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Efficient synthesis of pyrido[2,3-*d*]pyrimidine-7-carboxylic acids catalyzed by a TiO_2/SiO_2 nanocomposite in aqueous media at room temperature

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Abstract: A novel and efficient synthesis of eight 5-aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-7-carboxylic acids using a TiO_2/SiO_2 nanocomposite with a molar ratio of 1:1 as a recyclable heterogeneous catalyst is described. The desired products, five of which are new, are formed in short reaction times (2–3 h) with high to excellent yields (94%–98%) under very moderate reaction conditions (room temperature, aqueous media).

Keywords: 1,3-dimethyl barbituric acid; 4-substituted phenylmethylidenepyruvic acids; aqueous media; pyrido[2,3-*d*]pyrimidine-7-carboxylic acids; recyclability of catalyst; TiO_2/SiO_2 nanocomposite.

1 Introduction

Metal nanoparticles (NPs), especially metal oxide NPs, are increasingly considered to be an efficient and promising family of novel heterogeneous catalysts. They were shown to have notable advantages such as high catalytic activity, good reusability, improved selectivity, and generally a broad range of applications in various organic transformations [1]. Among them, TiO_2 NPs have been prepared with different particle sizes and crystalline modifications, and used as heterogeneous catalysts for various organic reactions [2–4]. Moreover, the catalytic activity of TiO_2 NPs was significantly improved after covering them with silica shells. TiO_2/SiO_2 nanocomposites are important for their unique properties such as electronic properties and large specific surface area, and can be used effectively in synthetic organic chemistry [5].

Pyrimidine derivatives constitute a privileged class of heterocycles because of their synthetic versatility and significant biological activities. Among the latter are antibacterial, antifungal [6], anticancer [7], analgesic, antiviral [8], antitubercular [9], anti-HIV [10], tyrosine kinase-inhibiting [11], antimalarial [12], anti-inflammatory [13], and diuretic [14] activities. Herein, we wish to report a successful synthesis of pyrido[2,3-*d*]pyrimidine-7-carboxylic acids **4** in aqueous media using a TiO_2/SiO_2 nanocomposite with a molar ratio of 1:1 as an efficient heterogeneous catalyst (Scheme 1). This catalytic protocol involves a cyclocondensation reaction of 4-substituted phenylmethylidenepyruvic acids, which are easily prepared according to a known procedure [15], with ammonium acetate and 1,3-dimethyl barbituric acid. Although two synthetic routes have been developed previously for the synthesis of these compounds, we consider this new procedure as an attractive synthetic alternative. The reported methods use the same starting materials in water as reaction media under reflux [16], or catalyzed by ZnO NPs at 70°C under solvent-free conditions [17]. Our efforts were aimed at the use of the catalytic abilities of TiO_2/SiO_2 nanocomposites in water under less harsh conditions for the synthesis of the compounds mentioned previously.

2 Results and discussion

A green and efficient preparation of 5-aryl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-7-carboxylic acid **4** was developed through the condensation of 4-substituted phenylmethylidenepyruvic acids **1**, ammonium acetate **2**, and 1,3-dimethyl barbituric acid **3**, in the presence of a catalytic amount of TiO_2/SiO_2 nanocomposite (15 mol%) at room temperature in water (Scheme 1).

TiO_2/SiO_2 nanocomposite in the molar ratio of 1:1 was prepared using a literature procedure [18]. The X-ray powder diffraction (XRD) pattern of the nanocomposite showed the existence of anatase-TiO_2 in an amorphous silica matrix. The transmission electron microscopy (TEM) image of the nanocomposite showed that all composites have a grainy structure with nanoparticle sizes of 5–9 nm. The chemical composition of as-prepared nanocomposite was determined by X-ray fluorescence (XRF) technique and the results showed that the composite consists of

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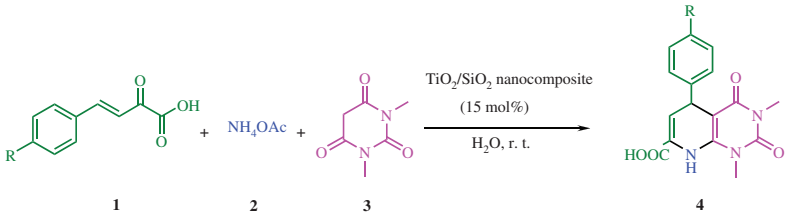


1a, 4a R = H, **1b**, **4b** R = Br, **1c**, **4c** R = Cl, **1d**, **4d** R = F, **1e**, **4e** R = OH, **1f**, **4f** R = OCH_3, **1g**, **4g** R = CH_3, **1h**, **4h** R = NO_2

Scheme 1: Synthesis of pyrido[2,3-*d*]pyrimidine-7-carboxylic acids (**4a–h**) using TiO_2/SiO_2 nanocomposites as catalyst.

55% TiO_2 and 45% SiO_2 (the molar ratio of TiO_2 to SiO_2 in the composite was approximately 1:1). Both XRD and TEM images of the as-synthesized nanocomposite have been presented in a previously published article [19].

In the present work, optimized reaction conditions were obtained in a model system using phenylmethylidenepyruvic acid (**1a**; R = H), ammonium acetate (**2**), and 1,3-dimethyl barbituric acid (**3**) to afford the corresponding product (**4a**; R = H) under various reaction conditions including different amounts of TiO_2/SiO_2 nanocomposite as catalyst (Scheme 1 and Table 1). In the absence of catalyst, 74% of the product was obtained after 5 h in refluxing H_2O (entry 1). The optimization of the catalyst loading showed that 15 mol% of catalyst was sufficient to effectively catalyze the reaction (entries 2–4). When comparing the catalytic efficiency of the TiO_2/SiO_2 nanocomposite with two commercial nanopowders, TiO_2 NPs (10–30 nm, anatase-TiO_2), and SiO_2 NPs (20 nm, nonporous), it was observed that the use of 20 mol% of the TiO_2 NPs and the SiO_2 NPs alone produced the desired product **4a** in 77% and 64% yields, respectively (entries 5 and 6).

In further tests, it was found that heating under reflux in H_2O did not improve the yield and the reaction time in the presence of the catalyst (entries 3 and 7). Finally, it was found that the best product yields were obtained in aqueous media (entries 3 and 8–10).

The generality of the method was corroborated using several 4-substituted phenylmethylidenepyruvic acids under optimized conditions (Table 2). The isolated compounds (**4a–h**) were characterized by infrared (IR), proton nuclear magnetic resonance (^{1}H NMR) and carbon-13

Table 1: Synthesis of pyrido[2,3-*d*]pyrimidine-7-carboxylic acid (**4a**; R = H) under different conditions (Scheme 1).[a]

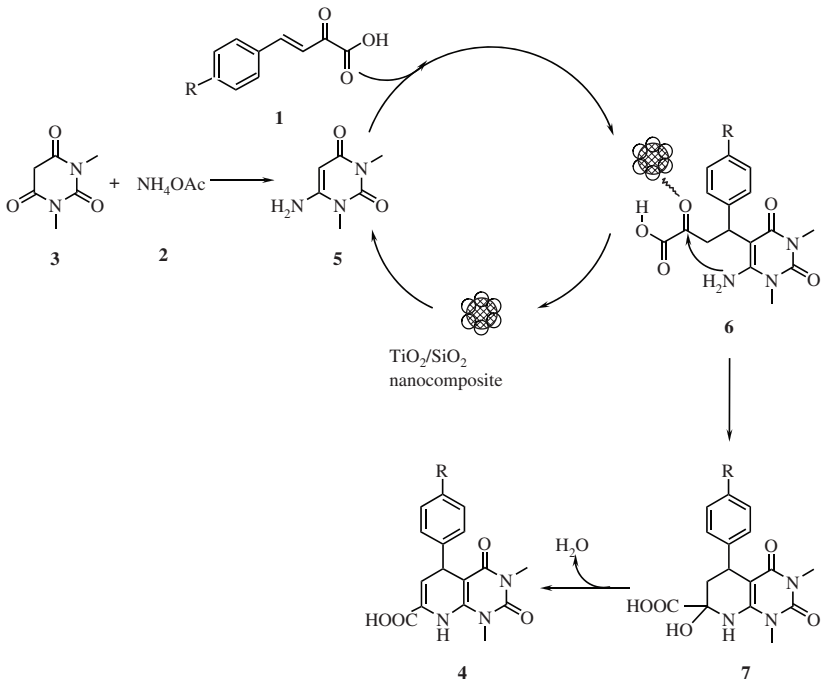
Entry	Nanocatalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)[b,c]
1	No catalyst	H_2O	Reflux	5	74
2	TiO_2/SiO_2 (10%)[a]	H_2O	r. t.	4	82
3	TiO_2/SiO_2 (15%)[a]	H_2O	r. t.	3	96
4	TiO_2/SiO_2 (20%)[a]	H_2O	r. t.	3	95
5	Nano-TiO_2 (20%)	H_2O	r. t.	5	77
6	Nano-SiO_2 (20%)	H_2O	r. t.	6	64
7	TiO_2/SiO_2 (15%)[a]	H_2O	Reflux	2	96
8	TiO_2/SiO_2 (15%)[a]	EtOH	r. t.	3	86
9	TiO_2/SiO_2 (15%)[a]	CH_3CN	r. t.	3	75
10	TiO_2/SiO_2 (15%)[a]	CH_2Cl_2	r. t.	3	71

[a]According to the molar ratio of the TiO_2 to the SiO_2 in the TiO_2/SiO_2 composite (1:1), the catalyst loadings in mol% with respect to TiO_2 were calculated to be 14, 21, and 28 mg for 10, 15, and 20 mol% of the catalyst, respectively; [b]reaction conditions: a mixture of phenylmethylidenepyruvic acid (**1a**; R = H) (1 mmol), ammonium acetate **2** (1.2 mmol), 1,3-dimethyl barbituric acid **3** (1 mmol), and TiO_2/SiO_2 nanocomposite in 3 mL of solvent was stirred at the indicated temperatures and times; [c]isolated yield.

Table 2: Synthesis of pyrido[2,3-*d*]pyrimidine-7-carboxylic acids (**4**; R = various) from 4-substituted phenylmethylidenepyruvic acids (**1**; R = various), ammonium acetate (**2**), 1,3-dimethyl barbituric acid (**3**), and a TiO_2/SiO_2 nanocomposite as catalyst (Scheme 1).[a]

Product	R	Yield (%)[b]	Time (h)	m. p. (°C)	
				Observed	Literature
4a	H	95	3	221–223	–
4b	Br	98	2	251–253	–
4c	Cl	96	2.5	237–239	236–238 [16]
4d	F	96	3	245–247	–
4e	OH	94	3	254–256	–
4f	OCH_3	94	2.5	226–228	228–229 [16]
4g	CH_3	96	2.5	248–250	248–249 [16]
4h	NO_2	97	2	239–241	–

[a]Reaction conditions: a mixture of 4-substituted phenylmethylidenepyruvic acids (**1**; R = various) (1 mmol), ammonium acetate **2** (1.2 mmol), 1,3-dimethyl barbituric acid 3 (1 mmol), and TiO_2/SiO_2 nanocomposite (15 mol%; 21 mg) in 3 mL of water was stirred at room temperature for the indicated times; [b]yields refer to those of pure isolated products that were characterized by IR, ^{1}H, and ^{13}C NMR spectral data and by elemental analyses.



Scheme 2: The proposed mechanism for the formation of **4**.

nuclear magnetic resonance (^{13}C NMR) data and also by elemental analyses.

A mechanism for the catalytic behavior of TiO_2/SiO_2 nanocomposite is provided in Scheme 2. This catalytic cycle is preceded by the reaction of 1,3-dimethyl barbituric acid (**3**) with ammonium acetate (**2**) to generate enaminone (**5**). Then, nanocatalyst participate in the subsequent Michael addition of **5** to phenylmethylidenepyruvic acid **1** to produce intermediate **6**. Further intermolecular cyclization of **6** affords the product **4** after dehydration.

The recyclability of the catalyst was explored using a simple procedure described in the Experimental section and reused up to four times for the synthesis of **4a** with a moderate decrease in catalytic activity (product yields: 95%, 93%, 91%, and 90%, respectively).

3 Conclusion

We found that TiO_2/SiO_2 nanocomposite successfully catalyzes the cyclocondensation reaction of 4-substituted phenylmethylidenepyruvic acids, ammonium acetate, and 1,3-dimethyl barbituric acid to afford pyrido[2,3-*d*] pyrimidine-7-carboxylic acids in aqueous media. Using the inexpensive, recyclable, and nontoxic catalyst mild reaction conditions, high yields and short reaction times at room temperature are the advantages of this protocol.

4 Experimental section

4.1 Materials and methods

All chemicals used in this work were purchased from Merck and Fluka in high purity (provided by Kimiaexir Chemical Company, Tehran, Iran). Melting points were determined with an Electrothermal 9100 apparatus (East Tehran Branch, Islamic Azad University, Tehran, Iran). FT-IR spectra were obtained using a Bruker Equinox 55 Golden Gate Micro-ATR spectrometer (Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 AVANCE at 300 and 75 MHz, respectively, using tetramethylsilane as an internal standard and deuterated dimethylsulfoxide as a solvent (Sharif University of Technology, Tehran, Iran). Elemental analyses were carried out using a Foss-Heraeus CHN-O-Rapid analyzer (Polymer and Petrochemical Institute, Tehran, Iran). The TEM image of the catalyst was obtained on a Philips EM208 transmission electron microscope under acceleration (Nuclear Science and Technology Research Institute AEOI, Tehran, Iran). Powder XRD data were determined on a Philips, X'Pert diffractometer using CuKα radiation ($\lambda = 1.54$ Å) (Nuclear Science and Technology Research Institute AEOI). The composition analysis of the catalyst was carried out by XRF spectroscopy using an Oxford

ED 2000 equipment (Nuclear Science and Technology Research Institute AEOI).

4.2 General procedure for the preparation of the TiO_2/SiO_2 nanocomposite catalyst [18]

Titanium tetrachloride (2 mL) was added dropwise into deionized water (200 mL) in an ice-water bath with strong magnetic stirring. After the hydrolysis was completed, the released HCl was neutralized by adding dilute NH_4OH to adjust the pH to 7. The produced solid was filtered and washed with distilled water. The precipitate was dispersed into a 0.3 M HNO_3 aqueous solution (200 mL) to remove all the chloride ions. The mixture was then refluxed under strong stirring at 70°C for 16 h, as the titania sol was prepared. Tetraethylorthosilicate (25 mL) was added dropwise into the above sol and stirred at 70°C for approximately 0.5 h. Finally, the TiO_2/SiO_2 nanocomposite powder was filtered and washed with distilled water and then dried in air at ambient temperature.

4.3 General procedure for the synthesis of compounds 4a–k

A mixture of 4-substituted phenylmethylidenepyruvic acids **1** (1 mmol), ammonium acetate (**2**, 1.2 mmol), 1,3-dimethyl barbituric acid (**3**, 1 mmol), and TiO_2/SiO_2 nanocomposite (21 mg, 15 mol%) in H_2O (3 mL) was stirred at room temperature for 3 h. After completion of the reaction [as monitored by thin layer chromatography in ethyl acetate-*n*-hexane (2:1) as thin layer chromatography solvent], the reaction mixture was filtered and the solid mass was diluted with dimethylformamide (2 mL). The resulting mixture was centrifuged at 2000–3000 rpm for 5 min to remove the TiO_2/SiO_2 nanocatalyst for reusing after drying at 80°C for several hours *in vacuo*. The organic solution was poured into ice-cold water (5 mL), filtered, and washed with aqueous ethanol to afford the pure products **4**.

4.4 Spectroscopic and physical data

4.4.1 1,3-Dimethyl-2,4-dioxo-5-phenyl-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-7-carboxylic acid (4a)

White solid; yield: 0.30 g (96%), m. p. 221°C–223°C. – ^{1}H NMR: $\delta = 3.05$ (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 4.61 (1H, d, $J = 5.0$ Hz, H-5), 5.99 (1H, d, $J = 5.0$ Hz, H-6), 7.49 (3H, m, H_{Ar}), 7.59 (1H, s, NH), 7.70 (2H, m, H_{Ar}), 13.51 (1H, s, COOH) ppm. – ^{13}C NMR: $\delta = 26.9$, 29.2, 37.4, 87.0, 116.2, 122.3, 123.8, 126.8, 129.1, 140.3, 146.7, 151.4, 160.2, 164.3 ppm. – IR (KBr): $\nu_{max} = 3339$, 3220, 2956, 2858, 1708, 1650, 1621 cm^{-1}. – Analysis calcd. for $C_{16}H_{15}N_3O_4$ (313.31): C 61.34, H 4.83, N 13.41; found C 61.23, H 5.03, N 13.27%.

4.4.2 5-(4-Bromophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-7-carboxylic acid (4b)

White solid; yield: 0.38 g (98%), m. p. 251°C–253°C. – ^{1}H NMR: $\delta = 3.06$ (3H, s, NCH_3), 3.44 (3H, s, NCH_3), 4.65 (1H, d, $J = 5.4$ Hz, H-5), 6.01 (1H, d, $J = 5.4$ Hz, H-6), 7.24 (2H, d, $J = 8.1$ Hz, H_{Ar}), 7.61 (1H, s, NH), 8.40 (2H, d, $J = 8.1$ Hz, H_{Ar}), 13.49 (1H, s, COOH) ppm. – ^{13}C NMR: $\delta = 27.6$, 29.1, 37.6, 86.5, 116.4, 126.7, 127.3, 128.2, 133.8, 139.5, 147.1, 151.2, 159.8, 163.1 ppm. – IR (KBr): $\nu_{max} = 3340$, 3294, 2963, 2860, 1711, 1663, 1564 cm^{-1}. – Analysis calcd. for $C_{16}H_{14}BrN_3O_4$ (392.21): C 49.00, H 3.60, N 10.71; found C 49.14, H 3.51, N 10.81%.

4.4.3 1,3-Dimethyl-2,4-dioxo-5-(4-fluorophenyl)-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-7-carboxylic acid (4d)

White solid; yield: 0.382 g (96%), m. p. 245°C–247°C. – ^{1}H NMR: $\delta = 3.02$ (3H, s, NCH_3), 3.43 (3H, s, NCH_3), 4.60 (1H, d, $J = 5.4$ Hz, H-5), 5.97 (1H, d, $J = 5.4$ Hz, H-6), 7.31 (4H, m, H_{Ar}), 7.58 (1H, s, NH), 13.38 (1H, s, COOH) ppm. – ^{13}C NMR: $\delta = 26.5$, 29.3, 38.1, 88.0, 116.1, 117.7, 126.1, 127.7, 141.9, 146.5, 151.5, 157.0, 158.7, 162.8 ppm. – IR (KBr): $\nu_{max} = 3339$, 3251, 2960, 2848, 1709, 1660, 1618 cm^{-1}. – Analysis calcd. for $C_{16}H_{14}FN_3O_4$ (331.30): C 58.01, H 4.26, N 12.88; found C 58.31, H 4.40, N 12.65%.

4.4.4 1,3-Dimethyl-2,4-dioxo-5-(4-hydroxyphenyl)-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-7-carboxylic acid (4e)

White solid; yield: 0.31 g (94%), m. p. 254°C–256°C. – ^{1}H NMR: $\delta = 3.05$ (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 4.595 (1H, d, $J = 5.2$ Hz, H-5), 6.03 (1H, d, $J = 5.2$ Hz, H-6), 6.98 (2H, d, $J = 8.3$ Hz, H_{Ar}), 7.22 (2H, d, $J = 8.3$ Hz, H_{Ar}), 7.60 (1H, s, NH), 9.17 (1H, s, OH), 13.46 (1H, s, COOH) ppm. – ^{13}C NMR: $\delta = 27.3$, 29.5, 37.6, 86.9, 115.9, 128.0, 130.4, 136.5, 140.6, 145.8, 148.3, 151.2, 160.0, 164.1 ppm. – IR (KBr): $\nu_{max} = 3464$, 3336, 3260, 2964, 2853, 1714, 1659, 1631 cm^{-1}. – Analysis calcd. for

$C_{16}H_{15}N_3O_5$ (329.31): C 58.36, H 4.59, N 12.76; found C 58.21, H 4.77, N 12.88%.

4.4.5 1,3-Dimethyl-2,4-dioxo-5-(4-nitrophenyl)-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-7-carboxylic acid (4h)

White solid; yield: 0.35 g (98%), m. p. 239°C–241°C. – ^{1}H NMR: $\delta = 3.07$ (3H, s, NCH_3), 3.44 (3H, s, NCH_3), 4.63 (1H, d, $J = 5.5$ Hz, H-5), 5.99 (1H, d, $J = 5.5$ Hz, H-6), 7.42 (2H, d, $J = 8.6$ Hz, H_{Ar}), 7.60 (1H, s, NH), 8.03 (2H, d, $J = 8.6$ Hz, H_{Ar}), 13.54 (1H, s, COOH) ppm. – ^{13}C NMR: $\delta = 27.4$, 29.3, 37.8, 88.1, 115.5, 124.1, 126.4, 126.8, 142.5, 144.0, 148.2, 150.8, 159.6, 164.0 ppm. – IR (KBr): $\nu_{max} = 3338$, 3246, 2955, 2852, 1709, 1657, 1618 cm^{-1}. – Analysis calcd. for $C_{16}H_{14}N_4O_6$ (358.31): C 53.63, H 3.94, N 15.64; found C 53.46, H 3.84, N 15.49%.

5 Supporting information

Copies of the NMR spectra of **4a**, **4b**, and **4h** are given as Supporting Information available online (https://doi.org/10.1515/znb-2018-0076).

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Graphical synopsis

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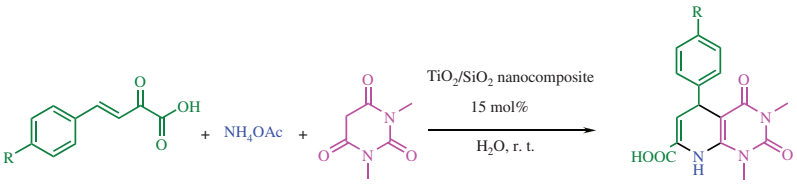

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