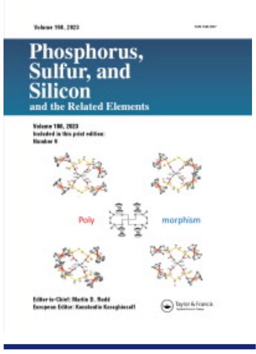

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Facile chemoselective dithioacetalization of carbonyl compounds promoted by Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs as an efficient magnetic nanostructured catalyst

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ABSTRACT

Dithioacetalization, as a well-known class of organic transformation, was carried out for protection of a wide variety of aromatic (with electron releasing and electron withdrawing substituents), heteroaromatic and aliphatic aldehydes as well as ketones by 1,2-ethanedithiol/or 1,3-propanedithiol in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs. The corresponding 1,3-dithiolanes and 1,3-dithianes were obtained chemoselectively in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs with hexagonal core-shell structure, superparamagnetic behavior, and average particle size of 8–25 nm under mild reaction conditions. The nanostructured catalyst could be separated easily from the reaction mixture using a magnetic bar and reused in several reaction runs without any remarkable reduction in its catalytic activity. Nearly neutral conditions, good to high yields of the products, operational simplicity, easy work-up procedure, compatibility with various functional groups make the present method valuable in addition to the known methodologies.

Abbreviations: Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II} NPs: Cu^{II} immobilized on aminated 3-glycidyloxypropyl trimethoxysilane anchored on magnetic mesoporous MCM-41 nanoparticle; TEOS: Tetraethyl orthosilicate; CTAB: Cetyltrimethylammonium bromide; GPTMS: 3-glycidyloxypropyltrimethoxysilane; Gu.HCl: Guanidine hydrochloride; $Cu(OAc)_2.H_2O$: Copper(II) acetate monohydrate; THF: Tetrahydrofuran; TLC: Thin-layer chromatography; NMR: Nuclear magnetic resonance; FT-IR: Fourier-transform infrared spectroscopy; XRD: X-ray powder diffraction; FE-SEM: Field emission scanning electron microscopy; ICP-OES: Inductively coupled plasma-optical emission spectrometry; TEM: Transmission electron microscopy; EDX: Energy dispersive x-ray; Vsm: Vibrating-sample magnetometer; BET: Brunauer–Emmett–Teller; TGA: Thermogravimetric analysis

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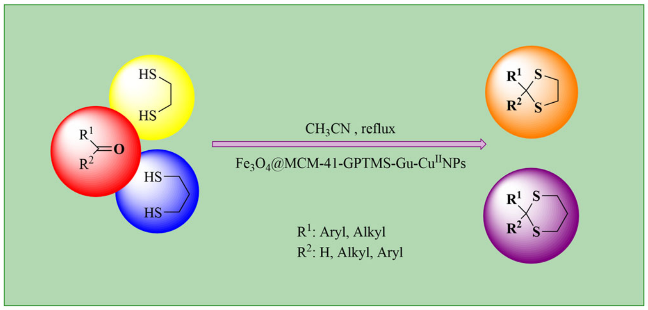
KEYWORDS
Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs; carbonyl compounds; dithiolanes; dithianes; dithioacetalization; nanostructured catalyst

GRAPHICAL ABSTRACT



1. Introduction

Due to the reactivity of carbonyl group toward a wide range of reagents with or without any activation, the chemistry of carbonyl group is very fascinating. In this regard, protecting carbonyl functionality is well known as one of the major challenging problems in the field of multistep total synthesis of multifunctional natural and non-natural products.[1–6] Protection of a carbonyl group in the form of 1,3-dithiolanes and 1,3-dithianes is useful as they are inherently stable in both acidic and basic conditions and to a wide variety of reagents as well.[7–14] Moreover, in organic synthesis *S*,*S*-acetals could be used as precursors of acyl anions[15,16] for the construction of carbon-carbon bonds and could be directly reduced to their parent hydrocarbons by reductive desulfurisation.[17] During the past decades, *S*,*S*-acetals were routinely prepared by the condensation reaction between aldehydes or ketones with 1,2-ethanedithiol or 1,3-propanedithiol using strong Brønsted acids,[18–27] Lewis acids,[28–41]

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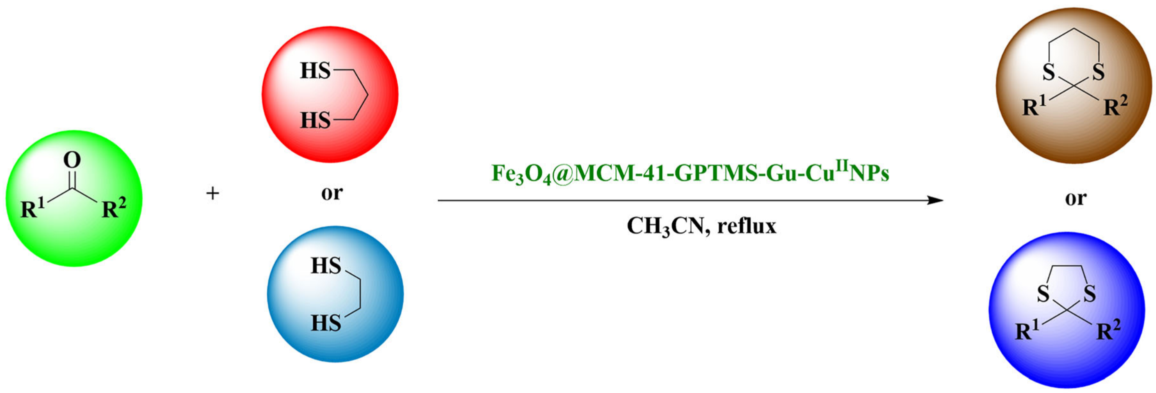


R^1= Phenyl, 4-Nitro C_6H_4, 4-F C_6H_4, 4-Chloro C_6H_4, 3-Bromo C_6H_4, 4-Methoxy C_6H_4,
Phenyl-CH=CH, 1-Naphtyl,C_4H_3O, C_4H_3S, CH_3, C_2H_5, C_3H_7, C_6H_{13}, R^2= H
R^1= C_2H_5, R^2= CH_3
R^1= C_5H_{11}, R^2= CH_3
R^1= R^2= $(CH_2)_4$
R^1= R^2= $(CH_2)_5$
R^1= Phenyl, R^2= CH_3
R^1= 4-Nitro C_6H_4, R^2= CH_3
R^1= R^2= Phenyl

Scheme 1. Protection of various types of carbonyl compounds with 1,2-ethanedithiol/or 1,3-propanedithiol in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs.

ionic liquids,[42–48] high energy microwave,[43,49,50] visible or UV light irradiation[51–53] and solid supports[54–62] to activate the carbonyl group. Although there are many methods in the literature for the protection of carbonyl compounds as 1,3-dithiolanes and 1,3-dithianes, it is still desirable to find more appropriate, mild, efficient, and chemoselective practical methods by emphasizing the Lewis acidity of the easily separable and recyclable catalysts. To follow the green chemistry principles, the focus of chemists has shifted toward the development of functionalized nano magnetic catalysts as useful catalysts in organic synthesis.[63–66]

Along the line of this idea and as a part of our continuing interest in the development of new synthetic methodologies,[67–69] very recently, we reported the preparation of Cu^{II} immobilized on functionalized magnetic mesoporous MCM-41(Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs). (Scheme S1, supplementary material) For this purpose, the prepared Fe_3O_4 NPs(**I**) *via* the co-precipitation method was coated with MCM-41 through the reaction with TEOS and CTAB to achieve the magnetic nanoparticles entrapped in mesoporous MCM-41(Fe_3O_4@MCM-41 (**II**)) after calcination at 550 °C for 6 h. Then Fe_3O_4@MCM-41 (**II**) was in turn treated with 3-glycidyloxypropyltrimethoxysilane (GPTMS) and guanidine hydrochloride to produce 3-glycidyloxypropyl trimethoxysilane anchored on magnetic nanoparticles entrapped in mesoporous MCM-41 (Fe_3O_4@MCM-41-GPTMS (**III**) and aminated 3-glycidyloxypropyl trimethoxysilane anchored on magnetic nanoparticles entrapped in mesoporous MCM-41(Fe_3O_4@MCM-41-GPTMS-Gu(**IV**)) respectively. After that, upon treatment of Fe_3O_4@MCM-41-GPTMS-Gu (**IV**) with an ethanolic solution of $Cu(OAc)_2.H_2O$, Cu^{II} immobilized on functionalized mesoporous MCM-41 (Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs (**V**)) (with 0.86 mmol.g^{-1} copper content according to the inductively coupled plasma optical emission spectroscopy (ICP-OES) measurement) was obtained. Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs (**V**) was fully characterized and evaluated toward the synthesis of structurally different 5-phenyl-5,10-dihydropyrido[2,3-d:6,5-d′] dipyrimidine-2,4,6,8 (1*H*,3*H*,7*H*,9*H*) tetraone derivatives through one-pot multicomponent condensation under green conditions.[70] (See supplementary material, characterization of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs″section)

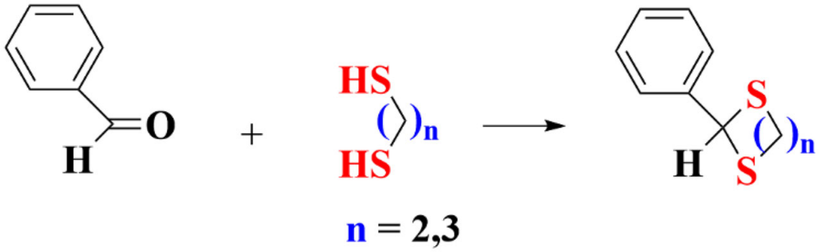
As an extension of our studies in protecting carbonyl functionality,[71,72] herein, we wish to disclose that Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs is also an efficient catalyst for the facile chemoselective dithioacetalization of various types of carbonyl compounds with 1,2-ethanedithiol/or 1,3-propanedithiol (Scheme 1).

2. Results and discussion

2.1. Protection of carbonyl compounds with1,2-ethanedithiol/or 1,3-propanedithiol promoted by Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs

As an initial attempt, the performance of the Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II} was investigated for the reaction of commercially available benzaldehyde (as a sample reaction) with 1,2-ethanedithiol/or 1,3-propanedithiol. Various conditions including the catalyst loading amount, temperature and solvent were tested to find the optimal reaction conditions (Table 1). According to the literature search, in the first reaction, protection of benzaldehyde was performed in refluxing CH_3CN. As we expected, by applying 1:2 molar ratio of benzaldehyde:1,2-ethanedithiol/or 1,3-propanedithiol, blank runs (in the absence of catalyst) provided no

Table 1. Optimization of various reaction parameters for protection of benzaldehyde with 1,2-ethanedithiol/or 1,3-propanedithiol.



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Molar ratio of benzaldehyde: dithiol	Time(h) 1,2-ethane dithiol/1,3-propane dithiol	Conversion (%)
1	–	CH_3CN	Reflux	1:2	24/24	0/0
2	1	CH_3CN	Reflux	1:2	6.5/6	100/100
3	2	CH_3CN	Reflux	1:2	2.5/2.15	100/100
4	3	CH_3CN	Reflux	1:2	2/1.5	100/100
5	**4**	**CH_3CN**	**Reflux**	**1:2**	**1.5/1**	**100/100**
6	4	CH_3CN	Reflux	1:1.5	1.45/1.5	100/100
7	4	CH_3CN	Reflux	1:1	2.45/2.15	100/100
8	4	CH_3CN	65	1:2	2/1.5	85/90
9	4	THF	Reflux	1:2	3/2	85/90
10	4	$CHCl_3$	Reflux	1:2	4/3	85/80
11	4	CH_2Cl_2	Reflux	1:2	3/2	100/100
12	4	*n*-Hexane	Reflux	1:2	4/3	85/80
13	4	1,4-dioxane	Reflux	1:2	2.5/2	75/80
14	4	–	78	1:2	10/10	0/0
15[a]	0.04(g)	CH_3CN	Reflux	1:2	15/14	50/50
16[b]	0.04(g)	CH_3CN	Reflux	1:2	6/5	50/50
17[c]	0.04(g)	CH_3CN	Reflux	1:2	6/5	50/50
18[d]	0.04(g)	CH_3CN	Reflux	1:2	6/5	50/50
19[e]	4	CH_3CN	Reflux	1:2	7.5/6.5	40/40

Reaction conditions: benzaldehyde (1 mmol), 1,2-ethanedithiol (2 mmol), 1,3-propanedithiol (2 mmol) and solvent(4 mL).

[a] The reaction was performed in the presence of Fe_3O_4NPs.

[b] The reaction was performed in the presence of Fe_3O_4@MCM-41.

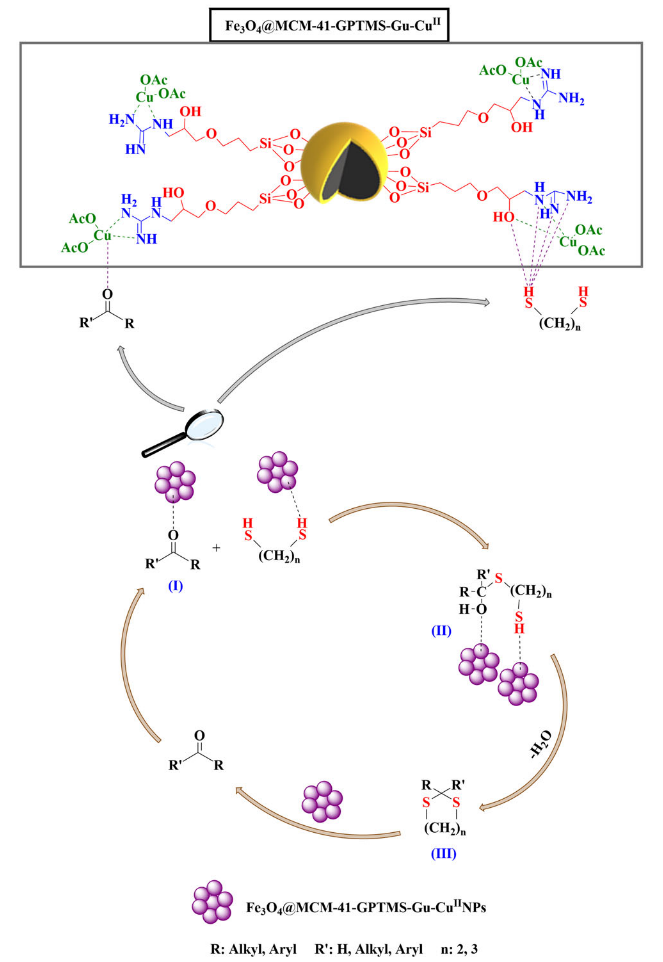
[c] The reaction was performed in the presence of Fe_3O_4@MCM-41-GPTMS.

[d] The reaction was performed in the presence of Fe_3O_4@MCM-41-GPTMS-Gu.

[e] The reaction was performed in the presence of $Cu(OAc)_2.H_2O$.

product (2-phenyl 1,3-dithiolane/or 2-phenyl 1,3-dithiane) after 24/or 24 h (Table 1, entry 1). Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs showed high efficiency for protection reaction of benzaldehyde with 1,2-ethanedithiol/or 1,3-propanedithiol in refluxing CH_3CN (Table 1, entry 2). To find out the optimum quantity of the catalyst, the protection reaction of benzaldehyde was carried out using different catalyst loading in refluxing CH_3CN. As shown in Table 1, the best yield of 2-phenyl 1,3-dithiolane/or 2-phenyl 1,3-dithiane was achieved using 4 mol% of Fe_3O_4@ MCM-41-GPTMS-Gu-Cu^{II} (Table 1, entries 2–5). To increase the efficacy of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs, other reaction parameters were tuned and optimized. The ratio of benzaldehyde:1,2-ethanedithiol/or 1,3-propanedithiol and temperature were also investigated, and it was found that the best conversion in short reaction time was achieved in refluxing CH_3CN by applying 1:2 molar ratio of reactants (Table 1, entries 6–8). To choose the appropriate medium for the transformation, we carried out the above model reaction in different solvents and solvent-free condition as well (Table 1, entries 9–14). The other solvents examined were tetrahydrofuran, chloroform, dichloromethane, *n*-hexane and 1,4-dioxane. It should be pointed out that in solvent-free condition the reaction did not proceed even after prolonged reaction times. These results implied that acetonitrile was the solvent of choice in terms of time and product yield.

To show the role of the Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs, further control experiments were conducted in the presence of Fe_3O_4NPs, Fe_3O_4@MCM-41, Fe_3O_4@MCM-41-GPTMS and Fe_3O_4@MCM-41-GPTMS-Gu (Table 1, entries 14–18). Surprisingly, in all cases the protection reaction of benzaldehyde with 1,2-ethanedithiol/or 1,3-propanedithiol under the optimized reaction conditions proceeded slowly and furnished the target product in lower yield. Fe_3O_4 nanoparticles slightly promoted the reaction while this transformation proceeded more efficiently in the presence of Fe_3O_4@MCM-41 due to the presence of a large number of hydroxy and silanol groups on the high surface area of MCM-41 comparing to the magnetite nanoparticles (Table 1, entry 15 vs. entry 16). Moreover, surface modification of Fe_3O_4@MCM-41 can be done easily because of the existence of a great number of silanol groups which increased the absorption capacity.[73] After, functionalization processes, high density of functional groups on the surface of Fe_3O_4@MCM-41 increases the active sites of the entire catalyst as the main factor in promoting the reaction (as displayed in the suggested mechanism illustrated in Scheme 2) resulting in boosted yields of the target product and increased the reaction rate. Furthermore, to better understand the catalytic activity of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs the reaction was carried out in the presence of $Cu(OAc)_2.H_2O$ (4/or 4 mol%). The desired product was



Scheme 2. The suggested mechanism for the protection reaction of aldehydes and ketones with1,2-ethanedithiol/or 1,3-propanedithiol in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs.

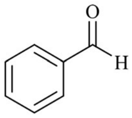
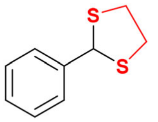
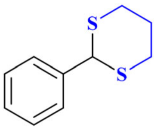
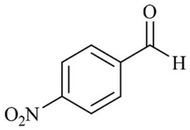
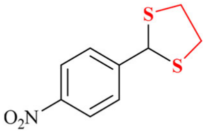
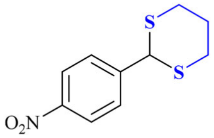
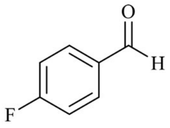
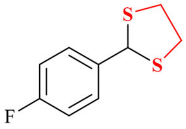
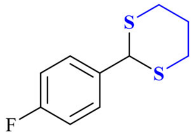
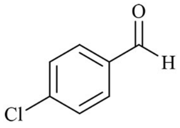
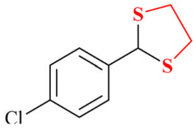
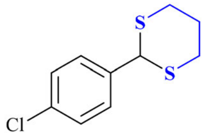
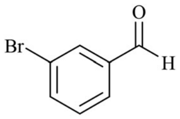
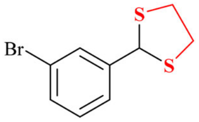
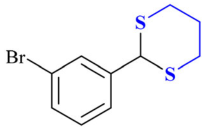
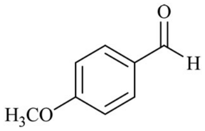
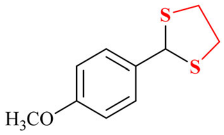
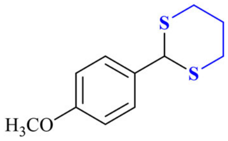
obtained with 40/or 40% yield after 7.5/or 6.5 h (Table 1, entry 19). This result leads to the conclusion that the immobilization of Cu^{II} on aminated 3-glycidyloxypropyl trimethoxysilane anchored on magnetic mesoporous MCM-41 nanoparticle improved the catalytic activity of Cu^{II} in dithioacetalization reaction of carbonyl compounds.

Encouraged by this promising result, we then explored the scope and limitations of this new procedure. The results of these studies are tabulated in Table 2. Aromatic aldehydes, with electron donating or electron withdrawing substituents could be protected to afford the corresponding 1,3-dithiolanes and 1,3-dithianes with high conversions under the optimized reaction conditions (Table 2, entries 1–6). The generality and versatility of this protocol has been proved with aldehydes bearing double bond like cinnamaldehyde. It was converted to the corresponding protected product without any reaction on the double bond (Table 2, entry 7). Interestingly, dithioacetalization of naphthaldehyde was also achieved efficiently with a catalytic amount of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs to afford the corresponding 1,3-dithiolanes/or 1,3-dithianes in high yield (Table 2, entry 8). Further, the usefulness of this methodology has also been extended for the protection of heteroaromatic aldehydes (Table 2, entries 9–10). As can be seen from Table 2, this method is also applicable for protecting of heteroaromatic aldehydes. Dithioacetalization of linear chain aldehydes were also examined in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs (Table 2, entries 11–14). Comparatively, high yield of the corresponding 1,3-dithiolanes and 1,3-dithianes were obtained in longer reaction time than aromatic ones. In spite of lower reactivity of carbonyl group of ketones, it is worthy to note that ketones can be protected by1,2-ethanedithiol/or 1,3-propanedithiol in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs under the optimized conditions (Table 2, entries 15–20). As shown in Table 2, although the reactivity of acetophenone seems to be slightly lower than that of cyclopentanone and cyclohexanone, protection of acetophenone was proceeded successfully by this method to afford the corresponding products in satisfactory yield. This method is not applicable for protecting of relatively unreactive and sterichindered ketone such as benzophenone (Table 2, entry 21).

The reaction progress was periodically monitored by the disappearance of the carbonyl compounds and further formation of the desired protected products on TLC. The obtained products were known and isolated as oil or solid after purification by column chromatography using *n*-hexane as eluent. All purified solid products were characterized by comparison of their melting points with those reported previously or with authentic samples prepared by the conventional methods. Moreover, the structure of certain selected products was successfully validated by surveying their high-field ^{1}H NMR, ^{13}C NMR, and FT-IR spectral data. FT-IR spectra of the obtained products did not contain stretching frequency of carbonyl group. Furthermore, FT-IR spectra exhibited a characteristic absorption band at 776–526 cm^{-1} due to the C-S bond of 1,3-dithiolane/or 1,3-dithiane ring. Additionally, the ^{1}H and ^{13}CNMR spectra are in good accord with the structure. The singlet resonating around 6.41–5.11 ppm established the protection of aldehydes. The signals related to the protons of the1,3-dithiolane/or 1,3-dithiane ring appear at around 3.89–1.56 ppm (as multiplets) (supplementary material).

Consistent with the literature survey[27,58] and our results, we would like to propose a plausible mechanism for the protection of aldehydes and ketones with 1,2-ethanedithiol/or 1,3-propanedithiol in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs (Scheme 2). The catalytic activity of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs in dithioacetalization of carbonyl compounds was established by performing the reaction in the absence of nanocatalyst. It could be seen that no product was obtained even after a long reaction time (Table 1, entry 1). Interestingly, lower yield of product was obtained upon performing the standard reaction in the presence of Fe_3O_4NPs, Fe_3O_4@MCM-41, Fe_3O_4@MCM-41-GPTMS and Fe_3O_4@MCM-41-GPTMS-Gu (Table 1, entries 15–18). It is speculated that the attached (=NH, -NH_2, -NH- and -OH) groups on the surface of Fe_3O_4@MCM-41 not only increase the nucleophilicity of 1,2-ethanedithiol/or 1,3-propanedithiol through hydrogen bonding but also activate the carbonyl group toward the nucleophilic attack. Accordingly from the result of Table 1, entry 4, it can be

Table 2. Protection reaction of various aldehydes and ketones with 1,2-ethanedithiol/or1,3-propanedithiol in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs.

Entry	Substrate	Product	Time (h)	Conversion %	Isolated yield %
1			1.5	100	95
			1	100	92
2			1	100	96
			0.5	100	97
3			3.15	95	87
			2.45	90	85
4			3.5	95	89
			3	90	85
5			4	95	90
			3.45	98	92
6			7	90	83
			6.5	92	85

(*continued*)

Table 2. Continued.

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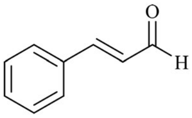
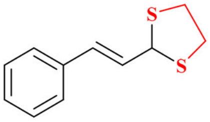
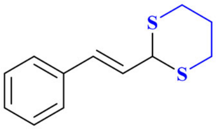
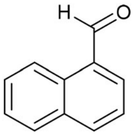
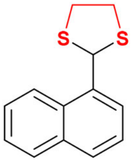
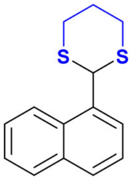
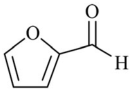
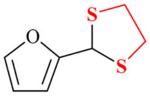
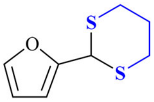
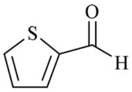
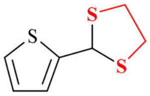
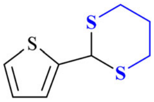
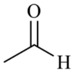
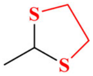
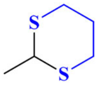
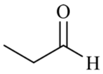
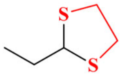
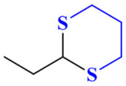
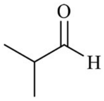
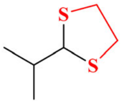
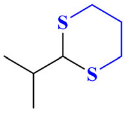
7			2.5	98	92
			1.45	95	89
8			28	75	70
			30	80	73
9			23	85	80
			20	80	74
10			23	85	80
			20	90	84
11			4	94	90
			3.5	96	90
12			4.15	95	90
			3.45	90	85
13			3.5	90	84
			4.5	85	80

(*continued*)

Table 2. Continued.

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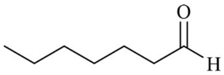
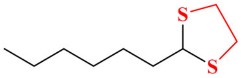
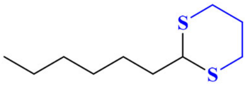
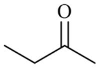
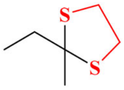
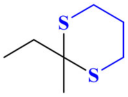
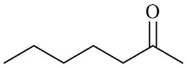
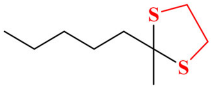
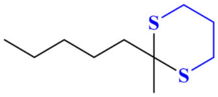
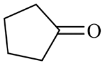
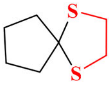
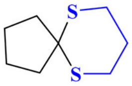
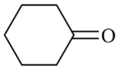
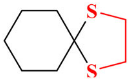
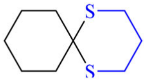
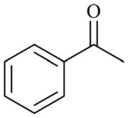
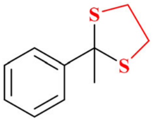
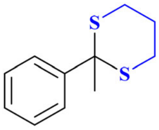
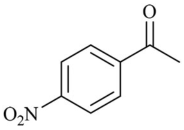
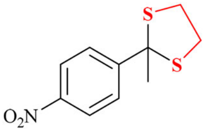
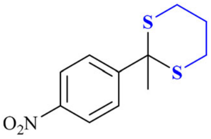
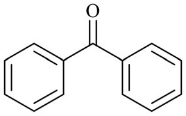
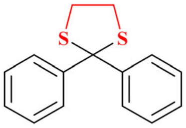
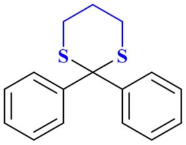
14			5	80	74
			4.5	80	73
15			14	90	85
			12	95	90
16			16	85	79
			15	90	84
17			26	80	73
			25	85	80
18			23	85	81
			22	90	86
19			33	70	65
			30	75	70
20			28	80	76
			25	85	79

(*continued*)

Table 2. Continued.

Entry	Substrate	Product	Time (h)	Conversion %	Isolated yield %
21			72	–	–
			72	–	–

concluded that Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs has a significant effect on all steps of protection reaction.

It is supposed that the acidic active sites (Cu^{II}) increase the electrophilicity of carbonyl group making it susceptible to attack by 1,2-ethanedithiol/or 1,3-propanedithiol to produce the formal hemithioacetal-type intermediate (**II**). In the following, losing an H_2O molecule (intramolecular cyclization) afforded the corresponding dithioacetal derivative (**III**) and regenerated Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs for the consecutive runs as well.

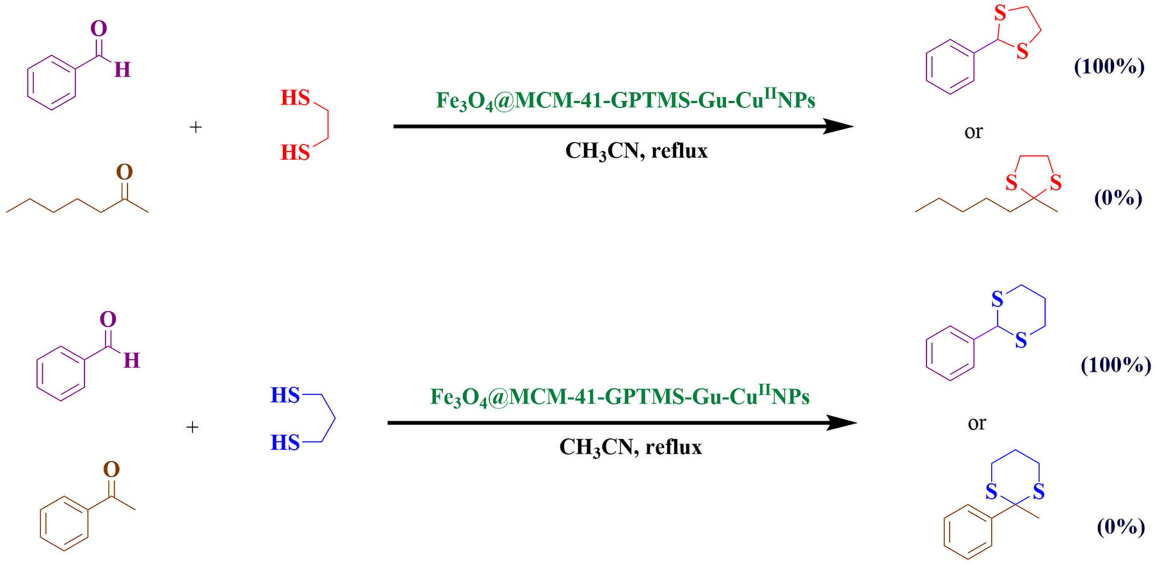
Due to the difference in reactivity of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs toward aldehydes and ketones, in the next stage of the present study, an equimolar mixture of benzaldehyde (1.0 mmol) and 2-heptanone/or acetophenone (1.0 mmol) was allowed to react with 1,2-ethanedithiol/or 1,3-propanedithiol (2 mmol) in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II} under the optimized reaction conditions (Scheme 3). By employing this catalytic system, after 3.5/or 2, h high selective conversion of benzaldehyde to 2-phenyl-1,3-dithiolane/or 2-phenyl-1,3-dithiane was observed, whereas the ketone is almost unreacted in the reaction mixture as evident from Scheme 3.

In the next part of the present study, the recovery and reusability of the nanostructured catalyst were also investigated. For this purpose, in a typical experiment (the protection reaction of benzaldehyde with 1,2-ethanedithiol/or 1,3-propanedithiol under the optimized reaction conditions) after completion of reaction, the catalyst was separated using an external magnetic field, washed successively with ethanol (4 × 5 mL) to remove the residual of organic compounds and then dried at ambient temperature for 16 h. Thereafter, the catalyst was subjected to another run under essentially the same reaction conditions. It is worth mentioning that the magnetic nanostructured catalyst could be recovered and reused for at least four consecutive reaction runs with reasonable yield in comparison to the fresh nanostructured catalyst. The practical recyclability of this magnetic nanostructured catalyst was clearly demonstrated by the average chemical yields for 4 runs to be 82/or 84.75% (Tables 3 and 4). The turn over frequency (TOF) and turn over number (TON) of the catalyst were also calculated and the results are shown in Tables 3 and 4.

The stability of the 4th reused Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs was confirmed by the FT-IR, XRD, FE-SEM and ICP-OES techniques (Figures S1(f, g), S2d, and S4(e, f), supplementary material). The resemblance between the FT-IR spectrum of the fresh and the 4th reused nanostructured catalyst from the reaction of benzaldehyde with 1,2-ethanedithiol/or 1,3-propanedithiol (Figure S1 (compare 1e with 1f and 1g), See supplementary material) is obvious interestingly. Moreover, the obtained results from XRD analysis showed no significant difference between the chemical structure of the fresh nanostructured catalyst and the reused Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs from the reaction of benzaldehyde with 1,3-propanedithiol even after four runs (Figure S2 (compare 2c with 2d), supplementary material). Likewise, FE-SEM images of the 4th reused nanostructured catalyst from the reaction of benzaldehyde with 1,3-propanedithiol are as the same as the freshly prepared nanostructured catalyst (Figure S4 (compare 4(e, f) with 4(c, d), See supplementary material). The obtained images recognized the stable morphology of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs with an approximately spherical shape and no agglomeration even after being used four times. Based on ICP-OES analysis, the fresh nanostructured catalyst contains 0.86 mmol of Cu per 1 g of catalyst, whereas this amount decreased to 0.65/or 0.70 mmol of Cu per 1 g of the 4th reused nanostructured catalyst from the reaction of benzaldehyde with 1,2-ethanedithiol/or 1,3-propanedithiol. The results demonstrated the 25/or 19% of Cu^{II} leaching from the structure of the catalyst after four runs. Consequently, the obtained results clearly authenticated good stability and reusability of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs with no significant loss in catalytic reactivity during the recycling process.

Then, the homogeneity or heterogeneity nature of Fe_3O_4@ MCM-41-GPTMS-Gu-Cu^{II} in the protection reaction of aldehydes and ketones with1,2-ethanedithiol/or 1,3-propanedithiol was investigated. For this purpose, in a set of experiments hot filtration test, kinetics study, and poisoning test were done.

The hot filtration test was performed for the protection reaction of benzaldehyde with 1,2-ethanedithiol/or1,3-propanedithiol under the optimized reaction conditions. In half time of the model reaction (45/or 30 min), the nanostructured catalyst was separated from the reaction medium by an external magnetic field. Then the reaction was continued for another 45/or 30 min, under similar conditions, while the progress of the reaction was monitored by thin-layer chromatography. According to the obtained results, in the



Scheme 3. Chemoselective conversion of aldehydes to corresponding1,3-dithiolanes and 1,3-dithianes in the presence of ketones using Fe$_3$O$_4$@MCM-41-GPTMS-Gu-Cu^{II}NPs as catalyst.

Table 3. The protection reaction of benzaldehyde with 1,2-ethanedithiol in the presence of the reused Fe$_3$O$_4$@MCM-41-GPTMS-Gu-Cu^{II}NPs.

Run	Time (h)	Conversion %	Isolated Yield %	TOF (h^{-1})	TON
1	1.5	100	95	0.16	0.24
2	1.5	100	95	0.16	0.24
3	1.5/2	80/100[a]	75/95	0.13/0.12	0.19/0.24
4	1.5/3	65/100[a]	63/95	0.11/0.08	0.16/0.24

[a]The first number in the third column corresponds to conversion after 1.5 h.

Table 4. The protection reaction of benzaldehyde with 1,3-propanedithiol in the presence of the reused Fe$_3$O$_4$@MCM-41-GPTMS-Gu-Cu^{II}NPs.

Run	Time (h)	Conversion %	Isolated yield %	TOF (h^{-1})	TON
1	1	100	92	0.23	0.23
2	1	100	92	0.23	0.23
3	1/1.15	85/100[a]	80/92	0.2/0.2	0.2/0.23
4	1/2	80/100[a]	75/92	0.19/0.12	0.19/0.23

[a]The first number in the third column corresponds to conversion after 1h.

second half of the reaction time no further substantial improvement in the yield of protection reaction was observed. Considering the ICP-OES analysis of the reaction mixture reveals the negligible leaching of Cu^{II} ions in the reaction mixture. It confirms the heterogeneous nature of catalyst as well as the stability during the catalytic reaction (Figures S11 and S12, supplementary material).

Additionally, poisoning test was performed to explore the true nature of the Fe$_3$O$_4$@MCM-41-GPTMS-Gu-Cu^{II}NPs. To this end, and in two separate flasks, the model protection reaction (reaction of benzaldehyde with 1,2-ethanedithiol/or 1,3-propanedithiol) was performed in the presence and in the absence of ethylenediaminetetraacetic acid (EDTA). EDTA with high affinity to take the homogeneous Cu^{II} ions forms the stable complex (Scheme S2, supplementary material), which deactivates the leached-out copper species. If the catalyst has a homogeneous behavior a complete loss in the catalytic activity should be observed. Interestingly, the protection reaction in the presence of EDTA was proceeded as the same as in the absence of EDTA (Figures S13 and S14, supplementary material). The obtained results confirmed no leaching of Cu^{II} ions was happened during the course of protection reaction. Thus, the heterogenous nature and stability of Fe$_3$O$_4$@MCM-41-GPTMS-Gu-Cu^{II}NPs was established truly under the described reaction conditions.

The catalytic quality of Fe$_3$O$_4$@MCM-41-GPTMS-Gu-Cu^{II}NPs in the protection reaction of benzaldehyde with 1,2-ethanedithiol/or 1,3-propanedithiol was compared with some reported results in the literature (Tables 5 and 6). With respect to the merits and superiority of most of the previously reported methods, the present catalytic system acts better rather than others in terms of mol% of catalyst (Table 5, entries 1, 4, Table 6, entries 1, 4), reaction time (Table 5, entries 2–4, Table 6, entries 2–4, 7, 8), and reusability (Table 5, entries 1–2, 4–6, Table 6, entries 1–2, 4–6) as well. Comparatively, among the other methods in Tables 5 and 6, the present investigation affords a truly mild process using a magnetic separable nanostructured catalyst with high yield of the product.

3. Material and methods

3.1. General

All chemical reagents and solvents (Benzaldehyde: for synthesis, ≥98%; 4-Nitrobenzaldehyde: for synthesis, ≥98%; 4-Fluorobenzaldehyde: for synthesis, ≥98%; 4-Chlorobenzaldehyde: for synthesis, ≥98%; 3-Bromobenzaldehyde: for synthesis, ≥97%; 4-Methoxybenzaldehyde: for synthesis, ≥98%; Cinnamaldehyde: for synthesis, ≥98%; 1-Naphthaldehyde: for synthesis, ≥97%; Furfural: for synthesis, ≥98%; Thiophene-2-carbaldehyde: for synthesis, ≥98%; Acetaldehyde: for synthesis, ≥99%; Propionaldehyde: for synthesis, ≥98%; Isobutyraldehyde: for synthesis, ≥98%; Heptanal: for synthesis, ≥97%; 2-Butanone: for synthesis, ≥98%; 2-Heptanone: for synthesis, ≥98%; Cyclopentanone: for synthesis, ≥99%; Cyclohexanone: for synthesis, ≥99%; Acetophenone: for synthesis, ≥98%; 4-Nitroacetophenone: for synthesis, ≥98%; Benzophenone: for synthesis, ≥99%; Silica gel: for column chromatography, 60;

Table 5. Comparison of the catalytic activity of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs with some literature precedents for protection reaction of benzaldehyde with 1,2-ethanedithiol.

Entry	Catalyst	Mol%	Solvent	Temperature (°C)	Time (min)	Isolated yield (%)	Reusability	Ref.
1	$Y(OTf)_3$	5	CH_3CN	RT	90	92	1	[41]
2	$NiCl_2$	1.3	CH_2Cl_2-MeOH	RT	2.75h	96	–	[35]
3a	$[Cu(2,3\text{-tmtppa})]^{4+}$	0.0017 gr	CH_3CN	Reflux	4 h	98	8	[71]
4b	TCM	10	CH_2Cl_2	RT	10 h	92	–	[26]
5	SBA-15-Ph-SO_3H	0.01 gr	CH_3CN	RT	30	96	–	[60]
6c	SPSA	0.5 gr	CH_3CN	RT	45	98	–	[54]
7	Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}	4	CH_3CN	Reflux	1.5 h	95	4	Present study

[a] N,N′,N″,N‴-tetramethyltetra-2,3-pyridinoporphyrazinato copper(II) methyl sulfate.
[b] Trichloromelamine.
[c] Silica phenyl sulfonic acid.

Table 6. Comparison of the catalytic activity of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs with some literature precedents for protection reaction of benzaldehyde with 1,3-propanedithiol.

Entry	Catalyst	Mol%	Solvent	Temperature (°C)	Time (min)	Isolated yield (%)	Reusability	Ref.
1	$Y(OTf)_3$	5	CH_3CN	RT	45	89	1	41
2	$NiCl_2$	1.3	CH_2Cl_2-MeOH	RT	2.5 h	94	–	35
3a	$[Cu(2,3\text{-tmtppa})]^{4+}$	0.0017 gr	CH_3CN	Reflux	3 h	96	8	71
4b	TCM	10	CH_2Cl_2	RT	9 h	94	–	27
5	SBA-15-Ph-SO_3H	0.01 gr	CH_3CN	RT	30	90	–	60
6c	SPSA	0.5 gr	CH_3CN	RT	45	90	–	54
7d	PMO-Py-IL	0.02 gr	–	RT	1.5 h	99	12	47
8e	IL@SBA-15-Pr-SO_3H	3	–	RT	2 h	98	8	48
9	Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}	4	CH_3CN	Reflux	1 h	92	4	Present Study

[a] N,N′,N″,N‴-tetramethyltetra-2,3-pyridinoporphyrazinato copper(II) methyl sulfate.
[b] Trichloromelamine.
[c] Silica phenyl sulfonic acid.
[d] Protic pyridinium ionic liquid silica.
[e] SBA-15 functionalized sulfonic acid confined hydrophobic and acidic ionic liquid.

1,2-Ethanedithiol: for synthesis, $\geq$99%; 1,3-Propanedithiol: for synthesis, $\geq$98%; Iron(III) chloride hexahydrate: for analysis EMSURE®, $\geq$99%; Iron(II) sulfate heptahydrate: for analysis EMSURE®, 99.5–102%; Cetyltrimethylammonium bromide: for analysis EMSURE®, $\geq$99%; Tetraethyl orthosilicate: for synthesis, $\geq$99%; 3-Glycidyloxypropyl trimethoxysilane: for synthesis, $\geq$98%; Guanidinium chloride: LAB, $\geq$99%; Sodium hydrogen carbonate: for analysis EMSURE®, 99–101%; Copper(II) acetate monohydrate: for analysis EMSURE®, $\geq$99%; Ammonia solution: for synthesis, $\geq$25%; Ethanol: for synthesis, $\geq$99.5%; Toluene: Emplura®, $\geq$99%; Acetonitrile: Emplura®, $\geq$99%; Tetrahydrofuran: Emplura®, $\geq$99%; Chloroform: Emplura®, $\geq$99%; Dichloromethane: Emplura®, $\geq$99%; *n*-hexane: Emplura®, $\geq$95%; 1,4-Dioxane: Emplura®, $\geq$99%) were purchased from Merck Chemical Company and were used as received without any further purification. The reaction progress was monitored by TLC on silica gel polygram STL G/UV 254 plates. The melting points of the products were determined with an Electrothermal Type 9100 melting point apparatus. The FT-IR spectra were recorded on an AVATAR 370 FT-IR spectrometer (Therma Nicolet spectrometer, USA) using KBr plates at room temperature in the range between 4000 and 400 cm^{-1} with a resolution of 4 cm^{-1}. The NMR spectra were recorded on a Bruker Avance 200, 250, 300, 400, 500 and 600 MHz instrument in $CDCl_3$ as solvent at room temperature. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 Series instrument (furnace: 900 °C, oven: 65 °C, flow carrier: 140 mL min^{-1}, flow reference: 100 mL min^{-1}). The crystal structure of the catalyst was analyzed by XRD using a D8 ADVANCE Bruker diffractometer operated at 40 kV and 30 mA utilizing Cu Kα radiation ($\lambda = 0.154$ A°). The BET surface area and pore size distribution were measured on a Belsorp-mini II system at -196 °C using N_2 as the adsorbate. Transmission electron microscopy (TEM) was performed with a Leo 912 AB microscope (Zeiss, Germany) with an accelerating voltage of 120 kV. The particles were first dispersed in ethanol for 30 minutes by applying a frequency of 40 KHz in an ultrasonic bath at room temperature. Then they were dripped on the GRID (Carbon coated 300 mesh copper) surface and after drying they were analyzed by TEM.

FE-SEM images, EDX and EDX-mapping were recorded using a TESCAN, model: MIRA3 scanning electron microscope operating at an acceleration voltage of 30.0 kV and a resolution of about 200, 500 nm and 1 μm (manufactured in the Czech Republic). The surface of sample was coated with gold and then analyzed. The magnetic properties of the catalyst were determined using a vibrating sample magnetometer (VSM, Magnetic Danesh Pajoh Inst). The sample was placed in the cap of sample holder and then a teflon layer was placed on it. Next, the powder was crammed by holding bar. The vibrator was linked to the holding bar, and the analysis was performed. Thermogravimetric analysis (TGA) was carried out using a Shimadzu Thermogravimetric Analyzer (TG-50) in the temperature range of 25–800 °C at a heating rate of 10 °C min^{-1}, under nitrogen atmosphere. ICP analysis was carried out on a Varian, VISTA-PRO, CCD, Australia. The sample (0.0358 g) was poured into a beaker and digested by aqua regia and hydrogen peroxide. Afterwards, the resulting mixture was heated at 120 °C and cooled before addition of deionized water to obtain a 100 mL suspension. After calibrating the device using the Cu 100 ppm approach, samples were injected into

ICP instrument and analyzed. All yields refer to the isolated products after purification by column chromatography. Fe_3O_4@MCM-41-GPTMS-Gu-CuIINPs was prepared by the method reported previously.[70] Supplementary material contains complete characterization of the NP and the known products (Figures S1–S11).

3.2. Typical procedure for dithioacetalization of benzaldehyde promoted in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs

To a solution of benzaldehyde (0.1061 g, 1 mmol) and 1,2-ethanedithiol/or 1,3-propanedithiol (0.1884 g, 2 mmol)/or (0.2164 g, 2 mmol) in acetonitrile (4 mL), Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs (4 mol%, 0.0880 g)/or (4 mol%, 0.0880 g) was added and the mixture was refluxed. After completion of the reaction (1.5/or 1 h), which was monitored by TLC, the nanostructured catalyst was separated using an external magnetic field, washed successively with ethanol (4 × 5 mL) to remove the residual of organic compounds and then dried at ambient temperature for 16 h (for using in the subsequent catalytic run). The obtained crude product was purified by column chromatography using *n*-hexane to afford the pure 2-phenyl 1,3-dithiolane/or 2-phenyl 1,3-dithiane (0.161 g, 95% yield/or (0.176 g, 92% yield).

4. Conclusion

In conclusion, in the present study, we have introduced an efficient and facile catalytic dithioacetalization of carbonyl compounds in the presence of the previously prepared and characterized Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs with superparamagnetic core-shell structure. Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs with average diameter of about 8–25 nm can be considered as bench-top reagent for the protection reaction of aldehydes and ketones with 1,2-ethanedithiol/or 1,3-propanedithiol with high chemoselectivity. A wide variety of aromatic (with electron releasing and electron withdrawing substituents), heteroaromatic and aliphatic aldehydes as well as ketones were protected by 1,2-ethanedithiol/or 1,3-propanedithiol in the presence of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs under mild reaction conditions. The present methodology can be considered as a promising candidate for potential applications in some organic reactions due to impressive catalytic activity of Fe_3O_4@MCM-41-GPTMS-Gu-Cu^{II}NPs in dithioacetalization of carbonyl compounds without any by-product formation, good to excellent yields of products, excellent functional group tolerability, mild reaction conditions as well as simple experimental and work-up procedures. Moreover, the catalyst can be easily separated from the reaction mixture by using an external magnetic field and reused in several reactions with only slight loss of its catalytic activity.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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