RESEARCH ARTICLE



A green and mild procedure to selective synthesis of diarylamine via domino reaction of aryl halides and arginine catalyzed by magnetic-MOF

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Abstract

Efficient and selective direct synthesis of diarylamines from aryl halides and arginine as a nitrogen-donor reagent is reported. Arginine, which is an oral supplement, acts as a useful nitrogen source donor in the copper-catalyzed reaction. $Fe_3O_4/Cu_3(BTC)_2$, which was easily separated and recycled with a magnet, improved the rate and facilitation of the synthesis of diarylamines selectively. The introduction of a new and available N-source, simple magnetic separation process, normal atmospheric conditions, and excellent yields under mild reaction conditions are other important features of this work.

1 | INTRODUCTION

Diarylamines are a very important class of chemicals that frequently utilized for pharmaceuticals, agricultural chemicals, dye preparation, stabilizers for explosives, as polymerization, corrosion inhibitors, and radical-trapping antioxidants.^[1] They are also found widely in a variety of biologically active molecules such as natural products and HIV-1 protease inhibitors.^[2] Thus, development of diverse procedures for their synthesis is of great importance.

The most classic method for amine synthesis is by using ammonia.^[3a] However, there are practical problems associated with the use of ammonia, including its storage, handling, and transportation.^[3b,c] Also, this reaction usually results in a mixture of primary, secondary, and tertiary amines.^[3d,e]

The general method for the synthesis of diarylamines is arylation of anilines using aryl halides and aryl metal or using aromatic C–H bond activation.^[4] Although these methods are very efficient, employment of aniline and its derivatives for the synthesis is often very annoying, because they undergo oxidation when exposed to air.^[5] Accordingly, the development of methods for the selective synthesis of amines is an obvious problem in organic chemistry.

Contract grant sponsor: Iranian National Science Foundation (INSF). Contract grant number: 96003528. Problems in working with ammonia and aniline have led organic chemists to use nitrogen-donor reagents.^[6] Compared to the impressive progress being made in the N-alkylation of organic amines, reports dealing with the direct synthesis of amines using nitrogen-donor reagents are scarcely available. After a successful presentation of sulfur-transfer reagents in our previous work,^[7] herein we wish to report an economical and environmentally friendly method for synthesis of diarylamines from aryl halides and arginine as a new nitrogendonor reagent.

Arginine is a very important biomolecule that is classified as an essential amino acid. Almost all dietary proteins contain arginine. They are also used widely in cell division, immune function, the healing of wounds, the release of hormones, and the removal of ammonia from the body.^[8] We herein report a new method of using arginine as a nitrogen-donor reagent that is an oral supplement, odorless, stable, non-toxic, and environmentally friendly. It is a basic, solid reagent that can be easily available and handled.

Traditionally, synthetic procedures for the preparation of diarylamines are under copper-mediated Ullmann-type conditions.^[9] Although these copper-catalyzed reactions are effective, the major drawbacks of this method are reaction harsh conditions and stoichiometric amounts of copper, and the yields are not reproducible.

TABLE 1 Optimization of the reaction conditions

PhI +	$H_{2N} \xrightarrow[OH]{H_2N} H_{NH_2}^{H_2NH}$	Cat (mol%) solvent, base temp, time	Ph ₂ NH			
Entry	Arginine (mmol)	Cat ^a (mol%)	Solvent	Base (mmol)	Temp (°C)	Yield (%) ^b
1	1	5	DMF	KOH (3)	130	76
2	1	10	DMF	KOH (3)	130	96
3	0.5	10	DMF	KOH (3)	130	95
4	0.5	10	DMF	KOH (2)	130	85
5	0.5	10	DMSO	KOH (3)	130	81
6	0.5	10	PEG	KOH (3)	130	98
7	0.5	10	H ₂ O	KOH (3)	130	Trace
8	0.5	10	PEG	KOH (3)	110	98
9	0.5	10	PEG	KOH (3)	80	98
10	0.5	10	PEG	KOH (3)	25	N.R.
11	0.5	10	PEG	$K_{2}CO_{3}(3)$	80	65
12	0.5	10	PEG	<i>t</i> -BuOK (3)	80	80
13	0.5	10	PEG	Et ₃ N (3)	80	58
14	0.5	10	PEG	-	80	N.R.

Notes. Reaction conditions: PhI (1.0 mmol), arginine (X mmol), base (X mmol), and time (2 h), in 2 mL solvent/H₂O (10:1).

Bold indicates optimization amount.

^aFe₃O₄/Cu₃(BTC)₂.

^bIsolated yield.

The Pd-catalyzed C-N coupling reaction of aryl halides has received much attention than other methods for laboratory-scale synthesis of the substituted arylamines. However, copper-catalyzed coupling is still the best choice for large and industrial scales.^[10]

The past few decades have witnessed an exponential growth in the number of research papers in the study of materials known as metal-organic frameworks (MOFs).^[11] In previous work, a highly porous metal-organic framework, $Cu_3 BTC_2$ (copper (II)-benzene-1,3,5-tricarboxylate), which is known as MOF-199, was used as an efficient and recyclable catalyst.^[12] In this study, a magnetic-MOF was synthesized and developed. Combinations of MOFs and magnetic nanoparticles have many advantages in adsorption and separation. Fe₃O₄/Cu₃(BTC)₂ exhibited both magnetic characteristics and high porosity.^[13] Magnetic characteristics led to easy to collect with an external magnet and high porosity



SCHEME 1 Selective synthesis of diarylamine compounds

characteristics led to an excellent catalyst for diarylamine synthesis.

Certainly, the use of suitable solvents and catalysts is very important in research areas of green chemistry.^[14] Herein magnetic-MOF and PEG have been used for advancing the goals of green chemistry.

On the basis of this approach, this study sought to synthesize symmetrical diarylamines via domino reaction of aryl halides and L-arginine through $Fe_3O_4/Cu_3(BTC)_2$ catalysis (Scheme 1).

2 | RESULTS AND DISCUSSION

The reaction of iodobenzene with L-arginine in the presence of $Fe_3O_4/Cu_3(BTC)_2$ was studied under normal atmospheric conditions in order to optimize the reaction condition in terms of temperature, type, and amount of base; amount of L-arginine and catalyst; and solvent. At first performed the optimization amount of $Fe_3O_4/Cu_3(BTC)_2$ for the C–N coupling reaction of iodobenzene and arginine. The reaction was not complete in the presence of 5 mol% $Fe_3O_4/$ $Cu_3(BTC)_2$. Diphenylamine was obtained in 98% yield with 10 mol% of catalyst (Table 1, Entries 1 and 2). We found that decreasing the amount of KOH from 3 to 2 mmol led

TABLE 2 Checking of the effect of catalysts

PhI + H ₂ N H_2 H_3							
Entry	Catalyst	ArNH ₂	Ar ₂ NH	Ar ₃ N			
1	-	-	-	-			
2	Fe ₃ O ₄ /Cu ₃ (BTC) ₂	-	97	-			
3	MOF-199	-	96	-			
4	CuCl	-	71 ^b	-			
5	NiCl ₂ ·6H ₂ O	Trace	Trace	Trace			
6	Fe ₃ O ₄	Trace	Trace	35			
7	K ₂ PdCl ₄	-	-	95			
8	K ₂ PdCl ₄	-	-	96 ^c			
9	K ₂ PdCl ₄	-	-	91 ^d			
10	K ₂ PdCl ₄	-	-	85 ^e			

Notes. Reaction conditions: PhI (1.0 mmol), arginine (0.5 mmol), cat (10 mol%), KOH (3 mmol), and time (2 h), in 2 mL PEG/H₂O (10:1).

^aIsolated yield.

^bReaction not complete.

^cAryl halide in this reaction is 2-iodotoluene.

^dAryl halide in this reaction is 4-iodoanisole.

^eAryl halide in this reaction is 2-iodothiophene.

to a decrease in the rate of reaction, and thus, 3 mmol KOH was selected as the optimum amount (Table 1, Entries 3 and 4). Changingthe solvents to DMSO led to decrease yields lightly, and the reaction proceeded in the presence of the

TABLE 3 The direct synthesis of symmetrical diarylamines

solvent of H_2O seldom. PEG was the best choice as a green and efficiency solvent (Table 1, Entries 5-7). We found that temperatures of 130°C, 110°C, and 80°C displayed a similar and good behavior, but the temperature of 80°C was used to be compatible with the principles of green chemistry.

The reaction did not proceed at 25°C (Table 1, Entries 8-10). The other bases, including K_2CO_3 , *t*-BuOK, and Et₃N, resulted in reducing yields significantly; thus, of the bases tested, KOH at a concentration of 3 mmol showed a superior effect on the reaction yields and the reaction did not proceed in the absence of a base (Table 1, Entries 11-14).

As shown in Table 2, the reaction did not proceed in the absence of catalyst. The different catalysts were evaluated, and it was found that MOF-199 as well as $Fe_3O_4/Cu_3(BTC)_2$ led to production of diarylamine. The reaction was not complete in the presence of CuCl salt (Table 2, Entries 1-4). The reaction produced a mixture of primary, secondary, and tertiary amines in the presence of NiCl₂·6H₂O and Fe₃O₄ (Table 2, Entries 5 and 6). The reaction had different pathways in the presence of palladium and moved forward to production of tertiary amine. This result was investigated with other derivatives, and the same result was obtained (Table 2, Entries 7-10).

After the optimized reaction conditions were established, a large number of aryl halides (and -OTs) were examined to explore the scope of this reaction. As summarized in Table 3, aryl iodides and aryl bromides were converted into the corresponding diarylamines in higher yields than their chloro and tosylate analogs (Table 3, Entries 1-4). The results show that the aryl halide derivatives with different functional groups, such as CH₃, OCH₃, and Br, provide good-to-excellent yields

Ar-X + H ₂	N OH H PEG/H PEG/H	$\begin{array}{c} \text{Cu}_{3}(\text{BTC})_{2} \\ \\ \text{H}_{2}\text{O}, \text{KOH} \end{array} \qquad \text{Ar}_{2}\text{NH} \\ \text{S0}^{\circ}\text{C} \qquad (a-1) \end{array}$		
Entry	Ar-X	Product	Time (h)	Yield (%)
1	PhI	а	2	97
2	PhBr	b	6	91
3	PhOTs	с	10	80
4	PhCl	d	12	73
5	o-MePh——I	e	3	86
6	p-MeOPh——I	j	10	90
7	o-MeOPh——I	k	7	74
8	<i>p</i> -BrPh——I	f	4	75
9	2-Iodothiophene	g	5	85
10	2-Bromothiophene	h	5	76
11	2-Chlorothiophene	i	10	68
12	<i>p</i> -MePh—Br	1	8	84

Note. Reaction conditions: Ar-X (1.0 mmol), arginine (0.5 mmol), $Fe_3O_4/Cu_3(BTC)_2$ (10 mol%), and KOH (3 mmol), in 2 mL PEG/H₂O (10:1).

(Table 3, Entries 5-8). The reaction was carried out with high chemoselectivity, and a single product was selectivity obtained of reaction substrates with two halide groups (Table 3, Entry 8).

In addition, symmetrical diheteroaryl amines were well synthesized from the corresponding heteroaryl iodides, bromides, and chlorides (Table 3, Entries 9-11).

Although we cannot clearly determine the catalytic reaction pathway for the synthesis of diarylamines from aryl halides and arginine, we proposed that the Cu-catalyzed reaction may proceed through the mechanism in Scheme 2. Initially, product (I) appears to be generated in the coupling reaction between aryl halide and arginine. Then, product (I) is hydrolyzed to the corresponding arylamine under the reaction conditions. Finally, diarylamines appear to have been generated in the coupling reaction between arylamine and aryl halide during the one-step reaction (Scheme 2).^[15]

2.1 | Characterization of Fe₃O₄/Cu₃(BTC)₂

Figure 1 shows the FT-IR spectra of (a) Fe_3O_4 , (b) $Cu_3(BTC)_2$, and (c) $Fe_3O_4/Cu_3(BTC)_2$. The Fe–O stretching vibration near 579 cm⁻¹ and O-H stretching vibration near 3401 cm⁻¹ were observed (Figure 1a). The spectrum of $Cu_3(BTC)_2$ shows absorption in the wave numbers 3423, 1640, and 1442 cm⁻¹ that they are related to water molecule, carbonyl group of benzene tricarboxylic acid, and double bonds of benzene, respectively (Figure 1b). For $Fe_3O_4/Cu_3(BTC)_2$, the band at 1622-1709 cm⁻¹ suggests the presence of BTC. The peaks observed at 1441 cm⁻¹ and 580 cm⁻¹ are related to N-H and O-H vibration, respectively. The broad peak at 3400 cm⁻¹ was due to water molecule and hydroxyl groups (Figure 1c).

Figure 2 shows the X-ray powder diffraction patterns of (a) $Cu_3(BTC)_2$, (b) Fe_3O_4 , and (c) $Fe_3O_4/Cu_3(BTC)_2$. The XRD pattern of the $Fe_3O_4/Cu_3(BTC)_2$ shows characteristic peaks



SCHEME 2 Possible mechanisms for synthesis of diarylamines



FIGURE 1 FT-IR spectra of (a) Fe_3O_4 , (b) $Cu_3(BTC)_2$, and (c) $Fe_3O_4/Cu_3(BTC)_2$

and relative intensity (Figure 2c), which match well with the reported XRD of Fe_3O_4 (magnetite) and XRD of $Cu_3(BTC)_2$. It implies that the spinal structure of Fe_3O_4 and $Cu_3(BTC)_2$ has been retained during the process of catalyst preparation.

Scanning electron microscopy (Figure 3) shows existence crystals in nano-size. This study showed diameters of ~30-90 nm for the magnetic nanoparticles. All of the data are similar to those of other $Fe_3O_4/Cu_3(BTC)_2$ samples previously mentioned in the literature.^[13b,c]

In view of green chemistry, the use of magnetic catalysis is important, because the magnetic catalysts offer several advantages, including easy catalyst separation, recovery, and recycling. As can be seen from Tables 1 and 3, the catalytic system worked exceedingly well in the selective synthesis of diarylamines with a wide range of substrates under the optimized reaction conditions. Also,



FIGURE 2 X-ray powder diffractogram of (a) Fe_3O_4 , (b) $Cu_3(BTC)_2$, and (c) $Fe_3O_4/Cu_3(BTC)_2$



FIGURE 3 SEM micrograph of Fe₃O₄/Cu₃(BTC)₂

the reusability is one of the important properties of this catalyst.

2.2 | Reusability

In order to consider the heterogeneity of the catalyst, we decided to investigate the recoverability and reusability of the Fe₃O₄/ Cu₃(BTC)₂ catalyst over five successive runs. The reaction was performed in PEG/H₂O (10:1) at 80°C, using iodobenzene (1 mmol), arginine (0.5 mmol), and KOH (3 mmol) in the presence of 10 mol% Fe₃O₄/Cu₃(BTC)₂ catalyst. After each run, the catalyst was separated from the reaction mixture by a magnetic field and washing and then reusing it. The recovered Fe₃O₄/Cu₃(BTC)₂ catalyst was dried and was then reused in the further reaction under identical conditions to those of the first run. The recyclability of Fe₃O₄/Cu₃(BTC)₂ was investigated for these reactions. The separated catalyst was reused for 5 runs in the synthesis of diphenylamine and without any significant loss of its activity, and it demonstrated excellent recoverability and reusability (Figure 4).

3 | CONCLUSION

In summary, we have developed a novel, effective and selective direct synthesis of diarylamines from aryl halides and arginine in PEG/H₂O. The important feature of this method is using $Fe_3O_4/Cu_3(BTC)_2$ as a recyclable, porous, and chemoselective catalyst and also using arginine as a nitrogen source donor that led to selective synthesis of diarylamines in high yield. This protocol has several advantages: normal atmospheric conditions, the use of a less amount of catalyst, an easily available and low-cost reagent, and the use of PEG as a green solvent instead of the usually used organic solvents to carry out the reactions.



FIGURE 4 Catalyst recycling studies

4 | EXPERIMENTAL

4.1 | Synthesis of Fe₃O₄/Cu₃(BTC)₂

The procedure to prepare MOF-199 was according to Ref. ^[13]. Fe₃O₄ nanoparticles were prepared by chemical coprecipitation of Fe³⁺ and Fe²⁺ ions with a molar ratio of 2:1 that has been reported previously. Then, 4 mmol/L mercaptoacetic acid (MAA) was added to Fe3O4 nanoparticles (1 g) and the resultant mixture was stirred for 24 hours. The resulting was isolated by magnetic decantation, washed twice with ethanol, and dried at 50°C under vacuum.

Briefly, 0.5 g MAA-functionalized Fe_3O_4 microspheres and 3.68 g Cu(NO₃)₂ were dispersed in 100 mL ethanol and ultrasonicated for 30 minutes. Then, 1.74 g benzene-1,3,5tricarboxylic acid (H₃BTC) was added to the above suspension and the mixture was stirred mechanically for 2 hours. The final product, $Fe_3O_4/Cu_3(BTC)_2$, was separated by an external magnet, washed with ethanol several times, and dried in an oven overnight.^[13b]

4.2 | Symmetrical diarylamine synthesis: typical experimental procedure

A mixture of aryl halide (1.0 mmol), arginine (0.5 mmol)and Fe₃O₄/Cu₃(BTC)₂ (10 mol%) were added to a flask containing 3 mmol KOH and 2 mL PEG/H₂O (10:1). The reaction continued at temperature 80°C under atmospheric conditions. The reaction progress was controlled by thinlayer chromatography. The solvent was evaporated under vacuum. Than crude reaction mixture was purified by column chromatography (*n*-hexane/ethyl acetate 4:1) to give the diaryl amines in good yields (see in Data S1)

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.S1

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