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An Efficient Method for the Synthesis of α -Amin Phosphonates with New Reusable Magnetic Nanocatalyst of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$

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$\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$ was prepared and applied as a heterogeneous nanocatalyst to synthesize α -aminophosphonate derivatives. The reaction was performed under solvent-free conditions at 80 °C. Synthesized compounds were characterized by FT-IR, ^1H NMR, and ^{13}C NMR. Magnetic properties lead to easy separation and reusability of the catalyst for several times. The simplicity of the procedure, easy workup, short reaction time, high efficiency, and toxic solvent removal are considerable advantages.

Keywords: α -Amin phosphonate, $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$, Heterogeneous nanocatalyst

INTRODUCTION

α -Aminophosphonate derivatives are compounds with a wide range of properties in organic chemistry, especially medicinal chemistry [1-3]. Most of α -aminophosphonate derivatives are known as antiviral[4], antifungal [5], antibacterial, and antitumor [6]. They are an important category of organic compounds with different biological activities [7-9]. In some literature, various activities such as peptidomimetic [10], enzyme inhibitors [11], pharmacogenic agent [12], herbicides [13], and inhibitors of serine hydrolases [14] have been reported for α -aminophosphonates [15,16]. The procedure for synthesizing these compounds is Kabachnik-Fields reaction which was discovered in 1952 independently by Kabachnik [17] and Fields [18]. Kabachnik-Fields is a one-pot three-component reaction that has been done to promote efficiency with different methods such as microwave irradiation, heating [19], and acidic or basic catalysts. Despite advancements, there are still considerable limitations in the Kabachnik-Fields reaction for synthesizing α -amino phosphonates, such as long reaction

time, expensive catalysts, and toxic solvents. Nowadays, replacing suitable catalysts in this reaction has been considered in organic chemistry. The difficulty in the separation process has made many of these catalysts unrecyclable. Also, most solvents used in many procedures are toxic and volatile, hazardous to the environment, causing air pollution, and risky for human health. Therefore, solvent-free conditions is essential in the synthesis of organic compounds [20,21]. In this research, $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$ is used as a heterogeneous catalyst for synthesizing α -aminophosphonates with solvent-free conditions. Moreover, it can be reused several times without considerable loss of activity.

EXPERIMENTAL

Materials and Instruments

All chemicals were obtained from Merck and Sigma-Aldrich without any purification. Infrared (IR) spectra were carried out by Shimadzu. Melting points were measured by an Electro thermal 9100 apparatus. Analytical TLC was monitored on Merck 0.2 mm silica gel 60 F-254 Al-plates.

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^1H NMR and ^{13}C NMR spectra were recorded by Bruker DRX-500 Avance, Bruker DRX-400 Avance, and Bruker DRX-250 Avance spectrometers.

The Procedure for the Synthesis of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$

First, 0.9 g $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ was dissolved in the mixture of distilled water and ethanol (2:1), transferred to a Teflon and heated in an oven at 150 °C for 10 h. Then, the mixture was filtered and washed with distilled water and ethanol and dried at 70 °C to obtain SnO_2 .

Afterward, Fe_3O_4 was prepared by the coprecipitation method. 5.41 g $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and 1.99 g $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ dissolved in 100 ml distilled water. While stirring, NaOH (1 M) was added to the mixture gradually until a black precipitate was formed. Then the mixture was filtered and dried at 70 °C.

In the next step, 0.88 g Fe_3O_4 and 0.88 g SnO_2 were poured into a mixture of distilled water and ethanol (2:1), transferred to a Teflon and heated in an oven at 150 °C for 10 h. Then, the mixture was filtered and dried at 70 °C.

In the final step, sulfuric acid solution (1 M) was added to the procedure and immersed for 1 h, and the $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$ was obtained.

General Procedure for the Synthesis of α -Aminophosphonate Derivatives

For preparing α -aminophosphonate, in a 5 ml dry balloon, a mixture of 100 mg catalyst ($\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$), 1 mmol aldehyde, 1 mmol amine, and 1.2 mmol dimethyl phosphite were added. The reaction refluxed under solvent-free conditions at 80 °C for an appropriate time. TLC monitored the progress of the reaction in a 1:1 hexane/ethyl acetate solvent. After the reaction was completed, the catalyst was filtered. Then the solvent was evaporated, and the intended product was purified by recrystallization.

Spectral Data of Representative Compound

Dimethyl[(2-chlorophenyl) (phenylamino)methyl] phosphonate (1b). M.p.: 134-136 °C, IR (KBr, ν_{max} , cm^{-1}): 3310, 1600, 1517, 1230, 1031. ^1H NMR (400 MHz, CDCl_3): δ 3.47 (d, $J = 10.5$ Hz, 3H), 3.89 (d, $J = 10.8$ Hz, 3H), 5.01 (br, NH, 1H), 5.43 (d, $J = 24.8$ Hz, 1H), 6.64-7.63 (m, $J = 7.7$ Hz, 9H) ppm. ^{13}C NMR (CDCl_3 -d) δC , ppm: 51.04, 52.27, 54.25, 114.02, 119.14, 127.88, 129.40, 129.73, 130.00, 134.19, 134.42, 145.88.

Dimethyl[naphthalen-1-yl(phenylamino)methyl] phosphonate (1e). M.p.: 143-145 °C, IR (KBr, ν_{max} , cm^{-1}): 3309, 3025, 1608, 1234, 1051, 832. ^1H NMR (400 MHz, CDCl_3): δ 3.18 (d, $J = 10.5$ Hz, 3H), 3.85 (d, $J = 10.6$ Hz, 3H), 5.69 (d, $J = 24.0$, 1H), 6.58 (d, $J = 8.0$ Hz, 2H), 6.69 (t, $J = 7.6$ Hz, 1H), 7.06-7.94 (m, $J = 7.7$ Hz, 8H), 8.26 (d, $J = 8.7$ Hz, 1H) ppm. ^{13}C NMR (CDCl_3 , 125 MHz): $\delta = 50.96, 52.18, 54.13, 114.04, 118.89, 123.03, 125.96, 126.95, 129.10, 129.55, 129.66, 131.79, 134.30, 146.30$ ppm.

RESULTS AND DISCUSSION

The FT-IR spectra of (a) Fe_3O_4 , (b) $\text{Fe}_3\text{O}_4@\text{SnO}_2$, and (c) $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$ in KBr in the range of 400-4000 cm^{-1} and shown in Fig. 1. Accordingly, broadened peak at 3400 cm^{-1} was observed, attributed to the O-H

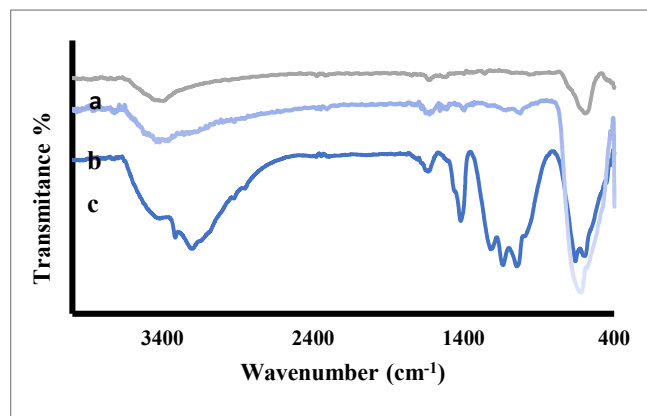


Fig. 1. FT-IR spectrum of a) Fe_3O_4 , b) $\text{Fe}_3\text{O}_4@\text{SnO}_2$ and c) $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$.

stretching vibration of water that adsorbed. The peak at 1630 cm^{-1} is attributed to the O-H bending mode of water associated with the sulfate group. A strong bond assigned to the stretching vibration of S=O was observed at 1130 cm^{-1} , and a middle peak at 1400 cm^{-1} was observed in the spectra assigned to the asymmetric covalent S=O bond. The peak at 650 cm^{-1} is attributed to the Sn-O bond, and the vibration peak of the Fe-O bond at 570 cm^{-1} [22,23].

The FE-SEM images of $\text{Fe}_3\text{O}_4@/\text{SnO}_2$ and $\text{Fe}_3\text{O}_4@/\text{SnO}_2/\text{SO}_4^{2-}$ (Figs. 2a, b) and the size distribution diagram (Fig. 2c) have shown the highest abundance of size distribution is in the range of 40-45 nm. According to the FE-SEM images, nanoparticles are spherical and have good uniformity.

XRD patterns are shown in Fig. 3a) Fe_3O_4 , b) SnO_2 , and c) $\text{Fe}_3\text{O}_4@/\text{SnO}_2/\text{SO}_4^{2-}$. Six characteristic peaks of Fe_3O_4 are $2\theta = 30.1, 35.4, 43.0, 53.5, 57.0,$ and 62.5 . The considerable similarity of the Fe_3O_4 peak with $\text{Fe}_3\text{O}_4@/\text{SnO}_2/\text{SO}_4^{2-}$ shows that the peak positions of Fe_3O_4 are unchanged during the production of $\text{Fe}_3\text{O}_4@/\text{SnO}_2/\text{SO}_4^{2-}$. It indicates that the crystalline structure of the magnetite is essentially maintained. Three characteristic peaks were observed in the SnO_2 X-ray diffraction, including $2\theta = 26.6, 33.8,$ and 51.78 , confirming the tetragonal structure [24-27].

According to the results of the magnetometer spectrum (Fig. 4), $\text{Fe}_3\text{O}_4@/\text{SnO}_2/\text{SO}_4^{2-}$ has super magnetic behavior, and It shows that after immobilization of SnO_2 on the surface of Fe_3O_4 , magnetic properties have been maintained successfully.

The Energy-Dispersive X-ray (EDX) spectra of the nanocatalyst are shown in Fig. 5. This spectrum displays the existence of Fe and Sn in the catalyst. The EDX spectra show a lack of impurity in the prepared nanocatalyst, as shown in Fig. 5.

Optimization of Synthesis Conditions

According to the reaction conditions, the reaction

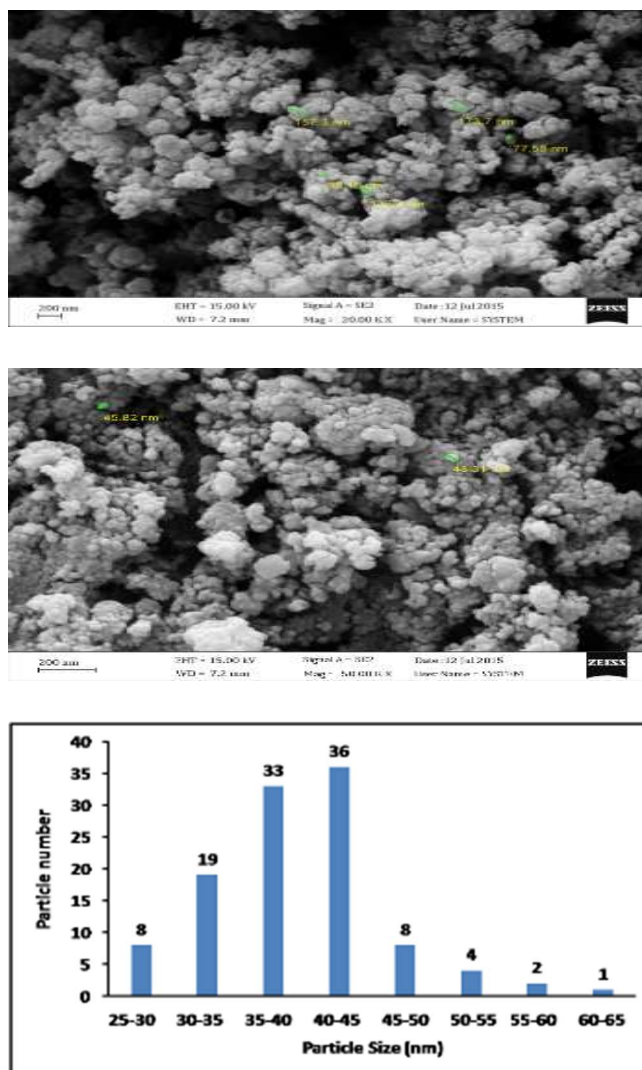


Fig. 2. FE-SEM images of nanoparticles include a) $\text{Fe}_3\text{O}_4@/\text{SnO}_2$, b) $\text{Fe}_3\text{O}_4@/\text{SnO}_2/\text{SO}_4^{2-}$ and c) size distribution of $\text{Fe}_3\text{O}_4@/\text{SnO}_2/\text{SO}_4^{2-}$.

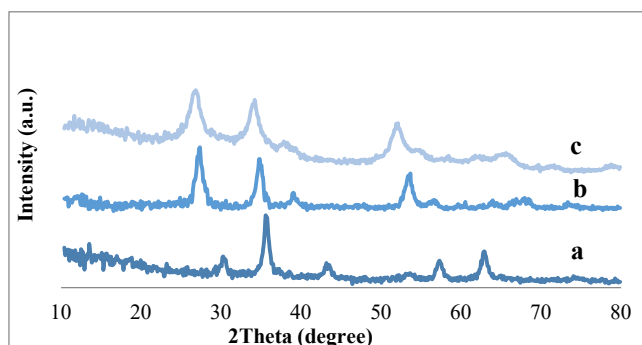


Fig. 3. The X-ray diffraction patterns of a) Fe_3O_4 , b) SnO_2 and c) $\text{Fe}_3\text{O}_4@/\text{SnO}_2/\text{SO}_4^{2-}$.

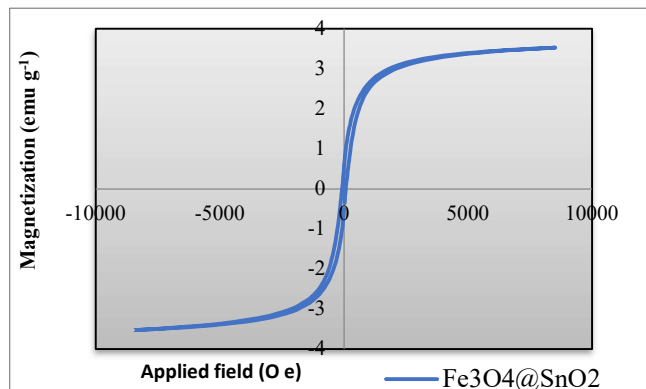


Fig. 4. VSM Spectra of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$.

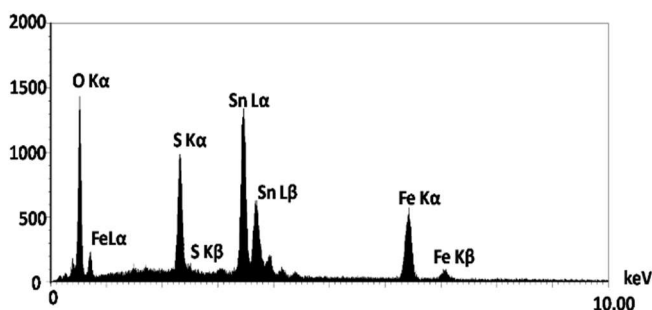


Fig. 5. EDX spectra of prepared composites $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$.

between 2-choloro benzaldehyde, aniline, and dimethyl phosphate in the presence of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$ as a model has been considered (Scheme 1).

The results of Table 1 vividly indicate the best consequence, which was obtained at 80 °C in solvent-free conditions.

According to Table 1, the yield percentage is not considered in the absence of the catalyst. The adequate amount of catalyst was measured with different concentrations, and the best result was obtained with 100 mg catalyst with 96% efficiency at 80 °C under solvent-free conditions.

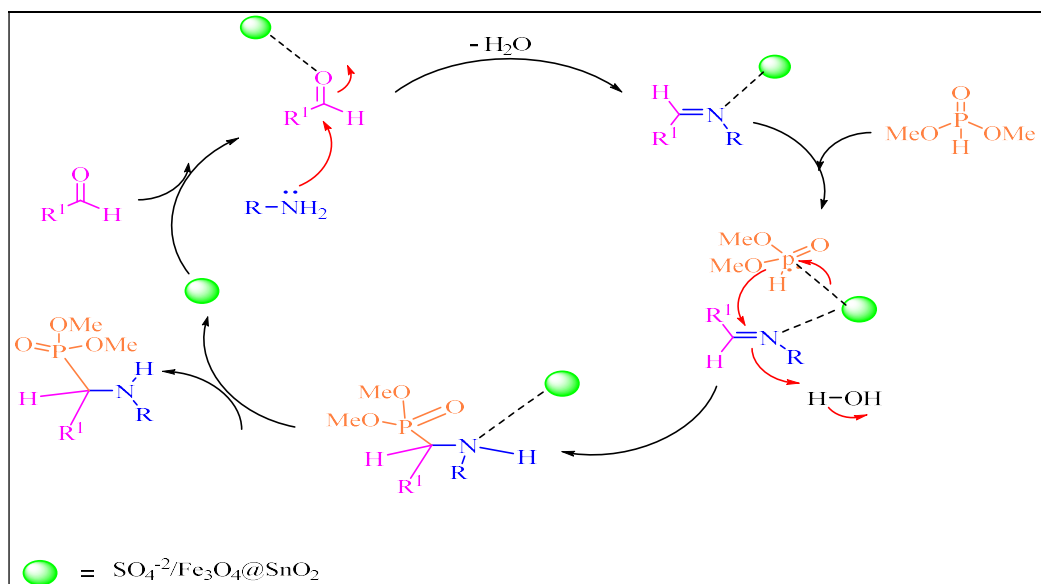
Proposed mechanism for synthesizing α -aminophosphonate in the presence of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$. The suggested mechanism for synthesizing α -aminophosphonate with $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$ is indicated in Scheme 2.

According to the mechanism, the catalyst leads to the facile formation of imine intermediate by activating the

Scheme 1. Reaction model to synthesis of α -aminophosphonate in the presence of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$

Table 1. Optimization of the Reaction Conditions to Synthesis of α -Aminophosphonate in the Presence of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$

Entry	Solvent	Cat (mg)	Time (min)	Temp (°C)	Yield (%)
1	EtOH	-	24h	25	30
2	EtOH	80	25	78	62
3	H ₂ O	80	25	100	20
4	CH ₃ CN	80	25	82	63
5	CHCl ₃	80	25	62	25
6	SF	80	25	90	95
7	SF	80	25	70	95
8	SF	80	25	50	62
9	SF	80	25	RT	10
10	SF	100	25	80	96
11	SF	60	25	70	73
12	-	40	25	70	65



Scheme 2. Suggested mechanism for synthesizing α -aminophosphonate in the presence of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$

amine and activated carbonyl group of aldehyde can form the imine intermediate. This intermediate has been carbonyl group. Nucleophilic addition between the reported in former similar research. The product was achieved with other nucleophilic addition of dimethyl phosphite with imine intermediate and then separation of nanocatalyst. In order to expand this method for synthesizing α -aminophosphonate derivatives investigated with versatile aldehydes and amines, the results are summarized in (Table 2). This table shows a wide range of aldehydes and amine derivatives for synthesizing α -amino phosphonate in the presence of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$.

There is a relationship between the reagent and the yield. For example, the reaction between 4-methoxy benzaldehyde with four different amines and different basicity, including benzylamine, P-toluidine, aniline, and 4-nitroaniline (Entries 13, 5, 15, and 17) has shown an increase in the basicity of amines and the efficiency has been decreased. The reaction between 4-choloro benzaldehyde, benzylamine, and aniline (Entries 16 and 3) yield more with high basicity. About the acidic nature of $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$, base reagents can be deactivated with the catalyst and yield lower than the other analogs.

Comparison of the synthesis of α -aminophosphonate by $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$ catalyst with other catalysts. The

efficiency of the produced catalyst with this method compared with other procedures is shown in Table 3. The table shows the catalyst's best efficiency and short reaction time compared with other methods.

CONCLUSION

$\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$, an environmentally friendly and heterogeneous solid acid nanocatalyst, synthesized α -aminophosphonates in a one-pot reaction. The optimized conditions were performed under solvent-free conditions at 80 °C. Reusability, simplicity of catalyst separation, easy work-up, short reaction time, high yield, and removal of toxic solvents are the advantages of using $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$ as the catalyst.

ACKNOWLEDGMENT

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Supplementary Information

This research has a supplementary file that all characterization, and selected spectra data files can be seen.

Table 2. The Synthesized Derivatives of α -Aminophosphonate Catalyzed by $\text{Fe}_3\text{O}_4@\text{SnO}_2/\text{SO}_4^{2-}$ ^a

Entry	Aldehydes	Amines	Phosphite	Products	Time (min)	Yield (%)	Mp (°C)	M _{Pref}
1a	PhCHO	Aniline			20	82	90-92	88-91 [28]
1b	2-(Cl)-PhCHO	Aniline			20	94	134-136	134-136 [29]
1c	4-(Cl)-C ₆ H ₄ -CHO	Aniline			20	95	148-150	148-150 [30]
1d	2,6-(Cl) ₂ -C ₆ H ₃ -CHO	Aniline			20	72	98-100	98-100 [31]
1e	1-naphthaldehyde	Aniline			25	93	143-145	144 [32]
1f	Terphthaldehyde	Aniline			10	80	170-172	170-173 [31]
1g	Thiophen-2-carbaldehyde	Aniline			85	70	92-94	92-94 [33]
1h	4-(Cl)-C ₆ H ₄ -CHO	4-Nitroaniline			10	88	161-163	162-165 [31]
1i	4-(OMe)-C ₆ H ₄ -CHO	4-Nitroaniline			15	93	149-151	148-150 [31]
1j	PhCHO	P-Toluidine			35	69	69-70	69-70 [34]
1k	4-(OMe)-C ₆ H ₄ -CHO	P-Toluidine			20	78	100-102	101-103 [34]

^a1 mmol aldehyde, 1 mmol amine, 1.2 mmol dimethylphosphate, and 100 mg catalyst under solvent-free conditions at 80 °C.

Table 3. The Comparison of Different Catalysts Efficiency in Synthesis of α -Aminophosphonate (1a)

Entry	Catalyst	Sol.	Time (min)	Temp. (°C)	Yield (%)	Ref.
1	MgFe ₂ O ₃	-	120 min	35	94	[35]
2	Oxalic acid	-	120 min	50	98	[36]
3	DHAA@Fe ₂ O ₃	-	120 min	40	93	[37]
4	Fe ₃ O ₄ @SnO ₂ /SO ₄ ²⁻	-	25 min	70	95	This work

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