

Selective Catalytic Transesterification, Transthiolesterification, and Protection of Carbonyl Compounds over Natural Kaolinitic Clay

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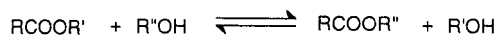
Transesterification and transthiolesterification of β -keto esters with variety of alcohols and thiols and selective protection of carbonyl functions with various protecting groups catalyzed by natural kaolinitic clay are described. The clay has been found to be an efficient catalyst in transesterifying long chain alcohols, unsaturated alcohols, and phenols to give their corresponding β -keto esters in high yields. For the first time, transthiolesterification of β -keto esters with a variety of thiols has been achieved under catalytic conditions. Clay also catalyzes selective transesterification of β -keto esters by primary alcohols in the presence of secondary and tertiary alcohols giving corresponding β -keto esters. A systematic study involving the reactivity of different nucleophiles (alcohols, amines, and thiols) toward β -keto esters is also described. Sterically hindered carbonyl groups as well as α,β -unsaturated carbonyl groups underwent protection without the deconjugation of the double bond. Chemoselective protection of aldehydes in the presence of ketones has also been achieved over natural kaolinitic clay.

1. Introduction

Transesterification is a process where an ester is transformed into another through interchange of the alkoxy moiety¹ (Scheme 1). Since the reaction is an equilibrium process, the transformation occurs essentially by simply mixing two components. However, it has been shown that the reaction is accelerated by Lewis acid catalysts (such as boron tribromide,² anhydrous aluminum trichloride embedded in polystyrene–divinyl benzene³), Bronsted acid catalysts (such as hydrochloric, phosphoric, sulfonic, sulfuric, or *p*-toluenesulfonic acid⁴), or basic catalysts (such as metal alkoxides,⁵ metal carbonates⁶).

Transesterification is more advantageous than the ester synthesis from carboxylic acid and alcohol, due to poor solubility of some of acids in organic solvents, whereas the esters are commonly soluble in most of the solvents. Some esters, especially methyl and ethyl esters, are readily or commercially available and thus serve conveniently as starting materials in transesterification.

Scheme 1



Transesterification is applicable in the paint industry for the curing of alkyl resin.¹ It also plays an important role in polymerization.¹

It is apparent, however, that the reaction under the acidic or basic conditions does not meet the requirements of modern synthetic chemistry, which needs highly efficient and selective reaction conditions. Also, efforts may be continued to make the reaction catalytic, milder, and more selective.

Among the catalysts developed, the distannoxane⁷ was found to be an effective one for transesterification of various types of esters; however, this catalyst is difficult to prepare. Titanate-mediated⁸ transesterification method is extremely mild but is found to be unsuccessful to give allyl ester from an ethyl ester. This may be due to the fact that transesterification of β -keto esters, especially with allylic alcohol, is rather difficult as it is offset by facile decarboxylation rearrangement. Although Taber's⁹ DMAP-promoted method is effective for transesterification of primary and secondary alcohols, it fails in the case of long chain alcohols due to the decomposition of the acetoacetate. A tin-based superacid¹⁰ was reported to be effective for the synthesis of alkyl β -keto esters although it failed with aromatic β -keto esters. Even though aromatic β -keto esters could be transesterified with H β -zeolite,¹¹ it fails to chemoselectively transesterify primary

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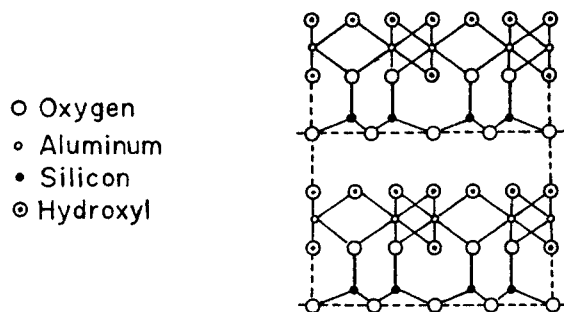


Figure 1.

alcohols in the presence of secondary ones. Commercially available Woelm, neutral chromatographic alumina,¹² has good chemoselectivity; however, it fails to transesterify phenols and 1,2 or 1,3 diols.

Thus, development of a new catalytic method, which can effectively overcome problems experienced in the transesterification reaction, should heighten the synthetic scope of the reaction. In this connection, the use of heterogeneous catalysts in the liquid-phase offers several advantages compared with their homogeneous counterparts, including ease of recovery, recycling, and enhanced stability.

2. Clay as Catalyst

Kaolinites,¹³ clays from which Chinaware is made, are 1:1 clays associating one tetrahedral and one octahedral layer, as shown in Figure 1. The aluminum(III) cations are bonded to an octahedral arrangement of oxygen anions. Repetition of these AlO_6 units in two dimensions forms an octahedral layer. Likewise, a tetrahedral layer is formed from SiO_4 silicate units. Clays stabilize high energy intermediates and can store energy in their lattice structures which can be released in the form of chemical energy.¹⁴ They have many advantages such as ease of handling, noncorrosiveness, low cost, and regeneration. Due to their Bronsted and Lewis acidities both in their natural and ion-exchanged forms, clays function as efficient catalysts for various organic transformations.¹⁵ We have recently reported the catalytic application of natural kaolinitic clay for the selective functional protection of aldehydes, ketones,¹⁶ and hydroxyl groups.¹⁷ In this paper we describe in detail the catalytic properties of the natural kaolinitic clay as an effective catalyst for transesterification, transthiol esterification, and selective protection of carbonyl compounds.

3. Results and Discussion

A. Transesterification of β -Keto Esters. β -Keto esters¹⁸ serve as important synthons by virtue of the ease with which they can be transformed to chiral building

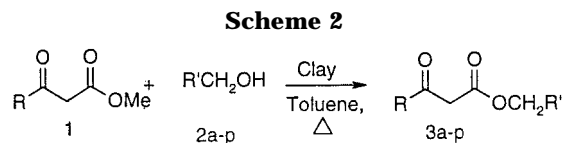


Table 1. Transesterification of β -Keto Esters with Different Alcohols Catalyzed by Natural Kaolinitic^a and Montmorillonite K10 Clays

| entry | substrate 1 R | alcohol 2 R ¹ | t/h | product (3) ^b kaolinitic | yield (%) ^c Mont. K10 |
|-------|------------------|-----------------------------|-----|--|-------------------------------------|
| a | Me | benzyl | 3 | 85 | 86 |
| b | Me | 2-phenylethyl | 3 | 87 | 80 |
| c | Me | furfuryl | 4 | 84 | 85 |
| d | Me | cinnamyl | 6 | 80 | 72 |
| e | Me | allyl | 6 | 75 | — |
| f | Me | cyclohexyl | 12 | 0 ^d | — |
| g | Me | geranyl | 8 | 70 | — |
| h | Me | crotyl | 8 | 80 | 75 |
| i | Me | propargyl | 7 | 79 | 80 |
| j | Me | dodecyl | 10 | 75 | 70 |
| k | Me | menthyl | 12 | 0 ^d | 0 ^d |
| l | Me | tert-butyl | 12 | 0 ^d | 0 ^d |
| m | Me | octadecyl | 11 | 71 | 70 |
| n | Me | tetrahydrofurfuryl | 4 | 90 | 84 |
| o | Me | 2-chloroethyl | 4 | 84 | 75 |
| p | Ph | propargyl | 9 | 51 | — |

^a Catalyst was recovered and reused three times without loss of activity. ^b Reaction was monitored on TLC, and all new compounds gave satisfactory data. ^c Isolated yield. ^d No reaction.

blocks by chemical, enzymatic transformations as well as a tool for chain extension reactions. When methyl β -keto esters were treated with an equimolar amount of primary alcohol in the presence of catalytic amount of natural kaolinitic clay under reflux in toluene using Dean–Stark apparatus to remove methanol, the corresponding esters were obtained in good to excellent yields (Scheme 2).

Table 1 attests the present method to be applicable for a wide range of compounds. Salient features of the methodology are as follows: (i) methyl acetoacetate is successfully transformed into synthetically useful esters; (ii) a variety of primary alcohols containing sensitive functional groups can be employed in this transformation; (iii) when β -keto esters with an aliphatic moiety were transesterified with alcohols, the corresponding transesterified products were obtained in high yields. However, for an aromatic moiety of β -keto ester, the corresponding transesterified product was obtained with moderate yield (entry p); (iv) a special feature of this method is that unsaturated alcohols such as crotyl, cinnamyl, propargyl and allyl underwent transesterification affording unsaturated esters in high yields, although it should be noted that transesterification with allylic alcohols is generally difficult with other catalysts; (v) Table 1 shows the preparation of long carbon chain ester which is often a starting material for the polymer industry (entries j & m); (vi) reaction fails in the case of secondary and tertiary alcohols, (entries f, k, l) and is selective only for primary alcohols; (vii) in agreement with Mori's procedure¹⁹ in which KCN was employed, no isomerization of double bond has occurred during transesterification (entry g); (viii) it is important to mention that the reaction appears to be specific only for transesterification of β -keto esters. Other esters such as normal esters, unsaturated esters, α -keto esters as well as γ -keto

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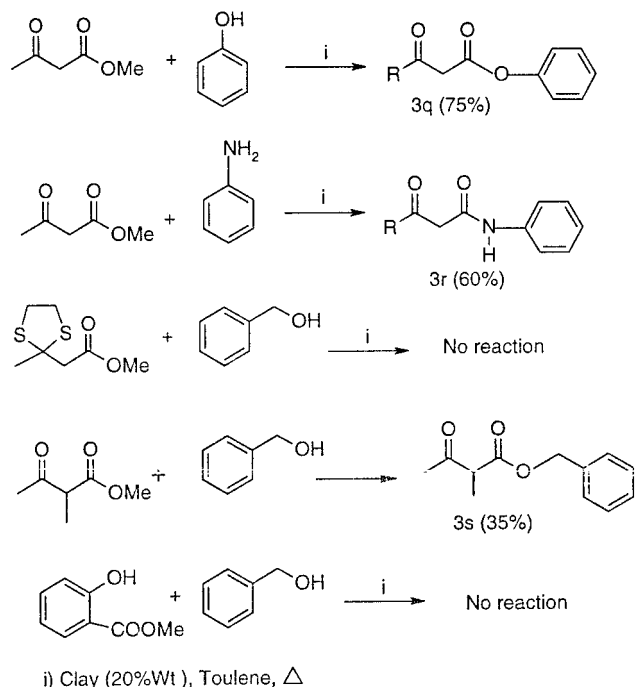
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Scheme 3



esters fail to undergo the reaction which is a limitation of the present method. This procedure works particularly well on multigram scale.

To gauge the scope and generality of the method, the following experiments were carried out as shown in Scheme 3.

One of the most important features of the methodology is that even phenols could be used to transesterify β -keto esters efficiently. In a similar manner, aniline underwent reaction to give the corresponding amidation product. When the keto group at the β -position is protected, then transesterification fails. In the case of α -methyl- β -keto ester the transesterification proceeds to give the product in low yield. Methyl salicylate failed to undergo transesterification.

B. Transesterification of β -Keto Esters. The role of thiol esters²⁰ as acylating agents in biochemical processes and their high reactivity with various nucleophiles has made them an attractive synthetic intermediate in a variety of chemical transformations. A comprehensive literature search has revealed that the exchange of normal ester with thiols is not reported in the literature. The conversion of a β -keto ester moiety to its thiol analogue is problematic as it always undergoes facile decarboxylation upon hydrolysis. Further, the preparation of such thiol esters generally requires multistep synthesis utilizing exotic reagents and drastic reaction conditions.²¹ However, this synthetic problem can now be conveniently solved by one to one exchange of thiols with β -keto esters to yield transesterified products catalyzed by natural kaolinitic clay. In our continuing interest in the application of natural kaolinitic

Scheme 4

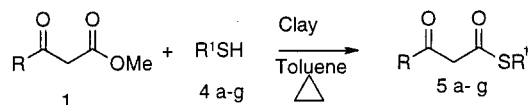


Table 2. Transesterification of Various β -Keto Esters Catalyzed by Natural Kaolinitic Clay with Different Thiols^a

| entry | substrate 1 R | thiol 4 R ¹ | t/h | product 5 ^b yield (%) ^c |
|-------|-------------------------|----------------------------------|-----|---|
| a | Me | phenyl | 8 | 70 |
| b | Me | 4-chlorophenyl | 6 | 75 |
| c | Me | 2-ethoxyphenyl | 8 | 64 |
| d | Me | benzyl | 6 | 71 (53) ^d |
| e | Me | 4-methoxyphenyl | 8 | 69 |
| f | Ph | benzyl | 12 | 42 (26) ^d |
| g | Ph | furfuryl | 12 | 51 |

^a Catalyst was recovered and reused three times without loss of activity. ^b All new compounds gave satisfactory spectral data. ^c Isolated yield. ^d Numbers in parentheses refers to yields using montmorillonite K10 clay as catalyst.

clay in synthetic transformations, we have subjected a variety of thiols for transesterification with β -keto esters, and the results are presented as shown in Scheme 4 and Table 2.

As evident from Table 2, this method appears to be quite general as a variety of thiols can be employed. The yields of the transesterified products are moderate, and the reaction time also ranges from 6 to 12 h.

C. Selectivity Study of Transesterification with Alcohols, Thiols, and Amines. Acylation of alcohols is one of the most fundamental reactions in synthetic organic chemistry. The chemoselective acylation of the primary hydroxyl group in the presence of a secondary one is often required, and a wide variety of methods with different reagents such as *N*-acetylimidazole,²² 2,2'-bipyridylcarboxylate–cesium fluoride,²³ iodotrimethylsilane,²⁴ triphenylphosphine–diethyl azodicarboxylate,²⁵ and neutral alumina have been developed for this purpose.

Since the catalyst is active toward transesterification and transesterification under the same catalytic condition, it is of interest to study the reactivity pattern of different kinds of diols, amino alcohols, and mercapto alcohols toward β -keto ester over natural kaolinitic clay, and the results of such a study are presented in Table 3. Major features are enumerated as follows: (i) in the case of aliphatic amino alcohols, amine being more nucleophilic than alcohol, it reacts faster with ester giving the corresponding amidation product (entry a), which is in agreement with Mukaiyama's procedure; (ii) it has been observed that the hydroxyl group of 2-mercaptoethanol (entry b) reacts preferentially over thiol; (iii) in the case of glycerol, the only product obtained was the ditransesterified product; however, excess of either the catalyst or the β -keto ester is used (entry d); (iv) another important feature of the methodology is that, unlike Posner's procedure which fails to selectively acylate 1,2 or 1,3

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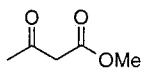
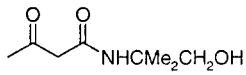
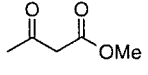
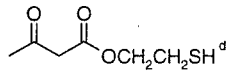
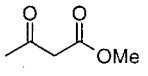
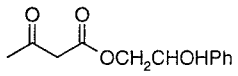
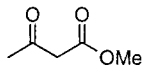
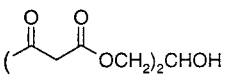
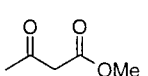
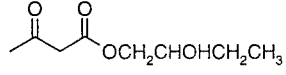
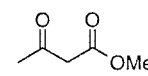
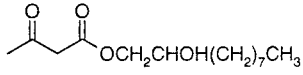
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Table 3. Selective Transesterification of β -Keto Esters with Amino Alcohol, Mercapto Alcohol, and Diols Catalyzed by Natural Kaolinitic Clay^a

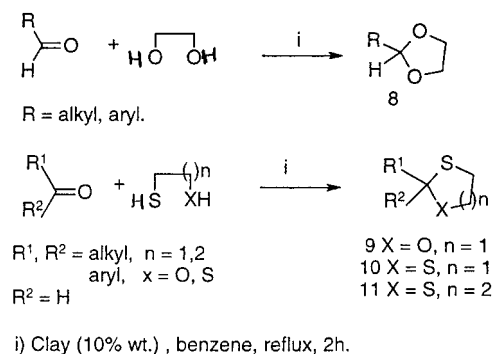
| Entry | β -Keto ester | Substrate | Product ^b | Yield (%) ^{c, e} |
|-------|---|--|--|---------------------------|
| | 1 | 6 | 7 | |
| a |  | H ₂ NMe ₂ CH ₂ OH |  | 61 (58) |
| b |  | HSCH ₂ CH ₂ OH |  | 49 (48) |
| c |  | PhCHOHCH ₂ OH |  | 48 |
| d |  | HOCH-(CH ₂ OH) ₂ |  | 55 |
| e |  | CH ₃ CH ₂ CHOHCH ₂ OH |  | 60 (54) |
| f |  | CH ₃ (CH ₂) ₇ CHOHCH ₂ OH |  | 55 (53) |

^a Catalyst was reused three times without loss of activity. ^b All compounds gave satisfactory spectral data. ^c Isolated yield. ^d Ketone-protected product also formed with almost equal amount 15 (see Scheme 7). ^e Numbers in parentheses refers to yields using montmorillonite K10 clay as catalyst.

diols, the clay catalyst efficiently transesterifies primary alcohols of 1,2 diols as shown in Table 3 (entries c, e, f).

D. Selective Functional Protection of Carbonyl Compounds over Natural Kaolinitic Clay. During a synthetic sequence a carbonyl group may have to be protected against attack by various reagents such as moderately strong nucleophiles including acidic, basic, catalytic, or hydride reducing agents and some oxidants. The most useful protective groups are the acyclic and cyclic acetal or ketal and the acyclic or cyclic thio acetals and ketals.²⁶ Further, the use of dithiolane and dithianes as blocking groups has raised a new strategy for electrophilic substitution at the carbonyl carbon.²⁷ Recently, many catalytic systems such as SOCl₂-SiO₂,²⁸ HY zeolite,²⁹ Mg-ZnTf,³⁰ and modified clays such as Mont-KSH³¹ and Ce-Mont³² have been developed for such synthetic transformations. However, the use of a reusable, heterogeneous catalyst such as natural clay, capable of achieving chemoselective protection of carbonyl function including hindered ketones and without shifting of the double bond to the β,γ -position while protecting the α,β -unsaturated carbonyl compounds, is of great interest.

We have found¹⁶ that natural kaolinitic clay catalyzes efficiently the chemoselective protection of a variety of aldehydes and ketones with ethane-1,2-diol, 1-hydroxy-

Scheme 5

ethane-2-thiol, ethane-1,2-dithiol, and propane-1,3-dithiol producing 1,3-dioxolane **8**, 1,3-oxathiolane **9**, 1,3-dithiolane **10**, and 1,3-dithiane **11** derivatives, respectively (Scheme 5).

Table 4 lists results of the protection of carbonyl functions catalyzed by clay. Evidently, the clay catalyzes the protection of a variety of aldehydes (aliphatic, aromatic, heteroaromatic, α,β -unsaturated) with ethane-1,2-diol. Ketones have, however, failed to undergo protection under such reaction conditions. In contrast, both aldehydes and ketones could be thioacetalized with ethane-1,2-dithiol, 1-hydroxyethane-2-thiol, and propane-1,3-dithiol in excellent yield. The major features of the protection of carbonyl compounds catalyzed by clay are as follows: the sterically hindered ketones such as camphor could be easily thioacetalized with ethane-1,2-dithiol and propane-1,3-dithiol (entry f); α,β -unsaturated ketones underwent protection without the shift of the double bond to β,γ -position (entries c-e).

Clay has also been found to be effective for the conversion of aldehydes and ketones into their corresponding acyclic acetals and ketals using ortho esters. In addition, benzaldehyde could also be thioacetalized

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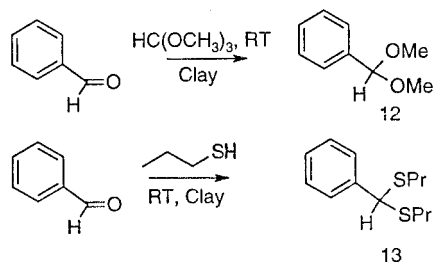
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Table 4. Protection of Carbonyl Functions with Ethane-1,2-diol, Hydroxy Thiol, Dithiol, and Propane-1,3-dithiol over Natural Kaolinitic Clay^a

| entry | substrate | 1,3-dioxolane (8) 1,3-oxathiolane (9) yield (%) ^b | | 1,3-dithiolane (10) 1,3-dithiane (11) yield (%) ^b | |
|-------|------------------------------|--|-----------------|--|----|
| | | 8 | 9 | 10 | 11 |
| a | 1-butanal | 91 | — | 92 | — |
| b | 1-hexanal | 90 | — | — | — |
| c | crotonaldehyde | 92 | — | 70 | — |
| d | 3-methylcyclohex-2-ene-1-one | 0 | — | 90 | — |
| e | (<i>R</i>)-carvone | 0 | — | 72 | — |
| f | (<i>R</i>)-camphor | 0 | — | 85 | 68 |
| g | cyclohexanone | 0 | — | 80 | — |
| h | menthone | 0 | — | 65 | 60 |
| i | benzaldehyde | 95 | 95 | 98 | 95 |
| j | 4-methoxybenzaldehyde | 92 | 86 | — | — |
| k | 4-chlorobenzaldehyde | 81 | — | — | — |
| l | 4-nitrobenzaldehyde | 75 | — | — | — |
| m | 4-hydroxybenzaldehyde | 40 ^c | — | 85 ^c | — |
| n | 1,4-benzenedicarboxaldehyde | 92 ^d | 94 ^d | 88 ^d | — |
| o | 3,4,5-trimethoxybenzaldehyde | 86 | — | — | — |
| p | furan-2-carboxaldehyde | 93 | — | 85 | 64 |
| q | pyridine-2-carboxaldehyde | 45 ^c | — | 92 ^c | — |
| r | cinnamaldehyde | 93 | — | — | — |
| s | acetophenone | 0 | 89 | 97 | 72 |
| t | benzophenone | 0 | 81 | 75 | 65 |

^a Catalyst was reused three times without loss of activity. ^b Isolated yield; characterized by IR, ¹H and ¹³C NMR, and MS. ^c 30% of catalyst used and requires 12 h for completion. ^d Underwent diprotection with 2 mol of reagent.

Scheme 6

with 1-propanethiol in very high yield (Scheme 6). To examine the selectivity of the present thioacetalization with use of the clay, an equimolar mixture of benzaldehyde, acetophenone, ethane-1,2-dithiol, and 10% (w/w) mass clay in benzene was refluxed for 2 h, and it was found that the protection proceeds chemoselectively at the aldehyde function only.

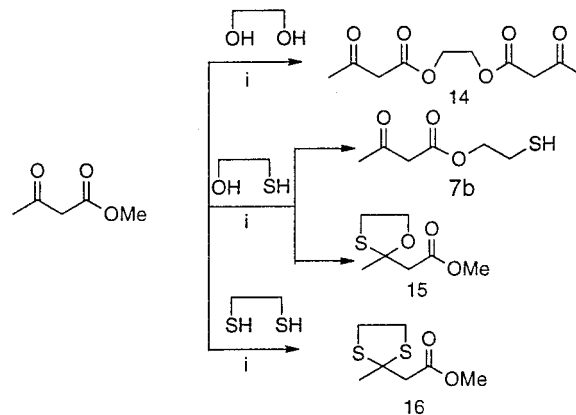
When a β -keto ester is treated with ethylene glycol, 1-hydroxyethane-2-thiol and ethane-1,2-dithiol, both transesterification and ketone protection could be possible. The results are as shown in Scheme 7.

From Scheme 7, it is evident that thiol being more nucleophilic than alcohol, dithiol under the clay condition undergoes selective protection with the ketone carbonyl while diol gets selectively transesterified with the β -keto ester to produce the ditransesterified product. In the case of hydroxy thiol, a mixture of both protected **15** as well as transesterified **7b** products are obtained in almost equal proportions (see Table 3, entry b).

It has been observed that commercially available Montmorillonite K 10 clay has also been found to be effective for transesterification and transthioesterification and thus exhibits the same selectivity and reactivity pattern of kaolinitic clay (Tables 1–3).

4. Mechanism

Natural kaolinitic clay has a surface acidity measuring between 1.5 to -3 in the Hammett H_0 acidity function scale. Simple washing of the clay with mineral acid such

Scheme 7^a

^a (i) Clay (20% wt), toluene, Δ .

as 0.1 M HCl brings down the H_0 between -6 and -8 , i.e., to values between that of concentrated HNO_3 and oleum.³³ We believe that the enhanced catalytic activity of the acid activated clay could be attributed to the significant amount of both Lewis acidity derived from Al remaining in the edges of the platelets and Bronsted acidity of coordinated hydroxyl groups of Al^{3+} , Fe^{3+} , and Ti^{4+} ions relocated in the interlammellar space of the clay.^{13,14}

The fact that both transesterification and transthioesterification are successful only for β -keto esters leads us to propose the following transition state model which could be responsible for bringing about such transformation (Figure 2). The cyclic enolate of the β -keto ester forms a stable enolate complex with Al^{3+} present in the clay by way of coordination so that the acyl oxygen bond of the β -keto ester is weakened, and the incoming nucleophile attacks the ester carbonyl leading to transesterified product. In the case of protection of the carbonyl compounds the Lewis acid center in the clay

(33) Sabu, K. R.; Sukumar, R.; Lalithambika, M. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3535–3541.

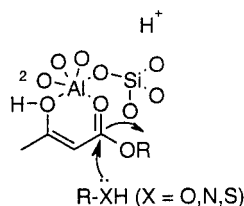


Figure 2.

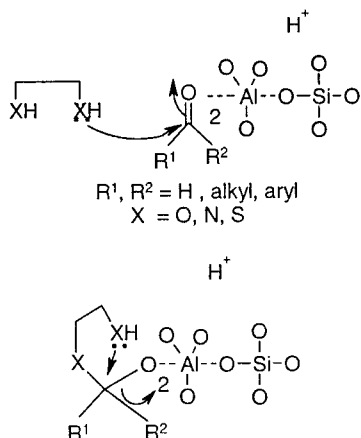


Figure 3.

activates the carbonyl compound by way of coordination so that the nucleophiles could approach the carbonyl group effectively to give the corresponding product (Figure 3).

5. Conclusion

In summary, we have shown that naturally occurring clay could efficiently catalyze transesterification of β -keto ester by a variety of alcohols, especially unsaturated alcohols and long chain alcohols. We have also studied, for the first time, transthioesterification of β -keto esters with various thiols. The reactivity of nucleophiles such as alcohols, thiols, and amines toward the transesterification reaction was systematically studied. Natural clay is an effective and convenient catalyst for acetalization and thioacetalization of carbonyl compounds, and the high chemoselectivity exhibited by the clay-catalyzed reaction should be useful for selective protection of aldehydes in the presence of keto carbonyl functions. Besides the high selectivity and reactivity exhibited by the clay, the method has other environmentally benign features: no inorganic wastes are produced and the catalyst can be reused a number of times.

6. Experimental Section

NMR spectra are listed in ppm and were measured in relation to internal TMS standard in solvent indicated. Commercial starting materials were obtained from Aldrich Chemical Co. Melting points were uncorrected.

Purification of Natural Kaolinitic Clay. The kaolinitic clay was procured from the Padappakara mine of Quilon District, Kerala, India, and it was subsequently purified³³ by separating coarser mineral impurities from clay particles, followed by drying and calcination. The 550 °C calcined clay sample (1 part by weight) are boiled with 2 M HCl (4 parts by weights) for 45 min. The leached samples are then washed free of chloride ions and dried at 110 °C for 12 h.

It was characterized by FT IR, XRD, UV, ESR, SEM, EDX, and chemical analysis by AAS. The composition of the clay has been determined by wet chemical analysis (in %): SiO₂ = 67.45, Al₂O₃ = 22.2, Fe₂O₃ = 6.1, TiO₂ = 3.45, and K = 0.8.

General Procedure for the Transesterification and Transthioesterification of β -Keto Esters. In a general reaction, a mixture of β -keto ester (10 mmol), alcohol or thiol (11 mmol), and clay 20% (w/w) in toluene (25 mL) was refluxed for 4–12 h under Dean–Stark conditions. After the reaction was complete (TLC), the clay catalyst was filtered off and the product purified by column chromatography to afford transesterified or transthioesterified product, respectively. They were identified by their physical and spectral properties and by comparison with the reported values.

General Procedure for Acetalization and Thioacetalization of Carbonyl Compounds. In a general reaction procedure, a mixture of carbonyl compounds (10 mmol), protecting groups such as ethane-1,2-diol, 1-hydroxyethane-2-thiol, ethane-1,2-dithiol, or propane-1,3-dithiol (11 mmol) and clay 10% (w/w) in benzene (25 mL) was refluxed for 2 h. After the reaction was complete (TLC), the clay was filtered off and the product purified by flash chromatography to afford 1,3-dioxolane, 1,3-oxathiolane, 1,3-dithiolane, and 1,3-dithiane, respectively.

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Supporting Information Available: ¹H and ¹³C NMR and mass spectra of selected compounds and the spectral data of 30 compounds (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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