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One-Pot Synthesis of Antitumor Agent PMX 610 by a Copper(II)-Incorporated Mesoporous Catalyst

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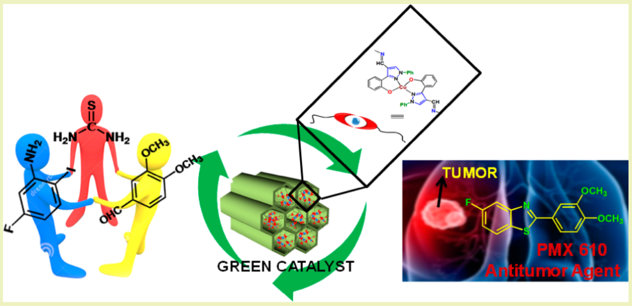
Supporting Information

ABSTRACT: PMX 610 ((2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole) is a benzothiazole derivative, which shows potent antitumor properties. In this study, copper(II)-chelated pyrazole functionalized SBA-15 mesoporous silica (Cu-Py-SBA-15) as a heterogeneous green catalyst was developed for the synthesis of substituted benzothiazole derivatives including PMX 610. The preparation of pyrazole functionalized SBA-15 (Py-SBA-15) was achieved by postsynthetic modification of mesoporous silica SBA-15 with 3-aminopropyltriethoxy-silane followed by the Schiff-base condensation with 1-phenyl-3-(2′-hydroxyphenyl)-4-formyl pyrazole. The reaction of Py-SBA-15 with $CuCl_2 \cdot 2H_2O$ in absolute ethanol afforded the Cu-Py-SBA-15 catalyst. The as-synthesized catalyst was fully characterized by several techniques including powder X-ray diffraction, high-resolution transmission electron microscopy, electron paramagnetic resonance spectroscopy, X-ray photoelectron spectroscopy, ^{13}C cross-polarization magic angle spinning NMR, Fourier transform infrared spectroscopy, field emission scanning electron microscopy, and N_2 adsorption/desorption measurements. A one-pot-three-component approach in aqueous medium using the Cu-Py-SBA-15 catalyst was exploited for direct synthesis of PMX 610. The novel heterogeneous green catalyst offers high catalytic recyclability without considerable loss of catalytic activity. The present synthetic strategy is valuable in the preparation of PMX 610 on account of the use of readily available and inexpensive starting materials, excellent recyclability of the catalyst, and sustainable catalytic protocol.



KEYWORDS: *Benzothiazole, Green synthesis, Heterogeneous catalysis, Mesoporous SBA-15, PMX 610*

INTRODUCTION

Benzothiazole and its derivatives exhibit a diverse range of biological activities and are primarily well-known on account of their antitumor properties.[1] In industry, these heterocyclic compounds are employed as antioxidants,[2] vulcanization accelerators,[3] and dopant in light-emitting organic electroluminescent devices.[4] For the preparation of derivatives with a benzothiazole framework, most common approaches include the condensations of 2-aminothiophenol with carboxylic acids, nitriles, or aldehydes. Conventionally, these reactions often suffer some problems such as drastic reaction conditions, low production yields, tedious workup procedures, and the instability of starting materials including 2-aminothiophenol.[5−11]

2-(3,4-Dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610, NSC 721648), formerly GW 610, is a potent antitumor agent to some human cancers including colon, lung, and breast cancers.[12] This 5-fluoro analogue of benzothaizole also functions as an arylhydrocarbon receptor (AhR), which translocates drugs to the cell nuclei.[13] Previously, PMX 610 was synthesized by the condensation of 2-aminothiophenol with corresponding aldehyde.[12] Later, this method was modified to the oxidative ring-opening of bis(2-aminophenyl) disulfide followed by the condensation with aromatic aldehyde.[14] Recently, the condensation of *N*-(2-iodophenyl)-benzamide derivative with ethylxanthogenate using homogeneous $Cu(OAc)_2$ catalyst was applied to synthesize PMX 610.[15] The limitations and drawbacks of previously adopted methods to synthesize PMX 610 are mainly associated with long reaction time, commercial unavailability of the starting materials, multistep synthetic methodology, and so on. To date, all reported synthetic procedures for the synthesis of PMX 610 are either homogeneous or multistep processes.[12,14,15] Hence, the development of a green heterogeneous catalyst for efficient synthesis of PMX610 is of great significance in industrial and academic point of view.

Owing to exceptionally high surface area, tunable pore size distribution, as well as thermal, hydrothermal, and mechanical stability, mesoporous materials have gained considerable research interest as appropriate host matrixes for grafting a wide range of catalytically active species.[16−21] In this work, we anchored newly prepared catalytic center, Cu^{2+}-chelated

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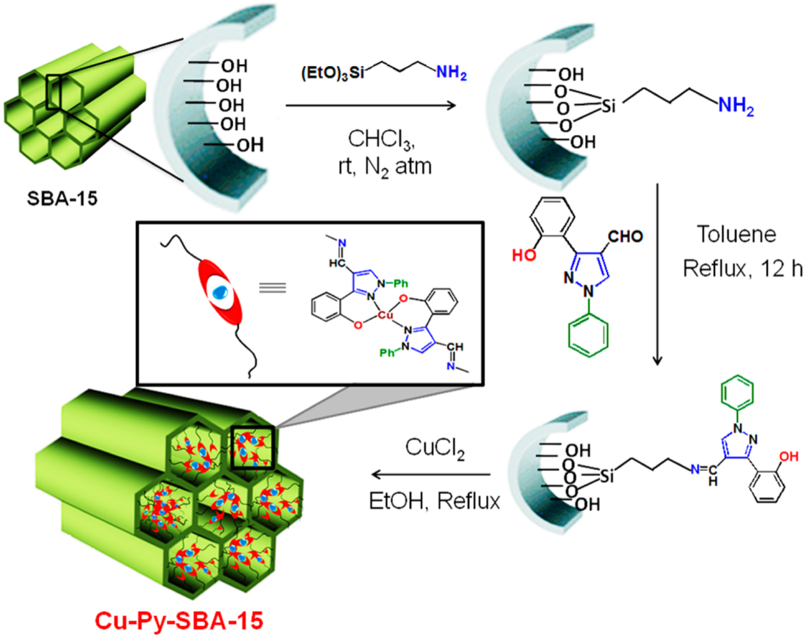
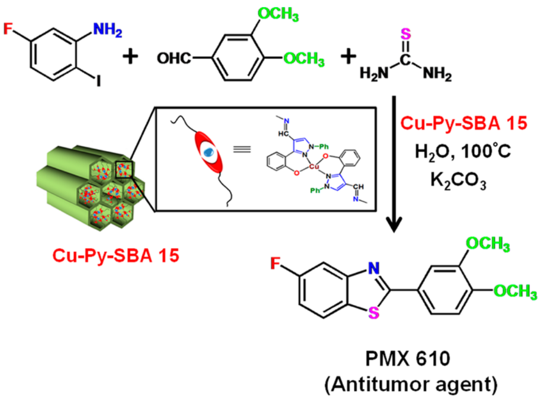
Scheme 1. Synthesis of Cu^{2+}-Chelated Pyrazole Appended Mesoporous Catalyst Cu-Py-SBA-15



pyrazole unit, onto SBA-15 type mesoporous silica, since pyrazole binds with Cu^{2+} more strongly than other metal ions.[20] Pyrazole functionalized SBA-15 (Py-SBA-15) was synthesized by post synthetic modification of SBA-15 with 3-aminopropyltriethoxy-silane (APTES) followed by the Schiff-base condensation with 1-phenyl-3-(2′-hydroxyphenyl)-4-formyl pyrazole. The treatment of Py-SBA-15 with $CuCl_2{\cdot}2H_2O$ in absolute ethanol led to the formation of Cu-Py-SBA-15 (Scheme 1).

Herein, we described a novel strategy for a one-pot-three-component catalytic reaction of 5-fluoro-2-iodoaniline, 3,4-dimethoxybenzaldehyde, and thiourea toward the synthesis of PMX 610 in water using efficient heterogeneous Cu-Py-SBA-15 catalyst (Scheme 2). To the best of our knowledge, this is the first example for one-pot direct synthesis of PMX 610 using a heterogeneous catalysis under sustainable conditions. This heterogeneous catalyst could be successfully recycled and reused for at least eight consecutive catalytic cycles without considerable loss of catalytic activity.

Scheme 2. One-Pot Three Component Synthesis of PMX 610 using Cu-Py-SBA-15 Heterogeneous Catalyst in Aqueous Medium



EXPERIMENTAL SECTION

Synthesis of Diphenylpyrazole Functionalized SBA-15 (Py-SBA-15). The synthesis of SBA-15 and 3-aminopropyl functionalized SBA-15 (NH_2-SBA-15) is presented in the Supporting Information (SI). NH_2-SBA-15 (0.1 g) was refluxed with substituted 4-formyl pyrazole (0.2 g) in dry toluene (10 mL) at 110 °C for 12 h. After 12 h, no further color change occurred in the reaction mixture. Then, the resulting mixture was allowed to cool down to 25 °C, and the product was collected by filtration followed by thoroughly washing with methanol in order to remove excess aldehyde. The light yellow colored material, Py-SBA-15, was dried in air.

Synthesis of Cu(II) Anchored Py-SBA-15 (Cu-Py-SBA-15). Py-SBA-15 (1 g) was suspended into $CuCl_2{\cdot}2H_2O$ (0.2 g) in ethanol (20 mL). The mixture was stirred at 25 °C to obtain a homogeneous light green colored solution, which was refluxed for about 8 h. The color of the mesoporous material slowly changed from yellow to light green, and no further color change occurred under further reflux. The reaction mixture was cooled down to 25 °C, and the resulting mesoporous solid was filtered through suction with thoroughly washing by ethanol. After washing, the product was dried under vacuum to afford Cu-Py-SBA-15. Schematic presentation of this catalyst is shown in Scheme 1.

Synthesis of PMX 610 Catalyzed by Cu-Py-SBA-15 in Aqueous Medium. At first, K_2CO_3 (4 mmol, 552 mg) dissolved in water (5 mL) was stirred in a round-bottomed flask (10 mL) at 25 °C. Then, a mixture of 5-fluoro-2-iodoaniline (1 mmol, 237 mg), 3,4-dimethoxy benzaldehyde (1.3 mmol, 215 mg), thiourea (3 mmol, 228 mg), and Cu-Py-SBA-15 (0.03 g) was added into the aqueous solution, and the resulting mixture was refluxed in an oil bath at 100 °C under aerobic condition for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled down to 25 °C. The mixture was filtered to remove the solid catalyst. The filtrate was diluted with EtOAc (20 mL) and then extracted with EtOAc. The combined organic layer was washed with water followed by brine solution (2 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford crude solid product. White colored solid compound PMX 610 (2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole) was separated by column chromatography. The isolated product was characterized by ^1H and ^{13}C NMR. The yield of the product is 68%.

General Procedure for Synthesis of 2-Substituted Benzothiazoles Catalyzed by Cu-Py-SBA-15 in Aqueous Medium. At first, K_2CO_3 (4 mmol, 552 mg) dissolved in water (5 mL) was stirred in a round-bottomed flask (10 mL) at 25 °C. Then, a mixture of 2-iodoaniline (1 mmol, 219 mg), corresponding benzaldehyde (1.3 mmol), thiourea (3 mmol, 228 mg), and Cu-Py-SBA-15 (0.03 g) was added into the aqueous solution, and the resulting mixture was refluxed in an oil bath at 100 °C under aerobic condition for appropriate reaction time. The progress of the reaction was monitored by TLC. After completing the reaction, the reaction mixture was cooled down to 25 °C, and the mixture was filtered to remove the solid catalyst. The filtrate was diluted with EtOAc (20 mL) and then extracted with EtOAc. The combined organic layer was washed with water followed by brine solution (2 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford crude solid product. The isolated product was characterized by ^1H and ^{13}C NMR. The NMR data of substituted benzothiazoles are in good agreement with reported values.

Characterization Techniques. Powder X-ray diffraction (XRD) patterns were recorded on a Bruker D-8 Advance SWAX diffractometer operated at 40 kV of voltage and 40 mA of current. The instrument was calibrated with a standard silicon sample using Ni-filtered Cu Kα (α = 0.15406 nm) radiation. Nitrogen adsorption/desorption isotherms were obtained using a Quantachrome Autosorb 1C at −196 °C. Prior to the gas adsorption, the sample was degassed at 120 °C for 10 h. A JEOL JEM 6700F field emission scanning electron microscope (FE-SEM) was used for determining the morphology of the samples. High resolution transmittance electron microscope (HR-TEM) images were recorded in a JEOL JEM 2010 transmission electron microscope. Cu loading in the samples was determined by using a Perkin-Elmer Optima 2100 DV inductive coupled plasma mass spectroscopy (ICP-MS). ^1H and ^{13}C NMR experiments were carried out on a Bruker DPX-300 NMR spectrometer. ^{13}C cross-polarization magic angle spinning (CP MAS) NMR experiments were performed on a JEOL ECA400 (ECA400) with a CPMAS probe. Electron paramagnetic resonance (EPR) measurements were performed on a Bruker EMX EPR spectrometer at X-band frequency of 9.46 GHz under liquid nitrogen temperature of −196 °C. Fourier transform infrared spectroscopy (FT-IR) was carried out using a Nicolet MAGNA-FT IR 750 Spectrometer Series II. X-ray photoelectron spectroscopy (XPS) analysis was carried out by a SPECS I3500 plus spectrometer using Mg X-ray source.

■ RESULTS AND DISCUSSION

As-prepared catalyst Cu-Py-SBS-15 was characterized using powder XRD, N_2 adsorption/desorption measurements, HR-TEM, FE-SEM, EPR, FT-IR, XPS, and ^{13}C CPMAS NMR. HR-TEM images of the Cu-Py-SBA-15 catalyst are shown in Figure 1. Figure 1A clearly presents mesoporous structures in a honeycomb-like hexagonal array with pore size diameter of 6−7 nm arranged uniformly throughout the sample.[22−26] Similarly, the channel directions are visible, which are parallel to the 110 reflection plane of Cu-Py-SBA-15 and perpendicular to the pore axis (Figure 1B and C). The fast Fourier transform (FFT) diffractogram of Cu-Py-SBA-15 (Figure 1D) reveals a two-dimensional hexagonal mesoporous channel pattern. The pore size observed from the TEM images is in a good agreement with the pore size calculated from the N_2 isotherm data (Figure S1 in the SI).

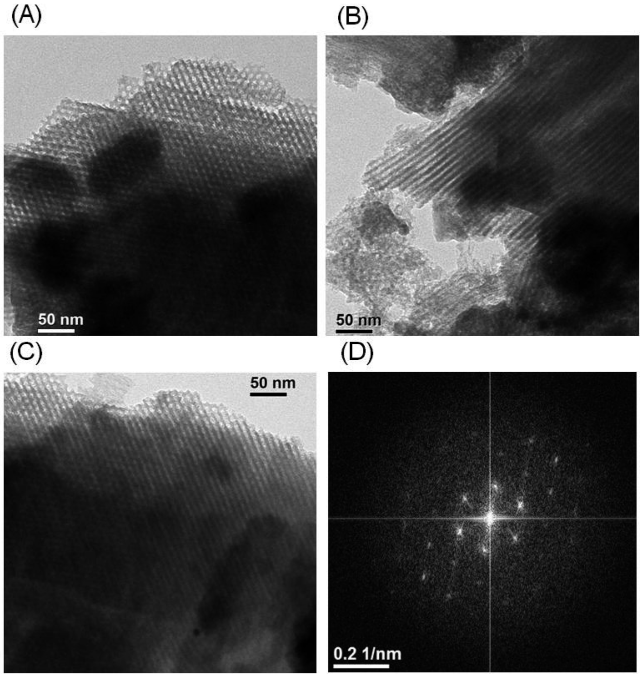


Figure 1. HR-TEM and FFT diffractogram of Cu-Py-SBA-15. HR-TEM images with (A) electron beam parallel to pore axis and (B and C) perpendicular to pore axis. (D) FFT pattern obtained from a selected area on image C.

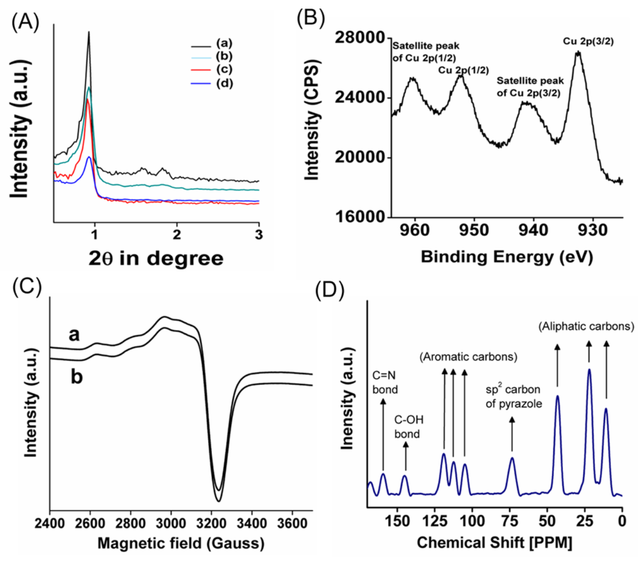


Figure 2. (A) Small angle powder XRD patterns of (a) SBA-15, (b) Py-SBA-15, (c) Cu-Py-SBA-15 catalyst, and (d) reused catalyst. (B) High resolution XPS spectrum of Cu-Py-SBA-15 at the Cu2p region. (C) EPR spectra of (a) Cu-Py-SBA-15 catalyst and (b) reused catalyst. (D) ^{13}C CP MAS NMR spectrum of Cu-Py-SBA-15.

The small angle powder XRD pattern of pure SBA-15 is shown in Figure 2A(a), which represents highly ordered mesoporous silica formation. The small angle powder XRD patterns of the Py-SBA-15 and Cu-Py-SBA-15 samples are given in Figure 2A. The powder XRD pattern of the Py-SBA-15 sample (Figure 2A(b)) exhibits three characteristic diffraction peaks centered at 2θ values of 0.90, 1.58 and 1.82°, respectively, which can be attributed to the 100 (strong), 110 (weak), and 200 (weak) reflections, corresponding to two-dimensional hexagonal mesostructure.[27] When this pyrazole imine functionalized mesoporous SBA-15 was treated with $CuCl_2$ to afford Cu-Py-SBA-15, considerable decreases in the intensities of the reflection pattern for the 110 and 200 planes were observed. The decreases can be assigned to the lowering of local order on account of the incorporation of Cu(II) complexes inside the pore channels of Py-SBA-15. The presence of a single intense peak around 0.92° (Figure 2A(c)) clarifies the preservation of the mesophase in Cu-Py-SBA-15. A slight shift of the single

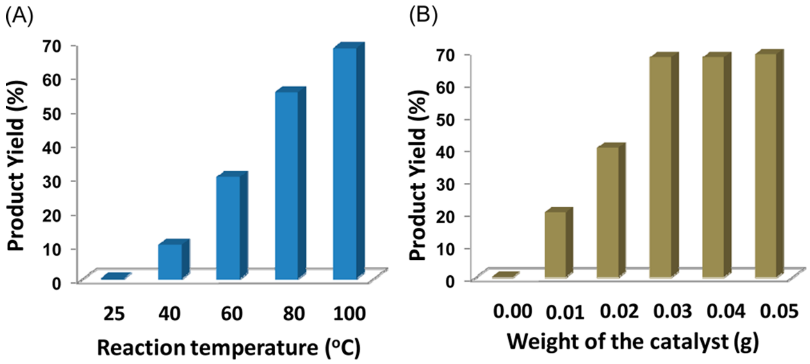


Figure 3. Effects of (A) temperature with 0.03 g of the catalyst and (B) the catalyst dose at 100 °C on the production yield of PMX 610.

peak for Cu-Py-SBA-15 can be ascribed to the contraction of the pore walls, which is responsible for the decrease in *d* spacing.

XPS is an indispensable tool to evaluate the oxidation state of Cu chelated to the pyrazole units in Cu-Py-SBA-15. The XPS spectrum of the Cu-Py-SBA-15 material is shown in Figure 2B. The binding energy $2p_{3/2}$ of Cu in Cu-Py-SBA-15 centered at 932.5 eV along with a characteristic satellite peak at 941.4 eV can be assigned to the existence of Cu in +2 oxidation state.[28−31] For pure CuO, the Cu($2p_{3/2}$) binding energy peak arises at 933.6 eV. A shift of 1.1 eV toward lower energy suggests the charge transfer from the pyrazole ligand of Py-SBA-15 to the Cu(II) ion (Figure 2B). Higher binding energy peak at 952.2 eV related to Cu($2p_{1/2}$) of Cu(II) ion along with the characteristic satellite peak at 960.4 eV were also observed.

Similarly, in the EPR spectrum (Figure 2C(a)), four hyperfine splitting patterns ($m_I = -3/2, -1/2, +1/2, +3/2$) in the low-field region for the parallel material of Cu-Py-SBA-15 were attributed to the coupling of unpaired electron with a nuclear spin of Cu ($I = 3/2$). However, the EPR signal for perpendicular components ($g_\perp = 2.064$) remained unresolved, indicating the presence of typical Cu(II) ion in axial symmetry. This EPR spectrum regarding the Cu(II) ion provides the information of spin Hamiltonian parameters in the range of $g_\parallel = 2.27$ and $A_\parallel = 160$ G.[32−34] The EPR studies of the Cu(II) complex suggest that the increase in $g_\parallel$ and decrease in $A_\parallel$ can be attributed to the tetragonal distortion of a square planar complex. Distortion factor (*f*) for the Cu-Py-SBA-15 catalyst is 152 cm, which clearly demonstrates that the Cu(II) centers are more distorted from the square planar geometry to the distorted tetragonal geometry. The EPR spectrum of the reused catalyst (Figure 2C(b)) indicates that the +2 oxidation state of Cu remained unchanged after the catalytic reactions. Thus, the XPS and EPR measurements reveal the oxidation state of the Cu metal centers inside the Cu-Py-SBA-15 catalyst.

^{13}C CP MAS NMR spectrum (Figure 2D) of Cu-Py-SBA-15 exhibits three strong signals in aliphatic region ranging from 10 to 43 ppm, which can be attributed to different aliphatic carbons on the bridging units. The signal centered at 73 ppm corresponds to sp^2 hybridized carbon atoms of the pyrazole units. Strong signals from 105 to 118 ppm can be assigned to the aromatic carbons on the phenyl ring. In addition, the peaks at 145 and 159 ppm were due to the carbons from aromatic C—OH and C═N groups of the incorporated organic ligand, respectively. The NMR spectrum provides solid evidence for successful incorporation of the organic ligand into the SBA-15 silica framework.[35−40] It is quite obvious that Cu^{2+} is chelated by two ligands. As Cu is present in the oxidation state of +2, the positive charges must be neutralized by negative charges of hydroxyl groups from the pyrazole ligands. The FE-SEM images (Figure S2 in the SI) provide the morphology of the Cu-Py-SBA-15 catalyst, and corresponding FT-IR spectra are shown in Figure S3 of the SI, further supporting the formation of Cu-Py-SBA-15.

For the synthesis of PMX 610, one-pot three component condensation was carried out using 3,4-dimethoxy benzaldehyde, 5-fluoro-2-iodoaniline, and thiourea as the starting materials in aqueous medium by employing the Cu-Py-SBA-15 catalyst. After 24 h of reaction, we can achieve a reaction yield of 68%. At this condition, 10% imine was isolated as a byproduct. The product was characterized by using ^{1}H and ^{13}C NMR spectra. The electrophilicity of the —CHO group of 3,4-dimethoxy benzaldehyde is very low due to the presence of two electron donating methoxy groups. As a result, the imine formation becomes very slow, which renders the moderate production yield after 24 h. In order to optimize the amount of the catalyst required to carry out the one-pot-three-component condensation in the synthesis of PMX-610, the catalytic reaction was performed by varying the amount of the catalyst from 0.01 to 0.05 g at 100 °C.

The effect of the catalyst dose and temperature for the synthesis of PMX 610 is depicted in Figure 3. It was evident that 0.03 g of the catalyst was the effective amount required to carry out the reaction. No substantial change in the product yield was observed with the increase of the catalyst dose. In this case, all the reactions were carried out at 100 °C. We then investigated the effect of temperature for this condensation by carrying out the reaction with 0.03 g of the catalyst at different temperatures. Figure 3A indicates that increasing temperature was essential for this one-pot three component condensation. Screening of catalysts and the control experiments were performed for the one-pot three component condensation in order to demonstrate high catalytic activity generated from Cu(II) complex grafted SBA-15 in the synthesis of PMX 610 (Table 1).

We performed the control experiments for the one-pot three component condensation of 5-fluoro-2-iodoaniline, 3,4-dimethoxybenzaldehyde, and thiourea in water to make sure that the catalytic activity was generated from the grafted Cu(II) complex nanoclusters inside the functionalized mesoporous SBA-15 (Table 1). At first, the catalytic reaction was performed without any catalyst at 25 °C in H_2O (Table 1, entry 1). No reaction was observed under this condition. Then, the temperature of the catalytic reaction was increased to 40 °C, while keeping other conditions unaltered (Table 1, entry 2). Again, no yield of the product was obtained. When the reaction

Table 1. Control Experiments with Other Catalysts for the Synthesis of PMX 610[a]

entry	catalyst	temperature (°C)	yield[b] (%)
1	no catalyst	25	no reaction
2	no catalyst	40	no reaction
3	no catalyst	60	no reaction
4	no catalyst	80	no reaction
5	no catalyst	100	no reaction
6	SBA-15	100	no reaction
7	Py-SBA-15	100	no reaction
8	CuI	100	25
9	$Cu(OAc)_2 \cdot H_2O$	100	30
10	$CuSO_4 \cdot 5H_2O$	100	35
11	$CuCl_2 \cdot 2H_2O$	100	37
12[41]	$Pd(dba)_2$	110	13
13[41]	$Ni(OAc)_2$	110	33
14	Py-SBA-15 + $CuCl_2 \cdot 2H_2O$	100	35
15	pyrazole ligand coordinated with Cu(II)	100	45
16	Cu-Py-SBA-15	100	68

[a] Reaction conditions: 3,4-dimethoxybenzaldehyde (1.3 mmol, 215 mg), 5-fluoro-2-iodoaniline (1 mmol, 237 mg), thiourea (3 mmol, 228 mg), K_2CO_3 (4 mmol, 552 mg), H_2O (5 mL), Cu-Py-SBA-15 (0.03g, 0.00306 mmol of Cu, the Cu loading in the Cu-Py-SBA-15 catalyst is 0.102 mmol g^{-1}); all the reactions were carried out for 12 h. [b] Isolated yield of product.

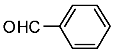
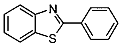
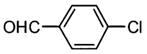
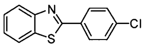
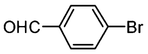
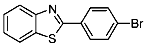
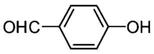
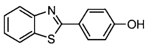
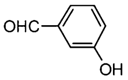
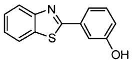
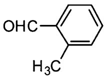
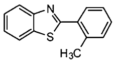
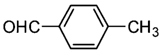
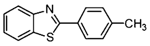
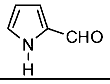
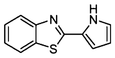
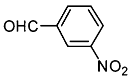
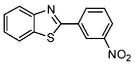
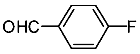
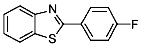
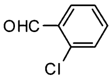
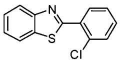
was performed in the absence of any catalyst at 60, 80, and 100 °C (Table 1; entries 3, 4, and 5), no catalytic reaction was observed, and the starting materials remained unreacted. Triggered by these unsatisfied results, we employed various materials as catalysts to perform this catalytic reaction. When we carried out the reaction in the presence of pure calcined SBA-15 and Py-SBA-15 materials (Table 1, entries 6 and 7) at 100 °C in H_2O, no product was observed. These results clearly indicate that the catalytic activity is generated from the metal active centers anchored with SBA-15. We then utilized various homogeneous Cu catalysts to perform this catalytic reaction. When the reaction was carried out in the presence of CuI, only 25% of product was obtained (Table 1, entry 8). In addition to the CuI catalyst, we also employed $Cu(OAc)_2 \cdot H_2O$ and $CuSO_4 \cdot 5H_2O$ as catalysts to perform this catalytic reaction (Table 1, entries 9 and 10). However, these catalysts also did not give satisfactory results. When the reaction was catalyzed by $CuCl_2 \cdot 2H_2O$, no obvious increase in the product yield was observed (Table 1, entry 11). The catalytic performance for the $Pd(dba)_2$ and $Ni(OAc)_2$ catalysts were also evaluated (Table 1, entries 12 and 13).[41] When a physical mixture of Py-SBA-15 and $CuCl_2 \cdot 2H_2O$ was used as a catalyst to synthesize PMX 610, we got the product yield of 35% (Table 1, entry 14). After that, we used the coordination complex of synthesized pyrazole ligand with Cu(II) ion as the catalyst under homogeneous conditions (Table 1, entry 15), and the product yield increased from 35% to 45%. This result signifies that the ligand plays a role for this catalytic reaction. The ligand coordinates with Cu(II) ion in such a way that the Cu(II) ion behaves as an active catalytic site. Since this catalyst is homogeneous in nature, we cannot reuse it for further catalysis. In order to make a heterogeneous catalyst, $CuCl_2 \cdot 2H_2O$ was anchored into mesoporous channels of Py-SBA-15 for the catalysis, and then, the product yield increased drastically to 68% (Table 1, entry 16). This result clearly indicates that the mesoporosity plays a significant role for performing this catalytic reaction. Large surface area and tunable pores facilitate the diffusion of large number of reagents into the mesoporous materials for interacting with the catalytic centers.

We then optimized the catalytic activity of the heterogeneous Cu-Py-SBA-15 catalyst by selecting suitable model reactions using substituted aldehydes and 2-iodoaniline in the presence of thiourea (Table 2). In these reactions, thiourea acts as a source for the inserted sulfur. We obtained isolated yields ranging from 70% to 78% for products **1−11**. The results indicate that the novel methodology could be employed to synthesize a library of 2-substituted benzothiazole derivatives. The imine generated initially in the reaction medium undergoes the C−S coupling reaction followed by intramolecular cyclization to afford benzothiazoles. Not all the formed imine was converted into benzothiazoles, and unreacted imine was isolated as a byproduct after the reactions. In addition, a trace amount of aldehydes that did not participate in the imine formation remained in the reaction mixture. It was also observed that the aromatic aldehydes attached with electron withdrawing groups and electron donating groups could participate in this condensation without any difficulty. All the product yields vary within 4%, from which we can conclude that the nature of functional groups on aldehydes does not significantly influence this type of catalytic reaction. A heterocyclic aldehyde, pyrrole-2-adehyde, also participated in the condensation reaction with equal efficiency (Table 2, entry 8). Various sensitive functional groups such as $-NO_2$, −F, and −Cl were well tolerated in the condensation reaction, providing moderate to excellent product yields.

The Cu content in fresh Cu-Py-SBA-15 catalyst was determined by employing ICP-MS technique, which was 0.102 mmol g^{-1}. We used an excess amount of $CuCl_2 \cdot 2H_2O$ during the preparation of Cu-Py-SBA-15 in order to achieve the maximum Cu(II) complexion with the diphenylpyrazole units. On the basis of the ICP-MS analysis, however, an incomplete coordination process was still observed. From the elemental analysis, the nitrogen content was determined to be 4.06 wt %, from which we quantified the amount of the diphenylpyrazole unit as 0.48 mmol g^{-1}. Theoretically, the amounts of Cu(II) for 1:1 and 1:2 complexion are 0.48 and 0.24 mmol g^{-1}, respectively. Therefore, the actual Cu(II) content of 0.102 mmol g^{-1} supports a 1:2 complexion rather than 1:1. The TON (turn over number) values calculated under this Cu-loading were relatively high ranging from 282 to 305 (Table 2). The high TON values suggest that the reaction is catalytically active and entirely catalyst-dependent.

Hence, a plausible mechanistic pathway was illustrated as shown in Figure 4. At first, 5-fluoro-2-iodoaniline undergoes the Schiff-base condensation with 3,4-dimethoxy benzaldehyde to give intermediate product (A). The heterogeneous catalyst generates reactive Cu(I) species under in situ base. Subsequently, the active Cu(I) species undergoes an oxidative addition with intermediate (A) to produce intermediate (B). Then, thiourea follows a ligand exchange via the formation of isothiouronium salt to provide complex (C), which is responsible for the generation of corresponding complex (D) through hydrolysis in the presence of base. Following step involves the reductive elimination of complex (D) to afford intermediate (E) with the formation of the active Cu(I) species. Aerobic oxidation of the active Cu(I) intermediate leads to the regeneration of the Cu(II) catalyst. The XPS analysis (Figure S5 in the SI) of the regenerated Cu(II) catalyst predicts the

Table 2. One-Pot-Three-Component Synthesis of Substituted Benzothiazoles with Different Aromatic Aldehydes Catalyzed by Cu-Py-SBA-15 under Optimized Conditions[a]

Entry	Aldehyde	Yield[b] (%)	Product	TON[c]
1		75		294
2		78		305
3		78		305
4		76		298
5		75		294
6		70		275
7		72		282
8		74		294
9		75		294
10		78		305
11		72		282

[a] Reaction conditions: aromatic aldehyde (1.3 mmol), 2-iodoaniline (1 mmol), thiourea (3 mmol, 228 mg), K_2CO_3 (4 mmol, 552 mg), H_2O (5 mL), Cu-Py-SBA-15 (0.03g, 0.00306 mmol of Cu, the Cu loading in the Cu-Py-SBA-15 catalyst is 0.102 mmol g^{-1}), 100 °C; all the reactions were carried out for 12 h. [b] Isolated yield of product. [c] TON = turn over number (mole of substrate converted per mole of active site).

oxidation state of Cu as +2, supporting the hypothesis.[42] Intramolecular cyclization of intermediate (E) leads to the formation of intermediate (F).[43−45] In the presence of air, the intermediate (F) gets oxidized to afford the final product PMX 610.[46]

Under optimized reaction conditions, the one-pot-three-component condensation was carried out again in order to demonstrate the recyclability and reusability of Cu-Py-SBA-15 during the synthesis of PMX 610. In this case, 30 mg of the Cu-Py-SBA-15 catalyst was used for the catalytic recycling experiments. The recovery rate of the catalyst after each catalytic cycle was calculated after drying it at 60 °C. The catalyst showed a constant weight and did not need further activations for the next reaction. Thus, the catalyst was recycled and reused for eight repetitive catalytic cycles without significant loss of catalytic activity, and the catalyst was also recovered in a constant rate in each catalytic cycle (Figure 5).

A little drop in the product yield was observed during the reuse experiments, which may be due to the plugging of the SBA-15 pores in the course of reaction (Figure 5). In order to investigate heterogeneous nature of the catalyst, a hot filtration test followed by leaching test were performed (see section S5 in the SI). The experiments clearly indicate that there was no leaching of copper during the reaction. The catalyst was characterized again after several cycles of catalytic reactions (see sections S6 and S7 in the SI), and the consistent results conclude that the heterogeneous catalyst is very stable during the preparation of PMX 610.

■ CONCLUSIONS

In conclusion, we have developed a novel synthetic strategy for aqueous synthesis of antitumor agent PMX 610 using an efficient mesoporous heterogeneous catalyst, Cu-Py-SBA-15, under sustainable conditions. In this approach, 5-fluoro-2-iodoaniline, 3,4-dimethoxybenzaldehyde, and thiourea undergo one-pot three component condensation to afford PMX 610. This synthetic protocol is environmentally friendly, as neat water is used as the solvent. Moreover, the protocol has also ruled out the necessity of synthesizing the starting materials as well as the isolation of intermediates. This heterogeneous

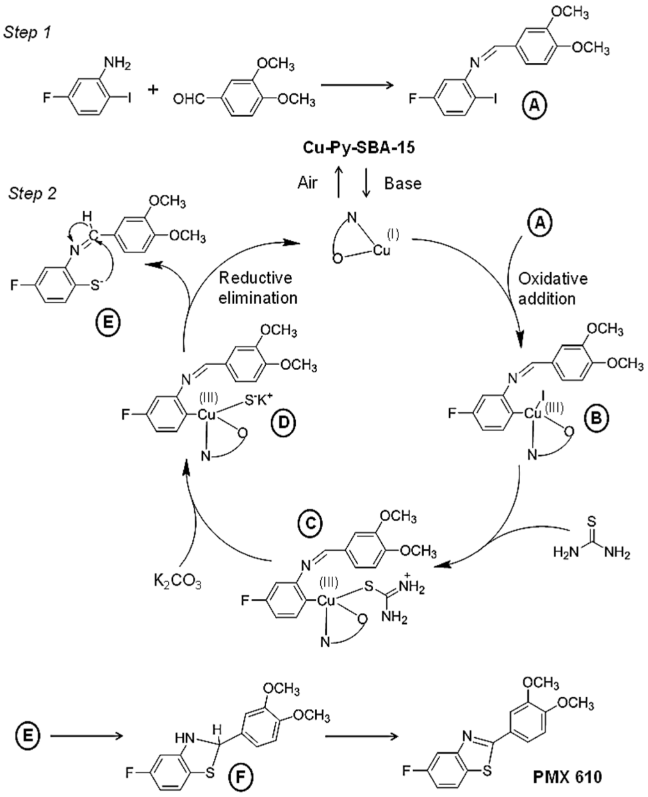


Figure 4. Plausible catalytic pathway of the Cu-Py-SBA-15 catalyst for the synthesis of PMX 610.

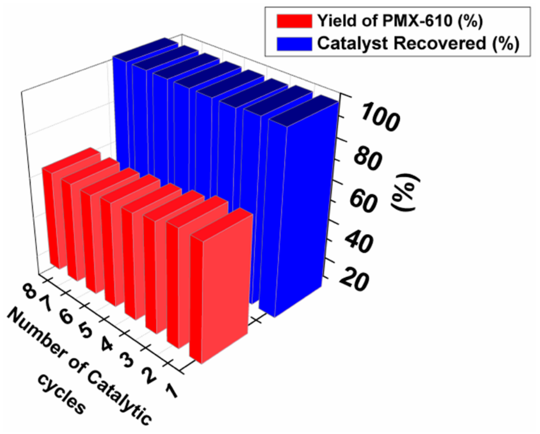


Figure 5. Recycling potential of the Cu-Py-SBA-15 catalyst for the synthesis of PMX 610.

catalyst has shown an excellent recyclability without considerable loss of catalytic activity. Thus, the efficient heterogeneous catalyst may find its way toward industrial applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic details, N_2 adsorption/desorption isotherms, wide angle powder XRD patterns, FE-SEM images, FT-IR analysis, XPS spectra, leaching and hot filtration tests, characterization of reused catalyst, and ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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