Synthesis of 4H-chromene Derivatives via Hantzsch Reaction Catalyzed by KH₂PO₄

Hu Xiaoyun¹ Wang Xueru¹ Shan Zixing²

¹ College of Chemistry and Materials, South-Central University for Nationalities, Wuhan 430074, China
² College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, China

Abstract 4H-chromene derivatives could be efficiently synthesized via Hantzsch reaction catalyzed by potassium dihydrogen phosphate, which is an inexpensive acidic inorganic salt. Under the optimized conditions, 4H-chromene derivatives could be directly separated in high yields via simple filtration. The filtrate containing potassium dihydrogen phosphate could be directly reused to catalyze this reaction for three times without appreciable loss of catalytic activity. It provided a practical and environmentally friendly method for the synthesis of 4H-chromene derivatives and had a good potential in industrial application.

Keywords Hantzsch reaction; 4H-chromene derivatives; potassium dihydrogen phosphate

4H-chromene derivatives have versatile biological and pharmacological properties such as anticoagulant, anticancer, antibacterial and anti-allergic activities, which have attracted considerable interest for chemists in the past decades. 4H-chromene derivatives are generally synthesized via three-component Hantzsch reaction of aromatic aldehydes, dimetone and malononitrile in presence of catalyst. Acidic catalysts such as silica-supported phosphomolybdic acid and KF-alumina were reported to catalyze Hantzsch reaction. Additionally, ionic liquid, ultrasonic and microwave irradiation were reported to promote Hantzsch reaction for synthesizing 4H-chromene derivatives. Recently silica nanoparticles and lipase were also reported as catalyst to synthesize 4H-chromene derivatives. Although many synthetic methodologies were reported and some of them have obtained excellent results, the limitations such as high cost, tedious work-up procedure, high reaction temperature and the requirement of special apparatus still existed. Therefore, a practical and environmentally friendly method for the synthesis of 4H-chromene derivatives continued to draw the attention of researchers.
KH₂PO₄ is an available inorganic salt, which is soluble in water and insoluble in ethanol. It is usually used as a buffer neutralizing agent in yeast food and also emerged as an effective heterogeneous acid catalyst used as a buffer.

2-amino-4-(4-chlorophenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4c) m. p. 208 ~ 210°C, 1H NMR (300 MHz, d₆-DMSO) δ: 7.26 (d [J = 8.1 Hz, 2H]) 7.18 (d [J = 8.1 Hz, 2H]), 4.57 (s 2H), 4.39 (s 1H), 2.4, 45 (s 2H), 2.21 ~ 2.23 (d [J = 4.2 Hz, 2H]), 1.11 (s 3H), 1.03 (s 3H).

2-amino-4-(2-hydroxyphenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4d) m. p. 263 ~ 239°C, 1H NMR (300 MHz, d₆-DMSO) δ: 7.45 (d [J = 8.1 Hz, 1H]) 7.35 (d [J = 8.1 Hz, 1H]) 7.27 ~ 7.22 (m 1H), 5.21 (s 2H), 4.36 (s 2H), 2.40 (s 2H), 2.28 ~ 2.04 (m 2H), 1.10 (s 3H), 0.98 (s 3H).

1 Experimental

1.1 Reagent and instrument

Potassium dihydrogen phosphate 5[B-dimethyl-1[B-cyclohexanone and various aldehydes were purchased from Aldrich Chemical Company and used directly.

NMR spectra were recorded at 300 MHz for 1H-NMR on a Varian Mercury VS 300; Mp were recorded at VEB Wägetechnik Rapido PHMK 05.

1.2 General procedure for the synthesis of 4H-chromene derivatives

In a test tube fitted with a magnetic bar, 5[B-dimethyl-1[B-cyclohexanone (1.1 mmol) aldehyde (1 mmol) malononitrile (1.1 mmol) and potassium dihydrogen phosphate (0.15 mmol) were added and followed by injection of about 5 ml 50% ethanol (volume ratio the same below) to obtain a transparent solution. The mixture was stirred at room temperature and monitored by TLC. The precipitate was filtrated directly and washed with 50% ethanol to give the expected product which usually was pure enough for NMR analysis. The crude product could be further recrystallized with ethanol if necessary. All the products are known compounds and characterization data are given below.

2-amino-4-phenyl-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4a) m. p. 227 ~ 230°C, 1H NMR (300 MHz, d₆-DMSO) δ: 7.22 ~ 7.59 (m 3H), 4.57 (s 2H), 4.40 (s 1H), 2.45 (s 2H), 2.23 (s 2H), 1.11 (s 3H), 1.04 (s 3H).

2-amino-4-(2-chlorophenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4b) m. p. 129 ~ 132°C, 1H NMR (300 MHz, d₆-DMSO) δ: 7.35 (d [J = 7.5 Hz, 1H]), 7.27 (d [J = 6.6 Hz, 1H]), 7.15 ~ 7.23 (m 2H), 7.00 (s 2H), 4.70 (s 1H), 2.51 (d [J = 5.1 Hz, 2H]), 2.04 ~ 2.26 (m 2H), 1.03 (s 3H), 0.97 (s 3H).

2-amino-4-(4-chlorophenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4c) m. p. 208 ~ 210°C, 1H NMR (300 MHz, d₆-DMSO) δ: 7.26 (d [J = 8.1 Hz, 2H]), 7.18 (d [J = 8.1 Hz, 2H]), 4.57 (s 2H), 4.39 (s 1H), 2.45 (s 2H), 2.21 ~ 2.23 (d [J = 4.2 Hz, 2H]), 1.11 (s 3H), 1.03 (s 3H).

2-amino-4-(2-hydroxyphenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4d) m. p. 236 ~ 239°C, 1H NMR (300 MHz, d₆-DMSO) δ: 7.45 (d [J = 8.1 Hz, 1H]), 7.35 (d [J = 8.1 Hz, 1H]), 7.27 ~ 7.22 (m 1H), 5.21 (s 2H), 4.36 (s 2H), 2.40 (s 2H), 2.28 ~ 2.04 (m 2H), 1.10 (s 3H), 0.98 (s 3H).

2-amino-4-(2-hydroxyphenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4e) m. p. 223 ~ 235°C, 1H NMR (300 MHz, d₆-DMSO) δ: 7.81 (d [J = 7.5 Hz, 1H]), 7.67 ~ 7.63 (m 1H), 7.44 ~ 7.33 (m 2H), 7.18 (s 1H), 4.93 (s 1H), 2.56 ~ 2.41 (m 2H), 2.22 ~ 1.98 (m 2H), 1.01 (s 3H), 0.98 (s 3H).

2-amino-4-(3-nitrophenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4f) m. p. 213 ~ 215°C, 1H NMR (300 MHz, d₆-DMSO) δ: 18.03 (d [J = 8.2 Hz, 1H]), 7.93 (s 1H), 7.60 ~ 7.57 (m 2H), 7.13 (s 2H), 4.37 (s 1H), 2.56 ~ 2.42 (2H), 2.25 ~ 2.04 (m 2H), 1.00 (s 3H), 0.91 (s 3H).

2-amino-4-(4-nitrophenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4g) m. p. 177 ~ 179°C, 1H NMR (300 MHz, d₆-DMSO) δ: 8.18 (d [J = 8.1 Hz, 2H]), 7.47 (d [J = 8.1 Hz, 2H]), 7.17 (s 2H), 4.40 (s 1H), 2.55 (s 2H), 2.10 ~ 2.30 (m 2H), 1.05 (s 3H), 0.97 (s 3H).

2-amino-4-(4-bromophenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4h) m. p. 203 ~ 204°C, 1H NMR (300 MHz, CDCl₃) δ: 8.42 (d [J = 8.1 Hz, 2H]), 7.12 (d [J = 8.1 Hz, 2H]), 4.60 (s 2H), 4.37 (s 1H), 2.45 (s 2H), 2.22 (d 2H), 1.22 (s 3H), 1.03 (s 3H).

2-amino-4-(4-methoxyphenyl)-7-7-dimethyl-5-oxo-5-6-[8-tetrahydro-4H-chromene-3-carbonitrile (4i)
Results and discussion

Considering high efficiency of solvent-free reaction, the reaction of benzaldehyde, 5\(\text{-dimethyl-1-3-cyclohexanedione}\) and malononitrile was firstly carried out under solvent-free condition. The mixture of reactants and 30\% KH\(_2\)PO\(_4\) (molar ratio\(\) the same below) was ground until it became solid (about 15 ~ 30 min). Saturated Na\(_2\)SO\(_3\) solution was added and stirred for 30 min until it became solid. Then, the solution was heated under reflux condition. It became turbid after 5 min and the reaction was completely finished for 30 min which was monitored by TLC. The expected product was directly separated out just by a simple filtering operation. The crude product was washed with 50\% ethanol\(\) and it was pure enough for NMR analysis. Influence of catalyst loading on the reaction was also examined\(\) which was 0.15 equiv. of potassium dihydrogen phosphate was enough to give high-yielding 4\(H\)-chromene derivative at room temperature.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>catalyst loading (%)</th>
<th>reaction time (\text{min})</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>water</td>
<td>30</td>
<td>180</td>
<td>42(^a)</td>
</tr>
<tr>
<td>2</td>
<td>dichloromethane</td>
<td>30</td>
<td>180</td>
<td>29(^a)</td>
</tr>
<tr>
<td>3</td>
<td>ethanol</td>
<td>30</td>
<td>180</td>
<td>47(^b)</td>
</tr>
<tr>
<td>4</td>
<td>50% ethanol</td>
<td>30</td>
<td>30</td>
<td>81(^b)</td>
</tr>
<tr>
<td>5</td>
<td>50% ethanol</td>
<td>15</td>
<td>30</td>
<td>79(^b)</td>
</tr>
<tr>
<td>6</td>
<td>50% ethanol</td>
<td>10</td>
<td>30</td>
<td>62(^b)</td>
</tr>
<tr>
<td>7</td>
<td>50% ethanol</td>
<td>5</td>
<td>30</td>
<td>49(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield after refluxing for 3 h and recrystallized with ethanol;\(^b\) Isolated yield after filtered and washed with 50\% ethanol.

It should be pointed out that catalytic effect would decrease (even under long reaction time or heating) if the catalyst loading was reduced. And potassium dihydrogen phosphate remained in the 50\% ethanol filtrate could be directly reused to catalyze the Hantzsch reaction for three times without significant loss of catalytic activity (Fig. 2). In 50\% ethanol filtrate there are potassium dihydrogen phosphate and a small amount of the reactants in the solution while the 4\(H\)-chromene derivative product was almost separated out quantitatively from the solution. So the 50\% ethanol filtrate could be directly recycled to catalyze three-component reaction and give high yields.

Then Hantzsch reaction of various aromatic

\[\text{Fig. 1 the Hantzsch reaction under solvent-free condition}\]

The yield of solvent-free reaction was not so satisfactory, it may be related to low grinding efficiency. So we tried to examine the Hantzsch reaction catalyzed by KH\(_2\)PO\(_4\) in the liquid phase. The reaction of benzaldehyde, 5\(\text{-dimethyl-1-3-cyclohexanedione}\) and malononitrile was set as a template to optimize reaction conditions.

Water dichloromethane and ethanol were first chosen as reaction medium. Benzaldehyde, 5\(\text{-dimethyl-1-3-cyclohexanedione}\) malononitrile and 30\% KH\(_2\)PO\(_4\) were refluxed for 3 h in the selected solvents. From Tab. 1 we could see that water dichloromethane and ethanol were not the suitable reaction medium in which reactants or catalyst were not well dissolved. So 50\% ethanol was chosen as reaction medium. The reactants and 30\% KH\(_2\)PO\(_4\) were added to 50\% ethanol to give a transparent solution then the reaction mixture was stirred at room temperature. It became turbid after 5 min and the reaction was completely finished for 30 min which was monitored by TLC. The expected product was directly separated out just by a simple filtering operation. The crude product was washed with 50\% ethanol\(\) and it was pure enough for NMR analysis. Influence of catalyst loading on the reaction was also examined\(\) which was 0.15 equiv. of potassium dihydrogen phosphate was enough to give high-yielding 4\(H\)-chromene derivative at room temperature.

\[\text{Tab. 1 Screening reaction conditions on the Hantzsch reaction}\]

\[\text{Fig. 1 the Hantzsch reaction under solvent-free condition}\]

\[\text{Table 1 Hantzsch and 4H-}\]

m. p. 199 ~ 201°C \(\text{H NMR (300 MHz, d6-DMSO)}\) \(\delta : 7.03 ~ 7.06 (d, J = 9.0 \text{Hz}, 2H)\), 6.93 \(s\), 6.81 ~ 6.84 \(d, J = 9.0 \text{Hz}\), 6.39 \(s\), 5.95 \(2.48 \text{ (m, 2H) \delta : 2.04 ~ 2.25 \text{ (m, 2H) \delta : 1.01 \text{ (s, 3H)} \delta : 0.93 \text{ (s, 3H)}}\).

2-amino-4-(4-dimethylaminophenyl)-7\(\text{-dimethyl-5-oxo-5H-chromene-3-carbonitrile} with the yield of 75.0\%.

\[\text{Fig. 1 the Hantzsch reaction under solvent-free condition}\]

The yield of solvent-free reaction was not so satisfactory it may be related to low grinding efficiency. So we tried to examine the Hantzsch reaction catalyzed by KH\(_2\)PO\(_4\) in the liquid phase. The reaction of benzaldehyde, 5\(\text{-dimethyl-1-3-cyclohexanedione}\) and malononitrile was set as a template to optimize reaction conditions.

Water dichloromethane and ethanol were first chosen as reaction medium. Benzaldehyde, 5\(\text{-dimethyl-1-3-cyclohexanedione}\) malononitrile and 30\% KH\(_2\)PO\(_4\) were refluxed for 3 h in the selected solvents. From Tab. 1 we could see that water dichloromethane and ethanol were not the suitable reaction medium in which reactants or catalyst were not well dissolved. So 50\% ethanol was chosen as reaction medium. The reactants and 30\% KH\(_2\)PO\(_4\) were added to 50\% ethanol to give a transparent solution then the reaction mixture was stirred at room temperature. It became turbid after 5 min and the reaction was completely finished for 30 min which was monitored by TLC. The expected product was directly separated out just by a simple filtering operation. The crude product was washed with 50\% ethanol\(\) and it was pure enough for NMR analysis. Influence of catalyst loading on the reaction was also examined\(\) which was 0.15 equiv. of potassium dihydrogen phosphate was enough to give high-yielding 4\(H\)-chromene derivative at room temperature.

\[\text{Tab. 1 Screening reaction conditions on the Hantzsch reaction}\]

\[\text{Table 1 Hantzsch and 4H-}\]

m. p. 199 ~ 201°C \(\text{H NMR (300 MHz, d6-DMSO)}\) \(\delta : 7.03 ~ 7.06 (d, J = 9.0 \text{Hz}, 2H)\), 6.93 \(s\), 6.81 ~ 6.84 \(d, J = 9.0 \text{Hz}\), 6.39 \(s\), 5.95 \(2.48 \text{ (m, 2H) \δ : 2.04 ~ 2.25 \text{ (m, 2H) \δ : 1.01 \text{ (s, 3H)} \δ : 0.93 \text{ (s, 3H)}}\).

2-amino-4-(4-dimethylaminophenyl)-7\(\text{-dimethyl-5-oxo-5H-chromene-3-carbonitrile} with the yield of 75.0\%.

\[\text{Fig. 1 the Hantzsch reaction under solvent-free condition}\]

The yield of solvent-free reaction was not so satisfactory it may be related to low grinding efficiency. So we tried to examine the Hantzsch reaction catalyzed by KH\(_2\)PO\(_4\) in the liquid phase. The reaction of benzaldehyde, 5\(\text{-dimethyl-1-3-cyclohexanedione}\) and malononitrile was set as a template to optimize reaction conditions.

Water dichloromethane and ethanol were first chosen as reaction medium. Benzaldehyde, 5\(\text{-dimethyl-1-3-cyclohexanedione}\) malononitrile and 30\% KH\(_2\)PO\(_4\) were refluxed for 3 h in the selected solvents. From Tab. 1 we could see that water dichloromethane and ethanol were not the suitable reaction medium in which reactants or catalyst were not well dissolved. So 50\% ethanol was chosen as reaction medium. The reactants and 30\% KH\(_2\)PO\(_4\) were added to 50\% ethanol to give a transparent solution then the reaction mixture was stirred at room temperature. It became turbid after 5 min and the reaction was completely finished for 30 min which was monitored by TLC. The expected product was directly separated out just by a simple filtering operation. The crude product was washed with 50\% ethanol\(\) and it was pure enough for NMR analysis. Influence of catalyst loading on the reaction was also examined\(\) which was 0.15 equiv. of potassium dihydrogen phosphate was enough to give high-yielding 4\(H\)-chromene derivative at room temperature.

\[\text{Tab. 1 Screening reaction conditions on the Hantzsch reaction}\]

\[\text{Table 1 Hantzsch and 4H-}\]
aldehydes catalyzed by 15% KH$_2$PO$_4$ in 50% ethanol were evaluated at room temperature. The results are listed in Tab. 2. From Tab. 2 it can be seen that in the presence of potassium dihydrogen phosphate all the reactions could finish high yields regardless of the steric (entries 4 and 10) or electronic effect (entries 7 and 9).

Fig. 2 The cyclic catalysis Hantzsch reaction by KH$_2$PO$_4$

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>R of aldehyde</th>
<th>t/min</th>
<th>product</th>
<th>Yield/% $^*$</th>
<th>m. p. /℃</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>30</td>
<td>4a</td>
<td>76</td>
<td>227–230</td>
</tr>
<tr>
<td>2</td>
<td>2-ClC$_6$H$_4$</td>
<td>30</td>
<td>4b</td>
<td>78</td>
<td>129–132</td>
</tr>
<tr>
<td>3</td>
<td>4-ClC$_6$H$_4$</td>
<td>30</td>
<td>4c</td>
<td>77</td>
<td>208–210</td>
</tr>
<tr>
<td>4</td>
<td>2,4-Cl$_2$C$_6$H$_4$</td>
<td>30</td>
<td>4d</td>
<td>72</td>
<td>236–239</td>
</tr>
<tr>
<td>5</td>
<td>2-N$_2$O$_2$C$_6$H$_4$</td>
<td>30</td>
<td>4e</td>
<td>75</td>
<td>233–235</td>
</tr>
<tr>
<td>6</td>
<td>3-N$_2$O$_2$C$_6$H$_4$</td>
<td>30</td>
<td>4f</td>
<td>76</td>
<td>213–215</td>
</tr>
<tr>
<td>7</td>
<td>4-N$_2$O$_2$C$_6$H$_4$</td>
<td>30</td>
<td>4g</td>
<td>77</td>
<td>177–179</td>
</tr>
<tr>
<td>8</td>
<td>4-BrC$_6$H$_4$</td>
<td>30</td>
<td>4h</td>
<td>79</td>
<td>203–204</td>
</tr>
<tr>
<td>9</td>
<td>4-CH$_3$OC$_6$H$_4$</td>
<td>30</td>
<td>4i</td>
<td>78</td>
<td>199–201</td>
</tr>
<tr>
<td>10</td>
<td>4-(CH$_3$)$_2$NC$_6$H$_4$</td>
<td>30</td>
<td>4j</td>
<td>74</td>
<td>207–210</td>
</tr>
</tbody>
</table>

* isolated yield after filtrated and washed with 50% ethanol

In summary we have developed a practical and environmentally friendly method for the synthesis of 4H-chromene derivatives which has a good potential in industrial application. KH$_2$PO$_4$ an available and inexpensive inorganic salt could efficiently catalyze three-component Hantzsch reaction in 50% ethanol to offer 4H-chromene derivatives in high yield and the product could be directly isolated from reaction system via a simple filtrating operation. KH$_2$PO$_4$ remained in the 50% ethanol filtrate could be recycled to catalyze Hantzsch reaction without significant loss of catalytic activity.

References


Table 2 KH$_2$PO$_4$-catalyzed synthesis of 4H-chromene derivatives

In summary we have developed a practical and environmentally friendly method for the synthesis of 4H-chromene derivatives which has a good potential in industrial application. KH$_2$PO$_4$ an available and inexpensive inorganic salt could efficiently catalyze three-component Hantzsch reaction in 50% ethanol to offer 4H-chromene derivatives in high yield and the product could be directly isolated from reaction system via a simple filtrating operation. KH$_2$PO$_4$ remained in the 50% ethanol filtrate could be recycled to catalyze Hantzsch reaction without significant loss of catalytic activity.