Article

Facile Synthesis of Iron-Based MOFs *MIL-100(Fe)* as Heterogeneous Catalyst in Kabachnick Reaction

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Abstract: An effective technique was proposed for the synthesis of novel α -aminophosphonates: a three-component one-pot condensation reaction of aniline, aromatic aldehydes, and triphenyl phosphite in the presence of (*MIL-100(Fe)*) as a heterogeneous catalyst. Initially, *MIL-100(Fe)* was synthesized using H_3BTC and ferric nitrate at low temperature and atmospheric pressure. Further, *MIL-100(Fe)* was characterized using various techniques such as XRD, BET surface area, scanning electron microscopy (SEM), Fourier-transform infrared (FT-IR), and thermogravimetric analysis (TGA). Herein, *MIL-100(Fe)* showed exceptional catalytic performance for the synthesis of α -aminophosphonate and its derivatives compared with conventional solid catalysts, and even homogeneous catalysts. The study demonstrated that *MIL-100(Fe)* is an ecofriendly and easily recyclable heterogeneous catalyst in Kabachnick reactions for α -aminophosphonate synthesis, with high yield (98%) and turnover frequency (TOF $\sim 3.60 \text{ min}^{-1}$) at room temperature and a short reaction time (30 min).

Keywords: metal-organic framework; catalyst; aldehydes; amines; α -aminophosphonates

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1. Introduction

Organophosphorus compounds, especially α -aminophosphonic acids (I) and their esters (II), possess the capacity for biological action because of their resemblance to α -amino acids (III). They are an important analog to α -amino acids (III); as such, we substituted a carboxylic group with a phosphonic acid ester moiety (Scheme 1) [1]. The advancement of existing synthetic techniques and the creation of novel derivatives are particularly relevant in the field of organophosphorus chemistry. Due to the amazing pharmacological and environmental applications of α -aminophosphonic acids and their related derivatives, α -aminophosphonate, and its analogs have recently attracted the attention of the scientific community [2,3].

Generally, these organophosphorus compounds have high biological efficiency, metabolic stability, and low toxicity in mammalian cells [2]. In fact, α -aminophosphonates have introduced many of medicinal benefits, possess antifungal [2], herbicidal [4], antibacterial [5,6] and antiviral [7] properties, and can function as enzyme inhibitors [8,9] and anticancer agents [10,11]. As a result, they become tremendously essential in medical and agricultural chemistry. Recently, Functionalized α -aminophosphonates placed on a solid support have been reported to have environmental and industrial uses in uranium and heavy metal removal. [12,13]. Interestingly, the synthesis of α -aminophosphonates can take a variety

of routes, depending on the reactants and catalysts used [14,15]. In particular, most of the catalysts utilized in α -aminophosphonates synthesis are homogeneous catalysts such as lithium perchlorate [16], aluminum chloride [17], and calcium bromide [18]. The drawbacks of the above-mentioned homogeneous catalysts are their smaller surface area, low porosity, the difficulty of purification from the reaction mixture, and the fact that they are not environmentally benign [19,20].

Scheme 1. Structures of α -aminophosphonic acids (I), α -aminophosphonic esters (II), and α -aminophosphonic acids (III).

In the past few decades, heterogeneous catalysts have been created to solve the aforementioned challenges thanks to several advantages, such as facile separation from the reaction mixture, environmental friendliness, and high reusability [21]. Interestingly, metal-organic frameworks (MOFs) have sparked interest in adsorption, biomedicine, molecular-based magnetism, drug delivery, sensing, and catalysis, among other uses [22–26], due to their characteristic properties of high porosity, crystallinity, ultrahigh specific surface area, low density, and high metal content [23,27]. However, the inhomogeneous blending of the components is one of the most challenging downsides of MOF-based composites, since the finished composite does not have a regular distribution throughout the product or demonstrate any well-enhanced performance in applications. One solution to this problem is to use well-shaped nanoparticles as hard templates that lead the next material component of the composite through a regulated bottom-up growth process, which assures uniformity. Hard templates can be used to create new nanoarchitectures with homogenous distribution of all material components throughout the composite [28]. Furthermore, internal diffusion occurs in these materials owing to the small size of their pores, a limitation which reduces their efficiency. Mesopores have been constructed in order to promote the transport of microporous materials in the manufacture of micro/mesoporous materials [29].

One of the most important applications of MOFs is heterogeneous catalysis [30]. The high metal content (active sites) and simple functionalization of organic linkers are primarily responsible for the catalytic activity of MOFs'. To the best of our knowledge, the literature rarely describes studies on MOFs as catalysts in kabachnick reactions. Among these, Sarika A. Rasal et al. [31] synthesized α -aminophosphonates by a three-component one-pot condensation of 3-(trifluoromethyl)aniline, substituting aromatic aldehydes and diethylphosphite using a nickel-based metal-organic framework (Ni-MOF), with a 95% yield in the solvent-free condition.

In this study, we facilitated the synthesis of *MIL-100(Fe)* from iron salts and trimesic acid. Remarkably, the iron center of *MIL-100(Fe)* introduces several merits compared with other metals due to its low cost, non-toxicity, and being mainly environmentally friendly with the exception of the Lewis acidity of the available unsaturated metal sites. *MIL-100(Fe)* was utilized as a recyclable catalyst in Kabachnik reactions for α -aminophosphonate synthesis, with high yields in mild conditions. N_2 sorption, X-ray diffraction (XRD), Fourier transform infrared (FTIR) spectroscopy, thermogravimetric (TGA), and scanning electron microscopy (SEM) were used to identify the prepared catalysts. Furthermore, the effect of optimized reaction parameters such as reaction temperature, catalyst loading, and different solvents and substrates on catalytic performance was investigated. To the best of our knowledge, hardly any study has been conducted on the synthesis of α -aminophosphonates catalyzed by MOFs.

2. Results and Discussion

2.1. Characterization of MIL-100(Fe) Catalyst

The structural integrity of MIL-100(Fe) was examined by XRD as displayed in Figure 1. The patterns of MIL-100(Fe) were entirely consistent with the characteristic patterns of pristine MIL-100(Fe). There are no further peaks, indicating that no new crystalline phase was formed.

Figure 1. XRD patterns for simulated MIL-100(Fe) and synthesized MIL-100(Fe).

The N₂ sorption isotherms of MIL-100(Fe) are shown in Figure 2. The samples show a typical type (I) isotherm in the relatively low-pressure regions, with a narrow hysteresis loop in the relative pressure (P/P_0) > 0.9 denoting the existence of micropores. The BET surface area and pore volume of MIL-100(Fe) are evaluated as 1804 m²/g and 1.1 cm³/g, respectively.

Figure 2. N₂ sorption isotherms of MIL-100(Fe) sample.

The SEM image of the MIL-100(Fe) sample is displayed in Figure 3. The SEM image in Figure 3a shows the irregular size of platy cleavages and the cauliflower-like shape of the MIL-100(Fe) particles. Additionally, we determined the average particle size distribution from SEM images using ImageJ software. The particles size is distributed in the range of 150–200 nm, as displayed in Figure 3a'.

Figure 3. (a) SEM image *MIL-100(Fe)* and (a') particle size distribution of *MIL-100(Fe)*.

The thermal stability of *MIL-100(Fe)* was explored by using thermogravimetric analysis; the subsequent TG curve is displayed in Figure 4. The *MIL-100(Fe)* exhibits three stages of weight loss: at temperature of 60–340 °C with 5% weight loss, at 340–400 °C with 34.20% weight loss, and at 400–680 °C with 38.90% weight loss. The first stage of thermal degradation corresponds to the removal of trapped water molecules followed by the decomposition of O-containing functional groups. The minimal weight loss (almost a plateau) at the first stage demonstrates that the *MIL-100(Fe)* is stable up to this range of temperature. Considerable weight loss was observed above the temperature of 340 °C; this is due to the structural collapse of *MIL-100(Fe)* as the ligand decomposes. The resulting extraordinary mass decrease began at 400 °C, which is brought about by the continuous decomposition of the framework accompanied by the reduction of iron [27,32]. The third stage of degradation ends at temperatures up to 680 °C, showing that *MIL-100(Fe)* is totally decomposed.

Figure 4. TGA of *MIL-100(Fe)* sample.

The FT-IR spectrum of *MIL-100(Fe)* is presented in Figure 5. The band in this spectrum is 1697 cm^{-1} , attributed to the C=O; those at 1379 and 1448 cm^{-1} are due to O-C-O stretching vibration. The bands at 1112 cm^{-1} can be attributed to the vibrations of the aromatic benzene ring of the BDC-linker.

Figure 5. FT-IR spectra of iron-based metal-organic framework (*MIL-100(Fe)*).

2.2. Catalytic Evaluation

Generally, α -aminophosphonates are produced from a one-pot reaction with an equivalent molar ratio of aldehydes, amines, and triphenylphosphite; we optimized the reaction conditions (catalyst amount, temperature, and solvent) in order to achieve the optimum conditions.

2.2.1. Effect of Catalyst Amount

To investigate the effect of catalyst quantity, the reactants (benzaldehyde, aniline, and triphenylphosphite) were utilized as the design model in the presence of *MIL-100(Fe)* catalyst (1–20 mol%, in light of the mol% of aldehyde) in CH_3CN at room temperature as in Scheme 2. When the reaction was carried out with 8 mol% loading of *MIL-100(Fe)* catalyst, we obtained a high yield (92%, Figure S1) in a short time (4 h), as exhibited in Table 1. This reaction progress was followed by using TLC. On the other hand, when the catalyst amount was more than 8%, the yield could not be increased further due to the hindrance due to mass transfer from the production of viscous slurries [31]. As a result, catalyst loading at 8 wt% was decided as the optimal condition for further series studies; according to the experimental results, we suggest one possible mechanism reaction in Scheme 3.

Scheme 2. Model system for a one—pot synthesis of α -aminophosphonates.

Table 1. Effect of catalyst amount in Kabachnick reaction at room temperature.

Reaction Conditions			
Entry	Catalyst Amount (wt%)	Time (h)	Isolated Yield (%)
1	1	24	77
2	3	4	83
3	5	24	95
4	8	4	92
5	10	4	84
6	13	6	90
7	15	24	68
8	18	6	90
9	20	4	72

Reactions conditions: benzaldehyde (a) (1.88 mmol), aniline (b) (1.93 mmol), triphenylphosphite (c) (1.87 mmol) and MIL-100(Fe) as catalyst. All reactions were done at room temperature under atmospheric conditions.

Scheme 3. The proposed mechanism of the one-pot reaction catalyzed by MIL-100(Fe).

2.2.2. Effect of Reaction Temperature

Generally, the Kabachnick reaction was carried out with 8 wt% of MIL-100(Fe) catalyst in a 10 mL glass vial at the temperature range of 298–333 K, starting with aldehyde, amine, and phosphite in a molar ratio (1:1:1) in CH_3CN . In this experiment, the reaction proceeded faster by increasing the temperature, at the expense of decreasing the yield (Figure 6). This might be due to depletion of the adsorption affinity of the reactants on the active sites of the

catalyst surface, which would result in a decrease in the conversion of the reactants to the product. Generally, the adsorption process is always an exothermic process ($\Delta H = -ve$). Therefore, the elevated temperature negatively affected the adsorption process of the reactants on the catalyst surface, and the reaction rate was decreased. Detailed outcomes are consistent with a standard deviation of ± 0.03 mass%. All data are from triplicated experiments [33].

Figure 6. Influence of reaction temperature on Kabachnik reaction; reaction conditions with a molar ratio of aldehyde: amine:phosphite 1:1:1 in CH_3CN , and $\text{MIL-100}(\text{Fe})$ catalyst (8 wt%).

2.2.3. Screening of Different Solvents in Kabachnik Reaction

We screened different solvents in order to upgrade the yield of a model reaction as despite in Scheme 4; the results are given in Table 2. Table 2 shows that Et_2O was the best solvent for the synthesis of α -aminophosphonate (yield ~ 98%, Figure S2). Et_2O is a polar aprotic solvent that is essential in the stabilization of metal catalysts via the lone electron pair in oxygen, hence increasing catalytic activity.

Scheme 4. Model reaction for improvement of solvent in synthesis α -aminophosphonates.

Table 2. Screening solvents in Kabachnick reaction.

Entry	Reaction Conditions		
	Types of Solvent	Time (min)	Isolated Yield (%)
1	THF	60 min	71
2	C ₂ H ₄ Cl ₂	30 min	74
3	Neat	60 min	91
4	CH ₃ CN	240 min	92
5	CH ₂ Cl ₂	120 min	96
6	Et ₂ O	45 min	98

All reactions were performed at room temperature in the presence of benzaldehyde (a) (1.88 mmol), aniline (b) (1.93 mmol), triphenylphosphite (c) (1.87 mmol and *MIL-100(Fe)* catalyst (8 wt%) under atmospheric conditions.

2.2.4. Effect of Substrates on Catalytic Activity

Due to the significance of the Kabachnick reaction in the preparation of α -aminophosphonates as key intermediates in the preparation of biologically active compounds we tested the reaction using different aldehydes, including electron-donating and electron-withdrawing groups in the para position to prevent steric hindrance effect under the same experimental conditions as seen in Scheme 5. The acquired results are shown in Table 3, Figures S3–S7. It was found that the electron structure and the size of the substituents affected the reaction yield. The aldehydes with electron-withdrawing substituents gave a good yield in a shorter reaction time (Table 3, Figure S4, 15 min, 94%) compared to that with electron-donating substituents (Table 3, Figure S5, 24 h, 59%). This was rationalized on the basis that electron-withdrawing substituents depleted the electrons on the carbonyl carbon of the aldehyde group which facilitates the formation of imine by attacking the nucleophilic nitrogen of amine.

Scheme 5. Schematic route for synthesis of functionalized α -aminophosphonates.**Table 3.** A model system for formation of α -aminophosphonates over *MIL-100(Fe)* as a catalyst, employing various aryl aldehydes.

Entry	R	Compound No.	Times (Min)	Isolated Yield (%)
1	C ₆ H ₅ -	4a	30	98
2	4-BrC ₆ H ₄ -	4b	5	81
3	4-HOC ₆ H ₄ -	4c	12	70
4	4-ClC ₆ H ₄ -	4d	6	84
5	4-NO ₂ C ₆ H ₄ -	4e	15	94
6	4-(CH ₃) ₂ N-C ₆ H ₄ -	4f	1440	59

All reactions were done at room temperature in the presence of (1) benzaldehyde or its derivatives (1.88 mmol), (2) aniline (1.93 mmol), (3) triphenylphosphite (1.87 mmol) and *MIL-100(Fe)* catalyst (8 wt%) under atmospheric conditions.

2.2.5. Comparison of Catalytic Performance of Different Catalysts

In order to provide a complete evaluation, the catalytic activity of several catalysts in the kabachnick reaction of aldehyde Scheme 6, is provided in Table 4. Notably, *MIL-100(Fe)* gave a yield of 98%. Therefore, Table 4 shows the superiority of *MIL-100(Fe)* compared to the reported catalysts in the kabachnick reaction because of its large surface area and enormous pore volume, which allow it to accommodate the reactants and stimulate the

reaction. Thus, we computed turnover frequency (TOF) in order to compare the catalytic activity of *MIL-100(Fe)* materials as heterogeneous solid catalysts for the production of α -aminophosphonate compounds. TOF is an important parameter in heterogeneous catalysis, gives quantitative insights into how catalytic cycles function, and compares the catalytic activity of *MIL-100(Fe)* materials, particularly in a system involving the transfer of bulky molecules. TOF is simply referred to the number of catalytic cycle uprisings per time, and was computed using Equation (1) [34,35]. Table 4 shows the activity of an Fe-based catalyst in terms of turnover frequency (TOF). All catalysts displayed mass transfer restriction at varying rates, with *MIL-100(Fe)* exhibiting the most activity.

$$\text{TOF} = \frac{X \cdot V_0 \cdot \rho \cdot M_C}{W_S \cdot M_r \cdot T} \quad (1)$$

where X , V_0 , ρ , M_C , M_r , W_S , and T are the conversion of the substrate, the volume (mL) of the substrate, the density (g/mL) of the substrate, the molar mass (g/mol) of the catalyst, the molar mass (g/mol) of substrate, the weight (g) of the catalyst, and the reaction time (min), respectively.

Scheme 6. Model reaction of comparison catalytic performance in preparation of α -aminophosphonates.

Table 4. Comparison of catalytic performance of different catalysts in Kabachnick reaction.

Entry	Catalyst	Time (h)	Isolated Yield (%)	TOF (h^{-1})	Ref
1	LiClO_4	48	86	0.017	This work
2	TiCl_4	30	55	0.018	[36]
3	AlCl_3	30	70	0.023	[36]
4	ZnCl_2	30	78	0.026	[36]
5	<i>MIL-100(Fe)</i>	4	98	3.6	This work

Reactions done at room temperature in the presence of benzaldehyde (a) (1.88 mmol), aniline (b) (1.93 mmol), triphenylphosphite (c) (1.87 mmol) and catalyst.

2.3. Reusability of Catalyst

The reusability of the catalysts is a significant advantage of this approach, making it suitable for commercial applications. Thus, the catalyst's recyclability was checked for the reaction between benzaldehyde, aniline, and triphenylphosphite with 8 wt% of *MIL-100(Fe)* at 25 °C, and with Et_2O as the solvent. Afterwards, the catalyst was separated by centrifugation and washed with CH_3CN to get rid of any residue which may be adsorbed onto the catalyst surface, then dried in an oven at 100 °C overnight and activated for 6 h at 150 °C under vacuum. The separated catalyst could then be reused for the next cycle. According to the findings, the catalyst can be utilized seven times, with slight loss in its catalytic activity (Figure 7) due to adsorbing of the final product and the remaining reactants onto the catalyst surface, as seen in the FT-IR analysis of the catalyst before and after reusability displayed in Figure S8.

Figure 7. Reusability of MIL 100-(Fe) in Kabachnick reaction at optimized reaction conditions.

3. Experimental

3.1. Materials

Trimesic acid 98% (LOBA Chemie, Mumbai, India), ferric nitrate nanohydrate 99% (LOBA Chemie, Mumbai, India), Lithium perchlorate 99% (LOBA Chemie, Mumbai, India), absolute ethanol 99% (Sigma Aldrich, MO, USA), Benzaldehydes 99% (Sigma Aldrich, MO, USA), Aniline 99% (LOBA Chemie, Mumbai, India), triphenylphosphite 97% (Sigma Aldrich, MO, USA), acetonitrile 99% (LOBA Chemie, Mumbai, India), Dichloromethane 98% (LOBA Chemie, Mumbai, India), Dichloroethane 98% (LOBA Chemie, Mumbai, India) and diethyl ether 99% (LOBA Chemie, Mumbai, India) compounds were utilized as supplied, with no additional purification.

3.2. Catalyst Preparation

MIL-100(Fe) was synthesized by a facile synthesis route with mild reaction conditions via the reaction of H_3BTC and ferric nitrate at the atmospheric pressure published in the literature [31], with some modifications. Typically, $Fe(NO_3)_3 \cdot 9H_2O$ (10 mmol), H_3BTC (9 mmol), and deionized water (30 mL) are mixed and charged in a two-neck round bottom flask (50 mL) fixed with a magnetic stirrer and a reflux condenser and kept at 95 °C for 12 h. The reaction product was centrifuged and rinsed three times with hot deionized water and ethanol at 70 °C for 1 h, then dried in an oven at 100 °C for 3 h and activated under vacuum at 150 °C for 24 h.

3.3. Characterization of Catalyst

Synthesized *MIL-100(Fe)* was identified by Nitrogen (N_2) Sorption, X-Ray Diffraction (XRD), Scanning Electron Microscopy (SEM) and Thermo-Gravimetric Analysis (TGA). XRD patterns were monitored on a Rigaku D/Max-2550 diffractometer equipped with a SolX Detector-Cu K radiation with $\lambda = 1.5418 \text{ \AA}$. The data were enrolled by step scanning at $2\theta = 0.02^\circ$ per second from 5° to 50° .

The Brunauer–Emmett–Teller (BET) and Barret–Joyner–Halenda (BJH) methods were utilized to evaluate surface area and pore volume. N_2 sorption isotherms for determining surface area and pore characteristics were performed at -196°C on a 3H-2000PS1 Gas Sorption and Porosimetry system. The sample was arranged for examination after degassing at 150 °C under vacuum until the final pressure reached 1×10^{-3} Torr.

Scanning electron microscopy (SEM) images were obtained on a SUPRA 55 fitted with an acceleration voltage of 20 kV.

Fourier transform infrared (FT-IR) spectra were examined on a NicoLET iS10 spectrometer. Thermogravimetric analysis (TGA) was conducted on Shimadzu TA-50.

Spectra of ^1H -NMR, ^{13}C -NMR, and ^{31}P -NMR were recorded on a Bruker Advance 400 MHz spectrometer with $\text{DMSO}-d_6$; chemical shifts (δ) are expressed in ppm.

3.4. Catalytic Reaction

A mixture of aldehydes (1.8 mmol) and amine (1.93 mmol) was added to triphenylphosphite (1.87 mmol) in acetonitrile by stirring in a little glass vial at room temperature. Then, the optimal weight of *MIL-100(Fe)* catalyst was added according to the weight of aldehyde. The progress of the reaction was checked by TLC using hexane:chloroform at a 1:9 ratio as an eluent until the reactants were consumed. Then, the catalyst was recovered by centrifugation followed by decantation. The acetonitrile decant was evaporated, and the remaining residue from the product was washed several times with diethyl ether to afford pure α -aminophosphonates, with excellent yields. The structure of the new compounds was determined by ^1H -NMR, ^{13}C -NMR, ^{31}P -NMR and FT-IR spectra; these are presented in the Supplementary Materials.

4. Conclusions

In this study, we successfully prepared *MIL-100(Fe)* via the facile method as an efficient and easily recyclable heterogeneous catalyst in Kabachnick reaction for α -aminophosphonates synthesis in excellent yields. The catalyst had an extremely good catalytic performance for condensation of different aldehydes, amines, and trialkyl/arylphosphites for the synthesis of α -aminophosphonates and their derivatives. The incredible catalytic performance of the catalyst for different reactants may be attributed to its suitable metal content, porosity, and high surface area, which greatly enhance the adsorption/diffusion of desirable reactants and the desorption of products. We believe that our research will open the path for the straightforward introduction of MOF heterogeneous catalysts instead of conventional ones for α -aminophosphonates synthesis, as these types of catalysts are becoming more environmentally and economically attractive.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/catal11121451/s1>: The novel compound structures as determined by the FT-IR, ^1H -NMR, ^{13}C -NMR and ^{31}P -NMR spectra and FT-IR of *MIL-100(Fe)*. Figures S1 and S7 (^1H -NMR, ^{31}P -NMR and FT-IR) for compounds 4a and 4j. Figures S2–S6 (FT-IR, ^1H -NMR, ^{13}C -NMR and ^{31}P -NMR) for compounds 4d to 4c. Figure S8 (FT-IR of *MIL-100(Fe)*).

Author Contributions: N.E.E., I.E.T.E.S. and A.S.A.-E. participated in the conceptualization and supervision; investigation, N.E.E., I.E.T.E.S. and A.S.A.-E.; writing—original draft, A.G.A.-S. and A.A.A.-G. funding acquisition, N.E.E., I.E.T.E.S. and A.S.A.-E.; writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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