A clean one-pot synthesis of 7-amino-5-aryl-6-cyano-1,5-dihydro-2*H*-pyrano[2,3-*d*] pyrimidine-2,4(3*H*)-diones in aqueous media under ultrasonic irradiation

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A novel approach to the synthesis of 7-amino-5-aryl-6-cyano-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-diones in aqueous media under ultrasonic irradiation without catalyst is described. This method provides several advantages such as being environmentally friendly, simple work-up procedure and milder condition. In addition, water was chosen as a green solvent.

Keywords: barbituric acid, dione, heterocyclic compounds, aqueous media

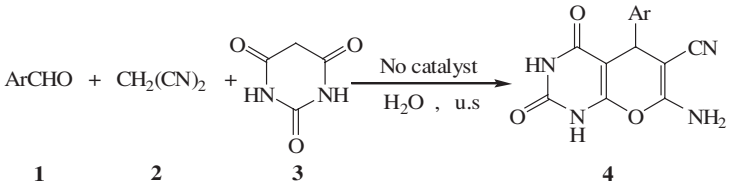
At the beginning of the new century, a shift in emphasis in chemistry is apparent with the desire to develop environmentally benign routes to a myriad of materials using non-toxic reagents, solvents and catalysts. Recently "ideal synthesis" was defined as one in which the target compound is generated in one step, in quantitative yield from readily available and inexpensive starting materials in a resource-effective and environmentally acceptable process. One-pot multicomponent condensations represent a possible instrument to perform a near ideal synthesis because they possess one of the aforementioned qualities, namely the possibility of building-up complex molecules with maximum simplicity and brevity. Recently organic reactions in water without use of harmful organic solvents have attracted much attention, because water is cheap, safe, and environmentally benign solvent.[1] In the course of our investigations to develop new synthetic methods in water, we examined the synthesis of 7-amino-5-aryl-6-cyano-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-diones in water, as a green solvent, which represents a remarkable benefit for its high polarity.

Ultrasound has increasingly been used in organic synthesis in last three decades, compared with traditional methods, this technique is more convenient and easily controlled.[2] A large number of organic reactions can be carried out in higher yields, shorter reaction time and milder conditions under ultrasound irradiation.[3,4]

Recently, people have paid much attention to the development of new methods for the synthesis of heterocyclic compounds, due to their potential importance in the fields of pharmaceutical and agricultural drugs.[5] Pyrimidine derivatives are generally used as antitumors,[6] analgetic substances,[7] bactericidals,[8] and fungicidal.[9] The synthesis of 7-amino-5-aryl-6-cyano-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-diones by the reaction of arylidenemalononitrile with barbituric acid under traditional hot reaction condition[10,11] or microwave irradiation[5] has been reported. Now we will directly one-pot synthesise 7-amino-5-aryl-6-cyano-1, 5-dihydro-2*H*-pyrano [2,3-*d*]pyrimidine-2,4(3*H*)-diones by the reaction of aromatic aldehydes, malononitrile with barbituric acid in aqueous media under ultrasound without catalyst. This method has not been reported before, it is environmentally friendly, the solvent is green, the operation is easier, the time is shorter (Scheme 1).

As summarised in Table 1, several aromatic aldehydes and malononitrile, barbituric acid were reacted in aqueous media under ultrasound without catalyst resulting corresponding 7-amino-5-aryl-6-cyano-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-diones in good yields.

The ultrasound plays an important role in the success of the reaction in terms of the rate and the yields. We have compared the reactions under ultrasound with those under hot conditions. For example, 4-nitrobenzoaldehyde reacted



Scheme 1

Table 1 Synthesis of 7-amino-5-aryl-6-cyano-1,5-dihydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-diones in aqueous media under ultrasound without catalyst

Entry	Ar	Time/h	Yield [a] /%	M.p. /°C	
				Found	Reported[10]
1	3–$NO_2C_6H_4$ **1a**	2	87	262–263	
2	4–$NO_2C_6H_4$ **1b**	1	66	237–238	237–238
3	2–$NO_2C_6H_4$ **1c**	2	67	265–266	
4	4–ClC_6H_4 **1d**	2	64	239–240	240–241
5	3–ClC_6H_4**1e**	2	68	241–242	
6	4–BrC_6H_4 **1f**	2	68	227–229	226–227
7	3–BrC_6H_4 **1g**	3	69	279–280	
8	4–$CH_3OC_6H_4$**1h**	2.5	62	281–282	280–281

[a]Isolated yield.

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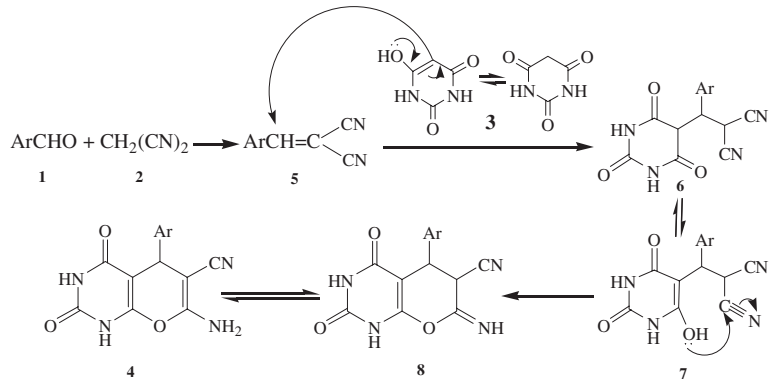

Scheme 2

with malononitrile and barbituric acid to give the product **4b** in modest yield (50%) under hot reaction conditions after 24 hours reaction time. Ultrasound results in raising the reaction yield to 66% after 1 h. Therefore, ultrasound was chosen as a reaction condition.

We propose the possible following mechanism to account for the reaction. One molecule of malononitrile **2** was firstly condensed with an aromatic aldehyde **1** to afford **5**. Then the active methylene of barbituric acid **3** reacted with **5** via Michael addition reaction to give the intermediate **6**, (**6**–**7**). Then the intermediate **7** cyclised by nucleophilic attack of the OH group on the nitrile group and gave the intermediate **8**. Finally, the expected products **4** tautomerised from **8** (Scheme 2).

In summary, we have described a practical and simple work-up procedure for the synthesis of 7-amino-5-aryl-6-cyano-1,5-dihyrano-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-diones through the three component reaction of aromatic aldehydes, malononitrile and barbituric acid without catalyst under ultrasonic irradiation. This procedure offers several advantages including mild reaction conditions, clear reaction as well as a simple experimental and isolated procedure. Mostly important, water has been chosen as a green solvent for these reactions.

Experimental

IR spectra were recorded on Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR spectra was measured on Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal standard and DMSO as solvent. Elemental analyses were measured on a HERAEUS (CHNO, Rapid) analyser. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25kHz and a nominal power 250W) and SK 250 LH ultrasonic cleaner (with a frequency of 40kHz, 59kHz and a nominal power 250W; Shanghai Kudos ultrasonic instrument Co., Ltd.). The reaction flasks were located in the maximum energy area in the cleaner, where the surface of reactants is slightly lower than the level of the water.

General procedure: A dry flask (50 ml) was charged with aromatic aldehydes (**1**, 1.0 mmol), malononitrile (**2**, 1.0 mmol), barbituric acid (**3**, 1.0 mmol), and 20 ml water. The mixture was irradiated in the water bath of the ultrasonic cleaner for a period as indicated in Table 1. After the completion of the reaction, the reaction mixture was laid for 12 hours and then it was heated to 90°C, filtered off, washed with 90°C water and ethanol, then the crude product was purified by recrystallisation from DMF–ethanol to afford the pure products **4**.

Data of the compounds are shown below:

4a: ν_{max}/cm^{-1} 3417, 3317, 3206, 2193, 1716, 1670, 1529; δ_H 4.47 (1H, s, CH), 7.26 (2H, s, NH_2), 7.59–8.10 (4H, m, ArH), 11.09 (1H, s, NH), 12.15 (1H, s, NH). Anal. Calcd for $C_{14}H_9N_5O_5$: C, 51.38; H, 2.77; N, 21.40. Found: C, 51.53; H, 2.89; N, 21.26.

4b: ν_{max}/cm^{-1} 3387, 3294, 3179, 2195, 1708, 1676, 1519; δ_H 4.46 (1H, s, CH), 7.26 (2H, s, NH_2), 7.54–8.21 (4H, m, ArH), 11.07 (1H, s, NH), 12.15 (1H, s, NH).

4c: ν_{max}/cm^{-1} 3387, 3238, 3080, 2194, 1734, 1690, 1518; δ_H 5.03 (1H, s, CH), 7.28 (2H, s, NH_2), 7.57–8.25 (4H, m, ArH), 11.05 (1H, s, NH), 12.14 (1H, s, NH). Anal. Calcd for $C_{14}H_9N_5O_5$: C, 51.38; H, 2.77; N, 21.40. Found: C, 51.46; H, 2.73; N, 21.28.

4d: ν_{max}/cm^{-1} 3385, 3300, 3250, 3175, 2195, 1728, 1675, 1533; δ_H 4.26 (1H, s, CH), 7.17 (2H, s, NH_2), 7.22 (2H, *J*=6.5 Hz, d, ArH), 7.34 (2H, *J*=6.5 Hz, d, ArH) 11.07 (1H, s, NH), 12.09 (1H, s, NH).

4e: ν_{max}/cm^{-1} 3415, 3320, 3194, 3099, 2194, 1714, 1671, 1527; δ_H 4.27 (1H, s, CH), 7.17 (2H, s, NH_2), 7.20–7.35 (4H, m, ArH), 11.07 (1H, s, NH), 12.08 (1H, s, NH). Anal. Calcd for $C_{14}H_9ClN_4O_3$: C, 53.10; H, 2.86; N, 17.69. Found: C, 53.22; H, 2.73; N, 17.60.

4f: ν_{max}/cm^{-1} 3387, 3305, 3248, 3169, 2195, 1730, 1674, 1585; δ_H 4.25 (1H, s, CH), 7.16 (2H, s, NH_2), 7.35 (2H, *J*=7.2 Hz, d, ArH), 7.91 (2H, *J*=7.2 Hz, d, ArH), 11.08 (1H, s, NH), 12.08 (1H, s, NH).

4g: ν_{max}/cm^{-1} 3432, 3204, 3081, 2195, 1750, 1682, 1583; δ_H 4.26 (1H, s, CH), 7.17 (2H, s, NH_2), 7.40–7.89 (4H, m, ArH), 11.07 (1H, s, NH), 12.08 (1H, s, NH). Anal. Calcd for $C_{14}H_9BrN_4O_3$: C, 46.56; H, 2.51; N, 15.51. Found: C, 46.67; H, 2.38; N, 15.62.

4h: ν_{max}/cm^{-1} 3425, 3253, 3102, 2197,1730, 1675, 1522; δ_H 3.96(3H, s, OCH_3), 4.19 (1H, s, CH), 7.08 (2H, s, NH_2), 7.17 (2H, *J*=7.2 Hz, d, ArH), 7.29 (2H, *J*=7.2 Hz, d, ArH), 11.12 (1H, s, NH), 11.35 (1H, s, NH).

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