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An efficient catalyst-free and chemoselective synthesis of azobenzenes from nitrobenzenes†

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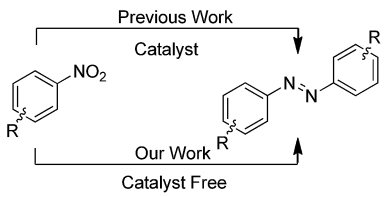
NaOH mediated reaction of nitrobenzenes in EtOH was performed at 80 °C temperature affording azobenzenes in excellent yield. This methodology presents an easy synthesis of a wide variety of azo compounds from readily available nitrobenzene derivatives.

Aromatic azobenzene derivatives as well as azoxybenzene compounds are important and central building blocks in the production of dyes and pigments,[1] agrochemicals, indicators in volumetric analysis,[2] pharmaceuticals,[3] polymers,[4] nanotubes,[5] and also in biological systems.[6] Various reagents and methodologies are reported for the formation of azobenzenes. Synthesis of symmetrical and unsymmetrical aromatic azo compounds have been developed using KOH at 150 °C.[7] Apart from conventional method, Mg and triethyl ammonium formate or ammonium bromide as a hydrogen source is a convenient reagent for the reduction of aromatic nitro compounds to symmetrically substituted azo compounds.[8] A novel route was developed to synthesize symmetric azobenzenes using Mg electrodes.[9] Many reports are available on metal catalyzed synthesis of azo compounds from nitrobenzene.[10] Recently, azoarenes are prepared from corresponding nitroarenes by using supported gold nanoparticles.[11]



An overview, some of the earlier reported methods is given in Table 1. All these methods gave good to better product yields as per their reaction conditions. However, they suffer from some limitations such as requirement of high pressure, high temperature, use of flammable hydrogen gas and use of toxic reagents. In some cases, transition metals are used as catalysts to achieve the desired yield of the product though these transition metals are not environmentally friendly and are very expensive. In some of the methods biologically harmful by-products are formed by using various reducing agents. It is also observed that in some of the methods, aniline is a major product whereas azobenzene is a minor products. In such processes azobenzene is very unstable and difficult to isolate.[13]

Therefore there is a need to develop a protocol which will overcome the above limitations by avoiding use of expensive metal catalysts and toxic reagents. Herein, we report an efficient, catalyst free, chemoselective route for the synthesis of aromatic azo compounds from substituted nitroarenes (Scheme 1). Ethanol which has no toxicity and is easily available from fermentation process is used as solvent as well as activated H-donor.[14] The major outcome of this protocol is the decrease in the yield of aniline which is a by-product and thereby making the system more atom economical. Moreover, this is the first catalyst free report on the synthesis of azo compounds from nitrobenzenes. Nitrobenzene was chosen as a starting material for optimizing various reaction conditions such as solvents, base, concentration of base, temperature and time.

First we carried out the experiments to select the most suitable solvent and got the maximum yield and better selectivity with ethanol which also acts as a hydrogen source (Table 2, entry 2). Other solvents such as methanol, 1-propanol, 2-propanol, 1-butanol, *tert*-butanol, isoamyl alcohol, THF, glycerol, water, benzyl alcohol and 1-hexanol were found to be less

Table 1 Comparison table of previous reports for the synthesis of azobenzene[a,12]

			Yield (%)		
Entry	Reaction parameters	Catalyst	II	III	IV
1[a]	Et_3SiH, DMF, 60 °C, N_2, 12 h	$In(OTf)_3$	Trace	—	84
2[b]	KOH, IPA, N_2, H_2O, 40 °C, 5 h	Au	2	3	95
3[c]	KOH, 40 °C, H_2, *p*-xylene, 3.5 h	Pt-NWs	7.3	—	92.7
4[d]	NaOH, EtOH, THF, 100 °C, 24 h	Ru/C	—	—	90
5[e]	KOH, 120 °C, H_2, *p*-xylene, 7 h	Nano-pd	12.6	—	84.4

[a] II-aniline, III-azoxybenzene, IV-azobenzene.

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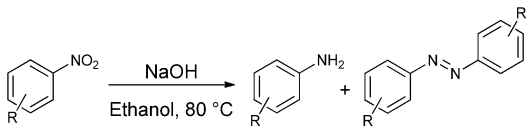
† Electronic supplementary information (ESI) available: Experimental procedures, mass, FT-IR and ^1H and ^{13}C NMR spectra of synthesized compound. See DOI: 10.1039/c4ra06027j



Scheme 1 Synthesis of aromatic azo compounds.

effective (Table 2, entries 1, 3–12). In this study we observed that 2-propanol and isoamyl alcohol gave aniline in 29% and 26% yields respectively, whereas in 1-butanol, azoxybenzene is formed as a major product giving 79% yield.

Our next step was to choose the most suitable base. We tested various inorganic bases such as NaOH, K_2CO_3, NaOEt, KOH and *t*-BuONa (Table 2, entries 2, 13–16). The better results are obtained with NaOH. Other bases did not yield any product, while KOH gave only 10% product yield. The reaction did not proceed in the absence of base (Table 2, entry 17). We examined exact quantity of NaOH and KOH required for complete conversion of nitrobenzene and the results are given in Table 3. Increase in concentration of NaOH from 1 mmol to 3 mmol increases the yield of azobenzene (Table 3, entries 1–3). When we used 5 mmol of NaOH the reaction time decreased significantly from 24 h to 18 h with negligible increase in the product yield. Further increase in concentration to 7 mmol decreased the reaction time to 12 h (Table 3, entries 4 and 5). When we replaced NaOH with 1 mmol of KOH, only azoxybenzene was obtained in 90% yield without formation of azobenzene (Table 3, entry 6). Increase in KOH concentration increases the yield of azobenzene, whereas it did not affect the yield of aniline (Table 3, entries 7 and 8). This base study reveals that base plays a crucial role in the formation of azobenzene as the selective reaction product.

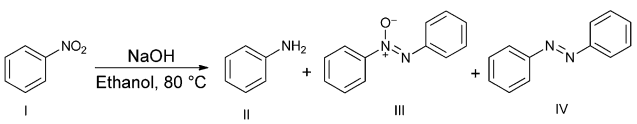
In further investigation, we carried out the standard reaction at different temperatures. The results showed that, 80 °C temperature is sufficient to get maximum yield of azobenzene (Table 3, entry 3). Whereas very little conversion of nitrobenzene to azoxybenzene is obtained at 30 °C (Table 3, entry 9). As the temperature is increased to 60 °C, approximately equal

Table 3 Optimization of reaction parameters for azobenzene synthesis[a]

					Yield[b] (%)		
Entry	Base	Base (mmol)	Temp. °C	Conv. (%)	II	III	IV
1	NaOH	1	80	100	8	34	58
2	NaOH	2	80	100	8	18	74
3	NaOH	3	80	100	8	—	92
4	NaOH	5	80	100	7	—	93[c]
5	NaOH	7	80	100	7	—	93[d]
6	KOH	1	80	100	10	90	—
7	KOH	3	80	100	13	77	10
8	KOH	5	80	100	14	59	27
9	NaOH	3	30	9	—	9	—
10	NaOH	3	60	78	5	39	34

[a] Reaction conditions: nitrobenzene (1 mmol), ethanol (1 mL) for 24 h. [b] GC yield. [c] 18 h. [d] 12 h.

Table 2 Formation of azobenzene with various solvents and bases[a]



					Yield[b] (%)		
Entry	Solvent	Base (mmol)	Temp. (°C)	Conv. (%)	II	III	IV
1	Methanol	NaOH	Reflux	—	—	—	—
2	Ethanol	NaOH	80	100	8	—	92
3	1-Propanol	NaOH	80	100	12	6	82
4	2-Propanol	NaOH	80	98	29	33	36
5	1-Butanol	NaOH	80	100	11	79	10
6	*tert*-Butanol	NaOH	80	—	—	—	—
7	Isoamyl alcohol	NaOH	80	100	26	25	49
8	THF	NaOH	Reflux	—	—	—	—
9	Glycerol	NaOH	80	44	12	26	6
10	Water	NaOH	80	—	—	—	—
11	Benzyl alcohol	NaOH	80	33	—	15	18
12	1-Hexanol	NaOH	80	86	7	4	75
13	Ethanol	K_2CO_3	80	—	—	—	—
14	Ethanol	EtONa	80	—	—	—	—
15	Ethanol	*t*-BuONa	80	—	—	—	—
16	Ethanol	KOH	80	100	13	77	10
17	Ethanol	—	80	—	—	—	—

[a] Reaction conditions: nitrobenzene (1 mmol), base (3 mmol), solvent (1 mL) for 24 h. [b] GC yield.

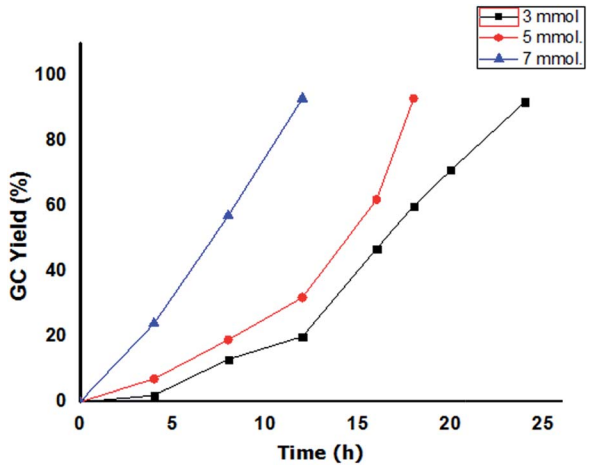


Fig. 1 Effect of NaOH concentration on yield of azobenzene.

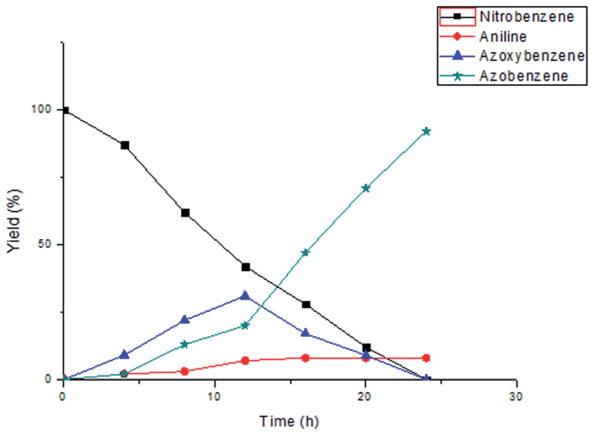


Fig. 2 Time conversion plot for synthesis of azobenzene.

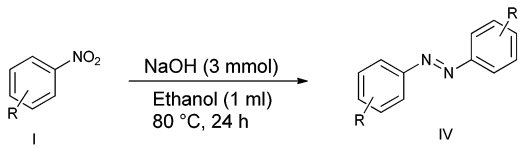
amounts of azoxy and azobenzene with small amount of aniline are obtained (Table 3, entry 10) (Fig. 1).

Conversion of nitrobenzene was monitored over the time of reaction by GC analysis and the results are depicted in Fig. 2. It is observed that aniline is formed only in initial few hours. As the reaction was continued further, the amount of aniline remained constant while that of azoxybenzene was increased. The conversion of nitrobenzene to azoxybenzene was maximum at 12 h which gradually decreased with further heating giving azobenzene. Azoxybenzene was completely converted to azobenzene after 24 h giving 92% yield with 100% conversion of nitrobenzene. This indicates that azoxybenzene being an intermediate undergoes dehydration which ultimately gets converted to azobenzene and hence azoxybenzene was not detected at the end of reaction.

Therefore, the optimum condition for formation of azobenzene from nitrobenzene is 3 mmol of NaOH as base, ethanol as a solvent, at 80 °C reaction temperature for 24 h giving 92% azobenzene and 8% aniline.

The applicability of the protocol to various substituted nitrobenzenes was tested and the results are shown in Table 4.

Table 4 Synthesis of azo compounds from substituted nitro compounds[a]



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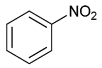
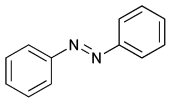
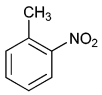
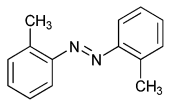
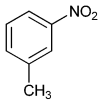
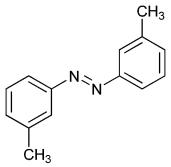
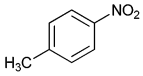
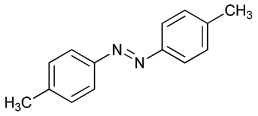
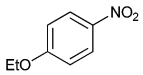
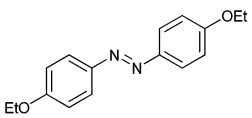
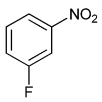
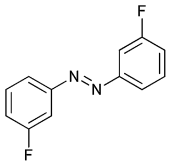
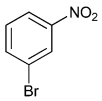
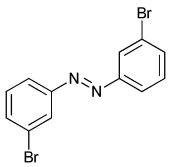
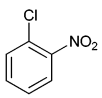
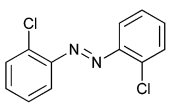
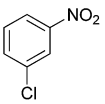
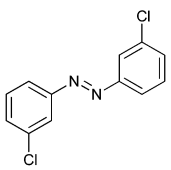
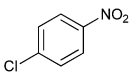
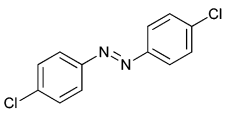
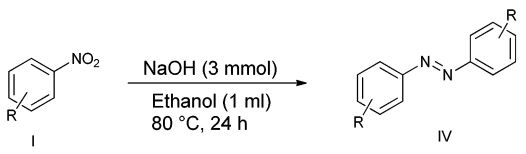
1			90
2			83
3			88
4			87
5			79
6			84
7			80
8			85
9			87
10			61

Table 4 (*Contd.*)



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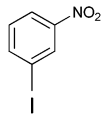
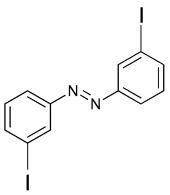
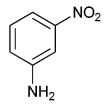
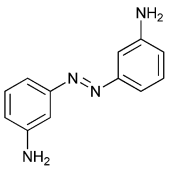
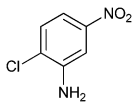
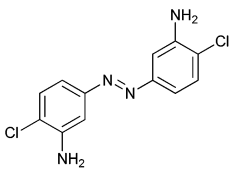
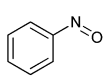
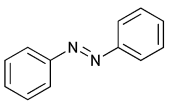
11			82
12			87
13			86
14			85

[a] Reaction conditions: nitroarene (1 mmol), NaOH (3 mmol), ethanol (1 mL) at 80 °C temperature for 24 h. [b] Isolated yield.

This substrate study helped to conclude that the reactions of substituted nitrobenzene having electron donating and electron withdrawing substituents show the significant effect on the progress of reaction. The groups like $-CH_3$, $-NH_2$, –OEt, –F, –Cl, –Br and –I gave good to excellent yield of product according to their position on aromatic ring (Table 4, entries 1–14). The $-CH_3$ group gave maximum yield of product at *meta* position while at *ortho* and *para* positions gave moderate yield of product. Similar results were obtained with –Cl group. Halogen at *ortho* position decreases the yield of desired product which may be due to the steric effect, whereas dehalogenation at *para* position affects the yield of desired product. The group likes –OEt at *para* and $-NH_2$ at *meta* position have positive effect in azo product formation, while $-NH_2$ group at *ortho* and *para* position have no reactivity. Dechlorination of 2-chloro-5-nitroaniline (Table 4, entry 13) at *para* position was not observed and gave excellent product yield. This may be due to the steric hindrance posed by '$-NH_2$' group for dechlorination.

We also carried out the reaction with nitrosobenzene as a starting compound and yielded 85% of azobenzene (Table 4, entry 14). This confirms that nitrosobenzene is formed as an intermediate during the course of reaction.

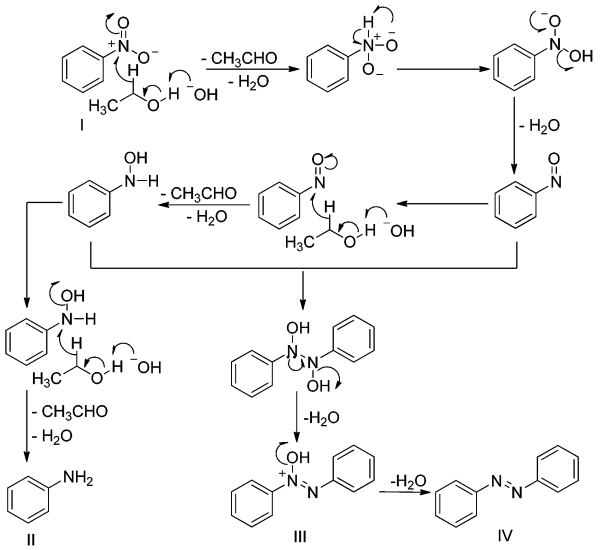
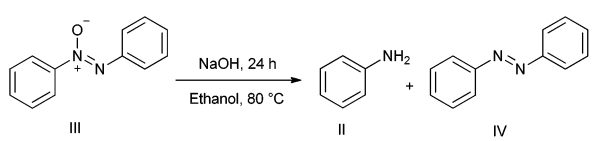


Fig. 3 Possible mechanistic pathway for formation of azobenzene.

Fig. 3 shows the mechanistic pathways involved in the formation of azobenzene and aniline. Excess of NaOH converts ethanol to ethoxide which is known as activated H-donor. The generated hydride ion from ethanol attacks on nitro group. Furthermore, intramolecular hydride transfer from 'N' to 'O' leads to the formation of nitrosobenzene. Thus the nitrobenzene gets reduced to aniline *via* formation of nitrosobenzene and *N*-phenylhydroxylamine as intermediates. On the other hand, these nitrosobenzene and *N*-phenylhydroxylamine immediately couples to give 1,2-dihydroxy-1,2-diphenylhydrazine which further dehydrates to azoxybenzene. Finally azobenzene is formed with release of water molecule from azoxybenzene. Results obtained from GC analysis (Fig. 2), clearly shows that azoxybenzene is the only stable intermediate in the whole process. In all the reactions, there is a formation of sodium acetate salt and it was analysed by FT-IR which matches with that of standard sodium acetate (see ESI†). Acetic acid is formed when the aqueous layer obtained during the work up was treated with HCl. The obtained acetic acid was analysed by GC-MS and ^{1}H-NMR (see ESI†).

We carried out the reaction of azoxybenzene, an intermediate, as a starting material under the optimised condition and obtained 2% aniline and 98% azobenzene as products (Scheme 2). Furthermore, the reaction of nitrobenzene was performed in benzyl alcohol as solvent under the optimized



Scheme 2 Synthesis of azobenzene from azoxybenzene intermediate.

reaction conditions. The aqueous layer after the work up was treated with dilute HCl and the obtained benzoic acid was analysed by GC-MS and ^{1}H NMR (see ESI†). These experiments were helpful to support the reaction mechanism.

In conclusion, a selective, controlled, cost effective, mild and highly efficient procedure is developed for the formation of synthetically important azobenzenes. The developed protocol can be considered as environmentally friendly as it avoids use of reducing agent and other additives and did not produce any hazardous by-products as well. The reaction operation is simple and easy to handle and it is suitable for large scale industrial production. Importantly, significant decrease in the yield of aniline as by-product is the noticeable achievement of this protocol.

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