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A ONE POT SYNTHETIC STRATEGY FOR THE CONSTRUCTION OF THE AROMATICCYANAMIDES

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ABSTRACT
An efficient and simple Methodology for the construction of aromatic cyanamides *via* desulphurization/*C-N* bond formation from thiourea with use of cheap, readily available and air stable copper catalyst has been described. Under optimized reaction conditions various bromobenzenes could give their respective *C-N* cross-coupled products in good to excellent yields.

KEYWORDS: Copper catalyst, Desulfurization, Bromobenzene, *C-N* Bond formation, Aryl Cyanamide.

INTRODUCTION
Cyanamide is an important functional group in synthetic organic chemistry because of its unique reactivity. In recent years, *N*-alkyl or *N*-aryl imides[1] and herbicides[2] were synthesized from cyanamides (RR^1N–CN), which are good intermediates for the synthesis of heterocyclic compounds that have biological, medicinal and pharmaceutical importance.[3] Especially, cyanamides exhibit apparent tumor growth inhibition activity[4] except for being a sole synthetic intermediate. Due to the easy removal of the cyano group from cyanamide, and N-alkyl or N-aryl imides,[5] they often serves as a useful protecting groups in the synthesis of secondary and tertiary amines containing heterocycles.[6] Apart from that, synthesis of many reagents has been developed from cyanamides.[7]

The frequently used method for the synthesis of cyanamides is the cyanation of amine using cyanogen halides, or synthon (CN^+).[8] The preparation of cyanamides is achieved by Traditional method from the reaction of gaseous cyanogen chloride or cyanogen bromide with amines or with imide salts.[9] In an alternative approach, cyanamides are obtained from ureas, thioureas[10] and amidoximes.[11] Recently, they were prepared from organic isocyanides and trimethylsilyl azide *via* Si–N bond cleavage catalyzed by $[(\eta^3\text{-}C_3H_5)PdCl)_2]$[12] and in one pot by reacting isocyanate or isothiocyanate with sodium bis(trimethylsilyl)amide as deoxygenating or desulfurizing agent in the presence of THF at room temperature.[13] Cyanamides were prepared from N, N-disubstituted glycylamide using a pentavalent iodine reagent in the presence of tetraethyl ammonium bromide at ambient temperature.[14] Recently, Patel and co-authors reported for the synthesis of cyanamides from thiocarbamate salts[15] using hyper valent Iodine (III) reagent and Yeh *et al.* demonstrated preparation of cyanamides from amines using sodium bis(trimethylsilyl)amide reagent.[16] Most of the reports have used cyano cation (CN^+), which gets from toxic cyanogen halides, strong alkaline conditions, toxic and expensive reagents, high reaction temperature. Other researchers have reported at high temperature, giving low yields and involving tedious purification procedures. To overcome the above referred disadvantages, the efficient method is needed. In this regard, here in we wish to report a high yielding one pot synthesis of cyanamides from thiourea using cheap, readily available and air stable copper source as catalyst under mild reaction conditions.

MATERIAL AND METHODS
Thiourea, DMSO, EtOH, EtOAC, n-Hexane, n-Heptane, L-Proline, CuI (98%), CuBr (98%), CuCl (99%), $Cu(NO_3)_2{\cdot}3H_2O$ (99%) and $Cu(OAc)_2{\cdot}H_2O$ (98%), Et_3N, $K_3PO_4{\cdot}3H_2O$, 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 (400 MHz) 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 substituted cyanamides.

EXPERIMENTAL SECTION

General procedure for the synthesis of aromatic cyanamide: To a stirred solution of DMSO solvent (2-3 ml), thiourea (1 mmol, 76 mg) was added slowly followed by Et_3N (1 mmol, 101 mg) and $Cu(NO_3)_2{\cdot}3H_2O$ (50 mol %, 242 mg) were added at room temperature. The whole reaction mixture was 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, bromobenzene (1 mmol, 157 mg), Cs_2CO_3 (1.5 equv, 488 mg), $Cu(NO_3)_2{\cdot}3H_2O$ (10 mol %, 48 mg) and L-Proline (20 mol %, 46 mg) were slowly added consecutively for several min and the reaction mixture was stirred for 15 h at 90°C. The progress of the reaction was monitered by TLC (5% ethylacetate in hexane). After finishing 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 5% ethylacetate in hexane as eluent to obtain a phenyl cyanamide **2a** as a white solid.

Characterization of the synthesized compounds

Phenylcyanamide 2a

Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.8; yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 2H), 7.29-7.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 130.6, 130.1, 128.9, 114.3; FT-IR (KBr) 3350, 3064, 2222, 1693, 1489, 1250, 1070, 909 cm^{-1}. Anal. Calcd. for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.28; H, 5.09; N, 23.62.

4-Methoxyphenylcyanamide 2b

Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.8; yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 9.6 Hz, 2H), 5.81 (br s, 1NH), 3.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 138.6, 131.9, 127.8, 121.7, 55.4; FT-IR (KBr) 3357, 3076, 2899, 2236, 1587, 1253, 1212, 1104, 1055, 941, 808 cm^{-1}. Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91; O, 10.80. Found: C, 64.99; H, 5.42; N, 18.85.

4-Methylphenylcyanamide 2c

Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.8; yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.17 (m, 2H), 7.01 (d, *J* = 9.6 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 132.4, 128.5, 124.6, 120.0, 21.3; FT-IR (KBr) 3378, 3097, 2896, 2835, 2200, 1601, 1580, 1503, 1252, 1179, 1028, 927 cm^{-1}. Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.79; H, 6.09; N, 21.12.

4-Chlorophenylcyanamide 2d

Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.6; yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.8, 2H), 6.97-6.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 132.5, 130.6, 129.1, 117.1; FT-IR (KBr) 3399, 3076, 2214, 1670, 1505, 1250, 1114, 1023, 959, 817 cm^{-1}. Anal. Calcd. for $C_7H_5ClN_2$: C, 55.10; H, 3.30; Cl, 23.24; N, 18.36. Found: C, 55.25; H, 3.28; N, 18.30.

4-Fluorophenylcyanamide 2e

Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.6; yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.39 (br s, 1NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 136.5, 126.2, 120.3, 114.9; FT-IR (KBr) 3359, 3056, 2217, 1654, 1554, 1394, 1279, 1140, 939, 822 cm^{-1}. Anal. Calcd. for $C_7H_5FN_2$: C, 61.76; H, 3.70; F, 13.96; N, 20.58. Found: C, 61.92; H, 3.67; N, 13.89.

4-(Cyanoamino)benzonitrile 2f

Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.5; yield 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.34-7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 132.7, 128.1, 120.0, 115.6, 115.0; FT-IR (KBr) 3355, 3100, 2256, 2217, 1667, 1526, 1348, 1277, 1078, 973, 892 cm^{-1}. Anal. Calcd. for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.35. Found: C, 67.20; H, 3.50; N, 29.29.

Methyl-4-(cyanoamino)benzoate 2g

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.5; yield 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.6 Hz, 2H), 7.38-7.33 (m, 2H), 5.91 (br s, 1NH), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 142.8, 134.4, 130.5, 130.0, 121.7, 54.8; FT-IR (KBr) 3415, 3082, 2896, 2234, 1749, 1675, 1607, 1524, 1459, 1345, 1261, 1145, 1099, 870 cm^{-1}. Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90; O, 18.16. Found: C, 61.50; H, 4.56; N, 15.84.

2-Nitrophenylcyanamide 2h

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.5; yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.2 Hz, 2 H), 7.65 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 141.6, 136.7, 134.0, 132.1, 120.9, 115.1; FT-IR (KBr) 3375, 3065, 2215, 1656, 1564, 1490, 1379, 1229, 1125, 1036, 941, 832 cm^{-1}. Anal. Calcd. for $C_7H_5N_3O_2$: C, 39.73; H, 3.33; N, 10.30. Found: C, 39.88; H, 3.30; N, 10.23.

o-Tolylcyanamide 2i

Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.8; yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (m, 1H), 7.17-7.12 (m, 2H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.09 (br s, 1NH), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 139.6, 137.8, 134.5, 130.9, 129.9, 117.0, 20.6; FT-IR (KBr) 3412, 3074, 2867, 2223, 1690, 1435, 1379, 1229, 1125, 1036, 941, 875 cm^{-1}. Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.80; H, 6.02; N, 21.12.

m-Tolylcyanamide 2j: Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.8; yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.22 (d, *J* = 8.8, 1H),

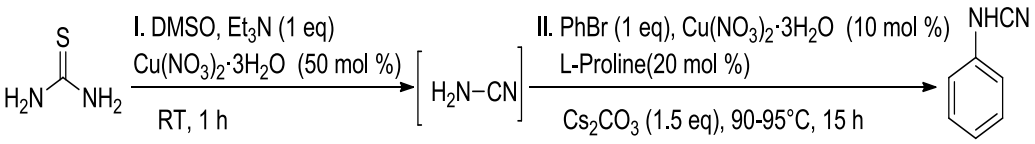
6.97-6.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 131.6, 131.3, 130.4, 120.3, 120.0, 115.4, 24.1; FT-IR (KBr) 3423, 3048, 2899, 2217, 1656, 1588, 1490, 1409, 1288, 1261, 1123, 1078, 823. Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.80; H, 6.02; N, 21.12.

2,4-Dimethylphenylcyanamide 2k

Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.8; yield 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 2.30 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 137.8, 134.5, 130.9, 129.9, 119.9, 113.9, 20.6, 18.2; FT-IR (KBr) 3368, 3077, 2888, 2863, 2212, 1635, 1599, 1513, 1491, 1287, 1215, 1027, 823 cm^{-1}. Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 74.02; H, 6.88; N, 19.09.

RESULTS AND DISCUSSIONS

Thiourea gave cyanamide, which is confirmed by IR analysis (-CN-2222 cm^{-1}) *via* desulphurization process using copper source as catalyst. It reacts with bromobenzene using copper source as catalyst under moderate reaction conditions to afford the target product as phenyl cyanamide (**Scheme 1**).



Scheme 1: Reaction pathway for the synthesis of arylcyanamides.

Initially, the optimization conditions of the first step reaction was performed using the readily available thiourea as model substrate with different copper sources and solvents at room temperature (**Table 1**). We were pleased to observe that the substrate proceeded reactions with 1 equivalent Et_3N and 50 mol % copper source (Both Cu (I) and Cu (II) slats) in the presence of EtOH, EtOAC, DMF and DMSO at room temperature to afford the corresponding unsubstituted cyanamide in complete conversion (**Table 1**, entries 1-2&6-7). The reaction using non polar solvents like n-hexane and n-heptane did not give unsubstituted cyanamide (**Table 1,** entries 3-4). Control experiment confirmed that the reaction did not proceed without copper source (**Table 1**, entry 14).

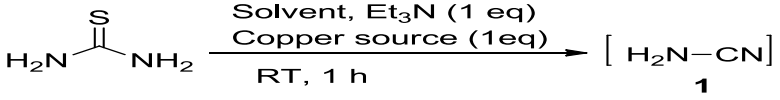
After finishing the first step optimization, we concentrated on the standardization of second step. In this connection, thiourea could provide unsubstituted cyanamide, that, gratifyingly, proceeded an intermolecular *N*-arylation with brombenzene using 10 mol % copper source, 20 mol % Ligand (L-Proline) and 1.5 equivalent Cs_2CO_3 at 90 °C temperature to give target product in complete conversion in the presence of DMSO(**Table 2,** entry 3). The reaction using Cs_2CO_3 exhibited greater reactivity compared to that of $K_3PO_4·3H_2O$, K_2CO_3 (**Table2**, entry1-3). In a set of ligands **L1**-**L2** screened, **L2** was found to be the most effective in comparison to **L1** (**Table 2**, entries 3-4). Both copper (I) and copper (II) sources (CuI, CuBr, CuCl, $Cu(NO_3)_2·3H_2O$ and $Cu(OAc)_2·H_2O$) exhibited a similar catalytic activity (**Table 2**, entries 3and 5-8). Lowering the amount of base (1 equiv) or the copper source (5 mol %) led to the *N*-arylation to afford target product in less conversion (**Table 2**, entries 9-10). Control experiments without the ligand and copper source confirmed that the formation of final product was not observed (**Table 2**, entry 12).

Getting the optimal conditions, the scope of the protocol was next explored to substituted cyanamides (**Table 3**). The process was common and a series of arylbromides were used to give corresponding aromatic cyanamides **2a-k** in moderate to good yield. The substrates having both electron donating and electron withdrawing substituents on the aryl rings could give their respective target product in moderate to high yield. Aryl bromide having electron donating substituents (4-Me, 2-Me, 4-OMe and 2,4-dimethyl) exhibited greater reactivity compared to that having electron withdrawing substituent's (4-Cl, 4-F, 4-CN and 4-COOMe groups). The phenyl ring having electron donating groups such as 4-OMe, 4-Me could give their respective aromatic cyanamides (**Table 2**, entries 2- 3) in 85% yield. The unsubstited phenyl ring also gave target product in good yield (**Table 2**, entry 1). Electron withdrawing groups such as 4-Cl and 4-F substituents gave their target products in 70% and 67% yields, respectively (**Table 2**, entries 4 and 5). Aryl ring bearing other strong electron withdrawing substituent's nitrile, ester and nitro could give target products (**Table 2**, entries 6-8) in moderate yield. Ortho and meta substituted methyl groups on aryl ring could give their respective target products in 74-72% yields (**Table 1**, entries 9-10). Di-Methyl substituent on aryl ring gave final product in 83% yield (**Table 2**, entry 11).

The mechanism of formation of aromatic cyanamides from thiourea is shown in **Scheme 4**. The mechanism is proposed based on experimental evidence and literature reports. Reduction of copper (II) with thiourea can give copper (I) species[17] which 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 unsubstituted cyanamide along with byproduct CuS and poly sulphide[18] via desulphurization.[19] On the other hand, oxidative

addition of aryl iodide with copper (I) species can lead to the formation of **K** which can undergo intermolecular *C-N* cross-coupling reaction[20] with unsubstituted cyanamide using base to give the intermediate **L** that can complete the catalytic cycle by reductive elimination to get target product aromatic cyanamide (**2a**).

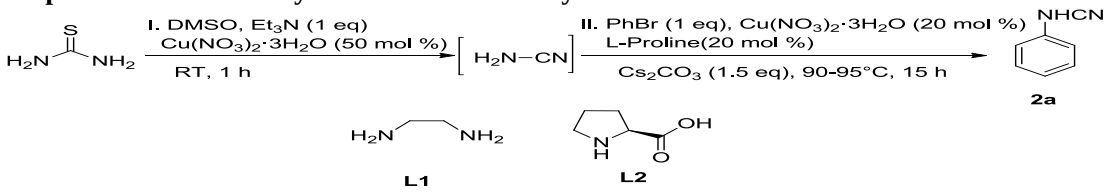
Table 1: Optimization for the synthesis of unsubstituted cyanamides[a]



Entry	Solvent	Copper source	Conversion (%)[a] 1
1	EtOH	CuI	100
2	EtOAc	CuI	100
3	*n*-Hexane	CuI	n.d
4	*n*-Heptane	CuI	n.d
5	H_2O	CuI	60
6	DMF	CuI	100
7	DMSO	CuI	100
8	DMSO	CuCl	100
9	DMSO	CuBr	100
10	DMSO	$Cu(NO_3)_2{\cdot}3H_2O$	100
11	DMSO	$Cu(OAc)_2.H_2O$	100
12[c]	DMSO	$Cu(NO_3)_2{\cdot}3H_2O$	100
13[d]	DMSO	$Cu(NO_3)_2{\cdot}3H_2O$	54
14	DMSO	-	n.d

[a]Reaction conditions: Thiourea (1 mmol), solvent (2 mL), Et_3N (1 eq), Copper source (1 eq), 1 h, room temperature.
[b]Conversion was confirmed by TLC.
[c]Copper source (50 mol %) used.
[d]Copper source (25 mol %) used. n.d. = not detected.

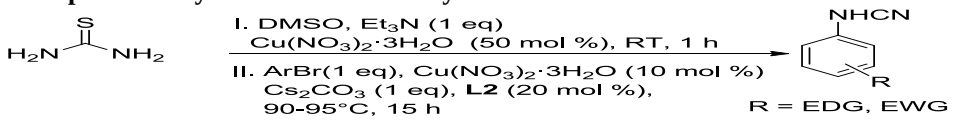
Table 2: Optimization for the synthesis of aromatic cyanamides[a]

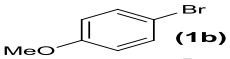
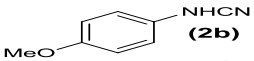
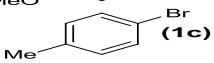
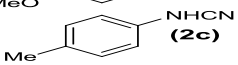
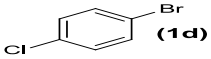
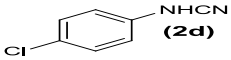
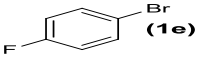
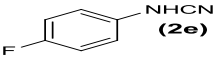
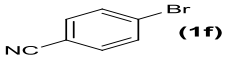
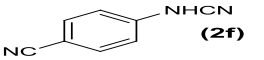
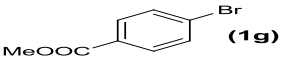
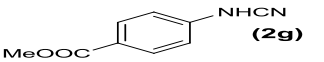
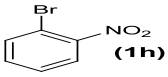
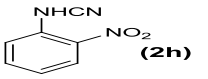
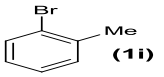
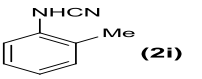
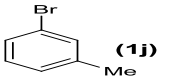
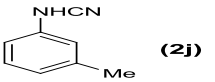
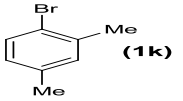
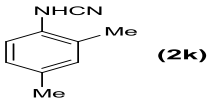


Entry	Solvent	Copper source	Base	Ligand	Conversion	
					1	2a
1	DMSO	CuI	$K_3PO_4{\cdot}3H_2O$	**L2**	30	70
2	DMSO	CuI	K_2CO_3	**L2**	40	60
3	DMSO	CuI	Cs_2CO_3	**L2**	n.d.	100
4	DMSO	CuI	Cs_2CO_3	**L1**	65	35
5	DMSO	CuBr	Cs_2CO_3	**L2**	n.d.	100
6	DMSO	CuCl	Cs_2CO_3	**L2**	n.d.	100
7	DMSO	$Cu(NO_3)_2{\cdot}3H_2O$	Cs_2CO_3	**L2**	n.d	100
8	DMSO	$Cu(OAc)_2{\cdot}H_2O$	Cs_2CO_3	**L2**	n.d.	100
9[c]	DMSO	$Cu(NO_3)_2{\cdot}3H_2O$	Cs_2CO_3	**L2**	35	65
10[d]	DMSO	$Cu(NO_3)_2{\cdot}3H_2O$	Cs_2CO_3	**L2**	35	75
11	DMSO	$Cu(NO_3)_2{\cdot}3H_2O$	Cs_2CO_3	-	75	25
12	DMSO	-	Cs_2CO_3	-	100	n.d.

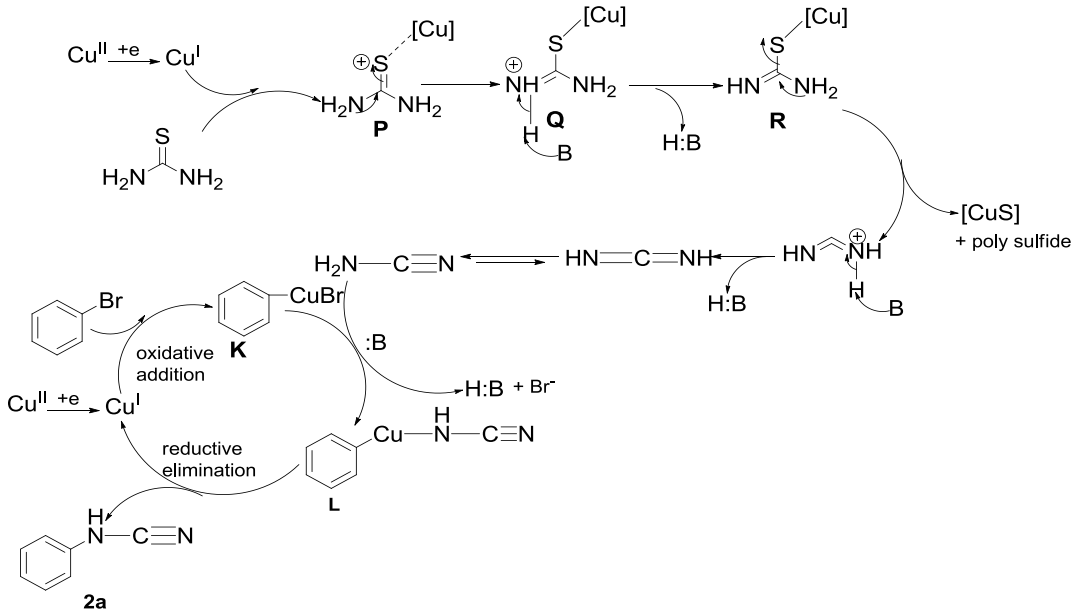
[a]Reaction conditions: Thiourea (1 mmol), solvent (2 mL), Et_3N (1 eq), $Cu(NO_3)_2{\cdot}3H_2O$ (50 mol %), 1 h, room temperature, then, catalyst (10 mol %), ligand (20 mol %), base (1.5 equiv), 15 h, 90-95°C.
[b]Conversion was confirmed crude ^1H NMR.
[c]Copper source (10 mol %) used.
[d]Cs_2CO_3 (1 equiv) used. n.d. = not detected.

Table 3: Substrate scope for the synthesis of aromatic cyanamides[a]



Entry	Substrate	Product	Yield[b]
1	 (1a)	 (2a)	80
2	 (1b)	 (2b)	85
3	 (1c)	 (2c)	85
4	 (1d)	 (2d)	70
5	 (1e)	 (2e)	67
6	 (1f)	 (2f)	40
7	 (1g)	 (2g)	40
8	 (1h)	 (2h)	55
9	 (1i)	 (2i)	74
10	 (1j)	 (2j)	72
11	 (1k)	 (2k)	83

[a]Reaction conditions: Thiourea (1 mmol), DMSO (3 mL), Et_3N (1 eq), $Cu(NO_3)_2{\cdot}3H_2O$ (50 mol %), 1 h, room temperature, then, $Cu(NO_3)_2{\cdot}3H_2O$ (10 mol %), ligand (20 mol %), base (1.5 eq.), 12 h, 90-95°C.
[b]Isolated yield.



Scheme 4: Proposed mechanism for formation of arylcyanamides.

CONCLUSION

In Conclusion we have developed a clean, neat and efficient methodology for the synthesis of aromatic cyanamides from thiourea using cheap, readily available and air stable copper source as catalyst under moderate reaction conditions. The reactions are rapid, facile and accomplished under mild reaction conditions. All the substrates could obtain their target products in good to excellent yields.

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