CHAPTER V

Boric acid catalyzed transition metal free efficient synthesis of azobenzenes

V.A. Introduction

Azobenzene are the class of chemical compounds having two phenyl rings linked through N=N double bond. Azobenzene exists in two isomeric forms, *trans*-azobenzene and *cis*-azobenzene. *Trans*-azobenzene is planer whereas *cis*-azobenzene is nonplaner. The N-N distance in *trans*-azobenzene and *cis*-azobenzene are 1.189Å and 1.251Å respectively. The *trans*-azobenzene is more stable than *cis*-azobenzene by about 50 KJ/mol. Trans form can be converted into the cis isomer by using an appropriate wavelength (UV at 300-400 nm) of light whereas different wavelength(visible blue light> 400 nm) can convert cis isomer back to trans form (Figure V.1).

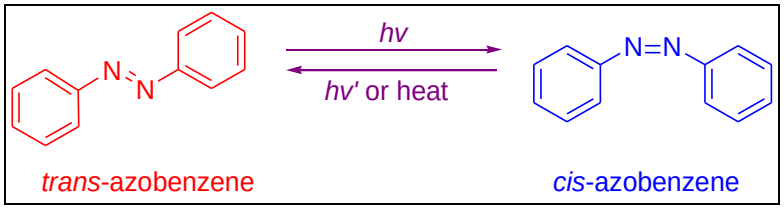


Figure V.1. Interconversion of *trans*-azobenzene and *cis*-azobenzene

For a long period of time, aromatic azo compound have received considerable amount of interest among the chemists. The main reason behind this is the tremendous array of application these compound promises in the field of food additives, indicators, organic dyes and therapeutic agents(Figure V.1).[1] Further, due to their exceptional photochemical response, these compounds have been extensively used as liquid crystals,[2] smart polymers,[3] photoswitches in biological systems[4] and photochromic ligands in optochemical genetics.[5] By C-H activation/functionalization, azo compounds has been recently reported to be used for synthesis of valuable compounds like o-alkoxyazobenzenes, [6] o-acylazobenzenes[7] and indole derivatives. [8] They are also used in the manufacture of proactive glass and filters.

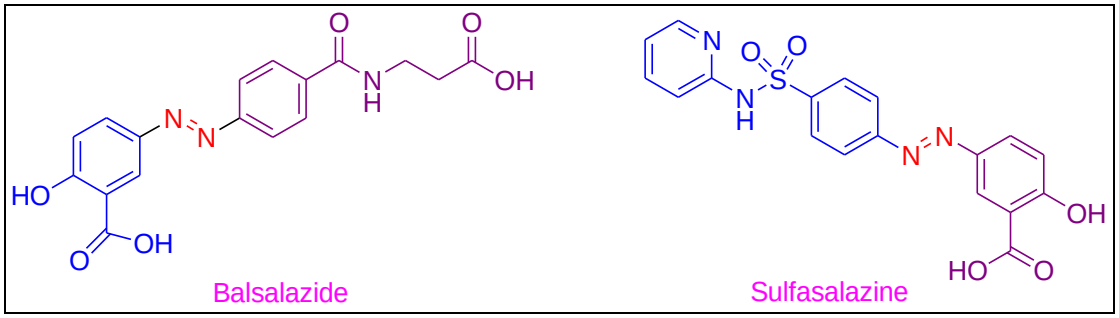


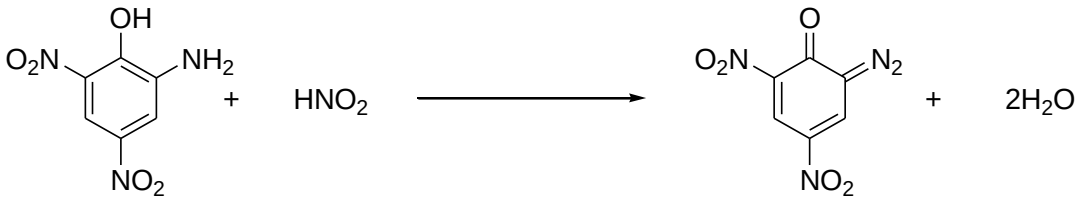
Figure V.2. Biologically active molecules having azo moiety

V.B. Background and objectives

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

V.B.1.1.Griess reaction

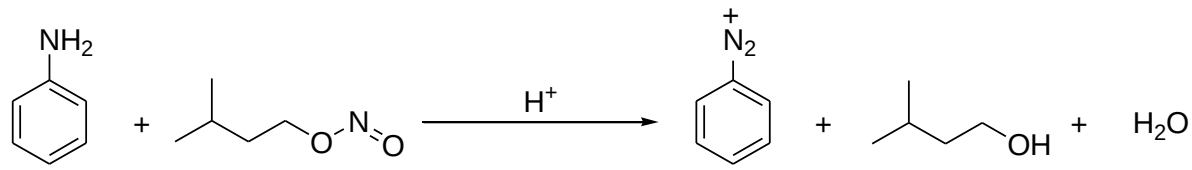
It was in the year of 1858, when Peter Griess[9] reported the first preparation of aromatic diazo compounds. In his work, he proposed the diazotization of o-aminophenol using nitric acid and arsenous acid. Here, nitrous acid was supposed to be generated in situ by the reaction of nitric acid and arsenous acid which was responsible for the conversion of o-aminophenol to the respective diazo-compound (Scheme V.1).



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

V.B.1.2. Knoevenagel method

Knoevenagel[10] modified Griess' original method by using nitrite esters. By using nitrite esters he found that transformation was more effective in preparing diazo-compounds in acid medium (Scheme V.2). Using this method he was able to convert aniline to diazo-benzene.



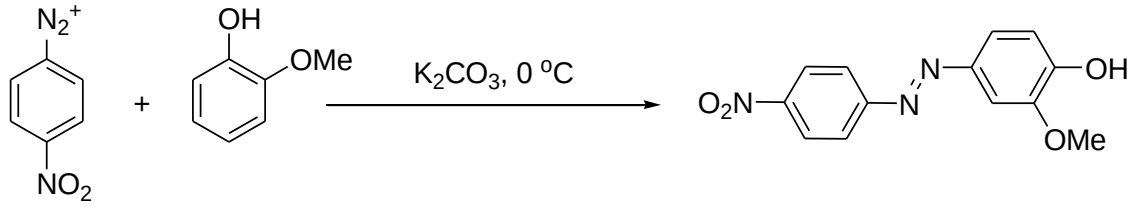
Scheme V.2. Knoevenagel method for synthesis of diazo-benzene

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

V.B.2.1. Azo coupling reaction

Majority of azobenzenes are usually synthesized using this method. The method involves diazotization of aromatic primary amines in low temperature and then reacting with electron rich aromatic nucleophile. Short reaction time and high yield are the main advantages of this reaction. K. Haghbeen *et al.*[11] were able to separate 92% yield of azo compound by reacting diazonium

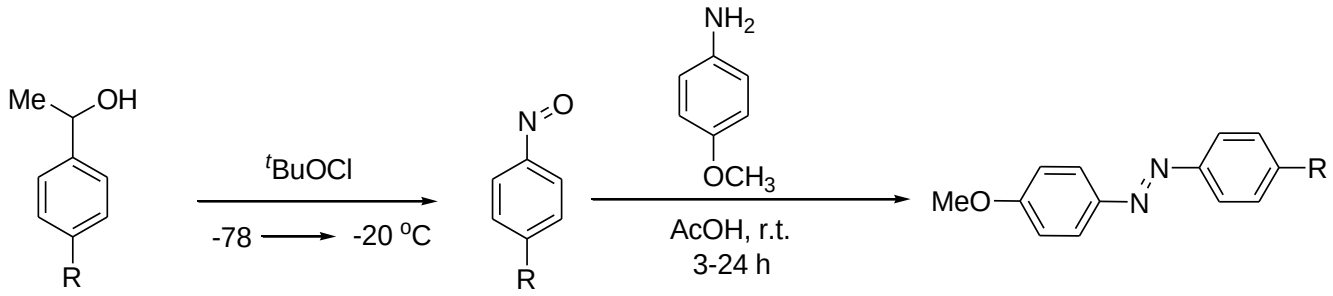
salt and phenol at 0^{o}C using K_2CO_3 as base (Scheme V.3). Diazonium salts are regarded as weak electrophiles and hence react with electron rich species like substituted arenes with electron donating groups such as amine or hydroxyl to form azobezene. Usually, reaction takes place at the para position to the electron donating group but when the para position is already occupied, the substitution takes placeat the the ortho position.



Scheme V.3. Azo coupling reaction for synthesis of azobenzene

V.B.2.2. Mills reaction

M. H. Davey *et al.*[12] reported the synthesis of azobenzene in excellent yield by the reaction between aromatic nitroso derivatives and anilines in presence of glacial acetic acid. Nitroso derivatives were prepared by oxidation of aromatic methylhydroxylamine with tert-butyl hypochlorite. The oxidation reaction needed to be carried out at -78 ^{o}C and high dilution since it is a very fast reaction and overoxidation takes place with the oxidation of nitrosobenzene to nitrobenzene (Scheme V.4).

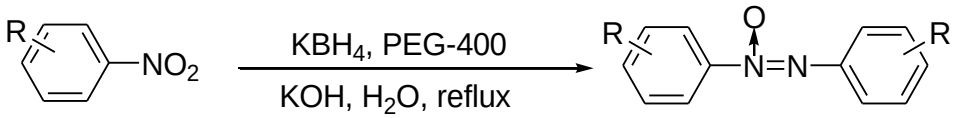


Scheme V.4. Mills reaction for synthesis of azobenzenes

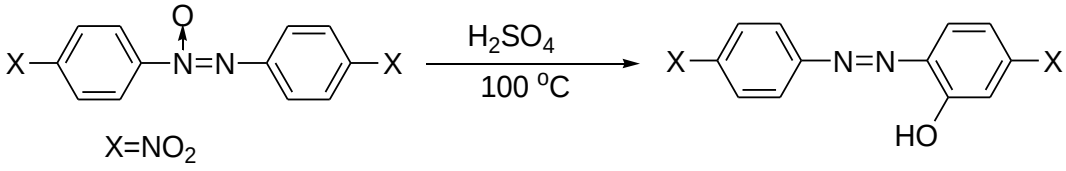
V.B.2.3. Wallach reaction

During 1880, O. Wallach[13] discovered that aromatic azoxy compound can be converted into azo compound using sulphuric acid or other strong acids. Here, one arene ring gets substituted with hydroxyl group on the para-position (Scheme V.6). Azoxy benzenes are usually prepared by the reduction of nitrobenzenes. A number of examples have been reported so far for the reduction of

nitrobenzene to azoxybenzene. Recently, Y. Liu *et al.*[14] have reported the reduction of nitrobenzenes into corresponding azoxybenzene using potassium borohydride as the reducing agent and water as the medium (Scheme V.5). PEG-400 was used as the phase transfer catalyst. It was found that the electronic effect played an important significance in the formation of azoxybenzene. The electron-withdrawing groups were found to accelerate the reaction whereas the electronic- releasing group retarded the reaction to various degrees.



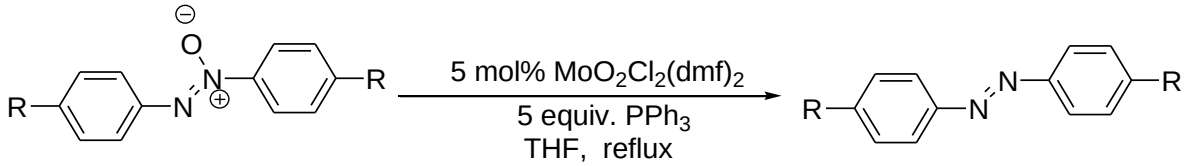
SchemeV.5. Reduction of nitro benzene to azoxybenzene



Scheme V.6. Wallach reaction for synthesis of azobenzenes

V.B.2.4 Reduction of azoxybenzenes

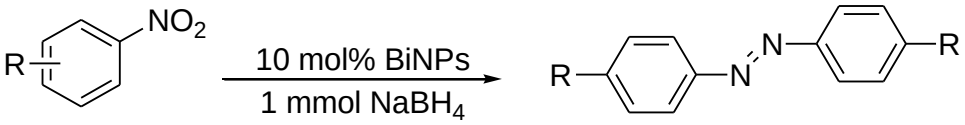
Reduction of azoxybenzenes can be used to synthesize azobenzenes. Recently, R. Sanz *et al.*[15] reported the reduction of azoxybenzene to azobenzene in excellent yield by using tertiary phosphines as a reducing agent (Scheme V.7). The reaction was performed using dichlorodioxomolybdenum (VI) as catalyst.



Scheme V.7. Reduction of azoxybenzene for synthesis of azobenzenes

V.B.2.5. Reductive coupling of aromatic nitro derivatives

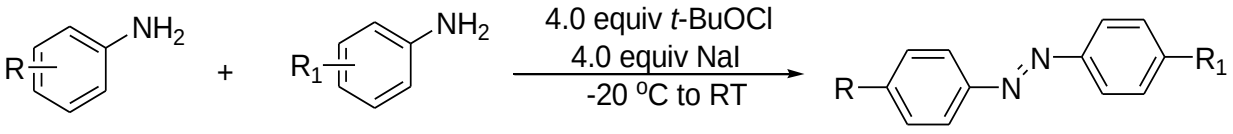
Reductive coupling reaction using suitable nitrobenzene has been an important tool for the synthesis of symmetrical aromatic azo compounds. A number of reducing agents have been used so far. Recently, in 2015, K. Pothula[16] and his co-workers have reported conversion of nitrobenzene to azobenzenes by using bismuth nanoparticles as catalyst. The conversion was carried out under environment friendly conditions with excellent yield of the product. Also, the catalyst was reported to be recovered and reused without losing much of its efficiency (Scheme V.8).



Scheme V.8. Reductive coupling of aromatic nitro derivatives for synthesis of azobenzenes

V.B.2.6. Oxidation of anilines

In 1972, a new methodology was reported for the synthesis of azobenzenes. S. Wawzonek *et al.*[17] reported synthesis of azobenzenes by electrolytic oxidation of aromatic amines. However the procedure was not as efficient as the yield obtained by them was very low. A number of protocols have been published which promised improvement of this synthesis using various reaction conditions, a number of oxidizing agents and a variety of catalysts. Recently, Y. Takeda *et al.*[17] have reported development cost-efficient procedure for oxidative dimerization of aromatic amines to azobenzenes using *tert*-butyl hypochlorite (*t*-BuOCl) and NaI (Scheme V.9). The advantage of this protocol as stated by them was the synthesis of unsymmetrical azobenzenes.

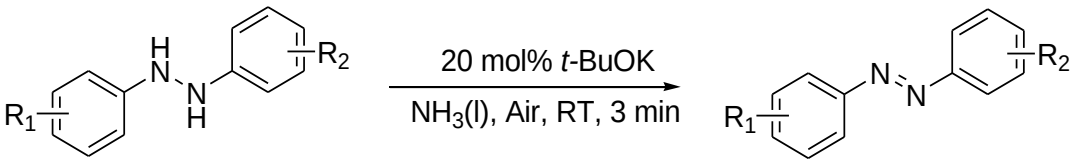


Scheme V.9. Oxidation of anilines for synthesis of azobenzenes

V.B.2.7. Dehydrogenation of arylhydrazines for synthesis of azobenzenes

Several examples of dehydrogenation of *N*,*N*-diarylhydrazines to corresponding azobenzenes have been reported in literature. In 2016, L. Wang and his co-workers[18] reported strategy for

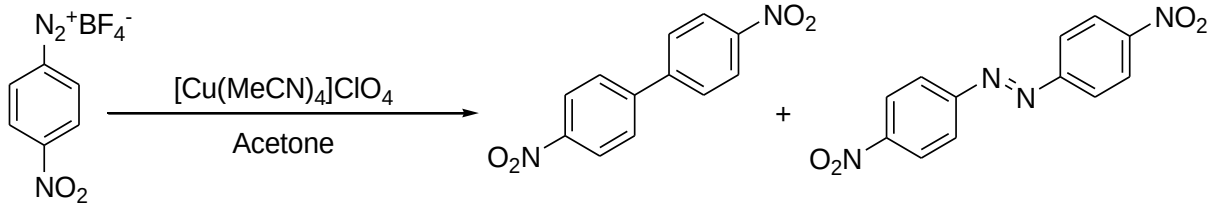
dehydrogenation of *N*,*N*-diarylhydrazines using potassium tert-butoxide in liquid ammonia. High efficiency of the methodology and very short reaction time was the main features of this synthesis (Scheme V.10). They further extended the methodology for the synthesis of diazirines.



Scheme V.10. Dehydrogenation of arylhydrazines for synthesis of azobenzenes

V.B.2.8. Dimerization reaction of diazonium salts

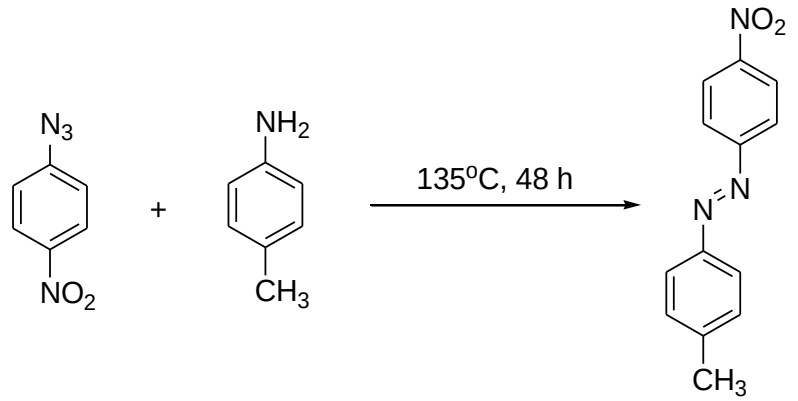
Dimerization of diazonium salts either in presence of copper and acid known to be Gatterman's method[19] or copper (I) salts leads to the formation of azobenzenes. The reaction is highly sensitive towards the nature of the aryl group present. In presence of electron-withdrawing group biaryl are obtained as the main product due to C-C coupling but in presence of electron-donating group, azobenzene dominates as the main product (Scheme V.11).



Scheme V.11. Dimerization reaction of diazonium salts for synthesis of azobenzenes

V.B.2.9. Thermolysis of azides

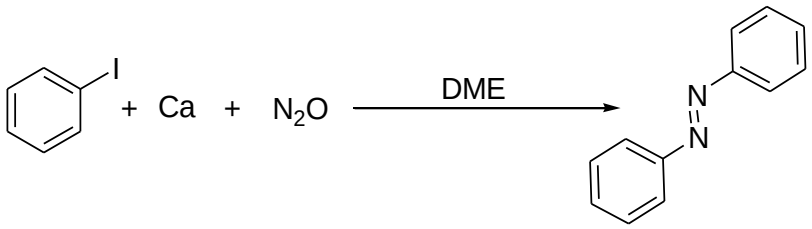
In presence of aniline, aromatic azides can be heated to give unsymmetrical azo compounds.[20] However the yield obtained in such reactions are always low. Also the azides are explosive in nature and are difficult to handle (Scheme V.12)



SchemeV.12. Thermolysis of azides for synthesis of azobenzenes

V.B.2.10. Reaction of arylcalcium derivatives with nitrous oxide

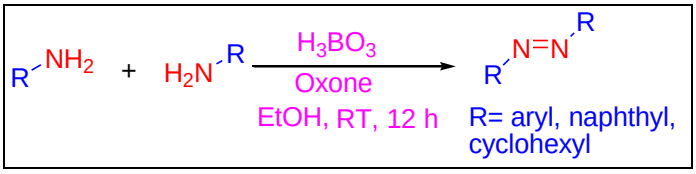
Aryl calcium derivatives act as a good precursor for the synthesis of azobenzenes. M.L. Hays and co-workers [21] have reported the synthesis of azobenzene in good yield by reacting iodobenzene with metallic calcium and nitrous oxide in presence of dimethoxyethane. The yield however became low when the reaction was carried out with organolithium compounds (Scheme V.13). Phenylcalcium iodide was supposed to be generated by the reaction of iodobenzene and calcium.



SchemeV.13. Reaction of arylcalcium derivatives with nitrous oxide for synthesis of azobenzenes

V.C. Present work

In this work boric acid has been used as an efficient, non toxic catalyst for the synthesis of azobenzenes. Oxone is used as an oxidant and ethanol the reaction medium. The reaction was performed at room temperature for 12 hours.



Scheme V.14. Synthesis of azobenzene from amines

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 started by taking 1 mmol of aniline, 0.5 mmol of oxone and 50 mol% of boric acid under neat condition for 12 hours. 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). With acetonitrile the yield was only 15% while chloroform gave a yield of 50% (Table V.1, Entry 3, 4). The yield further increased to 69% with toluene (Table V.1, Entry 5). Finally using ethanol furnished a good yield of 81% (Table V.1, Entry 6). Keeping the amount of oxone constant at 0.5 mmol further increasing the amount of the catalyst upto 100 mol% did not increased the yield significantly. Further, decreasing the amount to 20 mol% also decreased the yield to 52% (Table V.1, Entry 8). Hence, the amount of catalyst was optimized to 50 mol%. Now with the catalyst being constant at 50 mol%, we increase the amount of oxone to 1.0 mmol but here we were surprised to find that only trace amount of the product was only detected (Table V.1, Entry 9). It may be due to the oxidization 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 10). Hence finally we report that the optimal reaction condition is 1 mmol of aniline, 0.5 mmol of oxone and 50 mol% of boric acid in ethanol for 12 hours.

Table V.1. Optimization of reaction condition[a]

Entry	Oxone (mmol)	Catalyst (mol%)	Solvent	Yield (%)[b]
1	0.5	50	Neat	Trace
2	0.5	50	Water	trace
3	0.5	50	$CHCl_3$	50
4	0.5	50	Acetonitrile	15
5	0.5	50	Toluene	69
6	**0.5**	**50**	**Ethanol**	**81**
7	0.5	100	Ethanol	83
8	0.5	20	Ethanol	52
9	1.0	50	Ethanol	trace
10	0.25	50	Ethanol	38

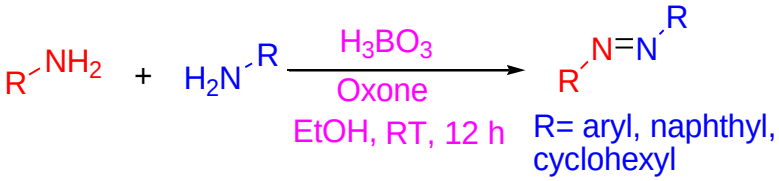
The bold significance represents the optimized protocol/conditions

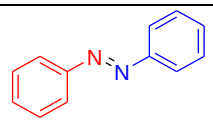
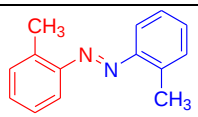
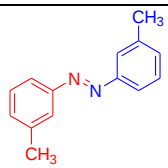
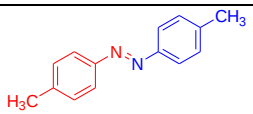
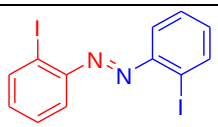
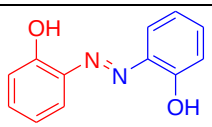
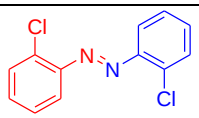
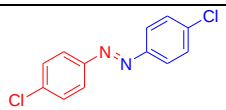
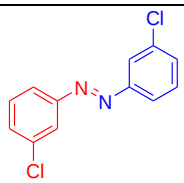
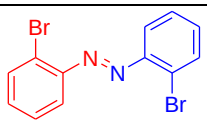
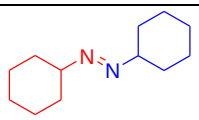
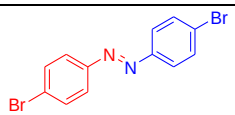
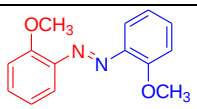
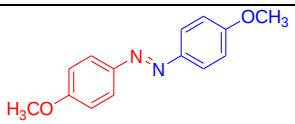
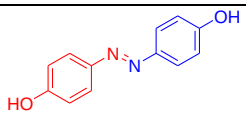
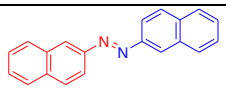
[a]Reaction of aniline (1 mmol)

[b]isolated yield of product by column chromatography.

Reaction was carried out at room temperature for 12 hours.

Table V.2. Boric acid catalyzed synthesis of azobenzenes

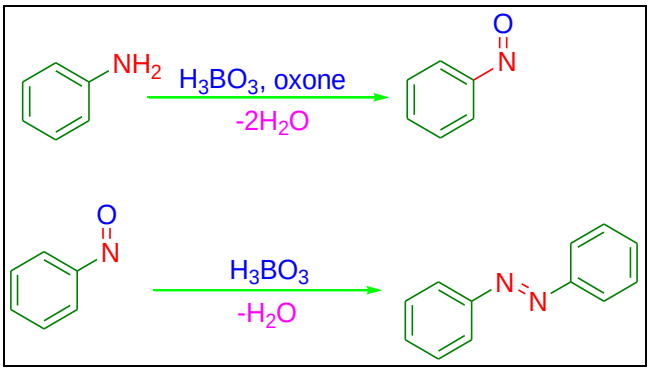


 81%, 12 h	 71%, 12 h	 83%, 12 h	 85%, 12 h
 59%, 12 h	 68%, 12 h	 64%, 12 h	 75%, 12 h
 65%, 12 h	 61%, 12 h	 70%, 12 h	 79%, 12 h
 66%, 12 h	 80%, 12 h	 72%, 12 h	 76%, 12 h

Amines having various substituents have been successfully converted into azobenzene in good yields as depicted in Table V.2. It is evident that ortho substituted amines gave fewer yields than the para substituted products. It may be due to the steric factor involved in ortho substituted products.

V.C.2. Mechanism

Boric acid may have oxidized aniline either through radical mechanism or via electrophilic oxygen transfer with the subsequent generation of unstable nitrosobenzene. Electrophilic attack by the second molecule of aniline to nitrosobenzene, followed by dehydration led to the formation of *trans*-azobenzenes.



Scheme.V.15. Plausible mechanism for azobenzene synthesis

C.3. Conclusion

In conclusion, we have developed an environmentally benign protocol for the single-step facile synthesis of azobenzenes from amines by using boric acid as a catalyst and ethanol as a solvent. The reaction protocol includes the use of an inexpensive and less toxic reagent, gives excellent yield of the desired products and has simple and easy reaction conditions and workup process.

V.D. Experimental

V.D.1. General Information

III. E.1. Material Apparatus

Most of the amines used were purchased from Sigma-Aldrich and some were purchased from Loba Chemie. All the products were purified by column chromatography on 60−120 mesh silica gel (SRL, India). For TLC, Merck plates coated with silica gel 60, IR spectra were recorded on using KBr pellets for solid compounds and under neat condition for liquid compounds in the range 4000-400 cm^{-1} on Shimadzu FT-IR 8300 Spectrometer. The ^{1}H & ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on Bruker AV 300 spectrometer in $CDCl_3$. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad) and m (multiplet).

V.D.2.Procedure for the synthesis of azobenzenes from aniline

In our general procedure, a mixture of aniline (1 mmol), oxone (0.5 mmol) and boric acid (50 mol%) in ethanol (1 mL) was stirred at room temperature and the progress of the reaction was monitored on the TLC. After completion of the reaction the reaction mass was cooled, then the

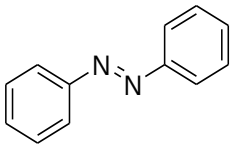
solution was poured into 100 mL water and extract with ethyl acetate, washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by column chromatography on silica gel 60–120 mesh using petroleum ether as eluent to afford the pure solid product. All compounds were analyzed by melting point, ^{13}C and ^{1}H-NMR techniques.

V.D.3. Spectroscopic data of synthesized azobenzenes

(E)-Azobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ =8.05-8.01 (m, 4H), 7.59-7.55 (m, 6H).

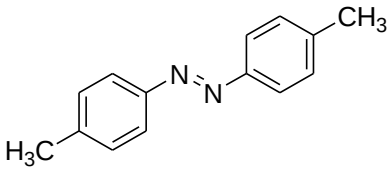
^{13}C NMR (75 MHz, $CDCl_3$): δ =152.6, 130.9, 129.1, 122.8.



(E)-4,4′-Dimethylazobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 6.9 Hz, 4H), 7.29 (d, *J* = 8.1 Hz, 4H), 2.42 (s, 6H).

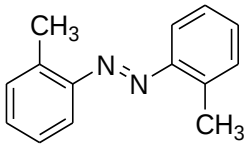
^{13}C NMR (75 MHz, $CDCl_3$): δ =150.8, 141.2, 129.7, 122.7, 21.5.



(E)-2,2′-Dimethylazobenzene

^{1}H NMR (300 MHz,$CDCl_3$): δ = 7.62-7.60(d, 2H),7.33-7.30(m, 4H),7.24-7.22(m, 2H),2.72(s, 6H).

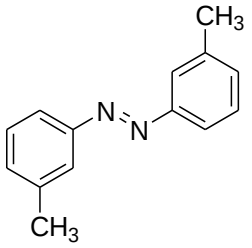
^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.31, 138.26, 130.92, 126.60, 116.07, 17.88.



(E)-3,3′-Dimethylazobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (s, 4H), 7.43-7.39 (m, 2H), 7.31-7.26 (d, 2H), 10 2.47 (s, 6H).

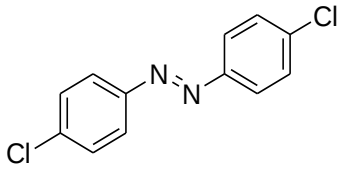
^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.97, 139.19, 131.91, 129.11, 123.04, 120.70, 21.61.



(E)-4,4′-Dicholroazobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ =7.86 (d, *J* = 8.6 Hz, 4H), 7.49 (d, *J* = 8.6 Hz, 4H).

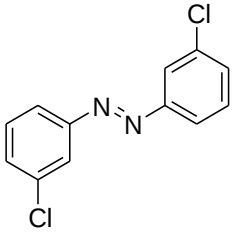
^{13}C NMR (75 MHz, $CDCl_3$): δ =150.9, 137.4, 129.6, 124.3.



(E)-3,3′-Dichloroazobenzene

^{1}H NMR (300 MHz,$CDCl_3$): δ = 7.78 (dd, *J* = 1.8, 7.8 Hz, 2H), 7.57 (dd, *J* = 1.5, 7.8 Hz, 2H), 7.39 (td, *J* = 2.9, 6.3 Hz, 4H).

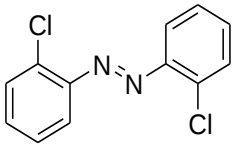
^{13}C NMR (75 MHz, $CDCl_3$): δ =148.7, 135.8, 132.2, 130.7, 127.4, 118.1.



(E)-2,2′-Dichloroazobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78-7.76 (d, 2H), 7.58-7.56 (d, 2H), 7.44-7.40 (m, 2H), 7.38-7.34 (m, 2H).

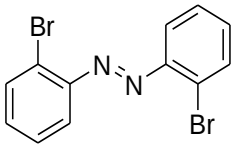
^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.47, 130.94, 127.61, 118.29.



(E)-2,2′-Dibromoazobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77-7.76 (d, 4H), 7.43-7.39 (m, 2H), 7.36-7.33 (m, 2H).

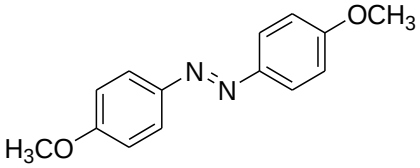
^{13}C NMR (75 MHz, CDCl3): δ = 134.02, 132.71, 128.33, 118.63.



(E)-2,2′-Dimethoxyazobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91-7.86 (m, 4H), 7.03-6.98 (m, 4H), 3.89 (s, 6H).

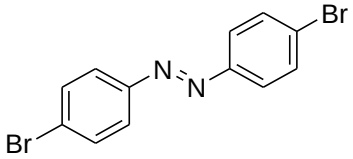
^{13}C NMR (75 MHz, $CDCl_3$): δ =161.6, 147, 124.4, 114.4, 55.6.



(E)-4,4′-Dibromoazobenzene

^{1} H NMR (300 MHz, $CDCl_3$): δ = 8.07-8.01 (2 H, m), 7.86 (2 H, d, *J* = 7.9 Hz), 7.60 (2 H, d, *J* = 7.9 Hz), 7.39 ppm (2 H, t, *J* = 7.9 Hz);

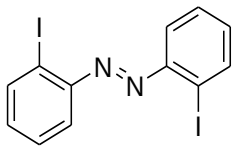
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.20, 134.12, 130.51, 124.77, 123.95, 123.19.



(E)-2,2′-Diiodoazobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.8 Hz, 2H,), 7.76 (d, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7 Hz, 2H).

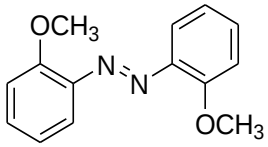
^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.7, 139.9, 132.7, 129, 118.2, 103.3.



(E)-2,2′-Dimethoxyazobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 7.9 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.00 (t, *J* = 7.6 Hz, 2H), 4.02 (s, 6H).

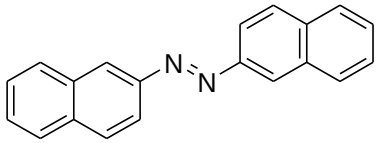
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 143.1, 132.3, 120.9, 117.6, 112.7, 56.4.



(E)-2,2′-Azonaphthalene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.04 (s, 1H), 8.79 (s, 1H), 7.45-8.00 (m, 8H), 7.51 (t, *J*=7.8Hz, 2H), 7.45 (t, *J*=7.2Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5, 134.6, 133.7, 133.2, 132.5, 129.6, 129.5, 128.8, 128.3, 128.1, 127.8, 127.5, 127.4, 127.2, 126.5, 124.9, 124.0, 122.2, 119.5.



V.D.4. Scan copies of ^{1}H NMR, ^{13}C NMR and FT-IR of compounds

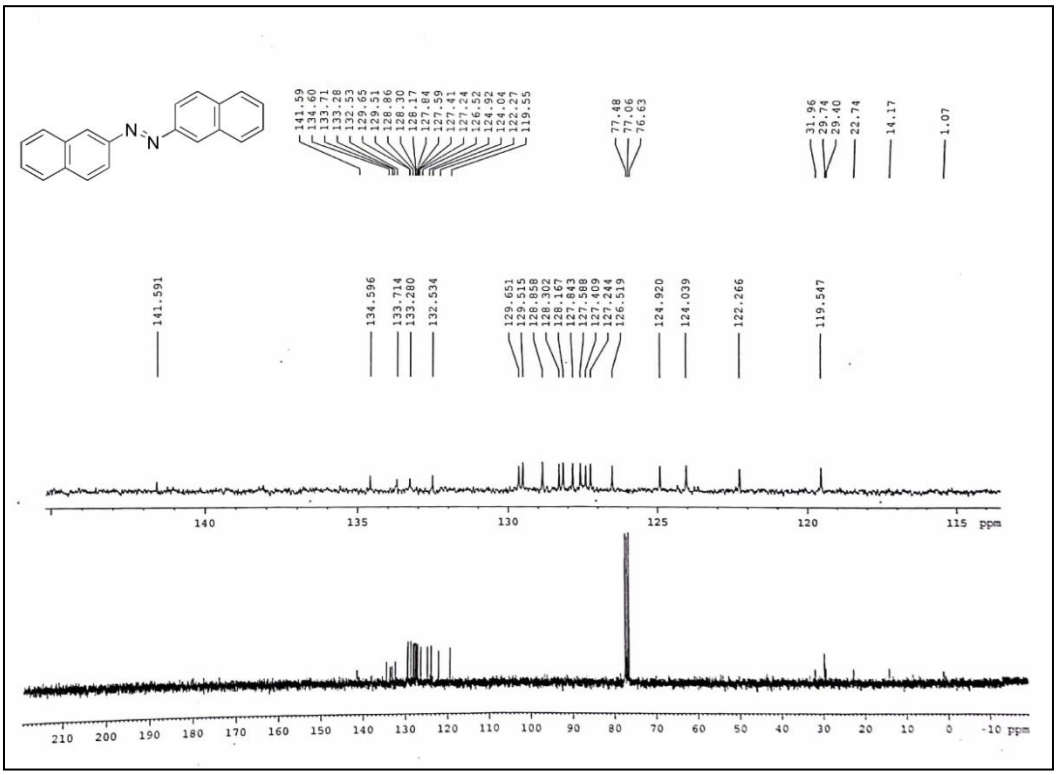


Figure V.3. Scan copy of ^{13}C NMR copy of 2,2'-Azonaphthalene

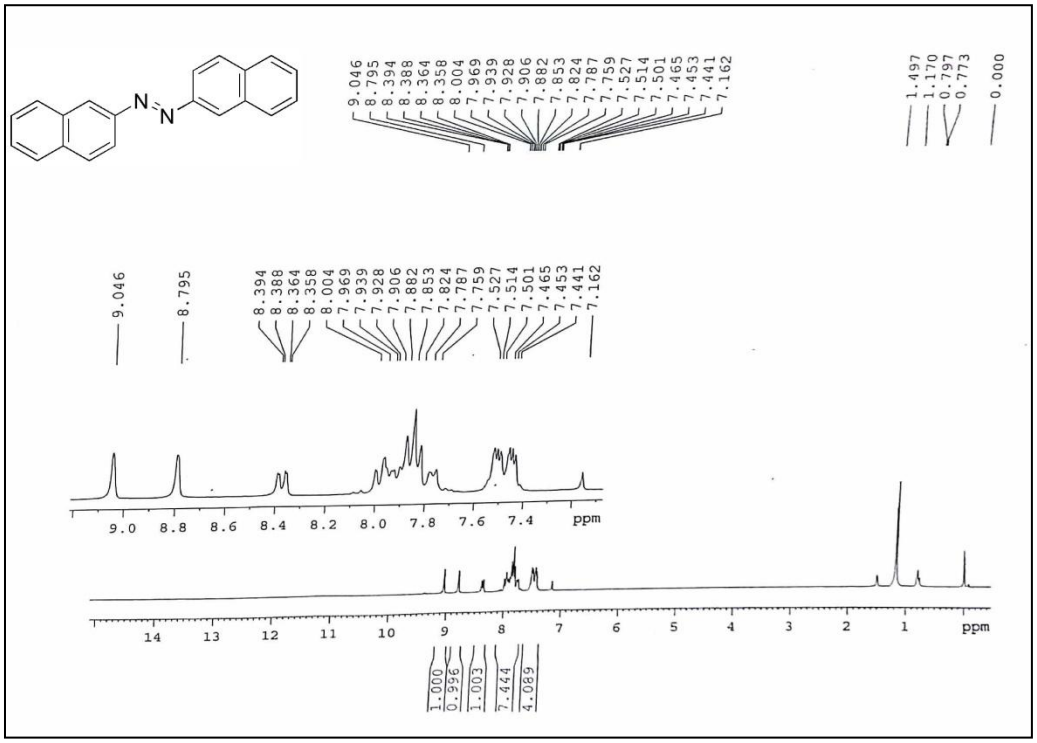


Figure V.4. Scan copy of ^{1}H NMR copy of 2,2'-Azonaphthalene

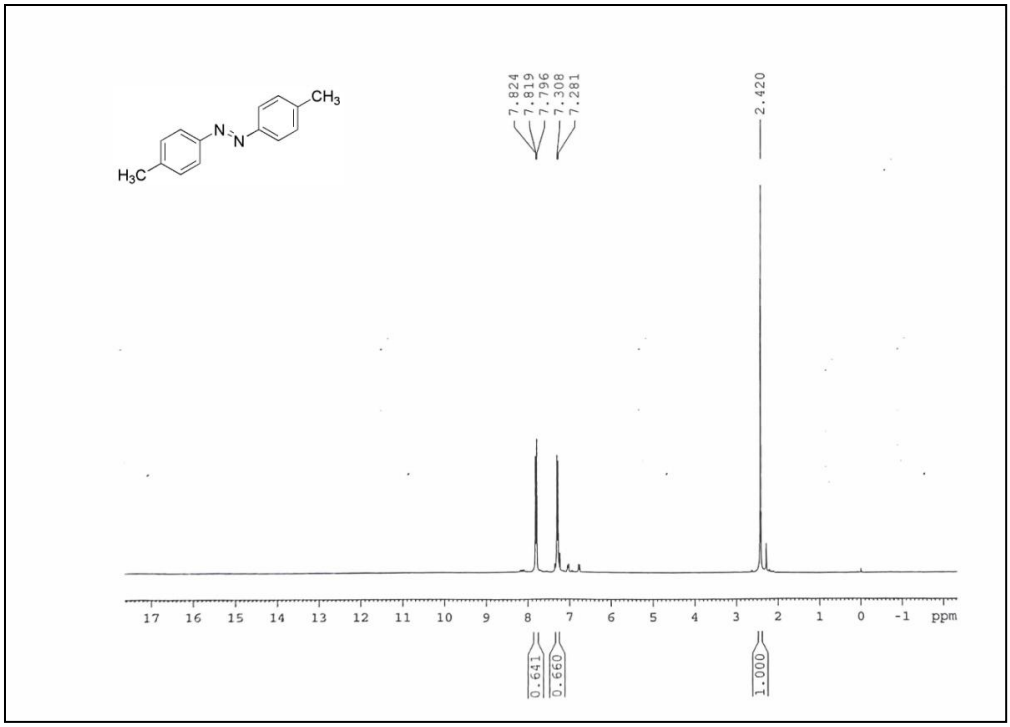


Figure V.5. Scan copy of ^{1}H NMR copy of 4,4'-Dimethylazobenzene

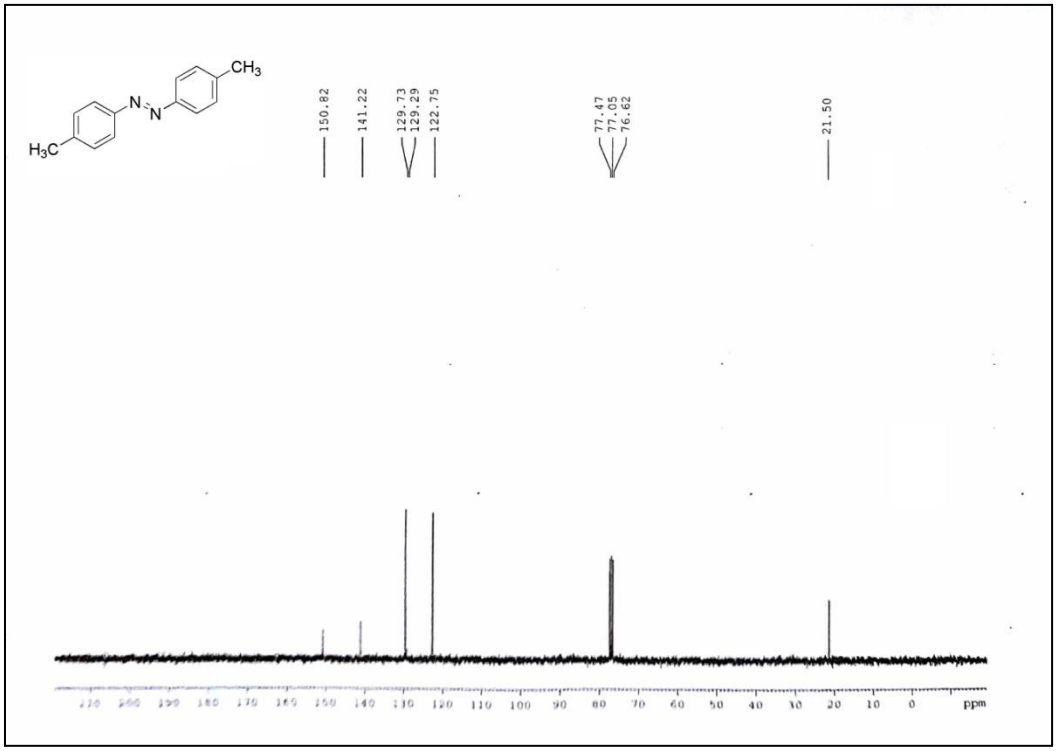


Figure V.6. Scanned ^{13}C NMR copy of 4,4'-Dimethylazobenzene

V.E. References

References are given in BIBLIOGRAPHY under Chapter V.