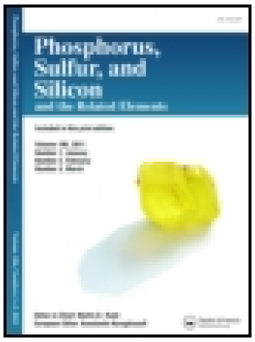

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Layered Double Hydroxides (LDHs): As Efficient Heterogeneous Catalyst for the Cyanosilylation of Aromatic Aldehydes

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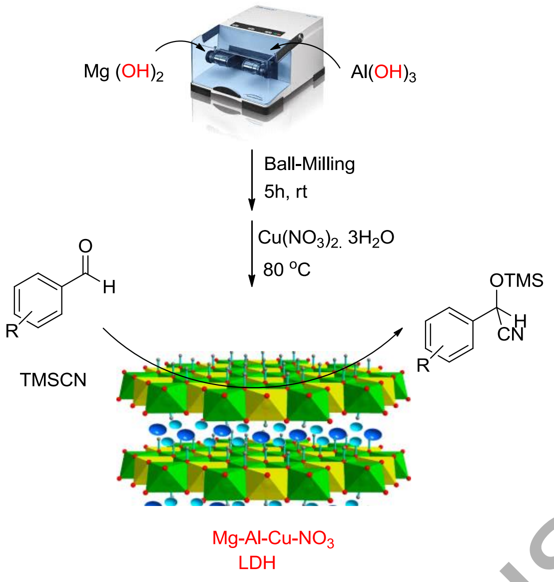
Abstract

We report the first application of Layered Double Hydroxides (LDHs) as efficient and novel heterogeneous catalyst for the cyanosilylation of aldehydes with excellent yields and simple work up. The reaction between different aldehydes with electron-withdrawing and releasing groups and trimethylsilyl cyanide (TMSCN) proceeds in dry CH_2Cl_2 at room temperature in the presence of Mg-Al-Cu LDH. The catalyst recycled and reused for four times without loss of catalytic activity. The structures of all compounds were corroborated spectroscopically (^{1}H- and ^{13}C-NMR, and elemental analysis). A plausible mechanism for this type of reaction is proposed.

Graphical Abstract



Keywords: Layered double hydroxide (LDH), cyanohydrin, cyanosilylation, heterogeneous catalyst

Introduction

From a synthetic point of view, the preparation of cyanohydrins is especially significant, because they serve as key intermediates in the synthesis of many biologically important compounds such as β-amino alcohols, α-hydroxy acids, β-hydroxy alcohols and α-hydroxy aldehydes [1-4]. The easiest suggested route for the synthesis of cyanohydrins is the catalytic cyanosilylation of carbonyl compounds [5-6]. Several catalysts have been used to this aim in which cyanohydrins have been produced from aldehydes and ketones. Some of these catalysts are; Lewis acids and bases [7-13], synthetic peptides [14, 15], helical poly (amino acid)s [16], enzymes [17,18], chiral metal complexes with various ligands like sulfoximines [19], Metal-Organic Frameworks (MOFs) [20], BINOLs [21, 22], β-amino alcohol [23], and other ligands [24-27]. However, some of these catalytic systems require multi-step preparation, high catalyst loading, inert atmosphere, long reaction times and laborious work-up procedure [7–27]. Therefore, development of new catalysts which operate under milder conditions is a challenge attracting much attention.

Doubled Layered Hydroxides (LDHs) are synthetic compounds that can be prepared in the laboratory. This term is used for synthetic compounds designed with natural hydroxides with basic layers containing two or more metal cations with anionic species in the inner layers [28].

The general formula proposed for LDH is $M(II)_{1-x}\ M(III)_{x}(OH)_2]^{+x}\ [(A^{-n})_{x/n}.mH_2O$, where M(II) and M(III) metal species are di- and tri- valent and A is an anion (Figure 1) [29].

Figure 1.General formula for LDHs [29b]

Such compounds have brucite-like structure in the center of the octahedral oxygen and two dimensional layers that are formed from sharing octahedral edges, organic or inorganic anions are placed between the layers in a way that balance is established between the charges [30, 31]. There are numerous applications for this class of compounds, such as good supporting for the different catalysts [32-34] and in organic synthesis including epoxidation reaction of styrene [35], Knoevenagel condensation [36, 37], Heck-Suzuki reaction [38], hydroxylation of phenol [39] and carbonylation of methanol to methyl acetate [40]. On the other hand this class of compound was used as environmental catalysis [41-43], ion exchange⁄adsorption [44] pharmaceutics [45-47], photochemistry [48-50] and electrochemistry [51-53].

Considering the catalytic activity of these compounds as mentioned above and as part of our ongoing work on the synthesis of cyanohydrins as a pharmacologically interesting intermediates by different salt of *N*-hydroxyl phthalimides [54], herein we report the first application of LDHs as efficient and novel heterogeneous catalyst for the cyanosilylation of carbonyl compounds.

Results and discussion

The goal of the present work was to propose simple and convenient method for the synthesis of Mg-Al-Cu LDH, and its application in the synthesis of cyanosilylethers from aldehydes and TMSCN. Mg-Al-Cu LDH has been used as a catalyst in different organic synthesis in recent years [55]. In the present work, the Mg-Al-Cu LDH was synthesized by ball-mill at room temperature under solvent-free condition. The process was completed within 0.5h and resulting in a white powder. To confirm the mechanochemical preparation of LDH, X-ray powder diffraction was performed. The observed peaks at 2Theta of 11, 22, 34, 38, 44, and 61 (Fig. S 1 Supplemental Materials) are in a good agreement with reported in literature [56]. Also in FT-IR spectrum, strong and broad peak at 3450 cm^{-1} indicates the presence of OH group. The peaks in 1639 cm^{-1} and 1365 cm^{-1} are related to CO_3^{2-} [57] and peaks from 400 to 1000 cm^{-1} were attributed to the stretching and bending vibrations of M-O and M-OH [58] (Fig. S 1 and S 2).

The synthesized Mg-Al-Cu LDH was employed as a heterogeneous catalyst in the cyanosilylation of aldehydes. Initially, for the optimization of reaction condition, the reaction of benzaldehyde with TMSCN was selected as a model reaction. The effect of various parameters such as catalyst loading and nature of the solvent on its cyanosilylation at room temperature was studied. The results have been summarized in Table 1. As shown in Table 1, LDH catalyst (20 mol%) was found to facilitate the cyanosilylation in quantitative yield within 30 min in CH_2Cl_2 (table 1, entry 2), while by increasing the catalyst up to 30 mg it still affords the desired products in quantitative yields within short reaction times (Table 1, entry 5). With decreasing the catalyst loading to 10 mg the yield decreased to 85%. Furthermore, no reaction was observed under similar reaction conditions in the absence of any LDH catalyst (Table 1, entry 6). Between CH_3CN and CH_2Cl_2 as a solvent, the best was CH_2Cl_2 and provided the product of the cyanosilylation in high isolated yield (Table 1, Entry 3, 4, 5).

Table 1. Optimization and comparison of the cyanosilylation of benzaldehyde in various conditions

Having optimal conditions of reaction (20 mg of LDH, TMSCN/aldehyde = 1.2 equiv., CH_2Cl_2, r.t.) in hand, the reactivity of different aldehydes were investigated in the next step. The results have been summarized in Table 2. Trimethylsilylcyanation of several aromatic aldehydes including electron-withdrawing and releasing groups was investigated and the results showed that type of substitution no significant change in the yields (Table 2, Entry 2-10), but steric hindrance at the ortho position results in lower yields (Table 2, Entry 6, 9, 10).

Table 2. Results of derivatives synthesis

One of the important properties of the heterogeneous catalyst is the reusability, so to confirm this for our catalyst, we performed recycling experiment; so the cyanosilylation of benzaldehyde was chosen as a model reaction with recycled catalyst; the reaction was completed after 0.5 h and the conversion and isolated yield of the reaction was 100 and 94 %, respectively. This experiment was performed for four more times and the result showed a negligible change in catalyst activity and yield of the product.

The mechanism of the LDH-catalyzed cyanosilylation probably involves the initial activation of carbonyl group in aldehyde at the unsaturated within M (II) or M (III) (Mg^{2+}, Cu^{2+}, Al^{3+}) sites and then activation of TMSCN by exposed OH^- of the LDH and subsequent release of the nucleophilic cyanide ion to add to the carbonyl moiety in a rate-determining step followed by silylation and formation of the product **3** (Scheme 1). Therefore, it is likely that both TMSCN and carbonyl compounds are activated by surface oxygen atoms (nucleophilically) and the Cu (II) (electrophilically), respectively [59].

Scheme 1. Postulated mechanism of the reaction

Experimental

All solvents and chemical materials were purchased from Sigma–Aldrich and Merck. Progress of reactions was monitored by thin layer chromatography while purification was effected by column chromatography, using silica-gel (Merck 230-240 mesh). X-ray powder diffraction (XRD) measurements were performed using an X'pert MPD. Philips diffractometer with Cu radiation source (λ = 1.54050 Å) at 40 kV voltage and 40 mA current. FT-IR spectra were recorded with a Shimadzu 8400s FT-IR spectrometer using potassium bromide pellets. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-500 AVANCE spectrometer at 500.13 and 125.8 MHz, with $CDCl_3$ as the solvent, respectively. Elemental analyses for C, H, and N: Heraeus CHN-O-Rapid analyzer. The Supplemental Materials contains sample ^1H and ^{13}C NMR spectra of the known products (Figures S 3 – S 9).

Synthesis of Mg-Al-Cu-NO_3 LDH

A mixture of $Mg(OH)_2$ (2.45 g, 42 mmol) and $Al(OH)_3$ (0.55 g, 7 mmol) with molar ratio of 6:1 were ball-milled at 28 Hz, for 5h at room temperature in solvent-free conditions. Then, resulting powder was added to 30 ml $Cu(NO_3)_2{\cdot}3H_2O$ (0.17mM) and the mixture was transferred to an autoclave and placed in the oven at 80 ^{o}C for 12 h. After that, the resulting precipitate was filtered or centrifuged and washed with water. The resulting cake was dried at oven for 12h in 60°C to yield 2.5 gr of Mg-Al-Cu-NO_3 LDH. The structure of synthesized LDH characterized and confirmed by comparison with the literature reports [56] (Fig. S 1 and S 2).

General procedure for cyanosilylation of carbonyl compounds catalyzed by LDH:

TMSCN (1.2 mmol, 0.15 ml) was added dropwise to the stirred solution of 1.0 mmol of a carbonyl compounds and 20 mg of LDH in dry CH_2Cl_2 (5 ml). The mixture was stirred at room temperature for 30 min. The reaction was monitored by TLC. Then, the reaction mixture was quenched by water (5 mL) and LDH filtered. The organic compound was extracted with CH_2Cl_2 (2×5.0 mL). The obtained organic phase was washed with water (5.0 mL) and dried over Na_2SO_4. The solvent was evaporated to afford the desired products which in some cases were essentially pure cyanohydrin TMS ethers. Further purification of the products was performed by silica gel column chromatography (EtOAc-Hexane, 1:8).

Conclusions

In summary, Mg-Al-Cu Layered double hydroxide (LDH) was found to be an good heterogenous catalyst for cyanosilylation of various aromatic aldehydes with electron-withdrawing and releasing group under mild conditions. Attractive features of the method include the general application, mild conditions and simplicity in the preparation, operation and separation of the catalyst by simple filtration. The catalytic ability of LDHs has been developed for the addition of TMSCN to carbonyl compounds for the first time. Further studies on preparation of other useful LDHs and development of its catalytic scope are in progress and will be presented in duecourse.

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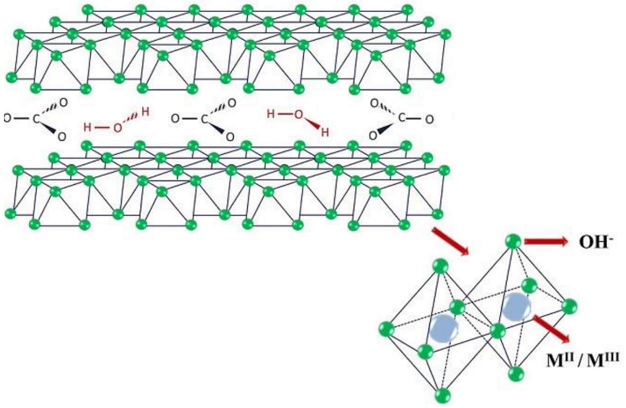
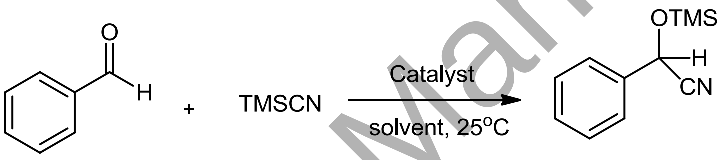


Figure 1.General formula for LDHs [30b]

Table 1. Optimization and comparison of the cyanosilylation of benzaldehyde in various conditions [a]

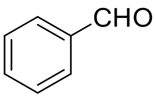
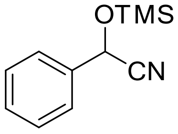
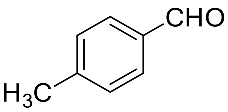
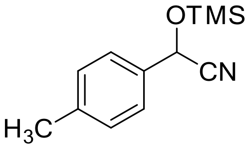
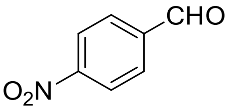
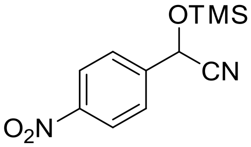
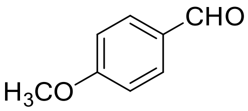
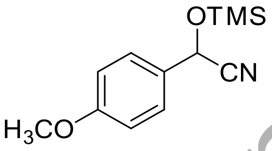
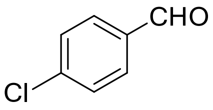
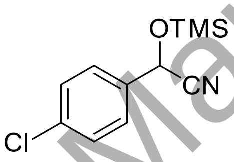
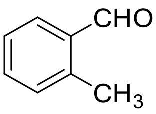
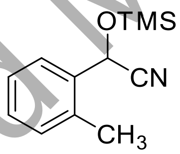
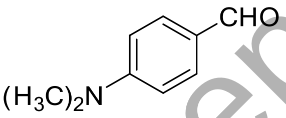
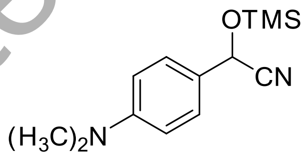
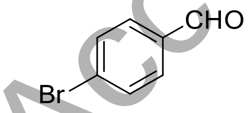
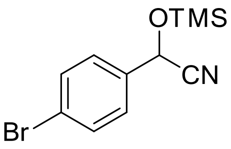
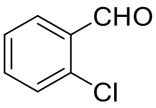
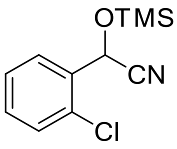
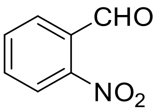
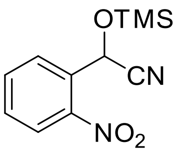


1 **2** **3**

Entry	Catalyst (mg)	Solvent	Time (h)	Yield (%)
1	10	CH_2Cl_2	0.5	85
2	**20**	$\mathbf{CH_2Cl_2}$	**0.5**	**95**
3	30	CH_2Cl_2	0.5	95
4	20	CH_3CN	8	65
5	40	CH_3CN	8	75
6	-	CH_2Cl_2	8	0

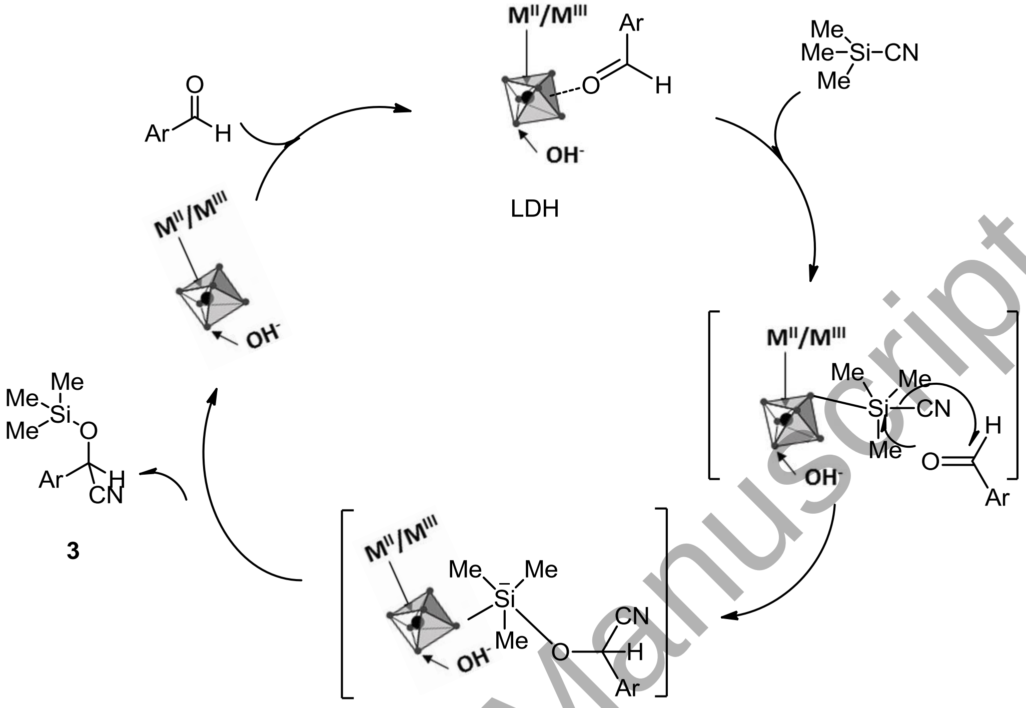
[a] Reaction conditions: 20 mol% of catalyst (Mg-Al-Cu LDH), solvent (5 mL), TMSCN (1.2 mmol) and aldehyde (1 mmol).

Table 2.Results of derivatives synthesis [a]

Entry	Aldehyde	Product	Yield (%)[b]	Lit. Ref.
1		 **3a**	95	60
2		 **3b**	96	60
3		 **3c**	92	61
4		 **3d**	93	61
5		 **3e**	95	61
6		 **3f**	89	60
7		 **3g**	90	62
8		 **3h**	92	54b
9		 **3i**	88	60
10		 **3j**	90	54b

[a] Reaction conditions: 20 mol% of catalyst (Mg-Al-Cu LDH), CH_2Cl_2 (5 mL), TMSCN (1.2 mmol) and aldehyde (1 mmol). Time: 0.5 h.

[b] Isolated yield



Scheme 1. Postulated mechanism of the reaction