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Original article

Synthesis of *N*-substituted-2-aminobenzothiazoles using nano copper oxide as a recyclable catalyst under ligand-free conditions, in reusable PEG-400 medium

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ABSTRACT

A simple and practical method for the synthesis of *N*-substituted-2-aminobenzothiazoles *via* a cross-coupling reaction of 2-iodo anilines with isothiocyanates is envisaged using nano copper oxide as a recyclable catalyst and Cs_2CO_3 as a base in PEG-400, as a bio-degradable, reusable, inexpensive and non-toxic reaction medium, under ligand-free conditions. The present tandem process underlines environmental acceptability to access a wide range of *N*-substituted-2-aminobenzothiazoles in good to excellent yields.

1. Introduction

In modern organic synthesis, biologically active benzothiazoles are considered privileged building blocks. In particular 2-aminobenzothiazoles like 2-(*N*-alkyl amino)benzothiazoles, 2-(*N*-acyl amino)benzothiazoles are involved in several applications in medicinal chemistry [1–3]. 2-Aminobenzothiazoles are unique scaffolds that are widely used in medicinal and biological chemistry [4]. A large number of 2-anilinobenzothiazole derivatives are found to be anticancer agents and represent an important pharmacophore as well as a reactive intermediate [5]. These compounds have remarkable biological activity and are widely employed for the treatment of various diseases such as tuberculosis [6], epilepsy [7], diabetes [8] and cancer [9] (Fig. 1).

Due to the pharmaceutical significance of the benzothiazole core structure, several synthetic approaches have been reported. These include coupling of 2-aminobenzothiazoles with aryl halides [10,11], coupling of aryl amine with 2-halobenzothiazoles [12–14], arylthioureas with liquid bromine [15], and oxidative cyclization of the intermediates generated by 2-amino thiophenol with isothiocyanates [16]. Recently, direct oxidative coupling between benzothiazoles and amines, Domino three-component reactions of carbon disulfides, amines, 2-halo anlines and intermolecular C–S bond formation in the synthesis of 2-aminobenzothiazoles catalyzed by Cu/Pd/Fe have been reported [17–22]. However, the reported catalytic systems or solvent media are not recyclable. In continuation of our work in cross-coupling reactions and heterogeneous catalysis [23–34], herein we describe an inexpensive, air-stable and recyclable nano copper oxide as a catalyst for the synthesis of 2-aminobenzothiazoles under ligand-free conditions (Scheme 1). In the present protocol, PEG-400 (polyethylene glycol) is employed as a low cost and reusable solvent. PEG has received attention of many research groups because it is a hydrophilic polymer. PEG-400 is inexpensive, recyclable, biodegradable, relatively nonflammable andnontoxic, miscible with a wide variety of organic solvents and can be used as an ecofriendly solvent for various organic transformations such as coupling [35], substitution [36], oxidation [37], addition [38] and reduction reactions [29–40].

The deployment of PEG in the organic synthesis could reduce the use of volatile organic solvents and environmental burden. PEG can be used as an alternate medium for different reactions with easy recyclability of solvent and catalysts, unlike several of the "neoteric solvents" such as the expensive ionic liquids (ILs).

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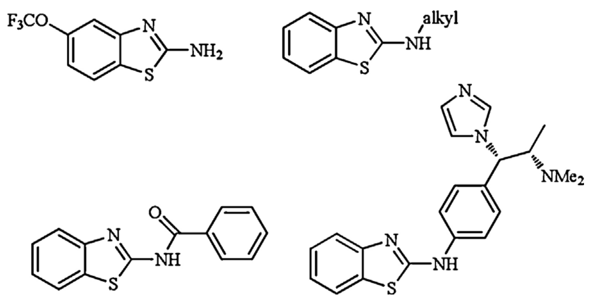
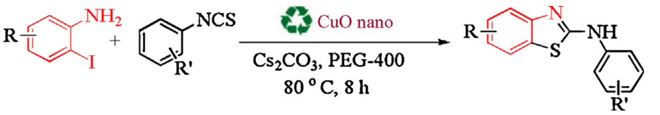


Fig. 1. Biologically active *N*-substituted-2-aminobenzothiazole derivatives.



Scheme 1. Recyclable nano CuO catalyzed synthesis of *N*-substituted-2-aminobenzothiazoles.

Recently, heterogeneous catalysts have become attractive both from economic and industrial points of view. The high surface area and reactive morphology of the nanomaterials allow them to be effective catalysts for organic synthesis. Nano copper oxides (CuO nps) have the advantages of improved recyclability, easier workup, and cleaner reaction profiles in addition to the lack of necessity of external ligands, which minimizes the organic waste generation, as compared to the conventional catalytic systems.

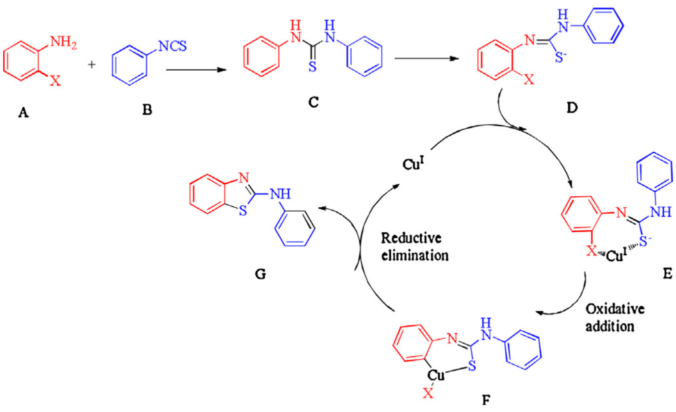
2. Experimental

All materials were purchased from Sigma Aldrich. Dry solvents and CuO nanopowders (<50 nm) were used for the reactions. Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F254 pre-coated plates. Column chromatography was carried out using silica gel (60–120 mesh size). Visualization was accomplished with UV lamp, I_2 stain, and Phosphomolybdic acid charring. ^{1}H NMR and ^{13}C NMR were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ using TMS as an internal standard. Chemical shifts were reported in parts per million (ppm) downfield from TMS.

General procedure: A mixture of 2-iodoaniline (0.5 mmol), isothiocyanate (0.6 mmol), CuO nanoparticles (0.05 mmol), and Cs_2CO_3 (1.5 mmol) in PEG-400 (3 mL) was stirred at 80 °C for 8 h (Scheme 1). After the reaction, the reaction mixture was centrifuged and catalyst was separated from the reaction mixture and then followed by washing with ethyl acetate and acetone, dried in vacuo and used directly for further catalytic reactions. The cooled solution was partitioned between ethyl acetate and water, and the organic layer was washed with water and brine, and then dried over Na_2SO_4. After the removal of the solvent in vacuo, the residue was purified by silica-gel chromatography to give the desired *N*-substituted-2-aminobenzothiazoles. All the compounds were characterized by comparison with authentic samples [41].

N-Phenylbenzo[d]thiazol-2-amine (Table 1, entry 1) [40]: White solid, mp 158–160 °C; yield 180 mg (80%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18–8.04 (m, 3H), 7.58–7.47 (m, 1H), 7.46–7.35 (m, 4H), 7.37–7.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4, 157.7,129.3, 126.6, 124.5, 122.0, 121.3, 120.0, 112.6; ESI-MS *m*/*z* 227 $(M+H)^+$.

4,6-Dimethyl-*N*-phenylbenzo[d]thiazol-2-amine (Table 1, entry 2) [40]: Yield 190 mg (85%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.45 (m, 2H), 7.41–7.33 (m, 2H), 7.29–7.25 (m, 1H), 7.19–7.05 (m, 2H), 6.199 (s, 1H), 2.58 (s, 3H) 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 139.9, 129.4, 128.8, 128.2, 123.6, 119.2, 117.9, 22.6, 21.2; ESI-MS *m*/*z* 255 $(M+H)^+$.



Scheme 2. Plausible mechanism for the formation of *N*-substituted-2-aminobenzothiazoles.

A model reaction was attempted under the optimized reaction conditions with 2-iodoaniline and isothiocyanates as a coupling partner. In general, the reaction proceeded well with these substrates to produce the 2-aminobenzothiazoles in good to excellent yields. It was found that both electron rich and electron poor aryl isothiocyanates underwent the tandem coupling reaction efficiently. The generality of the method was further explored by reacting a wide range of substituted 2-iodoanilines and substituted isothicyanates, resulting in the formation of the corresponding 2-*N*-substituted benzothiazole derivatives, as shown in (Table 1). All the products were confirmed by ^{1}H NMR, ^{13}C NMR spectroscopy, and compared spectroscopically with the authentic samples reported in the literature [41].

Recyclability of the nano copper oxide catalyst was examined under optimized reaction conditions and the results are described in (Table 2). After the reaction, the reaction mixture was centrifuged and catalyst was separated from the reaction mixture and then followed by washing with ethyl acetate and acetone, dried in vacuo and used directly for further catalytic reactions. No significant loss of catalyst activity was observed up to four cycles. The native and used nano copper oxide was analyzed by powder XRD. The powder XRD spectra confirmed that, the peaks of the both fresh and recovered nano copper oxide are identical. It is observed that the morphology of the catalyst remains the same even after four recycls.

3. Results and discussion

Initially, 2-iodo aniline and phenylisothiocyanates were used to optimize the reaction conditions such as base and solvent used and reaction temperature (Table 3), Among several bases screened, Cs_2CO_3 was found to be an excellent base (Table 3, entry 1). In presence of bases such as K_2CO_3, Na_2CO_3, and K_3PO_4, lesser amount of the desired product was obtained (Table 3, entries 2–4). The effect of solvent was also investigated and the highest yield was observed in PEG-400, while reaction in solvents such as THF, CH_3CN, and Toluene resulted in moderate yields (Table 3, entries 6–8). The experiment confirmed that the reaction did not occur in the absence of the base (Table 3, entry 9). When the reaction was conducted at room temperature a lower yield was obtained (Table 3, entry 5). The reaction did not occur in absence of the catalyst (Table 3, entry 10). Ideal temperature for the reaction was found to be 80 °C. The influence of the amount of catalyst on the yield of the product was also evaluated. It was observed that 0.05 mmol of CuO nano was ideal for the synthesis of *N*-substituted-2-aminobenzothiazoles in good to excellent yields.

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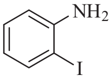
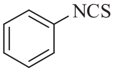
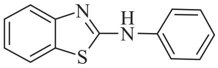
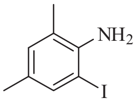
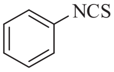
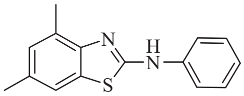
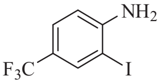
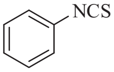
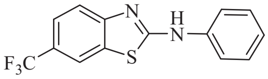
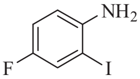
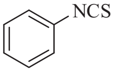
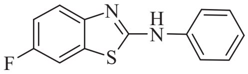
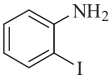
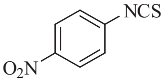
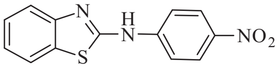
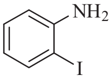
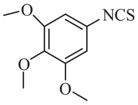
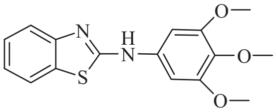
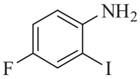
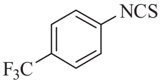
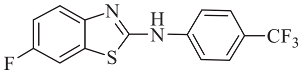
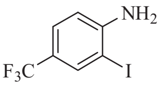
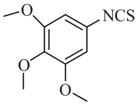
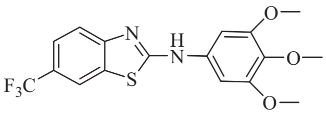
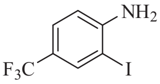
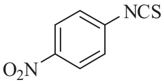
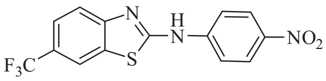
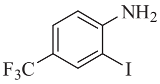
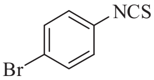
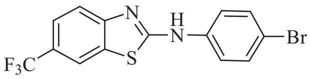
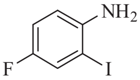
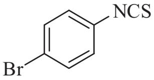
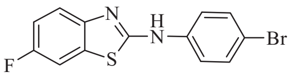
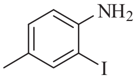
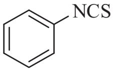
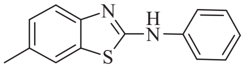
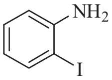
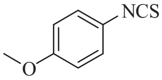
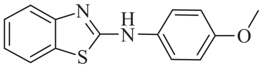
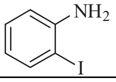
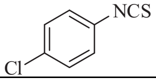
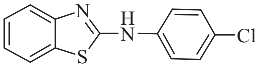
Table 1
Synthesis of *N*-substituted-2-aminobenzothiazoles.[a]

Entry	**1**	Substrates	Product	Yield (%)[b]
1				80
2				85
3				90
4				91
5				60
6				78
7				75
8				80
9				79
10				90
11				88
12				91
13				88
14				80

[a] Reaction conditions: 2-iodoaniline (0.5 mmol), isocyanate (0.6 mmol), nano copper oxide (0.05 mmol), and base (1.5 mmol) in solvent (3 mL) at 80 °C for 8 h.
[b] Isolated yield.

Table 2
Recyclability of CuO nanoparticles.[a]

Recycles	Yield (%)[b]	Catalyst recovery (%)
Native	91	97
1	89	95
2	87	92
3	85	90

[a] The conditions are same as that in Table 1.
[b] Isolated yield.

A plausible mechanism, which demonstrates the formation of *N*-substituted-2-aminobenzothiazoles from the 2-iodoanilines and isothiocyanates, is given in Scheme 2. [D] is formed by the reaction of 2-iodo aniline and isothiocyanate *via* the de protonation reaction. Then coordination of copper with [D] provides intermediate [E], which upon oxidative addition would form [F], which undergoes a reductive elimination to produce required final compound [G] with concomitant regeneration of the catalyst.

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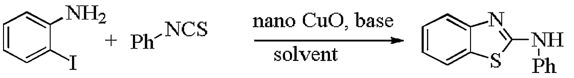
Table 3
Screening of nano copper oxide catalyzed synthesis of *N*-substituted-2-aminobenzothiazoles.[a]



Entry	Base	Solvent	Temp. (°C)	Yield (%)[b]
1	Cs_2CO_3	PEG	80	91
2	K_2CO_3	PEG	80	40
3	Na_2CO_3	PEG	80	20
4	K_3PO_4	PEG	80	Trace
5	Cs_2CO_3	PEG	r.t.	45
6	Cs_2CO_3	CH_3CN	80	60
7	Cs_2CO_3	Toluene	80	55
8	Cs_2CO_3	THF	80	0
9	–	PEG	80	0[c]
10	Cs_2CO_3	PEG	80	0
11	H_2O	PEG	80	0

[a] Reaction conditions: 2-iodo aniline (0.5 mmol), isocyanate (0.6 mmol), nano copper oxide (0.05 mmol), and base (1.5 mmol) in solvent (3 mL) at 80 °C for 8 h.
[b] Isolated yield.
[c] In absence of catalyst.

4. Conclusion

In conclusion, we have developed a novel protocol for the synthesis of *N*-substituted-2-aminobenzothiazoles by nanocrystalline CuO catalyzed coupling of 2-iodoanilnes and isothiocyanates under ligand-free conditions in good to excellent yields. This new protocol underlines the potential use of nanocrystalline CuO as user friendly, inexpensive, recyclable and efficient catalyst. This protocol also utilizes efficient, ecofriendly, recyclable, nontoxic, and biodegradable solvent PEG-400.

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