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# Amino acid intercalated layered double hydroxide catalyzed chemoselective methylation of phenols and thiophenols with dimethyl carbonate

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ABSTRACT

Sixteen different amino acids are intercalated into Mg–Al layered double hydroxides (LDHs) by the reconstruction method and are characterized by powder XRD and FT-IR. The intercalated amino acid–LDHs (AA-LDHs) are used as catalysts for chemoselective *O*-methylation of phenol and S-methylation of thiophenol with dimethyl carbonate (DMC) as a green methylating agent. The intercalation behavior of various amino acids is influenced by various structural features of amino acids, namely, carbon chain length, structure, and physicochemical properties. In particular, amino acids possessing a hydrophobic side-chain show higher catalytic activity. A suitable reaction mechanism is proposed. The catalyst can also be recycled.



In recent years, clay minerals have received considerable attention as support for the synthesis of new organic–inorganic nanohybrid materials.[1] Among the different types of clay minerals, layered double hydroxides (LDHs) are considered to be highly promising due to their easy preparation and broad uses as adsorbents.[2] In addition, LDHs are biocompatible and find application in pharmaceuticals such as non-viral vectors for delivery of antisense oligonucleotides, drug stabilizer, anticancer drugs in cancer treatment, therapy of digestive disorders, and support for controlled release formulations of pharmaceuticals.[3,4] Owing to the intercalation property of LDHs, many LDH composites with intercalated beneficial organic anions, such as DNA,[5] pesticide,[6] plant growth regulators,[7] and drugs[8] have been reported. Among them nucleotide,[9] deoxyribonucleic acid,[10] and amino acid[11] intercalated LDHs exhibit good catalytic activity and excellent chemoselectivity. Recently, Nakayama et al.[12] reported intercalated amino acids and oligopeptides over LDHs by the reconstruction method (memory effect) which proved the ability of LDHs to regenerate the layered structure when exposed to water and anions.

Protection and deprotection of fine chemicals through environmentally clean and economical processes is an emerging area with high commercial importance.[13] The protected *O*-methylated phenols (anisoles) are important intermediates in the field of fragrances, dyes, and agricultural chemicals and are widely used as antioxidants in oils and stabilizers for polymers.[14] Protection of thiol groups is yet another important reaction in organic synthesis and especially in peptide, protein, and β-lactam synthesis.[15] Various methylating agents such as iodomethane,[16] methanol,[17] methyl halide,[18] dimethyl sulfate,[19] trimethyl phosphate,[20] and tetramethylammonium chloride[21] have been used for methylation reaction. The traditional synthetic methodologies using some of these toxic alkylating reagents generate large quantities of waste. Safer, clean, and selective methylation protocols can be conceived with the use of non-toxic DMC.[22,23] This safe, green methylating agent enjoys advantages such as environmentally benign, cost-effective, can act as solvent, and above all produces $CO_2$ and methanol as by-products (which can be recycled back to DMC). Consequently, various approaches have been reported with different catalytic systems to obtain selective *O*-methylation of phenol with DMC, for example, fluorine-modified mesoporous Mg–Al mixed oxides,[22b] $ZnCl_2$ modified –$Al_2O_3$,[24] Cs-loaded MCM-41,[25] and [BMIM]$Cl^-$.[26]

Recently, we have reported L-methionine intercalated LDHs as catalysts for chemoselective *O*-methylation of phenol and esterification of aromatic carboxylic acids using DMC as methylating reagent.[27] In this context, we report the synthesis and characterization of sixteen different AA-LDHs with an aim to identify an ideal catalyst based on their activity derived through their structural interaction with LDHs in chemoselective methylation of phenol and thiophenol. Although, intercalation of amino acids onto the

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**Table 1**
Interlayer distance of amino acids intercalated LDHs

| Entry | Amino acid | | $d$ (nm) | Gallery height (nm) |
|---|---|---|---|---|
| 1 | —[a] | | 0.78 | 0.30 |
| 2 | Leucine | (Leu) | 1.44 | 0.96 |
| 3 | Isoleucine | (Ile) | 1.43 | 0.95 |
| 4 | α-Aminobutyric acid | (α-Aba) | 1.11 | 0.63 |
| 5 | Aspartic acid | (Asp) | 1.11 | 0.63 |
| 6 | Glutamic acid | (Glu) | 1.08 | 0.60 |
| 7 | Phenylalanine | (Phy) | 1.48 | 1.00 |
| 8 | Histidine | (His) | 1.72 | 1.24 |
| 9 | Tyrosine | (Tyr) | 1.08 | 0.60 |
| 10 | Alanine | (Ala) | 0.81 | 0.33 |
| 11 | Serine | (Ser) | 0.82 | 0.34 |
| 12 | Glycine | (Gly) | 0.79 | 0.31 |
| 13 | Cysteine | (Cys) | 0.79 | 0.31 |
| 14 | Proline | (Pro) | 0.77 | 0.29 |
| 15 | Arginine | (Arg) | 0.77 | 0.29 |
| 16 | Lysine | (Lys) | 0.77 | 0.29 |

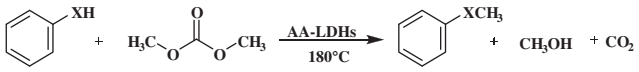
[a] LDHs.

layers of LDHs is a well known procedure to obtain inorganic–organic hybrid materials, their catalytic applications are quite limited. In this regard, we tried to intercalate various amino acids such as arginine, lysine, leucine, isoleucine, phenylalanine, α-aminobutyric acid, aspartic acid, glutamic acid, histidine, alanine, serine, glycine, tyrosine, cystine, and proline onto the layers of LDHs and their catalytic activity is tested in methylation of phenol and thiophenol with DMC.

The as prepared AA-LDHs are characterized by powder XRD and FT-IR (see Supplementary data). Characteristic reflections for Mg–Al LDHs are observed at 11.4°, 22.8°, and 34.8° with $d_{003}$ = 0.78 nm which indicates the existence of $CO_3^{2-}$ ions intercalated onto the interlayer space of LDHs. The thickness of the LDH basal layer is 0.48 nm and the interlayer space is calculated as 0.30 nm (Table 1, entry 1), and these values are in good agreement with previous report.[12] The diffraction peak Leu-LDHs ($d_{003}$ = 1.44 nm) (Fig. 1), Ile-LDHs ($d_{003}$ = 1.43 nm), α-Aba-LDHs ($d_{003}$ = 1.11 nm), Asp-LDHs ($d_{003}$ = 1.11 nm), and Glu-LDHs ($d_{003}$ = 1.08 nm) with the distinct expanded LDH structure (Table 1, entries 2–6) are observed. In the hydrophobic amino acids such as L-Phe-LDHs ($d_{003}$ = 1.48 nm) and L-His-LDHs ($d_{003}$ = 1.72 nm) expanded basal spacing (Table 1, entries 7 and 8) is observed. These values indicate that the amino acids are intercalated vertically onto the LDHs through the intercalation with carboxylate groups (Fig. 1). The diffraction peaks with unexpanded LDHs are also noticed with Ala-LDHs ($d_{003}$ = 0.81 nm), Ser-LDHs ($d_{003}$ = 0.82 nm), Gly-LDHs ($d_{003}$ = 0.79 nm), Tyr-LDHs ($d_{003}$ = 0.80 nm), Cys-LDHs ($d_{003}$ = 0.79 nm), and Pro-LDHs ($d_{003}$ = 0.77 nm) (Table 1, entries 9–14) which suggest the parallel arrangement over the interlayer due to the absence of the large hydrophobic group. The interlayer values after intercalation with amino acids are slightly higher compared to carbonate ions indicating the effective intercalation of amino acids into the interlayer space of LDHs. On the other hand, Arg and Lys are difficult to be intercalated into the LDHs due to the repulsion positive charge occurring between the LDH basal layer and the side-chain of Arg and Lys.[12]

The catalytic activity of these AA-LDHs was tested in the chemoselective methylation of phenol and thiophenol with DMC[31] and the observed results are summarized in Table 2. Phenol and thiophenol were selected as model substrates to optimize the reaction conditions using DMC as methylating reagent. LDHs resulted in 26% and 10% yields for the methylation of phenol and thiophenol respectively at 180 °C in 12 h. The amino acids possessing large hydrophobic pockets such as Leu-LDHs, Ile-LDHs, α-Aba-LDHs, Asp-LDHs, Glu-LDHs, His-LDHs, and Phy-LDHs were tested as catalysts for the *O*-methylation of phenol and afforded more than 90% yield (Table 2, entries 2–7). It is noteworthy to mention that no *C*-methylated products were observed as evidenced from $^1$H NMR and ESI-MS. On the other hand, amino acids intercalated with short side chain such as Ala, Ser, Gly, Tyr, Cys, and Pro resulted in low yield (Table 2, entries 9–14). However, complete conversion of phenol was observed with Arg-LDHs and Lys-LDHs along with high chemoselectivity (Table 2, entries 15 and 16). Although it was quite difficult to achieve intercalation of Arg and Lys over LDHs, the physical adsorption of these amino acids over LDHs showed higher activity and this is believed to be due to the hydrophobic pocket present in these amino acids. The catalytic activity of various amino acids was also tested and the observed results

**Table 2**
Chemoselective methylation of phenol and thiophenol with DMC in the presence of various AA-LDHs[a]




| Entry | AA-LDHs | Time (h) | Yield[b] (%) | |
|---|---|---|---|---|
| | | | X = O | X = S |
| 1 | LDHs | 12 | 26 | 10 |
| 2 | Leu-LDHs | 6 | 98 | 98 |
| 3 | Ile-LDHs | 6 | 82 | 95 |
| 4 | α-Aba-LDHs | 6 | 87 | 80 |
| 5 | Asp-LDHs | 6 | 96 | 82 |
| 6 | Glu-LDHs | 6 | 95 | 96 |
| 7 | Phy-LDHs | 6 | 88 | 85 |
| 8 | His-LDHs | 6 | 70 | 88 |
| 9 | Ala-LDHs | 12 | 03 | 36 |
| 10 | Ser-LDHs | 12 | 05 | 22 |
| 11 | Gly-LDHs | 12 | 02 | 19 |
| 12 | Tyr-LDHs | 6 | 89 | 90 |
| 13 | Cys-LDHs | 12 | 02 | 26 |
| 14 | Pro-LDHs | 12 | 27 | 29 |
| 15 | Arg-LDHs | 6 | 96 | 94 |
| 16 | Lys-LDHs | 6 | 95 | 94 |
| 17 | Met-LDH[c] | 6 | 92 | 97 |

[a] Reaction conditions: phenol/thiophenol (1 mmol), DMC (1.2 mL), AA-LDHs (100 mg), 180 °C in an autoclave.
[b] Determined by GC.
[c] Data taken from Ref. 27.

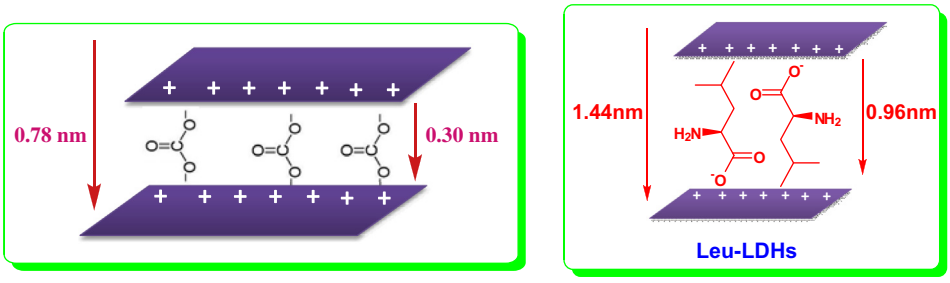


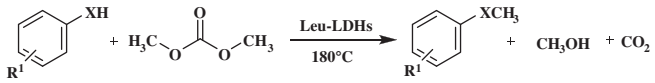

**Figure 1.** Schematic structural models of Mg–Al LDHs and Leu-LDHs.

**Table 3**
Chemoselective *O*-methylation of phenol with amino acids[a]

| Entry | Amino acid | Time (h) | Yield[b] (%) |
|---|---|---|---|
| 1 | Arginine | 6 | 3 |
| 2 | Glutamic acid | 6 | 4 |
| 3 | Lysine | 6 | 2 |
| 4 | Aspartic acid | 6 | 2 |
| 5 | Leucine | 6 | 2 |

[a] Reaction conditions: phenol (1 mmol), DMC (1.2 mL), amino acid (50 mg), 180 °C in an autoclave.
[b] GC yield.

**Table 4**
Leu-LDHs catalyzed chemoselective *O*-methylation of substituted phenols and thiophenols with DMC[a]




| Entry | $R^1$ | X | *T* (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | H– | O | 6 | 98 |
| 2 | *o*-$NO_2$– | O | 5 | 89 |
| 3 | *m*-$NO_2$– | O | 5 | 99 |
| 4 | *p*-$NO_2$- | O | 5 | 98 |
| 5 | *o*-Cl– | O | 6 | 86 |
| 6 | *p*-Cl– | O | 5 | 82 |
| 7 | *o*-Br– | O | 6 | 87 |
| 8 | *p*-Br– | O | 6 | 90 |
| 9 | *p*-I– | O | 6 | 92 |
| 10 | *p*-$OCH_3$– | O | 6 | 91 |
| 11 | *o*-$COCH_3$– | O | 6 | 89 |
| 12 | *p*-*t*Bu– | O | 6 | 94 |
| 13 | *p*-COOH– | O | 6 | 91 |
| 14 | 2-Naph–[c] | O | 6 | 98 |
| 15 | *m*-Isopropyl– | O | 6 | 95 |
| 16 | *p*-$C_6H_5CO$– | O | 6 | 92 |
| 17 | H– | S | 6 | 98 |
| 18 | *p*-Cl– | S | 6 | 87 |
| 19 | *p*-Br– | S | 6 | 81 |
| 20 | *p*-$OCH_3$– | S | 6 | 89 |

[a] Reaction conditions: substrate (1 mmol), DMC (1.2 mL), Leu-LDHs (100 mg), 180 °C in an autoclave.
[b] GC yield.
[c] 2-Naphthol.

are given in Table 3. It is surprising to note that those amino acids exhibiting higher activity within the interlayer space of LDHs showed negligible activity without LDHs. This clearly indicates that the intercalation of amino acids onto the layer of LDHs creates an environment which can facilitate the reaction in a facile manner with high conversion and selectivity.

These interesting preliminary results prompted us to expand the scope of Leu-LDHs with various substituted phenols and thiophenols and the observed results are given in Table 4. Phenols with electron withdrawing and donating substituents were converted to their corresponding anisoles in higher yields at short reaction time (5–6 h). *o*-, *m*-, *p*-Nitrophenols gave higher yields under the optimized condition. *p*-Bromo and *p*-iodophenols resulted in 90% and 92% yields of the respective anisoles. Increasing the steric hindrance on the aromatic ring showed not much influence on the reaction yield. For example, *o*-acetyl and *p*-*t*-butylphenol exhibited 89% and 94% yields to their respective anisoles. 2-Naphthol also gave 98% yield to its corresponding ether.

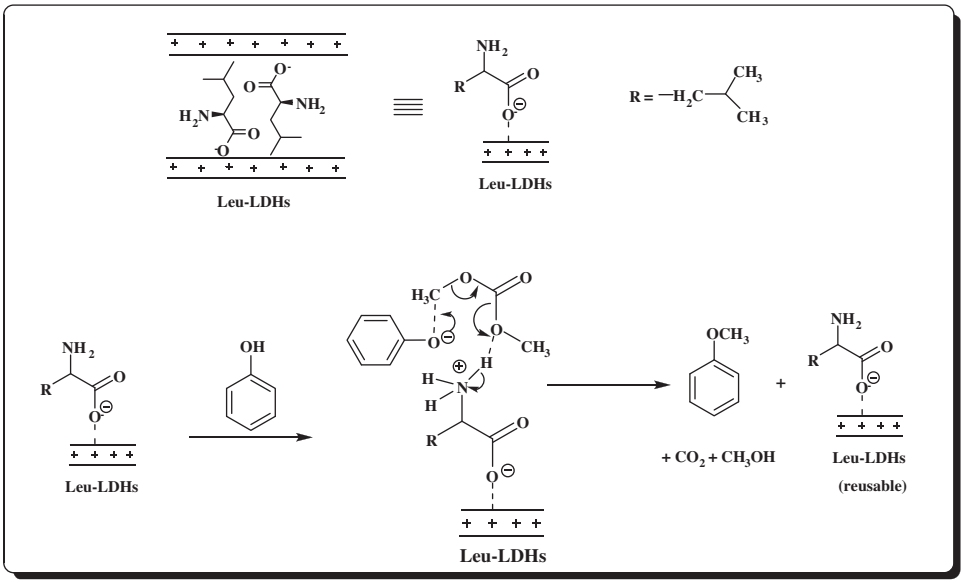
On the basis of the above results and also in accordance with our previous report,[27] a plausible reaction pathway is proposed for Leu-LDHs catalyzed chemoselective *O*-methylation of phenol with DMC as shown in Scheme 1. Leu is intercalated into anionic LDHs through $COO^-$ group in such a way that the amine group is exposed and the elongated side chain created a hydrophobic pocket. The free amine abstracts acidic hydrogen from phenol generating a softer phenolate anion, which in turn attacks DMC at the methyl group (softer electrophile) forming a six membered transition state inside the hydrophobic pocket, which further rearranges to give anisole and methanol as the end products.

One of the main advantages of heterogeneous catalysis is the recovery and reuse of the catalyst after the reaction. In this connection, the reusability of Leu-LDHs was tested in the *O*-methylation

**Table 5**
Reusability of the catalyst[a]

| Reuse | First | Second | Third | Fourth |
|---|---|---|---|---|
| Yield[b] (%) | 98 | 96 | 95 | 91 |

[a] Reaction conditions: phenol (1 mmol), DMC (1.2 mL), Leu-LDHs (100 mg), 180 °C, 6 h.
[b] GC yield.




**Scheme 1.** Plausible reaction mechanism for Leu-LDHs catalyzed *O*-methylation of phenol with DMC.

**Table 6**
Comparison of the present work with other reported catalytic systems for methylation of phenol

| Entry | Catalyst | Methylating agent | Base | Solvent | Time (h) | Yield (%) | Reusability of catalyst |
|---|---|---|---|---|---|---|---|
| 1 | —[28] | $(CH_3)_2SO_4$ | NaOH | EtOH | 1 | 89 | — |
| 2 | $Me_4NCl$[21] | —[a] | $K_2CO_3$ | DME[b] | 25–60 min | 19–91 | — |
| 3 | $BF_3$/ether[19b] | $P(OMe)_3$[a] | — | — | 1–3 min | 72–99 | — |
| 4 | [BMIm]Cl[26] | DMC | — | — | | >90 | 5 |
| 5 | DBU[29] | DMC | — | — | 10 min | 96 | — |
| 6 | Basic alumina[20] | $(CH_3)_2SO_4$ | KOH | — | 3–12 | 56–89 | — |
| 7 | F/Mg(Al)O[22b] | DMC | — | — | 8 | 99 | — |
| 8 | Calcined Mg–Al hydrotalcites[30] | DMC | — | — | 2 | 94 | — |
| 9 | Cs-MCM-41[25a] | MeOH | — | — | 1 | 96 | — |
| 10 | Leu-LDHs (present work) | DMC | — | — | 6 | 98 | 4 |

[a] Microwave mediated reaction.
[b] 1,2-dimethoxyethane.

of phenol with DMC. After completion of the reaction, Leu-LDHs were recovered by simple filtration after extracting with acetonitrile (10 mL) and activated in an air oven at 90 °C for 1 h then used for the next run. As it can be seen from Table 5, the catalyst can be reused four times with no significant loss in its activity.

The present catalytic system is compared with other reported works based on the reaction conditions employed, activity, and efficiency for methylation of phenol to delineate the merits and demerits of the present work and the data are shown in Table 6. These data indicate that our catalytic system (entry 10) exhibits a comparable performance to that of other conventional catalysts such as ionic liquid, fluorine modified magnesium aluminum oxide, and basic alumina. In addition, some of the catalytic systems required base (entries 1, 2, and 6), external solvent (entries 1 and 2), and higher reaction time (entries 6 and 7) while the current method does not require either base or solvent and the reaction completes in 6 h. In the present study, the catalyst was reused four times with no significant change in the overall yield while most of the reported systems did not enjoy these advantages.

In summary, different amino acids are intercalated into Mg–Al layered double hydroxides by the reconstruction method with the increase in interlayer space of LDHs, characterized by powder XRD and FT-IR techniques. The amino acids having large hydrophobic pocket exhibit high catalytic activity with excellent selectivity in *O*-methylation of phenol using DMC as methylating reagent and no *C*-methylated products are observed. The reaction has notable advantages from green chemistry point of view (1) it uses the cheap and non-toxic DMC; (2) no additional solvent is required; (3) catalyst can be prepared readily; (4) aryl methyl ethers are quantitatively obtained and waste of substrates is avoided; (5) Leu-LDHs can be easily recycled with no drop in its catalytic activity and (6) no hazardous wastes are produced. It is also relevant to emphasize that the products obtained needs no further purification.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.098.

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31. *General experimental procedure for AA-LDHs catalyzed methylation reactions*: In general, to 1 mmol of substrate, 100 mg of AA-LDHs and 1.2 mL of DMC were added. This mixture was kept in an autoclave at 180 °C for 6 h. The reaction mixture was extracted from the heterogeneous medium, upon stirring with acetonitrile for about 8 h, and filtered. The organic layer was dried over anhydrous sodium sulfate and the products were isolated and confirmed by their $^1$H NMR data.