RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, 4, 4286

Received 12th October 2013
Accepted 6th November 2013

DOI: 10.1039/c3ra45772a

www.rsc.org/advances

$Fe_2(SO_4)_3 \cdot xH_2O$ on silica: an efficient and low-cost catalyst for the direct nucleophilic substitution of alcohols in solvent-free conditions†

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$Fe_2(SO_4)_3 \cdot xH_2O$ on silica has been found to be a novel efficient catalyst for the direct nucleophilic substitution of alcohols in solvent-free conditions. In this reaction system, the alcohols can react with various nucleophilic reagents for the convenient construction of C–C bonds and C–N bonds with the benefits of high conversion, no requirement to use excessive amounts of the nucleophile, only a catalytic amount of iron catalyst required, solvent-free and benign reaction conditions, and the feasible reusability of the catalyst.

Alcohols are desirable substrates for nucleophilic substitution reactions to construct C–C and C–X bonds, and the activation of the hydroxyl group is essential for related reactions.[1,2] Numerous catalysis systems have been developed for this transformation, but they often suffer from low reactivity, low selectivity, the necessary use of organic volatile solvents and an anhydrous environment, the use of excessive amounts of the nucleophile, and difficulties in reusing the catalyst.[3–10] Recently, Cozzi *et al.*[11] found that when the substitution reactions of alcohols was conducted "on water", the hydroxyl group of the alcohol was activated by the water molecules on the surface, and converted to carbocations which reacted with the corresponding nucleophiles. However, the reaction substrates are very limited due to the strong nucleophilicity of water. In our previous work,[12] we also developed an interesting catalytic system based on ionic liquids for this transformation, but the reaction system still suffered from the use of high reaction temperatures partly due to the high viscosities of the ionic liquids themselves. Therefore, there is still a great necessity to develop efficient catalytic systems which allow this transformation to proceed under benign reaction conditions.

Benefiting from its low cost, relatively non-toxic nature, distinct Lewis acid character and feasible accessibility, iron is believed to be a rising star in metal catalysis.[13,14] Here, the commercial iron salt $Fe_2(SO_4)_3 \cdot xH_2O$ supported on silica gel was found to be an efficient heterogeneous catalyst for direct nucleophilic substitution reactions of alcohols under mild conditions. This catalytic system has a wide substrate tolerance with high conversion and selectivity, even in the water environment of the iron salt and hydroxyl groups on silica, and benefits from no requirement to use excessive amounts of the nucleophile, an easy work-up and the feasible reusability of the catalyst. The possible mechanism for the excellent performance of this catalytic system has also been proposed in this work.

The performances of different catalytic systems based on $Fe_2(SO_4)_3 \cdot xH_2O$ was studied using the reaction between benzoylacetone **1a** and benzhydryl alcohol **2a** as a model and the results are collected in Table 1. It was found that when this reaction was conducted in traditional solvents such as CH_2Cl_2 and CH_3NO_2 at room temperature or under reflux conditions, the reaction was sluggish and the target compounds were poorly obtained even after 5 hours. When the reaction was conducted in water at room temperature, the reaction did not proceed, but under reflux conditions, the target compound was produced in 10% yield after 5 hours, suggesting that water is not strictly forbidden in this reaction when catalysed with $Fe_2(SO_4)_3 \cdot xH_2O$. It is well known that silica gel has a high adsorptive ability and the hydroxyl groups together with adsorbed water on its surface can form local hydrophilic centers. This has found interesting applications in organic synthesis recently.[15,16] Interestingly, in this work, we found that when the iron salt $Fe_2(SO_4)_3 \cdot xH_2O$ was supported on silica, which has no obvious catalytic activity by itself (entry 11, Table 1), the yield of the target compound was significantly increased. Additionally, when the reaction was conducted at a temperature of 75 °C, the target compound was almost quantitatively isolated within 0.5 hours (entry 10, Table 1).

The high catalytic activity of $Fe_2(SO_4)_3 \cdot xH_2O$ supported on silica for the model reaction encouraged us to investigated the substrate scope of this method for the direct nucleophilic substitution of alcohols. The successful results are collected in

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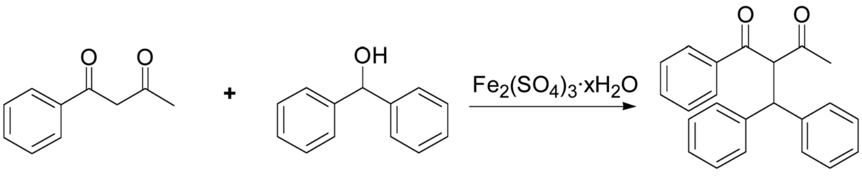
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra45772a

Table 1 $Fe_2(SO_4)_3 \cdot xH_2O$ catalyzed direct nucleophilic substitution reactions of benzhydryl alcohol



Entry[a]	Solvent or medium	Temperature (°C)	Time (h)	Isolated yield (%)
1	CH_2Cl_2	25	5	0
2	CH_2Cl_2	Reflux	5	0
3	CH_3NO_2	25	5	30
4	CH_3NO_2	Reflux	5	55
5	H_2O	25	5	0
6	H_2O	Reflux	5	10
7	Silica[b]	r.t.	5	10
8	Silica[b]	35	0.5	41
9	Silica[b]	55	0.5	89
10	Silica[b]	75	0.5	98
11[c]	Silica[b]	75	0.5	Trace

[a] **1a** (0.25 mmol), **2a** (0.25 mmol) and $Fe_2(SO_4)_3 \cdot xH_2O$ (12.5 mg, 0.025 mmol) in 5 mL of solvent were stirred at a certain temperature. [b] 200 mg silica gel was used as the reaction medium. [c] In the absence of $Fe_2(SO_4)_3 \cdot xH_2O$.

Table 2. It was found that, besides benzoylacetone **1a**, 1,3-dicarbonyl compounds such as acetylacetone **1b** and ethyl acetoacetate **1c** could also react with benzhydryl alcohol **2a** smoothly and gave excellent isolated yields within 0.5 hours (Table 2, entry 1–3). *N*-Nucleophiles such as nitroaniline **1d**, sulfonamide **1e**, amide **1f**, and 2,4-DNPH **1g** also reacted smoothly with a stoichiometric amount of the alcohol to give the *N*-alkylation products with good to excellent yields in 0.5–1 hour (Table 2, entry 4–7). The scope of this reaction with respect to the alcohol substrates was also examined (Table 2, entry 8–15). It was shown that the benzhydryl alcohol with chlorine substituents **2b** could react with the dicarbonyl compound **1a** and nitroaniline **1d** smoothly to give almost quantitative isolated yields (Table 2, entries 8 and 9). The benzhydryl alcohol with strong withdrawing substituents **2c** could react with nitroaniline **1d** at room temperature to give a quantitative isolated yield in 1 hour (Table 2, entry 10). Benzylic alcohols **2d–2f** could react with sulfonamide **1e** smoothly to give excellent yields under mild conditions (Table 2, entries 11–13). Allyl alcohol **2g** was also found to be a suitable substrate for this direct nucleophilic substitution reaction using this catalytic system, and gave the desired product in 93% yield within 0.5 hours (Table 2, entry 14). Moreover, primary alcohol **2h** could react effectively with **1a** to give product **3o** in 92% yield (Table 2, entry 15).

Additional experiments were designed to illustrate the role of $Fe_2(SO_4)_3 \cdot xH_2O$–silica on the promotion of the reaction procedure. Bis(4-methoxyphenyl)methanol **2c** was selected as a model, which could produce a red bis(4-methoxyphenyl) methyl cation **4**[+] (Fig. 1). By comparing photographs (a), (b) and (c) in Fig. 1, it can be concluded that $Fe_2(SO_4)_3 \cdot xH_2O$–silica promotes bis(4-methoxyphenyl)methanol to efficiently produce the bis(4-methoxyphenyl)methyl cation. The resulting mixture of $Fe_2(SO_4)_3 \cdot xH_2O$–silica and the bis(4-methoxyphenyl)methyl cation could keep the red colour for over 1 hour in an air atmosphere, which implied that $Fe_2(SO_4)_3 \cdot xH_2O$–silica can stabilize the active bis(4-methoxyphenyl)methyl cation. However, when a drop of ethyl acetate was added into this mixture, the red colour disappeared immediately, which indicated that organic solvent destabilized the bis(4-methoxyphenyl)methyl cation (photograph (d) in Fig. 1).

Based on the above experiments, a plausible reaction mechanism based on the model reaction is proposed, as illustrated in Fig 2. Water from $Fe_2(SO_4)_3 \cdot xH_2O$ or from the atmosphere is adsorbed on the surface of the silica gel, and forms hydrogen bonds with the surface hydroxyl groups of the silica, producing hydrophilic cores. The hydroxyl group of a benzhydryl alcohol molecule is attracted to a hydrophilic core through the formation of a hydrogen bond with the hydroxyl group of silica or the adsorbed water. It is then activated to its carbocation catalysed by the Lewis acid $Fe_2(SO_4)_3 \cdot xH_2O$. The formed carbocation, which is hydrophobic, then leaves the hydrophilic core and is attacked by a benzoylacetone molecule to form the target compound.

Furthermore, the reusability of this catalytic system for direct nucleophilic substitution reactions was also investigated from the point of green chemistry. The results are collected in Table 3. It was found that the supported iron salt, $Fe_2(SO_4)_3 \cdot xH_2O$, could be reused without any significant decrease in the catalytic activity. The 'cross reuse' experiment showed that the recovered catalyst could be reused for different

Table 2 Direct nucleophilic substitution reactions of alcohols with *N*-nucleophiles and *C*-nucleophiles catalyzed by $Fe_2(SO_4)_3 \cdot xH_2O$ on silica

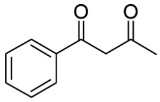
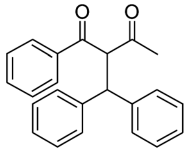
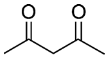
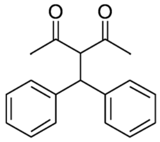
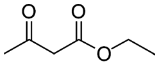
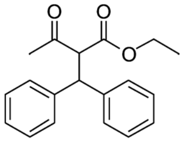
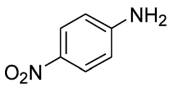
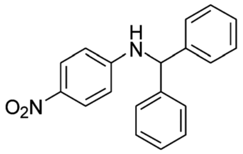
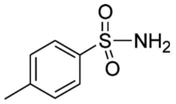
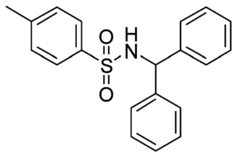
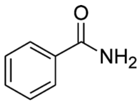
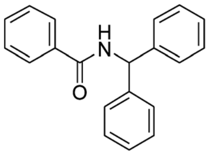
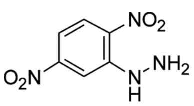
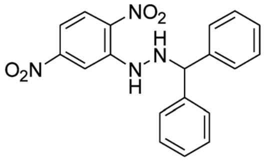
Entry[a]	Nucleophiles	Alcohol	Products	Temperature (°C)	Time (h)	Isolated Yield (%)
1	 **1a**	**2a**	 **3a**	75	0.5	98
2	 **1b**	**2a**	 **3b**	75	0.5	89
3	 **1c**	**2a**	 **3c**	75	0.5	90
4	 **1d**	**2a**	 **3d**	75	0.5	95
5	 **1e**	**2a**	 **3e**	75	0.5	92
6	 **1f**	**2a**	 **3f**	75	1	85
7	 **1g**	**2a**	 **3g**	75	0.5	81

Table 2 (*Contd.*)

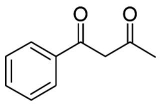
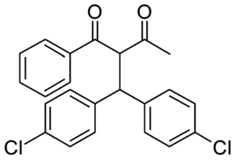
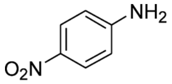
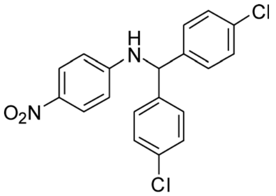
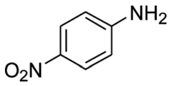
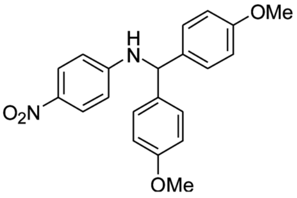
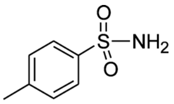
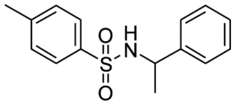
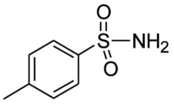
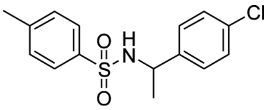
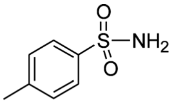
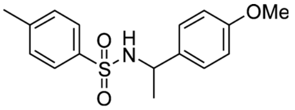
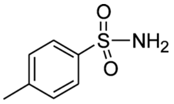
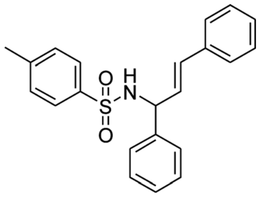
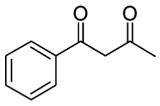
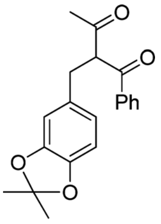
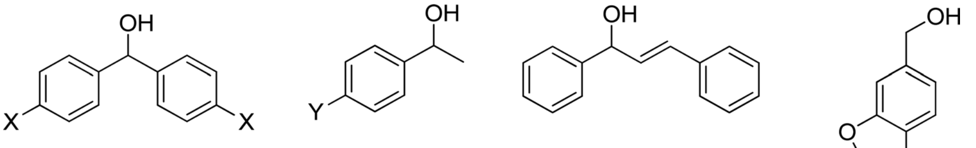
Entry[a]	Nucleophiles	Alcohol	Products	Temperature (°C)	Time (h)	Isolated Yield (%)
8	 **1a**	**2b**	 **3h**	75	0.5	97
9	 **1d**	**2b**	 **3i**	75	0.5	96
10	 **1d**	**2c**	 **3j**	r.t.	1	95
11	 **1e**	**2d**	 **3k**	75	0.5	90
12	 **1e**	**2e**	 **3l**	75	0.5	89
13	 **1e**	**2f**	 **3m**	r.t.	1	91
14	 **1e**	**2g**	 **3n**	75	0.5	93

Table 2 (*Contd.*)

Entry[a]	Nucleophiles	Alcohol	Products	Temperature (°C)	Time (h)	Isolated Yield (%)
15	 **1a**	**2h**	 **3o**	75	1	92

[a] *Reaction conditions*: **1** (0.25 mmol), **2** (0.25 mmol), $Fe_2(SO_4)_3 \cdot xH_2O$ (12.5 mg, 0.025 mmol), and silica gel (200 mg) were stirred under certain temperature.



2a : X = H
2b: X = Cl
2c: X = OMe

2d: Y = H
2e: Y = Cl
2f: Y = OMe

2g

2h

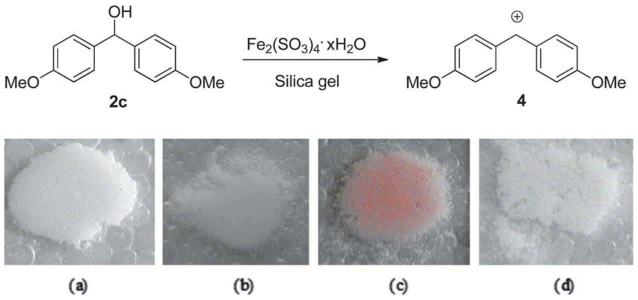


Fig. 1 (a) Mixture of the silica gel and **2c**; (b) mixture of $Fe_2(SO_4)_3 \cdot xH_2O$ on silica; (c) mixture of the $Fe_2(SO_4)_3 \cdot xH_2O$–silica gel and **2c**; (d) mixture of the $Fe_2(SO_4)_3 \cdot xH_2O$–silica gel and **2c** after adding ethyl acetate.

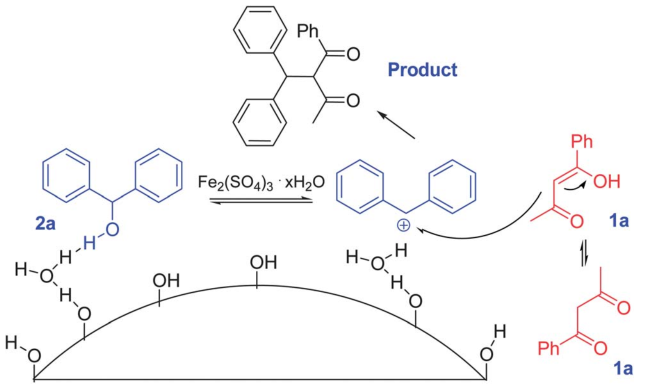


Fig. 2 A plausible reaction mechanism for $Fe_2(SO_4)_3 \cdot xH_2O$ on silica catalyzed direct nucleophilic substitution reactions of alcohols.

nucleophiles and alcohols with almost equivalent catalytic performances compared to using the fresh catalyst, suggesting its superior reusability.

In conclusion, this work has developed an efficient catalyst system based on $Fe_2(SO_4)_3 \cdot xH_2O$ on silica for direct nucleophilic substitution reactions of alcohols. The high conversion and selectivity, wide substrate tolerance, low cost of the catalyst, simple experimental process, solvent-free and benign reaction conditions, and reusability of the catalyst make this method attractive as a green chemistry process. Additionally, the plausible reaction mechanism may give some insight into the construction of novel alcohol activation systems.

Table 3 The reusability of $Fe_2(SO_4)_3 \cdot xH_2O$ on silica for direct nucleophilic substitution reactions of alcohols

Run[a]	NuH	Alcohol	Product	Time	Isolated yield (%)
1	1a	**2a**	**3a**	0.5	98
2	1a	**2a**	**3a**	0.5	95
3	1a	**2a**	**3a**	0.5	95
4	1a	**2b**	**3h**	0.5	96
5	1d	**2a**	**3d**	0.5	95

[a] All the reactions were conducted with the recovered $Fe_2(SO_4)_3 \cdot xH_2O$ on silica under 75 °C.

Experiment section

General

All of the alcohols, 1,3-dicarbonyl compounds, amide, sulfonamide and 2,4-DNPH were purchased from Aldrich, Alfa Aesar and Fluka and were used as received. Hydrated ferric sulfate of A. R. grade was purchased from Beijing Chemical Factory, and the content of Fe(III) was 21–23% (w/w). Melting points were measured using a XRC-1 Microscopic Melting Point Measurer (Sichuan University Instrument Factory) without correction. ^{1}H-NMR spectra were recorded on a BRUKER AV-400 instrument at room temperature. Chemical shifts (δ) are expressed in ppm downfield from the internal standard tetramethylsilane and coupling constants (J) are given in Hz. Mass spectra were obtained on either a VG-ZAB-HS or a Bruker APEX. High-resolution MS were performed using a Bruker BIFLEX III. An alternative procedure to prepare iron sulfate on silica is as follows: 1.25 g of $Fe_2(SO_4)_3 \cdot xH_2O$ and 20 g of silica were stirred in 10 mL of methanol at room temperature for 24 hours. Then the solvent was evaporated under reduced pressure. The resulting iron sulfate on silica was heated at 75 °C for 2 hours, and then cooled to room temperature.

Typical procedure for the $Fe_2(SO_4)_3 \cdot xH_2O$ on silica catalyzed direct nucleophilic substitution of alcohols

A mixture of alcohol **1a** (46 mg, 0.25 mmol), nucleophile **2a** (41 mg, 0.25 mmol), $Fe_2(SO_4)_3 \cdot xH_2O$ (12.5 mg, 0.025 mmol) and silica gel (200 mg, surface area = 200–300 m^2 g^{-1}, and pore size = 50–70 μm) was ground at room temperature or at 75 °C. After completion of the reaction, as indicated by TLC, the $Fe_2(SO_4)_3 \cdot xH_2O$ and silica gel were filtered off using EtOAc. The $Fe_2(SO_4)_3 \cdot xH_2O$ and silica gel obtained by drying the filtrate could be reused for another run. Evaporation of the solvent gave the corresponding product **3a**.

Yield: 98%. White solid, m.p. 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, J = 8 Hz, 2H), 7.77–7.03 (m, 13H), 5.62 (d, J = 12 Hz, 1H), 5.10 (d, J = 12 Hz, 1H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.3, 193.1, 140.6, 140.2, 136.1, 132.5, 128.2, 128.0, 127.9, 127.3, 126.9, 126.6, 125.9, 68.2, 50.1, 27.1. MS (ESI): m/z 328.1.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant 20903037, 21172058), and the Research Fund for the Doctoral Program of Higher Education of China (20094104120003).

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