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Hydration of aromatic terminal alkynes catalyzed by iron(III) sulfate hydrate under chlorine-free conditions



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ABSTRACT

The hydration of aromatic terminal alkynes performed in acetic acid in the presence of catalytic hydrate iron^{III} sulfate, $Fe_2(SO_4)_3 \cdot nH_2O$ (4–9 mol %), yields the derived aryl methyl ketones with good to excellent yields. Under comparable conditions (18 mol %, 95 °C, 24 h), bifunctional substrates were transformed into the monoacetyl or the diacetyl derivatives, depending on the structure of the aromatic diyne. The reaction is compatible with aryl substituents of different nature and ring positions, including hydroxyl, carbonyl groups, and cumulated hydrocarbons. The soft character of the non nucleophilic sulfate anion allows for activation of the triple bond toward carbon—oxygen bond formation in the Brønsted acidic medium. The proposed protocol is based on readily available and non toxic materials, in the absence of chlorine atoms in either the solvent or the metal catalyst.

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The addition of water to the triple bond allows for the transformation of alkynes into carbonyl derivatives. The process requires the use of an electrophilic catalyst for the activation of the unsaturated moiety toward the Markovnikov addition of oxygen nucleophiles with formation of a C–O bond.¹ Historically, mercuric ions in dilute acidic conditions were the promoters of choice for the synthesis of ketones from terminal and internal alkynes. Due to heavy environmental concerns, other catalysts, among which complexes of copper, silver, ruthenium, osmium, rhodium, palladium, platinum, and more recently gold, have been proposed as valid alternatives to toxic mercuric ion salts.² The transformation can also proceed in the presence of aqueous strong inorganic or organic acids without a metal catalyst,^{1,2} in which cases achieving mild reaction conditions remains a desirable goal.³ The metal catalyzed processes are often accelerated by protonic acids.

$$R \xrightarrow{} = \frac{H_2O}{cat} R \xrightarrow{} 0$$

In the search of increasingly sustainable and more affordable methodologies, iron salts have recently emerged as appropriate catalysts for the alkyne hydration process, while iron catalysis in general is witnessing a sort of renaissance in synthetic organic chemistry.⁴ After the discovery that phenylacetylene was converted into acetophenone in the presence of stoichiometric anhydrous FeCl₃ and H₂O in dichloromethane,⁵ Darcel and coworkers showed that catalytic FeCl₃ in 1,2-dichloroethane (DCE) can be used efficiently for the transformation of terminal alkynes into the corresponding methyl ketones,⁶ thus paving the way for the development of iron catalysts in this transformation. Recently, by combining FeCl₃ (10–20 mol %) with AgNTf₂ (30–60%) in dioxane, and generation in situ of catalytically active iron^{III} triflimide, Fe(NTf₂)₃, high regioselectivity was achieved in the water addition to both terminal and internal alkynes.⁷ Whereas iron^{III} salts are in general more active than iron^{II} species, FeCl₂·4H₂O in the presence of methansulfonic acid showed high reaction efficiency for the hydration of various alkynes in DCE.⁸

In this work, we have explored the reactivity of iron salts in acetic acid, a medium which provides a Brønsted acidic source other than being environmentally more benign than halogenated solvents.⁹ The use of acetic acid is common in the catalytic hydration of alkynes promoted by mercury^{1,10} and other catalytic systems,^{1,11} including a silver-catalyzed (AgBF₄) procedure recently reported.¹² In addition, phenylacetylene was transformed into acetophenone in high yield by reaction with stoichiometric amounts of both FeCl₃ and acetic acid.¹³ Starting from preliminary experiments based on FeCl₃, we wish to report that commercial iron^{III} sulfate is an efficient promoter of the hydration reaction, thus providing a simple procedure based on chlorine-free and readily available sources.

The catalytic activity of FeCl₃ (10 mol %) was tested using phenylacetylene (**1**) as the model substrate. At room temperature, formation of α -chlorostyrene as major product (**2**) and acetophenone (**3**) was observed under either nitrogen or oxygen





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$$Ph \xrightarrow{FeCl_3(10\%)}_{AcOH} Ph \xrightarrow{Fh}_{Ph} + \xrightarrow{O}_{Ph}_{Ph} Me$$

Scheme 1. Conversion of phenylacetylene in neat AcOH.

atmospheres, in the absence of added water (Scheme 1). The conversion proceeded slowly and no further changes occurred after 6 days, when the reaction mixture was composed of **1**, **2**, and **3** in relative GC percentages 53:32:10. An atmosphere of air or the addition of water inhibited the process.¹⁴ When the reaction was performed at 105 °C for 48 h, the values changed into 22:29:48 (**1:2:3**), indicating higher conversion and preferred transformation into acetophenone upon raising the temperature (Scheme 1).

The hydrochloration reaction constituted therefore a major drawback for the use of FeCl₃ in acetic acid. This competitive process yielding **2** is well documented in the addition of water to alkynes using stoichiometric or catalytic FeCl₃,^{5,6} whereas halovinyl derivatives were synthesized upon reaction of alkynes with iron^{III} halides in the presence of stoichiometric amounts of carboxylic acids.¹³

In spite of this chemoselectivity limitation, these experiments indicated that the iron-catalyzed hydration of phenylacetylene is feasable in AcOH, whereas other protic solvents which were screened in previous works proved to be unsuitable.^{5,6,7a} Therefore, we investigated the activities of other iron salts in oxidation states II and III and different ligand environments, the changes in the nature of the counteranions being specifically intended to suppress the competitive hydrochloration process. For direct comparison, the conversions were determined by GC after 24 h at 95 °C and the results are shown in Table 1. Traces or low yields of the ketone $\mathbf{3}$ were observed in the presence of iron^{II} salts (Table 1, entries 1-3), ferrous chloride being appreciably less active than FeCl₃ (Table 1, entries 1 and 5), while the catalytic activity varied largely within the series of ferric ions. Those complexes with bidentate oxygen donor ligands acetylacetonate (acac) or acetate were inactive (Table 1, entries 6 and 7), whereas the perchlorate or the nitrate salts induced extensive transformation of the alkvne. although with poor or no conversion into the desired ketone or other identifiable products (Table 1, entries 8 and 9). Remarkably, phenylacetylene was hydrated to acetophenone in the presence of iron^{III} sulfate hydrate, $Fe_2(SO_4)_3 \cdot nH_2O(I)$, with conversions larger than 80% and catalyst loadings as low as 4 mol % (8 mol % in iron). This iron salt exhibited similar activities under air or nitrogen, and in the presence of added water (Table 1, entries 10–12). Essentially full conversion is achieved using 8 mol % of I. The reactions promoted by $Fe_2(SO_4)_3 \cdot nH_2O$ proceeded in a milky gray heterogeneous mixture, with a progressive color change from neutral to orange. The use of methanol instead of acetic acid gave no evidence of the formation of acetophenone, as well as changing iron sulfate with iron phosphate (entry 14).

The activity of the catalytic system based on $Fe_2(SO_4)_3 \cdot nH_2O$ in AcOH was then investigated for different arylacetylenes. The substrates, conditions, products, and reaction yields are shown in Tables 2–4. The reaction time and yields depended largely on the nature of the aryl substituent. High conversions into ketone were observed with electron rich alkynes, such as those featuring dimethylamino or methoxy groups (Table 2, entries 1–4). In the case of 4-Me₂N—C₆H₄—C \equiv CH (**4a**), when kept in acetic acid for 24 h at 95 °C, the formation of the hydration product was observed even in the absence of the iron salt (**5a**, 57% isolated yield). These transformations can be regarded as a valid alternative to catalysis by gold complexes, as in the case of (NHC)AuBr₃ (10 mol %, NHC = *N*,*N*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) used in MeOH at reflux.¹⁵

4-Ethynylstyrene (**4e**) reacted regio-selectively at the triple bond affording 4-vinylacetophenone (**5e**). The reactivity decreased

Table 1

Hydration of phenylacetylene catalyzed by iron salts in acetic acid^a

$\frac{1}{1} \begin{array}{c} 1 \\ \frac{1}{2} \\ \frac{1}{2}$							
Entry	Salt (mol %)	Atmos	1 ^b (%)	$3^{\mathrm{b}}\left(2 ight)^{\mathrm{c}}\left(\% ight)$			
1	FeCl ₂ ·4H ₂ O (10)	Air	48	25 (11)			
2	FeS (10)	Air	23	1			
3	$FeSO_4 \cdot 7H_2O(10)$	Air	72	3			
4	FeCl ₃ (10)	N ₂	40	30 (29)			
5	FeCl ₃ (10)	Air	32	34 (32)			
6	$Fe(acac)_3$ (10)	N ₂	100	_ ` `			
7	Iron ^{III} acetate ^d (5)	Air	100	_			
8	Fe(ClO ₄) ₃ .9H ₂ O (10)	Air	_	10 ^e			
9	Fe(NO ₃) ₃ ·9H ₂ O (10)	Air	25	e			
10	$Fe_2(SO_4)_3 \cdot nH_2O(4)$	N ₂	5	84			
11	$Fe_2(SO_4)_3 \cdot nH_2O(4)$	Air	4	85			
12 ^f	$Fe_2(SO_4)_3 \cdot nH_2O(4)$	Air	7	90			
13	$Fe_2(SO_4)_3 \cdot nH_2O(8)$	Air	<1	99			
14	FePO ₄ (10)	Air	100	_			

 a Reaction conditions: $1~(300\,\mu\text{L},~2.73\,\text{mmol}),$ AcOH (10 mL), iron salt (4-10 mol %).

^b GC yield (±1%), determined by response factor vs 1,2-diphenylethane as internal standard.

^c Relative GC area %.

^d [Fe₃O(OAc)₃(H₂O)₃]OAc.

^e With formation of unidentified species.

 $^{\rm f}$ In the presence of H₂O (0.50 mL, 28 mmol).

Table 2

Hydration of arylalkynes catalyzed by iron^{III} sulfate hydrate (8 mol %) in acetic acid^a

$\overset{R}{\underset{A}{\longrightarrow}} = \underset{A \subset OH, 95 ^\circ C}{\overset{Pe_2(SO_4)_3 n H_2 O}_{SOH} \overset{R}{\underset{S}{\longrightarrow}} \overset{O}{\underset{S}{\longrightarrow}}$								
Entry	R Group	Time (h)	Ketone	Yield ^b (%)				
1	4-NMe ₂	6	5a	81				
2	4-OMe	7	5b	76				
3	2-OMe	7	5c	76				
4	3,4,5-(OMe) ₃	24	5d	75				
4	4-CH=CH ₂	24	5e	54				
5	4-Br	50	5f	70				
6 ^c	4-CF ₃	168	5g	28				

^a Reaction conditions: alkyne: 1-2 mmol (0.3–0.4 M in acetic acid), I (8 mol %), in air

^b Isolated yields, after column chromatography.

^c The reaction was performed at 120 °C.

with increasing electron-withdrawing character of the substituent, *p*-bromophenylacetylene (**4f**) requiring 50 h of reaction at 95 °C, and *p*-trifluoromethylphenylacetylene (**4g**, $\sigma_p - CF_3 = 0.53$) seven days at 120 °C for a poor conversion into methyl ketone **5g**. Along this trend, *p*-nitrophenylacetylene ($\sigma_p - NO_2 = 0.81$) gave no evidence of transformations when kept for several days at 120 °C.

The steric hindrance provided by adjacent phenyl rings in cumulated hydrocarbons did not hinder significantly the reactivity of the triple bond (Table 3). Only a modest reduction of yield was found in the transformation of the most congested 1-ethynylanthracene.

The scope of the reaction was investigated for substrates featuring hydroxyl functional groups, which may be sensitive to the acetic acid solvent and also hinder, as Lewis bases, the catalytic activity of the iron^{III} center.⁶ The reaction of the aliphatic alcohol **12** is outlined in Scheme 2.

The triple bond was hydrated with conversion comparable to that of the electron rich aromatic alkynes (overall 76% isolated yields of **13** and **14**), while the OH function was abundantly acetylated, as indicated by the signals of compound **13** at δ 2.52 (COMe) and 2.04 (OCOMe) ppm in the ¹H NMR spectrum, and

Table 3

Hydration of terminal alkynes catalyzed by iron ¹¹¹ sulfate hydrate in acetic acio	1 ^a
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 a Reaction conditions: Fe_2(SO_4)_3-nH_2O (8 mol %), 95 °C, 24 h. b Isolated yields, after column chromatography.

Table 4

Hydration of diethynyl substrates^a



^a Reaction conditions: Fe₂(SO₄)₃·*n*H₂O (I, 18 mol %), 95 °C, 24 h.

^b Isolated yields, after column chromatography.

^c Compound **25** (300 mg, 0.78 mmol), **I** (79 mg), AcOH (2.6 mL).

^d Compound **27** (160 mg, 0.37 mmol), **I** (37 mg), AcOH (1.2 mL).

the corresponding ones at δ 196.8 and 171.0 in the ¹³C NMR spectrum.¹⁶ By contrast, ethynyl phenol **15** was hydrated essentially to the corresponding ketone **16** and only to a minor extent to the bisacetylated product **17** (Scheme 3).

In the case of the propargylic alcohol 1-octyn-3-ol (**18**) treated under similar conditions (0.3 M, **I** 8 mol %, 95 °C, 24 h), the hydroxyl function was chemioselectively acetylated to afford compound **19**, $CH_3(CH_2)_4C(OCOMe)C\equiv CH$, isolated in 53% yield, with no evidence of hydration of the triple bond. The use of iron^{III} sulfate hydrate as catalyst for acetylation reactions has been previously documented.¹⁷

The catalytic system proved to be of lower efficiency for alkyl alkynes, requiring the use of more forcing conditions: 1-octyne was converted into 2-octanone in 18% yield (GC) after 5 days at 120 °C, with 10% load of the iron catalyst. However, by increasing



Scheme 2. Reaction of 2-{2-[2-(4-ethynylphenoxy) ethoxy]ethoxy}-ethanol (**12**, 0.4 M) in the presence of iron^{III} sulfate hydrate in acetic acid.

the substrate initial concentration from 0.3 to 2.0 M, the alkyne was consumed in 24 h at the same temperature and the yield of the ketone was raised to 57%.

The scope of the reaction of terminal aromatic alkynes was studied for bifunctional substrates. 1,4-Diethynlylbenzene (20) was allowed to react in the presence of $Fe_2(SO_4)_3 \cdot nH_2O$ (18 mol %) and afforded 1-(4-ethynylphenyl)ethanone (21) as the monohydrated product in 67% isolated yield (Table 4, entry 1). It is worth mentioning that the more active catalytic system based on indium^{III} trifluoromethanesulfonate and tosyl acid gave a mixture of products including 21 (29%) and 1,4-diacetylbenzene (46%).¹⁸ When the reaction was performed on 1,3-diethynlylbenzene (22) under the same conditions used for divne 20 (24 h, 95 °C), both triple bonds were hydrated to a good extent to afford the diacetyl derivative 24 along with a separable amount of the monoacetvlated product **23**. Along the same lines, the diethynyl compounds 25 and 27. featuring lipophilic alkyl chains, were transformed in excellent yields into the corresponding diacetyl derivatives **26**¹⁹ and **28**,²⁰ respectively (Table 4, entries 3 and 4). While 1,4-diacetylbenzene did not form from 20 due to the electronwithdrawing effect of the generated acetyl group of **21** in *para* position, the triple bonds at the 1,3 sites of the same ring, at the 1,4 positions of an electron rich dioctyloxybenzene moiety (25), or at the distant 2,7 positions in a fluorene skeleton (27) were both reactive. These reactions indicate the compatibility of the catalytic system with the carbonyl group.

Regarding the striking effect of the counteranions of the iron^{III} salts shown in Table 1, it is worth recalling that some of the most active mercury-based catalytic systems are those which involved the addition or generation in subscription of sulfate salts.² This is the case of the Hg^{2+}/H_2SO_4 catalysts,^{10a,21} of the sulfonated polystyrene resins,^{11a,22} or of mercury^{II} sulfate in sulfuric acid used in the industrial synthesis of acetaldeyde.²³ The switch of the iron^{III} counteranion from chloride to sulfate in the Brønsted acidic medium has provided a selective catalytic system for the hydration of terminal aromatic alkynes. This stems from the consequent elimination of the competitive hydrochloration process and from the presence of a soft low-coordinating anion in place of the hard chloride ligand. Non-nucleophilic sulfate anions can favor access of the alkyne to the metal center but also modulate the hard-soft character of the iron^{III} cation. In fact, proper interaction of the soft π -nucleophilic triple bond with the iron center, with activation toward oxygen-carbon bond formation, requires a relatively soft Lewis acidity of the metal which is favored by soft anions. A detailed description of the effect of low-coordinating ligands on the Lewisacid character of the iron^{III} center in the alkyne hydration process, and the possible role of Lewis/Brønsted co-catalysis, can be found in the article by Leyva-Pérez, Corma, and co-workers regarding the catalytic system based on Fe(NTf₂)₃ in 1,4-doxane.^{7a} Accordingly, an additional effect of $Fe_2(SO_4)_3 \cdot nH_2O$ can be that of a Lewis acid enhancing the acidity of the proton donor species in the reaction mixture, upon formation of hydrato or acetato complexes.

Since coordinated water molecules in $I (n \cong 9)$ and moisture in the medium can affect both the Lewis acid strength of the iron center, we wished to compare the efficiency of the reaction under standard conditions (hydrated salt I, glacial AcOH from the bottle, and air atmosphere) with one performed with attempted exclusion



Scheme 3. Reaction of 3-hydroxyphenylacetylene (**15**, 0.5 M) in the presence of iron^{III} sulfate hydrate in acetic acid.

of water. To this aim, a sample of the sulfate iron salt was kept at 120 °C under vacuum for 24 h, which changed the original whitish gray crystals into a pale yellow powder (II),²⁴ the resulting 19% mass reduction corresponding to an approximate loss of six water molecules from the pristine $Fe_2(SO_4)_3 \cdot nH_2O$. The reaction profiles for the hydration promoted by either salt I in air or by salt II under argon are shown in Figure 1. In the latter case, phenylacetylene was converted into the acetyl product by less than 50% after 24 h, thus indicating a marked lower activity of the 'dried' salt II. By contrast, the addition of extra water to the medium did not cause the expected full conversion of **1** into acetophenone (Table 1, entry 12). It is evident that coordinated water molecules influence the activity of the catalytic system, either by changing the Lewis acidity of the iron^{III} center, by assisting formation of intermediates as non-innocent ligands, or acting as attacking species to the activated triple bond. The key step, oxygen—carbon bond formation. may proceed by attack of H₂O, as most common in metal catalyzed hydration processes,^{1,2,5–8} and/or of AcOH. In fact, it is established that hydration reactions can proceed in organic acidic media in the absence of extra water, in which cases acetic acid under Lewis acid activation^{10b,c,25} or formic acid alone²⁶ react with the triple bond by addition and subsequent transformation of the resulting enol esters into the carbonyl products. Essentially, the organic acids act as formal water donors. The fact that vields near 80% cannot be achieved by exclusive direct addition of water to the triple bond using loadings of I of 4 mol % (almost 0.3 equiv H₂O; Table 1, entries 10, 11 and Fig. 1) supports the concurrence of an acid addition-vinyl ester hydrolysis sequence in the catalytic system formed by $Fe_2(SO_4)_3 \cdot nH_2O$ in acetic acid.

With regard to the activity of the iron sulfate hydrate catalyst in acetic acid in comparison with the previously reported iron-based systems, it is worth mentioning that FeCl₃ in DCE exhibited a similar but less pronounced electronic effect of the aryl substituents and that it is active for alkyl alkynes. By contrast, this system could not be used in the presence of coordinating hydroxyl or carbonyl groups in the substrates.⁶ The triflimide iron^{III} salt, obtained from FeCl₃ + 3AgNTf₂, works well for terminal alkyl alkynes and showed comparable efficiency to iron sulfate in the hydration of aryl



Figure 1. Conversion of phenylacetylene (2.73 mmol, \blacklozenge) into acetophenone (•), under the following conditions: (i) iron sulfate hydrate I (60 mg, 3.9 mol %), AcOH (9.1 mL), air (solid trace); or (ii) iron sulfate hydrate II (46 mg, 0.11 mmol, 3.7 mol %), AcOH (9.1 mL)/Ac₂O (20 µL), argon (dashed trace). Conversions were evaluated in the presence of 1,2-diphenylethane as internal standard.

alkynes, as for *p*-Br-phenylacetylene which was converted into **5f** (Table 2, entry 5) with 80% yield after 40 h at 80 °C in dioxane, although substrates with strongly electron-withdrawing groups were not tested. Remarkably, the system showed high efficiency and regioselectivity in the reaction of internal alkynes, either aromatic or aliphatic. FeCl₂·4H₂O catalyzes the hydration of various terminal arylalkynes, of aliphatic alkynes, of internal alkynes, and of propargylic alcohols under mild conditions (1–19 h, 60 °C), but still relies on the use of a halogenated solvent (DCE) and stoichiometric methansulfonic acid as a strong proton donor.⁸

The scope of this iron-based catalytic system for the hydration of internal alkynes is currently under investigation and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014. 01.083.

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- 16. 4- $\{2-[2-(2-Acetoxyethoxy)-ethoxy]-ethoxy\}$ acetophenone (13). ¹H NMR: $\delta = 7.91$ (d, 2H, J = 8.9 Hz), 6.93 (d, 2H, J = 9.0 Hz), 4.22 (m, 4H), 3.86 (m, 2H), 3.70 (m, 6H), 2.53 (s, 3H), 2.05 (s, 3H) ppm. ¹³C NMR: $\delta = 196.8$, 171.0, 162.6, 130.5, 130.3, 114.1, 70.7, 70.5, 69.5, 69.1, 67.5, 63.4, 26.6, 20.9 ppm. GC-MS (m/z, $M^* = 310.1$): 310 (19%), 162 (25%), 147 (15%), 121 (20%), 87 (100%), 43 (65%). FT-IR (neat, KBr): 3073, 2880, 1738, 1679, 1600, 1575, 1510, 1454, 1421, 1360, 1306, 1256, 1174, 1130, 1056, 958, 838, 594.
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- **19.** The diketone **15** is a coupling partner with dihalides in a palladium-catalyzed condensation polymerization to form polyketones Wang, D.; Wei, P.; Wu, Z. *Macromolecules* **2000**, *33*, 6896–6898.
- 20. 9,9-Bis(2'-ethylhexyl)-2,7-diacetylfluorene (**28**). Fe₂(SO₄)₃·nH₂O (**I**, 37 mg, 0.068 mmol), glacial acetic acid (1.2 mL), and 2,7-diethynyl-9,9-(di-2'-ethylhexyl)-fluorene (**27**, 0.160 g, 0.37 mmol) were introduced into a 25 mL Schlenk tube equipped with a magnetic bar and air condenser. The tube was immersed into an oil bath (95 °C) and the heterogeneous reaction mixture, slowly changing color from light yellow to bright orange, was kept under stirring for 24 h, when the TLC analysis showed consumption of the diyne. The mixture was poured into water/chloroform, extracted with chloroform, and the combined organic extracts washed with aqueous sodium bicarbonate (×2) and then water. After the addition of anhydrous sodium sulfate and filtration, the solvent was removed under vacuum and the crude oil purified by column chromatography over silica, using hexane/chloroform (8:2 to 1:1) as eluent. Removal of solvent under vacuum afforded 0.155 g of **28** (0.33 mmol, yield 88%). ¹H NMR (300 MHz, CDCl₃): δ = 8.07–7.85 (m, 4H), 7.85 and 7.82 (2 s, 2H), 2.673, 2.670 (2.667 (6H), 2.08 (d, *J* = 6 Hz, 4H), 0.9–0.6 (m, 22H), 0.52–0.36 (m, 8H). ¹³C NMR (75 MHz): δ = 197.82, 197.74, 197.66, 152.05, 152.02, 151.98,

144.6, 136.2, 127.99, 127.95, 127.91, 124.05, 123.98, 123.91, 120.5, 55.33, 44.16, 34.76, 33.70, 33.68, 28.03, 28.01, 27.04, 27.02, 26.81, 22.62, 13.88, 10.09, 10.07. FT-IR (neat on KBr): 2958, 2926, 2857, 1683, 1606, 1578, 1460, 1433, 1357, 1246, 956, 822, 755, 701, 592. Anal. Calcd for $C_{35}H_{50}O_2$: C, 83.61; H, 10.02. Found: C, 84.34; H, 10.76.

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- 24. The thermogravimetric analysis of **II** under nitrogen exhibited a 13% weight loss in the range 100–285 °C (see the Supplementary data), suggesting an approximate molecular formula Fe₂(SO₄)-3H₂O.
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