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Convenient One-pot Access to Pyrano[2,3-*d*]pyrimidine Derivatives *via* a $CuCl_2.2H_2O$ Catalyzed Knoevenagel-Michael Addition Reaction in Water/Ethanol Media

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Convenient procedure for the synthesis of corresponding pyrano[2,3-*d*]pyrimidine derivatives were developed *via* one-pot three-component reaction of aryl aldehyde derivatives, malononitrile with barbituric acids in the presence of copper(II) chloride dihydrate ($CuCl_2.2H_2O$) as highly efficient Lewis acid catalyst. This protocol has advantages such as including a readily and inexpensive catalyst, high reaction yields, eco-friendly solvent and high atom-economy.

Keywords: Sustainable procedure, Copper(II) chloride dihydrate ($CuCl_2.2H_2O$), Water/ethanol media, Pyrano[2,3-*d*]pyrimidine derivatives, One-pot reaction

INTRODUCTION

In recent years, multi-component reactions (MCRs) [1-12] have played crucial role in the combinatorial chemistry to assemble complex target structures with attractive biological aspects using simple and readily available starting materials, through a one-pot process. The one-pot character delivers fewer by-products, besides the lower costs, time and energy saving, in comparison with classical stepwise synthetic routes and leads to the formation of interesting heterocyclic scaffolds [13].

Synthesis of pyrimidine derivatives has attracted great attention recently in synthetic organic chemistry due to their therapeutic and pharmacological features. Various biological properties of pyranopyrimidine derivatives cause wide interest in the preparation of these compounds. Pyrano[2,3-*d*]pyrimidine derivatives, including attached rings of a uracil and a pyran are analogues of uracil which have different pharmacological properties such as antiallergic [14], antihypertensive [15], cardiotonic [16], bronchiodilator [17], antibronchitic [18] and antitumor activities [19]. Considering the importance of such compounds, many methods for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives have been reported. The conventional synthesis method involves condensation of barbituric acid/1,3-dimethylbarbituric acid with aromatic aldehyde and malononitrile using different catalytic systems such as DABCO-based ionic liquids [20], L-proline [21], iron ore pellet [22], nano-sawdust-OSO_3H [23], Al-HMS-20 [24], TSA/$B(OH)_3$ [25], Mn/ZrO_2 [26], green cellulose-based nanocomposite [27], DBA [28]. However, most of these synthetic approaches have restrictions, including the utilization of intense acidic or basic conditions, difficult work-up, toxic or expensive catalysts or reagents, low yields and prolonged reaction times. In continuation of our work to develop efficient catalytic systems to synthesize such compounds, we employed copper(II) chloride dihydrate ($CuCl_2.2H_2O$) as a catalyst to promote three-component reactions to obtain pyrano[2,3-*d*]pyrimidine derivatives. We report herein a cheap, efficient, $CuCl_2.2H_2O$-catalyzed procedure for the synthesis of pyrano[2,3-*d*]pyrimidine

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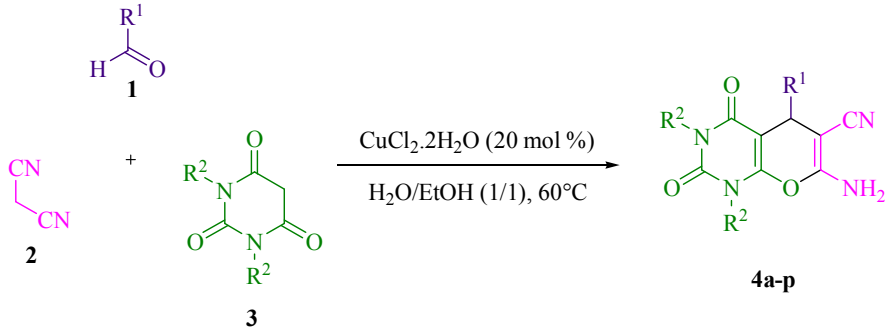


Scheme 1. Synthesis of pyrano[2,3-*d*]pyrimidine derivatives

derivatives *via* three-component and Knoevenagel-Michael addition reaction in water/ethanol media.

EXPERIMENTAL

General

Melting points and IR spectra of all compounds were determined using an Electro thermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer. Nuclear magnetic resonance, ^{1}H NMR spectra were also recorded on a Bruker DRX-400 Avance instrument with DMSO-d_6 as solvent. In this article, all reagents and solvents were purchased from Merck, Fluka and Acros chemical companies, and used without further purification.

General Procedure for Preparation of Pyrano[2,3-*d*]pyrimidine Derivatives (4a-p)

A mixture of aryl aldehyde derivatives (1, 1.0 mmol), malononitrile (2, 1.0 mmol), barbituric acid derivatives (3, 1.0 mmol), $CuCl_2.2H_2O$ (20 mol%) and 3 ml H_2O/EtOH (1/1) was heated at 60 °C for appropriate time. After completion of the reaction, as monitored by TLC using ethylacetate/n-hexane (3:7) as eluent, the mixture was cooled to rt, the precipitated product was filtered and washed with ethanol. The crude product was purified by recrystallization from ethanol to afford the desired product (4a-p). The products were characterized by melting points and ^{1}H NMR spectroscopy. Spectral data of the selected and known products are represented below:

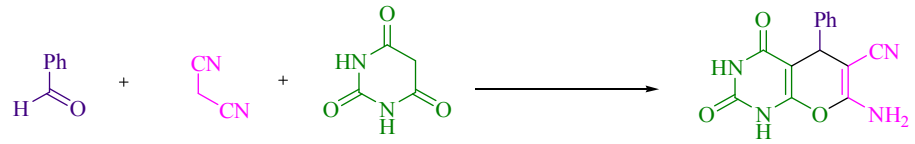
7-Amino-5-(4-bromophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4g). Solid powder; Yield: 79 %; m.p.: 211-213 °C; IR (KBr): ν 3375 (NH_2), 2275 (C≡N), 1705 (C=O), 1631 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 3.07 (3H, s, CH_3), 3.34 (3H, s, CH_3), 4.32 (1H, s, CHAr), 7.21 (2H, d, J = 8.4 Hz, ArH), 7.38 (2H, s, NH_2), 7.93 (2H, d, J = 8.4 Hz, ArH).

7-Amino-5-(4-methylphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4p). Solid powder; Yield: 87%; m.p.: 203-205 °C; IR (KBr): ν 3425 (NH_2), 2180 (C≡N), 1698 (C=O), 1674 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 2.25 (3H, s, CH_3), 3.07 (3H, s, CH_3), 3.34 (3H, s, CH_3), 4.27 (1H, s, CHAr), 7.07-7.12 (4H, m, ArH), 7.30 (2H, s, NH_2).

RESULTS AND DISCUSSION

Recently, we observed that the use of $CuCl_2.2H_2O$ as a catalyst resulted in a significant rate acceleration with a high yield in the synthesis of polysubstituted dihydro-2-oxopyrrols [29]. Accordingly, we evaluated the catalyst activity of $CuCl_2.2H_2O$ for the synthesis of pyrano[2,3 *d*]pyrimidine derivatives. The initially, catalytic activity of $CuCl_2.2H_2O$ was tested in a model system of a three-component reaction between a mixture of benzaldehyde (1.0 mmol), malononitrile (1.0 mmol) and barbituric acid (1.0 mmol). In the absence of a catalyst, only a trace of product was obtained at rt and 60 °C for a reaction time of about 240 min (Table 1, entries 1 and 2) indicating that the catalyst should be necessary for this transformation. The optimized conditions were determined by changing the parameters affecting the reaction such as amount of the catalyst, solvent and the temperature. Thereafter, for determining the

Table 1. Optimization of the Reaction Condition on the Synthesis of 4a[a]



Entry	$CuCl_2.2H_2O$ (mol %)	Solvent/Conditions	Time (min)	Isolated yields (%)
1	Catalyst free	H_2O/EtOH, r.t.	240	Trace
2	Catalyst free	H_2O/EtOH, 60 °C	240	Trace
3	5	H_2O/EtOH, 60 °C	120	28
4	10	H_2O/EtOH, 60 °C	90	46
5	15	H_2O/EtOH, 60 °C	55	72
6	20	H_2O/EtOH, 60 °C	35	87
7	20	H_2O/EtOH, r.t.	90	52
8	20	H_2O/EtOH, 40 °C	45	59
9	20	EtOH, 60 °C	35	67
10	20	EtOH, r.t.	65	51
11	20	Solvent free, 60 °C	50	38
12	20	H_2O, 60 °C	75	54
13	20	H_2O, r.t.	120	36
14	20	$CHCl_3$, r.t.	180	17
15	20	CH_2Cl_2, r.t.	180	23
16	20	MeOH, r.t.	75	35
17	20	CH_3CN, r.t.	90	29
18	25	EtOH/H_2O, 60 °C	35	89

[a]Reaction conditions: benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), barbituric acid (1.0 mmol), solvent (3 ml) and catalyst in various solvents and temperatures.

optimum quantity of catalyst, the model reaction was performed in the presence of different amounts of $CuCl_2.2H_2O$. Various loadings of catalyst, including 5, 10, 15, 20 and 25 mol% were screened in our model reaction. By lowering the catalyst loading to 5 mol%, the corresponding product was obtained in lower yield (Table 1, entry 3). By increasing the amount of catalyst from 5 to 10, 15 and 20 mol%, the reaction time was reduced and the yield of the product increased (Table 1, entries 3-6). So, among them, 20 mol% of $CuCl_2.2H_2O$ was proven to be the

most efficient catalyst for this reaction (Table 1, entry 6). The larger amount of the catalyst did not improve the yields (Table 1, entry 18). Following the reaction in the absence of solvent and in the presence of 20 mol% of the catalyst and at 60 °C, which resulted in the production of a reaction product with low yield and longer reaction time, indicated that the solvent plays an effective role in the development of this reaction (Table 1, entry 11). Therefore, choosing an appropriate solvent has crucial importance for the successful synthesis. To search for the optimal solvent, the model reaction was investigated in the presence of 20 mol% of $CuCl_2.2H_2O$ using various solvents. The results indicated that a low yield of the desired product is obtained when EtOH, H_2O, $CHCl_3$, CH_2Cl_2, MeOH and CH_3CN are used as solvents. The best yield was obtained when the reaction was performed in H_2O/EtOH (1/1) and it accelerated the reaction compared with other solvents and solvent-free condition. The results of these comparative experiments are summarized in Table 1. We also examined the influence of temperature on the reaction yield. Results indicated that when the reaction proceeds using $CuCl_2.2H_2O$ (20 mol%) at room temperature for 90 min, the yield of the corresponding product is low (52%) (Table 1, entry 7). The reaction time was decreased from 90 min to 35 min when the reaction temperature increased from r.t. to 60 °C, and the yield of 87% was obtained. Therefore, we employed the optimized conditions 20 mol% of $CuCl_2.2H_2O$ as a Lewis acid catalyst in 3 ml H_2O/EtOH (1/1) at 60 °C for the condensation reaction of aryl aldehyde derivatives 1, malononitrile 2 with barbituric acids 3 into the corresponding pyrano[2,3-*d*]pyrimidine derivatives (Scheme 1 and Table 2). Encouraged by the remarkable results obtained from the above conditions, and in order to show the generality and scope of this protocol, we used various aromatic aldehydes bearing either electron-withdrawing functional groups or electron-donating groups for the synthesis of corresponding pyrano[2,3-*d*]pyrimidine derivatives. The effects of substituents on the aromatic rings were found to be strong in terms of yields under these reaction conditions. Both classes of aromatic aldehydes containing electron-releasing and electronwithdrawing substituents in their aromatic rings gained the appropriate products in high reaction yields and short reaction times. The reaction times of aromatic aldehydes having electron-withdrawing groups and electron-donating groups had rather same results. We also applied 1,3-dimethylbarbituric acid. In each of these substitutions, no significant difference was observed in the reaction rate and product yields. The results are summarized in Table 2. The attractive features of this catalyst are easy to handle, mild and environmentally benign conditions, operational simplicity, high reaction yields and short reaction times.

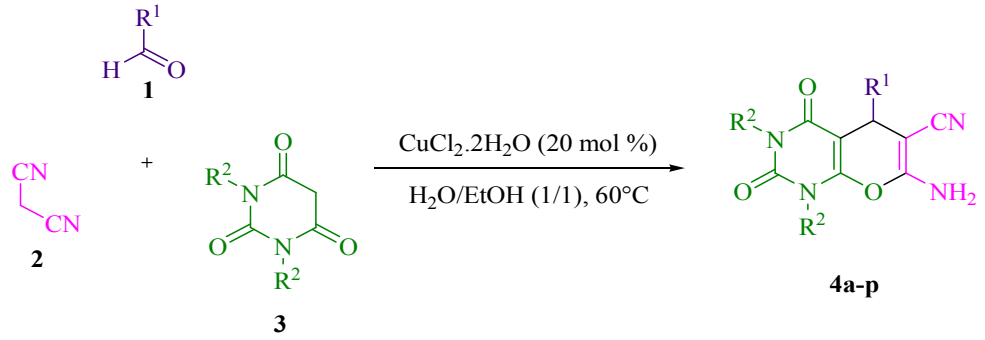
Proposed mechanism for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives are shown in Scheme 2. We suggest that $CuCl_2.2H_2O$ is an effective Lewis acid [29] for the facile knoevenagel condensation between aryl aldehyde 1 and malononitrile 2 which produces olefin A. $CuCl_2.2H_2O$ also catalyzes the generation of a proposed enolate intermediate B, which is formed from barbituric acid. An intermolecular cyclization of C from the enol form of B produces compound D. Finally, a tautomerization affords the target products 4.

Comparison of catalytic ability of some previously reported catalytic systems with $CuCl_2.2H_2O$ for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives is shown in Table 3. This study reveals that $CuCl_2.2H_2O$ has shown its extraordinary potential to be an alternative cheap, cost effective, eco-friendly and readily Lewis acid for the synthesis of these compounds. In addition, high reaction yields and short reaction times in the reaction are the notable advantages for the present methodology.

CONCLUSIONS

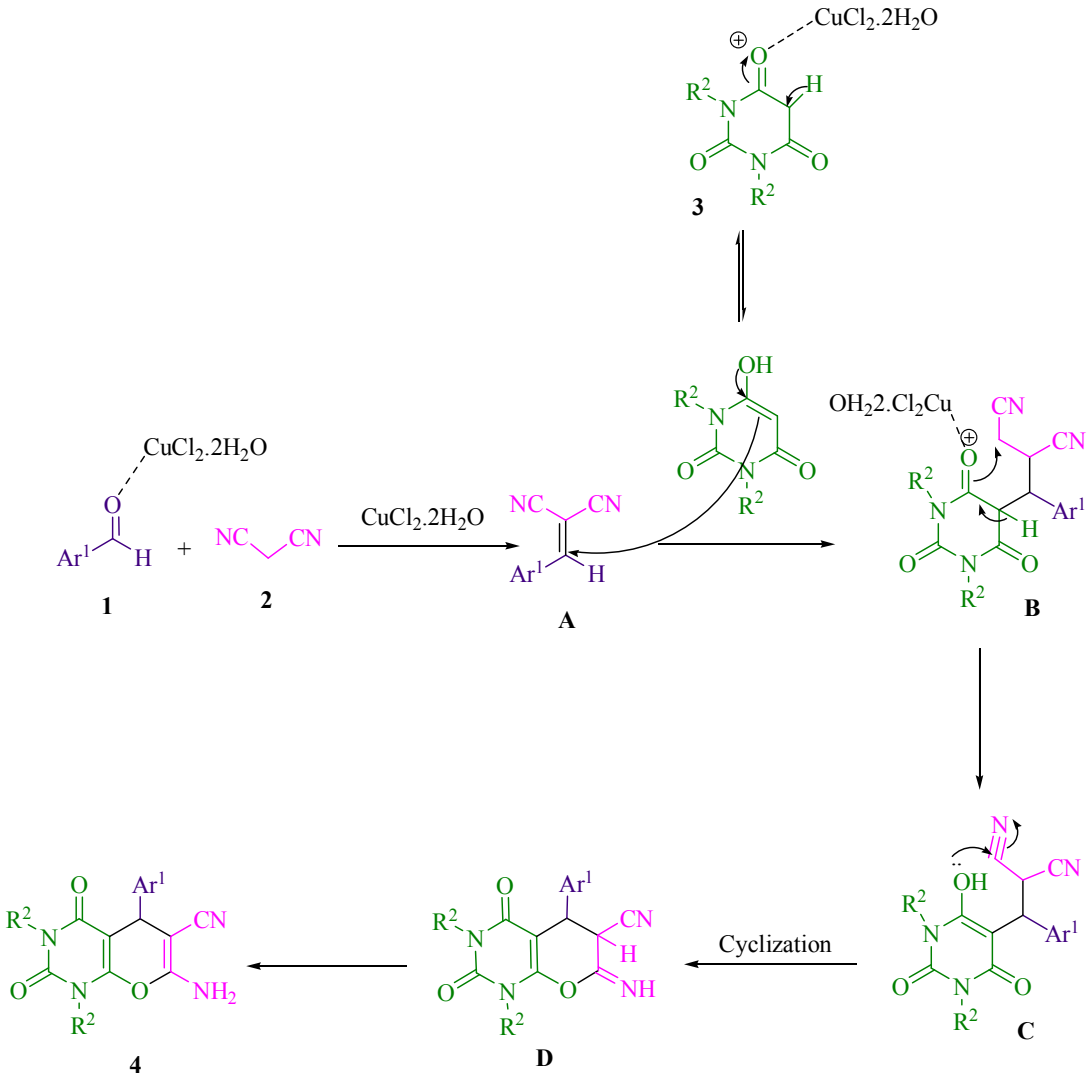
In conclusion, we have introduced copper(II) chloride dihydrate ($CuCl_2.2H_2O$) as an economical and highly efficient catalyst for facile one-pot three-component synthesis of pyrano[2,3-*d*]pyrimidine derivatives. The promising features that distinguish this approach from other reported methods regarding this transformation are using the high catalytic ability, low cost and readily catalyst, as well as simple reaction work-up, which make the present methodology more economical and industrially important. Furthermore, high reaction yields and short reaction times besides the water/ethanol media are the other advantages of the present protocol.

Table 2. $CuCl_2.2H_2O$ Catalyzed Synthesis of Pyrano[2,3-*d*]pyrimidine Derivatives[a]



Entry	R^1	R^2	Product	Time (min)	Isolated yields (%)	M.p. (°C)	Lit. M.p. (°C)
1	C_6H_5	H	4a	35	87	223-225	224-225[20]
2	C_6H_5	Me	4b	35	86	238-240	237-238[25]
3	4-Cl-C_6H_4	H	4c	50	81	234-236	235-237[25]
4	2-Cl-C_6H_4	H	4d	40	83	212-214	211-214[25]
5	2,4-$(Cl)_2$-C_6H_3	H	4e	55	78	242-244	241-242[21]
6	4-Br-C_6H_4	H	4f	45	82	243-245	240-245[22]
7	4-Br-C_6H_4	Me	4g	40	79	211-213	210-211[26]
8	3-OH-C_6H_4	H	4h	55	76	156-158	158-160[21]
9	2-OH-C_6H_4	H	4i	40	80	168-170	169-170[22]
10	4-O_2N-C_6H_4	H	4j	35	87	234-236	236-237[20]
11	4-O_2N-C_6H_4	Me	4k	30	84	215-217	214-216[25]
12	3-O_2N-C_6H_4	H	4l	35	89	257-259	259-261[23]
13	4-OMe-C_6H_4	H	4m	40	85	274-276	272-274[23]
14	2,4-$(OMe)_2$-C_6H_3	H	4n	45	86	225-227	227-228[22]
15	4-Me-C_6H_4	H	4o	35	90	226-228	226[25]
16	4-Me-C_6H_4	Me	4p	30	87	203-205	205-207[25]

[a]Reaction conditions: aryl aldehyde derivatives (1, 1.0 mmol), malononitrile (2, 1.0 mmol) with barbituric acid/1,3-dimethylbarbituric acid (3, 1.0 mmol) and $CuCl_2.2H_2O$ (20 mol%) as catalyst in 3 ml H_2O/EtOH (1/1) at 60 °C.



Scheme 2. Proposed mechanistic route for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives

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