Chapter V

Ethyl lactate mediated transition metal-free efficient synthesis of azobenzenes

V.A. Introduction

For a long period, aromatic azo compound has gained considerable amount of consideration among the chemists. The main motive behind this is the tremendous collection of application these motif promises in the field of indicators, food additives, organic dyes and therapeutic agents (Figure V.1)[1-4]. Moreover, due to their outstanding photochemical properties, these compounds have been widely used as smart polymers[5-7], liquid crystals[8], photochromic ligands in optochemical genetics[9-10] and photo switches in biological systems[11-14]. By C-H activation, azo compounds have been lately reported to be used for production of valued compounds like *o*-alkoxyazobenzenes[15], indole derivatives[16] and *o*-acylazobenzenes[17-20]. They are also used in the production of proactive glass and filters.

Azobenzenes are the group of chemical compounds having two phenyl rings coupled through N=N double bond. Azobenzene occurs in two geometrical isomeric forms, *trans* and *cis*-azobenzene. *Cis*-azobenzene is nonplanner but *trans*-azobenzene is planer in structure. The N-N distance in *cis*-azobenzene and *trans*-azobenzene are 1.251Å and 1.189Å respectively. The *cis*-azobenzene is less stable than *trans*-azobenzene by about 50 KJ/mol. *Cis* form can be changed into the *trans* isomer by using an suitable wavelength (visible blue light> 400 nm) of light whereas different wavelength (UV at 300-400nm) can convert *trans* isomer back to *cis* form (Figure V.2).

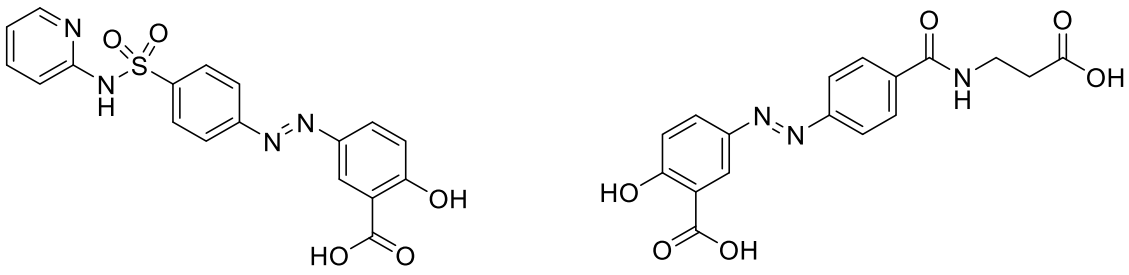


Figure V.1. Biologically active compounds having azo moiety.

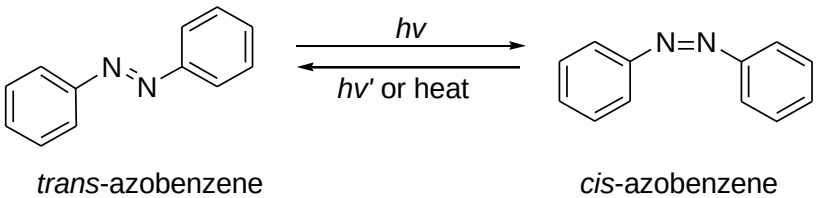


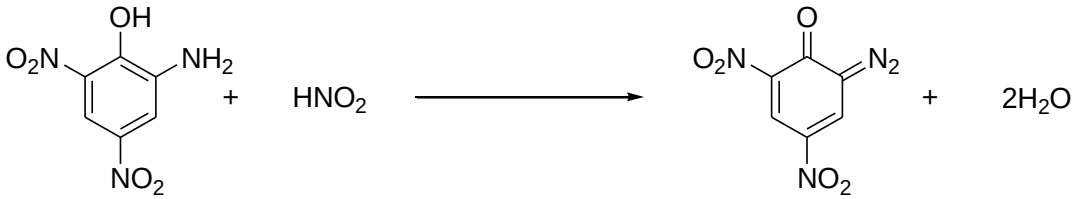
Figure V.2. Interconversion of *cis*-azobenzene and *trans*-azobenzene.

V.B. Background and objectives

From literature review, it has been documented that a number of approaches have been described so far for the production of azo compounds and their derivatives. Amid the few are Wallach reaction, Mills reaction, reduction of azobenzenes, oxidation of amines, opening of quinine acetals, reaction of quinine acetals with arylhydrazines, dehydrogenation of arylhydrazines, thermolysis of azides, metal catalyzed coupling of arylhydrazines, triazene rearrangements, oxidation of amines, opening of benzotriazoles and dimerization of diazonium salts. Comparing all these methods, the easiest methodology is the one step route in the synthesis of azocompounds by oxidation of amines. Literature survey shows that the synthesis of azo-compounds by oxidation of amines have been achieved by a number of catalysts[21-28].

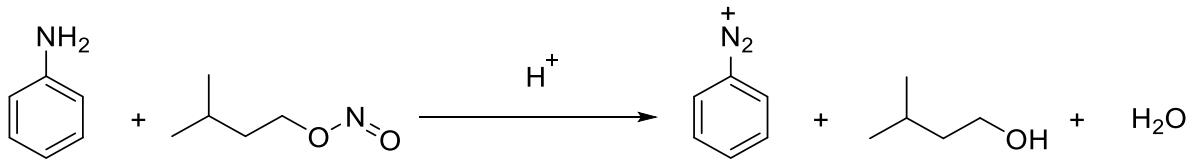
V.B.1. Classical method for Synthesis of azobenzenes

In 1858, Peter Griess *et al.* reported the first preparation of aromatic azo compounds[29-30]. In this reaction the diazotization of *o*-aminophenol using nitric acid and arsenous acid is produced. Nitrous acid was theoretically to be generated within the reaction mixture by the reaction of nitric acid and arsenous acid that converts *o*-aminophenol to the corresponding azo-compound (Scheme V.1).



Scheme V.1. Griess method for synthesis of diazo-compound.

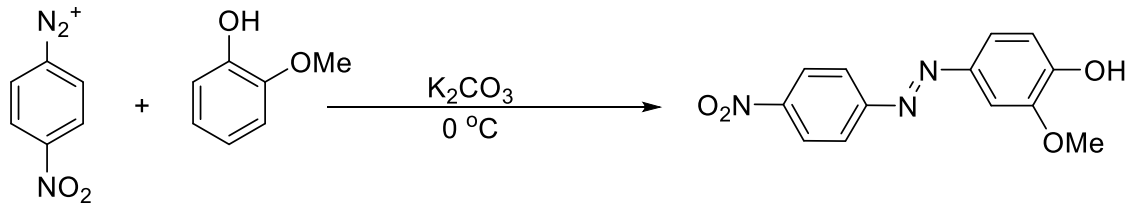
Later Knoevenagel *et al.* modified Griess's method by employing nitrite esters[31]. Transformation was more effective in this method in preparing azo-compounds in acidic medium (Scheme V.2). Using this method, he was able to convert aniline to corresponding diazo-benzene.



Scheme V.2. Knoevenagel reaction for synthesis of diazo-benzene.

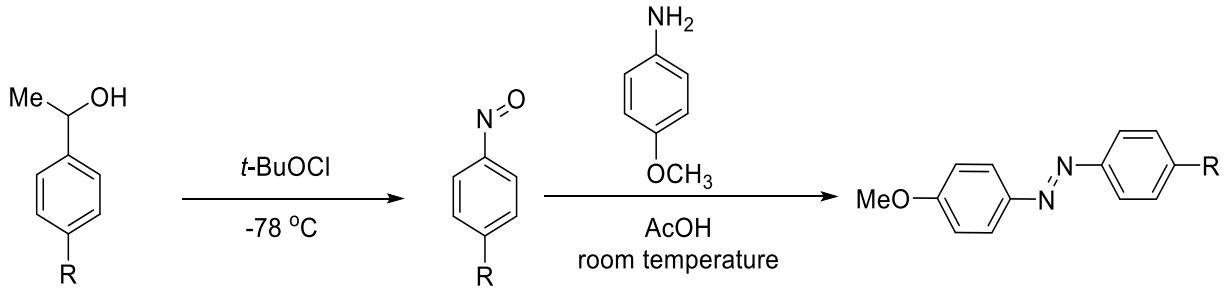
V.B.2. Modern approaches for synthesis of diazo compounds

Common azobenzenes are usually synthesized using azo coupling reaction method. The method includes diazotization of aromatic primary amines in very low temperature and at that point reacting with electron rich aromatic nucleophiles. Shorter reaction time and excellent yield are the main advantages of this method. K. Haghbeen *et al.* reported high yield of azo compound by reacting diazonium salt and phenol at 0 °C using base like K_2CO_3[32] (Scheme V.3). Diazonium salts are regarded as weak electrophiles and hence react with electron rich species like substituted arenes with electron donating groups such as amine or hydroxyl to form azobezenes. Usually, reaction takes place at the para position to the electron donating group but when the para position is already occupied, the substitution takes place at the the ortho position.



Scheme V.3. Azo coupling reaction for synthesis of azobenzenes by K_2CO_3

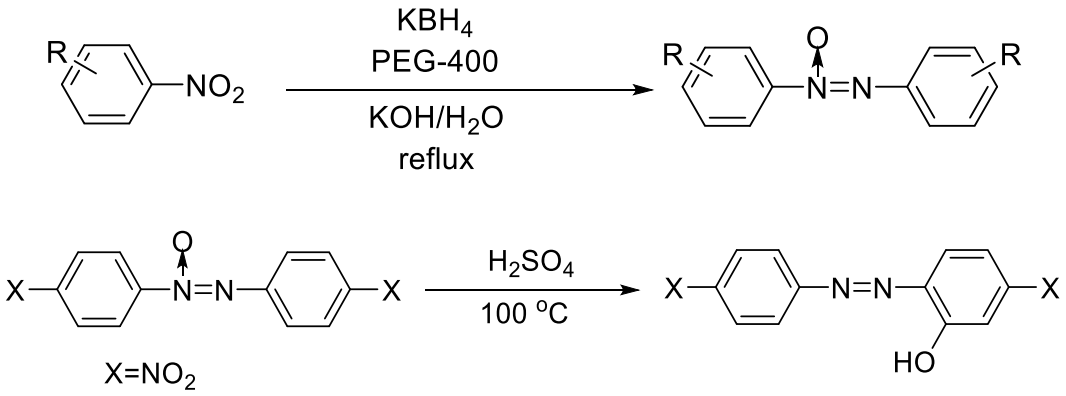
In a multistep reaction T.J. Marks *et al.* reported the synthesis of azobenzene by the reaction between aromatic nitroso compounds and aniline derivatives in presence of glacial acetic acid[33]. Previously, nitroso derivatives were arranged by oxidation of aromatic methylhydroxylamine by *tert*-butyl hypochlorite. The oxidation reaction needed to be carried out at very low temperature (-78 °C) and high dilution is required as it is a very fast reaction and often overoxidation takes place along with the oxidation of nitrosobenzene to nitrobenzene (Scheme V.4).



Scheme V.4. Synthesis of azobenzenes using *tert*-butyl hypochlorite

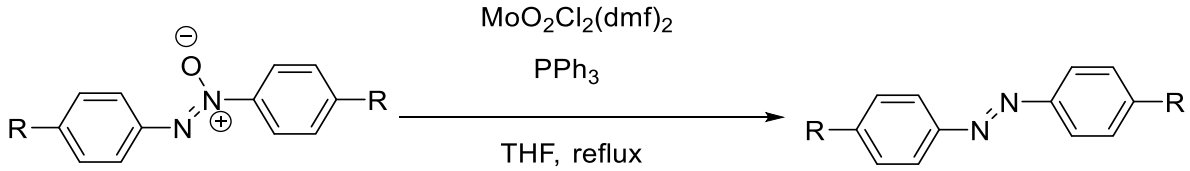
In 1880, O. Wallach discovered the process for convertion of aromatic azoxy compound into azo compound using strong acids[34]. Recently, Y. Lu *et al.* have extended the reduction of nitrobenzenes into corresponding azoxybenzene with potassium borohydride as the reducing

agent and water as medium[35] (Scheme V.5). PEG-400 was employed as the phase transfer catalyst in this reaction. The electron-withdrawing groups generally accelerate the reaction whereas the electronic- releasing group slows down the reaction to various degrees.



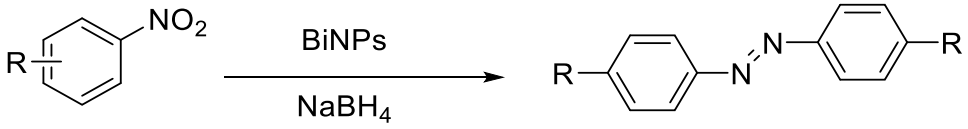
Scheme V.5. Synthesis of azobenzenes from nitro compounds by Wallach reaction by KBH_4/PEG-400 system.

Recently, F.J. Arnáiz *et al.* reported the conversion of azoxybenzene to azobenzene in good yield[36]. Tertiary phosphines are used as reducing agent in this reaction (Scheme V.6). The reaction was performed using dichlorodioxomolybdenum (VI) as catalyst in THF medium.



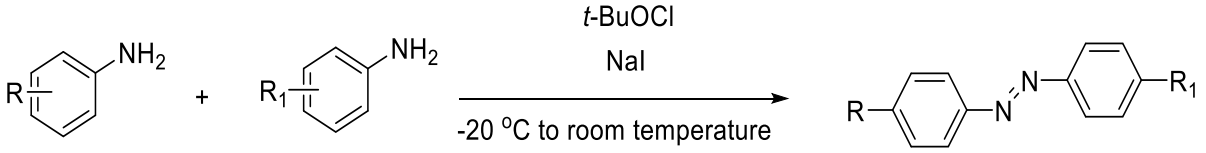
Scheme V.6. Reduction of azoxybenzene by tertiary phosphines for synthesis of azobenzenes using molybdenum (VI) catalyst.

A number of reducing agents have been used so far using suitable of nitrobenzene for the synthesis of symmetrical aromatic azo compounds. Recently, Z. Wang *et al.* reported transformation of nitrobenzene to azobenzenes by bismuth nanoparticles as catalyst[37]. The conversion was done under environmentally benign conditions with good yield of the product. Also, the catalyst was recoverable and reused without losing much of its efficiency (Scheme V.7).



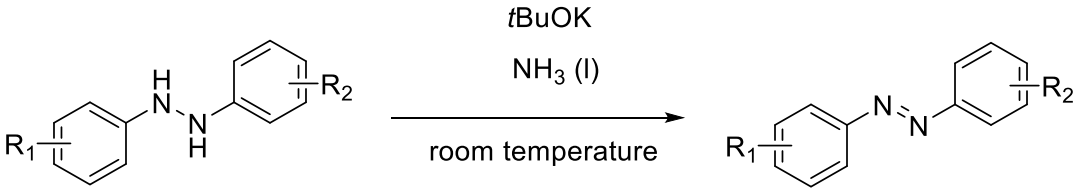
Scheme V.7. Synthesis of azobenzenes by reductive coupling of aromatic nitro derivatives using bismuth nanoparticles.

T.W. McIntyre *et al*. reported synthetic method for preparation of azobenzenes by electrolytic oxidation of aromatic amines[38]. However, the procedure was not efficient as the yield obtained by them was low. Numerous protocols have been published after that which assured improvement of this synthesis using several reaction conditions, various oxidizing agents and a wide range of catalysts. Recently, S. Minakata *et al.* reported development of cost-efficient and facile method for oxidative dimerization of azobenzenes from aromatic amines using *tert*-butyl hypochlorite (*t*-BuOCl) and NaI as catalyst[39] (Scheme V.8). Main advantage of this protocol is the synthesis of unsymmetrical azobenzenes as well.



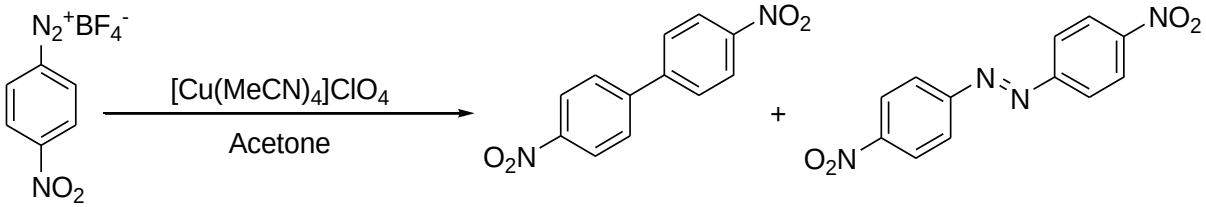
Scheme V.8. Oxidation of anilines for synthesis of azobenzenes by *tert*-butyl hypochlorite.

M. Hashimoto *et al.* have reported approach for dehydrogenation of *N*,*N*-diarylhydrazines by using potassium *tert*-butoxide in liquid ammonia[40]. High competence of the methodology and very short reaction time was one of the main features of this synthesis (Scheme V.9). The scope is further extended by the synthesis of diazirines.



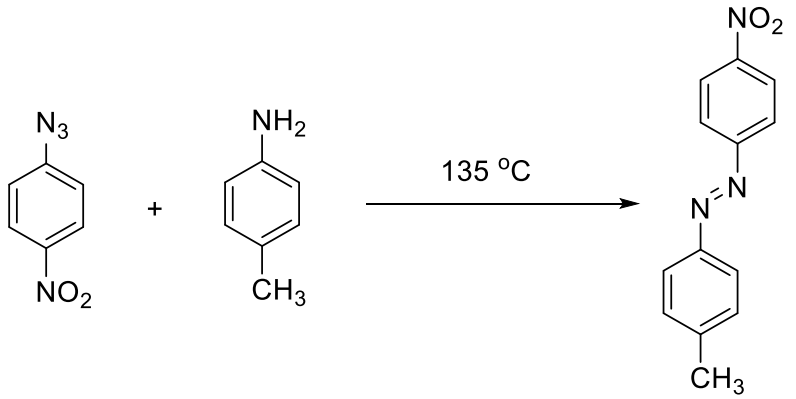
Scheme V.9. Synthesis of azobenzenes by *tert*-butoxide in liquid ammonia.

Dimerization of diazonium salts in presence of copper and acid is known as Gatterman's method or copper (I) salts moves to the formation of azobenzene. The reaction is highly delicate towards the nature of the aromatic group present. Due to C-C coupling, in presence of electron-withdrawing group, biaryl is the main product whereas in presence of electron-donating group, azobenzene governs as the main product (Scheme V.10).



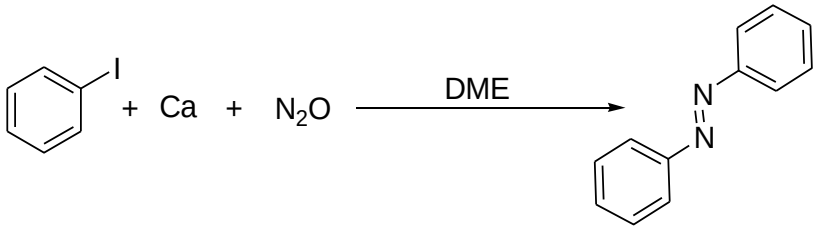
Scheme V.10. Dimerization reaction of diazonium salts for synthesis of azobenzenes using Cu (I) salt

Aromatic azides can be heated in presence of aniline to yield unsymmetrical azo compounds. However, the yield obtained in such reactions are often low. Also, the azides are explosive in nature and are difficult to handle. Such a reaction is reported by J. March *et al.*[41]. In this reaction azide condenses with aniline and its derivatives to yield corresponding azo compounds at 135 ^{o}C (Scheme V.11). Very long reaction time up to 48 hours is a drawback of this method.



Scheme V.11. Synthesis of azobenzenes by thermolysis of azides.

Aromatic calcium derivatives act as a good starting material for the synthesis of azobenzenes. T.P. Hanusa *et al.* have reported the synthesis of azobenzene in excellent yield by reacting iodobenzene with nitrous oxide and metallic calcium in presence of dimethoxethane[42]. Though the yield became low when the reaction is performed in presence of organolithium compounds (Scheme V.12). Phenylcalcium iodide was assumed to be generated by the reaction of iodobenzene and calcium.

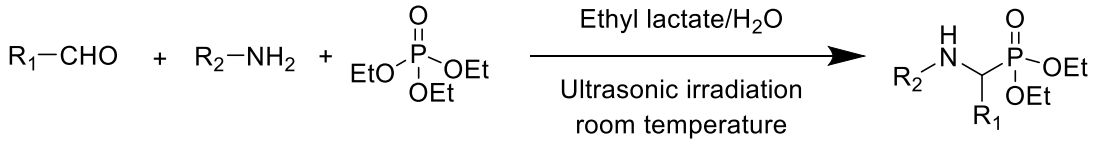


Scheme V.12. Synthesis of azobenzenes by dimethoxethane.

V.B.3. Background of Ethyl lactate in organic synthesis

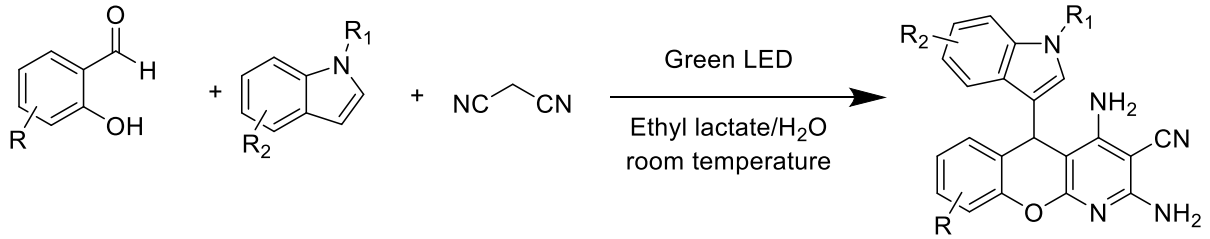
Ethyl lactate can be smoothly produced by fermentation of biomass raw materials[43]. As it is non-toxic, it has been permitted by European Food Safety Authorities and Food and Drug Administration (EFSA) for the use as pharmaceutical additives and food additives[44]. It also has been profitably engaged in the extraction of many bioactive compounds and diverse food such as polyphenols[45], carotenoids[46], caffeine[47], amino acids[48].

Ethyl lactate has effectively been employed as a green solvent in a number of prominent organic reactions. Recently, Z.H. Zhang *et al.* reported an efficient one-pot synthesis of α-aminophosphonates [49]. This reaction is done in metal -free condition in aqueous ethyl lactate medium. This reaction is a one-pot three-component reaction of wide range of aldehydes, amines and triethyl phosphate under ultrasonic irradiation conditions at room temperature (Scheme V.13).



Scheme V.13. Synthesis of α-aminophosphonates in aqueous ethyl lactate medium.

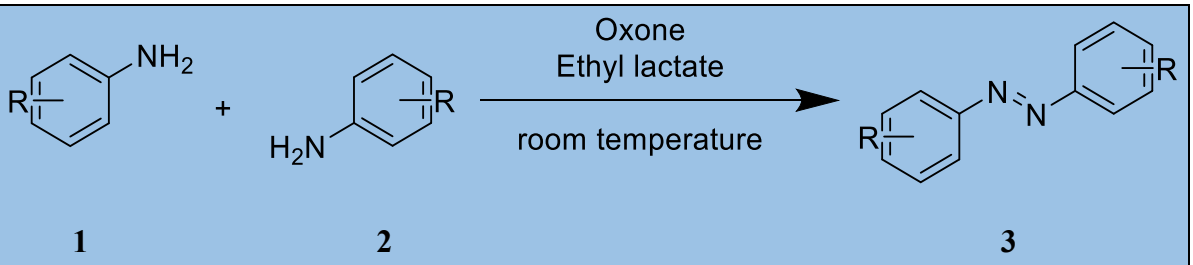
Another recent organic synthesis of 5-substituted indole chromeno[2,3]-bipyridines is reported by Z.H. Zhang *et al.*[50]. This innovative approach is catalyzed by green LED light in Ethyl lactate and water medium (Scheme V.14). It is described as a pseudo four-component one-pot reaction of salicylaldehydes, indole and malononitrile and good yield of corresponding pyridine derivatives are reported.



Scheme V.14. Synthesis of 5-substituted indole chromeno[2,3]-bipyridines by ethyl lactate/H_2O system.

V.C. Present Work

During the development of our research work, with an goal to develop a new procedure for our synthesis, we found that easily available, environmental benevolent and cost-effective solvent ethyl lactate can be explored as an excellent and effective mediator in the synthesis of azobenzenes from amines without using any additional catalyst. In our work, we report ethyl lactate as a green and efficient solvent for the synthesis of symmetric azobenzenes at room temperature (Scheme V.15). During the synthesis of symmetric azobenzenes, oxone accomplished the role of an oxidizing agent.



1 **2** **3**

Scheme V.15. Synthesis of azobenzene from amines by ethyl lactate at room temperature.

V.C.1. Result and discussion

To standardize the reaction protocol, aniline was taken as the starting material and the progress of the reaction was monitored by TLC. The reaction was first carried out by taking 1 mmol of aniline and 0.5 mmol of oxone under neat condition for 12 hours when only trace amount of the product was obtained (Table V.1, entry 1). Now with the same reaction conditions, different solvents were used to monitor the reaction. Water only furnished trace amount of the product (Table V.1, entry 2). However, with chloro- form the reaction gave encouraging yield of 50% (Table V.1, entry 3). PEG 400 further increased the yield to 74% (Table V.1, entry 4). Toluene and ethanol gave 55% and 59% of the yield respectively (Table V.1, entry 5, 6). However slightly fewer yields of 40% was obtained with methanol (Table V.1, entry 7). We then decided to use ethyl lactate as the solvent and we were excited to find the yield increased to 78% (Table V.1, entry 11). We also used the solution of ethyl lactate/H_2O at different ratios but yield remained almost the same (Table V.1, entry 10, 11, 12). Now with the solvent being optimized, we increased the amount of oxone to 1.0 mmol but here we were surprised to find that yield decreased considerably to 62% (Table V.1, entry 13). It may be due to the oxidation of aniline to nitrobenzene before undergoing coupling reaction. While reducing the amount of oxone to 0.25 mmol reduced the yield to 38% (Table V.1, entry 14). We further investigated the reaction by increasing the time to 24 hours which did not give any significant increase in the yield of the product (Table V.1, entry 15). However, decreasing the time to 6 hours decreased the yield to 60%. Increasing the temperature of the reaction to 90° C also showed a large decrease in the yield (Table V.1, entry 16). The decrease of yield to 35% may be due to the oxidation of aniline to nitrobenzene at high temperature. Hence finally we report that the optimal reaction condition is 1 mmol of aniline and 0.5 mmol of oxone in ethyl lactate for 12 hours.

Table V.1. [a]Optimization of reaction condition for symmetric azobenzene.

Entry	Oxone (mmol)	Solvent	Time (h)	Yield (%)[b]
1	0.5	Neat	12	Trace

2	0.5	Water	12	Trace
3	0.5	$CHCl_3$	12	50
4	0.5	PEG-400	12	74
5	0.5	Toluene	12	55
6	0.5	EtOH	12	59
7	0.5	MeOH	12	40
8	0.5	Ethyl lactate/H_2O (2:1)	12	76
9	0.5	Ethyl lactate/H_2O (1:1)	12	75
10	0.5	Ethyl lactate/H_2O (1:2)	12	73
11	0.5	Ethyl lactate	12	78
12	1.0	Ethyl lactate	12	62
13	0.25	Ethyl lactate	12	38
14	0.5	Ethyl lactate	24	78
15	0.5	Ethyl lactate	06	60
16	0.5	Ethyl lactate	12	35[c]

The bold significance represents the optimized protocol/conditions.

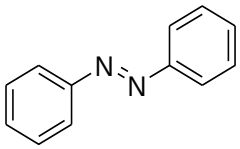
[a]Reaction of aniline (1 mmol).

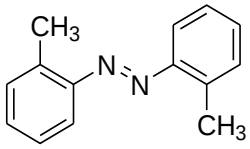
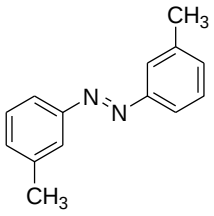
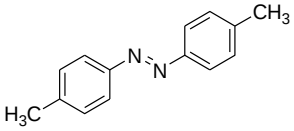
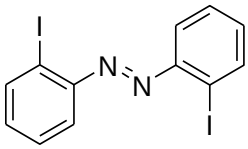
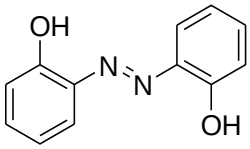
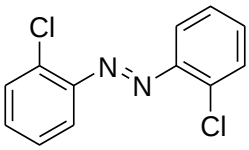
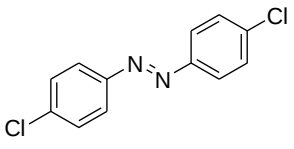
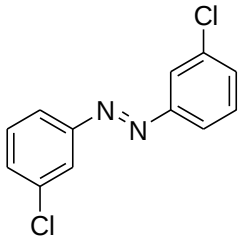
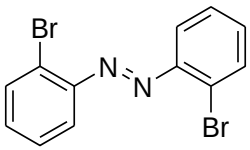
[b]Isolated yield of product by column chromatography.

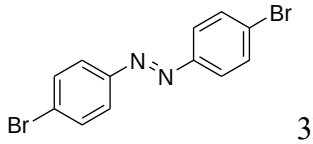
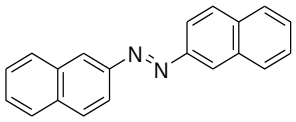
[c]Reaction carried out at 90° C.

A number of amines have been employed in the synthesis of symmetric azobenzenes in our methodology. As evidence from table 2, good yield of different products has been obtained all at room temperature. The procedure has been generalized for a range of amines having electron-donating, electron-withdrawing groups on benzene ring as well as naphthyl rings. Better results were obtained for amines having electron-donating effect compare to those having electron withdrawing effect. It may be due to the electron density on nitrogen atom making them more nucleophilic. It was also observed that ortho-product gave fewer yields than the other products. This may be due to steric factors at the ortho positions.

Table V.2. [a]Ethyl lactate mediated synthesis of symmetric azobenzenes.

Entry	Product	Yield (%)[b]
1	 3a	78

2	 3b	73
3	 3c	78
4	 3d	77
5	 3e	55
6	 3f	68
7	 3g	61
8	 3h	64
9	 3i	65
10	 3j	57

11	 3k	59
12	 3l	79

[a]Reaction conditions: Aniline (1 mmol), oxone (0.5 mmol) in ethyl lactate for 12 h at room temperature.

[b]Isolated yield of product by column chromatography.

V.D. Conclusion

In conclusion, we have developed an environmentally benign protocol for the single-step facile synthesis of symmetric azobenzenes from amines by using ethyl lactate as a solvent without the use of any catalyst. The reaction protocol includes the use of an inexpensive and non-toxic green solvent and gives excellent yield of the desired products with simple and easy reaction conditions and workup process.

V.E. Experimental

V.E.1. General Information

^{1}H NMR and ^{13}C NMR were recorded using 300 MHz, 400 MHz and 75 MHz, 100 MHz respectively on Bruker AV 300 NMR spectrometer and Bruker AV 400 NMR spectrometer using TMS as internal standard. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

V.E.2. General procedure for the synthesis of symmetric azobenzenes from amines

Aniline (1 mmol) and oxone (0.5 mmol) were mixed and stirred in ethyl lactate (1 mL) at room temperature for 12 hours. After completion of the reaction (observed on TLC), the reaction mixture was cooled down to room temperature. Then the solution was poured into 100 mL water and extract with ethyl acetate, washed several times with water. The combined 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 as eluent to afford the pure solid product. All the products were characterized by ^{1}H NMR and ^{13}C NMR.

V.E.3. Spectroscopy data

1. (*E*)-Azobenzene (Table V.2, entry 3a)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.93 (d, *J*=7.2, 4H), 7.54-7.49 (m, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):152.62, 131.00, 129.10, 122.84.

2. (*E*)-4,4′-Dimethylazobenzene (Table V.2, entry 3d)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.71 (d, *J* = 8.4 Hz, 4H), 7.19 (d, *J* = 8.1 Hz, 4H), 2.32 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):150.82, 141.22, 129.73, 122.75, 21.50.

3. (*E*)-2,2′-Dimethylazobenzene (Table V.2, entry 3b)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.74 (s, 4H), 7.43 (t, *J*=7.8, 2H), 7.20 (t, *J*=7.2, 4H), 2.28 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 149.46, 142.78, 131.23, 128.62, 121.56, 18.48.

4. (*E*)-3,3′-Dichloroazobenzene (Table V.2, entry 3i)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):7.42 (s, 1H), 7.37 (s, 1H), 7.31 (d, *J* = 7.8, 1H), 7.11(d, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 2H), 6.60-6.51 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):143.87, 134.18, 131.38, 129.27, 124.78, 119.98.

5. (*E*)-2,2′-Diiodoazobenzene (Table V.2, entry 3e)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.52 (d, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.8 Hz, 3H), 6.61 (d, *J* = 7.8 Hz, 2H), 6.36 (t, *J* = 7.2 Hz, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):146.83, 139.04, 129.44, 120.06, 114.87, 84.37.

6. (*E*)-2,2′-Dihydroxyazobenzene (Table V.2, entry 3f)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.13 (d, *J* = 8.4 Hz, 2H), 7.77 (t, *J* = 8.1 Hz, 2H), 7.30-7.40 (m, 2H), 6.93-7.09 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):152.35, 150.88, 133.35, 131.90, 126.27, 122.64, 118.92.

7. (*E*)-1,2-di(2-naphthyl)diazene (Table V.2, entry 3l)

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.04 (s, 1H), 8.79 (s, 1H), 8.38 (d, *J*=1.8 Hz, 1H), 8.00-7.75 (m, 7H), 7.51 (t, *J*=3.9, 2H), 7.44 (t, *J*=3.6, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 141.59, 134.59, 133.71, 132.53, 129.65, 128.85, 127.84, 126.51, 124.92, 119.54.

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

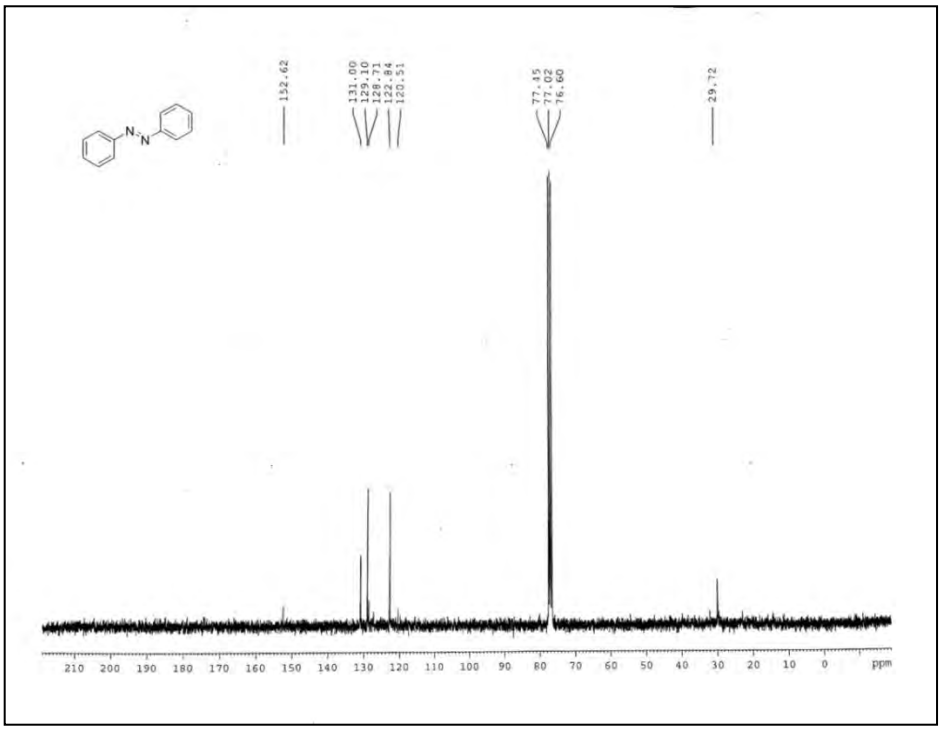


Figure V.3. Scan copy of ^{13}C NMR of (*E*)-Azobenzene.

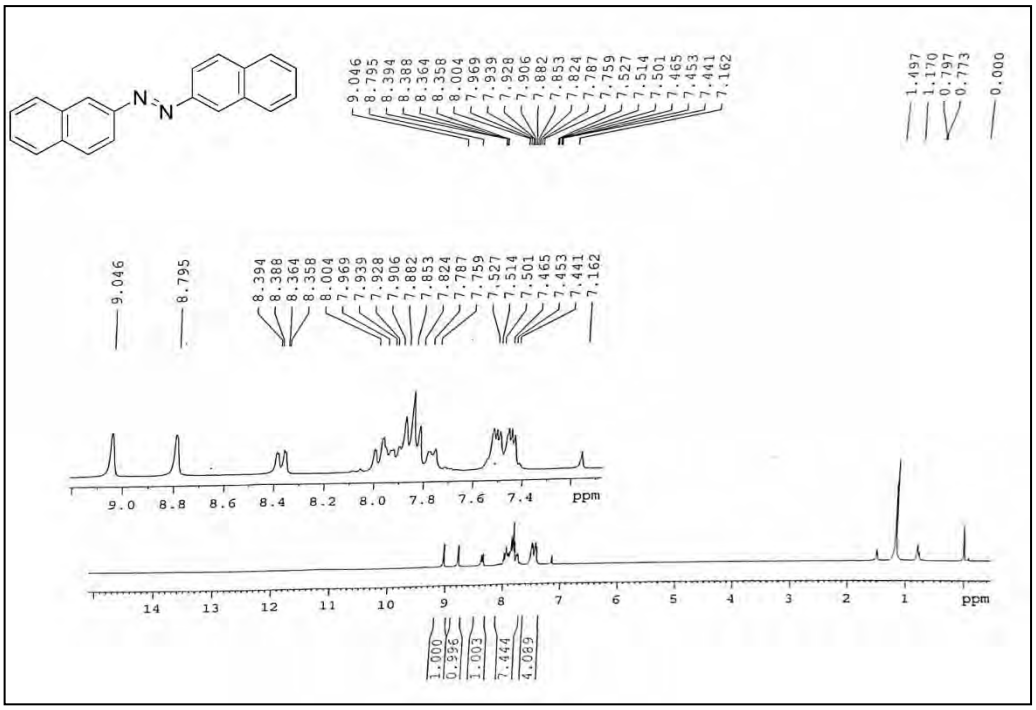


Figure V.4. Scan copy of ^{1}H NMR copy of (*E*)-2,2'-Azonaphthalene.

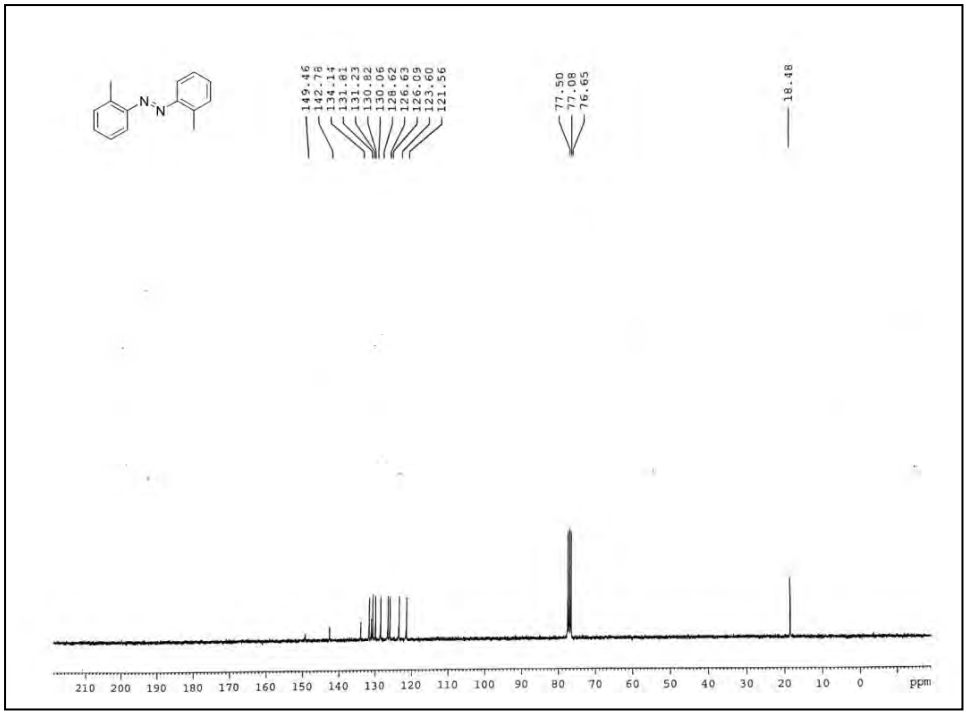


Figure V.5. Scan copy of ^{13}C NMR of (*E*)-2,2′-Dimethylazobenzene.

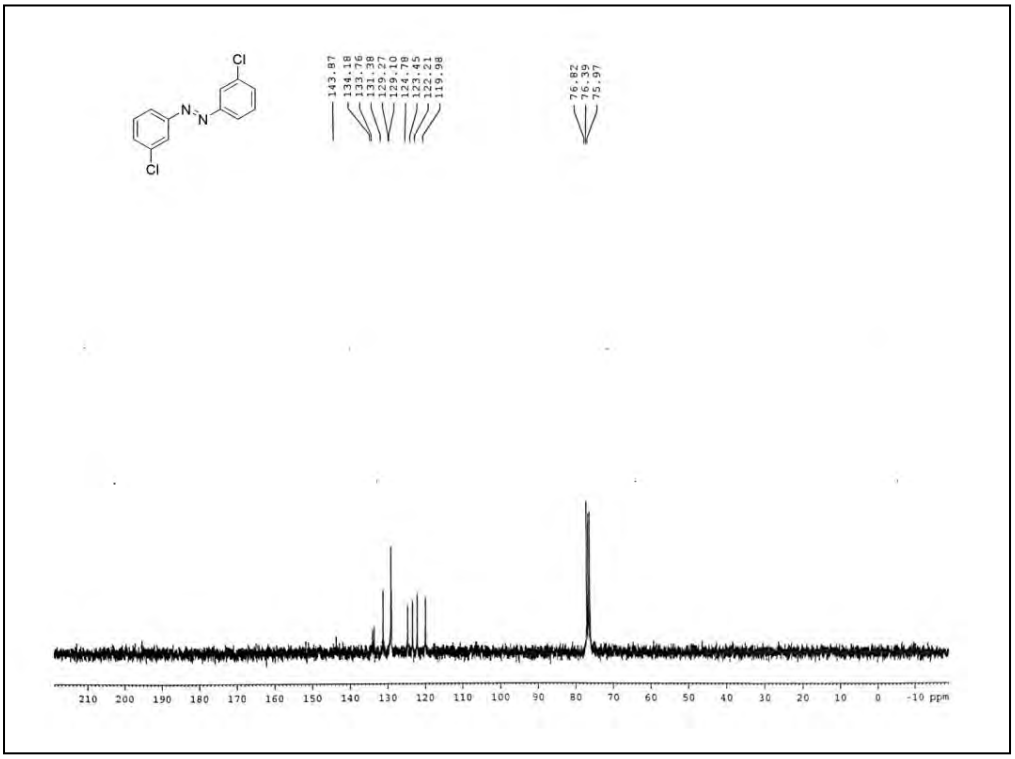


Figure V.6. Scan copy of ^{13}C NMR of (*E*)-3,3′-Dichloroazobenzene.

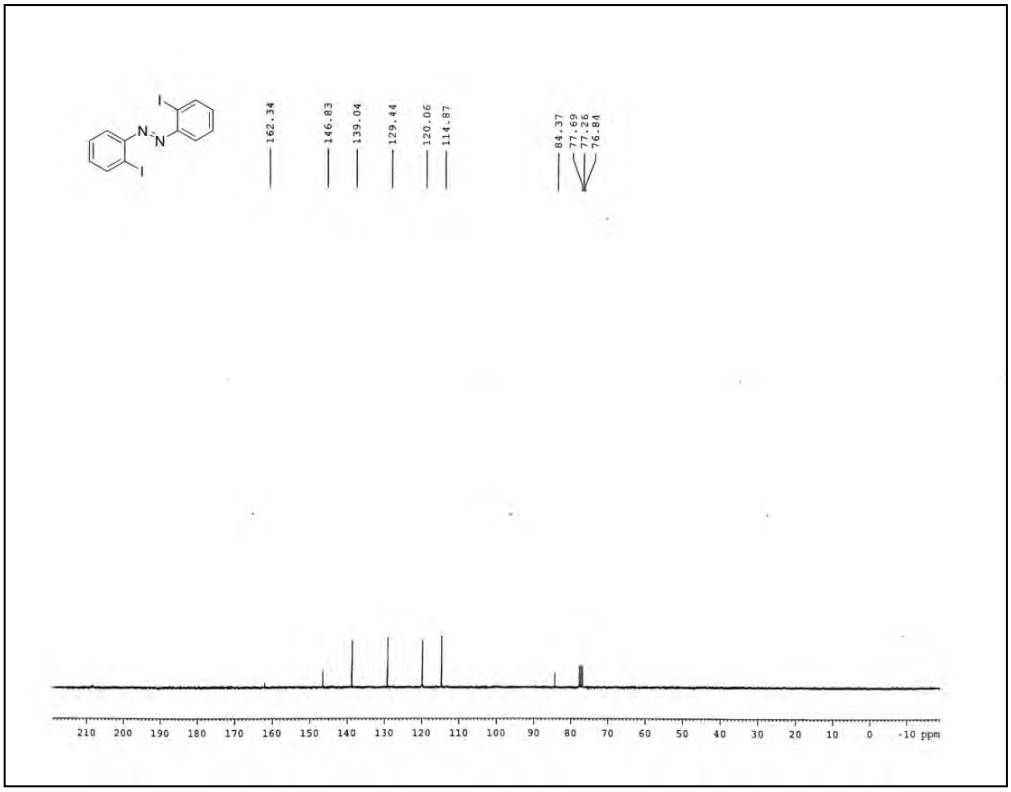


Figure V.7. Scan copy of ^{13}C NMR of (*E*)-2,2′-Diiodoazobenzene.

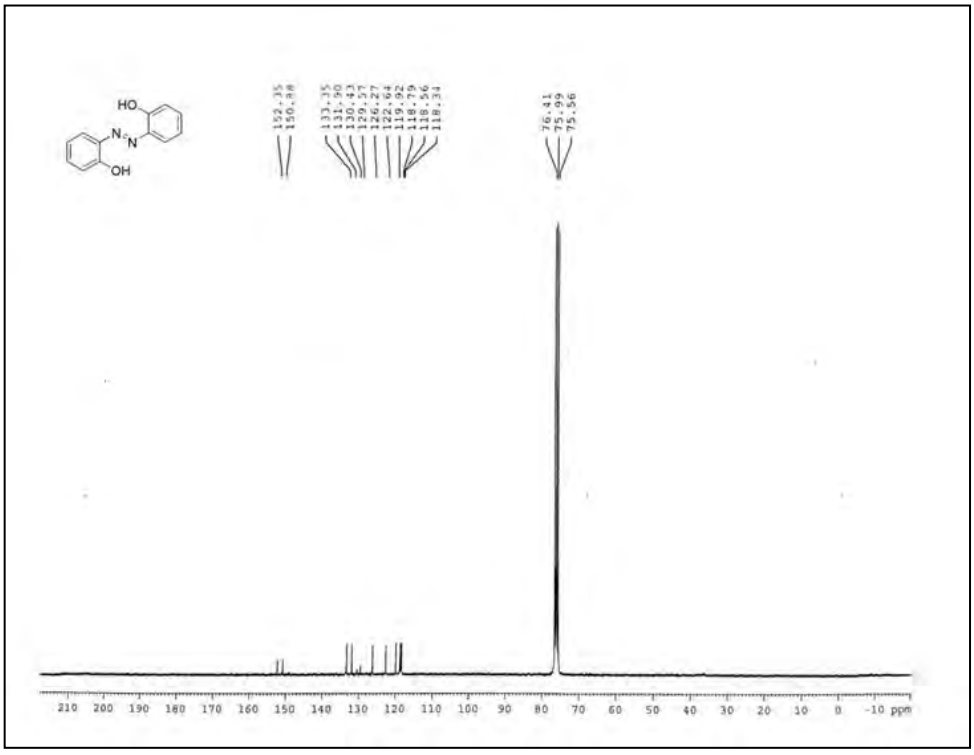


Figure V.8. Scan copy of ^{13}C NMR of (*E*)-2,2′-Dihydroxyazobenzene.

V.F. Reference

References are given in BIBLOGRAPHY under Chapter V.