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# Using titanium dioxide nanoparticles as recyclable catalyst for synthesis of 1-amidoalkyl-2-naphthols in solvent free condition

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## ABSTRACT

In this work a solvent-free and efficient method has been developed for the preparation of 1-amidoalkyl-2-naphthols from condensation of aldehydes with amides or urea and β-naphthol in the presence of nano-$TiO_2$ under thermal solvent-free conditions. The advantages of this procedure are good yields, easy work-up and purification, mild reaction conditions and reusability of the catalyst.

## KEYWORDS

Titanium dioxide nanoparticles;
1-amidoalkyl-2-naphthols;
Multi-component reactions;
Solvent free.

## INTRODUCTION

Multi-component processes have recently gained considerable economic and ecological interest as they address fundamental principles of synthetic efûciency and reaction design. Multi-component reactions (MCRs) have been proven to be a very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks and show high selectivity[1]. As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from two-component reactions in several aspects[2] and permitted rapid access to combinatorial libraries of organic molecules for efficient lead structure identification and optimization in drug discovery[3].

1-amidoalkyl 2-naphthols can be converted to useful and important biological building blocks and to 1-amino methyl 2-naphthols by an amide hydrolysis reaction, since compounds exhibit depressor and bradycardia effects in humans[4,5].

1-Amidoalkyl 2-naphthols can be prepared by multicomponent condensation of aldehydes, 2-naphthols and acetonitrile or different amides. Between reported methods, we can pointed to using of imidazolium salts[6], $Bi(NO_3)_3.5H_2O$[7], ultrasonic[8], thiamine hydrochloride[9], DMF/$POCl_3$[10], dodecylphosphonic acid[11], $FeCl_3.SiO_2$[12], ionic liquid[13], TCT[14], nano-$ZrSO_4$[15], $P_2O_5$[16].

In recent years, the use of heterogeneous solid acid catalysts has offered important advantages in organic synthesis, for example, operational simplicity, environmental compatibility, non-toxicity, reusability, low cost, and ease of isolation.

In this context, the use of nanoparticles as heterogeneous catalysts has attracted considerable attention because of the interesting structural features and high levels of catalytic activity associated with these materials[17,18]. The application of nanoparticles has extended to almost all possible field of science ranging from medicine to rocketry. Good catalytic activity of transition metal oxides (TMO) is attributed to their partially filled penultimate d orbitals and the subsequent binding sites provided to the intermediates formed during the reaction. The applications of TMO in industrial process as well as in thermal decomposition reactions are long known[19-21].

$TiO_2$ nanoparticles have been widely investigated in the past decades due to their multiple potential applications such as catalytic activity for esterification[22], sonocatalytic degradation of methyl parathion[23], photodecomposition of methylene-blue by highly dispersed on Ag[24], catalyst for rhodamine B degradation[25], photocatalytic degradation[26], crosslinking of cotton cellulose with succinic acid under UV[27] and synthesis of β-acetamido ketones[28].

## RESULT AND DISCUSSION

The nano-$TiO_2$ powder can be easily synthesized by hydrothermal method as reported in the literature[29]. Figure 1a shows the XRD patterns of nano-$TiO_2$ powder before modification. As it can be seen in Figure 1a, the main phase is nano-$TiO_2$ powder, which is observed without any phase. The size of the nano-$TiO_2$ powder was also determined from X-ray line broad using the Debye-Scherrer formula given as $D = 0.9\lambda/\beta\cos\theta$, where D is the average crystalline size, λ the X-ray wavelength used, β the angular line width at half maximum intensity and θ the Bragg's angle. The average size of the nano-$TiO_2$ powder for $2\theta = 25.303\,^{\circ}$ is estimated to be around 21.88 nm. Scanning electron microscopy (SEM) analysis were used for characterization of nano-$TiO_2$ powder (Figure 1b). The SEM image reveal the spherical nano-$TiO_2$ powder with average size 20-30 nm. The FT-IR spectra of nano-$TiO_2$ powder are shown in Figure 2. The absorbance bands at around 3350-3450 $cm^{-1}$ was certified to adsorbed water. The broad intense band blew 1200 $cm^{-1}$ as due to Ti-O-Ti vibration which are consistent with the reported IR spectra for nano-$TiO_2$[30].

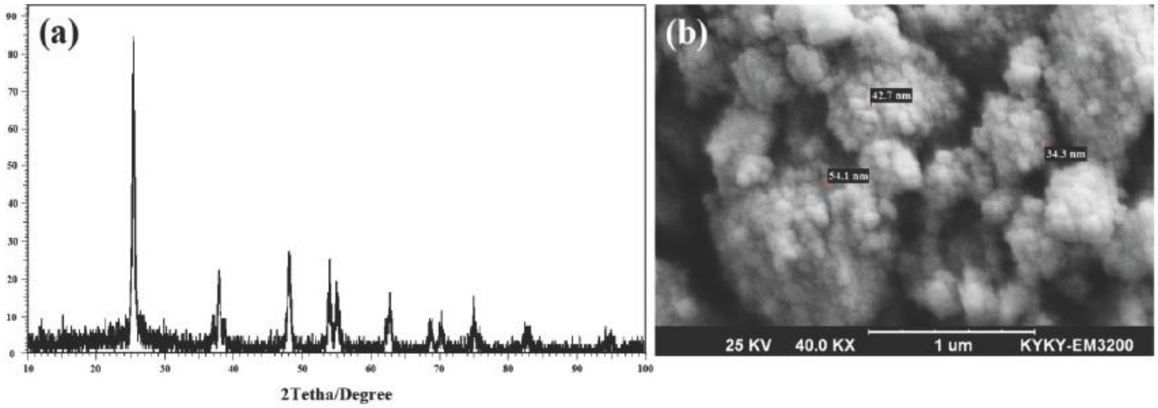


Figure 1 : (a) The X-ray diffraction patterns of the nano-$TiO_2$ powder, (b) the SEM image of nano-$TiO_2$.

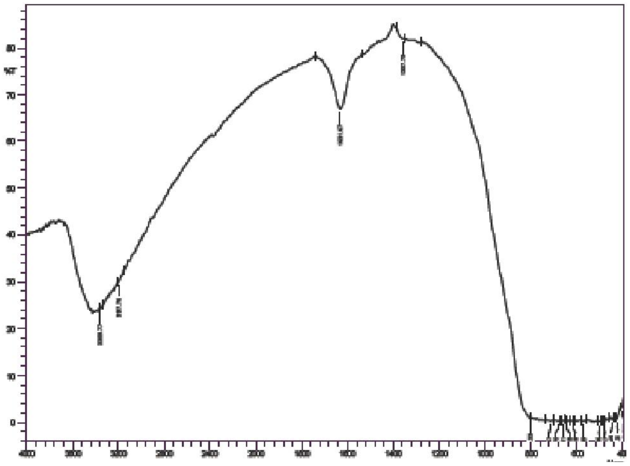
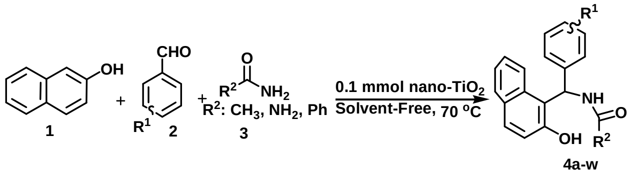


Figure 2 : The FT-IR spectra of nano-$TiO_2$ powder.

In continuation of our studies on developing inexpensive and environmentally benign methodologies for synthesis of organic compounds and reactions[31-33] and high efficient of nano-$TiO_2$, we decided to investigate the possibility of synthesizing 1-amidoalkyl-2-naphthols derivatives by one-pot condensation reaction strategy of β-naphthol, aromatic aldehydes and amide derivatives compounds in presents of nano-$TiO_2$ as an efficient and reusable heterogeneous catalysis as well as under solvent-free conditions (Scheme 1). To the best of our knowledge, there is no literature report on the



Scheme 1 : Synthesis of 1-amidoalkyl-2-naphthols by nan-$TiO_2$ as reusable catalyst.

multi-component condensation under these conditions. Because green chemistry is one of the most interesting aspects of organic synthesis, in the first glance we have decided to start with solvent free conditions.

Initially we started with condensation of β-naphthol, benzaldehyde and acetamide that had already been used vastly by other chemists in different conditions. In the first glance, we compared condensation between β-naphthol (1 mmol), benzaldehyde (1 mmol) and acetamide (1.2 mmol) in different solvents including MeCN, EtOH, MeOH, $CH_2Cl_2$ and $H_2O$ under reflux conditions or at 90 °C with the same reaction at 90 °C without solvent, shows that the best results can be obtained under solvent-free conditions (TABLE 1, entry 6). Using MeOH as solvent gave significantly lower yields and longer reaction times, while using others gave low yield. The results are presented in TABLE 1.

**TABLE 1 : Comparing solvent-free conditions with various solvents for synthesis of 1-amidoalkyl-2-naphthols derivatives[a].**

| Entry | Solvent | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | $H_2O$ | 1.5 | 42 |
| 2 | MeCN | 1.5 | 33 |
| 3 | EtOH | 1.5 | 54 |
| 4 | MeOH | 1.5 | 57 |
| 5 | $CH_2Cl_2$ | 1.5 | 46 |
| 6[b] | ---- | 1.5 | 84 |

[a]reaction condition: β-naphthol (1 mmol), benzaldehyde (1 mmol) and acetamide (1.2 mmol) in present of nano-$TiO_2$ (0.15 mmol).; [b]Solvent Free condition at 90 °C.

To study the limitation of catalyst amounts, we explored some reaction conditions in solvent free conditions which results are summarized in TABLE 2.

**TABLE 2 : Optimization of the amount of nano-$TiO_2$ in Synthesis of 1-amidoalkyl-2-naphthols derivatives[a].**

| Entry | Nano-$TiO_2$ (mmol) | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | 0.04 | 1.5 | 32 |
| 2 | 0.06 | 1.5 | 52 |
| 3 | 0.08 | 1.5 | 71 |
| 4 | 0.10 | 1.5 | 87 |
| 5 | 0.12 | 1.5 | 87 |
| 6 | 0.15 | 1.5 | 84 |

[a]reaction condition: β-naphthol (1 mmol), benzaldehyde (1 mmol) and acetamide (1.2 mmol) in solvent free conditions at 90 °C.

Our results showed that by increasing the catalytic load of nano-$TiO_2$ from 0.06 mmol to 0.10 mmol improved the yield from 52% to 87% (TABLE 2, entries 2-4). This showed that the catalyst concentration plays a major role in this reaction. But more increasing in the catalyst amount is not appropriate and the yield diminished (TABLE 2, entry 5).

To study the limitations of temperature, we explored some reaction conditions for condensation in presence of nano-$TiO_2$ in solvent free conditions. The results are summarized in TABLE 3.

**TABLE 3 : Optimization of temperature in synthesis of 1-amidoalkyl-2-naphthols derivatives[a].**

| Entry | T /°C | %Yield |
|---|---|---|
| 1 | 50 | 52 |
| 2 | 60 | 76 |
| 3 | 70 | 87 |
| 4 | 80 | 87 |
| 5 | 90 | 84 |

[a]reaction condition: β-naphthol (1 mmol), benzaldehyde (1 mmol), acetamide (1.2 mmol) and nano-$TiO_2$ (0.1 mmol) in solvent free conditions.

As indicated in Table 3, increasing the temperature until 70 °C, resulted a 87% yield (TABLE 3, entry 3). So we have followed our experiences at 70 °C.

Now, with different optimum conditions in hand, we selected the optimized reaction conditions to determine the scope of this procedure. The results are summarized in TABLE 4.

To study the scope of this procedure, the condensations of a series of different aromatic aldehydes with β-naphthol and amide derivatives at 70 °C have been studied (TABLE 4, entries 4a-4w). The results are summarized in TABLE 4. As indicated in Table 4, the reaction works easily for a variety of aldehydes with both electron-donating and electron-withdrawing groups to give corresponding 1-amidoalkyl-2-naphthols derivatives in good to excellent yields. In almost all cases, the reactions proceeded smoothly within 1-1.8 hours. It is important to note that it seems that aldehydes with electron-withdrawing groups (TABLE 4, entries 4b-e, 4h, 4i, 4k-4n, 4p-4s, 4w) react faster than aldehydes with electron-withdrawing groups (TABLE 4, entries 4f, 4g, 4l, 4t, 4u). In continuing studying upon scope of this method, we also to prepared 1-amidoalkyl-2-naphthols derivatives from urea and benzamide. The reaction of urea (TABLE 4, entries 4j-n) and benzamide (Table 4, entries 4o-w) resulted in the formation of the corresponding desired products in good yields.

**TABLE 4 : Titanium dioxide nanoparticles as recyclable catalyst for synthesis of 1-amidoalkyl-2-naphthols in solvent free condition[a].**

| Entry | R[1] | $R_2$ | Time (h) | Yield[b] (%) | Melting point (°C) | |
|---|---|---|---|---|---|---|
| | | | | | Found | Reported |
| 4a | -H | Me | 1.5 | 87 | 216-218 | 218-220 [13] |
| 4b | 2-Cl | Me | 1.2 | 89 | 210-212 | 213-215 [12] |
| 4c | 2-$NO_2$ | Me | 1.2 | 88 | 181-183 | 179-182 [12] |
| 4d | 3- $NO_2$ | Me | 1.1 | 90 | 242-243 | 241-242 [12] |
| 4e | 4- $NO_2$ | Me | 1 | 90 | 247-249 | 248-250 [12] |
| 4f | 4-Me | Me | 1.5 | 85 | 221-224 | 222-223 [12] |
| 4g | 4-OMe | Me | 1.6 | 86 | 182-184 | 183-185 [12] |
| 4h | 4-Cl | Me | 1.4 | 87 | 222-223 | 223-225 [12] |
| 4i | 4-F | Me | 1.2 | 89 | 228-230 | 230-232 [12] |
| 4j | -H | $NH_2$ | 1.4 | 88 | 175-177 | 176-178 [12] |
| 4l | 4-Me | $NH_2$ | 1.5 | 85 | 116-119 | 117-118 [15] |
| 4k | 4-Cl | $NH_2$ | 1.3 | 89 | 169-171 | 168-169 [8] |
| 4m | 3- $NO_2$ | $NH_2$ | 1.2 | 90 | 190-191 | 192-193 [13] |
| 4n | 4- $NO_2$ | $NH_2$ | 1.1 | 92 | 163-165 | 164-166 [15] |
| 4o | -H | Ph | 1.6 | 87 | 232-235 | 234-236 [8] |
| 4p | 2-Cl | Ph | 1.5 | 89 | 282-284 | 284-285 [16] |
| 4q | 2-$NO_2$ | Ph | 1.4 | 90 | 266-268 | 266-267 [16] |
| 4r | 3- $NO_2$ | Ph | 1.3 | 92 | 216-218 | 216-217 [8] |
| 4s | 4- $NO_2$ | Ph | 1.2 | 93 | 227-229 | 228-229 [16] |
| 4t | 4-Me | Ph | 1.7 | 87 | 190-191 | 192-193 [8] |
| 4u | 4-OMe | Ph | 1.8 | 89 | 206-208 | 206-208 [16] |
| 4v | 4-Cl | Ph | 1.8 | 89 | 175-177 | 177-178 [8] |
| 4w | 4-F | Ph | 1.4 | 91 | 192-194 | 193-194 [8] |

**[a]reaction condition: β-naphthol (1 mmol), benzaldehyde (1 mmol), acetamide (1.2 mmol) and nano-TiO$_2$ (0.1 mmol) in solvent free conditions at 70 °C; [b]Isolated yield.**

For testing reusable of catalyst and green chemistry perspective, experiments concerning the recycling and reuse of the catalyst were carried out. Then completion of the reaction (monitored by TLC), mixture of reaction washed with ethanol, catalyst separated with filtration and dried at 50 °C for 2h. The condensation of β-naphthol, benzaldehyde and acetamide was repeated with recovered catalyst. The catalyst could be efficiently recovered and recycled up to four times without suffering any significant drop in its catalytic activity or the yield for the reaction (TABLE 5).

**TABLE 5 : Recycling of nano-TiO$_2$.**

| Number of Cycle | Yield (%) |
|---|---|
| 1 | 87 |
| 2 | 87 |
| 3 | 85 |
| 4 | 83 |

Reaction condition: β-naphthol (1 mmol), benzaldehyde (1 mmol), acetamide (1.2 mmol) and nano-TiO-$_2$ (0.1 mmol) in solvent free condition at 70 ºC.

## EXPERIMENTAL SECTION

### General

Chemicals were purchased from the Merck and Aldrich chemical companies. Thin-Layer Chromatography (TLC) on commercial aluminum backed plates of silica gel 60 F254 was used to monitor the progress of reactions. The products were characterized by FT-IR spectra, $^1H$ NMR, $^{13}C$ NMR and CHN analyzer. FT-IR spectra were recorded on Shimadzo FT-IR-8400 instrument. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker Advance Spectrometer 300 MHz using $CHCl_3$-d as solvent. The chemical shifts are expressed in parts per million (ppm) and tetramethylsilane (TMS) was used as an internal reference. Elemental analyses were performed by Perkin Elmer CHN analyzer, 2400 series II. Melting points were recorded on a THERMO SCIENTIFIC 9100 apparatus. X-ray diffraction analyses were conducted using a Bruker D8 X-ray diffractometer (Cu-Ka radiation, k = 1.54 ) were obtained for characterization of the heterogeneous catalyst. Scanning electron microscopy (SEM) was carried out with a BAL-TEC SCD 005 instrument.

### Preparation of titanium dioxide nanoparticles

Nano-TiO$_2$ was prepared with hydrothermal method. The pH value of $TiCl_4$ solution was adjusted to 1.8 with $NH_3.H_2O$. After vigorously stirring at 70 °C for 2 h, the final pH of the solution was adjusted to 6. Then the resulting suspension was cooled down to room temperature and kept for 24 h. After filtration, the solid was firstly washed with $NH_4Ac$-HAc until no $Cl^-$ was detected, then separated out with a centrifuge and washed with ethanol, at last dried in vacuum. After 2 h treatment at 650 °C, nano-TiO$_2$ material was obtained[34].

### General procedure for the synthesis of 1-amidoalkyl-2-naphthols derivatives in presence of nano-TiO$_2$

β-naphthol (1.0 mmol), different aromatic Aldehyde (1.0 mmol), amide or urea (1.2 mmol) and nano-TiO$_2$ (0.1 mmol) were taken in a 10 mL round-bottomed flask. The mixture was stirred at 70 °C for an appropriate time as mentioned in TABLE 4. After completion of the reaction as monitored by TLC, the mixture was allowed to cool up to room temperature and washed with ethanol (5 mL). The mixture filtrated and collected nano-TiO$_2$ for reused. Then solvent evaporated under reduce pressure and the formed precipitate was collected by filtration. The crude product was recrystallized from ethanol to yield pure 1-amidoalkyl-2-naphthols derivatives. The formed crystals were collected by filtration at pump, washed with cool ethanol and dried. All the products were characterized by FT-IR, $^1$H NMR and $^{13}$C NMR, CHN and were identified by the comparison of the spectral data with those reported in literature.

## CONCLUSION

we have developed a one-pot, solvent free, efficient and environmentally benign method for the preparation of 1-amidoalkyl-2-naphthols derivatives by condensation between β-naphthol, different aromatic aldehydes and amide derivatives. This condensation reaction is efficiently catalyzed by nano-TiO$_2$ at 70 °C. The reaction works easily for a vast variety of aldehydes with both electron-donating and electron-withdrawing groups to give corresponding 1-amidoalkyl-2-naphthols derivatives from good to excellent yields. The significant advantages of this present method over other exiting methods are operational simplicity, mild reaction conditions, easy purification, economic viability of the catalyst and good isolated yields of the pure products.

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