

Short Communication

TiO₂ Nanoparticles: A Potent Heterogenous Nanocatalyst Mediated One-Pot Tandem Approach for the Environmentally Friendly Synthesis of 3,4-Dihydropyrimidin-2-(1H)-One/Thione Derivatives Under Solvent-Free Conditions

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Abstract

This procedure has developed the use of TiO₂ nanoparticles as an environmentally friendly and highly efficient heterogenous nanocatalyst for the eco-safe, facile and one-pot three-component Biginelli synthesis of biologically active corresponding 3,4-dihydropyrimidin-2-(1H)-one/thione derivatives under solvent-free conditions. This eco-friendly protocol provides high to excellent yields, short reaction times, clean reaction, simplicity and easy work up and mild conditions compared to the traditional method of synthesis. Furthermore, environment-friendly, readily available, low-cost and non-toxic nanocatalyst made this protocol economic and sustainable.

Keywords: TiO₂ Nanoparticles, 3,4-Dihydropyrimidin-2-(1H)-one/thione derivatives, High atom-economy, Environment-friendly procedure, Solvent-free conditions.

1. INTRODUCTION

Synthesis of heterocyclic compounds has attracted great interests due to their wide applicability in life and nature. The compounds with Pyrimidinone ring systems are reported as such, as calcium channel blockers, α -1a-antagonists [1], antihypertensive [2], anticancer [3], anti HIV [4], antibacterial and antifungal [5], antiviral [6], antioxidative [7] and anti-inflammatory [8] agents. In recent decades, a number of methodologies for preparation of 3,4-dihydropyrimidin-2-(1H)-one/thione derivatives via β -keto esters, aldehyde derivatives and urea/thiourea have been reported that is including various catalysts such as CaF [9], Cu(NH₂SO₃)₂ [10],

bakers'yeast [11], Mg–Al–CO₃ [12], [Al(H₂O)₆](BF₄)₃ [13], TBAB [14], Cu(BF₄)₂·xH₂O [15], [Btto][p-TSA] [16], TEAA [17], DBSA [18], Fe₃O₄-halloysite-SO₃H [19], [Et₃NH][HSO₄] [20], Dendrimer-PWA [21], GO-chitosan nanocomposite [22], [Simp]HSO₄ [23], NaNO₃-HPAIL [24], [pyridine-SO₃H]Cl [25] and Fe₃O₄@PEG-SO₃H [26]. Some of these methodologies have limitations such as difficult work-up, toxic and expensive catalysts, low yields, the use of strongly acidic conditions and long time reactions. Today, nanocatalysts [27-36] are a rapidly growing field which often employs nanoparticles in a variety of organic and

inorganic reactions. Due to a field of our program aimed at developing organic synthesis using of environmentally benign nature catalyst [37-43] and because of the above considerations and our interest in the development of Biginelli [44] reaction for the three-component synthesis of 3,4-dihydropyrimidin - 2- (1*H*)-one /thione derivatives with environmentally friendly procedures has become the most important aim of our researches. Finally, we have reported TiO₂ NPs as a highly efficient, readily available and economical heterogenous nanocatalyst for the synthesis of these compounds in high to excellent yields and short reaction times under solvent-free conditions. Environmentally friendly, low-cost, easy to handle and non-toxic catalyst, operational simplicity, purification of products without the need of column chromatography, one-pot and solvent-free conditions are the notable advantages of this eco-friendly procedure.

2. EXPERIMENTAL

2.1. Materials

Melting points of all compounds were determined using an Electro thermal 9100. ¹H NMR spectra were recorded on a Bruker DRX-400 Avance instrument with DMSO-*d*₆ as solvents. All reagents and solvents were purchased from Merck, Fluka and across chemical companies and used without further purification.

2.2. General procedure for preparation of 3,4-dihydropyrimidin – 2 - (1*H*) -one/thione derivatives (4a-r)

A mixture of aldehyde derivatives (**1**, 1.0 mmol; 1a: 0/140 g, 1b: 0/140 g, 1c: 0/120 g, 1d: 0/136 g, 1e: 0/136 g, 1f: 0/149 g, 1g: 0/106 g, 1h: 0/151 g, 1i: 0/136 g, 1j: 0/151 g, 1k: 0/106 g, 1l: 0/124 g, 1m: 0/122 g, 1n: 0/124 g, 1o: 0/122 g, 1p: 0/140 g, 1q: 0/120g , 1r: 0/151 g) and urea/thiourea (**2**, 1.5 mmol; 2a: 0.090 g, 2b: 0.114 g), ethyl/methyl acetoacetate (**3**, 1.0 mmol; 3a: 0.130 g, 3b: 0.116 g) was heated under solvent-free conditions at 70 °C for appropriate time in the presence of TiO₂

NPs (15 mol %; 0.01 g). After completion of the reaction (by thin layer chromatography TLC) the mixture was cooled to R.t and cold water was added and precipitates was separated by filtration. The solid residue was diluted with chloroform (4 ml) and the catalyst was separated. The solid which was dried crystallized from ethanol to afford the pure products (**4a- r**). The reusability of the nano-TiO₂ catalyst was also examined. After each run, the product was filtered, the solvent (CHCl₃) was evaporated and the catalyst residue was washed with CHCl₃ and reused. The catalyst was reusable, although a gradual decline in activity was observed.

2.3. Spectral data of the selected products

5-Methoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4b): Yield: 79%; M.p. 250-252 °C; ¹H NMR (400 MHz, DMSO-*d*₆): 2.31 (3H, s, CH₃), 3.46 (3H, s, OCH₃), 5.62 (1H, s, H_{benzylic}), 7.28-7.34 (3H, m, H_{Ar}), 7.42 (1H, d, *J*=7.2 Hz, H_{Ar}), 7.72 and 9.36(2H, 2s, 2NH).

5-Ethoxycarbonyl -6-methyl -4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4e): Yield: 80%; M.p.202-204°C; ¹H NMR (400 MHz, DMSO-*d*₆): 1.11 (3H , t, *J*= 9.6 Hz, CH₃CH₂), 2.24(3H, s, CH₃), 3.73 (3H, s, OCH₃), 3.99 (2H, q, *J*=9.6 Hz, CH₂O), 5.09 (1H, s, H_{benzylic}), 6.89 (2H, d, *J*= 8.4Hz, H_{Ar}), 7.15(2H, d, *J*= 8.8Hz, H_{Ar}), 7.70 and 9.18 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4- phenyl-3,4-dihydropyrimidin-2(1H)-one (4g): Yield: 85%; M.p. 200-202 °C; ¹H NMR (400 MHz, DMSO-*d*₆): 1.10 (3H, t, *J*= 7.2 Hz, CH₃CH₂), 2.26 (3H, s, CH₃), 3.99 (2H, q, *J*=7.2 Hz, CH₂O), 5.15 (1H, s, H_{benzylic}), 7.26 (3H, d, *J*= 7.2 Hz, H_{Ar}), 7.33 (2H, t, *J*=7.2 Hz, H_{Ar}), 7.76 and 9.21 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4h): Yield: 86%; M.p. 205-207 °C; ¹H NMR (400 MHz, DMSO-d₆): 1.10 (3H, t, *J*= 9.6 Hz, CH₃CH₂), 2.28(3H, s, CH₃), 3.99 (2H, q, *J*=9.2 Hz, CH₂O), 5.27 (1H, s, H_{benzylic}), 7.50-7.53 (2H, m, H_{Ar}), 7.23 (2H, d, *J*= 9.2Hz, H_{Ar}), 7.92 and 9.38 (2H, 2s, 2NH).

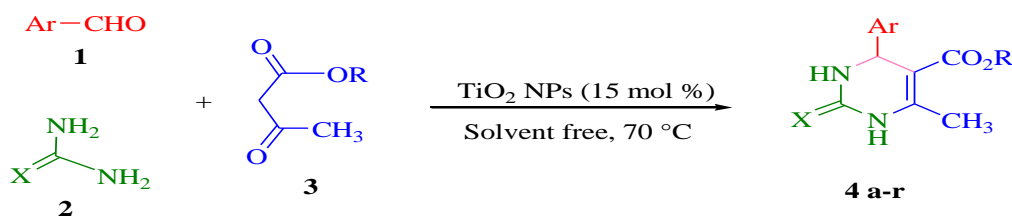
5-Methoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4j): Yield: 89%; M.p. 212-214 °C; ¹H NMR (400 MHz, DMSO-d₆): 2.28(3H, s, CH₃), 3.55 (3H, s, OCH₃), 5.28 (1H, s, H_{benzylic}), 7.52 (2H, d, *J*= 8.4Hz, H_{Ar}), 7.22 (2H, d, *J*= 8.8Hz, H_{Ar}), 7.93 and 9.40 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (4k): Yield: 83%; M.p. 207-209 °C; ¹H NMR (400 MHz, DMSO-d₆): 1.11 (3H, t, *J*= 7.2 Hz, CH₃CH₂), 2.31 (3H, s, CH₃), 4.02 (2H, q, *J*=7.2 Hz, CH₂O), 5.19 (1H, s, H_{benzylic}), 7.23 (2H, d, *J*=7.2 Hz, H_{Ar}), 7.28 (1H, t, *J*=7.2 Hz, H_{Ar}), 7.36 (2H, t, *J*=7.2 Hz, H_{Ar}), 9.68 and 10.36 (2H, 2s, 2NH).

3. RESULTS AND DISCUSSION

Due to the reasonable needs to efficient, readily and eco-safe catalyst, we explored TiO₂ NPs as an environmentally friendly and heterogenous nanocatalyst for synthesis of 3,4-dihydropyrimidin-2-(1H)-one/thione derivatives by the coupling of arylaldehyde derivatives (**1**, 1.0 mmol) and urea/thiourea (**2**, 1.5 mmol), ethyl/methyl acetoacetate (**3**, 1.0 mmol) (Scheme 1). In an initial endeavor benzaldehyde, ethyl acetoacetate and urea were selected as the model substrates and reacted under

different experimental variants. To obtain the optimized reaction conditions, we changed temperature and the amount of catalyst. To establish the catalytic role of TiO₂ NPs, endeavor benzaldehyde, ethyl acetoacetate and urea in the absence of a catalyst. It is important to note that in the absence of a catalyst, no product was observed (Table 1, entry 1). Good yields were obtained in the presence of a catalyst. The best amount of catalyst was 15 mol % (Table 1, entry 4). The higher amount of catalyst did not increase product yields (Table 1, entry 10). Also, the effect of temperature on the reaction has been investigated. No product could be detected in room temperature conditions (Table 1, entry 5). The reaction was investigated by changing temperature from 40-80°C and the high yield of product is obtained in 70 °C temperature (Table 1, entry 4). Consequently, among the tested temperature and the amount of catalyst, the condensation of endeavor benzaldehyde, ethyl acetoacetate and urea was best catalyzed by 15 mol % TiO₂ nanoparticles at 70 °C as the reaction was completed within high to excellent yield (Table 1, entry 4). To ascertain the scope and limitation of the present reaction, with optimized conditions in hand, variety of coupling of arylaldehyde derivatives (**1**, 1.0 mmol) and urea/thiourea (**2**, 1.5 mmol), ethyl/methyl acetoacetate (**3**, 1.0 mmol) under solvent-free conditions was examined and these results were summarized in Table 2. We were pleased to find that all substrates were converted to the corresponding products in high to excellent yields (72-90%).



Scheme 1. Synthesis of 3, 4-dihydropyrimidin-2-(1H)-one/thione derivatives.

Table 1. Optimization of the reaction condition on the synthesis of 4g^a.

Entry	TiO ₂ NPs (mol %)	Temperature (°C)	Time (min)	Isolated Yields (%)
1	Catalyst free	70	420	No product
2	5	70	75	34
3	10	70	40	67
4	15	70	25	85
5	15	rt	420	No product
6	15	40	90	30
7	15	50	65	46
8	15	60	40	68
9	15	80	25	85
10	20	70	25	87

^a Reaction conditions: benzaldehyde (1.0 mmol; 0.106 g), ethyl acetoacetate (1.0 mmol; 0.130 g), urea (1.5 mmol; 0.090 g) and TiO₂ NPs were heated under various temperatures for the appropriate time.

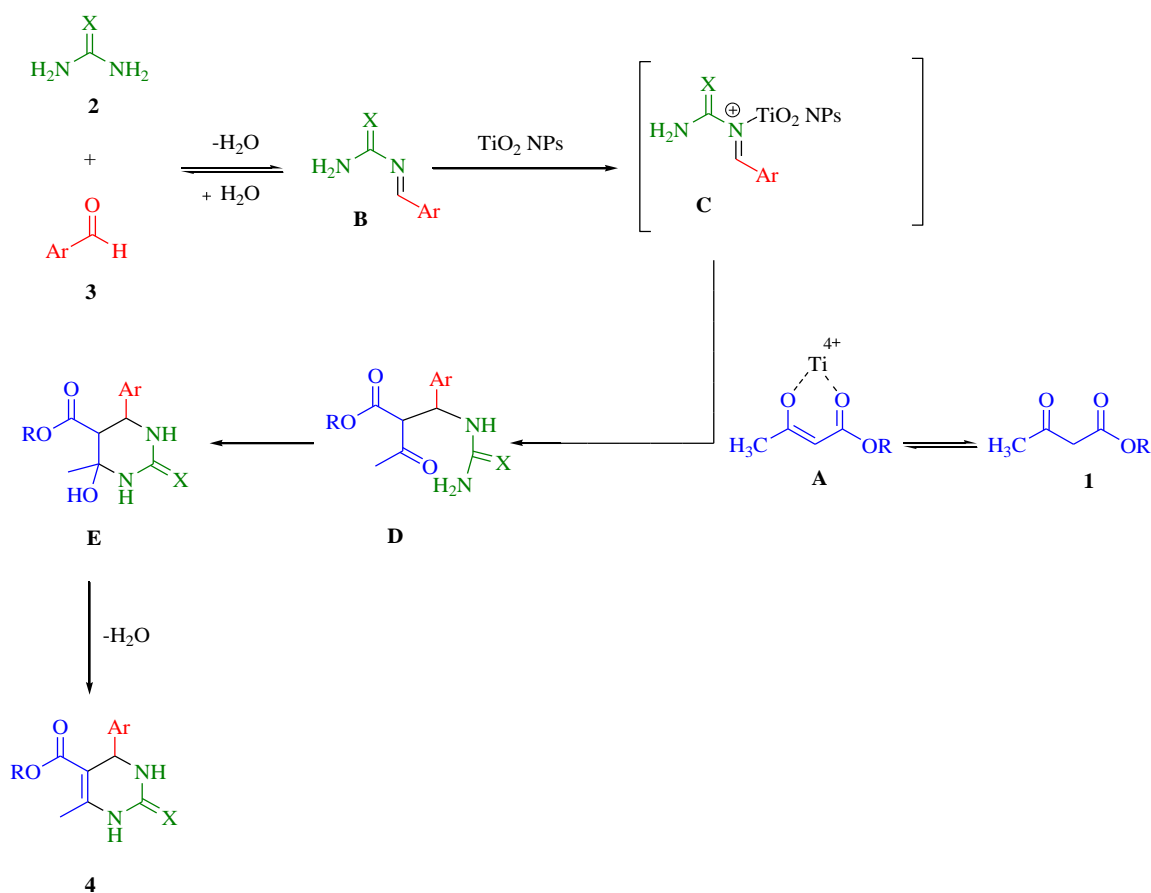
Table 2. TiO₂ NPs catalyzed synthesis of 3,4-dihydropyrimidin-2-(1H)-one/thione derivatives.

Entry	Ar	R	X	Product	Time (min)	Yield % ^a	M.p. °C	Lit. M.p. °C
1	2-Cl-C ₆ H ₄	C ₂ H ₅	O	4a	40	76	221-223	220-223 ¹⁰
2	2-Cl-C ₆ H ₄	CH ₃	O	4b	35	79	250-252	248-252 ¹⁰
3	4-Me-C ₆ H ₄	C ₂ H ₅	O	4c	25	88	203-205	204-205 ¹¹
4	3-MeO-C ₆ H ₄	C ₂ H ₅	O	4d	30	83	151-153	150-151 ¹¹
5	4-MeO-C ₆ H ₄	C ₂ H ₅	O	4e	30	80	202-204	202-203 ¹²
6	4-(Me) ₂ N-C ₆ H ₄	C ₂ H ₅	O	4f	30	84	256-258	255-257 ¹²
7	C ₆ H ₅	C ₂ H ₅	O	4g	25	85	200-202	200-202 ¹³
8	4-O ₂ N-C ₆ H ₄	C ₂ H ₅	O	4h	25	86	205-207	207-209 ¹³
9	4-MeO-C ₆ H ₄	C ₂ H ₅	S	4i	35	82	151-153	150-152 ¹³
10	4-O ₂ N-C ₆ H ₄	CH ₃	O	4j	20	89	212-214	214-216 ¹³
11	C ₆ H ₅	C ₂ H ₅	S	4k	25	83	207-209	208-210 ¹³
12	4-F-C ₆ H ₄	CH ₃	S	4l	20	85	209-211	208-210 ¹⁴
13	4-HO-C ₆ H ₄	C ₂ H ₅	O	4m	40	72	231-233	230-232 ¹⁴
14	4-F-C ₆ H ₄	C ₂ H ₅	O	4n	20	89	176-178	174-176 ¹⁴
15	3-HO-C ₆ H ₄	C ₂ H ₅	O	4o	40	75	166-168	163-166 ¹⁵
16	3-Cl-C ₆ H ₄	C ₂ H ₅	O	4p	40	73	192-194	191-193 ¹⁵
17	4-Me-C ₆ H ₄	CH ₃	O	4q	20	85	202-204	200-203 ¹⁵
18	2-O ₂ N-C ₆ H ₄	CH ₃	O	4r	20	90	274-276	274-277 ¹⁵

^a Isolated yield.

Although different mechanistic pathways have been previously proposed [45, 46], we believe that the reaction may proceed through an initial *N*-acylimine **B** formed from aldehyde **3** and urea **2** (Scheme 2). The coordination of the lone-pair of the nitrogen atom in the *N*-acylimine **B** with the TiO₂ NPs could lead to the *in situ*

formation of an *N*-carbamoyliminium ion **C**, which is sufficiently electrophilic to react with the enol form of ethyl acetoacetate **A** affording the open chain intermediate **D**. Further intramolecular cyclization, with lost of H₂O, produce the 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones **4**.



Scheme 2. Proposed mechanistic route for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones.

Also a comparison of catalytic ability of some of catalysts reported in the literature for synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one/thione derivatives are shown in Table 3. This study reveals that TiO₂ nanoparticles have shown its potential to be an alternative eco-safe, readily available and potent heterogenous nanocatalyst for the Biginelli reaction. In addition, the use of solvent-free conditions with high to excellent yields and short reaction times in the reaction with both urea and thiourea are the notable advantages of this present methodology.

4. CONCLUSION

In summary, a facile and environment-friendly methodology for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones using TiO₂ nanoparticles as a potent heterogenous nanocatalyst is described. The present protocol provides economical and efficient methodology for the synthesis of these compounds. And offers several notable advantages over the exiting methods, including low-cost, easy to handle, readily available and non-toxic nanocatalyst, environmentally friendly, short reaction times, operational simplicity,

high to excellent yields, purification of products without the need of column

chromatography, one-pot and solvent-free conditions.

Table 3. Comparison of catalytic ability some of catalysts reported in the literature for synthesis of 4g^a.

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	bakers' yeast	Room temperature	24h/84	[11]
2	Hydrotalcite	Solvent-free, 80 °C	35 min/84	[12]
3	[Al(H ₂ O) ₆](BF ₄) ₃	MeCN, Reflux	20 h/81	[13]
4	Cu(BF ₄) ₂ .xH ₂ O	Room temperature	30 min/90	[15]
5	[Btto][p-TSA]	Solvent-free, 90 °C	30 min/96	[16]
6	triethylammonium acetate	Solvent-free, 70 °C	45min/90	[17]
7	p-dodecylbenzenesulfonic acid	Solvent-free, 80 °C	3 h/94	[18]
8	TiO ₂ NPs	Solvent-free, 70 °C	25 min/85	This work

^aBased on reaction of benzaldehyde, ethyl acetoacetate and urea.

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