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A magnetically-separable $H_3PW_{12}O_{40}$@Fe_3O_4/EN-MIL-101 catalyst for the one-pot solventless synthesis of 2H-indazolo[2,1-*b*] phthalazine-triones

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ABSTRACT

A magnetic inorganic-organic catalyst, PTA@Fe_3O_4/EN-MIL-101 (EN = ethylenediamine, PTA = phosphotungstic acid) was fabricated and characterized by XRD, HRTEM, FESEM, UV–vis, TGA-DTA, FT-IR, XPS and porosimetry. PTA retained the parent Keggin structure upon dispersion throughout the amine-functionalized chromium terephthalate metal-organic framework, over which magnetic Fe_3O_4 nanoparticles were previously introduced. The resulting composite heterogeneous solid acid was an active catalyst for the one-pot synthesis of diverse 2H-indazolo[2,1-*b*] phthalazine-triones in good → excellent yields under mild, solventless condition, and offers facile separation and excellent recyclability.

1. Introduction

The design, synthesis and application of active and selective heterogeneous catalysts inspired by molecular analogues has been the focus of intensive recent research, resulting in the fabrication of diverse nanocomposites and nanoporous frameworks [1–4]. Critical design parameters for nanocomposite catalysts include ease of fabrication, separation and recycle and on-stream stability, which together influence their suitability for the large-scale commercial production of bulk and speciality chemicals and pharmaceuticals [5–7]. Of the many naturally occurring and synthetic catalytic materials available, metal-organic frameworks (MOFs) have risen in prominence for applications in organic synthesis due to their tunable microporosity (and more recently micro/mesoporosity [8]), extremely high surface areas, and wide range of pre- and post-synthetic routes to incorporate different chemical functionality [9–11].

Some MOFs offer vacant metal atom coordination sites which can be activated thermally, under vacuum, or through solvent exchange to enable their post-functionalization. Such coordinatively unsaturated MOFs are potential Lewis acid catalysts, and can act as structural building blocks in synergy with co-catalysts to generate multifunctional catalysts [12–15]. The attachment of magnetic nanoparticles to inorganic and organic backbones and fabrication of magnetic metal-organic frameworks (MMOFs) [16] unlocks opportunities to create novel multifunctional catalysts [17] amenable to facile separation and recycling.

The evolution of benign catalytic routes to the synthesis of structurally diverse active compounds for new therapeutic uses remains challenging [18–21]. Recently, phthalazine heterocyclic derivatives have attracted attention due to their high therapeutic value in analgesic, anti-inflammatory, antimicrobial, antithrombotic, antidepressant, diuretics, antihypertensive, antitubercular, and anti-HIV treatments [22]. Flexible synthetic routes to new scaffolds for generating various drug-based phthalazines thus represent a high of priority for catalyst design [22–24]. In this context, previous research has focused on catalytic functions immobilized on nanoparticles [25–30], wherein the catalytic surface area is related to the particle size and shape, and is generally too low

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to provide high activity. Nanoparticle catalysts may also require costly separation methods such as ultracentrifugation, although the application of magnetic Fe_3O_4 nanoparticles as a template can circumvent this issue [31–33]. Briefly, new composites made by immobilizing Fe_3O_4 nanoparticles onto functional MOFs could help in meeting the preceding goals, a high area catalyst offering facile, magnetic separation.

Here, we extend our recent efforts to develop efficient catalysts prepared from simple, low cost materials for atom economical and energy efficient organic synthesis [34–39], through the design of a MMOF incorporating $H_3PW_{12}O_{40}$ (phosphotungstic acid, PTA) guest molecules to introduce the Brönsted acidity required for one-pot 2H-indazolo[2,1-*b*]phthalazine-triones synthesis [40–43]. Chromium(III) terephthalate MOF, MIL-101(Cr) is a promising framework upon which to fabricate such catalysts, since it possesses a high surface area, good thermal and chemical stability, large mesopore channels (~2.9 and 3.4 nm) and wide pentagonal and hexagonal microporous windows (1.2 and 1.6 nm respectively) which facilitate rapid in-pore transport of substrate and products [15]. In MIL-101(Cr), Lewis acidic chromium vertices enable the coordination of ethylenediamine (EN) via simple post-modification. The large pore windows and channels facilitate subsequent in-pore anchoring of PTA to the amine moieties within EN-MIL-101(Cr) and hence Brønsted acidity, and the introduction of Fe_3O_4 nanoparticles which confer strong ferromagnetism and hence aid catalyst separation and re-use. This approach affords a magnetically separable, inorganic-organic hybrid catalyst for the one-pot condensation of phthalhydrazide, aromatic aldehydes, and dimedone to 2H-indazolo[2,1-*b*] phthalazine-trione derivatives (Scheme S1).

2. Experimental section

2.1. Materials and methods

All chemicals were obtained from commercial sources (Aldrich and Merck) and used without further purification. Scanning electron microscope (SEM) micrographs were taken using a KYKY-EM3200 microscope (acceleration voltage 26 kV). HRTEM measurements were performed on a Philips TECNAI-20T electronic microscope operated at 200 kV. Fourier transform infrared (FT-IR) spectra were recorded on a Bomem MB-Series FT-IR spectrometer. Ultraviolet–visible (UV–vis) spectra were obtained on a Shimadzu Model UV-2550 spectrophotometer. Melting points were recorded on a Barnstead electrothermal type 9200 melting point apparatus. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer. Typical ^{1}H NMR parameters were 10 scans averaged, 2 s delay time, 14.6 μs pulse length; and for ^{13}C NMR 1024 scans averaged; 2 s delay time, and 130 μs pulse length, using TMS as an internal reference. Thermal analysis (TGA-DTA) was carried out using a Bahr STA-503 instrument at a heating rate of 10 °C min^{-1} in air. Powder X-ray diffraction (XRD) patterns were obtained on a STOE diffractometer using Cu K_α radiation (λ = 0.15418 nm). XPS analysis was performed on a Kratos Axis HSi photoelectron spectrometer equipped with a charge neutralizer and magnetic focusing lenses, employing monochromatic Al K_α radiation (1486.6 eV) with energy referencing to the C 1s peak at 284.8 eV. Porosimetry measurements were conducted by N_2 physisorption on a Quantachrome Nova 4200e porosimeter with data analysis employing Novawin v11.0 software. Samples were degassed at 120 °C for 4 h prior to analysis by nitrogen adsorption at −196 °C, with BET surface areas calculated over the range P/P_0 = 0.05–0.35 where a linear relationship was maintained, while pore size distributions were calculated using the BJH model from the desorption isotherm. A freeze dryer (Model FD-10, Pishtaz Equipment Engineering Co, Iran) was utilized for occasional drying of samples if needed. Elemental analysis was performed with a Varian Vista-PRO ICP-OES and Thermo Scientific Flash 2000 organic elemental analyzer. Synthesis of MIL-101(Cr) was confirmed by comparison of its spectral and physical data with those of previously reported [44]. All prepared indazolophthalazine-triones were known compounds and their spectral data was compared with the literature to confirm successful synthesis [36].

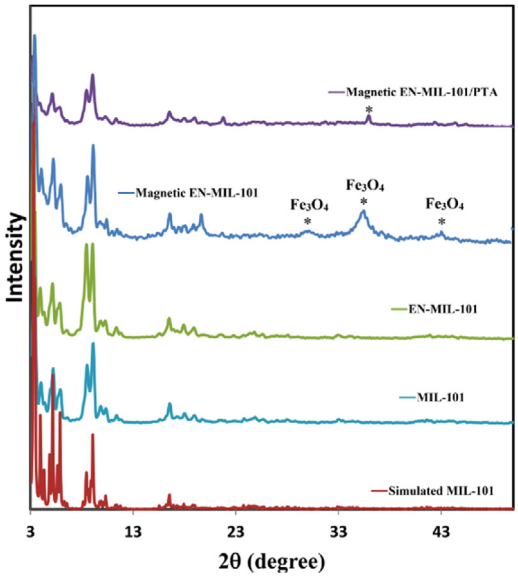

Fig. 1. X-ray diffraction patterns of parent and functionalized MOFs.

2.2. Preparation of chromium(III) terephthalate metal organic framework [MIL-101(Cr)]

MIL-101(Cr) was synthesized and purified according to the reported literature [45]. Briefly, 40 mL of deionized water was added to a mixture of ground, powdered terephthalic acid (1.66 g, 10 mmol) and $Cr(NO_3)_3{\cdot}9H_2O$ (4.0 g, 10 mmol). The mixture was sonicated resulting in a dark-blue suspension, which was then poured into a 100 mL Teflon-lined stainless steel autoclave; the autoclave was then sealed and heated to 220 °C (heating rate 1°/min) for 24 h. After hydrothermal processing, the autoclave was slowly cooled to ambient temperature, and the green suspension of MIL-101(Cr) thus obtained then separated by centrifugation (at 9000 rpm for 10 min). The crude product was rinsed with water, methanol, and acetone, then centrifuged and purified by 10 min ultrasonication with 25 mL *N*,*N*-dimethylformamide after which it was kept at 70 °C overnight. The final pure solid was obtained following additional centrifugation and repeated washing with methanol and acetone, and further overnight drying at 75 °C. The final isolated yield was 42%. MIL-101(Cr) was characterized by powder XRD and compared with the simulated single-crystal pattern from Mercury 3.8 software (Fig. 1) [44]. ICP-OES analysis gave the bulk Cr loading as 21 wt%.

2.3. Synthesis of EN-MIL-101

MIL-101 grafted with ethylenediamine (EN) was synthesized according to a previously reported procedure [46]. 1.0 g of MIL-101 was activated at 150 °C for 24 h and then added to anhydrous toluene (60 mL) and ethylenediamine (0.09 g, 1.4 mmol). The mixture was stirred under reflux for 12 h and then centrifuged and washed repeatedly with deionized water/ethanol (1:1) and finally