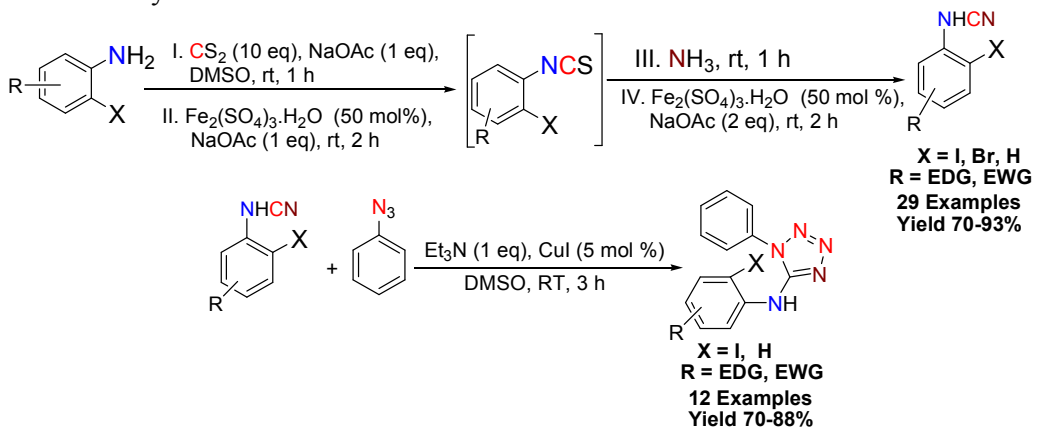
Heterocyclic Letters
Vol. 8| No.4|793-804|Aug-Oct|2018
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF CYANAMIDES LIBRARIES AND FURTHER CONVERSION INTO TETRAZOLE COMPOUNDS *VIA* CLICK-CHEMISTRY

Srinivasa rao Pinapati,[a] Usha rani Mandapati,[a] Ramana Tamminana[b] and Ramesh raju Rudraraju*[a]

[a] *Department of Chemistry, Acharya Nagarjuna University, Nagar,Guntur, AP-522510, India.*
[b] *Department of Chemistry, GIATM University, Bengaluru Campus, Karnataka-561203, India.*
Email: rameshrajurudraraju716@gmail.com

Abstract
The synthesis of 2-halo aromatic/aryl/alkyl cyanamides has been demonstrated in the presence of transition metal under mild reaction conditions. Further, tetrazole compounds have also been constructed from cyanamides through click-reaction. All electron donating and withdrawing substituent's readily underwent the reaction to give target products in good to excellent yield.



Keywords
Cyanamides; Tetrazole compounds; Iron catalyst; Desulphurization; Multistep reaction

Introduction

Due to its unique reactivity, cyano group is recognized as important building block and is found in various bioactive molecules and functionalized materials.[1] Cyanamides are useful precursors and important synthetic intermediates for the synthesis of biological, medicinal and pharmaceutically important heterocycles.[2] Since the cyano group is easy removal from

cyanamide and *N*-alkyl or *N*-aryl imides,[3] they often represent as a useful protecting groups in the synthesis of secondary and tertiary amines containing heterocycles.[4]

In recent times aromatic cyanamides are achieved from cyanogen halides, or its synthon (CN^-),[5] which are obtained from 2-chlorobenzyl thiocyanate,[6] 1-cyanoimidazole,[7] 2-cyanopyridazin-3-(2*H*)-ones,[8] 1-cyanobenzotriazole and me-tal cyanide,[9] 2-cyanopyridazin-3-(2*H*)-ones,[10] tosylcyanide,[11] thiocyanogen,[12] and cyanogens azide.[13] In an alternative approach, cyanamides are synthesized from ureas and thioureas.[14] The cyanamides are also prepared from organic isocyanides and trimethylsilyl azide via a Si–N bond cleavage catalyzed by $[\{(\eta^3\text{- } C_3H_5)PdCl\}_2]$,[15] 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[16] and from amidoximes through Tiemann rearrangement.[17] Very recently, Akamanchi and co- authors have developed method for the synthesis of cyanamides using a pentavalent iodine reagent in the presence of tetra ethyl ammonium bromide at ambient temperature,[18] Patel and co-authors also have demonstrated synthesis of cyanamides using hypervalent iodine (III) as catalyst.[19] Some other methods are known for the preparation of cyanamides.[20] However most of the reported methods required highly toxic cyanogen halides and using extremely alkaline reaction conditions, expensive reagents, high reaction temperatures giving low yields, and involving tedious purification procedure. To overcome the above mentioned draw backs, here in we report the synthesis of 2-haloaromatic/aryl/alkyl cyanamides through three component in one pot four steps reaction using iron source as catalyst under milder reaction conditions. Iron is cheap, readily available, air stable catalyst and it acts as a mild oxidizing capability similar to Mercury and Thallium based reagents and hence it is a suitable alternative to toxic, heavy metal-based reagents. Recently we also developed methodology for the synthesis of halo isothiocyanates in the presence of iron catalyst;[23a] therefore in order to extend of our chemistry herein we report methodology for the synthesis of 2-halo aromatic cyanamides from 2-halo amines using iron as catalyst. To the best of our knowledge no report is available for the synthesis of 2-halo aromatic cyanamides in the presence of iron catalyst.

Experimental

Aniline, CS_2, $FeCl_3$, $Fe(NO_3)_3.9H_2O$, $Fe_2(SO_4)_3.H_2O$, $FeCl_2$, Et_3N, Pyridine, sodium bicarbonate were purchased from Aldrich and used without further purification. The solvents were purchased and dried according to standard procedure prior to use. ^{1}H NMR (400 MHz) spectra were recorded with a Varian 400 spectrometer. Infrared (IR) spectra recorded on a Perkin Elmer Spectrum one FT-IR spectrometer. Elemental analyses were recorded with Perkin Elmer CHNS analyzer. VKSI Medico Centrifuge machine was used for our experimental procedure for the synthesis of 2-halo arylcyanamides.

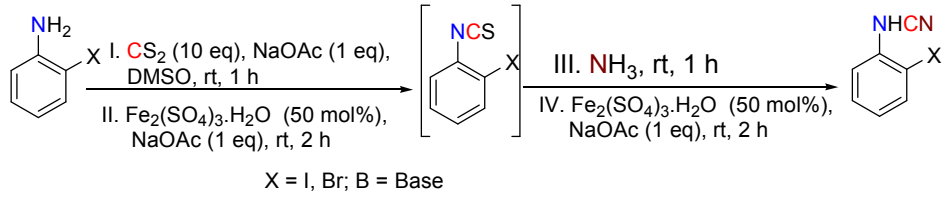
General Procedure for 2-haloarylcyanamide: To a stirred solution of DMSO (4-5 ml), respective 2-haloaniline (2 mmol) was added in slowly and followed by carbon disulphide (20 mmol (10 eq), 1520 mg or 1.21 ml) and sodium acetate (2 mmol (1 eq), 164 mg) were added at room temperature. The whole reaction mixture stirred for one hour (until get the yellow color solid) at room temperature. Thiocarbomate formation was monitored by TLC. To this, $Fe_2.(SO_4)_3.H_2O$ (50 mol%, 399 mg) was added slowly followed by sodium acetate (2 mmol (1 eq), 164 mg) was added slowly for 10 min and the reaction mixture was stirred for 1 h. During this period, a black color precipitate (FeS) was observed and settles at bottom of round bottom flask. The progress of the reaction was investigated by TLC (5% ethylacetate in hexane). After finish 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 removed from the centrifuged tubes. To that clear solution, Ammonia sol (2 ml) was added slowly. And then the reaction mixture stirred for 1 h. After 1 h, $Fe_2.(SO_4)_3.H_2O$

(50 mol%, 399 mg) and sodium acetate (2 mmol (1 eq), 164 mg) were added to that previous solution. The whole reaction mixture stirred for 2 h at room temperature. During this time black color precipitate (FeS) was observed. And it was removed by centrifugation. The clear solution was concentrated by using rotary evaporator and the crude mixture was purified by silica gel (60-120 mesh) column chromatography using Ethylacetate in Hexane as eluent to obtain a 2-halophenyl cyanamide as white solid.

General Procedure for the Synthesis of Diphenyl Tetrazole Amine: To a stirred solution of DMSO (4 ml), aryl cyanamide (1 mmol) was added slowly and followed by aryl azide (1 mmol) was added at room temperature. To that Et_3N (1 mmol, 121 mg) and CuI (5 mol %, 9.9 mg) were added. The whole reaction mixture stirred for 3 h. The resulted clear solution was washed with ethyl acetate (10 ml) and water (7 ml) for 3 times; and organic layer 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 a diphenyl tetrazole amine as a target product, which was characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy analysis.

Results and discussion

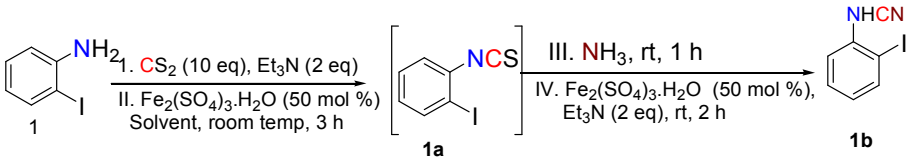
2-Haloaniline reacts with CS_2 followed by desulphurization using $Fe_2(SO_4)_3.H_2O$ to afford 2-halophenyl isothiocyanate, which is confirmed by IR analysis (-NCS: 2063 cm^{-1}).[21] It reacts with aqueous ammonia and followed by another desulfurization occurs to give target product as 2-halophenyl cyanamide using Fe_2 $(SO_4)_3.H_2O$ (Scheme 1).



Scheme 1. The reaction path way for the preparation of aromatic 2-halo cyanamides

The optimization of the reaction conditions was carried out with 2-iodoaniline as model substrate using different bases, solvents and iron at room temperature (Table 1). Initially, the reaction was checked in the presence of different solvents. In case of polar protic solvent EtOH, the reaction could give conversion 20%, which contains 10% isothiocyanate as intermediate **1a** and 10% target product **1b** (Table 1, entry 1). In order 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 DMSO solvent could give target product **1b** in 90% conversion (Table 1, entry 7). Rest of the percentage contains the mixture of isothiocyanate and starting material. Finally we have done the reaction in the presence of green solvent H_2O and it didn't give target

Table 1. Solvent optimization[a]



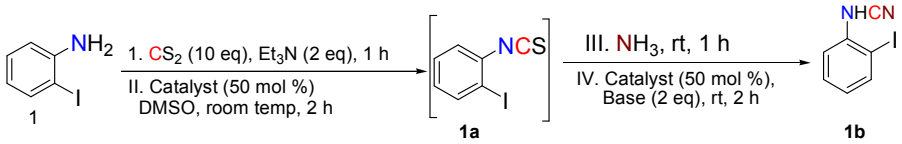
Entry	Solvent	Conversion (%)[b]	
		1a	1b

1	Ethanol	10	10
2	MeOH	10	10
3	Acetone	10	10
4	n-Hexane	NR	NR
5	n-Heptane	NR	NR
6	Ethyl acetate	40	35
7	DMSO	5	90
8	DMF	20	50
9	H_2O	NR	NR
10	Without solvent	NR	NR

[a]Reaction conditions: 2-Iodoaniline (2 mmol), CS_2 (10 eq), Et_3N (2 eq), $Fe_2(SO_4)_3.H_2O$ (50 mol %) were stirred at room temperature in the presence of respective solvent (4 ml) for 3 h, then, aq ammonia (2 ml), Et_3N (2 eq), $Fe_2(SO_4)_3.H_2O$ (50 mol %) were stirred at room temperature for 3 h. [b] conversion based on diagnostic peaks integration in ^{1}H NMR of crude react-ion mixture. NR: no reaction. (Note: 1. Entries 4-5 reactions didn't give thiocarbomate salt also. 2. The remaining percentage of all reactions exist thiocarbamate).

product (Table 1, entry 9). In continuous of our solvent optimization, we have also examined non polar solvents like n-hexane and n-heptane. Since 2-iodoaniline didn't dissolve in non-polar solvents, no thiocarbomate salt was occurred (Table 1, entry 4-5) and the starting material was recovered intact. Finally, the reaction was performed in the absence of solvent and the reaction didn't proceed 1st step also and the starting material was recovered intact.

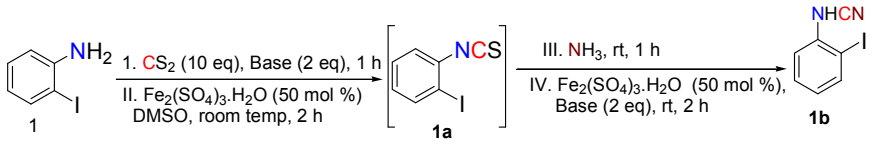
Table 2. Catalyst standardization



Entry	Catalyst	Conversion (%)[b]	
		1a	1b
1	$Fe_2(SO_4)_3.H_2O$	5	90
2	$Fe(NO_3)_3.9H_2O$	20	60
3	$FeCl_2$	30	40
4[c]	$Fe_2(SO_4)_3.H_2O$	40	30
5	Without catalyst	NR	NR

[a] Reaction conditions: 2-Iodoaniline (2 mmol), CS_2 (10 eq), Et_3N (2 eq), Catalyst (50 mol %) were stirred at room temperature in the presence of DMSO (4 ml) for 3 h, then, aq ammonia (2 ml), Et_3N (2 eq), Catalyst (50 mol %) were stirred at room temperature for 3 h. [b] conversion based on diagnostic peaks integration in ^{1}H NMR of crude reaction mixture. [c] Catalyst (25 mol %) was used

Table 3. Base optimization

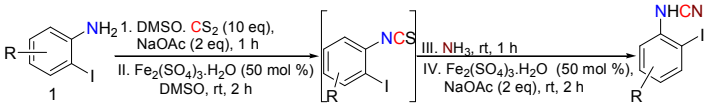


Entry	Base	Conversion (%)[b]	
		1a	1b

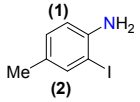
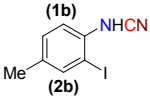
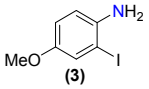
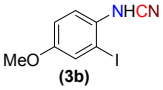
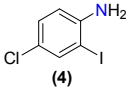
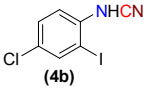
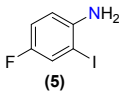
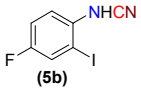
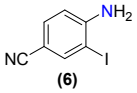
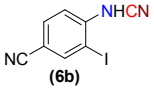
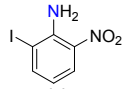
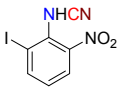
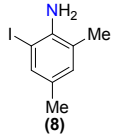
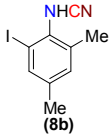
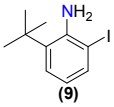
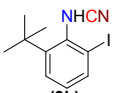
1	Et_3N	5	90
2	Pyridine	5	15
3	NaOAc	5	90
4	NaOH	20	50
5	$NaHCO_3$	30	50
6	Without base	NR	NR

Reaction conditions: 2-Iodoaniline (2 mmol), CS_2 (10 eq), base (2 eq), $Fe_2(SO_4)_3.H_2O$ (50 mol %) were stirred at room temperature in the presence of DMSO (4 ml) for 3 h, then, aq ammonia (2 ml), base (2 eq), [b] conversion based on diagnostic peaks integration in ^1H NMR of crude reaction mixture.

Table 4. Substrate scope for the construction of 2-iodo arylcyanamides



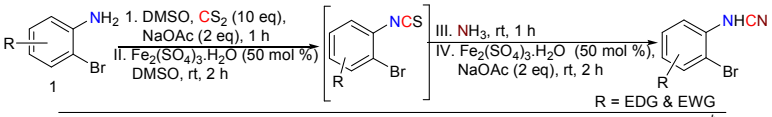
R = EDG & EWG

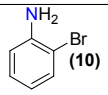
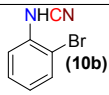
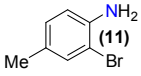
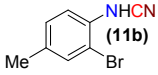
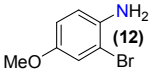
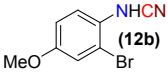
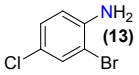
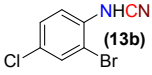
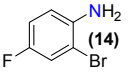
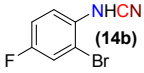
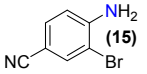
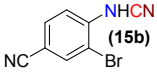
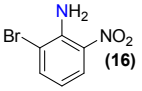
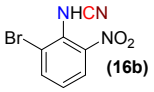
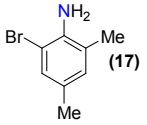
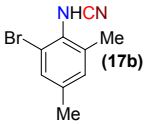
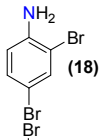
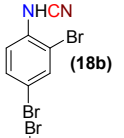
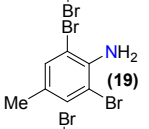
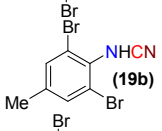
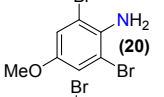
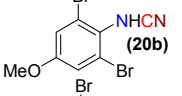
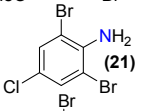
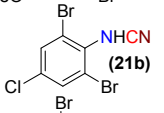
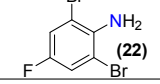
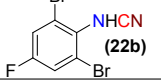
Entry	Substrate	Product	Isolated yield (%)[b]
1	 (1)	 (1b)	85
2	 (2)	 (2b)	85
3	 (3)	 (3b)	90
4[c]	 (4)	 (4b)	82
5[c]	 (5)	 (5b)	80
6[d]	 (6)	 (6b)	77
7[d]	 (7)	 (7b)	76
8	 (8)	 (8b)	80
9[c]	 (9)	 (9b)	79

[a] Reaction conditions: Substituted 2-iodoaniline (2 mmol), CS_2 (10 eq), NaOAc (2 eq), $Fe_2(SO_4)_3.H_2O$ (50 mol %) were stirred at room temperature in the presence of DMSO (4 ml) for 3 h, then, aq ammonia (2 ml), NaOAc (2 eq), $Fe_2(SO_4)_3.H_2O$ (50 mol %) were stirred at room temperature for 3 h. [b] Isolated yields. [c] The reactions were performed at 50 °C. [d] The reactions were performed at 70 °C and K_2CO_3

Later on, different iron sources effect was tested and $Fe_2(SO_4)_3.H_2O$ showed better activity (Table 2, entry 1) than other iron sources. We have also examined less amount of catalyst and the reaction could give expected product in less conversion (Table 2, entry 4). The reaction with other organic base pyridine could give expected product **1b** in 15% conversion (Table 3, entry 2). Later, the inorganic bases sodium bicarbonate, sodium acetate and sodium hydroxide activity was also checked. Among them sodium

Table 5. Substrate scope for the preparation of 2-bromoarylcyanamides[a]



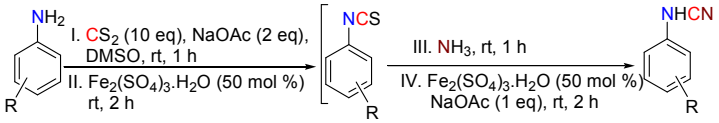
Entry	Substrate	Product	Isolated yield (%)[b]
1			80
2			80
3			85
4[c]			81
5[c]			77
6[d]			75
7[d]			72
8			75
9			70
10			80
11			80
12[c]			76
13[c]			74

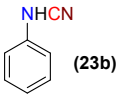
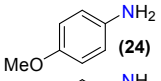
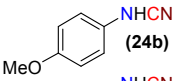
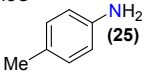
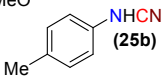
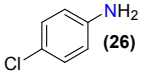
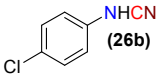
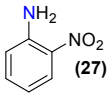
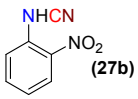
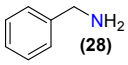
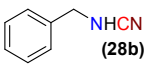
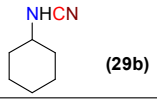
[a] Reaction conditions: Substituted 2-bromoaniline (2 mmol), CS_2 (10 eq), NaOAc (2 eq), $Fe_2(SO_4)_3.H_2O$ (50 mol %) were stirred at room temperature in the presence of DMSO (4 ml) for 3 h, then, aq ammonia (2 ml), NaOAc

(2 eq), $Fe_2(SO_4)_3.H_2O$ (50 mol %) were stirred at room temperature for 3 h. [b] Isolated yields. [c] The reactions were carried out at 60 °C. [d] The reactions were performed at 80 °C and K_2CO_3.

acetate is the best for this reaction and it could give target product **1b** in 90% conversion (Table 3, entry 3). The control experiment was confirmed that in the absence of solvent (Table 1, entry 10), iron salt (Table 2, entry 5) and base (Table 3, entry 6) no reaction was occurred.

Table 6. Substrate scope for the synthesis of aryl/alky cyanamides[a]

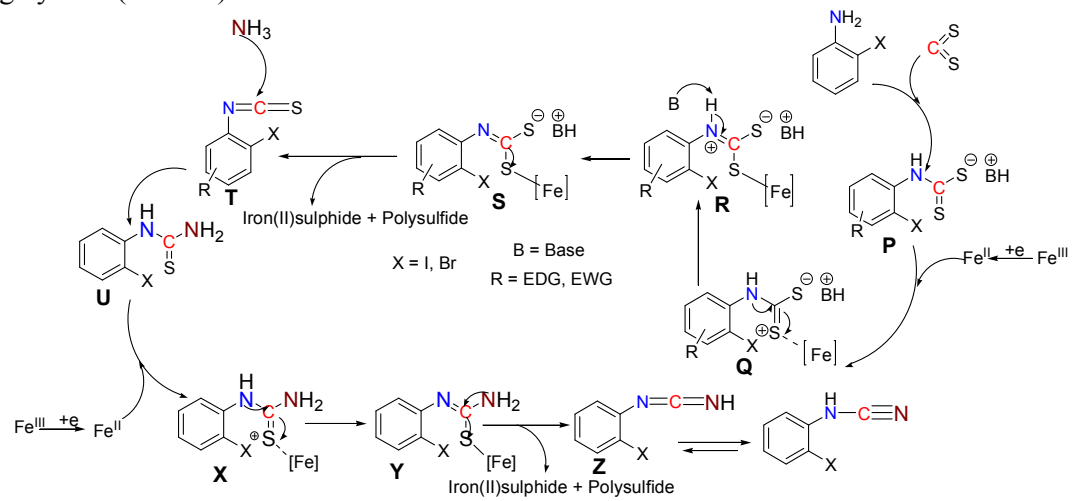


Entry	Substrate	Product	Isolated yield (%)[a]
1	 **(23)**	 **(23b)**	90
2	 **(24)**	 **(24b)**	93
3	 **(25)**	 **(25b)**	91
4[c]	 **(26)**	 **(26b)**	85
5[d]	 **(27)**	 **(27b)**	78
6	 **(28)**	 **(28b)**	92
7	 **(29)**	 **(29b)**	90

[a]Reaction conditions: Substituted amine (2 mmol), CS_2 (10 eq), NaOAc (2 eq), $Fe_2(SO_4)_3.H_2O$ (50 mol %) were stirred at room temperature in the presence of DMSO (4 ml) for 3 h, then, aq ammonia (2 ml), NaOAc (2 eq), $Fe_2(SO_4)_3.H_2O$ (50 mol %) were stirred at room temperature for 3 h. [b] Isolated yields. [c] The reaction were carried out at 60 °C. [d] The reactions were performed at 80 °C and K_2CO_3.

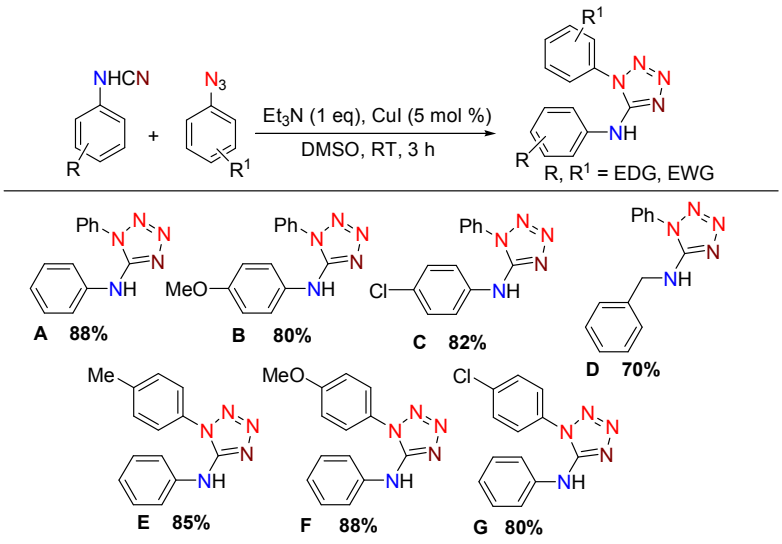
Having the optimal conditions in our hand, we explored the scope of this procedure for the substrates having electron donating and electron withdrawing substituent's on the aryl rings. The phenyl ring having electron donating groups such as 4-methyl (**2**), 4-methoxy (**3**) could give their respective aromatic cyanamides (**2b** and **3b**; Table 4, entries 2-3) in 85-90% yield. The unsubstituted phenyl ring (**1**) also gave target product in 85% yield (**1b**; table 4, entry 1). Electron withdrawing groups on aryl ring gave their respective target products in moderate yield under optimized reaction conditions. Therefore in order to increase the yield of them we have done the optimization. Very interestingly weak electron withdrawing substituents such as 4-chloro (**4**), 4-fluoro (**5**) gave their final products in high yield at 50 °C, where as the strong electron withdrawing groups like 4-cyano (**6**) and 2-nitro (**7**) gave expected products in good yield at 70 °C and using K_2CO_3 as strong base. Aryl ring bearing disubstituted methyl group (**8**) could give final cyanamide (**8b**) in 80% yield. Finally we have done the

reaction with the phenyl ring having bulky *t*-Bu group at ortho position and it could give their respective target product in 65% yield. It might be due to the presence of bulky *t*-Bu group near to the reactive site. But, yield of the reaction dramatically improved to 79%, when the reaction was performed at moderate temp 50 °C (Table 4, entry 9). Soon after successfully finish the synthesis of 2-iodoaromatic cyanamides, we became interested to develop the construction of bromo aromatic cyanamides. In this connection various substituted monobromo and dibromo aromatic cyanamides have been constructed under above shown reaction conditions and the results are shown in Table 5. All the substrates could obtain their respective cyanamides **10b-22b** in 70-85% yields.As we mentioned in the introduction, this is the new report for the synthesis of 2-haloaryl cyanamides. Therefore we could synthesize library of bromo/iodo aryl cyanamides. Finally, we have also checked with non-halogenated amines under optimized reaction conditions. Very interestingly both aryl/alkyl amines were carried out under optimized conditions to afford their respective target products in good to high yields (Table 6).

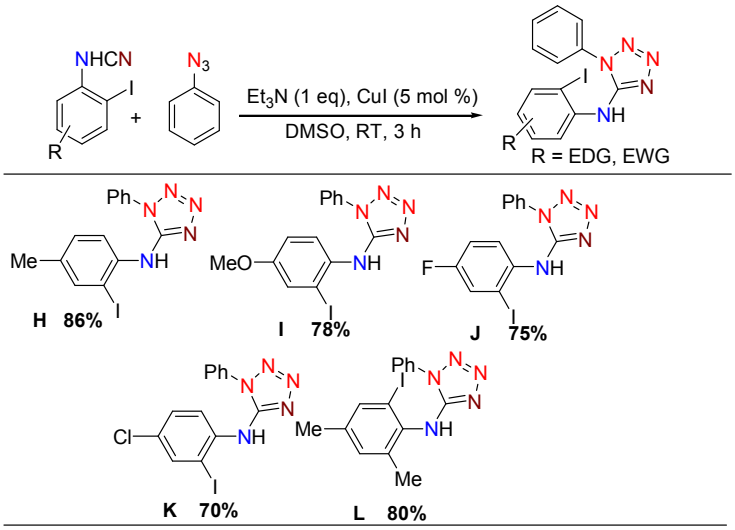


Scheme 2. Plausible mechanism

The mechanism of formation for cyanamides from amines is shown in scheme 2 (See supporting information). The experimental evidence and from the literature reports, the mechanism is proposed. As we shown in Scheme 1, 2-haloaniline reacts with carbondisulphide in the presence of base (sodium acetate) and respective solvent (DMSO) to give thiocarbonate salt **P**. It may help to reduce the iron (III) salt to iron (II) active species,[21] which may co-ordinate with thiocarbonate salt P and followed by remove the proton then afforded the intermediate **S** via intermediate complexes **Q** and **R**. The intermediate **S** may give isothiocyanate **T**, which reacts with ammonia to afford thiourea **U**. Desulfurization[22] of **U** afforded the target product **Z** along with byproducts FeS and polysulfide (the extra sulfur might have converted)[23] *via* intermediate complexes **X** and **Y** using iron salt. Still we are examining the mechanism for confirmation of FeS.



Scheme 3. The reaction between arylcyanamides and aryl azides



Scheme 4. The reaction between 2-iodoarylcyanamides and phenyl azide

Soon after successfully preparation of aryl/alkyl cyanamides, we have interested to make substituted diaryltetrazoleamine from cyanamides *via* click reaction. In chemical synthesis Click Chemistry[24]- is one of the approaches towards the assembly of nitrogen containing heterocyclic compounds,[25-26] which have been found to have industrial applications and biological applications.[27] Thus, several groups have demonstrated using Cu(I) salts along with triphenylphospine,[28] mono- or polydentate ligands,[29] as *N*-heterocyclic copper carbene complexes.[30] In addition, other groups have also developed Cu(I) species with various supports such as silica,[31] zeolites,[32] amine-functionalized polymers[33] and activated charcoal.[34] In this connection, we could make substituted diphenyl tetrazolamine using click reaction with our prepared starting precursors (aromatic cyanamides) and aryl azides under below shown reaction conditions (Scheme 3). The click reaction of both electron donating and electron withdrawing cyanamides with phenyl azide gave target products **A-D** in 70-88% yields. Similarly, the click reaction of substituted phenyl azides with phenyl cyanamide provide expected final products **E-G** in 80-88% yields. Additionally, we have also prepared

other substituted tetrazole compounds **H-L** from the reaction between 2-Iodoarylcyanamides and phenyl azide *via* click reaction (Scheme 4).

Conclusion

In conclusion, we have developed general, clean and efficient methodology for the synthesis of 2-halo aromatic/aryl/alkyl cyanamides. Although the overall isolated yields look moderate, considering that the reactions are multi processes, the yields are in fact good to excellent. Many reports are available for the preparation of cyanamides, however, the simplicity, environmental acceptability and cost effectiveness of the iron makes this method more practical. During the reaction process we couldn't observe any other byproducts (no other products could observe except cyanamide only).

Acknowledgments

Authors thank to the University Grants Commission-Hyderabad for giving opportunity to avail Faculty Development Programme and generous financial support and Acharya Nagarjuna University for providing place to carry out my experimental work.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Received on October 29, 2018,