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Catalyst free synthesis of fused pyrido[2,3-*d*]pyrimidines and pyrazolo[3,4-*b*]pyridines in water

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Abstract

A one-pot, three-component condensation reaction of an aldehyde, benzoyl acetonitrile (3-oxo-3-phenylpropane nitrile) and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione or 3-methyl-1-phenyl-1*H*-pyrazol-5-amine in water to give fused pyrido[2,3-*d*]pyrimidines and pyrazolo[3,4-*b*]pyridines in high yields without any catalyst, is described.

Keywords: Aminopyrazole; Aqueous media; 3-Methyl-1-phenyl-1*H*-pyrazol-5-amine; Pyrazolo[3,4-*b*]pyridine

Development of environmentally benign and clean synthetic procedure is one of the goals of organic synthesis [1]. In this way during the last two decades, water has been used as a green medium for organic reactions [2]. Because the use of water as solvent has several benefits; water is a cheap, plentiful, nontoxic, nonflammable, safe, neutral and natural solvent [3–6]. Also, one-pot multi-component reaction (MCR) strategies offer significant advantages over conventional linear-type syntheses by virtue of their convergence, productivity, facile execution and high yield [7]. Recently one-pot multi component have been used in drug discovery programs [8–12]. Therefore, the importance of accomplish of the MCRs in water and/or without any harmful organic solvents have been reported [13,14].

Pyrido[2,3-*d*]pyrimidine ring system is the main part of structure in a number of biologically active compounds which have antibacterial [15], anticancer [16], antipyretic [17], analgesic and anti-inflammatory [18], inhibitors of mTOR kinase [19], tyrosine kinase inhibitor [20,21] and adenosine kinase inhibitor [22] as well as anti-tumor activities [23]. As a consequence of the above reasons the synthesis of pyrido[2,3-*d*]pyrimidines compounds have been attracted great attention and several methods were reported for synthesis of these compounds [24–34]. Pyrazolo[3,4-*b*]pyridines rings have also displayed in wide range of biological and pharmaceutical activates [35]. Hence, the preparation of these compounds has been attracted great attention and numerous methods have been reported [36–40]. In spite of the potential utility of aforementioned routes for the synthesis of pyrido[2,3-*d*]pyrimidines and pyrazolo[3,4-*b*]pyridines compounds, many of these methods involve toxic and strong acidic/basic conditions, long reaction times and low yields as well as use of toxic organic reagents or catalysts. Therefore, to resolve these problems and limitations, the development of a new and efficient reaction with high catalytic activity, short reaction time and

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simple workup for the preparation of pyrido[2,3-*d*]pyrimidines and pyrazolo[3,4-*b*]pyridines under neutral, mild and practical conditions is of great interest.

In continuing our interest in MCRs [41] herein we wish to report a one-pot, an efficient approach for the synthesis of pyrido[2,3-*d*]pyrimidines and pyrazolo[3,4-*b*]pyridines; by three-component reaction of benzoyl acetonitrile (**1**), aminouracil (**2**) or 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3**), and an aldehyde (**4**) in water in the absence of any catalyst (Schemes 1).

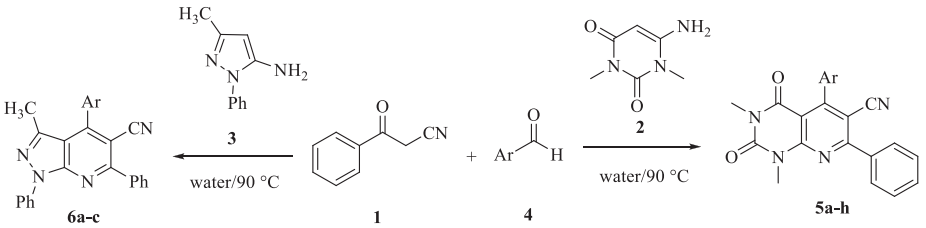
In order to optimize the reaction conditions, we carried out the reaction of benzoyl acetonitrile (**1**) with 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**2**) and 4-bromobenzaldehyde (**4b**) in water in the absence of catalyst in 24 h at room temperature. The results showed that the reaction could proceed as well. After, in order to obtain the best temperature, this reaction was carried out at various temperatures ranging from 25 to 90 °C under similar conditions in water. As disclose in Table 1, the maximum yield was observed at 90 °C (entry 6). Therefore, this temperature was chosen as the reaction temperature for all further reactions. At next step, the reaction was performed in different times, the results showed that amount of products at 8 h is maximum; the results of optimization process are summarized in Table 1.

After that, optimum conditions were obtained a variety of aldehydes were used for the scope and generality of this method (Scheme 2) and the results were listed in Table 2. It is demonstrated that all the aldehydes that used to give the product of pyrido[2,3-*d*]pyrimidines **5a–h** with satisfactory yields, and all the reactions were very clean. In order to further ability of method 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3**) were used instead of aminouracil. The result showed that reaction could proceed as well as amino uracil. Then different aldehydes was tested with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3**) in the presence of 3-oxo-3-phenylpropanenitrile in these conditions and pyrazolo[3,4-*b*]pyridines **6a–c** were obtained in excellent yields (Table 2).

In this study, we have successfully applied benzoyl acetonitrile in reaction with amino uracil or aminopyrazole using different aldehydes for one-pot three-component synthesis of pyrido[2,3-d]pyrimidine and pyrazolo[3,4-*b*]pyridine derivatives in water at 90 °C. The mild reaction conditions, less expensive of reaction medium, operational simplicity, environmental friendliness, and high yields are the advantages of the protocol. The present method may find some value in organic synthesis, because it is operationally very simple and the starting materials are readily available.

General procedure for the synthesis of compounds (***4a–h*** *and* ***6a–c***): A solution of 3-oxo-3-phenyl propanenitrile (1 mmol), aldehyde (1 mmol), amino uracil or 5-amino-3-phenyl-pyrazol (1 mmol) was heated in water (5 mL) for 8 h at 90 °C. After completion of the reactions, which has been followed by TLC, the reaction mixture was filtered and the pure products were obtained. In some of cases pure products were obtained by extra recrystallization from methanol.

1,3-Dimethyl-2,4-dioxo-7-phenyl-5-(3-methoxylphenyl)-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (**5h**): White crystals, mp: 163−165 °C. IR (KBr, cm^{-1}): 3064, 2930, 2223, 1716, 1669, 1555, 1476. ^1H NMR (400 MHz, DMSO-d_6): δ 3.30 (s, 3H, OCH_3), 3.77 (s, 3H, NCH_3), 3.78 (s, 3H, NCH_3), 6.75 (t, 1H, J = 2.0 Hz, CH^{arom}), 6.80 (ddd, 1H, J = 7.6 Hz, J = 1.6 Hz, J = 0.8 Hz, CH^{arom}), 6.99 (ddd, 1H, J = 8.4 Hz, J = 2.6 Hz, J = 0.8 Hz, CH^{arom}), 7.39 (t, 1H, J = 8.0 Hz, CH^{arom}), 7.49–7.52 (m, 3H, $3CH^{arom}$), 7.96 (dd, 2H, J = 4.0 Hz, J = 0.8 Hz, $2CH^{arom}$). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ 162.74, 158.70, 158.52, 158.04, 152.16, 150.65, 137.77, 136.41, 131.11, 129.30, 129.20, 128.61, 119.76, 116.27, 113.72, 113.49, 107.04, 103.76, 55.11, 30.04, 28.21. MS *m/z* (%): 398 (43) [M^+], 397 (35), 383 (5), 141 (26), 107 (39), 105 (49), 77 (60), 57 (100), 44 (57), 43 (92), and 42 (64). Anal. calcd. for $C_{23}H_{18}N_4O_3$: C, 69.34; H, 4.55; N, 14.06. Found: C, 69.30; H, 5.07; N, 14.34.

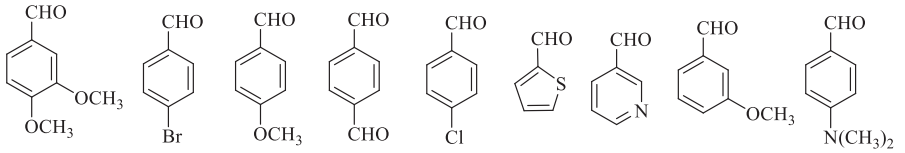


Scheme 1. Synthesis of pyrido[2,3-*d*]pyrimidines and pyrazolo[3,4-*b*]pyridines.

Table 1
Optimization of reaction conditions for synthesis of pyrido[2,3-*d*]pyrimidines (**5b**).[a]

Experimental number	Temperature (°C)	Time (h)	Isolated yield (%)
1	25	24	74
2	40	24	84
3	70	24	93
4	90	24	97
5	90	16	97
6	90	8	97
7	90	4	91
8	90	1	65

[a] 4-Bromo benzaldehyde(1 mmol), amino uracil (1 mmol), and 3-oxo-3-phenylpropanenitrile (1 mmol).



4a **4b** **4c** **4d** **4e** **4f** **4g** **4h** **4i**

Scheme 2. Various aldehydes.

Table 2
Synthesis of pyrido[2,3-*d*]pyrimidines **5a–h** and pyrazolo[3,4-*b*]pyridine **6a–c** in water.[a]

[a]Entry	CH-acid	Aldehyde	Product	Isolated yield (%)
1	**2**	**4a**	**5a**	90
2	**2**	**4b**	**5b**	97
3	**2**	**4c**	**5c**	86
4	**2**	**4d**	**5d**	83
5	**2**	**4e**	**5e**	93
6	**2**	**4f**	**5f**	82
7	**2**	**4g**	**5g**	84
8	**2**	**4h**	**5h**	96
9	**3**	**4c**	**6a**	98
10	**3**	**4i**	**6b**	96
11	**3**	**4e**	**6c**	95

[a] Aldehyde (1 mmol), amino uracil or aminopyrazole (1 mmol), and 3-oxo-3-phenylpropanenitrile (1 mmol).

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