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Layered Double Hydroxide-Supported L-Methionine-Catalyzed Chemoselective O-Methylation of Phenols and Esterification of Carboxylic Acids with Dimethyl Carbonate: A "Green" Protocol

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Alkylation of aromatics, an important reaction in organic chemistry, is widely used in the synthesis of petrochemicals, fine chemicals and pharmaceuticals.[1–4] Methyl halides, dimethyl sulfate and diazomethane are commonly used in methylation reactions.[5] The alkylation of a carboxylic acid to the corresponding methyl ester is also another fundamental transformation in organic chemistry.[6–7] A number of techniques including microwave applications[8–10] and zeolite-based catalysts[11–17] have been developed for the esterification process to prepare fine chemicals used in the synthesis of drugs, food preservatives, solvents, perfumes, pharmaceuticals, plasticizers and cosmetics.[18–19] Most of the reported procedures for esterification/etherification require use of sulfuric acid, hydrochloric acid and other toxic chemicals which are environmentally hazardous. Considering the impact of these chemicals on the environment, there is an urgent need to develop more ecofriendly methods for the production of methyl ethers/esters. During the past two decades, the non-toxic dimethyl carbonate (DMC) has emerged as a green alternative to replace the above toxic reagents and a number of methods have been reported for DMC-mediated processes with homogeneous and heterogeneous catalysts,[20–36] zeolite-based catalysts,[37–40] ionic liquids,[41–42] pentaalkylguanidines[43] and DBU.[44]

Generally, O-methylation of phenols is very slow at low temperatures as it requires a higher energy of activation and hence normally higher temperatures are necessary. Though it is a safe and efficient alternative, use of DMC in O-methylation needs rigorous conditions, as the major reaction is only methoxycarbonylation. The procedure is also not suitable for high boiling-point phenols. Consequently, various approaches have been reported[45–50] with different catalytic systems to obtain selective O-methylation of phenol with DMC as methylating agent. For example, O-methylation of phenol is achieved using alkyl methyl carbonates as methylating agent with a limitation of having bulky linear alkyl group (at least 3 carbon atoms) and a polar aprotic solvent.[45] 2-Naphthol is methylated with DMC and methanol and has resulted in a mixture of products (O-methylation and C-methylation) which mainly depends on the differences in the acid strengths of the zeolite and activation of 2-naphthol as well as the alkylating molecule.[46] As the ionic liquid, [BMIm]Cl is used for O-methylation of phenol selectively to anisole and the percentage conversion mainly depends on the imidazolium moiety of the ionic liquid.[47] Phenol is O-methylated by a continuous-flow method which requires poly(ethyleneglycol) 1000 as an anion activator along with K_2CO_3.[48] Fluorine-modified Mg-Al mixed oxides have been used for O-methylation of phenol and the percentage conversion depends on F/Mg ratio.[49] Ouk et al. have demonstrated O-methylation of phenol with DMC using potassium ion based bases.[50] In a continuous flow process use of alumina or alumina/silica as heterogeneous catalysts leads to the formation of aryl methyl ethers in good yield[51] but byproducts due to C-methylation are also observed. These results have prompted us to develop a process which can avoid the use of solvent, does not require an additional anion activator, selective towards O-methylation and applicable to a wide range of substrates with different functional groups.

Layered materials such as hydrotalcite-like layered double hydroxides (LDH) possess properties such as large surface area, high ion exchange capacity, swelling and intercalation which make them ideal supports for immobilization[52] of homogeneous catalysts such as chiral catalysts,[53] metal–salen complex,[54] Pd metal[55] and metal nanoparticles namely Pd^0,[56] Rh^0[57] and Pt^0[58] in their interlayer space. LDH has also been used to prepare highly oriented organic-LDH films.[59] In this work, we report the preparation of a novel LDH-supported L-methionine (based on a reported

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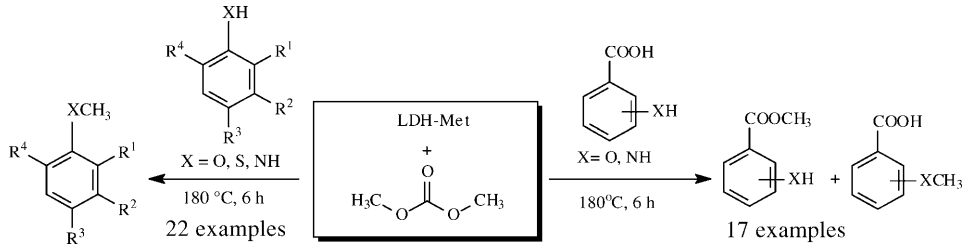
procedure[60]) and its successful use as a reusable catalyst for methylation of phenols and carboxylic acids with DMC (Scheme 1). The products are obtained by simple filtration of the catalyst after extracting with dichloromethane, which



Scheme 1. Chemoselective reactions of DMC in the presence of LDH-supported L-methionine catalyst.

makes this protocol suitable for various synthetic purposes. The prepared (LDH-Met) catalyst is characterized by powder XRD, FT-IR, TGA/DTA and EDX analysis (Supporting information).

Phenol is used as the substrate to optimize the reaction conditions. Without catalyst, O-methylation of phenol with DMC has afforded no product, while in the presence of catalyst, anisole is obtained in quantitative yield with 100% selectivity (Table 1). It is noteworthy that no C-methylated products are observed as evident from its ^{1}H NMR spectrum (Supporting Information). DMC acts as a solvent as well as methylating agent. Control experiments show that, the reaction fails at reflux temperature (90°C) and is very slow at 140°C. However, at 180°C the reaction leads to completion with 100% selectivity towards O-methylation. Also it is appropriate to note that the percentage conversion gradually increases as the reaction time increases and optimum conversion is realized in 6 h. It has been well established that the methyl group attached to the methionine sulfur atom in S-adenosyl methionine (SAM) is chemically reactive and this group gets readily transferred to an acceptor substrate in transmethylation reactions. More than 40 metabolic reactions involve this transfer of a methyl group from SAM to various substrates such as nucleic acids, proteins, and lipids.[61] In view of the importance of this methyl group transfer in SAM, we wish to study the effect of LDH-Met in methylation reactions involving DMC.

Further studies show that substituted phenols also found to be readily converted to the corresponding ethers under the present experimental conditions in the presence of LDH-Met as catalyst (Table 2, entries 1–4). Substituted polyphenolic compounds are also satisfactorily converted to its corresponding ethers (Table 2, entries 5,7,8), though low yields were observed with catechol. Resorcinol gives exclusively dimethylated product whereas quinol gives a mixture of mono- and dimethylated products (Table 2, entries 7 and 8). Under the present experimental conditions, 4-aminophenol yields both O- and N-methylated products (Table 2, entry 9). The reactivity of various phenols is found to depend on the substituents in the benzene ring. Phenols with electron-donating groups and/bulky substituents retard O-methylation (Table 2, entries 11–13).[47] This O-methylation protocol is also found to be suitable for ketones having hydroxyl groups (Table 2, entries 16–19). *o*-Hydroxyacetophenone results in low yield and this may be due to the intramolecular hydrogen bonding. This elegant methodology is also extended to prepare *p*-methoxystyrene in good yield (Table 2, entry 20).

To generalize this method further, S- and N-methylation are also carried out under identical conditions. S-Methylation is very efficient giving 97% yield with very little amount of diphenyl disulfide as byproduct. On the other hand, aniline reacts slowly and yields mono- as well as dimethylated products which is in accordance with previous report.[62] Though aniline is generally more nucleophilic than phenol, the decrease in reactivity in methylation observed here is attributed to a) facile ionization to more nucleophilic phenolate ion taking place readily under basic conditions and b) greater steric hindrance to methylation with the former. Based on the observed results, the following order of reactivity is (O-methylation $\approx$ S-methylation $>$ N-methylation) is rationalized.

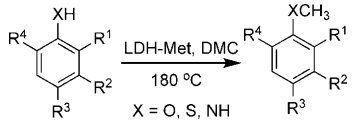
Table 1. O-Methylation of phenol to anisole with DMC in the presence of different catalysts.[a]

Run	Catalyst	*t* [h]	Yield [%][b]
1	none	4	0
2	L-methionine	4	0
3	hydrotalcite	6	23
4	K_2CO_3	6	39
5	Na_2CO_3	6	25
6	LDH-Met	4	90
7	LDH-Met	6	100
8	LDH-Met[c]	4	0
9	LDH-Met[d]	8	8

[a] Phenol (0.1 mL), DMC (1.2 mL), catalyst (100 mg), temperature (180°C) in an autoclave. [b] Determined by GC. [c] Reaction carried out at reflux temperature (90°C). [d] Methanol is used as methylating agent.

Recently, Selva et al. have reported zeolite-based chemoselective esterification of indolecarboxylic acids with DMC as methylating agent.[63] These observations have prompted us to extend the scope of this protocol for esterification of various carboxylic acids under identical conditions and it has been observed that simple carboxylic acids (Table 3, entries 1–4) are alkylated in good yields and excellent purities. When phenolic and amino groups are present, methylation occurs at both OH as well as at NH_2 group and the ratio of the products are determined by NMR spectroscopy (Table 3, entries 5–6). N-Protected amino acids such as N-acetylated *p*-aminobenzoic acid (Table 3, entry 3) can also

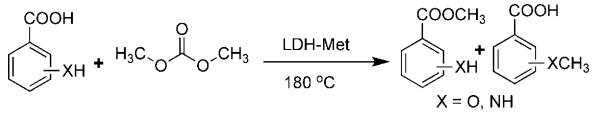
Table 2. O-Methylation of phenols with DMC in the presence of LDH-Met.[a]

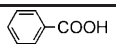
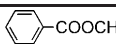
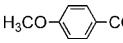
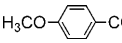
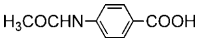
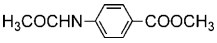


Entry	Substrate				Yield [%][b]
	R^1	R^2	R^3	R^4	
			X=O		
1	H	H	H	H	92
2	Cl	H	H	H	90
3	H	H	Br	H	95
4	H	H	NO_2	H	89
5	OH	H	NO_2	H	81[c]
6	OH	H	H	H	10
7	H	OH	H	H	89[c]
8	H	H	OH	H	88[d]
9	H	H	NH_2	H	90[e]
10	H	H	OCH_3	H	82
11	H	H	CH_3	H	10
12	*t*Bu	H	H	*t*Bu	05
13	*t*Bu	H	*t*Bu	H	06
14	H	H	C_3H_7	H	89
15			2-naphthol		94
16			4-hydroxybenzophenone		87
17	$COCH_3$	H	H	H	23[f]
18	H	$COCH_3$	H	H	86
19	H	H	$COCH_3$	H	89
20	H	H	$CH{=}CH_2$	H	80
			X=S		
21	H	H	H	H	97
			X=NH		
22	H	H	H	H	50

[a] Reaction conditions: Substrate (0.1 mL), DMC (1.2 mL), catalyst (100 mg), temperature (180 °C) in an autoclave, time (6 h). [b] Isolated yield and are characterized by ^{1}H NMR. [c] Both hydroxyl groups are methylated. [d] Combined yield of mixture of products and mono/di (84:16) methylation ratio is determined by GC. [e] Combined yield of mixture of products and O/N (52:48) methylation ratio is determined by NMR. [f] Yield determined by GC.

Table 3. Synthesis of carboxylic esters using LDH-Met as heterogeneous catalyst.[a]



Entry	Starting acid	Product	Yield [%][b]
1			89
2			88
3			90
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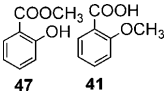
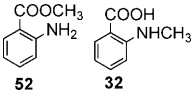
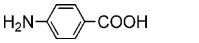
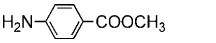
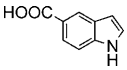
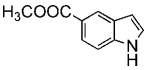
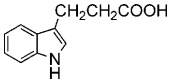
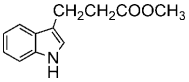
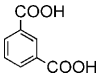
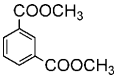
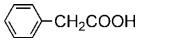
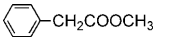
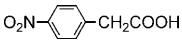
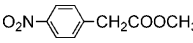
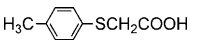
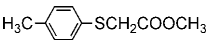
5		 **47** **41**	88
6		 **52** **32**	84
7			90
8			89
9			85
10			89
11			84
12			–
13			91
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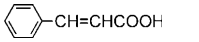
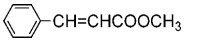
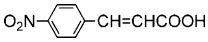
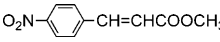
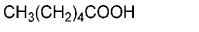
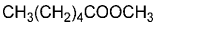
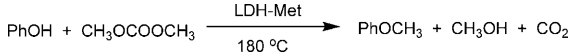
15			91
16			84
17			81

[a] Reaction conditions: Substrate (0.1 mL), DMC (1.2 mL), catalyst (100 mg), temperature (180 °C) in an autoclave, time (6 h).

Table 4. Recycling of LDH-Met. in the reaction of phenol with DMC.



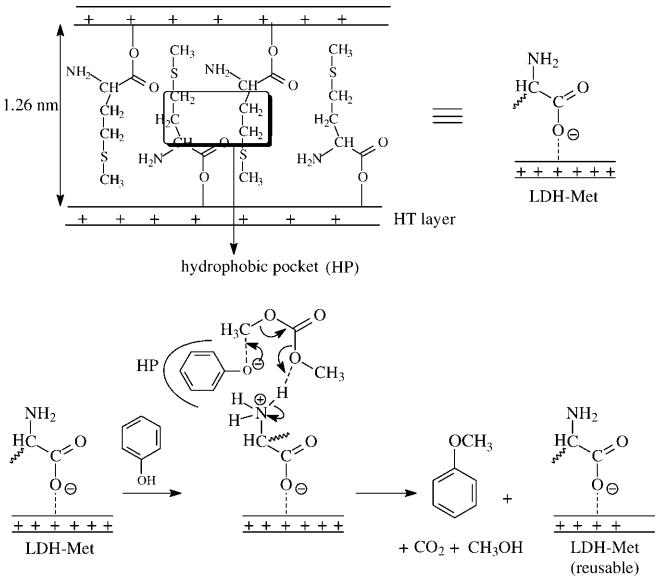
Cycle	1	2	3	4
Selectivity [%]	100	100	100	100
Yield [%]	90	91	88	89

be cleanly transformed to the corresponding esters. In addition indole derivatives are cleanly converted to the corresponding esters (Table 3, entries 8–9). Dicarboxylic acids are conveniently methylated at both carboxyl groups with the present catalytic system (Table 3, entry 10). 1-Phenyl, 1-naphthylacetic and also *p*-methylthiophenylacetic acids are converted to the corresponding esters successfully (Table 3, entries 11, 13 and 14). This protocol is also very much useful for the synthesis of cinnamic acid ester and its *p*-NO_2 substituted esters in very good yield without affecting the olefinic double bond (Table 3, entries 15 and 16). In all cases, products are obtained with >98% purity. The catalyst is also recycled. In the reaction of phenol with DMC, LDH-Met is recovered by filtration after extracting with dichloromethane (10 mL) and it is activated in an air oven at 90 °C for 1 h. In all the runs, the mass balance was >90%. This is reused for further runs as shown in Table 4.

Tundo et al. have demonstrated that nucleophilic substitution on DMC by various anions having different soft/hard character can be rationalized on the basis of HSAB principle.[36] For example, oxygen nucleophiles such as alcohols give mainly transesterification products either under gas–liquid phase-transfer catalysis at 180 °C[64] or under batch conditions. At 200 °C also, the reaction occurs at the carbonyl group only suggesting a hard acid/hard base interaction. On the other hand, methylation of alcohols is reported to

occur in the presence of tertiary amines[65] (e.g., (dimethylamino)pyridine, 1,4-diazabicyclo[2.2.2]octane). In this case, the catalyst modifies the hard–soft character of the two centers, thus allowing the nucleophilic displacement at the methyl group (softer acid) by the phenoxide ion (softer base) to occur. With *p*-substituted phenols, electron-withdrawing substituents in the ring, by facilitating the formation of softer phenoxide anion, give S_N2 displacement yielding once again methylation as the major reaction.

To find support for the observed selectivity in the present study, the following mechanism is proposed. L-Methionine is anchored onto anionic layered double hydroxide via its COO^- group in such a way that the amine group is exposed and the elongated side chain creates a hydrophobic pocket. The free amine abstracts acidic hydrogen of 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 rearranges to give anisole and methanol as the end products (Scheme 2). In control experiments, reaction of phenol with



Scheme 2. Plausible catalytic cycle for O-methylation of phenol with DMC.

excess (300 mg) LDH-Met results in negligible conversion of phenol in the absence of DMC, thus ruling out transfer of methyl group of methionine. However, additional experiments are needed to understand in detail the salient mechanistic features of the methylation involving this hybrid material.

In conclusion, the selective O-methylation of phenols with DMC has been studied in the presence of LDH-Met as an efficient organocatalyst. Phenols and carboxylic acids are converted into their corresponding aryl methyl ethers and aryl methyl esters, respectively, in high selectivities and yields, and no C-methylation products are obtained in the methylation of phenols. The reaction has notable advantages and remarkable environmentally benign features: 1) it uses cheap and non-toxic DMC; 2) DMC acts as a solvent and methylating agent; 3) catalyst can be prepared readily; 4) aryl methyl ethers and esters are quantitatively obtained and waste of substrates are avoided; 5) LDH-Met can be easily recycled and reused without decreasing catalytic activity; 6) no hazardous waste is produced. Finally, the products are obtained in high purity and this protocol does not require further purification.

Experimental Section

In general, to phenol (0.1 mL), LDH-Met (100 mg) and DMC (1.2 mL) were added. The mixture was kept in an autoclave at 180 °C for 6 h. The reaction mixture was extracted from the heterogeneous medium, upon stirring with dichloromethane for about 8 h, and filtered. The filtrate was washed with water and the organic layer was dried over anhydrous sodium sulfate. Products were isolated and were confirmed by their ^{1}HNMR spectra.

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Keywords: dimethyl carbonate · esterification · heterogeneous catalysis · layered double hydroxide · methylation

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