Chinese Chemical Letters 25 (2014) 308–312

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

A green multicomponent synthesis of bioactive pyrimido[4,5-b]quinoline derivatives as antibacterial agents in water catalyzed by $RuCl_3{\cdot}xH_2O$

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ARTICLE INFO

Article history:
Received 15 August 2013
Received in revised form 23 September 2013
Accepted 8 October 2013
Available online 12 November 2013

Keywords:
Pyrimido[4,5-b]quinoline
Reusable homogenous catalyst
One-pot multicomponent reaction
Antibacterial activity
Water

ABSTRACT

An efficient, convenient and environmentally benign one-pot multicomponent reaction for the preparation of pyrimido[4,5-b]quinoline derivatives as biologically, pharmacologically and antibacterially active products has been developed using $RuCl_3{\cdot}xH_2O$ as a reusable homogenous catalyst. Use of water as a green solvent, purification of products by non-chromatographic methods, reusability of transition metal homogenous catalyst, saving energy by employing multicomponent reactions, short reaction times and high yields, are some of the advantages of this process.

1. Introduction

In recent years, green chemistry has attracted considerable attention of organic and medicinal chemists. One of the most important roles of green chemistry is the invention, design and application of chemical reactions that reduce or eliminate the use of hazardous solvents [1]. In comparison with organic solvents, water is non-toxic, non-corrosive, non-explosive and is readily available at low cost. These properties along with the network of hydrogen bonds, large surface tension, high polarity and high specific heat capacity make it both economical and environmentally friendly and thus suitable as a green solvent [2,3].

Multicomponent reactions (MCRs) have emerged as a powerful synthetic tool for the preparation of biologically active compounds [4,5] and important drugs [6–8]. These types of reactions are especially attractive due to the features such as atom economy, operational simplicity and straightforward reaction design, reduced number of workups, extraction and purification processes and hence minimize waste generation. The combination of green chemistry and MCRs represents a very efficient method from both economical and environmental perspectives since the isolation of the intermediates is skipped, the overall reaction time is significantly decreased and higher yields of products are obtained.

1,4-Dihydropyridine compounds (1,4-DHPs) are a class of nitrogen containing heterocycles that have received much attention due to their wide range of pharmaceutical and biological properties [9–11]. A number of improved methods have been reported in the literatures for the synthesis of new compounds having substituents on the C_2, C_3, C_5, and C_6 positions of the 1,4-dihydropyridine ring, with enhanced biological activities [12–16]. In spite of potential utility of these methods, most of them suffer from disadvantages such as forcing conditions for catalyst preparation, long reaction times, low yields, formation of several side products, high temperature and the use of toxic solvents.

To overcome these drawbacks, we decided to introduce a new catalyst for more efficient and cleaner synthesis of pyrimido[4,5-b]quinoline derivatives with a potentially extensive range of biological and pharmacological properties such as antitumor [17], antiviral [18] and antioxidant [19] activities. These compounds can be used to produce bioactive drugs such as Quinine, Chloroquine, Luotonine-A and Camptothecin [20].

The transition metal complexes are well known as powerful, simple and efficient Lewis acid catalysts for various organic transformations [21,22]. $RuCl_3{\cdot}xH_2O$ salt as a homogenous environmentally friendly, mild, simple and efficient Lewis acid catalyst, has been used for various organic transformations [23–31]. The advantages of using $RuCl_3{\cdot}xH_2O$ salt are its stability

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http://dx.doi.org/10.1016/j.cclet.2013.10.021

at elevated temperatures, safety, mildness, non-volatility, low toxicity, reusability and biocompatibility.

In addition to the above mentioned characteristics, higher reactivity and excellent selectivity of this catalyst and along with the important role of nitrogen-containing heterocyclic compounds in medicinal chemistry also prompted us to explore the potential of $RuCl_3{\cdot}xH_2O$ in MCRs that could produce diversified heterocyclic products with practically important biological and pharmacological properties.

2. Experimental

IR spectra were obtained in KBr discs on a Perkin-Elmer model Spectrum One FT-IR Spectrometer. ^{1}H NMR spectra were obtained on a Bruker DRX-400 Avance spectrometer and ^{13}C NMR were obtained on a Bruker DRX-100 Avance spectrometer. Samples were analyzed in DMSO-d_6, and chemical shift values are reported in ppm relative to tetramethylsilane (TMS) as the internal reference. Melting points were measured on an Electrothermal apparatus and were uncorrected. Elemental analyses were made by a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values. Sonication was performed in an Elmasonic S 40H ultrasonic cleaning unit. All materials and solvents were purchased from Merck and used without further purification.

$RuCl_3{\cdot}xH_2O$ (3 mol%) was added to a mixture of aldehyde (1.0 mmol), 6-amino-1,3-dimethyluracil (1.0 mmol), and cyclic 1,3-diketone (1.0 mmol) in deionized water (10 mL). The reaction mixture was heated to 85 °C and stirred magnetically for an appropriate period of time. After the completion of the reaction as indicated by TLC analysis, the mixture was cooled to room temperature. The colored solid product was collected and washed with warm ethanol to afford the pure product. For further purification, some derivatives were recrystallized from ethanol. Spectroscopic data for the selected products are as follows:

5-(2-Chloro-6-fluorophenyl)-1,3,8,8-tetramethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline 2,4,6(1H,3H,5H)trione ***(7a)***: Light yellow solid, mp 302–304 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 (s, 3H), 1.04–1.08 (m, 3H), 1.98 (d, 2H, J = 16 Hz), 2.21 (d, 2H, J = 16.4Hz), 3.05 (s, 3H), 3.45 (s, 3H), 5.42 (s, 1H), 7.03 (t, 1H, ArH),7.122–7.154 (m, 2H, ArH) 9.06 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.53, 26.32, 28.15, 29.94, 30.20, 43.16, 50.52, 88.14, 113.46, 115.02, 122.27, 126.53, 127.94, 135.00, 146.16, 147.22, 150.01, 160.16, 161.42, 195.90. FT-IR (KBr, cm^{-1}): ν 3290, 3232, 3075, 2943, 2873, 1701, 1660, 1642, 1607, 1495, 1453, 1378, 1359, 1210, 886, 788, 730, 687. Anal. Calcd. for $C_{21}H_{21}ClFN_3O_3$: C 60.36, H 5.07, N 10.06; Found: C 60.23, H 4.90, N 9.8.

5-(3-Nitrophenyl)-1,3,8,8-tetramethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinolin2,4,6(1H,3H,5H)trione ***(8a)***: Yellow solid, mp 287–290 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.16 (m, 16H), 5.69 (s, 1H), 7.51 (t, 1H, J = 8 Hz, ArH), 7.60 (d, 1H, J = 8.0 Hz, ArH), 7.88 (s, 1H, ArH), 7.92 (d, 1H, J = 8.0 Hz, ArH), 10.15 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.81, 27.72, 30.11, 30.53, 37.55, 41.90, 50.41, 89.12, 113.53, 117.21, 122.71, 127.92, 133.74, 141.60, 146.00, 147.27, 148.25, 150.12, 160.93, 195.74. FT-IR (KBr, cm^{-1}): ν 3391, 3068, 2953, 1702, 1668, 1653, 1607, 1594, 1525, 1500, 1380, 1350, 1212, 904, 873, 790, 734, 681. Anal. Calcd. for $C_{21}H_{22}N_4O_5$: C 61.45, H 5.40, N 13.65; Found: C 61.32, H 5.28, N 13.44.

5-(2-Chloro,6-fluorophenyl)-1,3-dimethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-trione ***(2b)***: White solid, mp 298–300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.78 (m, 1H), 1.94 (m, 1H), 2.17–2.34 (m, 2H), 2.66 (m, 2H), 3.05 (s, 3H), 3.46 (s, 3H), 5.44 (s, 1H), 7.016 (t, 1H, J = 8.8 Hz, ArH), 7.123 (d, 1H, J = 8.0 Hz, ArH), 7.137 (d, 1H, J = 8.0 Hz, ArH), 9.11 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.00, 21.23, 26.96, 27.99, 30.76, 37.14, 87.81, 114.52, 116.55, 126.01, 128.20, 128.40, 136.71, 145.05, 145.36, 150.00, 153.00, 160.00, 195.06. FT-IR (KBr, cm^{-1}): ν 3555, 3405, 3173, 2955, 2872, 1697, 1660, 1607, 1606, 1506, 1467, 1356, 1205, 838, 793, 736, 693, 675. Anal. Calcd. for $C_{19}H_{17}ClFN_3O_3$: C 58.54, H 4.40, N 10.78; Found: C 58.40, H 4.22, N 10.55.

5-(4-Dimethylaminophenyl)-1,3-dimethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H)-trione ***(6b)***: Orange solid, mp 278–280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82, 1.81 (m, 1H), 1.92–1.99 (m, 1H), 2.22–2.26 (m, 2H), 2.58–2.63 (m, 1H), 2.73–2.75 (m, 1H), 3.10 (s, 3H), 3.34 (s, 6H), 3.45 (s, 3H), 4.82 (s, 1H), 6.55 (dd, 2H, J = 8.8, 4.8 Hz, ArH), 7.02 (dd, 2H, J = 8.4, 4.8 Hz, ArH), 9.029 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.24, 26.92, 28.11, 30.64, 32.66, 37.19, 40.38, 91.16, 112.6, 113.12, 128.45, 135.37, 143.83, 149.35, 151.3, 151.5, 161.24, 195.34. FT-IR (KBr, cm^{-1}): ν 3436, 3187, 3078, 2925, 2885, 1697, 1659, 1640, 1608, 1517, 1495, 1379, 1352, 1199, 825, 754, 702, 661. Anal. Calcd. for $C_{21}H_{24}N_4O_3$: C 66.30, H 6.36, N 14.73; Found: C 66.19, H 6.20, N 14.51.

3. Results and discussion

Our literature search revealed that there are no reports on the use of $RuCl_3{\cdot}xH_2O$ as an efficient and effective catalyst, without any toxic solvent in the synthesis of pyrimido[4,5-b]quinoline derivatives *via* a three-component reaction conditions.

In this methodology, cyclic 1,3-diketones, uracil and aldehyde react in one step in the presence of Lewis acid $RuCl_3{\cdot}xH_2O$ in water. Uracils are important compounds in the synthesis of anti-cancer and antiviral drugs. In this study, 6-amino-1,3-dimethyl uracil was used as an important partner in the synthesis of tricyclic fused ring derivatives. This agent provided C_5 and C_6 carbons in the products. Dimedone or 1,3-cyclohexanedione as a cyclic ketone with strong nucleophilic properties, provided C_2, C_3 carbons in the products.

In order to increase yield, the reaction conditions were optimized using 4-nitrobenzaldehyde, 6-amino-1,3-dimethyl uracil and dimedone under different temperatures and amount of the catalyst. (Scheme 1) The results are summarized in Table 1.

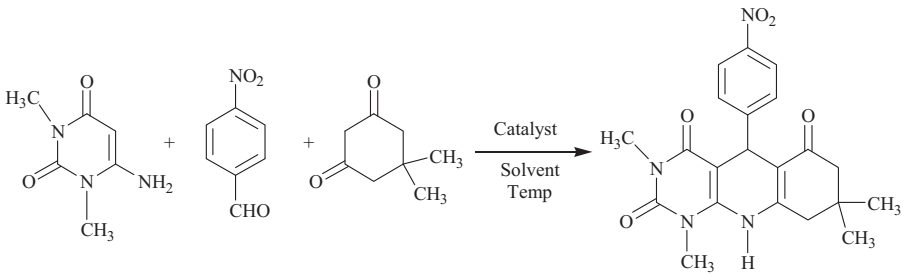
The optimum amount of $RuCl_3{\cdot}xH_2O$ was evaluated. The highest yield was obtained with 3 mol% of the catalyst. A further increase in the amount of $RuCl_3{\cdot}xH_2O$ did not have any significant effect on product yield. In order to establish the true effectiveness of the catalyst, a reaction of 4-nitrobenzaldehyde, dimedone and 6-amino-1,3-dimethyl uracil was performed at 90 °C without any catalyst in water. It was found that only trace amount of pyrimido[4,5-b]quinoline was obtained after 120 min of heating (Table 1, entry 6).

Choice of solvent plays an important role in most of the MCRs. To compare the efficiency of the solvent, various solvents, including nonpolar solvents such as *n*-hexane, protic solvents, such as water, ethanol and methanol, and aprotic polar solvents, such as acetonitrile, were tested. The results, presented in Table 2,

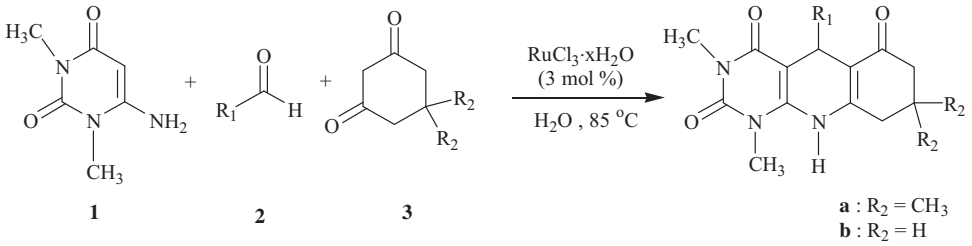
Table 1
Screening of the amount of the catalyst and temperature in one-pot synthesis of model reaction.[a]

Entry	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)[b]
1	20	90	60	80
2	10	90	50	85
3	7	90	50	89
4	5	90	40	90
5	3	90	30	94
6	–	90	120	Trace
7	3	70	60	71
8	3	80	45	85
9	3	85	30	95
10	3	100	30	92

[a] All reactions were run with 4-nitrobenzaldehyde (1.0 mmol), dimedone (1.0 mmol), and 6-amino-1,3-dimethyl uracil (1.0 mmol) in water (10 mL).
[b] Isolated yield.



Scheme 1. Synthesis of 5-(4-nitrophenyl)-1,3,8,8-tetramethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-trione as a model reaction.



Scheme 2. $RuCl_3{\cdot}xH_2O$ catalyzed synthesis of pyrimido[4,5-b]quinoline derivatives.

Table 2
Influence of the solvents on the synthesis of pyrimido[4,5-b]quinoline.[a]

Entry	Solvent	Temperature (°C)	Yield (%)[b]
1	Ethanol	Reflux	78
2	Methanol	Reflux	80
3	Water	85	95
4	Water/ethanol[c]	90	85
5	Water	100	92
6	Acetonitrile	Reflux	60
7	*n*-Hexane	Reflux	Trace
8	None	90	40

[a] Reaction condition: 4-nitrobenzaldehyde (1 mmol), dimedon (1 mmol), 6-amino-1,3-dimethyl uracil (1 mmol) and (3 mol%) $RuCl_3{\cdot}xH_2O$ for 30 min.
[b] Isolated yield.
[c] A mixture of 5 mL of water and 5 mL of ethanol was used as the solvent.

Table 3
Choice of the catalyst for pyrimido[4,5-b]quinoline formation. [a]

Entry	Catalyst (mol%) [Ref.]	Time (h)	Yield (%)[b]
1	$FeCl_3{\cdot}xH_2O$ [10]	2	56
2	$RuCl_3{\cdot}xH_2O$ [3]	0.5	95
3	$CoCl_2{\cdot}xH_2O$ [10]	2	48
4	$NiCl_2{\cdot}xH_2O$ [10]	2	43
5	$InCl_3$ (10) [12]	4	46
6	P_2O_5 (10) [12]	4	40

[a] All reactions were run with 4-nitrobenzaldehyde (1.0 mmol), dimedone (1.0 mmol), and 6-amino-1,3-dimethyl uracil (1.0 mmol) in water (10 mL).
[b] Isolated yield.

Table 4
Synthesis of pyrimido[4,5-b]quinoline derivatives using $RuCl_3{\cdot}xH_2O$ as the catalyst.[a]

Entry	R_1	R_2	Product[b]	Ultrasound		Reflux		Mp (°C)	
				Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]	Found	Reported [Ref.]
1	4-$MeOC_6H_4$	CH_3	**1a**	6	82	50	80	>300	>300 [13]
2	4-$O_2NC_6H_4$	CH_3	**2a**	3	96	30	95	303–305	– [12]
3	2-$MeOC_6H_4$	CH_3	**3a**	10	73	65	75	>300	>300 [13]
4	4-ClC_6H_4	CH_3	**4a**	4	91	30	90	291–293	292–294 [13]
5	2,4-$Cl_2C_6H_3$	CH_3	**5a**	3	92	25	91	>300	>300 [13]
6	4-MeC_6H_4	CH_3	**6a**	8	80	55	78	>300	>300 [13]
7	2-Cl-6-FC_6H_3	CH_3	**7a**	3	92	20	93	302–304	This work
8	3-$O_2NC_6H_4$	CH_3	**8a**	5	91	35	90	287–290	This work
9	2-ClC_6H_4	CH_3	**9a**	4	87	35	88	>300	>300 [13]
10	4-$(CH_3)_3CC_6H_4$	CH_3	**10a**	12	66	75	60	289–292	– [12]
11	Me	CH_3	**11a**	30	Trace	120	–	–	–
12	4-ClC_6H_4	H	**1b**	5	92	30	90	>300	310–313 [14]
13	2-Cl-6-FC_6H_3	H	**2b**	3	95	18	93	298–300	This work
14	4-$O_2NC_6H_4$	H	**3b**	4	92	25	91	300–302	301–303 [14]
15	4-FC_6H_4	H	**4b**	3	90	25	89	>300	311–313 [14]
16	4-MeC_6H_4	H	**5b**	8	80	45	78	281–284	284–285 [13]
17	4-$(CH_3)_2NC_6H_4$	H	**6b**	6	87	30	88	278–280	This work
18	2,4-$Cl_2C_6H_3$	H	**7b**	3	92	22	90	> 300	– [12]
19	Me	H	**8b**	30	Trace	120	–	–	–
20	4-$(CH_3)_3CC_6H_4$	H	**9b**	10	65	70	62	>300	– [12]

[a] Reaction conditions: aldehyde (1 mmol), cyclic ketone (1 mmol), 6-amino-1,3-dimethyluracil (1 mmol), $RuCl_3{\cdot}xH_2O$ (3 mol%), H_2O (10 mL), 85 °C.
[b] Isolated yield.
[c] Yields refer to those of pure isolated products characterized by spectroscopic data.

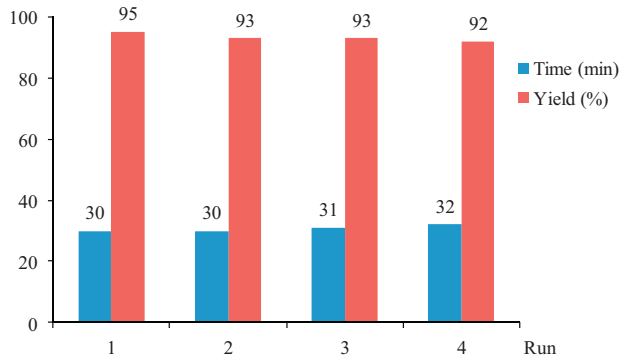


Fig. 1. Reusability of $RuCl_3{\cdot}xH_2O$ in the model reaction (Table 1, entry 2). Horizontal axe is usability times of the catalyst and vertical axe is time of the reaction and yield of the product.

indicate that solvents affected the efficiency of the catalyst. Yields were lower in acetonitrile and *n*-hexane (Table 2, entries 6 and 7).

When the reaction was performed under solvent-free conditions, the yield was low (40%), probably due to the absence of powerful interactions between the starting materials. However, among various solvents, fortunately, deionized water was found to give the best result at 85 °C (Table 2, entry 3). This solvent can have substantial effects in realizing the goals of green chemistry.

A comparison between various Lewis acids, including different metal salts, showed that $RuCl_3{\cdot}xH_2O$ was the best catalyst (yield 95%, Table 3, entry 2) for this reaction.

To determine the feasibility of this approach, particularly with regard to library construction, the protocol was applied to aromatic aldehydes with either electron-withdrawing groups (such as halide and nitro groups) or electron-donating groups (such as methyl and methoxy groups) (Scheme 2).

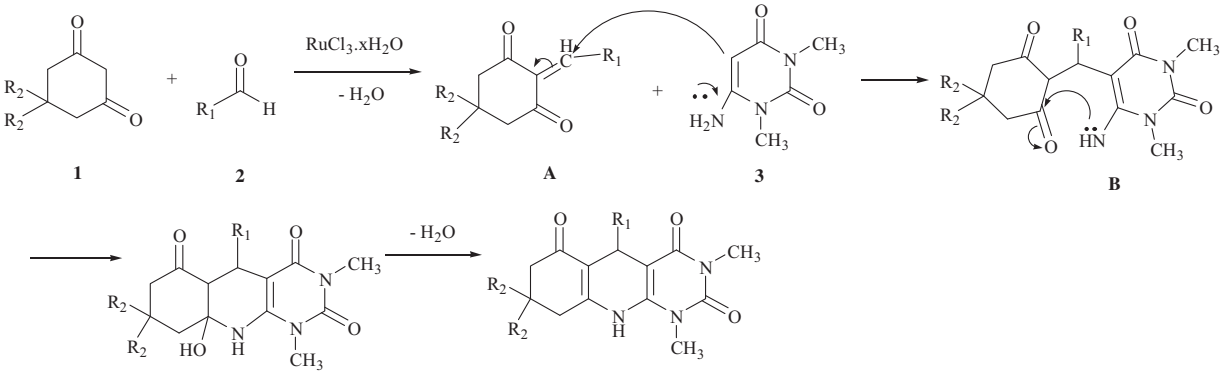
We therefore concluded that the electronic nature of the substituents of aldehydes have a significant effect on this reaction. Chloro-, flouro- and nitro-substituted aromatic aldehydes reacted well at faster rate and in higher yields, compared with corresponding methyl and methoxy substituted aldehydes. When an aliphatic aldehyde, such as acetaldehyde, was treated with cyclic ketone and 6-amino-1,3-dimethyl uracil in the presence of 3 mol% of $RuCl_3{\cdot}xH_2O$, the desired product was not obtained (Table 4, entries 11 and 19). The reaction of isopropyl benzaldehyde proceeds smoothly compared to other substituted aromatic aldehydes, in which the yields were lower due to steric factors (Table 4, entries 10 and 20).

Due to the benefits, such as higher yields, faster and cleaner reaction, sand environmentally friendliness, of using ultrasonic irradiations in MCRs, we investigated the effect of ultrasonic irradiations on the synthesis of targeted compounds. After optimization of the reaction conditions using 1:1:1 ratios of reactants, 2 mol% of $RuCl_3{\cdot}xH_2O$ as a catalyst, 2 mL deionized water under ultrasonic irradiations (40 kHz, 40 °C), we examined the generality of the reaction. As expected in all cases, an enhancement in the reaction rate was observed (Table 4).

The reusability of the catalysts is one of the most important advantages and potentiates their commercial applications. For this purpose, in the model reaction, the crude product was separated from the reaction mixture by filtration and more than 98% of $RuCl_3{\cdot}xH_2O$ could be easily transferred into the aqueous phase. Then the same substrates were added to the aqueous phase and experiments were repeated three times. In each step, the separated products were characterized by their melting point and IR spectra. The results indicated in Fig. 1 show that $RuCl_3{\cdot}xH_2O$ could be used for four times with only a slight decrease in the catalytic activity.

Table 5
Antimicrobial screening data (zone of inhibition in mm) of pyrimido[4,5-b]quinoline derivatives.

Entry	Compound	Concentration (μg/well)	Antimicrobial activity (zone of inhibition in mm)			
			Escherichia coli	*Staphylococcus aureus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*
1	**2a**	6	9	10	15	13
2	**4a**	6	8	10	22	25
3	**7a**	6	6	9	21	19
4	**8a**	6	8	12	14	13
5	**1b**	6	6	9	16	18
6	**2b**	6	8	10	18	20
7	**6b**	6	8	10	16	14
8	Erythromycin	15	16	10	12	10
9	Tetracycline	30	12	16	14	18



Scheme 3. Proposed mechanism for the formation of pyrimido[4,5-b]quinoline derivatives.

The formation of pyrimido[4,5-b]quinoline derivatives (**4**), can be explained by the proposed mechanism, presented in Scheme 3.

As shown, the reaction is initiated by a ruthenium salt-assisted Knoevenagel condensation to provide product **A**. Then product **A** reacted with 6-amino-1,3-dimethyl uracil (**3**) in a Michael-type fashion to give the corresponding product (**4**) [12].

Some of the synthesized pyrimido[4,5-b]quinoline derivatives were screened for antibacterial activity against four bacterial strains. The results can be seen in Table 5. In general, all the compounds exhibited good to excellent activity against all stains in comparison with standard drugs. Compounds **1a**, **2a**, **2b**, **4a**, **6b** and **7a** showed higher levels of antibacterial activity. *Bacillus subtilis* and *Pseudomonas aeruginosa* were more sensitive to all the compounds, in comparison to the other two species. In general, it seems that the presence of more polar groups enhances antibacterial activity.

The method provides an efficient, simple and environmentally friendly procedure for the synthesis of pyrimido[4,5-b]quinoline derivatives in high yields and very short period of time.

4. Conclusion

In conclusion, a convenient one-pot procedure for the synthesis of pyrimido[4,5-b]quinoline derivatives by a three-component coupling reaction of 6-amino-1,3-dimethyluracil, aldehydes, and cyclic 1,3-diketones in the presence of a catalytic amount of $RuCl_3{\cdot}xH_2O$ as a reusable homogenous catalyst in the absence of any organic solvents or additives, has been developed. The main advantages of this method are (i) easy and clean work-up for the isolation of the products without any chromatographic purification, (ii) high atom economy of the reaction by avoiding the use of hazardous organic solvents, (iii) reusability of the catalyst, and (iv) short reaction time, excellent yields and environmentally benign procedures. Several compounds showed extremely high levels of antibacterial activity. The mechanisms of this activity will be further investigated.

Acknowledgment

The authors are grateful to the Research Council of University of Guilan for partial support of this study.

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