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Synthesis of 2-arylthio arylcyanamides from 2-iodoaryl isothiocyanates *via* a one-pot three-component reaction†

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A one-pot three-component reaction has been described for the synthesis of substituted 2-arylthio arylcyanamides. A cheap and readily available iron source was used as a catalyst for this reaction. Consecutive addition and domino C–S cross-coupling reactions have been involved in this reaction.

Due to its unique reactivity, a cyano group is recognized as an important building block and found in various bioactive molecules and functionalized materials.[1] Cyanamides are useful precursors and important synthetic intermediates for the synthesis of biologically, medicinally, and pharmaceutically important heterocycles.[2] Since the cyano group can be easily removed from cyanamide and *N*-alkyl or *N*-aryl imides,[3] it often represents a useful protecting group 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 significant attention due to the presence of this moiety in many molecules that are of biological, pharmaceutical, and material interest.[7] Recently, the compounds, such as 2-(arylthio)arylcyanamides, containing the abovementioned moieties have been developed from 2-halophenyl thiourea *via* domino C–S cross-coupling reaction using copper as a catalyst.[8] To the best of our knowledge, no study has been reported on the synthesis of 2-(arylthio)arylcyanamides in the presence of iron as a catalyst. Therefore, herein, we report the one-pot synthesis of 2-(arylthio)arylcyanamides from 2-iodoaryl isothiocyanates and aryl iodides using a cheap, readily available, and air stable iron source as the catalyst under mild reaction conditions.

Initially, the optimization of the reaction conditions was performed using 4-Me-2-iodophenyl isothiocyanate as a model substrate with different solvents at room temperature (step 1). We could observe that the substrate reacted with aq. NH_3 in the presence of EtOH, EtOAc, DMF, and DMSO at room temperature to afford the corresponding thiourea **A** *via* complete conversion. Then, it took part in an domino intra- and intermolecular C–S cross-coupling reaction with iodobenzene with 10 mol% $Fe_2(SO_4)_3 \cdot H_2O$, 20 mol% ligand (1,10-phenanthroline), and 2 equiv. Cs_2CO_3 at 100 °C to form the target product **1A** *via* complete conversion. In case of solvent optimization, no reactions occurred in non-polar solvents such as *n*-hexane and *n*-heptane. Green solvent H_2O could afford thiourea (1st step) in 70% conversion, but the domino C–S cross-coupling reaction (2nd step) could not proceed. Various bases were examined and among them, Cs_2CO_3 could yield target product *via* complete conversion (Table 1, entry 10). Other bases gave less effective in the formation of target product. Among the set of three ligands L1–L3 screened, L3 was found to be more effective as compared to L1 and L2 (Table 1, entries 11 and 12). Both iron(II) and iron(III) sources ($Fe_2(SO_4)_3 \cdot H_2O$, $Fe(NO_3)_3 \cdot 9H_2O$, and $FeCl_2$) exhibited a similar catalytic activity (entries 10 and 13 and 14). The reaction, either lowering the amount of base (1.5 equiv.) or the iron source (5 mol%) gave target product in lower conversion. The reaction was also checked in the absence of ligand; unfortunately, the reaction could not yield target product and formed iodocyanamide in 25% conversion (Table 1, entry 17). The control experiment confirmed that the reaction did not proceed (step 2) in the absence of the catalyst. The ligand and thiourea were recovered intact (Table 1, entry 18).

Having the optimization reaction conditions in our hand, we further pursued the scope of the process with respect to the other substrates. Aryl iodides having the electron-donating groups 4-Me and 4-OMe proceeded reactions to afford their domino cross-coupled products **1B** and **1C** in 95% and 97% yield, respectively. Aryl iodides bearing weak electron withdrawing substituents 4-Cl and 4-F could give their respective target products **1D** and **1E** in 91% and 88% yield. Aryl iodides possessing strong electron-withdrawing groups 2-NO_2 and 4-CN

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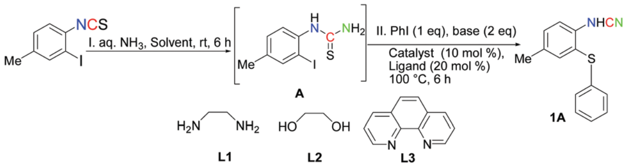
Table 1 Standardization for the reaction conditions[a]



Entry	Solvent	Catalyst	Base	Ligand	Conversion[b]	
					A	1A
1	EtOH	$Fe_2(SO_4)_3{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	100	n.d.
2	EtOAc	$Fe_2(SO_4)_3{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	100	n.d.
3	*n*-Hexane	$Fe_2(SO_4)_3{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	n.d.	n.d.
4	*n*-Heptane	$Fe_2(SO_4)_3{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	n.d.	n.d.
5	H_2O	$Fe_2(SO_4)_3{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	70	n.d.
6	DMF	$Fe_2(SO_4)_3{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	45	55
7	DMSO	$Fe_2(SO_4)_3{\cdot}H_2O$	$K_3PO_4{\cdot}3H_2O$	L3	45	55
8	DMSO	$Fe_2(SO_4)_3{\cdot}H_2O$	KOH	L3	25	75
9	DMSO	$Fe_2(SO_4)_3{\cdot}H_2O$	K_2CO_3	L3	40	60
10	DMSO	$Fe_2(SO_4)_3{\cdot}H_2O$	Cs_2CO_3	L3	n.d.	100
11	DMSO	$Fe_2(SO_4)_3{\cdot}H_2O$	Cs_2CO_3	L1	75	25
12	DMSO	$Fe_2(SO_4)_3{\cdot}H_2O$	Cs_2CO_3	L2	55	45
13	DMSO	$Fe(NO_3)_3{\cdot}9H_2O$	Cs_2CO_3	L3	n.d.	100
14	DMSO	$FeCl_2$	Cs_2CO_3	L3	n.d.	100
15[c]	DMSO	$Fe_2(SO_4)_3{\cdot}H_2O$	Cs_2CO_3	L3	55	50
16[d]	DMSO	$Fe_2(SO_4)_3{\cdot}H_2O$	Cs_2CO_3	L3	35	65
17[e]	DMSO	$Fe_2(SO_4)_3{\cdot}H_2O$	Cs_2CO_3	—	75	n.d.
18	DMSO	—	Cs_2CO_3	—	100	n.d.

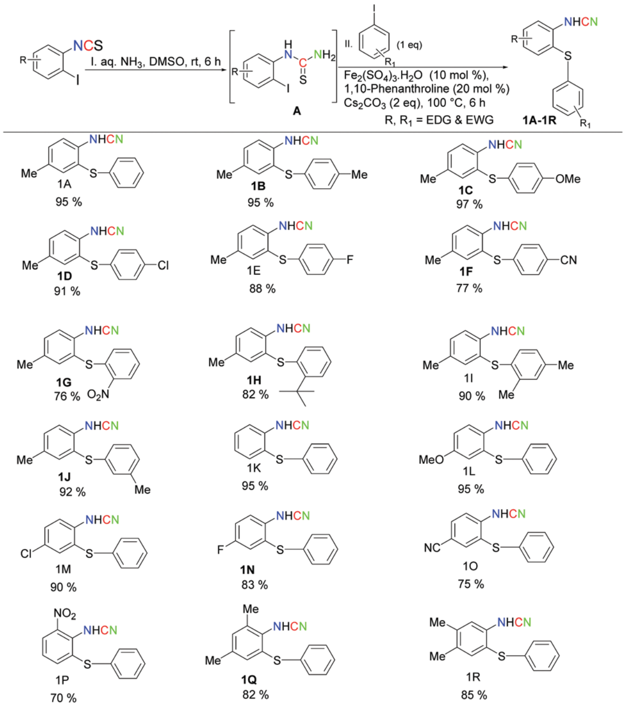
[a] Reaction conditions: 2-iodophenyl isothiocyanate (1 mmol), solvent (2 mL), aq. NH_3 (2 mL), 6 h, room temperature, then, iodobenzene (1 mmol), catalyst (10 mol%), ligand (20 mol%), base (2 mmol), 6 h, 100 °C. [b] Isolated yield. [c] Catalyst (5 mol%) was used. [d] Cs_2CO_3 (1.5 equiv.) was used. [e] The reaction gave 2-iodophenyl cyanamide in 25% conversion. n.d. = not detected.

gave their final products in lower yield. It might be occurred due to the strong electron-withdrawing group at reactive site. Aryl iodide containing disubstituted groups such as 2,4-di-Me gave desired product **1I** in 90% yield. Aryl iodide holding bulkier group 2-*t*Bu and 3-Me reacted under the optimized reaction conditions to give their respective final products **1H** and **1J** in 82% and 92% yield, respectively. Similarly, phenyl isothiocyanates 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 underwent the reaction with iodobenzene to give their final products **1K–R** in 70–95% yield. The abovementioned results clearly confirm that the substrates having electron-donating and electron-withdrawing groups are compatible with this process to afford the substituted 2-(arylthio)arylcyanamides in good to high yield.

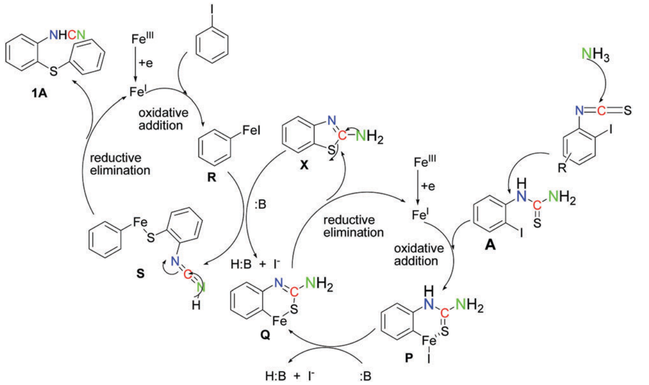
To reveal the mechanism, we carried out some control experiments (see the ESI†). In the absence of ligand, the reaction could give 2-iodophenyl cyanamide instead of target product at optimized temperature (eqn (1)) and room temperature (eqn (2)). The reaction could not proceed in the absence of both catalyst and ligand at 100 °C and room temperature (eqn (3)). Next, the reaction was performed in the presence of both catalyst and ligand at 50 °C, and the reaction could give intramolecular C–S cyclization product in 20% conversion (eqn (4)). The abovementioned results suggested that the catalyst ($Fe_2(SO_4)_3{\cdot}H_2O$) could act as a desulphurization reagent and the ligand was necessary for cyclization. The reaction gave a mixture of intramolecular C–S cyclization and domino C–S cyclization products when conducted at 80 °C (eqn (5)), whereas it could give exclusively domino C–S cyclized product in 100% conversion (eqn (6)) at 100 °C. Moreover, 2-amino benzothiozole readily underwent the reaction with iodobenzene under the optimized reaction conditions to provide final product **1A** in a quantitative yield (eqn (7)). The obtained results clearly suggest that thiourea first gives 2-amino benzothiozole as an intramolecular C–S cyclized product that may react with iodobenzene to afford the final product **1A** *via* intermolecular C–S cross-coupling reaction (Scheme 1).

According to the literature reports and experimental evidences, the mechanism has been proposed (Scheme 2, see the ESI†). 2-Iodophenyl isothiocyanate reacts with aq. NH_3 to provide *N*-2-iodophenyl thiourea **A**, which can undergo oxidative addition with Fe(I) species (thiourea may reduce Fe(III) to Fe(I) active species)[9] to yield the Fe(III) intermediate **P**. It may give 2-aminobenzothiozole **X** by intramolecular C–S cyclization using a base *via* the intermediate **Q**. On the other hand, iodobenzene can undergo oxidative addition with Fe(I) species to give intermediate **R**, which can undergo intermolecular C–S cross-coupling reaction with 2-aminobenzothiozole **X** to afford the intermediate **S**. This intermediate can complete catalytic cycle *via* reductive elimination to obtain the 2-arylthio aryl cyanamide **1A**.

As suggested by the reviewer, we have checked copper contamination in the iron sources using the AAS experiment. The results are shown in Table 2. The obtained results clearly proved that our catalyst (iron source) didn't contain any copper species. Therefore, we concluded that the reported reaction was catalyzed by iron source only. In addition, many researchers have developed cross-coupling reactions using Iron source as the catalyst.[10]



Scheme 1 Substrate scope for the synthesis of 2-arylthio arylcyanamides. Reaction conditions: substituted 2-iodophenyl isothiocyanate (1 mmol), DMSO (2 mL), aq. NH_3 (2 mL), 6 h, room temperature, then, substituted iodobenzene (1 mmol), $Fe_2(SO_4)_3{\cdot}H_2O$ (10 mol%), 1,10-phen (20 mol%), Cs_2CO_3 (2 mmol), 6 h, 100 °C.



Scheme 2 Proposed mechanism.

Table 2 Copper contamination in our catalyst (iron source)

S. no.	Sample	Absorbance of copper
1	Blank solution	0.0000
2	Sample solution-1 (1 ppm)	0.0000
3	Sample solution-2 (0.5 ppm)	0.0000
4	Sample solution-3 (0.25 ppm)	0.0000
5	Sample solution-4 (0.1 ppm)	0.0000
6	Sample solution-5 (0.01 ppm)	0.0000

Conclusions

In conclusion, we have developed a methodology for the synthesis of 2-arylthio arylcyanamides using a cheap and readily available iron source as a catalyst under mild reaction conditions. All the substrates reacted under the optimized reaction conditions to afford the desired products in good to high yield.

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