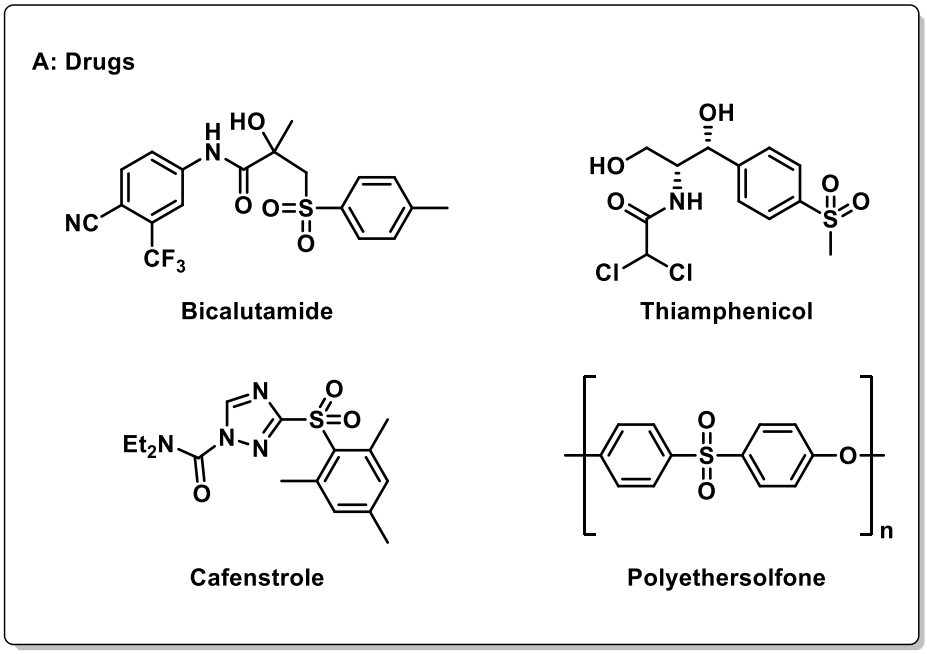
CHAPTER-5

Synthesis of α-arylsulfone propanamide from arylsulfinates with α-halohydroxamates under mild conditions

5.1 Introduction

Sulfones are an important class of organosulfur compounds used as precursors and intermediates in organic synthesis [1, 2]. Sulfones have been named “chemical chameleons” or “pluripotent” due to their versatile chemical properties and reactivity [3, 4]. Besides the synthetic applications, sulfones have found applications in different fields, including pharmaceuticals, agrochemicals, and functional materials [2, 5, 6]. Some of the biologically relevant sulfones are shown in (**Figure 5.1**), which include the anti-cancer drug bicalutamide, the antibiotic thiamphenicol, the herbicide cafestol, and polyethersulfone (PES), a high-performance polymer [5, 7] (**Figure 5.1A**).



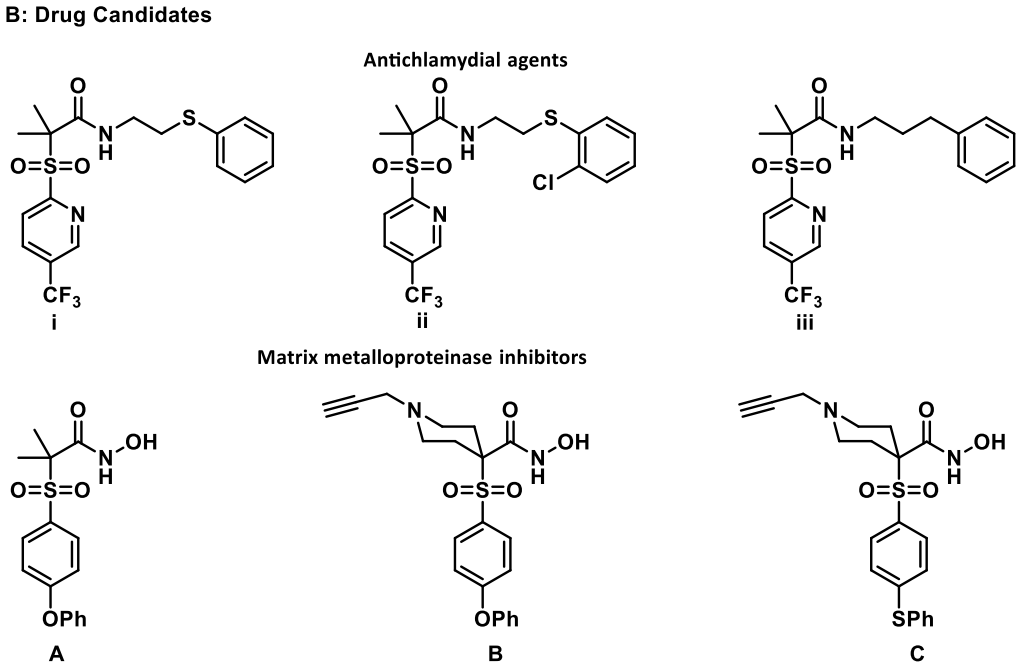
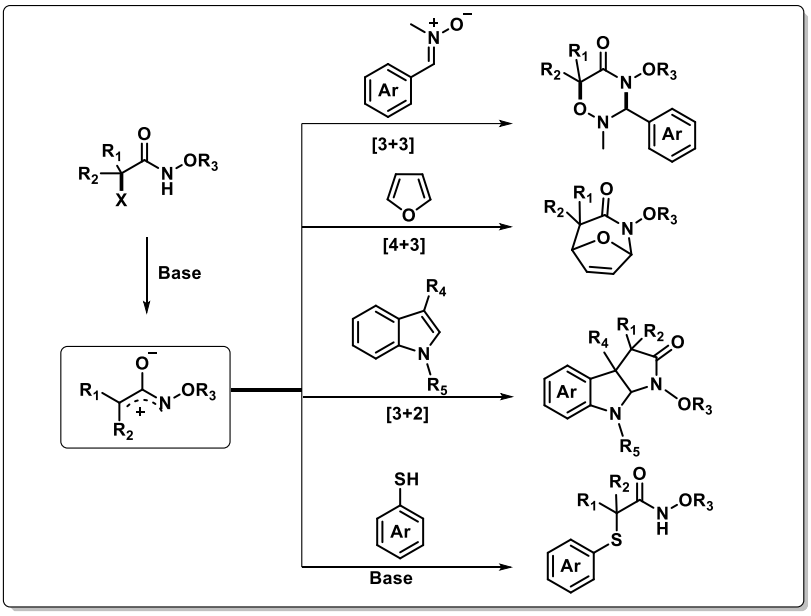


Figure 5.1 Biologically relevant sulfones.

Due to their high importance, considerable attention has been given to developing methods for synthesizing sulfones. Sulfones are typically synthesized from sulfides via oxidation reactions using various oxidants including peroxides [8]. Alternatively, Friedel-Crafts-type reactions with sulfonyl chlorides have been used for the construction of aryl sulfones [9]. Besides these traditional methods, i) the reaction of sulfinic acid salts with carbon electrophiles [10], ii) the addition of sulfonyl radicals to alkenes or alkynes [10], iii) fixation of sulfur dioxide, etc., provides aryl, alkyl, and aryl-alkyl mixed sulfones [11]. Among these methods, the synthesis of sulfones using sulfinic acid salts with different electrophilic

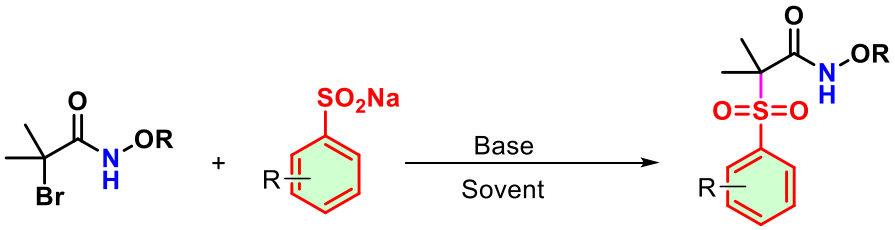
carbons received considerable attention in organic chemistry [12-14]. This approach provides high yields and selectivity over other methods.

α-Halohydroxamates are important precursors in organic synthesis [15-18]. The treatment of α-halohydroxamates with base in fluorinated solvents provides azaoxyallyl cations, a transient reactive species, which is used as intermediates for the [3+2]-Cycloaddition reactions [19-21]. These reactions provide a wide variety of biologically relevant nitrogen-containing heterocycles. Further, the insertion of different nucleophiles with azaoxyallyl cations provides sterically hindered amines, sulfides, ethers, etc, under different reaction conditions [22-26] (**Scheme 5.1**).



Scheme 5.1. Applications of α-halohydroxamates

In this context, the synthesis of sulfones from α-halohydroxamates and sulfinic acid salts has not been investigated. Nevertheless, developing such methods may provide quick access to sterically hindered sulfones in good yields under mild reactions. It is worth noting that such sterically hindered sulfones found applications as antichlamydial agents and Matrix metalloproteinase inhibitors [27, 28] (**Figure 5.1 B**). In this regard, we investigated the synthesis of sulfones from α-halohydroxamates and sodium sulfinate (**Scheme 5.2**).

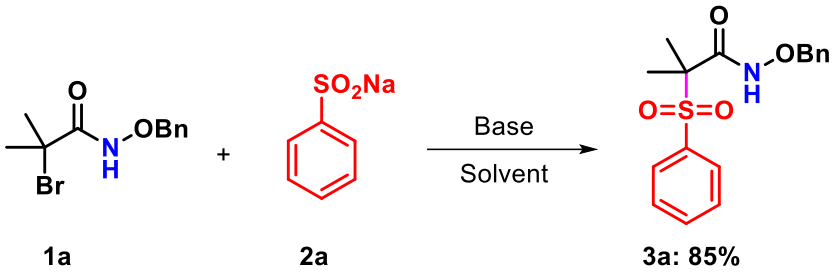


Scheme 5.2. Synthesis of sulfones from α-halohydroxamates

5.2 Results and Discussion

At the outset, the α-halo hydroxamate **1a** and sodium benzenesulfinate **2a** were chosen as the model substrates for the optimization study. The reaction was performed in different solvents at room temperature in the presence of different bases. Conventional solvents like DMF, DMSO, and acetonitrile failed to provide the desired sulfone **3a** after 24h using sodium carbonate as the base. Further, the optimization was investigated using fluorinated solvents like trifluorotoluene (TFT), hexafluoroisopropanol (HFIP), and 2,2,2-trifluoroethanol (TFE).

Table 5.1. Optimization table



1a **2a** **3a: 85%**

Entry	Solvent	Base	Time (h)	Yield (%)[b]
1	DMF	Na_2CO_3	24	NA
2	DMSO	Na_2CO_3	24	NA
3	CH_3CN	Na_2CO_3	24	NA
4	$PhCF_3$	Na_2CO_3	1	58
5	$PhCF_3$	Cs_2CO_3	1	45
6	$PhCF_3$	NaOAc	1	12
7	TFE	Na_2CO_3	1	65
8	**HFIP**	**Na_2CO_3**	**1**	**85**
9	HFIP	NaOAc	1	66
10	HFIP	Cs_2CO_3	1	78
11	HFIP	K_2CO_3	1	73
12	HFIP	*t*-BuOK	1	68
13	HFIP	Et_3N	1	80
14	HFIP	DBU	1	81
15	HFIP	DIEA	1	78

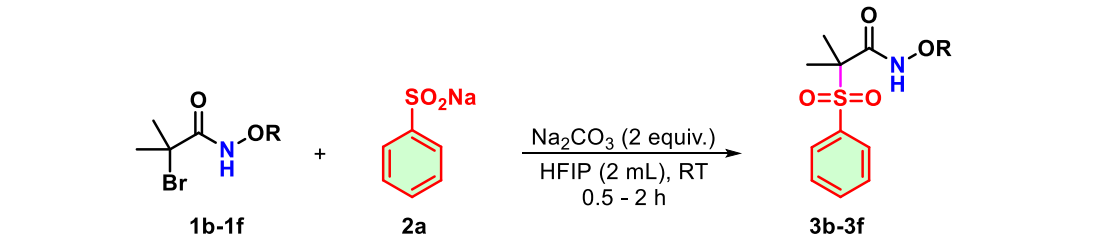
[a]**Reaction conditions:** substrate **1a** (100 mg, 0.36 mmol), **2a** (0.44 mmol) and sodium carbonate (0.73 mmol) were stirred in appropriate solvents (2 mL) for 0.5 h to 2 h at room temperature.
[b]Isolated yields.

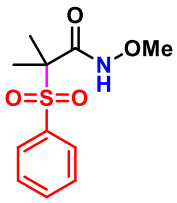
To our delight, the reaction in trifluorotoluene in the presence of sodium carbonate (Na_2CO_3) gave the desired product in 58% yield in one hour. However, low yields were observed with Cs_2CO_3 and NaOAc bases. Later, the reaction was investigated using 2,2,2-trifluoroethanol as a solvent in the presence of Na_2CO_3. This reaction gave the desired product in 3a in 65%

yield in 1 h. On the other hand, the reaction in HFIP in the presence of Na_2CO_3 gave the desired product **3a** in 85% yield in one hour. Later, the reaction condition was optimized using different organic and inorganic bases. However, Na_2CO_3 was found to be the best among all in terms of reaction yields. Overall, the optimization study reveals that a combination of HFIP-Na_2CO_3 would be suitable for the preparation of sterically hindered sulfones in good yields.

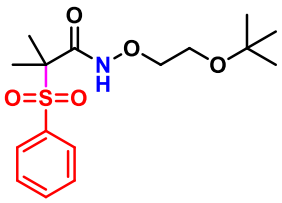
After the establishment of optimized conditions, the substrate scope was investigated using different aryl sulfonates and α-halo hydroxamates. Initially, α-halo hydroxamates bearing various hydroxylamine moieties were investigated for sulfone synthesis using sodium benzenesulfinate in HFIP solvent in the presence of sodium carbonate. N-methoxy, ethoxy, and benzyl protected α-halo hydroxamates were successfully coupled with sodium benzenesulfinate in good to excellent yields within 1-2 hours. Acid-sensitive tert-butyl group and electron donating and withdrawing groups functionalized benzyl groups on α-halo hydroxamates gave the products similar yields, indicating the versatile nature of the developed methodology.

Table 5.2: Substrate scope- α-halo hydroxamates.[a,b]

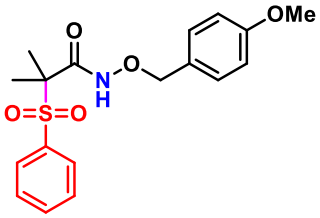




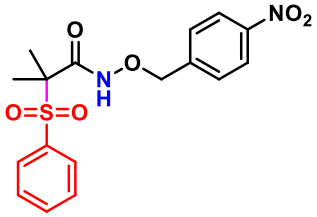
3b, 60%



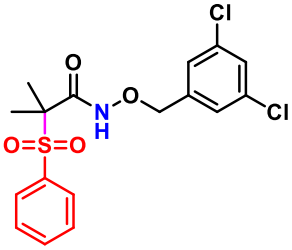
3c, 65%



3d, 64%



3e, 60%



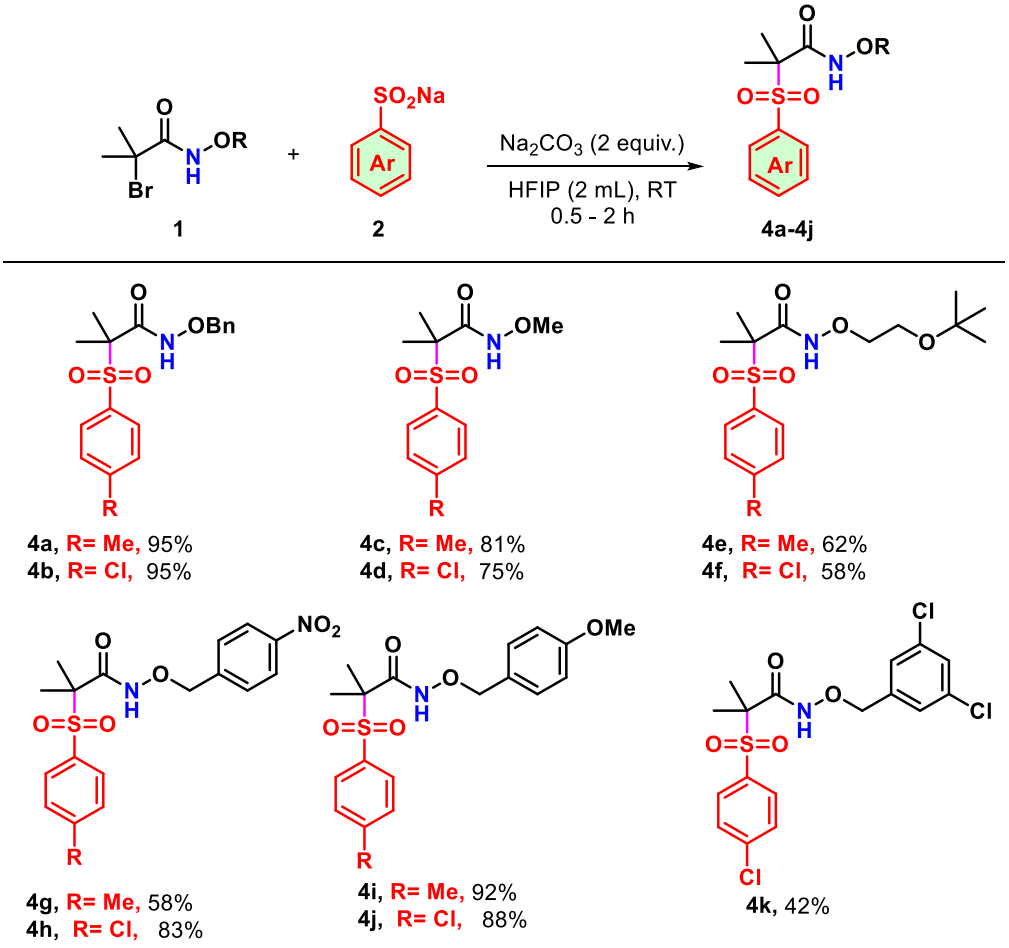
3f, 63%

[a]**Reaction condition:** substrate **1a** (100 mg, 0.36 mmol), **2a** (0.44 mmol) and sodium carbonate (0.73 mmol) were stirred in appropriate solvents (2 mL) for 0.5 h to 2 h at room temperature. [b]Isolated yields.

After investigating the scope of various α-halo hydroxamates, we studied the reactivity of various arylsulfinate salts in the preparation of aryl sulfones. Initially, the reaction of methyl and chloro-substituted sodium arylsulfinate salts with N-methoxy and N-benzyloxy functionalized α-bromo hydroxamates was attempted. To our delight, these reactions gave the desired products in good to excellent yields in a short span of time. Further, different N-

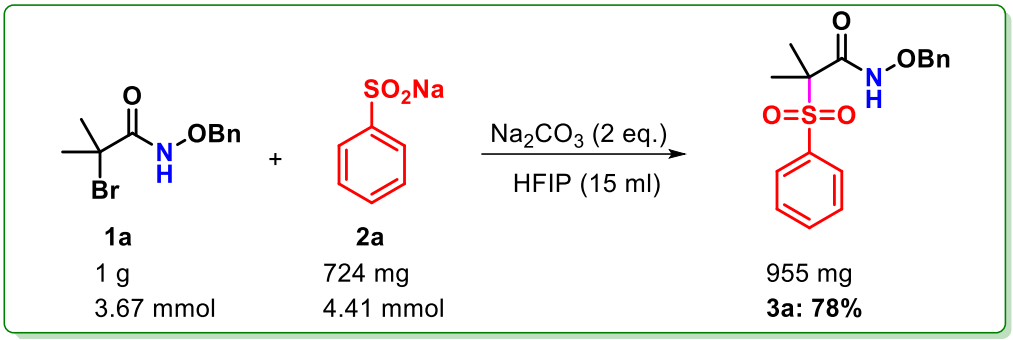
benzyloxy functionalized α-bromo hydroxamates were successfully coupled with methyl and chloro-substituted sodium arylsulfinate salts under optimized conditions.

Table 5.3: Substrate scope α-halo hydroxamates and arylsulfinate salts



[a]**Reaction conditions:** substrate **1a** (100 mg, 0.36 mmol), **2** (0.44 mmol) and sodium carbonate (0.73 mmol) were stirred in appropriate solvents (2 mL) for 0.5 h to 2 h at room temperature. [b]Isolated yields.

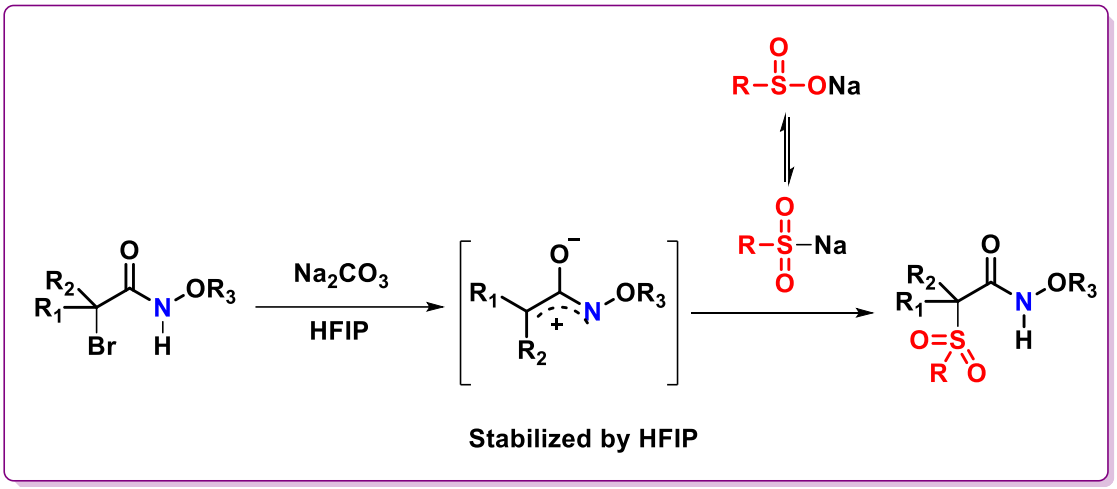
After the investigation of substrate scope, we attempted the gram scale reaction with model substrates. This reaction gave the desired product in 78% yield, indicating the suitability of the method for scale-up reactions (**Scheme 5.3**).



Scheme 5.3 Gram-scale synthesis.

5.3 Plausible Reaction Mechanism

The proposed mechanism of the reaction is shown in [15, 16] (**Scheme 5.4**). The α-bromo hydroxamates undergo HBr elimination in the presence of sodium carbonate due to the strong acetic character of HFIP. The resulting aza-oxy allyl cation is stabilized by HFIP through ion-pair effect. Further, sodium sulfinate reacts with carbocation to yield the desired sulfones, not O-alkylating product. Because, the nucleophilicity of sulfur is greater than that of oxygen due to the higher electronegativity of the oxygen atom in arylsulfinates. This might be explanation for obtaining the S-alkylation product. Nevertheless, we do not have any spectroscopic evidence.



Scheme 5.4 Plausible reaction mechanism.

5.4 Conclusions

Synthesis of sterically hindered sulfones was obtained from α-halohydroxamates and sulfinic acid sodium salts under mild conditions. The reaction proceeds at room temperature in the presence of sodium carbonate and HFIP. The desired products were obtained in excellent yields.

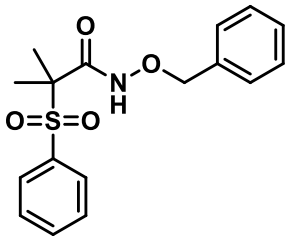
5.5 Experimental Procedure for Synthesis of *α*-Arylsulfone Propanamides

To a stirred solution of halohydroxamates (1.0 equiv.) in HFIP (hexafluoroisopropanol) in an oven-dried round-bottomed flask, 1.2 equivalents of sodium sulfinates were added.

Subsequently, 2.0 equivalents of sodium carbonate were introduced as the base. The reaction mixture was allowed to stir at room temperature for one hour. After completion, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate, filtered, and evaporated. Purification was carried out via column chromatography (SiO_2, 3:1, hexane: EtOAc).

5.6 Analytical Data

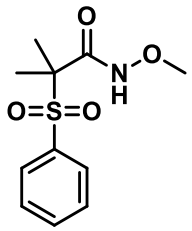
5.6.1 N-(benzyloxy)-2-methyl-2-(phenylsulfonyl)propanamide (3a):



3a

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.85-7.76 (m, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.45-7.30 (m, 5H), 4.94 (s, 2H), 1.52 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.88, 134.83, 134.51, 134.47, 129.98, 129.28, 129.14, 128.91, 128.61, 78.31, 67.91, 20.69. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{17}H_{20}NO_4S$: 334.1113; found: 334.1110.

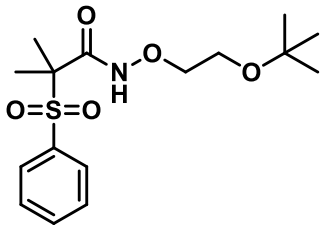
5.6.2 N-methoxy-2-methyl-2-(phenylsulfonyl)propenamide (3b):



3b

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.73 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H), 1.55 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.05, 145.74, 131.77, 130.39, 129.87, 77.71, 64.4, 20.8. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{11}H_{16}NO_4S$: 258.0800; found: 258.0780.

5.6.3 N-(2-(tert-butoxy)ethoxy)-2-methyl-2-(phenylsulfonyl)propenamide (3c):

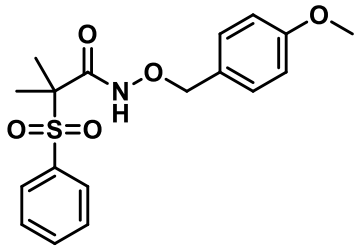


3c

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.73 (d, J = 4.0 Hz, 2H), 7.33 (m, 3H), 4.05 (t, J =

8 Hz, 2H), 3.66 (t, J = 4Hz, 2H), 1.55 (s, 6H), 1.27 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.05, 145.74, 131.77, 130.39, 129.87, 75.82, 74.04, 67.74, 61.54, 27.55, 20.62. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{16}H_{26}NO_5S$: 344.1532; found: 344.1540.

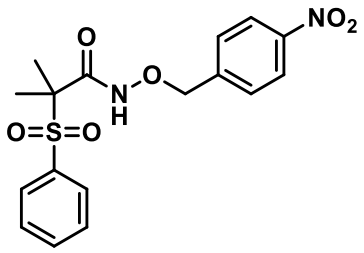
5.6.4 N-((4-methoxybenzyl)oxy)-2-methyl-2-(phenylsulfonyl)propenamide (3d):



3d

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.85-7.76 (m, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.45-7.30 (m, 4H), 4.94 (s, 2H), 3.85 (s, 3H), 1.52 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.88, 145.67, 134.8, 134.4, 129.9, 129.2, 128.9, 128.6, 115.78, 78.3, 70.9, 58.8, 20.6. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{18}H_{22}NO_5S$: 364.1219; found: 364.1210.

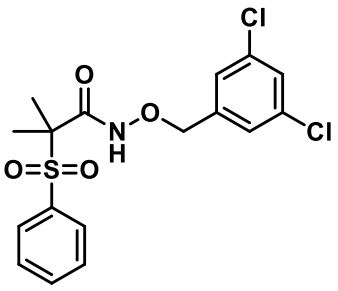
5.6.5 2-methyl-N-((4-nitrobenzyl)oxy)-2-(phenylsulfonyl)propanamide (3e):



3e

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.23 (d, J = 8.7 Hz, 2H), 7.81 (dd, J = 8.4, 1.2 Hz, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.63 – 7.55 (m, 4H), 5.03 (s, 2H), 1.52 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.60, 148.23, 142.24, 134.87, 134.37, 130.15, 129.73, 129.37, 123.89, 77.06, 68.18, 20.95. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{17}H_{19}N_2O_6S$: 379.0964; found: 379.0950.

5.6.6 N-((3,5-dichlorobenzyl)oxy)-2-methyl-2-(phenylsulfonyl)propenamide (3f):

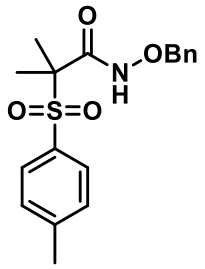


3f

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.81 (dd, J = 8.4, 1.2 Hz, 2H), 7.69 (t, J = 8.0 Hz, 1H), 7.56 (t, J = 7.8 Hz, 2H), 7.48-7.42 (m, 2H), 7.35-7.27 (m, 1H), 5.04 (s, 2H), 1.54 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.48, 135.54, 135.24, 134.49, 132.26, 131.54, 130.13,

129.63, 129.37, 74.69, 68.15, 20.89. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{17}H_{18}Cl_2NO_4S$: 402.0334; found: 402.0333.

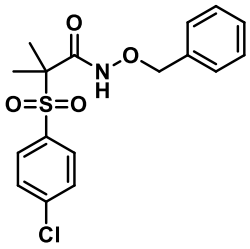
5.6.7 N-(benzyloxy)-2-methyl-2-tosylpropanamide (4a):



4a

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.85-7.76 (m, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.45-7.30 (m, 5H), 4.94 (s, 2H), 2.43 (s, 3H), 1.52 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.88, 134.8, 134.4, 131.5, 129.9, 129.2, 128.9, 128.6, 127.8, 78.3, 67.9, 21.3, 20.6. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{18}H_{22}NO_4S$: 348.1270; found: 348.1250.

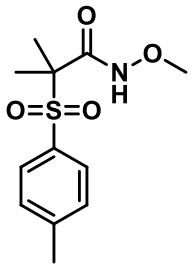
5.6.8 N-(benzyloxy)-2-((4-chlorophenyl)sulfonyl)-2-methylpropanamide (4b):



4b

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.67 (d, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.45-7.30 (m, 5H), 4.94 (s, 2H), 1.52 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.88, 135.7, 134.8, 134.4, 129.9, 129.2, 128.9, 128.6, 127.5 78.3, 67.9, 20.6. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{17}H_{19}ClNO_4S$: 368.0723; found: 368.0700.

5.6.9 N-methoxy-2-methyl-2-tosylpropanamide (4c):

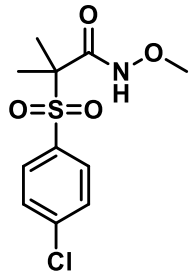


4c

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.73 (d, J = 4.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H),

3.89 (s, 3H), 2.33 (s, 3H), 1.55 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.05, 145.74, 131.77, 130.39, 129.87, 76.54, 64.4, 21.54, 20.8. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{12}H_{18}NO_4S$: 272.0957; found: 272.0960.

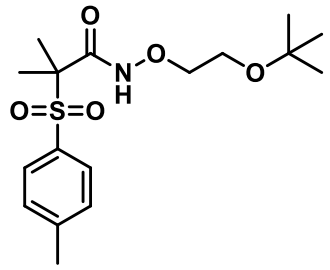
5.6.10 2-((4-chlorophenyl)sulfonyl)-N-methoxy-2-methylpropanamide (4d):



4d

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.73 (d, J = 4.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 3.85 (s, 3H), 1.55 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.05, 145.74, 131.77, 130.39, 129.87, 76.45, 64.63 20.8. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{11}H_{15}ClNO_4S$: 292.0410; found: 292.0402.

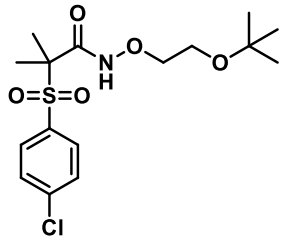
5.6.11 N-(2-(tert-butoxy)ethoxy)-2-methyl-2-tosylpropanamide (4e):



4e

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.73 (d, J = 4.0 Hz, 2H), 7.33 (m, 2H), 4.05 (t, J = 8 Hz, 2H), 3.66 (t, J = 4Hz, 2H), 2.81 (s, 3H), 1.55 (s, 6H), 1.27 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.05, 145.74, 131.77, 130.39, 129.87, 75.82, 74.04, 67.74, 61.54, 27.55, 21.3, 20.62. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{17}H_{28}NO_5S$: 358.1688; found: 358.1687.

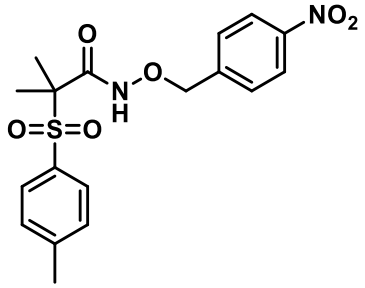
5.6.12 N-(2-(tert-butoxy)ethoxy)-2-((4-chlorophenyl)sulfonyl)-2-methylpropanamide (4f):



4f

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.73 (d, J = 4.0 Hz, 2H), 7.33 (m, 2H), 4.05 (t, J = 8 Hz, 2H), 3.66 (t, J = 4Hz, 2H), 1.55 (s, 6H), 1.27 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.05, 145.74, 131.77, 130.39, 129.87, 75.82, 74.04, 67.74, 61.54, 27.55, 20.62. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{16}H_{25}ClNO_5S$: 378.1142; found: 378.1140.

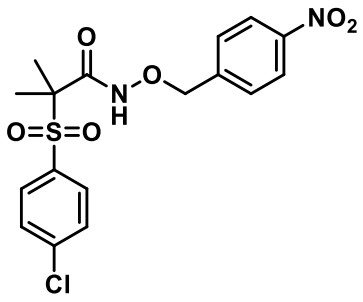
5.6.13 2-methyl-N-((4-nitrobenzyl)oxy)-2-tosylpropanamide (4g):



4g

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 9.70 (s, 1H), 8.23 (d, *J* = 8.7 Hz, 2H), 7.81 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.63-7.55 (m, 3H), 5.03 (s, 2H), 2.41 (s, 3H), 1.52 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) *δ* 166.60, 148.23, 142.24, 134.87, 134.37, 130.15, 129.73, 129.37, 123.89, 77.06, 68.18, 21.4, 20.95. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{18}H_{21}N_2O_6S$: 393.1120; found: 393.1119.

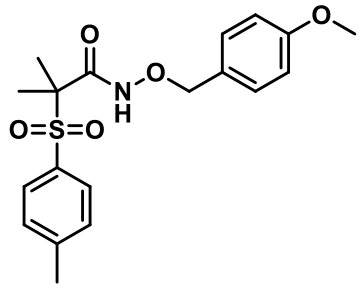
5.6.14 2-((4-chlorophenyl)sulfonyl)-2-methyl-N-((4-nitrobenzyl)oxy)propanamide (4h):



4h

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.23 (d, J = 8.7 Hz, 2H), 7.81 (dd, J = 8.4, 1.2 Hz, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.63-7.55 (m, 3H), 5.03 (s, 2H), 1.52 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.60, 148.23, 142.24, 134.87, 134.37, 130.15, 129.73, 129.37, 123.89, 77.06, 68.18, 20.95. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{17}H_{18}ClN_2O_6S$: 413.0574; found: 413.0570.

5.6.15 N-((4-methoxybenzyl)oxy)-2-methyl-2-tosylpropanamide (4i):

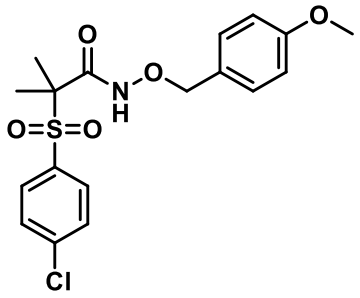


4i

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.85-7.76 (m, 2H), 7.54 (t, J = 7.8 Hz, 2H), 7.45-7.30 (m, 4H), 4.94 (s, 2H), 3.85 (s, 3H), 2.40 (s, 3H), 1.52 (s, 6H). **^{13}C NMR** (101 MHz,

$CDCl_3$) δ 165.88, 134.8, 134.4, 129.9, 129.2, 128.9, 128.6, 78.3, 76.5, 67.9, 58.8, 21.3, 21.2, 20.6. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{19}H_{24}NO_5S$: 378.1375; found: 378.1350.

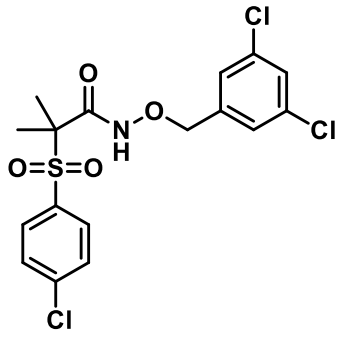
5.6.16 2-((4-chlorophenyl)sulfonyl)-N-((4-methoxybenzyl)oxy)-2-methylpropanamide (4j):



4j

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.85-7.76 (m, 2H), 7.67 (t, *J* = 7.5 Hz, 2H), 7.45-7.30 (m, 4H), 4.94 (s, 2H), 3.85 (s, 3H), 1.52 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.8, 140.7, 134.8, 134.4, 129.9, 129.2, 128.9, 128.6, 127.4, 78.3, 67.9, 58.8, 20.6. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{18}H_{21}ClNO_5S$: 398.0829; found: 398.0830.

5.6.17 2-((4-chlorophenyl)sulfonyl)-N-((3,5-dichlorobenzyl)oxy)-2-methylpropanamide (4k):



4k

The title of the compound is obtained as a reddish liquid using the general procedure. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.81 (dd, J = 8.4, 1.2 Hz, 2H), 7.56 (t, J = 7.8 Hz, 2H), 7.48-7.42 (m, 2H), 7.35-7.27 (m, 1H), 5.04 (s, 2H), 1.54 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.48, 135.54, 134.79, 134.49, 131.54, 130.13, 129.63, 129.37, 127.47, 74.69, 68.15, 20.89. HRMS (ESI): m/z $[M + H]^+$ calcd for : $C_{17}H_{17}Cl_3NO_4S$: 435.9944; found: 435.9940.

5.7 Spectra of Few Synthesized Compounds

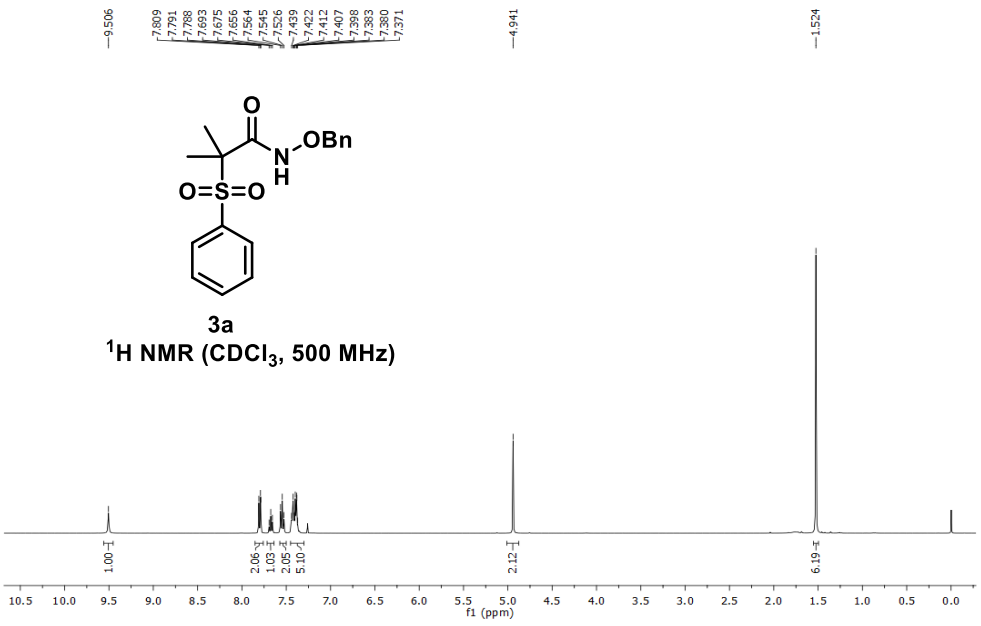


Figure 5.2 ^{1}H NMR Spectra of product 3a in $CDCl_3$

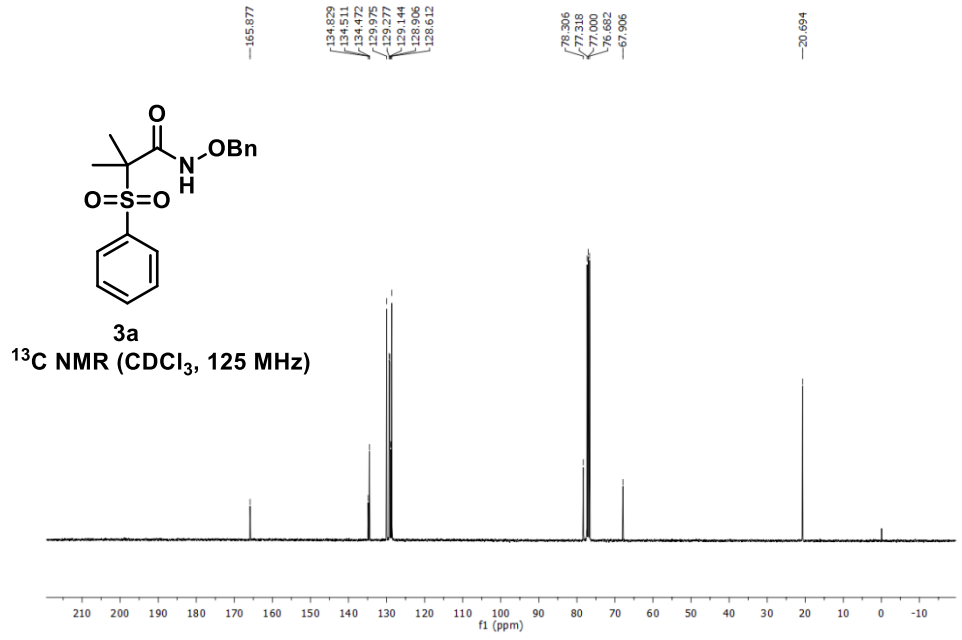


Figure 5.3 ^{13}C NMR Spectra of product 3a in $CDCl_3$

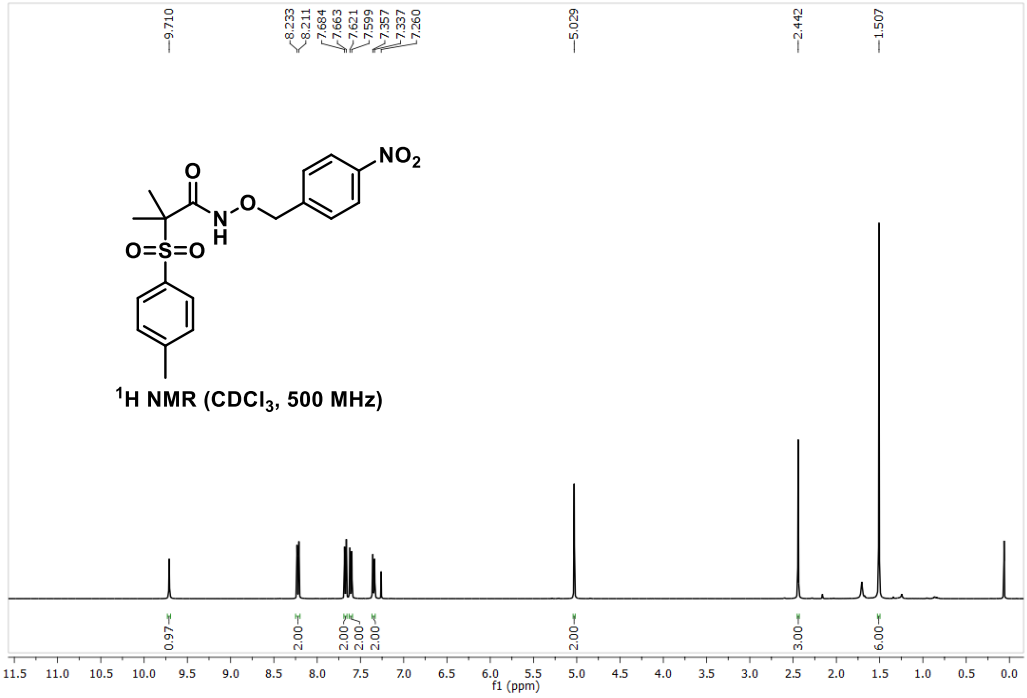


Figure 5.4 ^{1}H NMR Spectra of product 4g in $CDCl_3$

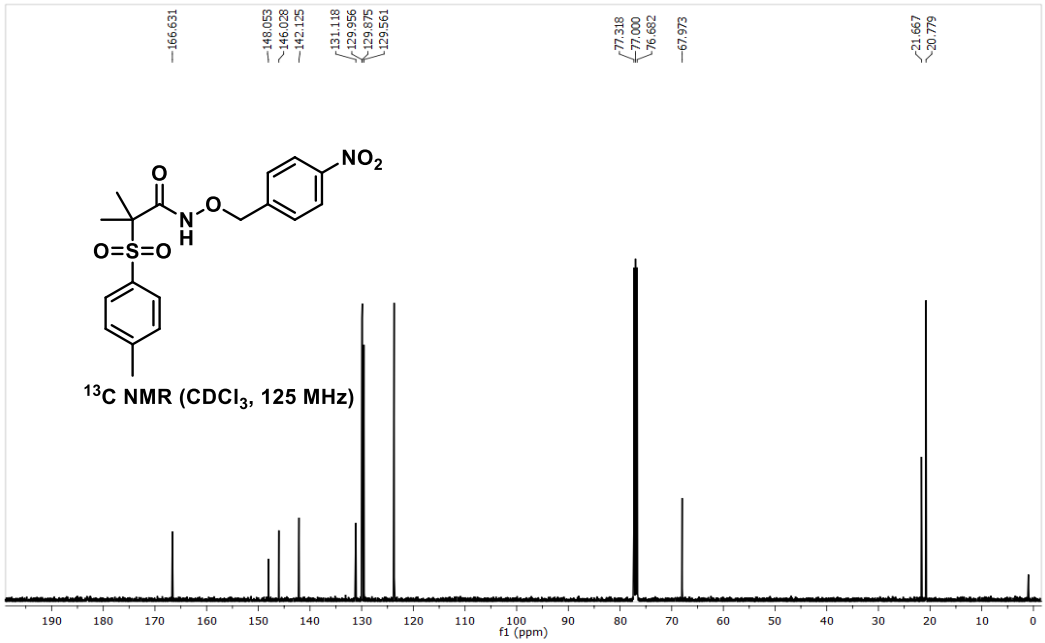


Figure 5.5 ^{13}C NMR Spectra of product 4g in $CDCl_3$

5.8 References

[1] R. J. Cremlyn," An introduction to organosulfur chemistry," *John Wiley and Sons: Chichester*, 1996.

[2] S. Patai, Z. Rappoport, C. J. M. Stirling, "The chemistry of sulphones and sulphoxides," *Wiley: New York*, 1986.

[3] A. E. Awa, M. N. Noshi, X. M. J. du, P. L. Fuchs, "Evolving organic synthesis fostered by the pluripotent phenylsulfone moiety," *Chemical Reviews*, **109** (2009) 2315-2349.

[4] B. M. Trost, C. A. Kalnmals, "Sulfones as chemical chameleons: versatile synthetic equivalents of small-molecule synthons," *Chemistry-A European Journal*, **25** (2019) 11193-11213.

[5] S. Liang, K. Hofman, M. Friedrich, J. Keller, G. Manolikakes, "Recent progress and emerging technologies towards a sustainable synthesis of sulfones," *ChemSusChem*, **14** (2021) 4878-4902.

[6] D. C. Meadows, J. Gervay-Hague, "Vinyl sulfones: synthetic preparations and medicinal chemistry applications," *Medicinal Research Reviews*, **26** (2006) 793-814.

[7] R. Ahmadi, S. Emami, "Recent applications of vinyl sulfone motif in drug design and discovery," *European Journal of Medicinal Chemistry*, **234** (2022) 114255.

[8] A. Podgoršek, M. Zupan, J. Iskra, "Oxidative halogenation with “green” oxidants: oxygen and hydrogen peroxide," *Angewandte Chemie*, **48** (2009) 8424-8450.

[9] B. M. Choudary, N. S. Chowdari, M. L. Kantam, "Friedel–crafts sulfonylation of aromatics catalyzed by solid acids: An eco-friendly route for sulfone synthesis," *Journal of the Chemical Society, Perkin Transactions* **1** (2000) 2689-2693.

[10] S. Liang, K. Hofman, M. Friedrich, G. Manolikakes, "Recent advances in the synthesis and direct application of sulfinate salts." *European Journal of Organic Chemistry*, **2020** (2020) 4664-4676.

[11] E. J. Emmett, M. C. Willis, "The development and application of sulfur dioxide surrogates in synthetic organic chemistry," *Asian Journal of Organic Chemistry*, **4** (2015) 602-611.

[12] W. Zhu, D. Ma, "Synthesis of aryl sulfones via L-proline-promoted CuI-catalyzed coupling reaction of aryl halides with sulfinic acid salts," *The Journal of Organic Chemistry*, **70** (2005) 2696-2700.

[13] R. J. Reddy, A. H. Kumari, "Synthesis and applications of sodium sulfinates (RSO 2 Na): a powerful building block for the synthesis of organosulfur compounds," *RSC Advances*, **11** (2021) 9130-9221.

[14] S. K. Aithagani, K. R. Yempalla, G. Munagala, R. A. Vishwakarma, P. P. Singh, "Metal-free, high yielding synthesis of unsymmetrical biaryl, bi (heteroaryl), aryl vinyl, aryl alkyl sulfones via coupling of aryne with sulfinic acid salts," *RSC Advances*, **4** (2014) 50208-50211.

[15] J. Xuan, X. Cao, X. Cheng, "Advances in heterocycle synthesis via [3+ m]-cycloaddition reactions involving an azaoxyallyl cation as the key intermediate," *Chemical Communications*, **54** (2018) 5154-5163.

[16] V. Jaiswal, B. Mondal, K. Singh, D. Das, J. Saha, "[3+ 2]-Annulation of azaoxyallyl cations and thiocarbonyls for the assembly of thiazolidin-4-ones," *Organic Letters*, **21** (2019) 5848-5852.

[17] A. El. Bouakher, A. Martel, S. Comesse, "α-Halogenoacetamides: versatile and efficient tools for the synthesis of complex aza-heterocycles," *Organic & Biomolecular Chemistry*, **17** (2019) 8467-8485.

[18] Deeksha, R. Singh, "Aza-oxyallyl cations and their applications in (3+ m) cycloaddition reactions," *European Journal of Organic Chemistry*, **2022** (2022) e202201043.

[19] C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff, C. R. Carson, "Generation and reactivity of aza-oxyallyl cationic intermediates: aza-[4+ 3] cycloaddition reactions for heterocycle synthesis," *Journal of the American Chemical Society*, **133** (2011) 7688-7691.

[20] Q. Jia, Z. Du, K. Zhang, J. Wang, "[3+ 2] Cycloaddition of aza-oxyallyl cations with aldehydes," *Organic Chemistry Frontiers*, **4** (2017) 91-94.

[21] I. M. Taily, D. Saha, P. Banerjee, "Aza-oxyallyl cation driven 3-amido oxetane rearrangement to 2-oxazolines: access to oxazoline amide ethers," *The Journal of Organic Chemistry*, **87** (2022) 2155-2166.

[22] Deeksha, E. S. Kiran, R. Singh, "Access to sterically hindered thioethers (α-thioamides) under mild conditions using α-halohydroxamates: application toward 1, 4-benzothiazinones and 4, 1-benzothiazepinones," *The Journal of Organic Chemistry*, **88** (2022) 901-908.

[23] Y. Kwon, S. Choi, H. S. Jang, S. G. Kim, "Rapid access to hindered α-amino acid derivatives and benzodiazepin-3-ones from aza-oxyallyl cations," *Organic Letters,* **22** (2020) 1420-1425.

[24] S. G. More, K. D. Mane, G. Suryavanshi, "A Metal-free access to hindered N-alkyl sulfoximines via in-situ generated aza-oxyallyl cations from functionalized alkyl bromide," *Asian Journal of Organic Chemistry,* **11** (2022) e202200210.

[25] C. Y. Lee, S. G. Kim, "Highly efficient DMSO-promoted α-hydrolysis of α-halohydroxamates under mild conditions," *European Journal of Organic Chemistry,* **2021** (2021) 1607-1614.

[26] E. C. Son, S. G. Kim, "Metal-free nucleophilic alkoxylation of in situ-generated azaoxyallyl cations: synthesis of hindered dialkyl ether derivatives," *Asian Journal of Organic Chemistry,* **9** (2020) 914-917.

[27] M. A. Seleem, N. R. de Almeida, Y. S. Chhonker, D. J. Murry, Z. d. R. Guterres, A. M. Blocker, S. Kuwabara, D. J. Fisher, E. S. Leal, M. R. Martinefski, M. Bollini, M. E. Monge, S. P. Ouellette, M. C. Sheridan, "Synthesis and antichlamydial activity of molecules based on dysregulators of cylindrical proteases," *Journal of medicinal chemistry,* **63** (2020) 4370-4387.

[28] D. P. Becker, C. I. Villamil, T. E. Barta, L. J. Bedell, T. L. Boehm, G. A. DeCrescenzo, J. N. Freskos, D. P. Getman, S. Hockerman, R. Heintz, S. C. Howard, M. H. Li, J. J. McDonald, C. P. Carron, C. L. Funckes-Shippy, P. P. Mehta, G. E. Munie, C. A. Swearingen, "Synthesis and structure-activity relationships of β-and α-piperidine sulfone hydroxamic acid matrix metalloproteinase inhibitors with oral antitumor efficacy," *Journal of medicinal chemistry,* **48** (2005) 6713-6730.