

Synthesis of Symmetrical Triaryl Amines by Nano-CuO Catalyzed Buchwald-Hartwig Cross-coupling Reaction: NH₂-Thiadiazole as a New N-source

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The one-pot synthesis of symmetrical triaryl amines using aryl halides and 5-methyl-1,3,4-thiadiazole-2-amine as a nitrogen-transfer reagent is reported. Copper nanoparticles improved rate and facility of the synthesis of triaryl amines without require the addition of any ligand. The introduction of a new N-source, using green solvents of PEG/H₂O, normal atmospheric conditions and excellent yields under mild reaction conditions are other important features of this work.

Keywords: Symmetrical triaryl amines, Selective N-arylation, Nitrogen-transfer reagent

INTRODUCTION

Aromatic amines are widely found in natural products, bioactive molecules, and industrial materials [1-3]. They are also widely employed in medicines, agricultural pesticides, dyes, synthetic rubber, pigments, *etc.* [4-6]. Moreover, they have numerous applications and are present in an extensive range of different materials. That is why; their synthesis has aroused the interest of many researchers [7-10]. Amines have numerous applications and are present in an extensive range of different materials. Yet the development of methods for the selective synthesis of amines is a serious challenge in organic chemistry.

The most reported methods for the synthesis of triaryl amines includes the reaction of an aromatic amine and an aryl halide mediated by palladium, copper, or nickel [11-13]. The Pd catalyzed C-N coupling reaction of aryl halides has received much attention than other methods for laboratory scale synthesis of the substituted aryl amines [14, 15].

However, copper-catalyzed coupling is still the best

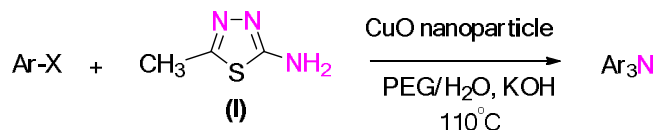
choice for large and industrial scales [16,17]. The major drawbacks of these methods are high temperature, stoichiometric or greater amount of copper reagent, sensitivity to catalyst type and low yield of triaryl amines [18,19].

Nanoparticles are bulk materials that have unique optical, electronic and chemical properties [20,21]. CuO is one of the most important transition metal oxides due to their captivating properties [22,23]. Also, copper oxide (CuO) nanoparticles have found many applications in lithium ion batteries, gas sensors, high-Tc superconductors and hydrogen detection [24-26].

The most widely used industrial method for amine synthesis is the reaction of aryl(alkyl)halides with ammonia [27]. However, there are practical difficulties associated with the use of ammonia, including its storage, handling, and transportation [28,29]. Further, this reaction usually results in a mixture of primary, secondary, and tertiary amines [30,31]. To solve these health and environmental risks and difficulty in working with ammonia, organic chemists have been trying to use nitrogen-transfer reagents to overcome these disadvantages [32-35].

Compared to the impressive progress made using the

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Scheme 1. Synthesis of triaryl amines compounds from aryl halides

arylation of organic amines, reports dealing with the direct synthesis of amines using nitrogen-transfer reagents are scarcely available. Nitrogen-containing compounds have been evaluated for their ability to transfer nitrogen in order to remove direct use of ammonia or aniline.

In continuation of our efforts to introduce sulfur/nitrogen-transfer reagents [36-38], herein we wish to report a new method for synthesis of symmetrical triaryl amines from aryl halides and 5-methyl-1,3,4-thiadiazole-2-amine (I) as a new nitrogen transfer reagent. In this process, N-source (I) is a basic, solid reagent which is easily available (Scheme 1).

EXPERIMENTAL

All reagents and starting materials were obtained from Sigma-Aldrich and Merck. Melting points were determined on an Electro thermal 9,100 apparatus. Fourier transform infrared (FT-IR) spectra were obtained on a Bruker VERTEX 70 instrument, with samples being dispersed on potassium bromide pallets. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance NMR spectrometer in CDCl_3 solution. The progress of the reaction was monitored by TLC using silica-gel SILG/UV 254 plates.

Typical Experimental Procedure for Triarylamines Synthesis

A mixture of aryl halide (1.0 mmol), 5-methyl-1,3,4-thiadiazole-2-amine (I) (0.5 mmol) and CuO nanoparticle (10 mol%) were added to a flask containing 3 mmol KOH and 2 ml PEG/ H_2O (20:1). The reaction continued at temperature 110 °C under atmospheric conditions. The reaction progress was controlled by the thin-layer chromatography. The solvent was evaporated under vacuum. Then, crude reaction mixture was purified by column chromatography (n-hexane/ethyl acetate 8:1) to give

the triaryl amines in good yields.

Synthesis of CuO Nanoparticles

The procedure to prepare CuO nanoparticles was according to Ref. [24]. $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ and citric acid with a molar ratio of 1:1 were dissolved in 100 ml deionized water. The solution was stirred in ultrasonic at temperature 60 °C for 45 min until gel formation. The gel was collected by filtration and allowed to burn at 200 °C. Subsequently, a light fluffy mass was obtained that combusted at 400 °C for 2 h.

Triphenylamine (Table 2, Entry 1). ^1H NMR (400 MHz, CDCl_3): δ = 7.001-7.186 (m, 15H-Ar) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 148.00, 129.34, 124.22, 122.91 ppm.

Tris(4-bromophenyl)amine (Table 2, Entry 6). ^1H NMR (400 MHz, CDCl_3): δ = 6.96-6.98 (m, 6H-Ar), 7.19-7.22 (m, 6H-Ar). ^{13}C NMR (100 MHz, CDCl_3): δ = 145.78, 130.01, 128.24, 125.20 ppm.

Tris(4-methoxyphenyl)amine (Table 2, Entry 11). ^1H NMR (400 MHz, CDCl_3): δ = 7.31-7.45 (m, 6H), 6.86-6.89 (d, 6H) 3.82 (s, 9H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 159.00, 137.45, 127.45, 114.76, 55.50 ppm.

Tri-p-tolylamine (Table 2, Entry 14). ^1H NMR (400 MHz, CDCl_3): δ = 6.71-7.00 (m, 12H-Ar), 1.91 (s, 9H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 141.02, 129.11, 127.55, 127.18, 20.02 ppm.

RESULTS AND DISCUSSION

Characterization of CuO Nanoparticles

CuO nanoparticles were investigated by X-Ray Diffractometry (XRD). The morphology was monitored by scanning electron microscope (SEM). Chemical properties investigated by Fourier transformation infrared spectroscopy (FT-IR) (Fig. 1) show absorption in the waves numbers 477, 522 and 603 cm^{-1} that they are related to the

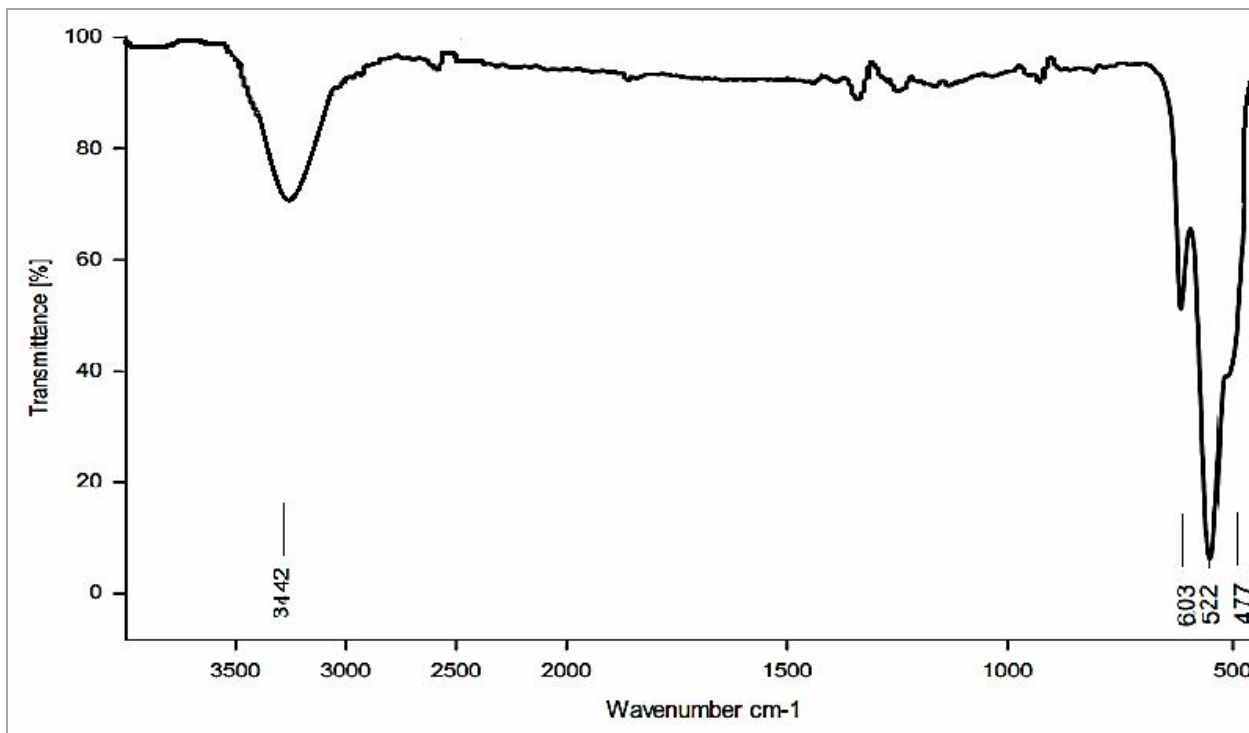


Fig. 1. FT-IR spectra of the CuO nanoparticles.

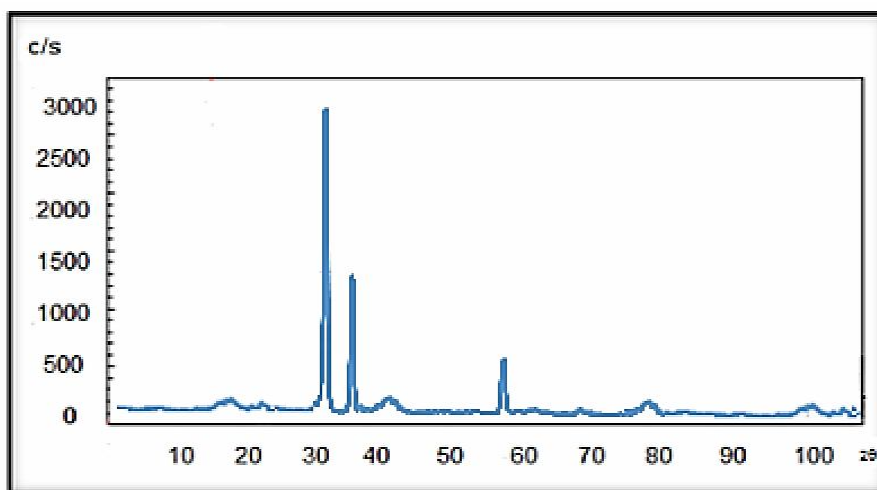


Fig. 2. Energy-dispersive X-ray spectroscopy of the CuO nanoparticles.

vibrations of Cu-O. The broad absorption peak at around 3442 cm⁻¹ highlights their relation to water molecules. X-ray powder diffraction patterns (Fig. 2) shows the presence

of the main diffraction peak in $2\theta = 37.30$, $2\theta = 34.45$. Scanning electron microscopy (Fig. 3) shows the existence of crystals in nano-size. All of the data are similar to those

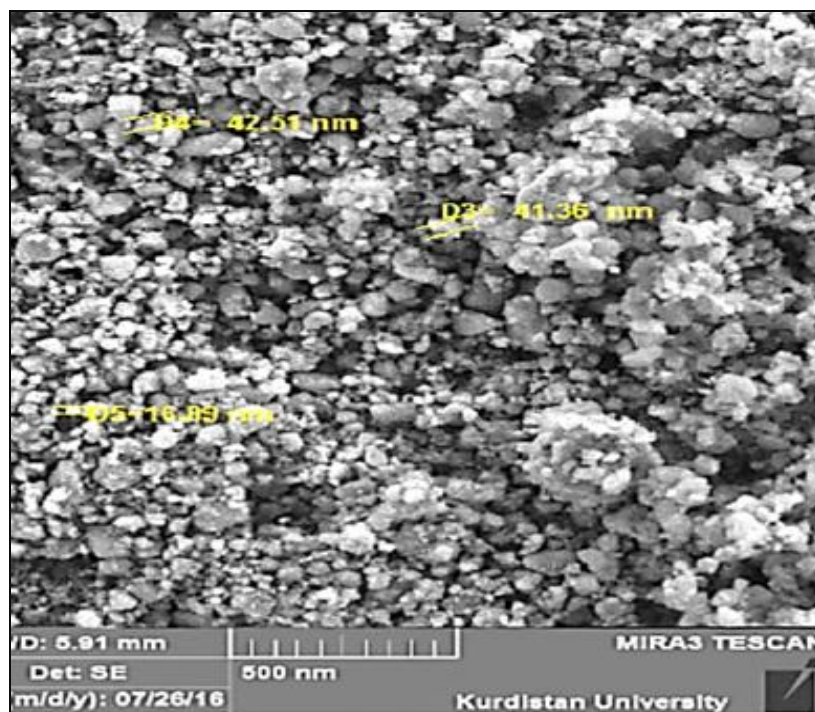


Fig. 3. SEM micrograph of the CuO nanoparticles.

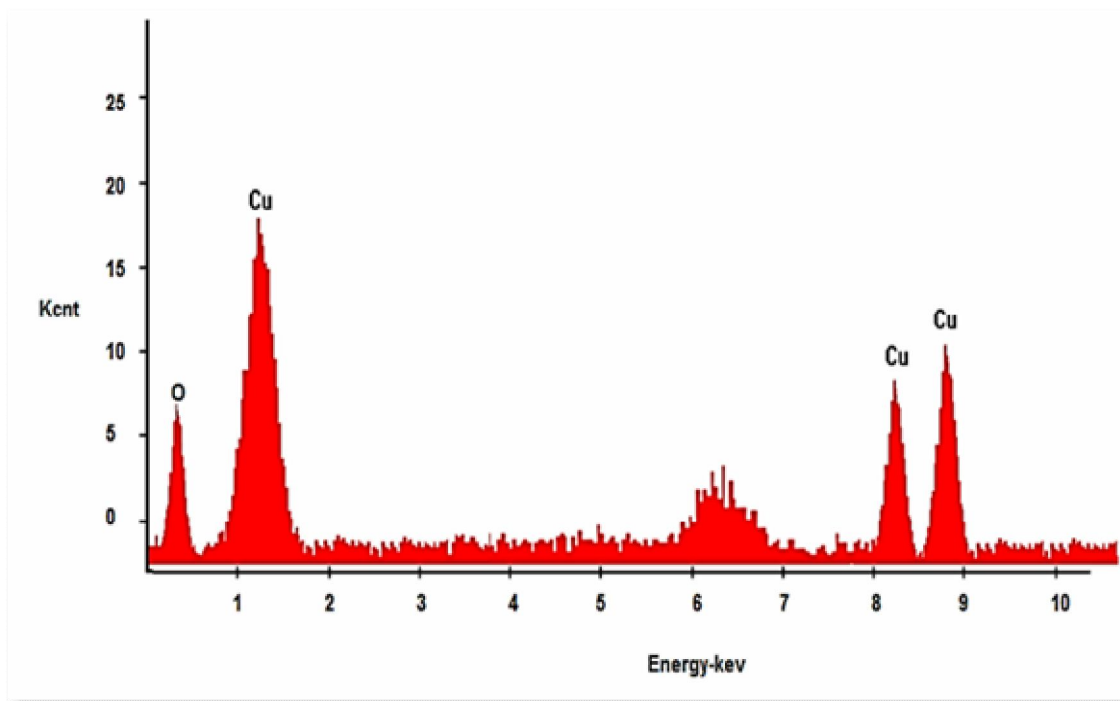


Fig. 4. X-ray powder diffractogram of the CuO nanoparticles.

Table 1. Optimization of the Reaction Conditions^a

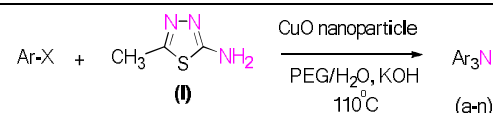














$\text{PhI} + \text{CH}_3\text{-C}_4\text{H}_2\text{N}_2\text{S}(\text{NH}_2) \xrightarrow[\text{solvent, base, temp, time}]{\text{Cat (mol\%)}} \text{Ph}_3\text{N}$

N-source (I)

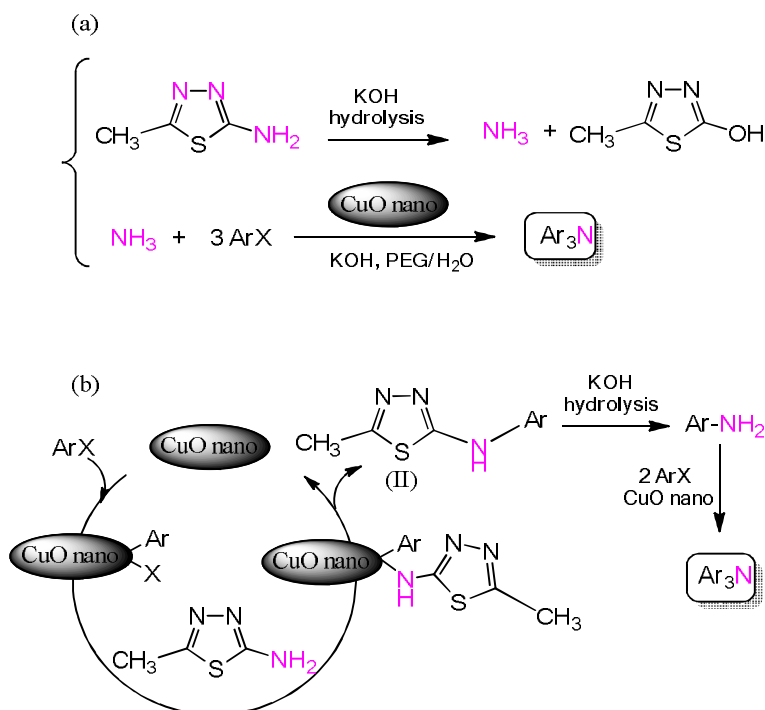
Entry	N-source (I) (mmol)	Cat. (mol%)	Solvent/H ₂ O (20:1)	Base (mmol)	Temp. (°C)	Time (h)	Yield (%)
1	0.5	CuO nano (5)	DMF	KOH (3)	130	2	72
2	0.5	CuO nano (10)	DMF	KOH (3)	130	2	96
3	0.5	CuO nano (10)	DMF	KOH (2)	130	2	86
4	1	CuO nano (10)	DMF	KOH (3)	130	2	87 ^b
5	0.5	CuO nano (10)	DMSO	KOH (3)	130	2	65 ^b
6	0.5	CuO nano (10)	PEG	KOH (3)	130	2	98
7	0.5	CuO nano (10)	H ₂ O	KOH (3)	130	2	Trace
8	0.5	CuO nano (10)	PEG	KOH (3)	25	24	Trace
9	0.5	CuO nano (10)	PEG	KOH (3)	80	24	91
10	0.5	CuO nano (10)	PEG	KOH (3)	110	2	98
11	0.5	CuO nano (10)	PEG	K ₂ CO ₃ (3)	110	2	68
12	0.5	CuO nano (10)	PEG	<i>t</i> -BuOK (3)	110	2	89
13	0.5	CuO nano (10)	PEG	Et ₃ N (3)	110	2	59
14	0.5	CuO nano (10)	PEG	-	110	2	N.R
15	0.5	-	PEG	KOH (3)	110	2	N.R
16	0.5	MOF-199 (10)	PEG	KOH (3)	110	2	95
17	0.5	CuCl (10)	PEG	KOH (3)	110	2	75
18	0.5	K ₂ PdCl ₂ (10)	PEG	KOH (3)	110	2	64 ^b
19	0.5	NiCl ₂ (10)	PEG	KOH (3)	110	2	Trace
20	0.5	Fe ₃ O ₄ nano (10)	PEG	KOH (3)	110	2	40

^aReaction conditions: iodobenzene (1 mmol), 5-methyl-1,3,4-thiadiazole-2-amine (I), catalyst, base in 2 ml solvent/H₂O (20:1) under normal atmospheric conditions. ^bThe reaction moved forward to generate the by-products.

Table 2. The Direct Synthesis of Symmetrical Triaryl Amines from Aryl Halides (and Tosylates)

Entry	Ar-X	Product ^a	Time (h)	Yield (%) ^b
				
1		a	2	98
2		b	5	95
3		c	8	82
4		d	18	76
5		e	3	65 ^b
6		f	3	74
7		g	6	86
8		h	6	81
9		i	7	70
10		j	10	72
11		k	10	91
12		l	8	62 ^b
14		m	8	89
15		n	1.5	56

^aAll the products are known compounds and were characterized by comparison of NMR, GC-Mass spectral data and melting points with those reported in the literature. ^bThe reactions moved forward to generate the by-products (diaryl amines).



Scheme 2. Proposed mechanisms for the synthesis of triaryl amines

previously documented for CuO nanoparticle samples [39, 40]. It also shows the incorporation of Cu metal and a uniform distribution of the particles, confirmed by EDX analysis (Fig. 4).

The reaction of iodobenzene with 5-methyl-1,3,4-thiadiazole-2-amine (I) was studied under normal atmospheric conditions in order to optimize the reaction conditions in terms of temperature, amount of reagent, the type of base and solvent.

According to the results shown in Table 1, it was found that increasing the amount of CuO from 5 mol% to 10 mol% allows to increase the yield of the reaction (Table 1, entries 1, 2). We found that by increasing the amount of N-source, the reaction moves forward to generate the by-products (aniline and diphenylamine) (Table 1, entries 3, 4). The solvents such as DMF, PEG, DMSO and H₂O were tested. It was found that DMF and PEG display similar and good performance, however, PEG was used because it is a green solvent (Table 1, entries 3-7). Different temperatures were studied under normal atmospheric conditions. 110 °C was found the most effective temperature (Table 1, entries 8-10).

Also, the amount of 3 mmol of bases showed a superior effect on the reaction conversion and reaction in less than 3 mmol of bases was incomplete (Table 1, entries 3, 4). Furthermore, the product is dependent on the type of base used. When a strong base such as KOH and *t*-BuOK were used, the main resultant product is triphenylamine (Table 1, Entries 10-13). No reaction was observed in the absence of a base and catalyst (Table 1, entries 14, 15).

The Cu salts were tested in this investigation, and it was found that MOF-199 (Cu₃BTC₂) as well as CuO nanoparticles lead to the production of triaryl amines. Since MOF-199 is more inexpensive than CuO nanoparticles, copper oxide nanoparticles were selected. The reaction was not completed in the presence of CuCl (10 mol%). The reaction moved forward to generate the by-products using Pd catalyst and in the presence of NiCl₂ and Fe₃O₄ nanoparticle not very good (Table 1, entries 16-20) (Table 1). Alkylhalides generated tertiary amines in very small amounts. This could be due to the steric hindrance. Thus, at the end, a mixture of alkene products, primary and secondary amines were produced.

The reaction efficiency for the synthesis of triaryl amines

was examined in the presence of aryl halides (1 mmol) using 0.5 mmol of 5-methyl-1,3,4-thiadiazole-2-amine (I) and 10 mol% CuO nanopowder at 110 °C under normal atmospheric conditions and KOH as base. Various types of arylhalides reacted very well with N-source (I) (Table 2, entries 1-14).

As can be seen, aryl iodides and aryl bromides were more effective than aryl chlorides and aryl tosylates (Table 2, entries 1-4). Symmetric triarylamines with different functional groups, such as CH₃, OCH₃, NO₂, NH₂, Br, were also synthesized in good to excellent yields. As a general result, under the optimal conditions, higher rate in reactions were obtained with electron-withdrawing groups such as NO₂ and Br (conversion 100%, Table 2, entries 6, 13). However, reactions were slowly completed in the presence of electron-donating groups such as OCH₃, NH₂ (Table 2, entries 10-12). It was observed that with ortho-substituted aryl halides the reactions moved forward to generate by-products (less than 10% diaryl amines) (Table 2, entries 5, 12).

Although we cannot clearly determine the reaction pathway for the synthesis of triaryl amines from aryl halides and N-source (I), two possible mechanisms have been proposed for this reaction.

In the first mechanism (a), using a strong base such as KOH, ammonia is generated in situ. Triaryl amine appears to be generated in the coupling reaction between ammonia and aryl halides during the two-step reaction (Scheme 2, a) [41].

In the second proposed mechanism, product (II) appears to be generated in the coupling reaction between N-source (I) and aryl halides. Then, primary amines are produced by hydrolysis. Finally, during the two-step coupling reaction, triaryl amines are generated (Scheme 2, b) [42].

CONCLUSIONS

We have developed a novel, effective and one-pot procedure for direct synthesis of triarylamines from various aryl halides and 5-methyl-1,3,4-thiadiazole-2-amine (I) under mild conditions. The important feature of this method is introduction of a new N-source. The reagent was a stable and nontoxic solid, which could be used to prepare all types of triaryl amines. This protocol has several advantages:

selective synthesis of triaryl amines, normal atmospheric conditions, ligand-free systems, easily available, low-cost reagents and using green solvent instead of the usually used organic solvents.

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REFERENCES

- [1] S.A. Lawrence, *Amines: Synthesis Properties, and Application*, Cambridge University Press, Cambridge (2004).
- [2] J. Louie, J.F. Hartwig, *J. Am. Chem. Soc.* 119 (1997) 11695.
- [3] R.A. Singer, S.L. Buld, *J. Am. Chem. Soc.* 120 (1998) 213.
- [4] *Pigment Handbook*, P.A. Lewis (Ed.), John Wiley & Sons, New York, 1988.
- [5] G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* 108 (2008) 3054.
- [6] B. Schlummer, U. Scholz, *Adv. Synth. Catal.* 346 (2004) 1599.
- [7] R.C. Jones, A.R. Katritzky, *Comprehensive Organic Functional Group Transformations II: Carbon with Two Attached Heteroatoms with at Least One Carbon-to-heteroatom Multiple Link*, Elsevier, 2005.
- [8] B. Mandal, B. Basu, *RSC Adv.* 4 (2014) 13854.
- [9] D. Witt, *Synthesis.* 16 (2008) 2491.
- [10] F. Esmaili-Marandi, M. Saeedi, M. Mahdavi, I. Yavari, A. Foroumadi, A. Shafiee, *Synlett.* 25(2014) 2605.
- [11] S.L. Buchwald, C. Mauger, G. Mignani, U. Scholz, *Adv. Synth. Catal.* 348 (2006) 23.
- [12] C. Desmarests, R. Schneider, Y. Fort, *J. Org. Chem.* 67 (2002) 3029.
- [13] F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* 48 (2009).
- [14] J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, John Wiley & Sons, New York, 2004.

- [15] J.F. Hartwig, *Angew. Chem. Int. Ed.* 37 (1998) 2046.
- [16] H.B. Goodbrand, N.-X. Hu, *J. Org. Chem.* 64 (1999) 670.
- [17] R.D. Fagan, E. Hauptman, R. Shaprio, A. Casalnuovo, *J. Am. Chem. Soc.* 122 (2000) 5043.
- [18] F. Ullmann, *Ber. Dtsch. Chem. Ges.* 36 (1903) 2382.
- [19] J. Hassan, M. Sevignon, C. Gozzi, C. Schulz, M. Lemaire, *Chem. Rev.* 102 (2002) 1359.
- [20] L. Mohammadi, M.A. Zolfigol, A. Khazaei, M. Yarie, S. Ansari, S. Azizian, M. Khosravi, *Appl Organometal Chem.* (2017) e3883.
- [21] M. Salavati-Nissari, F. Davar, *F. Mater. Lett.* 63 (2009) 441.
- [22] A. Azam, A.S. Ahmed, M. Oves, M.S. Khan, A. Memic, *Int. J. Nanomedicine.* 7 (2012) 3527.
- [23] J. Singh, G. Kaur, M. Rawat, *J. Biol. Elec. Nanotech.* 1 (2016) 9.
- [24] Q. Liu, H. Liu, Y. Liang, Z. Xu, G. Yin, *Mate. Res. Bull.* 41 (2006) 697.
- [25] R. Al-Gaashani, S. Radimana, N. Tabetc, A. RazakDaud, *J. Alloy. Comp.* 509 (2011) 8761.
- [26] M.S. Hassan, T. Amna, O.-B. Yang, M.H. El-Newehyd, S.S. Al-Deyab, M.-S. Khil, *Coll. Surf. B.* 97 (2012) 201.
- [27] W. Zhou, N. Jiao, *Nitrogenation Strategy for the Synthesis of Amines. In Nitrogenation Strategy for the Synthesis of N-containing Compounds*, Springer Singapore, 2017.
- [28] S. Das, B. Wendt, K. Möller, K. Junge, M. Beller, *Angew. Chem.* 124 (2012) 1694.
- [29] D.L.V. Katz, *Handbook of Natural Gas Engineering*. McGraw-Hill, 1959, p. 6954.
- [30] *Amines: Synthesis, Properties and Application*, ed. S. A. Lawrence, Cambridge University Press, Cambridge, 2004.
- [31] V. Azov, M. Beller, H. Butenschön, A. Börner, F.G. Couty, *Science of Synthesis*; Georg Thieme Verlag, 2014.
- [32] S. Liu, R. Chen, G.J. Deng, *Chem. Lett.* 40 (2011) 489.
- [33] L. He, Y. Qian, R.-S. Ding, Y.-M. Liu, H.-Y. He, K.N. Fan, Y. Cao, *Chem. Sus. Chem.* 5 (2012) 621.
- [34] A.M. Berman, J.S. Johnson, *J. Org. Chem.* 71 (2006) 219.
- [35] I.D. Watson, L. Yu, A.K. Yudin, *Acc. Chem. Res.* 39 (2006) 194.
- [36] M. Soleiman-Beigi, F. Mohammadi, *Tetrahedron Lett.* 53 (2012) 7028.
- [37] M. Soleiman-Beigi, F. Mohammadi, *Synlett.* 26 (2015) 911.
- [38] M. Soleiman-Beigi, F. Mohammadi, *Monatsh Chem.* 148 (2017) 2123.
- [39] K. Phiwdang, S. Suphankij, W. Mekprasart, W. Pecharapa, *Energy Procedia.* 34 (2013) 740.
- [40] J.M. Kshirsagar, R. Shrivastava, P.S. Adwani, *Therm. Sci.* 21 (2017) 233.
- [41] G.A. Artamkina, G.A. Sergeev, M.M. Stern, I.P. Beletskaya, *Synlett.* 02 (2006) 235.
- [42] V.K. Akkilagunta, R.R. Kakulapati, *J. Org. Chem.* 76 (2011) 6819.