (s, 3H), 1.60-1.53 (m, 2H), 1.39 (qt, *J* = 7.9, 6.9 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

The ^{1}H NMR spectrum was consistent with those previously reported.[16]

N-Butyl-4-methylbenzenesulfonamide (**3v**)



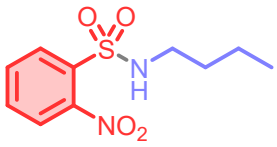
Compound **3v** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated

under vacuum to yield **3v** as a colorless oil (637 mg, 93%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 4.25 (br s, 1H), 2.94 (td, *J* = 7.1, 6.3 Hz, 2H), 2.43 (s, 3H), 1.44 (tt, *J* = 8.0, 6.7 Hz, 2H), 1.29 (qt, *J* = 7.9, 6.8 Hz, 2H), 0.86 (t, *J* = 7.3 Hz, 3H).

The ^{1}H NMR spectrum was consistent with those previously reported.[17]

N-Butyl-2-nitrobenzenesulfonamide (**3w**)



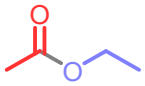
Compound **3w** was synthesized according to method A. The product solution from the flow experiment was extracted with dichloromethane (3 × 50 mL), washed with brine, dried by Na_2SO_4, and concentrated under vacuum to yield **3w** as a colorless oil (750 mg, 97%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.17-8.13 (m, 1H), 7.89-7.85 (m, 1H), 7.76-7.75 (m, 2H), 5.23 (t, *J* = 5.4 Hz, 1H), 3.10 (td, *J* = 7.1, 6.2 Hz, 2H), 1.51 (tt, *J* = 8.0, 6.8 Hz, 2H), 1.33 (tq, J = 8.1, 7.1 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz; $CDCl_3$) δ 147.9, 133.8, 133.3, 132.9, 130.9, 125.3, 43.5, 31.4, 19.5, 13.4.

HR-MS (FD): *m/z* = 258.06725 $[M]^+$ (calcd. 258.06688 for $C_{10}H_{14}N_2O_4S$).

Ethyl acetate (**3x**)



Compound **3x** was synthesized according to method C. The NMR yield was determined by ^{1}H NMR analysis of the crude mixture after extraction with dichloromethane (3 × 4 mL), using 1,3,5-trimethoxybenzene as an internal standard (WET solvent suppression). The structure of **3x** was confirmed by comparison of its ^{1}H NMR spectrum with that of an authentic (commercially available) sample.

3. Continuous synthesis of 7

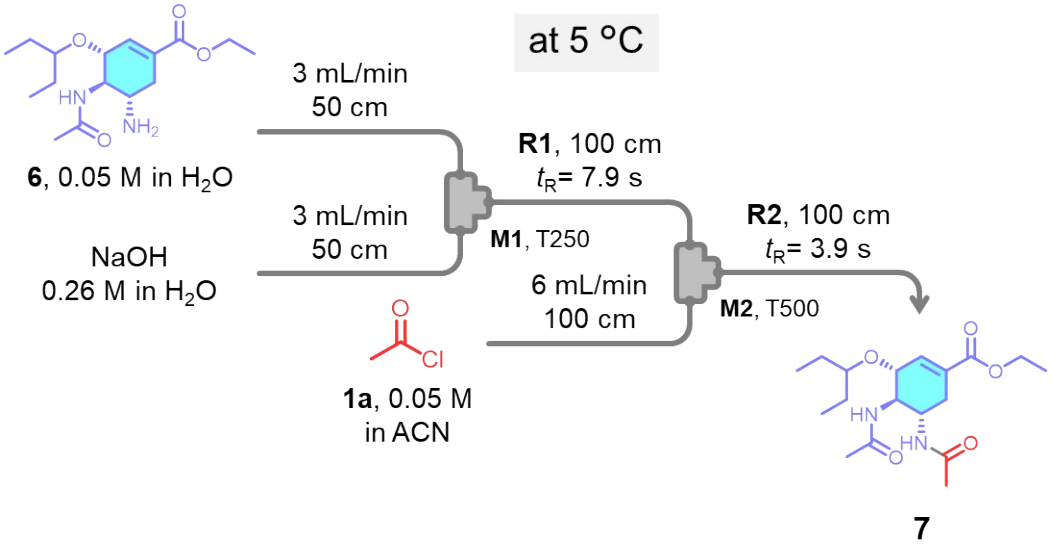
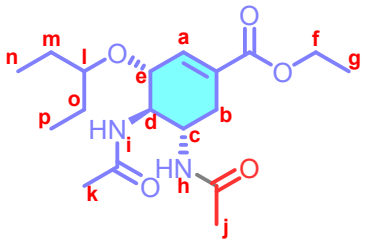


Figure S11. FMR setup of continuous synthesis of **7**.

A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), two microtube reactors (**R1**, **R2**) and three tube pre-temperature-retaining units ($\varnothing_{I.D.}$: 1000 μm, *L*: 50 or 100 cm) were used. The FMR system was immersed in a cooling bath (5 °C). A solution of oseltamivir **6** (0.05 M in H_2O, 3.0 mL/min) and NaOH (0.26 M in H_2O, 3.0 mL min^{-1}) were introduced to **M1** ($\varnothing_{M1}$ 250 μm) by syringe pumps. The resulting solution flowed through **R1** ($\varnothing_{R1}$: 1000 μm, L_1: 100 cm) and was mixed with carboxylic acid chloride **1a** (0.1 M in ACN, 6.0 mL min^{-1}) in **M2** ($\varnothing_{M2}$: 500 μm). The resulting solution flowed through **R2** ($\varnothing_{R2}$: 1000 μm, L_3 = 100 cm). After steady state was reached, the product solution was collected for 3.5 min in a vessel. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine, dried over $NaSO_4$, filtered, and concentrated under reduced pressure to give **7** as a white solid (147.6 mg, 79%).



^{1}H NMR (400 MHz; $CDCl_3$) δ 6.81 (s, 1H, H_a), 6.46 (d, *J* = 7.6 Hz, 1H, H_h), 5.74 (d, *J* = 7.7 Hz, 1H, H_i), 4.24–4.01 (m, 5H, H_c/H_d/H_e/H_f), 3.39 (quintet, *J* = 5.7 Hz, 1H, H_l), 2.77 (dd, *J* = 17.7, 4.6 Hz, 1H, H_b), 2.31 (m, 1H, H_b), 2.00 (s, 3H, H_j or H_k), 1.95 (s, 3H, H_j or H_k), 1.56–1.48 (m, 4H, H_m/H_o), 1.29 (t, *J* = 7.1 Hz, 3H, H_g), 0.90 (m, 6H, H_n/H_p).

^{13}C NMR (101 MHz; $CDCl_3$) δ 171.50, 170.73, 166.09, 137.58, 129.37, 82.30, 75.47, 61.09, 54.19, 48.56, 30.52, 26.31, 25.80, 23.33, 14.29, 9.65, 9.36.

HR-MS (ESI): *m/z* = 377.20587 $[M+Na]^+$ (calcd. 377.20469 for $C_{18}H_{30}N_2O_5Na$).

4. NMR spectra

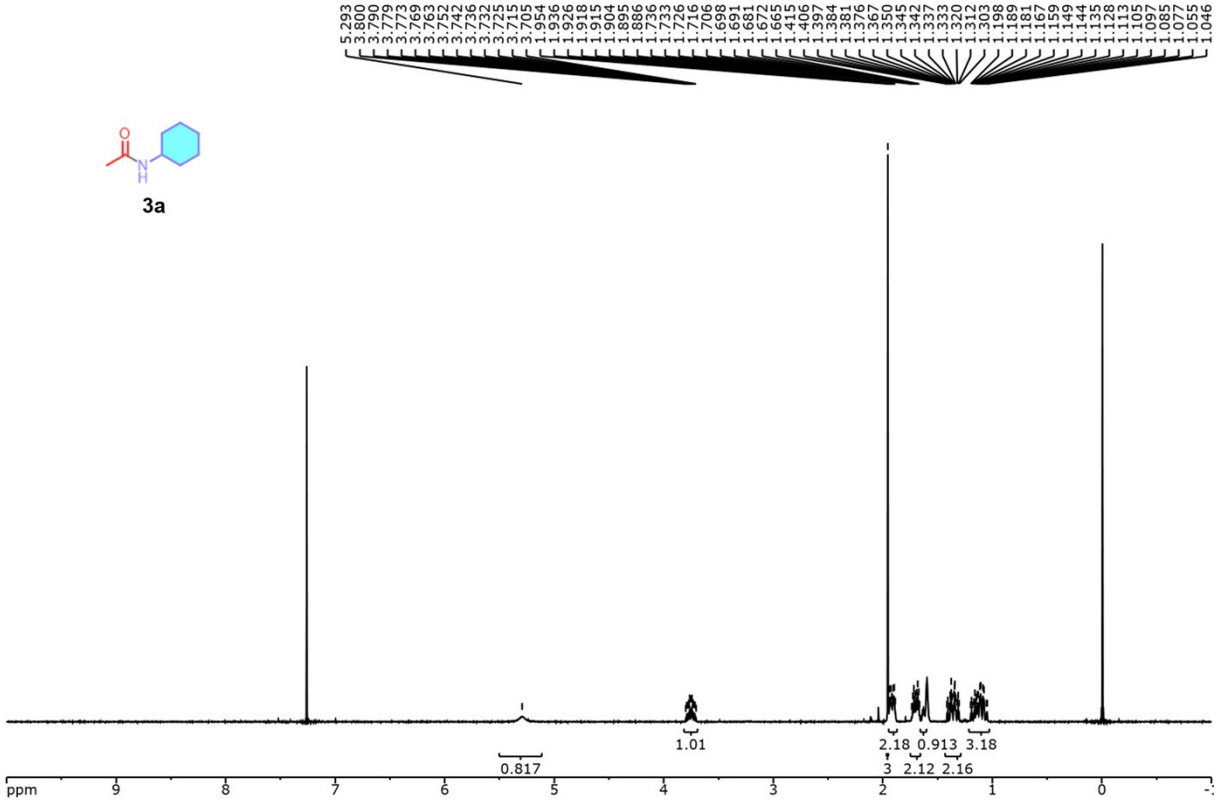


Figure S12. ^{1}H NMR spectrum of **3a** (400 MHz, $CDCl_3$).

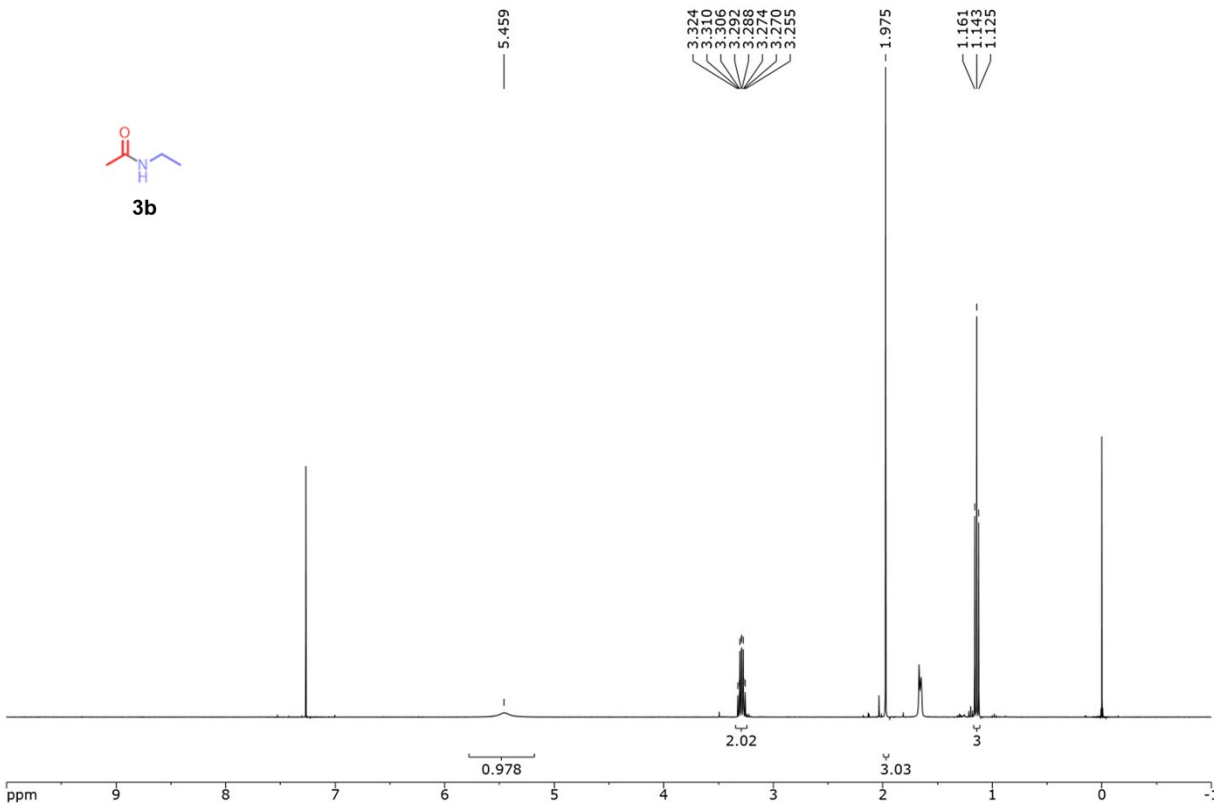


Figure S13. ^{1}H NMR spectrum of **3b** (400 MHz, $CDCl_3$).

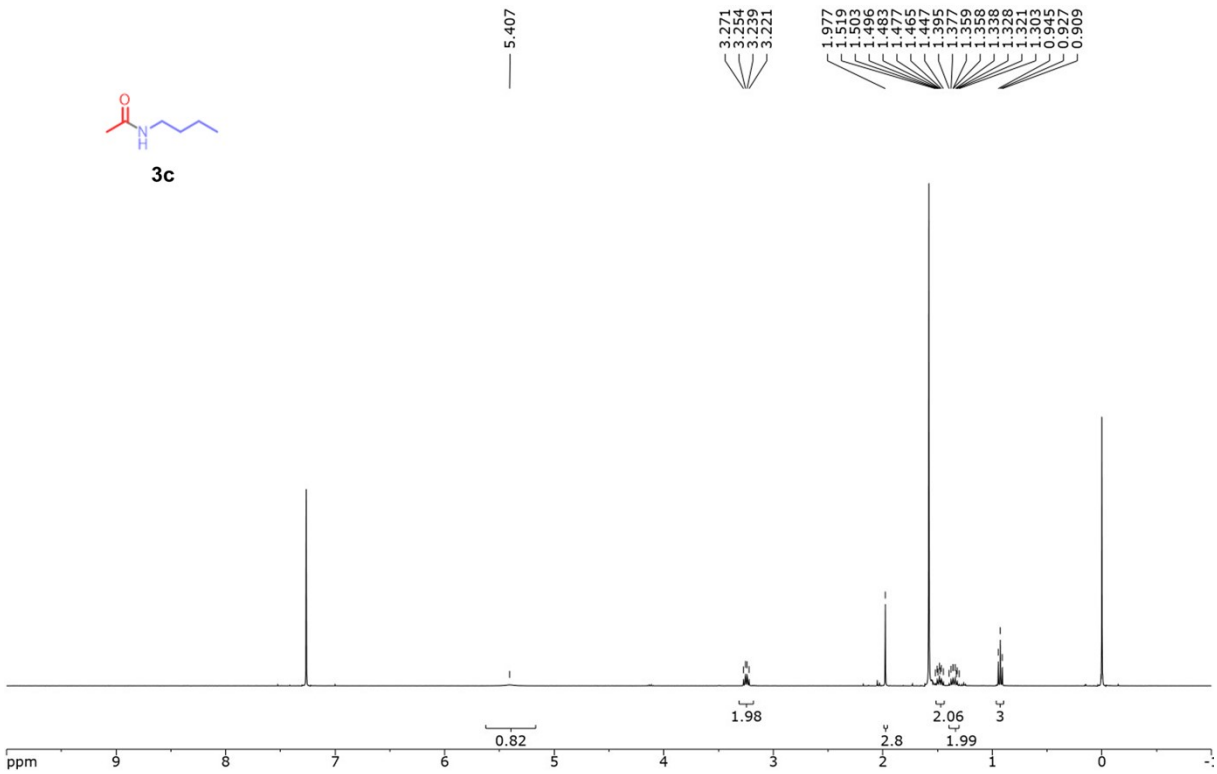


Figure S14. ^{1}H NMR spectrum of **3c** (400 MHz, $CDCl_3$).

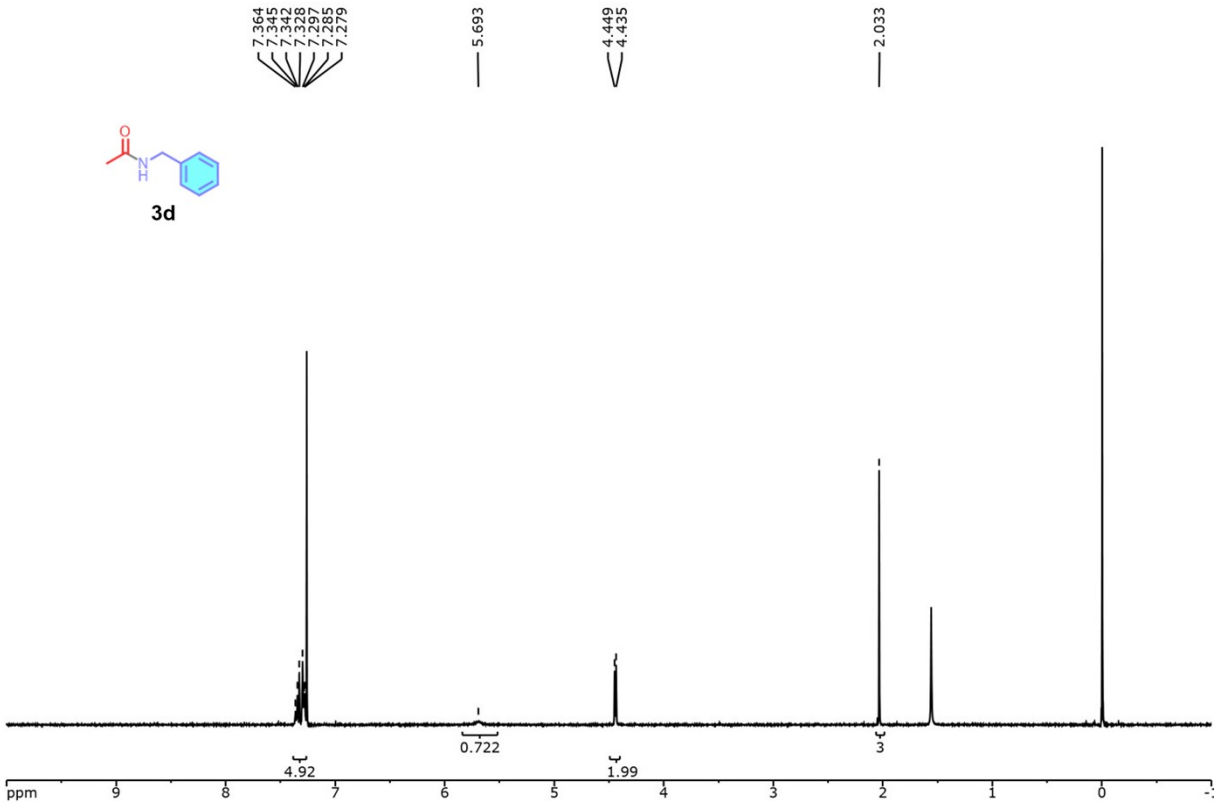


Figure S15. ^{1}H NMR spectrum of **3d** (400 MHz, $CDCl_3$).

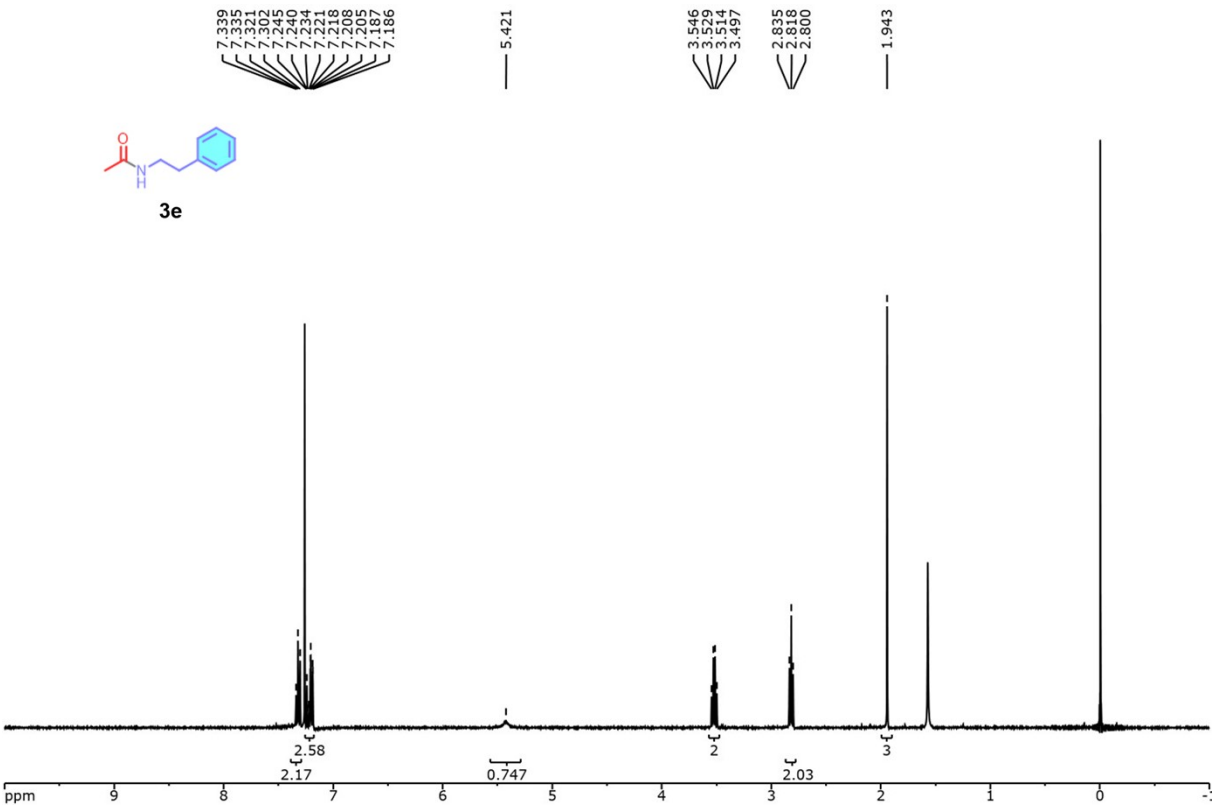


Figure S16. ^{1}H NMR spectrum of **3e** (400 MHz, $CDCl_3$).

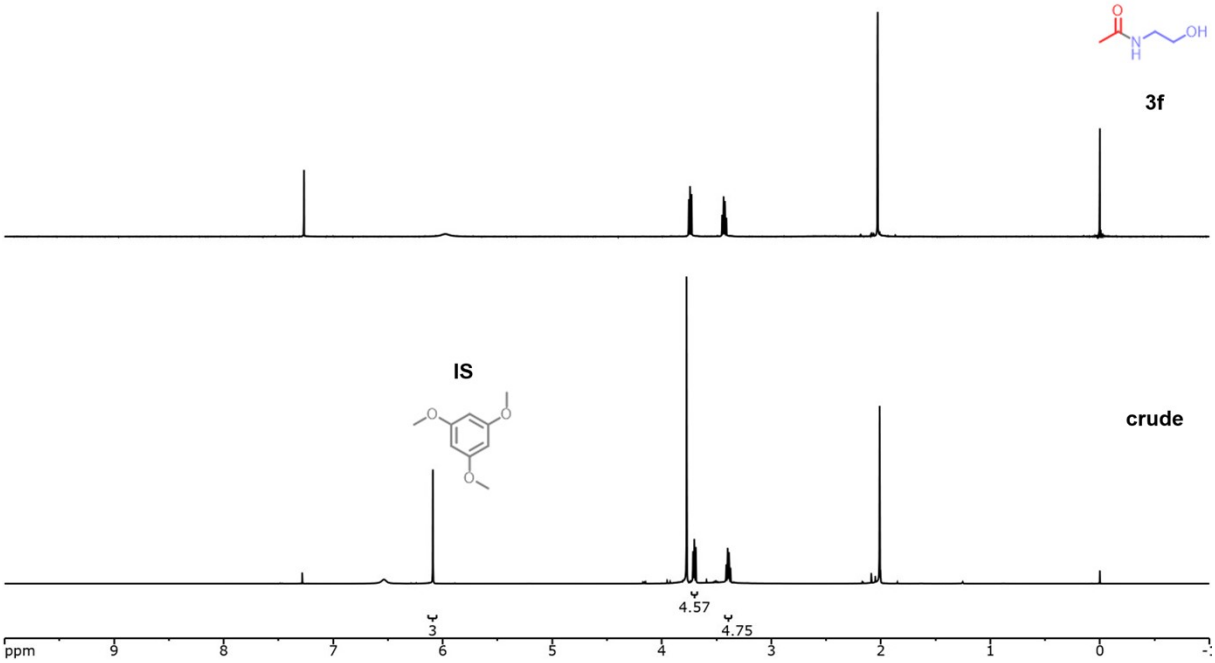


Figure S17. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of the crude of the flow synthesis of compound **3f** (bottom) and the authentic sample (top). The yield was determined using 1,3,5-trimethoxybenzene as an internal standard.

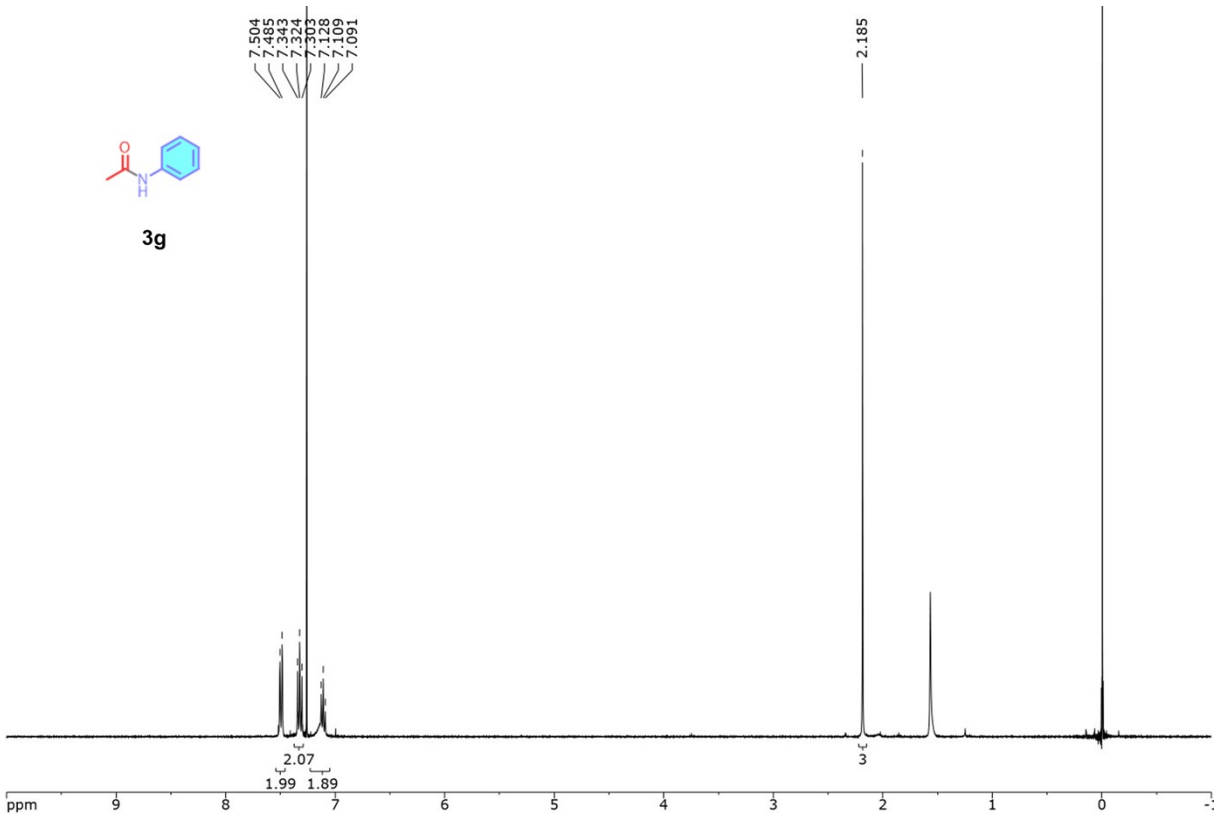


Figure S18. ^{1}H NMR spectrum of **3g** (400 MHz, $CDCl_3$).

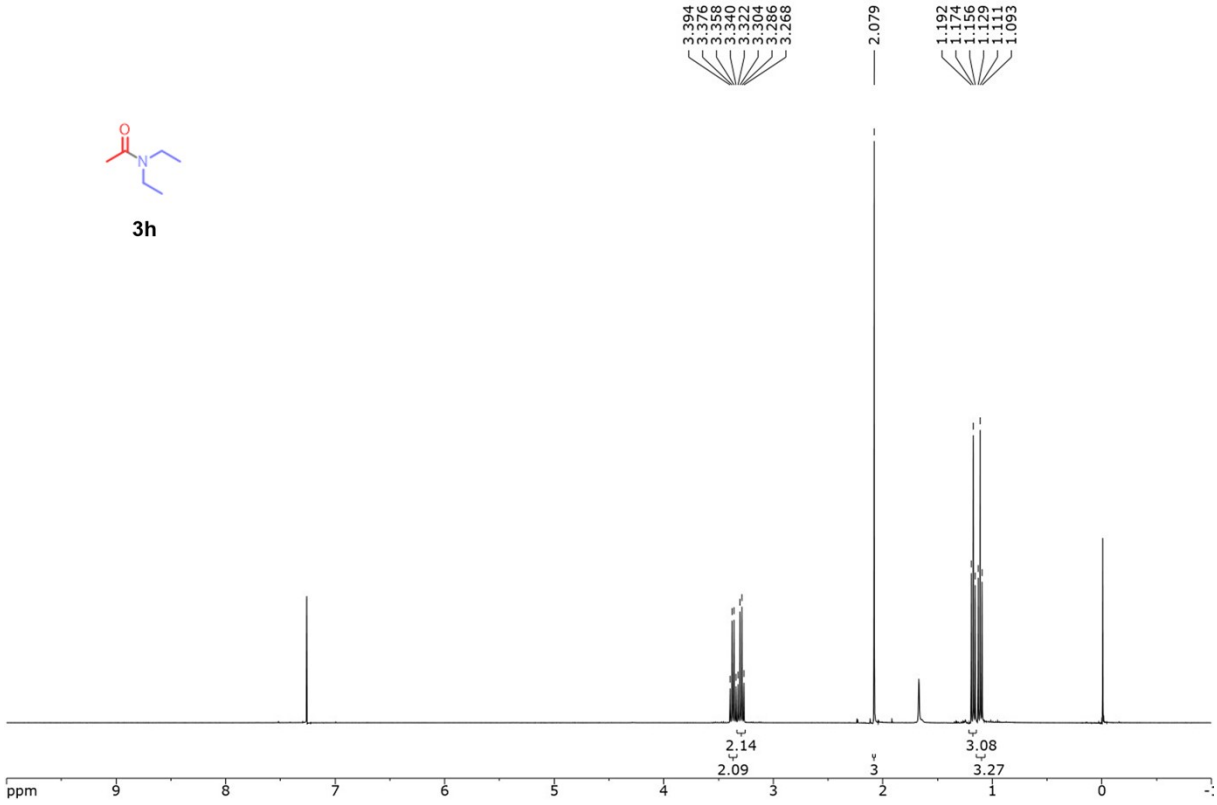


Figure S19. ^{1}H NMR spectrum of **3h** (400 MHz, $CDCl_3$).

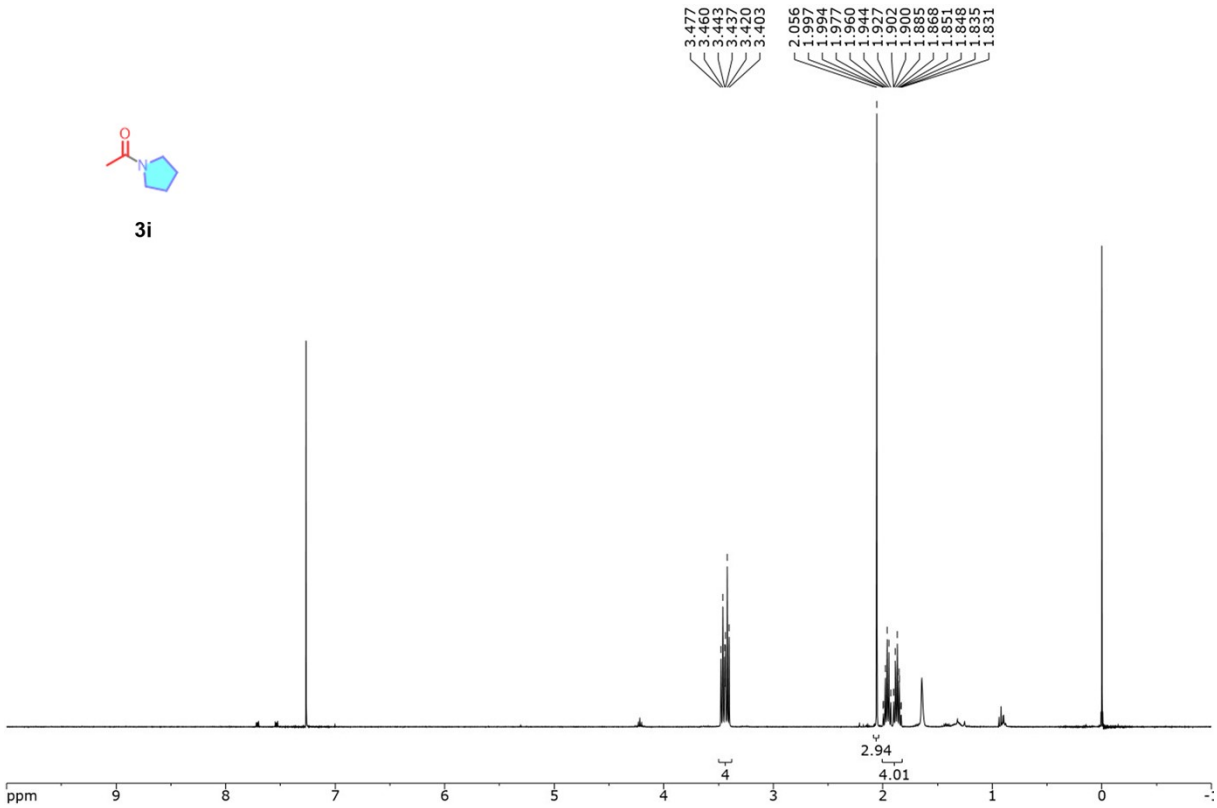


Figure S20. ^{1}H NMR spectrum of **3i** (400 MHz, $CDCl_3$).

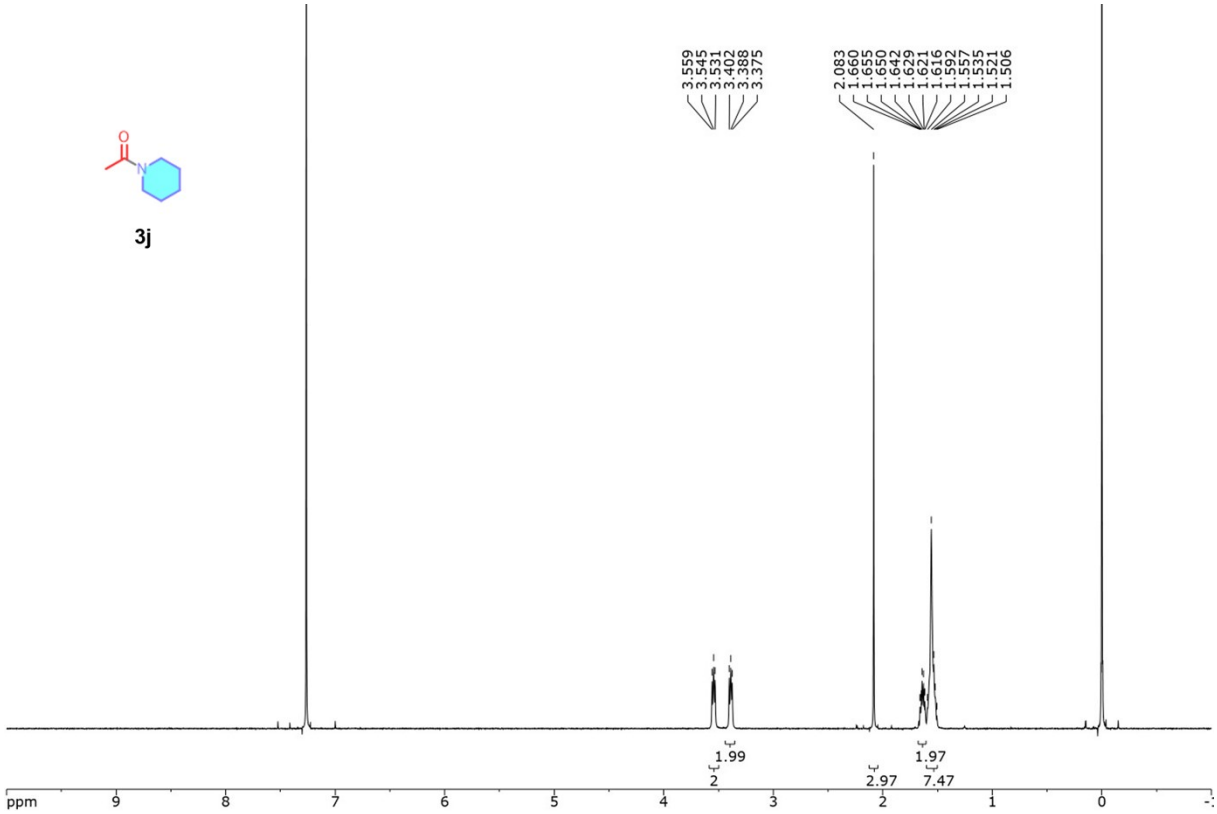


Figure S21. ^{1}H NMR spectrum of **3j** (400 MHz, $CDCl_3$).

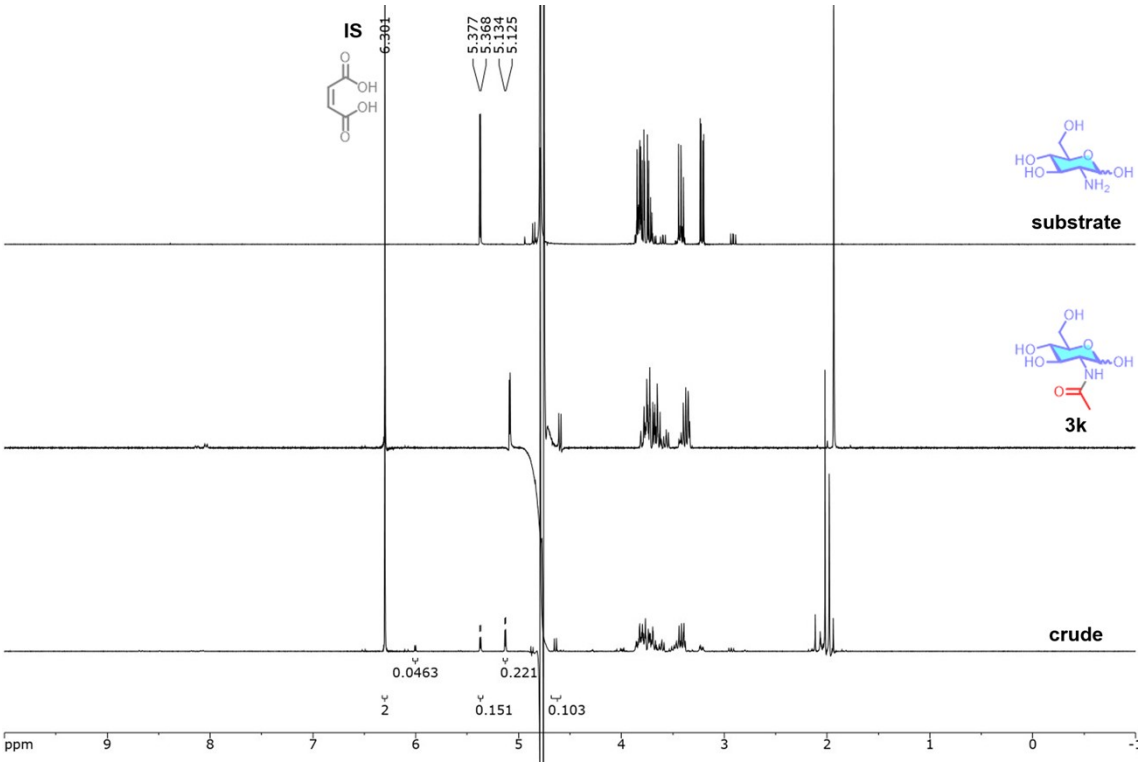


Figure S22. ^{1}H WET NMR spectra (400 MHz, D_2O/H_2O) of the crude reaction mixture from the flow synthesis of compound **3k** (bottom), the authentic sample (middle), and the substrate (top). The yield was determined using maleic acid as an internal standard.

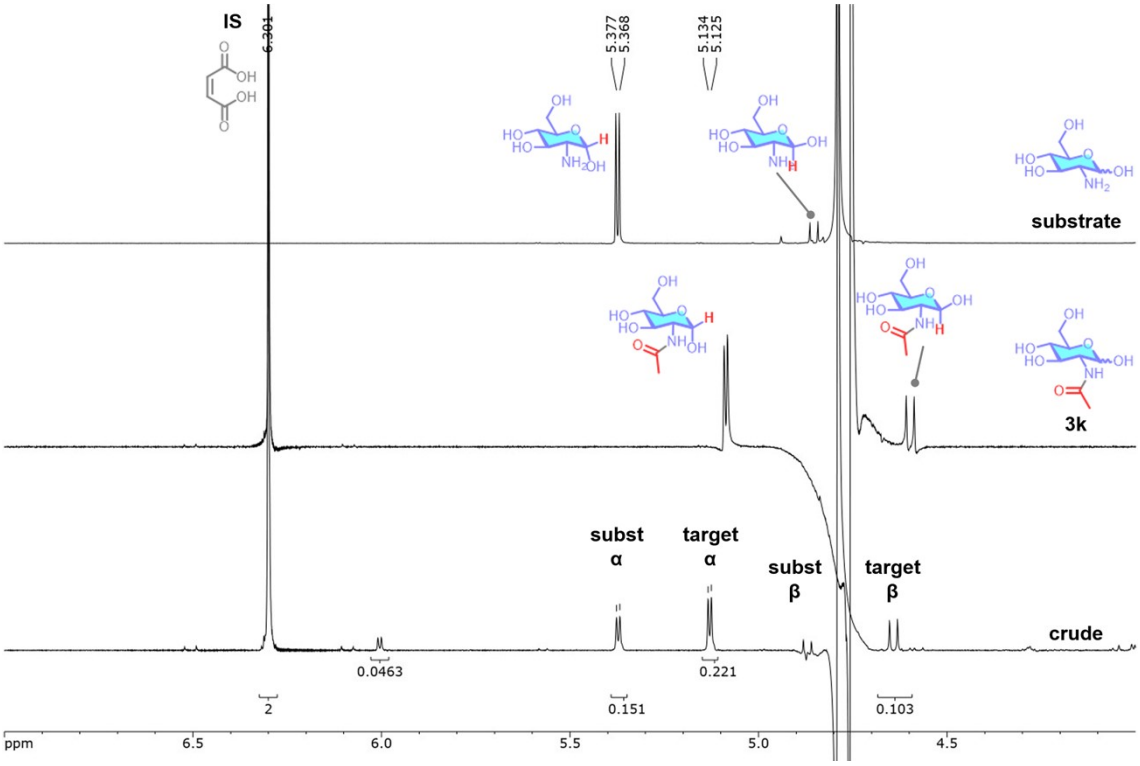


Figure S23. Partial ^{1}H WET NMR spectra (400 MHz, D_2O/H_2O) of the crude reaction mixture from the flow synthesis of compound **3k** (bottom), the authentic sample (middle), and the substrate (top).

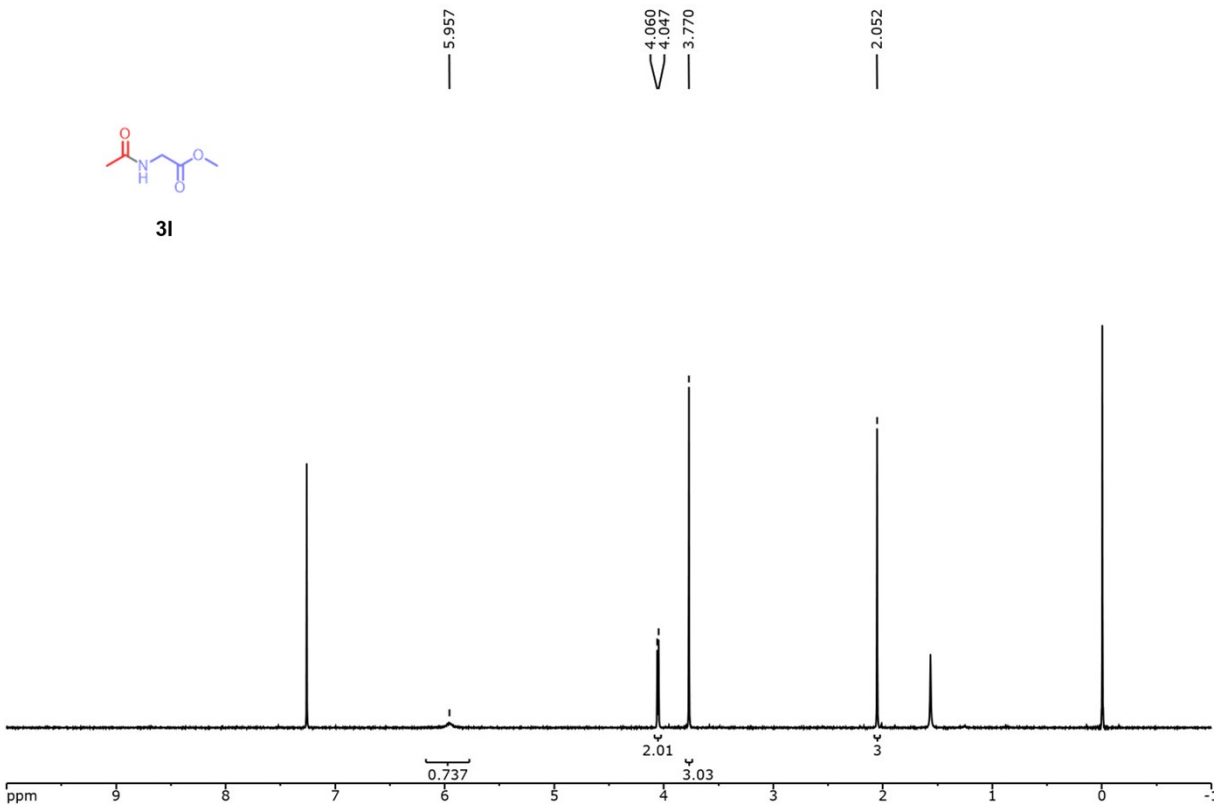


Figure S24. ^{1}H NMR spectrum of **3l** (400 MHz, $CDCl_3$).

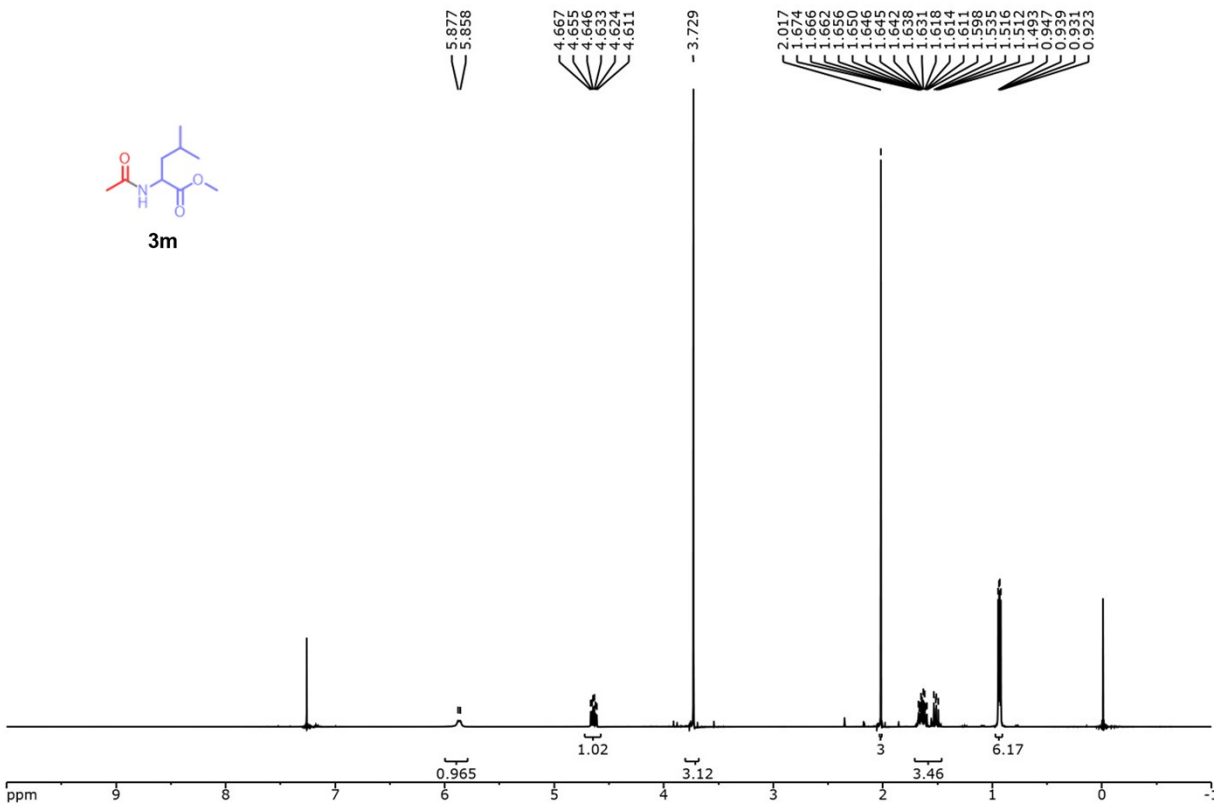


Figure S25. ^{1}H NMR spectrum of **3m** (400 MHz, $CDCl_3$).

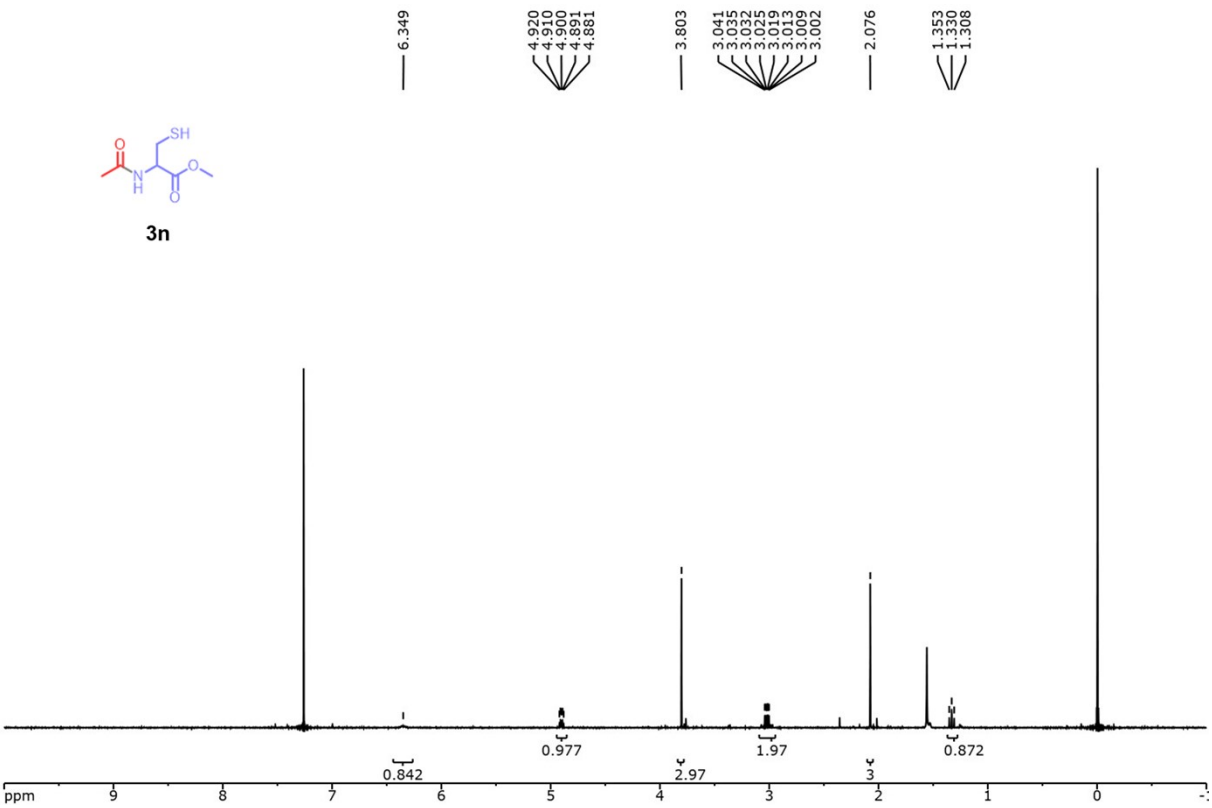


Figure S26. ^{1}H NMR spectrum of **3n** (400 MHz, $CDCl_3$).

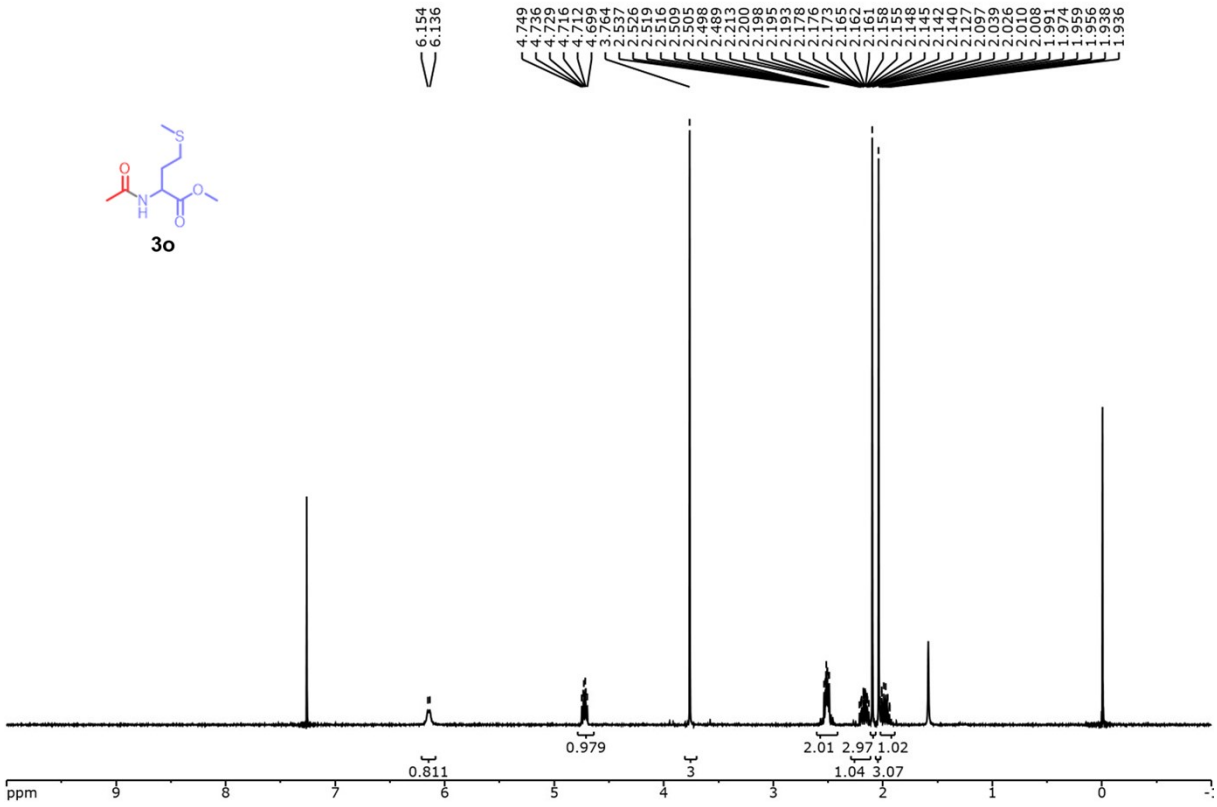


Figure S27. ^{1}H NMR spectrum of **3o** (400 MHz, $CDCl_3$).

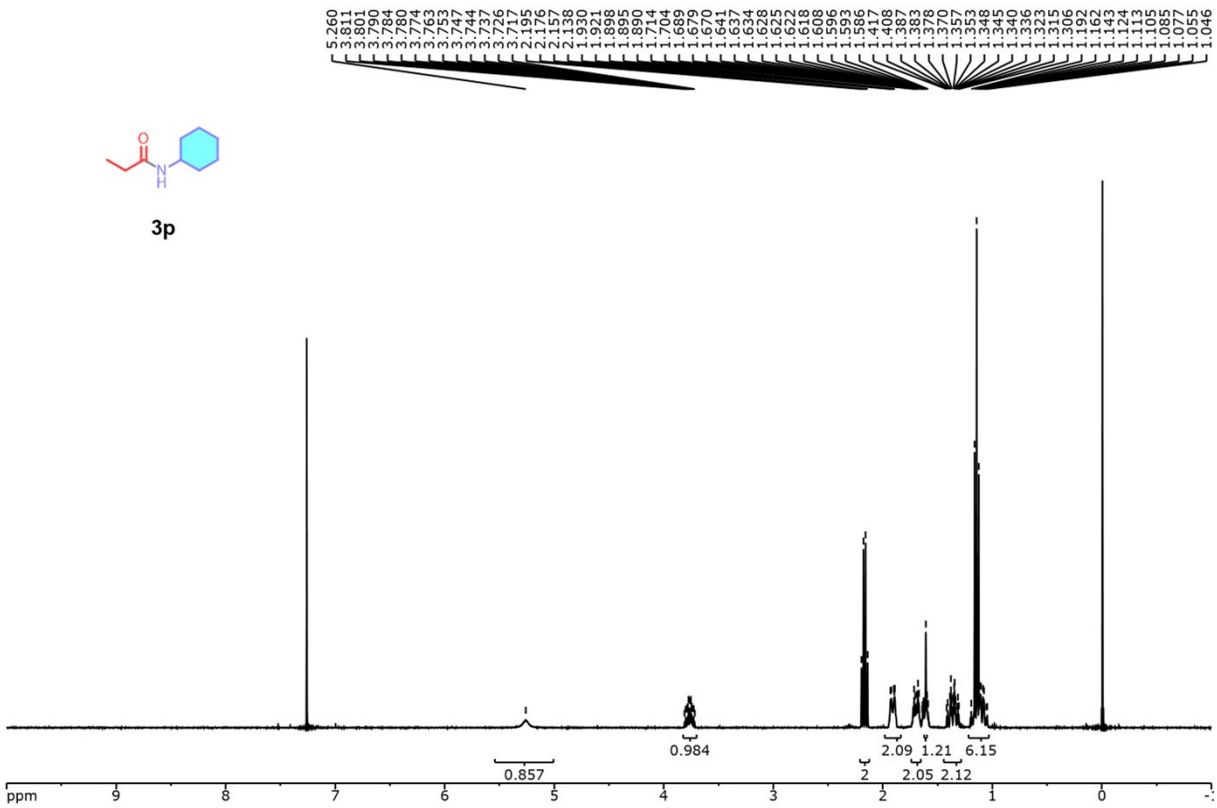


Figure S28. ^{1}H NMR spectrum of **3p** (400 MHz, $CDCl_3$).

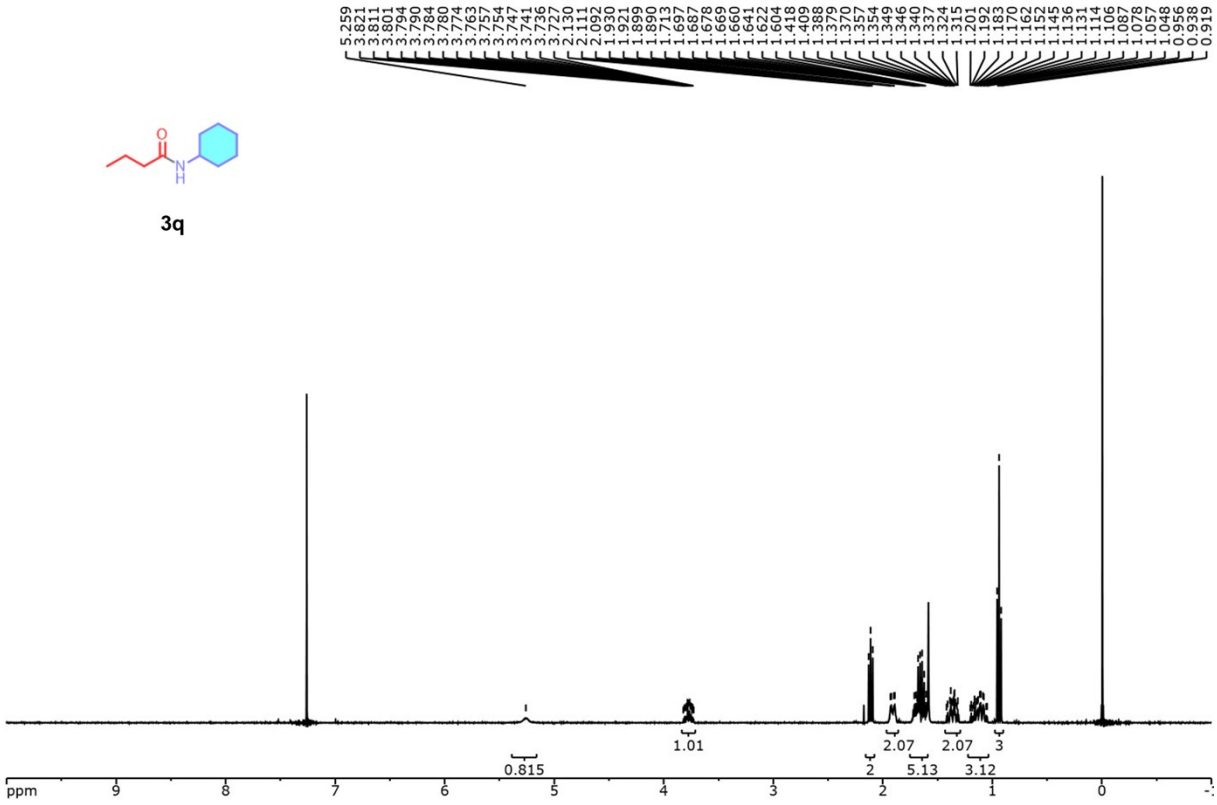


Figure S29. ^{1}H NMR spectrum of **3q** (400 MHz, $CDCl_3$).

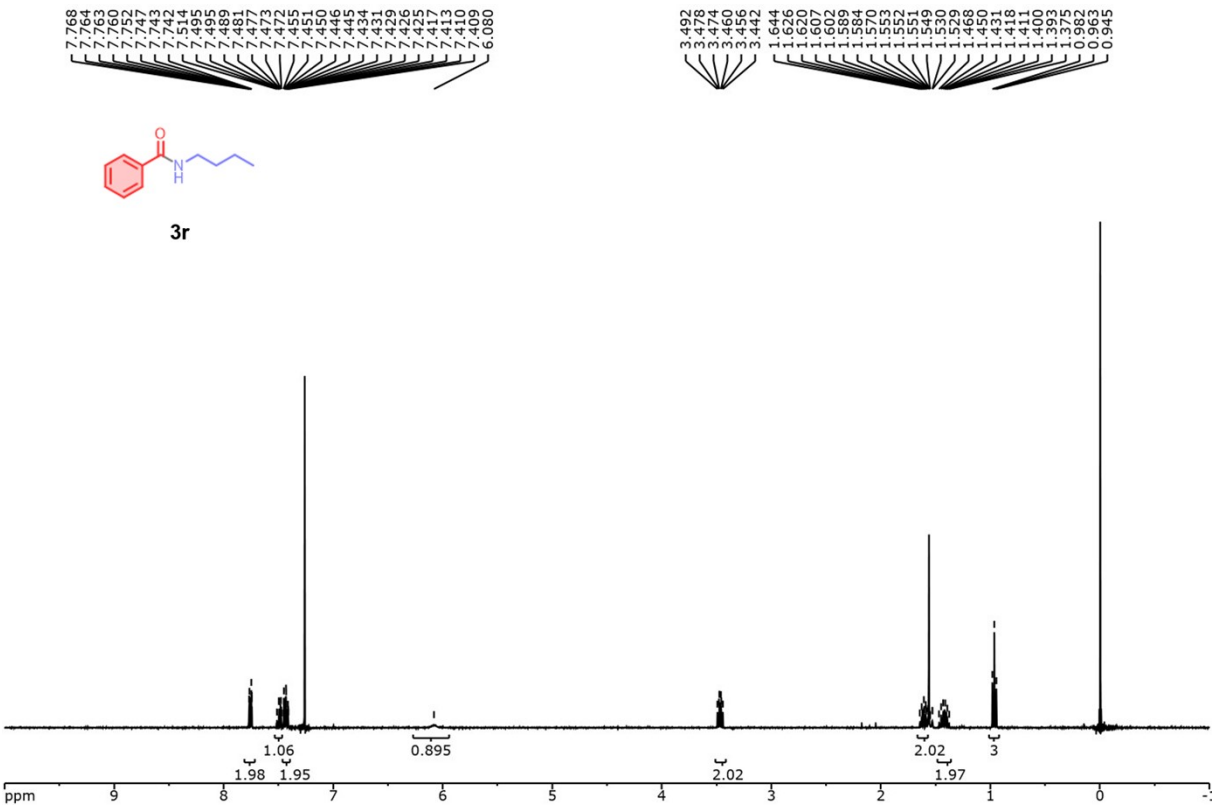


Figure S30. ^{1}H NMR spectrum of **3r** (400 MHz, $CDCl_3$).

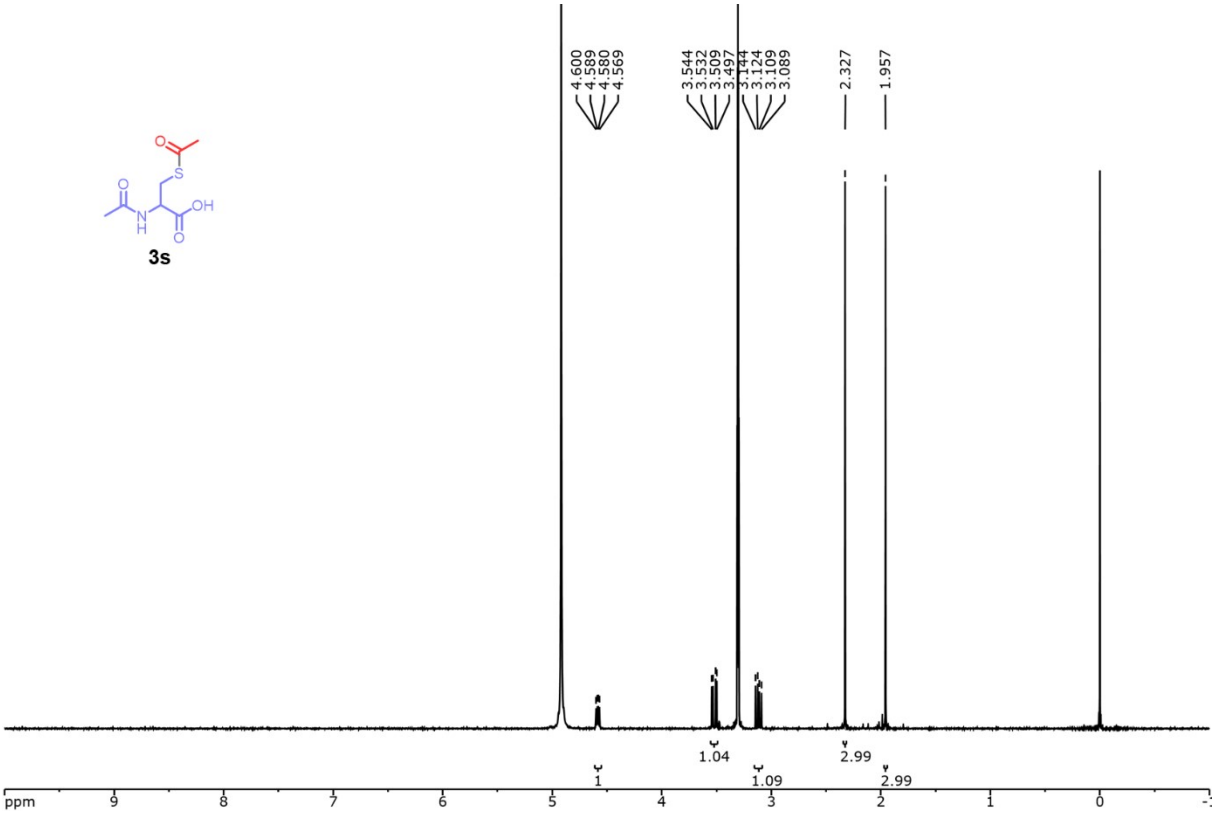


Figure S31. ^{1}H NMR spectrum of **3s** synthesized in a batch reactor (400 MHz, CD_3OD).

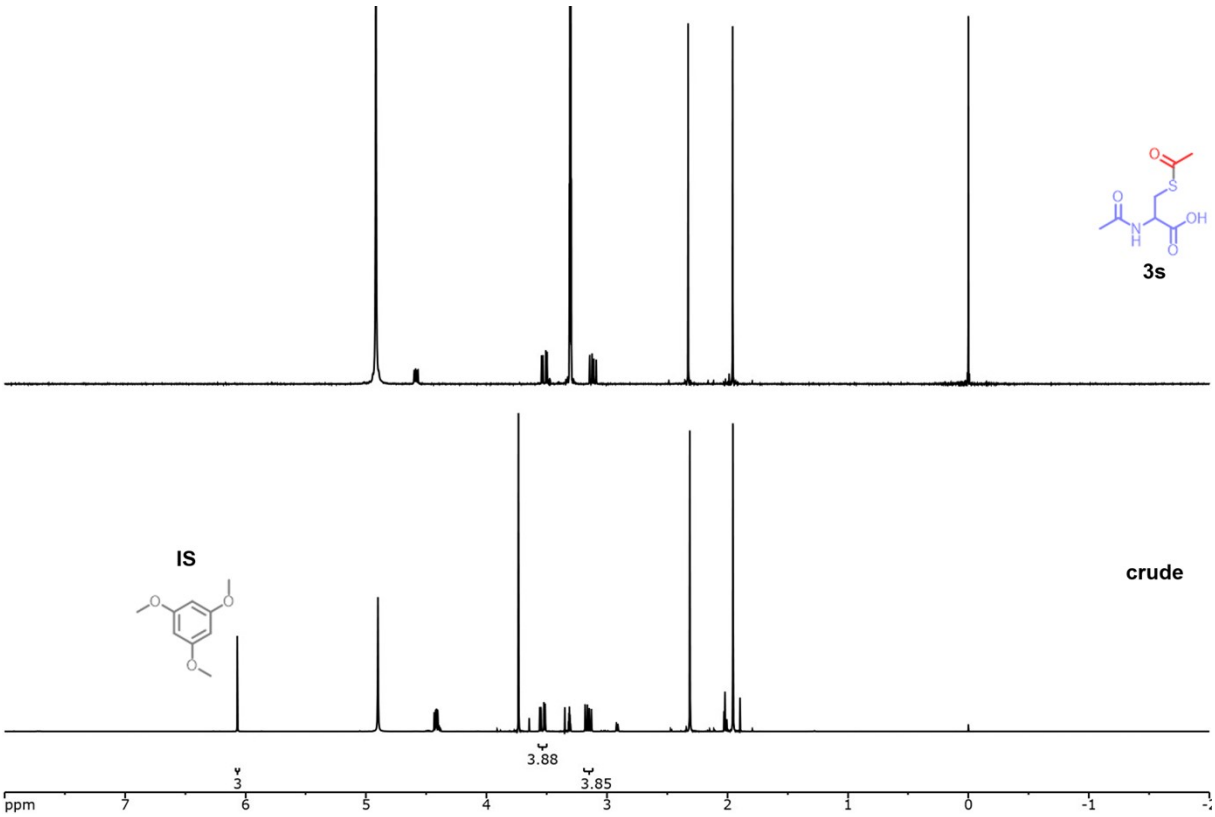


Figure S32. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of the crude of the flow synthesis of compound **3s** (bottom) and the batch-synthesized sample (top). The yield was determined using 1,3,5-trimethoxybenzene as an internal standard.

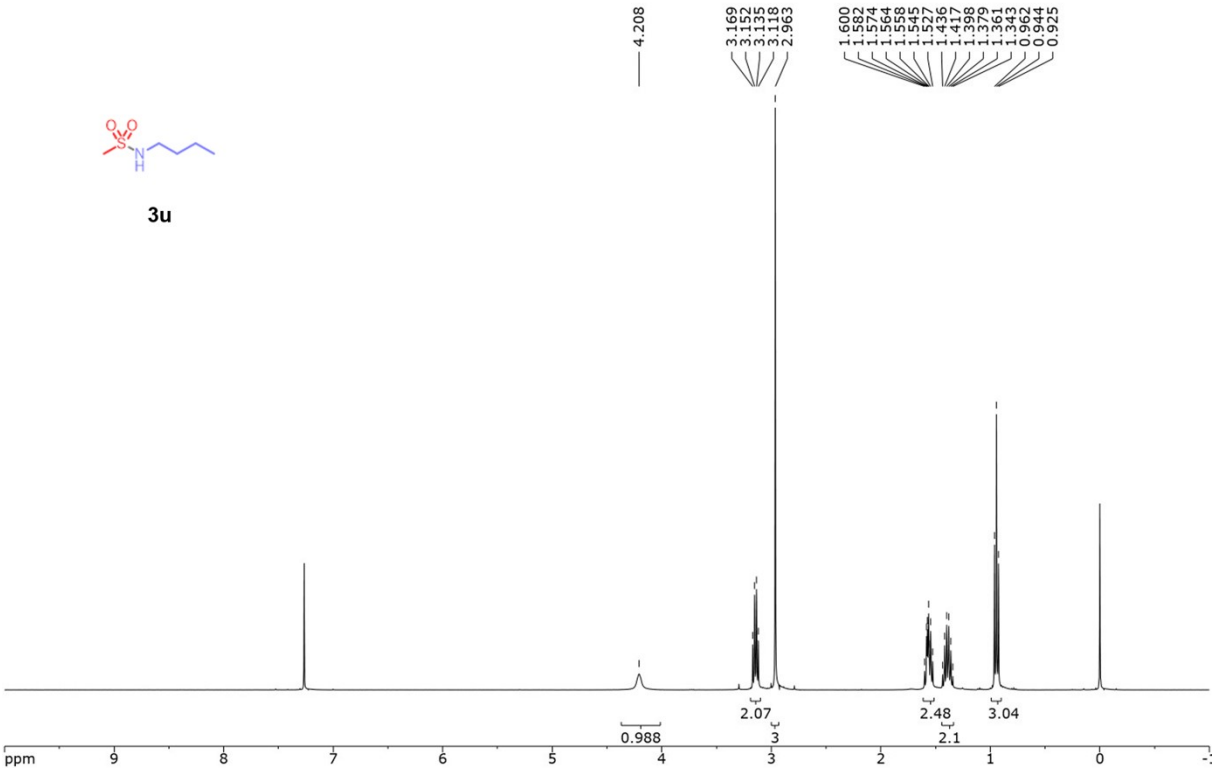


Figure S33. ^{1}H NMR spectrum of **3u** (400 MHz, $CDCl_3$).

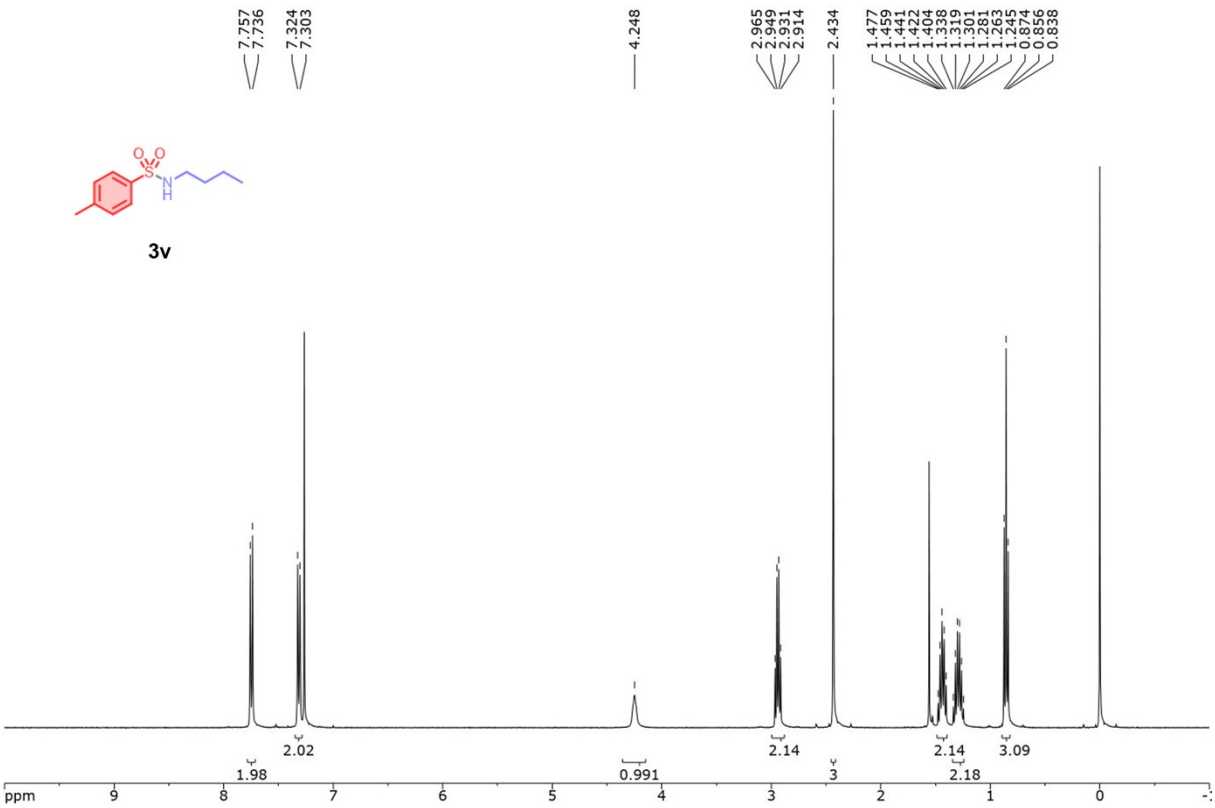


Figure S34. ^{1}H NMR spectrum of **3v** (400 MHz, $CDCl_3$).

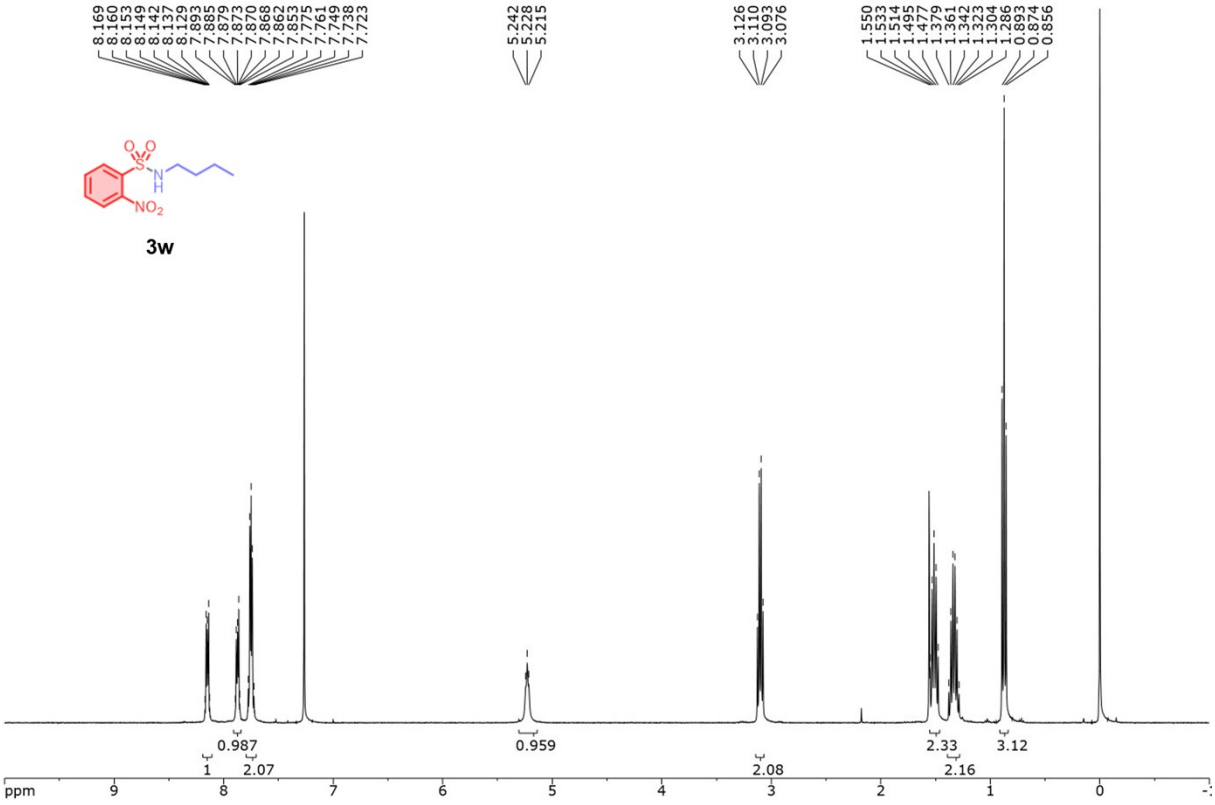


Figure S35. ^{1}H NMR spectrum of **3w** (400 MHz, $CDCl_3$).

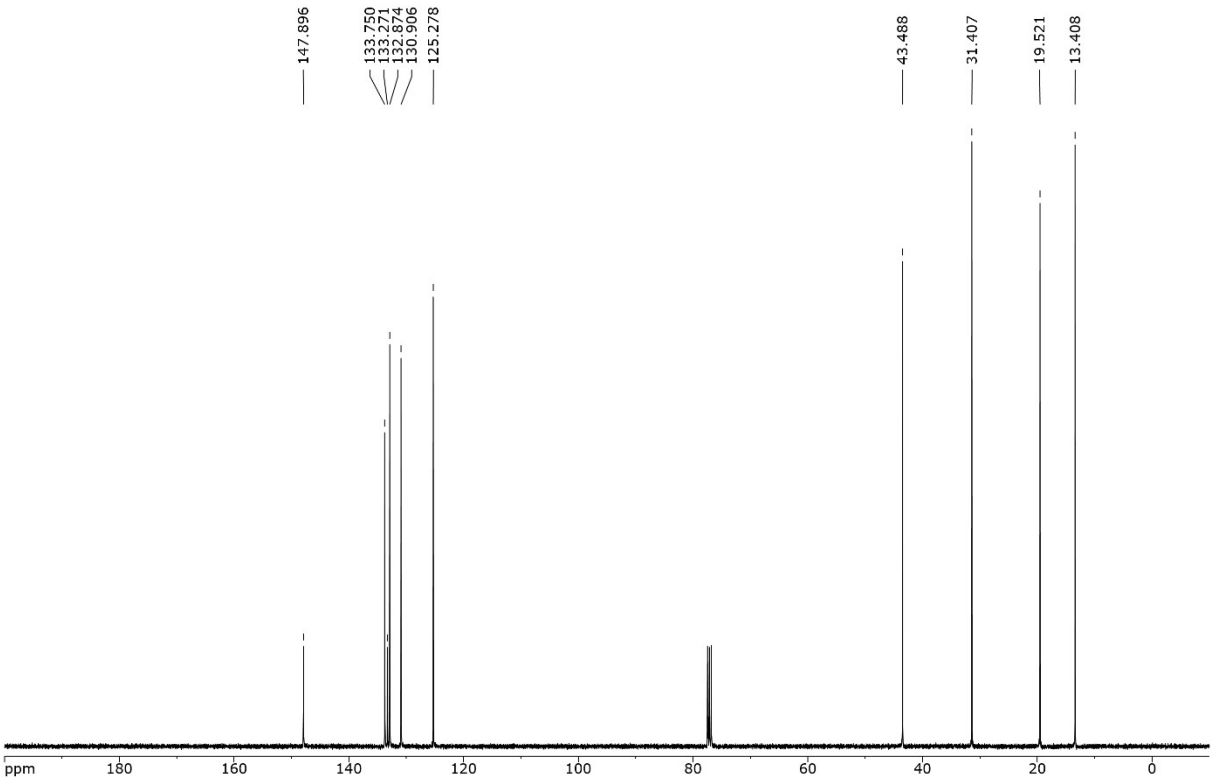


Figure S36. ^{13}C {^{1}H} NMR spectrum of **3w** (101 MHz, $CDCl_3$).

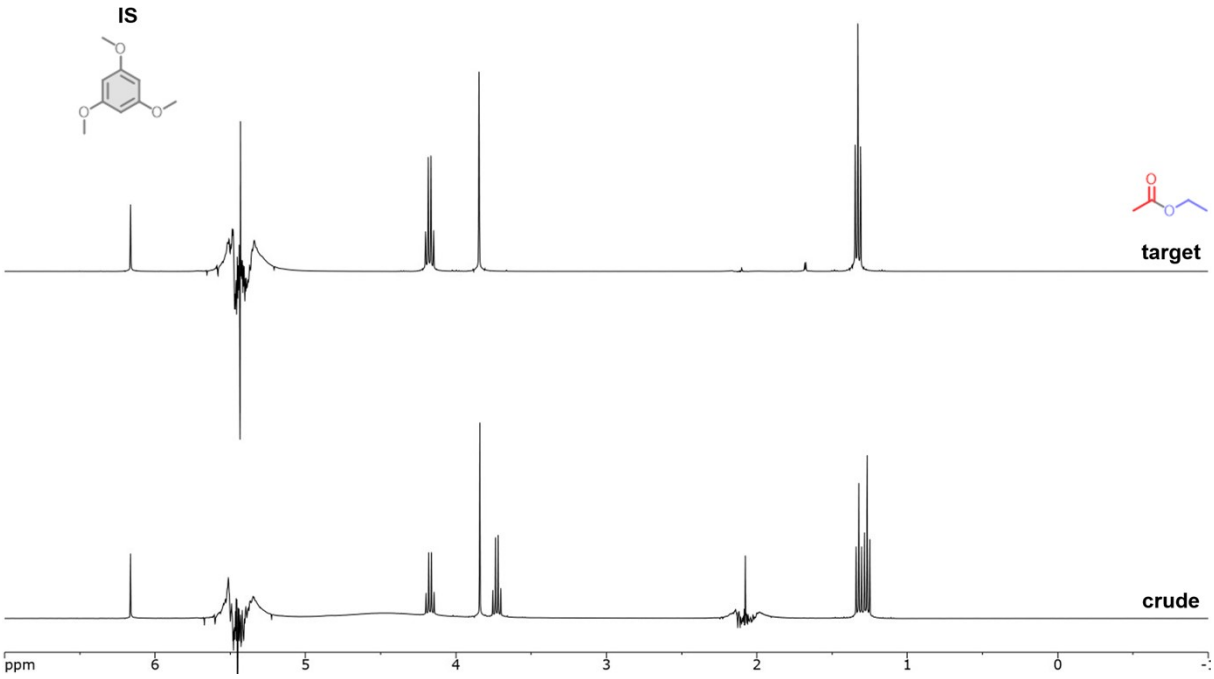


Figure S37. ^{1}H WET NMR spectra (400 MHz, CH_2Cl_2) of the crude reaction mixture from the flow synthesis of compound **3x** (bottom) and the authentic sample (top). The yield was determined using 1,3,5-trimethoxybenzene as an internal standard.

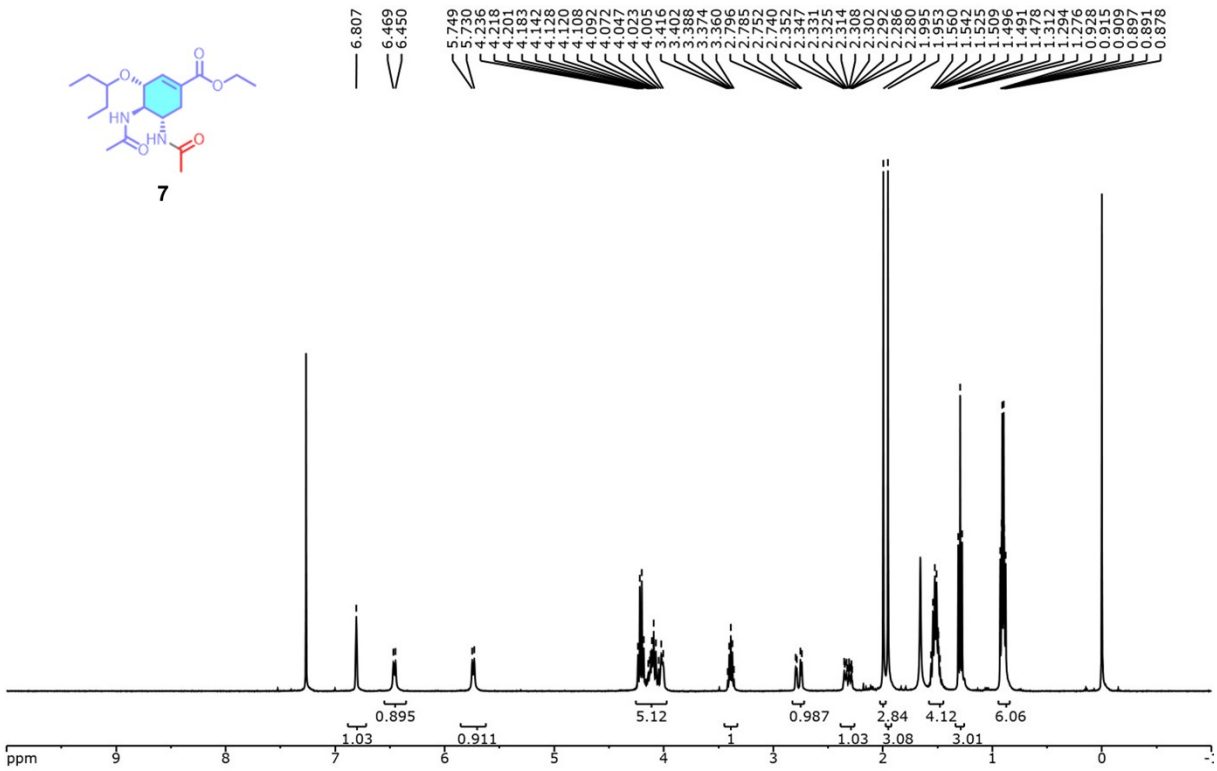


Figure S38. ^{1}H NMR spectrum of **7** (400 MHz, $CDCl_3$).

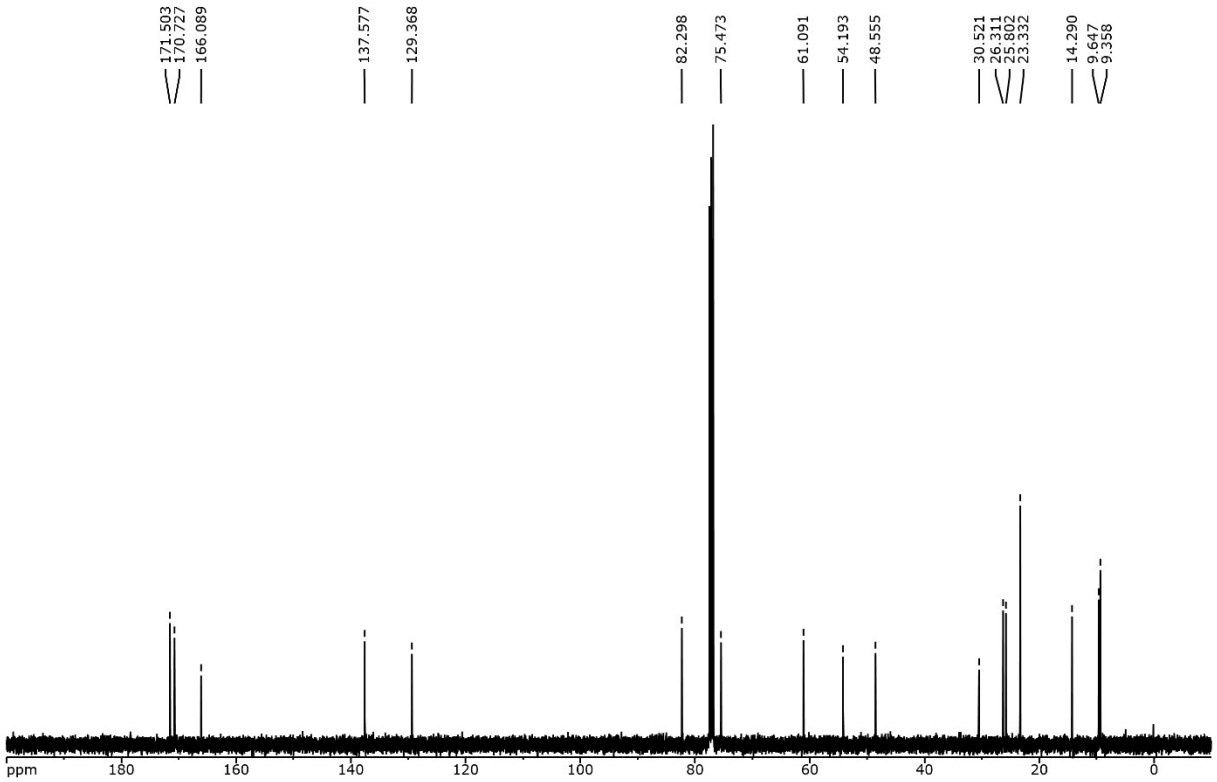


Figure S39. ^{13}C {^{1}H} NMR spectrum of **7** (101 MHz, $CDCl_3$).

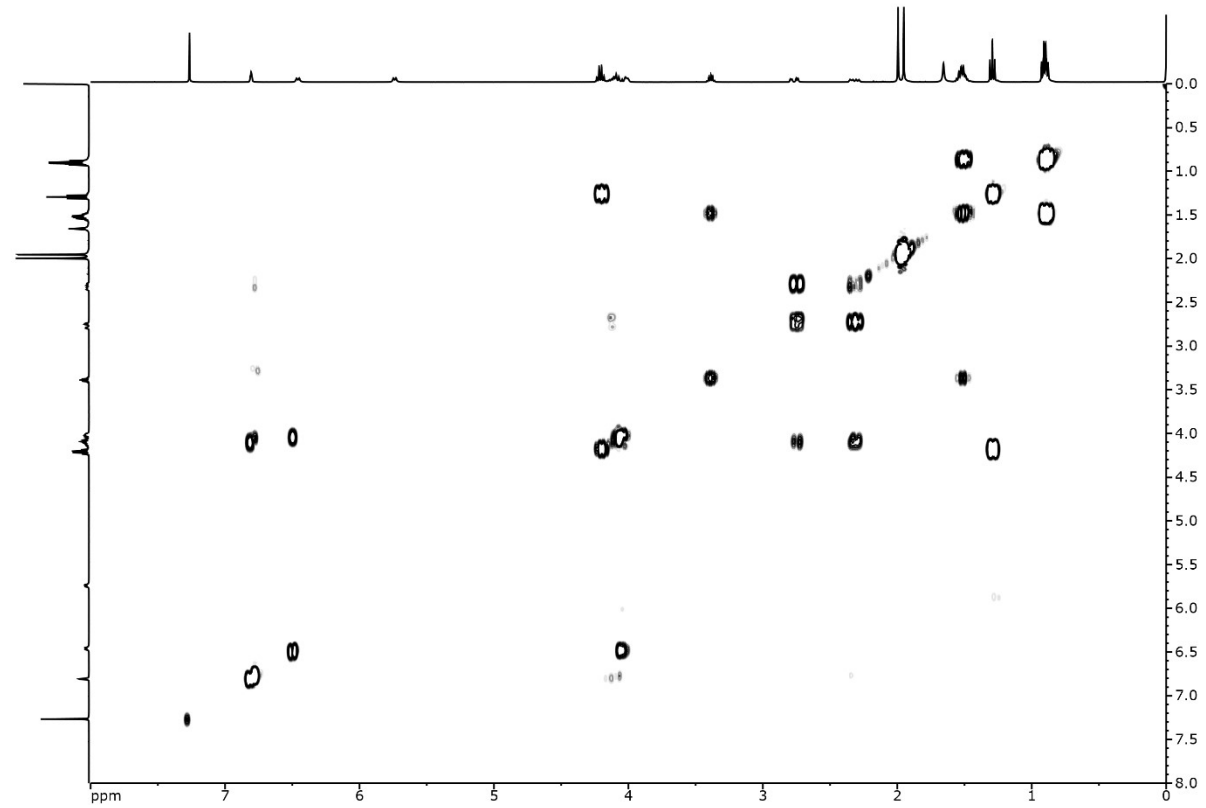


Figure S40. ^{1}H-^{1}H COSY NMR spectrum of **7** (400 MHz, $CDCl_3$).

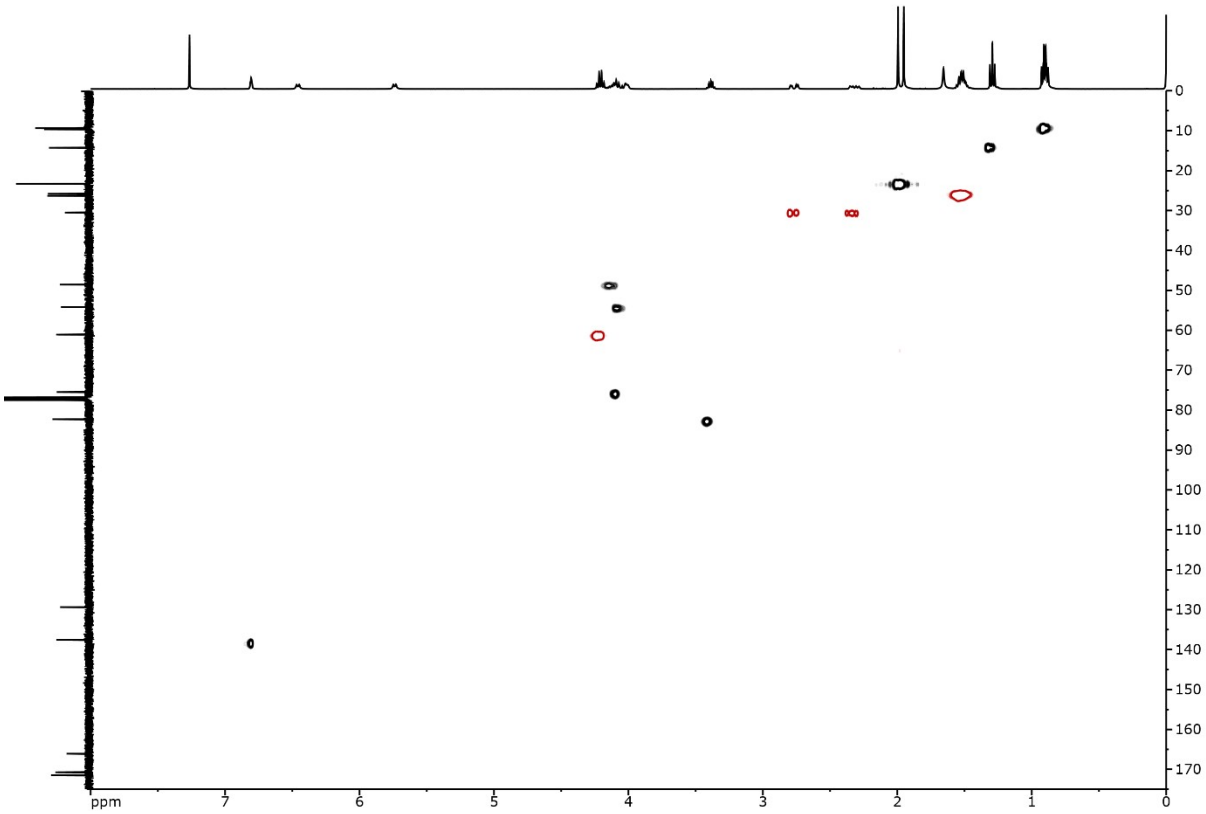


Figure S41. ^{1}H-^{13}C edited-HSQC NMR spectrum of **7** (400/101 MHz, $CDCl_3$).

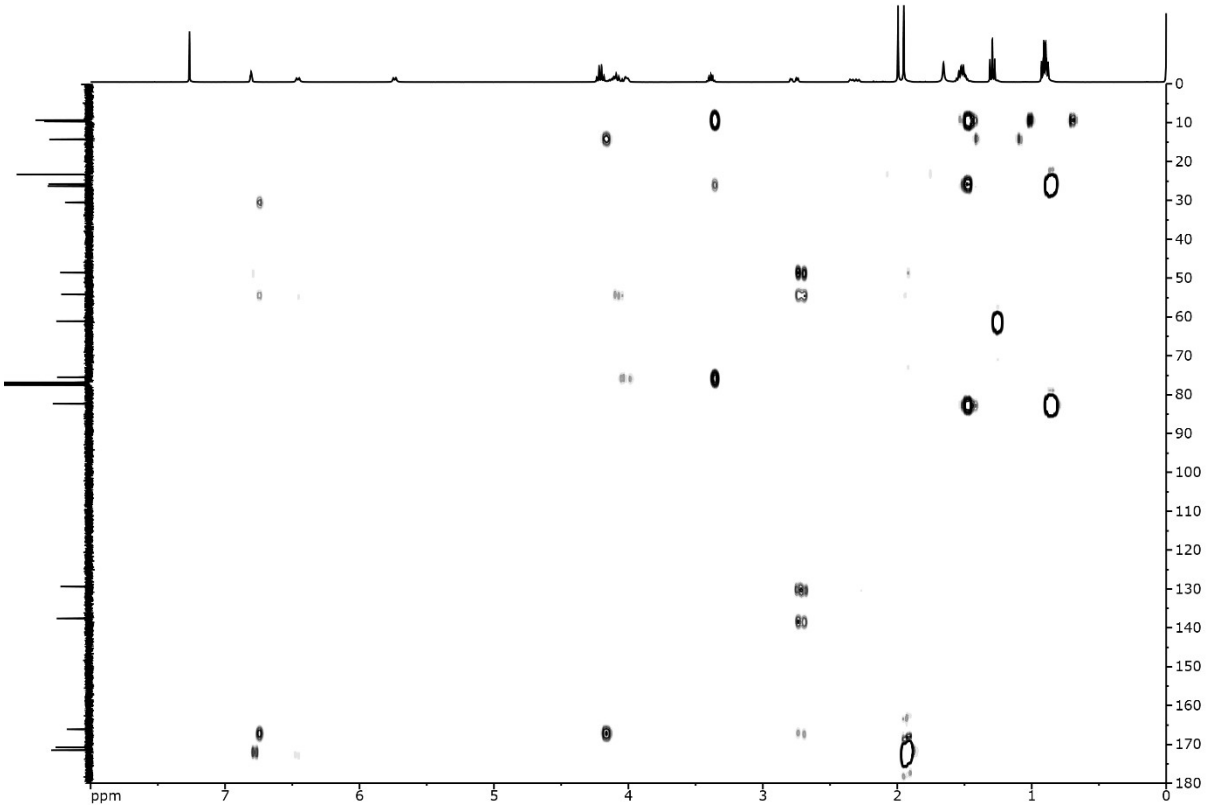


Figure S42. ^{1}H-^{13}C HMBC NMR spectrum of **7** (400/101 MHz, $CDCl_3$).

5. HRMS spectrum

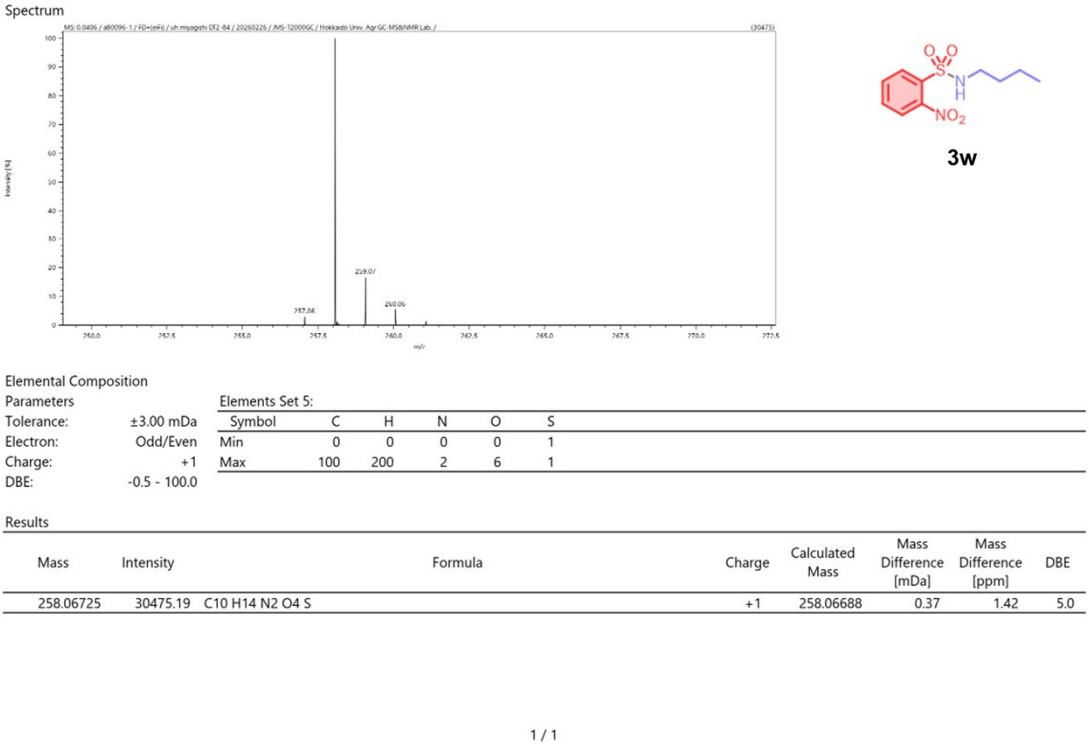


Figure S43. FD-MS spectrum and data of **3w**.

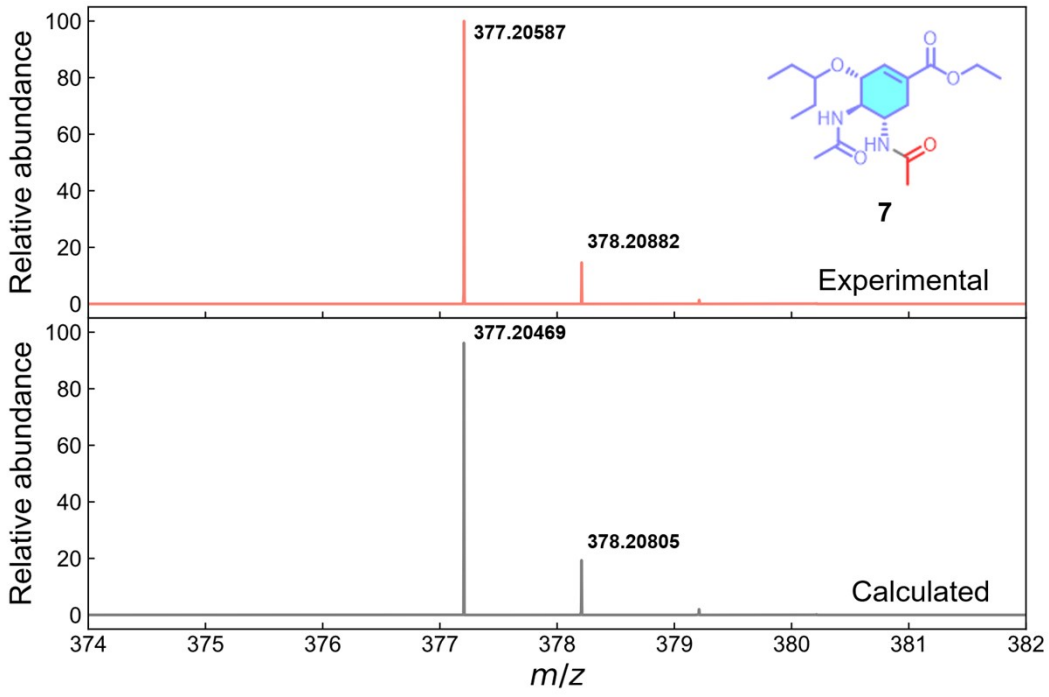


Figure S44. ESI-MS spectrum of **7**.

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