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Isothiocyanate-Directed Ortho-Selective Halogenation of Arenes via C–H Functionalization

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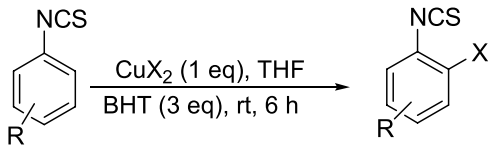
Abstract
Ortho-selective halogenation of arenes via C–H functionalization has been described under mild reaction conditions. In this reaction Cu(II)X_2 was used as a halide source. It is a simple, general and efficient method for the synthesis of 2-halo aromatic isothiocyanates. All the reactions are carried out under optimized reaction conditions to provide their respective desired products in good to high yield.

Graphical Abstract
We have developed a general, simple and efficient method for the synthesis of 2-halo arylisothiocyanates from isothiocyanates through ortho-selective halogenation under mild reaction conditions. Cu(II)X_2 was used as a halide source for this methodology. All the reactions are carried out under optimized reaction conditions to provide their respective desired products in good to high yield.



R = EDG and EWG

EDG-Electron Donating Group

EWG-Electron Withdrawing Group

Keywords Copper catalyst · Ortho halogenations · 2-Halo isothiocyanates · Room temperature · C–H Activation

1 Introduction

In recent years, the functionalization of C–H bonds have been developed towards the synthesis of heterocyclic compounds using transition-metal-catalysis (For recent reviews on directed C–H activation, see [1–9]). Especially, the selective activation of particular C–H bond has been developed through incorporation of directing group on aryl ring (For examples of diverse directing groups, see [10–31]). Recently, many researchers have developed selective

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ortho-halogenation due to incorporation of a directing group on aryl ring via C–H bond activation [32–38].

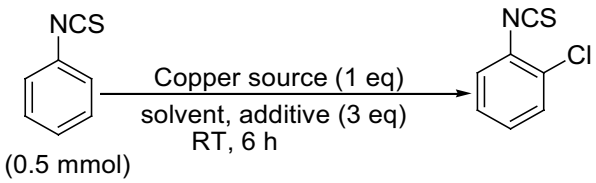
Isothiocyanate is an essential structural motif in many compounds that are important in biological and medicinal sciences. For example, the compounds having isothiocyanate core structure exhibit antiinflammatory, antiasthmatic, antiviral, antineoplastic, cognition disorder, and antibiotic properties [39–42]. These compounds could be synthesized by most regular methods [43–46] and recent ancient methods [40, 47–64]. However, most of the methods have drawbacks such as not readily available starting material, rigorous or hazardous conditions, intractable side reactions, evolved toxic gases, using expensive reagents, longer reaction time and required several steps. The development of a straightforward protocol for the direct ortho-halogenation of isothiocyanate on aryl ring is thus highly desirable.

In addition, aryl halides have been used as very precious starting materials for the synthesis of organometallic reagents and to construct carbon–carbon and carbon- heteroatom bonds via cross-coupling reactions (For examples, see [65–67]) towards the synthesis of heterocyclic compounds, that are biologically and medicinally active (For biological activity of halogen-containing compounds, see [68]). Therefore some conventional methods were used for the construction of aryl halides [69–71], however, they have suffered due to overhalogentaion and low regioselectivity [20, 27, 72–76]. Thus, considerable efforts have been recently made for the development of new methods for the regioselective C–H halogenation of arenes, employing directing groups in the presence of transition metal catalysis [32–38]. Palladium-based catalytic systems have been studied for the halogenation of arenes, employing carboxylic acid, amide, nitrile, and pyridine as the directing groups [32–37], while the rhodium-based systems have been demonstrated with amides and esters [38]. A few studies have been focused on the copper-catalyzed C–H functionalization reactions [72, 77–80]. Herein, we wish to report isothiocyanate-directed ortho-selective halogenation of arenes utilizing CuX_2 (X = Cl, Br) as a halogen source. This protocol is simple, general, and effective at moderate temperature to afford the target products in moderate to high yield.

2 Results and discussion

First, the optimization of the reaction conditions for chlorination was carried out using phenyl isothiocyanate as a model substrate. Initially the reaction was done with CuCl and NCS (*N*-Chloro succinimide) in the presence of DCE and CH_3CN at 60 °C (Table 1, entries 1–2). Unfortunately, no reaction could give target product and the starting material was recovered.

Table 1 Optimization for ortho-chlorination



Entry	Copper source	Solvent	Additive	Conversion (%)[a]
1	CuCl, NCS (1 eq)	DCE	–	n.d
2	CuCl, NCS (1 eq)	CH_3CN	–	n.d
3	$CuCl_2$, NCS (1 eq)	CH_3CN	–	< 10
4	$CuCl_2$	CH_3CN	–	< 10
5	$CuCl_2$	CH_3CN	BHT (1 eq)	< 15
6	$CuCl_2$	CH_3CN	BHT (3 eq)	80
7	$CuCl_2$	CH_3CN	BHT (2 eq)	45
8	$CuCl_2$	**THF**	BHT	87
9	$CuCl_2$	Toluene	BHT	n.d
10	$CuCl_2$	DCE	BHT	40
11	$CuCl_2$	DCM	BHT	43
12	$CuCl_2$	THF	CH_3COOAg	30
13	$CuCl_2$	THF	4-t-BuPhenol	52
14	$CuCl_2$	THF	PTSA	50
15	$CuCl_2$	THF	TFA	55
16	–	THF	BHT	n.d
17[b]	$CuCl_2$	THF	BHT	46
18	NCS (1 eq)	THF	BHT	n.d

Bold indicate best condition for this reaction

Reaction conditions: Phenyl isothiocyanate (0.5 mmol), copper source (1 eq), solvent (2 ml), additive (3 eq), rt, 6 h

[a]conversion based on diagnostic peaks integration in ^{1}H NMR of crude reaction mixture

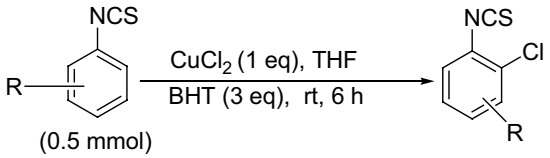
[b]$CuCl_2$ (0.5 eq) was used. (BHT: 2,6-bis(1,1-dimethylethyl)-4-methylphenol)

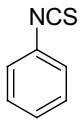
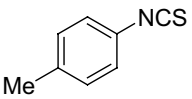
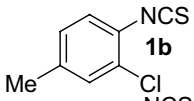
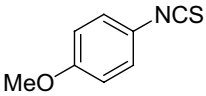
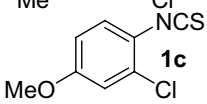
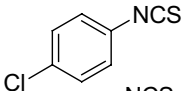
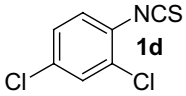
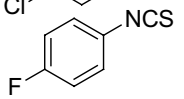
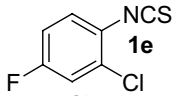
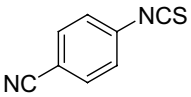
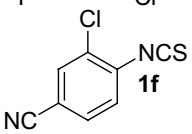
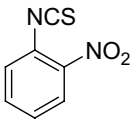
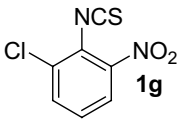
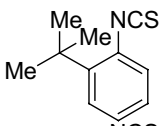
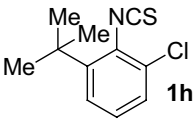
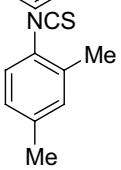
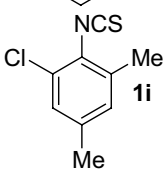
Later, the reaction was conducted with $CuCl_2$, however the reaction could give target product in less conversion (Table 1, entries 3–4). When we incorporate the additive (BHT, 1 eq) into the reaction, the conversion of the reaction was slightly improved (Table 1, entry 5). Very interestingly the conversion of the reaction was dramatically improved, when the reaction was performed with 3 eq BHT (Table 1, entry 6). The reaction was tested with less amount of additive, but unfortunately it gave target product in moderate conversion (Table 1, entry 7). Among the set of solvents tested, THF gave desired product in good conversion (Table 1, entry 8), while CH_3CN, DCM and DCE were found to be less effective in affording the target product in 40–80% and toluene was failed to produce target product (Table 1, entry 9). In case of various additives, BHT gave best results, whereas other additives

such as CH_3COOAg, 4-*t*-BuPhenol, PTSA and TFA gave inferior results. Finally the control experiment confirmed that the reaction couldn't give target product in the absence of copper source and the starting material was recovered intact (Table 1, entry 16). Lowering of catalyst afforded target product in 46% conversion (Table 1, entry 17). The reaction was also checked with NCS (N-Chloro succinimide) in the absence of copper source, however the reaction failed to obtain target product (Table 1, entry 18).

Having the optimal conditions in hand, we studied the scope of the protocol for the chlorination of a wide range of aryl isothiocyanate derivatives (Table 2). The reaction with unsubstituted phenyl isothiocyanate gave target product **1a** in 80% isolated yield (Table 2, entry 1). The substrates having electron donating groups

Table 2 Substrate scope for the synthesis of 2-chloroaryl isothiocyanate



Entry	Substrate	Product	Isolated yield (%)[a]
1		 **1a**	80
2		 **1b**	81
3		 **1c**	83
4		 **1d**	75
5		 **1e**	77
6[b]		 **1f**	78
7[b]		 **1g**	75
8[b]		 **1h**	75
9[b]		 **1i**	77

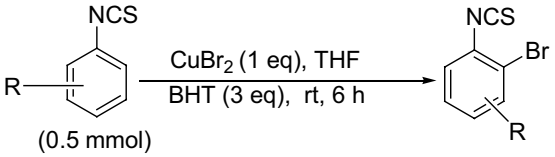
Reaction conditions: Aryl isothiocyanate (0.5 mmol), $CuCl_2$ (1 eq), THF (2 ml), BHT (3 eq), rt, 6 h

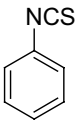
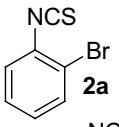
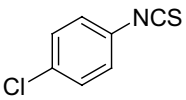
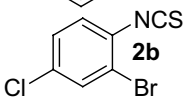
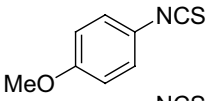
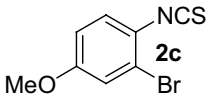
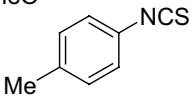
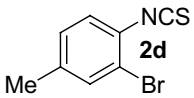
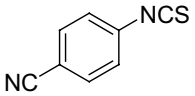
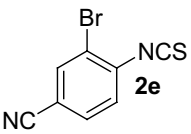
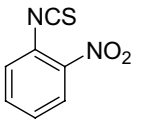
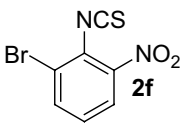
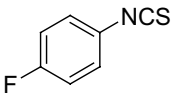
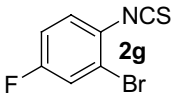
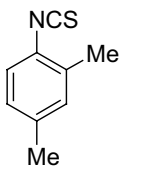
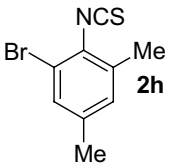
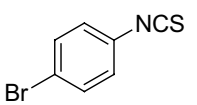
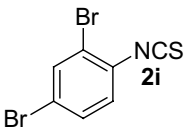
[a]Isolated yield

[b]Reaction time was 10 h. (BHT: 2,6-bis(1,1-dimethylethyl)-4-methylphenol)

4-Me and 4-OMe substituents on both aryl rings readily reacted to obtain their target products **1b** and **1c** in 81% and 83% yields, respectively (Table 2, entries 2–3). The substrates bearing weak electron withdrawing group's 4-Cl and 4-F readily underwent the reaction to get their respective desired products **1d** and **1e** in 75 and 77% yields, respectively (Table 2, entries 4–5). However, the substrates contain strong electron withdrawing groups 4-CN and 2-NO_2 required slightly longer reaction time to give their respective desired products **1f** and **1g** in good yield (Table 2, entries 6–7). Finally, we have also tried the reactions with the substrates having bulkier groups like 2-^{t}Bu and disubstituted groups such as 2,4-DiMe, as a result, both the substrates took longer reaction time to

Table 3 Substrate scope for the synthesis of 2-bromoaryl isothiocyanate

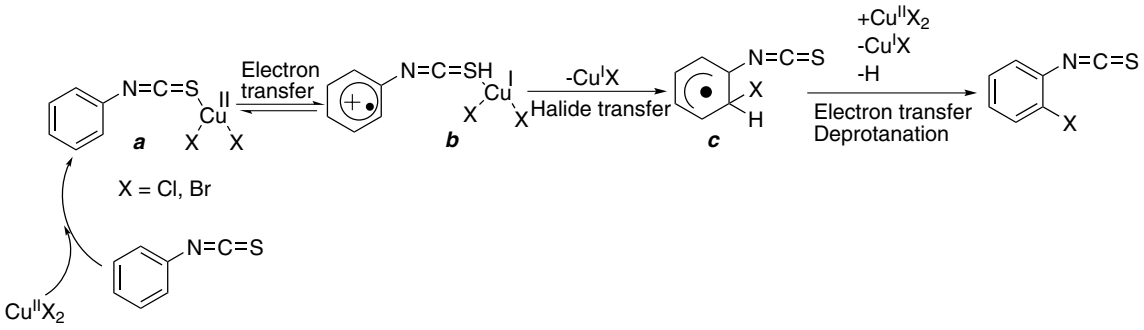


Entry	Substrate	Product	Isolated yield (%)[a]
1		 **2a**	78
2		 **2b**	75
3		 **2c**	81
4		 **2d**	79
5		 **2e**	79
6[b]		 **2f**	72
7		 **2g**	74
8[b]		 **2h**	71
9		 **2i**	72

Reaction conditions: Aryl isothiocyanate (0.5 mmol), $CuBr_2$ (1 eq), THF (2 ml), BHT (3 eq), rt, 6 h

[a]Isolated yield

[b]Reaction time was 10 h. (BHT: 2,6-bis(1,1-dimethylethyl)-4-methylphenol)



Scheme 1 Proposed mechanism

obtain their respective final products **1 h** and **1i** (Table 2, entries 8–9). It might be occurred due to steric effect at reactive site on aryl ring.

Next, the bromination of the substituted aryl isothiocyanate derivatives was studied $CuBr_2$ as a bromine source (Table 3). All the substrates having both electron donating and electron with.

drawing groups readily underwent the reaction under optimized reaction conditions to provide their target products **2a–2i** in 71–81% yields.

Based on experimental results and literature reports the mechanism is proposed (Scheme 1). The reaction may proceed via single-electron transfer pathway [81] which we shown in below scheme 1. Phenyl isothiocyanate reacts with CuX_2 to provide intermediate *a*, which gives another intermediate c via b through consecutive single electron transfer from phenyl ring and halide transfer. Electron transfer from intermediate *c* to Cu(II) species and followed by deprotonation to afford desired product as 2-halo phenylisothiocyanate. Not yet confirm any intermediate, which we shown in mechanism. Still many experiments need to be performed to confirm and propose the actual mechanism. For that mechanism studies are under process in our laboratory.

3 Conclusion

In conclusion we have developed general and efficient ortho-selective halogenation of arenes using Cu(II) halide as halide source under mild reaction conditions. The use of cheap, readily available and air stable copper source give a good method for the synthesis 2-halo isothiocyanates, which are good intermediates for the synthesis of hetero cyclic compounds. In addition the reaction exhibit good functional group tolerance in attaining product with good yield and high selectivity.

3.1 Experimental Section

3.1.1 General Information

$CuBr_2$ (99%), $CuCl_2$ (99%) and CuCl (98%), NCS, CH_3COOAg, 4-*t*-BuPhenol, PTSA, TFA and BHT were purchased from Aldrich and used without further purification. The solvents were purchased and dried according to standard procedure prior to use [64]. ^{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. Aromatic isothiocyanates have been synthesized by our recent reported literature [63].

3.1.2 General Procedure for 2-haloarylisothiocyanate

To a stirred solution of THF (2 ml), respective isothiocyanate (0.5 mmol) was added in slowly and followed by CuX_2 (1 eq) and BHT (3 eq) were added slowly and the reaction mixture was stirred for 6 h at room temperature. The progress of the reaction was investigated by TLC (5% ethylacetate in hexane). After finish the reaction, the reaction mixture was washed with water (4 ml) and ethylacetate (6 ml) for 3 times. Both organic and aqueous layers were separated and the organic layer 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 isothiocyanate as oily liquid

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