CHAPTER-2

Potassium Persulfate-Promoted *N*-Nitrosation of Secondary and Tertiary Amines with Nitromethane under Mild Conditions

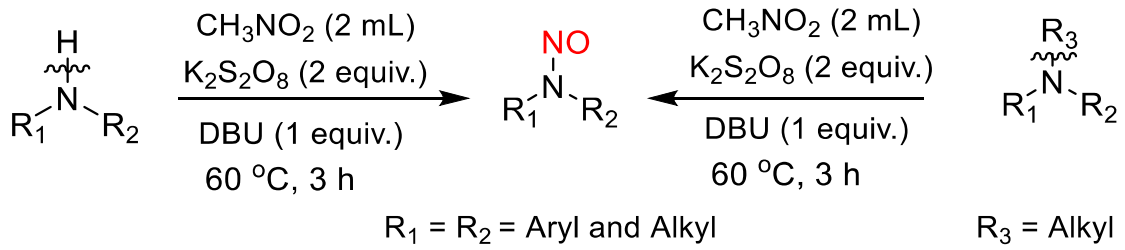
2.1 Introduction

N-Nitrosamines are versatile class of organic compounds that received continuous interest in biochemical research due to their unique carcinogenic and mutagenic properties [1, 2]. On the other hand, *N*-nitrosamines play an important role in organic synthesis as starting materials [3, 4], masking groups [5, 6], directing groups [7-13], etc. For example, synthesis of hydrazines, nitramines and sydnones were typically achieved from corresponding *N*-nitrosamines [3, 4, 14, 15]. In addition, recently *N*-nitroso functionality has been emerged as a traceless directing group for various metal catalyzed aryl C–H functionalization reactions [7-13].

The classical method of *N*-nitrosamine preparation involves the reaction of secondary amine with nitrous acid generated in situ by treating sodium nitrite with mineral acids [16]. Besides, a few other reagents such as nitrosonium tetrafluoroborate ($NOBF_4$) [17], nitrosyl chloride (NOCl) [18], nitrogen oxides (N_2O_3 or N_2O_4) [19-20] and Fremy's salt [21] were also employed. The major limitations of these reagents are the use of strong acidic medium, reagents that are difficult to handle and store, harsh reaction conditions, etc. In the last few years, our research group has focused on the chemistry of *N*-nitrosamines [22-24] and recently demonstrated *N*-nitrosation of various aryl, alkyl and benzylic secondary amines using *tert*-butyl nitrite under solvent free conditions [22].

Recently, nitromethane mediated *N*-nitrosation of secondary and tertiary amines in the presence of oxidizing agents such as IBX/TBAF [25], KI/TBHP [26] and $Cu(OTf)_2$/DBU/O_2 [27] have been demonstrated. In synthetic perspective, this

alternative approach is very interesting, because nitromethane is inexpensive and less toxic reagent widely used as a solvent in many organic transformations. However, the use of expensive oxidants, limited substrate scope, requirement of longer reaction time [27] and poor yields [25-27] make these protocols less attractive in organic synthesis. Therefore, identification of a suitable oxidant for the nitromethane mediated *N*-nitrosation of secondary and tertiary amines, is of great interest.



Scheme 2.1 Synthesis of *N*-nitrosamines from secondary as well as *tert*-amines

Potassium persulfate ($K_2S_2O_8$) is one of the most commonly used oxidants that enable many organic transformations under mild conditions [28]. Recently, potassium persulfate promoted direct C–H azidation of alkanes [29-30], carbonitration of alkenes [31], C–H oxidation of protonated aliphatic amines [32], oxidative coupling of sulfoximines with quinoxalinones [33], etc. were demonstrated [34-39]. The advantages of $K_2S_2O_8$ are (i) a stable crystalline material which is easy to handle and store, (ii) inexpensive and (iii) commercially available, hence, received a considerable interest in organic synthesis. In continuation to our previous work on *N*-nitrosamine chemistry, here we disclose iodine and metal-free route for the activation of nitromethane and subsequent *N*-nitrosation of secondary and tertiary amines in the presence of potassium persulfate and DBU under mild condition (Scheme 2.1).

2.2 Results and discussion

2.2.1 Optimization for *N*-nitrosation under different reaction conditions

At the outset, dihexylamine was chosen as a model substrate for the optimization study and subjected for *N*-nitrosation in the presence of $K_2S_2O_8$ in nitromethane under different reaction conditions (Table 2.1). Initially, the reaction was tested with $K_2S_2O_8$ alone with nitromethane as a solvent at room temperature (Table 2.1, entry 1). However, the desired product i.e. *N*-nitroso dihexylamine, was not observed even after 12 h. Therefore, the reaction was further investigated in the presence of different organic and inorganic bases including Et_3N, $Et(i\text{-}Pr)_2N$, K_2CO_3, KOH, CsF, 1,8–Diazabicyclo(5.4.0)undec-7-ene (DBU) and 1,4-diazabicyclo [2.2.2]octane (DABCO) (Table 2.1, entries 2–8).

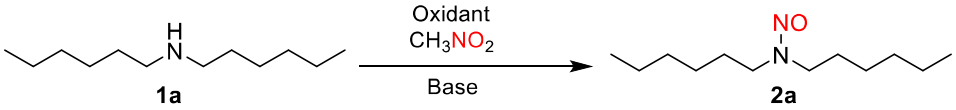
Among them, the bicyclic bases DBU and DABCO gave the desired product in 24% and 14% yield, respectively (Table 2.1, entries 7 and 8) while other bases failed to provide the desired product. Encouraged by the results, the *N*-nitrosation was further attempted in elevated temperature, i.e. 40–80 °C, in the presence of $K_2S_2O_8$ and DBU in nitromethane (Table 2.1, entries 9–11). From this investigation, it was identified that 60 °C would be optimum for the activation of nitromethane which provides *N*-nitroso dihexylamine in 80% yield within 3 h (Table 2.1, entry 10). In fact, no much difference was observed in the yield when the reaction was performed at 80 °C. Further, it was noticed that the reaction without DBU (i.e. only with $K_2S_2O_8$) gave the desired product in 15% yield at 60 °C, while in the absence of oxidant (i.e. only with DBU) no reaction underwent (Table 2.1, entries 12 and 13). Further to understand the credential of $K_2S_2O_8$, the *N*-nitrosation reaction was screened with different commonly used oxidants

in the presence of DBU (Table 2.1, entries 14–22). It is noteworthy that the other sulphur containing oxidants such as ammonium persulfate and oxone gave the desired product in low yields (i.e. 17–43%) when compared to potassium persulfate (Table 2.1, entries 14 and 15).

Further, we have tested the *N*-nitrosation with peracids such as *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl hydroperoxide (DTBP) and *meta*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of DBU (Table 2.1, entries 16–18). Surprisingly, the desired product was not observed with these oxidants. Furthermore, the nitrosation reaction was investigated with different hypervalent iodine reagents such as $PhI(OAc)_2$, 2-Iodoxybenzoic acid (IBX) and $NaIO_4$ (Table 2.1, entries 19–21).

These oxidants offered the desired product only in 32–40% yields. Finally, the reaction was tested with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), which provides the desired product in a negligible yield (Table 2.1, entry 22).

Table 2.1 Optimization for *N*-nitrosation under different reaction conditions



1a **2a**

S.No.	Oxidant	Equiv.	Base	Equiv.	Temp (°C)	Time (h)	Yield (%)[b]
1	$K_2S_2O_8$	2	-	-	rt	12	<5
2	$K_2S_2O_8$	2	Et_3N	1	rt	12	<5
3	$K_2S_2O_8$	2	Et(*i*-Pr)$_2$N	1	rt	12	<10
4	$K_2S_2O_8$	2	K_2CO_3	1	rt	12	<5
5	$K_2S_2O_8$	2	KOH	1	rt	12	nr
6	$K_2S_2O_8$	2	CsF	1	rt	12	<5
7	$K_2S_2O_8$	2	DBU	1	rt	12	24
8	$K_2S_2O_8$	2	DABCO	1	rt	12	14
9	$K_2S_2O_8$	2	DBU	1	40	6	58
10	**$K_2S_2O_8$**	**2**	**DBU**	**1**	**60**	**3**	**80**
11	$K_2S_2O_8$	2	DBU	1	80	3	78
12	$K_2S_2O_8$	2	-	-	60	3	15
13	-	-	DBU	1	60	3	nr
14	$(NH_4)S_2O_8$	2	DBU	1	60	3	43
15	Oxone	2	DBU	1	60	3	17
16	TBHP	2	DBU	1	60	3	nr
17	DTBP	2	DBU	1	60	3	nr
18	*m*-CPBA	2	DBU	1	60	3	nr
19	$PhI(OAc)_2$	2	DBU	1	60	3	39
20	IBX	2	DBU	1	60	3	40
21	$NaIO_4$	2	DBU	1	60	3	32
22	DDQ	2	DBU	1	60	3	<10

[a]Reaction conditions: Substrate (1 mmol), CH_3NO_2 (2 mL), DBU (1 mmol), Oxidant (2 mmol) at 60 °C. [b]Isolated yields.

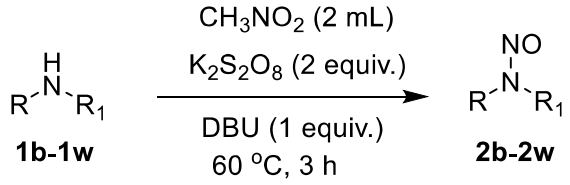
2.2.2 Substrate scope

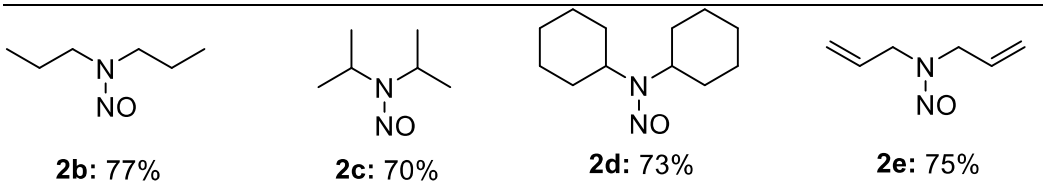
With optimized conditions in hand (Table 2.1, entry 10), the scope of the methodology was investigated with different secondary amines. Initially, different dialkyl amines such as dipropyl, diisopropyl and dicyclohexyl amines were subjected to *N*-nitrosation under optimized conditions. These reactions provided the corresponding *N*-nitrosamines 2b–2d in 70–77% yields. To our delight, similar to dialkyl amines, diallylamine also underwent *N*-nitrosation smoothly with 75% of the desired product 2e, while the double bonds were remained intact. Furthermore, the *N*-nitrosation of different cyclic secondary amines such as morpholine, pyrrolidine, piperidine, 1,2,3,4-tetrahydroisoquinoline was performed and obtained the desired products 2f–2i in 62–78% yields.

Likewise, *N*-nitrosation of *N*-methyl piperazine and *N*-diphenylmethyl piperazine was successfully accomplished in good yields (Table 2.2, 2j and 2k). This protocol is also found suitable for the *N*-nitrosation of diamine such as unprotected piperazine, which gave the dinitroso piperazine (2l) in 60% yield.

Further, we have investigated nitrosation of symmetrical and unsymmetrical dibenzyl amines as well as *N*-alkyl *N*-benzylamines under optimized conditions. Interestingly, the reactions were preceded with similar efficiency to that of dialkyl amines while the desired products 2m–2r were obtained in 69–75% yield. Having studied the nitrosation of dialkyl and benzyl amines, different *N*-aryl amines were subjected for *N*-nitrosation reactions (Table 2.3). To our delight, the optimized condition was found to be suitable to the task while *N*-nitroso aryl amines were obtained in 72–85% yield (Table 2.3, 2s–2w).

Table 2.2 *N*-Nitrosation of aliphatic secondary amines



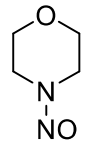


2b: 77%

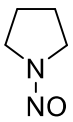
2c: 70%

2d: 73%

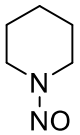
2e: 75%



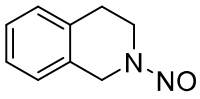
2f: 78%



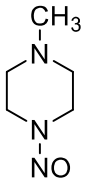
2g: 69%



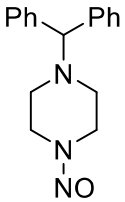
2h: 73%



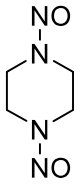
2i: 62%



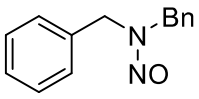
2j: 67%



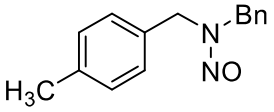
2k: 64%



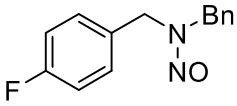
2l: 60%[c]



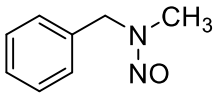
2m: 72%



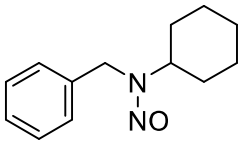
2n: 69%



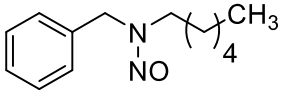
2o: 70%



2p: 75%



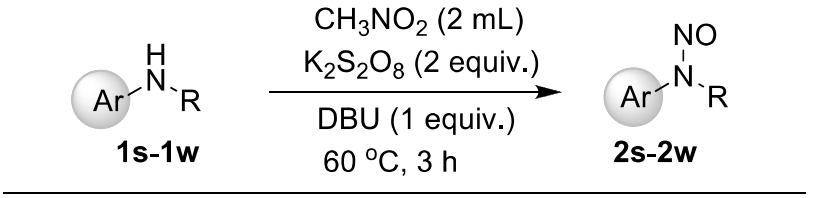
2q: 71%

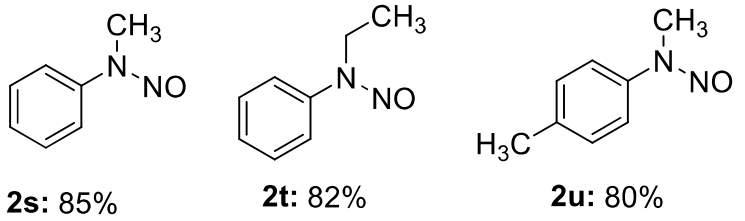


2r: 70%

[a]Reaction conditions: Substrate (1 mmol), CH_3NO_2 (2 mL), DBU (1 mmol), $K_2S_2O_8$ (2 mmol) at 60 °C. [b]Isolated yields. [c]Reaction was carried out with CH_3NO_2 (4 mL), $K_2S_2O_8$ (4 mmol), DBU (2 mmol) and required 6 h for completion of the reaction.

Table 2.3 *N*-Nitrosation of aromatic secondary amines





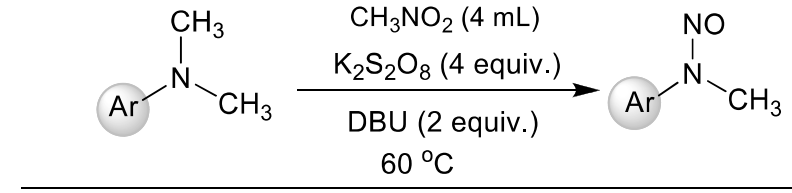
2s: 85% **2t:** 82% **2u:** 80%

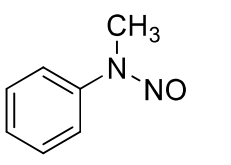
2v: 82% **2w:** 72%

[a]Reaction conditions: Substrate (1 mmol), CH_3NO_2 (2 mL), DBU (1 mmol), $K_2S_2O_8$ (2 mmol) at 60 °C. [b]Isolated yields.

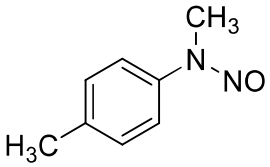
The optimized protocol was further applied for the dealkylative *N*-nitrosation of various *N,N*-dimethyl anilines (Table 2.4). Reactions were performed using 4 equiv. of oxidant and 2.0 equiv. base in nitromethane. To our delight, the desired *N*-nitrosated products were obtained in good yields within 3 h (Table 2.4, 2s, 2u and 4a–4c). Likewise, a dealkylative *N*-nitrosation of trialkylamines such as trihexylamine and tribenzylamine gave the desired products 2a and 2m in 74% and 62%, respectively (Table 2.5).

Table 2.4 *N*-Nitrosation of aromatic tertiary amines

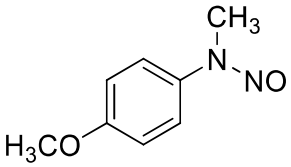




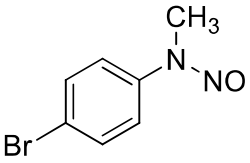
2s
(2 h, 70%)



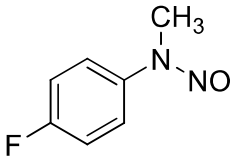
2u
(2 h, 72%)



4a
(2 h, 75%)



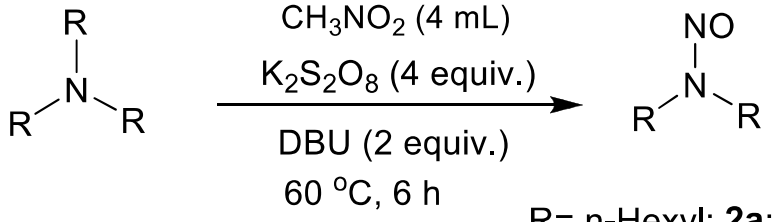
4b
(3 h, 65%)



4c
(3 h, 62%)

[a]Reaction conditions: Substrate (1 mmol), CH_3NO_2 (4 mL), DBU (2 mmol), $K_2S_2O_8$ (4 mmol) at 60 °C. [b]Isolated yields.

Table 2.5 *N*-Nitrosation of aliphatic tertiary amines

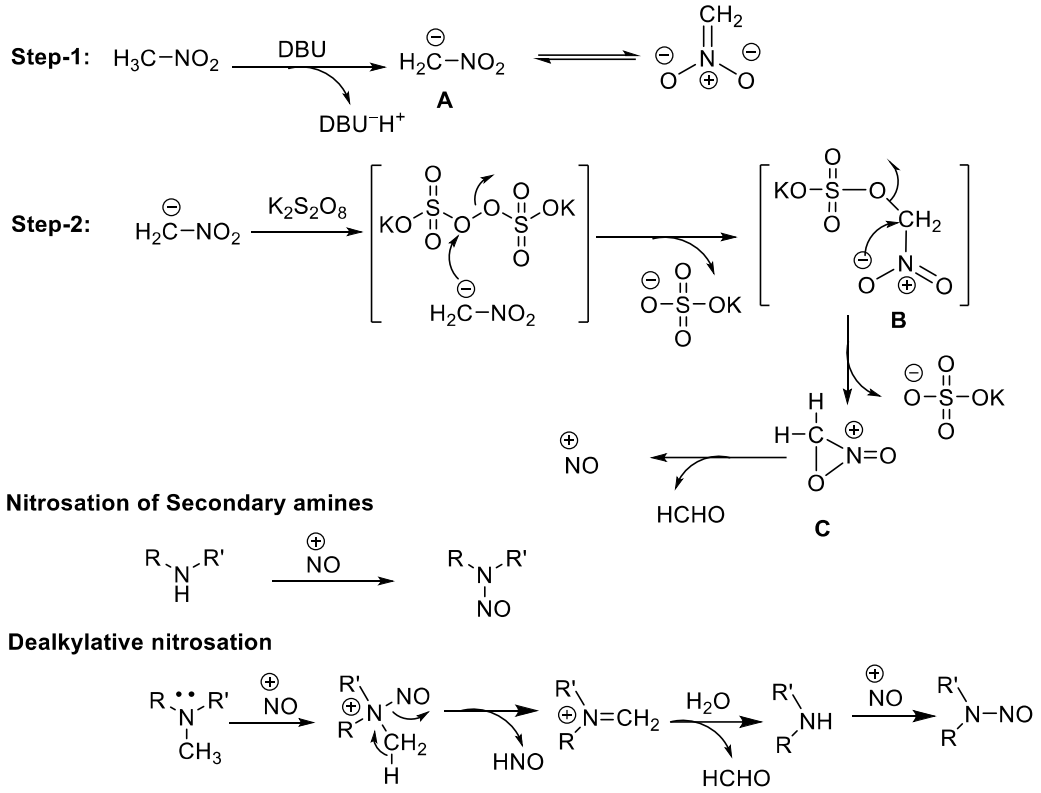


R= n-Hexyl: **2a**: 74%

R = Benzyl: **2m**: 62%

[a]Reaction conditions: Substrate (1 mmol), CH_3NO_2 (4 mL), DBU (2 mmol), $K_2S_2O_8$ (4 mmol) at 60 °C. [b]Isolated yields.

2.3 Plausible mechanism



Scheme 2.2 Proposed mechanism for *N*-nitrosation reaction

A plausible mechanism for the *N*-nitrosation of secondary amines with $K_2S_2O_8$ /DBU/CH_3NO_2 is depicted in Scheme 2.2. The base DBU abstracts a proton from nitromethane resulting into the formation of carbanion A in Step 1 [27]. Simultaneously, carbanion reacts with potassium persulfate and provides the intermediate B which leads to the formation unstable 2-oxo1,2-oxaziridin-2-ium (C) [Step 2] [26]. Later, the cyclic compound C undergoes decomposition into formaldehyde and nitrosonium ion (NO^+). Finally, the reaction of secondary amine with NO^+ yields the desired product. In the case of *tert*-amines, nitrosative dealkylation would take place in the first step [40] after which the resulted secondary amines undergo *N*-nitrosation.

2.4 Conclusion

In conclusion, we have demonstrated a simple and efficient route for the activation of nitromethane followed by *N*-nitrosation of various aryl and alkyl secondary amines in the presence of oxidant $K_2S_2O_8$ and the base DBU. The reactions proceed under mild condition and provide the desired products in good to excellent yields. Furthermore, a dealkylative *N*-nitrosation of *tert*-amines was successfully achieved under optimized condition. Broad substrate scope, simple reagents and efficient conversion make the current protocol attractive in organic synthesis, which will be an efficient alternative to the existing protocols.

2.5 Experimental section

2.5.1 Experimental procedure for the *N*-nitrosation of secondary amines

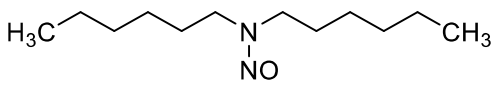
Potassium persulfate (2 mmol, 540 mg), nitromethane (2 mL) and DBU (1 mmol, 151 μL) were taken in a round bottom flask and allowed to stir for 10 minutes at room temperature. After that, secondary amine (1 mmol) was added to the reaction mixture and placed in pre-heated oil-bath at 60 °C. After completion, the reaction mixture was allowed to cool to room temperature and concentrated using rota-evaporator. Further, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulphate, concentrated and purified through column chromatography (SiO2: ethyl acetate/hexane) to obtain the corresponding *N*-nitrosamines.

2.5.2 Experimental procedure for the dealkylative *N*-nitrosation of *tert*-amines

Potassium persulfate (4 mmol, 1 g), nitromethane (4 mL) and DBU (2 mmol, 300 μL) were taken in a round bottom flask and allowed to stir for 10 minutes at room temperature. After that, tertiary amine (1 mmol) was added to the reaction mixture and placed in pre-heated oil-bath at 60 °C. After completion, the reaction mixture was allowed to cool to room temperature and concentrated using rota-evaporator. Further, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulphate, concentrated and purified through column chromatography (SiO2: ethyl acetate/hexane) to obtain the corresponding *N*-nitrosamines.

2.6 Analytical data for *N*-nitrosamines

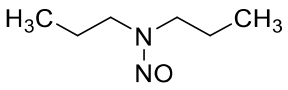
[2.6.1] *N*-Nitroso dihexylamine (2a)



2a

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 95:5, R_f= 0.66; Yield: 80%, (171 mg). IR (ν cm^{-1}): 2950, 2850, 1440, 1350, 1100.^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.02 (t, J = 7.3 Hz, 2H), 3.48 (t, J = 7.3 Hz, 2H), 1.71–1.66 (m, 2H), 1.45–1.42 (m, 2H), 1.28–1.21 (m, 12H), 0.86–0.82 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 52.1, 43.5, 31.2, 31.1, 29.5, 28.1, 26.7, 26.0, 25.8, 22.3, 22.3, 13.8. HRMS: Calc. for $C_{12}H_{27}N_2O$ $[M+H]^+$: 215.2123, Obser.: 215.2121.

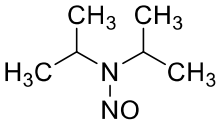
[2.6.2] *N*-Nitroso di-*n*-propylamine (2b)



2b

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.50; Yield: 77% (100 mg); IR (ν cm^{-1}): 2950, 2850, 1450, 1350, 1090. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.99 (t, J = 7.2 Hz, 2H), 3.45(t, J = 7.2 Hz, 2H), 1.76–1.69 (m, 2H), 1.50–1.42 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 53.7, 45.0, 21.5, 19.3, 11.4, 10.8. HRMS: Calc. for $C_6H_{15}N_2O$ $[M+H]^+$: 131.1184, Obser.: 131.1181.

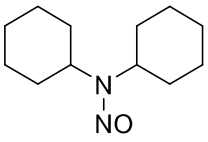
[2.6.3] *N*-Nitroso di-*iso*-propylamine (2c)



2c

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.45; Yield: 70% (91 mg); IR (ν cm^{-1}): 2950, 2850, 1450, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.01 (dt, J = 13.6, 6.8 Hz, 1H), 4.23 (dt, J = 13.4, 6.7 Hz, 1H), 1.48 (d, J = 6.8 Hz, 6H), 1.14 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 50.3, 44.3, 23.5, 18.9. HRMS: Calc. for $C_6H_{15}N_2O$ $[M+H]^+$: 131.1184, Obser.: 131.1183.

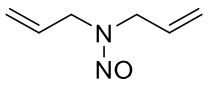
[2.6.4] *N*-Nitroso dicyclohexylamine (2d)



2d

The title compound was obtained as off white crystals. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 95:5, R_f= 0.60; Yield: 73% (153 mg); M.P = 94–96 °C. IR (ν cm$^{-1)}$: 2950, 2850, 1450, 1355, 1090. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.87–4.83 (m, 1H), 3.71–3.67 (m, 1H), 1.90 (dd, J = 24.8, 12.1 Hz, 6H), 1.77 (d, J = 13.0 Hz, 2H), 1.68 (dd, J = 18.1, 16.3 Hz, 2H), 1.57 (d, J = 11.5 Hz, 2H), 1.43–1.31 (m, 6H), 1.23 (dd, J = 7.1, 5.5 Hz, 1H), 1.13 (d, J = 12.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 58.4, 52.0, 34.2, 29.2, 26.0, 25.4, 25.2, 25.1. HRMS: Calc. for $C_{12}H_{23}N_2O$ $[M+H]^+$: 211.1810, Obser.: 211.1790.

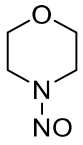
[2.6.5] *N*-Nitroso di-allylamine (2e)



2e

The title compound was obtained as light brown oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.45; Yield: 75% (95 mg); IR (ν cm^{-1}): 2950, 2850, 1637, 1572, 1420, 1090. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.91–5.83 (m, 1H), 5.62–5.54 (m, 1H), 5.31–5.27 (m, 2H), 5.16 (d, J = 10.2 Hz, 1H), 5.07 (d, J = 17.1 Hz, 1H), 4.69 (d, J = 6.1 Hz, 2H), 4.14 (d, J = 5.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 131.7, 129.1, 120.0, 119.0, 54.0, 45.0. HRMS: Calc. for $C_6H_{11}N_2O$ $[M+H]^+$: 127.0871 Obser.: 127.0851.

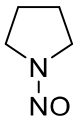
[2.6.6] *N*-Nitrosomorpholine (2f)



2f

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.50; Yield: 78% (90 mg); IR (ν cm^{-1}): 2950, 2850, 1450, 1310, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.25 (t, J = 5.1 Hz, 2H), 3.86–3.80 (m, 4H), 3.62 (t, J = 5.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 67.1, 65.7, 49.8, 40.1. HRMS: Calc. for $C_4H_9N_2O_2$ $[M+H]^+$: 117.0664, Obser.: 117.0658.

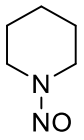
[2.6.7] *N*-Nitrosopyrrolidine (2g)



2g

The title compound was obtained as brown oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 85:15, R_f= 0.40; Yield: 69% (69 mg); IR (ν cm^{-1}): 2950, 2850, 1430, 1310, 1080. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.24 (t, J = 6.6 Hz, 2H), 3.55 (t, J = 6.9 Hz, 2H), 2.01 (dq, J = 27.4, 6.8 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 49.7, 45.1, 23.9, 22.5. HRMS: Calc. for $C_4H_9N_2O$ $[M+H]^+$: 101.0715, Obser.: 101.0712.

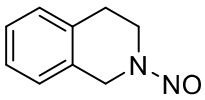
[2.6.8] *N*-Nitrosopiperidine (2h)



2h

The title compound was obtained as yellow solid crystals. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.60; Yield: 73% (83 mg); M.p. = 166–169 °C. IR (ν cm^{-1}): 2950, 2850, 1450, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.15–4.13 (m, 2H), 3.75–3.72 (m, 2H), 1.77–1.72 (m, 4H), 1.54–1.49 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 50.7, 39.6, 26.3, 24.6, 24.0. HRMS: Calc. for $C_5H_{11}N_2O$ $[M+H]^+$: 115.0871, Obser.: 115.0859.

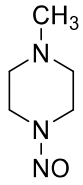
[2.6.9] *N*-Nitroso-1,2,3,4-tetrahydroisoquinoline (2i)



2i

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.50; Yield: 62% (100 mg); (mixture of two isomers in ≈ 2:1 ratio); IR (ν cm^{-1}): 3000, 2850, 1540, 1600, 1450, 1340, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29 (s, 1H), 7.26–7.20 (m, 4H), 7.17 (d, J = 7.1 Hz, 1H), 5.40 (s, 1H), 4.84 (s, 2H), 4.54 (t, J = 5.8 Hz, 2H), 3.88 (t, J = 6.5 Hz, 1H), 3.11 (t, J = 5.8 Hz, 2H), 2.97 (t, J = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 134.9, 133.8, 132.3, 129.9, 128.6, 128.0, 127.9, 127.3, 127.2, 126.1, 126.1, 51.2, 47.7, 44.4, 40.7, 29.7, 27.3. HRMS: Calc. for $C_9H_{11}N_2O$ $[M+H]^+$: 163.0871, Obser.: 163.0866.

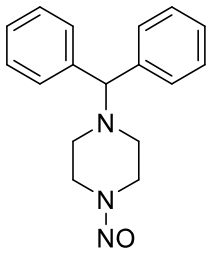
[2.6.10] 1-Methyl-4-nitrosopiperazine (2j)



2j

The title compound was obtained as brown oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 70:30, R_f= 0.30; Yield: 67% (86 mg); IR (ν cm^{-1}): 2950, 2850, 1445, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.26 (t, J = 5.0 Hz, 2H), 3.84 (t, J = 5.0 Hz, 2H), 2.62–2.60 (m, 2H), 2.38–2.35 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.0, 53.5, 49.4, 45.7, 39.2. HRMS: Calc. for $C_5H_{12}N_3O$ $[M+H]^+$: 130.0980, Obser.: 130.0954.

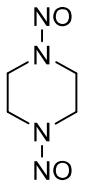
[2.6.11] 1-Benzhydryl-4-nitrosopiperazin (2k)



2k

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.50; Yield: 64% (179 mg); IR (ν cm^{-1}): 2950, 2850, 1520, 1600, 1450, 1340, 1080. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43 (d, J = 7.6 Hz, 4H), 7.31 (t, J = 7.6 Hz, 4H), 7.22 (t, J = 7.3 Hz, 2H), 4.32 (s, 1H), 4.26–4.24 (m, 2H), 3.84–3.82 (m, 2H), 2.63–2.61(m, 2H), 2.40–2.38 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 141.7, 128.7, 127.6, 127.3, 51.8, 50.4, 49.8, 39.7. HRMS: Calc. for $C_{17}H_{20}N_3O$ $[M+H]^+$: 282.1606, Obser.: 282.1607.

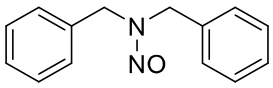
[2.6.12] *N*,*N*-Dinitrosopiperazine (2i)



2l

The title compound was obtained as yellow solid crystals. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 80:20, R_f= 0.30; (mixture of two isomers ≈ 1:1 ratio) Yield: 60% (86 mg); M.p. = 156–160 °C. IR (ν cm^{-1}): 2950, 2850, 1440, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.55 (s, 4H), 4.39 (t, J = 5.6 Hz 4H), 4.04 (t, J = 5.7 Hz 4H), 3.81 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 49.5, 47.0, 40.4, 37.7. HRMS: Calc. for $C_4H_8N_4O_2$ $[M+H]^+$: 145.0726, Obser.: 145.0721.

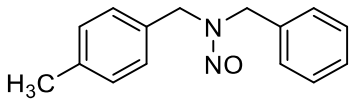
[2.6.13] *N*-Nitroso dibenzylamine (2m)



2m

The title compound was obtained as yellow solid crystals. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.50; Yield: 72 % (162 mg); M.p. = 58–61 °C. IR (ν cm^{-1}): 3100, 2900, 1500, 1600, 1450, 1320, 1100. ^{1}HNMR (500 MHz, $CDCl_3$) δ = 7.41 (d, J = 6.4 Hz, 3H), 7.32 (d, J = 6.4 Hz, 3H), 7.28 (d, J = 6.7 Hz, 2H), 7.08 (d, J = 6.9 Hz, 2H), 5.23 (s, 2H), 4.69 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 134.3, 133.7, 128.9, 128.7, 128.4, 128.3, 128.2, 127.7, 54.8, 44.7. HRMS: Calc. for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1184, Obser.: 227.1163.

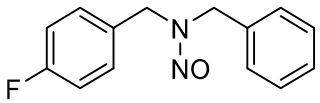
[2.6.14] *N*-(4-Methylbenzyl)-*N*-nitroso benzylamine (2n)



2n

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.50; Yield: 69% (165 mg); (mixture of two isomers in ≈1:1 ratio). IR (ν cm^{-1}): 3050, 2900, 1520, 1600, 1440, 1310, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40 (d, J = 6.5 Hz, 3H), 7.32 (d, J = 6.6 Hz, 3H), 7.27 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 7.15 (dd, J = 12.8, 7.8 Hz, 4H), 7.07 (d, J = 6.6 Hz, 2H), 6.97 (d, J = 7.5 Hz, 2H), 5.20 (s, 2H), 5.18 (s, 2H), 4.67 (s, 2H), 4.64 (s, 2H), 2.39 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.3, 137.6, 134.4, 133.8, 131.2, 130.7, 129.6, 129.4, 128.9, 128.7, 128.4, 128.4, 128.2, 127.7, 54.7, 54.6, 44.6, 44.4, 21.1, 21.0. HRMS: Calc. for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1341, Obser.: 241.1340

[2.6.15] *N*-(4-Fluorobenzyl)-*N*-nitroso benzylamine (2o)

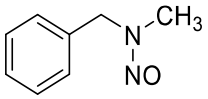


2o

The title compound was obtained as yellow oil, The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 80:20, R_f= 0.40; Yield: 70 % (170 mg); (mixture of two isomers in ≈ 1:1 ratio). IR (ν cm^{-1}): 3050, 2900, 1520, 1600, 1450, 1400, 1350, 1080. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37 (d, J = 5.9 Hz, 3H), 7.29 (d, J = 5.8 Hz, 3H), 7.26–7.19 (m, 4H), 7.07–6.94 (m, 8H), 5.20 (s, 2H),

5.17 (s, 2H), 4.65 (s, 2H), 4.62 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 63.4 (d, J = 62.6 Hz), 161.4 (d, J = 61.9 Hz), 134.2, 133.6, 130.2, 130.2, 130.1, 130.0, 129.9, 129.6, 128.9, 128.7, 128.5, 128.3, 128.2, 127.8, 115.9, 115.8, 115.7, 115.5, 55.0, 54.1, 44.8, 44.2. HRMS: Calc. for $C_{14}H_{14}FN_2O$ $[M+H]^+$: 245.1090, Obser.: 245.1062.

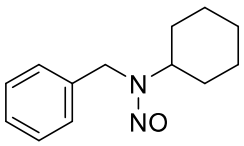
[2.6.16] *N*-Methyl-*N*-nitroso benzylamine (2p)



2p

The title compound was obtained as yellow oil, The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.50; Yield: 75 % (112 mg); (mixture of two isomers in ≈ 1:3 ratio). IR (ν cm^{-1}): 3050, 2900, 1500, 1600, 1450, 1320, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40 (d, J = 7.3 Hz, 3H), 7.34 d, J = 7.5 Hz, 1H), 7.29 (d, J = 6.6 Hz, 3H) 7.15 (d, J = 6.8 Hz, 0.54H), 4.83 (s, 0.60H), 3.71 (s, 1), 2.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 134.4, 133.7, 129.0, 128.8, 128.5, 128.3, 128.0, 127.9, 57.5, 47.7, 38.3, 30.8. HRMS: Calc. for $C_8H_{11}N_2O$ $[M+H]^+$: 151.0871, Obser.: 151.0866.

[2.6.17] *N*-Cyclohexyl-*N*-nitroso benzylamine (2q)

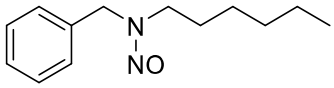


2q

The title compound was obtained as yellow oil, The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.50; Yield: 71% (154 mg); IR (ν cm^{-1}): 3050, 2900, 1520, 1600, 1440, 1350, 1100. ^{1}H NMR (500

MHz, $CDCl_3$) δ = 7.35–7.22 (m, 4H), 7.08 (d, J =7.5 Hz, 2H), 4.79 (s, 2H), 4.17–4.12 (m, 1H), 1.99 (d, J = 12.8 Hz, 2H), 1.86 (d, J = 13.5 Hz, 2H), 1.71 (dd, J = 12.3, 3.4 Hz, 2H), 1.34 (dd, J = 14.6, 11.8 Hz, 2H), 1.25–1.17 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 136.6, 135.0, 128.6, 128.5, 128.0, 127.7, 127.4, 127.3, 62.8, 53.4, 53.01, 45.9, 32.2, 29.4, 25.4, 25.3, 25.2, 25.1. HRMS: Calc. for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1497, Obser.: 219.1497.

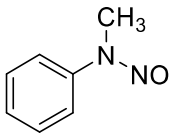
[2.6.18] *N*-Hexyl-*N*- nitroso benzylamine (2r)



2r

The title compound was obtained as pale yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.60; Yield: 70 % (154 mg); (mixture of two isomers in ≈ 1:1 ratio). IR (ν cm^{-1}): 3050, 2900, 1540, 1600, 1440, 1330, 1090. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36 (t, J = 7.9 Hz, 3H), 7.30–7.26 (m, 5H), 7.12 (d, J = 6.8 Hz, 2H), 5.26 (s, 2H), 4.80 (s, 2H), 4.04 (t, J = 7.3 Hz, 2H), 3.44–3.41 (m, 2H), 1.71–1.69 (m, 2H), 1.40–1.34 (m, 2H), 1.31–1.17 (m, 12H), 0.87–0.82 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 134.7, 134.1, 128.9, 128.9, 128.7, 128.7, 128.4,128.4, 128.2, 128.1, 128.1, 127.8, 127.7, 56.0, 51.5, 45.8, 43.0, 31.1, 27.9, 26.6, 26.0, 25.7, 22.4, 22.3, 13.9. HRMS: Calc. for $C_{13}H_{21}N_2O$ $[M+H]^+$: 221.1654, Obser.: 221.1629.

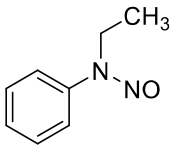
[2.6.19] *N*-Methyl-*N*-nitrosoaniline (2s)



2s

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.66; Yield: 85% (115 mg); IR (ν cm^{-1}): 3050, 2900, 1500, 1600, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.54 (d, J = 7.6 Hz, 2H), 7.48 (t, J = 7.9 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 3.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 142.2, 129.4, 127.2, 119.1, 31.4. HRMS: Calc. for $C_7H_9N_2O$ $[M+H]^+$:137.0715, Obser.: 137.0697.

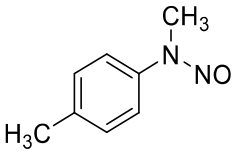
[2.6.20] *N*-Ethyl-*N*-nitrosoaniline (2t)



2t

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 95:5, R_f= 0.70; Yield: 82% (123 mg); IR (ν cm^{-1}): 3050, 2900, 1520, 1600, 1450, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 (d, J = 8.1 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 141.3, 129.4, 127.2, 119.4, 39.1, 11.6. HRMS: Calc. for $C_8H_{11}N_2O$ $[M+H]^+$: 151.0871, Obser.: 151.0841.

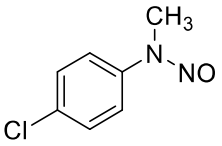
[2.6.21] *N*-Methyl-*N*-nitroso-*N*-(4-methylaniline) (2u)



2u

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 95:5, R_f= 0.66; Yield: 80% (120 mg); IR (ν cm^{-1}): 3050-3100, 2900, 1520, 1600, 1440, 1330, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42 (d, J = 8.4 Hz, 3H), 7.28–7.26 (m, 2H), 3.45 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 139.9, 137.3, 129.9, 119.2, 31.7, 20.9. HRMS: Calc. for $C_8H_{11}N_2O$ $[M+H]^+$: 151.0871, Obser.: 151.0866.

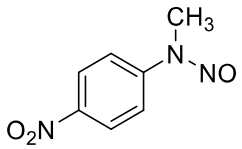
[2.6.22] *N*-Methyl- *N*-nitroso-*N*-(4-chloroaniline) (2v)



2v

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 95:5, R_f= 0.60; Yield: 82% (139 mg); IR (ν cm^{-1}): 3050, 2900, 1540, 1600, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 3.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 140.8, 132.8, 129.5, 120.1, 31.2. HRMS: Calc. for $C_7H_8ClN_2O$ $[M+H]^+$: 171.0325, Obser.: 171.0322.

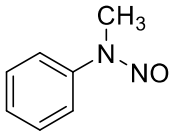
[2.6.23] *N*-Methyl- *N*-nitroso-*N*-(4-nitroaniline) (2w)



2w

The title compound was obtained as yellow solid. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 80:20, R_f= 0.40; Yield: 72% (130 mg); IR (ν cm^{-1}): 3050, 2900, 1500, 1600, 1450, 1320, 1080. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35–8.33 (m, 2H), 7.76–7.74 (m, 2H), 3.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 146.9, 145.8, 125.2, 117.8, 30.0. HRMS: Calc. for $C_7H_8N_3O_3$ $[M+H]^+$: 182.0566, Obser.: 182.0564.

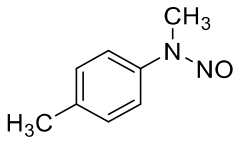
[2.6.24] *N*-Methyl-*N*-nitrosoaniline (2s)



2s

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 95:5, R_f= 0.66; Yield: 70% (95 mg); IR (ν cm^{-1}): 3050, 2900, 1500, 1600, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55–7.53 (m, 2H), 7.49–7.46 (m, 2H), 7.38–7.35 (m, 1H), 3.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 142.2, 129.4, 127.2, 119.1, 31.4. HRMS: Calc. for $C_7H_9N_2O$ $[M+H]^+$: 137.0715, Obser.: 137.0697.

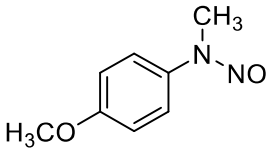
[2.6.25] *N*-Methyl-*N*-nitroso-*N*-(4-methylaniline) (2u)



2u

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 95:5, R_f= 0.66; Yield: 72% (108 mg); IR (ν cm^{-1}): 3050, 2900, 1540, 1600, 1450, 1330, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 3.46 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 139.9, 137.3, 129.9, 119.3, 31.7, 20.9. HRMS: Calc. for $C_8H_{11}N_2O$ $[M+H]^+$: 151.0871, Obser.: 151.0837.

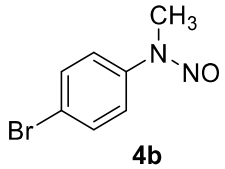
[2.6.26] *N*-Methyl- *N*-nitroso-*N*-(4-methoxyaniline) (4a)



4a

The title compound was obtained as brown oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.50; Yield: 75% (125 mg); IR (ν cm^{-1}): 3050, 2900, 1520, 1600, 1200, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 3.84 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.9, 135.7, 121.1, 114.5, 55.5, 32.1. HRMS: Calc. for $C_8H_{10}N_2NaO_2$ $[M+Na]^+$: 167.0821, Obser.: 167.0817.

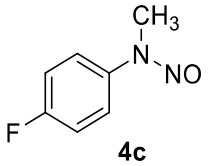
[2.6.27] *N*-Methyl-*N*-nitroso-*N*-(4-bromoaniline) (4b)



4b

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 90:10, R_f= 0.55; Yield: 65% (138 mg); IR (ν cm^{-1}): 3050–3100, 2900, 1520, 1600, 1350, 1080,700. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.60 (dd, J = 5.3, 3.7 Hz, 2H), 7.44 (dd, J = 5.3, 3.7 Hz, 2H), 3.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 141.3, 132.5, 120.6, 120.3, 31.0. HRMS: Calc. for $C_7H_8BrN_2O$ $[M+H]^+$: 214.9820, Obser.: 214.9787.

[2.6.28] *N*-Methyl- *N*-nitroso-*N*-(4-fluoroaniline) (4c)



4c

The title compound was obtained as yellow oil. The residue was purified by column chromatography in silica gel eluting with hexane: EtOAc 95:5, R_f= 0.60; Yield: 62% (95 mg); IR (ν cm^{-1}): 3050, 2900, 1500, 1600, 1400, 1350, 1100. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.50 (dd, J = 6.4, 4.5 Hz, 2H), 7.17 (t, J = 7.7 Hz, 2H), 3.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.6 (d, J = 247.3 Hz), 138.5, 121.1, 121.0, 116.4, 116.2, 31.7. HRMS: Calc. for $C_7H_8FN_2O$ $[M+H]^+$: 155.0621, Obser.: 155.0618.

2.7 Spectral data for few products

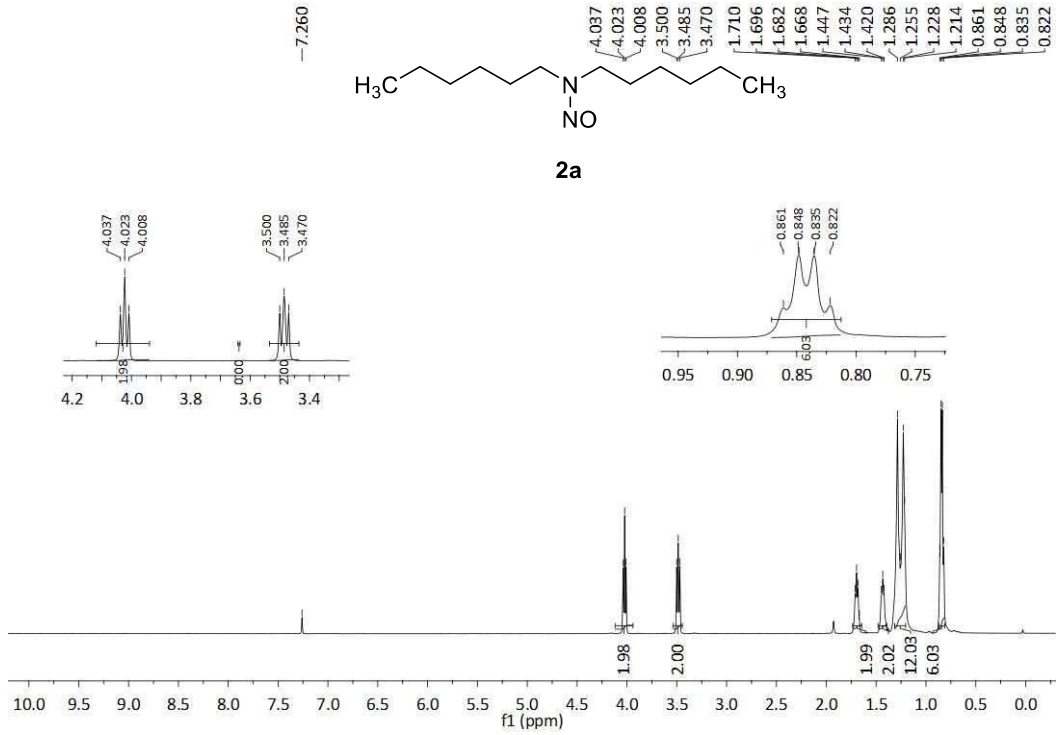


Figure 2.1 ^{1}H NMR of product **2a** in $CDCl_3$

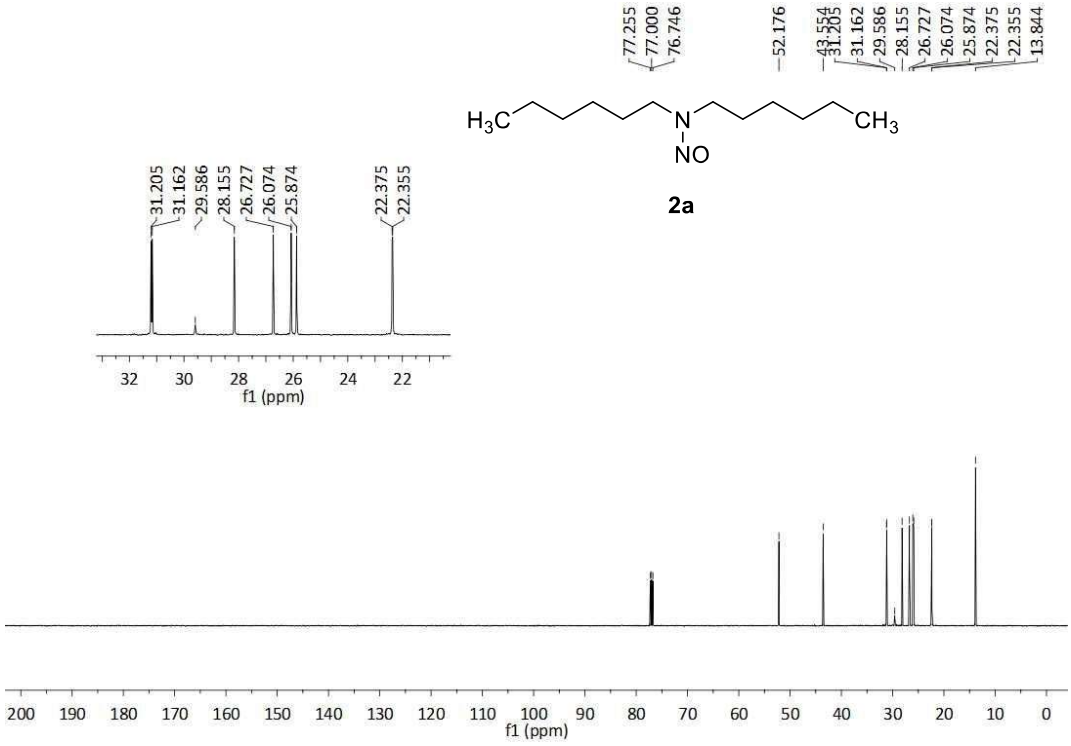


Figure 2.2 ^{13}C NMR of product **2a** in $CDCl_3$

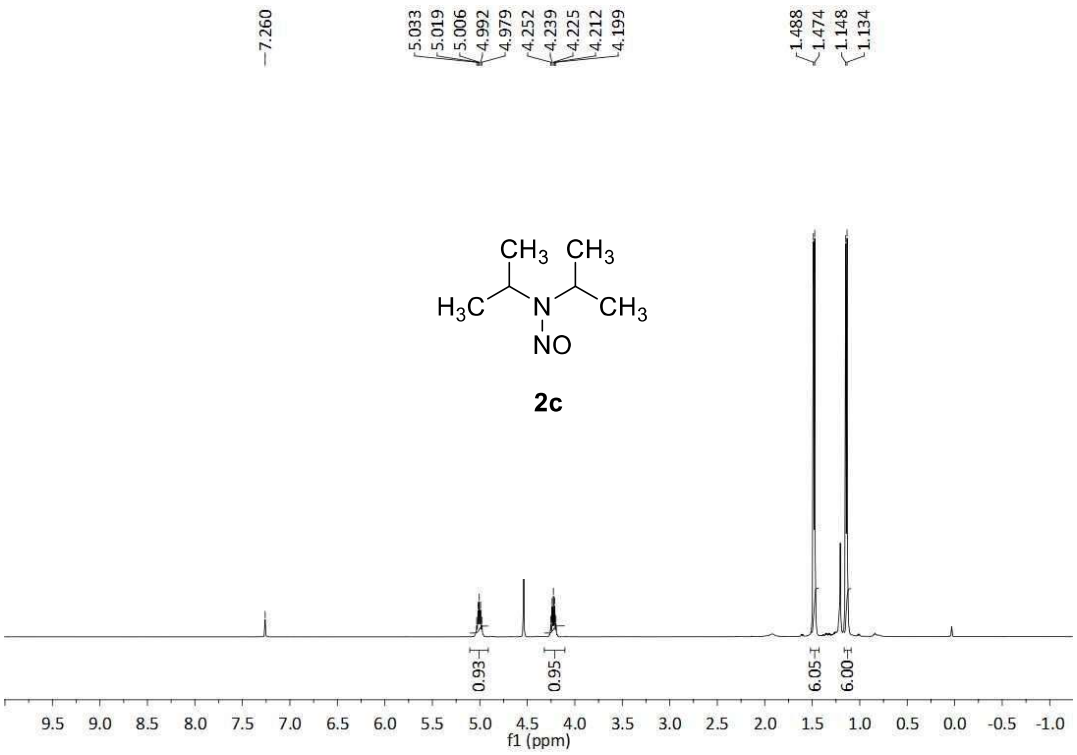


Figure 2.3 ^{1}H NMR of product **2c** in $CDCl_3$

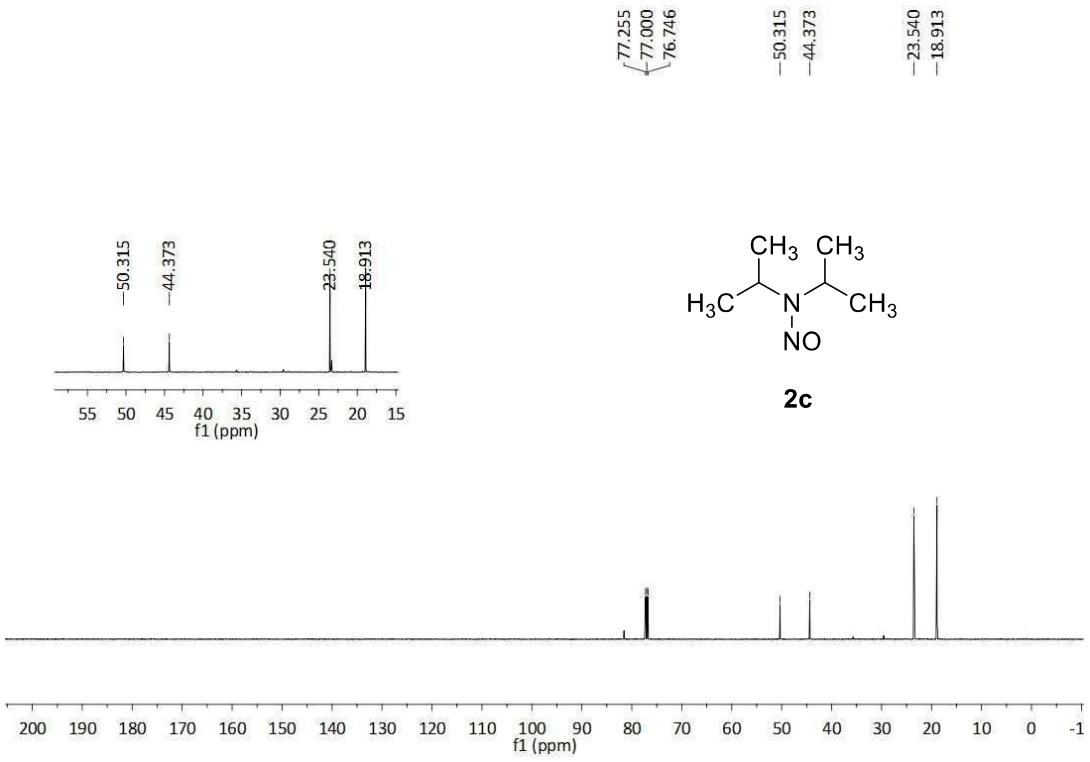


Figure 2.4 ^{13}C NMR of product **2c** in $CDCl_3$

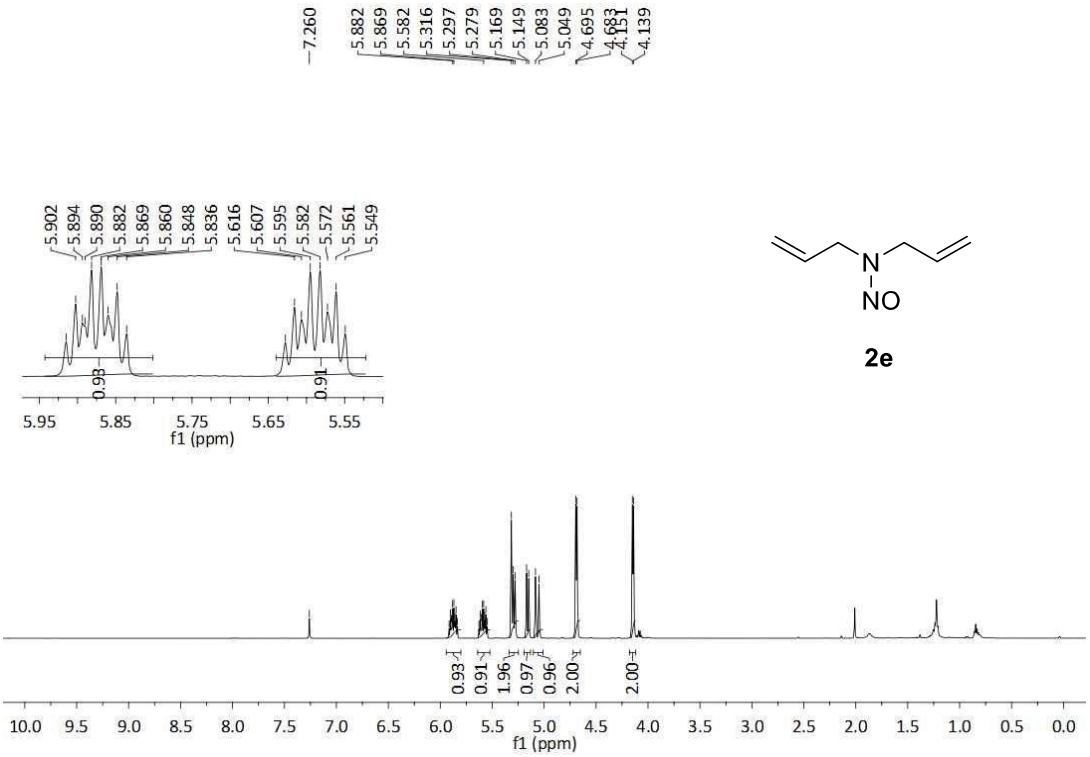


Figure 2.5 ^{1}H NMR of product **2e** in $CDCl_3$

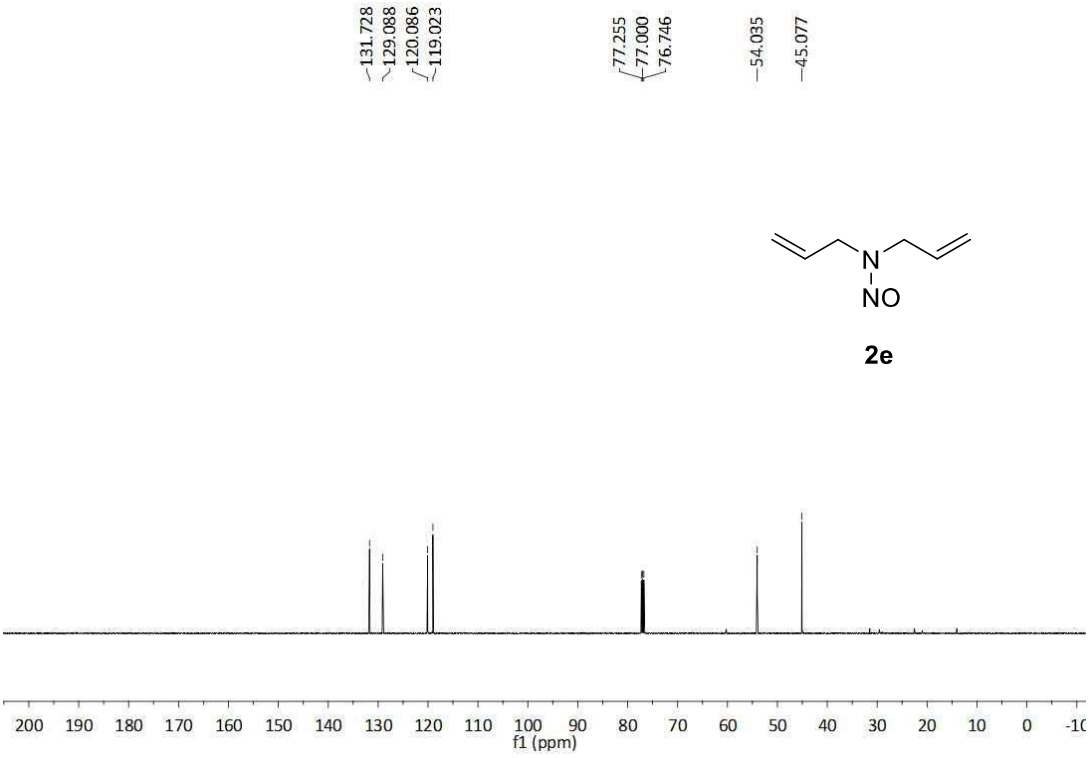


Figure 2.6 ^{13}C NMR of product **2e** in $CDCl_3$

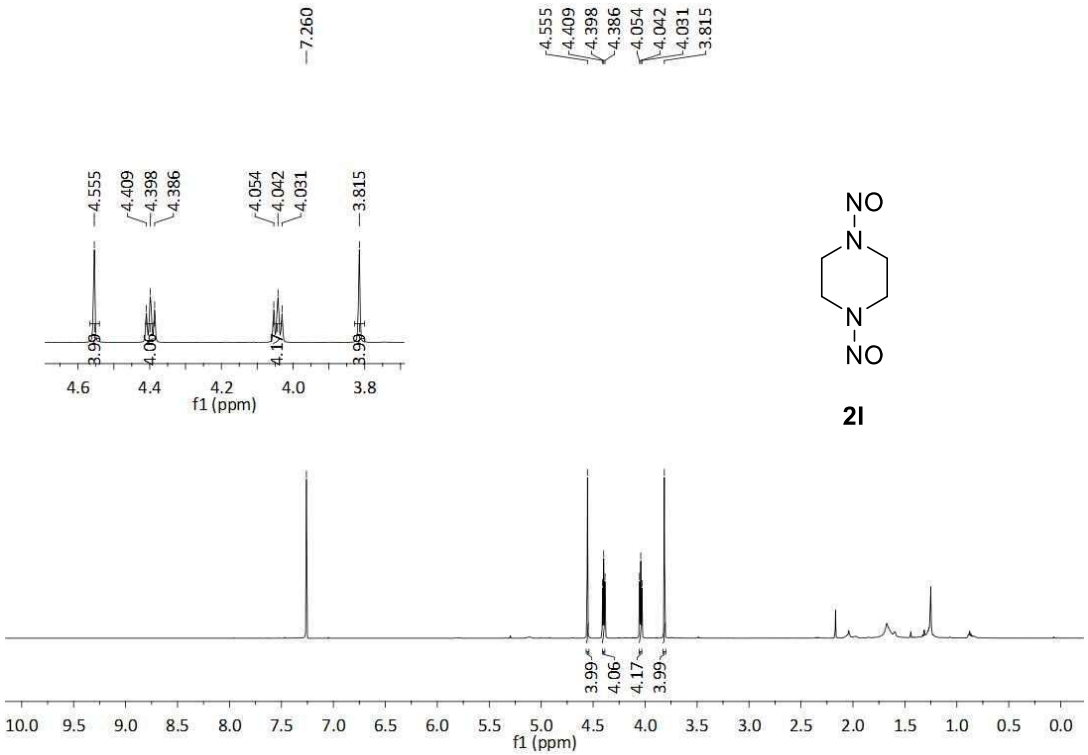


Figure 2.7 ^{1}H NMR of product **2l** in $CDCl_3$

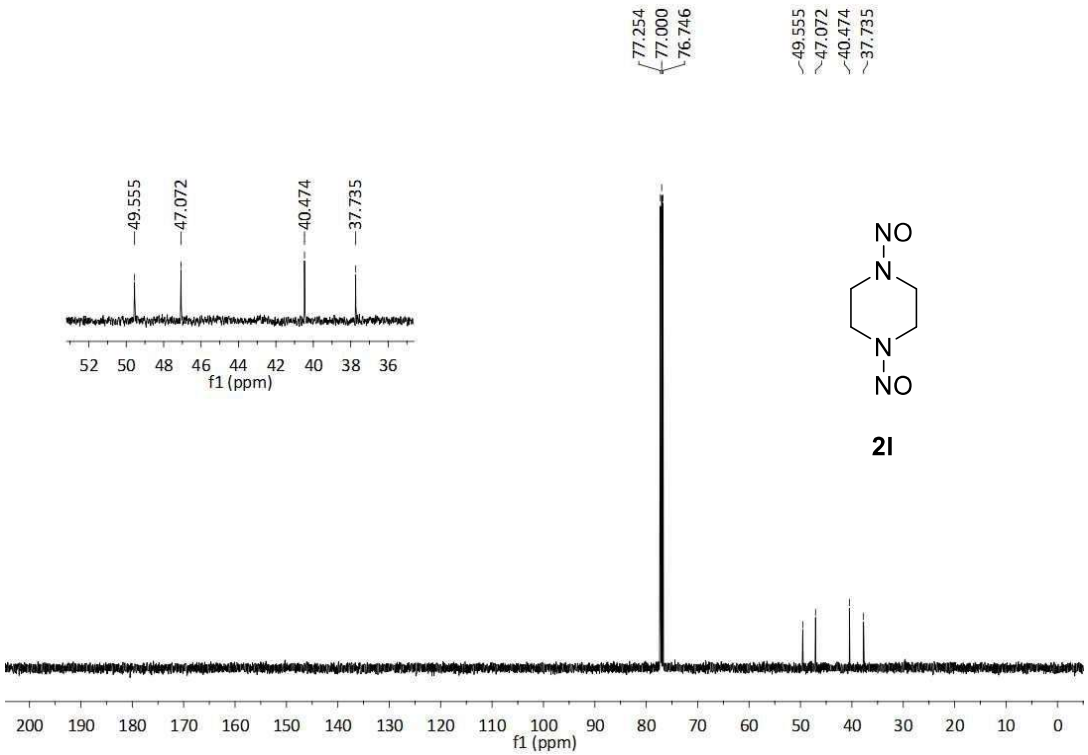


Figure 2.8 ^{13}C NMR of product **2l** in $CDCl_3$

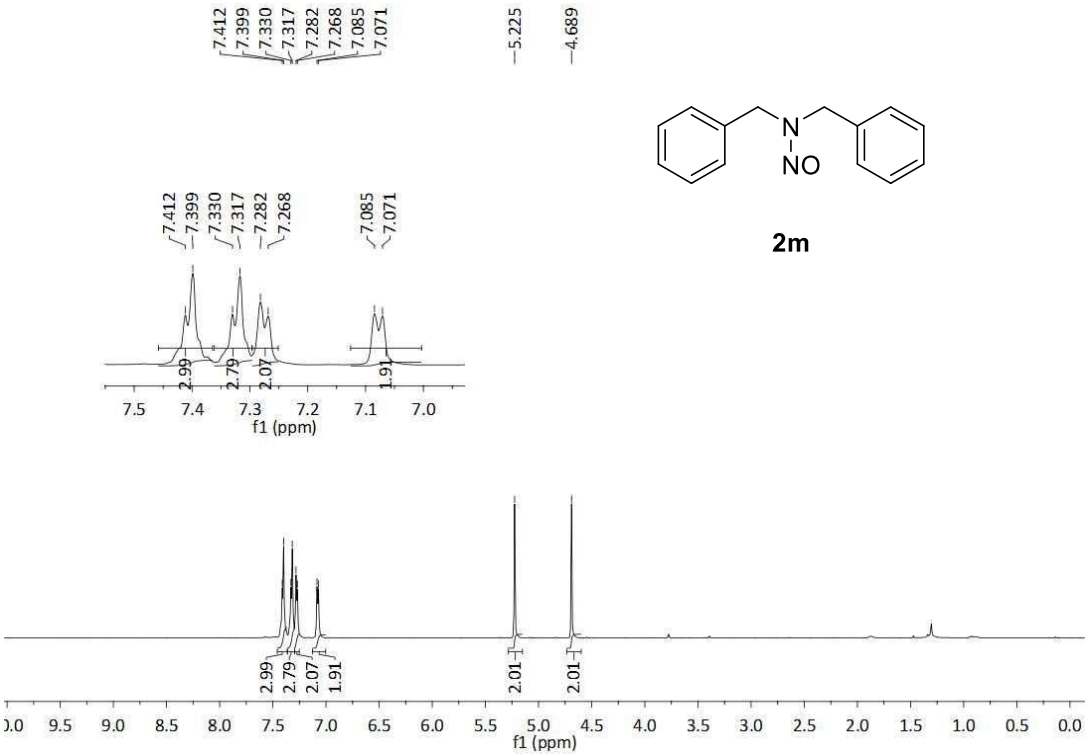


Figure 2.9 ^{1}H NMR of product **2m** in $CDCl_3$

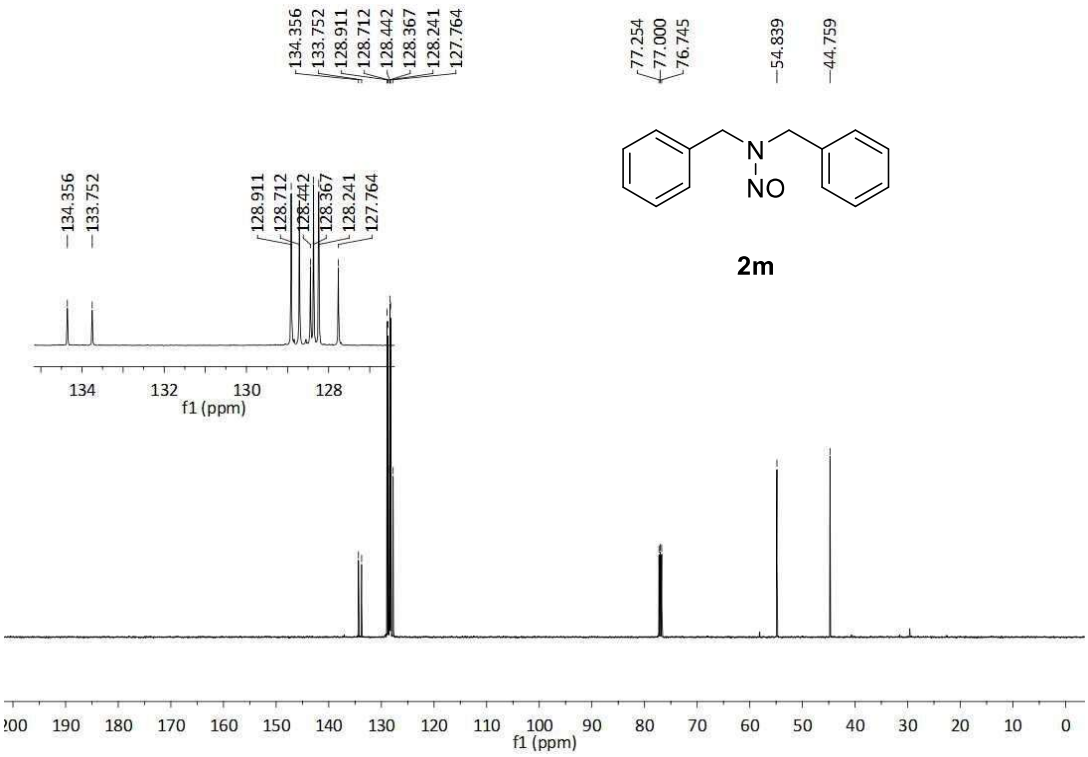


Figure 2.10 ^{13}C NMR of product **2m** in $CDCl_3$

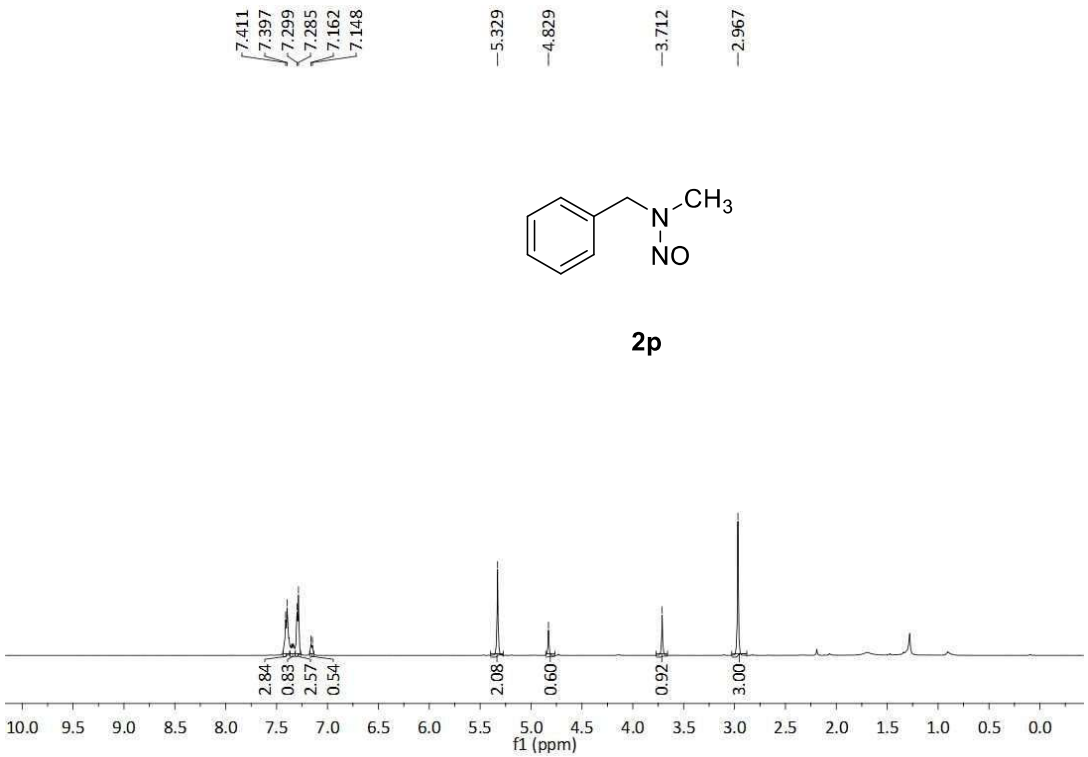


Figure 2.11 ^{1}H NMR of product **2p** in $CDCl_3$

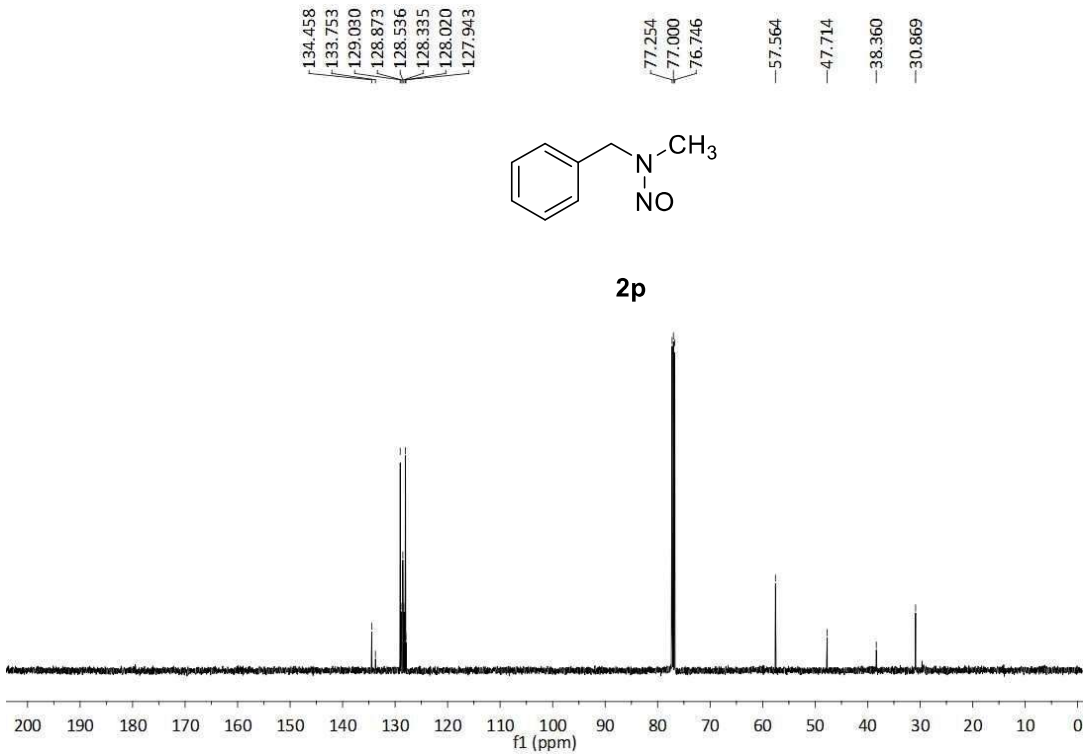


Figure 2.12 ^{13}C NMR of product **2p** in $CDCl_3$

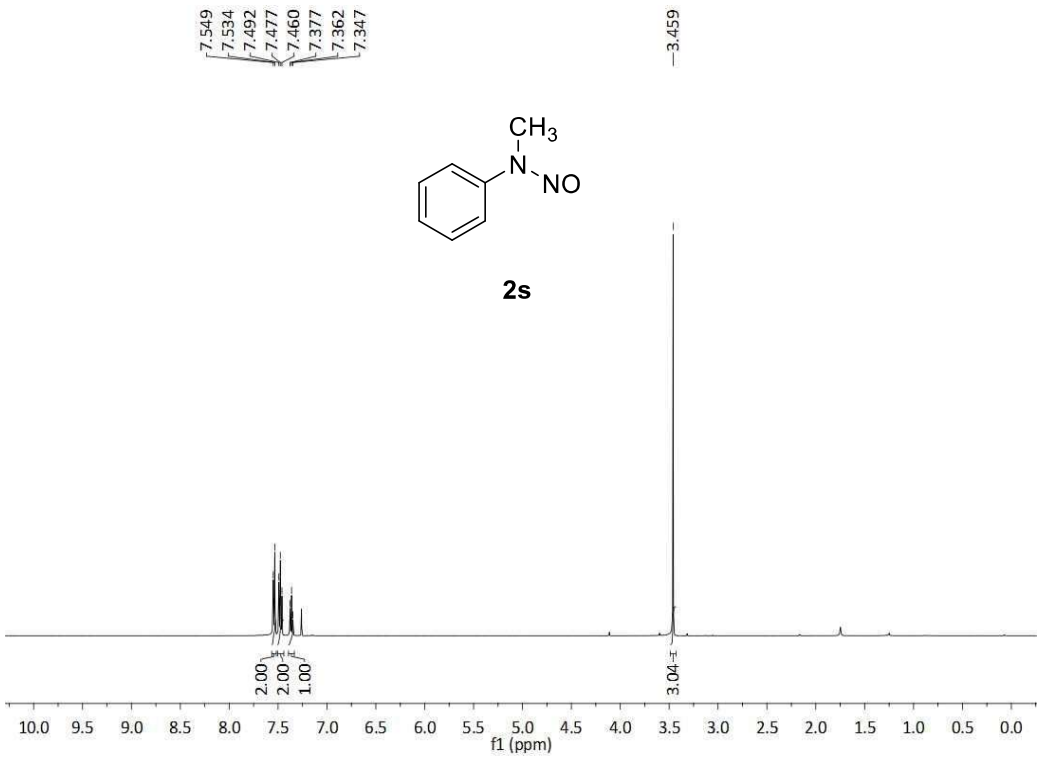


Figure 2.13 ^{1}H NMR of product **2s** in $CDCl_3$

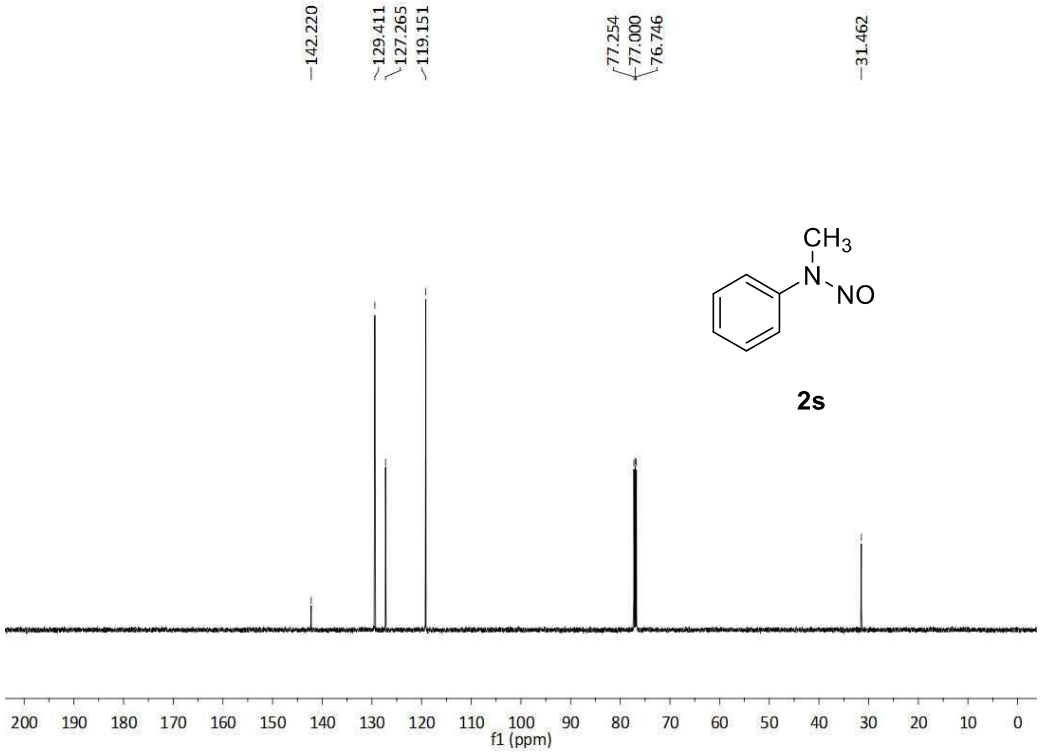


Figure 2.14 ^{13}C NMR of product **2s** in $CDCl_3$

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