

Supporting information

An integrated five-step continuous flow synthesis of 2-(1-cyclohexenyl)ethylamine: a key intermediate for morphinans

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1. General Information

All starting materials, reagents and solvents were purchased from commercial suppliers (Bide, Stream, Adamas etc.) and used as supplied unless otherwise stated. All the reactions were monitored by thin-layer chromatography (TLC), HPLC (Agilent 1260 Infinity II), ^1H NMR and GC-MS (Agilent 5975 equipped with HP-5MS column). Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 400 MHz and 100MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^1H NMR: TMS = 0.00 ppm, for ^{13}C NMR: CDCl_3 = 77.00 ppm, $\text{DMSO}-d_6$ = 39.52 ppm. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet, and br = broad. Analytical TLC was performed on precoated silica gel plates. High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

2. Flow Experimental Equipment Information

The continuous flow system was established, which include commercial available feeding equipments, continuous reactors and process control unit etc.

The main devices information is as follows:

The feeding equipments: HPLC pump (SANOTAC or OUSHISHENG), peristaltic pump (L/S easy-load II, Masterflex).

Continuous reactors: stainless steel coil reactor (0.8 mm i.d., 1.6 mm o.d. or 1.6 mm i.d., 3.2 mm o.d.), PTFE coil reactor (0.8 mm i.d., 1.6 mm o.d. or 1.6 mm i.d., 3.2 mm o.d.), PTFE fittings (RunZe Fluid), stainless steel fittings (Shang hai Xitai Fluid Technology Co., Ltd).

Process control unit: stainless steel one-way and two-way valve (SS-CVG01A-K1F, Shang hai Xitai Fluid Technology Co., Ltd), back-pressure valve (Shang hai Xitai Fluid Technology Co., Ltd), gas mass flow controller (MFC, Shen zhen E-Zheng tech Co., Ltd).

3. Flow synthesis of 2-(1-cyclohexenyl)ethylamine in separated steps

3.1 Flow synthesis of magnesium alkoxide and optimization of reaction conditions

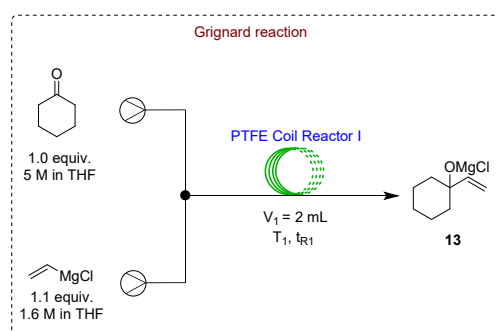


Table S1. Optimization of reaction conditions

| Entry | Grignard reagent (equiv.) | T_1 ($^{\circ}\text{C}$) | t_{R1} (min) | Conv. (%) ^a | Yield (%) ^a |
|-------|---------------------------|------------------------------|----------------|------------------------|------------------------|
| 1 | 1.1 | 0 | 2 | 80 | 76 |

| | | | | | |
|----------|------------|-----------|----------|---------------|-----------|
| 2 | 1.1 | 10 | 2 | 86 | 83 |
| 3 | 1.1 | 20 | 2 | 95 | 92 |
| 4 | 1.1 | 25 | 2 | >99 | 98 |
| 5 | 1.1 | 30 | 2 | >99 | 95 |
| 6 | 1.1 | 25 | 1.5 | 70 | 68 |
| 7 | 1.1 | 25 | 1 | 55 | 52 |
| 8 | 1.05 | 25 | 2 | 86 | 84 |
| 9 | 1.0 | 25 | 2 | 78 | 73 |

^aDetermined by ¹H NMR analysis.

Cyclohexanone (50 g, 0.5 mol, 5 M in THF (100 mL), 1.0 equiv.) and vinyl magnesium chloride (0.55 mol, 1.6 M in THF (344 mL), 1.1 equiv.) were introduced into a T-mixer to achieve the high mass-transfer efficiency using HPLC pumps at the flow rate of 0.23 mL/min and 0.77 mL/min respectively before entering the PTFE coil reactor (0.8 mm i.d., 1.6 mm o.d., 2 mL internal volume) to proceed the Grignard reaction. The reaction mixture was collected for 1 h after a residence time in a flask filled with nitrogen to avoid the decomposition of magnesium alkoxide.

3.2 Flow synthesis of (2-chloroethylidene)cyclohexane and optimization of reaction conditions

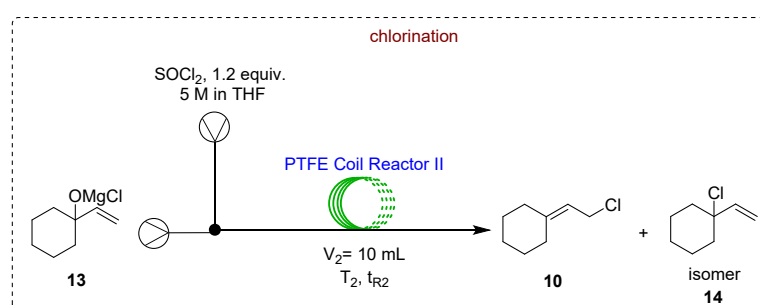


Table S2. Optimization of reaction conditions

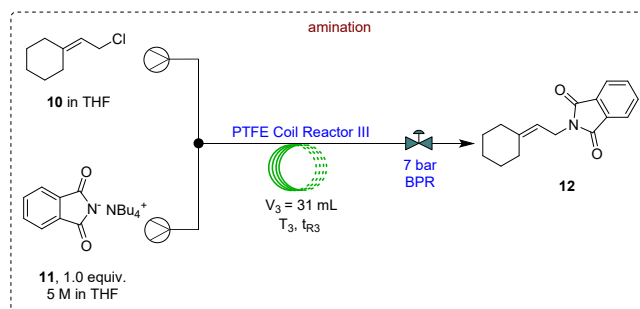
| Entry | Chlorinated reagent (equiv.) | T_2 ($^{\circ}\text{C}$) | t_{R2} (min) | Yield (%) ^a | isomer (%) ^b |
|----------|------------------------------|------------------------------|----------------|------------------------|-------------------------|
| 1 | 1.2 | 0 | 10 | 70 | 18 |
| 2 | 1.2 | 10 | 10 | 79 | 17 |
| 3 | 1.2 | 20 | 10 | 91 | 18 |
| 4 | 1.2 | 25 | 10 | 94 | 19 |
| 5 | 1.2 | 30 | 10 | 95 | 21 |
| 6 | 1.2 | 25 | 7.5 | 94 | 18 |
| 7 | 1.2 | 25 | 5 | 86 | 18 |
| 8 | 1.1 | 25 | 7.5 | 82 | 18 |
| 9 | 1.05 | 25 | 7.5 | 73 | 17 |

^a Crude isolated yield. ^b Determined by ¹H NMR analysis.

The reaction mixture from last step was mixed with SOCl_2 (5 M in THF, 1.2 equiv.) in a T-mixer at

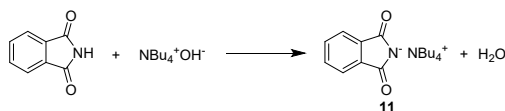
the flow rate of 1.0 mL/min and 0.27 mL/min respectively. The chlorination was proceeded at 25 °C in a PTFE coil reactor (1.6 mm i.d., 3.2 mm o.d., 10 mL internal volume). The reaction mixture was collected for 1 h after a residence time and quenched with 40% aq. NaOH (2.2 equiv.). The solution of (2-chloroethylidene)cyclohexane in THF was obtained after filtration to remove the undissolved inorganic salt.

3.3 Flow synthesis of 2-(2-cyclohexylideneethyl)isoindoline-1,3-dione



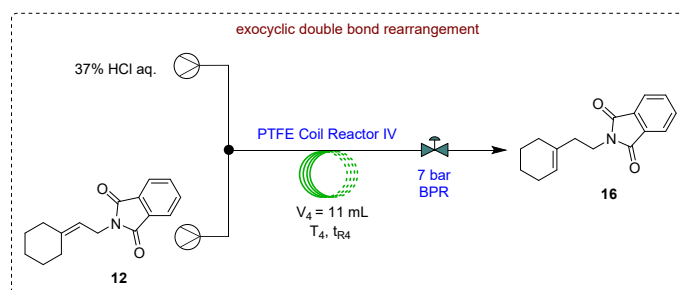
The acquired solution of (2-chloroethylidene)cyclohexane (1.11 M, 1.0 equiv.) from the previous step was introduced into a T-mixer by using HPLC pump (flow rate 0.9 mL/min) and mixed with tetrabutylammonium phthalimide (5 M in THF, 1.0 equiv., flow rate 0.67 mL/min). The amination was performed in a PTFE coil reactor (1.6 mm i.d., 3.2 mm o.d., 31 mL internal volume) at 120 °C under 7 bar back pressure. The reaction mixture was collected for 1 h after a residence time in a flask for the next step use.

Synthesis of tetrabutylammonium phthalimide



Suspension of phthalimide (7.35 g, 50 mmol) in methanol (50 mL) was mixed with a 40%(w/w) solution of tetrabutylammonium hydroxide in water (32.43 g, 50 mmol) and stirred for 5 minutes with the dissolution of the phthalimide. The solvent was removed by rotary evaporation under 45 °C to afford the colorless oil in 99% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.49 – 7.27 (m, 4H), 3.17 (t, *J* = 8.9 Hz, 8H), 1.66 – 1.45 (m, 8H), 1.31 – 1.22 (m, 8H), 0.87 (t, *J* = 7.3 Hz, 12H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 185.53, 139.83, 130.57, 119.82, 57.98, 23.55, 19.62, 13.90.

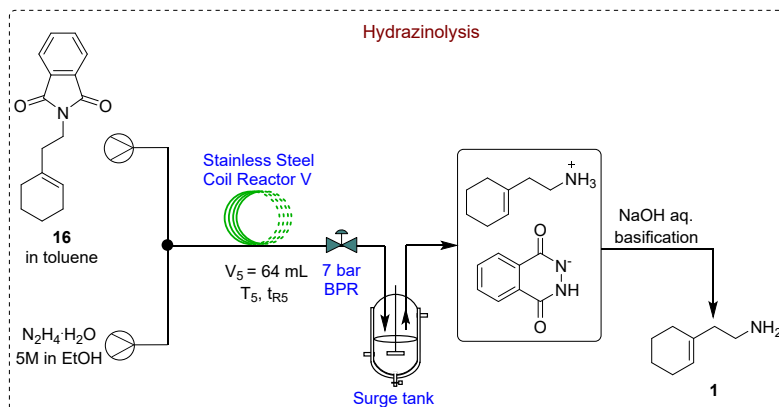
3.4 The exocyclic double bond rearrangement



The acquired solution of 2-(2-cyclohexylideneethyl)isoindoline-1,3-dione (0.64 M, 1.0 equiv.) from the previous step was introduced into a T-mixer by using HPLC pump (flow rate 1.57 mL/min) and mixed with 37% HCl aq. (12 M, 7.0 equiv., flow rate 0.58 mL/min). The rearrangement was performed in a PTFE coil reactor (1.6 mm i.d., 3.2 mm o.d., 11 mL internal volume) at 120 °C under

7 bar back pressure. The reaction mixture was mixed with toluene (3.14 mL/min) and water (1.57 mL/min) to transfer the product into toluene phase and dispose the acid aqueous phase. The toluene phase was collected for 1 h after a residence time in a flask for the next step use.

3.5 Flow synthesis of 2-(1-cyclohexenyl)ethylamine



The acquired toluene solution from the previous step was introduced into a T-mixer by using HPLC pump (flow rate 4.5 mL/min) and mixed with the solution of hydrazine hydrate (5 M in EtOH, 10.0 equiv., flow rate 1.89 mL/min). The hydrazinolysis was performed in a stainless steel coil reactor (1.6 mm i.d., 3.2 mm o.d., 64 mL internal volume) at 140 °C under 7 bar back pressure. The reaction mixture was collected in a tank and neutralized using 10% NaOH aq., then the organic phase was separated and concentrated in vacuo to afford the desired 2-(1-cyclohexenyl)ethylamine.

4. Integrated flow synthesis of 2-(1-cyclohexenyl)ethylamine from cyclohexanone

4.1 Procedures for the integrated flow synthesis of 2-(1-cyclohexenyl)ethylamine

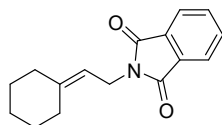
The cyclohexanone (30 g, 0.3 mol) in THF (60 mL, 5 M, 1.0 equiv.) as stream 1 at the flow rate of 0.23 mL/min and the vinyl magnesium chloride (0.33 mol) in THF (206 mL, 1.6 M, 1.1 equiv.) as stream 2 at the flow rate of 0.77 mL/min were introduced into a T-mixer using HPLC pumps before entering the PTFE coil reactor (0.8 mm i.d., 1.6 mm o.d., 2 mL internal volume). The Grignard addition and the chlorination were telescoped by introducing the reaction mixture of Grignard addition directly into another T-mixer to combine with the chlorination reagent SOCl₂ in THF (5 M, 1.2 equiv.) at the flow rate of 0.27 mL/min. The chlorination was performed at 25 °C in a PTFE coil reactor (1.6 mm i.d., 3.2 mm o.d., 10 mL internal volume) within a residence time of 7.5 min. The reaction was quenched using 40% NaOH aq. (2.2 equiv.) to afford the solution of (2-chloroethylidene)cyclohexane in THF for the next step use after filtration to remove the undissolved inorganic salt. The acquired solution of (2-chloroethylidene)cyclohexane (1.11 M, 1.0 equiv.) at the flow rate of 0.9 mL/min was mixed with tetrabutylammonium phthalimide (5 M in THF, 1.0 equiv.) at the flow rate 0.67 mL/min in a T-mixer. The amination was performed in a PTFE coil reactor (1.6 mm i.d., 3.2 mm o.d., 31 mL internal volume) at 120 °C within a residence time of 20 min under 7 bar back pressure. The amination and the exocyclic double bond rearrangement were telescoped by introducing the reaction mixture of amination directly into another T-mixer to combine with 37% HCl aq. (12 M, 7.0 equiv.) at the flow rate 0.58 mL/min. The rearrangement was performed in a PTFE coil reactor (1.6 mm i.d., 3.2 mm o.d., 11 mL internal volume) at 120 °C within a residence time of 5 min under 7 bar back pressure. The reaction mixture was mixed with toluene (3.14

mL/min) and water (1.57 mL/min) to transfer the product into toluene phase. The acid aqueous phase was separated using an in-line gravity liquid-liquid separator. The toluene phase was introduced into a T-mixer at the flow rate of 4.5 mL/min to mix with the ethanol solution of hydrazine hydrate (5 M, 10.0 equiv. at the flow rate 1.89 mL/min. The hydrazinolysis was performed in a PTFE coil reactor (1.6 mm i.d., 3.2 mm o.d., 64 mL internal volume) at 140 °C within a residence time of 10 min under 7 bar back pressure. After running the flow system for a whole residence time (44.5 min) to ensure the achievement of steady state, The reaction mixture was collected in a surge tank for 1 h to acquire the desired 2-(1-cyclohexenyl)ethylamine. The mixture was neutralized using 10% NaOH aq., then the organic phase was separated and concentrated in vacuo to afford the desired 2-(1-cyclohexenyl)ethylamine in 56% isolated yield and 94% purity over five steps.

4.2 Image of the flow system

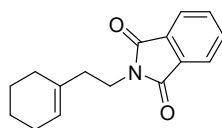


5. Characterization



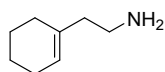
2-(2-cyclohexylideneethyl)isoindoline-1,3-dione

White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.87 – 7.79 (m, 2H), 7.74 – 7.65 (m, 2H), 5.21 (t, J = 7.3 Hz, 1H), 4.28 (d, J = 7.3 Hz, 2H), 2.35 (t, J = 5.8 Hz, 2H), 2.06 (t, J = 5.8 Hz, 2H), 1.64 – 1.45 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.13, 145.11, 133.90, 132.31, 123.13, 114.75, 36.90, 35.01, 28.88, 28.33, 27.70, 26.66. HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{17}\text{NaNO}_2$ $[\text{M}+\text{Na}]^+$: 278.1151, found: 278.1148.



2-(2-(cyclohex-1-en-1-yl)ethyl)isoindoline-1,3-dione

White solid. ^1H NMR (400 MHz, CDCl_3) δ 7.88 – 7.80 (m, 2H), 7.79 – 7.68 (m, 2H), 5.45 – 5.31 (m, 1H), 3.78 (t, J = 7.1 Hz, 2H), 2.29 (t, J = 7.2 Hz, 2H), 2.09 – 1.98 (m, 2H), 1.92 – 1.82 (m, 2H), 1.67 – 1.58 (m, 2H), 1.55 – 1.45 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.34, 134.23, 133.82, 132.16, 123.96, 123.11, 36.70, 36.62, 27.89, 25.28, 22.82, 22.19. HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{17}\text{NaNO}_2$ $[\text{M}+\text{Na}]^+$: 278.1151, found: 278.1149.

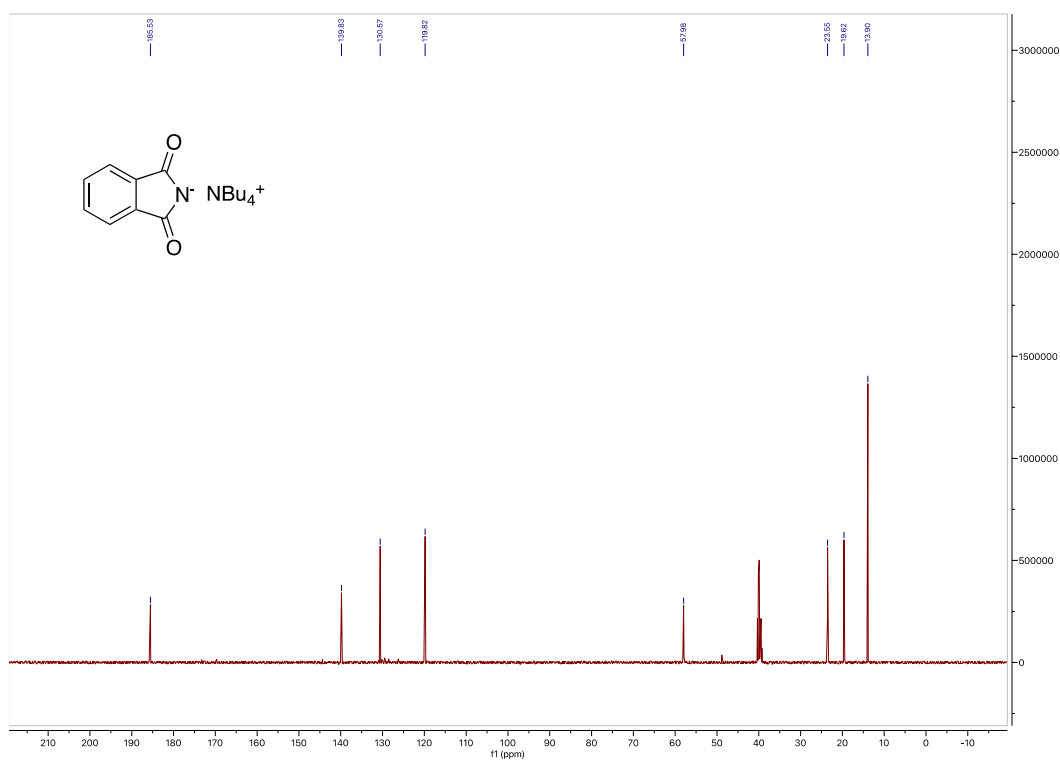
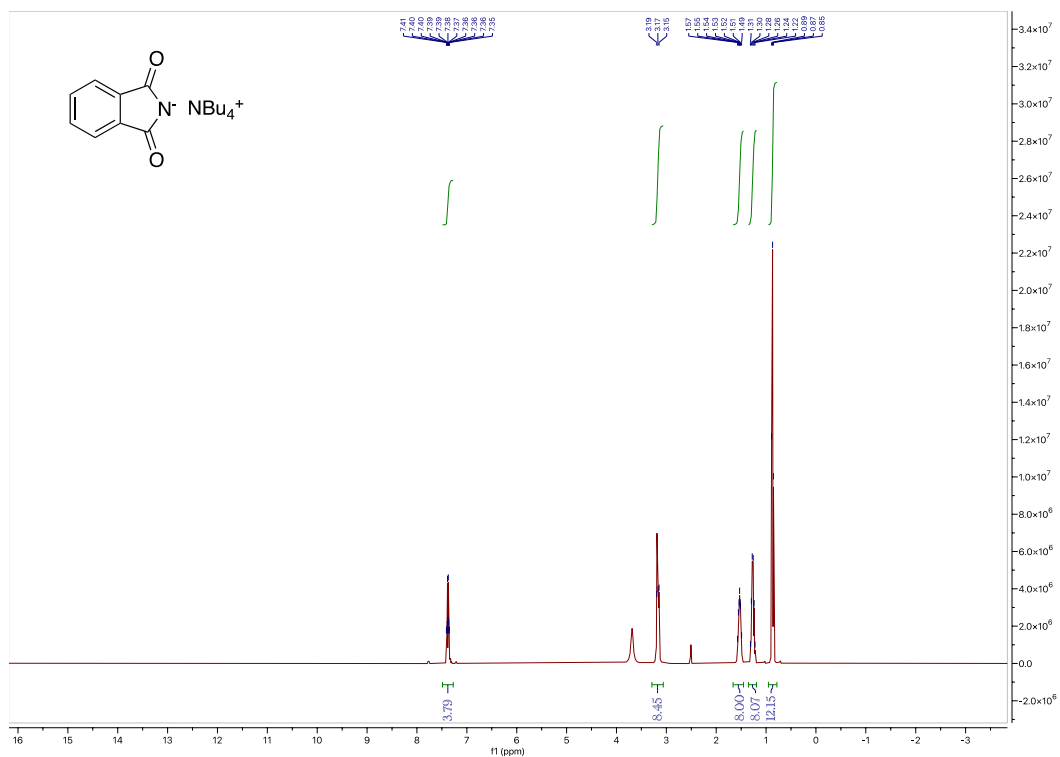


2-(1-cyclohexenyl)ethylamine

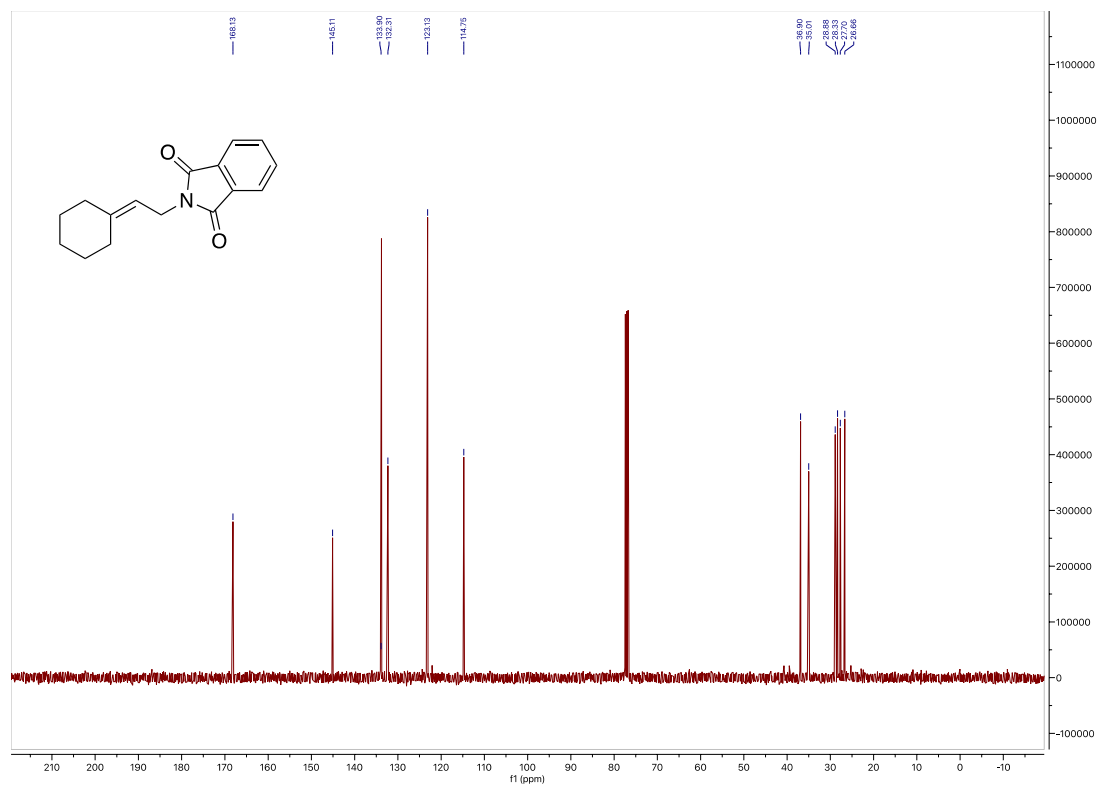
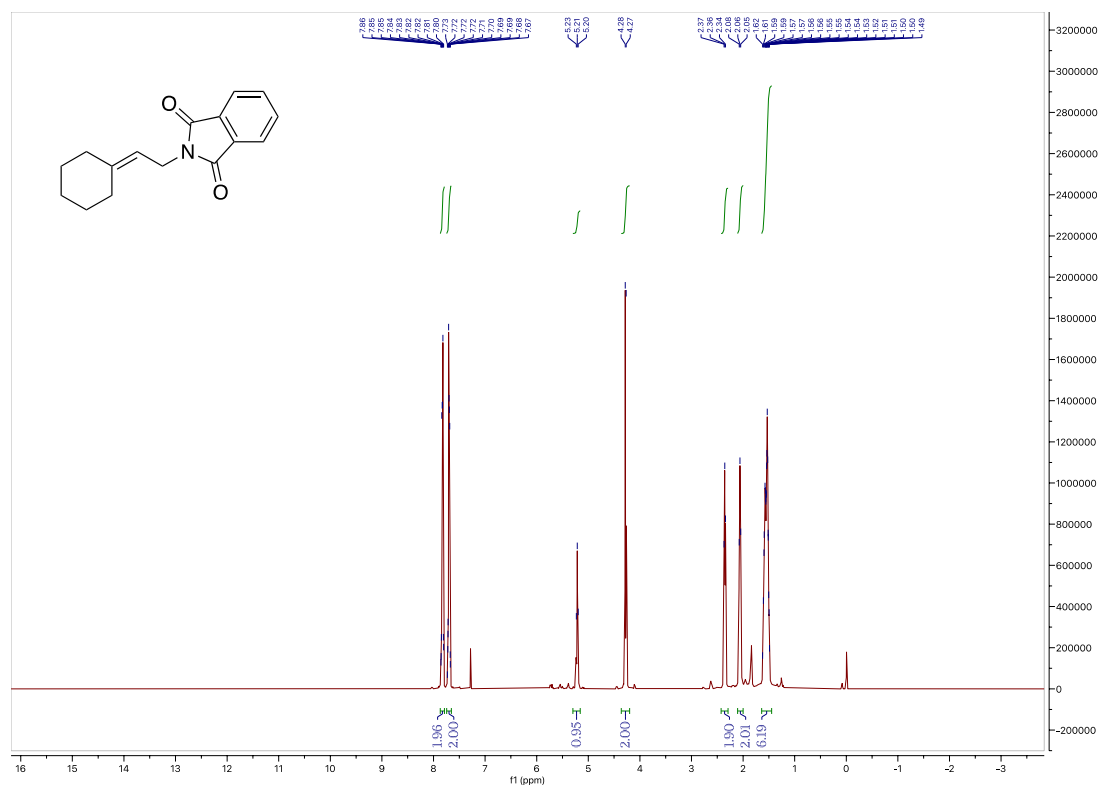
Pale yellow oil. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 5.36 (s, 1H), 2.57 (t, J = 7.0 Hz, 2H), 2.01 – 1.90 (m, 4H), 1.90 – 1.82 (m, 2H), 1.61 – 1.44 (m, 4H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 135.96, 121.96, 42.62, 40.52, 28.24, 25.18, 22.99, 22.56. HRMS (ESI-TOF) m/z Calcd for $\text{C}_8\text{H}_{16}\text{N}$ $[\text{M}+\text{H}]^+$: 126.1277, found: 126.1278.

6. ^1H and ^{13}C NMR spectra

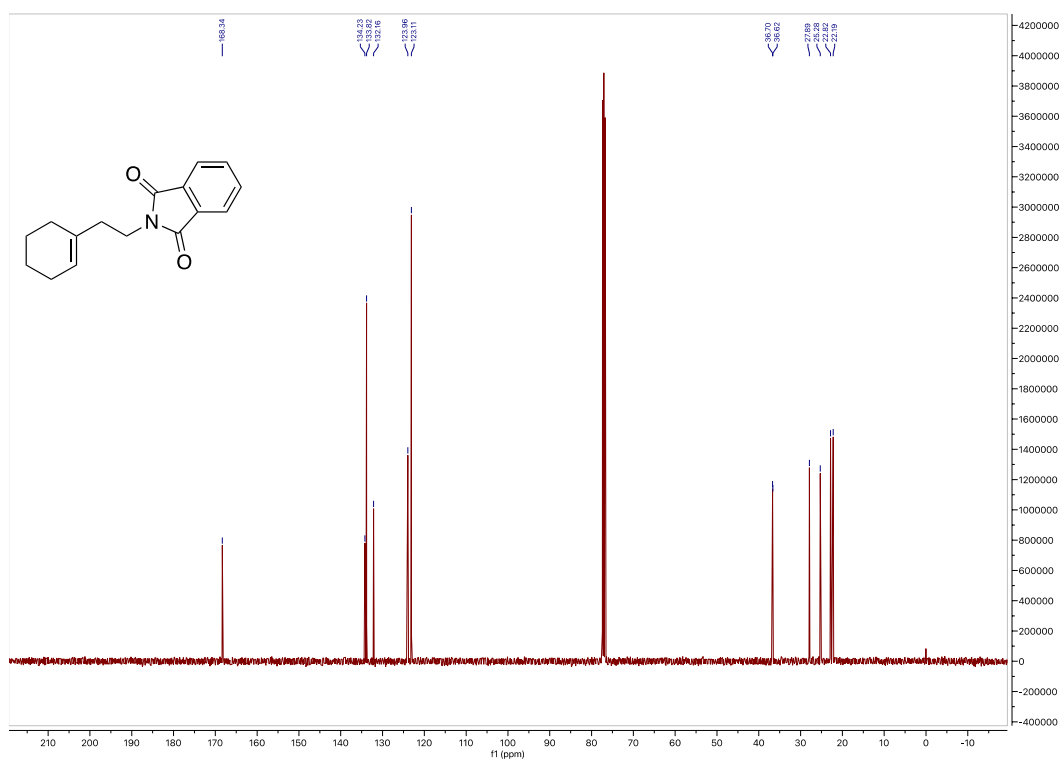
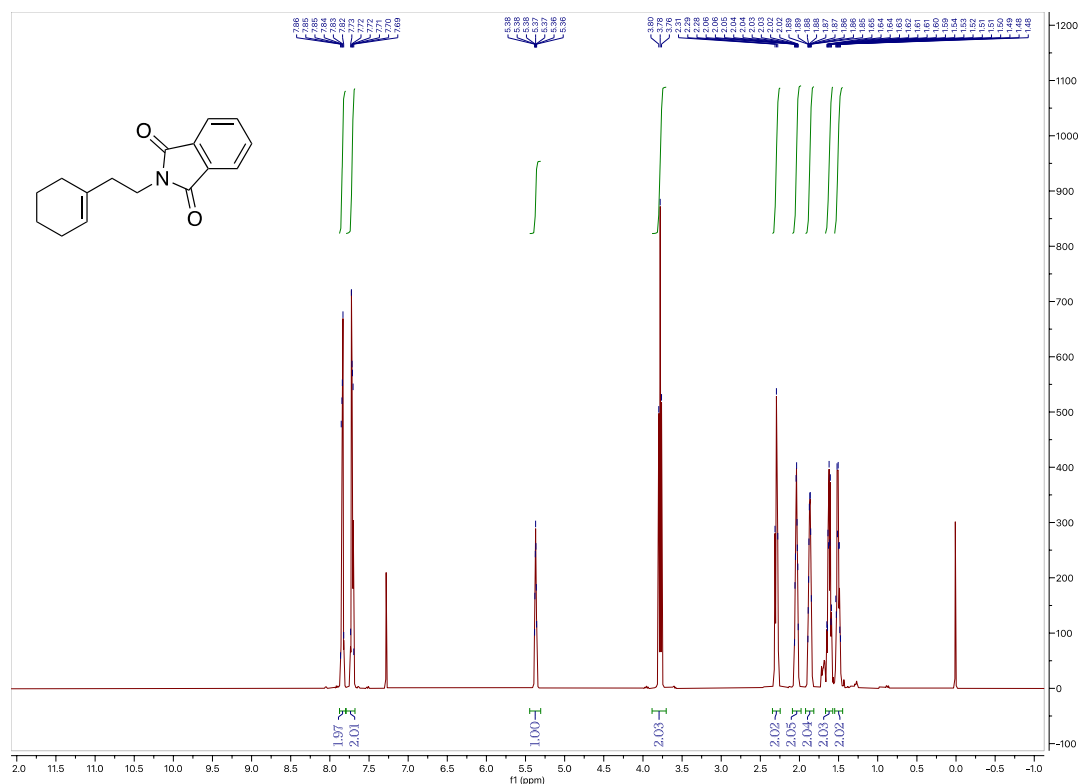
tetrabutylammonium phthalimide



2-(2-cyclohexylideneethyl)isoindoline-1,3-dione



2-(2-(cyclohex-1-en-1-yl)ethyl)isoindoline-1,3-dione



2-(1-Cyclohexenyl)ethylamine

