Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Synthesis of Substituted Oxazoles via Pd-Catalyzed Tandem Oxidative Cyclization

Wei Zhang,† Wenlong Yu,† Qiangqiang Yan,† Zhanxiang Liu,† Yuhong Zhang*,†,‡

†Department of Chemistry, Zhejiang University, Hangzhou 310027, China

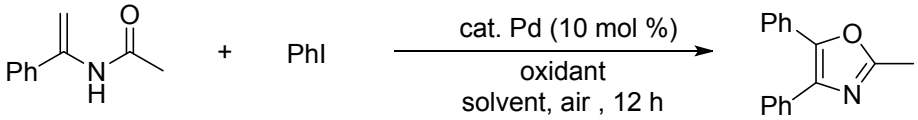
‡State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

E-mail: *yhzhang@zju.edu.cn*

General Information

All reactions were performed under air in a 25 mL tube. *N*-acyl enamides were synthesized according to reported procedures.[1] Other materials and solvents were purchased from common commercial sources and used without additional purification, if there is no special version. ^{1}H NMR spectra were recorded at 400 MHz using TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz using TMS as internal standard. The multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet of doublets (td), multiplet (m), triplet (t) and broad resonances (br). Mass spectroscopy data of the products were collected on an HRMS-TOF instrument.

Optimization of the Reaction Conditions[a]



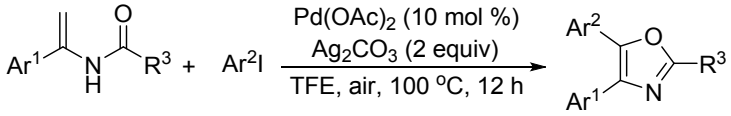
1a **2a** **3aa**

entry	catalyst (10 mol %)	oxidant (2 equiv)	solvent (1 mL)	temp (^{o}C)	yield (%)[b]
1	$PdCl_2$	Ag_2O	EtOH	100	10
2	$Pd(OAc)_2$	Ag_2O	EtOH	100	27
3	$PdCl_2$(dppf)	Ag_2O	EtOH	100	trace
4	$Pd(CH_3CN)_2(OTs)_2$	Ag_2O	EtOH	100	21
5	$Pd_2(dba)_3$	Ag_2O	EtOH	100	18
6	$Pd(TFA)_2$	Ag_2O	EtOH	100	22
7	$PdCl_2(CH_3CN)_2$	Ag_2O	EtOH	100	trace
8	$PdCl_2(PPh_3)_2$	Ag_2O	EtOH	100	10
9	$Pd(PPh_3)_4$	Ag_2O	EtOH	100	trace
10	$Pd(OAc)_2$	AgOTf	EtOH	100	NR
11	$Pd(OAc)_2$	AgOAc	EtOH	100	30
12	$Pd(OAc)_2$	Ag_2CO_3	EtOH	100	55
13	$Pd(OAc)_2$	CF_3COOAg	EtOH	100	33
14	$Pd(OAc)_2$	$AgSbF_6$	EtOH	100	NR
15	$Pd(OAc)_2$	$AgBF_4$	EtOH	100	NR
16	$Pd(OAc)_2$	AgOTFA	EtOH	100	31
17	$Pd(OAc)_2$	AgOPiv	EtOH	100	33
18	$Pd(OAc)_2$	C_6H_5COOAg	EtOH	100	37
19	$Pd(OAc)_2$	$AgNO_3$	EtOH	100	trace
20	$Pd(OAc)_2$	$AgPF_6$	EtOH	100	NR
21	$Pd(OAc)_2$	AgCl	EtOH	100	NR
22	$Pd(OAc)_2$	Ag_2S	EtOH	100	NR
23	$Pd(OAc)_2$	AgF_2	EtOH	100	NR

24	$Pd(OAc)_2$	AgF	EtOH	100	NR
25	$Pd(OAc)_2$	$Ag[(CF_3SO_2)_2N]$	EtOH	100	trace
26	$Pd(OAc)_2$	$CuSO_4$	EtOH	100	16
27	$Pd(OAc)_2$	$CuSO_4 \cdot 5H_2O$	EtOH	100	NR
28	$Pd(OAc)_2$	$Cu(OTFA)_2$	EtOH	100	NR
29	$Pd(OAc)_2$	CuI	EtOH	100	NR
30	$Pd(OAc)_2$	CuBr	EtOH	100	NR
31	$Pd(OAc)_2$	$CuCl_2$	EtOH	100	NR
32	$Pd(OAc)_2$	CuCl	EtOH	100	NR
33	$Pd(OAc)_2$	CuF_2	EtOH	100	NR
34	$Pd(OAc)_2$	IPrCuCl	EtOH	100	NR
35	$Pd(OAc)_2$	$Cu_2(OH)_2CO_3$	EtOH	100	NR
36	$Pd(OAc)_2$	Cu_2O	EtOH	100	NR
37	$Pd(OAc)_2$	CuO	EtOH	100	NR
38	$Pd(OAc)_2$	$Cu(OTf)_2$	EtOH	100	NR
39	$Pd(OAc)_2$	CuOAc	EtOH	100	NR
40	$Pd(OAc)_2$	$PhI(OAc)_2$	EtOH	100	NR
41	$Pd(OAc)_2$	Ag_2CO_3	CH_3CN	100	22
42	$Pd(OAc)_2$	Ag_2CO_3	DCE	100	24
43	$Pd(OAc)_2$	Ag_2CO_3	DMSO	100	trace
44	$Pd(OAc)_2$	Ag_2CO_3	1,4-dioxane	100	23
45	$Pd(OAc)_2$	Ag_2CO_3	MeOH	100	46
46	$Pd(OAc)_2$	Ag_2CO_3	$(CH_2OH)_2$	100	34
47	$Pd(OAc)_2$	Ag_2CO_3	*i*-PrOH	100	41
48	$Pd(OAc)_2$	Ag_2CO_3	$CH_3(CH_2)_4OH$	100	43
49	$Pd(OAc)_2$	Ag_2CO_3	*t*-AmOH	100	36
50	$Pd(OAc)_2$	Ag_2CO_3	PivOH	100	51
51	$Pd(OAc)_2$	Ag_2CO_3	TFE	100	78
52	$Pd(OAc)_2$	Ag_2CO_3	BzOH	100	trace
53	$Pd(OAc)_2$	Ag_2CO_3	HFIP	100	53
54	$Pd(OAc)_2$	Ag_2CO_3	Et_3N	100	32
55	$Pd(OAc)_2$	Ag_2CO_3	TFE	80	60
56	$Pd(OAc)_2$	Ag_2CO_3	TFE	120	64
57	-	Ag_2CO_3	TFE	100	NR
58	$Pd(OAc)_2$	-	TFE	100	NR

[a]Reaction conditions: substrate **1a** (0.1 mmol), iodobenzene **2a** (0.15 mmol), Pd catalyst (10 mol %), oxidant (2 equiv), solvent (1 mL), 100 °C, air, 12 h. [b]Isolated yields.

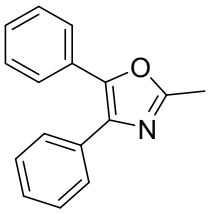
Typical Procedure for the Product



1 **2** **3**

A 25 mL tube was charged with *N*-(1-phenylvinyl)acetamide **1** (0.1 mmol), iodoarene **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2 equiv) and TFE (1 mL). The mixture was stirred at 100 °C for 12 h under air. The solvent was removed in vacuum and the product was isolated through column chromatography to afford the corresponding products **3**.

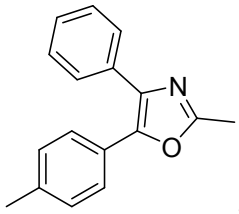
Analytical Data for Products



3aa

2-Methyl-4,5-diphenyloxazole

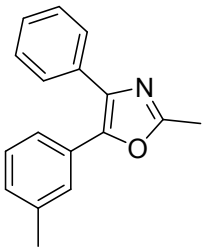
Yield: 78%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63, 7.65 (d, J = 8.4 Hz, 2H), 7.57, 7.59 (d, J = 8.4 Hz, 2H), 7.31-7.38 (m, 6H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 145.3, 136.2, 132.5, 129.1, 128.7, 128.6, 128.4, 128.0, 127.9, 126.4, 14.0. HRMS (EI-TOF) calcd for $C_{16}H_{13}NO$ (M^+): 235.0997, found: 235.1001



3ab

2-Methyl-4-phenyl-5-*p*-tolyloxazole

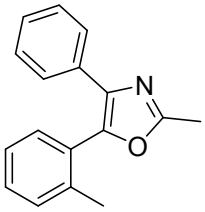
Yield: 55%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64, 7.65 (d, J = 1.6 Hz, 1H), 7.62-7.63 (m, 1H), 7.46 (s, 1H), 7.48 (s, 1H), 7.30-7.37 (m, 3H), 7.17 (s, 1H), 7.15 (s, 1H), 2.54 (s, 3H), 2.37(s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.0, 145.5, 138.4, 134.6, 132.7, 129.4, 128.5, 127.9, 127.8, 126.5, 126.3, 21.4, 14.0. HRMS (EI-TOF) calcd for $C_{17}H_{15}NO$ (M^+): 249.1154, found: 249.1150.



3ac

2-Methyl-4-phenyl-5-*m*-tolyloxazole

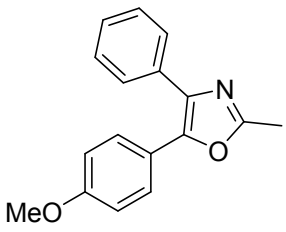
Yield: 56%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62, 7.65 (d, *J* = 7.2 Hz, 2H), 7.42 (s, 1H), 7.29-7.37 (m, 4H), 7.20-7.23 (t, *J* = 8.0 Hz, 1H), 7.11, 7.13 (d, *J* = 7.6 Hz, 1H), 2.53 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 145.5, 138.4, 135.0, 132.6, 129.2, 129.0, 128.5, 128.0, 127.8, 127.1, 123.7, 21.4, 14.0. HRMS (EI-TOF) calcd for $C_{17}H_{15}NO$ (M^+): 249.1154, found: 249.1157.



3ad

2-Methyl-4-phenyl-5-*o*-tolyloxazole

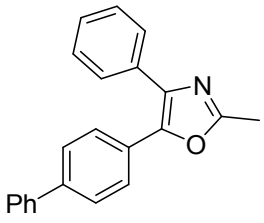
Yield: 55%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51, 7.52 (d, *J* = 1.6 Hz, 1H), 7.49, 7.50 (d, *J* = 1.2 Hz, 1H), 7.34-7.39 (m, 2H), 7.24-7.31 (m, 5H), 2.56 (s, 3H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 144.1, 136.9, 134.5, 131.0, 129.7, 129.5, 128.5, 127.9, 127.4, 126.5, 125.4, 125.1, 18.9, 13.0. HRMS (EI-TOF) calcd for $C_{17}H_{15}NO$ (M^+): 249.1154, found: 249.1158.



3ae

5-(4-Methoxyphenyl)-2-methyl-4-phenyloxazole

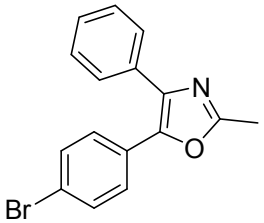
Yield: 77%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63, 7.64 (d, *J* = 1.2 Hz, 1H), 7.62 (s, 1H), 7.50, 7.51 (d, *J* = 2.0 Hz, 1H), 7.48, 7.49 (d, *J* = 1.6 Hz, 1H), 7.29-7.36 (m, 3H), 6.89, 6.90 (d, *J* = 1.6 Hz, 1H), 6.88 (s, 1H), 3.83 (s, 3H), 2.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.8, 159.7, 145.4, 133.9, 132.9, 128.5, 128.1, 127.8, 127.7, 121.9, 114.1, 56.3, 14.0. HRMS (EI-TOF) calcd for $C_{17}H_{15}NO_2$ (M^+): 265.1103, found: 265.1104.



3af

5-(Biphenyl-4-yl)-2-methyl-4-phenyloxazole

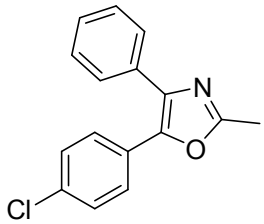
Yield: 60%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63-7.68 (m, 4H), 7.55-7.60 (t, *J* = 8.8 Hz, 4H), 7.32-7.44 (m, 6H), 2.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.3, 145.2, 141.0, 140.3, 135.4, 132.6, 128.9, 128.6, 128.1, 128.0, 127.6, 127.3, 127.0, 126.7, 14.0. HRMS (EI-TOF) calcd for $C_{22}H_{17}NO$ (M^+): 311.1310, found: 311.1310.



3ag

5-(4-Bromophenyl)-2-methyl-4-phenyloxazole

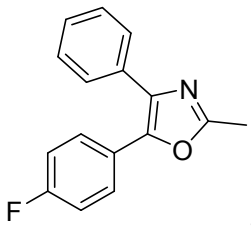
Yield: 52%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59-7.62 (t, 2H), 7.50-7.52 (m, 2H), 7.31-7.40 (m, 5H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.5, 144.3, 136.6, 134.1, 122.2, 128.9, 128.8, 128.3, 127.9, 127.7, 14.0. HRMS (EI-TOF) calcd for $C_{16}H_{12}BrNO$ (M^+): 313.0102, found: 313.0108.



3ah

5-(4-Chlorophenyl)-2-methyl-4-phenyloxazole

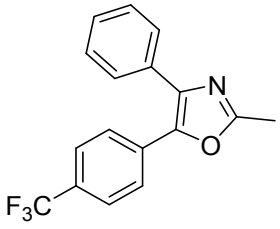
Yield: 58%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60, 7.61 (d, *J* = 2.0 Hz, 1H), 7.58, 7.59 (d, *J* =1.2 Hz, 1H), 7.43-7.49 (m, 4H), 7.32-7.40 (m, 3H), 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.6, 144.3, 135.7, 132.2, 131.9, 128.7, 128.3, 128.0, 127.9, 127.8, 122.3, 13.8. HRMS (EI-TOF) calcd for $C_{16}H_{12}ClNO$ (M^+): 269.0607, found: 269.0604.



3ai

5-(4-Fluorophenyl)-2-methyl-4-phenyloxazole

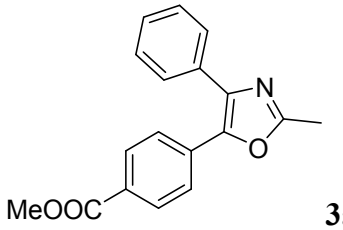
Yield: 59%; Orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61, 7.62 (d, J = 1.2 Hz, 1H), 7.60 (s, 1H), 7.53-7.57 (m, 2H), 7.34-7.39 (m, 3H), 7.03-7.07 (t, J = 8.8 Hz, 2H), 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 161.4, 160.2 (d, J_{C-F} = 9.5 Hz), 144.5, 134.9, 132.3, 128.6, 128.5, 128.4 (d, J_{C-F} = 8.1 Hz), 128.1, 127.8, 125.3, 115.9, 115.7 (d, J_{C-F} = 21.8 Hz), 14.0. HRMS (EI-TOF) calcd for $C_{16}H_{12}FNO$ (M^+): 253.0903, found: 253.0902.



3aj

2-Methyl-4-phenyl-5-(4-(trifluoromethyl)phenyl)oxazole

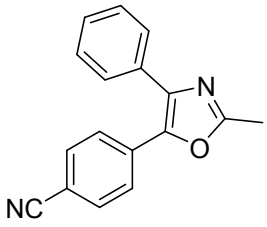
Yield: 68%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69, 7.71 (d, J = 4.0 Hz, 2H), 7.58-7.62 (m, 4H), 7.36-7.43 (m, 3H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.1, 143.9, 137.0, 132.0, 129.8, 128.8, 128.6, 128.1, 126.1, 125.7, 125.6, 122.6, 122.4 (d, J_{C-F} = 19.3 Hz), 14.0. HRMS (EI-TOF) calcd for $C_{17}H_{12}F_3NO$ (M^+): 303.0871, found: 303.0872.



3ak

Methyl 4-(2-methyl-4-phenyloxazol-5-yl)benzoate

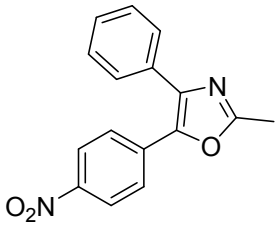
Yield: 57%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (s, 1H), 8.00 (s, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.61-7.63 (m, 2H), 7.36-7.42 (m, 3H), 3.92 (s, 3H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 161.0, 144.3, 137.1, 133.2, 132.2, 129.9, 128.7, 128.5, 128.1, 125.8, 52.2, 14.0. HRMS (EI-TOF) calcd for $C_{18}H_{15}NO_3$ (M^+): 293.1052, found: 293.1055.



3al

4-(2-Methyl-4-phenyloxazol-5-yl)benzonitrile

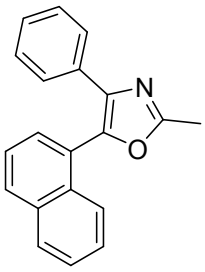
Yield: 66%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.70 (m, 2H), 7.58-7.62 (m, 4H), 7.40-7.42 (m, 3H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.5, 136.1, 133.2, 132.5, 128.9, 128.2, 126.1, 118.8, 111.3, 14.1. HRMS (EI-TOF) calcd for $C_{17}H_{12}N_2O$ (M^+): 260.0950, found: 260.0952.



3am

2-Methyl-5-(4-nitrophenyl)-4-phenyloxazole

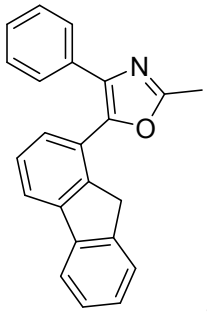
Yield: 20%; Orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 1H), 8.18 (s, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.59-7.61 (m, 2H), 7.42-7.46 (m, 3H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.8, 146.9, 143.2, 138.8, 135.0, 129.0, 128.9, 128.2, 126.2, 124.1, 14.1. HRMS (EI-TOF) calcd for $C_{17}H_{12}N_2O_3$ (M^+): 280.0848, found: 280.0844.



3an

2-Methyl-5-(naphthalen-1-yl)-4-phenyloxazole

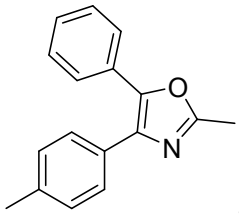
Yield: 73%; Orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.91-7.97 (m, 2H), 7.77, 7.79 (d, *J* = 8.4 Hz, 1H), 7.60, 7.62 (d, *J* = 7.2 Hz, 1H), 7.47-7.53 (m, 4H), 7.41-7.45 (m, 1H), 7.17-7.25 (m, 3H), 2.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.0, 144.2, 136.7, 133.9, 131.7, 131.6, 130.2, 129.0, 128.5, 128.4, 127.5, 127.0, 126.9, 126.7, 126.4, 125.6, 125.4, 14.1. HRMS (EI-TOF) calcd for $C_{20}H_{15}NO$ (M^+): 285.1154, found: 285.1159.



3ao

5-(9*H*-fluoren-1-yl)-2-methyl-4-phenyloxazole

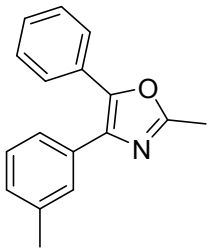
Yield: 31%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72-7.78 (t, *J* = 8.0 Hz, 3H), 7.66-7.68 (m, 2H), 7.58, 7.60 (d, 1H), 7.52, 7.54 (d, 1H), 7.29-7.39 (m, 5H), 3.87 (s, 2H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 145.9, 143.6, 143.5, 142.0, 141.1, 134.9, 132.7, 128.6, 127.9, 127.4, 127.1, 126.9, 125.4, 125.1, 123.1, 120.1, 120.0, 37.0, 14.0. HRMS (EI-TOF) calcd for $C_{23}H_{17}NO$ (M^+): 323.1310, found: 323.1313.



3ba

2-Methyl-5-phenyl-4-(*p*-tolyl)oxazole

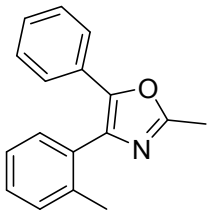
Yield: 72%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50, 7.52 (d, *J* =8.0 Hz, 2H), 7.44, 7.46 (d, *J* =8.4 Hz, 2H), 7.22-7.27 (m, 3H), 7.08-7.10 (d, *J* =8.0 Hz, 2H), 2.47 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 145.0, 137.8, 136.2, 129.6, 129.3, 128.6, 128.2, 127.8, 126.4, 21.3, 14.0. HRMS (EI-TOF) calcd for $C_{17}H_{15}NO$ (M^+): 249.1154, found: 249.1153.



3ca

2-Methyl-5-phenyl-4-(*m*-tolyl)oxazole

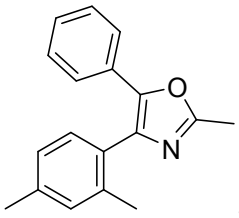
Yield: 61%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58, 7.59 (d, *J* =7.2 Hz, 2H), 7.50 (s, 1H), 7.38-7.40 (d, *J* =8.0 Hz, 1H), 7.31-7.36 (m, 3H), 7.21-7.25 (t, *J* =7.6 Hz, 1H), 7.12, 7.14 (d, *J* =7.6 Hz, 1H), 2.54 (s, 3H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 145.3, 138.3, 135.3, 132.4, 129.2, 128.8, 128.6, 128.5, 128.4, 128.3, 126.4, 124.9, 21.4, 14.0. HRMS (EI-TOF) calcd for $C_{17}H_{15}NO$ (M^+): 249.1154, found: 249.1157.



3da

2-Methyl-5-phenyl-4-(*o*-tolyl)oxazole

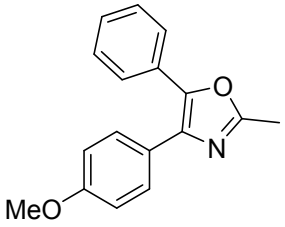
Yield: 12%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.39 (m, 3H), 7.21-7.31 (m, 6H), 2.56 (s, 3H), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.8, 145.7, 137.3, 134.9, 132.4, 130.5, 130.3, 128.9, 128.2, 128.6, 127.7, 126.1, 124.7, 19.9, 14.1. HRMS (EI-TOF) calcd for $C_{17}H_{15}NO$ (M^+): 249.1154, found: 249.1157.



3ea

4-(2,4-Dimethylphenyl)-2-methyl-5-phenyloxazole

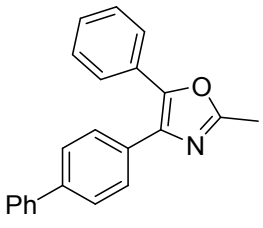
Yield: 57%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37, 7.39 (d, *J* =7.2 Hz, 2H), 7.20-7.27 (m, 4H), 7.10 (s, 1H), 7.03, 7.05 (d, *J* =8.0 Hz, 1H), 2.55 (s, 3H), 2.36 (s, 3H), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.7, 145.5, 138.3, 137.0, 135.0, 131.2, 130.1, 129.5, 129.0, 128.6, 127.6, 126.8, 124.7, 21.3, 19.8, 14.1. HRMS (EI-TOF) calcd for $C_{18}H_{17}NO$ (M+): 263.1310, found: 263.1309.



3fa

4-(4-Methoxyphenyl)-2-methyl-5-phenyloxazole

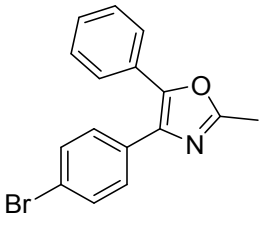
Yield: 67%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55-7.59 (m, 4H), 7.27-7.36 (m, 3H), 6.89, 6.91 (d, J = 9.2 Hz, 2H), 3.83 (s, 3H), 2.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 159.5, 144.5, 135.0, 129.3, 129.2, 128.6, 128.1, 126.3, 125.0, 114.0, 55.3, 14.0. HRMS (EI-TOF) calcd for $C_{17}H_{15}NO_2$ (M^+): 265.1103, found: 265.1107.



3ga

4-(Biphenyl-4-yl)-2-methyl-5-phenyloxazole

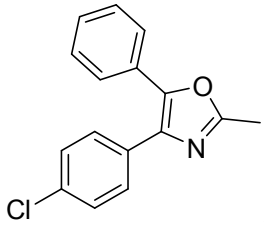
Yield: 78%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71-7.73 (m, 2H), 7.59 -7.62 (m, 6H), 7.42-7.46 (t, J = 7.6 Hz, 2H), 7.33-7.40 (m, 4H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.3, 145.5, 140.6, 134.8, 131.5, 129.1, 128.8, 128.7, 128.5, 128.2, 127.4, 127.2 127.0, 126.6, 14.0. HRMS (EI-TOF) calcd for $C_{22}H_{17}NO$ (M^+): 311.1310, found: 311.1315.



3ha

4-(4-Bromophenyl)-2-methyl-5-phenyloxazole

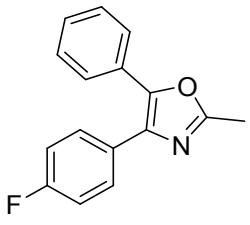
Yield: 66%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50-7.55 (m, 4H), 7.46, 7.48 (d, J = 8.4 Hz, 2H), 7.32-7.37 (m, 3H), 2.53 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 145.6, 134.1, 131.7, 131.5, 129.4, 128.8, 128.7, 128.6, 126.6, 122.0, 13.9. HRMS (EI-TOF) calcd for $C_{16}H_{12}BrNO$ (M^+):313.0102, found: 313.0106.



3ia

4-(4-Chlorophenyl)-2-methyl-5-phenyloxazole

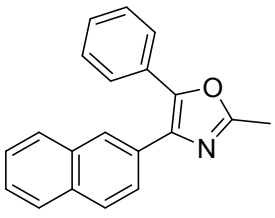
Yield: 65%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58, 7.59 (d, 1H), 7.56, 7.57 (d, 2H), 7.54-7.55 (m, 1H), 7.32-7.39 (m, 5H), 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 145.6, 134.0, 133.8, 121.0, 129.1, 128.8, 128.7, 128.6, 126.6, 14.0. HRMS (EI-TOF) calcd for $C_{16}H_{12}ClNO$ (M^+): 269.0607, found: 269.0608.



3ja

4-(4-Fluorophenyl)-2-methyl-5-phenyloxazole

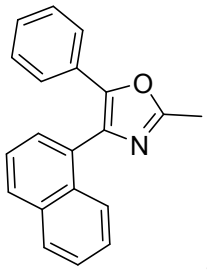
Yield: 54%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54-7.63 (m, 4H), 7.30-7.39 (m, 3H), 7.03-7.08 (t, J = 8.8 Hz, 2H), 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 160.3, 161.3 (d, $J_{C\text{-}F}$ = 102.7 Hz), 145.2, 134.2, 129.6, 129.7 (d, $J_{C\text{-}F}$ = 8.2 Hz), 128.9, 128.7, 128.6, 128.5, 126.4 115.5, 115.7 (d, $J_{C\text{-}F}$ = 4.1 Hz), 14.0. HRMS (EI-TOF) calcd for $C_{16}H_{12}FNO$ (M^+): 253.0903, found: 253.0900.



3ka

2-Methyl-4-(naphthalen-2-yl)-5-phenyloxazole

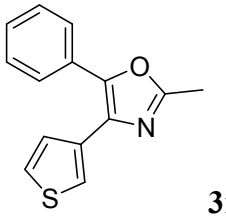
Yield: 74%; Orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (s,1H), 7.80-7.84 (m, 3H), 7.67, 7.70 (d, J = 9.2 Hz, 1H), 7.62-7.60 (d, J = 8.0 Hz 2H), 7.48-7.46 (m, 2H), 7.37, 7.34 (d, 3H), 2.59 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.5, 145.8, 140.7, 136.1, 133.5, 128.7, 128.5, 128.3, 128.1, 127.7, 126.9 126.6, 126.3, 126.2, 125.6, 14.1. HRMS (EI-TOF) calcd for $C_{20}H_{15}NO$ (M^+): 285.1154, found: 285.1158.



3la

2-Methyl-4-(naphthalen-1-yl)-5-phenyloxazole

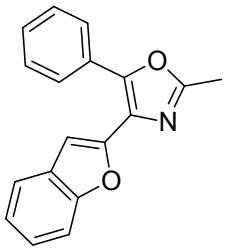
Yield: 56%; Orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86-7.94 (m, 3H), 7.57, 7.59 (d, J = 3.2 Hz, 1H), 7.49-7.53 (m, 2H), 7.39-7.43 (m, 1H), 7.34-7.36 (m, 2H), 7.18-7.19 (m, 3H), 2.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 146.7, 133.9, 133.8, 131.7, 130.3, 129.2, 128.5, 128.4, 128.3, 128,2 127.9, 126.5, 126.1, 125.8, 125.5, 125.2, 14.1. HRMS (EI-TOF) calcd for $C_{20}H_{15}NO$ (M^+): 285.1154, found: 285.1152 .



3ma

2-Methyl-5-phenyl-4-(thiophen-3-yl)oxazole

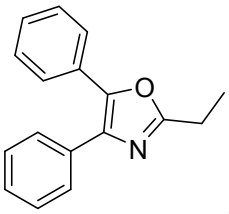
Yield: 52%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69, 7.70 (d, J = 1.6 Hz, 1H), 7.68 (s, 1H), 7.33-7.42 (m, 5H), 7.00-7.03 (dd, J_1 = 0.4 Hz, J_2 = 1.6 Hz, 1H), 2.53, (S, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 144.9,134.7, 129.9, 128.8, 128.7, 127.5, 126.8, 125.7, 125.2, 13.9. HRMS (EI-TOF) calcd for $C_{14}H_{11}NOS$ (M^+): 241.0561, found: 241.0561.



3na

4-(benzofuran-2-yl)-2-methyl-5-phenyloxazole

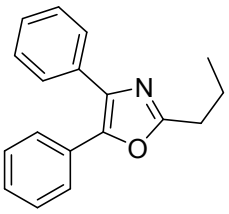
Yield: 37%; Orange liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84, 7.86 (d, J = 7.2 Hz, 2H), 7.56, 7.58 (d, J = 7.2 Hz, 1H), 7.39-7.49 (m, 4H), 7.20-7.29 (m, 2H), 7.11 (s, 1H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.9, 154.7, 149.3, 147.0, 129.0, 128.6, 128.3, 127.2, 126.8, 124.6, 123.1, 121.0, 111.3, 104.8, 13.9. HRMS (EI-TOF) calcd for $C_{18}H_{13}NO_2$ (M^+): 275.0946, found: 275.0944.



3oa

2-Ethyl-4,5-diphenyloxazole

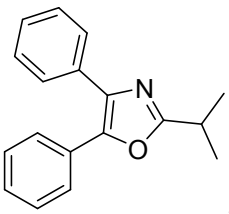
Yield: 67%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64-7.66 (d, J = 12.0 Hz, 2H), 7.58-7.60 (d, J = 4.0 Hz, 2H), 7.30-7.39 (m, 6H), 2.86-2.92 (m, 2H), 1.40-1.45 (td, J_1 = 2.0 Hz; J_2 = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 145.1, 135.0, 132.6, 129.2, 128.7, 128.6, 128.3, 128.0, 127.9, 126.4, 21.8, 11.4. HRMS (EI-TOF) calcd for $C_{17}H_{15}NO$ (M^+): 249.1154, found: 249.1155.



3pa

4,5-Diphenyl-2-propyloxazole

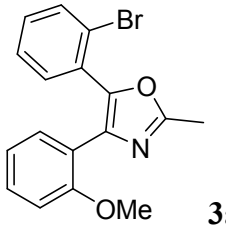
Yield: 66%; Yellow solid; mp = 52.6-53.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (s, 1H), 7.50-7.55 (m, 4H), 7.30-7.39 (m, 6H), 6.75 (s, 1H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 138.8, 136.0, 134.7, 128.7, 128.3, 128.2, 127.8, 127.2, 125.6, 122.7, 22.8. HRMS (EI-TOF) calcd for $C_{18}H_{17}NO$ (M^+): 263.1310, found: 263.1309.



3qa

2-Isopropyl-4,5-diphenyloxazole

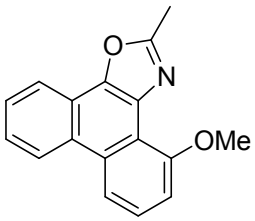
Yield: 69%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63-7.66 (m, 2H), 7.57-7.59 (m, 2H), 7.31-7.36 (m, 6H), 3.13-3.23 (m, 1H), 1.43-1.44 (d, J = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.7, 144.8, 134.9, 132.8, 129.3, 128.6, 128.5, 128.3, 128.1, 128.0, 126.4, 28.6, 20.6. HRMS (EI-TOF) calcd for $C_{18}H_{17}NO$ (M^+): 263.1310, found: 263.2309.



3ap

5-(2-Bromophenyl)-4-(2-methoxyphenyl)-2-methyloxazole

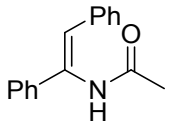
Yield: 42%; Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62, 7.64 (d, *J* = 7.2 Hz, 2H), 7.32-7.42 (m, 3H), 7.17-7.22 (m, 1H), 6.97-7.01 (m, 1H), 6.78, 6.80 (d, *J* = 8.0 Hz, 1H), 3.33 (s, 3H), 2.57 (S, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.5, 156.4, 145.6, 133.8, 132.9, 132.4, 131.2, 130.3, 129.8, 129.4, 126.8, 123.1, 121.5, 120.6, 110.7, 54.5, 14.0. HRMS (EI-TOF) calcd for $C_{17}H_{14}BrNO_2$ (M^+): 343.0208, found: 343.0211.



4a

4-Methoxy-2-methylphenanthro[9,10-*d*]oxazole

Yield: 43%; Light yellow solid; mp = 145.8-149.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.71, 8.73 (d, *J* = 8.0 Hz, 1H), 8.35, 8.38 (d, *J* = 8.4 Hz, 1H), 8.22, 8.24 (d, *J* = 7.6 Hz, 1H), 7.58-7.72 (m, 3H), 7.18, 7.20 (d, *J* = 8.0 Hz, 1H), 4.18 (s, 3H), 2.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3, 156.2, 145.5, 132.7, 130.7, 128.7, 127.5, 126.3, 126.1, 124.2, 121.1, 120.5, 116.5, 115.9, 107.9, 56.4, 14.9. HRMS (EI-TOF) calcd for $C_{17}H_{13}NO_2$ (M^+): 263.0946, found: 263.0944.



6a

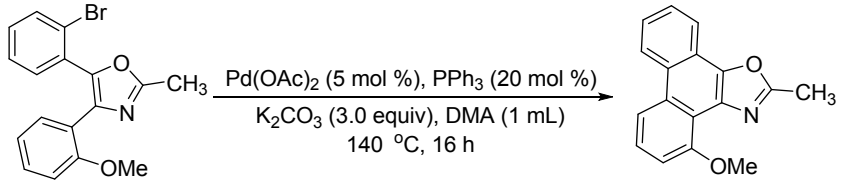
(*Z*)-*N*-(1,2-diphenylvinyl)acetamide

Yield: 42%; Light yellow solid; mp = 166.7-167.9 °C; ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 9.60 (br, 1H), 7.50-7.55 (m, 4H), 7.35-7.39 (m, 5H), 7.23-7.32 (m, 2H), 6.75 (s, 1H), 2.03, (S, 3H). ^{13}C NMR (DMSO-*d6*, 100 MHz) δ 168.8, 138.6, 136.0, 134.7, 128.7, 128.3, 128.2, 127.8, 127.2, 125.5, 122.7, 40.1, 39.9, 39.7, 39.5, 39.3, 39.0, 38.8, 22.8. HRMS (EI-TOF) calcd for $C_{16}H_{15}NO$ (M^+): 237.1154, found: 237.1154.

Gram-scale Synthesis of 3aa

A 25 mL sealed tube was charged with *N*-(1-phenylvinyl)acetamide **1** (1.0 mmol), iodoarene **2** (1.5 mmol), $Pd(OAc)_2$ (15 mg, 0.5 mmol), Ag_2CO_3 (550 mg, 2 mmol), TFE (3 mL), and stirred at 120 °C for 18 h. The mixture was then cooled to room temperature, diluted with EtOAc (25 mL), filtered through a celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/ petroleum ether (1:50~1:20, v/v), to afford the product **3aa** (yield = 61%).

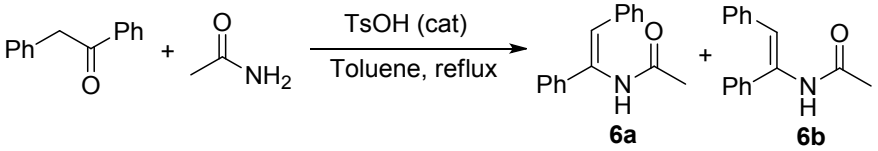
Derivatization Experiment



3ap **4a**

Under air atmosphere, 5-(2-bromophenyl)-4-(2-methoxyphenyl)-2-methyloxazole (64 mg, 0.2 mmol), potassium carbonate (84 mg, 0.6 mmol), palladium acetate (2mg, 0.01 mmol), and tricyclohexylphosphine (10 mg, 0.04 mmol) were solved in DMA (1.0 mL) in a 20 mL tube. The resulting mixture was stirred for 16 h at 140 ˚C. The mixture was then cooled to room temperature. Silica gel column purification with hexane and ethyl acetate as an eluent afforded 4-methoxy-2-methylphenanthro[9,10-*d*]oxazole (**4a**, 23 mg, 0.09 mmol, 43% yield).[2]

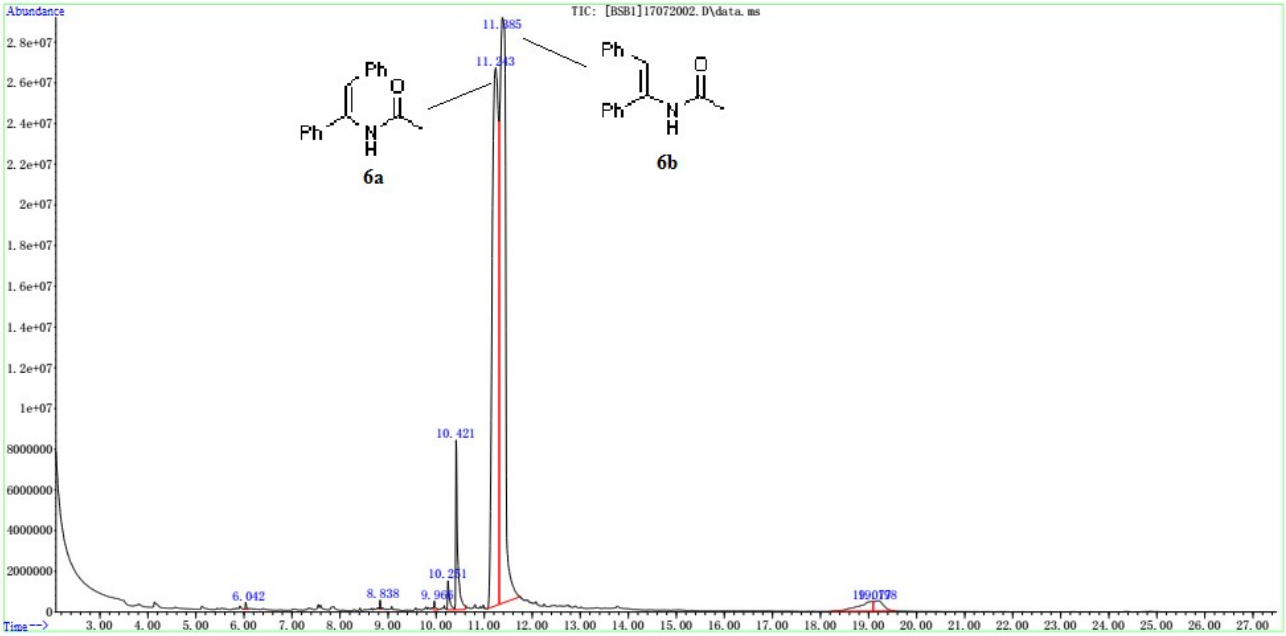
Control Experiments



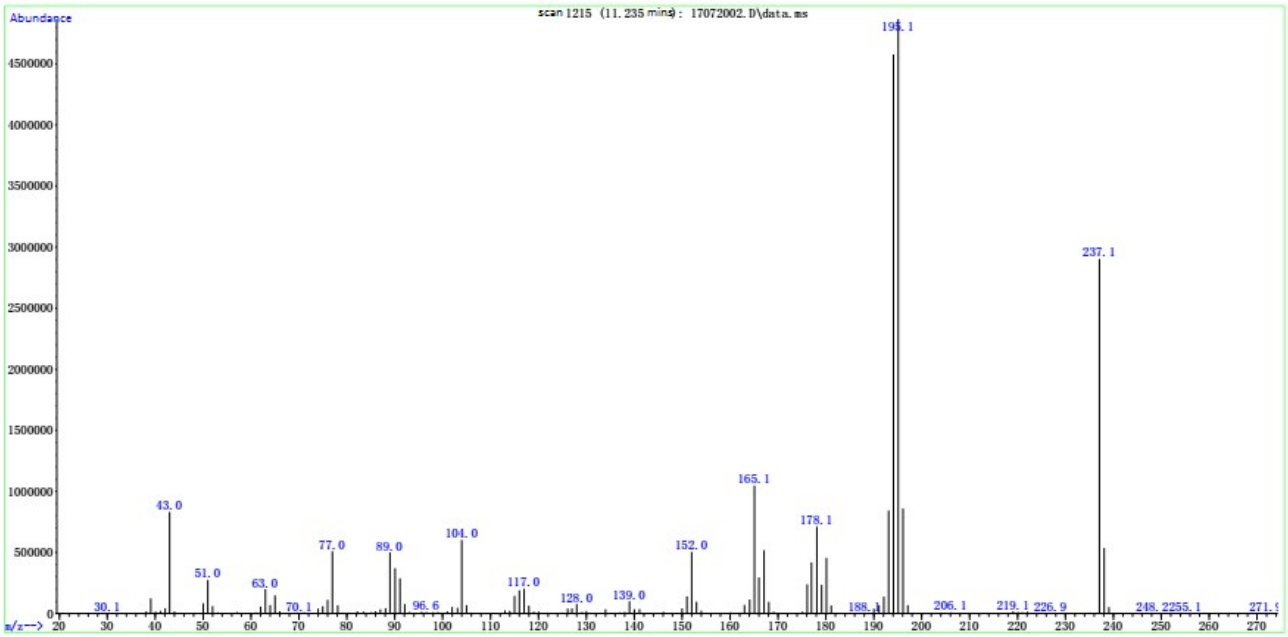
6a **6b**

The arylated intermediate **6a** and **6b** were synthesized according to literature procedures.[3] The mixture of the **6a** and **6b** was analyzed by GC-MS and the results showed that the retention time of those compounds were different as shown Figure 1. The retention time of **6a** is 11.322 mins, however, the retention time of **6b** is 11.472 mins.

File: D:\MS5973\lan\1707\BSB\17072002.D
Operator: [BSB1]
Captured: 20 Jul 2017 16: 47, acquisition method LAN2-2.M
Equipment: 5973N
Sample Description: ZW2-005-6
Additional Information:
Vial:1



File: D:\MS5973\lan\1707\BSB\17072002.D
Operator: [BSB1]
Captured: 20 Jul 2017 16: 47, acquisition method LAN2-2.M
Equipment: 5973N
Sample Description: ZW2-005-6
Additional Information:
Vial:1



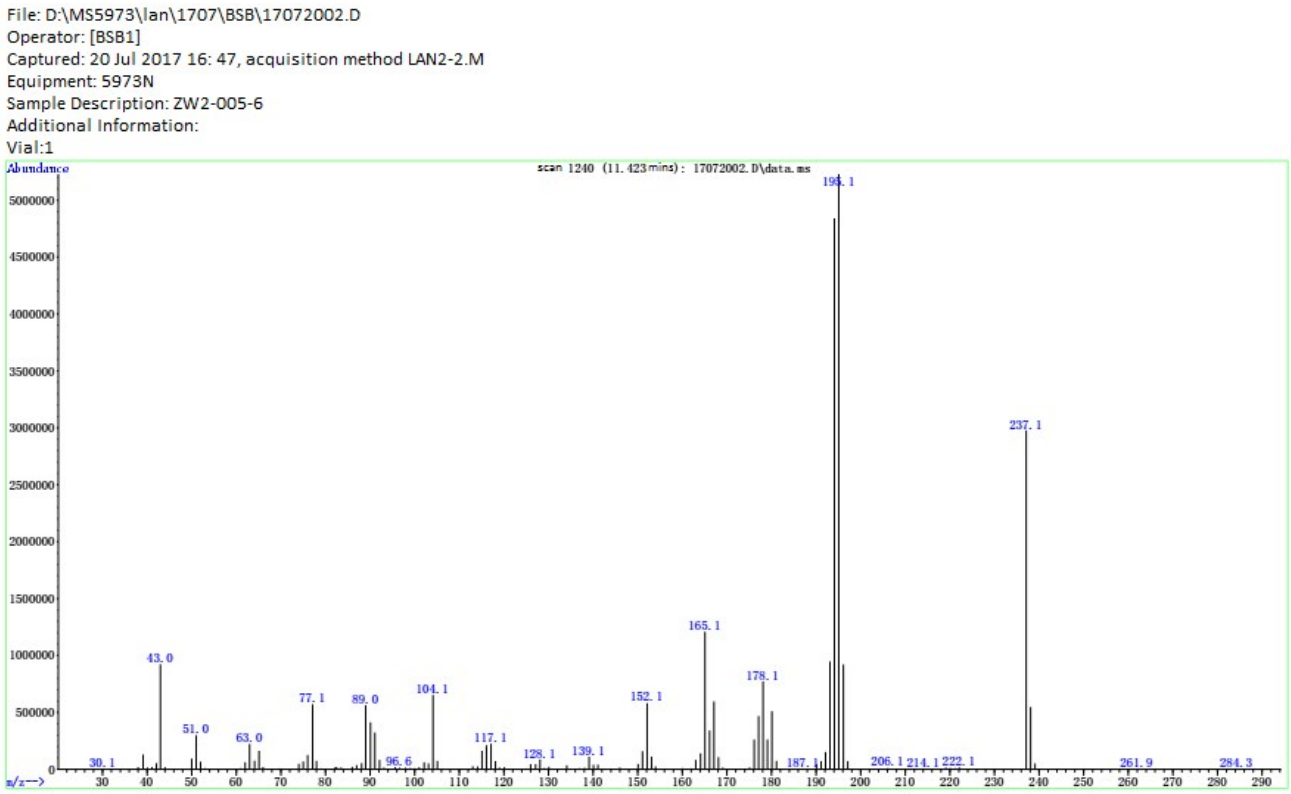
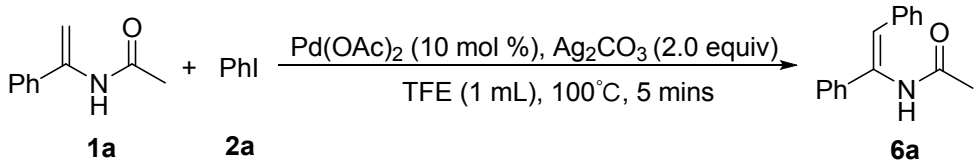
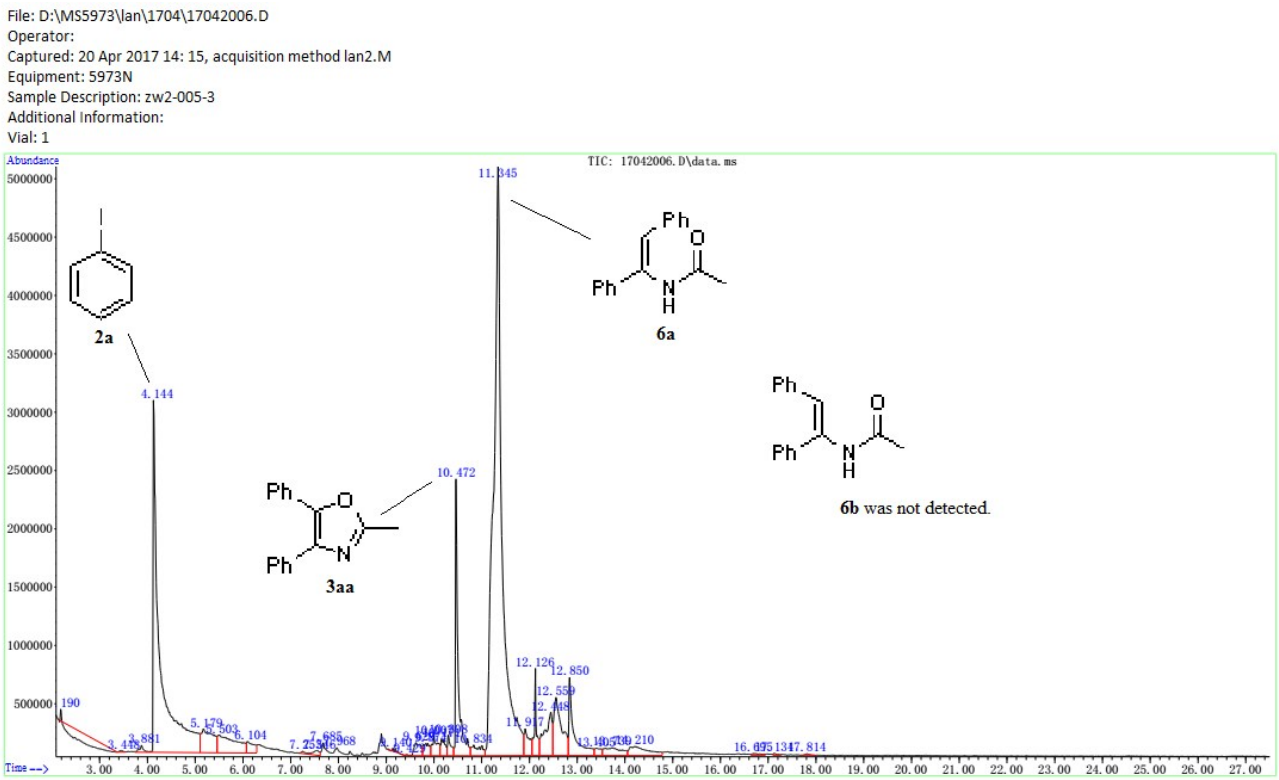


Figure 1: GC-MS of mixture **6a** and **6b**



1a **2a** **6a**

N-(1-phenylvinyl)acetamide **1a** and iodobenzene **2a** were treated in the presence of 10 mol % $Pd(OAc)_2$ and Ag_2CO_3 (2 equiv) in TFE at 100 °C. After 5 minutes, the reaction was terminated and reaction mixture was analyzed by the GC-MS. The result of the GC-MS demonstrated that *Z*-configuration arylated intermediate **6a** was formed exclusively and the *E*-configuration intermediate **6b** was not observed (Figure 2). Silica gel column purification afforded the desired product *N*-(1,2-diphenylvinyl)acetamide **6a** in 42% yield. The configuration of **6a** was further confirmed by X-ray crystallography.



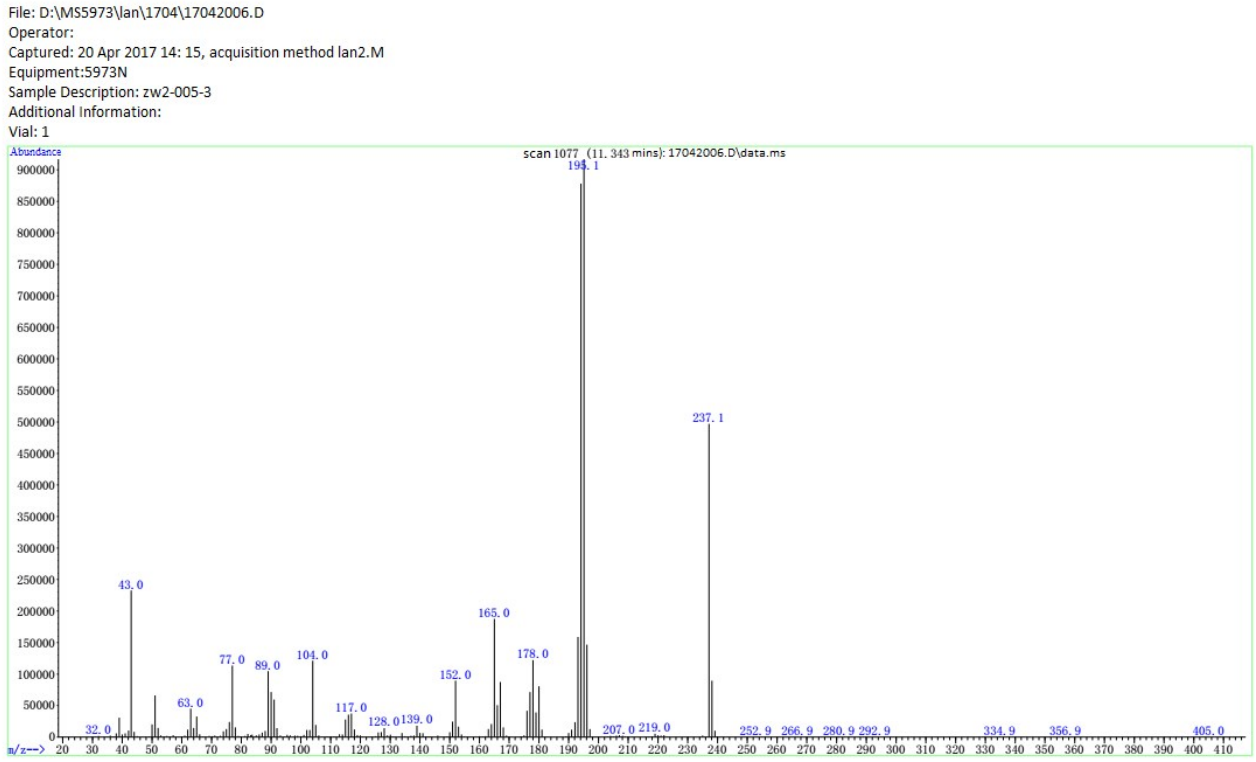
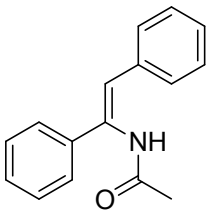
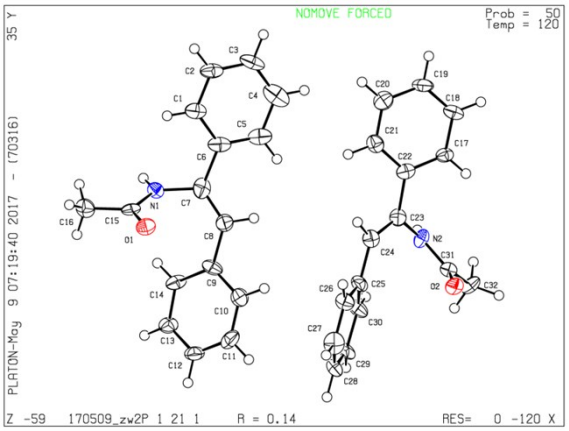


Figure 2: GC-MS of mixture **6a**

X-Ray Crystallographic Data



6a (CCDC 1549336)



Datablock: 170509_zw2_005_3_1

Bond precision: C-C = 0.0154 A Wavelength=0.71073

Cell: a=6.9086(8) b=9.5831(7) c=19.453(2)
alpha=90 beta=96.737(10) gamma=90
Temperature: 120 K

	Calculated	Reported
Volume	1279.0(2)	1279.0(2)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C16 H15 N O	C16 H15 N O
Sum formula	C16 H15 N O	C16 H15 N O
Mr	237.29	237.29
Dx,g cm-3	1.232	1.232
Z	4	4
Mu (mm-1)	0.077	0.077
F000	504.0	504.0
F000'	504.20	
h,k,lmax	8,11,23	8,11,23
Nref	4680[2493]	3782
Tmin,Tmax	0.968,0.973	0.854,1.000
Tmin'	0.968	

Correction method= # Reported T Limits: Tmin=0.854 Tmax=1.000
AbsCorr = MULTI-SCAN

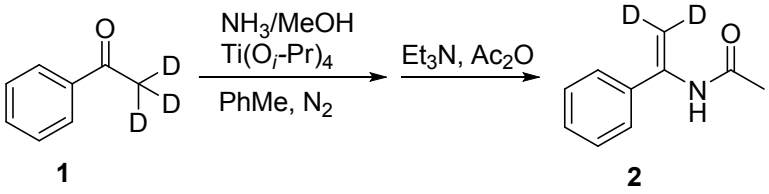
Data completeness= 1.52/0.81 Theta(max)= 25.346

R(reflections)= 0.1365(3115) wR2(reflections)= 0.3583(3782)

S = 1.333 Npar= 327

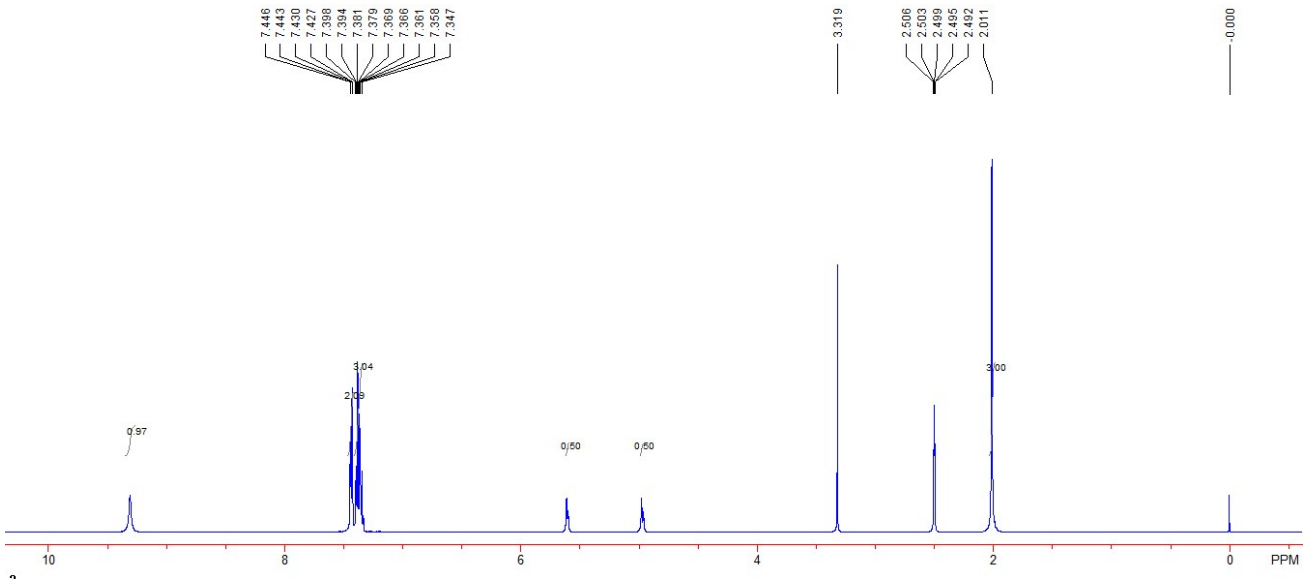
Isotope kinetic experiment

1. The synthesis of *N*-(1-phenylvinyl-2,2-d_2)acetamide[1a]



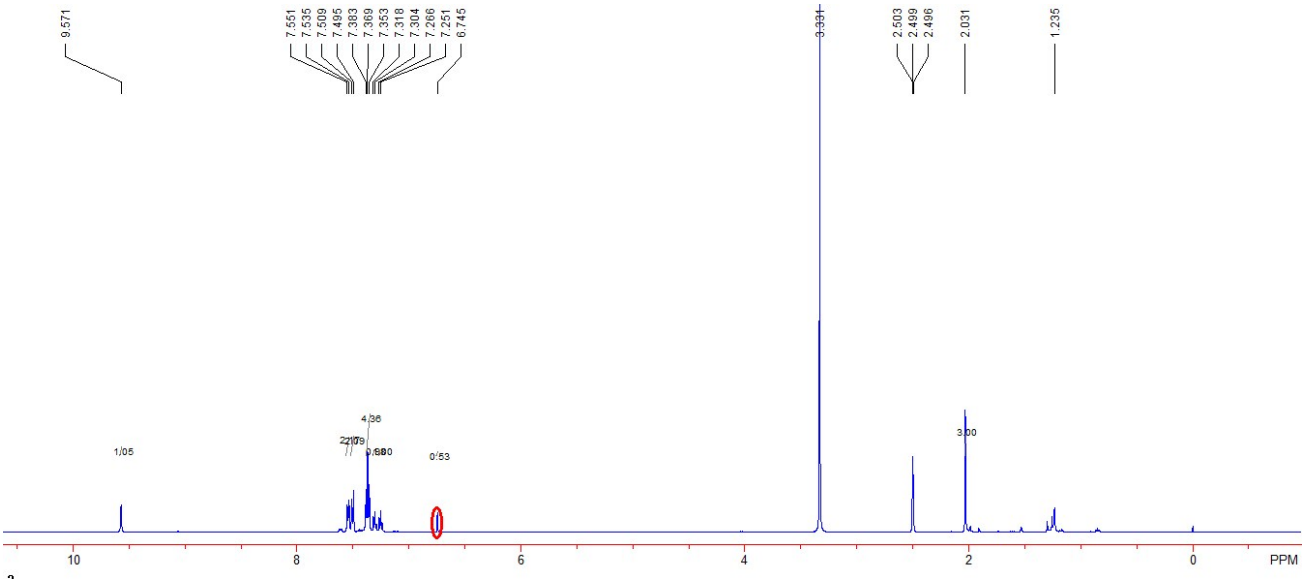
1 **2**

Under N_2 atmosphere, deuterated acetophenone (1.17 mL, 10.0 mmol, 1 equiv) were solved in toluene (6 mL) in a dry three-neck 50 mL round bottom flask. The solution was stirred and cooled in an ice/water bath and added 7N NH_3 in MeOH (2.14 mL, 15.0 mmol, 1.5 equiv) followed by dropwise addition of Ti(O*i*-Pr)$_4$ (5.92 mL, 20.0 mmol, 2.0 equiv). After 10 mins, the ice/water cooling bath was removed, and the solution was stirred at room temperature for 24 h. Then, the reaction mixture was then cooled in an ice/water bath and treated with Et_3N (5.58 mL, 40.0 mmol, 4.0 equiv) followed by Ac_2O (1.89 mL, 20.0 mmol, 2.0 equiv). The cooling bath was then removed and the solution was stirred at room temperature for 3 h. The reaction mixture was then treated with EDTE (4.51 mL, 21.0 mmol, 2.1 equiv) at room temperature and heated at about 55 °C for 15 mins. The reaction mixture was allowed to cool to room temperature, and was then poured into a separatory funnel containing a solution made from water (30 mL) and NH_4OH (10 mL) and EtOAc (50 mL). The combined organic layer was concentrated under reduced pressure and purification by flash chromatography on silica gel (hexane/EtOAc, 5:1 to 3:1) gave **2** (1.03 g, 64% yield) as a light yellow solid with 50% deuterium.

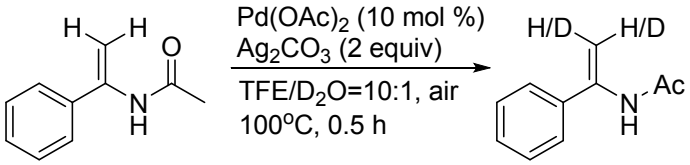


2. Intermolecular kinetic isotopic effect (KIE) study

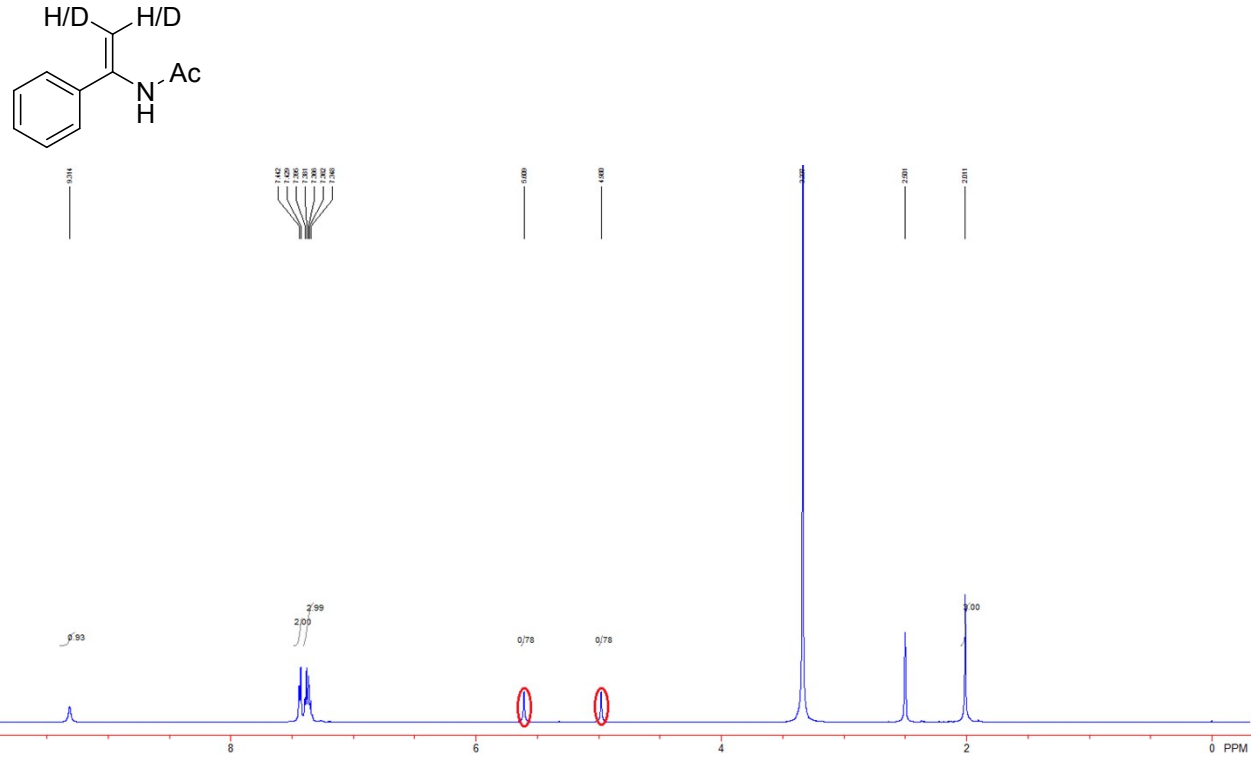
33 mg (0.2 mmol) of the deuterated enamide was dissolved in 1mL TFE in a tube. 6 mg (10 mol %) of $Pd(OAc)_2$, 110 mg (2 equiv) Ag_2CO_3 were added. The solution was heated at 100 ^oC for 20 mins. The solvent was removed in vacuum and the product was isolated through flash column chromatography (hexane/ethyl acetate) to furnish 5 mg (10%) of the product mixture as light yellow solid. The KIE value (K_H/K_D = 1.13) was determined from the ^{1}H-NMR.



Deuteration Experiments



32 mg (0.2 mmol) of the protonated enamide was dissolved in 1mL TFE/D_2O (v_1 /v_2 = 9/1) in a tube. 6 mg (10 mol %) of $Pd(OAc)_2$, 110 mg (2 equiv) Ag_2CO_3 were added. The solution was heated at 100 °C for 0.5 hours. The start material was recovered and analysised by ^{1}H-NMR.



Reference

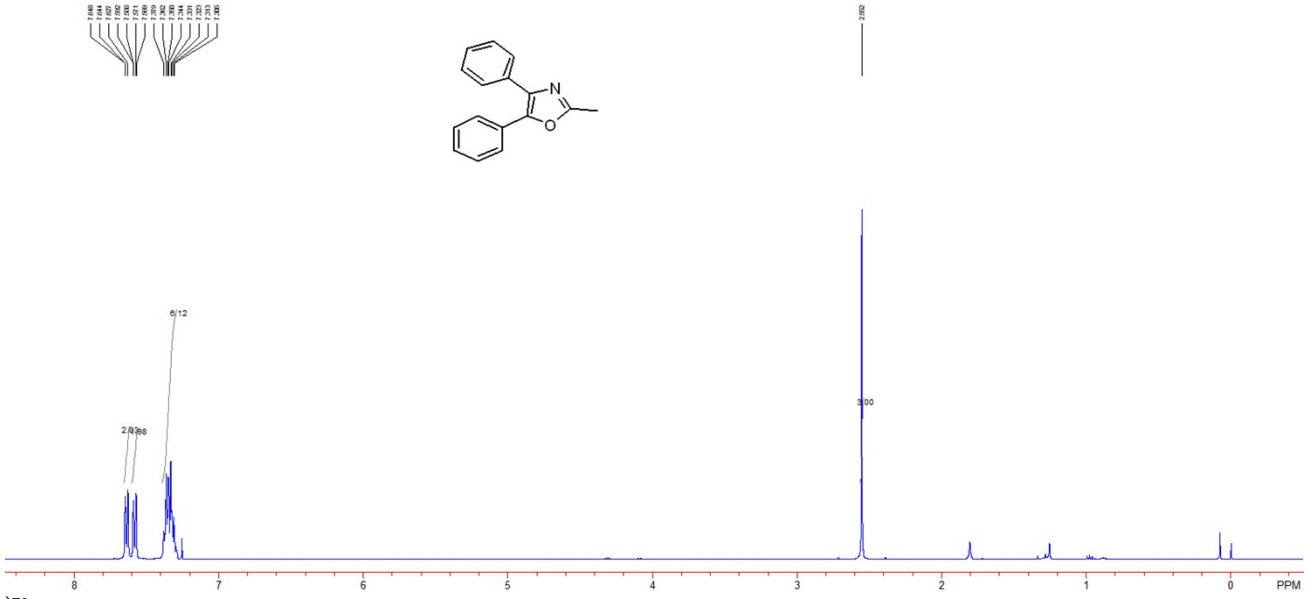
1 (*a*) J. T. Reeves, Z. Tan, Z. Han, G. Li, Y. Zhang, Y. Xu, D. C. Reeves, D. C. Gonnella, S. L. Ma, H. W. Lee, B. Z. Lu and C. H. Senanayake, *Angew. Chem. Int. Ed.*, 2012, **51**, 1400; (*b*) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Chem. Commun.*, 2012, **48**, 8105.

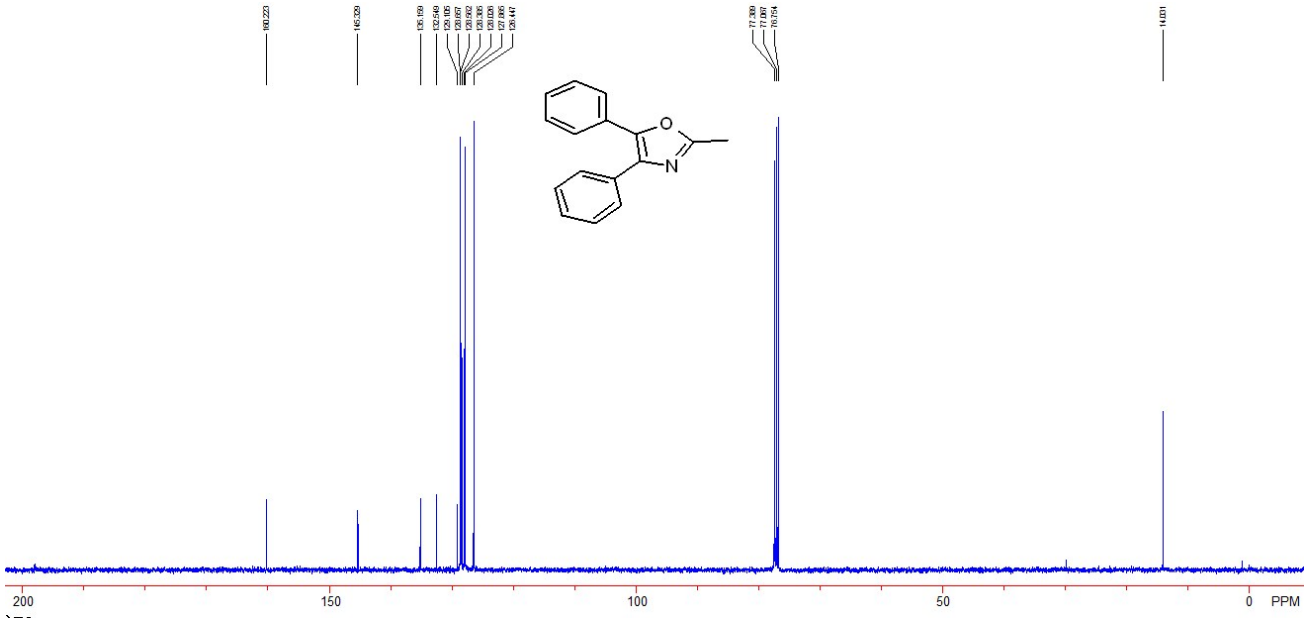
2 (*a*) D. García-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2006, **128**, 1066; (*b*) D. García-Cuadrado, P. Mendoza, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2007, **129**, 6880; (*c*) M. Iwasaki, S. Iino and Y. Nishihara, *Org. Lett.*, 2013, **15**, 5326; (*d*) M. Iwasaki, Y. Araki, S. Iino and Y. Nishihara, *J. Org. Chem.*, 2015, **80**, 9247.

3 J. Chen, W. Zhang, H. Geng, W. Li, G. Hou, A. Lei and X. Zhang, *Angew. Chem. Int. Ed.,* 2009, **48**, 800.

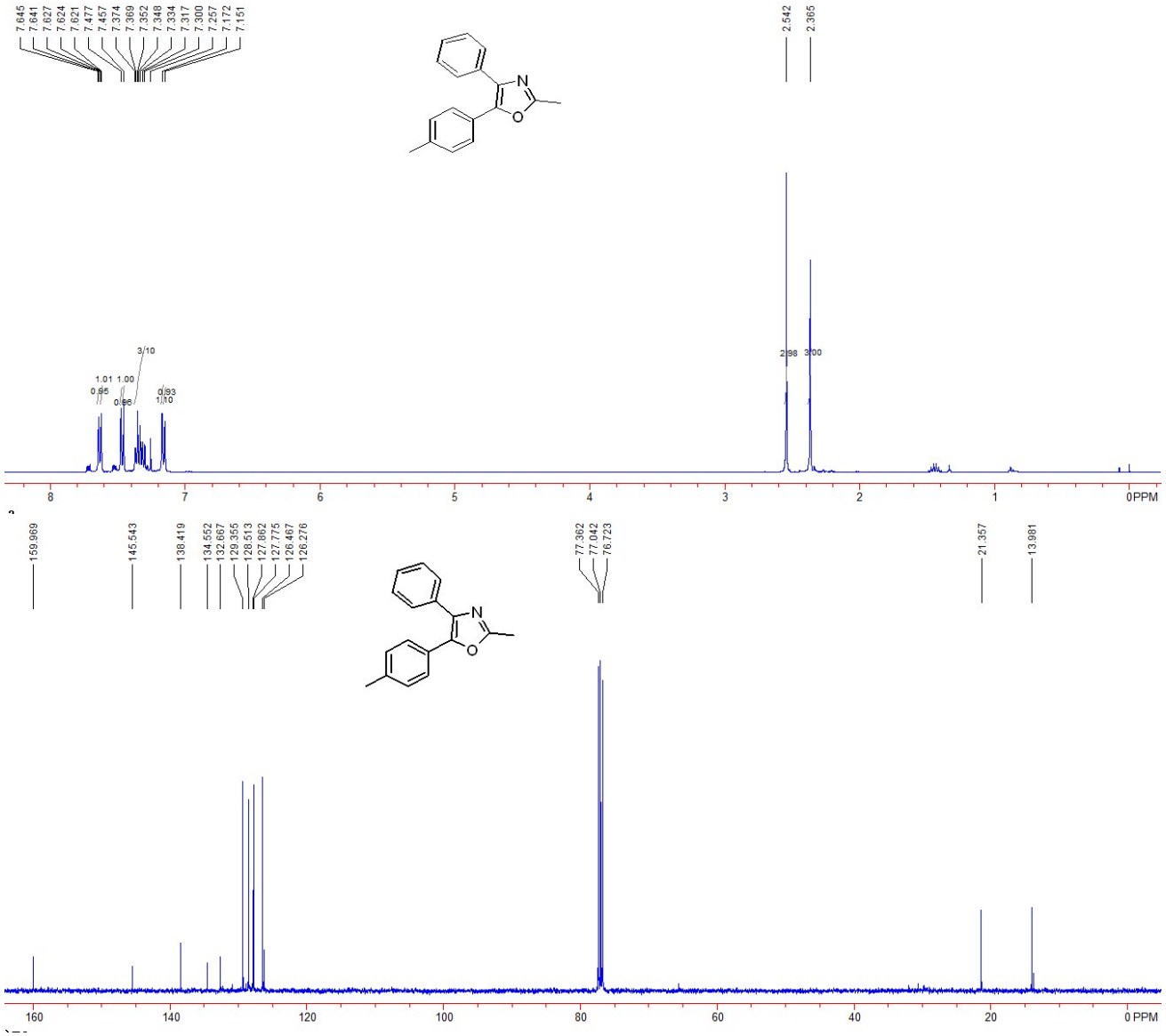
^{1}H and ^{13}C NMR Spectra

3aa 2-Methyl-4,5-diphenyloxazole

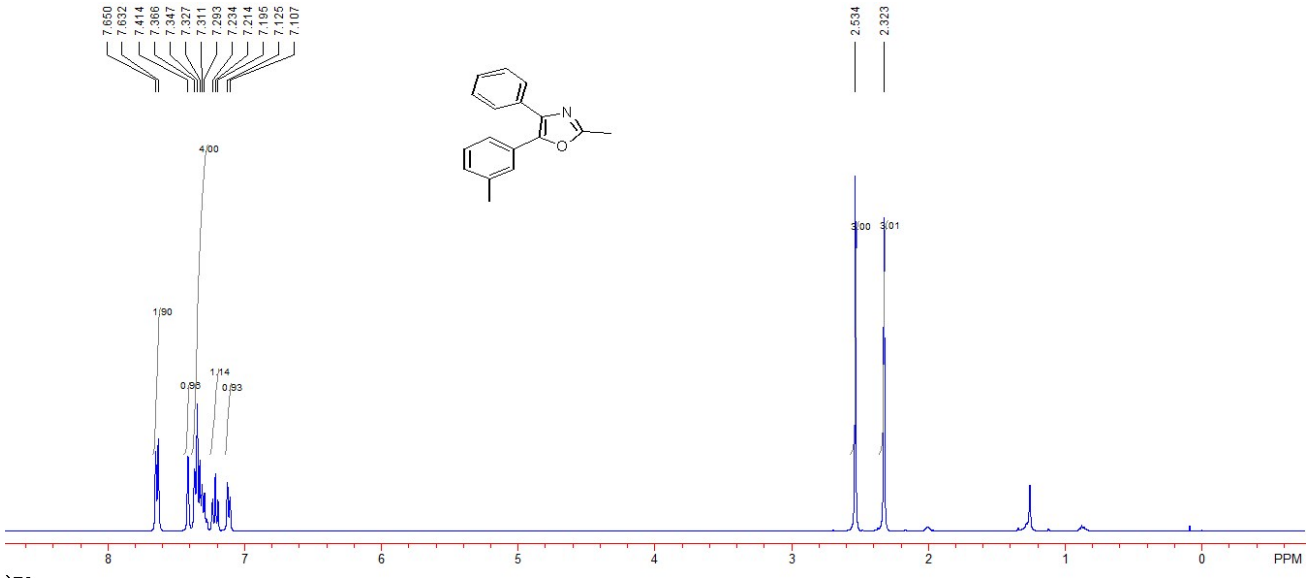


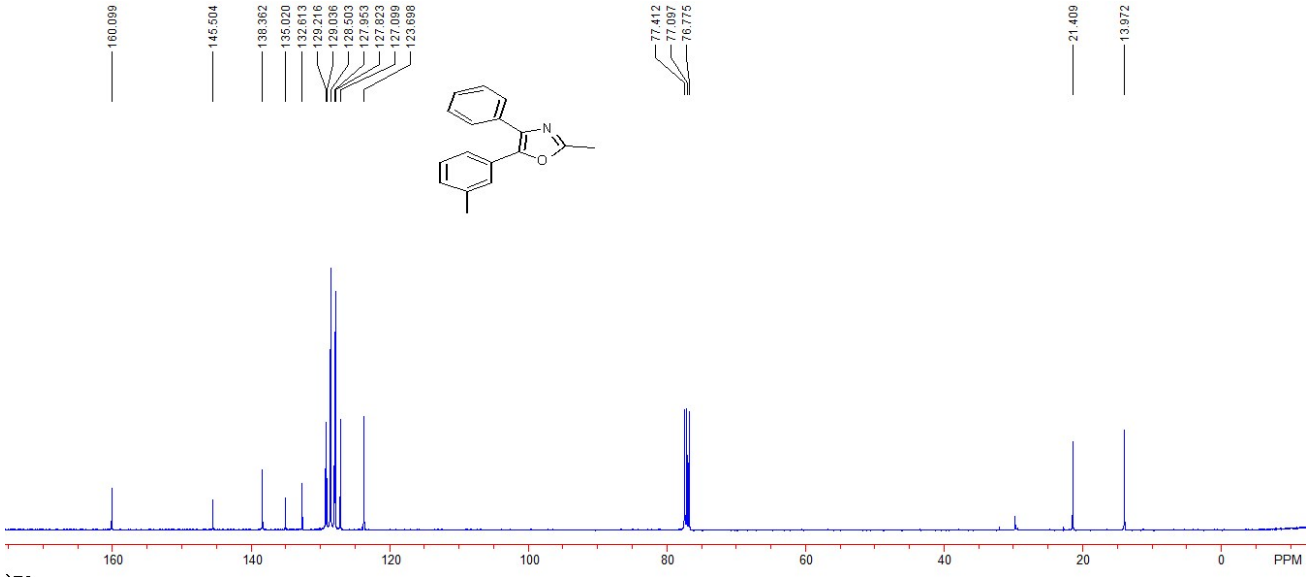


3ab 2-Methyl-4-phenyl-5-*p*-tolyloxazole

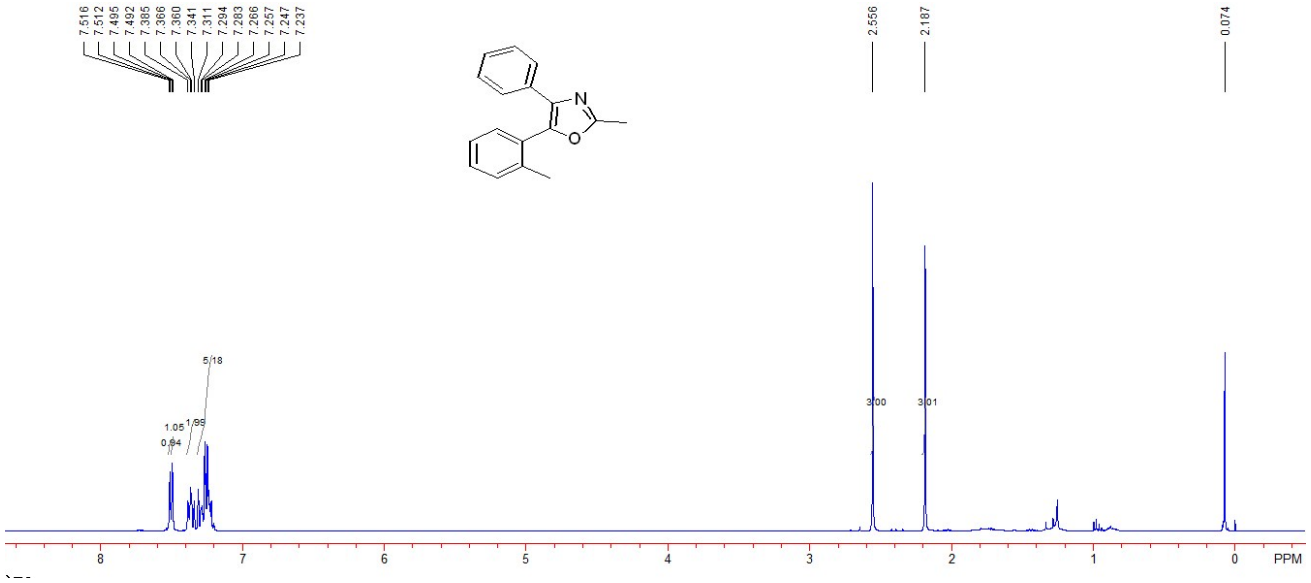


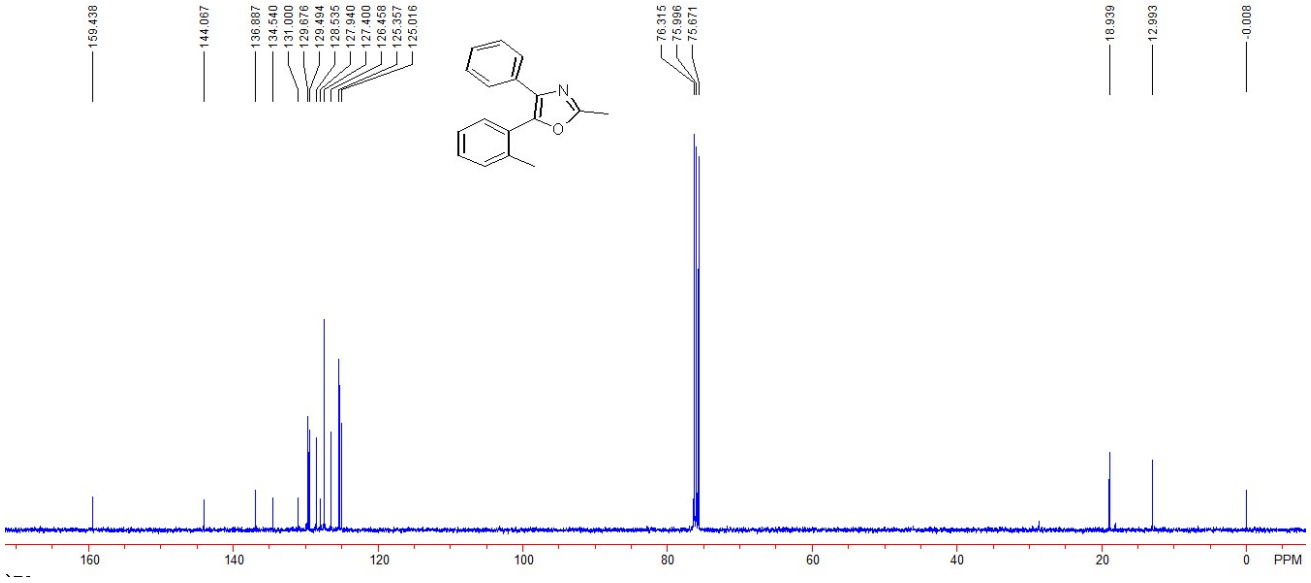
3ac 2-Methyl-4-phenyl-5-*m*-tolyloxazole



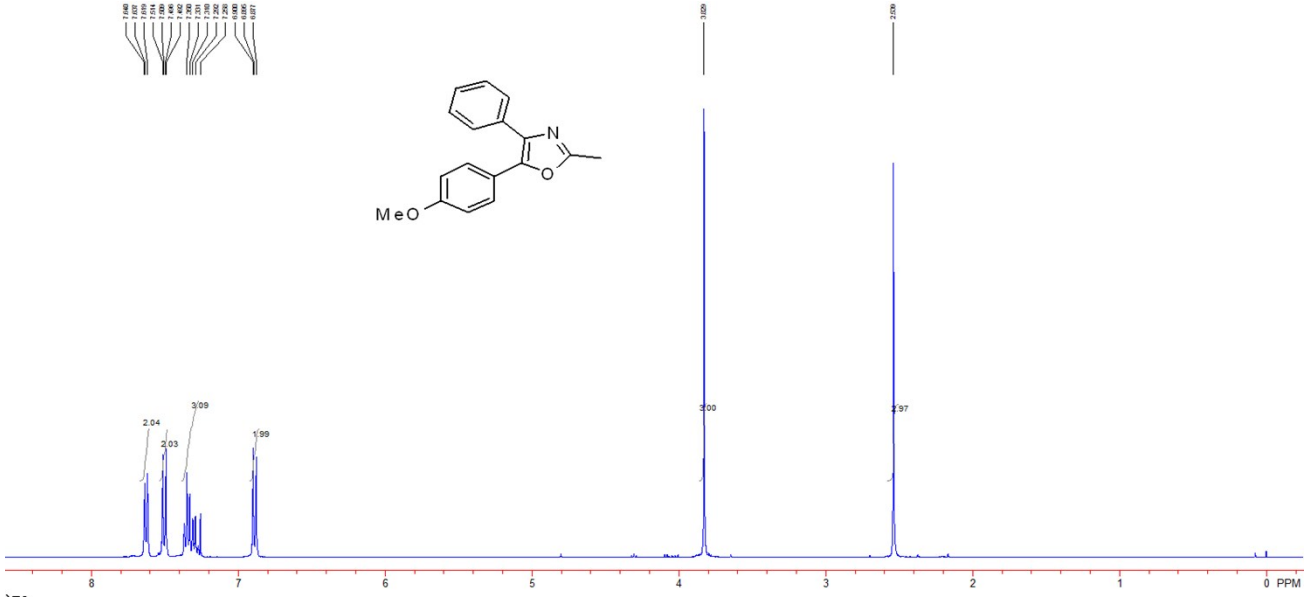


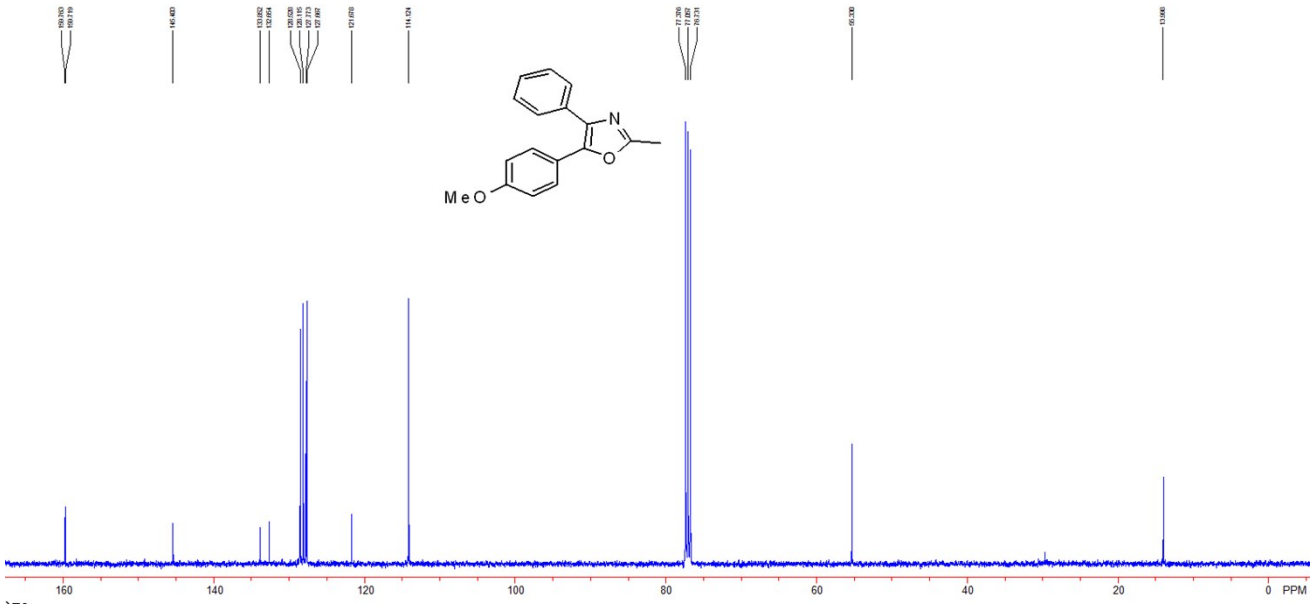
3ad 2-Methyl-4-phenyl-5-*o*-tolyloxazole



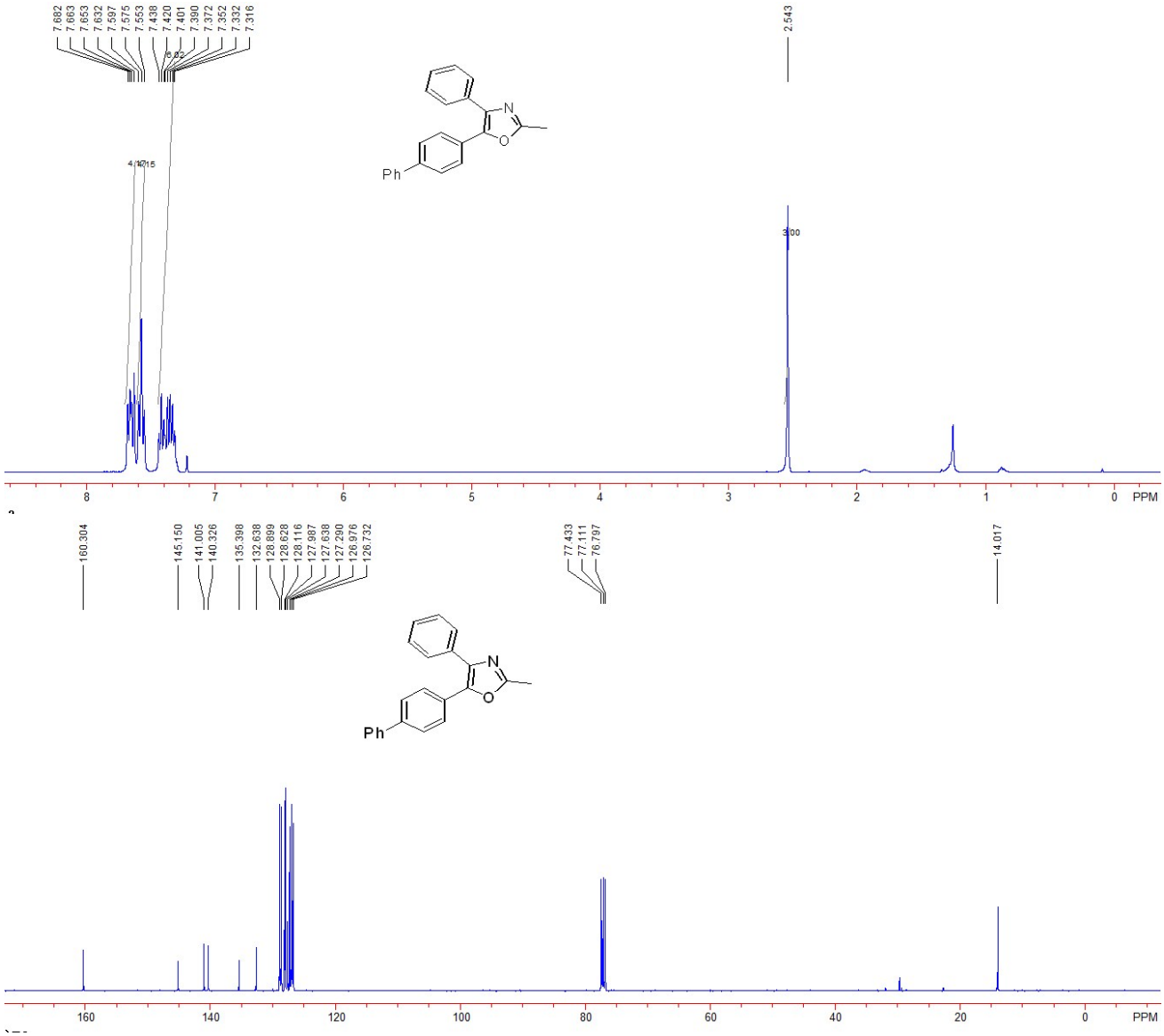


3ae 5-(4-Methoxyphenyl)-2-methyl-4-phenyloxazole

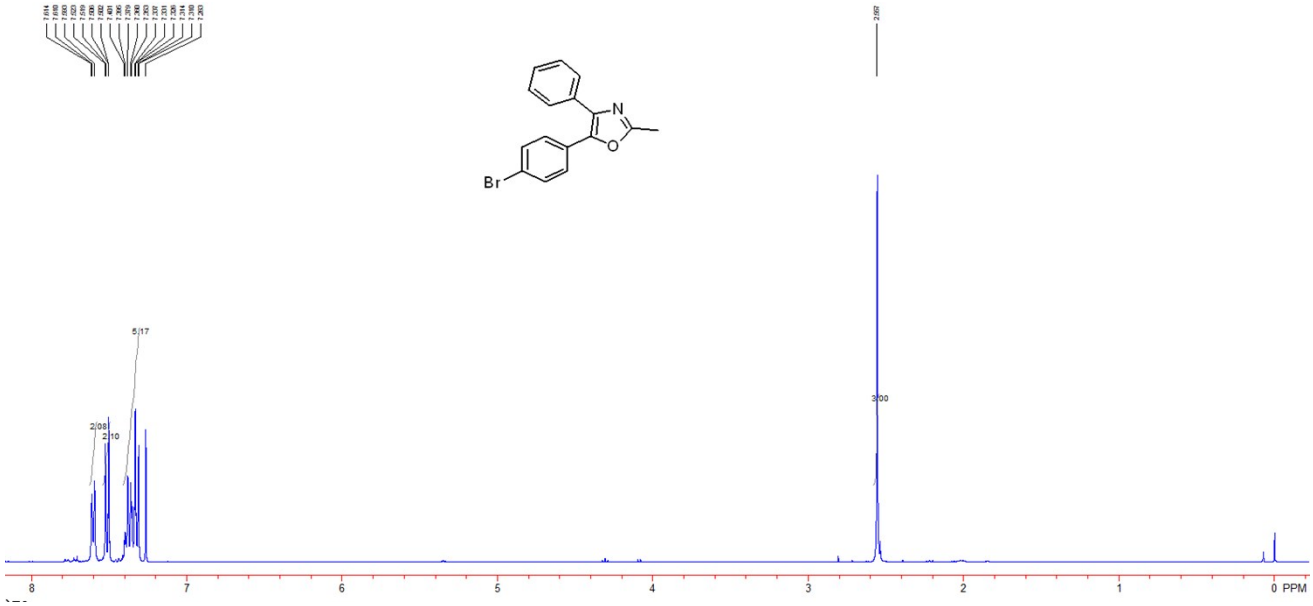


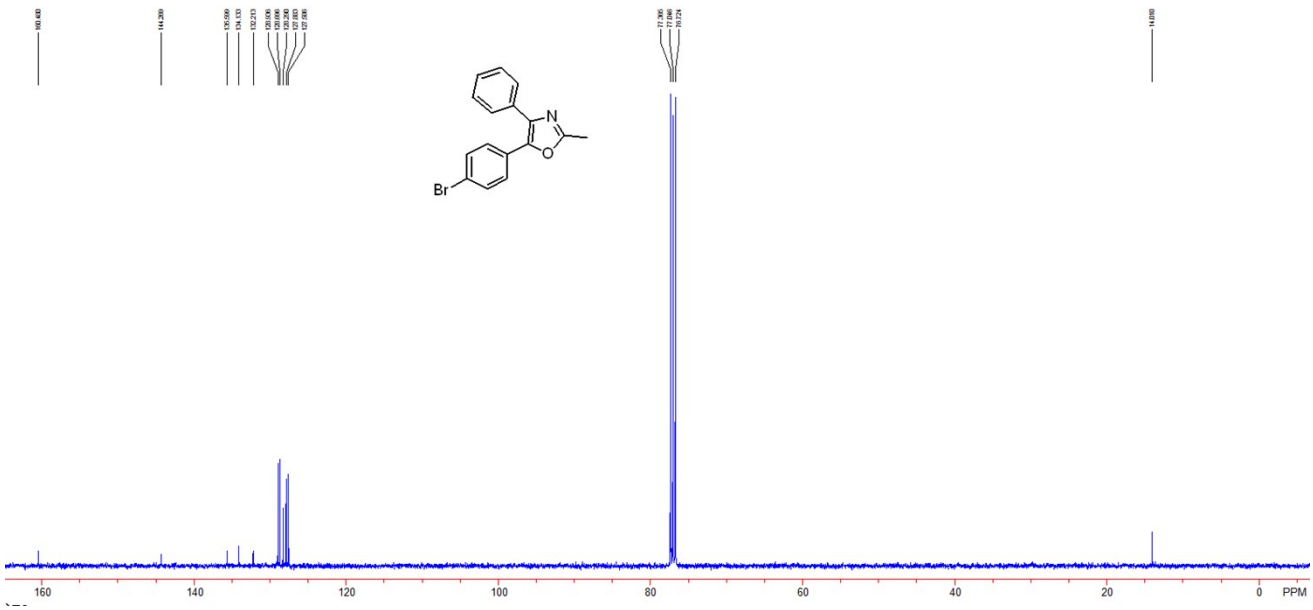


3af 5-(Biphenyl-4-yl)-2-methyl-4-phenyloxazole

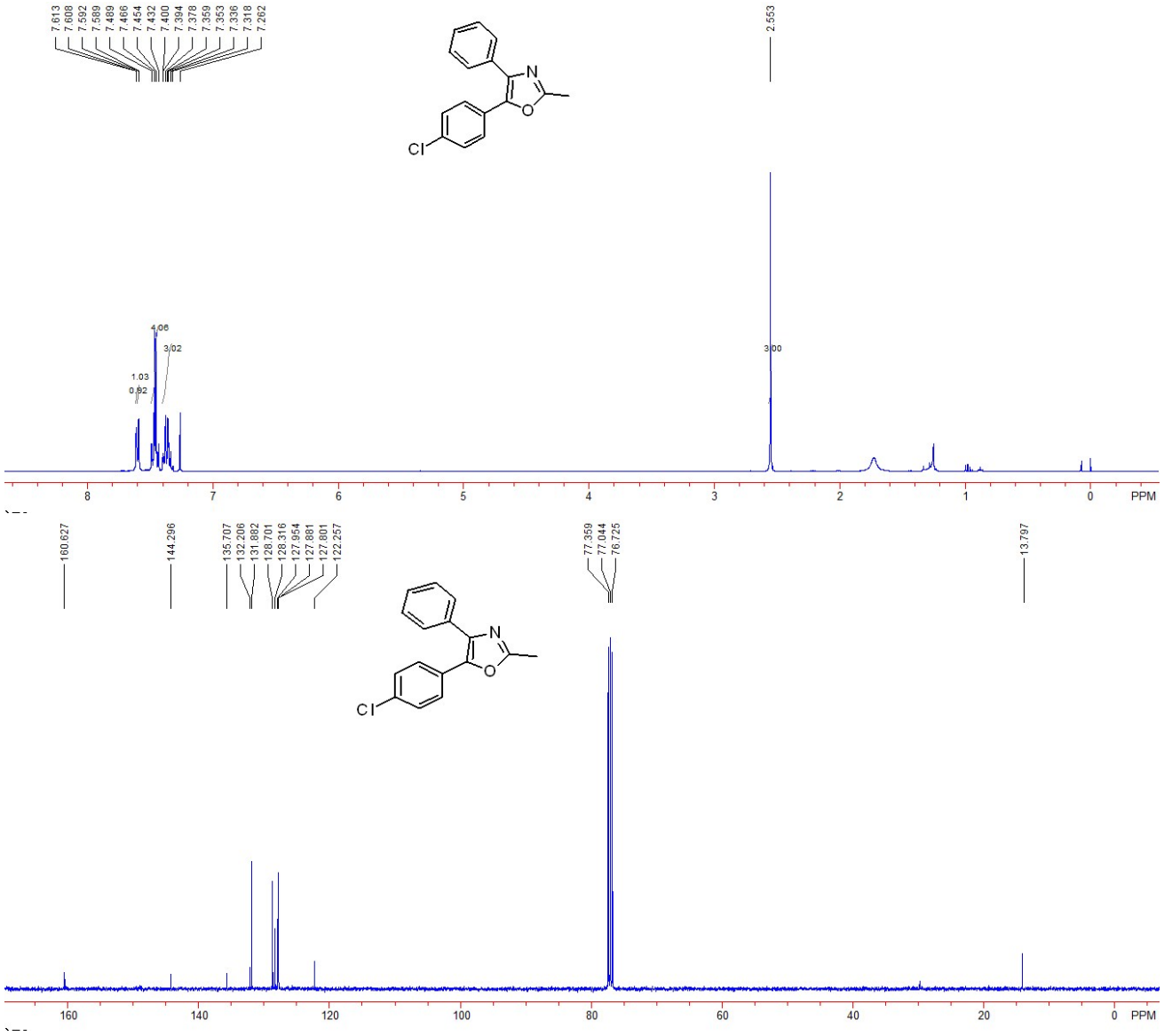


3ag 5-(4-Bromophenyl)-2-methyl-4-phenyloxazole

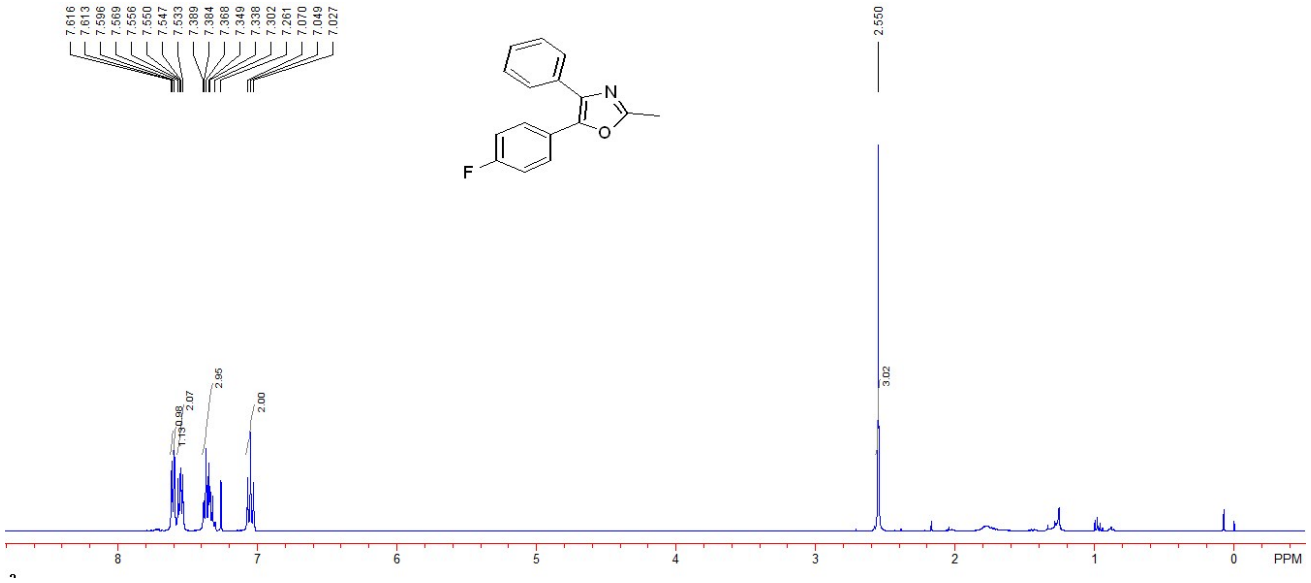


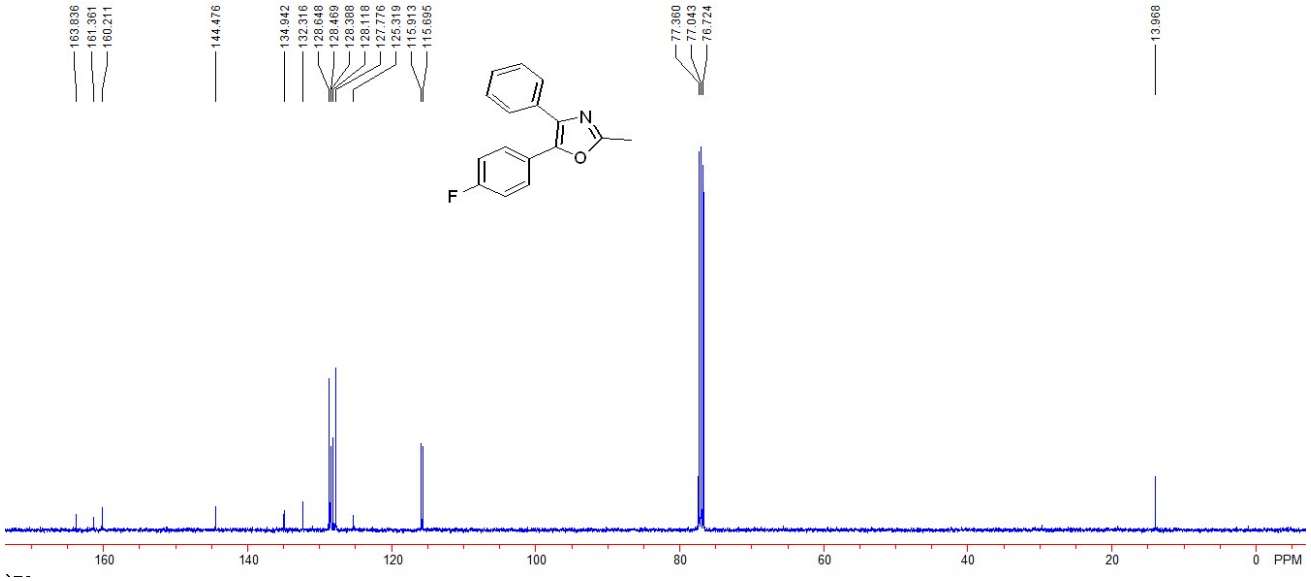


3ah 5-(4-Chlorophenyl)-2-methyl-4-phenyloxazole

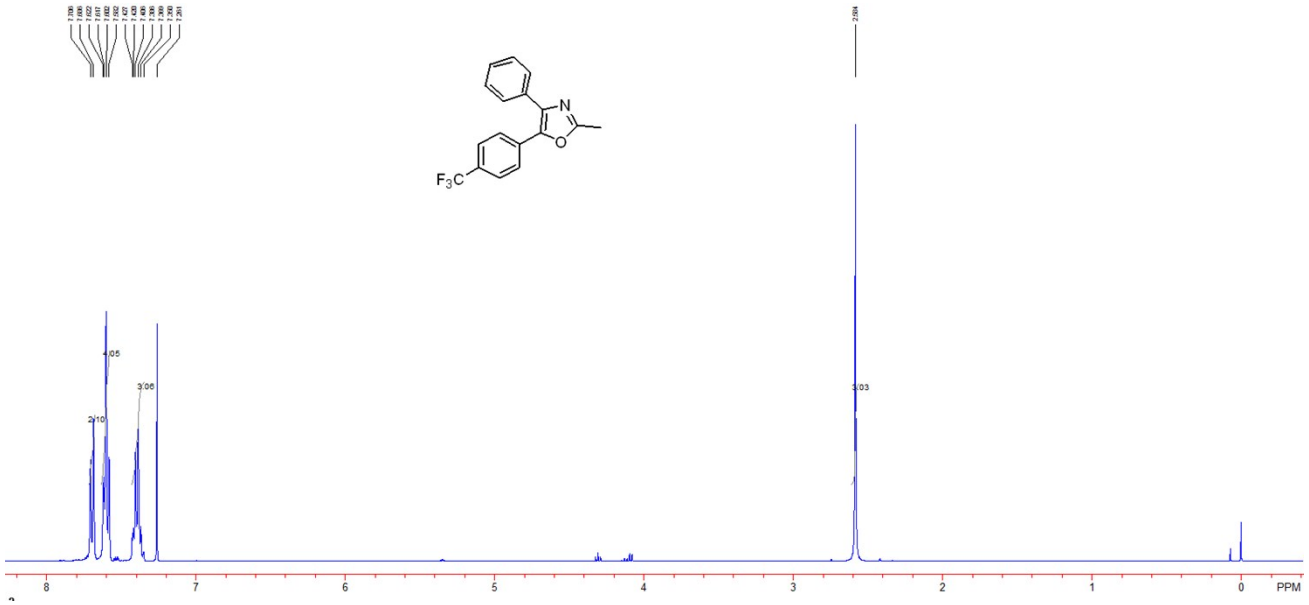


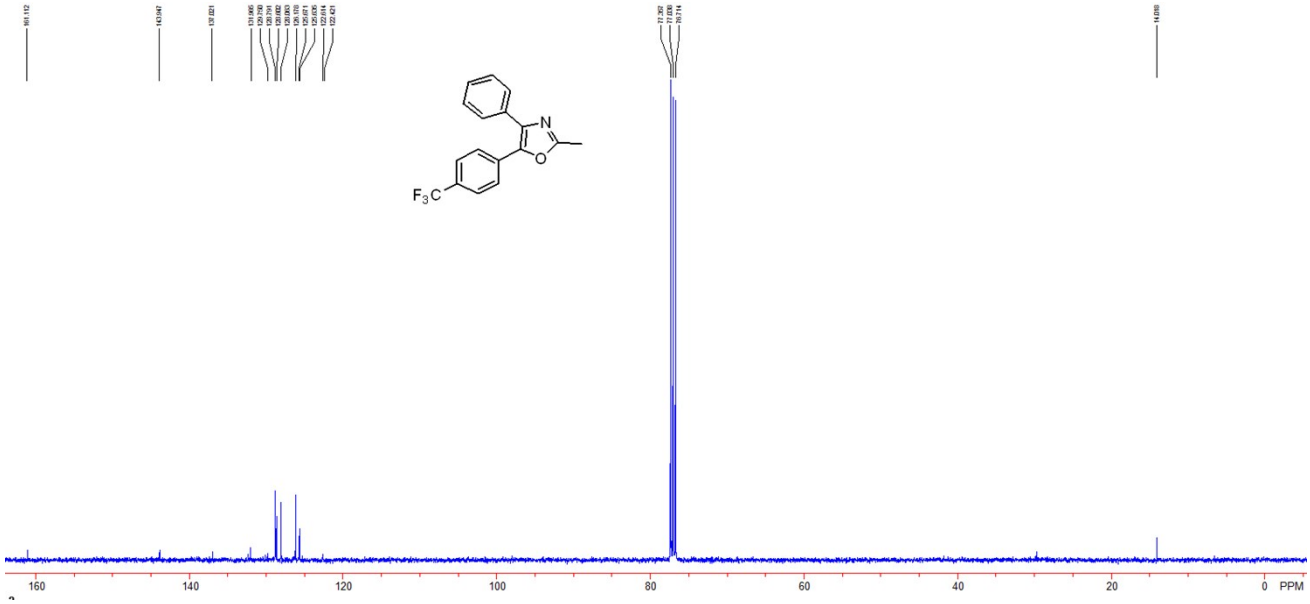
3ai 5-(4-Fluorophenyl)-2-methyl-4-phenyloxazole



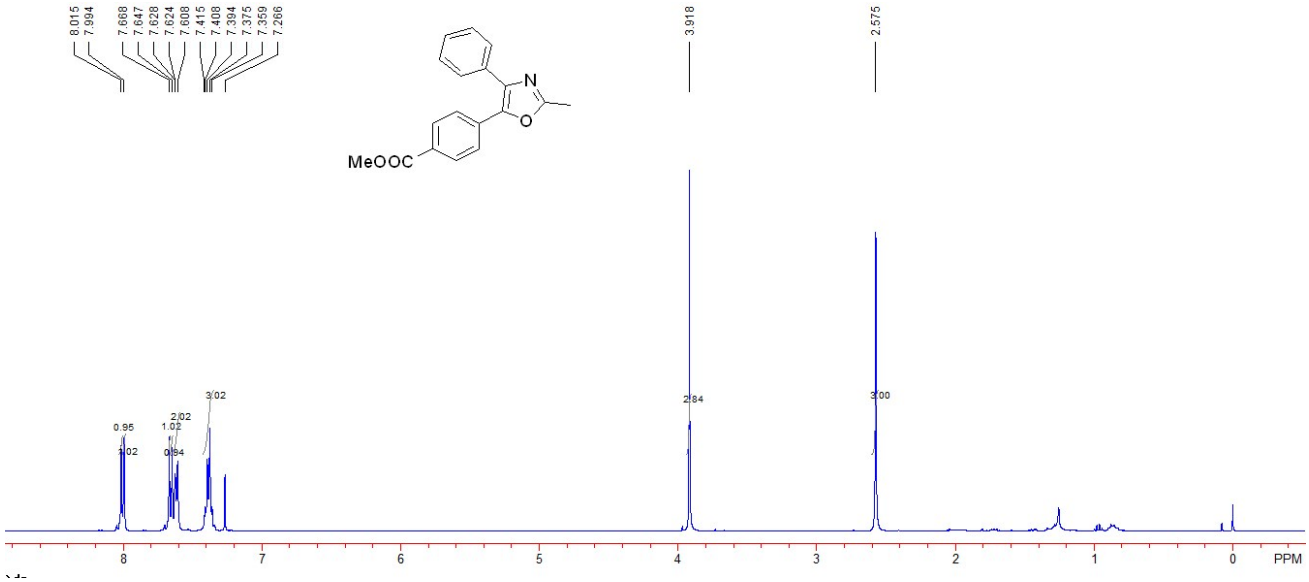


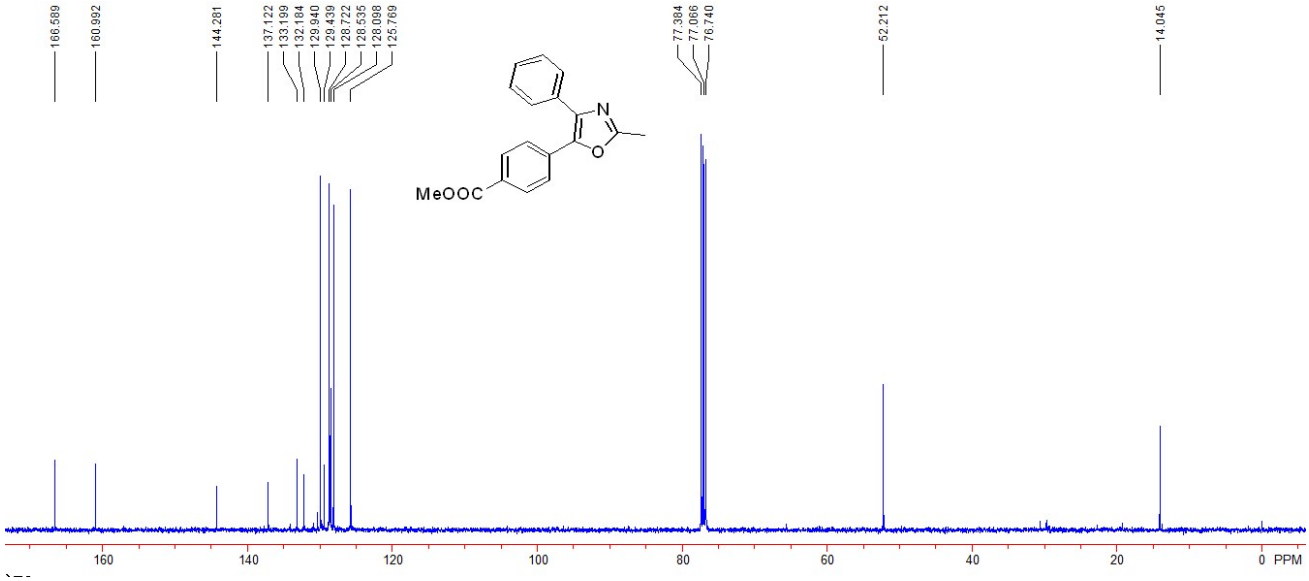
3aj 2-Methyl-4-phenyl-5-(4-(trifluoromethyl)phenyl)oxazole



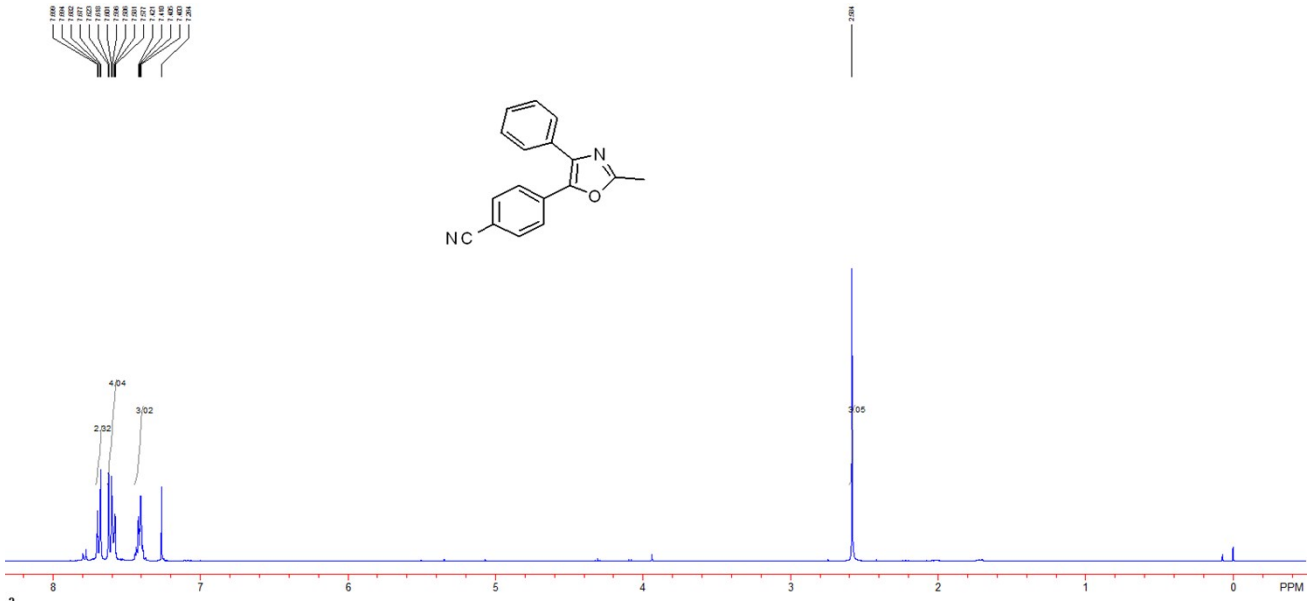


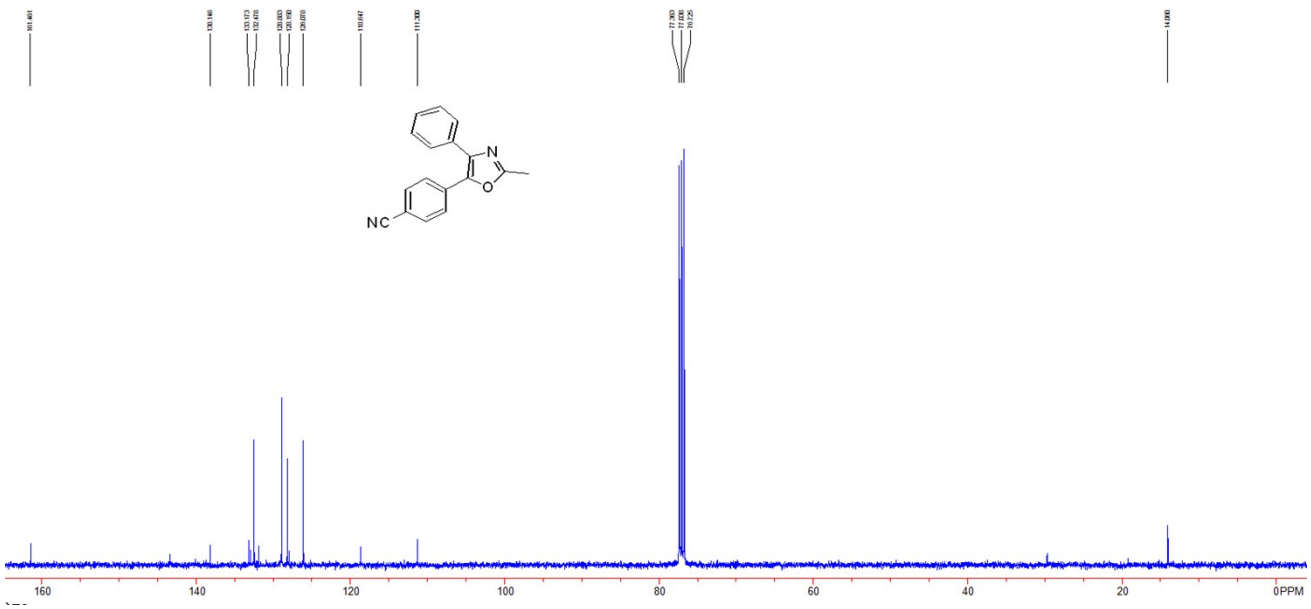
3ak Methyl 4-(2-methyl-4-phenyloxazol-5-yl)benzoate



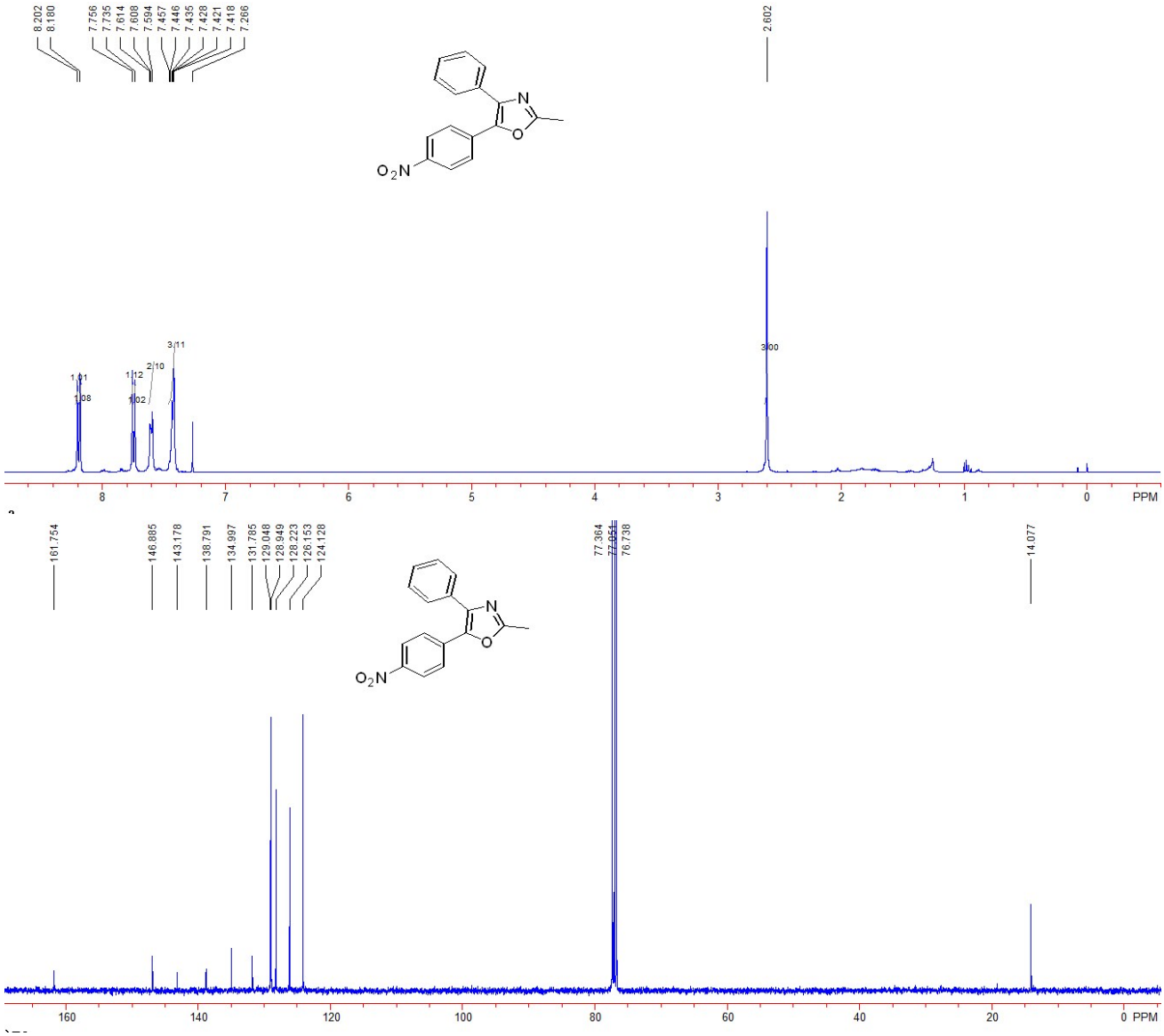


3al 4-(2-Methyl-4-phenyloxazol-5-yl)benzonitrile

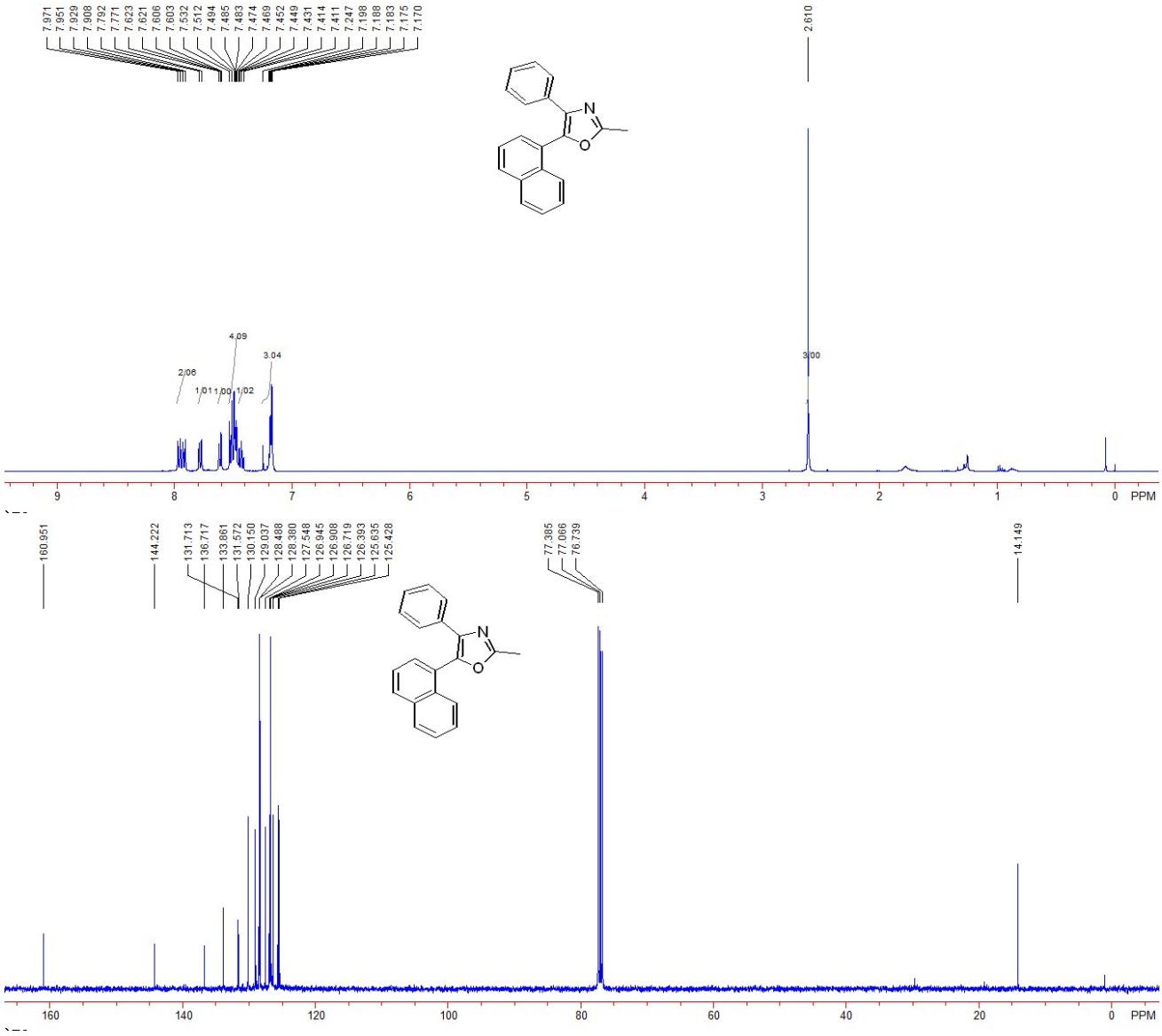




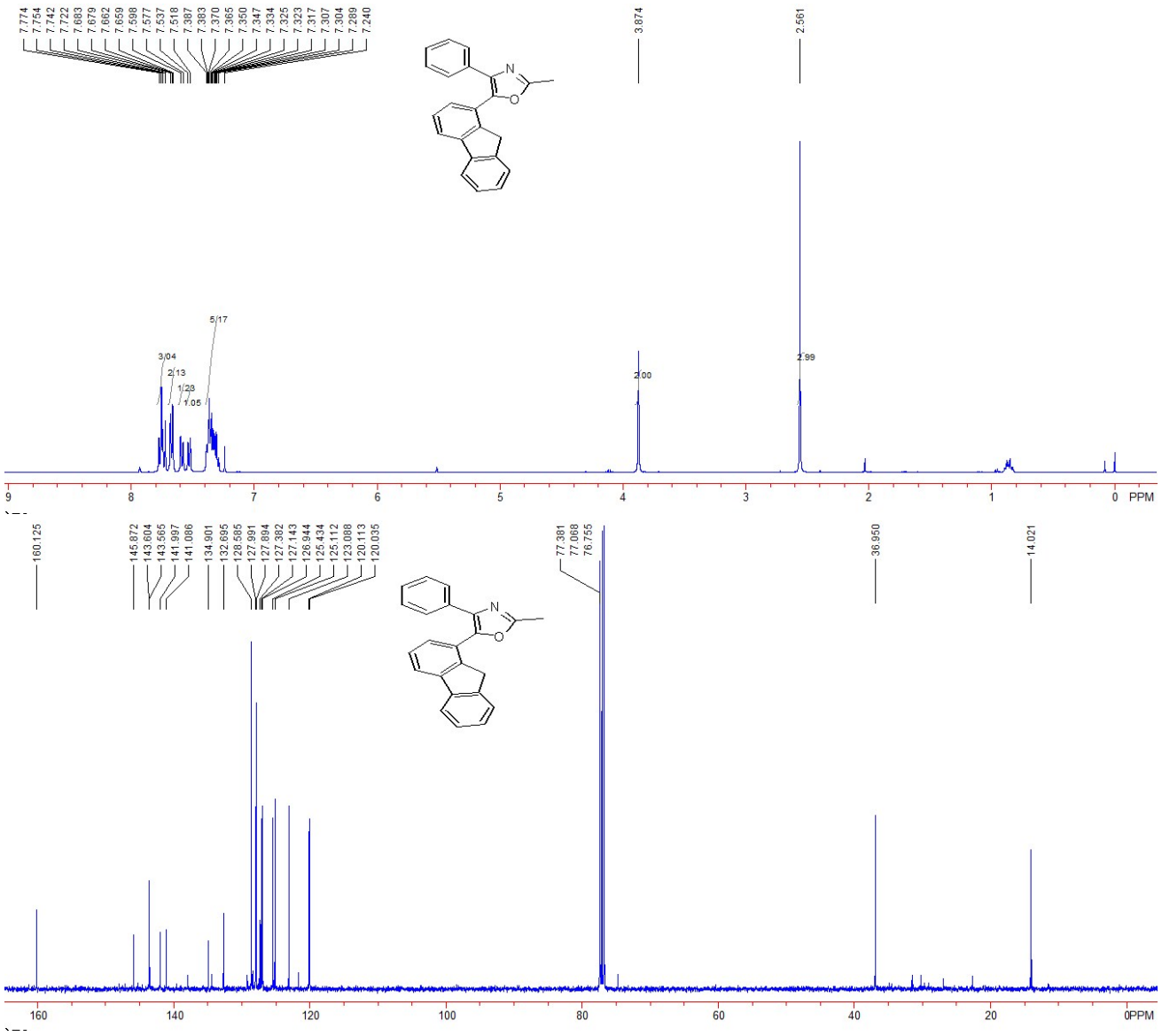
3am 2-Methyl-5-(4-nitrophenyl)-4-phenyloxazole



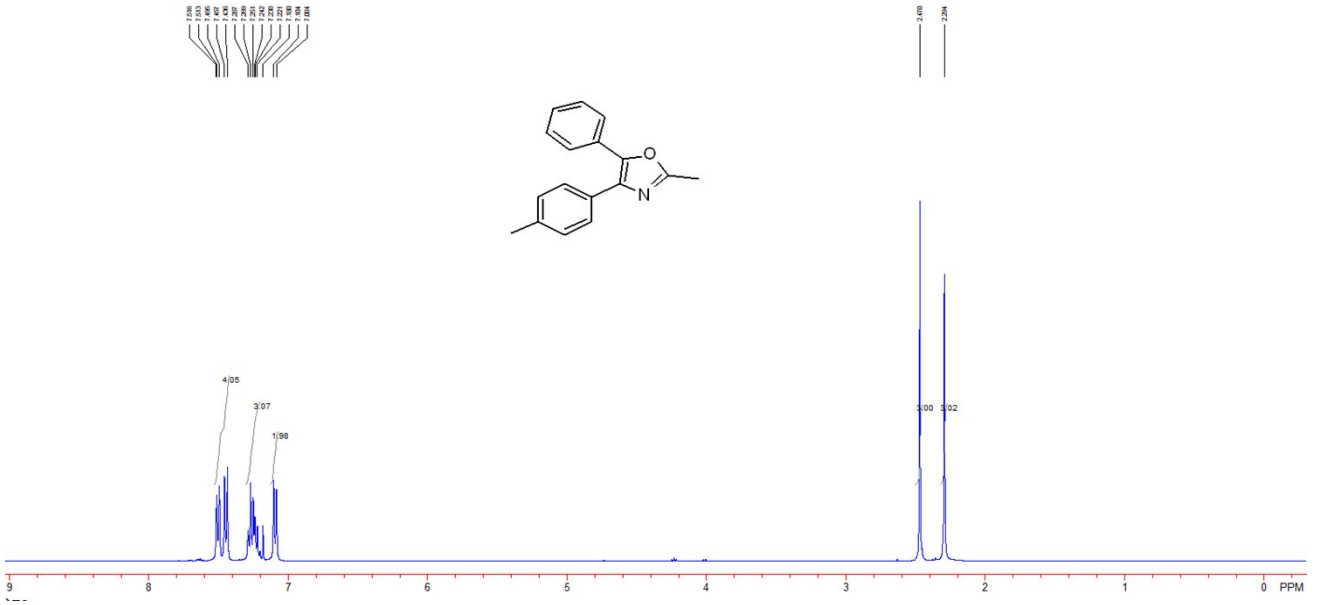
3an 2-Methyl-5-(naphthalen-1-yl)-4-phenyloxazole

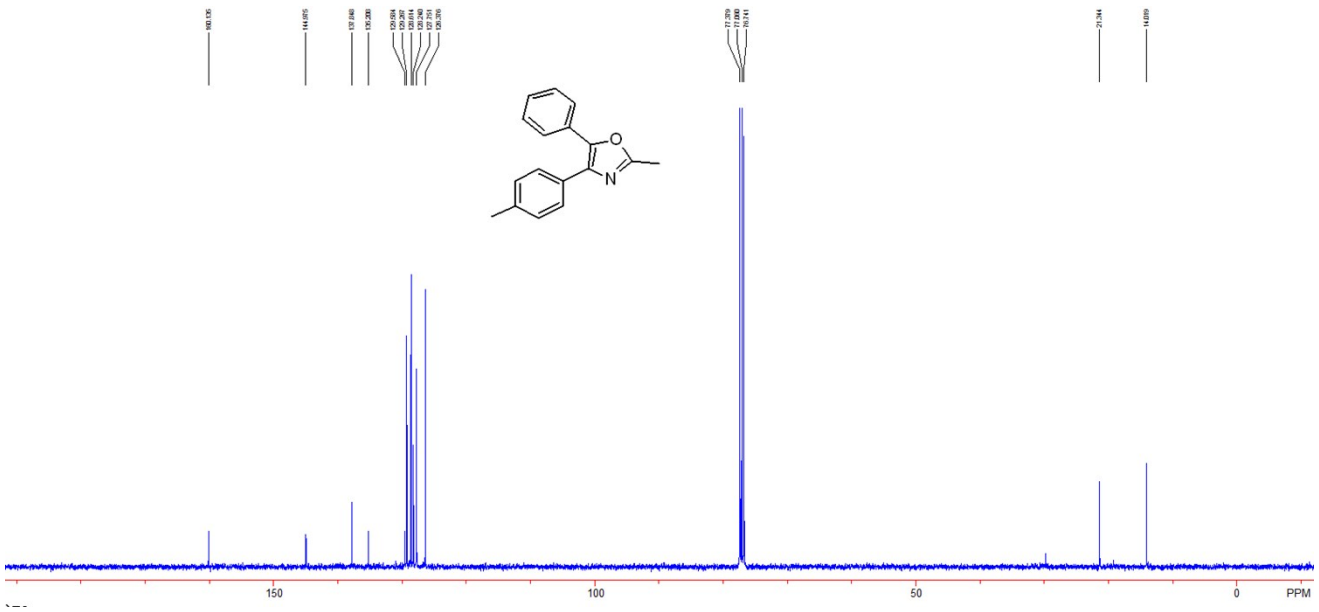


3ao 5-(9*H*-fluoren-1-yl)-2-methyl-4-phenyloxazole

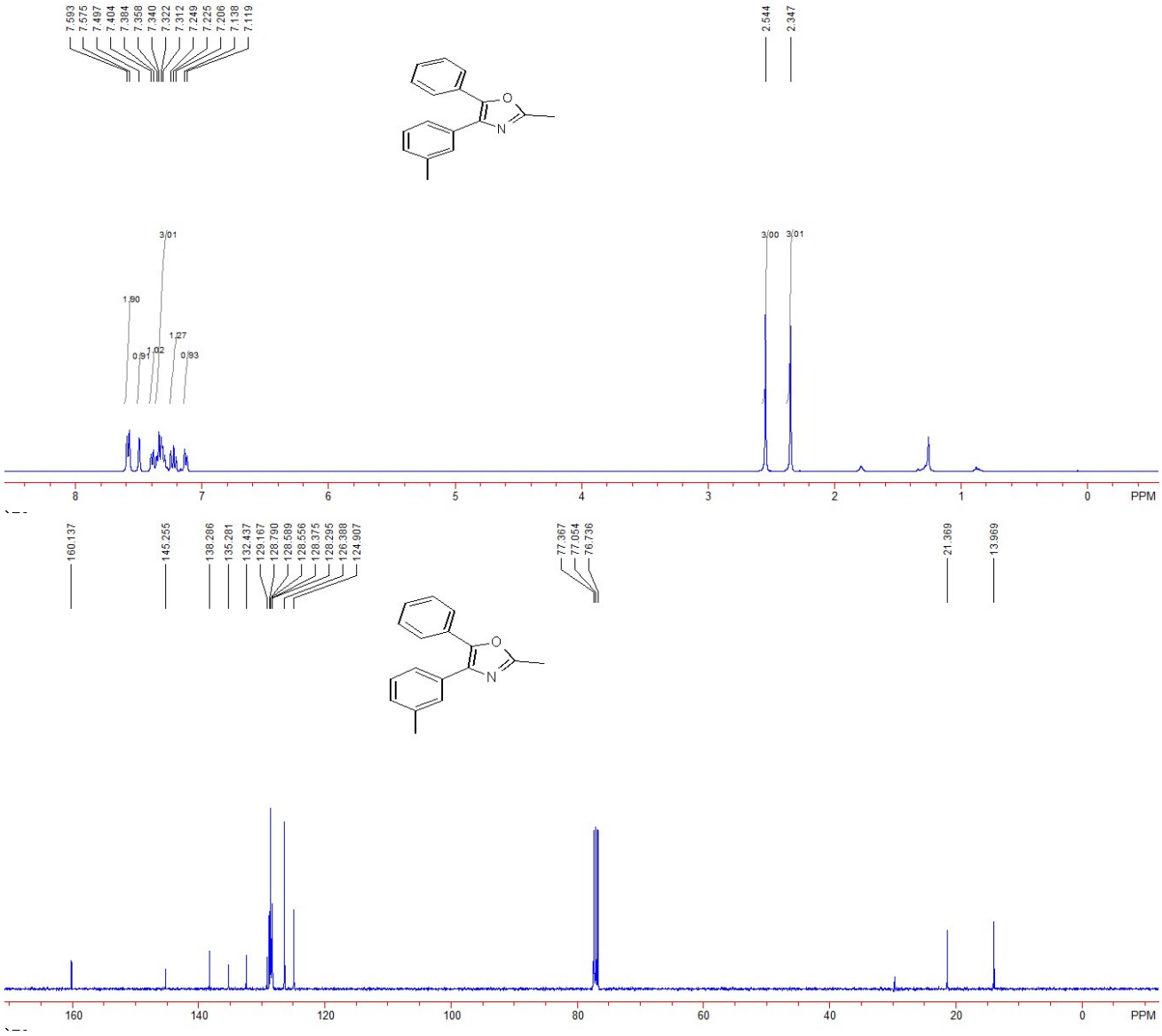


3ba 2-Methyl-5-phenyl-4-(*p*-tolyl)oxazole

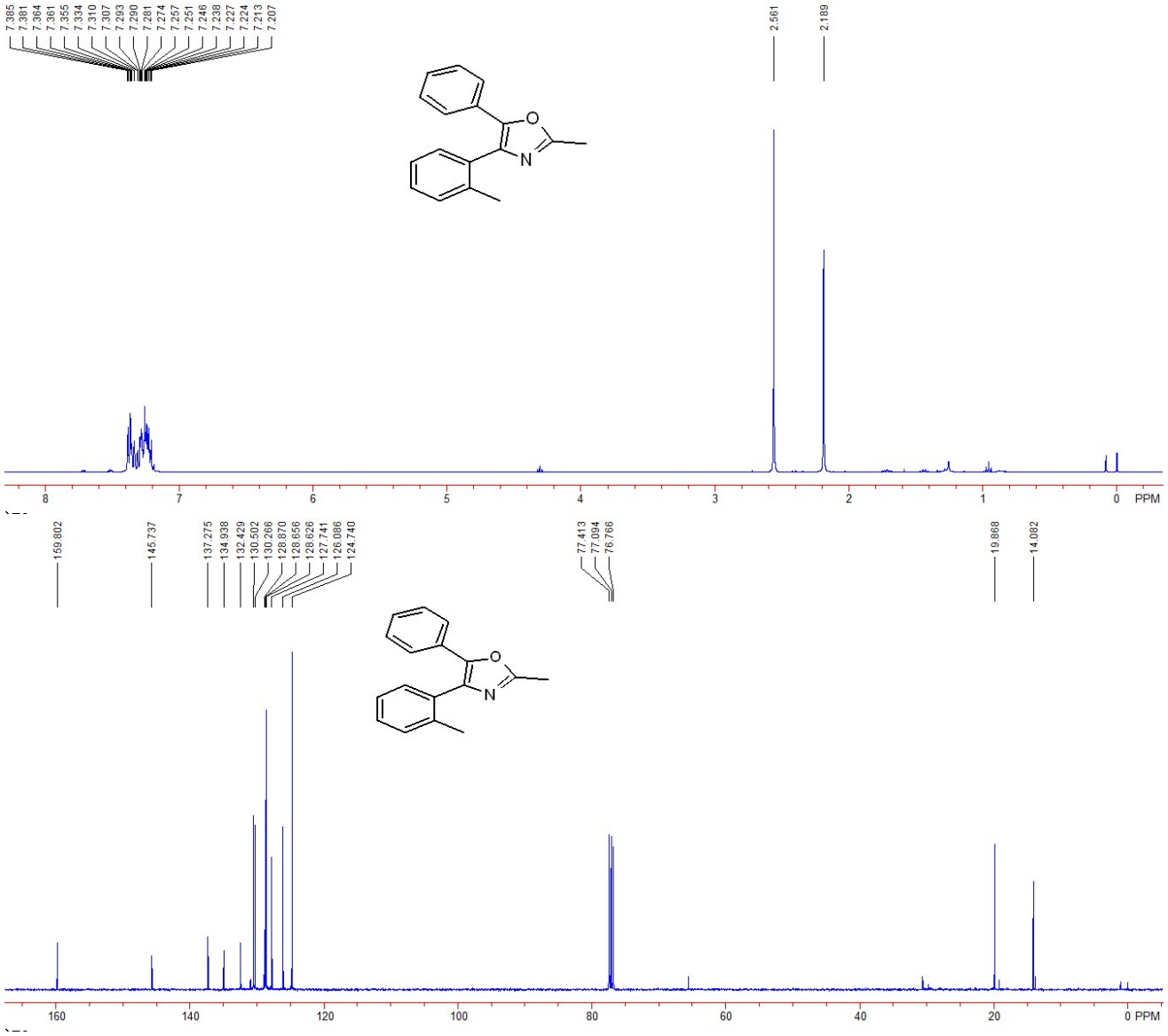




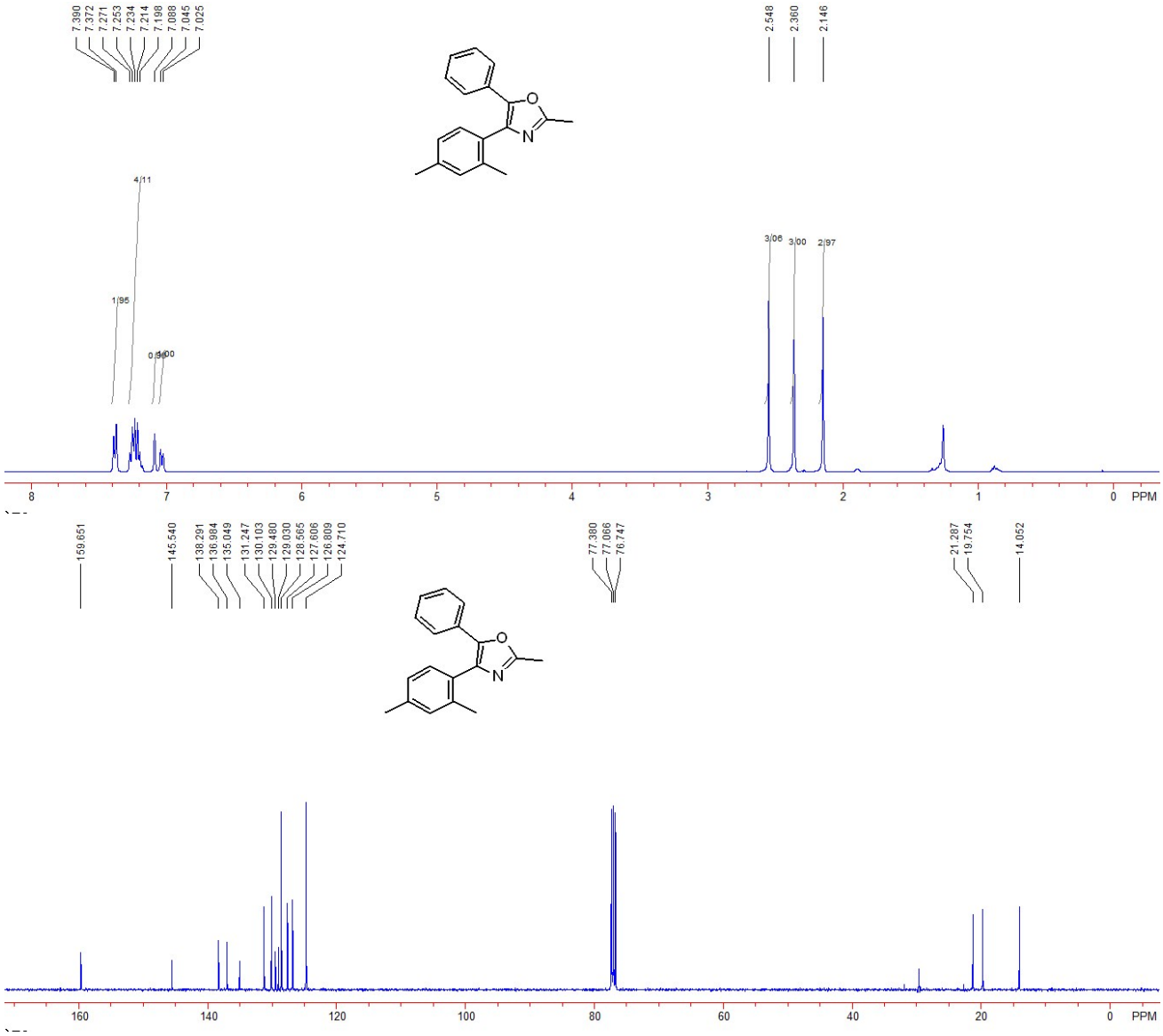
3ca 2-Methyl-5-phenyl-4-(*m*-tolyl)oxazole



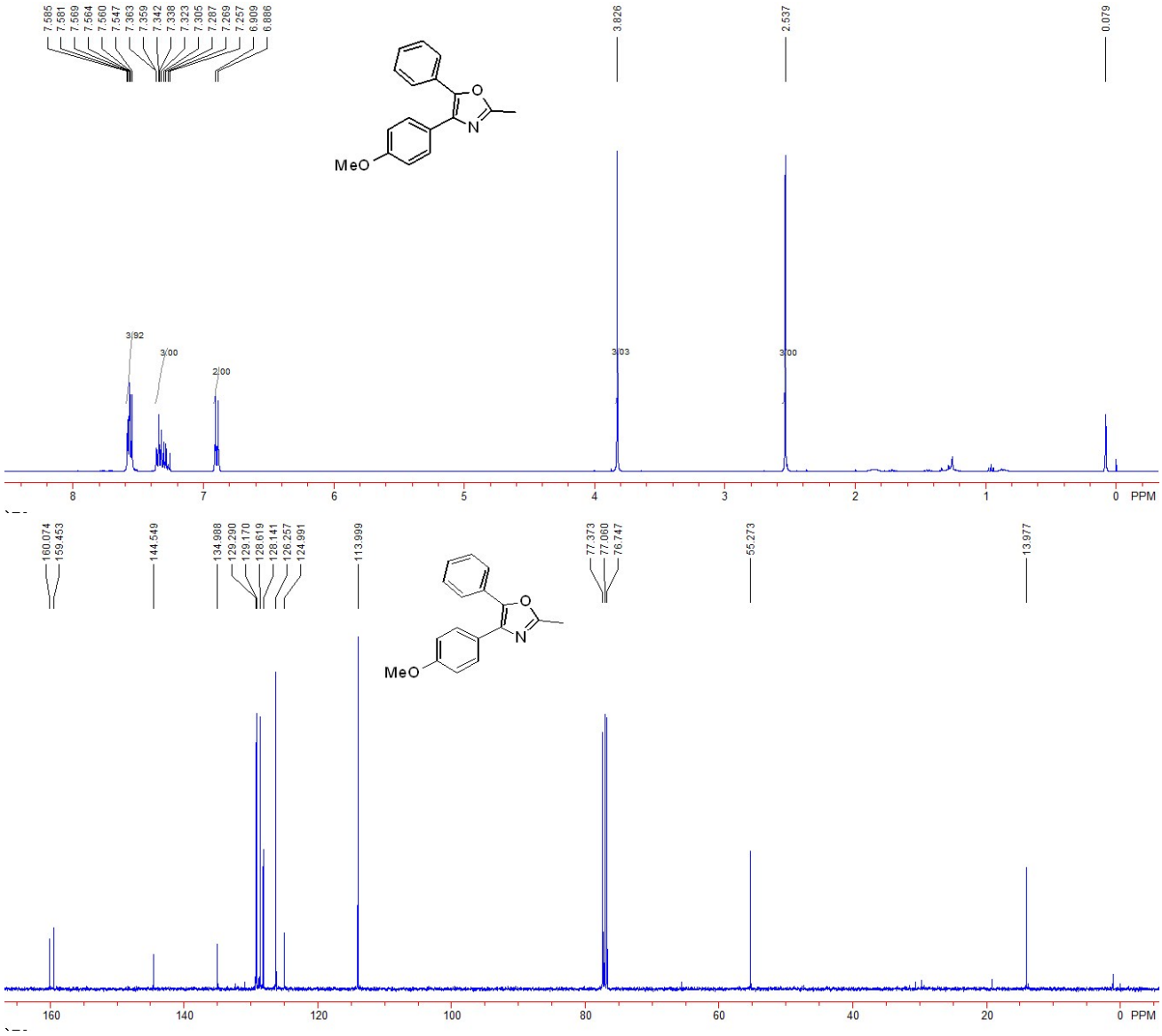
3da 2-Methyl-5-phenyl-4-(*o*-tolyl)oxazole



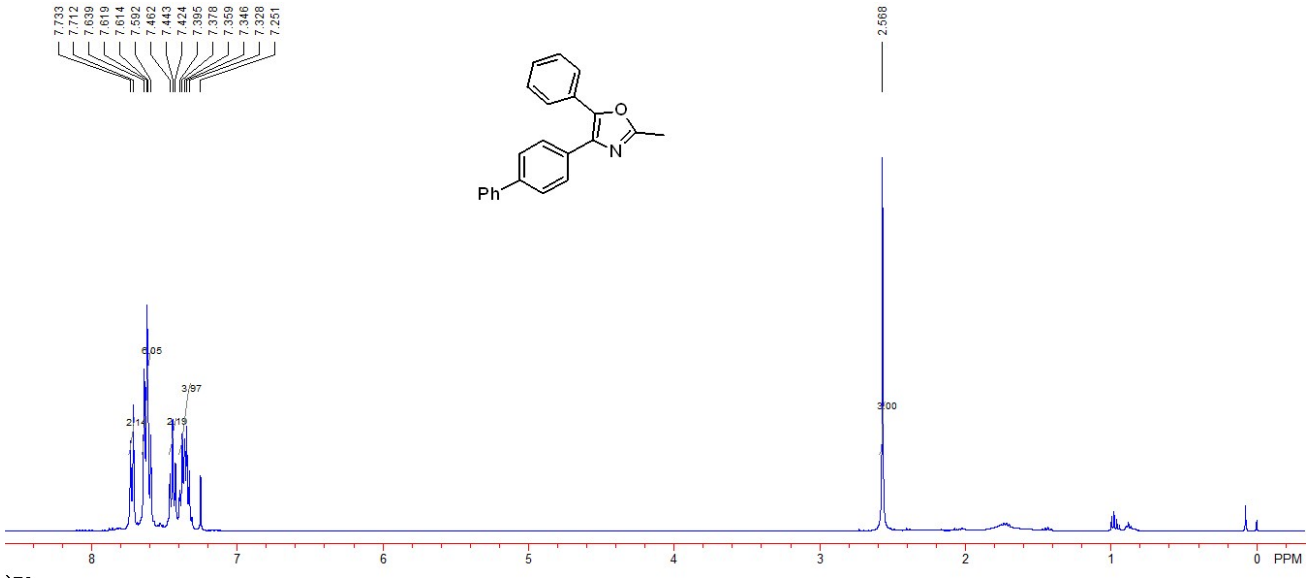
3ea 4-(2,4-Dimethylphenyl)-2-methyl-5-phenyloxazole

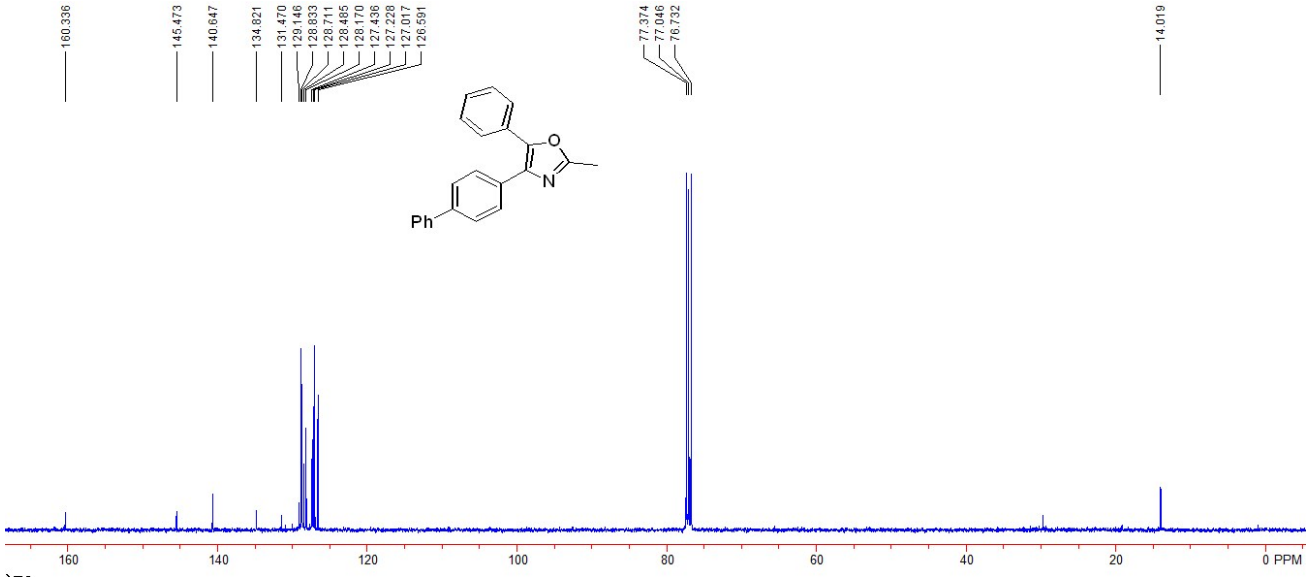


3fa 4-(4-Methoxyphenyl)-2-methyl-5-phenyloxazole

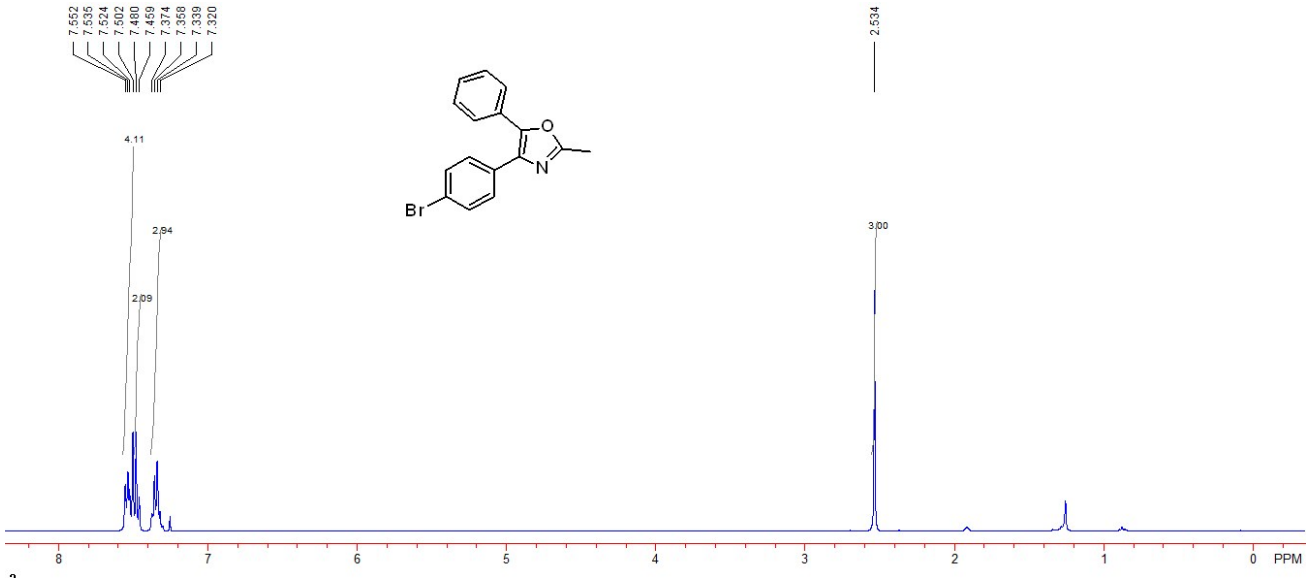


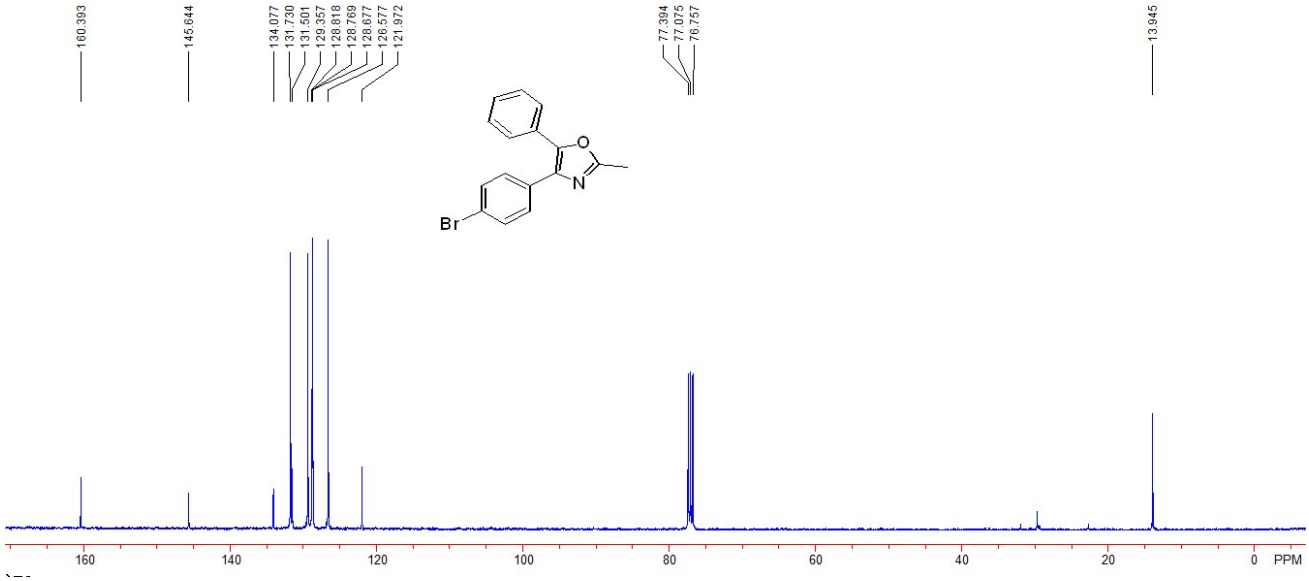
3ga 4-(Biphenyl-4-yl)-2-methyl-5-phenyloxazole



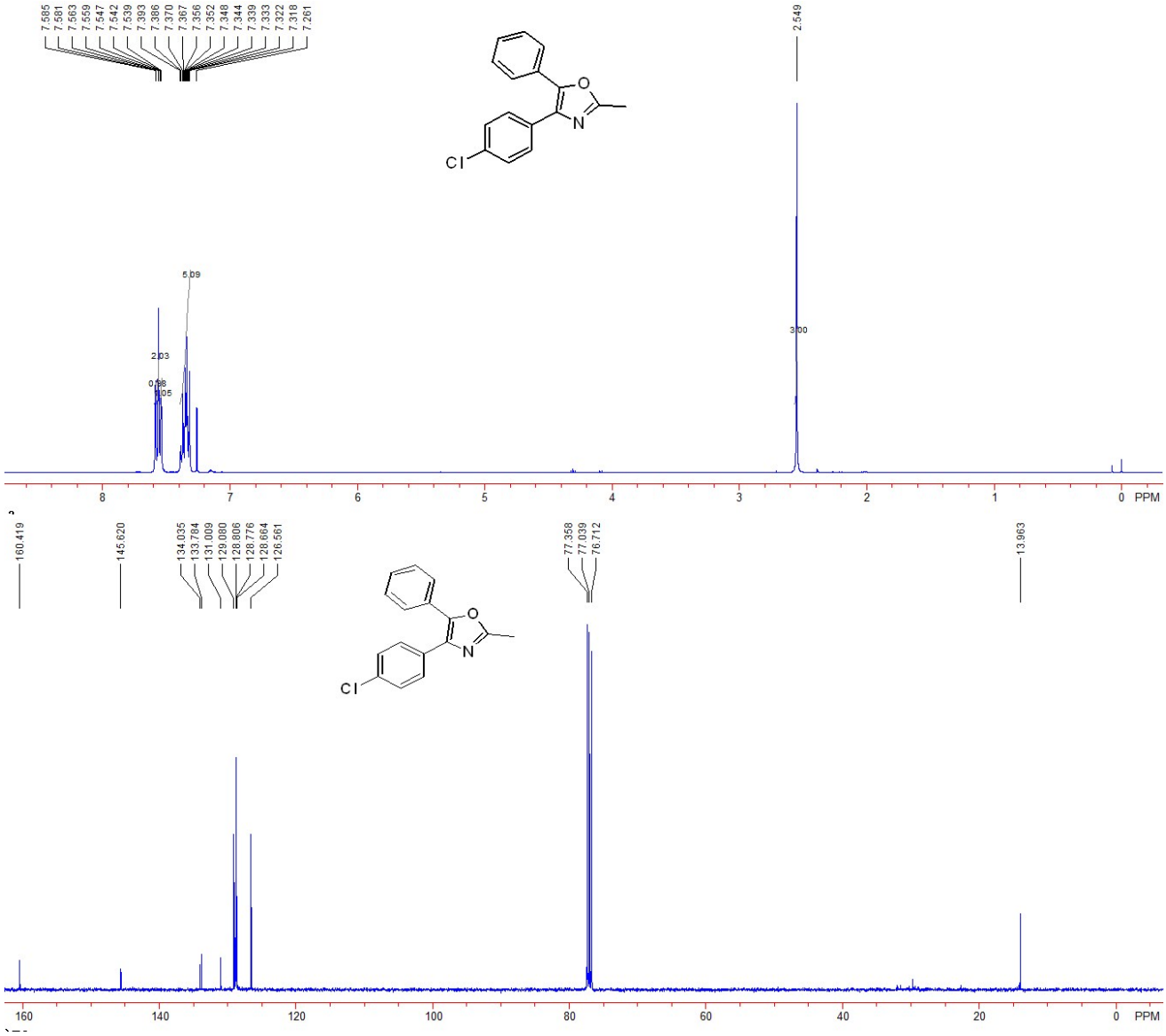


3ha 4-(4-Bromophenyl)-2-methyl-5-phenyloxazole

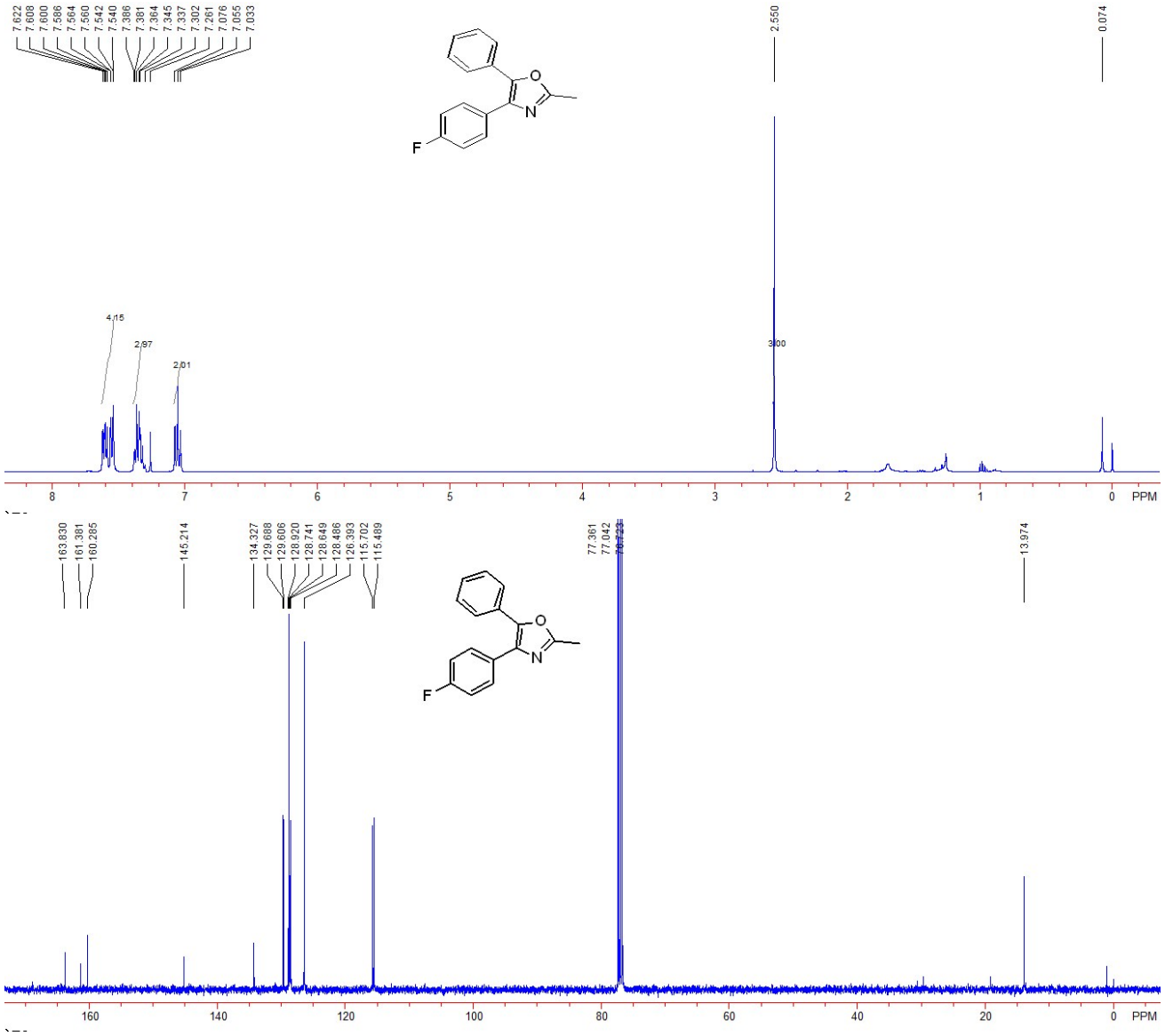




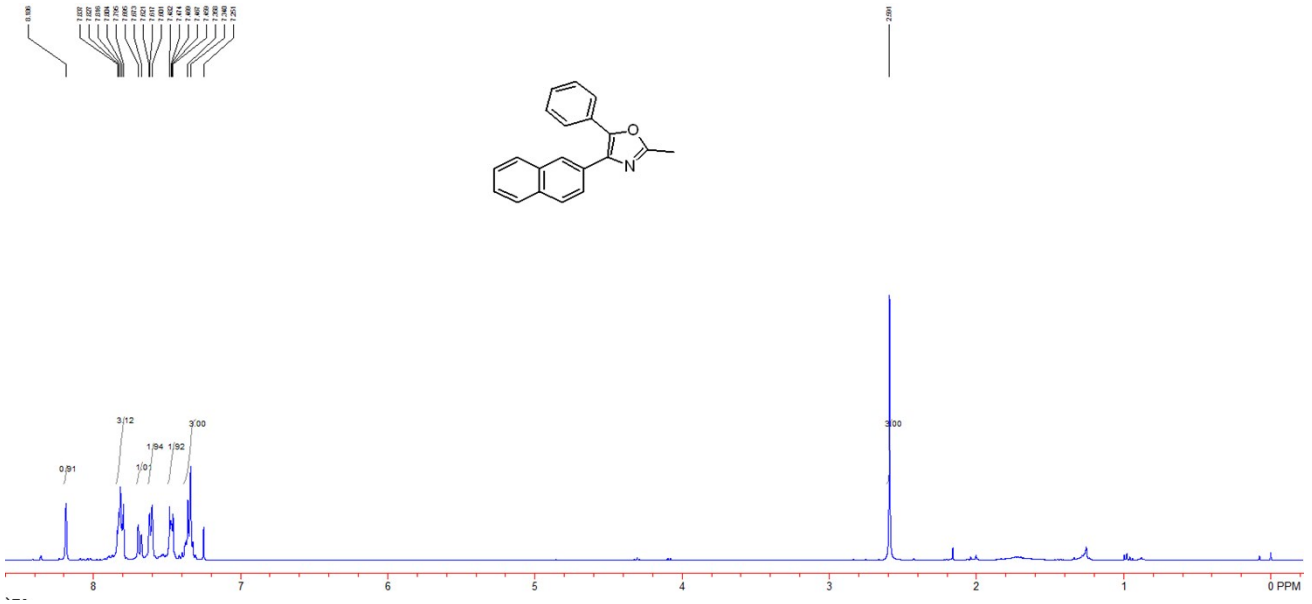
3ia 4-(4-Chlorophenyl)-2-methyl-5-phenyloxazole

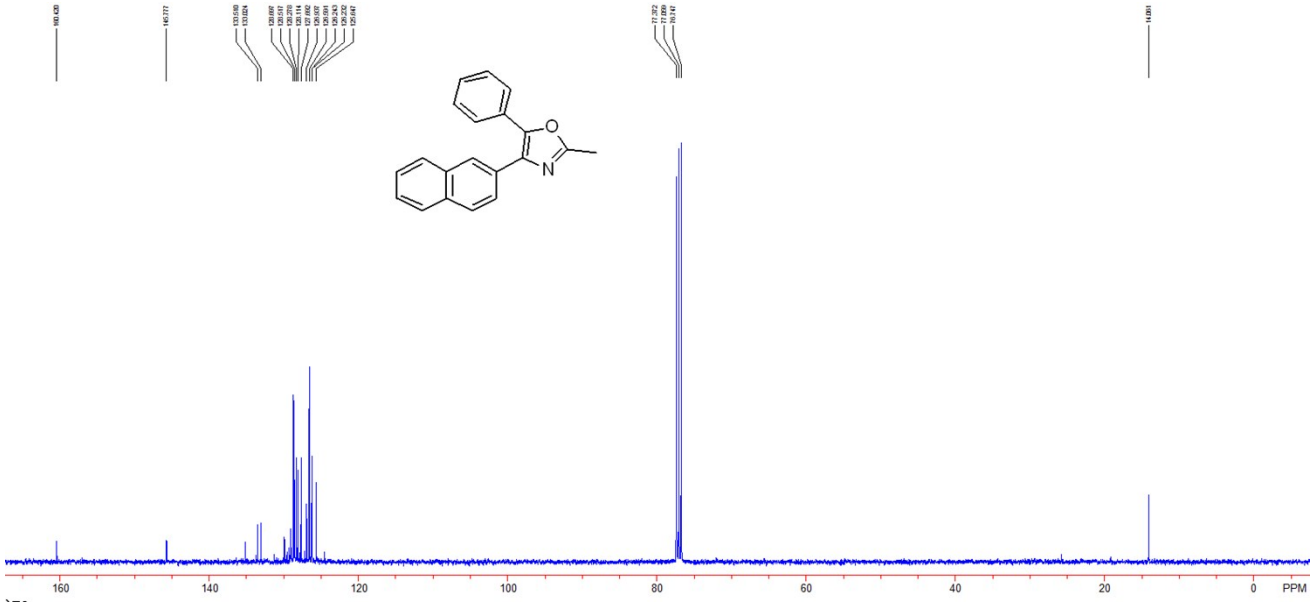


3ja 4-(4-Fluorophenyl)-2-methyl-5-phenyloxazole

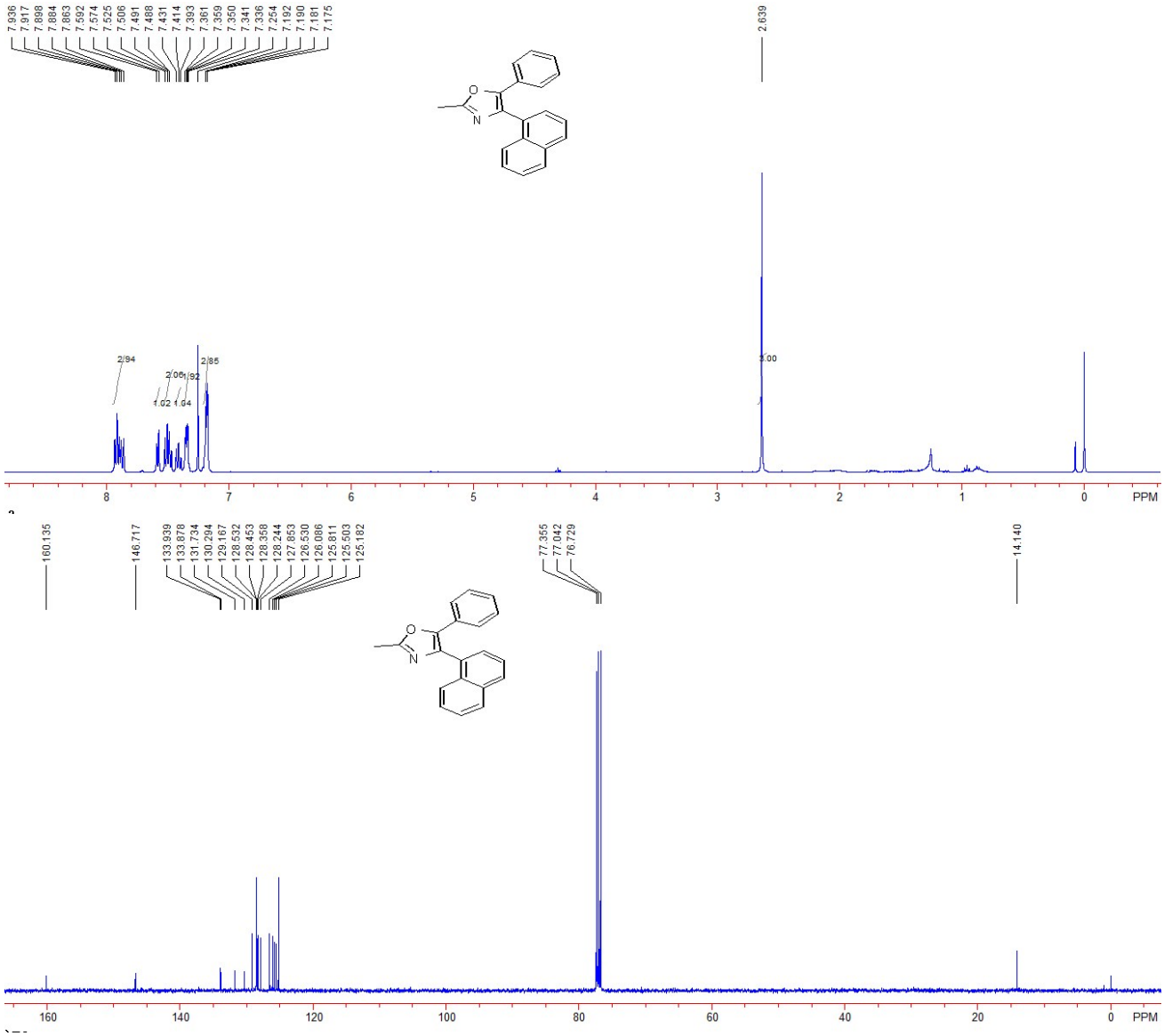


3ka 2-Methyl-4-(naphthalen-2-yl)-5-phenyloxazole

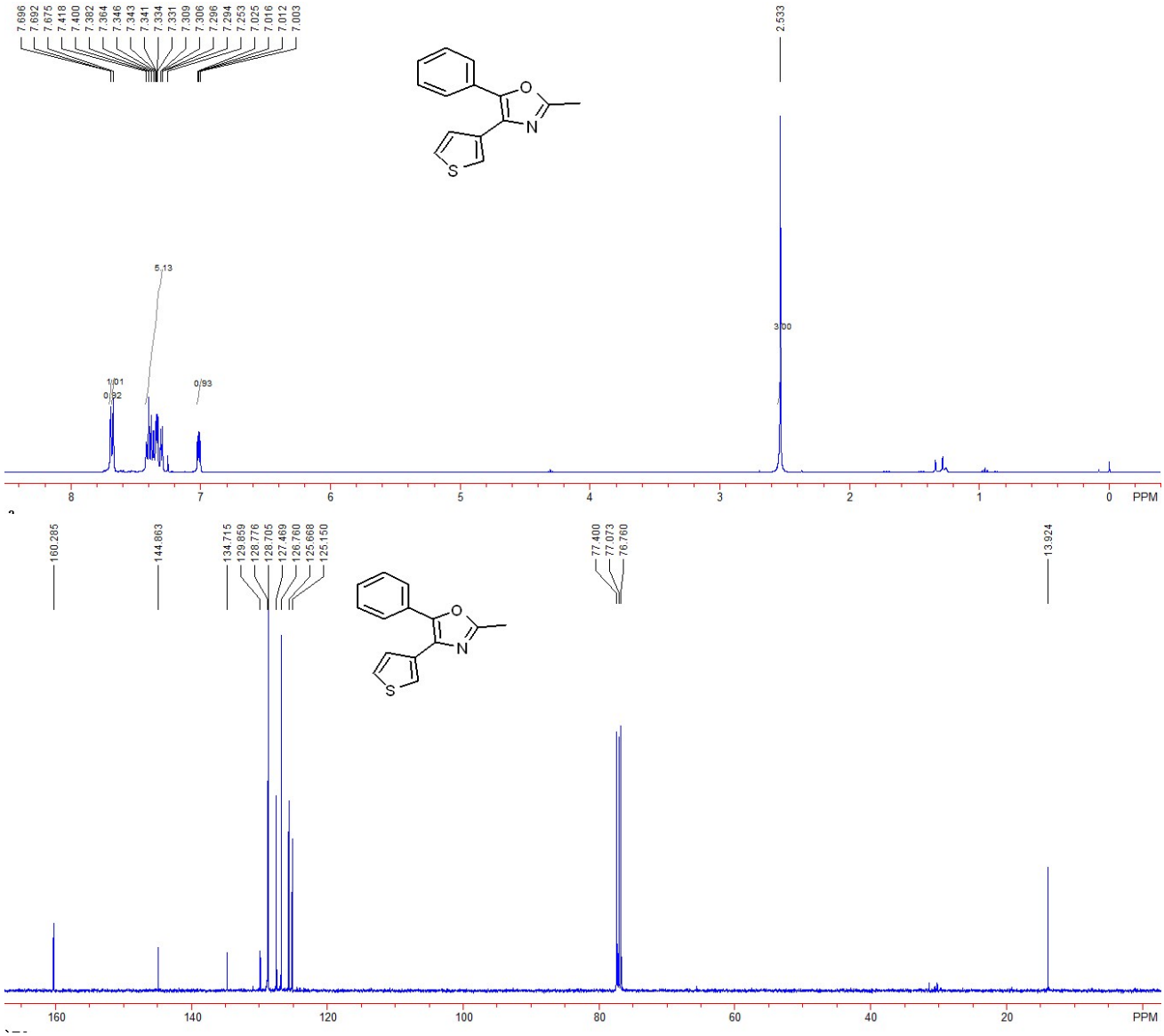




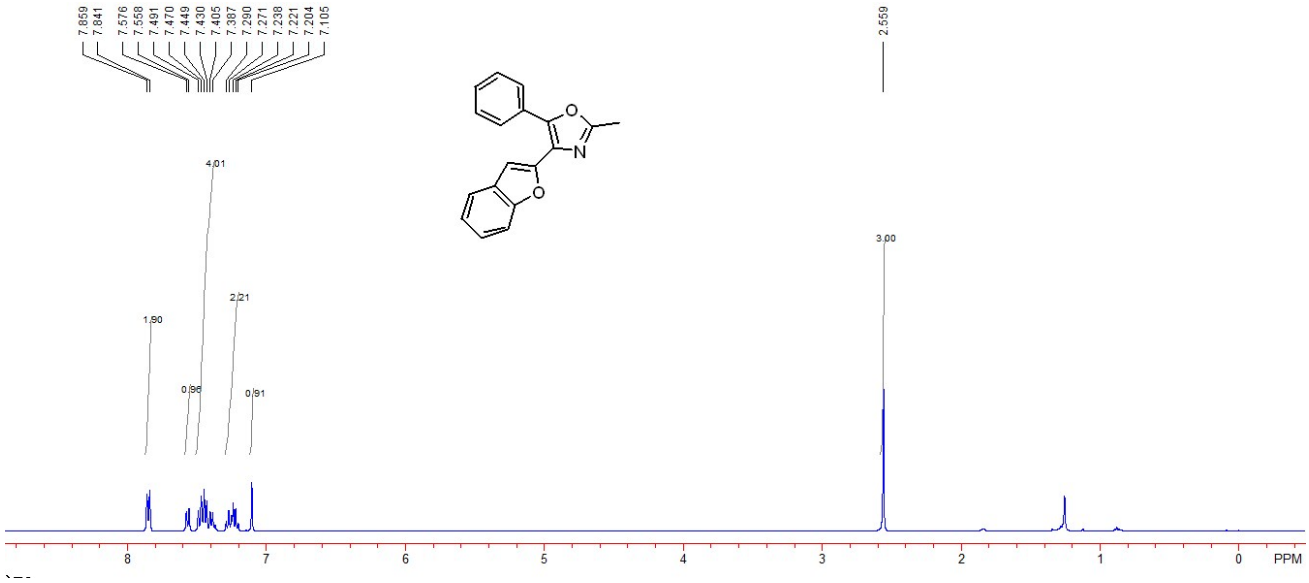
3la 2-Methyl-4-(naphthalen-1-yl)-5-phenyloxazole

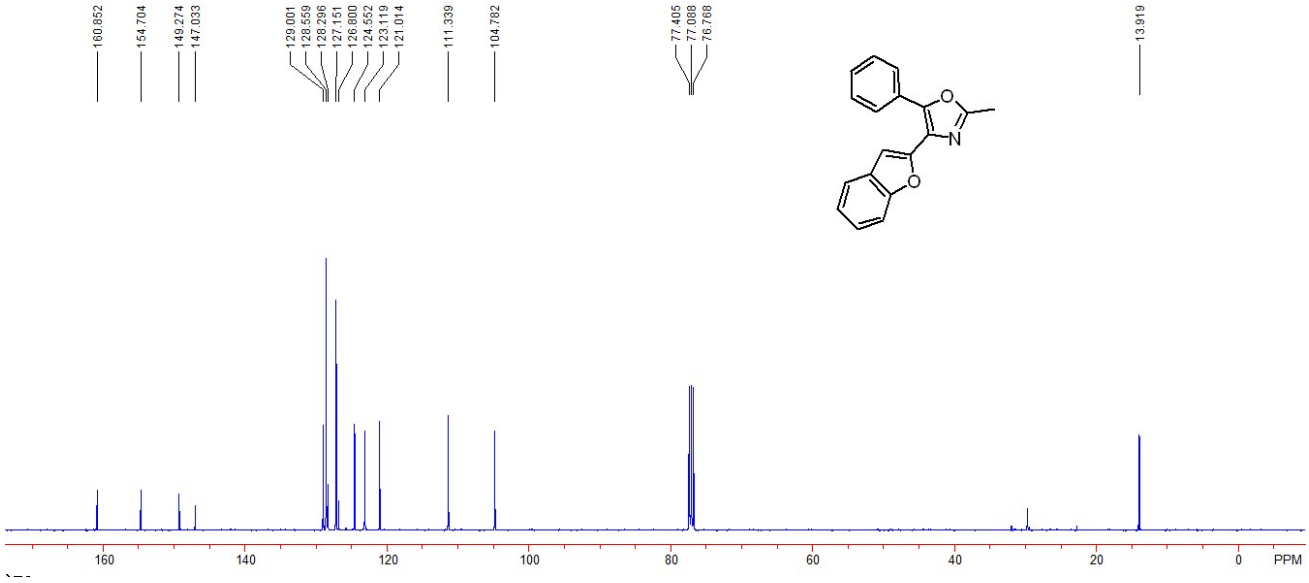


3ma 2-Methyl-5-phenyl-4-(thiophen-3-yl)oxazole

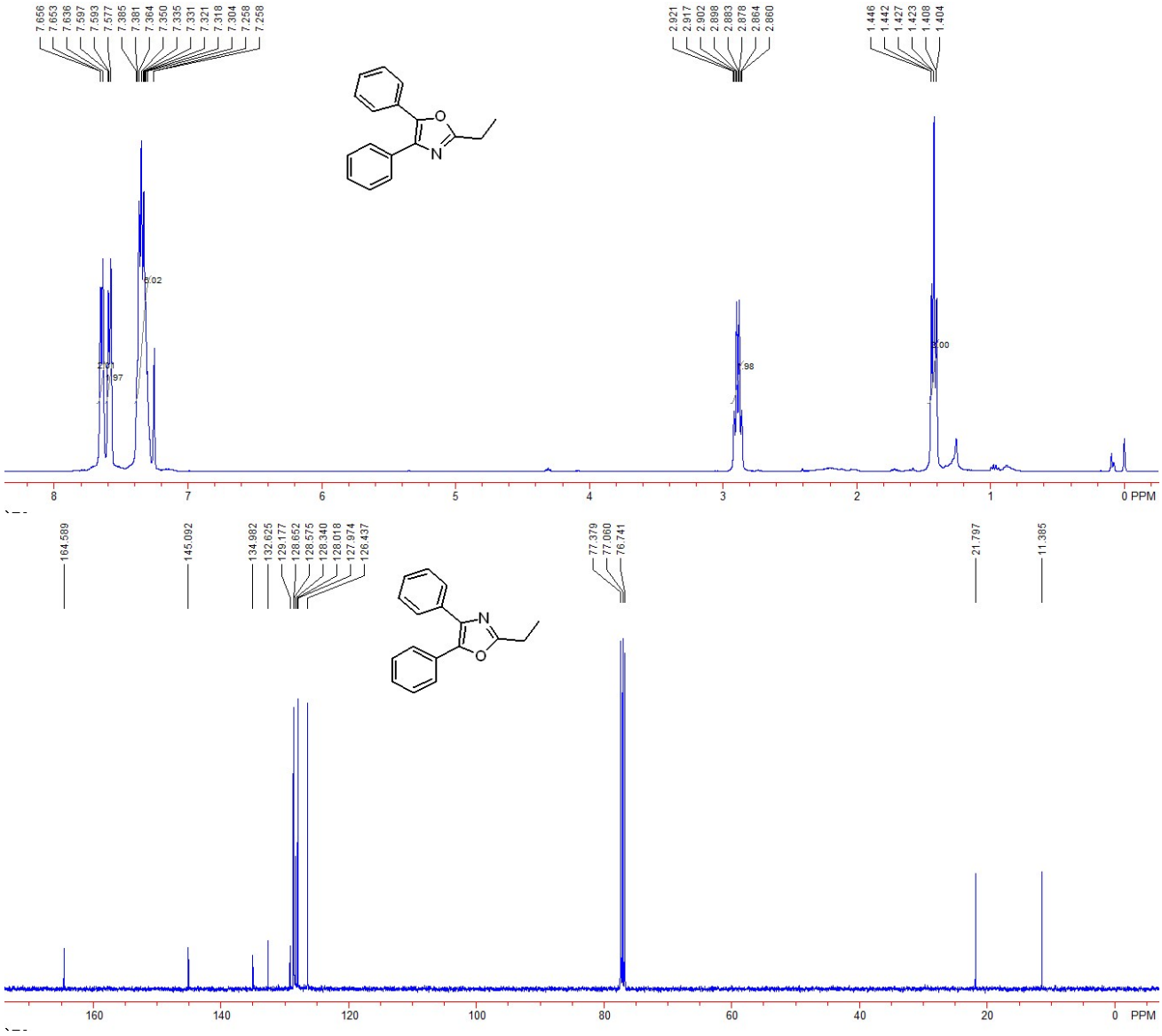


3na 4-(benzofuran-2-yl)-2-methyl-5-phenyloxazole

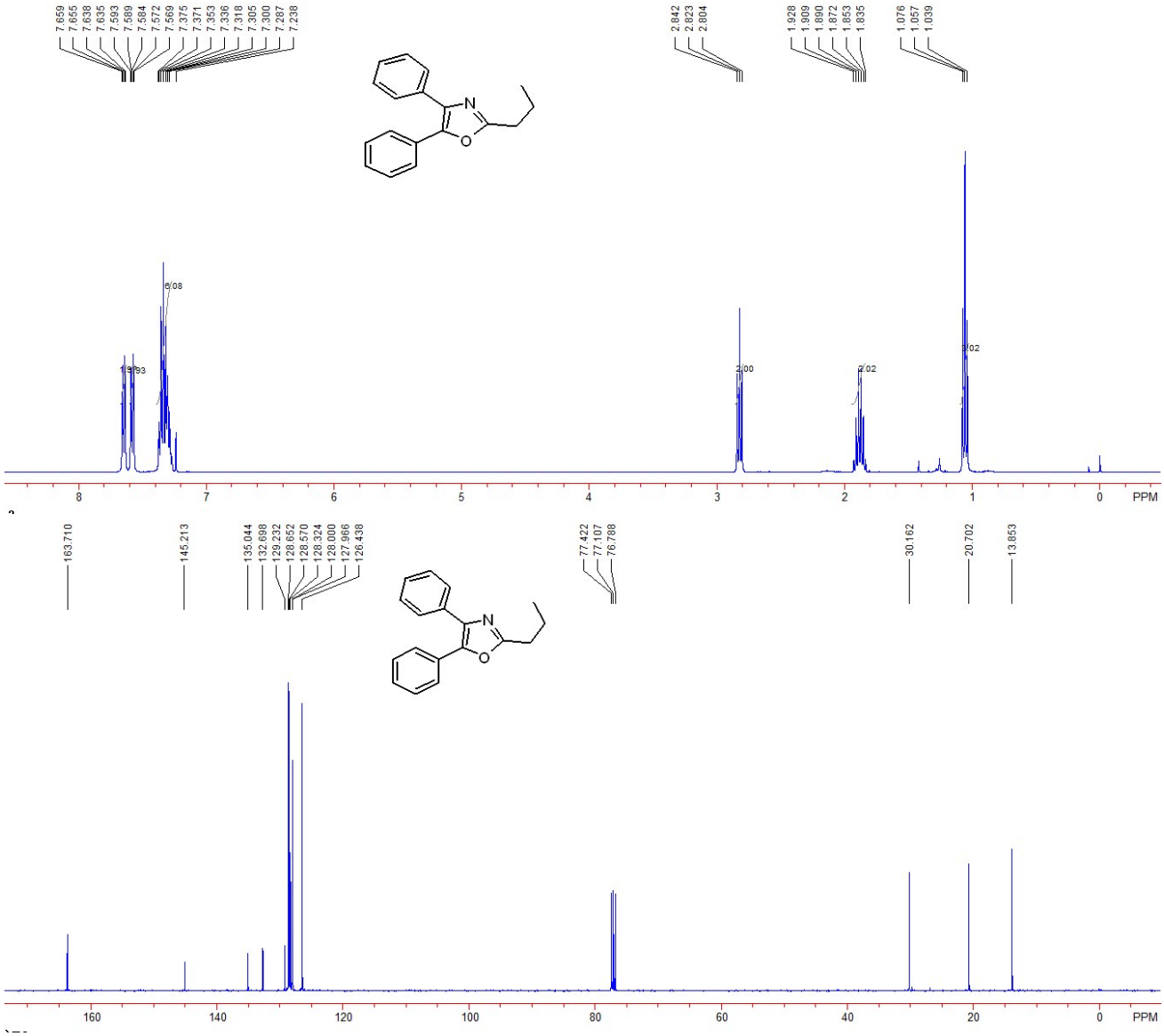




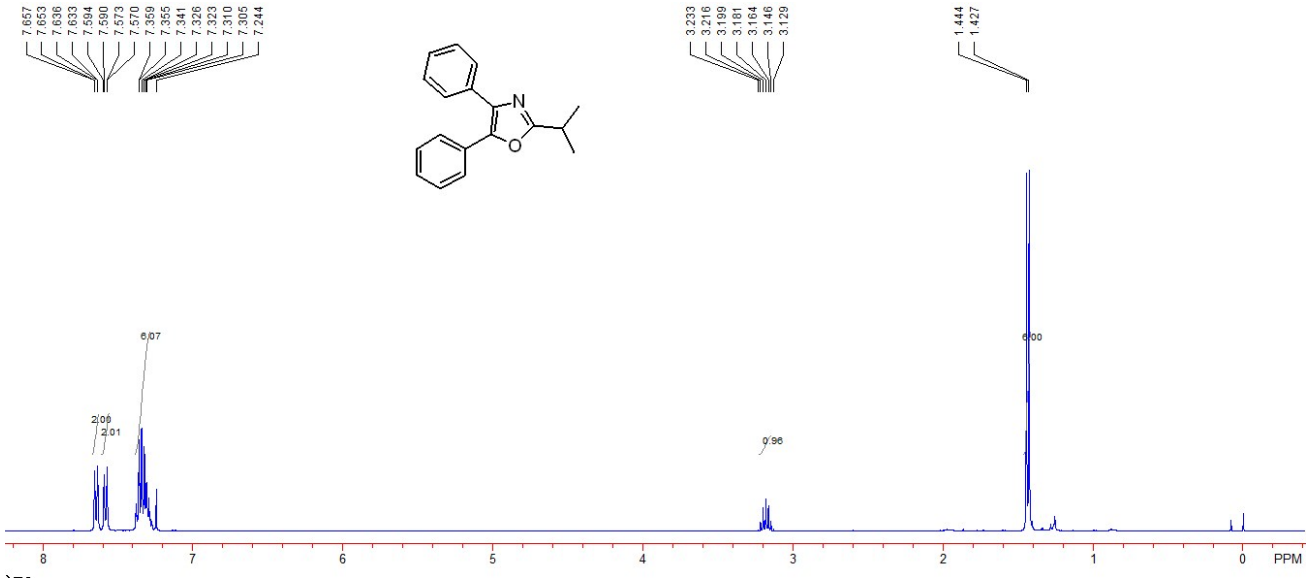
3oa 2-Ethyl-4,5-diphenyloxazole

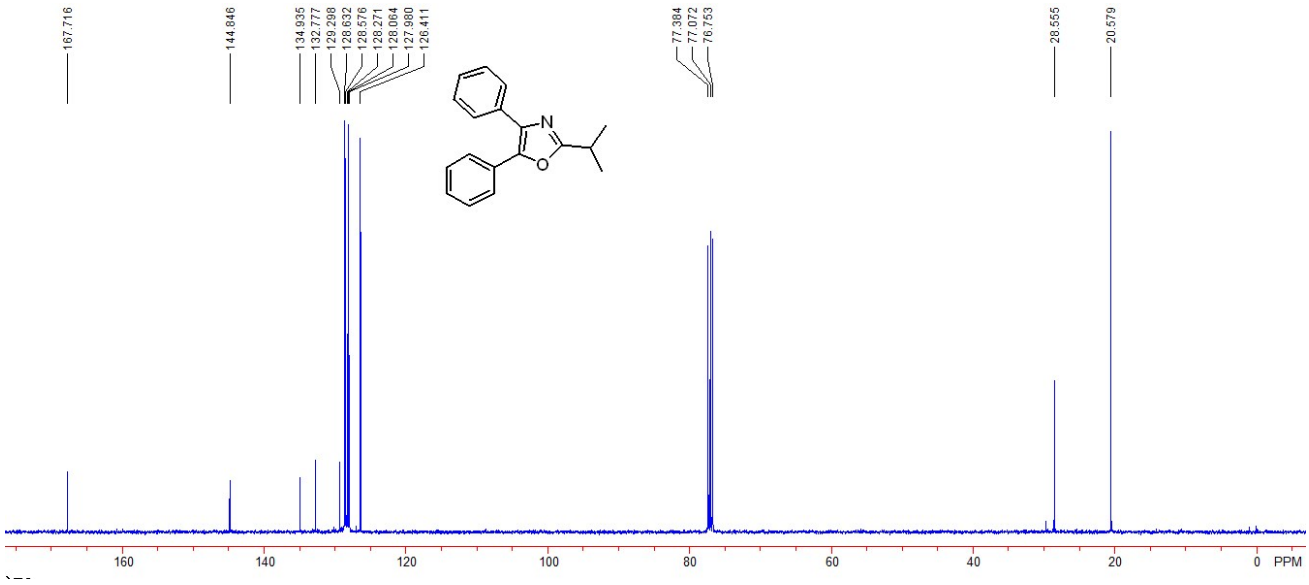


3pa 4,5-Diphenyl-2-propyloxazole

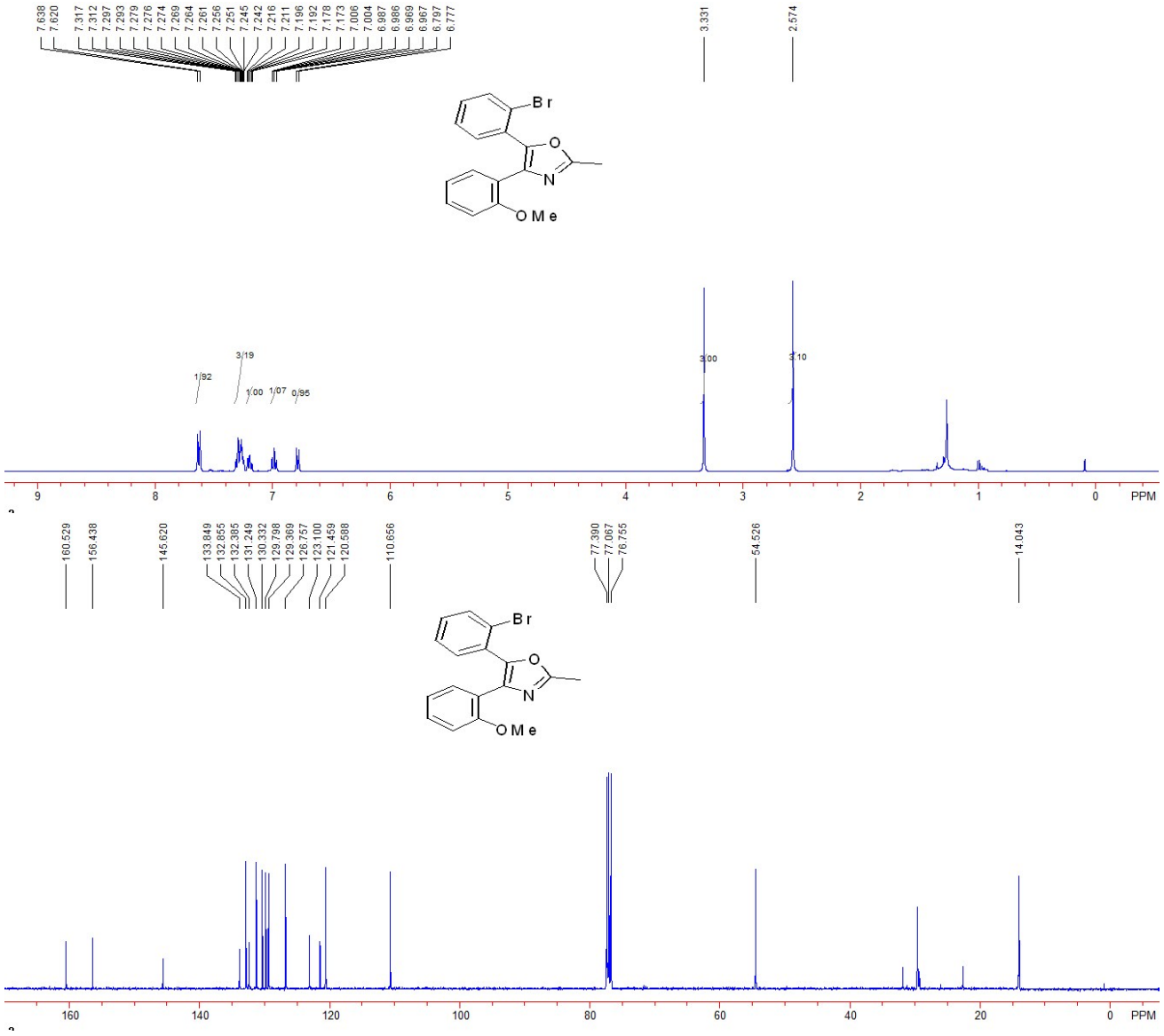


3qa 2-Isopropyl-4,5-diphenyloxazole

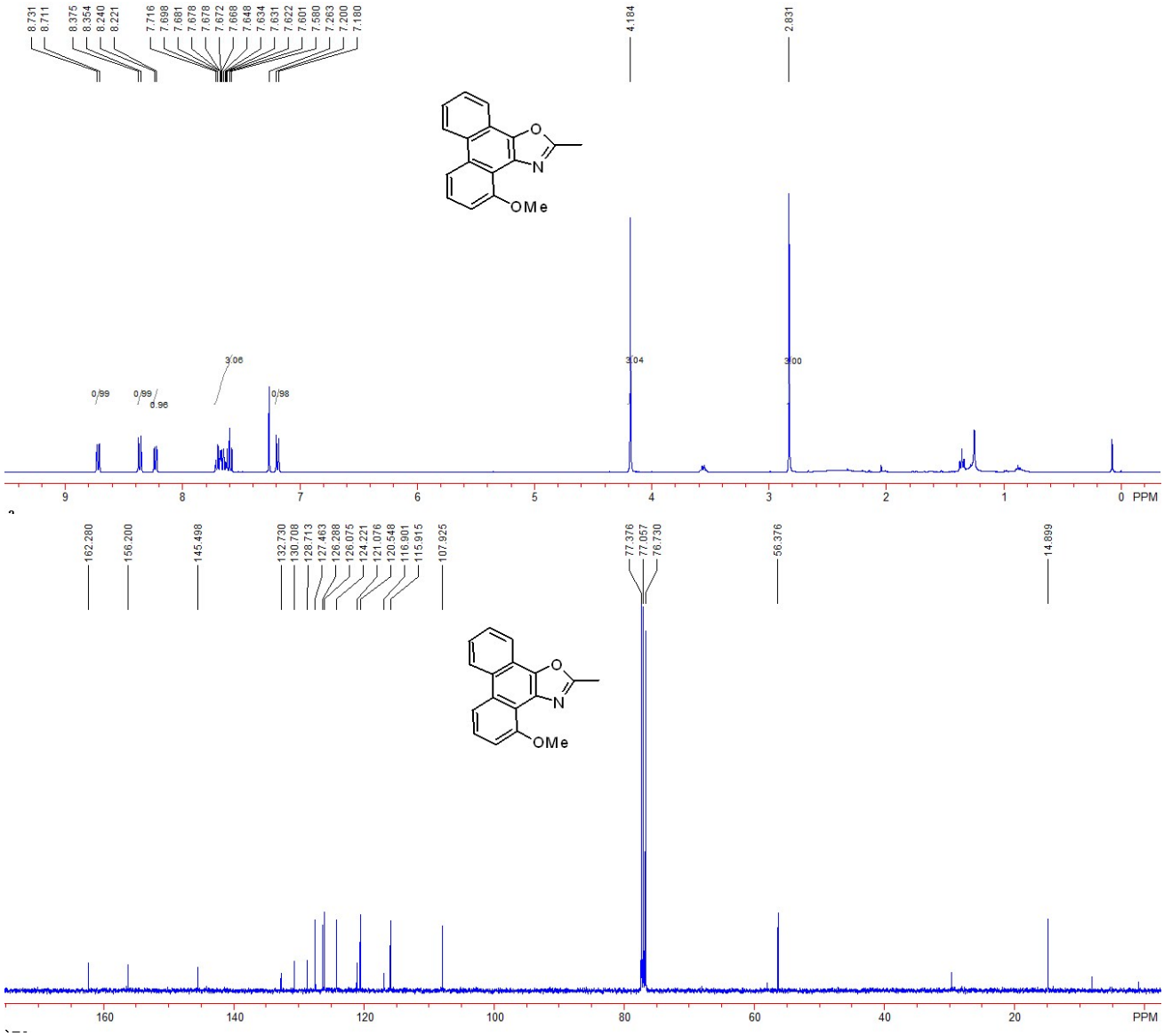




3ap 5-(2-Bromophenyl)-4-(2-methoxyphenyl)-2-methyloxazole



4a 4-Methoxy-2-methylphenanthro[9,10-*d*]oxazole



6a (*Z*)-*N*-(1,2-diphenylvinyl)acetamide