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SYNTHESIS OF 2-ARYL THIO ARYL CYANAMIDES FROM 2-IODO ARYL ISOTHIOCYANATES IN ONE POT THREE COMPONENT REACTION BY USING IRON AS A CATALYST

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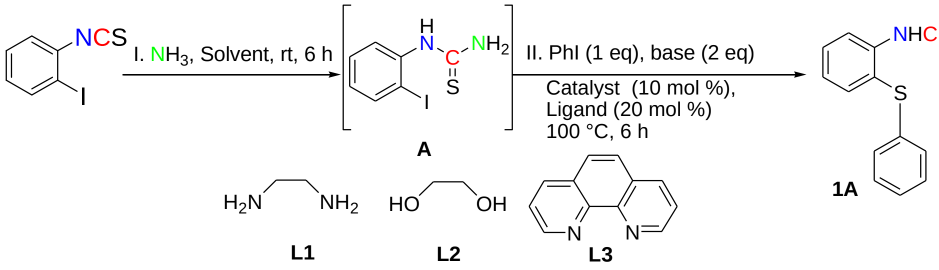
INTRODUCTION

Due to its unique reactivity, cyno 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 hetero-cycles.[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] Aromatic cyanamides have also been prepared by both classical and ancient methods.[5]

In recent years, the formation of carbon-heteroatom bonds[6] towards the synthesis of heterocyclic compounds has been developed through cross-coupling reactions using transition-metal-catalysis. Among these, carbon-sulfur bond formation has received much attention due to the presence of this moiety in many molecules that are of biological, pharmaceutical and material interest.[7] Recently the above said moieties containing compounds like 2-(arylthio) aryl cyan-amides from 2-halophenyl thiourea via domino C-S cross-coupling reaction using copper as catalyst.[8] But to the best of our knowledge no one has reported in the presence of iron.

Therefore, herein, we wish to demonstrate the one-pot synthesis of 2-(arylthio) aryl cyanamides from 2-iodoaryl isothiocyanate and aryl iodides using cheap, readily available and air stable iron source as catalyst under milder conditions.

Table 1: Standardization for the reaction conditions.

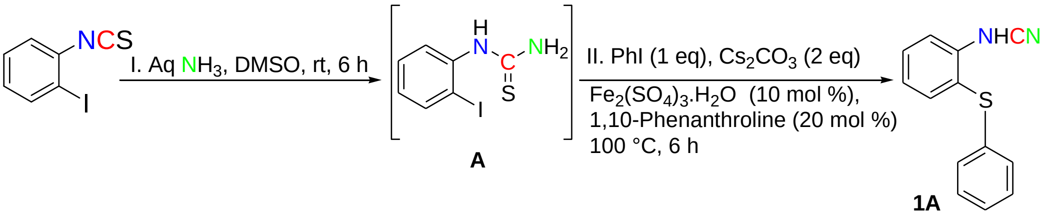


Entry	Solvent	Catalyst	Base	Ligand	Conversion[b]	
					A	1A
1	EtOH	$Fe_2(SO_4)_3.\ H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	100	n.d.
2	EtOAc	$Fe_2(SO_4)_3.\ H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	100	n.d.
3	n-Hexane	$Fe_2(SO_4)_3.\ H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	n.d.	n.d.
4	n-Heptane	$Fe_2(SO_4)_3.\ H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	n.d.	n.d.
5	H_2O	$Fe_2(SO_4)_3.\ H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	70	n.d.
6	DMF	$Fe_2(SO_4)_3.\ H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	45	55
7	DMSO	$Fe_2(SO_4)_3.\ H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	45	55

8	DMSO	$Fe_2(SO_4)_3$. H_2O	KOH	L3	25	75
9	DMSO	$Fe_2(SO_4)_3$. H_2O	K_2CO_3	L3	40	60
10	DMSO	$Fe_2(SO_4)_3$. H_2O	Cs_2CO_3	L3	n.d.	100
11	DMSO	$Fe_2(SO_4)_3$. H_2O	Cs_2CO_3	L1	75	25
12	DMSO	$Fe_2(SO_4)_3$. H_2O	Cs_2CO_3	L2	55	45
13	DMSO	$Fe(NO_3)_3.9H_2O$	Cs_2CO_3	L3	n.d.	100
14	DMSO	$FeCl_2$	Cs_2CO_3	L3	n.d.	100
15[c]	DMSO	$Fe_2(SO_4)_3$. H_2O	Cs_2CO_3	L3	50	50
16[d]	DMSO	$Fe_2(SO_4)_3$. H_2O	Cs_2CO_3	L3	35	65
17	DMSO	$Fe_2(SO_4)_3$. H_2O	Cs_2CO_3	-	79	21
18	DMSO	-	Cs_2CO_3	-	100	n.d.

[a]Reactionconditions: 2-Iodophenyl isothiocyanate (1 mmol), solvent (2 mL), Aq NH_3 (2 ml), 6h, room temperature, then, iodo benzene (1 mmol), catalyst (10 mol %), ligand (20 mol %), base (2 mmol), 6 h, 100 °C. [b] Isolated yield. [c] Catalyst (5 mol %) was used. [d] Cs_2CO_3 (1.5 equiv) was used. n.d. = not detected.

2-Iodo phenyl isothiocyanate reacts with aq ammonia in the presence of DMSO to afford 2-iodo phenyl thiourea as an intermediate, which reacts with iodo benzene using iron source as catalyst under below shown reaction conditions to obtain the target product as 2-phenylthio phenyl cyanamide via domino intra and inter molecular C-S cross-coupling reaction (**Scheme 1**).



Scheme 1

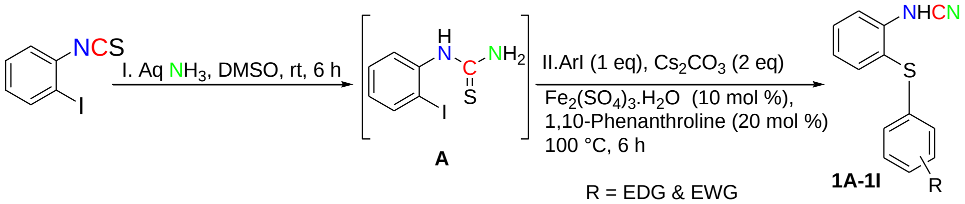
Initially, the optimization of the reaction conditions was performed using 2-iodophenyl isothiocyanate as model substrates with different solvents at room temperature (Step 1). We could observe that that the substrate proceeded reactions with aq NH_3 and in the presence of EtOH, EtOAc, DMF and DMSO at room temperature to get the corresponding thiourea A in complete conversion, that, gratifyingly, proceeded an domino intra and inter molecular C-S cross-coupling reaction with iodobenzene using 10 mol % $Fe_2(SO_4)_3$. H_2O, 20 mol % Ligand (1,10-Phenthralene) and 2 equiv Cs_2CO_3 at 100 °C temperature to give target product 1A in complete conversion. In case of solvent optimization, non-polar solvents like n-hexane and n-heptane couldn't proceed the reaction. Green solvent H_2O could give thiourea (1st step) in 70% conversion, that couldn't proceed the domino C-S cross-coupling reaction (2nd step). Various bases were examined and among them Cs_2CO_3 could give target product in complete conversion (Table 1, entry 10). Other bases ($K_3PO_4·3H_2O$, K_2CO_3 and KOH) could give less effect for the formation of target product. In a set of ligands L1-L3 screened, L3 was found to be the most effective in comparison to L1-L2 (Table 1, entries 11-12). Both iron (II) and iron (III) sources ($Fe_2(SO_4)_3$. H_2O, Fe $(NO_3)_3.9H_2O$ and FeCl2) exhibited a similar catalytic activity (entries 10 and 13-14). Lowering the amount of base (1.5 equivalent) or the iron source (5 mol %) led to the domino C-S cross-coupling reaction to afford target product in less conversion (Table 1, entries 15-16). The reaction was also checked in the absence of ligand, unfortunately, the reaction could give target product in 21% conversion only (Table 1, entry 17). Control experiments confirmed that the reaction didn't proceed (step 2) in the absence of the catalyst and ligand and the thiourea was recovered intact (Table 1, entry 18).

Having optimization reaction conditions in our hand, we further pursued the scope of the process with respect to the other substrates. Aryl iodides having electron donating groups 4-Me and 4-OMe proceeded reactions to afford their domino coupled products 1B and 1C in 95% and 97% yields, respectively. Aryl iodides bearing weak electron withdrawing substituent's 4-Cl and 4-F could give their respective target products 1D and 1E in 91% and 88%. Aryl iodides possess strong electron withdrawing groups 2-NO_2 and 4-CN gave their final products in less yield. It might be occurred as these have strong electron withdrawing capacity. Finally, we have also checked reaction with 2,4-diMe iodobenzene and it could give target product in decent yield. Aryl iodide contain bulkier group 2-^{t}Bu carried out the reaction under optimized reaction conditions to give respective 2-(arylthio) aryl cyanamide 1I in 82% yield. Similarly, phenyl isothiocyanate bearing 4-Me, 4-OMe, 4-Cl, 4-F, 4-CN, 2-NO_2, 2,4-di-Me, 3,4-di-Me and 2-^{t}Bu substituents readily carried out reaction with iodobenzene to give their final products 1J-R in 70-95% yields. The above-mentioned results clearly confirm that the substrates having electron donating

and –withdrawing groups are compatible with this process to afford the substituted 2-(arylthio) aryl cyanamides in good to high yield.

According to literature reports and experimental evidence the mechanism is proposed (Scheme 2). 2-Iodophenyl isothiocyanate reacts with aqueous NH_3 to provide *N*-2-iodophenyl thiourea A, which can undergo oxidative addition with Iron(I) species (thiourea may reduce Iron (III) to Iron(I) active species) to yield Iron(III) intermediate P. It may give 2-aminobenzothiozole X through intramolecular *C-S* cyclization using base via intermediate Q. On the other hand, iodobenzene can undergo oxidative addition with Iron(I) species to give intermediate R, which can carry out inter molecular *C-S* cross-coupling reaction with 2-aminobenzothiozole X to afford intermediate S that can complete catalytic cycle via reductive elimination to obtain 2-arylthio aryl cyanamide 1A.

Table 2: Substrate scope for the synthesis of 2-arylthio aryl cyanamides.



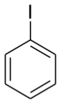
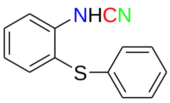
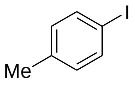
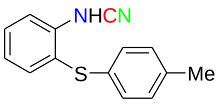
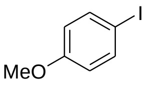
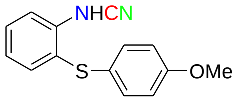
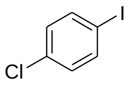
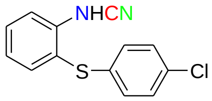
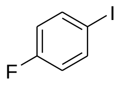
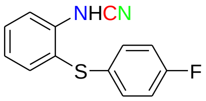
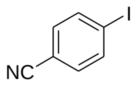
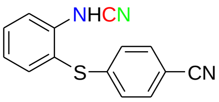
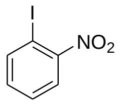
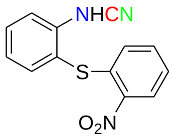
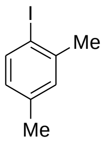
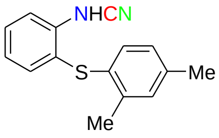
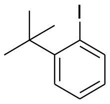
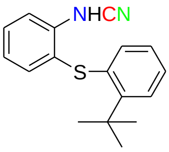
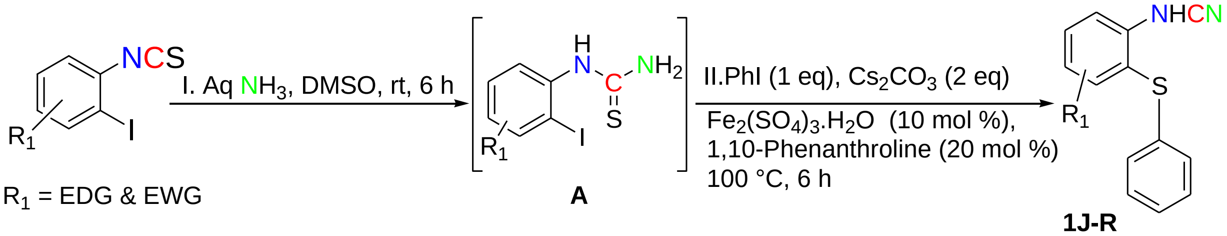
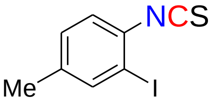
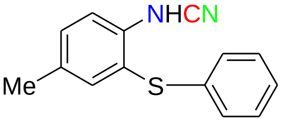
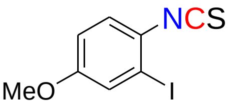
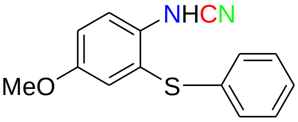
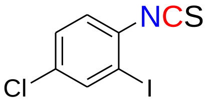
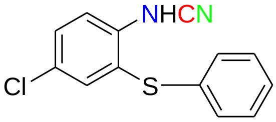
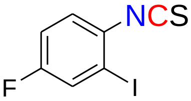
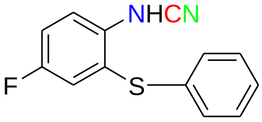
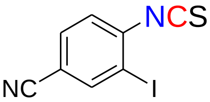
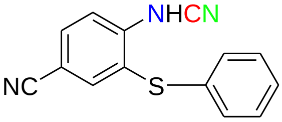
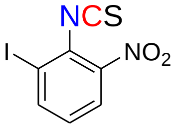
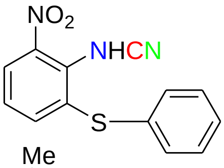
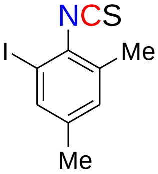
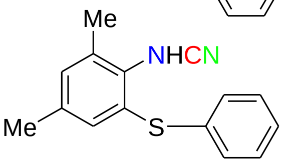
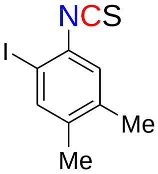
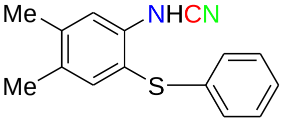
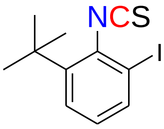
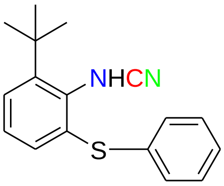
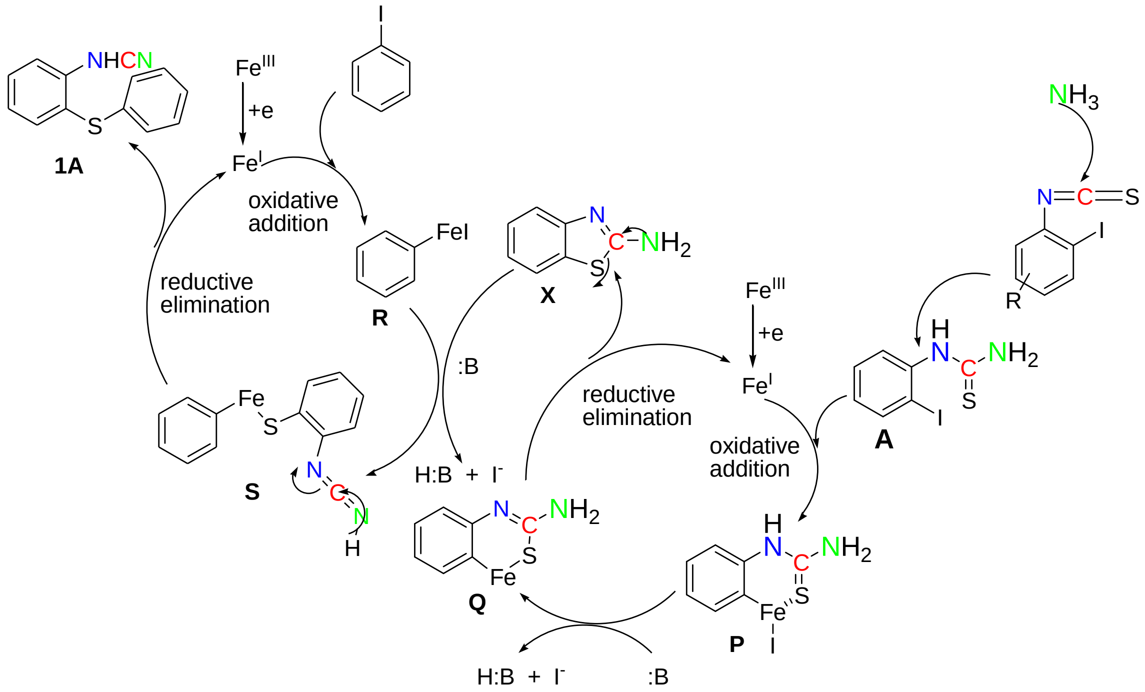
Entry	Substrate	Product		Isolated yield (%)^b
1			1A	95
2			1B	95
3			1C	97
4			1D	91
5			1E	88
6			1F	77
7			1G	76
8			1H	90
9			1I	82

Table 3: Substrate scope for the synthesis of 2-arylthio arylcyanamides.



1J-R

Entry	Substrate	Product		Isolated yield (%)^b
1			**1J**	95
2			**1K**	95
3			**1L**	90
4			**1M**	83
5			**1N**	75
6			**1O**	70
7			**1P**	82
8			**1Q**	85
9			**1R**	77



Scheme 2: Proposed mechanism.

We have developed neat, clean and efficient methodology for the synthesis of 2-halo aromatic cyanamides. During the reaction process we couldn't observe any other byproducts (no other products could observe except cyanamide only). The reactions are rapid and facile and accomplished under mild reaction conditions. All the substrates could obtain their target products in good to excellent yields.

ACKNOWLEDGMENT

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