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Cu-Catalyzed Aerobic Oxygenation of 2-Phenoxyacetophenones to AlkyloxyAcetophenones

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1. Experimental section.

Materials

All reagents and solvents were purchased from Acros, Tci, Alfa-Aesar, Sigma-Aldrich and Beijing Chemical Company, Ltd.Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.Lignin model compoundwere prepared following procedures reported in the literaturewith some modifications.

Instrumentation

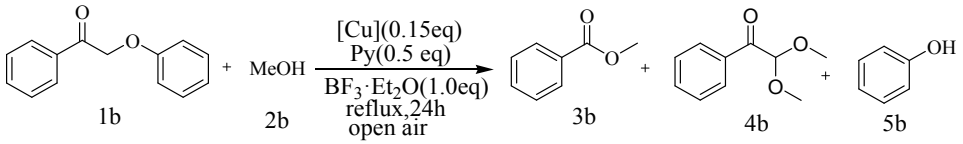
Products were purified by flashchromatography on silica gel.Electron Impact Mass (EI MS) Spectra were performed on DFS Mass Spectrometer.Analysis of crude reaction mixture was performed on an Agilent 7890BGCSystem with a HP-INNOWAX capillary column (30 m×0.25 mm×0.25 μm)and an FID detector. The following GC temperature program was used: 50 °C hold for 2 min, ramp 20 °C/min to a final temperature of 260 °C, and hold for 8 min. Nitrogen was used as a carrier gas. The injector temperature was held at 250 °C.GC-MS analysis was carried out on a SHIMADZU GCMS-QP2010 with a DB-5 capillary column (30 m×0.25 mm×0.25 μm). ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO using internal reference (the residue proton peaks of $CHCl_3$ at 7.26 ppm and DMSO at 2.5 ppm) on Bruker 400 spectrometer. Liquid ^{13}C NMR was recorded at 100.6 MHz in $CDCl_3$ using residual $CHCl_3$ as internal reference (the residue proton peaks of $CHCl_3$ at 77.02ppm and DMSO at 40.03 ppm).X-Ray photoelectron spectroscopy (XPS) data were collected on an ESCALab220i-XL electron spectrometer from VG Scientific using 300 W Al-Kα radiation. The base pressure was about 3×10^{-9} mbar. The binding energies were referenced to the C1s line at 284.8 eV from adventitious carbon.

Catalytic reaction

Typically, substrate(0.5 mmol), alcohol (1 mL), catalyst (0.075 mmol), ligand (0.25 mmol), additive (0.5 mmol) were introduced into a 5 mL glass reactor. The reaction mixture was heated to the designated temperature in an oil bath and kept at that temperature for desired reaction time.After that, an aqueous solution of HCl (10mL, 1.0M) was added to the reaction system, and then 3*10 mL CH_2Cl_2 was added to extract organic compounds.The organic phase with n-dodecane as an internal standard was analysed by GC, affording the GC product yield. Then, the organic phase was purified by column chromatographyover silica gel to obtain the desired product(eluent: petroleum ether/ethyl acetate = 100/1), and the product yield was denoted as isolated yield. The isolated products were identified by NMR.

2. Additionalscreening of reaction conditions

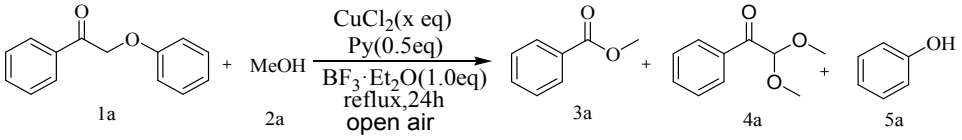
Table S1.Evaluation of Cu catalysts [a]



Entry	[Cu]	Yield (%)[b]			Conversion (%)
		3a	4a	5a	
1	$CuBr_2$	36.2	25.0	71.5	85.9
2	CuBr	44.9	4.3	84.5	96.3
3	$CuCl_2$	36.8	62.7	99.5	99.9
4	CuCl	30.1	23.4	65.6	99.9
5	CuO	11.2	38.5	82.2	90.6
6	Cu_2O	24.1	28.4	14.3	45.9
7	CuI	15.7	8.8	75.0	83.1
8	CuOAc	13.5	21.4	53.4	59.0
9	$CuCl_2·2H_2O$	29.4	48.7	88.8	89.9

[a]Reaction conditions: 1a (0.5mmol), 2a (1.0mL), Cu salts (0.15equiv.),pyridine (0.5 equiv.), BF_3•Et_2O (1.0 equiv.). [b]GC yield.

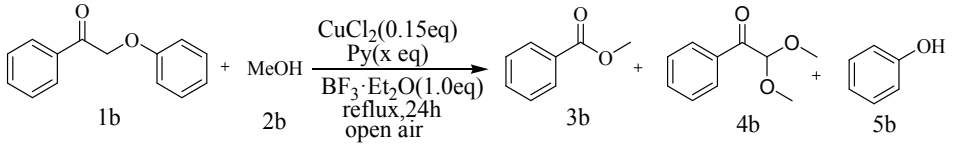
Table S2. The effects of $CuCl_2$loading[a]



Entry	$CuCl_2$(x eq)	Yield (%)[b]			Conversion (%)
		3a	4a	5a	
1	0.05	9.1	6.3	71.6	71.6
2	0.1	29.4	44.1	93.8	93.8
3	0.15	36.8	62.7	99.5	99.9

[a]Reaction conditions: 1a (0.5mmol), 2a (1.0mL), $CuCl_2$, Pyridine (0.5equiv.), BF_3•Et_2O (1.0equiv.). [b]GC yield.

Table S3. The effects of pyridine loading[a]



Entry	Py(x eq)	Yield (%)[b]			Conversion (%)
		3a	4a	5a	
1	0.1	39.4	36.4	87.8	99.9
2	0.2	41.3	44.0	83.4	99.9
3	0.5	36.8	62.7	99.5	99.9
4	1	38.4	47.7	98.3	99.9

[a]Reaction conditions: 1a (0.5mmol), 2a (1.0mL), $CuCl_2$ (0.15equiv.),pyridine, BF_3•Et_2O (1.0equiv.). [b]GC yield.

3. Control experiments

Some potential intermediates were subjected to the reaction system.

When we shorten the reaction time, we could make the reaction stay at incomplete stage. We found I (phenylglyoxal) was an intermediate through GC-MS. (Figure S1)

And D could further reacted to form 4a.

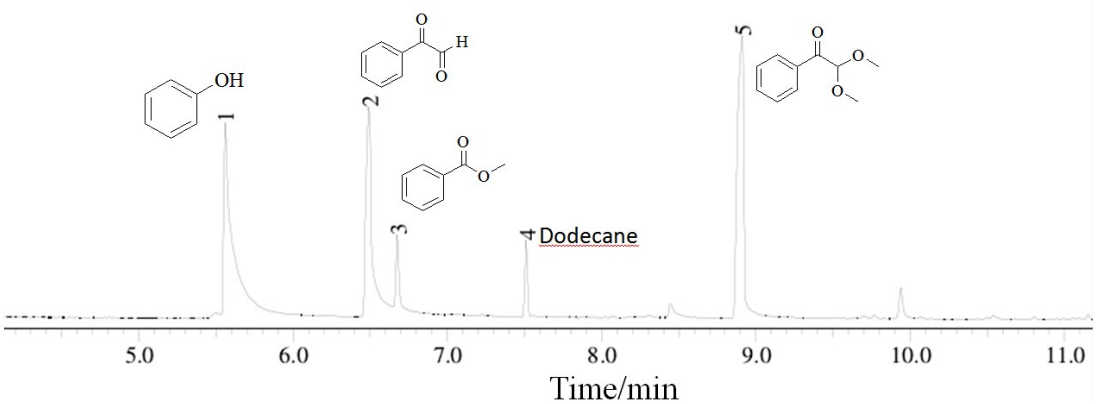


Figure S1 GC-MS of the reaction solution. Conditions: 1a (0.5 mmol), 2a (1 ml), $CuCl_2$ (0.075 mmol), Py (0.25 mmol), $BF_3 \cdot Et_2O$ (0.5 mmol), 12h.

4. Detection by GC

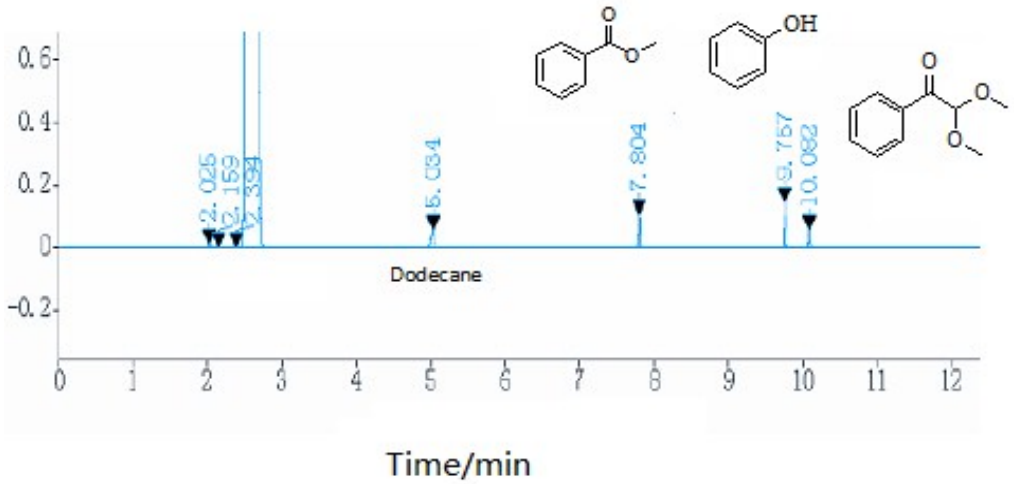
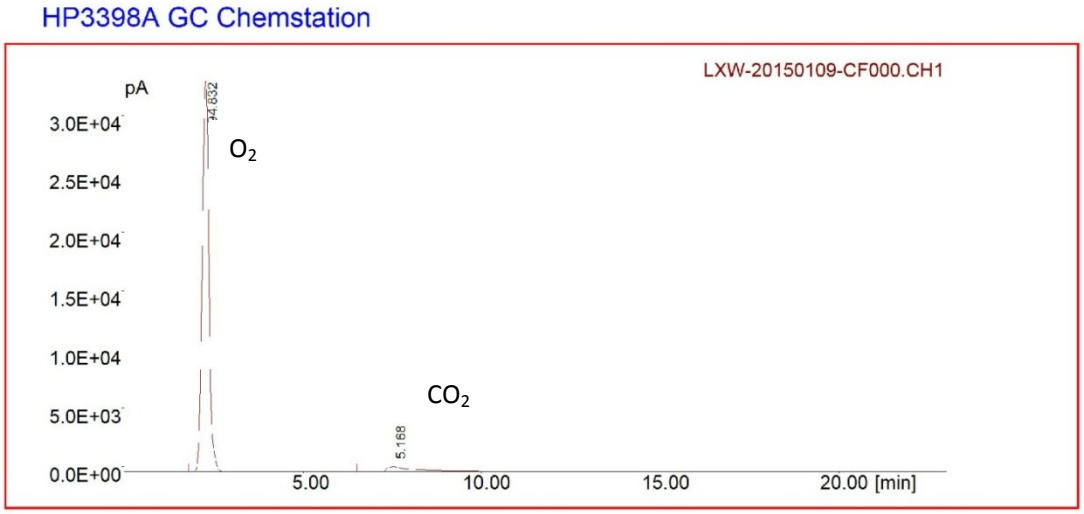


Figure S2 GC spectrum of the liquid phase of the reaction solution. Conditions: 1a (0.5 mmol), 2a (1 ml), $CuCl_2$ (0.075 mmol), Py (0.25 mmol) and $BF_3 \cdot Et_2O$ (0.5 mmol), 24h.

Tail gas detection by GC

Under the environment of pure oxygen, tail gas was collected and detected by GC.

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File Information :
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Curr. Date :  8-Jun-2015  17:18:26

Acquisition Time : 23.00 [mins]
Injection Volume = 1.0000
Dilution(%) = 100.000
Multiplier = 1.000
Vial # = 1

Instrument Method : WUCY
Analysis Method :
Calculation Mode : % Area
Nb of integration :  0
Date of last Integration :
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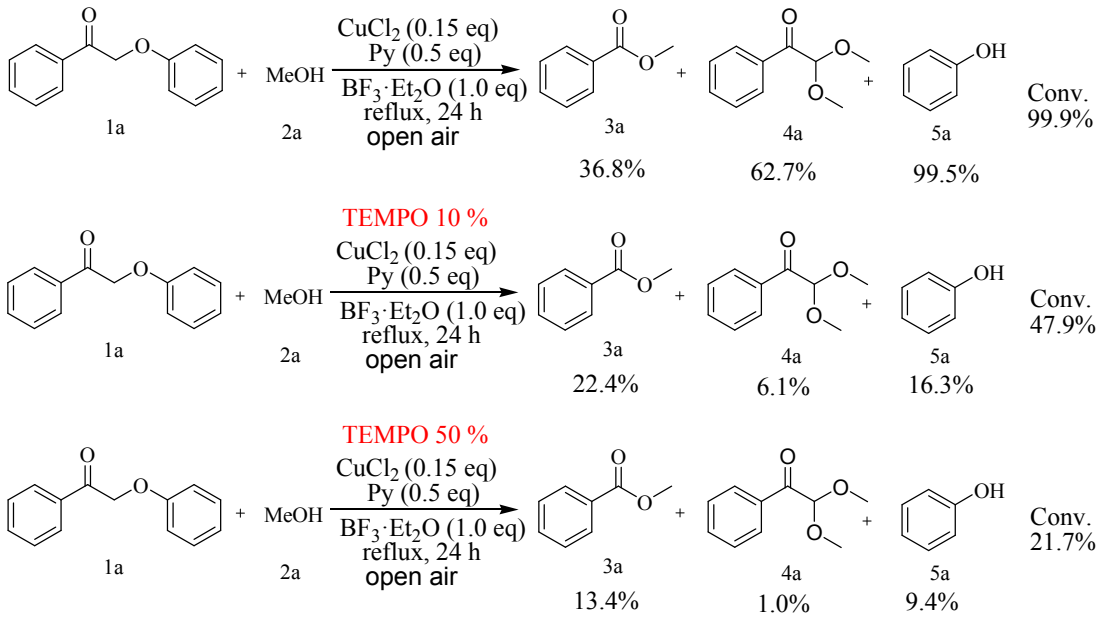
#	Name	RT [min]	Area [pA*s]	Amount [%]
1		2.281	412361	94.8324
2		7.539	22470	5.1676

Figure S3 GC profile of the gas phase of the reaction solution. Conditions: 1a (0.5 mmol), 2a (1 ml), $CuCl_2$ (0.075 mmol), Py (0.25 mmol) and $BF_3{\cdot}Et_2O$ (0.5 mmol), 24h.

5. Radical trapping experiments



Scheme S1 Control experimentswithTEMPO

6. EPR spectrum

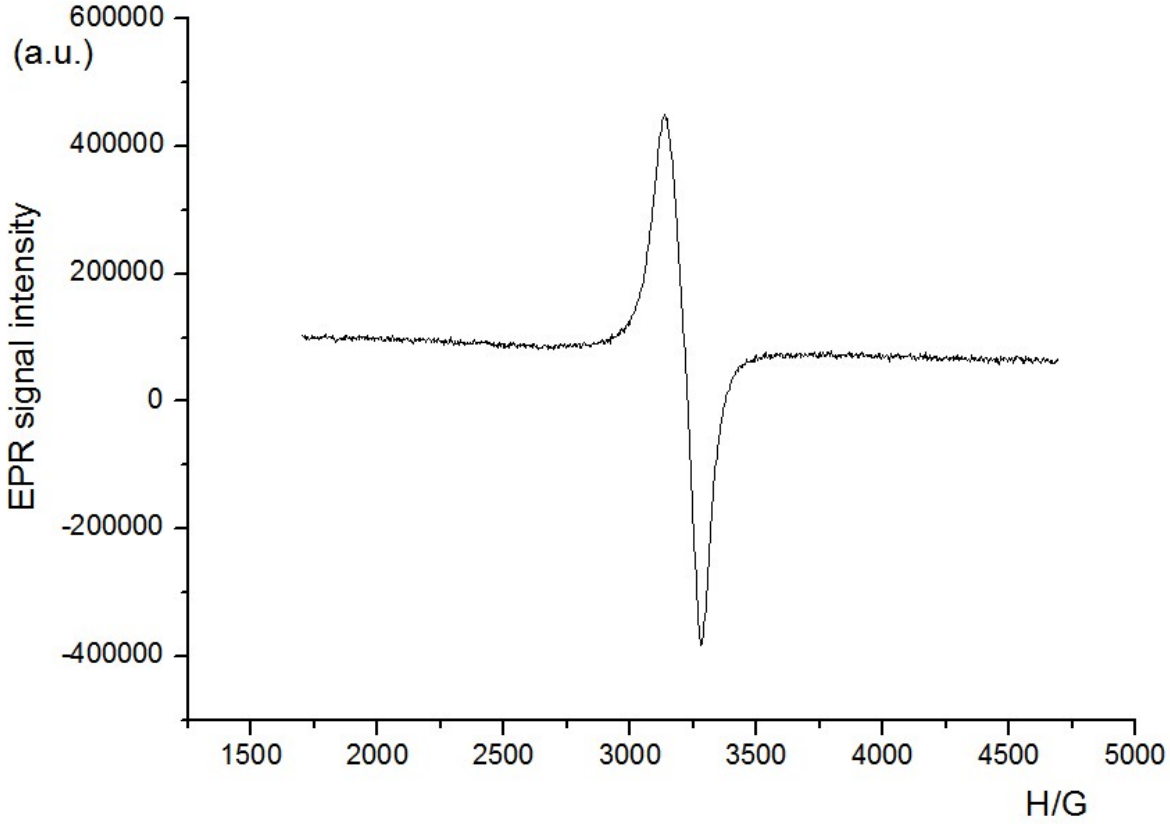


Figure S4 EPR spectrum of the reaction solution. Reaction conditions:1a (0.5 mmol), 2a (1 ml), $CuCl_2$ (0.075 mmol), Py (0.25 mmol), $BF_3 \cdot Et_2O$,methanol,12h.

7. Cu2p XPS spectrum of the recovered Cu catalyst

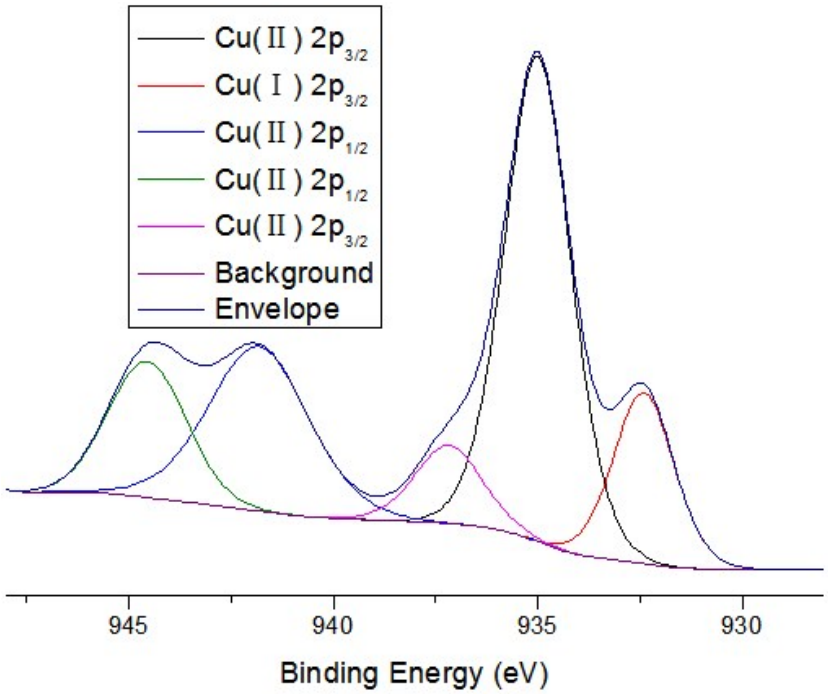
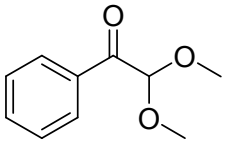


Figure S5 Cu2p XPS spectrum of the recovered Cu catalyst.

8. ESI-MS spectrumcharts of compounds

2,2-dimethoxyacetophenone



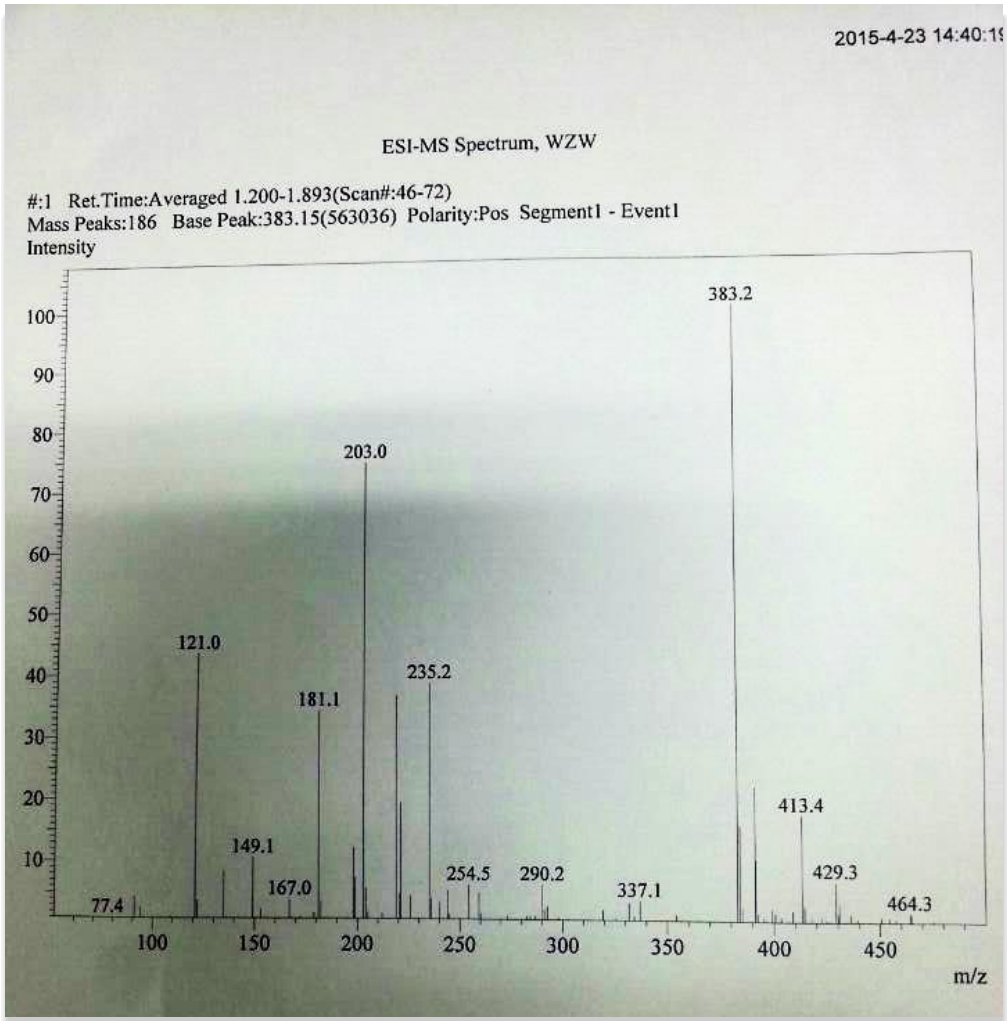
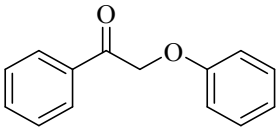


Figure S6ESI-MS spectrum of 2,2-dimethoxyacetophenone.

9. NMRdata for starting materials

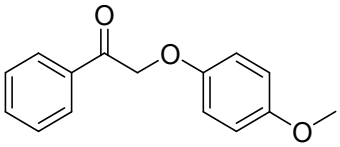
2-Aryloxy-1-acetophenone derivatives were prepared based on the reported procedures,[1] which were examined by NMR analysis. The NMR data for these compounds are listed as follows.

2-phenyloxy-acetophenone



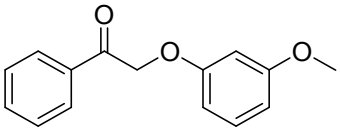
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.94 (m, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.35 – 7.19 (m, 2H), 6.98 (dd, *J* = 18.9, 7.7 Hz, 1H), 5.28 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.55 (s), 158.03 (s), 134.65 (s), 133.82 (s), 129.56 (s), 128.81 (s), 128.15 (s), 121.65 (s), 114.83 (s), 70.84 (s).

2-(4-methoxyphenyl)oxy-acetophenon



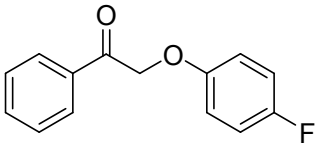
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.23 (m, 5H), 6.98 (dd, *J* = 19.0, 7.7 Hz, 3H), 5.28 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.74 (s), 154.38 (s), 152.14 (s), 134.55 (s), 133.68 (s), 128.69 (s), 128.00 (s), 115.89 (s), 114.60 (s), 77.32 (s), 77.00 (s), 76.68 (s), 71.63 (s), 55.55 (s).

2-(3-methoxyphenyl)oxy-acetophenon



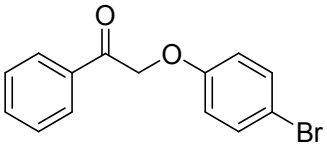
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.3 Hz, 4H), 7.62 (t, *J* = 7.4 Hz, 3H), 7.50 (t, *J* = 7.7 Hz, 5H), 7.18 (t, *J* = 8.5 Hz, 6H), 6.66 – 6.47 (m, 6H), 5.26 (s, 4H), 3.78 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.28 (s), 160.82 (s), 159.17 (s), 134.52 (s), 133.77 (s), 129.92 (s), 128.75 (s), 128.03 (s), 125.10 (s), 107.27 (s), 106.55 (s), 101.46 (s), 77.32 (s), 77.00 (s), 76.68 (s), 70.69 (s), 55.21 (s).

2-(4-fluor-phenyl)oxy-acetophenon



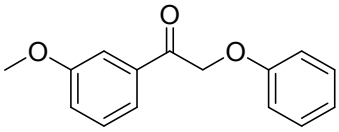
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 6.92 (ddd, *J* = 12.0, 9.2, 6.7 Hz, 4H), 5.25 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.30 (s), 158.86 (s), 156.48 (s), 154.12 (d, *J* = 2.1 Hz), 134.41 (s), 133.91 (s), 128.82 (s), 128.01 (s), 115.94 (dd, *J* = 15.7, 7.5 Hz), 77.32 (s), 77.00 (s), 76.68 (s), 71.37 (s).

2-(4-bromo-phenyl)oxy-acetophenon



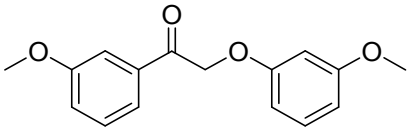
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 5.17 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.96 (s), 157.13 (s), 134.37 (s), 133.97 (s), 132.36 (s), 128.85 (s), 128.03 (s), 116.60 (s), 113.87 (s), 70.82 (s).

2-phenyloxy-3'-methoxy acetophenone



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.50 (m, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.28 (dd, *J* = 14.6, 6.4 Hz, 2H), 7.16 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.05 – 6.89 (m, 3H), 5.26 (s, 2H), 3.86 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.21 (s), 159.90 (s), 157.96 (s), 135.80 (s), 129.75 (s), 129.49 (s), 121.56 (s), 120.48 (s), 120.25 (s), 114.76 (s), 112.37 (s), 77.32 (s), 77.00 (s), 76.68 (s), 70.74 (s), 55.39 (s).

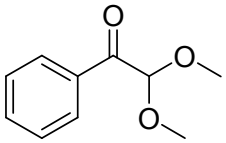
2-(3-methoxyphenyl)oxy-3'-methoxyacetophenone



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.39 (m, 2H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.13 – 7.00 (m, 2H), 6.50 – 6.37 (m, 3H), 5.14 (s, 2H), 3.76 (s, 3H), 3.68 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.06 (s), 160.85 (s), 159.93 (s), 159.21 (s), 135.83 (s), 129.84 (d, *J* = 16.3 Hz), 120.48 (s), 120.27 (s), 112.39 (s), 107.29 (s), 106.60 (s), 101.51 (s), 77.26 (d, *J* = 11.7 Hz), 77.00 (s), 76.68 (s), 70.77 (s), 55.33 (d, *J* = 18.7 Hz).

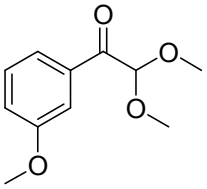
10. NMRdata for the products

2,2-Dimethoxyacetophenone



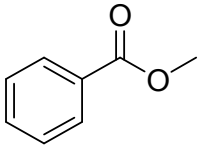
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 2H), 5.14 (s, 1H), 3.37 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.22 (s), 133.47 (s), 129.34 (s), 128.29 (s), 103.13 (s), 54.36 (s).

2,2-Dimethoxy-1-(3-methoxyphenyl)



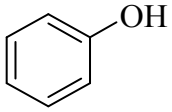
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.7 Hz, 1H), 7.51 (s, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 8.2, 1.8 Hz, 1H), 5.12 (s, 1H), 3.72 (s, 3H), 3.36 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 192.90 (s), 159.41 (s), 134.90 (s), 129.22 (s), 121.89 (s), 119.88 (s), 113.37 (s), 102.93 (s), 55.10 (s), 54.23 (s).

benzoic acid methyl ester



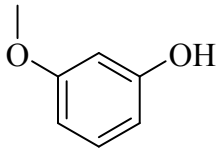
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.99 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 3.92 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.13 (s), 132.91 (s), 130.22 (s), 129.59 (s), 128.37 (s), 52.09 (s).

Phenol



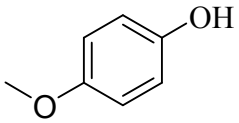
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 9.6, 6.2 Hz, 3H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 2H), 5.35 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.46 (s), 129.67 (s), 120.81 (s), 115.28 (s).

3-methoxyphenol



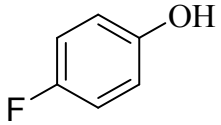
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.0 Hz, 1H), 6.51 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 1.3 Hz, 2H), 4.77 (s, 1H), 3.78 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.94 (s), 156.69 (s), 130.15 (s), 107.81 (s), 106.49 (s), 101.56 (s), 77.26 (d, *J* = 11.5 Hz), 77.00 (s), 76.68 (s), 55.27 (s), -0.03 (s).

4-methoxyphenol



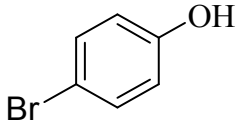
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.67 (m, 1H), 3.76 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.86 (s), 149.41 (s), 116.02 (s), 114.85 (s), 55.78 (s).

4-fluorophenol



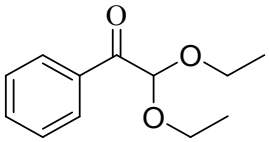
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 11.9, 5.4 Hz, 1H), 6.85 – 6.68 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.51 (s), 156.14 (s), 151.44 (d, *J* = 2.2 Hz), 116.37 – 116.00 (m), 115.87 (s).

4-bromophenol



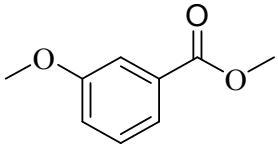
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.9 Hz, 1H), 5.35 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.59 (s), 132.48 (s), 117.19 (s), 112.93 (s).

2,2-diethoxyacetophenone



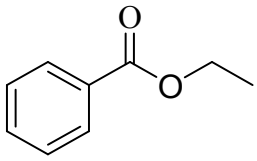
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.10 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 5.28 (s, 1H), 3.88 – 3.52 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.04 (s), 133.81 (s), 133.41 (s), 129.73 (s), 128.31 (s), 102.48 (s), 63.20 (s), 15.18 (s).

3-methoxybenzoate



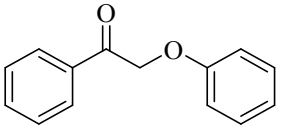
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 1H), 7.56 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.10 (ddd, *J* = 8.2, 2.7, 0.8 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.95 (s), 159.57 (s), 131.47 (s), 129.35 (s), 121.97 (s), 119.48 (s), 113.98 (s), 55.41 (s), 52.12 (s).

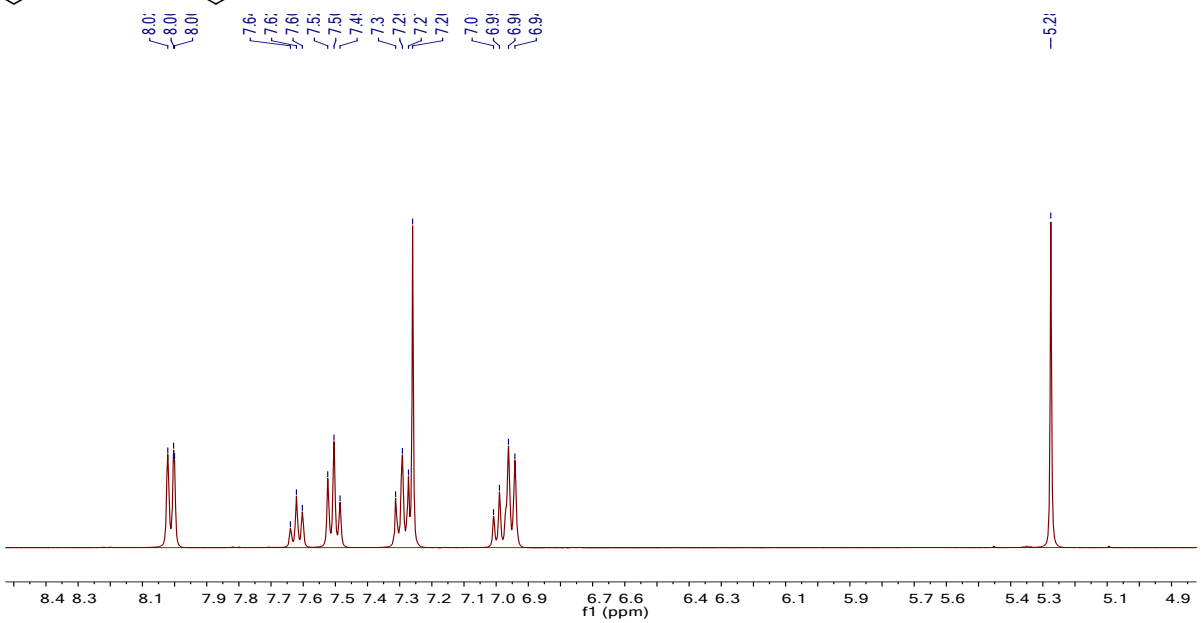
Ethyl benzoate



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.01 (m, 2H), 7.62 – 7.50 (m, 1H), 7.42 (dd, J = 10.6, 4.7 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.55 (s), 132.71 (s), 130.51 (s), 129.47 (s), 128.23 (s), 60.85 (s), 14.26 (s).

11. ^{1}H NMR and ^{13}C NMR spectra of compounds





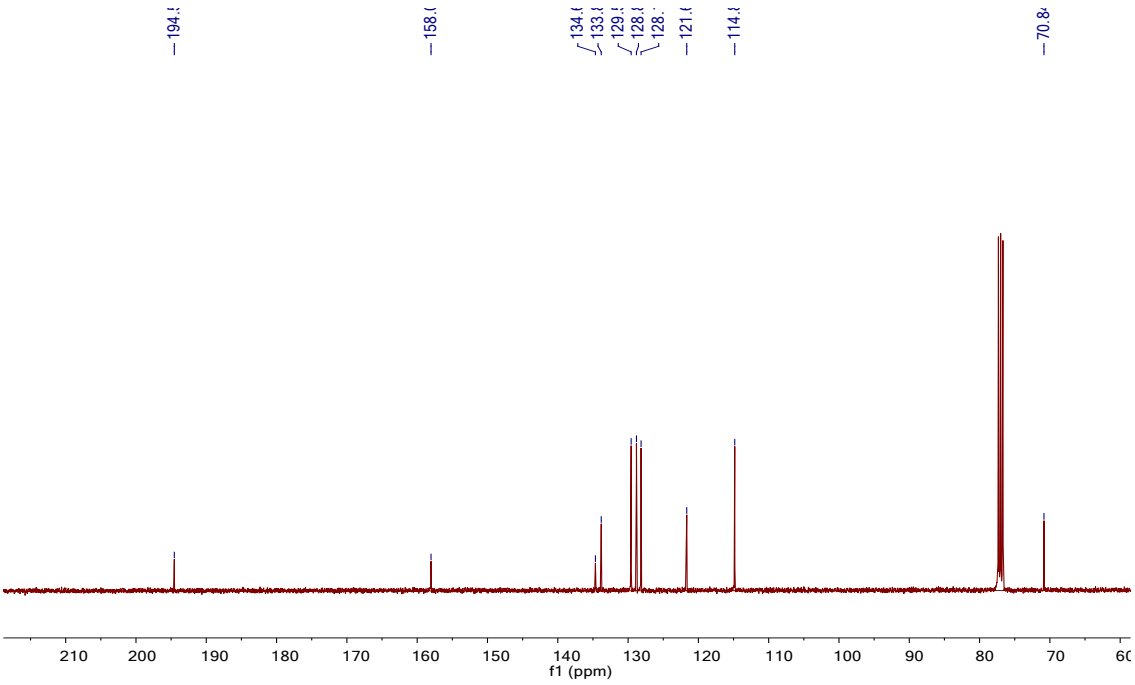
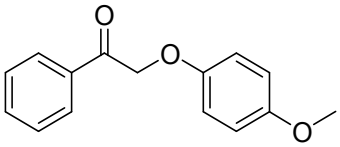
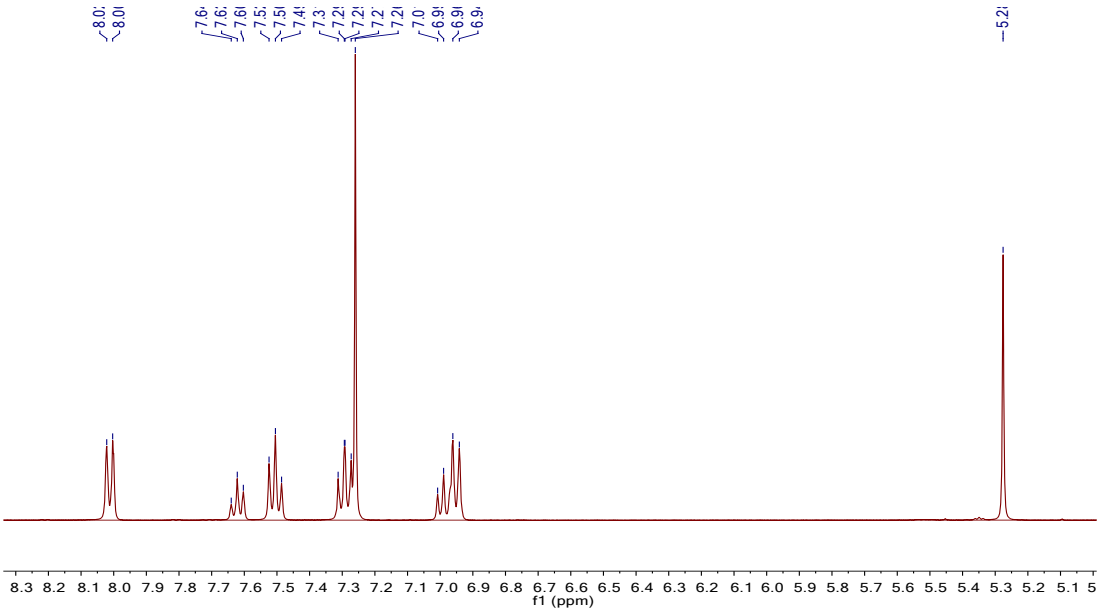


Figure S7^{1}H (top) and ^{13}C (bottom) NMR spectra of 2-phenyloxy-acetophenone





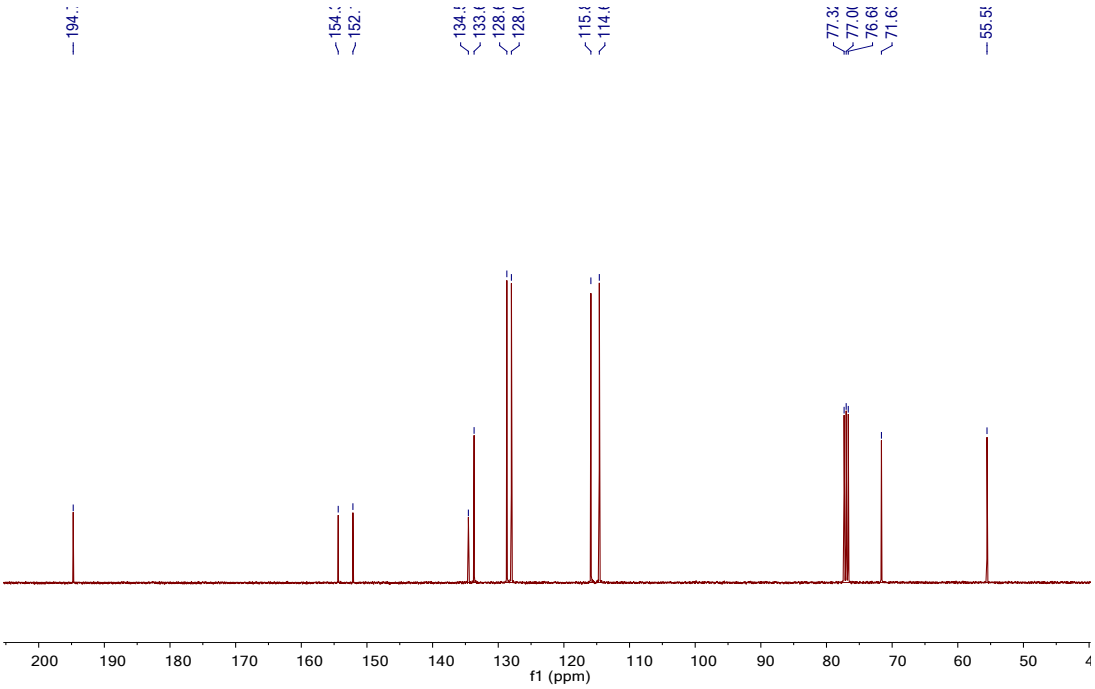


Figure S8[1]H (top) and ^{13}C (bottom) NMR spectra of 2-(4-methoxyphenyl)oxy-acetophenon

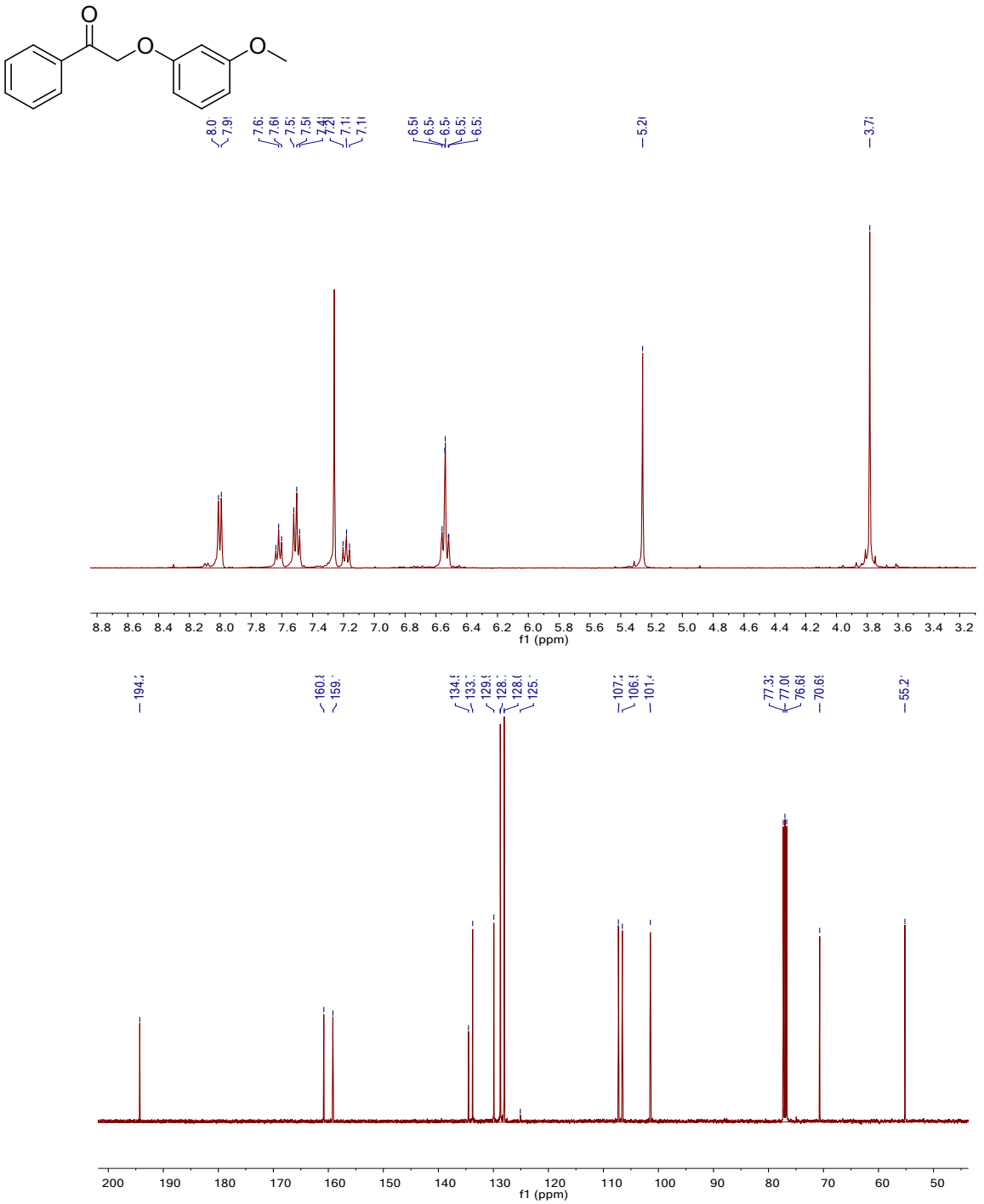
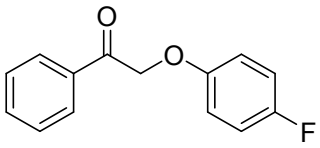
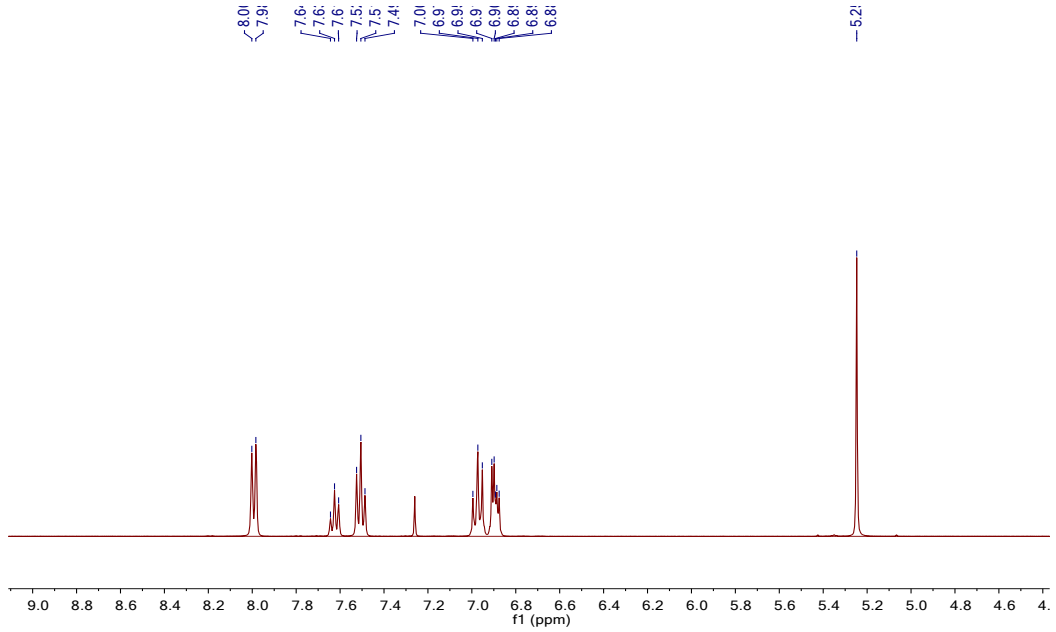


Figure S9[1]H (top) and ^{13}C (bottom) NMR spectra of 2-(3-methoxyphenyl)oxy-acetophenon





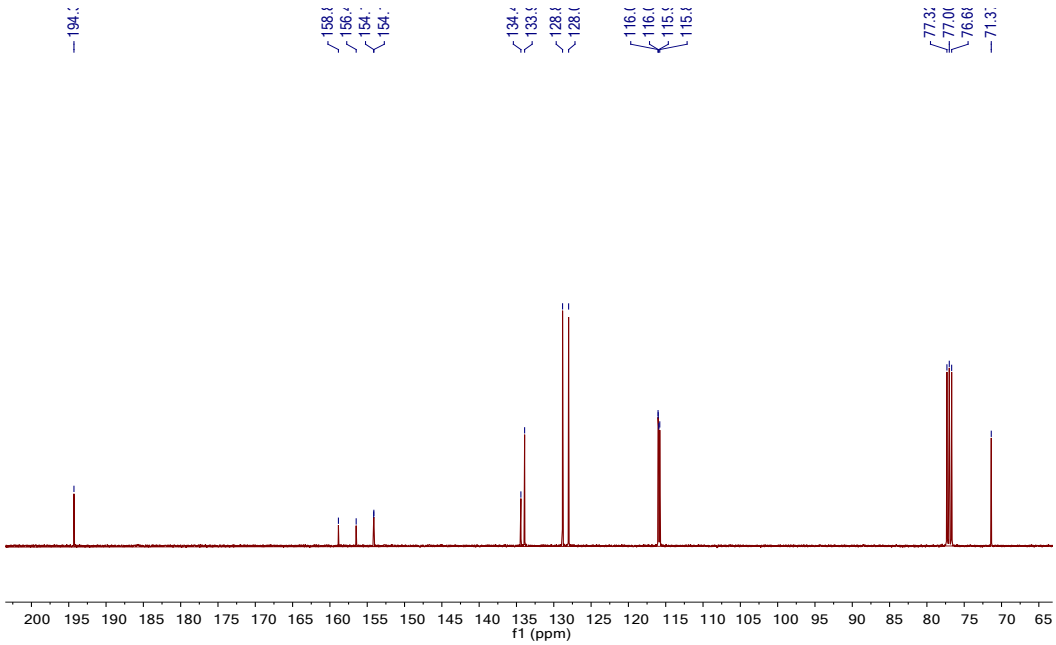


Figure S10 ^{1}H (top) and ^{13}C (bottom) NMR spectra of 2-(4-fluor-phenyl)oxy-acetophenon

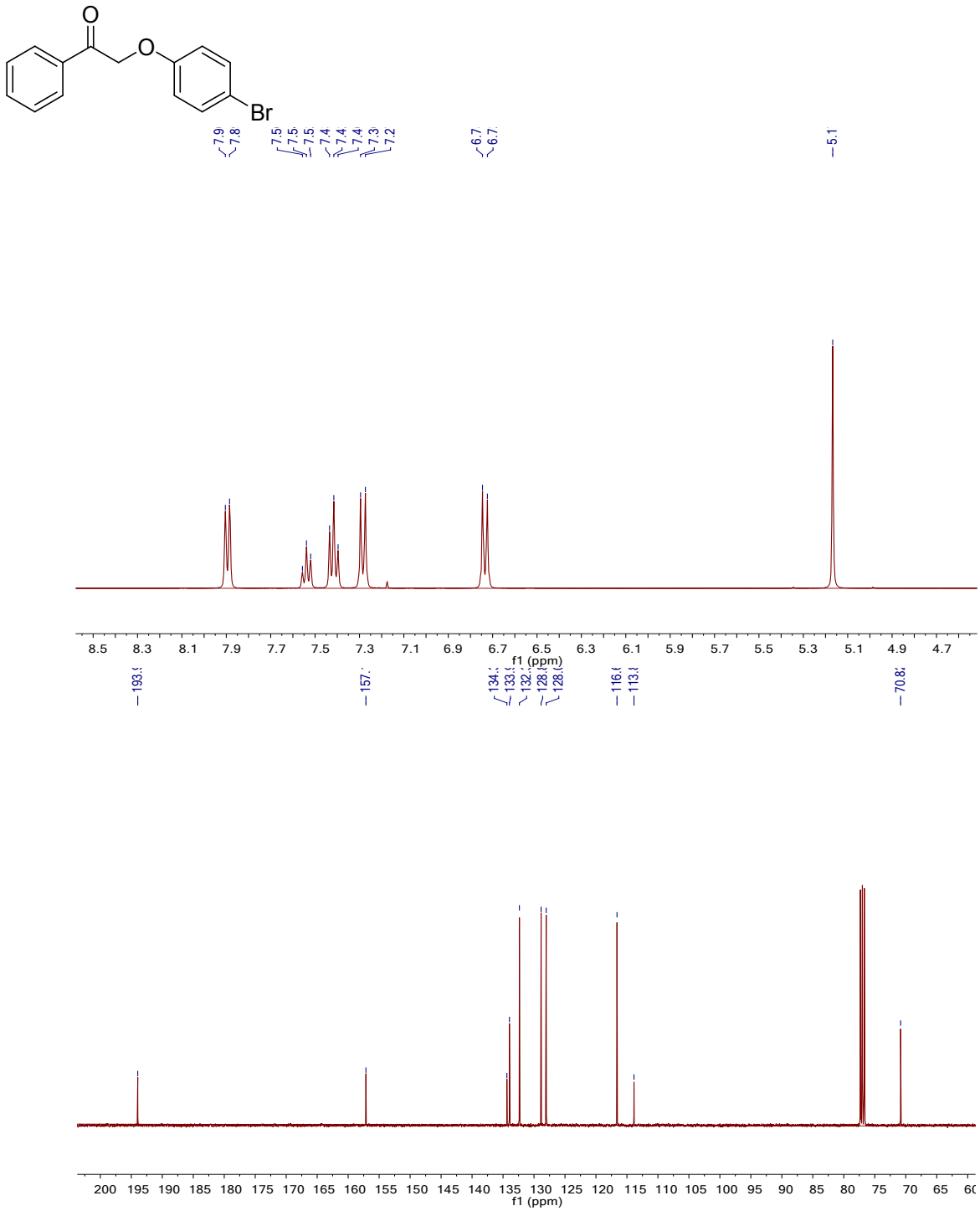


Figure S11 ^{1}H (top) and ^{13}C (bottom) NMR spectra of 2-(4-bromo-phenyl)oxy-acetophenon

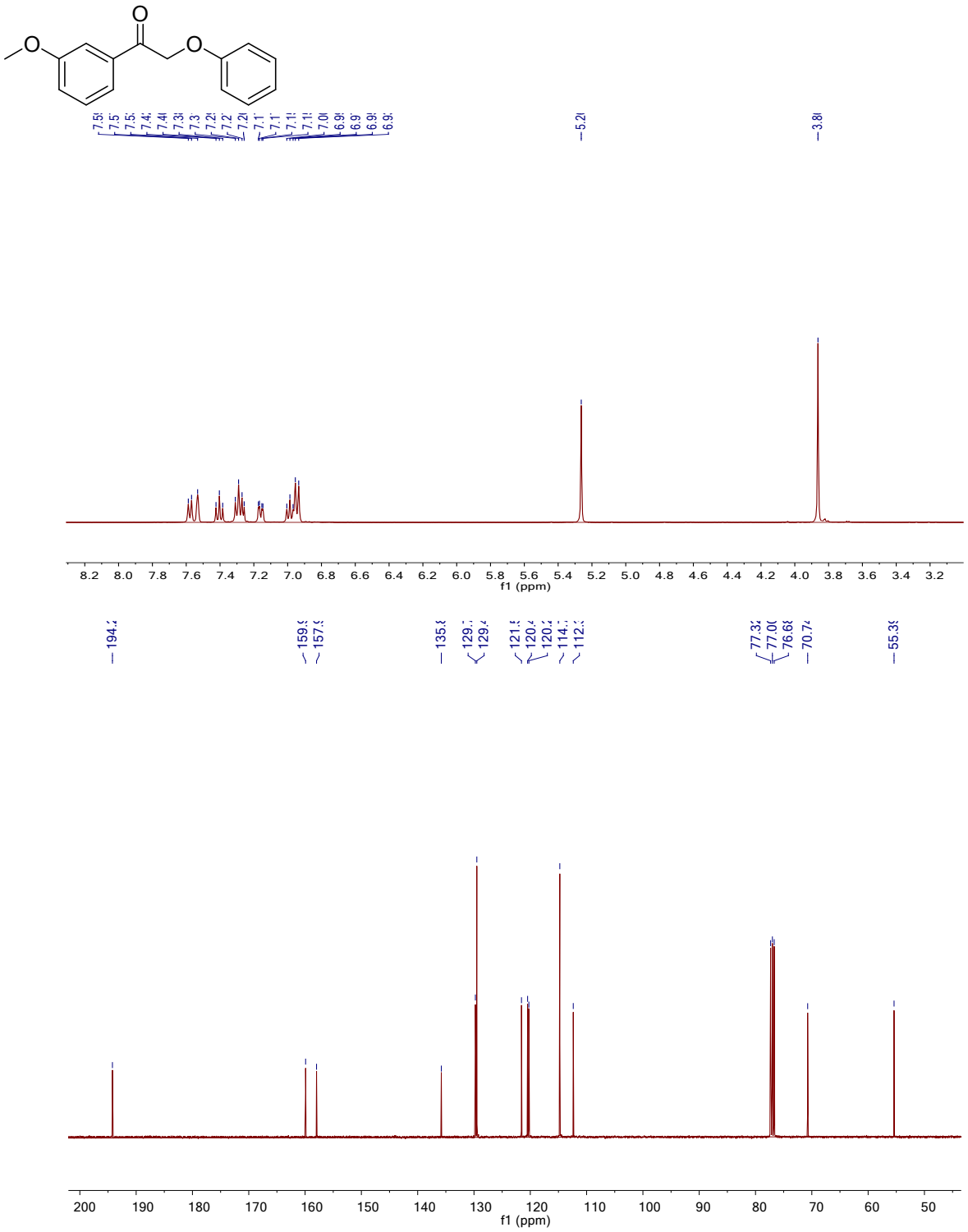


Figure S12 ^{1}H (top) and ^{13}C (bottom) NMR spectra of 2-phenyloxy-3'-methoxy acetophenone

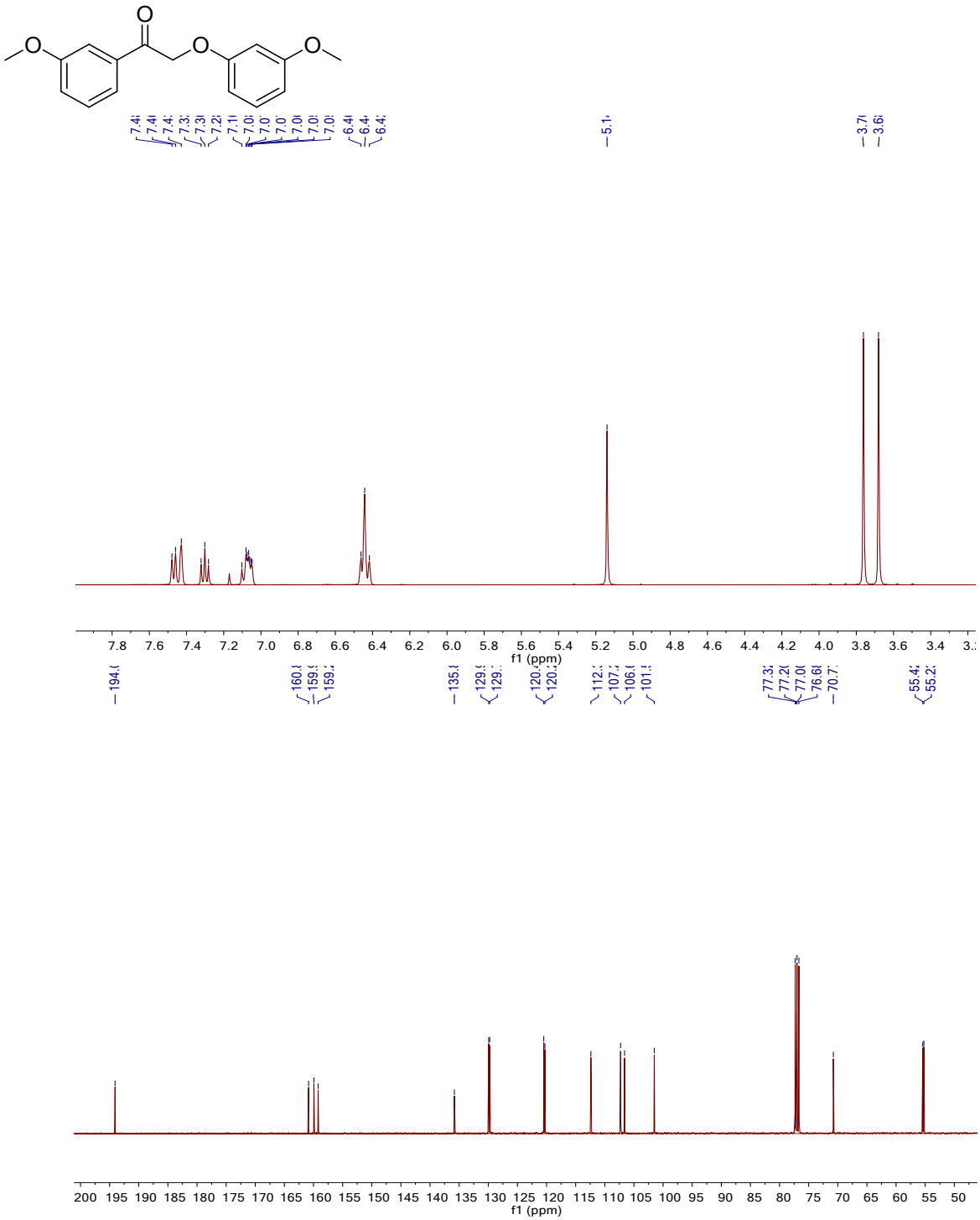


Figure S13 ^{1}H (top) and ^{13}C (bottom) NMR spectra of 2-(3-methoxyphenyl)oxy-3'-methoxyacetophenone

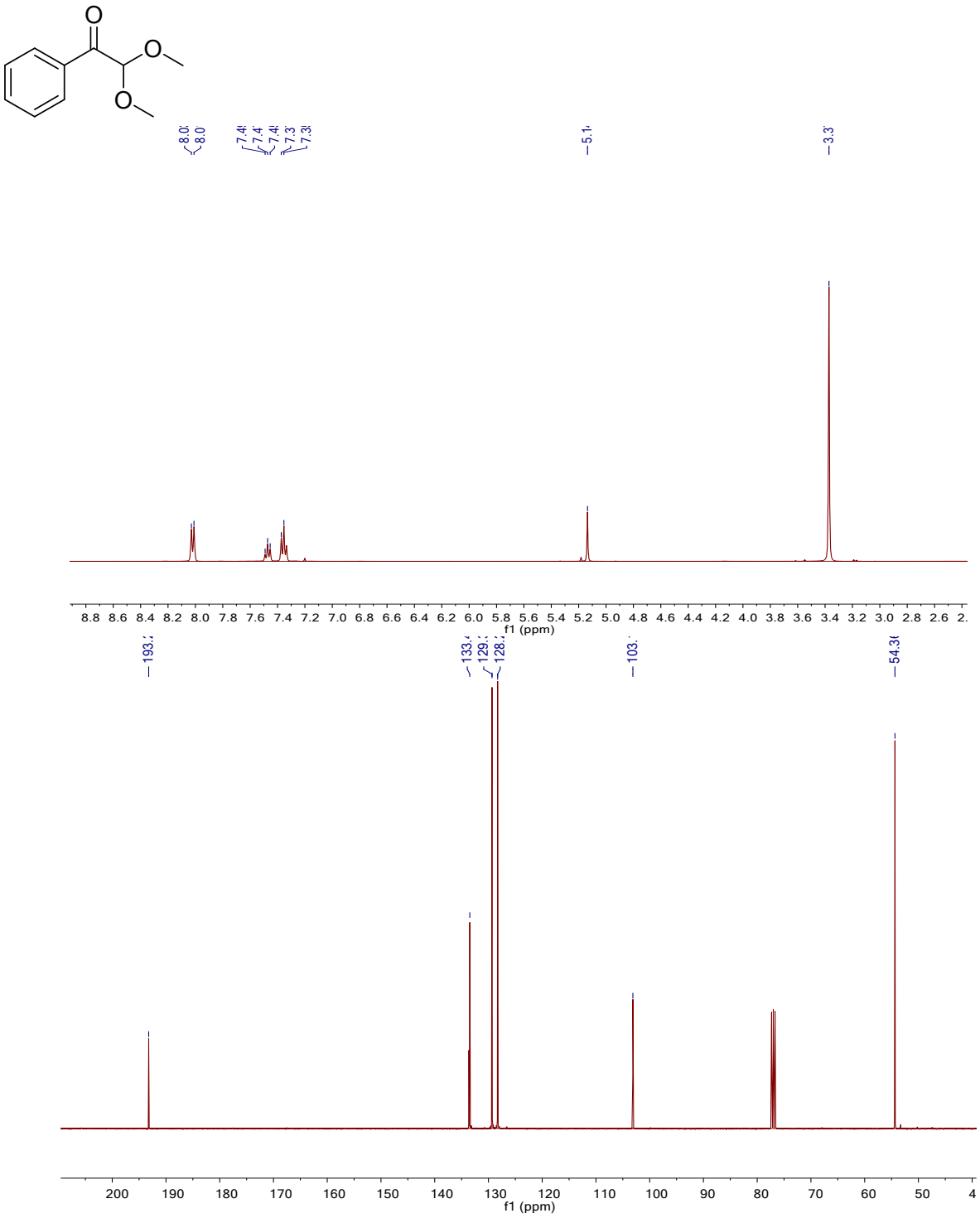
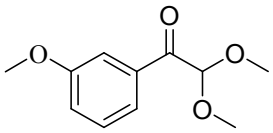


Figure S14 ^{1}H (top) and ^{13}C (bottom) NMR spectra of the isolated product 2,2-dimethoxyacetophenone



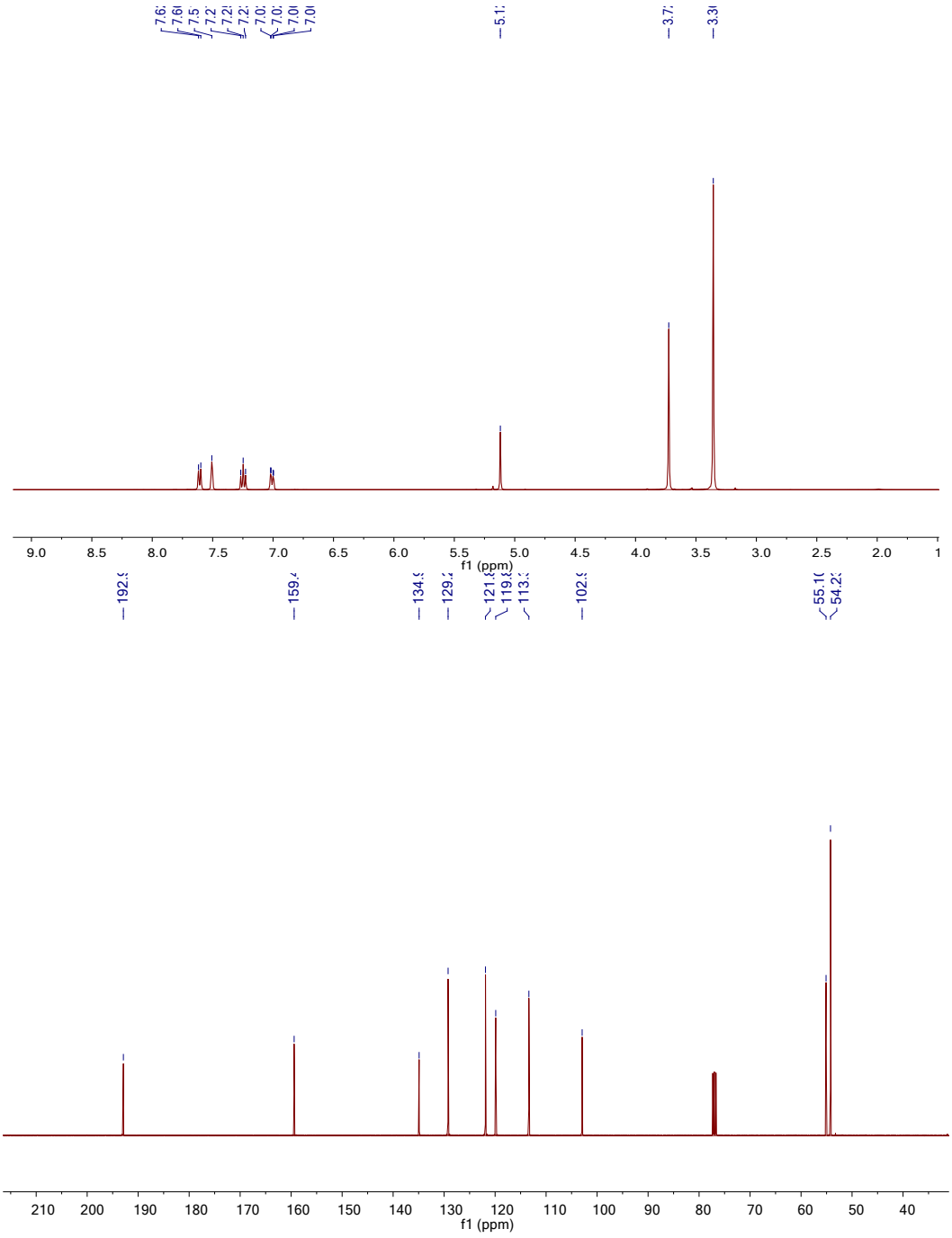
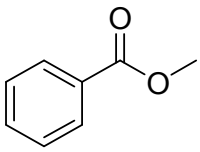


Figure S15 ^{1}H (top) and ^{13}C (bottom) NMR spectra of the isolated product 2,2-dimethoxy-1-(3-methoxyphenyl)



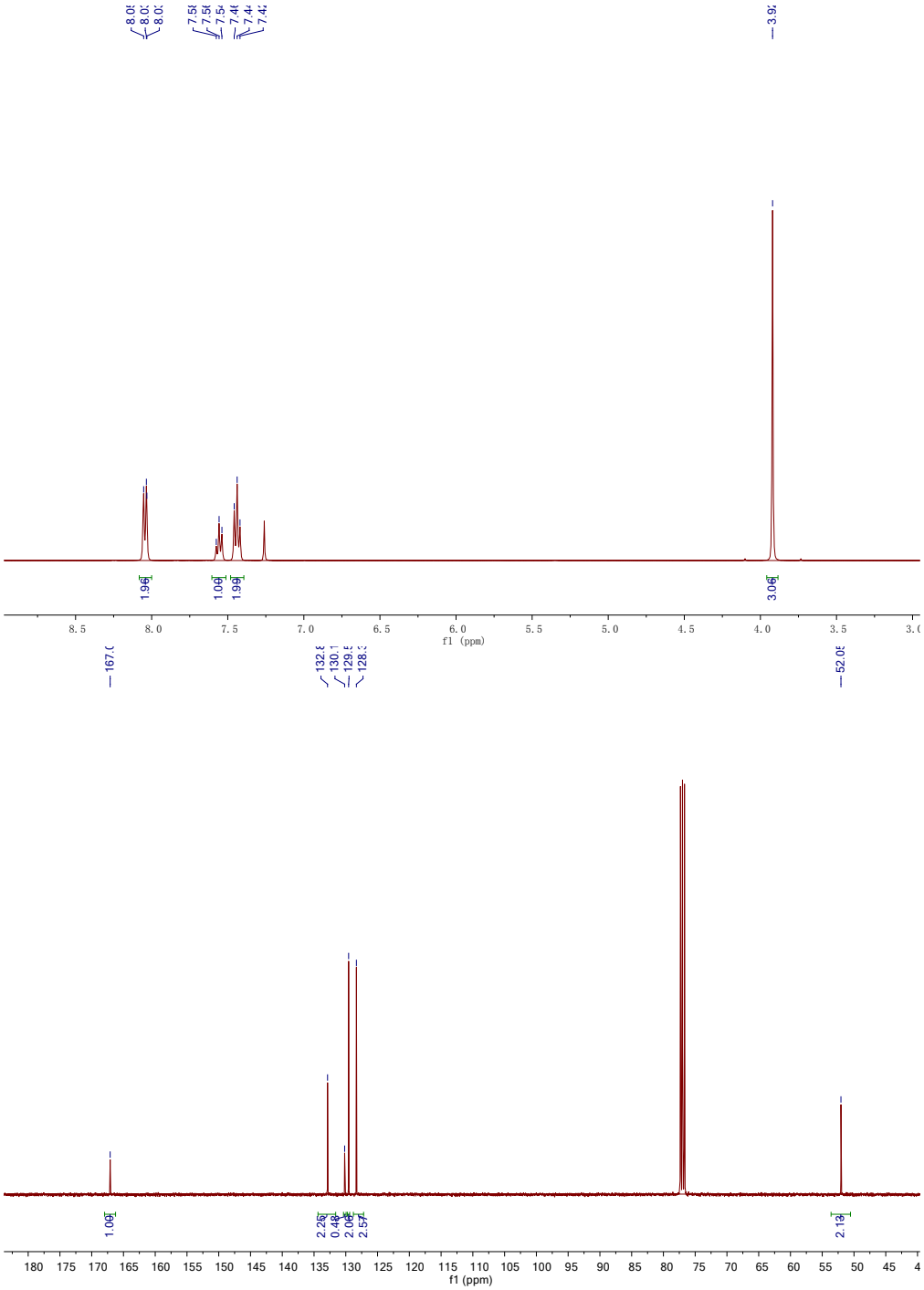


Figure S16^{1}H (top) and ^{13}C (bottom) NMR spectra of the isolated benzoic acid methyl ester

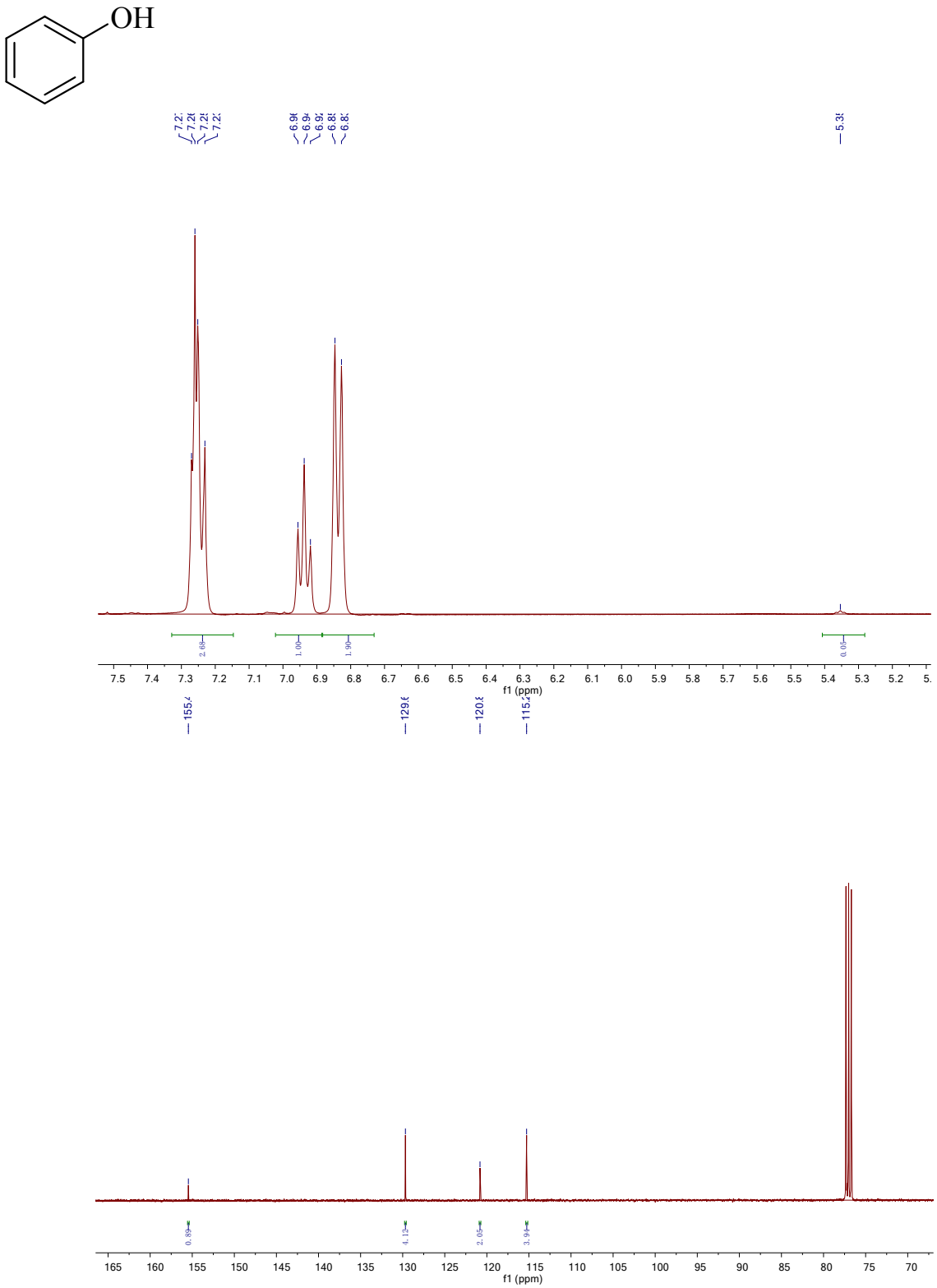
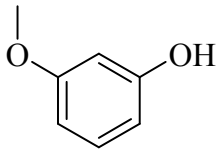


Figure S17[1]H (top) and ^{13}C (bottom) NMR spectra of the isolated product Phenol



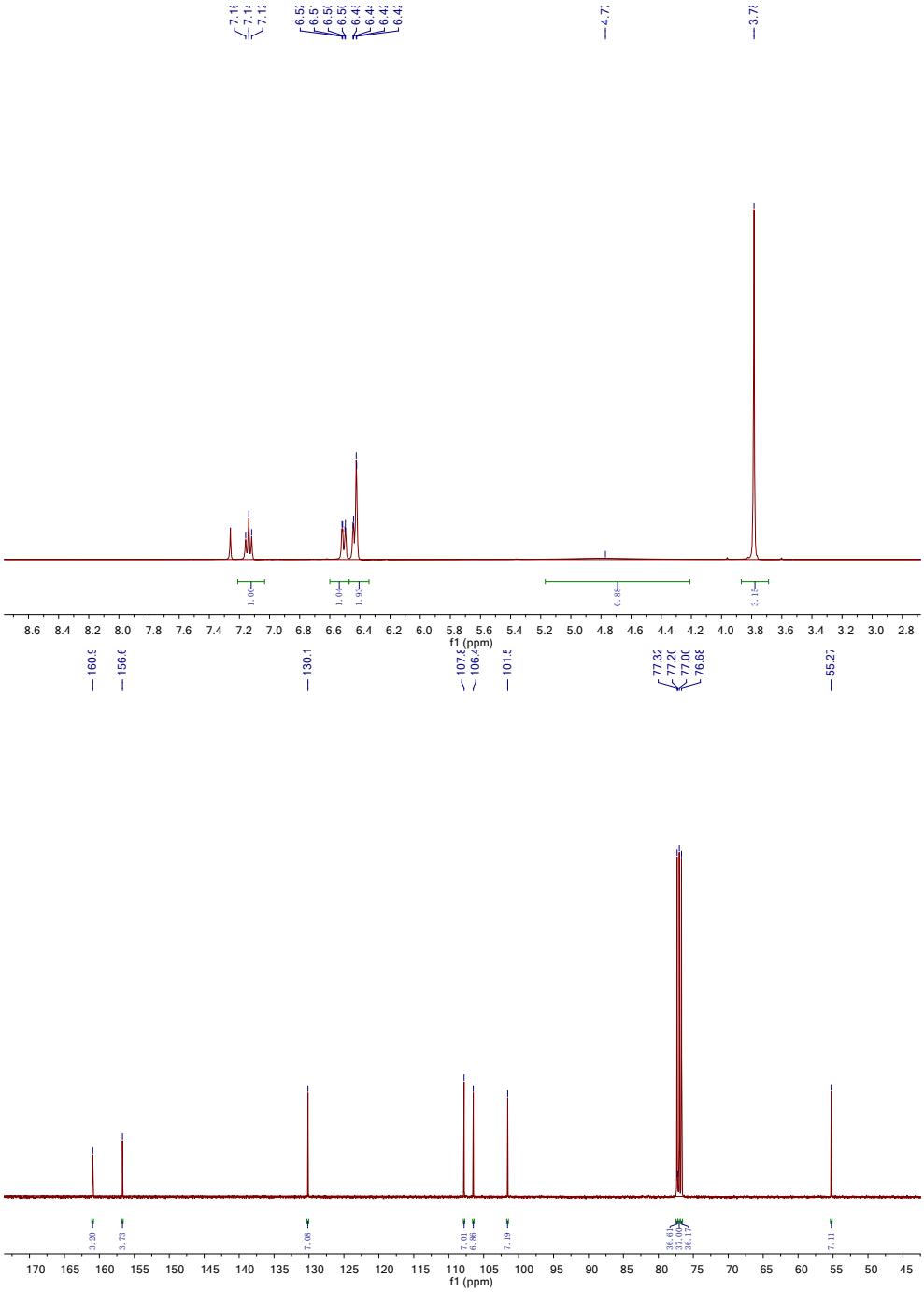
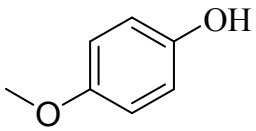


Figure S18[1]H (top) and ^{13}C (bottom) NMR spectra of the isolated product 3-methoxyphenol



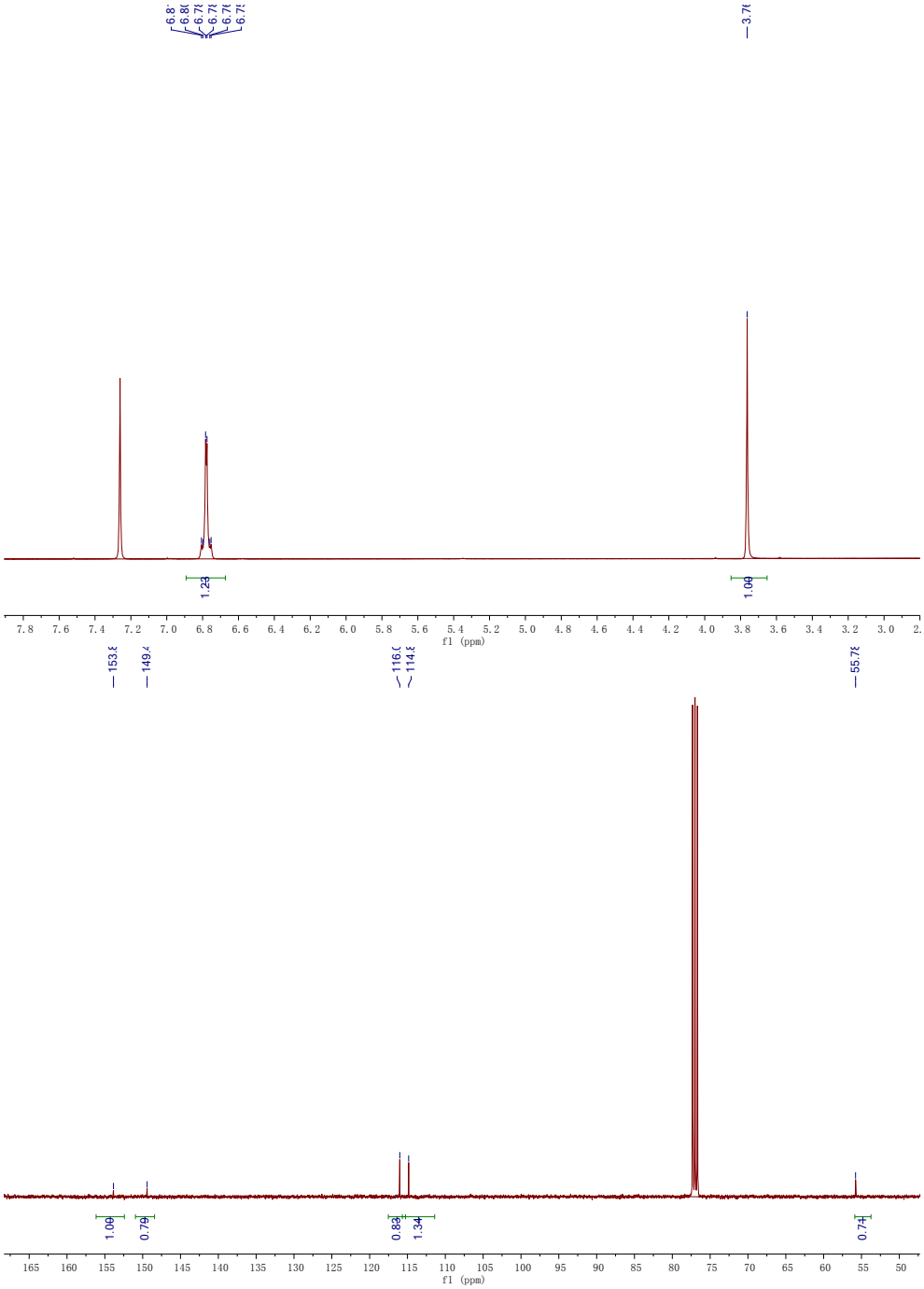
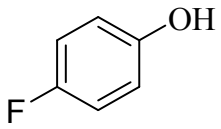
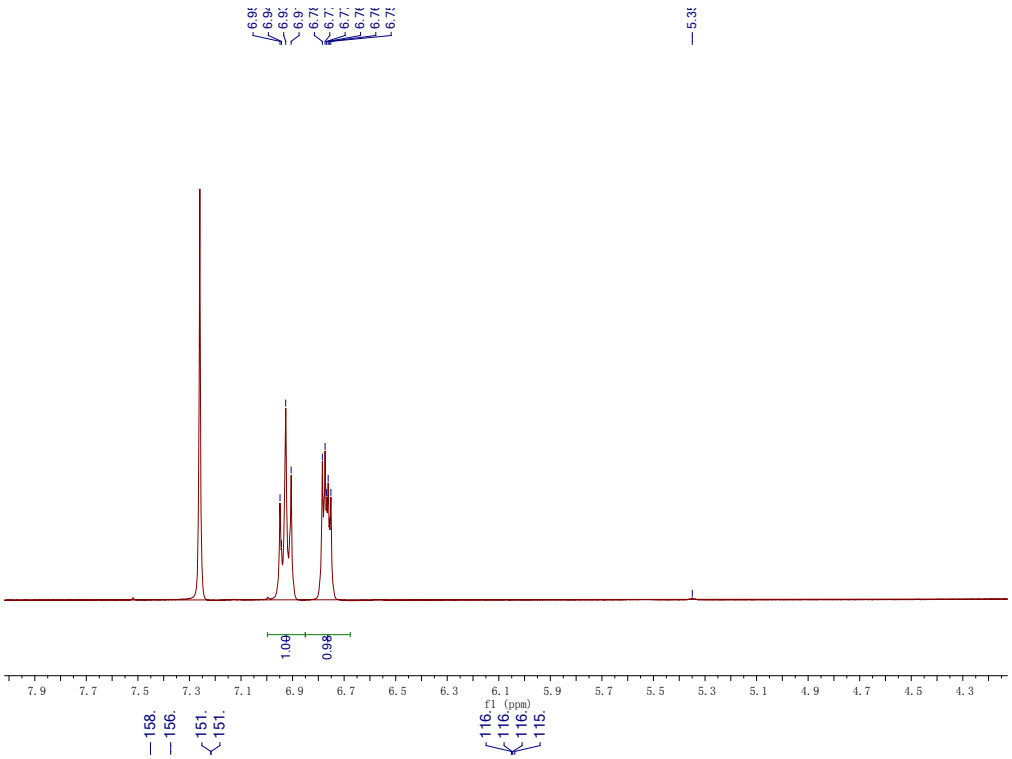


Figure S19 ^{1}H (top) and ^{13}C (bottom) NMR spectra of the isolated product 4-methoxyphenol





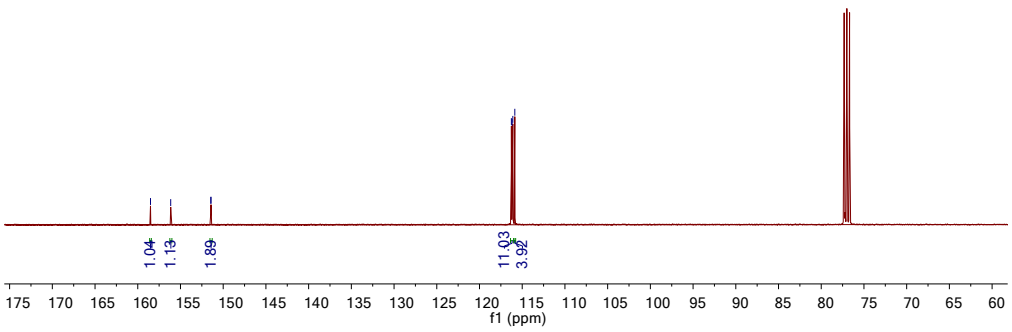
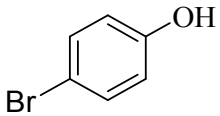
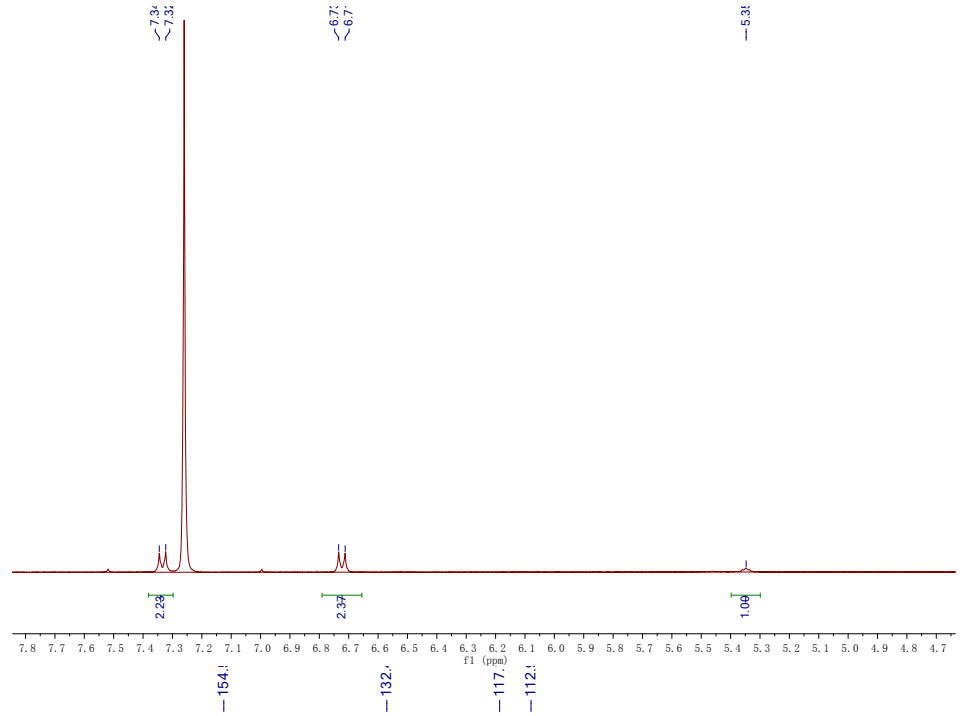


Figure S20[1]H (top) and ^{13}C (bottom) NMR spectra of the isolated product 4-fluorophenol





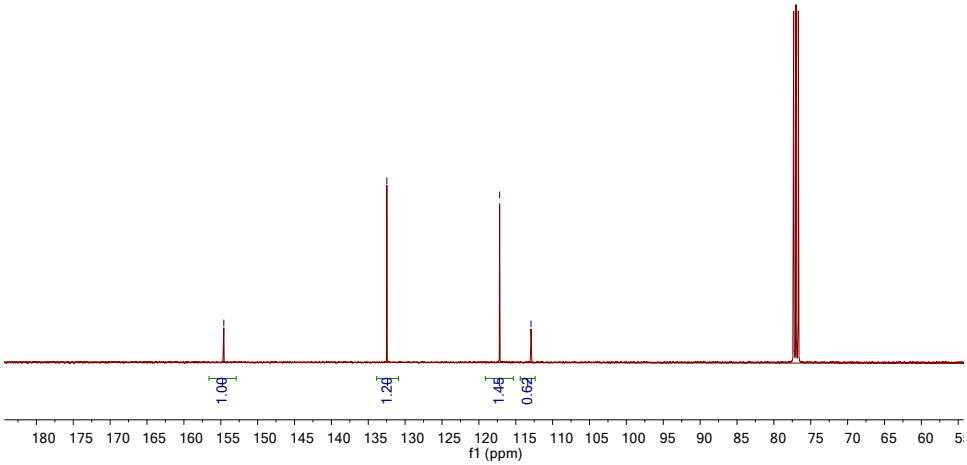


Figure S21 ^{1}H (top) and ^{13}C (bottom) NMR spectra of the isolated product 4-bromophenol

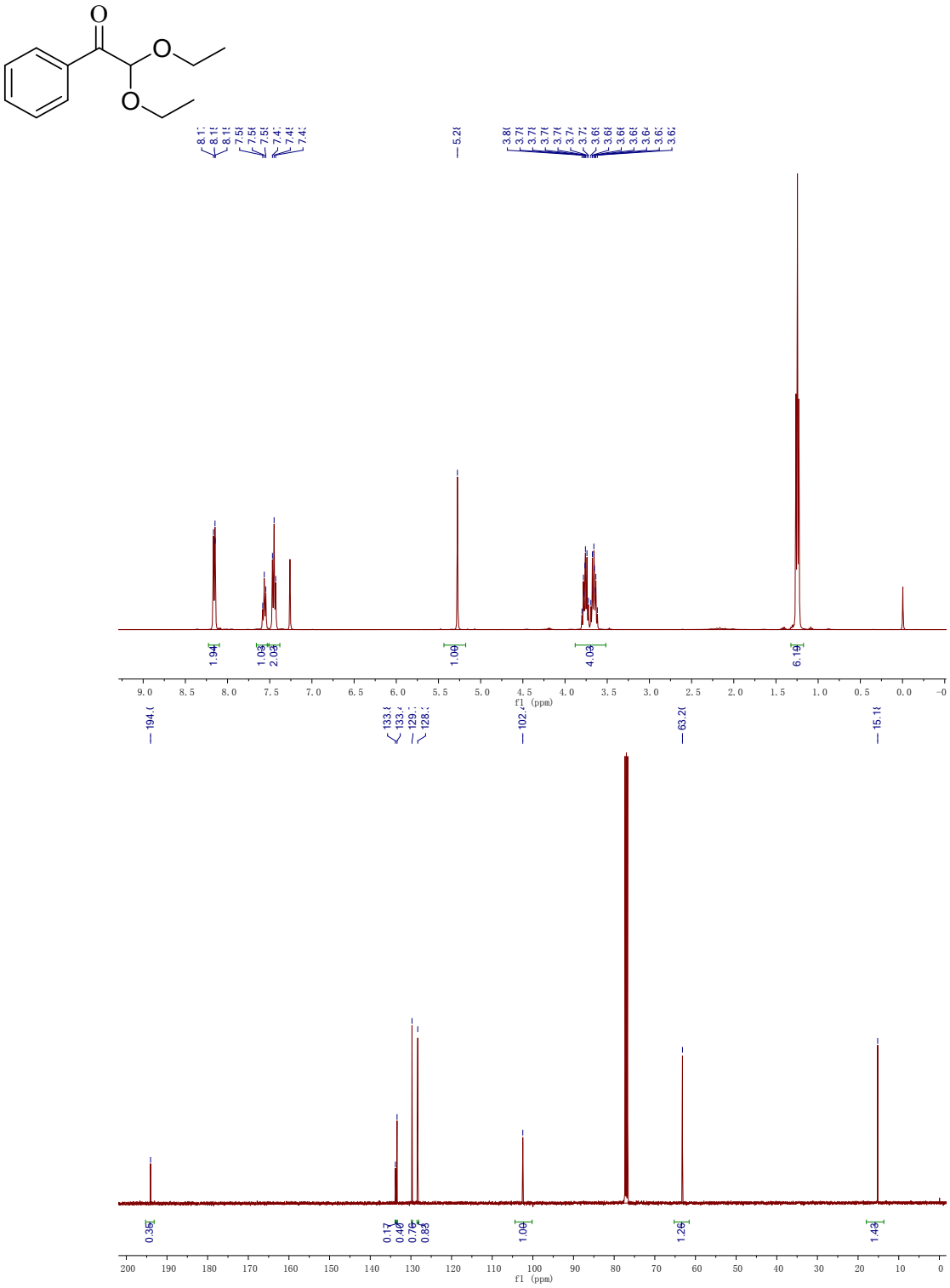
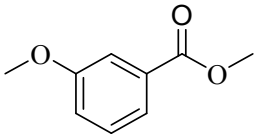


Figure S22 ^{1}H (top) and ^{13}C (bottom) NMR spectra of the isolated 2,2-diethoxyacetophenone



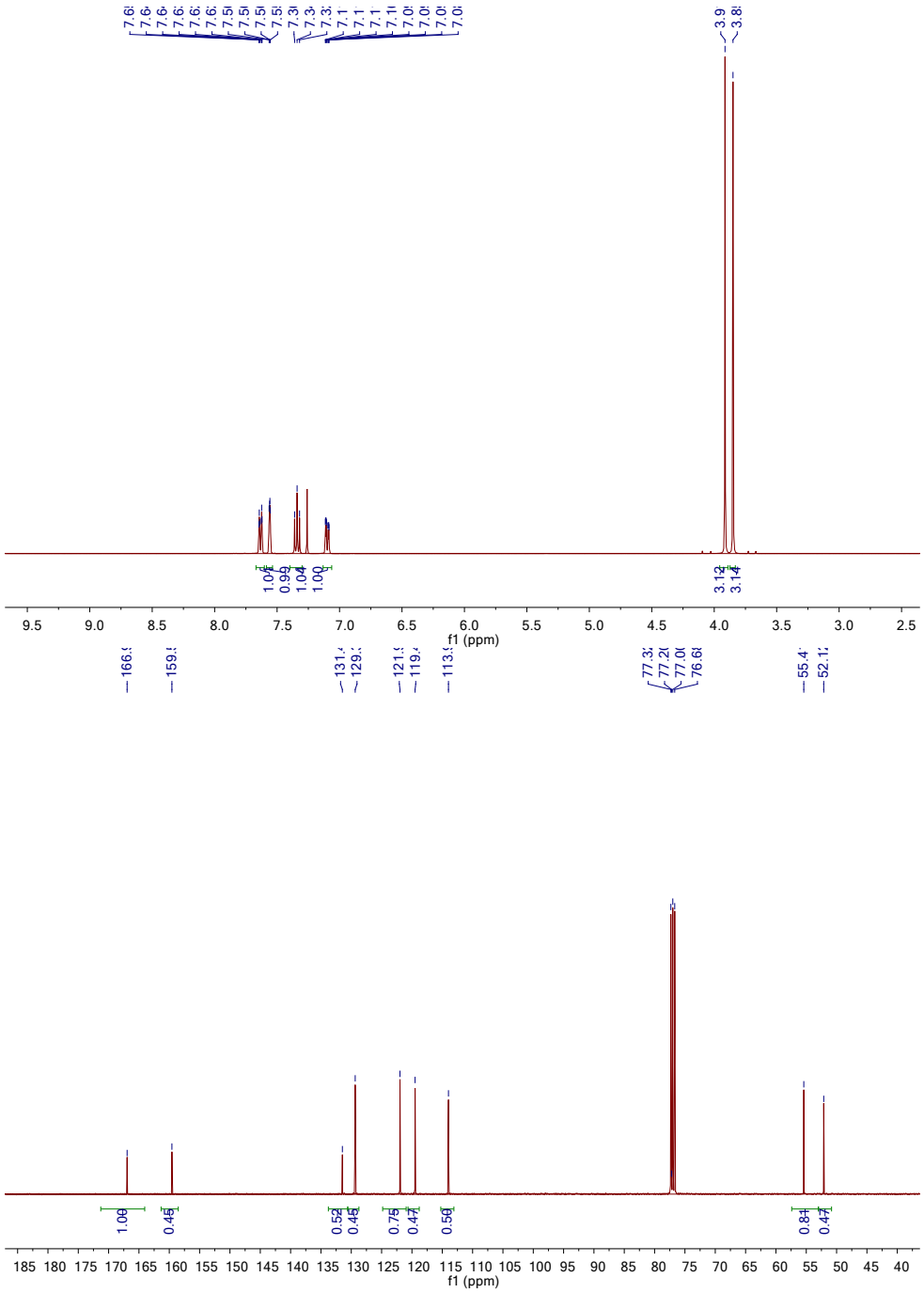
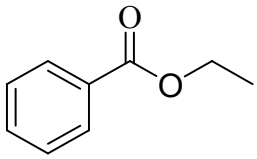
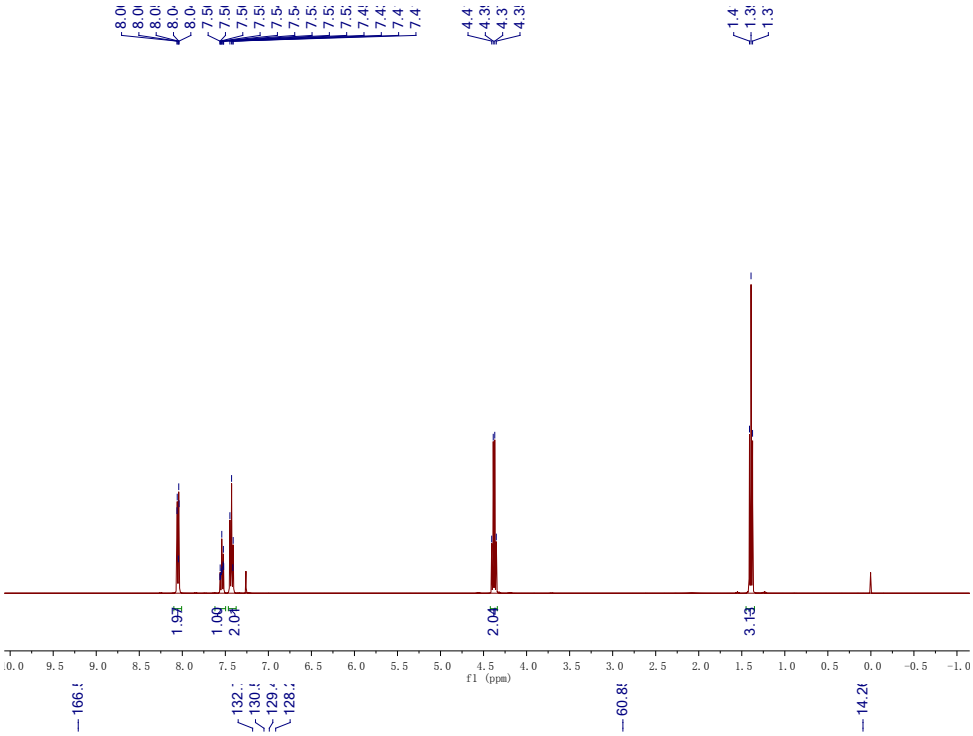


Figure S23 ^{1}H (top) and ^{13}C (bottom) NMR spectra of the isolated product 3-methoxybenzoate





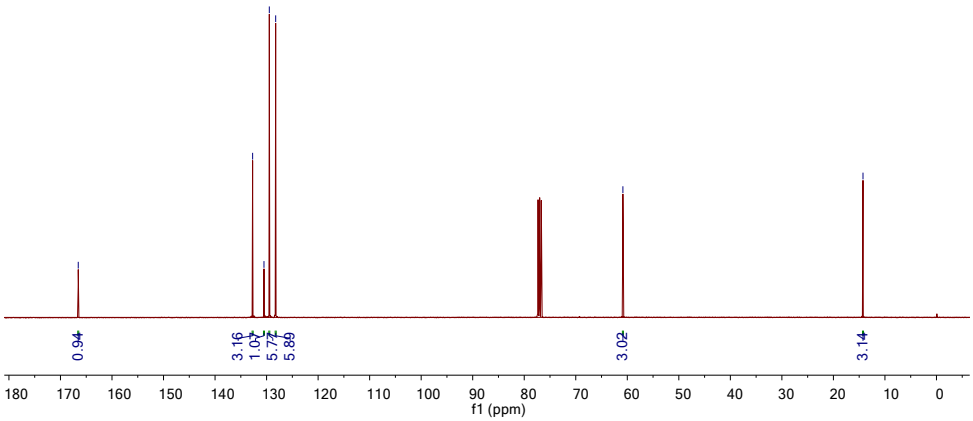


Figure S24^{1}H (top) and ^{13}C (bottom) NMR spectra of the isolated product Ethyl benzoate

12. References

S1.J. M.Nichols,L. M. Bishop,R. G.Bergman, and J. A. Ellman, *J. Am. Chem. Soc*, 2010, **132**, 12554-12555.

S2. P.Panunzi, L. Rotiroti, andM. Tingoli, *Tetrahedron Lett.*, 2003, **49**, 8753-8756.