Chapter II

Room Temperature Direct Reductive Amination of Carbonyl compounds by L-ascorbic acid – $NaBH_4$ in Water

II.A. Introduction

Amines are functional groups containing basic nitrogen atom. As the nitrogen bears a lone pair of electrons, it is a lewis base. Amines are previously prepared from ammonia where one or more hydrogen atoms are replaces by alkyl or aryl groups. Presence of hydrogen bond influences the property of primary and secondary amines significantly but tertiary amines do not have any influence of hydrogen. Due to that amine shows good solubility in water owing to hydrogen bonding, though amines with larger substituents are lipophilic in nature. Amines are ubiquitous in biological field as they are structural units of amino acids. For instance, a decaying fish smells of trimethyl amine as a result of breakdown in amino acids present in it. Neurotransmitters like norepinephrine, epinephrine, serotonin, dopamine and histamine are amines.

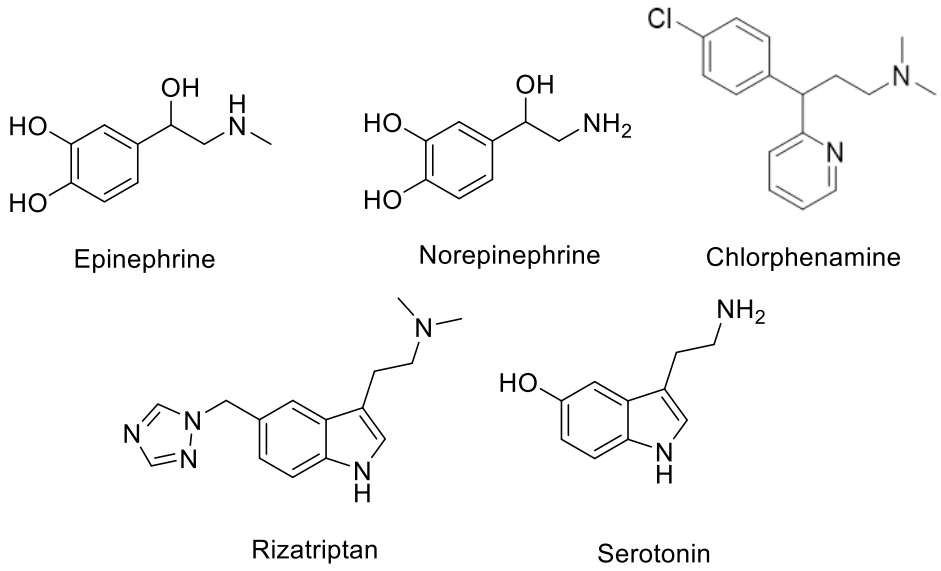


Figure II.1. Neurotransmitters containing amines.

Most common positively charged moieties in proteins are protonated amino groups ($-NH_3^+$). Specially in amino acids like lysine. Further, the anionic polymer of DNA is also bound to different amine containing proteins. Primary amines are also used majorly as starting material of many azo dyes such as Methyl orange, Ponceau, Direct brown 138, Sunset yellow FCF etc. Around the world approximately 40-42% drugs contain amine functional groups it their structure. A few examples are, opiate analgesics like codeine, morphine and heroin are tertiary amines. Amoxapine, nortriptyline and desipramine are secondary amines and tricyclic antidepressants. Ephedrine and phenylephrine are amine hydrochlorides and are applied as decongestants. Chlorpromazine is a tranquilizer that sedates but without inducing sleep. Chlorpheniramine is an antihistamine that aids to discharge allergic conditions due to cold, insect bites, hay fever, itchy skin and stings.

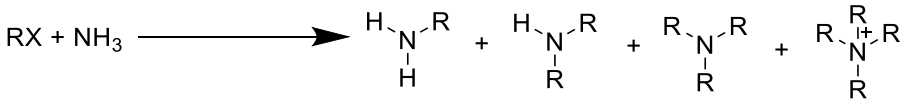
In natural gas industry, to remove CO_2 and H_2S in refining process various amines are employed such as, Aqueous monoethanolamine (MEA), diglycolamine (DGA), diisopropanolamine (DIPA) diethanolamine (DEA) and methyldiethanolamine (MDEA). Amines also posess the ability to reduce greenhouse gasses from the environment. This type of gas treatment by amines are also known as amine scrubbing, gas sweetening and acid gas removal.

Dimethylethylamine, cyclohexylamine, a variety of diamines such as 4,4-diaminodicyclohexylmethane and multifunctional amines like triethylenetetramine tetraethylenepentamine are often used as epoxy resin curing agents. The lone pair electrons present on nitrogen in amine attacks the outermost carbon in oxirane ring of the epoxy resin that relieves stress on the epoxide and leads to the reaction.

Though amines are easily handleable compounds, low molecular weight amines are often slightly toxic in nature whereas complex members of the class like heroin or strychnine can also be extremely bioactive in nature.

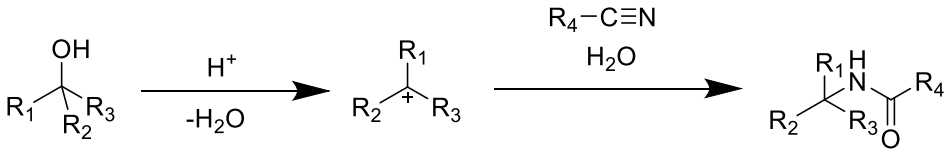
II.B. Background and objectives

In large scale alkyl amines are prepared by amination of alcohols by ammonia. In laboratory another facile route is formation of amines by alkylation of ammonia by haloalkanes (Scheme II.1). But in such reactions a major drawback is formation of mixture of primary, secondary and tertiary amines as a product along with ammonium salt formation. Use of excess ammonia often elevates the yield of primary amine formation but lacks in formation of secondary and tertiary amines in the process. Further, the reaction is not completely -free of unwanted byproducts. Also following the route, a huge amount of ammonia is often wasted considering the reaction requirements.



Scheme II.1. Preparation of amines by amination of alkyl halides.

To overcome the hurdles another method is suggested in Ritter's reaction[1] in which disubstituted alkenes reacts with HCN in a strong acid catalyzed condition (Scheme II.2). This method is also employed industrially for production of mainly tertiary amines. Clearly this reaction lacks in ease of handling of the reactants and definitely a hazardous alternative.

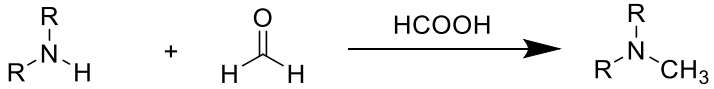


Scheme II.2. Synthesis of amine from cyanide in presence of strong acid.

Hydroamination has also been practiced as an alternate catalyzed by zeolite based solid acids. Many reductive routes have also been explored like hydrogenation using hydrogen and nickel as catalyst. *N*-containing functional groups from which amines have been prepared are azides, imines, oximes, amides, nitriles and nitro groups. But these protocols suffer from functional group sensitivity as it reduces other functional groups too. Further use of metal is always a limitation towards green synthetic approach. $LiAlH_4$ is also commonly applied for reduction purpose.

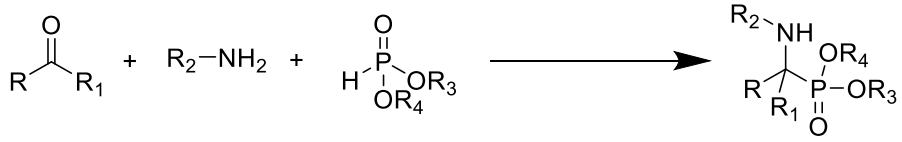
II.B.1. Specialized methods for synthesis of substituted amines

Many advancements have been reported for synthesis of amines and their derivatives. W. Eschweiler *et al.* reported in 1905 preparation of amines from aldehyde using formic acid as catalyst[2]. This simple reaction allows the synthesis of tertiary methyl amines from secondary amines by treating it with formaldehyde (Scheme II.3). In this reaction the formate ion is utilised as hydride donor for the reduction of iminium ion formed. So overall it can be termed as reductive amination too. By this process formation of quaternary salts of amines is not possible.



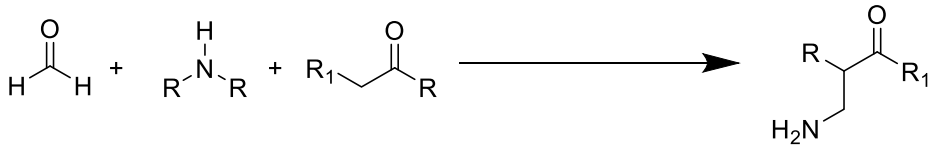
Scheme II.3. Synthesis of amine from formaldehyde and secondary amines catalyzed by formic acid.

The Kabachnik-Fields Reaction shows vast importance in drug discovery research for the formation of peptidomimetic compounds. In this reaction carbonyl compound couples with amine and a hydrophosphoryl compound which leads to the formation of α-aminophosphonates[3]. Initially very few aldehydes were successfully used in this method for preparation of respective α-aminophosphonates. But advancement of this reaction now permits use of various carbonyl compound even sterically hindered carbonyl compounds can be used as starting materials (Scheme II.4).



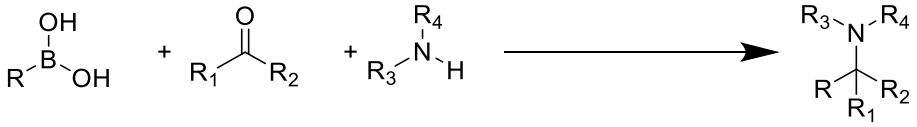
Scheme II.4. Synthesis of α-aminophosphonates by condensation of carbonyl, amine and hydrophosphoryl compound.

Another multi component condensation of aldehyde having no alpha hydrogens with primary and secondary amine and another enolizable carbonyl compound produces aminomethylated corresponding products (Scheme II.5). This reaction is well known as Mannich reaction[4] and in this reaction the iminium derivative of the aldehyde acts as the acceptor. Mannich reaction is vastly involved in many biosynthetic pathways mainly for alkaloids.



Scheme II.5. Multicomponent condensation to produce aminomethylated products.

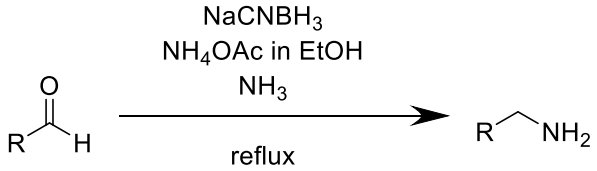
An advancement of previous process is known as Petasis reaction or also known as Boronic Acid Mannich Reaction[5]. In this multicomponent reaction, amines and their derivatives are prepared via reaction of imine with organic ligands of boronic acids, where boronic acid acts as a nucleophile (Scheme II.6). The role of boronic acid is very much similar to the role of enolizable carbonyl compound in mannich reaction.



Scheme II.6. Multicomponent synthesis of amine and its derivatives by boronic acid.

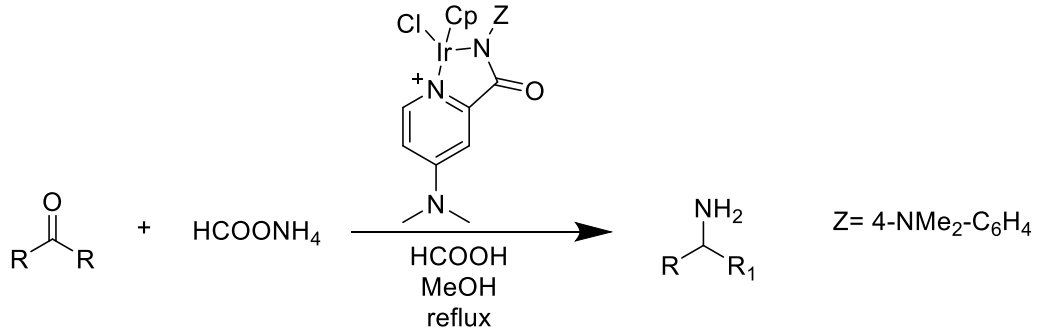
II.B.2. Modern approach towards reductive amination

M. S. M. Timmer *et al.* reported metal hydride ammonia mediated reductive amination of aldehydes[6]. In this reaction primary amines are selectively prepared without forming any unwanted byproducts such as secondary and tertiary amines. This protocol is applicable on a range of aldehydes, even on in situ formed aldehydes produced by Vasella reaction[7].



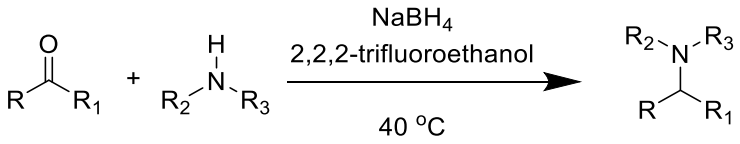
Scheme II.7. Synthesis of primary amines in metal hydride/ammonia.

M. Watanabe *et al.* reported another facile method recently for synthesis of primary amines from ketones by direct reductive amination[8]. The reaction is catalyzed by Cp*Ir complexes bearing a 2-picolinamide moiety. In this reaction ammonium formate acts as both nitrogen and hydrogen source (Scheme II.8).



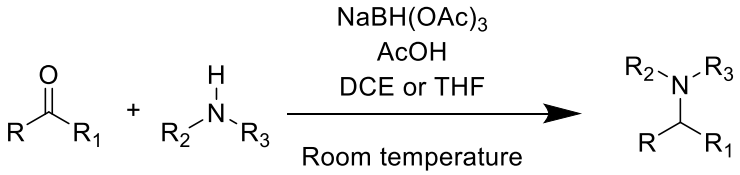
Scheme II.8. Synthesis of primary amine by Cp-Ir complex from ketones.

S. Khaksar *et al.* reported alternative way of synthesis of substituted amine by a mild and convenient procedure[9]. This method starts with primary and secondary amines and ketones to produce *N*,*N*-dimethyl tertiary amines. Sodium borohydride is used as reducing agent without use of any catalyst in 2,2,2-trifluoroethanol at 40 ^{o}C (Scheme II.9). An advantage of this method is the reusability of the solvent.



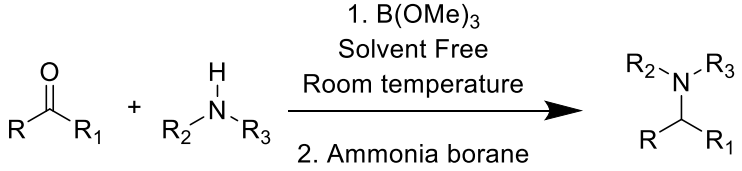
Scheme II.9. Synthesis of tertiary amine from primary and secondary amines by sodium borohydride in 2,2,2-trifluoroethanol.

Sodium triacetoxyborohydride has also been employed as selective reducing agent for reductive amination of various aldehydes and ketones by R. D. Shah *et al.*[10]. 1,2-Dichloroethane (DCE) is used as solvent in this reaction. But this reaction also shows prominent result with tetrahydrofuran and even acetonitrile (Scheme II.10). In special cases of ketones as reactants, acetic acid can be used as catalyst too. This reaction has a huge functional group tolerance such as nitro, cyano and even unsaturation of C-C bond.



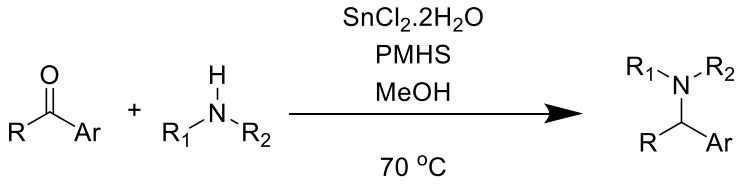
Scheme II.10. Synthesis of substituted amines by Sodium triacetoxyborohydride.

A very recent study on reductive amination successfully achieves the desired product in a solvent -free condition by using trimethyl borate as catalyst. This reaction was reported by A. Singh *et al.*[11] (Scheme II.11). This reductive amination process successfully converts aromatic and aliphatic aldehydes and ketones into aliphatic and aromatic substituted amines respectively in which borane itself acts as reductant as well. The only drawback of this process being its time requirement which is up to 36 hours.



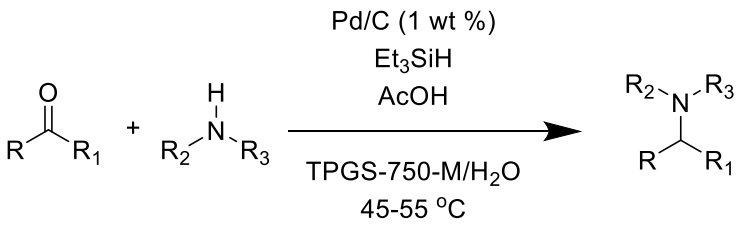
Scheme II.11. Synthesis of substituted amines in solvent -free condition by trimethyl borate.

N. Kumar *et al.* developed Chemoselective reductive amination process using stannous chloride as catalyst in presence of polymethylhydrosiloxane as reductant[12]. Methanol is used as solvent in this reaction and the reaction is optimized at 70 ºC (Scheme II.12). Various aromatic carbonyl compounds produce respective secondary and tertiary amines in good yield in this process.



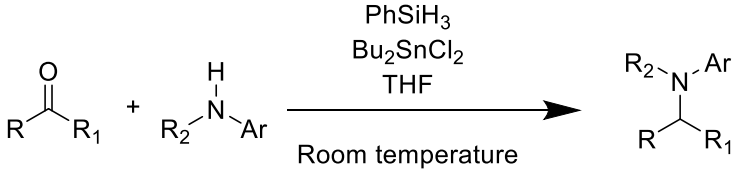
Scheme II.12. Synthesis of substituted amines by stannous chloride.

Another very recent exploration of reductive amination has been reported by B. H. Lipshutz *et al.*[13].This reaction is mediated by hydrophobic cores of nanomicelles, an environmentally benign surfactant TPGS-750-M, in water. A broad range of aldehydes, ketones with amines undergo this protocol under mild condition. Presence of 0.20 mol % Pd/C and triethylsilane is required for satisfactory yield of desired product of secondary and tertiary amines (Scheme II.13). The use of TPGS-750-M makes this protocol costly which can be a downside of this methodology.



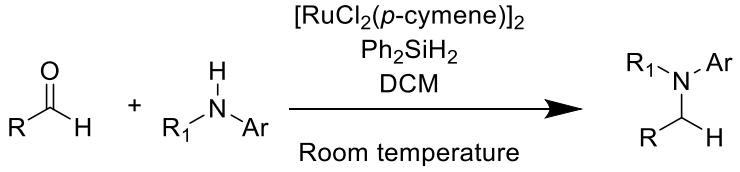
Scheme II.13. Synthesis of substituted amines by hydrophobic cores of nanomicelles in water.

W. Xiao *et al.* developed dibutyltin dichloride catalyzed direct reductive amination of aldehydes and ketones[14]. Phenylsilane is used as reductant in this case in presence of THF as solvent. The reaction produces good yield of desired product even at room temperature (Scheme II.14). Anilines and dialkyl amines give good product yield in this reaction but an exception for monoalkylamines is a boundary of the reaction. Further this reaction reveals a time requirement of up to 24 hours which is another limitation of this methodology.



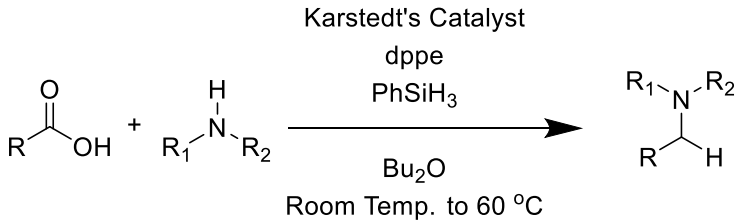
Scheme II.14. Direct reductive amination of aldehydes and ketones in the presence of phenylsilane.

Reductive amination using $[RuCl_2(p\text{-cymene})]_2/Ph_2SiH_2$ catalytic system has been introduced by L. Chen *et al.*[15]. Aldehydes with various substituted anilines produced good yield of desired product in this reaction protocol. DCM is used as solvent at room temperature for this protocol (Scheme II.15). Secondary as well as tertiary amines has been successfully synthesized by this reaction. In terms of functional group tolerance this reaction exhibits wide range of functional groups tolerance such as, CN, NO_2, COOMe, F, Cl, OMe, Me, Br, alkyl and furyl. The only notable drawback is difficulty to produce $[RuCl_2(p\text{-cymene})]_2/Ph_2SiH_2$ catalytic system in economic condition.



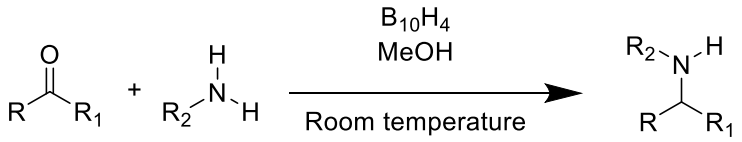
Scheme II.15. Synthesis of secondary and tertiary amines in $[RuCl_2(p\text{-cymene})]_2/Ph_2SiH_2$ catalytic system.

Another route of *N*-alkyl amine formation is suggested by M. Beller *et al.* This methodology starts with carboxylic acid in presence of silanes, 1,2-Bis(diphenylphosphino)ethane (dppe) and Karstedt's catalyst [16]. The hydride source as silane enables C-N bond construction in an efficient and mild way in this reaction (Scheme II.16). A wide range of alkylated secondary and tertiary amine can be achieved by this reaction process. Some notable amines like bioactive compound Cinacalcet HCl and fluoroalkyl-substituted anilines has been successfully prepared by this process.



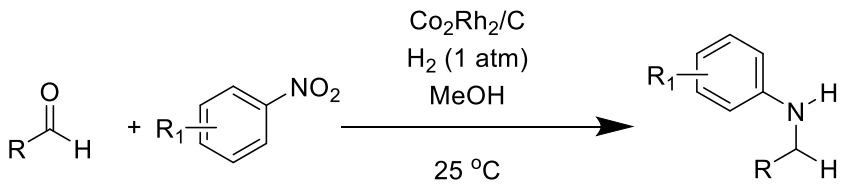
Scheme II.16. Synthesis of alkylated secondary and tertiary amines using Karstedt's catalyst and silanes.

An easy and efficient reductive amination of carbonyls with amines is reported by C. M. Yoon *et al.* using decaborane in methanol[17]. Room temperature is maintained during the process under nitrogen atmosphere to control high reactivity of decaborane (Scheme II.17). Another limitation of the reaction is inability to produce tertiary amines.



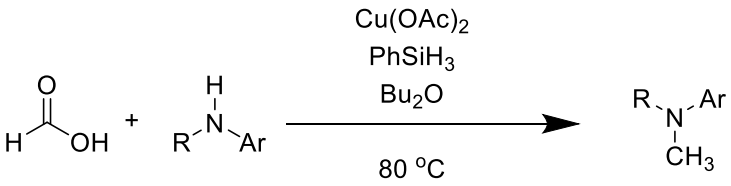
Scheme II.17. Synthesis of secondary amines using decaborane in methanol.

A distinct methodology for synthesis of substituted amines by reductive amination is reported by Y. K. Chung *et al.* using Cobalt-rhodium heterobimetallic nanoparticles[18]. Aromatic nitro compounds are used as precursor of desired substituted amines and the nitro compounds are reacted with aldehydes under mild condition at 25 °C. 1 atm of H_2 pressure is required throughout the reaction for reduction purpose. Reusability of catalyst and gram scale production of substituted amines are two major highlights of this reaction methodology (Scheme II.18). But use of metal catalyst and costly reaction setup can be considered as limitation of the process.



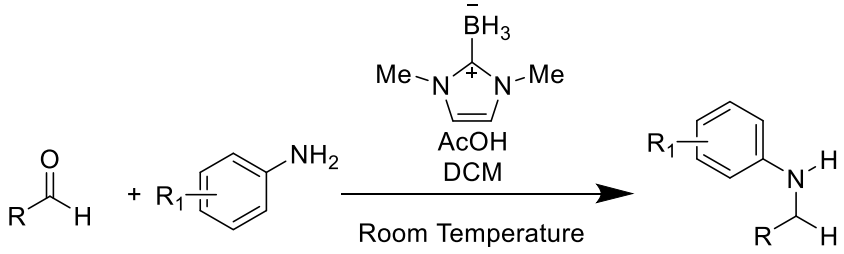
Scheme II.18. Synthesis of secondary amines using Cobalt-rhodium heterobimetallic nanoparticles.

Another copper catalyzed protocol for reductive methylation was formulated by L.N. He *et al.*[19]. By this protocol amines and imines were successfully condensed with formic acid in presence of phenyl silane as reducing agent to produce corresponding substituted amines. Bu_2O is applied as solvent at 80 °C. Copper acetate is used as catalyst in this method (Scheme II.19). Use of metal catalyst is a drawback in this case.



Scheme II.19. Synthesis of methylated anilines catalyzed by copper in presence of phenyl silane.

D. P. Curran *et al.* proposed reductive amination by *N*-heterocyclic carbene boranes (NHC-boranes)[20]. Carbene boranes like diMe-Imd-BH_3 are one of the most nucleophilic classes of neutral hydride donors. Definitely this heterocycle is yet to be explored to its full potential. Highly electron poor bonds like C=N and C=C provide hydrogenation products in addition with stable borylated products. Various aldehydes with aniline produce corresponding substituted amines in this process. Difficulty in catalyst preparation can be a drawback in this process.



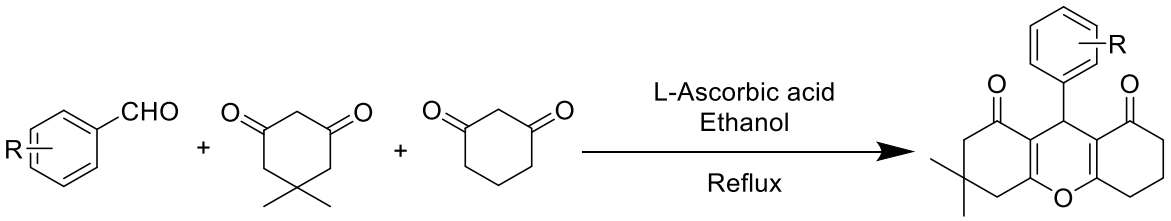
Scheme II.20. Synthesis of substituted anilines using diMe-Imd-BH_3.

II.B.3. Background of L-ascorbic acid in organic synthesis

In recent times organo catalyts mediated reaction have gained ample interest due to its greener approach towards synthesis of organic compounds as a substitute to metal catalysts. The superiority of organ catalysts over metal catalysts lies within their inexpensiveness, ease of

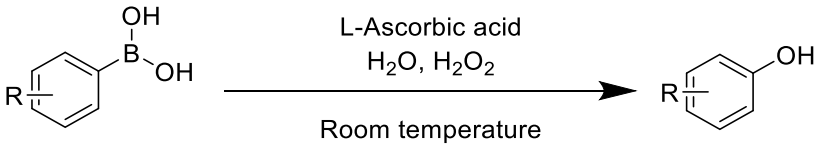
availability, environmental sustainability, easy handling, nontoxic nature[21]. L-ascorbic acid is known to mankind for a very long time as vitamin-C. L-ascorbic has exceptional medicinal values to cure numerous diseases. However, application of L-ascorbic acid as organo catalyst was very little explored up to later part of twentieth century. After that period of time L-ascorbic acid has been proven to be effective organo catalyst for modelling synthetic route to many biologically significant compounds and chemotherapeutic agents.

In 2014 E.H Chung *et al.* synthesis of 3,4,6,7- tetrahydro-3,3-dimethyl-9-phenyl-2*H*-xanthene-1,8(5*H*,9*H*)-diones with ascorbic acid as catalyst in ethanol[22]. The reaction takes place in reflux condition and reported good yields of desired xanthene dione derivatives (Scheme II.21).



Scheme II.21. Synthesis of 3,4,6,7-tetrahydro-3,3-dimethyl-9-phenyl- 2*H*-xanthene-1,8(5*H*,9*H*)-diones catalyzed by ascorbic acid.

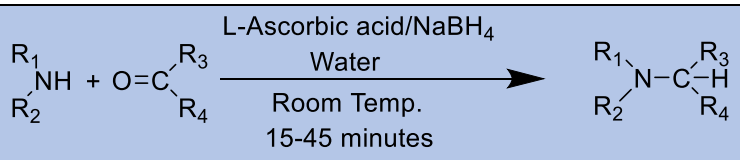
Another prominent organic synthesis of phenol derivatives reported by U. Bora *et al.* catalyzed by L-ascorbic acid in water and hydrogen peroxide[23]. Aryl boronic acids were used as precursor for the reaction and good yield of corresponding phenols were reported at room temperature (Scheme II.22).



Scheme II.22. Synthesis of phenols from aryl boronic acid by using ascorbic acid.

II.C. Present Work

Here we are reporting a novel, biomimetic concept for the direct reductive amination of aldehyde and ketones is developed which uses largely available, low cost and harmless L-ascorbic acid as sustainable, versatile, non-toxic catalyst and $NaBH_4$ as a reductant. Described herein is a one -pot conversion of effortlessly accessible primary and secondary amines to biologically active higher degree amines in water at room temperature. The mild condition, environmentally benign by-products and broad scope of makes this transformation very useful.



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Scheme II.23. Direct reductive amination in L-ascorbic acid and water at room temperature.

II.C.1 Result and discussion

Preliminary study was carried out to study the feasibility and reaction conditions of the imine reduction and direct reductive amination. $NaBH_4$ is selected as reducing agent over other available options due to its ability to rapidly reduce the imine to corresponding desired amine. The obstructing possibility is the $NaBH_4$ with water produces a low hydrogen yield due to pH stabilization of reaction medium, which is caused by formation of strongly basic metaborate ions. The addition of L-ascorbic acid delays the formation of the metaborate ions by shifting the pH of the reaction medium to lower values which eventually increases the H-Yield[24]. In order to establish superiority of L-ascorbic acid over other reducing agents we attempted various catalyst or reductant couples like PTSA/$NaBH_4$ (Table II.1, entry 1), H_3BO_3/ $NaBH_4$ (Table II.1, entry 2), Ph-COOH/$NaBH_4$ (Table II.1, entry 4), CH_3COOH/ $NaBH_4$ (Table II.1, entry 5). Among these PTSA/$NaBH_4$ (Table II.1, entry 1) and H_3BO_3/$NaBH_4$ (Table II.1, entry 2) shows prominent yield but L-ascorbic acid/$NaBH_4$ (Table II.1, entry 3) reducing couple proves to be the best couple in terms of yield. We also tried to carry out the scheme solely employing L-ascorbic acid and $NaBH_4$ but failed to generate any desired product. This suggests the enhancement in catalytic activity of L-ascorbic acid/$NaBH_4$ (Table II.1, entry 3) couple as reducing agent.

Table II.1. [a]Optimization of the reducing agent for direct reductive amination for the synthesis of *N*-benzylaniline

Entry	Reductant	Yield [%][b]
1	PTSA/$NaBH_4$	95%
2	H_3BO_3/ $NaBH_4$	92%
3	**L-ascorbic acid/$NaBH_4$**	**97%**
4	Ph-COOH/ $NaBH_4$	60%
5	CH_3COOH/ $NaBH_4$	50%
6	L-ascorbic acid	-
7	$NaBH_4$	-

The bold signifies most optimized condition.

[a] Reaction of Benzaldehyde (1 mmol), aniline (1 mmol) in presence of reducing agent and 5 ml of water as solvent at room temperature.

[b] Isolated yield

Our investigation for direct reductive amination of carbonyls and primary and secondary amines by L-ascorbic acid/$NaBH_4$ has been tested initially in neat condition (Table II.2, entry 8). Dissatisfied by the % yield in neat condition, we tried with various other solvents like methanol (Table II.2, entry 1), ethanol (Table II.2, entry 2), acetonitrile (Table II.2, entry 3), water (Table II.2, entry 6), glycerol (Table II.2, entry 4), PEG-300 (Table II.2, entry 5). Even mixtures of water/ethanol (1:1) (Table II.2, entry 7) was also tested. From our observation, water and acetonitrile both shows prominent results. Among all the other solvents water (Table II.2, entry 6) is the cheapest, non-flammable, non-toxic and environmentally benign solvent. Further, reaction in water eliminates the additional efforts of preparing anhydrous substances before use. So, water is selected as our suitable catalyst for its superiority over other organic solvents.

Table II.2. [a]Optimization of solvent for direct reductive amination for the synthesis of *N*-benzylaniline.

Entry	Solvent[b]	Yield [%][c]
1	CH_3OH	80%
2	C_2H_5OH	85%
3	Acetonitrile	98%
4	Glycerol	30%
5	PEG-300	45%
6	**H_2O**	**97%**
7	H_2O+ C_2H_5OH (1:1)	90%
8	Neat	~20%

The bold signifies most optimized condition.

[a] Reaction of Benzaldehyde (1 mmol), aniline (1 mmol) in presence of reducing agent at room temperature.

[b] 5 ml of solvent is taken

[c] Isolated yield

Room temperature is maintained during the reaction. This not only simplifies the reaction conditions but also terminates the reducing probability of aldehydes. After knowing the important role played by L-ascorbic acid/$NaBH_4$ couple we examined the optimum amount required for the direct reductive amination process. We started with 0.5 mmol of each L-ascorbic acid/$NaBH_4$ (1:1) (Table II.3, entry 1) reducing couple but failed to generate desired

significant yield. After several attempts 3 mmol of L-ascorbic acid/$NaBH_4$ in 1:2 (Table II.3, entry 3) ratio provided 97% yield, which is the highest among the other results.

Table II.3: [a]Optimization of amount of catalyst for direct reductive amination for the synthesis of *N*-benzylaniline.

Entry	L-ascorbic acid (mmol)	$NaBH_4$ (mmol)	Yield [%][b]
1	0.5	0.5	40%
2	1	1	80%
3	**1**	**2**	**97%**
4	2	1	75%
5	2	2	95%

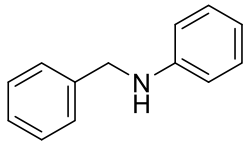
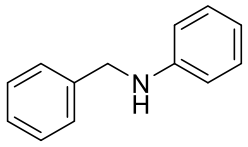
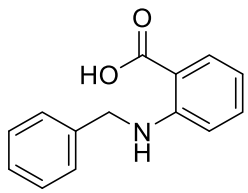
The bold signifies most optimized condition.

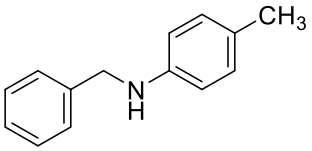
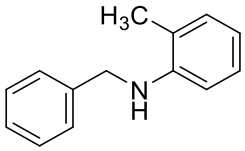
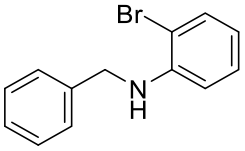
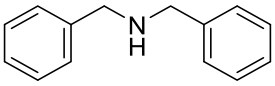
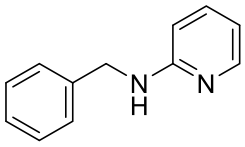
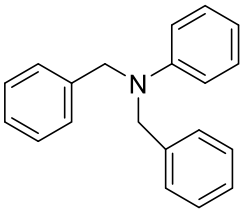
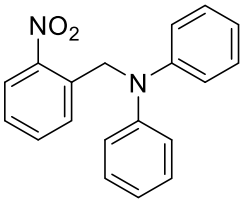
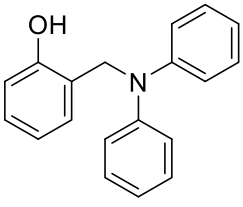
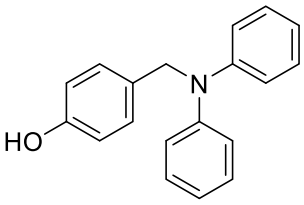
[a] Reaction of Benzaldehyde (1 mmol), aniline (1 mmol) in presence of reducing agent at room temperature.

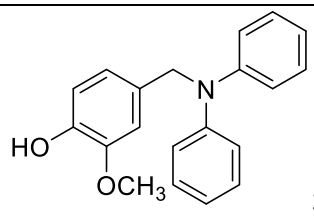
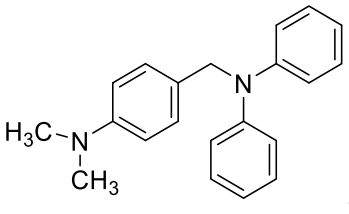
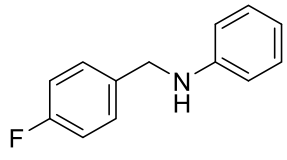
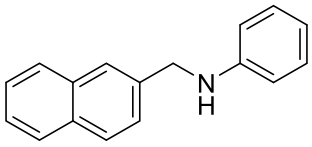
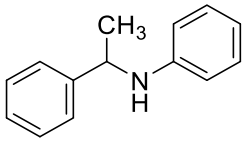
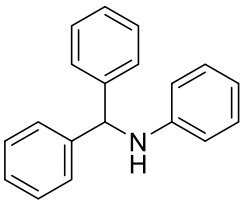
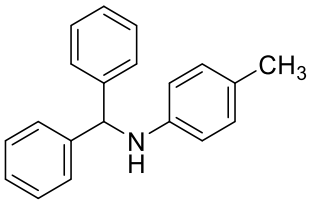
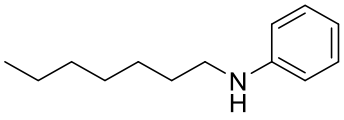
[b] Isolated yield

After achieving the optimum condition for the reaction, we then started to explore the reaction with various aldehydes and amines. The aldehydes (entry 3a-3p) and amines used were aromatic (entry 3a-3p) (containing electron withdrawing and electron donating groups) and aliphatic (entry 3t) both. Aromatic amine and aldehydes produce better result in the reaction (entry 3a – 3s). Electron withdrawing groups present in amines results in slightly lower yield whereas electron withdrawing group present in aldehyde escalates the yield. This is probably due to the increase in positive character of the carbonyl carbon atom. We further investigated the protocol exploring ketones (entry 3q - 3s) and the received yield was very satisfying.

Table II.4: [a]Synthesis of *N*-benzylaniline derivatives.

Entry	Product	Yield (%)[b]
1	 3a	97
2	 3b	82
3	 3c	84

4	 3d	92
5	 3e	93
6	 3f	88
7	 3g	83
8	 3h	86
9	 3i	82
10	 3j	85
11	 3k	87
12	 3l	88

13	 3m	75
14	 3n	92
15	 3o	89
16	 3p	65
17	 3q	85
18	 3r	83
19	 3s	90
20	 3t	72

[a]Reaction conditions: Aldehyde/ ketone (1.0 mmol), amine (1.0 mmol), in presence of reducing agent in water as the solvent (5 mL), at room temperature.

[b]Isolated yield of product measured by column chromatography.

Lower yield observed in some cases may be due to presence of electron withdrawing groups (entry 3b, entry 3c, entry 3j) or steric hindrance between the phenyl rings present in close vicinity (entry 3i, entry 3m, entry 3r). Presence of larger rings like naphthalene (entry 3p)

decreases the yield considerably. Also, the scheme produced less yield with aliphatic aldehydes like heptanal (entry 3t). Heterocyclic products also have shown promising yield (entry 3h).

II.D. Conclusion

In conclusion we have developed a simple, relevant, benign and eco-friendly facile strategy for the direct reductive amination using L-ascorbic acid and $NaBH_4$ without any transition metal catalysts. Use of water as solvent further enhances the advantage of the protocol. Replacement of expensive and toxic metal catalysts by environment friendly L-ascorbic acid is the highlight of this protocol. Further achievement of good yield with ketones and production of 3° amines in less reaction time and at room temperature has added further advantages to this protocol. Therefore, we expect this protocol to achieve wide application in natural product synthesis and in pharmaceutical industry.

II.E. Experimental

II.E.1. General Information

^{1}H NMR were recorded using 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

II.E.2. General procedure for the Direct reductive amination

A mixture of Carbonyl (1 mmol) and amine (1 mmol) in the presence of L-ascorbic acid (1 mmol) and $NaBH_4$ (2 mmol) was stirred at room temperature in water as solvent (5 ml). After completion of the reaction (observed by TLC), the reaction mixture was cooled down to room temperature. The solution was poured into 100 ml water and extracted with ethyl acetate, and washed several times with water. The organic mixture was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ ethyl acetate as eluent to afford the pure product. All products were characterized by ^{1}H NMR and ^{13}C NMR.

II.E.3. Spectroscopy data

1. *N*-benzylaniline [25] (Table II.4, entry 3a) (97% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.22 (br s, 1H), 4.35 (s, 2H), 6.67 (d, *J*= 7.9 Hz, 2H),6.75 (t, *J*= 7.3 Hz, 1H), 7.20 (t, *J*= 7.9 Hz, 2H), 7.26 - 7.47 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.4, 112.9, 117.7, 127.2, 127.5, 128.6, 129. 2, 139.3, 147.9 ppm.

2. *N*-benzyl-2-nitroaniline (Table II.4, entry 3b) (82% yield). ^{1}H NMR (300MHz, $CDCl_3$) : δ = 4.32 (s, 2H), 6.81 (br s, 1H), 7.08 (t, *J*= 7.5Hz, 1H), 7.31-7.46 (m, 6H), 7.67 (t, *J*= 7.5 Hz, 1H), 8.20 (d, *J*= 7.5 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.0, 114.4, 118.0, 125.9, 126.7, 126.9, 128.5, 131.7, 135.6, 139.9, 146.7 ppm.

3. 2-(Benzylamino)benzoic acid (Table II.4, entry 3c) (84% yield). ^{1}H NMR (300MHz, $CDCl_3$) : δ = 4.32 (s, 2H), 6.92 (br s, 1H), 7.03 (d, 1H, *J* = 7.5 Hz), 7.29- 7.38 (m, 5H, *J* = 7.3Hz), 7.53 (t, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 7.5Hz, 1H), 13.11 (br s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.1, 107.4, 113.4, 117.0, 126.7, 126.8, 126.9, 128.5, 128.6, 131.1, 139.9, 150.1, 169.3 ppm.

4. *N*-benzyl-4-methylaniline (Table II.4, entry 3d) (93% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (s, 3H), 4.02 (br s, 1H), 4.36 (s, 2H) 6.47 -6.57 (m, 2H), 6.60 (d, *J* = 6.9 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.28 - 7.45 (m, 5H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.6, 48.4, 110.0, 113.1, 113.7, 118.6, 127.2, 127.5, 128.6, 129.1, 129.7, 139.0, 139.5, 148.2 ppm.

5. *N*-benzyl-2-methylaniline[25] (Table II.4, entry 3e) (93% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.16 (s, 3H), 3.96 (br s, 1H), 4.37 (s, 2H), 6.62 (d, *J* = 7.9 Hz, 1H), 6.68 (t, *J* = 7.3 Hz, 1H), 7.09 (dd, *J* = 15.1, 7.5 Hz, 2H), 7.28 (t, *J* = 7.0 Hz, 1H), 7.31 - 7.41 (m, 4H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.5, 48.4, 110.1, 117.3, 122.0, 127.2, 127.3, 127.6, 128.6, 130.1, 139.4, 145.9 ppm.

6. *N*-benzyl-2-bromoaniline[26] (Table II.4, entry 3f) (88% yield): H^1 NMR ($CDCl_3$, 300 MHz) δ= 7.43-7.39 (m, 1H), 7.33-7.23 (m, 5H), 7.12-7.06 (m, 1H), 6.58-6.51 (m, 2H), 4.64 (br, 1H), 4.34 (s, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz) δ=144.9, 138.8, 132.5, 128.8, 128.6, 127.4, 127.3, 118.1, 111.7, 109.8, 48.1 ppm.

7. *N*-(phenylmethyl)-benzenemethanamine (Table II.4, entry 3g) (83% yield): H^1 NMR ($CDCl_3$, 300 MHz) δ= 3.76 (s, 2H), 5.01 (br s, 1H), 7.29-7.61 (m, 10H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 57.8, 127.0, 127.9, 128.5, 140.2 ppm.

8. *N*-benzylpyridin-2-amine (Table II.4, entry 3h) (86% yield): H^1 NMR ($CDCl_3$, 300 MHz) δ= 4.35 (s,1H), 6.41-6.58 (m, 1H), 6.93 (br s, 1H), 7.13 – 7.42 (m, 5H), 7.86-7.98 (m, 2H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 46.4, 106.5, 126.7, 126.9, 128.5, 138.3, 139.9, 148.1, 158.5 ppm.

9. *N, N*-dibenzylaniline[27] (Table II.4, entry 3i) (82% yield): ^{1}H NMR (400MHz, $CDCl_3$): δ 7.15-7.34 (m, 12H), δ 6.68-6.74 (m, 3H), δ 4.65 (s, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ= 149.15, 138.57, 129.20, 128.61, 126.85, 126.62, 116.68, 112.41, 54.15 ppm.

10. *N*-(2-nitrobenzyl)-*N*-phenylaniline (Table II.4, entry 3j) (85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.20 (s, 2H), 7.06-7.21 (m, 2H), 7.33- 7.61 (m, 10H), 7.72-7.87 (m, 1H), 7.99 (d, *J* = 7.3 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 52.4, 119.1, 121.9, 124.7, 126.1, 127.6, 129.6, 131.2, 142.6, 149.1 ppm.

11. 2-((diphenylamino)methyl)phenol (Table II.4, entry 3k) (87% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.17 (s, 2H), 6.73-6.83 (m, 2H), 7.06-7.11 (m, 4H), 7.33-7.67 (m, 8H), 10.12 (br s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 50.8, 115.7, 119.1,121.1, 121.9, 128.1, 128.3, 128.9, 129.6, 149.1, 156.6 ppm.

12. 4-((diphenylamino)methyl)phenol (Table II.4, entry 3l) (88% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.29 (s, 2H), 6.71 (d, *J*= 7.4 Hz, 2H), 6.95 (d, *J*= 7.5 Hz, 2H), 7.06-7.10 (m, 2H), 7.33 – 7.40 (m, 8H), 9.06 (br s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 57.0, 115.7, 119.1, 121.9, 129.6, 130.7, 130.9, 149.1, 156.5 ppm.

13. 4-((diphenylamino)methyl)-2-methoxyphenol (Table II.4, entry 3m) (75% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.77 (s, 3H), 4.28 (s, 2H), 6.63 (d, *J*= 7.3Hz, 1H), 6.81 (t, *J* = 7.4Hz, 2H), 7.06 (t, *J*= 6.9 Hz, 2H), 7.31- 7.47 (m, 8H), 9.92 (br s, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 56.1, 57.3, 109.6, 115.4, 119.1, 121.9, 123.2, 129.6, 135.2, 146.7, 147.3, 149.1 ppm.

14. 4-((diphenylamino)methyl)-*N*,*N*-dimethylaniline (Table II.4, entry 3n) (92% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.02 (s, 6H), 4.20 (s 2H), 6.71 (d, *J* = 6.9, 2H), 7.03-7.12 (m, 4H), 7.33 – 7.47 (m, 8H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 41.3, 57.0, 112.3, 119.1, 121.9, 127.6, 127.8, 129.8, 148.7, 149.1 ppm.

15. *N*-(4-fluorobenzyl)benzenamine[26] (Table II.4, entry 3o) (92% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ= 7.31-7.26 (m, 2H), 7.18-7.12 (m, 2H), 7.03-6.96 (m, 2H), 6.73-6.68 (m, 1H), 6.60-6.57 (m, 2H), 4.24 (s, 2H) 3.84 (br, 1H) ppm.

^{13}C NMR ($CDCl_3$, 75MHz) δ= 163.8, 160.6, 148.2, 135.5, 129.5, 129.2, 129.1, 117.9, 115.7, 115.4, 113.1, 47.6 ppm.

16. *N*-(naphthalen-2-ylmethyl)aniline[27] (Table II.4, entry 3p) (65% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ= 7.72 (m, 4H),7.38 (m, 3H), 7.08 (m, 2H), 6.63 (d, *J* = 9.0 Hz, 1H), 6.57 (d, *J*=10.3 Hz, 2H), 4.39 (d, *J* = 6.7 Hz, 2H), 4.21 (br s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ= 148.59, 137.36, 133.90, 133.17, 129.69, 128.77, 128.16, 128.10, 126.55, 126.31, 126.13, 126.12, 118.03, 113.34, 48.90.

17. *N*-(1-phenylethyl)aniline[28] (Table II.4, entry 3q) (85% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ= 1.54 (d, *J* = 6.8 Hz, 3H), 4.19 (br s, 1H), 4.51 (q, *J* = 6.7 Hz, 1H), 6.55 (dd, *J*= 8.7, 0.9 Hz, 2H), 6.67 (tt, *J*= 7.3, 1.0 Hz, 1H), 7.11 (dd, *J*= 8.5, 7.3 Hz, 2H), 7.20- 7.28 (m, 1H), 7.29-7.43 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.9, 53.4, 113.4, 117.3, 125.8, 126.9, 128.6, 129.1, 145.1, 147.1 ppm.

18. *N*-benzhydrylaniline[29] (Table II.4, entry 3r) (83% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (br, 1H), 5.48 (s, 1H), 6.51-6.52 (m, 2H), 6.67 (s, 1H), 7.07-7.09 (m, 2H), 7.22-7.24 (m, 2H), 7.29-7.33 (m, 8H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.1, 113.6, 117.7, 127.4, 127.5, 128.9, 129.2, 143.0, 147.4 ppm.

19. *N*-benzhydryl-4-methylaniline[29] (Table II.4, entry 3s) (90% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 4.11 (br, 1H), 5.47 (s, 1H), 6.45-6.47 (m, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 7.21-7.25 (m, 2H), 7.28-7.32 (m, 4H), 7.36 (d, *J* = 7.6 Hz, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 63.4, 113.7, 126.8, 127.4, 127.5, 128.8, 129.7, 143.2, 145.2 ppm.

20. *N*-heptylaniline[30] (Table II.4, entry 3s) (72% yield): ^{1}H NMR (300MHz, $CDCl_3$): δ = 7.08 (t, *J* = 6.79 Hz, 2H), 6.60 (t, *J* = 6.04 Hz, 1H), 6.51 - 6.49 (m, 2H), 3.40 (br s, 1H), 3.06 (t, *J* = 6.79 Hz, 2H), 1.63 - 1.54 (m, 2H), 1.40 - 1.22 (m, 8H), 0.91 - 0.87 (m, 3H) ppm.

^{13}C NMR (75MHz, $CDCl_3$): δ = 148.4, 129.1, 116.9, 112.5, 43.9, 31.7, 29.5, 29.0, 27.0, 22.5, 14.0 ppm.

II.E.4. Scanned copies of ^{1}H and ^{13}C NMR of the derivatives

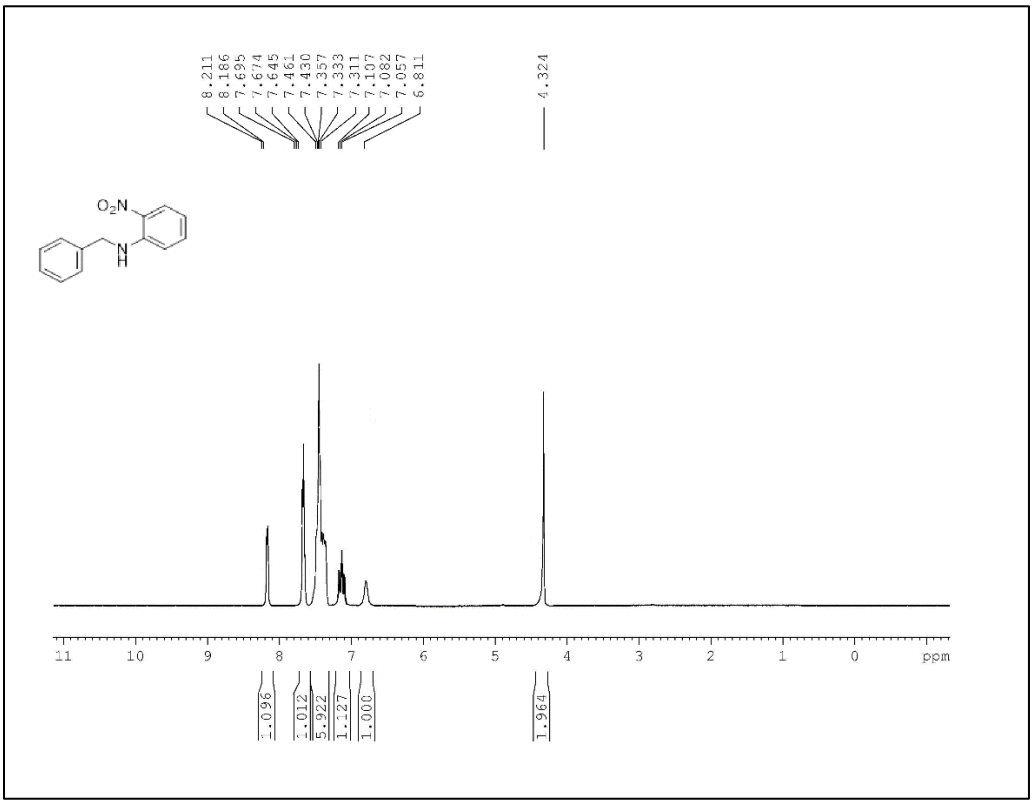


Figure II.2. Scan copy of ^{1}H NMR of *N*-benzyl-2-nitroaniline.

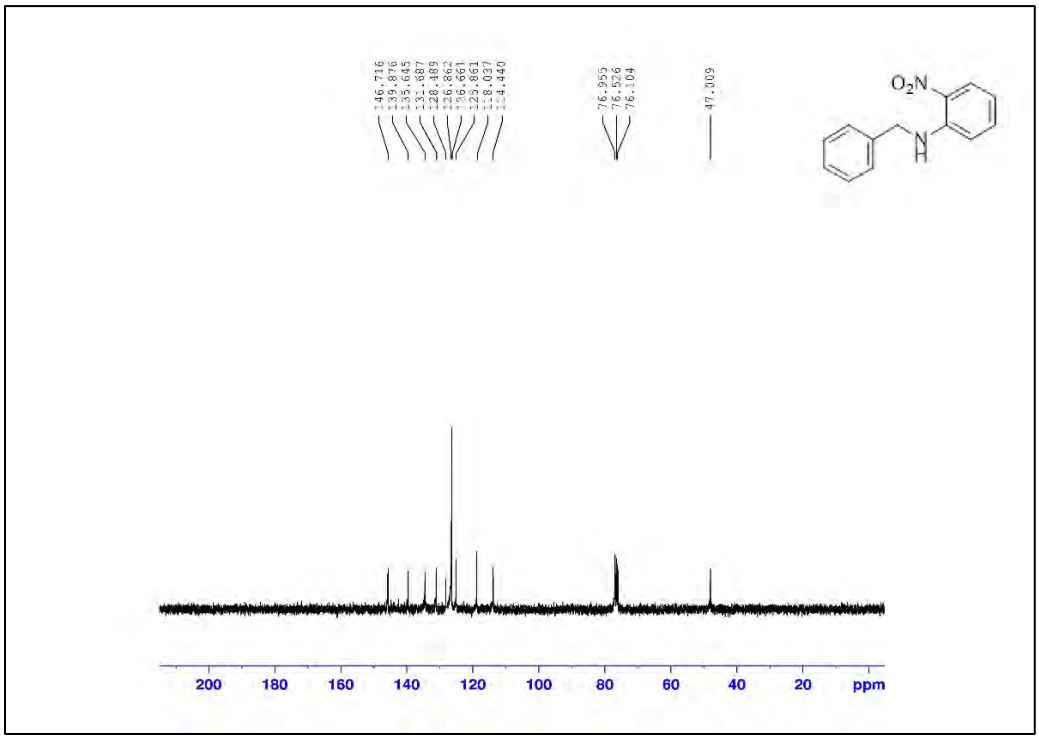


Figure II.3. Scan copy of ^{13}C NMR of *N*-benzyl-2-nitroaniline.

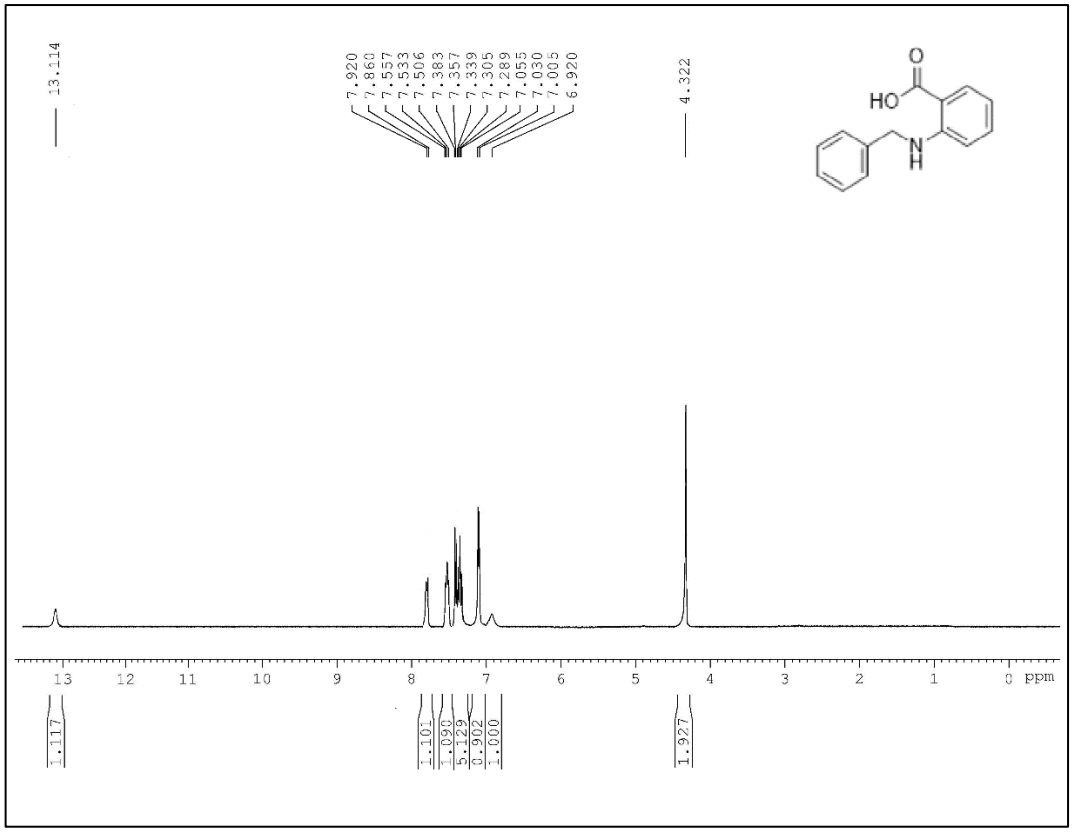


Figure II.4. Scan copy of ^{1}H NMR of 2-(Benzylamino)benzoic acid.

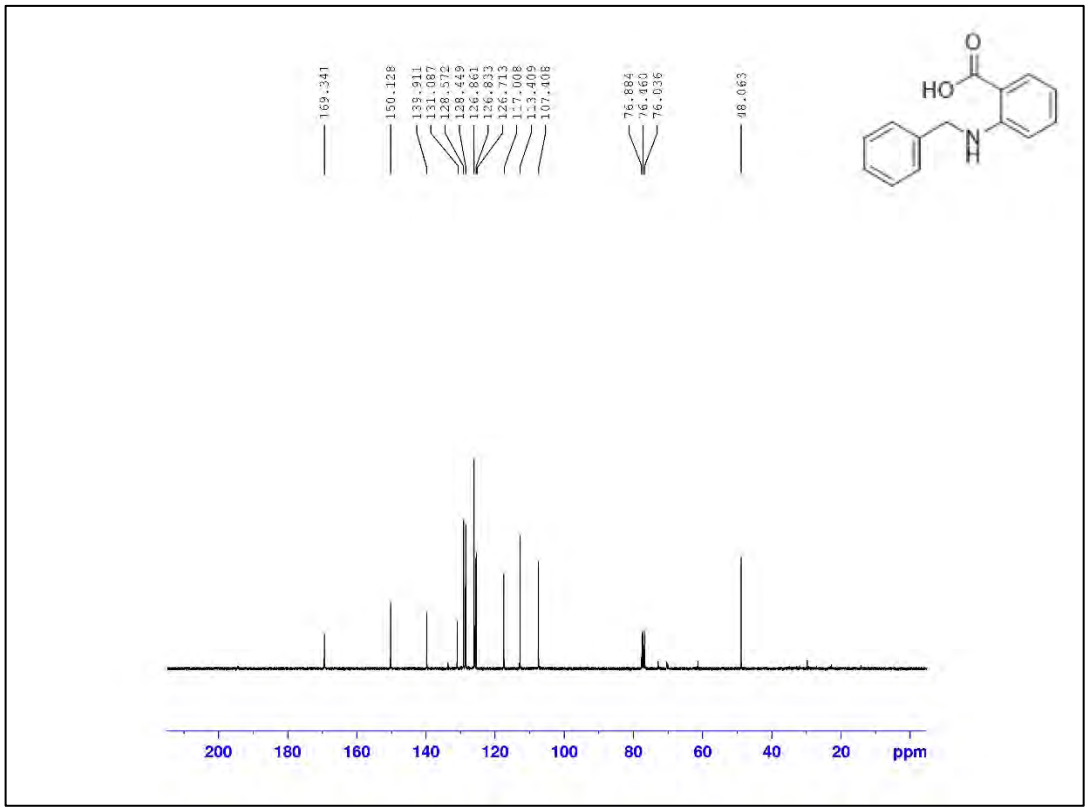


Figure II.5. Scan copy of ^{13}C NMR of 2-(Benzylamino)benzoic acid.

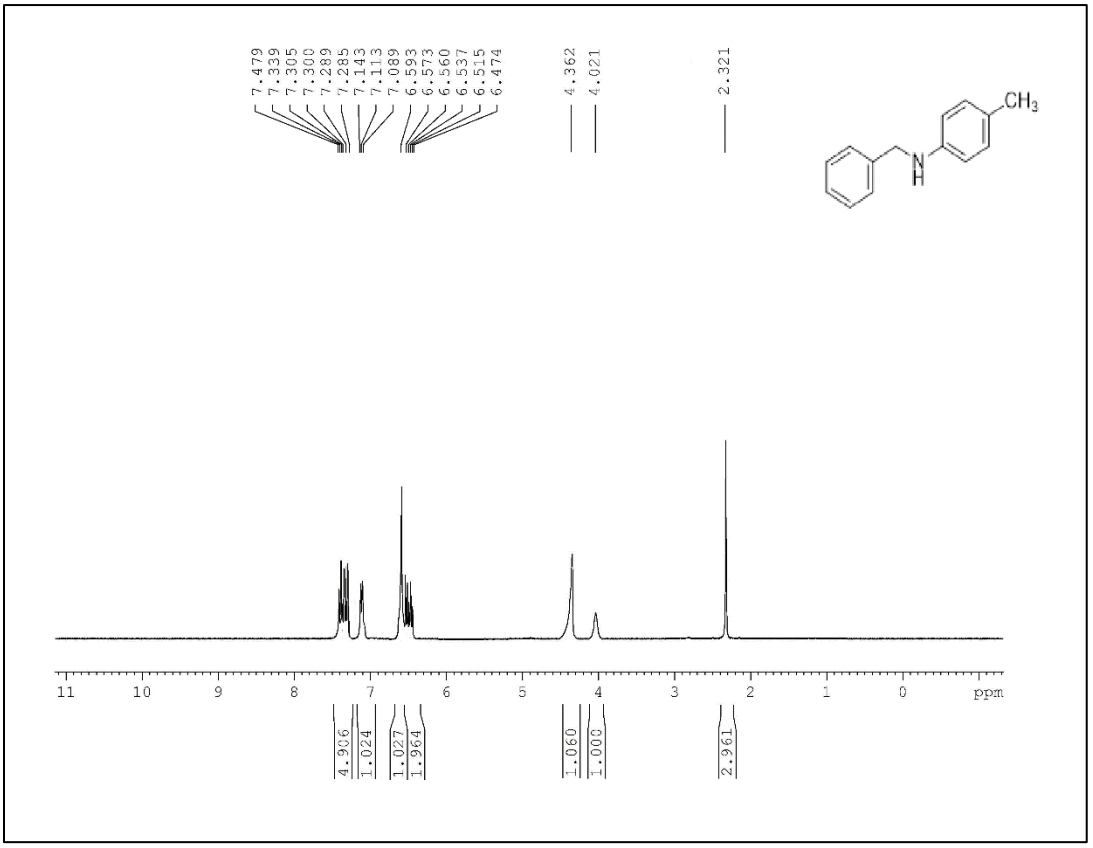


Figure II.6. Scan copy of ^{1}H NMR of *N*-benzyl-4-methylaniline.

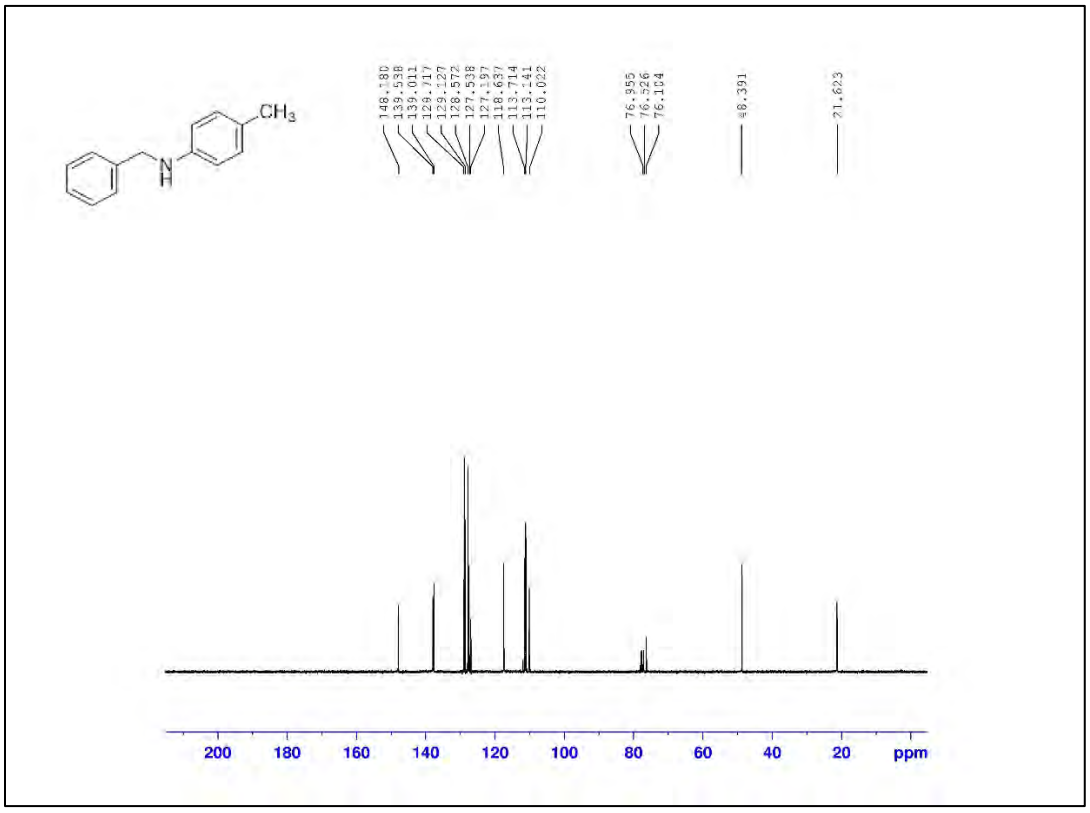


Figure II.7. Scan copy of ^{13}C NMR of *N*-benzyl-4-methylaniline.

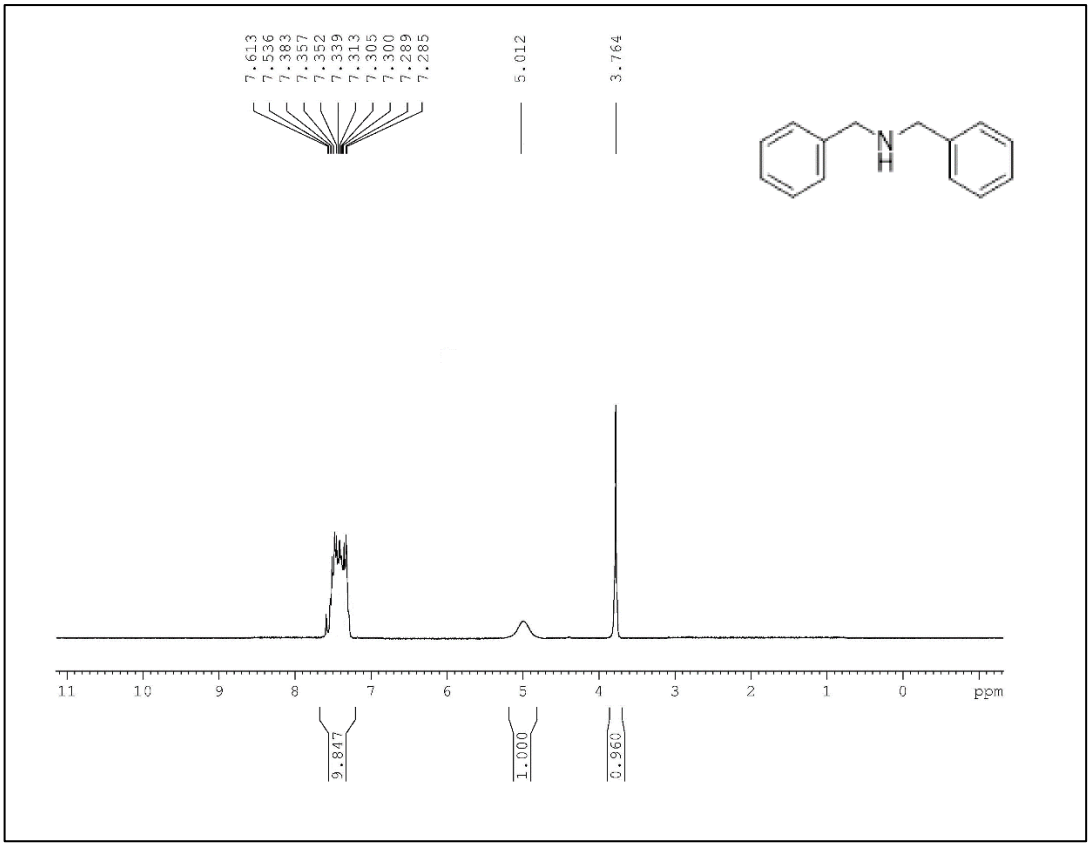


Figure II.8. Scan copy of ^{1}H NMR of *N*-(phenylmethyl)-benzenemethanamine.

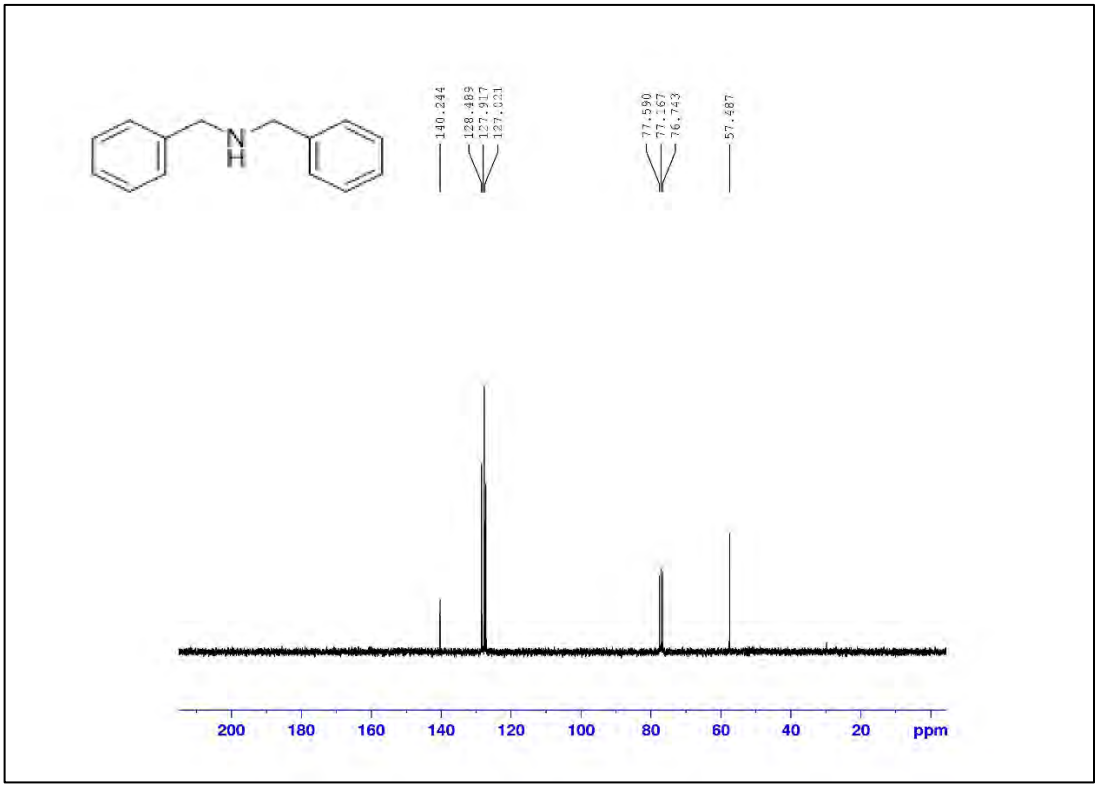


Figure II.9. Scan copy of ^{13}C NMR of *N*-(phenylmethyl)-benzenemethanamine.

II.F. Reference

References are given in BIBLOGRAPHY under Chapter II.