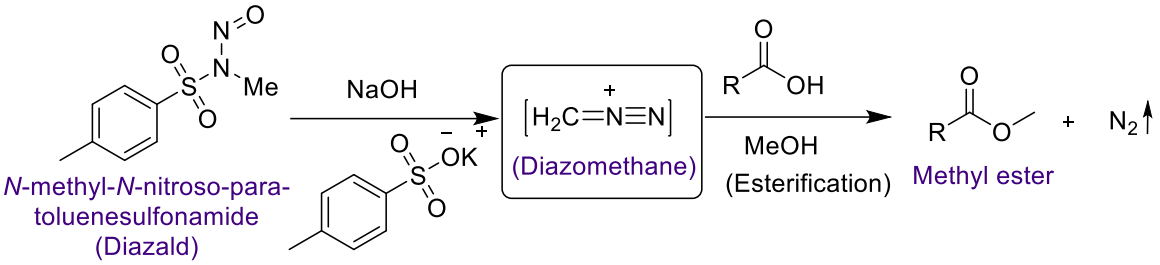
CHAPTER-4

Synthesis of *N*-nitroso sulfonamides from sulfonamides and tert-Butyl nitrite under mild reaction conditions

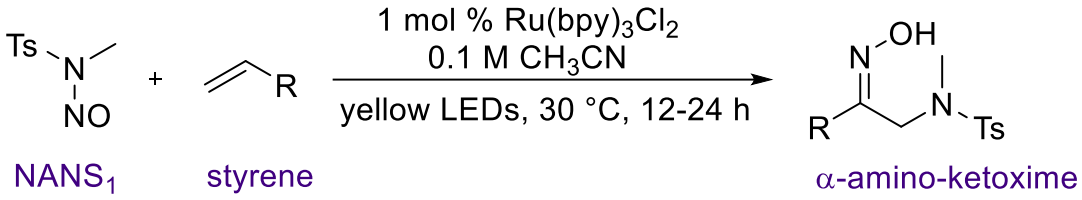
4.1 Introduction

N-Nitroso compounds, including *N*-Nitrosamines and *N*-Nitrosamides, play important roles in human health and diseases. In particular, *N*-Nitroso compounds possess a strong carcinogenic and mutagenic property [1]. On the other hand, some *N*-Nitrosamines have been used in various treatments including cancer, cardiovascular diseases, central nervous disorders, diseases related to immunity and physiological disorders, etc [1, 2]. Besides their biological importance, *N*-Nitrosamines have become valuable precursors and intermediates in organic synthesis [11]. Besides their traditional synthetic applications, they have been recently used as the directing group in *C*-H activation reactions [3]. Unlike *N*-Nitrosamines, the chemistry of *N*-Nitrosamides is less explored [12]. There are two types of *N*-Nitrosamides, namely i) *N*-Nitroso acyl amides and ii) *N*-Nitroso sulfonamides [4, 5]. In terms of synthesis and applications, the chemistry of *N*-Nitroso acyl amides is better explored when compared with *N*-Nitroso sulfonamides [5]. For instance, *N*-Nitroso acyl amides have been synthesized using various nitrosating reagents (e.g. sodium nitrite-acetic anhydride, [6, 7] nitrosyl chloride, [8a] nitrogen trioxide, nitrogen tetraoxide, [8b] tert-butyl nitrite [7c], etc.) and have been used in the acyl transfer reactions, *C*-H activation reactions, rearrangement reactions, etc. On the other hand, only limited methods are available for the synthesis and applications of *N*-Nitroso sulfonamides. In general, *N*-Nitroso sulfonamides have been synthesized using sodium nitrite and hydrochloric acid [5]. However, the use of strong acidic conditions, excess amounts of sodium nitrite, and low yields are the major problems of the existing methodology. As far as the applications are concerned, *N*-Methyl-*N*-Nitroso-*p*-Toluenesulfonamide (Diazald) has been used as the diazomethane precursor **(Scheme**

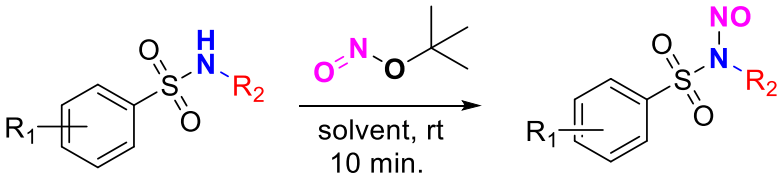
4.1) [9]. Very recently, synthesis of α-amino-ketoximes has been reported from *N*-Nitrososulfonamides and aryl alkenes **(Scheme 4.2)** [5].



Scheme 4.1 Diazomethane is used for esterification.



Scheme 4.2 *N*-Methyl-*N*-Nitroso sulfonamide is used for the synthesis of α-Amino-ketoximes.



Scheme 4.3 Nitrosation of sulfonamide with TBN.

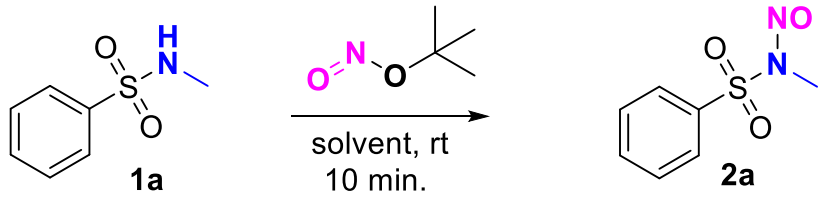
Our group research is mainly focused on the chemistry of *N*-Nitrosamines [10]. In this context, we have reported tert-butyl nitrite (TBN)-mediated solvent-free synthesis of *N*-Nitrosamines, [13] radical dimerization of thiobenzamide, [13b] transamidation of

secondary amides, [13c] and nitration of *N*-Alkyl anilines [13d]. Recently, we have reported the synthesis of benzotriazoles and benzimidazoles from o-phenylenediamine using tert-butyl nitrite [14]. It is important to mention here that tert-butyl nitrite is a commercially available, inexpensive, and easy-to-handle multi-tasking reagent found in various applications in organic synthesis [15, 16, 17]. In continuation of our previous works using TBN, here we report the synthesis of *N*-Nitroso sulfonamides from sulfonamides and TBN and their synthetic applications in nitroso transfer reactions under mild reaction conditions **(Scheme 4.3)**.

4.2 Results and Discussion

At the outset, the reaction conditions were optimized using *N*-Phenyl *N*-Methyl sulfonamide **1a** as a model substrate with tert-Butyl nitrite (TBN) (1.0 equiv.) used as the nitrosating agent and the reactions were performed in different solvents including methanol, tetrahydrofuran (THF), acetonitrile, dichloromethane (DCM) and water at room temperature. However, the reactions in methanol and THF gave the desired product **2a** only (5-10%) yields (**Table 4.1,** entries 1-2). On the other hand, the reactions in acetonitrile, dichloromethane (DCM), and water (**Table 4.1,** entries 3-5) gave product **2a** (68-98%) yields. In particular, a quantitative yield (98%) was obtained in dichloromethane solvent. The reaction also proceeded under solvent-free conditions, (**Table 4.1,** entries 6-7) however, relatively in low yields. We further used the other alkyl nitrites including n-butyl nitrite and amyl nitrite. The reactions proceed well with these alkyl nitrites (**Table 4.1,** entries 8-9) and the product was obtained (94-96%) in comparable yields to that of TBN.

Table 4.1: Optimization study[a, b]



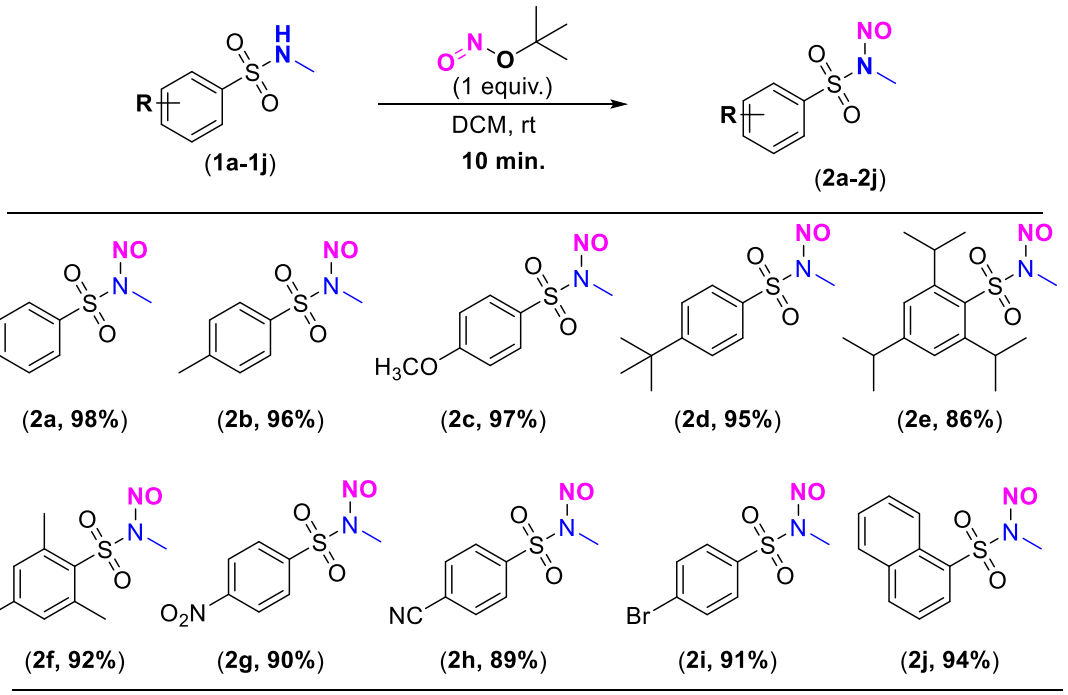
S.No.	Solvent	TBN (equiv.)	Yield[b] (%)
1	CH_3OH	1.0	<5
2	THF	1.0	<10
3	CH_3CN	1.0	85
4	DCM	1.0	98
5	H_2O	1.0	68
6	Solvent Free	1.0	81
7	Solvent Free	2.0	93
8	DCM (n-butyl nitrite)	1.0	96
9	DCM (n-amyl nitrite)	1.0	94

[a]**Reaction conditions**: Substrate **1a** (1mmol) and TBN (1.0 equiv.) in DCM (2.0 mL) were stirred at room temperature for 10 minutes. [b]Isolated yields.

Having optimized the reaction conditions, we investigated the scope of the reaction concerning sulfonamides (**Table 4.2**). Initially, various aryl *N*-Methyl sulfonamides were prepared and subjected to the *N*-Nitrosation reaction with TBN under optimization conditions. Aryl groups bearing various electron-donating functional groups such as methyl, methoxy, and tert-butyl groups underwent *N*-Nitrosation within 10 min. and provided the desired products **2a-2f** in (86-97%) good to excellent yields. It is worth noting that the sterically hindered *ortho* tert-butyl groups functionalized substrate also

gave the desired product **2e** in 86% good yield. Similarly, the electron-withdrawing groups such as nitro and cyano-containing substrates also underwent *N*-Nitrosation smoothly and gave the desired product **2g-2h** in (89-94%) excellent yields. Moreover, the substrates bearing halogen functional groups underwent *N*-Nitrosation, and the desired products **2i** in (91%) good yields. *N*-Methyl naphthalene sulfonamide also underwent *N*-Nitrosation very smoothly and gave the desired product **2j** in (94%) excellent yield.

Table 4.2: *N*-Nitrosation of various *N*-Methyl sulphonamides using TBN[a, b]

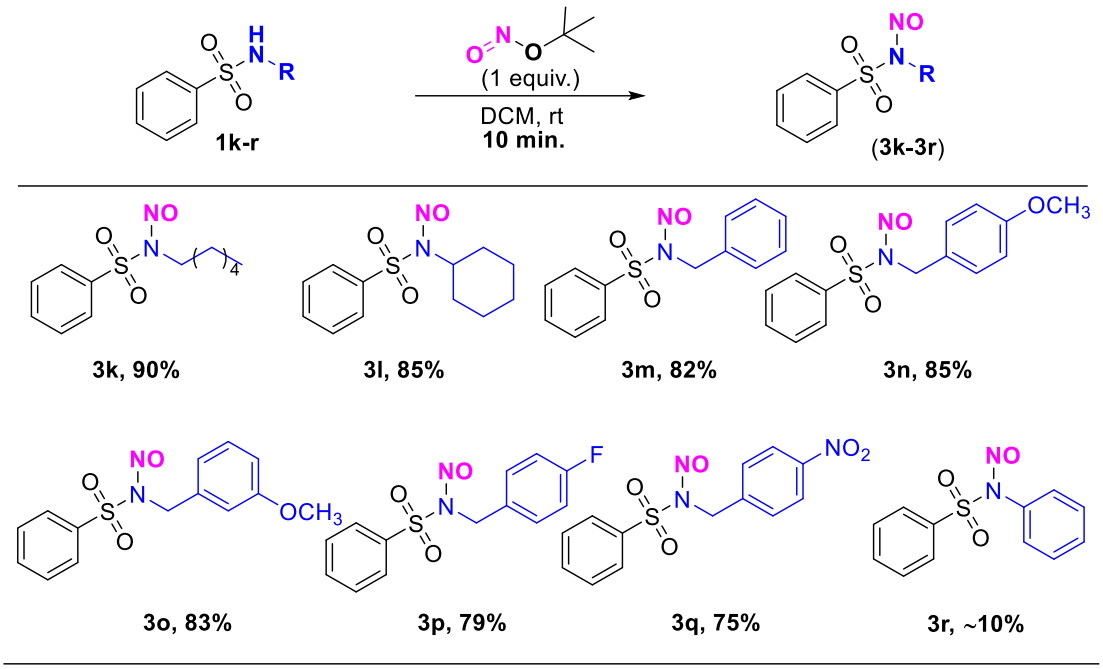


[a]**Reaction conditions**: Substrates (**1a-1j**, 1 mmol) and TBN (1.0 equiv.) in DCM (2.0 mL) were stirred at room temperature for 10 minutes. [b]Isolated yields.

After exploring the scope of the aryl *N*-Methyl sulfonamides, we have investigated the *N*-Nitrosation of various *N*-Alkyl benzenesulfonamides (**Table 4.3**). The substrates bearing liner and cyclic alkyl groups such as hexyl and cyclohexyl underwent *N*-Nitrosation smoothly and the desired products **3k-3l** were obtained in good yields (90-85%). Further,

we investigated the *N*-Nitrosation of various phenyl *N*-Benzyl sulfonamides. It was observed that the sulfonamides bearing various *N*-Benzyl groups such as 4-methoxy, 3-methoxy, 4-fluoro and 4-nitro benzyl moiety underwent *N*-Nitrosation and gave the corresponding *N*-Nitroso sulfonamides **3m-3q** in good to excellent yields (75-85%). However, the substrate, *N*-Phenyl benzene sulfonamide gave the desired product **3r** in low yield (~10%).

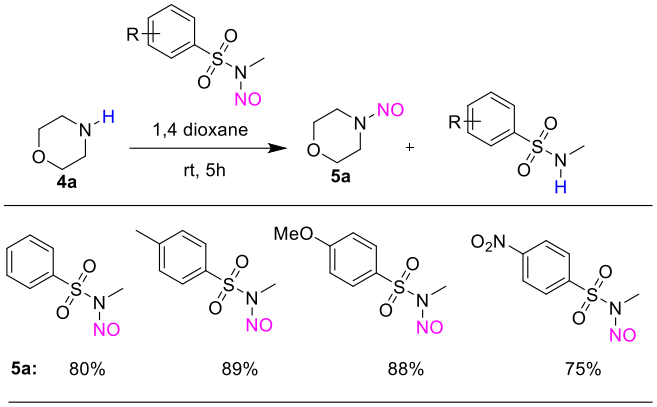
Table 4.3: *N*-Nitrosation of various *N*-substituted benzenesulfonamides using TBN[a,b]



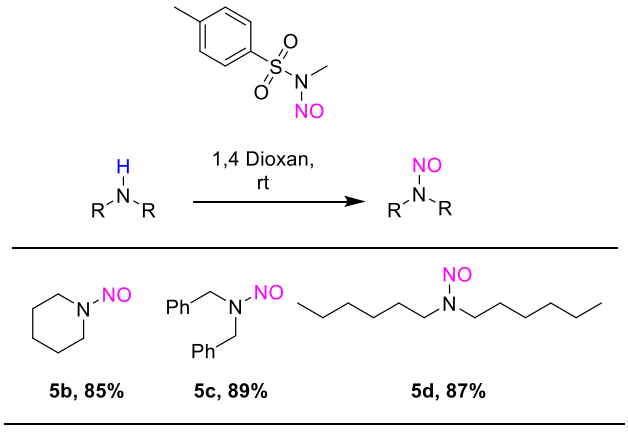
[a]**Reaction conditions**: Substrates (**1k-1r**, 1 mmol, 1.0 equiv.) and TBN (1.0 equiv.) in DCM (2.0 mL) with different amines were stirred at room temperature for 10 minutes. [b]Isolated yields.

Having generated various *N*-Nitroso sulfonamides, we investigated the applications of these compounds. In this context, we have investigated the use of *N*-Nitroso sulfonamides as nitrosating agents for the secondary amines. We have used morpholine as the model

substrate and investigated nitrosation using aryl *N*-Methyl *N*-Nitroso benzene sulfonamides in 1, 4 dioxane at room temperature. The reaction was performed in the 1, 4 dioxane solvent at room temperature. It was observed that *N*-Methyl *N*-Nitroso *p*-Tolyl sulfonamide gave the desired product in good yield when compared with other sulfonamides **(Scheme 4.4)**. We further extended the study and *N*-Nitrosation of various other secondary amines were investigated using *N*-Methyl *N*-Nitroso *p*-Tolyl sulfonamide. The secondary amides including piperidine, dibenzyl amine, and dihexyl amine were successfully nitrosated using the developed methodology **(Scheme 4.5)**.



Scheme 4.4 Nitrosation of morpholine with different *N*-Methyl *N*-Nitroso sulfonamides.



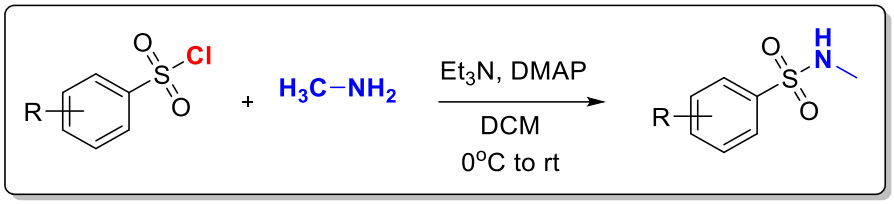
Scheme 4.5 Transnitrosation with *N*-Methyl *N*-Nitroso sulfonamide with secondary amines.

4.3 Conclusion

In conclusion, we have successfully developed a simple and highly efficient method for the preparation of *N*-Nitroso sulfonamides from sulfonamides and *tert*-butyl nitrite at room temperature. The reactions gave the desired products good to excellent yields. The application of *N*-Nitroso sulfonamides was explored for the nitrosation of secondary amines under mild reaction conditions. The developed methodology is attractive in terms of reaction conditions, yields, and execution of the reactions.

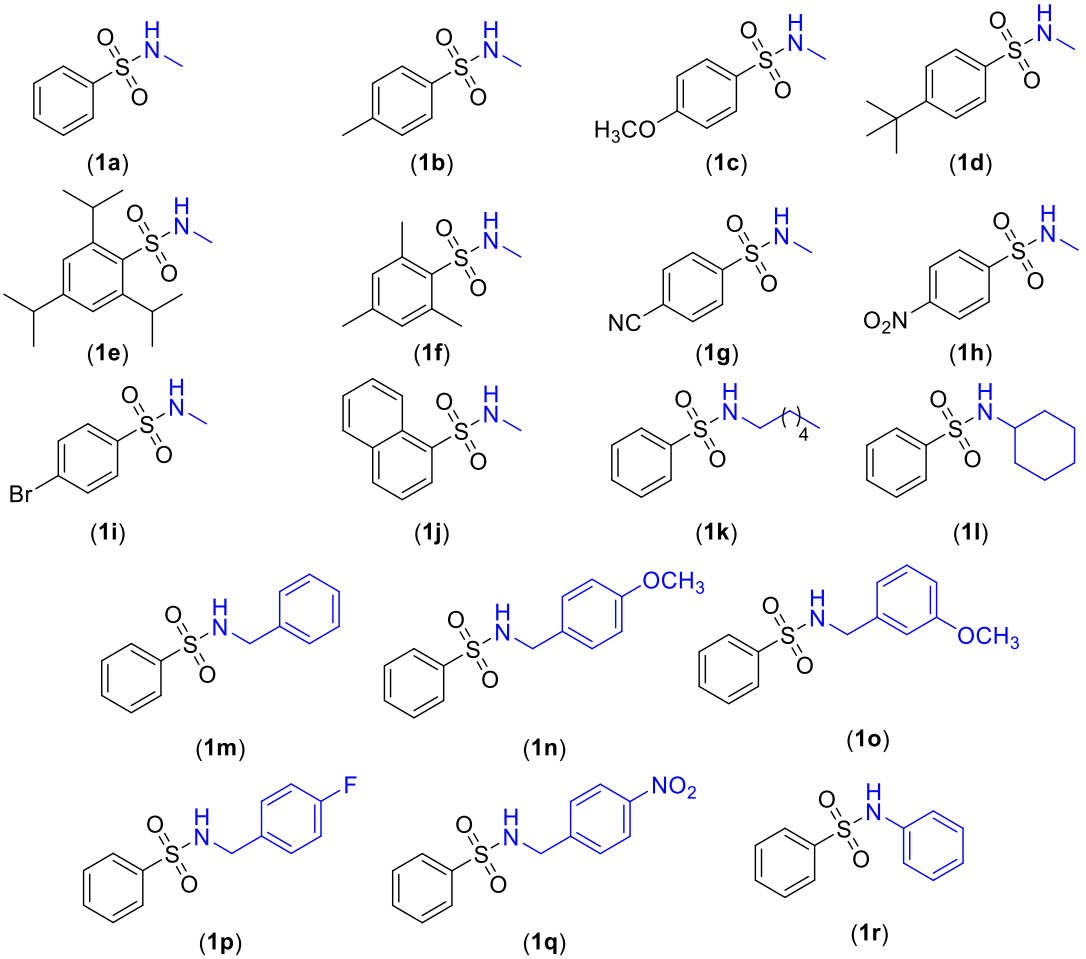
4.4 Experimental Section

4.4.1. General procedure of preparation of *N*-Alkyl sulfonamides from sulfonyl chlorides: [5]

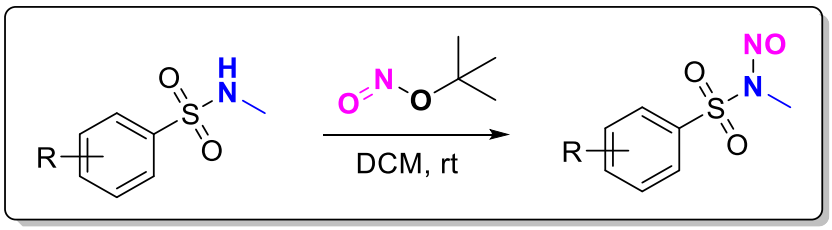


Substrate primary amine (methylamine: 25–30% in water, 2 equiv.) was dissolved in dichloromethane (DCM) and cooled to 0 °C. Triethylamine (2 equiv.) and dimethyl aminopyridine (0.1 equiv.) were added. In the end, the sulfonyl chloride (1 equiv.) was added piece of the action. Then the solution was slowly warmed to room temperature and stirred for an additional 12 hours. Once complete, the reaction was quenched with 1 M hydrochloric acid. The aqueous layer was washed with dichloromethane, dried over sodium sulphate, and concentrated under reduced pressure. The residue was obtained as a white solid or colourless oil liquid in 90–98% yield and used directly without further purification.

4.4.2. Starting materials prepared: [5, 18]



4.4.3. Procedure of preparation of *N*-nitroso-*N*-Alkyl-sulfonamides from *N*-Alkyl-sulfonamides:



To a well oven-dried round bottom flask, *N*-Methylsulfonamide (0.5 mmol, 1.0 equiv.) and *tert*-butyl nitrite (1.0 equiv.) were added and allowed to stir at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was dissolved in the DCM, washed with water (2 x 20 mL), and dried over anhydrous

$NaSO_4$. Further, DCM was evaporated in vacuo and subjected to silica gel (100-200 mesh) column chromatography purification (SiO_2: ethyl acetate/hexane) to obtain the corresponding *N*-nitroso-*N*-methyl sulfonamides. Some sulfonamide was confirmed by NMR and mass in previous literature [5].

4.5: Analytical data:

4.5.1: *N*-methyl-*N*-nitrosobenzenesulfonamide (2a) [5]

The title compound was obtained as a pale yellow liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f = 0.70; Yield: 98% (206 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (m, *J* = 8.7, 1.8, 1.2 Hz, 2H), 7.62 (m, *J* = 8.1, 7.3, 1.2 Hz, 1H), 7.50 (m, *J* = 7.5, 2.5, 1.2 Hz, 2H), 3.04 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.92, 134.68, 129.66, 127.74, 28.83.

4.5.2: *N*,4-dimethyl-*N*-nitrosobenzenesulfonamide (2b) [5]

The title compound was obtained as a pale yellow liquid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 92:8, R_f = 0.68; Yield: 96% (210 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.04 (s, 3H), 2.38 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.12, 134.05, 130.32, 127.94, 28.83, 21.67.

4.5.3: 4-methoxy-*N*-methyl-*N*-nitrosobenzenesulfonamide (2c) [5]

The title compound was obtained as pale yellow viscous. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f = 0.60; Yield: 88% (230 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.1 Hz, 2H), 6.96 (d, *J* = 9.1

Hz, 2H), 3.82 (s, 3H), 3.05 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.56, 130.34, 128.18, 114.90, 55.82, 28.77.

4.5.4: 4-(tert-butyl)-*N*-methyl-*N*-nitrosobenzenesulfonamide (2d) [5]

The title compound was obtained as a pale yellow solid. Melting point 85 °C. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 92:8, R_f = 0.65; Yield: 95% (246 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 3.06 (s, 3H), 1.27 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.95, 133.97, 127.82, 126.75, 35.39, 30.90, 28.90. HRMS-ESI (m/z): calcd for $C_{11}H_{16}N_2O_3S$, $[M + H]^+$: 257.0960, found 257.0950.

4.5.5: 2,4,6-triisopropyl-*N*-methyl-*N*-nitrosobenzenesulfonamide (2e)

The title compound was obtained as a pale yellow foam. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 94:6, R_f = 0.82; Yield: 86% (280 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 2H), 3.97 (m, *J* = 6.7 Hz, 2H), 3.13 (s, 3H), 2.85 (m, *J* = 13.8, 6.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 12H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.36, 152.21, 129.26, 124.47, 34.29, 29.63, 27.75, 24.50, 23.41. HRMS-ESI (m/z): calcd for $C_{16}H_{26}N_2O_3S$, $[M + Na]^+$: 349.1562, found 349.1553.

4.5.6: *N*,2,4,6-tetramethyl-*N*-nitrosobenzenesulfonamide (2f)

The title compound was obtained as pale yellow viscous. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 92:8, R_f = 0.75; Yield: 88% (229 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.94 (s, 2H), 3.11 (s, 3H), 2.54 (d, *J* = 2.2

Hz, 6H), 2.25 (d, *J* = 1.9 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.05, 141.08, 132.48, 130.76, 28.22, 22.84, 21.10. HRMS-ESI (m/z): calcd for $C_{10}H_{14}N_2O_3S$, $[M + Na]^+$: 265.0623, found 265.0615.

4.5.7: *N*-methyl-4-nitro-*N*-nitrosobenzenesulfonamide (2g) [5]

The title compound was obtained as a pale yellow foam. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 79:21, R_f = 0.42; Yield: 90% (220 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H), 3.11 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.18, 142.75, 129.36, 124.93, 29.08.

4.5.8: 4-cyano-*N*-methyl-*N*-nitrosobenzenesulfonamide (2h) [5]

The title compound was obtained as a pale yellow foam. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 88:12, R_f = 0.45; Yield: 89% (210 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.7 Hz, 2H), 7.83 (d, *J* = 8.7 Hz, 2H), 3.09 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.30, 133.44, 128.56, 118.44, 116.64, 29.08.

4.5.9: 4-bromo-N-methyl-*N*-nitrosobenzenesulfonamide (2i) [5]

The title compound was obtained as a pale yellow viscous. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 87:13, R_f = 0.52; Yield: 91% (250 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 3.06 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.12, 133.10, 130.29, 129.34, 28.92.

4.5.10: *N*-methyl-*N*-nitrosonaphthalene-1-sulfonamide (2j)

The title compound was obtained as a pale yellow solid. Melting point 105 °C The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 80:20, R_f = 0.52; Yield: 94% (240 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.67 – 8.60 (m, 1H), 8.42 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.61 (m, *J* = 8.6, 6.9, 1.4 Hz, 1H), 7.56 (dd, *J* = 10.8, 4.8 Hz, 2H), 3.03 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.75, 134.28, 131.97, 131.23, 129.44, 129.27, 128.00, 127.55, 124.16, 123.78, 28.73. HRMS-ESI (m/z): calcd for $C_{11}H_{10}N_2O_3S$, $[M + Na]^+$: 273.0310, found 273.0302.

4.5.11: *N*-hexyl-*N*-nitrosobenzenesulfonamide (3k)

The title compound was obtained as colourless. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 92:8, R_f = 0.72; Yield: 90% (240 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 7.71 (td, *J* = 7.6, 1.0 Hz, 1H), 7.62 – 7.58 (m, 2H), 3.77 – 3.67 (m, 2H), 1.44 (dd, *J* = 14.5, 7.3 Hz, 2H), 1.27 – 1.19 (m, 6H), 0.88 – 0.85 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.99, 134.54, 129.59, 127.95, 43.24, 31.03, 27.58, 26.38, 22.33, 13.88. HRMS-ESI (m/z): calcd for $C_{29}H_{33}NO_6$, $[M + H]^+$: 271.1116, found 271.1120.

4.5.12: *N*-cyclohexyl-*N*-nitrosobenzenesulfonamide (3l)

The title compound was obtained as a pale yellow viscous. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 92:8, R_f = 0.75; Yield: 85% (235 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 2H), 7.58 – 7.54 (m, 1H),

7.49 – 7.44 (m, 2H), 4.49 – 4.43 (m, 1H), 1.74 – 1.69 (m, 2H), 1.64 (m, *J* = 9.9, 5.3, 2.7 Hz, 2H), 1.50 – 1.43 (m, 2H), 1.38 (m, *J* = 7.3, 6.7, 3.5 Hz, 1H), 1.24 – 1.17 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.76, 133.36, 129.08, 127.49, 81.98, 32.28, 24.77, 23.32. HRMS-ESI (m/z): calcd for $C_{12}H_{17}N_2O_3S$, $[M + H]^+$: 269.0960, found 269.0985.

4.5.13: *N*-benzyl-*N*-nitrosobenzenesulfonamide (3m)

The title compound was obtained as a yellow foam. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f = 0.68; Yield: 82% (229 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.38 (q, *J* = 7.7 Hz, 2H), 7.15 – 7.10 (m, 3H), 7.01 (dd, *J* = 6.5, 2.6 Hz, 2H), 4.86 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.01, 134.45, 129.38, 128.58, 128.30, 128.05, 127.90, 127.06, 47.26. HRMS-ESI (m/z): calcd for $C_{13}H_{13}N_2O_3S$, $[M + H]^+$: 277.0647, found 277.0655.

4.5.14: *N*-(4-methoxybenzyl)-*N*-nitrosobenzenesulfonamide (3n)

The title compound was obtained as a dark red viscous. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 85:15, R_f = 0.52; Yield: 85% (260 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.70 – 6.64 (m, 2H), 4.81 (s, 2H), 3.69 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.37, 138.15, 134.39, 130.05, 129.36, 127.90, 125.49, 113.91, 55.25, 45.49. calcd for $C_{14}H_{15}N_2O_4S$, $[M + H]^+$: 307.0753, found 307.0755.

4.5.15: *N*-(3-methoxybenzyl)-*N*-nitrosobenzenesulfonamide (3o)

The title compound was obtained as red viscous. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 85:15, R_f = 0.52; Yield: 83% (250 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.5, 1.1 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.42 – 7.38 (m, 2H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.69 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.50 (s, 1H), 4.84 (s, 2H), 3.62 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.67, 138.04, 134.45, 129.62, 129.38, 127.94, 120.52, 113.80, 113.52, 55.13, 47.24. calcd for $C_{14}H_{15}N_2O_4S$, $[M + H]^+$: 307.0753, found 307.0759.

4.5.16: *N*-(4-fluorobenzyl)-*N*-nitrosobenzenesulfonamide (3p)

The title compound was obtained as pale yellow viscous. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 75:25, R_f = 0.48; Yield: 79% (240 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.5, 1.1 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.06 – 7.00 (m, 2H), 6.85 – 6.79 (m, 2H), 4.81 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.37, 134.59, 130.42, 130.35, 129.47, 127.87, 115.59, 115.42, 45.17. calcd for $C_{13}H_{11}FN_2NaO_3S$, $[M + Na]^+$: 317.0372, found 317.0380.

4.5.17: *N*-(4-nitrobenzyl)-*N*-nitrosobenzenesulfonamide (3q)

The title compound was obtained as a pale yellow foam. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 75:25, R_f = 0.42; Yield: 75% (240 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.6 Hz, 2H), 7.88 – 7.84 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 4.89 (s, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 147.52, 140.36, 137.45, 135.00, 129.72, 128.90, 127.95, 123.84, 46.34. calcd for $C_{13}H_{12}N_3O_5S$, $[M + H]^+$: 322.0498, found 322.0505.

4.5.18: *N*-nitroso-*N*-phenylbenzenesulfonamide (3r)

The title compound was obtained as a pale yellow foam. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 85:15, R_f = 0.79; Yield: 10% (25 mg); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.03 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.80 – 7.75 (m, 3H), 7.54 – 7.49 (m, 2H), 7.40 (dd, *J* = 10.7, 4.9 Hz, 2H), 7.09 (m, *J* = 8.5, 7.4, 1.2 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.58, 135.87, 133.70, 129.38, 127.16, 126.15, 123.95, 121.09. calcd for $C_{12}H_{11}N_2O_3S$, $[M + H]^+$: 263.0490, found 263.0495.

4.6 Spectra of Few Synthesized Compounds

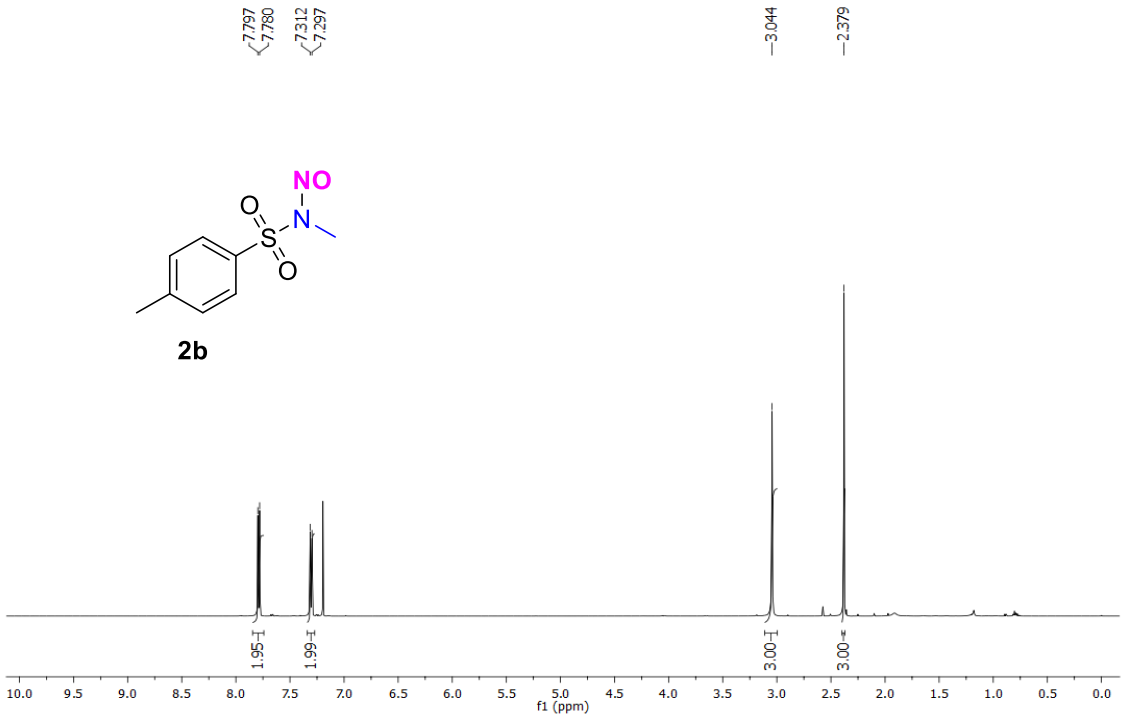


Figure 4.1 ^{1}H NMR Spectra of product 2b in $CDCl_3$

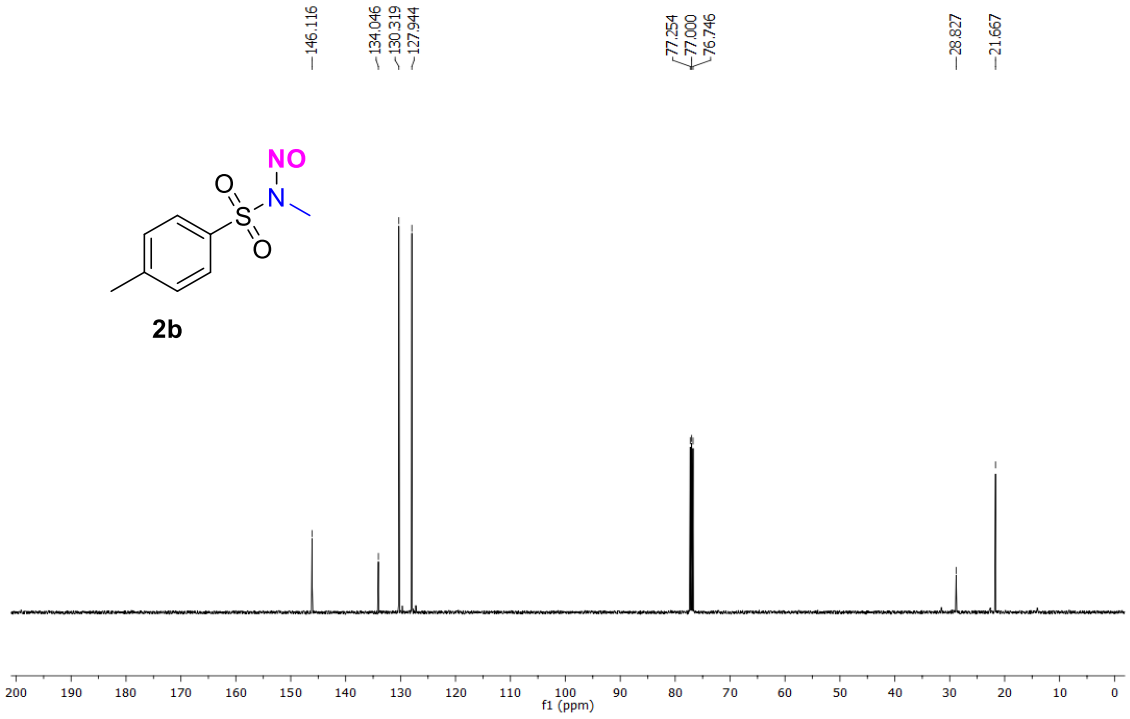


Figure 4.2 ^{13}C NMR Spectra of product 2b in $CDCl_3$

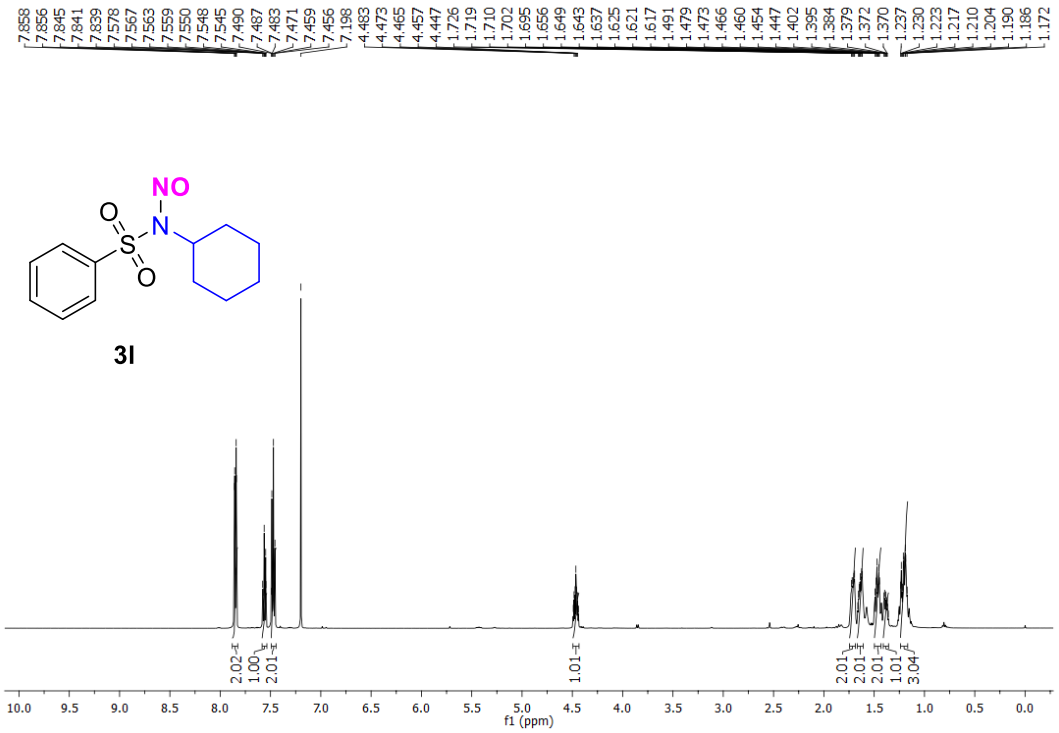


Figure 4.3 ^{1}H NMR Spectra of product 3l in $CDCl_3$

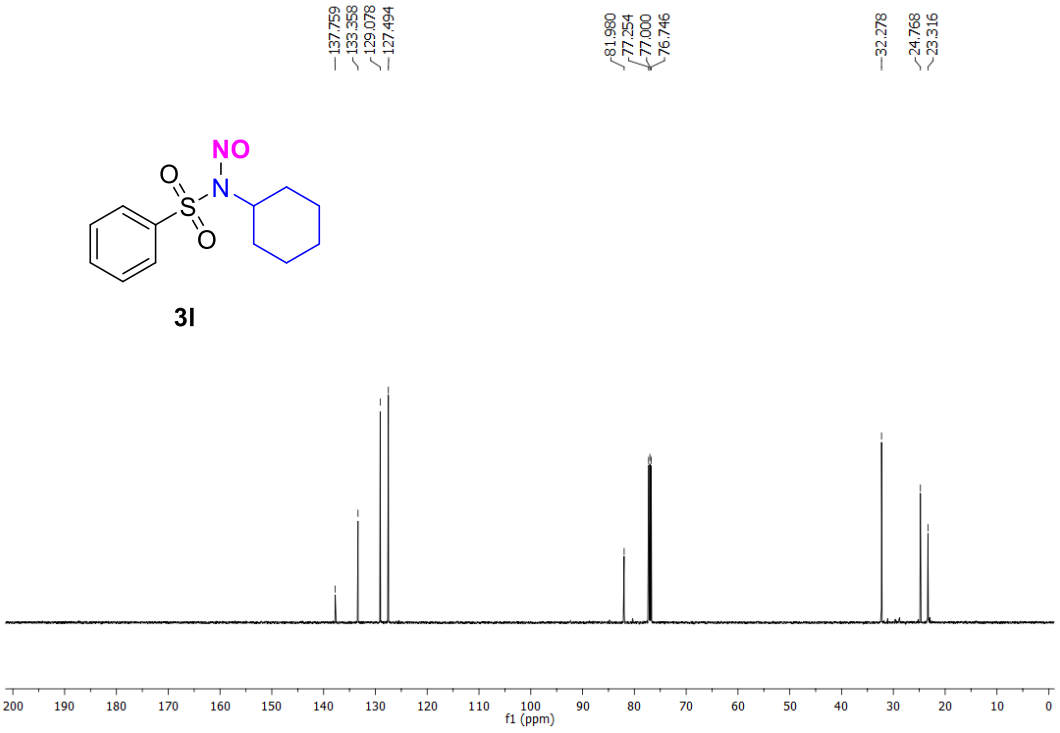


Figure 4.4 ^{13}C NMR Spectra of product 3l in $CDCl_3$

4.7 References

1. (a) P. G. Wang, T. B. Cai and N. Taniguchi, "Nitric Oxide Donor, For Pharmaceutical and Biological Applications," WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, 2005 (b) P. G. Wang, M. Xian, X. Tang, X. Wu, Z. Wen, T. Cai, A. J. Janczuk, "Nitric oxide donors: chemical activities and biological applications," *Chemical reviews*, **102**(2002) 1091-1134.
2. R. N. Loeppky, C. J. Michejda, "Nitrosamines and Related N-Nitroso Compounds: Chemistry and Biochemistry," ACS Symposium Series, American Chemical Society, Washington, DC, 1994.
3. a) B. Liu, Y. Fan, Y. Gao, C. Sun, C. Xu, & J. Zhu, "Rhodium (III)-catalyzed N-nitroso-directed C–H olefination of arenes. High-yield, versatile coupling under mild conditions," *Journal of the American Chemical Society*, **135**(2013) 468-473; b) J. Chen, P. Chen, C. Song, J. Zhu , "Rhodium (III)-Catalyzed N-Nitroso-Directed C- H Addition to Ethyl 2-Oxoacetate for Cycloaddition/Fragmentation Synthesis of Indazoles," *Chemistry–A European Journal*, **20**(2014) 14245-14249; c) Y. Wu, L. J. Feng, X. Lu, F. Y. Kwong, H. B. Luo, "Palladium-catalyzed oxidative C–H bond acylation of N-nitrosoanilines with toluene derivatives: a traceless approach to synthesize N-alkyl-2-aminobenzophenones," *Chemical Communications*, **50**(2014) 15352-15354; d) F. Xie, Z. S. Qi, S. J. Yu, X. W. Li, "Rh (III)-and Ir (III)-catalyzed C–H alkynylation of arenes under chelation assistance," *Journal of the American Chemical Society*, **136**(2014) 4780-4787; e) S. Yu, X. Li, "Rhodium (III)-catalyzed C–C coupling of arenes with 2-vinyloxiranes: synthesis of allylic alcohols," *Organic letters*, **16**(2014) 1200-1203; f) D. D. Li, Y. X. Cao, G. W. Wang, "Palladium-catalyzed ortho-acyloxylation of N-nitrosoanilines via direct sp2 C–H bond activation," *Organic & Biomolecular Chemistry*, **13**(2015) 6958-6964.
4. S. Azeez, P. Chaudhary, P. Sureshbabu, S. Sabiah, J. Kandasamy, "Potassium Persulfate-Promoted N-Nitrosation of Secondary and Tertiary Amines with Nitromethane under Mild Conditions," *Asian Journal of Organic Chemistry*, **7**(2018) 2113-2119.
5. P. F. Yuan, T. Huang, J. He, X. T. Huang, X. L. Jin, C. Sun, L. Z. Wu, Q. Liu, "Controllable Z/E-selective synthesis of α-amino-ketoximes from N-nitrososulfonamides and aryl alkenes under neutral conditions," *Organic Chemistry Frontiers*, **8**(2021) 5785-5792.
6. Y. Wang, Y. Wu, Y. Li and Y. Tang, "Denitrogenative Suzuki and carbonylative Suzuki coupling reactions of benzotriazoles with boronic acids," *Chemical science*, **8**(2017) 3852-3857.
7. (a) J. Fu, Y. Yang, X. W. Zhang, W. J. Mao, Z. M. Zhang, H. L. Zhu, "Discovery of 1H-benzo [d][1, 2, 3] triazol-1-yl 3, 4, 5-trimethoxybenzoate as a potential

antiproliferative agent by inhibiting histone deacetylase," *Bioorganic & medicinal chemistry*, **18**(2010) 8457-8462. (b) Y. Luo, Z.-J. Liu, G. Chen, J. Shi, J.-R. Li and H.-L. Zhu, "1, 3, 4-Oxadiazole derivatives as potential antitumor agents: discovery, optimization and biological activity valuation," *MedChemComm*, **7**(2016) 263-271. (c) S. L. Yedage, B. M. Bhanage, "tert-Butyl nitrite-mediated synthesis of N-nitrosoamides, carboxylic acids, benzocoumarins, and isocoumarins from amides," *The Journal of Organic Chemistry*, **82**(217), 5769-5781.

8. a) M. A. Zolfigol, F. Shirini, A. G. Choghamarani, A. Taqian Nasab, H. Keypour, S. Salehzadeh, "Chemoselective N-nitrosation of secondary amines under mild and heterogeneous conditions via in situ generation of NOCl," *Journal of Chemical Research*, **9**(2000) 420-422. b) E. H. White, "The chemistry of the N-alkyl-N-nitrosoamides. I. Methods of preparation," *Journal of the American Chemical Society*, **77**(1955), 6008-6010; c) B. C. Challis, S. A. Kyrtopoulos, "The chemistry of nitroso-compounds. Part 11. Nitrosation of amines by the two-phase interaction of amines in solution with gaseous oxides of nitrogen," *Journal of the Chemical Society, Perkin Transactions,* **1**(1979) 299-304.
9. J. D. Galloway, C. Sarabia, J. C. Fettinger, H. P. Hratchian, R. D. Baxter, "Versatile New Reagent for Nitrosation under Mild Conditions," *Organic Letters*, **23**(2021) 3253-3258.
10. (a) P. Chaudhary, S. Gupta, N. Muniyappan, S. Sabiah, J. Kandasamy, "An efficient synthesis of N-nitrosamines under solvent, metal and acid free conditions using tert-butyl nitrite," *Green Chemistry*, **18**(2016), 2323-2330; (b) P. Chaudhary, S. Gupta, P. Sureshbabu, S. Sabiah and J. Kandasamy, "A metal free reduction of aryl-N-nitrosamines to the corresponding hydrazines using a sustainable reductant thiourea dioxide," *Green Chemistry*, **18**(2016), 6215-6221; (c) P. Chaudhary, R. Korde, S. Gupta, P. Sureshbabu, S. Sabiah, J. Kandasamy, "An Efficient Metal-Free Method for the Denitrosation of Aryl N-Nitrosamines at Room Temperature," *Advanced Synthesis & Catalysis*, **360**(2018) 556-561; (d) S. Chauhan, P. Chaudhary, A. K. Singh, P. Verma, S. Vandana and J. Kandasamy, "tert-Butyl nitrite induced radical dimerization of primary thioamides and selenoamides at room temperature, *Tetrahedron letters*, **59**(2018) 272-276.
11. (a) R. N. Loeppky, C. J. Michejda, "Nitrosamines and Related N-Nitroso Compounds: Chemistry and Biochemistry, American Chemical Society," Washington, DC, 1994; (b) R. L. Hinmap and K. L. Hamm, "Synthesis of Some 1, 1-Dibenzylhydrazines1," *The Journal of Organic Chemistry*, **23**(1958), 529-531.; (c) D. Seebach and D. Enders, "Umpolung of amine reactivity. Nucleophilic α-(secondary amino)-alkylation via metalated nitrosamines," *Angewandte Chemie International Edition in English*, **14(**1975), 15-32; (d) B. Liu, Y. Fan, Y. Gao, C.

Sun, C. Xu, J. Zhu, "Rhodium (III)-catalyzed N-nitroso-directed C–H olefination of arenes. High-yield, versatile coupling under mild conditions," *Journal of the American Chemical Society*, **135**(2013), 468-473; (e) J. W. Dong, Z. J. Wu, Z. Y. Liu, P. Liu, P. P. Sun, "Rhodium (III)-Catalyzed Direct Cyanation of Aromatic C–H Bond to Form 2-(Alkylamino) benzonitriles Using N-Nitroso as Directing Group," *The Journal of Organic Chemistry*, **80**(2015), 12588-12593.

12. (a) R. W. Darbeau and E. H. White, "A Study of N-Nitrosoamide-Mediated Friedel− Crafts Type Benzylation of Benzene− Toluene and Benzene− Anisole," *The Journal of Organic Chemistry*, **65**(2000), 1121-1131; (b) R. W. Darbeau, N. Alvarez, R. N. Aymond, "N-nitrosoamide-mediated N→O nitroso transfer to alcohols with subsequent denitroxylation," *The Journal of Organic Chemistry*, **70**(2005), 3225-3230; (c) J. R. Hwu, J. J. T. Huang, F. Y. Tsai, S. C. Tsay, M. H. Hsu, K. C. Hwang, J. C. Horng, J. A. A. Ho, C. C. Lin, Photochemical Activities of N-Nitroso Carboxamides and Sulfoximides and Their Application to DNA Cleavage," *Chemistry–A European Journal*, **15**(2009), 8742-8750; (d) E. H. White, R. W. Darbeau, Y. L. Chen, S. Chen, D. Chen, "A New Look at the Friedel− Crafts Alkylation Reaction," *The Journal of Organic Chemistry*, **61**(1996), 7986-7987; (e) J. Garcia and J. Vilarrasa, "New synthetic "tricks" using old reagents. A mild method for the conversion of RCONHR′ to RCONHR," *Tetrahedron Letters*, **23**(1982) 1127-1128; (f) J. Garcia, J. Gonzalez, R. Segura, F. Urpi and J. Vilarrasa, "Reaction of N-Nitroso-and N-Nitro-N-alkylamides with Amines," *The Journal of Organic Chemistry*, **49**(1984) 3322-3327; (g) D. T. Glatzhofer, R. R. Roy and K. N. Cossey, "Conversion of N-aromatic amides to O-aromatic esters," *Organic Letters*, **4**(2002) 2349-2352; (h) W. R. Li, "Synthesis of Amides with Retention of the Functional Group," *Science of Synthesis*, **21**(2005) 179–257.
13. (a) P. Chaudhary, S. Gupta, N. Muniyappan, S. Sabiah, & J. Kandasamy, "An efficient synthesis of N-nitrosamines under solvent, metal and acid free conditions using tert-butyl nitrite," *Green Chemistry*, **18**(2016) 2323-2330; (b) S. Chauhan, P. Chaudhary, A. K. Singh, P. Verma, V. Srivastava, J. Kandasamy, "tert-Butyl nitrite induced radical dimerization of primary thioamides and selenoamides at room temperature," *Tetrahedron letters*, **59**(2018), 272-276; (c) P. Sureshbabu, S. Azeez, P. Chaudhary, J. Kandasamy, "tert-Butyl nitrite promoted transamidation of secondary amides under metal and catalyst free conditions," *Organic & Biomolecular Chemistry*, *17*(4), 845-850," *Organic & Biomolecular Chemistry*, **17**(2019) 845-850; (d) P. Chaudhary, S. Gupta, N. Muniyappan, S. Sabiah, J. Kandasamy, "Regioselective nitration of N-alkyl anilines using tert-butyl nitrite under mild condition," *The Journal of Organic Chemistry*, **84**(2018) 104-119.

14. S. Azeez, P. Chaudhary, P. Sureshbabu, S. Sabiah, J. Kandasamy, "tert-Butyl nitrite mediated nitrogen transfer reactions: synthesis of benzotriazoles and azides at room temperature," *Organic & Biomolecular Chemistry*, **16**(2018) 8280-8285.
15. A. Dahiya, A. K. Sahoo, T. Alam, B. K. Patel, "tert-Butyl Nitrite (TBN), a Multitasking Reagent in Organic Synthesis," *Chemistry–An Asian Journal*, **14**(2019) 4454-4492.
16. R. López-Rodríguez, J. A. McManus, N. S. Murphy, M. A. Ott, M. J. Burns, "Pathways for N-nitroso compound formation: secondary amines and beyond," *Organic Process Research & Development*, **24**(2020) 1558-1585.
17. P. Chaudhary, J. Kandasamy, A. P. G. Macabeo, R. J. I. Tamargo, Y. R. Lee, Recent Advances and Strategies for the Transition-Metal-Catalyzed C− H Functionalization of N-Nitrosoanilines," *Advanced Synthesis & Catalysis*, **363**(2021) 2037-2060.
18. W. Wei, C. Liu, D. Yang, J. Wen, J. You, H. Wang, "Metal-Free Direct Construction of Sulfonamides via Iodine-Mediated Coupling Reaction of Sodium Sulfinates and Amines at Room Temperature," *Advanced Synthesis & Catalysis*, **357**(2015) 987-992.