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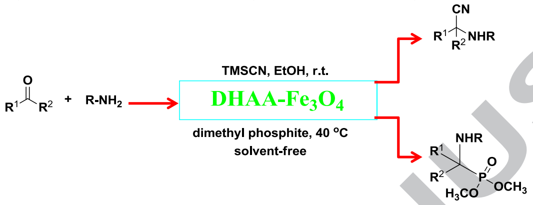

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ABSTRACT

A dehydroascorbic acid capped magnetite (DHAA-Fe_3O_4) catalyst is prepared and used for the one-pot synthesis of α-aminonitriles and α-aminophosphonates. Different derivatives of these compounds are synthesized in good yields.

Nitrogen-containing compounds such as amines, α-aminonitriles, α-aminophosphonates, etc., are very common substrates in organic synthesis. α-Aminonitriles constitute a class of compounds some of which display anticancer, antibacterial, antifungal and antiviral activities.[1] They also serve as efficient precursors for the synthesis of natural and unnatural α-amino acids.[2] α-Aminophosphonic acids act as antibiotics,[3] herbicides,[4] pharmacological agents[5] and enzyme inhibitors.[6] Owing to their widespread applications, the synthesis of these compounds has gained a great deal of attention. Among all the procedures leading to these compounds, three-component condensation reactions are very attractive. In this context, the addition of nucleophiles to *in situ* generated C=N bonds has emerged as an extremely useful tool for the synthesis of such nitrogen-containing molecules. Two renowned approaches in this field are the Strecker reaction[7] and Kabachnik–Fields reaction.[8] In the former, condensation of a carbonyl compound (generally an aldehyde), an amine and a cyanide ion source leads to the direct one-pot synthesis of α-aminonitriles. In the latter, which is the most frequently used for the synthesis of α-aminophosphonates, an amine, an aldehyde and a di- or tri-alkyl phosphite react in a one-pot fashion in the presence of either a Lewis acid or a Brønsted acid. As is common for classical Strecker reactions, an aqueous solution of KCN is used as the cyanide source which poses difficulties, especially in the work-up stage. Thus a number of alternative cyanide sources have been introduced to overcome problems associated with using KCN.[9] Among these, trimethylsilyl cyanide (TMSCN) was found to be a promising choice, due to its nature as an effective, easily-handled, and relatively safe cyanation reagent.[10] It is noteworthy that TMSCN is able to transfer the cyanide ion only in the presence of a catalyst. Hence, different types of catalysts have been developed including various Lewis and Brønsted acids such as $Yb(OTf)_3$,[11a] $Cu(OTf)_2$,[11b] $BiCl_3$,[11c] $RuCl_3$,[11d] $Sc(OTf)_3$,[11e] K_2PdCl_4,[11f] $GdCl_3.6H_2O$,[11g] InI_3,[11h] $CeCl_3$,[11i] $ZrCl_4$[11j] $K_4[Fe(CN)_6]$[11k] and *p*-toluenesulfonic acid,[11l] which catalyze homogeneously the Strecker reaction. Incidentally, several heterogeneous catalysts have also been proposed, which are more advantageous in terms of catalyst/product separation.[12] Similarly, diverse catalytic systems for the synthesis of α-aminophosphonates have been reported,[13] but most of them suffer from at least one of the following disadvantages: harsh reaction conditions, air sensitivity, the use of stoichiometric, toxic and relatively expensive reagents or catalysts, poor product yields, long reaction times and tedious separation procedures. To compensate for these deficiencies, numerous endeavors have been made giving rise to satisfactory results in terms of efficiency and rate of the reaction, but still two major problems remained. Firstly, the presence of a metal (free or complex) as the catalyst, hence posing environmental problems and as an impurity in the final product. Secondly, the matter of recycling and reusability of the catalyst. Other shortcomings include the low selectivity of most of the catalysts. Thus, green, selective and metal-free catalytic systems, which can be easily recycled are still required for these reactions.

The emergence of organocatalysts has interested chemists by virtue of them often being waste-free, environmentally benign, easily-handled, and highly efficient.[14] Nevertheless, developing such catalysts is a challenging issue.

Herein, we introduce Vitamin C (in its oxidized form, DHAA) as a green and biocompatible organocatalyst which can promote the three-component coupling reactions of aldehydes (ketones), amines (both primary and secondary), and TMSCN or dimethyl phosphite to afford of α-aminonitriles and α-aminophosphonates. To avoid problems arising during separation of the catalyst from the reaction medium, and also to facilitate the purification process, DHAA is mounted on magnetite nanoparticles. In this way, a reusable magnetic organocatalyst is formed, which is easily separated from the reaction medium simply by applying an external magnet.

DHAA-capped magnetite nanoparticles (DHAA-Fe_3O_4) were synthesized according to a previously reported procedure.[15] Briefly, a 0.1 M $Fe(OH)_3$ colloidal solution was prepared by adding 10 mL of $FeCl_3.6H_2O$ aqueous solution to 20 mL of a 0.45 M $NaHCO_3$ solution, and the obtained solution stirred for 30 minutes. Subsequently, 10 mL of an aqueous solution of vitamin C in a molar ratio of 1:6 was added gradually to the Fe^{3+}. The mixture was stirred for another 10 minutes and then transferred into a steel-lined Teflon autoclave to a volume of 50 mL and the autoclave kept at 150 °C for 4 hours. The particles were washed three times with water and ethanol and then collected by centrifugation (0.42 mmol DHAA/g catalyst). It is worth mentioning that in this synthetic process, not only does vitamin C act as the reducing agent by its C=C bond being oxidized, but also its oxidation product (dehydroascorbic acid, DHAA) serves as a stabilizer and capping ligand due to the interactions of its carbonyl groups with FeO_x particles.[15]

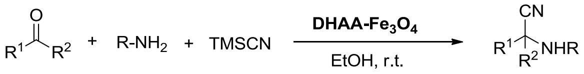
To assess the efficacy of the synthesized catalyst, the one-pot reaction between benzaldehyde, aniline and TMSCN was carried out in the presence of vitamin C (17.6 mg, 10 mol%), in EtOH as the solvent, at room temperature, which gave rise to approximately 20% conversion after 3 hours. Much to our surprise, when DHAA-Fe_3O_4 (20 mg, 0.9 mol% DHAA) was used as the catalyst, the reaction went to completion in 15 minutes and 90% of the product was isolated. To investigate the role of Fe_3O_4 as a catalyst, the same reaction was performed in the presence of Fe_3O_4 (23 mg, 10 mol%), which resulted in a 90% yield after 150 minutes. Next, the effects of the solvent and catalyst loading were investigated (Table 1). The best results were obtained when the reaction was conducted in EtOH with 20 mg of the catalyst.

Table 1: The effect of the solvent and catalyst loading on the Strecker reaction[a]

Entry	Solvent	Amount of Cat. (mg)	Time (min)	Yield (%)[b]
1	**EtOH**	**20**	**15**	**90**
2	CH_2Cl_2	20	60	68
3	CH_3CN	20	60	80
4	H_2O	20	60	70
5	DMSO	20	60	75
6	toluene	20	60	50
7	THF	20	60	60
8	EtOH	10	15	70
9	EtOH	25	15	90

[a]Reaction conditions: benzaldehyde (1 mmol), aniline (1.2 mmol), TMSCN (1.2 mmol), room temperature. [b]Isolated yield.

Having established optimum conditions, a series of α-aminonitriles was synthesized by reacting various aldehydes or ketones and amines with TMSCN in the presence of DHAA-Fe_3O_4 in EtOH in order to showcase the broad scope and generality of this method (Scheme 1).



Scheme 1: Strecker reaction in the presence of the DHAA-Fe_3O_4 catalyst

Irrespective of the aldehyde used, the reaction proceeded to furnish the corresponding product with varying degrees of success (Table 2). Substituted aromatic aldehydes provided good results. Acid-sensitive heterocycles such as furfural and an unsaturated aldehyde such as cinnamaldehyde, produced excellent yields, without any decomposition or polymerization (Table 2, entries 4 and 7). Aliphatic aldehydes were also used, which afforded very good yields under these conditions (Table 2, entries 5 and 6). The cyclic amine, morpholine, gave a high yield of product in a short time (Table 2, entry 15).

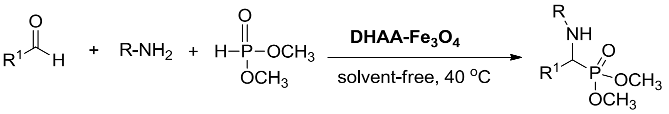
Table 2: Strecker reaction of various aldehydes or ketones and amines in the presence of DHAA-Fe_3O_4 as the catalyst [a]

Entry	R	R^1	R^2	Time (min)	Yield (%)[b]	Ref.
1	Ph	Ph	H	15	90	11g
2	Ph	4-Me-C_6H_4	H	45	80	12b
3	Ph	4-MeO-C_6H_4	H	30	92	12b
4	Ph	PhCH=CH	H	80	78	11i
5	Ph	C_3H_7	H	30	83	13h
6	Ph	^{i}Pr	H	60	75	11g
7	Ph	furan-2-yl	H	100	82	11d
8	Ph	cyclohexyl	H	100	85	16
9	Ph	$R^1,R^2= (CH_2)_5$		60	90	11k
10	4-Me-C_6H_4	Ph	H	45	83	11f
11	4-MeO-C_6H_4	Ph	H	30	90	16
12	4-Br-C_6H_4	Ph	H	180	80	11f
13	4-I-C_6H_4	Ph	H	180	78	-
14	4-O_2N-C_6H_4	Ph	H	180	<10[c]	17
15	RNH_2 = $O(CH_2CH_2)_2NH$	Ph	H	60	85	11c
16	Ph	Ph	Me	180	trace	11k

[a]Reaction conditions: aldehyde or ketone (1 mmol), amine (1.2 mmol), TMSCN (1.2 mmol), catalyst (20 mg), room temperature.[18] [b]Isolated yield. [c]Conversion

In the case of 4-nitroaniline, due to its low nucleophilicity, only 10 mol% of the starting material was converted into the corresponding product after 3 hours (Table 2, entry 14). By applying these conditions to cyclohexanone, a 90% yield of the corresponding product was obtained (Table 2, entry 9). In contrast, in the case of acetophenone the progress of the reaction was negligible (Table 2, entry 16).

As a second target, we explored the effectiveness of DHAA-Fe_3O_4 as a reusable catalyst for the generation of α-aminophosphonates (Scheme 2).



Scheme 2: Kabachnik–Fields reaction in the presence of the DHAA-Fe_3O_4 catalyst.

The reaction between dimethyl phosphite and the *in situ* generated imine from benzaldehyde and aniline was chosen as a model system. Having screened parameters such as solvent, temperature and amount of catalyst loading (Table 3), the following conditions offered the maximum yield of product: aldehyde (1 mmol), amine (1 mmol), dimethyl phosphite (1 mmol), catalyst (20 mg), 40 °C, and solvent-free conditions.

Several α-aminophosphonates were prepared (Table 4). Simple aldehydes and acid-sensitive aldehydes such as thiophene-2-carbaldehyde and cinnamaldehyde underwent the reaction with aniline and dimethyl phosphite to produce the corresponding α-aminophosphonates. Several other aniline derivatives were coupled with benzaldehyde and dimethyl phosphite to give good yields of the desired products. Cyclohexanone also underwent this one-pot reaction with aniline and dimethyl phosphite to give the desired product in good yield (Table 4, entry 10).

Table 3: Optimization of the reaction conditions for the Kabachnik–Fields reaction catalyzed by DHAA-Fe_3O_4[a]

Entry	Temp.	Solvent	Catalyst (mg)	Time (h)	Yield (%)[b]
1	40	EtOH	20	3.5	40
2	40	CH_2Cl_2	20	3.5	60
3	40	H_2O	20	3.5	40
4	40	CH_3CN	20	3.5	50
5	**40**	**Solvent-free**	**20**	**2**	**93**
6	r.t.	Solvent-free	20	2	10
7	60	Solvent-free	20	2	93
8	40	Solvent-free	15	2	70
9	40	Solvent-free	25	2	95

[a] Reaction conditions: benzaldehyde (1 mmol), aniline (1 mmol), dimethyl phosphite (1 mmol). [b] Isolated yield

Table 4: Kabachnik–Fields reaction of various aldehydes or ketones and amines in the presence of DHAA-Fe_3O_4 as the catalyst.[a]

Entry	R^1	R	Time (h)	Yield (%)[b]	Ref.
1	Ph	Ph	2	93	13n
2	4-Me-C_6H_4	Ph	2	91	13e
3	4-Cl-C_6H_4	Ph	2	90	13n
4	4-MeO-C_6H_4	Ph	1	95	13l
5	thien-2-yl	Ph	2	80	13r
6	PhCH=CH	Ph	2	80	13r
7	Ph	4-Me-C_6H_4	2	90	13s
8	Ph	4-Br-C_6H_4	2	83	13d
9	Ph	RNH_2 = $O(CH_2CH_2)_2NH$	2	75	13t
10	R^1CHO = cyclohexanone	Ph	2	85	13t

[a] Reaction conditions: aldehyde (1 mmol), amine (1 mmol), dimethyl phosphite (1 mmol), solvent-free, 40 °C.[18] [b] Isolated yield

The reusability of the catalyst was also tested in the reaction between benzaldehyde, aniline and TMSCN. When the stirring was stopped, the catalyst was adsorbed onto the surface of the stir bar. The nanoparticles were then washed with EtOH, air-dried and used directly for the next reaction without further purification. The DHAA-Fe_3O_4 nanoparticles could be recovered and reused 6 times without any significant loss of the catalytic activity (Figure 1).

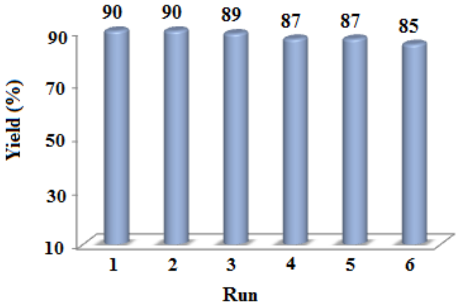
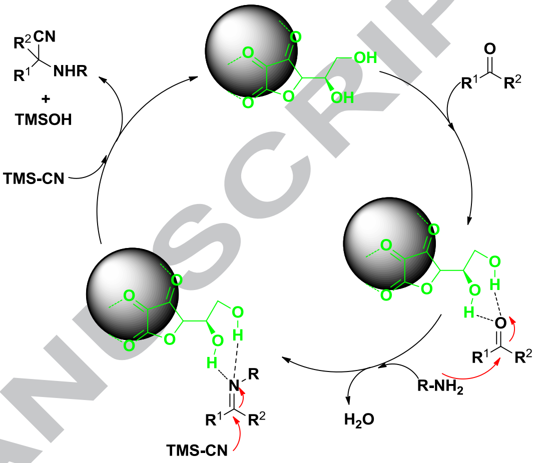


Figure 1: Reusability of the DHAA-Fe_3O_4 catalyst in the Strecker reaction between benzaldehyde, aniline and TMSCN. Reaction time: 15 min.

A plausible mechanism for the one-pot, three-component condensation reaction of aldehydes, amines and TMSCN to produce α-aminonitriles in the presence of DHAA-Fe_3O_4 is shown in Scheme 3. According to this mechanism, DHAA-Fe_3O_4 nanoparticles catalyze the *in situ* formation of the imine intermediate through generation of hydrogen bonds between the hydroxyl groups of DHAA and the oxygen atom of the carbonyl group. In the presence of the magnetic catalyst, the imine carbon is attacked by cyanide to give the product. This mechanism is thought to also occur in the formation of α-aminophosphonates. A more significant issue is that the catalyst used is enantiomerically pure and so it is possible that the cyanide ion attack on both sides of the imine is not equal. Consequently, the reaction may be enantioselective. Although this is a very important issue, unfortunately it was not possible to examine this aspect in detail.



Scheme 3: A plausible mechanism for the one-pot synthesis of α-aminonitriles catalyzed by DHAA-Fe_3O_4

Finally, a comparative study of this catalytic system with other recent reports on one-pot reactions between benzaldehyde, aniline and TMSCN was undertaken, which revealed that our catalyst was comparable with others in terms of the reaction time and yields, but required less catalyst (Table 5).

Table 5: A comparison of the efficiency of DHAA-Fe_3O_4 with several reported procedures on the condensation of benzaldelyde, aniline, and TMSCN

Entry	Catalyst	Catalyst loading	Time (min)	Yield (%)[a]	Ref.
1	sulfamic acid	20 mol%	240	90	19
2	Ph_3P/DEAD	100 mol%	20	98	20
3	Ga-TUD-1	4 mol%	30	95	21
4	oxalic acid	10 mol%	60	97	22
5	K_2PdCl_4	10 mol%	12	95	11f
6	RhI_3	2 mol%	10	95	23
7	Montmorillonite KSF	1 g	150	90	12b
8	DHAA-Fe_3O_4	0.9 mol%	15	90	Present work

In conclusion, we have shown that DHAA supported on magnetite nanoparticles can act as a novel, effective, heterogeneous and biocompatible organocatalyst for the one-pot synthesis of α-aminonitrile and α-aminophosphonate derivatives from commercially available starting materials. Various aldehydes and ketones and amines gave the corresponding products in high yields. Recovery of the catalyst was simple using a magnet, allowing its reuse without significant loss of its catalytic activity (over 6 cycles).

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18. *General procedure for the synthesis of α-aminonitriles:*
    To a 10 mL round-bottomed flask were added sequentially the aldehyde (1.0 mmol), amine (1.2 mmol), TMSCN (1.2 mmol), EtOH (2 mL) and DHAA-Fe_3O_4 (20 mg, 0.9 mol% with respect to the aldehyde). The reaction was stirred vigorously at room temperature and the progress of the reaction was monitored by TLC. After stirring for the time shown in Table 2, the catalyst was adsorbed onto the surface of the stir bar and was separated from the solution. The product was obtained by evaporation of the volatiles under reduced pressure and the residue purified by column chromatography, if necessary. All the products are known. The identity of the products was confirmed by comparison of their spectroscopic data with literature data.

    General procedure for the synthesis of α-aminophosphonates:
    To a 10 mL round-bottomed flask were added sequentially the aldehyde (1.0 mmol), amine (1 mmol), dimethyl phosphite (1.0 mmol) and DHAA-Fe_3O_4 (20 mg, 0.9 mol%). The reaction was stirred vigorously at 40 °C and the progress of the reaction was monitored by TLC. After stirring for the time shown in Table 4, the catalyst was adsorbed onto the surface of the stir bar and was separated from the solution. The product was obtained by evaporation of the volatiles under reduced pressure and the residue purified by column chromatography, if necessary. All the products are known. The identity of the products was confirmed by comparison of their spectroscopic data with literature data.
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