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Organobase catalyzsed, simple and highly efficient one-pot three-component synthesis of pyrano[2,3-*d*]pyrimidin-diones in water

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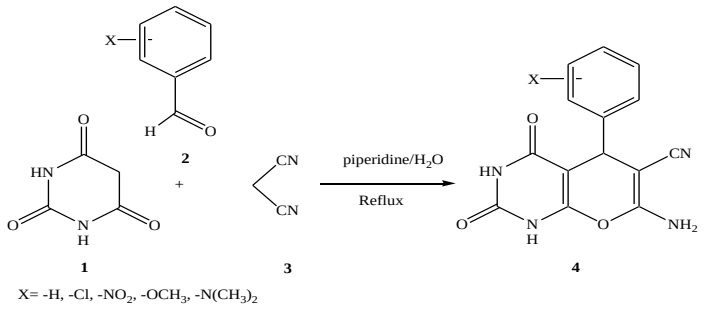
ABSTRACT

An efficient and inexpensive synthesis of pyrano[2,3-*d*]pyrimidin-diones by a piperidine catalyzed one-pot three-component condensation reaction consisting of aromatic aldehydes, malononitrile and barbituric acid in water at reflux is described. The method is simple and the products are obtained in excellent yield in a very short duration.



Key words: Pyrano[2,3-*d*]pyrimidin-diones; malononitrile; barbituric acid; aromatic aldehydes; piperidine; water.

1. Introduction

Development of clean and green chemical processes, search for new and less hazardous chemical catalysts and their use in environmentally safe solvents has become a priority in modern organic synthesis.[1] Reactions in water are generally environmentally safe, comparatively easy to operate, devoid of any carcinogenic effects, less expensive and are therefore important in industries.[2] Dramatic rate enhancement of many organic reactions such as: aldol condensations, Claisen rearrangements, and Diels–Alder cycloaddition reactions[3] have been achieved in water as a solvent.

Pyrimidinone and its derivatives have displayed various biological[4] and pharmaceutical[5] activities such as anti-tumor activity in the treatment of B16 melanoma and P388 leukemia,[6]

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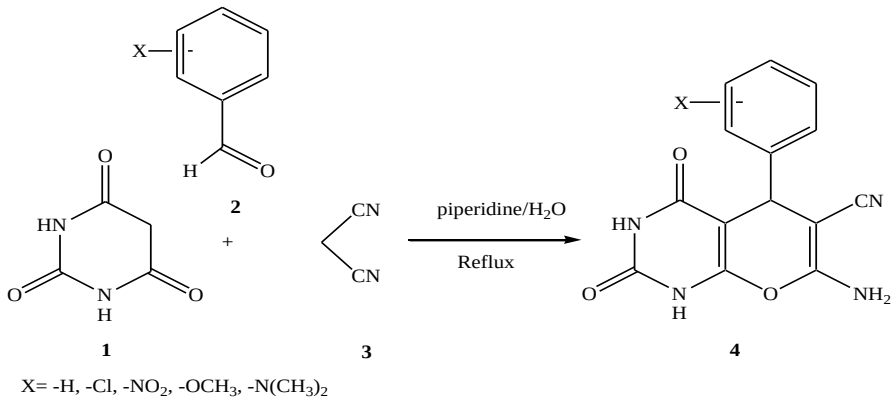
antagonize cell proliferation and induce cell differentiation by inhibiting (a non-telomeric) endogenous reverse transcriptase.[7] It is also known that, compounds with an uracil moiety in the skeleton of an organic molecule shows antitumor, vasodilator, bronchiodilator, antibacterial, antihypertensive, hepatoprotective, cardiotonic, and antiallergic activities. Some of them also exhibit antifungal, analgesics, antimalarial and herbicidal properties.[8–15] As a result, synthesis of these heterocycles as well as their analogues is very important in organic, pharmaceutical and medicinal chemistry.

Preparation of pyrano[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-diones generally involves the reaction of arylmethylidenemalononitriles with barbituric acid under traditional thermal conditions[16,17] or under microwave irradiation.[18] In these methods the requisite arylmethylidenemalononitriles are prepared previously from malononitrile and respective aldehydes; the drawbacks of these methods are: they require an additional step in the preparation of arylmethylidenemalononitriles, needs specialized equipment and high thermal microwave activation. There is another report on microwave-assisted one-pot three-component cyclocondensation of barbituric acid, benzaldehyde derivatives, and alkylnitriles in the absence or presence of triethylamine,[19] and the method exhibits some disadvantages such as: harsh conditions, long reaction durations, low yield of the products and environmental pollution. A few reports are also available for the synthesis of pyrano[2,3-*d*]pyrimidin-diones by the one-pot condensation of aromatic aldehydes, malononitrile and barbituric acid employing catalysts such as: diammonium hydrogen phosphate in aqueous ethanol[20] or *N*-methylmorpholine in DMF.[21] The limitation of these two methods are: i) the reaction is possible only in organic solvents which are hazardous to environment; and ii) isolation procedure is tedious and requires longer durations. There are a few more methods in the literature for the synthesis of pyrano-pyrimidin-dione derivatives involving ionic liquids,[22] a mechanochemical method where we require a special ball mill set up which includes circulation of boiling water/steam,[23] use of $KAl(SO_4)_2{\cdot}12H_2O$ (alum) in water,[24] L-proline,[25] sulfonic acid nanoporous silica (SBA-Pr-SO_3H),[26] DABCO in aqueous medium[27] and basic ionic liquid under *Grindstone* method.[28]

Organocatalysis involves use of small organic molecules predominantly made up of C, H, O, N, S and P to accelerate chemical reactions. The advantages associated with the use of organocatalysts include: their lack of sensitivity to moisture and atmospheric oxygen, their ready availability and low cost which confers a huge and direct benefit in the production of pharmaceutical intermediates and products when compared with metal (transition metal) catalysed reactions.[29] We have worked earlier on the synthesis of heterocyclic compounds of biological interest such as: 5-aryl-1*H*-tetrazoles,[30] 4,6-diarylpyrimidin-2(1*H*)-ones,[31] pyranopyrazoles,[32] 1,2,4,5-tetraaryl-imidazoles[33] and 5-arylmethylidene-2-phenyloxazol-4-ones[34] following the *green-chemistry* principles. To expand our work and to develop new synthetic methods involving use of readily available and simple catalysts, herein, we report a new, efficient and convenient method for the one-pot three-component synthesis of pyrano[2,3-*d*]pyrimidin-diones catalyzed by an organocatalyst: piperidine, as shown in the **Scheme 1**.

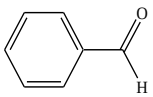
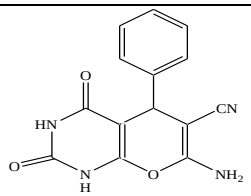
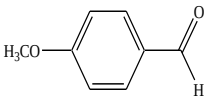
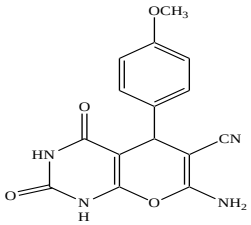
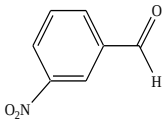
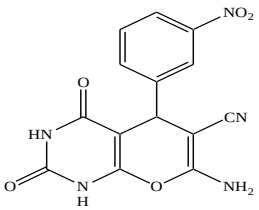


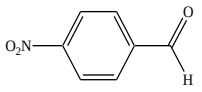
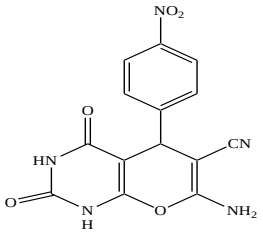
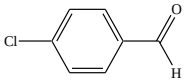
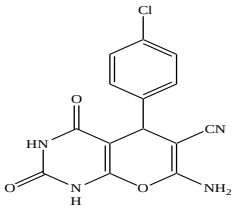
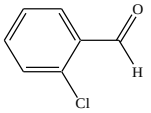
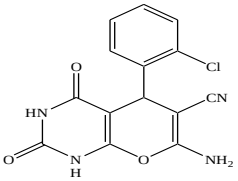
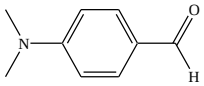
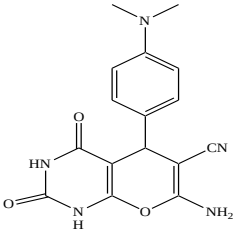
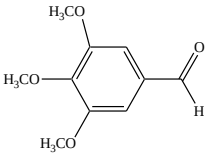
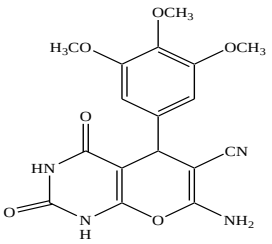
Scheme 1: Synthesis of pyrano[2,3-*d*]pyrimidin-diones

2. Results and Discussion

As a representative example, the reaction of anisaldehyde, malononitrile and barbituric acid (in equimolar ratios) was carried out for 60 min at reflux in the presence of piperidine (2 mol %) in water to get the corresponding pyrano[2,3-*d*]pyrimin-dione (**4b**) in 95% yield. Even though the reactants did not solubilize completely, water was chosen as solvent as it is environmentally safe and readily available. Selection of water as a solvent for the present reaction can be explained on the basis of 'on water' protocol developed by Sharpless *et al*.[35] According to Sharpless the organic substrates initially float on top of the water, when the mixture is stirred vigorously, the reactants disperse as small droplets and lead to a large increase in the surface area between the reactants and the aqueous phase and then reaction takes place to give the product either as a solid precipitate or an oil which floats on top of the water which can be separated easily. Thus, a series of pyrano[2,3-*d*]pyrimidin-diones were prepared in very high to excellent yields by using this standardized procedure. In this study, the aryl aldehydes containing both electron-withdrawing and electron donating substituents were found to be equally reactive towards the condensation with malononitrile and barbituric acid. The results of this study are summarized in the **Table 1**. The products **4a**–**4f** (Table 1) are known and were characterized by their melting points or by comparing them on TLC with authentic samples prepared by known procedure.[23] Products **4g** and **4h** are novel compounds and were characterized by ^{1}H NMR, ^{13}C NMR, HRMS and FT IR (ATR) spectral analysis.

Table 1: Synthesis of pyrano[2,3-*d*]pyrimidin-diones from aldehyde, malononitrile and Barbituric acid.

Entry	Aldehyde (**2**)	Product (**4**)	Time (min)	Yield[a] (%)	M. P (°C)	
					Observed	Reported
a			30	90	207–209	206–209
b			30	95	286–287	287–288
c			35	90	255–257	255–257

d			35	90	226–228/227–229
e			30	90	235–237 /234–237
f			35	85	213–215/213–215
g			30	90	170–172[†]
h			30	95	228–230[†]

[a]Isolated yields; [†]Novel compound.

3. Experimental

3.1 Materials and Methods

The chemicals used were commercial reagents. Melting points were determined using a Ragaa, Indian make melting point apparatus. Reactions were monitored on TLC by comparison with the authentic samples. Nuclear magnetic resonance spectra were obtained on a Bruker AMX instrument in DMSO-d_6 using TMS as an internal standard. HRMS was done using Q-Tof mass-micro mass spectrometer. The Infrared spectra were recorded in the solid phase on a Bruker Optics Alpha-P ATR FT-IR spectrophotometer.

3.2 General procedure for the synthesis of pyrano[2,3-d]pyrimidin-diones:

A mixture of barbituric acid (0.256g, 2 mmol), malononitrile (0.132g, 2 mmol), corresponding aromatic aldehyde (2 mmol) and piperidine (2 mol %) in water (5 mL) was vigorously stirred at reflux for 30–35 min, and the solid thus separated was filtered, washed with ethyl acetate/light petrol (2 : 8, 2 ×10 mL) to get nearly pure products. The products of desired purity were obtained by recrystallization from ethanol.

3.3 Spectral Data of novel compounds

3.3.1 7-Amino-6-cyano-5-(4´-dimethylaminophenyl)-4H-pyrano[2,3-d]pyrimidin-2,4(1H,3H)-dione (**4g**):

Mp: 170–172 °C;
IR (ATR): ν 2206.77 cm^{-1} (CN);
^{1}H NMR (400 MHz, DMSO-d_6): δ10.98 (d, *J* = 48 Hz, 1H, NH), 8.43 (d, *J* = 8 Hz, 2H, NH_2), 8.11 (d, *J* = 40 Hz, 1H, NH), 7.85 (d, *J* = 8 Hz, 2H, Ar-H), 6.865 (d, *J* = 12 Hz, 2H, Ar-H), 6.79 (s, 1H, CH), 3.12 (s, 6H, 2 × CH_3) ppm.
^{13}C NMR (100 MHz, DMSO-d_6): δ 55.83, 58.76, 59.85, 88.14, 104.52, 119.15, 136.36, 139.73, 149.44, 152.26, 152.64, 157.60, 162.46 ppm.
HR-MS: 326.1253 (M+H).

3.3.2 7-Amino-6-cyano-5-(3´,4´,5´-trimethoxyphenyl)-4H-pyrano[2,3-d]pyrimidin-2,4(1H,3H)-dione (**4h**):

Mp: 228–230 °C;
IR (ATR): ν 2196.27 cm^{-1} (CN);
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (s, 1H, NH), 11.05 (s, 1H, NH), 7.08 (s, 2H, Ar-H), 6.47 (s, 2H, NH_2), 4.21 (s, 1H, CH) 3.32 (s, 9H, 3 × OCH_3) ppm.
^{13}C NMR (100 MHz, DMSO-d_6): δ 68.64, 109.54, 111.13, 111.76, 115.46, 116.20, 118.70, 119.94, 133.54, 138.96, 150.23, 154.10, 154.30, 155.39, 158.82, 162.64, 164.61 ppm.
HR-MS: 395.0968 (M+Na).

4. Conclusions

In conclusion, we have successfully developed a simple and an efficient method to prepare a variety of known and new pyrano[2,3-*d*]pyrimidin-diones *via* the cyclocondensation of different substituted aromatic aldehydes, barbituric acid and malononitrile using a readily available organocatalyst-piperidine in water as a solvent. In addition to its efficiency and simplicity, this method is highly cost-effective. After looking into the advantages of this protocol, we feel that, it is a valuable method for the preparation of pyrano[2,3-*d*]pyrimidin-diones.

5. Conflict of Interest

The authors declare that, there is no conflict of interest in the publication of this work.

6. Acknowledgement

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