TiO$_2$ Nanoparticles as an Efficient Catalyst for the One-pot Preparation of Tetrahydrobenzo[c]acridines in Aqueous Media

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A series of tetrahydrobenzo[c]acridinone derivatives have been prepared by a one-pot four-component reaction of 1-naphthol, aromatic aldehydes, dimedone, and ammonium acetate in aqueous media using a catalytic amount of titanium dioxide nanoparticles (TiO$_2$ NPs). The advantages of this novel protocol include the excellent yields, operational simplicity, short reaction time, easy work-up, reusability of the catalyst and an environmentally friendly procedure.

Key words: Aqueous Media, Domino Knoevenagel-Michael Condensation, Tetrahydrobenzo[c]acridinones, TiO$_2$ Nanoparticles

Introduction

The utility of heterogeneous catalysts in synthetic chemistry has been increasingly recognized in the last few years [1–6]. It was shown that one of the efficient synthetic methods is to perform reactions on the surface of metal oxides such as SiO$_2$, Al$_2$O$_3$, ZnO, etc. [7–15]. The most preferred solids would be those which are easy to handle, inexpensive, non-toxic and easily removed during work-up. TiO$_2$ nanoparticles (TiO$_2$ NPs) as an inexpensive, non-toxic, moisture-stable, reusable, commercially available colorless powder has been of great interest to many scientists in recent years. Several applications of these nanoparticles as effective catalysts in green synthetic organic chemistry have been already highlighted in the literature [16–23]. It has been our interest to elaborate another significant catalytic activity of TiO$_2$ NPs for the synthesis of tetrahydrobenzo[c]acridinone derivatives 5a–h by a one-pot four-component reaction of 1-naphthol, aromatic aldehydes, dimedone, and ammonium acetate in aqueous media.

It is well known that the acridine core structure is an important heterocyclic framework that can be found in numerous biologically active compounds, which are widely used as antibacterial, antifungal [24], antimalarial [25], and anticancer [26, 27] agents. The most prominent members of this group have been used as chemotherapeutic agents against cancer cells [28]. In the field of antitumor DNA-binding agents, this class of acridine derivatives play an important role regarding both the number of active compounds and their DNA binding affinity [29]. Although several methods have been reported previously [30–37] there is always a need for efficient methods for the synthesis of these biologically important compounds. In the present study, we designed a new simple one-pot four-component reaction of 1-naphthol (1), aromatic aldehydes 2, dimedone (3), and ammonium acetate (4) to afford 7-aryl-10,10-dimethyl-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-ones 5, which is catalyzed by 10 mol-% of commercially available TiO$_2$ NPs with an average particle size of 15 nm, in aqueous media at 80°C (Scheme 1).

Results and Discussion

As a starting point of this investigation, we chose the reaction of 1-naphthol (1), 3-nitrobenzaldehyde (2h), dimedone (3), and ammonium acetate (4), as a model to explore the appropriate conditions (Scheme 2). A summary of the optimization experiments is shown in Table 1.
The results have shown that the use of just 10 mol-% of TiO₂ NPs is sufficient to push the reaction forward (Table 1, entries 1 – 4). To evaluate the optimum reaction temperature, the reaction was examined at different temperatures. The optimal reaction temperature was found to be 80 °C (Table 1, entries 3 and 5 – 6).

In the absence of any solvent and catalyst the reaction proceeded poorly (Table 1, entry 7). When the same reaction was carried out in various solvents such as CH₃CN, CH₂Cl₂, H₂O and also under solvent-free conditions, it was revealed that the reaction performed in aqueous media gave the best results (Table 1, entries 3 and 8 – 10).

To explore the scope of this novel efficient method, a reaction of 1-naphthol, dimedone and ammonium acetate with various substituted aryl aldehydes was evaluated (Table 2).

According to both Lewis acid and Lewis base character of metal oxides [38], a suggested mechanism for the formation of tetrahydrobenzo[c]acridinone derivatives 5 is shown in Scheme 3. It is reasonable to assume that TiO₂ NPs are coordinated to the oxygen atom of the aromatic aldehyde 2 activating it for nucleophilic attack [39]. Knoevenagel condensation between 2 and enamine 6, previously formed from the reaction of dimedone (3) and ammonium acetate (4), generates alkene 7. 1-Naphthol (1) adds to intermediates 8 – 10 (Table 1, entries 1 – 4). To evaluate the optimum reaction temperature, the reaction was examined at different temperatures. The optimal reaction temperature was found to be 80 °C (Table 1, entries 3 and 5 – 6).

To check the recyclability the catalyst (TiO₂ NPs) was centrifuged from the reaction mixture after adding DMF, and dried in vacuo. It could then be reused for further catalytic reactions. In each cycle > 81% of the catalyst was easily recovered. As shown in Table 3, the yields of the model reaction after the second and third uses of the catalyst were almost the same without loss of catalytic activity.

### Conclusion

In conclusion, an efficient green method for the preparation of 7-aryl-10,10-dimethyl-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives by a domino Knoevenagel-Michael condensation of 1-naphthol, aromatic aldehydes, dimedone, and ammonium acetate, catalyzed by TiO₂ NPs in aqueous media, was achieved. This novel method has the advantages of high yields, mild reaction conditions, short re-

Table 1. The synthesis of acridin-8(9H)-one 5h from 1-naphthol (1), 3-nitrobenzaldehyde (2h), dimedone (3), and ammonium acetate (4) under different conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol-%)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no catalyst</td>
<td>H₂O</td>
<td>80</td>
<td>10</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>TiO₂ NPs (5%)</td>
<td>H₂O</td>
<td>80</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>TiO₂ NPs (10%)</td>
<td>H₂O</td>
<td>80</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>TiO₂ NPs (20%)</td>
<td>H₂O</td>
<td>80</td>
<td>2</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>TiO₂ NPs (10%)</td>
<td>H₂O</td>
<td>60</td>
<td>6</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>TiO₂ NPs (10%)</td>
<td>H₂O</td>
<td>90</td>
<td>4</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>no catalyst</td>
<td>neat</td>
<td>80</td>
<td>8</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>TiO₂ NPs (10%)</td>
<td>neat</td>
<td>80</td>
<td>2</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>TiO₂ NPs (10%)</td>
<td>CH₂CN</td>
<td>80</td>
<td>4</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>TiO₂ NPs (10%)</td>
<td>CH₂Cl₂</td>
<td>80</td>
<td>5</td>
<td>76</td>
</tr>
</tbody>
</table>

*Isolated yield.*

Table 2. Synthesis of acridin-8(9H)-ones 5a–h catalyzed by TiO₂ NPs.

<table>
<thead>
<tr>
<th>Product</th>
<th>Ar</th>
<th>Time (h)</th>
<th>M. p. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>4-BrC₆H₄</td>
<td>2</td>
<td>277 – 278</td>
<td>98</td>
</tr>
<tr>
<td>5b</td>
<td>2-ClC₆H₄</td>
<td>3</td>
<td>275 – 277</td>
<td>97</td>
</tr>
<tr>
<td>5c</td>
<td>4-ClC₆H₄</td>
<td>2.5</td>
<td>263 – 265</td>
<td>98</td>
</tr>
<tr>
<td>5d</td>
<td>2.4-Cl₂C₆H₄</td>
<td>3</td>
<td>279 – 280</td>
<td>95</td>
</tr>
<tr>
<td>5e</td>
<td>3.4-Cl₂C₆H₄</td>
<td>2.5</td>
<td>285 – 287</td>
<td>96</td>
</tr>
<tr>
<td>5f</td>
<td>4-HOC₆H₄</td>
<td>2</td>
<td>315 – 317</td>
<td>97</td>
</tr>
<tr>
<td>5g</td>
<td>4-CH₂O₂C₆H₄</td>
<td>2.5</td>
<td>259 – 260</td>
<td>95</td>
</tr>
<tr>
<td>5h</td>
<td>3-NO₂C₆H₄</td>
<td>2</td>
<td>268 – 270</td>
<td>98</td>
</tr>
</tbody>
</table>

*Yields refer to those of pure isolated products.*
action time, easy work-up, recyclability of the catalyst, and an environmentally friendly procedure.

**Experimental Section**

**Materials and methods**

All of the chemical materials used in this work were purchased from Merck and Sigma-Aldrich and used without further purification. Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were obtained on an ABB FT-IR (FTLA 2000) spectrometer. 1H NMR spectra were recorded on a Bruker DRX-500 AVANCE instrument at 500 MHz, using TMS as internal standard and [D$_6$]DMSO as solvent. Elemental analyses were carried out using a Heraeus CHN rapid analyzer.

**General procedure for the preparation of compounds 5a–h**

A mixture of 1-naphthol (1, 1 mmol), an aromatic aldehyde 2 (1 mmol), dimedone (3, 1 mmol), ammonium acetate (4, 1 mmol), and commercially available TiO$_2$ NPs (Sigma-Aldrich) with an average diameter of 15 nm (7.9 mg, 10 mol-%) was stirred at 80 °C in water (10 mL). After completion of the reaction (TLC), the reaction mixture was filtered. The solid mass was eluted with DMF (5 mL), and the mixture was centrifuged at 2000–3000 rpm for 5 min to remove the nano TiO$_2$ catalyst. The organic solution was then poured into cold water (15 mL), filtered and washed with aqueous ethanol to afford the pure products 5 in high yields.

**Table 3. Reuse of TiO$_2$ NPs for the synthesis of 5h.**

<table>
<thead>
<tr>
<th>Recycles</th>
<th>Yield (%)$^a$</th>
<th>Recovery of catalyst (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>93</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
<td>81</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield.
7-(2,4-Dichlorophenyl)-10,10-dimethyl-
7,10,11,12-tetrahydrobenzoc[7]acridin-8(9H)-one (5d)

Colorless powder; yield 0.401 g (95%); m.p. 279 – 280 °C (lit.: 280 – 282 °C [37]). – IR (KBr): ν = 3313, 2952, 1682, 1589, 1517 cm⁻¹. – ¹H NMR: δ = 1.02 (s, 3H, CH₃), 1.10 (s, 3H, CH₃), 2.02 (d, 1H, H-11, J = 16.1 Hz), 2.24 (d, 1H, H-11, J = 16.1 Hz), 2.63 (d, 1H, H-9, J = 16.4 Hz), 2.73 (d, 1H, H-9, J = 16.4 Hz), 5.71 (s, 1H, CH), 7.20 (d, 1H, H₆, J = 8.4 Hz), 7.26 (m, 2H, H₈), 7.45 (d, 1H, H₅, J = 8.2 Hz), 7.55 (m, 3H, H₆ – H₈), 7.81 (d, 1H, H₄, J = 7.4 Hz), 8.47 (d, 1H, H₈, J = 7.4 Hz), 9.30 (s, 1H, NH) ppm. – Anal. for C₂₅H₁₉Cl₂N₂O (422.47): calcld. C 71.10, H 5.01, N 3.32; found C 71.03, H 5.21, N 3.24%.

7-(3,4-Dichlorophenyl)-10,10-dimethyl-
7,10,11,12-tetrahydrobenzoc[7]acridin-8(9H)-one (5e)

Colorless powder; yield 0.405 g (96%); m.p. 285 – 287 °C (lit.: 284 – 286 °C [37]). – IR (KBr): ν = 3319, 2952, 1684, 1583, 1520 cm⁻¹. – ¹H NMR: δ = 1.00 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 2.07 (d, 1H, J = 16.2 Hz, H-11), 2.26 (d, 1H, J = 16.2 Hz, H-11), 2.67 (d, 1H, J = 17.2 Hz, H-9), 2.76 (d, 1H, J = 17.2 Hz, H-9), 5.28 (s, 1H, CH), 7.17 (dd, 1H, J = 8.4, 2.0 Hz, H₆), 7.30 (d, 1H, J = 8.2 Hz, H₅), 7.48 (m, 5H, H₈), 7.84 (d, 1H, J = 8.1 Hz, H₄), 8.48 (d, 1H, J = 8.6 Hz, H₃), 9.54 (s, 1H, NH) ppm. – Anal. for C₂₅H₁₉Cl₂N₂O (422.47): calcld. C 71.10, H 5.01, N 3.32; found C 71.19, H 5.08, N 3.28%.

7-(4-Hydroxyphenyl)-10,10-dimethyl-
7,10,11,12-tetrahydrobenzoc[7]acridin-8(9H)-one (5f)

Colorless powder; yield 0.455 g (97%); m.p. 315 – 317 °C (lit.: 312 – 315 °C [37]). – IR (KBr): ν = 3293, 2986, 2910, 1668, 1574, 1521 cm⁻¹. – ¹H NMR: δ = 1.00 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 2.04 (d, 1H, H-11, J = 16.0 Hz), 2.23 (d, 1H, H-11, J = 16.0 Hz), 2.64 (d, 1H, H-9, J = 16.4 Hz), 2.72 (d, 1H, H-9, J = 16.4 Hz), 5.08 (s, 1H, CH), 6.55 (d, 2H, H₆, J = 8.2 Hz), 6.99 (d, 2H, H₆, J = 8.2 Hz), 7.24 (d, 1H, H₅, J = 8.4 Hz), 7.48 (m, 3H, H₄), 7.81 (d, 1H, H₅, J = 7.4 Hz), 8.44 (1H, d, H₃, J = 8.2 Hz), 9.08 (s, 1H, OH), 9.20 (s, 1H, NH) ppm. – Anal. for C₂₅H₁₉NO (398.44): calcld. C 75.36, H 5.75, N 7.03; found C 75.44, H 5.51, N 7.10%.

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