

Copper-catalyzed, hypervalent iodine mediated C=C bond activation of enaminones for the synthesis of α -keto amides

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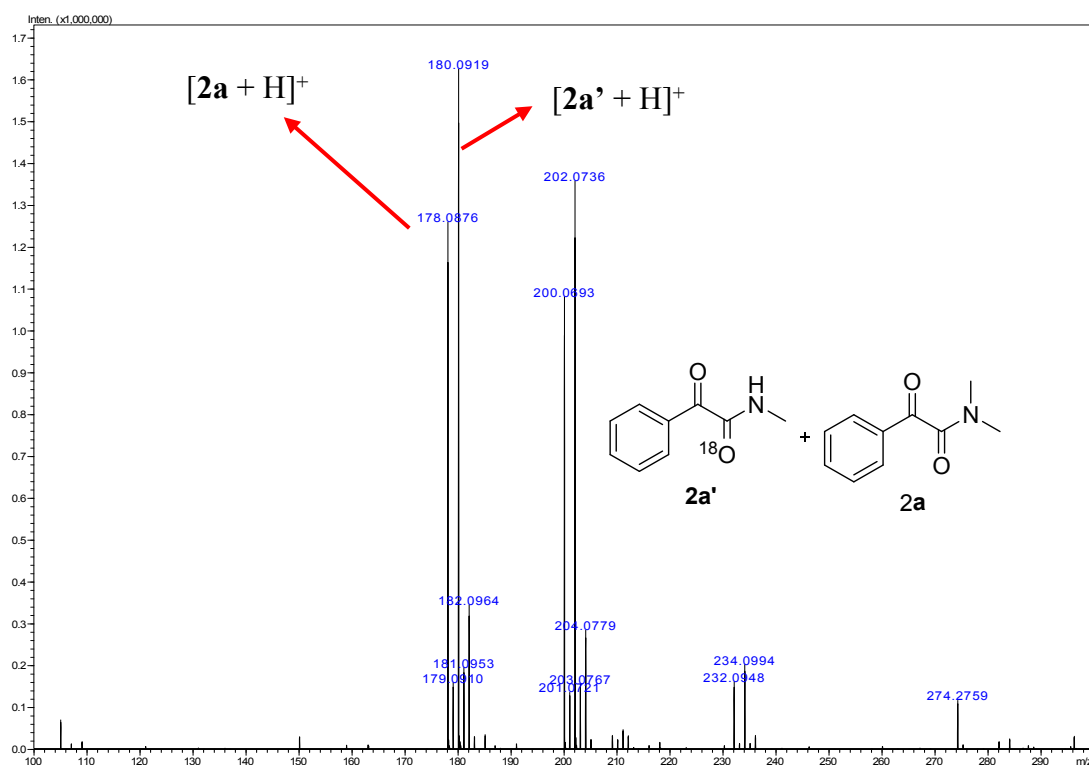
General experimental information

Enaminones **1** were prepared following literature process.¹⁻³ All other chemicals and solvents used in the experiments were acquired from commercial sources and used directly without further treatment. ¹H and ¹³C NMR were recorded in 400 or 600 MHz spectrometer using CDCl₃ as solvent and TMS as internal standard. The chemical shifts were reported in ppm, and the frequencies for ¹H and ¹³C NMR test were 400/600 MHz and 100/150 MHz, respectively. High resolution mass spectrometry (HRMS) data for all new products were obtained under ESI model in a apparatus equipped with TOF analyzer. The melting points were tested with X-4A apparatus without correcting the temperature. Thin-layer chromatography was performed on GF254 plates.

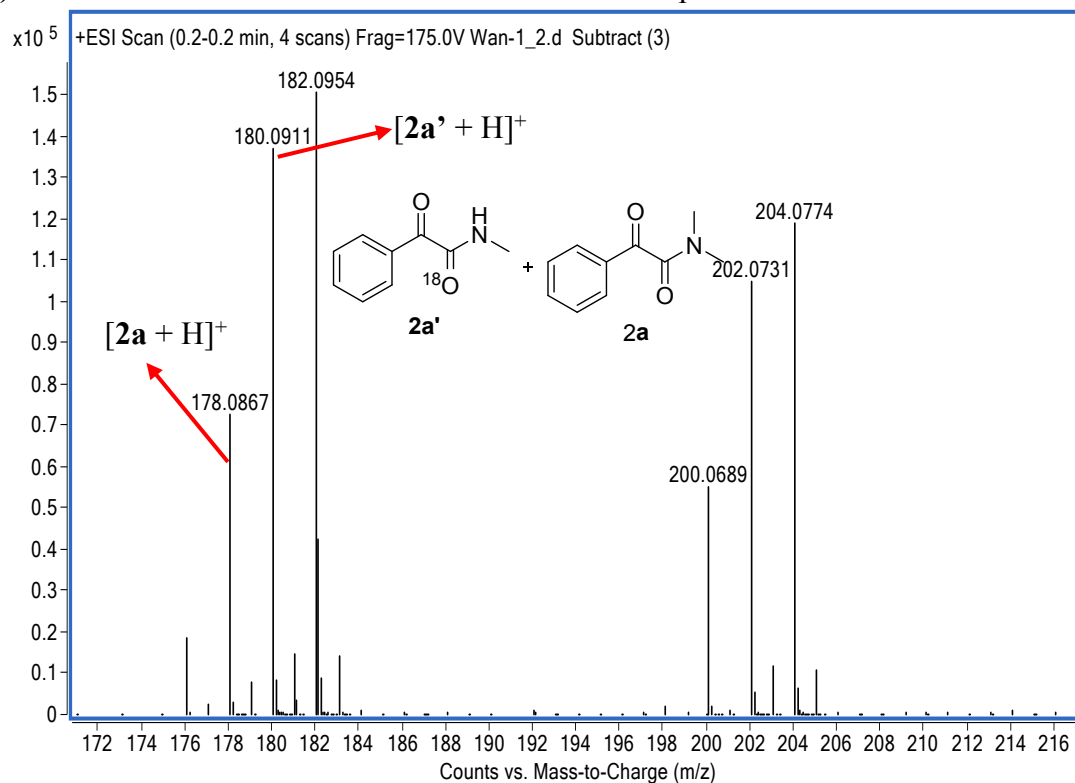
General procedure for the synthesis of α -ketoamides **2**

Enaminone **1** (0.3 mmol), CuI (0.18 mmol) and PhI(AcO)₂ (0.3 mmol) or oxygen balloon (for **2o** and **2p**) were charged in a 25 ml round bottom flask equipped with stirring bar (0.09 mmol morpholine was additionally employed in the synthesis of **2t** and **2u**). DMSO (2 mL) was added and the mixture was stirred at 120 °C under open air for 12 h or 16 h (TLC). After cooling down to room temperature, 5 mL water was added, and the resulting mixture was extracted with ethyl acetate (3 × 8 mL). The organic layers were combined and dried overnight with anhydrous Na₂SO₄. After removing the solvent under reduced pressure, the residue was subjected to silica gel chromatography to provide pure product by using mixed ethyl acetate/petroleum ether as eluent (v/v = 1/4).

HMRS spectra for products 2a+2a' from the reaction employing H₂¹⁸O

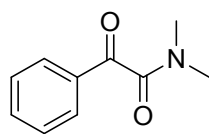


a) The reaction with untreated DMSO under air atmosphere

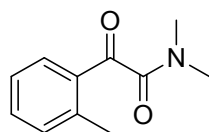


b) The reaction with dry DMSO under nitrogen atmosphere (unlabeled product came from the H₂O mixed in commercial H₂¹⁸O and few air because the experiment could not guarantee full moisture-free condition during the operation and long time stirring).

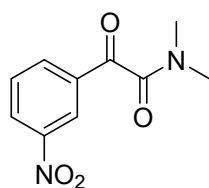
Characterization data of all products



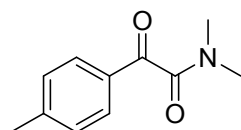
***N,N*-Dimethyl-2-oxo-2-phenylacetamide (2a).**⁴ Yellow oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.94 (d, 2 H, *J* = 7.2 Hz), 7.64 (t, 1 H, *J* = 7.6 Hz), 7.51 (t, 2 H, *J* = 7.6 Hz), 3.11 (s, 3 H), 2.95 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 191.3, 166.6, 134.2, 132.5, 129.1, 128.5, 36.5, 33.4.



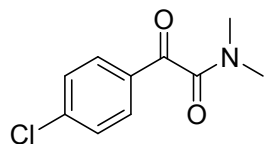
***N,N*-Dimethyl-2-oxo-2-o-tolylacetamide (2b).**⁴ Yellow oil; ¹H NMR (600 MHz, CDCl₃) δ = 7.69 (d, 1 H, *J* = 7.2 Hz), 7.49-7.47 (m, 1 H), 7.33-7.30 (m, 2 H), 3.11 (s, 3 H), 2.98 (s, 3 H), 2.66 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ = 196.4, 170.4, 144.1, 136.3, 135.3, 135.2, 134.2, 128.8, 39.7, 36.7, 24.4.



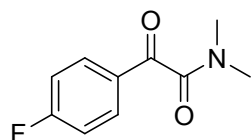
***N,N*-Dimethyl-2-(3-nitrophenyl)-2-oxoacetamide (2c).** White solid; mp.: 92-93 °C; ¹H NMR (600 MHz, CDCl₃) δ = 8.79 (t, 1 H, *J* = 1.8 Hz), 8.49-8.48 (m, 1 H), 8.31 (d, 1 H, *J* = 7.8 Hz), 7.74 (t, 1 H, *J* = 7.8 Hz), 3.17 (s, 3 H), 3.03 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ = 191.3, 168.1, 151.2, 137.8, 137.3, 132.9, 131.3, 127.1, 39.8, 37.0; ESI-HRMS: Calcd for C₁₀H₁₀N₂NaO₄[M+Na]⁺: 245.0533; Found: 245.0543.



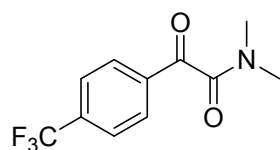
***N,N*-Dimethyl-2-oxo-2-p-tolylacetamide (2d).**⁴ Yellow oil; ¹H NMR (600 MHz, CDCl₃) δ = 7.83 (d, 2 H, *J* = 7.8 Hz), 7.30 (t, 2 H, *J* = 7.8 Hz), 3.11 (s, 3 H), 2.95 (s, 3 H), 2.43 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ = 194.2, 169.9, 148.6, 133.3, 132.38, 132.35, 39.7, 36.6, 24.5.



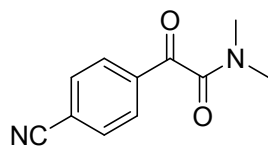
2-(4-Chlorophenyl)-N,N-dimethyl-2-oxoacetamide (2e).⁴ Yellow oil; ¹H NMR (600 MHz, CDCl₃) δ = 7.90 (d, 2 H, J = 8.4 Hz), 7.49 (d, 2 H, J = 8.4 Hz), 3.12 (s, 3 H), 2.97 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ = 192.9, 169.1, 144.0, 134.1, 133.7, 132.0, 39.7, 36.7.



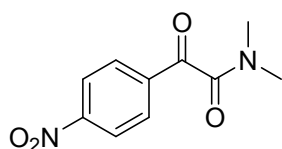
2-(4-Fluorophenyl)-N,N-dimethyl-2-oxoacetamide (2f).⁴ Pale Yellow gummy compound; ¹H NMR (600 MHz, CDCl₃) δ = 7.99 (dd, 2 H, J = 5.4 Hz, 3.0 Hz), 7.19 (t, 2 H, J = 8.4 Hz), 3.12 (s, 3 H), 2.97 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ = 192.6, 169.30, 169.29 (d, 1 C, J = 256.2 Hz), 135.1 (d, 1 C, J = 9.8 Hz), 132.2 (d, 1 C, J = 2.7 Hz), 119.0 (d, 1 C, J = 22.2 Hz), 39.7, 36.7.



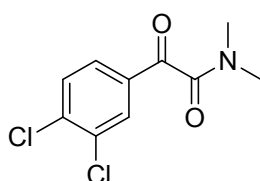
N,N-Dimethyl-2-oxo-2-(4-(trifluoromethyl)phenyl)acetamide (2g). Yellow oil; ¹H NMR (400 MHz, CDCl₃) δ = 8.09 (d, 2 H, J = 7.6 Hz), 7.78 (d, 2 H, J = 8.4 Hz) 3.14 (s, 3 H), 2.99 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 190.3, 166.1, 135.8, 135.5, 130.0, 126.01, 125.98, 124.7, 122.0, 37.0, 34.1; ESI-HRMS: Calcd for C₁₁H₁₀F₃NNaO₂ [M+Na]⁺: 268.0556; Found:268.0538.



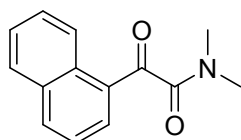
2-(4-Cyanophenyl)-N,N-dimethyl-2-oxoacetamide (2h). White solid; mp.: 131-134 °C; ¹H NMR (400 MHz, CDCl₃) δ = 8.08 (d, 1 H, J = 8.4 Hz), 7.82 (d, 1 H, J = 8.0 Hz), 3.15 (s, 3 H), 3.00 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 189.6, 165.7, 136.1, 132.7, 130.0, 117.67, 117.62, 37.0, 34.2; ESI-HRMS: Calcd for C₁₁H₁₀N₂NaO₂⁺ [M+Na]⁺: 225.0634; Found: 225.0651.



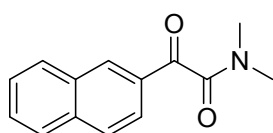
***N,N*-Dimethyl-2-(4-nitrophenyl)-2-oxoacetamide (2i).**⁴ Pale yellow solid; mp.: 135-136 °C [lit. 136-138 °C]; ¹H NMR (600 MHz, CDCl₃) δ = 8.35 (d, 2 H, *J* = 9.0 Hz), 8.15 (d, 2 H, *J* = 8.4 Hz), 3.15 (s, 3 H), 3.01 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ = 189.8, 166.1, 151.6, 138.1, 131.3, 124.6, 37.6, 34.9.



2-(3,4-Dichlorophenyl)-*N,N*-dimethyl-2-oxoacetamide (2j). White solid; mp.: 81-82 °C; ¹H NMR (600 MHz, CDCl₃) δ = 8.04 (d, 1 H, *J* = 2.4 Hz), 7.79 (d, 1 H, *J* = 4.2 Hz), 7.60 (d, 1 H, *J* = 8.4 Hz), 3.13 (s, 3 H), 2.98 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ = 191.7, 168.5, 142.1, 136.4, 135.4, 134.0, 133.8, 131.2, 39.7, 36.9; ESI-HRMS: Calcd for C₁₀H₉Cl₂NNaO₂ [M+Na]⁺: 267.9903; Found: 267.9921.

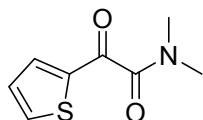


***N,N*-Dimethyl-2-(naphthalen-1-yl)-2-oxoacetamide (2k).**⁴ Pale yellow oil; ¹H NMR (600 MHz, CDCl₃) δ = 9.25 (d, 1 H, *J* = 8.4 Hz), 8.10 (d, 1 H, *J* = 7.8 Hz), 7.99 (d, 1 H, *J* = 7.8 Hz), 7.90 (d, 1 H, *J* = 7.8 Hz), 7.68 (t, 1 H, *J* = 7.2 Hz), 7.58 (t, 1 H, *J* = 7.2 Hz), 7.53 (d, 1 H, *J* = 7.8 Hz), 3.14 (s, 3 H), 3.00 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ = 196.9, 170.3, 138.5, 137.0, 136.7, 133.6, 131.9, 131.4, 131.1, 129.6, 128.4, 127.2, 39.8, 36.8.

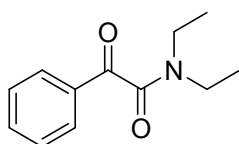


***N,N*-Dimethyl-2-(naphthalen-2-yl)-2-oxoacetamide (2l).**⁵ Pale yellow solid; mp.: 112-113 °C [lit. 112-114 °C] ¹H NMR (600 MHz, CDCl₃) δ = 8.44 (s, 1 H), 8.00 (d, 1 H, *J* = 8.4 Hz), 7.97 (d, 1 H, *J* = 7.8 Hz), 7.93 (d, 1 H, *J* = 9.0 Hz), 7.88 (d, 1 H, *J* =

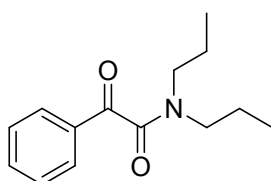
7.8 Hz), 7.64 (dd, 1 H, $J = 7.2$ Hz, 1.2 Hz), 7.56 (t, 1 H, $J = 7.8$ Hz), 3.17(s, 3 H), 2.99 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) $\delta = 194.5, 169.8, 139.0, 135.6, 135.1, 133.1, 132.5, 132.0, 131.7, 130.6, 129.8, 126.3, 39.8, 36.8$.



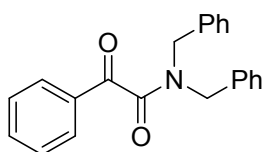
***N,N*-Dimethyl-2-oxo-2-(thiophen-2-yl)acetamide (2m).**⁵ Pale yellow gummy compound; ^1H NMR (600 MHz, CDCl_3) $\delta = 7.82$ (d, 1 H, $J = 3.6$ Hz), 7.79 (d, 1 H, $J = 4.8$ Hz), 7.18 (t, 1 H, $J = 4.8$ Hz), 3.10 (s, 3 H), 3.04 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) $\delta = 186.1, 168.5, 143.0, 139.1, 138.8, 131.3, 40.0, 37.1$.



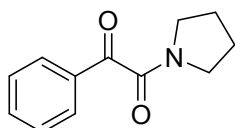
***N,N*-Diethyl-2-oxo-2-phenylacetamide (2n).**⁴ Yellow oil; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.94$ (d, 2 H, $J = 8.0$ Hz), 7.64 (t, 1 H, $J = 7.2$ Hz), 7.51 (t, 2 H, $J = 8.0$ Hz), 3.57 (q, 2 H, $J = 7.2$ Hz), 3.24 (q, 2 H, $J = 7.2$ Hz), 1.29 (t, 3 H, $J = 7.2$ Hz), 1.15 (t, 3 H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 191.6, 166.8, 134.6, 133.2, 129.6, 129.0, 42.1, 38.8, 14.1, 12.8$.



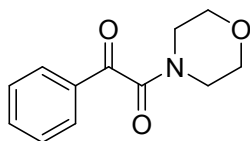
2-Oxo-2-phenyl-*N,N*-dipropylacetamide (2o).⁶ Pale yellow oil; ^1H NMR (400 MHz, CDCl_3) $\delta = 7.94$ (d, 2 H, $J = 8.0$ Hz), 7.63 (t, 1 H, $J = 8.0$ Hz), 7.50 (t, 2 H, $J = 8.0$ Hz), 3.47 (t, 2 H, $J = 7.6$ Hz), 3.13 (t, 2 H, $J = 7.6$ Hz) 1.73 (q, 2 H, $J = 7.6$ Hz), 1.59 (q, 2 H, $J = 7.6$ Hz), 1.00 (t, 3 H, $J = 7.6$ Hz), 0.79 (t, 3 H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 191.5, 167.2, 134.5, 133.3, 129.6, 128.9, 49.3, 45.8, 21.8, 20.6, 11.4, 11.0$.



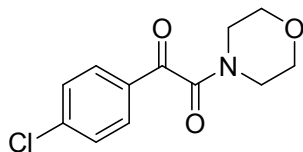
***N,N*-Dibenzyl-2-oxo-2-phenylacetamide (2p).**⁷ Pale Yellow gummy compound; mp.:
¹H NMR (400 MHz, CDCl₃) δ = 7.99 (d, 2 H, J = 8.0 Hz), 7.64-7.60 (m, 1H), 7.49 (t, 2 H, J = 7.2 Hz), 7.40-7.22 (m, 10 H), 4.62 (s, 2 H), 4.27 (s, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ = 191.2, 167.4, 136.0, 134.8, 134.7, 133.4, 129.8, 129.0, 128.93, 128.86, 128.7, 128.3, 128.2, 127.9, 50.2, 46.1



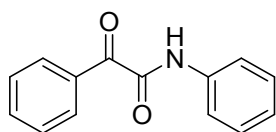
1-Phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione (2q).⁷ Yellow gummy compound; ¹H NMR (600 MHz, CDCl₃) δ = 8.00 (d, 2 H, J = 6.6 Hz), 7.64 (t, 1 H, J = 7.2 Hz), 7.51 (t, 2 H, J = 7.8 Hz), 3.66 (t, 2 H, J = 6.6 Hz), 3.43 (t, 2 H, J = 6.6 Hz), 1.98-1.93 (m, 4 H); ¹³C NMR (150 MHz, CDCl₃) δ = 194.2, 167.6, 137.2, 135.6, 132.5, 131.6, 49.3, 47.9, 28.6, 26.7.



1-Morpholino-2-phenylethane-1,2-dione (2r).⁴ Yellow oil; ¹H NMR (600 MHz, CDCl₃) δ = 7.97 (d, 2 H, J = 8.4 Hz), 7.66 (t, 1 H, J = 7.8 Hz), 7.53 (t, 2 H, J = 7.8 Hz), 3.80 (s, 4 H), 3.66 (t, 2 H, J = 4.8 Hz), 3.39 (t, 2 H, J = 4.8 Hz); ¹³C NMR (150 MHz, CDCl₃) δ = 193.8, 168.1, 137.6, 135.7, 132.3, 131.7, 69.4, 69.3, 48.9, 44.3.

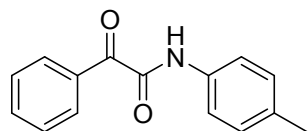


1-(4-Chlorophenyl)-2-morpholinoethane-1,2-dione (2s).⁵ Yellow gummy compound; ¹H NMR (400 MHz, CDCl₃) δ = 7.91 (d, 2 H, J = 8.0 Hz), 7.50 (d, 2 H, J = 8.4 Hz), 3.79 (s, 4 H), 3.66 (t, 2 H, J = 4.0 Hz), 3.39 (t, 2 H, J = 4.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ = 189.7, 164.9, 141.6, 131.5, 131.0, 129.5, 66.7, 66.6, 46.3, 41.7.



2-Oxo-N-2-diphenylacetamide (2t).⁸ Yellow solid; mp.:44-45 °C [lit. 43-45 °C]; ¹H

NMR (400 MHz, CDCl₃) δ = 8.98 (s, 1 H), 8.40 (d, 2 H, J = 8.0 Hz), 7.71-7.63 (m, 3 H), 7.50 (t, 2 H, J = 8.0 Hz), 7.39 (t, 2 H, J = 8.0 Hz), 7.19 (t, 1 H, J = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ = 187.5, 158.9, 136.7, 134.6, 133.1, 131.5, 129.2, 128.5, 125.3, 120.0.



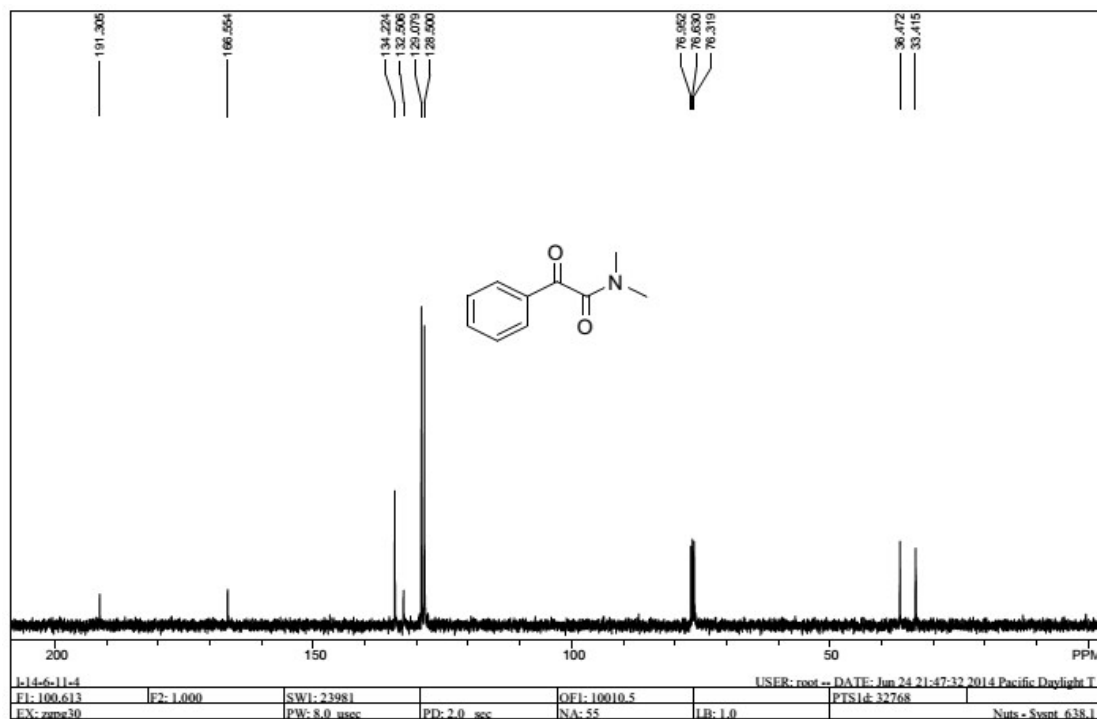
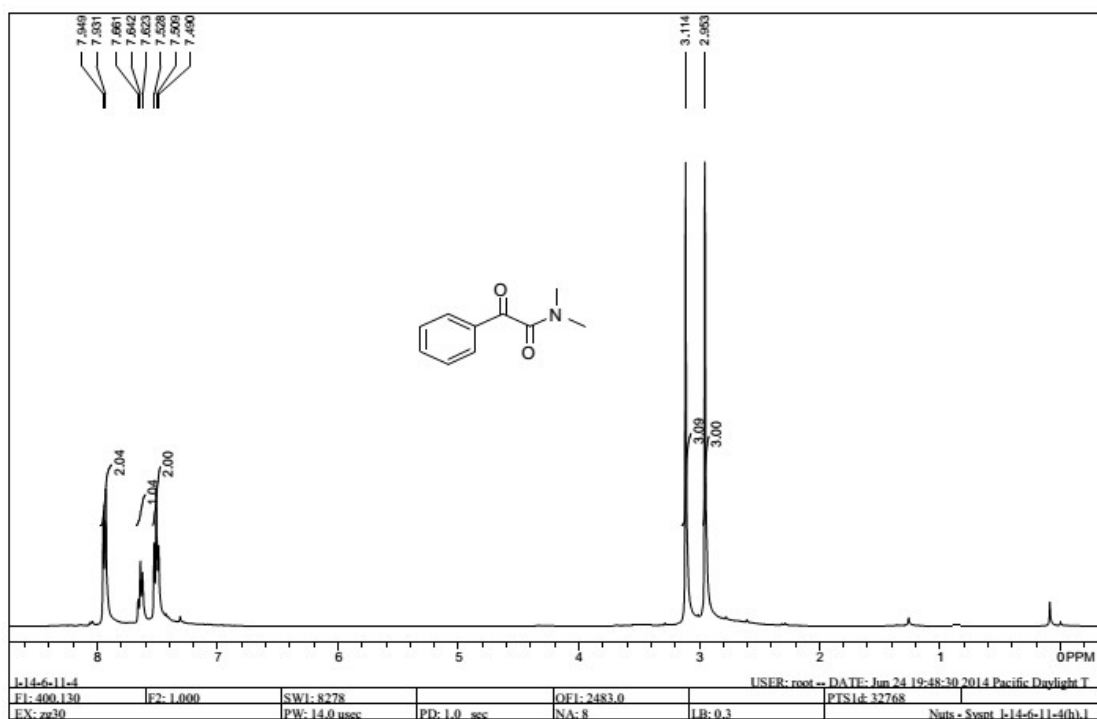
2-oxo-2-phenyl-N-p-tolylacetamide (2u).⁸ Pale yellow solid; mp.: 114-115 °C [lit. 114.5-116.4 °C]; ¹H NMR (400 MHz, CDCl₃) δ = 8.91 (s, 1 H), 8.41 (d, 2 H, J = 7.2 Hz), 7.65 (t, 1 H, J = 8.8 Hz), 7.59 (d, 2 H, J = 8.8 Hz), 7.50 (t, 2 H, J = 7.6 Hz), 7.20 (t, 2 H, J = 8.0 Hz), 2.35 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 187.5, 158.8, 135.1, 134.6, 134.2, 133.2, 131.5, 129.7, 128.5, 119.9, 21.0.

Reference

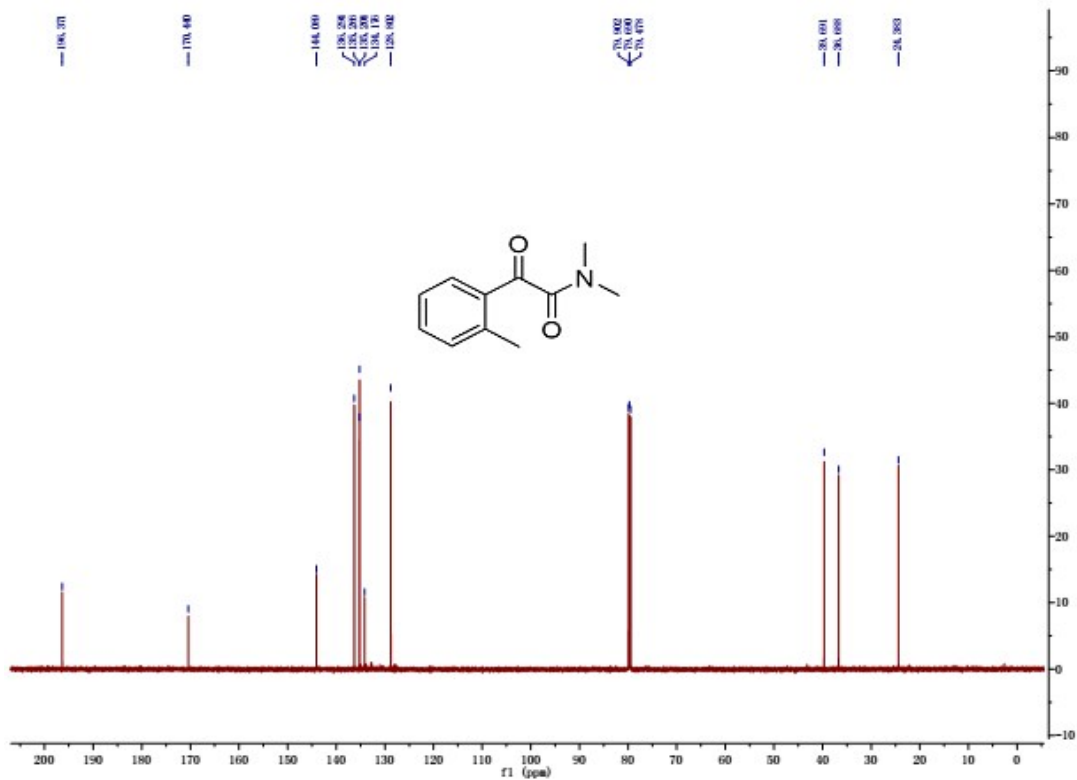
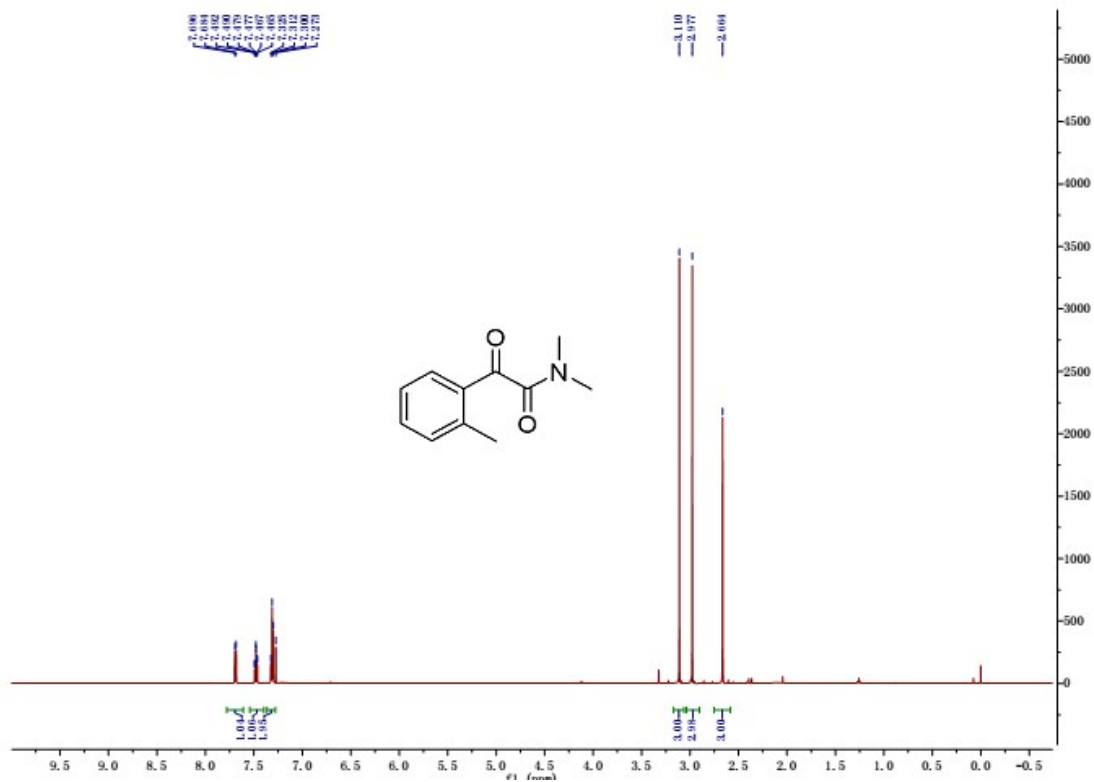
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¹H and ¹³C NMR spectra of all products

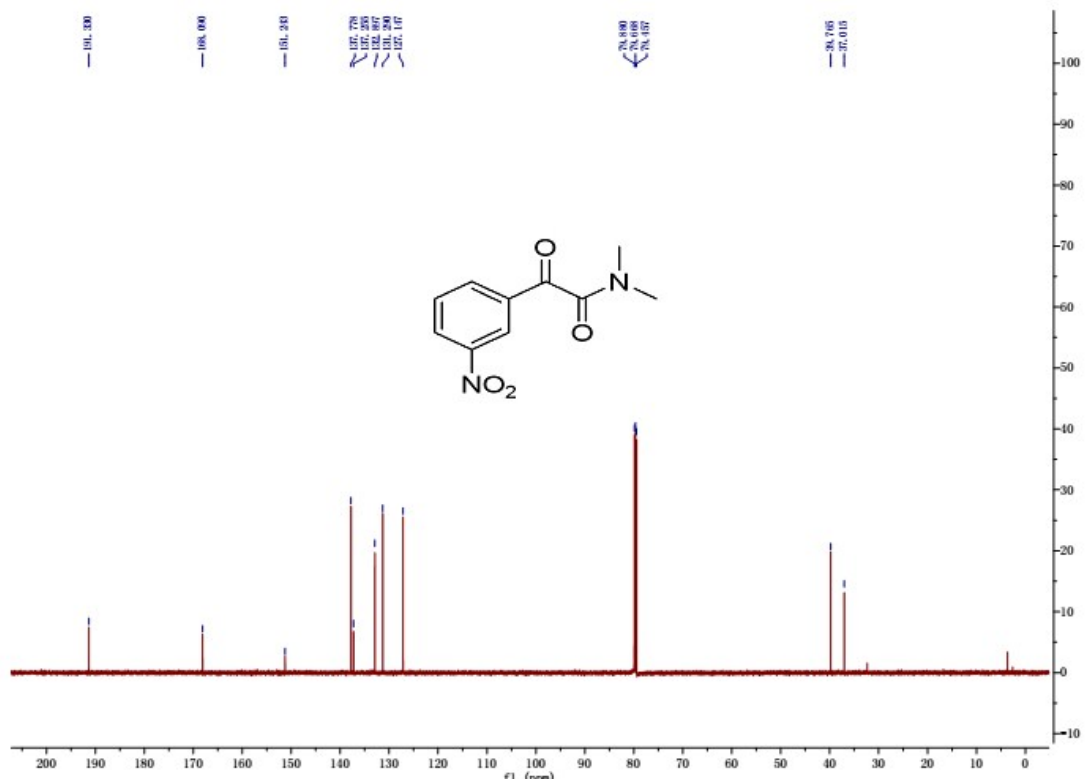
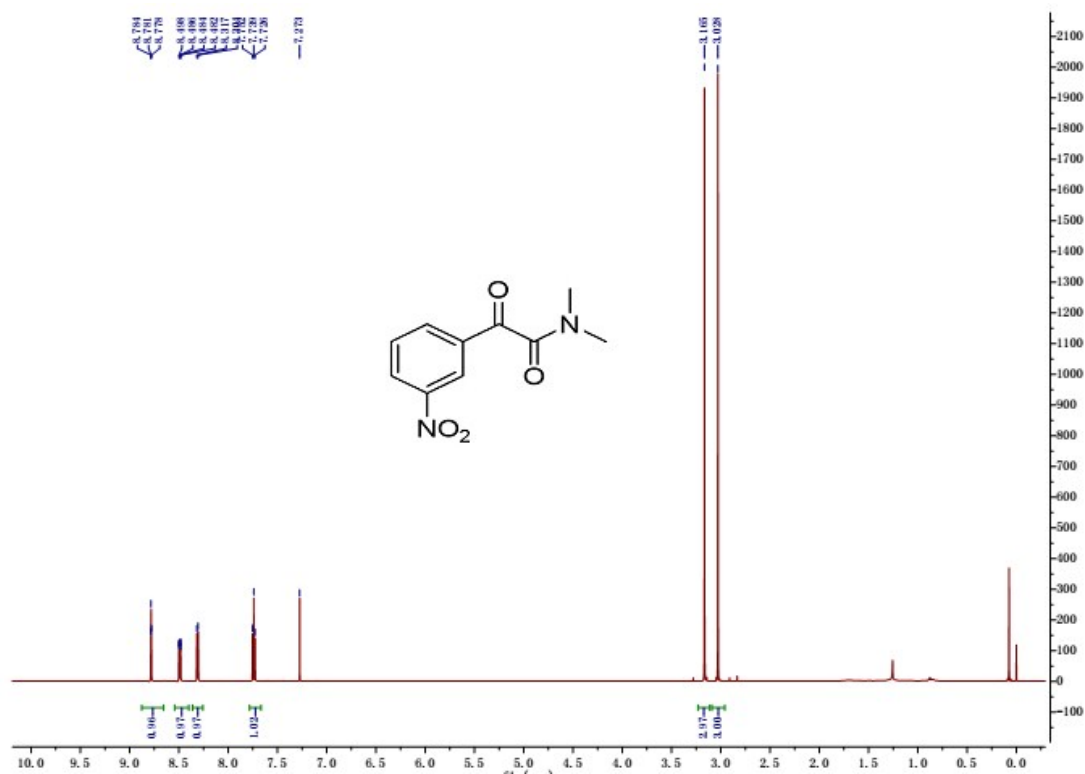
^1H and ^{13}C NMR spectra of **2a** (recorded in 400 MHz NMR apparatus)



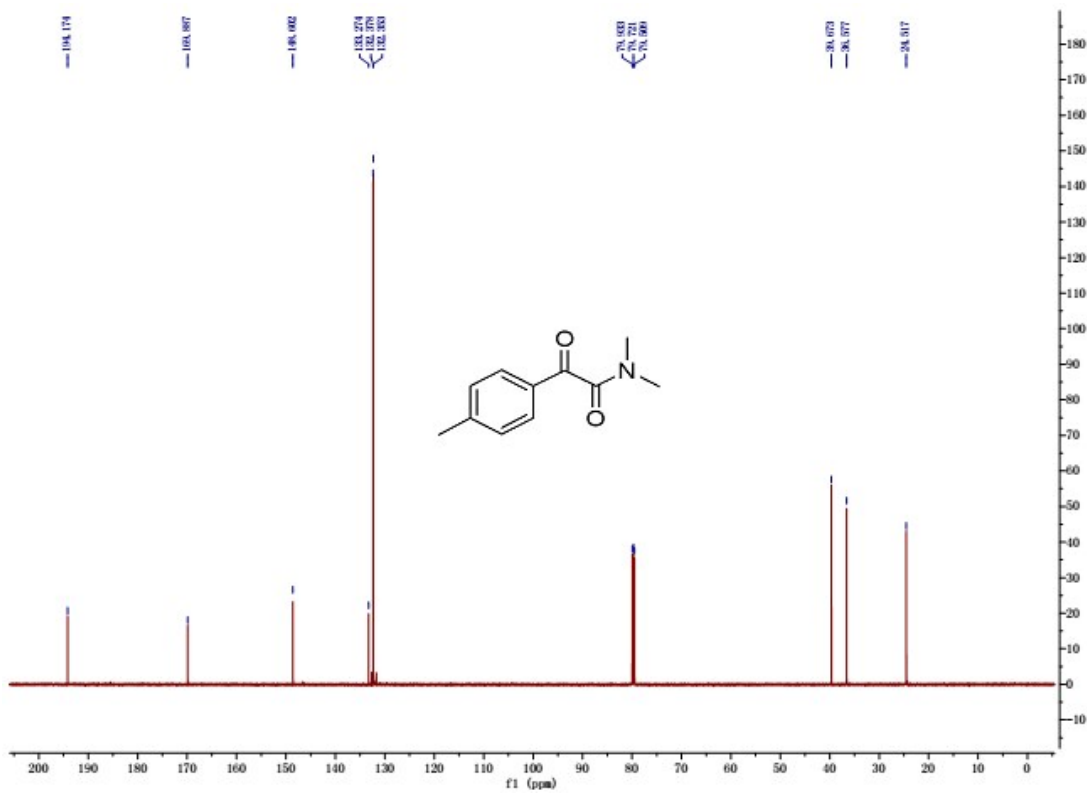
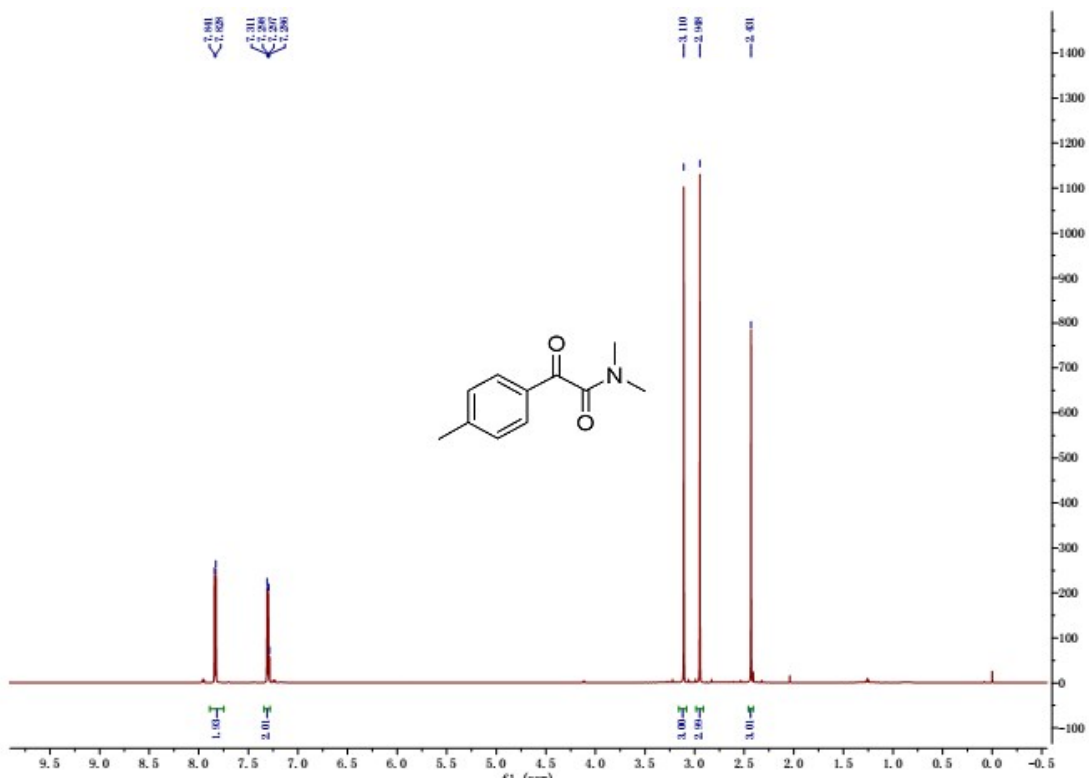
^1H and ^{13}C NMR spectra of **2b** (recorded in 600 MHz NMR apparatus)



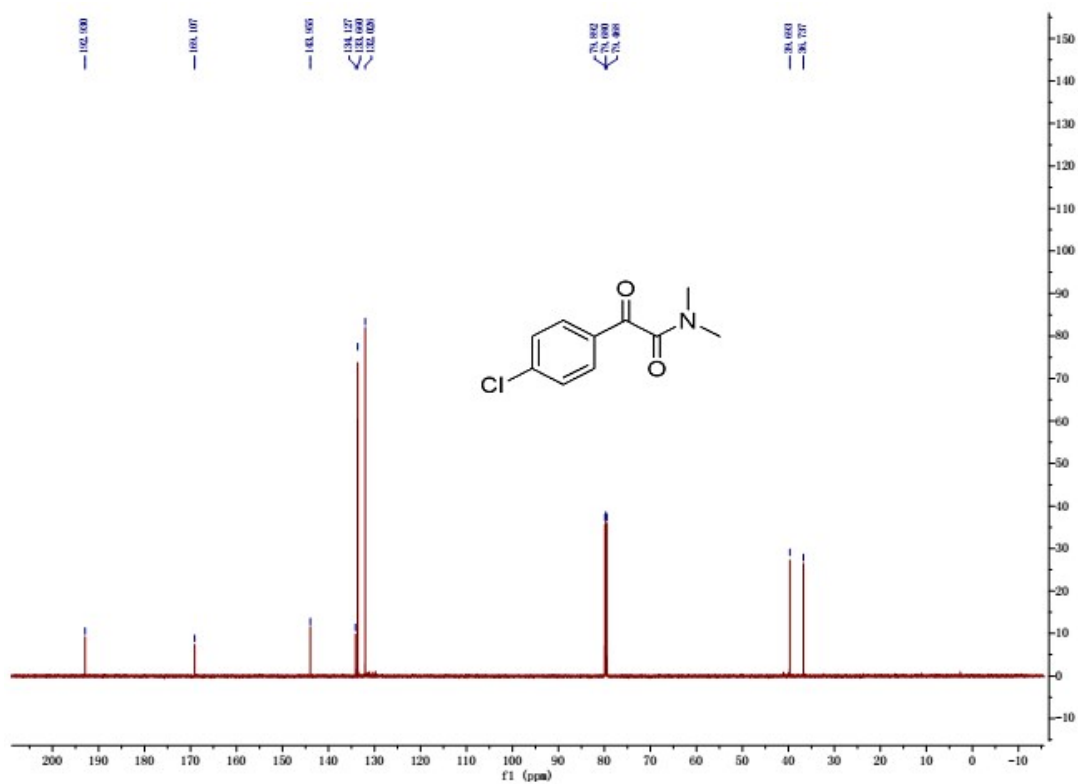
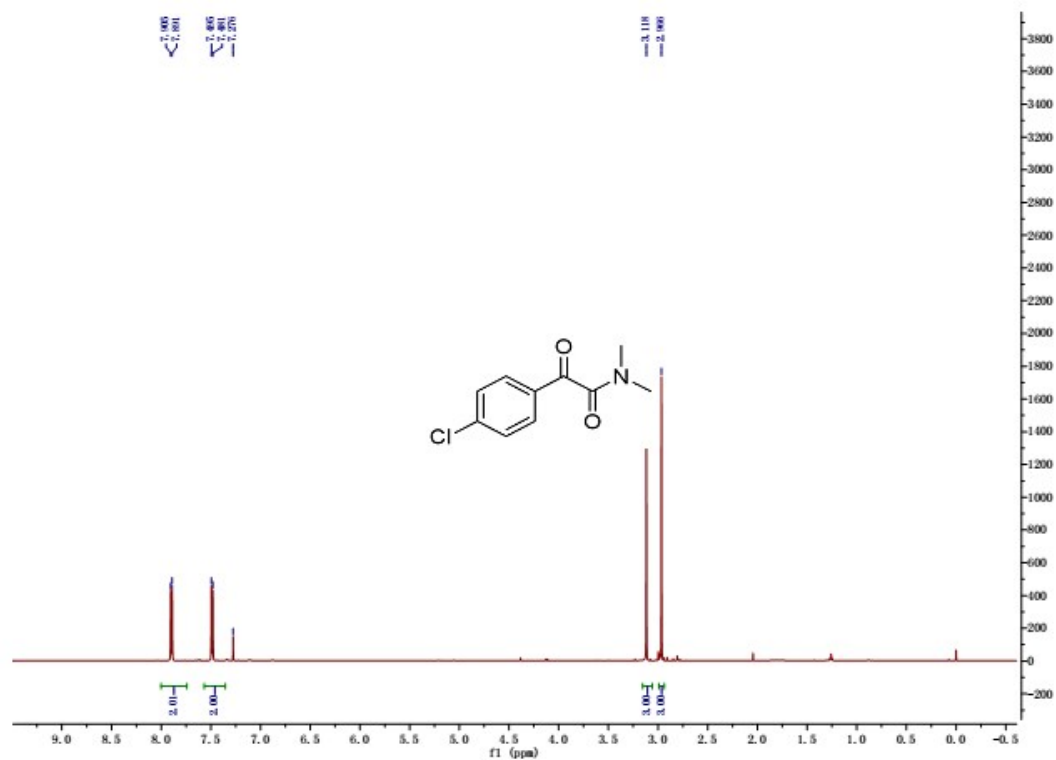
¹H and ¹³C NMR spectra of **2c** (recorded in 600 MHz NMR apparatus)



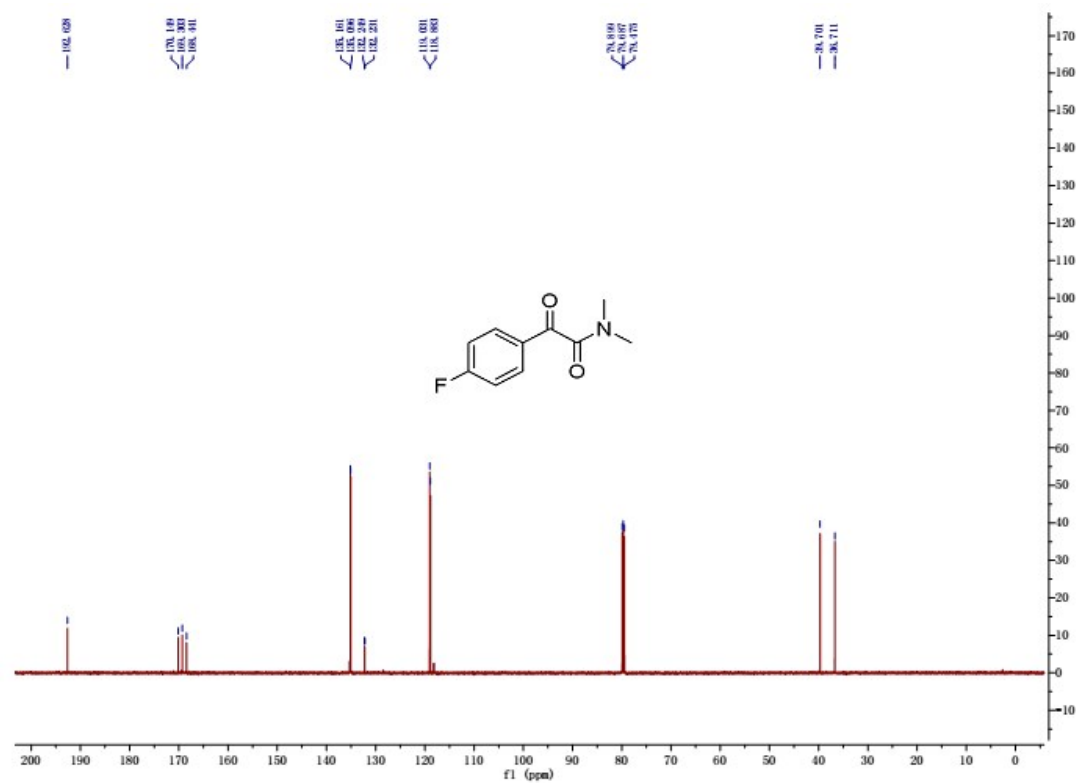
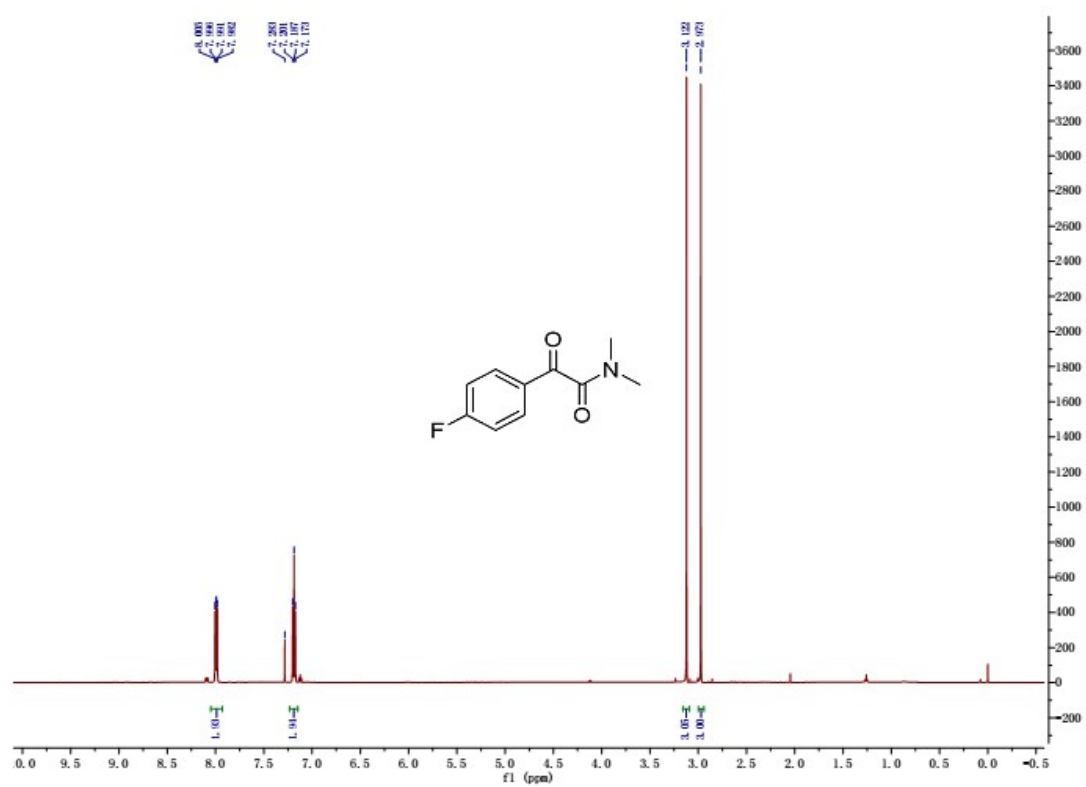
¹H and ¹³C NMR spectra of **2d** (recorded in 600 MHz NMR apparatus)



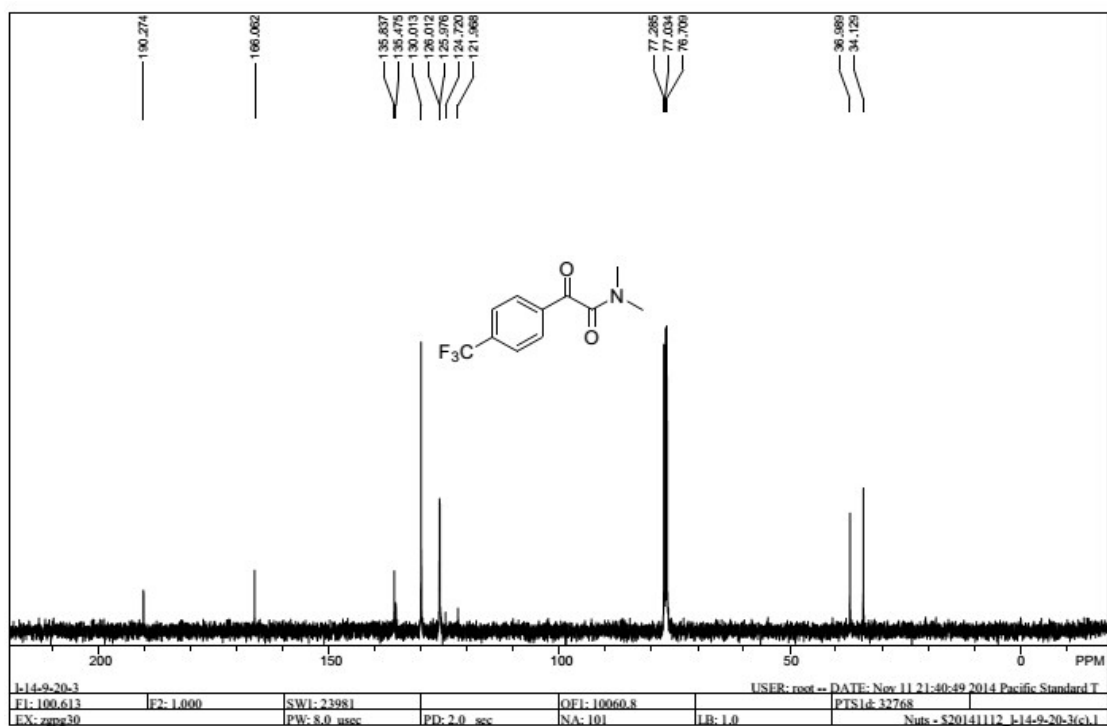
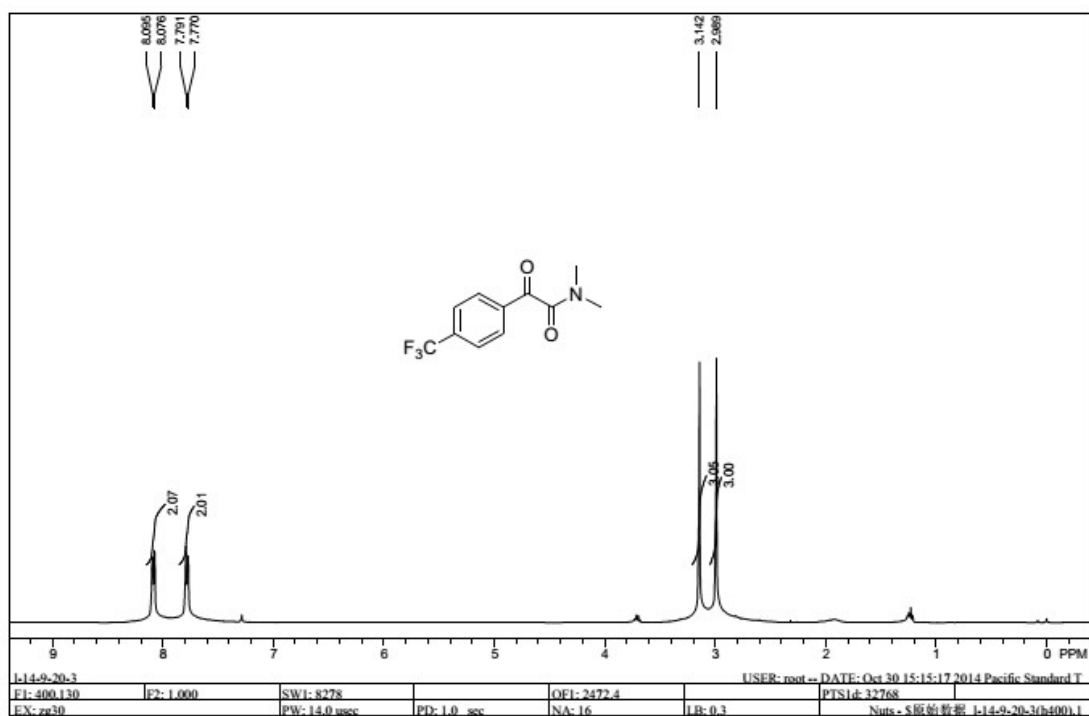
¹H and ¹³C NMR spectra of **2e** (recorded in 600 MHz NMR apparatus)



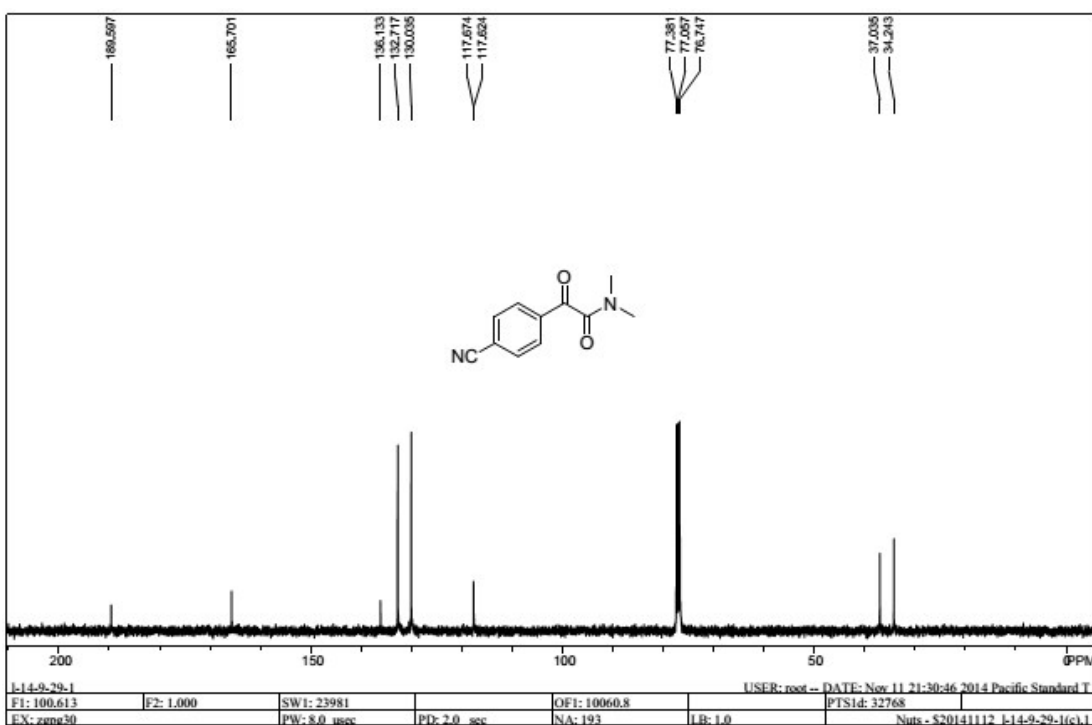
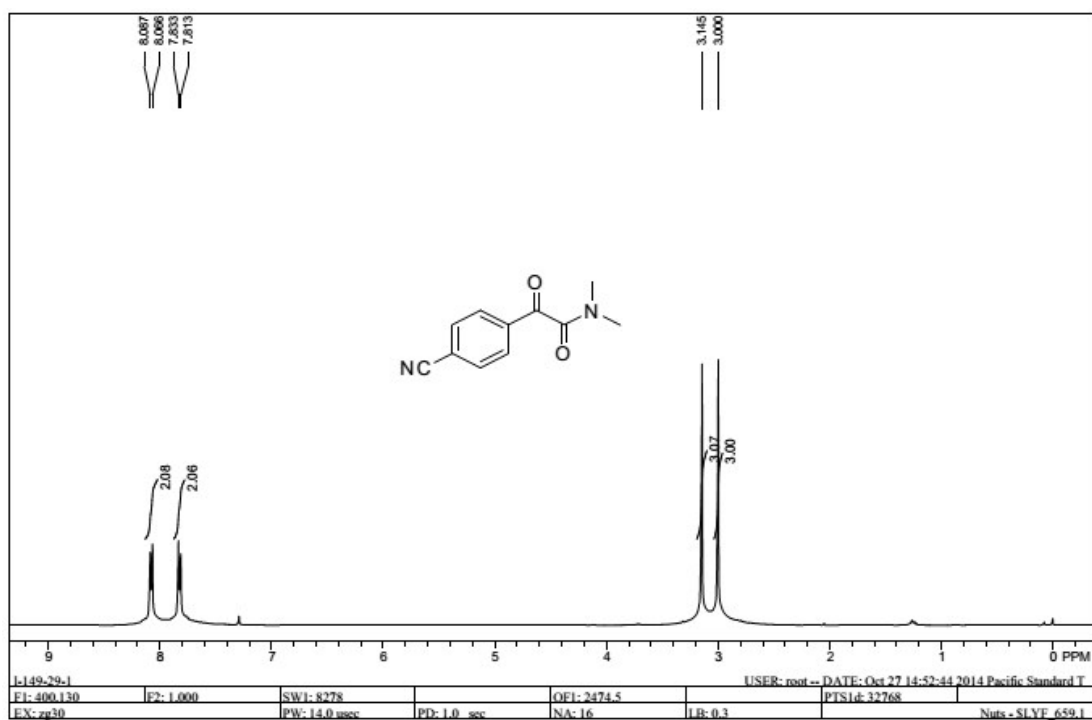
¹H and ¹³C NMR spectra of **2f** (recorded in 600 MHz NMR apparatus)



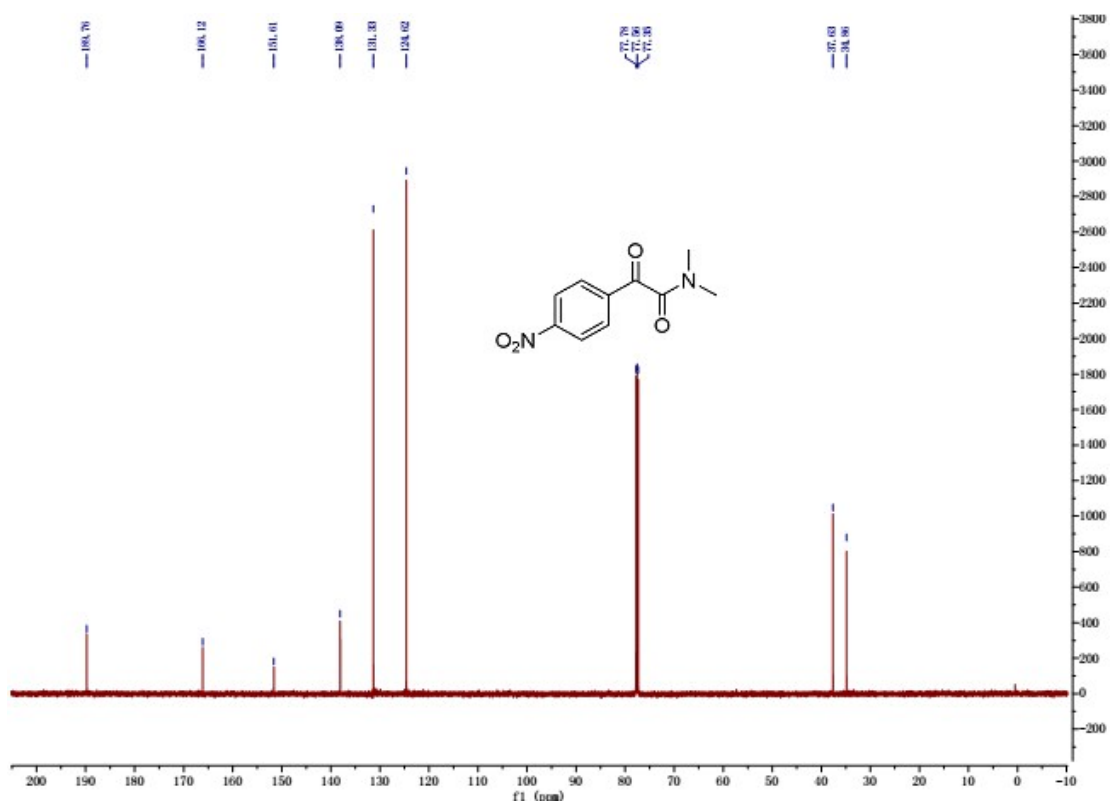
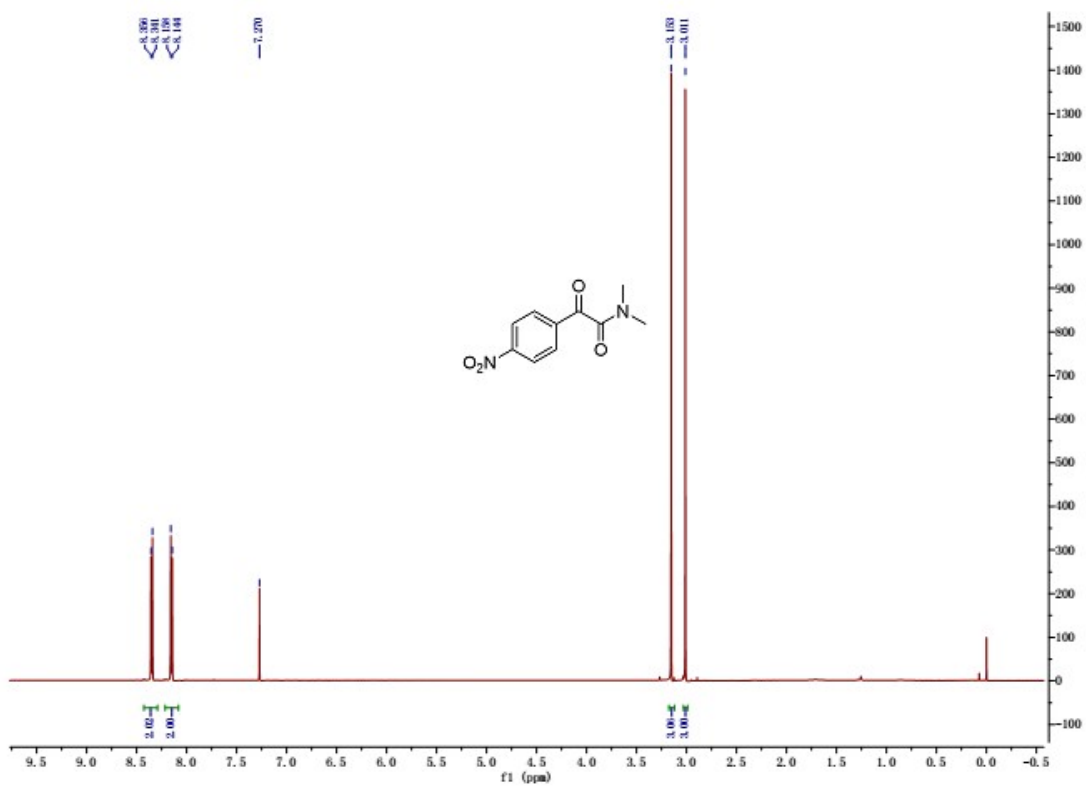
¹H and ¹³C NMR spectra of **2g** (recorded in 400 MHz NMR apparatus)



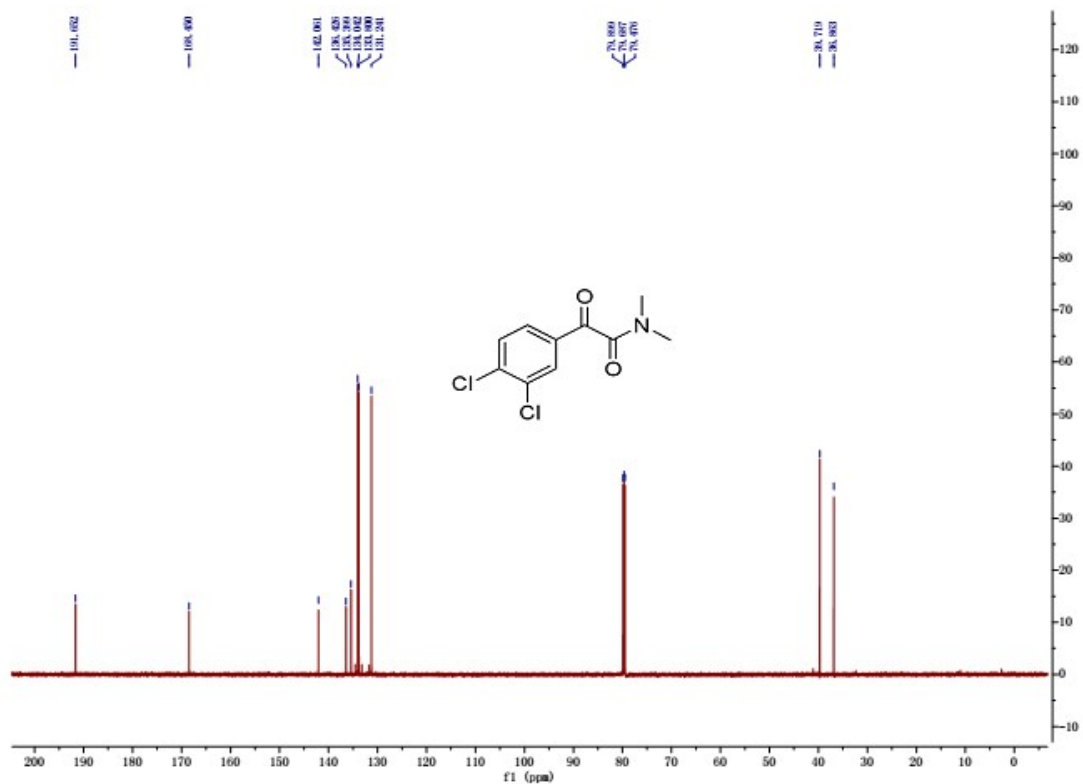
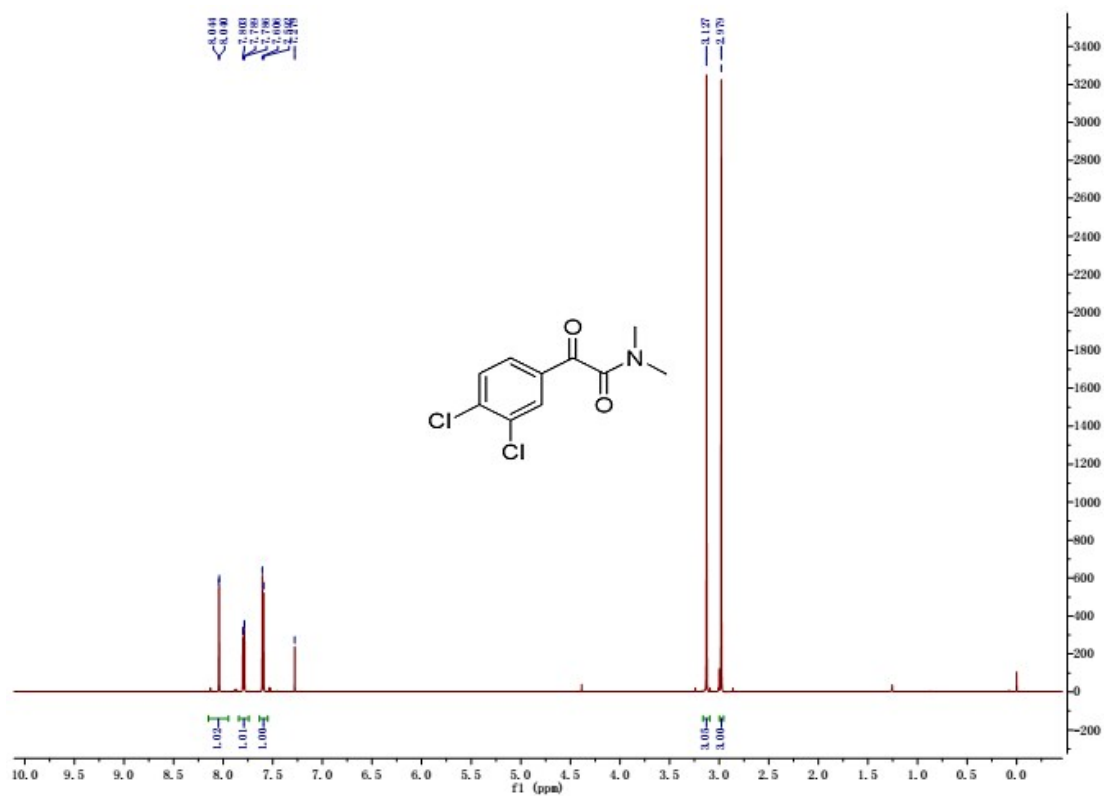
¹H and ¹³C NMR spectra of **2h** (recorded in 600 MHz NMR apparatus)



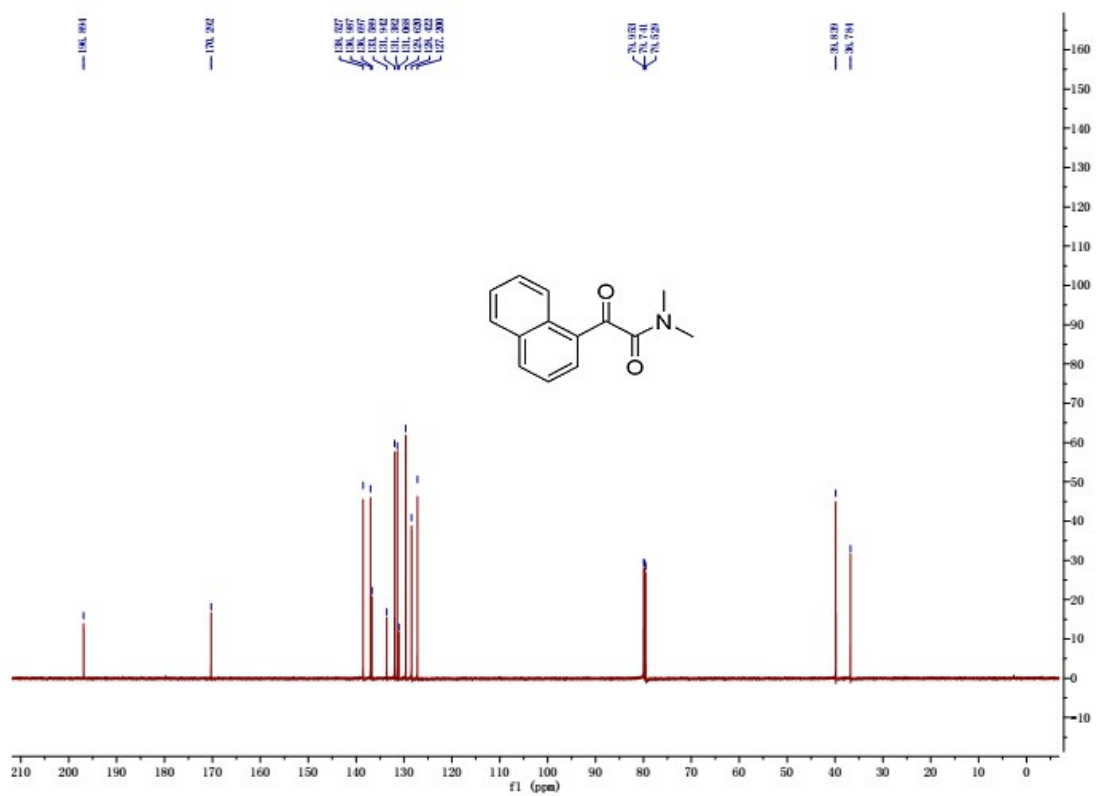
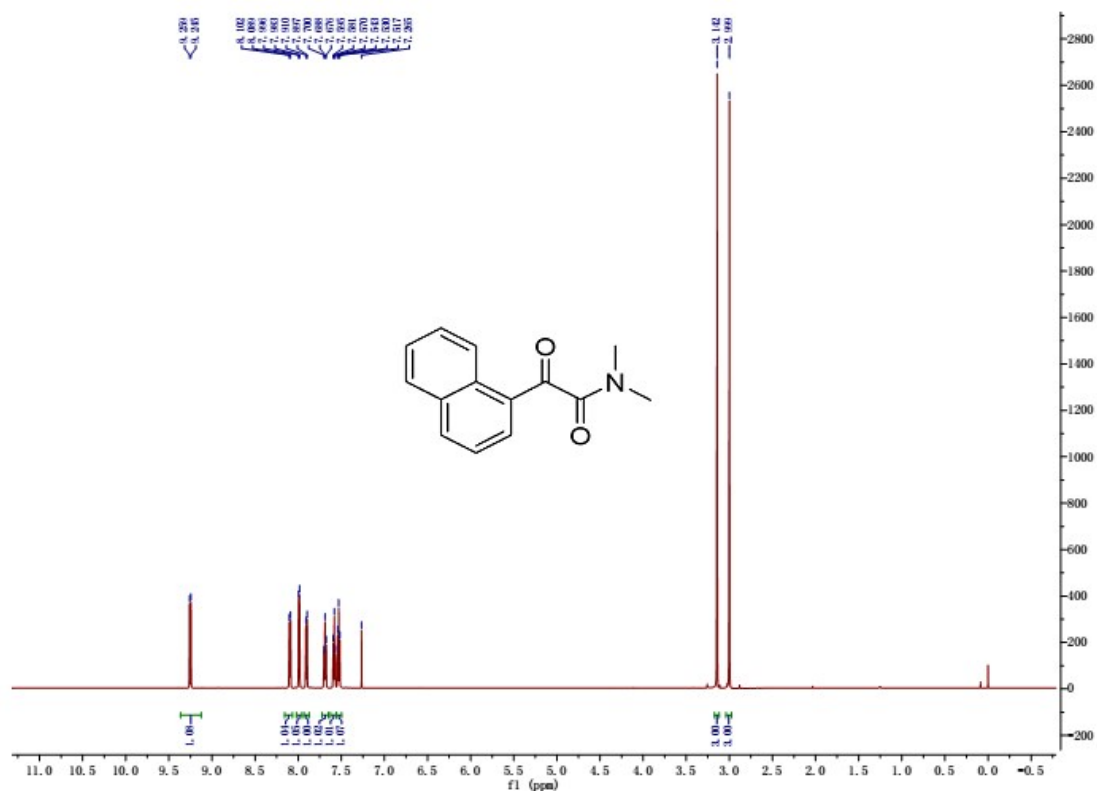
¹H and ¹³C NMR spectra of **2i** (recorded in 600 MHz NMR apparatus)



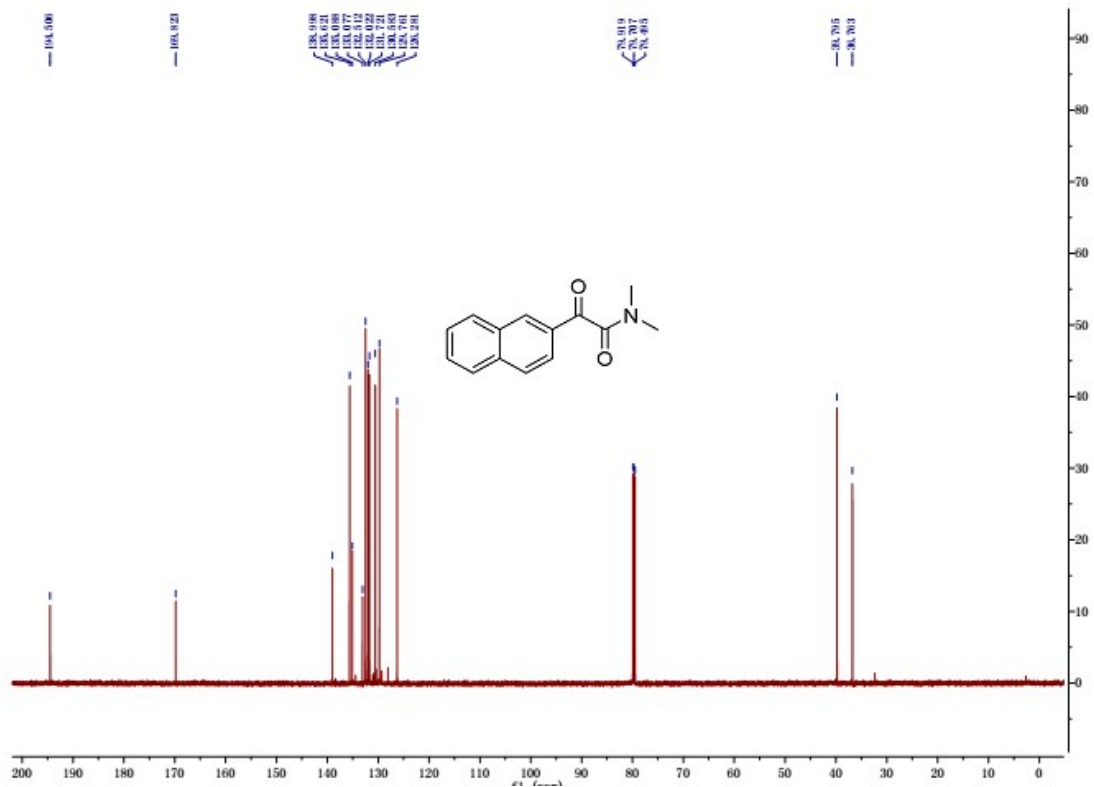
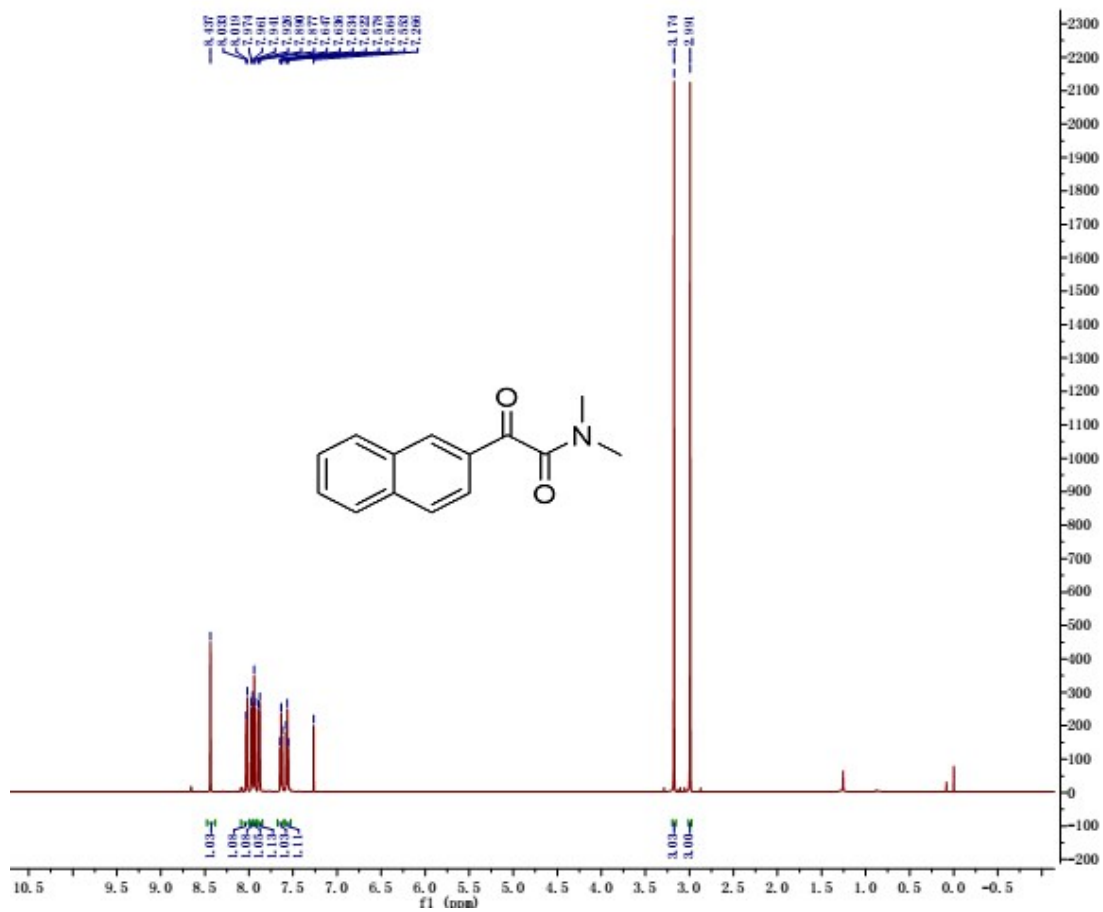
¹H and ¹³C NMR spectra of **2j** (recorded in 600 MHz NMR apparatus)



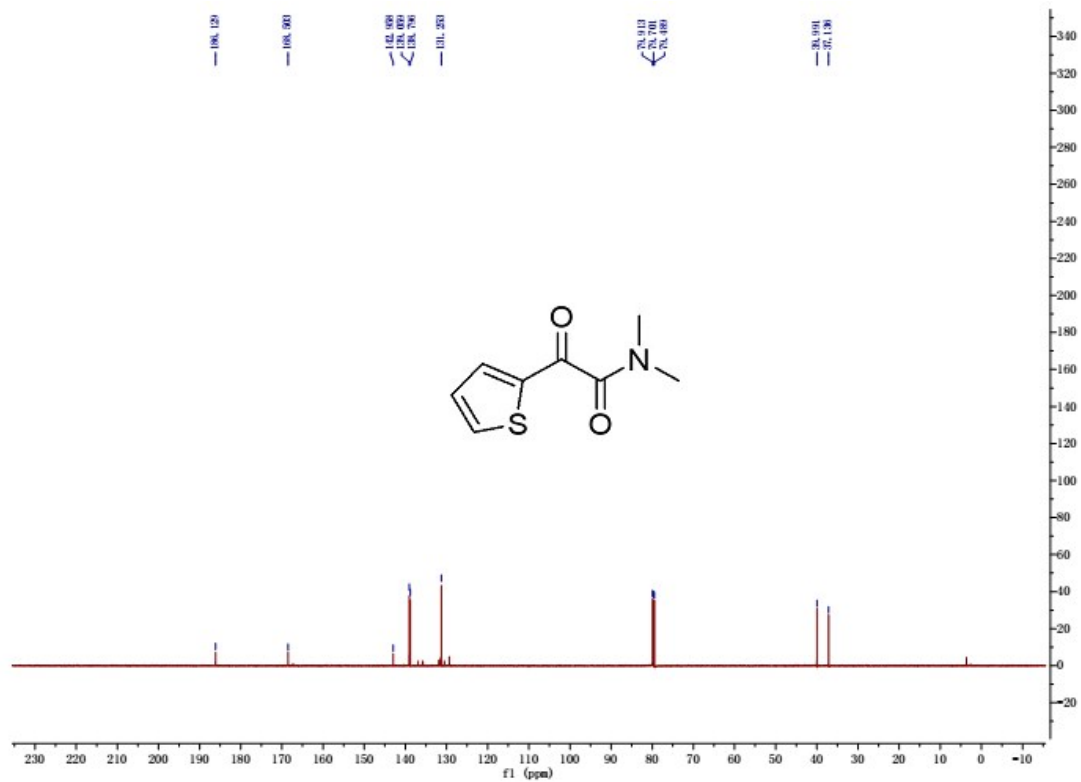
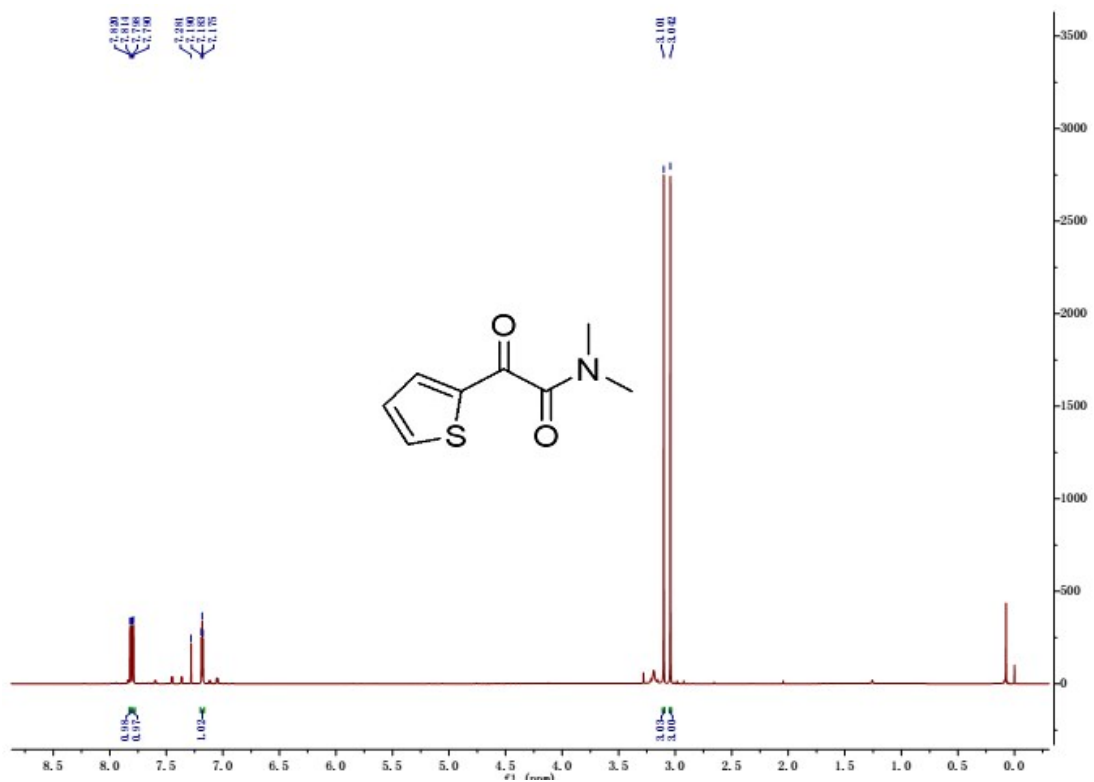
¹H and ¹³C NMR spectra of **2k** (recorded in 600 MHz NMR apparatus)



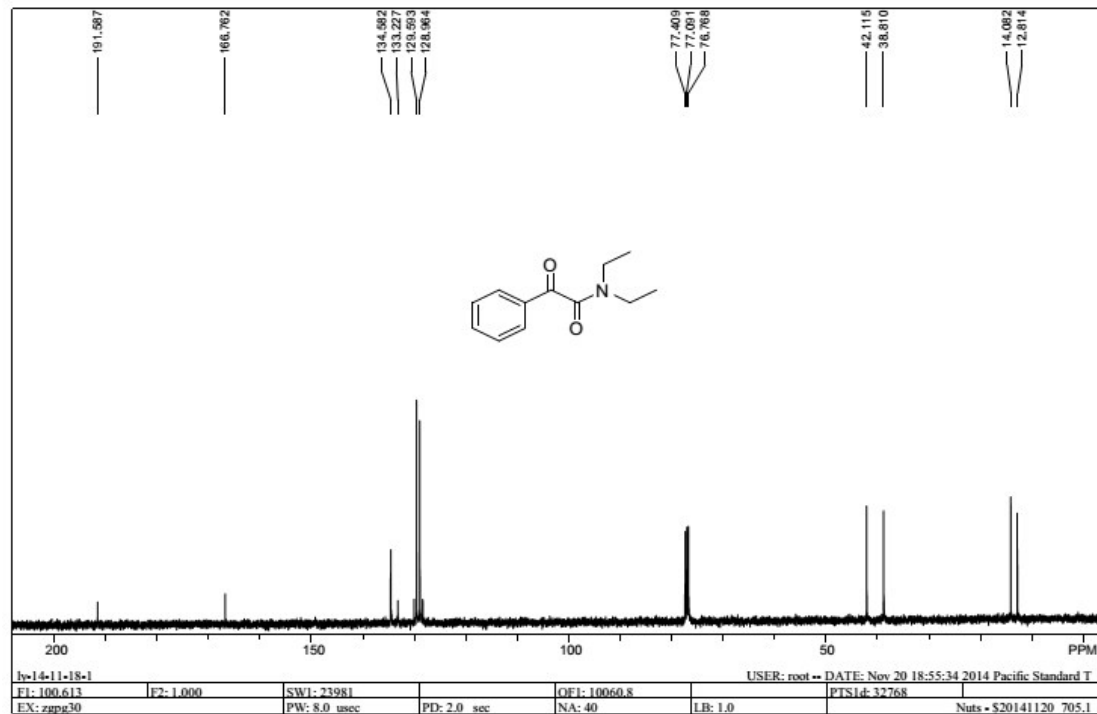
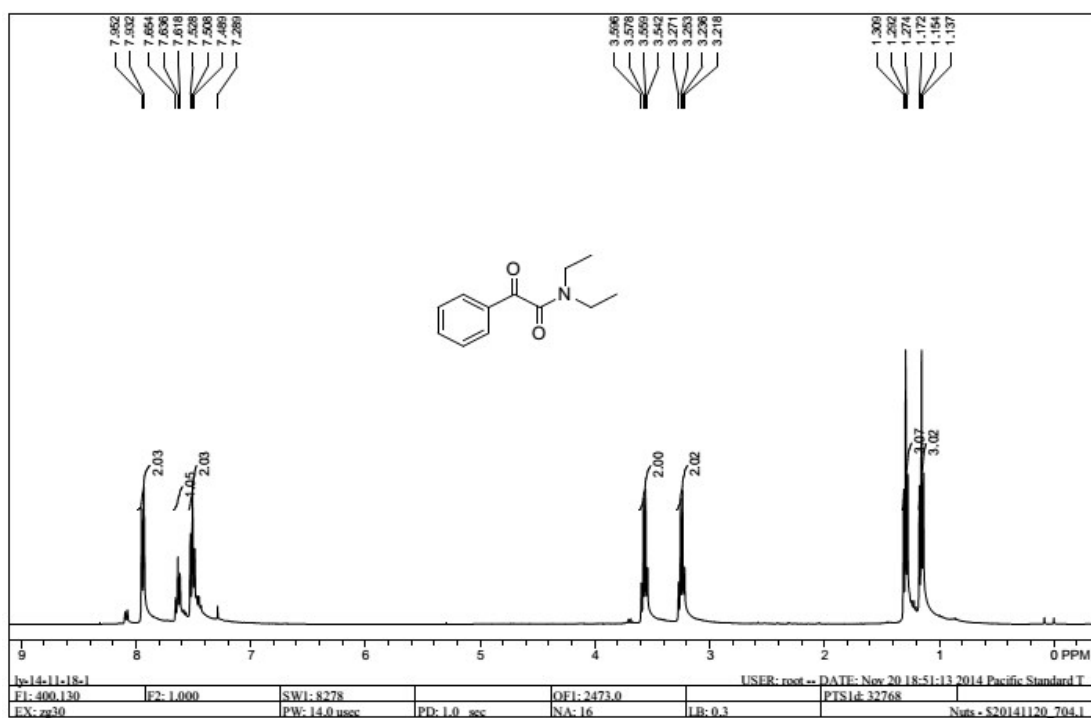
¹H and ¹³C NMR spectra of **2I** (recorded in 600 MHz NMR apparatus)



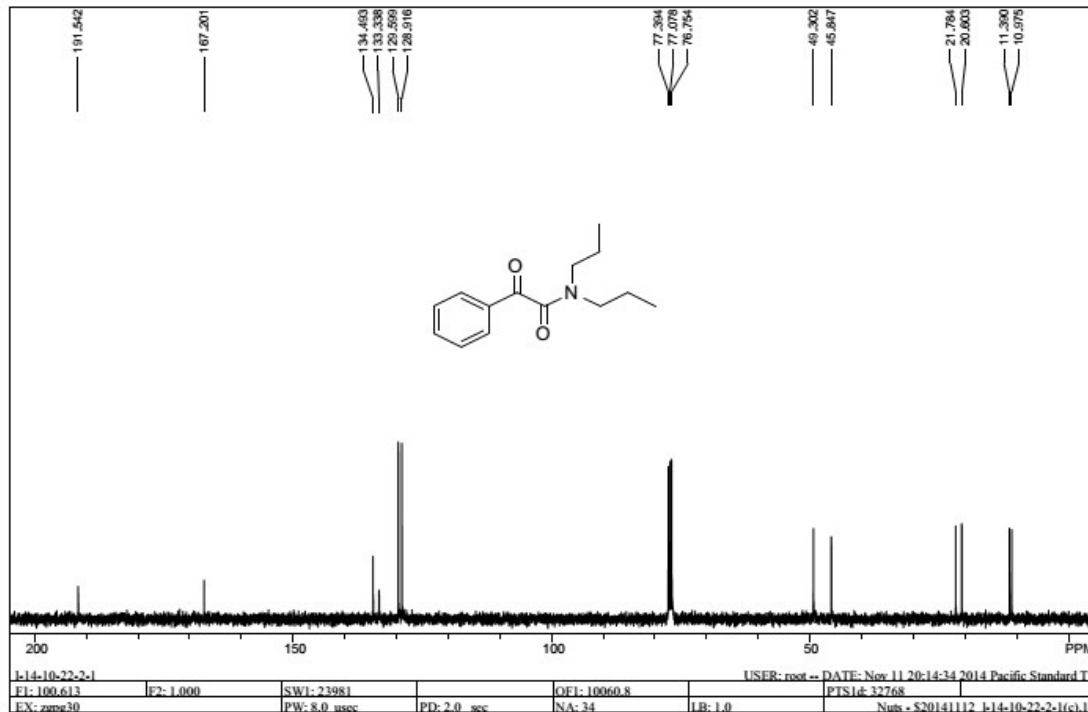
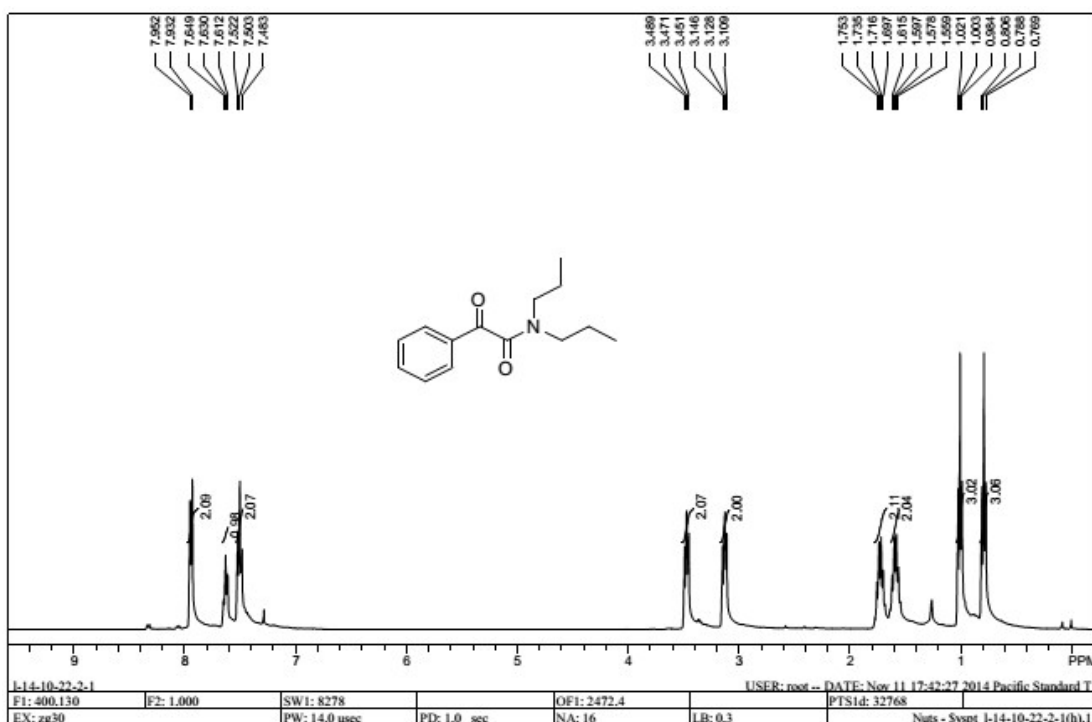
¹H and ¹³C NMR spectra of **2m** (recorded in 600 MHz NMR apparatus)



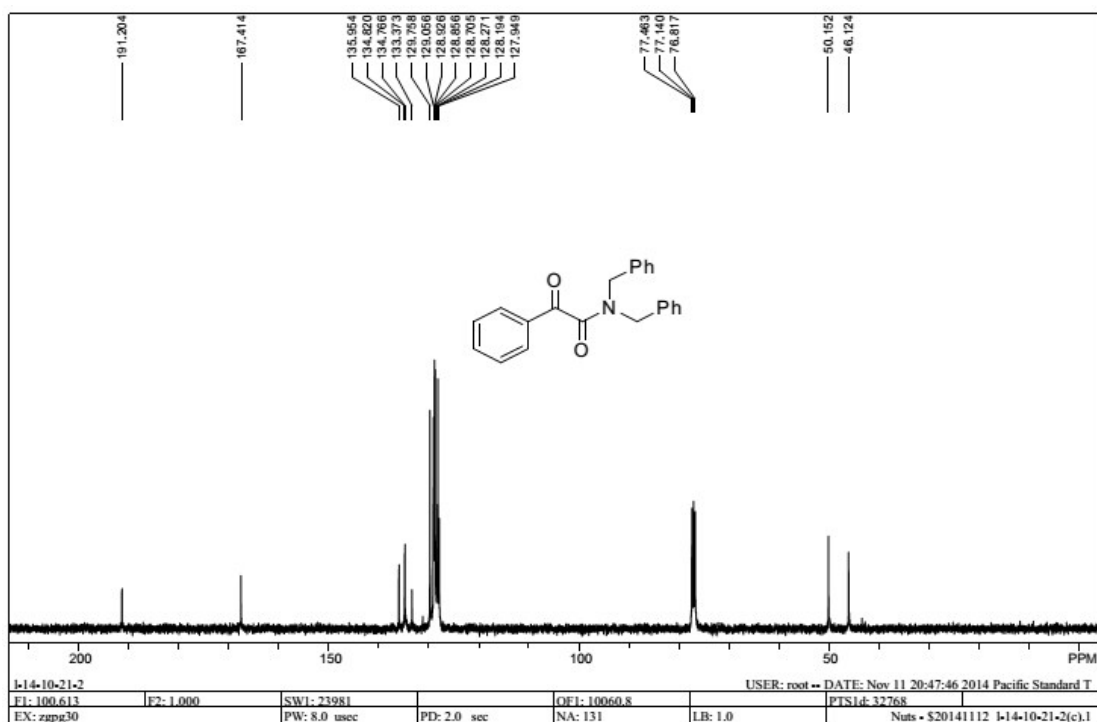
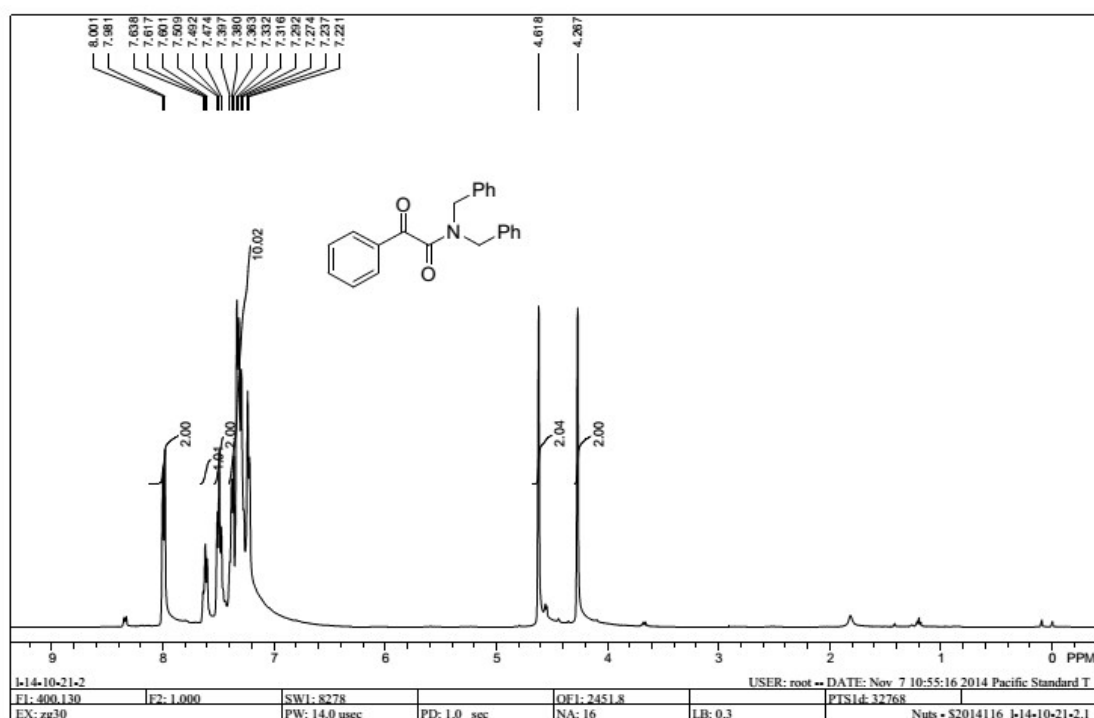
¹H and ¹³C NMR spectra of **2n** (recorded in 400 MHz NMR apparatus)



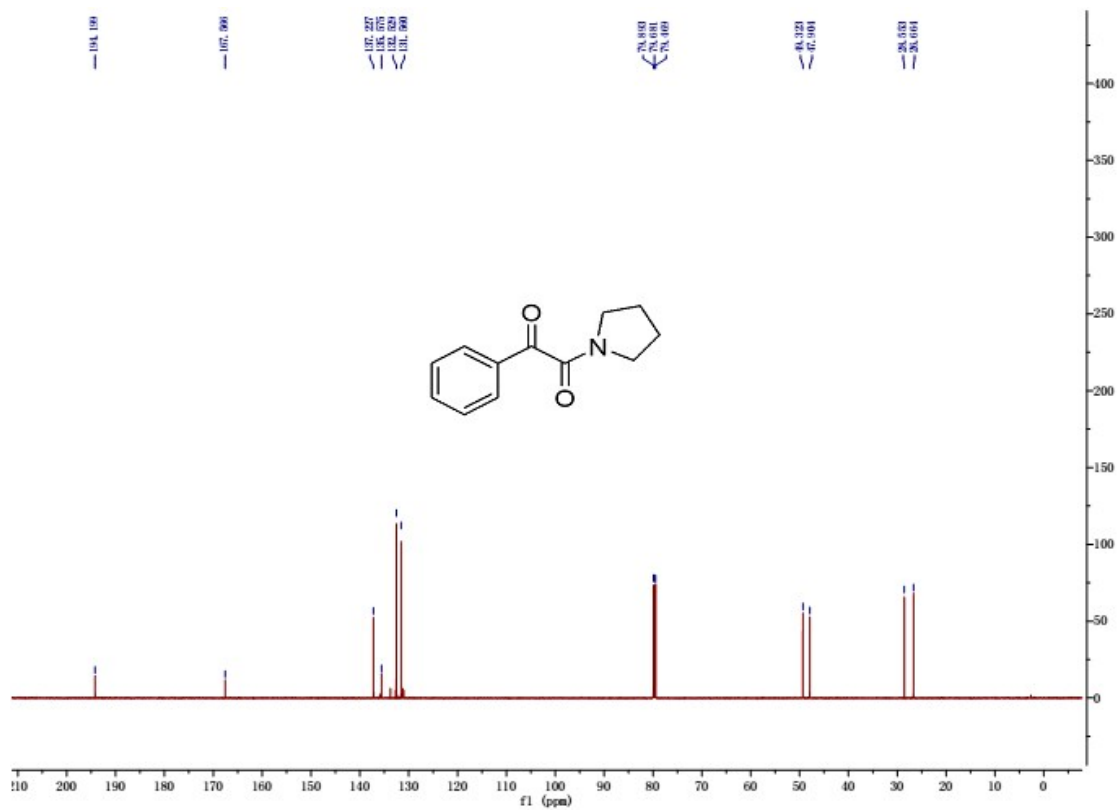
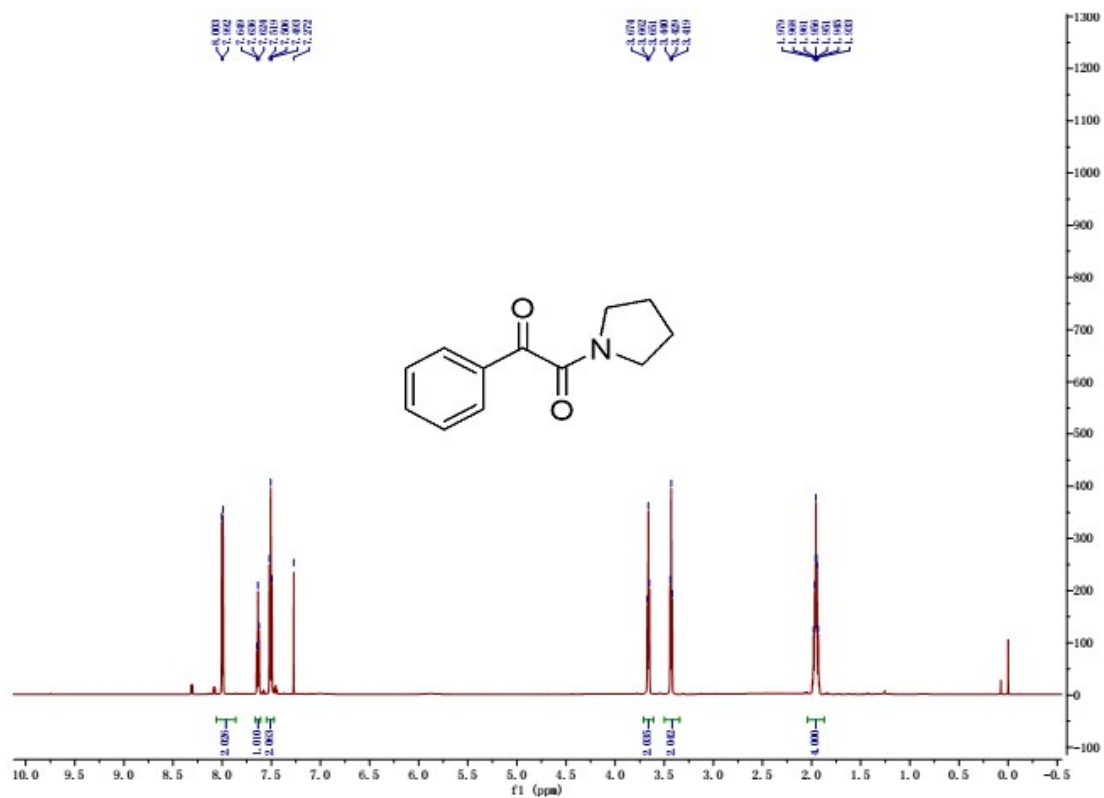
¹H and ¹³C NMR spectra of **2o** (recorded in 400 MHz NMR apparatus)



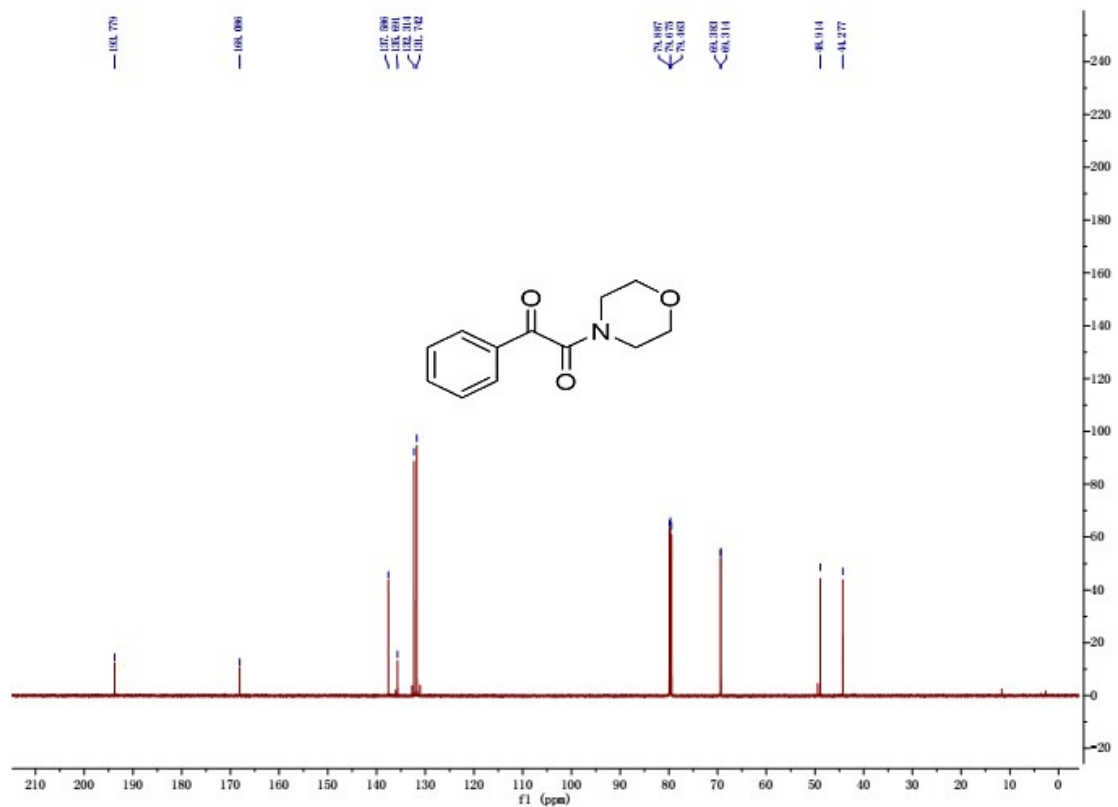
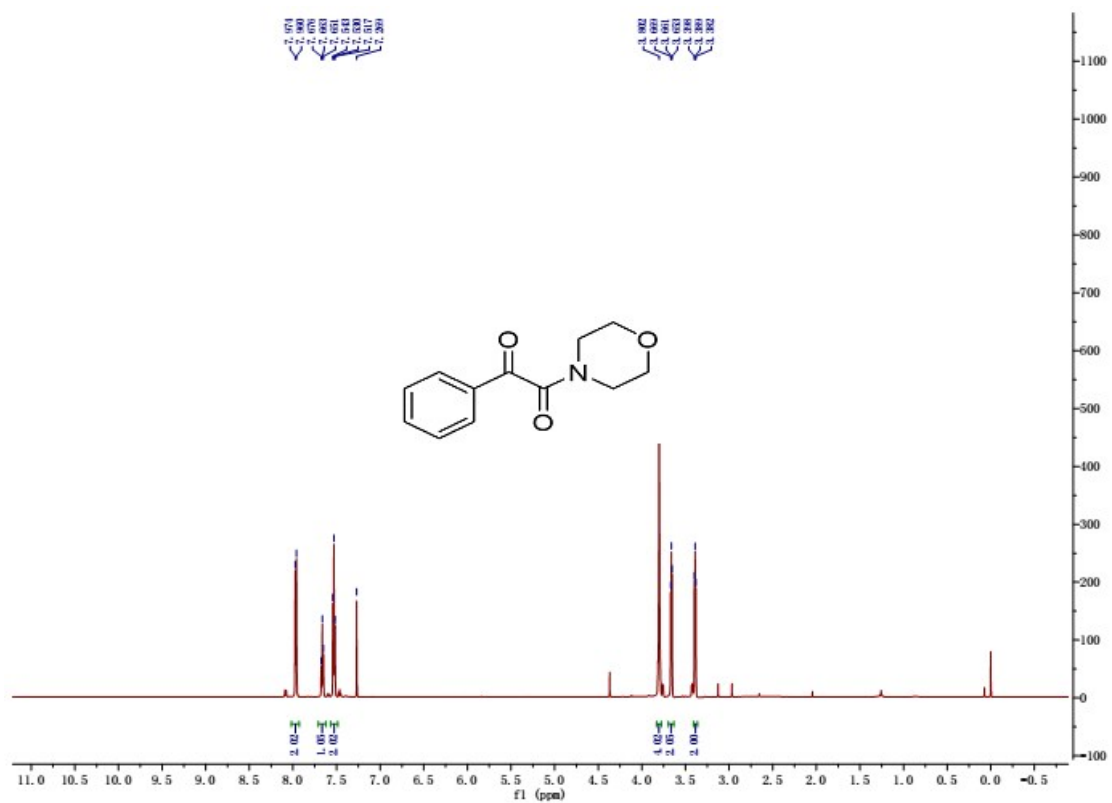
¹H and ¹³C NMR spectra of **2p** (recorded in 400 MHz NMR apparatus)



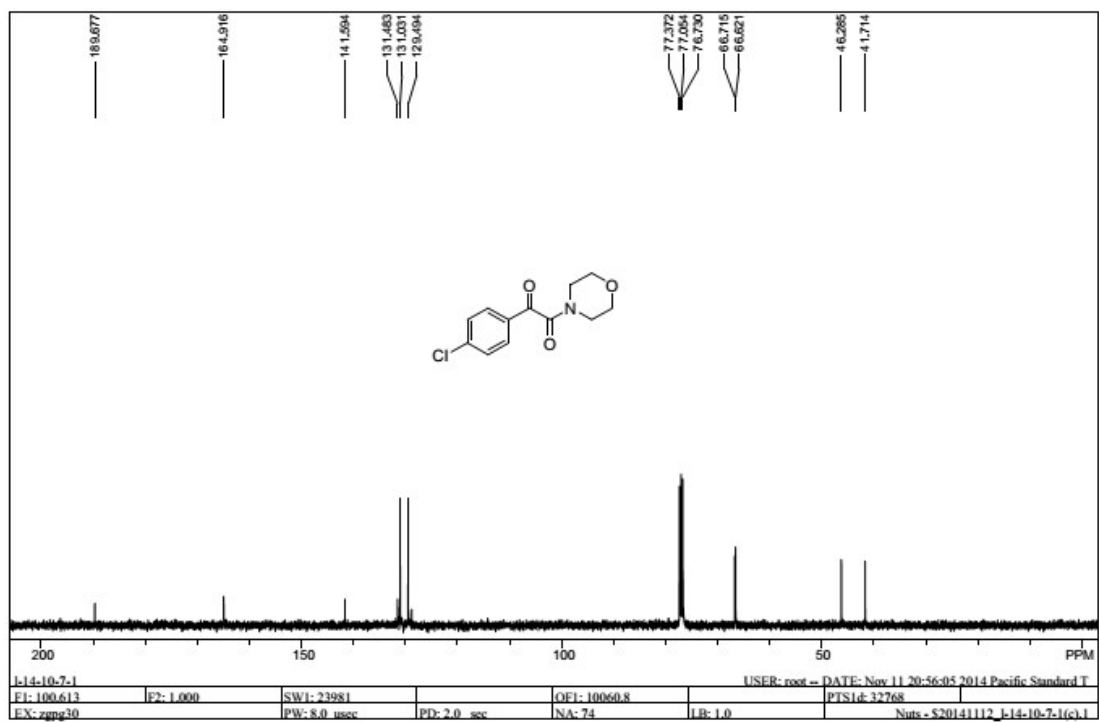
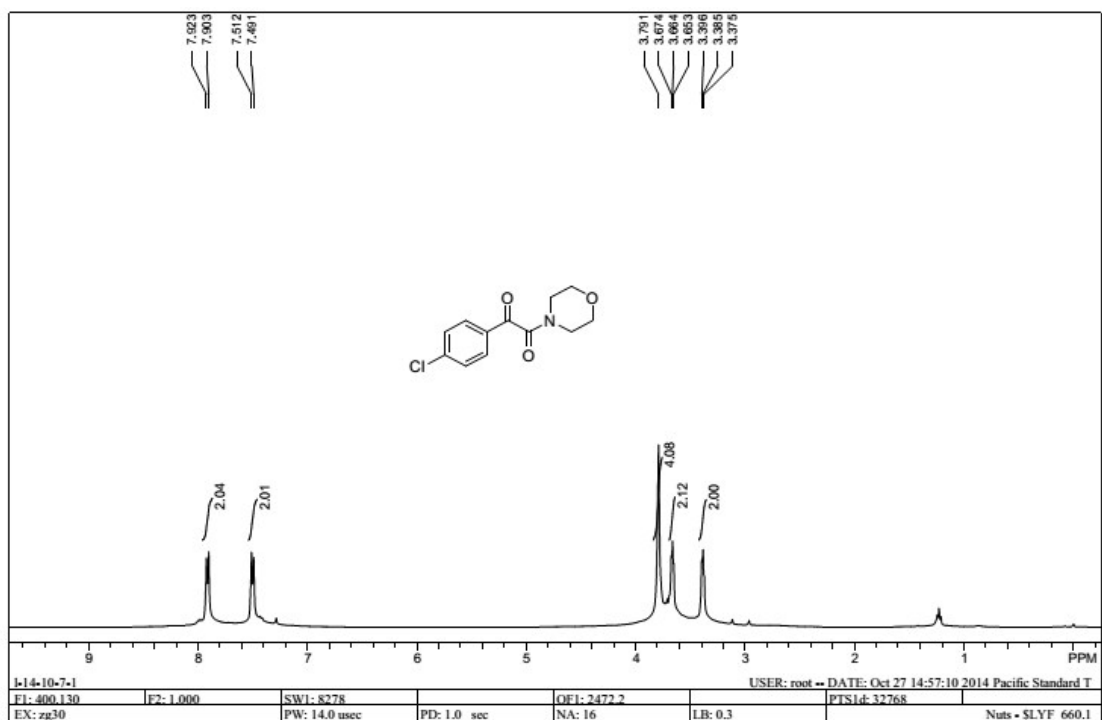
^1H and ^{13}C NMR spectra of **2q** (recorded in 600 MHz NMR apparatus)



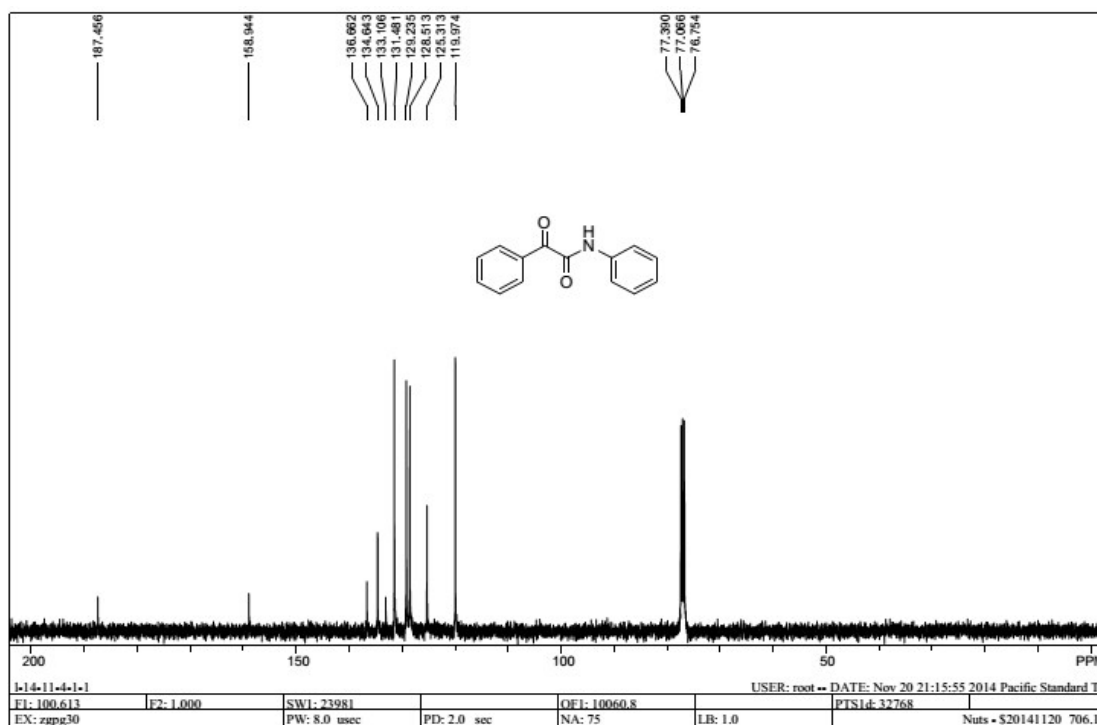
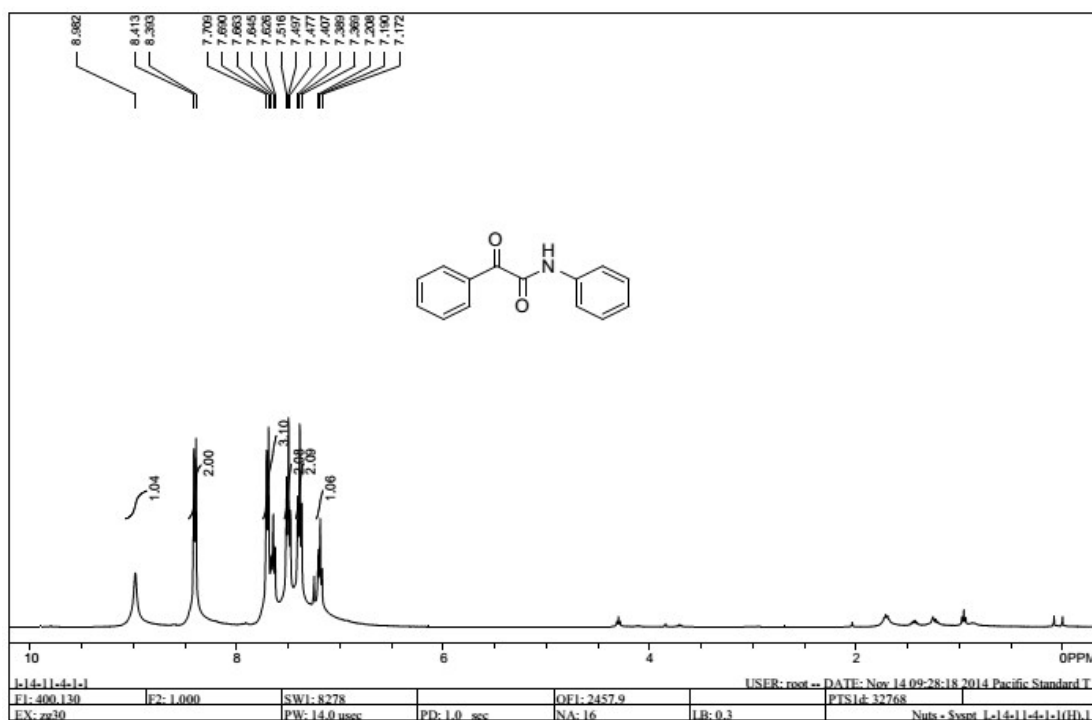
¹H and ¹³C NMR spectra of **2r** (recorded in 600 MHz NMR apparatus)



¹H and ¹³C NMR spectra of **2s** (recorded in 400 MHz NMR apparatus)



^1H and ^{13}C NMR spectra of **2t** (recorded in 400 MHz NMR apparatus)



^1H and ^{13}C NMR spectra of **2u** (recorded in 400 MHz NMR apparatus)

