CHAPTER-5

A METAL FREE REDUCTION OF ARYL-*N*-NITROSAMINES TO THE CORRESPONDING HYDRAZINES USING A SUSTAINABLE REDUCTANT THIOUREA DIOXIDE

5.1 Introduction

Hydrazines, hydrazones and hydrazides are the N-N bond containing organic compounds exhibiting a wide range of biological properties including antibacterial, anticonvulsant, analgesic, anti-inflammatory, antiplatelet, antitubercular and antitumour activities (Figure 5.1) [1-3]. On the other hand, hydrazine is the primary structural unit required for generating various hydrazones and hydrazides of interest and therefore synthesis of hydrazines is still an active area of research in organic chemistry [4].

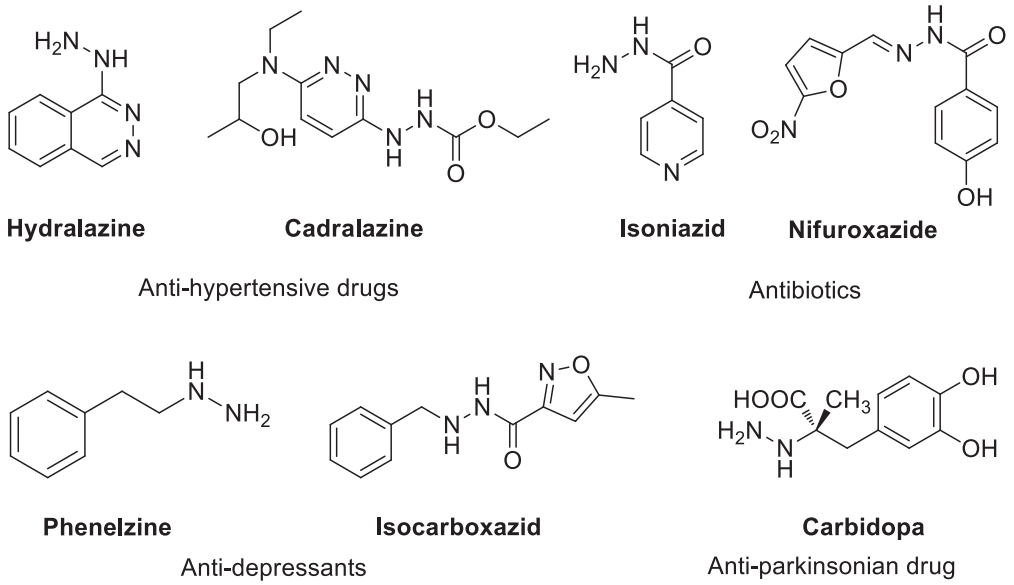


Figure 5.1 Biologically relevant hydrazines, hydrazones and hydrazides.

Among the different subclasses of hydrazines, aryl hydrazines have received considerable attention due to their synthetic as well as biological importance [4-6]. Aryl hydrazines are versatile intermediates and starting materials in organic synthesis, frequently used for the preparation of not only hydrazones and hydrazides but also various bioactive heterocyclic compounds including indoles, benzimidazoles, pyrazoles, indazoles, etc. (Figure 5.2) [7-12]. Besides the biological and synthetic importance, aryl

hydrazines are used in the preparation of molecular glasses for various applications [13, 14].

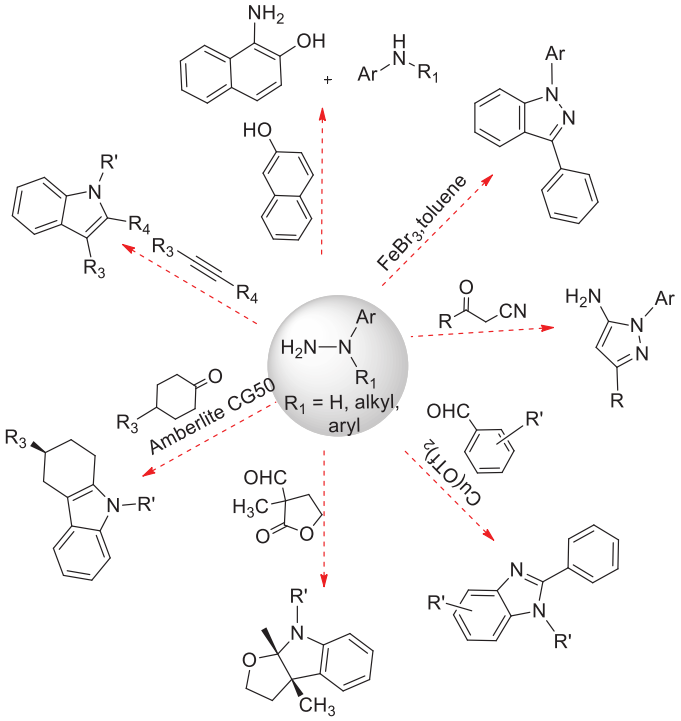


Figure 5.2 Synthetic importance of aryl hydrazines.

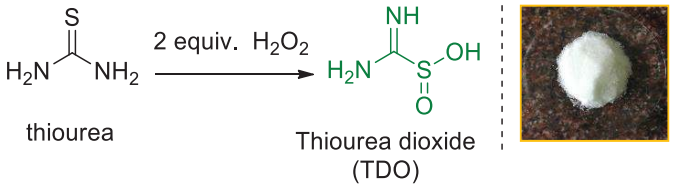
Unsubstituted aryl hydrazines are easily achieved from corresponding anilines *via* formation of diazonium salts followed by reduction using tin (II) chloride or sodium sulfite in good yield [15]. In contrast, synthesis of α-substituted aryl hydrazines (e.g. *N*, *N*-disubstituted aryl alkyl hydrazines or diaryl hydrazines) is a difficult task, because they are unstable and usually required multi-step synthesis [15] Nevertheless, over the past decade α-substituted aryl hydrazines have been utilized in a large number of reactions as one of the substrates to construct various bioactive molecules [15].

In general, three different approaches have been used for the preparation of α-substituted aryl hydrazines. These include **i)** α-alkylation of aryl hydrazines with the alkyl halides using strong bases like alkali metals or alkali amides in liquid ammonia, [16-19] **ii)** metal catalyzed cross coupling reactions of protected alkyl/aryl hydrazines with aryl halides or arylboronic acids [20-23] and **iii)** reduction of aryl *N*-nitrosamines [24-27]. Of these, the first two approaches have drawbacks like low yields (due to poor selectivity), harsh reaction conditions, use of protecting groups, limited substrate scope, etc. Therefore, the third approach i.e. the synthesis of aryl hydrazines from their corresponding *N*-nitrosamines is considered to be a general and straight forward approach, because it requires only two steps from the corresponding secondary amines without the need for any protecting groups. In this approach, the preparation of aryl-*N*-nitrosamines is the first step which can be easily achieved from the corresponding secondary amines under mild conditions.

In fact, we have recently developed a very efficient and greener method for the preparation of aryl-*N*-nitrosamines under solvent free conditions using *tert*-butyl nitrite [28].The second step is the reduction of *N*-nitrosamines to the corresponding hydrazines. The frequently used reagents for this transformation are lithium aluminium hydride ($LiAlH_4$) [24], a low valent titanium reagent (i.e. $TiCl_4$/Mg) [25] and zinc-acetic acid (Zn/AcOH) [26] In fact, the handling of $LiAlH_4$ or $TiCl_4$/Mg requires more precautions, because both reagents are highly sensitive to air and moisture which requires anhydrous solvents and an inert atmosphere in order to perform the reduction reaction. On the other hand, the zinc-acetic acid system is easy to handle, but unfortunately this method provides the desired products in lower yields along with a

significant amount of denitrosation products (i.e. parent secondary amines), perhaps due to a strong acidic medium [24, 26]. Moreover, all these reduction methods are considered to be non-ecofriendly methods since they produce a large amount of metallic waste which is harmful to the environment. With the increase in environmental awareness with respect to green chemistry, there is an urgent need for the development of suitable greener methods for the reduction of *N*-nitrosamines.

Thiourea dioxide (TDO) is an organo sulphur compound widely known as a "green industrial reductant", with various applications in chemistry and biology [29]. TDO is known to reduce various metallic ions (e.g. Cd^{2+}, Cu^{2+}, Ni^{2+} and Fe^{3+}) to corresponding metals and biochemical substrates (e.g. ferredoxin, cytochrome C and methemoglobin) into their reduced form [29, 30]. Recently, thiourea dioxide has been explored as an efficient chemiluminescence coreactant for the selective detection of cobalt ions with luminol [31]. On the other hand, thiourea dioxide (TDO) has also found wide application in organic synthesis not only as a reducing agent [29] but also as an organo catalyst for oxidation [32], multi-component (MCR) [33], and imine hydrolysis reactions [34]. Thiourea dioxide reduces various organic functional groups including epoxides, *N*-oxides, aldehydes, ketones, aromatic nitro, azo and azoxy compounds, quinones, etc. under alkaline medium [29, 35-37]. However, the reduction of *N*-nitrosamines to corresponding hydrazines has not been well explored with thiourea dioxide (TDO).



Scheme 5.1 Preparation of thiourea dioxide.

Thiourea dioxide is very stable crystalline material which can be prepared in a large quantity from thiourea in the presence of hydrogen peroxide (Scheme 5.1) [29]. On the other hand, thiourea dioxide is also commercially available at a cheaper price, and is easy to handle and store. Moreover, during the reduction, thiourea dioxide produces only nontoxic commercial wastes such as urea and sodium sulphite as byproducts [29] which is an important advantage of TDO. Due to its eco-friendly nature, TDO has been extensively used in the photographic, textile, paper, dye and leather industries as a reducing agent [29, 31]. In this context, here we report an efficient and practical method for the reduction of aryl *N*-nitrosamines into corresponding hydrazines using thiourea dioxide under metal free condition in aqueous medium. To the best of our knowledge, it is the first green approach disclosed for the reduction of aryl-nitrosamines.

5.2 Results and Discussions

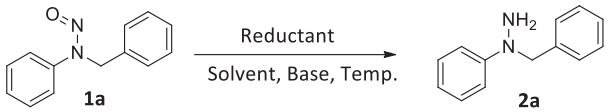
5.2.1 Optimization for reduction of *N*-Nitrosamines

At the outset, *N*-nitroso *N*-benzylaniline (**1a**) was chosen as a model substrate for the optimization while the reactions were performed at different temperatures and by varying the amount of TDO and sodium hydroxide in methanol (Table 5.1). It was observed that at room temperature the reaction does not proceed to completion even

after prolonged reaction time (Table 5.1, entries 1-3). The desired product *N*-benzyl *N*-phenylhydrazine (**2a**) was obtained only in 37% yield after 12 h with 3 equiv. of TDO (Table 5.1, entry 3). Therefore, the reaction temperature was increased to 50 °C with 3 equiv. of TDO in the presence of sodium hydroxide in methanol. Interestingly, the reaction leads to completion within three hours to provide 81% of the desired product (Table 5.1, entry 4). Nevertheless, further increase in the reaction time, temperature and the equivalents of reductant did not bring a significant change in the reaction yield (Table 5.1, entries 5-7).

It is also important to note that in the absence of either reductant (i.e. TDO) or base (NaOH) no reaction takes place (Table 5.1, entries 8 and 9). Similarly, by replacing thiourea dioxide with thiourea no reaction was observed (Table 5.1, entry 10). Further, the reaction was tested in different protic and aprotic solvents using 3.0 equiv. of TDO at 50 °C. Among the protic solvents, ethanol gave the desired product in a comparable yield (i.e. 78%) to that of methanol while H_2O, *iso*-propanol, *n*-butanol and *tert*-butanol gave lower yields (Table 5.1, entries 11-15). In addition, no reaction was observed when hexafluoro-2-propanol (HFIP) was used as a solvent (Table 5.1, entry 16). Similarly, aprotic solvents such as acetonitrile and THF were also found to be inefficient medium for the reduction reaction with TDO (Table 5.1, entries 17-18).

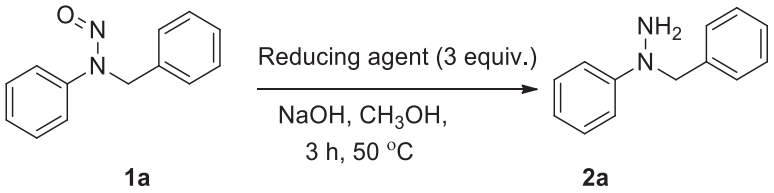
Table 5.1 Reduction of *N*-nitrosamines under various reaction conditions.[a,b]



S.No.	Reductant	Equiv.	Solvent	Base	Temp	Time (h)	Yield (%)[b]
1	TDO	1	CH_3OH	NaOH	RT	12	<10%
2	TDO	2	CH_3OH	NaOH	RT	12	15
3	TDO	3	CH_3OH	NaOH	RT	12	37
4	**TDO**	**3**	**CH_3OH**	**NaOH**	**50 °C**	**3**	**81**
5	TDO	4	CH_3OH	NaOH	50 °C	3	83
6	TDO	3	CH_3OH	NaOH	50 °C	4	80
7	TDO	3	CH_3OH	NaOH	75 °C	3	71
8	TDO	3	CH_3OH	---	50 °C	3	N.R.
9	---	3	CH_3OH	NaOH	50 °C	3	N.R
10	Thiourea	3	CH_3OH	NaOH	50 °C	3	N.R
11	TDO	3	H_2O	NaOH	50 °C	3	47
12	TDO	3	C_2H_5OH	NaOH	50 °C	3	78
13	TDO	3	*i*-Propanol	NaOH	50 °C	3	36
14	TDO	3	*n*-Butanol	NaOH	50 °C	3	27
15	TDO	3	*tert*-Butanol	NaOH	50 °C	3	20
16	TDO	3	HFIP	NaOH	50 °C	3	N.R.
17	TDO	3	CH_3CN	NaOH	50 °C	3	N.R.
18	TDO	3	THF	NaOH	50 °C	3	N.R.
19	TDO	3	CH_3OH	KOH	50 °C	3	73
20	TDO	3	CH_3OH	CsOH	50 °C	3	78
21	TDO	3	CH_3OH	NH_4OH	50 °C	3	21
22	TDO	3	CH_3OH	Bu_4NOH	50 °C	3	30
23	TDO	3	CH_3OH	NaOMe	50 °C	3	N.R.

[a]Reaction conditions: *N*-nitrosamine (1mmol), 2.0 equiv. base (1M aqueous solution) per one equiv. of reductant, solvent (2 mL), stirred at appropriate temperature. [b]Isolated yield. N.R.- No Reaction.

Further, the reaction was examined using different bases like KOH, CsOH, NH_4OH, Bu_4NOH and NaOMe (Table 5.1, entries 19-23). Potassium hydroxide and cesium hydroxide gave the desired hydrazine in 73% and 78% respectively (Table 5.1, entries 19 and 20) while ammonium hydroxides gave less than 30% of the desired hydrazine (Table 5.1, entries 21 and 22). Interestingly, there was no reaction observed when sodium methoxide used as a base (Table 5.1, entry 23).



1a **2a**

Reductant:	TDO	Sodium bisulfite	Sodium sulfite	Sodium dithionite
Yield (Isolated):	81%	<5%	<5%	57%

Scheme 5.2 Reduction of *N*-nitroso *N*-benzyl aniline with different sulphur containing reducing agents.

Besides the thiourea dioxides, other sulphur containing reducing agents which are frequently used in organic synthesis [37, 38] such as sodium sulfite, sodium bisulfite and sodium dithionite have been studied for the reduction of *N*-nitroso *N*-benzylaniline (Scheme 5.2). Among them, sodium dithionite gave 57% of the desired hydrazine [39] while sodium sulfite and bisulfite gave a negligible amount. Over all, thiourea dioxide (TDO) was found to be superior among the sulphur containing reducing agents for the reduction of *N*-nitroso *N*-benzylaniline. Further, it was observed

that 3.0 equiv. of thiourea dioxide would be optimal for achieving high yield of the hydrazine in the presence of sodium hydroxide in methanol at 50 °C.

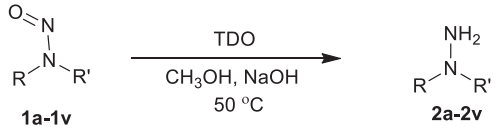
5.2.2 Substrate scope

With optimized conditions in hand, we have studied the scope of this methodology by attempting the reduction of various α-substituted aryl *N*-nitrosamines using thiourea dioxide in methanol (Table 5.2). At the beginning, various *N*-nitroso *N*-benzyl anilines bearing electron donating (e.g. methyl and methoxy) as well as withdrawing substituents (e.g. fluorine, chlorine and bromine) were prepared from corresponding secondary amines using *tert*-butyl nitrite and subjected to the reduction.

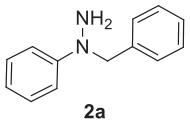
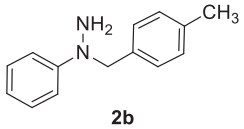
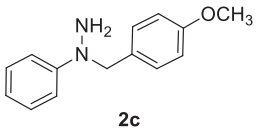
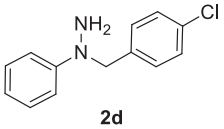
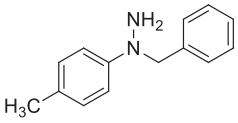
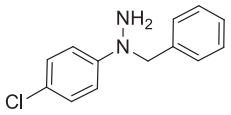
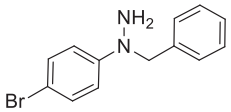
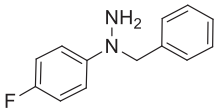
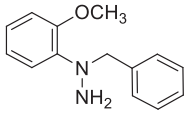
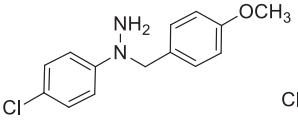
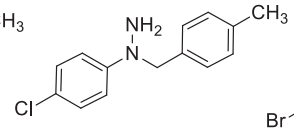
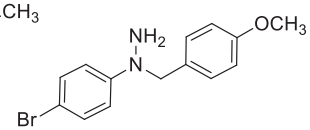
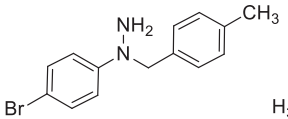
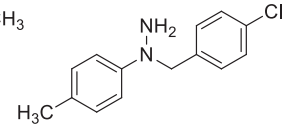
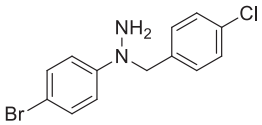
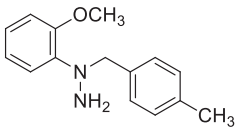
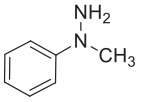
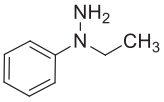
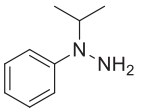
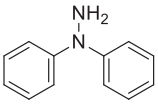
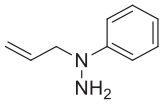
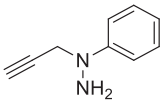
All these *N*-nitrosamines underwent reduction smoothly irrespective of their electronic nature and provided the corresponding hydrazines in high yields (Table 5.2, **2b**-**2p**). Interestingly, aryl halides such as fluorides, chlorides and bromides were found to be very stable during the reduction and there was no observation of dehalogenation or nucleophilic substitutions.

Overall, the time required for the reduction of *N*-nitroso *N*-benzylanilines to corresponding hydrazines was about 3 to 4 hours while the desired products were obtained in 69%-81% isolated yield. Particularly, sterically hindered *N*-nitrosamines i.e. *ortho*-substituted *N*-benzyl *N*-nitroso anilines took slightly longer time to yield the desired hydrazines (**2i** and **2p**), however in a comparable yields (i.e. 69-70%). As a matter of fact, all these phenyl hydrazines were found to be quite stable in the reaction medium (*i.e.* alkaline medium), but underwent a small amount of decomposition during the purification process.

Table 5.2 Reduction of *N*-nitrosamines using thiourea dioxide.[a,b]



1a-1v **2a-2v**

 **2a** (3 h, 81%)	 **2b** (3 h, 78%)	 **2c** (3 h, 76%)	 **2d** (3 h, 80%)
 **2e** (3 h, 78%)	 **2f** (3 h, 71%)	 **2g** (3 h, 75%)	 **2h** (3 h, 72%)
 **2i** (4 h, 69%)	 **2j** (3 h, 74%)	 **2k** (3 h, 75%)	 **2l** (3 h, 77%)
 **2m** (3 h, 79%)	 **2n** (3 h, 73%)	 **2o** (3 h, 76%)	 **2p** (4 h, 70%)
 **2q** (3 h, 89%)	 **2r** (3 h, 87%)	 **2s** (4 h, 73%)	 **2t** (3 h, 81%)
 **2u** (3 h, 69%)	 **2v** (3 h, 71%)		

[a]Reaction conditions: *N*-nitrosamine (1 mmol), TDO (3 equiv.), CH_3OH (2 mL), NaOH (1 molar, 6 equiv.) were stirred at 50 °C. [b]Isolated yield.

5.2.3 Comparative study of current protocol with the previous approach

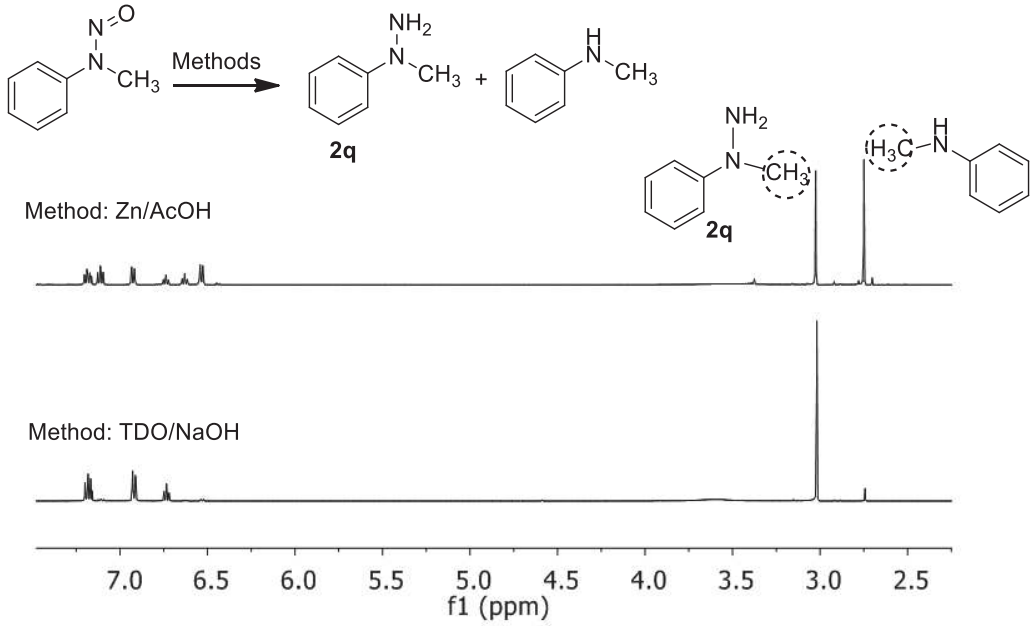


Figure 5.3 Comparative ^{1}H NMR (in $CDCl_3$) of *N*-methyl *N*-phenyl hydrazine obtained from the reduction of *N*-nitroso *N*-methyl aniline using TDO-NaOH and Zn-AcOH systems.

It is also worthy to note that the current protocol was found to be superior when compared to the common method *i.e.* zinc-acetic acid system (Scheme 5.3) [26]. For instance, the comparative crude ^{1}H NMR spectra of *N*-methyl-*N*-phenyl hydrazine (**2q**) which was obtained from the reduction of *N*-nitroso *N*-methyl aniline by using both TDO-NaOH and Zn-AcOH system is shown in Figure 5.3.

The spectra clearly shows that TDO provides the desired hydrazine with minimal amount of denitrosation product (<5 %) while Zn-AcOH gave approximately 1:1 ratio of the desired product and de-nitrosation product (Scheme 5.3). Similarly, *N*-ethyl *N*-phenylhydrazine (**2r**) was obtained from the corresponding *N*-nitroso compound in 94%

(crude yield) by using TDO while Zn/AcOH system gave only 42% yield (Scheme 5.3) [26]. These results clearly reveal the merits and the efficiency of TDO in the reduction of aryl *N*-nitrosamines.

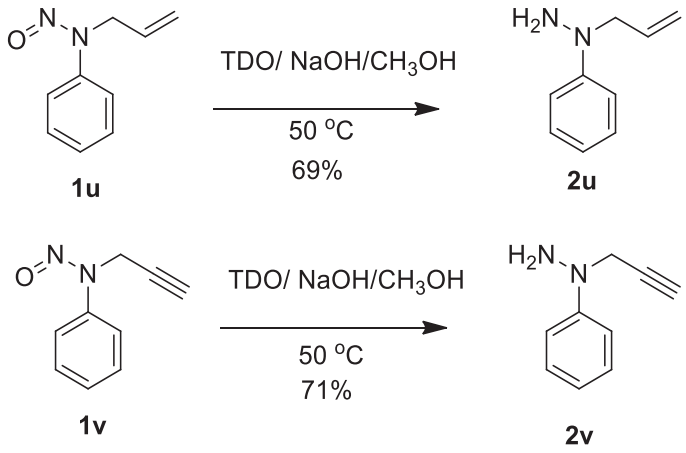
R	Yield (%)[a]	
	Zn/AcOH RT-80 °C 3 h	TDO/ NaOH 50 °C 3 h
Me (**2q**)	50	95
Et (**2r**)	42	94

[a]Crude yields as seen in the ^{1}H NMR

Scheme 5.3 Reduction of *N*-nitroso-*N*-alkyl anilines.

Organic syntheses are facilitated and controlled by the functional groups of the reactants. Therefore, the stability of different functional groups under standard reaction conditions plays a major role in organic synthesis. Functional groups like olefin and alkyne are known to undergo reduction in the presence of different reducing agents [40]. In order to see their stability under the present reaction condition, *N*-nitroso *N*-allyl and *N*-nitroso *N*-anilines (**1u** and **1v**, respectively) were prepared and subjected to the reduction with TDO (Scheme 4). Remarkably, both allyl and propargyl functionalities were found to be stable during the reduction while *N*-nitrosamines selectively converted to corresponding hydrazines (Table 2, **2u** and **2v**, respectively) in good yield. It is noteworthy that *N*-

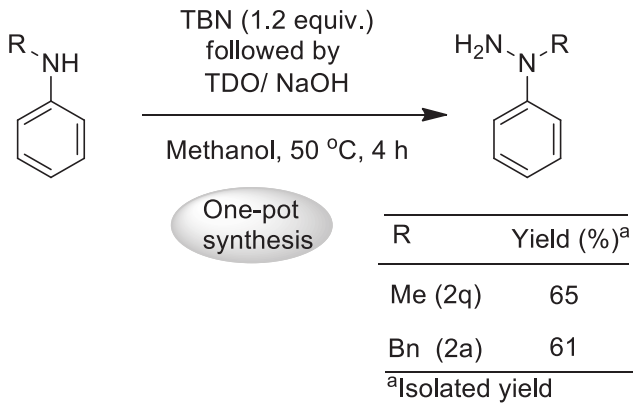
propargyl hydrazine derivatives have been shown to have various biological properties and used as monoamine oxidase inhibitors and neuroprotective agents [6].



Scheme 5.4 Reduction of *N*-nitroso-*N*-allyl and propargyl anilines.

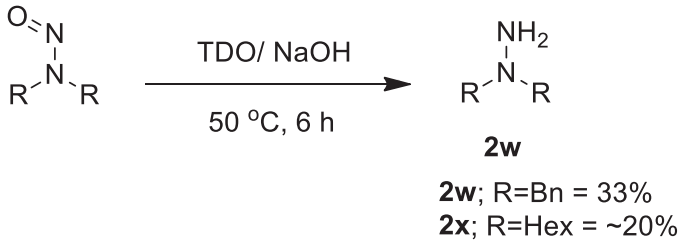
5.3 One-Pot Synthesis of Aryl-*N*-hydrazines

One-pot reactions have received considerable interest in organic synthesis, because they significantly reduce the labour and time [41]. We have attempted one-pot synthesis of α-substituted arylhydrazines starting from secondary amines *via* *N*-nitrosation followed by reduction using *tert*-butyl nitrite and thiourea dioxide, respectively (Scheme 5.5). *N*-Methyl and *N*-benzyl anilines were successfully converted to corresponding hydrazines in 65% and 61%, respectively, within four hours.



Scheme 5.5 One-pot synthesis of α-substituted aryl hydrazines.

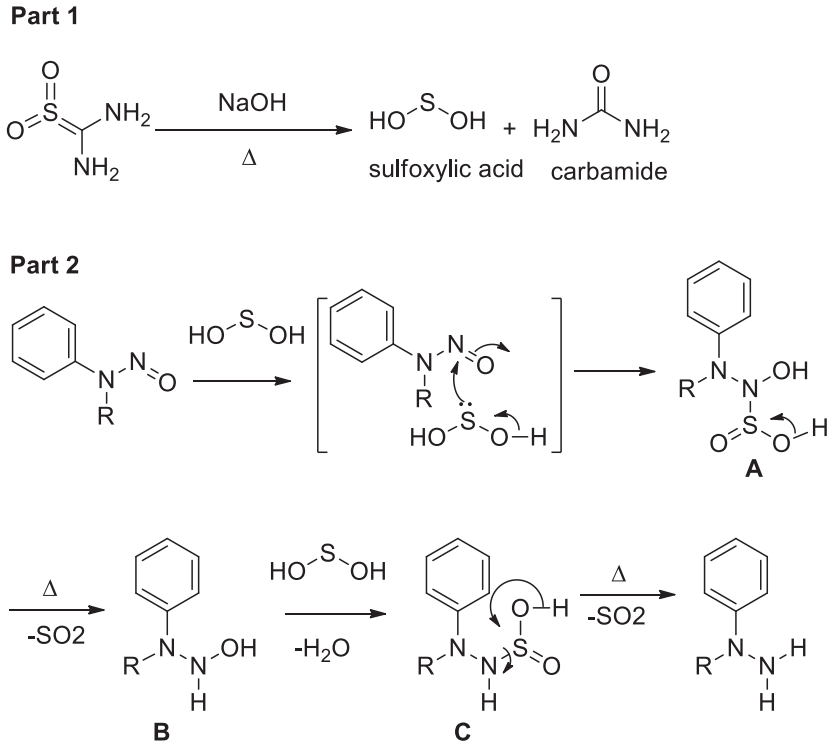
In general, unlike aryl-*N*-nitrosamines, reduction of dialkyl and dibenzyl *N*-nitrosamines to corresponding hydrazines required strong reducing agents (e.g. $LiAlH_4$) [15]. In order to check the capability of TDO in this transformation, the reduction of dibenzyl and dihexyl *N*-nitrosamines were examined under the optimized condition. Although dibenzyl *N*-nitrosamine was reduced to the corresponding hydrazine **2w** in 33% yield (Scheme 5.6), the reduction of dihexyl *N*-nitrosamine provided the desired hydrazine **2x** in very low yield (~ 20% yield) [42]. It clearly suggests that the current optimized condition is not suitable for the reduction of dialkyl/dibenzyl *N*-nitrosamines and further optimization may be necessary.



Scheme 5.6 Reduction of dibenzyl and dihexyl *N*-nitrosamine.

5.4 Plausible Mechanism

Although the reduction mechanism of TDO is not well understood, a proposed mechanism for the reduction of *N*-nitrosamine is shown in Scheme 5.7. The reaction of sodium hydroxide with thiourea dioxide is known to provide sulfoxylic acid, which has a potent role in the reduction of *N*-nitrosamines (Scheme 5.7, **Part 1**)[29,37]. We believe that sulfoxylic acid will undergo addition reaction with the nitroso moiety to provide an intermediate **A** which will release the sulphur dioxide (SO_2) upon heating to provide a partially reduced hydroxylamine derivative **B** (Scheme 5.7, **Part 2**). The reaction of another molecule of sulfoxylic acid with intermediate **B** would provide the desired hydrazines *via* intermediate **C** as shown in the scheme 5.7.



Scheme 5.7 Proposed mechanism for the reduction of *N*-nitrosamines with thiourea dioxide.

5.5 Conclusion

In conclusion, we have demonstrated an efficient and practical method for the preparation of α-substituted aryl hydrazines from corresponding *N*-nitroso compounds using eco-friendly reductant thiourea dioxide. Thiourea dioxide is found to be superior among the sulphur containing reducing agents and provides a high yield of desired hydrazines. Moreover, sensitive functional groups such as aryl halides, olefin and alkyne are found to be stable during the reduction. Innocuous reagent, convenient procedure and high yield make the protocol attractive for the preparation of aryl hydrazines from simple starting materials.

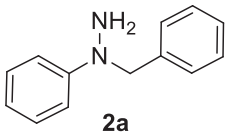
5.6 Experimental Section

5.6.1 Experimental procedure for the reduction of *N*-nitrosamines

N-nitrosamine (1.0 mmol) was allowed to stir in methanol (2 mL) approximately for 5 min at 50 °C to which aqueous solution of sodium hydroxide (1 M, 6 equiv.) followed by thiourea dioxide (TDO) (3 equiv.) was added. The reaction was allowed to stir for 3-4 h and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with chloroform and washed with water. The organic layer was dried over anhydrous sodium sulphate, concentrated and subjected for column chromatography (SiO_2: ethyl acetate/hexane) to obtain corresponding pure substituted *N*-aryl hydrazines.

5.7 Analytical Data of Products

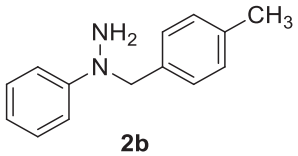
5.7.1 *N*-Benzyl *N*-phenyl hydrazine (2a)



2a

The title compound was obtained as white solid. M.p.164-166 °C. Yield: 81% (160 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.35; IR (neat): 3367, 2936, 1465, 1260, 1080 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.17 (m, 7H), 7.02 (d, J = 7.7 Hz, 2H), 6.74 (t, J = 7.3 Hz, 1H), 4.52 (s, 2H), 3.47 (brs, 2H, NH_2).^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 137.5, 129.0, 128.6, 127.8, 127.3, 118.5, 113.6, 60.3. HRMS: Calc. for $C_{13}H_{14}N_2$ $[M+H]^+$: 199.1235, Obser.: 199.1226.

5.7.2 *N*-(4-Methylbenzyl)-*N*-phenylhydrazine (2b)

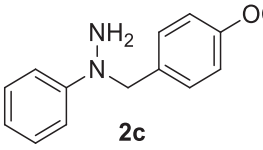


2b

The title compound was obtained as yellow solid. M.p. 39-40 °C. Yield: 78% (180 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.33. IR (neat): 3290, 2978, 1590, 1490, 1035 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.22 (m, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 7.7 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 6.80 (t, J = 7.3 Hz, 1H), 4.53 (s, 2H), 3.50 (brs, 2H, NH_2),

2.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 137.0, 134.3, 129.3, 129.0, 127.9, 118.5, 113.7, 60.1, 21.0. HRMS: Calc. for $C_{14}H_{16}N_2$ $[M+H]^+$: 213.1392, Obser.: 213.1385.

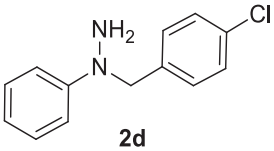
5.7.3 *N*-(4-Methoxybenzyl)-*N*-phenylhydrazine (2c)



2c

The title compound was obtained as white solid. M.p. 71-72 °C. Yield: 76% (173 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15. R_f = 0.35. IR (neat): 3275, 2879, 1652, 1473, 1081 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.82 (t, *J* = 7.2 Hz, 1H), 4.52 (s, 2H), 3.80 (s, 3H), 3.49 (brs, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 151.7, 129.2, 129.0, 118.6, 114.0, 113.9, 59.8, 55.2. HRMS: Calc. for $C_{14}H_{16}N_2O$ $[M+H]^+$: 229.1341, Obser.: 229.1332.

5.7.4 *N*-(4-Chlorobenzyl)-*N*-phenylhydrazine (2d)

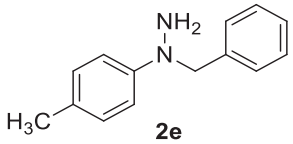


2d

The title compound was obtained as white solid. M.p. 40 °C. Yield: 80% (186 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.33. IR (neat): 3352, 2987,

2756, 1576, 1075 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.14 (m, 6H), 6.96 (d, *J* = 7.7 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 4.47 (s, 2H), 3.50 (brs, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 136.2, 133.0, 129.1, 128.7, 7, 118.8, 113.5, 59.7. HRMS: Calc. for $C_{13}H_{13}ClN_2$ $[M+H]^+$: 233.0846, Obser.: 233.0835.

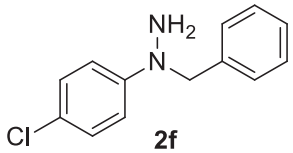
5.7.5 *N*-Benzyl-*N*-(4-methylphenyl) hydrazine (2e)



2e

The title compound was obtained as white solid. M.p. 37-38 °C. Yield: 78% (165 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.33. IR (neat): 3248, 2938, 1689, 1478, 1001 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 4.52 (s, 2H), 3.49 (brs, 2H, NH_2), 2.27 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 137.6, 129.5, 128.6, 128.1, 128.0, 127.3, 114.1, 61.0, 20.3. HRMS: Calc. for $C_{14}H_{16}N_2$ $[M+H]^+$: 213.1392, Obser.: 213.1382.

5.7.6 *N*-Benzyl-*N*-(4-chlorophenyl) hydrazine (2f)

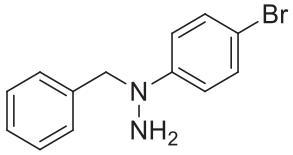


2f

The title compound was obtained as white solid. M.p. 40 °C. Yield: 71% (165 mg). The residue was purified by column chromatography in silica gel eluting with

hexane:EtOAc 85:15, R_f = 0.32. IR (neat): 3350, 2972, 1756, 1456, 1027, 786 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.3 Hz, 2H), 7.32-7.24 (m, 3H), 7.19 (d, *J* = 8.9 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 2H), 4.56 (s, 2H), 3.53 (brs, 2H, NH_2).^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 136.8, 128.8, 128.7, 127.8, 127.5, 123.2, 114.8, 60.2. HRMS: Calc. for $C_{13}H_{13}ClN_2$ $[M+H]^+$: 233.0846, Obser.: 233.0833.

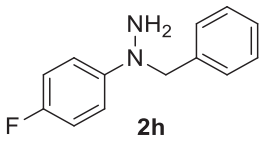
5.7.7 *N*-(4-Bromobenzyl)-*N*-phenylhydrazine (2g)



2g

The title compound was obtained as white solid. M.p. 57 °C. Yield: 75% (207 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 80:20, R_f = 0.30. IR (neat): 3247, 2978, 1657, 1452, 1026, 587 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 7.26 (d, *J* = 7.4 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 4.57 (s, 2H), 3.53 (brs, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 136.8, 131.7, 128.7, 127.7, 127.5, 115.2, 110.3, 60.0. HRMS: Calc. for $C_{13}H_{13}BrN_2$ $[M+H]^+$: 277.0340, Obser.: 277.0333.

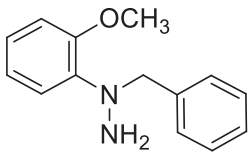
5.7.8 *N*-Benzyl-(4-fluorophenyl) hydrazine (2h)



2h

The title compound was obtained as yellow solid. M.p. 67 °C. Yield: 72% (156 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 80:20, R_f = 0.28. IR (neat): 3235, 2978, 1876, 1456, 1123 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 8.4 Hz, 2H), 7.24-7.21 (m, 3H), 7.04-6.96 (m, 2H), 6.88 (t, *J* = 8.7 Hz, 2H), 4.43 (s, 2H), 3.41 (brs, 2H, NH_2).^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6 (d, J_{C-F} =237.5 Hz), 148.3, 148.3, 137.0, 128.7, 128.1, 127.5, 115.6 (d, J_{C-F} =7.4 Hz), 115.3 (d, J_{C-F} =22.2 Hz) , 61.7. HRMS: Calc. for $C_{13}H_{13}FN_2$ $[M+H]^+$: 217.1141, Obser.: 217.1145.

5.7.9 *N*-Benzyl-(2-methoxyphenyl) hydrazine (2i)

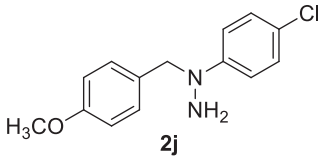


2i

The title compound was obtained as yellow solid. M.p. 48 °C Yield: 69% (157 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.34. IR (neat): 3256, 2965, 1467, 1200, 1001 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.29 (m, 4H), 7.29 (dd, *J* = 5.9, 2.9 Hz, 1H), 7.15 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.06-7.01 (m, 1H), 6.95-6.90 (m, 2H), 4.31 (s, 2H), 3.93 (s, 3H), 3.52 (brs, 2H, NH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 141.9, 137.5, 129.1, 128.3, 127.3, 123.6, 120.8, 119.7, 111.3, 63.4, 55.5. HRMS: Calc. for $C_{14}H_{16}N_2O$ $[M+H]^+$: 229.1341, Obser.: 229.1334.

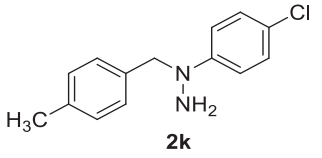
5.7.10 *N*-(4-Methoxybenzyl)-(4-chlorophenyl) hydrazine (2j)



2j

The title compound was obtained as pale brown solid. M.p. 78 °C. Yield: 74% (194 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.33. IR (neat): 3345, 2989, 1678, 1458, 879 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.17 (m, 4H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 4.46 (s, 2H), 3.79 (s, 3H), 3.45 (brs, 2H, NH_2).^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 150.3, 129.2, 128.7, 128.6, 123.2, 115.1, 114.1, 59.6, 55.2. HRMS: Calc. for $C_{14}H_{15}ClN_2O$ $[M+H]^+$: 263.0951, Obser.: 263.0947.

5.7.11 *N*-(4-Chlorobenzyl)-(4-methylphenyl) hydrazine (2k)

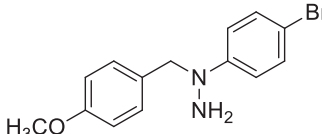


2k

The title compound was obtained as pale yellow solid. M.p. 55 °C Yield: 75% (185 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.32. . IR (neat): 3378, 2976, 1604, 1257, 799 cm^{-1}. ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 4.41 (s, 2H), 3.44 (brs, 2H, NH_2), 2.20 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 136.3, 133.0, 129.6, 129.3, 128.7, 128.3, 114.0, 60.3, 20.3. HRMS: Calc. for $C_{14}H_{15}ClN_2$ $[M+H]^+$: 247.1002, Obser.: 247.0990.

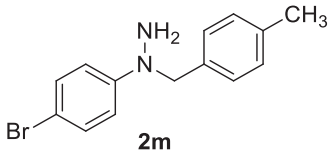
5.7.12 *N*-(4-Bromophenyl)-*N*-(4-methoxybenzyl) hydrazine (2l)



2l

The title compound was obtained as white solid. M.p. 89 °C. Yield: 77% (236 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.30. IR (neat): 3256, 2978, 1653, 1253, 567 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* =8.1 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 7.7 Hz, 2H), 4.47 (s, 2H), 3.78 (s, 3H), 3.45 (brs, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 150.7, 131.6, 129.2, 128.5, 115.5, 114.1, 110.4, 59.5, 55.2. HRMS: Calc. for $C_{14}H_{15}BrN_2O$ $[M+H]^+$: 307.0446, Obser.: 307.0431.

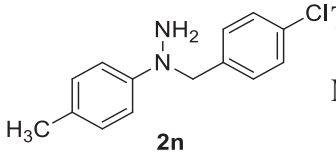
5.7.13 *N*-(4-Methylbenzyl)-(4-bromophenyl) hydrazine (2m)



2m

The title compound was obtained as yellow solid. M.p. 97 °C. Yield: 79% (229 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.35. IR (neat): 3248, 2988, 1678, 1451, 1232, 567 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 9.0 Hz, 2H), 7.13 (s, 4H), 7.01 (d, *J* = 9.0 Hz, 2H), 4.49 (s, 2H), 3.47 (brs, 2H, NH_2), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 137.2, 133.6, 129.4, 128.7, 127.8, 123.1, 114.9, 60.0, 21.0. HRMS: Calc. for $C_{14}H_{15}BrN_2$ $[M+H]^+$: 291.0497, Obser.: 291.0491.

5.7.14 *N*-(4-Chlorobenzyl)-*N*-4-methyl hydrazine (2n)

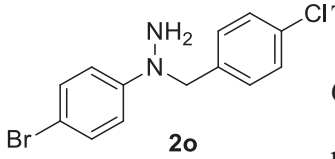


2n

The title compound was obtained as white solid. M.p.56 °C. Yield: 73% (179 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.34. IR (neat): 3349, 2988, 1678, 1451, 1232, 567 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 9.0 Hz, 2H), 7.14 (m, 4H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.51 (s, 2H), 3.49 (brs, 2H, NH_2), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 137.2, 133.6, 129.3, 128.7,

127.8, 123.1, 114.9, 60.2, 21.0. HRMS: Calc. for $C_{14}H_{15}ClN_2$ $[M+H]^+$:247.1002, Obser.: 247.0997.

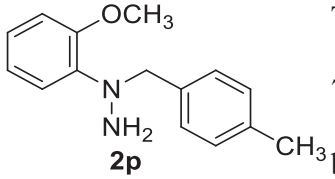
5.7.15 *N*-(4-Bromophenyl)-*N*-(4-chlorobenzyl) hydrazine (2o)



2o

The title compound was obtained as white solid. M.p. 68 °C. Yield: 76% (234 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.33. IR (neat): 3245, 2967, 1654, 1453, 1090, 879 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.25 (m, 4H), 7.18 (d, *J* = 6.3 Hz, 2H), 6.92 (d, *J* = 6.6 Hz, 2H), 4.52 (s, 2H), 3.53 (brs, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 135.4, 133.3, 131.7, 129.0, 128.9, 115.2, 110.7, 59.5. HRMS: Calc. for $C_{13}H_{12}BrClN_2$ $[M+H]^+$: 310.9951, Obser.: 310.9927.

5.7.16 *N*-(4-Methylbenzyl)-*N*-(4-methoxyphenyl) hydrazine (2p)

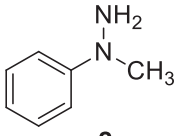


2p

The title compound was obtained as red liquid. M.p. 78 °C. Yield: 70% (169 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.35. IR (neat): 3245, 2987, 1441, 1253, 1101 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (m, 2H), 7.16-7.11 (m, 3H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 2H), 4.27 (s, 2H),

3.93 (s, 3H), 3.38 (brs, 2H, NH_2), 2.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 141.9, 136.9, 134.3, 129.1, 129.0, 123.5, 120.8, 119.7, 111.3, 63.1, 55.5, 21.1. HRMS: Calc. for $C_{15}H_{18}N_2O$ $[M+H]^+$: 243.1497, Obser.: 243.1419.

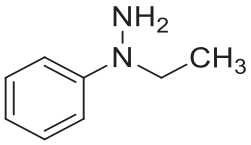
5.7.17 *N*-Methyl–*N*-phenyl hydrazine (2q)



2q

The title compound was obtained as yellow liquid. Yield: 89% (112 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.37. IR (neat): 2970, 1679, 1490, 1120, 690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.11 (m, 2H), 6.93 (d, *J* = 7.7 Hz, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 3.62 (brs, 2H, NH_2), 3.03 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 128.9, 118.5, 113.4, 44.5. HRMS: Calc. for $C_7H_{10}N_2$ $[M+H]^+$: 123.0922, Obser.: 123.0929.

5.7.18 *N*-Ethyl-*N*-phenyl hydrazine (2r)

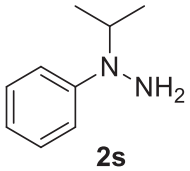


2r

The title compound was obtained as yellow liquid. Yield: 87% (118 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.33. IR (neat): 2989, 1689, 1587, 1250, 597 cm^{-1}. ^1H NMR (500 MHz,

$CDCl_3$) δ 7.18 (m, 2H), 6.91 (d, *J* = 7.2 Hz, 2H), 6.71 (m, 1H), 3.39 (q, *J* = 7.1 Hz, 4H (together CH_2 and broad peak of amine)), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 129.1, 117.1, 112.7, 38.4, 14.8. HRMS: Calc. for $C_8H_{12}N_2$ $[M+H]^+$: 137.1079, Obser.: 137.1068.

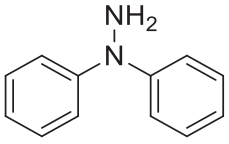
5.7.19 *N*-Isopropyl-*N*-phenyl hydrazine (2s)



2s

The title compound was obtained as yellow liquid. Yield: 73% (109 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.35. IR (neat): 2789, 1567, 1465, 1233, 585 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.20-7.15 (m, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.70 (t, *J* = 7.4 Hz, 1H), 4.00 (q, *J* = 6.4 Hz, 1H), 3.17 (s, 2H), 1.08 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 129.0, 118.0, 113.7, 50.6, 17.6. HRMS: Calc. for $C_9H_{14}N_2$ $[M+H]^+$: 151.1235, Obser.: 151.1227

5.7.20 *N*-Diphenyl hydrazine (2t)

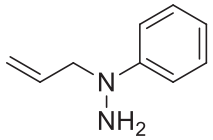


2t

The title compound was obtained as white solid. M.p. 89 °C.Yield: 81% (144 mg). The residue was purified by column chromatography in silica gel eluting with

hexane:EtOAc 85:15, R_f = 0.35. IR (neat): 2980, 1579, 1320, 1178, 620 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$). δ 7.28 (t, *J* = 7.8 Hz, 4H), 7.25-7.17 (m, 4H), 6.97 (t, *J* = 7.3 Hz, 2H), 3.77 (brs, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 129.0, 121.9, 119.4. HRMS: Calc. for $C_{12}H_{12}N_2$ $[M+H]^+$:185.1079, Obser.: 185.1067

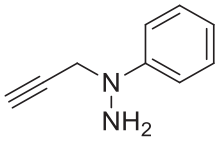
5.7.21 *N*-Allyl *N*-phenyl hydrazine (2u)



2u

The title compound was obtained as yellow liquid. Yield: 69% (102 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.35. IR (neat): 3325, 2986, 1673, 1210, 1108 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 5.80 (m, 1H), 5.27-5.17 (m, 2H), 3.95 (d, *J* = 5.8 Hz, 2H, CH_2), 3.50 (brs, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 132.6, 128.9, 118.6, 118.5, 113.7, 58.8. HRMS: Calc. for $C_9H_{12}N_2$ $[M+H]^+$: 149.1079, Obser.: 148.1068

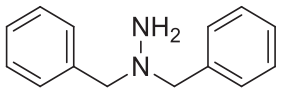
5.7.22 *N*-Propargyl-*N*-phenyl hydrazine (2v)



2v

The title compound was obtained as brown liquid. Yield: 71% (103 mg) The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 85:15, R_f = 0.33. IR (neat): 3520, 3278, 2289, 1659, 1429, 1243 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 4.18 (d, *J* = 2.3 Hz, 2H), 3.77 (brs, 2H, NH_2), 2.18 (t, *J* = 2.3 Hz, 1H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 128.9, 120.0, 115.1, 78.0, 73.2, 46.0. HRMS: Calc. for $C_9H_{10}N_2$ $[M+H]^+$: 147.0922, Obser.: 147.0915.

5.7.23 *N*,*N*-Dibenzyl hydrazine (2w)



2w

The title compound was obtained as white solid. M.p. 65 °C. Yield: 33% (74 mg). The residue was purified by column chromatography in silica gel eluting with hexane:EtOAc 80:20, R_f = 0.25. IR (neat): 3246, 29978, 1656, 1457, 1002 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.25 (m, 10H), 3.73 (s, 4H), 2.81 (brs, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 129.0, 128.3, 127.2, 64.8. HRMS: Calc. for $C_{14}H_{11}N_2$ $[M+H]^+$: 213.1392, Obser.: 213.1384.

5.8 Spectral Data of Few Products

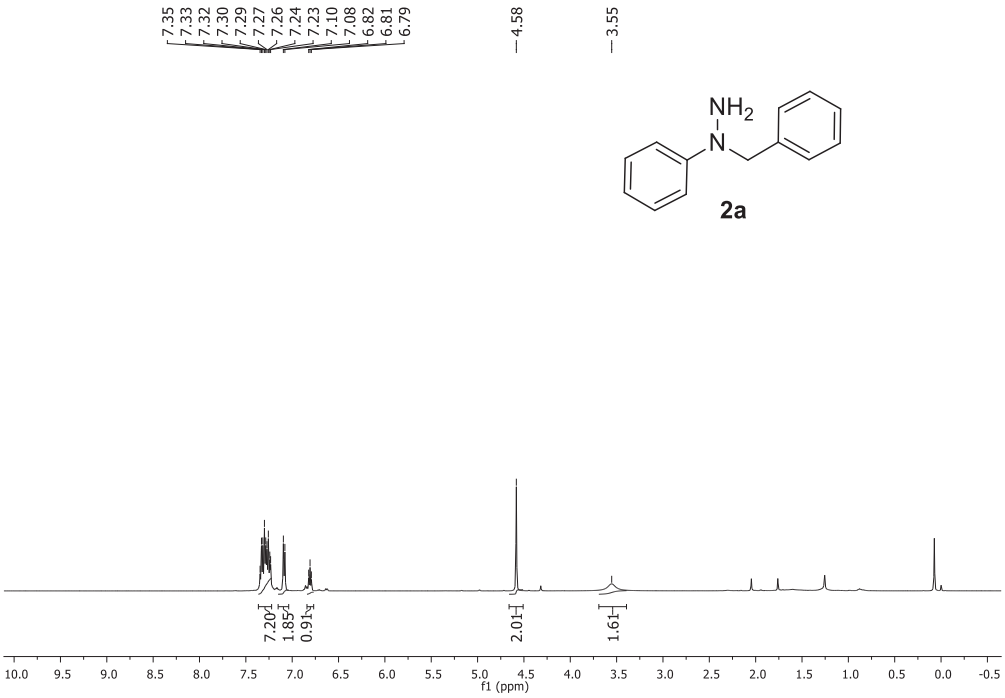


Figure 5.4 ^{1}H NMR of product **2a** in $CDCl_3$

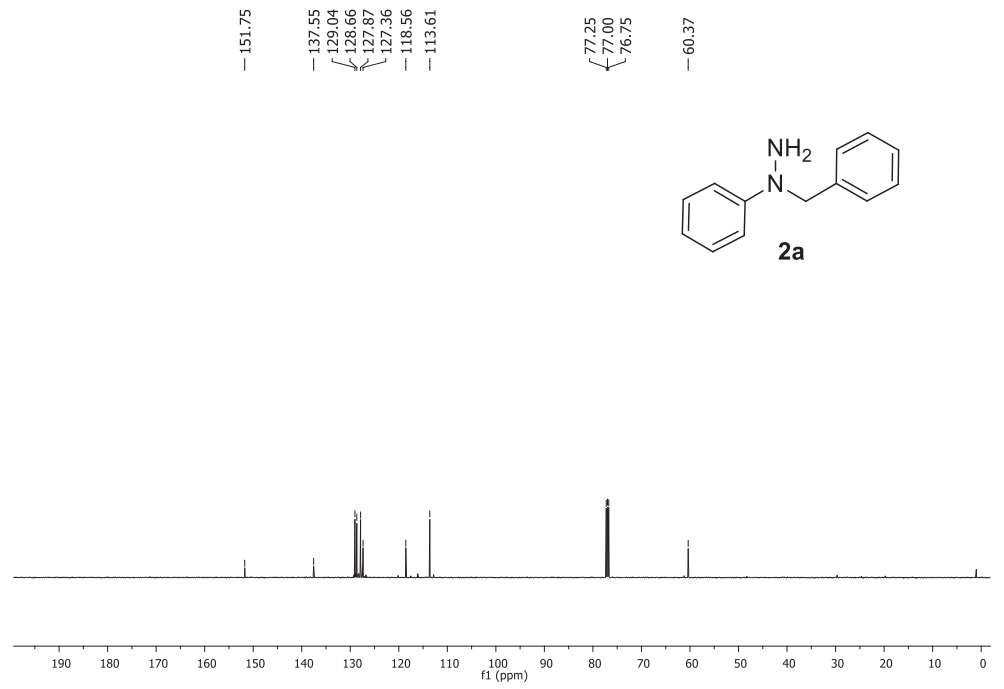


Figure 5.5 ^{13}C NMR of product **2a** in $CDCl_3$

5.9 References

[1] G. Le Goff, J. Ouazzani, "Natural hydrazine-containing compounds: Biosynthesis, isolation, biological activities and synthesis," *Bioorganic and Medicinal Chemistry*, **22**(2014) 6529-6544.

[2] R. Narang, B. Narasimhan, S. Sharma, "A review on biological activities and chemical synthesis of hydrazide derivatives," *Current medicinal Chemistry*, **19**(2012) 569-612.

[3] G. Verma, A. Marella, M. Shaquiquzzaman, M. Akhtar, M. R. Ali, M. M. Alam, "A review exploring biological activities of hydrazones," *Journal of Pharmacy and Bioallied Sciences*, **6**(2014) 69-80.

[4] U. Ragnarsson, "Synthetic methodology for alkyl substituted hydrazines," *Chemical Society Reviews*, **30**(2001) 205-213.

[5] T. K. Sasikumar, D. A. Burnett, H. Zhang, A. Smith-Torhan, A. Fawzi, J. E. Lachowicz, "Hydrazides of Clozapine: A new class of D1 dopamine receptor subtype selective antagonists," *Bioorganic and Medicinal Chemistry Letters*, **16**(2006) 4543-4547.

[6] S. S. Hong, S. A. Bavadekar, S. I. Lee, P. N. Patil, S. G. Lalchandani, D. R. Feller, D. D. Miller, "Bioisosteric phentolamine analogs as potent α-adrenergic antagonists," *Bioorganic and Medicinal Chemistry Letters,* **15**(2005) 4691-4695.

[7] C. P. Kordik, C. Luo, B. C. Zanoni, S. L. Dax, J. J. McNally, T. W. Lovenberg, S. J. Wilson, A. B. Reitz, "Aminopyrazoles with high affinity for the human neuropeptide Y5 recepto," *Bioorganic and Medicinal Chemistry Letters*, **11**(2001) 2283-2286.

[8] K. Xu, T. Gilles, B. Breit, "Asymmetric synthesis of *N*-allylic indoles *via* regio- and enantioselective allylation of aryl hydrazines," *Nature Communications*, **6**(2015) 7616.

[9] C. Cao, Y. Shi, A. L. Odom, "Intermolecular alkyne hydroaminations involving 1,1-disubstituted hydrazines," *Organic letters*, **4**(2002) 2853-2856.

[10] S. Muller, M. J. Webber, B. List, "The catalytic asymmetric Fischer indolization," *Journal of the American Chemical Society*, **133(**2011) 18534-18537.

[11]M. M. Guru, M. A. Ali, T. Punniyamurthy, "Copper-mediated synthesis of substituted 2-aryl-*N*-benzylbenzimidazoles and 2-arylbenzoxazoles *via* C-H functionalization/C-N/C-O bond formation," *Journal of Organic Chemistry*, **76**(2011) 5295-5308.

[12] Q. Tang, C. Zhang, M. Luo, "A new method for N-N bond cleavage of N,N-disubstituted hydrazines to secondary amines and direct *ortho* amination of naphthol and its analogues," *Journal of the American Chemical Society*, **130**(2008) 5840-5841.

[13] K. Nishimura, T. Kobata, H. Inada, Y. Shirota, Arylaldehyde, arylketone hydrazones as a new class of amorphous molecular materials," *Journal of Material Sciences*, **1**(1991) 897-898

[14] P. Strohriegl, J. V. Grazulevicius, "Charge-transporting molecular glasses," *Advanced Materials*, **14**(2002) 1439-1452.
[15] L.K.Rasmussen (Editior), Compounds with two carbon-heteroatom bonds, Science of Synthesis: Houben-Weyl methods of molecular transformations, Vol 40a, Georg Themie Verlag KG, Stuttgart. New York, 2007.
[16] A. Ali, P. Fisara, J. A. Freemont, S. Kyi, A. G. Meyer, A. G. Riches, R. M. Sargent, D. G. Sawutz, K. A. Turner, K. N. Winzenberg, Q. Yang, "Discovery of ectoparasiticidal hydrazonotrifluoromethanesulfonanilides," *Bioorganic and Medicinal Chemistry Letters*, **20**(2010) 649-652.
[17] U. Lerch, J. König, "Selective alkylation of phenylhydrazine: A facile and efficient synthesis of 1-alkyl-1-phenylhydrazines," *Synthesis*, **2**(1983) 157-158.
[18] C. G. Neochoritis, K. Wang, N. E.-Ortiz, E. Herdtweck, K. Kubica, A. Twarda, K. M. Zak, T. A. Holak, A. Domling, "2,30-Bis(10H-indole) heterocycles: New p53/MDM2/MDMX antagonists," *Bioorganic and Medicinal Chemistry Letters*, **25**(2015) 5661-5666.
[19] L. F. Audrieth, J. R. Weisiger, H. E. Carter, "Alkylation of phenylhydrazine in liquid ammonia," *Journal of Organic Chemistry,* **6**(1941) 417-420.
[20] L. Q. Jiang, X. Lu, H. Zhang, Y. W. Jiang, D. W. Ma, CuI/4-Hydro-l-proline as a more effective catalytic system for coupling of aryl bromides with N-Boc hydrazine and aqueous ammonia," *Journal of Organic Chemistry,* **74**(2009) 4542-4546
[21] M. S. Lam, H. W. Lee, A. S. C. Chan, F. Y. Kwong, "Copper(I)-picolinic acid catalyzed *N*-arylation of hydrazides," *Tetrahedron Letters*, **49**(2008) 6192-6194
[22] K. Kisseljova, O. Tsubrik, R. Sillard, S. Maeorg, U. Maeorg, "Addition of arylboronic acids to symmetrical and unsymmetrical azo compounds," *Organic letters*, **8**(2006) 43-45
[23] K. Y. Kim, J. T. Shin, K. S. Lee, C. G. Cho, "Cu(I) mediated one-pot synthesis of azobenzenes from *bis*-Boc aryl hydrazines and aryl halides," *Tetrahedron Letters*, **45**(2004) 117-120.
[24] R. H. Poirier, F. Benington, "Reduction of *N*-nitrosodiphenylamine to unsym-diphenylhydrazine by lithium aluminum hydride," *Journal of Chemical Society,* **74**(1952) 3192–3192.
[25] I. D. Entwistle, R. A. W. Johnstone, A. H. Wilby, "Metal-assisted reactions-Part II: Rapid reduction of *N*-nitrosoamines to *N*,*N*-disubstituted hydrazines; the utility of some low-valent titanium reagents," *Tetrahedron*, **38**(1982) 419-423.
[26] W. W. Hartman, L. J. Roll, "α-Methyl-α-phenylhydrazine," *Organic Syntheses,* **13**(1933) 66-67.
[27] S. Liu, Y. Liu, H. Wang, Y. Ding, H. Wu, J. Dong, A. Wong, S. H. Chen, G. Li, M. Chan, N. Sawyer, F. G. Gervais, M. Henault, S. Kargman, L. L. Bedard, Y. Han, R. Friesen, R. B. Lobell, D. M. Stout, "Design, synthesis, and evaluation of novel 3-amino-4-hydrazine-cyclobut-3-ene-1,2-diones as potent and selective CXCR2 chemokine receptor antagonists," *Bioorganic and Medicinal Chemistry Letters,* **19(**2009) 5741-5745.

[28] 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.
[29] S. V. Makarov, A. K. Horvath, R. Silaghi-Dumitrescu, Q. Gao, "Recent developments in the chemistry of thiourea oxides," *Chemistry: A European Journal*, **20**(2014) 14164-14176.
[30] V. E. Shashoua, "Formamidine sulfinic acid as a biochemical reducing agent," *Biochemistry,* **3**(1964) 1719-1720.
[31] W. Y. Gao, W. J. Qi, J. P. Lai, L. M. Qi, S. Majeed, G. B. Xu, "Thiourea dioxide as a unique eco-friendly coreactant for luminol chemiluminescence in the sensitive detection of luminol, thiourea dioxide and cobalt ions", *Chemical Communications*, **51**(2015) 1620-1623.
[32] S. Verma, R. Singh, D. Tripathi, P. Gupta, G. M. Bahuguna, S. L. Jain, "Thiourea dioxide with TBHP: A fruitful and greener recipe for the catalytic oxidation of alcohols," *RSC Advances*, **3**(2013) 4184-4188.
[33] S. Verma, S. Kumar, S. L. Jain, B. Sain, "Thiourea dioxide promoted efficient organocatalytic one-pot synthesis of a library of novel heterocyclic compounds," *Organic and Biomolecular Chemistry*, **9**(2011) 6943-6948.
[34] S. Kumar, S. L. Jain, B. Sain, "Thiourea dioxide promoted cobalt-catalyzed hydrolysis of imines: Dual activation *via* organocatalysis and metal catalysis," *RSC Advances*, **2**(2012) 789-791.
[35] R. Caputo, L. Mangoni, P. Monaco, G. Palambo, L. Previtera, "The role of thiourea S-S-dioxide in the reduction of steroidal ketones," *Tetrahedron Letters*, **12**(1975) 1041-1042.
[36] K. Nakagawa, K. Minami, "Reduction of organic compounds with thiourea dioxide. I. Reduction of ketones to secondary alcohols," *Tetrahedron Letters*, **13**(1972) 343-346.
[37] S. V. Makarov, "Recent trends in the chemistry of sulfur-containing reducing agents," *Russian Chemical Reviews*, **70**(2001) 885-895.
[38] R. Ayazi-Nasrabadi, "Thiourea Dioxide: A multi-purpose reagent," *Synlett*, **26**(2015) 1281-1282.
[39] C. G. Overberger, J. G. Lombardino, R. G. Hiskey, "Novel reductions of *N*-nitrosodibenzylamines-A new reaction," *Journal of American Chemical Society*, **80**(1958) 3009-3012.
[40] J. March, Advanced Organic Chemistry reactions, mechanisms and structure (3rd ed.). New York: John Wiley and Sons, inc. 1985
[41] Y. Hayashi, "Pot economy and one-pot synthesis," *Chemical Sciences*, **7**(2016) 866-880.
[42] The crude yield of *N*,*N*-dihexylhydrazine was judged based on the ^{1}H NMR.