Supporting Information

Pd-Catalyzed Amidation of 1,3-Diketones with CO and Azides via Nitrene Intermediate

Zheng-Yang Gu[1,2], Jie Chen,[2,3] Ji-Bao Xia[2]*

[1] College of Textiles and Clothing & Key Laboratory for Advanced Technology in Environmental Protection of Jiangsu Province, Yancheng Institute of Technology, Jiangsu, 224003, China.

[2] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Center for Excellence in Molecular Synthesis, Suzhou Research Institute of LICP, Lanzhou Institute of Chemical Physics (LICP), University of Chinese Academy of Sciences, Chinese Academy of Sciences, Lanzhou 730000, China

[3] Suzhou Kintor Pharmaceuticals, Inc. Suzhou, China, 215123

*Corresponding Author: jibaoxia@licp.cas.cn

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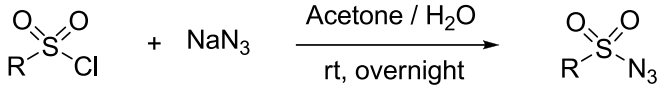
I. General Information

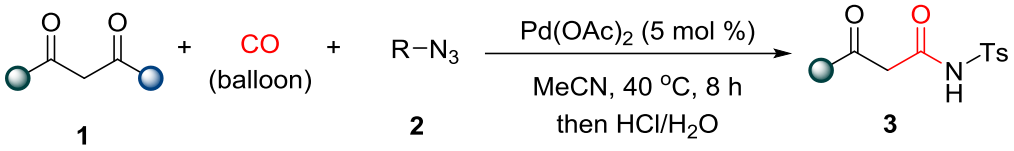
All intermolecular amidation reactions were carried out under atmospheric pressure of carbon monoxide in oven-dried Schlenk tube. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200-300 mesh silica gel in petroleum (bp. 60-90 ^{o}C). The High Resolution MS analyses were performed on Thermo Fisher Scientific LTQ FT Ultra with DART Positive Mode or Agilent 6530 Accurate–Mass Q-TOF LC/MS with ESI mode. NMR spectra were recorded on a 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, using tetramethylsilane as an internal reference DMSO-d_6 and $CDCl_3$ as solvent. Chemical shift values for protons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual proton of DMSO-d_6 (δ 2.50) and residual proton (δ 7.24) in $CDCl_3$. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); p (pentet); m (multiplet); br (broad). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz. Chemical shifts for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of DMSO-d_6 (δ 39.51) and $CDCl_3$ (77.23). Materials were purchased from Tokyo Chemical Industry Co., Aldrich Inc., Alfa Aesar, Adamas, or other commercial suppliers and used as received unless otherwise noted.

II. General Procedure for the Preparation of Sulfonyl Azides

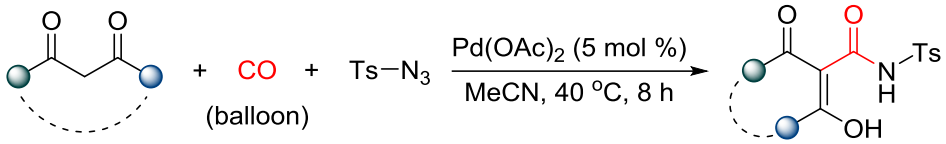


To the solution of sodium azide (2.0 g, 30 mmol) in water (10 mL) was added a solution of sulfonyl chloride (20 mmol) in acetone (20 mL) dropwise over 1 h at 0 ℃. The reaction mixture was warmed up to room temperature and stirred for 11 h. Acetone was removed under reduced pressure and the reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Crude product was used directly without further purification.

III. General Procedure for the Pd-Catalyzed Amidation Reaction

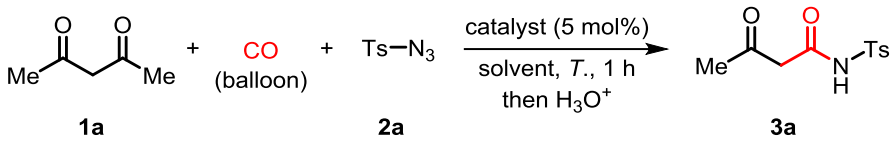


To an oven-dried Schlenk tube (10 mL) was added the organic azide **2** (1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %), and 1,3-diketones **1** (0.5 mmol). The tube was purged and backfilled with CO (3 cycles) from a balloon. Anhydrous CH_3CN (3.0 mL) was injected into the tube. After stirring at 40 °C for 8 h under CO atmosphere (balloon), the reaction mixture was quenched with 2.0 M HCl (2 mL) and stirred for another 1 h. The mixture was extracted with EtOAc (3×5 mL), dried over $NaSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc 3:1~1:1) to give the desired product **3**.



To an oven-dried Schlenk tube (10 mL) was added the organic azide **2a** (1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %), and 1,3-dicarbonyl compound **1** (0.5 mmol). The tube was purged and backfilled with CO (3 cycles) from a balloon. Anhydrous CH_3CN (3.0 mL) was injected into the tube. After stirring at 40 °C for 8 h under CO atmosphere (balloon), the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc 3:1~1:1) to give the desired product **4**.

IV. Table S1. Optimization of the Reaction Conditions[a]



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

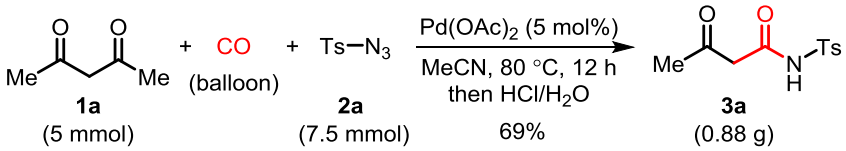
entry	catalyst	solvent	T (℃)	yield (%)[b]
1	$[Rh(cod)Cl]_2$	MeCN	80	32
2	$Co(OAc)_2$	MeCN	80	trace
3	$Cu(OAc)_2$	MeCN	80	trace
4	$Pd(OAc)_2$	MeCN	80	57
5	$PdCl_2$	MeCN	80	trace
6	$Pd(PPh_3)_4$	MeCN	80	trace
7	$Pd(dba)_2$	MeCN	80	trace
8	$Pd(TFA)_2$	MeCN	80	58
9	$Pd(OPiv)_2$	MeCN	80	67
10	$Pd(OAc)_2$	toluene	80	8
11	$Pd(OAc)_2$	THF	80	trace
12	$Pd(OAc)_2$	1,4-dioxane	80	11
13	$Pd(OAc)_2$	DCE	80	trace
14[d]	$Pd(OAc)_2$	MeCN	80	87
15[d]	$Pd(OAc)_2$	MeCN	40	85 (82)[c]
16[d]	$Pd(OAc)_2$	MeCN	25	61
17[d]	-	MeCN	40	N.R.

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), CO (balloon), catalyst (5 mol%), solvent (3 mL), 8 h, then 2N HCl (2 mL), 25 °C, 1 h. [b]Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield. [d]**2a** (1.0 mmol) was used.

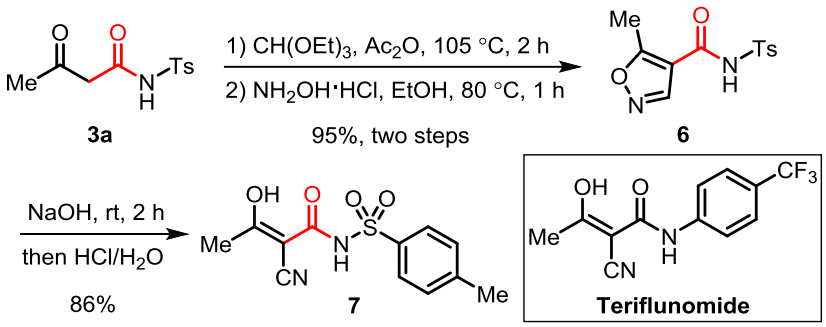
[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), CO (balloon), $Pd(OAc)_2$ (5 mol%), MeCN (3 mL), 40 ℃, 8 h, isolated yield was provided. [b]80 ℃, 18 h.

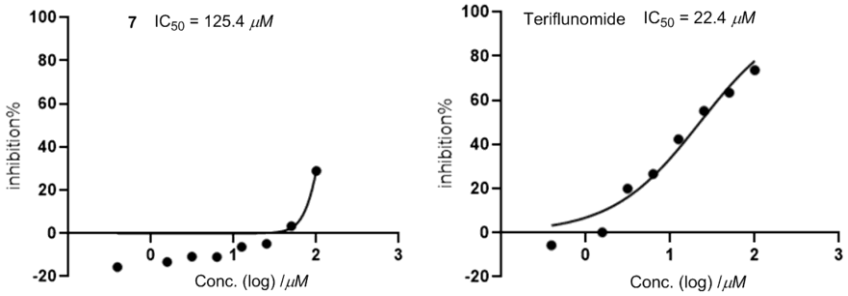
Scheme S1. Synthetic Applications

a) Scale-up reaction for the synthesis of **3a**

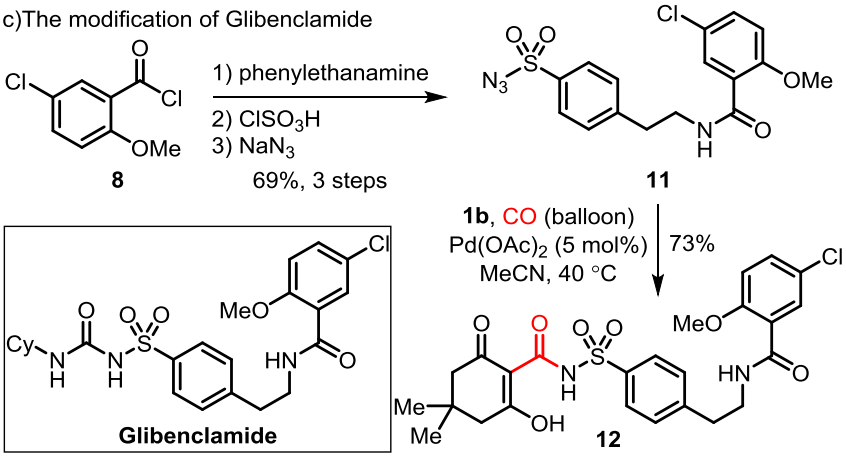


b) Derivatization of **3a** for the synthesis of Tefiflunomide analoge **7**

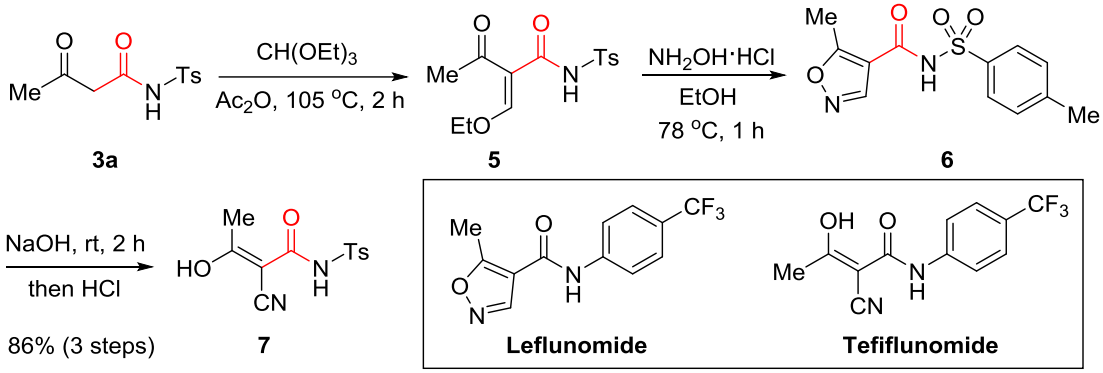




c)The modification of Glibenclamide



V. Synthesis and Bioactivity Evaluation of Sulfonamide Analoge of Leflunomide and Teriflunomide: 6 and 7



Amide **3a** (127.6 mg, 0.5 mmol), acetic anhydride (3 equiv) and triethylorthoformate (1.2 equiv) were stirred at 105 ℃. The reaction were monitored by TLC (Hexanes/EtOAc: 70/30) until its completion. The mixtures were then concentrated to dryness. The residue was dissolved in CH_2Cl_2 and washed with cold brine. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated affording product **5** and used directly for the next step.

To a solution of above product **5** in ethanol (3 mL) was slowly added an ice cooled solution of hydroxylamine hydrochloride (1.2 equiv) in 2 M NaOH (2 mL). The mixture was heated to reflux for 1 hour, then cooled to room temperature, and evaporated to dryness. The residue was dissolved in EtOAc (20 mL) and water (10 mL). The organic layer was separated, extracted with water to remove inorganics, dried with Na_2SO_4 and the organic layer was evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc 3:1~1:1) to give the desired product **6** (133.1 mg, 95%).

To a solution of above product **6** in 2 M NaOH (2 mL), the mixture was stirred for 2 h until the solution transparent. Then pH value of the solution was adjusted to 6 with hydrochloric acid, accompanied by a large amount of white solids. The solution was filtered, washed with water, and dried affording the product **7** (120.5 mg, 86%).

Bioactivity Evaluation of 6, 7, and Teriflunomide

Cell Culture

The Jurkat cell lines were obtained Chinese Academy of Sciences (Shanghai, China) and cultured in RPMI1640 medium supplemented with 20% or 10% fetal bovine serum and 1% Penicillin-streptomycin. All cells were maintained in CO_2 incubator with a controlled humidified atmosphere composed of 95% air and 5% CO_2 at 37 ℃.

Cell Viability Assay

The Jurkat cells were plated in 96-well plate at 2×10^4 cells /well and the test concentrations were adjusted and multiple concentrations were set within the range of 0.39 μM to 100 μM for 72 h. Then the cell viability was assessed using

CellTiter-Glo® Luminescent Cell Viability (Promega) that measures ATP levels.

Result

To evaluate whether inhibition the dihydroorotate dehydrogenase (DHODH) has the antiproliferation effect in vitro, the DHODH inhibition by compounds **6**, **7**, and Teriflunomide was tested for Jurkat cell, providing the IC_{50} of 112.8, 125.4, and 22.4 μM, respectively.

Compound **6**

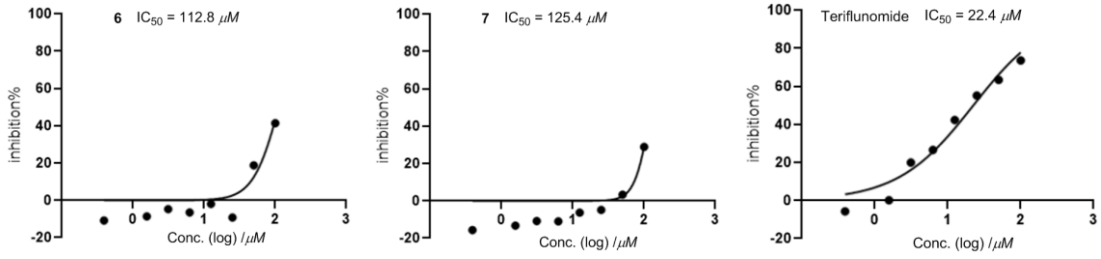
Conc. (μM)	100	50	25	12.5	6.25	3.125	1.5625	0.78125	0.390625	DMSO
run 1	428503	571717	971954	840580	871823	854092	911722	808679	908649	865991
run 2	499226	738037	865532	858270	878769	879234	903278	848788	923592	867861
run 3	544436	730725	905218	861564	923713	897869	913819	862225	952103	779310
average	490721.7	680159.7	914234.7	853471.3	891435	877065	909606.3	839897.3	928114.7	837720.7
inhibition%	41.42	18.81	-9.13	-1.88	-6.41	-4.70	-8.58	-0.26	-10.79	

Compound **7**

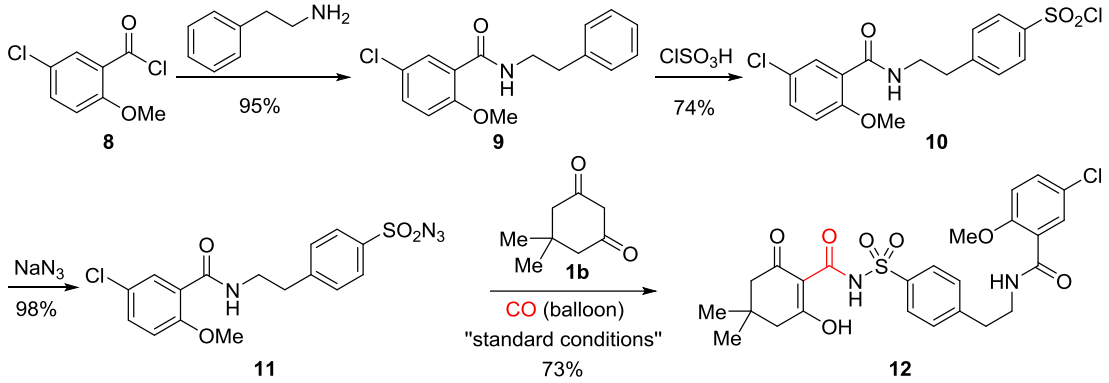
Conc. (μM)	100	50	25	12.5	6.25	3.125	1.5625	0.78125	0.390625	DMSO
run 1	606323	791339	882608	873386	915174	892538	922020	846551	941127	847569
run 2	610794	840406	905049	867986	928719	914754	923581	833836	942626	839385
run 3	519959	730781	824807	856406	892081	899708	870324	807654	888453	756823
average	579025.3	787508.7	870821.3	865926	911991.3	902333.3	905308.3	829347	924068.7	814592.3
inhibition%	28.92	3.32	-6.90	-6.30	-11.96	-10.77	-11.14	-1.81	-13.44	

Teriflunomide

Conc. (μM)	100	50	25	12.5	6.25	3.125	1.5625	0.78125	0.390625	DMSO
run 1	181908	275338	329273	421881	548100	607392	733781	800699	796389	715234
run 2	219025	290801	355858	466704	585660	660978	790467	822836	817190	810792
run 3	202629	271265	341788	430563	545913	564122	761019	960515	804602	-
average	201187.3	279134.7	342306.3	439716.0	559891.0	610830.7	761755.7	861350.0	806060.3	763013.0
inhibition%	73.63	63.42	55.14	42.37	26.62	19.94	0.16	-12.89	-5.64	



VI. The modification of Glibenclamide



To a 100 mL round bottom flask was added 5-chloro-2-methoxybenzoic acid (1.12 g, 6 mmol) and CH_2Cl_2 (25 mL). The flask was cooled in an ice bath, and oxalyl chloride (3.05 g, 24 mmol) was added dropwise. The solution was stirred at room temperature for 12 h. Then the solvent was removed in vacuum to give 5-chloro-2-methoxybenzoyl chloride as a colorless solid. CH_2Cl_2 (30 mL), 2-phenylethylamine (0.66 g, 5.4 mmol), and NEt_3 (2.43 g, 24 mmol) were added in a 150 mL round bottom flask. The flask was cooled in an ice bath. Then the solution of above 5-chloro-2-methoxybenzoyl chloride in CH_2Cl_2 (10 mL) was added dropwise into the 150 mL flask through an aonstant pressure drop funnel. The solution was stirred at room temperature for 6 h. The solvent was then evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with 10% HCl solution, 10% $NaHCO_3$ solution and water. After separation, the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was further purified by column chromatography over silica gel using hexanes and EtOAc as eluent to afford **9** as a white solid (1.48 g, 95%).

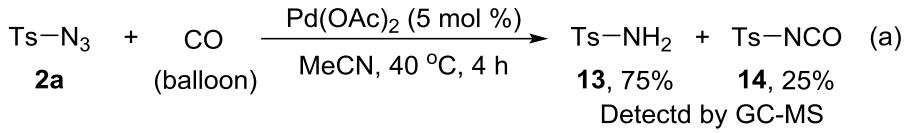
To an ice bath cooled 100 mL round bottom flask containing 20 mL of DCE was added **9** (1.48 g, 5.1 mmol). Then chlorosulfonic acid (2 mL) was added dropwise cautiously. The solution was stirred at 50 ℃ until **9** disappeared monitored by TLC. Then the reaction mixture was washed with dry CH_2Cl_2 to remove the residual acid, and dried over Na_2SO_4, evaporated under reduced pressure. The crude product was further purified by column chromatography over silica gel using hexanes and EtOAc as eluent to afford **10** as a white solid (1.46 g, 74%).

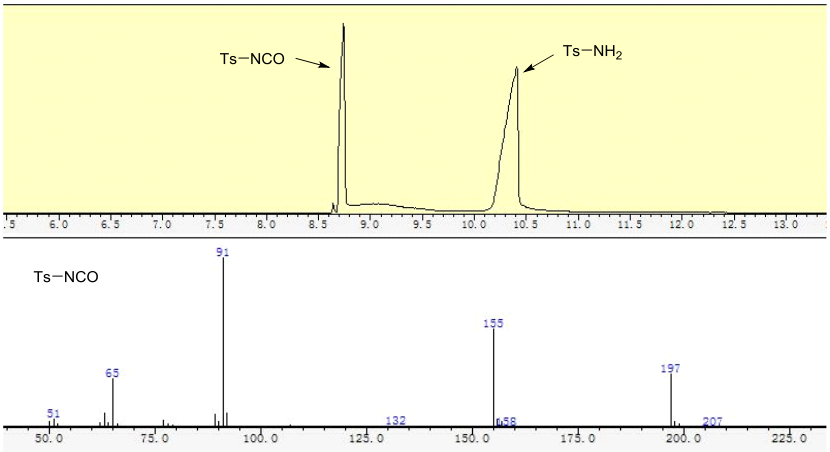
To the solution of sodium azide (0.74 g, 11.4 mmol) in water (10 mL) was added a solution of sulfonyl chloride **10** (1.46 g, 3.8 mmol) in acetone (20 mL) dropwise over 1 h at 0 ℃. The reaction mixture was warmed up to room temperature and stirred for 11 h. Acetone was removed under reduced pressure and the residue was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Crude product **11** was obtained and used directly in the next step without further purification.

To an oven-dried Schlenk tube (10 mL) was added the organic azide **11** (394.8 mg, 1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol %), and 5,5-dimethylcyclohexane-1,3-dione **1b** (70.1 mg, 0.5 mmol). The tube was purged and backfilled with CO (3 cycles) from

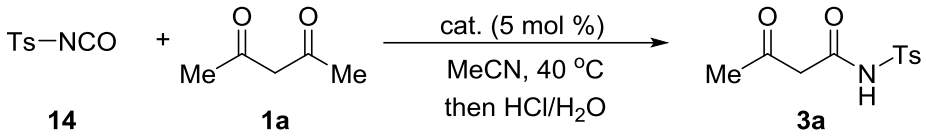
a balloon. Anhydrous CH_3CN (3.0 mL) was injected into the tube. After stirring at 80 ^oC for 8 h under CO atmosphere (balloon). The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc 3:1~1:1) to give the desired product **12** as white powder (193.7 mg, 73 %).

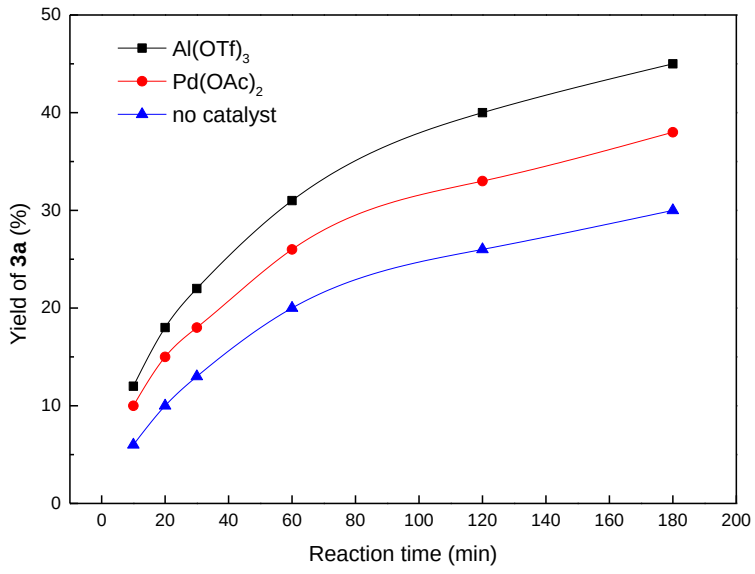
VII. Mechanistic Studies





Scheme S1. Control experiments.





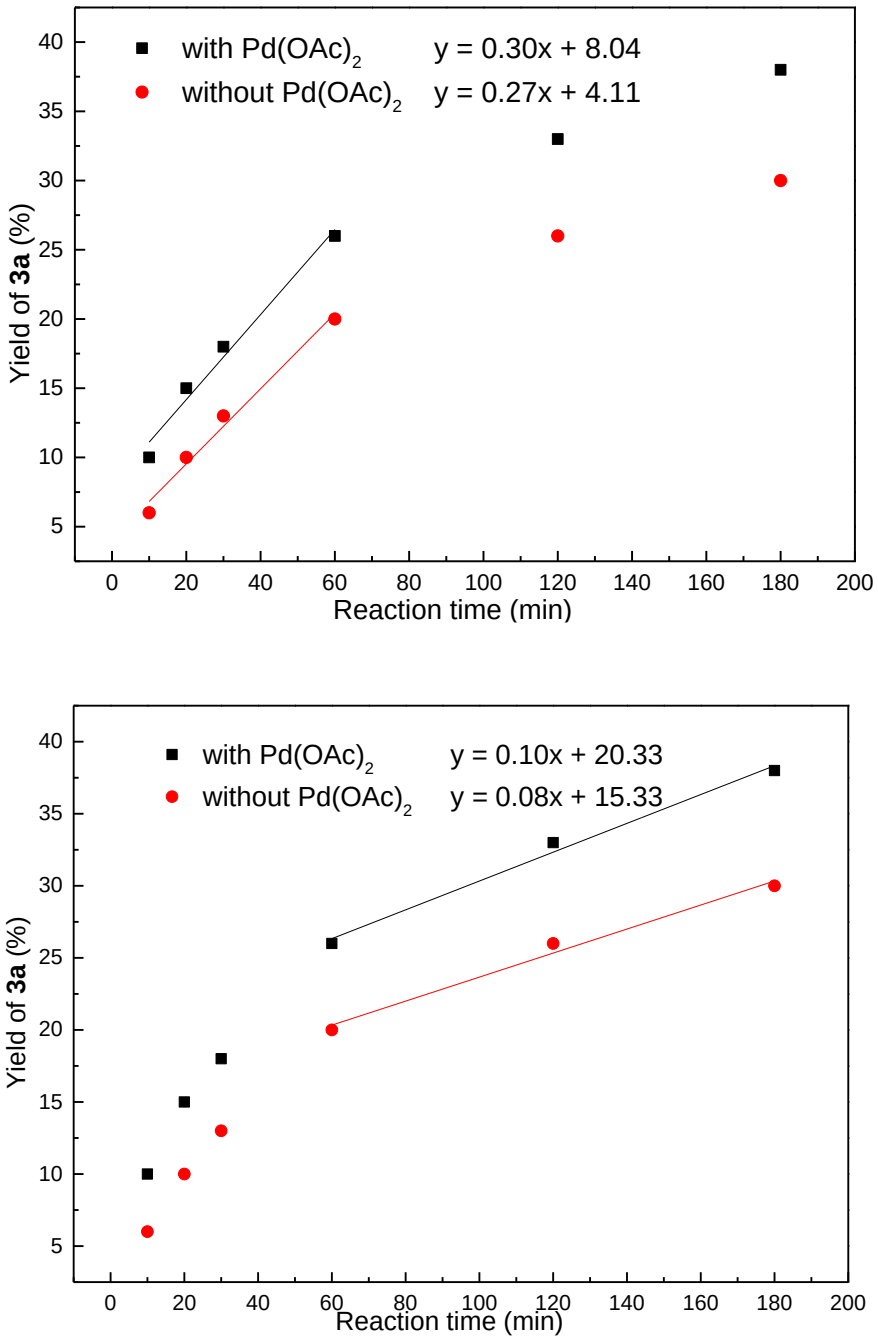
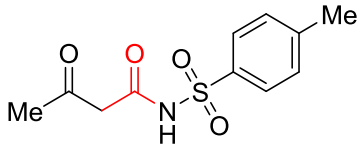
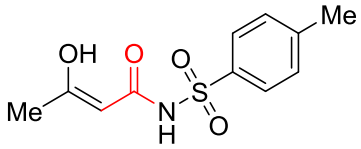


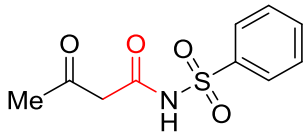
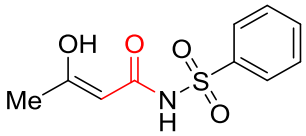
Figure S1. The rate curve experiment of reaction 1a and 14 w/wt Pd catalyst.

VIII. Characterization Data of Compounds 3a–12

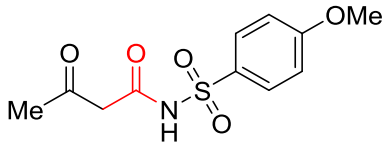
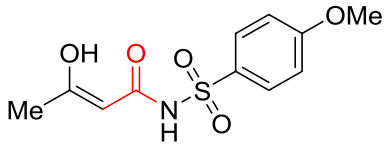
3-Oxo-*N*-tosylbutanamide 3a and 3-Hydroxy-*N*-tosylbut-2-enamide 3a' (3a/3a'=4.3/1)

Yield = 82% (104.7 mg). White solid. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.49 (s, 2H), 2.43 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 164.3, 145.2, 135.5, 129.6, 128.4, 49.6, 30.8, 21.7. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.76 (s, 1H), 5.07 (s, 1H), 2.44 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 169.4, 145.0, 136.1, 129.7, 128.1, 89.9. The other analytical data are in accordance with the literature.[1]

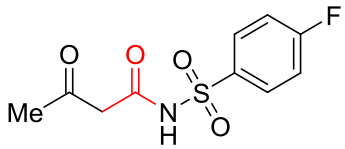
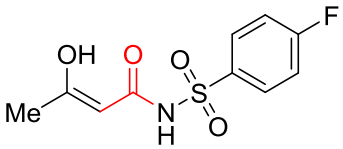
3-Oxo-*N*-(phenylsulfonyl)butanamide 3b and 3-hydroxy-*N*-(phenylsulfonyl)but-2-enamide 3b' (3b/3b'=10/1)

Yield = 80% (96.5 mg). White powder. For ketone: ^{1}H NMR (400 MHz, CD_3CN) δ 8.04 – 8.02 (m, 2H), 7.76 – 7.69 (m, 1H), 7.65 –7.61 (m, 2H), 3.48 (s, 2H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, CD_3CN) δ 202.6, 165.8, 139.7, 134.7, 129.7, 128.6, 51.2, 30.3. For enolate: ^{1}H NMR (400 MHz, CD_3CN) δ 5.10 (s, 1H), 1.94 (s, 3H); ^{13}C NMR (101 MHz, CD_3CN) δ 90.4, 21.4. HRMS (ESI) m/z calculated for $C_{10}H_{11}NO_4S$, $[M+Na]^+$ 264.0301; found 264.0296.

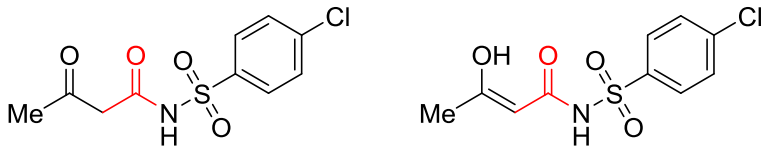
***N*-((4-Methoxyphenyl)sulfonyl)-3-oxobutanamide 3c and 3-hydroxy-*N*-((4-methoxyphenyl)sulfonyl)but-2-enamide 3c' (3c/3c'=5/1)**

Yield = 86% (116.6 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 3H), 3.86 (s, 3H), 3.49 (s, 2H), 2.22 (s, 3H),; ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 164.1, 130.8, 130.5, 129.8, 114.2, 55.7, 49.4, 30.9. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.78 (s, 1H), 5.04 (s, 1H), 3.87 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 89.9, 21.7. HRMS (ESI) m/z calculated for $C_{11}H_{13}NO_5S$, $[M+Na]^+$ 294.0407; found 294.0401.

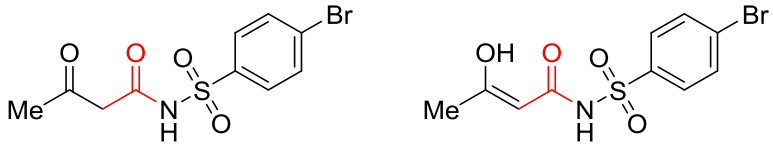
***N*-((4-Fluorophenyl)sulfonyl)-3-oxobutanamide 3d and *N*-((4-fluorophenyl)sulfonyl)-3-hydroxybut-2-enamide 3d' (3d/3d'=5/1)**

Yield = 76% (98.5 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.04 (m, 2H), 7.22 – 7.18 (m, 2H), 3.52 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 166.0 (d, *J* = 255.2 Hz), 164.3, 134.3 (d, *J* = 3.0 Hz), 131.5 (d, *J* = 9.6 Hz), 116.3 (d, *J* = 22.9 Hz), 49.5, 30.8. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (s, 1H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 169.3, 165.8 (d, *J* = 254.4 Hz), 134.9 (d, *J* = 2.9 Hz), 131.2 (d, *J* = 9.8 Hz), 116.3 (d, *J* = 23.0 Hz), 89.8, 21.7. HRMS (ESI) m/z calculated for $C_{10}H_{10}FNO_4S$, $[M+Na]^+$ 282.0207; found 282.0205.



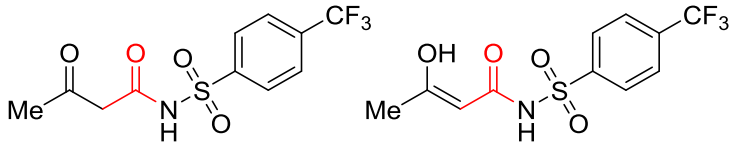
***N*-((4-Chlorophenyl)sulfonyl)-3-oxobutanamide 3e and *N*-((4-chlorophenyl)sulfonyl)-3-hydroxybut-2-enamide 3e' (3e/3e'=5/1)**

Yield = 71% (97.9 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.50 (m, 2H), 3.54 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 164.4, 140.9, 136.8, 130.0, 129.3, 49.5, 30.9. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.69 (s, 1H), 5.05 (s, 1H), 1.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 169.3, 140.6, 137.3, 129.7, 127.9, 89.8, 21.7. HRMS (ESI) m/z calculated for $C_{10}H_{10}ClNO_4S$, $[M+Na]^+$ 297.9911; found 297.9908.



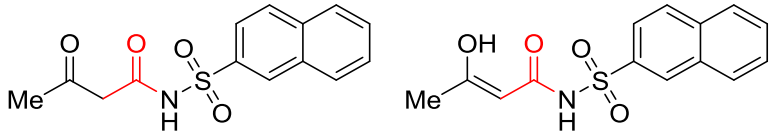
***N*-((4-Bromophenyl)sulfonyl)-3-oxobutanamide 3f and *N*-((4-bromophenyl)sulfonyl)-3-hydroxybut-2-enamide 3f' (3f/3f'=5/1)**

Yield = 62% (99.2 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 3.51 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5, 164.0, 137.4, 132.3, 130.0, 129.5, 49.2, 31.0. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.68 (s, 1H), 5.03 (s, 1H), 1.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 169.1, 137.9, 132.4, 129.7, 129.2, 89.7, 21.7. HRMS (ESI) m/z calculated for $C_{10}H_{10}BrNO_4S$, $[M+Na]^+$ 341.9406; found 341.9403.



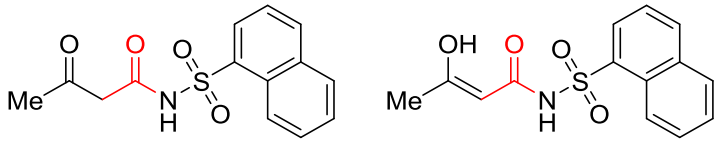
3-Oxo-*N*-((4-(trifluoromethyl)phenyl)sulfonyl)butanamide 3g and 3-hydroxy-*N*-((4-(trifluoromethyl)phenyl)sulfonyl)but-2-enamide 3g' (3g/3g'=5/1)

Yield = 59% (91.2 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 3.54 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5, 164.2, 141.8, 135.6 (q, *J* = 32.8 Hz), 129.1, 126.2 (q, *J* = 3.8 Hz), 123.1 (q, *J* = 271.4 Hz), 49.2, 30.9. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.64 (s, 1H), 5.05 (s, 1H), 1.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 169.1, 128.8, 89.7, 21.7. HRMS (ESI) m/z calculated for $C_{11}H_{10}F_3NO_4S$, $[M+Na]^+$ 332.0175; found 332.0169.



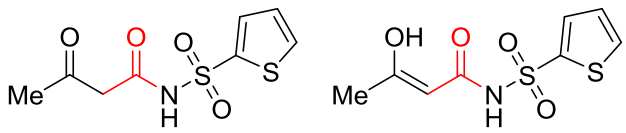
_N_-(Naphthalen-2-ylsulfonyl)-3-oxobutanamide 3h and 3-hydroxy-_N_-(naphthalen-2-ylsulfonyl)but-2-enamide 3h' (3h/3h'=11/1)

Yield = 74% (107.8 mg). White powder. For ketone: ^{1}H NMR (400 MHz, CD_3CN) δ 8.63 (s, 1H), 8.10 – 8.06 (m, 2H), 8.00 – 7.94 (m, 2H), 7.72 – 7.64 (m, 2H), 3.45 (s, 2H), 2.09 (s, 3H); ^{13}C NMR (101 MHz, CD_3CN) δ 202.5, 165.7, 136.6, 135.9, 132.4, 130.5, 130.1, 130.0, 129.8, 128.5, 128.4, 123.3, 51.2, 30.2. For enolate: ^{1}H NMR (400 MHz, CD_3CN) δ 5.09 (s, 1H), 1.88 (s, 3H); ^{13}C NMR (101 MHz, CD_3CN) δ 90.4. HRMS (ESI) m/z calculated for $C_{14}H_{13}NO_4S$, $[M+Na]^+$ 314.0457; found 314.0460.



_N_-(Naphthalen-1-ylsulfonyl)-3-oxobutanamide 3i and 3-hydroxy-_N_-(naphthalen-1-ylsulfonyl)but-2-enamide 3i' (3i/3i'=4.2/1)

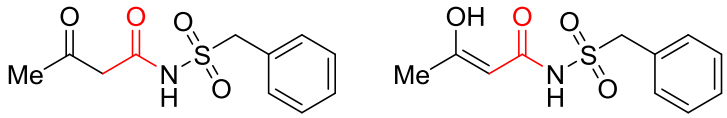
Yield = 79% (115.1 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 9.4 Hz, 1H), 8.50 (d, *J* = 7.4 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.60 (m, 1H), 7.56 (m, 2H), 3.44 (s, 2H), 2.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 164.6, 135.8, 134.1, 133.1, 132.2, 129.3, 128.9, 128.0, 127.1, 124.2, 123.8, 49.5, 30.7. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.61 (s, 1H), 5.04 (s, 1H), 1.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 169.5, 135.6, 134.1, 133.7, 131.7, 90.0, 21.6. HRMS (ESI) m/z calculated for $C_{14}H_{13}NO_4S$, $[M+Na]^+$ 314.0457; found 314.0452.



3-Oxo-_N_-(thiophen-2-ylsulfonyl)butanamide 3j and 3-hydroxy-_N_-(thiophen-2-ylsulfonyl)but-2-enamide 3j' (3j/3j'=5/1)

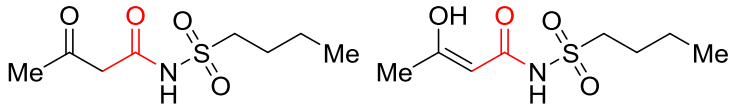
Yield = 76% (94.0 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 3.8 Hz, 1H), 7.69 (d, *J* = 5.0 Hz, 1H), 7.10 (dd, *J* = 4.0, 4.4 Hz, 1H), 3.55

(s, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 164.4, 135.3, 134.3, 127.5, 49.4, 30.9. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.76 (s, 1H), 5.13 (s, 1H), 1.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 169.3, 138.6, 134.8, 133.9, 90.0, 21.8. HRMS (ESI) m/z calculated for $C_8H_9NO_4S_2$, $[M+Na]^+$ 269.9865; found 269.9865.



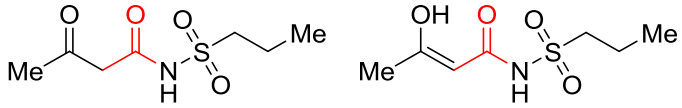
***N*-(Benzylsulfonyl)-3-oxobutanamide 3k and *N*-(benzylsulfonyl)-3-hydroxybut-2-enamide 3k' (3k/3k'=3.7/1)**

Yield = 75% (95.7 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (brs, 1H), 7.38 – 7.36 (m, 5H), 4.61 (s, 2H), 3.47 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 165.4, 130.8, 129.3, 129.0, 127.6, 77.0, 59.2, 49.5, 30.8. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.89 (s, 1H), 4.95 (s, 1H), 4.62 (s, 2H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 170.2, 130.8, 129.3, 129.0, 127.9, 89.6, 59.5, 21.8. HRMS (ESI) m/z calculated for $C_{11}H_{13}NO_4S$, $[M+Na]^+$ 278.0457; found 278.0457.



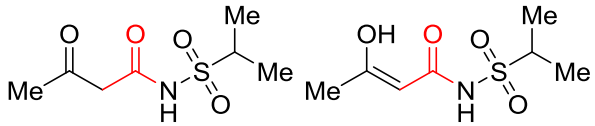
***N*-(Butylsulfonyl)-3-oxobutanamide 3l and *N*-(butylsulfonyl)-3-hydroxybut-2-enamide 3l' (3l/3l'=4.2/1)**

Yield = 66% (73.0 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 2H), 3.42 – 3.38 (m, 2H), 2.27 (s, 3H), 1.83 – 1.76 (m, 2H), 1.48 – 1.42 (m, 2H), 0.95 – 0.91 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 165.7, 53.2, 50.0, 30.8, 24.9, 21.3, 13.5. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.81 (s, 1H), 5.08 (s, 1H), 1.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 170.2, 89.9, 53.7, 49.9, 25.0, 25.0, 21.7. HRMS (ESI) m/z calculated for $C_8H_{15}NO_4S$, $[M+Na]^+$ 244.0614; found 244.0609.



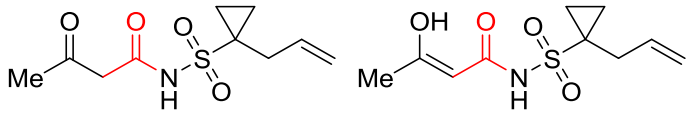
3-Oxo-*N*-(propylsulfonyl)butanamide 3m and 3-hydroxy-*N*-(propylsulfonyl)but-2-enamide 3m' (3m/3m'=5/1)

Yield = 71% (73.6 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (brs, 1H), 3.59 (s, 2H), 3.41 – 3.37 (m, 2H), 2.29 (s, 3H), 1.90 – 1.84 (m, 2H), 1.09 – 1.05 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0, 165.3, 55.1, 49.7, 30.9, 16.8, 12.7. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.85 (s, 1H), 5.07 (s, 1H), 1.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 89.8, 55.7, 29.7, 21.8, 17.0. HRMS (ESI) m/z calculated for $C_7H_{13}NO_4S$, $[M+Na]^+$ 230.0457; found 230.0457.



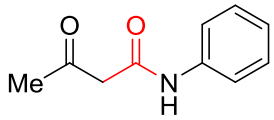
***N*-(Isopropylsulfonyl)-3-oxobutanamide 3n and 3-hydroxy-*N*-(isopropylsulfonyl)but-2-enamide 3n' (3n/3n'=4/1)**

Yield = 70% (72.5mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 – 3.70 (m, 1H), 3.60 (s, 2H), 2.26 (s, 3H), 1.41-1.38 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8, 165.7, 54.1, 50.3, 30.7, 15.8. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.84 (s, 1H), 5.12 (s, 1H), 1.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 170.3, 89.8, 54.5, 21.7, 15.9. HRMS (ESI) m/z calculated for $C_7H_{13}NO_4S$, $[M+Na]^+$ 230.0457; found 230.0456.



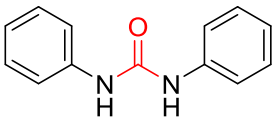
***N*-((1-Allylcyclopropyl)sulfonyl)-3-oxobutanamide 3o and *N*-((1-allylcyclopropyl)sulfonyl)-3-hydroxybut-2-enamide 3o' (3o/3o'=3.8/1)**

Yield = 74% (90.8 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 – 5.70 (m, 1H), 5.25 – 5.14 (m, 2H), 3.61 (s, 2H), 2.71 (d, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 1.70 (t, *J* = 6.4 Hz, 2H), 1.03 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 158.7, 127.0, 114.0, 44.5, 34.8, 29.5, 25.6, 6.0. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.99 (s, 1H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 164.3, 126.6, 114.5, 84.5, 44.5, 35.7, 29.7, 6.3. HRMS (ESI) m/z calculated for $C_{10}H_{15}NO_4S$, $[M+Na]^+$ 268.0614; found 268.0610.



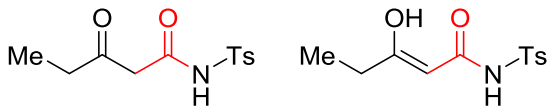
3-Oxo-*N*-phenylbutanamide 3p

Yield = 31% (27.5 mg). White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.55 – 7.52 (m, 2H), 7.34 – 7.26 (m, 2H), 7.14 – 7.10 (m, 1H), 3.57 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.2, 163.5, 137.5, 129.0, 124.6, 120.2, 49.8, 31.2. The other analytical data are in accordance with the literature.[2]



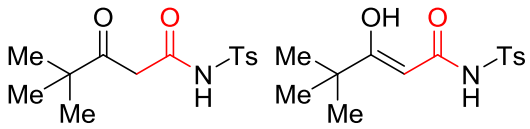
1,3-Diphenylurea 3p'

Yield = 53% (28.1 mg). White powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 2H), 7.45 (d, *J* = 8.0 Hz, 4H), 7.28 (dd, *J* = 7.6, 8.0 Hz, 4H), 6.96 (dd, *J* = 7.2, 7.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 153.0, 140.2, 129.3, 122.3, 118.7. The other analytical data are in accordance with the literature.[3]



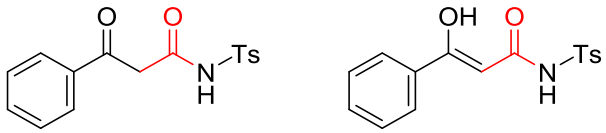
3-Oxo-*N*-tosylpentanamide 3q and 3-hydroxy-*N*-tosylpent-2-enamide 3q' (3q/3q'=7.7/1)

Yield = 71% (95.6 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.34 – 7.31 (m, 2H), 3.45 (s, 2H), 2.53 – 2.48 (m, 2H), 2.43 (s, 3H), 1.07 – 1.03 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2, 163.9, 145.2, 135.6, 129.6, 128.5, 48.2, 37.2, 21.7, 7.3. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.7, 128.2. HRMS (ESI) m/z calculated for $C_{12}H_{15}NO_4S$, $[M+Na]^+$ 292.0614; found 292.0610.



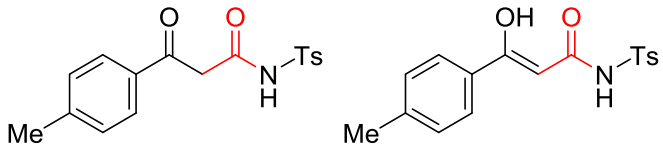
4,4-Dimethyl-3-oxo-*N*-tosylpentanamide 3r and 3-hydroxy-4,4-dimethyl-*N*-tosylpent-2-enamide 3r' (3r/3r'=3.3/1)

Yield = 76% (113.0 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0, 2H), 7.31 (d, *J* = 8.8, 2H), 3.55 (s, 2H), 2.41 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7, 164.7, 145.1, 135.6, 129.6, 128.4, 43.9, 27.3, 25.8, 21.7. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.00 (s, 1H), 5.12 (s, 1H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.3, 170.1, 144.9, 136.1, 129.6, 128.2, 85.7, 45.1, 37.0. HRMS (ESI) m/z calculated for $C_{14}H_{19}NO_4S$, $[M+Na]^+$ 320.0927; found 320.0927.



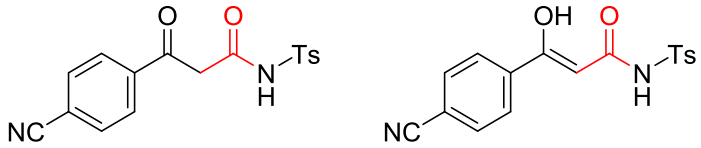
3-Oxo-3-phenyl-*N*-tosylpropanamide 3s and 3-hydroxy-3-phenyl-*N*-tosylacrylamide 3s' (3s/3s'=2/1)

Yield = 80% (126.9 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 2H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.71 – 7.69 (m, 1H), 7.61 – 7.57 (m, 1H), 7.46 – 7.42 (m, 1H), 7.38 – 7.26 (m, 2H), 4.03 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5, 165.0, 145.2, 135.4, 134.6, 131.9, 129.6, 129.0, 128.6, 128.5, 45.3, 21.7. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.25 (s, 1H), 5.75 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 170.0, 145.0, 136.0, 135.5, 133.0, 129.7, 128.6, 128.2, 126.3, 87.3. HRMS (ESI) m/z calculated for $C_{16}H_{15}NO_4S$, $[M+H]^+$ 318.0795; found 318.0788.



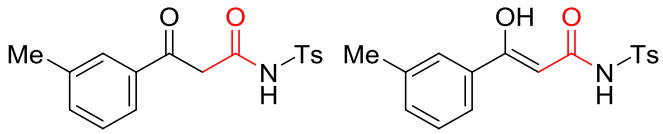
3-Oxo-3-(*p*-tolyl)-*N*-tosylpropanamide 3t and 3-hydroxy-3-(*p*-tolyl)-*N*-tosylacrylamide 3t' (3t/3t'=2.4/1)

Yield = 86% (142.5 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 3.99 (s, 2H), 2.35 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 165.4, 145.7, 145.1, 135.6, 133.0, 129.6, 129.6, 128.8, 128.4, 45.3, 21.7, 21.6. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.26 (s, 1H), 7.95 (d, *J* = 6.4 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.72 (s, 1H), 2.38 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 170.2, 144.9, 142.5, 136.2, 130.2, 129.3, 128.2, 126.3, 86.7, 21.5. HRMS (ESI) m/z calculated for $C_{17}H_{17}NO_4S$, $[M+Na]^+$ 354.0770; found 354.0772.



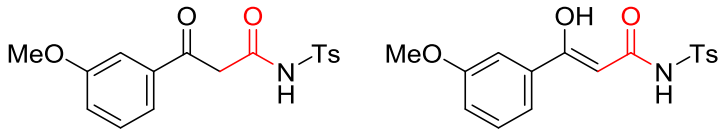
3-(4-cyanophenyl)-3-oxo-N-tosylpropanamide 3u and 3-(4-cyanophenyl)-3-hydroxy-N-tosylacrylamide 3u' (3u/3u'=2/1)

Yield = 42% (71.9 mg). White powder. For ketone: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 8.00 – 7.94 (m, 4H), 7.88 – 7.80 (m, 2H), 7.46 – 7.42 (m, 2H), 4.13 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 193.5, 166.1, 144.8, 139.5, 136.7, 133.3, 130.0, 129.3, 128.1, 118.5, 116.0, 48.0, 21.5. For enolate: ^{1}H NMR (400 MHz, DMSO) δ 13.24 (s, 1H), 5.92 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 170.5, 169.8, 145.0, 137.4, 136.9, 133.4, 130.2, 128.0, 127.0, 118.7, 114.3, 90.8. HRMS (ESI) m/z calculated for $C_{17}H_{14}N_2O_4S$, $[M+Na]^+$ 365.0566; found 365.0558.



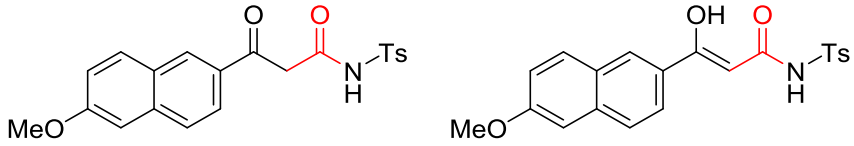
3-oxo-3-(*m*-tolyl)-*N*-tosylpropanamide 3v and 3-hydroxy-3-(*m*-tolyl)-*N*-tosylacrylamide 3v' (3v/3v'=2.2/1)

Yield = 84% (139.2 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 2H), 7.69 – 7.66 (m, 2H), 7.35 – 7.25 (m, 4H), 4.00 (s, 2H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8, 164.7, 145.1, 138.9, 135.4, 129.7, 129.6, 129.0, 128.9, 128.5, 128.2, 125.8, 45.1, 21.7, 21.3. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.25 (s, 1H), 7.53 – 7.48 (m, 2H), 7.41 – 7.39 (m, 2H), 5.74 (s, 1H), 2.42 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 170.0, 145.0, 138.4, 136.2, 135.6, 135.5, 133.0, 132.7, 128.5, 126.9, 123.5, 87.2, 21.3. HRMS (ESI) m/z calculated for $C_{17}H_{17}NO_4S$, $[M+H]^+$ 354.0770; found 354.0762.



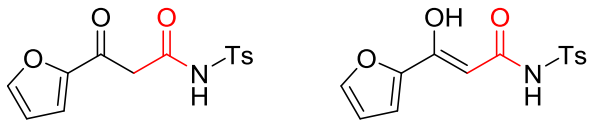
3-(3-Methoxyphenyl)-3-oxo-*N*-tosylpropanamide 3w and 3-hydroxy-3-(3-methoxyphenyl)-*N*-tosylacrylamide 3w' (3w/3w'=2/1)

Yield = 85% (147.6 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.39 – 7.24 (m, 5H), 7.14 – 7.11 (m, 1H), 4.01 (s, 2H), 3.80 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 164.8, 160.0, 145.2, 136.8, 135.5, 130.0, 129.6, 128.5, 121.2, 118.7, 112.6, 55.5, 45.3, 21.7. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.24 (s, 1H), 7.44 – 7.43 (m, 2H), 7.00 – 6.96 (m, 1H), 5.73 (s, 1H), 3.78 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 170.0, 159.8, 145.0, 136.1, 134.4, 129.7, 129.7, 128.2, 121.2, 117.9, 111.4, 87.5, 55.4. HRMS (ESI) m/z calculated for $C_{17}H_{17}NO_5S$, $[M+H]^+$ 348.0900; found 348.0891.



3-(6-Methoxynaphthalen-2-yl)-3-oxo-*N*-tosylpropanamide 3x and 3-hydroxy-3-(6-methoxynaphthalen-2-yl)-*N*-tosylacrylamide 3x' (3x/3x'=5/1)

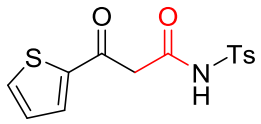
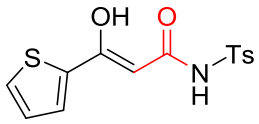
Yield = 78% (155.0 mg). White powder. For ketone: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.49 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.91 – 7.84 (m, 4H), 7.41 – 7.36 (m, 3H), 7.28 – 7.21 (m, 1H), 4.17 (s, 2H), 3.90 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 193.4, 166.6, 160.1, 144.7, 137.6, 136.9, 131.7, 131.6, 131.0, 130.0, 128.0, 127.8, 127.6, 124.6, 120.1, 106.6, 55.9, 47.6, 21.5. For enolate: ^{1}H NMR (400 MHz, DMSO) δ 13.51 (s, 1H), 8.27 (s, 1H), 7.65 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 1H), 3.90 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 172.7, 171.0, 88.2, 55.9. HRMS (ESI) m/z calculated for $C_{21}H_{19}NO_5S$, $[M+Na]^+$ 420.0876; found 420.0876.



3-(Furan-2-yl)-3-oxo-*N*-tosylpropanamide 3y and 3-(furan-2-yl)-3-hydroxy-*N*-tosylacrylamide 3y' (3y/3y'=5.9/1)

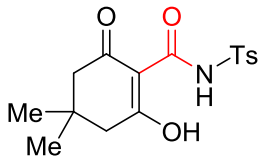
Yield = 71% (109.1 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (brs, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 1H), 7.34 – 7.29 (m, 3H), 6.57 – 6.49 (m, 1H), 3.88 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.2, 163.9, 151.3, 148.3, 145.2, 135.5, 129.6, 128.5, 120.2, 113.2, 44.8, 21.6. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.83 (s, 1H), 7.48 (s, 1H), 6.96 – 6.95 (m, 1H), 5.69 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 164.2, 147.9, 145.6, 145.0,

136.1, 129.7, 128.2, 114.0, 112.3, 86.0. HRMS (ESI) m/z calculated for $C_{14}H_{13}NO_5S$, $[M+Na]^+$ 330.0407; found 330.0400.

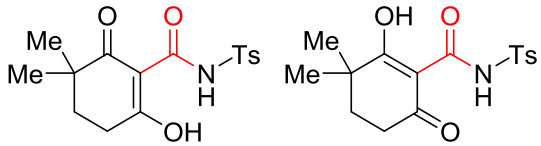
3-Oxo-3-(thiophen-2-yl)-*N*-tosylpropanamide 3z and 3-hydroxy-3-(thiophen-2-yl)-*N*-tosylacrylamide 3z' (3z/3z'=11/1)

Yield = 76% (122.9 mg). White powder. For ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 4.4 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 4.4 Hz, 1H), 3.95 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.7, 164.0, 145.2, 142.4, 136.5, 135.5, 134.4, 129.6, 128.8, 128.5, 45.6, 21.7. For enolate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.20 (s, 1H), 7.55 (d, *J* = 3.6 Hz, 2H), 7.46 (d, *J* = 4.8 Hz, 2H), 7.06 (t, *J* = 4.8 Hz, 1H), 5.66 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 168.9, 145.0, 137.0, 136.1, 130.5, 129.7, 128.9, 128.2, 86.3. HRMS (ESI) m/z calculated for $C_{14}H_{13}NO_4S_2$, $[M+Na]^+$ 346.0178; found 346.0177.



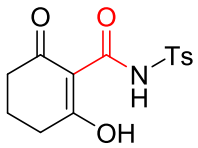
2-Hydroxy-4,4-dimethyl-6-oxo-*N*-tosylcyclohex-1-ene-1-carboxamide 4a

Yield = 85% (143.4 mg). White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.60 (s, 1H), 12.32 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.49 (s, 2H), 2.43 (s, 3H), 2.35 (s, 2H), 1.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 194.1, 169.1, 145.1, 136.0, 129.6, 128.6, 102.8, 50.8, 44.8, 31.0, 28.0, 21.7. HRMS (ESI) m/z calculated for $C_{16}H_{19}NO_5S$, $[M+Na]^+$ 360.0876; found 360.0876.



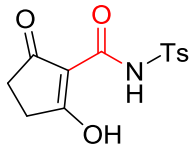
2-Hydroxy-5,5-dimethyl-6-oxo-*N*-tosylcyclohex-1-ene-1-carboxamide 4b and 2-hydroxy-3,3-dimethyl-6-oxo-*N*-tosylcyclohex-1-ene-1-carboxamide 4b' (1.6/1)

Yield = 71% (119.8mg). White powder. Major: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.66 (s, 1H), 12.55 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.42 (s, 3H), 1.80 – 1.76 (m, 2H), 1.13 (s, 6H). Minor: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 16.23 (s, 1H), 12.59 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.52 (t, *J* = 6.8 Hz, 2H), 2.42 (s, 3H), 1.80 – 1.76 (m, 2H), 1.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 201.3, 197.5, 194.1, 169.9, 169.8, 145.0, 136.1, 129.5, 128.6, 101.9, 101.8, 77.4, 77.1, 76.8, 40.8, 37.7, 33.8, 33.3, 32.2, 28.0, 25.3, 24.7, 21.7. HRMS (ESI) m/z calculated for $C_{16}H_{19}NO_5S$, $[M+Na]^+$ 360.0876; found 360.0873.



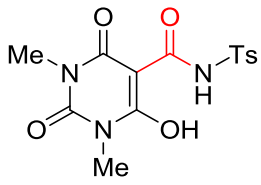
2-Hydroxy-6-oxo-*N*-tosylcyclohex-1-ene-1-carboxamide 4c

Yield = 84% (130.0 mg). White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.63 (s, 1H), 12.34 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 2.58 (t, *J* = 6.4 Hz, 2H), 2.44 (t, *J* = 6.4 Hz, 2H), 2.37 (s, 3H), 1.90 (tt, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 195.5, 169.3, 145.1, 136.0, 129.6, 128.5, 103.8, 77.4, 77.1, 76.8, 37.0, 31.3, 21.7, 18.8. HRMS (ESI) m/z calculated for $C_{14}H_{15}NO_5S$, $[M+H]^+$ 310.0744; found 310.0740.



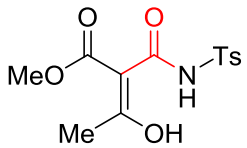
2-Hydroxy-5-oxo-*N*-tosylcyclopent-1-ene-1-carboxamide 4d

Yield = 60% (88.6 mg). Yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.78 – 2.75 (m, 2H), 2.57 – 2.55 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.1, 200.3, 163.8, 145.3, 135.9, 135.9, 129.6, 128.5, 107.6, 33.1, 27.6, 21.7. HRMS (ESI) m/z calculated for $C_{13}H_{13}NO_5S$, $[M+Na]^+$ 318.0407; found 318.0403.



6-Hydroxy-1,3-dimethyl-2,4-dioxo-*N*-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide 4e

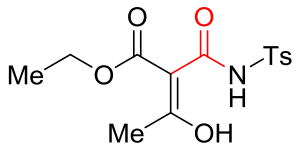
Yield =74% (130.7 mg). White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 17.07 (s, 1H), 12.15 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.35 (s, 3H), 3.30 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.9, 162.5, 149.1, 145.4, 135.7, 129.7, 128.5, 81.9, 77.4, 77.1, 76.8, 28.4, 28.1, 21.7. HRMS (ESI) m/z calculated for $C_{14}H_{15}N_3O_6S$, $[M+H]^+$ 354.0754; found 354.0752.



Methyl-3-hydroxy-2-(tosylcarbamoyl)but-2-enoate 4f

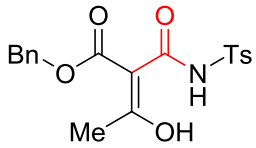
Yield = 71% (111.2 mg). White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.53 (s, 1H), 11.87 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 170.8, 168.7, 145.0, 136.0,

129.5, 128.6, 95.6, 52.2, 25.8, 21.6. HRMS (ESI) m/z calculated for $C_{13}H_{15}NO_6S$, $[M+Na]^+$ 336.0512; found 336.0511.



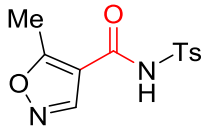
Ethyl-3-hydroxy-2-(tosylcarbamoyl)but-2-enoate 4g

Yield = 70% (114.6 mg). White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.50 (s, 1H), 11.93 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 193.1, 170.9, 168.3, 144.9, 136.0, 129.5, 128.6, 95.8, 61.7, 25.9, 21.7, 14.2. HRMS (ESI) m/z calculated for $C_{14}H_{17}NO_6S$, $[M+Na]^+$ 350.0669; found 350.0657.



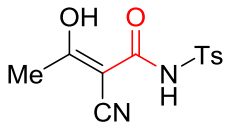
Benzyl-3-hydroxy-2-(tosylcarbamoyl)but-2-enoate 4h

Yield = 68% (132.4 mg). White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.57 (s, 1H), 11.89 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.41 – 7.32 (m, 7H), 5.26 (s, 2H), 2.44 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 170.8, 168.1, 145.0, 136.0, 134.9, 129.5, 128.8, 128.8, 128.7, 128.6, 95.6, 67.5, 26.1, 21.7. HRMS (ESI) m/z calculated for $C_{19}H_{19}NO_6S$, $[M+Na]^+$ 412.0825; found 412.0821.



5-Methyl-*N*-tosylisoxazole-4-carboxamide 6

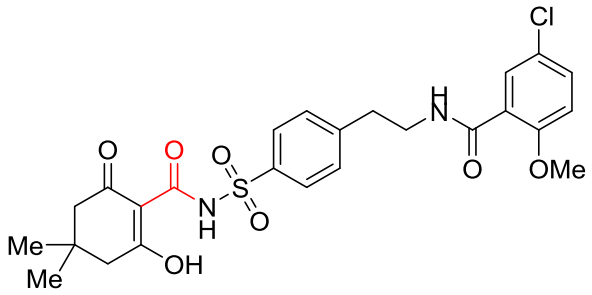
Yield = 95% (133.1 mg). White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (brs, 1H), 8.62 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 2.65 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 158.4, 147.6, 145.7, 135.0, 129.9, 128.5, 109.7, 21.8, 12.9. HRMS (ESI) m/z calculated for $C_{12}H_{12}N_2O_4S$, $[M+Na]^+$ 303.0410; found 303.0406.



2-Cyano-3-hydroxy-*N*-tosylbut-2-enamide 7

Yield = 86% (120.5 mg). White powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 190.4, 164.6, 143.6, 138.5, 129.7, 127.8, 122.6, 77.5, 26.7, 21.5.

HRMS (ESI) m/z calculated for $C_{12}H_{12}N_2O_4S$, $[M+Na]^+$ 303.0410; found 303.0402.



5-Chloro-*N*-(4-(*N*-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-ene-1-carbonyl)sulfamoyl)phenethyl)-2-methoxybenzamide 12

Yield = 73% (195.3 mg). White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.52 (s, 1H), 12.37 (s, 1H), 8.14 (d, *J* = 2.8 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.80 (t, *J* = 6.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.36 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 3.78 – 3.71 (m, 5H), 3.01 (t, *J* = 6.8 Hz, 2H), 2.50 (s, 2H), 2.35 (s, 2H), 1.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 194.2, 169.1, 164.0, 155.9, 146.3, 137.1, 132.4, 131.9, 129.5, 128.8, 126.8, 122.7, 112.9, 102.8, 56.2, 50.7, 44.8, 40.6, 35.6, 31.0, 28.0. HRMS (ESI) m/z calculated for $C_{25}H_{27}ClN_2O_7S$, $[M+Na]^+$ 557.1120; found 557.1116.

IX. References

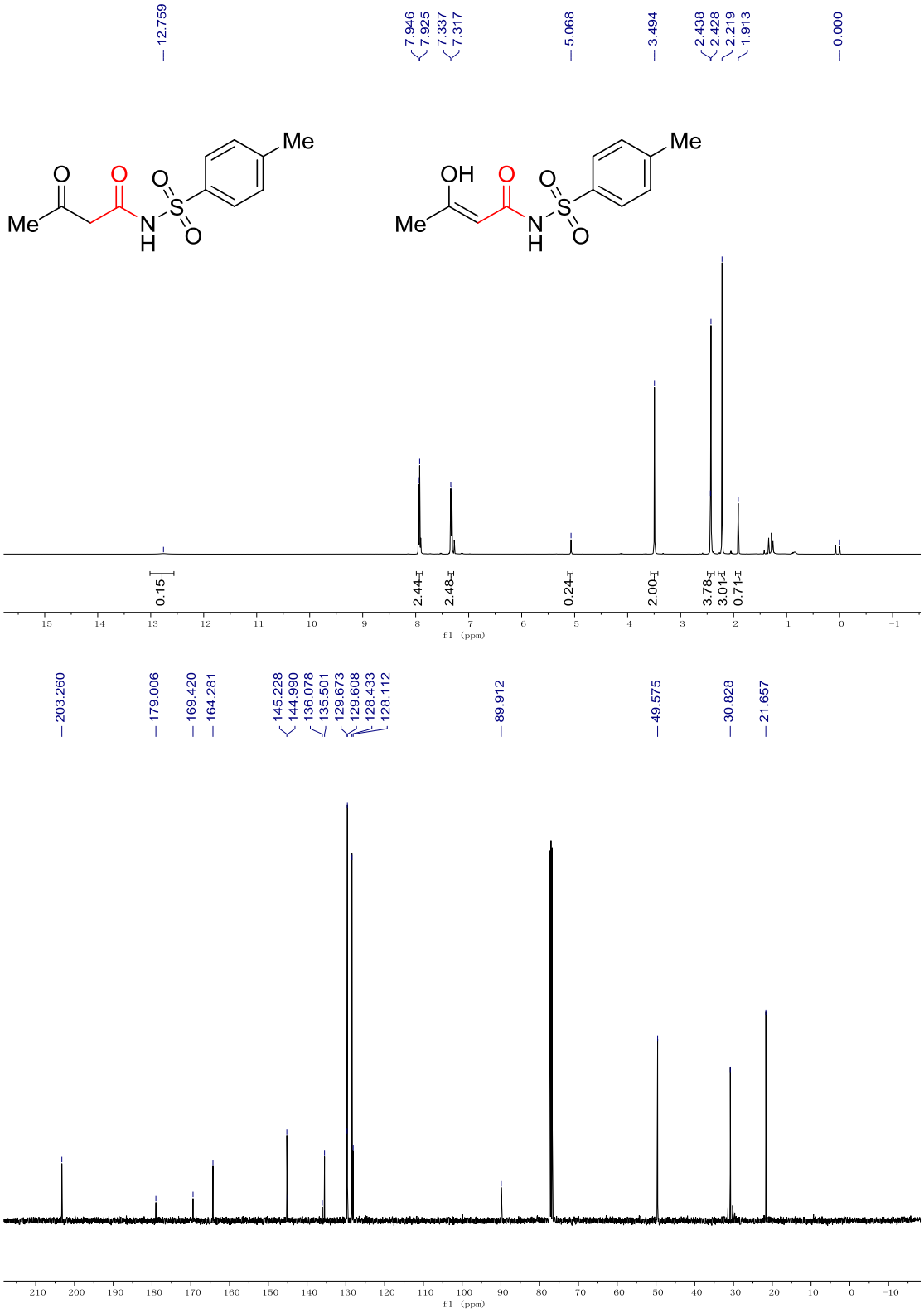
[1] Liu, Y.; Mao, Z.; Pradal, A.; Huang, P.-Q.; Oble, J.; Poli, G. Palladium-Catalyzed [3+2]-C–C/N–C Bond-Forming Annulation. *Org. Lett.* **2018**, *20*, 4057-4061.

[2] Gama, F. H. S.; de Souza, R. O. M. A.; Garden, S. J. An Efficient Green Protocol for the Preparation of Acetoacetamides and Application of the Methodology to a One-pot Synthesis of Biginelli Dihydropyrimidines. Expansion of Dihydropyrimidine Topological Chemical Space. *RSC Adv.* **2015**, *5*, 70915-70928.

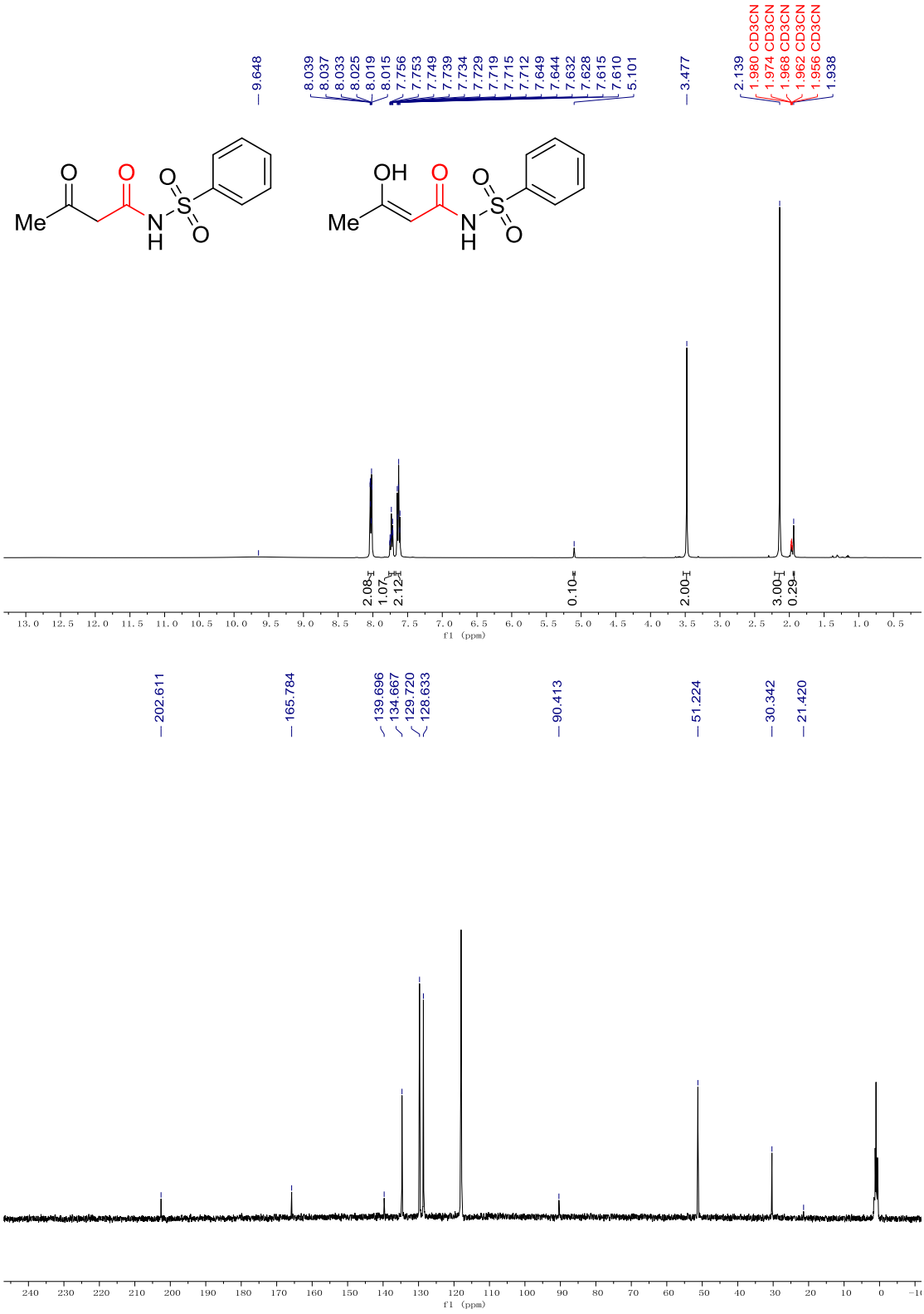
[3] Li, Z.; Xu, S.; Huang, B.; Yuan, C.; Chang, W.; Fu, B.; Jiao, L.; Wang, P.; Zhang, Z. Pd-Catalyzed Carbonylation of Acyl Azides. *J. Org. Chem.* **2019**, *84*, 9497-9508.

X. NMR Spectra

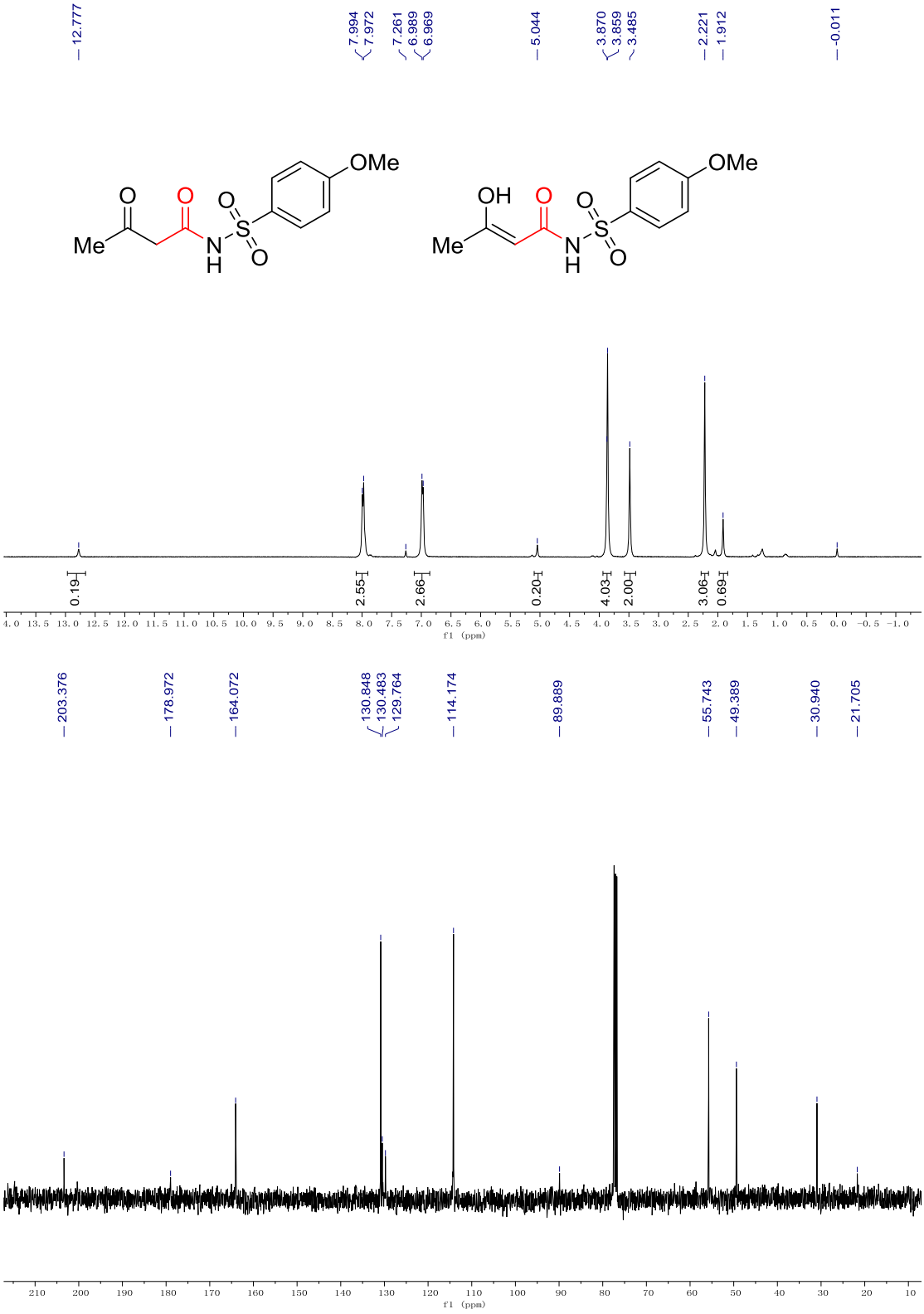
3-Oxo-*N*-tosylbutanamide 3a and 3-Hydroxy-*N*-tosylbut-2-enamide 3a' (3a/3a'=4.3/1)



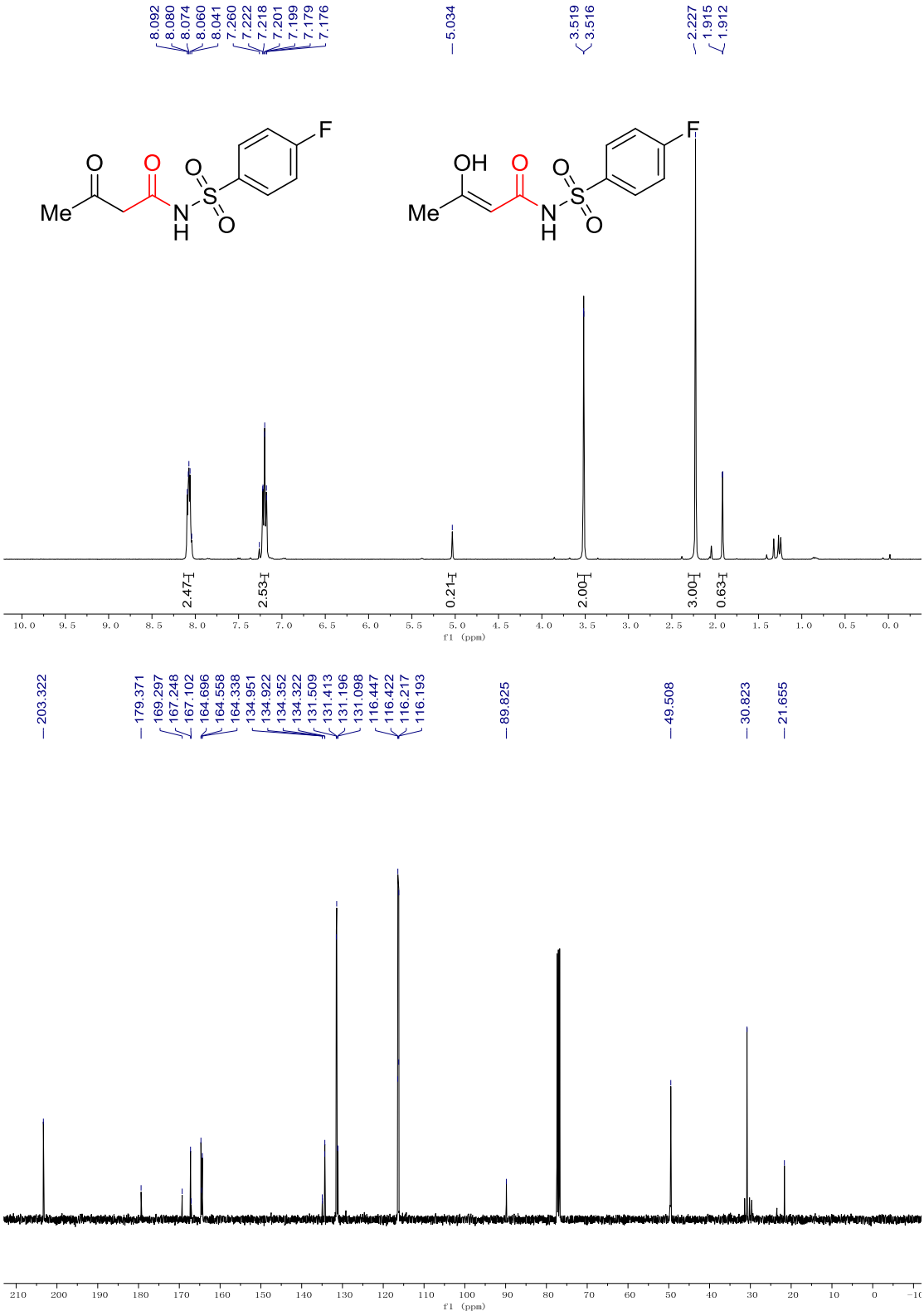
3-Oxo-*N*-(phenylsulfonyl)butanamide 3b and 3-hydroxy-*N*-(phenylsulfonyl)but-2-enamide 3b' (3b/3b'=10/1)



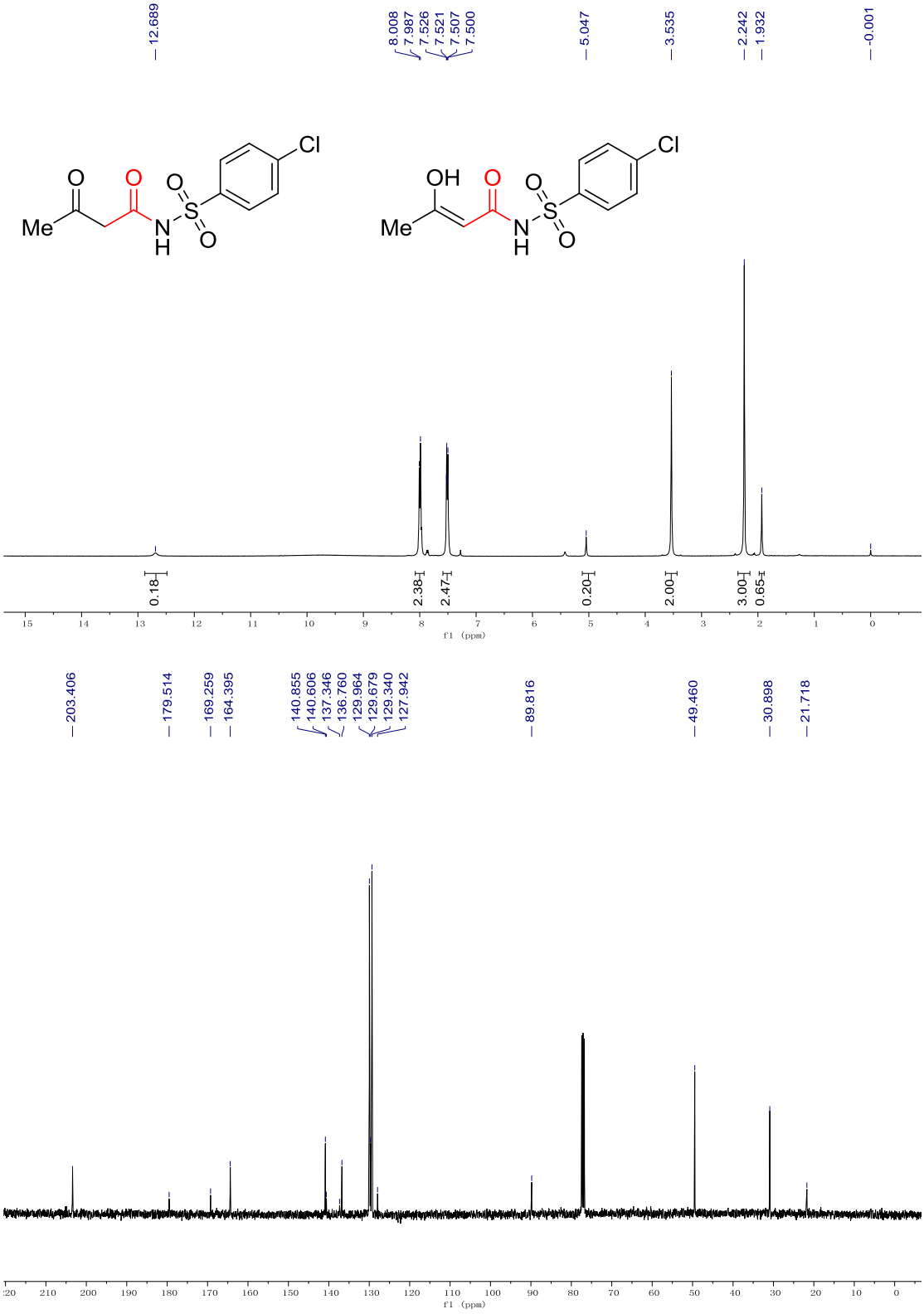
***N*-((4-Methoxyphenyl)sulfonyl)-3-oxobutanamide 3c and 3-hydroxy-*N*-((4-methoxyphenyl)sulfonyl)but-2-enamide 3c' (3c/3c'=5/1)**



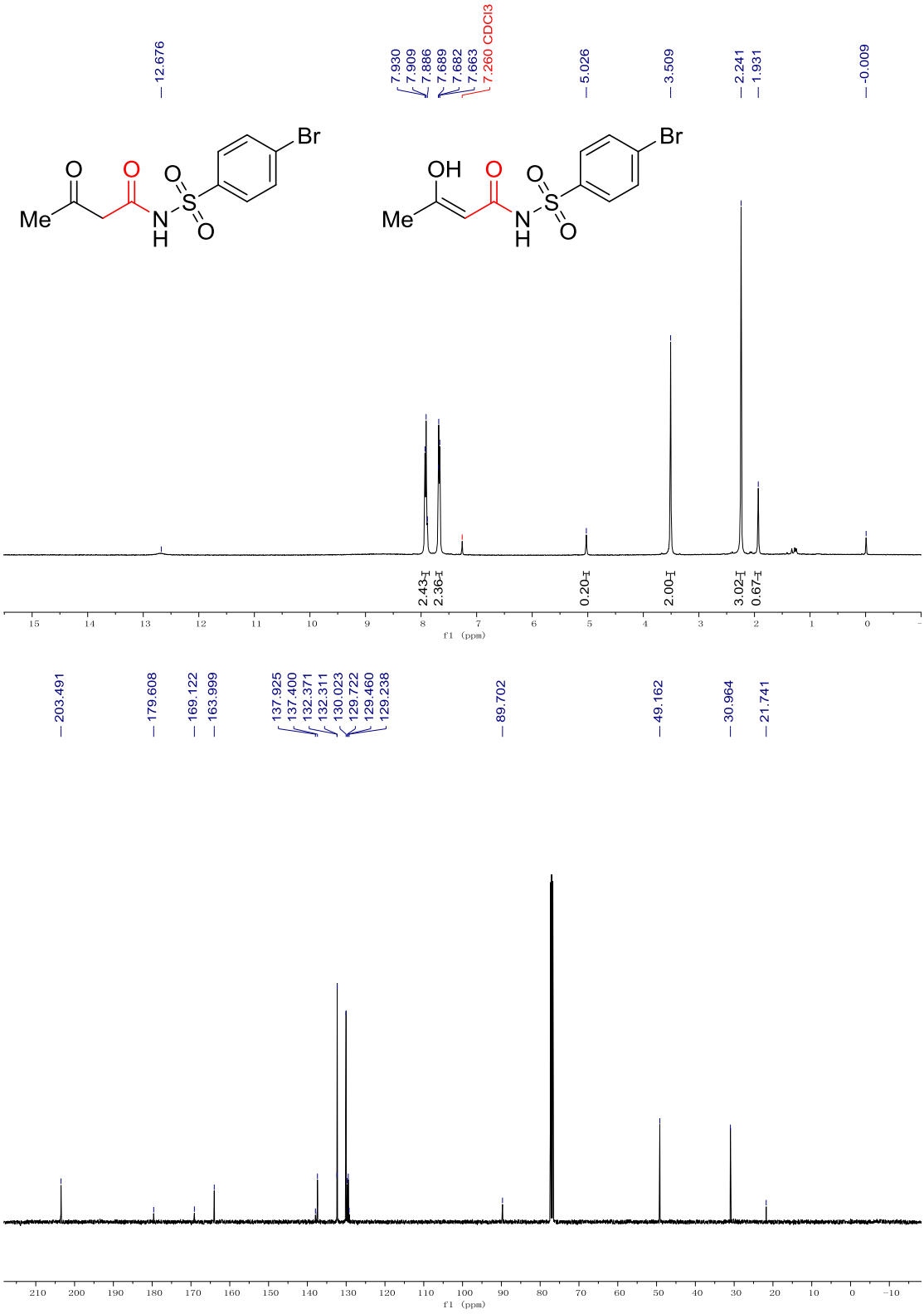
_N_-((4-Fluorophenyl)sulfonyl)-3-oxobutanamide 3d and _N_-((4-fluorophenyl)sulfonyl)-3-hydroxybut-2-enamide 3d' (3d/3d'=5/1)



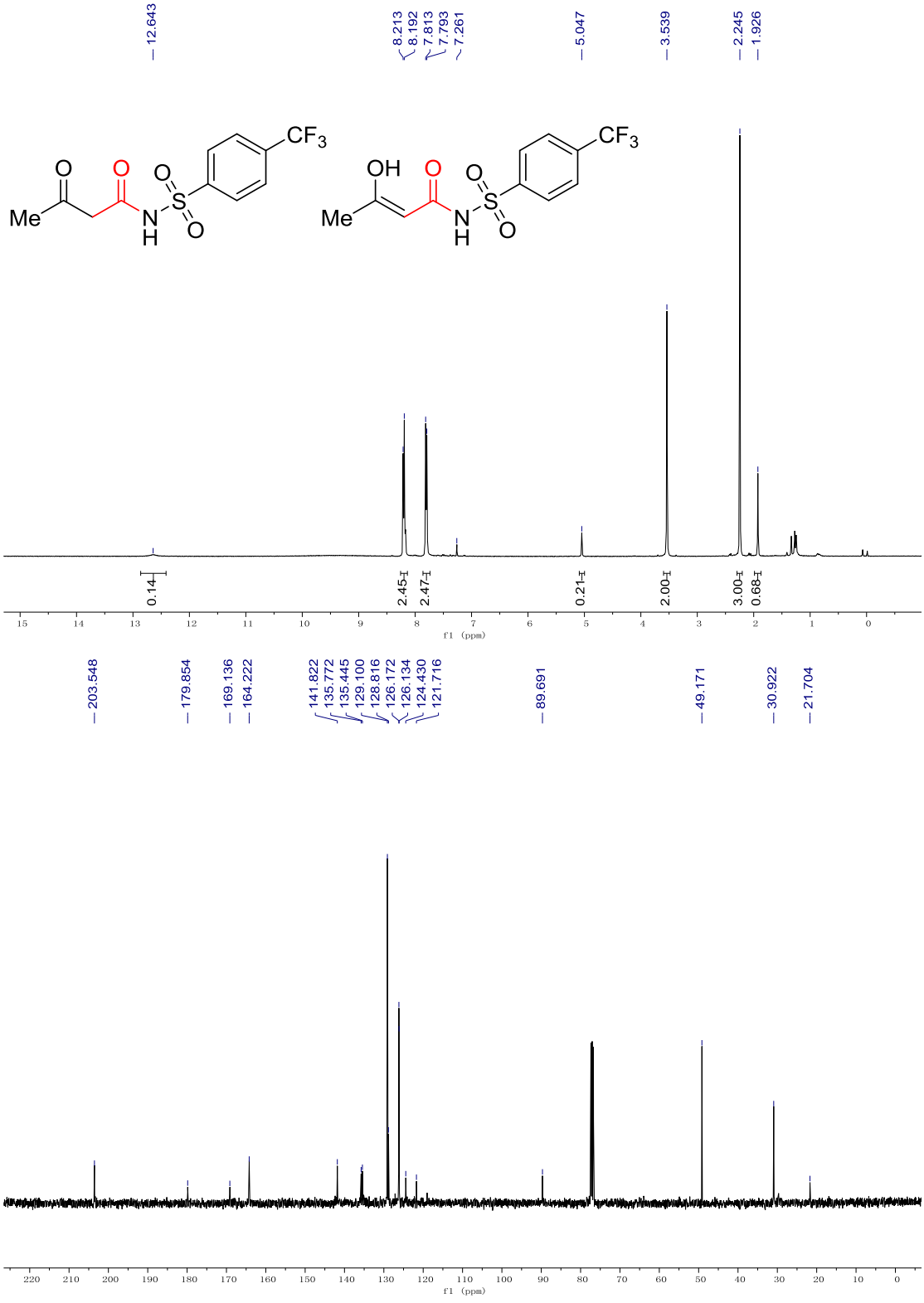
***N*-((4-Chlorophenyl)sulfonyl)-3-oxobutanamide 3e and *N*-((4-chlorophenyl)sulfonyl)-3-hydroxybut-2-enamide 3e' (3e/3e'=5/1)**



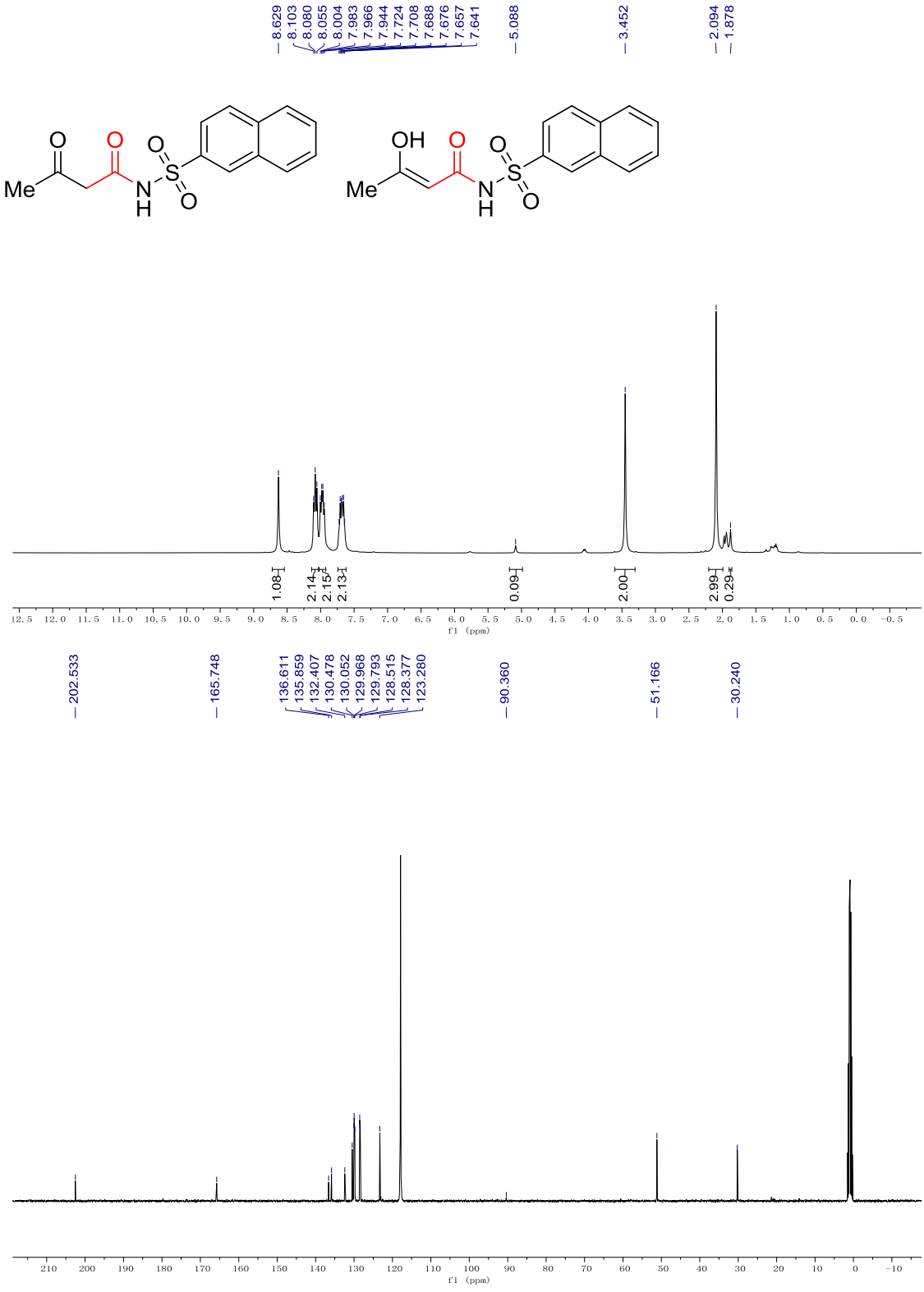
_N_-((4-Bromophenyl)sulfonyl)-3-oxobutanamide 3f and _N_-((4-bromophenyl)sulfonyl)-3-hydroxybut-2-enamide 3f' (3f/3f'=5/1)



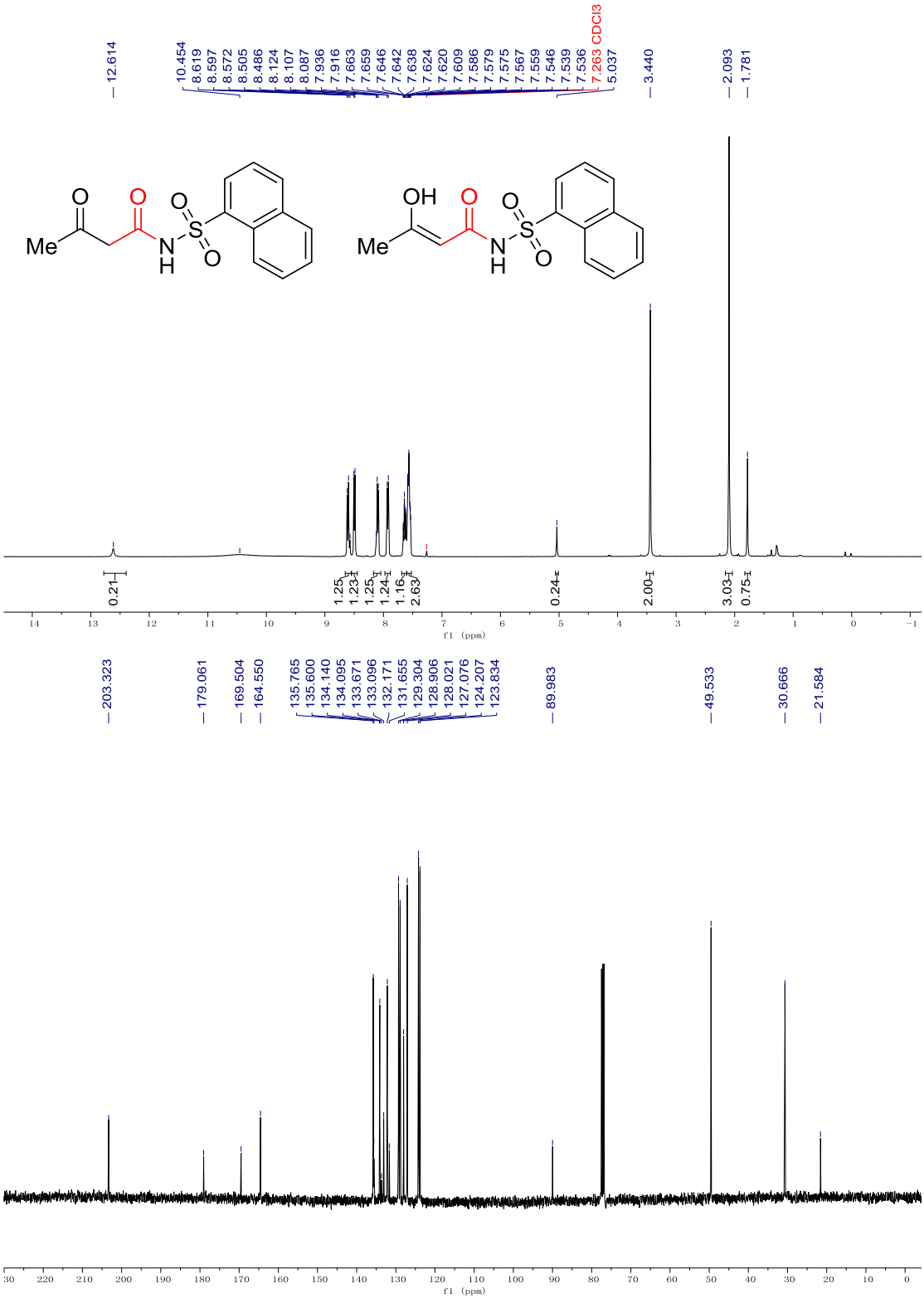
3-Oxo-*N*-((4-(trifluoromethyl)phenyl)sulfonyl)butanamide 3g and 3-hydroxy-*N*-((4-(trifluoromethyl)phenyl)sulfonyl)but-2-enamide 3g' (3g/3g'=5/1)



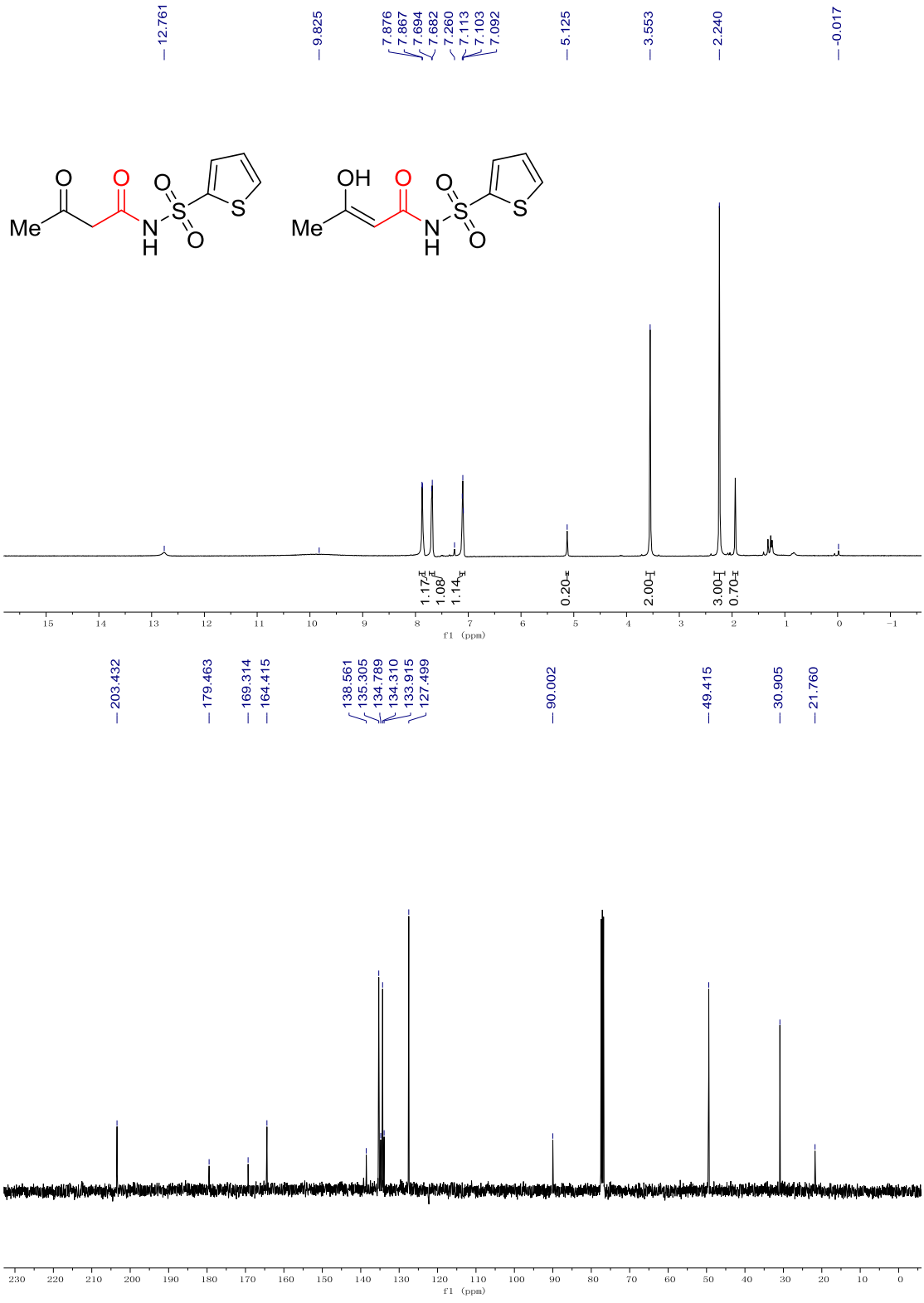
_N_-(Naphthalen-2-ylsulfonyl)-3-oxobutanamide 3h and 3-hydroxy-_N_-(naphthalen-2-ylsulfonyl)but-2-enamide 3h' (3h/3h'=11/1)



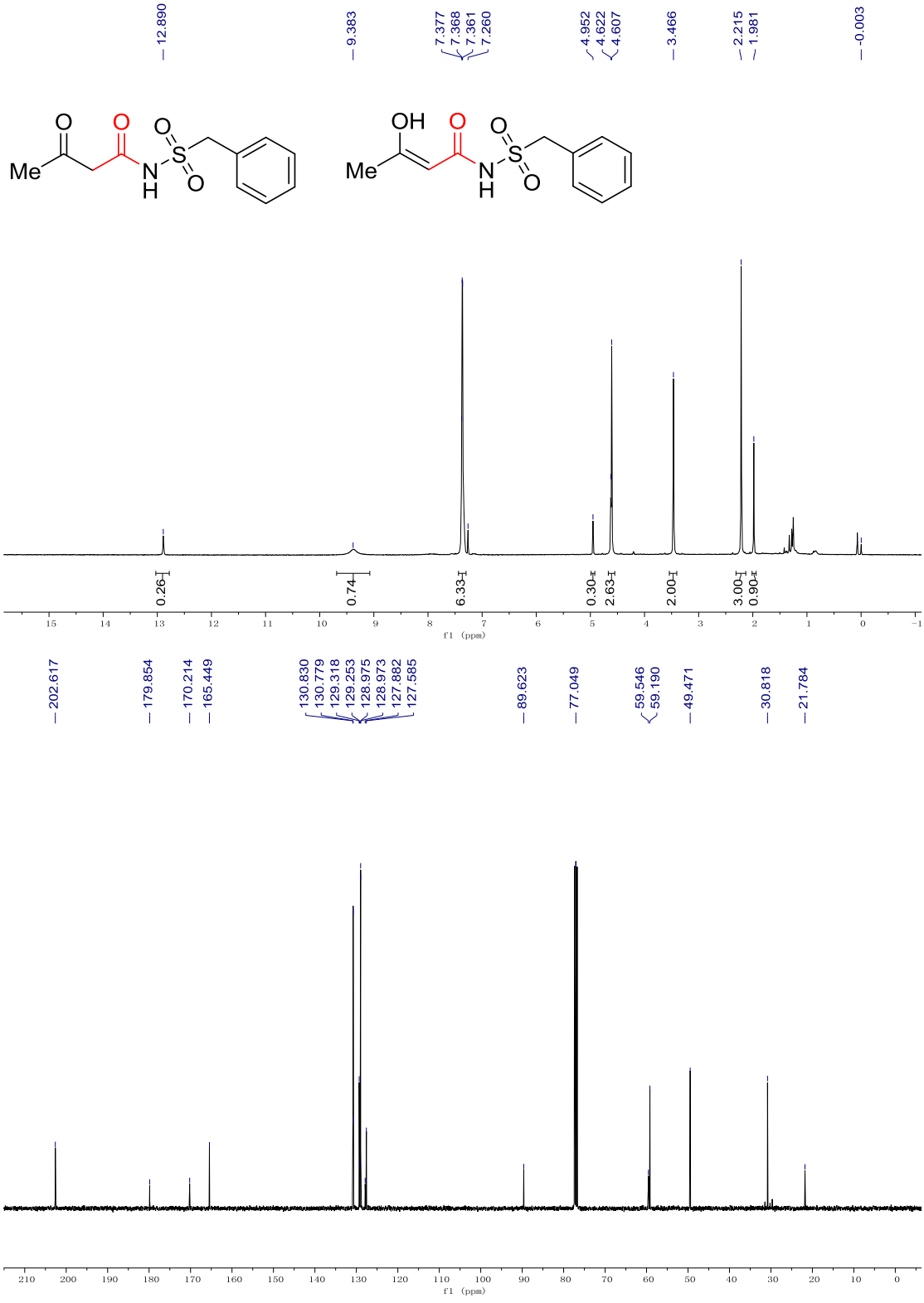
_N_-(Naphthalen-1-ylsulfonyl)-3-oxobutanamide 3i and 3-hydroxy-_N_-(naphthalen-1-ylsulfonyl)but-2-enamide 3i' (3i/3i'=4.2/1)



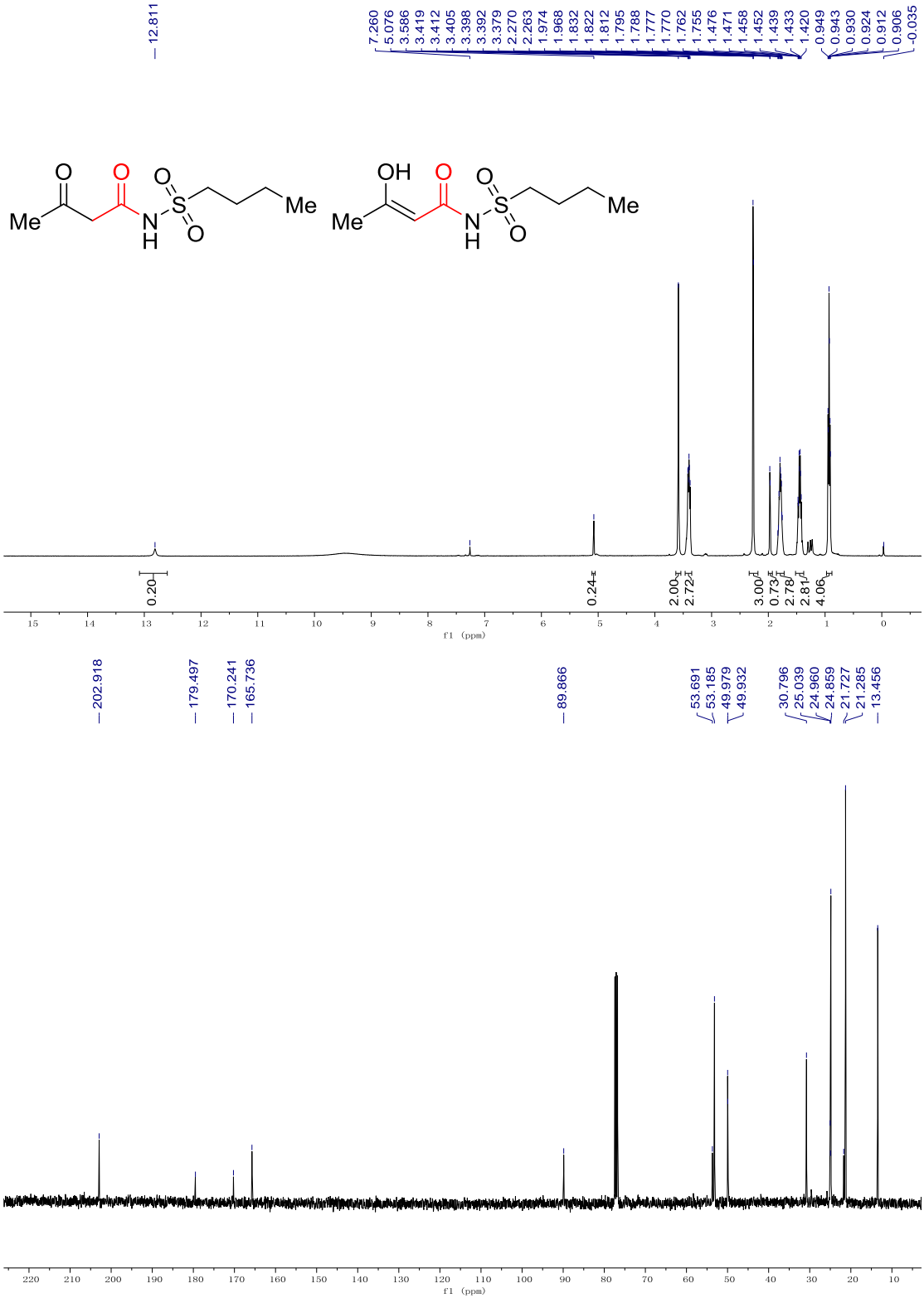
3-Oxo-*N*-(thiophen-2-ylsulfonyl)butanamide 3j and 3-hydroxy-*N*-(thiophen-2-ylsulfonyl)but-2-enamide 3j' (3j/3j'=5/1)



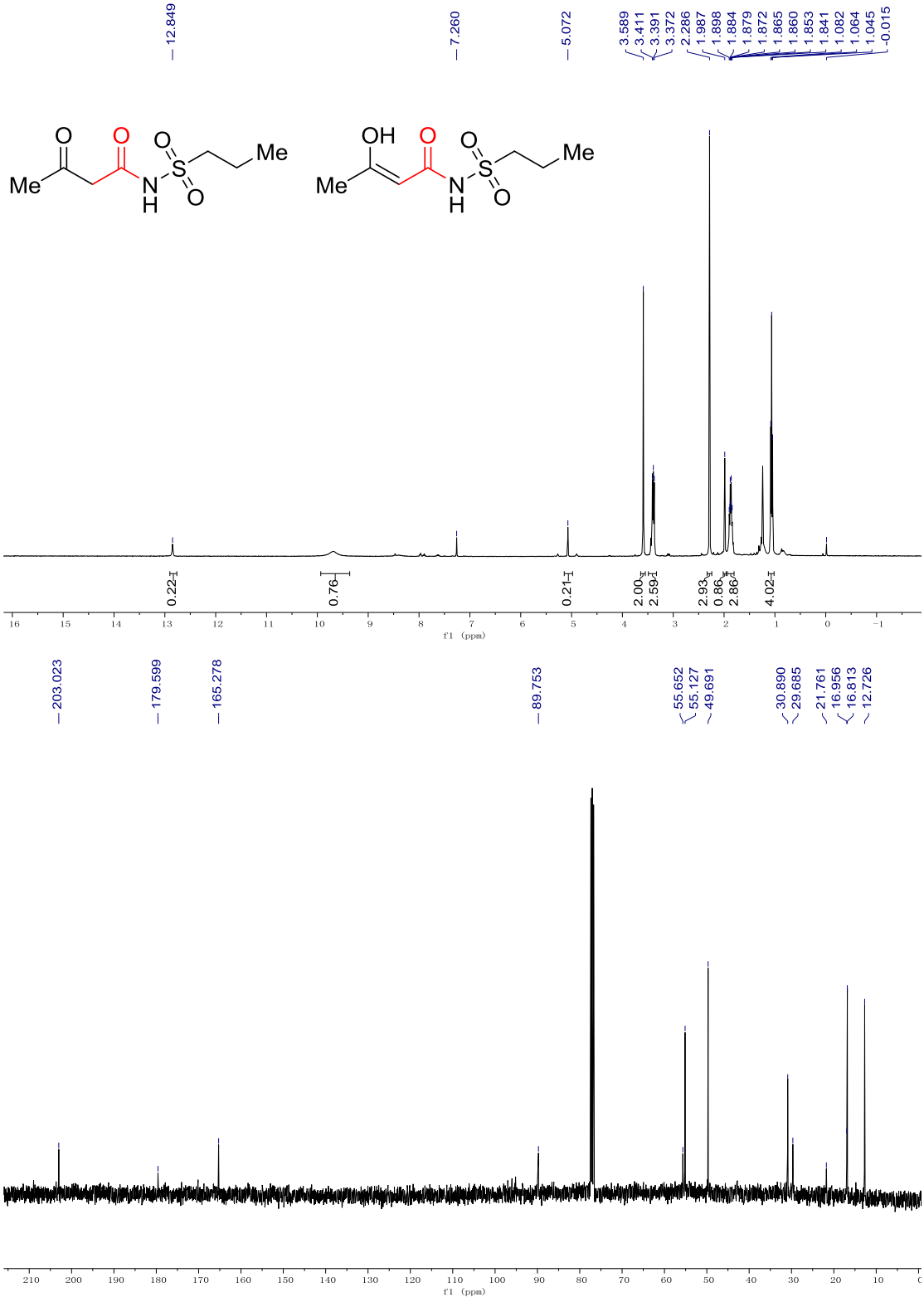
***N*-(Benzylsulfonyl)-3-oxobutanamide 3k and *N*-(benzylsulfonyl)-3-hydroxybut-2-enamide 3k' (3k/3k'=3.7/1)**



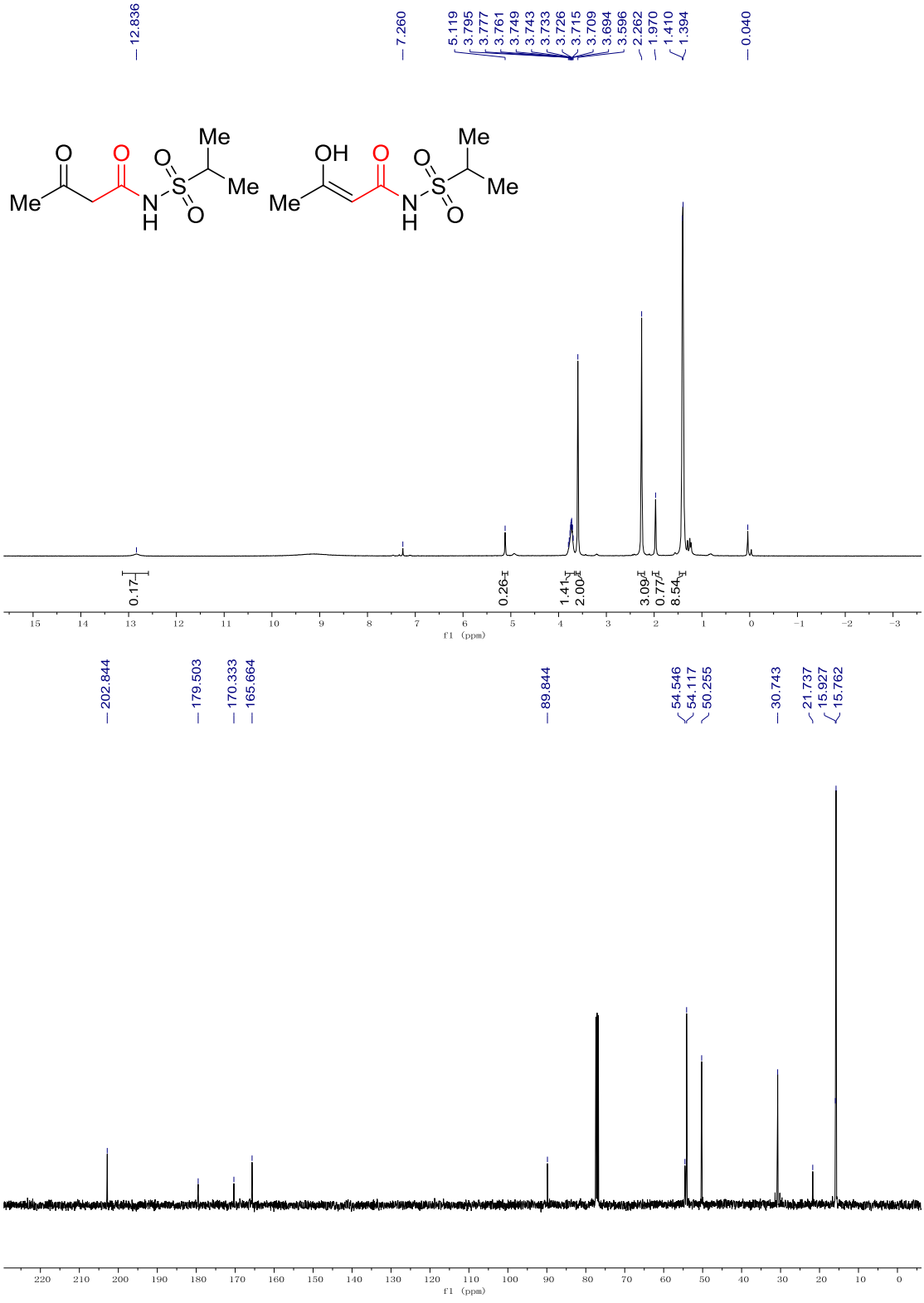
***N*-(Butylsulfonyl)-3-oxobutanamide 3l and *N*-(butylsulfonyl)-3-hydroxybut-2-enamide 3l' (3l/3l'=4.2/1)**



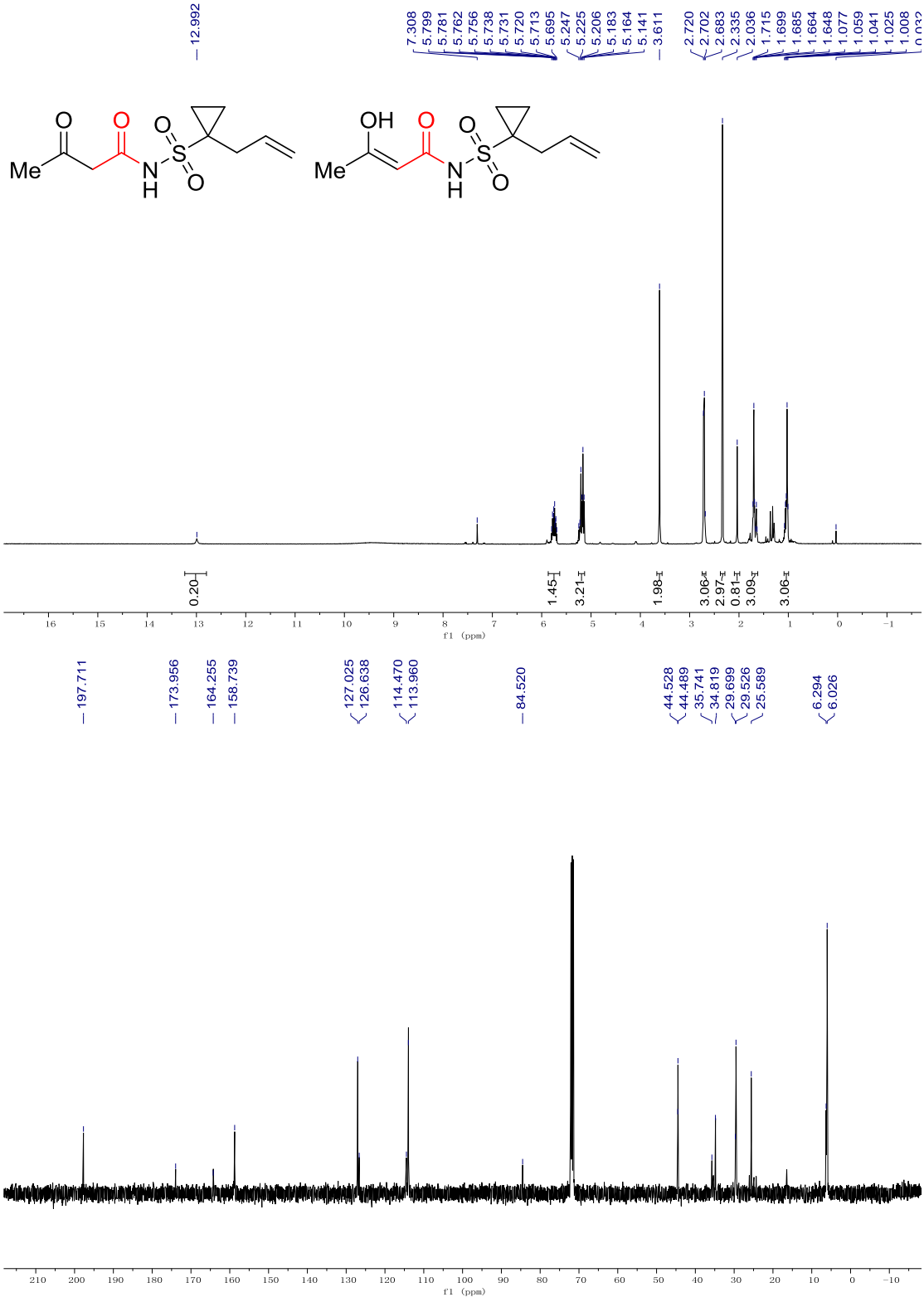
3-Oxo-*N*-(propylsulfonyl)butanamide 3m and 3-hydroxy-*N*-(propylsulfonyl)but-2-enamide 3m' (3m/3m'=5/1)



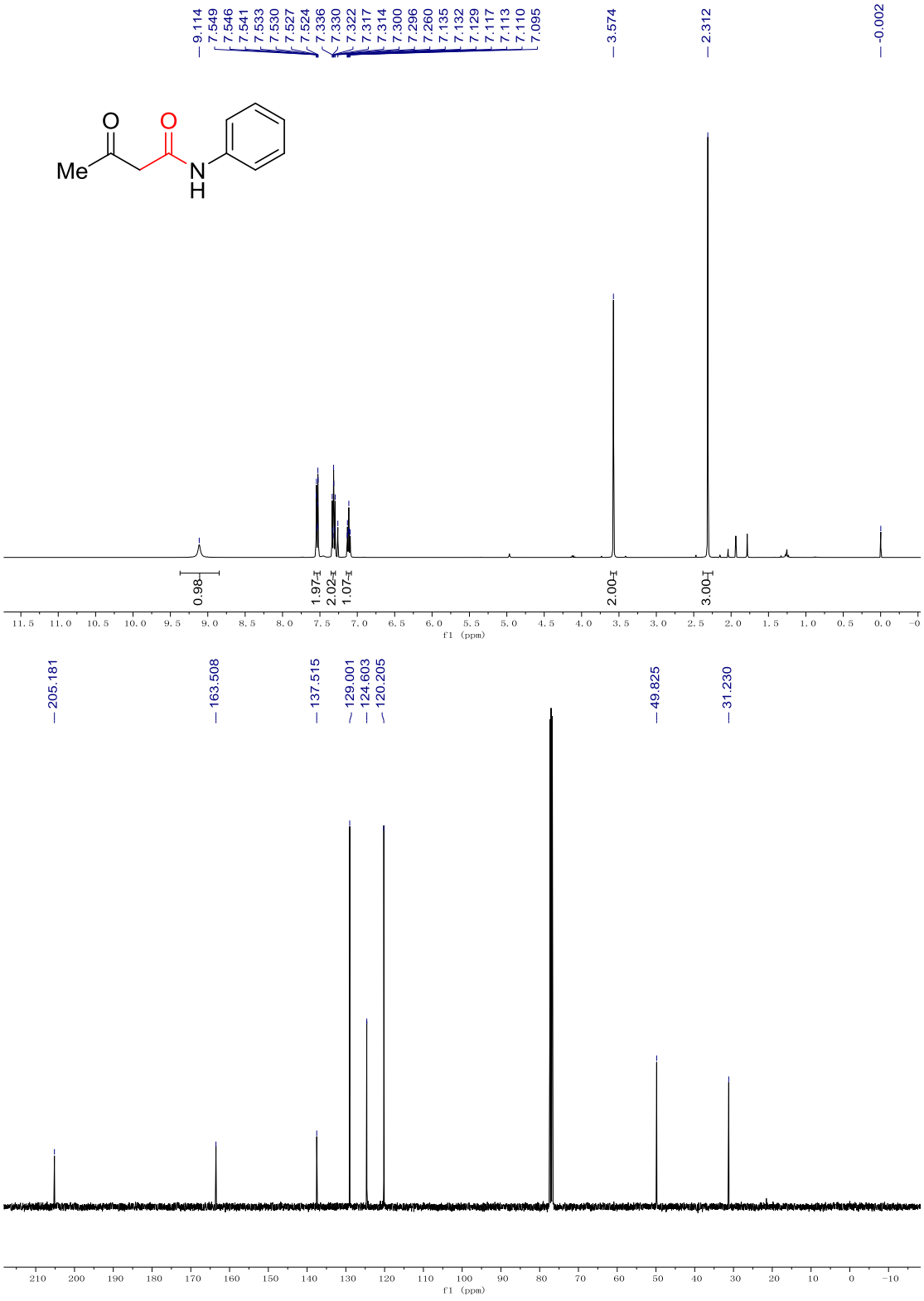
***N*-(Isopropylsulfonyl)-3-oxobutanamide 3n and 3-hydroxy-*N*-(isopropylsulfonyl)but-2-enamide 3n' (3n/3n'=4/1)**



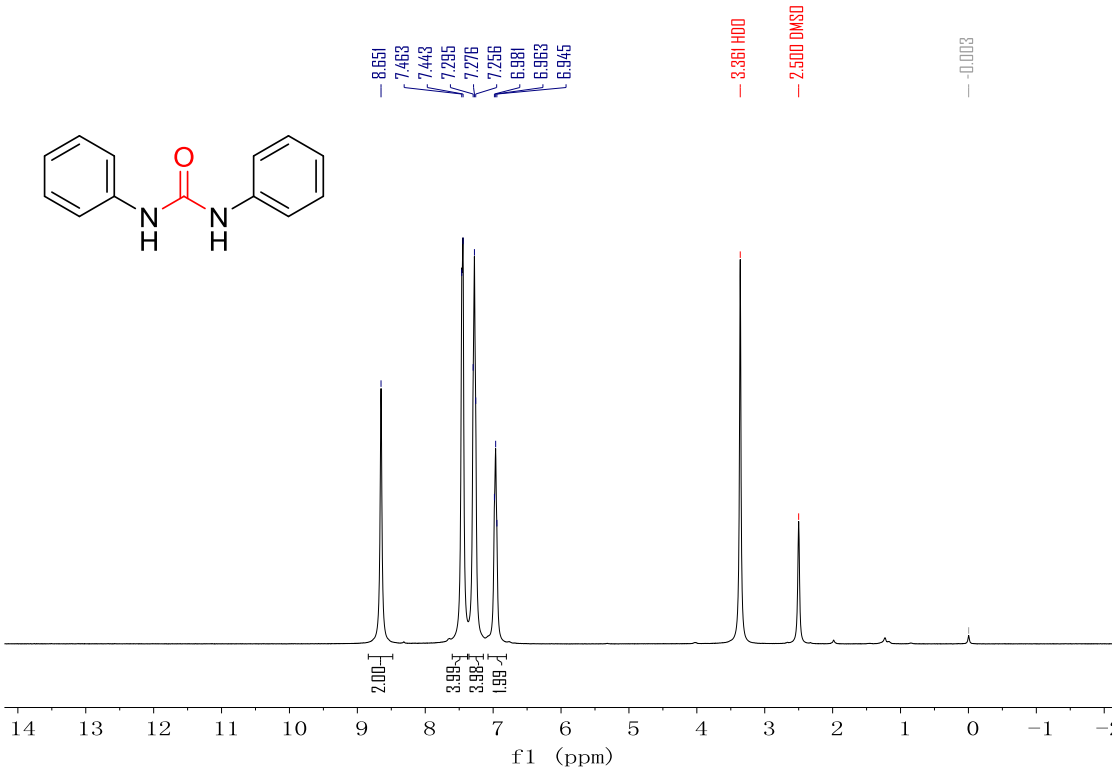
_N_-((1-Allylcyclopropyl)sulfonyl)-3-oxobutanamide 3o and _N_-((1-allylcyclopropyl)sulfonyl)-3-hydroxybut-2-enamide 3o' (3o/3o'=3.8/1)

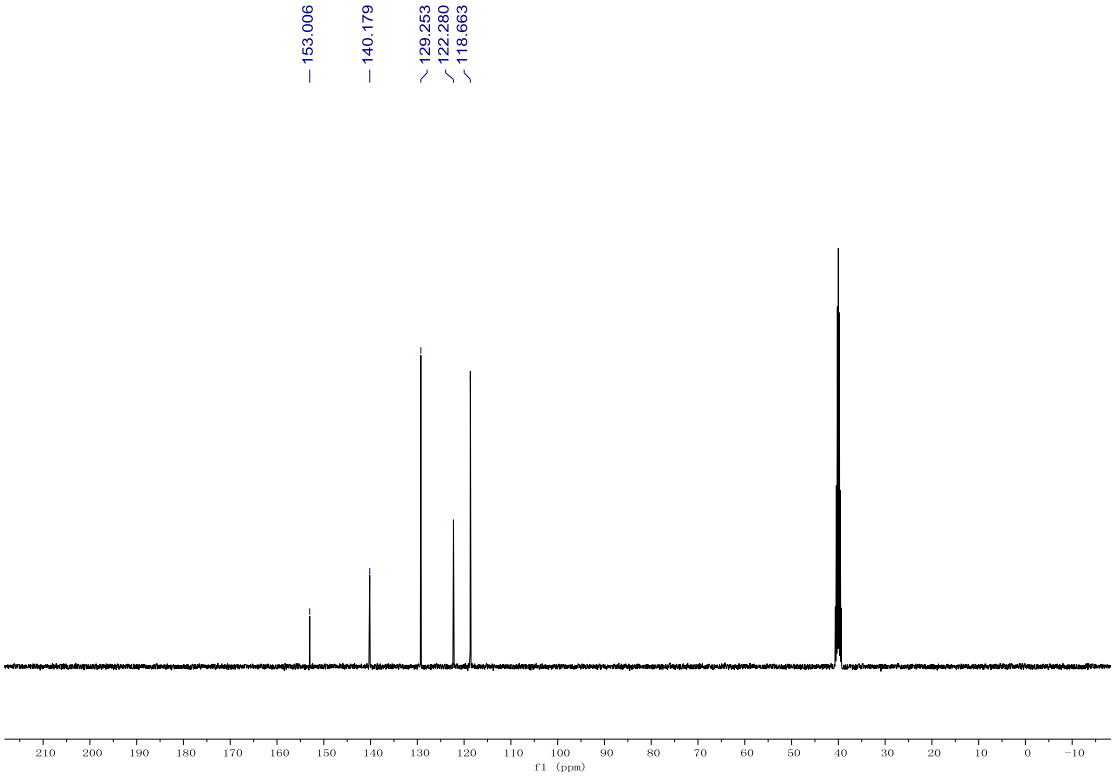


3-Oxo-*N*-phenylbutanamide 3p

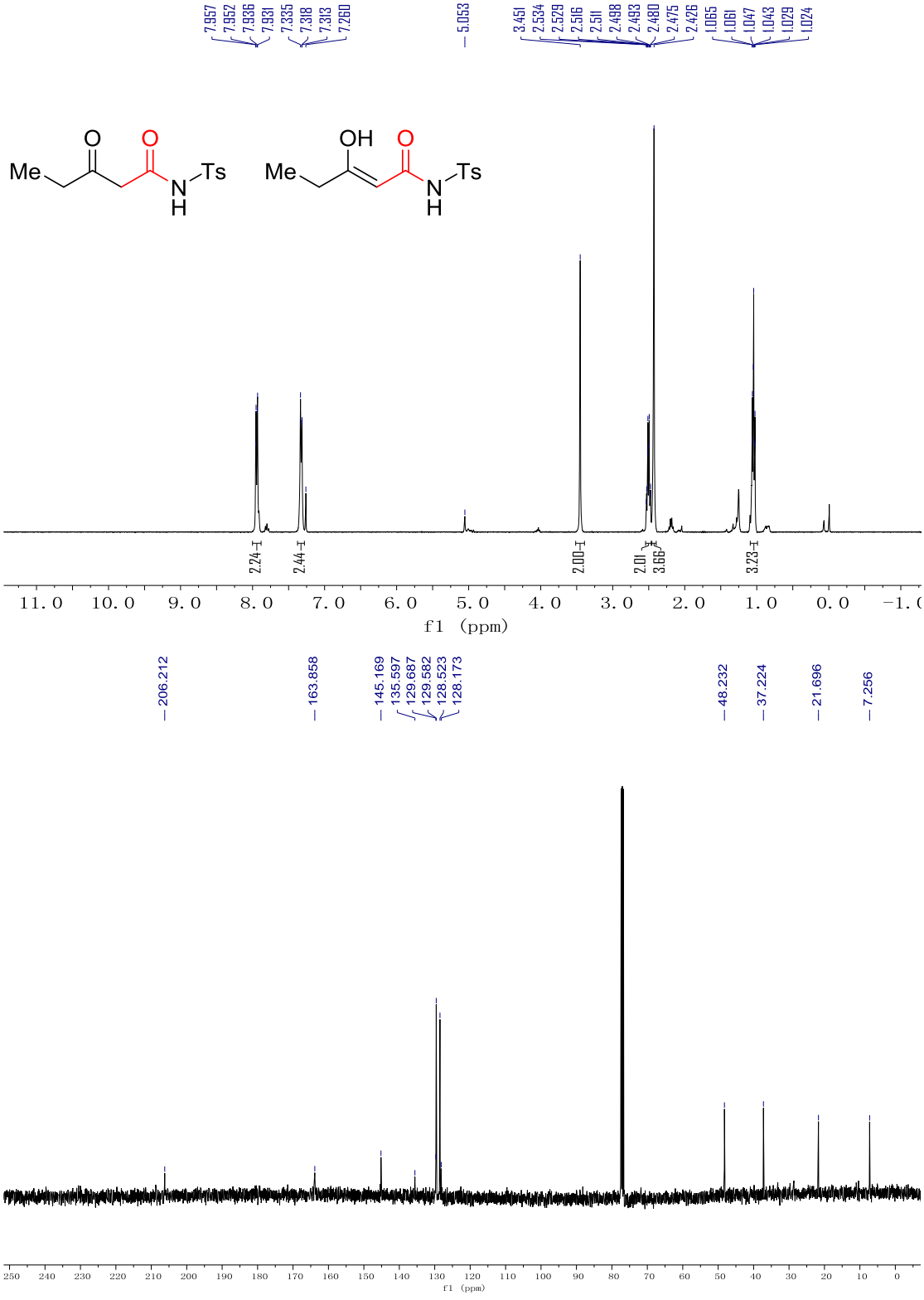


1,3-Diphenylurea 3p’

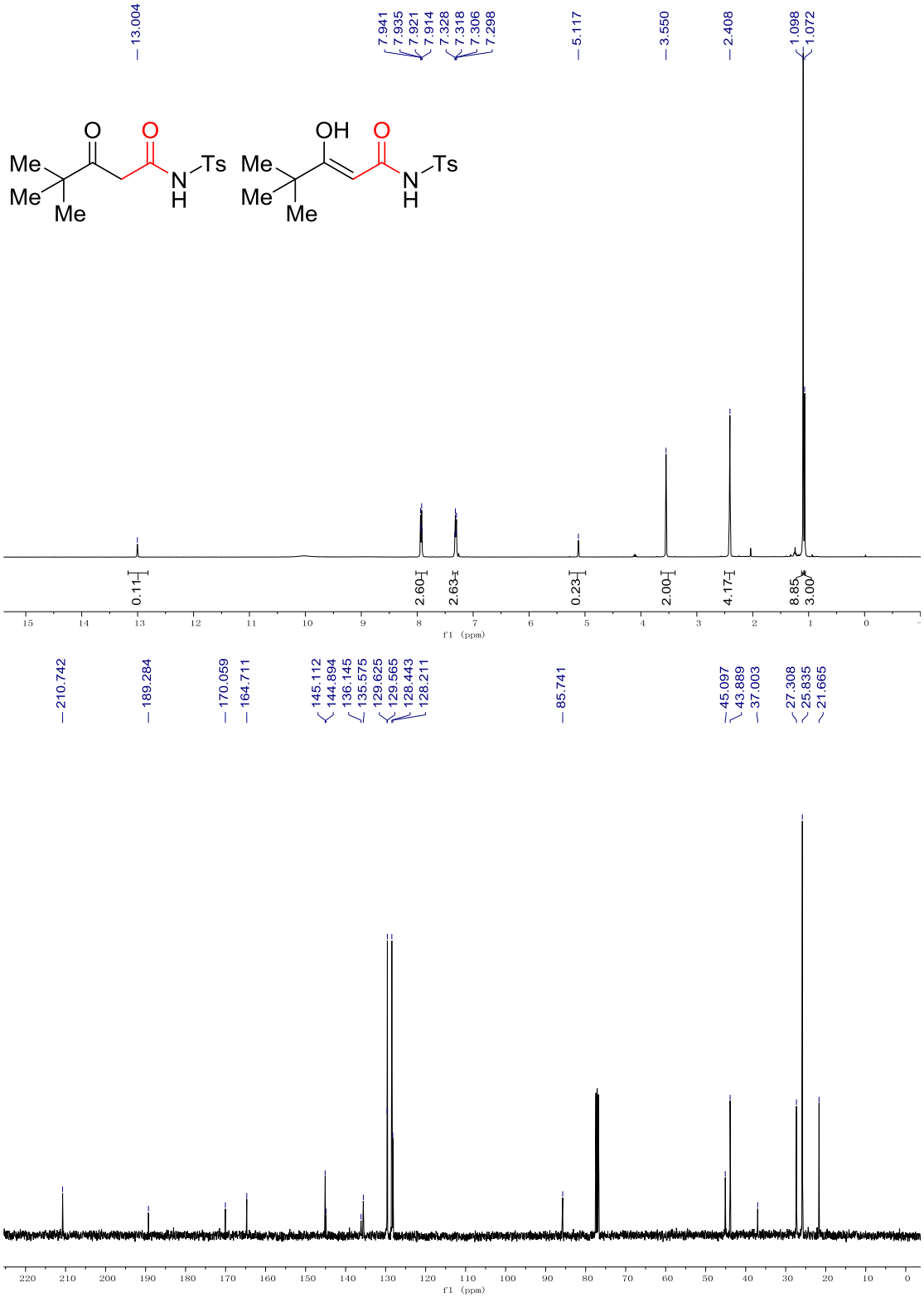




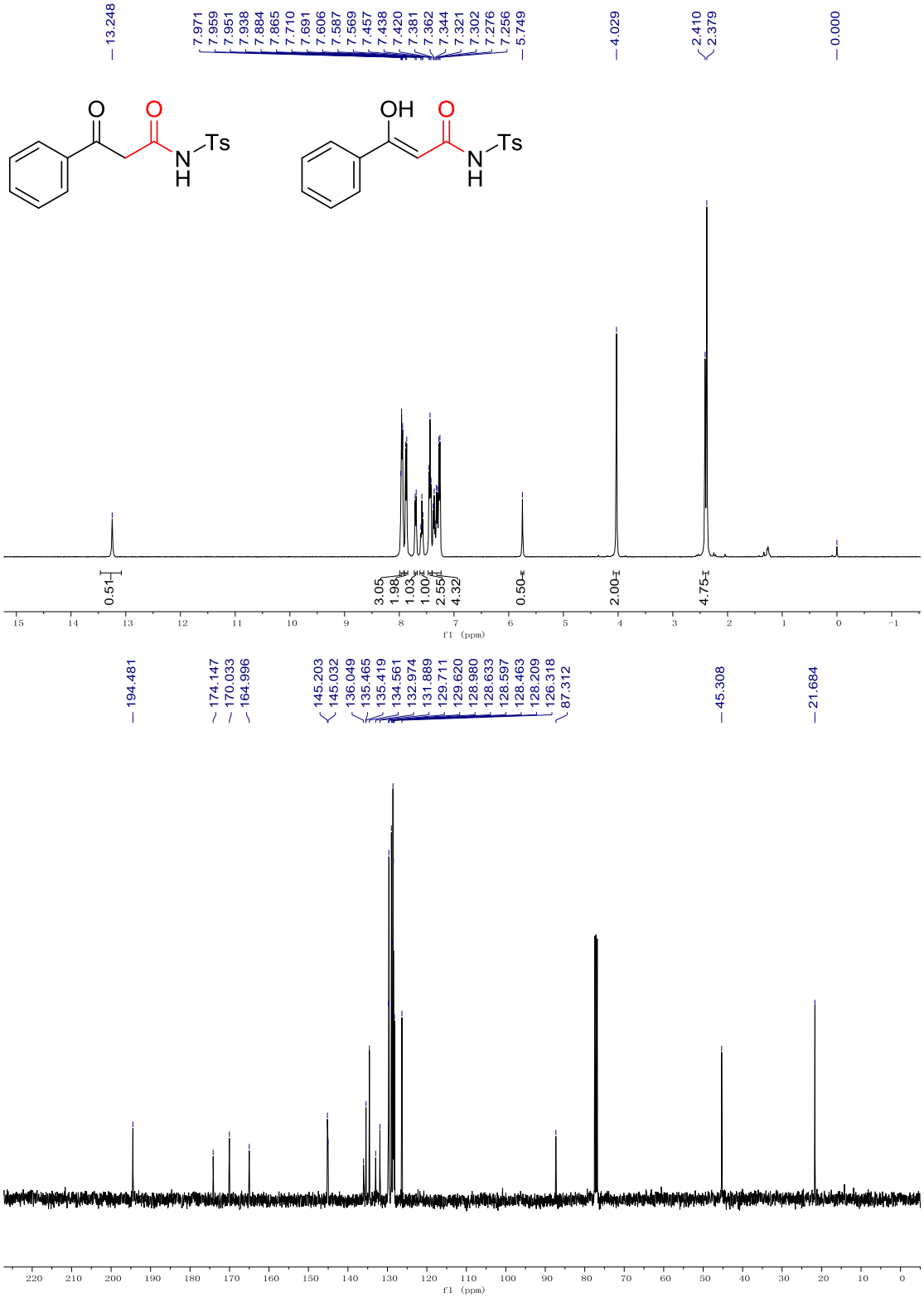
3-Oxo-*N*-tosylpentanamide 3q and 3-hydroxy-*N*-tosylpent-2-enamide 3q' (3q/3q'=7.7/1)



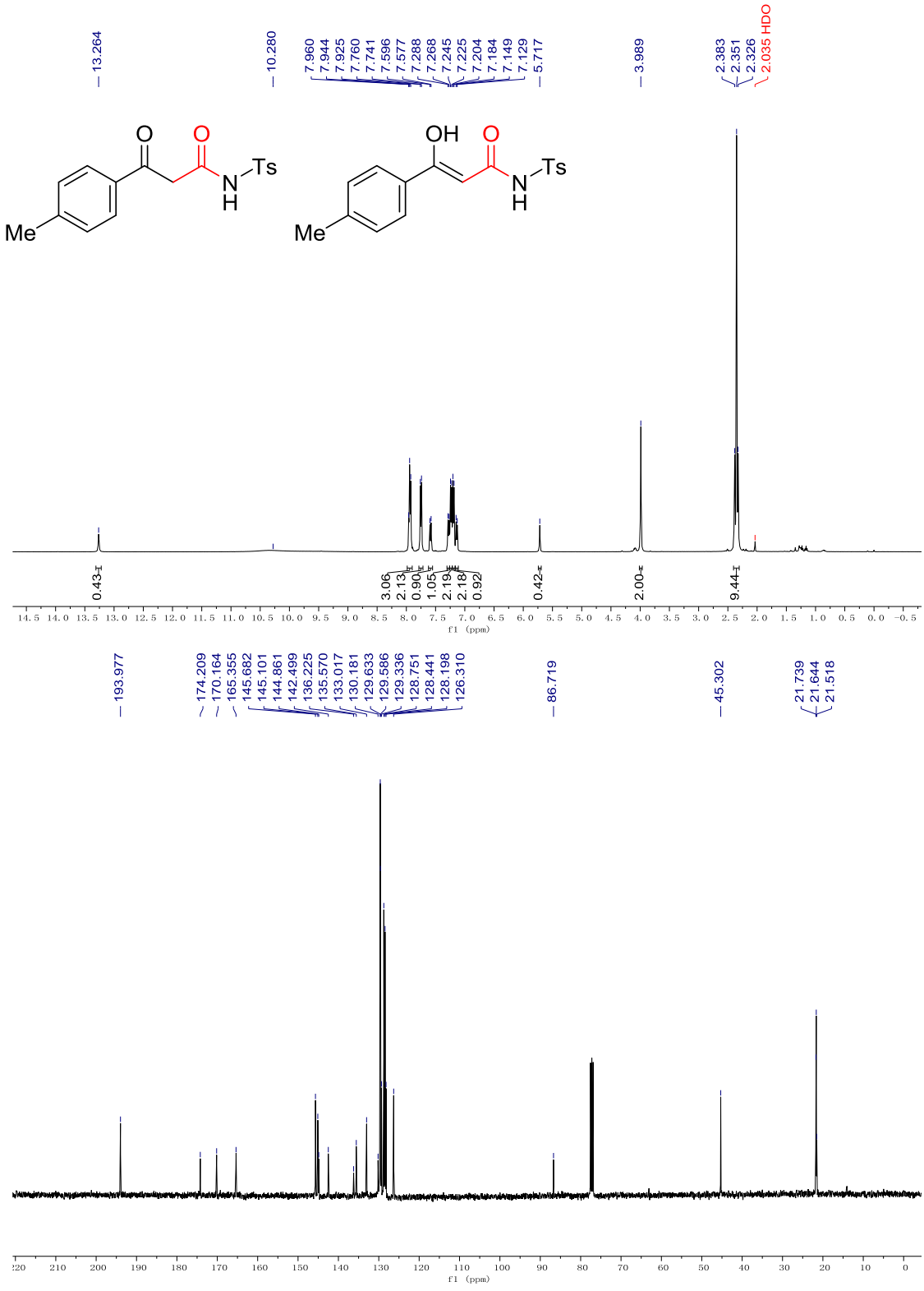
4,4-Dimethyl-3-oxo-*N*-tosylpentanamide 3r and 3-hydroxy-4,4-dimethyl-*N*-tosylpent-2-enamide 3r' (3r/3r'=3.3/1)



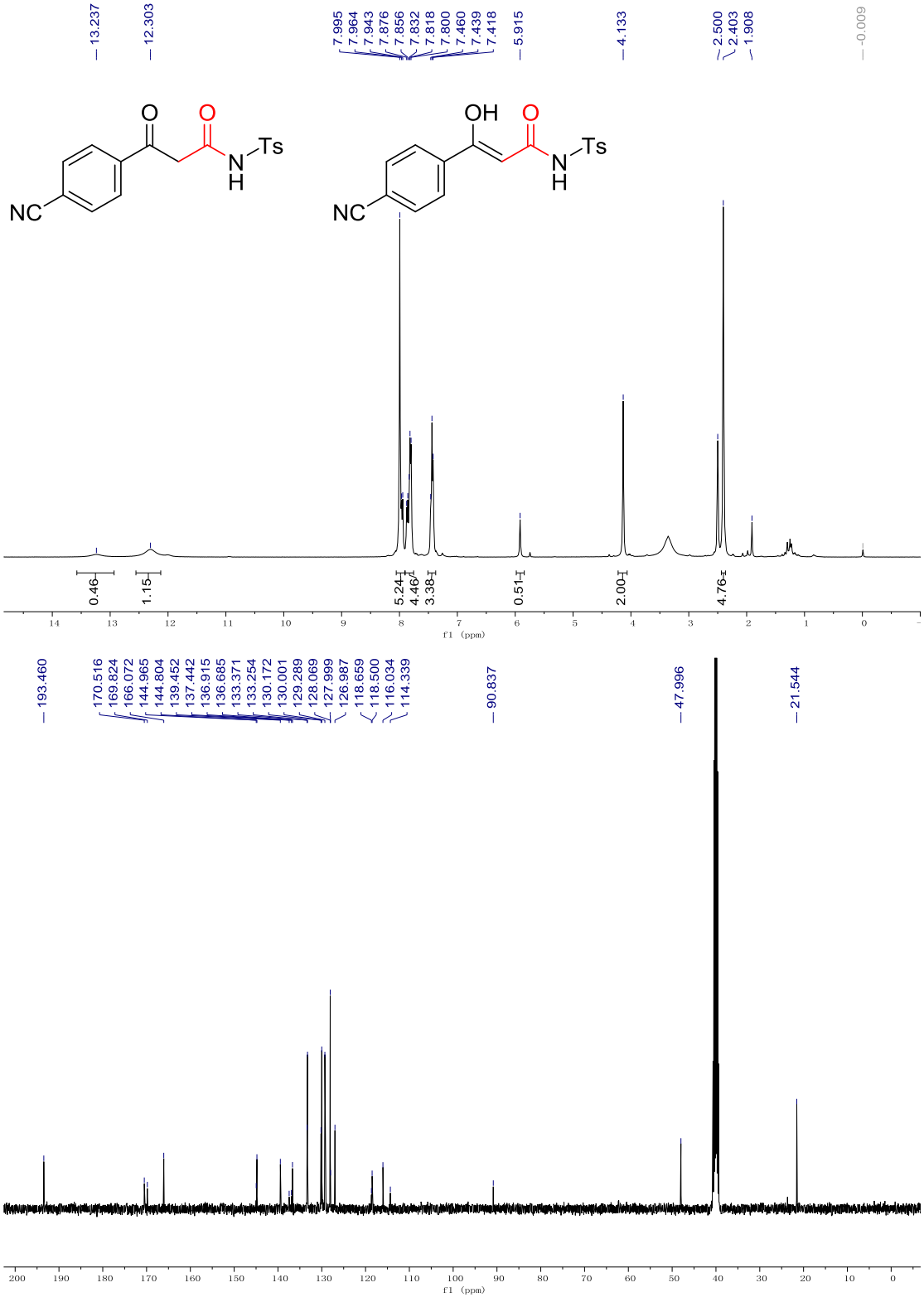
3-Oxo-3-phenyl-*N*-tosylpropanamide 3s and 3-hydroxy-3-phenyl-*N*-tosylacrylamide 3s' (3s/3s'=2/1)



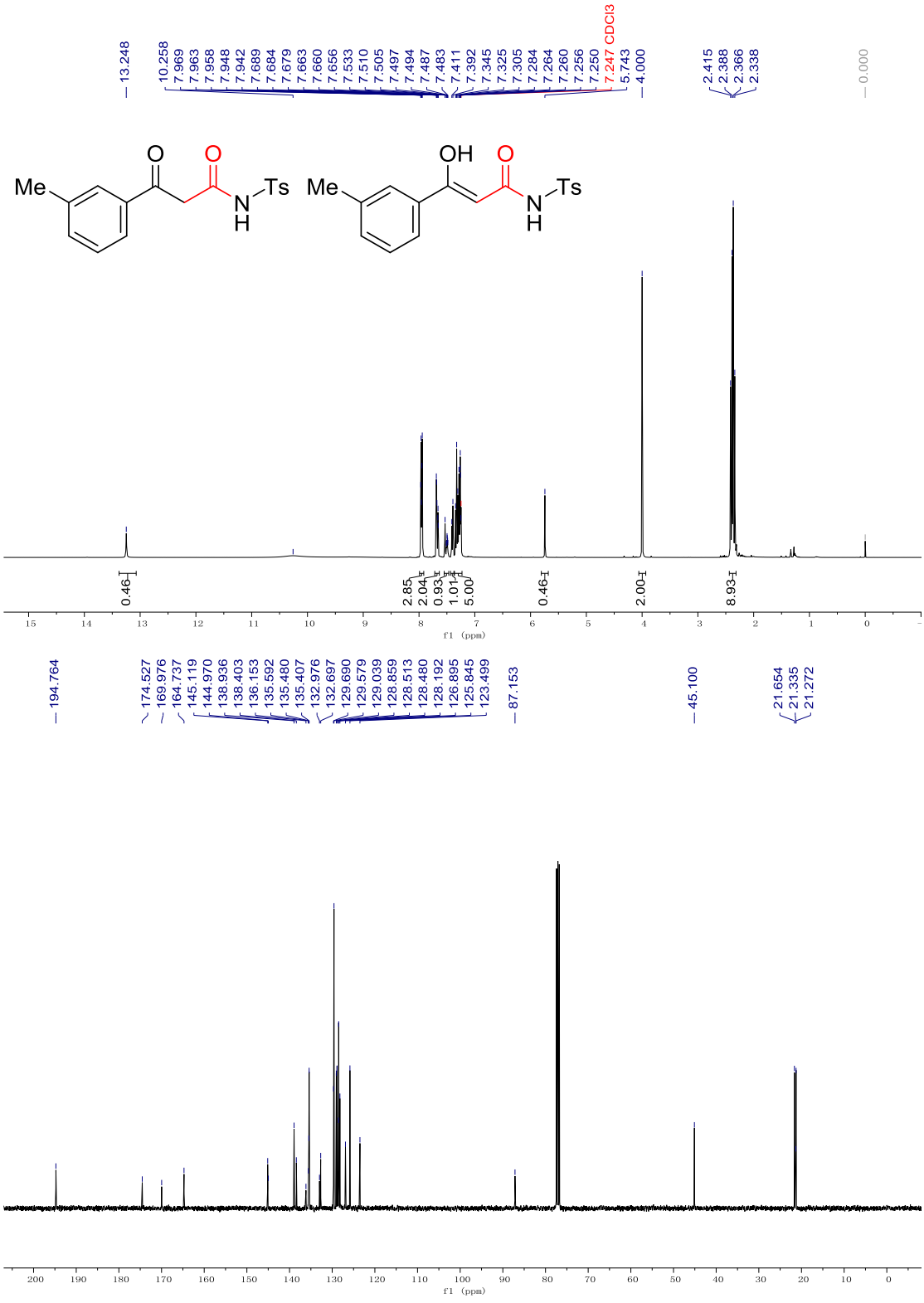
3-Oxo-3-(*p*-tolyl)-*N*-tosylpropanamide 3t and 3-hydroxy-3-(*p*-tolyl)-*N*-tosylacrylamide 3t' (3t/3t'=2.4/1)



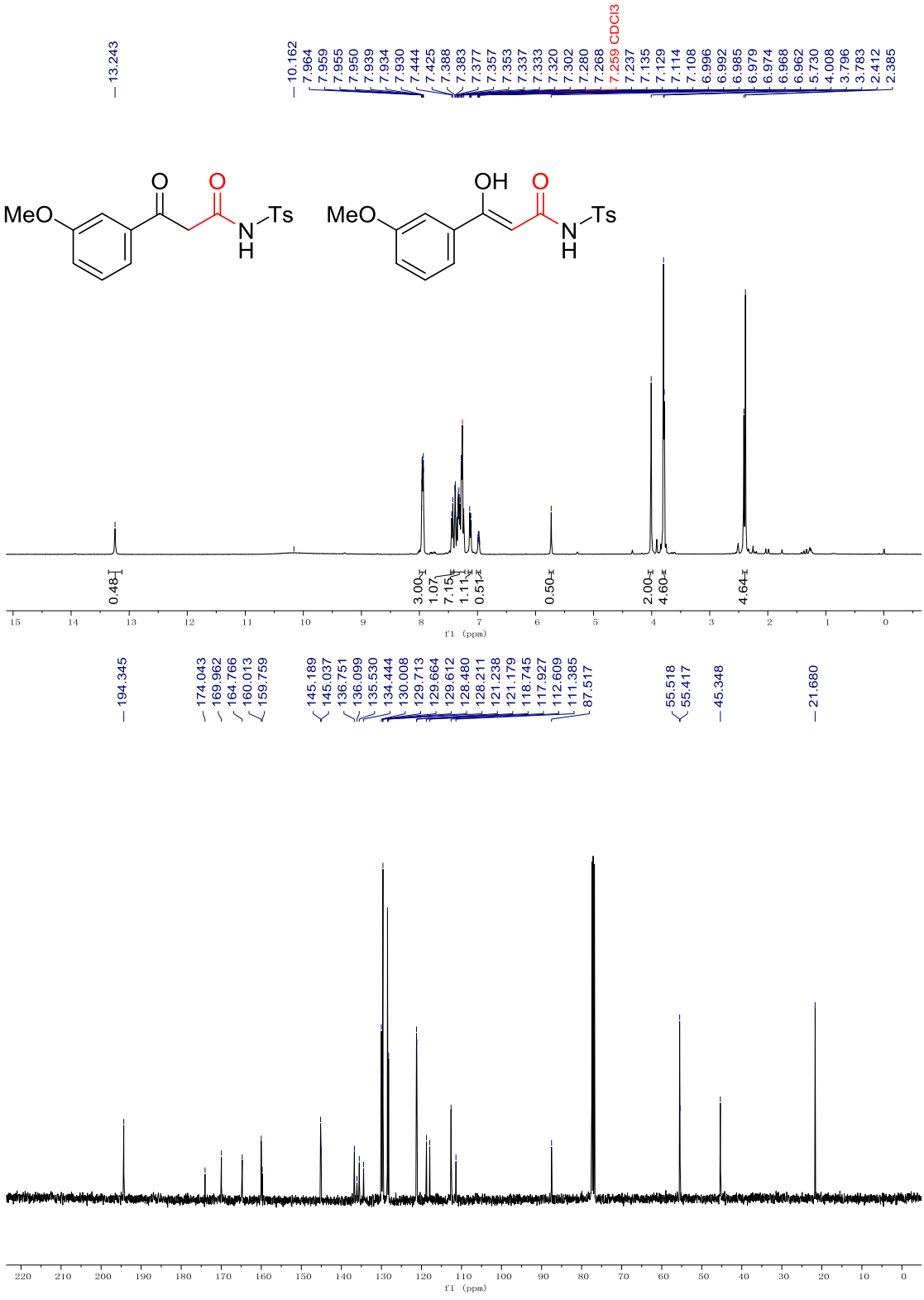
3-(4-Cyanophenyl)-3-oxo-*N*-tosylpropanamide 3u and 3-(4-cyanophenyl)-3-hydroxy-*N*-tosylacrylamide 3u' (3u/3u'=2/1)



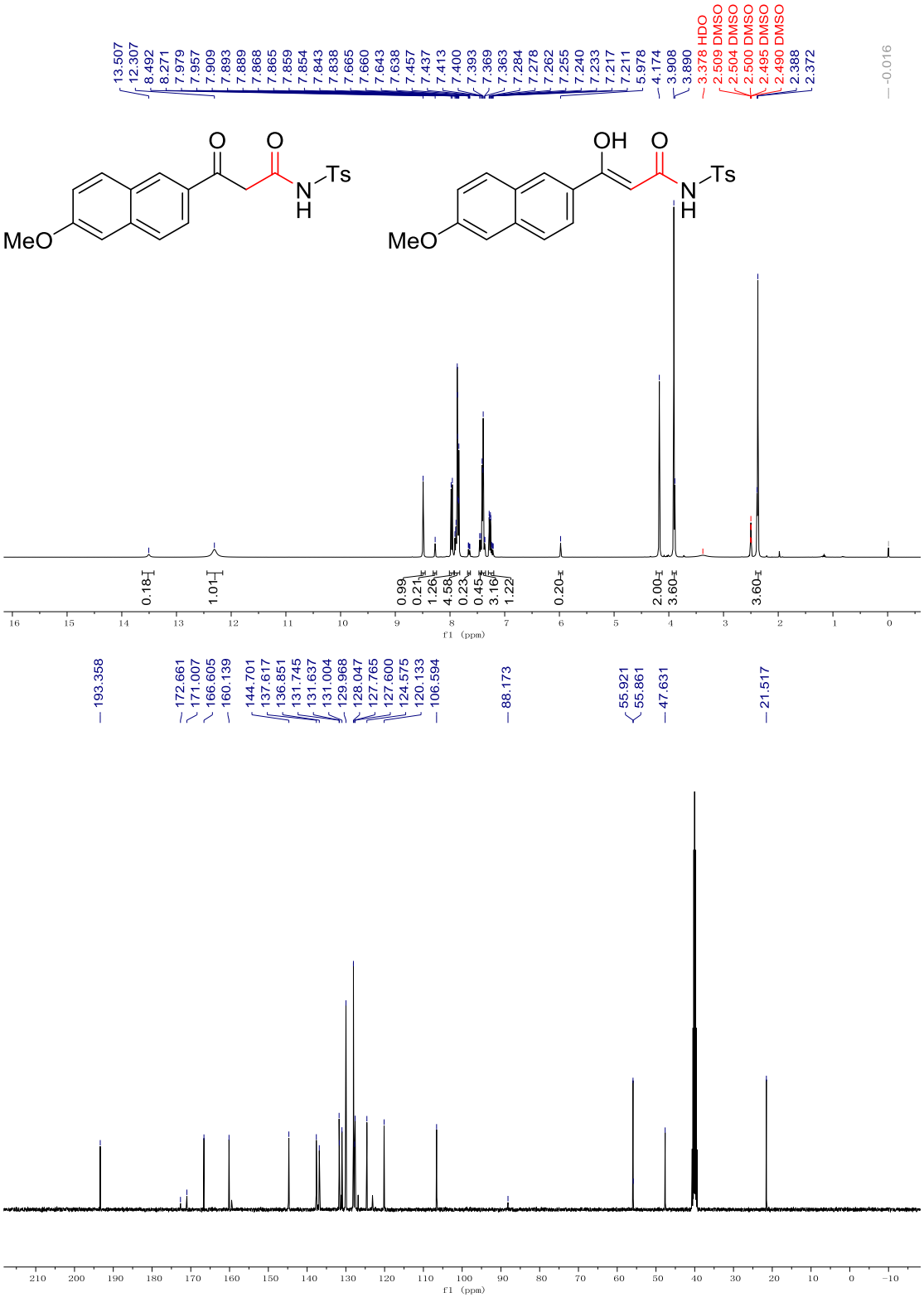
3-Oxo-3-(*m*-tolyl)-*N*-tosylpropanamide 3v and 3-hydroxy-3-(*m*-tolyl)-*N*-tosylacrylamide 3v' (3v/3v'=2.2/1)



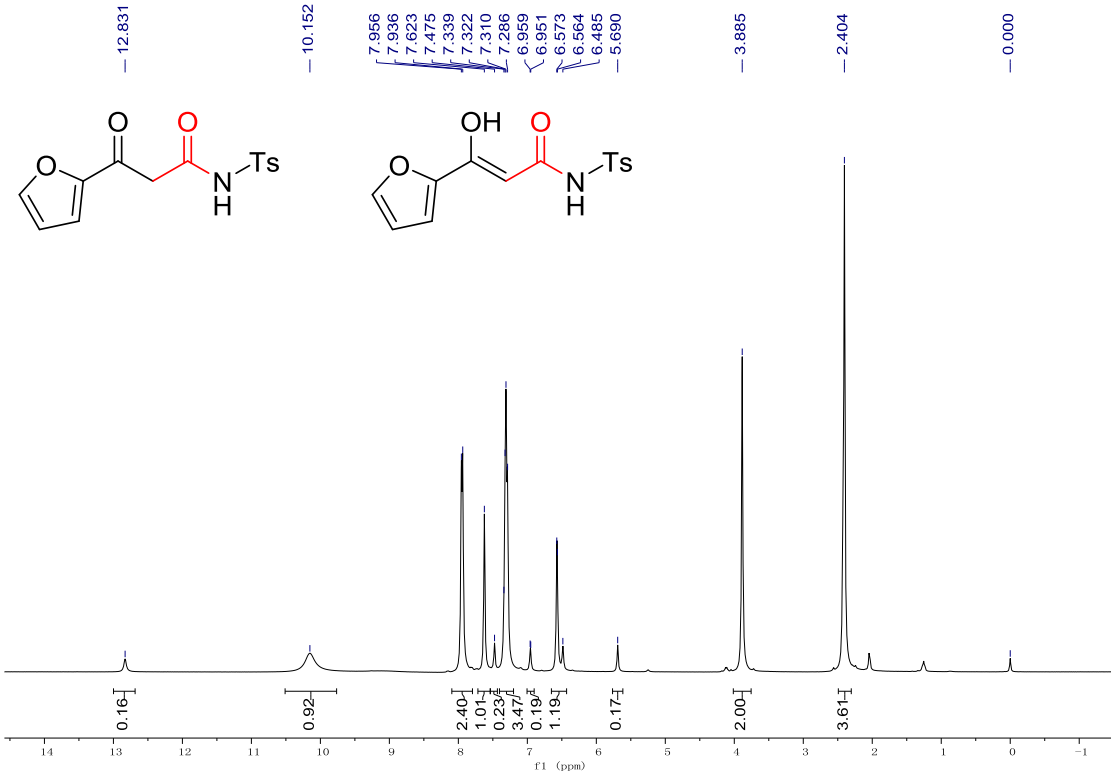
3-(3-Methoxyphenyl)-3-oxo-*N*-tosylpropanamide 3w and 3-hydroxy-3-(3-methoxyphenyl)-*N*-tosylacrylamide 3w' (3w/3w'=2/1)

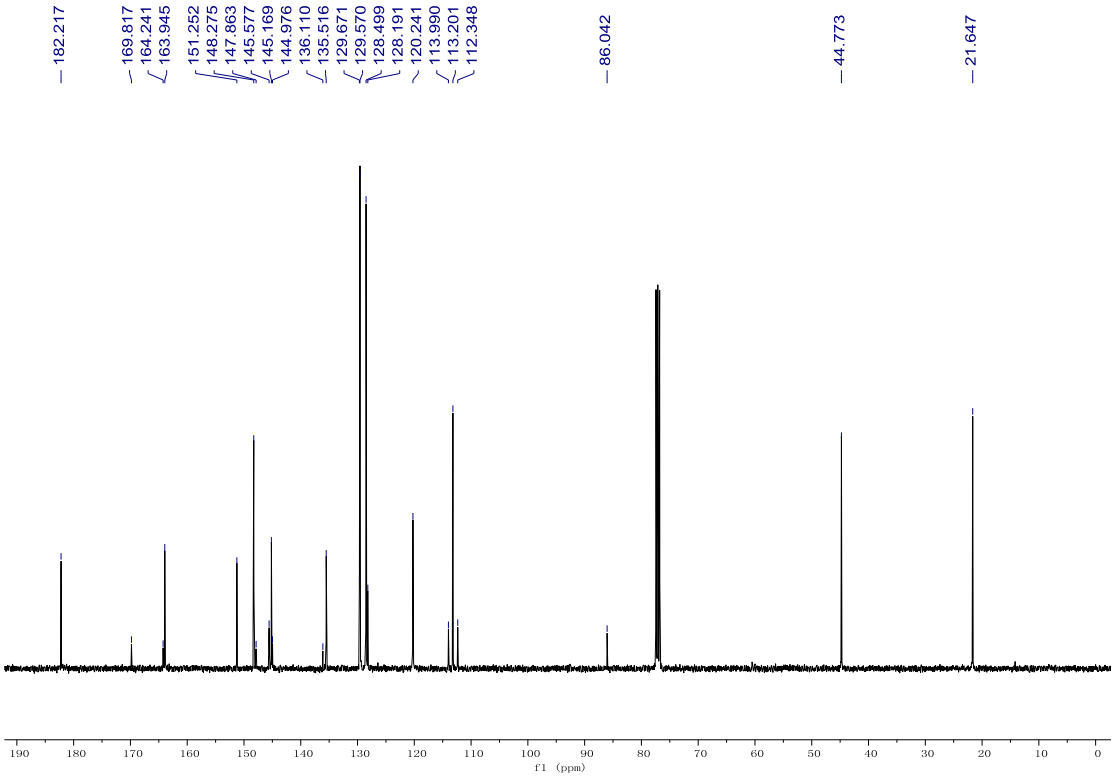


3-(6-Methoxynaphthalen-2-yl)-3-oxo-*N*-tosylpropanamide 3x and 3-hydroxy-3-(6-methoxynaphthalen-2-yl)-*N*-tosylacrylamide 3x' (3x/3x'=5/1)

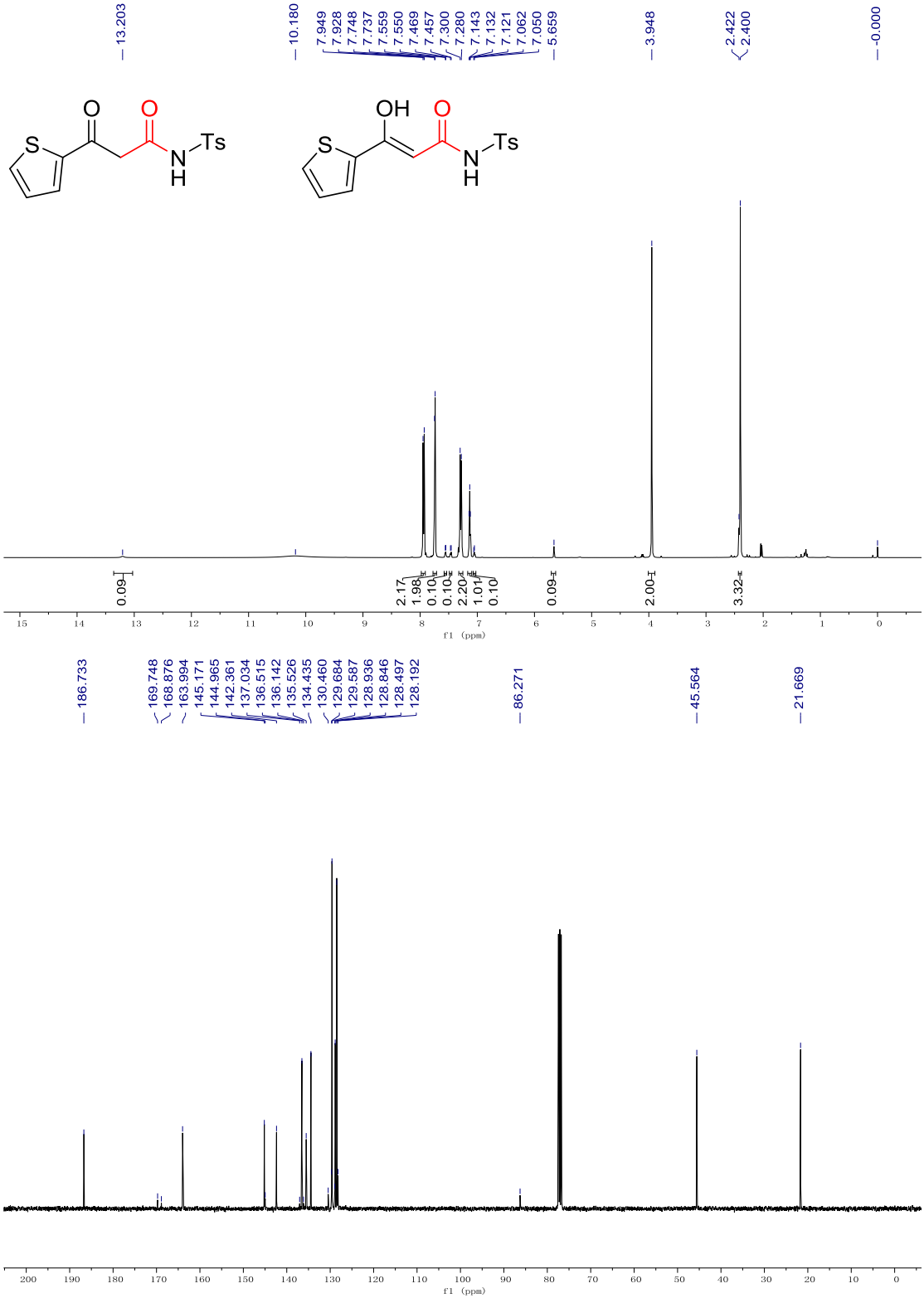


3-(Furan-2-yl)-3-oxo-*N*-tosylpropanamide 3y and 3-(furan-2-yl)-3-hydroxy-*N*-tosylacrylamide 3y' (3y/3y'=5.9/1)

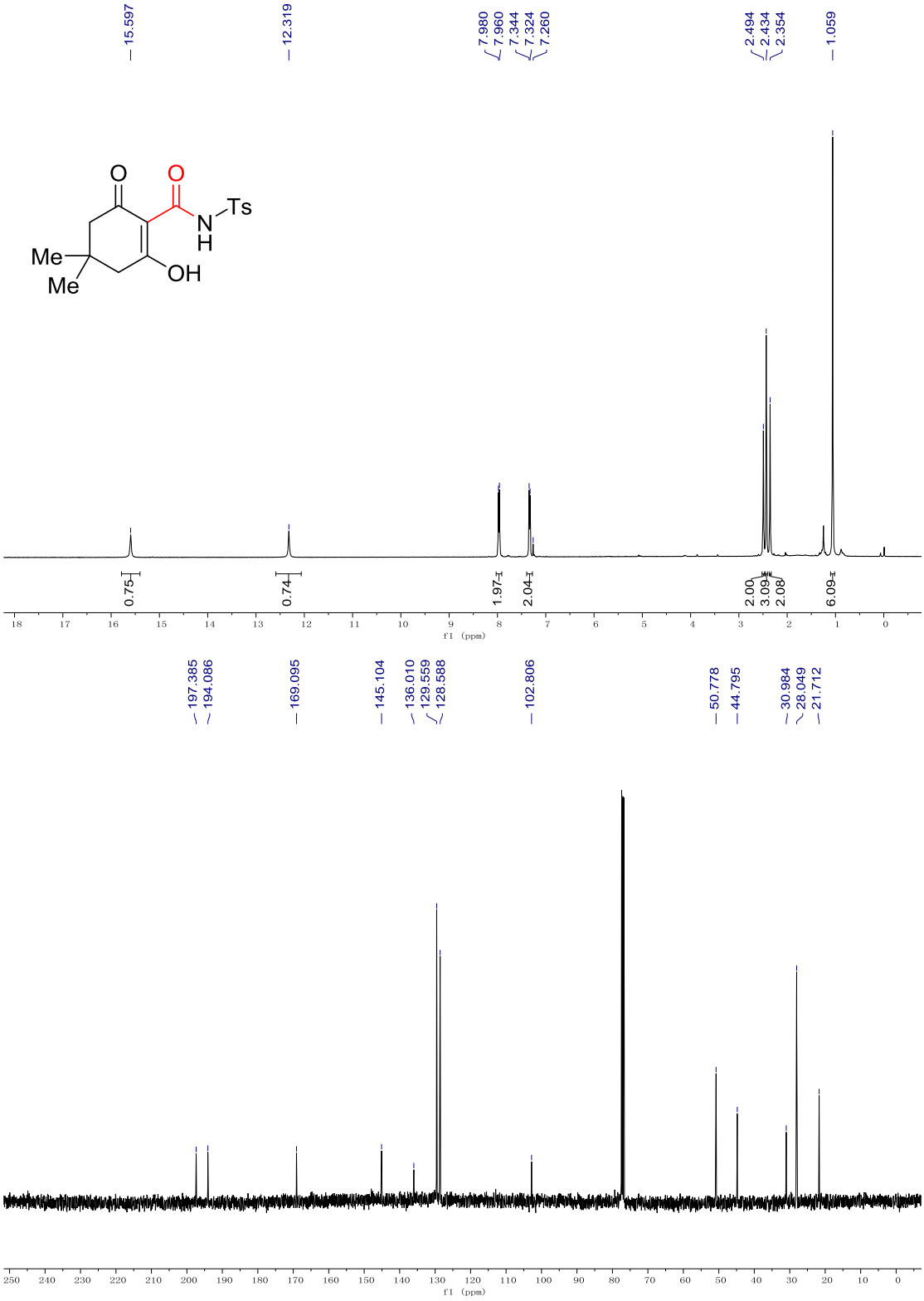




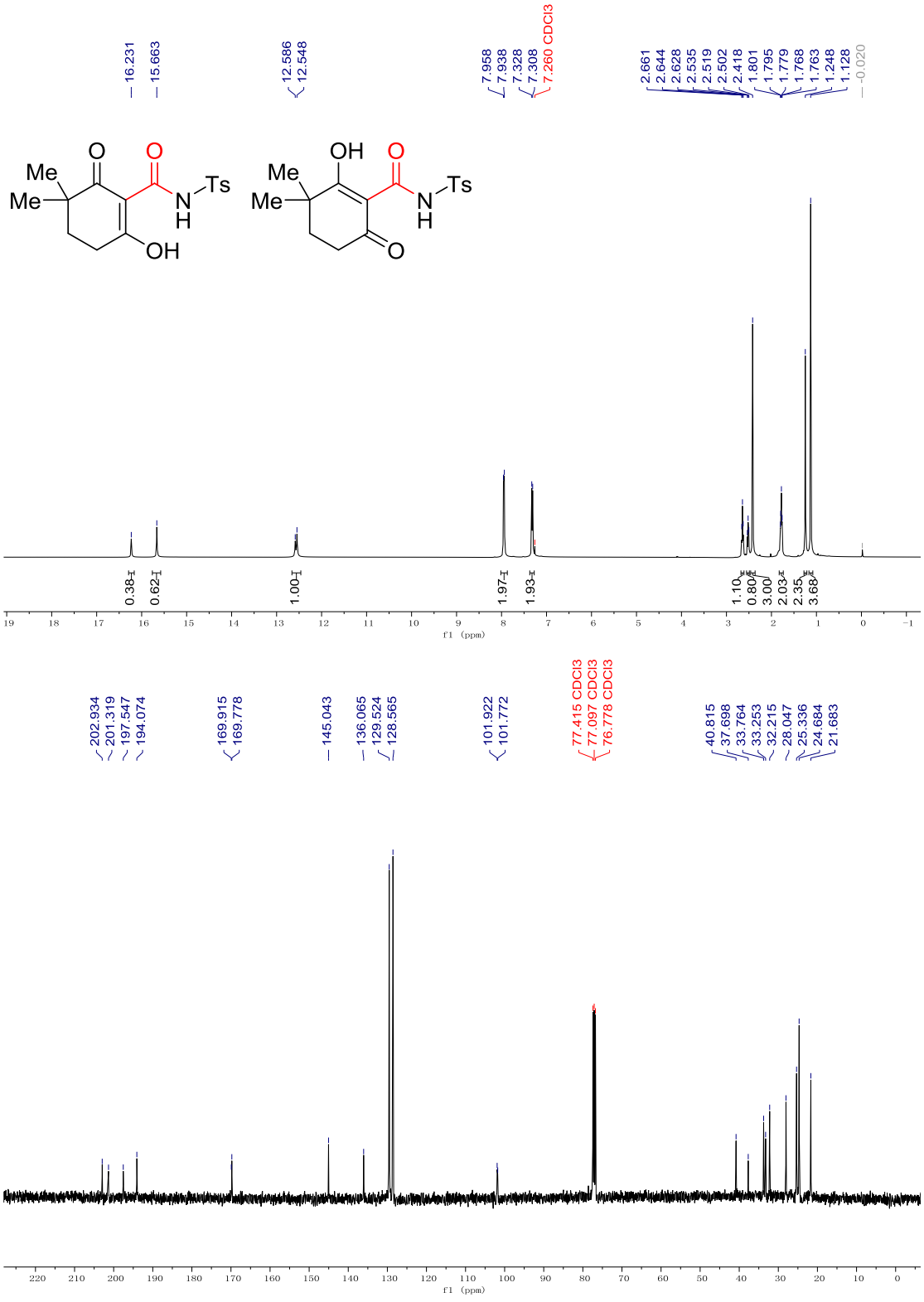
3-Oxo-3-(thiophen-2-yl)-*N*-tosylpropanamide 3z and 3-hydroxy-3-(thiophen-2-yl)-*N*-tosylacrylamide 3z' (3z/3z'=11/1)



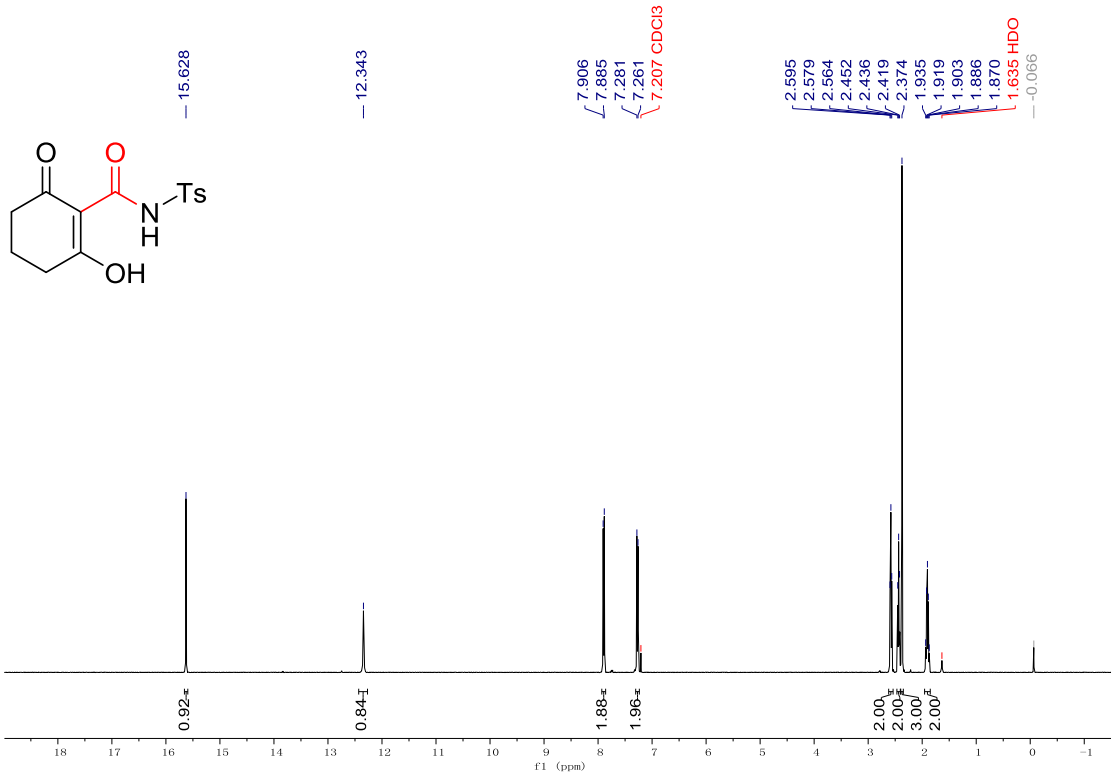
2-Hydroxy-4,4-dimethyl-6-oxo-*N*-tosylcyclohex-1-ene-1-carboxamide 4a

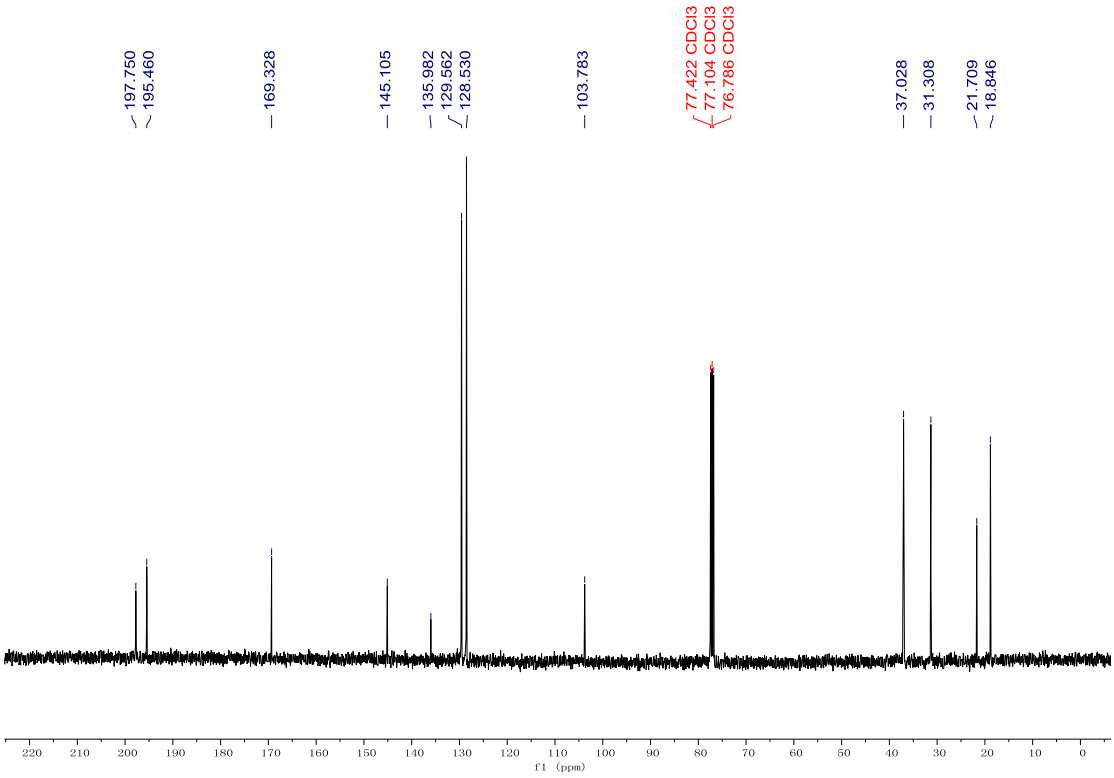


2-Hydroxy-5,5-dimethyl-6-oxo-*N*-tosylcyclohex-1-ene-1-carboxamide 4b and 2-hydroxy-3,3-dimethyl-6-oxo-*N*-tosylcyclohex-1-ene-1-carboxamide 4b' (1.6/1)

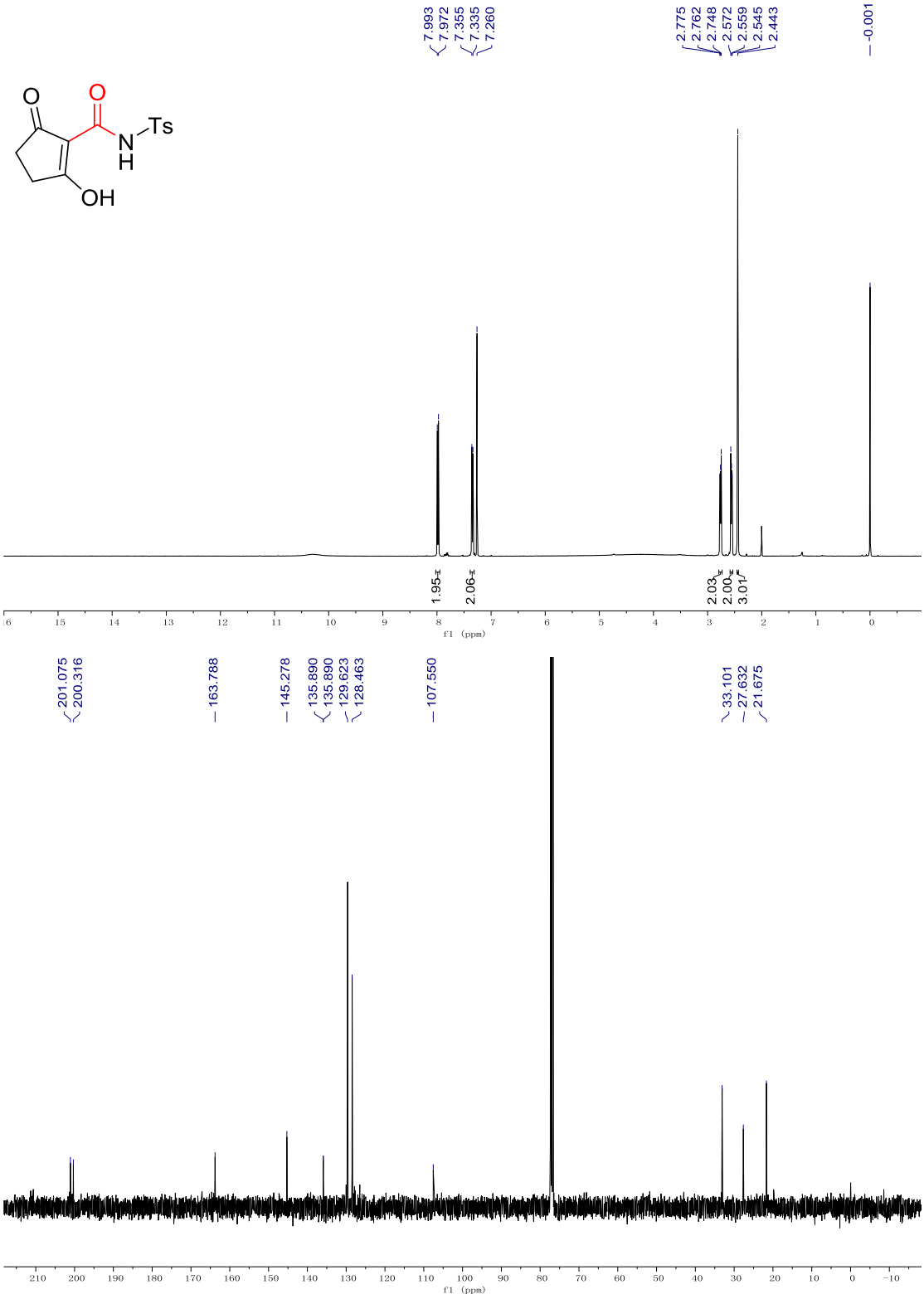


2-Hydroxy-6-oxo-*N*-tosylcyclohex-1-ene-1-carboxamide 4c

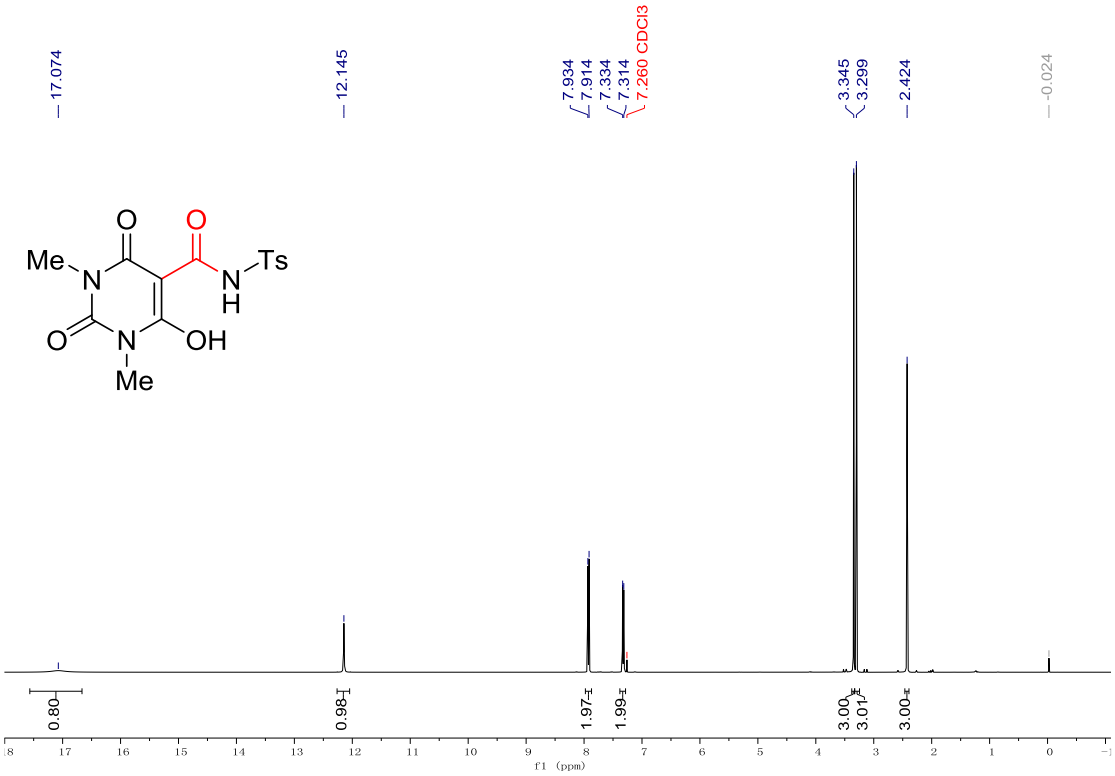


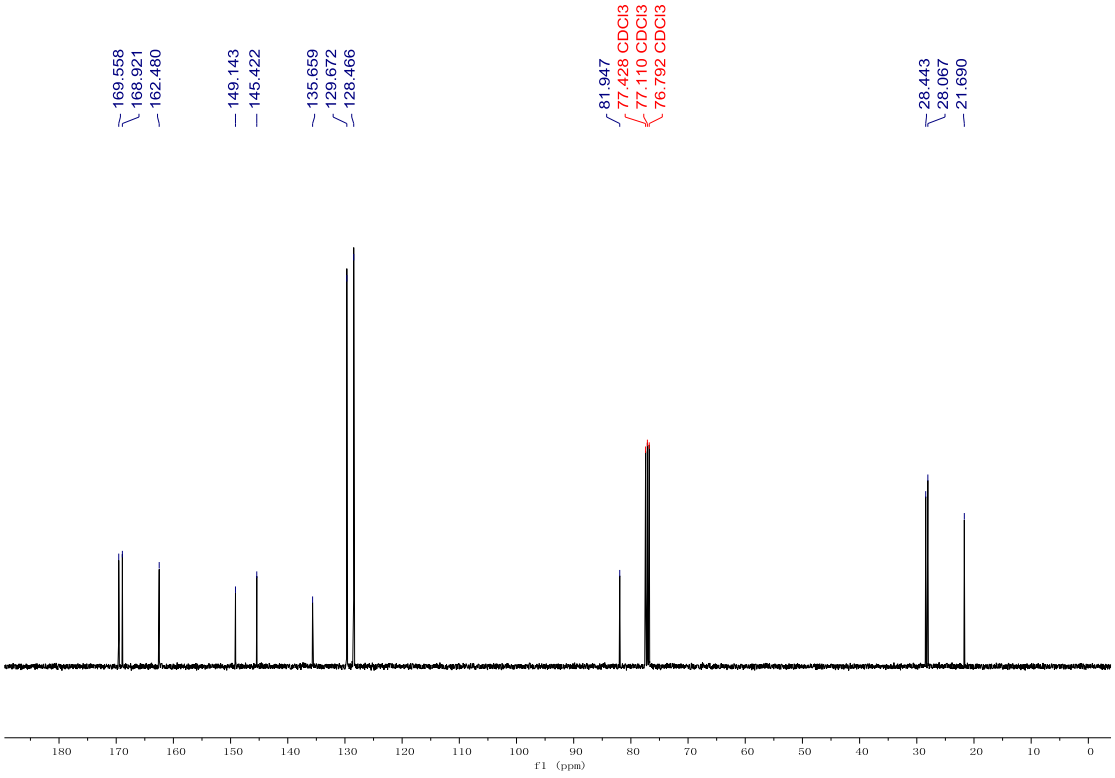


2-Hydroxy-5-oxo-*N*-tosylcyclopent-1-ene-1-carboxamide 4d

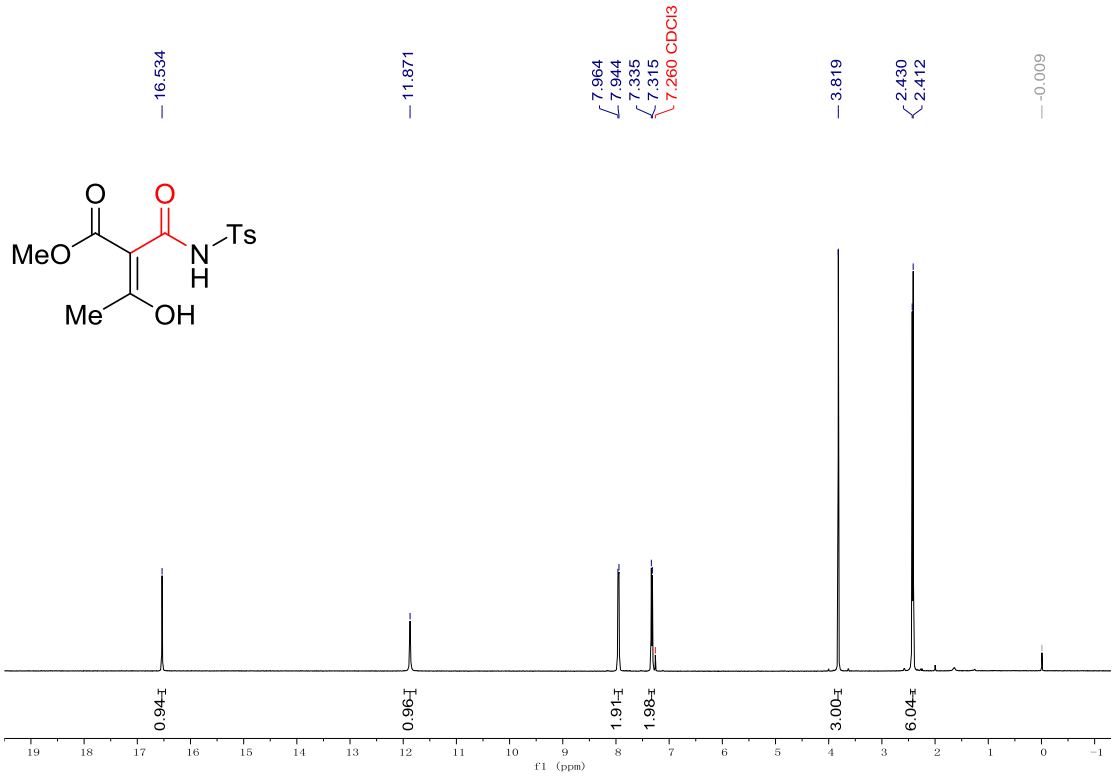


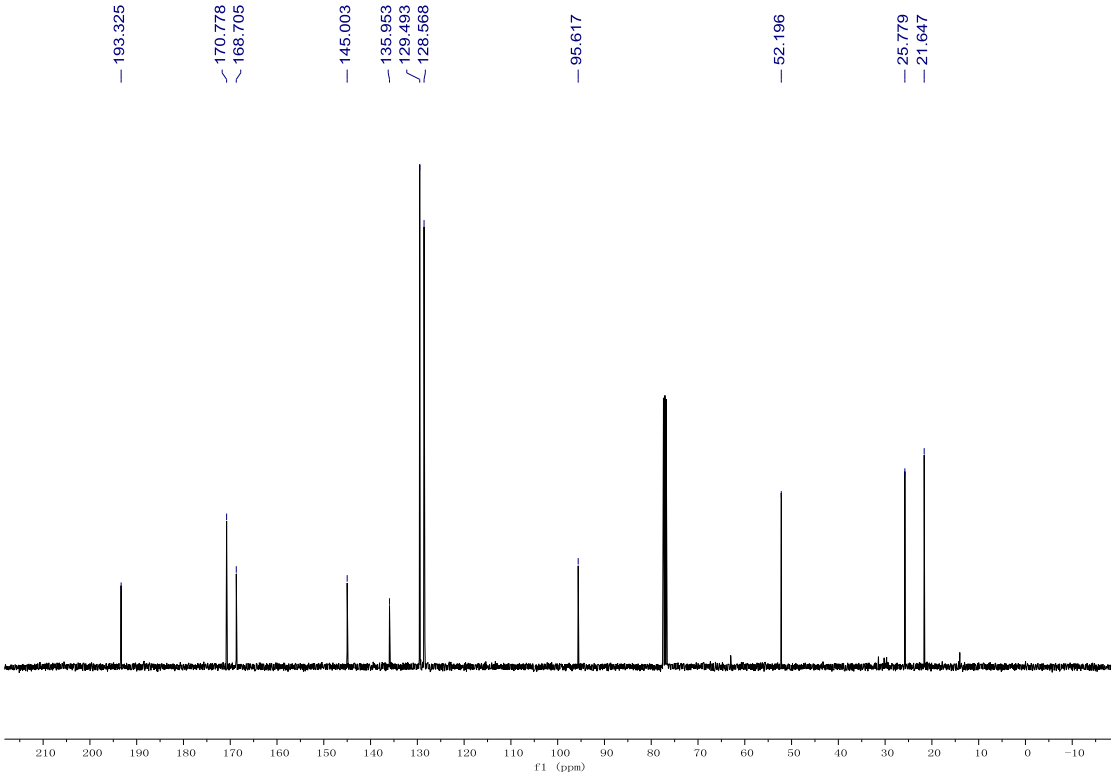
6-Hydroxy-1,3-dimethyl-2,4-dioxo-*N*-tosyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide 4e



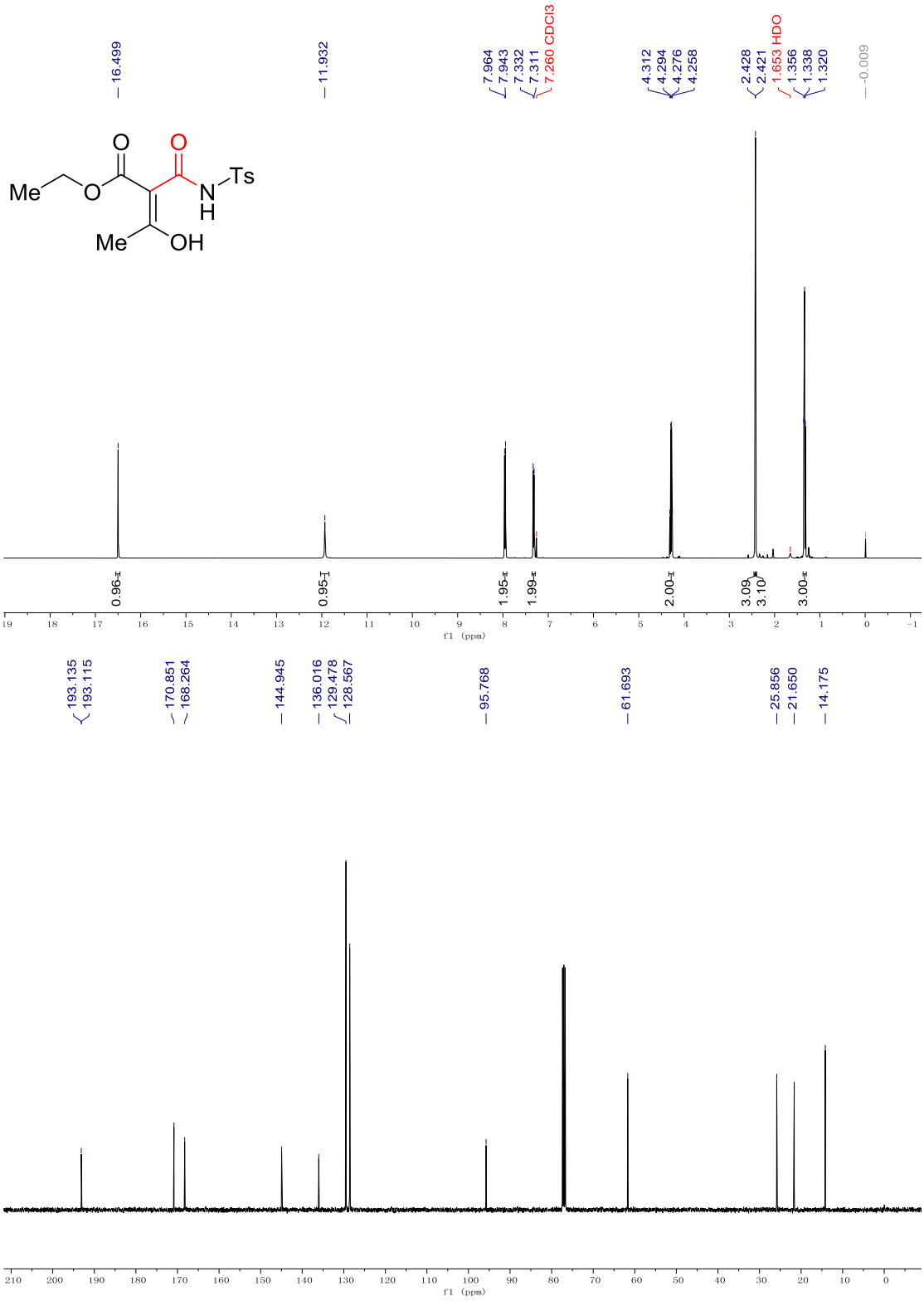


Methyl-3-hydroxy-2-(tosylcarbamoyl)but-2-enoate 4f

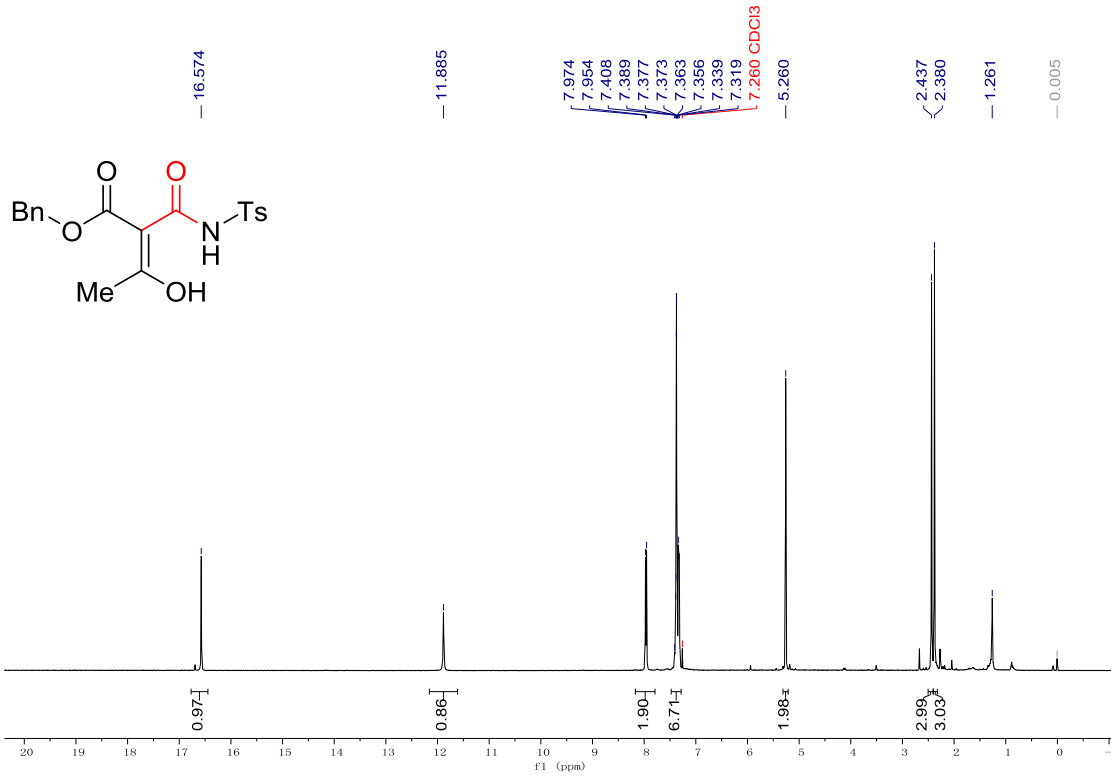


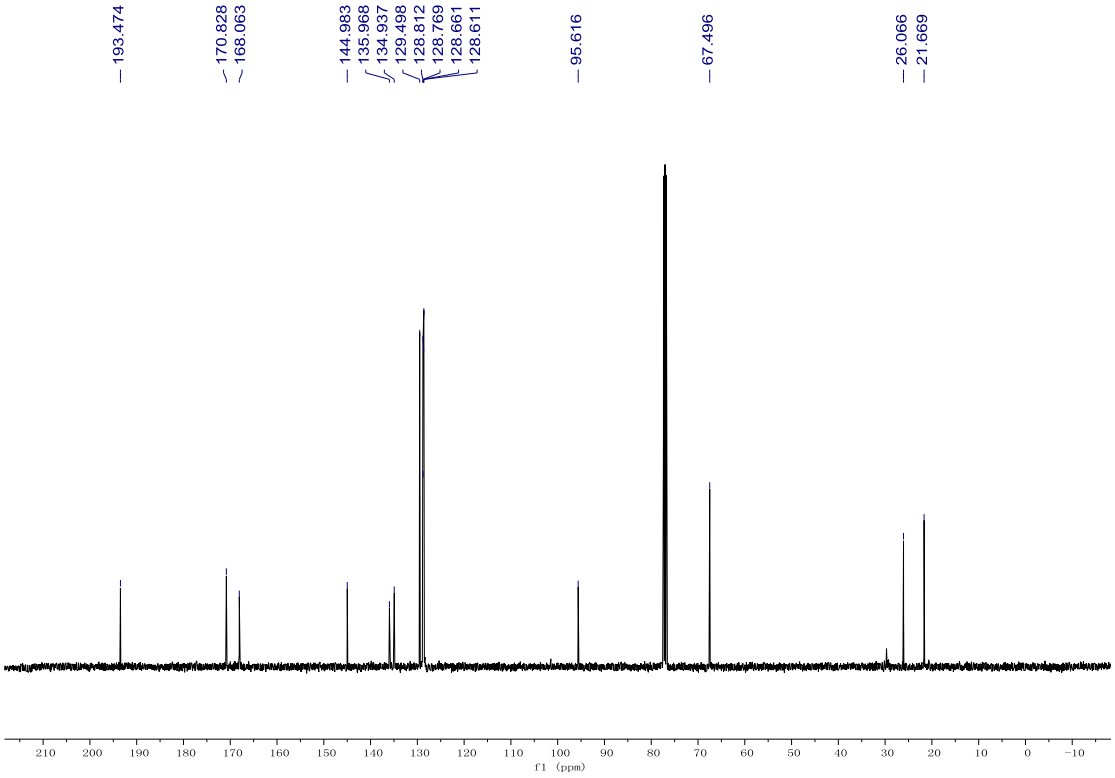


Ethyl-3-hydroxy-2-(tosylcarbamoyl)but-2-enoate 4g

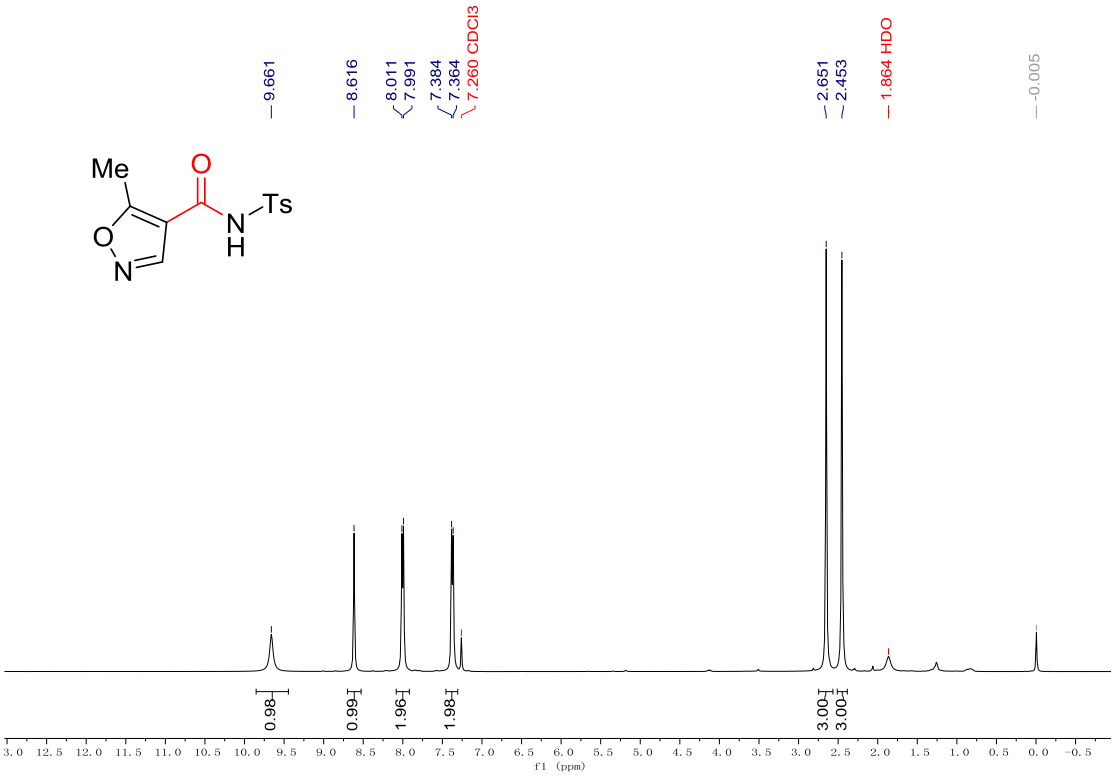


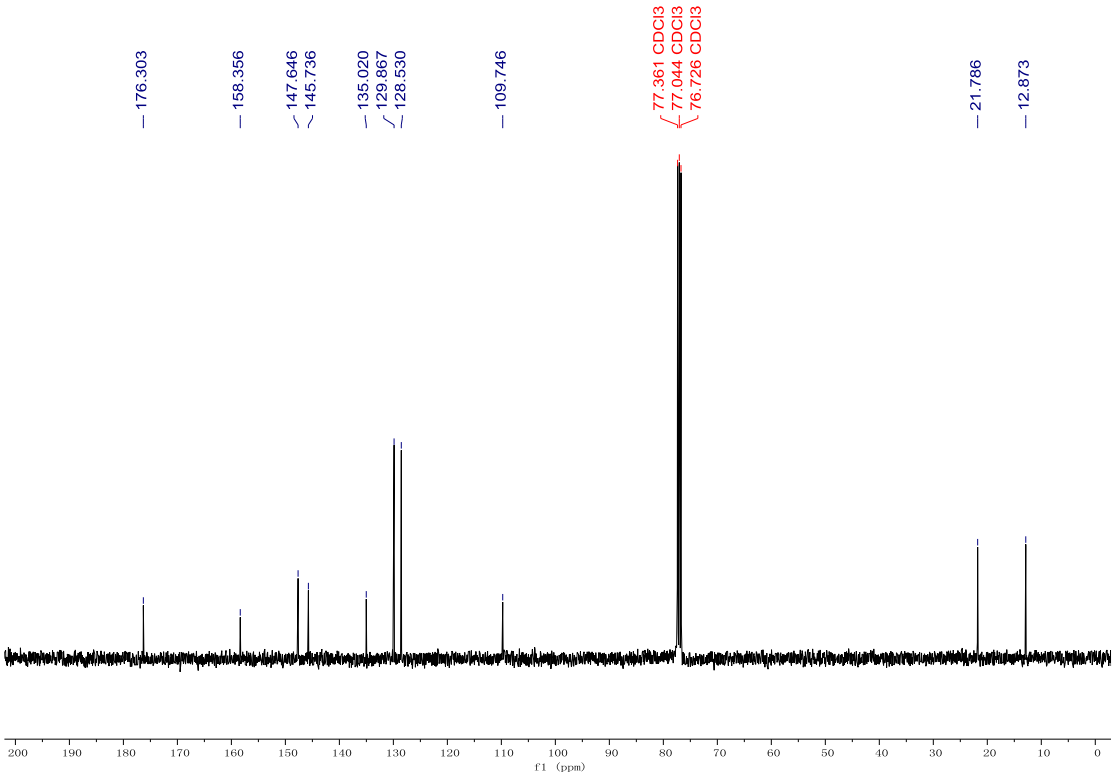
Benzyl-3-hydroxy-2-(tosylcarbamoyl)but-2-enoate 4h



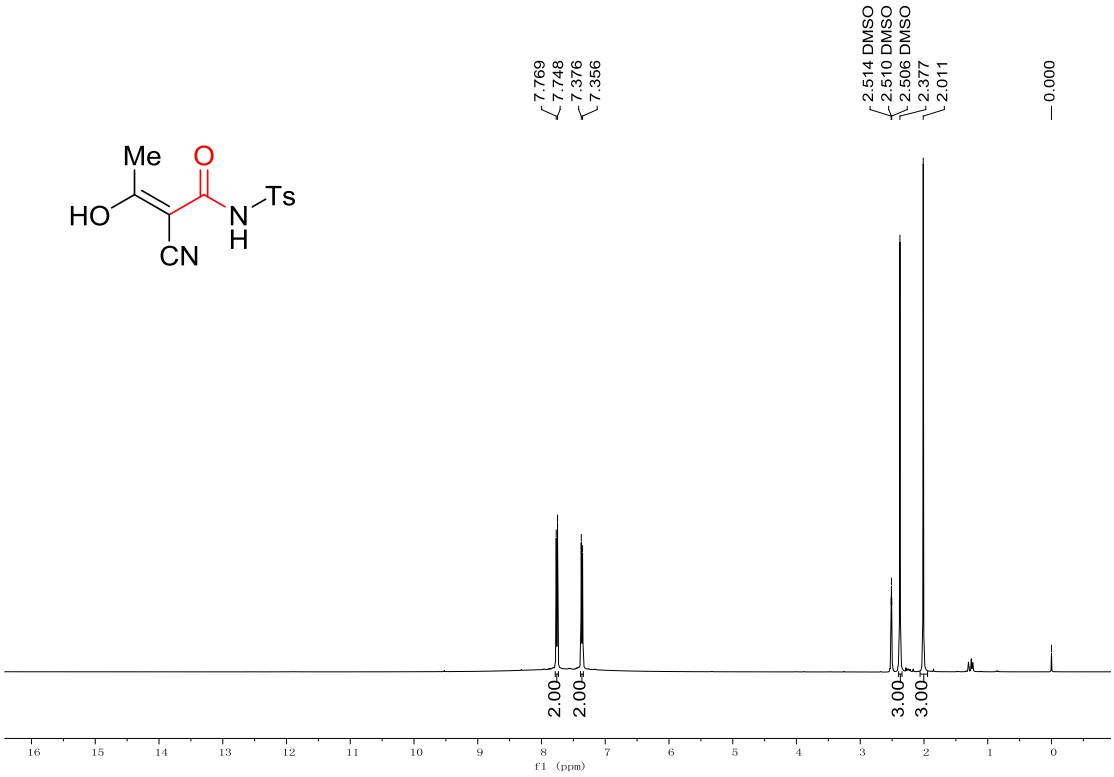


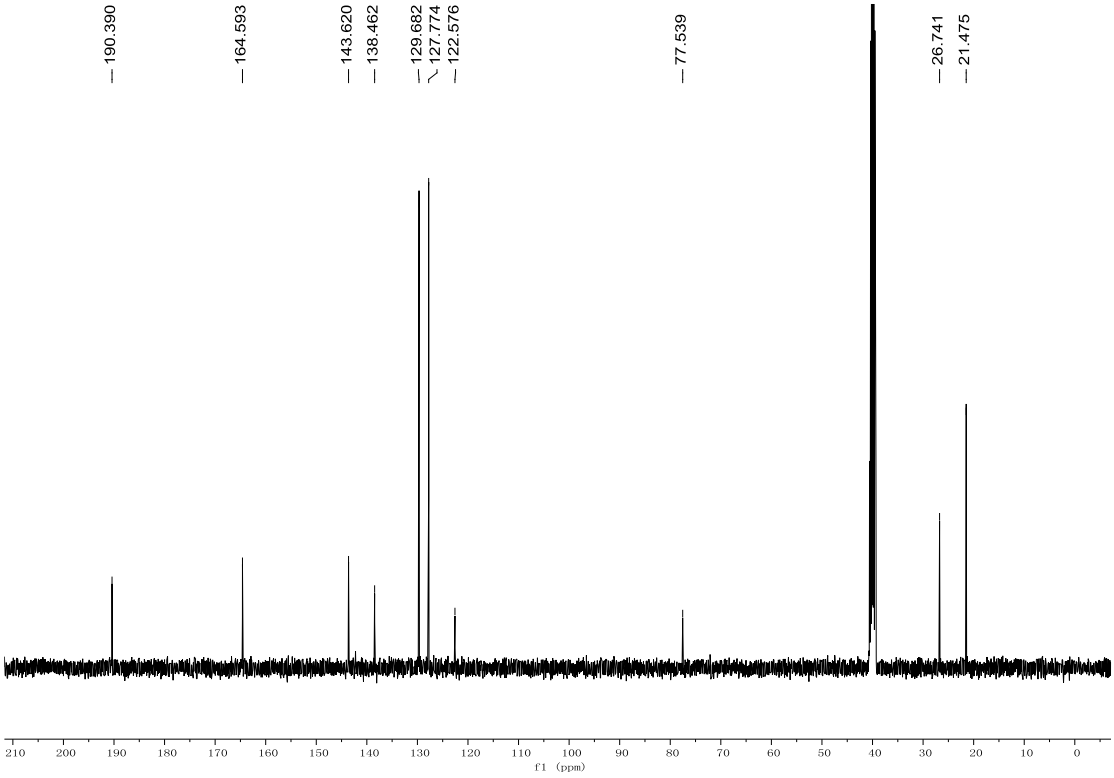
5-Methyl-*N*-tosylisoxazole-4-carboxamide 6





2-Cyano-3-hydroxy-*N*-tosylbut-2-enamide 7





5-Chloro-*N*-(4-(*N*-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-ene-1-carbonyl)sulfamoyl)phenethyl)-2-methoxybenzamide 12