Electronic Supplementary Information

Organocatalytic Amination of Alkyl Ethers via *n*-Bu_4NI/*t*-BuOOH-mediated Intermolecular Oxidative C(sp^3)–N Bond Formation: Novel Synthesis of Hemiaminal Ethers

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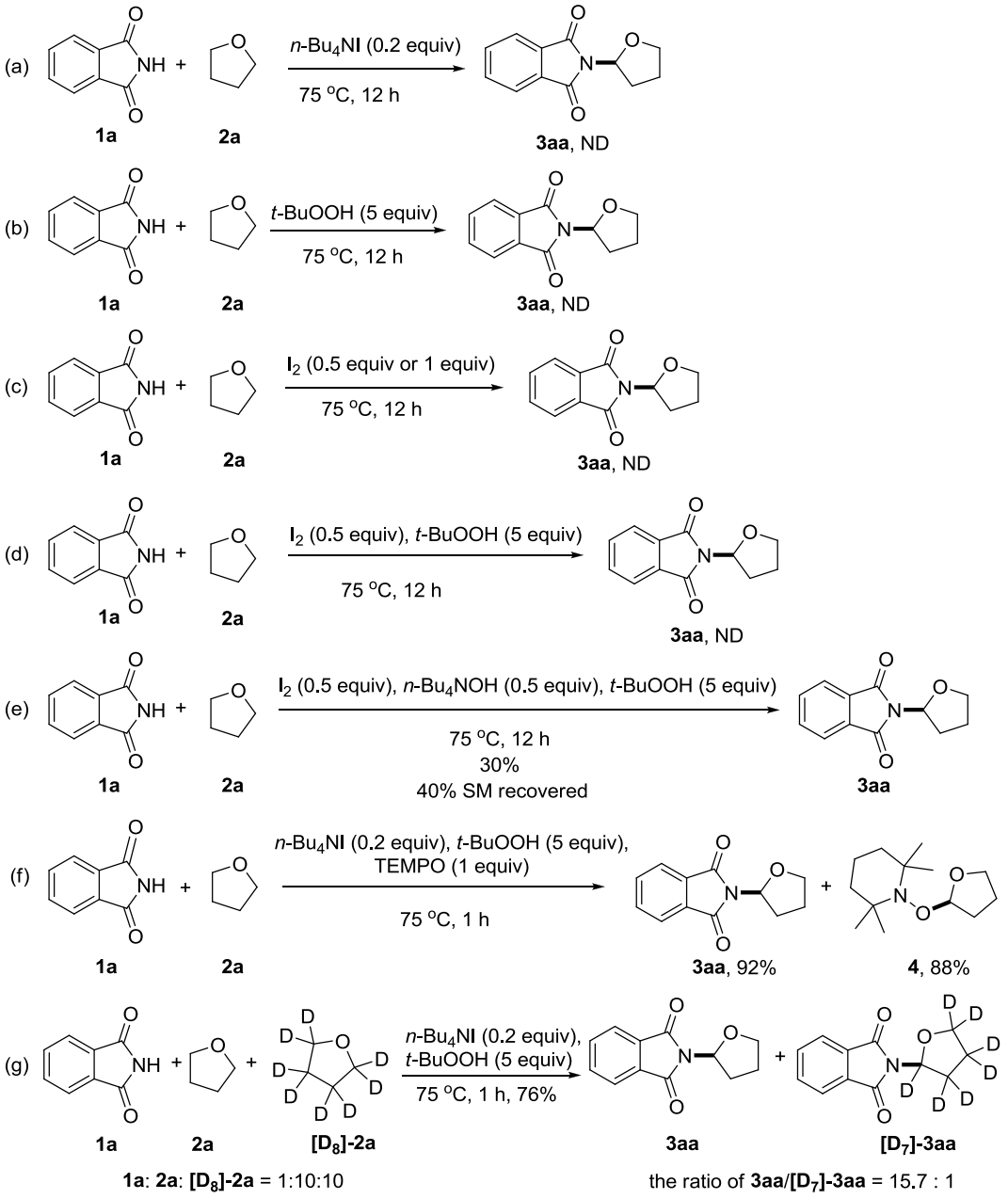
1. General Information

^{1}H NMR spectra were recorded on 600 MHz or 400 MHz spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained at 150 MHz or 100 MHz spectrometers and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$). $CDCl_3$ was used as the NMR solvent. High resolution mass spectrometry (HRMS) was obtained on a Q-TOF micro spectroMeter. Melting points were determined with a MicroMelting point apparatus without corrections. Organic solutions were concentrated by rotary evaporation below 40 ℃ in vacuum. TLC plates were visualized by exposure to ultraviolet light.

Reagents and solvents were purchased as reagent grade and were used without further purification unless otherwise stated. Flash column chromatography was performed over silica gel 200-300 m and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE).

2. Experimental Section

2.1 Mechanistic Studies

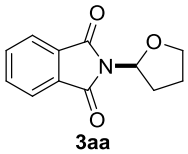


Scheme 1. Investigation of the reaction mechanism. Reaction conditions: **1a** (1 mmol), **2a** (20 mmol), catalyst and oxidant, heated in a sealed tube at 75 °C.

2.1.1 General procedure for trapping experiment:

To a mixture of phthalimide **1a** (0.5 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 0.5 mmol) and *n*-Bu_4NI (0.2 mmol), tetrahydrofuran **2a** (20 mmol) was added. Then anhydrous *t*-BuOOH (5 mmol) was dropped into the mixture. The reaction mixture was heated in a sealed tube at 75 ^oC and the process of the reaction was monitored by TLC. Upon completion, the reaction mixture was transferred to a round-bottom flask then the solvent was removed under vacuum without any workup and the residue was purified by silica gel chromatography (5% EA/PE) to afford the desired product **3aa** and **4**.

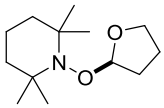
2-(Tetrahydrofuran-2-yl)isoindoline-1,3-dione (3aa)



3aa

3aa, 92% yield (based on **1a**), white solid, mp. 73-75 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.05 (dd, *J* = 8.0, 4.9 Hz, 1H), 4.21 (dd, *J* = 14.8, 7.7 Hz, 1H), 3.96 (td, *J* = 7.8, 4.7 Hz, 1H), 2.59-2.52 (m, 1H), 2.45-2.35 (m, 1H), 2.32-2.26 (m, 1H), 2.04-1.95 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 134.1, 131.9, 123.3, 80.8, 69.7, 29.1, 26.0. HRMS (ESI) m/z calcd for $C_{12}H_{11}NNaO_3$ [M + Na^+] 240.0631, found 240.0640.

2,2,6,6-Tetramethyl-1-(tetrahydrofuran-2-yloxy)piperidine (4)[1]



4

4, 88% yield (based on TEMPO), yellow oil. ^1H NMR (600 MHz, $CDCl_3$) δ 5.42 – 5.30 (m, 1H), 3.87 (dd, *J* = 14.8, 7.1 Hz, 1H), 3.82 (td, *J* = 7.8, 5.1 Hz, 1H), 2.05 – 1.86 (m, 3H), 1.84 – 1.73 (m, 1H), 1.60 – 1.39 (m, 5H), 1.32 (d, *J* = 12.2 Hz, 1H), 1.22 (s, 3H), 1.11 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H).

2.1.2 Procedure of competition experiments between THF and [D_8]-THF:

To a mixture of phthalimide **1a** (0.25 mmol) and *n*-Bu_4NI (0.05 mmol, 20 mol%), tetrahydrofuran **2a** (2.5 mmol, 10 equiv.) and d8-tetrahydrofuran **[D_8]-2a** (2.5 mmol,

10 equiv.) was added followed by the dropwise addition of anhydrous *t*-BuOOH (1.25 mmol, 5 equiv.). Then the reaction mixture was stirred at 75 ^{o}C under air atmosphere in a sealed tube and the process of the reaction was monitored by TLC. Upon completion, the reaction mixture was transferred to a round-bottom flask then the solvent was removed under vacuum without any workup and the residue was purified by silica gel chromatography, using a mixture of PE/EA to afford the desired product **3aa and [D_7]-3aa** in 76% yield. The ratio (**3aa/[D_7]-3aa=**15.7 : 1) was calculated from ^{1}H NMR spectra.

2.2 A Full Description of the Reaction Optimization Conditions.[a]

entry	Catalyst (mol%)	Oxidant (equiv.)	Time (h)	T (^{o}C)	yield (%)[b]
1	None	PhIO	12	Rt	NR
2	None	PIFA	12	RT	Decomposed
3	none	PIDA (2.0)	12	rt	NR[c]
4	None	PIDA (2.0)	12	75	5
5	I_2 (20)	PIDA (2.0)	5	75	20
6	PhI (20)	*m*-CPBA (2.0)	10	75	NR
7	PhI (20)	H_2O_2 (2.0)	10	75	NR
8	*n*-Bu_4NI (10)	H_2O_2 (5.0)	5	75	NR
9	*n*-Bu_4NI (10)	*t*-BuOOH (3.0)	5	75	67
10	*n*-Bu_4NI (20)	*t*-BuOOH (3.0)	2	75	85
11	***n*-Bu_4NI (20)**	***t*-BuOOH (5.0)**	**1**	**75**	**92**
12	*n*-Bu_4NBr (20)	*t*-BuOOH (5.0)	12	75	NR
13	KI (20)	*t*-BuOOH (5.0)	12	75	NR
14	I_2 (20)	*t*-BuOOH (5.0)	12	75	NR
15	CuBr (20)	*t*-BuOOH (5.0)	12	75	trace
16	$FeCl_3{\cdot}6H_2O$ (20)	*t*-BuOOH (5.0)	12	75	5%
17	none	*t*-BuOOH (5.0)	12	75	NR
18	*n*-Bu_4NI (20)	DTBP (5.0)	12	75	NR
19	*n*-Bu_4NI (20)	O_2	12	75	NR
20	*n*-Bu_4NI (20)	*t*-BuOOH (5.0)[c]	1	75	70
21[d]	*n*-Bu_4NI (20)	*t*-BuOOH (5.0)	1	75	76
22[e]	*n*-Bu_4NI (20)	*t*-BuOOH (5.0)	1	75	60

[a] Reaction conditions: **1a** (1 mmol), **2a** (20 mmol), catalyst and oxidant were heated in a sealed tube at 75 ^{o}C unless otherwise stated. *t*-BuOOH: anhydrous *tert*-butyl hydroperoxide, H_2O_2 30% in water, DTBP: *di-tert*-butyl peroxide 98%. [b] Isolated yields. [c] *t*-BuOOH, 70% in H_2O. [d] EtOAc (0.3 M) was used as the solvent. [e] DCE was used as the solvent.

2.3 General Procedure

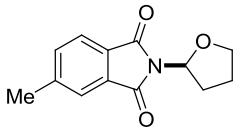
All the known amides **1b**,[2] **1c**,[3] **1d**[3], **1g**[4] and **3i**[5] were prepared following literature procedure and the analytical data were in agreement with those that have been previously reported.

2.3.1 General procedure for the amination of alkyl ethers

To the mixture of ether **2** (10 mmol) and *n*-Bu_4NI (0.1 mmol, 36.9 mg) into a sealed tube, amine **1** (0.5 mmol) and *t*-BuOOH (2.5 mmol) were added. The reaction mixture was stirred at 75 ^oC under air atmosphere in a sealed tube and the process of the reaction was monitored by TLC. Upon completion, the reaction mixture was transferred to a round-bottom flask. Then the solvent was removed under vacuum and the residue was purified by silica gel chromatography, using a mixture of PE/EA to afford the desired product **3**.

2.3.2 Data and references.

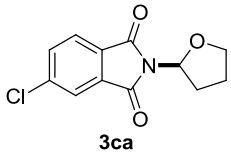
5-Methyl-2-(tetrahydrofuran-2-yl)isoindoline-1,3-dione (3ba)



3ba

Following the general procedure, **3ba** was purified by silica gel chromatography (10% EA/PE). Yield: 80%. **3ba**, white solid, mp. 74-76 ^oC. ^1H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 6.03 (dd, *J* = 8.0, 5.0 Hz, 1H), 4.20 (dd, *J* = 14.9, 7.7 Hz, 1H), 3.95 (td, *J* = 7.8, 4.7 Hz, 1H), 2.59-2.52 (m, 1H), 2.51 (s, 3H), 2.43-2.35 (m, 1H), 2.32-2.22 (m, 1H), 2.06-1.95 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 167.7, 145.3, 134.6, 132.2, 129.2, 123.6, 123.0, 80.7, 69.5, 28.9, 25.9, 21.8. HRMS (ESI) m/z calcd for $C_{13}H_{13}NNaO_3$ [M+Na^+] 254.0788, found 254.0790.

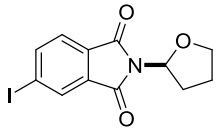
5-Chloro-2-(tetrahydrofuran-2-yl)isoindoline-1,3-dione (3ca)



3ca

Following the general procedure, **3ca** was purified by silica gel chromatography (10% EA/PE). Yield: 87%. **3ca**, white solid, mp. 90-93 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 1.4 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.03 (dd, *J* = 7.9, 4.9 Hz, 1H), 4.20 (dd, *J* = 14.8, 7.7 Hz, 1H), 3.96 (td, *J* = 7.8, 4.7 Hz, 1H), 2.53 (tdd, *J* = 13.0, 7.9, 5.0 Hz, 1H), 2.39 (dt, *J* = 10.1, 6.1 Hz, 1H), 2.34-2.23 (m, 1H), 2.03 (ddd, *J* = 11.8, 8.3, 4.3 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 166.4, 140.7, 134.2, 133.5, 129.9, 124.6, 123.7, 81.0, 69.8, 29.0, 25.9. HRMS (ESI) m/z calcd for $C_{12}H_{10}{}^{35}ClNNaO_3$ [M + Na^+] 274.0241, found 274.0243.

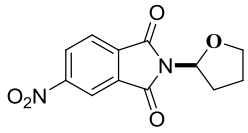
5-Iodo-2-(tetrahydrofuran-2-yl)isoindoline-1,3-dione (3da)



3da

Following the general procedure, **3da** was purified by silica gel chromatography (10% EA/PE). Yield: 58%. **3da**, white solid, mp. 100-103 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 0.7 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 6.02 (dd, *J* = 7.9, 4.9 Hz, 1H), 4.19 (dd, *J* = 14.8, 7.7 Hz, 1H), 3.96 (td, *J* = 7.8, 4.7 Hz, 1H), 2.57-2.47 (m, 1H), 2.43-2.33 (m, 1H), 2.33-2.22 (m, 1H), 2.02 (ddd, *J* = 11.9, 8.3, 4.3 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 166.4, 143.1, 133.2, 132.4, 131.0, 124.6, 101.1, 81.0, 69.8, 29.1, 26.0. HRMS (ESI) m/z calcd for $C_{12}H_{10}INNaO_3$ [M + Na^+] 365.9598, found 365.9601.

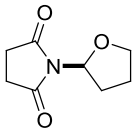
5-Nitro-2-(tetrahydrofuran-2-yl)isoindoline-1,3-dione (3ea)



3ea

Following the general procedure, **3ea** was purified by silica gel chromatography (10% EA/PE). Yield: 24%, 89% brsm. **3ea**, white solid, mp. 75-78 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.62 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 6.07 (dd, *J* = 7.6, 5.0 Hz, 1H), 4.26-4.15 (m, 1H), 3.98 (dd, *J* = 7.5, 5.0 Hz, 1H), 2.59-2.47 (m, 1H), 2.47-2.26 (m, 2H), 2.11-1.97 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 165.4, 151.7, 136.2, 133.2, 129.4, 124.6, 118.8, 81.4, 70.0, 29.2, 25.9. HRMS (ESI) m/z calcd for $C_{12}H_{10}N_2NaO_5$ [M+Na^+] 285.0482, found 285.0485.

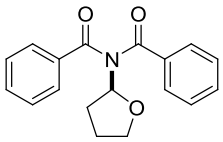
1-(Tetrahydrofuran-2-yl)pyrrolidine-2,5-dione (3fa)



3fa

Following the general procedure, **3fa** was purified by silica gel chromatography (10% EA/PE). Yield: 90%. **3fa**, colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 7.7, 5.3 Hz, 1H), 4.16 (dd, *J* = 15.0, 7.4 Hz, 1H), 3.92 (td, *J* = 7.6, 4.8 Hz, 1H), 2.68 (s, 4H), 2.41 (dt, *J* = 17.1, 6.5 Hz, 1H), 2.35-2.26 (m, 1H), 2.24-2.14 (m, 1H), 2.03-1.91 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.8, 81.3, 70.0, 28.2, 28.0, 26.0. HRMS (ESI) m/z calcd for $C_8H_{11}NNaO_3$ [M + Na^+] 192.0631, found 192.0640.

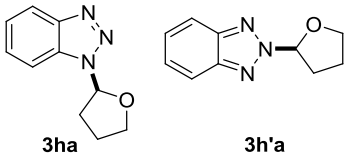
_N_-benzoyl-_N_-(tetrahydrofuran-2-yl)benzamide (3ga)



3ga

Following the general procedure, **3ga** was purified by silica gel chromatography (10% EA/PE). Yield: 59%. **3ga**, white solid, mp. 92-94 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 4H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 4H), 6.42-6.26 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 1H), 3.91 (dd, *J* = 12.9, 7.5 Hz, 1H), 2.56 (dd, *J* = 12.5, 5.2 Hz, 1H), 2.43-2.19 (m, 2H), 2.13-1.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 137.1, 131.9, 128.7, 128.3, 88.6, 69.6, 30.2, 25.6. HRMS (ESI) m/z calcd for $C_{18}H_{17}NNaO_3$ [M + Na^+] 318.1101, found 318.1007.

1-(Tetrahydrofuran-2-yl)-1*H*-benzo[*d*][1,2,3]triazole (3ha) and 2-(tetrahydrofuran-2-yl)-2*H*-benzo[*d*][1,2,3]triazole (3h′a)[6]

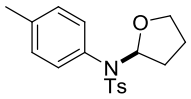


3ha 3h'a

Following the general procedure, **3ha** and **3h′a** was purified by silica gel chromatography (10% EA/PE). Yield: **3ha**, 67% and **3h′a**, 20%, 87% in total. **3ha**, colorless oil.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 6.52 (dd, *J* = 6.8, 1.8 Hz, 1H), 4.11 (dd, *J* = 14.8, 7.7 Hz, 1H), 4.04 (dd, *J* = 14.5, 8.1 Hz, 1H), 3.25-3.13 (m, 1H), 2.53 (dt, *J* = 15.5, 8.7 Hz, 1H), 2.46-2.34 (m, 1H), 2.19 (dd, *J* = 9.3, 4.7 Hz, 1H). **3h′a**, white solid, mp. 47-50 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.39 (dd, *J* = 6.6, 3.1 Hz, 2H), 6.60 (dd, *J* = 6.5, 2.0 Hz, 1H), 4.34 (dd, *J* =

13.9, 7.8 Hz, 1H), 4.15 (dd, *J* = 14.5, 7.4 Hz, 1H), 2.76 (ddd, *J* = 8.0, 6.6, 2.5 Hz, 1H), 2.61-2.44 (m, 2H), 2.25-2.08 (m, 1H).

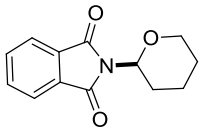
4-Methyl-*N*-(tetrahydrofuran-2-yl)-N-*p*-tolylbenzenesulfonamide (3ia)



3ia

Following the general procedure, **3ia** was purified by silica gel chromatography (10% EA/PE). Yield: 42%, 61% brsm. **3ia**, white solid, mp. 98-100 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 7.4 Hz, 2H), 6.25 (t, *J* = 5.7 Hz, 1H), 3.62 (dd, *J* = 16.5, 7.6 Hz, 2H), 2.42 (s, 3H), 2.33 (s, 3H), 2.18-2.06 (m, 1H), 1.74-1.60 (m, 2H), 1.22 (dt, *J* = 12.9, 6.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.0, 138.7, 136.9, 132.5, 131.8, 129.3, 129.0, 128.1, 89.3, 68.3, 30.2, 24.6, 21.5, 21.1. HRMS (ESI) m/z calcd for $C_{18}H_{21}NNaO_3S$ [M + Na^+] 354.1134, found 354.1140.

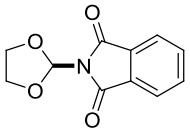
2-(Tetrahydro-2H-pyran-2-yl)isoindoline-1,3-dione (3ab)



3ab

Following the general procedure, **3ab** was purified by silica gel chromatography (10% EA/PE). Yield: 54%, white solid, mp. 115-118 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.33 (dd, *J* = 11.4, 2.2 Hz, 1H), 4.17-4.05 (m, 1H), 3.66 (td, *J* = 12.1, 2.2 Hz, 1H), 2.76 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.04 (dd, *J* = 13.3, 2.3 Hz, 1H), 1.80-1.51 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 134.2, 131.8, 123.5, 79.3, 69.0, 27.9, 24.9, 23.6. HRMS (ESI) calcd for $C_{13}H_{13}NNaO_3$ [M + Na^+] 254.0788, found 254.0782.

2-(1,3-Dioxolan-2-yl)isoindoline-1,3-dione (3ac)

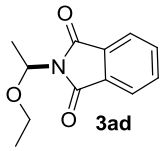


3ac

Following the general procedure, **3ac** was purified by silica gel chromatography (10% EA/PE). Yield: 65%, white solid, mp. 95-98 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz,

2H), 6.79 (s, 1H), 4.46 (t, *J* = 6.6 Hz, 2H), 4.10 (t, *J* = 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 134.3, 131.7, 123.5, 100.5, 66.5. HRMS (ESI) calcd for $C_{11}H_9NNaO_4$ [M + Na^+] 242.0424, found 242.0431.

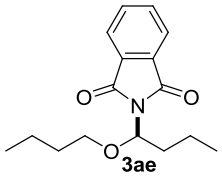
2-(1-Ethoxyethyl)isoindoline-1,3-dione (3ad)[7]



3ad

Following the general procedure, **3ad** was purified by silica gel chromatography (10% EA/PE). Yield: 90%, white solid, mp. 63-65 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.59 (q, *J* = 6.3 Hz, 1H), 3.59-3.45 (m, 2H), 1.79 (d, *J* = 6.3 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 134.1, 131.9, 123.3, 80.8, 69.7, 29.1, 26.0. HRMS (ESI) m/z calcd for $C_{12}H_{13}NNaO_3$ [M + Na^+] 242.0788, found 242.0790.

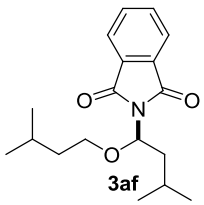
2-(1-Butoxybutyl)isoindoline-1,3-dione (3ae)



3ae

Following the general procedure, **3ae** was purified by silica gel chromatography (10% EA/PE). Yield: 72%, colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.38 (t, *J* = 7.1 Hz, 1H), 3.52-3.39 (m, 2H), 2.32-2.21 (m, 1H), 2.15-2.04 (m, 1H), 1.55 (td, *J* = 13.4, 6.8 Hz, 2H), 1.50-1.40 (m, 1H), 1.39-1.28 (m, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 134.2, 131.7, 123.5, 82.0, 68.9, 34.6, 31.4, 19.3, 18.9, 13.8, 13.6. HRMS (ESI) m/z calcd for $C_{16}H_{21}NNaO_3$ [M + Na^+] 298.1414, found 298.1415.

2-(1-(Isopentyloxy)-3-methylbutyl)isoindoline-1,3-dione (3af)

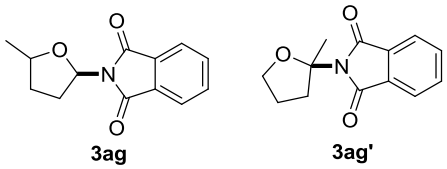


3af

Following the general procedure, **3af** was purified by silica gel chromatography (10% EA/PE). Yield: 72%, colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.4,

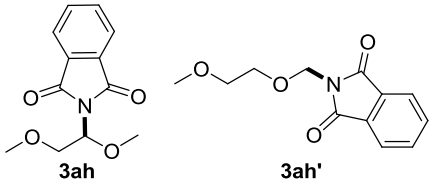
3.0 Hz, 2H), 7.75 (dt, *J* = 5.4, 2.7 Hz, 2H), 5.55 – 5.35 (m, 1H), 3.50 – 3.44 (m, 1H), 2.22 – 2.13 (m, 1H), 2.05 – 1.93 (m, 1H), 1.70 – 1.60 (m, 2H), 1.45 (dt, *J* = 14.1, 6.9 Hz, 2H), 0.98-0.92 (m, 6H), 0.88 – 0.79 (m, 7H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 134.1, 131.5, 123.3, 80.6, 67.1, 41.0, 37.9, 24.7, 24.6, 22.3, 22.2. HRMS (ESI) m/z calcd for $C_{18}H_{25}NNaO_3$ [M + Na^+] 326.1727, found 326.1735.

5-Methyltetrahydrofuran-2-yl)isoindoline-1,3-dione (3ag) and
2-(2-methyltetrahydrofuran-2-yl)isoindoline-1,3-dione (3ag′)



Following the general procedure, **3ag and 3ag′** was purified by silica gel chromatography (10% EA/PE). Yield: 63%. **3ag**, white solid, mp. 103-105 ^{o}C, a mixture of two diastereomers (dr=1.6:1). Major: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90-7.81 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.3, 3.0 Hz, 2H), 6.11 (dd, *J* = 7.8, 6.0 Hz 0.6H), 5.99 (dd, *J* = 8.6, 3.5 Hz, 0.4H), 4.62-4.50 (m, 0.6H), 4.13-4.10 (m, 0.4H), 2.71-2.60 (m, 0.6H), 2.58-2.49 (m, 0.4H), 2.45-2.27 (m, 1.6H), 2.21-2.14 (m, 0.4H), 2.10-2.02 (m, 1H), 1.64-1.57 (m, 0.6H), 1.37 (d, *J* = 6.0 Hz, 1.1H), 1.28 (d, *J* = 6.1 Hz, 1.9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 167.3, 134.0, 131.7, 131.7, 123.1, 123.1, 80.4, 80.0, 77.1, 33.8, 32.3, 29.7, 29.3, 20.6, 20.1. HRMS (ESI) calcd for $C_{13}H_{13}NNaO_3$ [M + Na^+] 254.0788, found 254.0783. **3ag′**, white solid, mp. 84-85 ^{o}C ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H), 4.13-3.97 (m, 2H), 3.31-3.15 (m, 1H), 2.11-1.91 (m, 3H), 1.86 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.3, 133.8, 132.0, 122.9, 97.0, 68.8, 37.2, 25.7, 24.6. HRMS (ESI) calcd for $C_{13}H_{13}NNaO_3$ [M + Na^+] 254.0788, found 254.0786.

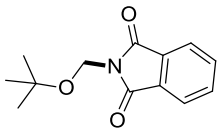
2-(1,2-Dimethoxyethyl)isoindoline-1,3-dione (3ah) and
2-((2-methoxyethoxy)methyl)isoindoline-1,3-dione (3ah′)



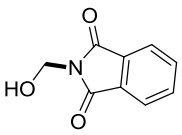
Following the general procedure, **3ah** and **3ah′** was purified by silica gel chromatography (10% EA/PE). Yield: **3ah**, 48% and **3ah′**, 32%, 80% in total. **3ah**, colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.48 (t, *J* = 6.5 Hz, 1H), 4.01 (dd, *J* = 12.4, 6.5 Hz, 2H), 3.42 (s,

3H), 3.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 134.3, 131.6, 123.6, 81.2, 70.9, 59.2, 56.9. HRMS (ESI) m/z calcd for $C_{12}H_{13}NNaO_4$ [M + Na^+] 258.0737, found 258.0744. **3ah′**, white solid, mp. 78-80 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.77 (dd, *J* = 5.4, 2.9 Hz, 2H), 5.19 (s, 2H), 3.83-3.72 (m, 2H), 3.58-3.48 (m, 2H), 3.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 134.3, 131.9, 123.6, 71.6, 69.4, 67.7, 59.0. HRMS (ESI) m/z calcd for $C_{12}H_{13}NNaO_4$ [M + Na^+] 258.0737, found 258.0742.

2-(Tert-butoxymethyl)isoindoline-1,3-dione (3ai)[8] **and**
2-(hydroxymethyl)isoindoline-1,3-dione (3ai′)[9]



3ai



3ai'

Following the general procedure, **3ai** and **3ai′** was purified by silica gel chromatography (10% EA/PE). Yield: 65% in total. **3ai**, white solid, mp. 80-83 °C. ^{1}H NMR (600 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.12 (s, 2H), 1.31 (s, 9H). **3ai′**, white solid, mp. 140-145 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.27 (s, 2H).

3. Reference

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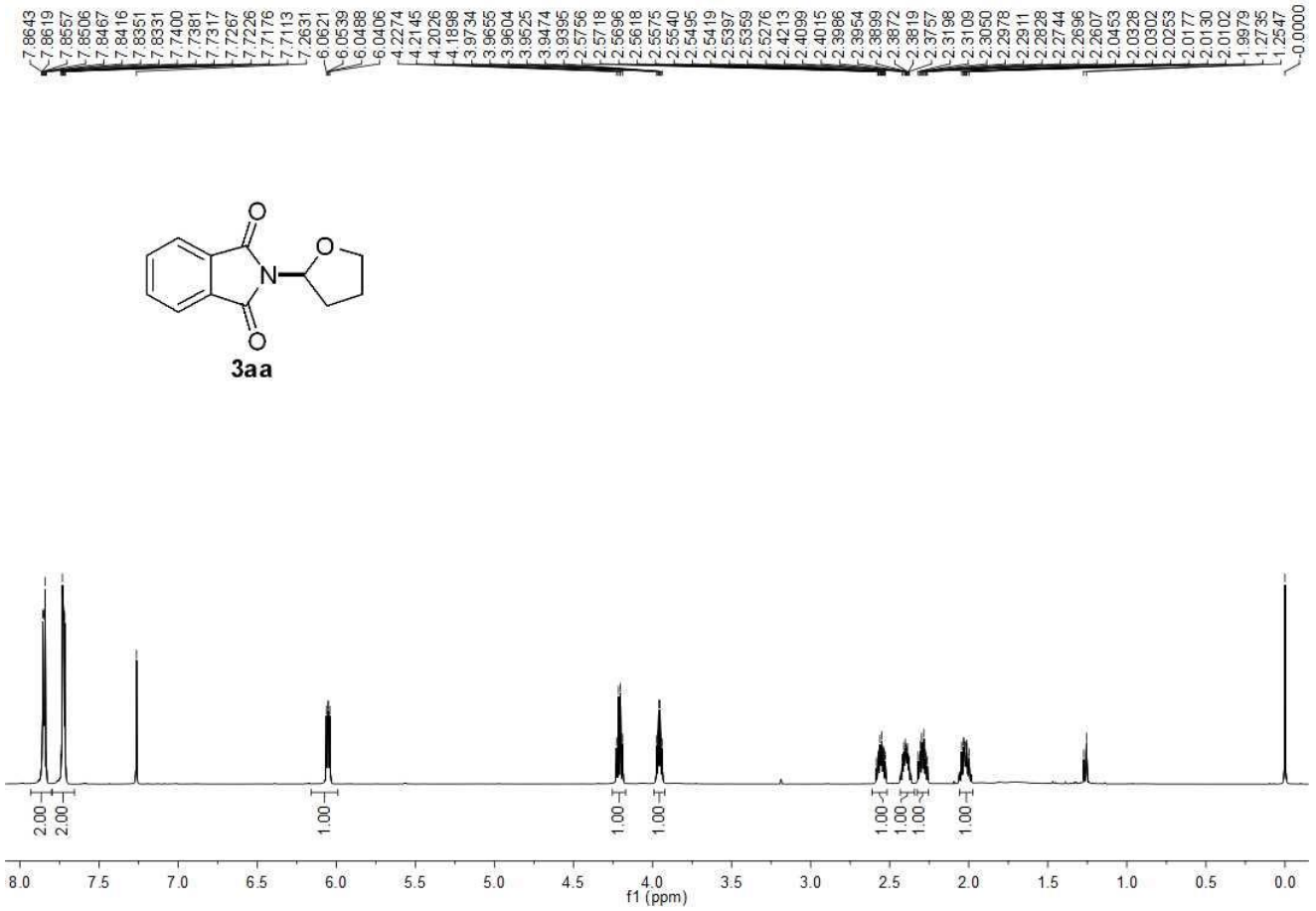
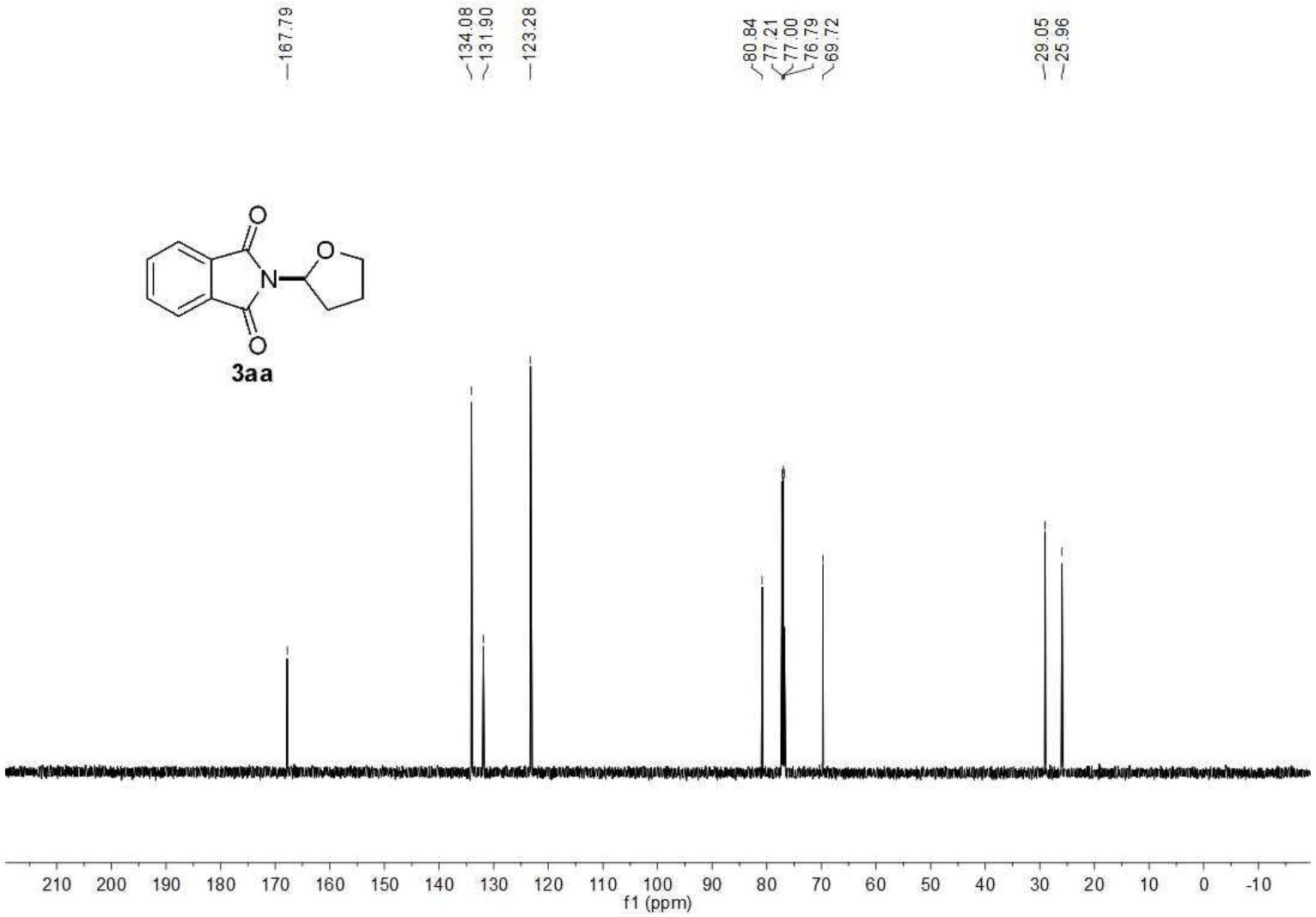
4. ^{1}H NMR and ^{13}C NMR Spectra of the Products

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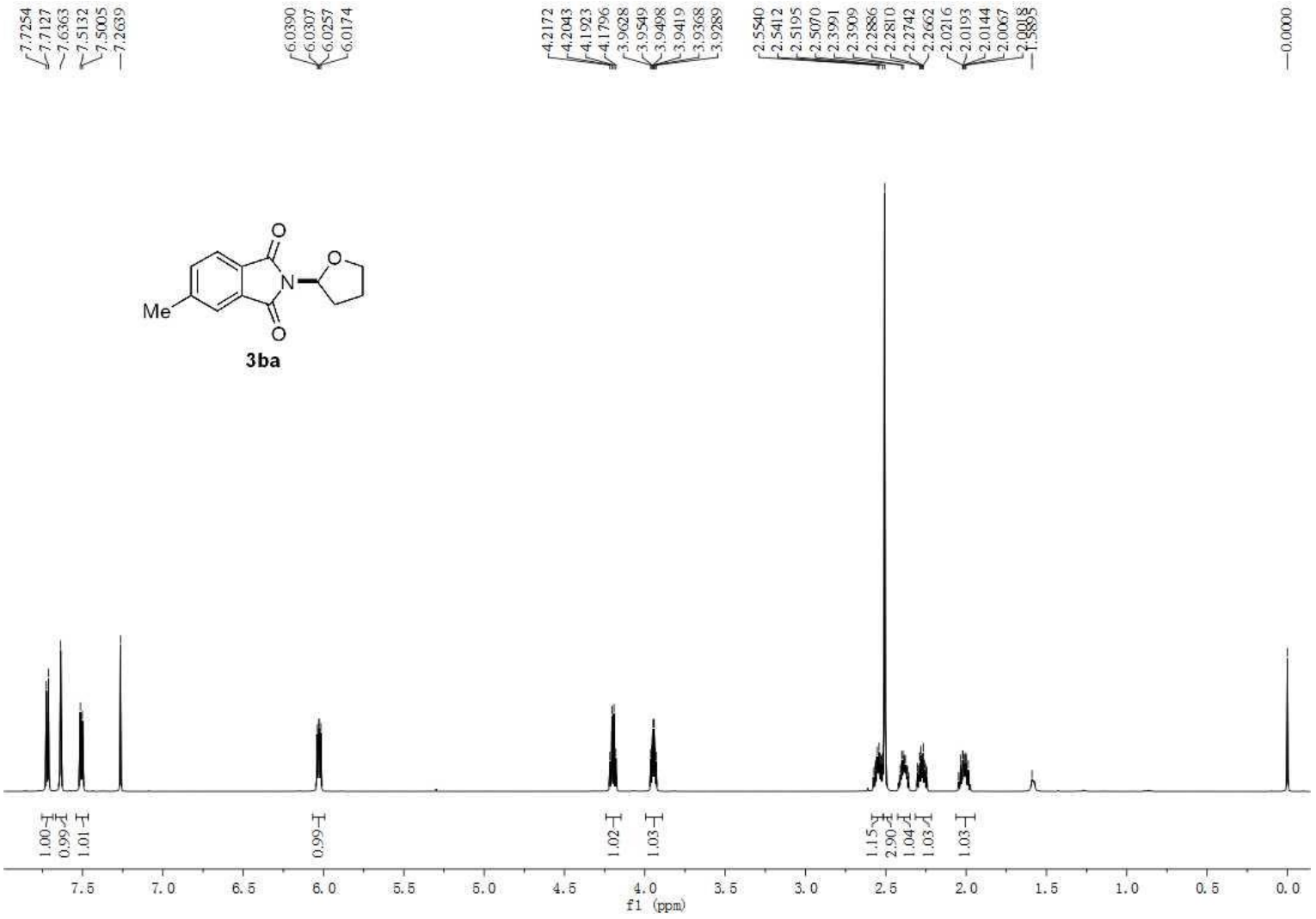
134.08
131.90
123.28
80.84
77.21
77.00
76.79
69.72
29.05
25.96
O
O
N
O
O
3aa
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.7127
7.6363
7.5132
7.5005
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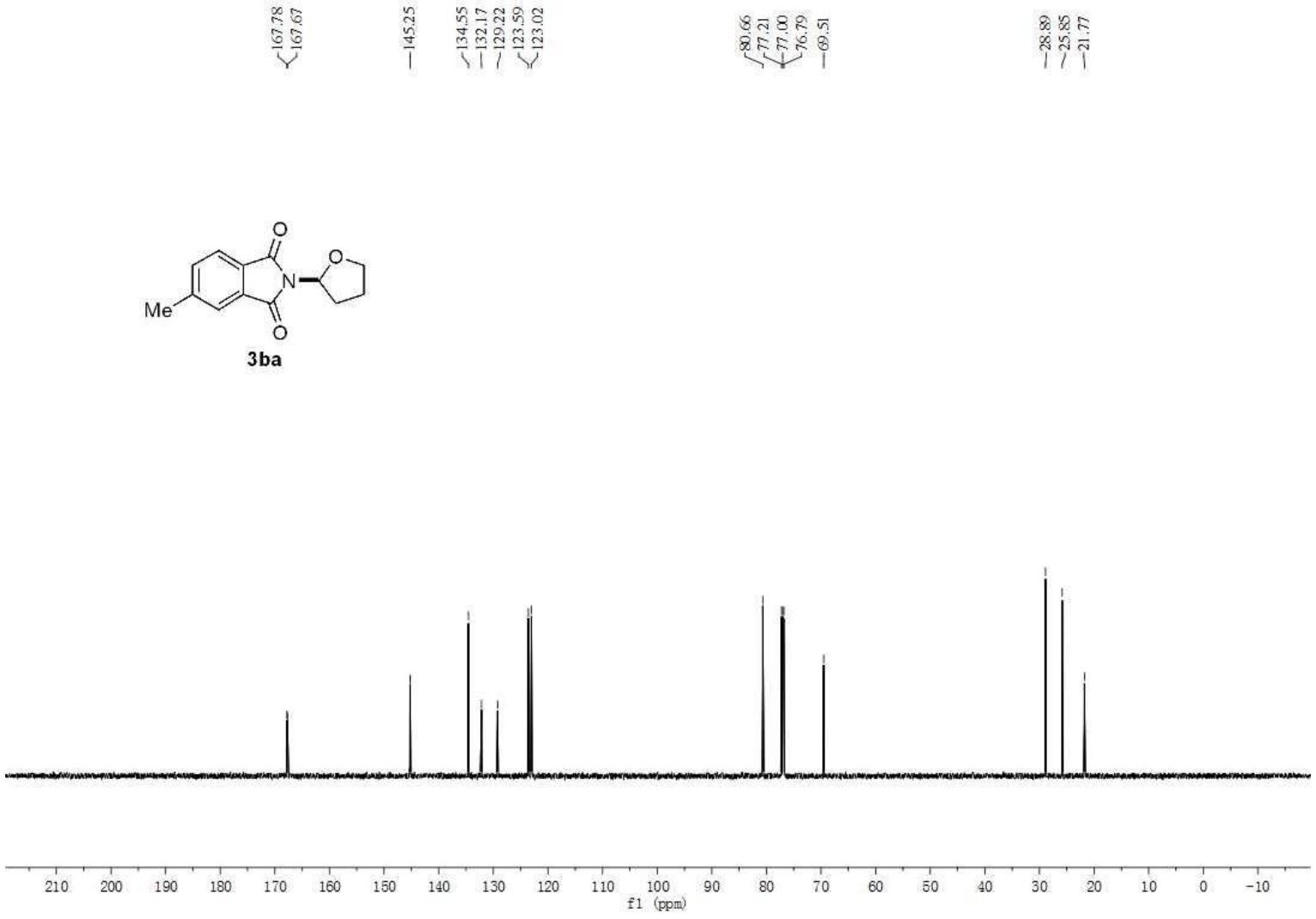
6.0390
6.0307
6.0257
6.0174
4.2172
4.2043
4.1923
4.1796
3.9628
3.9549
3.9498
3.9419
3.9368
3.9289
2.5540
2.5412
2.5195
2.5070
2.3991
2.3909
2.2886
2.2810
2.2742
2.2662
2.0216
2.0193
2.0144
2.0067
2.0018
1.5885
0.0000
Me
O
N
O
O
3ba
1.00
0.99
1.01
0.99
1.02
1.03
1.15
2.90
1.04
1.03
1.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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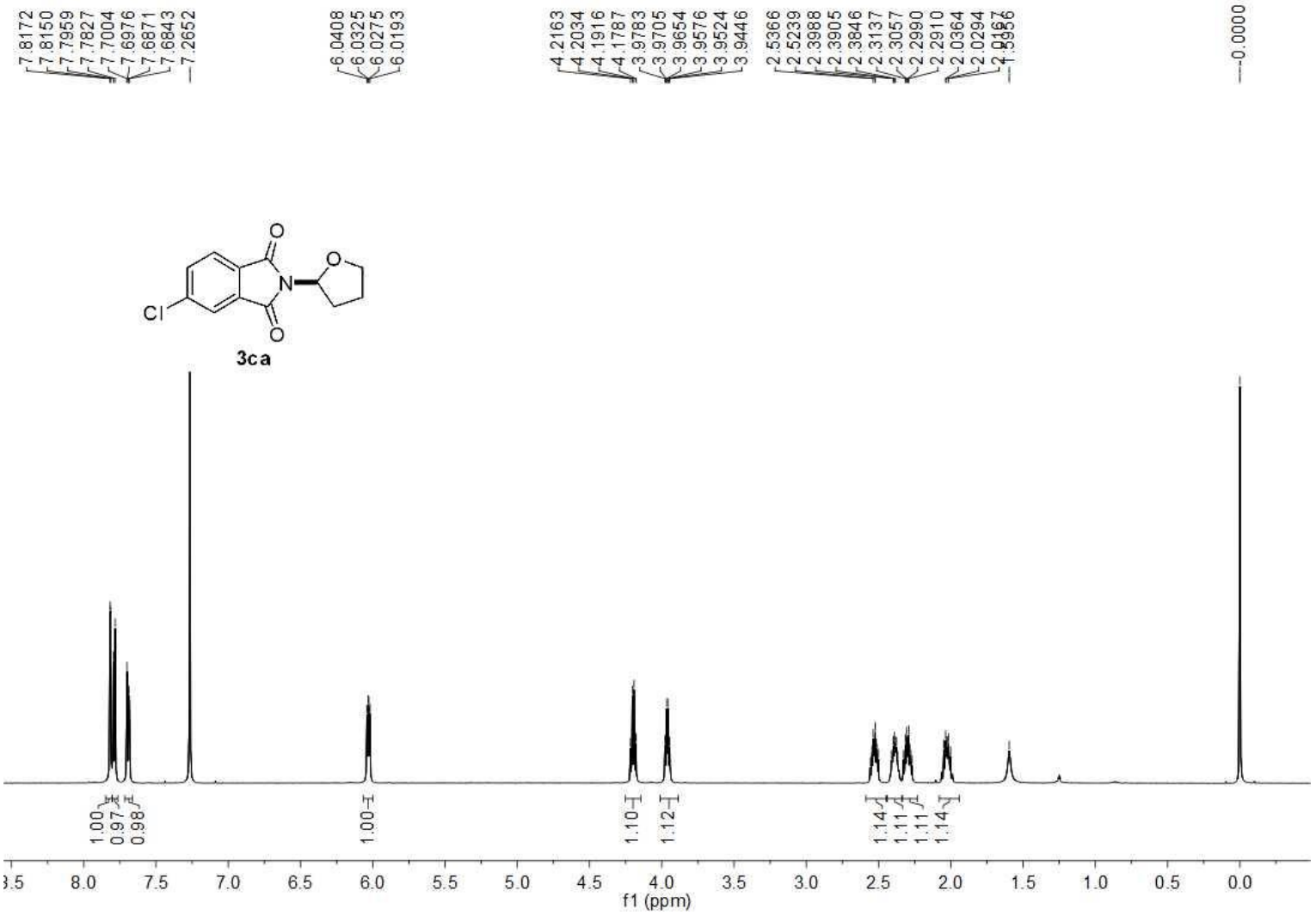
167.67
145.25
134.55
132.17
129.22
123.59
123.02
80.66
77.21
77.00
76.79
69.51
28.89
25.85
21.77
O
N
O
O
Me
3ba
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.7959
7.7827
7.7004
7.6976
7.6871
7.6843
7.2652
6.0408
6.0325
6.0275
6.0193
4.2163
4.2034
4.1916
4.1787
3.9783
3.9705
3.9654
3.9576
3.9524
3.9446
2.5366
2.5239
2.3988
2.3905
2.3846
2.3137
2.3057
2.2990
2.2910
2.0364
2.0294
0.0000
Cl
O
N
O
O
3ca
1.00
0.97
0.98
1.00
1.10
1.12
1.14
1.14
1.11
1.14
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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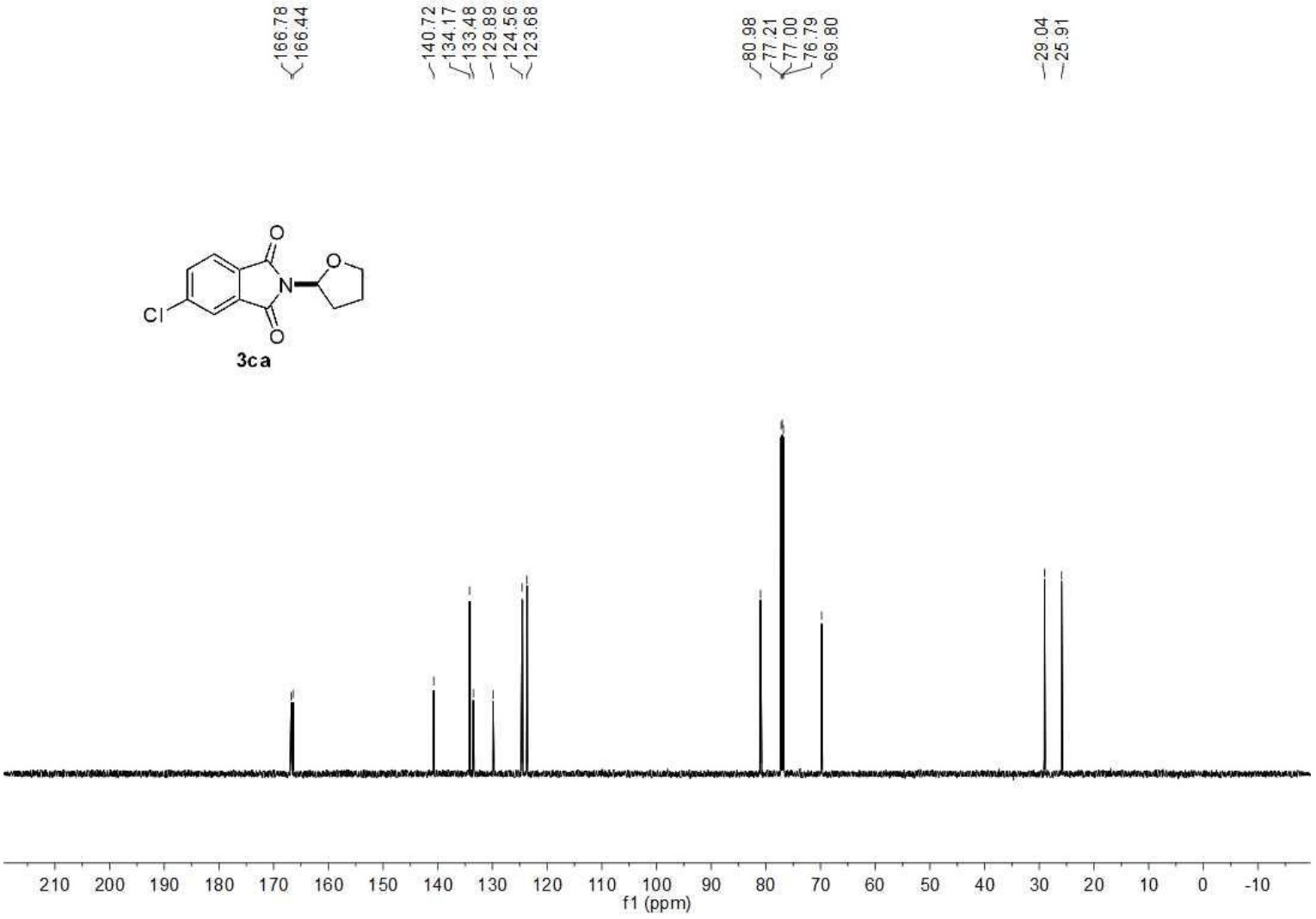
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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129.89
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123.68
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77.00
76.79
69.80
29.04
25.91
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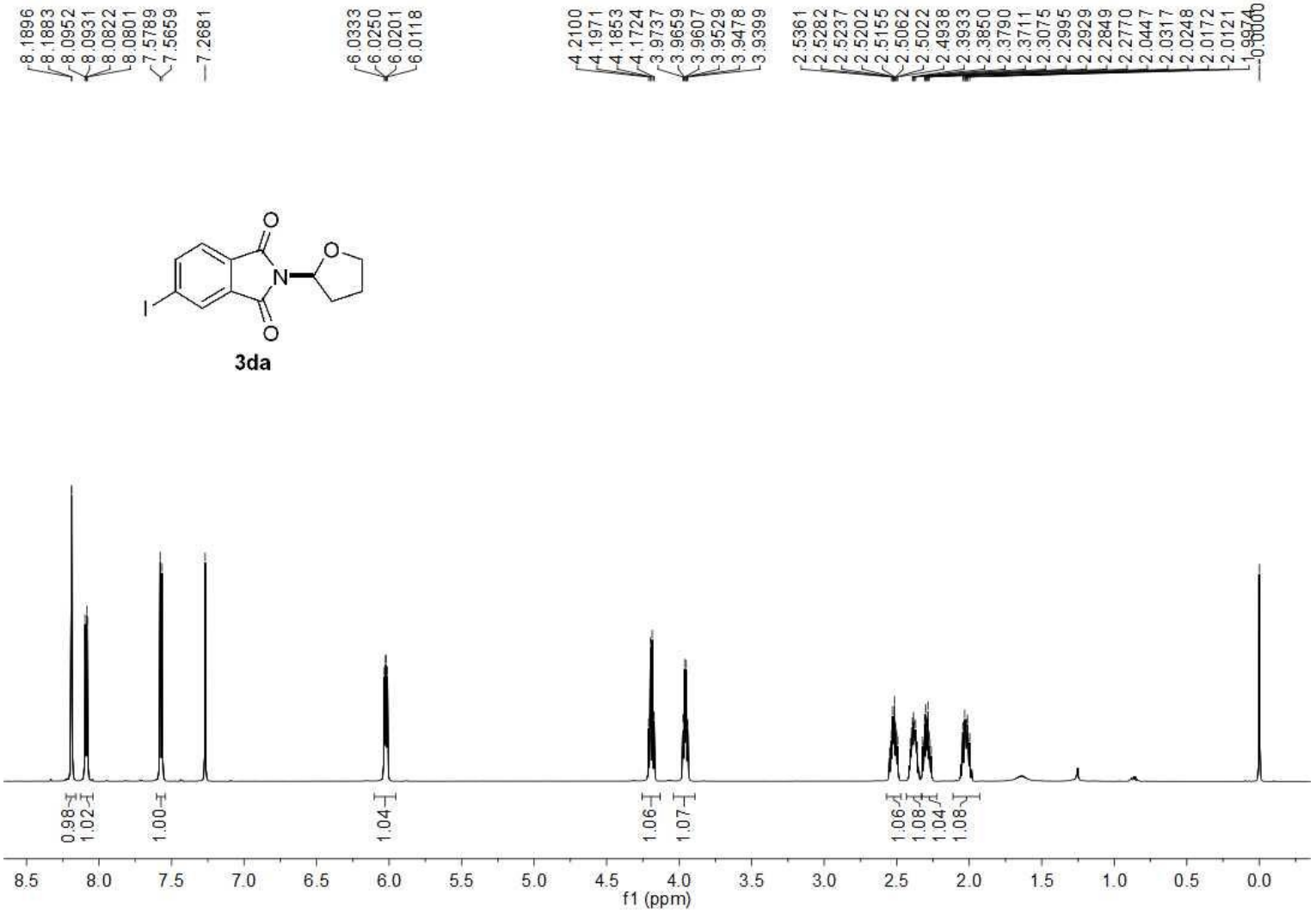
O
N
O
Cl
O
3ca
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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8.1883
8.0952
8.0931
8.0822
8.0801
7.5789
7.5659
7.2681
6.0333
6.0250
6.0201
6.0118
4.2100
4.1971
4.1853
4.1724
3.9737
3.9659
3.9607
3.9529
3.9478
3.9399
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2.5155
2.5062
2.5022
2.4938
2.3933
2.3850
2.3790
2.3711
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2.2995
2.2929
2.2849
2.2770
2.0447
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2.0172
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1.9974
0.0000
O
O
N
O
I
3da
0.98
1.02
1.00
1.04
1.06
1.07
1.06
1.08
1.04
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7.0
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6.0
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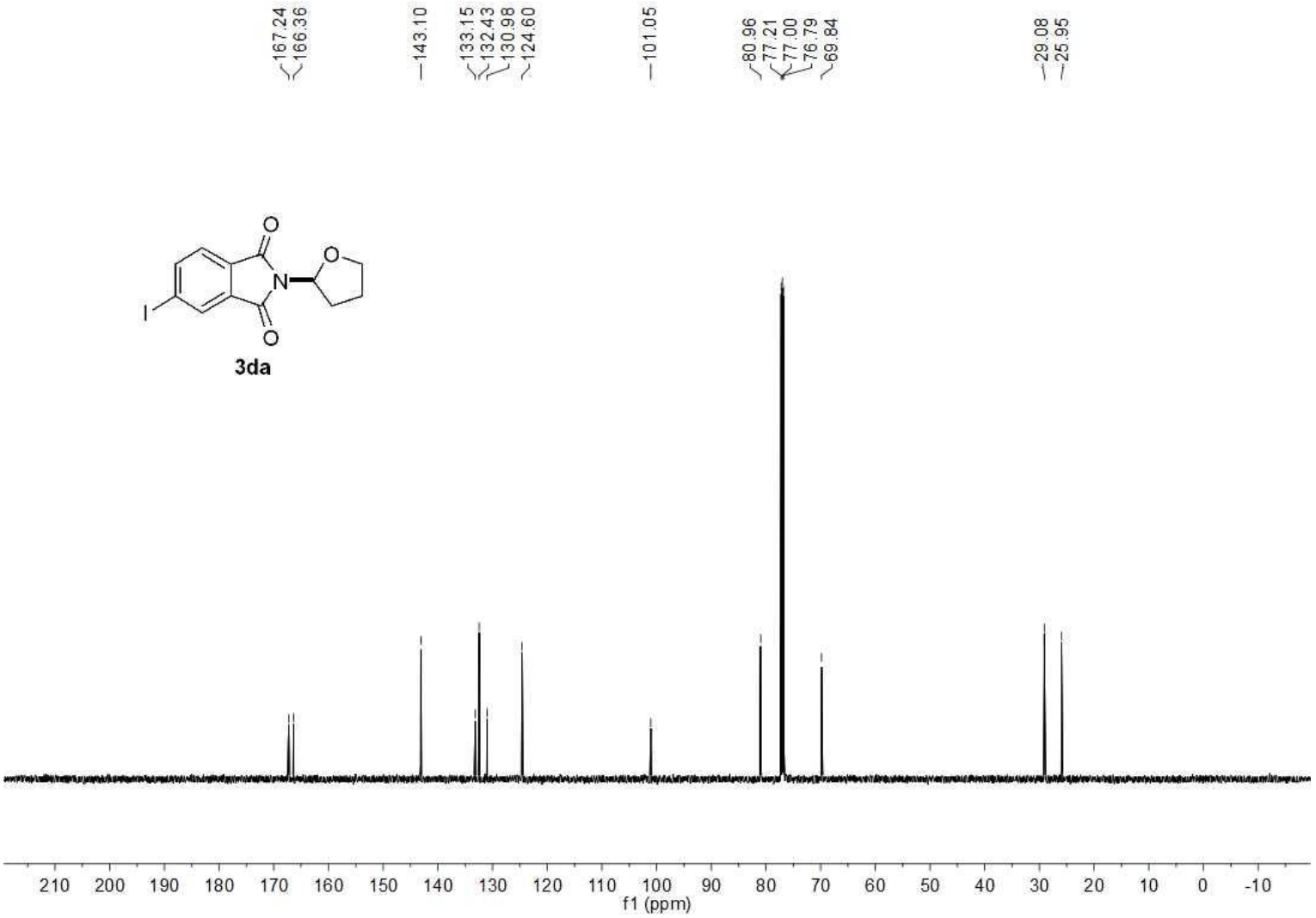
0.0
f1 (ppm)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69.84
29.08
25.95
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O
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O
I
O
3da
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


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8.6095
8.0643
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6.0616
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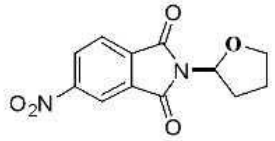
O
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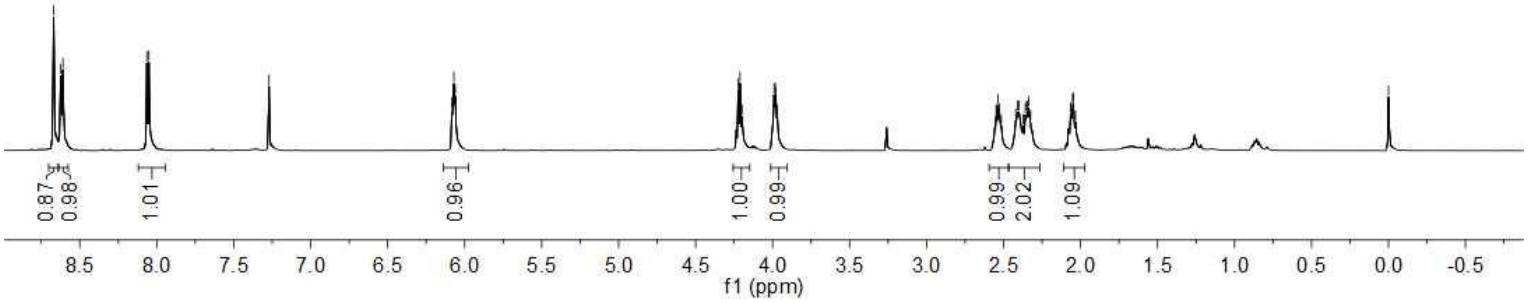
O
O2N

3ea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7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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3.0
2.5
2.0
1.5
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0.5
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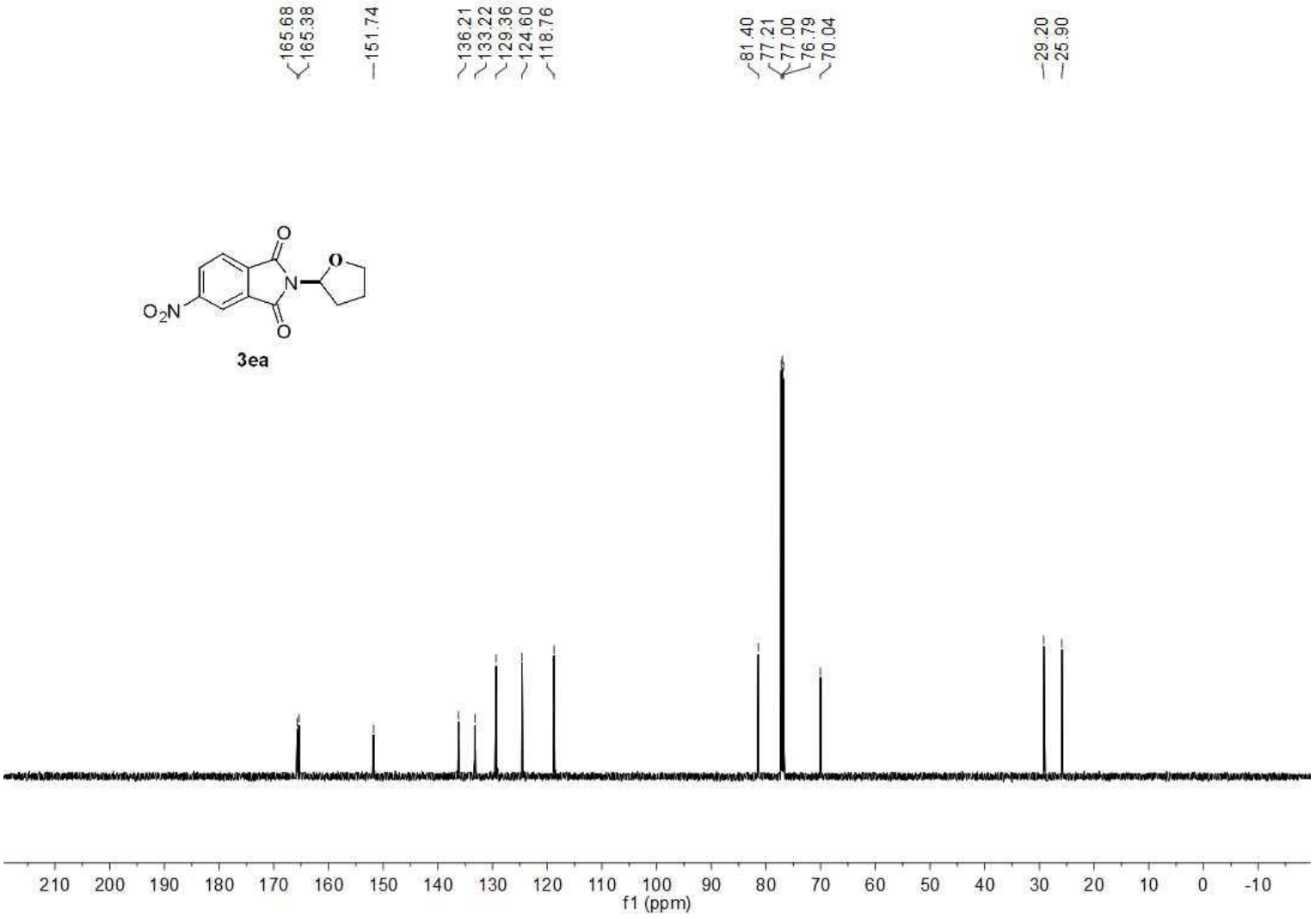
f1 (ppm)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77.21
77.00
76.79
70.04
29.20
25.90
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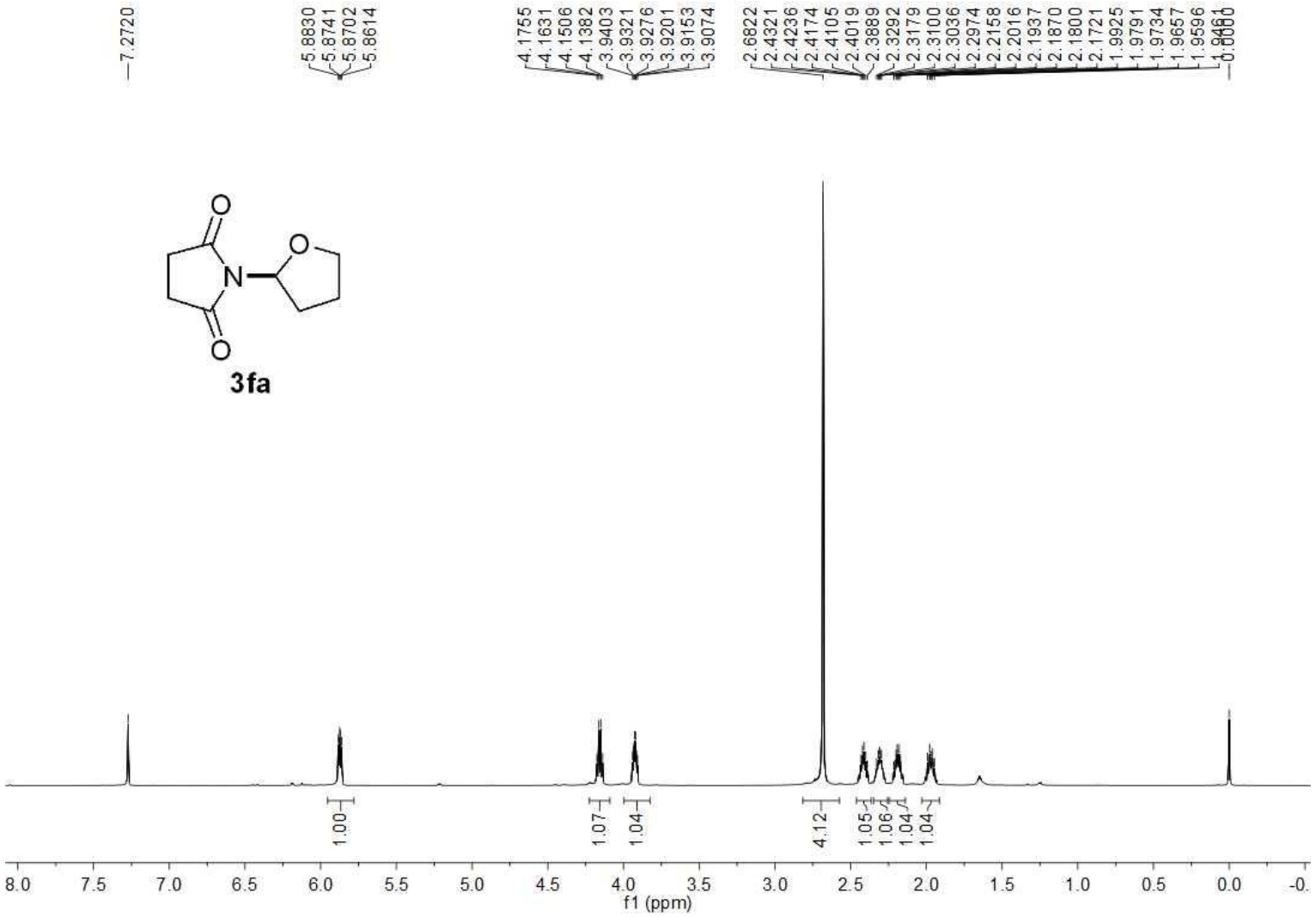
N
O
O
O2N
3ea
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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O
O
3fa
1.00
1.07
1.04
4.12
1.05
1.06
1.04
1.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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2.0
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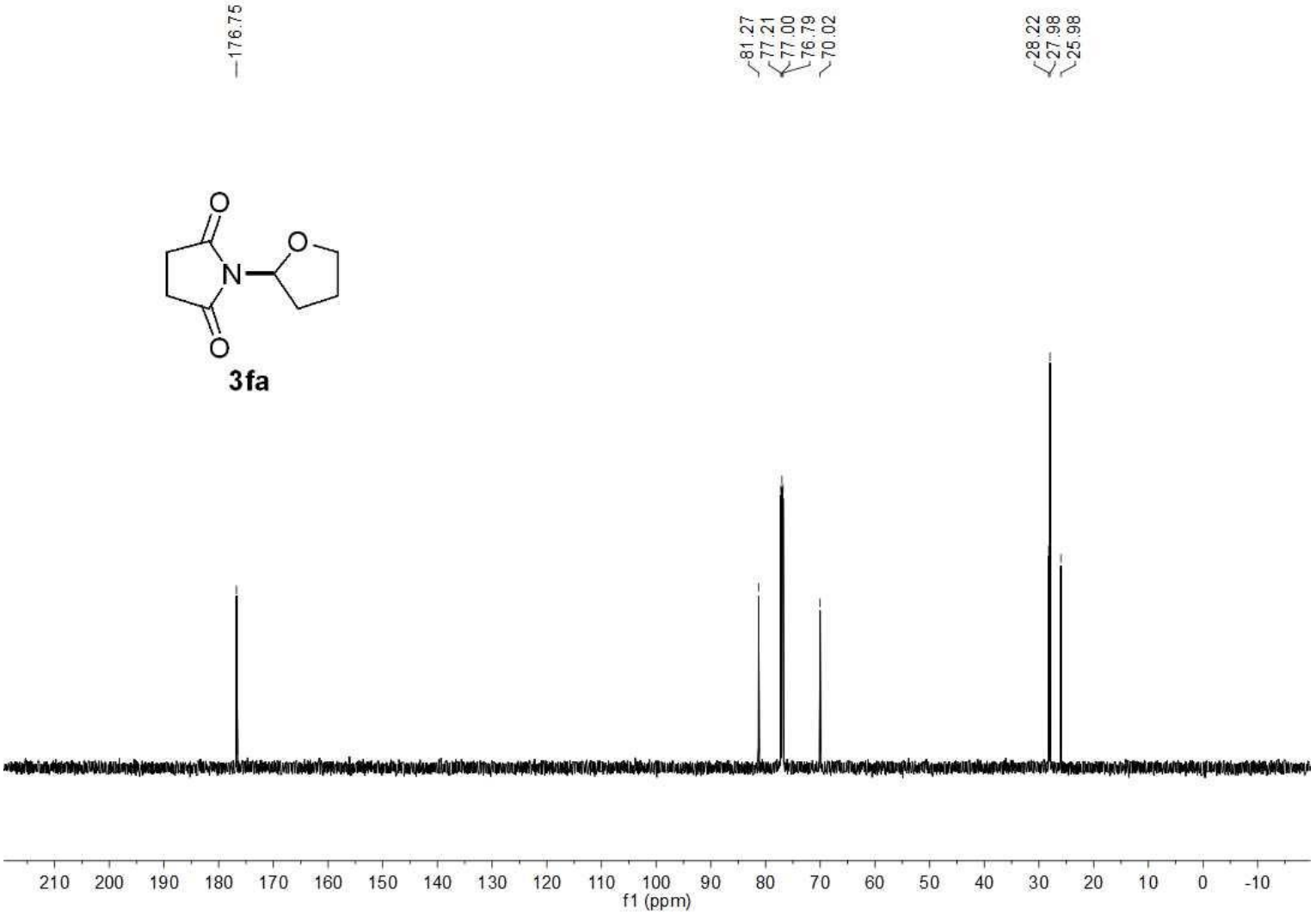
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28.22
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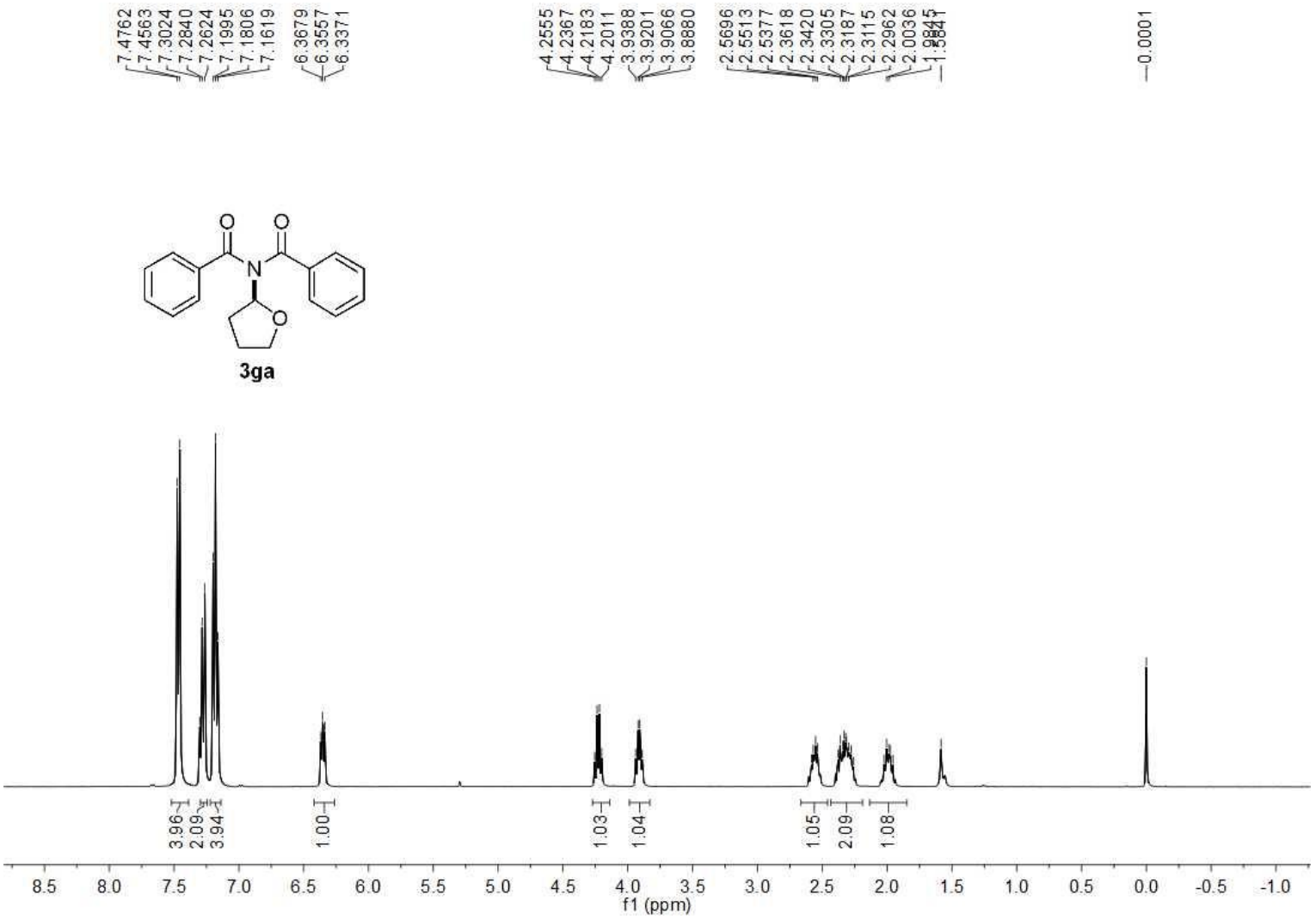
O
O
N
O
3fa
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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6.3371
4.2555
4.2367
4.2183
4.2011
3.9388
3.9201
3.9066
3.8880
2.5696
2.5513
2.5377
2.3618
2.3420
2.3305
2.3187
2.3115
2.2962
2.0036
0.0001
3ga
3.96
2.09
3.94
1.00
1.03
1.04
1.05
2.09
1.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
2.0
1.5
1.0
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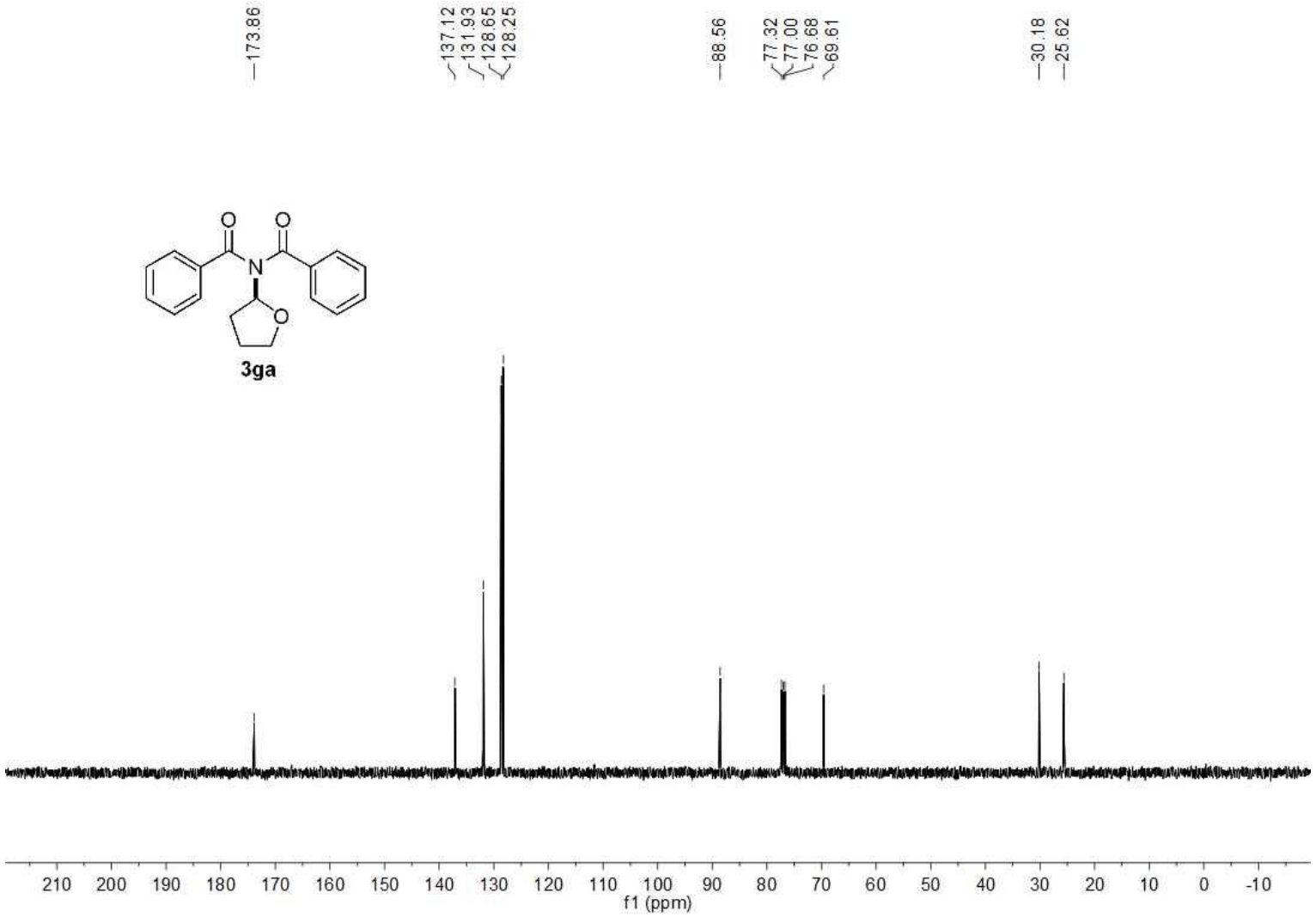
0.0
-0.5
-1.0
f1 (ppm)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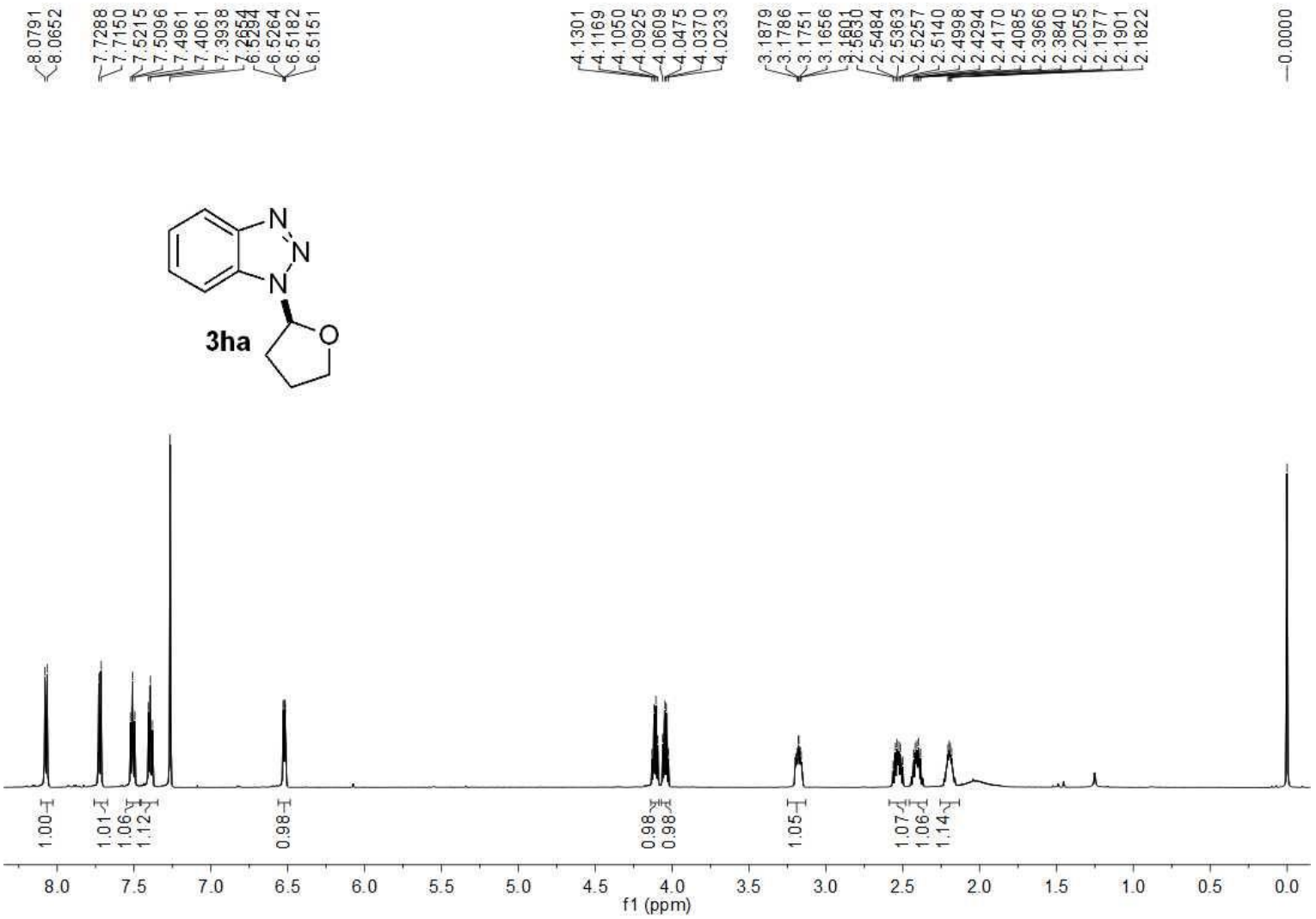
131.93
128.65
128.25
88.56
77.32
77.00
76.68
69.61
30.18
25.62
3ga
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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6.5182
6.5151
4.1301
4.1169
4.1050
4.0925
4.0609
4.0475
4.0370
4.0233
3.1879
3.1786
3.1751
3.1656
2.5484
2.5363
2.5257
2.5140
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2.4294
2.4170
2.4085
2.3966
2.3840
2.2055
2.1977
2.1901
2.1822
0.0000
3ha
1.00
1.01
1.06
1.12
0.98
0.98
0.98
1.05
1.07
1.06
1.14
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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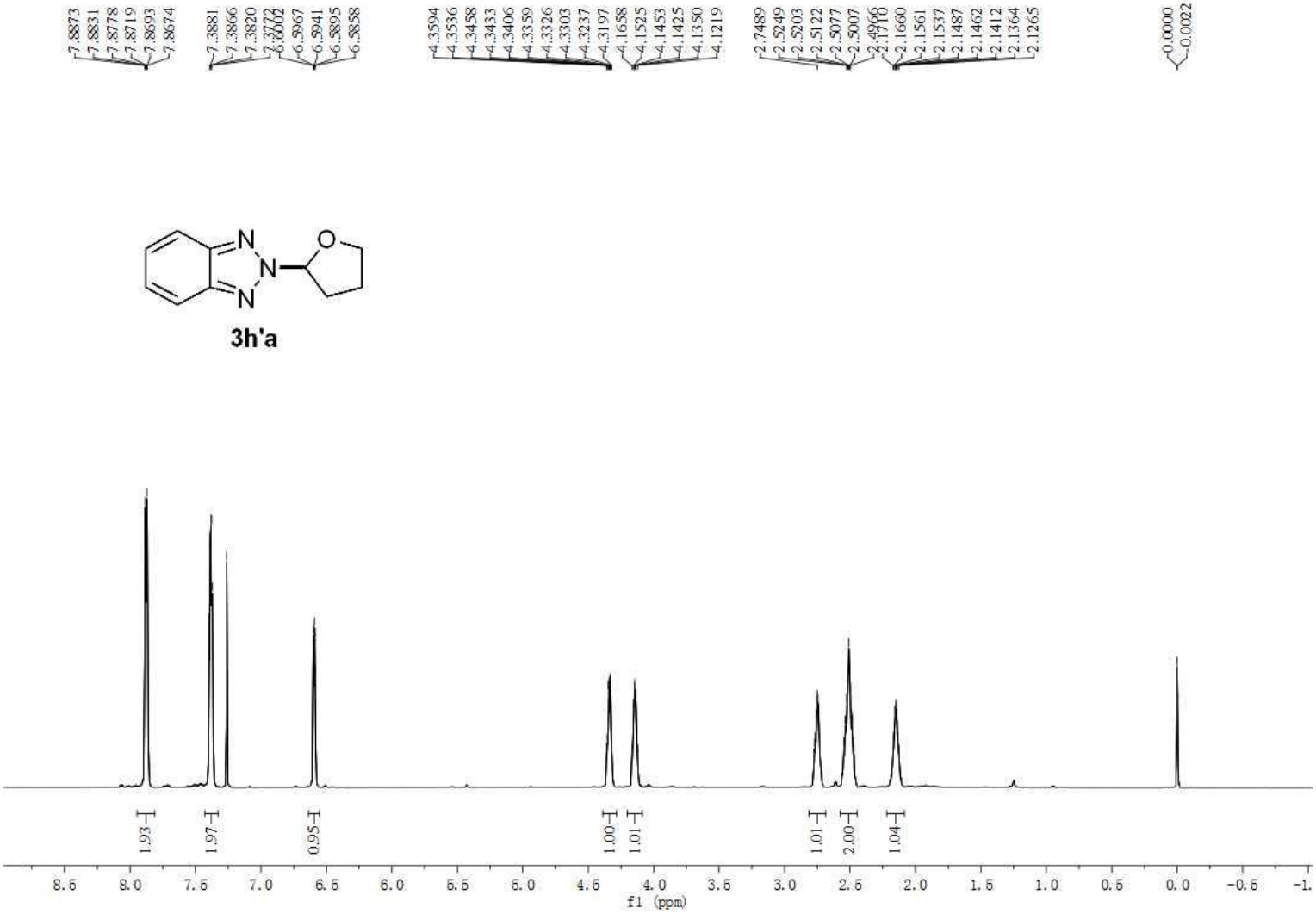
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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7.8693
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7.3881
7.3866
7.3820
7.3772
6.6002
6.5967
6.5941
6.5895
6.5858
4.3594
4.3536
4.3458
4.3433
4.3406
4.3359
4.3326
4.3303
4.3237
4.3197
4.1658
4.1525
4.1453
4.1425
4.1350
4.1219
2.7489
2.5249
2.5203
2.5122
2.5077
2.5007
2.4966
2.1710
2.1660
2.1561
2.1537
2.1487
2.1462
2.1412
2.1364
2.1265
0.0000
-0.0022
N
N
N
O
3h'a
1.93
1.97
0.95
1.00
1.01
1.01
2.00
1.04
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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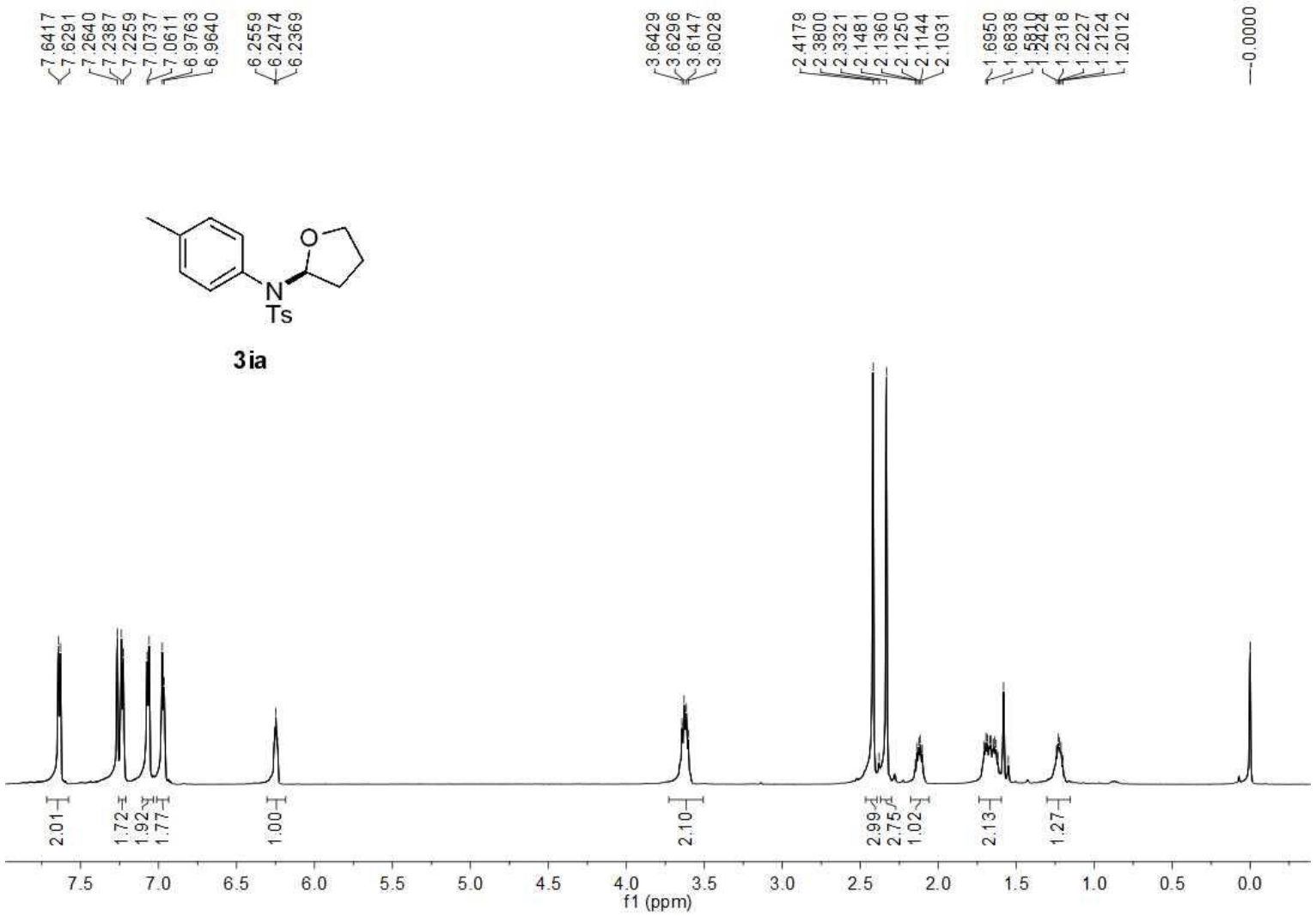
f1 (ppm)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7.0611
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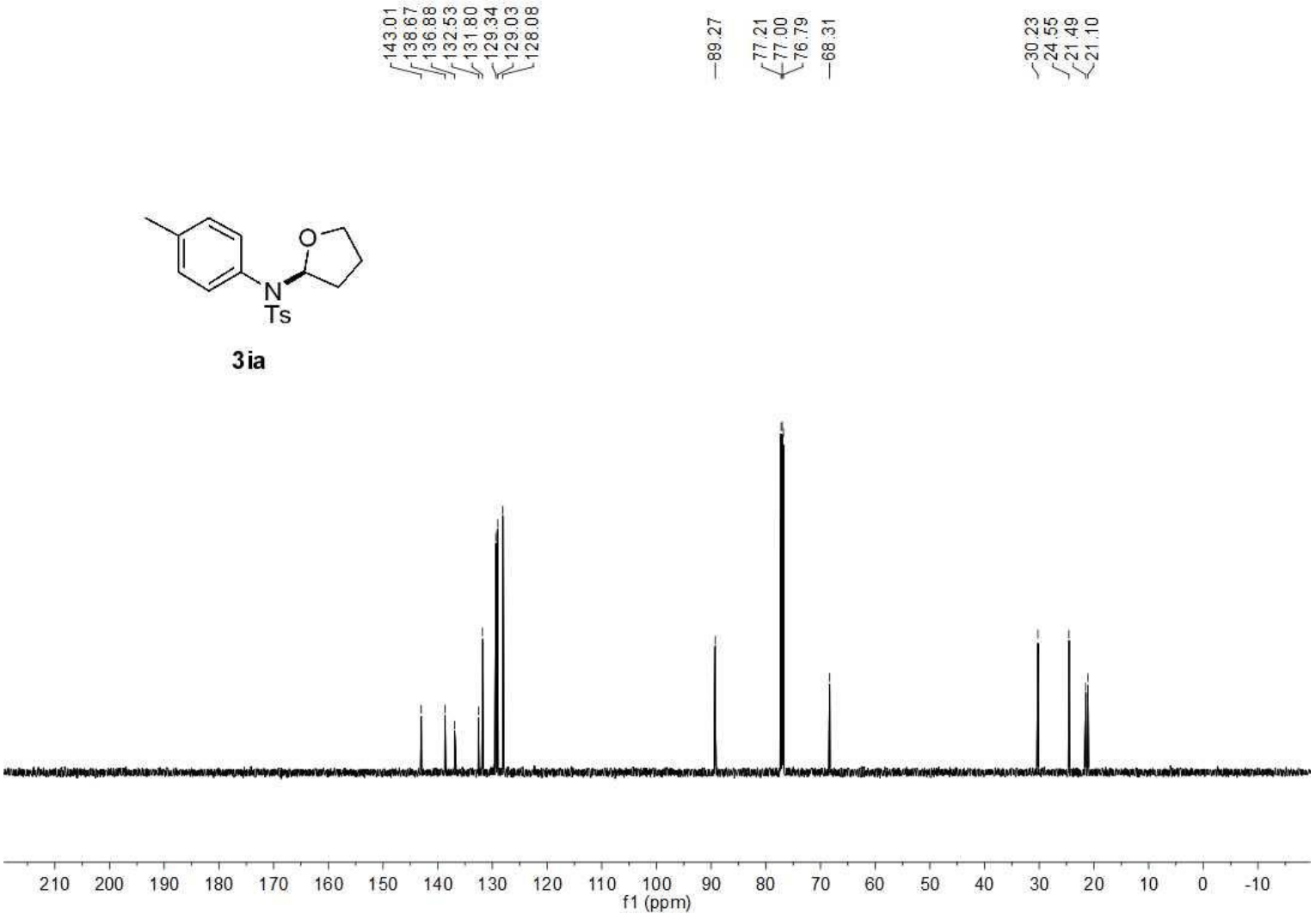
6.9640
6.2559
6.2474
6.2369
3.6429
3.6296
3.6147
3.6028
2.4179
2.3800
2.3321
2.1481
2.1360
2.1250
2.1144
2.1031
1.6950
1.6838
1.2318
1.2227
1.2124
1.2012
0.0000
O
N
Ts
3ia
2.01
1.72
1.92
1.77
1.00
2.10
2.99
2.75
1.02
2.13
1.27
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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136.88
132.53
131.80
129.34
129.03
128.08
89.27
77.21
77.00
76.79
68.31
30.23
24.55
21.49
21.10
O
N
Ts
3ia
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.8754
7.8715
7.8664
7.7454
7.7404
7.7364
7.7314
7.2700
5.3447
5.3412
5.3257
5.3220
4.1357
4.1320
4.1283
4.1165
4.1128
4.1090
3.6892
3.6857
3.6690
3.6660
3.6493
2.7694
2.7626
2.7501
2.7432
2.7286
2.7224
2.0558
2.0522
2.0336
2.0299
1.7671
1.7528
1.7457
1.7027
1.6808
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1.6335
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1.6213
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1.5454
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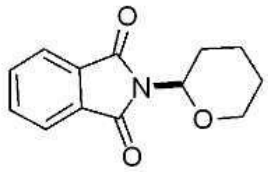

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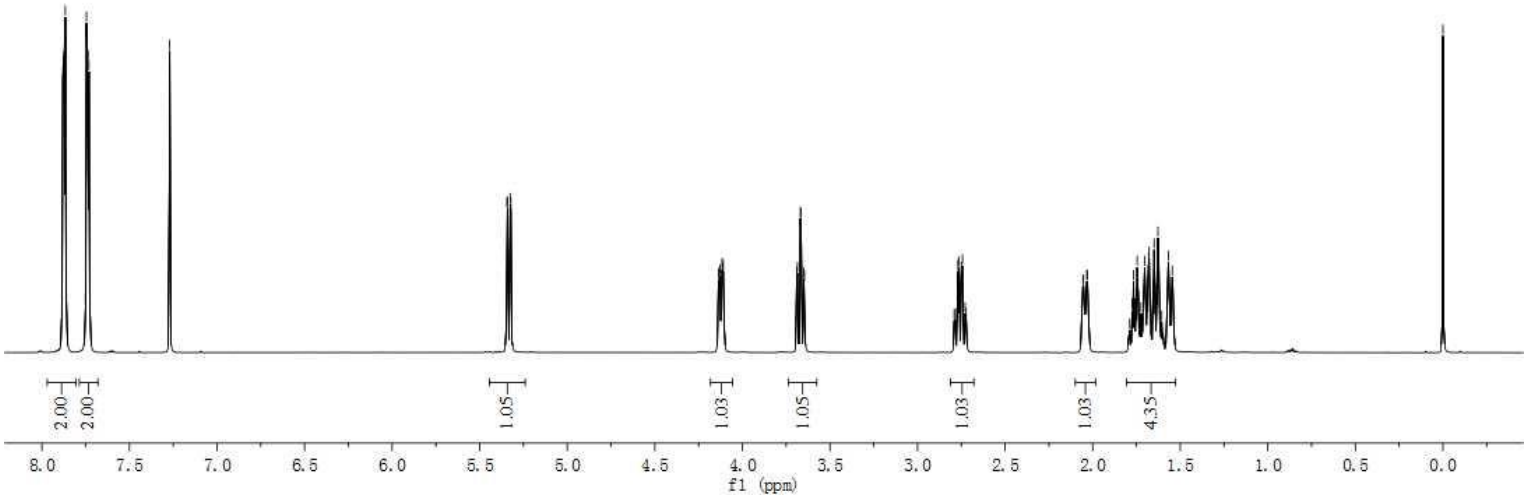
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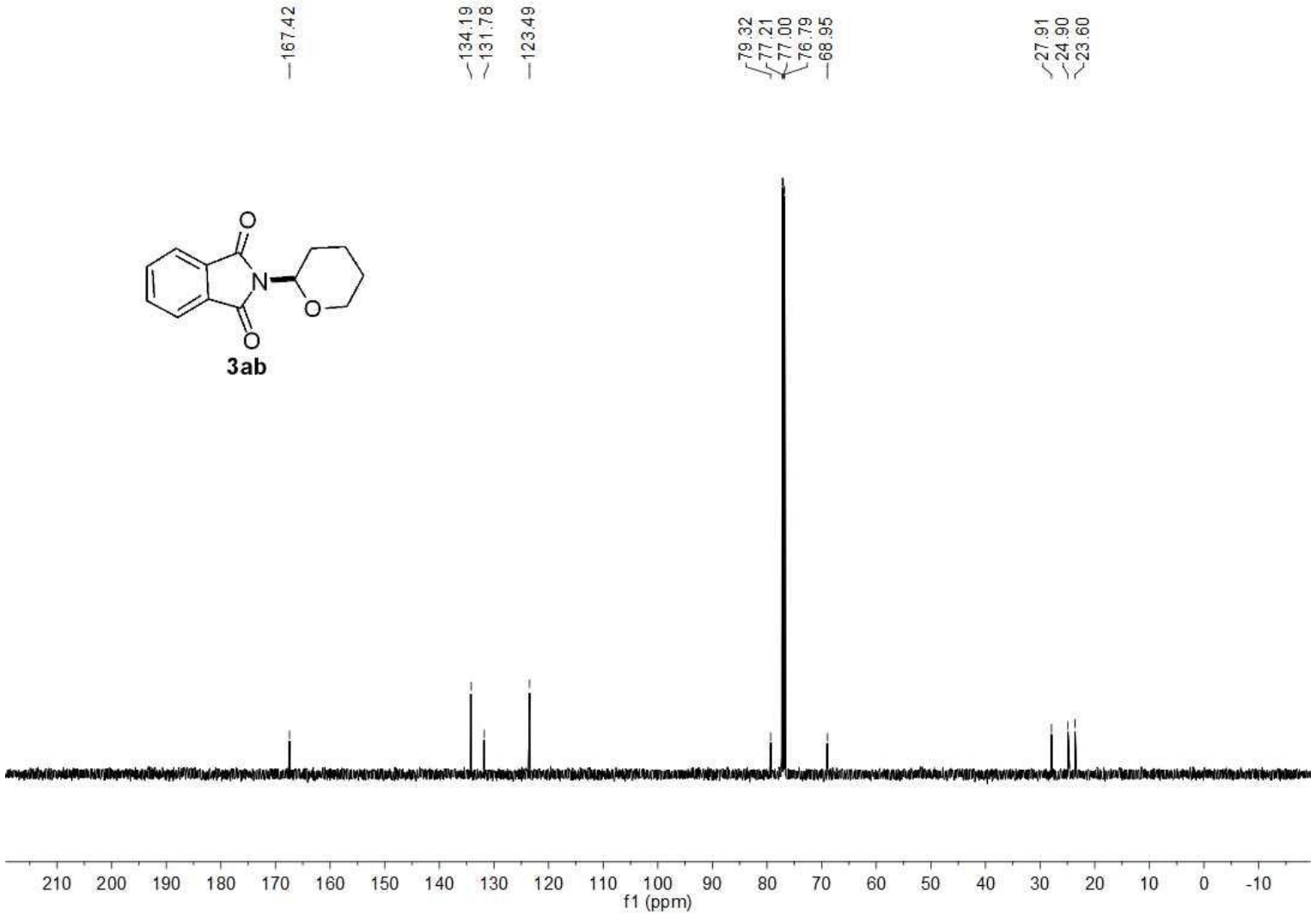
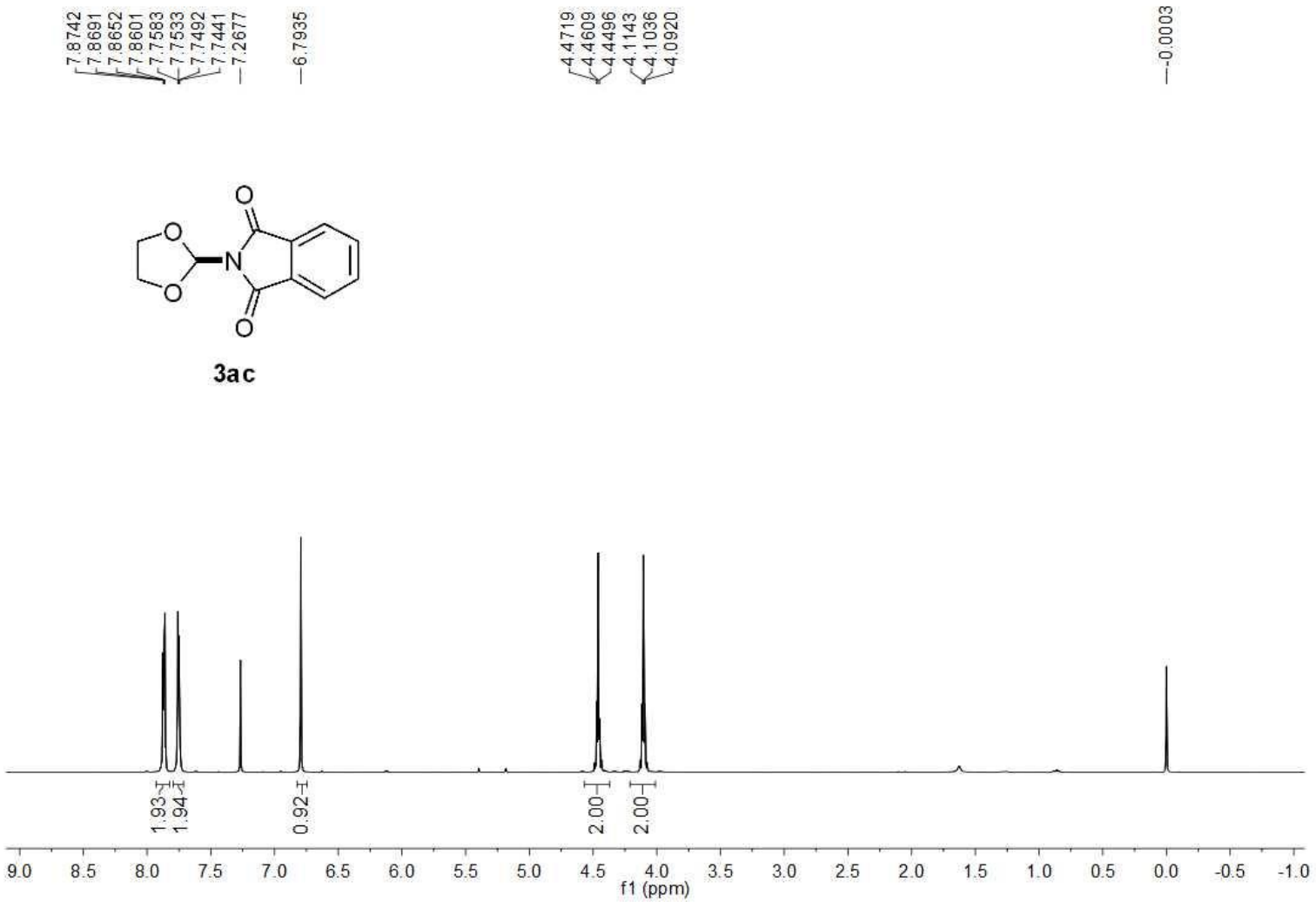
1.05
1.03
1.03
4.35
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


167.42
134.19
131.78
123.49
79.32
77.21
77.00
76.79
68.95
27.91
24.90
23.60
O
N
O
O
3ab
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.7441
7.2677
6.7935
4.4719
4.4609
4.4496
4.1143
4.1036
4.0920
0.0003
O
O
N
O
O
1.93
1.94
0.92
2.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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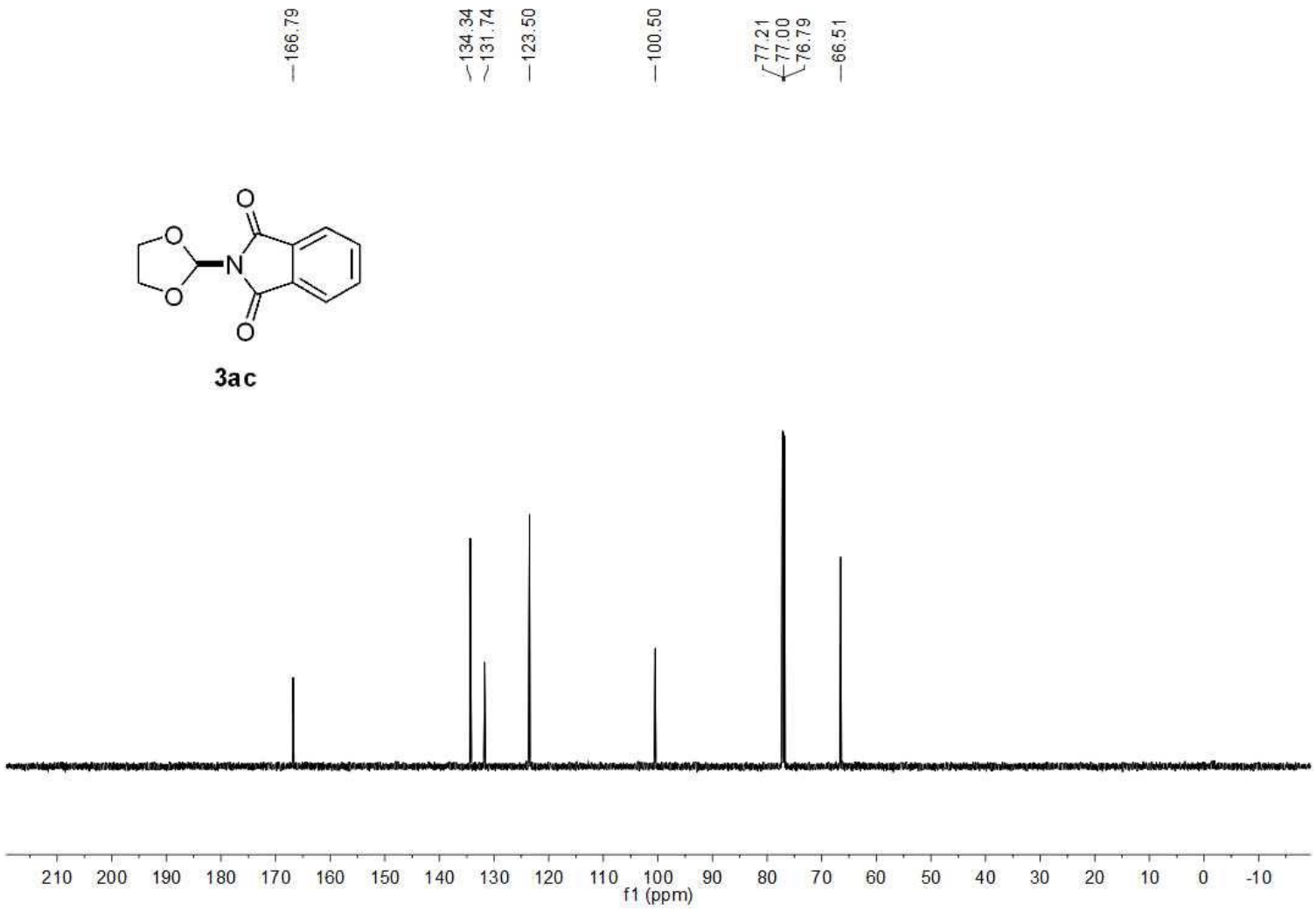
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

3ac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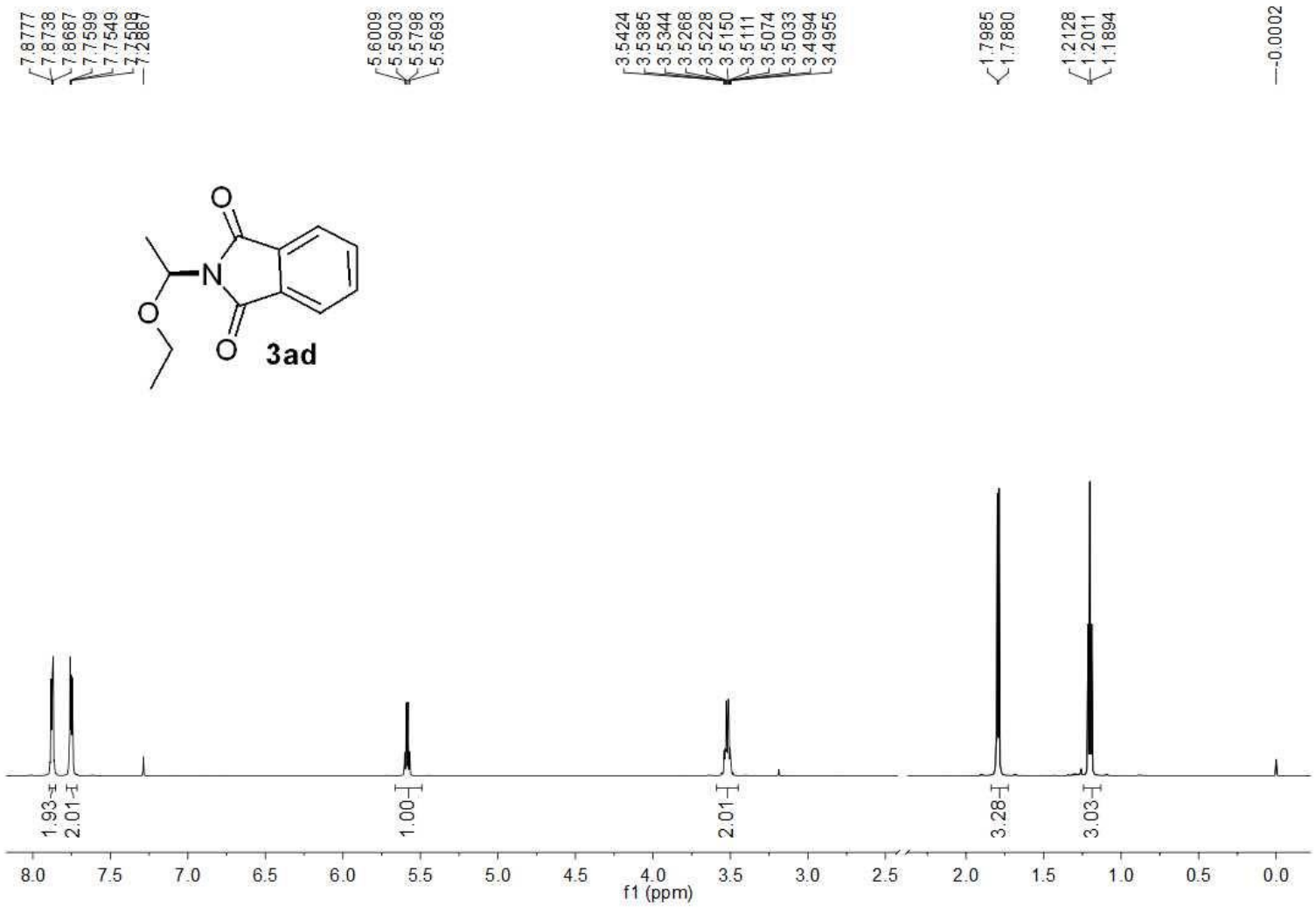
100.50
77.21
77.00
76.79
66.51
O
O
N
O
O
3ac
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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3.5385
3.5344
3.5268
3.5228
3.5150
3.5111
3.5074
3.5033
3.4994
3.4955
1.7985
1.7880
1.2128
1.2011
1.1894
-0.0002
O
N
O
O
O
3ad
1.93
2.01
1.00
2.01
3.28
3.03
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
2.0
1.5
1.0
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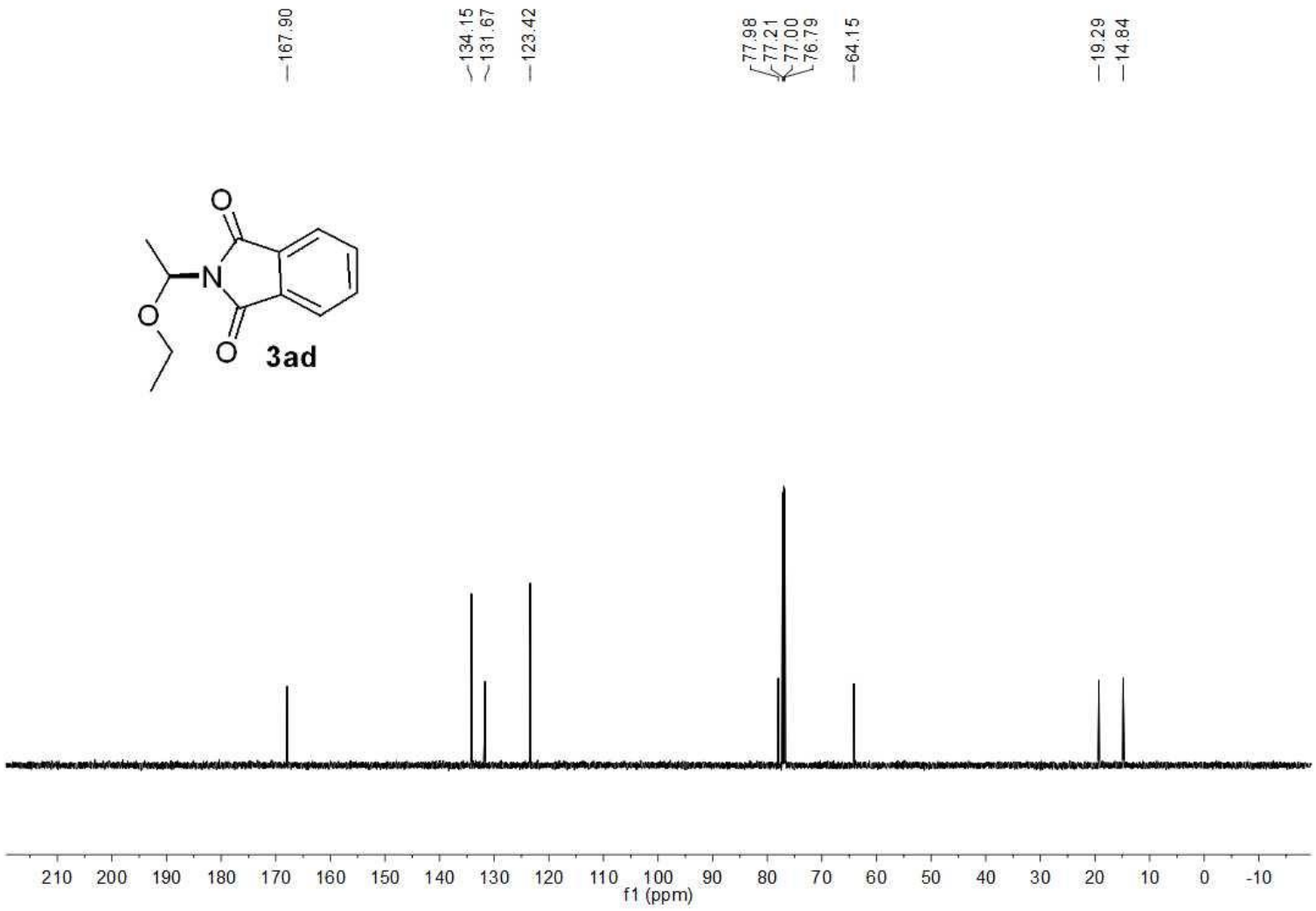
0.0
f1 (ppm)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77.21
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19.29
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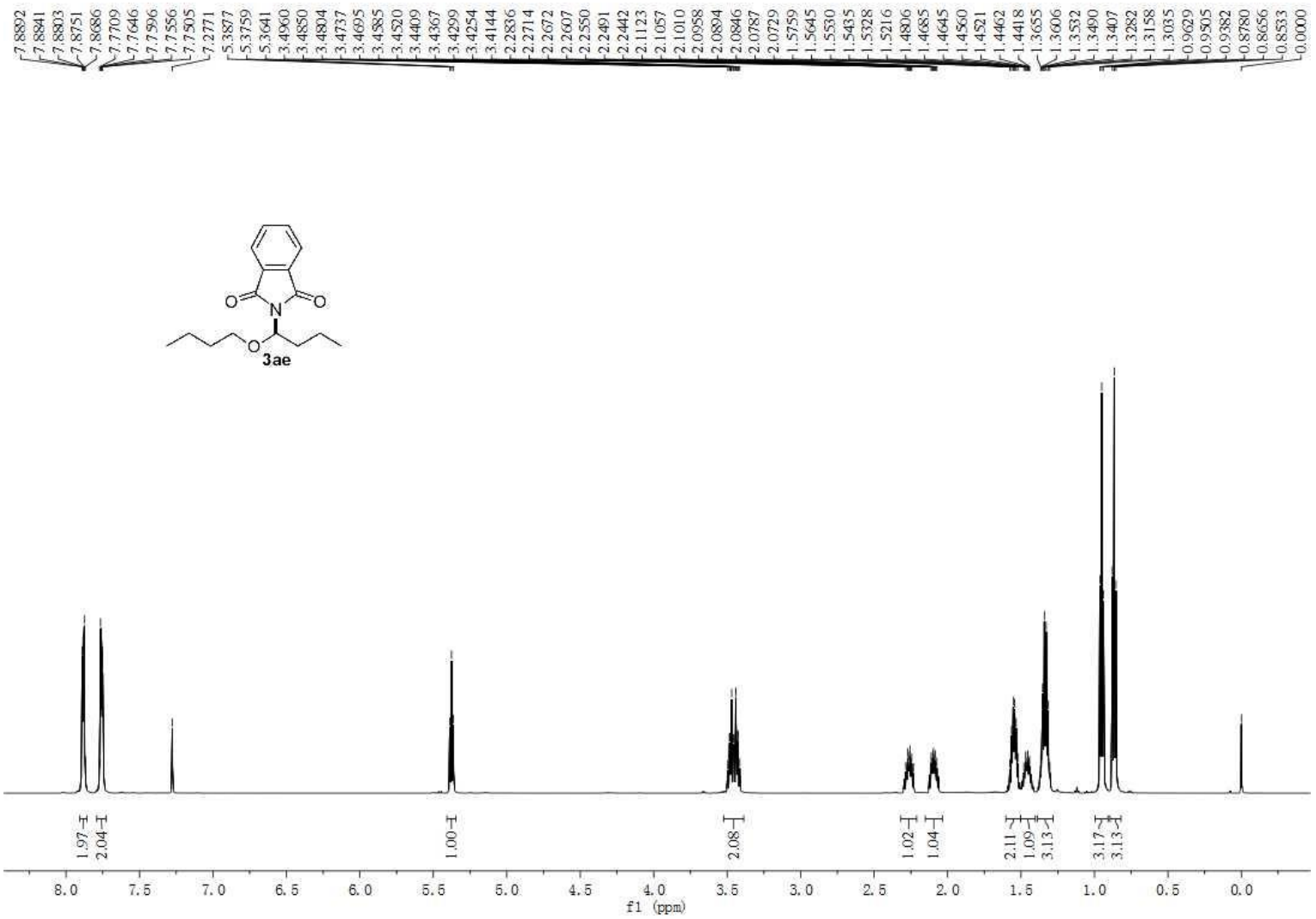
f1 (ppm)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7.7556
7.7505
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5.3887
5.3759
5.3641
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3.4850
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3.4737
3.4695
3.4585
3.4520
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3.4367
3.4299
3.4254
3.4144
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2.2672
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2.2550
2.2491
2.2442
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2.0729
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1.4418
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1.3490
1.3407
1.3282
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1.3035
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0.9505
0.9382
0.8780
0.8656
0.8533
0.0000
O
N
O
O
3ae
1.97
2.04
1.00
2.08
1.02
1.04
2.11
1.09
3.13
3.17
3.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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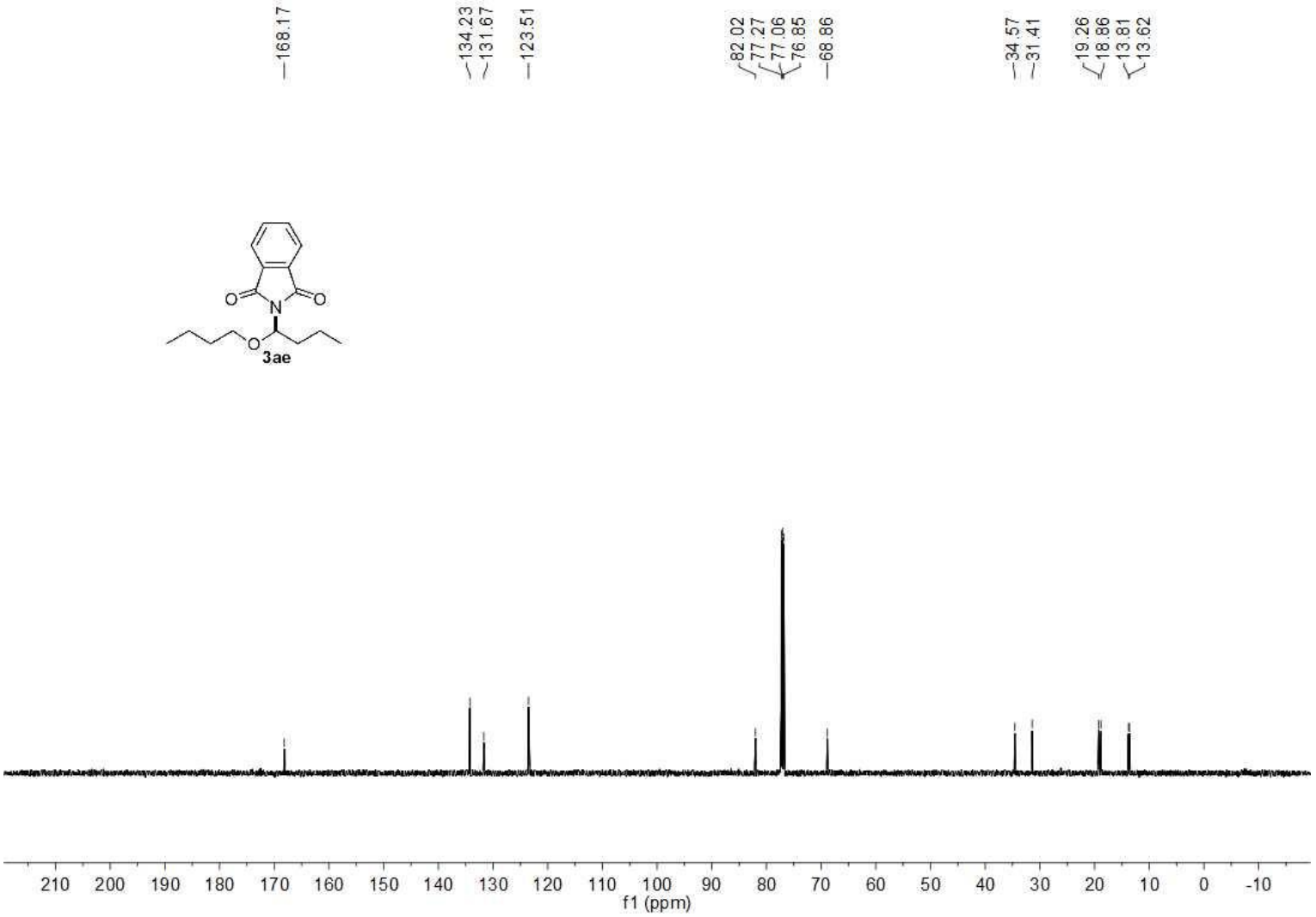
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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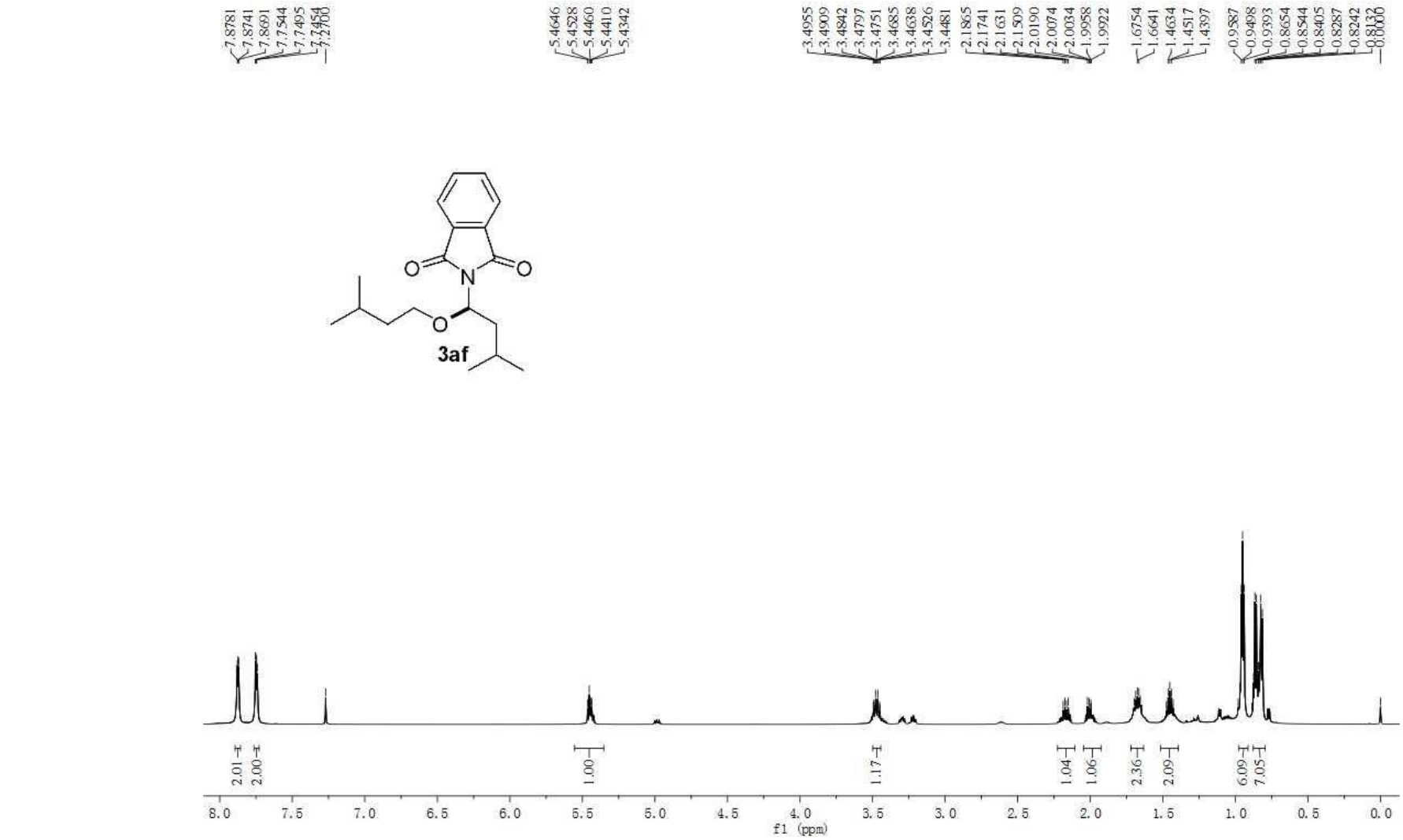
34.57
31.41
19.26
18.86
13.81
13.62
3ae
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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3.4638
3.4526
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2.1631
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2.0074
2.0034
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1.9922
1.6754
1.6641
1.4634
1.4517
1.4397
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0.9393
0.8654
0.8544
0.8405
0.8287
0.8242
0.8132
0.0000
O
N
O
O
3af
2.01
2.00
1.00
1.17
1.04
1.06
2.36
2.09
6.09
7.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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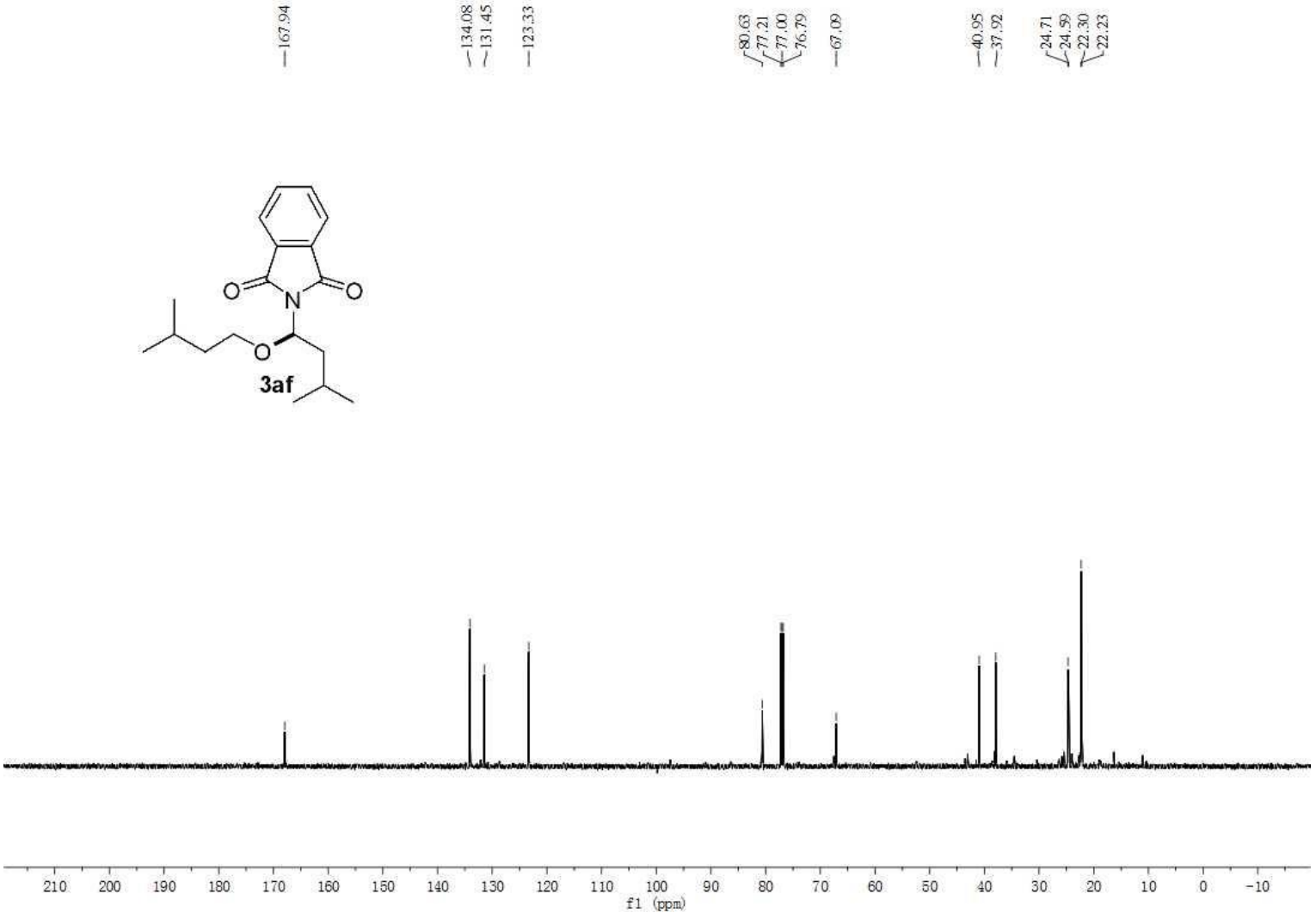
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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40.95
37.92
24.71
24.59
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22.23
O
N
O
O
3af
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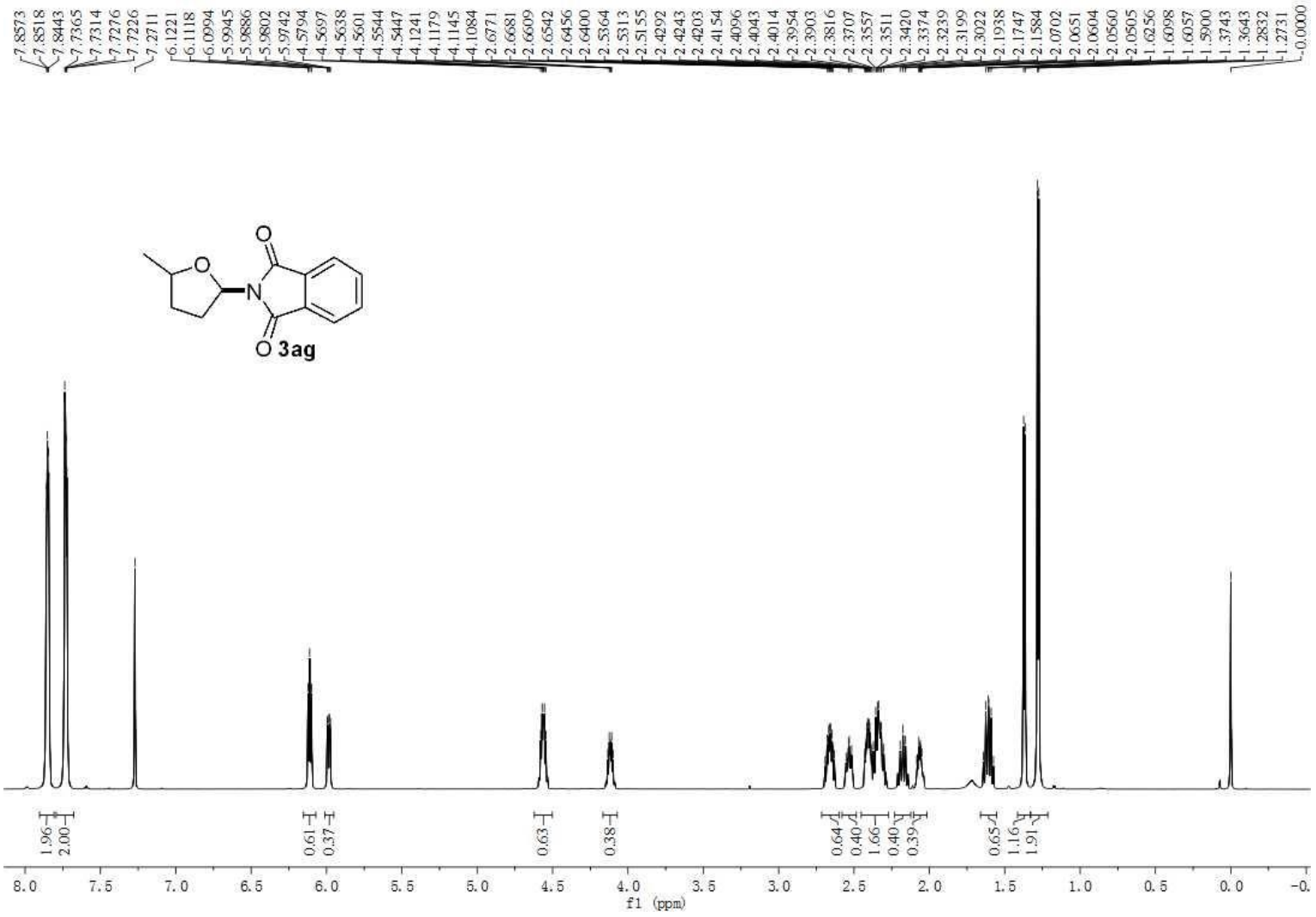
f1 (ppm)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5.9742
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4.5601
4.5544
4.5447
4.1241
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4.1145
4.1084
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2.6456
2.6400
2.5364
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2.4243
2.4203
2.4154
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2.4043
2.4014
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2.3903
2.3816
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2.3557
2.3511
2.3420
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2.3239
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2.3022
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1.6057
1.5900
1.3743
1.3643
1.2832
1.2731
0.0000
O
O
N
O
O
3ag
1.96
2.00
0.61
0.37
0.63
0.38
0.64
0.40
1.66
0.40
0.39
0.65
1.16
1.91
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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2.0
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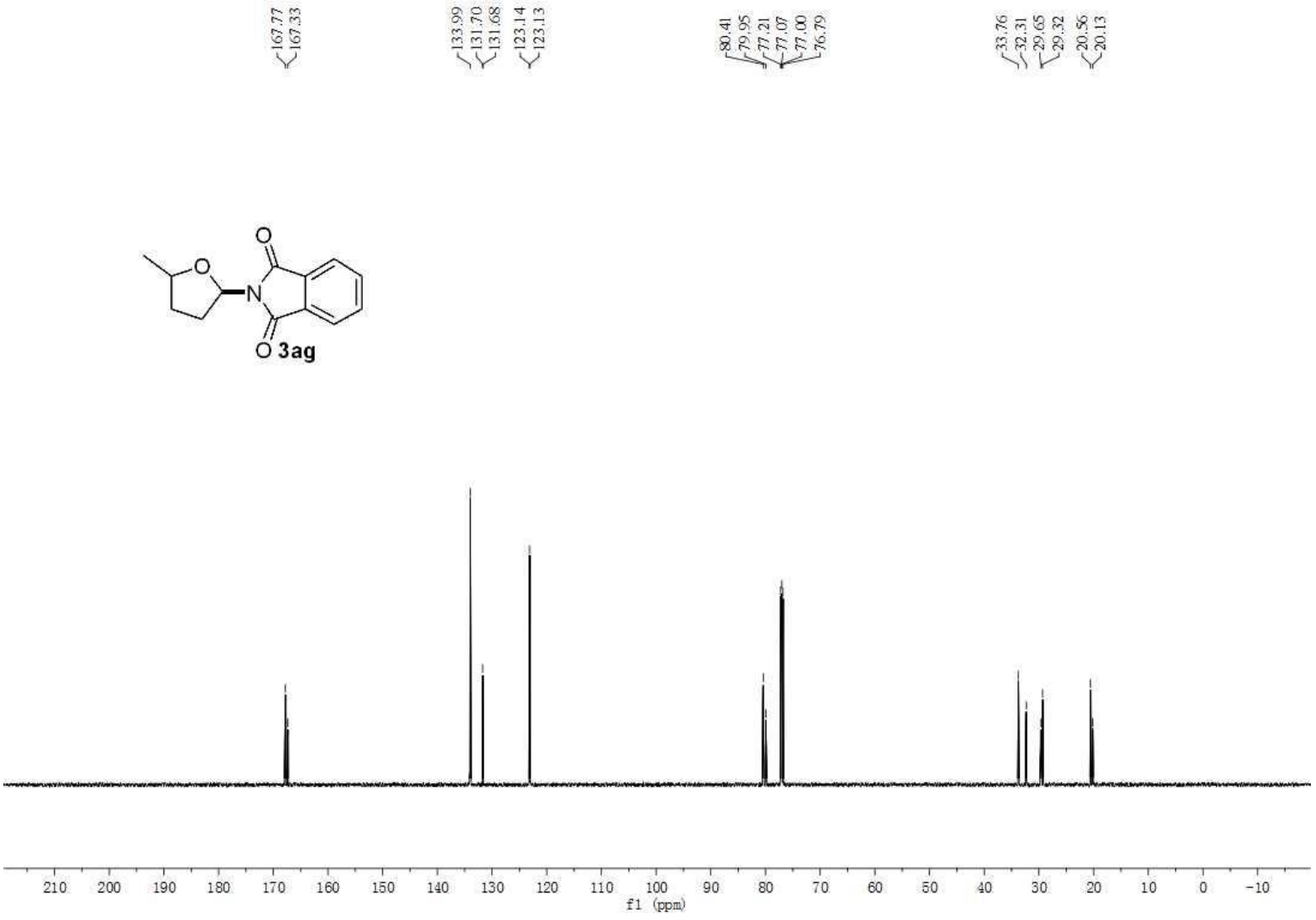
0.5
0.0
-0.
f1 (ppm)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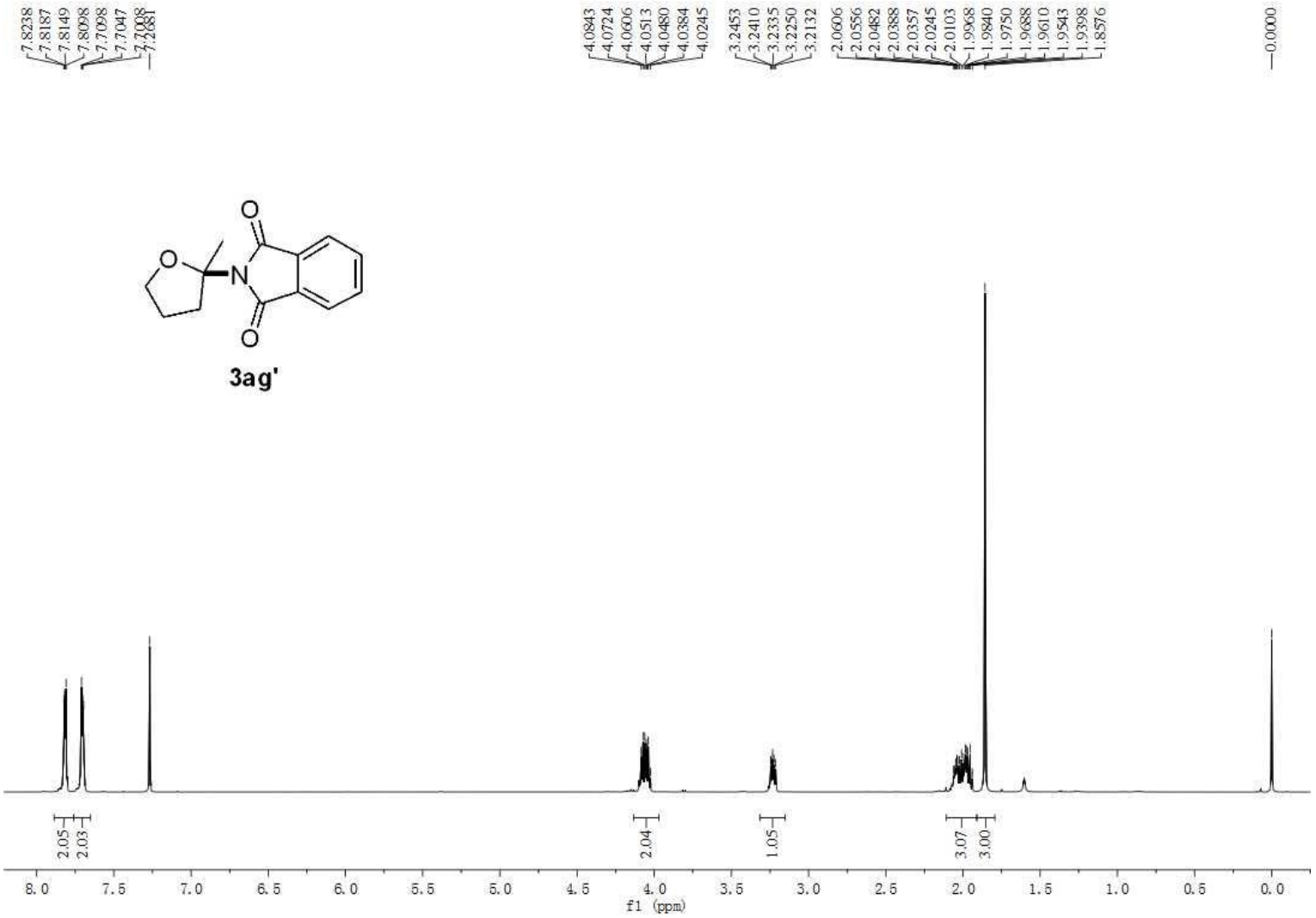
77.07
77.00
76.79
33.76
32.31
29.65
29.32
20.56
20.13
O
O
N
O
O
3ag
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)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4.0513
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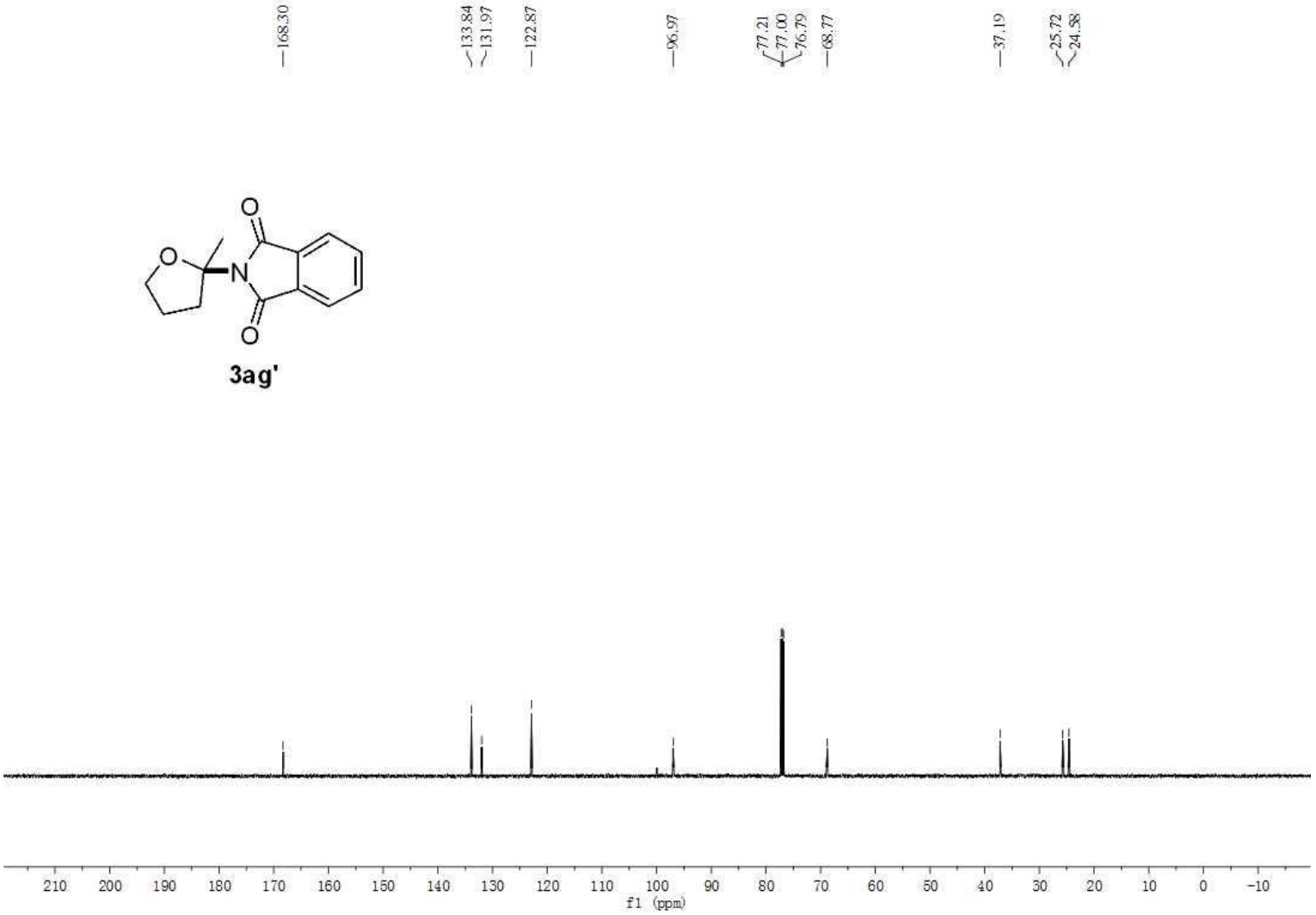
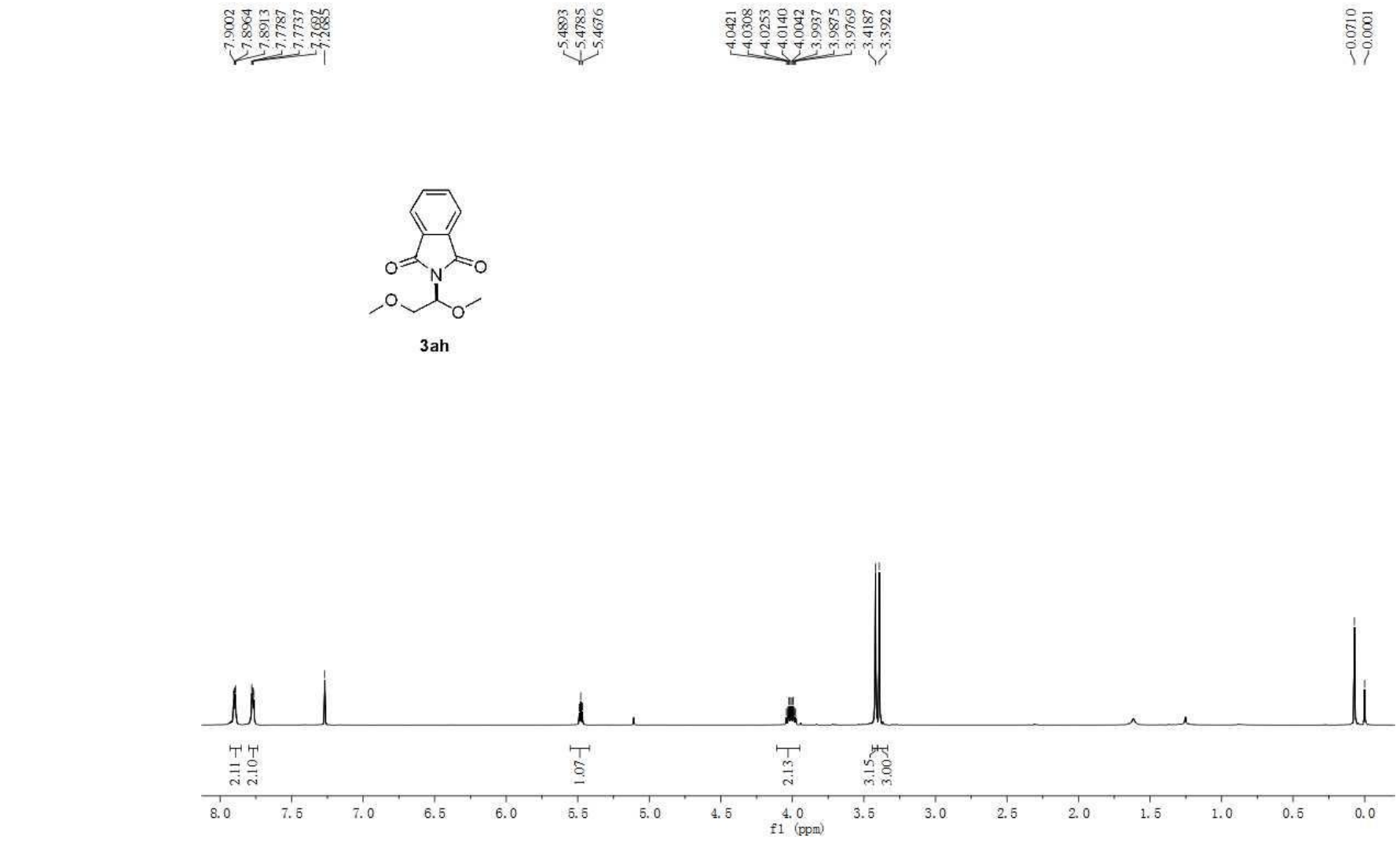
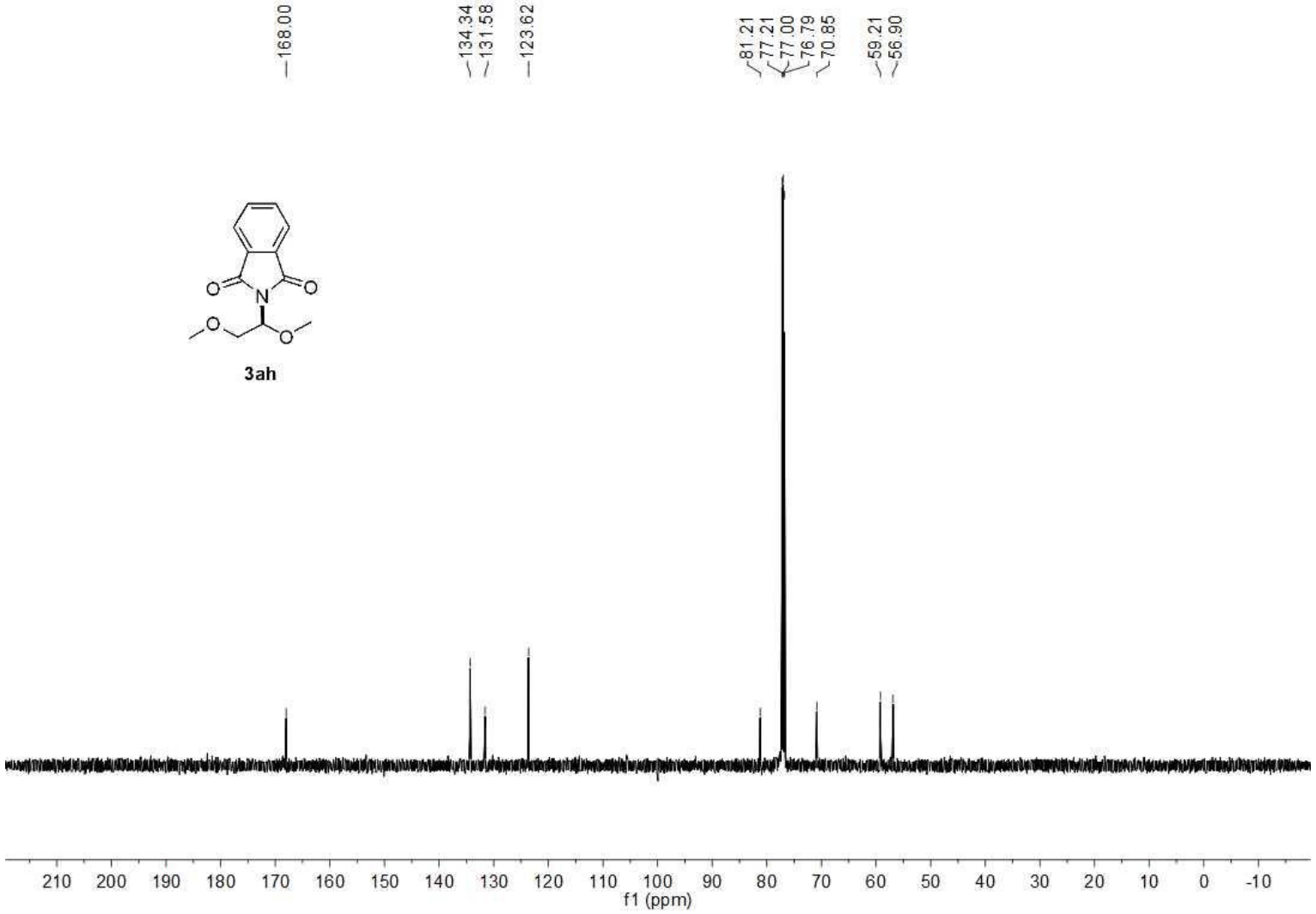
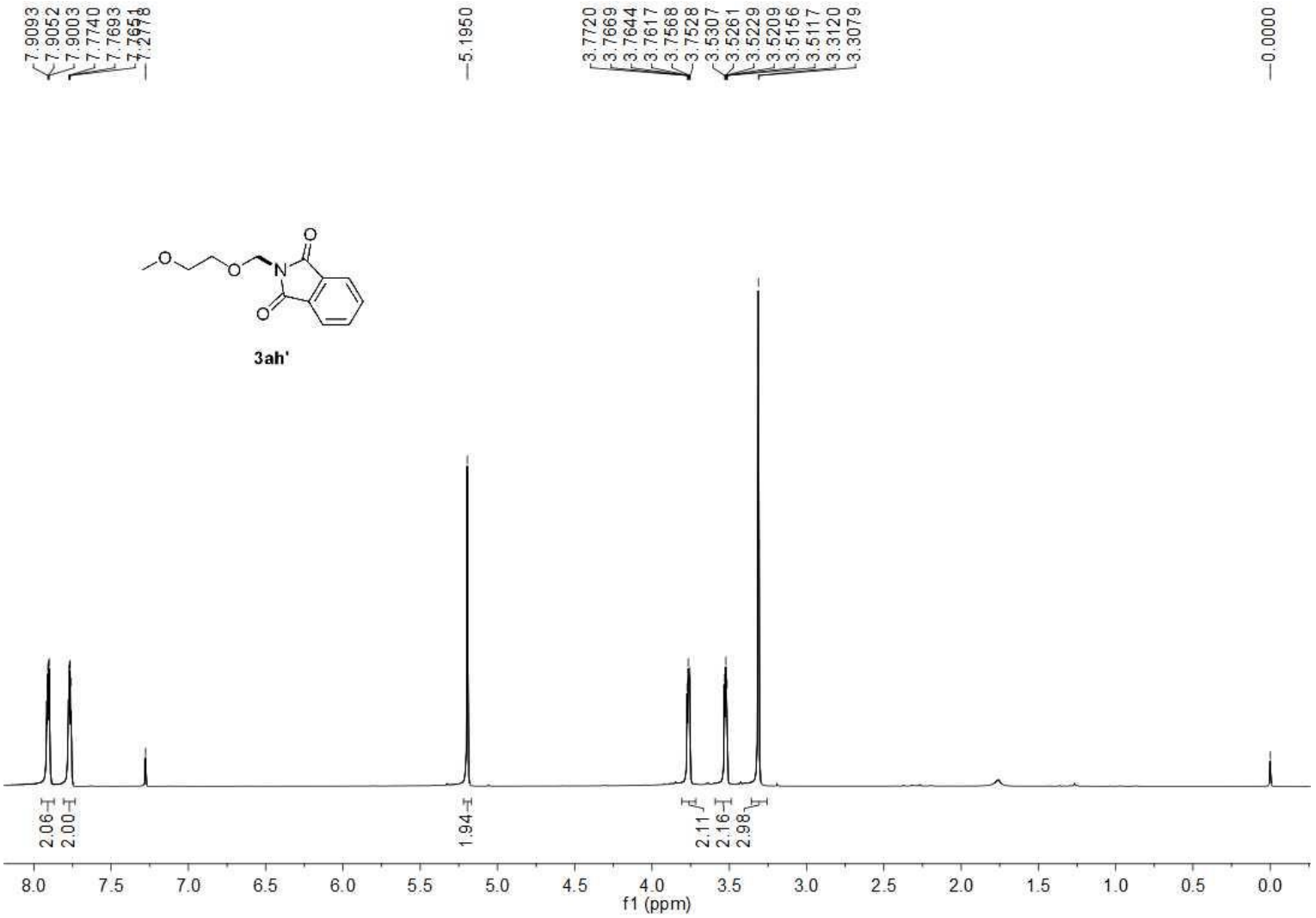
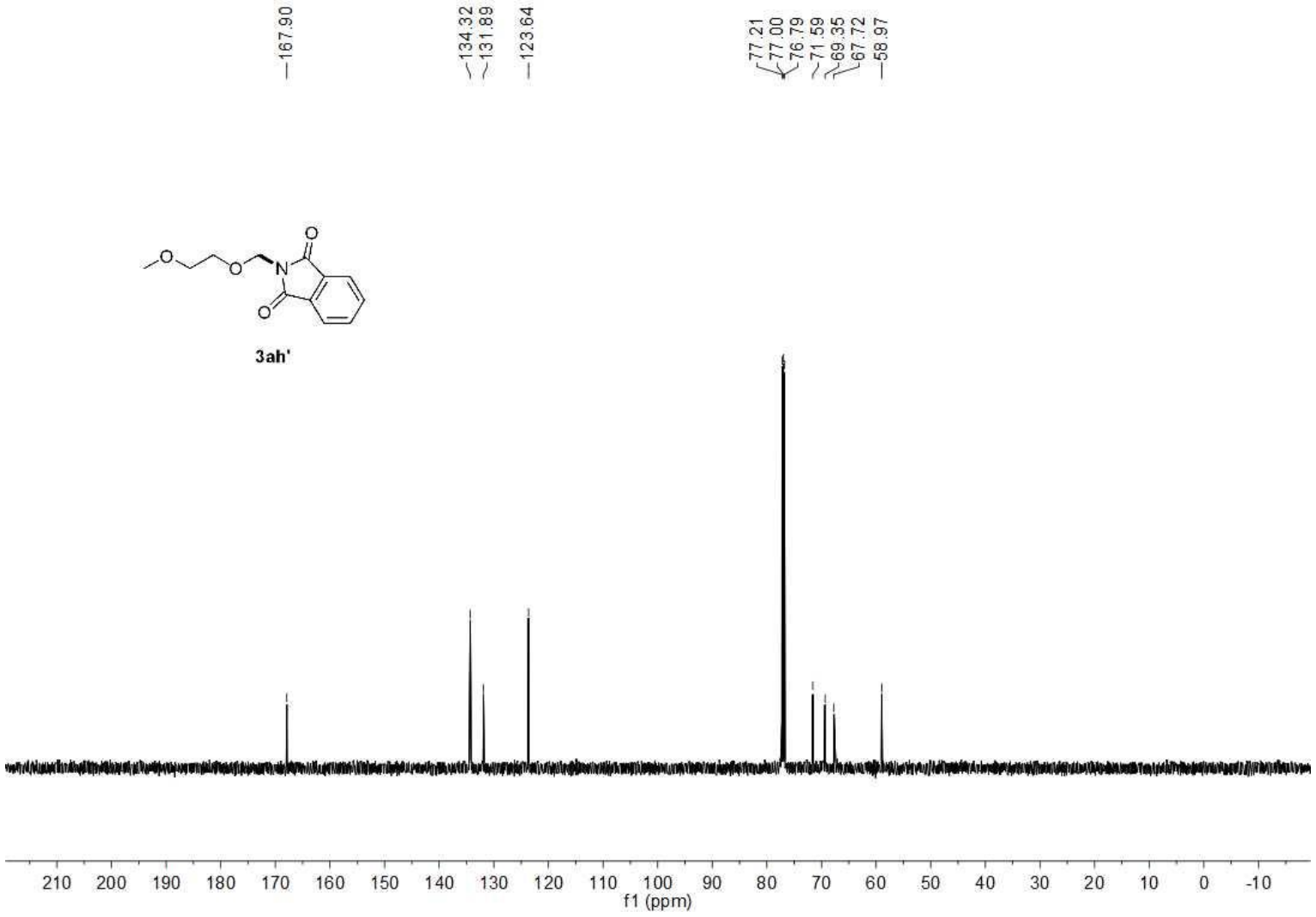
2.0556
2.0482
2.0388
2.0357
2.0245
2.0103
1.9968
1.9840
1.9750
1.9688
1.9610
1.9543
1.9398
1.8576
0.0000
O
O
N
O
3ag'
2.05
2.03
2.04
1.05
3.07
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

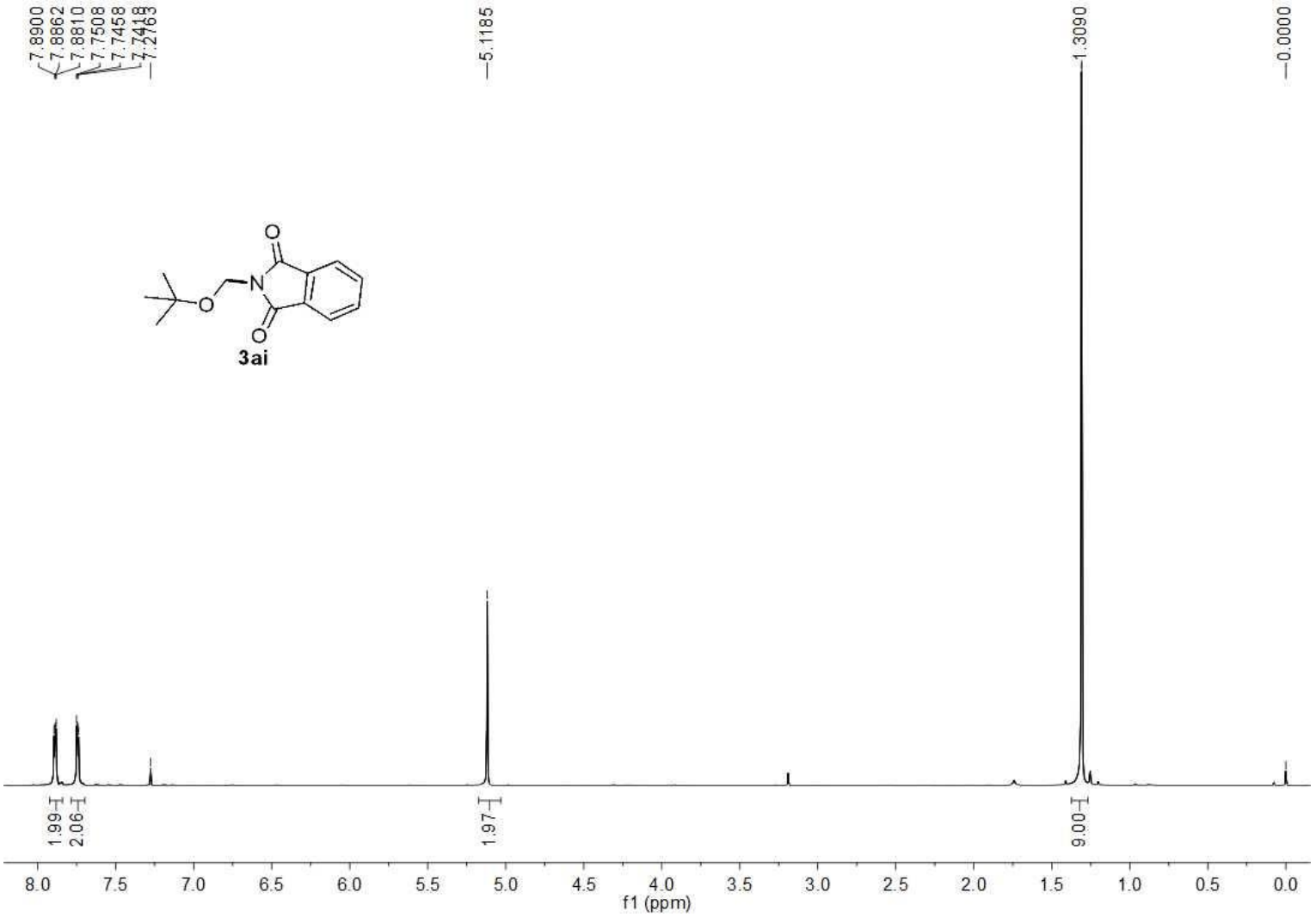

168.30
133.84
131.97
122.87
96.97
77.21
77.00
76.79
68.77
37.19
25.72
24.58
O
O
O
N
3ag'
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

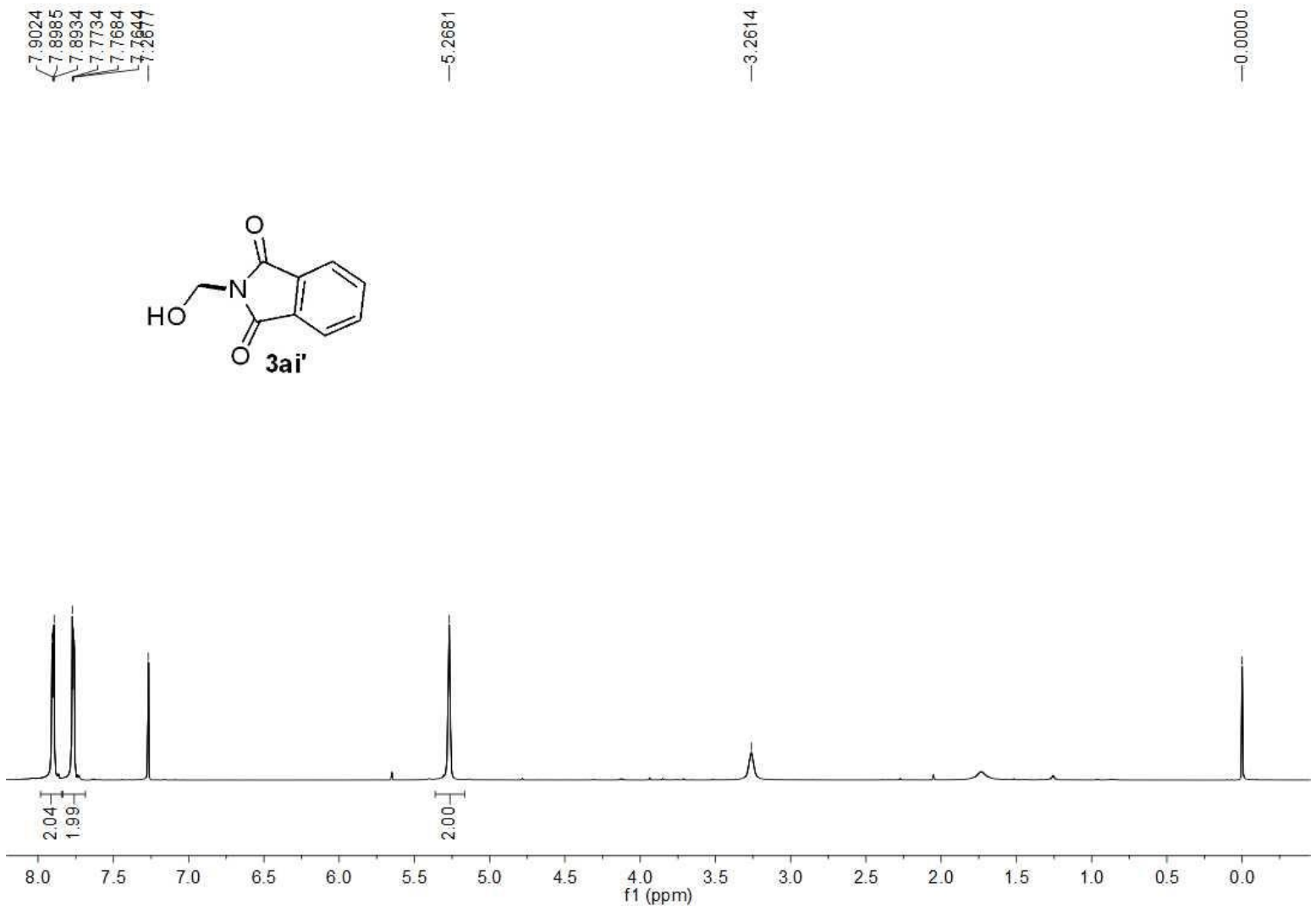

7.9002
7.8964
7.8913
7.7787
7.7737
5.4893
5.4785
5.4676
4.0421
4.0308
4.0253
4.0140
4.0042
3.9937
3.9875
3.9769
3.4187
3.3922
0.0710
0.0001
3ah
2.11
2.10
1.07
2.13
3.15
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

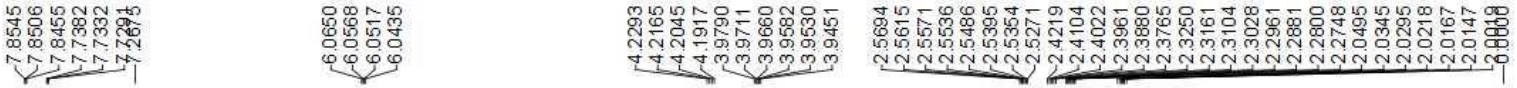

168.00
134.34
131.58
123.62
81.21
77.21
77.00
76.79
70.85
59.21
56.90
3ah
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

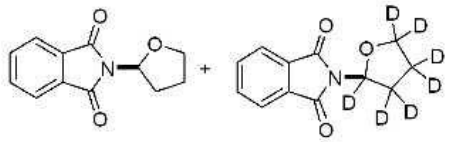

7.9093
7.9052
7.9003
7.7740
7.7693
5.1950
3.7720
3.7669
3.7644
3.7617
3.7568
3.7528
3.5307
3.5261
3.5229
3.5209
3.5156
3.5117
3.3120
3.3079
0.0000
3ah'
2.06
2.00
1.94
2.11
2.16
2.98
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


167.90
134.32
131.89
123.64
77.21
77.00
76.79
71.59
69.35
67.72
58.97
O
O
O
N
O
3ah'
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.8900
7.8862
7.8810
7.7508
7.7458
7.7418
7.2763
5.1185
1.3090
0.0000
3ai
1.99
2.06
1.97
9.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.9024
7.8985
7.8934
7.7734
7.7684
7.2677
5.2681
3.2614
0.0000
HO
N
O
O
3ai'
2.04
1.99
2.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)





3aa **[D_7]-3aa**

the ratio of **3aa**/**[D_7]-3aa** = 15.7 : **1**