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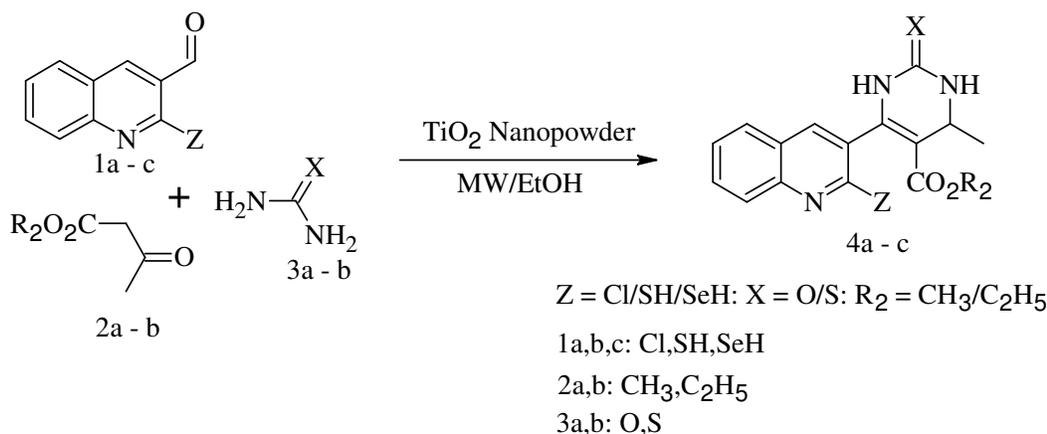
# Nano-Titanium dioxide (TiO<sub>2</sub>) mediated simple and efficient modification to Biginelli reaction

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We report an efficient titanium dioxide (TiO<sub>2</sub>) nanopowder catalyzed and microwave induced, much improved modification to original Biginelli reaction reported in 1893 involving fast reaction kinetics.



**Key words:** Titanium dioxide, biginelli reaction, microwave, fast kinetics.

## INTRODUCTION

The functionalized quinolines are attractive compounds for drug discovery since many of them have been shown to exhibit excellent biological activities (Balasubramanian and Keay, 1996; Catoen-Chackal et al., 2004; Vazquez et al., 2004; Chen et al., 2004; Chen et al., 2001). Therefore, the development of facile methodologies for the synthesis of highly functionalized quinoline derivatives represents a challenge in medicinal chemistry (Gilchrist et al., 1997; Jones, 1984; Jones, 1996; Kouznetsov et al., 2005; Ishkawa et al., 2004; Sangu et al., 2004; Kobayashi et al., 2004; Wang et al., 2004; Palimkar et al., 2003; Du and Curran, 2003; Jiang and Yui-Gui, 2002; Amii et al., 2001). For example,

oxoindeno[1,2-*b*]quinolines have shown strong binding to DNA and efficient inhibition DNA topoisomerase 1 that were associated with their well pronounced anticancer activities (Deady et al., 2001; Chen et al., 2000; Deady et al., 2000; Deady et al., 1997), 3-Benzoylquinolines (Ryabukhin et al., 2007; Basavaiah et al., 2006; Yoon, 2005; Patteux et al., 2003; Mahata et al., 2003; Singh et al., 2002; Singh et al., 2002; Harrowven et al., 2001; Ishar et al., 1998) are inhibitors of HIV-1 replication (Normand-Bayle et al., 2005) and cathepsin D (Whitesitt et al., 1996) and possess antianaphylactic activity (Evans et al., 1987). The Combes synthesis is one of the most efficient approaches to the quinolines.

Organic synthesis through semiconductor photocatalysis has become an important research area in photochemistry in the last two decades (Fox, 2001; Kisch and Hopfner, 2001). Significant examples of organic transformations employed for synthetic purposes are

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oxidation and reduction reactions, isomerization reactions, C–H bond activations and C–C and C–N bond forming reactions (Mills and LeHunte, 1997; Robertson, 1996; Maldotti et al., 2002). Metal oxide semiconductor colloids are of considerable interest because of their photocatalytic properties and resistance against corrosion. Titanium dioxide, in particular, could be the photocatalyst of choice for a large variety of applications because it is cheap, non-toxic, and has redox properties which are favorable both for oxidation of many organics and for reduction of a number of metal ions or organics in aqueous solution. Absorption of light having energy greater than the band gap (3.2 eV for titanium dioxide) results in the promotion of electrons from the valence band to the conduction band of the metal oxide particle, leaving positively charged holes in the valence band. These photogenerated electrons and holes ( $E_{cb/vb} \sim -0.5/+2.7$  V at pH 8, respectively for  $\text{TiO}_2$ ) (Nozik, 1978; Hagfeldt and Gratzel, 1995) can recombine nonproductively, or they can migrate to surface trapping sites where they can react with redox species in solution. Surface derivatization strategies have been developed for enhancing the reaction lifetimes, trapping efficiency and reaction selectivity of the trapped electrons and holes (Hara and Mallouk, 2000; Rajh et al., 2003). For example, in titanium dioxide colloids, light-induced chemistry produces electron–hole pairs that can be used to drive external redox chemistry with surface derivatized particles (Jakob et al., 2003).

At the beginning of the new century, a shift in emphasis in chemistry is apparent with the desire to develop environmentally benign routes to a myriad of materials (Anastas and Williamson, 1998). Green chemistry approaches hold out significant potential not only for reduction of byproducts, a reduction in the waste produced, and lowering of energy costs but also in the development of new methodologies toward previously unobtainable materials, using existing technologies (Cave et al., 2001). Of all of the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally large volume of waste/product ratio, are perhaps the most ripe for greening (Sheldon, 1997).

Our Approach is to develop a rapid and efficient scientifically based framework for greener preparation of these dihydropyrimidinone fused benzoquinolines in a manner that renders the materials less mobile in the environment and reduces or eliminates the use and generation of hazardous substances. The areas of opportunity are being exploited to engage green chemistry: (i) Choice of solvent, (ii) The catalytic agent employed, finally we found microwave (MW) irradiation as an efficient and selective mode of activation in rapid and efficient synthesis.

## Experimental section

All reagents were used as obtained commercially. Thin-layer

chromatography was performed using commercially prepared 60-mesh silica gel plates and visualization was effected with short wavelength UV light (254 nm).  $^1\text{H}$  NMR spectra were recorded in  $\text{DMSO-d}_6$  on EM-390 (400MHz) NMR spectrometer and mass spectra were recorded on MASPEC low resolution instrument operating at 70eV and JELO JSM-35 JF instrument was used to take SEM photographs.

## Preparation of semiconductor titanium dioxide nanoparticles in colloidal solutions

Titanium dioxide nanoparticles used in the experiments above were produced according to the reported procedure (Fendler, 1998) in the following manner.  $\text{TiO}_2$  nanoparticles are prepared by the hydrolysis of titanium tetrachloride.  $\text{TiCl}_4 + 2\text{H}_2\text{O} = \text{TiO}_2\downarrow + 4\text{HCl}$

Obtained stable colloidal solution of nanoparticles, were then centrifuged for a length of time dependent on the expected particle size and density as well as the centrifuge rotor dimensions and revolutions per minute (rpm) selected. The well defined below 100 nm sized  $\text{TiO}_2$  particles were obtained by mixing the reactants for 2 h followed by 30 min centrifugation at 10000 rpm in a Centra-CL2 equipped with a swinging bucket rotor.

A dry, 50-mL flask was charged with 2-chloro/mercapto/seleno-3-formylquinoline (5 mmol), methyl acetoacetate (5 mmol), urea/thiourea (5 mmol), and titanium dioxide ( $\text{TiO}_2$ ) nanopowder (500 mg) in presence of 10 ml of ethanol. The mixture was well mixed and then irradiated in a SANYOEM-350S microwave oven at 300W or 150W for a designated time as required for completing the reaction (determined by TLC) in Table 1. Then, after being cooled to room temperature, under these conditions, the reaction mass was poured on crushed ice solid material was filtered off and the crude product was purified by recrystallization from DMF. The similar reaction procedure has been followed for other derivatives.

### Methyl [6-(2-chloroquinolin-3-yl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4a of 2a&3a)

Yield 81%, pale yellow solid, mp( $^{\circ}\text{C}$ ) 211-213,  $^1\text{H}$  NMR ( $\text{DMSO d}_6$ ),  $\delta$  8.08 (d, 1H, Ar-H), 7.60 (d, 1H, Ar-H), 7.46 (d, 1H, Ar-H), 7.61 (d, 1H, Ar-H), 8.38 (d, 1H, Ar-H), 2.8 (s, 2H,  $\text{CH}_2$ ), 3.61 (s, 3H,  $\text{CH}_3$ ), 1.25 (t, 3H,  $\text{CH}_3$ ), 2.1 (s, 1H, NH), 3.45 (s, 1H, CH); 2.2 (s, 1H, NH); m/z (%)  $[\text{M}]^+$  : [345] $^+$ ; Elemental analysis, Found: C, 59.12; H, 4.57; N, 12.06. Calculated for  $\text{C}_{17}\text{H}_{16}\text{ClN}_3\text{O}_3$ : C, 59.05; H, 4.66; N, 12.15.

### Methyl [6-(2-chloroquinolin-3-yl)-4-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4a of 2a&3b)

Yield 86%, pale yellow solid, mp ( $^{\circ}\text{C}$ ) 215-217,  $^1\text{H}$  NMR ( $\text{DMSO d}_6$ ),  $\delta$  8.05 (d, 1H, Ar-H), 7.61 (d, 1H, Ar-H), 7.43 (d, 1H, Ar-H), 7.68 (d, 1H, Ar-H), 8.33 (d, 1H, Ar-H), 2.9 (s, 2H,  $\text{CH}_2$ ), 3.67 (s, 3H,  $\text{CH}_3$ ), 1.20 (t, 3H,  $\text{CH}_3$ ), 2.0 (s, 1H, NH), 3.48 (s, 1H, CH); 2.0 (s, 1H, NH); m/z (%)  $[\text{M}]^+$  : [361] $^+$ ; Elemental analysis, Found: C, 56.34; H, 4.40; N, 11.68. Calculated for  $\text{C}_{17}\text{H}_{16}\text{ClN}_3\text{O}_2\text{S}$ : C, 56.43; H, 4.46; N, 11.61.

### Ethyl [6-(2-chloroquinolin-3-yl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4a of 2b&3a)

Yield 79%, pale yellow solid, mp( $^{\circ}\text{C}$ ) 219-221,  $^1\text{H}$  NMR ( $\text{DMSO d}_6$ ),  $\delta$  8.01 (d, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 7.41 (d, 1H, Ar-H), 7.58 (d, 1H, Ar-H), 8.35 (d, 1H, Ar-H), 2.85 (s, 2H,  $\text{CH}_2$  COO), 3.66 (s, 3H,  $\text{CH}_3$ ), 4.25 (q, 2H,  $\text{CH}_2$ ), 1.25 (t, 3H,  $\text{CH}_3$ ), 6.1 (br, s, 1H, NH), 3.49 (s, 1H, CH); 6.4 (br, s, 1H, NH); m/z (%)  $[\text{M}]^+$  : [359] $^+$ ; Elemental analysis, Found: C, 59.91; H, 5.12; N, 11.76. Calculated for  $\text{C}_{18}\text{H}_{18}\text{ClN}_3\text{O}_3$ : C, 60.09; H, 5.04; N, 11.68.

**Table 1.** Reaction time data of both conventional and MW methods.

Compound	Time (Hours)-Conventional heating	Time (Minutes)-MW
4a of 2a and 3a	1.5	5 - 8
4a of 2a and 3b	1.7	6 - 9
4a of 2b and 3a	2.1	5 - 9
4a of 2b and 3b	1.6	7 - 10
4b of 2a and 3a	1.8	6 - 9
4b of 2a and 3b	2.0	5 - 8
4b of 2b and 3b	2.1	6 - 7
4b of 2b and 3a	1.8	5 - 9
4c of 2a and 3b	1.6	6 - 8
4c of 2a and 3a	1.8	7 - 10
4c of 2b and 3a	2.3	6 - 7
4c of 2b and 3b	2.2	7 - 10

**Ethyl [6-(2-chloroquinolin-3-yl)-4-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4a of 2b&3b)**

Yield 75%, pale yellow solid, mp(°C) 225-226, <sup>1</sup>H NMR (DMSO d<sub>6</sub>), δ 7.95 (d, 1H, Ar-H), 7.68 (d, 1H, Ar-H), 7.45 (d, 1H, Ar-H), 7.55 (d, 1H, Ar-H), 8.39 (d, 1H, Ar-H), 2.81 (s, 2H, CH<sub>2</sub>), 3.59 (s, 3H, CH<sub>3</sub>), 4.21 (q, 2H, CH<sub>2</sub>), 1.26 (t, 3H, CH<sub>3</sub>), 2.0 (s, 1H, NH), 3.41 (s, 1H, CH); 2.1 (s, 1H, NH); m/z (%) [M]<sup>+</sup> : [375]<sup>+</sup>; Elemental analysis, Found: C, 57.48; H, 4.75; N, 11.10. Calculated for C<sub>18</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>2</sub>S: C, 57.52; H, 4.83; N, 11.18.

**Methyl [6-(2-mercaptoquinolin-3-yl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4b of 2a&3a)**

Yield 65%, pale yellow solid, mp(°C) 232-234, <sup>1</sup>H NMR (DMSO d<sub>6</sub>), δ 7.91 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H), 7.43 (d, 1H, Ar-H), 7.68 (d, 1H, Ar-H), 7.38 (d, 1H, Ar-H), 2.9 (s, 2H, CH<sub>2</sub>), 3.65 (s, 3H, CH<sub>3</sub>), 1.27 (t, 3H, CH<sub>3</sub>), 2.0 (s, 1H, NH), 3.41 (s, 1H, CH), 2.1 (s, 1H, NH), 11.1 (s, 1H, SH); m/z (%) [M]<sup>+</sup> : [343]<sup>+</sup>; Elemental analysis, Found: C, 59.39; H, 4.88; N, 12.15. Calculated for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>S: C, 59.46; H, 4.99; N, 12.24.

**Methyl [6-(2-mercaptoquinolin-3-yl)-4-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4b of 2a&3b)**

Yield 68%, pale yellow solid, mp(°C) 218-220, <sup>1</sup>H NMR (DMSO d<sub>6</sub>), δ 7.98 (d, 1H, Ar-H), 7.61 (d, 1H, Ar-H), 7.38 (d, 1H, Ar-H), 7.71 (d, 1H, Ar-H), 7.35 (d, 1H, Ar-H), 2.7 (s, 2H, CH<sub>2</sub>), 3.6 (s, 3H, CH<sub>3</sub>), 1.21 (t, 3H, CH<sub>3</sub>), 2.1 (s, 1H, NH), 3.45 (s, 1H, CH), 2.2 (s, 1H, NH), 11.4 (s, 1H, SH); m/z (%) [M]<sup>+</sup> : [359]<sup>+</sup>; Elemental analysis, Found: C, 56.85; H, 4.68; N, 11.59. Calculated for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: C, 56.80; H, 4.77; N, 11.69.

**Ethyl [6-(2-mercaptoquinolin-3-yl)-4-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4b of 2b&3b)**

Yield 63%, pale yellow solid, mp(°C) 205-207, <sup>1</sup>H NMR (DMSO d<sub>6</sub>), δ 8.2 (d, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 7.49 (d, 1H, Ar-H), 7.62 (d, 1H, Ar-H), 7.8 (d, 1H, Ar-H), 2.75 (s, 2H, CH<sub>2</sub>), 3.51 (s, 3H, CH<sub>3</sub>), 4.18 (q, 2H, CH<sub>2</sub>), 1.23 (t, 3H, CH<sub>3</sub>), 2.3 (s, 1H, NH), 3.48 (s, 1H, CH), 2.0 (s, 1H, NH), 11.3 (s, 1H, SH); m/z (%) [M]<sup>+</sup> : [373]<sup>+</sup>; Elemental analysis, Found: C, 57.95; H, 5.05; N, 11.27. Calculated for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>: C, 57.88; H, 5.13; N, 11.25.

**Ethyl [6-(2-mercaptoquinolin-3-yl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4b of 2b&3a)**

Yield 61%, pale yellow solid, mp(°C) 213-214, <sup>1</sup>H NMR (DMSO d<sub>6</sub>), δ 7.85 (d, 1H, Ar-H), 7.79 (d, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H), 7.7 (d, 1H, Ar-H), 2.71 (s, 2H, CH<sub>2</sub>), 3.55 (s, 3H, CH<sub>3</sub>), 4.22 (q, 2H, CH<sub>2</sub>), 1.21 (t, 3H, CH<sub>3</sub>), 2.1 (s, 1H, NH), 3.35 (s, 1H, CH), 2.2 (s, 1H, NH), 11.7 (s, 1H, SH); m/z (%) [M]<sup>+</sup> : [357]<sup>+</sup>; Elemental analysis, Found: C, 60.39; H, 5.29; N, 11.81. Calculated for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S: C, 60.49; H, 5.36; N, 11.76.

**Methyl [6-(2-selenoquinolin-3-yl)-4-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4c of 2a&3b)**

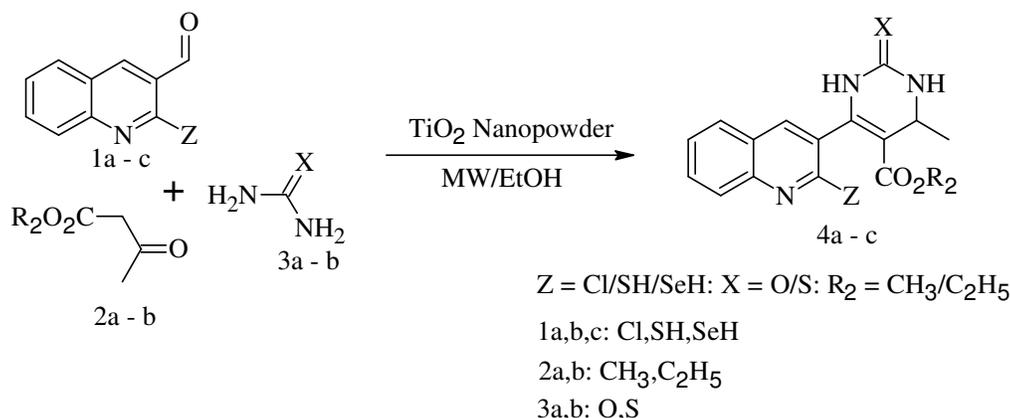
Yield 58%, pale brown solid, mp(°C) 236-237, <sup>1</sup>H NMR (DMSO d<sub>6</sub>), δ 7.91 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H), 7.31 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H), 7.31 (d, 1H, Ar-H), 2.6 (s, 2H, CH<sub>2</sub>), 3.5 (s, 3H, CH<sub>3</sub>), 1.25 (t, 3H, CH<sub>3</sub>), 2.0 (s, 1H, NH), 3.45 (s, 1H, CH), 2.2 (s, 1H, NH), 11.5 (s, 1H, SH); m/z (%) [M]<sup>+</sup> : [406]<sup>+</sup>; Elemental analysis, Found: C, 50.31; H, 4.15; N, 10.28. Calculated for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>SSe: C, 50.25; H, 4.22; N, 10.34.

**Methyl [6-(2-selenoquinolin-3-yl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4c of 2a&3a)**

Yield 52%, pale brown solid, mp(°C) 245-247, <sup>1</sup>H NMR (DMSO d<sub>6</sub>), δ 7.91 (d, 1H, Ar-H), 7.59 (d, 1H, Ar-H), 7.31 (d, 1H, Ar-H), 7.75 (d, 1H, Ar-H), 7.31 (d, 1H, Ar-H), 2.75 (s, 2H, CH<sub>2</sub>), 3.5 (s, 3H, CH<sub>3</sub>), 1.26 (t, 3H, CH<sub>3</sub>), 2.1 (s, 1H, NH), 3.41 (s, 1H, CH), 2.0 (s, 1H, NH), 11.3 (s, 1H, SH); m/z (%) [M]<sup>+</sup> : [390]<sup>+</sup>; Elemental analysis, Found: C, 52.25; H, 4.31; N, 10.70. Calculated for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>Se: C, 52.31; H, 4.39; N, 10.77.

**Ethyl [6-(2-selenoquinolin-3-yl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4c of 2b&3a)**

Yield 49%, pale brown solid, mp(°C) 262-265, <sup>1</sup>H NMR (DMSO d<sub>6</sub>), δ 8.05 (d, 1H, Ar-H), 7.75 (d, 1H, Ar-H), 7.41 (d, 1H, Ar-H), 7.69 (d, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 2.72 (s, 2H, CH<sub>2</sub>), 3.6 (s, 3H, CH<sub>3</sub>), 4.3 (q, 2H, CH<sub>2</sub>), 1.26 (t, 3H, CH<sub>3</sub>), 2.3 (s, 1H, NH), 3.38 (s, 1H, CH), 2.2 (s, 1H, NH), 11.4 (s, 1H, SeH); m/z (%) [M]<sup>+</sup> : [404]<sup>+</sup>; Elemental analysis, Found: C, 53.41; H, 4.81; N, 10.30. Calculated for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>Se: C, 53.47; H, 4.74; N, 10.39.



**Scheme 1.** synthetic route for the synthesis of quinoline conjugated dihydropyrimidinones.

**Ethyl [6-(2-selenoquinolin-3-yl)-4-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetate (4c of 2b&3b)**

Yield 51%, pale brown solid, mp(°C) 251-253,  $^1\text{H}$  NMR (DMSO  $d_6$ ),  $\delta$  7.86 (d, 1H, Ar-H), 7.7 (d, 1H, Ar-H), 7.5 (d, 1H, Ar-H), 7.6 (d, 1H, Ar-H), 7.4 (d, 1H, Ar-H), 2.75 (s, 2H,  $\text{CH}_2$ ), 3.7 (s, 3H,  $\text{CH}_3$ ), 4.41 (q, 2H,  $\text{CH}_2$ ), 1.21 (t, 3H,  $\text{CH}_3$ ), 2.2 (s, 1H, NH), 3.32 (s, 1H, CH), 2.1 (s, 1H, NH), 11.6 (s, 1H, SeH); m/z (%)  $[\text{M}]^+$  : [420] $^+$ ; Elemental analysis, Found: C, 51.39; H, 4.51; N, 9.85. Calculated for  $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2\text{SSe}$ : C, 51.43; H, 4.56; N, 10.00.

## RESULTS AND DISCUSSION

Over recent years, semiconductor oxide nanoparticles mediated catalytic reactions have attracted tremendous interest throughout scientific communities due to their higher efficiency, ease of handling, low cost, stability, and recoverability of the reagent from water. In this paper, we describe a general and practical route for the Biginelli cyclocondensation reaction using  $\text{TiO}_2$  nanoparticles as the efficient photo-catalyst under microwave irradiation technique. Two different sets of reaction conditions were examined: (i) Traditional ethanol reflux; (ii) Microwave conditions. This is a novel, one-pot combination that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produces excellent yields of the dihydropyrimidine-2(1*H*)-ones (Scheme 1). In a typical general experimental procedure by using traditional conditions, a solution of  $\alpha$ -dicarbonyl compound, an aldehyde, and urea in ethanol was heated under reflux in the presence of a catalytic amount of  $\text{TiO}_2$  nanoparticles for a certain period of time required to complete the reaction (TLC), resulting in the formation of dihydropyrimidinone. The reaction mixture was then poured into crushed ice, and the solid product separated was filtered and recrystallized. To study the generality of this process, times taken for the synthesis of dihydropyrimidinones were studied and are summarized in Table 1. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be

introduced with high efficiency. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes carrying either electron-donating or - withdrawing substituents afforded high yields of products in high purity. Acid sensitive aldehydes such as furfural worked well without the formation of any side products. Thiourea has been used with similar success to provide the corresponding dihydropyrimidine-(2*H*)-thiones, which are also of much interest with regard to biological activity. Thus, variations in all three components have been accommodated very comfortably. However, under the present reaction conditions  $\alpha$ -ketoaldehydes do not produce the corresponding dihydropyrimidinones; instead they lead to multiple products whose identities are yet to be established.

Here, in continuation of our work (Prakash Naik et al. 2009; Prakash Naik et al. 2009; Prakash Naik et al. 2009) the  $\text{TiO}_2$  nanoparticles were prepared according to the reported procedure, so just to check their size we went for SEM and AFM images finally we found their size is well below 100 nm (Figure 1). Use of just  $\text{TiO}_2$  nanoparticles in refluxing EtOH is sufficient to push the reaction forward. Higher amounts of  $\text{TiO}_2$  nanoparticles improved the result to a greater extent.

The yields are, in general, very high regardless of the structural variations in dicarbonyl compound, aldehyde, or urea. The crude products obtained are of high purity (>95% by  $^1\text{H}$  NMR). Another important aspect of this procedure is survival of a variety of functional groups such as  $\text{NO}_2$ , Cl, OH,  $\text{OCH}_3$  and conjugated  $\text{C}=\text{C}$  double bond under the reaction conditions. Presumably, the reaction may proceed through the  $\text{TiO}_2$  nanoparticles catalyzed formation of an acyl imine intermediate or *N*-alkylidene urea formed by reaction of the aldehyde with urea, the key rate-determining step. Interception of the iminium ion by ethyl acetoacetate produces an openchain ureide which subsequently cyclizes to the dihydropyrimidinones. Because of the 4f empty orbital in the titanium ion, a complex can be formed through a

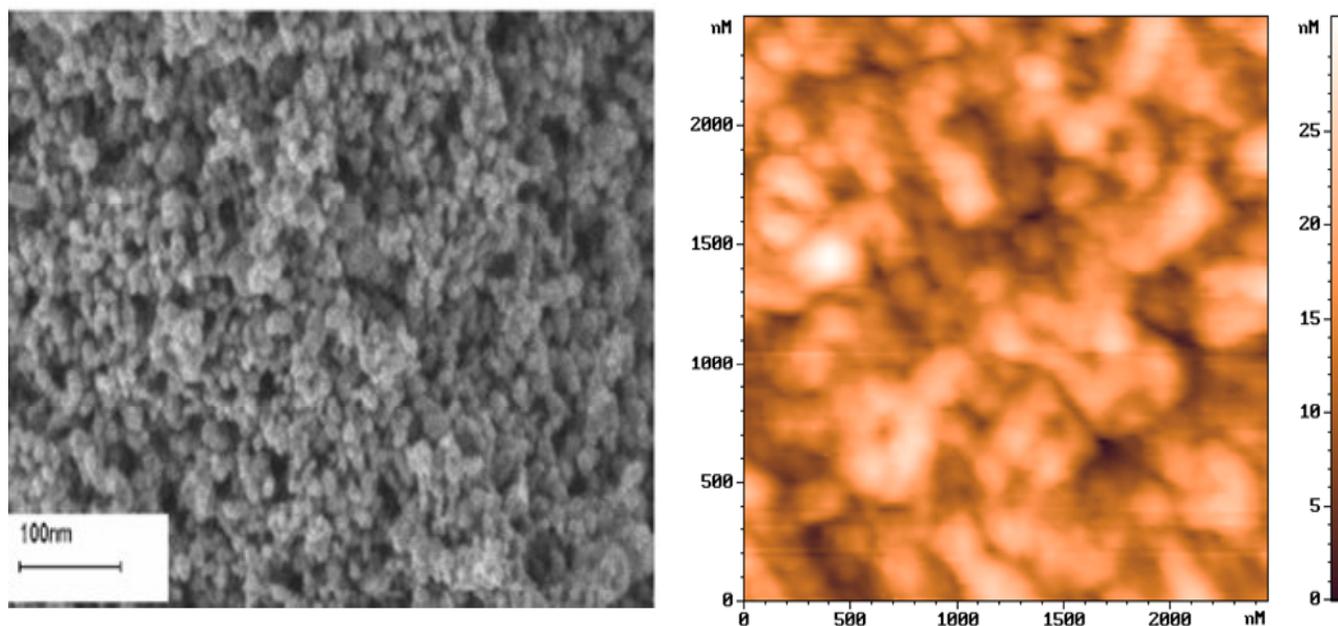
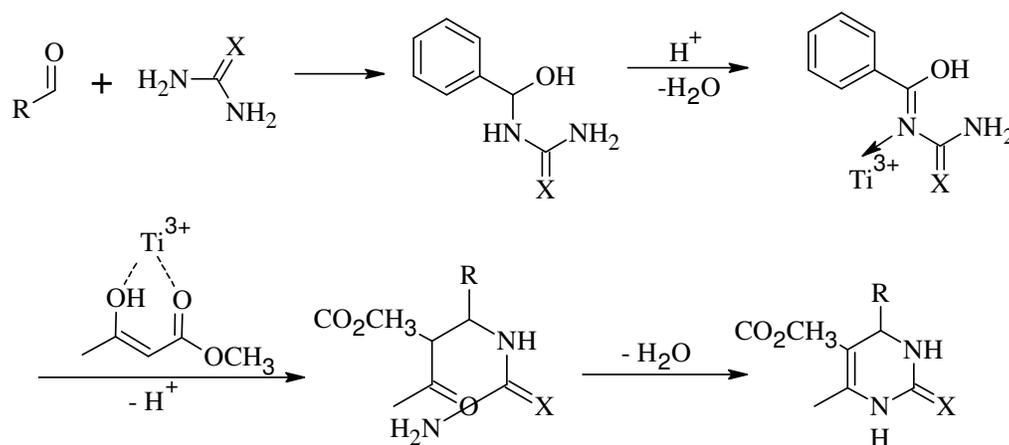


Figure 1. SEM and AFM images of  $\text{TiO}_2$  nanoparticles.



Scheme 2. Proposed reaction mechanism where R=quinoline.

coordinative bond and stabilized by titanium dioxide. So we propose a mechanism similar to that of Kappe (Kappe et al., 1998; Singh et al., 1999) for the Biginelli reaction as in Scheme 2.

## Conclusion

In conclusion, we developed novel pathway for the synthesis of dihydropyrimidin-2(1*H*)-ones by nano  $\text{TiO}_2$  catalyzed, three-component condensation provides an efficient and much improved modification of Biginelli's reaction. Moreover, this method offers several advantages including high yields, short reaction times, and a simple work-up procedure.

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