Supporting Information

Copper-catalyzed direct oxidative synthesis of α-ketoamides from aryl methyl ketones, amines, and molecular oxygen

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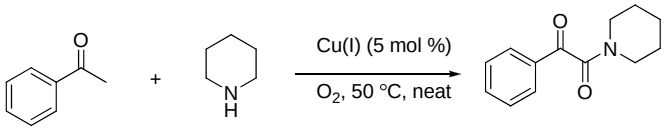
1. General remarks

CuI (98%) was purchased from Alfa Aesar Chemical Company and used as received. 5,5-dimethyl-1-yrroline *N*-oxide (DMPO) was purchased from Acros chemical company. Superoxide dismutase (SOD) and $H_2{}^{18}O$ (97%) were purchased from Aldrich chemical company. $^{18}O_2$ (97%) was purchased from Beijing Gaisi Chemical Gases Center. The catalyst $[Cu(CH_3CN)_4]OTf$ was prepared from commercially available $Cu(CF_3SO_3)_2$ according to a previously reported procedure.[1] Enamine **4a** was prepared from acetophenone and piperidine by a previously reported procedure.[2] All other commercially available reagents were purchased from Acros, Aldrich and Alfa Aesar Chemical Company and used without further purification unless otherwise stated. All reactions were carried out under an oxygen atmosphere unless otherwise stated. All solvents were dried according to standard procedures. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Bruker Avance 600 spectrometer with TMS as internal standard (600 MHz ^1H, 150 MHz ^{13}C) at room temperature, and the chemical shifts (δ) were expressed in ppm and *J* values were given in Hz. The following abbreviations are used to indicate the multiplicity: s (singlet), d (doublet), t (triplet), m (multiplet), br (broad). EPR spectra were recorded at room temperature on a JEOL JES-FA200 EPR spectrometer (300K, 9.07 GHz, X-band). Mass analyses and HRMS were obtained on a Finnigan-LCQDECA mass spectrometer and a Bruker Daltonics Bio-TOF-Q mass spectrometer by the ESI method, respectively. LC-MS were obtained on Waters Acquity HPLC (PDA Detector)/Quattro Premier XE triquadrupole mass spectrometer. HPLC analysis was performed on Agilent 1200 with a DAD detector. Column chromatography was performed on silica gel (100-200 mesh).

2. Experimental section

2.1 Investigations on the catalytic activity of Cu(I) and Cu(II) salts under neat conditions

Table S1. Cu(I)-catalyzed reaction of **1a** and **2a** under neat conditions[a]



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

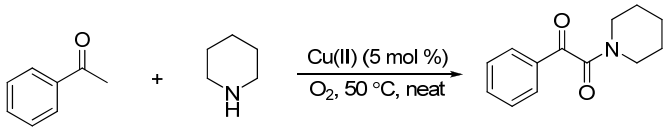
Entry	Catalyst	Yield[b] (%)
1	CuBr	15
2	CuCl	9
3	$(CuOTf)_2{\cdot}PhCH_3$	9
4	$[Cu(CH_3CN)_4]PF_6$	8
5	CuI	71
6	$[Cu(CH_3CN)_4]OTf$	11[c]

[a] Reaction conditions: **1a** (2 mmol), **2a** (6 mmol), catalyst (5 mol%), O_2 (balloon), 50 ºC, 48 h. [b] Isolated yields. [c] 20 mol% catalyst was used.

Cu(I) salts were investigated in the model reaction of acetophenone with piperidine under neat conditions. As shown in Table S1, CuI turned out to be the best choice, while others such as CuBr, CuCl, $(CuOTf)_2{\cdot}PhCH_3$, $[Cu(CH_3CN)_4]PF_6$, and $[Cu(CH_3CN)_4]OTf$ were less effective. The influence of the anions on the catalytic activity of Cu was not clear at the present stage. However, based on the further investigation on the mechanism by EPR experiments and previous reports,[3] we speculated that, compared with other Cu(I) salts, the better catalytic activity of CuI might be explained by the difference in the electron density on Cu. I anion is less electronegative than Cl,

Br, OTf, and PF_6 anions. The higher electron density on Cu might promote the reaction of Cu(I) with dioxygen to form superoxide radical ($O_2^{\bullet-}$) more easily. These indicate that CuI is more reactive than other Cu(I) salts in our reaction system.

Table S2. Cu(II)-catalyzed reaction of **1a** and **2a** under neat conditions[a]



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

Entry	Catalyst	Yield[b] (%)
1	$CuCl_2$	12
2	$CuBr_2$	16
3	$Cu(OTf)_2$	7
4	$Cu(ClO_4)_2 \cdot 6H_2O$	3
5	$Cu(OAc)_2$	2

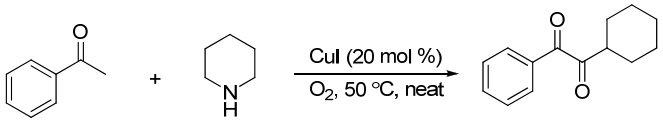
[a] Reaction conditions: **1a** (2 mmol), **2a** (6 mmol), catalyst (5 mol%), O_2 (balloon), 50 ºC, 48 h. [b] Isolated yields.

As shown in Table S2, Cu(II) salts could also promote the reaction, albeit in low yields. Based on our experiments (more details see EPR experiments on pages S14-15) and previous reports,[4] we speculated that Cu(II) might be reduced to Cu(I) by enamine generated in our reaction system. Subsequently, the produced Cu(I) reacted with O_2 to produce Cu(II) and superoxide radical ($O_2^{\bullet-}$), which would undergo the subsequent reactions to generate α-ketoamides.

2.2 Investigations on the catalytic activity of CuI with different source and purity

The catalytic activity of CuI with different source and purity has been investigated in the model reaction of acetophenone with piperidine under standard conditions. As shown in Table S3, the products of α-ketoamides were almost equally obtained when three different kinds of CuI were used, which indicated that the source and purity of CuI have not obvious effect on the reaction efficiency.

Table S3. Studies on the catalytic activity of CuI with different source and purity[a]



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

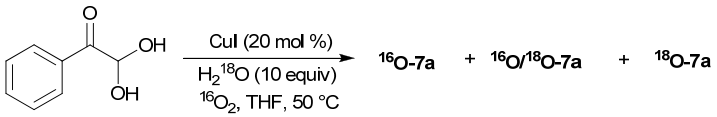
Entry	CuI		Yield[b] (%)
	Source	Purity	
1	Alfa Aesar	99.999%	87
2	Alfa Aesar	98%	87
3	Acros	98%	86

[a] Reaction conditions: **1a** (2mmol), **2a** (6 mmol), CuI (20 mol%), O_2, 50 ºC, 20 h. [b] Isolated yields.

2.3 Labeling experiments

The experimental procedures and copies of HRMS spectra for isotope labeling experiments

(1) Oxygen exchange experiment of phenylglyoxal monohydrate with $H_2{}^{18}O$ (10 equiv)



$H_2{}^{18}O$ (50 mg, 2.5 mmol) was added to a mixture of CuI (9.5 mg, 0.05 mmol) and phenylglyoxal monohydrate (38 mg, 0.25 mmol) in THF (2 mL) at room temperature under $^{16}O_2$ (balloon). The resulting mixture was stirred at 50 ºC for 20 h. Then, the reaction mixture was cooled to room temperature and purified by flash column chromatography on a short silica gel (petroleum ether/ethyl acetate = 2:1) to give the products, which were measured by HRMS.

Elemental Composition Report Page 1

Single Mass Analysis
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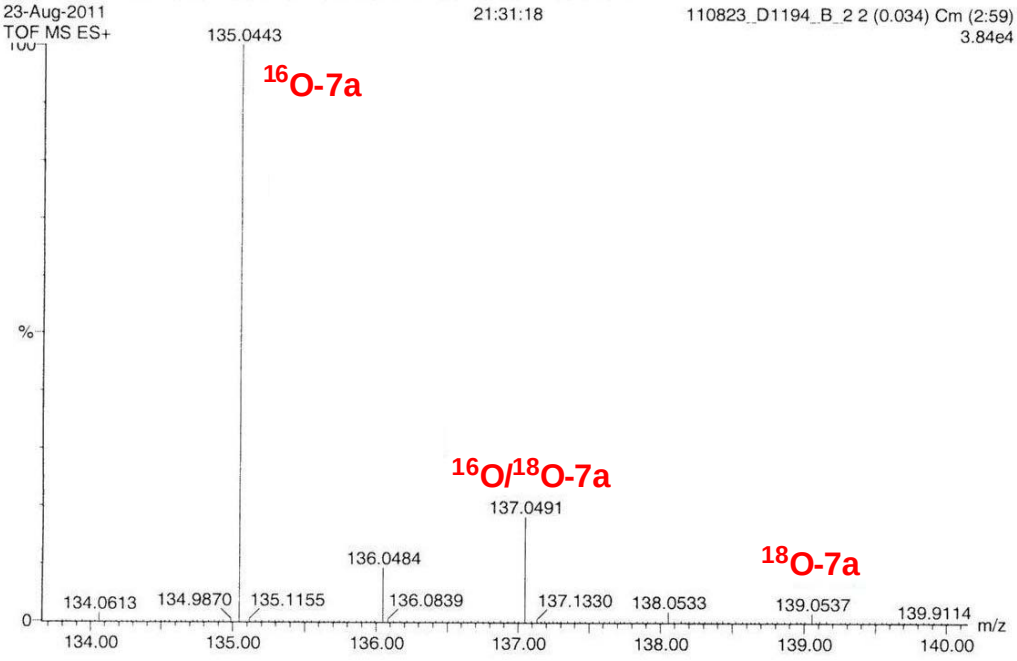
Selected filters: None

Monoisotopic Mass, Even Electron Ions
74 formula(e) evaluated with 6 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-200 H: 0-200 N: 0-1 16O: 0-2 18O: 0-2 Na: 0-1

23-Aug-2011 21:31:18 110823_D1194_B_2 2 (0.034) Cm (2:59)
TOF MS ES+ 3.84e4



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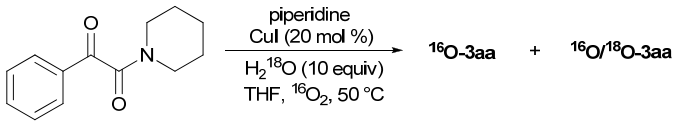
Maximum:		5.0	100.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
135.0443	135.0446	-0.3	-2.2	5.5	3201.4	C8 H7 16O2
137.0491	137.0488	0.3	2.2	5.5	40.5	C8 H7 16O 18O
139.0537	139.0531	0.6	4.3	5.5	79665.6	C8 H7 18O2

(2) Oxygen exchange experiment of **^{16}O-3aa** with $H_2{}^{18}O$ (10 equiv)



$H_2{}^{18}O$ (50 mg, 2.5 mmol) was added to a mixture of CuI (9.5 mg, 0.05 mmol), α-ketoamide (54 mg, 0.25 mmol) and piperidine (75 μL, 0.75 mmol) in THF (2 mL) at room temperature under $^{16}O_2$ (balloon). The resulting mixture was stirred at 50 ºC for 20 h. Then, the reaction mixture was directly determined by HRMS without purification by flash column chromatography.

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 100.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
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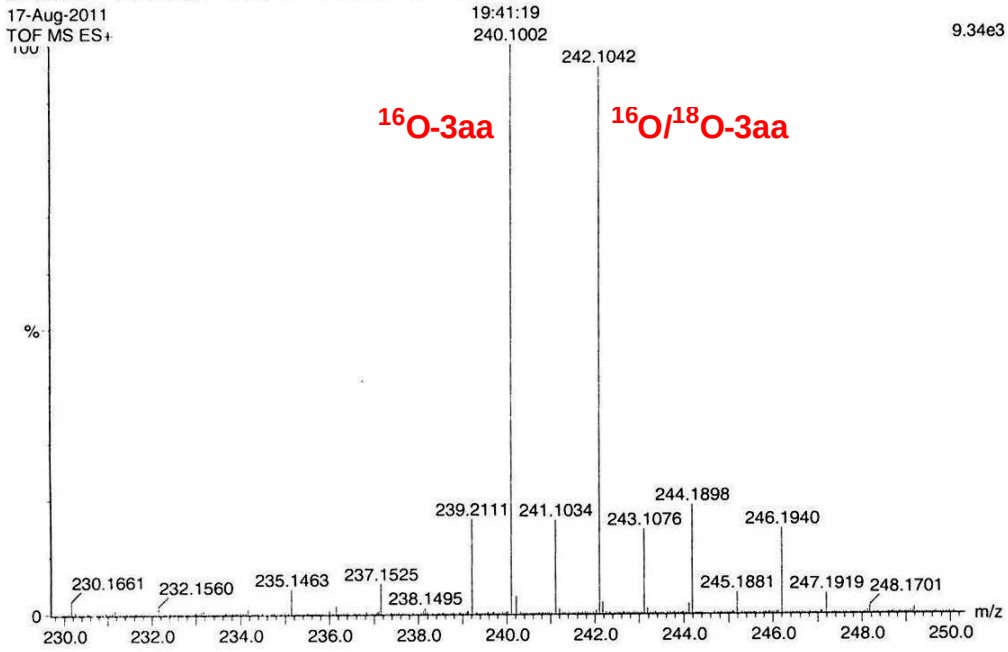
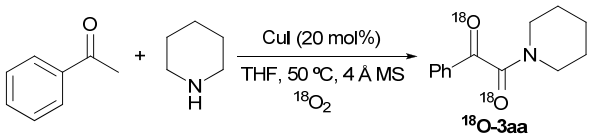


Minimum:				-1.5		
Maximum:		5.0	100.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
240.1002	240.1000	0.2	0.8	6.5	4352.0	C13 H15 N 1602 Na
242.1042	242.1043	-0.1	-.4	6.5	184.0	C13 H15 N 160 180 Na

(3) Labeling experiment in the presence of 4 Å MS



Acetophenone (117 μL, 1 mmol) was added to a mixture of CuI (38 mg, 0.2 mmol), 4 Å MS (0.3 g) and piperidine (297 μL, 3 mmol) in THF (1 mL) at room temperature under $^{18}O_2$ (balloon). The resulting mixture was stirred at 50 ºC for 20 h. The reaction mixture was directly determined by HRMS without purification by flash column chromatography.

Elemental Composition Report

Single Mass Analysis
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Selected filters: None

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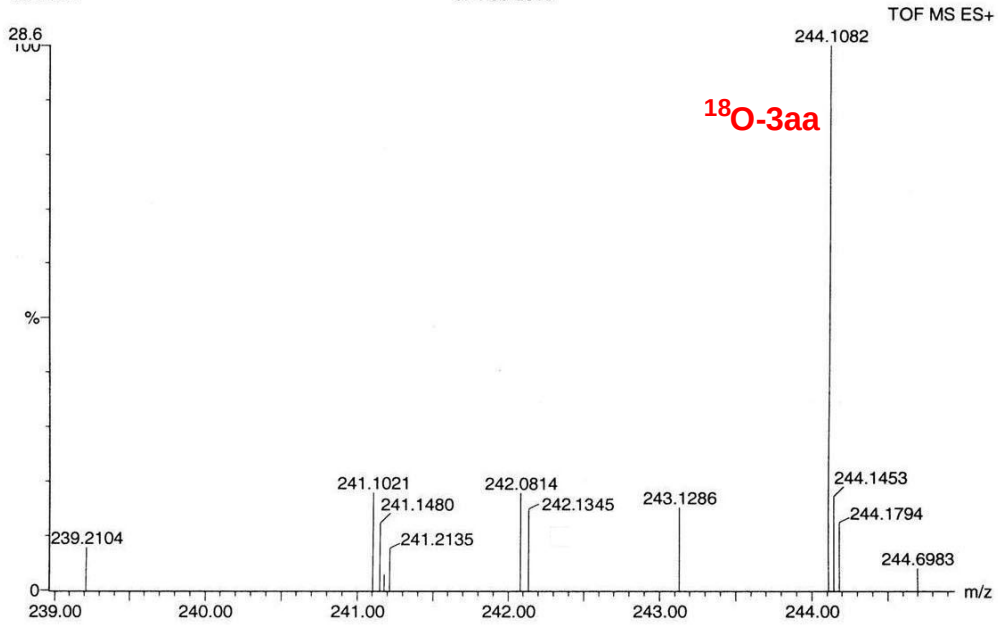
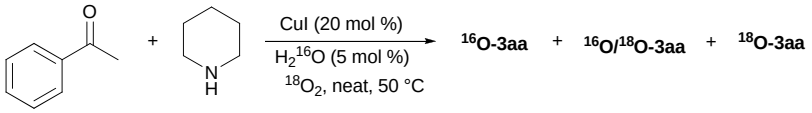
10:32:40 07-Feb-2010



Minimum:				-1.5		
Maximum:		5.0	100.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
244.1082	244.1085	-0.3	-1.2	6.5	1328.7	C13 H15 N 18O2 Na

(4) Oxygen exchange experiment in the presence of $H_2{}^{16}O$ (5 mol%) under $^{18}O_2$



Acetophenone (234 µL, 2 mmol) was added to a mixture of CuI (76 mg, 0.4 mmol), piperidine (594 µL, 6 mmol) and $H_2{}^{16}O$ (1.8 mg, 5 mol%) at room temperature under $^{18}O_2$ (balloon). The resulting mixture was stirred at 50 ºC for 20 h. Then, the reaction mixture was directly determined by HRMS without purification by flash column chromatography.

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 100.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
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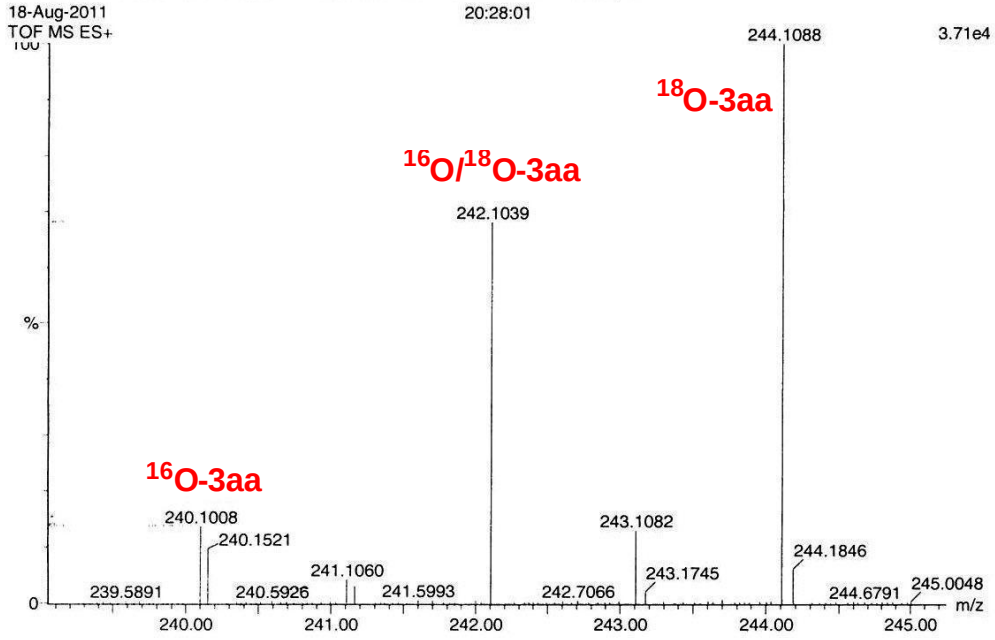
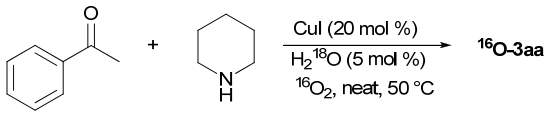


Minimum:				-1.5		
Maximum:		5.0	100.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
240.1008	240.1000	0.8	3.3	6.5	12753.2	C13 H15 N 16O2 Na
242.1039	242.1043	-0.4	-1.7	6.5	901.1	C13 H15 N 16O 18O Na
244.1088	244.1085	0.3	1.2	6.5	172747O.6	C13 H15 N 18O2 Na

(5) Oxygen exchange experiment in the presence of $H_2{}^{18}O$ (5 mol%) under $^{16}O_2$



Acetophenone (234 µL, 2 mmol) was added to a mixture of CuI (76 mg, 0.4 mmol), piperidine (594 µL, 6 mmol) and $H_2{}^{18}O$ (2 mg, 5 mol%) at room temperature under $^{16}O_2$ (balloon). The resulting mixture was stirred at 50 ºC for 20 h. Then, the reaction mixture was directly determined by HRMS without purification by flash column chromatography.

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 100.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
117 formula(e) evaluated with 10 results within limits (up to 1 closest results for each mass)
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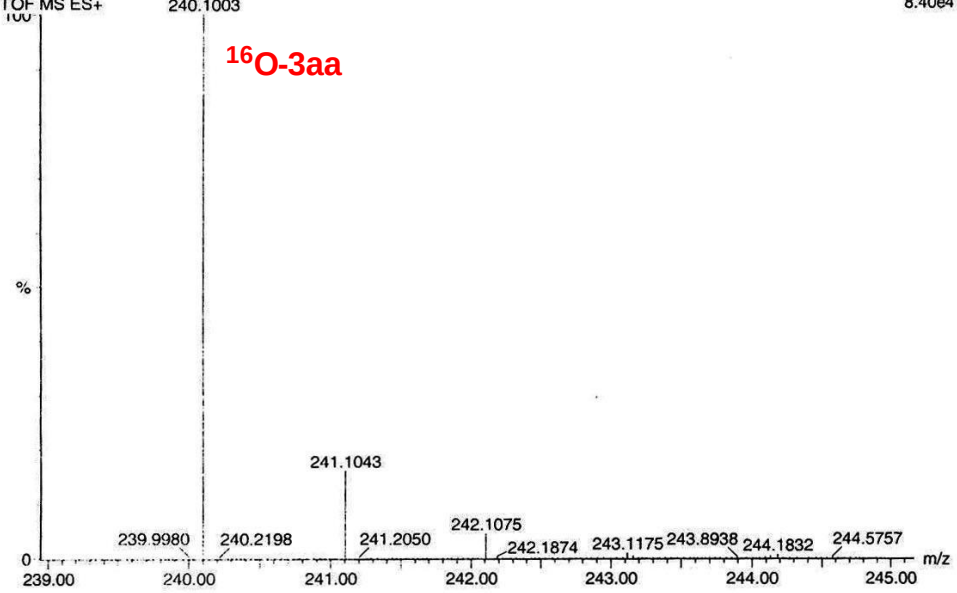
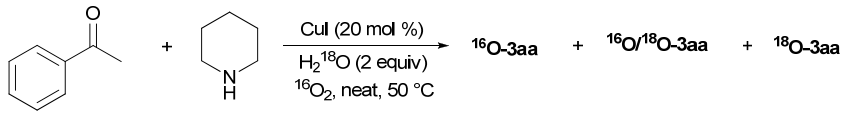


Minimum:				-1.5		
Maximum:		5.0	100.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
240.1003	240.1000	0.3	1.2	6.5	856.7	C13 H15 N 1602 Na

(6) Oxygen exchange experiment in the presence of $H_2{}^{18}O$ (2 equiv) under $^{16}O_2$



Acetophenone (234 µL, 2 mmol) was added to a mixture of CuI (76 mg, 0.4 mmol), piperidine (594 µL, 6 mmol) and $H_2{}^{18}O$ (80 mg, 4 mmol) at room temperature under $^{16}O_2$ (balloon). The resulting mixture was stirred at 50 ºC for 20 h. Then, the reaction mixture was directly determined by HRMS without purification by flash column chromatography.

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 100.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
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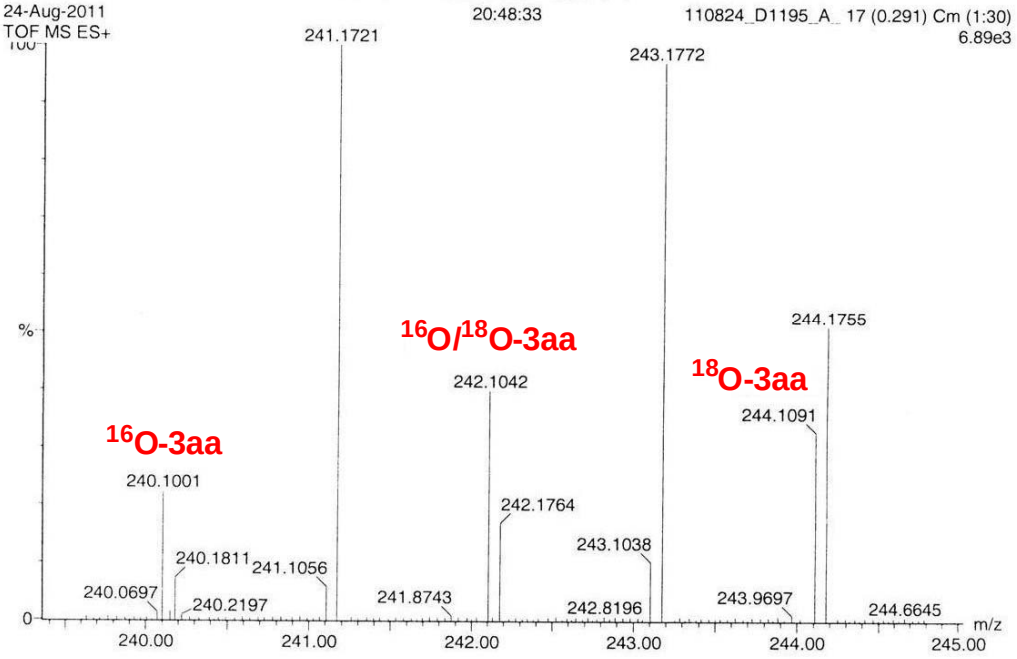
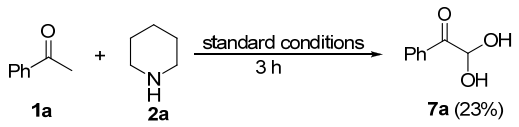


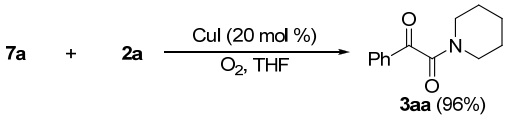
Minimum:				-1.5		
Maximum:		5.0	100.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
240.1001	240.1000	0.1	0.4	6.5	1372.7	C13 H15 N 16O2 Na
242.1042	242.1043	-0.1	-0.4	6.5	169.2	C13 H15 N 16O 18O Na
244.1091	244.1085	0.6	2.5	6.5	103990.8	C13 H15 N 18O2 Na

2.4 Isolation of intermediate 7a



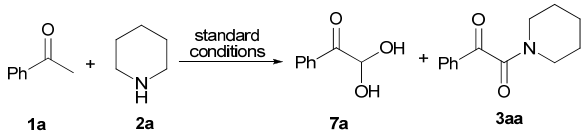
Acetophenone (234 μL, 2 mmol) was added to a mixture of CuI (76mg, 0.4 mmol) and piperidine (594 μL, 6 mmol) at room temperature under O_2 (balloon). The resulting mixture was stirred at 50 ºC for 3 h. Then, the reaction mixture was cooled to room temperature, filtered through silica gel, and washed with CH_2Cl_2. The resulting solution was concentrated in vacuo and the residue was purified by flash column chromatography (hexanes/ethyl acetate = 5:1) to afford the intermediate **7a** (70 mg, 23%). ^{1}H NMR (CD_3OD, 600 MHz, ppm): δ = 8.10-8.08 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.67-7.63 (t, *J* = 7.5 Hz, 1H), 7.55-7.51 (t, *J* = 7.9 Hz, 2H), 5.57 (s, 1H); ^{13}C NMR (CD_3OD, 150 MHz, ppm): δ = 193.6, 132.9, 132.6, 128.3, 127.4, 94.3. The NMR characterization data of **7a** is coincidence with that of commericially available reagent.

2.5 Conversion of 7a into α-ketoamide 3aa



Phenylglyoxal monohydrate (38 mg, 0.25 mmol) was added to a mixture of CuI (9 mg, 0.05 mmol) and piperidine (74 μL, 0.75 mmol) in THF (1 mL) at room temperature under O_2 (balloon). The resulting mixture was stirred at 50 ºC for 1 h. Then the reaction mixture was cooled to room temperature, filtered through silica gel, and washed with CH_2Cl_2. The resulting solution was concentrated in vacuo and the residue was purified by flash column chromatography (hexanes/ethyl acetate = 5:1) to yield the product **3aa** (52 mg, 96%).

2.6 The variation of phenylglyoxal intermediate and α-ketoamide with reaction time in the reaction of acetophenone 1a with piperidine 2a.



The experimental conditions of HPLC analysis: Agilent 1200, DAD detector: 220 nm; Luna C_{18} (4.6×150mm, 5μm); 25ºC. flow rate: 1 mL/min; The mobile phase consisted of A (Water) and B (acetonitrile), gradient elution: 0-20 min, 10-40% B (acetonitrile); 20-30 min, 40% B (acetonitrile).

Eight parallel reactions of acetophenone (2 mmol) and piperidine (6 mmol) was performed under standard conditions. The reactions were stopped at 0.5 h, 1 h, 2 h, 3 h, 6 h, 12 h, 20 h, 24 h, cooled to room temperature, and diluted with methanol to 100 mL, respectively. The diluted mixtures were detected by HPLC via external standard method.

The amount of phenylglyoxal monohydrate **7a** and α-ketoamide **3aa** varied with reaction time are demonstrated in Fig. S1. At the beginning of the reaction (0.5 h), phenyl glyoxal **7a** intermediate was produced in 40% yield along with a trace amount of product α-ketoamide. The amount of phenyl glyoxal intermediate gradually decreased and the product increased with the prolonging of reaction time. After 6 h, only a small amount

of phenyl glyoxal intermediate was detected and the rate of product formation has also become slow. After 20 h, the amount of product almost did not increase.

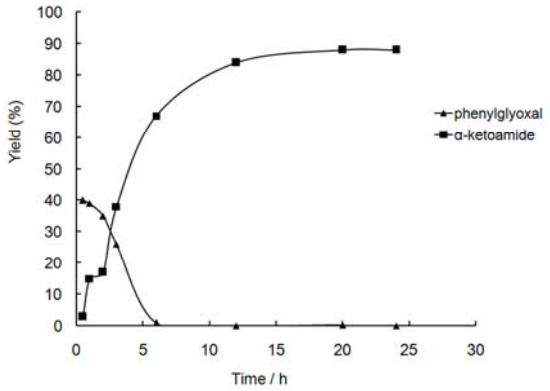
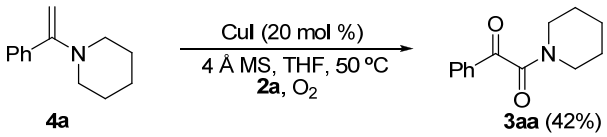


Fig. S1 The variation of phenylglyoxal intermediate and α-ketoamide with reaction time in the reaction of acetophenone (**1a**) with piperidine (**2a**). Yields of phenylglyoxal and α-ketoamide were determined by HPLC.

2.7 Conversion of enamine 4a into 3aa



Enamine **4a** (47 mg, 0.25 mmol) was added to a mixture of CuI (9.5 mg, 0.05 mmol), 4 Å MS (50 mg), piperidine (50 μL, 0.5 mmol) in THF (1 mL) at room temperature under O_2 (balloon). The resulting mixture was stirred at 50 ºC for 20 h. Then the reaction mixture was cooled to room temperature, filtered through silica gel, and washed with CH_2Cl_2. The resulting solution was concentrated in vacuo and the residue was purified by flash column chromatography (hexanes/ethyl acetate = 5:1) to yield the product **3aa** (23 mg, 42%).

2.8 EPR experiments

EPR spectra were recorded at room temperature on a JEOL JES-FA200 EPR spectrometer (300K, 9.07 GHz, X-band). Typical instrument settings were as follows: microwave power, 1 mW ($O_2^{\bullet-}$) and 2 mW (Cu^{2+}); field set, 3240 ($O_2^{\bullet-}$) and 3230 (Cu^{2+}); sweep width, 3100-3300 G ($O_2^{\bullet-}$) and 2200-4400 G (Cu^{2+}); modulation frequency, 100 kHz; modulation amplitude, 1G ($O_2^{\bullet-}$) and 3.5 G (Cu^{2+}); sweep time, 60 s.

Table S4. EPR investigation

entry	EPR sample	signals of DMPO-OO(H)	superoxide radical	concentration of DMPO-OO(H) (mM)
1	standard sample (acetophenone (0.25 mmol), piperidine (0.75 mmol), CuI (20 mol%), O_2, DMPO)	yes	Yes	1.09
2	standard sample without CuI	no	no	-
3	standard sample without piperidine	no	no	-
4	standard sample without CuI and piperidine	no	no	-
5	standard sample without acetophenone	yes	yes	1.05

Reaction conditions: The mixture of acetophenone (29 μL, 0.25 mmol), piperidine (75 μL, 0.75 mmol) and CuI (9.5 mg, 0.05 mmol) in THF (2 mL) was stirred at 50 ºC under O_2 for 30 min. 30 μL of the reaction mixture was taken out into a small

tube, followed by the addition of 10 μL DMPO (0.1 M). Then, the resulting mixture was tested by EPR.

Measured concentration of DMPO-OO(H) was determined by the following formula:

$C = \{[(S_{DMPO\text{-}OO(H)}/S_{TEMPOL})\times(2.408\times10^{15})]/(6.02\times10^{23})\}/V$

Notes:

The double integration area of standard sample: $S_{DMPO\text{-}OO(H)}=38.21$

The double integration area of standard sample without acetophenone: $S'_{DMPO\text{-}OO(H)}=36.86$

The double integration area of TEMPOL (400 μL, 10 μM): $S_{TEMPOL}=3.5$

The number of spins of TEMPOL (400 μL, 10 μM) was 2.408×10^{15}

V=40 μL

The double integration area of sample was obtained by an EPR software (version: 3.3.34 XB) of JEOL JES-FA200 EPR spectrometer

The standard sample TEMPOL was provided by JEOL company.

(1) When the reaction of acetophenone (**1a**) with piperidine (**2a**) was recorded for the EPR spectra using 5,5-dimethyl-1-yrroline *N*-oxide (DMPO) as a spin trap, the signals corresponding to DMPO-OO(H) were observed (EPR spectrum see Fig. S2). The calculated hyperfine splittings are g_0 (2.006), α_N (15.8 G), α^{β}_H (13.4 G), and α^{γ}_H(1.9 G), which indicated the presence of the superoxide radical during the transformation.

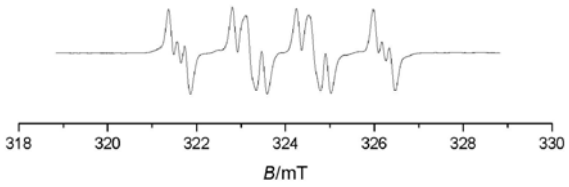


Fig. S2 EPR spectrum obtained from the reaction system: acetophenone (29 μL, 0.25 mmol), piperidine (75 μL, 0.75 mmol) and CuI (9.5 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min. 30 μL of the reaction mixture was taken out into a small tube, followed by the addition of 10 μL DMPO (0.1 M). Then, this mixture was tested by EPR.

(2) Definitely, the signals completely disappeared with the addition of superoxide dismutase (SOD), which further confirmed the existence of superoxide radical in the present reaction system (EPR spectrum see Fig. S3).

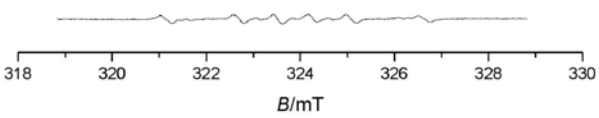


Fig. S3 EPR spectrum obtained from the reaction system: acetophenone (29 μL, 0.25 mmol), piperidine (75 μL, 0.75 mmol) and CuI (9.5 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min. 30 μL of the reaction mixture was taken out into a small tube, mixed well with 10 μL SOD (0.1 mg/mL), folllwed by the addition of 10 μL DMPO (0.1 M). Then, this mixture was tested by EPR.

(3) When the EPR was tested in the absence of CuI catalyst (EPR spectrum see Fig. S4) or piperidine (EPR

spectrum see Fig. S5), the signals corresponding to DMPO–OO(H) did not appear, which indicated that the superoxide radical was produced in the presence of Cu(I) catalyst and amine.

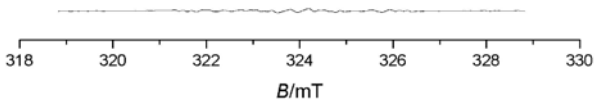


Fig. S4 EPR spectrum obtained from the reaction system: acetophenone (29 μL, 0.25 mmol) and piperidine (75 μL, 0.75 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min. 30 μL of the reaction mixture was taken out into a small tube, followed by the addition of 10 μL DMPO (0.1 M). Then, this mixture was tested by EPR.

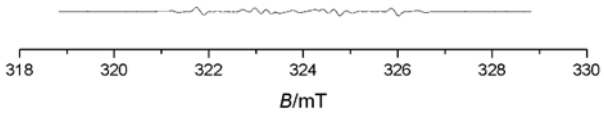


Fig. S5 EPR spectrum obtained from the reaction system: acetophenone (29 μL, 0.25 mmol) and CuI (9.5 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min. 30 μL of the reaction mixture was taken out into a small tube, followed by the addition of 10 μL DMPO (0.1 M). Then, this mixture was tested by EPR..

(4) Indeed, when the CuI was stirred with piperidine under dioxygen, the signals corresponding to DMPO-OO(H) were observed through EPR experiment. The calculated hyperfine splittings are g_0 (2.006), α_N (15.8 G), α^{β}_H (13.5 G), and α^{γ}_H (1.8 G).

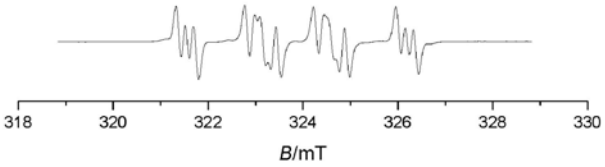


Fig. S6 EPR spectrum obtained from the reaction system: piperidine (75 μL, 0.75 mmol) and CuI (9.5 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min. 30 μL of the reaction mixture was taken out into a small tube, followed by the addition of 10 μL DMPO (0.1 M). Then, this mixture was tested by EPR.

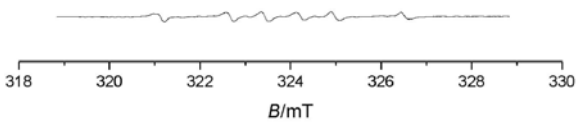


Fig. S7 EPR spectrum obtained from the reaction system: piperidine (75 μL, 0.75 mmol) and CuI (9.5 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min. 30 μL of the reaction mixture was taken out into a small tube, mixed well with 10 μL SOD (0.1 mg/mL), folllwed by the addition of 10 μL DMPO (0.1 M). Then, this mixture was tested by EPR.

(5) Importantly, the signals of Cu(II) were also detected by EPR from the standard reaction system (EPR spectrum see Fig. S8) and the mixtures of CuI with piperidine under dioxygen (EPR spectrum see Fig. S9), which indicated that Cu(I) was oxidized into Cu(II) in our reaction system.

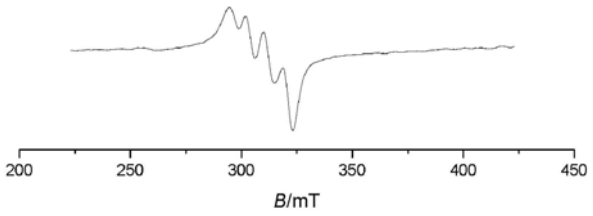


Fig. S8 EPR spectrum obtained from the reaction system: acetophenone (29 μL, 0.25 mmol), piperidine (75 μL, 0.75 mmol) and CuI (9.5 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min, and texted by EPR.

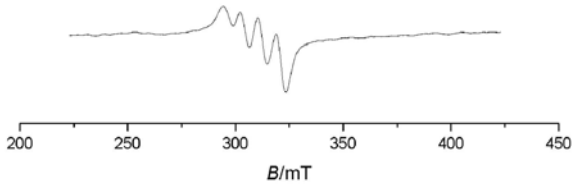


Fig. S9 EPR spectrum obtained from the reaction system: piperidine (75 μL, 0.75 mmol) and CuI (9.5 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min, and texted by EPR.

(6) When the reactions of **1a** with **2a** catalyzed by $CuBr_2$ or $CuCl_2$ were performed under standard conditions, superoxide radical ($O_2^{\bullet-}$) were detected by EPR experiments (EPR spectra see Fig. S10 and S11). Superoxide radical ($O_2^{\bullet-}$) was also detected by EPR analysis when the reaction of enamine **4a** with $CuBr_2$ was performed in the presence of piperidine in dry THF under oxygen atmosphere (EPR spectrum see Fig. 12). While, superoxide radical was not detected when $CuBr_2$ was directly stirred with piperidine in dry THF under oxygen atmosphere. Based on our experiments and previous reports about the reduction of Cu(II) by enamine or enol ether to Cu(I),[21f,25] we speculated that Cu(II) might be reduced to Cu(I) by enamine generated in our reaction system. Subsequently, the produced Cu(I) reacted with O_2 to produce Cu(II) and superoxide radical ($O_2^{\bullet-}$).

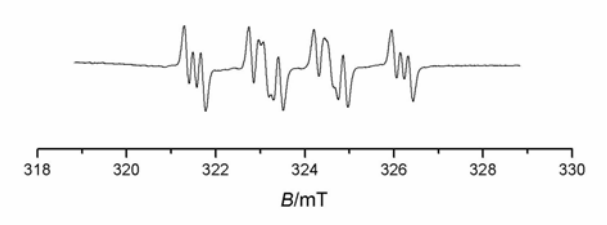


Fig. S10 EPR spectrum obtained from the reaction system: acetophenone (29 μL, 0.25 mmol), piperidine (75 μL, 0.75 mmol) and $CuBr_2$ (11 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min. 30 μL of the reaction mixture was taken out into a small tube, followed by the addition of 10 μL DMPO (0.1 M). Then, this mixture was tested by EPR.

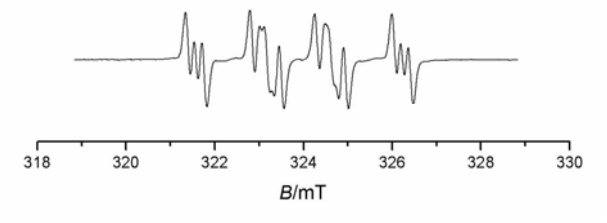


Fig. S11 EPR spectrum obtained from the reaction system: acetophenone (29 μL, 0.25 mmol), piperidine (75 μL, 0.75 mmol)

and $CuCl_2$ (7 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min. 30 μL of the reaction mixture was taken out into a small tube, followed by the addition of 10 μL DMPO (0.1 M). Then, this mixture was tested by EPR.

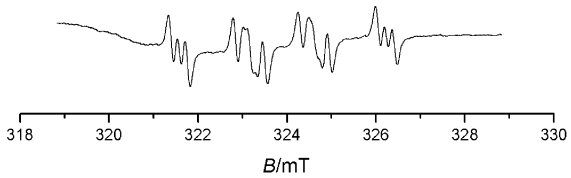


Fig. S12 EPR spectrum obtained from the reaction system: enamine (47mg, 0.25 mmol), piperidine (50 μL, 0.5 mmol), 4Å MS (55mg) and $CuBr_2$ (11 mg, 0.05 mmol) in THF (2 mL) under O_2. The reaction mixture was stirred at 50 ºC for 30 min. 30 μL of the reaction mixture was taken out into a small tube, followed by the addition of 10 μL DMPO (0.1 M). Then, this mixture was tested by EPR.

2.9 LC-MS analysis experiments

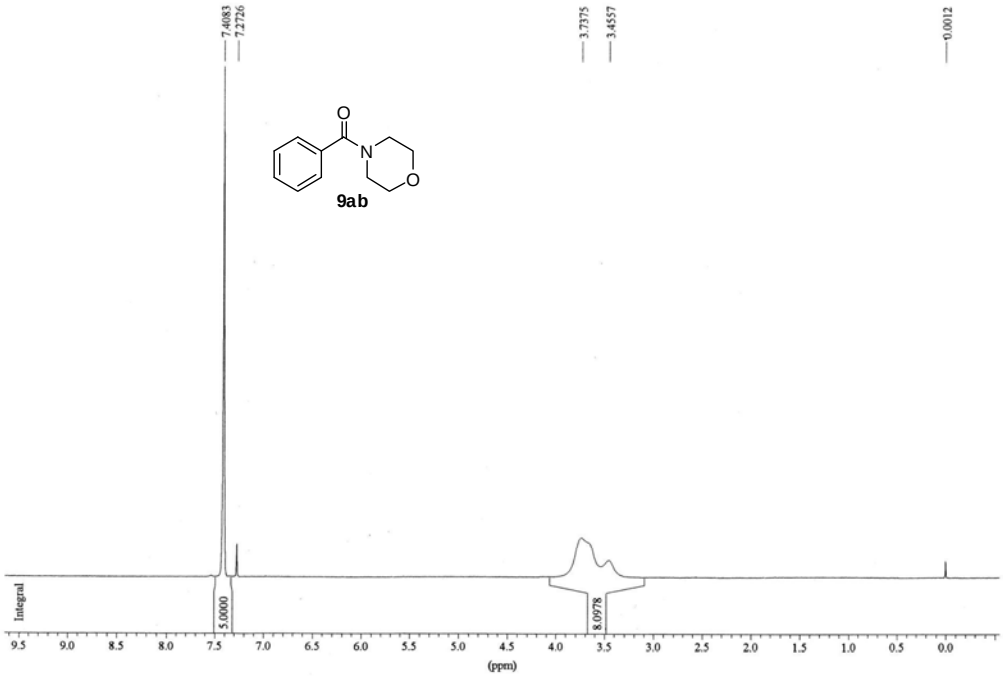
The experimental conditions of LC-MS analysis:

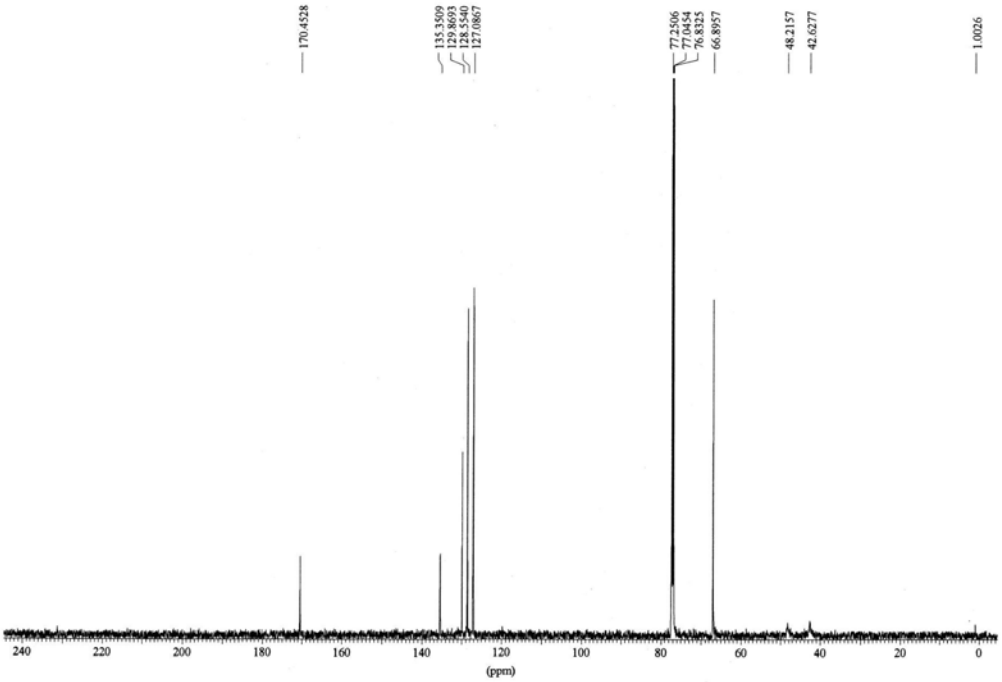
HPLC: Waters BEH C18 column, 2.1×100 mm, 1.7 μm; PDA detector: 220 nm; 30 ^oC; flow rate: 0.25 mL/min; The mobile phase consisted of A (Water with 0.1% acetic acid) and B (methanol), gradient elution: 50% B(methanol) or 75% B(methanol).

MS: Capillary 3.0 kv; Cone 40.v; Extraction cone 3 v; Source temperature 100 ^oC; Desolvation temperature 250 ^oC; Cone gas flow 40 L/h; Desolvation gas flow 600 L/h. Scan 100~800 m/z.

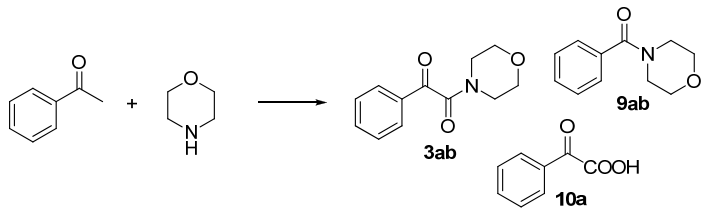
Amide (**9ab**) could be isolated (8% yield) from the reaction system of acetophenone (**1a**) with morpholine (**2b**) in the standard conditions.

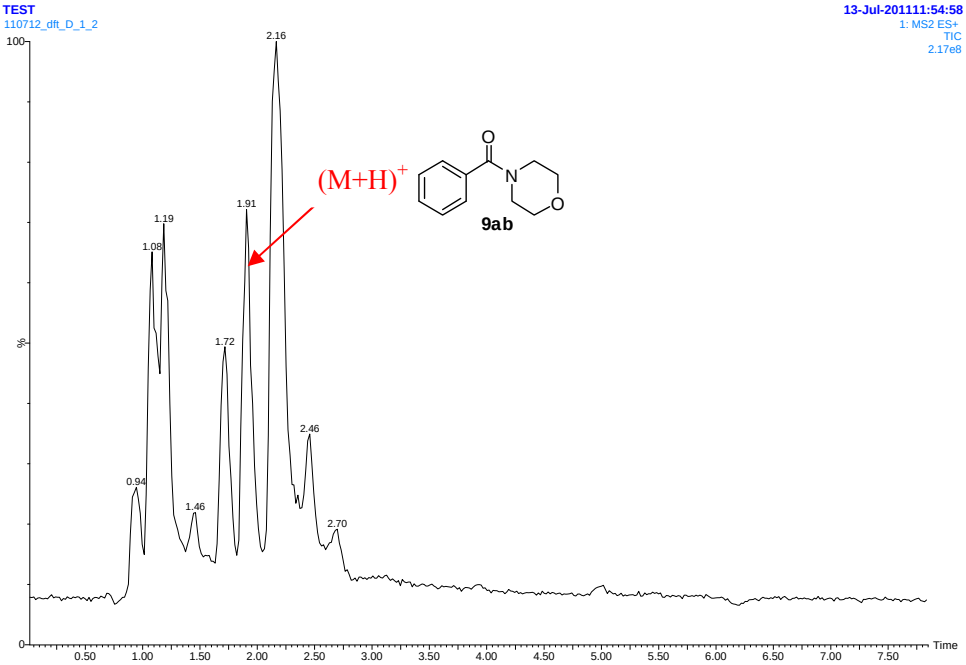
Copies of ^{1}H NMR and ^{13}C NMR of isolated amide (**9ab)**.

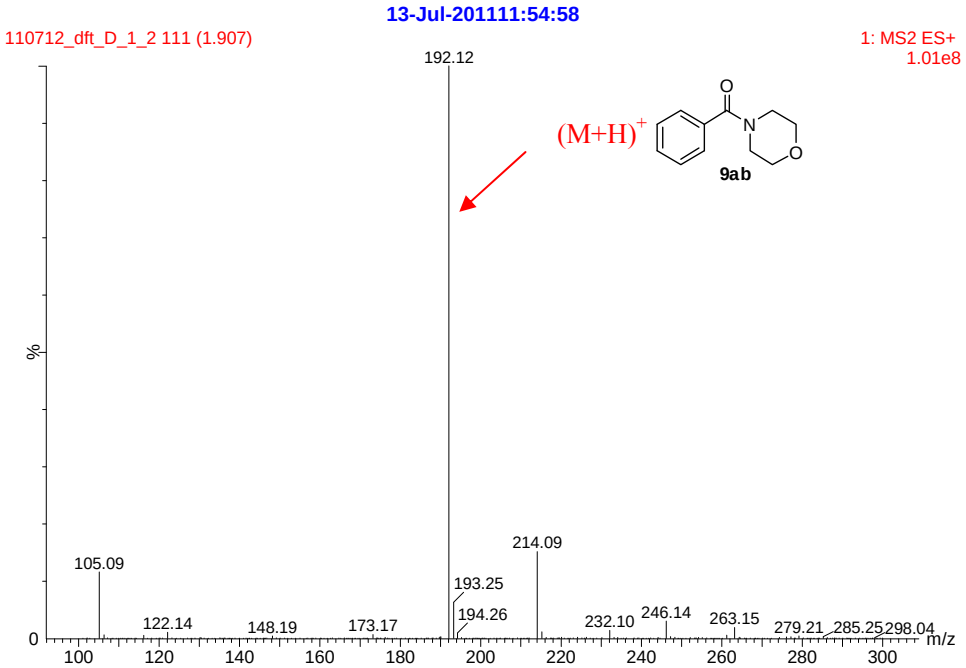


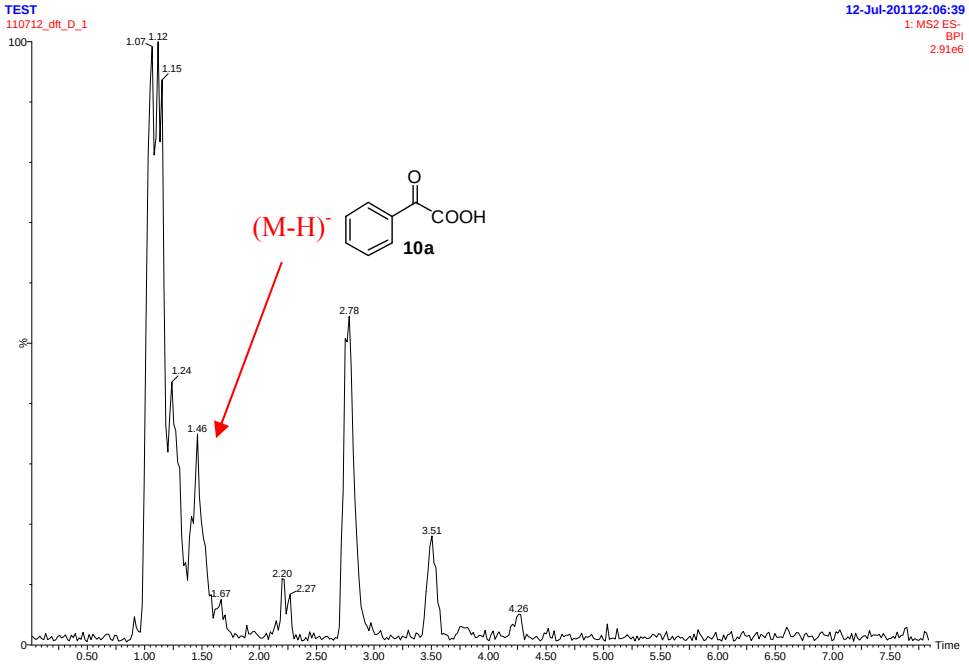


Copies of LC-MS spectra









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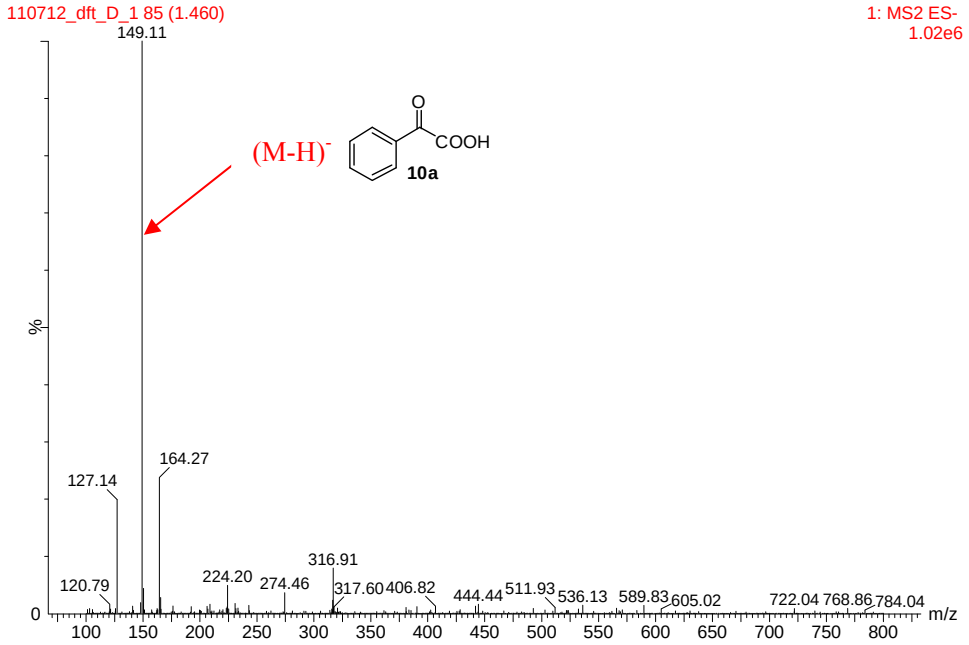

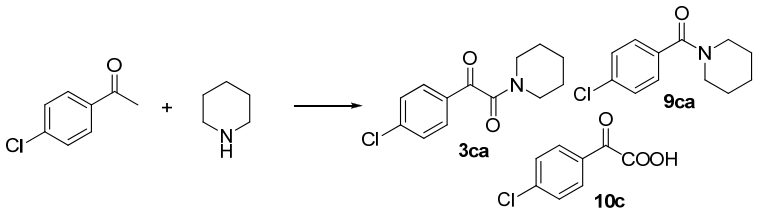
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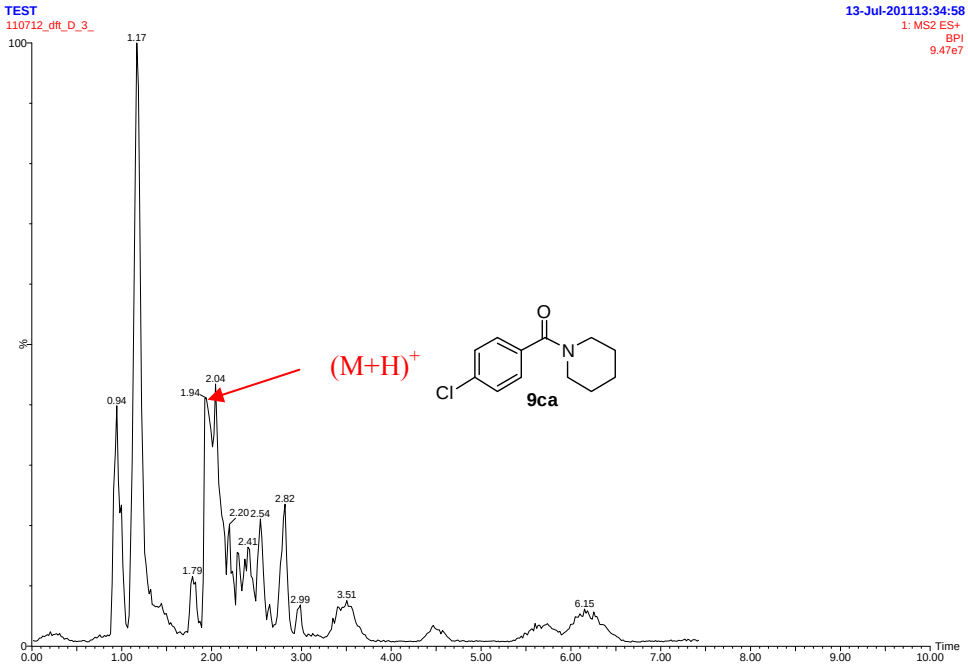
N
H
O
N
Cl
3ca
9ca
COOH
10c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%
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1.94
2.04
1.79
2.20
2.54
2.41
2.82
2.99
3.51
6.15
0.00
1.00
2.00
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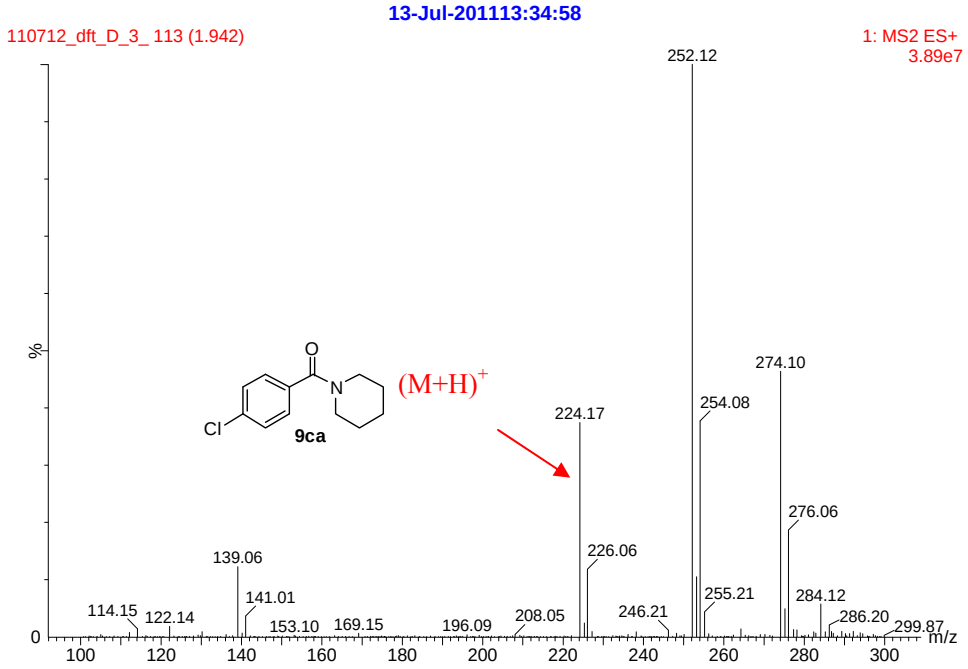
6.00
7.00
8.00
9.00
10.00
Time
(M+H)+
9ca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255.21
284.12
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114.15
122.14
153.10
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196.09
208.05
246.21
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260
280
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m/z
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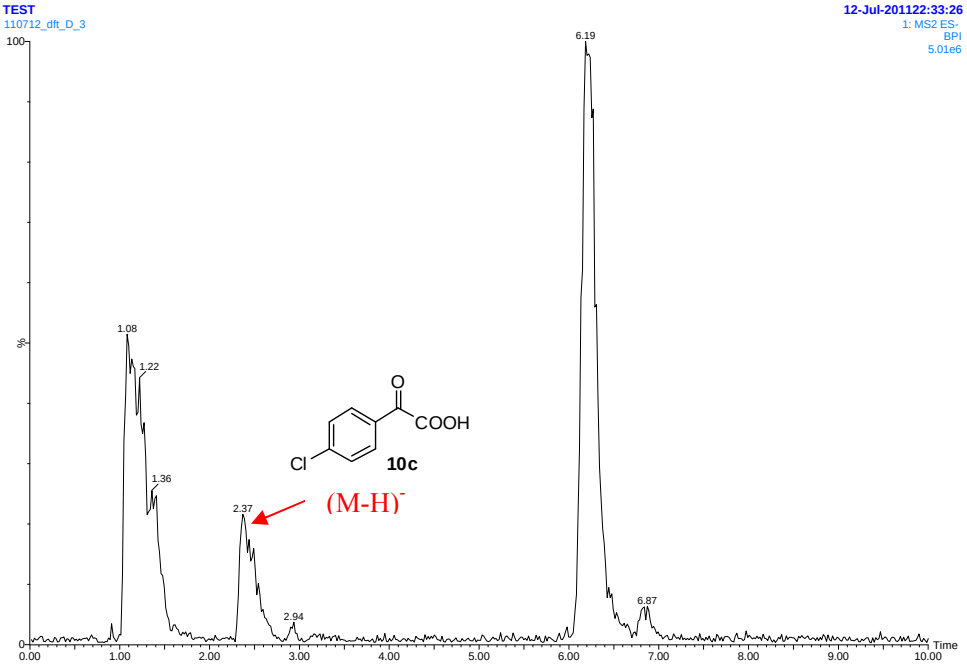
9ca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9.00
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Cl
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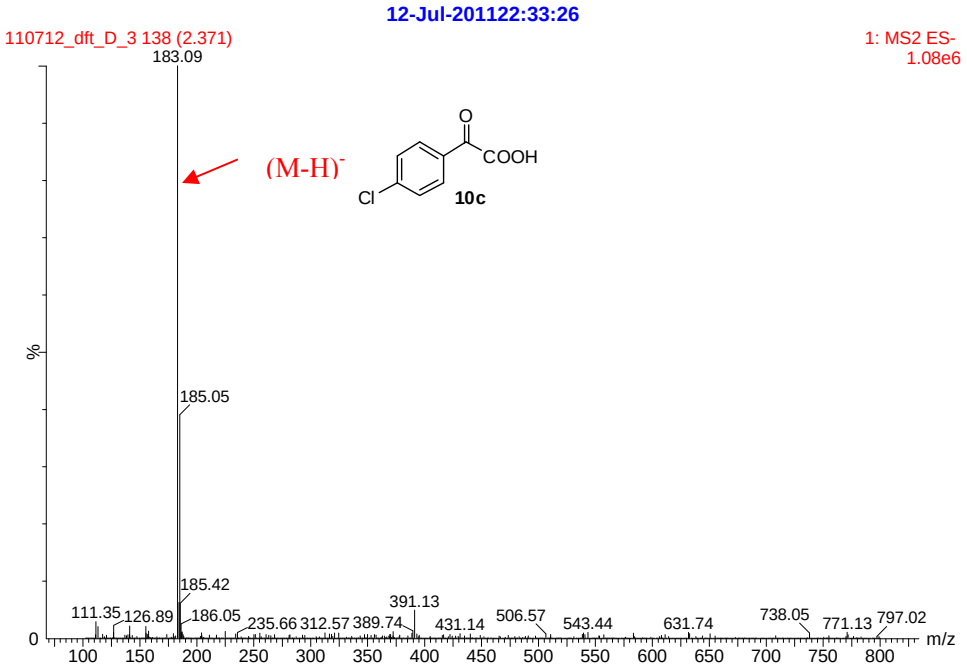
(M-H)-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506.57
543.44
631.74
738.05
771.13
797.02
%
0
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150
200
250
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350
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600
650
700
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m/z
(M-H)-
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COOH
Cl
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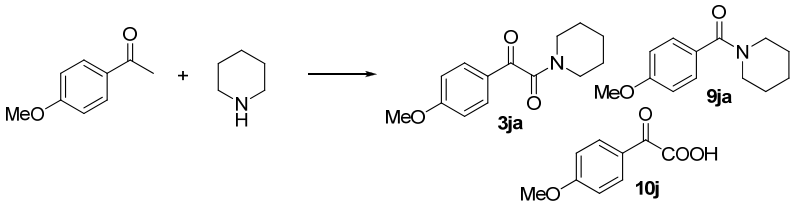

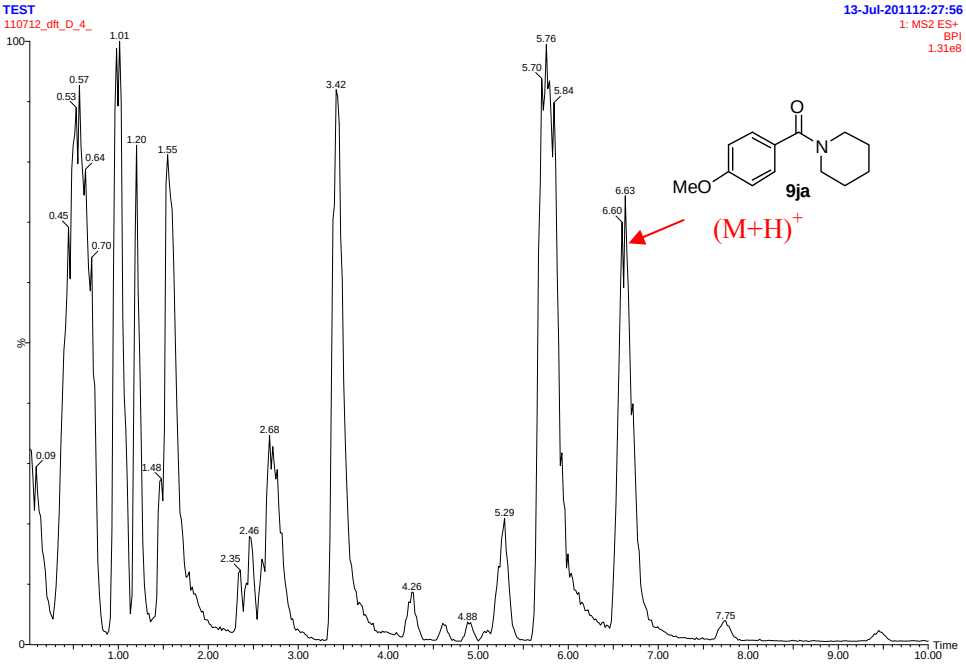

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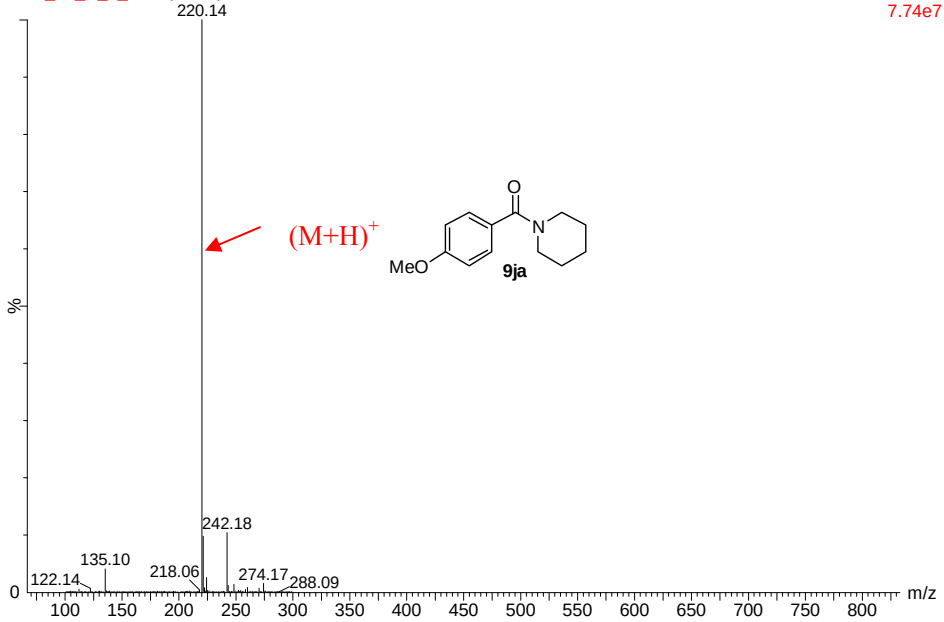

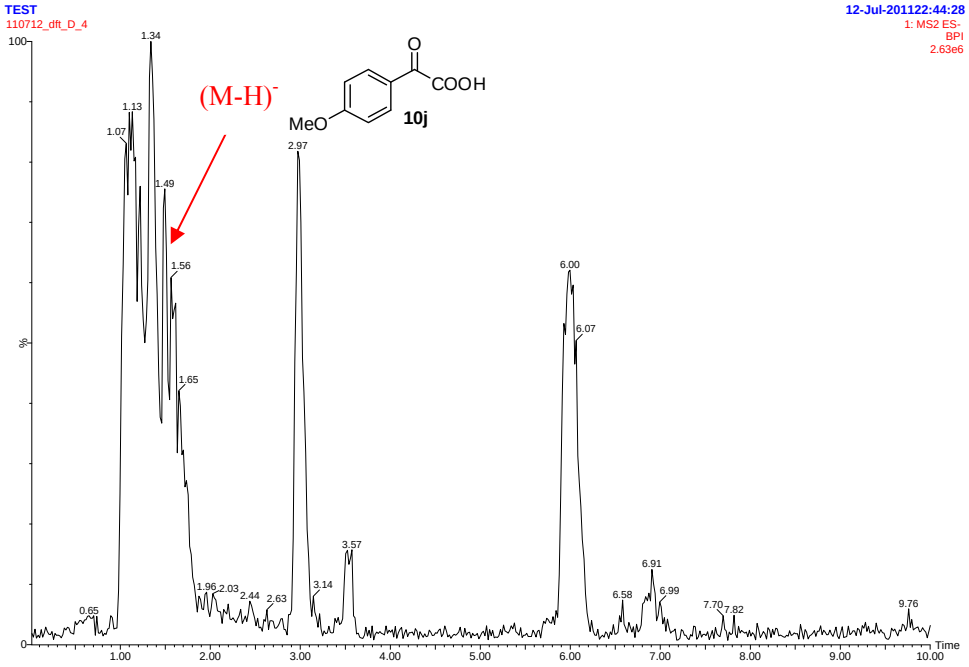

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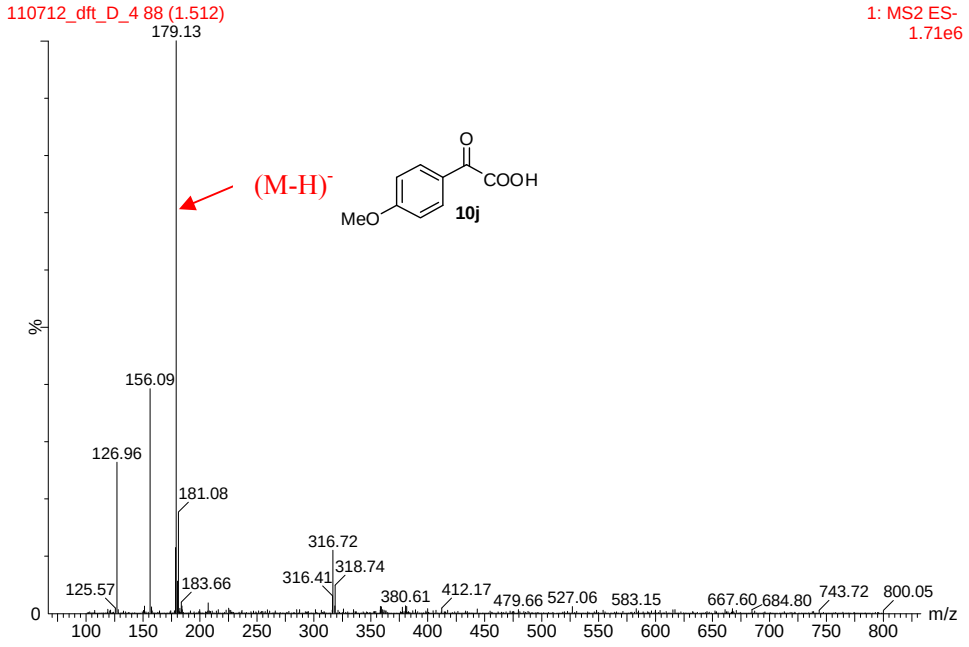

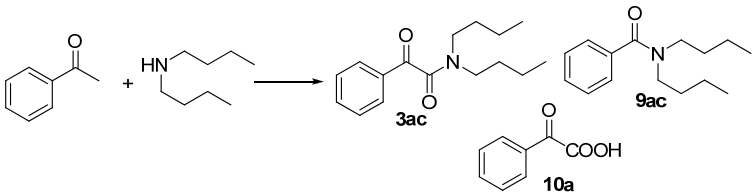

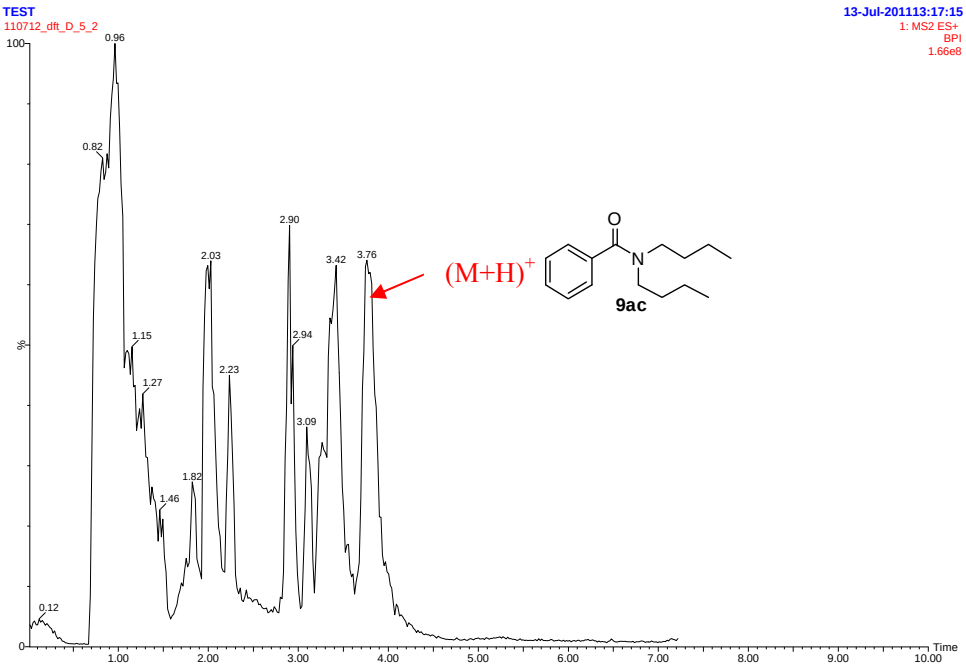

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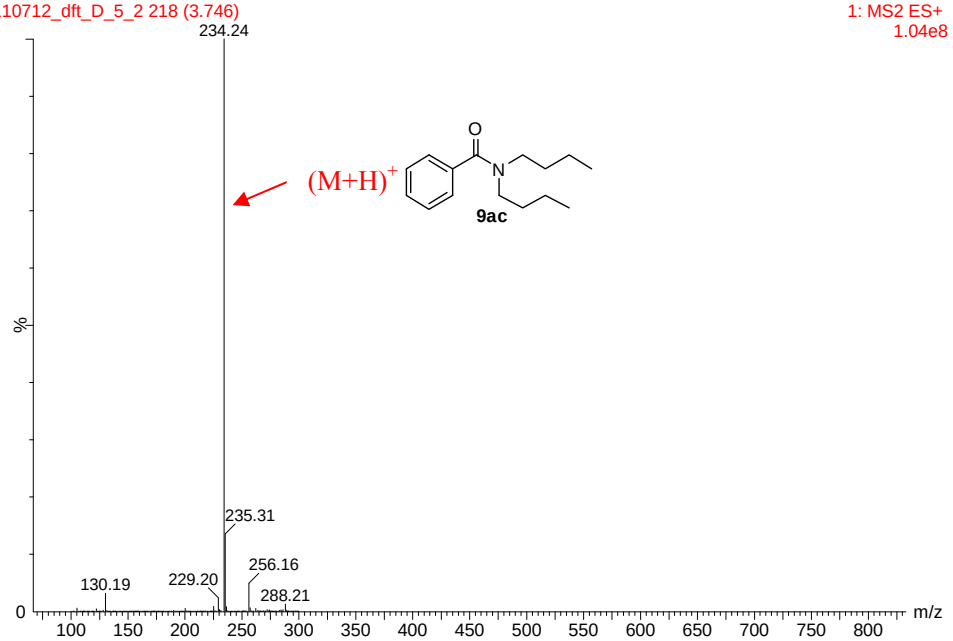

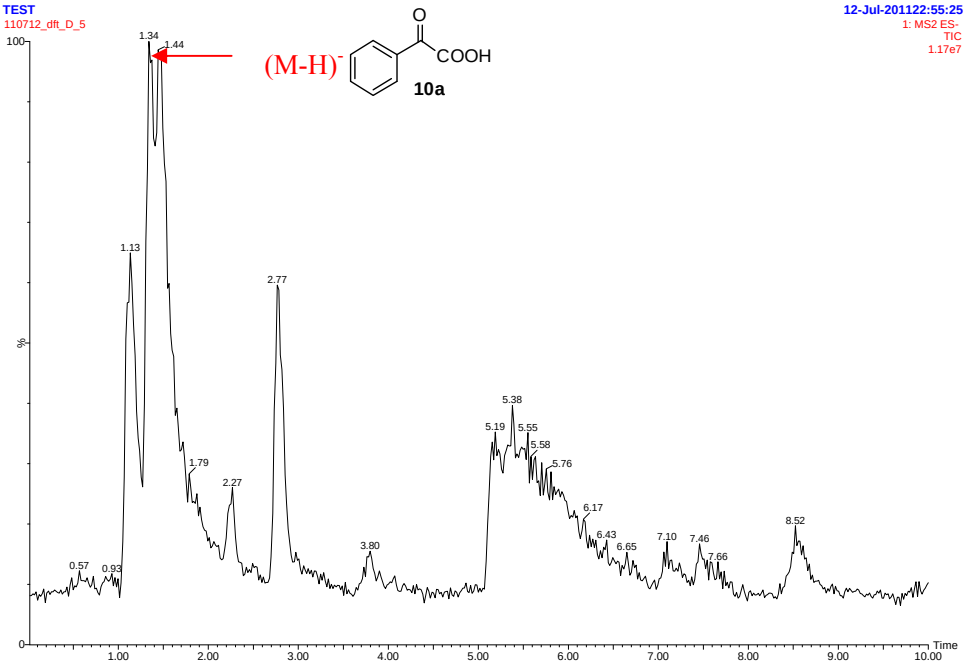

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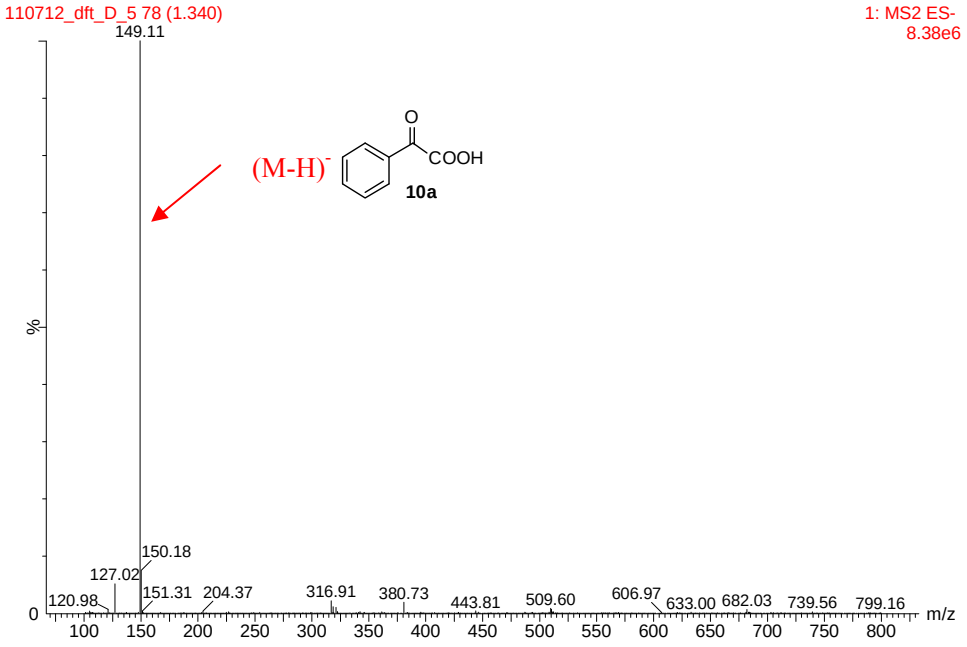

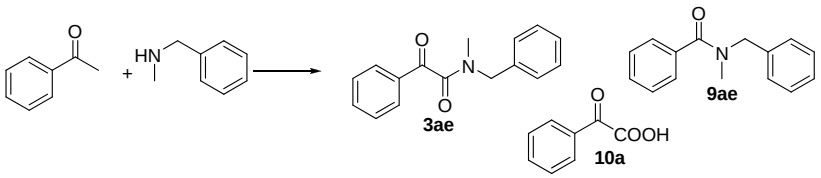

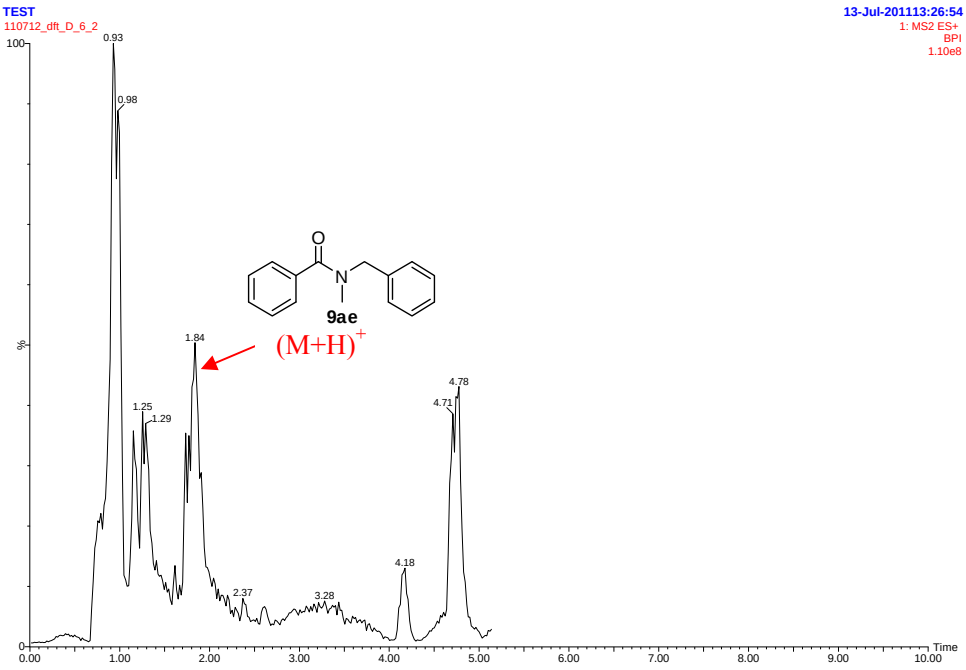

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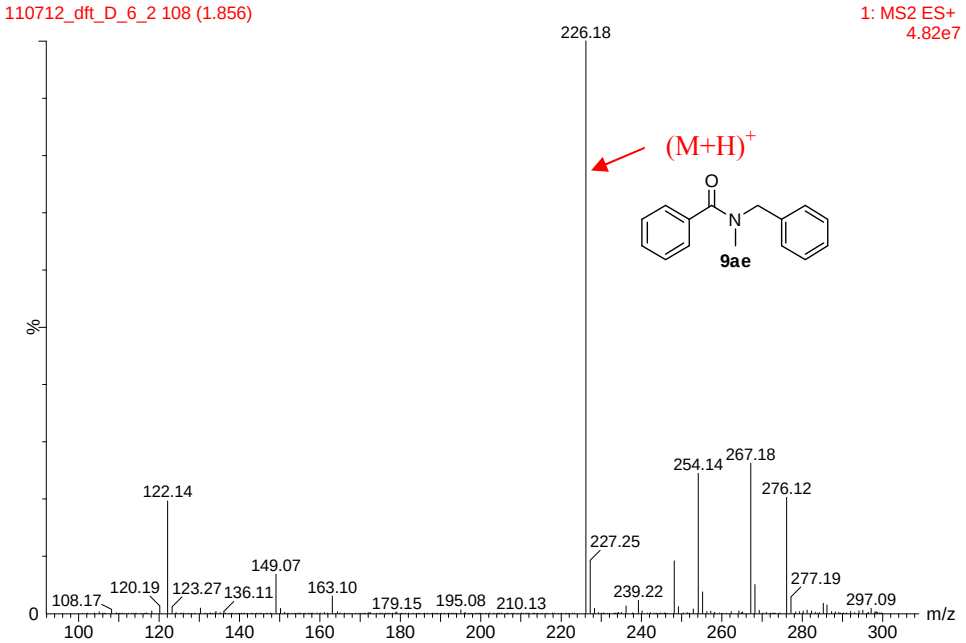

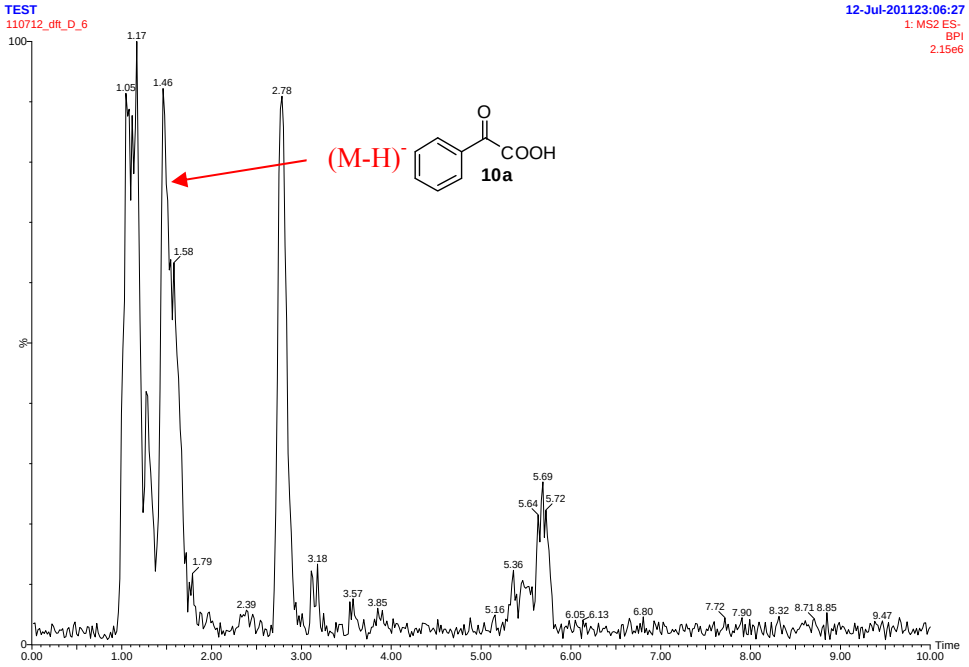
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3.57
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1.00
2.00
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8.00
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Time
(M-H)-
O
COOH
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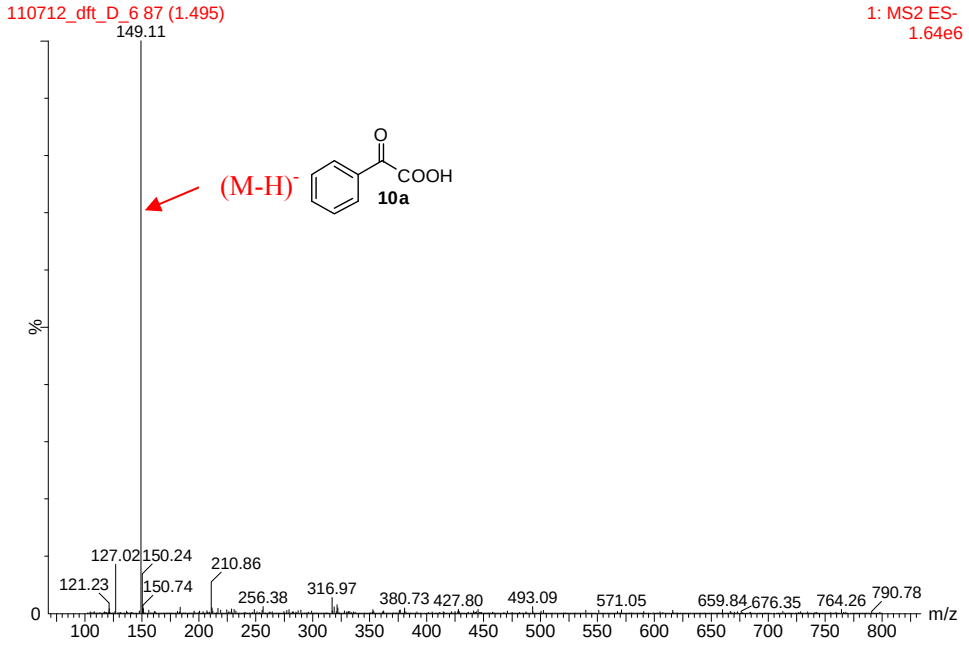
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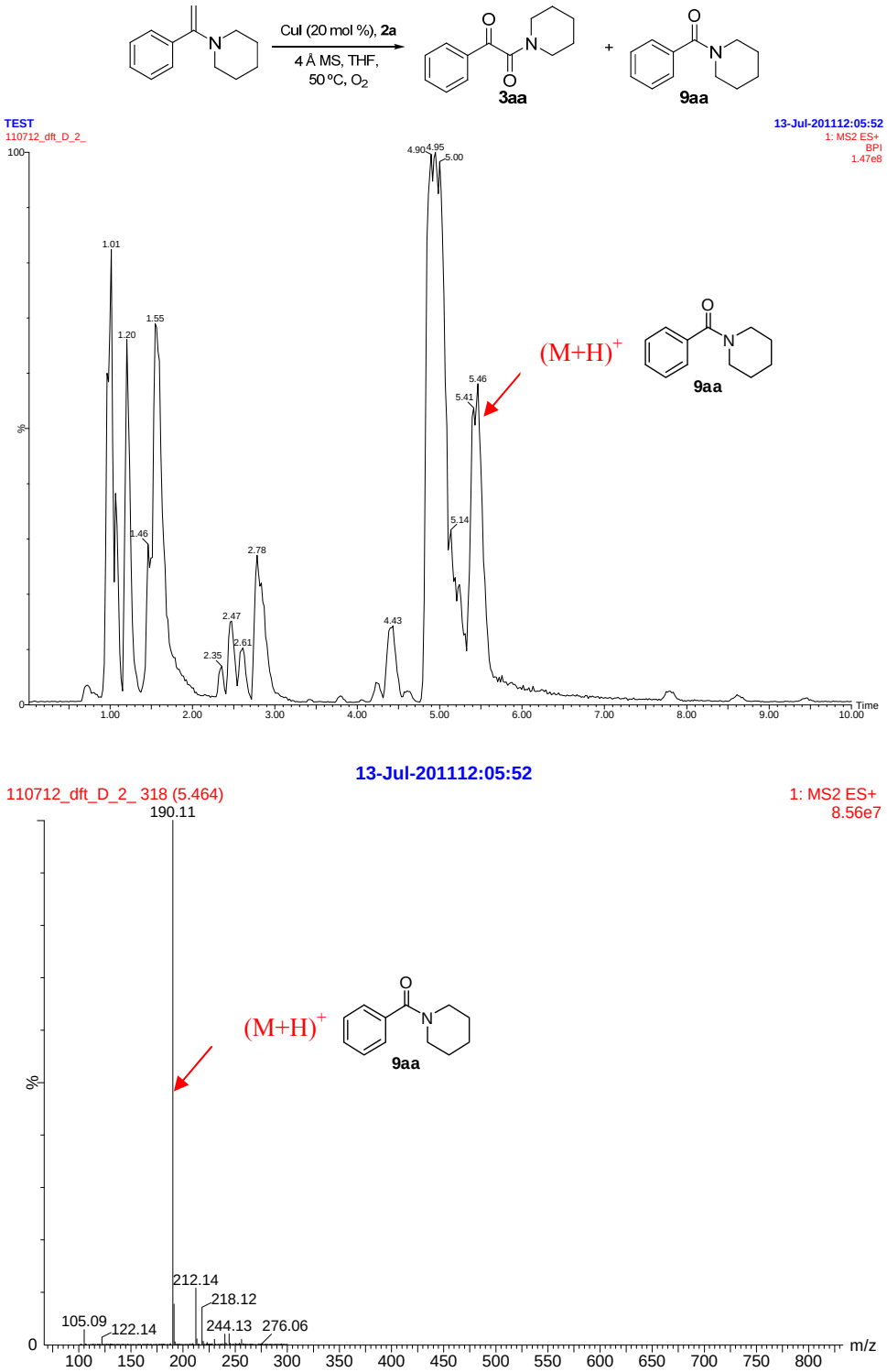
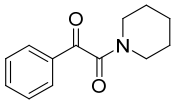


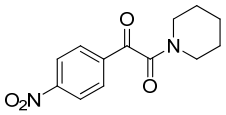
2.10 General procedure for the synthesis of α-ketoamides

Aryl methyl ketone (2 mmol) was added to a mixture of CuI (76 mg, 0.4 mmol) and amine (6 mmol) at room temperature under O_2 (balloon). The resulting mixture was stirred at 50 ºC for 5-48 h. Then the reaction mixture was cooled to room temperature, filtered through silica gel, and washed with CH_2Cl_2. The resulting solution was concentrated in vacuo and the residue was purified by flash column chromatography.

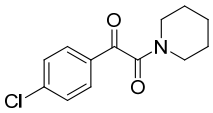
3. Characterization data of α-ketoamides



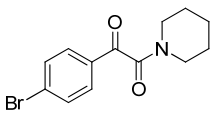
1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (3aa). According to the general procedure, afforded the desired product as a yellowish solid after 20 h (381 mg, 88%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.97-7.95 (d, *J* = 7.4 Hz, 2H), 7.67-7.63 (t, *J* = 7.4 Hz, 1H), 7.54-7.51 (t, *J* = 7.7 Hz, 2H), 3.72 (brs, 2H), 3.32-3.29 (t, *J* = 5.6 Hz, 2H), 1.72-1.70 (m, 4H), 1.56 (brs, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 191.9, 165.5, 134.6, 133.3, 129.6, 129.0, 47.0, 42.2, 26.2, 25.5, 24.4; HRMS calcd for $C_{13}H_{15}NNaO_2$ $(M + Na)^+$ 240.0995, found 240.1001.



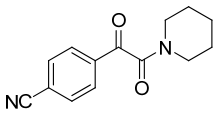
1-(4-nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3ba). The reacetion of 4-nitroacetophenone (1 mmol), piperidine (2 mmol) and CuI (5 mol %) in toluene (1 mL), afforded the product as a yellowish solid after 10 h (238 mg, 91%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 8.36-8.34 (d, *J* = 8.8 Hz, 2H), 8.15-8.13 (d, *J* = 8.8 Hz, 2H), 3.74-3.72 (brd, 2H), 3.33-3.30 (t, *J* = 5.5 Hz, 2H), 1.73 (brs, 4H), 1.59 (brs, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 189.5, 164.1, 151.1, 137.8, 130.6, 124.1, 47.1, 42.5, 26.3, 25.4, 24.3; HRMS calcd for $C_{13}H_{14}N_2NaO_4$ $(M + Na)^+$ 285.0846, found 285.0851.



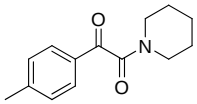
1-(4-chlorophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3ca). According to the general procedure, afforded the desired product as a yellow oil after 20 h (413 mg, 82%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.91-7.88 (d, *J* = 8.5 Hz, 2H), 7.50-7.47 (d, *J* = 8.5 Hz, 2H), 3.71-3.69 (t, *J* = 5.2 Hz, 2H), 3.30-3.27 (t, *J* = 5.6 Hz, 2H), 1.73-1.67 (m, 4H), 1.58-1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 190.5, 164.9, 141.2, 131.7, 130.9, 129.4, 47.1, 42.3, 26.3, 25.4, 24.4; HRMS calcd for $C_{13}H_{14}ClNNaO_2$ $(M + Na)^+$ 274.0605, found 274.0604.



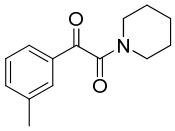
1-(4-bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3da). According to the general procedure, afforded the desired product as a yellow oil after 20 h (450 mg, 76%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.83-7.80 (d, *J* = 8.5 Hz, 2H), 7.67-7.64 (d, *J* = 8.7 Hz, 2H), 3.71-3.68 (t, *J* = 5.2 Hz, 2H), 3.29-3.27 (t, *J* = 5.6 Hz, 2H), 1.72-1.66 (m, 4H), 1.57-1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 190.7, 164.9, 132.4, 132.1, 130.9, 130.1, 47.0, 42.2, 26.2, 25.4, 24.3; HRMS calcd for $C_{13}H_{14}BrNNaO_2$ $(M+Na)^+$ 318.0100, found 318.0106.



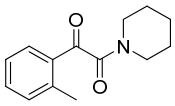
4-(2-oxo-2-(piperidin-1-yl)acetyl)benzonitrile (3ea). According to the general procedure, afforded the desired product as a yellowish solid after 7 h (360 mg, 74%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 8.07-8.05 (d, *J* = 8.6 Hz, 2H), 7.83-7.80 (d, *J* = 8.6 Hz, 2H), 3.73-3.70 (t, *J* = 5.2 Hz, 2H), 3.32-3.29 (t, *J* = 5.6 Hz, 2H), 1.75-1.68 (m, 4H), 1.60-1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 189.8, 164.2, 136.3, 132.7, 129.9, 117.6, 47.1, 42.4, 26.3, 25.4, 24.3; HRMS calcd for $C_{14}H_{14}N_2NaO_2$ $(M + Na)^+$ 265.0947, found 265.0942.



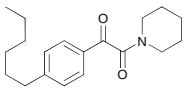
1-(piperidin-1-yl)-2-p-tolylethane-1,2-dione (3fa). According to the general procedure, afforded the desired product as a yellowish oil after 20 h (363 mg, 79%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.85-7.83 (d, *J* = 8.0 Hz, 2H), 7.32-7.29 (d, *J* = 8.0 Hz, 2H), 3.71-3.69 (brd, 2H), 3.29-3.26 (t, *J* = 5.5 Hz, 2H), 2.43 (s, 3H), 1.70-1.68 (m, 4H), 1.54 (brs, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 191.7, 165.7, 145.8, 130.9, 129.70, 129.67, 47.0, 42.1, 26.2, 25.5, 24.4, 21.9; HRMS calcd for $C_{14}H_{17}NNaO_2$ $(M + Na)^+$ 254.1151, found 254.1147.



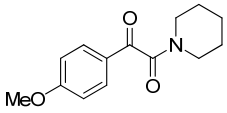
1-(piperidin-1-yl)-2-m-tolylethane-1,2-dione (3ga). According to the general procedure, afforded the desired product as a yellow oil after 20 h (346 mg, 75%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.76-7.73 (m, 2H), 7.46-7.43 (d, *J* = 7.6 Hz, 1H), 7.41-7.37 (t, *J* = 7.6 Hz, 1H), 3.72-3.70 (brd, 2H), 3.30-3.27 (t, *J* = 5.6 Hz, 2H), 2.42 (s, 3H), 1.72-1.67 (m, 4H), 1.56-1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 192.2, 165.6, 138.9, 135.5, 133.3, 129.8, 128.9, 126.9, 47.0, 42.1, 26.2, 25.5, 24.4, 21.2; HRMS calcd for $C_{14}H_{17}NNaO_2$ $(M + Na)^+$ 254.1151, found 254.1161.



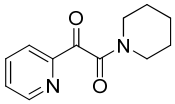
1-(piperidin-1-yl)-2-o-tolylethane-1,2-dione (3ha). According to the general procedure, afforded the desired product as a yellow solid after 20 h (345 mg, 75%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.73-7.71 (d, *J* = 7.6 Hz, 1H), 7.49-7.45 (t, *J* = 7.5 Hz, 1H), 7.33-7.29 (m, 2H), 3.70-3.68 (t, *J* = 4.9 Hz, 2H), 3.32-3.29 (t, *J* = 5.6 Hz, 2H), 2.67 (s, 3H), 1.70-1.67 (m, 4H), 1.57-1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 193.9, 166.1, 141.4, 133.6, 132.7, 132.6, 131.7, 126.1, 47.0, 42.1, 26.1, 25.4, 24.4, 21.8; HRMS calcd for $C_{14}H_{17}NNaO_2$ $(M + Na)^+$ 254.1151, found 254.1160.



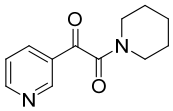
1-(4-hexylphenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3ia). According to the general procedure, afforded the desired product as a light yellow oil after 20 h (368 mg, 64%); eluent: hexanes/EtOAc = 7:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.85-7.84 (d, *J* = 8.1 Hz, 2H), 7.30-7.29 (d, *J* = 8.1 Hz, 2H), 3.70 (brs, 2H), 3.29-3.27 (t, *J* = 5.6 Hz, 2H), 2.68-2.65 (t, *J* = 7.7 Hz, 2H), 1.69-1.68 (m, 4H), 1.63-1.61 (m, 2H), 1.54 (brs, 2H), 1.32-1.29 (m, 6H), 0.88-0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 191.7, 165.7, 150.8, 131.1, 129.7, 129.1, 47.1, 42.1, 36.2, 31.6, 31.0, 28.9, 26.2, 25.5, 24.4, 22.5, 14.0; HRMS calcd for $C_{19}H_{27}NNaO_2$ $(M + Na)^+$ 324.1939, found 324.1936.



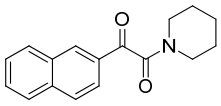
1-(4-methoxyphenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3ja). According to the general procedure, afforded the desired product as a yellow oil after 48 h (302 mg, 61%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.93-7.91 (d, *J* = 8.8 Hz, 2H), 6.99-6.96 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.71-3.69 (brd, 2H), 3.30-3.27 (t, *J* = 5.6 Hz, 2H), 1.70-1.68 (m, 4H), 1.54 (brs, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 190.7, 165.8, 164.8, 131.9, 126.4, 114.3, 55.6, 47.0, 42.0, 26.2, 25.4, 24.4; HRMS calcd for $C_{14}H_{17}NNaO_3$ $(M + Na)^+$ 270.1101, found 270.1098.



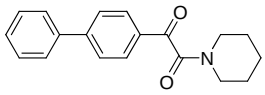
1-(piperidin-1-yl)-2-(pyridin-2-yl)ethane-1,2-dione (3ka). According to the general procedure, afforded the desired product as a yellow oil after 7 h (262 mg, 60%); eluent: hexanes/EtOAc = 2:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 8.76-8.74 (d, *J* = 4.6 Hz, 1H), 8.12-8.10 (d, *J* = 7.7 Hz, 1H), 7.91-7.88 (t, *J* = 7.6 Hz, 1H), 7.53-7.50 (m, 1H), 3.72 (brs, 2H), 3.29-3.26 (t, *J* = 5.5 Hz, 2H), 1.72-1.70 (m, 4H), 1.59 (brs, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 192.1, 166.2, 151.5, 149.9, 137.1, 127.9, 123.1, 47.0, 42.1, 25.9, 25.2, 24.5; HRMS calcd for $C_{12}H_{14}N_2NaO_2$ $(M + Na)^+$ 241.0947, found 241.0962.



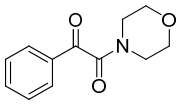
1-(piperidin-1-yl)-2-(pyridin-3-yl)ethane-1,2-dione (3la). According to the general procedure, afforded the desired product as a light yellow oil after 5 h (306 mg, 70%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.11-9.10 (d, *J* = 1.4 Hz, 1H), 8.82-8.81 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.23-8.22 (d, *J* = 7.9 Hz, 1H), 7.45-7.43 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.70-3.68 (t, *J* = 5.0 Hz, 2H), 3.31-3.29 (t, *J* = 5.6 Hz, 2H), 1.69 (m, 4H), 1.56 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 190.3, 164.3, 154.7, 151.2, 136.6, 129.0, 123.9, 47.1, 42.4, 26.3, 25.4, 24.3. HRMS calcd for $C_{12}H_{14}N_2NaO_2$ $(M + Na)^+$ 241.0953, found 241.0956.



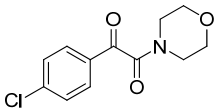
1-(naphthalen-2-yl)-2-(piperidin-1-yl)ethane-1,2-dione (3ma). According to the general procedure, afforded the desired product as a yellow oil after 30 h (428 mg, 80%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 8.45 (s, 1H), 8.04-8.01 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.99-7.96 (d, *J* = 8.3 Hz, 1H), 7.95-7.93 (d, *J* = 8.5 Hz, 1H), 7.91-7.88 (d, *J* = 8.0 Hz, 1H), 7.66-7.62 (t, *J* = 7.6 Hz, 1H), 7.59-7.56 (t, *J* = 7.5 Hz, 1H), 3.78-3.75 (t, *J* = 5.1 Hz, 2H), 3.34-3.32 (t, *J* = 5.5 Hz, 2H), 1.73 (brs, 4H), 1.58-1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 192.1, 165.6, 136.3, 132.8, 132.5, 130.7, 129.9, 129.3, 129.1, 127.9, 127.1, 123.7, 47.1, 42.3, 26.2, 25.5, 24.4; HRMS calcd for $C_{17}H_{17}NNaO_2$ $(M + Na)^+$ 290.1151, found 290.1138.



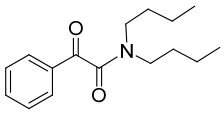
1-(biphenyl-4-yl)-2-(piperidin-1-yl)ethane-1,2-dione (3na). According to the general procedure, afforded the desired product as a yellow oil after 20 h (276 mg, 47%); eluent: hexanes/EtOAc = 7:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.99-7.98 (d, *J* = 8.3 Hz, 2H), 7.69-7.68 (d, *J* = 8.3 Hz, 2H), 7.58-7.57 (d, *J* = 7.4 Hz, 2H), 7.43-7.41 (t, *J* = 7.6 Hz, 2H), 7.37-7.34 (t, *J* = 7.2 Hz, 1H), 3.68 (brs, 2H), 3.28-3.26 (t, *J* = 5.5 Hz, 2H), 1.66 (brs, 4H), 1.52 (brs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 191.6, 165.5, 147.3, 139.5, 132.0, 130.1, 129.0, 128.6, 127.6, 127.3, 47.0, 42.1, 26.2, 25.5, 24.4. HRMS calcd for $C_{19}H_{19}NNaO_2$ $(M + Na)^+$ 316. 1313, found 316.1313.



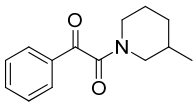
1-morpholino-2-phenylethane-1,2-dione (3ab). According to the general procedure, afforded the desired product as a yellow oil after 20 h (305 mg, 70%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.98-7.95 (d, *J* = 7.8 Hz, 2H), 7.68-7.64 (t, *J* = 7.5 Hz, 1H), 7.54-7.51 (t, *J* = 7.8 Hz, 2H), 3.82-3.78 (m, 4H), 3.67-3.65 (t, *J* = 4.8 Hz, 2H), 3.40-3.37 (t, *J* = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 191.1, 165.5, 134.9, 133.1, 129.7, 129.1, 66.8, 66.7, 46.3, 41.6; HRMS calcd for $C_{12}H_{13}NNaO_3$ $(M + Na)^+$ 242.0788, found 242.0785.



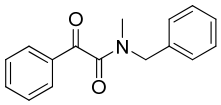
1-(4-chlorophenyl)-2-morpholinoethane-1,2-dione (3cb). According to the general procedure, afforded the desired product as a yellow solid after 20 h (314 mg, 62%); eluent: hexanes/EtOAc = 5:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.89-7.87 (d, *J* = 8.5 Hz, 2H), 7.48-7.46 (d, *J* = 8.5 Hz, 2H), 3.78-3.74 (m, 4H), 3.64-3.62 (t, *J* = 4.8 Hz, 2H), 3.37-3.34 (t, *J* = 4.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 189.7, 164.9, 141.6, 131.5, 131.0, 129.5, 66.7, 66.6, 46.3, 41.7; HRMS calcd for $C_{12}H_{12}ClNNaO_3$ $(M + Na)^+$ 276.0403, found 276.0397.



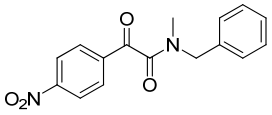
***N*,*N*-dibutyl-2-oxo-2-phenylacetamide (3ac).** According to the general procedure, afforded the desired product as a yellow oil after 20 h (279 mg, 53%); eluent: hexanes/EtOAc = 15:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.95-7.92 (d, *J* = 7.3 Hz, 2H), 7.64-7.61 (t, *J* = 7.5 Hz, 1H), 7.52-7.48 (t, *J* = 7.7 Hz, 2H), 3.52-3.48 (t, *J* = 7.7 Hz, 2H), 3.17-3.13 (t, *J* = 7.7 Hz, 2H), 1.70-1.64 (m, 2H), 1.57-1.51 (m, 2H), 1.46-1.38 (m, 2H), 1.22-1.15 (m, 2H), 1.01-0.98 (t, *J* = 7.4 Hz, 3H), 0.83-0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 191.6, 167.1, 134.4, 133.4, 129.6, 128.9, 47.4, 44.0, 30.6, 29.5, 20.2, 19.8, 13.8, 13.5; HRMS calcd for $C_{16}H_{23}NNaO_2$ $(M + Na)^+$ 284.1621, found 284.1618.



1-(3-methylpiperidin-1-yl)-2-phenylethane-1,2-dione (3ad). According to the general procedure, afforded the desired product (a mixture of s-cis and s-trans isomers) as a yellow oil after 20 h (400 mg, 87%); eluent: hexanes/EtOAc = 15:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.96-7.94 (d, *J* = 8.3 Hz, 4H), 7.65-7.62 (td, *J* = 7.4, 1.2 Hz, 2H), 7.52-7.49 (t, *J* = 7.5 Hz, 4H), 4.53-4.46 (m, 2H), 3.49-3.40 (m, 2H), 3.04-2.99 (m, 1H), 2.85-2.79 (td, *J* = 12.5, 3.1 Hz, 1H), 2.72-2.67 (m, 1H), 2.53-2.48 (m, 1H), 1.89-1.47 (m, 8H), 1.24-1.18 (m, 2H), 1.00-0.98 (d, *J* = 6.6 Hz, 3H), 0.82-0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 191.9, 191.8, 165.4, 134.6, 133.34, 133.31, 129.57, 129.55, 129.0, 53.3, 48.4, 46.5, 41.6, 32.91, 32.85, 31.6, 31.1, 25.6, 24.7, 18.9, 18.7; HRMS calcd. for $C_{14}H_{17}NNaO_2$ $(M+Na)^+$, 254.1151; found, 254.1161.

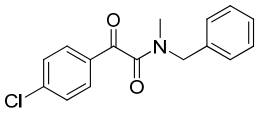


***N*-benzyl-*N*-methyl-2-oxo-2-phenylacetamide (3ae).** According to the general procedure, afforded the desired product (a mixture of s-cis and s-trans isomers) as a yellow oil after 30 h (373 mg, 74%); eluent: hexanes/EtOAc = 8:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 8.01-7.96 (m, 4H), 7.66-7.63 (t, *J* = 7.5 Hz, 2H), 7.53-7.50 (t, *J* = 7.8 Hz, 4H), 7.41-7.24 (m, 10H), 4.74 (s, 2H), 4.40 (s, 2H), 3.00 (s, 3H), 2.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 191.5, 167.3, 167.2, 135.8, 135.0, 134.7, 133.3, 133.1, 129.8, 129.7, 129.1, 129.0, 128.9, 128.8, 128.3, 128.2, 127.9, 127.8, 53.6, 49.9, 34.5, 31.4; HRMS calcd for $C_{16}H_{15}NNaO_2$ $(M + Na)^+$ 276.0995, found 276.0999.



***N*-benzyl-*N*-methyl-2-(4-nitrophenyl)-2-oxoacetamide (3be).** The reacetion of 4-nitroacetophenone (1 mmol), *N*-benzylmethylamine (2 mmol) and CuI (5 mol %) in toluene (1 mL), afforded the product as a yellowish oil after 20 h (245 mg, 82%); eluent: hexanes/EtOAc = 10:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 8.36-8.31 (m, 4H), 8.17-8.13 (m, 4H), 7.42-7.22 (m, 10H), 4.75 (s, 2H), 4.45 (s, 2H), 3.06 (s, 3H), 2.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 189.1, 166.1, 165.8, 151.13, 151.05, 137.7, 137.6, 135.4, 134.7, 130.9, 130.8, 129.01, 128.96,

128.4, 128.3, 128.2, 127.7, 124.2, 124.0, 53.6, 50.2, 34.5, 32.1; HRMS calcd for $C_{16}H_{14}N_2NaO_4$ $(M + Na)^+$ 321.0851, found 321.0843.



***N*-benzyl-2-(4-chlorophenyl)-*N*-methyl-2-oxoacetamide (3ce).** According to the general procedure, afforded the desired product (a mixture of s-cis and s-trans isomers) as a yellowish oil after 20 h (436 mg, 76%); eluent: hexanes/EtOAc = 10:1. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ = 7.94-7.89 (m, 4H), 7.49-7.46 (m, 4H), 7.40-7.18 (m, 10H), 4.72 (s, 2H), 4.39 (s, 2H), 2.99 (s, 3H), 2.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ = 190.1, 166.8, 166.6, 141.4, 135.7, 134.9, 131.7, 131.6, 131.1, 131.0, 129.5, 129.4, 128.93, 128.89, 128.3, 128.2, 128.0, 127.8, 127.0, 53.5, 50.0, 34.5, 31.6; HRMS calcd for $C_{16}H_{14}ClNNaO_2$ $(M + Na)^+$ 310.0611, found 310.0599.

4. References

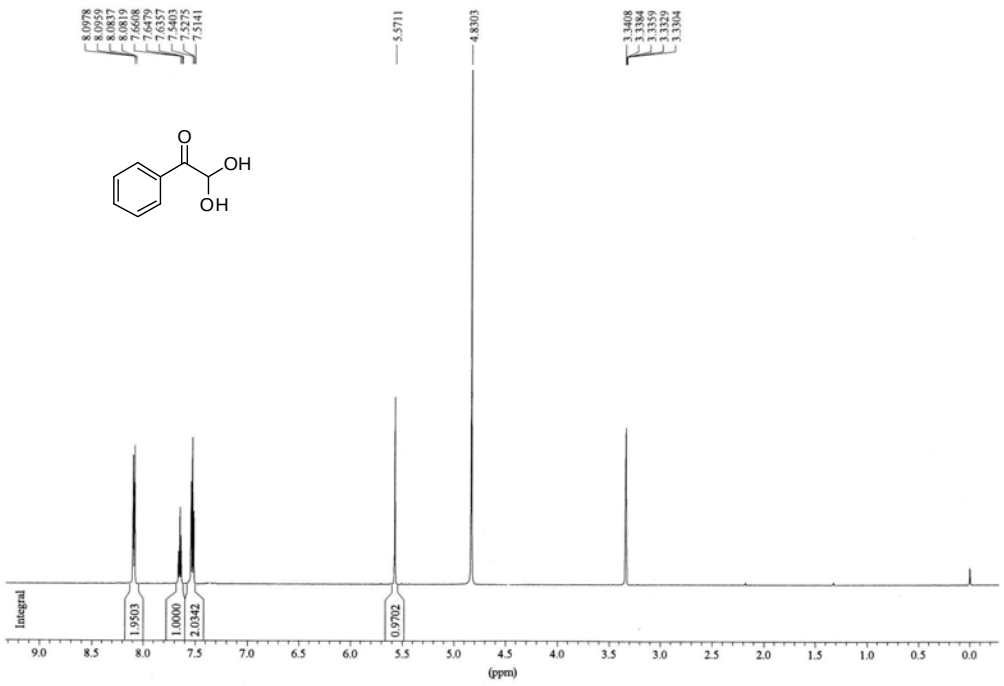
1. W. Caseri, T. Sauer and G. Wegner, *Makromol. Chem., Rapid Commun.*, 1988, **9**, 651-657.

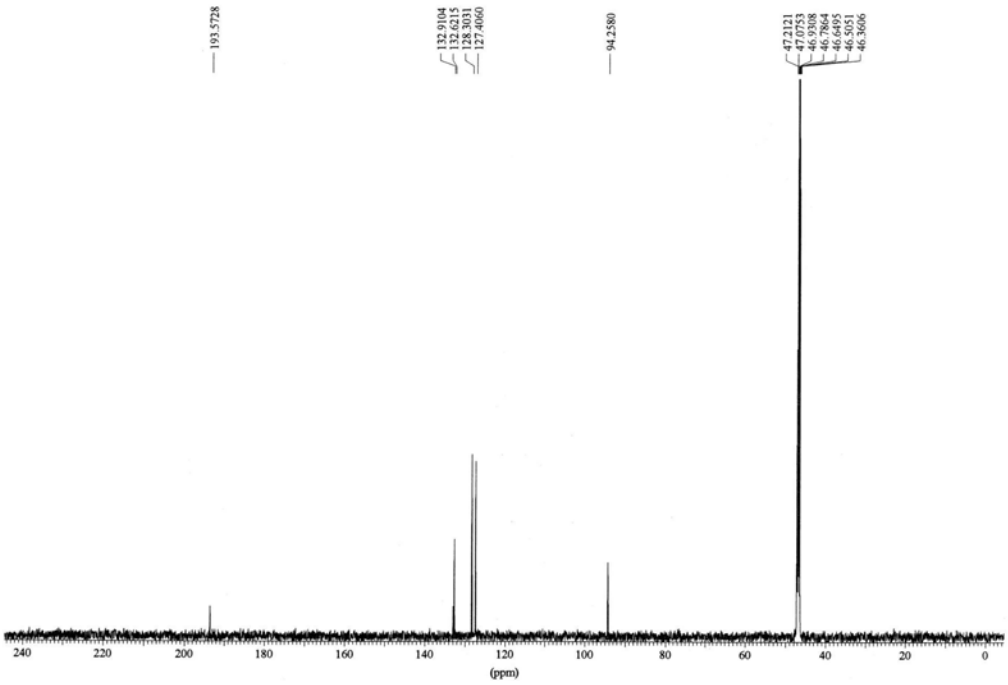
2. J. Paleček and O. Paleta, *Synthesis*, 2004, 521-524.

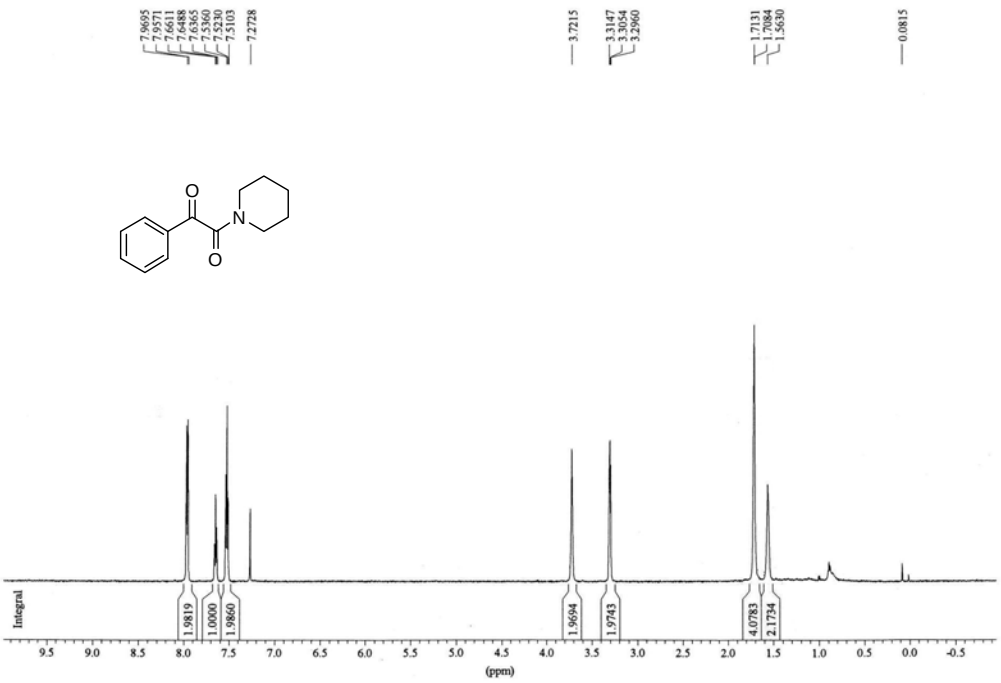
3. W. L. Mo, H. Xiong, J. L. Hua, Y. M. Ni and G. X. Li, *Appl. Organometal. Chem.* 2010, **24**, 576-580.

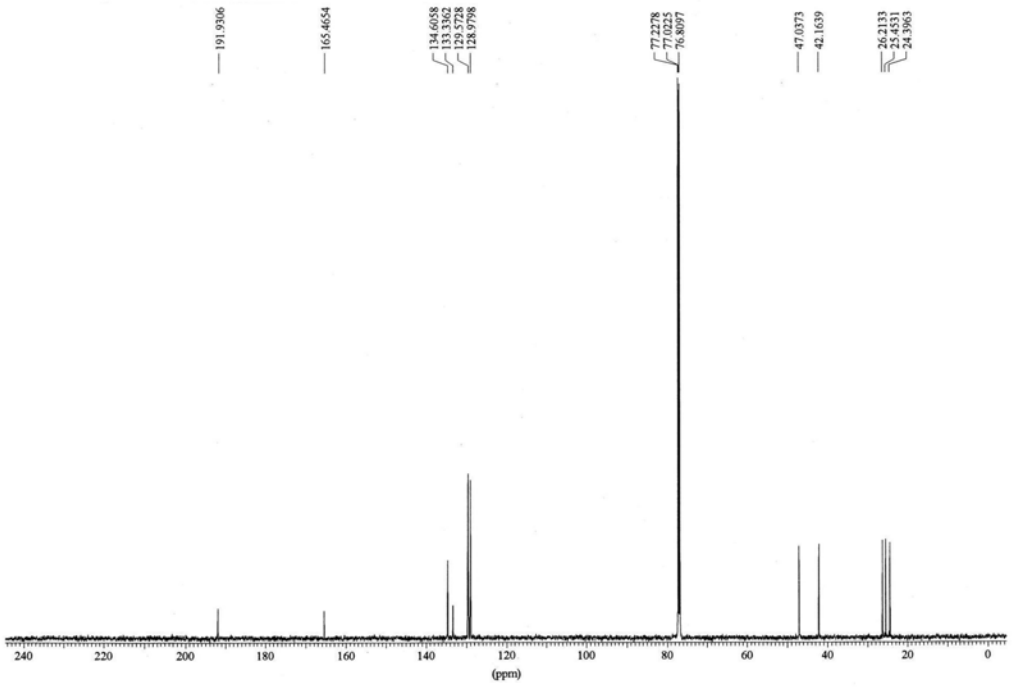
4. (*a*) K. Kaneda, T. Itoh, N. Kii, K. Jitsukawa and S. Teranishi, *J. Mol. Catal.*, 1982, **15**, 349-365; (*b*) M. Tokunaga, Y. Shirogane, H. Aoyama, Y. Obora and Y. Tsuji, *J. Organomet. Chem.*, 2005, **690**, 5378-5382.

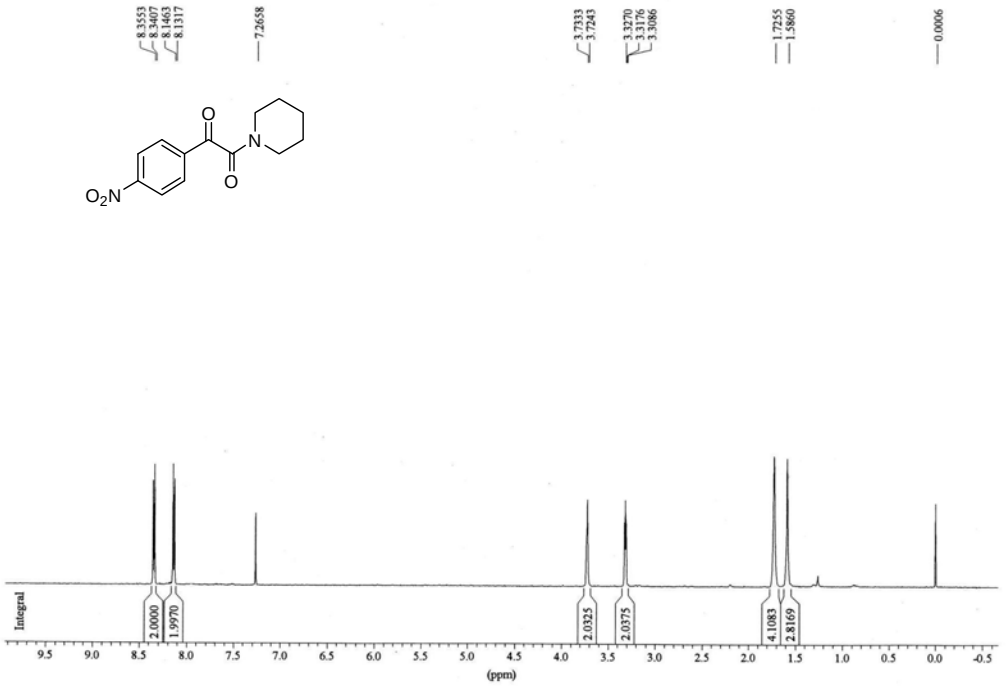
5. Copies of ^{1}H NMR and ^{13}C NMR spectra for all compounds

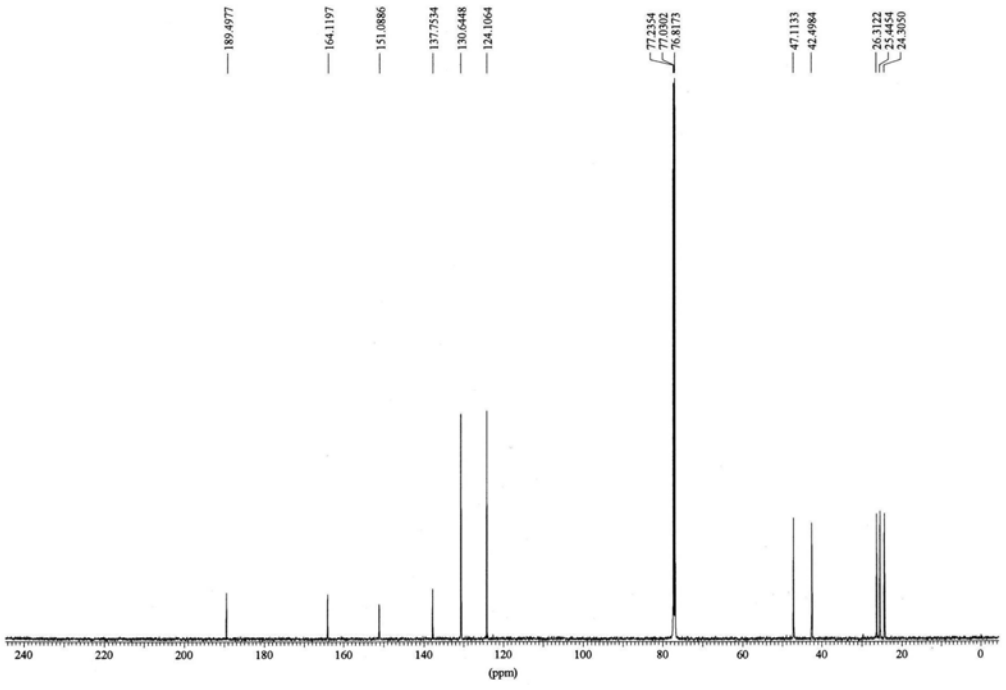


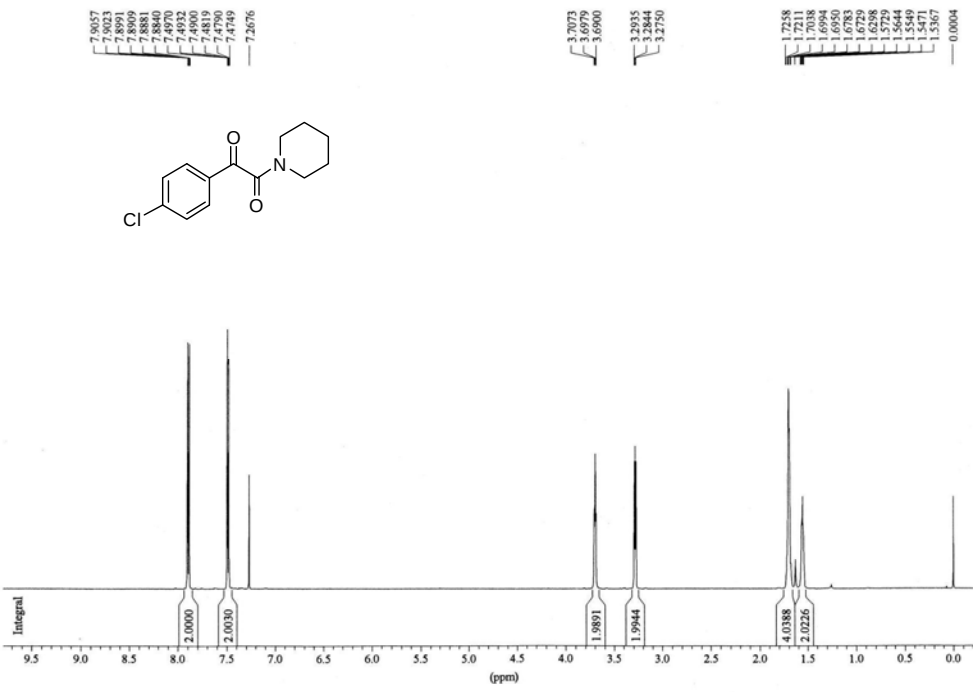


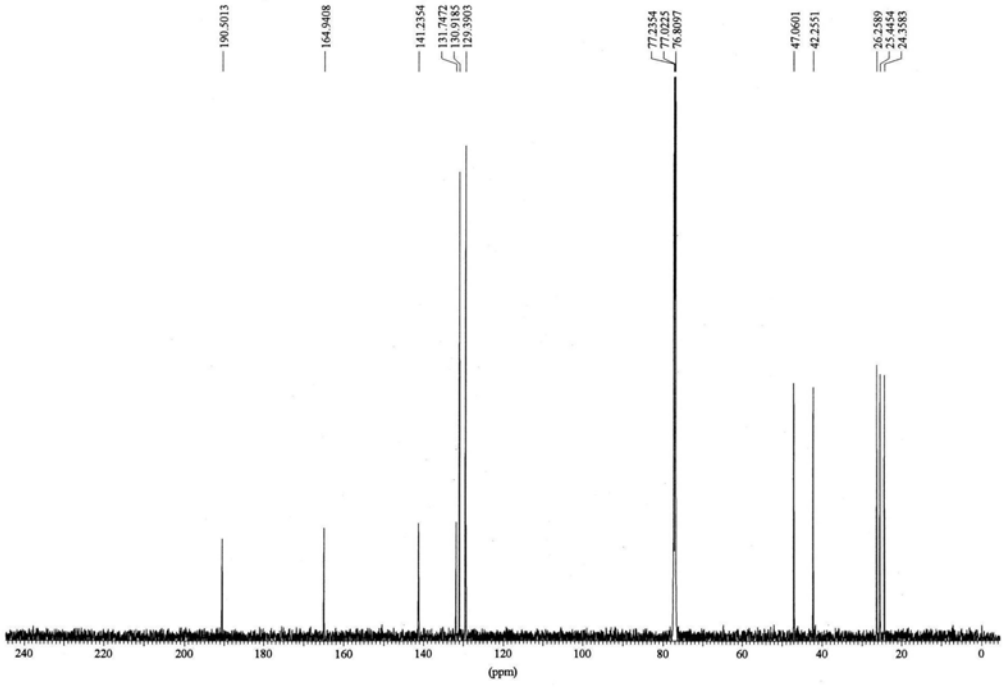


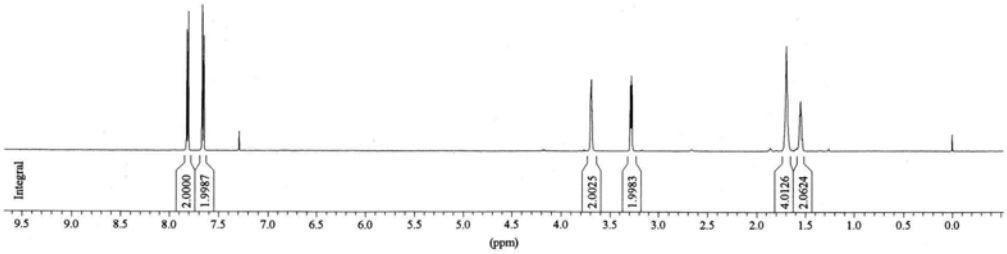


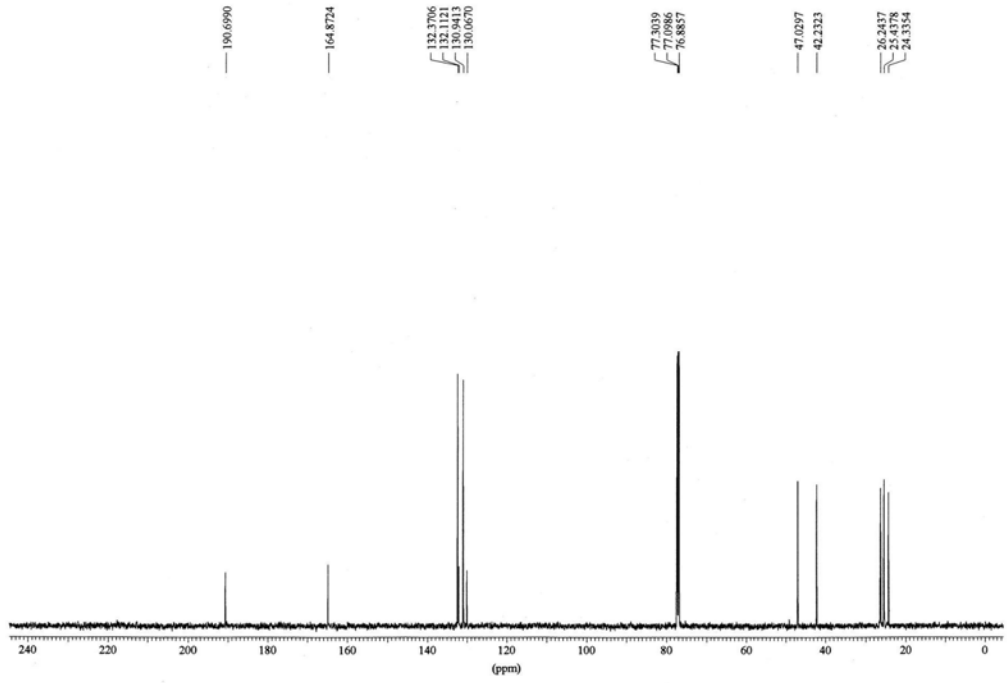


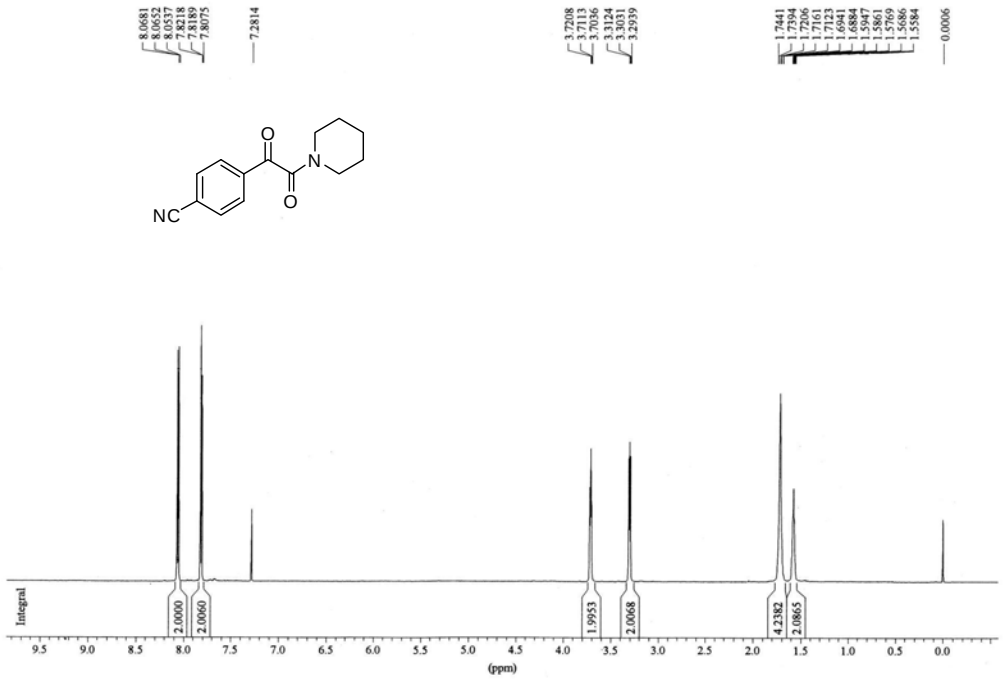








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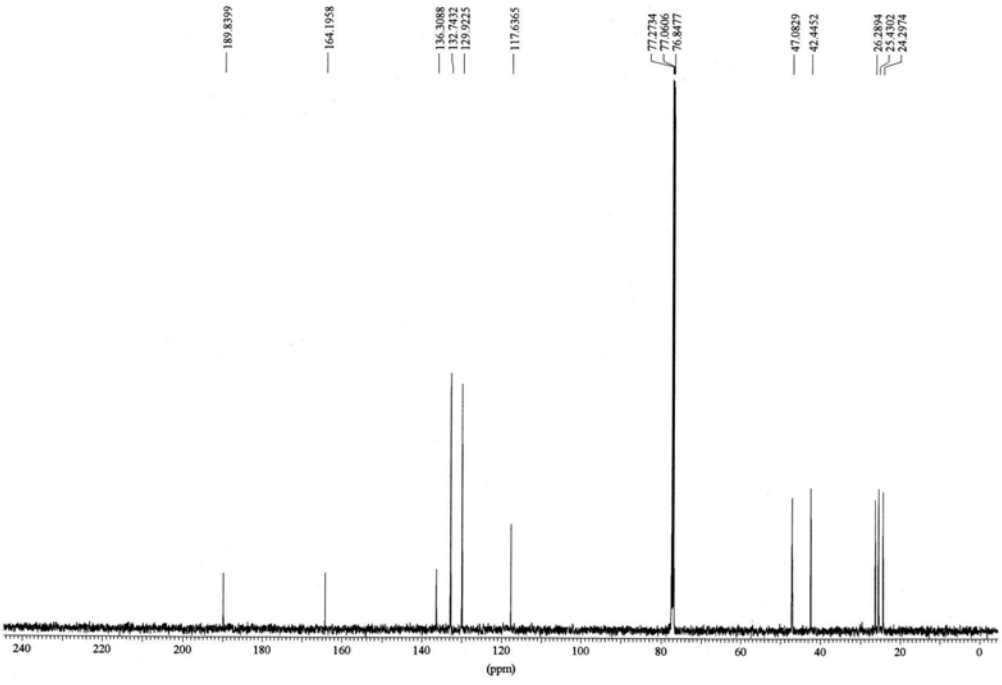
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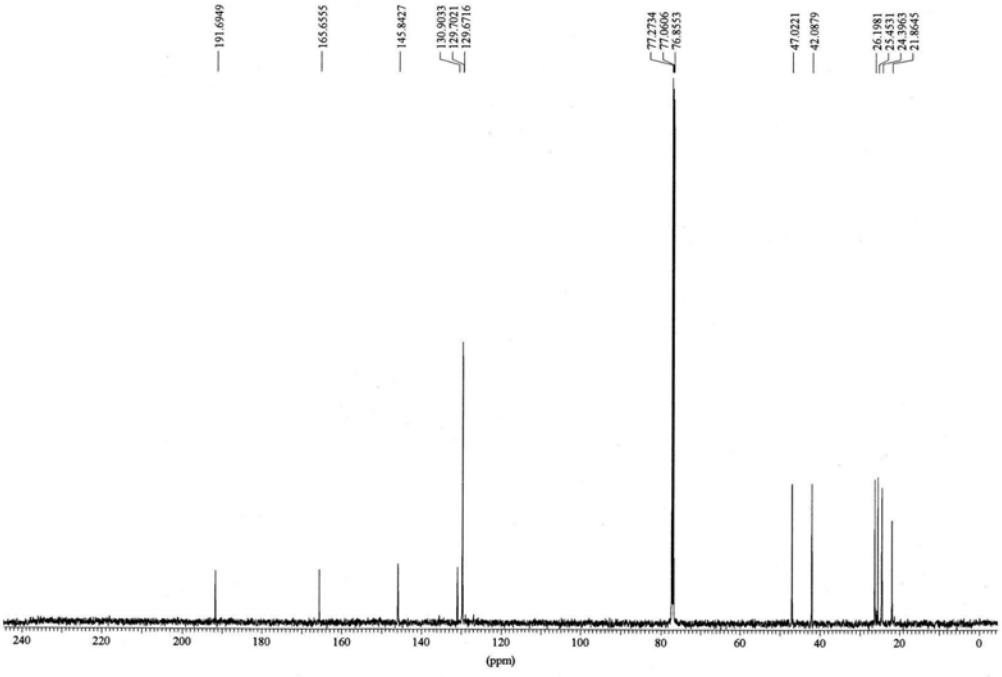
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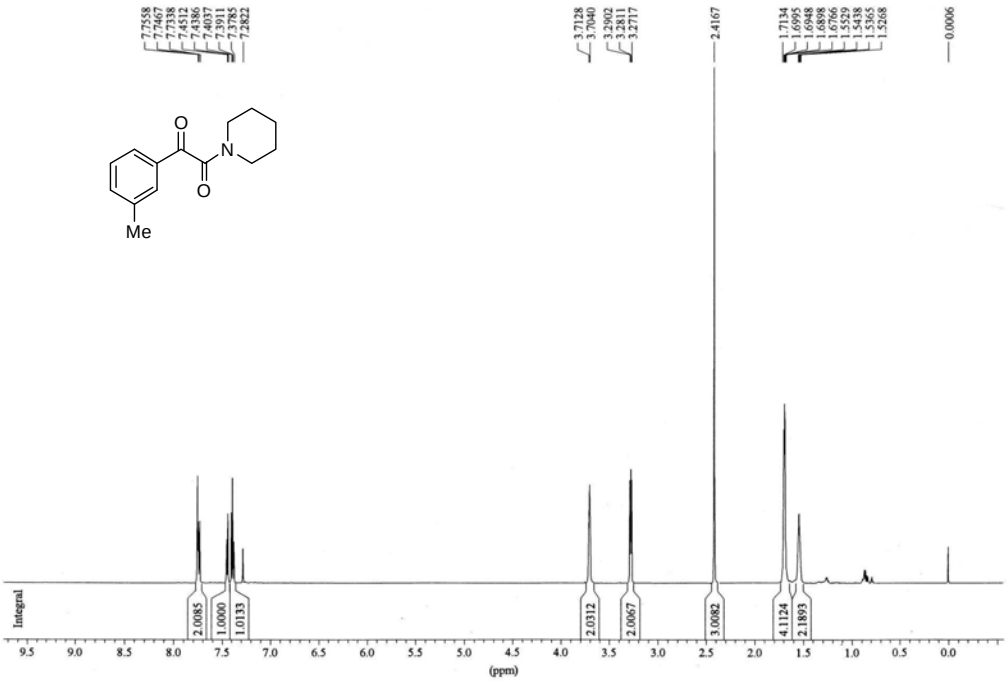

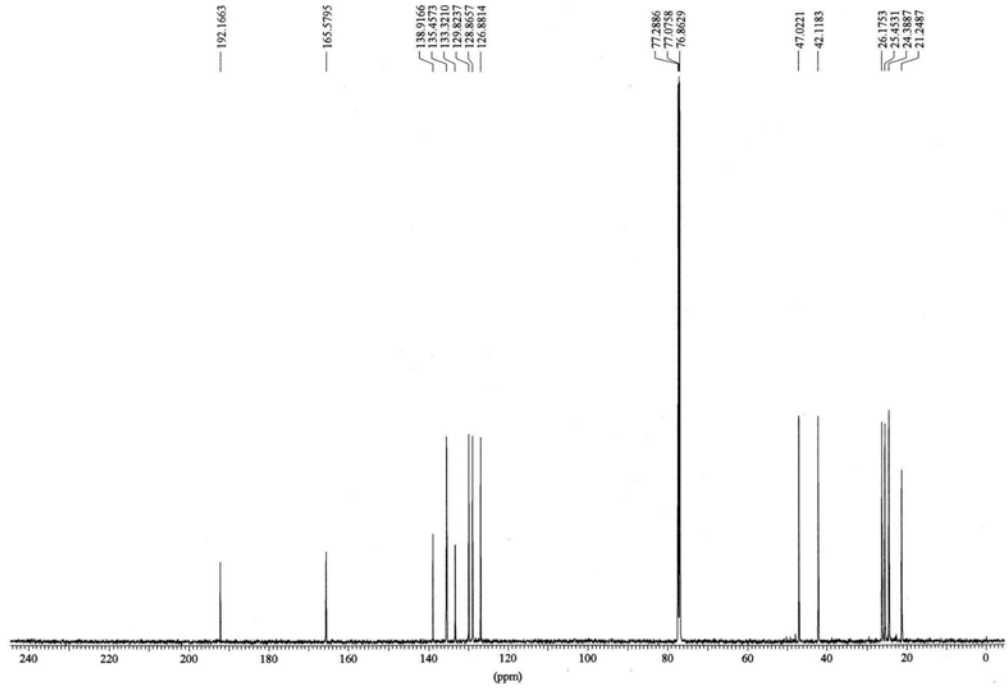

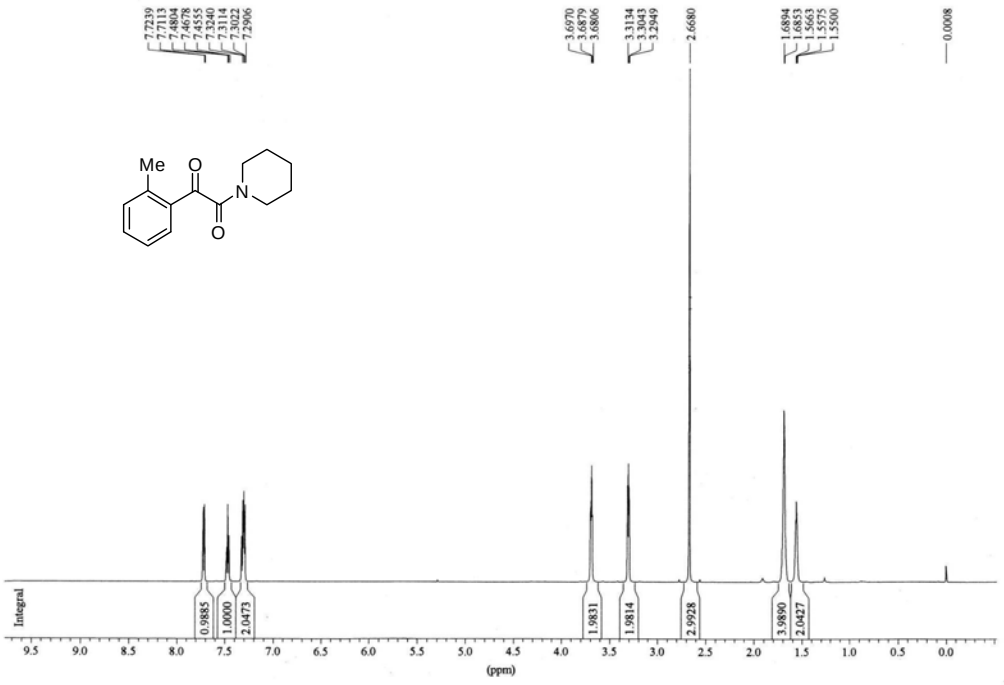
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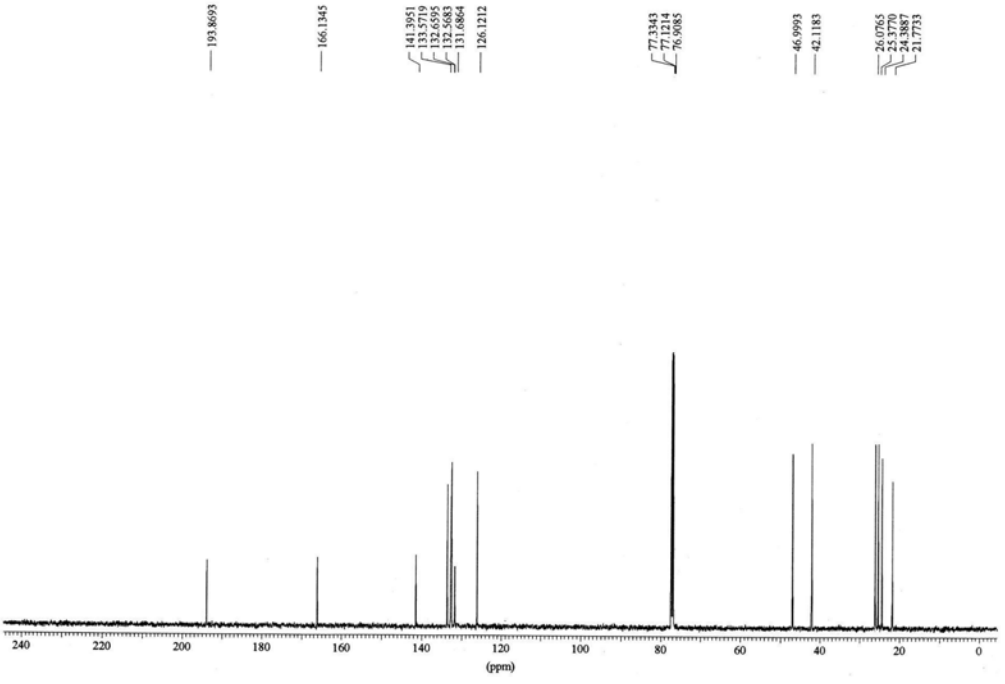
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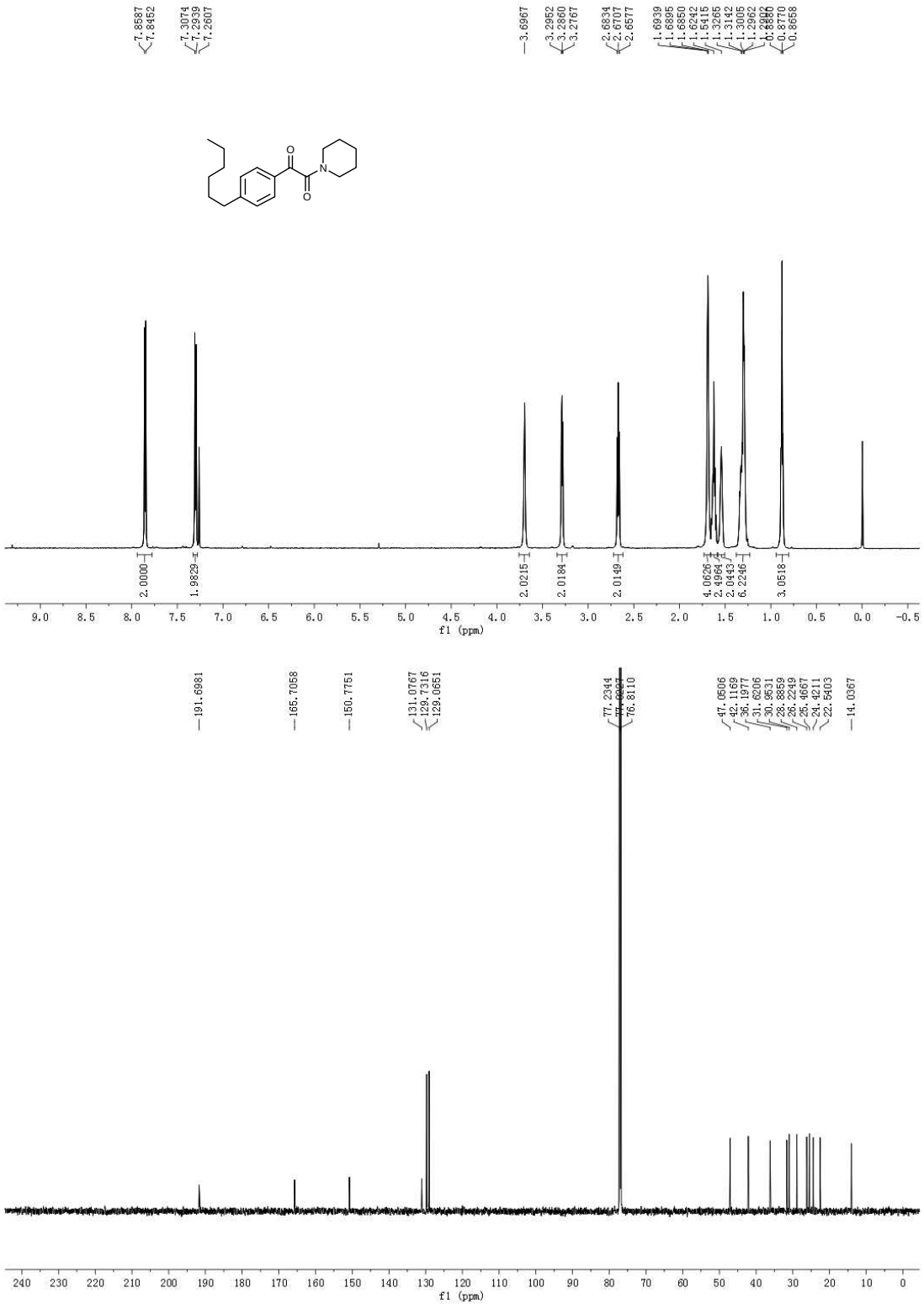
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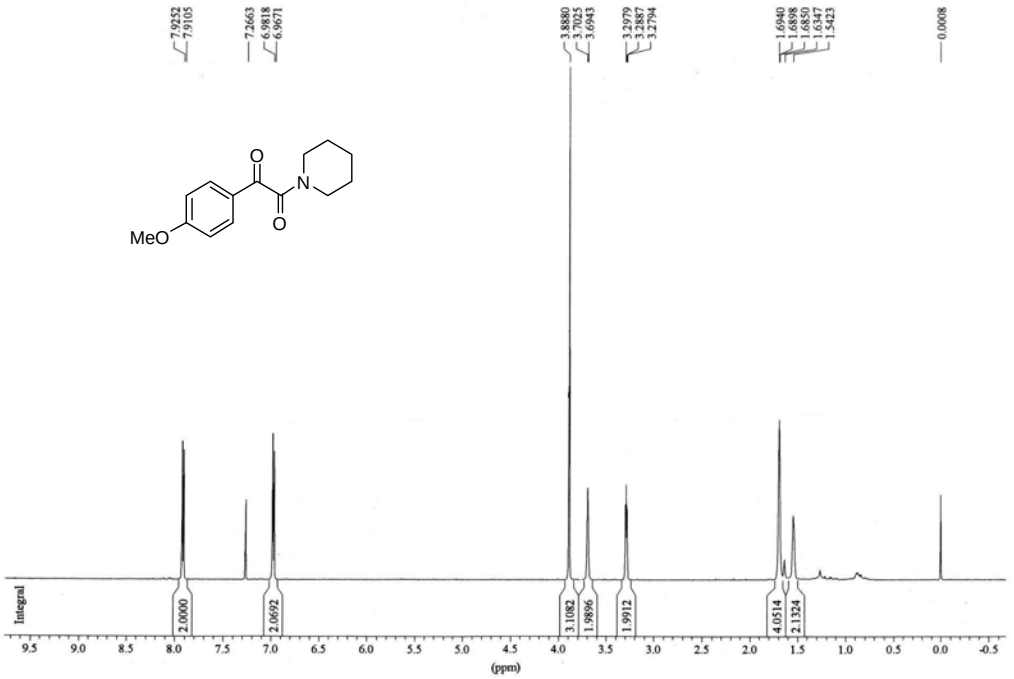
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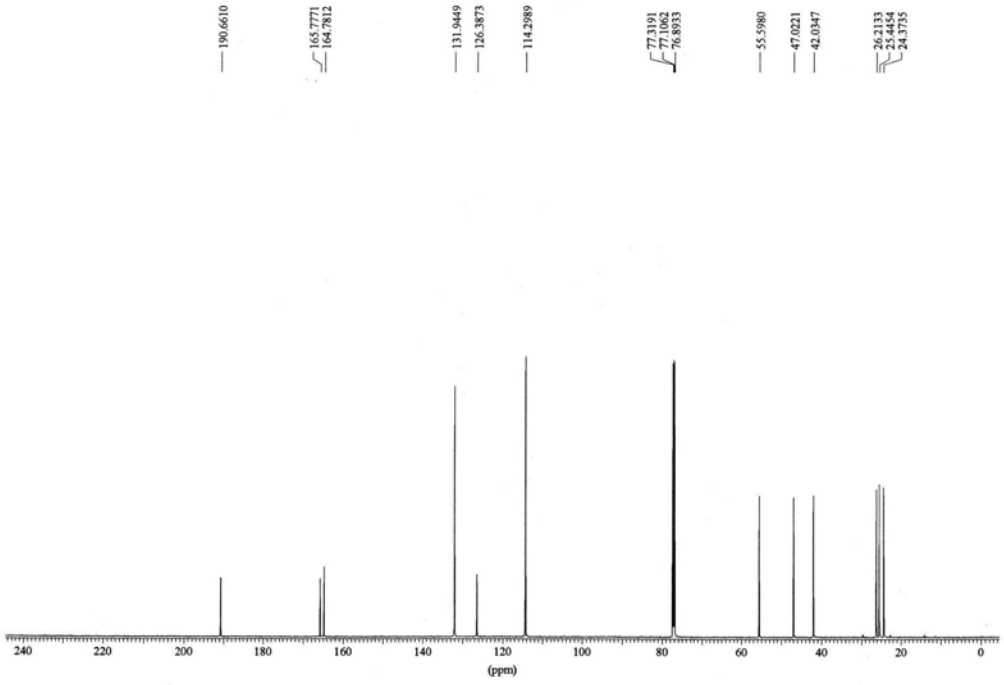
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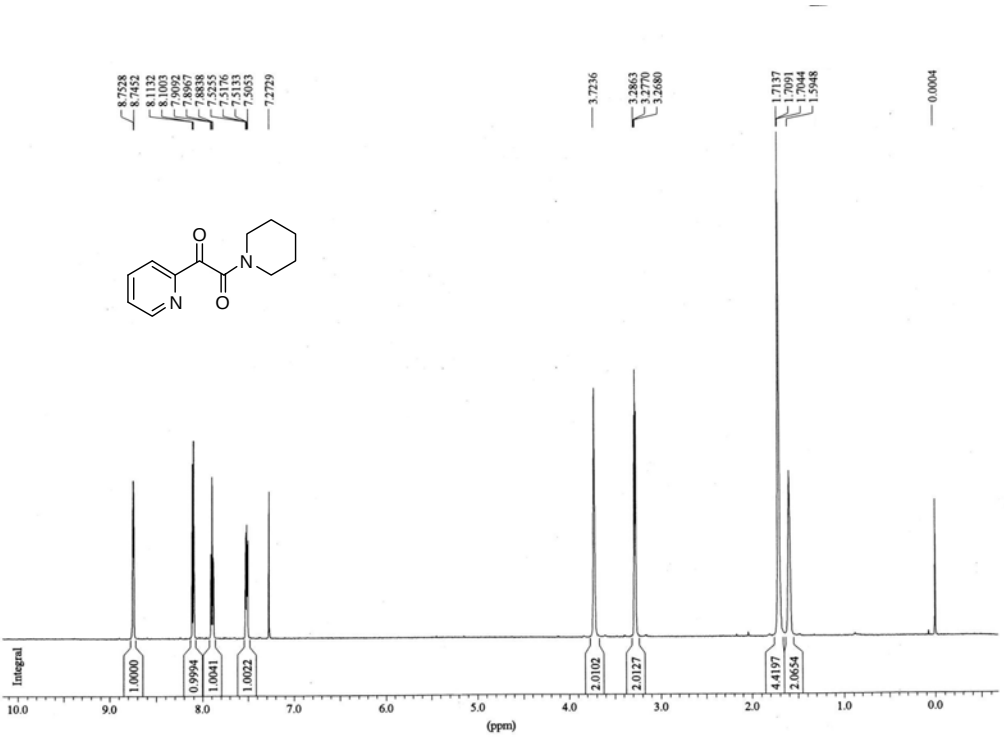

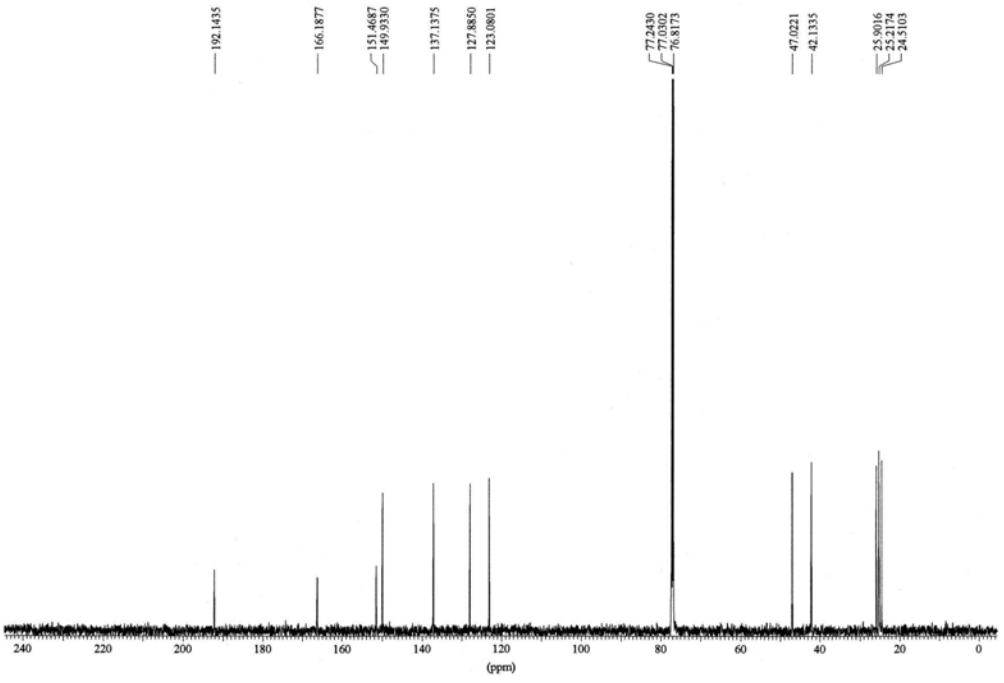

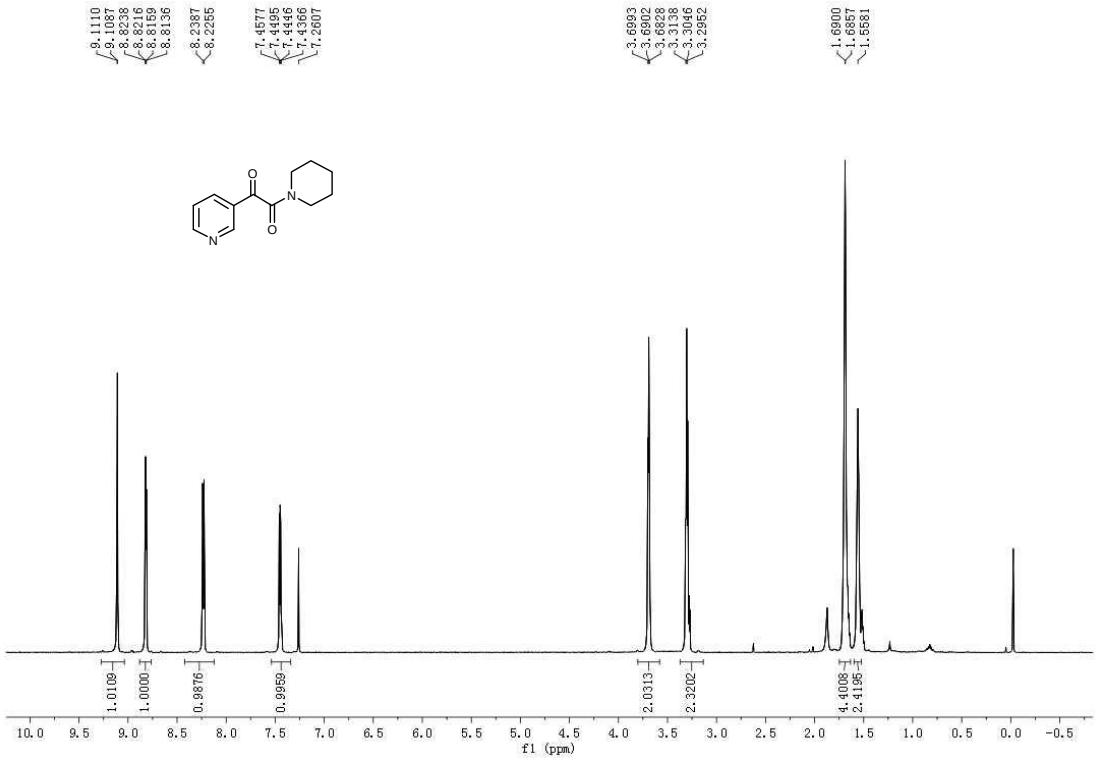
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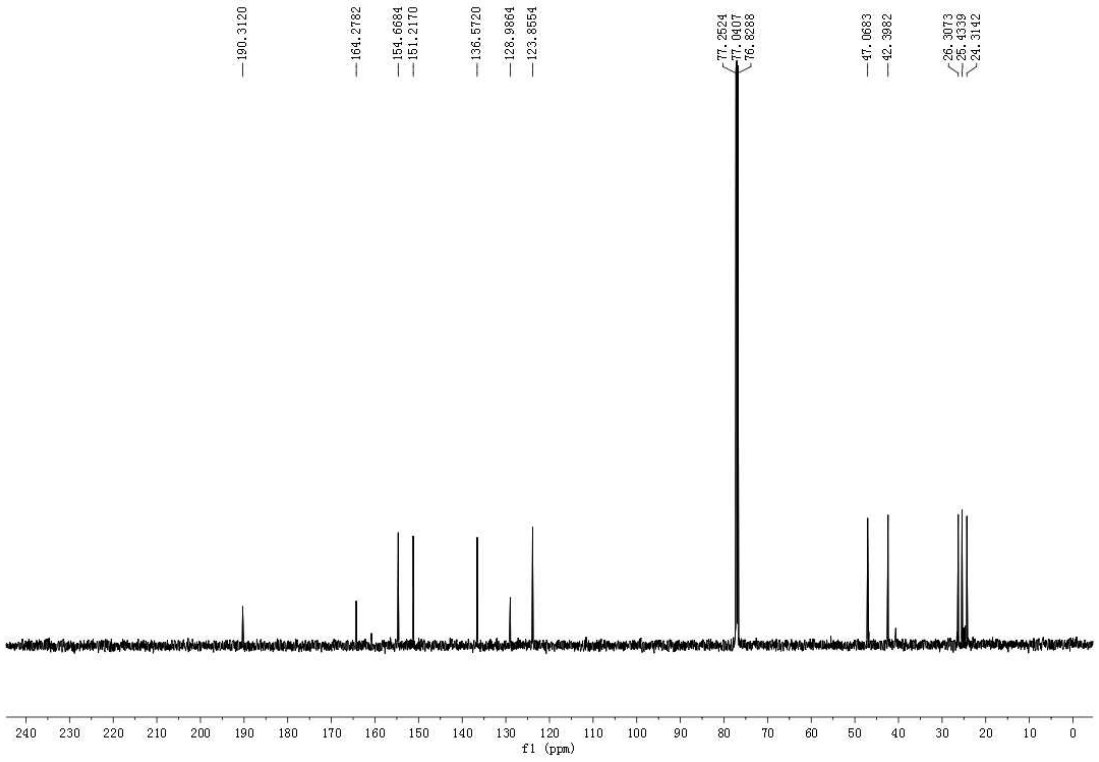
8.8238
8.8216
8.8159
8.8136
8.2387
8.2255
7.4577
7.4495
7.4446
7.4366
7.2607
3.6993
3.6902
3.6828
3.3138
3.3046
3.2952
1.6900
1.6857
1.6581
O
N
O
N
1.0109
1.0000
0.9876
0.9959
2.0313
2.3202
4.4008
2.4195
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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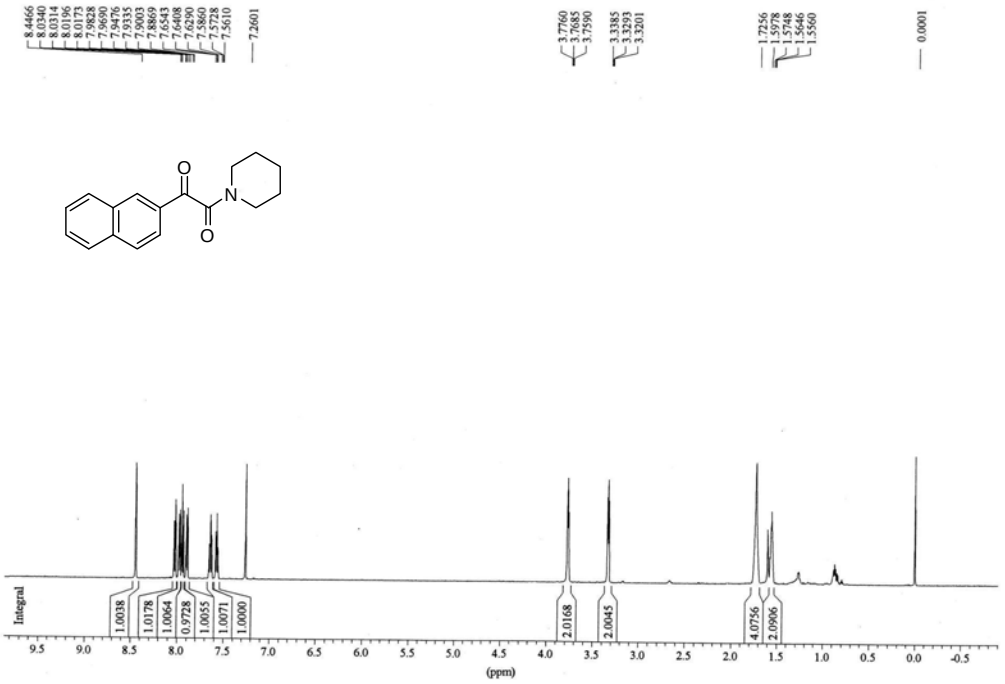
154.6684
151.2170
136.5720
128.9864
123.8554
77.2524
77.0407
76.8288
47.0683
42.3982
26.3073
25.4339
24.3142
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.0340
8.0314
8.0196
8.0173
7.9828
7.9660
7.9476
7.9335
7.9003
7.8869
7.6543
7.6408
7.6290
7.5860
7.5728
7.5610
7.2601
3.7760
3.7685
3.7590
3.3385
3.3293
3.3201
1.7256
1.6978
1.5748
1.5646
1.5560
0.0001
O
N
O
Integral
1.0038
1.0178
1.0064
0.9728
1.0055
1.0071
1.0000
2.0168
2.0045
4.0756
2.0906
(ppm)
192.0523
165.5947
136.3469
132.7584
132.4923
130.6828
129.8617
129.3295
128.9658
127.9438
127.1095
123.6655
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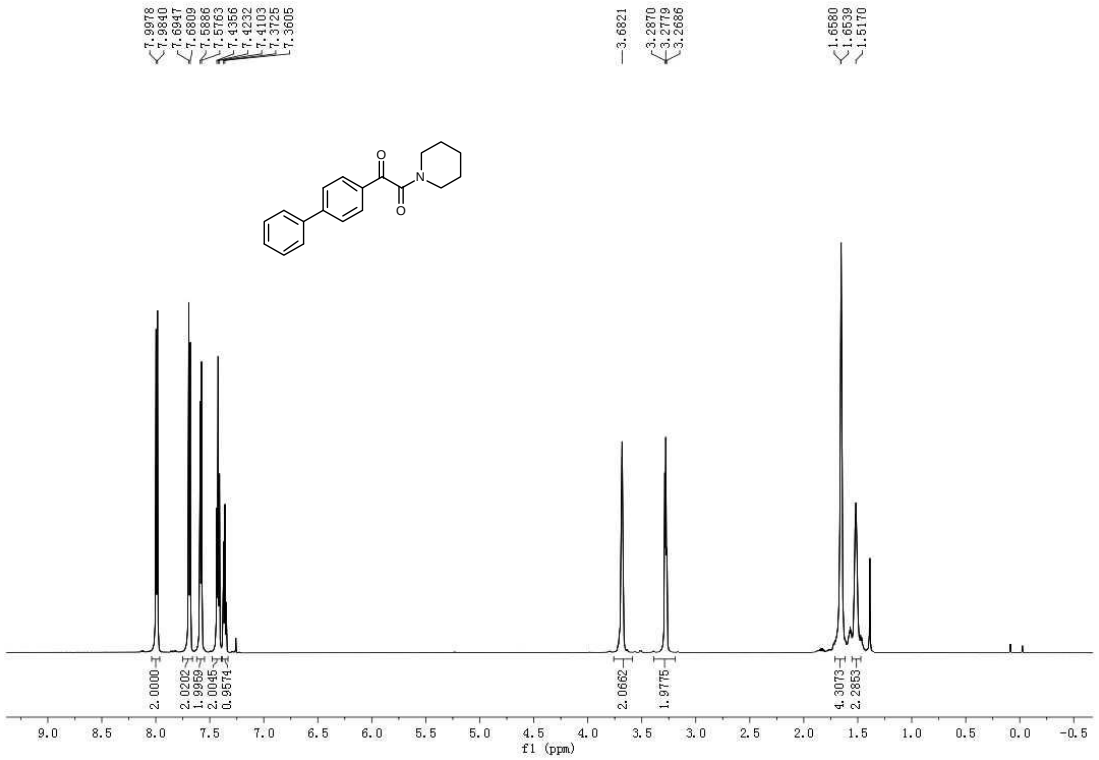
77.0986
76.8857
47.1437
42.2551
26.2437
25.5215
24.4115
(ppm)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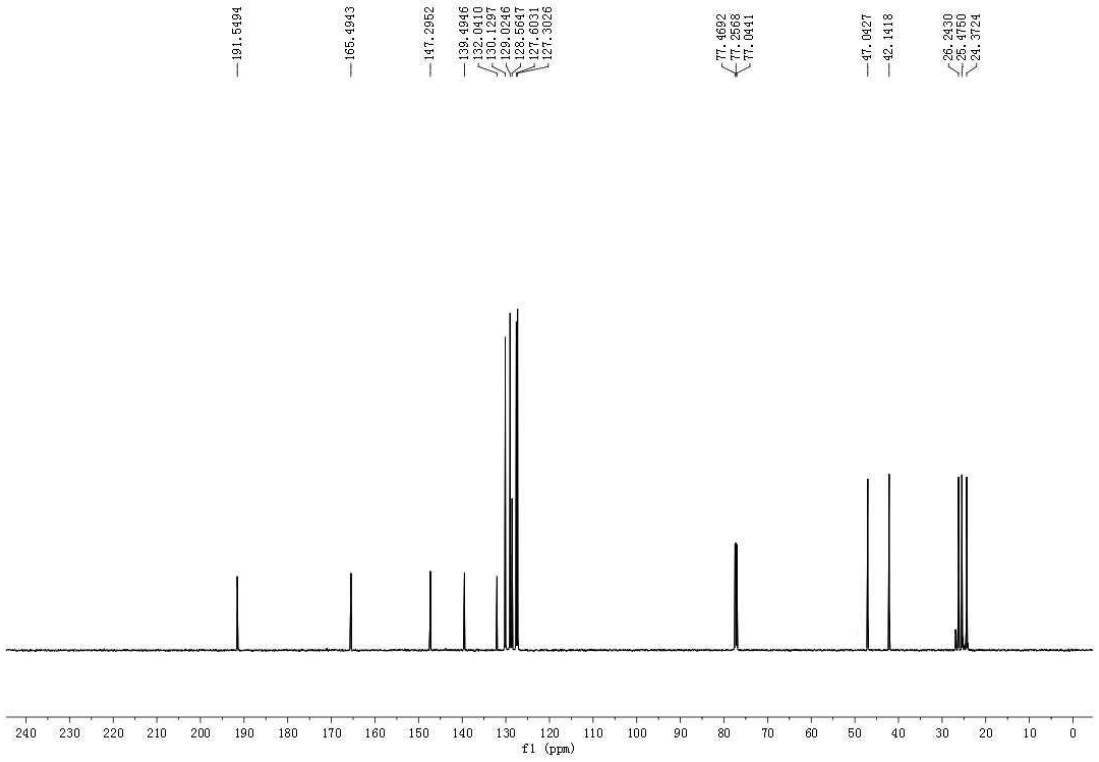
7.9940
7.6947
7.6809
7.5886
7.5763
7.4356
7.4232
7.4103
7.3725
7.3605
3.6821
3.2870
3.2779
3.2686
1.6580
1.6539
1.5170
O
O
N
2.0000
2.0202
1.9959
2.0045
0.9574
2.0662
1.9776
4.3073
2.2853
f1 (ppm)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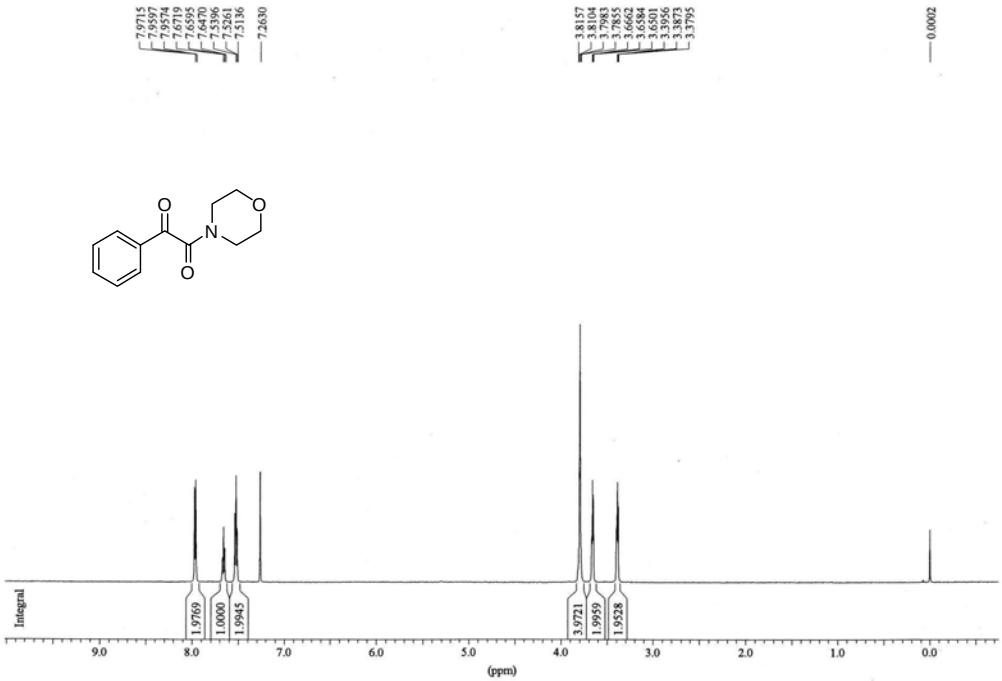
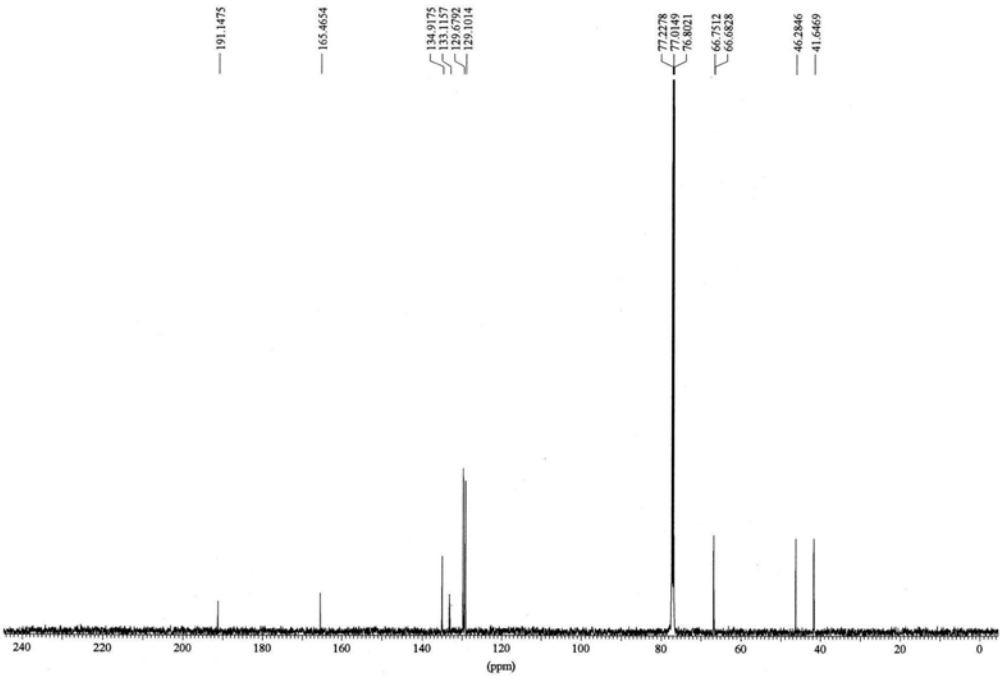
165.4943
147.2952
139.4946
132.0410
130.1297
129.0246
128.5647
127.6031
127.3026
77.4692
77.2568
77.0441
47.0427
42.1418
26.2430
25.4750
24.3724
f1 (ppm)






7.8900
7.8759
7.4781
7.4639
7.2523
3.7733
3.7611
3.7551
3.7432
3.6393
3.6316
3.6234
3.3624
3.3544
3.3466
O
O
N
O
Cl
2.0000
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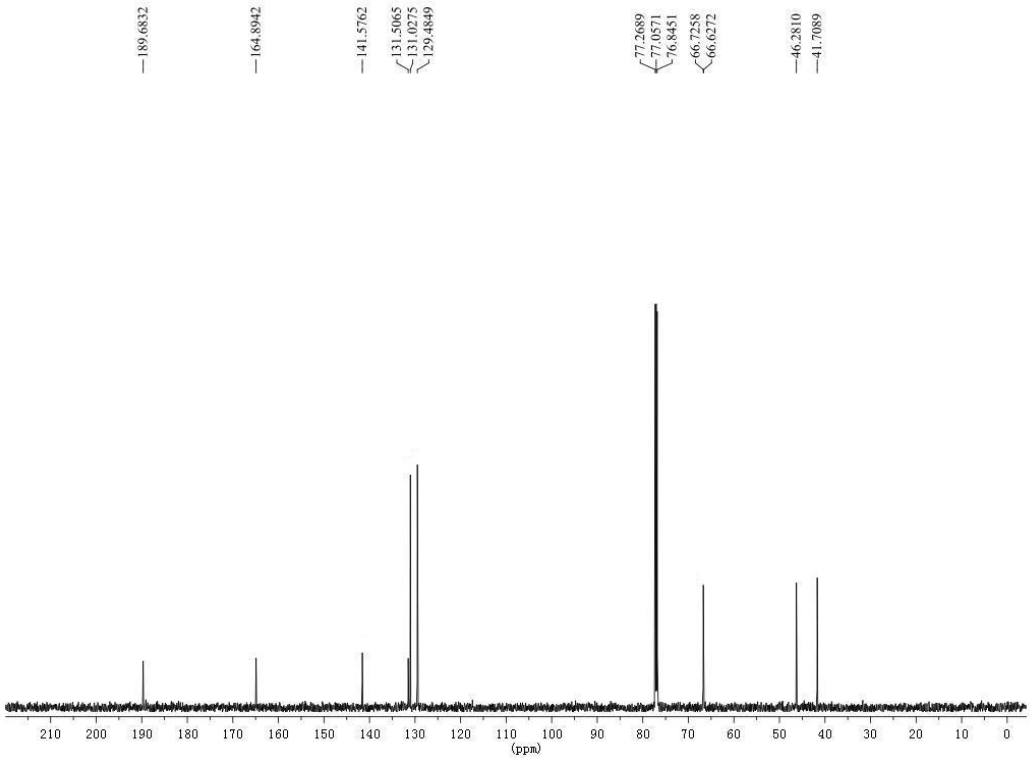
4.0149
2.0337
1.9975
(ppm)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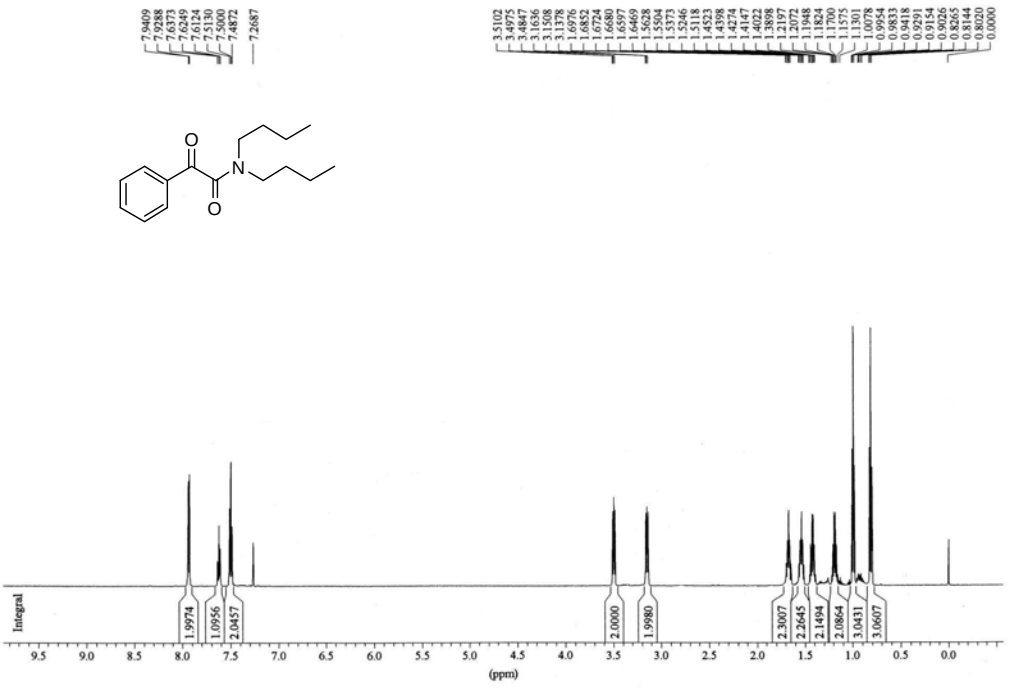
141.5762
131.5065
131.0275
129.4849
77.2689
77.0571
76.8451
66.7258
66.6272
46.2810
41.7089
(ppm)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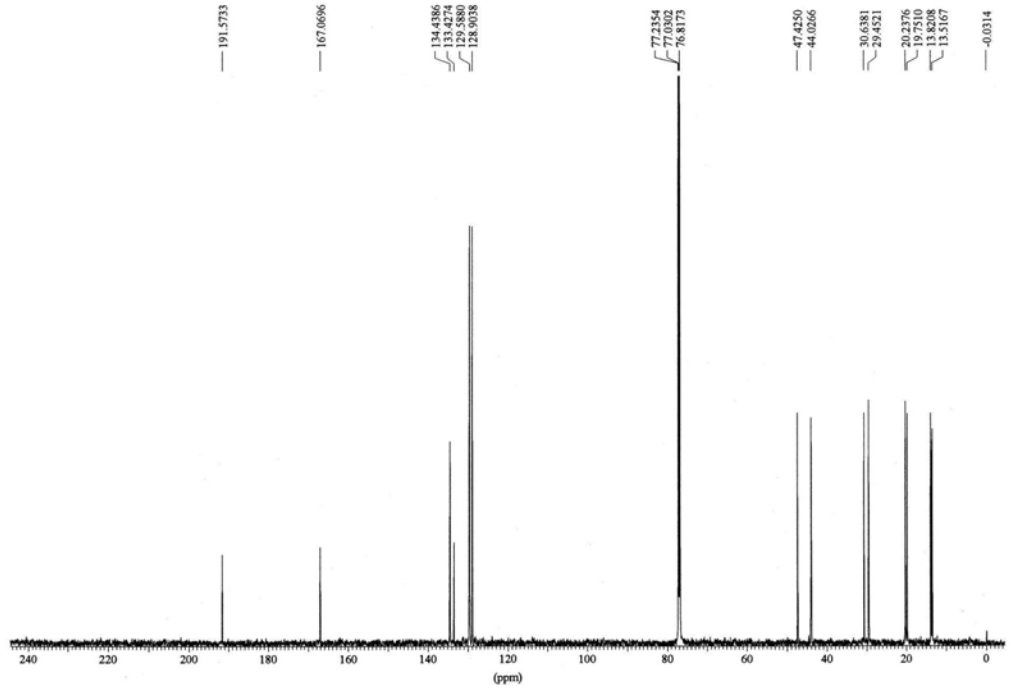
7.9288
7.6373
7.6249
7.6124
7.5130
7.5000
7.4872
7.2687
3.5102
3.4975
3.4847
3.1636
3.1508
3.1378
3.1246
1.6976
1.6852
1.6724
1.6680
1.6597
1.6469
1.5628
1.5504
1.5373
1.5246
1.5118
1.4523
1.4398
1.4274
1.4147
1.4022
1.3898
1.3197
1.2072
1.1948
1.1824
1.1700
1.1575
1.1301
1.0078
0.9954
0.9833
0.9418
0.9291
0.9154
0.9026
0.8265
0.8144
0.8020
0.0000
O
N
O
Integral
1.9974
1.0956
2.0457
2.0000
1.9980
2.3007
2.2645
2.1494
2.0864
3.0431
3.0607
(ppm)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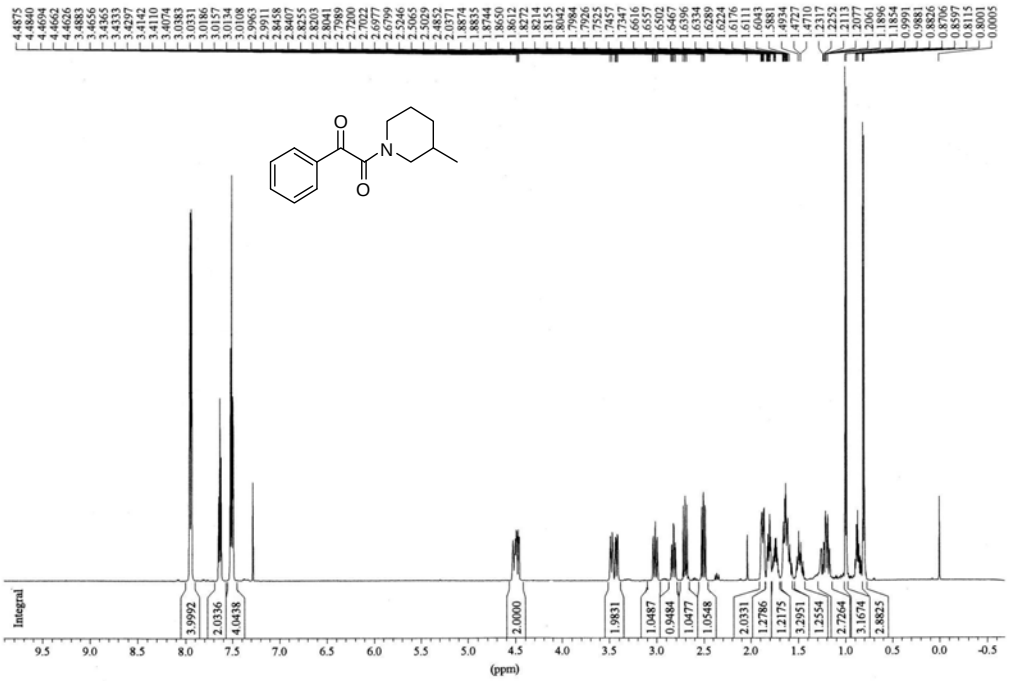
167.0696
134.4386
133.4274
129.5880
128.9038
77.2354
77.0302
76.8175
47.4250
44.0266
30.6381
29.4521
20.2376
19.7510
13.8208
13.5167
-0.0314
(ppm)


O
N
O
Integral
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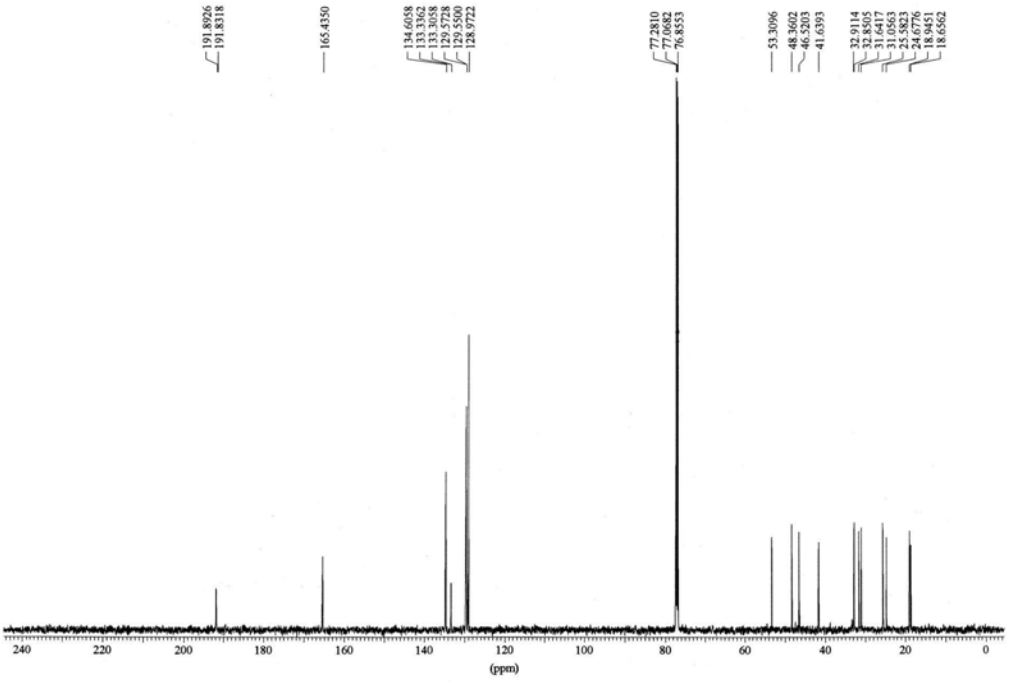
2.0336
4.0438
2.0000
1.9831
1.0487
0.9484
1.0477
1.0548
2.0331
1.2786
1.2175
3.2951
1.2554
2.7264
3.1674
2.8825
(ppm)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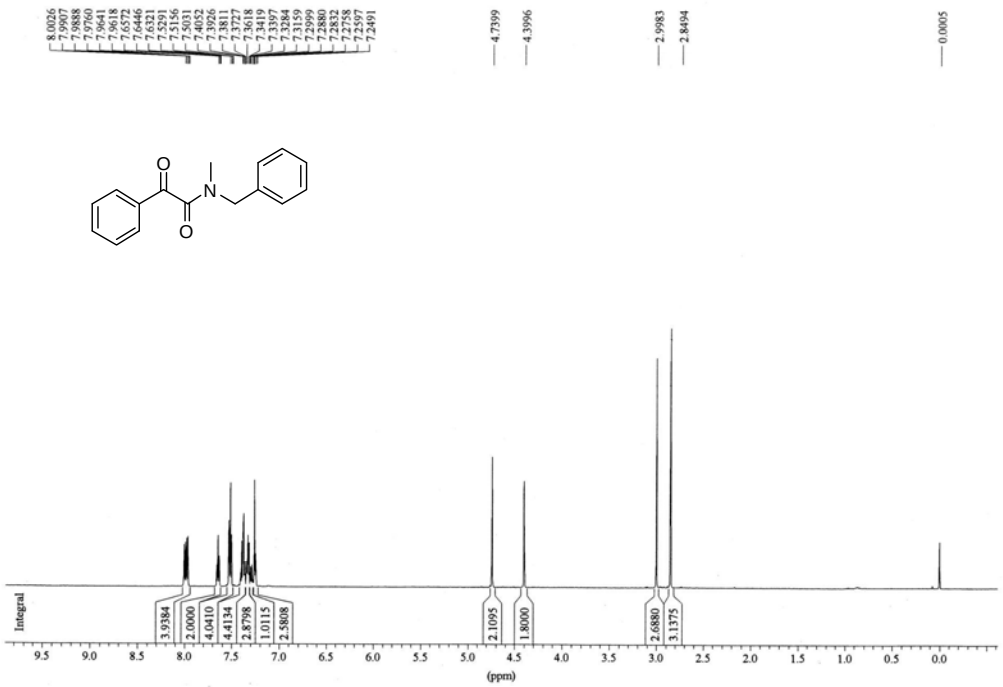
191.8318
165.4350
134.6058
133.3362
133.3038
130.3728
129.5500
128.9722
77.2810
77.0682
76.8553
53.3096
48.3602
46.5203
41.6393
32.9114
32.8505
31.6477
31.0565
25.5823
24.6776
18.9451
18.6562
(ppm)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7.9888
7.9760
7.9641
7.9618
7.6572
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7.5531
7.5291
7.5156
7.5031
7.4052
7.3926
7.3811
7.3727
7.3618
7.3419
7.3397
7.3284
7.3159
7.2999
7.2880
7.2852
7.2758
7.2597
7.2491
4.7399
4.3996
2.9983
2.8494
0.0005
O
N
O
Integral
3.9384
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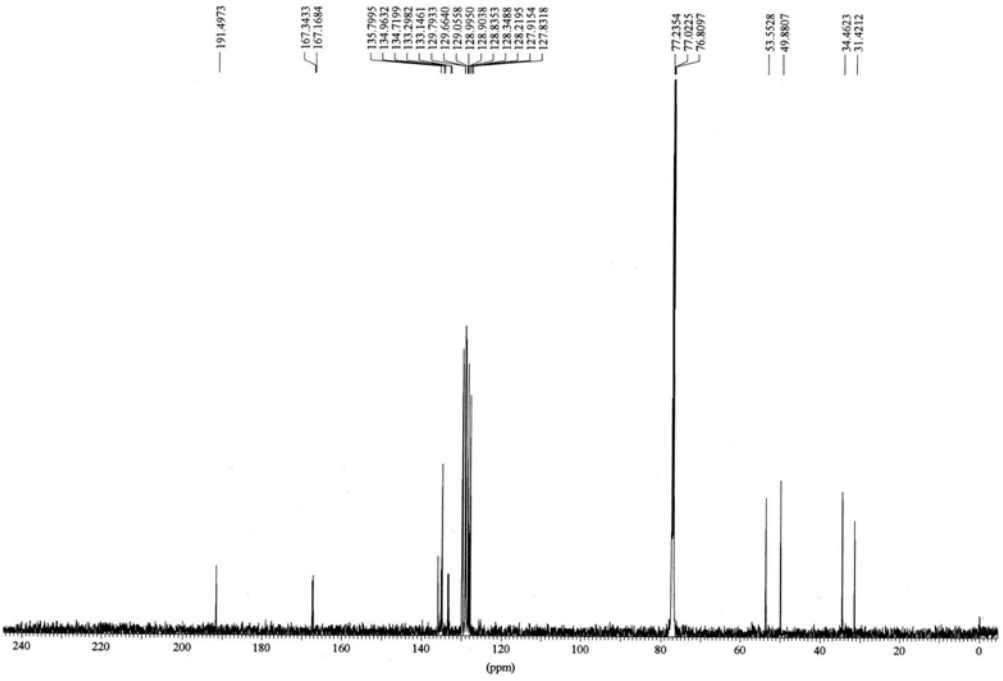
4.4134
2.8798
1.0115
2.5808
2.1095
1.8000
2.6880
3.1375
(ppm)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167.1684
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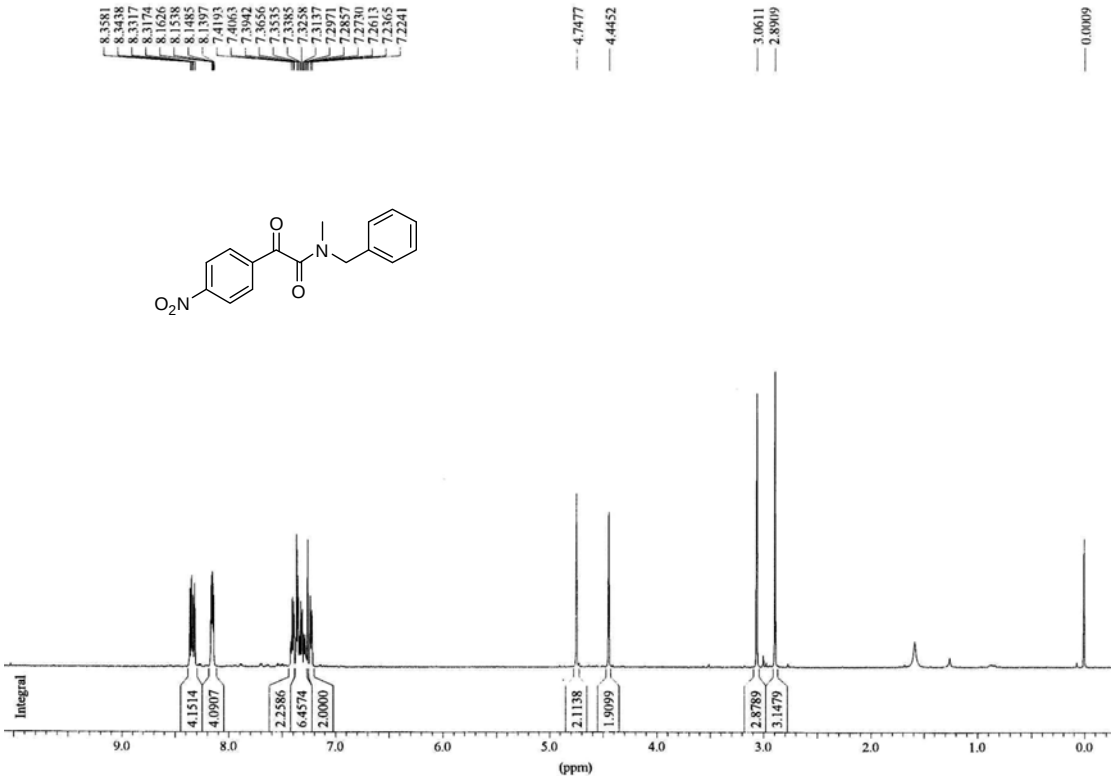
134.9632
134.7199
133.2982
133.1461
129.7933
129.6640
129.0558
128.9950
128.9038
128.8353
128.3488
128.2195
127.9154
127.8318
77.2354
77.0225
76.8097
53.5528
49.8807
34.4623
31.4212
(ppm)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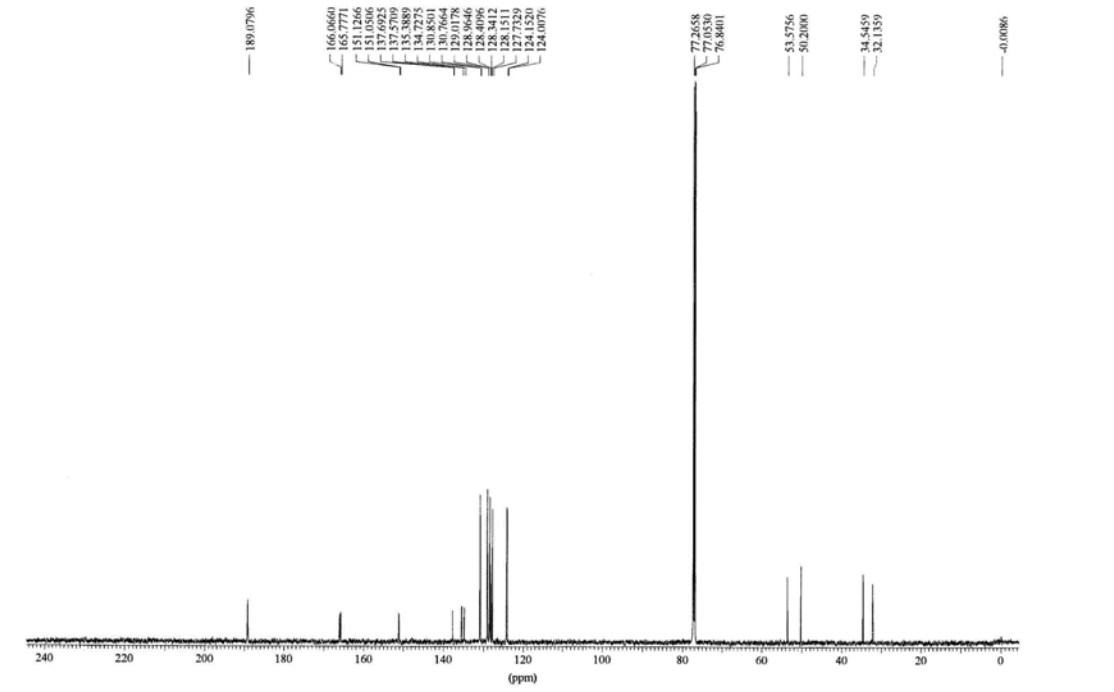
8.3438
8.3317
8.3174
8.1626
8.1538
8.1485
8.1397
7.4193
7.4063
7.3942
7.3656
7.3535
7.3385
7.3258
7.3137
7.2971
7.2857
7.2730
7.2613
7.2365
7.2241
4.7477
4.4452
3.0611
2.8909
0.0009
O
N
O
O2N
Integral
4.1514
4.0907
2.2586
6.4574
2.0000
2.1138
1.9099
2.8789
3.1479
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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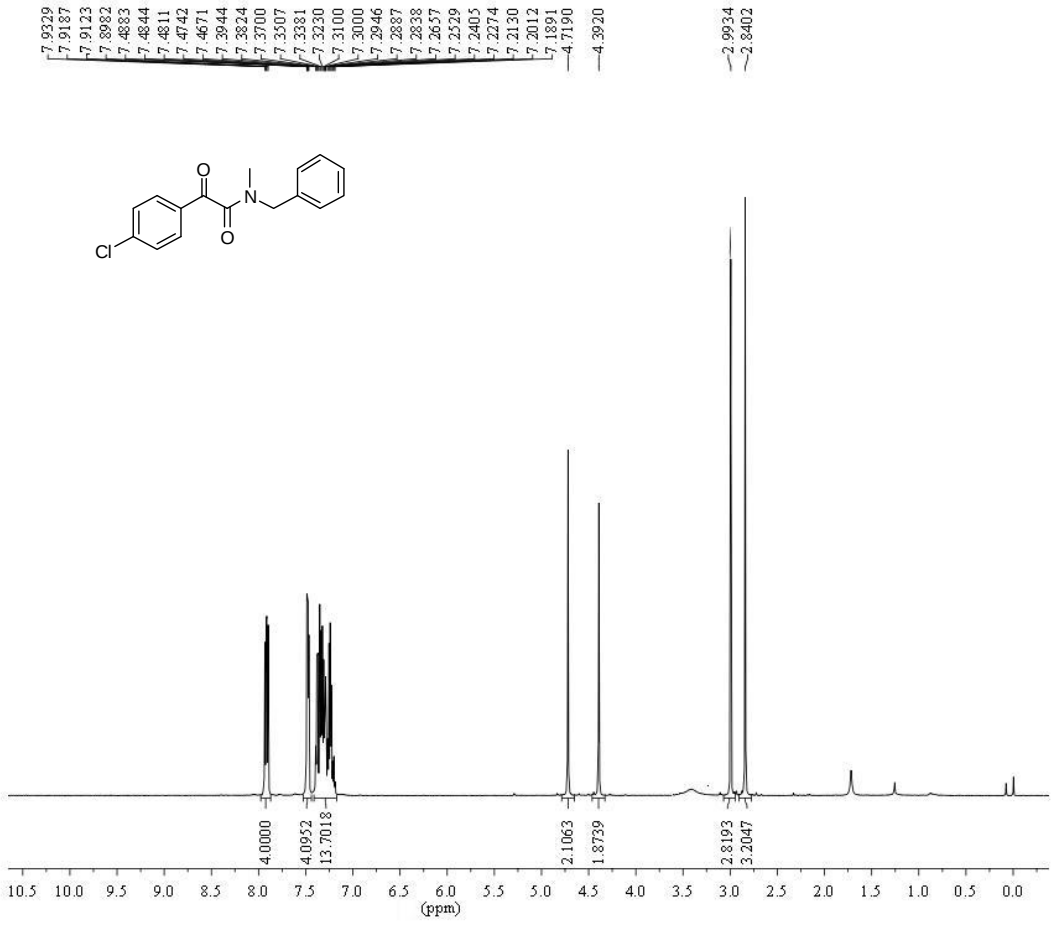
165.7771
151.1266
151.0506
137.6925
137.5709
135.3889
134.7275
130.8501
130.7664
129.0178
128.9646
128.4096
128.3412
128.1511
127.7329
124.1520
124.0076
77.2658
77.0530
76.8401
53.5756
50.2080
34.5459
32.1359
-0.0086
240
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)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7.9187
7.9123
7.8982
7.4883
7.4844
7.4811
7.4742
7.4671
7.3944
7.3824
7.3700
7.3307
7.3381
7.3230
7.3100
7.3000
7.2946
7.2887
7.2838
7.2657
7.2529
7.2405
7.2274
7.2130
7.2012
7.1891
4.7190
4.3920
2.9934
2.8402
O
N
O
Cl
4.0000
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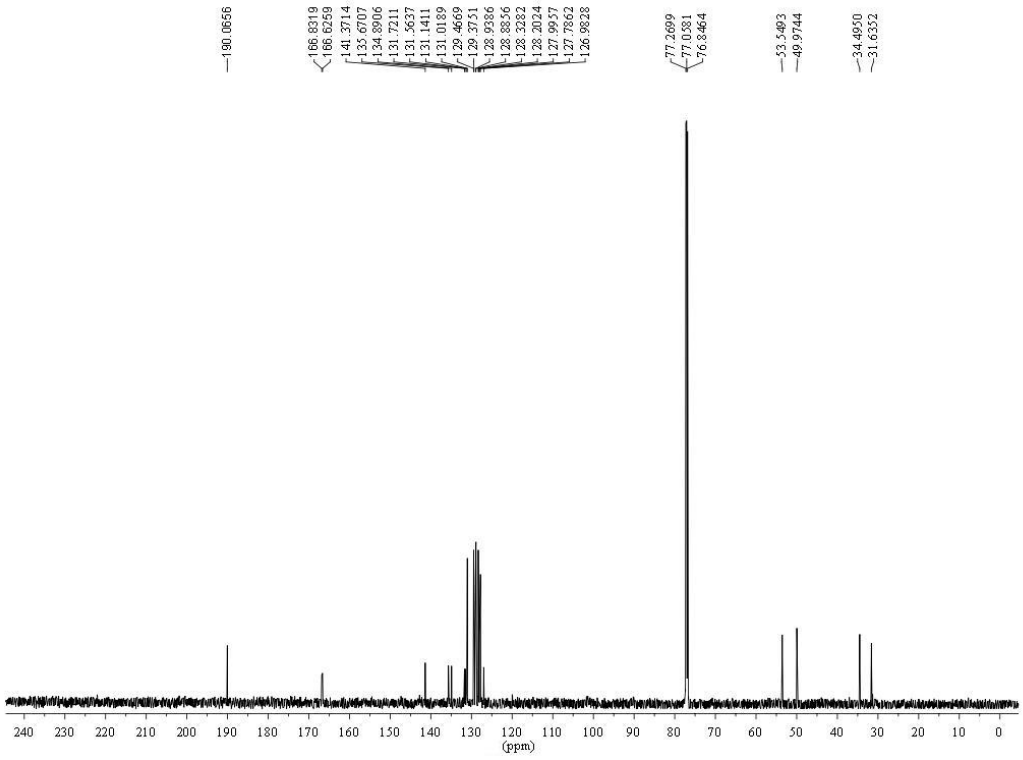
13.7018
2.1063
1.8739
2.8193
3.2047
(ppm)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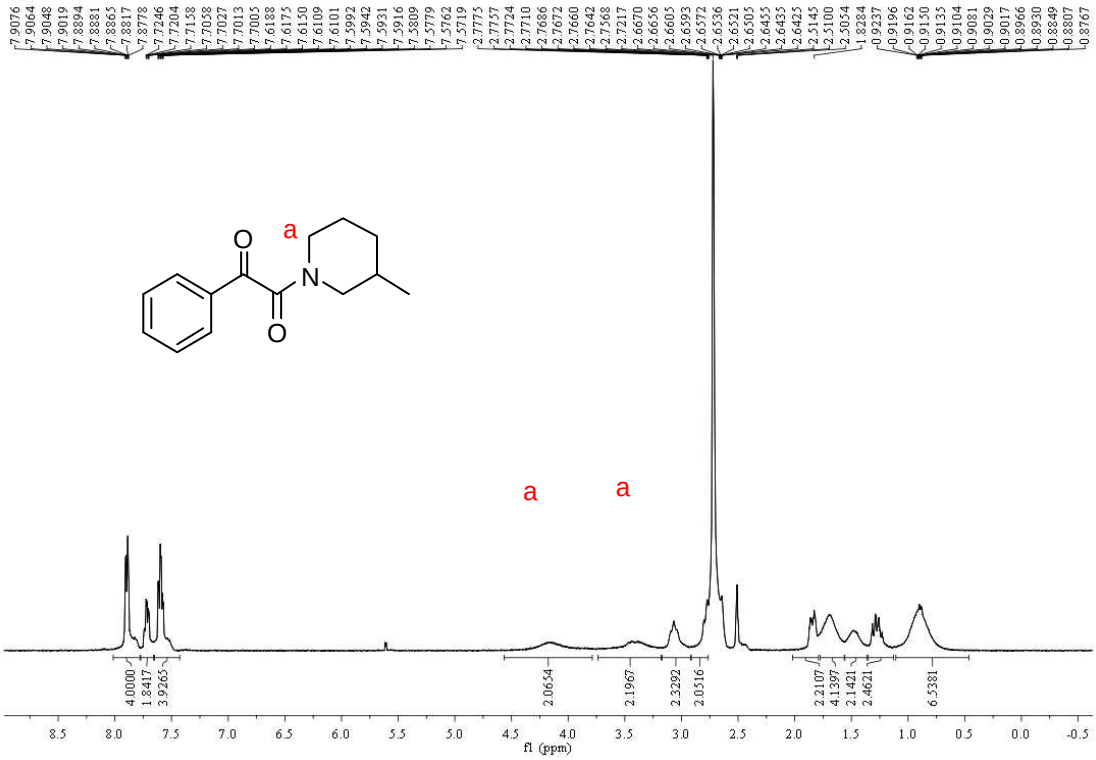
166.8319
166.6259
141.3714
133.6707
134.8906
131.7211
131.5637
131.1411
131.0189
129.4669
129.3751
128.9386
128.8856
128.3282
128.2024
127.9957
127.7862
126.9828
77.2699
77.0381
76.8464
53.5493
49.9744
34.4950
31.6332
(ppm)

6. Copies of high temperature (160 ºC) ^{1}H NMR spectra of α-ketoamides **3ad** and **3ae**

The high temperature (160 ºC) ^{1}H NMR spectrum of **3ad**



The high temperature (160 ºC) ^{1}H NMR spectrum of **3ae**