Development of a Safe and Economical Synthesis of Methyl 6-chloro-5-(trifluoromethyl)nicotinate: Trifluoromethylation on Kilogram Scale

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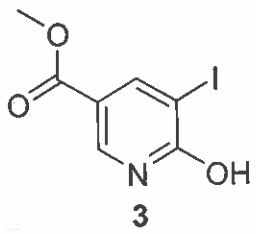
Chemical Development, U.S., Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd., Ridgefield, CT 06877, United States

Supporting Information:

3
proton NMR



3

BRUKER

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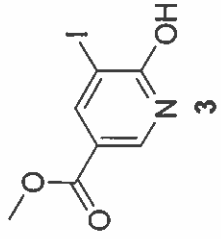
3
13C NMR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PCPD2 80.00 usec
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PL12 15.14 dB
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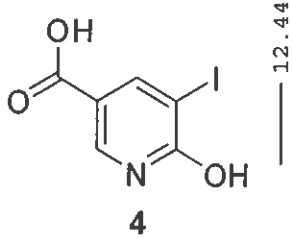
4
proton NMR



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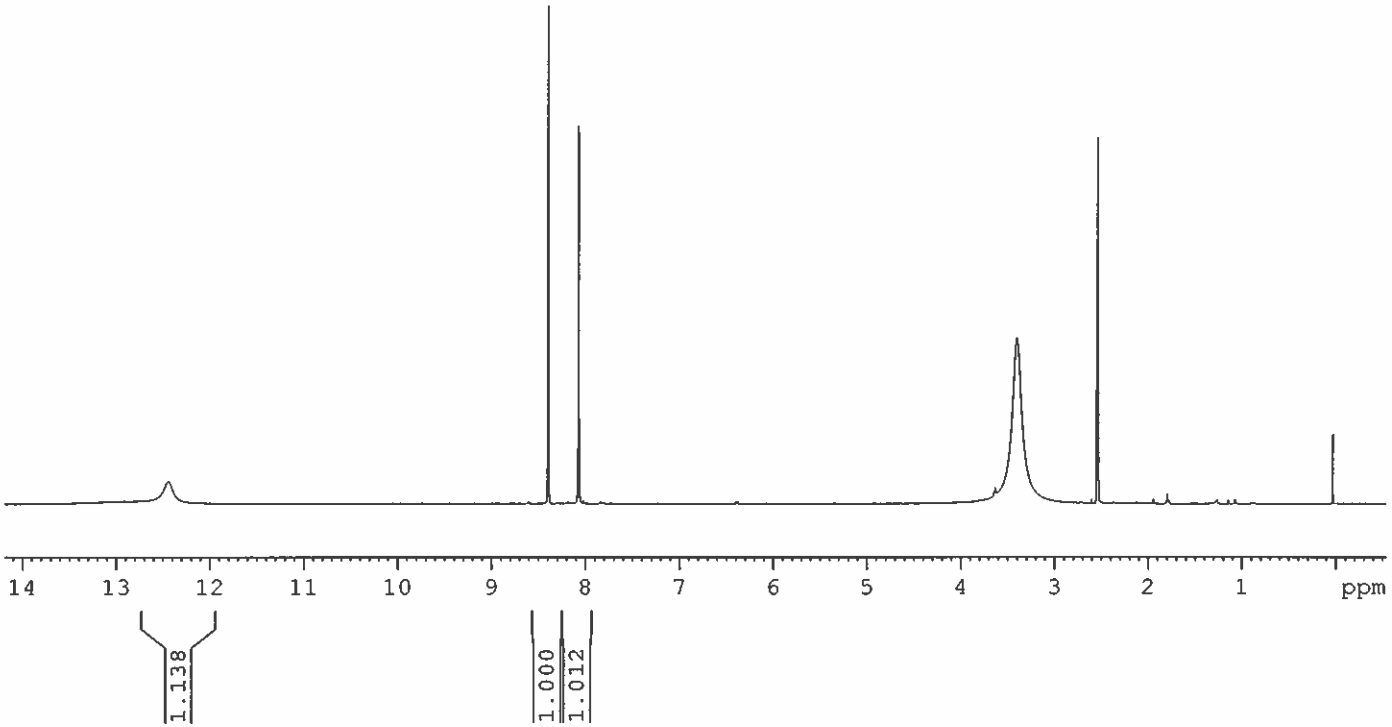
0.030



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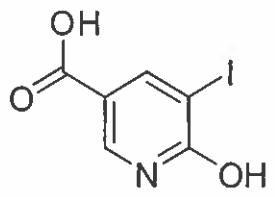
4
13C NMR



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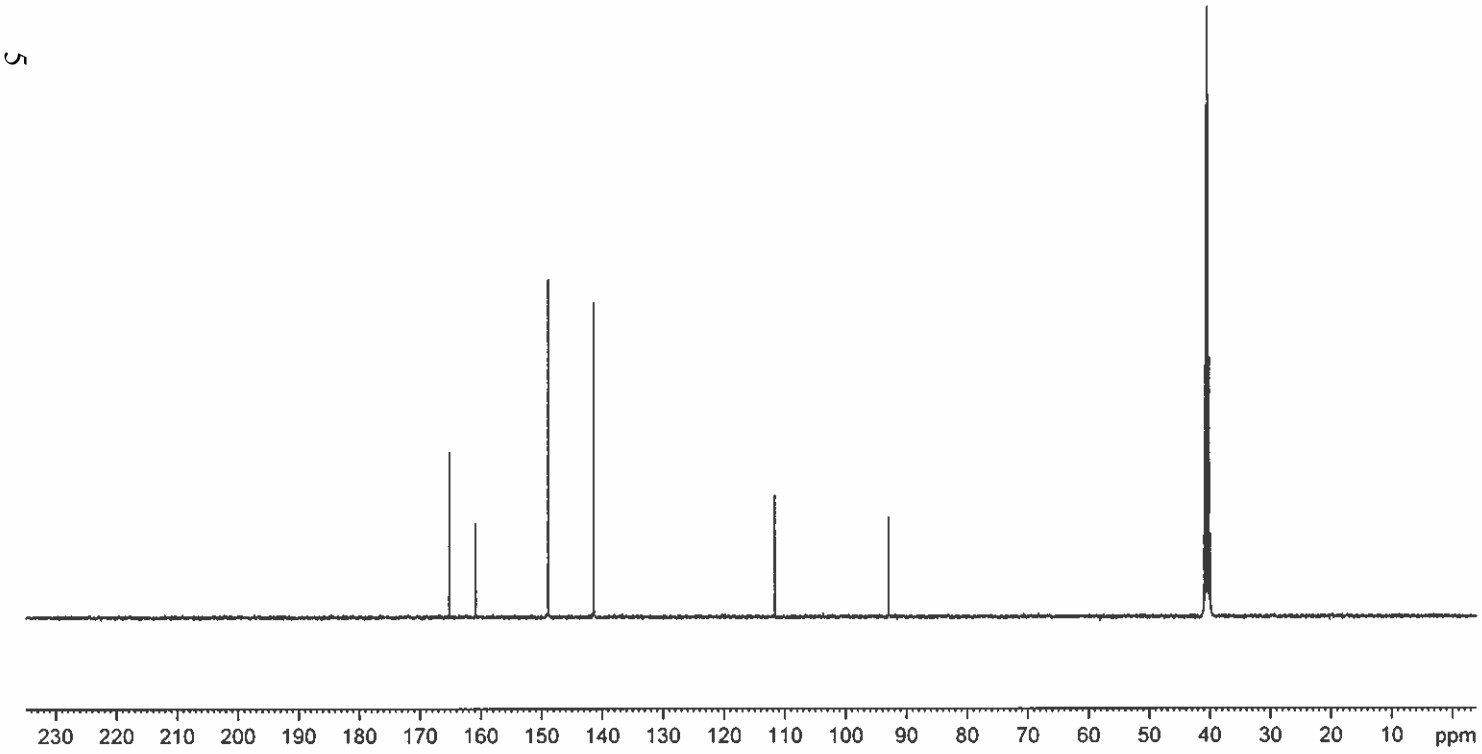

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FIDRES              0.733596 Hz
AQ                  0.6816244 sec
RG                       287
DW                    20.800 usec
DE                     6.50 usec
TE                     298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                      9.75 usec
PL1                    -1.00 dB
PL1W              43.00697708 W
SFO1              100.6243395 MHz

======== CHANNEL f2 ========
CPDPRG2               waltz16
NUC2                      1H
PCPD2                  80.00 usec
PL2                     0.00 dB
PL12                   15.14 dB
PL13                   15.14 dB
PL2W              10.49968529 W
PL12W              0.32149649 W
PL13W              0.32149649 W
SFO2              400.1316005 MHz

F2 - Processing parameters
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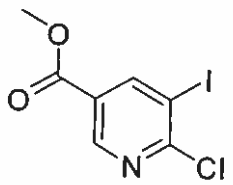
5
proton NMR



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TD                32768
SOLVENT            DMSO
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DS                     4
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FIDRES        0.179939 Hz
AQ            2.7787764 sec
RG                   406
DW              84.800 usec
DE               6.50 usec
TE               298.0 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                14.00 usec
PL1                0.00 dB
PL1W        10.49968529 W
SFO1        400.1327209 MHz

F2 - Processing parameters
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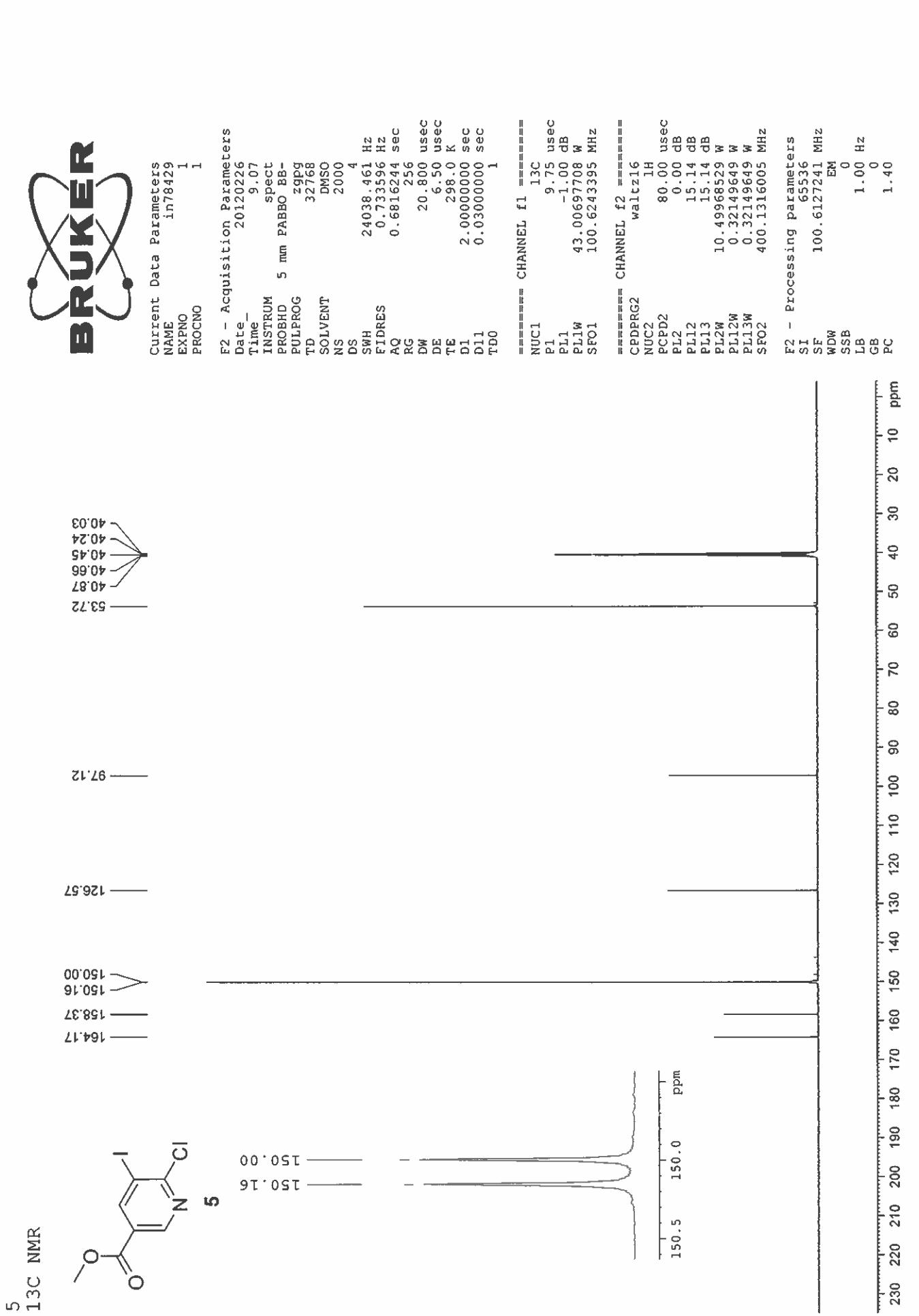
5
13C NMR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DS 4
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FIDRES 0.733596 Hz
AQ 0.6816244 sec
RG 256
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.75 usec
PL1 -1.00 dB
PL1W 43.00697708 W
SFO1 100.6243395 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 15.14 dB
PL13 15.14 dB
PL2W 10.49968529 W
PL12W 0.32149649 W
PL13W 0.32149649 W
SFO2 400.1316005 MHz
F2 - Processing parameters
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WDW EM
SSB 0
LB 1.00 Hz
GB 0
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ppm
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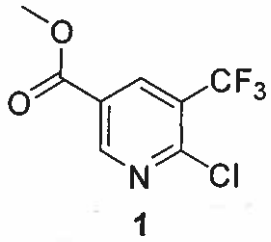
ppm

1
proton NMR



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SOLVENT DMSO
NS 256
DS 4
SWH 5896.227 Hz
FIDRES 0.179939 Hz
AQ 2.7787764 sec
RG 406
DW 84.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 0.00 dB
PL1W 10.49968529 W
SFO1 400.1327209 MHz

F2 - Processing parameters
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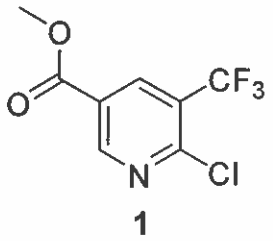
1
13C NMR



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FIDRES	0.733596 Hz
AQ	0.6816244 sec
RG	287
DW	20.800 usec
DE	6.50 usec
TE	298.0 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	13C
P1	9.75 usec
PL1	-1.00 dB
PL1W	43.00697708 W
SFO1	100.6243395 MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	15.14 dB
PL13	15.14 dB
PL2W	10.49968529 W
PL12W	0.32149649 W
PL13W	0.32149649 W
SFO2	400.1316005 MHz

F2 - Processing parameters

SI	65536
SF	100.6127225 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

Data Collection by ARSST Instrument:

Advanced Reactive Systems Screening Tool (ARSST) calorimeter is manufactured by Fauske and Associates. ARSST is a quasi-adiabatic calorimeter that works on basis of heat loss compensation principle. The basic component of the ARSST instrument includes a spherical 10-mL glass test cell (*), its surrounding "bottom heater" jacket and insulation, thermocouple, pressure transducer, and a 350-mL containment vessel that serves as both pressure simulator and safety vessel. Tests are usually performed in the open test cell in closed containment. Nitrogen pressure in the containment vessel is used to suppress the boiling point of the sample. The sample temperature is measured by a thermocouple inside the test cell. A magnetic stir bar is placed inside the test cell and driven by an external magnetic stirrer. A key feature of the apparatus is its low effective heat capacity relative to that of the sample (low φ factor). Thus, the heat released by chemical reaction goes to heat up the sample with negligible energy absorbed by the test cell itself. A fill tube is used to add the mixture to the purged test cell.
For screening purposes, ARSST data is usually collected with the use of 2 °C/min temperature ramp polynomial and approximately 10 mL of the reaction mixture. All data points in the plots are smoothed over five data points.
It is worth to mention, that the fill level in ARSST cell is about 3% of the total vessel volume (open cell in closed containment. 10 ml of reaction mixture in a containment volume of 350 ml). This fact needs to be considered for pressure increase and pressure rates.
(*) Options for performing tests in other cell volume and cell materials are available. Experiments in closed test cells are also possible.

Figure A1: Temperature vs. Time Profile; Preparation of "**1"** in Batch mode; ARSST experiment

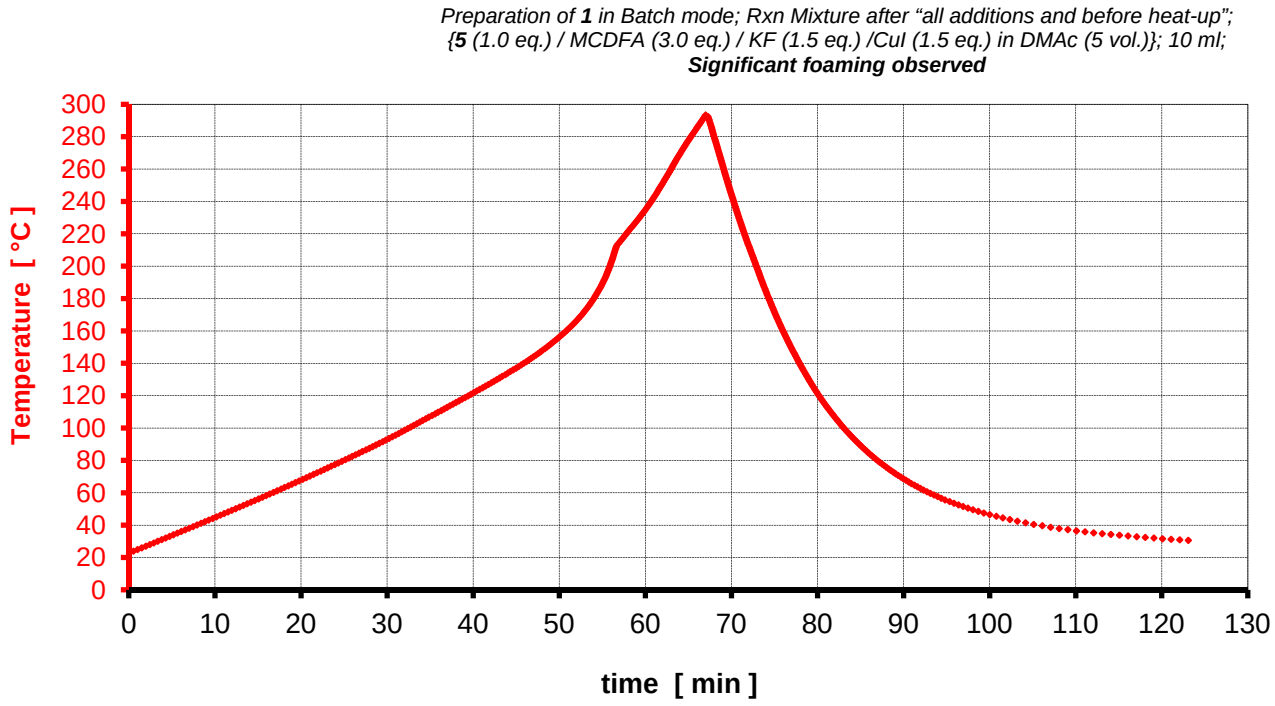


Figure A2: Pressure vs. Time Profile; Preparation of "**1"** in Batch mode; ARSST experiment

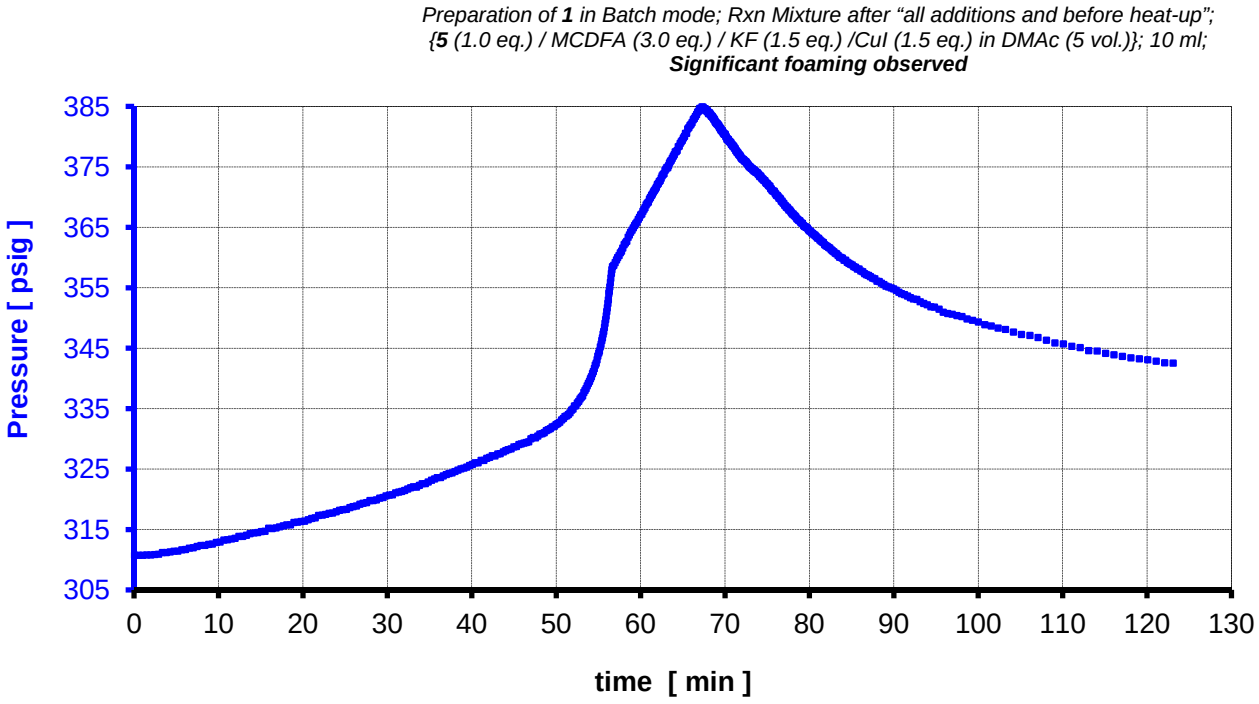


Figure A3: Pressure vs. Temperature Profile; Preparation of "**1**" in Batch mode; ARSST experiment

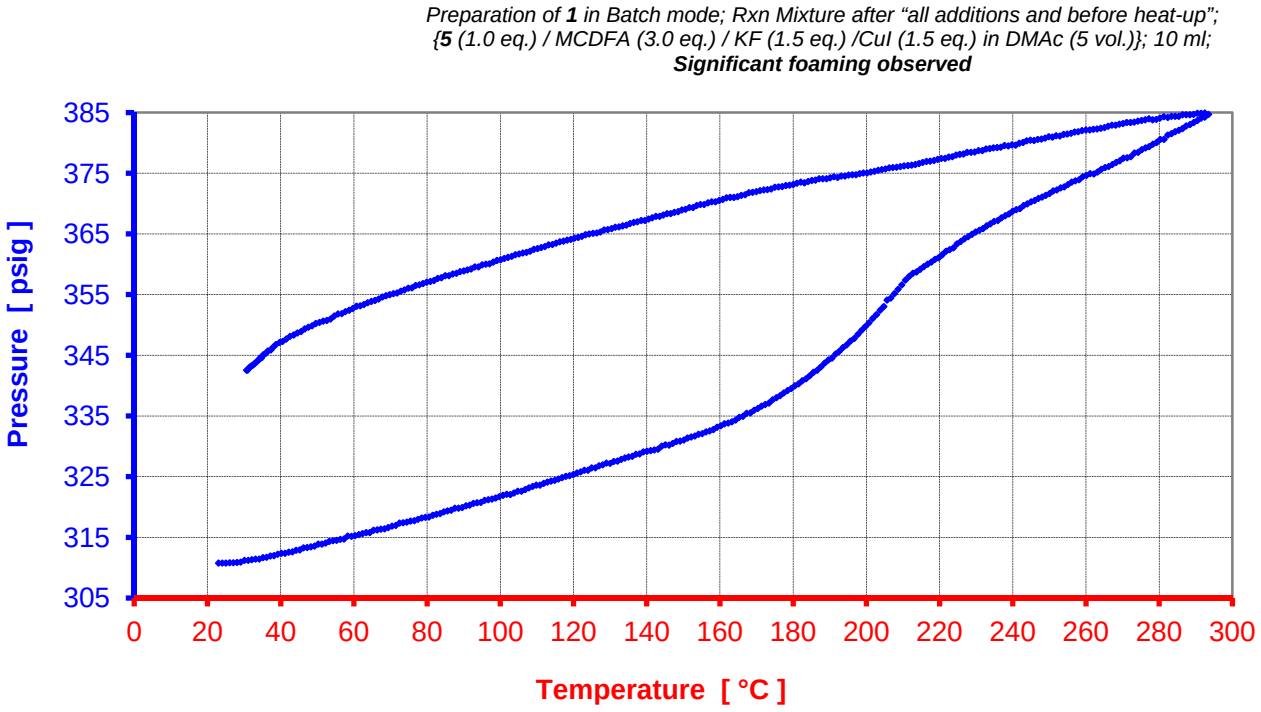


Figure A4: Time Derivative of Temperature vs. Temperature Profile; Preparation of "**1**" in Batch mode; ARSST experiment; only heat-up part of the curve is shown here.

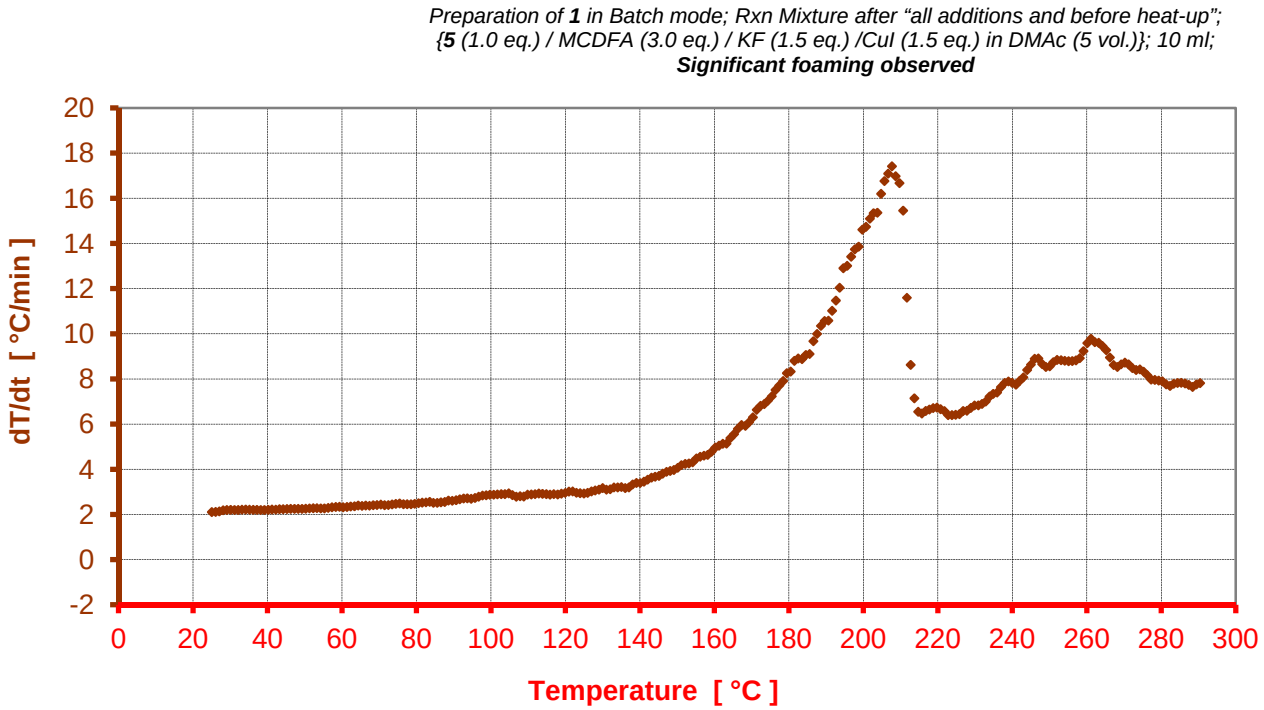


Figure A5: Time Derivative of Temperature (Self Heat Rate) vs. Time Profile; Preparation of "**1"** in Batch mode; ARSST experiment

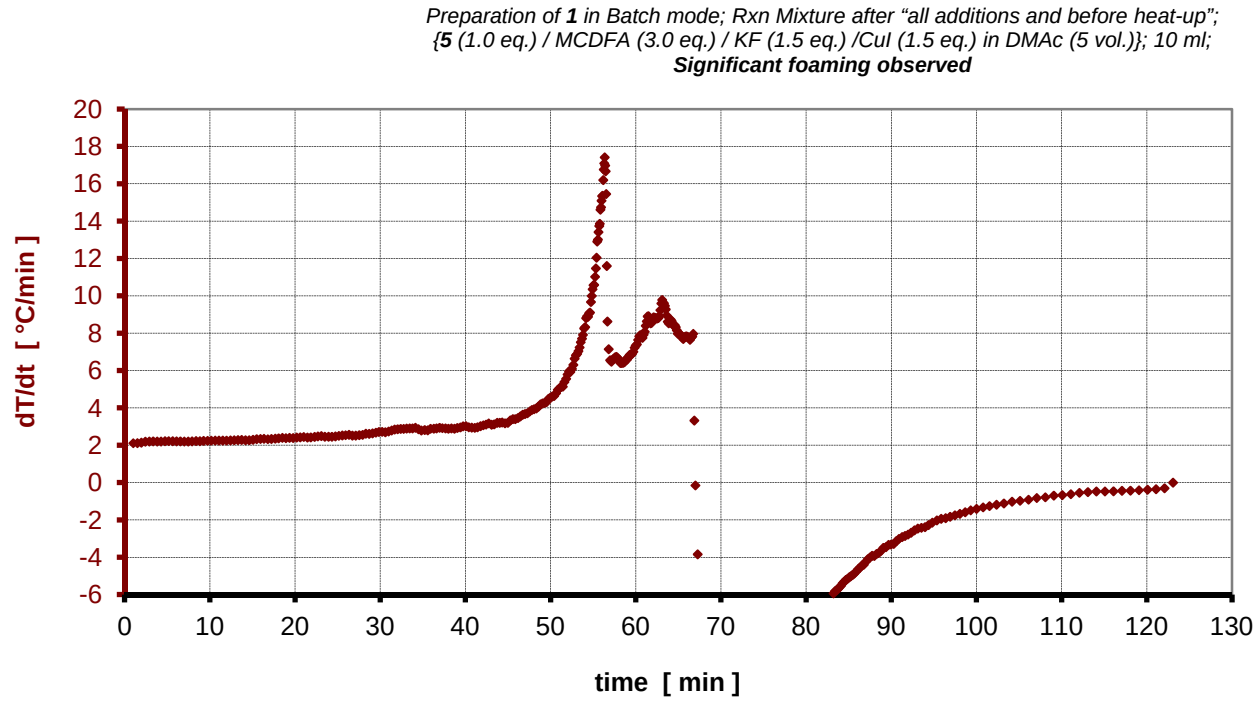


Figure A6: Time Derivative of Pressure (Pressure-rise Rate) vs. Time Profile; Preparation of "**1"** in Batch mode; ARSST experiment

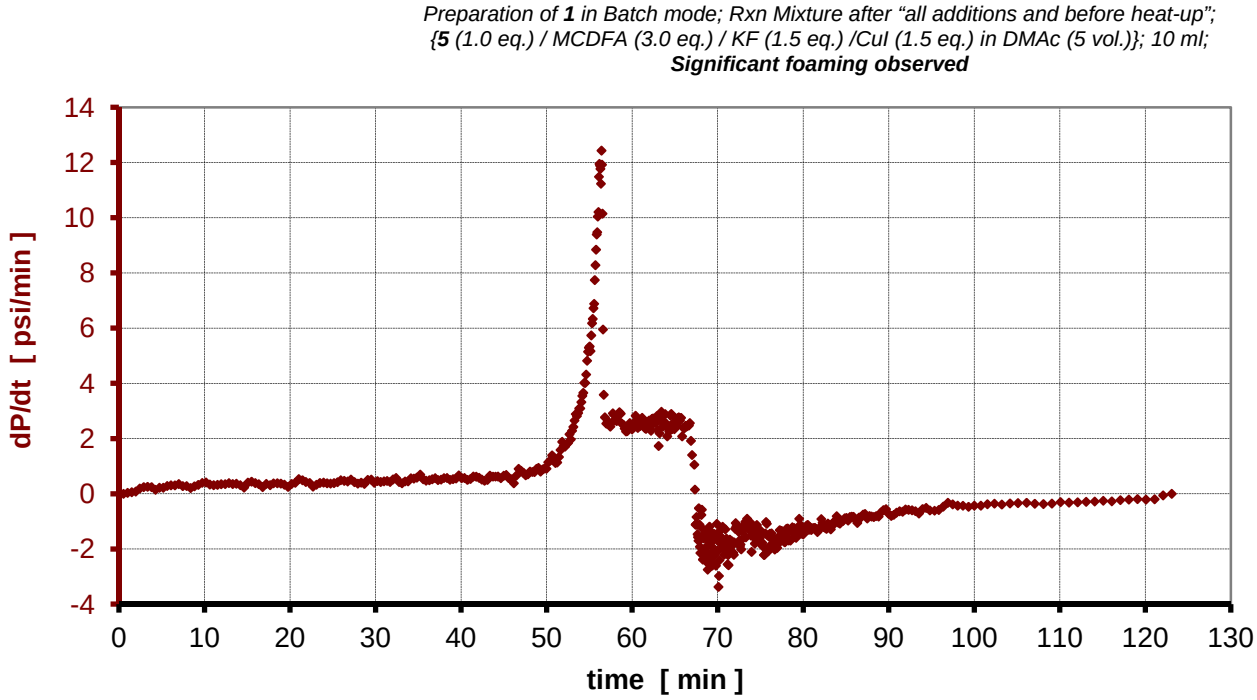


Figure A7: Time Derivative of Temperature (Self Heat Rate) vs. Temperature Profile; Preparation of "**1"** in Batch mode; ARSST experiment

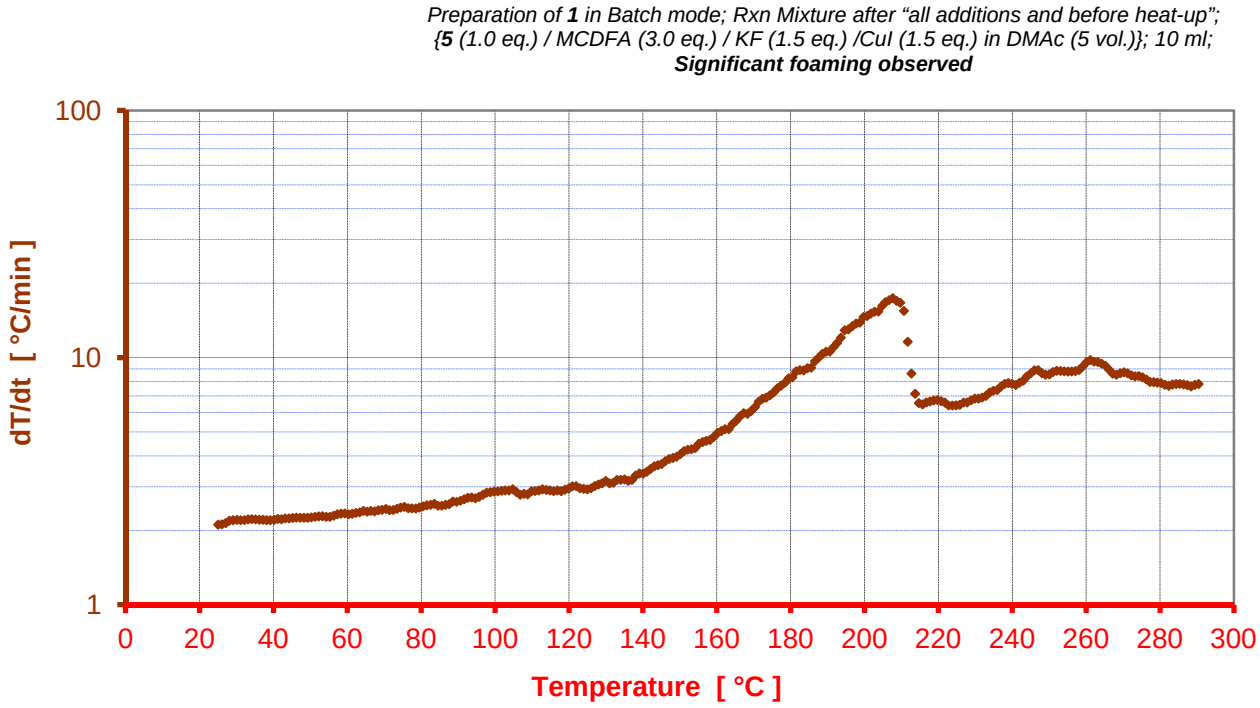


Figure A8: Time Derivative of Pressure (Pressure-rise Rate) vs. Temperature Profile; Preparation of "**1"** in Batch mode; ARSST experiment

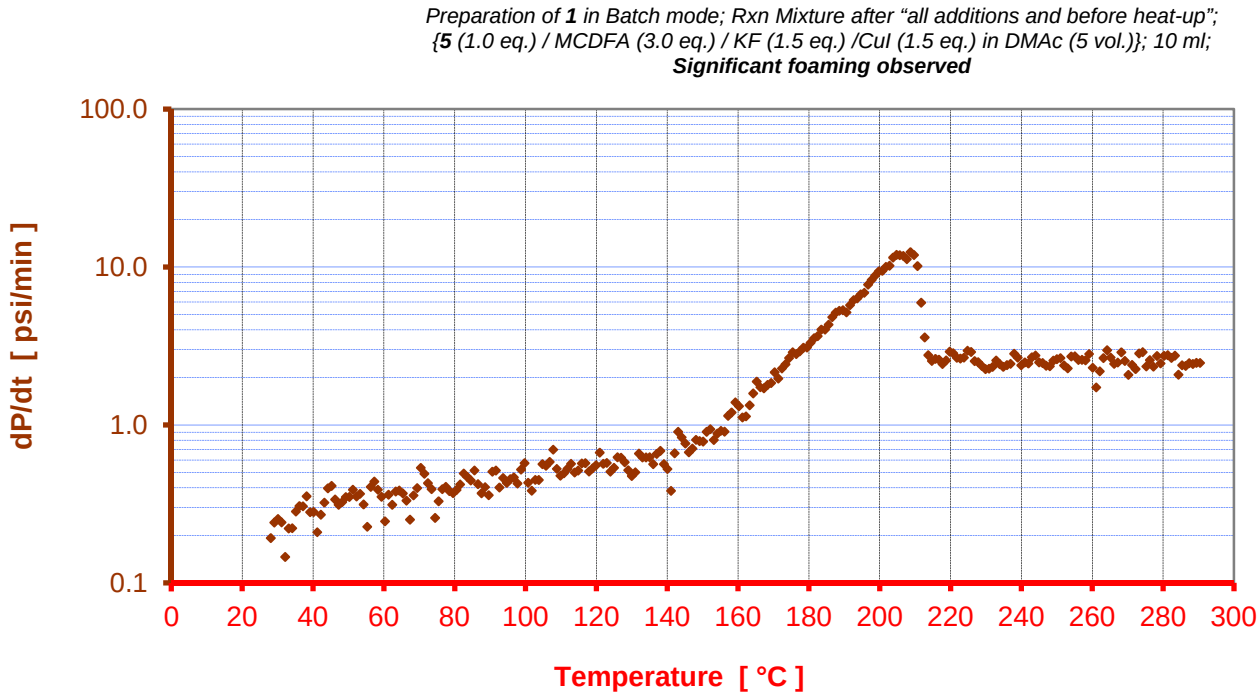


Figure B1: Temperature vs. Time Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

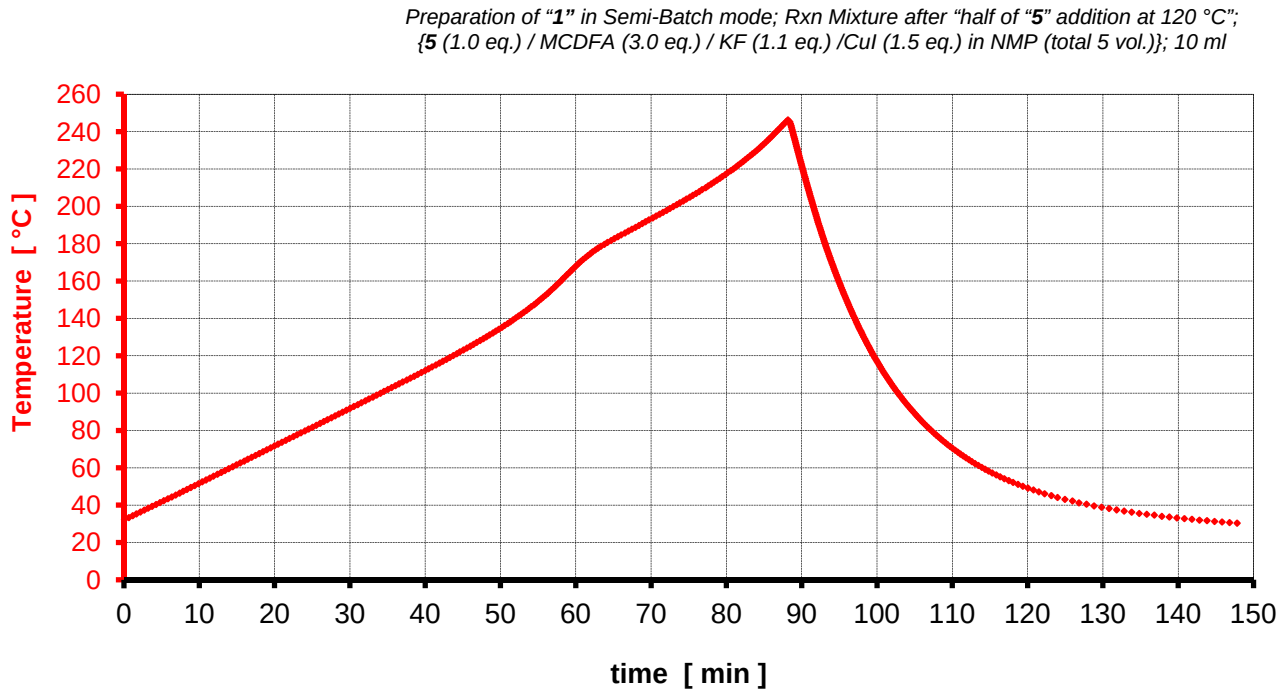


Figure B2: Pressure vs. Time Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

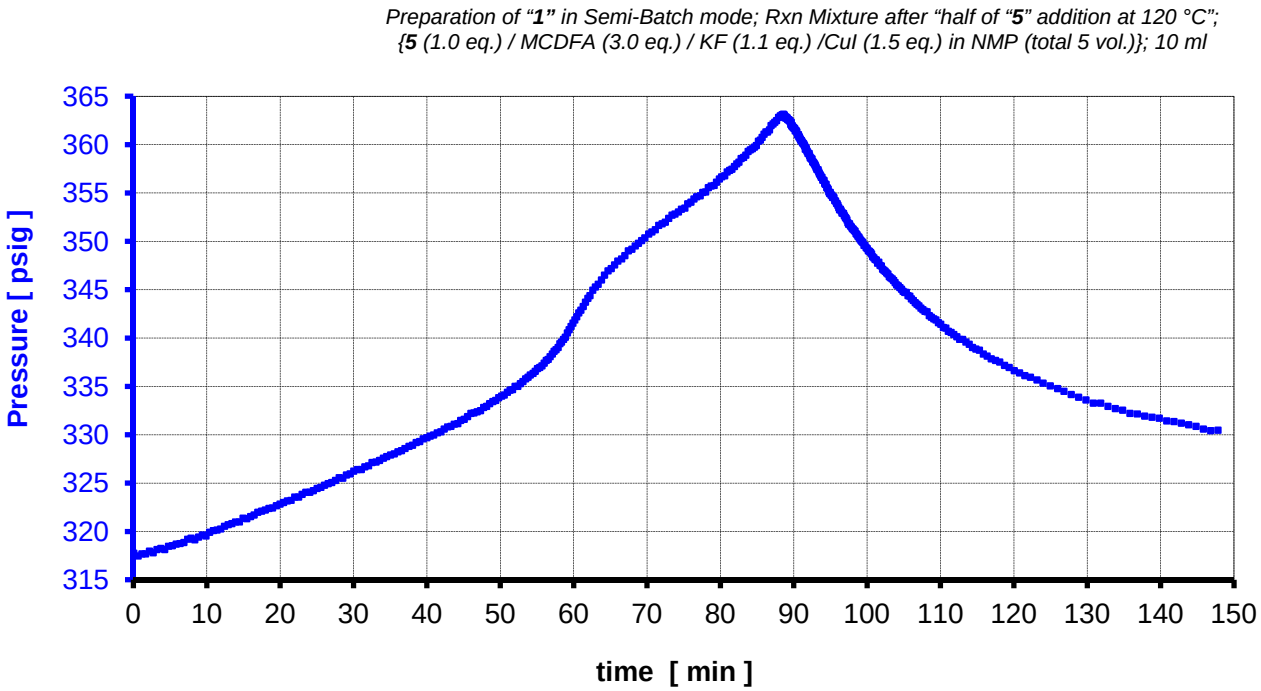


Figure B3: Pressure vs. Temperature Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

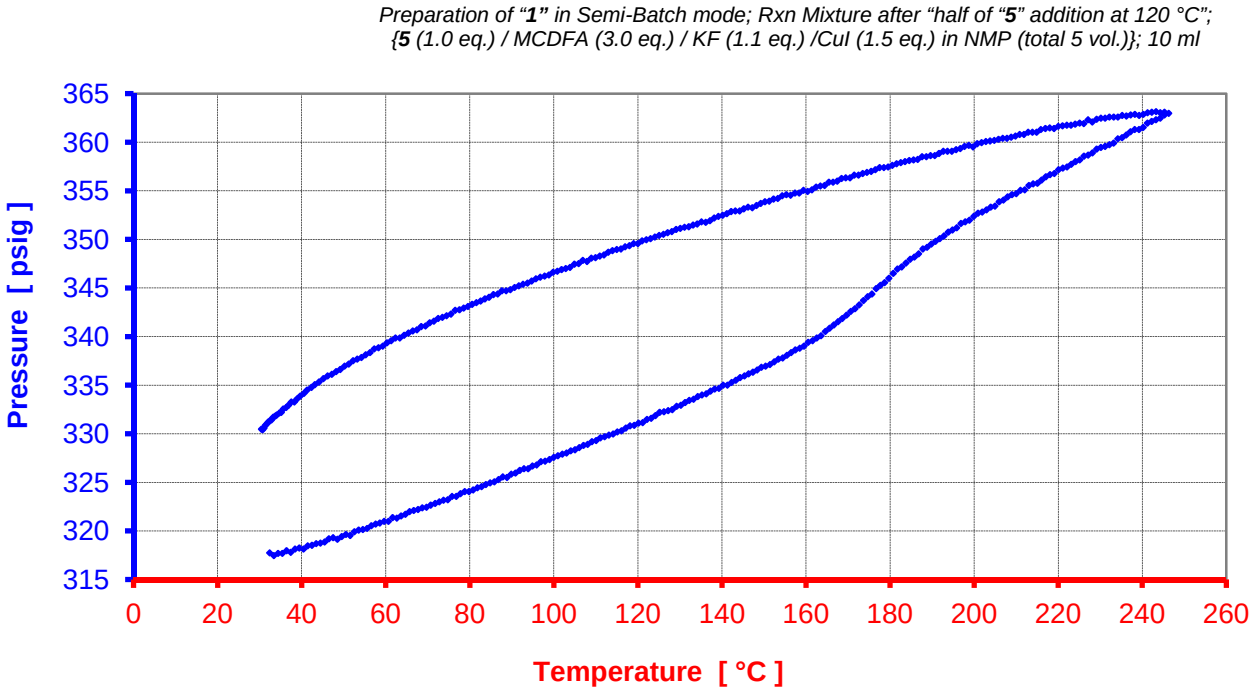


Figure B4: Time Derivative of Temperature vs. Temperature Profile: Preparation of "**1"** in Semi-Batch mode; ARSST experiment; only heat-up part of the curve is shown here.

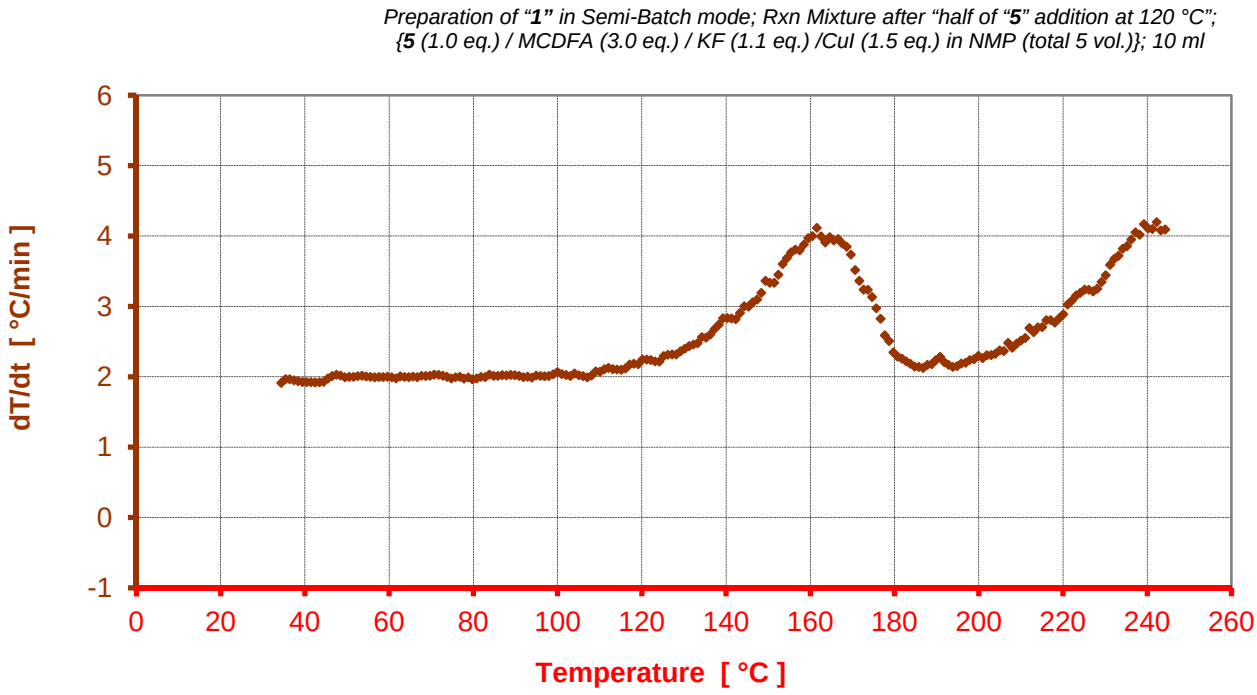


Figure B5: Time Derivative of Temperature (Self Heat Rate) vs. Time Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

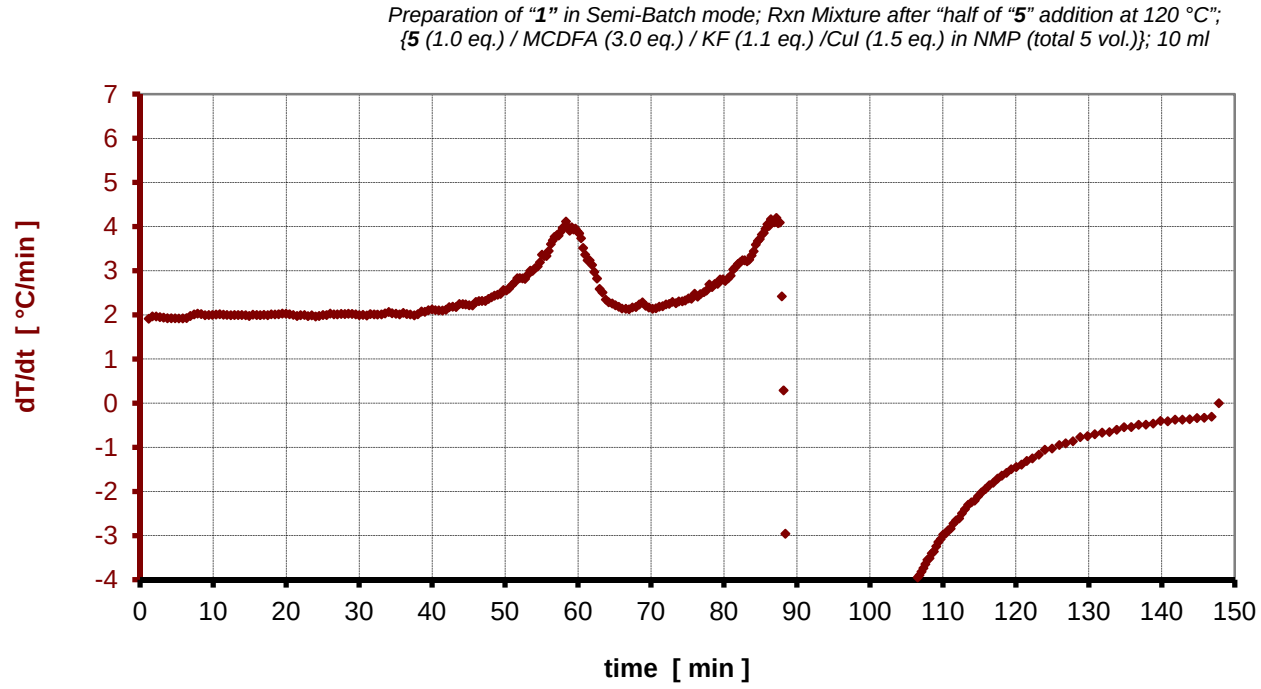


Figure B6: Time Derivative of Pressure (Pressure-rise Rate) vs. Time Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

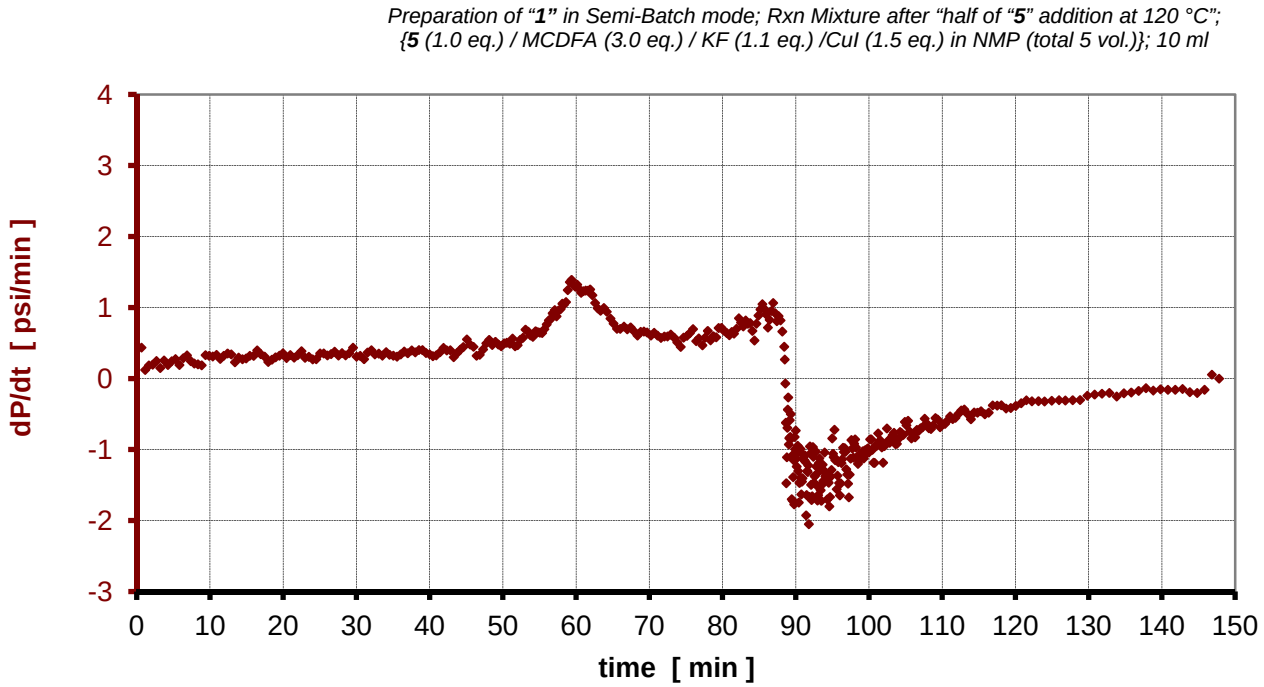


Figure B7: Time Derivative of Temperature (Self Heat Rate) vs. Temperature Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

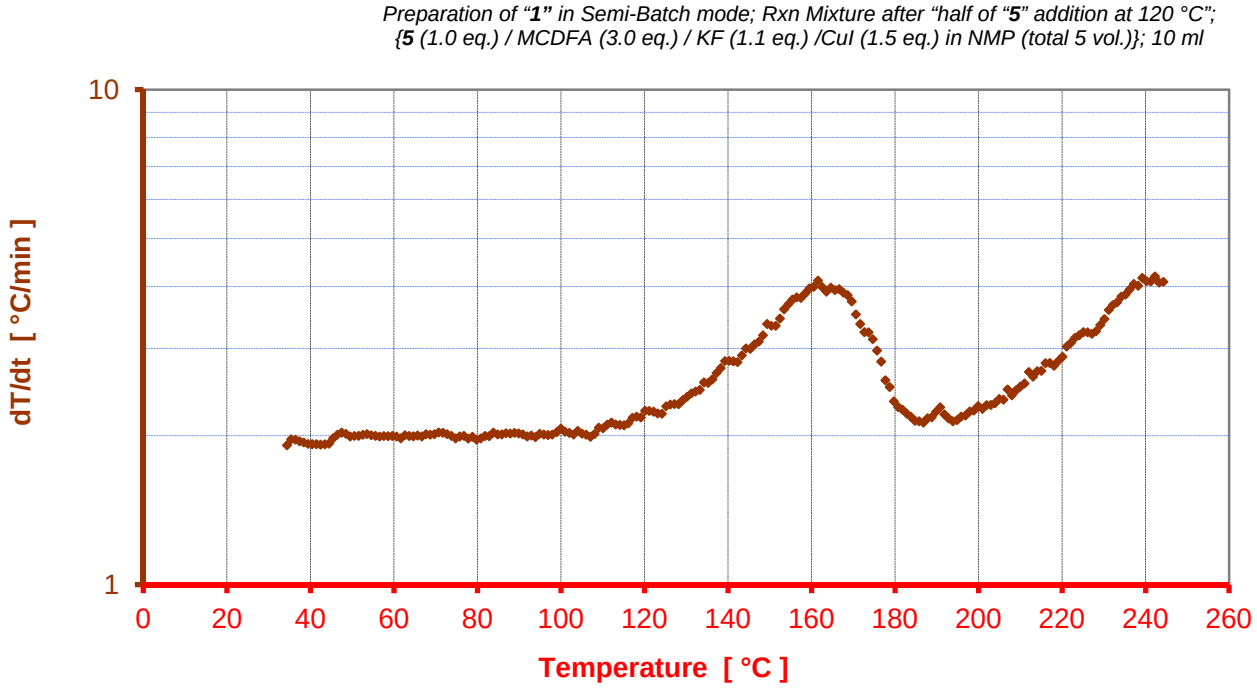


Figure B8: Time Derivative of Pressure (Pressure-rise Rate) vs. Temperature Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

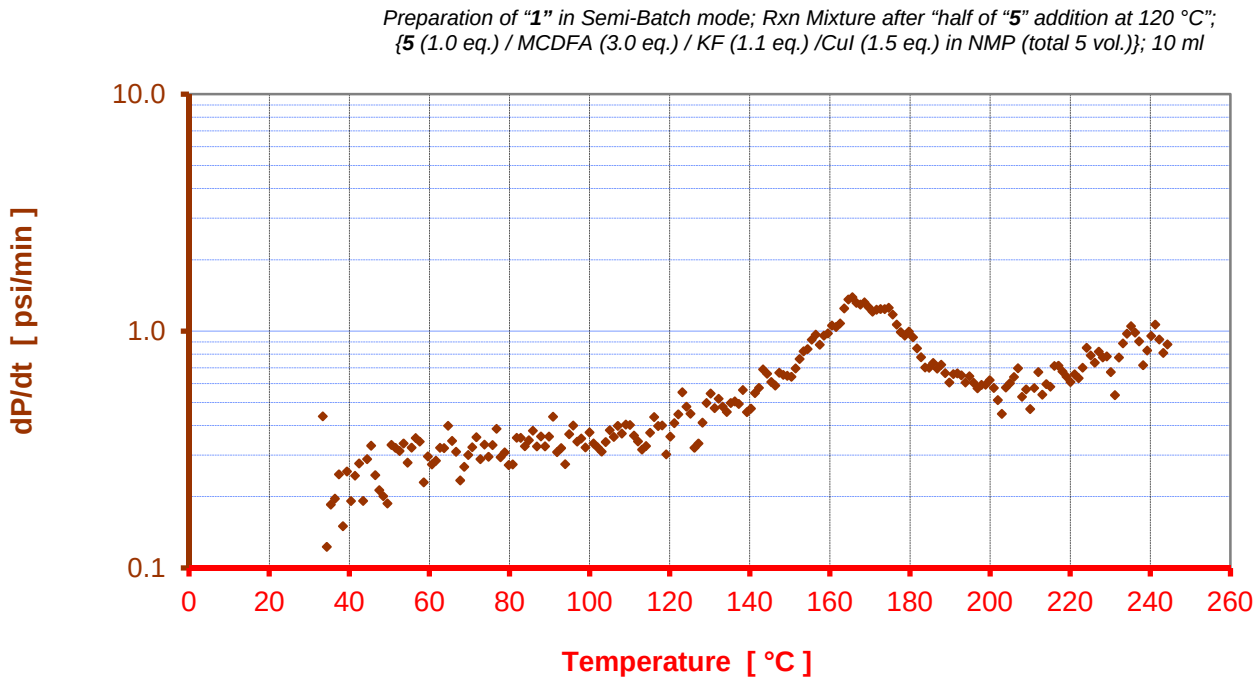


Figure C1: Temperature vs. Time Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

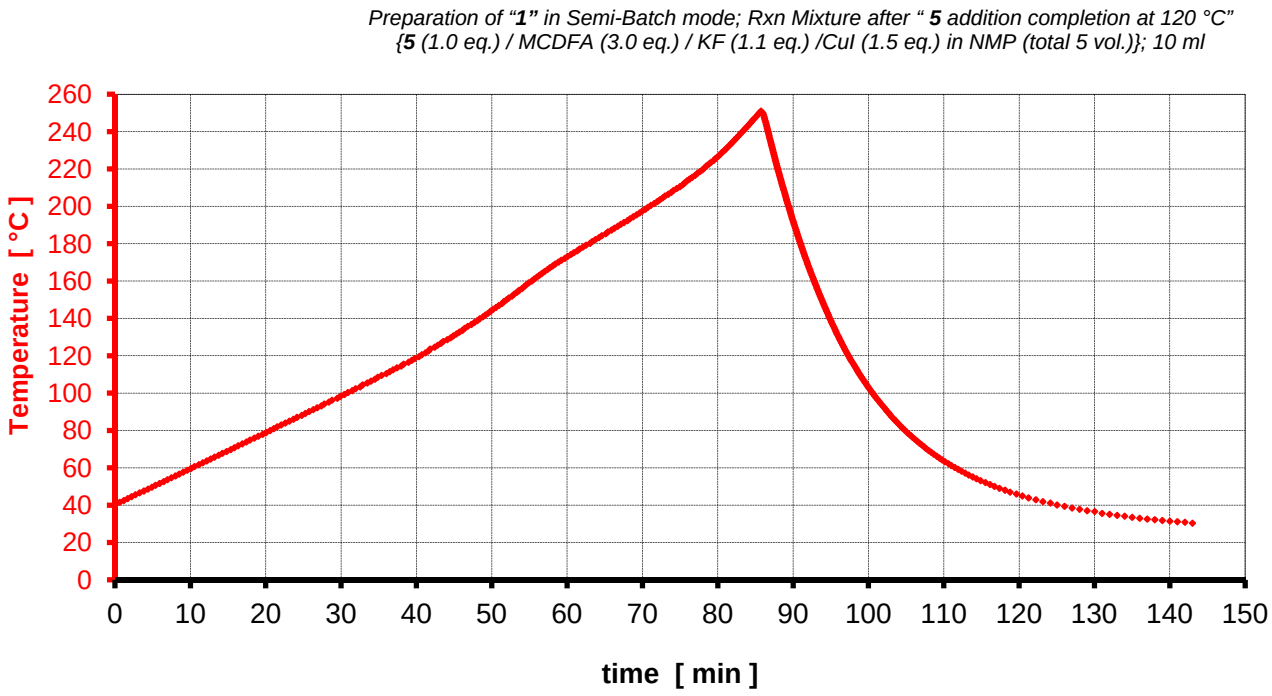


Figure C2: Temperature vs. Time Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

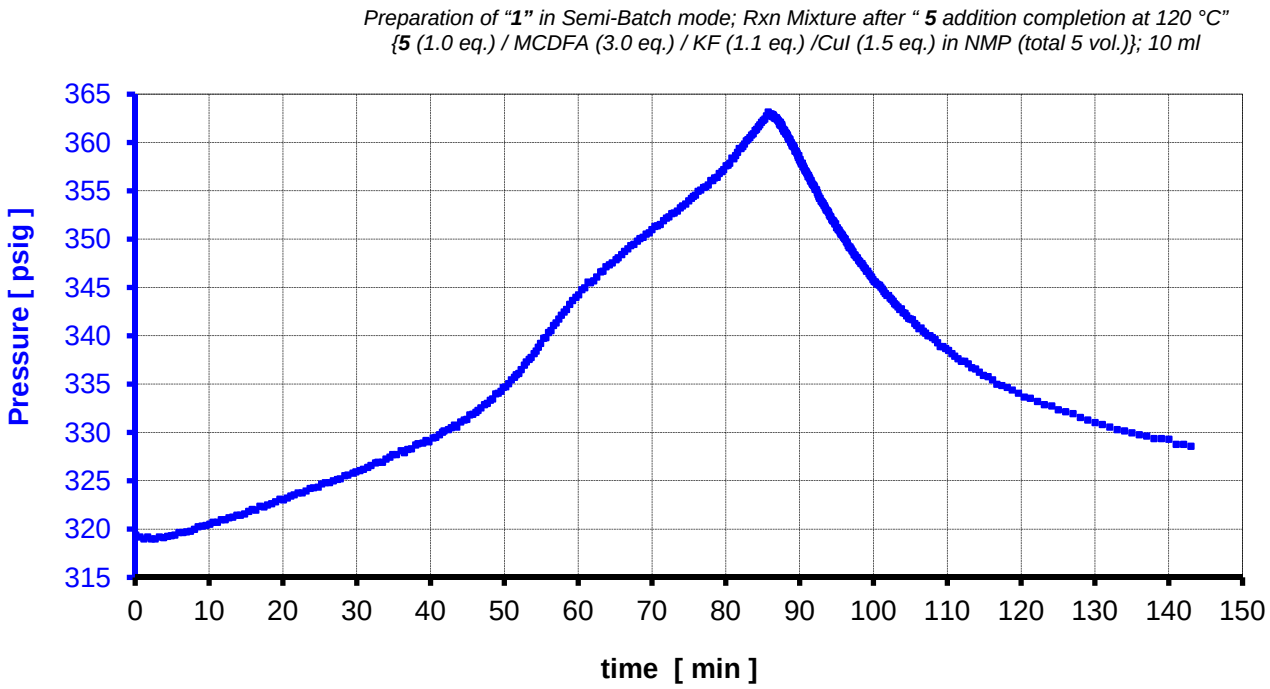


Figure C3: Temperature vs. Time Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

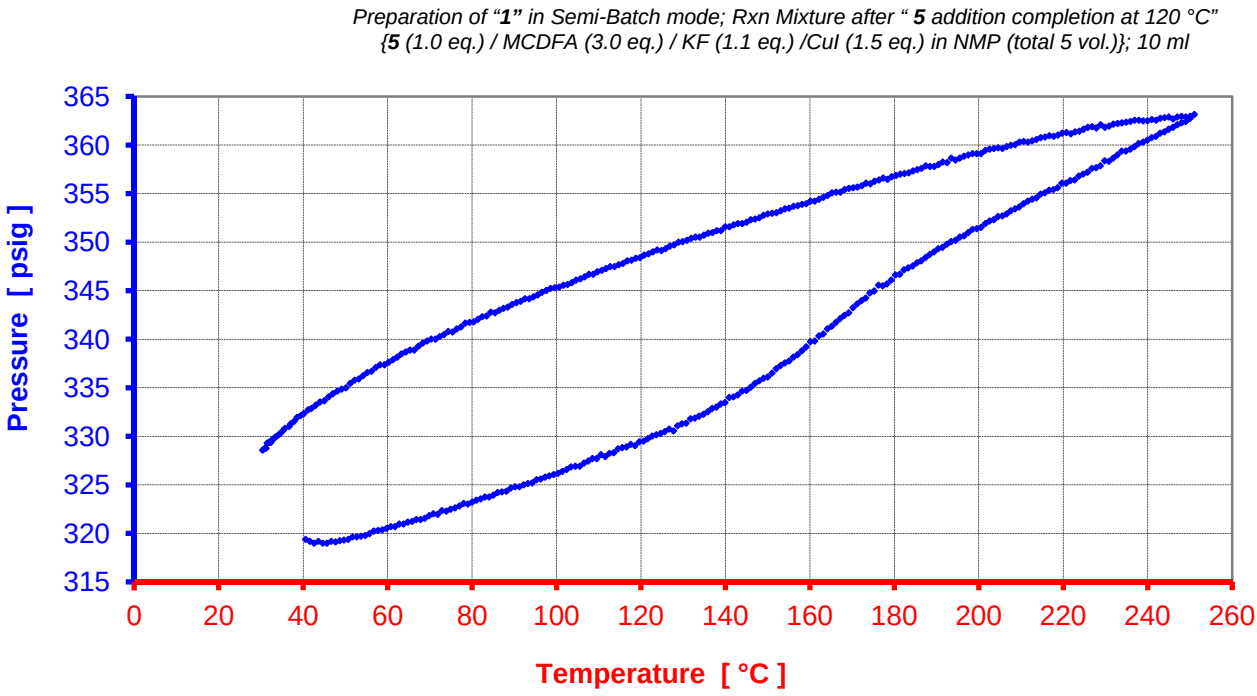


Figure C4: Time Derivative of Temperature vs. Temperature Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment; only heat-up part of the curve is shown here.

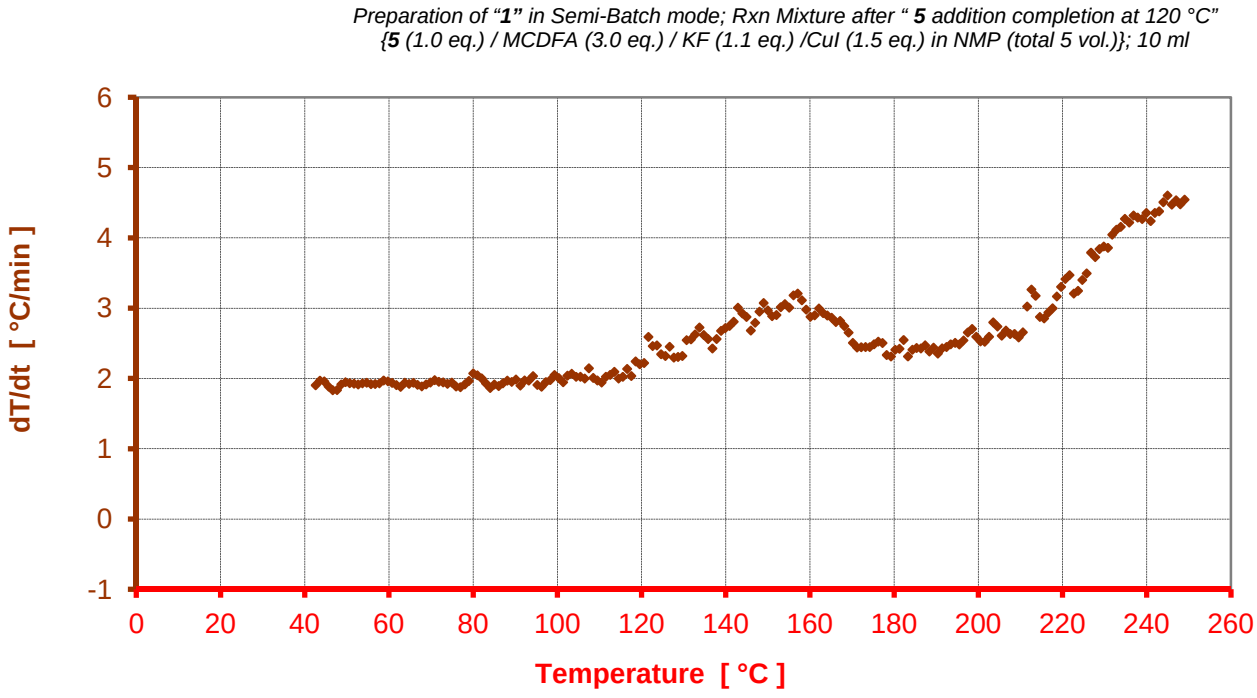


Figure C5: Time Derivative of Temperature (Self Heat Rate) vs. Time Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

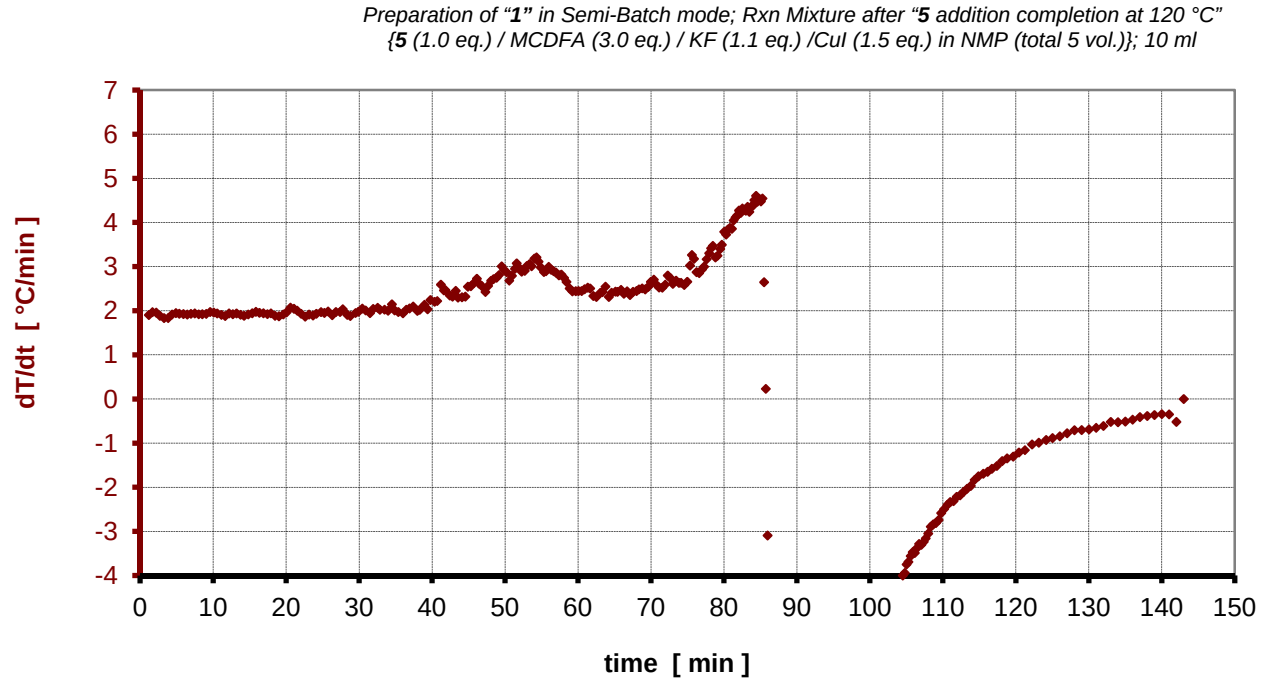


Figure C6: Time Derivative of Pressure (Pressure-rise Rate) vs. Time Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

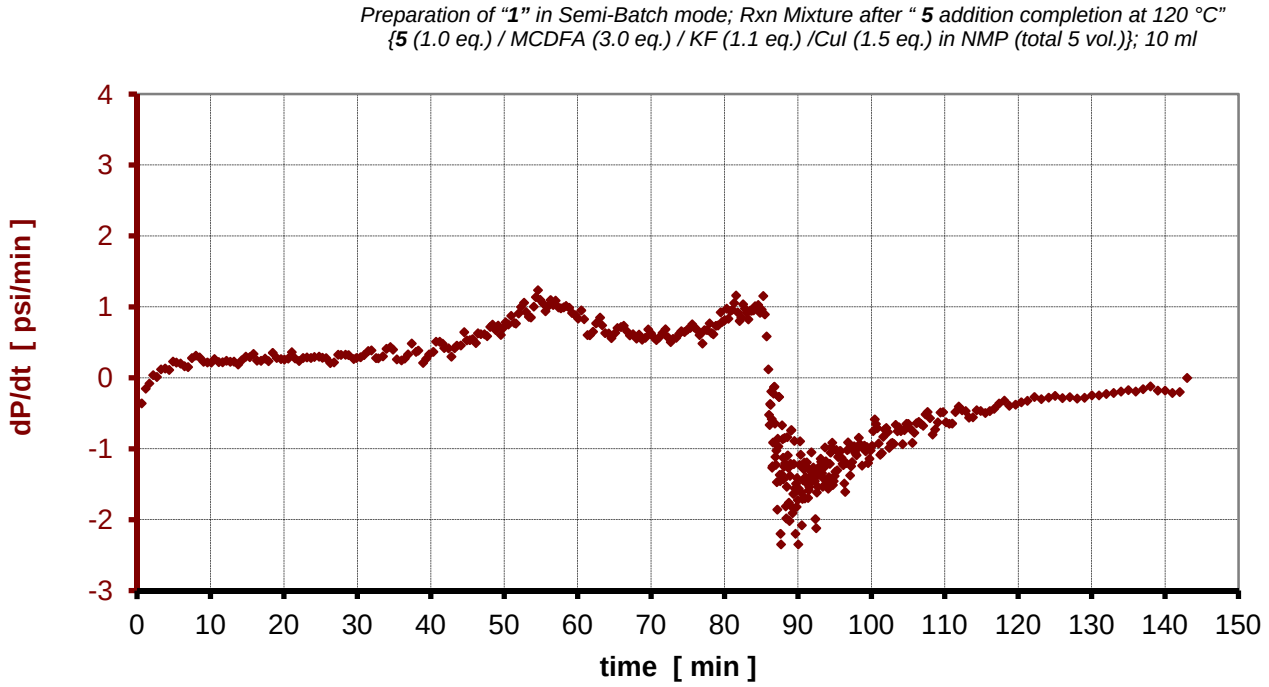


Figure C7: Time Derivative of Temperature (Self Heat Rate) vs. Temperature Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment

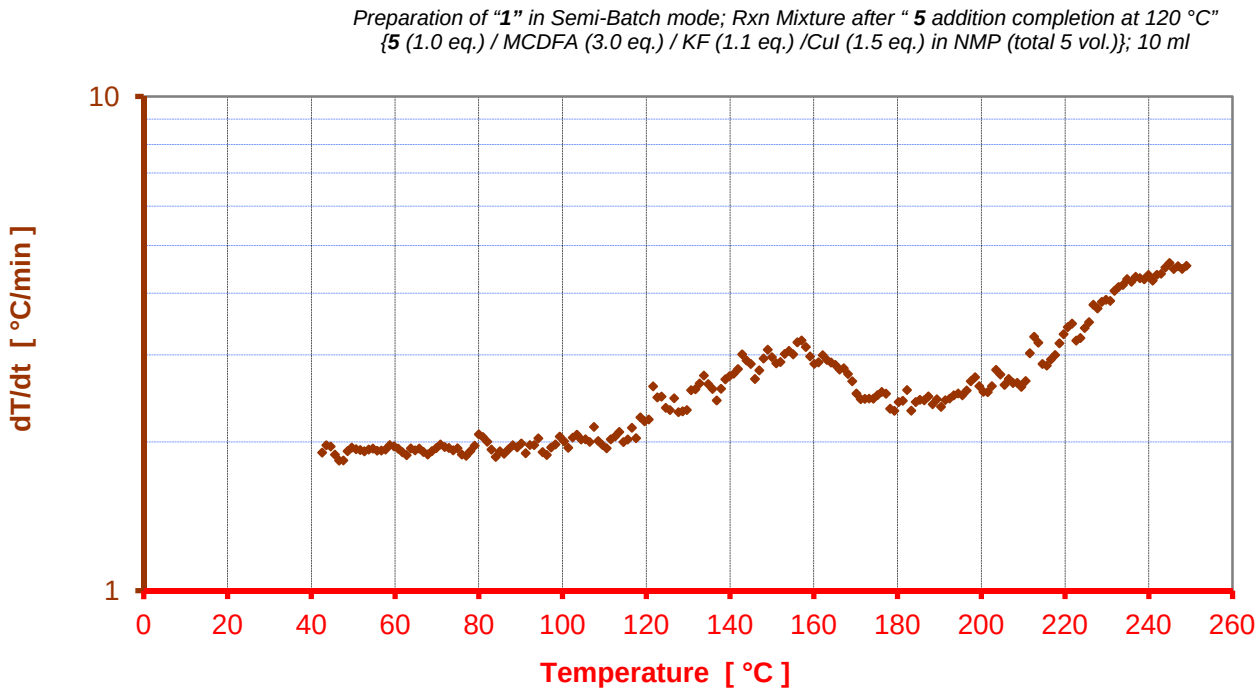
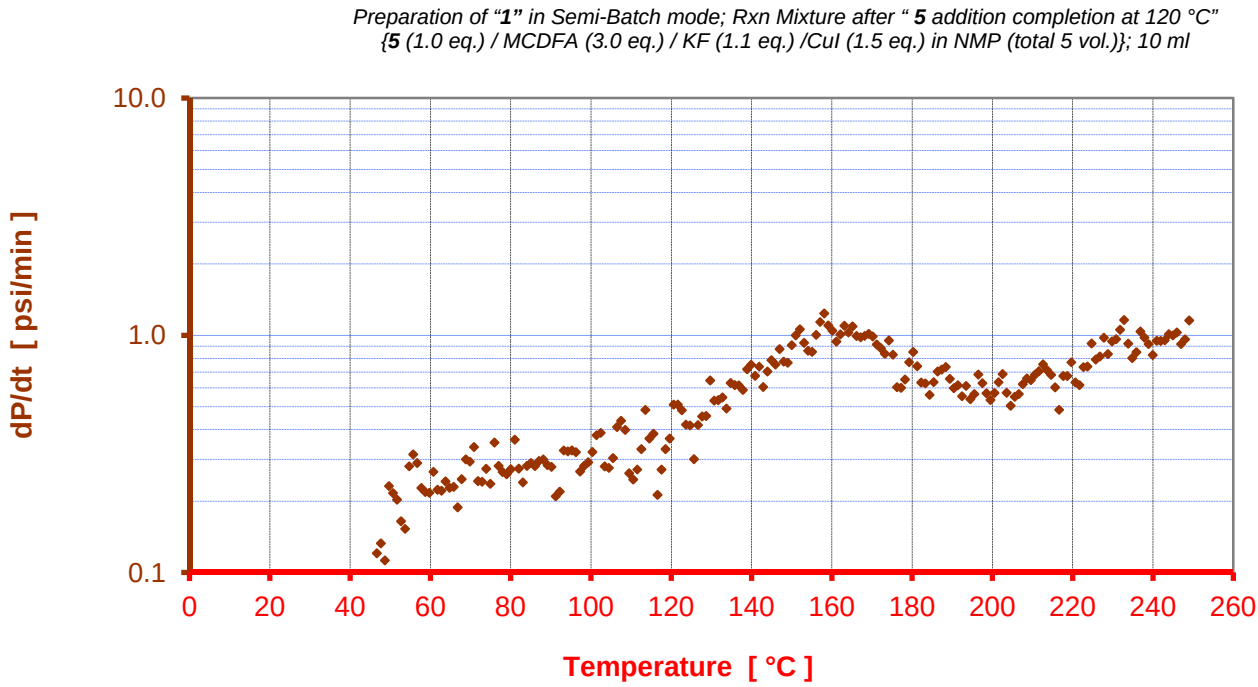
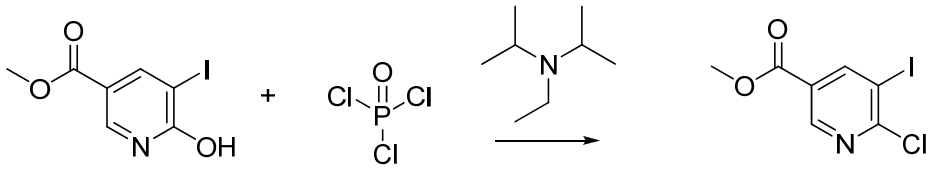


Figure C8: Time Derivative of Pressure (Pressure-rise Rate) vs. Temperature Profile; Preparation of "**1"** in Semi-Batch mode; ARSST experiment



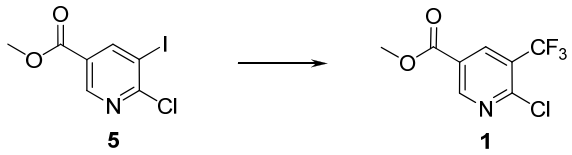


3 **5**

Chlorination in 10V solvent, 2 equiv $POCl_3$, 1 equiv Hunig base. (200 mg scale) (220 nm)

Entry	solvent	temp	time	conv	pdt	SM	assay
1	ACN	80 °C	12h	99.6%	99.3%	0.4%	-
2	dioxane	100 °C	12h	100%	100%	0	97%
3	anisole	100 °C	12h	98.7%	97.9%	1.3%	94%
4	anisole	105 °C	14h	84.7%	77.4%	15.3%	-
5	fluorobenzene	100 °C	12h	40%	15%	60%	-
6	CPME	100 °C	12h	96.3%	96.1%	3.7%	88%
7	CPME	105 °C	14h	96.3%	95.1%	3.7%	-
8	toluene	100 °C	12h	40%	20%	60%	--
9	diethoxyethane	100 °C	12h	98.5%	97.9%	1.5%	90%
10	diethoxyethane	105 °C	14h	99.8%	99%	0.2%	98%
11	DMF	100 °C	12h	94.6%	89%	5.4%	84%
12	DMF	105 °C	14h	86.2%	54.6%	13.8%	
13	MeTHF	80 °C	14h	76.0%	67.3%	24.0%	-
14	2-butanone	80 °C	14h	91.2%	85.7%	8.8%	-
15	DME	85 °C	14h	99.6%	98.3%	0.4%	99%
16	NMP	105 °C	14h	39.9%	27.6%	60.1%	-
17	*Sec*-butylacetate	105 °C	14h	97.0%	93.2%	3.0%	-
18	DMAc	100 °C	12h	messy	trace		-

TRIFLUOROMETHYLATION USING STOICHIOMETRIC COPPER: SELECTED SCREENING DATA



Summary of observations:

- Copper iodide is superior to other copper sources for the trifluoromethylation using stoichiometric copper.
- NMP is inferior to DMAc (entry 3 vs entry 1)
- 3v, 5v, 10v give similar yield, there is a minor concentration effect (entries 1, 5, 8), some difficulty stirring observed with 3v.
- Reducing CuI below 1.5 equiv. is detrimental to the reaction (entries 6, 7 vs entry 5). More than 1.5 equiv. is not beneficial (entry 4 vs entry 5).
- 70% assay yield was obtained with 1.5 h slow addition of ClF_2CCO_2Me (entry 5), longer addition time (3h in entry 2) is detrimental.
- Addition of ligand (1,10 phenanthroline) is detrimental under stoichiometric copper conditions (entry 9 vs entry 6).
- A major by-product is hydro-deiodination of **5** (des-I).

Table A: Stoichiometric Trifluoromethylation: Copper Source Screen

	copper reagent	DMAc	conv. 3h	pdt. (**1**) (HPLC A%)	des-I (HPLC A%)	notes
1	CuI	5v	98%	80.3%	7.7%	
2	$Cu(II)(acac)_2$	5v	75% (3h) 79% (6h)	47% (3h) 52% (6h)	85.% (3h) 11% (6h)	
3	$Cu(II)(OTf)_2$	5v	37%	1%	1.5%	5,6 Bis-Cl 22%
4	$Cu(I)Br(1,10\text{-phen})(PPh_3)$	10v	98%	18%	63%	
5	$Cu(I)(NO_3)(1,10\text{-phen})(PPh_3)$	5v	99%	0	37%	5,6 Bis-Cl 7%
6	$Cu(I)(ACN)_4(PF_6)$	5v	40%	2%	20%	5,6 Bis-Cl 11% Dimer 6%
7	$(Cu(II)(OTf))_2.C_6H_6$ (90%)	5v	72%	2%	14%	5,6 Bis-Cl 16% Dimer 38%
8	CuBr	5v	95%	41%	5%	5,6 Bis-Cl 3% 5-Br, 6-Cl 40%
9	Cu(TC) TC=thiophene-2-carboxylate	5v	55%	1%	25%	5,6 Bis-Cl 3% Dimer 4% + 2 unknown
10	$Cu(II)Br_2(1,10\text{-phen})$	5v	96%	38%	25%	Dimer major

0.5g (**5**) in DMAc at 120 ^oC, KF 1.2 equiv, $ClCF_2CCOOMe$ 3 equiv, HPLC A% (220 nm).

Table B: Stoichiometric Trifluoromethylation With CuI: Reagent / Condition Screening

	solvent (vol)	F_2ClCCO_2Me Add. Time	CuI	KF	conv.	sm (**5**) (A%)	pdt. (**1**) (A%)	des-I (A%)	assay
1	DMAc 10v	1.5h	1.5	1.5	97%	1%	82.5%	5.4%	68%
2	DMAc 10v	3h	1.5	1.5	86%	14%	76.5%	6.5%	61%
3	NMP 10v	1.5h	1.5	1.5	98%	2.4%	69%	4.5%	57%
4	DMAc 5v	1.5h	2	1.2	97.7%	3.0%	83.3%	5.1%	68.1%
5	DMAc 5v	1.5h	1.5	1.2	98.6%	3.6%	82.8%	7.1%	70.5%
6	DMAc 5v	1.5h	1.2	1.2	97%	4.5%	80.7%	3.0%	62.3%
7	DMAc 5v	1.5h	1.0	1.2	98%	8.4%	72.5%	10.3%	54%
8	DMAc 3v	1.5h	1.5	1.2	98.7%	4.3%	81.5%	8.6%	66.6%

0.5g (**5**) at 120 ^oC, $ClF_2CCOOMe$ 3 equiv, HPLC A% (220 nm), assay is wt% based on an HPLC standard. *Added 10% 1,10-phenanthroline

TRFLUOROMETHYLATION USING CATALYTIC COPPER: SELECTED SCREENING DATA

More than 20 copper (I) and copper (II) sources and a variety of CF_3 (:CF_2) sources were screened, below is some additional data as a supplement to the information provided in the manuscript.

Table C: Trifluoromethylation Catalytic in Copper: Reagent Screen

entry	copper reagent	ligand	CF_3 reagent	conv.	sm (**5**) (A%)	pdt.(**1**) (A%)	des-I (A%)	assay
1	Cu(TC)	1,10-phenanthroline (1,10-phen)	$ClF_2CCOOMe$	100%	0%	71%	6%	63%
2	Cu(TC)	2,2'-Bipyridine	$ClF_2CCOOMe$	92%	8%	72%	4%	58%
3	Cu(TC)	2-(2-thienyl)pyridine	$ClF_2CCOOMe$	42%	58%	24%	5%	
4	Cu(TC)	1,10-phen	$CF_3COONEt_4$	25%	75%	0%	6%	
5	Cu(TC)	1,10-phen	CF_3COOEt	22%	78%	0%	6%	
6	Cu(TC)	1,10-phen	CF_3TMS	91%	9%	4%	54%	
7	Cu(TC)	1,10-phen	$FSO_2CF_2CO_2Me$	100%	0%	81%	2%	

8	CuI	2-(2-thienyl)pyridine	$ClF_2CCOOMe$	47%	53%	42%	1%	
9	CuI	1,10-phen	$ClF_2CCOOMe$	91%	9%	68%	6%	67%
10	CuI	2,2'-Bipyridine	$ClF_2CCOOMe$	84%	16%	70%	2%	64%
11	CuI	1,10-phen	$CF_3COONEt_4$	33%	67%	0%	4%	
12	CuI	1,10-phen	CF_3COOEt	2%	98%	1%	1%	
13	CuI	1,10-phen	CF_3TMS	92%	8%	2%	66%	
14	CuI	1,10-phen	TFAA	20%	80%	0%	2%	
15	CuI	1,10-phen	$FSO_2CF_2CO_2Me$	100%	0%	80%	1%	55%
16	$Cu(II)Br_2$(1,10-phen)	2-(2-thienyl)pyridine	$ClF_2CCOOMe$	43%	57%	33%	5%	
17	$Cu(II)Br_2$(1,10-phen)	1,10-phen	$ClF_2CCOOMe$	55%	45%	34%	12%	
18	$Cu(II)Br_2$(1,10-phen)	2,2'-Bipyridine	$ClF_2CCOOMe$	94%	6%	70%	7%	69%
19	$Cu(II)Br_2$(1,10-phen)	1,10-phen	$CF_3COONEt_4$	42%	58%	0%	4%	
20	$Cu(II)Br_2$(1,10-phen)	1,10-phen	CF_3COOEt	5%	95%	3%	0%	
21	$Cu(II)Br_2$(1,10-phen)	1,10-phen	CF_3TMS	53%	47%	16%	2%	
22	$Cu(I)(ACN)_4(PF_6)$	2-(2-thienyl)pyridine	$ClF_2CCOOMe$	40%	60%	36%	1%	
23	$Cu(I)(ACN)_4(PF_6)$	1,10-phen	$ClF_2CCOOMe$	95%	5%	75%	5%	73%
23	$Cu(I)(ACN)_4(PF_6)$	2,2'-Bipyridine	$ClF_2CCOOMe$	72%	28%	40%	14%	
25	$Cu(I)(ACN)_4(PF_6)$	1,10-phen	$CF_3COONEt_4$	22%	78%	0%	2%	
26	$Cu(I)(ACN)_4(PF_6)$	1,10-phen	CF_3COOEt	9%	91%	0%	2%	
27	$Cu(I)(ACN)_4(PF_6)$	1,10-phen	CF_3TMS	62%	38%	22%	17%	
28	$Cu(I)(ACN)_4(PF_6)$	1,10-phen	$FSO_2CF_2CO_2Me$	99%	1%	76%	1%	72%
29	$Cu(II)(NO_3)_2$(1,10-phen)	2-(2-thienyl)pyridine	$ClF_2CCOOMe$	76%	24%	46%	16%	
30	$Cu(II)(NO_3)_2$(1,10-phen)	1,10-phen	$ClF_2CCOOMe$	65%	35%	41%	8%	
31	$Cu(II)(NO_3)_2$(1,10-phen)	1,10-phen	$ClF_2CCOOMe$	65%	35%	41%	8%	
32	$Cu(II)(NO_3)_2$(1,10-phen)	1,10-phen	$CF_3COONEt_4$	5%	95%	5%	0%	
33	$Cu(II)(NO_3)_2$(1,10-phen)	1,10-phen	CF_3COOEt	5%	95%	2%	0%	
34	$Cu(II)(NO_3)_2$(1,10-	1,10-phen	CF_3TMS	42%	58%	18%	8%	

	phen)							
35	$Cu(II)(acac)_2$	2-(2-thienyl)pyridine	$ClF_2CCOOMe$	33%	67%	30%	1%	
36	$Cu(II)(acac)_2$	1,10-phen	$ClF_2CCOOMe$	100%	1%	86%	5%	76%
37	$Cu(II)(acac)_2$	2,2'-Bipyridine	$ClF_2CCOOMe$	94%	6%	83%	2%	74%
38	$Cu(II)(acac)_2$	1,10-phen	$CF_3COONEt_4$	37%	63%	0%	29%	
39	$Cu(II)(acac)_2$	1,10-phen	CF_3COOEt	16%	84%	0%	10%	
40	$Cu(II)(acac)_2$	1,10-phen	CF_3TMS	93%	7%	0%	75%	
41	$Cu(II)(acac)_2$	1,10-phen	$FSO_2CF_2CO_2Me$	62%	38%	45%	1%	
42	$Cu(II)(OAc)_2$	2-(2-thienyl)pyridine	$ClF_2CCOOMe$	22%	78%	17%	1%	
43	$Cu(II)(OAc)_2$	1,10-phen	$ClF_2CCOOMe$	99%	1%	84%	2%	71%
44	$Pd(acac)_2$	1,10-phen	$ClF_2CCOOMe$	31%	69%	22%	3%	
45	$Pd(acac)_2$	1,10-phen	TFAA	35%	65%	0%	0%	
46	$Pd(acac)_2$	2-(2-thienyl)pyridine	TFAA	33%	67%	0%	0%	

Trifluoromethylation: 50 mg at 80-90 ^oC, $CF_2ClCOOMe$ 3 equiv, KF 2 equiv. HPLC A% (220 nm).

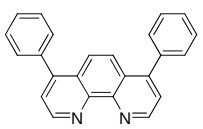
A wide variety of ligands were tested. A subset of these results is shown below. The variety of copper sources should not skew the results as CuI, Cu(TC), and $Cu(I)(CH_3CN)_4PF_6$ all show good results (entries 1-3) at this scale using the 1,10-phenanthroline ligand.

Table D: Trifluoromethylation Catalytic in Copper: Ligand Survey

entry	scale	catalyst	ligand		equiv	sm (A%)	pdt (A%)	des-I (A%)
1	50 mg	Cu(TC)	1,10-phen	KF	2	18%	**71%**	11%
2	50 mg	CuI	1,10-phen	KF	2	34%	**58%**	8%
3	50 mg	$Cu(I)(ACN)_4(PF_6)$	1,10-phen	KF	2	5%	**75%**	5%
4	50 mg	CuI	**L1**	KF	2	69%	**29%**	2%
5	50 mg	CuI	**L2**	KF	2	51%	**42%**	8%
6	50 mg	**cat1**	-	KF	2	21%	**69%**	10%
7	50 mg	**cat2**	-	KF	2	50%	**39%**	11%
8	50 mg	Cu(TC)	**L3**	KF	2	54%	**38%**	8%
9	0.2g	Cu(TC)	**L4**	KF	2	94%	**5%**	1%
10	0.2g	Cu(TC)	**L5**	KF	2	97%	**2%**	1%
11	0.2g	Cu(TC)	**L6**	KF	2	97%	**1%**	1%
12	50 mg	Cu(TC)	**L7**	CsF	2	80%	**1%**	2%
13	0.2g	Cu(TC)	**L8**	KF	2	97%	**1%**	2%
14	0.2g	Cu(TC)	**L8 (1 eq.)**	KF	2	93%	**4%**	2%
15	0.2g	$Cu(I)(CH_3CN)_4PF_6$	**TBTA**	KF	2	79%	**18%**	2%
16	0.2g	$Cu(I)(CH_3CN)_4PF_6$	**BINAP**	KF	2	97%	**2%**	1%
17	0.2g	$Cu(I)(CH_3CN)_4PF_6$	**L9**	KF	2	99%	**0**	1%

18	0.2g	$Cu(I)(CH_3CN)_4PF_6$	**L10**	KF	2	99%	**1%**	0%
19	0.2g	$Cu(I)(CH_3CN)_4PF_6$	**2,2'-Bipyridine**	KF	2	99%	**0**	1%
20	0.2g	$Cu(I)(CH_3CN)_4PF_6$	**Proline**	KF	2	99%	**0**	1%

10 v DMAc at 80 ^oC, 3h, 10 mol% Cu, 10 mol% ligand (if applicable), KF 2 equiv., ClF_2CCO_2Me 3-4 equiv. (HPLC A% 220 nm)



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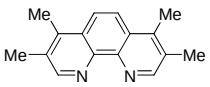

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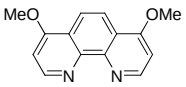

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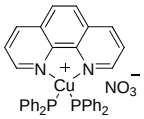

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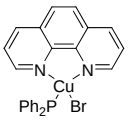

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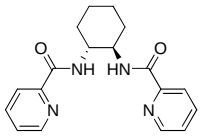
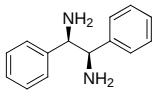
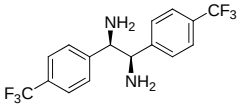


L4

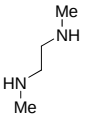


L5

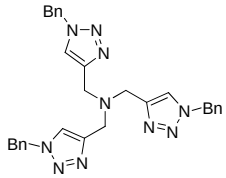
L6



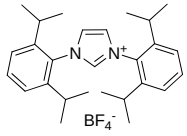
L7



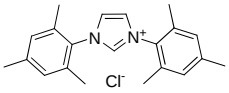
L8



TBTA



L9



L10