Supporting Information to

High Pressure Initiated Solvent and Catalyst-free Instant Paal-Knorr Reactions

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Materials and Methods

Materials: All amines and 2,5-hexanedione were purchased from Aldrich and used without any purification. NH_4OH (a 28-30% aqueous solution) was a ThermoFisher Scientific product. $CDCl_3$ used as a solvent (99.8%) for NMR studies was an Aldrich product. Ethyl acetate used for product isolation in the NH_4OH reactions (minimum purity of 99.5%) was purchased from ThermoFisher Scientific. The small scale reactor tubes were made of teflon and obtained from Pressure BioSciences Inc. while the larger scale bulbs were made of polyethylene and purchased from ThermoFisher Scientific.

Analysis: The ^{1}H and ^{13}C spectra were obtained on a 400 MHz Agilent MM2 NMR spectrometer, in $CDCl_3$ with either using the signal of tetramethylsilane or the residual solvent signal as reference. The temperature was 25 °C (accuracy ±1 °C) . All products were known compounds and the NMR spectra were in agreement with earlier sources. The mass spectrometric identification and purity determination of the products have been carried out by an Agilent 6850 gas chromatograph-5973 mass spectrometer system (70 eV electron impact ionization) using a 30m long DB-5 type column (J&W Scientific).

General procedure for the catalyst and solvent-free reaction of hexan-2,5-dione and aq. NH_4OH under High Hydrostatic Pressure.

To a 150 µL high-pressure teflon reaction tube was added hexan-2,5-dione (41.0 mg, 0.360 mmol) and 2.0 eq 28-30% NH_4OH (83.9 mg, 0.720 mmol) which could just fill up the entire reaction tube, then the tube was sealed by teflon PCT MicroCaps. Afterward, the tube was placed in the chamber compartment of Barocycler 2320EXT (Pressure BioSciences Inc.). The chamber was filled up with water and pressurized up to 3.8 kbar. The mixture of **1** and **2** was reacted under 3.8 kbar at room temperature for 10 seconds. After removing the reaction tube, from the pressure chamber, the organic materials were extracted with ethyl acetate. After extraction the organic phase was dried and the solvent removed and the yield was determined by an Agilent 6850 gas chromatograph 5973 mass spectrometer system (70 eV electron impact ionization) using a 30 m long DB-5 column (J&W Scientific).

Figure SI 1: The test Paal-Knorr reaction for the optimization of the reaction conditions

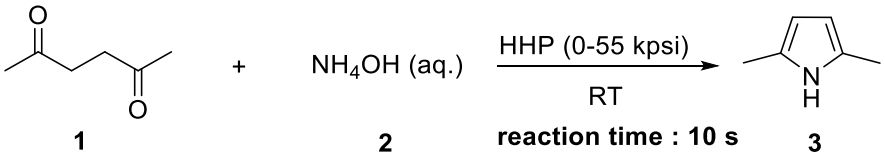
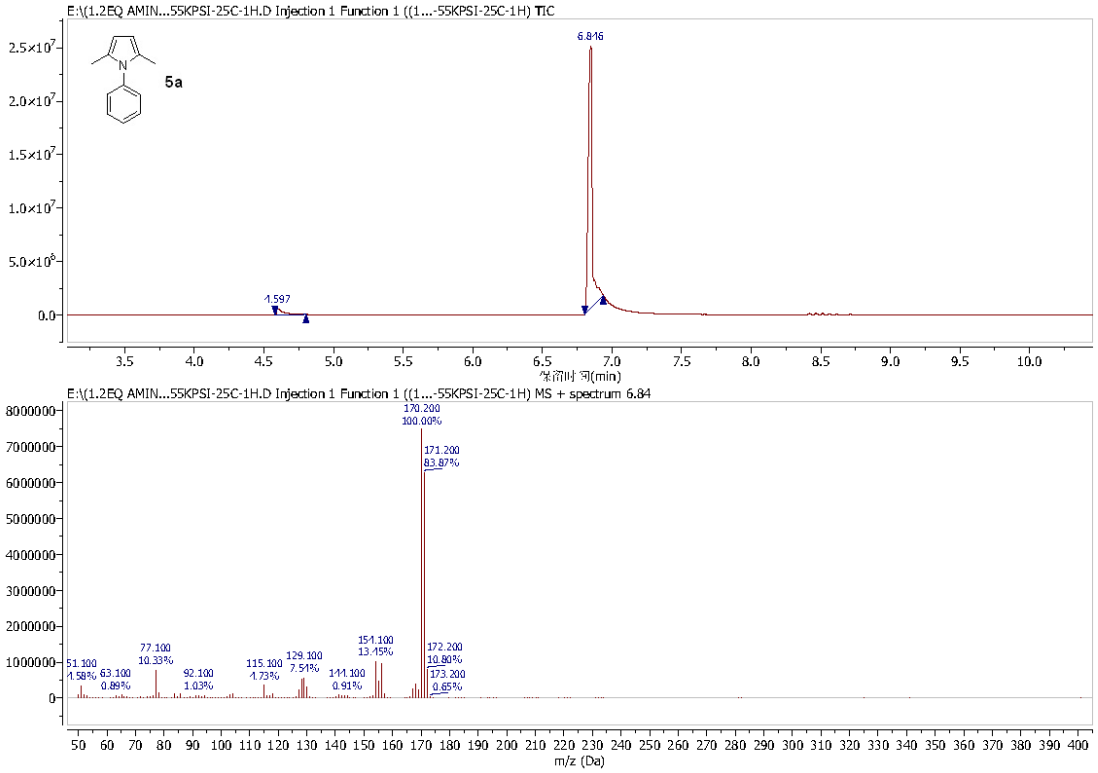
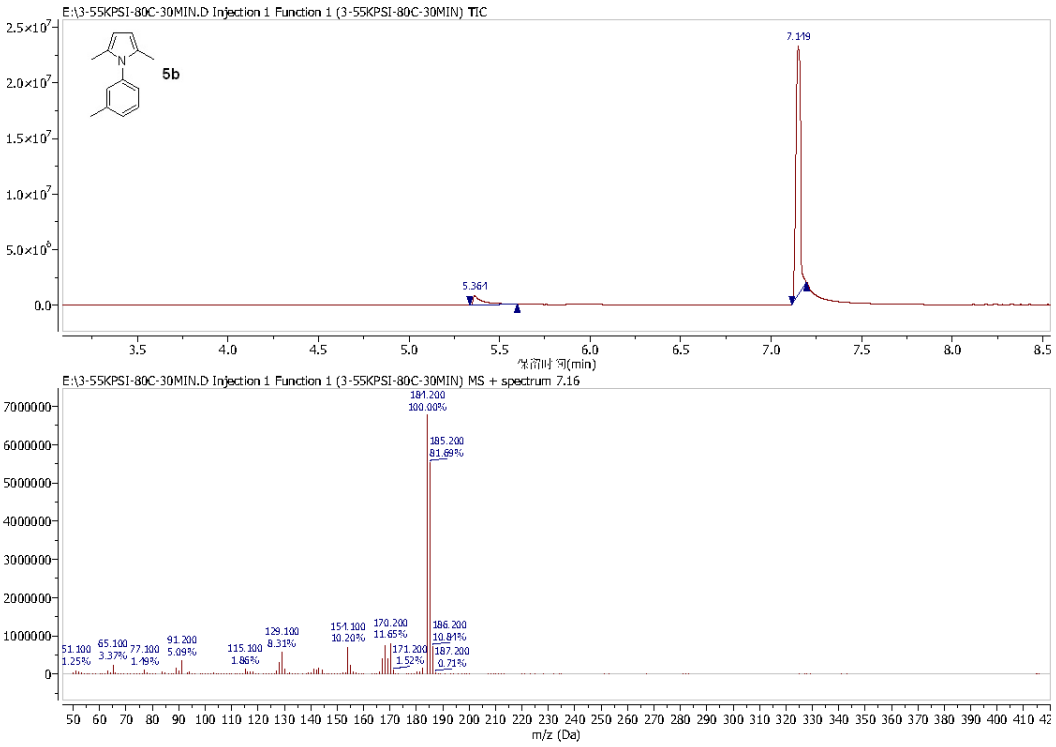
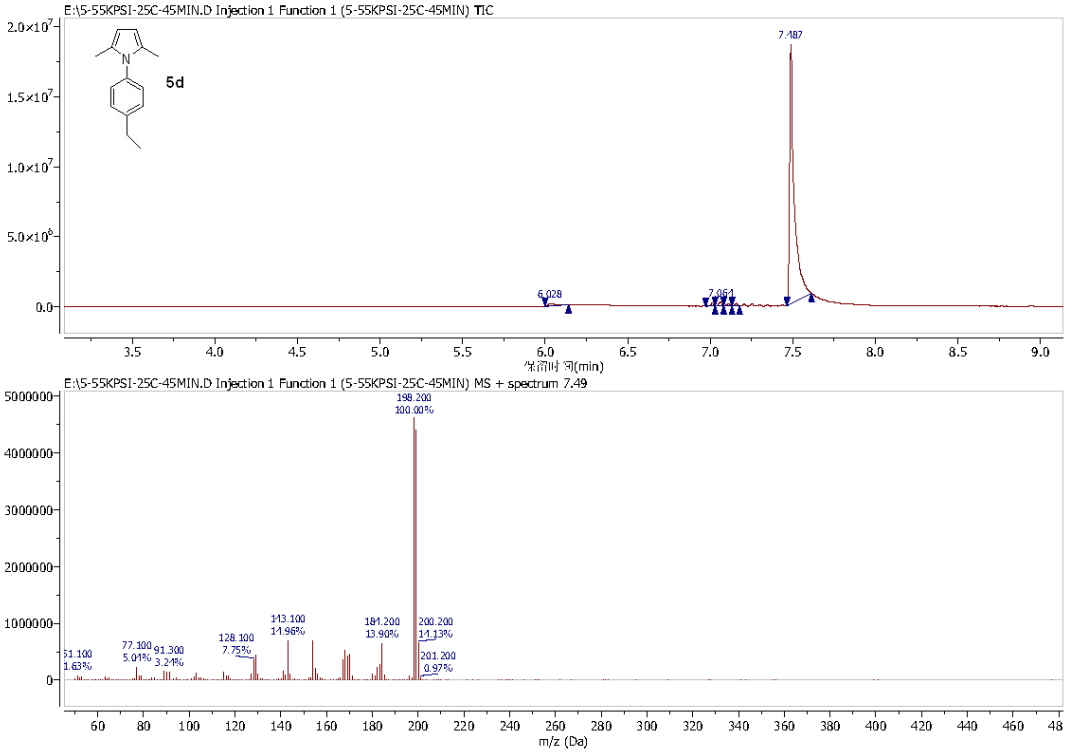


Figure SI 2: GC-MS total ion chromatogram and mass spectrum of selected products as isolated without purification.




E:\3-55KPSI-80C-30MIN.D Injection 1 Function 1 (3-55KPSI-80C-30MIN) TIC
5b
7.149
5.361
保留时间(min)
E:\3-55KPSI-80C-30MIN.D Injection 1 Function 1 (3-55KPSI-80C-30MIN) MS + spectrum 7.16
181.200
100.00%
185.200
81.69%
m/z (Da)


E:\5-55KPSI-25C-45MIN.D Injection 1 Function 1 (5-55KPSI-25C-45MIN) TIC
5d
7.487
6.028
保留时间(min)
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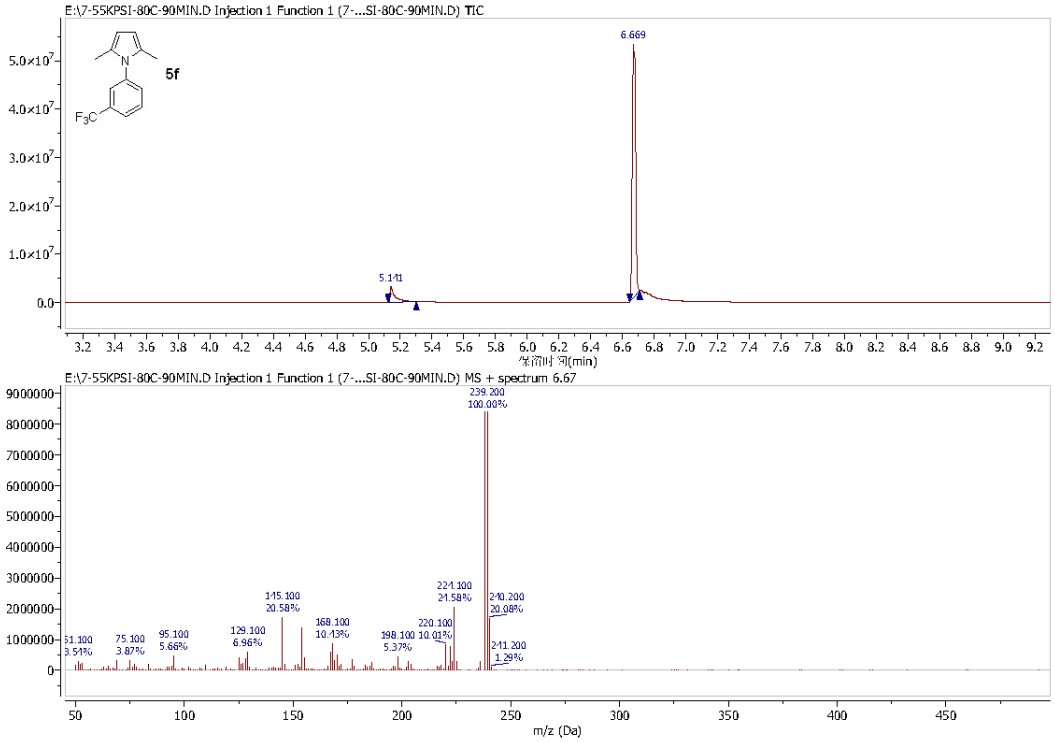
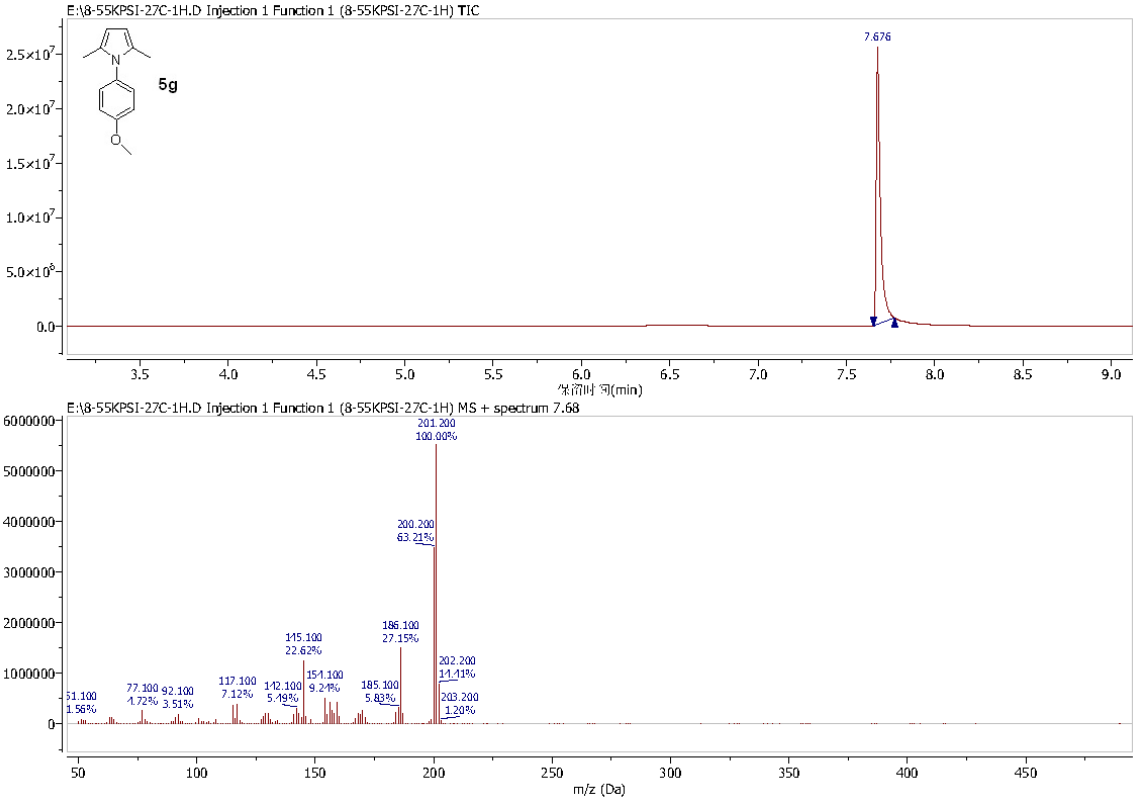
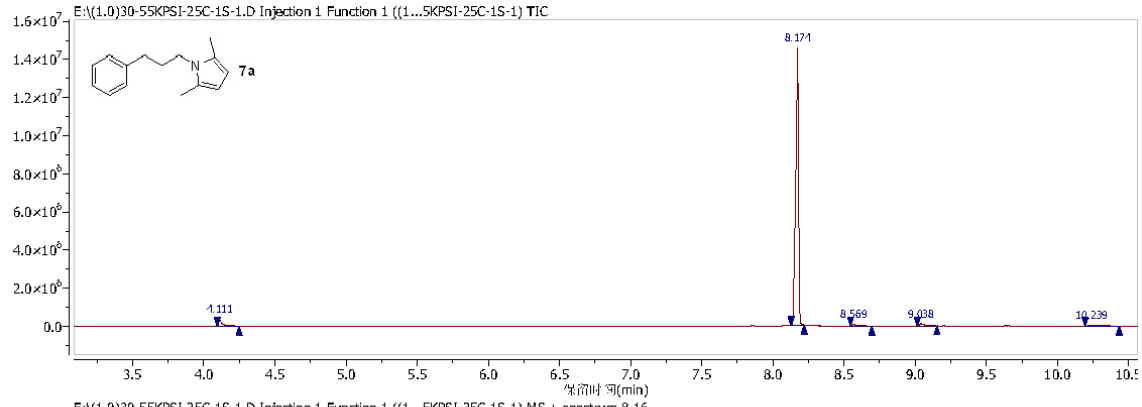
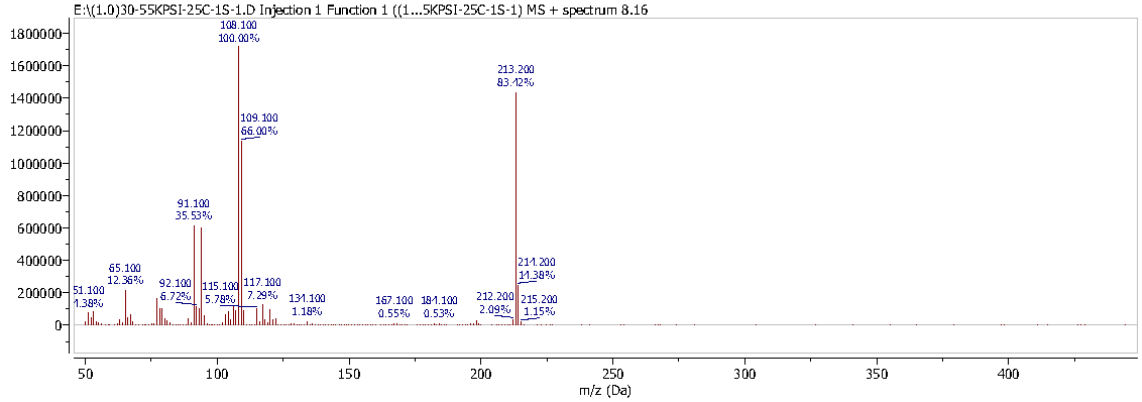
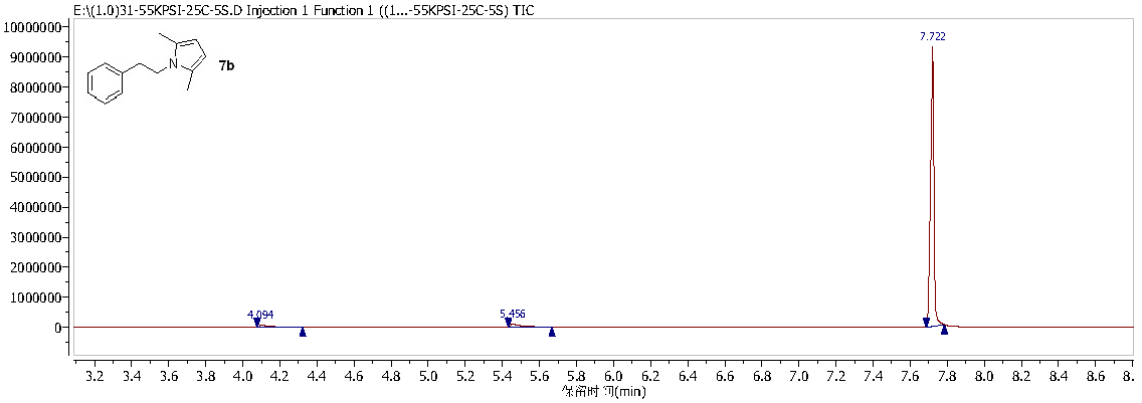
198.200
100.00%
m/z (Da)

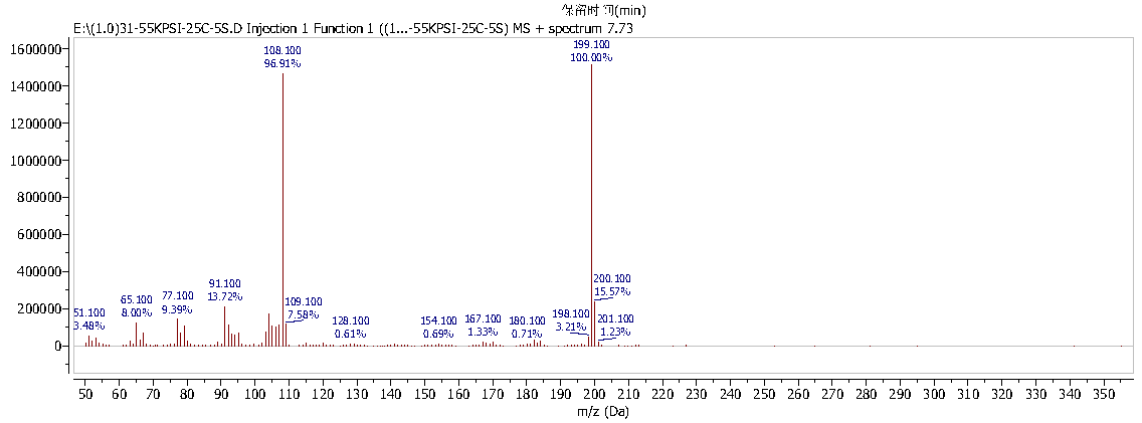

E:\7-55KPSI-80C-90MIN.D Injection 1 Function 1 (7-...SI-80C-90MIN.D) TIC
5f
6.669
5.141
E:\7-55KPSI-80C-90MIN.D Injection 1 Function 1 (7-...SI-80C-90MIN.D) MS + spectrum 6.67
239.200
100.00%
145.100
20.58%
224.100
21.58%
240.200
20.08%
168.100
10.13%
220.100
10.01%
129.100
6.96%
95.100
5.66%
75.100
3.87%
198.100
5.37%
241.200
1.29%
m/z (Da)

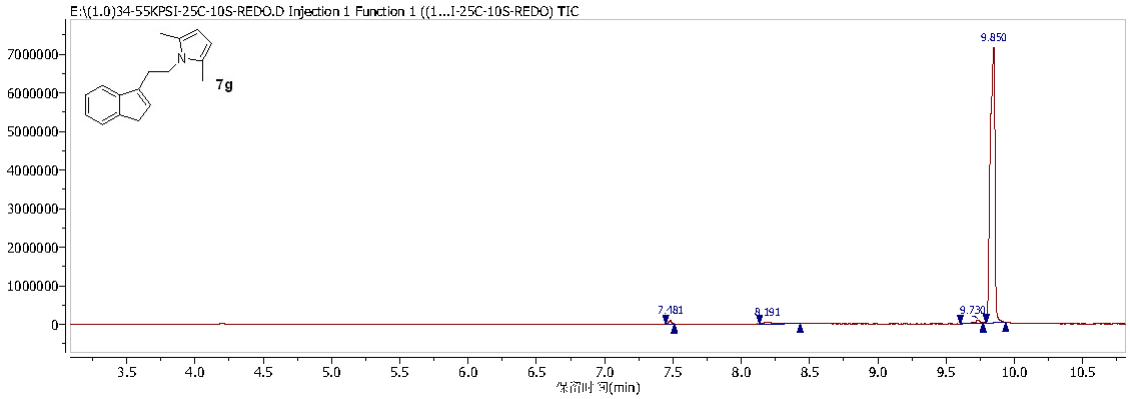

E:\8-55KPSI-27C-1H.D Injection 1 Function 1 (8-55KPSI-27C-1H) TIC
5g
7.676
E:\8-55KPSI-27C-1H.D Injection 1 Function 1 (8-55KPSI-27C-1H) MS + spectrum 7.68
201.200
100.00%
200.200
63.21%
145.100
22.62%
186.100
27.15%
202.200
11.11%
151.100
9.24%
117.100
7.12%
185.100
5.83%
77.100
1.72%
92.100
3.51%
203.200
1.20%
m/z (Da)

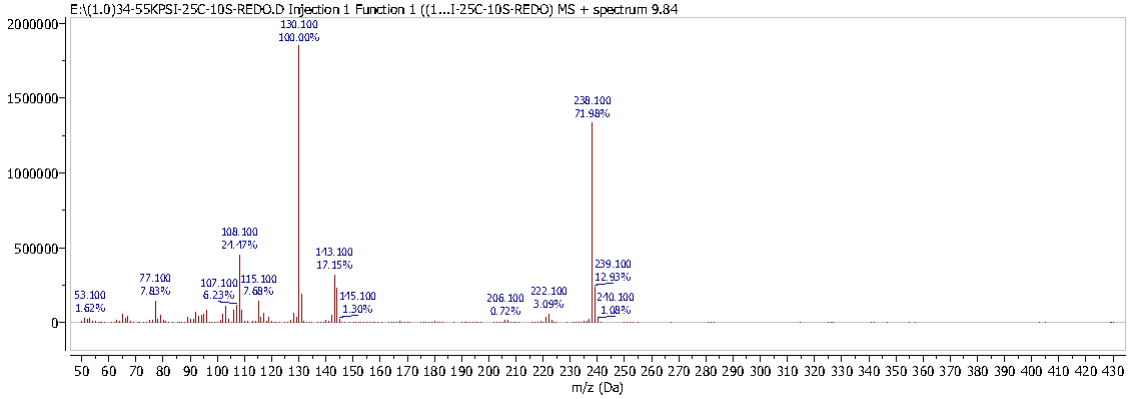

E:\(1.0)30-55KPSI-25C-1S-1.D Injection 1 Function 1 ((1...5KPSI-25C-1S-1) TIC
7a
8.171
1.111
8.569
9.038
10.239
保留时间(min)


E:\(1.0)30-55KPSI-25C-1S-1.D Injection 1 Function 1 ((1...5KPSI-25C-1S-1) MS + spectrum 8.16
108.100
100.00%
213.200
83.42%
109.100
66.00%
91.100
35.53%
65.100
12.36%
214.200
14.38%
m/z (Da)


E:\(1.0)31-55KPSI-25C-5S.D Injection 1 Function 1 ((1...-55KPSI-25C-5S) TIC
7b
7.722
4.094
5.456
保留时间(min)


E:\(1.0)31-55KPSI-25C-5S.D Injection 1 Function 1 ((1...-55KPSI-25C-5S) MS + spectrum 7.73
108.100
96.91%
199.100
100.00%
91.100
13.72%
65.100
8.00%
77.100
9.39%
109.100
7.58%
200.100
15.57%
m/z (Da)


E:\(1.0)34-55KPSI-25C-10S-REDO.D Injection 1 Function 1 ((1...I-25C-10S-REDO) TIC
7g
9.850
7.481
8.191
9.730
保留时间(min)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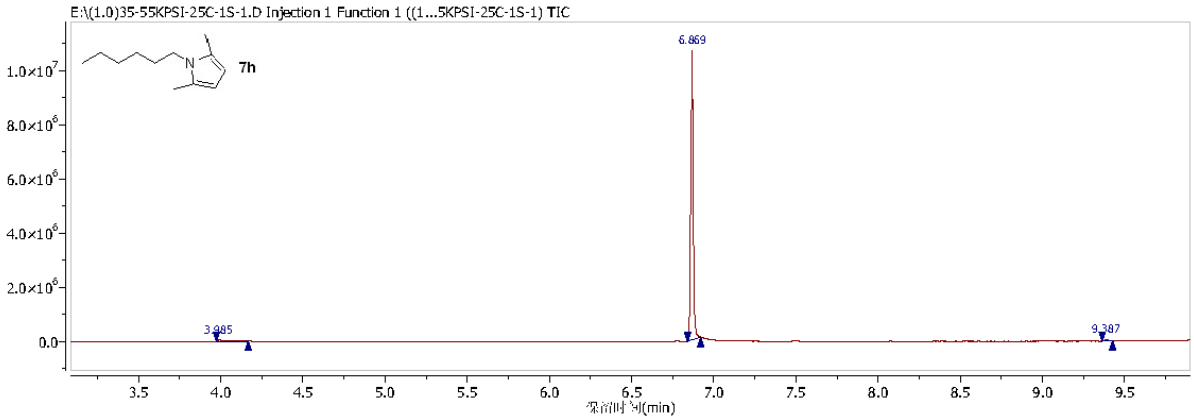
130.100 100.00%
238.100 71.98%
108.100 24.17%
143.100 17.15%
239.100 12.93%
77.100 7.83%
107.100 6.23%
115.100 7.68%
53.100 1.62%
145.100 1.30%
206.100 0.72%
222.100 3.09%
240.100 1.08%
m/z (Da)


E:\(1.0)35-55KPSI-25C-1S-1.D Injection 1 Function 1 ((1...5KPSI-25C-1S-1) TIC
7h
6.869
3.985
9.387
保留时间(min)

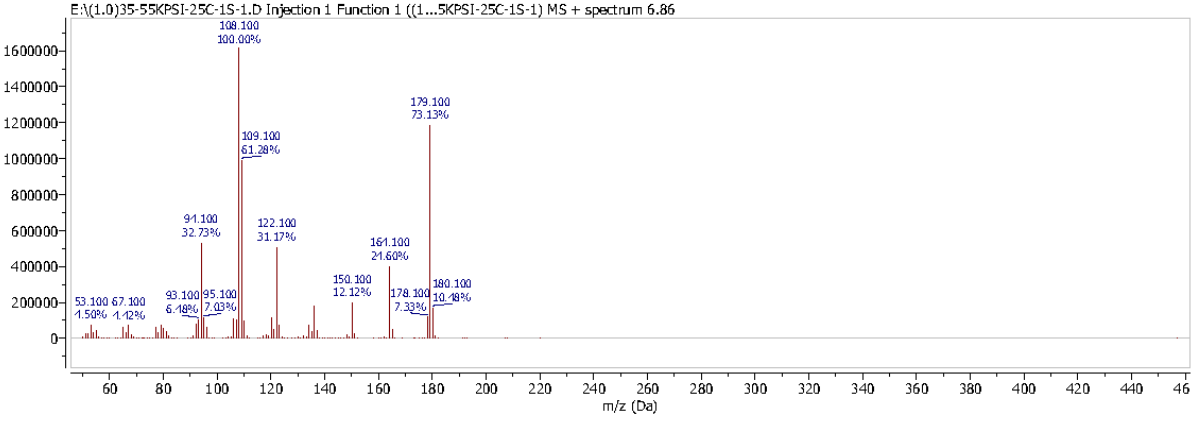

E:\(1.0)35-55KPSI-25C-1S-1.D Injection 1 Function 1 ((1...5KPSI-25C-1S-1) MS + spectrum 6.86
108.100 100.00%
179.100 73.13%
109.100 61.28%
91.100 32.73%
122.100 31.17%
161.100 21.60%
150.100 12.12%
180.100 10.48%
178.100 7.33%
93.100 6.48%
95.100 7.03%
53.100 1.50%
67.100 1.42%
m/z (Da)

Figure SI 3: Illustration of selected examples of the small (~150-200 mg) scale reactions.

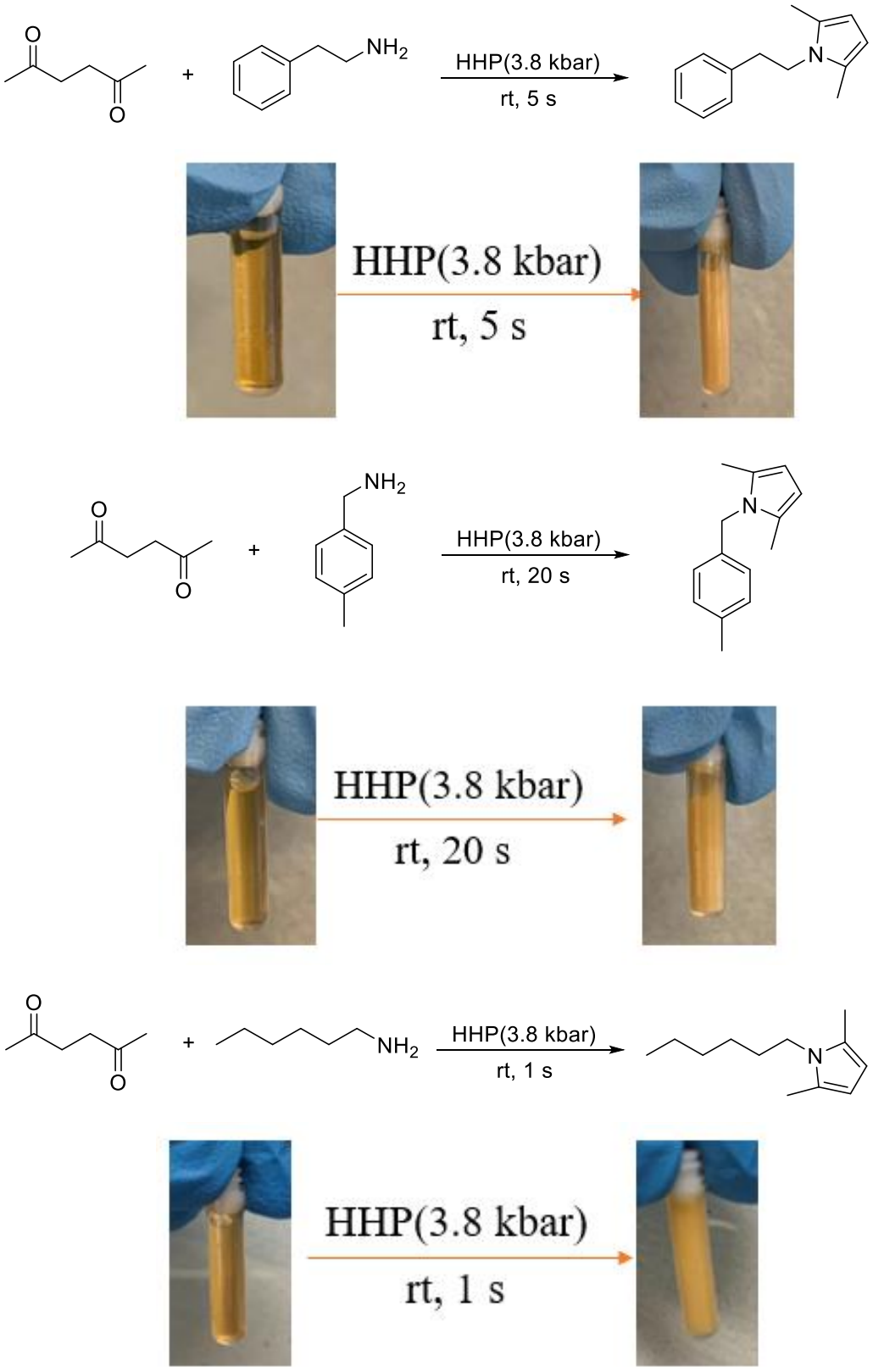
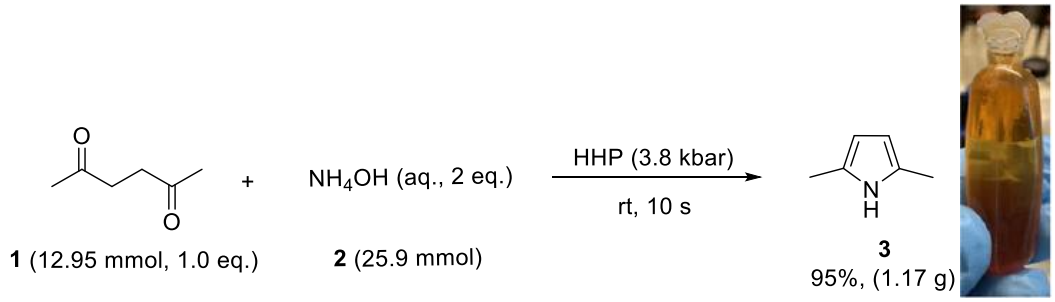
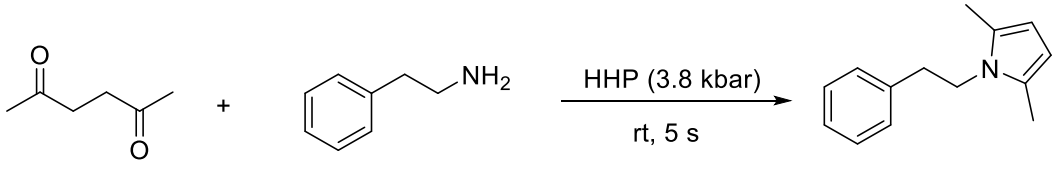


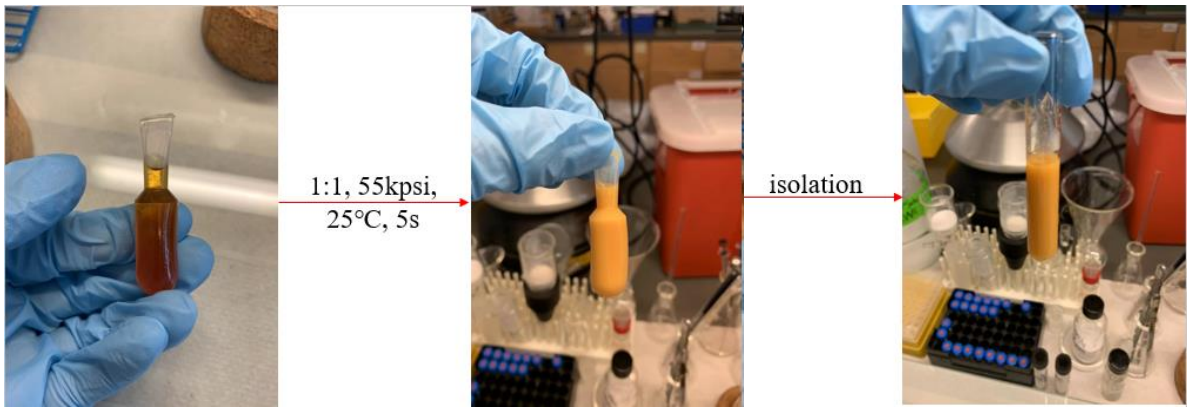
Figure SI 4: Illustration of selected examples of the scale up reactions (~1.17-2.65 g).

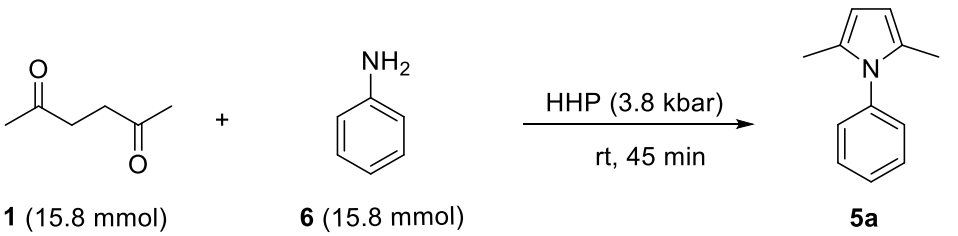


1 (12.95 mmol, 1.0 eq.) **2** (25.9 mmol) **3** 95%, (1.17 g)



1 (13.2 mmol) **6** (13.2 mmol) **7b** 96%, (2.52 g)





1 (15.8 mmol) **6** (15.8 mmol) **5a** 98%, (2.65 g)

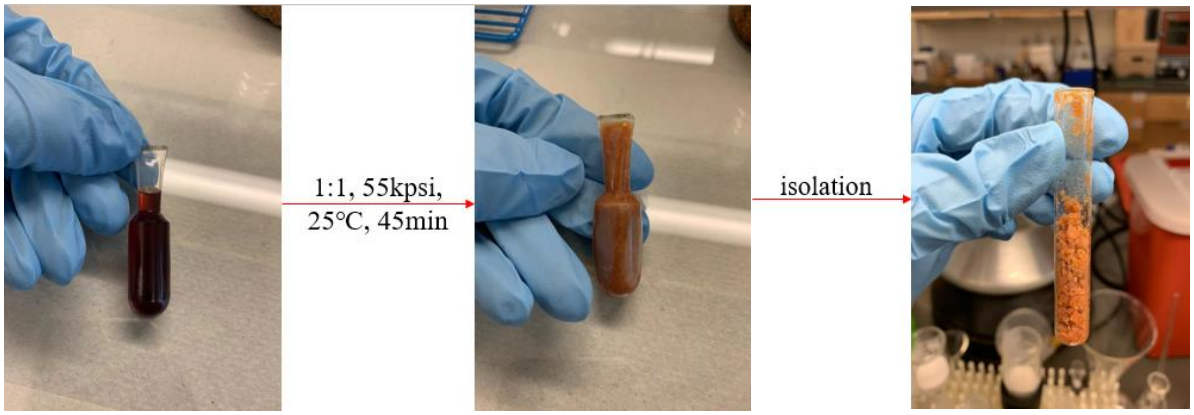
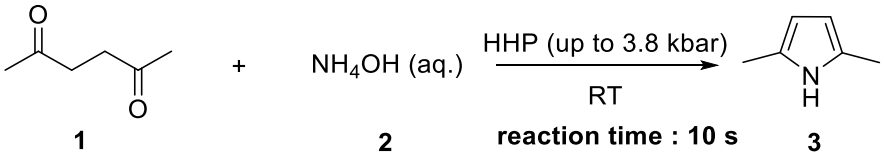


Table SI 1: Synthesis of **3** under normal pressure (NP) and high hydrostatic pressure

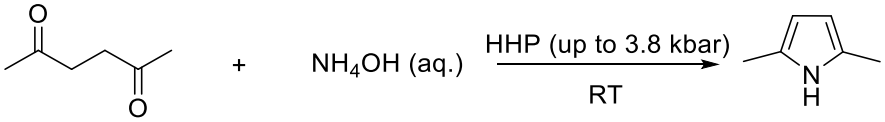


1 **2** **3**

Entry[a]	Pressure (kbar)	Time (s)	T (ºC)	Yield (%)[b]
1	NP[c]	10	25	0
2	0.7	10	25	14
3	1.4	10	25	36
4	2.1	10	25	48
5	2.8	10	25	50
6	3.4	10	25	67
7	3.8	10	25	71

[a]**1/2** molar ratio is 1:1. [b] isolated yield, [c] 1 bar pressure

Table SI 2: Optimization of synthesis of **3** under high hydrostatic pressure

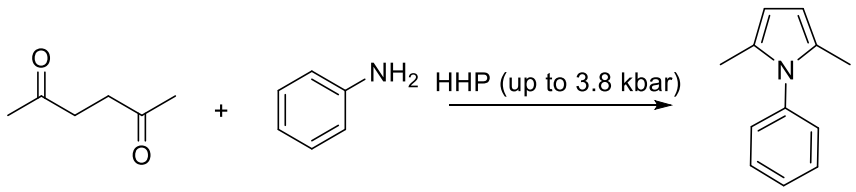


1 **2** **3**

Entry[a]	Pressure (kbar)	Time (s)	T (ºC)	Yield (%)[b]
1	NP	10	25	3
2	0.7	10	25	54
3	1.4	10	25	56
4	2.1	10	25	61
5	2.8	10	25	74
6	3.5	10	25	97
7	3.8	10	25	97
8	3.4	5	25	79
9	3.8	5	25	97

[a]**1/2** molar ratio is 1:2. [b] isolated yield

Table SI 3: Synthesis of **5a** under normal pressure (NP) and high hydrostatic pressure.[a]

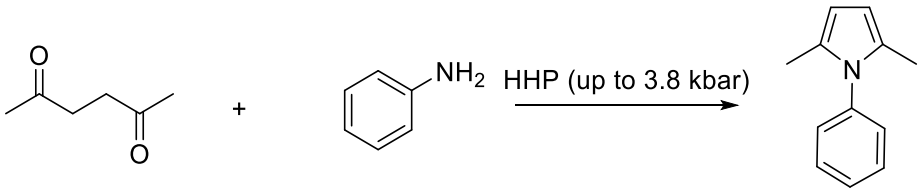


4 **5a**

Entry	Pressure (kbar)	Time (s)	T (ºC)	Yield (%)[b]
1	NP	10	25	0
2	NP	30	25	0
3	NP	45	25	0
4	NP	60	25	0
5	NP	300	25	9
6	3.8	10	25	52
7	3.8	30	25	58
8	3.8	45	25	60
9	3.8	60	25	71
10	3.8	300	25	77

[a] Reaction conditions: 1 equiv. aniline, 1 equiv. diketone, at room temperature. [b] isolated yield

Table SI 4: Optimization in the synthesis of **5a** under high hydrostatic pressure[a]



5a

Entry	Pressure (kbar)	Time (min)	T(ºC)	Yield (%)
1	0.7	15	25	79
2	1.4	15	25	80
3	2.1	15	25	83
4	2.8	15	25	85
5	3.4	15	25	88
6	3.8	15	25	90
7	3.8	30	25	92
8	3.8	45	25	99
9[b]	3.8	30	25	99

[a] 0.692 mmol aniline, 0.692 mmol diketone, both neat. [b] 1.2eq aniline