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Clay Montmorillonite K10 Catalyzed Aldol-type Reaction of Aldehydes with Silyl Enol Ethers in Water

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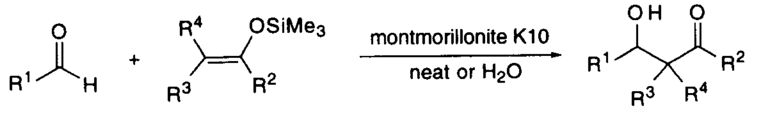
Abstract: An environmentally friendly method for the cross aldol reaction of silyl enol ethers and ketene silyl acetal with various aldehydes using montmorillonite K10 is described. Cheap and commercially available montmorillonite K10 can be used without the need of an ion exchange process under solvent-free conditions or in water. Hydrate of aldehydes such as glyoxylic acid can be used directly. Thermal treatment of K10 increased the catalytic activity. The catalytic activity was supposed due to the properties of the structure of K10 and its inherent Brönsted acidity. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Clays, Aldol Reactions, Aldehydes, Environmentally Friendly, Water

Introduction

There is an urgent need to develop safe, practical and environmentally friendly processes.[1] Among the many methods, the use of solid acids such as clay and zeolites as catalysts in organic reactions which can minimize waste emission and the formation of large quantities of environmentally hazardous toxic substances is one of the most attractive methods to establish clean chemical processes.[2] Although ion-exchanged clay has been used successfully for the catalysis of various C-C bond formation reactions, the use of cheap, commercially available montmorillonite K10 for C-C bond formation reactions has not been well-studied.[3] In addition, the many possible advantages of performing carbon-carbon bond formation in aqueous media has also encouraged us to investigate the use of K10 for the catalysis in water.[4] This relatively unfamiliar territory, especially using commercially available montmorillonite K10 without organic solvents, lends itself to exploration in terms of reaction characteristics and stereochemical behaviour therenin.[5] Here, we report that the cheap, commercially available clay K10 itself can serve as an efficient promoter for the cross aldol reaction of silyl enol ethers and ketene silyl acetal with various aldehydes under solvent-free conditions or in water (eq. 1).



(eq. 1)

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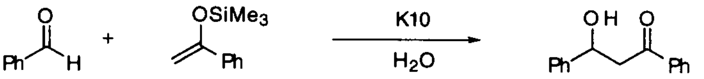
Results and Discussion

The reaction of benzaldehyde with 1-phenyl-silyl enol ether was initially carried out with various quantities of K10 to optimize the reaction conditions (eq. 2). The results are summarized in Figure 1.



(eq. 2)

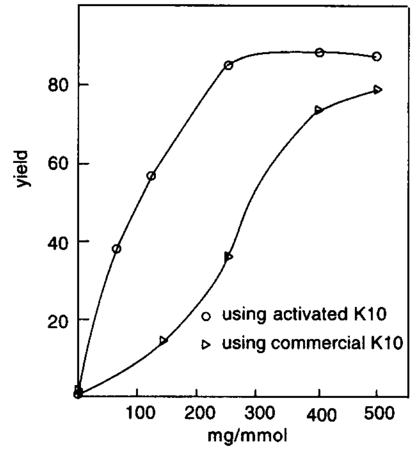
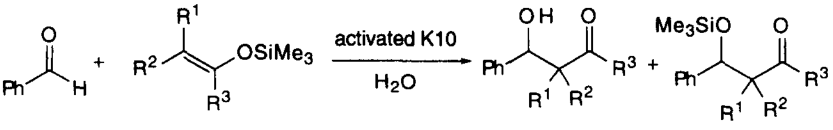


Figure 1. The effect of the amount of K10 used on the %yield of reaction

In the absence of montmorillonite K10, no reaction was observed even after the reaction mixture was stirred at room temperature in water for 18 hours. Interestingly, the aldol reaction in water proceeded smoothly in the presence of montmorillonite K10. This result shows that K10 is essential for the success of the reaction. It was found that the reaction yield correlated with the amount of added montmorillonite K10 until it peaked at 500 mg/mmol. Furthermore, in all cases, leaving the reaction to proceed longer (>1 hour) did not improve the yield of the reaction. A mixture of OTMS and OH products was obtained when the amount of montmorillonite K10 was decreased to less than 400 mg/mmol. Interestingly, decreasing the amount of K10 to 50 mg/mmol afforded only the OTMS aldol product in much lower yield (Figure 1).

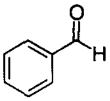
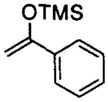
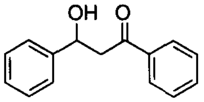
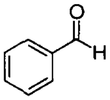
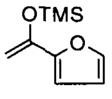
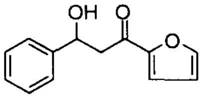
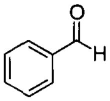
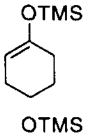
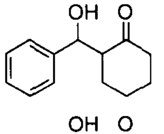
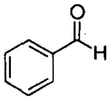
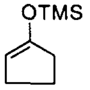
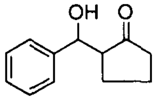
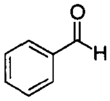
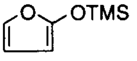
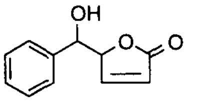
According to known studies, there is some intercalating water present between the silicate interlayers of montmorillonite K10.[1,2] We envisaged that thermal treatment to remove the physisorbed water may increase the catalytic ability of K10. Thus, commercial K10 was heated at 120-130 °C in an oven for 1 hour. The treated K10 was cooled to room temperature and immediately used in the Mukaiyama-aldol reaction of benzaldehyde with 1-phenyl silyl enol ether. Using this activated clay, only half of the previous amount of K10 (250 mg/mmol) was needed to completely convert the aldehydes to the corresponding products. For comparison purposes, the results are also shown in Figure 1. Thus, thermal treatment of K10 increases the catalytic activity for the Mukaiyama-Aldol reaction. However, if the montmorillonite K10 was treated at a temperature higher than 150 °C for a few hours, the catalytic ability was found to be dramatically reduced.

With the optimized conditions, the aldol reactions of benzaldehyde with various silyl enol ethers were carried out using activated clay at room temperature in water (eq. 3). The results are summarized in Table 1.



(eq. 3)

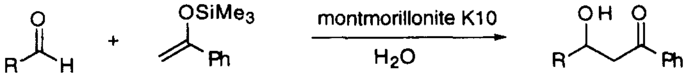
Table 1 Clay-Catalyzed Reaction of Benzaldehyde with Silyl enol ethers in Water[a]

Entry	Aldehyde	Silyl enol ether	Product	Yield (%)[b]
1				87[c]
2				82[d]
3				65[d] (*syn: anti* 44:56)
4				90[d] (*syn: anti* 58:42)
5				62[c] (64:36)[e]

a. All reactions were carried out on 0.2-0.5 mmol scale. b. Isolated yield. c. Only OH product was obtained. d. A mixture of OH and OTMS products was obtained. e. Relative stereochemistry has not been determined.

In all cases, the reactions proceeded smoothly to afford the corresponding aldol products in moderate to good yields. It was observed that cyclic silyl enol ethers also reacted with benzaldehyde smoothly to afford the corresponding products in good yields. However, the diastereoselectivities were low (entries 3 and 4). It is noteworthy that the clay-catalyzed reaction between 2-trimethylsilyloxy-furan and benzaldehyde gave the γ-lactone product (entry 5). Interestingly, a mixture of OH and OTMS products were collected (Table 1, entries 2, 3 and 4). With equal amounts of K10, the ratio of the two products obtained depends on the silyl enol ether used.

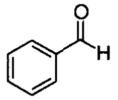
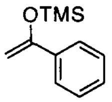
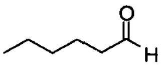
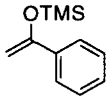
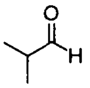
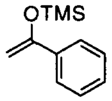
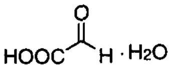
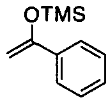
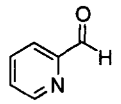
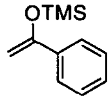
Following these good results obtained in the reaction of benzaldehyde with silyl enol ethers, we explored the performance of various aldehydes in this clay montmorillonite K10 catalyzed Mukaiyama-aldol reaction. 1-Phenyl silyl enol ether was chosen as the representative starting material to react with a variety of aldehydes (eq. 4)



(eq. 4)

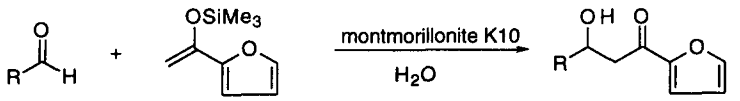
Similar to the reaction of benzaldehyde, we found that aliphatic aldehydes can also react with 1-phenyl-silyl enol ether smoothly using the optimized conditions (Table 2, entries 2, 3). When the hydrate of glyoxylic acid was employed as the starting aldehyde, the reaction proceeded even when commercially available montmorillonite K10 was used directly. It was also found that only 50 mg/mmol of K10 is sufficient to catalyze the aldol reaction to afford the product in good yield (entry 4). However, in the case of aromatic aldehydes bearing a heteroatom such as 2-pyridinecarboxaldehyde, the reaction was incomplete affording the aldol product in much lower isolated yield (entry 5). In this reaction, we have tried using different amounts of K10 to promote the conversion of aldehyde to aldol product. Unfortunately, there is no improvement in conversion even when more than 50 mg/mmol montmorillonite K10 was used. It can be easily rationalized that the strong coordination between the nitrogen atom in the pyridine ring and the clay Brönsted acid sites resulted in the loss of catalytic activity. Interestingly, if the amount of K10 was increased to 250 mg/mmol, only a trace of the product was observed.

Table 2 Clay-Catalyzed Reaction of Aldehydes with 1-Phenyl-silyl enol ether[a]

Entry	Aldehyde	Silyl enol ether	Conditions	Yield (%)[b]
1			250 mg/mmol[c] rt, H_2O, 1 h	87
2			250 mg/mmol[c] rt, H_2O, 4 h	62
3			250 mg/mmol[c] rt, H_2O, 4 h	71
4			50 mg/mmol[d] rt, H_2O, 4 h	74
5			50 mg/mmol[c] rt, H_2O, 15 h	51

a. All reactions were carried out on 0.2-0.5 mmol scale. b. Isolated yield. c. Using activated montmorillonite K10 (120 °C-130 °C, 1 h). d. Using commercially available montmorillonite K10 in this reaction.

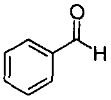
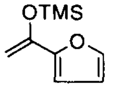
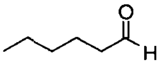
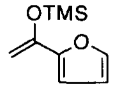
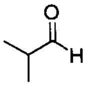
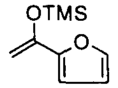
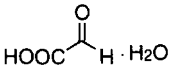
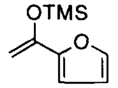
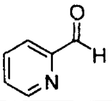
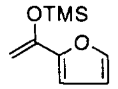
Furthermore, the feasibility of this methodology was also observed with the montmorillonite K10 catalyzed Mukaiyama-aldol reaction of a variety of aldehydes with 1-(2-furyl)-silyl enol ether (eq. 5).



(eq. 5)

Similarly, these reactions with various aldehydes and this silyl enol ether catalyzed by montmorillonite K10 proceeded smoothly to afford the corresponding aldol products in moderate to high yields (Table 3). The side-product produced from the excess 1-(2-furyl)-silyl enol ether which makes purification difficult can be reduced by performing the reaction at 0 °C. In most cases, the OH product was obtained as the sole product. However, the reaction of benzaldehyde with 1-(2-furyl)-silyl enol ether gave a mixture of OTMS and OH products (53 : 47).

Table 3 Clay Catalyzed Aldol Reaction of Aldehydes with 1-(2-Furyl)-silyl enol ether[a]

Entry	Aldehyde	Silyl enol ether	Conditions[b]	Yield (%)[c]
1			250 mg/mmol rt, H_2O, 1 h	82[d]
2			250 mg/mmol rt, H_2O, 1 h	65[e]
3			250 mg/mmol rt, H_2O, 1 h	63[e]
4			250 mg/mmol rt, H_2O, 4 h	71[e]
5			250 mg/mmol rt, H_2O, 4 h	51[e]

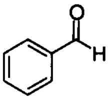
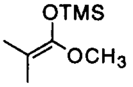
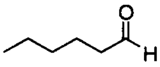
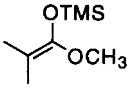
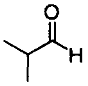
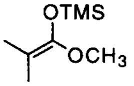
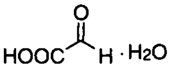
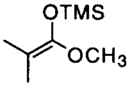
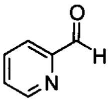
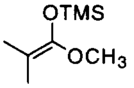
a. All reactions were carried out on 0.2-0.5 mmol scale. b. Using activated montmorillonite K10 (120 °C-130 °C, 1 hour). c. Isolated yield. d. A mixture of OTMS and OH products was obtained. e. Only OH product was obtained.

As an important extension of this methodology, we replaced the silyl enol ethers with ketene silyl acetal. The commercially available 1-methoxy-2-methyl-1-trimethylsiloxypropene was employed to explore the reaction with a wide variety of aldehydes (eq. 6).

(eq. 6)

Similar to those of silyl enol ethers, in all cases, the reactions proceeded very fast in water at room temperature to afford the corresponding aldol products in good yields (Table 4). The reaction of a hetero aromatic compound such as 2-pyridinecarboxaldehyde was also found to be positive. The high reactivity of this reaction allowed the product to be obtained in high yield regardless of the possible negative effect of the coordination of nitrogen with K10 acidic sites (entry 5). The aliphatic aldehydes were also highly reactive towards ketene silyl acetal in the presence of activated clay montmorillonite K10 (entries 2, 3). Commercially available glyoxylic acid hydrate could be used directly (entry 4). In all these cases, only the β-hydroxyl ester was collected without detection of the possible OTMS product.

Table 4 Clay Catalyzed Mukaiyama Aldol Reaction of Ketene silyl acetal[a]

Entry	Aldehyde	Ketene silyl acetal	Conditions[b]	Yield (%)[c]
1			250 mg/mmol rt, H_2O, 1 h	75
2			250 mg/mmol rt, H_2O, 4 h	65
3			250 mg/mmol rt, H_2O, 4 h	84
4			50 mg/mmol rt, H_2O, 4 h	52
5			50 mg/mmol rt , H_2O, 1 h	89

a All reactions were carried out on 0.2-0.5 mmol scale. b Using activated clay montmorillonite K10 (120 °C-130 °C, 1 hour). c Isolated yield.

As a good environmentally friendly catalyst, montmorillonite K10 was found to be reusable. After the reaction of benzaldehyde and 1-phenyl silyl enol ether, K10 was separated by centrifugation and washed with ethanol, deionized water a few times and then reactivated in an oven at 120-130 °C for 2 hours. When the recycled K10 was used in this reaction of benzaldehyde, it was noted that the reaction occured smoothly and the corresponding aldol product was obtained in 65% yield. Although the yield is slightly lower, it proved that montmorillonite K10 can be activated and reused again.

Mechanistic Aspects

Although the mechanism of the ion exchanged montmorillonite "Kunipia F" catalyzed Mukaiyama-aldol reaction in organic solvent has been proposed by Onaka and co-workers,[5] the real catalytic species affecting the C-C bond formation is still ambiguous. In our work, the catalyst used is montmorillonite K10 which only has Brönsted acid sites.[2, 6] Therefore, the acidic characteristics of K10 must be responsible for its catalytic activity. The lower yields obtained in the reactions of heteroaromatic aldehydes such as 2-pyridinecarboxaldehyde with silyl enol ethers also supported this mechanism. However, there are differences between our reactions using K10 as catalyst and the reported reactions using ion-exchanged montmorillonite "Kunipia F".

(1) The structure of montmorillonite.[2, 7] Unlike ion-exchanged montmorillonite "Kunipia F" which has a laminated structure, the commercially available montmorillonite K10 is produced from the parent clay montmorillonite tonsil 13 through acid treatment.[6] The lamellar structure has been disrupted to a large extent after acid treatment. Therefore, K10 has a card-house-like structure.[2b, 8] The reaction may occur on the acidic surface of interlamellar space or mesopores of montmorillonite K10.

(2) Water effect. The ion-exchanged clays used in reported reactions[5] have to be predried at 20 °C/1 Torr for 6 hours then 20 °C/0.5 Torr for 24 hours. The reactions have to be carried out in organic solvents under strictly

anhydrous conditions. In our montmorillonite K10 catalyzed Mukaiyama-aldol reaction, both commercially available K10 without pretreatment or activated by heating K10 at 120-130 °C for 1 hour (Table 5, entries 1, 2, 3 and 5) can be used. Furthermore, the reactions were performed in water. These differences encouraged us to study the effect of water including the intercalating water of clay montmorillonite K10 and the water added during the reaction.

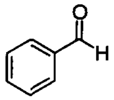
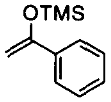
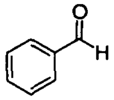
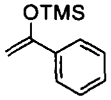
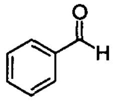
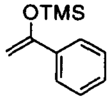
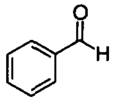
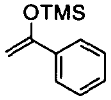
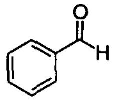
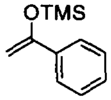
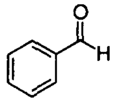
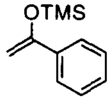
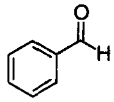
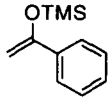
Compared to commercial montmorillonite K10, the activated K10 pretreated by heating at 120-130 °C for 1 hour has significantly increased catalytic ability. Study on the humidity effect on the acidity of K10 has shown that after by heating K10 in an oven at 120 °C for a few hours, the H_0 for the K10 was decreased from a range of -3.7 to -4.3 (in humid air) to the range of -5.6 to -5.9.[2e, 9] Therefore, the increased acidity of K10 may explain the higher activity of activated K10. As well as removing the physisorbed water it also induces lower polarity, thus, organic molecules such as aldehydes and the silyl enol ethers may diffuse to the catalytic sites easier for the cross coupling reaction. Similarly, the Al-Mot successfully used in the reported reactions was predried in vacuum (25 °C/0.5 torr for 24 hours) in order to get stronger acidity ($-8.2 < H_0 <= -5.6$ in CH_2Cl_2), which enhances the reactivity of clay.[5] On the other hand, treatment of montmorillonite at higher temperature (> 150 °C) as we have discussed above, lowers the catalytic activity due to the partial loss of the catalytic sites of montmorillonite K10. The observation that surface radical sites of the O_3SiO-silyoxy type can be generated during dehydrative activation process of a clay when it was heated in an oven at temperature of 150-300 °C has been reported.[2b, 10]

To study the effect of added water, the representative reaction of benzaldehyde with 1-phenyl silyl enol ether under neat conditions was performed. The commercially bought K10 and activated K10 were used. The results are listed in Table 5. Comparing entries 3 and 4 which used the commercial available K10, it was found that the reaction without added water gave the product in lower yield (entry 4). Similar results were also observed in entries 5 and 6 which used activated K10. These results suggest that the added water indeed has a positive effect on the reaction of aldehyde with silyl enol ether regardless of the clay K10 used. However, if water was added to the K10 followed by the aldehyde and silyl enol ether, no reaction was observed (entry 7).

(3) OTMS vs OH aldol product. In the previous reported ion-exchanged clay catalyzed Mukaiyama-aldol reactions, only the -OTMS products were obtained exclusively.[5] In contrast, only the -OH Mukaiyama-aldol coupling products were obtained in most of our reactions even in the case of the reaction using non-activated K10 as a catalyst under neat conditions. The only exception is when the reaction using activated K10 is carried out under neat condition when the OTMS substituted aldol product was obtained exclusively. These results indicate that the acidic sites in the predried ion-exchanged montmorillonite cannot hydrolyze the -OTMS coupling product to form the -OH product. This is similar to our reaction using activated K10 in the absence of added water. Noteworthy is that both intercalating water (in humid K10, Table 5, entry 4) and water added to activated K10 (Table 5, entry 5) have the same function to convert the -OTMS product to -OH product.

Based on these observations and the reported explanation for ion-exchanged clay catalyzed Mukaiyama-aldol reactions in organic solvents,[5] the mechanism of reaction catalyzed by commercially available K10 under neat conditions and in the presence of water is proposed as follows (Figure 2): In the commercially available K10, H_3O^+ exists in the interlamellar space to balance the negative charge of the silicate sheet. A number of water molecules are intercalated in the interlamellar space. This physisorbed water can be removed by thermal activation which results in higher Brönsted acidity of K10. The H_3O^+ may readily react with the silyl enol ether and produced the TMS^+. Some may be hydrolyzed by free water molecules, while others may coordinate to the oxygen of aldehyde in the interlayers or mesopores of K10. In the latter case, the formation of TMS-aldehyde complex activates the aldehyde for the reaction with silyl enol ether to afford the -OTMS aldol product. In the presence of physisorbed water molecules, the OTMS product may be hydrolyzed to give the -OH product.

Table 5 Effect of Water on Clay Catalyzed Mukaiyama-Aldol Reaction[a]

Entry	Aldehyde	Silyl enol ether	Conditions[b]	yield (%)[c]
1			400 mg/mmol non-activated K10 rt, H_2O, 1 h	72 (-OH)
2			400 mg/mmol, activated K10 rt, H_2O, 1 h	88 (-OH)
3			250 mg/mmol non-activated K10 rt, H_2O, 1 h	35 (-OH and -OTMS)
4			250 mg/mmol non-activated K10 rt, neat, 1 h	22 (-OH)
5			250 mg/mmol activated K10 rt, H_2O, 1 h	87 (-OH)
6			250 mg/mmol activated K10 rt, neat, 1 h	53 (-OTMS)
7			250 mg/mmol non-activated K10, H_2O then aldehyde and silyl enol ether, 1 h[d]	no reaction

a All reactions were carried out on 0.5 mmol scale. b The starting materials were added consequently as following: clay, silyl enol ether, aldehyde, and water. c. Isolated yield. d. The starting materials were added consequently as indicated.

Based on the proposed mechanism, the catalytic effect of montmorillonite K10 can be recognized in the following two aspects: First, it provides the H_3O^+ which initializes the reaction to form active TMS^+. Secondly, the TMS^+ produced can be rapidly transferred to the aldehyde molecule to activate it. This process may involve the help of the negatively charged oxygen atoms on the clay surface. This function may also be due to the two-dimensional structure of the montmorillonite which facilitates the transportation of TMS^+ to the aldehyde. The facts that the presence of intercalated water in commercially available K10 did not hinder the Mukaiyama-aldol reaction completely and the negative effect of the intercalating water can be compensated by the increasing amount of K10 used indicating that the clay montmorillonite K10 in the Mukaiyama-aldol reaction did not only work as normal mineral acid. The special structure of K10 is of considerable importance.

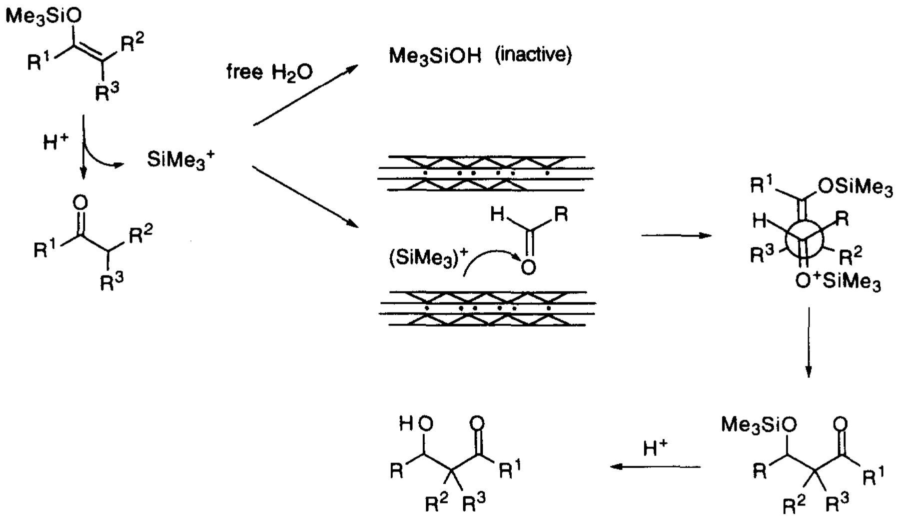


Figure 2 The possible mechanism involved in the montmorillonite K10 catalyzed aldol reaction

Conclusion

We have found that clay montmorillonite K10 catalyzes the Mukaiyama-aldol reactions of aldehydes with silyl enol ethers or ketene silyl acetals in water. This methodology has the following advantages: (1) practical ease and convenience. Commercially available montmorillonite K10 can be used without the need of ion-exchange processes. (2) Aldol-type reactions can be successfully performed in water. It avoids strict anhydrous and non-protic conditions. (3) Hydrates of aldehydes such as glyoxylic acid can be used directly. (4) Montmorillonite K10 can be activated and reused again after the reaction. (5) The experimental procedure is extremely simple; simply mix the montmorillonite K10, aldehyde and silyl enol ether in water for a number of hours and the corresponding aldol product is usually obtained in good yield.

On the other hand, this study showed that aldol reactions can occur in the presence of only clay and water. In conclusion, the basic C-C bond formation involving the condensation of silyl enol ethers with various aldehydes can occur in the presence of clay montmorillonite K10 and water. We believe that this mild and environmentally friendly process will find wide applications in organic synthesis.

Experimental Section

Materials and Methods. Clay montmorillonite K10 was purchased from Aldrich Chemical company. Flash chromatography was performed using Merck silica gel 60 (40 - 63 µm particle size) and distilled solvents. Columns were typically packed as a slurry and equilibrated with the appropriate solvents prior to use. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker ACF 300 nuclear magnetic resonance spectrometer at the frequency indicated. Mass spectral analyses were carried out on a VG7035 Micromass mass spectrometer and were reported in unit of mass to charge (*m/z*). Electron impact (EI) at an ion current of 70 eV was used for fragmentation of molecules.

The representative procedure of aldol reaction of aldehydes with 1-phenyl-1-(trimethylsilyloxy)ethylene catalyzed by commercially available montmorillonite K10 in water: A round bottom flask containing commercially available montmorillonite K10 (125 mg) was placed in an oven at 120-130 °C for 1 hour then it was cooled to room temperature under nitrogen protection. To the activated K10 was added 1-phenyl-1-(trimethylsilyloxy)ethylene (0.205 mL, 1.0 mmol) and benzaldehyde (0.050 mL, 0.5 mmol) followed by deionized water (5 mL). The resulting suspension was stirred at room temperature for 1 hour. The ethyl acetate (20 mL) was added. The mixture was centrifuged at 8000 rpm for 5 min. The liquid phase was separated with separating funnel to give organic extraction. To the solid phase was added ethyl acetate (20 mL). The suspension was stirred for 1 hour or placed for overnight to get better extraction of product from the clay interlayers. The resulting suspension was centrifuged again. The combined ethyl acetate extraction was washed with brine, dried over anhydrous $MgSO_4$. After filtration, the ethyl acetate was removed in vacuum. The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate 10:1) to afford the pure product in 87% yield (98.3 mg).

3-Hydroxy-1,3-diphenylpropan-1-one: white solid, m.p. 49-50 °C (lit.[11] m. p. 50-50.5 °C); R$_f$ (20% ethyl acetate/hexane) 0.31; FTIR (KBr) : ν 3452, 1679, 1597, 1449, 1212 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 3.37 (1 H, d, *J* 4.4 Hz, $\mathrm{COC\underline{H}_2}$) 3.38 (1 H, d, *J* 7.4 Hz, $\mathrm{COC\underline{H}_2}$), 3.69 (1H, brs, $\mathrm{O\underline{H}}$), 5.33-5.37 (1 H, dd, *J* 4.4, 7.4 Hz, $\mathrm{C\underline{H}OH}$), 7.26-7.59 (8 H, m, aryl-$\underline{\mathrm{H}}$), 7.94-7.97 (2 H, m, aryl-$\underline{\mathrm{H}}$); δ_C (75.4 MHz, $CDCl_3$) 47.3, 69.9, 125.7, 127.6, 128.1, 128.5, 128.6, 133.6, 136.5, 143.0, 200.1; HRMS (EI): M$^+$ found 226.0994. $C_{15}H_{14}O_2$ requires 226.0994.

3-Hydroxy-1-phenyloctan-1-one: colourless oil, R$_f$ (20% ethyl acetate/hexane) 0.35; FTIR (thin film): ν 3440, 1632, 1449, 1275 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.87–0.92 (3 H, t, *J* 6.6 Hz, $\mathrm{C\underline{H}_3}$), 1.10-1.66 (8 H, m, 4-$\mathrm{C\underline{H}_2}$), 2.99-3.08 (1 H, dd, *J* 8.9 17.6 Hz, $\mathrm{COC\underline{H}_2}$), 3.14-3.20 (1 H, dd, *J* 2.8, 17.6 Hz, $\mathrm{COC\underline{H}_2}$), 3.22 (1 H, brs, $\mathrm{O\underline{H}}$), 4.19-4.24 (1 H, m, $\mathrm{C\underline{H}OH}$), 7.44-7.49 (2 H, m, aryl-$\underline{\mathrm{H}}$), 7.55-7.60 (1 H, m, aryl-$\underline{\mathrm{H}}$),7.94-7.97 (2 H, m, aryl-$\underline{\mathrm{H}}$); δ_C (75.4 MHz, $CDCl_3$) 13.9, 22.5, 25.2, 31.7, 36.4, 44.9, 67.7, 128.0, 128.6, 133.4, 136.7, 200.9. HRMS (EI): M$^+$ found 220.1456 $C_{14}H_{20}O_2$ requires 220.1463.

3-Hydroxy-4-methyl-1-phenylpentan-1-one: colourless oil, [Found: C, 74.02; H, 7.84. $C_{12}H_{16}O_2$ requires C, 74.95; H, 8.39%]; R$_f$ (20% ethyl acetate/hexane) 0.38; FTIR (thin film) : ν 3452, 1678, 1597, 1448, 1279, 1211 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.00 (3 H, d, *J* 6.6 Hz, $\mathrm{C\underline{H}_3}$), 1.01 (3 H, d, *J* 6.6 Hz, $\mathrm{C\underline{H}_3}$), 1.78-1.82 (1 H, m, $\mathrm{C\underline{H}}$), 3.02-3.15 (1 H, dd, *J* 9.4, 17.5 Hz, $\mathrm{COC\underline{H}_2}$), 3.17-3.21 (1 H, dd, *J* 2.3, 17.5 Hz, $\mathrm{COC\underline{H}_2}$), 3.17 (1 H, brs, $\mathrm{O\underline{H}}$), 3.97-4.02 (1 H, m, $\mathrm{C\underline{H}OH}$), 7.45-7.50 (2 H, m, aryl-$\underline{\mathrm{H}}$), 7.56-7.59 (1 H, m, aryl-$\underline{\mathrm{H}}$),7.95-7.98 (2 H, m, aryl-$\underline{\mathrm{H}}$); δ_C (75.4 MHz, $CDCl_3$) 17.8, 18.5, 33.0, 41.9, 72.3, 128.0, 128.6, 133.4, 136.8, 201.3.

2-Hydroxy-4-oxo-4-phenylbutanoic acid: white solid, m.p. 129-131 °C; R$_f$ (0.4 % acetic acid/20% hexane/ethyl acetate) 0.17; FTIR (KBr) : ν 3426, 1726, 1679, 1598, 1450, 1218, 1105 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.50–3.58 (1 H, dd, *J* 6.3, 18.2 Hz, $\mathrm{COC\underline{H}_2}$), 3.59-3.67 (1 H, dd, *J* 4.5, 18.2 Hz, $\mathrm{COC\underline{H}_2}$), 3.75 (1 H, brs, $\mathrm{O\underline{H}}$), 4.71-4.74 (1 H, dd, *J* 4.5, 6.3 Hz, $\mathrm{C\underline{H}OH}$), 7.48-7.53 (2 H, m, aryl-$\underline{\mathrm{H}}$), 7.61-7.66 (1 H, m, aryl-H),7.96-7.99 (2 H, m, aryl-H); δ_C (75.4 MHz, $CDCl_3$) 42.0, 66.9, 128.4, 128.9, 134.1, 136.0, 176.1, 198.8. HRMS (EI): M+ found 194.0578 $C_{10}H_{10}O_4$ requires 194.0579.

3-Hydroxy-1-phenyl-3-(2-pyridyl)propan-1-one:[12] white solid, mp 84-86 °C; Rf (50% ethyl acetate/hexane) 0.35; FTIR (KBr): υ 3426, 1704, 1597, 1449, 1252, 1204, 1073 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.45-3.50 (1 H, dd, *J* 8.2, 17.4 Hz, $COCH_2$), 3.62-3.66 (1 H, dd, *J* 3.7, 17.4 Hz, $COCH_2$), 4.30 (1 H, brs, OH), 5.40-5.42 (1 H, dd, *J* 3.7, 8.2 Hz, CHOH), 7.20-7.22 (1 H, m, aryl-H), 7.45-7.48 (2 H, m, aryl-H), 7.55-7.60 (2 H, m, aryl-H), 7.71-7.74 (1 H, m, aryl-H), 7.97-8.00 (2 H, m, aryl-H), 8.55-8.56 (1 H, d, *J* 4.8 Hz, aryl-H); δ_C (75.4 MHz, $CDCl_3$) 46.0, 70.3, 120.5, 122.5, 128.3, 128.7, 133.5, 136.8, 136.9, 148.6, 161.6, 200.0. HRMS (EI): M+ found 227.0943 $C_{14}H_{13}NO_2$ requires 227.0946.

2-(Hydroxyphenylmethyl)cyclohexan-1-one:[13] white solid, Rf (20% ethyl acetate/hexane) 0.27, 0.33; FTIR (KBr): υ 3426, 1709, 1451, 1128 cm^{-1}; *syn* δ_H (300 MHz, $CDCl_3$) 1.47-1.87 (5 H, m, CH_2), 2.05-2.11 (1 H, m, CH_2), 2.33-2.48 (2 H, m, $COCH_2$), 2.58-2.62 (1 H, m, COCH), 3.00-3.01 (1 H, d, *J* 3.3 Hz, OH), 5.39-5.40 (1 H, t, *J* 2.1 Hz, CHOH), 7.23-7.35 (5 H, m, aryl-H); δ_C (75.4 MHz, $CDCl_3$) 24.9, 26.0, 28.0, 42.7, 57.2, 70.7, 125.8, 127.0, 128.2, 141.5, 214.8. *anti*: δ_H (300 MHz, $CDCl_3$) 1.26–1.35 (1 H, m, CH_2), 1.51-1.81 (4 H, m, CH_2), 2.06-2.11 (1 H, m, CH_2), 2.32-2.51 (2 H, m, $COCH_2$), 2.59-2.65 (1 H, m, COCH), 3.94 (1 H, d, *J* 2.0 Hz, OH), 4.78-4.80 (1 H, dd, *J* 2.0, 8.8 Hz, CHOH), 7.28-7.36 (5 H, m, aryl-H); δ_C (75.4 MHz, $CDCl_3$) 24.8, 27.8, 30.9, 42.7, 57.5, 74.8, 125.8, 127.1, 127.9, 128.2, 128.4, 141.0, 215.6. HRMS (EI): M+ found 204.1144 $C_{13}H_{16}O_2$ requires 204.1150.

2-(Hydroxyphenylmethyl)cyclopentan-1-one: colourless oil, Rf (20% ethyl acetate/hexane) 0.26, 0.29; FTIR (thin film): υ 3453, 1738, 1453, 1274, 1156 cm^{-1}; *syn* δ_H (300 MHz, $CDCl_3$) 1.25-2.32 (6 H, m, 3-CH_2), 2.39-2.44 (1 H, m, COCH), 4.53 (1H, brs, OH), 5.28 (1 H, d, *J* 2.7 Hz, CHOH), 7.25-7.34 (5 H, m, aryl-H); δ_C (75.4 MHz, $CDCl_3$) 22.7, 26.3, 36.2, 56.0, 71.4, 125.5, 127.2, 128.2, 142.7, 220.3. *anti*: δ_H (300 MHz, $CDCl_3$) 1.26–2.35 (6 H, m, 3-CH_2), 2.38-2.44 (1 H, m, COCH), 2.62 (1 H, brs, OH), 4.68-4.72 (1 H, dd, *J* 1.3, 9.2 Hz, CHOH), 7.26-7.35 (5 H, m, aryl-H); δ_C (75.4 MHz, $CDCl_3$) 20.3, 26.9, 38.6, 55.2, 75.1, 126.5, 127.9, 128.3, 141.3, 222.9. HRMS (EI): M+ found 190.0992 $C_{12}H_{14}O_2$ requires 190.0994.

5-(Hydroxyphenylmethyl)-5-hydrofuran-2-one: colourless oil, FTIR (thin film): υ 3426, 1755, 1453, 1168, 1042 cm^{-1}; *major* Rf (50% ethyl acetate/hexane) 0.33; δ_H (300 MHz, $CDCl_3$) 3.22 (1 H, brs, OH), 4.70 (1 H, d, *J* 7.0 Hz, CHOH), 5.15 (1 H, ddd, *J* 1.7, 1.7, 7.0 Hz, CH), 6.08 (1 H, dd, *J* 1.7, 6.2 Hz, CH=), 7.16 (1 H, dd, *J* 1.7, 6.2 Hz, CH=), 7.36 (5 H, m, aryl-H). δ_C (75.4 MHz, $CDCl_3$) 75.4, 86.8, 122.8, 126.6, 128.6, 128.8, 137.8, 153.1, 172.5. *minor* Rf (50% ethyl acetate/hexane) 0.38; δ_H (300 MHz, $CDCl_3$) 2.90 (1 H, brs, OH), 5.06 (1 H, brs, CHOH), 5.16 (1 H, m, CH), 6.16 (1 H, m, CH=), 7.34-7.40 (6 H, m, aryl-H and CH=). δ_C (75.4 MHz, $CDCl_3$) 73.0, 86.4, 121.5, 126.0, 128.5, 128.6, 138.5, 152.8, 172.2. HRMS (EI): M+ found 190.0652 $C_{11}H_{10}O_3$ requires 190.0630.

1-(2-Furyl)-3-hydroxy-3-phenylpropan-1-one: colourless oil, Rf (20% ethyl acetate/hexane) 0.14; FTIR (thin film): υ 3452, 1666, 1468, 1258, 1021 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.22-3.26 (2 H, m, $COCH_2$), 4.08 (1 H, brs, OH), 5.29-5.33 (1 H, dd, *J* 4.4, 7.7 Hz, CHOH), 6.53-6.55 (1 H, dd, *J* 1.7, 3.5 Hz, CH=), 7.21 (1

H, d, *J* 3.5 Hz, CH=), 7.28-7.43 (5 H, m, aryl-H), 7.58 (1 H, d, *J* 1.7 Hz, CH=). δ_C (75.4 MHz, $CDCl_3$) 46.9, 69.9, 112.4, 117.9, 125.6, 127.6, 128.4, 142.8, 146.8, 152.4, 188.5. HRMS (EI): M$^+$ found 216.0777 $C_{13}H_{12}O_3$ requires 216.0786.

1-(2-Furyl)-3-hydroxyoctan-1-one: colourless oil, Rf (20% ethyl acetate/hexane) 0.16; FTIR (thin film): 3439, 1667, 1469, 1026 cm^{-1}, δ_H (300 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 7.0 Hz, CH_3), 1.26-1.44 (8 H, m, 4-CH_2), 2.86-2.94 (1 H, dd, *J* 8.8, 17.1 Hz, $COCH_2$), 3.00-3.08 (1 H, dd, *J* 3.1, 17.1 Hz, $COCH_2$), 4.19 (1 H, m, CHOH), 6.54-6.56 (1 H, dd, *J* 3.5, 1.7 Hz, CH=), 7.22 (1 H, d, *J* 3.5 Hz, CH=), 7.60 (1 H, d, *J* 1.7 Hz, CH=). δ_C (75.4 MHz, $CDCl_3$) 13.9, 22.5, 25.1, 31.7, 36.6, 44.8, 67.8, 112.3, 117.6, 146.6, 152.6, 189.5. HRMS (EI): M$^+$ found 210.1262 $C_{12}H_{18}O_3$ requires 210.1256.

1-(2-Furyl)-3-hydroxy-4-methylpentan-1-one: colourless oil, Rf (20% ethyl acetate/hexane) 0.17; FTIR (thin film): 3426, 1666, 1567, 1469, 1392, 1030 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.98 (6 H, t, *J* 6.6 Hz, 2-CH_3), 1.77 (1 H, m, CH), 2.84-2.92 (1 H, dd, *J* 9.2, 16.7 Hz, $COCH_2$), 2.99-3.07 (1 H, dd, *J* 2.6, 16.7 Hz, $COCH_2$), 3.96 (1 H, m, CHOH), 6.54-6.56 (1 H, dd, *J* 3.5, 1.7 Hz, CH=), 7.23 (1 H, d, *J* 3.5 Hz, CH=), 7.60 (1 H, d, *J* = 1.7 Hz, CH=); δ_C (75.4 MHz, $CDCl_3$) 17.7, 18.3, 33.2, 41.8, 72.4, 112.3, 117.5, 146.6, 152.6, 189.9. HRMS (EI): $(M-H_2O)^+$ found 164.0834 $C_{10}H_{12}O_2$ requires 164.0837.

4-(2-Furyl)-2-hydroxy-4-oxobutanoic acid: colourless oil, Rf = 0.15 (0.4% acetic acid/20% hexane/ethyl acetate); FTIR (thin film): 3416, 1729, 1666, 1568, 1469, 1258, 1103 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.31-3.39 (1 H, dd, *J* 6.6, 7.6 Hz, $COCH_2$), 3.40-3.48 (1 H, dd, *J* 4.4, 7.6 Hz, $COCH_2$), 4.69-4.73 (1 H, dd, *J* 4.4,.6.6 Hz, CHOH), 6.54-6.56 (1 H, dd, *J* 3.5, 1.7 Hz, CH=), 7.26 (1 H, d, *J* 3.5 Hz, CH=), 7.60 (1 H, d, *J* 1.7 Hz, CH=). δ_C (75.4 MHz, $CDCl_3$) 41.7, 66.5, 112.5, 118.5, 147.2, 151.9, 176.8, 186.6. HRMS (EI): M$^+$ found 184.0382 $C_8H_8O_5$ requires 184.0372.

1-(2-Furyl)-3-Hydroxy-3-(2-pyridyl)propan-1-one: colourless oil, Rf (50% ethyl acetate/hexane) 0.20; FTIR (thin film): 3426, 1660, 1594, 1470, 1071 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.26-3.34 (1 H, dd, *J* 8.4, 16.7 Hz, $COCH_2$), 3.39-3.46 (1 H, dd, *J* 4.0, 16.7 Hz, $COCH_2$), 4.28 (1 H, brs, OH), 5.33-5.37 (1 H, dd, *J* 4.0, 8.4 Hz, CHOH), 6.51-6.54 (1 H, dd, *J* 1.7, 3.5 Hz, CH=), 7.18-7.20 (1 H, m, aryl-H), 7.23 (1 H, d, *J* 3.5 Hz, CH=), 7.49 (1 H, d, *J* 7.9 Hz, aryl-H), 7.58 (1 H, d, *J* 1.7 Hz, CH=), 7.67-7.73 (1 H, m, aryl-H), 8.53 (1 H, d, *J* 4.8 Hz, aryl-H). δ_C (75.4 MHz, $CDCl_3$) 45.9, 69.9, 112.3, 118.2, 120.4, 122.4, 136.8, 146.8, 148.4, 152.5, 161.2, 188.1. HRMS (EI): M$^+$ found 217.0737 $C_{12}H_{11}NO_3$ requires 217.0739.

Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate:[14] colourless oil, Rf (20% ethyl acetate/hexane) 0.43; FTIR (thin film): 3453, 1728, 1681, 1598, 1454, 1260, 1132 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.11 (3 H, s, CH_3), 1.14 (3 H, s, CH_3), 3.11 (1 H, brs, OH), 3.72 (3 H, s, OCH_3), 4.90 (1 H, s, CHOH), 7.27-7.33 (5 H, m, aryl-H). δ_C (75.4 MHz, $CDCl_3$) 18.9, 22.9, 47.6, 52.0, 78.6, 127.3, 127.6, 127.7, 139.9, 178.1.

Methyl 3-hydoxy-2,2-dimethyloctanoate: colourless oil, Rf (20% ethyl acetate/hexane) 0.46; FTIR (thin film): 3467, 1726, 1469, 1267, 1141 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.5 Hz, CH_3), 1.16 (3 H, s, CH_3), 1.18 (3 H, s, CH_3), 1.22-1.65 (8 H, m, 4-CH_2), 2.36 (1 H, d, *J* 6.8 Hz, OH), 3.57-3.63 (1 H, m, CH̲OH), 3.70 (3 H, s, OCH̲3). δ_C (75.4 MHz, $CDCl_3$) 13.9, 20.3, 22.2, 22.5, 26.2, 31.6, 31.7, 47.1, 51.8, 76.6, 178.1. HRMS (EI): (M^+-OH) found 185.1549 $C_{11}H_{21}O_2$ requires 185.1542.

Methyl 3-hydoxy-2,2,4-trimethylpentanoate: colourless oil, Rf (20% ethyl acetate/hexane) 0.45; FTIR (thin film): 3475, 1719, 1467, 1263, 1142 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.80 (3 H, d, *J* 6.8 Hz, CH̲3), 0.96 (3 H, d, *J* 6.9 Hz, CH̲3), 1.18 (3 H, s, CH̲3), 1.27 (3 H, s, CH̲3), 1.85 (1 H, m, CH̲), 2.83 (1 H, d, *J* 8.2 Hz, OH̲), 3.38 (1 H, m, CH̲OH), 3.69 (3 H, s, OCH̲3). δ_C (75.4 MHz, $CDCl_3$) 16.0, 21.6, 22.3, 23.7, 29.8, 45.8, 51.5, 81.5, 178.5. HRMS (EI): (M^+-OH) found 157.1224. $C_9H_{17}O_2$ requires 157.1229.

2-Hydroxy-3-(methoxycarbonyl)-3-methylbutanoic acid: colourless oil, Rf (0.4% acetic acid/20% hexane/ethyl acetate) 0.42; FTIR (thin film): 3451, 1724, 1439, 1272, 1094 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26 (3 H, s, CH̲3), 1.31 (3 H, s, CH̲3), 3.74 (3 H, s, OCH̲3), 4.41 (1 H, s, CH̲OH). δ_C (75.4 MHz, $CDCl_3$) 20.5, 21.6, 46.6, 52.4, 74.9, 176.0, 176.7. HRMS (EI): MH^+ found 177.0767 $C_7H_{13}O_5$ requires 177.0763.

Methyl 3-hydoxy-2,2-dimethyl-3-(2-pyridyl)propanoate: colourless oil, [Found: C, 62.77; H, 7.22, N, 6.57. $C_{11}H_{15}NO_3$ requires C, 63.16; H, 7.18; N, 6.70%]; Rf (20% ethyl acetate/hexane) 0.38; FTIR (thin film) Rf (50% ethyl acetate/hexane) 0.42; FTIR (thin film): 3426, 1738, 1593, 1470, 1258, 1134 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.08 (3 H, s, CH̲3), 1.16 (3 H, s, CH̲3), 3.72 (3 H, s, OCH̲3), 4.95 (1 H, s, CH̲OH), 7.16-7.23 (2 H, m, aryl-H̲), 7.62-7.67 (1 H, m, aryl-H̲), 8.54-8.55 (1 H, m, aryl-H̲). δ_C (75.4 MHz, $CDCl_3$) 20.8, 48.4, 51.8, 76.9, 122.1, 122.7, 136.1, 148.0, 158.3, 177.1. HRMS (EI): (M^+-OH) found 192.1007 $C_{11}H_{14}NO_2$ requires 192.1025.

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