TiO₂/nanoclinoptilolite, a recyclable and high efficient heterogeneous nanocatalyst, for the synthesis of 2-amino-4H-chromene derivatives

Farzad Javadi, Reza Tayebee*

Department of Chemistry, School of Sciences, Hakim Sabzevari University, Sabzevar, 96179-76487, Iran.

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ABSTRACT

The synthesis of pharmaceutically and biologically active 2-amino-4H-chromenes was described using TiO₂/nanoclinoptilolite (TiO₂/NCP) as an efficient nanocatalyst under solvent-free condition. The TiO₂/NCP was fabricated through modification of NCP with HDTMA, then the surface modified NCP was impregnated with titanium tetrachloride solution. Finally, the material incorporated with titanium was calcinated at 500 ºC and was characterized by FT-IR, ICP-OES, SEM, and XRD. The experimental conditions have been completely optimized and established, providing an increase in the rate and high yields. This procedure provides several merits such as a simple workup, economical, environmentally benign, short reaction time and excellent yields. Moreover, the prepared nanocomposite showed very high stability and reusability in the synthetic method under solvent-free and mild conditions.

Keywords: TiO₂/nanoclinoptilolite, 4H-chromene, Nanocomposite, Nanocatalyst, Solvent-free.

1. Introduction

Considering the growing concern about environmental pollution troubles, the development of eco-friendly catalysts and solvents for chemical synthesis and finding neutral conditions have gained much attention. From both economic and environmental aspects, the use of heterogeneous catalysis and green solvents in chemical industries is very promising [1,2]. Multicomponent reactions (MCRs), in which multiple reactions are combined into a single synthetic operation, have attracted much attention in both combinatorial and medicinal chemistry research due to the creation of several new bonds in a one-pot reaction, synthetic convergence, low number of reaction and purification steps, variable and high bond forming efficiency, selectivity, and simplicity [3-5]. Therefore, industrial and academic research has focused on the use of MCRs to synthesize a broad range of products [6-8].

Recently, the synthesis of 4H-chromene derivatives has been of considerable interest due to their useful pharmacological and biological properties such as antitumor, antifungal, anticoagulant, anticancer, antibacterial, diuretic and antianaphylactin compounds [3,4,9-11]. These compounds are important heterocyclic compounds that are found in many natural products. Moreover, they can be applied as cognitive enhancers for the treatment of neurodegenerative diseases including Huntington’s disease, Alzheimer’s disease, amytrophic lateral sclerosis and Parkinson’s disease, and also for the treatment of myoclonus and schizophrenia [12,13]. Furthermore, 4H-chromenes have played key roles in synthetic approaches to fabrication of promising compounds in the area of medicinal chemistry [14].

A well-known method for the synthesis of 4H-chromene derivatives employs a three-component (aryl aldehydes, cyclic 1,3-diketones, and malononitrile) reaction under different reaction conditions [15,16]. A number of strategies have been reported for the synthesis of these substances including the use of ultrasonic irradiations [17] and microwave irradiations [5]. In addition, a variety of reagents such as hexadecyldimethyl benzyl ammonium bromide [18], LiBr [19], Na₂CO₃ under grinding [20], diammonium hydrogen phosphate [21], nano-sized MgO [22], Mg/Al hydrotalcite [23], KF/Al₂O₃ [24], sodium selenite [25], heteropolyacids [26], TiCl₄ [27],
tetrabutylammonium bromide [23], cerium (III) chloride [28], ionic liquids [29,30], and ZnO-beta zeolite [11] have been employed as catalysts. However, despite the merits of these protocols, many proposed methods for the synthesis of these compounds suffer from drawbacks such as low product yield, high reaction time, effluent pollution, use of toxic solvents, expensive and non-reusable catalysts, harsh reaction conditions, and tedious work-up. Therefore, it is necessary to overcome these limitations to develop efficient, eco-friendly and green synthetic protocols for 4H-chromenes.

Clinoptilolite, which belongs to the class of aluminosilicates, is one of the most plentiful and beneficial natural zeolites [31]. It has a monoclinic structure with ten-membered and two eight-membered rings including water molecules and replaceable metal cations in the internal crystalline cages. Clinoptilolite has extensive surface area and numerous active sites which enabled this material to be used as a molecular sieve, nourishment, food additive, smell and gas adsorbent and as catalyst in a variety of organic transformations [32-34].

In continuation of our interest in developing the one-pot synthesis of various biologically important compounds [8,35] and considering the importance of substituted 2-amino-4H-chromenes, TiO$_2$/NCP nano-composite was performed as a highly efficient heterogeneous, low-cost and reusable nano-catalyst for the preparation of these derivatives under solvent-free conditions at 70°C (Scheme 1).

2. Experimental

2.1. Materials and methods

All reagents and starting materials were supplied from commercial resources and used without further purification. Melting points were recorded on a Bamstead electrothermal type 9200 melting point apparatus. SEM pictures were taken by XL-30 Phillips (1992). The crystalline structures of the samples were assessed by XRD analysis on a PW1800-PHILIPS diffractometer with Cu Kα radiation ($\lambda$= 1.5418 Å) at 40 keV and 40 mA. FT-IR spectra were recorded on a 8700 Shimadzu spectrophotometer in the area of 400 to 4000 cm$^{-1}$ utilizing KBr pellets. $^1$H- and $^{13}$CNMR spectra were recorded on a Bruker AVANCE 400 and 100 MHz spectrometer, respectively. A freeze dryer (Model FD-10, Pishhaz Equipment Engineering Co, Iran) was used for drying the sample. The chemical composition of the examined materials was determined using an inductively coupling plasma spectrometer (ICP-MS) model Vista-pro. All products were recognized by comparison of their spectral and physical data with those previously reported.

2.2. Preparation of TiO$_2$/NCP by the mediation of HDTMA as surfactant

TiO$_2$/NCP was prepared through the in-situ preparation of TiO$_2$ nanoparticles immobilized on the surface of the NCP. Accordingly, TiCl$_4$ (0.5 M) solution prepared in 30 ml deionized water was stirred for 30 min. NaOH (2 M) was added dropwise to the solution to reach pH= 12. Simultaneously, one gram of NCP was homogeneously dispersed in 10 ml of HDTMA (0.1 M) solution and stirred at 75°C for 24 h to obtain HDTMA/NCP. Then, the prepared aqueous mixture of TiCl$_4$ and NaOH solution was added dropwise to the suspension of HDTMA/NCP with continuous stirring at 75°C and the obtained mixture could react for 24 h. Then, the resulting precipitate was separated by filtration, washed several times with deionized water, and dried at 50 ºC for 3 days in an oven. In the next step, the obtained solid product was calcined at 500°C in a furnace for 20 h to achieve TiO$_2$/NCP nano-composite. Also, the amount of TiO$_2$ in the prepared TiO$_2$/NCP was 32% that was analyzed by ICP-OES [31].

2.3. General procedure for the synthesis of 2-amino-4H-chromene derivatives

One mmol of appropriate benzaldehyde, 1 mmol of malononitrile and 1 mmol dimerdone were mixed. Then, 0.01 g of TiO$_2$/NCP was added and the mixture was heated to 70°C with good stirring for the required time. After completion of the reaction monitored by TLC, the reaction was stopped and the favorable product was achieved by the addition of 5 ml of hot ethanol. Then the catalyst was separated by simple filtration. Soon after, the reaction mixture was poured into 50 ml of ice water and the precipitate was filtered off, washed with cold water, and dried.

![Scheme 1](image-url)

Scheme 1. General formulation for the synthesis of substituted 2-amino-4H-chromenes.
3. Results and Discussion

3.1. FT-IR analysis

The FT-IR spectra of NCP, TiO$_2$/NCP nanocomposite and TiO$_2$ nanoparticles are depicted in Fig. 1. In the FT-IR spectrum of NCP, four bands included (i) the bands attributed to the zeolitic water in the region of 1600–3700 cm$^{-1}$, (ii) the bands due to the internal Si–O (Si) and Si–O (Al) vibration modes in the range of 400–1200 cm$^{-1}$, (iii) the bands related to the pseudo-lattice vibrations of structural units situated in the scope of 500–700 cm$^{-1}$, and (iv) the bands associated with lattice vibrations appeared below 400 cm$^{-1}$ [36,37]. In the FT-IR of NCP a broad band, about 1070 cm$^{-1}$ due to the asymmetric stretching vibrations of –Si–O–Si– was overlapped with the stretching vibrations of Al–O and Al–O–Si bonds [8]. The bands located at 1629 and 3614 cm$^{-1}$ were assigned to the OH stretching vibrations of water molecules in the NCP framework.

3.2. XRD investigation

The NCP and prepared TiO$_2$/NCP nanocomposites were characterized by X-ray diffraction as demonstrated in Fig. 2. The original clinoptilolite showed a pattern similar to the crystalline structure, which has been introduced in the X-ray data file (JCPDS no. 39-1383) [38]. This pattern showed a strong and main diffraction peak situated at 2θ value of 22.5, related to the d$_{004}$ reflection and the crystalline framework of NCP was identified [8]. Comparing the XRD pattern of TiO$_2$/NCP with that reported for TiO$_2$ demonstrated that new diffraction peaks appeared at 22º and 48º were associated with TiO$_2$ nanoparticles in the anatase phase (JCPDS no.: 84-1286) and the diffraction peaks at 45º, 58º and 67º were bound up with TiO$_2$ nanoparticles in the rutile phase (JCPDS no.: 88-1175) [38,39]. It is proved that, when the metal oxides are located in the channel or pores of zeolite, the related diffraction peaks almost disappear because of the shielding effects of the surrounding framework [40,41]. Comparison of the XRD patterns of NCP and TiO$_2$/NCP showed absence of any structural destruction in the nanoclinoptilolite during ion exchange and calcination processes. The particle size of the TiO$_2$/NCP was measured by the X-ray line broadening method using the Scherrer equation [42]. The crystallite size of the particles was calculated to be 46 nm.

3.3. SEM investigation

The morphology of the NCP and TiO$_2$/NCP were studied by scanning electron microscope as demonstrated in Fig. 3. SEM images of NCP (Fig. 3a) and TiO$_2$/NCP (Fig. 3b) samples showed that titanium dioxide nanoparticles were successfully immobilized on the surface of NCP. As indicated by the SEM image of the nano-composite, it seems that the pores of NCP were blocked by TiO$_2$ nanoparticles and the porosity of the nano-composite was diminished [44].

Fig. 1. FT-IR spectra of the NCP, TiO$_2$/NCP and nano TiO$_2$. 
Fig. 2. XRD patterns of NCP (a) and TiO$_2$/NCP (b), reproduced from ref. [43].

Fig. 3. SEM images of NCP (a) and TiO$_2$/NCP (b).
3.4. Effect of catalyst amount on the three-component condensation reaction

In this study, a simple and efficient one-step procedure for the synthesis of 4H-chromene derivatives in the presence of a catalytic amount of TiO2/NCP was conducted. To find the optimized conditions, a systematic investigation considering different variables affecting the reaction yield was carried out for the reaction of benzaldehyde, malononitrile and dimecone (molar ratio, 1:1:1) as the model reaction. For this goal, initially, the catalytic efficiency of TiO2/NCP for the preparation of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile was studied and the obtained results are tabulated in Table 1.

According to these results, in the absence of a catalyst, only 25% yield was obtained after 120 min. But, in the presence of nanocatalyst (0.005 g), yield was increased from 25 to 80% in ten minutes. Enhancing the amount of nanocatalyst improved the yield by the increased contact opportunity of nanocatalyst surface with the reactant molecules. Although further increase in the catalyst amount, from 0.03 to 0.05 g, led to a decrease in yield from 95 to 90%. These results would be explained considering the fact that the agglomeration of the nanocatalyst active sites was increased by enhancing the catalyst amount, resulting in a reduction in concentration of the reactant molecules at the active sites and a decrease in yield. Thus, 0.01 g of the nanocatalyst was enough to reach the high conversion.

3.5. Influence of reaction temperature on the three-component condensation reaction

To find the best temperature for condensation reaction, the reaction of benzaldehyde, dimecone, and malononitrile (molar ratio 1:1:1) was studied in the presence of TiO2/NCP (0.01 g) as a nano-catalyst for 15 minutes and the obtained results are demonstrated in Fig 4.

![Fig. 4. Yield (%) as a function of reaction temperature.](image)

The results showed that increasing temperature from 25 to 70°C could increase yield while increasing temperature to 100°C decreased yield from 95 to 90%. Therefore, the temperature of 70°C was chosen as the best temperature for the reaction.

3.6. Investigation catalytic efficiency of the nano-composite ingredients

Table 2 compares the catalytic activity of TiO2/NCP with those of NCP, bulk TiO2, HDTMA, and HDTMA/NCP, separately, in the preparation of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile under the optimum conditions. The obtained results reveal that in the presence of NCP and Bulk TiO2 (0.01 g), yield (%) was enhanced to 74 and 75%, respectively, but it is interesting to note that 0.01 g of prepared TiO2/NCP nanocomposite led to higher yield compared to other ingredients.

3.7. Synthesis of substituted 2-amino-4H-chromenes derivatives catalyzed by TiO2/NCP

To assess the generality and versatility of the present procedure, different substituted 2-amino-4H-chromenes were synthesized via the three-component

Table 2. Studying catalytic activity of the ingredients comprising the nanocomposite in the syntheses of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst (g)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NCP</td>
<td>0.01</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>Bulk TiO2</td>
<td>0.01</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>HDTMA</td>
<td>0.01</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>HDTMA/NCP</td>
<td>0.01</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>Ti/HDTMA/NCP</td>
<td>0.01</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>TiO2/NCP</td>
<td>0.01</td>
<td>95</td>
</tr>
</tbody>
</table>

Reaction condition: Reaction time 15 min, solvent- free.
reaction of an appropriate aldehyde, dinedone and malononitrile in the presence of a catalytic amount of TiO$_2$/NCP (0.01 g) under solvent-free conditions. The overall results have been summarized in Table 3. Results showed that under the optimum conditions, benzaldehydes with electron-donating or withdrawing groups reacted successfully and gave high yields of the product in short reaction times [4,45].

3.8. The reusability of TiO$_2$/NCP nano-catalyst

The recoverability of the heterogeneous catalyst is one of the most important benefits and this makes them useful for industrial applications. Thus, the recovery and reusability of the TiO$_2$/NCP were studied in the reaction of benzaldehyde, dinedone, and malononitrile under the present reaction conditions (Table 1, entry 3). After completion of the reaction, the catalyst was removed by simple filtration and washed with hot ethanol (5 mL) and dried in an oven at 100°C for 2 h. The recycled catalyst was reused successively 5 times without any significant loss of activity for the synthesis of 2- amino- 7,7- dimethyl- 5- oxo- 4- phenyl- 5,6,7,8- tetrahydro-4H-chromene-3-carbonitrile (The yields were 92, 90, 88, 88 and 88 %, respectively).

According to the results, a very slight loss in the reaction yields would be explained by agglomeration of some nanoparticles during reaction which decreased the active surface of the nanocomposite.

3.9. Comparison of the catalytic activity of TiO$_2$/NCP with other catalysts

To show the merit of this work, this procedure was compared to same procedures with other catalysts reported for the syntheses of 2-amino-4H-chromene derivatives. The obtained results in relation to the reaction time, reaction conditions, and yield % of the products are demonstrated in Table 4. Obviously, the present procedure offers several merits such as easy workup, short reaction time, excellent yields, environmentally benign and economic protocol over the reported methods.

3.10. Plausible mechanism for TiO$_2$/NCP catalyzed synthesis of 4H-chromenes

A plausible mechanism for the synthesis of 2-Amino-4H-chromenes is shown in Scheme 2. In the first step, aldehyde was condensed with activated malononitrile to afford the α-cyanocinnamonic derivative.

Table 3. Synthesis of derivatives of 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-benzo[b]pyrans in the presence of TiO$_2$/NCP.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCHO</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CHO</td>
<td><img src="image1.png" alt="Image" /></td>
<td>10</td>
<td>92</td>
<td>227-229</td>
<td>[1]</td>
</tr>
<tr>
<td>2</td>
<td>CHO-Cl</td>
<td><img src="image2.png" alt="Image" /></td>
<td>12</td>
<td>95</td>
<td>208-210</td>
<td>[15]</td>
</tr>
<tr>
<td>3</td>
<td>CHO-Cl</td>
<td><img src="image3.png" alt="Image" /></td>
<td>10</td>
<td>82</td>
<td>235-238</td>
<td>[12]</td>
</tr>
</tbody>
</table>

![Image](image4.png)
Table 3. (Continued)

<table>
<thead>
<tr>
<th>No.</th>
<th>smiles</th>
<th>N (%)</th>
<th>T (°C)</th>
<th>T ′ (°C)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>-</td>
<td>6</td>
<td>88</td>
<td>207-209</td>
<td>285-210 [1]</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>7</td>
<td>89</td>
<td>225-227</td>
<td>224-226 [25]</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>10</td>
<td>89</td>
<td>200-203</td>
<td>200-202 [12]</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>5</td>
<td>90</td>
<td>180-182</td>
<td>179-180 [1]</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>12</td>
<td>97</td>
<td>192-194</td>
<td>194-196 [45]</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>20</td>
<td>60</td>
<td>130-132</td>
<td>174-176 [12]</td>
</tr>
</tbody>
</table>
Table 3. (Continued)

| Reaction conditions: Dimedone (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol), TiO$_2$/NCP (0.01 g), T= 70°C, solvent-free conditions. |  
| --- | --- | --- | --- | --- | --- |
| 10 | ![Molecule 1] | 12 | 84 | 192-194 | 194-196 [12] |
| 11 | ![Molecule 2] | 10 | 96 | 219-220 | 219-221 [3] |
| 12 | ![Molecule 3] | 8 | 94 | 204-206 | 203-205 [25] |
| 14 | ![Molecule 5] | 15 | 50 | 209-211 | 210-212 [3] |
Table 4. Comparison of the catalytic activity of TiO$_2$/NCP with some reported catalysts for the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Condition</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TiO$_2$/NCP</td>
<td>10</td>
<td>92</td>
<td>Solvent-free</td>
<td>This work</td>
</tr>
<tr>
<td>2</td>
<td>aminopropylated silica gel</td>
<td>90</td>
<td>93</td>
<td>H$_2$O/reflux</td>
<td>[10]</td>
</tr>
<tr>
<td>3</td>
<td>Nano TiO$_2$</td>
<td>540</td>
<td>91</td>
<td>H$_2$O/50 °C</td>
<td>[1]</td>
</tr>
<tr>
<td>4</td>
<td>N-methylimidazole</td>
<td>90</td>
<td>90</td>
<td>H$_2$O/reflux</td>
<td>[3]</td>
</tr>
<tr>
<td>5</td>
<td>RE(PFO)$_3$</td>
<td>300</td>
<td>90</td>
<td>EtOH/90 °C</td>
<td>[46]</td>
</tr>
<tr>
<td>6</td>
<td>TEBA</td>
<td>240</td>
<td>95</td>
<td>H$_2$O/90 °C</td>
<td>[47]</td>
</tr>
<tr>
<td>7</td>
<td>DIB (5 mol%)</td>
<td>60</td>
<td>83</td>
<td>H$_2$O/EtOH</td>
<td>[12]</td>
</tr>
<tr>
<td>8</td>
<td>Lipase</td>
<td>60</td>
<td>94</td>
<td>H$_2$O-EtOH/rt</td>
<td>[14]</td>
</tr>
<tr>
<td>9</td>
<td>ZnO-beta zeolite</td>
<td>35</td>
<td>95</td>
<td>EtOH/reflux</td>
<td>[11]</td>
</tr>
<tr>
<td>10</td>
<td>CeCl$_3$.7H$_2$O</td>
<td>90</td>
<td>90</td>
<td>EtOH/reflux</td>
<td>[28]</td>
</tr>
<tr>
<td>11</td>
<td>SBPPSP</td>
<td>25</td>
<td>90</td>
<td>H$_2$O/EtOH</td>
<td>[48]</td>
</tr>
<tr>
<td>12</td>
<td>SBNPTT</td>
<td>15</td>
<td>93</td>
<td>Solvent-free</td>
<td>[49]</td>
</tr>
</tbody>
</table>

In the next step, the nucleophilic attack of activated dimeredone on the electrophilic C=C double bond of a-cyanocinnammonitrile took place to give the cyclized intermediate via an intramolecular cyclization. Finally, the expected product was provided by tautomerization of the prepared cyclized intermediate. Dual catalytic roles are suggested for TiO$_2$/NCP in the above pathway. First, TiO$_2$, on the surface of nano-clinoptilolite, would activate the carbonyl group of aromatic aldehyde by attaching the oxygen atom and then increase activity of the carbonyl group. Second, the Lewis basic sites of the nanocomposite (O$^-$) would deprotonate and then activate malononitrile. Afterwards the nucleophilic attack on the activated carbonyl group pushes the reaction forward [8].

Scheme 2. Plausible mechanism for TiO$_2$/NCP catalyzed the synthesis of 4H- chromene.
4. Conclusions

In this work, a highly efficient procedure for the synthesis of 2-amino-4H-chromenes in the presence of TiO2/NCP as a heterogeneous and reusable nanocatalyst was performed under solvent-free conditions. Moreover, the obtained results including high yields of products and mild reaction conditions. Furthermore, the obtained results demonstrated good reusability of the catalyst.

Acknowledgements

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References