Direct condensation of carboxylic acids with alcohols: The atom economic protocol catalysed by Fe^{3+}-montmorillonite [*]

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Received 17 July 2001; accepted 3 October 2001

Fe^{3+}-montmorillonite clay catalyst was used for the first time to esterify various aliphatic, aromatic, α,β-unsaturated mono- and dicarboxylic acids and long chain fatty acids with alcohols under mild reaction conditions in good to excellent yields. The present heterogeneous catalytic system is a potential candidate not only for laboratory practice but also for commercial application and offers an environmentally safer alternative to the existing processes.

KEY WORDS: esterification; carboxylic acids; condensation; azeotrope; Fe^{3+}-montmorillonite catalyst

1. Introduction

Esterifications are among the most fundamental and important organic reactions in organic synthesis, because of their ubiquitous applications as intermediates in the synthesis of fine chemicals, drugs, plasticizers, perfumes, food preservatives, cosmetics, pharmaceuticals, solvents and chiral auxiliaries. Recent reports [1] include improved variation of well-established procedures, either innovative and/or applications of entirely new ones, but are restricted to laboratory scale and lack of commercial viability in economic terms. The established process using sulfuric acid, *p*-toluenesulfonic acid (PTSA) as a catalyst or dry hydrochloric acid [2] passed through a methanolic solution of the carboxylic acid leads to highly acidic waste streams posing environmental problems. Alternatives such as cationic exchangers like Amberlyst-15 [3], heteropolyacids supported on carbon [4], SiO_2–Al_2O_3 and zeolites [5], sulphated zirconia and titania [6], Nafion-H [7] and niobic acid in vapour phase reactions [8] have been developed. The esterification of carboxylic acids with alcohols or olefins in the presence of Zr^{4+}-montmorillonite to corresponding esters [9] and etherification of Me_2CHOH catalysed by Al^{3+}-montmorillonite to $(Me_2CH)_2O$ [10] are reported. An esterification process patented by the Texaco Chemicals Co. described the esterification of tertiary butanol with methanol in the presence of phosphoric-acid-treated montmorillonite to methyl-*tert*-butyl ether [11]. But, the use of high pressures and temperatures made the above processes unattractive. Ballantine *et al.* demonstrated the etherification of alkenes with different nucleophiles in the presence of metal-ion-exchanged montmorillonite clay catalysts successfully [12]. Alkylation of free carboxylic acids with alkyl halide in the presence of H^+-montmorillonite at higher temperature [13], CsF and hexamethylphosphoramide (HMPA) was also demonstrated [14]. Hafnium(IV) salts [15] have been found very effective in condensation of acids with alcohols to afford a wide spectrum of esters with high atom economy. Although most of these solid acid catalysts offer distinct advantages over conventional methods in terms of product separation and recycling, they suffer from certain drawbacks such as high cost, long reaction times, poor selectivity and lower yields of the desired products.

In continuation with our investigations in catalytic activity of the montmorillonite clays, a class of inexpensive and non-corrosive solid acids [16], we herein report on Fe^{3+}-exchanged montmorillonite clay for esterification of carboxylic acids that include mono- and di-carboxylic acids and long chain fatty acids. The experimental procedure is very simple and the catalyst can be recycled for several times without loss of activity.

2. Experimental

2.1. Preparation of the catalysts

Metal-exchanged montmorillonite K10 clays were prepared by adopting literature methods [17], and dried in an oven at 120 °C overnight.

2.2. Characterisation

The metal content of Fe^{3+}-, Zn^{2+}-, Cu^{2+}- and Al^{3+}-exchanged montmorillonite catalysts was analysed according to Vogel's procedure [18] and found to be 6.3, 1.79, 1.28 and 7.82 wt%, respectively. The maximum acid strength for K10 montmorillonite with Hammett indicators in benzene is known ($-8.2 \geqslant H_0$) [19]. As it is difficult to judge colour changes of Hammett indicators for the coloured Fe^{3+}- and

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1011-372X/02/0300-0185/0

Cu^{2+}-montmorillonites, the acidity of Fe^{3+}-, Zn^{2+}-, Cu^{2+}- and Al^{3+}-exchanged montmorillonites and montmorillonite K10 was estimated by the temperature-programmed desorption of ammonia gas (NH_3-TPD) analysis and was found to be 1.029, 0.547, 0.350 and 0.524 μmol/g catalyst, respectively. Specific surface areas of the montmorillonite K10, Fe^{3+}-, Zn^{2+}-, Cu^{2+}- and Al^{3+}-exchanged montmorillonites are calculated from BET nitrogen isotherms determined at $-196\,^\circ$C (Micrometrics ASAP 2000) on samples degassed at $250\,^\circ$C for 12 h before the experiment and found to be 212, 248, 228, 234 and 226 m^2/g, respectively.

The products of the reactions were characterised by NMR and mass spectroscopic methods. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Gemini-Varian (200 MHz) NMR spectrometer, using TMS as an internal standard. Mass spectroscopic analysis was performed with a Micromass VG 7070H spectrometer.

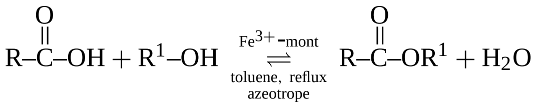
3. Catalytic reactions

3.1. Typical procedure

A two-necked round bottom flask equipped with a Dean–Stark trap is charged with a mixture of phenylacetic acid (1.36 g, 10 mmol), methanol (25 mmol), toluene (10 ml) and Fe^{3+}-montmorillonite clay (250 mg). The solution is heated under reflux with stirring. On completion of the reaction (followed by TLC), the reaction mixture is filtered and the catalyst is washed with ethyl acetate (2×10 ml). Ethyl acetate is used to extract the product and to wash off the ester adhered on the surface of the catalyst. The combined filtrate fractions are washed with saturated sodium bicarbonate and brine, dried on anhydrous magnesium sulphate and concentrated under reduced pressure to obtain pure product. Yield 1.47 g, 98%; ^{1}H NMR ($CDCl_3$): δ 3.6 (s, 2H), 3.7 (s, 3H), 7.2–7.35 (m, 5H); MS: $(m/z) = 150$ (M^+).

3.2. Results and discussion

Since the esterification reaction proceeds via an acyl-oxygen cleavage bimolecular ($A_{AC}2$) mechanism through a tetrahedral intermediate, it can be expected that a multivalent metal ion could affect the rate of esterification reaction due to transient complexation with the carbonyl group. To explore the possibilities of enhancing the catalytic efficacy, various metal-ion-exchanged montmorillonite K10 [17–19] were prepared and employed for the formation of a chiral auxiliary (+)-dimethyl (L)-tartarate, a widely used chiral intermediate from (L)-tartaric acid and methanol as a part of preliminary screening. The order of the activity in the esterification of the tartaric acid is Fe^{3+}-mont > H^+-mont > Zn^{2+}-mont > Al^{3+}-mont > K10-mont > Cu^{2+}-mont (table 1). The order of activity is in the increased order of acidity of the metal-exchanged montmorillonite clay catalysts as determined by TPD studies. The catalyst is recycled six times, which shows consistent activity.



$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH} + \mathrm{R^1{-}OH} \underset{\text{toluene, reflux azeotrope}}{\overset{Fe^{3+}\text{-mont}}{\rightleftharpoons}} \mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OR^1} + H_2O$$

R = aliphatic, aromatic, α,β-unsaturated, fatty, mono- and di-carboxylic acids; R^1 = methanol, ethanol, butanol, hexanol and octanol.

Scheme 1.

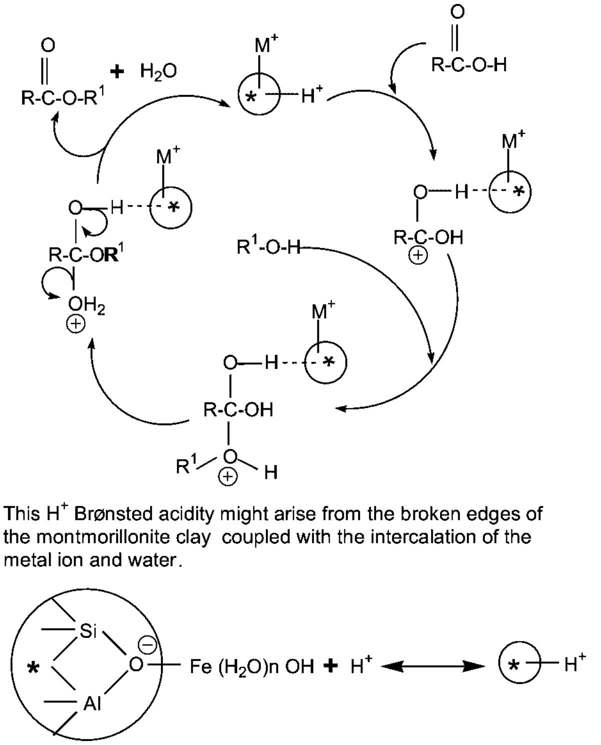
According to the reaction mechanism, the density of the Brønsted acid sites in the acid-treated montmorillonite K10, specially chosen for the studies, is increased over natural montmorillonite because of the increased number of broken edges resulting from the broken layers to favour the formation of esters assumed to proceed *via* the $A_{AC}2$ mechanistic pathway. Introduction of metal *via* ion exchange process in montmorillonite K10 catalyst enhances not only the Lewis acidity but also Brønsted acidity. The enhancement of the Brønsted acidity is due to the interaction of the metal–aqua complex formed in montmorillonite K10 with water present/formed during the reaction. The formation of the right admix of Brønsted and Lewis acid sites is able to facilitate the esterification reaction as described in the reversible reaction

$$M^+(H_2O)_n + H_2O \rightleftharpoons M^+(OH)(H_2O)_{n-1} + H_3^+O$$

Indeed, the hydrated cations of montmorillonite are more reactive than their corresponding homogeneous analogues. The interlayer acidity increases with increasing ratio of charge to ionic radius of the cation [20,21]. Therefore, the Fe^{3+}-montmorillonite is the most superior catalyst compared to other metal-ion-exchanged montmorillonites. Moreover, the Fe^{3+} ion has lower redox potential which can polarise the carboxylic acid more strongly than the other exchanged metals. The sustained and long lasting activity of the catalyst over the number of cycles is ascribed to the generation of the Brønsted acid site as described and the regeneration of Brønsted acid sites to achieve high turnover number is explained in scheme 2. Moreover, the cationic aqua-complexes located in interlayers of montmorillonite have been countered with an array of negative layered charges that do not allow the cationic complex to go out of the interlayers. This is also attributed to the long lasting activity of the catalyst for the number of cycles.

Table 1
Esterification of L-tartaric acid with MeOH (1 : 2.5 molar ratio) in presence of toluene using various metal-exchanged montmorillonite clay catalysts

Entry	Catalyst	Time (h)	Isolated yield (%)
1	Fe^{3+}-mont	3.0	85
2	Cu^{2+}-mont	15.0	85
3	Zn^{2+}-mont	4.5	85
4	Al^{3+}-mont	5.0	85
5	Ce^{3+}-mont	4.5	85
6	H^+-mont	3.5	85
7	K10-mont	9.0	60
8	Blank	15.0	–



Scheme 2.

It can be easily seen that the product (+)-dimethyl-(L)-tartarate is obtained in high yields 85% and the reaction periods are shorter 3–5 h than the uncatalysed reaction (no progress in reaction even after 15 h). Loss in isolated product, *i.e.*, ~15% may be attributed to the high solubility of (+)-dimethyl-(L)-tartarate in water. The yield drops to 60–65% and reaction periods are also significantly longer 8–9 h when K10-montmorillonite as such is used. The above obtained (+)-dimethyl-(L)-tartrate was crystallized in benzene, dried in abderholden (Vacuum drier), and checked for optical purity. The enantiomeric excess was found to be >99%.

With this success, we further esterified other dicarboxylic acids such as malonic, succinic, glutaric and adipic acid with methanol and the corresponding dimethyl esters were obtained in ~70% yields (table 2) in 4–5 h. In the case of adipic acid, higher yields (90%) are obtained on prolonged reaction time (10 h). The selective formation of dimethyl maleate is observed when the reaction is performed in the presence of H$^+$- montmorillonite (table 2).

Table 2
Esterification of dicarboxylic acids with MeOH (1 : 5 molar ratio) in presence of toluene using Fe^{3+}-montmorillonite clay catalyst

Entry	Substrate	Reaction time (h)	Product	Yield (%)	
				NMR	Isolated
1	Malonic acid	3.0	Dimethyl malonate	75.0	70.0
2	Succinic acid	4.5	Dimethyl succinate	76.0	70.0
3	Glutaric acid	5.0	Dimethyl glutarate	75.0	68.0
4	Adipic acid	10.0	Dimethyl adipate	96.0	90.0
5	Maleic acid[a]	5.0	Dimethyl maleate	78.0	71.0
			Monomethyl maleate	22.0	–
		12.0[b]	Dimethyl maleate	66.0	–
			Monomethyl maleate	–	–
6	Phthalic acid	5.0	Dimethyl phthalate	72.0	60.0

[a] 1 : 10 molar ratio (acid to alcohol).
[b] In the presence of H$^+$-montmorillonite catalyst.

Aromatic monocarboxylic acids such as cinnamic acid and *p*-isobutyl-2-methyl phenylacetic acid (ibuprofen) corresponding methyl esters are obtained in 5–6 h with >70% conversion (table 3). It has also been observed that the nature of the alcohol used plays a vital role in determining the course of the reaction, *i.e.*, in the case of chloroacetic acid, the esterification reaction is more efficient when ethanol is used instead of methanol; the yields are improved from 65 to 80% (table 3). Optimum yields are obtained when toluene is used as an entrainer in place of benzene.

Esterification of long chain fatty acids is an important industrial process since the fatty acid esters are extensively used in the food and cosmetic industries. Fe^{3+}-montmorillonite clay catalyses the esterification of long chain fatty acids like stearic acid, lipoic acid and azelaic acid with good efficiency (table 4). It should also be noted that Fe^{3+}-montmorillonite clay functions as an excellent catalyst even in the case of sensitive fatty acids like lipoic acid with two sulfur atoms providing the lipoate es-

Table 3
Esterification of monocarboxylic acids with alcohols (1 : 2.5 molar ratio) in presence of toluene using Fe^{3+}-montmorillonite clay catalyst

Entry	Acid	Alcohol	Reaction time (h)	Product	Yield[a] (%)
1	Phenyl acetic acid	Methanol	6.5	Methyl phenyl acetate	100
2	Cinnamic acid	Methanol	5.0	Methylcinnamate	72
3	*p*-isobutyl, 2-methyl, phenyl acetic acid	Methanol	6.5	*p*-isobutyl, 2-methyl, phenyl methyl acetate	71
4	2-(6-methoxy-2-naphthyl) propionic acid	Methanol	12.0	2-(6-methoxy-2-naphthyl) methyl propionate	12
5	2-(6-methoxy-2-naphthyl) propionic acid	Ethanol	12.0	2-(6-methoxy-2-naphthyl) ethyl propionate	52
6	Cyano acetic acid	Methanol	4.5	Methyl cyano acetate	68
7	Cyano acetic acid	Ethanol	5.0	Ethyl cyano acetate	85
8	Chloro acetic acid	Methanol	5.0	Methyl chloro acetate	65
9	Chloro acetic acid	Ethanol	5.5	Ethyl chloro acetate	80
10	Chloro acetic acid	Ethanol	6.0	Ethyl chloro acetate	55[b]
11	Furan-2-carboxylic acid	Methanol	12	No reaction	–

[a] NMR yields.
[b] Benzene used as solvent.

Table 4
Esterification of fatty acids with various alcohols using Fe^{3+}-montmorillonite catalyst

Entry	Acid	Alcohol	Reaction time (h)	Product	Yield (%)	
					NMR	Isolated
1	Stearic acid	Methanol	5	Methyl stearate	100	98
2	Azelic acid	Methanol	6	Dimethyl azelate	66	62
3	Lipoic acid	Methanol	12	Methyl lipoate	76	–
4	Lipoic acid	Butanol	5	Butyl lipoate	100	98
5	Lipoic acid	Hexanol	3	Hexyl lipoate	100	98
6	Lipoic acid	Octanol	3	Octyl lipoate	77	–

ters without any by-product formation. The esterification with methanol results in moderate yields (reaction period 12 h, yield $>75\%$), whereas quantitative yields are obtained with the other higher alcohols like *n*-butanol and *n*-hexanol within the short time of 3–5 h.

4. Conclusions

In our methodology, Fe^{3+}-montmorillonite is found to be an excellent catalyst for esterification reaction. Notably the aspect of effluent treatment does not arise, as water is the only by-product. The advantages include the operational simplicity, recyclability of the catalyst, high atom economy and the mild reaction conditions. The present heterogeneous catalytic system can be a potential candidate not only for laboratory practice but also for commercial applications and offers an environmentally safer alternative to the existing processes.

Acknowledgment

VB thanks the Council of Scientific and Industrial Research, New Delhi, for the award of Senior Research Fellowship.

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