A Clean Procedure for Synthesis of Pyrido[*d*]Pyrimidine Derivatives Under Solvent-Free Conditions Catalyzed by ZrO_2 Nanoparticles

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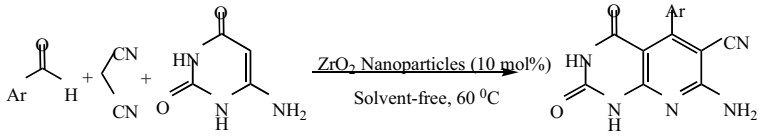
Abstract: A simple one-pot method for the preparation of 7-amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitriles **4** from aromatic aldehydes, malononitrile and 4(6)-aminouracil in the presence of ZrO_2 nanoparticles (ZrO_2 NPs) as an efficient heterogeneous catalyst is described. The procedure has the advantages of high yields (86-97%), short reaction time (2h) and an environmentally friendly specificity.



Keywords: Solvent-free, tandem knoevenagel-michael addition, tetrahydropyrido[d]pyrimidine, ZrO_2 nanoparticles.

INTRODUCTION

Pyridopyrimidine and its derivatives are of considerable interest. They possess a wide range of biological properties such as antibacterial [1], antiasthmatic, antiallergic, antifolate [2], tyrosine kinase [3], antimicrobial [4], calcium channel antagonists [5], anti-inflammatory and analgesic [6], antihypertensive [7], antileishmanial [8], tuberculostatic [9], anticonvulsants [10], diuretic and potassium-sparing [11], antiaggressive [12] activities. In this paper, we have described a very simple procedure for the preparation of 7-amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives **4** (Fig. **1**) under solvent-free conditions.

In recent years, it has been recognized a gradual change from classical reaction conditions to more environmentally friendly routes [13]. One of these efficient synthetic methods is to perform reactions on the surface of solid which holds significant potential for several reasons such as: (a) higher reactivity in comparison to usual solution counterpart, (b) easier isolation of products, (c) easier separation and recycling of the catalysts, (d) reduction of the waste generation and (e) selectivity and reactivity of the catalysts which often are comparable to those of enzymes [14-18]. Several inorganic oxides such as SiO_2, Al_2O_3, etc. have commonly been used for surface organic chemistry [19]. Thus, in continuation of our previous study on the development of new facile routes in heterocyclic synthesis, we considered ZrO_2 nanoparticles (ZrO_2 NPs) to be an efficient catalyst for the synthesis of tetrahydropyrido [*d*]pyrimidine derivatives as a class of important biologically active compounds *via* a three-component reaction of aromatic aldehydes, malononitrile and 4(6)-aminouracil.

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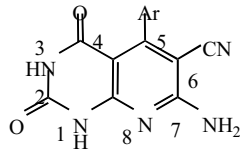

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Fig. (1). Structure of pyrido[*d*]pyrimidine derivatives.

The method that we present here includes the reaction of benzaldehyde derivatives **1**, malononitrile **2** and 4(6)-aminouracil **3** in the presence of catalytic amounts of ZrO_2 NPs (10 mol%) under solvent-free conditions for 2 hours to give the corresponding products **4**(**a-h**) in high yields (86-97%) (Scheme **1**).

RESULT AND DISCUSSION

Following up our previous works on the development of new and efficient methods for the preparation of heterocyclic compounds [20], herein, we describe a convenient, simple and clean procedure to 7-amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitriles **4**, under solvent-free conditions in the presence of ZrO_2 NPs as an efficient, inexpensive, reusable, moisture stable, commercially available and environmentally benign catalyst.

Table **1** shows the results obtained in the reaction of a series of representative aldehydes with malononitrile and 4(6)-aminouracil. Substituent on the aromatic ring did not show any electronic effects in terms of yields under these reaction conditions.

In order to optimize the reaction conditions, first we used 3-nitrobenzaldehyde, **2** and **3** as a model. The experimental results are summarized in Table **2**. After 2 h with 5, 10 and 15 mol% of ZrO_2 NPs, yields of 68, 96 and 96%, respectively, were obtained. It is important to note that in the

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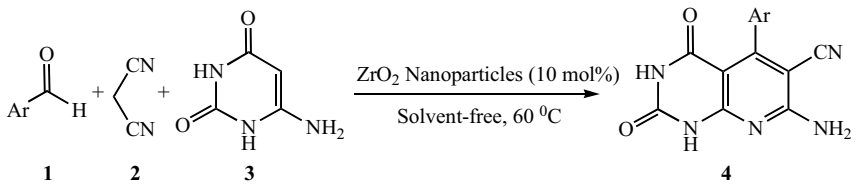


1 2 3 4

Scheme 1. Synthesis of pyrido[*d*]pyrimidine derivatives.

absence of ZrO_2 NPs the reaction time was increased, meanwhile the yield decreased (Table **2**, entries 1-4).

Table 1. ZrO_2 NPs Catalyzed Synthesis of Pyrido[*d*] Pyrimidines 4(a-h) in Solvent-Free Condition

Product	Ar	Yield (%)[a,b]
4a	C_6H_5	89
4b	2-Cl-C_6H_4	91
4c	2,4-Cl_2-C_6H_3	90
4d	3-OH-C_6H_4	97
4e	4-OCH_3-C_6H_4	86
4f	4-CH_3-C_6H_4	91
4g	3-NO_2-C_6H_4	96
4h	4-NO_2-C_6H_4	97

[a]Yields refer to those of pure isolated products characterized by IR, ^{1}H and ^{13}C NMR spectroscopic data and mass spectrometry.
[b]In all cases, reaction time was 2 h stirring at 60°C.

In comparison to the efficiency of catalytic activity of the ZrO_2 NPs with commercially available ZrO_2 bulk, using ZrO_2 NPs, the reaction time was reduced by four times with higher yield than ZrO_2 bulk (Table **2**, entries 3 and 5).

The increasing of temperature to more than 60°C did not play an important role in the yield of product (Table **2**, entries 3 and 6).

A comparison of the same reaction in various reaction media is also presented in Table **2**. Using solvents such as CH_2Cl_2, DMF and EtOH/H_2O were less effective versus solvent-free conditions (Table **2**, entries 3 and 7-9).

Although it is not clear how ZrO_2 NPs act as catalyst for the reaction, on the basis of the surface of metal oxides which exhibit both lewis acid and lewis base character [21], a plausible mechanism for the ZrO_2 catalyzed one-pot reaction of aromatic aldehydes, malononitrile and 4(6)-aminouracil is outlined in Scheme **2**. It is suggested that, ZrO_2 NPs are coordinated to the oxygen of the aromatic aldehyde **1** and activate it for nucleophilic attack [22] by malononitrile **2** to produce alkene **5**, via a Knoevenagel condensation. On the other hand, ZrO_2 NPs also facilitate the Michael addition between alkene **5** and 4(6)-aminouracil **3**, by coordination assistance to generate the Michael adduct **6**. Cyclization of **6** gives intermediate **7**, which could be easily oxidized to corresponding aromatization product **4** after tautomerization of intermediate **8**.

The structure of compounds **4**(**a-h**) were deduced from their ^{1}H NMR, ^{13}C NMR and IR spectral data and their molecular weight confirmed by mass spectrometry. ^{1}H NMR and ^{13}C NMR spectroscopy was especially useful to elucidate the structures of products. The mass spectra of these compounds showed the expected molecular ion signals, selected spectroscopic data have been given in general procedure section.

In order to demonstrate that ZrO_2 can catalyze the two steps of the proposed mechanism, we tried the reaction into two separate steps. In the absence of ZrO_2, the alkene formation is occurred in a long reaction time and in a very low yield. Also, when we used preformed alkene **5** in the reaction with 4(6)-aminouracil **3**, it shows that there was no reaction in the absence of catalyst.

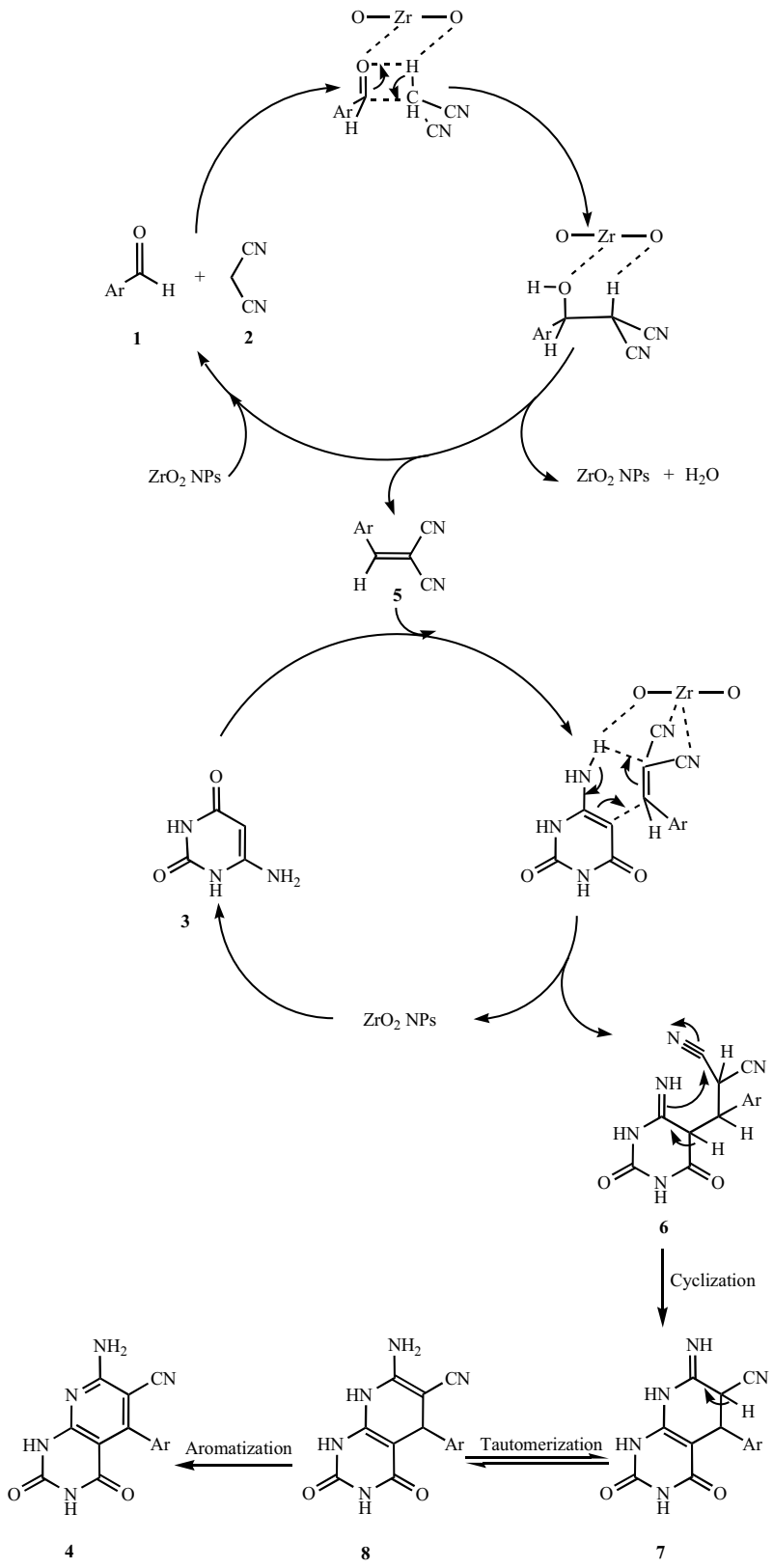
MATERIAL AND METHODS

All chemicals used in this work purchased from Fluka and used without further purification. Melting points were

Table 2. Synthesis of 7-Amino-2,4-Dioxo-5-(3-Nitrophenyl)-1,2,3,4-Tetrahydropyrido[2,3-d]Pyrimidine-6-Carbonitrile (4g) Through the Reaction of 3-Nitrobenzaldehyde, Malononitrile and 4(6)-Aminouracil Under Different Conditions

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	No catalyst	none	60	6	38
2	ZrO_2 NPs (5%)	none	60	2	68
3	ZrO_2 NPs (10%)	none	60	2	96
4	ZrO_2 NPs (15%)	none	60	2	96
5	ZrO_2 bulk (10%)	none	60	8	42
6	ZrO_2 NPs (10%)	none	80	2	97
7	ZrO_2 NPs (10%)	CH_2Cl_2	70	5	45
8	ZrO_2 NPs (10%)	DMF	100	5	58
9	ZrO_2 NPs (10%)	EtOH/H_2O	80	5	73

[a]Isolated yield.



Scheme 2. Proposed mechanism for the one-pot synthesis of tetrahydropyrido[*d*]pyrimidines catalyzed by ZrO_2 NPs under solvent-free conditions.

determined with *Electrothermal 9100* melting point apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR (FTLA 2000) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Bruker DRX-500 AVANCE at 500 and 125 MHz, respectively using TMS as internal standard and DMSO-d_6 as solvent. Mass spectra data were obtained by using GC-MS Hewlet Packard (EI, 70 eV) instrument.

General Procedure

A mixture of aromatic aldehyde **1** (1 mmol), malononitrile (**2**, 1.2 mmol), 4(6)-aminouracil (**3**, 1 mmol) and ZrO_2 NPs (12.3 mg, 10 mol%) was stirred at 60ºC for 2 h. The progress of the reaction was monitored with TLC in 1:1 ethanol–ethyl acetate as TLC solvent. Upon completion of the reaction, DMF (5 mL) was added to the reaction mixture, and ZrO_2 NPs was removed by filtration. The organic solution was then poured into cold water (20 mL), filtered and washed with aqueous ethanol to give the pure product.

7-amino-2,4-dioxo-5-phenyl-1,2,3,4-tetrahydropyrido[2, 3-d]pyrimidine-6-carbonitrile (**4a**): White solid, yield: 0.248 g (89%), m.p.>300ºC. IR (KBr) (ν_{max}/cm^{-1}): 3403, 3331 (NH_2), 3174 (br, 2 NH), 2224 (CN), 1707, 1643 (2 CO) cm^{-1}. ^{1}H-NMR: δ = 7.24 (m, 2 H, H_{Ar}), 7.40 (m, 3 H, H_{Ar}), 7.59 (br s, 2 H, NH_2), 10.89 (s, 1 H, NH), 11.44 (s, 1 H, NH) ppm. ^{13}C-NMR: δ = 88.71 (*C*-CN), 98.32 (C), 115.51 (CH), 127.53(C≡N), 127.65 (2 CH), 128.26 (2 CH), 136.76 (C), 150.31 (C=O), 155.57 (C), 159.03 (C), 160.05 (C-NH_2), 160.86 (C=O) ppm. Mass: ($C_{14}H_9N_5O_2$) *m/z* (*%*)= 278 (M-H)$^+$, 235 (M$^+$-HNCO), 208 (M$^+$-C_2HNO_2), 118 $(C_6H_4N_3)^+$, 77, 57, 43.

7-amino-2,4-dioxo-5-(2-chlorophenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**4b**): White solid, yield: 0.285 g (91%), m.p.>300ºC. IR (KBr) (ν_{max}/cm^{-1}): 3390, 3311 (NH_2), 3188, 3091 (2 NH), 2228 (CN), 1699, 1648 (2 CO) cm^{-1}. ^{1}H-NMR: δ = 7.28 (dd, 1 H, H_{Ar}, ^3J = 7.4, ^4J = 1.5 Hz), 7.38 (t, 1 H, H_{Ar}, ^3J = 7.9 Hz), 7.43 (dt, 1 H, H_{Ar}, ^3J = 7.4, ^4J = 1.5 Hz), 7.51 (d, 1 H, H_{Ar}, ^3J = 7.9 Hz,), 7.75 (br s, 2 H, NH_2), 10.99 (s, 1 H, NH), 11.55 (s, 1 H, NH) ppm. ^{13}C-NMR: δ = 88.32 (*C*-CN), 98.47 (C), 114.78 (CH), 126.90 (C≡N), 128.76 (CH), 128.95 (CH), 129.91 (CH), 130.49 (C), 135.87 (C-Cl), 150.12 (C=O), 155.38 (C), 155.76 (C), 159.72 (C-NH_2), 160.94 (C=O) ppm. Mass: ($C_{14}H_8ClN_5O_2$) *m/z* (*%*)= 313 (M)$^+$, 278 (M$^+$-Cl), 188 $(C_8H_4N_4O_2)^+$, 153, 111, 77, 57, 43.

7-amino-2,4-dioxo-5-(2,4-dichlorophenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**4c**): White solid, yield: 0.312 g (90%), m.p.>300ºC. IR (KBr) (ν_{max}/cm^{-1}): 3377, 3318 (NH_2), 3143, 3068 (2 NH), 2206 (CN), 1699, 1648 (2 CO) cm^{-1}. ^{1}H-NMR: δ = 7.34 (d, 1 H, H_{Ar}, ^3J = 8.2 Hz), 7.50 (d, 1 H, H_{Ar}, ^3J = 8.2 Hz), 7.72 (br s, 1 H, H_{Ar}), 7.81 (br s, 2 H, NH_2), 11.06 (s, 1 H, NH), 11.58 (s, 1 H, NH) ppm. ^{13}C-NMR: δ = 88.10 (*C*-CN), 98.41 (C), 114.68 (CH), 127.21 (C≡N), 128.38 (C-Cl), 130.33 (CH), 131.73 (CH), 133.69 (C), 134.97 (C-Cl), 150.07 (C=O), 154.61 (C), 155.38 (C), 159.79 (C-NH_2), 160.88 (C=O) ppm. Mass: ($C_{14}H_7Cl_2N_5O_2$) *m/z* (*%*)= 348 (M+H)$^+$, 312 (M$^+$-Cl), 277 (M$^+$- C_2HNO_2), 77, 57, 43.

7-amino-2,4-dioxo-5-(3-hydroxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**4d**): Brick-red solid, yield: 0.286 g (97%), m.p.>300ºC. IR (KBr) (ν_{max}/cm^{-1}): 3391, 3322 (NH_2), 3164, 3071 (2 NH), 2237 (CN), 1686, 1649 (2 CO) cm^{-1}. ^{1}H-NMR: δ = 6.59 (s, 1 H, H_{Ar}), 6.62 (d, 1 H, H_{Ar}, ^3J = 7.4 Hz), 6.78 (dd, 1 H, H_{Ar}, ^3J = 8.0, ^4J = 1.9 Hz), 7.18 (t, 1 H, H_{Ar}, ^3J = 8.0 Hz), 7.58 (br s, 2 H, NH_2), 9.46 (s, 1 H, OH), 11.06 (s, 2 H, 2NH) ppm. ^{13}C-NMR: δ = 88.53 (*C*-CN), 98.25 (C), 114.34 (CH), 115.15 (CH), 115.39 (CH), 118.06 (CH), 128.77 (C≡N), 137.92 (C), 150.19 (C=O), 155.43 (C), 156.57 (C), 158.95 (C-OH), 159.79 (C-NH_2), 160.76 (C=O) ppm. Mass: ($C_{14}H_9N_5O_3$) *m/z* (*%*)= 294 (M-H)$^+$, 266 (M$^+$-CO), 251 (M$^+$- HNCO), 118$(C_6H_4N_3)^+$, 77, 57, 43.

7-amino-2,4-dioxo-5-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**4e**): Brick-red solid, yield: 0.266 g (86%), m.p.>300ºC. IR (KBr) (ν_{max}/cm^{-1}): 3404, 3328 (NH_2), 3188, 3150 (2 NH), 2219 (CN), 1700, 1645 (2 CO) cm^{-1}. ^{1}H-NMR: δ = 3.80 (s, 3 H, OCH_3), 6.94 (m, 2 H, H_{Ar}), 7.19 (m, 2 H, H_{Ar}), 7.57 (br s, 2 H, NH_2), 10.59 (s, 1 H, NH), 10.73 (s, 1 H, NH) ppm. ^{13}C-NMR: δ = 55.02 (OCH_3), 88.80 (*C*-CN), 98.32 (C), 112.93 (2 CH), 115.67 (2 CH), 128.55 (C≡N), 129.23 (C), 150.13 (C=O), 155.51 (C), 158.84 (C-O), 159.29 (C), 160.02 (C-NH_2), 160.82 (C=O) ppm. Mass: ($C_{15}H_{11}N_5O_3$) *m/z* (*%*)= 309 (M)$^+$, 265 (M$^+$-HNCO), 121, 77, 57, 43.

7-amino-2,4-dioxo-5-(4-methyphenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**4f**): White solid, yield: 0.267 g (91%), m.p.>300ºC. IR (KBr) (ν_{max}/cm^{-1}): 3394, 3281 (NH_2), 3167, 3031 (2 NH), 2222 (CN), 1699, 1645 (2 CO) cm^{-1}. ^{1}H-NMR: δ = 2.36 (s, 3 H, CH_3), 7.12 (d, 2 H, H_{Ar}, ^3J = 8.0 Hz), 7.20 (d, 2 H, H_{Ar}, ^3J = 8.0 Hz), 7.60 (br s, 2 H, NH_2), 10.89 (s, 1 H, NH), 11.43 (s, 1 H, NH) ppm. ^{13}C-NMR: δ = 20.88 (CH_3), 88.70 (*C*-CN), 98.26 (C), 115.51 (2 CH), 127.48 (2 CH), 128.11(C≡N), 133.70 (C), 137.43 (C), 150.12 (C=O), 155.46 (C), 159.06 (C), 159.94 (C-NH_2), 160.79 (C=O) ppm. Mass: ($C_{15}H_{11}N_5O_2$) *m/z* (*%*)= 292 (M-H)$^+$, 249 (M$^+$-HNCO), 77, 57, 43.

7-amino-2,4-dioxo-5-(3-nitrophenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**4g**): Pale Yellow solid, yield: 0.311 g (96%), m.p.>300ºC. IR (KBr) (ν_{max}/cm^{-1}): 3384, 3321 (NH_2), 3172, 3081 (2 NH), 2216 (CN), 1718, 1662 (2 CO) cm^{-1}. ^{1}H-NMR: δ = 7.75 (m, 2 H, H_{Ar}), 7.77 (br s, 2 H, NH_2), 8.29 (qd, 1 H, H_{Ar}, ^3J = 7.0, ^4J = 1.1 Hz), 11.00 (s, 1 H, NH), 11.54 (s, 1 H, NH) ppm. ^{13}C-NMR: δ = 88.33 (*C*-CN), 98.33 (C), 115.19 (CH), 122.79 (CH), 123.13 (CH), 129.40 (C≡N), 134.43 (CH), 138.36 (C), 147.14 (C), 150.11 (C=O), 155.45 (C), 156.10 (C), 160.19 (C-NH_2), 160.76 (C=O) ppm. Mass: ($C_{14}H_8N_6O_4$) *m/z* (*%*)= 324 (M)$^+$, 277 (M$^+$-HNCO), 77, 57, 43.

7-amino-2,4-dioxo-5-(4-nitrophenyl)-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (**4h**): Brick-red solid, yield: 0.314 g (97%), m.p.>300ºC. IR (KBr) (ν_{max}/cm^{-1}): 3607, 3534 (NH_2), 3297, 3070 (2 NH), 2222 (CN), 1703, 1590 (2 CO) cm^{-1}. ^{1}H-NMR: δ = 7.58 (d, 2 H, H_{Ar}, ^3J = 8.6 Hz), 7.75 (br s, 2 H, NH_2), 8.27 (d, 2 H, H_{Ar}, ^3J = 8.6 Hz), 11.00 (s, 1 H, NH), 11.55 (s, 1 H, NH) ppm. ^{13}C-NMR: δ = 87.88 (*C*-CN), 98.16 (C), 115.06 (2 CH), 122.89 (2 CH), 129.15 (*C*-CN), 143.96 (C), 147.33 (C), 150.18 (C=O), 155.47 (C), 156.62 (C), 160.13 (C-NH_2), 160.76 (C=O) ppm. Mass: ($C_{14}H_8N_6O_4$) *m/z* (*%*)= 324 (M)$^+$, 277 (M$^+$-HNCO), 77, 57, 43.

CONCLUSION

In conclusion, we found a novel method available for the synthesis of 7-amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitriles, meanwhile the new method also expands the application of the catalyst of ZrO_2 NPs in organic synthesis. Compared with previous methods for the synthesis of these biologically active compounds

[23], this method has the advantages of high yields, mild reaction conditions, short reaction time, easy work-up, inexpensive reagents and environmentally friendly procedure.

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CONFLICT OF INTEREST

Declared none.

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