

Cite this: *RSC Sustainability*, 2025, 3, 4746

Fe(MIL-53) metal–organic framework as a facile and sustainable Lewis acidic catalyst for the one-pot synthesis of xanthene derivatives

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The catalytic application of the easily preparable Fe(MIL-53) MOF was demonstrated as a sustainable solid Lewis acidic catalyst in synthesising pharmaceutically essential xanthenes under mild conditions. The Fe(MIL-53) MOF catalyst was synthesised and characterised using various analytical tools such as PXRD, FTIR, SEM, TGA and ICP-OES. The presence of a high concentration of coordinatively unsaturated Fe³⁺ sites in Fe(MIL-53) can efficiently catalyse the formation of xanthenes in the presence of a catalytic amount (1.36 mg) of MOF using environmentally friendly, non-toxic and renewable ethanol as the medium. A series of substituted xanthenes were synthesised in good to excellent yield with wide functional group tolerance. The present methodology avoids the usage of any strong reagents and uses stoichiometric amounts of the catalyst. The catalytic comparison studies with other homogeneous and heterogeneous catalytic systems proved the efficiency of the present Fe(MIL-53) MOF catalyst. The hot-filtration test and reusability profile prove the stability and sustainability of this catalyst, which were also supported by PXRD, FTIR and SEM analysis of the reused catalyst.

Received 17th March 2025
Accepted 6th August 2025

DOI: 10.1039/d5su00191a

rsc.li/rscsus

Sustainability spotlight

Iron is one of the most abundant metals in nature, and iron-based metal–organic frameworks (MOFs) have garnered significant attention due to their remarkable reactivity, stability, ease of handling, relatively low toxicity, and environmental friendliness while being cost-effective. Earlier-generation catalysts were largely based on precious metals, often homogeneous, and suffered from significant recyclability challenges. Xanthenes are a crucial class of organic compounds with diverse pharmacological properties. However, their synthesis presents challenges, particularly due to their acid-sensitive groups. The use of iron-based MOFs offers a sustainable approach to overcoming these limitations. This work aligns with the United Nations Sustainable Development Goals (SDGs) 7 and 12, which emphasize affordable and clean energy as well as sustainable consumption and production patterns, promoting a more environmentally responsible approach to catalysis.

1. Introduction

Xanthenes are an important class of organic compounds with several pharmacological properties, such as anti-coagulant, spasmolytic, anticancer, antiviral, anti-inflammatory, antibacterial, antifungal, antiproliferative, antioxidant, and specific IK_{Ca} channel blocking activities.^{1–7} These compounds were widely used as synthetic precursors for many valuable organic compounds,⁸ dyes,⁹ and photoactive materials¹⁰ and in laser technologies¹¹ and fluorescent materials for the visualisation of biomolecules¹² and detection of metal ions.¹³ Tetraketones and their tautomeric enol forms are also considered to be important biologically active compounds, being assessed as tyrosinase

inhibitors, and also leading intermediates in the preparation of fused heterocyclic systems such as xanthendione, acridindione and 4*H*-1-benzopyran derivatives.¹⁴ Xanthene derivatives can be prepared generally *via* the condensation between aldehydes and 1,3-dicarbonyl compounds. To obtain xanthenes, this type of condensation reactions has been reported in the literature using homogeneous catalysts, including protonic acids,¹⁵ Lewis acids such as InCl₃·4H₂O,¹⁶ indium triflate,¹⁷ FeCl₃·8H₂O,¹⁸ CuCl₂,¹⁹ and NaHSO₄,²⁰ and heterogeneous catalysts, such as Dowex-50W,²¹ polyaniline *p*-toluenesulfonate,²² *p*-toluenesulfonic acid,²³ sulfamic acid@MCM-41,²⁴ PPA-SiO₂,²⁵ TiO₂/SO₄,²⁶ nano-Fe₃O₄-TiO₂-SO₃H,²⁷ Fe₃O₄@NFC@NNSM-Mn(III),²⁸ Fe₃O₄@SiO₂@APTES@MPIB-Mn(II),²⁹ TMP-PECH-COOH,³⁰ CuCeO₂ NPs,³¹ ZrO₂ NPs,³² Fe₃O₄ NPs,³³ Cu(II) NPs,³⁴ CuS quantum dots,³⁵ and Amberlyst-15.³⁶ In general, heterogeneous solid acid catalysts have more advantages over homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused several times

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yield (74–88%). Conversely, in protic polar solvents such as methanol, ethanol, and isopropanol, the reaction proceeds smoothly and yields good to excellent (85–98%). Further, to explore the greener aspects, water was employed as the solvent; however, the result was not encouraging, giving a lower yield of 45% and revealing that the MOF catalyst was not stable at the end of the reaction (refer to SI, Fig. S54).

According to the overall analysis of the solvent screening results, the readily available and renewable ethanol was identified as the optimum reaction medium for the Fe(MIL-53) (1)-catalysed synthesis of xanthene (4a). Compared to the other solvent systems, in recent days, ethanol was found to be a benign reaction medium⁶¹ owing to its renewable and non-toxic nature; besides, it is cheap and readily available.

In the present synthesis of xanthene (4a), temperature plays a crucial role, as inferred from the solvent optimisation. During the solvent screening, most of the solvents were used at their boiling point. The optimised ethanol was also used at its boiling point; however, to find the optimum temperature, the reactions were carried out at different temperatures.

The product yield fluctuated while tuning the temperature (Fig. 1). Initially, at room temperature, an inferior product (<2%) was noted. When the temperature increased, an enhancement in yield was observed (Fig. 1) and it increased proportionally with temperature. When the temperature reached 60 °C and 70 °C, it offered a reasonable yield (75% and 83%, respectively); however, complete conversion and the expected yield were not achieved. Further, the reaction temperature increased up to the reflux temperature of the solvent (at the boiling point of 80 °C) and gave the maximum yield (98%). To investigate the reaction at 90 °C, a sealed vessel was used to prevent solvent loss. The yield obtained under this condition did not influence the yield and gave the maximum yield of 98%. According to the temperature optimisation study, the reflux condition (80 °C) was fixed as the optimum temperature.



Fig. 1 Temperature optimisation for Fe(MIL-53) MOF-catalysed synthesis of xanthene (4a).

In heterogeneous catalysis, time optimisation is another important factor that determines the efficiency of catalysts. In the present reaction, the reaction was performed for 3 h for the initial screening of the catalyst. With the optimised solvent and temperature, the actual time required to attain the maximum yield was studied by monitoring the reaction conversion at certain intervals. Only 58% of product formation was observed after 30 min of reaction (Fig. 2). Further studied reactions after 60 min, 90 min and 120 min showed 75%, 84% and 98% yield, respectively. After 120 min and further allowing the reaction to proceed for an additional 60 min, no notable enhancement in the yield was observed. According to the above-mentioned results, 120 min (2 h) is sufficient for the complete conversion of the reactant and to achieve the maximum product (4a, 98%). Hence, 120 min (2 h) was fixed as the optimised time for the Fe(MIL-53) (1) MOF-catalysed synthesis of xanthene (4a).

After optimising the solvent, time and temperature, another crucial parameter, the exact quantity of catalyst required for the maximum product formation, was screened. In heterogeneous catalysis, the amount of catalyst used determines the efficiency and endorses the greener nature of the catalyst.

In the initial optimisation studies, 25 mg of the Fe(MIL-53) MOF (1) catalyst was employed; however, further screening started with 5% catalyst load, which resulted in moderate (70%) product (4a) formation (Fig. 3). Further, to identify the appropriate catalyst loading, the amount of catalyst was increased from 5% to 30 wt% and the isolated yield was calculated with an increase in the catalyst load in every additional 5% load. The screening results showed that 20 wt% catalyst loading provides the maximum yield of 98%. Further increasing the catalyst load to 25 and 30 wt% showed no remarkable improvement. This screening study demonstrated that 20 wt% of Fe(MIL-53) (1) catalyst load is adequate to get the maximum yield of xanthene (4a).

All the above-mentioned preliminary screening studies disclosed that Fe(MIL-53) (1) acts as an efficient heterogeneous catalyst for the synthesis of xanthene (4a) with 20 wt% (1.36 mg of Fe, 0.0243 mmol) of catalyst in renewable ethanolic medium



Fig. 2 Time optimisation for Fe(MIL-53) MOF (1)-catalysed synthesis of xanthene (4a).



Table 2 Fe(MIL-53) (1) MOF-catalysed synthesis of xanthene derivatives^a

Entry	Aldehyde	Xanthene	Yield ^b (%)
1			98%, 94% (Gram-scale synthesis)
2			89%
3			95%
4			97%
5			97%
6			94%
7			92%
8			95%



Table 2 (Contd.)

Fe(MIL-53) (1)
(20 wt %)
Ethanol, reflux, 2 h

2a-t + 3 → 4a-t (82-98%)

Entry	Aldehyde	Xanthone	Xanthene	Yield ^b (%)	
9		2i		4i	89%
10		2j		4j	91%
11		2k		4k	90%
12		2l		4l	84%
13		2m		4m	87%
14		2n		4n	89%
15		2o		4o	82%
16		2p		4p	91%



Table 2 (Contd.)

Entry	Aldehyde	Xanthene	Yield ^b (%)
17			90%
18			92%
19			85%
20			93%

^a Reaction conditions: aldehyde (0.71 mmol, 1.0 eq.), dimedone (1.42 mmol, 2.0 eq.), Fe(MIL-53) (20 wt%), ethanol (2.0 mL), reflux (80 °C), 2 h. ^b All are isolated yields. ^c Gram-scale synthesis.

terephthalic acid (precursors of Fe(MIL-53) MOF) as a catalyst in xanthene synthesis under the optimised conditions. The physical mixture also catalysed the reaction but only gave 17% yield. This catalytic performance of the physical mixture unambiguously confirms that the presence of the framework is responsible for the high catalytic efficiency in the synthesis of xanthene derivatives.

After successfully exploring the true catalytic efficiency of the present catalyst **1**, it was necessary to understand the stability of the heterogeneous catalyst under the screened reaction conditions, and thus hot filtration studies were carried out under the optimised conditions. During the heterogeneity test, the catalyst was removed from the reaction medium by simple filtration after 30 min under hot conditions.

Aliquots of the reaction mixture were subjected to HPLC analysis at 30 min. Extended intervals showed no further increase in the yield (Fig. 5). The hot filtration test strongly evidenced that the catalyst is highly stable and acts in a truly heterogeneous manner under the optimised reaction conditions without breaking or deforming the framework of Fe(MIL-

53) (**1**). The result obtained from the hot filtration studies was strongly endorsed by the inductively coupled plasma optical emission spectroscopy (ICP-OES) measurements of the filtrate from the reaction mixture in ethanol. The catalyst was filtered from the reaction medium after 30 min, and then the filtrate was subjected to ICP-OES analysis, where no proof of iron leaching was observed, manifesting the true heterogeneity of the Fe(MIL-53) MOF (**1**).

The reusability aspect determines the stability and sustainability of a heterogeneous catalyst. This is considered one of the indispensable parameters for a reliable heterogeneous catalytic system. Due to this, the catalyst was recovered by simple filtration at the end of the reaction, dried under vacuum at 120 °C for 2 h and reused. This procedure was repeated at the end of each cycle, and the recovered catalyst was reused up to 5 times without any remarkable loss in its activity (Fig. 6). In addition, the stability of the catalyst was confirmed by subjecting the recovered catalyst to analytical confirmations such as FTIR, powder XRD and SEM.



Table 3 Effect of different iron sources in xanthenone (4a) synthesis^a


Entry	Iron source	Yield ^b (%)
1	—	—
2	Fe(NO ₃) ₃ ·9H ₂ O	22 ^c
3	FeCl ₃	38 ^c
4	Fe ₃ O ₄	29 ^c
5	Fe(III)acac	35 ^c
6	Fe(MIL-53)	98 ^d

^a Reaction conditions: catalyst (0.71 mmol), benzaldehyde (0.71 mmol, 1.0 eq.), dimedone (1.42 mmol, 2.0 eq.), ethanol (2.0 mL), reflux.

^b Isolated yield. ^c 24 h. ^d Catalyst (20 wt%).



Fig. 5 Hot filtration test for understanding the true heterogeneity of Fe(MIL-53) MOF (1).

The recovered catalyst was analysed by FTIR spectroscopy before the next catalytic cycle. The FTIR analysis of the reused catalyst showed that the vibrational bands are almost identical to the as-synthesised MOF without the appearance of any new peaks, even after reusing five times. In the FTIR spectrum of Fe-MIL-53 (1) (Fig. 7), the absence of strong vibrational bands in the range of 1760–1690 cm⁻¹ confirmed that the framework did not undergo any decomposition under the reaction conditions, and the carboxylate groups are still coordinated with the iron metal centre and exist as organic linkers coordinating with the secondary building units.

The observed stability results of the recovered catalyst from FTIR were further supported by the PXRD analysis. The powder XRD patterns of the recovered catalyst are identical to the fresh catalyst even after five consecutive reuses.

The presence of sharp diffraction patterns located nearly at $2\theta = 12.68^\circ$ and 25.44° (Fig. 8) indicates that the reused MOF



Fig. 6 Reusability profile of Fe(MIL-53) MOF (1) for the catalytic synthesis of xanthenone (4a).



Fig. 4 Optimisation of different MOFs as catalysts for the synthesis of xanthenone (4a). ^aReaction conditions: catalyst (20 wt%), benzaldehyde (0.71 mmol, 1.0 eq.), dimedone (1.42 mmol, 2.0 eq.), ethanol (2.0 mL), reflux. Reaction monitored by HPLC.





Scheme 1 Plausible mechanism for the Fe(MIL-53) MOF (1)-catalysed synthesis of xanthene (4a).

Table 4 Comparison of catalytic potential of Fe(MIL-53) MOF (1) in the synthesis of xanthene derivatives^a

Entry	Catalyst	Solvent	Catalyst load	Temp (°C)	Time	Yield (%)	Reusability	Ref.
1	FeCl ₃ ·6H ₂ O	[bmim][BF ₄]	0.1 mmol	80	6 h	92	5	18
2	Fe ₃ O ₄ NPs	EtOH	0.1 mmol	rt	2.45 h	82	5	33 ^c
3	Indium triflate [In(CF ₃ SO ₃) ₃]	Neat	0.02 mmol		1 h	95	5	17
4	<i>p</i> -Toluene sulfonic acid	Toluene	0.07 mmol	110	30 min	82	—	23 ^b
5	Nano-Fe ₃ O ₄ -TiO ₂ -SO ₃ H (<i>n</i> -FTSA)	Neat	0.01 g	110	50 min	90	5	27
6	Fe ₃ O ₄ @NFC@NNSM-Mn(III)	EtOH	0.5 mol%	45	10 min	98	6	28 ^c
7	Fe ₃ O ₄ @SiO ₂ @APTES@MPIB-Mn(II)	Neat	0.05 g	100	10 min	100	6	29
8	TMP-PECH-COOH polymer	Water	8 mg	50	10 min	97	6	30
9	CuCeO ₂ NPs	Water	10 mol%	80	12 min	98	5	31
10	ZrO ₂ NPs	Neat	20 mg	100	20 min	85	5	32
11	Cu(II) NPs	EtOH	0.2 g	Reflux	3.5 h	98	5	34
12	CuS quantum dots	Neat	6 mg	80	6 min	95	5	35
13	Amberlyst-15	CH ₃ CN	200 mg	Reflux	5 h	92	3	36
14	NaHSO ₄	[bmim]BF ₄	0.2 mmol	100	1 h	93	5	20
15	Fe-MIL(53)	EtOH	20 wt%	80 (reflux)	2 h	98	5	This work

^a NPs-nanoparticles, 1-*n*-butyl-3-methylimidazolium tetrafluoroborate-[bmim]BF₄. ^b *N*-tosylhydrazone. ^c carboxylic acid.

3. Conclusions

In summary, a simple, facile, economical and efficient methodology for the synthesis of xanthenes was developed using an iron-based metal-organic framework Fe(MIL-53) (1) as a sustainable heterogeneous catalyst. The presence of coordinatively unsaturated Fe³⁺ in the secondary building unit catalyses the present heterocyclic synthesis through its inherent Lewis acidic nature. This catalyst offers a straightforward

catalytic methodology to access a wide range of xanthene derivatives without any influence from the electronic nature of the substituents on aldehydes. The catalyst could be easily recovered by simple filtration and reused up to five times without any remarkable loss in its activity. The hot filtration test proved the stability and true heterogeneity of the catalyst. This Fe(MIL-53) MOF (1) replaces the homogeneous and non-reusable Lewis acid catalyst and acts as a solid-heterogeneous Lewis acid catalyst, replacing iron-salt-based catalysts. A



