Dicalcium phosphate dehydrate DCPD as a highly efficient and reusable catalyst for Knoevenagel condensation

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ABSTRACT
We have described the catalytic activities of dicalcium phosphate dihydrate (DCPD) in the condensation reaction of various substituted benzaldehydes with active methylene compound malononitrile. The influences of reaction conditions on the corresponding catalytic behavior have been investigated. The results showed that the DCPD exhibited high catalytic activity and versatility and that it can be recycled without significant loss of its activity for the condensation reactions, which shows the material is a promising new type of heterogeneous catalyst for the condensation reactions. Meanwhile, the catalytic results of DCPD compared favorably with those of other materials for Knoevenagel reactions reported previously.

GRAPHICAL ABSTRACT

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Introduction
The Knoevenagel condensation reaction is a useful transformation that has been widely employed for carbon–carbon bond formation in organic synthesis. In recent years, a wide array of catalysts, including Lewis acids, solid bases, ionic liquids, organometallic catalysts, Sevelamer, and solid-supported catalysts have been used to catalyze the Knoevenagel condensation reaction. However, most of these methods suffer from one disadvantage or another, such as using hazardous and carcinogenic solvents, high catalyst loading, or unrecoverable catalysts that sometimes contain toxic metals. Therefore, there is a great need for new catalytic methods that do not have these problems. Functional phosphates catalysts have recently attracted significant attention for organic synthesis because of their ease of recovery, reuse, and simplified product isolation and purification. Using phosphates catalysts is an efficient way to achieve economically advantageous and
environmentally friendly processes. The Knoevenagel condensation is a powerful method to construct a carbon–carbon bond and has been widely used in the production of fine chemicals, such as cosmetics, drugs, and other substances.\cite{9-11} A wide range of catalysts have recently been used in the Knoevenagel condensation.\cite{12-28} but several disadvantages remain regarding to the use of these catalysts, such as difficulties in catalyst recovery and reuse, longer reaction time, or harsh reaction conditions. Therefore, the study of a catalyst for Knoevenagel condensation based on a functional phosphate catalyst is challenging.

The phosphate compound is an environmentally friendly solid material with excellent mechanical strength and stability. Several heterogeneous catalysts have been reported for the Knoevenagel condensation reaction, but few of them are based on phosphate calcium catalyst. Herein, we report our work on dicalcium phosphate dihydrate (DCPD) to catalyze the Knoevenagel condensation reaction with high efficiency and excellent reusability. The catalyst can be easily recovered and still retains catalytic activity. The optimal reaction conditions were obtained after screening the catalyst loading, reaction time, solvent, and temperature for the Knoevenagel condensation reaction between benzaldehyde and malononitrile.

**Results and discussion**

**General information for the catalyst**

Dicalcium phosphate dihydrate CaHPO$_4$·2H$_2$O (DCPD) can be obtained in aqueous medium either by neutralization of phosphoric acid by calcium hydroxide\cite{29} or by double decomposition of a calcium salt and a phosphate salt.\cite{30} The crystal structure of this compound has been described through x-ray diffraction (XRD)\cite{31} and using neutron diffraction.\cite{32} DCPD crystallizes in the monoclinic system (space group: Ia) and its crystallographic parameters are $a = 5.812$ Å, $b = 15.180$ Å, $c = 6.239$ Å, and $\beta = 116.25$.

A schematic representation of its structure is given in Fig. 1. The structure of DCPD consists of corrugated sheets consist of Ca-PO$_4$-Ca-Ca-PO$_4$ chains oriented parallel. The crystals are in the form of platelets and sometimes in the form of needles.\cite{33}

![Figure 1. Schematic representation of the corrugated sheet in DCPD structure. The arrows show the direction of the Ca-PO$_4$ chains.](image-url)
Dicalcium phosphate dihydrate (DCPD) was synthesized by double decomposition of calcium nitrate tetrahydrate and ammonium di-hydrogenophosphate. After 2 h of maturation, the suspension was filtered, washed, and freeze dried.

The appropriate physical methods used to confirm the identity of the product are IR absorption spectroscopy, XRD, elemental analyses of calcium and phosphate concentrations, scanning electron microscopy, and specific surface by BET (Brunauer Emmett and Teller). The IR spectrum shows well-defined bands that can be easily identified from their wave number (Fig. 2). It is analogous to that described by Berry et al.\cite{34} Note the presence of the bands due to the HPO$_4^{2-}$ ions (875 to 1185 cm$^{-1}$) and high intensities of absorption bands due to the vibration of OH groups of water molecules (1645, 3155, 3280 cm$^{-1}$). The XRD pattern is reported in Fig. 3. The interplanar spacings and intensities of the main diffraction lines correspond to those reported on the ASTM (American Society for Testing and Materials) card (JCPDS No. 11-293).\cite{35}

The Ca/P of synthesized DCPD equals 1.00 ± 0.01 and has a very low specific surface area of 2 m$^2$/g. Scanning electron microscopy (SEM) shows that the prepared sample is in the form of large platelets (Fig. 4).
Catalytic activity of DCPD in Knoevenagel reaction

Initial studies were undertaken using benzaldehyde 1a and malonitrile 2a as a model reaction (Scheme 1). The reaction was performed at 25 °C with different mass of catalyst. The best result of 96% yield was achieved by using 0.058 mmol (0.01 g) of the catalyst after 1 h (Table 1). Moreover, the blank experiment was also performed under identical reaction conditions, and it only gave the product in yield of 54% after 3 h. It was obvious that DCPD was the most effective catalyst among the tested catalysts.

Effect of solvents

Based on the concept that catalysts phosphates can work in organic media, and they acquire remarkable properties such as enhanced stability and altered substrate specificity,

![Figure 4. Scanning electron microscopy of synthesized DCPD.](image)

**Scheme 1.** Knoevenagel condensation reaction between 4-chlorobenzaldehyde and Malononitrile.

**Table 1.** Effect of mass catalyst DCPD on the reaction of 1a with 2a.

| Entry | Mass DCPD (g) | Time (h) | Yield (%)b |
|-------|---------------|----------|-------------|
| 1     | No catalyst   | 3        | 54          |
| 2     | 0.01          | 1        | 96          |
| 3     | 0.02          | 1        | 92          |
| 4     | 0.03          | 1        | 90          |
| 5     | 0.05          | 1        | 86          |
| 6     | 0.075         | 1        | 84          |
| 7     | 0.1           | 1        | 80          |
| 8     | 0.2           | 1        | 74          |

aReaction conditions: 1a (1 mmol), 2a (1 mmol), EtOH (5 mL), rt.
bIsolated yield of the pure product.
we investigated the effect of different solvents on the model reaction. We found that the catalytic activity of DCPD was remarkably influenced by solvents (Table 2).

The reaction in EtOH gave the best yield of 96% while the reactions in water and methanol provided the yields of 90% and 92% respectively. The other tested solvents including dioxane, acetonitrile, and tetrahydrofuran (THF) gave poor yields. Moreover, only 84% yield was obtained under solvent-free conditions. The clear correlation between the solvent polarity and the DCPD activity was observed. This result may be attributed to specific interactions between the solvent and catalyst. Based on the results of solvent screen, EtOH was chosen as the optimum solvent for the DCPD-catalyzed Knoevenagel condensation.

**Effect of volume of ethanol**

EtOH was selected to examine the effect of volume of the solvent (Table 3). The reaction in 3 mL EtOH at room temperature for 1 h gave 96% of 3a. However, when the volume of ethanol was increased, the yield of 3a begins to decline.

**Effect of time reaction**

EtOH was selected to examine the effect of time on the reaction (Table 4). The reaction in EtOH at room temperature for a short reaction time gave 75% of 3a. However, when the reaction time was increased, the yield of 3a began to increase. Compound 3a was obtained in 96% yield at room temperature after 10 min of reaction.

### Table 2. Solvent effects on the reaction of 1a with 2a using DCPD catalyst.$^{a}$

| Entry | Solvent   | Time (h) | Yield (%) |
|-------|-----------|----------|-----------|
| 1     | EtOH      | 1        | 96        |
| 2     | MeOH      | 1        | 92        |
| 3     | Water     | 1        | 90        |
| 4     | Dioxane   | 1        | 70        |
| 5     | Acetonitrile | 1       | 68        |
| 6     | THF       | 1        | 80        |
| 7     | Chloroform| 1        | 74        |
| 8     | Dichloromethane | 1   | 74        |
| 9     | Solvent-free | 1     | 84        |

$a$Reaction conditions: 1a (1 mmol), 2a (1 mmol), catalyst (0.058 mmol), solvent (5 mL), rt for 1 h.

$b$Isolated yield of the pure product.

### Table 3. Volume of ethanol effects on the reaction of 1a with 2a using DCPD catalyst.$^{a}$

| Entry | Volume (mL) | Time (h) | Yield (%) |
|-------|-------------|----------|-----------|
| 1     | Solvent-free| 1 h      | 84        |
| 2     | 1           | 1 h      | 85        |
| 3     | 3           | 1 h      | 96        |
| 4     | 5           | 1 h      | 96        |
| 5     | 7           | 1 h      | 92        |
| 6     | 10          | 1 h      | 90        |
| 7     | 15          | 1 h      | 90        |

$a$Reaction conditions: 1a (1 mmol), 2a (1 mmol), catalyst (0.058 mmol), specified volume of EtOH, rt for 1 h.

$b$Isolated yield of the pure product.
**Table 4.** Effect of reaction time and temperature on the reaction of 1a with 2a using DCPD catalyst.\(^a\)

| Entry | Time (min) | Temperature (°C) | Yield (\%)\(^b\) |
|-------|------------|------------------|------------------|
| 1     | 3          | rt               | 75               |
| 2     | 5          | rt               | 90               |
| 3     | 7          | rt               | 94               |
| 4     | 10         | rt               | 96               |
| 5     | 20         | rt               | 96               |
| 6     | 30         | rt               | 96               |
| 7     | 60         | rt               | 96               |
| 8     | 3          | Reflux           | 98               |
| 9     | 5          | Reflux           | 98               |
| 10    | 7          | Reflux           | 98               |
| 11    | 10         | Reflux           | 98               |
| 12    | 20         | Reflux           | 98               |

\(^a\)Reaction conditions: 1a (1 mmol), 2a (1 mmol), catalyst (0.058 mmol), solvent (3 mL), specified temperature for specified time.

\(^b\)Isolated yield of the pure product.

**Effect of reaction temperature**

Temperature also plays an important role in DCPD-catalyzed reactions because of its effects on the reaction rate. Thus, a temperature screening was performed (Table 4). It was found that the activity of DCPD in the Knoevenagel reaction could be increased by raising the temperature, and reached the best yield of 98% at refluxing after only 3 min. Based on the temperature screening, we chose the reflux as the optimum temperature for the reaction.

**Reusability of the catalyst**

Finally, the recovery and reusability of the catalyst were examined. After the completion of a condensation reaction between benzaldehyde and malonitrile, the catalyst was recovered by simple filtration and then washed with ethanol (2 × 10 mL) to remove any residue that had adhered to the catalyst. The recycled catalyst was reused directly in the next cycle without any additional treatments. The efficiency of the recovered catalyst was measured again using the same model reaction. As shown in Table 5, the reaction yield of 80% was achieved after seven cycles, which suggests that there is no loss of activity of the catalyst in the process. To the best of our knowledge, the reusability of this catalyst is significantly better than most of the reported supported catalysts.

**Table 5.** Reusability of the fiber catalyst in Knoevenagel condensation reaction between benzaldehyde and malonitrile.\(^a\)

| Entry | No. of recycling runs | Yield (\%)\(^b\) |
|-------|-----------------------|------------------|
| 1     | 1                     | 96               |
| 2     | 2                     | 96               |
| 3     | 3                     | 92               |
| 4     | 4                     | 90               |
| 5     | 5                     | 88               |
| 6     | 6                     | 86               |
| 7     | 7                     | 80               |

\(^a\)Conditions: 1a (1 mmol), 2a (1 mmol), catalyst (0.058 mmol), EtOH (3 mL), rt for 10 min.

\(^b\)Isolated yield of the pure product.
Generalization of Knoevenagel reaction to other aldehydes

The DCPD was employed in the reaction, where the catalyst activity is mainly due to the structural basicity. To demonstrate the versatility of DCPD for Knoevenagel condensation, we submitted various substituted aldehydes and substrates containing active methylene groups with the molar ratio 1:1 under the optimum conditions (Scheme 2, Table 6). Both electron-rich and electron-deficient aromatic aldehydes worked well and produced good product yields. Nonetheless, when the reactions were realized at reflux for 3 min, good yields were also achieved (Table 6, entries 12–14). All compounds were identified by comparison to reference samples.

Comparison with other reported systems

Many synthetic methods have been developed to accomplish the Knoevenagel condensation reaction successfully.\[36\] From Table 7, it is seen that present catalyst exhibited greater yields compared to the other reported system.\[37–49\] For reactions conducted at room temperature, shorter reaction times were required when using the DCPD catalyst.

Experimental

A 10-mL round-bottomed flask was charged with the carbonyl compound (1 mmol), active methylene compound (1 mmol), DCPD (0.01 g, 5.8 \(10^{-2}\) mmol), and ethanol
(3 mL). The reaction mixture was stirred at room temperature for 10 min (or 3 min at reflux). Progress of the reaction was monitored by thin-layer chromatography (TLC) using n-hexane–EtOAc (5:1) as eluent. After completion of the reaction, 5 mL of water was added and the mixture was extracted three times with dichloromethane. The catalyst was removed by filtration and washed with ethanol–H2O. The solid product was obtained after solvents were removed under vacuum. The product 3a was purified through recrystallization from ethanol.

The DCPD could be recycled after vaporizing water–ethanol. The recycled DCPD could be used repeatedly under the same reaction conditions.

The products prepared 3 are known compounds [47,50,51] and were confirmed by comparing the IR, 1H NMR, 13C NMR, and mass spectral data with authentic samples reported in the literature.

### Conclusions

In conclusion, DCPD was employed as a new and efficient catalyst for the Knoevenagel condensation of aromatic aldehydes with active methylene compounds in ethanol. Furthermore, the attractive features of this method are the green and mild reaction conditions, short reaction times, excellent yields, and operational simplicity. The catalyst can be recycled more than seven times without obvious loss of catalytic activity.
The easy and safe preparation, which is economical and environmentally benign, as well as the reusability, selectivity, and efficiency of the heterogeneous catalyst DCPD proves it has great potential for application in synthetic organic chemistry. Thus, we believe that this simple and efficient procedure will be a practical method to meet the needs of academia. In addition, the catalytic results of DCPD compared favorably with those of other materials for Knoevenagel reactions reported previously.

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