

# Transesterification of $\beta$ -ketoesters catalyzed by hybrid materials based on silica sol–gel

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## Abstract

This work shows an alternative process for  $\beta$ -ketoester transesterification using new silica-based hybrid materials as heterogeneous catalysts. The catalysts were synthesized using silica and 3-aminopropyltriethoxysilane or 1,1,1,3,3,3-hexamethyldisilazane as functionalizing agents.  $\beta$ -Ketoesters and alcohols were transesterified in refluxing toluene with reaction times between 4 h and 14 h. Different ketoesters with good performance were obtained. The influence of the catalysts and starting materials on the reaction rate was studied. In all cases, coproduct formation was not observed; the catalysts were recovered and reused without loss of catalytic activity.

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## 1. Introduction

The transesterification reaction is a useful tool in organic synthesis, having wide application both in academic and in industrial research [1]; for example, in the preparation of  $\beta$ -ketoesters used as chemical intermediates in pharmaceutical, agrochemical, chemical, and polymer industries [2]. A non-catalytic transesterification of  $\beta$ -ketoesters requires the use of either excess of  $\beta$ -ketoesters or longer reaction time, and employs high boiling alcohols. In addition, this reaction is currently catalyzed by strong acids such as hydrochloric, sulphuric, and *p*-toluenesulphonic acids [3,4]. The transesterification has also reported to be effectively catalyzed by soluble basic catalysts such as DMAP [5], DBU [6], metal alkoxides [7], carbonates [8], and enzymes [9].

The reaction conditions involving soluble acids or bases are contradictory to the aim of current synthetic industrial chemistry, which prefers processes being highly efficient, selective, ecofriendly, and preferably catalytic with high

efficiency and selectivity. From the environmental point of view, heterogeneous catalysts such as clays [10], Mo–ZrO<sub>2</sub> [11], FeSO<sub>4</sub> or CuSO<sub>4</sub> [12], zinc [13], K-10 montmorillonite [14], B<sub>2</sub>O<sub>3</sub>/ZrO<sub>2</sub> [15], Mg–Al–O–*t*-Bu hydrotalcite [16], and amine grafted on silica gel [17] are much more desirable. Nowadays attention is focused on the development of basic solids, which are still scarcely used in comparison to the solid acid catalysts employed for transesterification [18].

On the other hand, the modification of the surface of silica materials through the covalent bonding with organic species is being studied for the design of hybrid materials with properties focused on advanced technological applications. The inorganic–organic functionalities inside silica network present different advantages in heterogeneous catalysis, in our case for the transesterification reaction. These hybrid materials were obtained by the sol–gel technique. The sol–gel process was used for the first time by Steven S. Kistler in 1931 [19]. From that time, the procedure has been further changed to obtain gels by hydrolysis of sodium silicate. This reaction gives salts in the wet gel, their elimination being possible with successive and complicate washing. Nowadays, these aerogels are prepared by alkoxide precursors. The innovation of this study is the preparation of silica having a high number of superficial silanol

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groups but a very low number of adsorbed water molecules. The synthesis procedure consisted in obtaining a sol–gel silica co-synthesized or functionalized by covalent attachment of 3-aminopropyltriethoxysilane and 1,1,1,3,3,3-hexamethyldisilazane, respectively. These compounds present organic functional groups with different properties than that of the silica precursors employed, tetraethylorthosilicate in this study, and they are incorporated to the silica network to modify the surface and mechanical properties of these hybrid materials [20].

In this paper, we focused on a further effect of the catalytic activity of hybrid materials based on silica sol–gel; we report a mild and sustainable transesterification of  $\beta$ -ketoesters with various alcohols.

## 2. Experimental

### 2.1. Preparation of catalysts

#### 2.1.1. Silica preparation

Silica (S) preparation by sol–gel technique: all the experiences were made with a final molar ratio of tetraethylorthosilicate (TEOS), TEOS/EtOH/H<sub>2</sub>O equal to 1:1:4. The TEOS–EtOH–AcOH sols were stirred at an atmospheric pressure at room temperature (rt) for 30 min. Then, the hydrolysis process began with the slow addition of distilled water. After water addition, gelation of the sols was carried out at rt, and the wet gels were then aged in the same medium until dry silica particles were obtained. These solids were washed with distilled water, and subsequently dried at rt.

#### 2.1.2. Modified silicas

These catalysts were synthesized by addition of 3-aminopropyltriethoxysilane (AP) [5] or 1,1,1,3,3,3-hexamethyldisilazane (HS) to a suspension of silica previously prepared in refluxing toluene. The mixture was then stirred for 5 h. The solid was filtered, washed in a soxhlet apparatus with diethyl ether and dichloromethane and then dried at 120 °C. The nomenclature of samples is SAF (modified silica with AP) and SHF (modified silica with HS), respectively.

#### 2.1.3. Characterization of samples

The characterization of catalysts was realized by different techniques: FT-IR, XRD,  $S_{BET}$ , DTA-TGA, TEM, EDX, SEM, and wet ability, although not all of them are presented in this work.

### 2.2. Catalytic test: typical experimental procedure

$\beta$ -Ketoester (1 mmol), alcohol (1 mmol), catalyst (150 mg), and toluene (4 ml) were placed in a 50-ml round bottom flask fitted with a reflux condenser. The reaction mixture was heated to 110 °C (silicone oil bath temperature) for a period of time. The reaction was monitored by TLC (hexane–ethyl acetate 4:1) and after completion the mixture was cooled, the catalyst was removed by filtration and washed twice with toluene (2 ml). The organic extract was

evaporated to dryness giving a residue, which was purified by column chromatography on silica gel to give the pure  $\beta$ -ketoester. The catalyst was reused in subsequent reactions. Characterization of the products was performed by <sup>13</sup>C NMR using a Varian 250 MHz spectrometer, with TMS as an internal standard. The <sup>13</sup>C NMR spectra of representative products are shown below:

- *Benzyl acetoacetate*: <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  30.41, 50.28, 67.40, 128.39, 128.63, 128.89, 135.55, 167.22, 200.70.
- *2-Phenoxyethyl acetoacetate*: <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  30.33, 50.13, 63.86, 65.82, 114.84, 121.54, 129.81, 158.58, 167.32, 200.61.
- *3-Phenoxypropyl acetoacetate*: <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  30.32, 30.45, 32.28, 50.28, 64.95, 126.33, 128.68, 128.73, 141.26, 167.45, 201.00.
- *Geranyl acetoacetate*: <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.24, 17.56, 25.84, 26.44, 30.25, 39.69, 50.32, 59.16, 123.84, 124.12, 132.05, 143.29, 167.34, 200.83.
- *2-(Ethylthio)ethyl acetoacetate*: <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.95, 26.30, 29.99, 30.36, 50.10, 64.36, 167.03, 200.57.

### 2.3. Recycling of catalyst

After the reaction endpoint, the catalyst is filtered, washed thoroughly with toluene, dried under vacuum and reused for the transesterification reaction, following the procedure described above.

## 3. Results and discussion

### 3.1. Characterization of samples

In Fig. 1 are shown TEOS (precursor of silica), AP and HS (modifiers that depend on the desired properties of silica prepared by sol–gel) structures and in Fig. 2 are shown TEM micrographs of pure silica with 200 nm, 100 nm, and 20 nm of magnifications, respectively. In these pictures, it can be seen that silica presents a majority spherical particles with size about 12 nm.

In Fig. 3 are shown TEM micrographs of SHF and SAF, with a magnification of 50 nm and EDX analysis of the relation Si/O ratio in the SHF sample (in Fig. 3, numbers 1 and 2); the results for EDX analysis of relation of the Si/O ratio in the SHF sample are shown in Table 1. In the SHF sample, which contains only HS modifier, it can be seen that size of silica increases in relation to pure silica. Besides, the presence of flocculates inside the silica network indicates excess of HS. Then, these results illustrate that the modifier not only is on the surface but also in the crystalline silica network. In relation to SAF sample (Fig. 3) a different morphology can be seen, such as sheets characteristic of growing silica particles containing AP in the structure. This distinctive morphology could be assigned to the amino groups in AP, having an important interaction with the silanol groups of silica. Besides, EDX analysis corroborates the presence of the two modifiers inside silica framework.

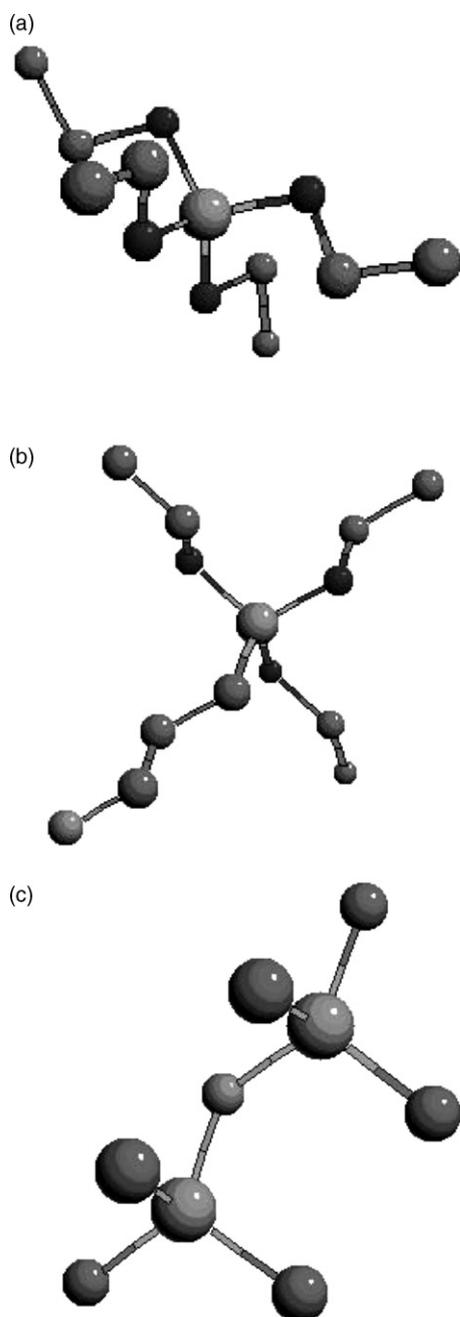


Fig. 1. Scheme of TEOS (a), AP (b), and HS (c).

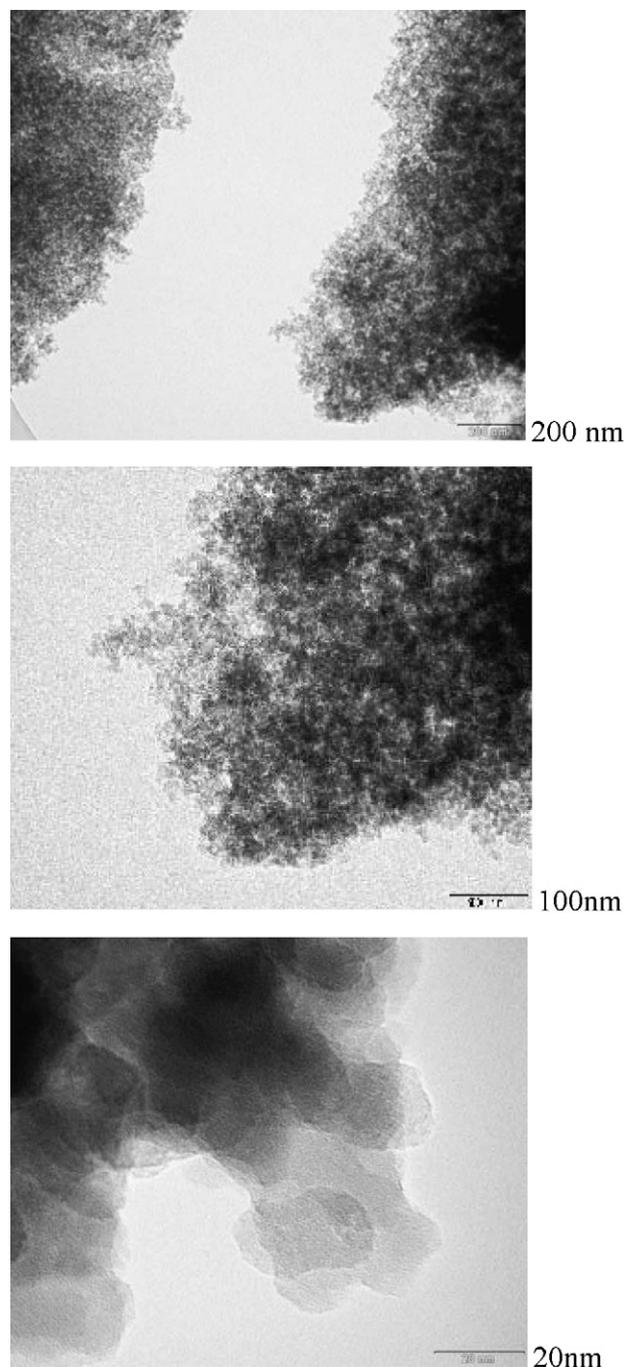


Fig. 2. TEM micrographs of pure silica at different magnifications.

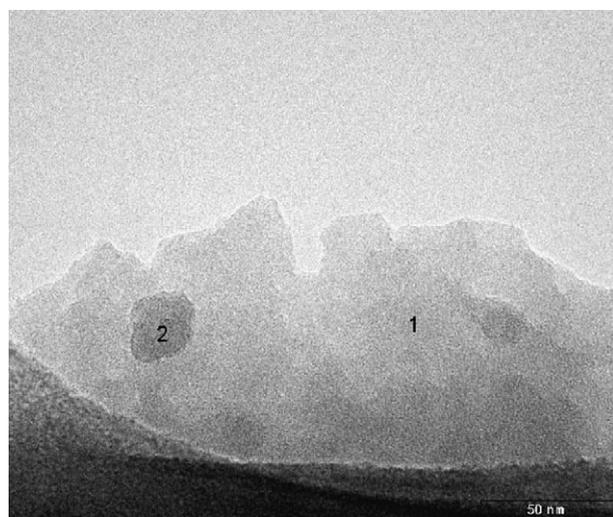
The modifiers are identified in particular form, as can be observed in micrographs and EDX analysis (Table 1).

In addition, the effect of AP and HS upon the framework of silica was studied by  $S_{\text{BET}}$ , as well as the pore volume and the pore diameter of different catalysts used. The results are shown in Table 2. The functionalized samples present a decreased  $S_{\text{BET}}$  in relation to pure silica, as well as a change in other two parameters (Table 2). For SAF sample, the  $S_{\text{BET}}$  decreases from 507.2 m<sup>2</sup>/g (pure silica) to 210 m<sup>2</sup>/g because of the reaction between AP with TEOS, and steric effects due to their structure (Fig. 1). SHF presents a value of 459.1 m<sup>2</sup>/g, this decrease could be due to the presence of agglomeration of HS inside the silica network.

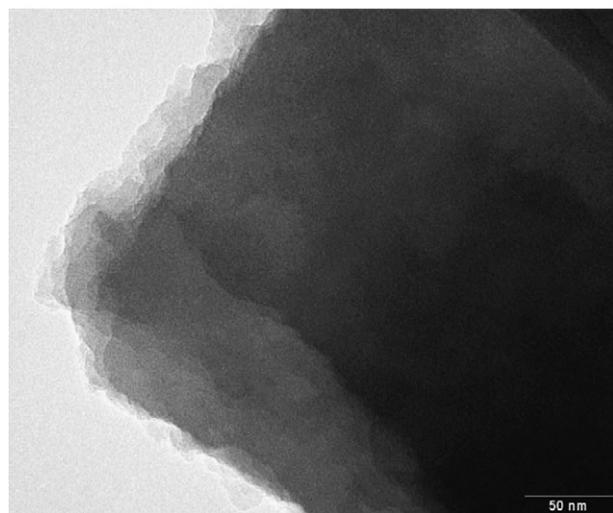
### 3.2. Transesterification reaction

This research describes a sustainable method for transesterification of  $\beta$ -ketoesters (Scheme 1) catalyzed by hybrid materials described. A variety of  $\beta$ -ketoesters was treated with alcohols in the presence of catalyst to give the corresponding ester by transesterification in good to excellent yields.

Optimum reaction conditions were examined employing ethyl acetoacetate and 3-phenylethanol as substrates. Initially, silica gel (S) was used as catalyst in refluxing toluene, and substrates were consumed completely after 10 h. Besides, a



SHF



SAF

Fig. 3. TEM micrographs of synthesized catalysts.

secondary product was detected from alcohol intermolecular etherification through the silica gel acid sites (Scheme 2).

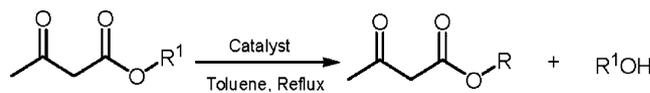
Afterward, the synthesized catalyst SHF was used. The results of the transesterification reaction between  $\beta$ -ketoesters and alcohols at 110 °C in refluxing toluene are given in Table 3. All the reactions are carried out with standard substrates such as methyl acetoacetate and ethyl acetoacetate and various alcohols (3-phenyl-1-propanol, (–)-menthol and benzyl alcohol). When methyl or ethyl acetoacetate are heated at 110 °C with 3-phenyl-1-propanol in the presence of 150 mg of SHF (in toluene), the corresponding  $\beta$ -ketoesters are obtained. For these

Table 1  
Determination of Si and O contents by EDX (catalyst: SHF)

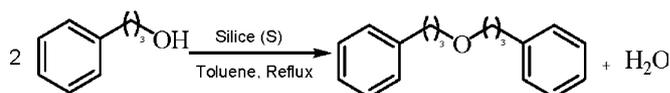
| Reference numbers on micrographs | Element | Atomic% | Weight% |
|----------------------------------|---------|---------|---------|
| 1 (SiO <sub>2</sub> )            | Si      | 33.1    | 47.4    |
|                                  | O       | 57.7    | 47.0    |
| 2 (HS)                           | Si      | 42.6    | 57.1    |
|                                  | O       | 53.3    | 40.6    |

Table 2  
Results of  $S_{\text{BET}}$  of catalysts

| Catalyst         | $S_{\text{BET}}$ (m <sup>2</sup> /g) | Pore volumes (cm <sup>3</sup> /g) | Pore diameter (Å) |
|------------------|--------------------------------------|-----------------------------------|-------------------|
| SiO <sub>2</sub> | 507.2                                | 0.77                              | 67.3              |
| SHF              | 459.1                                | 0.21                              | 19.4              |
| SAF              | 210.0                                | 0.11                              | 20.7              |



Scheme 1. Transesterification reaction: general scheme.



Scheme 2. Ether formation reaction.

Table 3  
Transesterification reaction, using SHF as catalyst during 4 h in reflux toluene

| Entry | $\beta$ -Ketoester  | Alcohol             | Yields (%) |
|-------|---------------------|---------------------|------------|
| 1     | Methyl acetoacetate | 3-Phenyl-1-propanol | 97         |
| 2     | Ethyl acetoacetate  | 3-Phenyl-1-propanol | 98         |
| 3     |                     | (–)-Menthol         | 94         |
| 4     |                     | Benzyl alcohol      | 92         |

conditions, the reaction time was 4 h, which gave excellent yields: 97% and 98%, respectively, without detecting the formation of secondary products (Table 3, entries 1 and 2).

In fact, the partial protection of silica OH by  $-\text{Si}(\text{CH}_3)_3$  groups decreases the Brønsted nature of SHF catalyst. In this case, no subproduct is obtained as it occurs when silica is used as catalyst. For this reason SHF is a selective hybrid catalyst.

In all the examples the yields are excellent (92–97%, entries 1–4) showing that most of the chosen alcohols have no considerable effect on the reaction yields.

The SHF catalyst was reused intact without reactivation up to four times as is shown in Table 4. In addition, the high efficient and stable nature of the catalyst is shown in Table 4: in entry 1, 98% yield and in entry 4, 97% yield in the reaction of ethyl acetoacetate with 3-phenyl-1-propanol, in refluxing toluene for 4 h. This methodology of reaction using SHF as catalyst shows a selective, reusable, and easy to synthesize catalyst; the silica-based hybrid solid with these properties can be characterized as a sustainable catalyst.

Table 4  
Reused SHF catalyst for transesterification of ethyl acetoacetate with 3-phenyl-1-propanol

| Cycle | Time (h) | Yields (%) |
|-------|----------|------------|
| 1     | 4        | 98         |
| 2     | 4        | 98         |
| 3     | 4        | 97         |
| 4     | 4        | 97         |

Table 5  
Methyl acetoacetate transesterification using SAF as catalyst

| Entry | Alcohol               | Time (h) | Yields (%) |
|-------|-----------------------|----------|------------|
| 1     | 3-Phenyl-1-propanol   | 8        | 88         |
| 2     | Cholesterol           | 11       | 98         |
| 3     | (-)-Menthol           | 10       | 74         |
| 4     | 2-Phenoxy ethanol     | 10       | 98         |
| 5     | Benzyl alcohol        | 6        | 77         |
| 6     | 2-(Ethyl)-thioethanol | 14       | 72         |

Table 6  
Ethyl acetoacetate transesterification reaction using SAF as catalyst

| Entry | Alcohol                 | Time (h) | Yields (%) |
|-------|-------------------------|----------|------------|
| 1     | 3-Phenyl-1-propanol     | 8        | 92         |
| 2     | 4-Methoxybenzyl alcohol | 7        | 92         |
| 3     | Geraniol                | 6        | 95         |
| 4     | Linalool                | 7        | 52         |
| 5     | (-)-Menthol             | 10       | 77         |

Table 7  
Transesterification reaction using different  $\beta$ -ketoesters with 3-phenyl-1-propanol, using SAF as catalyst

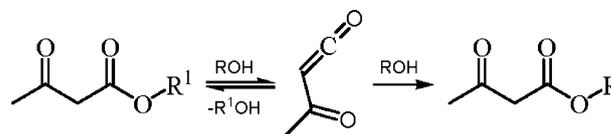
| Entry | $\beta$ -Ketoester   | Yields (%) |
|-------|----------------------|------------|
| 1     | Methyl acetoacetate  | 88         |
| 2     | Ethyl acetoacetate   | 92         |
| 3     | Ethyl benzoylacetate | 80         |

The results of the transesterification reaction between  $\beta$ -ketoesters and alcohols at 110 °C under solvent-free conditions using SAF solid base catalyst are given in Tables 5–7. All the reactions are carried out with standard substrates such as methyl acetoacetate with various alcohols such as primary, secondary, tertiary, and benzyl alcohols under similar conditions.

When methyl acetoacetate is heated with 3-phenyl-1-propanol at 110 °C in the presence of 150 mg of SAF in toluene, the corresponding  $\beta$ -ketoesters are obtained, requiring 8 h to attain excellent yields of 88%, without the formation of secondary products (Table 5, entry 1). In all the examples the yields are very good showing that most of the chosen alcohols have an effect on the reaction yields, for example: benzylic alcohols at 6 h (Table 5, entry 5) in comparison to 2-ethylthioethanol at 14 h (Table 5, entry 6).

In Table 6 are summarized the results of the reaction of ethyl acetoacetate with different alcohols in refluxing toluene using SAF as catalyst. No considerable effect on the yields of the reaction was detected when ethyl acetoacetate was replaced by methyl acetoacetate (Tables 5 and 6, respectively). But an important effect on the yields can be seen with the alcohol structures: benzyl > primary > secondary > tertiary (Table 6).

Transesterification with tertiary alcohols is often problematic in the acid-catalyzed reaction. This reaction proceeded also with tertiary alcohol with moderate yield (Table 6, entry 4), which is another advantageous feature of the method.



Scheme 3. Reaction mechanism via acetylketene.

Finally, the results for the studied reaction of different acetoacetates with 3-phenyl-1-propanol, in refluxing toluene using SAF, are summarized in Table 7. No considerable effect on the yields was detected when ethyl acetoacetate was replaced by methyl acetoacetate (92% and 88%, entries 1 and 2 in Table 7, respectively). When benzoylacetate was used (80%, entry 3 Table 7) it an important effect on yields can be seen.

It is important to mention that a similar activity was obtained for SAF, also in relation to catalyst reuse.

The structural characteristic of the catalyst suggests that the reaction proceeds via the activation of the carbonyl group of the  $\beta$ -ketoester leading to the formation of acylketene as proposed by Campbell and co-workers [21,22] (Scheme 3).

#### 4. Conclusions

In conclusion, we have demonstrated that hybrid materials based on silica gel serve as an efficient, selective, inexpensive, friendly and general heterogeneous catalysts for the transesterification of  $\beta$ -ketoesters with various alcohols. These catalysts can be recycled several times without appreciable loss of reactivity. Simplicity of the operation coupled with simple work-up and the environmentally benign nature of the reaction would allow their application for a variety of substrates.

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