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Cu(II) catalysed chemoselective oxidative transformation of thiourea to thioamidoguanidine/2-aminobenzothiazole†

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2-Haloaryl-*sec*-alkyl unsymmetrical thioureas (Tu) (halo = –F, –Cl) with a catalytic amount of Cu(II) salt get oxidised *in situ* to their disulfide intermediates followed by an imine-disulfide rearrangement to give thioamidoguanidino (Tag) moieties at room temperature. During this process Cu(II) gets reduced to Cu(I) and forms a complex with the Tag moiety from which Tag moiety can be isolated upon treatment with ammonia. However, when the same reaction was performed at an elevated temperature with a catalytic quantity of Cu(II) salt, Tu bearing *o*-halogens (–F, –Cl) gave 2-aminobenzothiazoles *via* a dehalogenative heteroarylation path and not by the Hugerschoff path involving an electrophilic substitution reaction. For thioureas containing reactive *ortho* halogens (such as –Br, –I) the reaction proceeds at room temperature giving 2-aminobenzothiazoles *via* a dehalogenative path requiring a catalytic quantity of Cu(II). No transformation of thiourea (Tu) to Tag was observed with Cu(I) salts suggesting the requirement of an oxidising Cu(II) salt for this oxidative transformation. Mild reaction conditions, environmentally benign reagents and solvent, high yields, tolerance of various functional groups are some of the essential features of this methodology.

Introduction

2-Aryl-*sec*-alkyl unsymmetrical thioureas (Tu) on treatment with thiophilic oxidising agents such as bromine (or its equivalent)[1a] or iodine[1b] give thioamidoguanidine products (Tag) for most thiourea (Tu) substrates instead of giving the expected 2-aminobenzothiazoles. These results of ours are in contrast with the classical Hugerschoff reaction known since 1901[2] and the recent reports by Jordan and Le *et al.*[3] Of course, unsymmetrical thioureas (Tu) containing activating group(s) in the aryl rings are susceptible towards intramolecular reactions in the presence of suitable thiophiles giving 2-aminobenzothiazoles (Hugerschoff product).[1a]

A competitive formation of 2-aminobenzothiazole (Hugerschoff product) and thioamidoguanidine (anti-Hugerschoff product) was observed for the moderately activated substrates.[1] The formation of the thioamidoguanidine (Tag) product from 2-aryl-*sec*-alkyl unsymmetrical thioureas goes *via* an oxidative dimerization (S–S bond formation) followed by an intramolecular imine-disulfide rearrangement.[1a] On the other hand the formation of 2-aminobenzothiazole involves an intramolecular aromatic electrophilic substitution reaction (Hugerschoff path) facilitated by activation of the sulfur atom of the thiourea with a thiophilic reagent.[1] In order to circumvent the competitive formation of 2-aminobenzothiazole and allow exclusive formation of the Tag product, the redox active metal Cu(II) is expected to promote only oxidative dimerisation of thiourea (S–S bond formation). This is then followed by an intramolecular iminedisulfide rearrangement leading to the formation of Tag. Thiophilic redox active metal Cu(II) would not activate the sulphur atom of thiourea towards an intramolecular electrophilic substitution reaction (Hugerschoff path). Indeed this strategy was quite successful and the unsymmetrical thiourea (Tu) was transformed into a thioamidoguanidine (Tag) moiety with concomitant reduction of Cu(II) to Cu(I) which however formed a $[Cu_2^{I}(\mu_2\text{-Br})_2Tag_2]$ complex.[4] Furthermore, we know that 2-halothioureas prefer a dehalogenative path during the formation of an intramolecular C–S bond formation giving 2-aminobenzothiazoles for the entire range of halogens where as Pd favors a C–H activation path.[5] Recently, we have engineered a greener strategy for the synthesis of 2-aminobenzothiazole from *ortho*-halo (–F, –Cl, –Br and –I) substituted unsymmetrical thioureas using CuO nanoparticles.[6] In this strategy for *ortho* –I and –Br substituted thioureas the reaction affords 2-aminobenzothiazoles under metal free conditions *via* a base promoted intramolecular nucleophilic aromatic sub-

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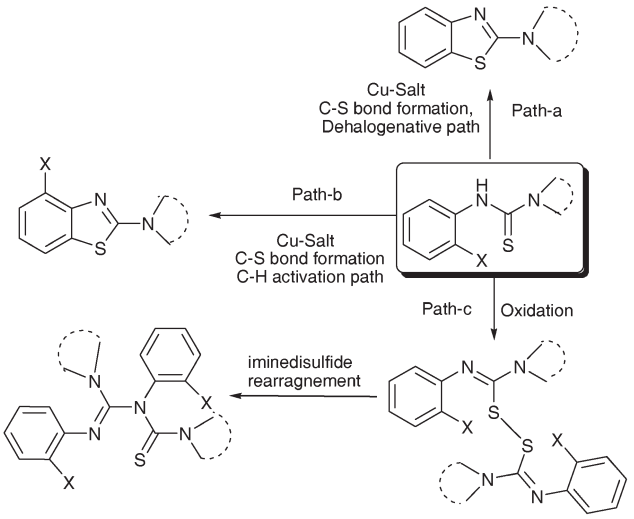
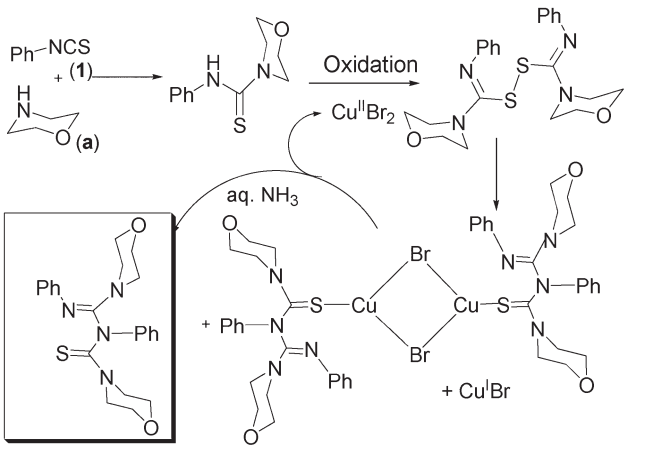
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra and HRMS spectra. CCDC reference numbers 894067 and 894068. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ra22240j



Scheme 1 Various possible reaction pathways of 2-halo thiourea.



Scheme 2 Formation of thioamidoguanidino moiety from thiourea.

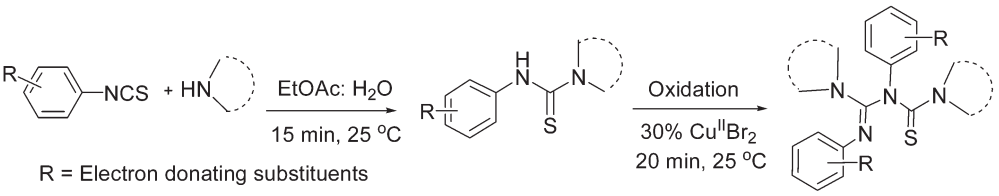
stitution. However, base and Cu catalyst were essential for the relatively inert *ortho* –Cl and –F substrates.[6]

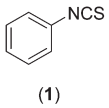
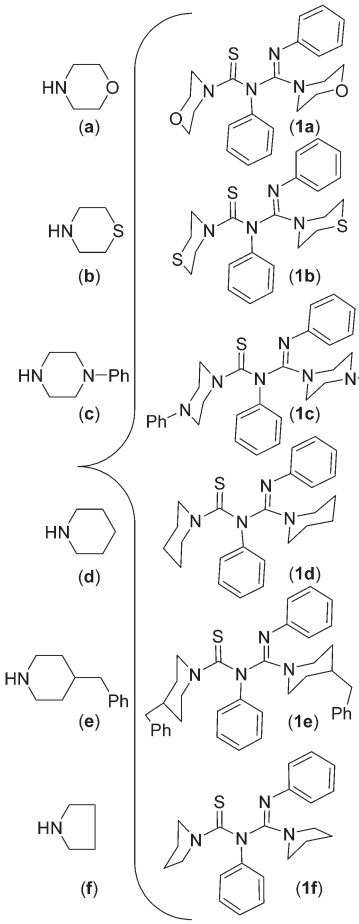
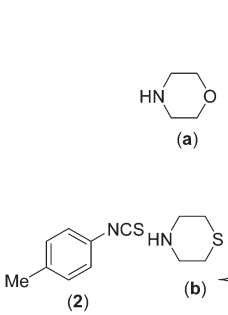
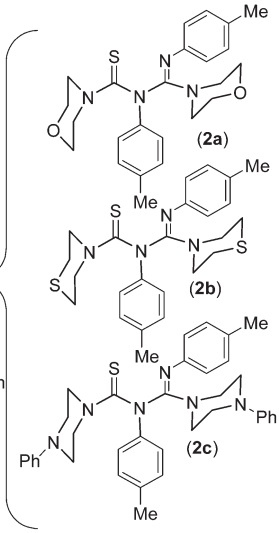
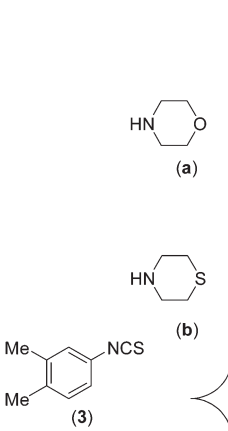
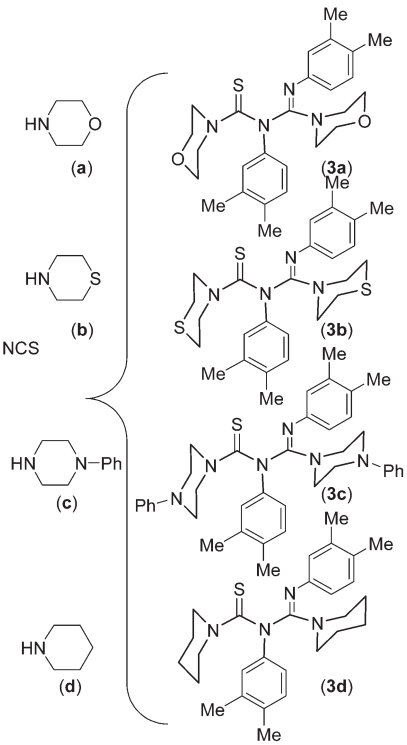
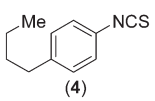
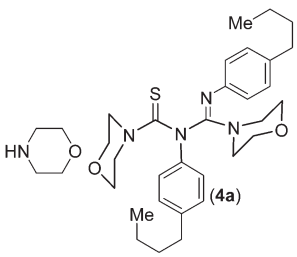
2-Haloaryl-*sec*-alkyl unsymmetrical thioureas (Tu) on treatment with Cu(II) salts there exists several possible reaction pathways as shown in Scheme 1. In path-a, it can undergo an intramolecular C–S bond formation *via* a dehelogenative path giving 2-aminobenzothiazole. Depending on the nature of the 2-halo substituents, particularly inert halogens (–Cl, –F) or in the absence of any halo substituents it may furnish 2-aminobenzothiazole *via* a C–H activation strategy (path-b). The possibility of an oxidative dimerisation (S–S bond formation) of a thiourea (Tu) in the presence of a redox active metal Cu(II) cannot be ruled out as shown in path-c which would eventually lead to the formation of a Tag moiety after an intramolecular imine-disulfide rearrangement. Thus we wish to investigate which of the above paths would operate when 2-haloaryl-*sec*-alkyl unsymmetrical thioureas (Tu) are treated with Cu(II) salt and also whether *o*-halogens would have any affect on the outcome of the product. For substrates without *o*-halo groups, would path-b (C–H activation) or path-c (S–S bond formation) be followed when treated with a redox active Cu(II) salt? If path-c operates, then a library of guanidine class of molecules can be generated. The molecules containing guanidine moieties have shown number of biological and pharmaceutical applications. Furthermore, guanidine possessing molecules are also capable of catalysing organic reactions, can be used as a super bases and they exhibit a variety of coordination modes leading to compatibility with a wide range of metal ions.[7]

Results and discussion

We directly adopted our recently established procedure[4] for the preparation of the Tag moiety from thiourea but the solvent system was switched to EtOAc : H_2O (3 : 1) instead of ethanol because of the convenience in work up at a later stage. The *in situ* generated unsymmetrical thiourea (Tu) obtained by reacting phenylisothiocyanate (**1**) with morpholine (**a**) (Scheme 2) in EtOAc : H_2O (3 : 1) medium was treated with an aqueous solution of $CuBr_2$ (1 equiv.). The green colour of $CuBr_2$ disappeared immediately giving a yellow solution along with yellow precipitate. From our earlier report we know that the yellow compound formed is a bimetallic $[Cu_2^{I}(\mu_2\text{-Br})_2Tag_2]$ complex.[4] The co-ordinated copper was removed from the complex by treating the crude reaction mixture with an aqueous ammonia solution. The isolated ligand was found to be the expected thioamidoguanidino moiety (Tag) (**1a**) and no traces of 2-aminobenzothiazole (**11′a**) formation (Table 4) was observed. It may be mentioned here that the use of bromine equivalent, 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) gave a mixture of thioamidoguanidino moiety (Tag) and 2-aminobenzothiazole (**11′a**). Thus our envisioned strategy was indeed successful in suppressing the formation of 2-aminobenzothiazole (**11′a**). Our group has been actively involved in the synthesis of various *N*, *O*, *S* heterocycles using Cu catalyst.[8] From a green chemistry perspective, it is desirable to have a catalytic quantity of Cu instead of stoichiometric amount for any transformations. The reaction when carried out with 10, 20, 30 and 40 mol% of $CuBr_2$ it was found that 30 mol% of $CuBr_2$ was optimum in converting the starting material into the product. As evident from our recent result when thiourea is treated with Cu(II) salt, it is first oxidised to its disulfide intermediate which then undergo an intramolecular rearrangement giving Tag and during the process the Cu(II) gets reduced to Cu(I). The *in situ* generated Cu(I) is reoxidised to Cu(II) by the atmospheric oxygen and the catalytic cycle continues. The amount of catalyst required is more (30 mol%) compared to any typical catalytic reactions because of the propensity of the *in situ* generated Cu(I) species to form a complex with the *in situ* generated Tag unit thereby making part of the catalyst unavailable.[4] Other divalent Cu(II) salts like $CuSO_4\cdot5H_2O$, $Cu(OAc)_2\cdot2H_2O$, $Cu(NO_3)_2\cdot3H_2O$,

Table 1 Synthesis of thioamidoguanidino products from arylisothiocyanates and *sec* amines[a]



Substrate	Product	Yield[b]	Substrate	Product	Yield[b]
 (1)	 (a) (1a)	89%	 (2)	 (a) (2a)	86%
	(b) (1b)	80%		(b) (2b)	71%
	(c) (1c)	83%		(c) (2c)	73%
	(d) (1d)	88%	 (3)	 (a) (3a)	86%
	(e) (1e)	85%		(b) (3b)	73%
	(f) (1f)	78%		(c) (3c)	74%
 (4)	 (4a)	85%		(d) (3d)	83%

[a] Reaction monitored by TLC. [b] Confirmed by IR, ^{1}H, ^{13}C NMR spectra.

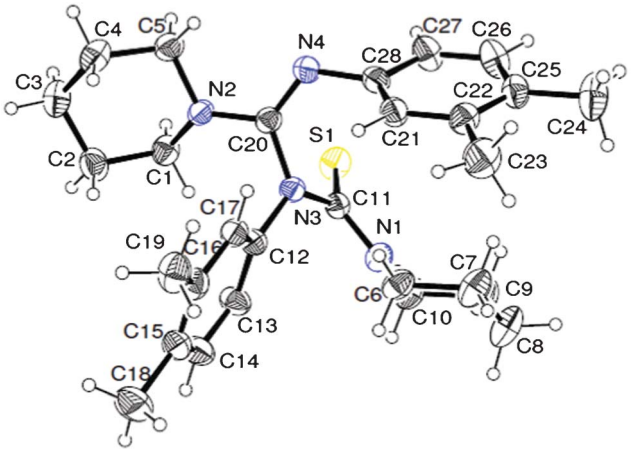


Fig. 1 ORTEP view (30% probability ellipsoids) of compound **3d**.

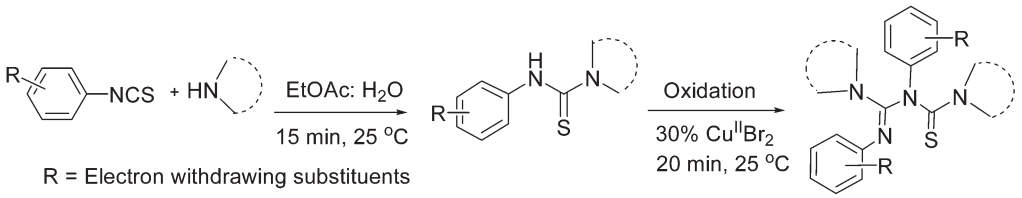
$CuCl_2 \cdot 2H_2O$, CuI_2 were tested and gave the desired transformations, but were found to be inferior to $CuBr_2$.

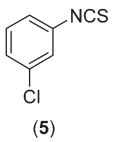
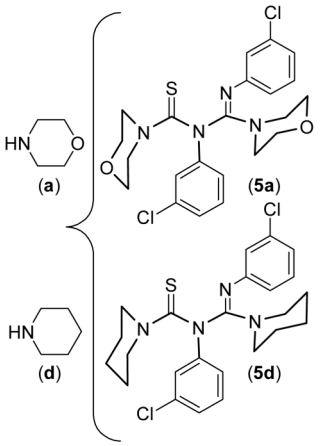
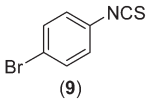
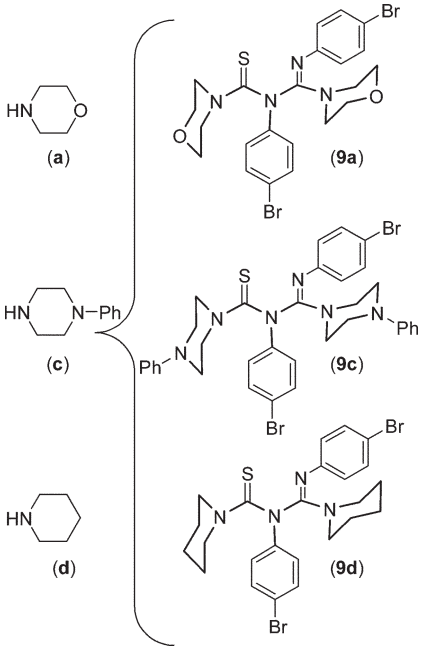
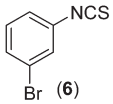
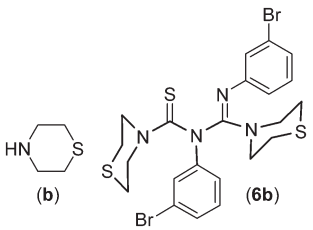
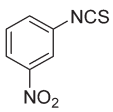
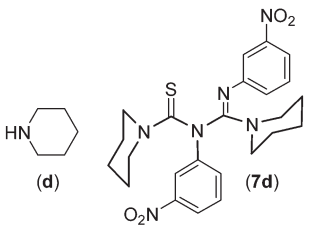
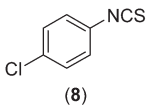
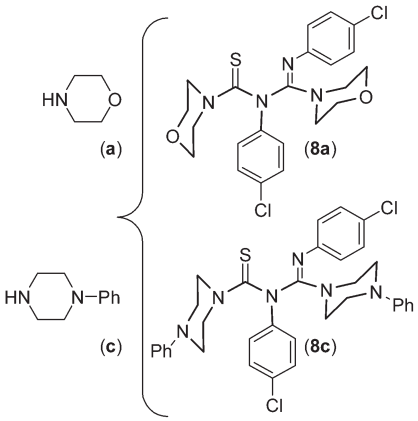
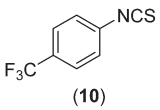
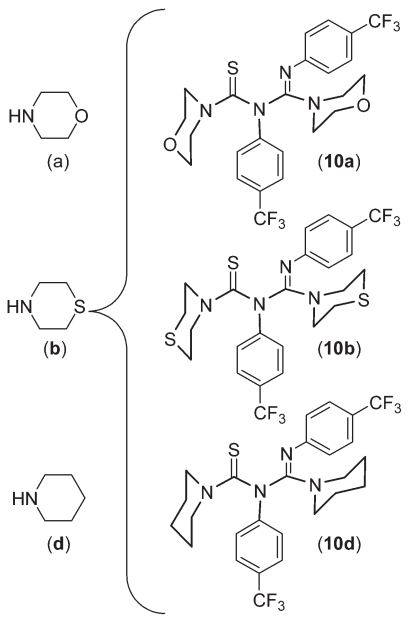
Despite their use as efficient vulcanising and herbicide agents, prior to our greener strategies there is only one synthetic method reported using 2-aryl-*sec*-alkyl unsymmetrical thioureas (Tu) and iodine in chloroform.[9a] Another report is on the crystal structure determination.[9b] Beside this report there are two more methods reported for the synthesis of thioamido guanidine in the literature. Both methods are from our group only, starting from aryl-*sec*-alkyl unsymmetrical thiourea using thiophilic reagents such as bromine or iodine.[1] Thus we wished to synthesize a series of thioamidoguanidine (Tag) moieties by varying the secondary aliphatic amines in thioureas keeping the aryl part constant. Thiomorpholine (**b**), *N*-phenyl piperazine (**c**), piperidine (**d**), 4-benzylpiperidine (**e**) and pyrrolydine (**f**) derived thioureas from phenyl isothiocyanate (**1**) all gave good yields of their corresponding Tag products (**1b**), (**1c**), (**1d**), (**1e**), and (**1f**), respectively as shown in Table 1. From the present study it was found that the aliphatic secondary amines in thioureas seem to have little or no effect on the outcome of the product yields. Thus we planned to investigate whether the substituents present in the aryl rings would influence the reaction path. Besides being an oxidising agent, copper(II) salts are also thiophilic in nature, so the presence of activated substituents in the aryl rings of thioureas (Tu) might promote an intramolecular aromatic electrophilic substitution (Hugerschoff path), path-b as was observed using bromine equivalent or iodine.[1] Alternatively, some of the substrates might exert C–H activation (path-b) giving 2-aminobenzothiazole. With this objective thioureas derived from *p*-methyl phenylisothiocyanate (**2**) and morpholine (**a**) was treated with $CuBr_2$ and the product isolated after an aqueous ammonia treatment was found to be the Tag product (**2a**) (Table 1) exclusively and no traces of corresponding 2-aminobenzothiazole was observed. Similarly thioureas derived from *p*-methyl phenylisothiocyanate (**2**) and other secondary amines such as thiomorpholine (**b**), *N*-phenyl piperazine (**c**) gave only their respective Tag products (**2b**) and (**2c**). Thioureas derived from aromatic isothiocyanate containing two weakly activating (methyl) substituents such as 3,4-dimethyl phenylisothiocyanate (**3**) and various secondary aliphatic amines like morpholine (**a**), thiomorpholine (**b**), *N*-phenyl piperazine (**c**) and piperidine (**d**) all afforded Tag products (**3a**), (**3b**), (**3c**), and (**3d**) respectively under the present reaction conditions. Structure of the product (**3d**) has been confirmed by single crystal X-ray crystallography as shown in Fig. 1. It may be worth mentioning here that the same thiourea derived from 3,4-dimethylphenylisothiocyanate (**3**) and morpholine (**a**) gave a regioisomeric mixture of two 2-aminobenzothiazoles and no traces of Tag product (**3a**) was observed when bromine equivalent (EDPBT) was used as the thiophilic reagent.[1] Thus, the oxidising ability (S–S bond formation) of Cu(II) predominates over its thiophilicity. Furthermore, the absence of any intramolecular aromatic electrophilic substitution product (2-aminobenzothiazole) using Cu(II) salt confirms its lower thiophilicity as compared to EDPBT. Thus, the use of Cu(II) as an oxidising agent is advantageous over EDPBT in giving Tag products. Not surprisingly, thiourea derived from *p*-butyl phenylisothiocyante (**4**) and morpholine (**a**) yielded the corresponding Tag product (**4a**).

Unsymmetrical thioureas (Tu) possessing activating groups in the aryl rings are prone towards intramolecular aromatic electrophilic substitution reaction in the presence of a thiophilic reagent thereby enhancing the chances of forming 2-aminobenzothiazoles *via* a Hugerschoff path. However, the use of Cu(II) salt gave exclusively Tag products for substrates containing not only for deactivating substrates but also for activating substrates. However, the presence of weakly deactivating substituents in the aryl ring of the thiourea is more likely to give Tag products only. To verify this fact and demonstrate the versatility of the method thioureas derived from 3-chloro phenylisothiocyanate (**5**) and aliphatic secondary amines such as morpholine (**a**) and piperidine (**d**) on treatment with $CuBr_2$ gave exclusively Tag products (**5a**) and (**5d**) respectively in excellent yields (Table 2). The treatment of the thiourea derived from 3-bromo phenylisothiocyanate (**6**) and thiomorpholine (**b**) with Cu(II) gave Tag product (**6b**) in a modest yield. Thioureas derived from sets of arylisothiocanates such as 3-nitro phenylisothiocyanate (**7**), 4-chloro phenylisothiocyanate (**8**), 4-bromo phenylisothiocyanate (**9**) and 4-trifluoromethyl phenylsiothiocyanate (**10**) and sets of aliphatic secondary amines (**a–d**) all gave their expected Tag products in good to excellent yield under the present reaction conditions as shown in Table 2.

2-Halo substituted thioureas undergoing copper catalysis are prone to intramolecular heteroarylation *via* a dehalogenative path.[5,6,8b,10] All the substrates examined in Table 1 and 2 are devoid of 2-halosubstituents thus we wish to examine the effect of 2-halo substituents on the outcome of the products where all the three possibilities (path-a, path-b and path-c) exist equally as shown in Scheme 1. Recently, we have demonstrated that the use of Cu(I) gave 2-aminobenzothiazoles *via* a dehalogenative path for the entire range of 2-halo (–F, –Cl, –Br, and –I) substituted thioureas.[5] It is further

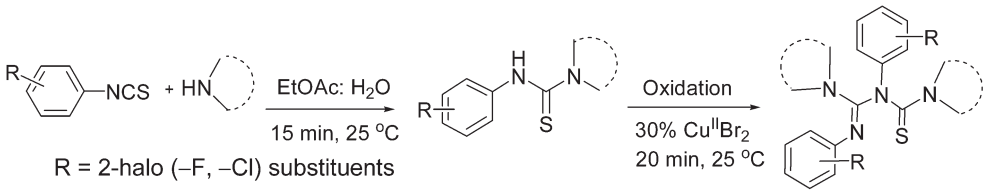
Table 2 Synthesis of thioamidoguanidino products from arylisothiocyanates and *sec* amines[a]

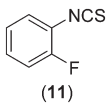
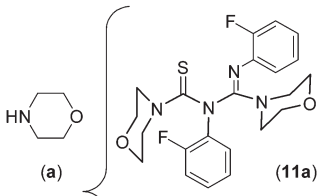
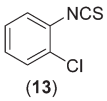
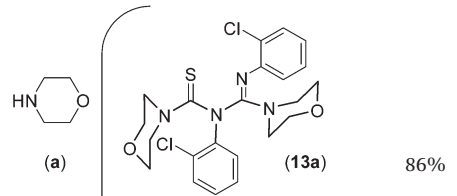
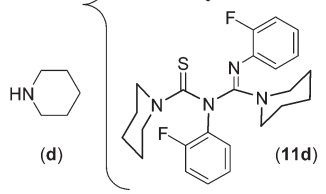
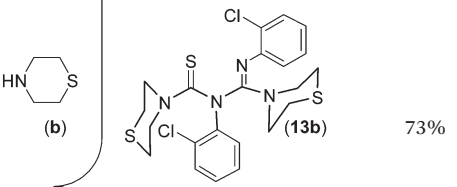
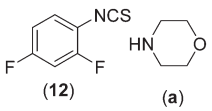
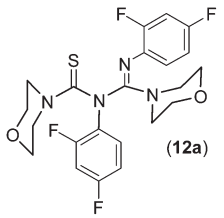
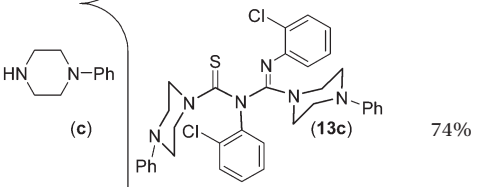
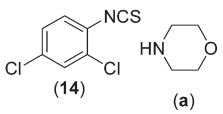
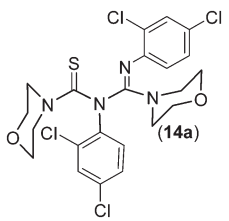
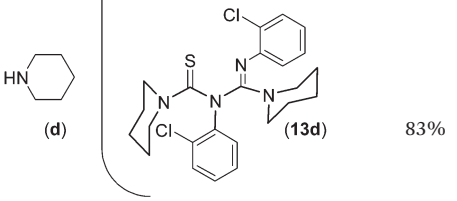


Substrate	Product	Yield[b]	Substrate	Product	Yield[b]
 (5)	 (a) (5a) (d) (5d)	91% 79%	 (9)	 (a) (9a) (c) (9c) (d) (9d)	92% 78% 82%
 (6)	 (b) (6b)	71%			
 (7)	 (d) (7d)	79%			
 (8)	 (a) (8a) (c) (8c)	93% 74%	 (10)	 (a) (10a) (b) (10b) (d) (10d)	85% 70% 80%

[a] Reaction monitored by TLC. [b] Confirmed by IR, ^{1}H, ^{13}C NMR spectra.

Table 3 Synthesis of thioamidoguanidino products from arylisothiocyanates and *sec* amines[a]



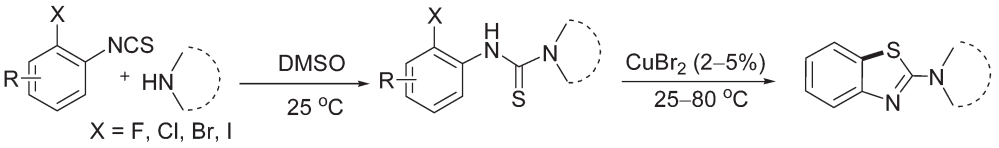
Substrate	Product	Yield[b]	Substrate	Product	Yield[b]
 (11)	 (a) (11a)	92%	 (13)	 (a) (13a)	86%
	 (d) (11d)	87%		 (b) (13b)	73%
 (12) (a)	 (12a)	81%		 (c) (13c)	74%
 (14) (a)	 (14a)	85%		 (d) (13d)	83%

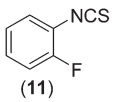
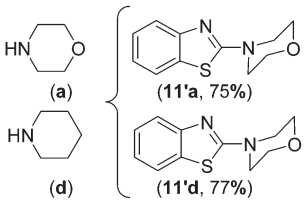
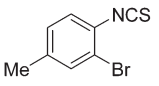
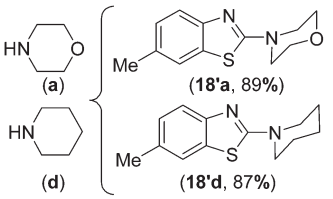
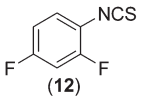
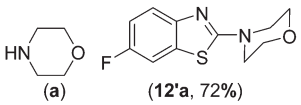
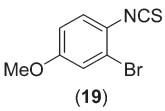
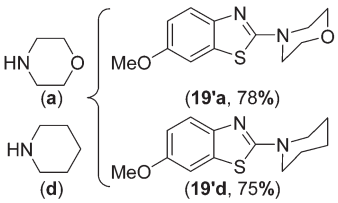
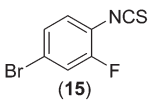
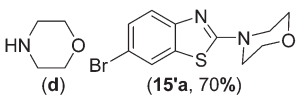
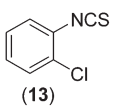
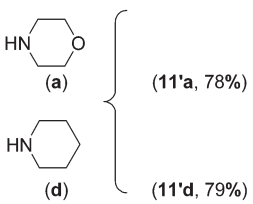
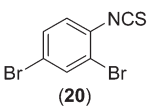
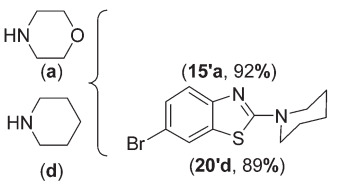
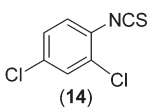
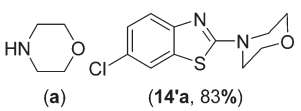
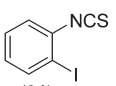
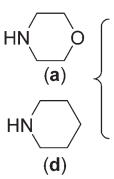
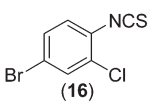
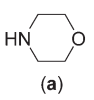
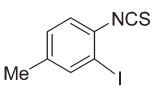
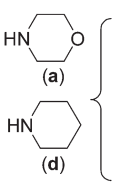
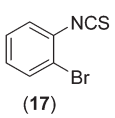
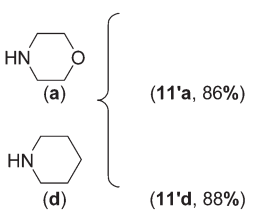
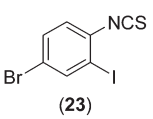
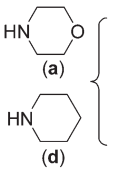
[a] Reaction monitored by TLC. [b] Confirmed by IR, ^{1}H, ^{13}C NMR spectra.

demonstrated that the dehaloganative path is preferred even for less reactive halogens (–F, –Cl) using CuO nanoparticles in an aqueous medium at an elevated temperature.[6] In the present case thioureas derived from 2-fluoro phenylisothiocyanate with morpholine (**a**) and piperidine (**d**) when treated with Cu(II) salt gave Tag products (**11a**) and (**11d**) and not the expected 2-aminobenzothiazoles. Thus with lesser reactive halogens (–F, –Cl) Cu(II) behaves better as an oxidising (S–S bond forming) agent at room temperature resulting in the formation of Tag. Formation of 2-aminobenzothiazoles were not observed either *via* an intramolecular C–S bond forming path (dehalogenation path-a, Scheme 1) or *via* a C–H activation path (path-b, Scheme 1). Thus, the thioureas derived from isothiocyanates (**12**), (**13**) and (**14**) and aliphatic secondary amines such as morpholine (**a**), thiomorpholine (**b**), *N*-phenyl piperazine (**c**) and piperidine (**d**) all gave only their corresponding Tag products as shown in Table 3 confirming the preferential oxidative path for 2-halo (–F, –Cl) possessing substrates.

The results in Table 3 are in contrast to our recent reports where Cu as a catalyst has more propensities towards intramolecular C–S bond formation *via* a dehalogenative path even for lesser activated halogens (such as –F, –Cl).[5] A reaction temperature of 80 °C was used in our previous investigation with a catalyst loading of 5 mol%, but in the present case the reaction is carried out at room temperature requiring 30 mol% of the catalyst. Thus an increase in the temperature to 80 °C might result in the formation of 2-aminobenzothiazoles from

Table 4 Synthesis of 2-aminobenzothiazoles from 2-halo arylisothiocyanates and *sec* amines[a]



Substrate	Product[b,c,d]	Substrate	Product[b,c,d]
 (**11**)	 (**a**) (**11'a**, 75%); (**d**) (**11'd**, 77%)	 (**18**)	 (**a**) (**18'a**, 89%); (**d**) (**18'd**, 87%)
 (**12**)	 (**a**) (**12'a**, 72%)	 (**19**)	 (**a**) (**19'a**, 78%); (**d**) (**19'd**, 75%)
 (**15**)	 (**d**) (**15'a**, 70%)		
 (**13**)	 (**a**) (**11'a**, 78%); (**d**) (**11'd**, 79%)	 (**20**)	 (**a**) (**15'a**, 92%); (**d**) (**20'd**, 89%)
 (**14**)	 (**a**) (**14'a**, 83%)	 (**21**)	 (**a**) (**11'a**, 93%); (**d**) (**11'd**, 90%)
 (**16**)	 (**a**) (**15'a**, 79%)	 (**22**)	 (**a**) (**18'a**, 91%); (**d**) (**18'd**, 89%)
 (**17**)	 (**a**) (**11'a**, 86%); (**d**) (**11'd**, 88%)	 (**23**)	 (**a**) (**15'a**, 95%); (**d**) (**20'd**, 94%)

[a] Isolated yield. [b] Confirmed by IR, ^{1}H, ^{13}C NMR spectra. [c] $CuBr_2$ (5 mol%), Na_2CO_3 (1 equiv.), DMSO, 85 °C, 22 h, (when X = F, Cl). [d] $CuBr_2$ (2–5 mol%), 0.5–2 h, room temperature (when X = Br, I).

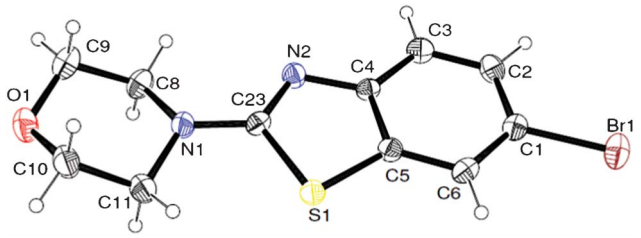
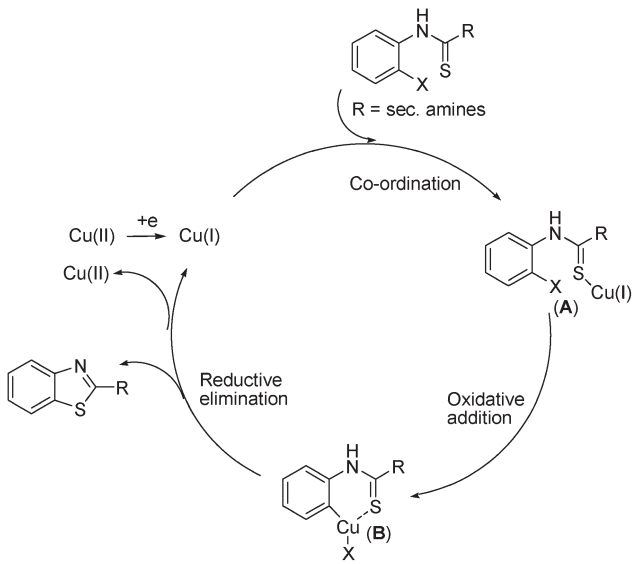


Fig. 2 ORTEP view (30% probability ellipsoids) of compound **15′a**.

2-halo (–F, –Cl) thioureas *via* a dehalogenative path as was observed earlier.[5] With this objective the *in situ* generated thiourea obtained by reacting 2-fluoro phenylisothiocyanate (**11**) and morpholine (**a**) when treated with a catalytic quantity (5 mol%) of $CuBr_2$ at 80 °C gave 2-aminobenzothiazole (**11′a**) in a poor yield of 40% when EtOAc : H_2O was used as the solvent. Thus differential reactivity of 2-fluoro thiourea was observed at two different temperatures, at 80 °C path-a is followed and at room temperature path-c is followed (Scheme 1). Further experiments revealed that the use of DMSO as the solvent gave superior yield 75% of (**11′a**) compared to other solvents such as CH_3CN, DMF, toluene, dioxane, EtOH and DMA tested. Similarly the thiourea generated from 2-fluoro phenylisothiocyanate (**11**) and piperidine (**d**) gave corresponding 2-aminobenzothiazole (**11′d**) in good yield. This dehalogenative strategy at higher temperatures was also equally successful for other *in situ* generated 2-fluoro thioureas as shown in Table 4. The structure of the product (**15′a**) has been further confirmed by crystal X-ray crystallography (Fig. 2). Not surprisingly the *in situ* generated 2-chloro thioureas underwent similar dehalogenative path giving the corresponding 2-aminobenzothiazoles as shown in Table 4. From this study it is clear that using a catalytic amount of $CuBr_2$ (5 mol%) at higher temperatures a dehalogenative path is preferred giving 2-aminobenzothiazole, while a lower temperature favors an oxidative dimerisation path giving Tag products. It is well documented that thioureas derived from more activated halogens such as 2–Br or 2–I undergo intramolecular C–S bond formation under ligand and catalyst free conditions at 130 °C in the presence of Cs_2CO_3.[11] For 2-bromo thiourea derived from 2-bromo phenylisothiocyanate (**17**) and morpholine (**a**) the reaction proceeded at room temperature with just 5 mol% of the catalyst. It may be mentioned here that the use of EDPBT gave exclusively the *anti*-Hugerschoff product (Tag) for the same substrate. Other 2-bromo substituted thioureas derived from respective isothiocyanates (**18**), (**19**) and (**20**) and secondary amines such as, morpholine (**a**) and piperidine (**d**) gave the respective 2-amino benzothiazoles *via* a dehalogenetive path as shown in Table 4. 2-Iodo thioureas derived from respective arylisothiocyanates (**21**), (**22**) and (**23**) and secondary amines morpholine (**a**) and piperidine (**d**) were found to be much more reactive than their bromo analogues and the reaction goes at room temperature with just 2 mol% of the catalyst.

A proposed catalytic cycle for the synthesis of 2-amino benzothiazole using Cu(II) can be envisaged taking cues from the literature as shown in Scheme 3. The copper(II) salt is initially reduced *in situ* to a copper(I) species by thiourea.[12] Co-ordination of thioureas with thiophilic copper(I) gives intermediate (**A**) which is then followed by an oxidative addition giving a copper(III) intermediate (**B**). Subsequent reductive elimination provides benzothiazole with concomitant regeneration of catalytic copper species for the next cycle.



Scheme 3 Proposed mechanism for the formation of 2-aminobenzothiazole.

Conclusion

In conclusion 2-haloaryl-*sec*-alkyl unsymmetrical thioureas (Tu) (halo = –F, –Cl) with a catalytic amount of Cu(II) salt at room temperature gives thioamidoguanidino (Tag) which is obtained *via* a oxidative dimerisation followed by an imine-disulfide rearrangement. Changing the reaction temperature to 80 °C gives 2-aminobenzothiazole *via* a dehelogenative path and not by the Hugerschoff path involving an electrophilic substitution reaction. For thioureas containing reactive *ortho* halogens such as (–Br, –I) the reaction proceeds at room temperature giving 2-aminobenzothiazoles *via* a dehalogenative path. Failure to transform thiourea (Tu) to Tag with Cu(I) salts suggests the requirement of oxidising Cu(II) salts for this oxidative transformation. Thus this method gives an easy access to a variety of Tag moieties using environmentally benign reagents. These Tag moieties might find applications as metal scavengers and may be used as vulcanising agents. Mild reaction conditions, high yields and tolerance of various functional groups are some of the main attributes of this methodology.

General experimental procedure

Phenylisothiocyanates were prepared using our greener procedures.[13]

Experimental procedure for the synthesis of *anti*-Hugerschoff product (1a)

Morpholine (3 mmol) was added to a mixture of phenylisothiocyanate (**1**) (3 mmol, 666 mg) in EtOAc/H_2O (25 mL, (3 : 1) and stirred at room temperature. Formation of phenyl morpholine-4-carbothiamide (**1a**) was observed within 15 min as judged from TLC. To this was added an aqueous solution of $CuBr_2$ (0.9 mmol, 201 mg) and the resultant reaction mixture was stirred at room temperature for 20 min. During this period a pale yellow solution along with yellow precipitate was obtained. After completion of the reaction, ethyl acetate (20 mL) was added to the reaction mixture. Aqueous ammonia (20%, 10 mL), was added to the above ethyl acetate suspended reaction mixture and the heterogeneous mixture was stirred at room temperature. During this time (10 min) the suspended insoluble yellow solid got dissolved into the ethyl acetate layer leaving the ammonia layer blue in color. The ethyl acetate layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product is further purified by recrystallisation using ethyl acetate and pentane (9 : 1) (551 mg, 89%). Alternatively, if desired the product can be purified by passing through silica gel column and eluted with hexane : ethylacetate (8 : 2) containing 1% triethylamine to give the desire product (551 mg, 89%).

General procedure for preparation of 2-morpholin benzo[d]-thiazole (11′a) from *N*-(2-fluoro phenyl)morpholine-4-carbothiamide (5a) using $CuBr_2$.

2-Fluoro phenylisothiocyanate (**11**) (2 mmol) in DMSO (2 mL) was added morpholine (2 mmol) and stirred at room temperature complete formation of *N*-(2-fluoro phenyl) morpholine-4-carbothiamide **11′a** was observed within 15 min. To this was added Na_2CO_3 (2 mmol), $CuBr_2$ (0.01 mmol, 5 mol%) and the reaction mixture was heated in an oil bath at 80 °C. The progress of the reaction was monitored by TLC. After 22 h the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified over a column of silica gel with EtOAc : pentane (2 : 8) as the eluents to give the product **1a** in 0.330 g 75% isolated yield.

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