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Superparamagnetic iron oxide as an efficient catalyst for the one-pot, solvent-free synthesis of α-aminonitriles

Mohammad M. Mojtahedi *, M. Saeed Abaee *, Tooba Alishiri

Chemistry and Chemical Engineering Research Center of Iran, Pajouhesh Blvd, 17th Km Tehran-Karaj Highway, PO Box 14335-186, Tehran, Iran

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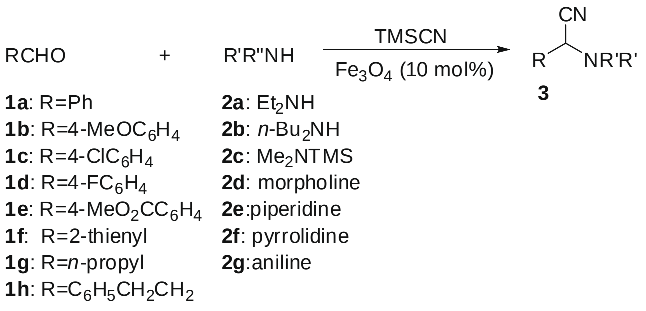
ABSTRACT

Superparamagnetic Fe_3O_4 is shown to act as a very efficient catalyst for the one-pot, three-component synthesis of α-aminonitriles from aldehydes, amines, and TMSCN. The catalyst is easily recovered by the use of an external magnet and reused in several reactions without any noticeable loss of activity. The products are obtained rapidly at room temperature in good purity upon separation of the catalyst and evaporation of the volatiles of the reaction mixture.

Lewis acid-catalyzed reactions allow smooth transformation of various functional groups in modern synthetic organic chemistry.[1,2] However, there are limitations associated with the use of conventional homogeneous Lewis acids. For example, work-up usually results in complete decomposition of the catalyst and in addition, the resulting inorganic salts are usually harmful to the environment. To avoid these drawbacks, heterogeneous catalytic systems have been used extensively in recent years in various synthetic transformations.[3–7] Mild reaction conditions, straightforward experimental procedures, minimal waste disposal, and reusability of catalysts are advantages of heterogeneous systems. In this context, magnetic particles have emerged as a useful group of heterogeneous catalysts due to their numerous applications in nanocatalysis,[8,9] biotechnology,[10,11] and medicine.[12,13] Additionally, the magnetic property of such particles provides the opportunity for quantitative recovery of the catalyst by the use of an external magnetic field.[14–16]

We recently presented an efficient protocol for the rapid room temperature protection of alcohols and phenols with HMDS using superparamagnetic Fe_3O_4 particles.[17] After separation of the catalyst using an external magnet, the silyl ether products were easily obtained in good purity by evaporation of the volatiles. No additive or co-catalyst, and no solvent during the reaction or work-up were required. The ease of accessibility of the catalyst at low cost along with its full recovery upon completion of the reactions and the chemoselectivity of the process are advantages of this method. This has encouraged us to study other organic functional group transformations. In this Letter, we report the three-component Strecker reaction of an aldehyde, an amine, and a 'cyanide' (Scheme 1).[18,19] Although this important carbon–carbon bond forming reaction has witnessed much recent progress,[20–24] there are still demands for the development of efficient procedures involving inexpensive, recyclable catalytic systems under solvent-free conditions.

Table 1 summarizes the results of the Fe_3O_4-catalyzed reaction of TMSCN with various aldehydes and amines. Initial experiments were carried out under solvent-free conditions involving the reaction of benzaldehyde, Et_2NH, and TMSCN at room temperature catalyzed by Fe_3O_4 (Table 1).[25,26] Complete disappearance of the aldehyde and rapid formation of the product were monitored by TLC. The use of various amounts of the Lewis acid was investigated to optimize the reaction conditions. A catalytic quantity of Fe_3O_4 (10 mol %) proved to be effective for complete conversion of the starting materials to the desired product **3aa** within 20 min (entry 1). The use of lower amounts of the catalyst (down to 2 mol %) prolonged the reaction time up to 2 h whilst still giving an almost quantitative yield of **3aa**. Omission of Fe_3O_4 from the reaction medium led to formation of only trace quantities of **3aa** after several hours indicating the crucial role of the catalyst. Similar reactions of benzaldehyde with other acyclic (entries 2 and 3), cyclic (entries 4 and 5), and aromatic amines (entry 6) were conducted under the same conditions affording high yields of the respective



Scheme 1.

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* Corresponding authors. Tel.: +98 21 44580720; fax: +98 21 44580762 (M.M.M.).
E-mail addresses: mojtahedi@ccerci.ac.ir (M.M. Mojtahedi), abaee@ccerci.ac.ir (M. Saeed Abaee).

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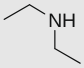
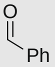
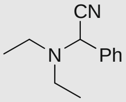
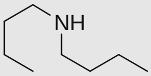
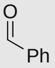
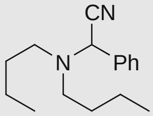
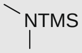
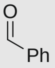
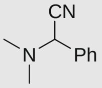
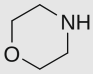
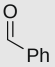
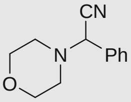
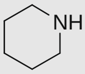
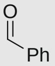
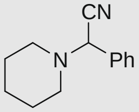
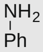
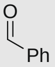
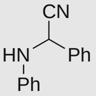
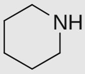
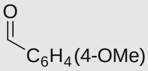
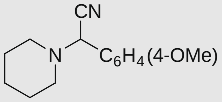
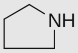
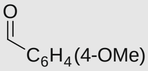
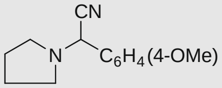
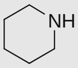
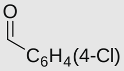
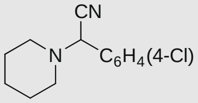
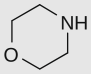
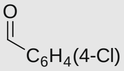
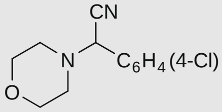
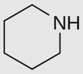
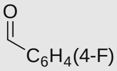
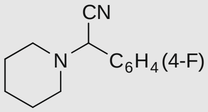
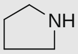
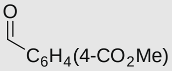
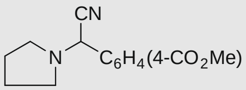
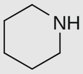
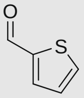
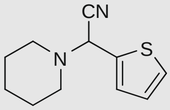
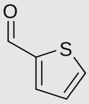
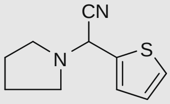
Table 1
Strecker reaction of TMSCN and various aldehydes and amines catalyzed by Fe_3O_4

Entry	Amine	Aldehyde	Product		Yield[a] (%)
1				**3aa**	89[20]
2				**3ab**	95[20]
3				**3ac**	93[20]
4				**3ad**	95[27]
5				**3ae**	90[28]
6				**3ag**	95[27]
7				**3be**	89[20]
8				**3bf**	90[20]
9				**3ce**	93[20]
10				**3 cd**	87[20]
11				**3de**	94[20]
12				**3ef**	92[20]
13				**3fe**	90[21]
14				**3ff**	86[21]

[a] Isolated yields.

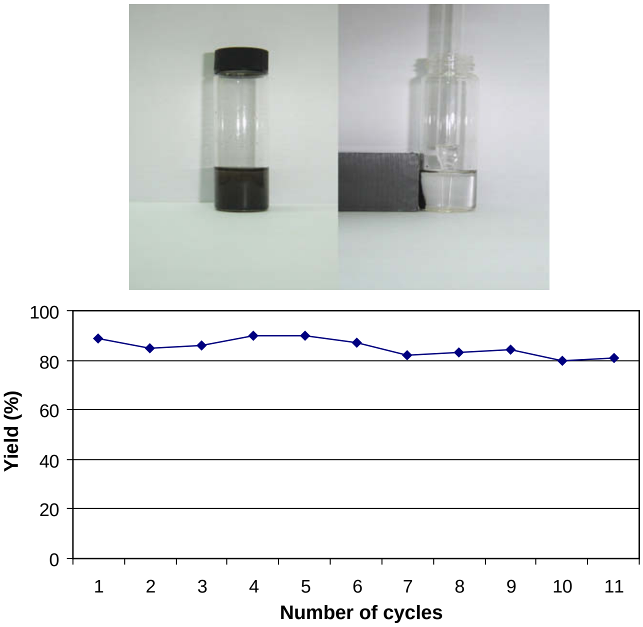


Figure 1. A typical reaction mixture in the presence or absence of a magnetic field (top). Efficient recovery of the catalyst (bottom).

products within the same time period. Other aromatic aldehydes bearing electron-withdrawing groups and electron-releasing groups reacted equally well with various amines under the same conditions (entries 7–14).

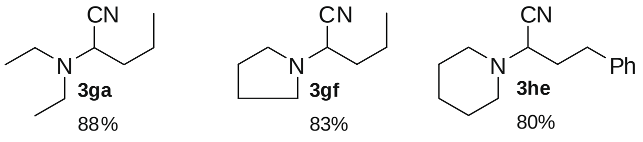
Upon completion of the reactions, the catalyst was recovered from the reaction mixture simply by applying an external permanent magnet as shown in Figure 1 (top) and the products were isolated in good purity by removing the volatiles under reduced pressure. Further, the recovered Fe_3O_4 was reused successfully in 10 subsequent reactions without significant loss of catalytic performance as illustrated in Figure 1 (bottom).

A flame atomic absorption spectroscopy (FAAS) experiment was designed to study the stability of the Fe_3O_4 catalyst during the reaction and the recycling process. Consequently, when a reaction mixture filtrate was subjected to FAAS analysis, only 0.6 ppm Fe was detected in the mixture which is equal to 0.1% of the starting Fe_3O_4 used for catalysis. This illustrates that Fe_3O_4 initiates a heterogeneous catalytic cycle and does not undergo degradation during the reactions allowing its successful reuse.

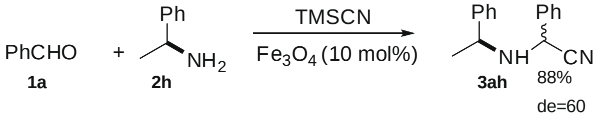
In the next step, the procedure was further explored by smooth conversion of the aliphatic aldehydes butyraldehyde or 3-phenylpropionaldehyde into their corresponding α-aminonitriles **3ga**,[20] **3gf**,[31] and **3he**,[20] respectively, in high yields (Scheme 2).

Finally, the diastereoselectivity of the process was examined for the reaction between (*S*)-1-phenylethylamine **2h** and benzaldehyde **1a**. Under the above conditions, formation of **3ah**[24] was observed in 83% yield within 20 min. The ^{1}H NMR spectrum of the reaction mixture revealed the formation of both possible products with moderate 4:1 diastereoselectivity (Scheme 3).

In conclusion, an efficient protocol for the rapid room temperature Strecker reaction using Fe_3O_4 as an inexpensive and easily accessible catalyst is presented. After separation of the catalyst with an external magnet, the reaction products are easily obtained in good purity by evaporation of the volatiles. A comparison of the performance of the present catalyst for the Strecker reaction with some other recent reports[27–31] on the condensation of benzaldehyde with aniline and TMSCN is shown in Table 2.



Scheme 2.



Scheme 3.

Table 2
Fe_3O_4-catalyzed Strecker reaction of benzaldehyde, aniline, and TMSCN in comparison with other methods

Catalyst	Solvent	Yield (%)	Reference
Fe_3O_4	–	95	Present work
RhI_3	CH_3CN	95	Majhi et al.[30]
InI_3	Et_2O	95	Shen et al.[27]
Montmorillonite	CH_2Cl_2	90	Yadav et al.[29]
Silica sulfuric acid	CH_2Cl_2	88	Chen et al.[28]
$NiCl_2$	CH_3CN	92	De et al.[31]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.199.

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26. *Typical procedure*: *Caution*! TMSCN is very toxic and could produce hydrogen cyanide in contact with water. All operations should be performed with special care under a well-ventilated fume hood. A mixture of aldehyde (4 mmol), amine (8 mmol), and Fe_3O_4 (10 mol % with respect to aldehyde) was stirred at

room temperature for 1 min. TMSCN (4.8 mmol) was added to this mixture and stirring was continued for another 15–20 min when TLC showed completion of the reaction. A conventional permanent magnet (dimensions: 8 mm × 25 mm × 40 mm) was applied externally to the outside of the reaction tube to separate the solid catalyst from the solution. The products were obtained by evaporation of the volatiles under reduced pressure and residues were purified by column chromatography, when necessary. All products are known compounds. The identity of the products was confirmed by comparison of their spectroscopic data with literature data. The isolated yields of the products were 80–95%.

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