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Chinese Chemical Letters 23 (2012) 257–260

CHINESE CHEMICAL LETTERS

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Facile one-pot synthesis of pyrido[2,3-*d*]pyrimidine derivatives over ZrO_2 nanoparticles catalyst

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Received 23 August 2011
Available online 24 January 2012

Abstract

An efficient synthesis of hexahydropyrido[2,3-*d*]pyrimidinetrione derivatives is achieved *via* tandem Knoevenagel–Michael addition of aromatic aldehydes, methylcyanoacetate and 4(6)-aminouracil in solvent-free conditions in the presence of 10 mol% of ZrO_2 nanoparticles (ZrO_2 NPs) as a heterogenous catalyst. The procedure is formed in high yields, short reaction time and an environmentally friendly specificity.

Keywords: Pyrido[2,3-*d*]pyrimidines; Solvent-free; Tandem Knoevenagel–Michael addition; ZrO_2 nanoparticles

Pyridopyrimidine and its derivatives have been studied for over a century because of a variety of chemical and biological significance. They have been reported as antibacterial [1], antiasthmatic, antiallergic [2], antifolate [3], tyrosine kinase [4], antimicroibial [5], calcium channel antagonists [6], anti-inflammatory and analgesic [7], antihypertensive [8], antileishmanial [9], tuberculostatic [10], anticonvulsants [11], diuretic and potassium-sparing [12], antiaggressive [13] activities. Various synthetic approaches have been reported for the synthesis of hexahydropyrido[2,3-*d*]pyrimidinetrione derivatives, such as traditional thermal methods using KF/Al_2O_3 [14], or TEBAC [15] as catalyst. However, there is always the need for better methods.

In the last few years the application of metal oxide nanoparticles as an efficient catalyst have proved to be useful in several scientific and technological areas due to the activation of adsorbed compounds and reaction rate enhancement, easier wok-up, reusability of the catalyst and the environmentally friendly reaction conditions [16,17]. Currently, application of these nanocatalysts in organic and inorganic reactions has emerged as a rapidly growing field [18–21]. These facts encouraged us to explore other clean method using ZrO_2 nanoparticles (ZrO_2 NPs) commercially available with an average size of 15 nm, for the synthesis of an important class of the pyrido-pyrimidinetrione derivatives **4**(**a**–**g**) at 70 °C in solvent-free conditions (Scheme 1 and Table 1). Although, this is the first report of using Lewis acid catalyst for the synthesis of these biologically active compounds, compared with previous methods [14,15], this method has the advantages of high yields, mild reaction conditions, short reaction time, easy work-up, inexpensive reagents and environmentally friendly procedure.

In continuation of our previous works on the development of novel and efficient catalytic methods for the synthesis of heterocyclic compounds [22–24], herein has been reported a novel and highly efficient solvent-free protocol for the

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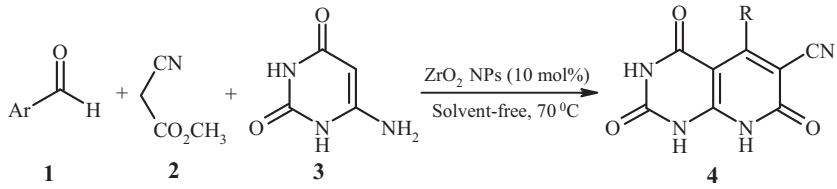
1001-8417/$ – see front matter
doi:10.1016/j.cclet.2012.01.001



Scheme 1. Synthesis of hexahydropyrido[2,3-*d*]pyrimidine derivatives in solvent-free conditions.

Table 1
Synthesis of hexahydropyrido[2,3-*d*]pyrimidines **4(a–g)** in solvent-free conditions using ZrO_2 NPs as catalyst.

Product	Ar	mp (°C)	Yield[a] (%)
4a	4-BrC_6H_4	>300	97
4b	2-ClC_6H_4	>300	90
4c	3-ClC_6H_4	>300	92
4d	2,4-$Cl_2C_6H_3$	>300	93
4e	4-HOC_6H_4	>300	94
4f	4-$CH_3OC_6H_4$	>300	93
4g	4-$CH_3C_6H_4$	>300	96

[a] Yields refer to pure isolated products characterized by IR, ^{1}H NMR spectroscopy, mass spectrometry and elemental analysis.

synthesis of pyrido[*d*]pyrimidine derivatives **4** *via* a three-component reaction of aromatic aldehydes, methylcyanoacetate and 4(6)-aminouracil in the presence of ZrO_2 NPs as an efficient, inexpensive, moisture stable, commercially available and environmentally benign catalyst. We also tried to use this procedure for aliphatic aldehydes but unfortunately the yields were low because of the low boiling points of aldehydes so they vaporize fast.

As shown in Table 2, the reaction of 4-hydroxybenzaldehyde, **2** and **3** as a model was examined under various reaction conditions. After 1 h with 5, 10 and 15 mol% of ZrO_2 NPs, yields of 67, 94 and 95%, respectively, were obtained. To show that ZrO_2 NPs is an efficient catalyst, we tried the reaction in the absence of ZrO_2 NPs, but the reaction time increased, meanwhile the yield decreased mainly (Table 2, entries 1–4).

The effect of the temperature was studied by carrying out the model reaction in the presence of ZrO_2 NPs (10 mol%) at 70 °C and at 90 °C in solvent-free conditions. It was observed that the yield was not increased as the reaction temperature was raised (Table 2, entries 3 and 5).

ZrO_2 bulk also was evaluated for the model reaction. Clearly, the reaction time using ZrO_2 NPs has been reduced by ten times with higher yield than ZrO_2 bulk (Table 2, entries 3 and 6).

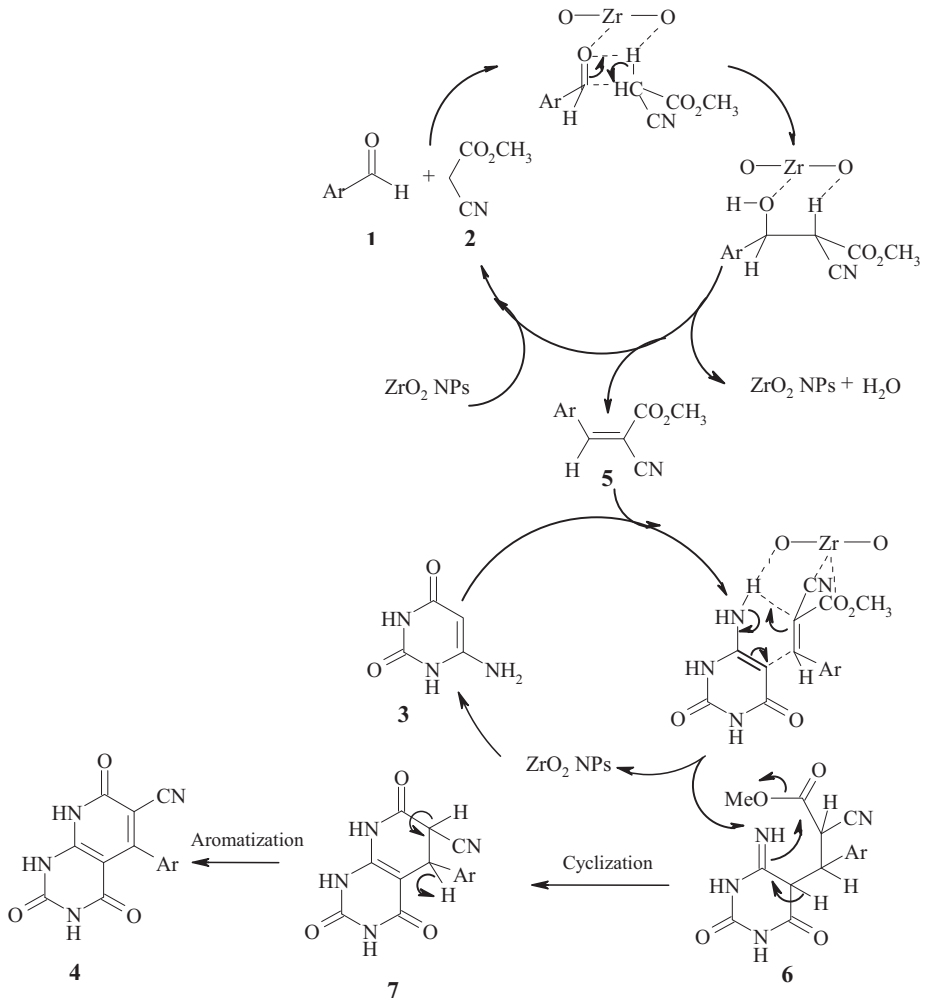
Investigation of the effect of solvents showed that the best results were obtained in solvent-free conditions (Table 2, entries 3 and 7–9).

Although it is not clear how ZrO_2 acts as a catalyst for the reaction, on the basis of the surface of metal oxides exhibit both Lewis acid and Lewis base character [25], the proposed mechanism for the ZrO_2 catalyzed one-pot reaction of aromatic aldehydes, methylcyanoacetate and 4(6)-aminouracil is shown in Scheme 2. It is suggested that, ZrO_2 NPs are coordinated to the oxygen of the aromatic aldehyde **1** and active it for nucleophilic attack [26] by

Table 2
Optimization of the ZrO_2 NPs catalyzed model reaction of 4-hydroxybenzaldehyde, methylcyanoacetate and 4(6)-aminouracil for the synthesis of product **4e**.

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	No catalyst	None	70	6	28
2	ZrO_2 NPs (5%)	None	70	1	67
3	ZrO_2 NPs (10%)	None	70	1	94
4	ZrO_2 NPs (15%)	None	70	1	95
5	ZrO_2 NPs (10%)	None	90	1	94
6	ZrO_2 bulk (10%)	None	70	10	35
7	ZrO_2 NPs (10%)	CH_2Cl_2	70	5	42
8	ZrO_2 NPs (10%)	DMF	100	5	48
9	ZrO_2 NPs (10%)	EtOH/H_2O	80	10	68

[a] Isolated yield.



Scheme 2. The proposed mechanism for the synthesis of hexahydropyrido[*d*]pyrimidines in solvent-free conditions catalyzed by ZrO_2 NPs (10%).

methylcyanoacetate **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 **4** after aromatization of intermediate **7**.

In order to demonstrate the ZrO_2 can be catalyses both of 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.

The structure of compounds **4**(**a**–**g**) were deduced from their ^{1}H NMR and IR spectral data and also by elemental analysis. Spectroscopic data have been given in general procedure section.

In summary, We have demonstrated that ZrO_2 NPs efficiently catalyzes the one-pot three-component synthesis of 2,4,7-trioxo-5-aryl-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitriles in high yields.

1. General procedure for preparation of compounds *4a–g*

A mixture of aromatic aldehyde 1 (1 mmol), methylcyanoacetate (2, 1.2 mmol), 4(6)-aminouracil (3, 1 mmol) and ZrO_2 NPs (12.3 mg, 10 mol%) was stirred at 70 °C for 1 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.

2,4,7-Trioxo-5-(4-bromophenyl)-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitriles (**4a**): pale yellow solid; mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 7.12 (d, 2H, H_{Ar}, J = 8.4 Hz), 7.49 (d, 2H, H_{Ar}, J = 8.4 Hz), 10.10 (s, 1H, NH), 10.14 (s, 1H, NH), 10.33 (s, 1H, NH). IR (KBr): ν_{max} 3NH 3135 br, CN 2217, 3CO 1653, 1575, 1533 cm^{-1}. Anal. Calcd. for $C_{14}H_7BrN_4O_3$ (359.14): C, 46.82; H, 1.96; N, 15.60. Found: C, 46.91; H, 1.85; N, 15.52.

2,4,7-Trioxo-5-(2-chlorophenyl)-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitriles (**4b**): pale yellow solid; mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 7.29 (m, 1H, H_{Ar}), 7.41 (m, 1H, H_{Ar}), 7.53 (m, 1H, H_{Ar}), 10.12 (s, 1H, NH), 10.18 (s, 1H, NH), 10.29 (s, 1H, NH). IR (KBr): ν_{max} 3NH 3133 br, CN 2221, 3CO 1695, 1573, 1513 cm^{-1}. Anal. Calcd. for $C_{14}H_7ClN_4O_3$ (314.69): C, 53.43; H, 2.24; N, 17.80. Found: C, 53.35; H, 2.28; N, 17.62.

2,4,7-Trioxo-5-(2,4-dichlorophenyl)-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitriles (**4d**): pale yellow solid; mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 7.29 (d, 1H, H_{Ar}, J = 8.0 Hz), 7.38 (dd, 1H, H_{Ar}, J = 8.0 Hz, J' = 2.0 Hz), 7.60 (d, 1H, H_{Ar}, J = 2.0 Hz), 10.07 (s, 1H, NH), 10.16 (s, 1H, NH), 10.24 (s, 1H, NH). IR (KBr): ν_{max} 3NH 3394 br, 3042, CN 2161, 3CO 1718, 1565, 1480 cm^{-1}. Anal. Calcd. for $C_{14}H_6Cl_2N_4O_3$ (349.13): C, 48.16; H, 1.73; N, 16.05. Found: C, 48.19; H, 1.85; N, 15.92.

2,4,7-Trioxo-5-(4-hydroxyphenyl)-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitriles (**4e**): pale yellow solid; mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 6.96 (d, 2H, H_{Ar}, J = 8.4 Hz), 7.24 (d, 2H, H_{Ar}, J = 8.4 Hz), 9.63 (s, 1H, OH), 10.05 (s, 1H, NH), 10.14 (s, 1H, NH), 10.38 (s, 1H, NH). IR (KBr): ν_{max} 3NH 3335, 3157 br, CN 2211, 3CO 1707, 1643, 1522 cm^{-1}. Anal. Calcd. for $C_{14}H_8N_4O_4$ (296.24): C, 56.76; H, 2.72; N, 18.91. Found: C, 56.56; H, 2.53; N, 18.78.

2,4,7-Trioxo-5-(4-methoxyphenyl)-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitriles (**4f**): pale yellow solid; mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 6.90 (d, 2H, H_{Ar}, J = 8.0 Hz), 7.12 (d, 2H, H_{Ar}, J = 8.0 Hz), 10.03 (s, 1H, NH), 10.11 (s, 1H, NH), 10.34 (s, 1H, NH). IR (KBr): ν_{max} 3NH 3390, 3128, 2955, CN 2221, 3CO 1720, 1645, 1603 cm^{-1}. Anal. Calcd. for $C_{15}H_{10}N_4O_4$ (310.27): C, 58.07; H, 3.25; N, 18.06. Found: C, 58.19; H, 3.15; N, 18.22.

2,4,7-Trioxo-5-(4-methylphenyl)-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-6-carbonitriles (**4g**): pale yellow solid; mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.22 (d, 2H, H_{Ar}, J = 8.0 Hz), 7.32 (d, 2H, H_{Ar}, J = 8.0 Hz), 10.04 (s, 1H, NH), 10.10 (s, 1H, NH), 10.33 (s, 1H, NH). IR (KBr): ν_{max} 3NH 3152 br, 3024, CN 2220, 3CO 1656, 1542, 1513 cm^{-1}. Anal. Calcd. for $C_{15}H_{10}N_4O_3$ (294.27): C, 61.22; H, 3.43; N, 19.04. Found: C, 61.39; H, 3.25; N, 19.21.

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