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Selective *N*-Alkylation of Imidazole with Alcohols over Calcined Layered Double Hydroxides

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Vapor-phase *N*-alkylation syntheses of imidazole were carried out with MeOH and EtOH over a series of calcined $\mathrm{Mg^{II}}$–$\mathrm{Al^{III}}$ layered double hydroxides (LDHs) selectively produced in high yields of *N*-methyl (70%) and *N*-ethyl (63%) imidazoles only on the 3 : 1 atomic ratio of $\mathrm{Mg^{II}}$–$\mathrm{Al^{III}}$ calcined LDH. Attempts on C-alkylation and dialkylation reactions over the same catalysts proved to be unsuccessful.

N-alkylated imidazole derivatives serve as potential precursors in the complex and multistep syntheses of several chemotherapeutic agents with trichomonad anesthetic, hypnotic and antimycotic activities.1) Hence, selective *N*-alkylation transformations of imidazoles in the vapor phase have become an industrially important synthesis. The utility of common alkylating agents, such as alkyl halides or dimethyl sulfates, have proven to be futile due to their toxicity and corrosiveness. They are eco-deadlier and are required in higher amounts of $\mathrm{NaNH_2}$ and NaOH as additives.2) For similar reasons, of late, the formations of 1,4 (or 5)-dialkylimidazole from tautomeric 4(5)-methylimidazole with alcohols in the vapor phase have been reported over zeolites. Also, the presence of a methyl substituent in imidazole with a+I effect seem to aid the process over Y-type zeolites.3—5) In the present work, attempts concerning the possibility of direct and selective *N*-alkylation reactions of unsubstituted imidazole in the vapor phase with MeOH and EtOH over calcined $\mathrm{Mg^{II}}$–$\mathrm{Al^{III}}$ layered double hydroxides (CLDHs) in various mole ratios have been reported.

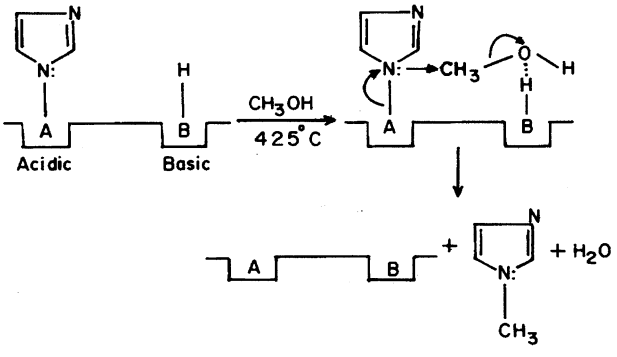
Anionic clays with a hydrotalcite-like (HT) structure, also known as LDH, represent the counterpart of the well-known cationic clays; their general formula can be written as $[\mathrm{M}^{\mathrm{II}}_{1-x}\text{–}\mathrm{M}^{\mathrm{III}}_{x}(\mathrm{OH})_2]^{x+}[\mathrm{A}^{n-}]_{x/n}\cdot m\mathrm{H_2O}$, where ‘M’ is the respective metal cation; ‘x’ is the mole ratio of $\mathrm{M^{II}}$–$\mathrm{M^{III}}$, usually lying between 0.2 and 0.33; ‘A’ is the interlayer anionic carbonate and ‘n’ is crystalline water. Calcination removes the interlayer carbonate and water from LDH, resulting in a high specific surface area, a porous nature and a strongly basic solid solution, CLDH. Applications of LDH and CLDHs over a wide range of fields are due to the tunable “acidity–basicity” of the solids via M(II) : M(III) composition formulations.6) Also, CLDHs have been reported as being efficient and selective catalysts for the alkylation of anilines,7) phenols, C-alkylation,8) and for some miscellaneous reactions, such as aldol condensation, epoxidation, alkene isomerization and alcohol oxidation.6,9) The characterization methods of CLDHs, product optimizations with the reactor temperature, time on stream, % conversions and probable reaction pathway (Scheme 1) have been briefly discussed.

Experimental

Freshly distilled and dried MeOH and EtOH (E-Merck) were used. Analar-grade samples of the metal nitrates were used to prepare aqueous solutions. A sequential precipitation method was adopted to prepare the LDHs.6) To an aqueous solution containing $\mathrm{Mg(NO_3)_2\cdot 6H_2O}$ and $\mathrm{Al(NO_3)_3\cdot 9H_2O}$ mixed at the desired mole ratio, an aqueous solution of NaOH was added dropwise with stirring until the pH reached 10.0. The resulting white slurry was stirred at 313 K for 20 h, then filtered and washed with deionized and decarbonated water until the pH of the filtrate became equal to 7.0 and dried at 373 K. The samples were stored in a desiccator before use.

The characterizations of LDH and CLDHs were carried out using X-ray powder diffraction, thermogravimetry and BET specific surface-area determinations. The ICPES method was adopted to estimate the molar ratios of M(II) and M(III) ions in LDHs. The organic products were analysed through conventional GC, ^{1}H NMR and IR measurements.

The LDHs used were 1 : 1, 2 : 1, 3 : 1, 4 : 1, 5 : 1, 7 : 1, and 9 : 1 mole ratios of $\mathrm{Mg^{II}}$–$\mathrm{Al^{III}}$ carbonates hydroxides, were calcined by heating at 698 K for 12 h in air. A solution of imidazole in methanol and ethanol in various mole ratios was fed into a vertical fixed bed



Scheme 1. Reaction pathway.

(2 cm i.d., 28 cm long) reactor loaded with 1.5 g of CLDH without any carrier gas at 698 K, by using a motor-driven syringe at various flow rates. The products were collected on an ice trap and analyzed by gas chromatography and by ^{1}H NMR in $CDCl_3$. The catalyst activities were tested by carrying out the reaction continuously for six hours. Reactivation of the catalyst was made in a N_2 atmosphere at 723 K for 7 h prior to each run. The reaction conditions based on the % yield of the product were optimized using various feedmix mole ratios (imidazole : alcohols) on a series of Mg : Al mole ratio CLDHs at 573, 648, 698, and 748 K reactor temperatures.

Results and Discussion

Typical XRD, IR TGA, and DTA patterns of LDH of Mg–Al are shown in Fig. 1. Two-stage weight losses corresponding to the desorption of physically adsorbed H_2O and decarboxy-hydroxylations were observed for LDHs.

The IR and TGA patterns indicate the LDHs.[10—13] Upon heating up to 473 K, the interstitial water loss was reversible, and during 548—723 K the decarboxylated and dehydrated CO_2 and H_2O regenerated the HT lattice framework insitu. Heating to and above 873 K resulted in a loss of the HT lattice framework. The catalytic efficiency in the CLDH, calcined at around 723 K is due to activated surfacial MgO and $MgO\text{–}Al_2O_3$.[14,15] In the overall basic CLDH, Al sites result in an acidic behaviour, and mixture of $MgO\text{–}Al_2O_3$ produces a combination of neighbouring acidic–basic sites in such a manner that the 3 : 1 CLDH behaves as a better catalyst in the presence of a series of catalysts. Other surface reaction characterizations, like surface area, reactor temperatures, and % conversions at various mole ratio CLDHs, are presented Table 1. Considering the % conversion dependency with mole ratios $Mg^{II}\text{–}Al^{III}$ in CLDHS, the 3 : 1 sample proves to result in the maximum (70%) conversion. A study on the effect of the reactor temperatures on a 3 : 1 catalyst shows that the maximum conversion occurs at around 698 K. A further increase in the reactor temperature to 723 K only results in a lower % conversion. In all of the cases studied the end-product analyses clearly indicated single-product formations with the corresponding *N*-alkyl substituents in imidazole with C-alkylation being almost nil.

Table 1. *N*- Alkylation of Imidazole with Alcohols over Calcined $Mg^{II}\text{–}Al^{III}$ Layered Double Hydroxides (Selectivity 100%)

Catalyst molar ratio	Reactor temperature	Surface area	% Conversion	
Mg^{II} : Al^{III}	K	$m^2\,g^{-1}$	*N*-Methyl-imidazole	*N*-Ethyl-imidazole
1 : 1	698	110.0	43	37
2 : 1	698	119.1	41	39
3 : 1	573	110.0	52	51
	648	126.1	62	58
	698	136.0	70	63
	748	138.0	60	53
4 : 1	698	118.5	55	47
5 : 1	698	145.5	50	45
9 : 1	698	135.0	47	41

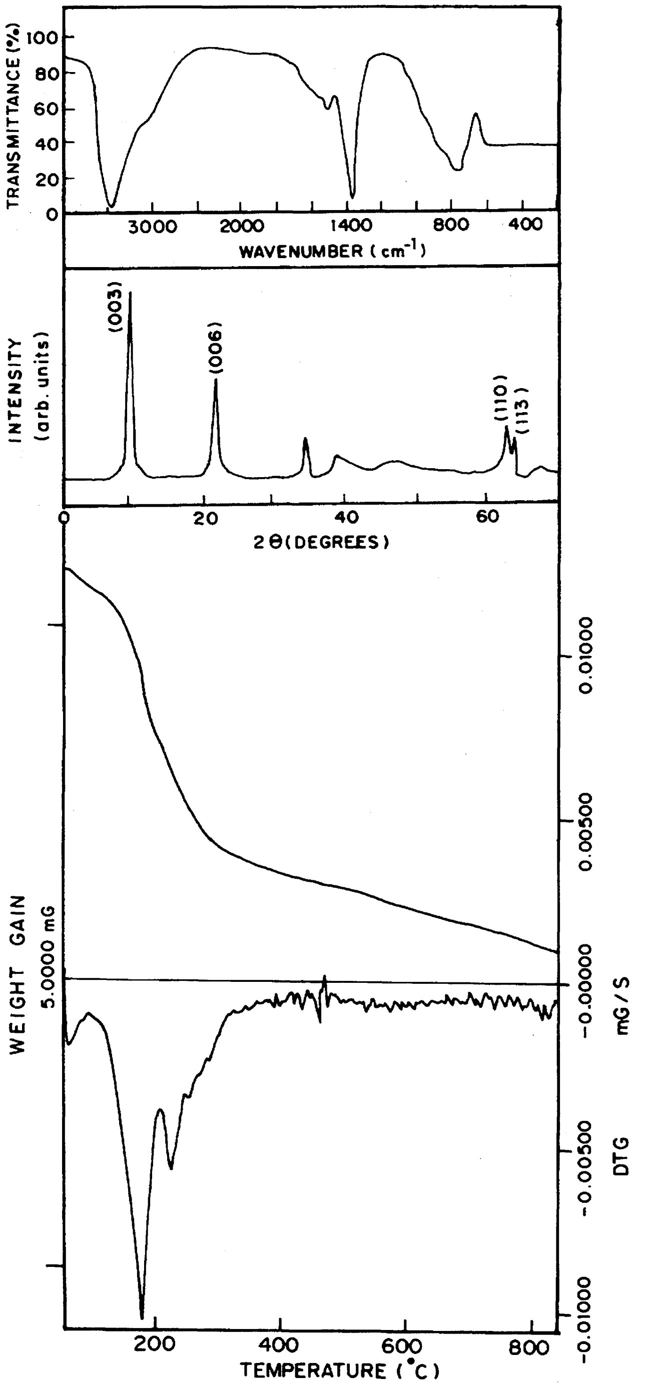


Fig. 1. XRD, IR, and TGA-DTA patterns of LDH.

When MeOH and EtOH were used, *N*-methyl and *N*-ethyl imidazoles were obtained, respectively, as a single product in each case. When the catalyst mole ratio and reactor temperature were kept constant as 3 : 1 and 698 K, the *N*-methyl products yield were found to be more than that of the *N*-ethyl product.

A study on the variations in the feed-mix mole ratio indicates a 1 : 10 (imidazole : alcohol) ratio to yield the maximum % conversion. The percentage yield in Table 1 refers to only the 1 : 10 feed mix ratio. Among the various flow rates adopted, 7 ml h^{-1} has been found to yield the maximum conversions. Regarding the efficiency of the 3 : 1 catalyst, no deactivations after numerous reaction cycles were detected. The specificity and efficiency of 3 : 1 CLDHs towards single-product formation may be attributed to the higher specific surface area obtained at 698 K, compared to that of other mole-ratio catalysts (Table 1). The high specific surface area results from the decarboxylations and dehydroxylations, which proportionate to the chemically adsorbed CO_2 (as $CO_3{}^{2})$ and H_2O molecules, which, in turn, balance the net basicity of the LDH.[16)]

The *N*-alkylation process proceeding via a concerted type, as shown in the scheme, has been confirmed by the absence of C-alkylated products.

The mechanism invokes the activity of a nitrogen atom on the imidazole (though neutralized on the acid site), caused by hydrogen abstraction of the neighbouring bronsted basic site. Interactions such as hydrogen bonding binds and orients the alkylating agents in a manner such that the electromeric shifts make the N-atom at the acid site nucleophilic. This results in the *N*-alkylation of imidazole. Similar *N*-alkylation reactions of imidazole carried out over magnesia and alumina, physically mixed in various mole ratios, showed lower activities in terms of the yield, longevity and recycling of the catalyst.

Absolute selectivity towards *N*-methylimidazole and *N*-ethylimidazole formations may also be caused by the specific value of the resultant basicity of the 3 : 1 CLDHs. However, the results of this work pave the way to a series of selective *N*-alkylation reactions of imidazoles using calcined Mg^{II}–Al^{III} LDHs. Depending on the basicity of the substrate and the mole ratio of Mg^{II}–Al^{III} in CLDHs, the product selectivity and yield may vary, since 'acidity–basicity' functions are governed by the CLDH compositions. When 1-propanol is used, fragmentation of the alcohol may result, thus leading to different *N*-alkylated products. Research along this line is under progress. Also, an estimation and correlation of the resultant basicity of the CLDHs to the *N*-alkylation of various amines are under investigation.

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