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A mild CuBr-NMO oxidative system for the coupling of anilines leading to aromatic azo compounds

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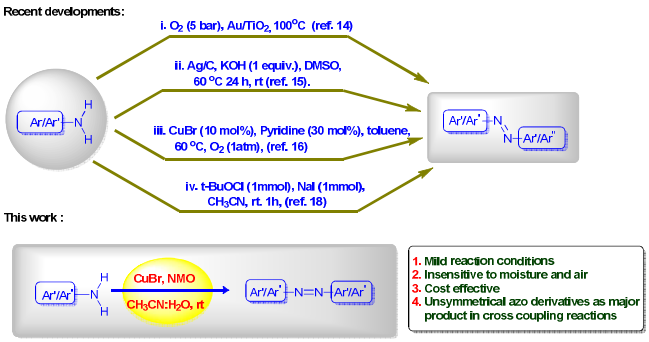
An efficient, mild and cost-effective method has been developed utilizing CuBr with N-methylmorpholine N-oxide (NMO/NMMO) for the oxidative coupling of anilines to access symmetrical and unsymmetrical azo compounds in high yield. The reactivity was found to be governed by electronic and steric factors of anilines.

Aromatic azo compounds have attracted considerable attention for a long time due to their wide range of applications such as organic dyes, indicators, food additives, pigments and therapeutic agents.[1] These motifs are extensively used as smart polymers,[2] liquid crystals[3] and photoswitches[4] in biological system because of their exclusive cis/trans isomerisation.[5] Recently the azo group has been used successfully as a directing group for ortho C-H activation/functionalization,[6] for the synthesis of valuable o-acylazobenzenes,[6a-d] o-alkoxyazobenzenes[6e] and indazole derivatives.[6f]

Innumerable methods[7] are available for the synthesis of these azo derivatives, however, development of new methods with mild reaction conditions and the improvement of the existing methodologies is in high demand. Traditional methods for the preparation of symmetrical azo derivatives include oxidation of primary amines[8] and reductive homodimerization of nitroarenes.[9] These methods have some limitations such as in the oxidative preparation method use of environmentally unfriendly heavy metals[10] (Hg,[10d] Mn[10e] and Pb[10f] salts) in stoichiometric amount and poor control of product distribution (the azo and azoxybenzene ratio) in reductive homodimerization of nitroarenes. Diazonium coupling[11], Mills reaction[12] and Wallach reaction[13] are the most common methodologies used to synthesize unsymmetrical azo compounds, but these methods require explosive and hazardous diazonium salts and toxic nitrosobenzenes. More specifically the problem lies in the substrate scope as it is limited to the electron donating amines. In this regard Corma *et al*. reported an efficient path to synthesize aromatic azo compounds by gold nanoparticles catalyzed process under O_2 (3-5 bar) as an oxidant at 100 °C, however, high temperature and pressure limits this methodology.[14] Again silver nanoparticles catalyzed oxidative dimerization of amines suffers from the use of stoichiometric amount of strong base KOH.[15] Jiao's group proposed Cu/Pyridine catalyzed aerobic oxidation of aniline derivatives at 60 °C, where an excess use of electron deficient anilines was required for the synthesis of unsymmetrical azobenzene derivatives.[16] Ma *et al*. developed an organomettallic approach using hypervalent iodine (III).[17] Furthermore, Minakata group used *t*-BuOI in different reaction conditions (temperature and solvents) for different substrates under nitrogen atmosphere for oxidative dimerization of aromatic amines leading to azo derivatives (Scheme 1).[18]



Scheme 1 Strategies for the synthesis of azobenzenes

Here we developed an efficient and a mild synthetic methodology for the preparation of symmetrical and unsymmetrical azo compounds from aromatic anilines in a moderate to good yield. N-Methylmorpholine N-oxide (NMO) is mostly utilized as a co-oxidant or a sacrificial oxidant with TPAP,[19] Osmium tetraoxide[20] in various oxidation reactions and

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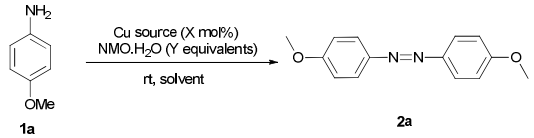
also is used as a solvent for dissolution of cellulose in Lyocell process.[21] Herein, we have utilized CuBr catalyst in the presence of NMO as an oxidant (Scheme 1) and it was found to be a better and mild oxidative system for the synthesis of various azo derivatives as compared to some other previously reported methods, where high temperature, pressure, excess use of strong base and explosive or toxic intermediate were the main limitations.

Table 1 Optimization of catalyst for coupling reaction[a]



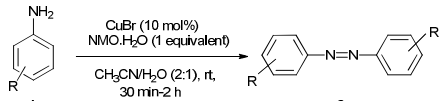
1a 2a

Entry	Cu source	X	Y	Solvent	Time	Yield (%)[b]
1	CuBr	10	-	CH_3CN	5 h	25
2	-	-	5	CH_3CN	3 h	-
3	CuBr	10	1	CH_3CN	30 min	48
4	CuBr	20	1	CH_3CN	1 h	62
5	**CuBr**	**10**	**1**	**CH_3CN/ H_2O(2:1)**	**30 min**	**86**
6	CuBr	10	-	CH_3CN/ H_2O(2:1)	3 h	30
7	CuBr	10	1	CH_3CN/ H_2O(1:2)	3 h	35
8	$CuBr_2$	10	-	CH_3CN	1 h	32
9	$CuBr_2$	20	1	CH_3CN	1 h	56
10	$CuBr_2$	20	1	CH_3CN/ H_2O(2:1)	1 h	59
11	$CuBr_2$	20	1	CH_3CN/ H_2O(1:2)	1.5 h	30
12	$Cu(OAc)_2$	20	1	CH_3CN	1.5 h	42
13	$Cu(OAc)_2$	20	1	CH_3CN/ H_2O(2:1)	2 h	48
14	CuCl	20	1	CH_3CN	1 h	40
15	CuCl	20	1	CH_3CN/ H_2O(2:1)	1 h	55
16	CuBr	20	1	Toluene/ H_2O(2:1)	1 h	-

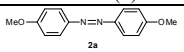
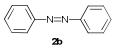
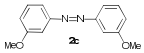
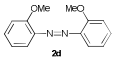
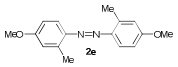
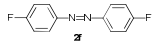
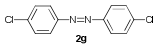
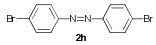
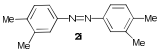
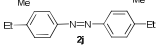
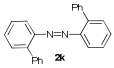
[a]Reaction condition: **1a** (0.81 mmol), catalyst (X mol%), NMO (Y equivalents), solvent (6 mL) at rt. [b]Isolated yields.

To optimize the reaction condition oxidation of 4-methoxy aniline was chosen as a model reaction (Table 1). Various copper salts were investigated among them copper bromide gave the best conversion of 4-methoxy aniline to bis(4-methoxyphenyl)diazene in 30 minutes (entry 5, Table 1). NMO was essential for the reaction along with CuBr since in the absence of any one of these showed lack of reactivity. Other copper salts such as CuCl and copper acetate showed less efficiency as compared to CuBr (entry 12-15, Table 1). $CuBr_2$ gave a moderate yield (entry 8-11, Table 1). The decrease reaction yields in case of Cu(II) salts may be linked with the tendency of Cu(II) salts to directly react with NMO leading to its decomposition into morpholine and formaldehyde.[20] Selection of solvent system was crucial for the reaction, as most of the copper-catalyzed reactions are conducted in acetonitrile,[22] we started observing the reaction in neat acetonitrile (6 mL), which gave 48% and 62% yield with 10 mol% and 20 mol% CuBr respectively (entry 3-4, Table 1). Interestingly, when the reaction was carried out in 2:1 (v/v) acetonitrile and water solvent mixture, reaction yield was abruptly increased to 86% (entry 5, Table 1). When the amount of water was increased in the solvent mixture the reaction yield was decreased (entry 7, Table 1). It may be due to enhanced disproportionation of Cu(I) salt in the aqueous solution into Cu and Cu(II).[21] When toluene was used instead of acetonitrile in a solvent mixture to form biphasic solvent no product was observed (entry 16, Table 1). Other solvents such as DMSO, DMF, THF and ethanol were not effective in the conversion. NMO was essential for the reaction since its absence resulted in a profound decrease in the reaction yield (entry 1, 6 and 8, Table 1).

Table 2 Homocoupling of substituted anilines[a]



1 2

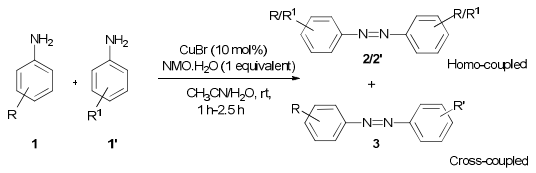
Entry	R	Product (**2**)	Time	Yield (%)[b]
1	4-OMe	 **2a**	30 min	86
2	H	 **2b**	45 min	78
3	3-OMe	 **2c**	45 min	83
4	2-OMe	 **2d**	40 min	84
5	2-Me-4-OMe	 **2e**	1 h	72
6	4-F	 **2f**	30 min	79
7	4-Cl	 **2g**	45 min	83
8	4-Br	 **2h**	1 h	73
9	3,4-Di-Me	 **2i**	1 h	74
10	4-Et	 **2j**	30 min	90
11	2-Ph	 **2k**	2 h	69

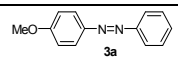
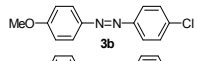
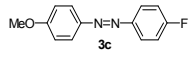
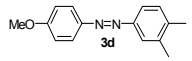
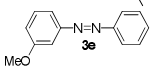
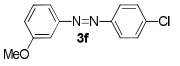
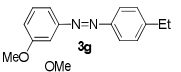
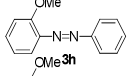
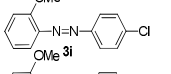
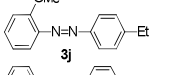
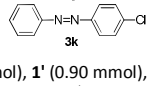
[a]Reaction condition: **1a** (0.81 mmol), CuBr (10 mol%), NMO (1 equivalent), CH_3CN/H_2O (2:1) (6 mL) at rt. [b]Isolated yields mixture of cis:trans isomers.

Under the optimized reaction condition, the scope of different anilines was investigated. The electronic and steric factors were found to be crucial for the reactivity. The experiment showed that anilines with electron donating substituents gave corresponding azo compounds in excellent yield (Table 2). Halogenated anilines (**2f-2h**) easily reacted under the optimized reaction condition to afford respective halogenated azo derivatives in good to high yield which can be further utilized for functionalization (entry 6-8, Table 2).

Successful results for homodimerization motivated us to find out the scope of cross-dimerization reaction, since it is quite challenging to couple two different anilines to afford unsymmetrical azo benzenes as a major product due to existed Competitive homodimerization over cross dimerization reaction. Thus to check the applicability of our protocol we applied this methodology for the synthesis of the unsymmetrical azobenzenes and gratifyingly, successfully we could synthesize various unsymmetrical azo derivatives (Table 3).

Table 3 Cross-coupling of substituted anilines[a]

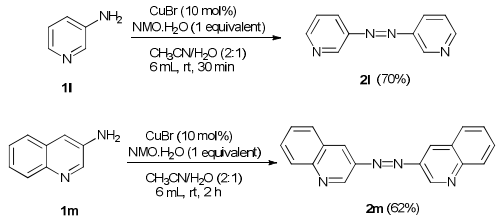


Entry	R	R^1	Cross coupling product (**3**)	Time	Yield (%)[b] (**3, 2, 2'**)
1	4-OMe	H	 **3a**	1 h	45[c]
2	4-OMe	Cl	 **3b**	1.5 h	54, 20, 26
3	4-OMe	4-F	 **3c**	1 h	50[c]
4	4-OMe	3,4-DiMe	 **3d**	2.5 h	52, 33, 15
5	3-OMe	H	 **3e**	2.5 h	48[c]
6	3-OMe	4-Cl	 **3f**	1.5 h	53, 27, 20
7	3-OMe	4-Et	 **3g**	1 h	50, 41, 9
8	2-OMe	H	 **3h**	2 h	45, 40, 15
9	2-OMe	4-Cl	 **3i**	2.5 h	51, 49, -[d]
10	2-OMe	4-Et	 **3j**	2 h	49, 42, 9
11	H	4-Cl	 **3k**	1.5 h	50, 45, 5

[a]Reaction condition: **1** (0.81 mmol), **1'** (0.90 mmol), CuBr (10 mol%), NMO (1 equivalent), CH_3CN/H_2O (2:1) (6 mL) at rt. [b]HPLC yields, [c]Isolated yield, [d]Not resolved in HPLC.

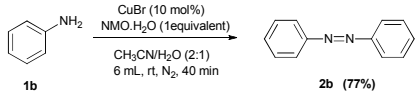
Anilines substituted at ortho, meta and para position smoothly afforded unsymmetrical azobenzenes in moderate to good yield. Halogen substituted anilines smoothly reacted to give cross-dimerized halo substituted azo derivatives in high yield over homodimerized products (Table 3). Unfortunately, nitro, cyano, or ester substituted anilines did not afford azo derivative and remained in a dormant state. Except these, In all other cases cross-coupled azobenzene were the major product over the homodimerized products and were easily purified by column chromatography.

Azo-pyridines have been widely utilized as photodissociable axial ligands (PDL),[23] photoactive liquid crystals[24] and an efficient reagent for esterification reaction.[25] Thus, we tried to explore the scope of our methodology to synthesize 3-azopyridine (**2l**) from 3-aminopyridine (**1l**). It was our delight that the desired product was obtained in good yield within 30 minutes. Similarly, 3-azoquinoline was also prepared within 2 h using the present protocol (Scheme 2).



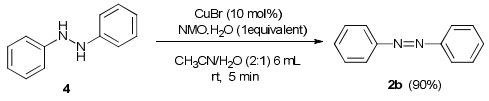
Scheme 2 Synthesis of 3-azopyridine and 3-azoquinoline

In order to understand the reaction mechanism and to exclude the possibility of dioxygen as an oxidant, we used our optimized reaction condition and allowed **1b** to react under nitrogen atmosphere (Scheme 3). The corresponding azobenzene **2b** was observed within 10 min of the reaction and full conversion was obtained after 40 min. However, in the absence of NMO, the reaction yielded only 14% of the product. From these observations, it was clear that dioxygen was not acting as an oxidant and NMO was responsible for the oxidative coupling of the aniline along with CuBr.



Sheme 3 Homodimerization of aniline under N_2 atmosphere

1,2-diphenylhydrazine (**4**) was oxidized under the optimized reaction condition and it was found that **4** was easily transformed to corresponding azobenzene (**2b**) within 5 min (Scheme 4). Although, it could be converted by CuBr alone, but the full conversion of azobenzene was obtained after 6 h. Thus, it showed that NMO played an important role in the oxidative coupling of anilines.



Scheme 4 Oxidation of 1, 2-phenylhydrazine

Through the studies reported above, we postulated a plausible mechanism (Figure 1). Firstly, in the primary step a single electron transfer from Cu(I) to NMO resulted in the homolytic cleavage of N-O bond which subsequently produced aminyl radical (**5**) and Cu(II) salt.[21] This aminyl radical was

stabilized by single electron transfer by Cu(I) to give N-methylmorpholine (NMM, **6**) and Cu(II) salt. Cu(II) salt coordinated to aniline to give corresponding complex **A** which after one electron transfer resulted in radical cation **B**. Dimerizaton of radical cations afforded respective hydrazine **C**, which upon dehydrogenation gave corresponding azobenzene.

In the presence of excess of Cu(II), NMO decomposed to morpholine and formaldehyde, this was also responsible for the decrease in the reaction yield when Cu(II) salts were used instead of Cu(I) salts in the reaction.[21] In situ generated Cu(II) salt oxidizes NMM to generate Cu(I) and aminyl radical which further starts the catalytic cycle.

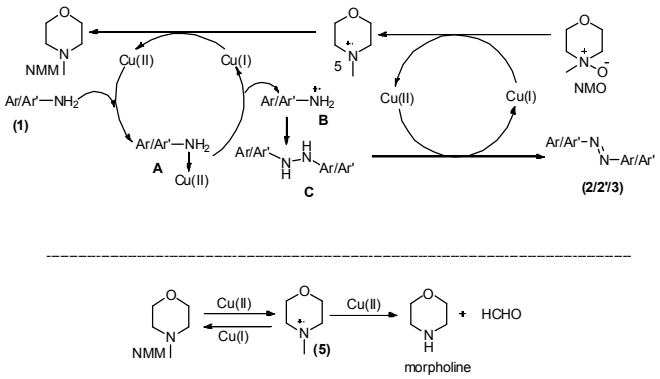


Figure 1 Proposed mechanism

Conclusions

In summary, an efficient and a low cost CuBr-NMO oxidative system was developed for the synthesis of symmetrical and unsymmetrical azobenzenes under mild reaction condition. Anilines were converted to corresponding homo and cross-coupled azo products in good to excellent yield. Furthermore, 3-Azopyridine a highly valued hetero azo derivative was successfully synthesized by our methodology. Studies are ongoing in our lab for the further synthetic application of this protocol.

Acknowledgements

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