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Majid M. Heravi [a], Azadeh Ghods [a], Khadijeh Bakhtiari [a] & Fatemeh Derikvand [a]

[a] Department of Chemistry, School of Sciences, Alzahra University, Vanak, Tehran, Iran

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Zn[(L)PROLINE]$_2$: AN EFFICIENT CATALYST FOR THE SYNTHESIS OF BIOLOGICALLY ACTIVE PYRANO[2,3-*d*]PYRIMIDINE DERIVATIVES

Majid M. Heravi, Azadeh Ghods, Khadijeh Bakhtiari, and Fatemeh Derikvand

Department of Chemistry, School of Sciences, Alzahra University, Vanak, Tehran, Iran

Biologically active pyrano[2,3-d]pyrimidine derivatives were efficiently synthesized in excellent yields by a three-component, one-pot condensation reaction of malononitrile, benzaldehydes, and barbituric acid using a catalytic amount of Zn[(L)proline].

Keywords: Barbituric acid; pyrano[2,3-*d*]pyrimidine derivatives; three-component one-pot reaction; Zn[(L)proline]$_2$

INTRODUCTION

Pyrano[2,3-*d*]pyrimidine derivatives are annulated uracils that have received great attention during the past years because of their wide range of biological activity. Compounds with these ring systems have various pharmacological activities such as antitumor, cardiotonic, hepatoprotactive, antihypertensive, antibronchitic, and antifungal activities.[1–4] Therefore, for the preparation of these complex molecules, great efforts have been directed toward the synthetic manipulation of uracils. A number of methods have been developed for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives from two-component condensation of 2-benzylidene-malononitrile with barbituric acid.[5–7] However, most of these methods suffer from some disadvantages such as long reaction times and complex synthetic pathways. Therefore, the development of improved methods for the synthesis of these compounds has relevance in current research.

The role of bis[(L)prolinato-N,O]Zn complex, Zn[(L)proline]$_2$, in organic chemistry has been documented elsewhere.[8] Recently, we have also reported the use of this catalyst for the synthesis of quinoxaline derivatives.[9]

Multicomponent reactions (MCRs) have been considered in modern medicinal chemistry.[10] We have been interested in development of the efficient and environmentally benign synthetic methodologies using economical and ecofriendly catalysts.[11–13] Herein, we report the synthesis of pyrano[2,3-*d*]pyrimidine derivatives from a

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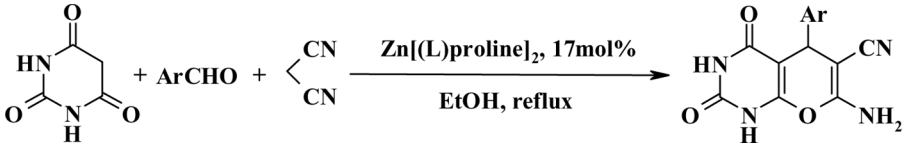
Address correspondence to Majid M. Heravi, Department of Chemistry, School of Sciences, Alzahra University, Vanak, Tehran 1234, Iran. E-mail: mmh1331@yahoo.com



Scheme 1. Synthesis of pyrano[2,3-*d*]pyrimidine derivatives in the presence of Zn[(L)proline]$_2$ as catalyst.

three-component, one-pot condensation of benzaldehyde derivatives, malononitrile, and barbituric acid in the presence of Zn[(L)proline]$_2$ as catalyst (Scheme 1).

RESULTS AND DISCUSSION

The procedure is very simple: 1 equiv of an appropriate aromatic aldehyde was mixed with 1.2 equiv of malononitrile, 1 equiv of barbituric acid, and Zn[(L)proline]$_2$ (17 mol%) in ethanol (3 mL) and magnetically stirred in a round-bottomed flask under reflux conditions.

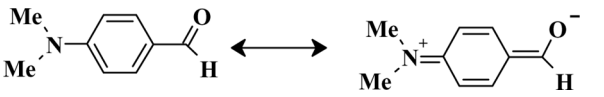
The scope and generality of this method are illustrated with respect to various aromatic aldehydes. As shown in Table 1, the electron-withdrawing or electron-donating group on the phenyl rings did not affect the reaction. Unfortunately, the reaction did not proceed using propionaldehyde and acetaldehyde as aliphatic aldehydes (Table 1, entries 12 and 13).

Interestingly, in the case of 4-*N,N*-dimethylamino-benzaldehyde and 3,4-dimethoxy-benzaldehyde, we did not obtain any product. However, the desired products were obtained in very good yields by 2- or 4-methoxybenzaldehyde. Therefore, it cannot be due to the complexation–deactivation of the Zn metal by these substituent groups. It could be due to the strong electron-donating nature of these substituents, which make the carbonyl ineffective, as shown in Scheme 2.

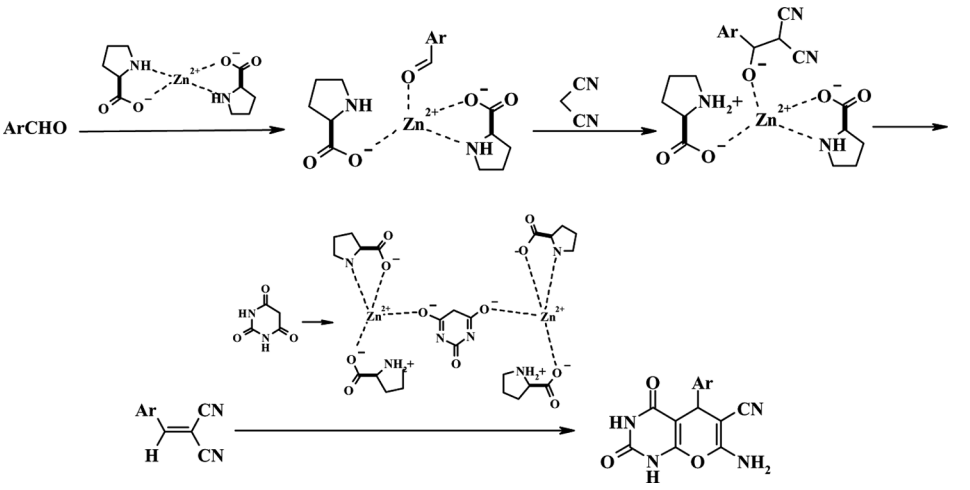
Table 1. Zn[(L)proline]-catalyzed synthesis of pyrano[2,3-*d*]pyrimidine derivatives

				Mp (°C)	
Entry	Aldehyde	Time (min)	Yield (%)[a]	Found	Reported
1	PhCHO	60	85	223	224–225[6]
2	4-Me-PhCHO	70	82	225	—
3	2-Me-PhCHO	85	80	235	—
4	4-MeO-PhCHO	45	88	280	280–281[7]
5	2-MeO-PhCHO	50	85	230	—
6	3-NO_2-PhCHO	30	90	265	262–263[15]
7	4-NO_2-PhCHO	30	92	245	238–239[7]
8	4-Cl-PhCHO	50	90	245	242–244[6]
9	4-CF_3-PhCHO	40	88	250	250–251[16]
10	3,4-$(MeO)_2$-PhCHO	12 h	0	—	—
11	4-$N(Me)_2$-PhCHO	12 h	0	—	—
12	EtCHO	12 h	0	—	—
13	MeCHO	12 h	0	—	—

[a]Yields refer to isolated pure products.



Scheme 2. The strong electron-donating nature of 4-*N,N*-dimethylamino-benzaldehyde.



Scheme 3. Plausible mechanism.

We have not established an exact mechanism for the formation of pyrano[2,3-*d*]pyrimidine derivatives; however, a reasonable possibility is shown in Scheme 3. The reaction does not afford any enantioselectivity, and it could be due to the production of a symmetric intermediate as shown in Scheme 3.

In summary, we report here a high-yielding, one-pot synthesis of pyrano[2,3-*d*]pyrimidine derivatives from the condensation of aldehydes, barbituric acid, and malononitrile under simple and convenient conditions. The conditions are mild and a wide range of functional groups can be tolerated. Use of Zn[(L)proline] as catalyst offers advantages including simplicity of operation, easy workup, and excellent yields of products.

EXPERIMENTAL

All the chemicals were purchased from Merck. Melting points were measured by using the capillary tube method with a Bamstead Electrothermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker AQS Avance 300-MHz spectrometer using tetramethylsilane (TMS) as an internal standard ($CDCl_3$ solution). Infrared (IR) spectra were recorded on a Fourier transform (FT)–IR Bruker Tensor 27 (KBr disk). Optical rotation was recorded on an A-Kruss-Optronic (polaremeter P1000) instrument.

Synthesis of Bis[(L)prolinato-N,O]Zn Complex

The catalyst was prepared according to the reported procedure in the literature.[14]

Synthesis of Pyrano[2,3-*d*]pyrimidine Derivatives: General Procedure

A mixture of an appropriate aromatic aldehyde (1 mmol), malononitrile (1.2 mmol), barbituric acid (1 mmol), and Zn[(L)proline] (17 mol%) in ethanol (3 mL) was magnetically stirred in a round-bottomed flask under reflux conditions. The progress of the reaction was monitored by thin-layer chromatography (TLC) using chloroform/ethyl acetate as the eluent. Upon completion of the reaction, the mixture was cooled to room temperature. The precipitated solid was collected by filtration. For further purification, the product was washed with water and recrystallized from ethanol. Pure products were obtained in excellent yields as summarized in Table 1.

Spectroscopic Data for New Products

7-Amino-6-cyano-5-(4-methylphenyl)-5H-pyrano[2,3-*d*]pyrimidine-2,4(1-H,3H)-diones (entry 2). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 2.25$ (s, 3H, CH_3), 4.17 (s, 1H, CH), 7.07 (s, 6H, ArH & NH_2), 11.046 (s, 1H, NH), 12.043 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 36.55$, 59.83, 89.38, 120.03, 127.58, 128.15, 129.15, 130.02, 145, 150.37, 153.15, 158.51, 163 ppm. Anal. calcd. (%): C, 60.81; H, 4.05; N, 18.92. $C_{15}H_{12}N_4O_3$ found: C, 60.65; H, 4.22; N, 18.93.

7-Amino-6-cyano-5-(2-methylphenyl)-5H-pyrano[2,3-*d*]pyrimidine-2,4(1H,3H)-diones (entry 3). IR (KBr): $\upsilon_{max} = 3431$, 3345, 3262, 3170, 3061, 2201, 1719, 1680, 1673, 1587 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.48$ (s, 3H, CH_3), 4.54 (s, 1H, CH), 7.01–7.1 (m, 6H, ArH & NH_2), 11.03 (s, 1H, NH), 12.05 (s, 1H, NH) ppm. Anal. calcd. (%): C, 60.81; H, 4.05; N, 18.92. $C_{15}H_{12}N_4O_3$ found: C, 60.15; H, 4.31; N, 18.61.

7-Amino-6-cyano-5-(2-methoxy-phenyl)-5H-pyrano[2,3-*d*]pyrimidine-2,4(1H,3H)-diones (entry 5). IR (KBr): $\upsilon_{max} = 3388$, 3306, 3258, 3187, 3076, 3008, 2196, 1717, 1676, 1638, 1604 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 3.75$ (s, 3H, CH_3), 4.5 (s, 1H, CH), 6.8–7.2 (m, 6H, ArH & NH_2), 10.99 (s, 1H, NH), 11.98 (s, 1H, NH) ppm. Anal. calcd. (%): C, 57.69; H, 3.85; N, 17.95. $C_{15}H_{12}N_4O_4$ found: C, 58.01; H, 3.96; N, 18.11.

7-Amino-6-cyano-5-(3-nitrophenyl)-5H-pyrano[2,3-*d*]pyrimidine-2,4(1H, 3H)-diones (entry 6). ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 4.48$ (s, 1H, CH), 7.27 (s, 2H, NH_2), 7.59–7.64 (m, 1H, ArH), 7.74–7.76 (m, 1H, ArH), 8.07–8.12 (m, 2H, ArH), 11.09 (s, 1H, NH), 12.15 (s, 1H, NH) ppm.

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