The potassium pyrophosphate $K_2CaP_2O_7$, a new and efficient catalyst for the conjugate addition of thiols onto chalcones

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Citation

Abstract
The synthetic potassium pyrophosphate $K_2CaP_2O_7$ is a new solid support, catalyze the Michael addition of mercaptans onto $\alpha,\beta$-unsaturated carbonyl compounds in heterogeneous media, leading to quantitative yields in a short reaction time. Products of undesirable side reactions resulting from $1,2$-addition, polymerisation and bis-addition are not observed. The work-up procedure is simplified so she gives a cleaner product.

1. Introduction

The conjugate addition [1] of thiols to electron deficient alkenes is one of the most effective methods for carbon-sulphur bond formation [2] and has been the subject of a number of studies about various uses involving synthesis of anti-tuberculosis drug [3], anti-fungal drug [4], biochemistry [5], agrochemistry [6], anti-corrosion [7] and lubrication [8] among others.

In classic methods, this reaction catalysed by strong bases such alkali metal alkoxides [9], hydroxides [10] and amines [11].

The employment of these strong bases and acids in these reactions [12], however, leads to two main problems affecting the environment; the necessity to dispose of huge amounts of organic waste due to formation of undesirable side products resulting from polymerization, bis-addition and self condensation, and total dissolved salts formed following the neutralization of soluble bases with acids.

The replacement of liquid basic catalysts by solid bases in the synthesis [13] of fine and intermediate organic chemicals allows one to avoid corrosion and environmental problems [14].

A new methodology to overcome these problems has been devised by the use of heterogeneous catalyst [15] like alumina [16], zeolites [17], montmorillonite [18], Mg-Al hydrotalcite [19], Perlite [20], animal bone meal [21], $Na_2CaP_2O_7$ [22], $Na_3P_2O_7$ [23], fluorapatite [24], hydroxyapatite [25], natural phosphate [26].
In continuation of our investigations on the use of heterogeneous catalysts for fine chemicals preparation, we wish to report here a mild, heterogeneous catalytic method for the Michael addition between chalcones derivatives and mercaptans catalyzed by synthetic potassium pyrophosphate K$_3$CaP$_2$O$_7$ in mild reaction condition.

2. Materials and Methods

2.1. Chemicals and Instrumentations

All commercial reagents and solvents were used without further purification. Potassium pyrophosphate K$_3$CaP$_2$O$_7$ is prepared in powder state. X-ray diffraction (XRD) patterns of the catalysts were obtained on a Philips 1710 diffractometer using Cu-Kα radiation. Surface areas were determined at 77 K using a Coulter SA 31000 instrument with an automated gas volumetric method employing nitrogen as the adsorbate. NMR spectra were recorded on a Bruker ARX 300 spectrometer. Mass spectra were recorded on a VG Autospec spectrometer. FTIR spectra were recorded on an ATI Mattson-Genesis Series spectrophotometer using the KBr disc method.

2.2. Preparation and Characterization of Catalyst

The Potassium pyrophosphate K$_3$CaP$_2$O$_7$ [27] was synthesized by heating stoichiometric quantities of K$_2$CO$_3$, CaCO$_3$ and NH$_4$H$_2$PO$_4$ (purity greater than 99%). The starting materials were carefully mixed in an agate mortar and heated by steps of 150°C in a porcelain crucible up to 800°C. This solid state technique allows ammonia, water and carbon dioxide to evolve progressively according to the following equation (Figure 1).

$$K_3CO_3 + CaCO_3 + 2NH_4H_2PO_4 \xrightarrow{\Delta} K_3CaP_2O_7 + 3H_2O + 2CO_2$$

**Figure 1. Preparation of potassium pyrophosphate**

After the final grinding, the powder is heated at 820°C for 48hours. The purity of the final powder was controlled by X-ray diffraction, using a D 500 Diffractometer (CuKα radiation, 1,540 Å).

The powder pattern of K$_3$CaP$_2$O$_7$ available in the literature (monoclinic system, space group P2$_1$/n, a = 9.79 Å, c = 12.97 Å, β = 104.3°), and by comparison to those of its two isomorphic diphasphates Cs$_2$CaP$_2$O$_7$ and Rb$_2$CaP$_2$O$_7$ [28].

The powder was dried for 2 hours at 100°C before use in order to eliminate possible water molecules adsorbed on the surface of the sample which may affect catalytic.

2.3. General Procedure

The general procedure for synthesis of β-mercapto carbonyl derivatives is reported in Figure 2, as follows: To a flask containing an equimolar mixture (1 mmol) of chalcones derivatives as Michael acceptors and thiols as Michael donors in methanol catalyzed by K$_3$CaP$_2$O$_7$ was added and the mixture was stirred at room temperature until completion of the reaction, as monitored by thin layer chromatography.

![Figure 2. Thia-Michael addition catalyzed by K$_3$CaP$_2$O$_7$](image)

The catalyst was filtered, washed with dichloromethane and the filtrate was concentrated under reduced pressure. The crude product was purified by recrystallization [29]. The product was analyzed by $^1$H, $^{13}$C NMR and IR spectrometry.

1,3-Diphenyl-3-phenylsulfenylpropan-1-one (3a). White solid, mp 116-118 °C; Rf (10% AcOEt/hexane) 0.36; umax (KBr)1680 cm-1; $\delta$H (400 MHz CDCl3) 3.5 (H, CH$_2$, dd, J$_1$ = 7.5 Hz, J$_2$ = 17.2 Hz), 3.2 (H, CH$_2$, dd, J$_1$ = 8.1 Hz, J$_2$ =17.2 Hz); 4.98 (H, CH, t, J = 7.2 Hz); 7.2-7.6 (13H, arom, m); 7.9 (2H, arom, d, J = 7.5); δC (100 MHz CDCl3) 44.7; 48.3; 127.4; 127.6; 127.9; 128.1; 128.5; 128.6; 128.9; 132.8; 133.3; 134.6; 136.8; 141.3; 197.9; MS (m/z): 318 (M+); 206; 109.

3-(4-Nitrophenyl)-1-phenyl-3-phenylsulfenylpropan-1-one (3b). White solid; 84-87 °C; Rf (10% AcOEt/hexane) 0.2; IR (KBr): 1720 cm-1; 1H NMR (400 MHz CDCl3) δ; 3.6 (2H, d, J$_1$=7.5 Hz, CH$_2$), 4.91 (H, t, J$_1$ = 7.5 Hz, CH$_3$), 7.13-7.5 (10H, m, arom), 7.79 (2H, d, J = 7.5 Hz, arom), 8 (2H, d, J = 7.5 Hz, arom), 13C NMR (100 MHz CDCl3) δ; 196.11, 149.17, 146.94, 136.28, 134.68, 134.38, 134.37, 129.13, 128.79, 128.73, 128.36, 128.05, 123.66, 47.90, 44.07; MS (m/z): 363 (M+); 253, 109.

3-(4-Chlorophenyl)-1-phenyl-3-phenylsulfenylpropan-1-one (3c). White solid; mp 64-67 °C; Rf (10% AcOEt/hexane) 0.35; umax (KBr) 1730 cm-1; δH (400 MHz CDCl3) 3.6 (2H, CH, m, J = 7.2 Hz); 7.2-7.5 (12H, arom, m); 7.9 (2H, arom, d, J = 7.5 Hz); δC (100 MHz CDCl3) 44.2; 47.8; 122.3; 122.7; 128.1; 128.3; 128.8; 129.1; 129.3; 132.9; 133.4; 134.2; 136.3; 143.8; 148.2; 196.1; MS (m/z): 353 (M+) 241.91; 109.

3-(4-Methoxyphenyl)-1-phenyl-3-phenylsulfenylpropan-1-one (3d). White solid; mp 126-128 °C; Rf (10% AcOEt/hexane) 0.26; IR (KBr, ν cm$^{-1}$) 1703 cm-1; 1H NMR (400 MHz CDCl3) δ; 3.62 (2H, d, J$_1$= 7.5 Hz, J$_2$= 15.2 Hz, CH$_2$), 3.76 (3H, s, OCH$_3$); 4.2 (2H, NH$_2$, bs); 4.73 (H, CH, t, J = 7.5 Hz, CH$_3$); 7.13-7.5; 137.2; 136.8; 134.8; 134; 123.6; 134.2; 136.3; 143.8; 148.2; 196.1; MS (m/z): 348 (M+) 239,238, 237, 109.

3-(2-Aminophenylsulfenyl)-1,3-diphenylpropan-1-one (3e). White solid; mp 126-128 °C; Rf (10% AcOEt/hexane) 0.20; umax (KBr) 1710; 3410 cm-1 δH (400 MHz CDCl3) 3.5 (H, CH$_2$, d, J = 7.0 Hz, J$_2$ = 17.4 Hz); 3.7 (H, CH$_2$, dd, J$_1$ = 7.3 Hz, J$_2$ = 17.4 Hz); 4.3 (2H, NH$_2$, bs); 4.73 (H, CH, t, J = 7.1 Hz, CH$_3$); 6.53-7.54 (12H, arom, m); 7.9 (2H, arom, d, J = 7.2 Hz); δC (100 MHz CDCl3) 44.1; 47.1; 114.9; 115.3; 115.7; 118.0; 118.2; 127.3; 127.6; 128.1; 128.4; 128.6; 130.6; 131.6; 133.3; 136.8; 137.7; 141.7; 148.7; 149.5; 197.2; MS (m/z): 333 (M+); 207, 126.
(3-(2-Aminophenylsulfenyl)-3-(4-nitrophenyl)-1-phenylpropan-1-one (3f). White solid; mp 78-81 °C; RF (10% AcOEt/hexane) 0.33; umax (KBr) 1700; 3470, 1680 cm⁻¹; 6H (400 MHz CDCl₃) 3.4 (H, CH₂, dd, J₁ = 7.1 Hz, J₂ = 17.5 Hz); 3.6 (H, CH₂, dd, J₁ = 7.2 Hz, J₂ = 17.5 Hz); 4.2 (2H, NH₂, bs); 4.9 (1H, CH, q, J = 7.1 Hz); 7.3 – 8.2 (11H, m); 129.97, 128.10, 127.49, 127.19, 125.32, 123.01, 118.07, 114.88, 114.09, 113.77, 55.30, 46.32, 44.32; MS (m/z): 363 (M⁺), 239, 238, 237, 125.

(3-Oxo-1,3-diphenylsulfanyl)-1-phenylpropan-1-one (3g). White solid; mp 108-111 °C; RF (10% AcOEt/hexane) 0.24; IR (KBr, v cm⁻¹): 3420, 1730 cm⁻¹; 1H NMR (400 MHz CDCl₃) δ : 3.52 (2H, dd, J₁ = 7.5 Hz, J₂ = 15.2 Hz); J₃ = 17.3 Hz, CH₂); 3.76 (2H, CH₃, q, J = 14.9 Hz); 4.2 (2H, CH₂, s, NO₂); 4.8 (H, dd, J₁ = 6.2 Hz, J₂ = 8.1 Hz, CH); 6.48-7.76 (11H, m, arom); 7.95 (2H, d, J = 7.4 Hz, arom); 13C NMR (100 MHz CDCl₃) δ : 19736, 158.74, 149.5, 137.69, 136.33, 135.10, 133.25, 131.13, 130.62, 129.71, 129.72, 128.10, 127.49, 127.19, 125.32, 123.01, 118.07, 114.88, 114.09, 113.77, 55.30, 46.32, 44.32; MS (m/z): 363 (M⁺), 239, 238, 237, 125.

1-(4-Nitro-phenyl)-3-oxo-3-phenylpropylsulfanyl-ethyl acetate (3j). IR (KBr, v cm⁻¹): 1690; 1740. RMN ¹H (CDCl₃, δ en ppm) : 1.2 (3H, CH₃, q, J = 7.0 Hz); 3.0 (2H, CH₂, t, J = 14.9 Hz); 3.55 (2H, CH₂, d, J = 10.7 Hz); 4.8 (H, CH, t, J = 6.7 Hz); 7.3 – 8.1 (8H, arom, m); 8.1 (1H, arom, d, J = 7.7 Hz); 8.3 (1H, arom, s). RMN ¹³C (CDCl₃, δ en ppm) : 13.6; 33.5; 37.7; 47.6; 118.0; 118.2; 128.0; 128.5; 128.7; 129.0; 130.8; 131.6; 132.9; 133.4; 133.6; 136.8; 137.6; 140.3; 149.4; 196.9.

1-(4-Chloro-phenyl)-3-oxo-3-phenylpropylsulfanyl-ethyl acetate (3k). Liquid, IR (KBr, v cm⁻¹): 1680; 1730. RMN ¹H (CDCl₃, δ en ppm) : 1.2 (3H, CH₃, q, J = 7.2 Hz); 2.9 (2H, CH₂, q, J = 14.9 Hz); 3.55 (2H, CH₂, d, J = 7.5 Hz); 4.05 (2H, CH₂, q, J = 10.7 Hz); 4.72 (H, CH, t, J = 7.5 Hz); 7.3 – 8.3 (9H, arom, m). RMN ¹³C (CDCl₃, δ en ppm) : 14.1; 22.6; 29.3; 29.6; 33.0; 43.8; 44.4; 61.5; 122.5; 122.9; 128.0; 128.7; 129.4; 133.6; 134.6; 136.2; 143.5; 148.4; 169.7; 176.2; 195.75.

1-(4-Methoxy-phenyl)-3-oxo-3-phenylpropylsulfanyl-ethyl acetate (3l). IR (KBr, v cm⁻¹): 1695; 1740. RMN ¹H (CDCl₃, δ en ppm) : 1.3 (3H, CH₃, q, J = 7.1 Hz); 3 (2H, CH₂, q, J = 14.9 Hz); 3.6 (2H, CH₂, d, J = 7.4 Hz); 4.25 (2H, CH₂, q, J = 10.7 Hz); 4.8 (H, CH, t, J = 7.3 Hz); 7.3 – 8.05 (9H, arom, m). RMN ¹³C (CDCl₃, δ en ppm) : 13.66; 41.08; 47.78; 55.36; 61.01; 113.93; 114.05; 114.46; 128.14; 128.45; 128.57; 129.02; 130.03; 132.27; 132.81; 133.43; 140.03; 143.30; 159.01; 172.90; 195.75.

3. Results and Discussion

Chalcone and Thiophenol catalyzed by the potassium pyrophosphate K₂Ca₃P₅O₁₀ (0.1g), were chosen as model substrates to determine suitable reaction conditions for thia-Michael addition.

Therefore, we carried out the reaction in various quantities of methanol. The yields obtained of product 3a are 81%; 92%; 93%; 87%; and 73% with 0.75; 1.5; 3; 5; and 10 ml of methanol, respectively.

This result confirms the crucial role played by the solvent used to carry out the reaction. It would appear that best solvent for this reaction is the methanol and ethanol. The same result has been observed with natural phosphate [30].

To determine the scope and limitation of Michael addition, the optimum conditions were applied to other substrates as shown in Table 1.

| Table 1. | Synthesis of products 3 catalyzed by K₂Ca₃P₅O₁₀ |
| Products | R₂ | R-SH | Yield (%/min) |
| 3a | Ph | PhSH | 92 (25) |
| 3b | p-NO₂-Ph | PhSH | 96 (15) |
| 3c | p-CI-Ph | PhSH | 94 (20) |
| 3d | p-OMe-Ph | PhSH | 92 (120) |
| 3e | Ph | 2-NO₂-Ph | 94 (05) |
| 3f | p-NO₂-Ph | 2-NO₂-Ph | 95 (98) |
| 3g | p-CI-Ph | 2-NO₂-Ph | 94 (05) |
| 3h | p-OMe-Ph | 2-NO₂-Ph | 92 (06) |
| 3i | Ph | EtO₂CH₂SH | 68 (75) |
| 3j | p-NO₂-Ph | EtO₂CH₂SH | 92 (75) |
| 3k | p-CI-Ph | EtO₂CH₂SH | 76 (75) |
| 3l | p-OMe-Ph | EtO₂CH₂SH | 52 (90) |

For this study, we carried out the Michael addition of chalcones as acceptors with various mercaptans such as...
thiophenol, 2-aminothiophenol and ethyl thioglycolate catalysed by K$_2$CaP$_2$O$_7$ (0.1g) in the presence of methanol (1.5 ml) at room temperature.

The products of undesirable side reactions resulting from 1,2 addition, polymerization and bis-addition are not observed.

The use of synthetic diphosphate K$_2$CaP$_2$O$_7$ as heterogeneous catalyst for Michael reaction has allowed the isolation of products 3 rapidly and with good yields except for products 3i, 3k and 3l.

The results observed with different Michael acceptors shown that the presence of an electron-donors group (-OMe) decreases their activity whereas the electron-acceptors group (-NO$_2$, -Cl) increases the activity of the Michael acceptors.

In order to test their possible synthetic application, ketone 3a was converted to oxime 4a catalyzed by the Potassium pyrophosphate K$_2$CaP$_2$O$_7$ (Figure 3).

The oxime was subjected to the reaction by thionyl chloride and the chemoselective Bekmann rearrangement gave the anilide of 3a. Its alcoholysis furnished the corresponding ethyl ester 6a, while compound 6a is a direct precursor of β-thio acid 7a.

We next investigated the sability of the catalyst in order to recycle it. The used and recovered K$_2$CaP$_2$O$_7$ has been shown to be reusable after drying at 150 °C in vacuum, and more efficiently after washing with acetone followed by calcinations at 600 °C. In the last case, the catalyst can be recovered and reused at least five times without appreciable loss of activity.

4. Conclusion

In summary, we believe that K$_2$CaP$_2$O$_7$ is a new heterogeneous catalytic for effecting carbon-sulphur bond formation and represent an important breakthrough in the development of solid catalysts. The high reactivity and specificity of our catalyst coupled with their ease of use and reduced environmental problems makes them attractive alternatives to homogeneous basic reagents.

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References


