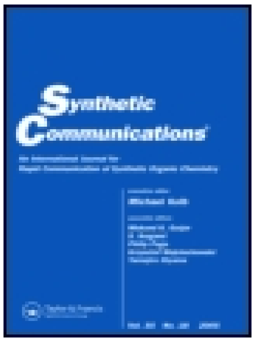

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One-pot three-component tandem reaction: Synthesis of aryl/alkyl cyanamides libraries and their further conversion into tetrazole derivatives

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ABSTRACT

We have developed methodology for the synthesis of aryl/alkyl cyanamides from amines in one-pot four steps reaction using cheap, readily available and air stable copper source as catalyst under mild reaction conditions. We have also studied the application of cyanamides. In this connection, we could construct aryl tetrazolamine from cyanamides using click reaction

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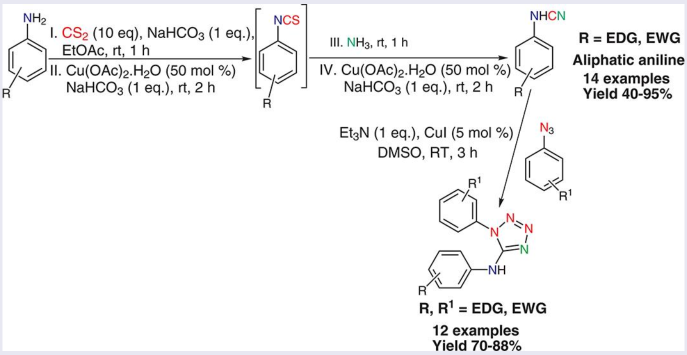
KEYWORDS
Copper catalyst; desulphurization; mild reaction conditions; room temperature; substituted cyanamides; tandem reaction

GRAPHICAL ABSTRACT



Introduction

In recent years, *N*-alkyl or *N*-aryl imides[1] and herbicides[2] were synthesized from cyanamides (RR^{1}N–CN), which are good intermediates and these are also useful for the synthesis of heterocyclic compounds that have biologically, medicinally and pharmaceutical importance.[3] It acts as a not only synthetic intermediate but also show apparent tumor growth inhibition activity.[4] Since the cyano group is easy removal from cyanamide, they regularly perform as a protecting groups in the construction of heterocycles, which are having secondary and tertiary amines.[5] Apart from that, synthesis of many reagents has been developed from cyanamides.[6]

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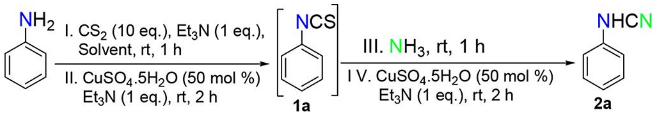
The classical method has been developed for the synthesis of cyanamides from the reaction between gaseous cyanogen halides and amines or imide salts.[7] In addition substituted cyanamides were prepared by the most general method through cyanation of amine using cyanogen halides, or synthon (CN^+).[8] Cyanamides are also obtained from different starting precursors such as ureas, thioureas,[9] amidoxims,[10] organic isocyanides, trimethylsilyl azide,[11] and *N,N*-disubstituted glycyclamide.[12] Recently, Yeh et al.[13] have developed in one-pot reaction for the manufacturing of cyanamides from isocyanate and isothiocyanate using deoxygenating or desulfurizing agent like sodium bis(trimethylsilyl)amide. Later, Patel et al.[14] reported for the synthesis of cyanamides from thiocarbamate salts using hyper valent iodine(III) reagent and Yeh et al.[15] demonstrated preparation of cyanamides from amines using sodium bis(trimethylsilyl)amide reagent. Most of the reports have used cyano cation (CN^+), which gets from toxic cyanogens 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 these referred disadvantages, the efficient method is needed. In this context, we wish to report high yielding one-pot synthesis of cyanamides from amines using cheap, readily available and air stable copper source as catalyst under mild reaction conditions.

Results and discussion

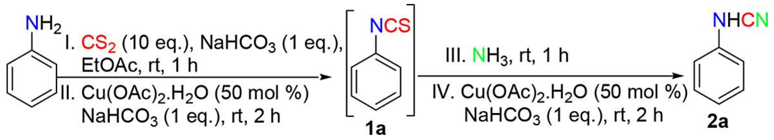
The optimization of the reaction conditions was performed with aniline as model substrate using different bases, solvents and copper sources at varied temperatures (Table 1). Aniline reacts with CS_2 followed by desulphurization using $Cu(OAc)_2 \cdot H_2O$ to afford phenyl isothiocyanate, which is confirmed by IR analysis (–NCS–2063 cm^{-1}) and it was reported by our group in recently.[17c] It reacts with aqueous ammonia solution and subsequent

Table 1. Solvent optimization.[a]



Entry	Solvent	Yield[b]	
		1a	**2a**
1	Ethanol	10	70
2	MeOH	10	70
3	Acetone	20	70
4	*n*-Hexane	NR	NR
5	*n*-Heptane	NR	NR
6	EtOAc	5	90
7	DMSO	5	85
8	DMF	20	50
9	H_2O	NR	NR
10	EtOAC/H_2O (1:1)	NR	NR
11	EtOAC/H_2O (1:2)	NR	NR
12	EtOAC/H_2O (2:1)	15	80
13	No solvent	NR	NR

[a] Reaction conditions: anline (2 mmol), CS_2 (10 eq.), Et_3N (2 eq.), $CuSO_4 \cdot 5H_2O$ (50 mol%) were stirred at room temperature in the presence of respective solvent for 3 h. Then, Aq NH_3 (2 mL), Et_3N (2 eq.), $CuSO_4 \cdot 5H_2O$ (50 mol%), rt, 3 h.
[b] Isolated yield. NR = no reaction.

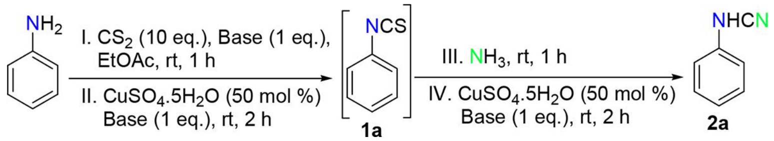


Scheme 1. Path way for the synthesis of aryl cyanamides.

desulfurization occurs in the presence of $Cu(OAc)_2 \cdot H_2O$ to give target product as phenyl cyanamide (Scheme 1).

Initially, the reaction was checked in the presence of different solvents. In case of polar protic solvent EtOH, the reaction could give target product **2a** in 70% yield (Table 1, entry 1) along with **1a** as intermediate in 10% yield. To increase the yield of the reaction we have checked the reaction in the presence of MeOH, acetone, ethyl acetate, DMSO, and DMF. Among them ethyl acetate gave better result than others. Finally we have done the reaction in the presence of green solvent H_2O and it did not give target product (Table 1, entry 9). In continuous of our solvent optimization, we have also examined non polar solvents like *n*-hexane and *n*-heptane. Unfortunately no conversion of the reaction could observe (Table 1, entries 4–5) and the starting material was recovered intact. Later, we have also examined the reaction in the presence of combination of solvents (Table 1, entries 10–12). The system, which contains lower amount of water than ethyl acetate (Table 1, entry 12) could give target product in good yield. Whereas other two solvent combinations [EA:H_2O (1:1 and 1:2)] did not give expected product. These results confirmed that little high amount of water gives negative effect. Later, various bases were also tested for this reaction. In case of organic base pyridine could give moderate yield. On the other hand all inorganic bases could give expected product in high yield (Table 2, entries 3–5). Control experiment is confirmed that no target product could observe in the absence of base and the starting material is recovered. Different copper sources were tested, both copper(I) and copper(II) sources could show similar effect (Table 3, entries 1–6). Less amount of catalyst could give target product in moderate yield (Table 3, entry 7). No reaction could observe in the absence of catalyst (Table 3, entry 8).

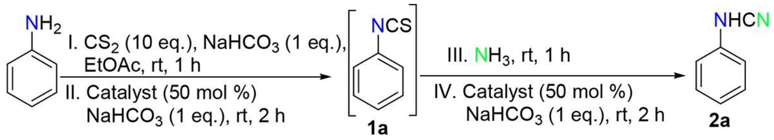
Table 2. Base standardization.[a]



Entry	Base	Yield[b] 1a	Yield[b] 2a
1	Et_3N	5	90
2	Pyridine	30	60
3	NaOAc	5	90
4	NaOH	5	90
5	$NaHCO_3$	5	90
6	No base	NR	NR

[a] Reaction conditions: anline (2 mmol), CS_2 (10 eq.), base (2 eq.), $CuSO_4 \cdot 5H_2O$ (50 mol%) were stirred at room temperature in the presence of EtOAc for 3 h. Then, Aq NH_3 (2 mL), base (2 eq.), $CuSO_4 \cdot 5H_2O$ (50 mol%), rt, 3 h.
[b] Isolated yield. NR = no reaction.

Table 3. Catalyst standardization.[a]



Entry	Catalyst	Yield[b]	
		1a	2a
1	$CuSO_4 \cdot 5H_2O$	5	90
2	$Cu(NO_3)_2 \cdot 3H_2O$	5	90
3	$Cu(OAc)_2 \cdot H_2O$	5	90
4	CuI	5	90
5	CuBr	5	90
6	CuCl	5	90
7[c]	$Cu(OAc)_2 \cdot H_2O$	15	60
8	No catalyst	ND	ND

[a] Reaction conditions: anline (2 mmol), CS_2 (10 eq.), $NaHCO_3$ (2 eq.), catalyst (50 mol%) were stirred at room temperature in the presence of EtOAc for 3 h. Then, Aq NH_3 (2 mL), $NaHCO_3$ (2 eq.), catalyst (50 mol%), rt, 3 h.

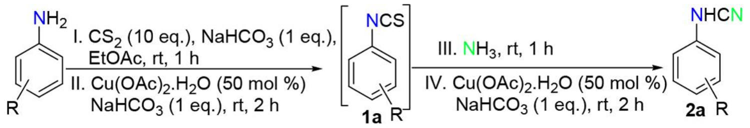
[b] Isolated yield.

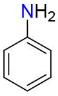
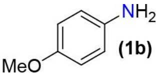
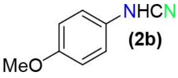
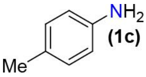
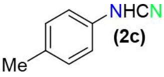
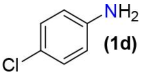
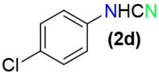
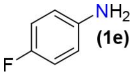
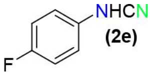
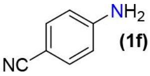
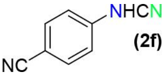
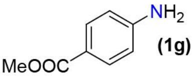
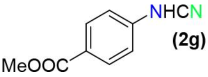
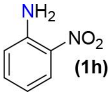
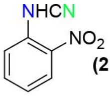
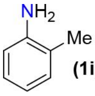
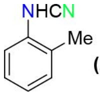
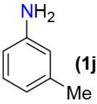
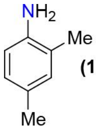
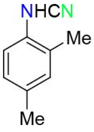
[c] Catalyst (25 mol%) was used. NR = no reaction.

Having the optimal conditions in our hand, we explored the substrate scope (Table 4). The amines having both electron donating and electron withdrawing substituents on the aryl rings could give their respective target products in moderate to high yield. The phenyl ring having electron donating groups such as 4-methoxy, 4-methyl could give their respective aromatic cyanamides (Table 4, entries 2–3) in 95% yield. The unsubstituted phenyl ring also gave target product in excellent yield (Table 4, entry 1). Electron withdrawing groups such as 4-chloro and 4-fluoro substituents gave their target products in 80 and 72% yields, respectively (Table 4, entries 4 and 5). Aryl ring bearing other strong electron withdrawing substituent's nitrile and ester could not give target products under optimized reaction conditions. But, very interestingly the reactions could give target product in moderate yield at higher temperature 70 °C (Table 4, enries 6-7). The aryl ring having strong electron withdrawing group $-NO_2$ on second position gave their final product in 60% yield at 80 °C (Table 4, entry 8). Ortho and meta substituted methyl groups on aryl ring could give their respective target products in 82–93% yields (Table 4, entries 9–10). Di-methyl substituent on aryl ring gave final product in 80% yield (Table 4, entry 11). Finally we have also studied about aliphatic anilines. The aliphatic substrates readily underwent the reaction to produce the target products in high yields (Table 4, entries 9–11).

The mechanism of formation for cyanamides from anilines is shown in Scheme 3. From the experimental evidence and from the literature reports the mechanism is proposed. As we shown in Scheme 3, aniline reacts with carbon disulfide using base and in the presence of solvent to give thiocarbomate salt **K**. It may help to reduce the copper(II) salt to copper (I) active species,[16] which may co-ordinate with thiocarbomate salt **K** and followed by the removal of proton to afford the intermediate **N** through other intermediates **L** and **M**. The desulphurization of **N** to get isothiocyanante, that reacts with ammonia to afford phenyl thiourea. It co-ordinates with Cu(I) species and followed by desulphurization to give target product along with byproduct CuS[17] and poly sulfide (the extra sulfur might have converted into sulfide) through intermediates **O** and **P**.

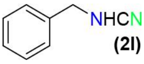
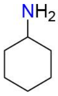
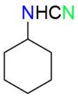
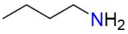
Table 4. Substrate scope for the synthesis of aryl/alkyl cyanamides.[a]



Entry	Substrate	Product	Isolated yield (%)[a] reported	Mp observed
1	 **(1a)**	 **(2a)**	90	Gummy
2	 **(1b)**	 **(2b)**	95	Gummy
3	 **(1c)**	 **(2c)**	95	Gummy
4	 **(1d)**	 **(2d)**	80	110–111 °C 111–112 °C
5	 **(1e)**	 **(2e)**	72	125–126 °C 124–126 °C
6	 **(1f)**	 **(2f)**	40	140–141 °C 141–142 °C
7	 **(1g)**	 **(2g)**	40	156–157 °C 157–158 °C
8	 **(1h)**	 **(2h)**	60	133–135 °C 134–135 °C
9	 **(1i)**	 **(2i)**	82	Gummy
10	 **(1j)**	 **(2j)**	93	Gummy
11	 **(1k)**	 **(2k)**	80	Gummy

(*Continued*)

Table 4. Continued.

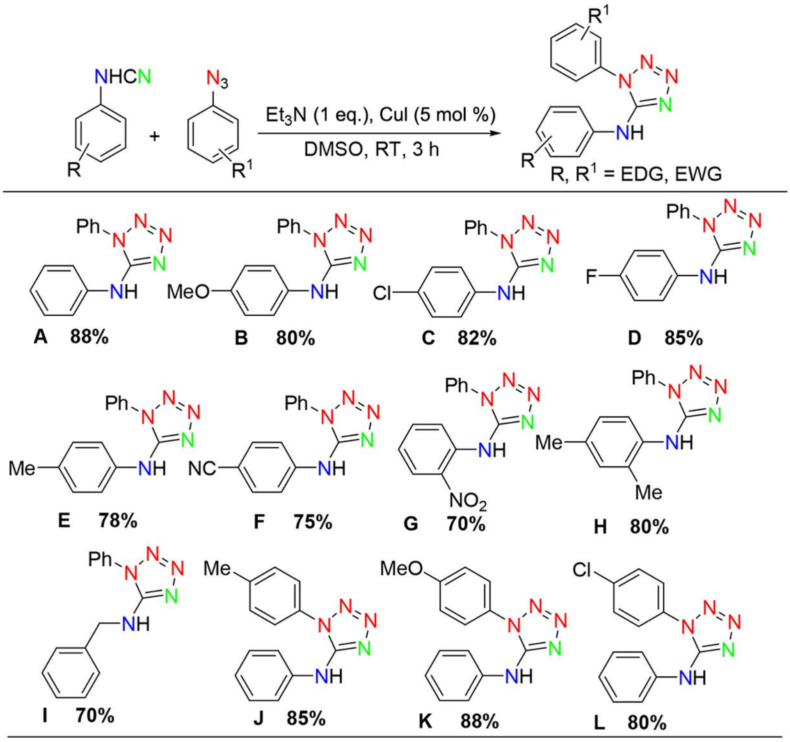
Entry	Substrate	Product	Isolated yield (%)[a] reported	Mp observed
12	 (1l)	 (2l)	92	Gummy
13	 (1m)	 (2m)	90	Gummy
14	 (1n)	 (2n)	90	Gummy

[a]Reaction conditions: amine (2 mmol), CS_2 (10 eq.), $NaHCO_3$ (2 eq.), $Cu(OAc)_2 \cdot H_2O$ (50 mol%) were stirred at room temperature in the presence of EtOAc for 3 h. Then, Aq NH_3 (2 mL), $NaHCO_3$ (2 eq.), $Cu(OAc)_2 \cdot H_2O$ (50 mol%), rt, 3 h.
[b]Isolated yield.

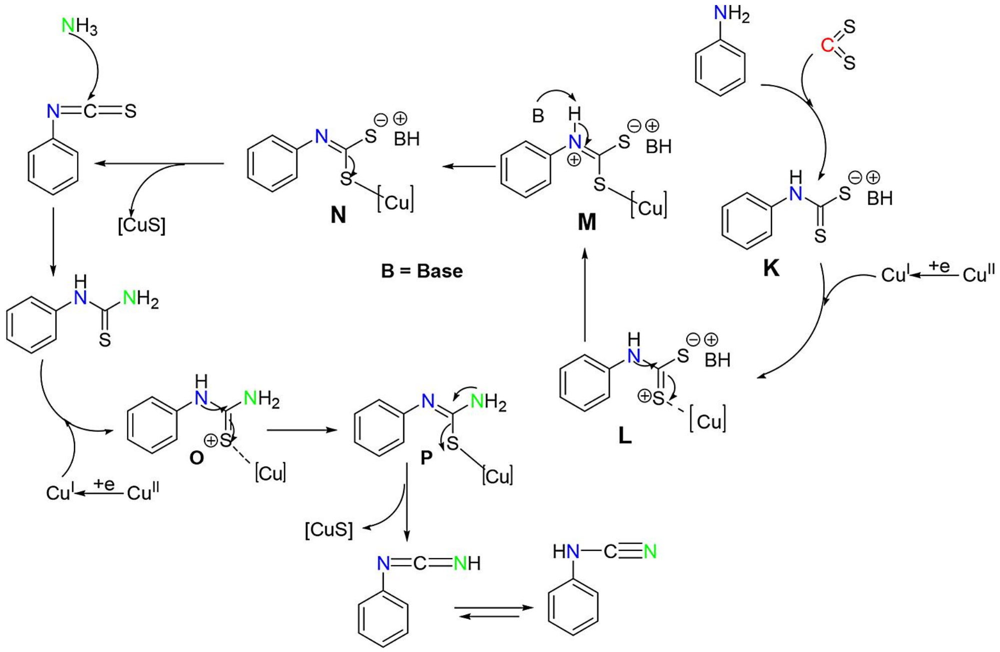
Soon after successfully preparation of aryl/alkyl cyanamides, we have interested to make substituted diaryltetrazoleamine from cyanamides through click reaction. Click chemistry[18]—"a modular synthetic approach toward the assembly of new molecular entities"—finds extensive applications, ranging from functionalizing biological molecules,[19] solubilizing carbon nanotubes,[20] to forming supramolecular assemblies.[21] Among these, in particular, five-membered nitrogen containing heterocyclic compounds substituted with 1,2,3-triazoles have been found to have industrial applications and biologically importance.[22] These compounds have been synthesized by Huisgen[23] 1,3-dipolar cycloaddition of azides with alkynes. Out of these, the copper(I)-catalyzed [3 + 2]-cycloaddition also known as click chemistry of organic azides and terminal alkynes is emerged method for the synthesis of substituted 1,2,3-triazole compounds.[24] Thus, this method has been developed by several groups using Cu(I) salts along with triphenylphospine,[25] mono- or polydentate ligands,[26] as *N*-heterocyclic copper carbene complexes.[27] Recently, few groups have also demonstrated through Cu(I) species with various supports such as silica,[28] zeolites,[29] amine-functionalized polymers,[30] and activated charcoal.[31] Cu(II) salts have been used in which the designed reaction conditions reduce the Cu(II) to Cu(I) by reducing agents such as sodium ascorbate,[32] elemental copper,[33] and phosphorus(III) agents.[34]

Tetrazoles are of noticeable interest in medicinal[35] applications and also applied as ligands in coordination chemistry,[36] and these are found in compounds bearing antiasthmatic,[37] antiviral, anti-inflammatory,[38] and antineoplastic.[39] Tetrazoles having pharmacological,[40] antiviral,[41] and receptor modulator[42] activities. Moreover, substituted tetrazoles (RCN_4H), may serve as a nonclassical isostere for the carboxylic acid moiety in biological active compounds.[43] Owing to their synthetic and medicinal importance the continuous and significant efforts are being made in this area.[44] In this contribution, we would like to report the compounds contain the above said moieties like diaryl tetrazoleamine from cyanamides using copper as catalyst.

In this connection, we could make substituted diphenyl tetrazolamine using click reaction under below shown reaction conditions (Scheme 2). The click reaction of both electron donating and electron withdrawing cyanamides with phenyl azide gave target products **A–I** in 70–88% yields. Similarly, the click reaction of substituted phenyl azides with phenyl cyanamide provide expected final products **J–L** in moderate to good yield.



Scheme 2. Synthesis of phenyl tetrazolamine.



Scheme 3. Proposed mechanism.

Experimental section

Representative experimental procedure for the synthesis of phenyl cyanamide

To a stirred solution of ethyl acetate (4–5 mL), aniline (2 mmol, 186 mg) was added in slowly and followed by carbon disulfide [20 mmol (10 eq.), 1520 mg or 1.21 mL] and sodium bicarbonate [2 mmol (1 eq.), 168 mg] were added at room temperature. The whole reaction mixture stirred for 1 h (until get the yellow color solid) at room temperature. Thiocarbomate formation was monitored by TLC. To this, $Cu(OAc)_2 \cdot H_2O$ (50 mol%, 199 mg) was added slowly followed by sodium bicarbonate [2 mmol (1 eq.), 168 mg] was added slowly for 10 min and the reaction mixture was stirred for 1 h. During this period, a black color precipitate (CuS) was observed and settles at bottom of round bottom flask. The progress of the reaction was investigated by TLC (5% ethyl acetate in hexane). After completion of the reaction, the reaction mixture was transferred into centrifuged tubes and the mixture was centrifuged for 10 min using centrifugation machine. Black color solid was removed from the centrifuged tubes. To that clear solution, ammonia sol (2 mL) was added slowly, and the reaction mixture stirred for 1 h. Later, $Cu(OAc)_2 \cdot H_2O$ (50 mol%, 199 mg) and sodium bicarbonate [2 mmol (1 eq.), 168 mg] were added to that previous solution. The whole reaction mixture stirred for 2 h at room temperature. During this period black color precipitate (CuS) was observed, and it was removed by centrifugation. The clear solution was concentrated using rotary evaporator and the crude mixture was purified by silica gel (60–120 mesh) column chromatography using ethyl acetate in hexane as eluent to obtain a phenyl cyanamide as gummy.

Phenylcyanamide **2a** (Table 4, entry 1)[45]: Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.8$; yield 90%; ^{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, 23.63.

Conclusion

In conclusion, the synthesis of various aromatic and aliphatic cyanamide's has been demonstrated. All the substrates performed under optimized reaction conditions and they could give their respective target product in moderate to good yield. To extend our chemistry we have also accomplished the click reaction between cyanamides and azides.

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