Sterically-Controlled Intermolecular Friedel-Crafts Acylation with Twisted Amides via Selective N–C Cleavage under Mild Conditions

Yongmei Liu, Guangrong Meng, Ruzhang Liu, and Michal Szostak*

College of Chemistry and Chemical Engineering, Yangzhou University, 180 Siwangting Road, Yangzhou, Jiangsu 225002, China and Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States

michal.szostak@rutgers.edu

Electronic Supplementary Information

Table of Contents 1

Y. Liu, R. Liu
College of Chemistry and Chemical Engineering
Yangzhou University, 180 Siwangting Road, Yangzhou, Jiangsu 225002, China

Y. Liu, G. Meng, M. Szostak
Department of Chemistry, Rutgers University
73 Warren Street, Newark, NJ 07102, United States
Corresponding Author:
E-mail: michal.szostak@rutgers.edu

List of Known Compounds/General Methods

All starting materials reported in the manuscript have been previously described in literature and prepared by the method reported previously. Amides were prepared by standard methods.[1-14] All products reported in the manuscript have been previously described in literature.[15-26] All experiments were performed using standard Schlenk techniques under argon or nitrogen atmosphere unless stated otherwise. All solvents were purchased at the highest commercial grade and used as received or after purification by passing through activated alumina columns or distillation from sodium/benzophenone under nitrogen. All other chemicals were purchased at the highest commercial grade and used as received. Reaction glassware was oven-dried at 140 °C for at least 24 h or flame-dried prior to use, allowed to cool under vacuum and purged with argon or nitrogen (three cycles). All products were identified using ^{1}H NMR analysis and comparison with authentic samples. GC and/or GC/MS analysis was used for volatile products. All yields refer to yields determined by ^{1}H NMR and/or GC or GC/MS using an internal standard (optimization) and isolated yields (preparative runs) unless stated otherwise. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker spectrometers at 500 (^{1}H NMR) and 125 MHz (^{13}C NMR). All shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ peak (7.27 and 77.2 ppm, ^{1}H NMR and ^{13}C NMR, respectively). All coupling constants (J) are reported in hertz (Hz). Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; brs, broad singlet. GC-MS chromatography was performed using Agilent HP6890 GC System and Agilent 5973A inert XL EI/CI MSD using helium as the carrier gas at a flow rate of 1 mL/min and an initial oven temperature of 50 °C. The injector temperature was 280 °C. The detector temperature was 280 °C. For runs with the initial oven temperature of 50 °C, temperature was increased with a 10 °C/min ramp after 50 °C hold for 3 min to a final temperature of 280 °C, then hold at 280 °C for 10 min (splitless mode of injection, total run time of 33.00 min). All flash chromatography was performed using silica gel, 60 Å, 300 mesh. TLC analysis was carried out on glass plates coated with silica gel 60 F254, 0.2 mm thickness. The plates were visualized using a 254 nm ultraviolet lamp or aqueous potassium permanganate solutions. *^{1}H NMR, ^{13}C NMR, and MS data are given for all compounds in the Supporting Experimental for characterization purposes. ^{1}H NMR, ^{13}C NMR, MS and HRMS data are reported for all new compounds.*

Experimental Procedures and Characterization Data

General Procedure for Amide Synthesis. An oven-dried round-bottomed flask (100 mL) equipped with a stir bar was charged with amine (8.84 mmol, 1.0 equiv), triethylamine (typically, 2.0 equiv), 4-dimethylaminopyridine (typically, 0.25 equiv) and dichloromethane (typically, 50 mL), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acyl chloride (typically, 1.1 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred overnight at room temperature. After the indicated time, the reaction mixture was diluted with Et_2O (20 mL) and filtered. The organic layer was washed with HCl (1.0 *N*, 30 mL), brine (30 mL), dried, and concentrated. Unless stated otherwise, the crude product was purified by recrystallization (toluene) to give analytically pure product.

General Procedure for Friedel-Crafts Acylation. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), placed under a positive pressure of nitrogen, and subjected to three evacuation/backfilling cycles. Solvent (typically, 0.10 M), and trifluoromethanesulfonic acid (typically, 3.0 equiv) were sequentially added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for an indicated time. After the indicated time, the reaction mixture was diluted with saturated $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 20 mL), the organic layers were combined, dried, filtered, and concentrated. A sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Unless stated otherwise, purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

Representative Procedure for Friedel-Craft Acylation. An oven-dried vial equipped with a stir bar was charged with benzoylpiperidine-2,6-dione (0.217 g, 1.0 mmol, 1.0 equiv), placed under a positive pressure of nitrogen, and subjected to three evacuation/backfilling cycles. Benzene (0.10 M) and trifluoromethanesulfonic acid (0.27 mL, 3.0 mmol, 3.0 equiv) were added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with saturated $NaHCO_3$, extracted

with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated. A sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product (0.143 g). White solid. Characterization data are included in the section below.

Characterization Data for Starting Materials

All starting materials have been previously reported.[15-17] Spectroscopic data matched literature values.

Benzoylpiperidine-2,6-dione (1a).[15] White solid. GC: rt = 17.94 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (q, *J* = 6.5 Hz, 2 H), 2.80 (t, *J* = 6.6 Hz, 4 H), 7.52 (t, *J* = 7.7 Hz, 2 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 7.89 (d, *J* = 7.8 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.51, 32.41, 129.14, 130.16, 131.78, 134.97, 170.74, 171.90. MS= 217.1 (EI).

1-Benzoylpyrrolidine-2,5-dione (1b).[15] White solid. GC: rt = 16.90 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (s, 4 H), 7.53 (t, *J* = 7.8 Hz, 2 H), 7.69 (t, *J* = 7.5 Hz, 1 H), 7.88 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.08, 128.97, 130.53, 131.40, 135.15, 167.62, 174.54. MS = 203.1 (EI).

***N*-Methyl-*N*-phenylbenzamide (1c).**[16] Oil. GC: rt = 15.80 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.52 (s, 3 H), 7.06 (d, *J* = 7.5 Hz, 2 H), 7.17 (dd, *J* = 12.4, 7.5 Hz, 3 H), 7.21-7.27 (m, 3 H), 7.32 (d, *J* = 7.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.41, 126.48, 126.91, 127.72, 128.72, 129.14, 129.58, 135.94, 144.93, 170.68. MS = 211.1 (EI).

***tert*-Butyl benzoyl(benzyl)carbamate (1d).**[16] Oil. GC: rt = 19.66 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 9 H), 5.02 (s, 2 H), 7.29 (d, *J* = 9.6 Hz, 1 H), 7.36 (t, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.48 (dd, *J* = 18.6, 7.5 Hz, 3 H), 7.54 (d, *J* = 7.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.35, 48.88, 83.18, 127.40, 127.46, 128.06, 128.16, 128.45, 131.04, 137.73, 137.86, 153.46, 173.09. MS = 311.1 (EI).

***N*-Phenyl-*N*-tosylbenzamide (1e).**[17] Yellow solid**.** GC: rt = 22.09 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 7.19 (t, *J* = 7.9 Hz, 4 H), 7.30 (d, *J* = 5.1 Hz, 4 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 7.46 (d, *J* = 7.4 Hz, 2 H), 7.86 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.73, 127.98, 128.60, 129.03, 129.10, 129.25, 129.48, 130.40, 131.74, 133.67, 135.25, 137.43, 144.81, 169.90. MS = 351.1 (EI).

***N*-Methoxy-*N*-methylbenzamide (1f).**[15] Oil. GC: rt = 10.67 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (s, 3 H), 3.55 (s, 3 H), 7.42-7.37 (m, 2 H), 7.45-7.43 (m, 1 H), 7.68 (dt, *J* = 7.0, 1.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.79, 61.01, 128.00, 128.10, 130.55, 134.09, 169.94. MS = 165.1 (EI).

(2-Methylaziridin-1-yl)(phenyl)methanone (1g).[15] Oil. GC: rt = 10.49 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (d, *J* = 5.4 Hz, 3 H), 2.17 (d, *J* = 3.6 Hz, 1 H), 2.66-2.54 (m, 2 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 7.57 (td, *J* = 7.2, 1.5 Hz, 1 H), 8.08-8.02 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.79, 32.14, 34.61, 128.40, 129.05, 132.62, 133.54, 179.30. MS = 161.1 (EI).

Azetidin-1-yl(phenyl)methanone (1h).[15] Oil. GC: rt = 13.71 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41-2.25 (m, 2 H), 4.26 (dt, *J* = 15.0, 7.8 Hz, 4 H), 7.51-7.35 (m, 3 H), 7.68-7.57 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.03, 30.92, 127.78, 128.31, 130.82, 133.26, 170.24. MS = 161.1 (EI).

1-(4-Methylbenzoyl)piperidine-2,6-dione (1i).[17] White solid. GC: rt = 19.26 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (p, *J* = 6.6 Hz, 2 H), 2.79 (t, *J* = 6.6 Hz, 4 H), 2.45 (s, 3 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.78 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.52, 21.89, 32.42, 129.24, 129.87, 130.32, 146.32, 170.39, 171.87. MS = 231.1 (EI).

1-(4-Methoxybenzoyl)piperidine-2,6-dione (1j).[15] White solid. GC: rt = 20.72 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (p, *J* = 6.6 Hz, 2 H), 2.78 (t, *J* = 6.6 Hz, 4 H), 3.90 (s, 3 H), 6.99-6.94 (d, *J* = 7.5 Hz, 2 H), 7.87-7.82 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.52, 32.45, 55.69, 114.49, 124.51, 132.75, 165.09, 169.48, 171.88. MS =247.1 (EI).

1-(4-(Trifluoromethyl)benzoyl)piperidine-2,6-dione (1k).[15] White solid. GC: rt = 17.11 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20 (q, *J* = 6.6 Hz, 2 H), 2.83 (t, *J* = 6.5 Hz, 4 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 8.00 (d, *J* = 8.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.27 (q, J^1 = 272.4 Hz), 126.21 (q, J^3 = 3.5 Hz), 130.36, 134.80, 135.93 (q, J^2 = 36.7 Hz), 170.17, 171.97. ^{19}F (471 MHz, $CDCl_3$) δ -63.4. MS = 285.1 (EI).

1-(4-Fluorobenzoyl)piperidine-2,6-dione (1l).[15] White solid. GC: rt = 11.90 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (p, *J* = 6.5 Hz, 2 H), 2.79 (t, *J* = 6.5 Hz, 4 H), 7.18 (t, *J* = 8.4 Hz, 2 H), 7.91 (dd, *J* = 8.5, 5.2 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.46, 32.37, 116.52 (d, J^2 = 22.1 Hz), 128.30 (d, J^4 = 2.7 Hz), 133.01 (d, J^3 = 10.2 Hz), 166.84 (d, J^1 = 258.4 Hz), 169.59, 171.94. ^{19}F (471 MHz, $CDCl_3$) δ -101.31. MS = 235.1 (EI).

1-(4-Chlorobenzoyl)piperidine-2,6-dione (1m).[15] White solid. GC: rt = 19.33 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (p, *J* = 6.6 Hz, 2 H), 2.80 (t, *J* = 6.5 Hz, 4 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 7.81 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.47, 32.40, 129.55, 130.31, 131.44, 141.68, 169.89, 171.91. MS = 251.0 (EI).

1-(4-Bromobenzoyl)piperidine-2,6-dione (1n).[17] White solid. GC: rt = 20.31 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (p, *J* = 6.6 Hz, 2 H), 2.80 (t, *J* = 6.5 Hz, 4 H), 7.66 (d, *J* = 8.6 Hz, 2 H), 7.74 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.47, 32.39, 130.51, 130.76, 131.45, 132.55, 170.12, 171.85. MS = 295.0 (EI).

1-(2-Fluorobenzoyl)piperidine-2,6-dione (1o).[15] White solid. GC: rt = 17.76 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (p, *J* = 6.6 Hz, 2 H), 2.76 (t, *J* = 6.5 Hz, 4 H), 7.13 (ddd, *J* = 12.0, 8.4, 1.1 Hz, 1 H), 7.36-7.30 (m, 1 H), 7.63 (dddd, *J* = 8.3, 7.1, 5.0, 1.8 Hz, 1 H), 8.11 (td, *J* = 7.8, 1.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.24, 32.41, 117.08 (d, J^2 = 23.6 Hz), 120.36 (d, J^3 = 7.0 Hz), 125.09 (d, J^4 = 3.6 Hz), 132.95, 136.79 (d, J^3 = 10.0 Hz), 161.79 (d, J^1 = 255.9 Hz), 166.86, 171.68. ^{19}F NMR (471 MHz, $CDCl_3$) δ -113.49. MS = 235.1 (EI).

Methyl 4-(2,6-dioxopiperidine-1-carbonyl)benzoate (1p).[16] White solid. GC: rt = 21.52 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (q, *J* = 6.5 Hz, 2 H), 2.81 (q, *J* = 6.5 Hz, 4 H), 3.98 (s, 3 H), 7.94 (d, *J* = 8.2 Hz, 2 H), 8.16 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.47, 32.40, 52.64, 129.58, 129.95, 130.21, 135.42, 165.75, 170.38, 171.90. MS = 275.1 (EI).

1-(3,4-Difluorobenzoyl)piperidine-2,6-dione (1q).[16] White solid. GC: rt = 17.02 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14-2.23 (m, 2 H), 2.81 (t, *J* = 5.7 Hz, 4 H), 7.32 (t, *J* = 9.0 Hz, 1 H), 7.66 (s, 1 H), 7.72 (t, *J* = 8.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.43, 32.36,

118.25 (J^2 = 17.5 Hz), 119.43 (J^2 = 18.8 Hz), 127.37, 129.08, 150.73 (J^1 = 237.5 Hz), 154.87 (J^1 = 243.8 Hz), 168.94, 171.86. ^{19}F NMR (471 MHz, $CDCl_3$) δ = -125.85, -134.81. MS = 253.1 (EI).

1-(2-Naphthoyl)piperidine-2,6-dione (1r).[15] White solid. GC: rt = 23.08 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (p, *J* = 6.6 Hz, 2 H), 2.85 (t, *J* = 6.5 Hz, 4 H), 7.59 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1 H), 7.66 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.99-7.93 (m, 3 H), 8.37 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.57, 32.50, 124.75, 127.17, 127.91, 129.20, 129.51, 129.83, 132.45, 132.65, 136.42, 170.89, 172.02. MS = 267.1 (EI).

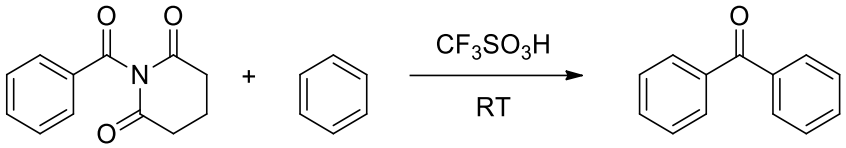
1-(Benzo[*d*][1,3]dioxole-5-carbonyl)piperidine-2,6-dione (1s).[16] White solid. GC: rt = 21.77 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (p, *J* = 6.5 Hz, 2 H), 2.79 (t, *J* = 6.5 Hz, 4 H), 6.11 (s, 2 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 7.36 (s, 1 H), 7.46 (d, *J* = 8.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.49, 32.43, 102.39, 108.55, 109.60, 126.25, 127.29, 148.62, 153.60, 169.22, 171.83. MS = 261.1 (EI).

1-(Thiophene-2-carbonyl)piperidine-2,6-dione (1t).[16] White solid. GC: rt = 18.14 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (p, *J* = 6.6 Hz, 2 H), 2.79 (t, *J* = 6.6 Hz, 4 H), 7.39 (dd, *J* = 5.3, 2.9 Hz, 1 H), 7.50 (d, *J* = 5.2 Hz, 1 H), 8.08 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.50, 32.43, 127.43, 127.77, 136.39, 136.54, 164.49, 171.73. MS = 223.0 (EI).

1-(Cyclohexanecarbonyl)piperidine-2,6-dione (1u).[16] White solid. GC: rt = 16.95 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19-1.32 (m, 3 H), 1.49 (qd, *J* = 11.9, 3.4 Hz, 2 H), 1.64-1.70 (m, 1 H), 1.84 (q, *J* = 3.4 Hz, 2 H), 1.97-2.08 (m, 4 H), 2.62 (dq, *J* = 13.2, 3.5 Hz, 1 H), 2.68 (t, *J* = 6.6 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.39, 25.37, 25.56, 28.05, 32.37, 48.73, 171.84, 180.84. MS = 223.1 (EI).

Friedel-Crafts Reactions of Amides: Twist Angle Optimization (Scheme 1)

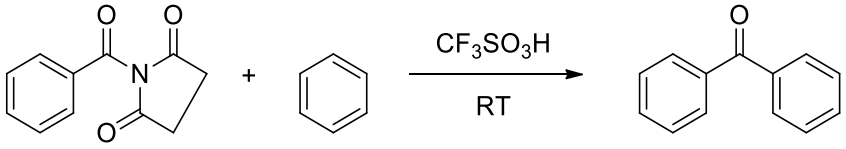
1-Benzoylpiperidine-2,6-dione (Scheme 1, Entry 1)



1a **2a** **3a**

According to the general procedure, 1-benzoylpiperidine-2,6-dione (0.20 mmol) was reacted with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h. After the standard work-up as described above, the sample was analyzed by ^{1}H NMR and GC-MS to obtain conversion and yield using internal standard: conversion >98%; yield of **3a** >90%, indicating high reactivity of amides **1a** in Friedel-Crafts acylation under these conditions.

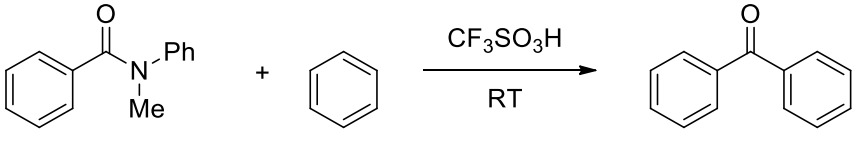
1-Benzoylpyrrolidine-2,5-dione (Scheme 1, Entry 2)



1b **2a** **3a**

According to the general procedure, 1-benzoylpyrrolidine-2,5-dione (0.20 mmol) was reacted with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h. After the standard work-up as described above, the sample was analyzed by ^{1}H NMR and GC-MS to obtain conversion and yield using internal standard: conversion >98%; yield of **3a** 68%, indicating high reactivity of amides **1b** in the Friedel-Craft reaction under these conditions.

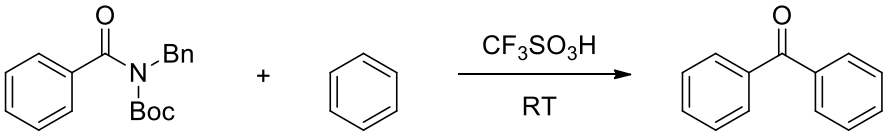
***N*-Methyl-*N*-phenylbenzamide** (Scheme 1, Entry 3)



1c **2a** **3a**

According to the general procedure, *N*-methyl-*N*-phenylbenzamide (0.20 mmol) was reacted with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h. After the standard work-up as described above, the sample was analyzed by ^{1}H NMR and GC-MS to obtain conversion and yield using internal standard: conversion <5.0%; yield of **3a** <5.0%. At this stage, further optimization of Friedel-Crafts acylation of amides **1c** was not performed.

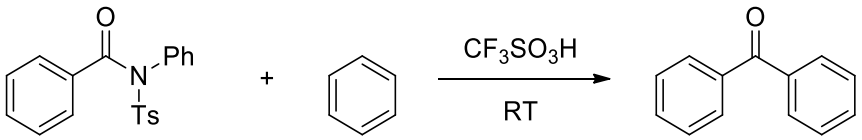
***tert*-Butyl benzoyl(benzyl)carbamate** (Scheme 1, Entry 4)



1d **2a** **3a**

According to the general procedure, *tert*-butyl benzoyl(benzyl)carbamate (0.20 mmol) was reacted with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature overnight. After the standard work-up as described above, the sample was analyzed by ^{1}H NMR and GC-MS to obtain conversion and yield using internal standard: conversion >95.0%; yield of **3a** <5.0%. At this stage, further optimization of Friedel-Crafts acylation of amides **1d** was not performed.

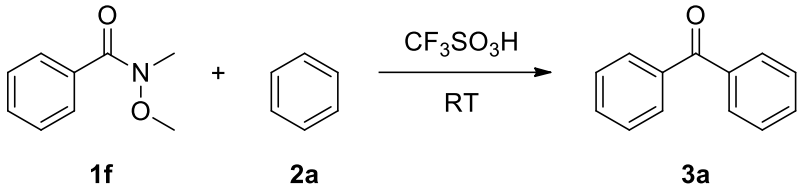
***N*-Phenyl-*N*-tosylbenzamide** (Scheme 1, Entry 5)



1e **2a** **3a**

According to the general procedure, *N*-phenyl-*N*-tosylbenzamide (0.20 mmol) was reacted with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h. After the standard work-up as described above, the sample was analyzed by ^{1}H NMR and GC-MS to obtain conversion and yield using internal standard: conversion 20%; yield of **3a** <5.0%. At this stage, further optimization of Friedel-Crafts acylation of amides **1e** was not performed.

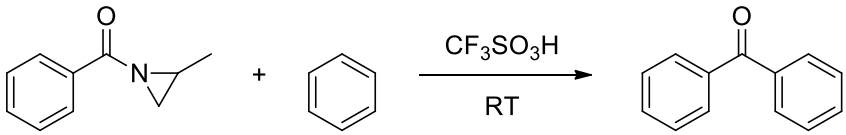
***N*-Methoxy-*N*-methylbenzamide** (Scheme 1, Entry 6)



1f **2a** **3a**

According to the general procedure, *N*-methoxy-*N*-methylbenzamide (0.20 mmol) was reacted with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h. After the standard work-up as described above, the sample was analyzed by ^{1}H NMR and GC-MS to obtain conversion and yield using internal standard: conversion 25%; yield of **3a** <5.0%. At this stage, further optimization of Friedel-Crafts acylation of amides **1f** was not performed.

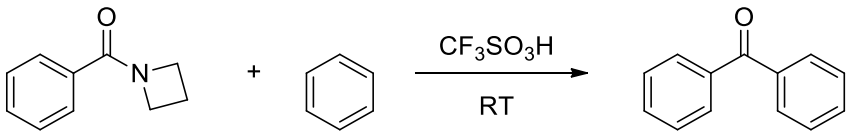
(2-Methylaziridin-1-yl)(phenyl)methanone (Scheme 1, Entry 7)



1g **2a** **3a**

According to the general procedure, (2-methylaziridin-1-yl)(phenyl)methanone (0.20 mmol) was reacted with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h. After the standard work-up as described above, the sample was analyzed by ^{1}H NMR and GC-MS to obtain conversion and yield using internal standard: conversion <5.0%; yield of **3a** <5.0%. At this stage, further optimization of Friedel-Crafts acylation of amides **1g** was not performed.

Azetidin-1-yl(phenyl)methanone (Scheme 1, Entry 8)



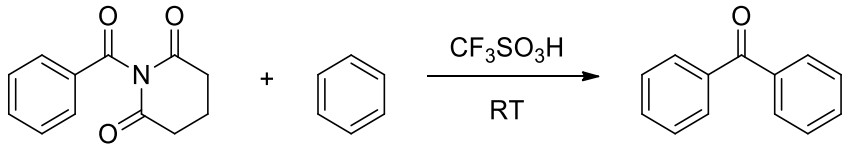
1h **2a** **3a**

According to the general procedure, azetidin-1-yl(phenyl)methanone (0.20 mmol) was reacted with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h. After the standard work-up as described above, the sample was analyzed by ^{1}H NMR and GC-MS to obtain conversion and yield using internal standard: conversion <5.0%; yield of **3a** <5.0%. At this stage, further optimization of Friedel-Crafts acylation of amides **1h** was not performed.

Friedel-Crafts Reactions of Amides: Variation of Amides (Scheme 2)

All products have been previously reported.[15-26] Spectroscopic data matched literature values.

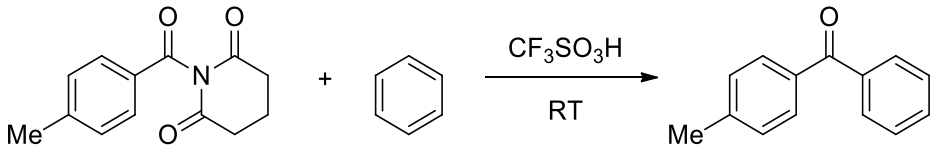
1-Benzoylpiperidine-2,6-dione (Scheme 2, **3a**)



1a **2a** **3a**

According to the general procedure, the reaction of 1-benzoylpiperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 93% yield (33.8 mg). White solid. GC: rt = 13.71 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.7 Hz, 4 H), 7.59-7.64 (m, 2 H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.28, 130.06, 132.41, 137.62, 196.73. MS = 182.1 (EI).[15]

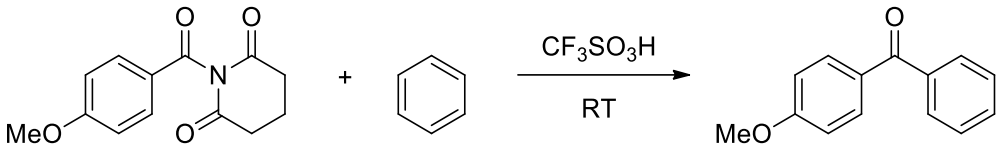
1-(4-Methylbenzoyl)piperidine-2,6-dione (Scheme 2, **3b**)



1i **2a** **3b**

According to the general procedure, the reaction of 1-(4-methylbenzoyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 74% yield (29.8 mg). White solid. GC: rt = 15.32 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.56-7.63 (m, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.81 (dd, *J* = 8.2, 1.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.67, 128.21, 128.98, 129.94, 130.32, 132.16, 134.89, 137.96, 143.24, 196.51. MS = 196.1 (EI).[18]

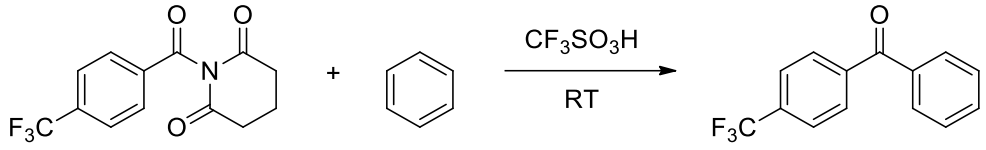
1-(4-Methoxybenzoyl)piperidine-2,6-dione (Scheme 2, **3c**)



1j **2a** **3c**

According to the general procedure, the reaction of 1-(4-methoxybenzoyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 77% yield (32.8 mg). White solid. GC: rt = 17.19 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 7.50 (t, *J* = 7.6 Hz, 2 H), 7.59 (t, *J* = 7.4 Hz, 1 H), 7.78 (d, *J* = 7.3 Hz, 2 H), 7.86 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.50, 113.56, 128.19, 129.73, 130.18, 131.88, 138.31, 132.56, 163.23, 195.55. MS = 212.1 (EI).[15]

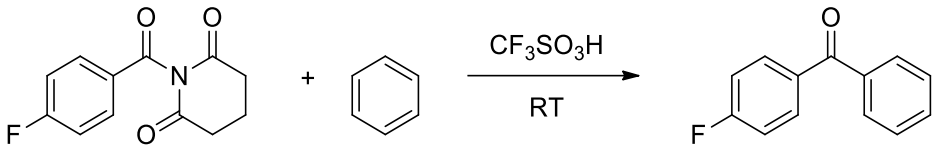
1-(4-(Trifluoromethyl)benzoyl)piperidine-2, 6-dione (Scheme 2, **3d**)



1k **2a** **3d**

According to the general procedure, the reaction of 1-(4-(trifluoromethyl)benzoyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 97% yield (48.4 mg). White solid. GC: rt = 13.27 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (t, *J* = 7.7 Hz, 2 H), 7.66 (t, *J* = 7.4 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 2 H), 7.83 (d, *J* = 7.7 Hz, 2 H), 7.92 (d, *J* = 8.2 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.68 (q, J^1 = 273.4 Hz), 125.35 (q, J^1 = 3.8 Hz), 128.53, 130.10, 130.13, 133.09, 133.73 (q, J^2 = 32.8 Hz), 136.74, 140.74, 195.52. ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.02. MS = 250.1 (EI).[15]

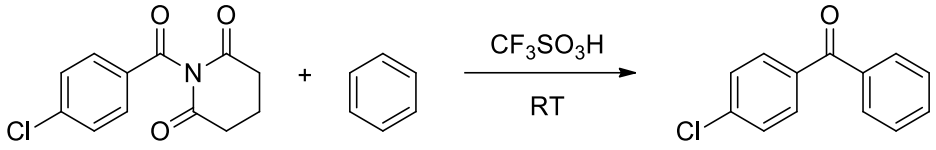
1-(4-Fluorobenzoyl)piperidine-2,6-dione (Scheme 2, **3e**)



1l **2a** **3e**

According to the general procedure, the reaction of 1-(4-fluorobenzoyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 95% yield (38.0 mg). Oil. GC: rt = 13.67 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 2 H), 7.52 (d, *J* = 7.7 Hz, 2 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.80 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.85-7.91 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.46 (d, J^2 = 21.4 Hz), 128.36, 129.87, 132.47, 132.67 (d, J^3 = 8.8 Hz), 133.81, 137.52, 165.40 (d, J^1 = 254.5 Hz), 195.26. ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.01. MS = 200.1 (EI).[15]

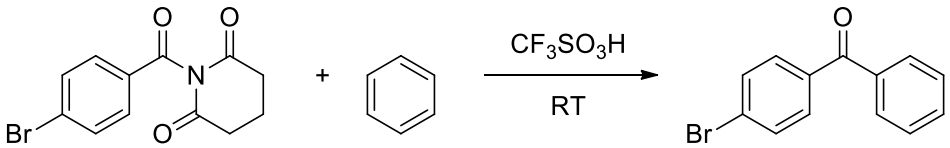
1-(4-Chlorobenzoyl)piperidine-2,6-dione (Scheme 2, **3f**)



1m **2a** **3f**

According to the general procedure, the reaction of 1-(4-chlorobenzoyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 83% yield (35.8 mg). Oil. GC: rt = 15.87 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.54 (m, 4 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.79 (t, *J* = 8.0 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.40, 128.64, 129.92, 131.46, 132.64, 135.89, 137.26, 138.90, 195.48. MS = 216.0 (EI).[15]

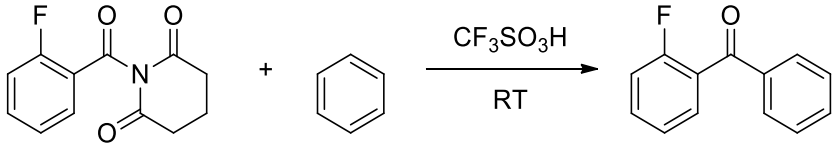
1-(4-Bromobenzoyl)piperidine-2,6-dione (Scheme 2, **3g**)



1n **2a** **3g**

According to the general procedure, the reaction of 1-(4-bromobenzoyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 68% yield (35.8 mg). White solid. GC: rt = 16.93 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (t, *J* = 7.7 Hz, 2 H), 7.62 (d, *J* = 7.5 Hz, 1 H), 7.66 (d, *J* = 8.6 Hz, 2 H), 7.71 (d, *J* = 8.6 Hz, 2 H), 7.80 (dd, *J* = 8.3, 1.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.51, 128.41, 129.94, 131.56, 131.62, 132.67, 136.33, 137.19, 195.62. MS = 260.0 (EI).[19]

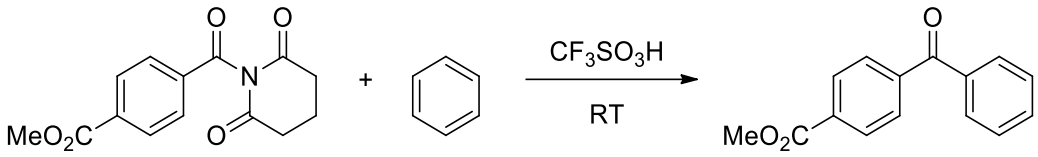
1-(2-Fluorobenzoyl)piperidine-2,6-dione (Scheme 2, **3h**)



1o **2a** **3h**

According to the general procedure, the reaction of 1-(2-fluorobenzoyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 73% yield (29.2 mg). Oil. GC: rt = 13.64 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (t, *J* = 9.1 Hz, 1 H), 7.30 (d, *J* = 7.5 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.53-7.61 (m, 2 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.87 (d, *J* = 8.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.28 (d, J^2 = 21.4 Hz), 124.28 (d, J^4= 3.8 Hz), 127.06 (d, J^2 = 15.1 Hz), 128.46, 129.81, 130.76 (d, J^3= 3.8 Hz), 133.05 (d, J^3 = 8.8 Hz), 133.40, 137.42, 160.10 (d, J^1 = 253.3 Hz), 193.45. ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.04. MS = 200.1 (EI).[15]

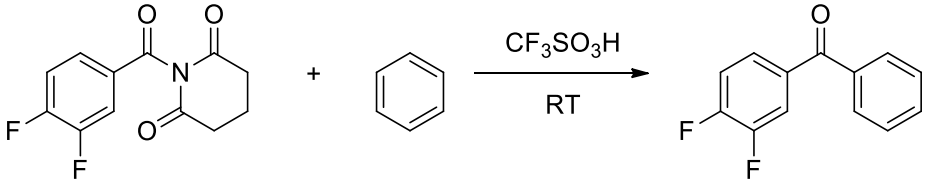
Methyl 4-(2,6-dioxopiperidine-1-carbonyl)benzoate (Scheme 2, **3i**)



1p **2a** **3i**

According to the general procedure, the reaction of methyl 4-(2,6-dioxopiperidine-1-carbonyl)benzoate (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 75% yield (36.0 mg). White solid. GC: rt = 18.34 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (s, 3 H), 7.52 (t, *J* = 7.7 Hz, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.83 (d, *J* = 7.2 Hz, 2 H), 7.86 (d, *J* = 8.4 Hz, 2 H), 8.17 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.49, 128.47, 129.51, 129.78, 130.11, 132.96, 133.22, 136.95, 141.32, 166.33, 196.05. MS = 240.1 (EI).[15]

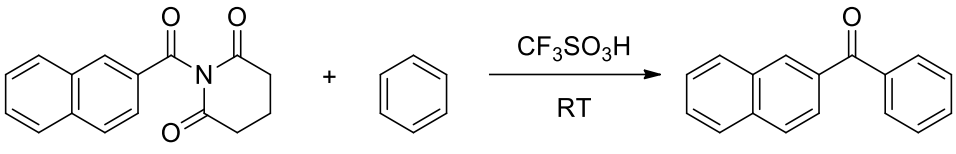
1-(3,4-Difluorobenzoyl)piperidine-2,6-dione (Scheme 2, **3j**)



1q **2a** **3j**

According to the general procedure, the reaction of 1-(2-fluorobenzoyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 95% yield (41.3 mg). White solid. GC: rt = 13.40 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dt, *J* = 9.7, 7.5 Hz, 1 H), 7.53 (t, *J* = 7.8 Hz, 2 H), 7.59-7.67 (m, 2 H), 7.71 (ddd, *J* = 10.2, 7.7, 2.1 Hz, 1 H), 7.79 (dd, *J* = 8.3, 1.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 117.28 (J^2 = 17.5 Hz), 119.33 (J^2 = 18.8 Hz), 127.10 (J^3 = 7.5 Hz), 128.50, 129.85, 132.81, 134.45 (J^4 = 3.8 Hz), 136.88, 150.21 (J^1 = 248.8 Hz), 152.79 (J^1 = 255.0 Hz), 194.09. ^{19}F NMR (471 MHz, $CDCl_3$) δ -136.19, -136.15, -130.61, -130.56. MS = 218.1 (EI).[20]

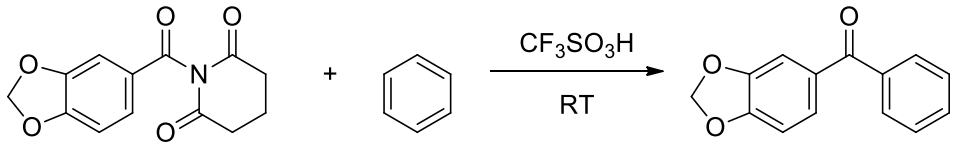
1-(2-Naphthoyl)piperidine-2,6-dione (Scheme 2, **3k**)



1r **2a** **3k**

According to the general procedure, the reaction of 1-(2-naphthoyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 78% yield (36.3 mg). White solid. GC: rt = 19.90 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dt, *J* = 15.4, 7.8 Hz, 3 H), 7.62-7.68 (m, 2 H), 7.90 (d, *J* = 7.3 Hz, 2 H), 7.95 (dd, *J* = 8.1, 2.9 Hz, 2 H), 7.98 (s, 2 H), 8.30 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.80, 126.81, 127.84, 128.31, 128.34, 128.35, 129.43, 130.11, 131.87, 132.28, 132.39, 134.85, 135.29, 137.93, 196.74. MS = 232.1 (EI).[15]

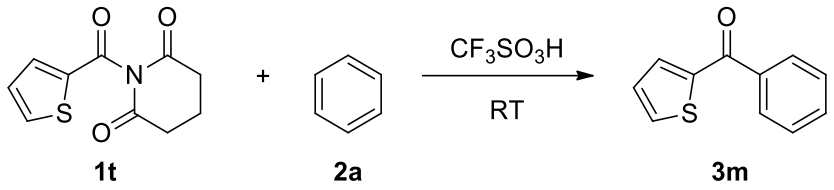
1-(Benzo[*d*][1,3]dioxole-5-carbonyl)piperidine-2,6-dione (Scheme 2, **3l**)



1s **2a** **3l**

According to the general procedure, the reaction of 1-(benzo[*d*][1,3]dioxole-5-carbonyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 50% yield (22.8 mg). Yellow solid. GC: rt = 18.11 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (s, 2 H), 6.88 (d, *J* = 7.9 Hz, 1 H), 7.37-7.43 (m, 2 H), 7.49 (t, *J* = 7.7 Hz, 2 H), 7.56-7.61 (m, 1 H), 7.75-7.79 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 101.86, 107.70, 109.92, 126.87, 128.21, 129.71, 131.91, 131.99, 138.13, 147.95, 151.52, 195.15. MS = 226.1 (EI).[21]

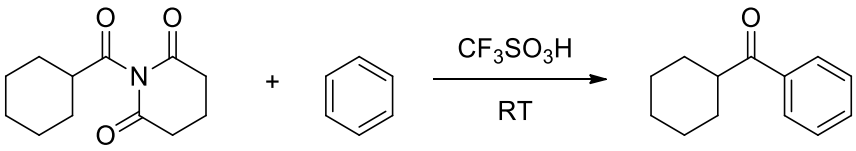
1-(Thiophene-2-carbonyl)piperidine-2,6-dione (Scheme 2, **3m**)



1t **2a** **3m**

According to the general procedure, the reaction of 1-(thiophene-2-carbonyl)piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 64% yield (24.2 mg). White solid. GC: rt = 14.59 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.21 (m, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.67 (dd, *J* = 3.8, 1.0 Hz, 1 H), 7.75 (dd, *J* = 4.9, 1.0 Hz, 1 H), 7.89 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.97, 128.42, 129.18, 132.28, 134.22, 134.86, 138.16, 143.65, 188.25. MS = 188.0 (EI).[22]

1-(Cyclohexanecarbonyl)piperidine-2,6-dione (Scheme 2, **3n**)

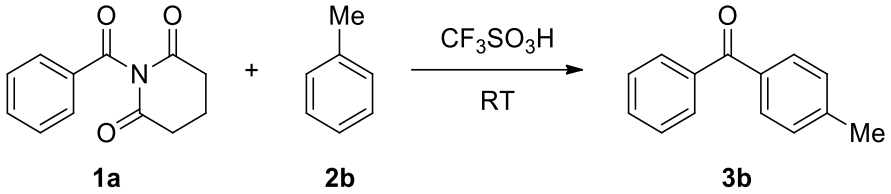


1s **2a** **3n**

According to the general procedure, the reaction of methyl 1-(cyclohexanecarbonyl) piperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 50% yield (18.9 mg). White solid. GC: rt = 13.62 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24-1.36 (m, 2 H), 1.42 (qt, *J* = 12.7, 3.1 Hz, 2 H), 1.52 (qd, *J* = 12.6, 2.8 Hz, 2 H), 1.83-1.95 (m, 4 H), 3.29 (tt, *J* = 11.5, 3.2 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.97 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.88, 25.98, 29.44, 45.65, 128.25, 128.58, 132.72, 136.36, 203.91. MS = 188.1 (EI).[23]

Friedel-Crafts Reactions of Amides: Variation of Nucleophiles (Scheme 3)

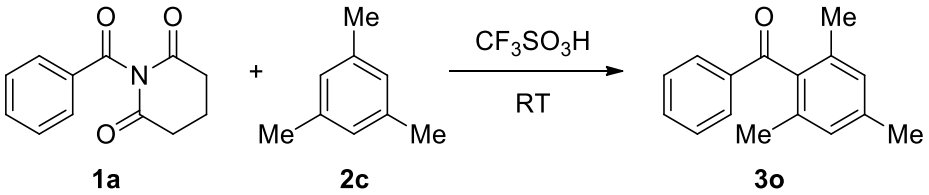
Toluene (Scheme 3, Entry 1)



1a **2b** **3b**

According to the general procedure, the reaction of 1-benzoylpiperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in toluene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 75% yield (29.6 mg). White solid. GC: rt = 15.33 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.75 (d, *J* = 8.1 Hz, 2 H), 7.81 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.68, 128.21, 128.98, 129.94, 130.32, 132.16, 134.89, 137.96, 143.25, 196.52. MS = 196.1 (EI).[15]

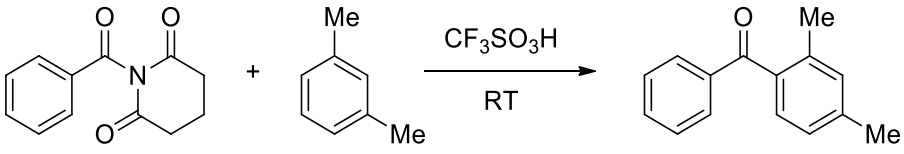
Mesitylene (Scheme 3, Entry 2)



1a **2c** **3o**

According to the general procedure, the reaction of 1-benzoylpiperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in mesitylene (0.40 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 64% yield (28.7 mg). Oil. GC: rt = 15.86 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (s, 6 H), 2.36 (s, 3 H), 6.93 (s, 2 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.84 (d, *J* = 7.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.37, 21.17, 128.34, 128.80, 129.41, 133.55, 134.20, 136.89, 137.32, 138.50, 200.77. MS = 224.1 (EI).[24]

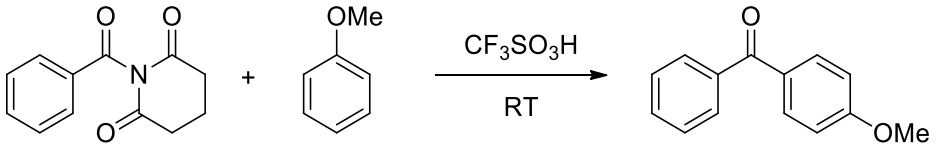
***m*-Xylene** (Scheme 3, Entry 3)



1a **2d** **3p**

According to the general procedure, the reaction of 1-benzoylpiperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in *m*-xylene (0.10 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 65% yield (27.3 mg). White solid. GC: rt = 15.59 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.41 (s, 3 H), 7.07 (d, *J* = 7.7 Hz, 1 H), 7.14 (s, 1 H), 7.24-7.30 (m, 1 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 7.59 (t, *J* = 7.4 Hz, 1 H), 7.82 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.12, 21.40, 125.79, 128.36, 129.27, 130.10, 131.91, 132.85, 135.61, 137.30, 138.22, 140.65, 198.55. MS = 210.1 (EI).[25]

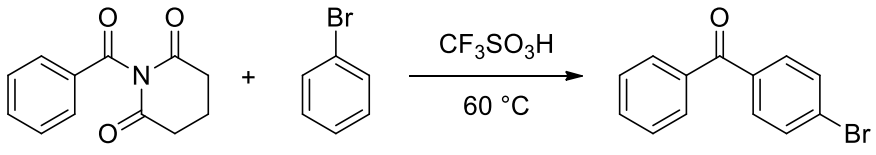
Anisole (Scheme 3, Entry 4)



1a **2e** **3c**

According to the general procedure, the reaction of 1-benzoylpiperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in anisole (0.40 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 57% yield (24.4 mg). White solid. GC: rt = 17.20 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 7.78 (d, *J* = 7.1 Hz, 2 H), 7.85 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.50, 113.56, 128.19, 129.73, 130.16, 131.89, 132.56, 138.30, 163.23, 195.55. MS = 212.1 (EI).[15]

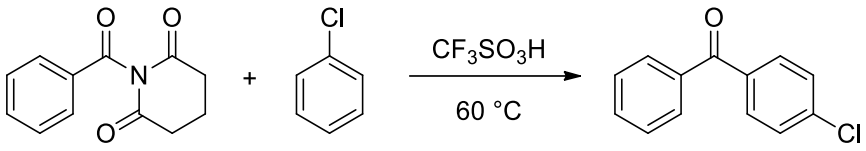
Bromobenzene (Scheme 3, Entry 5)



1a **2f** **3g**

According to the general procedure, the reaction of 1-benzoylpiperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in bromobenzene (0.40 M) at 60 °C for 15 h, afforded after the standard work-up as described above the title compound in 64% yield (33.2 mg). Yellow solid. GC: rt = 17.07 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.7 Hz, 2 H), 7.63 (dd, *J* = 16.4, 8.0 Hz, 3 H), 7.70 (d, *J* = 8.5 Hz, 2 H), 7.80 (d, *J* = 7.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.52, 128.42, 129.95, 131.57, 131.62, 132.69, 136.31, 137.17, 195.64. MS = 260.0 (EI).[19]

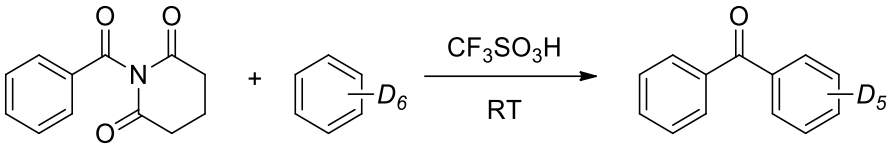
Chlorobenzene (Scheme 3, Entry 6)



1a **2g** **3f**

According to the general procedure, the reaction of 1-benzoylpiperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in chlorobenzene (0.40 M) at 60 °C for 15 h, afforded after the standard work-up as described above the title compound in 57% yield (24.5 mg). White solid. GC: rt = 16.00 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.55 (m, 4 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 7.79 (t, *J* = 8.1 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.41, 128.62, 128.64, 129.93, 131.47, 132.65, 135.87, 137.25, 138.90, 195.50. MS = 216.0 (EI).[15]

Benzene-*D_6*

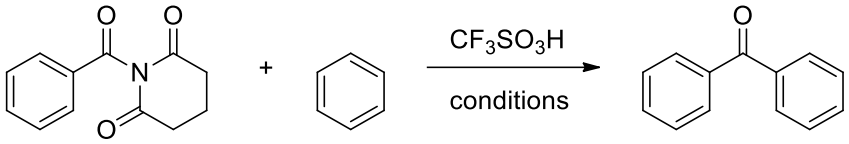


1a **2a-*D_6*** **3a-*D_5***

According to the general procedure, the reaction of 1-benzoylpiperidine-2,6-dione (0.20 mmol) with trifluoromethanesulfonic acid (3.0 equiv) in benzene-*d_6* (0.20 M) at room temperature for 15 h, afforded after the standard work-up as described above the title compound in 72% yield (27.0 mg). White solid. GC: rt = 13.88 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.6 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.83 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.29, 130.06, 132.42, 137.62, 196.74. MS = 187.1 (EI).[26]

Detailed Optimization Experiments

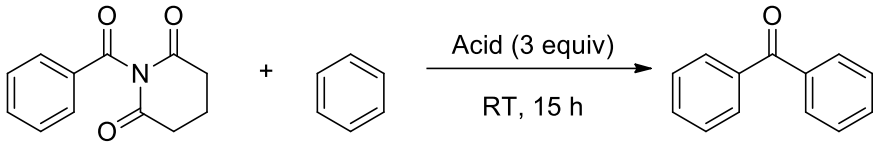
Table SI-1. Optimization Studies in the Friedel-Craft reaction of Sterically-Distorted Amides.[a]



Entry	Benzene (M)	CF_3SO_3H (equiv)	Temperature (°C)	Time (h)	Additives	Conv.[b] (%)	Yield[b] (%)
1	0.10	3.0	rt	15	-	>95	93[c]
2	0.10	2.0	rt	15	-	>95	66
3	0.10	1.0	rt	15	-	64	<10
4	0.10	0.2	rt	15	-	13	<5
5	0.10	5.0	rt	15	-	>95	53
6	0.10	3.0	rt	15	DCE (1/1)	46	29
7	0.10	3.0	rt	15	4 Å MS	>95	11
8	0.10	3.0	rt	3	-	>95	54
9[d]	0.10	3.0	rt	15	-	>95	53
10	0.40	3.0	rt	15	-	>95	52
11	0.04	3.0	rt	15	-	>95	44
12	0.10	3.0	65	15	-	>95	67
13	0.10	3.0	0 to rt	15	-	>95	71

[a]Conditions: **1a** (1 equiv), benzene (x M), acid (x equiv). All reactions carried out using standard Schlenk techniques under nitrogen. [b]Determined by ^{1}H NMR and/or GC-MS. [c]Isolated yield. [d]Reverse addition.

Table SI-2. Influence of Acids in the Friedel-Craft reaction of Sterically-Distorted Amides.[a]



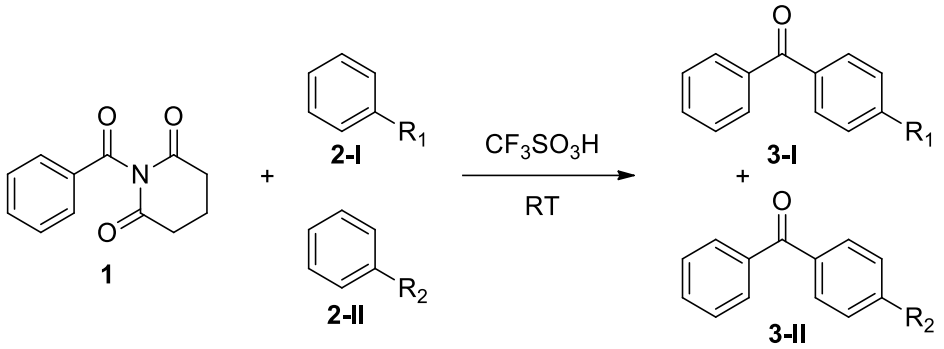
Entry	Acids (3.0 equiv)	Conv.[b] (%)	Yield[b] (%)
1	CF_3SO_3H	>95	93[c]
2	$TiCl_4$	<5	<5
3	$BF_3{\cdot}Et_2O$	<5	<5
4	TFA	<5	<5
5	HCl	<5	<5
6	HBF_4	<5	<5

[a]Conditions: **1a** (1 equiv), benzene (0.10 M), acid (3.0 equiv), rt, 15 h. All reactions carried out using standard Schlenk techniques under nitrogen. [b]Determined by ^{1}H NMR and/or GC-MS. [c]Isolated yield.

Selectivity Studies – Nucleophiles[27-29]

General Procedure. An oven-dried vial equipped with a stir bar was charged with an amide substrate (1.0 equiv), placed under a positive pressure of nitrogen, and subjected to three evacuation/backfilling cycles. Nucleophile (1/1 mmol ratio to a total volume of 0.10 M) and trifluoromethanesulfonic acid (3.0 equiv) were added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 15 h. After the indicated time, the reaction mixture was quenched with saturated $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 20 mL), the organic layers were combined, dried, filtered, and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion and yield using internal standard and comparison with authentic samples.

Table SI-3. Selectivity Study in the Friedel-Crafts Reaction of Sterically-Distorted Amides.[a]



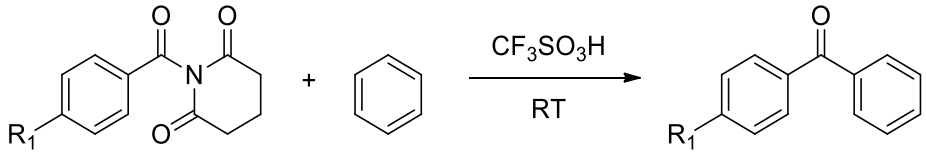
Entry	**2-I** (R_1)	**2-II** (R_2)	CF_3SO_3H (equiv)	**3-I**:**3-II** (R_1:R_2)[b]
1	H-	Me-	3.0	1:34.4
2	H-	Br-	3.0	25.0:1

[a]Conditions: Solvent (2 mL), CF_3SO_3H (3.0 equiv), rt, 15 h. All reactions carried out using standard Schlenk techniques under nitrogen. [b]Determined by ^1H NMR and/or GC-MS.

Selectivity Studies – Amides[27-29]

General Procedure. An oven-dried vial equipped with a stir bar was charged with an amide substrate (1.0 equiv), placed under a positive pressure of nitrogen, and subjected to three evacuation/backfilling cycles. Benzene (0.10 M) and trifluoromethanesulfonic acid (3.0 equiv) were added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 5.0 min. After the indicated time, the reaction mixture was quenched with saturated $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 20 mL), the organic layers were combined, dried, filtered, and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion and yield using internal standard and comparison with authentic samples.

Table SI-4. Selectivity Study in the Friedel-Crafts Reaction of Sterically-Distorted Amides.[a]



1-I **2** **3-I**

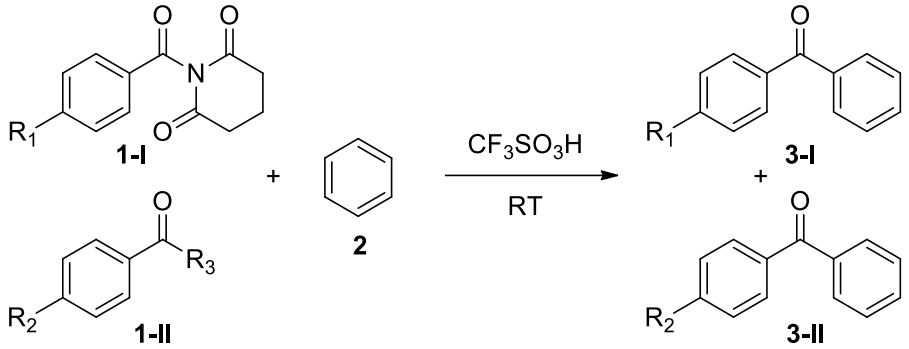
Entry	**1-I** (R_1)	Conv.[b] (%) (k_X/k_H)	Yield[b] (%)
1	MeO-	>95 (0.94)	29.5
2	H-	>95 (1.00)	31.6
3	CF_3-	>95 (1.22)	38.5

[a]Conditions: Solvent (2 mL), CF_3SO_3H (3.0 equiv), rt, 5 min. All reactions carried out using standard Schlenk techniques under nitrogen. [b]Determined by ^1H NMR and/or GC-MS.

Selectivity Studies – Other Electrophiles[27-29]

General Procedure. An oven-dried vial equipped with a stir bar was charged with two substrates (each 1.0 equiv), placed under a positive pressure of nitrogen, and subjected to three evacuation/backfilling cycles. Benzene (0.10 M) and trifluoromethanesulfonic acid (3.0 equiv) were added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 15 h. After the indicated time, the reaction mixture was quenched with saturated $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 20 mL), the organic layers were combined, dried, filtered, and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion and yield using internal standard and comparison with authentic samples.

Table SI-5. Selectivity Study in the Friedel-Crafts Reaction of Sterically-Distorted Amides.[a]



Entry	**1-I** (R_1)	**1-II** (R_2/R_3)	CF_3SO_3H (equiv)	**3-I**:**3-II** (R_1:R_2)[b]
1	Me-	H-/Cl-	3.0	1:1.16
2	Me-	H-/OCOPh	3.0	1.12:1

[a]Conditions: Solvent (2 mL), CF_3SO_3H (3.0 equiv), rt, 15 h. All reactions carried out using standard Schlenk techniques under nitrogen. [b]Determined by ^1H NMR and/or GC-MS.

Kinetic Isotope Studies[30]

General Procedure. An oven-dried vial equipped with a stir bar was charged with an amide substrate (0.20 mmol), placed under a positive pressure of nitrogen, and subjected to three evacuation/backfilling cycles. Benzene/benzene-d_6 (1/1, 0.10 M) and trifluoromethanesulfonic acid (3.0 equiv) were added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for 15 h. After the indicated time, the reaction mixture was quenched with saturated $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 20 mL), the organic layers were combined, dried, filtered, and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) to obtain conversion and yield using internal standard and comparison with authentic samples. The amount of each species was determined by ^1H NMR (500 MHz, $CDCl_3$) and HRMS analysis. Kinetic isotope effect, k_H/k_D = 2.9, indicating that proton transfer might be involved in the rate determining step of the reaction.

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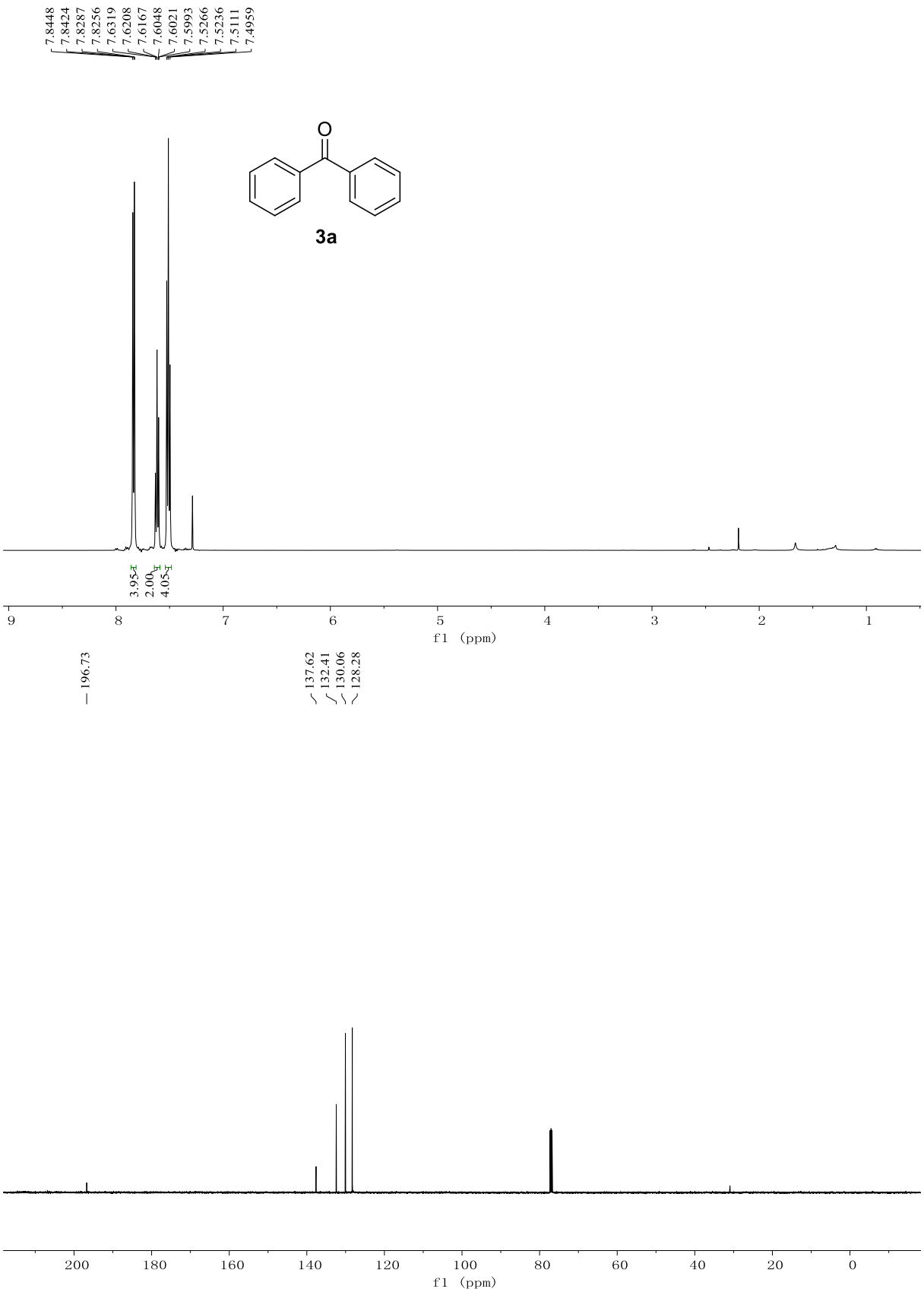
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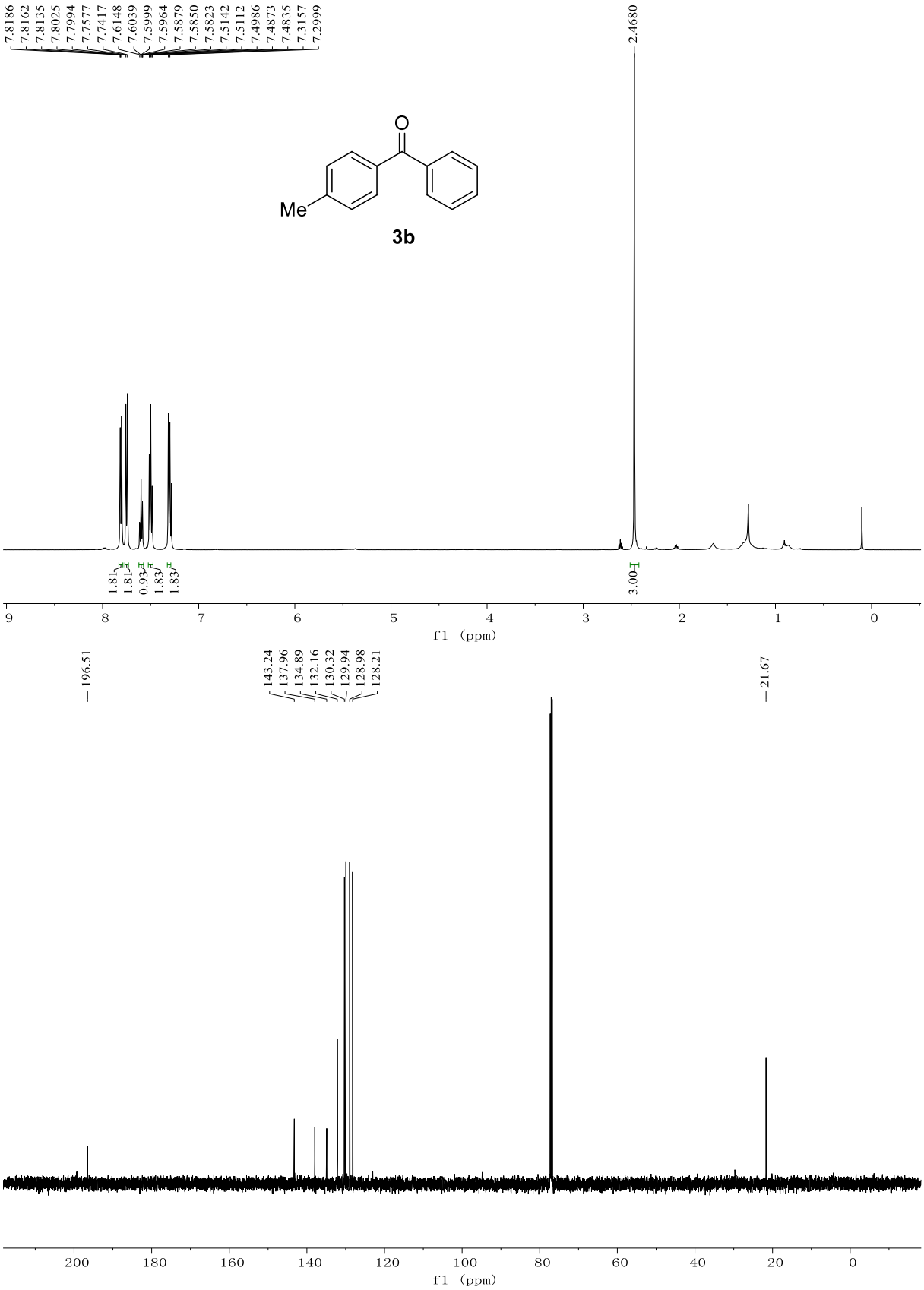
f1 (ppm)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1.83
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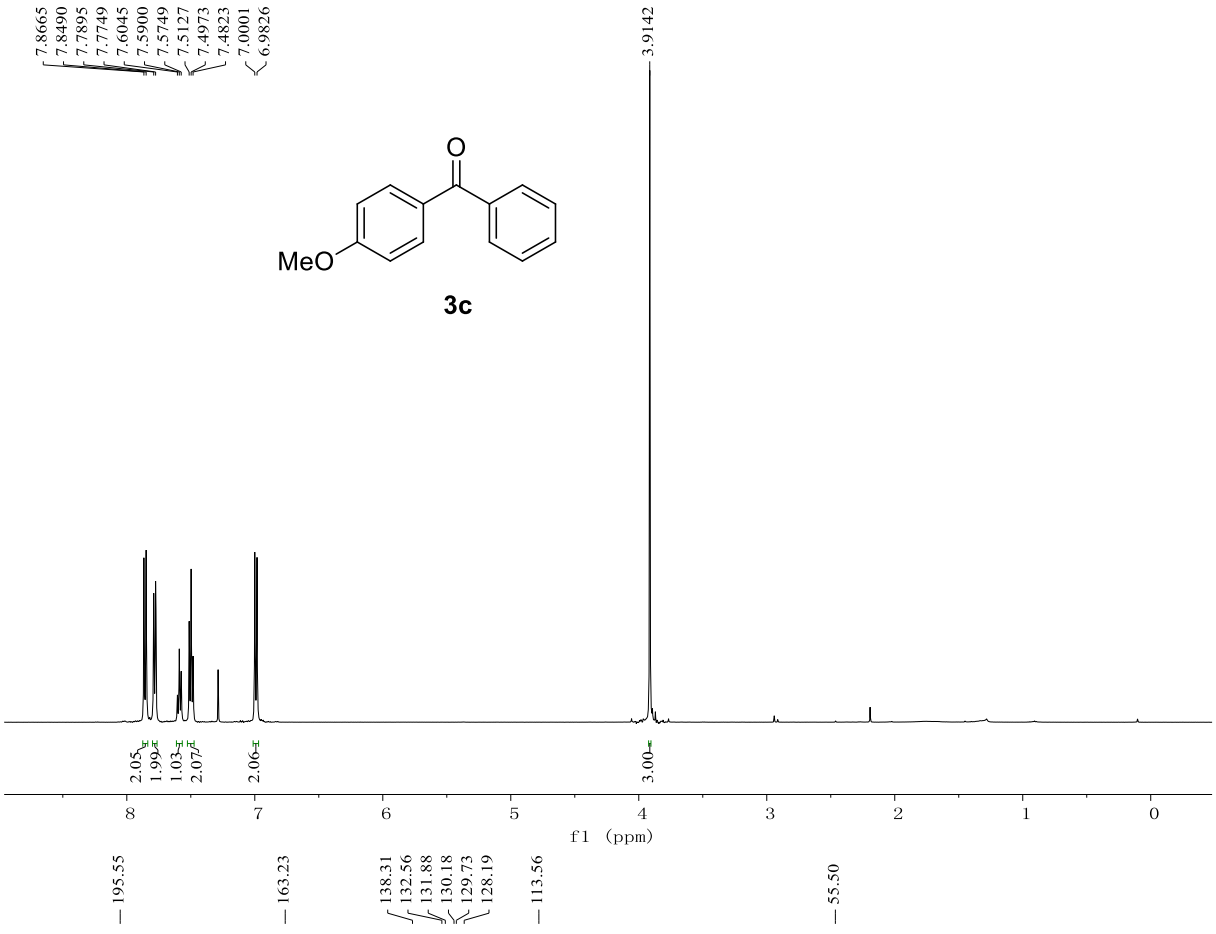
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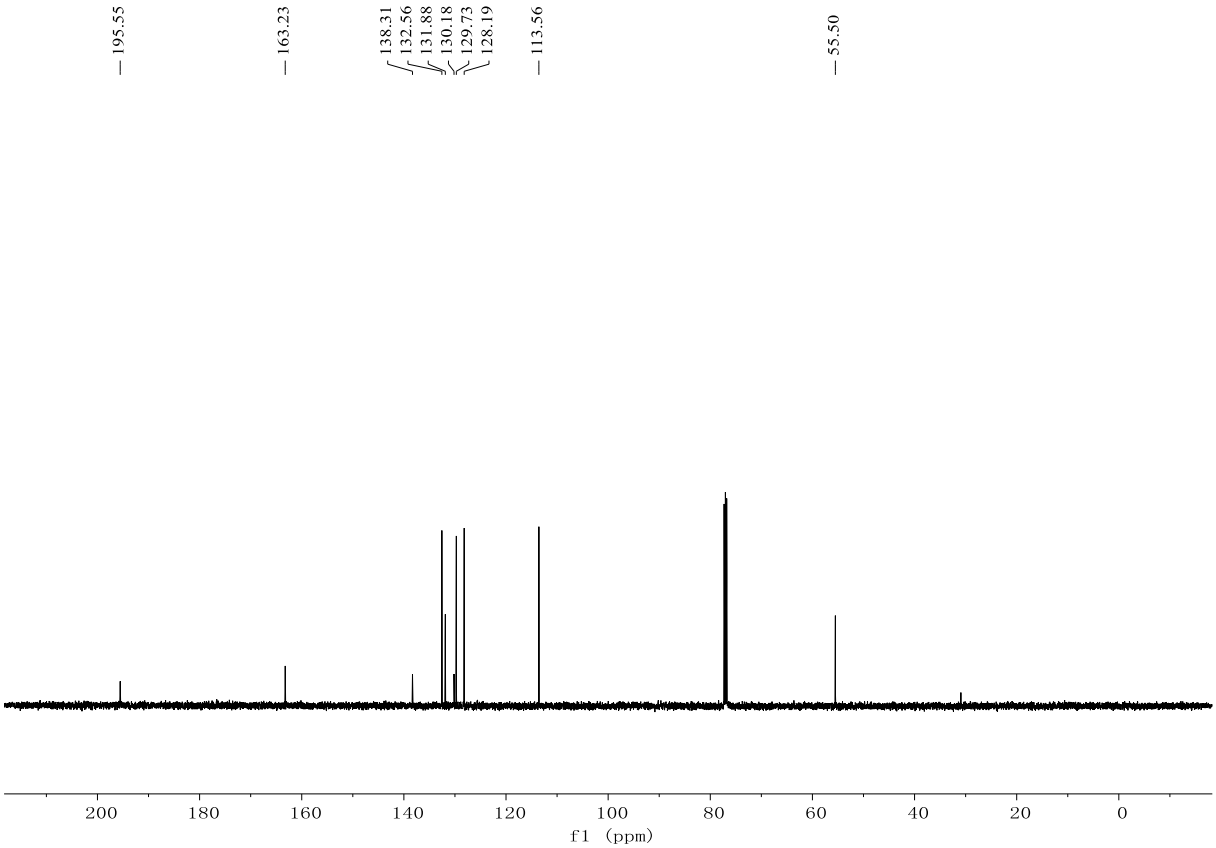
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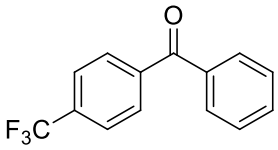
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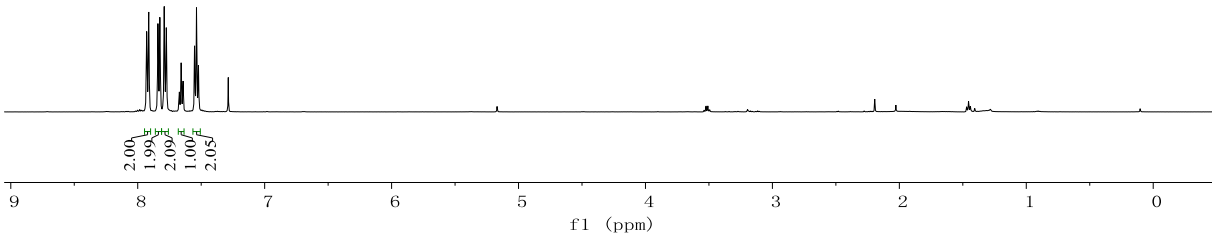
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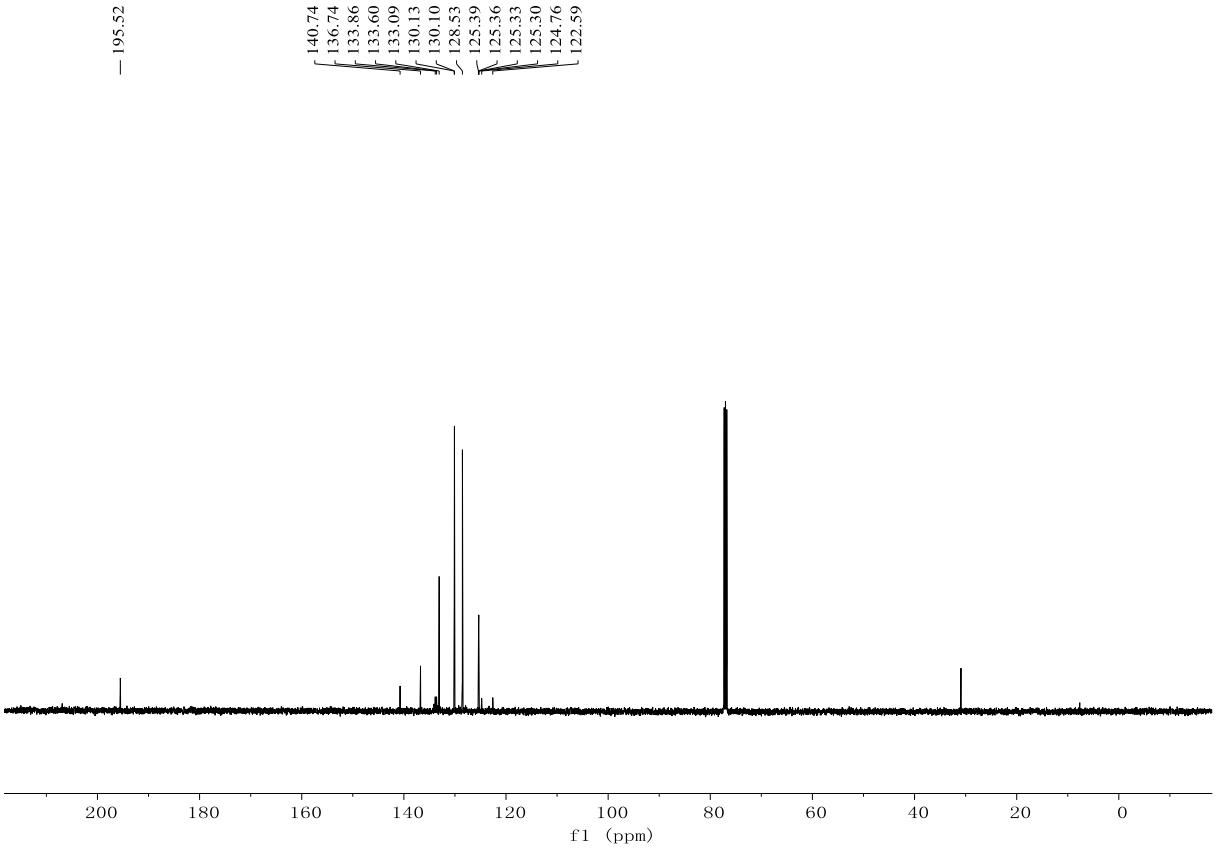
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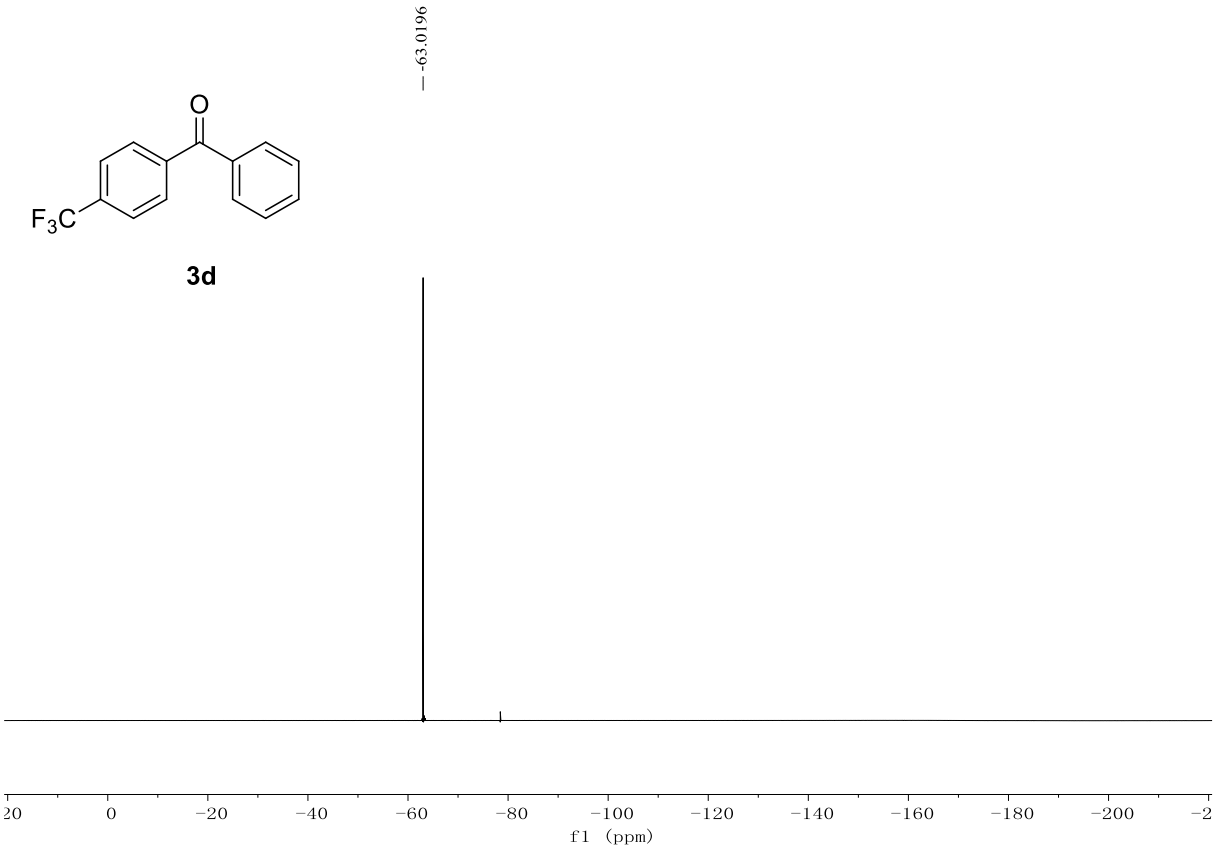
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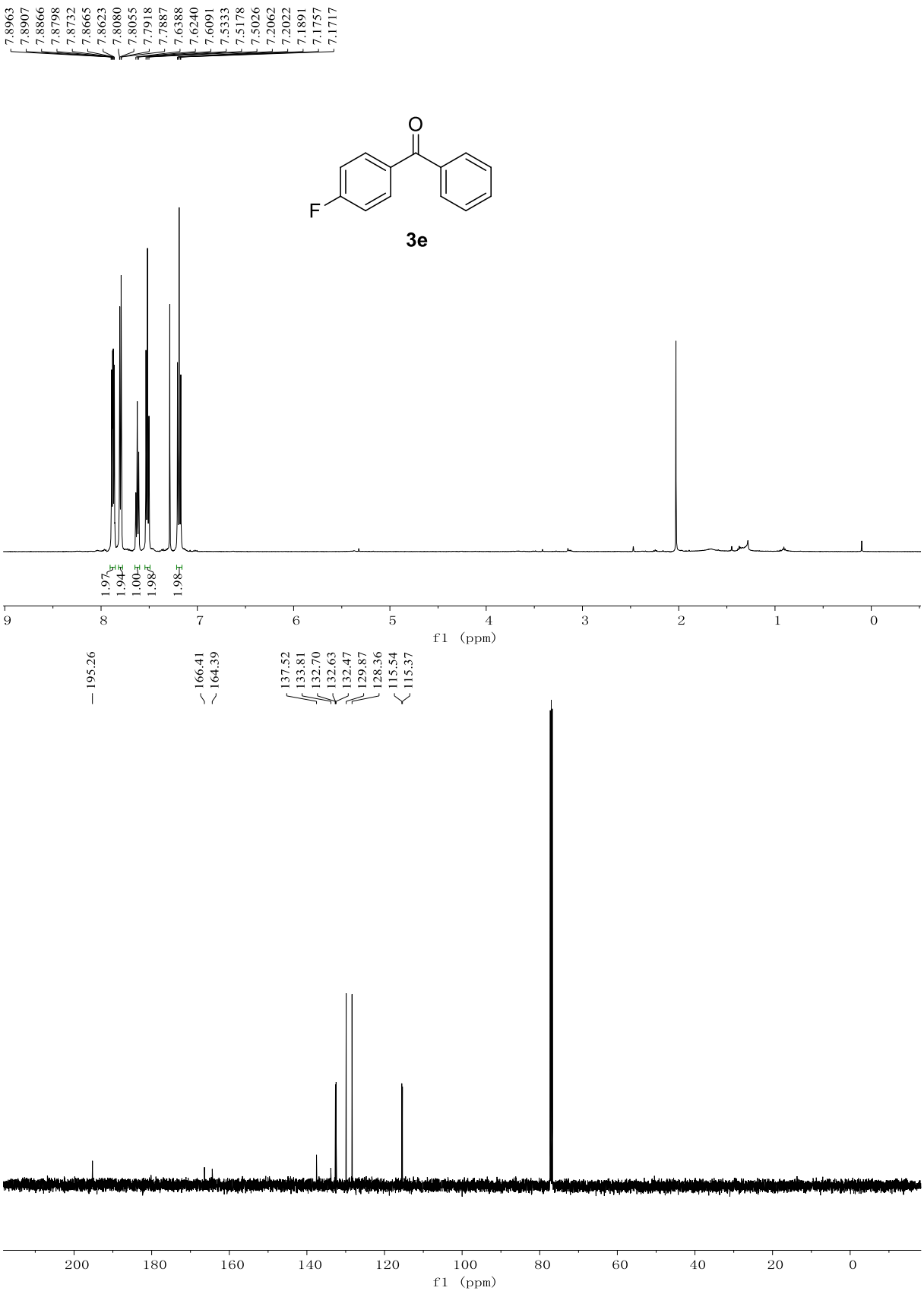
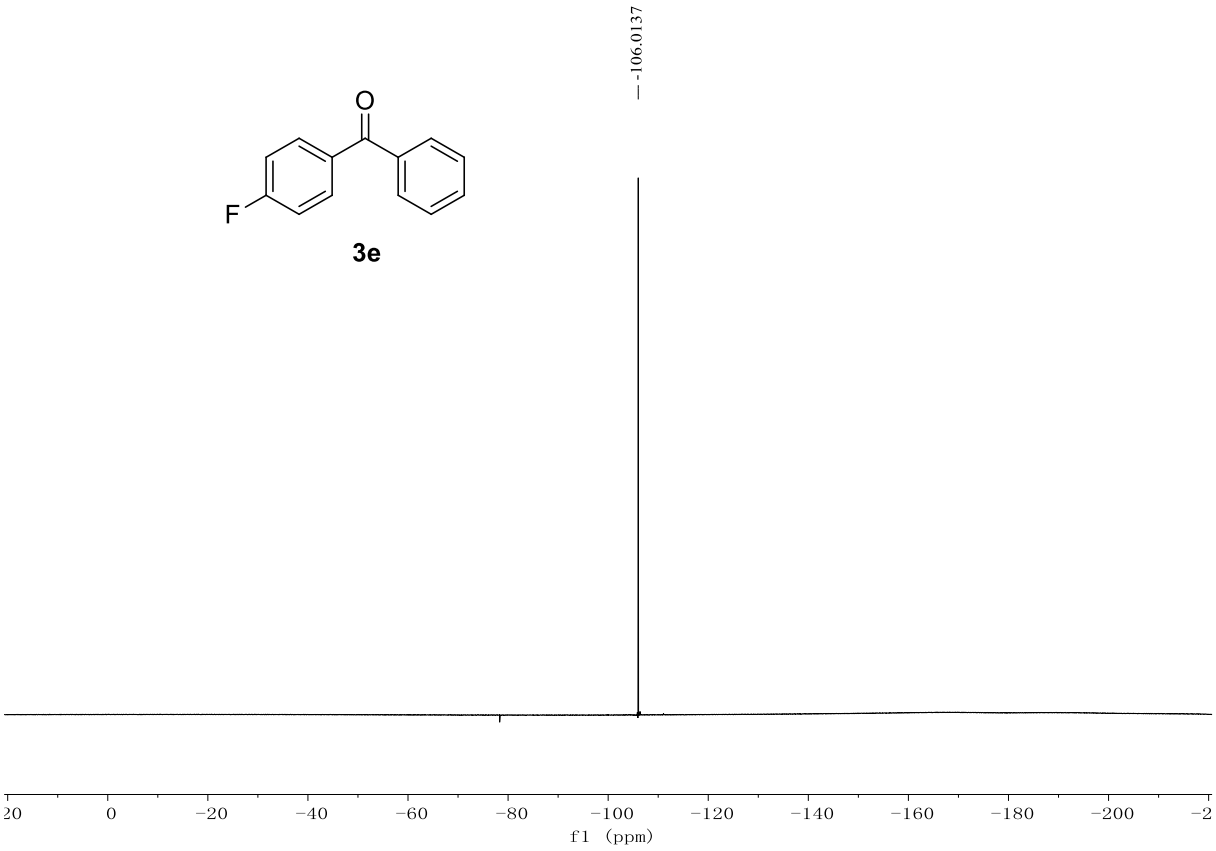
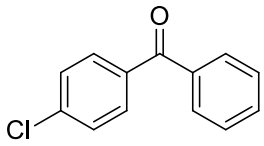
−100
−120
−140
−160
−180
−200
−2
f1 (ppm)

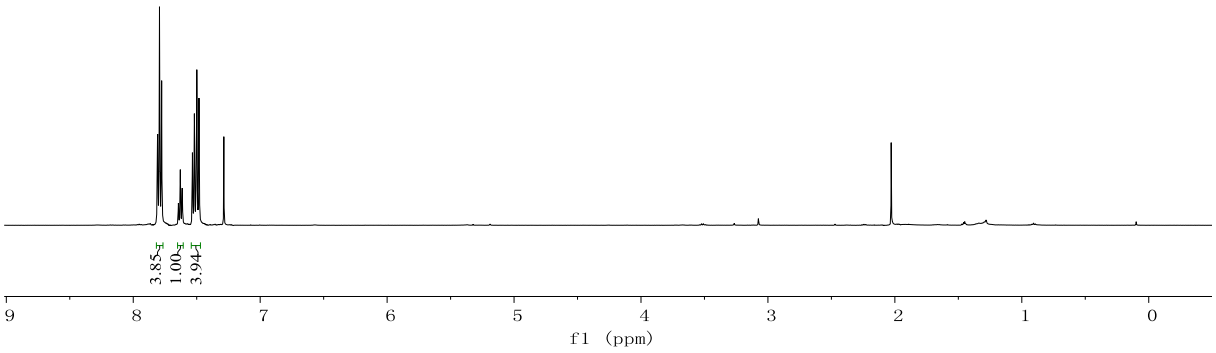

7.8963
7.8907
7.8866
7.8798
7.8732
7.8665
7.8623
7.8080
7.8055
7.7918
7.7887
7.6388
7.6240
7.6091
7.5333
7.5178
7.5026
7.2062
7.2022
7.1891
7.1757
7.1717
O
F
3e
1.97
1.94
1.00
1.98
1.98
f1 (ppm)
195.26
166.41
164.39
137.52
133.81
132.70
132.63
132.47
129.87
128.36
115.54
115.37
f1 (ppm)

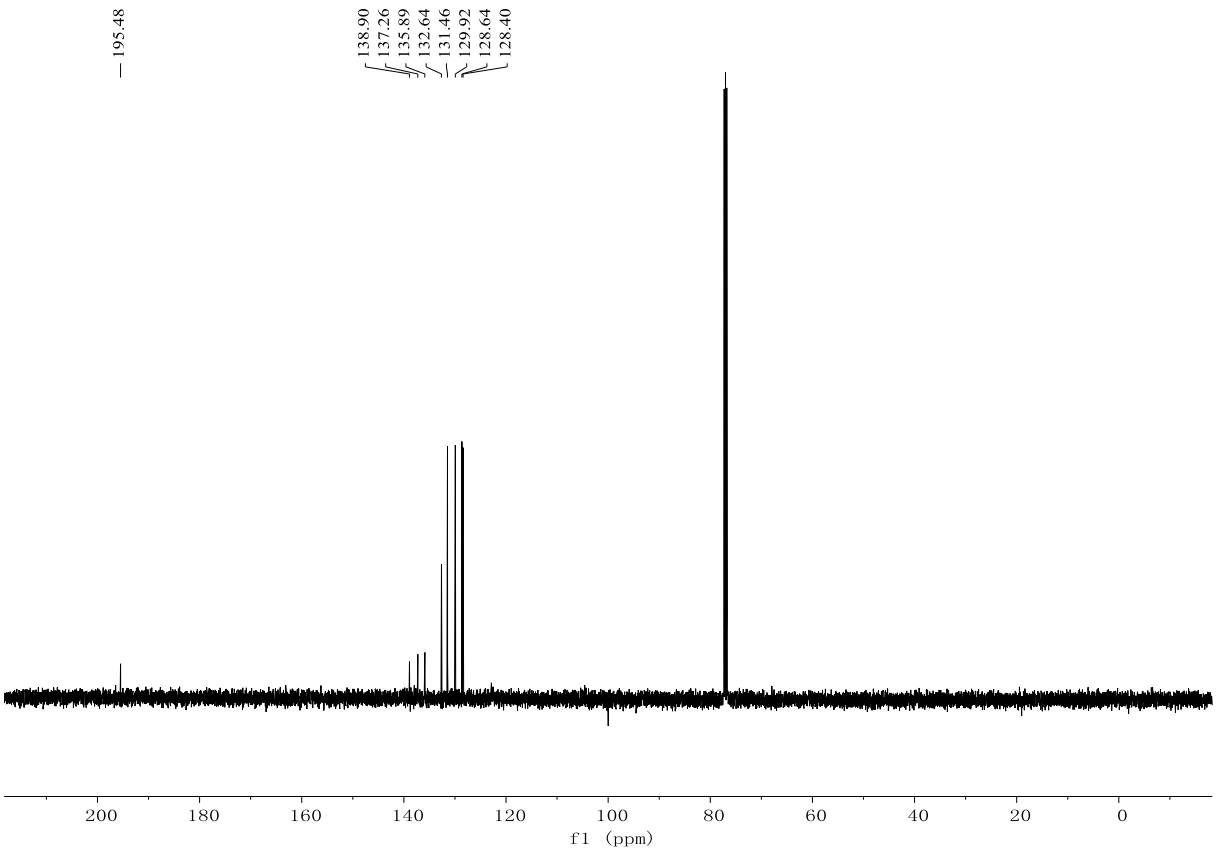

-106.0137
O
F
3e
20
0
−20
−40
−60
−80
−100
−120
−140
−160
−180
−200
−2
f1 (ppm)


7.8080
7.7934
7.7761
7.6441
7.6292
7.6143
7.5340
7.5308
7.5184
7.5068
7.5035
7.4992
7.4952
7.4861
7.4822
7.4772

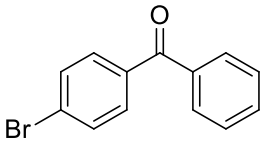

O
Cl

3f

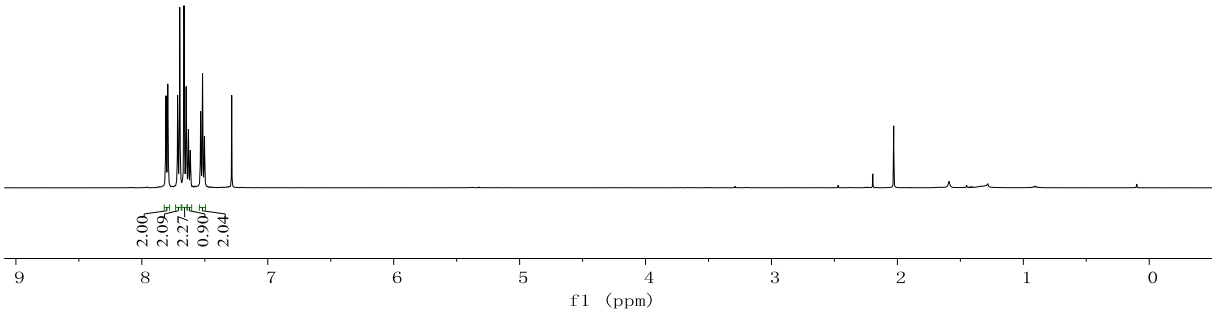

3.85
1.00
3.94
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

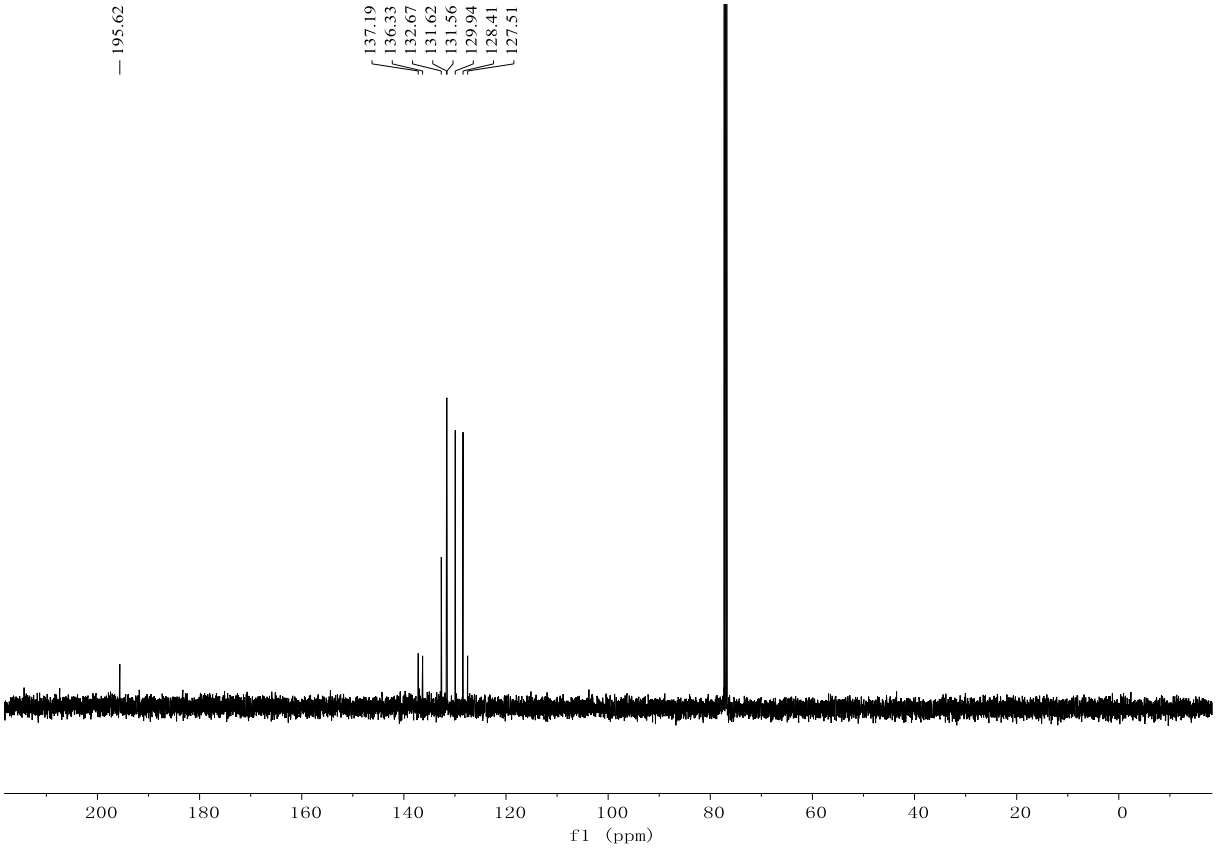

195.48
138.90
137.26
135.89
132.64
131.46
129.92
128.64
128.40
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

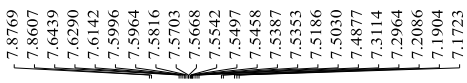

7.8105
7.8079
7.7942
7.7912
7.7163
7.7035
7.6992
7.6650
7.6608
7.6479
7.6301
7.6151
7.5334
7.5304
7.5178
7.5060
7.5024

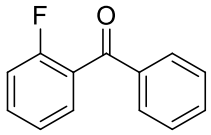

O
Br

3g

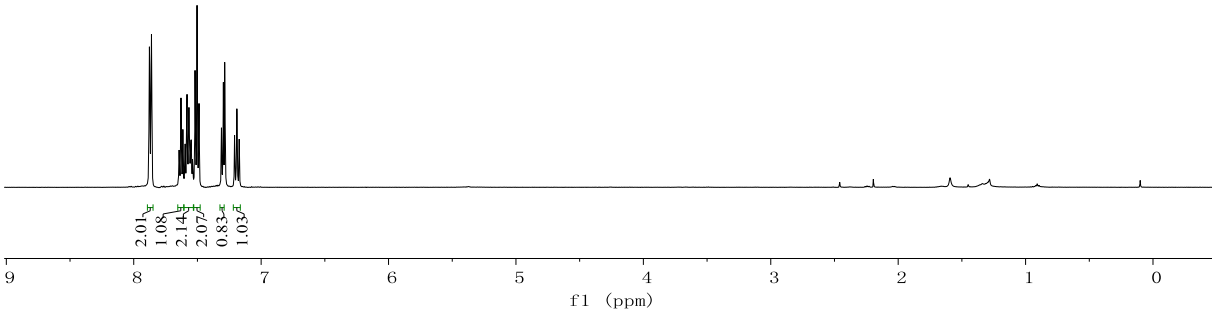

2.00
2.09
2.27
0.90
2.04
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

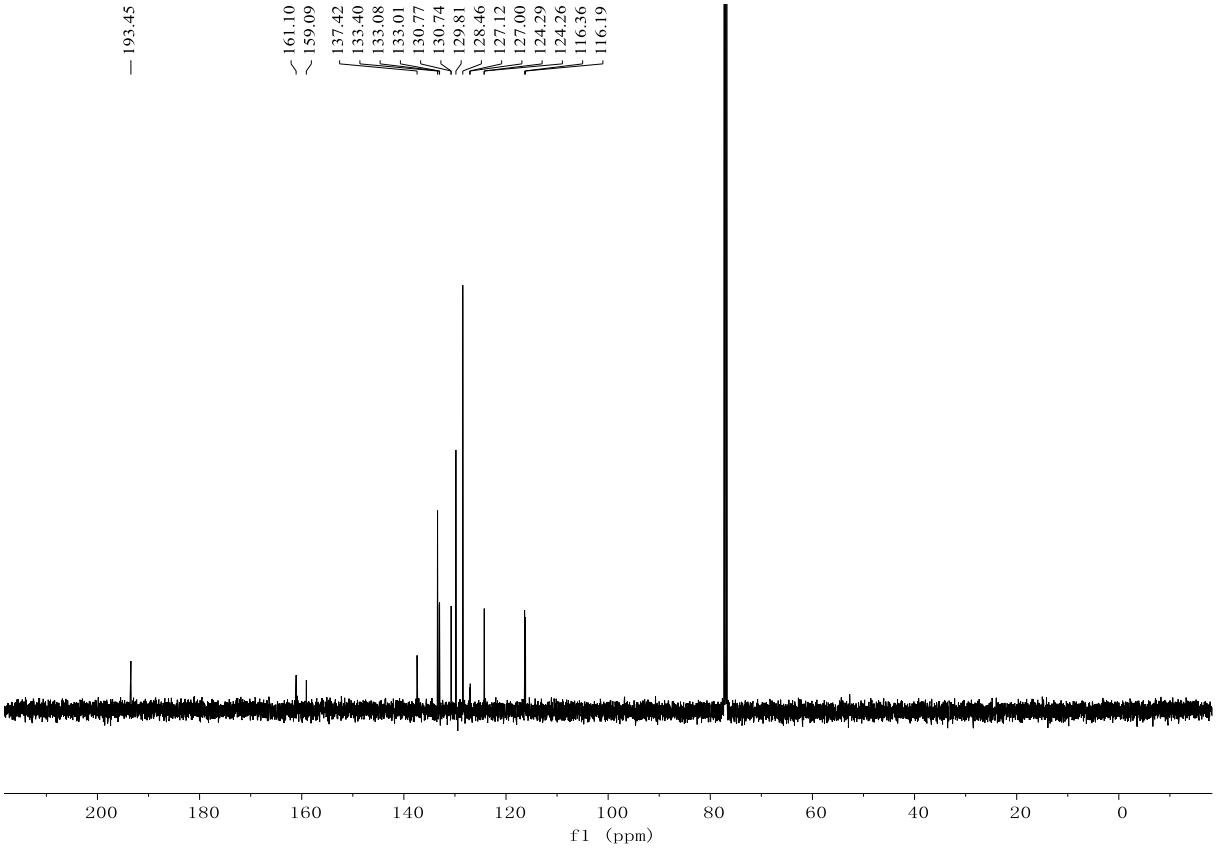

195.62
137.19
136.33
132.67
131.62
131.56
129.94
128.41
127.51
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

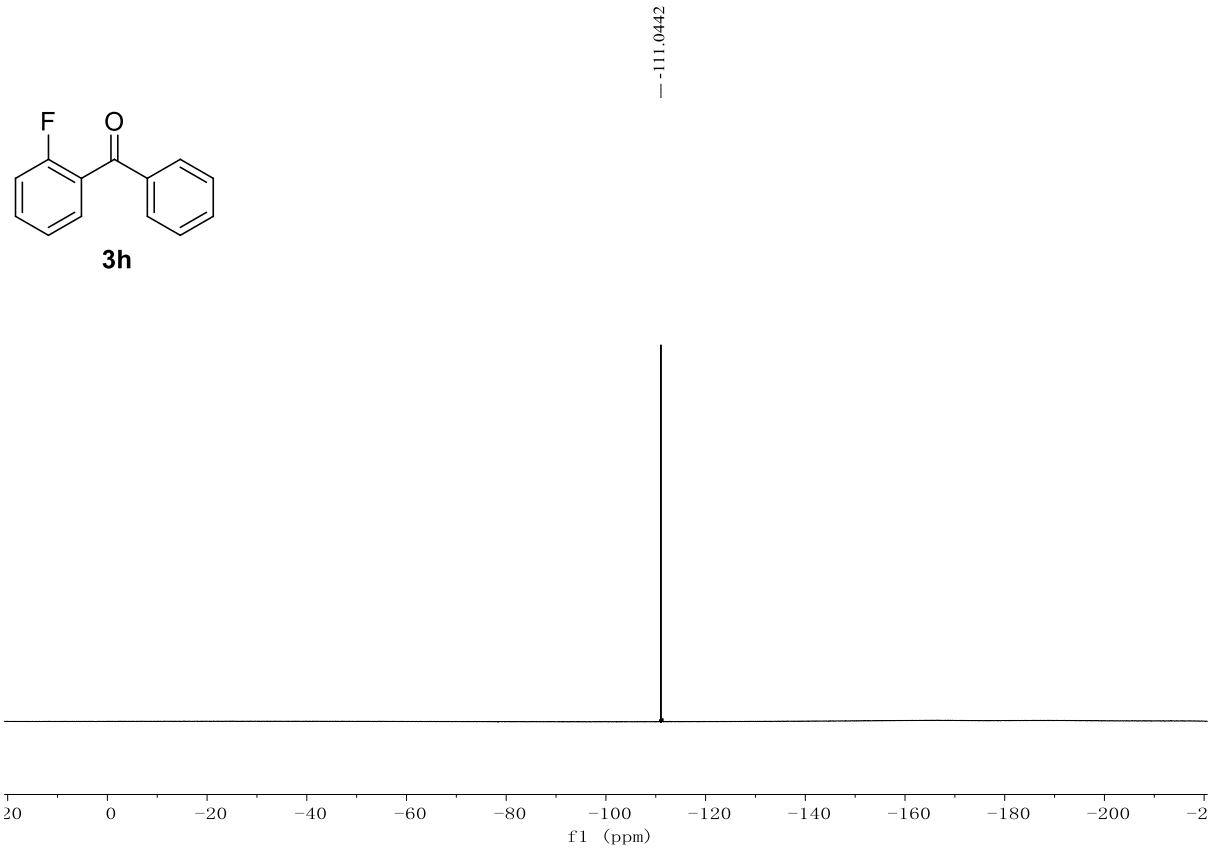

7.8769
7.8607
7.6439
7.6290
7.6142
7.5996
7.5964
7.5816
7.5703
7.5668
7.5542
7.5497
7.5458
7.5387
7.5353
7.5186
7.5030
7.4877
7.3114
7.2964
7.2086
7.1904
7.1723

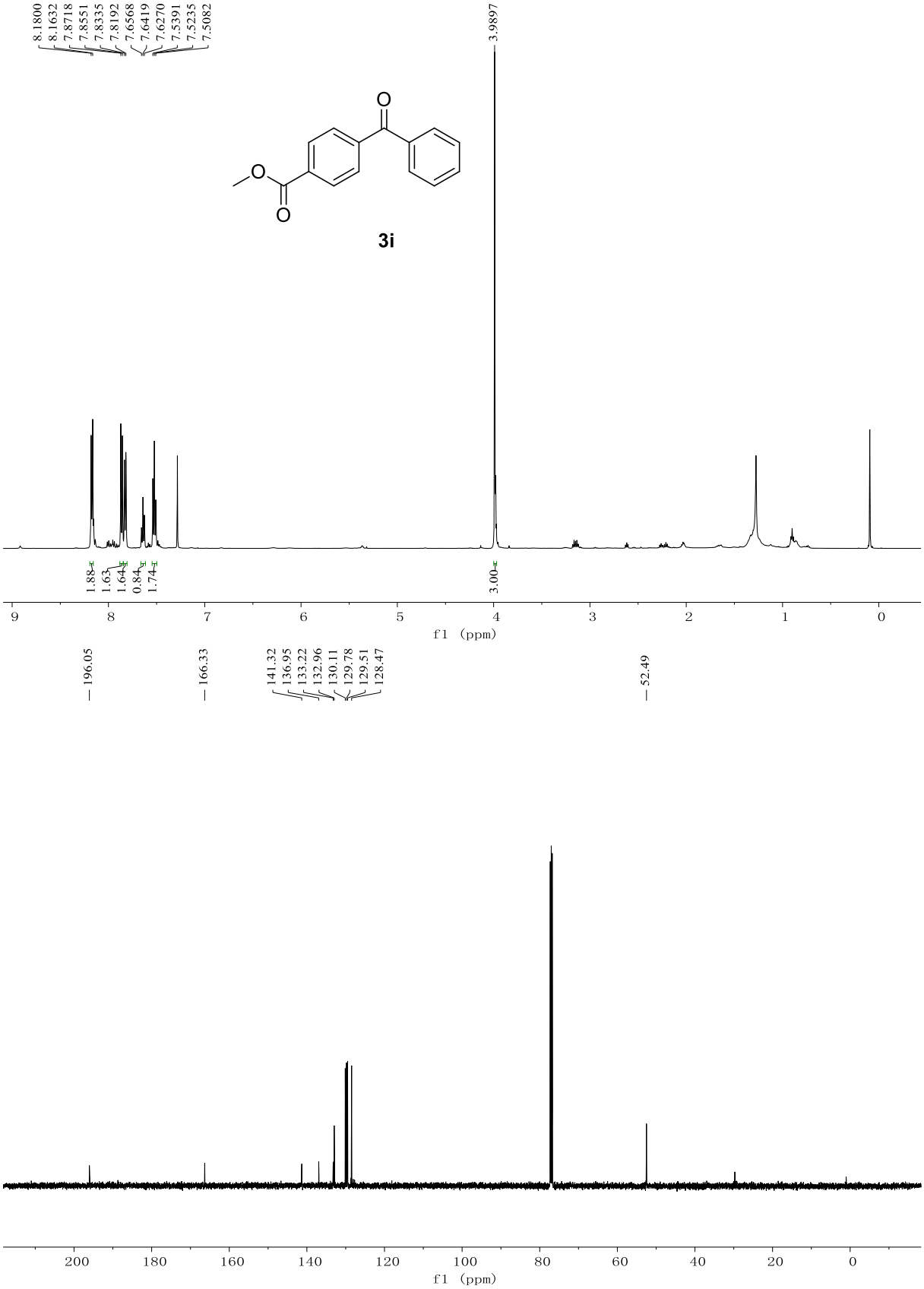

F
O

3h

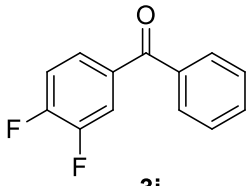

2.01
1.08
2.14
2.07
0.83
1.03
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


193.45
161.10
159.09
137.42
133.40
133.08
133.01
130.77
130.74
129.81
128.46
127.12
127.00
124.29
124.26
116.36
116.19
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

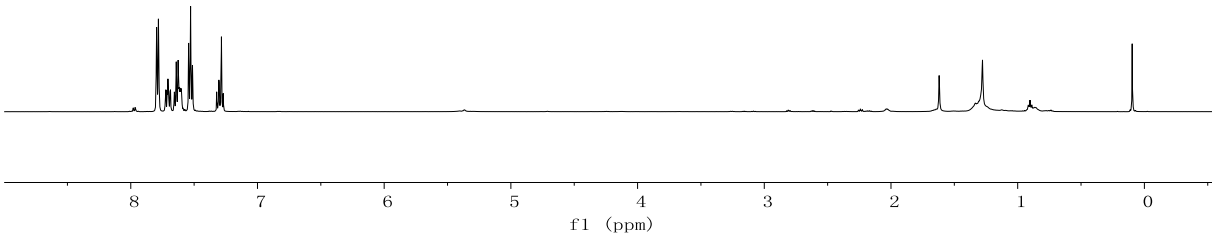

-111.0442
F
O
3h
20
0
−20
−40
−60
−80
−100
−120
−140
−160
−180
−200
−2
f1 (ppm)

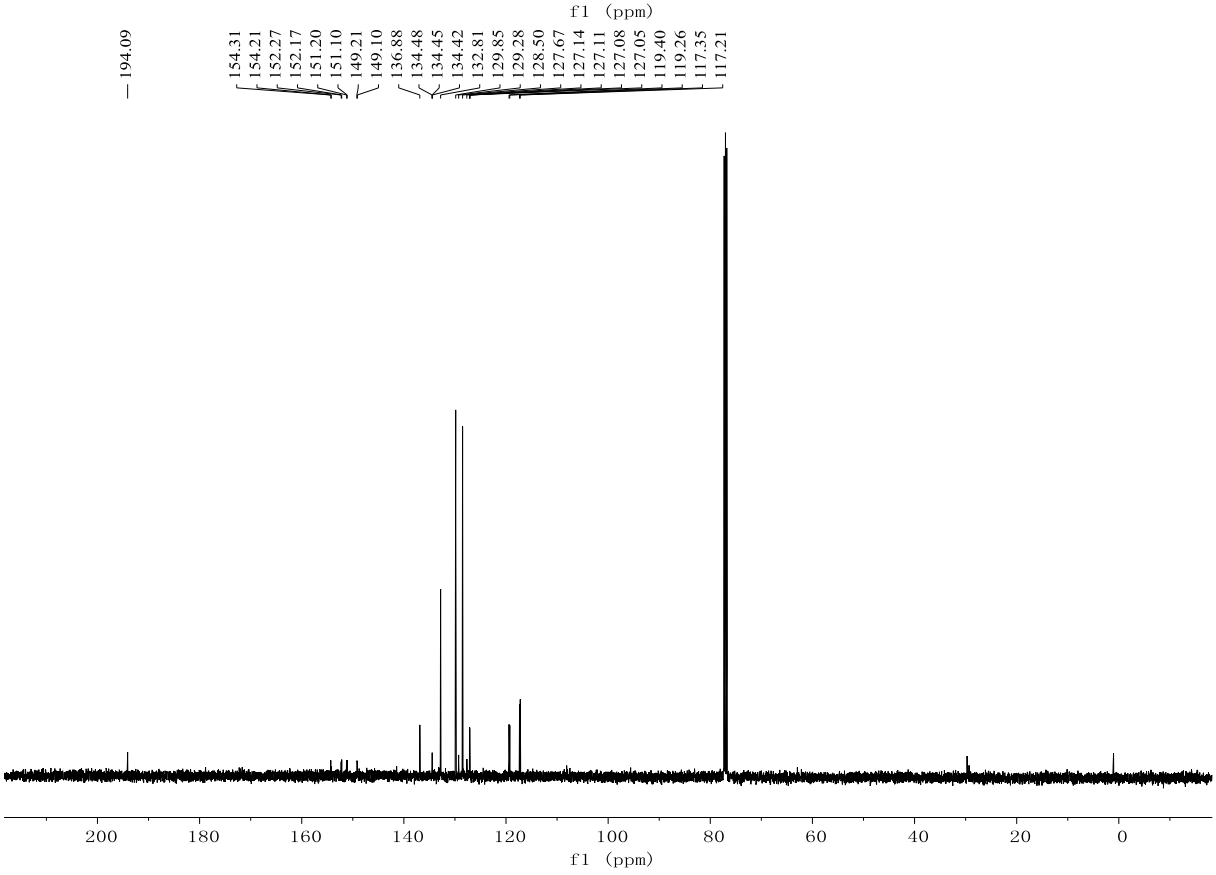

8.1800
8.1632
7.8718
7.8551
7.8335
7.8192
7.6568
7.6419
7.6270
7.5391
7.5235
7.5082
3.9897
O
O
O
3i
1.88
1.63
1.64
0.84
1.74
3.00
f1 (ppm)
196.05
166.33
141.32
136.95
133.22
132.96
130.11
129.78
129.51
128.47
52.49
f1 (ppm)

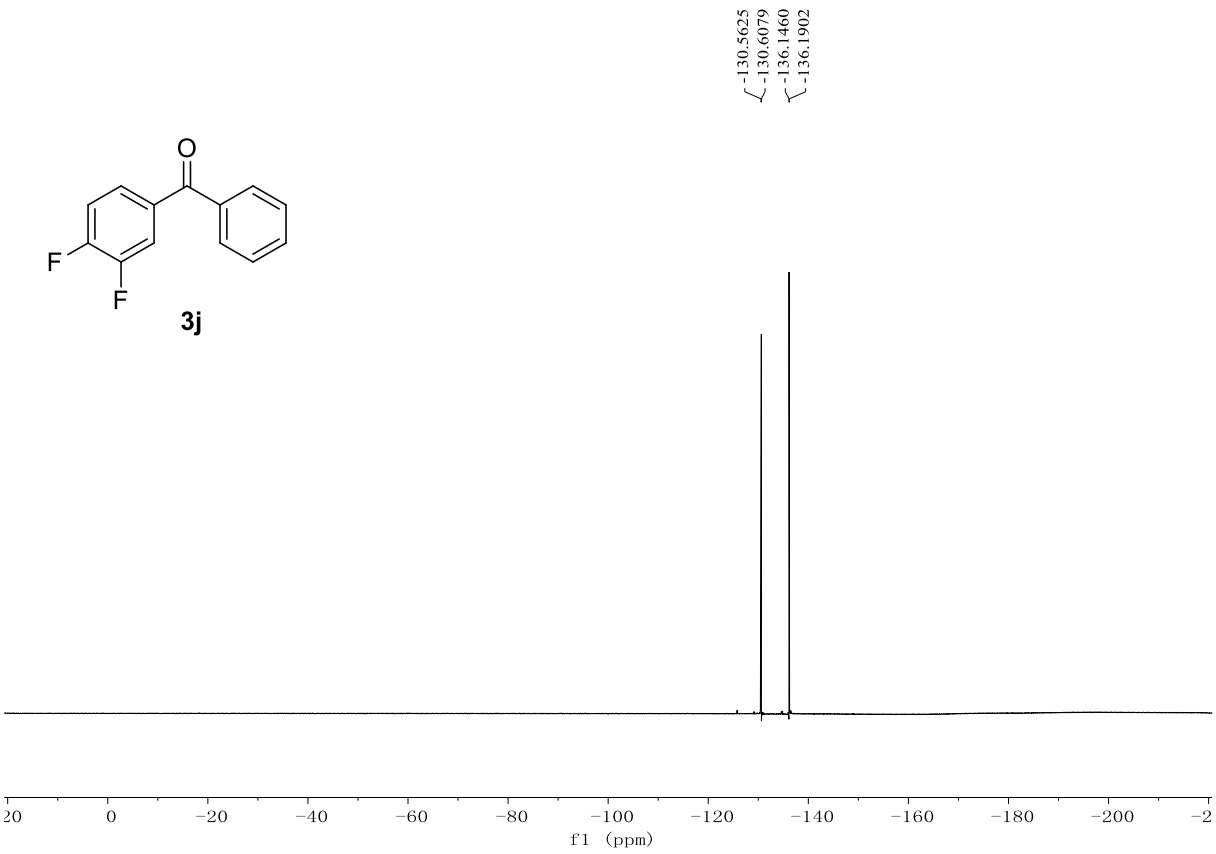

7.7960
7.7818
7.7271
7.7231
7.7118
7.7068
7.7020
7.6907
7.6866
7.6559
7.6410
7.6261
7.5436
7.5280
7.5129
7.3219
7.3051
7.2844
7.2702

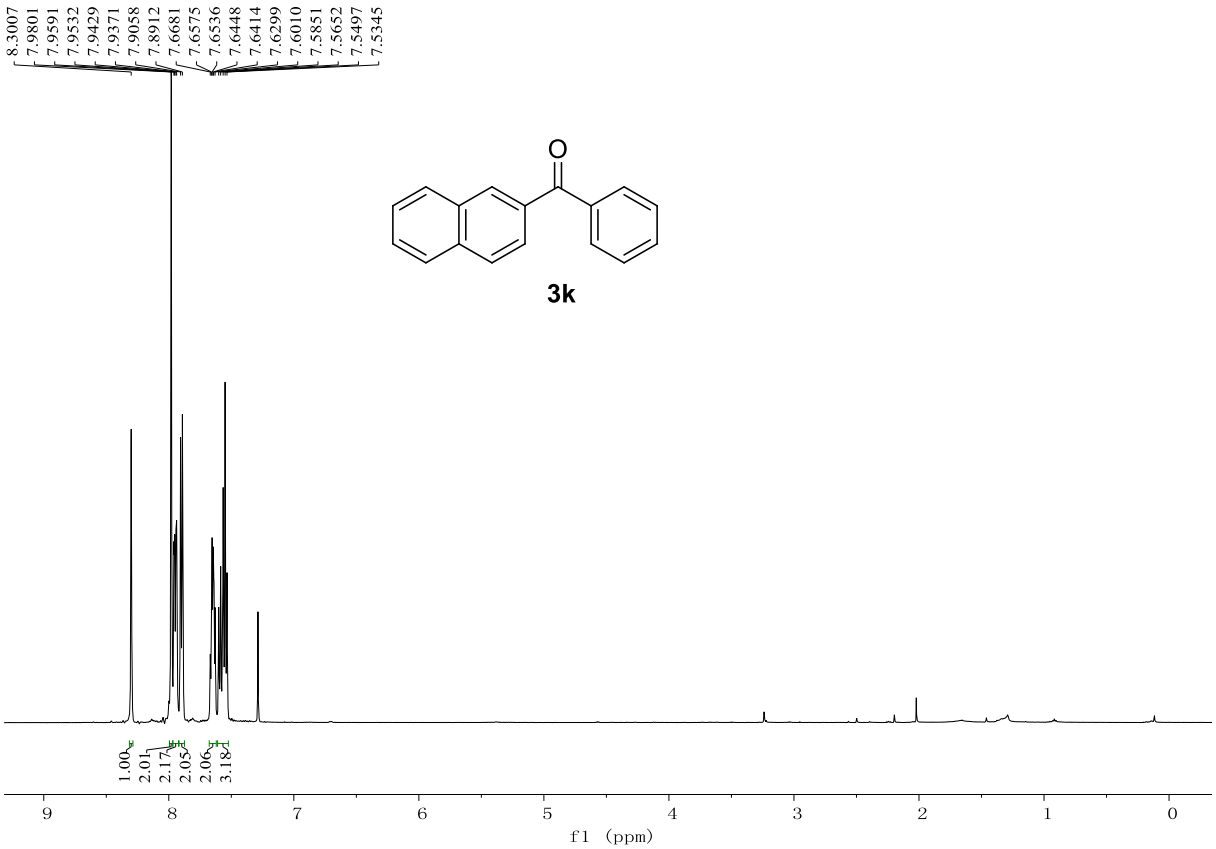

O
F
F

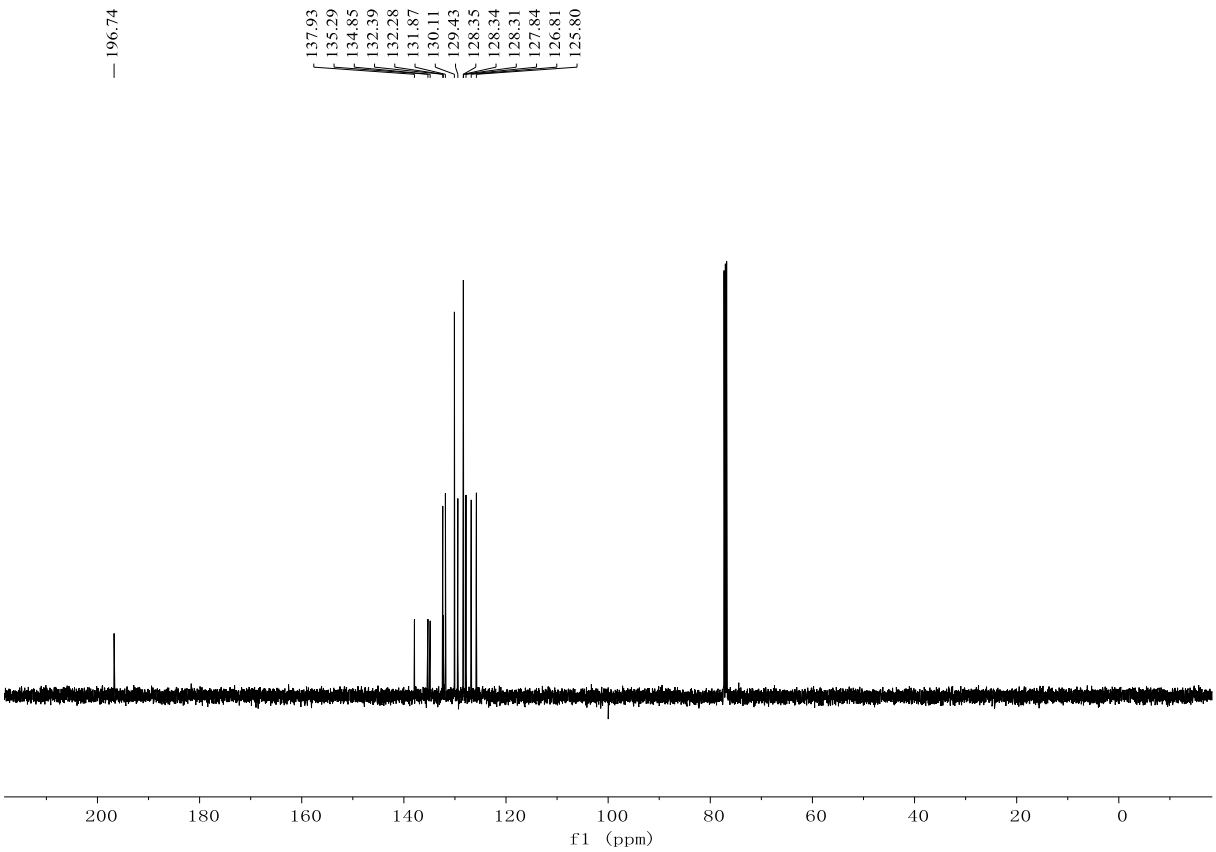
3j

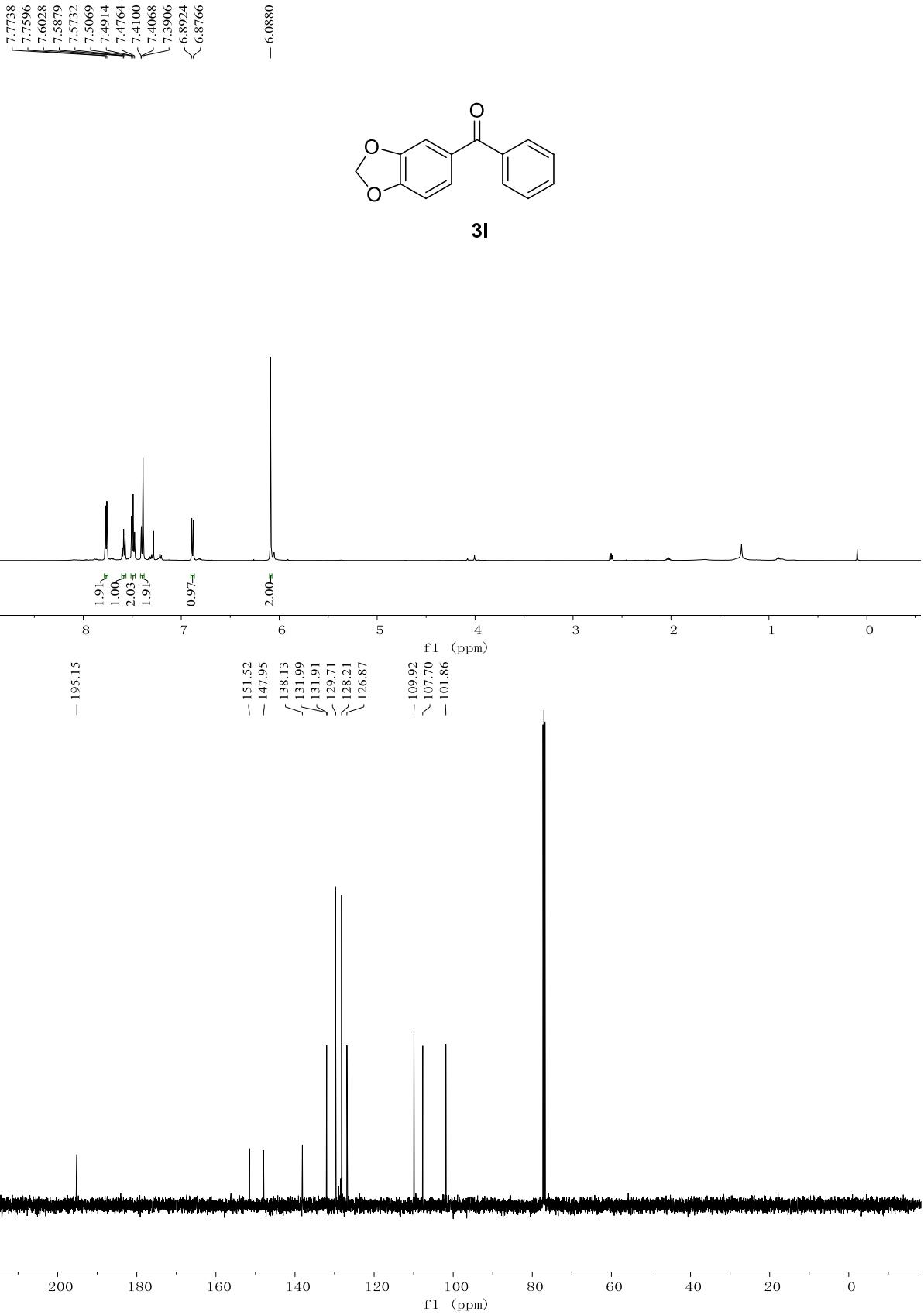

8
7
6
5
4
3
2
1
0
f1 (ppm)


194.09
154.31
154.21
152.27
152.17
151.20
151.10
149.21
149.10
136.88
134.48
134.45
134.42
132.81
129.85
129.28
128.50
127.67
127.14
127.11
127.08
127.05
119.40
119.26
117.35
117.21
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


-130.5625
-130.6079
-136.1460
-136.1902
O
F
F
3j
20
0
−20
−40
−60
−80
−100
−120
−140
−160
−180
−200
−2
f1 (ppm)


8.3007
7.9801
7.9591
7.9532
7.9429
7.9371
7.9058
7.8912
7.6681
7.6575
7.6536
7.6448
7.6414
7.6299
7.6010
7.5851
7.5652
7.5497
7.5345
O
3k
1.00
2.01
2.17
2.05
2.06
3.18
f1 (ppm)


196.74
137.93
135.29
134.85
132.39
132.28
131.87
130.11
129.43
128.35
128.34
128.31
127.84
126.81
125.80
f1 (ppm)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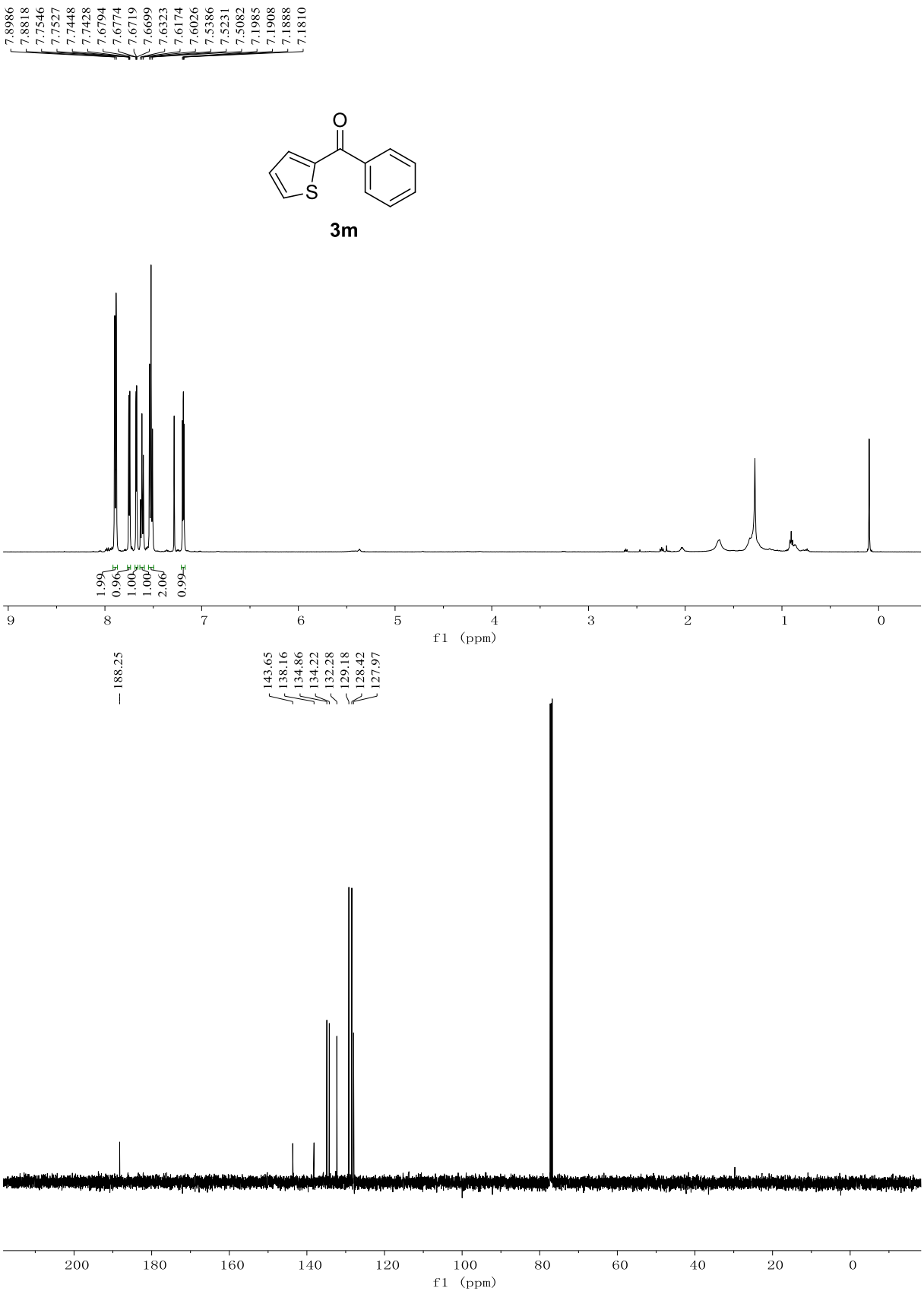
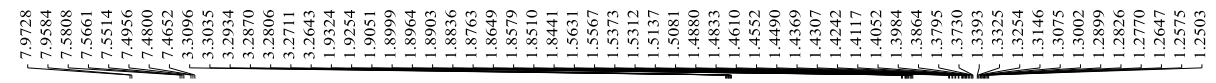
7.7596
7.6028
7.5879
7.5732
7.5069
7.4914
7.4764
7.4100
7.4068
7.3906
6.8924
6.8766
6.0880
O
O
O
3l
1.91
1.00
2.03
1.91
0.97
2.00
f1 (ppm)
195.15
151.52
147.95
138.13
131.99
131.91
129.71
128.21
126.87
109.92
107.70
101.86
f1 (ppm)


7.8986
7.8818
7.7546
7.7527
7.7448
7.7428
7.6794
7.6774
7.6719
7.6699
7.6323
7.6174
7.6026
7.5386
7.5231
7.5082
7.1985
7.1908
7.1888
7.1810
O
S
3m
1.99
0.96
1.00
1.00
2.06
0.99
f1 (ppm)
188.25
143.65
138.16
134.86
134.22
132.28
129.18
128.42
127.97
f1 (ppm)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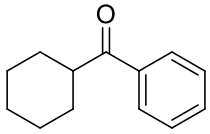
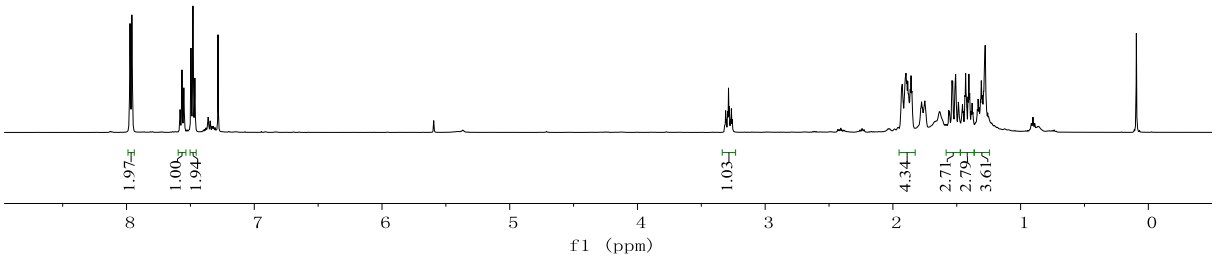
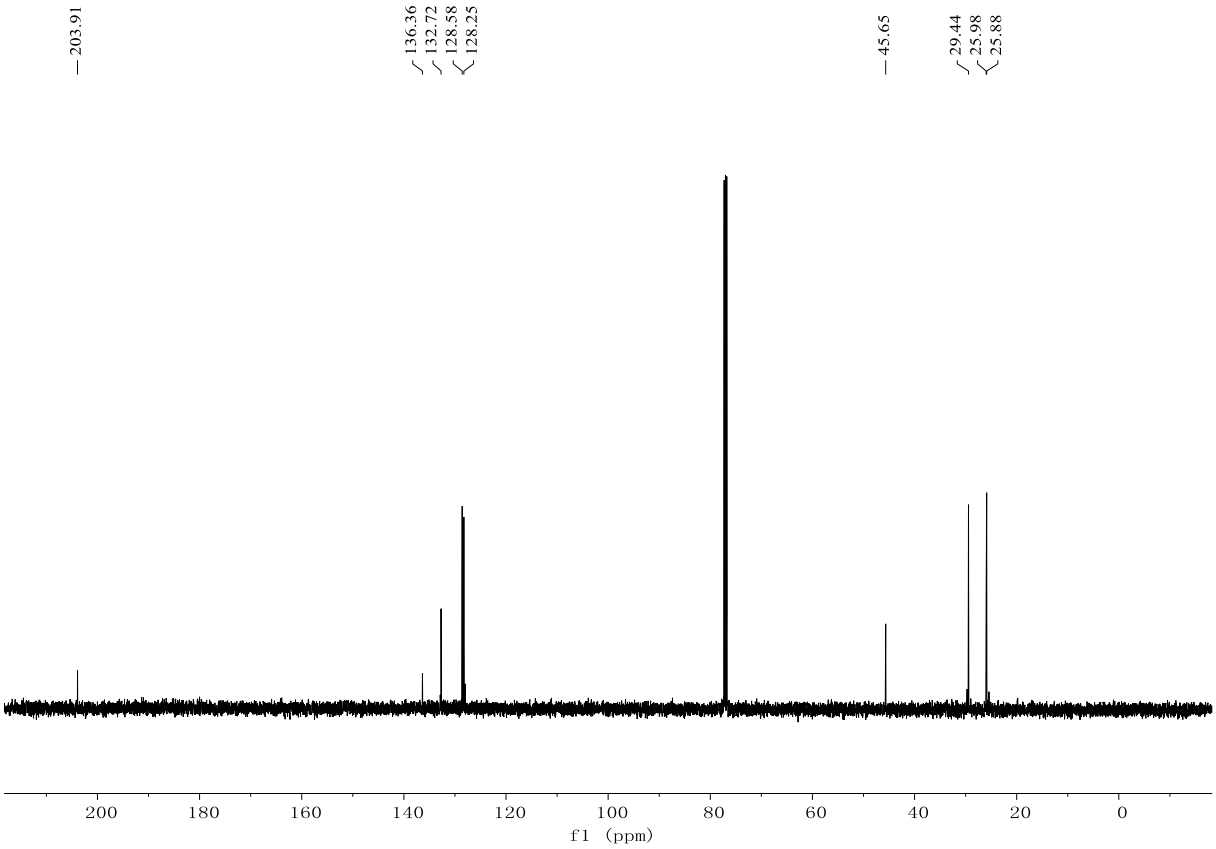
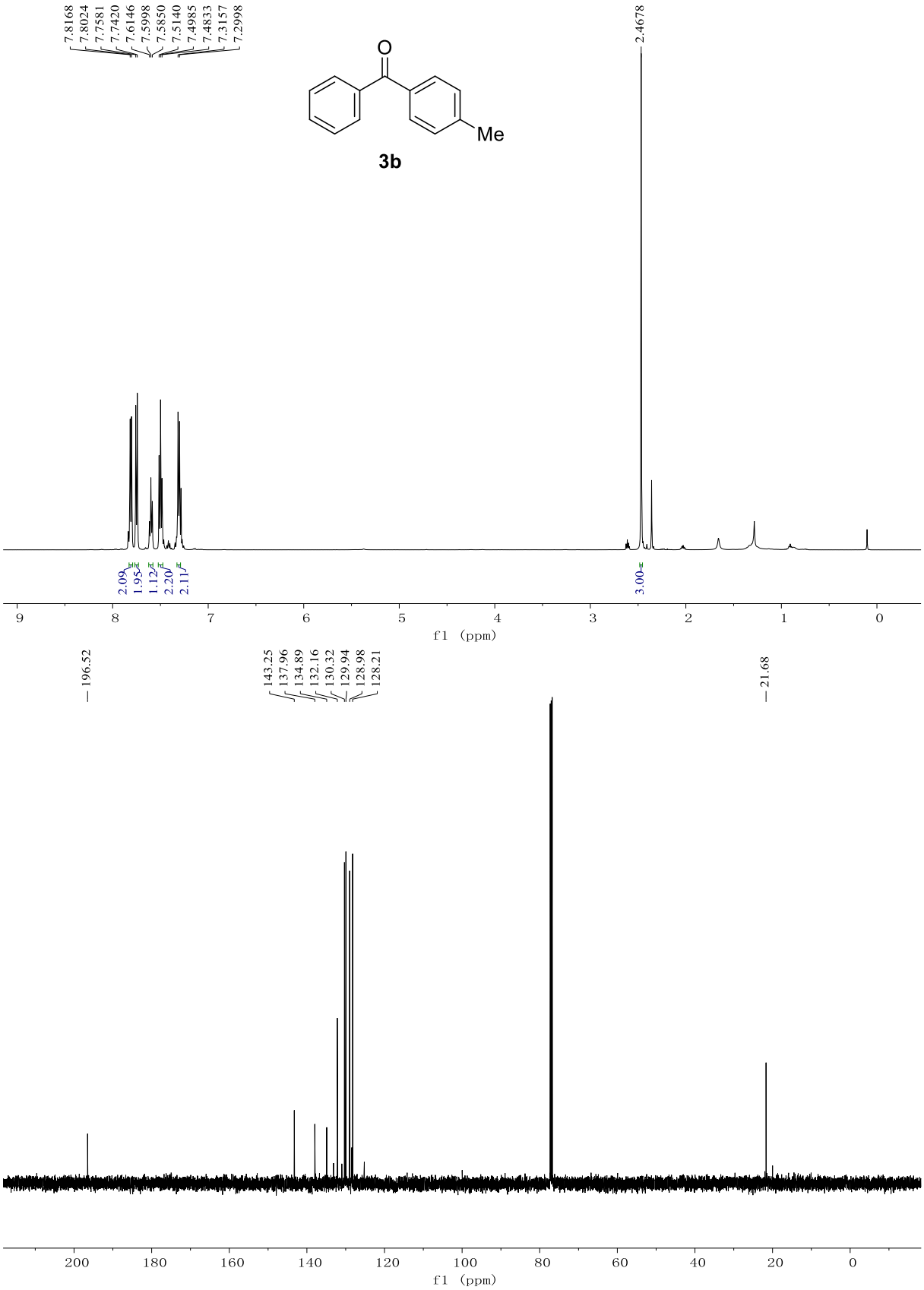
7.9584
7.5808
7.5661
7.5514
7.4956
7.4800
7.4652
3.3096
3.3035
3.2934
3.2870
3.2806
3.2711
3.2643
1.9324
1.9254
1.9051
1.8999
1.8964
1.8903
1.8836
1.8763
1.8649
1.8579
1.8510
1.8441
1.5631
1.5567
1.5373
1.5312
1.5137
1.5081
1.4880
1.4833
1.4610
1.4552
1.4490
1.4369
1.4307
1.4242
1.4117
1.4052
1.3984
1.3864
1.3795
1.3730
1.3393
1.3325
1.3254
1.3146
1.3075
1.3002
1.2899
1.2826
1.2770
1.2647
1.2575
1.2503


O

3n


1.97
1.00
1.94
1.03
4.34
2.71
2.79
3.61
8
7
6
5
4
3
2
1
0
f1 (ppm)


203.91
136.36
132.72
128.58
128.25
45.65
29.44
25.98
25.88
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)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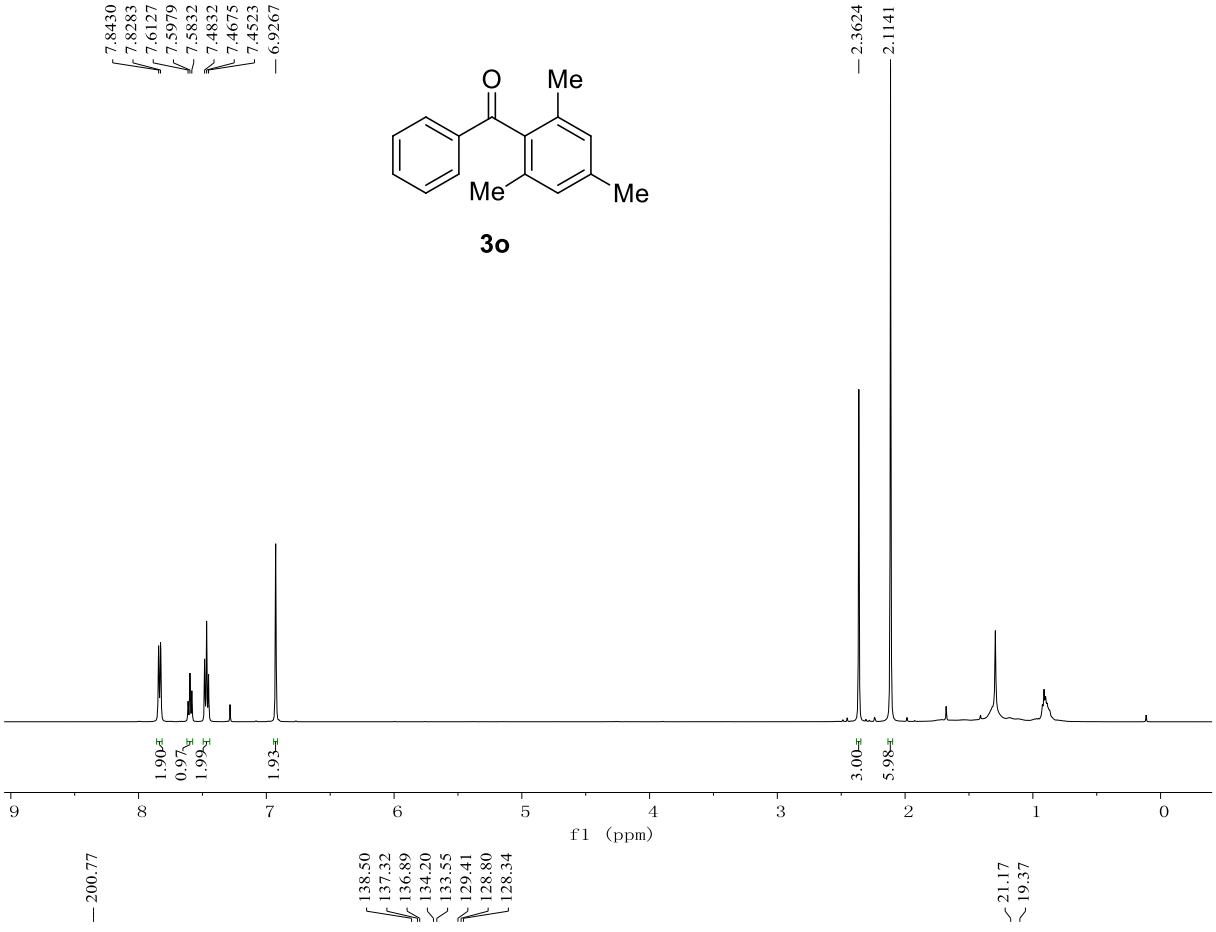
7.7581
7.7420
7.6146
7.5998
7.5850
7.5140
7.4985
7.4833
7.3157
7.2998
2.4678
O
Me
3b
2.09
1.95
1.12
2.20
2.11
3.00
f1 (ppm)
196.52
143.25
137.96
134.89
132.16
130.32
129.94
128.98
128.21
21.68
f1 (ppm)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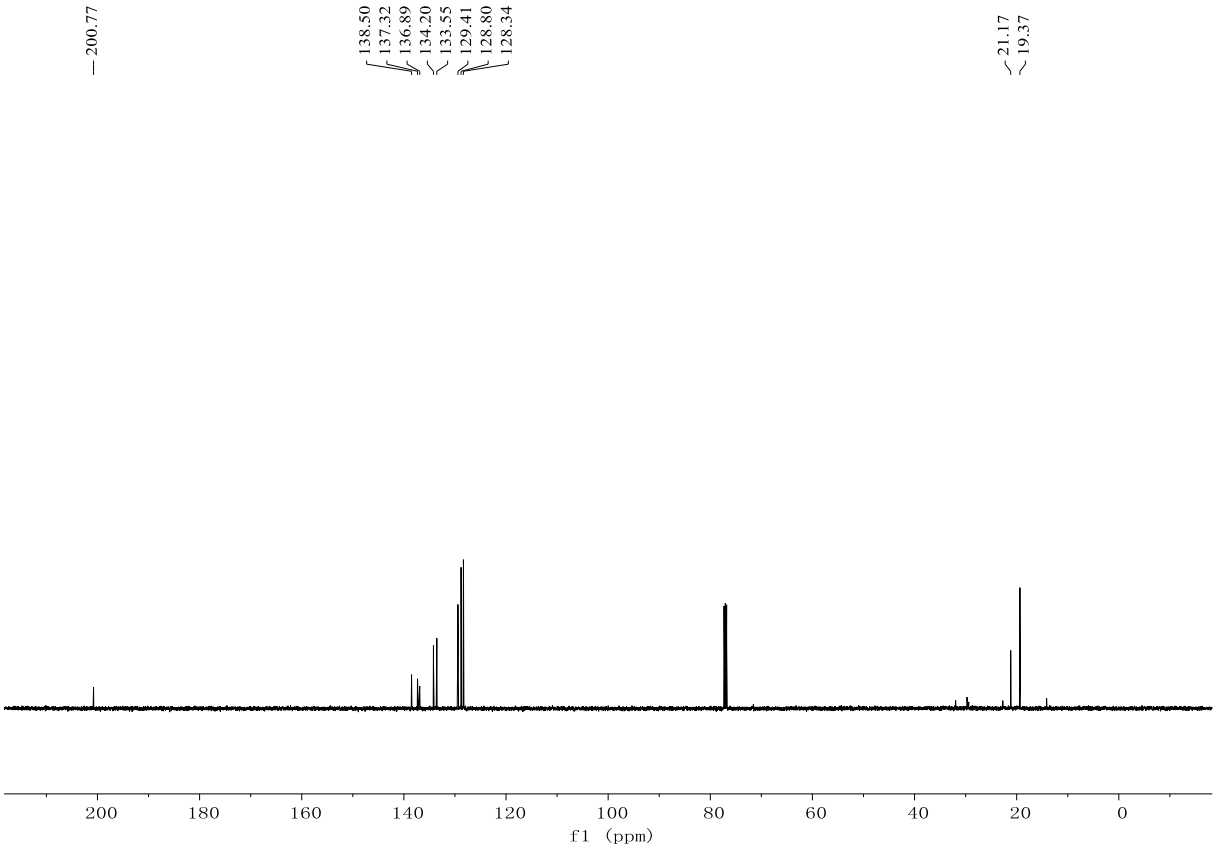
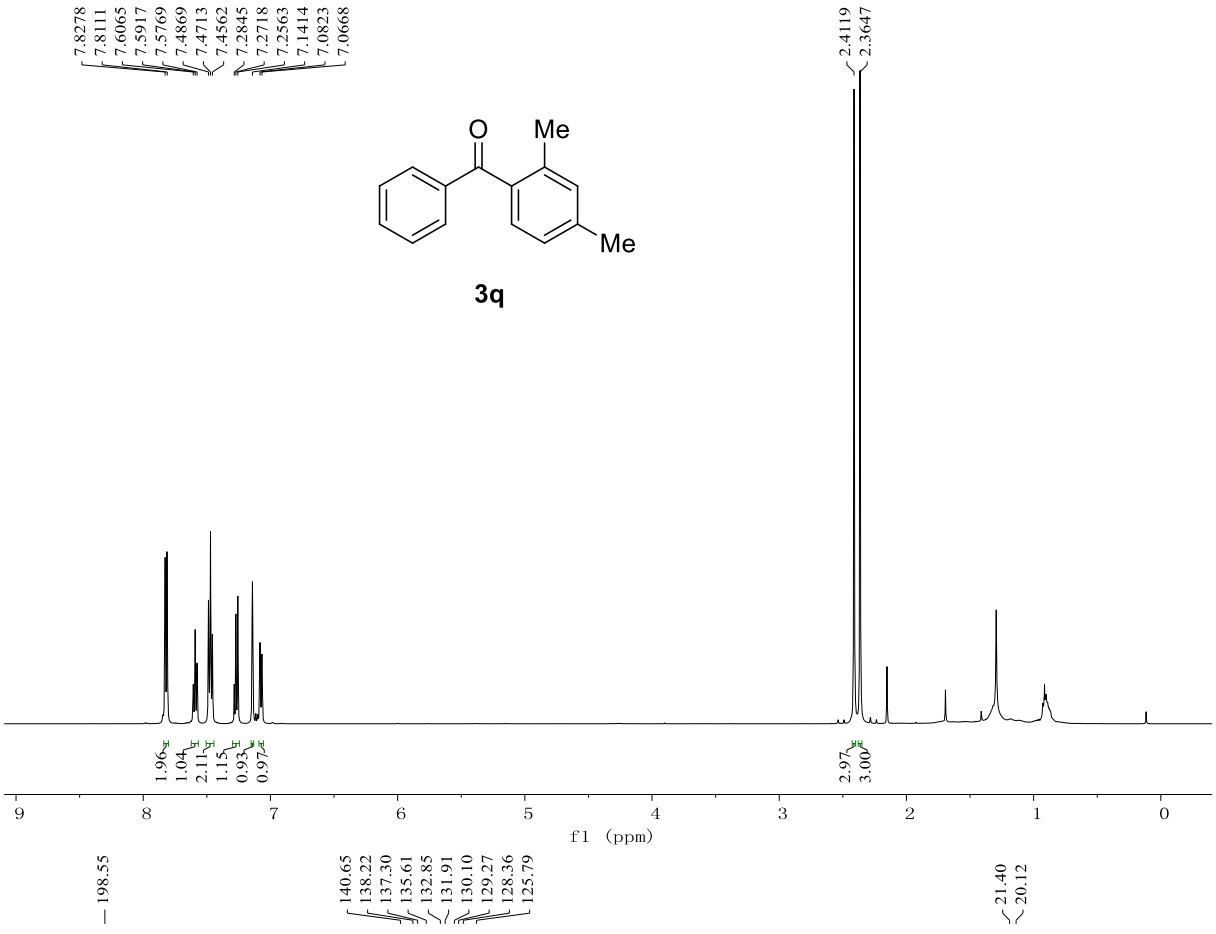
7.8283
7.6127
7.5979
7.5832
7.4832
7.4675
7.4523
6.9267
2.3624
2.1141
O
Me
Me
Me
1.90
0.97
1.99
1.93
3.00
5.98
f1 (ppm)

3o


200.77
138.50
137.32
136.89
134.20
133.55
129.41
128.80
128.34
21.17
19.37
f1 (ppm)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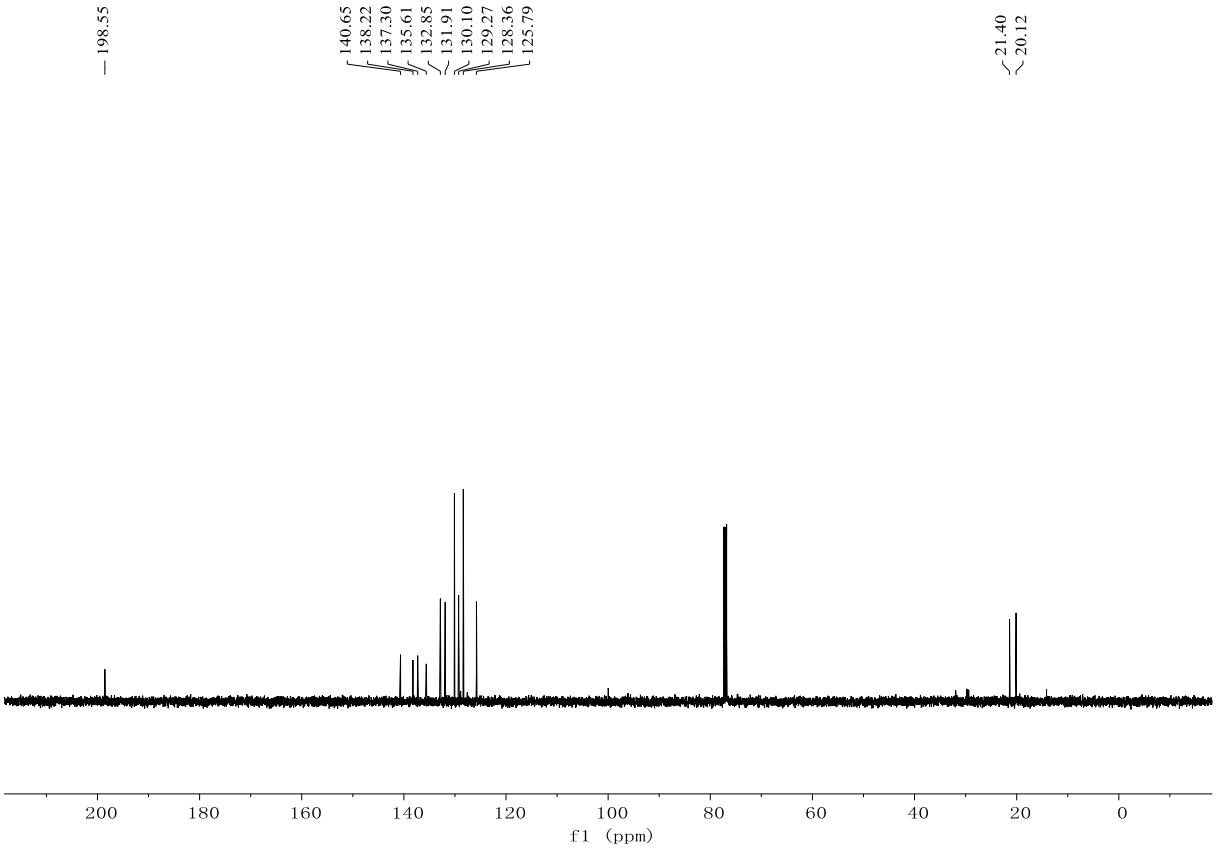
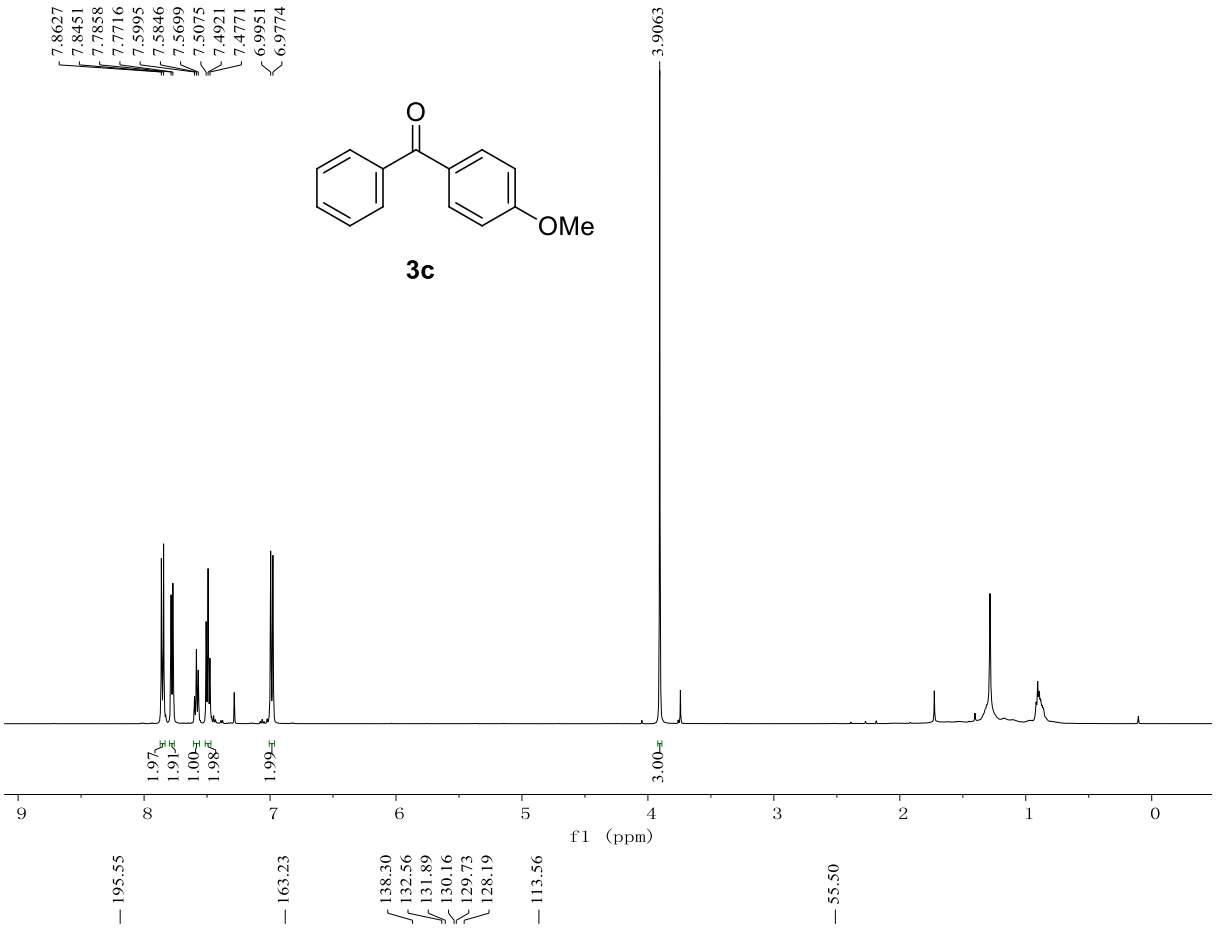
7.6065
7.5917
7.5769
7.4869
7.4713
7.4562
7.2845
7.2718
7.2563
7.1414
7.0823
7.0668
2.4119
2.3647
O
Me
Me
3q
1.96
1.04
2.11
1.15
0.93
0.97
2.97
3.00
f1 (ppm)


198.55
140.65
138.22
137.30
135.61
132.85
131.91
130.10
129.27
128.36
125.79
21.40
20.12
f1 (ppm)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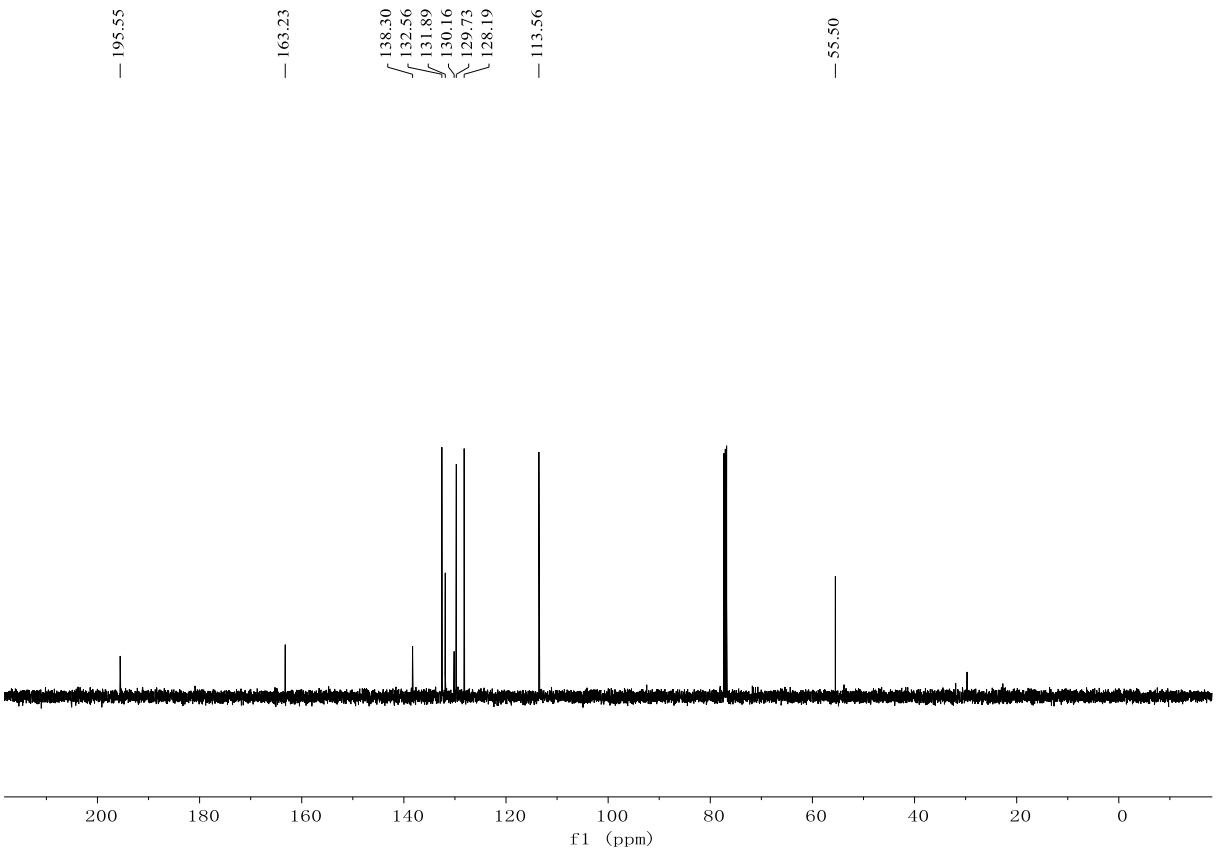
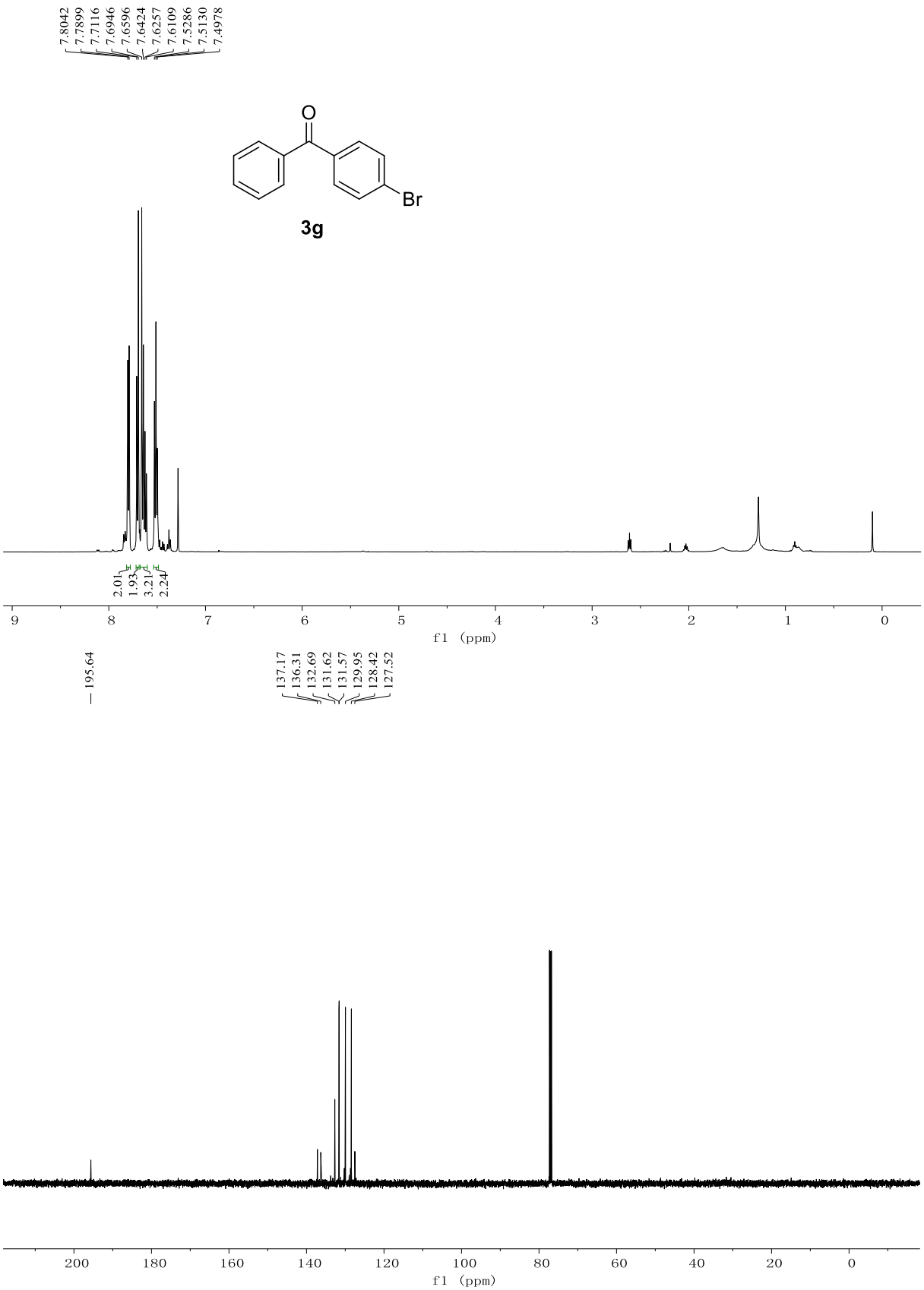
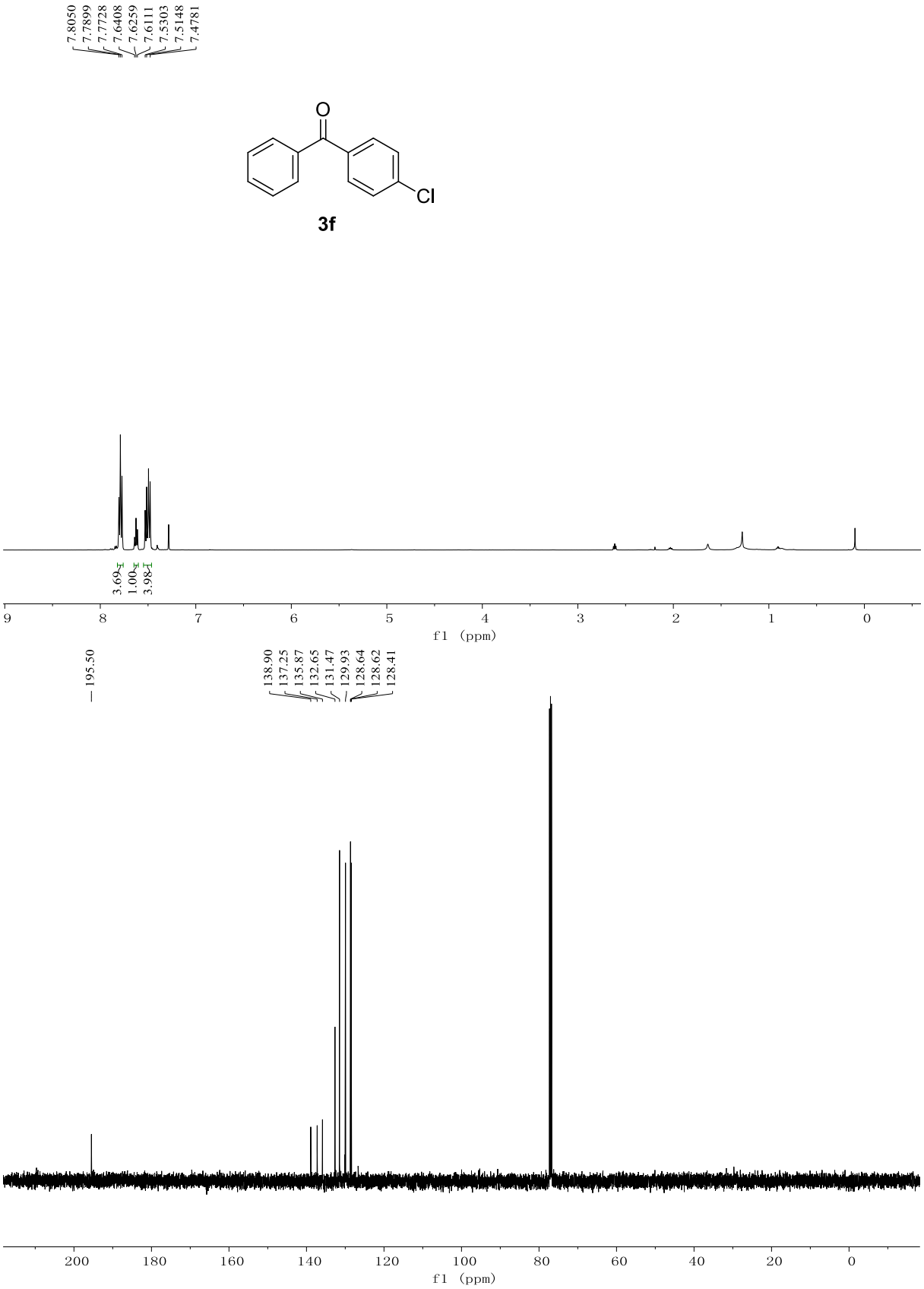
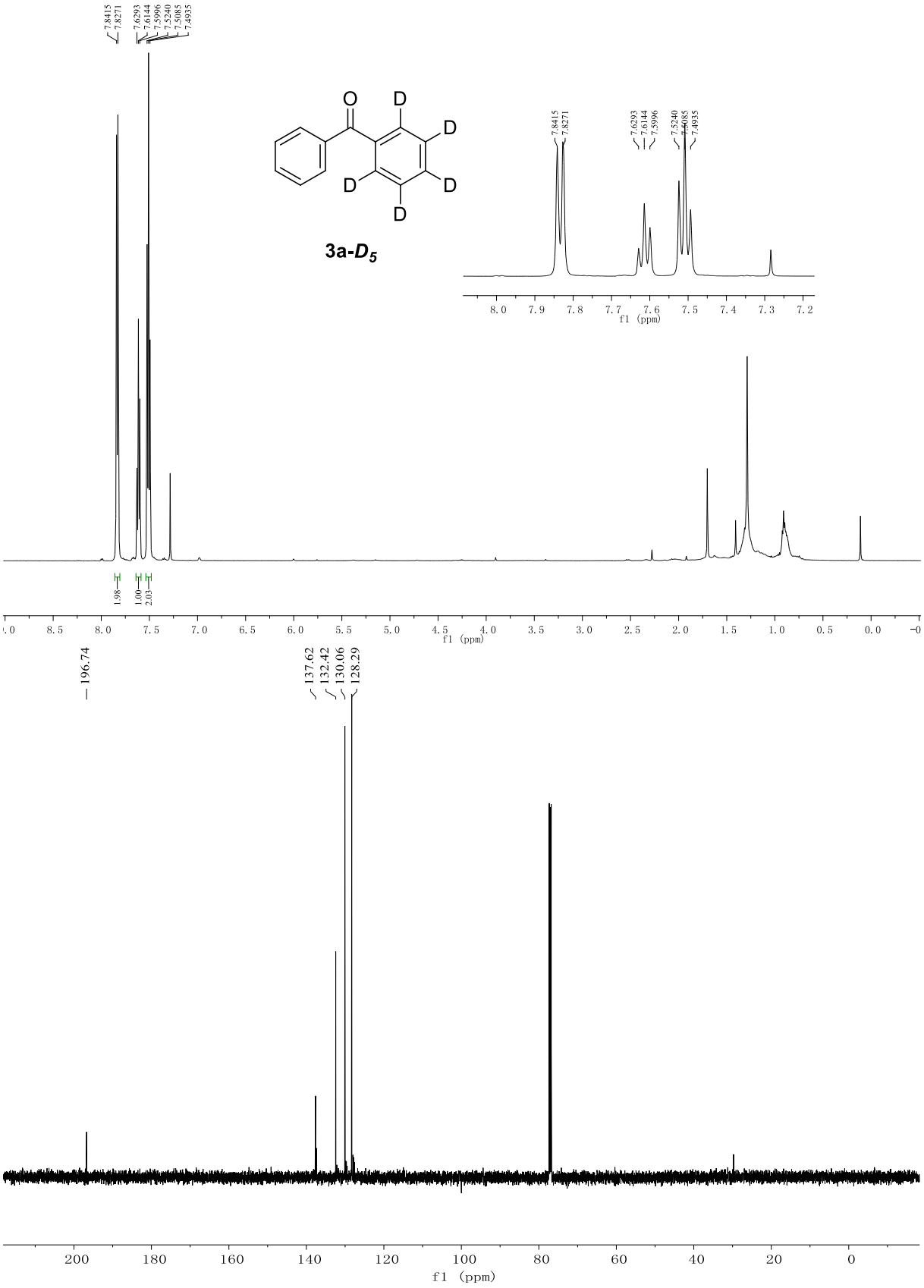
7.8451
7.7858
7.7716
7.5995
7.5846
7.5699
7.5075
7.4921
7.4771
6.9951
6.9774
3.9063
O
OMe
3c
1.97
1.91
1.00
1.98
1.99
3.00
f1 (ppm)


195.55
163.23
138.30
132.56
131.89
130.16
129.73
128.19
113.56
55.50
f1 (ppm)


7.8042
7.7899
7.7116
7.6946
7.6596
7.6424
7.6257
7.6109
7.5286
7.5130
7.4978
O
Br
3g
2.01
1.93
3.21
2.24
f1 (ppm)
195.64
137.17
136.31
132.69
131.62
131.57
129.95
128.42
127.52
f1 (ppm)


7.8050
7.7899
7.7728
7.6408
7.6259
7.6111
7.5303
7.5148
7.4781
O
Cl
3f
3.69
1.00
3.98
f1 (ppm)
195.50
138.90
137.25
135.87
132.65
131.47
129.93
128.64
128.62
128.41
f1 (ppm)


7.8415
7.8271
7.6293
7.6144
7.5996
7.5240
7.5085
7.4935
O
D
D
D
D
D
3a-D_5
1.98
1.00
2.03
f1 (ppm)
196.74
137.62
132.42
130.06
128.29
f1 (ppm)