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A novel one-pot three component approach to 6-substituted 2,4-diamino-1,3,5-triazines using nano-sized copper/zinc-modified MCM-41 (Cu/Zn-MCM-41) as a new heterogeneous mesoporous catalyst

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ABSTRACT

The nano-sized copper/zinc-modified MCM-41 (Cu/Zn-MCM-41) was successfully prepared and applied as a new heterogeneous mesoporous nano-catalyst in a more benign and novel one-pot three component strategy for the synthesis of 6-substituted 2,4-diamino-1,3,5-triazines from aryl-aldehydes, hydroxylamine and 2-cyanoguanidine under microwave irradiation. Using this method, the major problems of previously reported methods (very low diversity of available starting materials and the production of explosive byproducts) have been solved and all desired products were obtained in good to excellent yields in very short times.

Introduction

Heterocyclic compounds are the main backbone of many natural products and important synthetic molecules and have numerous applications in biology and industry [1–5]. The widespread interest in heterocycles makes the synthesis of these compounds one of the most important research areas in synthetic chemistry, resulting in the development of several classic named reactions [6]. Many of these classical synthetic methodologies have broad scopes, however, they are simply no longer acceptable by current environmental and safety standards. Recent developments in discovery and process chemistry emphasize new sustainable synthetic routes, introducing rapid and environmentally acceptable alternatives to the classic methods. Twelve principles of Green Chemistry are one of the best guide lines to gain more benign and sustainable synthetic strategies [7].

Triazines are one of the important class of heterocycles due to their varied bioactivities such as anticancer [8], antimalarial [9], antibacterial [10], antiviral [11], antiprotozoal [11] and antileshmanial [11]. Between various types of triazines, 6-aryl-2,4-diamino derivatives are mostly studied in view of their potentially interesting molecular recognition [12], agrochemicals and medicinal [13] properties. The most commonly used synthetic strategy to 6-substituted 2,4-diamino-1,3,5- triazines is a base-catalyzed condensation of aryl-nitriles with 2-cyanoguanidine [14] that is highly limited to the low diversity of commercial available nitriles and suffer from the need to excess amounts of strong bases such as KOH that leads to the generation of hazardous waste. More recently, a new one-pot strategy has been reported with the direct conversion of alcohols and aldehydes to corresponding nitriles that is followed with microwave-assisted condensation of prepared nitriles with 2-cyanoguanidine [15]. In spite of enhanced diversity of available starting materials, application of molecular iodine in saturated aqueous ammonia leads to the preparation of hazardous and explosive NI_3 that limits this method to the small scale synthesis and completely is contrary to the *Green Chemistry* point of view. So, introducing a new synthetic strategy for the diversity-oriented synthesis of titled compounds under more benign conditions without the formation of dangerous or toxic byproducts is still of a great interest.

Another key area of clean technology is the replacement of hazardous acids, bases, metals and other hazardous traditional reagents widely used in the specialty chemical and pharmaceutical industries. Between various introduced alternatives, mesoporous solids have been gained much attention and have been widely used

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in chemistry as catalyst, reagent, trapping material and transporting agents. Since the first report of the synthesis of MCM-41 as a periodic mesoporous silica material, this compound has attracted much attention and its synthesis, characterization and applications as heterogeneous catalyst and support in organic processes [16–19] are the main research interest of many research groups. In spite of the fact that MCM-41 provides ideal conditions for organic reactions due to its unique properties such as high surface area and uniform 2D hexagonal channels and tunable pore diameters in the range of 2–10 nm [20–22], its catalytic activity is low due to the lack of potent acid or base active sites. This low catalytic activity has been lead to the synthesis of some novel modified MCM-41 with special catalytic activities [23–27]. One useful method to gain modified MCM-41 with enhanced catalytic activity is the replacement of some Si atoms with transition metals such as V [28], Fe [29], Cu [30], Mn [31], Co [32], Ni [33] and Mo [34].

Recently, Abdollahi-Alibeik and co-workers reported the application of *in situ* generated oximes instead of nitriles for the synthesis of tetrazoles using Cu-MCM-41 as a new mesoporous catalyst [35]. Considering obtained results by Abdollahi-Alibeik and co-workers, our research background on the introducing more benign methods in organic synthesis [36] and the importance of transition metal-modified MCM-41 materials in heterogeneous catalysis, herein we tried to introduce a new strategy for the synthesis of 6-aryl-2,4-diamino-1,3,5- triazines *via* a novel one-pot three component reaction of aryl-aldehydes (**1**), hydroxylamine (**2**) and 2-cyanoguanidine (**3**) in the presence of nano-sized copper/zinc-modified MCM-41 (Cu/Zn-MCM-41) as a new heterogeneous catalyst under microwave irradiation. (Scheme 1)

Experimental

All chemicals were purchased from Merck or Aldrich companies. All reactions were monitored by TLC and all yields refer to isolated products. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance (250 MHz for ^{1}H and 62.5 MHz for ^{13}C) spectrometer with tetramethylsilane (TMS) as an internal standard. Infrared spectra of the catalysts and reaction products were recorded on a Bruker FT-IR Equinax-55 spectrophotometer in KBr disks. XRD patterns were recorded on a Bruker D8 ADVANCE X-ray diffractometer using nickel filtered Cu K_α radiation ($\lambda = 1.5406$ Å). Scanning Electron Micrograms (SEM) was obtained using KYKY-EM3200 Instrument. The high resolution transmittance electron microscopy was performed with JEOL, JEM-2100F, 200 KV TEM. All reactions were carried out using a laboratory microwave oven (MicroSYNTH, Milestone Company, Italy). The reactions were performed in a glass tube sealed with a septum. The reported reaction temperature was monitored using a calibrated infrared temperature control mounted under the reaction vessel. The reaction mixture was magnetically stirred. Melting points were determined in open capillary tubes with a Büchi B-545 melting point apparatus. Microanalysis was performed on a Perkin-Elmer 240-B microanalyzer. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. The hydroxylamine solution 50 wt. % in water by Sigma-Aldrich was applied.

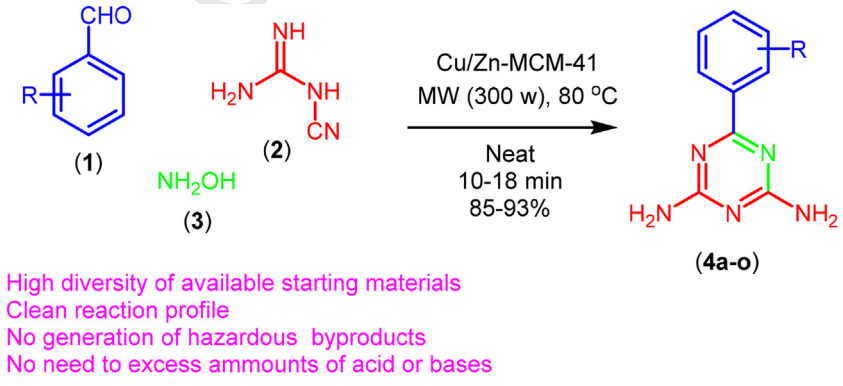
The preparation of nano-sized Cu/Zn-MCM-41

The synthesis of nano-sized Cu/Zn-MCM-41 was performed with the method of direct insertion of the Cu and Zn ions in the sol–gel preparation step at room temperature. This synthesis was performed using tetraethyl orthosilicate (TEOS) as the Si source, cetyltrimethylammonium bromide (CTAB) as the template, ammonia as the pH control agent, $Cu(OAc)_2{\cdot}H_2O$ as the copper source and $Zn(OAc)_2{\cdot}2H_2O$ as the zinc source with the gel composition (molar ratio) of SiO_2: CTAB: NH_4OH: H_2O: $Cu(OAc)_2{\cdot}H_2O$: Zn $(OAc)_2{\cdot}2H_2O$ = 1.000: 0.127: 0.623: 508.000: 0.033: 0.033 for typical synthesis of Cu/Zn-MCM-41 with both Si/Cu and Si/Zn molar ratios of 30 and 1.000: 0.127: 0.623: 508.000: 0.033: 0.0165 for typical synthesis of Cu/Zn-MCM-41 with Si/Cu and Si/Zn molar ratios of 30 and 60 respectively.

In a typical procedure for the synthesis of Cu/Zn-MCM-41 with both Si/Cu and Si/Zn molar ratios of 30, cetyltrimethylammonium bromide (1040 mg) was dissolved in deionized water (200 mL) under constant vigorous stirring and temperature was adjusted to 60 °C for 15 min. Tetraethyl orthosilicate (5 mL) was added dropwise during 60 min gradually. Then, a solution content of $Cu(OAc)_2{\cdot}H_2O$ (150 mg) and $Zn(OAc)_2{\cdot}2H_2O$ (165 mg) in 5 mL of deionized water was prepared and added dropwise to the previous solution. This solution was kept under vigorous stirring for 1 h at 25 °C and then pH of the solution was adjusted to 10.5 by adding 25 wt.% ammonia solution. The mixture was stirred for 12 h at 25 °C. The gel was recovered by centrifuging and washed with ethanol (20 mL) and deionized water (40 mL). The obtained solid was dried at 120 °C for 2 h and calcined in air at 550 °C for 4 h. This procedure was also applied for the preparation of Cu/Zn-MCM-41 with Si/Cu molar ratio of 30 and Si/Zn molar ratio of 60 and only 82 mg of $Zn(OAc)_2.2H_2O$ was applied. The obtained samples were named as Cu/Zn-MCM-41-x-y that x and y are the Si/Cu and Si/Zn molar ratios in their initial gel compositions, respectively.

General procedure for the synthesis of 6-aryl-2,4-diamino-1,3,5-triazines

A mixture of aryl-aldehyde (**1**) (1 mmol), aqueous solution of hydroxylamine (**2**) (1.1 mmol, 0.07 mL), 2-cyanoguanidine (**3**) (1 mmol) and Cu/Zn-MCM-41 (20 mg) was placed in a pressure-resistance microwave glass tube sealed with a septum. The mixture



Scheme 1. The novel and more benign strategy to 6-aryl-2,4-diamino-1,3,5- triazines in the presence of nano-sized Cu/Zn-MCM-41 as a new mesoporous catalyst.

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