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PAPER

An "on-water" exploration of CuO nanoparticle catalysed synthesis of 2-aminobenzothiazoles†‡

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An "on-water" one-pot process has been engineered for the preparation of 2-aminobenzothiazole from *ortho*-halo (–F, –Cl, –Br and –I) substituted unsymmetrical thioureas. For *ortho* –I and –Br substrates the reactions afford 2-aminobenzothiazoles under metal free condition promoted by base. However, the relatively inert *ortho* –Cl and –F substrates undergo intramolecular arylthiolation only in the presence of CuO nanoparticles yielding 2-aminobenzothiazoles. This methodology provides easy access to aminobenzothiazoles utilising even the *ortho* –Cl and –F substrates. The catalyst is recyclable several times without loss of substantial activity. Other remarkable features include the wide range of functional group tolerance, absence of chromatographic purification (for *ortho* –I and –Br substrates) and providing moderate to excellent yield of the products under mild conditions, thus rendering the methodology as a highly eco-friendly alternative to the existing methods.

Introduction

In recent years, many efforts have been devoted towards sustainable reaction media, and notably the use of water as solvent has grabbed considerable interest among the synthetic community.[1] Indeed, water as a solvent offers many advantages because it is cheap, readily available, non-toxic and non-flammable, thus being very attractive from both an economical and environmental point of view. In addition, water is also recognized as an effective reaction medium with unique properties for many organic reactions that cannot be attained in conventional organic solvents.[1d,e,2] It is believed, particularly for on-water reactions, that the hydrophobic effect of water generates an internal pressure which brings the reactants into close proximity and promotes the association of reactants in solvent cavities during reaction processes and thus accelerates reactions.[1c,h,3] As a result, tremendous efforts have been implemented in the development of catalytic processes by employing water as a medium to accomplish greener syntheses. A query that exists is how far the on-water catalytic processes could be engineered to benefit the synthesis of biologically important pharmacophores. To speak of bioactive molecules, substituted benzothiazoles display a diverse array of such compounds. In this regard, 2-aminobenzothiazoles have attracted particular attention as they comprise the privileged motifs prevalent in various pharmaceutical and agrochemical compounds.

Various pharmacophores bearing this heterocyclic unit have revealed a broad spectrum of biological activities that encompass anti-inflammatory, anti-microbial, anti-tumour, neuroprotective and anti-convulsant activities.[4] Instances of the recent developments of the pharmacophores possessing the 2-aminobenzothiazole as the core unit include a potent inhibitor of all *trans*-retinoic acid metabolism (**1**),[4d] the antibacterial compound (**2**),[5] the PPAR agonist (**3**),[6] the H3-receptor ligand (**4**),[7] the nicotinic-acetylcholine-receptor ligand (**5**),[8] and activity for enhancing the atRA-induced expression of CYP26B1 (**6**)[4e] as shown in Fig. 1.

The potential of the 2-aminobenzothiazoles has led to them being encountered through the development of various synthetic protocols. The classical methodologies employed for their synthesis involve (i) transition metal-catalyzed intramolecular

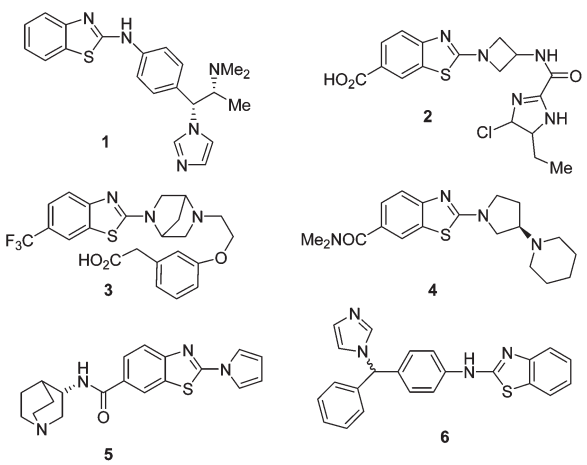

Fig. 1 Structures of bioactive 2-*N*-substituted benzothiazoles.

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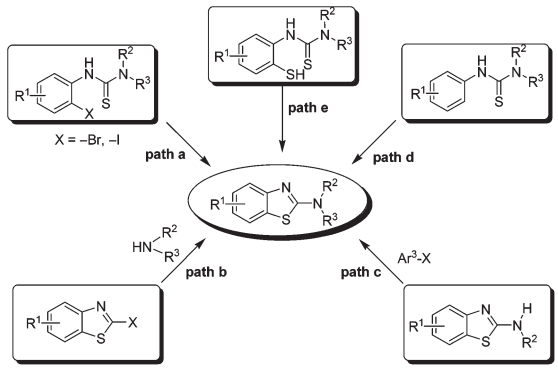
†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra and HRMS spectra. CCDC 876212 and 829313. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2gc35575b

‡This manuscript is dedicated to Prof. Rajani Kanta Behera on the occasion of his 60th birthday.



Scheme 1 Available literature methods for the preparation of 2-amino benzothiazoles.

cyclisation of 2-halobenzothioureas (path a, Scheme 1),[9] (ii) coupling of arylamines with preformed 2-halobenzothiazoles (path b, Scheme 1)[10] or 2-aminobenzothiazoles with aryl halides, (path c, Scheme 1)[11] and (iii) oxidative cyclisation of thiobenzanilides including Jacobson's and Hugerschoff's methods (path d, Scheme 1)[12] or the intermediates generated by 2-aminothiophenols with isothiocyanates (path e, Scheme 1).[13]

Although these methods are generally efficient and high yielding, a careful scrutiny would entail that most of the strategies suffer some setback owing to their limited utility and applicability in large and industrial scale applications. This is because they usually employ highly toxic and corrosive reagents, expensive catalyst systems, drastic reaction conditions or generate environmentally hazardous wastes. To circumvent these disadvantages various modified protocols were being explored that involve the use of recyclable catalysts under ligand-free conditions[13a,14] the C–H activation strategy[15] or the metal-free base-mediated conditions[16] to promote intramolecular C–S bond forming reactions. Despite there being a subtle improvement of the reaction conditions through these strategies, somewhere down the line they still lack the versatility. The most concerning outcome is the detrimental effect of environmentally non-compatible solvents. Secondly, the catalyst systems are usually non-recoverable, thereby reducing the turn over number (TON) or turn over frequency (TOF) which are important from an industrial point of view. Also worth mentioning is that most of the literature methods focused on the cross-coupling reactions of more labile *o*-iodo or *o*-bromo substrates. Hence they are devoid of substrate generality as the inert C–Cl and C–F bonds are overlooked most of the time. In this regard the C–H activation strategy seems advantageous due to operational simplicity and avoiding the arduous substrate pre-activation steps, however, they make use of highly oxidised conditions which are undesirable in pharmaceuticals. Therefore it is of utmost importance to develop economically and environmentally more viable procedures for the synthesis of 2-aminobenzothiazoles.

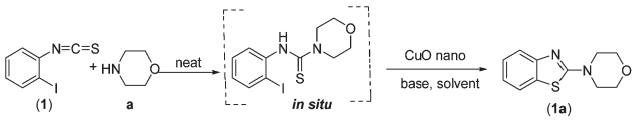
On the other hand, nano-crystalline metal oxides bearing high surface area and reactive morphologies find excellent applications as catalysts for various organic transformations.[17] Furthermore, the nano-material catalysed reactions provide the advantages of high atom efficiency, simplified isolation of product, and easy recovery and recyclability of the catalysts. These features of the nano-materials, in particular the salts of copper have been successfully exploited for various C–N, C–O, C–S cross-coupling reactions.[14,18] It is worth mentioning here that CuO nanoparticles as catalysts have been able to provide the platform to realise the carbon heteroatom bond formation through a dehalogenative path of the relatively inert C–F and C–Cl bond under mild conditions.[18d,e] The tendency of Cu as compared to Pd towards dehalogenative path over a C–H activation has been very recently demonstrated by us.[19]

Hence, judging the rationale behind the development of a versatile and sustainable methodology and our interest on the exploration of expeditious synthesis of heterocyclic frameworks,[19,20] we have envisioned a practical, greener route to 2-aminobenzothiazoles *via* a water mediated tandem reaction of 2-haloarylisothiocyanates with various amines. Herein, we report our observations in this regard.

Results and discussion

To examine the feasibility of CuO catalysed reaction on water, an initial experiment was performed with *o*-iodophenyl isothiocyanate (**1**) and morpholine (**a**) as the model substrate. Upon treatment of *o*-iodophenylisothiocyanate **1** (1 equiv.) with morpholine (**a**) (1 equiv.) under neat condition provided the intermediate thiourea which was then subjected to cross-coupling reaction following subsequent addition of K_2CO_3 (1 equiv.) and catalyst CuO nanoparticles (2.5 mol%) in aqueous medium. No reaction was observed at room temperature but by performing the reaction at 80 °C (Table 1, entry 2) encouragingly the reaction afforded the corresponding product 2-aminobenzothiazole **1a** *via* intramolecular cyclisation in 80% yields within 1.5 h. With further increase in temperature to 100 °C the yield increased to 95% within a shorter span of 30 min (Table 1, entry 3). A decrease in the catalyst amount to 2 mol% provided a consistent result without alteration of yield (Table 1, entry 4). With the initial results in hand, a series of experiments were performed by varying solvents, temperature, catalyst quantity and bases to arrive at the best optimal reaction conditions and establish the superiority of water as solvent compared to commonly employed organic solvents. The results are summarised in Table 1. Entries 4 and 9 (Table 1) show that both water and DMSO were equally effective in giving good yields in short reaction time while both K_2CO_3 (Table 1, entry 4) and Cs_2CO_3 (Table 1, entry 6) could be used as the base of choice when 2 mol% of the catalyst was used. It is noteworthy that when a blank reaction (without CuO) was performed (Table 1, entry 13) a low conversion of the product (**1a**) was obtained. On increasing the base quantity to 3 equivalents the yield enhanced to 94% within 3 h (Table 1, entry 15). Hence considering the Green Chemistry criteria, we opted to choose water as solvent and K_2CO_3 as the base under metal-free conditions (Table 1, entry 15) for subsequent studies of the *o*-iodo substrates. It may be mentioned here that a metal free synthesis of 2-substituted benzothiazoles has been achieved *via* base promoted cyclisation in organic solvent dioxane having 2-bromo and 2-iodo substrates at 130 °C in a sealed tube.[16c] In this "on water" reaction the starting materials thiourea remains insoluble in water and so is the product which can be filtered out. Alternatively it can be extracted out from the reaction mixture with ethyl acetate leaving behind the aqueous

Table 1 Optimisation of reaction conditions[a]



Entry	Catalyst (mol%)	Solvent	Base (equiv.)	Temp	Time (h)	Yield[b] (%)
1.	CuO (2.5)	H_2O	K_2CO_3 (1)	30 °C	5	00
2.	CuO (2.5)	H_2O	K_2CO_3 (1)	80 °C	1.5	80
3.	CuO (2.5)	H_2O	K_2CO_3 (1)	100 °C	0.5	95
4.	CuO (2)	H_2O	K_2CO_3 (1)	100 °C	0.5	95
5.	CuO (1)	H_2O	K_2CO_3 (1)	100 °C	2	77
6.	CuO (2)	H_2O	Cs_2CO_3 (1)	100 °C	0.5	96
7.	CuO (2)	H_2O	NaOH (1)	100 °C	2	65
8.	CuO (2)	H_2O	Et_3N (1)	100 °C	2	40
9.	CuO (2)	DMSO	K_2CO_3 (1)	100 °C	0.5	92
10.	CuO (2)	DMF	K_2CO_3 (1)	100 °C	2	70
11.	CuO (2)	Toluene	K_2CO_3 (1)	100 °C	2	55
12.	CuO (2)	Dioxane	K_2CO_3 (1)	100 °C	2	63
13.	Nil	H_2O	K_2CO_3 (1)	100 °C	7	20
14.	Nil	H_2O	K_2CO_3 (2)	100 °C	5	60
15.	**Nil**	**H_2O**	**K_2CO_3 (3)**	**100 °C**	**3**	**94**

[a] Reactions were monitored by TLC. [b] Isolated yield.

suspension CuO catalyst for further round of reaction, thus an excellent demonstration of "on water" reaction.

With the optimal "on water" reaction conditions established, we sought to investigate the scope and generality of this methodology. The results shown in Table 2 attest that this methodology is compatible with a broad range of substituents in the amines or the *o*-iodo isothiocyanate. Aliphatic secondary amines (**a–c**, Table 2) and primary amines (**d**, Table 2) were particularly effective providing an excellent yield of the desired products (**1a**, **1b**, **1c** and **1d**) through sequential formation of the respective thioureas and subsequent intramolecular arylthiolation. The structure of the product (**1b**) has been further confirmed by X-ray crystallographic analysis as shown in Fig. 2. The reaction of 2-iodoisothiocyanates (**1**) with various substituted aryl amines (**e–g**) examined also proceeded well to afford the 2-aminobenzothiazoles (**1e–1g**) in good yields (Table 2). Both electron rich (**f**, Table 2) and electron deficient (**g**, Table 2) aromatic amines successfully rendered the corresponding benzothiazoles (**1f**) and (**1g**) respectively. Substituted 2-iodo isothiocyanates possessing electron-donating group (**2**) and an electron-withdrawing group (**3**) with morpholine yielded corresponding thiourea *in situ* which were efficiently transformed to their respective benzothiazoles (**2a**) and (**3a**) in excellent yield under the basic aqueous medium.

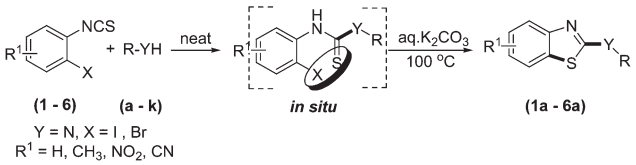
A few notable characteristics of these reactions include the observation that the reactions were faster for the substrates thioureas (*in situ* generated) derived from aliphatic secondary amines (**a–c**, Table 2). For primary arylamines having electron-donating (**f**) or electron-withdrawing substituents (**g**) there seem to be either little or no effect on either reaction time or on the product yields. A similar result was observed with thioureas derived from isothiocyanates containing electron-donating (**2**) or electron withdrawing substituents (**3**) (Table 2).

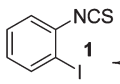
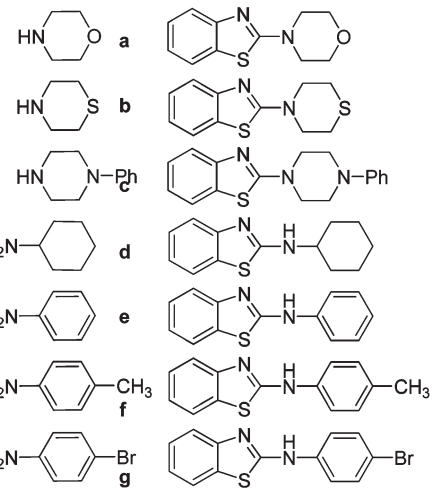
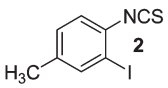
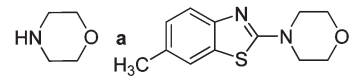
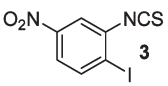
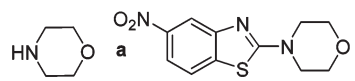
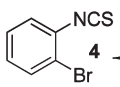
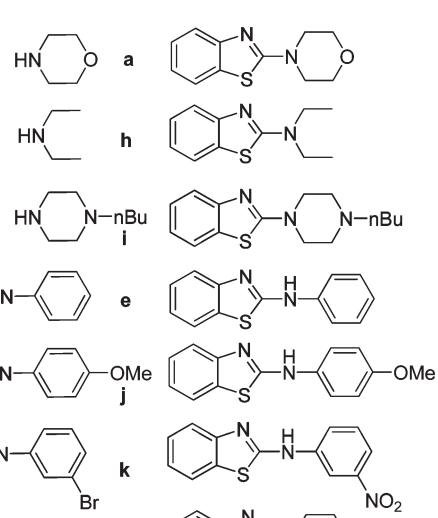
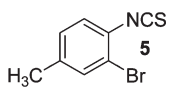
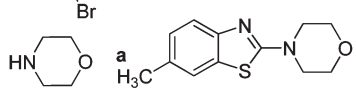
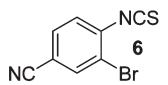
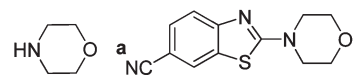
After having successfully established the reaction with the *o*-iodo substrates, next we executed the reaction onto the *o*-bromo substrates. It was delightful to observe that the optimised condition could be equally applicable to the 2-bromo substituted thioureas however being slightly sluggish comparative to the *o*-iodo substrates. The reaction of 2-bromophenylisothiocyanate (**4**) with either aliphatic secondary amines (**a**, **h–i**) or primary amines (**e**, **j–k**) afforded corresponding thioureas *in situ* which underwent the intramolecular cyclisation providing the desired products in good to excellent yields. This reveals the versatility of this protocol.

In order to reveal further scope of this methodology we turned our attention to the *ortho*-chloro substrates. An attempt to effect the intramolecular arylthiolation with the *in situ* generated *o*-chlorothiourea obtained by reacting 2-chlorophenylisothiocyanate (**7**) and morpholine (**a**) (Table 3, entry 1) under the above standardised condition provided inferior results as no conversion was observed at all even after 24 h. This observation indicates the degree of inertness of the C–Cl bond toward the intramolecular cyclisation (C–Cl bond energy 95 kcal mol^{-1}) under metal free condition. Hence, the use of the catalytic CuO nanoparticle was thought to facilitate the transformation. To examine the effect of catalyst the *in situ* generated *o*-chloro thiourea obtained by reacting 2-chlorophenylisothiocyanate (**7**) and morpholine (**a**) with 2 mol% of the catalyst provided the desired product (**1a**) in decent yield of 68% (Table 3, entry 2) along with the formation of undesired decomposition products. When the catalyst amount was increased to 2.5 mol% there was marginal improvement of yield up to 72% (Table 3, entry 3). Surprisingly, increase in catalyst loading (beyond 5 mol%) had rather adverse effect on the product yield. The yield dropped resulting in the formation of undesirable side products (Table 3, entry 6 and entry 7). It is worth mentioning that the increase in catalyst quantity increased the rate of conversion, however, it was disadvantageous with respect to the formation of side products. Hence to suppress the formation of the multitude of undesired products, for subsequent investigation 2.5 mol% of the catalyst was used along with 1.5 equivalent of base (Table 3, entry 5). 2-Chloroisothiocyanate (**7**) was treated with different aliphatic secondary (**a**, **l**, **m**, Table 4) and primary (**e**, **n–p**, Table 4) amines to generate corresponding thioureas *in situ*. The reaction of resulting *in situ* thioureas in the presence of CuO nanoparticle catalyst proceeded well to give their respective benzothiazoles in moderate to good yields as shown in Table 4. Also, the *in situ* generated thioureas derived from electron-rich (**8**) and electron-deficient (**9**) isothiocyanates and aliphatic secondary amine (**a**) underwent this transformation giving corresponding benzothiazoles (**8a**) and (**9a**) respectively, in modest yield.

Likewise, when 2-fluoroarylisothiocyanates (Table 4, **10–13**) were treated with various primary and secondary amines, the resultant *o*-fluoroaryl thioureas underwent the intramolecular heteroarylation reaction well in the presence of the catalyst. However the reaction rate was more sluggish compared to its –I, –Br or –Cl-analogues. This counts to the high bond energy of the C–F bond (C–F bond energy 124 kcal mol^{-1}) and attributes to reluctance of the intramolecular cyclisation. Usually a very moderate yield of the product was obtained with the *o*-fluoro counterpart. This observation further supports our recent observation that Cu prefers the dehalogenative path over a C–H

Table 2 Synthesis of 2-aminobenzothiazoles *via* base-mediated intramolecular arylthiolation[a]



Substrate	Amine	Product[b]	Time (h)	Yield[c] (%)
		**1a**	3	96
		1b	3	94
		1c	3.5	91
		1d	5	90
		1e	8	82
		1f	7	85
		1g	10	78
		**2a**	4	95
		**3a**	2	97
		**1a**	4	95
		4h	5	90
		4i	5	92
		1e	10	78
		4j	10	81
		4k	12	75
		**2a**	4	92
		**6a**	3	96

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

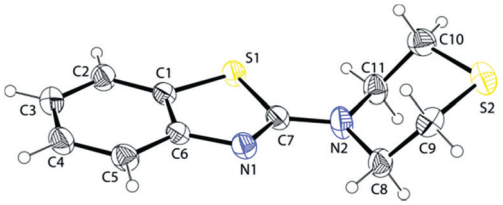
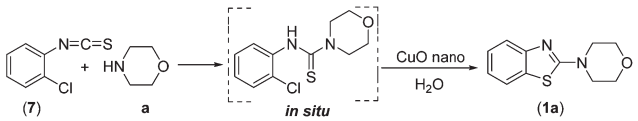


Fig. 2 Ortep view of structure **1b**.

Table 3 Optimisation of reaction conditions[a]



Entry	Catalyst (mol%)	Base (equiv.)	Time (h)	Yield[b] (%)
1	Nil	K_2CO_3 (3)	24	0
2	CuO (2)	K_2CO_3 (1)	24	68
3	CuO (2.5)	K_2CO_3 (3)	24	72
4	CuO (2.5)	K_2CO_3 (2)	24	72
5	**CuO (2.5)**	**K_2CO_3 (1.5)**	**24**	**72**
6	CuO (5)	K_2CO_3 (1.5)	18	60
7	CuO (7.5)	K_2CO_3 (1.5)	16	54

[a] Reactions were monitored by TLC. [b] Isolated yield.

activation as compared to Pd which prefers mostly C–H activation for less reactive halogens (–F, –Cl).[19] The formation of dehalogenation product has also been unambiguously established by the X-ray crystallography of the product (**10q**) possessing the chiral amine (Fig. 3). To generalise few observations, it was found that with both the 2-chloro or the 2-fluoro substituted thioureas the reactions occurred rather smoothly with the electron-withdrawing groups on the aryl moiety possessing the halogen while hardly was there any effect of the substituents on the aryl amines. However, as with the *o*-iodo and *o*-bromo analogues, the reactions with the aliphatic amines were far superior.

The substrates consisting of *o*-iodo and *o*-bromo substituents underwent the cyclisation in the presence of base without the requirement of metal catalyst (Table 2). Hence, from this observation, it could be concluded that for iodo and bromo substrates the reaction proceeded through a base promoted intramolecular nucleophilic aromatic substitution (INASOB) of *o*-halothioureas as has been proposed by others.[16] However, the possibility of a benzyne mechanism for iodo and bromo substrates could not be ruled out since the halide reactivity follows the order I > Br > Cl > F when cleavage of C–X bond is the rate determining step.[21] For those containing *o*-chloro and *o*-fluoro the cyclisation was affected by the metal catalyst and there was no reaction without it. Furthermore, the reaction proceeded smoothly with an electron-withdrawing group on the aryl moiety bearing the halide. Hence it is presumed that the mechanistic path goes *via* an oxidative addition subsequently followed by a reductive elimination. CuO nanoparticles (**A**) bearing highly reactive morphologies expectedly form an active cluster intermediate (**B**) which on oxidative addition at the C–X bond may give intermediate (**C**) (Scheme 2). The excess positive charge is being dispersed among the CuO nanoparticles present on the surface cluster. The intermediate (**D**) then undergoes an intramolecular arylthiolation *via* a reductive elimination of the catalyst, which continues the catalytic cycle along with the formation of the cross coupled product.[14,18e]

An assessment of the efficacy of the catalyst toward further catalytic cycles was being performed through a series of reactions involving thiourea derived from 2-chlorophenylisothiocyanate (**7**) and amine (**a**). In the first cycle 80% conversion (by G.C.) was obtained after 24 h under the optimised conditions. The product was then extracted out with ethyl acetate and the aqueous layer containing the dispersed CuO nanoparticles were then subjected to next run by adding thiourea and K_2CO_3. In this cycle 75% yield was obtained. This process of recycling the catalyst was repeated for three more cycles and the result is summarised in Table 5. The catalyst was found to be effective up to five cycles giving a conversion up to 73%, however, with relatively longer reaction time for increasing cycles.

After five cycles the aqueous layer containing the catalyst was centrifuged and its morphology was determined by TEM and powder XRD. A comparative study of the TEM and powder XRD of the fresh catalyst and the recovered catalyst after five cycles (Fig. 4 and 5) shows that the catalyst does not undergo substantial leaching or agglomeration during the recycling process.

Conclusion

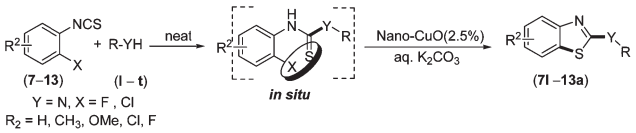
In conclusion, we have developed a simple, versatile, efficient on water one-pot methodology for the synthesis of 2-aminobenzothiazoles from the *in situ* generated 2-halothioureas. In the case of *o*-iodo and *o*-bromo substrates, reactions were, in general, very clean and high yielding without the assistance of any metal catalyst. However, *o*-chloro and *o*-fluoro substrates undergo intramolecular arylthiolation only in the presence of CuO nanoparticles. Use of an ecologically favourable base, recyclable catalyst and water as the reaction medium makes this methodology a benign alternative to the existing methods.

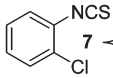
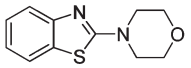
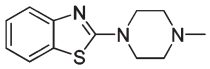
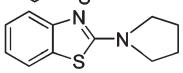
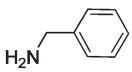
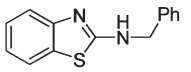
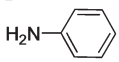
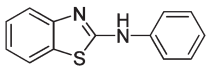
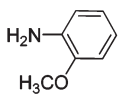
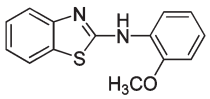
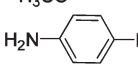
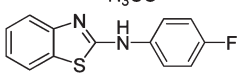
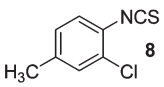
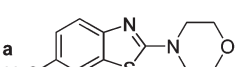
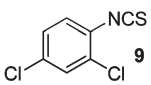
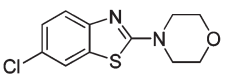
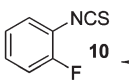
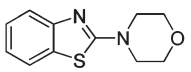
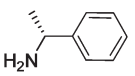
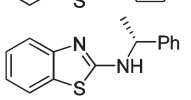
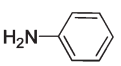
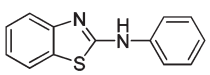
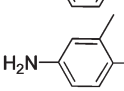
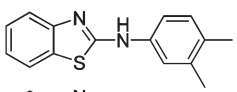
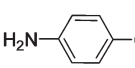
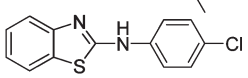
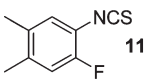
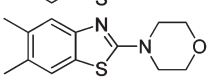
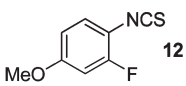
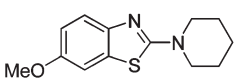
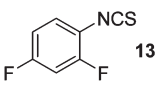
General procedure

Synthesis of 2-morpholinbenzo[d]thiazole (1a) from 2-iodo isothiocyanate(1)

2-Iodophenyl isothiocyanate (**1**) (1 mmol) was treated with morpholine (**a**) (1 mmol) under neat conditions and immediate formation of the corresponding thiourea was observed. To this *in situ* generated thiourea, was subsequently added H_2O (5 mL) and K_2CO_3 (3 mmol) and the mixture was subjected to reflux in a preheated oil bath at 100 °C. The progress of the reaction was monitored by TLC each time by extracting a small aliquot from the aqueous medium containing dispersed particles using ethyl acetate. On completion of the reaction (3 h) as judged from TLC the reaction mixture was cooled to room temperature and extracted with ethyl acetate (2 × 10 mL). The combined ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was recrystallised to give the pure product **1a** (202 mg, 92% yield).

Table 4 CuO-nanoparticles catalysed one-pot synthesis of 2-aminobenzothiazoles[a]



Substrate	Amine	Product[b]	Time (h)	Yield[c] (%)
	 a		**1a**	24	72
	 l		**7l**	24	70
	 m		**7m**	24	71
	 n		**7n**	30	64
	 e		**7e**	33	63
	 o		**7o**	33	60
	 p		**7p**	34	61
	 a		**8a**	28	62
	 a		**9a**	23	74
	 a		**1a**	29	65
	 q		**10q**	44	51
	 e		**10e**	43	52
	 r		**10r**	43	53
	 s		**10s**	44	48
	 a		**11a**	33	61
	 t		**12t**	35	60
	a		**13a**	29	67

[a] Reactions were monitored by TLC. [b] Confirmed by IR and ^{1}H and ^{13}C NMR. [c] Isolated yield.

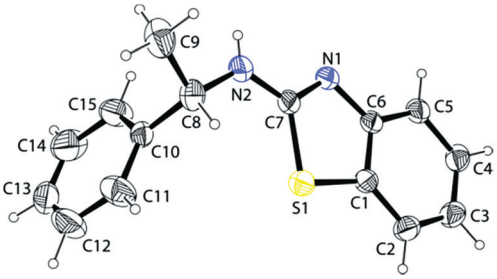
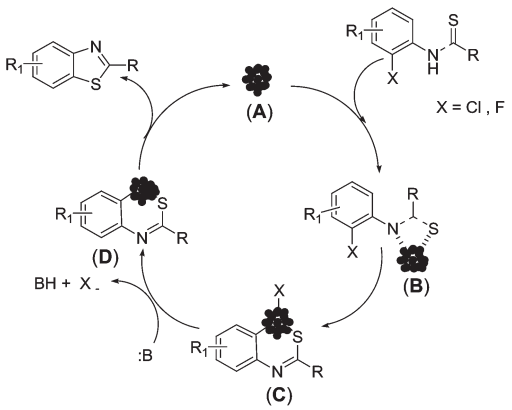


Fig. 3 ORTEP view of structure **10q**.



Scheme 2 Proposed catalytic cycle for intramolecular arylthiolation.

Table 5 Recycling of the catalyst[a]

No of cycle	Conversion[b] (%)	Time (h)
1	80	24
2	78	25
3	75	28
4	73	29
5	73	31

[a] Reactions were monitored by TLC. [b] GC yield.

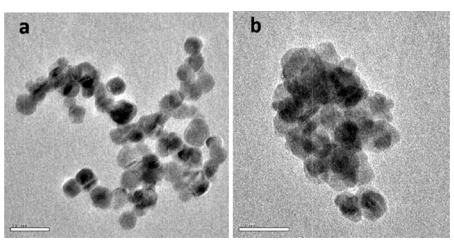


Fig. 4 TEM images of (a) fresh CuO nanoparticles and (b) CuO nanoparticles after the fifth catalytic cycle.

Synthesis of 2-morpholinbenzo[d]thiazole (1a) from 2-chloroisothiocyanate (7) using copper nano catalyst

2-Chlorophenyl isothiocyanate (**7**) (1 mmol) was treated with morpholine (**a**) (1 mmol) under neat conditions to provide the corresponding thiourea. To this *in situ* generated thiourea, was

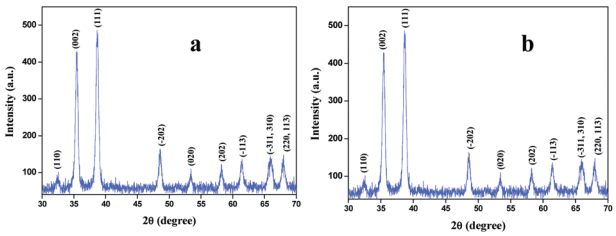


Fig. 5 Powder X-ray diffraction patterns of (a) fresh CuO nanoparticles and (b) CuO nanoparticles after fifth cycle.

subsequently added CuO nanoparticles (2.5 mol%), K_2CO_3 (1.5 mmol) in H_2O (5 mL) and the reaction mixture was subjected to reflux in a preheated oil bath at 100 °C. The progress of the reaction was monitored by TLC each time by extracting small aliquot of the aqueous medium containing dispersed particles using ethyl acetate. After 24 h, on completion of the reaction (judged by TLC) the reaction mixture was cooled to room temperature and extracted with ethyl acetate (2 × 10 mL). The insoluble CuO nanoparticles that remain suspended in the water can be reused as such for next round of reaction if desired. The combined ethyl acetate layer was then dried over anhydrous Na_2SO_4 and removed under reduced pressure. The crude product was purified over a column of silica gel eluting with (2 : 8, EtOAc–petroleum ether) to give the pure product **1a** (145 mg, 72% yield).

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