ORIGINAL ARTICLE

Natural halloysite nanotubes as an efficient catalyst in strecker reaction: the synthesis of *α*-amino nitriles under solvent-free conditions

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Abstract

In this work, a green and cost-effective method based on halloysite as natural catalyst for the synthesis of α-amino nitriles via Strecker three-component reaction is introduced. The chemical and physical structure of natural halloysite has characterized thoroughly, and then the effect of different parameters such as the amount of catalyst, solvent, and temperature was optimized in the synthesis of 2-phenyl-2-(phenylamino)acetonitrile as the model reaction. Then, various substituted benzaldehydes and anilines were converted to the desired α-amino nitriles under the optimized conditions. Electronic properties of substituents on aldehydes and aromatic amines have been affected the reaction efficiency. For all substrates, good to excellent yields of the corresponding α-amino nitriles were obtained under solvent-free conditions at room temperature. The catalyst has been recovered and reused five times in successive Strecker reaction.

Graphical abstract
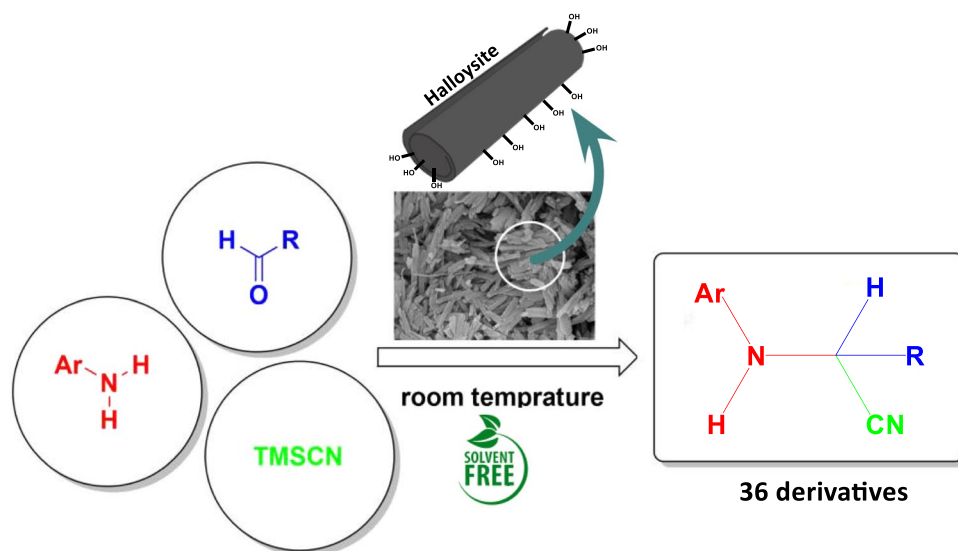
Introduction

Carbon–carbon bond formation reactions are one of the most important methods in the synthesis of drugs, natural products, and fine chemicals [1, 2]. Among them, the Strecker

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reaction is one of the well-known classical multicomponent reactions to afford α-aminonitriles via a carbon–carbon bond formation reaction between imines and cyanides [3, 4]. *α*-Amino nitriles as the key valuable precursors have been used for the synthesis of various organic compounds, drugs, and bioactive scaffolds such as saframycin A and its derivative [5], anagliptin (Fig. 1), saxagliptin, vildagliptin (Fig. 1) [6], odanacatib [7], ecteinascidin [8], (±)-phthalascidin 622 [9], HCV NS3 serine protease inhibitors [10], and clopidogrel [11]. Moreover, α-amino nitriles can be converted to the corresponding α-amino acids, amines, enamines, ketones, α-amino amides, amino alcohols, and nitrogen-containing heterocyclic compounds, which have been reviewed by Enders and his coworkers [5].

Because of the importance and variety of applications of nitriles, several methods have been reported for this purpose. As it has been mentioned in the previous reports, synthetic routes have been extended by using different sources of cyanide ions, amine substrates, catalysts, and solvents [12]. In recent decades, a wide range of methods and catalysts has been conducted in which the followings are some noteworthy special reports. Hazardous and toxic cyanide sources such as KCN, NaCN, and HCN [13] have been replaced by Bu_3SnCN [14], $(EtO)_2P(O)CN$ [15], Et_2AlCN [16], $Me_2C(OH)CN$ [17], ferro/ferric-cyanides [18], thiocyanates [19], $K_4[Fe(CN)_6]$ [20], and TMSCN [21] in recent years. In addition, the efficiency of zinc oxide [22], chloride salts of indium [23], bismuth [24], nickel [25], ruthenium [26], gallium [27], cerium [28], iron [28], sulfonium salts [29], lanthanum isopropoxide [30], copper triflate [31], indium/MOF [32], MCM-41 [33], chitosan [34], montmorillonite KSF6 [35], I_2 [36], g-C_3N_4-anchored sulfonic acid [37], and

$CdFe_2O_4@SiO_2@ZrO_2/SO_4^{2-}/Cu/Ni$ [38] has been investigated in metal-catalyzed or metal-free approaches for the production of α-amino nitriles. Electrochemical [39] and photochemical pathways [40] in the presence of different ionic liquids [41], as well as organic solvents, were also developed in this area. The use of cost-effective and recyclable catalysts [42, 43] along with avoiding toxic or volatile organic solvents [44] can be a major effort to improve the clean and green synthesis of α-amino nitriles. Most of the mentioned methods are suffering from a few drawbacks. These drawbacks include the use of expensive and inaccessible catalysts—the use of materials that are not environmentally friendly, as well as the need for high energy to perform the reaction, which sometimes does not yield good results. Therefore, finding cost-effective and reusable catalysts along with the use of nontoxic or nonvolatile solvents can improve these methods to synthesize α-amino nitriles via the clean and green procedure. For a greener methodology, finding an active natural catalyst for organic transformation can minimize the catalyst preparation steps, production of toxic wastes, and the use of toxic solvents or precious materials.

Halloysite nanotubes as a natural aluminosilicate have been used in various methods due to their unique features such as low cost, accessibility, easy modification, stability, biocompatibility, and porosity [45]. Halloysite was used as a nanocontainer for biological molecules [46], adsorbent of wastewater pollutions [47, 48], nanofiller [49], and supported catalysts [50–53]. Several nanocomposites of magnetic metal oxides [54, 55], zinc oxide [56], poly(ethylene imine) [57], and chitosan [58] have been synthesized with halloysite for organic transformations, photocatalysis, and environmental and biomedical applications [59–62].

Herein, in continuation of our previous studies [63–70], a novel and green method is reported for the synthesis of α-amino nitriles starting from the appropriate substituted aldehydes, aromatic amines, and trimethylsilyl cyanide (TMSCN) in the presence of halloysite as a highly active natural catalyst (Scheme 1).
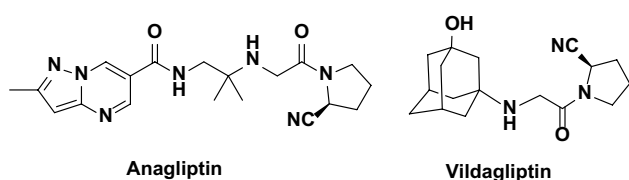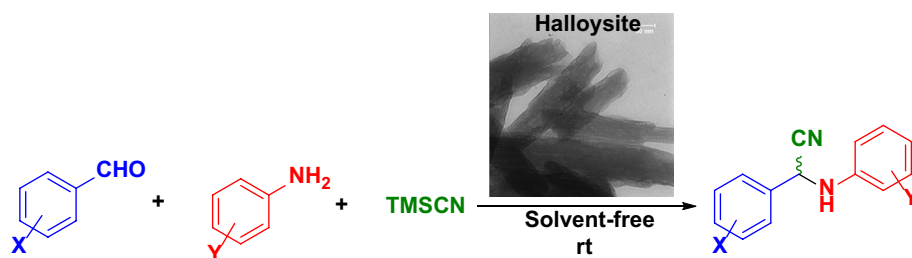

Fig. 1 Examples of existing *α*-amino nitrile moiety in drugs

Scheme 1 Schematic pathway of the Strecker reaction

Experimental

Materials and apparatuses

Halloysite nanotube, solvents, and all substrates needed for the synthesis of α-amino nitriles are obtained from Merck and Aldrich companies. All materials and solvents were used without any further purification. For the morphological studies of the halloysite, transmittance electron microscopy (TEM) (Leo 912AB microscope operated at 120 kV) and scanning electron microscopy (SEM) (Leo 1450VP microscope) analyses were used. Thermal stability of halloysite was evaluated by thermogravimetric analysis (TGA, Mettler Toledo LF-Switzerland). Fourier transform infrared spectroscopy (FT-IR) spectra (Nicolet Fourier spectrophotometer, using KBr pellets) were used for the chemical structure study of the catalyst. The crystalline structure of halloysite was also measured by the energy-dispersive X-ray analysis (XRD). ^{1}H NMR and ^{13}C NMR in CDCl$_3$ (Bruker DRX-300 AVANCE spectrometer at 300 and 75 MHz, respectively) were used to confirm the chemical structure of the synthesized α-amino nitriles.

General procedure for the synthesis of α-amino nitriles

In a round bottom flask, a mixture of the appropriate aldehyde (1 mmol), amine (1 mmol), trimethylsilyl cyanide (TMSCN) (1.2 mmol), and halloysite (10 mg) was stirred in solvent-free condition at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC) using (n-hexane/ethyl acetate) as eluent (10/1). After the completion of the reaction, the mixture was diluted with dichloromethane. The catalyst was separated from the reaction mixture by simple filtration and washed with dichloromethane (3×5 ml) and ethanol (3×5 ml) to recover the catalyst. The desired product was either recrystallized in ethanol or, if necessary, subjected to preparative thin layer chromatography on silica gel to achieve the pure α-amino nitrile compounds. The structures of the products were elucidated by ^{1}H NMR and ^{13}C NMR spectroscopy.

Results and discussion

Commercially, obtained halloysite was used as a heterogeneous green natural catalyst for the one-pot three-component synthesis of α-amino nitriles from various aldehydes, amines, and TMSCN in solvent-free condition at room temperature (Scheme 1).

FTIR analysis is used for the chemical composition study of the natural halloysite (Fig. 2). In the FTIR spectrum of halloysite, the stretching vibrations of perpendicular surface -OH groups are observed at 3696 cm^{-1} as well as the stretching vibration of the inner-surface -OH groups coordinated with the tetrahedral sheet and octahedral sheet of halloysite is observed at 3620 cm^{-1}. These peaks confirm the connection of inner surface hydroxyl groups to the aluminum sheets, which caused the occurrence of the hydrogen bonds with oxygen groups of the next layer. Also, the stretching vibration of Si–O bonds has appeared around 1089 cm^{-1}. The peak observed at 1031 cm^{-1} can be attributed to the Si–O–Si bonds. The bending vibration of Al–O–Si bonds has appeared at 538 cm^{-1}, whereas the peaks at 911 and 470 cm^{-1} are corresponded to bending vibrations of Al–OH and Si–O–Si bonds, respectively. Typically, the characteristic peak at 1637 is due to the deformation of water. The FTIR analysis confirms the existence of the characteristic vibrational peaks of the halloysite in accordance with the corresponding references [71, 72].

Fig. 2 FTIR spectra of natural halloysite
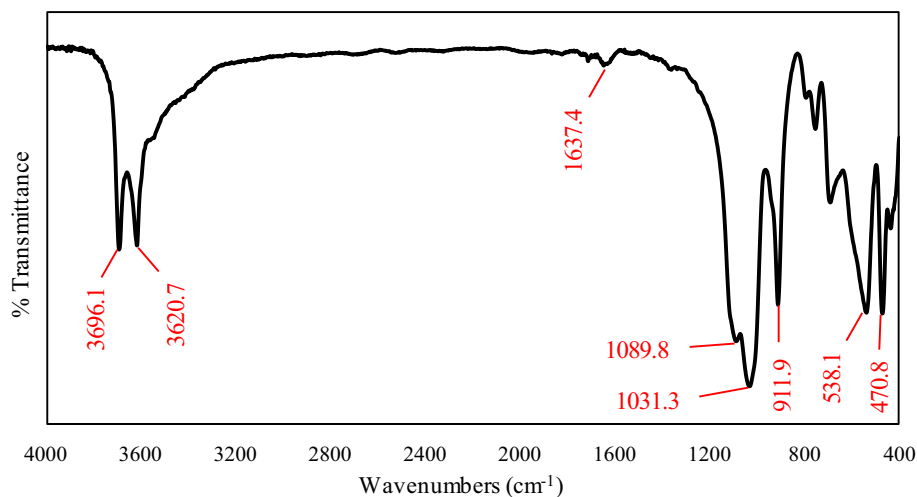
To testify thermal stability of natural halloysite, thermogravimetric analysis was carried out. As shown in Fig. 3, a weight loss below 100 °C can be attributed to the removal of surface adsorbed water molecules, which is about 2.5 wt% of halloysite. Also, an intense weight loss of 13% is observed from 400 to 550 °C related to the decomposition of the OH groups of aluminum-hydroxide moieties. Based on the TGA curve, halloysite is stable up to 400 °C [73].

The morphology of the natural halloysite was evaluated by transmittance electron microscopy (TEM). Most halloysite particles have cylindrical hollow tubular structures (Fig. 4). Generally, halloysite tubes length is in the range of 200–1000 nm. Also, the outer diameter of tubes varies from 10 to 100 nm, and the lumen diameter ranges from 5 to 50 nm (Fig. 4b). The nonuniform size distribution of nanoparticles is due to the unequal hydroxyl group density and uncommon charge distributions, which caused the formation of unequaled crystals [74].

For further study of the natural halloysite structure, scanning electron microscopy (SEM) was used. SEM image and EDX analysis are represented in Fig. 5. The SEM image indicates the polydispersity of halloysite particles in length. Also, the open-ended lumen of the cylindrically shaped
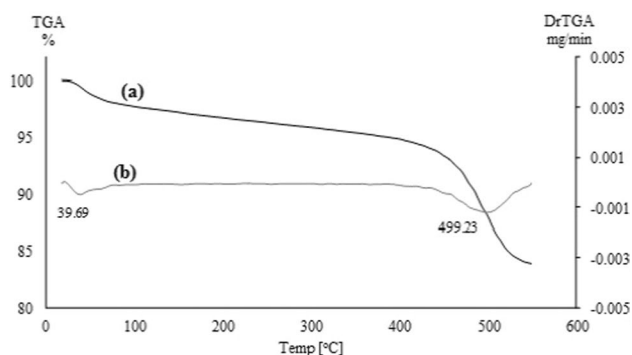

Fig. 5 **a** SEM image and **b** EDX analysis of halloysite

Fig. 3 TGA (**a**) and differential TGA (DrTGA) (**b**) curve of halloysite

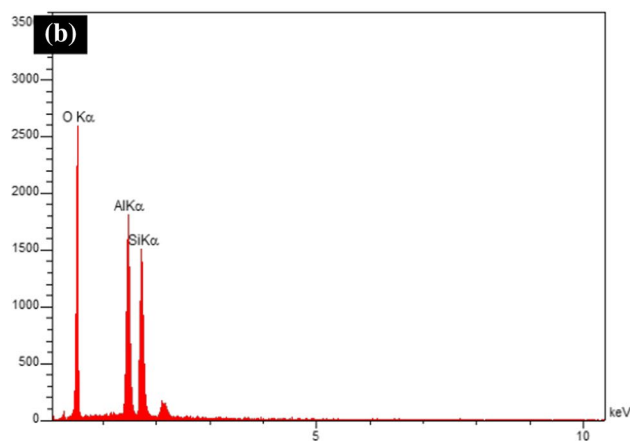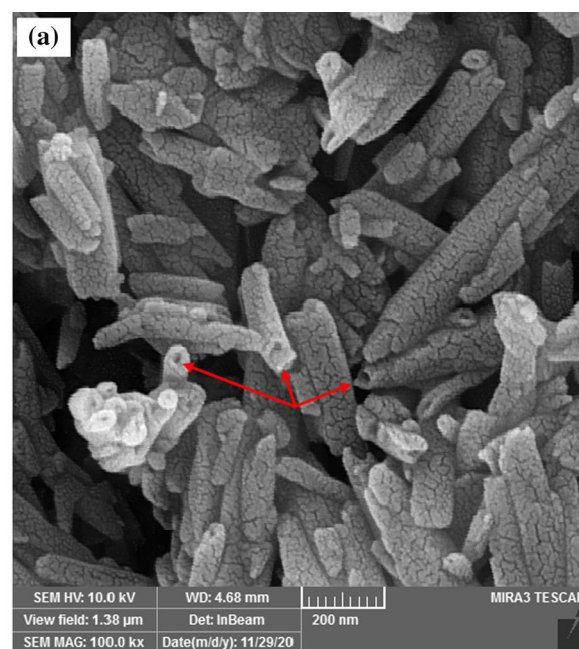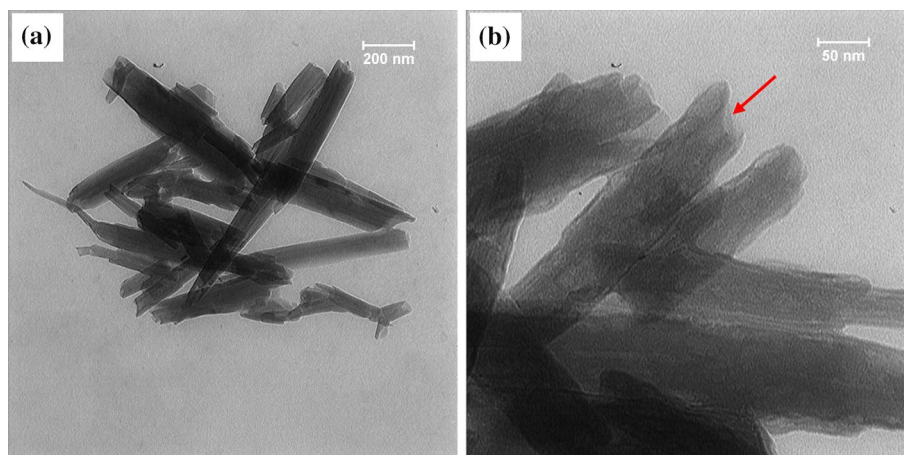**Fig. 4** TEM images of natural halloysite

tubes can be clearly observed (Fig. 5a). To recognize the elemental composition of halloysite, EDX analysis was also applied. In Fig. 5b, the characteristic peaks of Si, Al, and O have been presented as the main elements of halloysite, which are attributed to the SiO_2 and Al_2O_3 composition of halloysite [75].

The WAXRD pattern was used to study the crystalline structure of the natural halloysite (Fig. 6). In the WAXRD of halloysite, characteristic peaks of halloysite $[Al_2Si_2O_5(OH)_4]$ were observed in accordance with JCPDS card number 00-029-1487. Diffraction peaks at 2θ values of 11.8°, 20.1°, 24.5°, 35.8°, and 54.9° correspond to the (001), (110), (002), (100), and (210) planes are presented. The observed sharp peak at 2θ of 20.1° confirms the tubular structure of the halloysite sample. Other minerals such as cristobalite (C,

JCPDS card number 04-008-7642) kaolinite (K, JCPDS card number 00-005-0143), and quartz (Q, JCPDS card number 00-046-1045) as impurities are also observed [76].

After structural characterization of the natural halloysite, the feasibility of the three-component reaction among aldehyde, amine, and trimethylsilyl cyanide known as Strecker reaction in the presence of halloysite catalyst was explored. The model reaction using benzaldehyde, aniline, and TMSCN was carried out under different reaction conditions to achieve the optimized procedure. The effectiveness of various factors, including the amount of catalyst, solvent, and reaction temperature was investigated (Table 1). The effect of the solvent on the reaction process was illustrated using polar and nonpolar solvents such as DMSO, EtOH, n-hexane, and H_2O at room temperature/reflux conditions. In
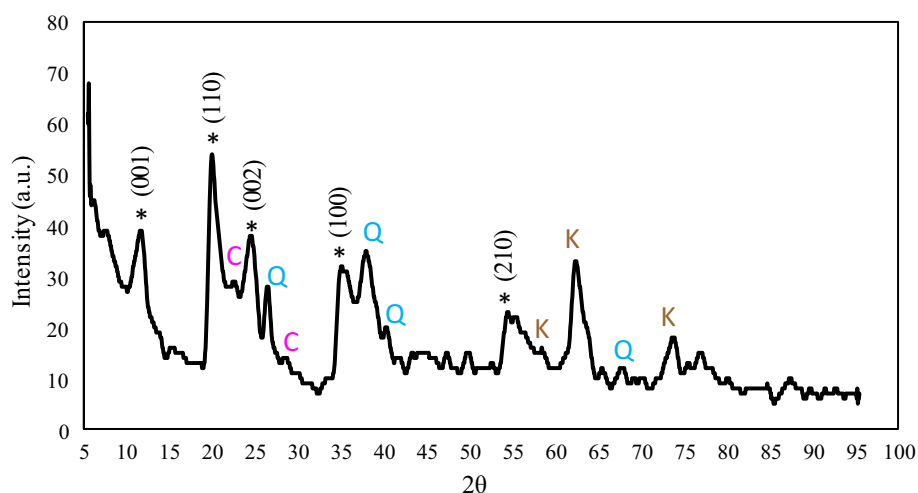
Fig. 6 WAXRD pattern of natural halloysite

Table 1 The optimization of the reaction conditions
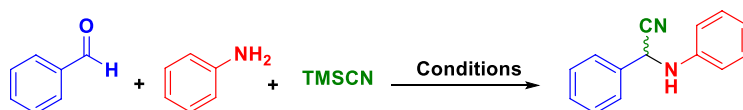
Entry	Solvent	Catalyst (mg)	Temperature (ºC)	Time (h)	Yield (%)[a]
1	DMSO	10	Room temp./Reflux	2	80/83
2	EtOH	10	Room temp./Reflux	2	92/96
3	Hexane	10	Room temp./Reflux	4	75/65
4	H_2O	10	Room temp./Reflux	3	90/93
5	solvent-free	–	Room temp	24	0
6	solvent-free	15	Room temp	1	95
7	**solvent-free**	**10**	**Room temp**	**1**	**97**
8	solvent-free	5	Room temp	4	85
9	solvent-free	2.5	Room temp	7	60
10	solvent-free	1	Room temp	12	30

Conditions: benzaldehyde (1 mmol), aniline (1 mmol), TMSCN (1.2 mmol), solvent (2 ml), and catalyst

[a]Isolated yield
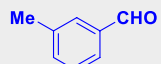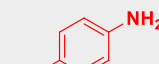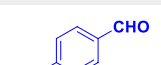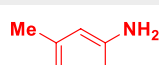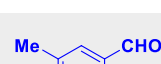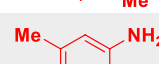
Table 2 The substrate scope of halloysite catalyzed α-amino nitrile in Strecker reaction

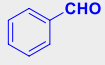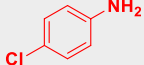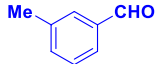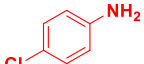| Entry	Aldehyde	Amine	Time (min)	Yield (%)
1	benzaldehyde	aniline	60	97
2	4-Cl-benzaldehyde	aniline	60	96
3	4-Br-benzaldehyde	aniline	70	93
4	4-Me-benzaldehyde	aniline	60	95
5	3-Me-benzaldehyde	aniline	60	92
6	4-O_2N-benzaldehyde	aniline	80	95
7	4-MeO-benzaldehyde	aniline	60	95
8	benzaldehyde	4-Me-aniline	60	95
9	4-Cl-benzaldehyde	4-Me-aniline	60	93
10	4-Br-benzaldehyde	4-Me-aniline	75	91
11	4-Me-benzaldehyde	4-Me-aniline	70	92
12	3-Me-benzaldehyde	4-Me-aniline	75	90
13	4-O_2N-benzaldehyde	4-Me-aniline	85	96
14	4-MeO-benzaldehyde	4-Me-aniline	65	92
15	benzaldehyde	3-Me-aniline	60	93
16	4-Cl-benzaldehyde	3-Me-aniline	60	91
17	4-Br-benzaldehyde	3-Me-aniline	80	89
18	benzaldehyde	4-Br-aniline	65	92
19	4-Cl-benzaldehyde	4-Br-aniline	65	91
20	4-Br-benzaldehyde	4-Br-aniline	70	90
21	4-Me-benzaldehyde	4-Br-aniline	75	91
22	3-Me-benzaldehyde	4-Br-aniline	80	88
23	4-O_2N-benzaldehyde	4-Br-aniline	90	93
24	4-MeO-benzaldehyde	4-Br-aniline	70	90
25	benzaldehyde	3,4-diMe-aniline	70	91
26	4-Cl-benzaldehyde	3,4-diMe-aniline	70	89
27	4-Br-benzaldehyde	3,4-diMe-aniline	85	85
28	4-Me-benzaldehyde	3,4-diMe-aniline	85	89
29	3-Me-benzaldehyde	3,4-diMe-aniline	85	86
30	4-O_2N-benzaldehyde	3,4-diMe-aniline	100	95
31	4-MeO-benzaldehyde	3,4-diMe-aniline	80	88

Table 2 (continued)

Table 2 (continued)

32	[structure: benzaldehyde with CHO]	[structure: 4-Cl aniline NH2]	60	94
33	[structure: Me-substituted benzaldehyde CHO]	[structure: 4-Cl aniline NH2]	60	90
34	[structure: Me-substituted benzaldehyde CHO]	[structure: 4-MeO aniline NH2]	60	85
35	[structure: O2N benzaldehyde CHO]	[structure: dimethyl aniline NH2]	100	92
36	[structure: Me benzaldehyde CHO]	[structure: dimethyl aniline NH2]	80	80

Conditions: aldehyde (1 mmol), amine (1 mmol), TMSCN (1.2 mmol) and halloysite (10 mg) at room temperature in solvent-free condition

the progress of the reaction, the tested solvents were not significantly different from the solvent-free condition (Table 1, entries 1–4). Without any catalyst, the imine product was only detected, and the reaction did not further proceed to produce the desired α-amino nitrile even after 24 h in solvent-free conditions (Table 1, entry 5). This is concluded that the presence of a catalyst is necessary for this reaction. The model reaction with 10 mg of halloysite was completed in 1 h with 97% of product yield under solvent-free conditions (Table 1, entry 7). It is notable that no cyanohydrin was produced as by-product in the model reaction. After the confirmation of the efficiency of halloysite in the model reaction, the effect of catalyst amount was evaluated. For this purpose, 15, 5, 2.5, and 1 mg of the catalyst were used (Table 1, entries 6–10). The yield of the final product was decreased to 95, 85, 60, and 30%, respectively. Therefore, 10 mg of the catalyst at room temperature under solvent-free conditions was selected as the optimized reaction conditions (entry 7).

Based on Table 1 results, the natural halloysite is catalytically active for the synthesis of α-amino nitrile. In the following, the scope of this method was explored with various substituted benzaldehydes and anilines in order to synthesize various rang of α-amino nitriles under the optimized reaction conditions which is summarized in Table 2. Both electron-donating and electron-withdrawing substituents on aromatic aldehydes have affected the reaction efficiencies. Substituted benzaldehydes with electron-withdrawing/donating groups were efficiently active in this reaction, and desired products were achieved with excellent yields (Table 2, entries 1–7). The electronic nature of the substituents on aromatic amines influences the efficiency of this method (Table 2, entries 8–33).

The reusability of the natural halloysite catalyst was also tested in the optimized model reaction. After the first catalytic run, the halloysite was filtered off and successively washed with water and ethyl acetate. The recovered halloysite was dried at 100 °C in an electric oven and used for the next run with fresh substrates. The recovered catalyst was active for five consecutive runs. The yield of the final product was 97% in the first run, which was decreased to 90% in the fifth run (Fig. 7). After the fifth run, the catalyst was deactivated due to the catalyst poisoning with substrates and products.

Figure 8 shows the plausible reaction mechanism in which aldehyde interacts with the catalyst to increase the electrophilicity of the carbonyl group to form the intermediate which reacts with the amine to make in situ generations of aldimine (I). It consecutively interacts with hydroxyl group and increases the electrophilicity of the carbon of the imine to form a reactive intermediate (II). This hydroxyaldimine intermediate reacts with trimethyl-silylcaynide (TMSCN) as the nucleophile to form N-silylated product along with the generation of the active pre-catalysts. The N-silylated product is converted to the α-aminonitrile as final product after aqueous workup of N-silylated product by elimination of Me_3SiOH.

Eventually, the comparison of the natural halloysite nanotubes (HNTs) as a suitable catalyst in the synthesis

Table 3 Comparison of halloysite nanotubes with previously reported catalysts

| Entry	Catalyst	Amount	Solvent	Temp	Time	Yield (%)	Ref.
1	Zinc Complex	35 mg	neat	r.t	6 h	90	[77]
2	Fe_3O_4@SiO_2-NH_2-GA	40 mg	EtOH	r.t	10 min	98	[78]
3	Fe_3O_4@SiO_2–APTES–TFA	50 mg	EtOH	r.t	50 min	96	[79]
4	ionic liquid [PMIm]Br	10 wt%	IL	r.t	30 min	97	[41]
5	CN-Bu-SO_3H	20 mg	EtOH	r.t	20 min	94	[37]
6	ZnO	5 mol%	CH_3CN	80 °C	45 min	94	[22]
7	CMK-5-SO_3H	46 mg	Solvent free	r.t	45 min	96	[80]
8	**Halloysite nanotubes**	**10 mg**	**Solvent free**	**r.t**	**60 min**	**97**	**This work**
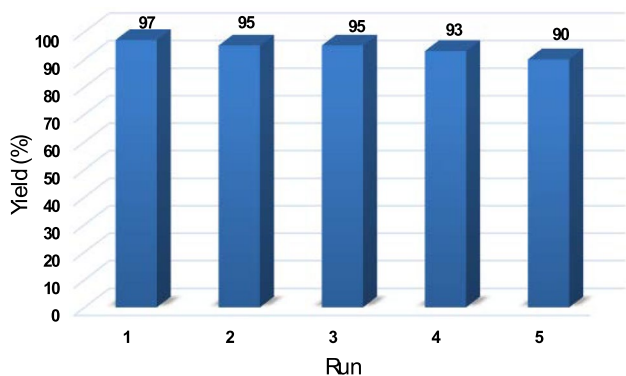
Fig. 7 Recycling study of halloysite catalyzed model reaction

Conclusions

The natural halloysite is active for the one-pot synthesis of α-amino nitriles by a three-component condensation of various benzaldehydes, anilines, and TMSCN. This green natural catalyst can produce a variety of α-amino nitriles in a facile and cost-effective method in solvent-free condition at room temperature. Both electron-donating and electron-withdrawing substitutions on benzaldehyde and aniline substrates have been affected the reaction efficiency. Electron-withdrawing groups on benzaldehyde and electron-donating groups on aniline were converted to the desired α-amino nitriles in excellent yields. The catalyst was active for five consequent runs.
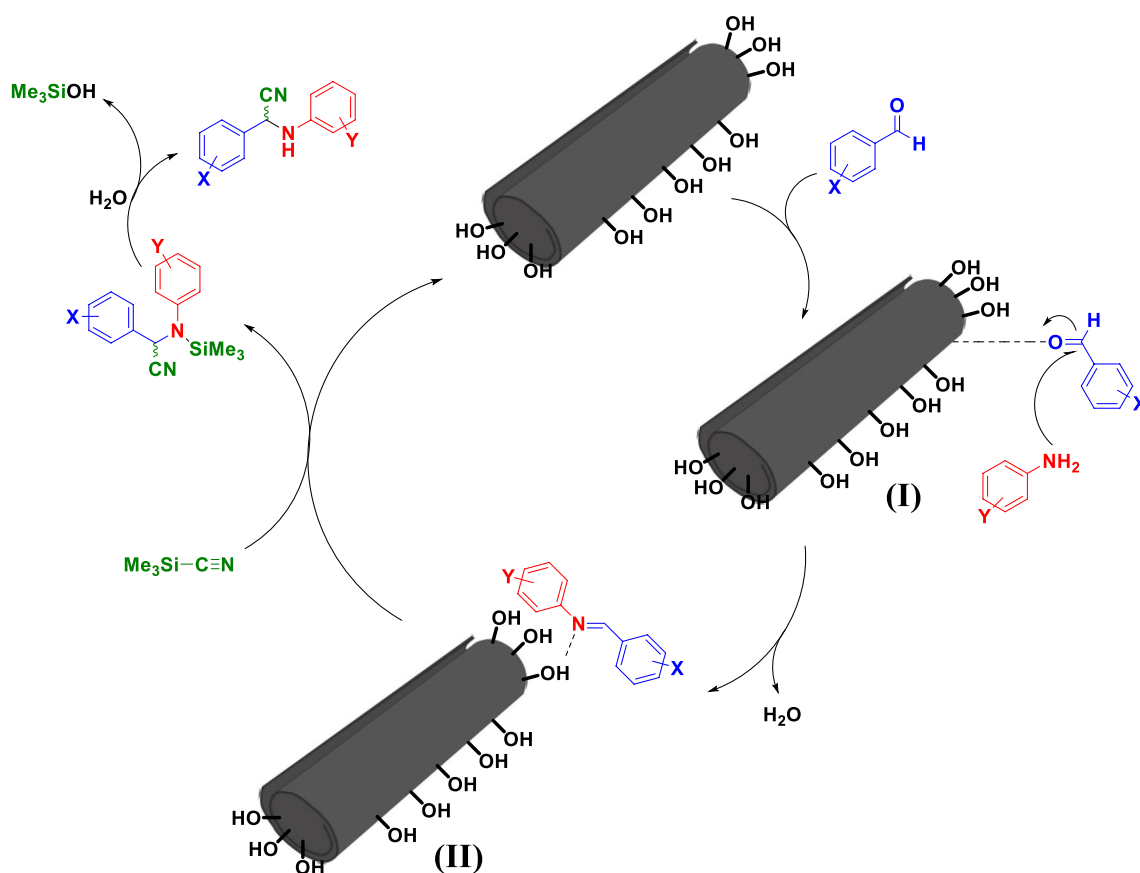

Fig. 8 The possible mechanism of halloysite catalyzed α-amino nitrile in Strecker reaction

of α-amino nitriles (Strecker reaction) with the previously reported ones demonstrates that this procedure has the advantages of low catalyst loadings, solvent-free conditions at room temperature, high yields of final products, short reaction times, and easy catalyst recovery with the eco-friendly nature (Table 3).

The catalyst used for this reaction can cover the disadvantages of previous reports of catalytic work of this reaction and synthesize the desired products with the least amount of energy and cost.

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