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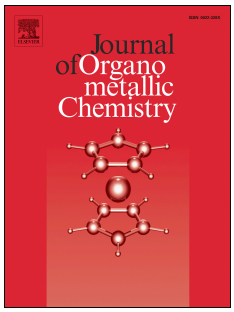

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Temperature dependent regioselective synthesis of aryl tetrazole amines using copper source

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ABSTRACT

One pot highly efficient and simple protocol for the construction of aryl tetrazole amines *via* desulphurization/substitution/electro cyclization/*C-N* cross coupling reactions from thiourea with the use of cheap, readily available and air stable copper source as catalyst has been described. The reaction proceeds through the *in situ* formation of amino tetrazole followed by successive *C-N* cross-coupling reaction with aryl iodide. Further the temperature dependent regioselectivity in *N*-arylation of tetrazole amines has been described.

KEYWORDS

- Aryl tetrazole amines
- Regioselective synthesis
- Copper catalyst
- Desulphurization
- *C-N* Cross-Coupling Reaction

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1. Introduction

Tandem reactions have gained vital role in the construction of small molecule libraries [1]. Generally, in case of tandem reactions the intermediate need not be stable enough to be isolated that follows further reaction to provide multiple organic compounds. In recent times, various organic molecules which contain biological and pharmalogical activities were constructed *via* tandem reaction and carbon-heteroatom cross coupling reaction using transition metal [2]. In this connection we are also interested to make hetero cyclic compounds such as substituted aryl tetrazole amines through tandem reaction.

Tetrazole is found in compounds having anti-allergic/anti-asthmatic [3],antiviral and anti-inflammatory [4], anti-neoplastic [5] activities (**Figure 1**). In addition tetrazoles are also used as ligands in coordination chemistry and they were shown in medicinal applications [6]. Therefore, synthetic organic chemists have drawn immense attention for the preparation of substituted tetrazoles. In this connection, researchers have developed traditional methods for the construction of tetrazoles. Especially, the preparation of tetrazoles is achieved by addition of $NaNO_2$ to aminoguanidine [7c], addition of NaN_3 to carbodiimides or cyanamides [8], reaction of amines with a leaving group in tetrazoles 5thposition[9], nucelophilic substitution by N_3^- of (a) chlorine in α-chloroformamidines [10] and (b) sulfur from thioureas in presence of mercury [11] or lead salts [7c] or iodine [12]. 5-Substituted-1*H*-tetrazoles have also prepared from the reaction between corresponding nitriles and NaN_3 *via* [3+2] cycloaddition using Zn (II) salts [13] and ZnO nanocrystal [14]. Later, substituted tetrazole have been prepared from the reaction between substituted nitriles and $TMSN_3$ using TBAF [15] and copper catalyst [16].

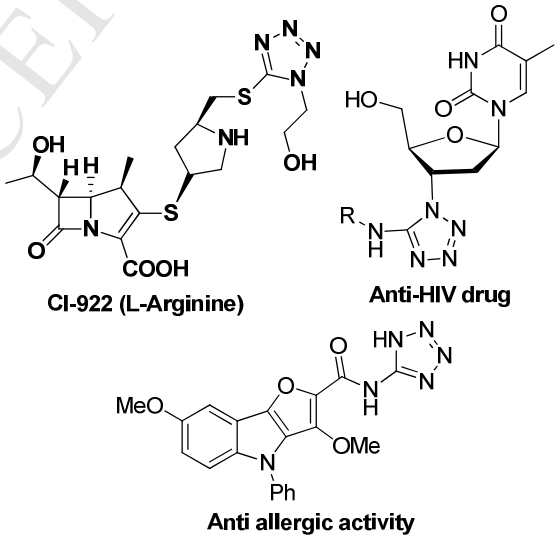


Fig 1: Some of the biologically important aminotetrazoles

Often thesemethods useeither toxic reagents or harsh reaction conditions such as high temperature, using toxic reagents, unavailable starting precursors and lack of regioselectivity [17]. Hence to overcome the above mentioned draw backs we wish to develop an efficient methodology for the synthesis of substituted tetrazoles from thiourea using copper *via* desulphurization/substitution/electro cyclization/*C-N* cross-coupling reaction. To the best of our knowledge no report is available for the synthesis of aryl tetrazole amines from thiourea using copper.

2. Materials and methods

***2.1 General information*:** Thiourea, DMSO, EtOH, EtOAC, n-Hexane, n-Heptane, 1,10-Phenanthroline, $CuSO_4 \cdot 5H_2O$ (98%), CuI (98%), CuBr (98%), Cu_2O (97%), CuCl(99%), and $Cu(OAc)_2 \cdot H_2O$ (98%), Et_3N, sodium azide, $K_3PO_4 \cdot 3H_2O$, KOH, K_2CO_3, Cs_2CO_3 were purchased from Aldrich and used without further purification. The solvents were purchased and dried according to standard procedure prior to use. ^1H NMR (400MHz) spectra were recorded with a Varian 400 spectrometer. Infrared (IR) spectra recorded on a Perkin Elmer Spectrum one FT-IR spectrometer. VKSI Medico centrifuge machine was used for our experimental procedure for the synthesis of resulting compounds

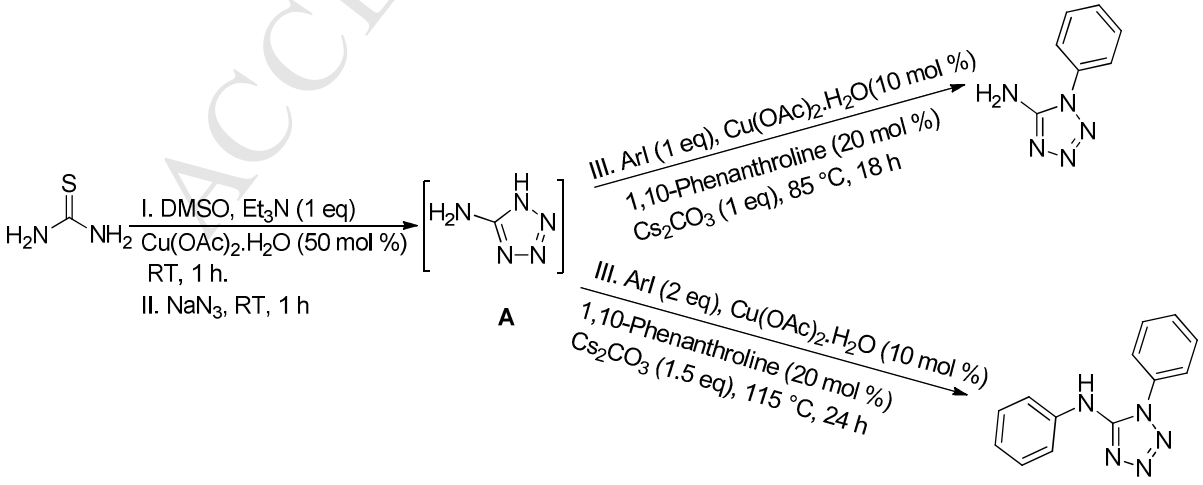
2.2. Representative experimental procedure for the synthesis of Phenyl tetrazole amine 1a:

To a stirred solution of DMSO (2-3 mL), thiourea (1 mmol, 76 mg) was added in slowly and followed by Et_3N (1 mmol, 101 mg) and $Cu(OAc)_2.H_2O$ (50 mol %, 100 mg) were added at room temperature. The whole reaction mixture stirred for one hour (until get the black color) at room temperature. The reaction was monitored by TLC. After completion of the reaction (monitored by TLC), to this, NaN_3 (2 mmol, 130 mg) was added. Then, the reaction mixture stirred for 1 h. Later, iodobenzene (1 mmol, 204 mg), Cs_2CO_3 (1 mmol, 325 mg), $Cu(OAc)_2.H_2O$ (10 mol %, 19.9 mg) and 1,10-phenanthroline (20 mol %, 36 mg) were added consecutively for several min and the reaction mixture was stirred for 18 h at 85 °C. The progress of the reaction was investigated by TLC (5% ethylacetate in hexane). After completion of the reaction, the reaction mixture was transferred into centrifuged tubes and the mixture was centrifuged for 10 min by using centrifugation machine. Black color solid was settled in the bottom of centrifuged tubes. The clear solution was concentrated by using rotary evaporator and the crude mixture was purified by silica gel (60-120 mesh) column chromatography using 20% ethylacetate in hexane as eluent to obtain a phenyl tetrazole amine **1a** as a white solid.

2.3 General Procedure for the Synthesis of Diphenyl Tetrazole amine 2a: To a stirred solution of DMSO (2-3 ml), thiourea (1 mmol, 76 mg) was added in slowly and followed by Et_3N (1 mmol, 101 mg) and $Cu(OAc)_2.H_2O$ (50 mol %, 100 mg) were added at room temperature. The whole reaction mixture stirred for one hour (until get the black color) at room temperature. The reaction was monitored by TLC. After completion of the reaction (monitored by TLC), to this, NaN_3 (2 mmol, 130 mg) was added. Then, the reaction mixture stirred for 1 h. Later, iodobenzene (2 mmol, 408 mg), Cs_2CO_3 (1.5 mmol, 485 mg), $Cu(OAc)_2.H_2O$ (10 mol %, 19.9 mg) and 1,10-phenanthroline (20 mol %, 36 mg) were added consecutively for several min and the reaction mixture was stirred for 24 h at 115 °C. The progress of the reaction was investigated by TLC (5% ethylacetate in hexane). After completion of the reaction, the reaction mixture was transferred into centrifuged tubes and the mixture was centrifuged for 10 min by using centrifugation machine. Black color solid was settled in the bottom of centrifuged tubes. The clear solution was concentrated by using rotary evaporator and the crude mixture was purified by silica gel (60-120 mesh) column chromatography using 30% ethylacetate in hexane as eluent to obtain thediphenyl tetrazole amine **2a** as a white solid.

3. Results and discussions

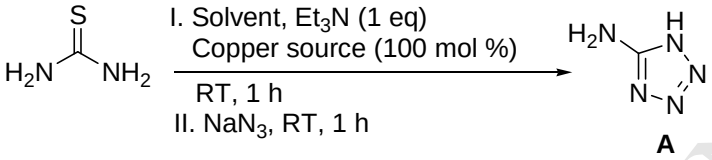
Thiourea gave 1*H*-tetrazol-5-amine *via* desulfurization using copper source fallowed by substitution and electro cyclizationreactions with NaN_3. Further, 1*H*-tetrazol-5-amine reacts with iodobenzene using a copper source as catalyst under moderate reaction conditions to afford the target products phenyltetrazolamine and 1-phenyl-5-(*N*-phenyl amino) tetrazole (**Scheme 1**).



Scheme 1. Synthetic route for aryltetrazolamine and 1-aryl-5-(*N*-aryl amino) tetrazole.

Firstly, the optimization was started for the synthesis of tetrazole amine using thiourea as a model substrate with various solvents and copper sources at room temperature. Among the solvents protic polar solvents like EtOH and EtOAc (**Table 1**, entries 1-2), aprotic solvents DMSO and DMF (**Table 1**, entries 6-7) gave final product **A** in complete conversion. The reaction didn't provide the target product in the presence of nonpolar solvents *n*-hexane and *n*-heptane (**Table 1**, entries 3-4). The reaction using both copper (I) and (II) sources to afford final product **A** in complete conversion. The reaction using the lower amount of catalyst 50 mol % and 25 mol % to give final product in 100% and 65% conversion, respectively (**Table 1**, entries13-14). Control experiment confirmed that the reaction did not provide target product in the absence of catalyst (**Table 1**, entry 15).

Table 1: Optimization for the synthesis of tetrazole amine[a]



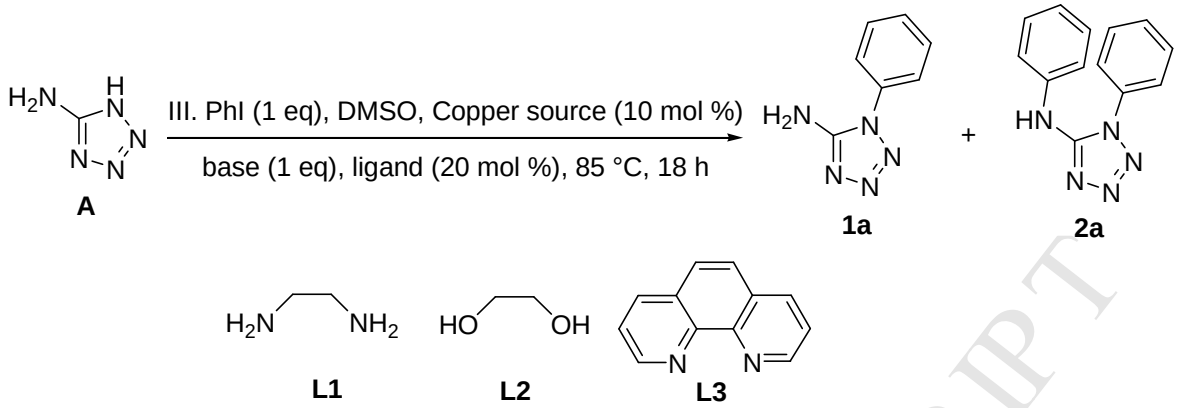
A

Entry	Solvent	Copper source	Conversion(%)[b] **A**
1	EtOH	CuI	100
2	EtOAc	CuI	100
3	*n*-Hexane	CuI	n.d
4	*n*-Heptane	CuI	n.d
5	H_2O	CuI	56
6	DMF	CuI	100
7	DMSO	CuI	100
8	DMSO	CuCl	100
9	DMSO	CuBr	100
10	DMSO	Cu_2O	100
11	DMSO	$CuSO_4.5H_2O$	100
12	DMSO	$Cu(OAc)_2.H_2O$	100
13[c]	DMSO	$Cu(OAc)_2.H_2O$	100
14[d]	DMSO	$Cu(OAc)_2.H_2O$	65
15	DMSO	-	n.d

[a]Reaction conditions: Thiourea (1 mmol), solvent (2 mL), Et_3N (1 eq),Copper source (100 mol %), 1 h, room temperature, then, NaN_3 (2 mmol) room temperature, 1h. [b]Conversion based on diagnostic peaks integration in ^1H NMR of crude reaction mixture. [c] Copper source (50 mol %) wasused. [d] Copper source (25 mol %) was used. n.d. = not detected.

Later, the optimization reaction conditions were performed for the synthesis of phenyltetrazole amine using tetrazole amine and iodobenzene as model substrates with various bases, ligands and copper sources. We were glad to observe that the reaction could give target product **1a** incomplete conversion using 10 mol % copper source, 20 mol % ligand (1,10-phenanthroline)and 1 equiv. Cs_2CO_3 at 85 °C temperature in the presence of DMSO solvent (**Table2**, entry 4)

Table 2: Optimization for the synthesis of phenyltetrazole amine[a]

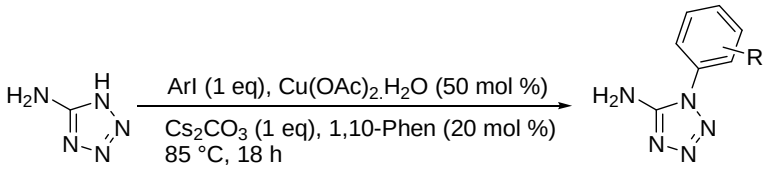


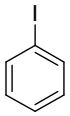
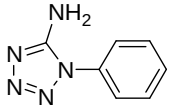
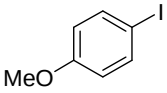
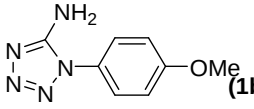
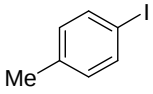
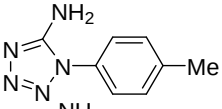
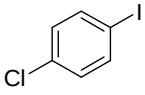
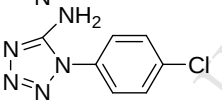
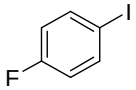
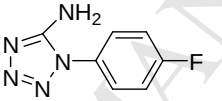
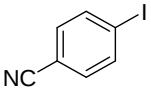
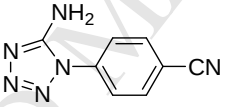
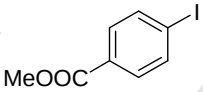
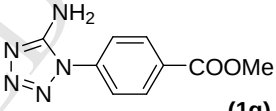
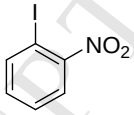
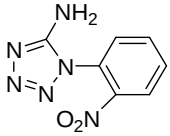
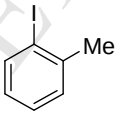
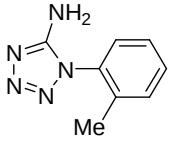
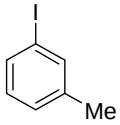
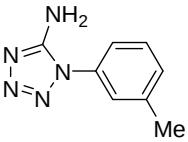
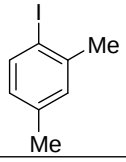
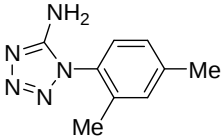
Entry	Copper source	Base	Ligand	Conversion[b]	
				1a	**2a**
1	CuI	$K_3PO_4 \cdot 3H_2O$	**L3**	68	n.d
2	CuI	KOH	**L3**	72	n.d
3	CuI	K_2CO_3	**L3**	62	n.d
4	CuI	Cs_2CO_3	**L3**	100	n.d
5	CuBr	Cs_2CO_3	**L3**	100	n.d
6	CuCl	Cs_2CO_3	**L3**	100	n.d
7	$CuSO_4 \cdot 5H_2O$	Cs_2CO_3	**L3**	100	n.d
8	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	**L3**	100	n.d
9	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	**L1**	70	n.d
10	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	**L2**	55	n.d
11[c]	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	**L3**	40	n.d
12[d]	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	**L3**	35	n.d
13	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	-	20	n.d
14	-	Cs_2CO_3	-	n.d.	n.d
15[e]	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	**L3**	100	n.d
16[f]	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	**L3**	85	15
17[g]	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	**L3**	50	50
18[h]	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	**L3**	n.d	100

[a] Reaction conditions: Amino tetrazole (1 mmol), DMSO (2 mL), iodo benzene (1 mmol), catalyst (10 mol %), ligand (20 mol %), base (1 mmol), 18 h, 85 °C. [b]Conversion based on diagnostic peaks integration in ^{1}H NMR ofcrude reaction mixture. [c] Copper source (5 mol %) used. [d] Cs_2CO_3 (0.5 equiv) used. [e] Iodobenzene (2 eq) was used. [f] Iodobenzene (2 eq) and temp 100 °C were used. [g] Iodobenzene (2 eq), temp 100 °C, 24h and Cs_2CO_3(1.5 eq) were used. [h] Iodobenzene (2 eq), temp 115 °C, 24h and Cs_2CO_3 (1.5 eq) were used. n.d. = not detected.

The reaction using Cs_2CO_3 exhibited greater reactivity compared to that of $K_3PO_4 \cdot 3H_2O$, K_2CO_3 and KOH. In a set of ligands **L1-L3** screened, **L3** (**Table 2**, entry 4) was found to be the most effective in comparison to **L1-L2** (**Table 2**, entries 9-10). Both copper (I) and (II) sources (CuI, CuBr, CuCl, $Cu(OAc)_2.H_2O$ and $CuSO_4.5H_2O$) exhibited a similar catalyticactivity (**Table 2**, entries 4-8). Lowering the amount of base (0.5 equiv) or the copper source (5 mol %) led to the *N*-arylation to afford target product in less conversion (**Table 2**, entries 11 and 12).

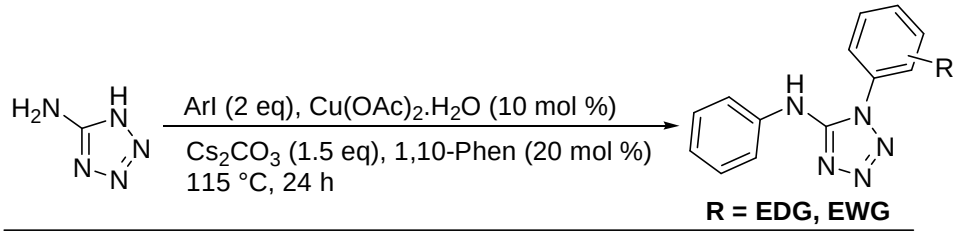
Table 3: Substrate scope for the synthesis of substituted aryltetrazole amines[a]

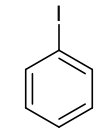
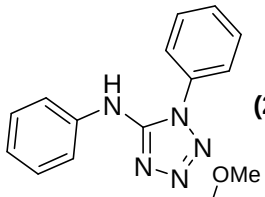
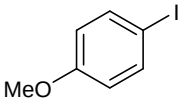
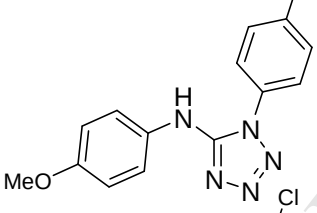
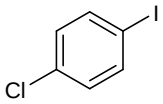
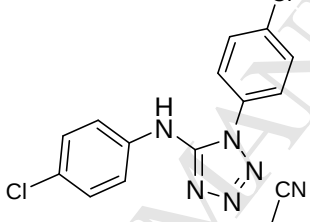
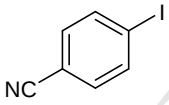
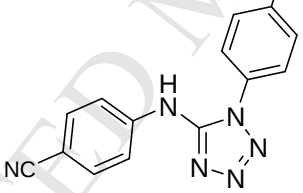
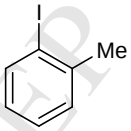
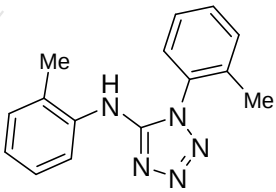
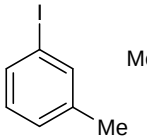
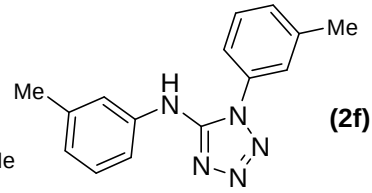


Entry	Substrate	Product	Yield[b]
1		 **(1a)**	96
2		 **(1b)**	98
3		 **(1c)**	97
4		 **(1d)**	87
5		 **(1e)**	80
6		 **(1f)**	47
7		 **(1g)**	46
8		 **(1h)**	52
9		 **(1i)**	87
10		 **(1j)**	90
11		 **(1k)**	87

[a] Reaction conditions: Tetrazole amine (1 mmol), DMSO (2 mL), $Cu(OAc)_2.H_2O$ (10 mol %), ArI (1 mmol), ligand(20 mol %), Cs_2CO_3 (1 mmol), 18 h, 85 °C. [b] Isolated yield.

Table 4: Substrate scope for the synthesis of substituted 1-aryl-5-(*N*-arylamino) tetrazole[a]



Entry	Substrate	Product	Yield[b]
1		 **(2a)**	95
2		 **(2b)**	97
3		 **(2c)**	78
4		 **(2d)**	43
5		 **(2e)**	76
6		 **(2f)**	80

[a] Reaction conditions: Tetrazole amine (1 mmol), DMSO (2 mL), Aryl iodide (2 mmol), $Cu(OAc)_2.H_2O$ (10 mol %), ligand(20 mol %), Cs_2CO_3 (1.5 mmol), 24 h, 115 °C. [b] Isolated yield.

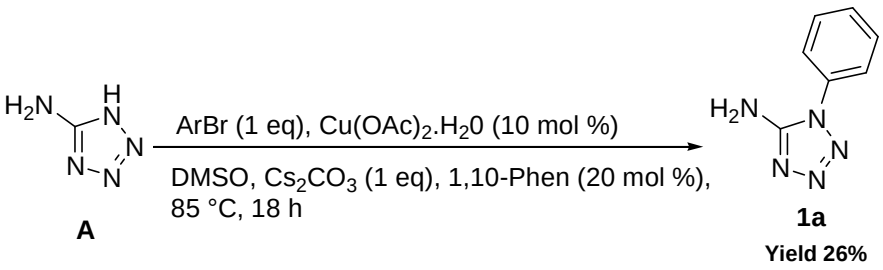
In order to know the role of ligand, the reaction was also performed without ligand (**Table 2**, entry 13) and it gave the target product in very less yield even for prolonged

reaction times. Control experiments without ligand and the copper source confirmed that the formation of final product was not observed (**Table 2**, entry 14).

In order to optimize for another target product **2a**, addition experiments were conducted with high amount of iodobenzene and base at 100 °C and 115 °C. The results shown in **Table 2** clearly suggest that increasing temperature, base and iodobenzene increases the yield of target product **2a** (**Table 2**, entry 18).

Having the optimal conditions in hand, the scope of the protocol was next explored to substituted phenyltetrazoleamines (**Table 3**). The substrates having both electron donating and electron with drawing groups on the aryl rings could give their respective target products **1a-1k** in moderate to high yield. Aryl iodide having electron donating substituents (4-Me, 2-Me, 4-OMe and 2,4-dimethyl) showed greater reactivity compared to that bearing electron withdrawing substituent's (4-Cl, 4-F, 4-CN and 4-COOMe groups). The phenyl ring having electron donating groups such as 4-methoxy, 4-methyl could give their respective aromatic cyanamides **1b** and **1c** in 98 and 97 % yield (**Table 3**, entries 2 and 3). The unsubstited phenyl ring also gave target product **1a** in excellent yield. Electron withdrawing groups such as 4-chloro and 4-fluoro substituents provide their target products **1d** and **1e** in 87% and 80% yields, (**Table 3**, entries 4 and 5) respectively. Aryl ring bearing other strong electron withdrawing substituents such as nitrile, ester and nitro could give target products **1f-1h** in moderate yield (**Table 3**, entries 6-8). Aryl iodides bearing ortho and meta substituted methyl groups readily underwent the reaction to give final products **1i-1j** in 87 and 90% yields respectively (**Table 3**, entries 9 and 10). 2,4-Di-Methyl substituents on aryl ring gave targetproduct **1k** in 87% yield (**Table 3**, entry 11).

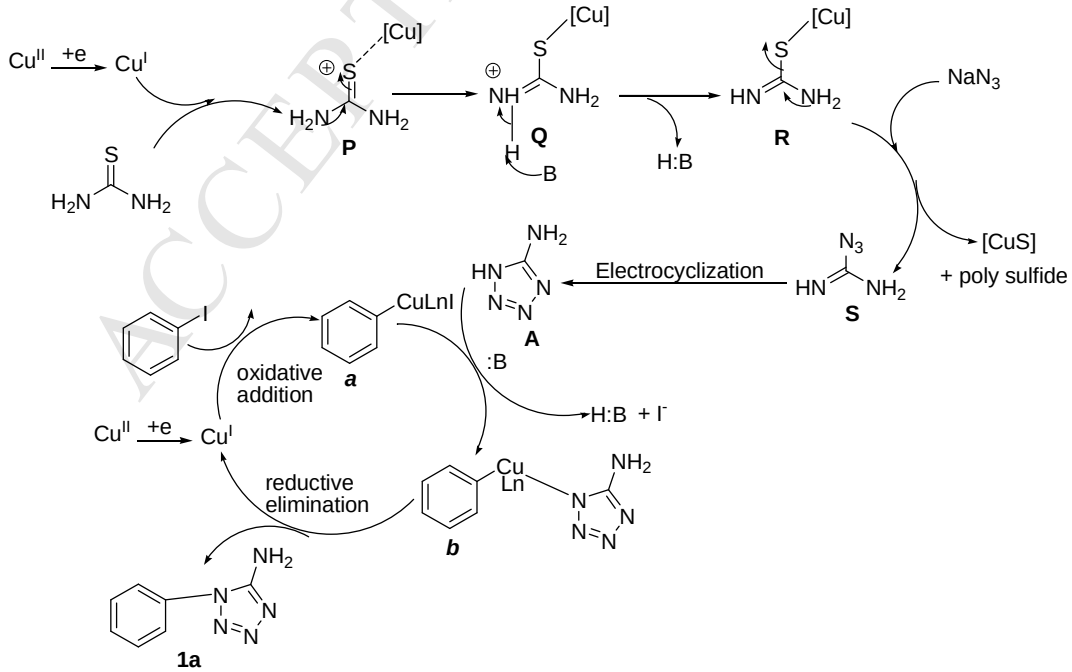
Further, we have also explored for the construction of substituted 1-aryl-5-(*N*-arylamino) tetrazole under optimized reaction conditions (**Table 4**). The reaction of tetrazoleamine with aryl iodides containing both electron donating, electron withdrawing groups were investigated. Aryl iodide having electron donating substituents (4-OMe, 3-Me and 2-Me) showed greater reactivity compared to that bearing electron withdrawing substituent's (4-Cl and 4-CN groups). The phenyl ring having electron donating groups such as 4-methoxy, 3-methyl and 2-methyl could give their respective 1-aryl-5-(*N*-aryl amino) tetrazole **2b-2d** in 97-78% yield (**Table 4**, entries 2-4). The unsubstituted phenyl ring also gave target product **2a** in excellent yield (**Table 4**, entry 1). Electron withdrawing groups such as 4-chloro and 4-cyano substituents provide their target products **2e** and **2f** in 76% and 43% yields, respectively (**Table 4**, entries 5 and 6).



Scheme 2. Reaction with aryl bromide

Moreover, we also check the employability of the reaction with aryl bromide instead of aryl iodide under optimized reaction conditions (**Scheme 2**). Very unfortunately, the reaction gave target product in fewer yields. It might be occurred due to very hard to formation of aryl bromide and copper complex [18].

The mechanism of formation for substituted aryltetrazole amine from thiourea is shown in below **Scheme 3**. The experimental evidence and from the literature reports the mechanism is proposed. Copper can co-ordinate with thiourea and followed by removal of protons to afford intermediate **R** *via* intermediates **P** and **Q**. The intermediate **R** may provide tetrazole amine **A** along with by-products CuS and poly sulphide [19] *via* desulphurization/substitu-tion/electrocyclization [20]. On the other hand, oxidative addition of aryl iodide with copper (I) species (it could be formed from copper (II) species) [21] can lead to the formation of ***a*** which can undergo intermolecular *C-N* cross-coupling reaction [22] with tetrazole amine using base to give the intermediate ***b*** that can complete the catalytic cycle by reductive elimination to get target product aryltetarzole amine **1a**.



Scheme 3: Proposed mechanism for aryl tetrazolamine.

4. Conclusion

In conclusion, we have developed methodology for the regioselective synthesis of aryltetrazoleamines from thiourea in one pot multistep reaction. It is a general, efficient and easy method. Although the overall isolated yields look moderate, considering that the reactions are multiprocesses, the yields are in fact good to excellent. Many reports are available for the preparation of aminotetrazoles, however, the simplicity, environmental acceptability and cost effectiveness of the copper makes this method more practical. The reactions were involved desulphurization/substitution/electrocyclization followed by inter molecular *C-N* cross-coupling reaction.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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Highlights

- An efficient methodology for the synthesis of substituted tetrazoles has been described.
- The reactions are general, clean and efficient.
- Desulfurization is developed by cheap, available and air stable copper catalyst.
- All the substrates could obtain their target products in good to excellent yields.