



Short Communication

Cu(I) catalyzed dehydrogenative homo coupling of aromatic amines under simple and mild reaction conditions



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ABSTRACT

An efficient protocol for the synthesis of a variety of azobenzenes and hydrazines from aromatic amines under mild reaction conditions is developed using Cu(I) catalyst. The copper catalyst used in this study comprises of CuBr, DMAP and AIBN. The plausible proposed mechanism for this dehydrogenative homo coupling of aromatic amines is depicted.

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1. Introduction

N–N bond bearing compounds are of high importance in the synthesis of polymers [1], dendrimers [2] and bio-active molecules [3–5] (Fig. 1, i–v) due to more applicability, cost effectiveness and their being environmentally benign. Besides their numerous applications in therapeutics [6], aromatic azo compounds are also widely used as ligands (due to their being easy in complexation with metal ions), indicators, dyes, pigments [7] and radical initiators (e.g. Mitsunobu reaction) [8]. Recently, Hoogenboom et al. and several other groups [9] employed azo compounds as raw materials in the construction of stimuli responsive polymers, which have a wide range of applications in biotechnology, drug delivery systems, optical sensing agents and smart sensors. Though the developed methods for the synthesis of N–N bond containing compounds are synthetically useful [10–14], they do have drawbacks like commercial non-availability of reagents, longer reaction times (>24 h), and high operating reaction conditions (>90 °C), which make them undesirable and inconvenient.

Despite numerous efforts toward the synthesis of azo derivatives, the reduction of nitro-aromatic compounds and oxidative cyclization still remains a big challenge for synthetic chemists [15,16]. Indeed, most of the traditional methods suffer from the practical difficulties such as use of stoichiometric reagents and toxic metals, less selectivity, and formation of by-products, which make the isolation of desired product difficult. As part of our ongoing research efforts toward the total synthesis of N–N bond containing natural products and

developing novel oxidation methods under mild reaction conditions [17, 18], we are actively looking for facile methods for dehydrogenative coupling of aromatic amines, since most of literature methods suffer from several disadvantages as discussed above. Herein we report an efficient protocol for the synthesis of a variety of azobenzenes and hydrazines under mild reaction conditions using easily available CuBr, 2,2'-azobisisobutyronitrile (AIBN) and 4-dimethylaminopyridine (4-DMAP) in acetonitrile at room temperature. Both azobenzenes and hydrazines were obtained in good to excellent yields (Scheme 1) [19].

2. Result and discussions

To optimize the reaction conditions, a series of experiments (Table 1) were performed using *p*-toluidine as starting substrate. The first set (Table 1, Entries, 1–3) of experiments was carried out using CuI as catalyst, 2,2'-bipyridyl as ligand and K₂CO₃ as base under atmospheric oxygen using a variety of oxidants and radical initiators such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), urea hydrogen peroxide (UHP) and aqueous *tert*-butyl hydroperoxide solution (TBHP). Notably, no reaction has taken place with complete recovery of starting materials. The second set (Table 1, Entries 4 and 5) of reactions was performed using 10 mol% of CuI and CuBr, 20 mol% of 2,2'-bipyridyl and AIBN (40 mol%), which resulted in compound **2** in moderate yields of 24% and 52% respectively. The third set (Table 1, Entries 6–8) of reactions was executed using 10 mol% of CuBr by varying ligands such as bipyridyl, 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-DMAP, and N,N,N',N'-tetramethyl ethylenediamine (TMEDA) in CH₃CN at room temperature. Product **2** was obtained in excellent yields when DMAP (or) DABCO was used as a ligand (Table 1, Entries 7 and 8). Because DMAP acts as both

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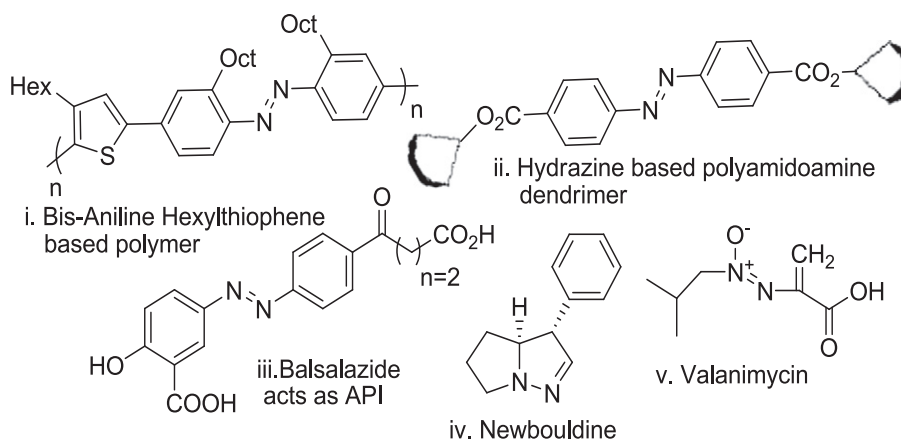
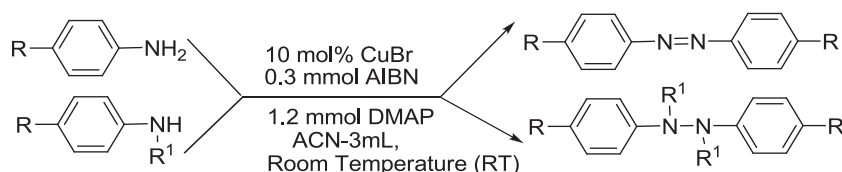


Fig. 1. Some of the important N–N bond carrying polymers, dendrimers and bio active compounds.

ligand and base, the further experiments (Table 1, Entry 9) were carried out without additional base (i.e. K_2CO_3) by varying with the amounts of DMAP. Interestingly, the yield of the product improved from 52% to 72%, when the reaction was carried out under nitrogen atmosphere (Table 1, Entry 10) and was better than that of atmospheric oxygen or oxygen balloon. Furthermore, in order to obtain the maximum yield of the product different mole ratios of DMAP were tested (Table 1, Entries 12–13). It was observed that, 10 mol% of CuBr, 0.3 mmol of AIBN, 1.2 mmol of 4-DMAP in dry acetonitrile at room temperature under N_2 (commercial grade) atmosphere gave compound **2** in 97% isolated yield. (Table 1, Entry 13). It was noticed that under atmospheric oxygen, the reaction was not selective (5% of unidentified products were noticed along with desired product **2** in 88% yield). However when the reaction was performed under complete degassed acetonitrile and high pure nitrogen conditions instead of commercial grade N_2 , it was observed that the reaction was slower even after 12 h, and 10% of starting material was recovered along with 81% of product **2**. The absence of AIBN in the reaction mixture gave compound **2** in only 10% of isolated yield even after 24 h.

Next, the scope of the newly developed protocol was extended to other primary aromatic amines to produce a series of diverse azo compounds under optimized reaction conditions (Table 2). In case of aromatic amines without any substituent i.e. aniline, the corresponding azo compound was obtained in excellent yield (**2a**). Similarly, the presence of electron donating groups such as methyl and methoxy substitution at *para*-position of aniline gave the corresponding azo compound in excellent yields (Table 1, Entry 13; Table 2, **2b**). This oxidative coupling was extended to mono and dihalogen substituted anilines (fluoro, chloro and bromo). In case of fluoro substituted aniline (**1c**) the corresponding azobenzene (**2c**) was obtained in high yield (88%). However, for chloro (**1d**), bromo (**1e**) and 4-bromo-3-fluoro aniline (**1f**), the reaction rate was slower and resulted in reasonable yields of products (**2d–2f**).

However, in elevated temperature i.e. at 60 °C, high yields (62–76%) of desired products were obtained. Remarkably, in all the above cases only azo products were formed selectively and no by-products (e.g. Ullmann coupled products, N-oxides and hydroxyl amine compounds) were noticed [20].



Scheme 1. Synthesis of azobenzenes and hydrazines from various primary and secondary amines using copper (I) catalyst.

Table 1

Optimizing the conditions for direct oxidation of *p*-toluidine to 1,2-di-*p*-tolylidiazene

Entry	Metal catalyst	Ligand (mmol)	Additives (mmol)	Medium	Temp.	Time	Yield ^a
1 ^b	CuI	bpy(0.2)	TEMPO(0.1)	–	50 °C	24	–
2 ^b	CuI	bpy(0.2)	UHP(2)	–	50 °C	24	–
3 ^b	CuI	bpy(0.2)	aqTBHP(4)	–	50 °C	24	–
4 ^b	CuI	bpy(0.2)	AIBN(0.3)	–	RT	24	24
5 ^b	CuBr	bpy(0.2)	AIBN(0.4)	–	RT	8	52
6 ^b	CuBr	TMEDA(0.2)	AIBN(0.4)	–	RT	24	28
7 ^b	CuBr	DABCO(0.2)	AIBN(0.4)	–	RT	8	84
8 ^b	CuBr	DMAP(0.2)	AIBN(0.4)	–	RT	8	88
9 ^c	CuBr	DMAP (0.2)	AIBN(0.4)	–	RT	8	52
10 ^c	CuBr	DMAP (0.2)	AIBN(0.4)	N_2	RT	6	72
11 ^c	CuBr	DMAP (0.5)	AIBN(0.4)	N_2	RT	8	76
12 ^c	CuBr	DMAP (1.0)	AIBN(0.3)	N_2	RT	7	94
13 ^c	CuBr	DMAP (1.2)	AIBN(0.3)	N_2	RT	6	97

Note: entries 1–9 reactions were carried out at atmospheric oxygen.

^a All the reactions were carried out using 1 mmol of **1**, 10 mol% catalyst, 3 mL CH_3CN . Where bpy = 2,2'-bipyridyl.

^b Entries 1–8 K_2CO_3 (2 mmol) used as base.

^c Entries 9–13 without base.

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