# Highly efficient heterogeneous copper-catalysed coupling of oxime acetates with isothiocyanates leading to 2-aminothiazoles

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The heterogeneous coupling reaction of oxime acetates with isothiocyanates was achieved at 110  $^{\circ}$ C in toluene in air in the presence of a bidentate nitrogen-functionalised MCM-41-immobilised copper(I) complex (MCM-41-2N-CuI) with Cs<sub>2</sub>CO<sub>3</sub> as base to afford a variety of 2-aminothiazoles in good yields. The MCM-41-2N-CuI catalyst can be easily recovered by a simple filtration and reused at least eight times without significant loss of activity.

Keywords: copper, oxidative coupling, functionalised MCM-41, oxime acetate, heterogeneous catalysis

The 2-aminothiazole motif is a useful structural element in medicinal chemistry and has been widely used in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia and bacterial and HIV infections.1-3 Many methods have been developed for the synthesis of 2-aminothiazole and their derivatives, such as those of such as Hantzsch, Cook-Heilbron and Tchernic.<sup>4</sup> Among these, the Hantzsch reaction, which uses  $\alpha$ -halocarbonyl compounds to couple with thiourea or thioamides, is one of the most widely used protocols.<sup>5-8</sup> Recently, 2-aminothiazole derivatives were also prepared by using various catalysts such as iodine,9 silica chloride,10 1,3-di-n-butylimidazolium tetrafluoroborate,<sup>11</sup> ammonium 12-molybdophosphate and cyclodextrin.<sup>12,13</sup> Reactions starting directly from ketones and thioureas have also been reported for the synthesis of 2-aminothiazoles.14-16 However, they suffer from some drawbacks such as harsh reaction conditions, poor functional group tolerance or limited starting materials. Therefore, the development of more green reagents and new efficient methods for the synthesis of 2-aminothiazoles is highly desirable. Very recently, Jiang and co-workers reported a novel route to 2-aminothiazoles by the copper-catalysed coupling of oxime acetates with isothiocyanates under mild conditions.<sup>17</sup> The proposed mechanism involved an oxidative reaction of an intermediate due a to Cu(II) species. Although the Cu-catalysed oxidative coupling of oxime acetates with isothiocyanates was highly efficient for the construction of 2-aminothiazoles, the use of 0.2 equiv. of CuI was required to obtain good yields. Moreover, a homogeneous copper salt is difficult to separate from the reaction mixture and it cannot be reused in consecutive reactions. It is well-known that homogeneous catalysis may result in heavy metal contamination of the desired isolated product due to the coordination of the product to the metal, which restricts the application of such systems in electronics and biomedicine. These problems are of particular

environmental and economic concern in large-scale syntheses and in industry. To overcome these problems, from the standpoint of green and sustainable chemistry, the development of highly efficient and recyclable heterogeneous catalysts, for example by immobilisation of catalytically active species onto an ideal solid support to produce a molecular heterogeneous catalyst, is essential.<sup>18–20</sup> The use of immobilised catalysts could result in easy recovery and reusability of the copper catalyst, thereby minimising copper contamination of the desired isolated products and of wastes derived from reaction workup.

The mesoporous MCM-41 material has emerged as an ideal heterogeneous support for the immobilisation of homogeneous catalysts due to its high surface area, large and defined pore size, big pore volume and rich silanol groups in the inner channel walls.<sup>21-23</sup> To date, MCM-41-immobilised palladium,<sup>24-27</sup> rhodium,28 molybdenum,29 gold30-32 and copper33-35 complexes have been successfully utilised as potentially green and sustainable catalysts in organic synthesis. Recently, we reported the first synthesis of an MCM-41-immobilised bidentate nitrogen copper(I) complex (MCM-41-2N-CuI) and its successful application to the *N*-arylation of indoles<sup>33</sup> and the A<sup>3</sup> reaction of tetrahydroisoquinoline, aldehydes and alkynes.<sup>35</sup> In continuing our efforts to develop greener synthetic pathways for organic transformations, we wish to report here a highly efficient heterogeneous copper-catalysed coupling reaction of oxime acetates with isothiocyanates using 20 mol% of the MCM-41-2N-CuI complex as catalyst and yielding a variety of 2-aminothiazoles in good isolated yields (Scheme 1). This heterogeneous copper catalyst can easily be recovered by a simple filtration of the reaction solution and its catalytic efficiency remains essentially unaltered even after recycling eight times.

## **Results and discussion**

A series of MCM-41-immobilised bidentate nitrogen copper(I) or copper(II) complexes  $(MCM-41-2N-CuX_n)$  were easily



Scheme 1

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Toluene

Toluene

<sup>a</sup>All reactions were performed using 1a (0.5 mmol), 2a (0.5 mmol), base (0.25 mmol) and copper catalyst (20 mol%) in solvent (3.0 mL) at 110 °C in air for 12 h. <sup>b</sup> Isolated yield.

Cs CO

Cs<sup>2</sup>CO

° Under Ar.

С

123456789

18

prepared starting from commercially available and inexpensive 3-(2-aminoethylamino)propyltrimethoxysilane and simple copper salts such as  $CuX_n$  (X = Cl, Br, I, OAc, OTf) according to our previous procedure (Scheme 2).<sup>33</sup> Firstly, the mesoporous material MCM-41 was condensed with 3-(2-aminoethylamino) propyltrimethoxysilane in toluene at 100 °C for 24 h, followed by silvlation with Me<sub>2</sub>SiCl in dry toluene at room temperature for 24 h to afford 3-(2-aminoethylamino)propyl-functionalised MCM-41 (MCM-41-2N). The latter was subsequently treated with various copper salts in DMF at room temperature for 7 h to give a series of MCM-41-immobilised bidentate nitrogen copper(I) or (II) complexes (MCM-41-2N-CuX<sub>n</sub>) as pale blue powders.

In our initial screening experiments, the reaction of acetophenone oxime acetate (1a) with phenyl isothiocyanate (2a) was investigated to optimise the reaction conditions and the results are summarised in Table 1. First, the effect of various immobilised copper complexes on the model reaction was examined by using Cs<sub>2</sub>CO<sub>3</sub> as base and toluene as solvent at 110 °C and a significant catalytic effect was observed (Table 1, entries 1–7). It is evident that good yields were obtained when MCM-41-2N-CuBr [B], MCM-41-2N-CuI [C], MCM-41-2N-Cu(OAc), [F] or MCM-41-2N-Cu(OTf), [G] were used as the catalyst and MCM-41-2N-CuI [C] gave the best result (Table 1, entry 3), whilst MCM-41-2N-CuCl [A], MCM-41-2N-CuCl<sub>2</sub> [D] and MCM-41-2N-CuBr<sub>2</sub> [E] were substantially less efficient. MCM-41-2N-CuI [C] was therefore selected as the catalyst for the reaction. Our next studies focused on the effects of bases and solvents on the model reaction. For the bases tested (K<sub>2</sub>CO<sub>2</sub>, Cs<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, KOBu<sup>t</sup>, DBU and Na<sub>2</sub>SO<sub>3</sub>), Cs<sub>2</sub>CO<sub>3</sub> gave the best result and other bases afforded low yields (Table 1, entries 3, 8–12). When DMSO or DMF was used as solvent, the reaction did not occur and 1,4-dioxane gave a low yield (Table 1, entries 13-15). The control experiments showed that no desired product **3a** was detected in the absence of a base or a copper catalyst (Table 1, entries 16 and 17). When the reaction was carried out under an argon atmosphere, the result was not improved significantly (Table 1, entry 18). Therefore, the optimal catalytic system involved the use of MCM-41-2N-CuI [C] (20 mol%) and Cs<sub>2</sub>CO<sub>2</sub> (0.5 equiv.) in toluene at 110 °C in air for 12 h (Table 1, entry 3).

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Table 2 Heterogeneous copper-catalysed synthesis of 2-aminothiazoles from various oxime acetates and isothiocyanates<sup>a</sup>



<sup>a</sup> The reactions were performed at 110 °C using 1 (0.5 mmol), 2 (0.5 mmol), MCM-41-2N-Cul (20 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (0.25 mmol) in toluene (3 mL) in air for 12 h. <sup>b</sup> Isolated vield.

° Isolated yield in parentheses was obtained<sup>17</sup> with Cul (20 mol%) and Cs<sub>a</sub>CO<sub>a</sub> (0.25 mmol) in toluene at 105 °C for 8 h.

With the optimal reaction conditions established, we tried to investigate the scope and limitations of this heterogeneous copper-catalysed coupling reaction of oxime acetates with isothiocyanates and the results are summarised in Table 2 and yields compared with the homogeneous method.<sup>17</sup> Firstly, the reactions of various oxime acetates with phenyl isothiocyanate were examined. The reactions of para-substituted acetophenone oxime acetates bearing both electron-donating groups and electron-withdrawing groups with phenyl isothiocyanate proceeded smoothly, leading to the desired 2-aminothiazoles **3b-e** in good yields. The results indicated that the electronic natures of the substituents on acetophenone oxime acetates have limited influence on this heterogeneous copper-catalysed coupling reaction. Besides, acetophenone oxime acetates with a fluoro, chloro or bromo group at the meta- or orthoposition could also participate in this reaction well to give the corresponding coupled products **3f-i** in good yields. In general, electron-rich acetophenone oxime acetates showed higher reactivity than electron-deficient ones. However, a strong electron-withdrawing group such as a nitro group was not tolerated in this transformation. Ester and cyano groups were also unsuitable substituents. The disubstituted acetophenone oxime acetate proved to be a suitable substrate and the desired product 3j was formed in 78% yield. It is noteworthy that a heteroaryl-containing oxime acetate was compatible for this reaction and was transformed into the corresponding product 3k in 73% yield. To our delight, 4,5-disubstituited 2-aminothiazoles **3l-o** could be easily obtained in good yields from other oxime acetates. Encouraged by the above results, we next examined the scope of isothiocyanates for this reaction. For various para-substituted phenyl isothiocyanates bearing either electron-donating or electron-withdrawing substituents on the aromatic ring, the reactions proceeded smoothly to give the expected products **3p-t** in high yields. When 3-methylphenyl isothiocyanate was used as the substrate, the desired product 3u was obtained in 76% yield. Additionally, the reactions of alkyl or benzyl isothiocyanates with acetophenone oxime acetate also proceeded effectively to afford the corresponding products 3v-x in 75–88% yields.

To determine whether the observed catalysis was due to the heterogeneous catalyst MCM-41-2N-CuI or to a leached copper species in solution, a hot filtration test was performed.<sup>36</sup> We focused on the coupling reaction of acetophenone oxime acetate (**1a**) with phenyl isothiocyanate (**2a**). The MCM-41-2N-CuI complex was filtered off after 5 h of reaction time and the filtrate was allowed to react further by addition of 0.5 equiv. of Cs<sub>2</sub>CO<sub>3</sub>. The catalyst filtration was performed at the reaction temperature (110 °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, indicating that leached copper species from the catalyst (if any) are not responsible for the observed activity.

For a heterogeneous transition metal catalyst system, it is important to examine its ease of separation, recoverability and reusability. This heterogeneous copper catalyst can be easily recovered by simple filtration of the reaction solution. We next investigated the recyclability of the catalyst by using the coupling reaction of 4'-methoxyacetophenone oxime acetate with phenyl isothiocyanate in air. After carrying out the reaction, the catalyst was separated by simple filtration and washed with distilled water, DMF and ethanol. After being air-dried, it can be reused directly without further purification. The recovered catalyst was used in the next run and almost consistent activity was observed for eight consecutive cycles (Fig. 1). The high stability and excellent reusability of the catalyst should result from the chelating action of the bidentate nitrogen ligand on copper and the mesoporous structure of the MCM-41 support. The result is important from industrial and environmental points of view.



Fig. 1 Recycling of the MCM-41-2N-Cul complex. Where 1 indicates the original catalyst before the first recycling.

In conclusion, we have developed a novel, environmentally friendly and economic catalyst system for the oxidative coupling reaction of oxime acetates with isothiocyanates by using an MCM-41-immobilised bidentate nitrogen copper(I) complex (MCM-41-2N-CuI) as catalyst. The reactions generated a variety of 2-aminothiazoles in good yields and were applicable to various oxime acetates and different isothiocyanates. This heterogeneous copper catalyst could be easily recovered by a simple filtration of the reaction solution and recycled at least eight times without significant loss of catalytic activity. The present methodology provides a green and practical route to 4-substituted or 4,5-disubstituted 2-aminothiazoles.

## Experimental

All reagents were used as received without further purification. The MCM-41-2N-CuCl [A], MCM-41-2N-CuBr [B], MCM-41-2N-CuI [C], MCM-41-2N-CuCl<sub>2</sub> [D], MCM-41-2N-CuBr<sub>2</sub> [E], MCM-41-2N-Cu(OAc)<sub>2</sub> [F] and MCM-41-2N-Cu(OTf), [G] were prepared according to our previous procedure<sup>33</sup> and the copper contents were determined to be 0.44 mmol g<sup>-1</sup>, 0.42 mmol g<sup>-1</sup>, 0.45 mmol g<sup>-1</sup>, 0.47 mmol g<sup>-1</sup>, 0.49 mmol g<sup>-1</sup>, 0.51 mmol g<sup>-1</sup> and 0.50 mmol g-1 respectively. Oxime acetates were prepared according to the literature procedure.37 All reactions were carried out in air in oven-dried glassware with magnetic stirring. FTIR spectra were obtained on a Nicolet MAGNA-IR 750 spectrometer. <sup>1</sup>H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer with TMS as an internal standard using CDCl, as the solvent. 13C NMR spectra were recorded on a Bruker Avance 400 (100 MHz) spectrometer using CDCl<sub>2</sub> as the solvent. Melting points are uncorrected. Copper content was determined using inductively coupled plasma atom emission spectrometry on an Atomscan16 instrument (TJA Corporation).

## Synthesis of MCM-41-2N-CuI; general procedure<sup>33</sup>

A solution of 3-(2-aminoethylamino)propyltrimethoxysilane (1.54 g) in dry chloroform (18 mL) was added to a suspension of MCM-41 (2.2 g) in dry toluene (180 mL). The mixture was stirred for 24 h at 100 °C. The solid was filtered off, washed with CHCl<sub>3</sub> (2 × 20 mL) and dried under reduced pressure at 160 °C for 5 h. The dried white solid was then soaked in a solution of Me<sub>3</sub>SiCl (3.1 g) in dry toluene (100 mL) at room temperature under stirring for 24 h. The solid was filtered off, washed with acetone (3 × 20 mL) and diethyl ether (3 × 20 mL) and then dried under reduced pressure at 120 °C for 5 h to obtain the hybrid material MCM-41-2N (3.49 g). The nitrogen content was found to be 1.84 mmol g<sup>-1</sup> by elemental analysis.

In a small Schlenk tube, the above-functionalised MCM-41 (MCM-41-2N) (1.0 g) was mixed with CuI (0.1 g, 0.52 mmol) in dry DMF

(10 mL). The mixture was stirred at room temperature for 7 h under an argon atmosphere. The solid product was filtered off by suction, washed with DMF and acetone and dried at 40 °C/26.7 Pa under Ar for 5 h to give a pale blue copper complex (MCM-41-2N-CuI) (1.07 g). The nitrogen and copper contents were found to be 1.67 mmol  $g^{-1}$  and 0.45 mmol  $g^{-1}$  respectively.

Coupling reaction of oxime acetates with isothiocyanates; general procedure

A mixture of the oxime acetate (0.5 mmol), the isothiocyanate (0.5 mmol),  $Cs_2CO_3$  (0.25 mmol), toluene (3 mL) and the MCM-41-2N-CuI complex (222 mg, 20 mol%) was stirred at 110 °C in air for 12 h. The reaction mixture was cooled to room temperature and quenched with H<sub>2</sub>O (10 mL) and extracted with EtOAc (3 × 10 mL). The MCM-41-2N-CuI catalyst was recovered by filtration, washed with distilled water (2 × 5 mL), DMF (2 × 5 mL) and EtOH (2 × 5 mL) and could be reused in the next run. The combined organic layers were dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate) on silica gel.

All the products **3a–x** are known compounds and the melting points of the solids are given in Table 2 and compared with literature values.

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## **Electronic Supplementary Information**

The ESI (FTIR and NMR data of the products) is available through:

stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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