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A practical synthesis of 2-aminobenzothiazoles via the tandem reactions of 2-haloanilines with isothiocyanates catalyzed by immobilization of copper in MCM-41

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ABSTRACT

The heterogeneous tandem reactions of 2-haloanilines with isothiocyanates were achieved in DMSO using Et_3N as base at 80 °C in the presence of a 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized copper(II) complex [MCM-41-2N-$CuSO_4$], yielding a variety of 2-aminobenzothiazoles in good to excellent yields. This heterogeneous copper catalyst exhibited higher activity than $CuSO_4$ and can be recovered and recycled by a simple filtration of the reaction solution and used for at least 10 consecutive trials without any decreases in activity.

1. Introduction

2-Aminobenzothiazoles, one of the important classes of heterocyclic compounds, are broadly found in biological chemistry and medicinal areas [1–3]. A great amount of 2-anilinobenzothiazoles derivatives are proven to be anticancer active and the 2-aminobenzothiazole moieties are privileged pharmacophores as well as valuable reactive intermediates [4–10]. Therefore, considerable effort has been made in the development of efficient strategies for their construction. The majority of efficient methods include the palladium- or copper-catalyzed intramolecular cyclization of 2-bromobenzothioureas [8,11,12]. Castillon and coworkers reported Pd-catalyzed cyclization of 2-bromophenylthioamides using the $Pd_2(dba)_3$/(2-biphenyl)P(*t*-Bu)$_2$ catalytic system [11]. However, both a ligand and a base are required to promote the reaction, and the substrates are not readily available. Recently, the transition-metal-catalyzed tandem reactions of 2-halobenzenamines and isothiocyanates for the synthesis of 2-aminobenzothiazoles have received considerable attention because of their efficiency and low costs. For example, Wu and coworkers described a copper-catalyzed tandem reaction between 2-halobenzenamines and isothiocyanates using the CuI (10 mol %)/1,10-phenanthroline (20 mol%) catalytic system to prepare 2-aminobenzothiazoles [10]; Li and Ding's groups reported iron-catalyzed tandem reactions of 2-halobenzenamines and isothiocyanates leading to 2-aminobenzothiazoles [13,14]. Meanwhile, the ligand-free copper-catalyzed tandem reactions of 2-halobenzenamines and isothiocyanates were also reported [15,16].

Although these transition-metal-catalyzed tandem reactions of 2-halobenzenamines and isothiocyanates are highly efficient for the synthesis of 2-aminobenzothiazoles, the problem with homogeneous catalysis is the difficulty to separate the catalyst from the reaction mixture and the impossibility to reuse it in consecutive reactions. In addition, homogeneous catalysis might result in unacceptable metal contamination of the desired isolated product, which is a particularly significant drawback for its application in the pharmaceutical industry. In contrast, heterogeneous catalysts can be easily separated from the reaction mixture by a simple filtration of the reaction solution and reused in successive reactions provided that the active sites have not become deactivated. Heterogeneous catalysis also helps to minimize wastes derived from reaction workup, contributing to the development of green chemical processes [17–20]. From industrial and environmental points of view, the development of a cheap, efficient and environmentally benign catalyst is challenging and important. In an ideal system, they can be recovered by simple filtration and reused infinitely, and contamination of products by the metal is prevented.

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Polymer-supported palladium complexes catalysts have successfully been used in a variety of carbon–carbon bond or carbon–heteroatom bond formation reactions [20–23], however, polymer-supported copper complexes catalysts for organic transformations have received less attention [24,25]. Recently, Yang and coworkers reported the reaction of 2-haloanilines with isothiocyanates catalyzed by Merrifield resin-supported phenan throline–Cu(I) complex for the synthesis of 2-aminobenzothiazoles. However, the preparation of this heterogeneous copper catalyst required use of expensive and unavailable 5-amine-1,10-phenanthrolin and the catalytic activity decreased gradually with repeated uses [26]. Therefore, the development of new and easily accessible heterogeneous copper catalysts having a high activity and good stability is a topic of enormous importance. Our approach was guided by three imperatives: the polymeric ligand should be easily accessible (1), starting from readily available and cheap reagents (2). The polymeric copper catalyst should be air stable, which should allow its storage in normal bottles with unlimited shelf life (3). Developments on the mesoporous material MCM-41 provided a new possible candidate for a solid support for immobilization of homogeneous catalysts [27]. MCM-41 has a regular pore diameter of *ca.* 5 nm and a specific surface area $>700\ m^2\ g^{-1}$ [28]. Its large pore size allows passage of large molecules such as organic reactants and metal complexes through the pores to reach to the surface of the channel [29–31]. To date, some palladium and rhodium complexes on functionalized MCM-41 support have been prepared and successfully used in organic reactions [32–38]. However, no immobilization of copper in MCM-41 has been described in the open literature. It is generally believed that high surface area of heterogeneous catalyst results in high catalytic activity. Considering the fact that MCM-41 support has an extremely high surface area and the catalytic copper species is anchored on the inner surface of the mesopore of MCM-41, we expect that MCM-41-supported copper catalyst will exhibit high activity and good reusability. In continuing our efforts to develop greener synthetic pathways for organic transformations, our new approach, described in this paper, was to design and synthesize a new 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized copper complex (MCM-41-2N-$CuSO_4$), which was used as an effective copper catalyst for the tandem reactions of 2-halobenzenamines and isothiocyanates leading to 2-aminobenzothiazoles.

2. Experimental

2.1. General remarks

All chemicals were reagent grade and used as purchased. All solvents were dried and distilled before use. The products were purified by flash chromatography on silica gel. IR spectra were determined on a Perkin–Elmer 683 instrument. ^{1}H NMR spectra were recorded on a Bruker Avance (400 MHz) spectrometer with TMS as an internal standard in $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded on a Bruker Avance (100 MHz) spectrometer in $CDCl_3$ as solvent. Melting points are uncorrected. Copper content was determined with inductively coupled plasma atom emission Atomscan16 (ICP-AES, TJA Corporation). X-ray powder diffraction was obtained on Damx-rA (Rigaka). Microanalyses were measured by using a Yanaco MT-3 CHN microelemental analyzer. The mesoporous material MCM-41 was easily prepared according to a literature procedure [39].

2.2. Preparation of the catalyst

2.2.1. Preparation of MCM-41-2N

A solution of 1.54 g of 3-(2-aminoethylamino)propyltrimethoxysilane in 18 mL of dry chloroform was added to a suspension of 2.2 g of the MCM-41 in 180 mL of dry toluene. The mixture was stirred for 24 h at 100 °C. Then the solid was filtered and washed by $CHCl_3$ (2×20 mL), and dried in vacuum at 160 °C for 5 h. The dried white solid was then soaked in a solution of 3.1 g of Me_3SiCl in 100 mL of dry toluene at room temperature under stirring for 24 h. Then the solid was filtered, washed with acetone (3×20 mL) and diethyl ether (3×20 mL), and dried in vacuum at 120 °C for 5 h to obtain 3.49 g of hybrid material MCM-41-2N. The nitrogen content was found to be 1.84 mmol/g by elemental analysis.

2.2.2. Preparation of MCM-41-2N-$CuSO_4$

In a small Schlenk tube, 1.28 g of the above-functionalized MCM-41 (MCM-41-2N) was mixed with 0.106 g (0.66 mmol) of $CuSO_4$ in 10 mL of dry DMF. The mixture was stirred at room temperature for 7 h under an argon atmosphere. The solid product was filtered by suction, washed with DMF, distilled water and acetone and dried at 40 °C/26.7 Pa under Ar for 5 h to give 1.323 g of a pale blue copper complex (MCM-41-2N-$CuSO_4$). The nitrogen, sulfur and copper content were found to be 1.70 mmol/g, 0.45 mmol/g and 0.43 mmol/g, respectively.

2.3. General procedure for the synthesis of 2-aminobenzothiazoles

A mixture of 2-halobenzenamine (1.0 mmol), isothiocyanate (1.2 mmol), Et_3N (2.0 mmol) and MCM-41-2N-$CuSO_4$ (0.0025 mmol) in DMSO (2 mL) was stirred under an air atmosphere at 80 °C for 5–24 h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature. The solution was diluted with ethyl acetate (30 mL) and filtered. The catalyst was washed with ethyl acetate (2×5 mL) and Et_2O (2×5 mL) and reused in the next run. The organic layer was washed with water (2×10 mL) and dried over anhydrous Na_2SO_4. After evaporating under vacuum, the residue was purified by flash chromatography on silica gel (petroleum/ethyl acetate = 10:1 to 4:1) to provide the corresponding pure product **3**.

2.3.1. N-Phenylbenzo[d]thiazol-2-amine, ***3a***

White solid, mp 162–164 °C (lit [15]. mp 161–164 °C). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.59$ (s, 1H), 7.91 (d, $J = 7.2$ Hz, 2H), 7.83 (d, $J = 7.2$ Hz, 1H), 7.69 (d, $J = 7.2$ Hz, 1H), 7.44–7.35 (m, 3H), 7.19 (t, $J = 6.4$ Hz, 1H), 7.07 (t, $J = 6.4$ Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 162.1$, 152.7, 141.2, 130.5, 129.5, 126.3, 122.7, 122.5, 121.5, 119.7, 118.3 ppm.

2.3.2. N-(p-Tolyl)benzo[d]thiazol-2-amine, ***3b***

White solid, mp 178–179 °C (lit [15]. mp 178–179 °C). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.42$ (s, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.71 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.13 (t, $J = 7.6$ Hz, 1H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 162.2$, 152.7, 138.7, 131.5, 130.4, 129.8, 126.3, 122.6, 121.4, 119.5, 118.4, 20.9 ppm.

2.3.3. N-(4-Methoxyphenyl)benzo[d]thiazol-2-amine, ***3c***

White solid, mp 152–154 °C (lit [13]. mp 154–155 °C). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.35$ (s, 1H), 7.78–7.73 (m, 3H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.31 (t, $J = 7.6$ Hz, 1H), 7.12 (t, $J = 7.4$ Hz, 1H), 6.97 (d, $J = 8.8$ Hz, 2H), 3.74 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 162.6$, 155.2, 152.8, 134.5, 130.5, 126.3, 122.4, 121.4, 120.2, 119.4, 114.7, 55.6 ppm.

2.3.4. N-(4-Fluorophenyl)benzo[d]thiazol-2-amine, ***3d***

White solid, mp 215–216 °C (lit [40]. mp 216–217 °C). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.55$ (s, 1H), 7.88–7.83 (m, 2H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H),

7.26–7.12 (m, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.1, 157.8 (d, $^1J_{CF}$ = 237.0 Hz), 152.5, 137.6, 130.5, 126.3, 122.7, 121.5, 119.9, 119.7 (d, $^3J_{CF}$ = 16.0 Hz), 116.0 (d, $^2J_{CF}$ = 23 Hz) ppm.

2.3.5. N-(4-Chlorophenyl)benzo[d]thiazol-2-amine, ***3e***

White solid, mp 204–206 °C (lit [13]. mp 206–207 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.68 (s, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.8, 152.4, 140.0, 130.5, 129.3, 126.4, 125.9, 123.0, 121.6, 119.8, 119.7 ppm.

2.3.6. N-(4-Nitrophenyl)benzo[d]thiazol-2-amine, ***3f***

Orange solid, mp 225–226 °C (lit [13]. mp 225–227 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.24 (s, 1H), 8.28 (d, J = 9.2 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.1, 151.9, 146.9, 141.3, 130.8, 126.6, 125.9, 123.7, 121.8, 120.5, 117.6 ppm.

2.3.7. N-Cyclohexylbenzo[d]thiazol-2-amine, ***3g***

Pale oil [41]. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.22–7.17 (m, 1H), 7.01–6.96 (m, 1H), 3.72–3.68 (m, 1H), 2.00–1.97 (m, 2H), 1.74–1.71 (m, 2H), 1.60–1.56 (m, 1H), 1.40–1.14 (m, 5H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.6, 153.2, 130.6, 125.9, 121.2, 121.1, 118.3, 53.2, 32.8, 25.7, 24.9 ppm.

2.3.8. N-Phenyl-6-(trifluoromethyl)benzo[d]thiazol-2-amine, ***3h***

White solid, mp 160–161 °C (lit [41]. mp 163–165 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.72 (s, 1H), 8.19 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 7.8 Hz, 2H), 7.00 (t, J = 7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.4, 155.0, 140.2, 130.7, 129.0, 124.6 (q, $^1J_{CF}$ = 270.0 Hz), 122.7 (q, $^3J_{CF}$ = 3.0 Hz), 122.6, 122.4 (q, $^2J_{CF}$ = 33.0 Hz), 119.0, 118.6 (q, $^3J_{CF}$ = 4.0 Hz), 118.3 ppm.

2.3.9. N-(4-Methoxyphenyl)-6-(trifluoromethyl)benzo[d]thiazol-2-amine, ***3i***

White solid, mp 200–201 °C (lit [41]. mp 200–202 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.63 (s, 1H), 8.25 (s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.5, 155.7, 133.9, 131.1, 125.2 (q, $^1J_{CF}$ = 270.0 Hz), 123.2 (q, $^3J_{CF}$ = 4.0 Hz), 122.5 (q, $^2J_{CF}$ = 32.0 Hz), 120.8, 119.2, 119.1 (q, $^3J_{CF}$ = 4.0 Hz), 115.0, 114.7, 55.7 ppm.

2.3.10. N-(4-Fluorophenyl)-6-(trifluoromethyl)benzo[d]thiazol-2-amine, ***3j***

White solid, mp 200–201 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.83 (s, 1H), 8.28 (s, 1H), 7.90–7.86 (m, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.9, 158.2 (d, $^1J_{CF}$ = 238.0), 155.4, 137.1, 131.2, 125.1 (q, $^1J_{CF}$ = 270.0 Hz), 123.2 (q, $^3J_{CF}$ = 4.0 Hz), 122.9 (q, $^2J_{CF}$ = 32.0 Hz), 120.4 (d, $^3J_{CF}$ = 8.0 Hz), 119.5, 119.2 (q, $^3J_{CF}$ = 4.0 Hz), 116.0 (d, $^2J_{CF}$ = 23.0) ppm. Anal. Calcd. for $C_{14}H_8N_2F_4S$: C, 53.84; H, 2.58. Found: C, 53.58; H, 2.74.

2.3.11. N-(4-Chlorophenyl)-6-(trifluoromethyl)benzo[d]thiazol-2-amine, ***3k***

White solid, mp 190–192 °C (lit [13]. mp 191–192 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.93 (s, 1H), 8.30 (s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.1, 154.8, 139.0, 130.7, 128.7, 126.1, 124.6 (q, $^1J_{CF}$ = 270.0 Hz), 122.7 (q, $^3J_{CF}$ = 4.0 Hz), 122.6 (q, $^2J_{CF}$ = 32.0 Hz), 119.6, 119.2, 118.7 (q, $^3J_{CF}$ = 4.0 Hz) ppm.

2.3.12. N-(4-Nitrophenyl)-6-(trifluoromethyl)benzo[d]thiazol-2-amine, ***3l***

Yellow solid, mp 250–252 °C (lit [14]. mp 253–254 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.38 (s, 1H), 8.33 (s, 1H), 8.25 (d, J = 7.2 Hz, 2H), 8.00 (d, J = 7.2 Hz, 2H), 7.82 (d, J = 7.2 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.1, 154.7, 146.3, 141.8, 131.5, 125.7 (q, $^3J_{CF}$ = 8.0 Hz), 125.0 (q, $^1J_{CF}$ = 272.0 Hz), 123.8 (q, $^2J_{CF}$ = 33.0 Hz), 123.5, 120.5, 119.6, 118.0 (q, $^3J_{CF}$ = 7.0 Hz) ppm.

2.3.13. N-Phenyl-6-chlorobenzo[d]thiazol-2-amine, ***3m***

White solid, mp 187–189 °C (lit [13]. mp188–189 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.56 (s, 1H), 7.92 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.35–7.32 (m, 2H), 7.04 (t, J = 7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.7, 151.5, 140.9, 132.2, 129.5, 126.6, 126.5, 122.8, 121.2, 120.6, 118.4 ppm.

2.3.14. N-(p-Tolyl)-6-chlorobenzo[d]thiazol-2-amine, ***3n***

White solid, mp 197–198 °C (lit [13]. mp 198–200 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.46 (s, 1H), 7.91 (s, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 7.6 Hz, 2H), 2.28 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.9, 151.6, 138.4, 132.1, 131.8, 129.9, 126.5, 126.4, 121.2, 120.4, 118.6, 20.9 ppm.

2.3.15. N-(4-Methoxyphenyl)-6-chlorobenzo[d]thiazol-2-amine, ***3o***

White solid, mp 185–187 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.28 (s, 1H), 7.80 (s, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 3.66 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.8, 154.9, 151.2, 133.7, 131.6, 125.9, 125.7, 120.6, 119.9, 119.7, 114.2, 55.2 ppm. Anal. Calcd. for $C_{14}H_{11}N_2SOCl$: C, 57.82; H, 3.81. Found: C, 57.59; H, 3.67.

2.3.16. N-(4-Fluorophenyl)-6-chlorobenzo[d]thiazol-2-amine, ***3p***

White solid, mp 213–214 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.63 (s, 1H), 7.99 (s, 1H), 7.91–7.82 (m, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.3, 157.4 (d, $^1J_{CF}$ = 237.0 Hz), 150.9, 136.8, 131.7, 126.1, 121.4, 120.8, 120.1, 119.6 (d, $^3J_{CF}$ = 7.0 Hz), 115.5 (d, $^2J_{CF}$ = 22.0 Hz) ppm. Anal. Calcd. for $C_{13}H_8N_2FSCl$: C, 56.01; H, 2.89. Found: C, 55.79; H, 2.63.

2.3.17. N-(4-Chlorophenyl)-6-chlorobenzo[d]thiazol-2-amine, ***3q***

White solid, mp 206–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.68 (s, 1H), 7.91 (s, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.4, 151.3, 139.7, 132.2, 129.3, 126.8, 126.6, 126.2, 121.2, 120.7, 119.8 ppm. Anal. Calcd. for $C_{13}H_8N_2SCl_2$: C, 52.88; H, 2.73. Found: C, 52.67; H, 2.91.

2.3.18. N-Phenyl-6-methylbenzo[d]thiazol-2-amine, ***3r***

White solid, mp 171–172 °C (lit [41]. mp 154–155 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.45 (s, 1H), 7.85 (d, J = 7.6 Hz, 2H), 7.63 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 8.0 Hz, 2H), 7.19–7.16 (m, 1H), 7.06 (t, J = 7.2 Hz, 1H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.8, 150.0, 140.7, 131.5, 130.0, 128.9, 126.9, 121.8, 120.8, 118.8, 117.6, 20.8 ppm.

2.3.19. N-(4-Methoxyphenyl)-6-methylbenzo[d]thiazol-2-amine, ***3s***

White solid, mp 168–169 °C (lit [41]. mp 160 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.18 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.55

(s, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 8.0$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 2H), 3.75 (s, 3H), 2.35 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 161.3$, 154.6, 150.2, 134.2, 131.1, 130.0, 126.8, 120.8, 119.5, 118.5, 114.1, 55.1, 20.8 ppm.

2.3.20. N-(4-Chlorophenyl)-6-methylbenzo[d]thiazol-2-amine, ***3t***

Colorless oil [15]. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.60$ (s, 1H), 7.88 (d, $J = 7.6$ Hz, 2H), 7.65 (s, 1H), 7.56 (d, $J = 7.2$ Hz, 1H), 7.45 (d, $J = 7.6$ Hz, 2H), 7.19 (d, $J = 7.2$ Hz, 1H), 2.41 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 161.0$, 150.3, 140.1, 132.3, 130.5, 129.2, 127.5, 125.7, 121.4, 119.5, 119.4, 21.3 ppm.

2.3.21. N-(4-Nitrophenyl)-6-methylbenzo[d]thiazol-2-amine, ***3u***

Yellow solid, mp 272–273 °C (lit [14]. mp 271–273 °C). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 11.09$ (s, 1H), 8.23 (d, $J = 9.0$ Hz, 2H), 7.97 (d, $J = 9.0$ Hz, 2H), 7.65 (s, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 2.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 159.7$, 149.3, 146.4, 140.9, 132.7, 130.4, 127.3, 125.2, 121.0, 119.6, 117.0, 20.8 ppm.

2.3.22. N-Cyclohexyl-6-methylbenzo[d]thiazol-2-amine, ***3v***

White solid, mp 173–174 °C (lit [42]. mp 173–175 °C). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.82$ (d, $J = 6.8$ Hz, 1H), 7.42 (s, 1H), 7.25 (d, $J = 7.6$ Hz, 1H), 7.00 (d, $J = 7.6$ Hz, 1H), 3.72–3.63 (m, 1H), 2.30 (s, 3H), 2.00–1.96 (m, 2H), 1.74–1.70 (m, 2H), 1.60–1.55 (m, 1H), 1.38–1.14 (m, 5H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 165.0$, 151.1, 130.7, 130.2, 126.9, 121.2, 117.9, 53.2, 32.8, 25.8, 24.9, 21.2 ppm.

3. Results and discussion

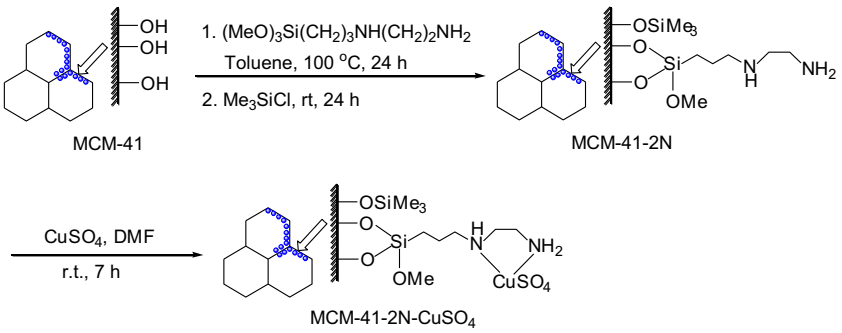
3.1. Synthesis and characterization of MCM-41-2N-CuSO$_4$

A novel 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper complex catalyst (MCM-41-2N-CuSO$_4$) was very conveniently synthesized starting from commercially available and cheap 3-(2-aminoethylamino)propyltrimethoxysilane and CuSO$_4$ according to Scheme 1. Firstly, the MCM-41 support reacted with 3-(2-aminoethylamino)propyltrimethoxysilane in toluene at 100 °C for 24 h, followed by the silylation with Me$_3$SiCl in toluene at room temperature for 24 h to generate 3-(2-aminoethylamino)propyl-functionalized MCM-41 (MCM-41-2N). Then the MCM-41-2N reacted with CuSO$_4$ in DMF at room temperature for 7 h to generate the 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized copper complex catalyst (MCM-41-2N-CuSO$_4$) as a pale blue powder, the copper content of the catalyst was found to be 0.43 mmol/g according to the ICP-AES measurements. The X-ray powder diffraction (XRD) analysis of the new MCM-41-immobilized copper complex catalyst (MCM-41-2N-CuSO$_4$) indicated that, in addition to an intense diffraction peak (100), two higher order peaks (110) and (200) with lower intensities were also detected, and therefore the chemical bonding procedure did not diminish the structural ordering of the MCM-41. In order to confirm that MCM-41-2N-CuSO$_4$ is a neutral complex with the SO_4^{2-} moiety on the metal, the sulfur content of MCM-41-2N-CuSO$_4$ was determined to be 0.45 mmol/g, which is close to the copper content of 0.43 mmol/g. In addition, we prepared the neutral analog [CuSO$_4$/$H_2NCH_2CH_2NH_2$ (1:1)] from the reaction of CuSO$_4$ with ethylenediamine in DMF. FT-IR spectrum of the analog [CuSO$_4$/$H_2NCH_2CH_2NH_2$ (1:1)] includes the characteristic absorptions of SO_4^{2-} at 1085 and 621 cm^{-1}, FT-IR spectrum of the MCM-41-2N-CuSO$_4$ also includes the characteristic absorptions of SO_4^{2-} at 1069 and 622 cm^{-1}. These results indicated that a neutral copper complex with the SO_4^{2-} moiety on the metal is formed from the reaction of MCM-41-2N with CuSO$_4$.

3.2. Heterogeneous tandem reactions of 2-haloanilines with isothiocyanates

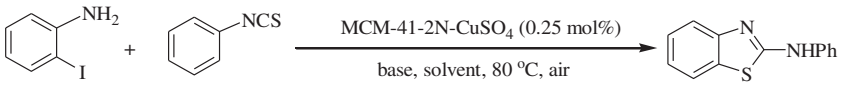
In order to test the catalytic activity of the MCM-41-2N-CuSO$_4$, the tandem reactions of 2-haloanilines with isothiocyanates were investigated under an air atmosphere. The reaction of 2-iodoaniline with phenyl isothiocyanate (1.2 equiv) was chosen as a model reaction, and the influences of various reaction parameters such as solvent, base, and copper catalyst quantity on the reaction were tested. The results are summarized in Table 1. For the solvents evaluated such as EtOH, DMSO, DMF, dioxane, NMP, H_2O, toluene and DCE, DMSO was found to be the most effective. Our next studies focused on the effect of base on the model reaction. Among the bases examined, Et$_3$N was found to be the most effective (Table 1, entry 1), DBU and pyridine also afforded good yields (Table 1, entries 9–11, 19). While other bases such as K_2CO_3, Na_2CO_3, K_3PO_4 and Cs_2CO_3 were ineffective (Table 1, entries 13–16), Et$_2$NH, piperidine and NaOAc were substantially less effective (Table 1, entries 12, 17, 18). The amount of supported copper catalyst was also screened, and 0.25 mol% loading of copper was found to be optimal, a lower yield was observed when the amount of the catalyst was decreased (Table 1, entry 20). Increasing the amount of copper catalyst could shorten the reaction time, but did not increase the yield of *N*-phenylbenzo[*d*]thiazol-2-amine (Table 1, entry 21). Thus, the optimized reaction conditions for this tandem reaction are MCM-41-2N-CuSO$_4$ (0.25 mol%) in DMSO using Et$_3$N as base at 80 °C under air for 8 h (Table 1, entry 1).

With this promising result in hand, we started to investigate the scope of both 2-halobenzenamines and isothiocyanates under the optimized conditions, and the results are summarized in Table 2. As showed in Table 2, a variety of isothiocyanates **2** were investigated by reacting with 2-iodoaniline in the presence of 0.25 mol% MCM-41-2N-CuSO$_4$ and Et$_3$N (2.0 equiv) at 80 °C under aerobic



Scheme 1. Preparation of MCM-41-2N-CuSO4.

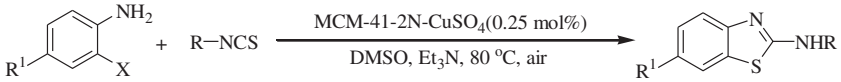
Table 1
Reaction condition screening for the reaction of 2-iodoaniline with phenyl isothiocyanate.[a]



Entry	Solvent	Base	Time (h)	Yield[b] (%)
1	DMSO	Et_3N	8	95
2	DMF	Et_3N	10	80
3	EtOH	Et_3N	24	76
4	Toluene	Et_3N	12	83
5	Dioxane	Et_3N	24	58
6	DCE	Et_3N	24	67
7	NMP	Et_3N	10	72
8	H_2O	Et_3N	24	10
9	DMF	DBU	24	65
10	DMSO	DBU	24	89
11	Toluene	DBU	24	70
12	DMSO	Et_2NH	24	58
13	DMSO	K_2CO_3	24	Trace
14	DMSO	Na_2CO_3	24	Trace
15	DMSO	K_3PO_4	24	Trace
16	DMSO	Cs_2CO_3	24	Trace
17	DMSO	Piperidine	24	44
18	DMSO	NaOAc	24	39
19	DMSO	Pyridine	24	67
20[c]	DMSO	Et_3N	16	85
21[d]	DMSO	Et_3N	5	94

[a] Reaction conditions: 2-iodoaniline (1.0 mmol), phenyl isothiocyanate (1.2 mmol), MCM-41-2N-$CuSO_4$ (0.25 mol%), base (2.0 mmol) in solvent (2.0 mL) at 80 °C under an air atmosphere.
[b] Isolated yield.
[c] 0.13 mol% of copper catalyst was used.
[d] 0.5 mol% of copper catalyst was used.

Table 2
Heterogeneous tandem reaction of 2-halobenzenamines with isothiocyanates.[a]

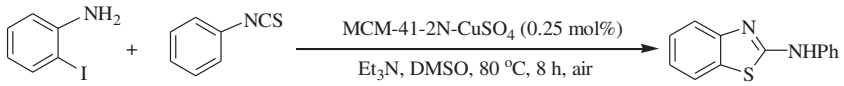


1 **2** **3**

Entry	R^1/X	R	Time (h)	Product	Yield[b] (%)
1	H/I	C_6H_5	8	**3a**	95
2	H/I	4-$CH_3C_6H_4$	8	**3b**	94
3	H/I	4-$CH_3OC_6H_4$	10	**3c**	92
4	H/I	4-FC_6H_4	8	**3d**	90
5	H/I	4-ClC_6H_4	8	**3e**	89
6	H/I	4-$NO_2C_6H_4$	5	**3f**	80
7	H/I	Cyclohexyl	8	**3g**	85
8	CF_3/I	C_6H_5	10	**3h**	94
9	CF_3/I	4-$CH_3OC_6H_4$	10	**3i**	91
10	CF_3/I	4-FC_6H_4	10	**3j**	92
11	CF_3/I	4-ClC_6H_4	14	**3k**	90
12	CF_3/I	4-$NO_2C_6H_4$	10	**3l**	78
13	Cl/I	C_6H_5	8	**3m**	92
14	Cl/I	4-$CH_3C_6H_4$	8	**3n**	88
15	Cl/I	4-$CH_3OC_6H_4$	11	**3o**	91
16	Cl/I	4-FC_6H_4	8	**3p**	90
17	Cl/I	4-ClC_6H_4	8	**3q**	89
18	CH_3/I	C_6H_5	8	**3r**	96
19	CH_3/I	4-$CH_3OC_6H_4$	8	**3s**	90
20	CH_3/I	4-ClC_6H_4	8	**3t**	91
21	CH_3/I	4-$NO_2C_6H_4$	6	**3u**	85
22	CH_3/I	Cyclohexyl	8	**3v**	83
23	H/Br	C_6H_5	24	**3a**	81

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), MCM-41-2N-$CuSO_4$ (0.25 mol%), Et_3N (2.0 mmol) in DMSO (2.0 mL) at 80 °C under an air atmosphere.
[b] Isolated yield.

Table 3
Tandem reaction of 2-iodoaniline with phenyl isothiocyanate catalyzed by recycled catalyst.[a]



Cycle	Yield[b] (%)	Cycle	Yield[b] (%)
1	95	2	95
3	94	4	93
5	94	6	94
7	93	8	93
9	92	10	93

[a] Reaction conditions: 4-iodoaniline (10 mmol), phenyl isothiocyanate (12 mmol), MCM-41-2N-$CuSO_4$ (0.025 mmol), Et_3N (20 mmol) in DMSO (20 mL) at 80 °C for 8 h under an air atmosphere.
[b] Isolated yield.

conditions. The results demonstrated that several functional groups, such as methyl, methoxy, fluoro, chloro and nitro groups, on the aryl moiety were tolerated well, and both electron-rich and electron-poor aryl isothiocyanates underwent the tandem reaction successfully in good to excellent yields (entries 2–6). 4-Methoxyphenyl isothiocyanate, for example, was treated with 2-iodoaniline to give the target product **3c** in 92% yield (entry 3), and the reaction of 4-nitrophenyl isothiocyanate with 2-iodoaniline afforded the corresponding product **3f** in 80% yield (entry 6). To our delight, alkyl isothiocyanates were also suitable substrates for the tandem reactions. Cyclohexyl isothiocyanate, for instance, was treated with 2-iodoaniline under the same conditions to afford the desired product **3g** in 85% yield (entry 7). This heterogeneous copper catalyst exhibited higher catalytic activity than $CuSO_4$. For example, the tandem reaction of 2-iodoaniline with phenyl isothiocyanate in the presence of 0.25 mol% of MCM-41-2N-$CuSO_4$ in DMSO using Et_3N as base at 80 °C under air for 8 h gave a 95% yield of *N*-phenylbenzo[*d*]thiazol-2-amine **3a** (entry 1), the same reaction in the presence of 1 mol% $CuSO_4$ in DMSO using Et_3N as base at 80 °C under air for 10 h gave **3a** in 91% yield.

Substituted 2-iodoanilines were subsequently investigated to react with a variety of isothiocyanates under the optimized conditions, and the results are also summarized in Table 2. We were pleased to find that the optimized conditions were compatible with various 2-iodoanilines bearing chloro, methyl and trifluoromethyl groups. 4-Chloro-2-iodoaniline, for instance, underwent the tandem reaction with phenyl isothiocyanate or substituted phenyl isothiocyanates, smoothly in high yields (entries 13–17). 2-Iodo-4-methylaniline was a suitable substrate under the same conditions (entries 18–22). It was observed that the tandem reactions of electron-withdrawing 2-iodo-4-(trifluoromethyl)aniline with various isothiocyanates were also successful to afford the desired products **3h**–**l** in good to excellent yields (entries 8–12). Interestingly, a less active substrate, 2-bromoaniline, also displayed high activity for the tandem reaction with phenyl isothiocyanate in 81% yield (entry 23).

A further objective of our studies was to determine whether the catalysis was due to the MCM-41-2N-$CuSO_4$ complex or to a homogeneous copper complex that comes off the support during the reaction and then returns to the support at the end. To test this, we performed the hot filtration test [43]. We focused on the tandem reaction of 2-iodoaniline with phenyl isothiocyanate. We filtered off the MCM-41-2N-$CuSO_4$ complex after 2 h of reaction time and allowed the filtrate to react further. The catalyst filtration was performed at the reaction temperature (80 °C) in order to avoid possible recoordination or precipitation of soluble copper upon cooling. We found that, after this hot filtration, no further reaction was observed and no copper could be detected in the filtered solution by ICP-AES. This result points to a process of heterogeneous nature.

3.3. Recycling of the catalyst

For a heterogeneous transition-metal catalyst, it is very important to examine its ease of separation, good of recoverability and reusability. We also investigated the recyclability of the MCM-41-2N-$CuSO_4$ by using the reaction of 2-iodoaniline with phenyl isothiocyanate. This heterogeneous copper catalyst can be easily recovered by simple filtration and washed with ethyl acetate and diethyl ether. After being air-dried, it can be reused directly without further purification. The recovered copper catalyst was used in the next run, and almost consistent activity was observed for ten consecutive cycles (Table 3). In addition, copper leaching in the supported catalyst was also determined. The copper content of the catalyst was found by ICP analysis to be 0.42 mmol/g after ten consecutive runs, only 2% of copper had been lost from the MCM-41 support. The high stability and excellent reusability of the catalyst should result from the chelating action of bidentate 2-aminoethylamino ligand on copper and the mesoporous structure of the MCM-41 support. The result is important from a practical point of view. The high catalytic activity, excellent reusability and the easy accessibility of the MCM-41-2N-$CuSO_4$ make them a highly attractive heterogeneous copper catalyst for the parallel solution phase synthesis of diverse libraries of compounds.

4. Conclusion

In summary, we have developed a novel, practical and environmentally friendly catalyst system for the tandem reactions of 2-haloanilines with isothiocyanates by using 0.25 mol% 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized copper complex as catalyst under an air atmosphere. The reactions generated the corresponding 2-aminobenzothiazoles in good to excellent yields. This novel heterogeneous copper catalyst can be conveniently prepared by a simple two-step procedure from commercially available and cheap reagents and exhibits higher activity than $CuSO_4$ and can be reused at least 10 times without any decreases in activity. The tandem reactions of 2-haloanilines with isothiocyanates catalyzed by the MCM-41-2N-$CuSO_4$ complex provide a better and practical procedure for the synthesis of a variety of 2-aminobenzothiazoles.

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