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FULL PAPER

Mild and eco-friendly chemoselective acylation of amines in aqueous medium using a green, superparamagnetic, recoverable nanocatalyst †

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[†]This article is dedicated to memory of Khalil Motaharniya

Copper-grafted guanidine acetic acid-modified magnetite nanoparticles $(Fe_3O_4@GAA-Cu(II))$ as a green, superparamagnetic and recoverable nanocatalyst is found to promote quantitative *N*-acylation of various amines in a very short time with an equimolar amount of thioacetic acid in water at room temperature. This method is found to be highly selective for amines and not sensitive to other functional groups. Mild reaction condition, high selectivity, efficiency, simple workup and excellent yields are some of the major advantages of the procedure.

KEYWORDS

heterogeneous catalyst, magnetic nanoparticles, N-acylation reaction, organocatalyst

1 | INTRODUCTION

Acylation of amines is a basic and important reaction in organic chemistry. Many pharmacological molecules possess at least one amide bond.^[1] N-Acyl derivatives of amines are used for the synthesis of amides and their derivatives, as starting materials for various transformations and for protecting -- NH and -- OH group functionality in multi-step syntheses.^[2] Several methods for acylation have been developed including: (a) direct reaction of an amine and an acid, (b) reaction of a readily available acid derivative (e.g. simple methyl ester) with an amine, (c) formation of an activated carbonyl compound (e.g. acid chloride, anhydride or active ester) followed by condensation with an amine and (d) onepot reaction of a carboxylic acid with an amine in which a coupling reagent activates the acid component in situ.^[3] Among various synthetic protocols,^[4] N-acylation reaction is commonly carried out with acetic anhydride or acetyl chloride in the presence of either acidic or basic catalysts under various conditions.^[5] However, there are a number of problems associated with N-acylation reactions using acyl chlorides and acid anhydrides. For example, anhydrides can form imides as side products when reacted with primary amines,^[6] while reactions of acyl chlorides with amines can be highly exothermic. In addition, many acid chlorides and

anhydrides react rapidly with water and alcohols leading to the corresponding acids and esters, respectively. The selective acylation of amines in the presence of other functional groups is a rather difficult process. Numerous strategies including the direct and metal-mediated condensation of unactivated carboxylic acids and amines,^[7] acylation through N-acyl DBN tetraphenyl borate salts,^[8] mercury- and ruthenium-catalysed Beckman rearrangements.^[9] oxidative amidation,^[10] triazole- and imidazole-mediated acyl transfer reactions^[11] and acylation through acylbenzotriazoles^[12] have been developed to circumvent the inherent problems. These reactions suffer from some drawbacks such as the requirement of more expensive reagents, relatively harsh reaction conditions and long reaction times. Thus, there is still a great need to find various alternative reagents for acylation of amines.

In contrast to carboxylic acids, thioacids have been of considerable interest due to their unique reactivity and selectivity in amide bond formations. Various authors^[13–17] have reported elegant methods for *N*-acylation of amines in peptide synthesis. In 2013, Gopi and co-workers^[18] used copper(II) acetate as a catalyst for acylation of amines. But this methodology suffers from using a large amount of catalyst and cumbersome procedures for separation of the resulting product. Filtration and expensive ultracentrifugation

are available methods to recover heterogeneous catalysts, but these routes can result in loss of catalyst. Magnetic nanoparticle-supported catalysts have been successfully deployed in a variety of important organic reactions due to their high stability and the easy separation of the catalyst from the reaction mixture using an external magnet. Recently, magnetic nanoparticles have served as highly promising supports of organocatalysts.^[19]

Guanidine acetic acid (GAA) is the essential precursor of creatine, and belongs to the class of guanidino compounds that are characterized by the presence of a basic guanidine group. GAA has a carboxylic acid group that facilitates the easy linkage of the compound to a magnetite support and the guanidino group renders it suitable to serve as a complexing agent for most transition metal ions. Herein, we report the rapid and highly selective *N*-acylation of amines using thioacids in water at room temperature mediated by copper-grafted GAA-modified magnetite nanoparticles (Fe₃O₄@GAA-Cu(II)). Studies with amines containing various other functional groups such as thiols, carboxylic acids and alcohols suggest that the reactions are highly selective for amines, and other functional groups are unaffected.

2 | **RESULTS AND DISCUSSION**

Some spectroscopic and microscopic techniques were used for characterization of the catalyst structure. The organic moieties anchored on the surface of Fe₃O₄ were investigated using Fourier transform infrared (FT-IR) spectroscopy. Figure 1 shows FT-IR spectra of GAA, bare Fe₃O₄, Fe₃O₄@GAA and Fe₃O₄@GAA-Cu(II). Typical band ascribed to the Fe–O stretching vibration appears at 561 cm⁻¹ for the bare magnetic nanoparticles. Immobilization of GAA on the surface of the magnetic nanoparticles is proved with the appearance of peaks at 1626 and 1400 cm⁻¹, assigned to the stretching vibration of C=O and C–N respectively. Comparison of the C–N vibration



FIGURE 1 FT-IR spectra of catalyst and its components

in the FT-IR spectrum of $Fe_3O_4@GAA$ at 1400 cm⁻¹ with that of $Fe_3O_4@GAA$ -Cu(II) at 1408 cm⁻¹ confirms formation of the complex.

The morphology of $Fe_3O_4@GAA$ and $Fe_3O_4@GAA$ -Cu(II) was investigated using scanning electron microscopy (SEM). The SEM images confirm that the synthesized $Fe_3O_4@GAA$ and $Fe_3O_4@GAA$ -Cu(II) present uniform nanoparticles. Regarding the incorporation of Cu(II), the image obtained (Figure 2b) does not reveal significant changes in the $Fe_3O_4@GAA$ morphology (Figure 2a).

As illustrated in Figure 3, the magnetic properties of the catalyst were investigated at room temperature using a vibrating sample magnetometer. The magnetic hysteresis loop of $Fe_3O_4@GAA-Cu(II)$ was measured in an applied magnetic field of 15 000 Oe at 298 K. The hysteresis loop of the $Fe_3O_4@GAA-Cu$ (II) nanoparticles shows a superparamagnetic behaviour with its redispersion stability in solution, without aggregation.



 $\label{eq:FIGURE 2} FIGURE \ 2 \quad SEM \ images \ of \ (a) \ Fe_3O_4@GAA \ nanoparticles \ and \ (b) \ Fe_3O_4@GAA-Cu(II) \ nanoparticles$



FIGURE 3 Magnetization curve of Fe₃O₄@GAA-Cu(II) nanoparticles

X-ray diffraction (XRD) was applied to determine the crystal structure of the superparamagnetic nanoparticles. The obtained lattice parameters of $Fe_3O_4@GAA$ and $Fe_3O_4@GAA$ -Cu(II) coincide with the standard parameters of magnetite. Comparison of the patterns of $Fe_3O_4@GAA$ and $Fe_3O_4@GAA$ -Cu(II) indicates retention of the crystalline cubic spinel structure during functionalization of the magnetic nanoparticles (Figure 4).

The amount of GAA supported on the surface of Fe₃O₄ was determined using thermogravimetric analysis (TGA) of Fe₃O₄@GAA-Cu(II). As depicted in Figure 5, the TGA curve of Fe₃O₄@GAA-Cu(II) shows a weight loss of 2% below 200 °C, which is due to the loss of adsorbed water in the sample. The mass loss of about 3.3% by weight in the range 200–400 °C is attributed to the thermal decomposition of GAA, which is estimated to be about 0.28 mmol of GAA per gram of catalyst. The TGA curve indicates the successful supporting of the GAA complex onto the magnetic surface. The copper content of the catalyst was determined as 0.55 mmol g⁻¹ using inductively coupled plasma (ICP) analysis.



FIGURE 4 XRD pattern of catalyst



FIGURE 5 TGA curves of catalyst

The hydrodynamic diameter of the nanoparticles was measured using dynamic light scattering (DLS), with the nanoparticles being sonicated in water before the measurement (Figure 6). DLS characterization shows that the average sizes of nanoparticles are about 65.8 and 114 nm before and after the reaction, respectively.

Acylation of amines was chosen to evaluate the catalytic behaviour of the $Fe_3O_4@GAA-Cu(II)$ nanoparticles. Initially, acylation of aniline (1.0 mmol) with thioacetic acid (1.0 mmol) was studied as a model reaction in the presence of 40 mg of $Fe_3O_4@GAA-Cu(II)$ nanoparticles at room temperature in water (Scheme 1).

When the reaction is carried out using these conditions, the desired product is obtained in 95% isolated yield. Based on these findings, we further investigated other reaction parameters, such as acylation agent, solvent and amount of catalyst in order to achieve a better chemoselectivity and a higher chemical yield. It should be noted that the use of common organic solvents, such as ethanol, methanol and CH_2Cl_2 , results in low to moderate yields. In the absence of any catalyst, no reaction is observed even after prolonged reaction time. The acylation of amines proceeds smoothly in the presence of unsupported Fe_3O_4 (Table 1, entry 8). It is found that 40 mg of Fe₃O₄@GAA is enough to progress the reaction. When acetic acid is used as acylation agent, no product is observed. Under these optimized conditions, the acylation of various amines was examined using Fe₃O₄@GAA-Cu(II) nanoparticles in water at room temperature. The obtained results are summarized in Table 1.

The selective acylation of amines in the presence of other functional groups is a rather difficult process. In order to understand the selectivity and the reactivity of the protocol under investigation, we subjected 2-aminothiophenol (Table 2, entry 5) and *p*-aminophenol (Table 2, entry 6) to N-acetylation (Scheme 2). The reaction proceeds with the same rate as that of aniline. When 2-aminothiophenol and *p*-aminophenol are treated with one equivalent of thioacetic



FIGURE 6 DLS analysis of nanoparticles (a) before and (b) after reaction

acid under identical conditions, corresponding acetamides are obtained in high yield and no O,S-acylation and S–S disulfide dimer product are observed in the reaction mixture. Similar result is obtained with *m*-aminobenzoic acid (Table 2, entry 7), where exclusive *N*-acetylation is achieved with excellent yield. We also examined the tolerance of this reaction to phenylhydrazine in the presence of the catalyst (Table 2, entry 10). It is observed that only primary amino group will undergo *N*-acylation under this condition. This method was applied for the formation of amide bond in amino acids (Table 2, entry 14). Tryptophan is successfully *N*-acetylated with excellent yield in a short time.

Further, to understand the role of electron-withdrawing groups in the reaction, we subjected *p*-nitroaniline (Table 2, entry 3) and *p*-iodoaniline (Table 2, entry 4) to *N*-acetylation. Except for *p*-nitroaniline, all other *N*-acetylated products are isolated in excellent yields.

In order to establish the reusability of the catalyst for *N*-acylation, the model reaction was repeated under standard conditions. For this, after completion of the reaction, the catalyst was recovered by magnetic decantation, washed with deionized water, dried and used for the next cycle. The catalytic activity does not decrease considerably after six catalytic cycles (Figure 7).



SCHEME 1 *N*-acylation of amine using thioacetic acid

No leaching of copper ion from the catalyst surface was determined according to ICP analysis. Any possible change in catalyst structure was studied using FT-IR spectroscopy and XRD (Figure 8). The FT-IR spectrum shows no significant changes compared to that of the fresh catalyst. The XRD pattern shows the characteristics peaks of magnetite and additional peaks of sulfur precipitated on the surface of the catalyst in the course of the reaction.

TABLE 1 Optimization of reaction conditions^a

	$ \begin{array}{c} $		
Entry	Catalyst (mg)	Solvent	Yield (%) ^b
1	40	CH_2Cl_2	40
2	40	CH ₃ OH	85
3	40	EtOH	75
4	40	H ₂ O	95
5	35	H_2O	90
6	30	H ₂ O	88
7	25	H_2O	85
8	40 ^c	H_2O	25
9	_	H_2O	—

^aReaction conditions: thioacetic acid (1.0 mmol), amine (1.0 mmol) in solvent (1.0 ml).

^bIsolated yield.

^c40 mg of Fe₃O₄ nanoparticles

TABLE 2Ace	ylation (of amines	with	thioacetic	acid
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^aReaction conditions: thioacetic acid (1.0 mmol), amine (1.0 mmol) in solvent (1.0 ml).

^bIsolated yield.

The proposed mechanism is presented in Scheme 3. Copper chelated to the guanidine moiety supported on the magnetite nanoparticles interacts with thioacetic acid and



SCHEME 2 Selective acylation of amines in the presence of other functional groups



FIGURE 7 Recyclability of catalyst

consequently weakens the C–S bond. Following substitution of amine to copper atom, hydrogen sulfide gas is released and the acylated amine is liberated in the final step.

3 | EXPERIMENTAL

All chemicals and solvents were purchased from commercial suppliers and used without further purification. FT-IR spectra were obtained over the region 400–4000 cm^{-1} with a Nicolet IR100 FT-IR with spectroscopic grade KBr. XRD patterns were obtained at room temperature with a Philips X-pert 1710 diffractometer with Co K_{α} ($\lambda = 1.78897$ Å), 40 kV voltage, 40 mA current and in the range 10-90° (2θ) with a scan speed of 0.020° s⁻¹. SEM (Philips XL 30) and S-4160) was used to study the catalyst morphology and size. Magnetic saturation of the catalyst was investigated using a vibrating magnetometer/alternating gradient force magnetometer (VSM/AGFM, MDK Co., Iran). TGA was conducted using a thermal analyser with a heating rate of 20 °C min⁻¹ over a temperature range of 25–1100 °C under flowing nitrogen. The hydrodynamic diameter of the nanoparticles was measured using a Zetasizer Nano-MAL1001767 (Malvern Instruments, Malvern, UK) by DLS with the nanoparticles sonicated in water before the measurement. ¹H NMR spectra were recorded with a Bruker Avance (DRX 500 MHz, DRX 250 MHz) in pure deuterated dimethylsulfoxide solvent with tetramethylsilane as internal standard.

3.1 | Preparation of GAA supported on Fe₃O₄

3.1.1 | Preparation of Fe₃O₄@GAA nanoparticles

Amounts of 5.0 mmol of $FeCl_3 \cdot 6H_2O$ and 2.5 mmol of $FeCl_2 \cdot 4H_2O$ salts were dissolved in 100 ml of deionized



FIGURE 8 FT-IR spectrum and XRD pattern of catalyst (after sixth run)

water under vigorous stirring. Then 2.0 mmol of GAA and NH₄OH solution (25% w/w, 30 ml) were added to the mixture until the pH was raised to 11 at which a black suspension was formed. This suspension was then refluxed at 100 °C for 6 h, with vigorous stirring. Fe₃O₄@GAA nanoparticles were separated from the aqueous solution by magnetic decantation, and washed with deionized water several times before being dried in an oven overnight.

3.1.2 | Preparation of Fe₃O₄@GAA-Cu(II) nanoparticles

An amount of 2.0 mmol of Cu(OAc)₂·2H₂O in 50 ml of water was added to Fe₃O₄@GAA nanoparticles and stirred at room temperature for 2 h. The suspension was refluxed for 2 h. Finally, the nanoparticles were separated from the aqueous solution by magnetic decantation, and washed with water, ethanol and diethyl ether several times before being dried in an oven overnight.



SCHEME 3 Proposed mechanism of N-acylation of amine using thioacetic acid

3.2 | General procedure for acylation of amines

To a mixture of catalyst (40 mg) and amine (1.0 mmol) in water (1.0 ml) was added thioacetic acid (1.0 mmol). The mixture was stirred at room temperature for 5 min. Completion of the reaction was confirmed by TLC. After completion of the reaction, the nanoparticles were collected with a permanent magnet from the reaction mixture and washed with distilled water and methanol repeatedly. Water (50 ml) was added to the reaction mixture and extracted with EtOAc $(2 \times 20 \text{ ml})$ and dried over Na₂SO₄. The solvent was removed under reduced pressure to give the crude product. The residue was recrystallized from ethanol to afford the pure product.

CONCLUSIONS 4

Fe₃O₄@GAA-Cu(II) Robust and effective as а green, superparamagnetic and recoverable nanocatalyst for N-acylation of a variety of amines was synthesized and studied. When thioacetic acid is used as the acylation agent in water, N-acylation can be carried out to afford corresponding products in excellent yields and short time. This method is found to be highly selective for amines and not sensitive to other functional groups such as thiol, phenol and amino acids. Mild reaction conditions, high selectivity, efficiency, simple workup and excellent yields are some of the major advantages of the procedure.

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SUPPORTING INFORMATION

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