Supporting Information for

Vitamin B$_{12}$-Catalyzed Coupling Reaction of Nitroalkanes and Diazo Compounds

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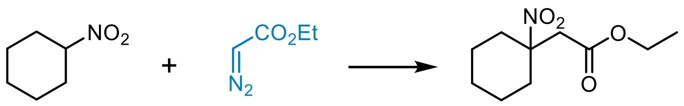
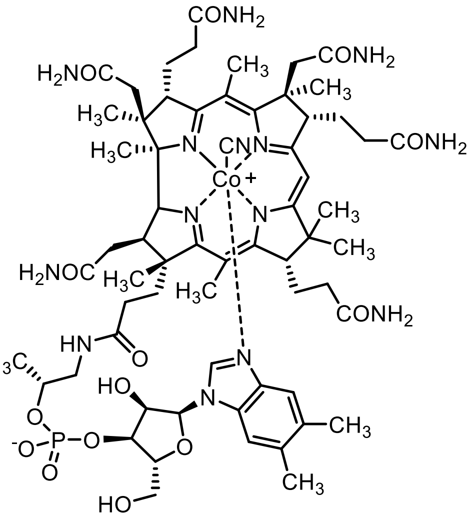
1. General information

The reactions were carried out under an argon atmosphere unless otherwise indicated. All reactions were performed using 10 mL glass vials sealed with rubber septa. Reaction process monitoring using thin-layer chromatography (TLC) on Yantai Chemical Industry Research Institute silica gel (GF254, 0.23 mm thickness). Observations were made using UV light (254 nm) or potassium permanganate for color development. The crude product was separated and purified by column chromatography using Qingdao Ocean Chemical silica gel (200-300 mesh). ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker 400 MHz instrument with TMS as an internal standard. Liquid chromatograph mass spectrums (LC-MS) data were obtained on an Water Xevo G2 QTof Liquid Chromatograph Mass Spectrometer and a SilGreen 100 C18 column. All commercial reagents and solvents are to be used as received unless otherwise indicated.

Zn needs to be activated before use. The activation process was as follows: 1) grinding in 10% HCl, 2) washing with water, methanol and water, 3) drying in vacuum. Activation of Zn has a great influence on the reaction yield.

2. Optimisation of reaction conditions





*All yields from the optimization studies involving 2-(1-nitrocyclohexyl)-ethyl acetate were determined by **HPLC**.*

2.1 HPLC analysis

Mobile phase: water : acetonitrile =0.4 : 0.5

Total flow rate: 0.9 mL/min

Temperature: 30 °C

Uv detection wavelength: 230 nm

2-(1-nitrocyclohexyl)-ethyl acetate, with 2 mg/mL N-(tert-butyl)-2-methylbenzamide as internal standard, at 230 nm.

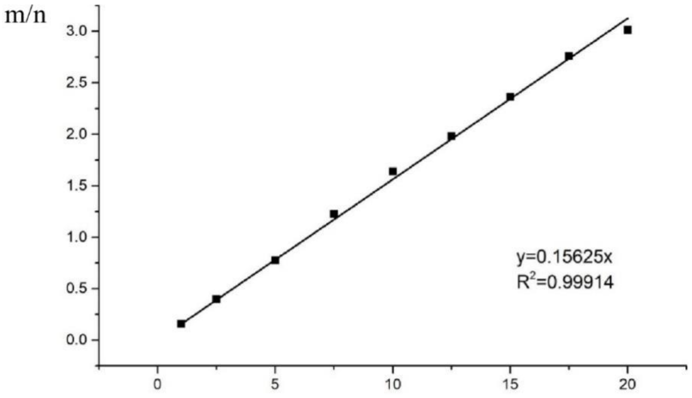


Fig. S1 Standard curve for ethyl 2-(1-nitrocyclohexyl)-acetate (a/b: internal standard concentration/internal standard concentration; m/n: standard peak area/internal standard peak area)

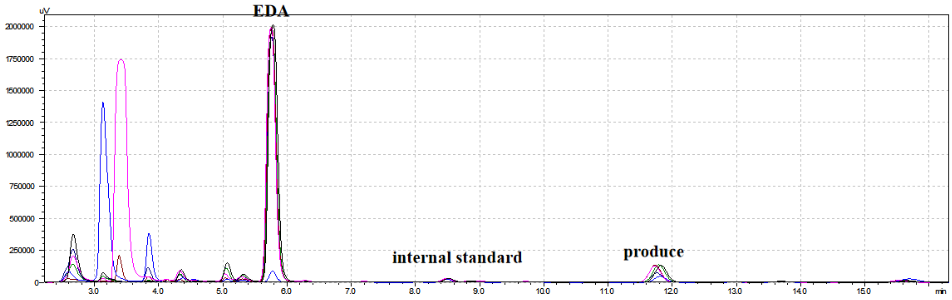


Fig. S2 HPLC spectra of vitamin B_{12}-catalyzed reaction

2.2 Table S1. Background reactions [a]

No	Deviation from reaction conditions	yield (%)
1	no Vitamin B_{12}	0
2	no Zn	0
3	no H_2O	36
4	Mn as reductant	0
5	add NH_4Cl	13
6	open to air	0
7	O_2	0

[a] Reaction conditions: nitrocyclohexane (0.25 mmol), EDA (2 equiv.), Zn (6 equiv.), vitamin B_{12} (2 mol %), solvent (DMSO:H_2O = 1:1, 2.5 mL), 50°C, 24 h.

2.3 Table S2. Optimization of the solvent pH [a]

No	pH	yield (%)
1	H_2O	38
2	5.0	35
3	7.0	23
4	9.0	23
5	11.0	23

[a] Reaction conditions: nitrocyclohexane (0.25 mmol), EDA (2 equiv.), Zn (6 equiv.), vitamin B_{12} (2 mol %), solvent (KPi buffer:DMSO=1:1, 2.5 mL), 50°C, 24 h.

2.4 Table S3. Optimization of the temperature [a]

No	Temperature(°C)	yield (%)
1	50	38
2	45	28
3	37	21

[a] Reaction conditions: nitrocyclohexane (0.25 mmol), EDA (2 equiv.), Zn (6 equiv.), vitamin B_{12} (2 mol %), solvent (DMSO:H_2O = 1:1, 2.5 mL), 24 h.

2.5 Table S4. Optimization of the zinc [a]

No	Zn [equiv.]	yield (%)
1	2.0	18
2	4.0	30
3	6.0	38

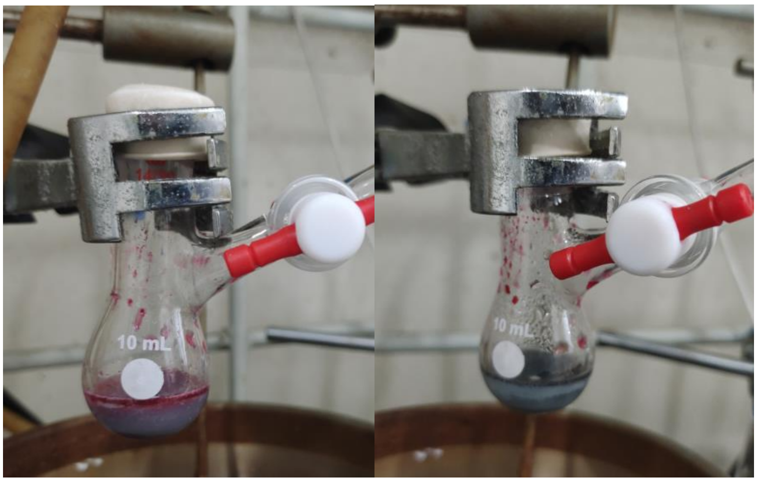
[a] Reaction conditions: nitrocyclohexane (0.25 mmol), EDA (2 equiv.), Zn, vitamin B_{12} (2 mol%), solvent (DMSO:H_2O = 1:1, 2.5 mL), 24 h.

3. General procedures

3.1 General procedure for Vitamin B_{12}-catalysed reaction

Vitamin B_{12} (2 mol%, 7 mg), Zn (196 mg, 6.0 mmol) were accurately weighed in a 10 mL two-necked flask using an electroanalytical balance. Degassed dimethyl sulfoxide and water (DMSO:H_2O = 1:1, 2.5 mL) were added to the reaction flask, and the reaction mixture was stirred vigorously under argon gas at 50 °C until the vitamin B_{12} was completely reduced (colour changed from red to green). Nitrocyclohexane (0.25 mmol, 1.0 equiv) and ethyl diazoacetate (0.50 mmol, 1.1 equiv) dissolved in dimethylsulfoxide were added to the reaction system with a syringe and the reaction was carried out for 24 h. The reaction was carried out under argon conditions.

The mixture was filtered on diatomaceous earth, the crude reaction mixture was extracted with EA, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum.. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 30: 1, V/V) to afford the product.

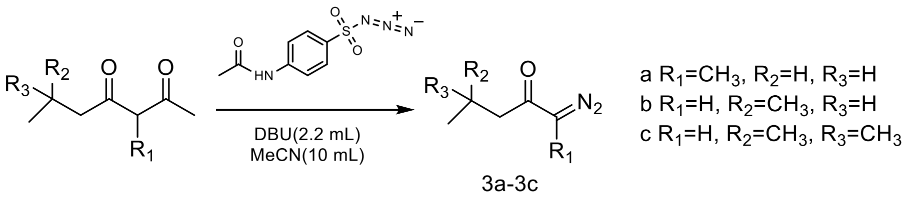


a **b**

Fig. S3 a) Initial reaction mixture, **b)** the reaction mixture after vitamin B_{12} is completely reduced

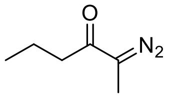
3.2 General procedure for diazo compounds

3.2.1 Synthetic routes for compounds 3a-3c



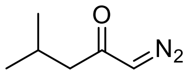
At 0°C, 1,8-Diazabicyclo[5.4.0]undec-7-ene (2.2 mL) was added dropwise to a solution of Ethyl 2-methylacetoacetate (5.0 mmol) and 4-Acetamido-benzenesulfonyl azide (1.80 g, 7.50 mmol) in 10 mL MeCN. The reaction was stirred at room temperature for 10 h and then added HCl to extinguish the reaction. The reaction was extracted with DCM, washed with saturated aqueous $NaHCO_3$ and brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 20: 1, V/V) to afford the product **3a-3c**.

Ethyl 2-diazopropionate (3a)



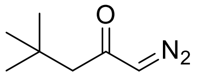
Yellow oil, 70% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.22(q, *J*= 8.0 Hz, 2H), 1.96 (s, 3H), 1.27 (t, *J* = 8.0 Hz, 3H).

Isopropyl 2-diazoacetate (3b)



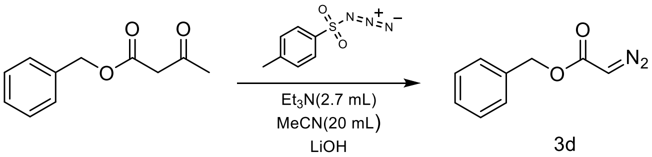
Yellow oil, 67% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.09 (s, *J* = 8.0 Hz, 1H), 4.69 (s, 1H), 1.26 (d, *J* = 8.0 Hz, 6H).

Tert-Butyl 2-diazoacetate (3c)



Yellow oil, 55% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.60 (s, 1H), 1.47 (s, 9H).

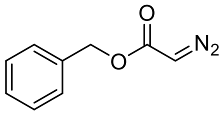
3.2.2 Synthetic routes for compounds 3d



3d

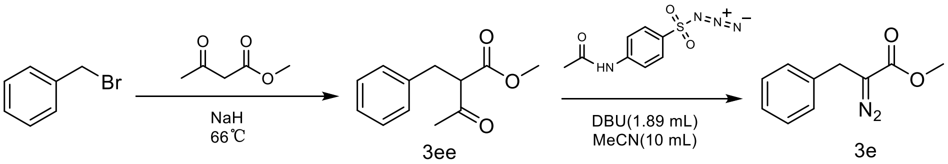
Tosyl azide (2.67 g, 13.53 mmol) was added dropwise to a solution of Butanoic acid, 3-oxo-, phenylmethyl ester (2.0 g, 10.41 mmol) and Et_3N (2.16 mL) in 20 mL MeCN. The reaction was stirred at room temperature for 8 h. Upon completion (monitored by TLC), slowly add 0.1 mol LiOH aqueous solution and stirred at room temperature for 6 h. The reaction was extracted with DCM, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 20: 1, V/V) to afford the product **3d**.

Isopropyl 2-diazoacetate (3d)



Clear oil, 75% yield, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.46-7.33 (m, 5H), 5.20 (s, 2H), 4.80 (s, 1H).

3.2.3 Synthetic routes for compounds 3e



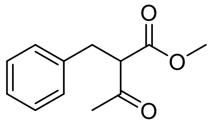
3ee

3e

At 0°C, NaH (60%, 0.69 g, 17.24 mmol) was added dropwise to a solvent anhydrous THF (12 mL), followed by the addition of methyl acetoacetate (2.0 g, 17.24 mmol) dropwise to the suspension, and the reaction mixture was slowly warmed up to room temperature, followed by the addition of benzyl bromide (1.96 g, 11.49 mmol) dropwise, and refluxed for 3 h at 66 °C. Upon completion (monitored by TLC), the reaction was quenched by adding saturated NH_4Cl aqueous solution at 0°C, extracted and partitioned by DCM, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 20: 1, V/V) to afford the product **3ee**.

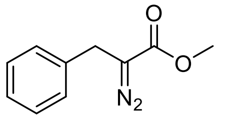
At 0°C, 1,8-Diazabicyclo[5.4.0]undc-7-ene (1.89 mL) was added dropwise to a solution of **3ee** (0.876 g, 4.21 mmol) and 4-Acetamido-benzenesulfonyl azide (1.52 g, 6.32 mmol) in 10 mL MeCN. The reaction was stirred at room temperature for 10 h and then added HCl to extinguish the reaction. The reaction was extracted with DCM, washed with saturated aqueous $NaHCO_3$ and brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 20: 1, V/V) to afford the product **3e**.

Intermediate (3ee)



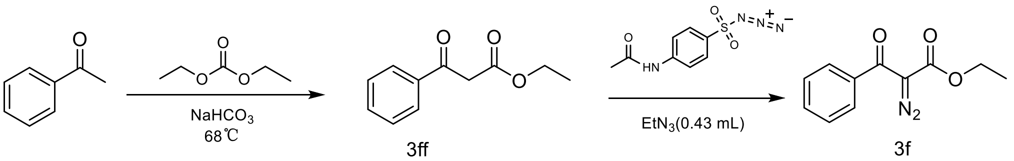
65% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (m, 2H), 7.23-7.17 (m, 3H), 4.04 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.59 (s, 3H), 3.05 (m, 2H), 2.16 (s, 3H).

2-diazo-3-phenylpropionate methyl ester (3e)



Yelloe oil, 70% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34-7.24 (m, 5H), 3.79 (s, 3H), 3.64 (s, 2H).

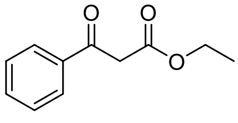
3.2.4 Synthetic routes for compounds 3f



At 0°C, $NaHCO_3$ (1.66 g, 41.61 mmol) and diethyl carbonate (5.5 g, 46.61 mmol) was added dropwise to a solvent anhydrous THF (24 mL), the reaction mixture was slowly warmed up to 68°C, followed by the addition of acetophenone (2.0 g, 16.64 mmol) dropwise. Upon completion (monitored by TLC), the reaction was quenched by adding saturated NH_4Cl aqueous solution at 0°C, extracted and partitioned by DCM, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 10: 1, V/V) to afford the product **3ff**.

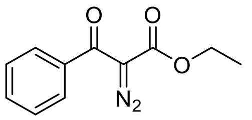
At 0°C, EtN_3 (0.43 mL) was added dropwise to a solution of **3ff** (0.5 g, 2.60 mmol) and p-ABSA (0.75 g, 3.12 mmol) in 10 mL MeCN. The reaction was stirred at room temperature for 12 h. The mixture was filtered on diatomaceous earth, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 15: 1, V/V) to afford the product **3f**.

Intermediate (3ff)



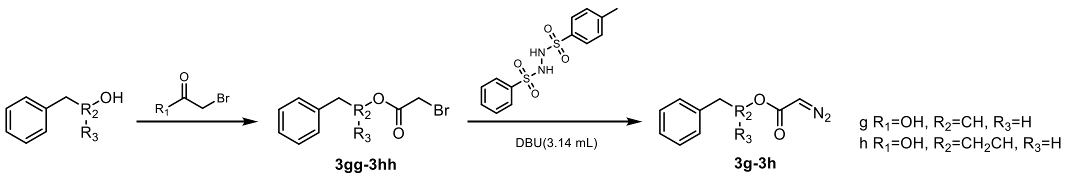
66% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94-7.87 (m, 2H), 7.55 (m, 1H), 7.44-7.42 (m, 2H), 4.18 (q, *J* = 8.0 Hz, 2H), 3.96 (s, 2H), 1.22 (t, *J* = 8.0 Hz, 3H).

Ethyl 2-diazo-3-oxo-3-phenylpropanoate (3f)



Clear oil, 43% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (m, 2H), 7.56-7.47 (m, 1H), 7.42 (m, 2H), 4.25 (q, *J* = 16.0, 8.0 Hz, 2H), 1.26 (t, *J* = 16.0, 8.0 Hz, 3H).

3.2.5 Synthetic routes for compounds 3g-3h

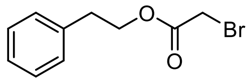


Bromoacetic acid (4.1 g, 29.49 mmol), EDCl (8.0 g, 41.78 mmol) and DMAP (0.3 g, 2.46 mmol) was added dropwise to a solution of phenylethyl alcohol (3.0 g, 24.58 mmol) in 30 mL DCM. The reaction was heated at 32 °C for 6 h. Upon completion (monitored by TLC), the reaction was quenched by adding saturated H_2O, extracted and partitioned by DCM, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 20: 1, V/V) to afford the product **3gg**.

Bromoacetic acid (3.68 g, 26.45 mmol), DCC (5.45 g, 26.45 mmol) and DMAP (0.27 g, 2.2 mmol) was added dropwise to a solution of 3-Phenyl-1-propanol (3.0 g, 22.04 mmol) in 30 mL DCM. The reaction was heated at 32 °C for 6 h. Upon completion (monitored by TLC), the reaction solution was diluted with DCM, washed with water, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum to afford the product **3hh**.

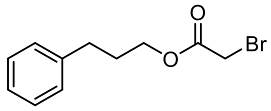
At 0°C, DBU (3.14 mL) was added dropwise to a solution of N,N'-Bis(p-toluenesulfonyl)hydrazine (2.68 g, 7.89 mmol) and **3gg-3hh** (5.26 mmol) in 20 mL THF. The reaction was stirred at room temperature for 1 h and then added water to extinguish the reaction. The reaction was extracted with DCM, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 20: 1, V/V) to afford the product **3g-3h**.

Intermediate (3gg)



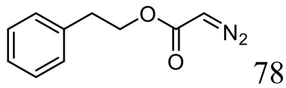
53% yield, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.32 (m, 2H), 7.28-7.20 (m, 3H), 4.41 (t, *J* = 8.0 Hz, 2H), 4.04 (s, 2H), 2.99 (t, *J* = 8.0 Hz, 2H).

Intermediate (3hh)



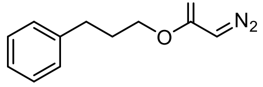
67% yield, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.31-7.28 (m, 2H), 7.22-7.18(m, 3H), 4.20 (t, *J* = 8.0 Hz, 2H), 3.82 (s,2H), 2.72 (t, *J* = 8.0 Hz, 2H), 2.06-1.95 (m, 2H).

2-diazoacetic acid-2-phenyl ethyl ester (3g)



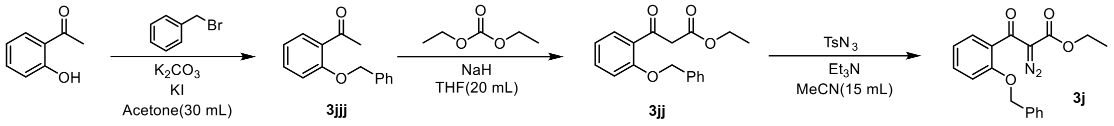
78% yield, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.26 (m, 5H), 4.72 (s, 1H), 4.37 (t, *J* = 8.0 Hz, 2H), 2.96 (t, *J* = 8.0 Hz, 2H).

2-diazoacetate-3-phenylpropyl ester (3h)



69% yield, ^1H NMR (400MHz, Chloroform-*d*) δ 7.31-7.27 (m, 2H), 7.22-7.18 (m, 3H), 4.74 (s, 2H), 4.19 (t, *J* = 8.0 Hz, 2H), 2.69 (t, *J* = 8.0 Hz, 2H), 2.02-1.94 (m, 2H).

3.2.6 Synthetic routes for compounds 3j

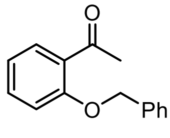


KCO_3 (4.06 g, 29.4 mmol), KI (2.48 g, 14.69 mmol) and bromobenzyl (5.03 g, 29.38 mmol) were added successively to a solution of 2'-hydroxyacetophenone (2.0 g, 14.6 mmol) in 30 mL acetone. The reaction was stirred at 60°C for 12 h. Upon completion (monitored by TLC), the reaction was quenched with water and the aqueous layer was extracted with EA, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 40: 1, V/V) to afford the product **3jjj**.

At 0°C, NaH (60%, 0.98 g, 24.45 mmol) and diethyl carbonate (1.93 g, 16.3 mmol) were added successively to a solution of **3jjj** (3.71 g, 16.3 mmol) in 10 mL acetonitrile. The reaction was stirred at 0°C for 5 min and then heated at 66°C for 3 h. Upon completion (monitored by TLC), the reaction was quenched with water at 0°C and the aqueous layer was extracted with EA, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 10: 1, V/V) to afford the product **3jj**.

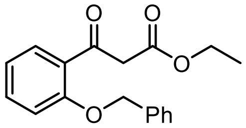
TsN_3 (1.21 g, 6.11 mmol) was added dropwise to a solution of **3jj** (1.82 g, 6.11 mmol) and Et_3N (0.85 mL) in 15 mL acetonitrile. The reaction was stirred at 28°C for 18 h. Upon completion (monitored by TLC), the solvent was removed in vacuum. The crude product was dissolved in EA (10 mL) and then washed with 25% KOH (25 mL) and 6% KOH (20 mL). Organic phase was dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 20: 1, V/V) to afford the product **3j**.

Intermediate (3jjj)



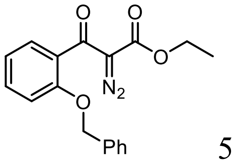
54% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78-7.76 (m, 1H), 7.46-7.34 (m, 6H), 7.04-7.00 (m, 2H), 5.17 (s, 2H), 2.62 (s, 3H).

Intermediate (3jj)



25% yield, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.86 (dd, J = 7.8, 1.8 Hz, 1H), 7.46-7.37 (m, 6H), 7.02 (dd, J = 14.3, 7.6 Hz, 2H), 5.18 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.99 (s, 2H), 1.18 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.60, 168.12, 158.18, 135.89, 134.50, 131.19, 128.81, 128.39, 127.57, 126.97, 121.11, 112.87, 70.71, 60.94, 50.53, 14.06. HRMS (ESI): $[M+H]^+$ *m/z*: calculated: 299.1278, found: 299.1259.

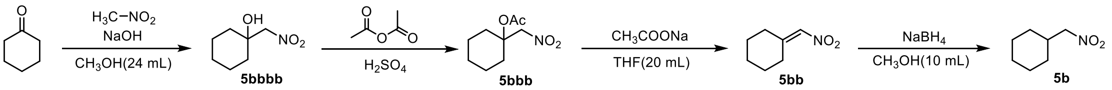
3-(2-(benzoxy) phenyl)-2-diazo-3-oxo-propionate ethyl ester (3j)



54% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43-7.31 (m, 7H), 7.05-7.01 (m, 1H), 6.98-6.66 (m, 1H), 5.09 (s, 2H), 4.11 (q, 2H), 1.13 (t, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 186.33, 160.84, 156.15, 136.57, 132.36, 128.57, 128.64, 127.96, 126.98, 121.00, 112.26, 70.53, 61.27, 14.10. HRMS (ESI): $[M+H]^+$ *m/z*: calculated: 325.1188, found: 325.1189.

3.3 General procedure for nitro-compounds

3.3.1 Synthetic routes for compounds 5b



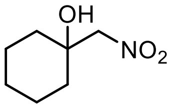
At 0°C, 16% aqueous sodium hydroxide (12 mL) was added dropwise to a solution of cyclohexanone (4.0 g, 40.76 mmol) and nitromethane (2.49 g, 40.76 mmol) in 24 mL methanol. The reaction was stirred at 0°C for 3 h. Upon completion (monitored by TLC), the reaction mixture was filtered to collect the white solid crude product， and then dissolved crude product into water, stirred, added acetic acid (12 mL) and water (20 ml), the aqueous layer was extracted with EA, washed with saturated aqueous $NaHCO_3$ and brine, then dried with Na_2SO_4, the solvent was removed in vacuum to afford the product **5bbbb**.

At 0°C, acetic anhydride (2.29 g, 22.43 mmol) and concentrated sulfuric acid (0.22 mmol) were added dropwise to **5bbbb** (3.57 g, 22.43 mmol). The reaction was stirred at 50°C for 2 h. Upon completion (monitored by TLC), the reaction was quenched with water, the aqueous layer was extracted with EA, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum to afford the product **5bbb.**

CH_3COONa (1.80 g, 21.91 mmol) was added to a solution of **5bbb** (3.8 g, 18.89 mmol) in 20 mL THF. The reaction was stirred at 66°C for 6.5 h. Upon completion (monitored by TLC), the reaction was filtered, and then the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 20: 1, V/V) to afford the product **5bb**.

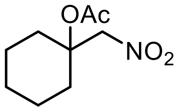
At 0°C, $NaBH_4$ (0.54 g, 14.46 mmol) was added to a solution of **5bb** (2.04 g, 14.46 mmol) in 10 mL methanol. The reaction was stirred at room temperature for 2 h. Upon completion (monitored by TLC), the reaction was quenched with saturated aqueous NH_4Cl and water (20 mL), and then, the aqueous layer was extracted with EA, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 10: 1, V/V) to afford the product **5b**.

Intermediate (5bbbb)



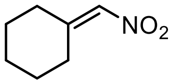
55% yield, ^{1}H NMR(400 MHz, $CDCl_3$) δ 4.42 (s, 2H), 2.77 (s, 1H), 1.73-1.44 (m, 9H), 1.35-1.22 (m, 1H).

Intermediate (5bbb)



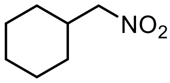
84% yield, ^{1}H NMR(400 MHz, $CDCl_3$) δ 4.93 (s, 2H), 2.22-2.19 (m, 2H), 2.07 (s, 3H), 1.65-1.46 (m, 7H), 1.35-1.22 (m, 1H). ^{13}C NMR(101 MHz, $CDCl_3$) δ 170.67, 79.46, 79.42, 32.69, 24.92, 21.98, 21.19. HRMS (ESI): $[M+H]^+$ *m/z*: calculated: 202.1074, found: 202.1090.

Intermediate (5bb)



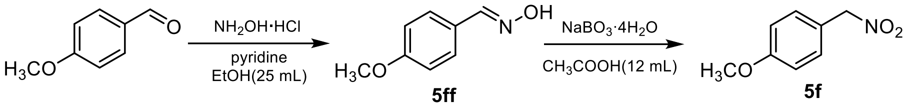
50% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.89 (s, 1H), 2.85-2.82 (m, 2H), 2.21-2.18 (m, 2H), 1.73-1.61 (m, 6H).

(Nitromethyl) cyclohexane (5b)



49% yield, ^1H NMR (400 MHz, Chloroform-*d*) δ 4.22 (d, 2H), 2.22-2.11 (m, 1H), 1.79-1.73 (m, 5H), 1.36-1.29 (m, 2H), 1.28-1.18 (m, 1H), 1.17-1.00 (m, 2H).

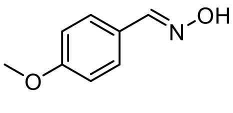
3.3.2 Synthetic routes for compounds 5f



Hydroxylamine hydrochloride (3.24 g, 46.61 mmol) and pyridine (4.74 g, 59.92 mmol) were added to a solution of p-anisaldehyde (33.29 mmol) in 25 mL ethanol. The reaction was stirred at room temperature for 10 h. Upon completion (monitored by TLC), the solvent was removed in vacuum. The crude product was dissolved in EA (10 mL) and then a solution of 2.0 M HCl was added until the pH of the solution has been adjusted to 6. The mixture was washed with saturated aqueous $NaHCO_3$ and brine. Organic phase was dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 20: 1, V/V) to afford the product **5ff**.

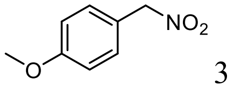
Sodium perborate tetrahydrate (10.25 g, 66.60 mmol) were added to a solution of **5ff** (22.20 mmol) in 25 mL acetic acid. The reaction was stirred at 55°C for 20 h. Upon completion (monitored by TLC), the reaction was quenched with water at 0°C, removed acetic acid by the addition of aqueous sodium hydroxide, and then, the aqueous layer was extracted with EA, washed with brine, then dried with Na_2SO_4, filtered, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 30: 1, V/V) to afford the product **5f**.

Intermediate (5ff)



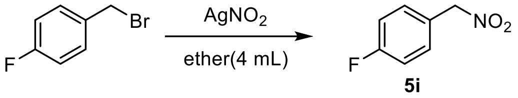
90% yield, ^1H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 8.15 (s, 1H), 7.55 (d, 2H), 6.95 (d, 2H), 3.85 (s, 3H).

1-methoxy-4-(nitromethyl) benzene (5f)



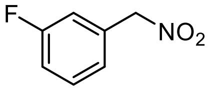
36% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 (d, 2H), 6.94 (d, 2H), 5.37 (s, 2H), 3.82 (s, 3H).

3.3.3 Synthetic routes for compounds 5i



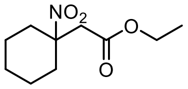
The reaction was carried out in a tinfoil wrapped round-bottom flask. At 0°C, 3-fluorobenzyl bromide (1.06 mmol) was added dropwise to a solution of silver nitrite (0.21 g, 1.38 mmol) in 8 mL ether. The mixture was stirred at 0°C for 1 h, subsequently allowed to react for 4 h at room temperature. Upon completion (monitored by TLC), the mixture was filtered on diatomaceous earth, the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 30: 1, V/V) to afford the product **5i**.

1-fluoro-3 -(nitromethyl) benzene (5i)

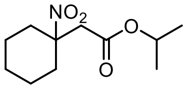


37% yield, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45-7.30 (m, 1H), 7.27-7.21 (m, 1H), 7.19-7.14(m, 2H), 5.44 (s, 2H).

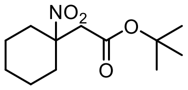
4. Specific synthetic procedures



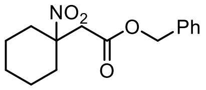
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.13 (q, 2H), 2.91 (s, 2H), 2.35-2.29 (m, 2H), 1.88-1.83 (m, 2H), 1.61-1.38 (m, 6H), 1.22 (t, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.62, 88.50, 61.02, 42.83, 34.27, 24.60, 22.29, 14.02. HRMS (ESI): [M+H]$^{+}$ *m/z*: calculated: 216.1230, found: 216.1217.



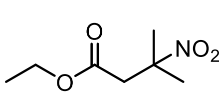
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.04-4.94 (m, 1H), 2.89 (s, 2H), 2.37-2.31 (m, 2H), 1.90-1.84 (m, 2H), 1.61–1.41(m, 6H), 1.22 (d, J=6.3 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.13, 88.55, 68.75, 43.23, 34.30, 24.64, 22.30, 21.65. HRMS (ESI): [M+H]$^{+}$ *m/z*: calculated: 230.1387, found: 230.1385.



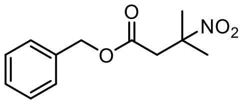
^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.83 (s, 2H), 2.35-2.30 (m, 2H), 1.88-1.82 (m, 2H), 1.63–1.49 (m, 6H), 1.42 (s. 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.82, 88.58, 81.88, 44.31, 34.32, 27.90, 24.67, 22.30. HRMS (ESI): [M+H]$^{+}$ m/z: calculated: 244.1543, found: 244.1548.



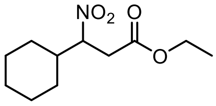
^{1}HNMR (400 MHz, Chloroform-*d*) δ 7.36-7.32 (m, 5H), 5.11 (s, 2H), 2.99 (s, 2H), 2.37-2.30 (m, 2H), 1.91-1.84 (m, 2H), 1.60-1.41 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.54, 135.26, 128.62, 128.46, 128.38, 88.52, 66.91, 42.65, 34.28, 29.71, 24.60, 22.31. HRMS (ESI): [M+H]$^{+}$ *m/z*: calculated: 278.1387, found: 278.1386.



^{1}H NMR (400 MHz, Chloroform-d) δ 4.15 (q, J = 7.1 Hz, 2H), 2.97 (s, 2H), 1.69 (s, 6H), 1.25 (t, J = 7.1 Hz, 3H). 13C NMR (101 MHz, Chloroform-d) δ 168.83, 84.95, 61.05, 44.00, 26.31,14.05.



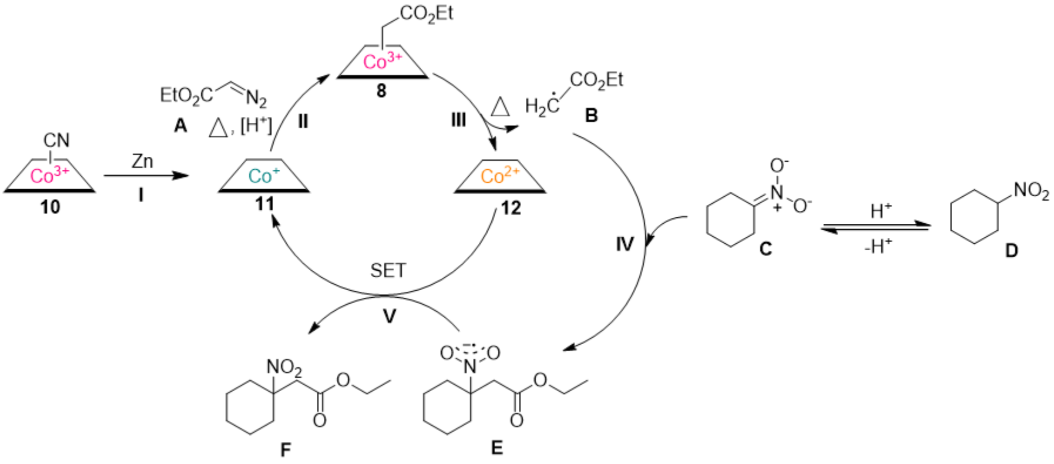
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40-7.32 (m, 5H), 5.13 (s, 2H), 3.03 (s, 2H), 1.69 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.70, 135.26, 128.64, 128.49, 128.36, 84.94, 66.86, 43.89, 26.33. HRMS (ESI): [M+H]$^{+}$ *m/z*: calculated: 238.1074, found: 238.1088.



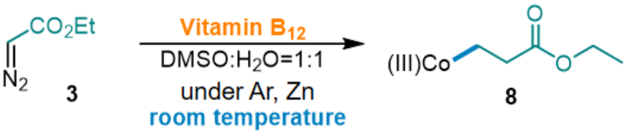
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.73 (ddd, 1H), 4.13 (q, 2H), 3.10 (dd, 1H), 2.66 (dd, 1H), 1.91-1.76 (m, 1H), 1.69-1.63 (m, 5H), 1.26-1.02 (m, 8H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.75, 88.16, 61.24, 41.33, 34.37, 29.17, 28.53, 25.73, 14.00. HRMS (ESI): $[M+H]^+$ *m/z*: calculated: 230.1387, found: 230.1382.

5. Mechanistic considerations

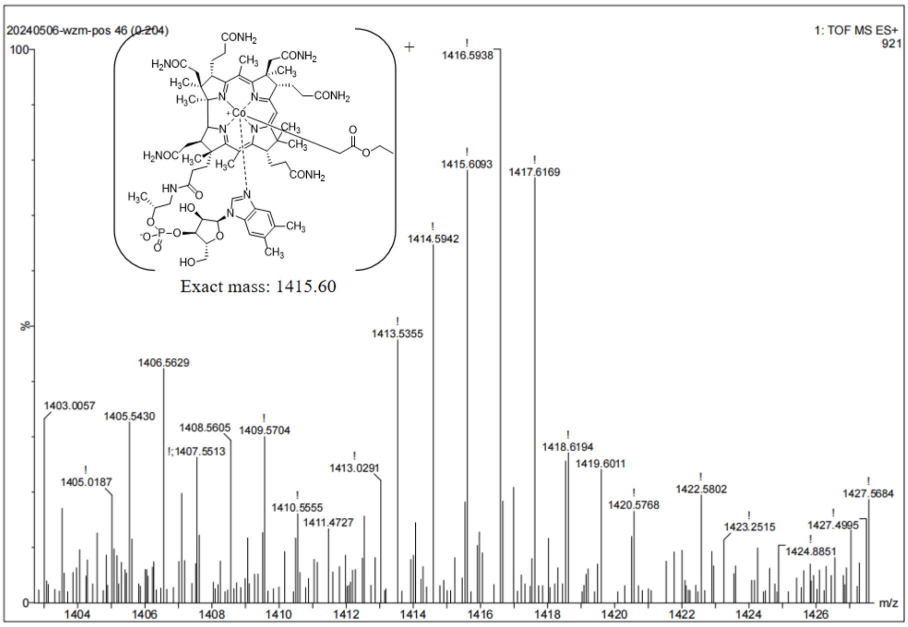
5.1 Proposed Mechanism



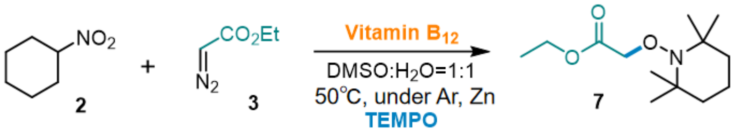
5.2 Reaction with no heat



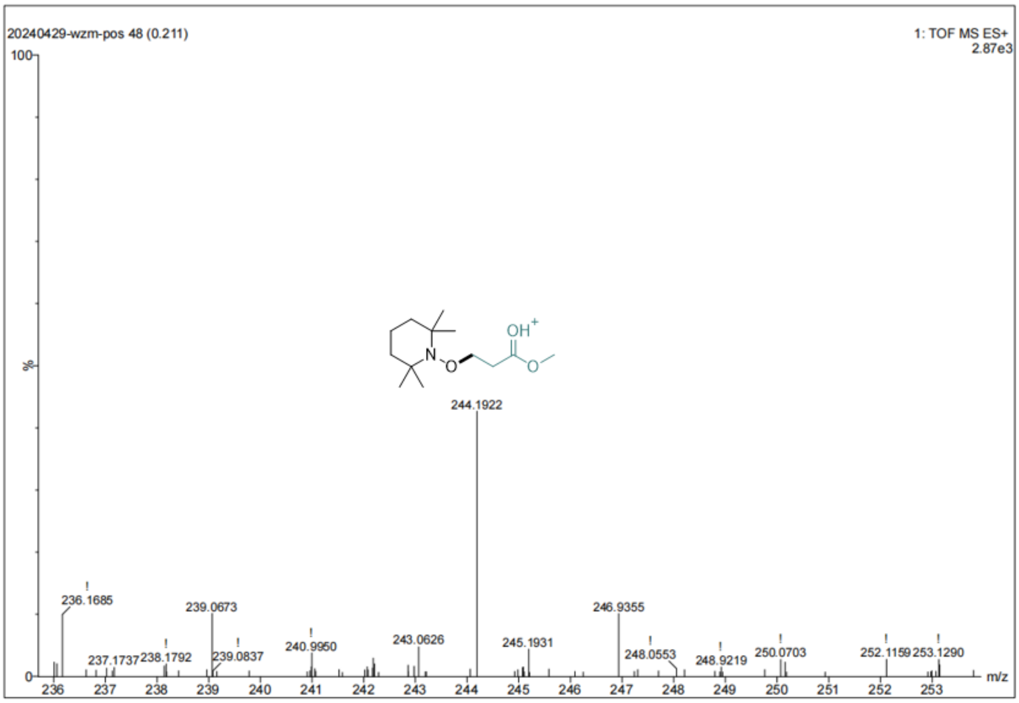
The reaction was performed at room temperature. After vitamin B_{12} was fully reduced, EDA was added. Afte stirring at room temperature for 30 min, a sample of crude reaction mixture was taken and monitored by MS. Signal at 1415.60 corresponds to the alkyl complex.



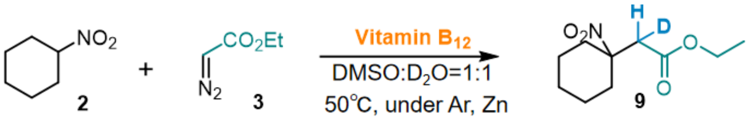
5.3 Reaction with radical trap



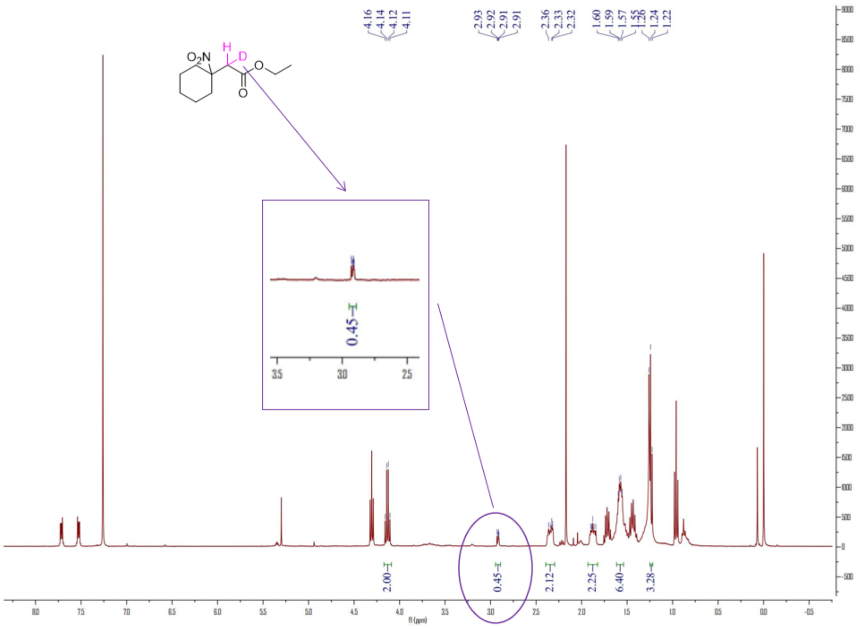
The reaction was performed according to the general procedure with addition of 2 equiv of TEMPO. Reaction was monitored by MS. After 24 hours product was not detected. The MS spectra of the reaction mixture showed peaks at 244.1922 corresponds to adduct **5.2**.



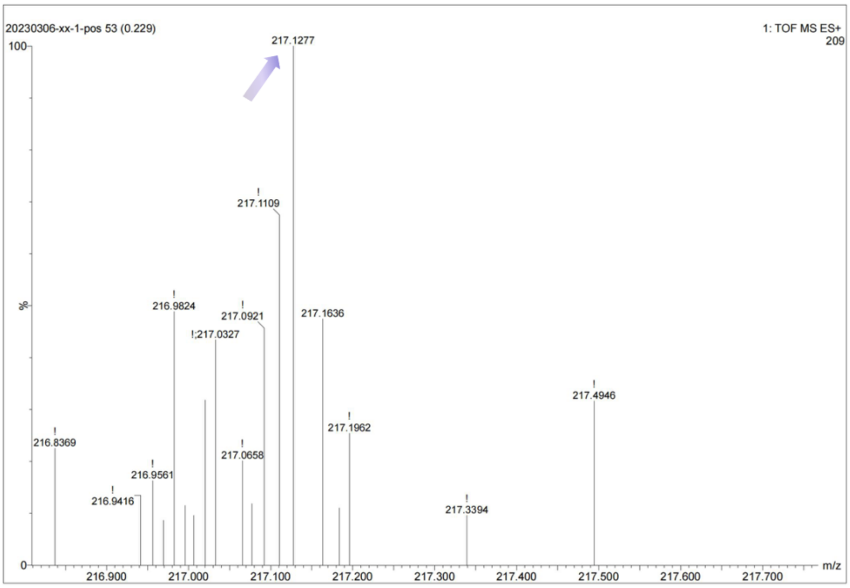
5.4 Experiment with deuterated reagents



Reaction conditions: Nitrocyclohexane (0.25 mmol), EDA (2 equiv.), Zn (6 equiv.), vitamin B_{12} (2 mol%), solvent (2.5 mL), 24 h.

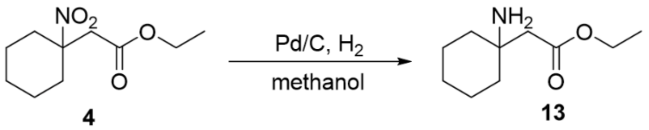


To prove the hypothesis of the external proton in alkylcobalamin(9) originated from H_2O, the experiment in D_2O was performed. The integral of the signal at 2.92 ppm changed from 2 to 0.45 demonstrates that the deuterated substrate is present, and the peak shape was changed from the single peak to multiple peaks.

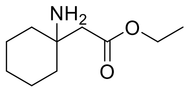


The mass spectrum data changed from 216.1230 to 217.1277. The above results confirmed that an original H atom in the product was replaced by a D atom.

6. Product Derivatization



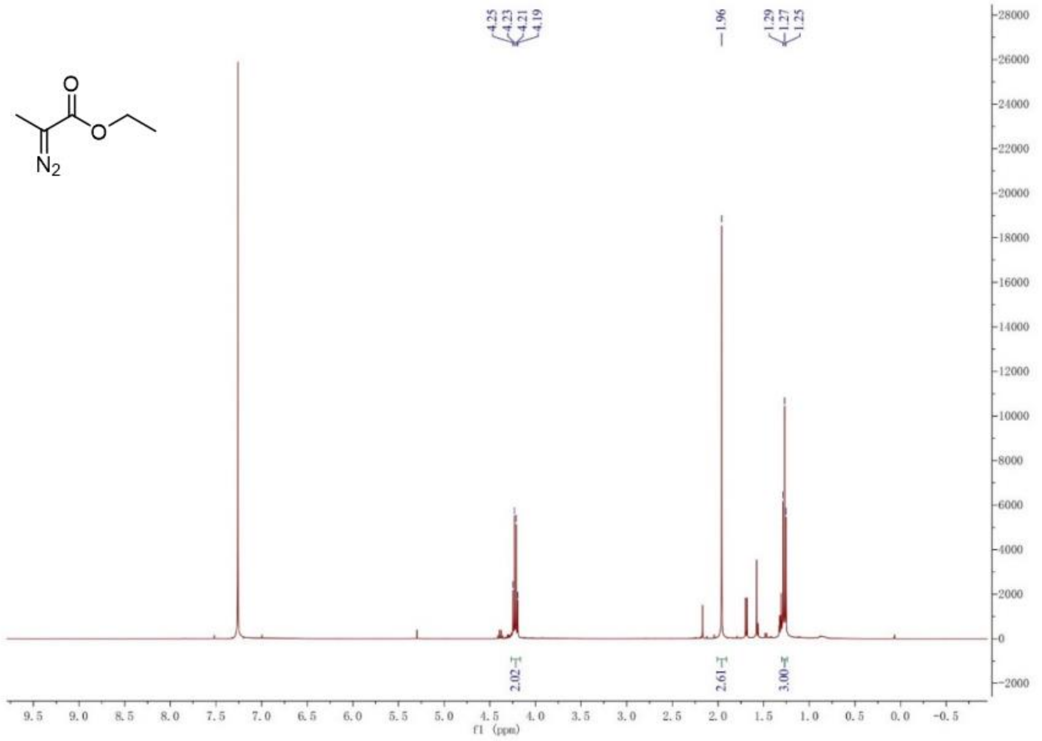
10% Pd/C was added to a solution of 2-(1-nitrocyclohexyl) ethyl acetate (43 mg, 0.2 mmol) in 10 mL methanol. The reaction was stirred at room temperature for 20 h under a hydrogen atmosphere (50 psi). Upon completion, the mixture was filtered and the solvent was removed in vacuum. The crude reaction mixture was purified by chromatography on silica gel (PE: EA = 1: 1, V/V) to afford the product **13**.



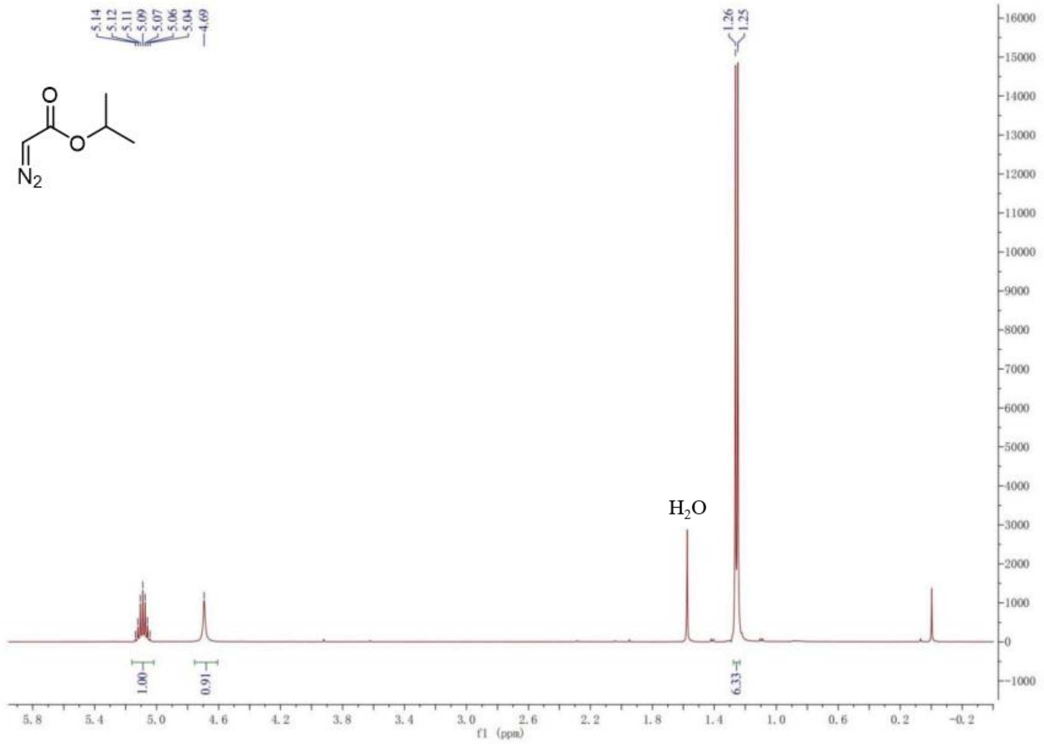
^{1}H NMR (400 MHz, CDCl$_3$) δ 4.14 (q, J = 7.1 Hz, 2H), 2.39 (s, 2H), 1.64 – 1.42 (m, 10H), 1.26 (t, J = 7.1 Hz, 3H).

7. ^{1}H and ^{13}C NMR spectra

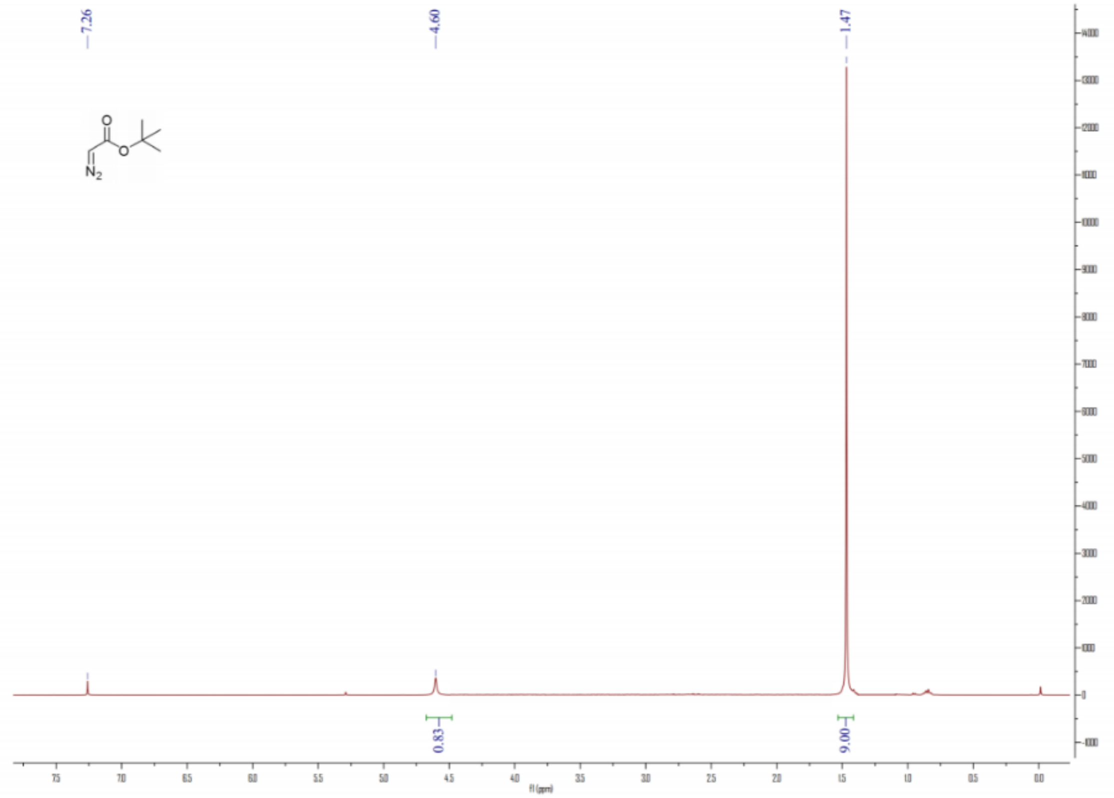
(3a) ^{1}H NMR (400 MHz, $CDCl_3$)



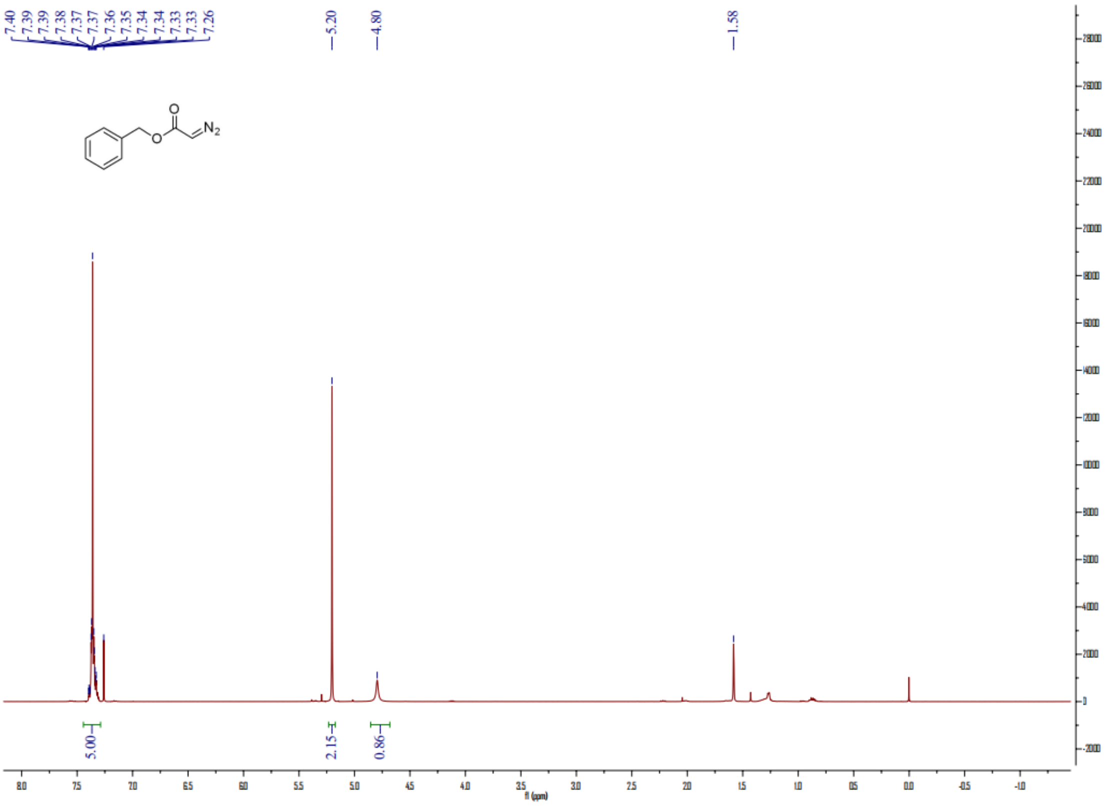
(3b) ^{1}H NMR (400 MHz, $CDCl_3$)



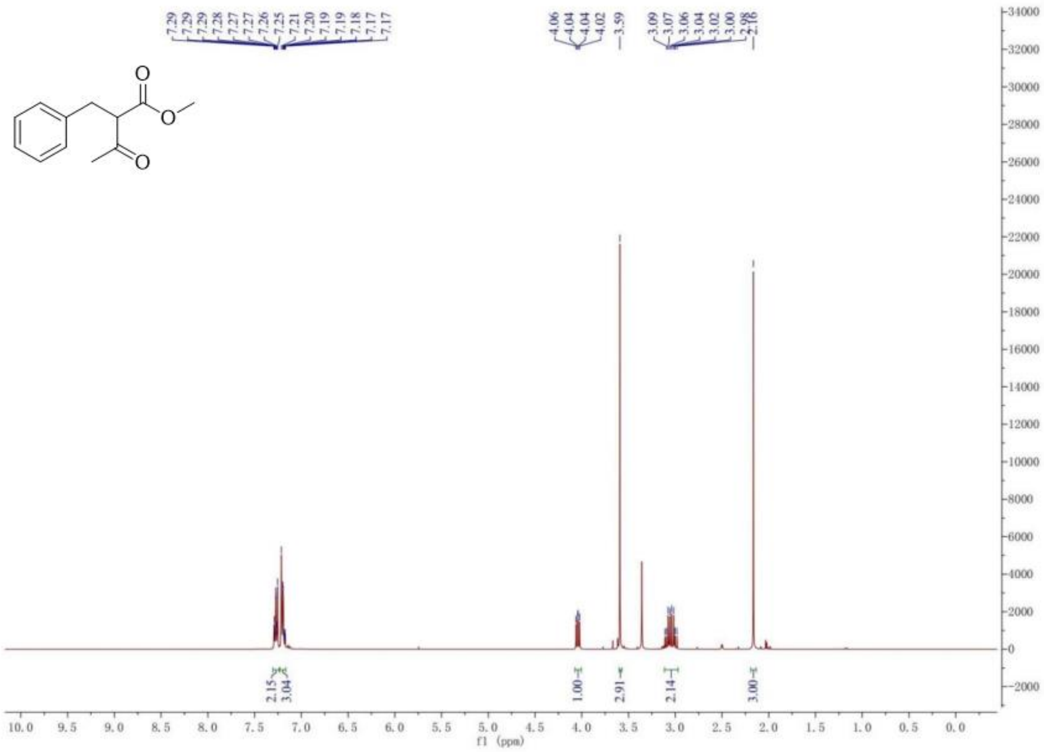
(3c) ^{1}H NMR (400 MHz, CDCl$_3$)



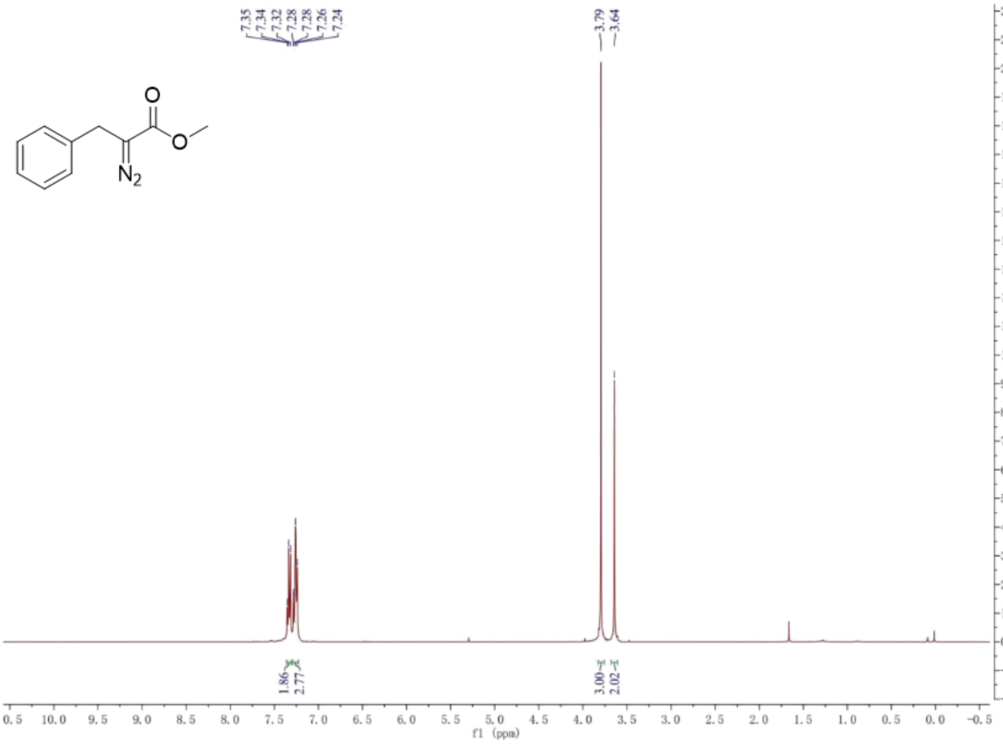
(3d) ^{1}H NMR (400 MHz, CDCl$_3$)



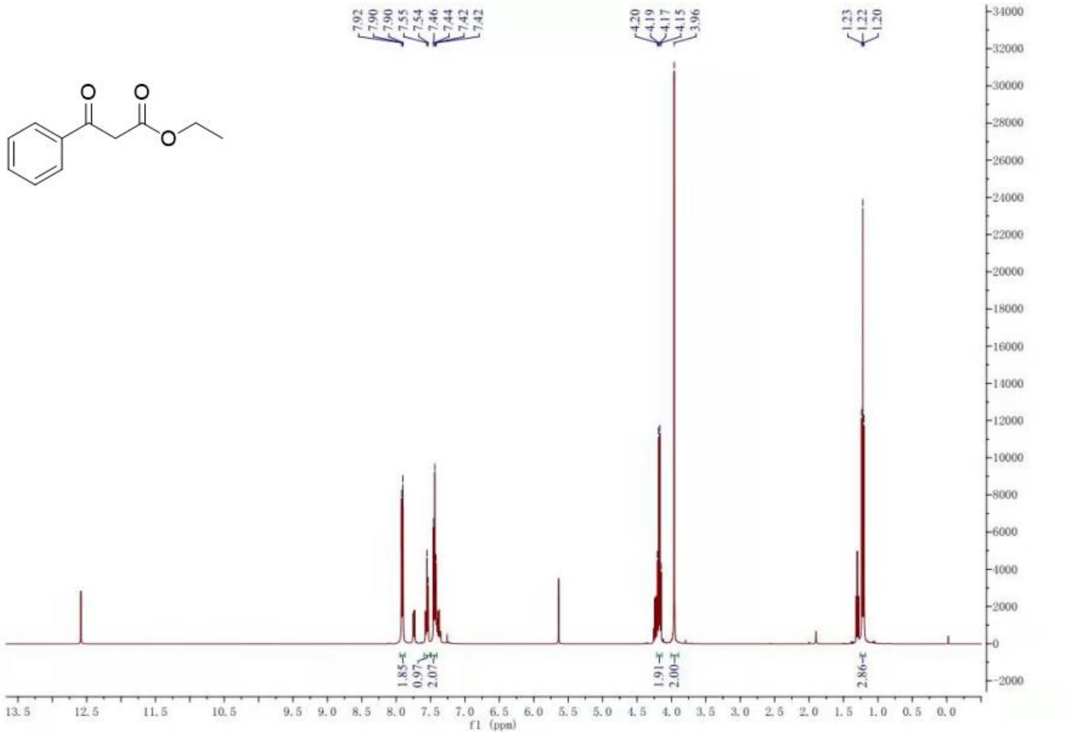
(3ee) ^{1}H NMR (400 MHz, CDCl$_3$)



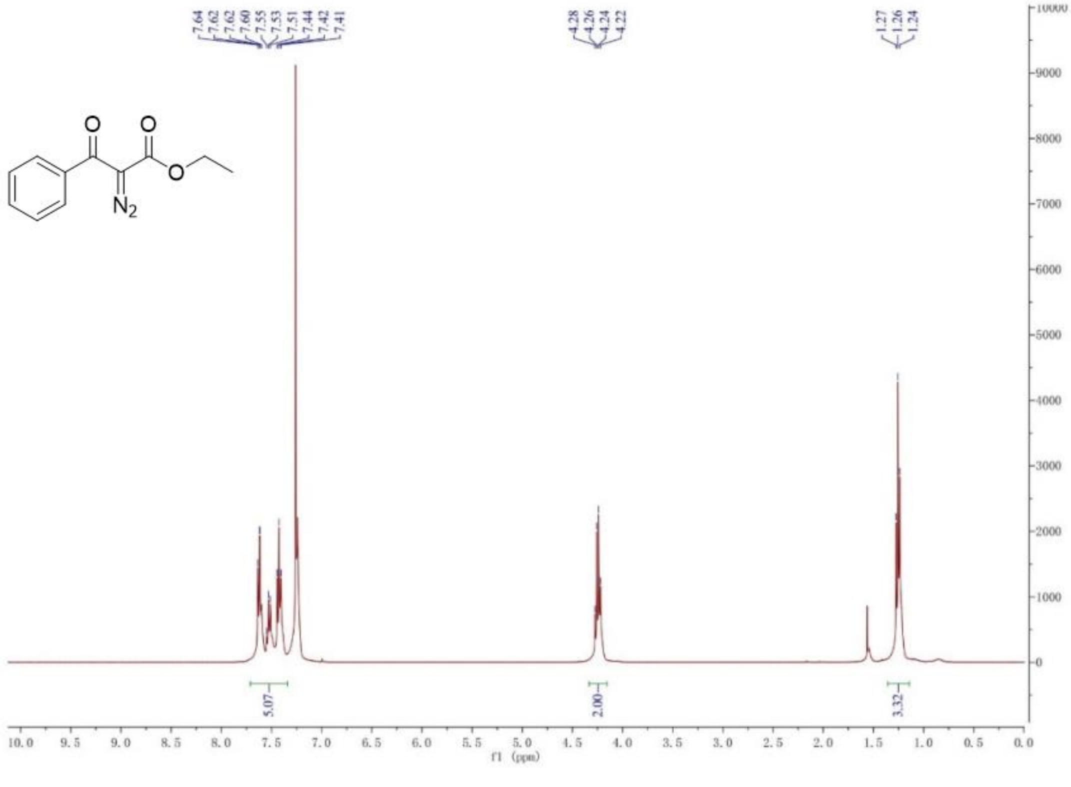
(3e) ^{1}H NMR (400 MHz, CDCl$_3$)



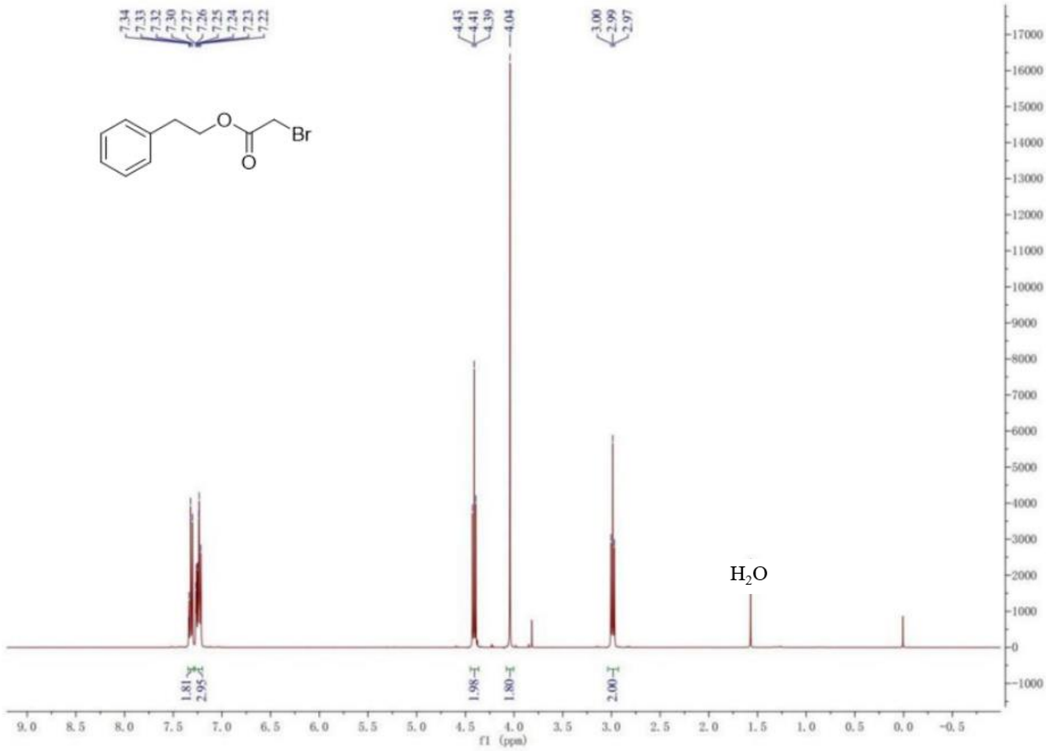
(3ff) ^{1}H NMR (400 MHz, CDCl$_3$)



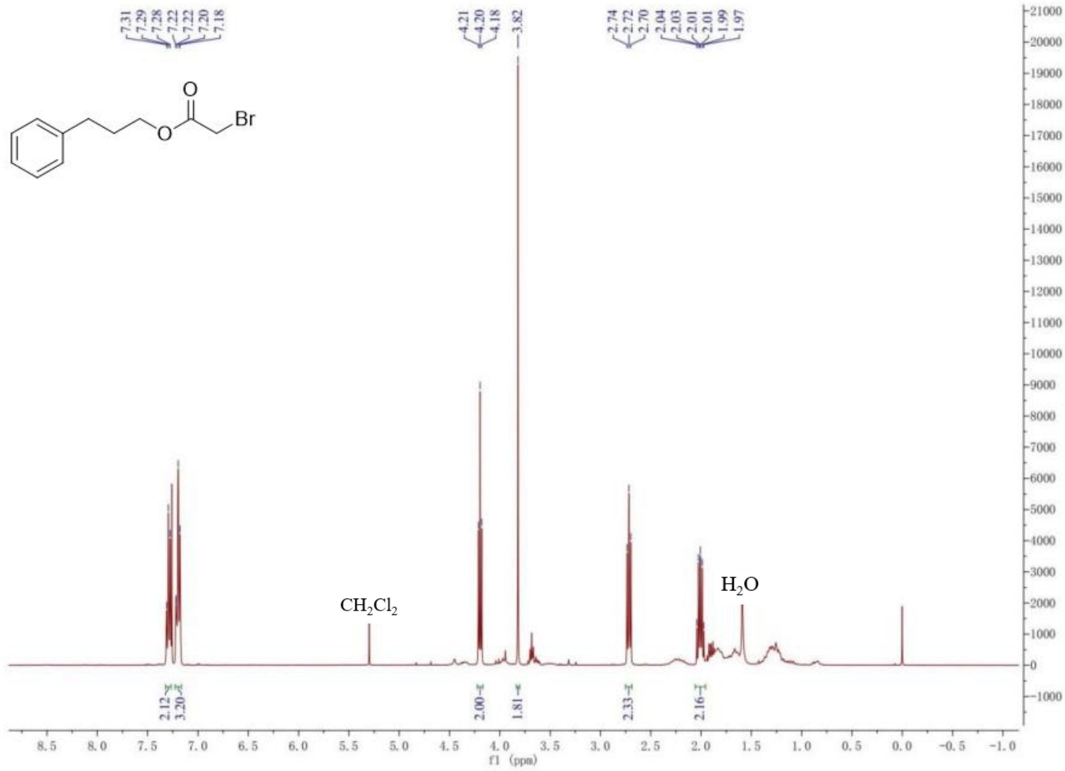
(3f) ^{1}H NMR (400 MHz, CDCl$_3$)



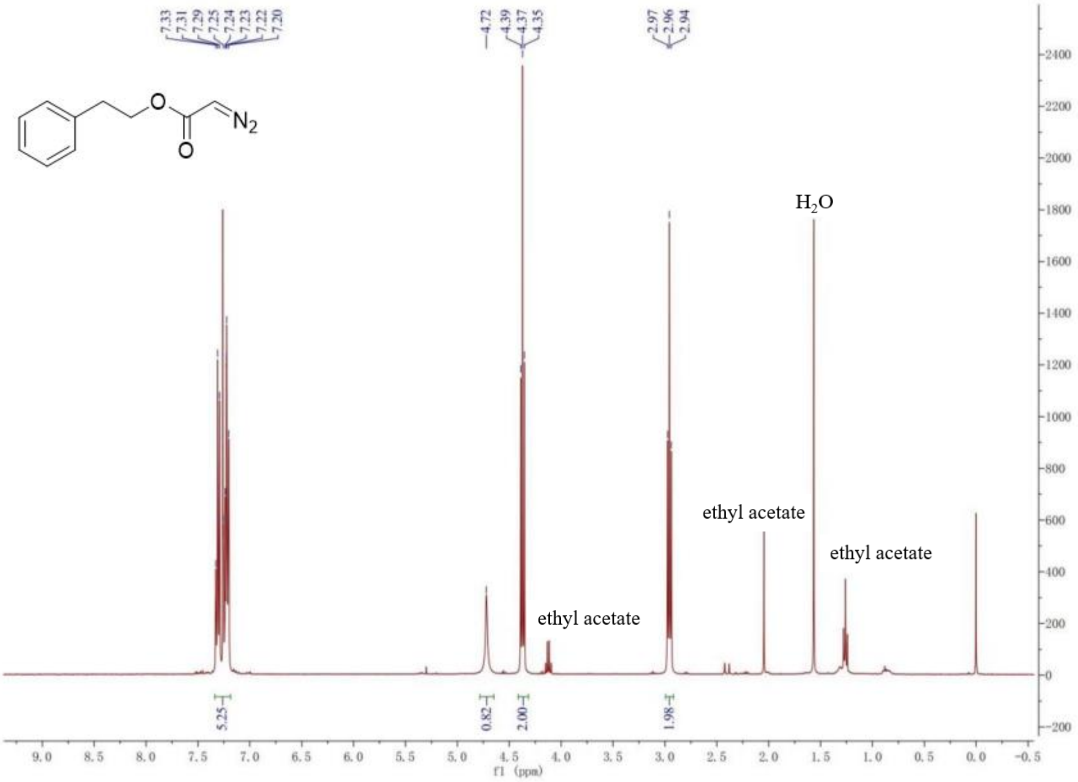
(3gg) ^{1}H NMR (400 MHz, CDCl$_3$)



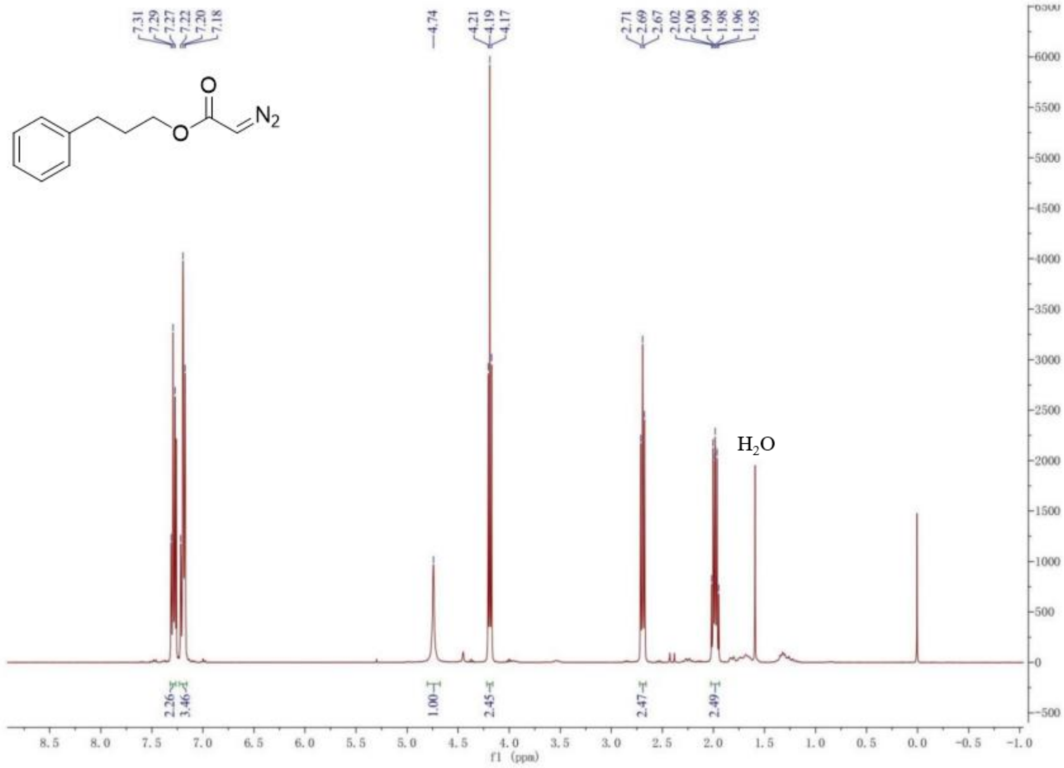
(3hh) ^{1}H NMR (400 MHz, CDCl$_3$)



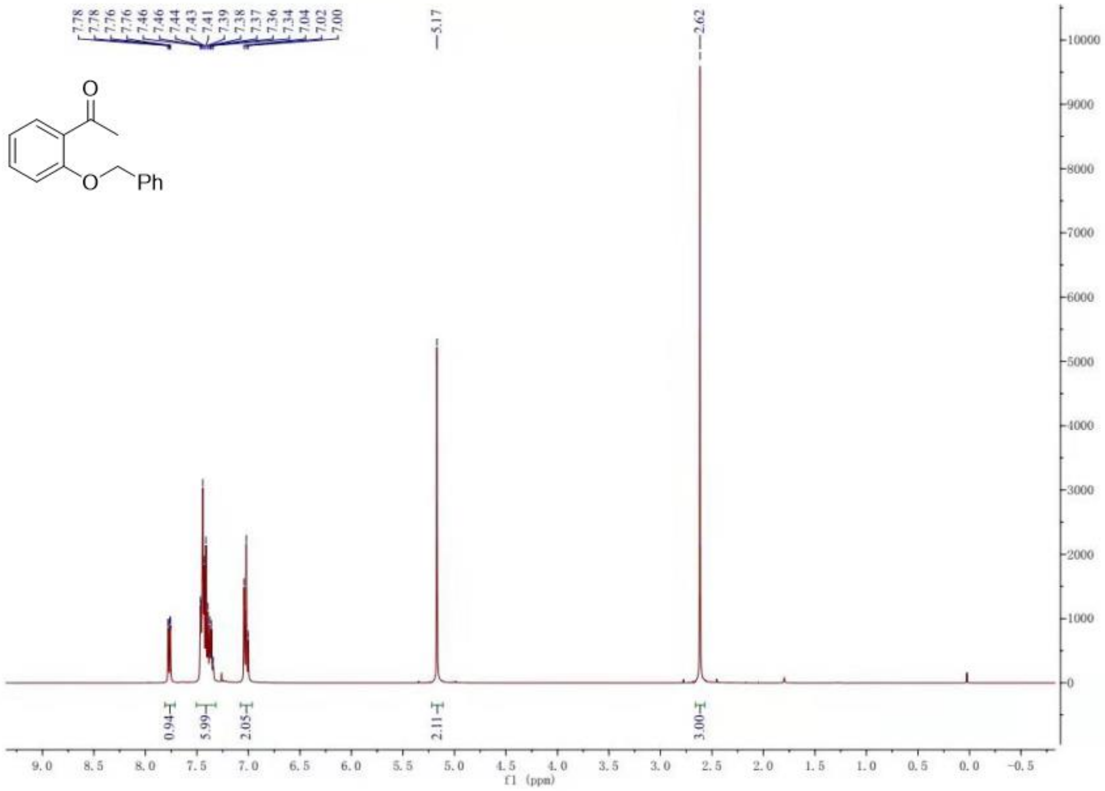
(3g) ^{1}H NMR (400 MHz, CDCl$_3$)



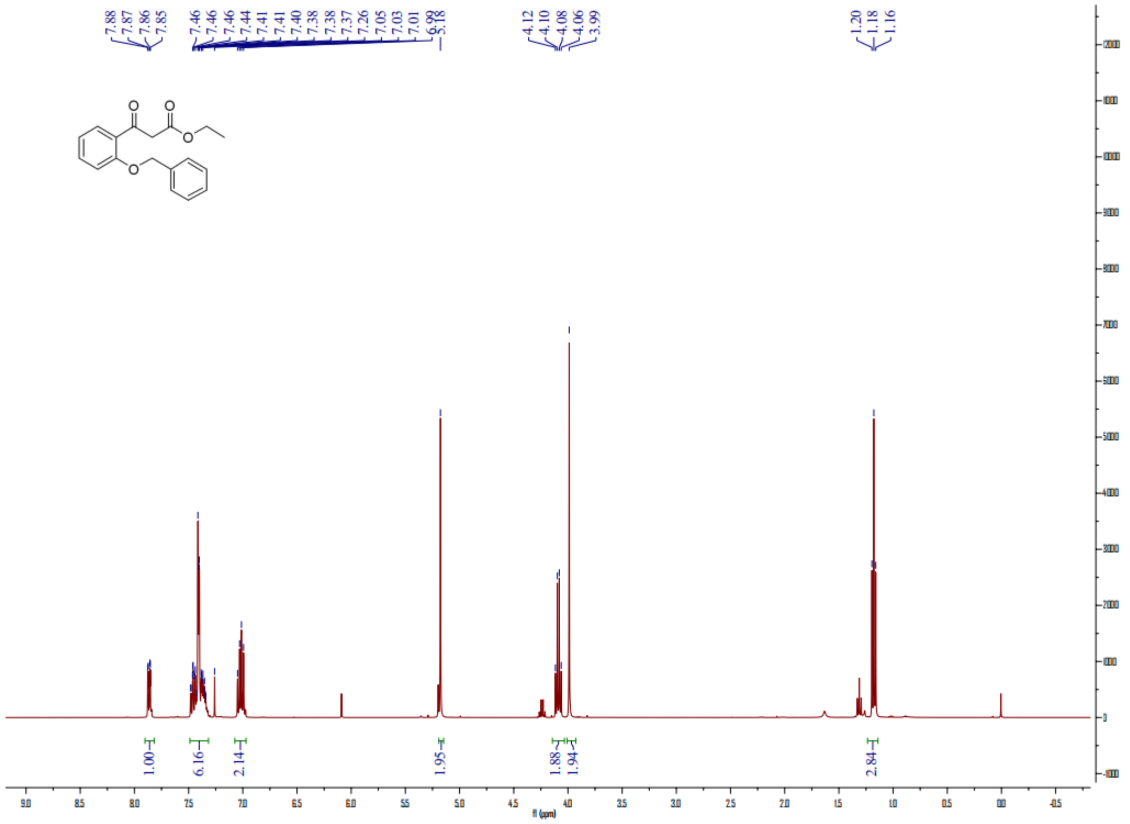
(3h) ^{1}H NMR (400 MHz, CDCl$_3$)



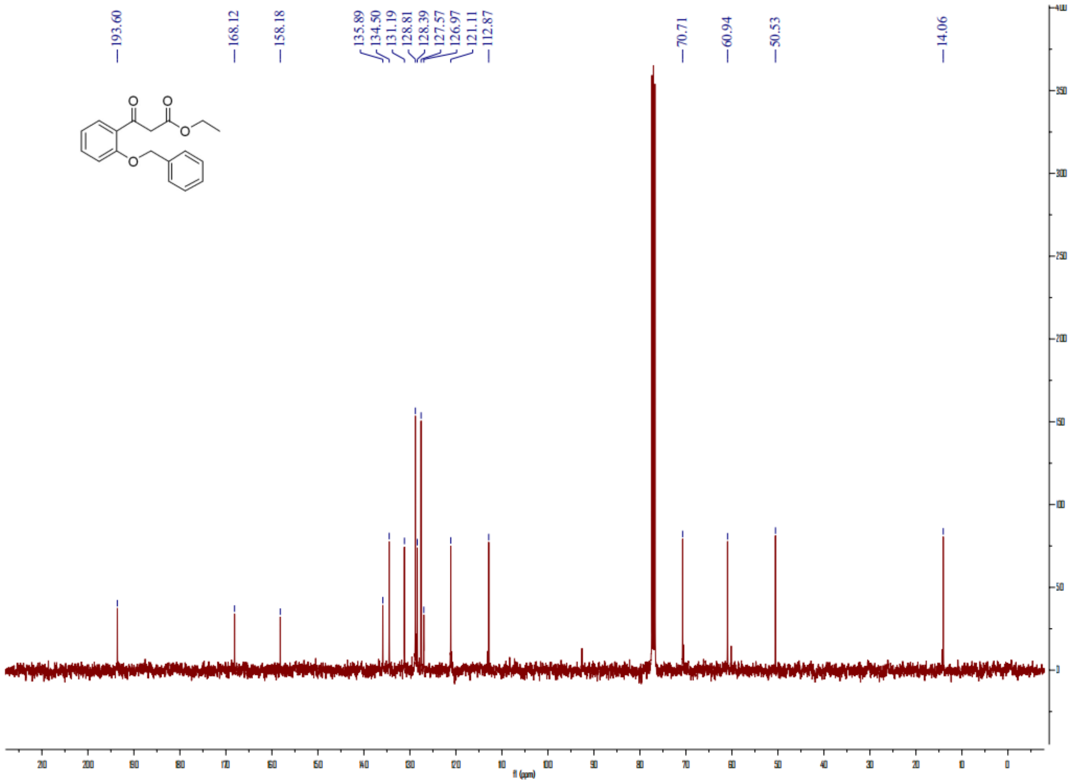
(3jjj) ^{1}H NMR (400 MHz, $CDCl_3$)



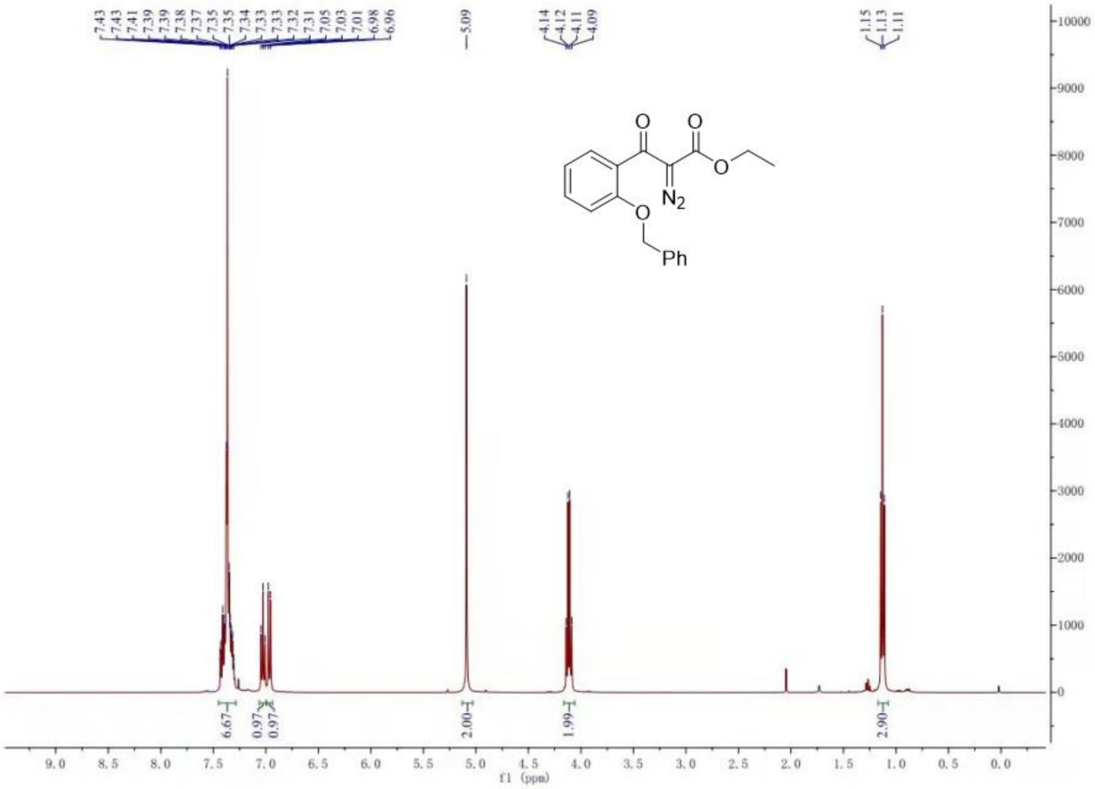
(3jj) ^{1}H NMR (400 MHz, $CDCl_3$)



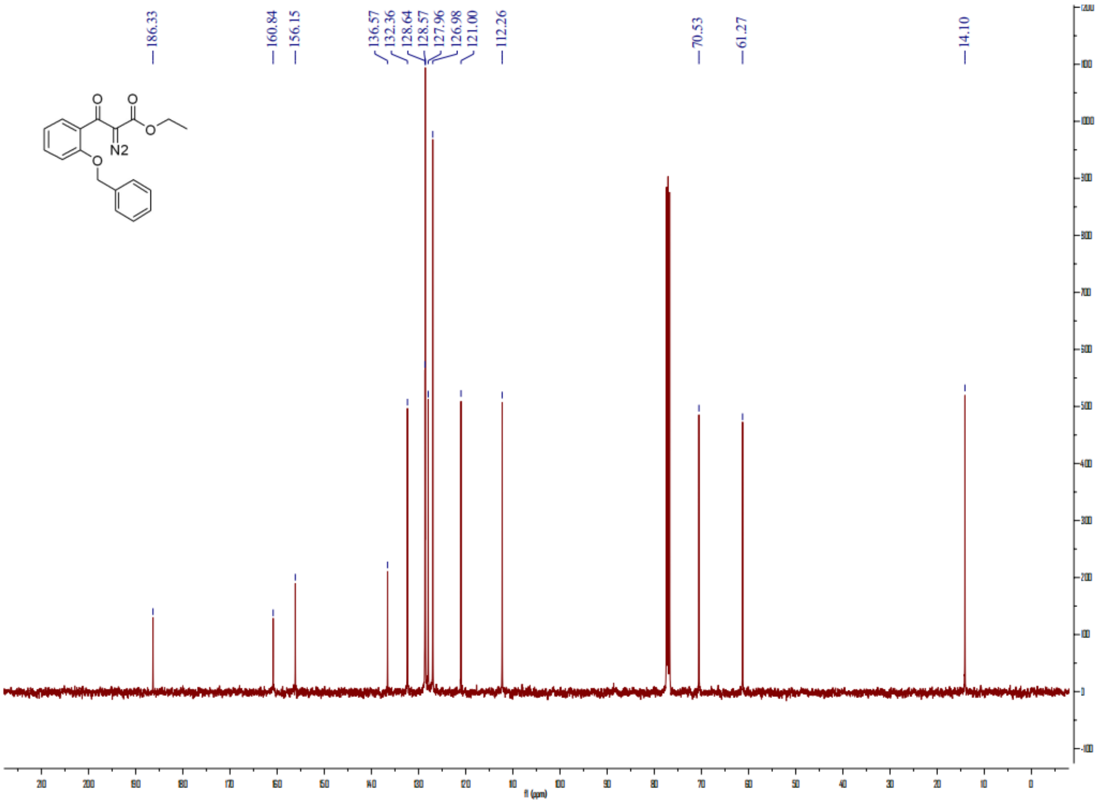
(3jj)^{13}C NMR (100 MHz, CDCl$_3$)



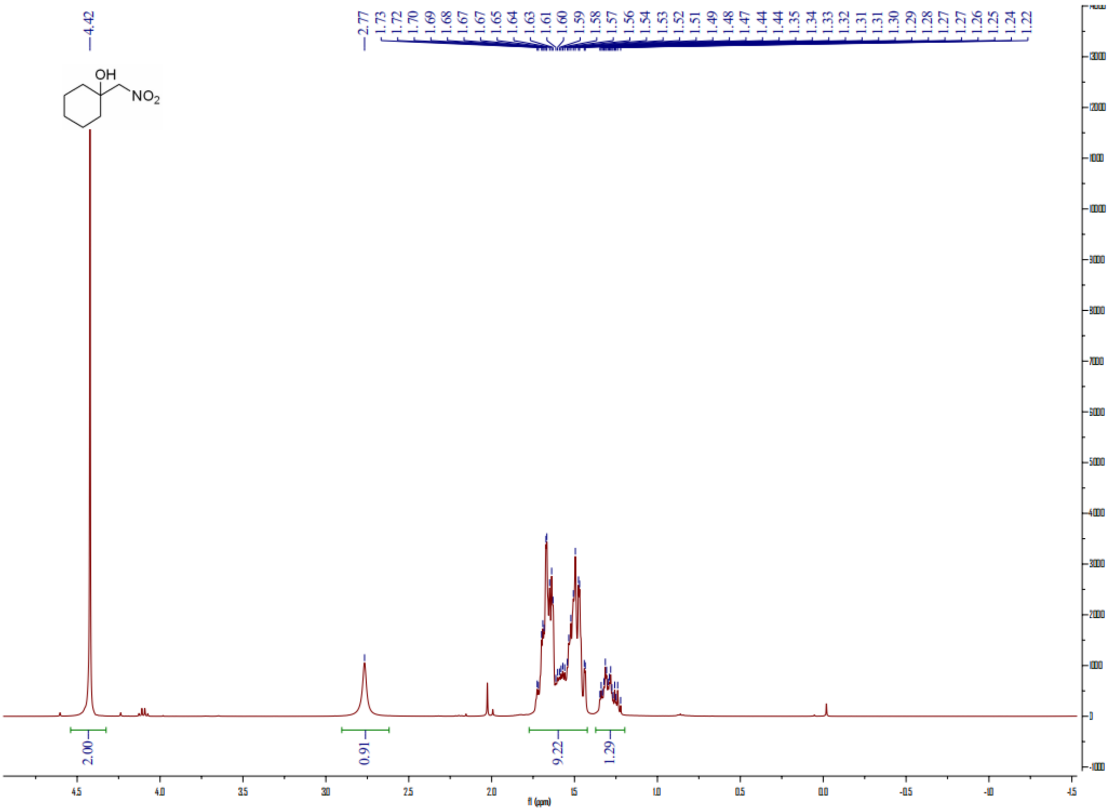
(3j) ^{1}H NMR (400 MHz, CDCl$_3$)



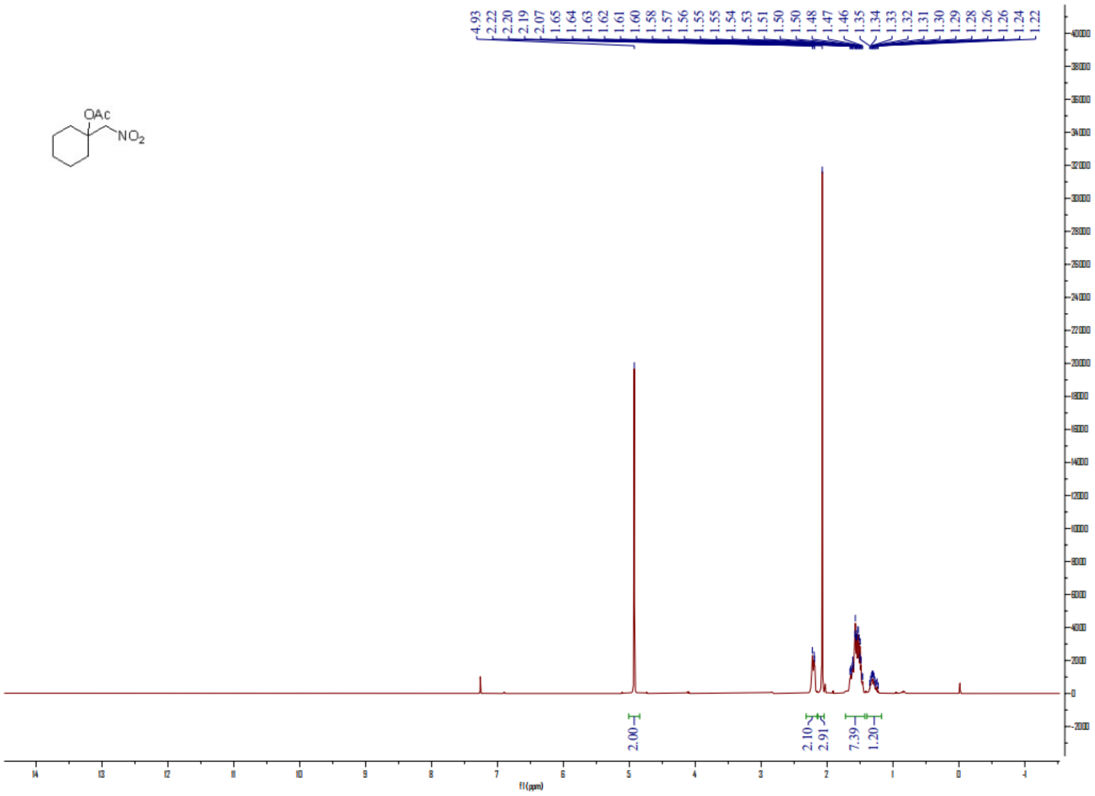
(3j) ^{13}C NMR (100 MHz, CDCl$_3$)



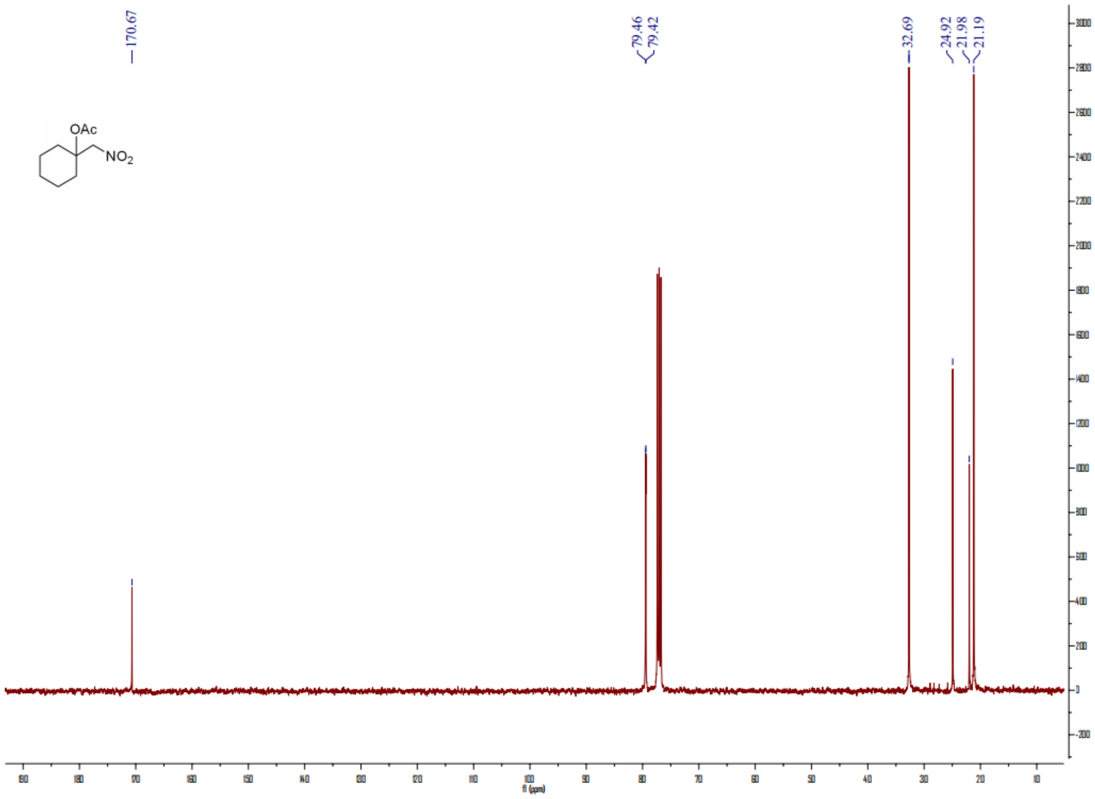
(5bbbb) ^{1}H NMR (400 MHz, CDCl$_3$)



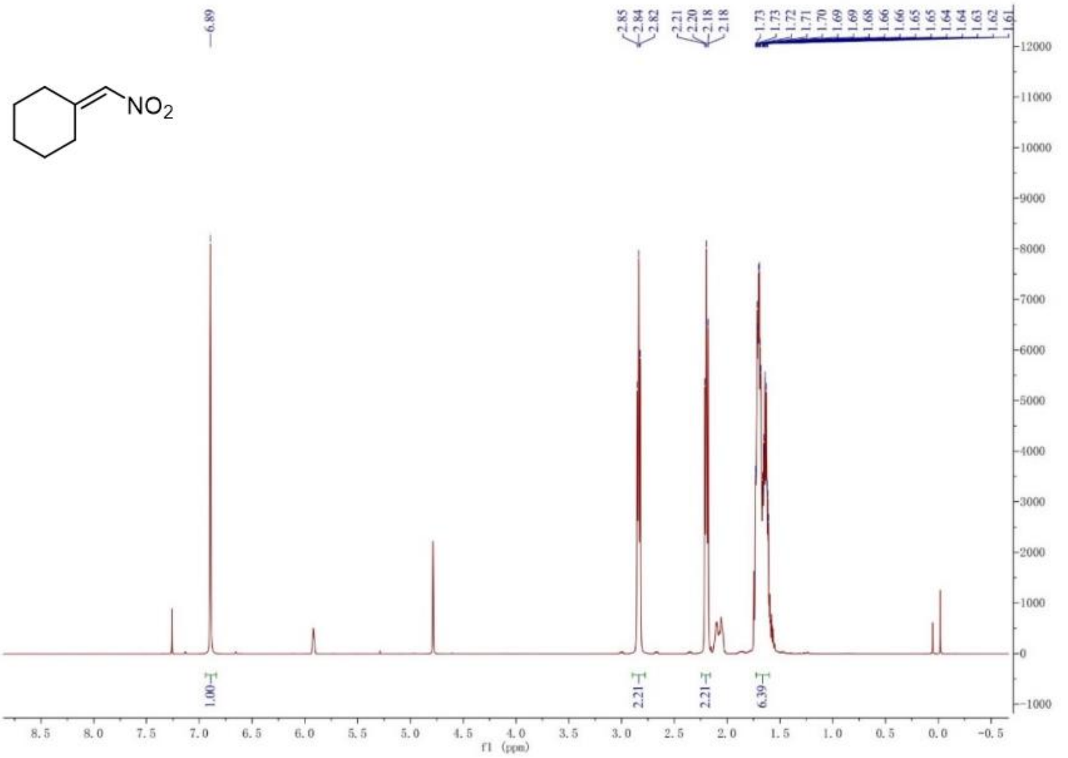
(5bbb) ^{1}H NMR (400 MHz, CDCl$_3$)



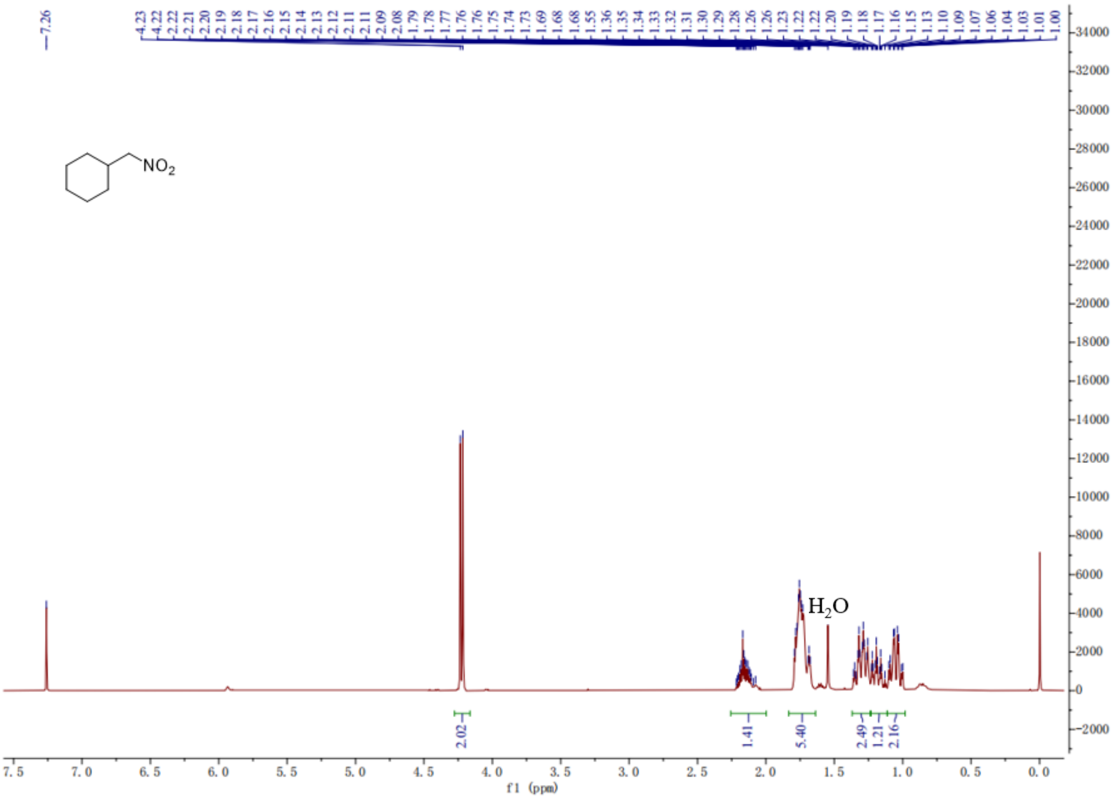
(5bbb) ^{13}C NMR (400 MHz, CDCl$_3$)



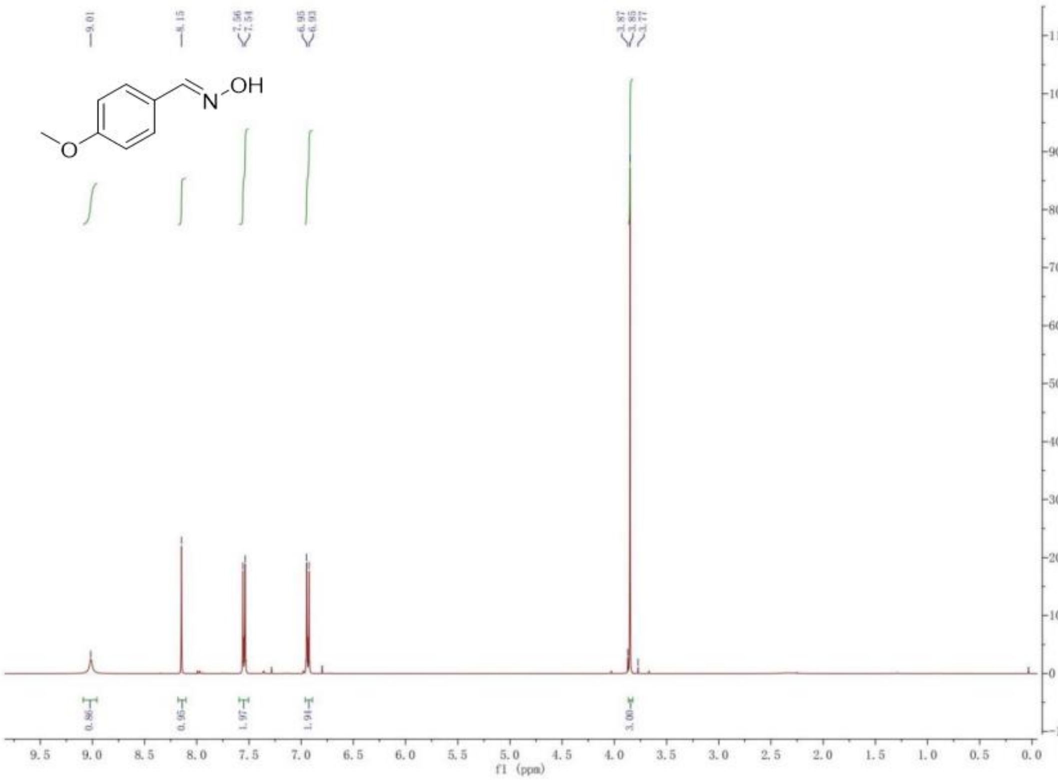
(5bb) ^{1}H NMR (400 MHz, CDCl$_3$)



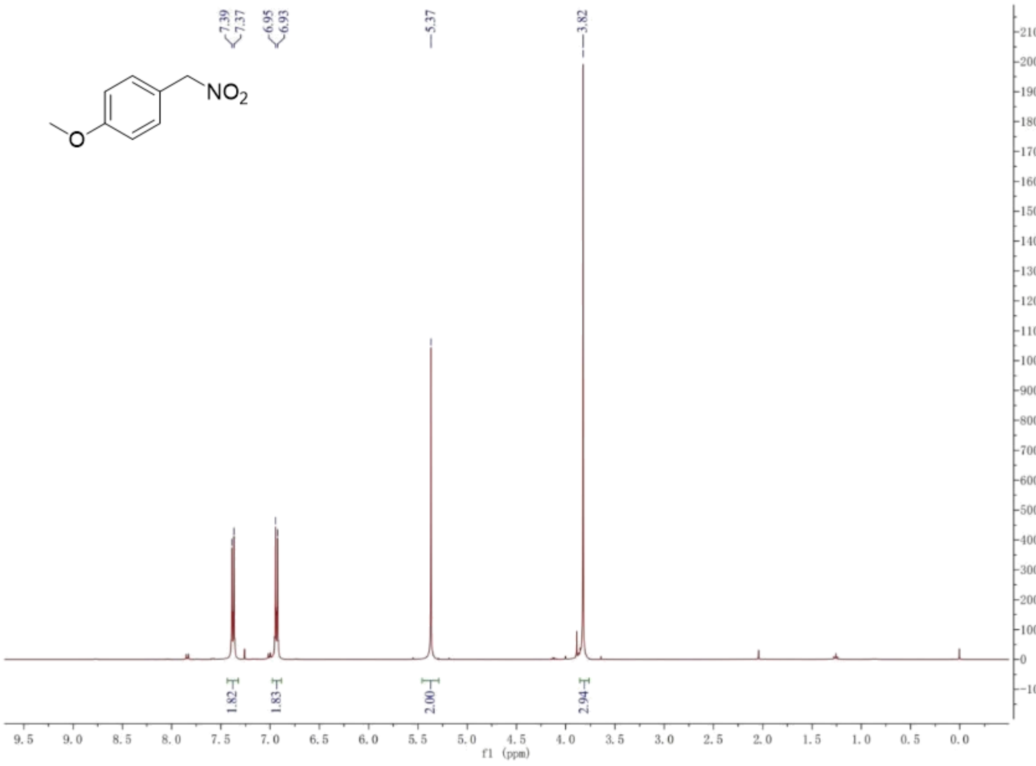
(5b) ^{1}H NMR (400 MHz, CDCl$_3$)



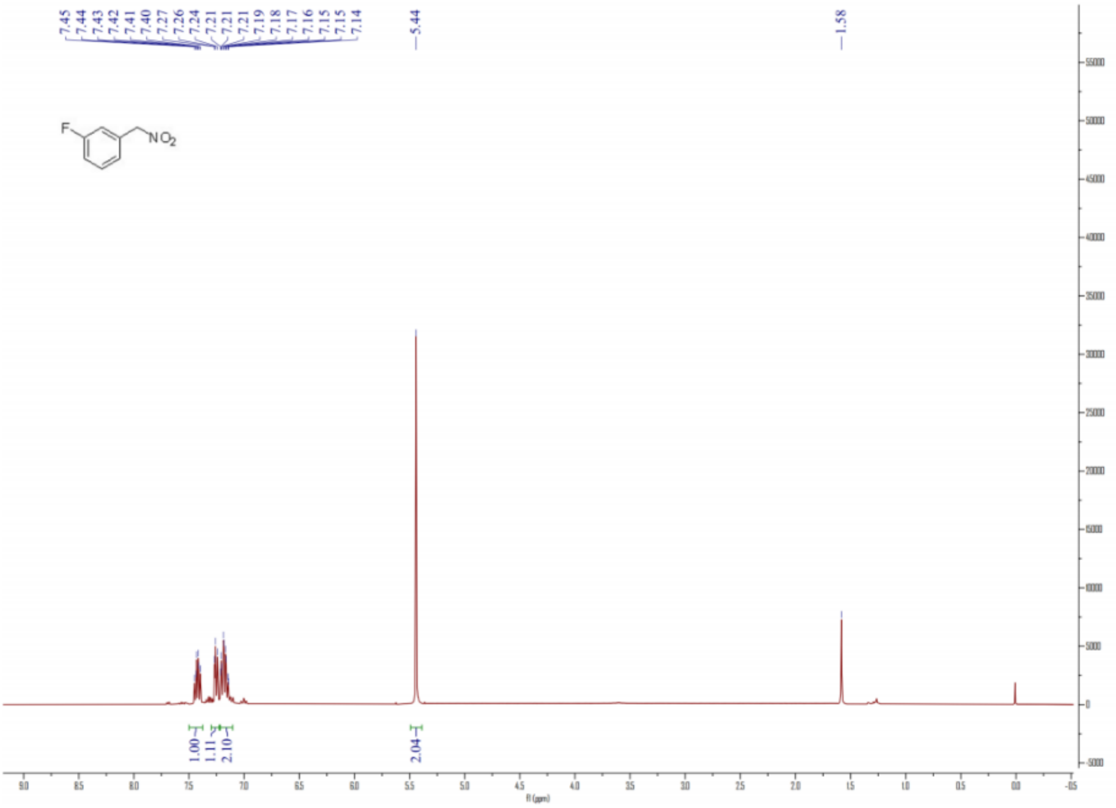
(5ff) ^{1}H NMR (400 MHz, CDCl$_3$)



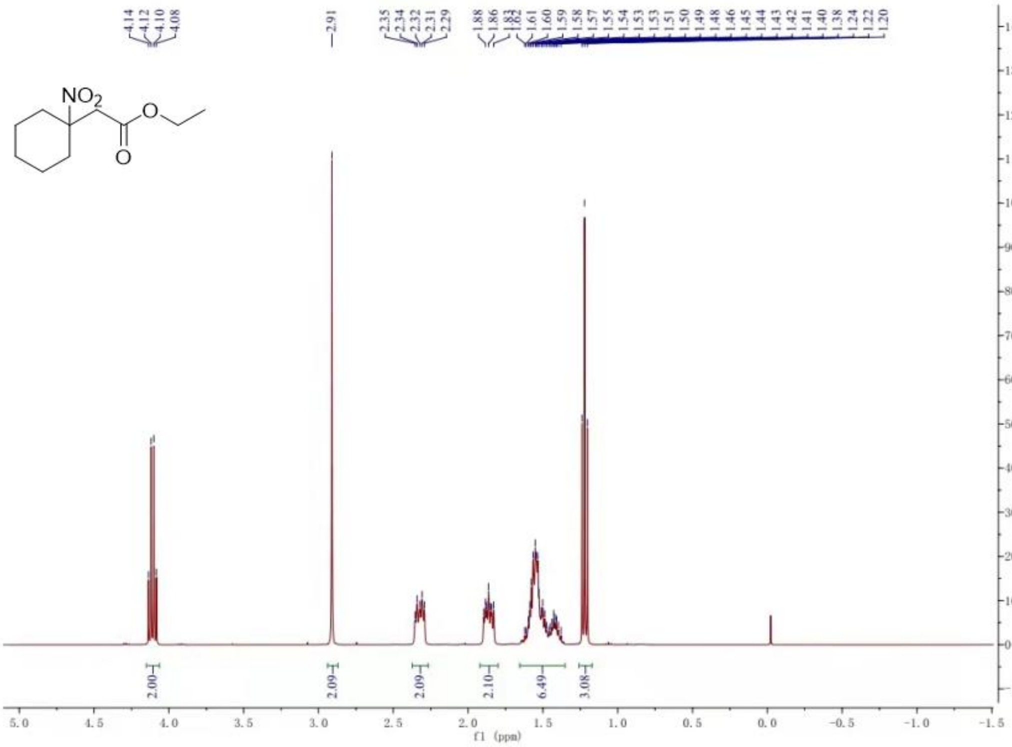
(5f) ^{1}H NMR (400 MHz, CDCl$_3$)



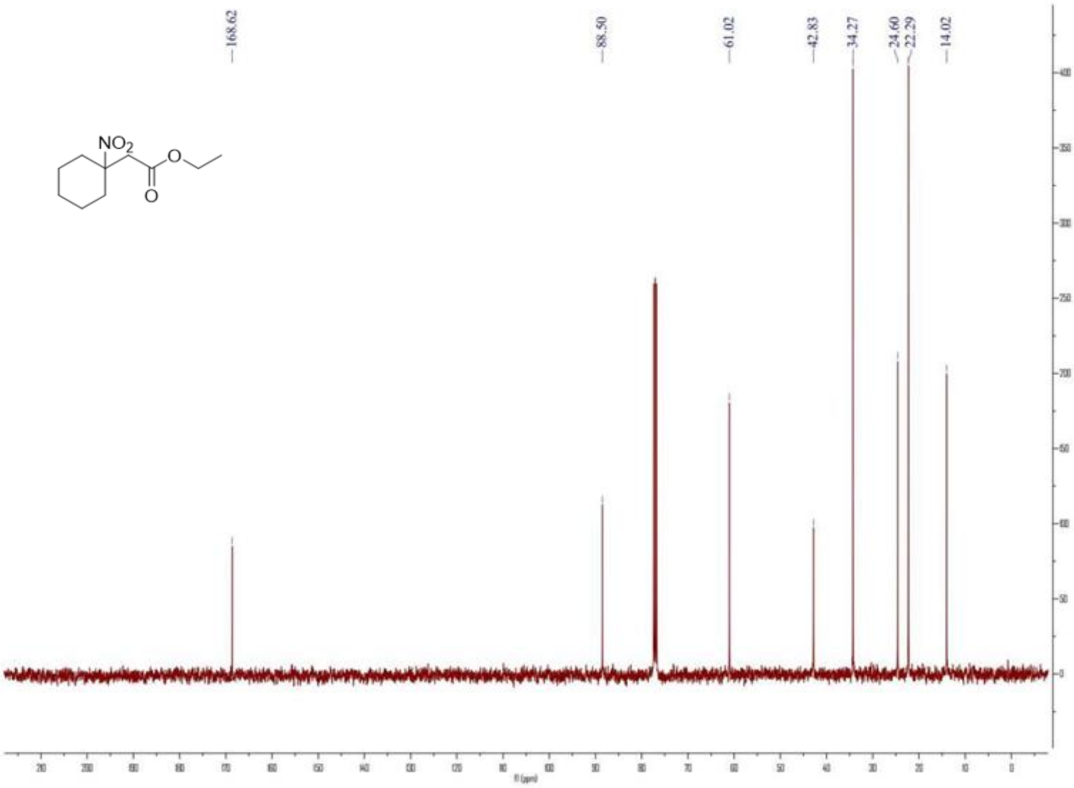
(5i) ^{1}H NMR (400 MHz, $CDCl_3$)



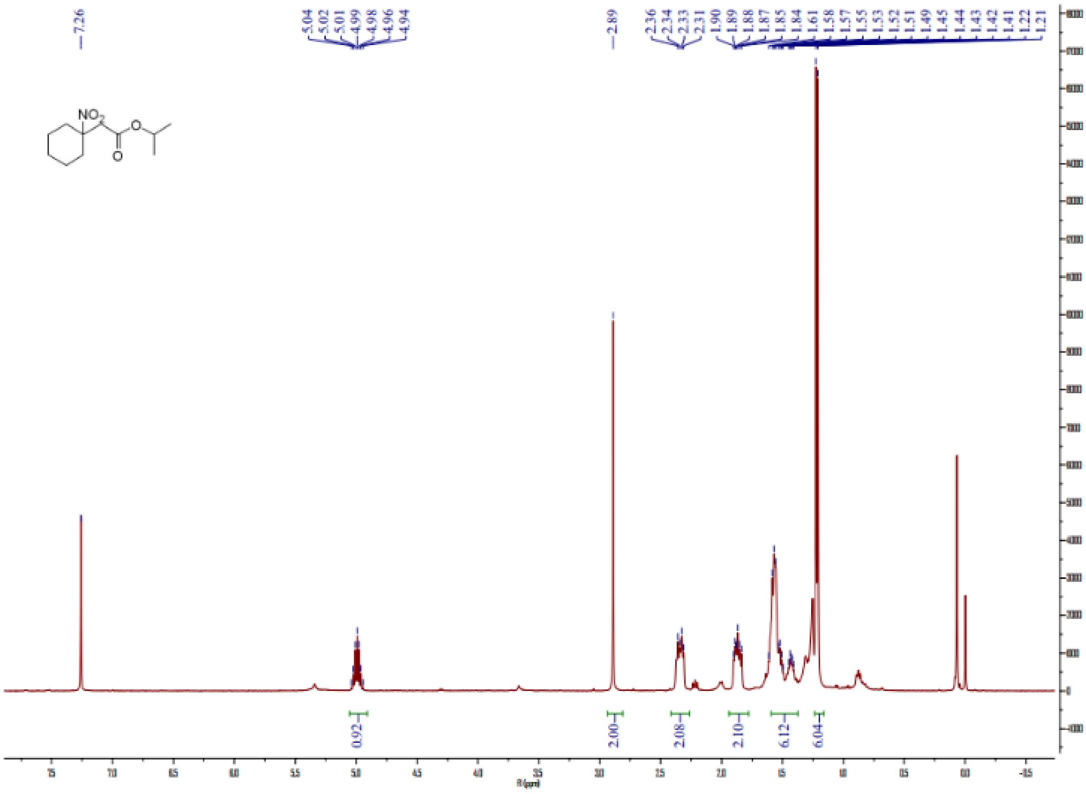
(4) ^{1}H NMR (400 MHz, $CDCl_3$)



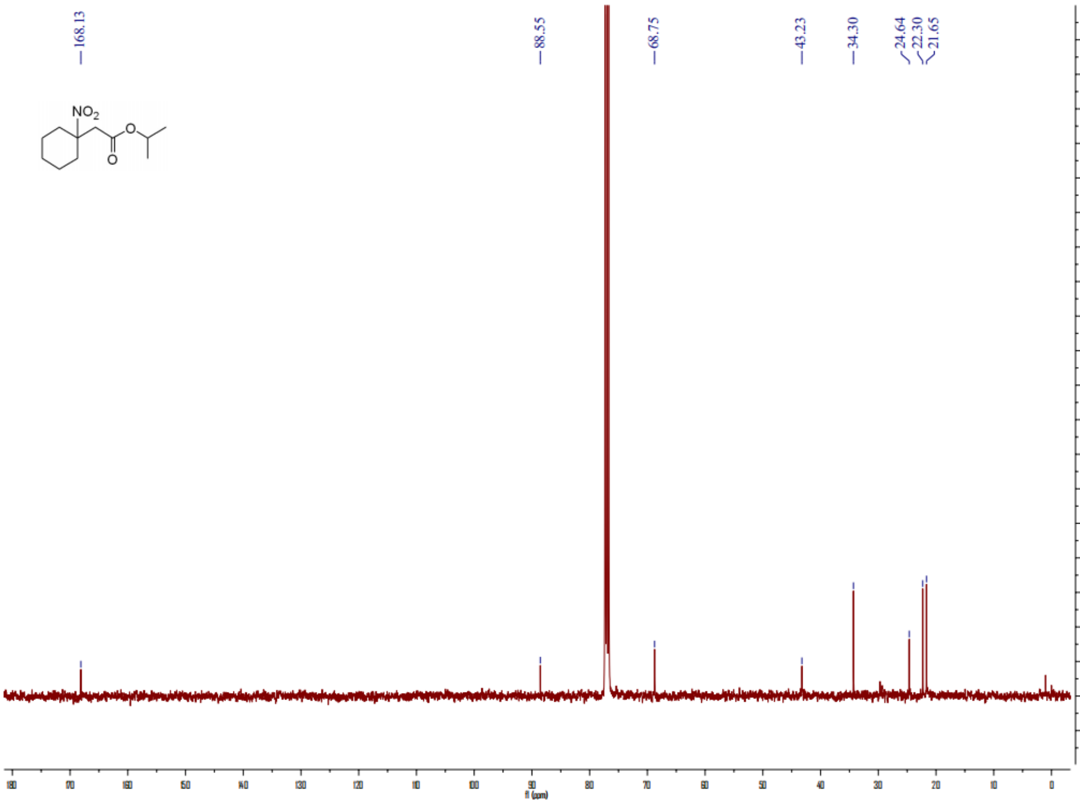
(4) ^{13}C NMR (100 MHz, $CDCl_3$)



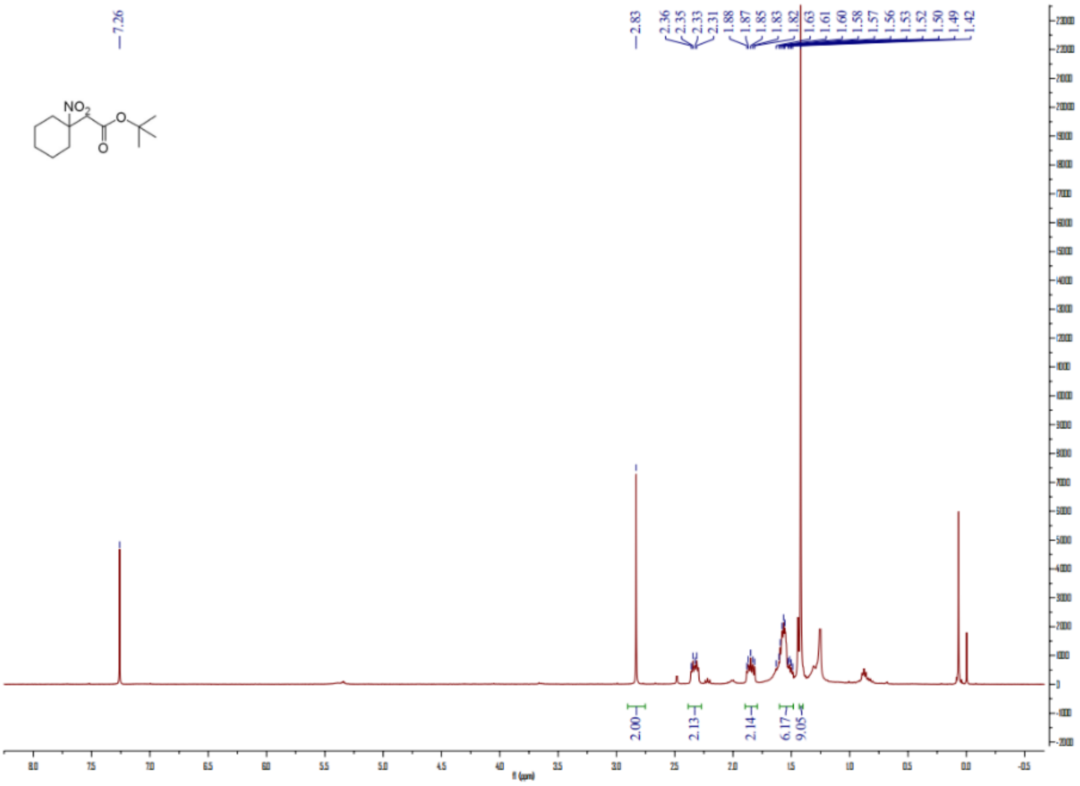
(4b) ^{1}H NMR (400 MHz, CDCl$_3$)



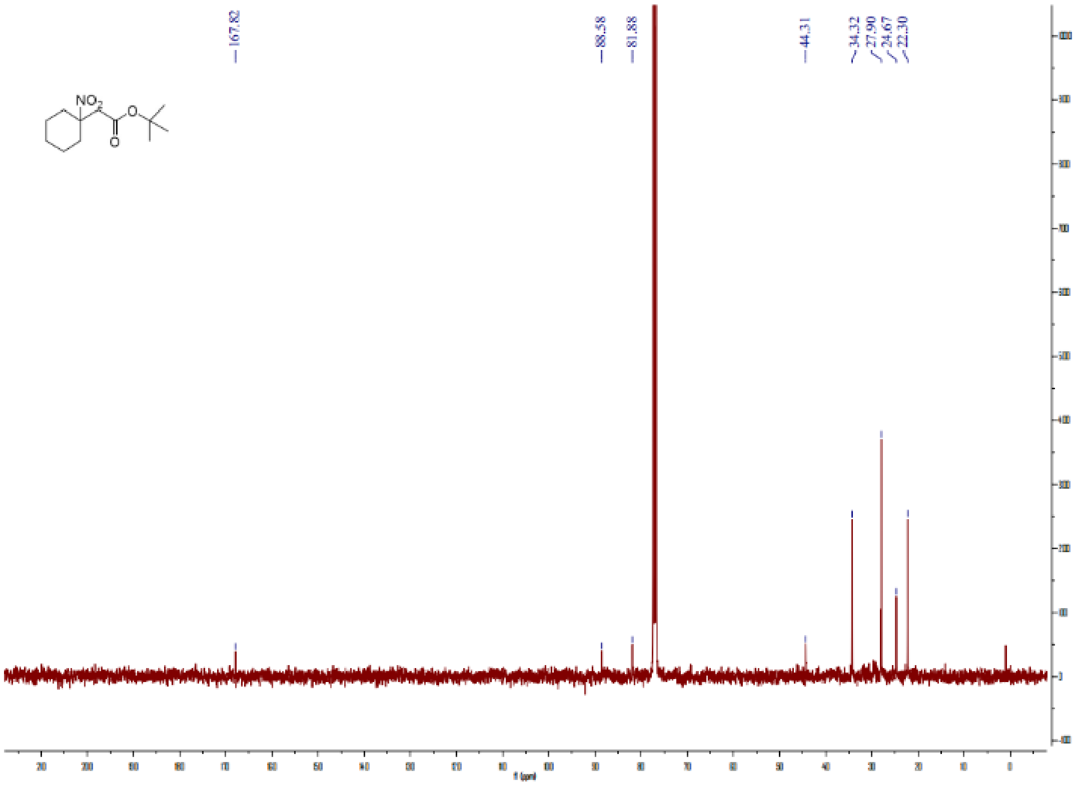
(4b) ^{13}C NMR (100 MHz, CDCl$_3$)



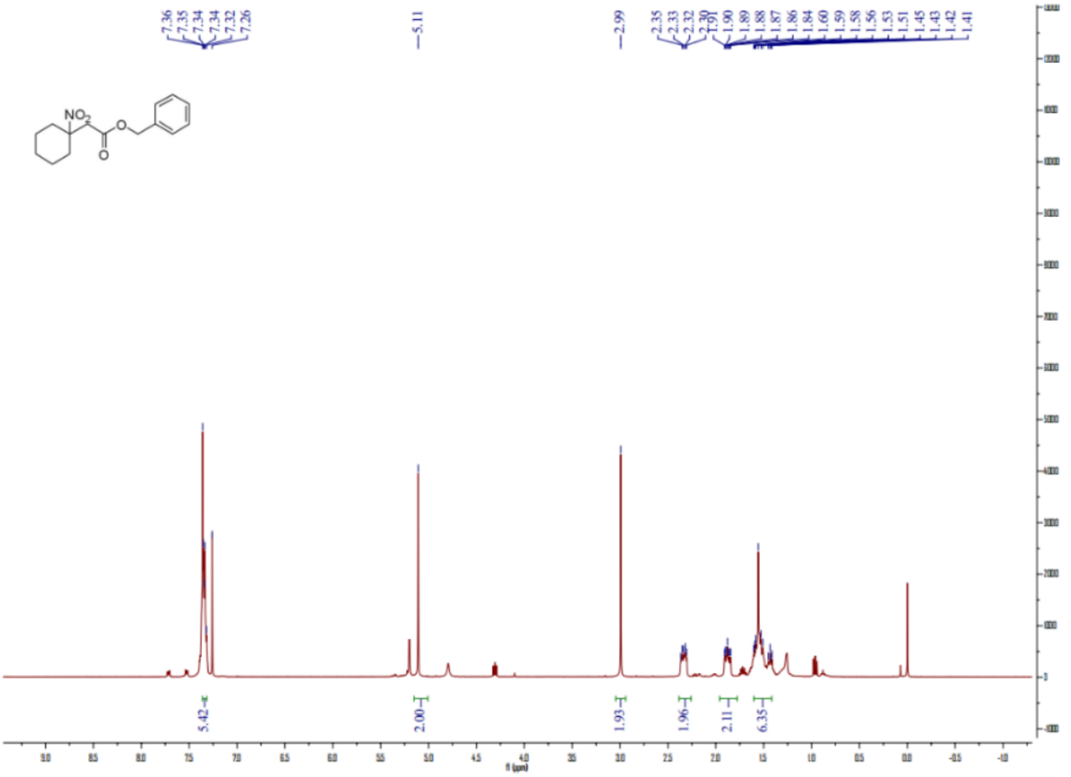
(4c) ^{1}H NMR (400 MHz, CDCl$_3$)



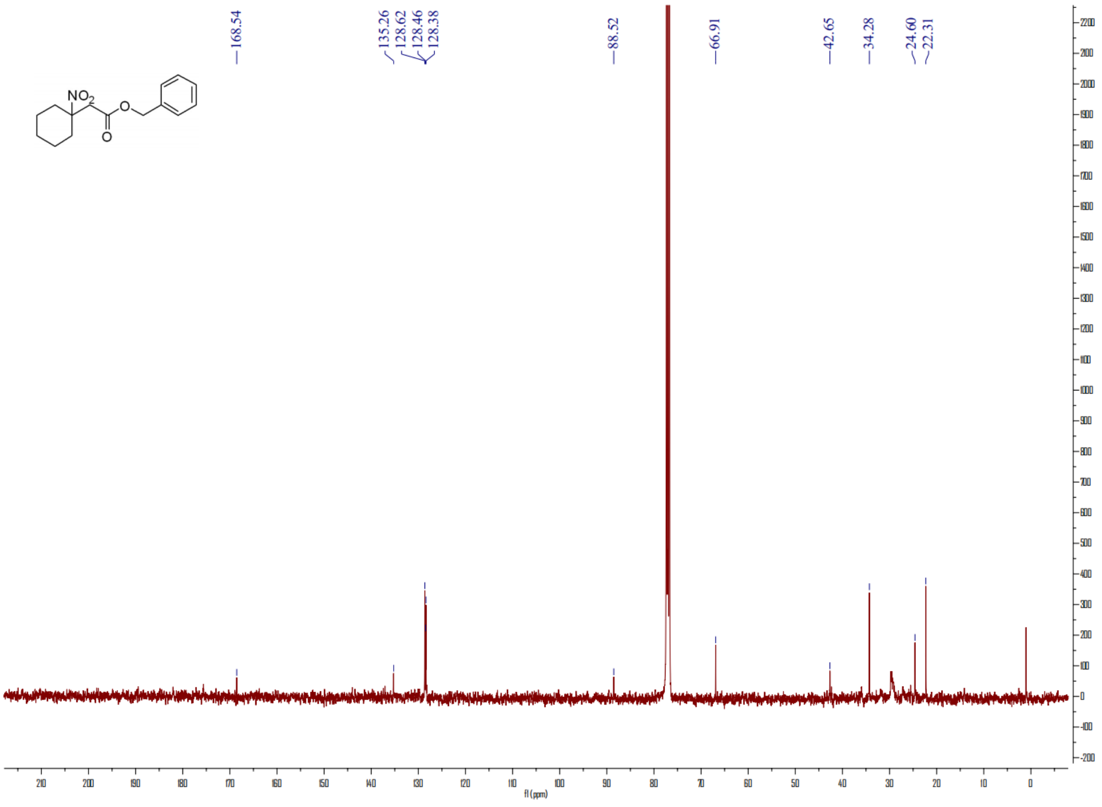
(4c) ^{13}C NMR (400 MHz, CDCl$_3$)



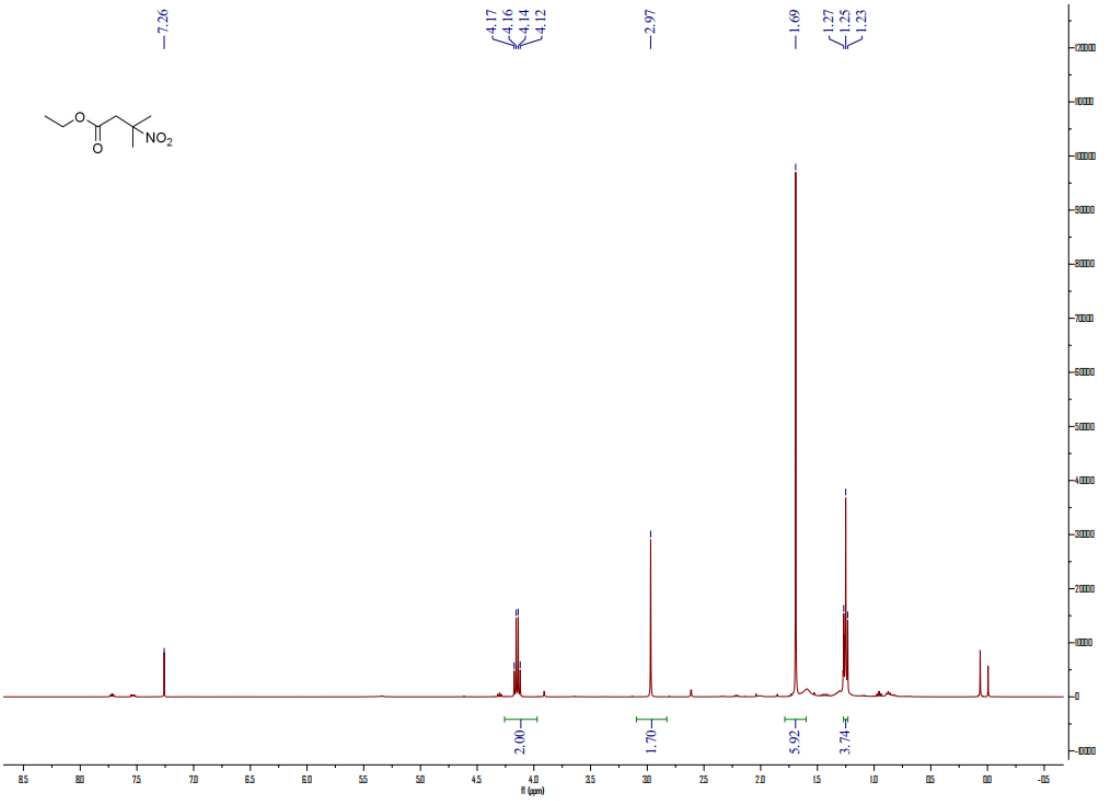
(4d) ^{13}H NMR (400 MHz, CDCl$_3$)



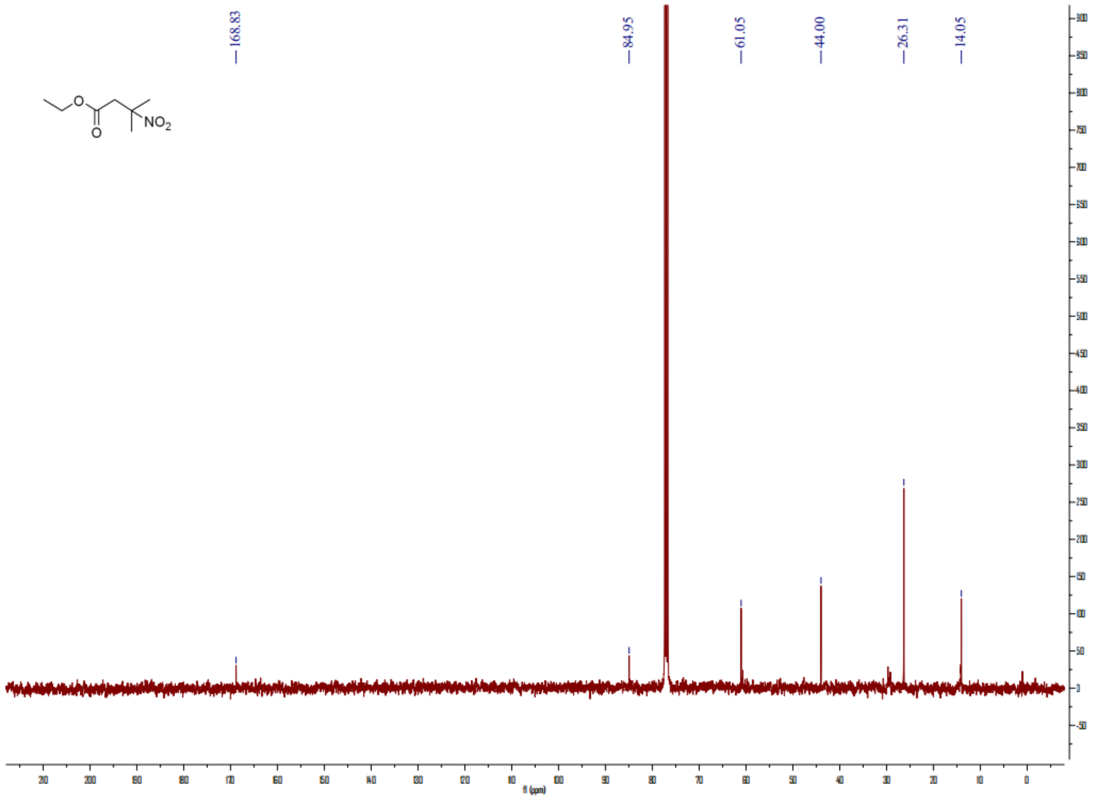
(4d) ^{13}C NMR (400 MHz, CDCl$_3$)



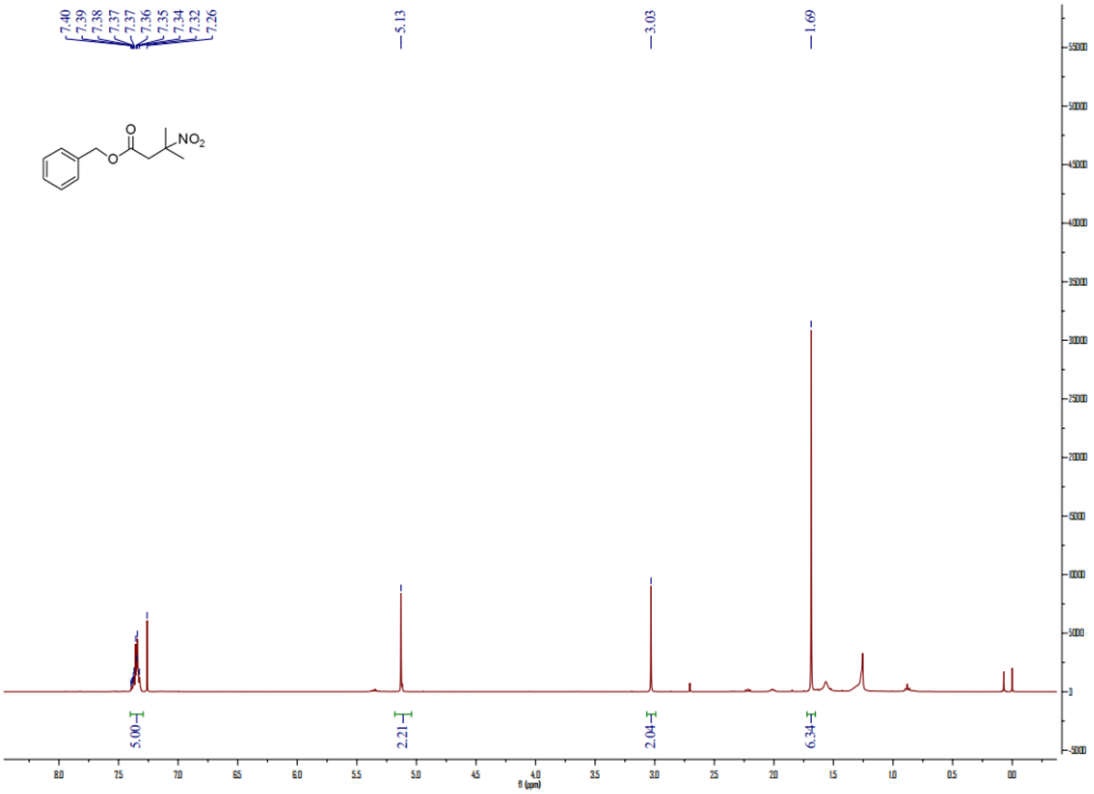
(6a) ^{1}H NMR (400 MHz, CDCl$_3$)



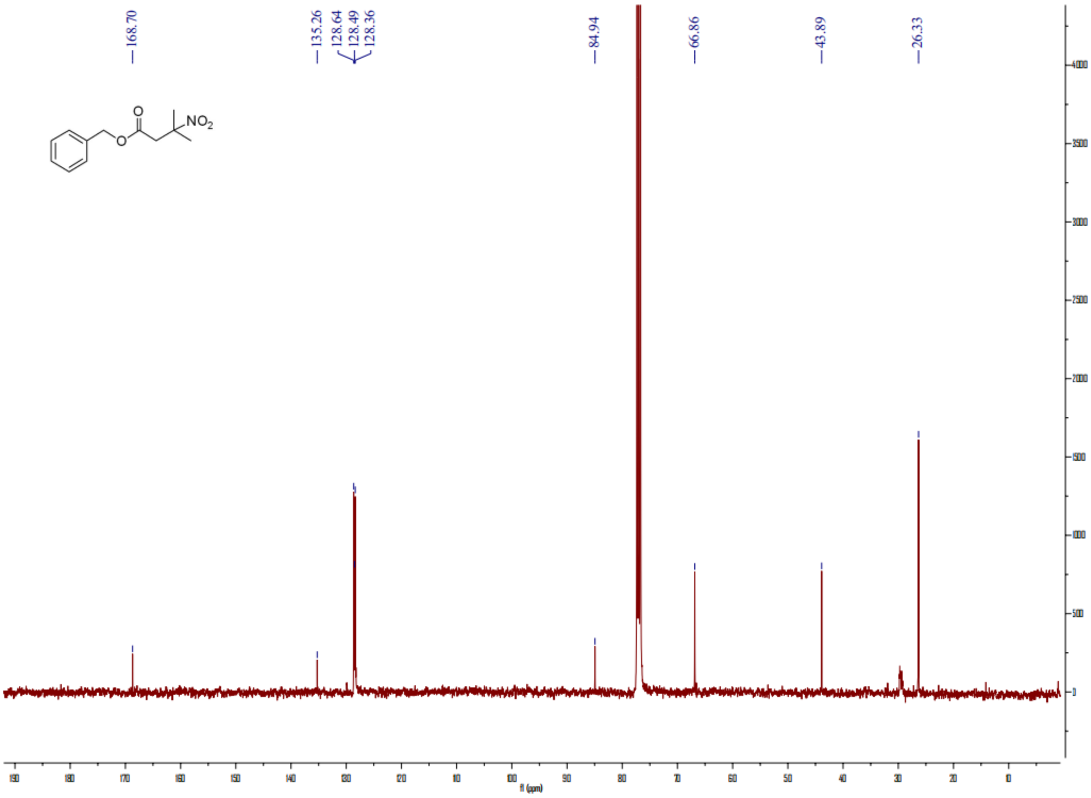
(6a) ^{13}C NMR (400 MHz, CDCl$_3$)



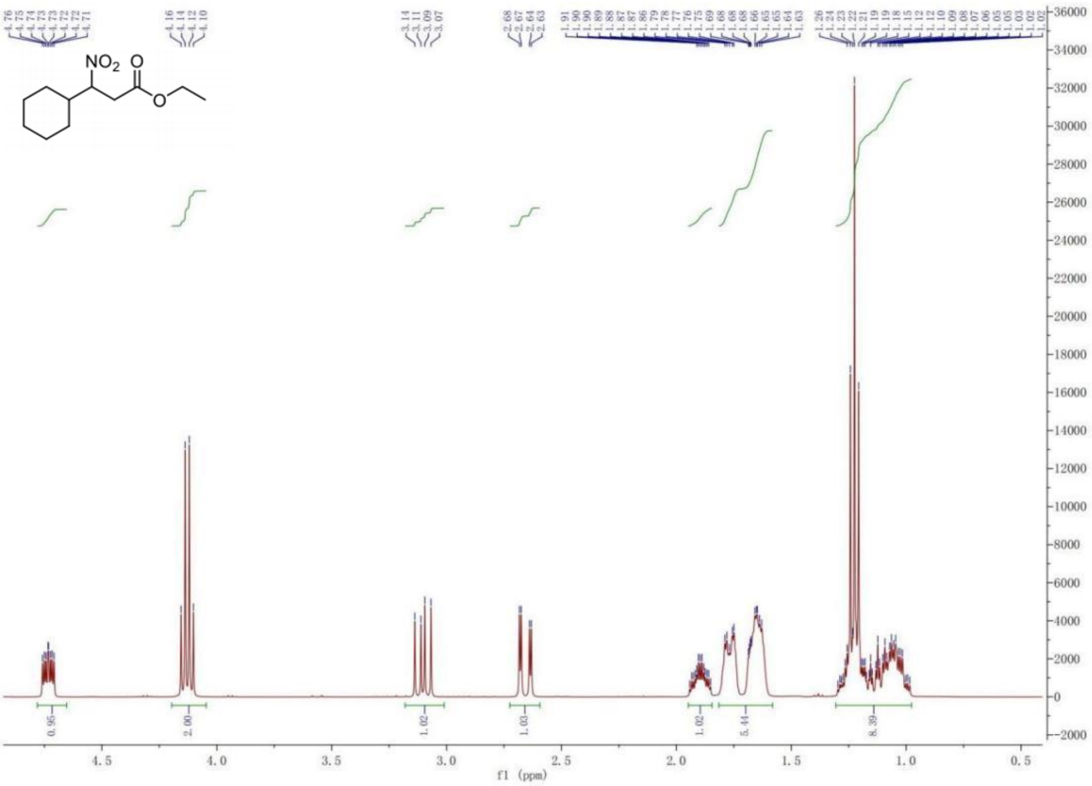
(6ad) ^{1}H NMR (400 MHz, CDCl$_3$)



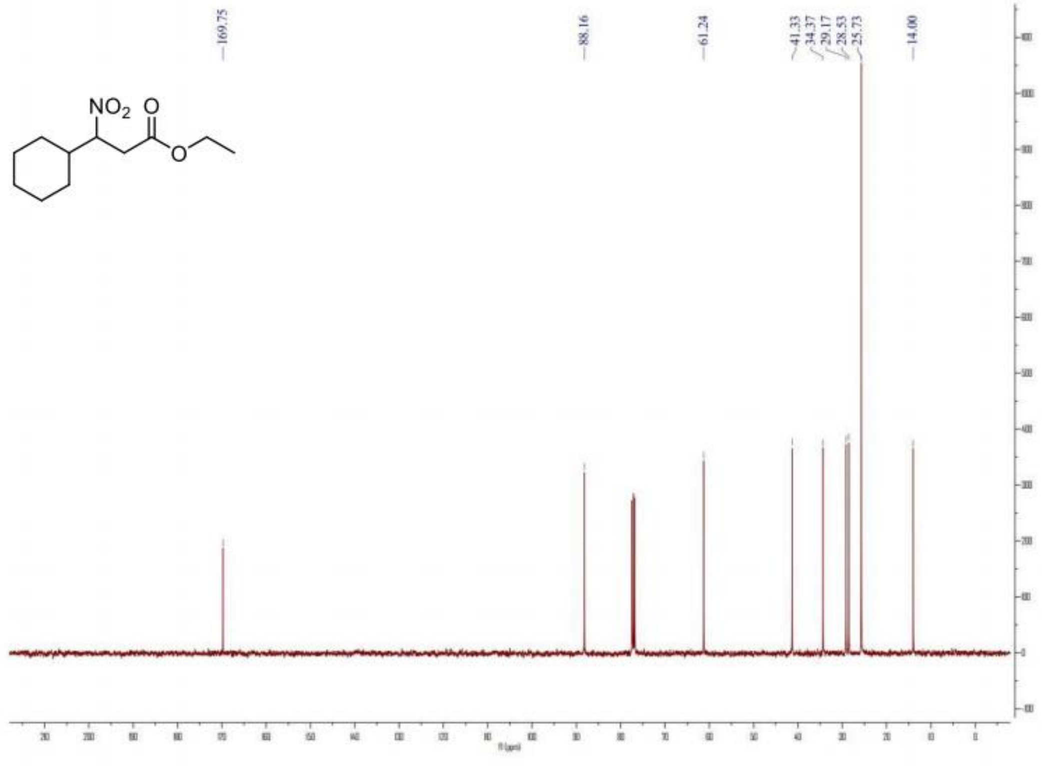
(6ad) ^{13}C NMR (400 MHz, CDCl$_3$)



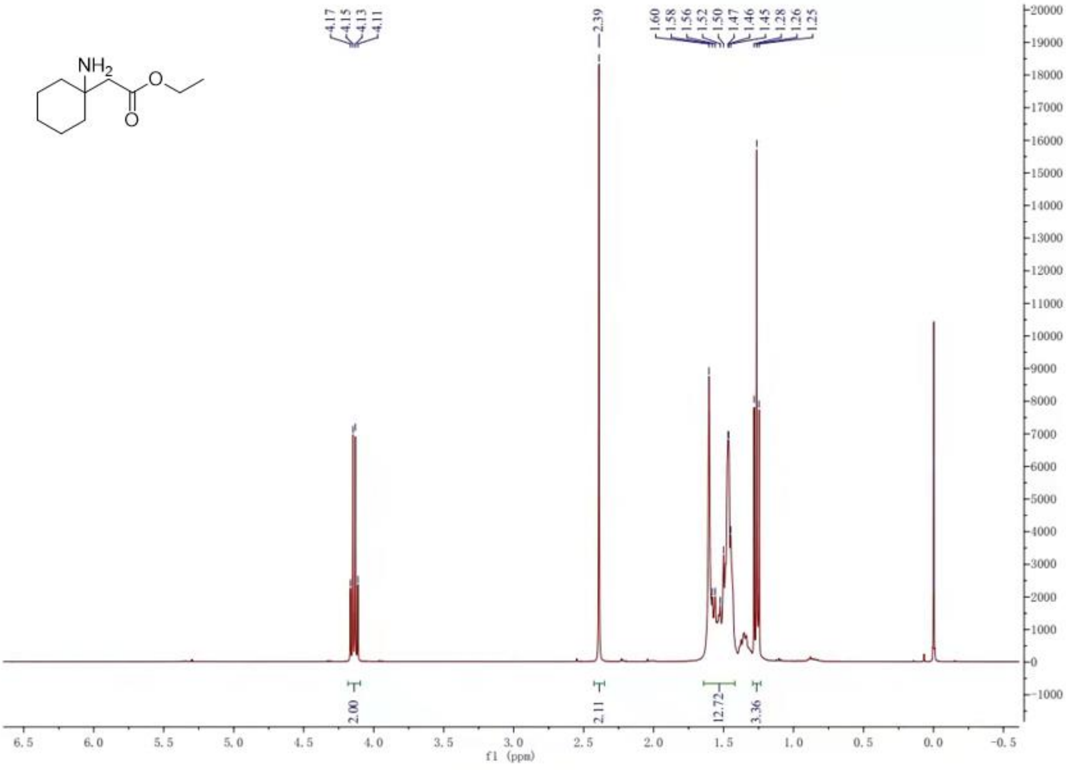
(6b) ^{1}H NMR (400 MHz, CDCl$_3$)



(6b) ^{13}C NMR (400 MHz, CDCl$_3$)

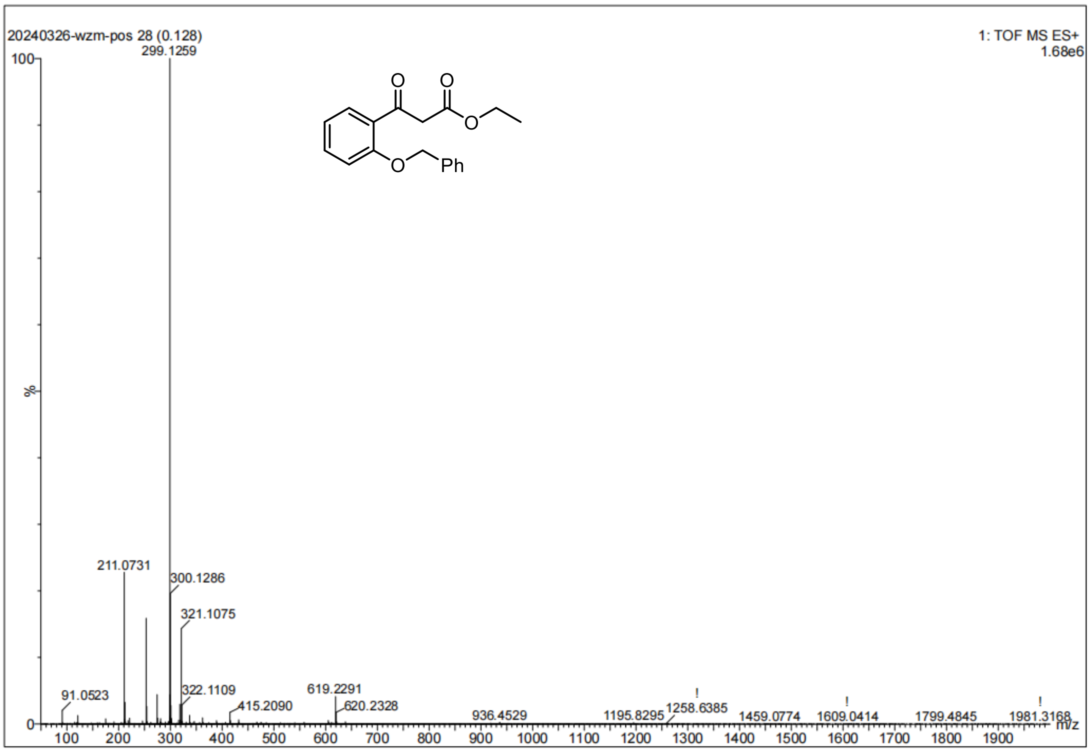


(13) ^{1}H NMR (400 MHz, CDCl$_3$)

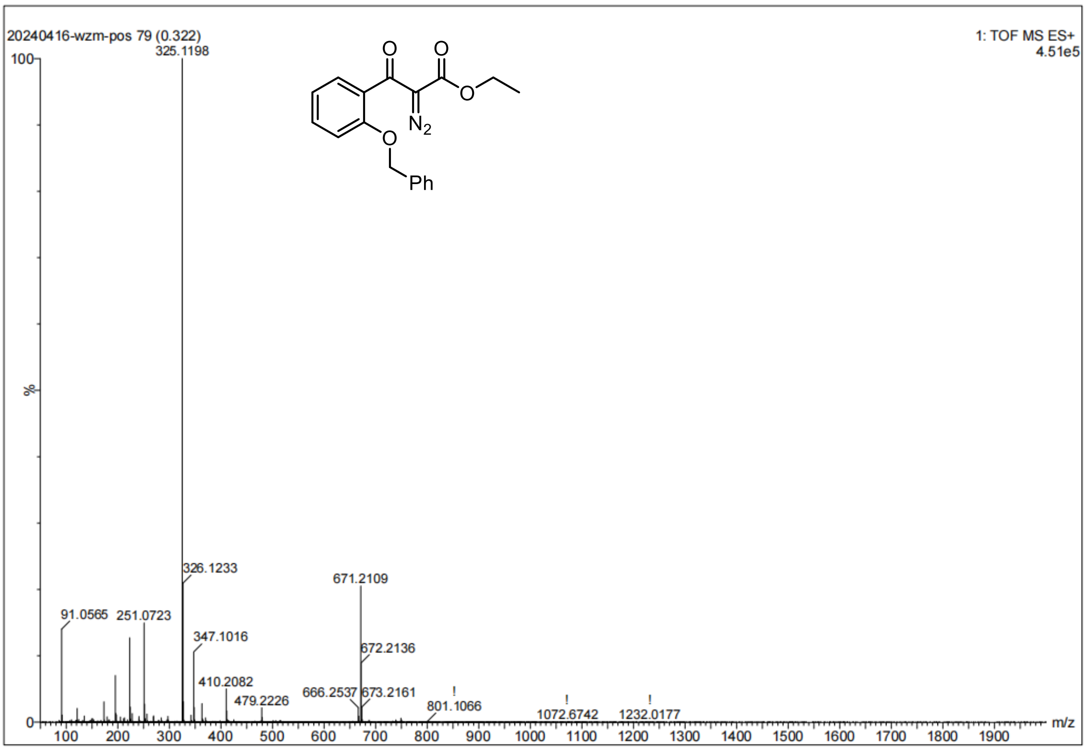


8. HRMS spectra

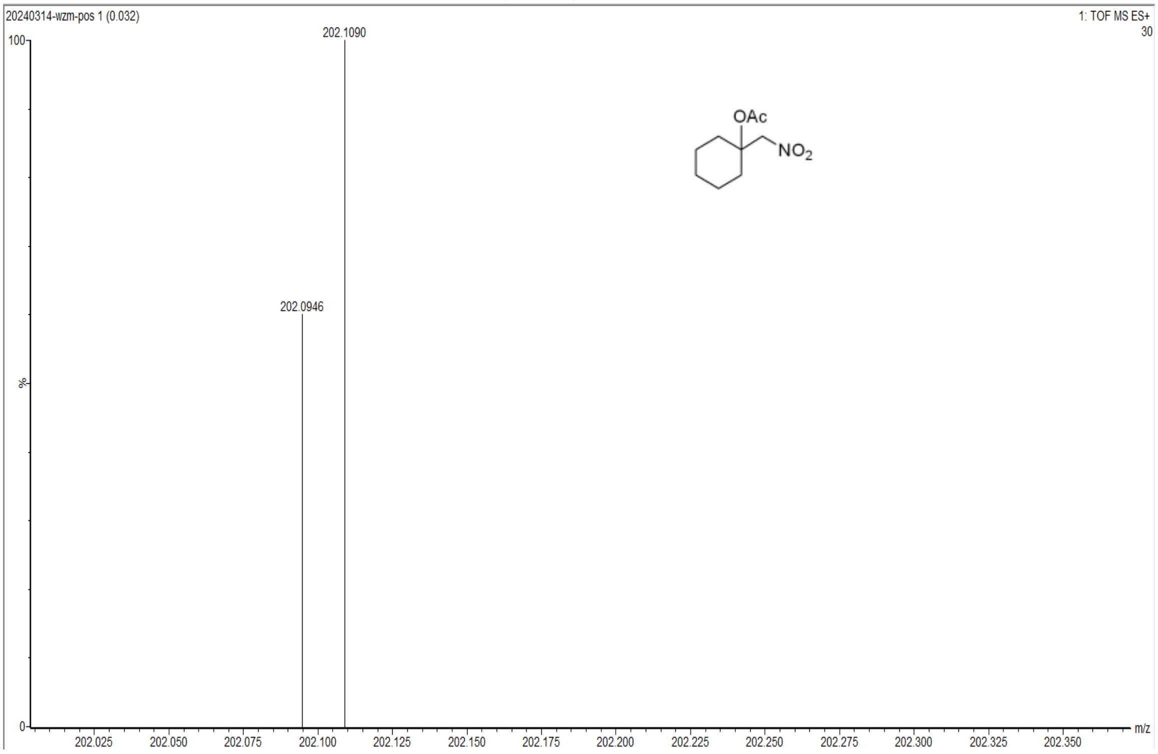
HRMS (ESI+) of **(3jj)**



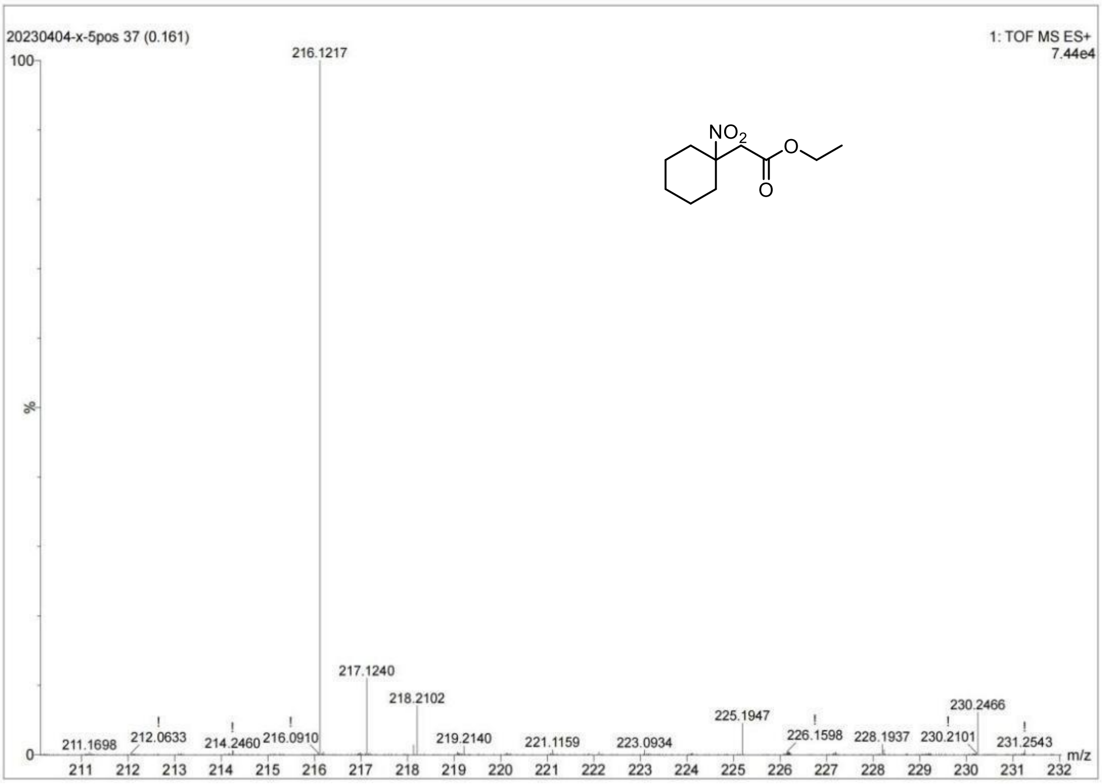
HRMS (ESI+) of **(3j)**



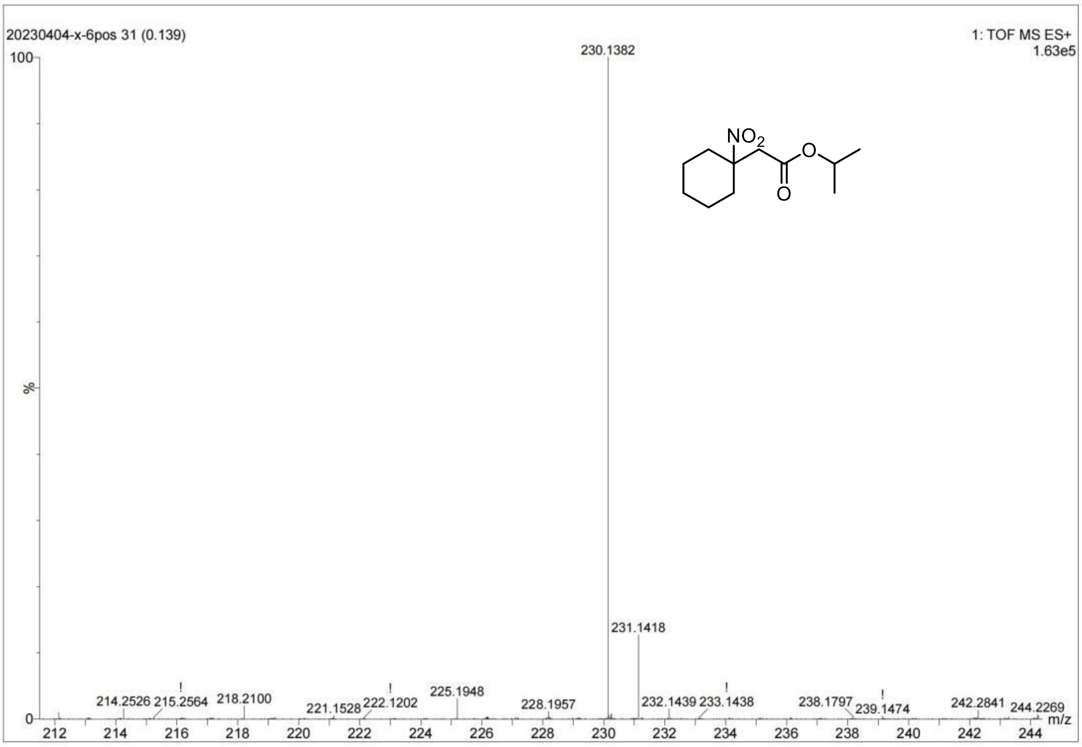
HRMS (ESI+) of **(5bbb)**



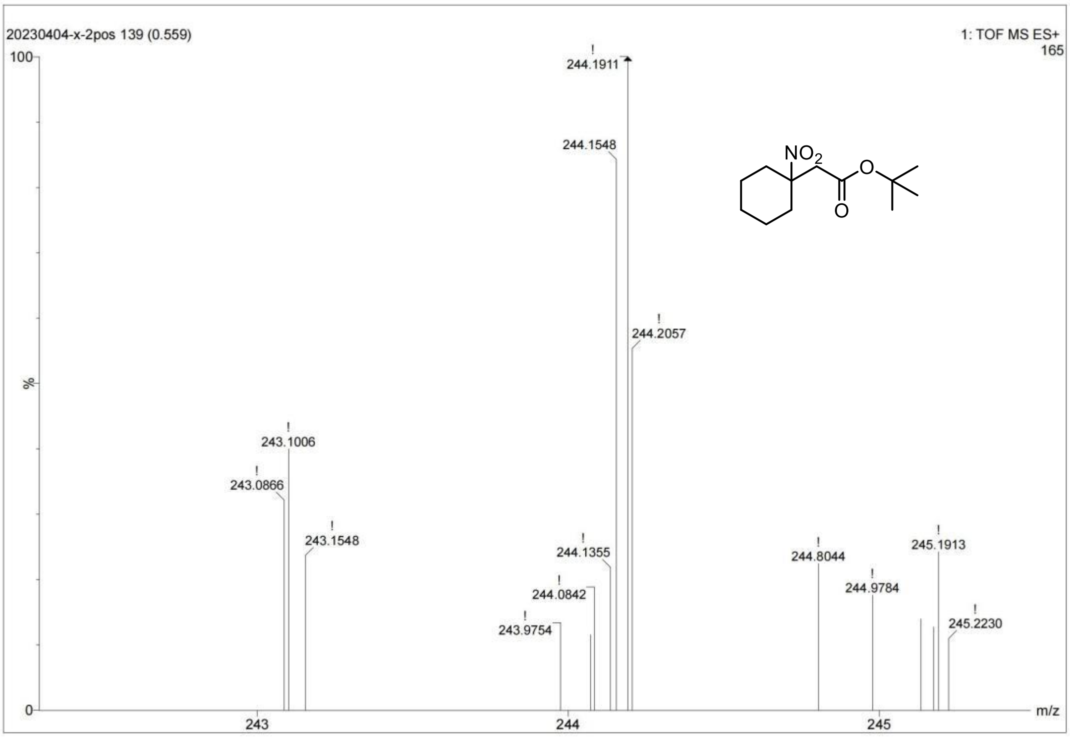
HRMS (ESI+) of **(4)**



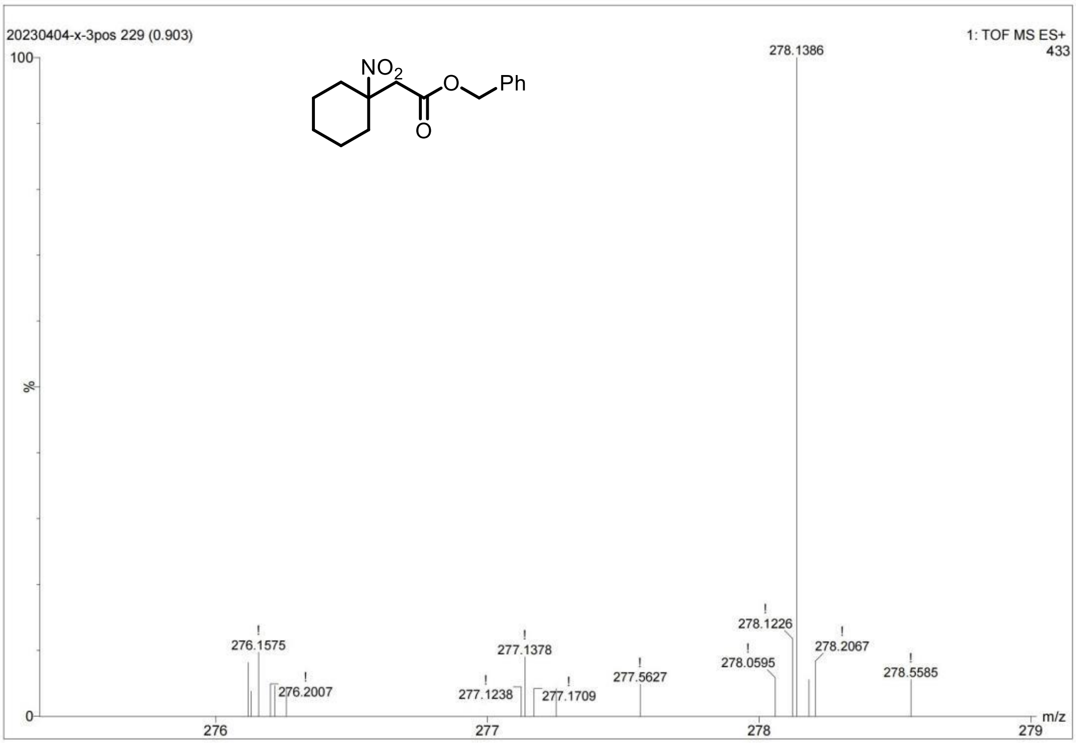
HRMS (ESI+) of **(4b)**



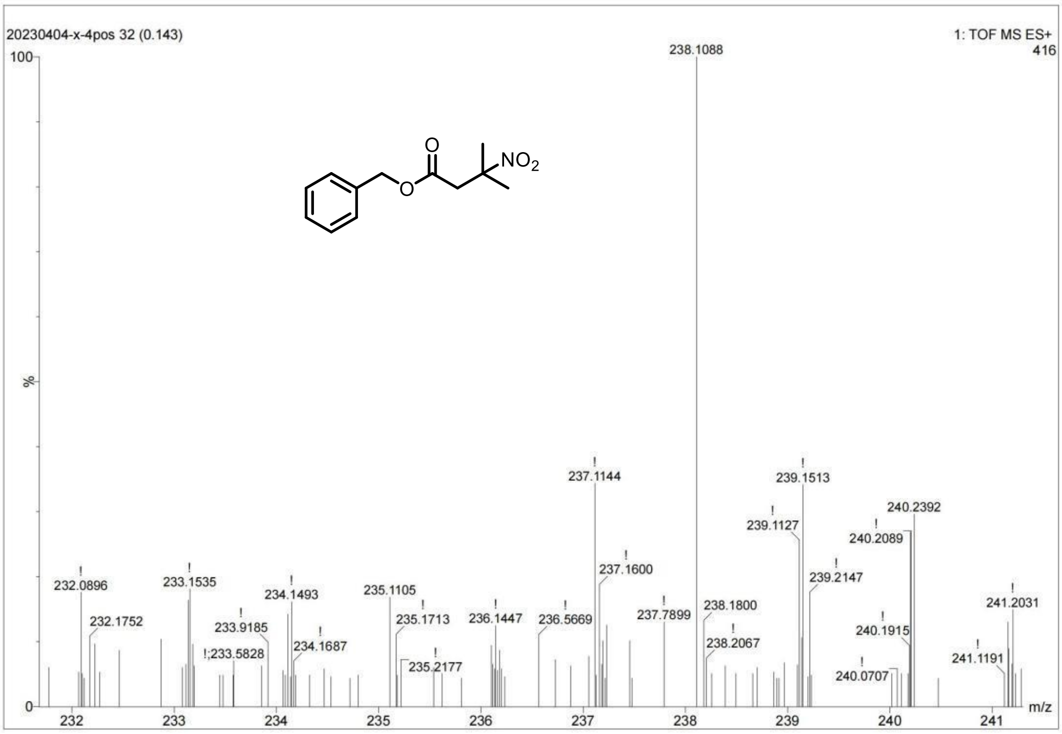
HRMS (ESI+) of **(4c)**



HRMS (ESI+) of **(4d)**



HRMS (ESI+) of **(6ad)**



HRMS (ESI+) of **(6b)**