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Nano-organocatalyst: magnetically retrievable ferrite-anchored glutathione for microwave-assisted Paal–Knorr reaction, aza-Michael addition, and pyrazole synthesis

Vivek Polshettiwar *,†, Rajender S. Varma *

Sustainable Technology Division, National Risk Management Research Laboratory, U.S. Environmental Protection Agency, MS 443, Cincinnati, OH 45268, USA

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ABSTRACT

Postsynthetic surface modification of magnetic nanoparticles by glutathione imparts desirable chemical functionality and enables the generation of catalytic sites on the surfaces of ensuing organocatalysts. In this article, we discuss the developments, unique activity, and high selectivity of nano-organocatalysts for microwave-assisted Paal–Knorr reaction, aza-Michael addition, and pyrazole synthesis. Their insoluble character coupled with paramagnetic nature enables easy separation of these nano-catalysts from the reaction mixture using external magnet, which eliminates the requirement of catalyst filtration.
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1. Introduction

Manufacturing protocols can be made economic, greener, and more sustainable, by designing and vigilant use of catalysts, which reduces the chemical waste harmful to human health and the environment. In this regard, magnetic nano-materials showed major impacts on catalysis and many other areas, such as medicine, drug delivery, and remediation.[1,2] These inexpensive materials are accessible via simple synthesis and they can be easily enhanced/tuned by postsynthetic surface modifications.[3] Functionalized nanoparticles have emerged as feasible substitute to conventional materials as a robust, active, high-surface-area catalyst support.[4–8] In view of their nano-size, the contact between reactants and catalyst increases dramatically thus mimicking the homogeneous catalysts. They offer an added advantage of being magnetically separable, thereby eliminating the requirement of catalyst filtration after completion of the reaction.

During the past decade, another exciting field of organocatalysis has become a very significant area of research and this metal-free approach to the synthesis of organic molecules has attracted worldwide attention.[9–12] A diverse set of reactions, including enantioselective C–C, C–N, C–O bond formation,[13] Diels–Alder,[14,15] Baylis–Hilman,[16,17] Mannich,[14,18–20] Michael,[14,21,22] Friedel–Crafts alkylation,[23] oxidation,[24,25] and carbohydrate synthesis,[26] has benefited from the developments in this area.[27–29] This relatively green approach has been rendered even greener by efforts in immobilization and recycling of the organocatalysts on supports, which involve their adsorption, covalent linkage, and dissolution in various matrices.[30–33] Newer strategies include the use of non-traditional methods such as light,[34] mechanochemical mixing, microwave (MW), and ultrasonic irradiation.[35] Most of these reactions are generally carried out in organic solvents, with a few aqueous phase organocatalytic processes as recent exceptions.[36–39] Although water is an environmental benign solvent,[40] and addition of water often accelerates the reaction, isolation of final organic product from the reaction mixture is tedious. Most of the reactions described in published reports use excessive amounts of toxic organic solvents for workup and the total amount of water used in the process is much less. As stated by Blackmond, 'A holistic approach that consider not only the reaction step but also the economics and environmental impact of product workup and reagent preparation', is the key aspect in deciding about the greenness of aqueous protocol.[41]

Although extensive amount of research has been carried out over organocatalysis, following aspects still remained unexplored;

* Corresponding authors. Tel.: +1 513 487 2701; fax: +1 513 569 7677.
E-mail addresses: vivekpol@yahoo.com, vivek.polshettiwar@kaust.edu.sa (V. Polshettiwar), varma.rajender@epa.gov (R.S. Varma).
† Present address: KAUST Catalysis Center (KCC), King Abdullah University of Science and Technology Thuwal 23955-6900, Kingdom of Saudi Arabia.

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(i) totally benign aqueous protocol without using any organic solvent even in workup step; (ii) magnetic nanoparticle-supported organocatalyst; (iii) use of naturally abundant and benign organocatalyst, glutathione. Engaged in the development of greener and sustainable pathways for organic transformations[42–45] and nanomaterials[46–48] and after our initial success with nano-organocatalyst,[49] herein, we report a simple and efficient synthesis of nano-ferrite-supported, magnetically recyclable organocatalyst for microwave-assisted Paal–Knorr, Aza-Michael reactions, and pyrazole synthesis.

2. Result and discussion

2.1. Design and synthesis of nano-organocatalyst

The first step in the realization of this concept was the selection of amino acids for the functionalization of magnetic nanoparticles. We decided to explore cysteine and glutathione, since they have highly reactive thiol group, which can be used for anchoring to the nano-ferrite surfaces, keeping active sites free for catalysis. Initially, both of the amino acids were tested for Paal–Knorr reaction under homogeneous condition in water medium, to compare their catalytic activity and glutathione appeared to be more active in comparison to cysteine. Glutathione is a highly benign tripeptide, an essential component of plants and human cell systems. The nano-organocatalyst was then prepared in high yield using our recently developed post-functionalization method[46] (Fig. 1).

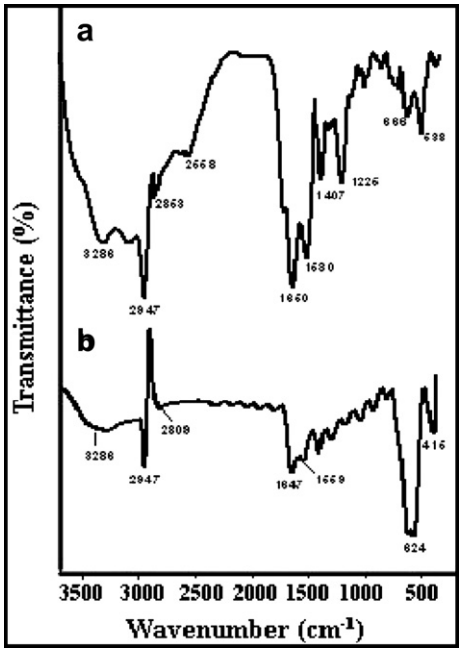


Figure 2. FTIR spectra (a) glutathione and (b) nano-organocatalyst.

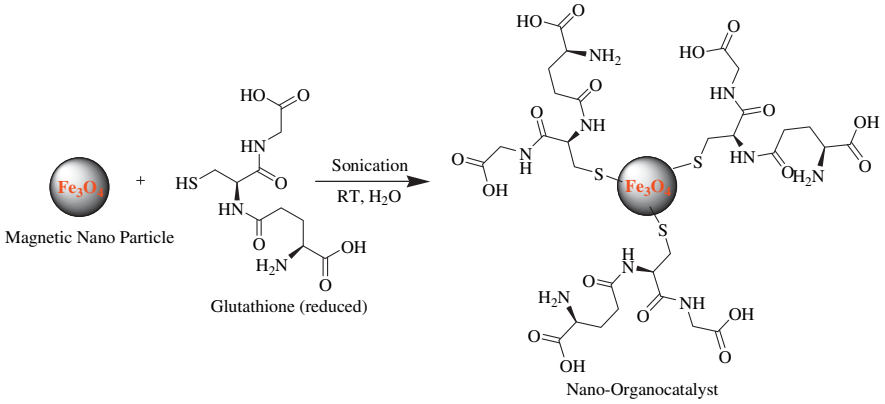


Figure 1. Synthesis of nanoparticle-supported glutathione as an organocatalyst.

Anchoring of glutathione on the surface of magnetic nanoparticles was examined by FTIR spectroscopy (Fig. 2). Three characteristic bands 2947 cm^{-1} (C–H stretching), 1648 cm^{-1} (cysteine-carbonyl), and 1629 cm^{-1} (glutamic acid-carbonyl) confirmed the attachment of glutathione on nano-ferrite surfaces. The molecule was firmly anchored via the thiol group, as the IR band at 2558 cm^{-1} for S–H stretching was diminished in the catalyst. A strong absorption band at 592 cm^{-1} was due to the vibration of the Fe–O bond of ferrite. The crystalline structures of the organocatalyst were determined by powder X-ray diffraction (XRD) (Fig. 3a); the diffraction patterns and relative intensities of all the peaks matched well with those of magnetite (JCPDS card no. 00-002-1035). Other oxide or hydroxide phases were not observed and the broad XRD peaks clearly indicate the nano-crystalline nature of the material. Transmission electron microscopy (TEM) analysis (Fig. 3b) of the organocatalyst showed uniform-sized particles with spherical morphology with an average size range of 10–12 nm. This is comparable to the crystallite size (10.11 nm) calculated from X-ray spectrum using Scherer formula for the full width at half-maximum (fwhm) of the (311) reflection.

2.2. MW-assisted Paal–Knorr reaction using nano-organocatalyst in aqueous medium

Paal–Knorr reaction in which amines are converted to pyrrole in one step has gained great interest in the synthetic organic chemistry, as these heterocycles are intermediates for various pharmaceutical drugs.[50] A range of clean protocols have been developed by using solid supported catalyst such as alumina,[51] zeolites,[52] phosphates,[53] and ionic liquids.[54] The use of non-conventional energy sources such as microwave[55] and ultrasound[56] was studied. However, most of the above methods involve the use of excess amounts of catalyst, toxic organic solvents, and tedious workup and cannot be considered as real green protocols. Hence, we decided to explore, this glutathione-coated material as a nano-organocatalyst for Paal–Knorr reactions (Scheme 1) as this reaction has never been accomplished using an organocatalyst.

Reaction conditions were optimized for the Paal–Knorr reaction using benzylamine as a substrate, using nano-organocatalyst under

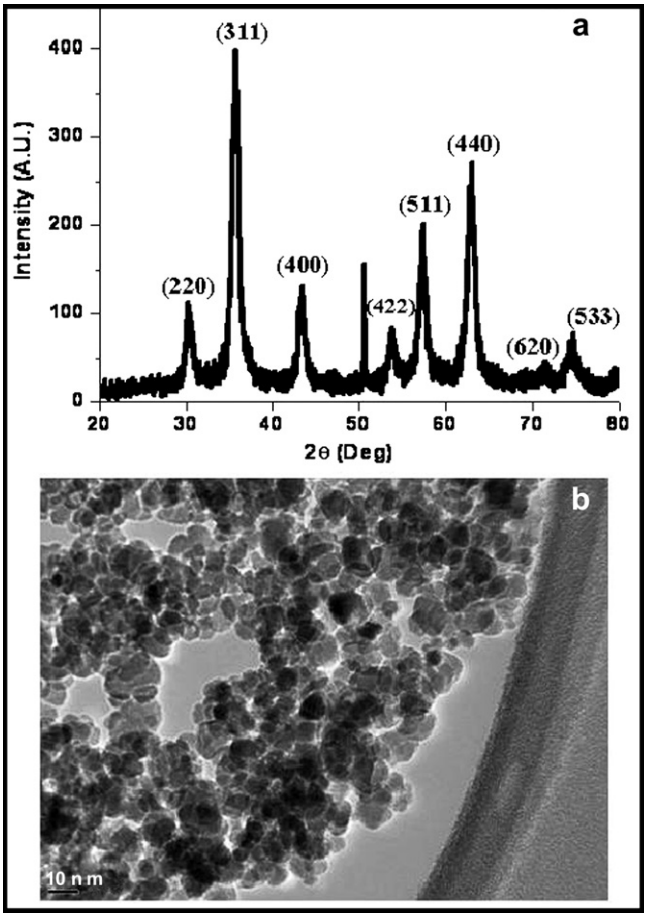
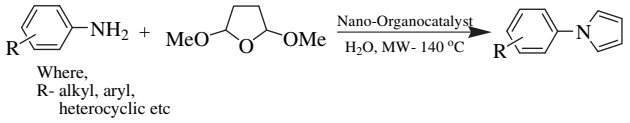


Figure 3. (a) Powder XRD pattern and (b) TEM image of as-synthesized nano-organocatalyst.



Scheme 1. Nano-organocatalyst promoted Paal–Knorr reactions.

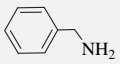
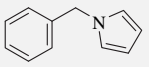
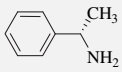
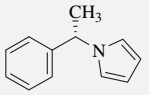
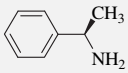
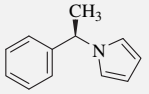
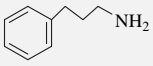
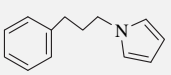
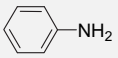
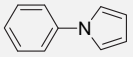
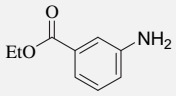
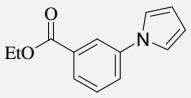
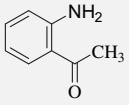
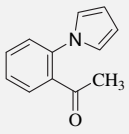
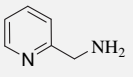
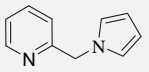
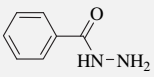
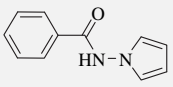
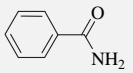
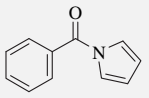
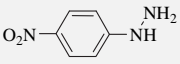
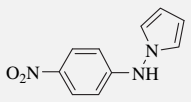
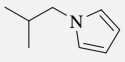
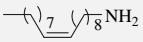
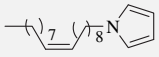
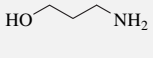
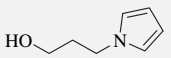
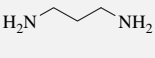
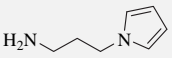
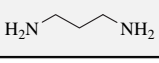
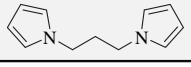
Table 1
Optimization of reaction conditions[a]

No.	Solvent	R. temp (°C)	R. time (min)	Conversion (%)
1	Toluene	120	30	>5
2	Toluene	140	30	>5
3	Toluene+H_2O	140	30	80
4	H_2O	120	30	70
5	H_2O	140	20	92
6	H_2O	140	30	95

[a] 1 mmol of benzylamine, 25 mg of nano-organocatalyst.

MW irradiation conditions (Table 1). MW-assisted chemistry was used due to the efficiency of the interaction of MWs with the polar nano-catalyst,[42] as it allows rapid heating of the reaction mixture to required temperatures and the precise control of the reaction temperature. The reaction was first conducted in toluene as a reaction medium at 120 °C and a poor conversion was observed (entry 1). Increasing the reaction temperature to 140 °C provided no significant increase in conversion (entry 2). Interestingly, when the reaction was carried out in a mixture of toluene and water, good conversion was achieved (entry 3). Encouraged from this result, we decided to carry out the reaction in pure water; 92% conversion was achieved in 20 min at 140 °C under MW irradiation (entry 5).

Table 2
Paal–Knorr reaction of amines using nano-organocatalyst[a]

Entry	Substrate	Product	Yield (%)
1			92
2			90
3			90
4			86
5			88
6			85
7			82
8			78
9			72
10			NR
11			NR
12			90
13			84
14			86[b]
15			85[b]
16			72[c]

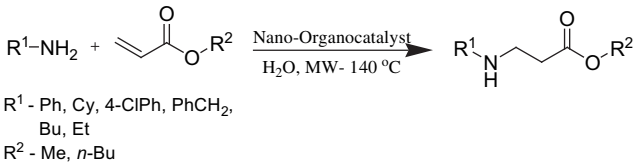
[a] Reactions were carried out with 1 mmol of amines, 1.1 mmol of tetrahydro-2,5-dimethoxyfuran, and 25 mg of nano-organocatalyst in 1.5 mL of water at 140 °C for 20 min under MW irradiation.
[b] Solvent extraction was needed to isolate the product.
[c] 2.2 mmol of tetrahydro-2,5-dimethoxyfuran, reaction temperature 150 °C, time 90 min.

Deploying the above optimized reaction conditions, the scope of this catalyst was then investigated for Paal–Knorr reaction using a variety of amines (Table 2).

The nano-organocatalyst displayed high catalytic activity for Paal–Knorr reactions and a variety of amines reacted efficiently with tetrahydro-2,5-dimethoxyfuran to afford the desired pyrrole derivatives in good yields (Table 2). The rates were essentially the same for both the aliphatic or aromatic nature of the amines, showing the high activity of the catalyst. Chiral (*S*)-α-methylbenzylamine and (*R*)-α-methylbenzylamine yielded corresponding pyrroles without racemization (entries 2 and 3). Heterocyclic amine underwent Paal–Knorr reaction with good yield of the respective pyrrole (entry 8). This protocol is also suitable for acid hydrazide (entry 9); however, our attempts to use amide (entry 10) and hydrazine (entry 11) as substrates yielded no product. Significantly, substituted amines were selectively converted to pyrroles while keeping other reactive functional groups, such as ester (entry 6), ketone (entry 7), olefinic bond (entry 13), alcohol (entry 14), and amine (entry 15) intact. For diamines, by changing the mole ratio and reaction time, mono- (entry 15) and di- (entry 16) pyrrole derivatives were obtained. It is important to point out that these biphasic reactions functioned well in an aqueous medium without the need for any phase-transfer catalyst, which is due to the selective absorption of microwaves by reactants, polar nano-catalyst, and aqueous medium.[42]

2.3. MW-assisted aza-Michael reaction using nano-organocatalyst in aqueous medium

Aza-Michael addition is a vital carbon–nitrogen bond-forming reaction and has been intensively examined as a powerful tool in organic synthesis.[57] However, most of the aza-Michael additions are performed in organic solvents. Recently β-cyclodextrin,[58] ytterbium triflate,[59] and surfactant-type asymmetric organocatalyst (STAO) type catalyst,[60] has been used in aqueous medium. Although today's environmental concerns encourage the development of such greener synthetic methodology in aqueous medium, many of these methods suffer from limitations such as the use of expensive and toxic catalyst, harsh reaction conditions. In order to study the versatility of the developed organocatalyst, we examined it for MW-assisted aza-Michael reaction in aqueous medium (Scheme 2).



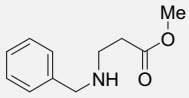
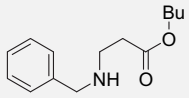
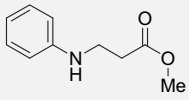
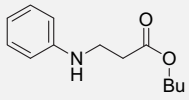
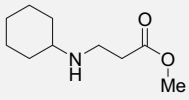
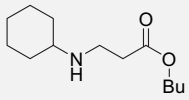
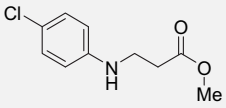
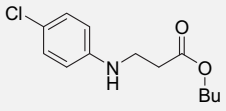
Scheme 2. Nano-organocatalyst promoted aza-Michael reactions.

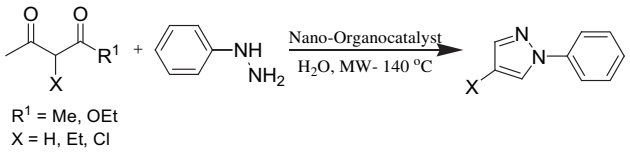
Using the optimized reaction conditions (developed for Paal–Knorr reaction), the scope and efficiency of this aqueous approach were explored for the reaction of various amines with methyl and butyl acrylate (Table 3). All reactions proceeded expeditiously and delivered excellent product yields. However, no phase separation was observed in these reactions, because of the high solubility of the product in water due to the presence of free –NH group.

2.4. MW-assisted pyrazole synthesis using nano-organocatalyst in aqueous medium

Pyrazoles are an important class of bio-active drug targets in the pharmaceutical industry, in both lead identification and lead optimization processes.[61] Recently, several efficient methods have been developed[62]; however most of these utilize a circuitous route requiring longer reaction time, and are often conducted in organic solvents. We decided to extend the exploration of nano-organocatalyst for the synthesis of pyrazole derivatives (Scheme 3).

Table 3
Aza-Michael addition using nano-organocatalyst

Entry	R1	R2	Product	Yield (%)
1	$PhCH_2$	Me		92
2	$PhCH_2$	Bu		90
3	Ph	Me		92
4	Ph	Bu		90
5	Cy	Me		90
6	Cy	Bu		92
7	4-ClPh	Me		90
8	4-ClPh	Bu		90



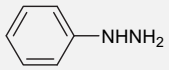
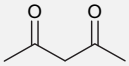
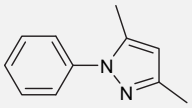
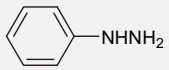
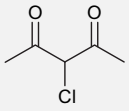
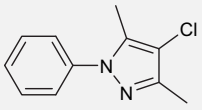
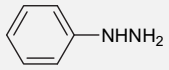
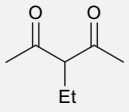
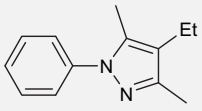
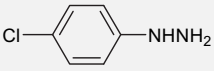
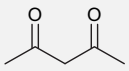
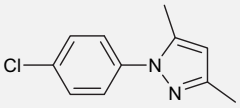
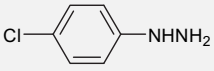
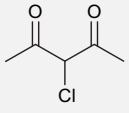
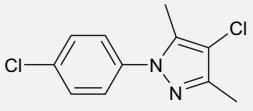
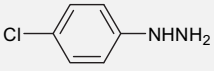
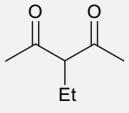
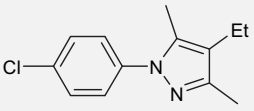
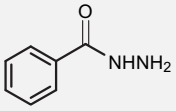
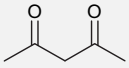
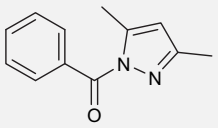
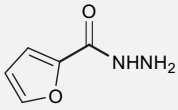
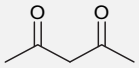
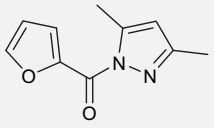
Scheme 3. Nano-organocatalyst promoted pyrazole synthesis.

Various hydrazines and hydrazides reacted efficiently with 1,3-diketones to afford the desired pyrazoles in good yields (Table 4). The β-keto esters can also be used as a substitute for diketones in this synthesis. All these reactions proceeded efficiently in aqueous medium and were completed in a 20 min. Product was isolated by simple decantation (in some cases) as well as extraction by ethyl acetate.

2.5. Recovery and reuse of nano-organocatalyst

Separation of the catalyst and isolation of products are the main operations in aqueous organocatalysis.[41] Catalyst recovery is often

Table 4
Pyrazole synthesis using nano-organocatalyst

Entry	Hydrazine	Diketone	Product	Yield (%)
1				96
2				80
3				84
4				82
5				78
6				84
7				88
8				84

performed by filtration that reduces efficiency and extractive isolation of products requires large amount of organic solvents. In the case of Paal–Knorr reaction, because of the super-paramagnetic nature of the material, within a few seconds after stirring was stopped, the reaction mixture turned clear and catalyst was deposited on the magnetic bar, which was easily removed using an external magnet. We observed that after completion of the reactions, the phase separation of the desired product from the aqueous media occurred (Fig. 4) in most cases, thus facilitating the isolation of crude product by simple decantation rather than tedious extraction processes. Consequently, the use of volatile organic solvents is reduced during product workup. In a few cases, solid product precipitated out; the product could then be isolated by simple filtration.

To evaluate lifetime and level of reusability of the catalyst, we conducted the experiments using the recycled nano-organocatalyst for the Paal–Knorr reaction of benzylamine. After the completion of the first reaction, the product layer was removed by decantation and the catalyst was recovered magnetically, washed with water and methanol, and dried. A new reaction was then conducted with fresh reactants under similar conditions. It was found that the developed catalyst could be used at least five times without any change in activity. Alternatively, the reaction could be carried out

Figure 4. Paal–Knorr reaction of benzylamine using magnetic nano-organocatalyst in water, after completion of the reaction.

by simply removing the product layer and adding fresh benzylamine and tetrahydro-2,5-dimethoxyfuran, and similar results were obtained.

3. Conclusions

Novel concept of nano-organocatalyst was developed, by supporting totally benign and naturally abundant glutathione on magnetic nanoparticles. The catalyst showed excellent activity for microwave-assisted Paal–Knorr, Aza-Michael reactions, and pyrazole synthesis. Importantly, in the case of Paal–Knorr reaction of amines, the entire process was carried out in aqueous medium, without using organic solvent in the reaction or during the workup. This novel nano-organocatalyst bridges the gap between homogeneous and heterogeneous catalysis thus preserving the desirable attributes of both the systems.[63]

4. Experimental

4.1. General

All the solvents and reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Gas chromatography (GC) was used to monitor the reactions. The crude products were identified by GC–MS qualitative analysis using a GC system with a mass selective detector. CEM Discover focused microwave synthesis system was used to carry out all aforementioned organic transformations.

4.2. Anchoring of glutathione on nano-ferrite surfaces

Nano-Fe_3O_4 (0.5 g) was dispersed in water (15 mL) and methanol (5 mL) and sonicated for 15 min. Glutathione (reduced form) (0.4 g) dissolved in water (5 mL) was added to this solution and again sonicated for 2 h. The glutathione-functionalized nanomaterial (nano-organocatalyst) was then isolated by centrifugation, washed with water and methanol, and dried under vacuum at 50–60 °C.

4.3. Paal–Knorr reaction of amines using nano-organocatalyst

The amines (1 mmol), tetrahydro-2,5-dimethoxyfuran (1.1 mmol), and nano-organocatalyst (25 mg) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. Water (2 mL) was added and the reaction mixture was thoroughly mixed. The reaction tube was then placed inside the cavity of a CEM Discover focused MW synthesis system, operated at 140±5 °C (temperature monitored by a built-in infrared sensor), power 50–250 W, and pressure 50–180 psi for 20 min (Table 2). After completion of the reaction, the phase separation of the desired product from the aqueous medium occurred, facilitating the isolation of crude product by simple decantation, which was further purified by simply passing through short silica column. All products are known in the literature and were identified by comparison of their GC–MS spectra with standard Wiley mass spectral library.

4.4. Aza-Michael reaction using nano-organocatalyst

The amines (1 mmol) and alkyl (1.2 mmol) and nano-organocatalyst (25 mg) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. Water (2 mL) was added and the reaction mixture was mixed thoroughly. The reaction tube was then placed inside the cavity of a CEM Discover focused MW synthesis system, operated at 140±5 °C (temperature monitored by a built-in infrared sensor), power 50–250 W, and pressure 50–180 psi for 20 min (Table 3). After completion of the reaction, products were extracted with ethyl acetate and washed with sodium bicarbonate solution. After concentrated in vacuum, the crude product was subjected to flash column chromatography for further purification. All products are known in the literature and were identified by comparison of their GC–MS spectra with standard Wiley mass spectral library.

4.5. Pyrazole synthesis using nano-organocatalyst

1.0 equiv of 1,3-diketone, 1.1 equiv of hydrazines and nano-organocatalyst (25 mg) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. Water (2 mL) was added and the reaction mixture was mixed thoroughly. The reaction tube was then placed inside the cavity of a CEM Discover focused MW synthesis system, operated at 140±5 °C (temperature monitored by a built-in infrared sensor), power 50–250 W, and pressure 50–180 psi for 20 min (Table 3). After completion of the reaction, products were extracted with ethyl acetate and washed with sodium bicarbonate solution. After concentrated in vacuum, the crude product was subjected to flash column chromatography for further purification. All products are known in the literature and were identified by comparison of their GC–MS spectra with standard Wiley mass spectral library.

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