Iranian Journal of Catalysis 4(2), 2014, 113-120

IRANIAN JOURNAL OF CATALYSIS

Cellulose sulfuric acid catalyzed multicomponent reaction for efficient synthesis of pyrimido and pyrazolo[4,5-*b*]quinolines under solvent-free conditions

Seyyedeh Cobra Azimi*

Young Researchers and Elites Club, Rasht Branch, Islamic Azad University, Rasht, Iran.

Received 4 May 2014; received in revised form 3 June 2014; accepted 5 June 2014

ABSTRACT

Cellulose sulfuric acid was used as an efficient biopolymer-based catalyst for the synthesis of tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-triones and hexahydro-2*H*-pyrazolo[5,4-*b*]quinoline-6-ones via three component reaction of aldehyde, 5,5-dimethyl-1,3-cyclohexadione and 6-amino-1,3-dimethyluracil or 5-amino-3-methyl-1-phenypyrazole under solvent-free conditions at 90 °C. The major advantages of the present method are simple experimentation, use of inexpensive and eco-friendly reusable catalyst with good yields and short reaction times.

***Keywords**: 6-Amino-1,3-dimethyluracil, 5-Amino-3-methyl-1-phenypyrazole, Solvent-free, Cellulose sulfuric acid.*

1. Introduction

Designing for more efficient processes which allow for the rapid generation of molecular complexity and diversity from simple and readily accessible starting materials have attracted much attention of organic chemists [1]. Among them, multicomponent reactions (MCRs) are effictive methods in heterocyclic scaffolds for the creation of different chemical libraries of drug-like advanced compounds [2]. The developing of new multicomponent reactions (MCRs) and improving the known MCRs are an area of considerable current interest in organic and medicinal chemistry [3,4].

As opposed to the classical way to synthesize complex molecules by sequential synthesis, MCRs allow the assembly of complex molecules in one-pot and show a facile execution, high atom-economy and high selectivity [5-8]. As a one-pot reaction, MCRs generally obtain good yields and are fundamentally various from two-component and stepwise reactions in several aspects and permitted a rapid access to combinatorial libraries of complex organic molecules for an efficient lead structure identification and optimization in drug discovery [9]. Hence, most of the scientific efforts have been focused on the develpment of multicomponent processes to prepare diverse heterocyclic compound libraries [10].

Quinolines and their derivatives an important class of heterocyclic alkaloids, are significant synthetic targets both in pharmaceutical industries and in academic laboratories displaying modern chemistry [11] and various useful biological activities such as DNA binding capability [12], antitumor [13], and DNA-intercalating carrier [14]. They are widely present as key structural motifs in a large number of bioactive drugs such as Quinine, Chloroquine, Luotonine-A, and Camptothecin. Many of these compounds have proved to be active anticancers [15], anti-inflammatories [16], antiallergics [17] and antimicrobials [18].

Furthermore, quinoline derivatives find applications in flavoring agents [19], in luminescence chemistry [20] and in the manufacture of some dyes and pigments [21]. In addition quinolines are valuable synthons for the preparation of nano-and meso-structures with enhanced electronic as well as photonic functions [22].

Pyrimido quinolines are a class of naturally occurring fused uracils occupying a special place in synthetic and medicinal chemistry due to their wide range of pharmacological and biological properties.

It has established broad application in drug development for the treatment as antibacterial, anti-inflammatory, antiviral, antitumoral, and antimalarial agent [23].

*Corresponding author: cobra.azimi@gmail.com
Tel/Fax: +981312233271

Pyrazolo quinoline derivatives, one of the important kind of fused heterocyclic compounds, possess significant bioactivities such as antiviral, antimalarial and antibacterial activities, acting as potent remedies for treating atherosclerosis or restenosis, inflammatory disorders, demyelinating disorders and cancers [24].

Literature search disclose that the synthesis of pyrimido quinoline derivatives can be achieved using [BMIm]Br [25], *p*-toluenesulfonic acid (*p*-TSA) [26], indium(III) chloride ($InCl_3$) [27], magnetic nanoparticles supported silica sulfuric acid (Fe_3O_4@SiO_2-SO_3H) [28], pyrazolo quinolines using ethylene glycol under MW irradiation [29], or diammonium hydrogen phosphate [30], *L*-proline [31], and indium(III) chloride ($InCl_3$) [27], as a catalyst.

In recent decades, the direction of technology and science has been shifting toward eco-friendly, natural product resources and reusable catalysts. Thus, natural biopolymers such as cellulose are most abundant natural biopolymers, biodegradable materials and a renewable resource. Because of its unique properties cellulose sulfuric acid (CSA) has emerged as a promising biopolymeric recyclable solid support acid catalyst for acid-catalyzed reactions, such as the synthesis of aryl-14*H*-dibenzo[*a.j*]xanthenes [32], 1,4-dihydropyridines [33], quinoxaline [34], α-amino nitriles [35], imidazoazines [36], quinolines [37], 2,4,5-triarylimidazoles [38], oxazolines, imidazolines and thiazolines [39].

As part of our continuing efforts on the development of new strategies for the synthesis of heterocyclic compounds [40], we decided to investigate the synthesis of pyrimido and pyrazolo quinoline derivatives via three component reaction of aldehyde, 5,5-dimethyl-1,3-cyclohexadione and 6-amino-1,3-dimethyluracil or 5-amino-3-methyl-1-phenypyrazole under solvent-free conditions by cellulose sulfuric acid (CSA) at 90 ˚C (Scheme 1).

2. Experimental

2.1. General

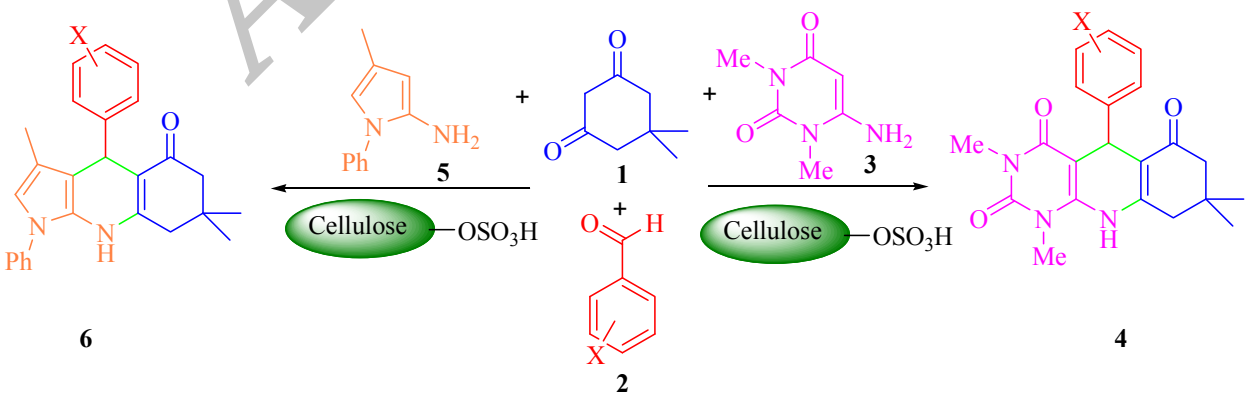
All chemicals were purchased from Merck or Fluka Chemical Companies. All products were characterized by physical data (m.p.), and spectral data (IR, ^{1}HNMR). Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were obtained on a Shimadzu FTIR-8400S spectrometer. ^{1}H and ^{13}CNMR spectra was determined on a BRUKER DRX-400 AVANCE spectrometer.

2.2. Catalyst preparation

To a magnetically stirred mixture of cellulose (5.00 g, DEAE for column chromatography, Merck) in $CHCl_3$ (20 mL), chloro sulfonic acid (1.00 g, 9 mmol) was added drop wise at 0 °C during 2 h. After addition was complete, the mixture was stirred for 2 h until HCl was removed from reaction vessel. Then, the mixture was filtered and washed with methanol (30 mL) and dried at room temperature to obtain cellulose sulfuric acid as white powder (5.13 g) [35].

2.3. General procedure for the preparation of tetrahydropyrimido[4,5-b]quinoline-2,4,6-trione ***(4a)*** *and hexahydro-2H-pyrazolo[5,4-b]quinoline-6-one* ***(6a)***

To a mixture of benzaldehyde (1 mmol, 0.106 g), 5,5-dimethyl-1,3-cyclohexadione (1 mmol, 0.140 g), and 6-amino-1,3-dimethyluracil (1 mmol, 0.155 g), or 5-amino-3-methyl-1-phenypyrazole (1 mmol, 0.172 g) under solvent-free conditions (0.06 g) cellulose sulfuric acid was added. The reaction mixture was heated at 90 ˚C for the stipulated period of time till the full consumption of the starting materials (monitored by TLC). After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The solid obtained was filtered and washed with CH_2Cl_2 (10 mL) to separate the catalyst.



Scheme 1. Synthesis of tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-triones and hexahydro-2*H*-pyrazolo[5,4-*b*]quinoline-6-ones in the presence of cellulose sulfuric acid (CSA).

Then the filtrate's solvent was evaporated under reduced pressure and recrystallized from ethanol to afford the pure product **(4a)** or **(6a)**. The same procedure was also used for the other products listed in Table 2.

Selected spectral data

5-(3-Nitrophenyl)-1,3,8,8-tetramethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-trione ***(4g):***

m.p.= 219-221 °C. IR (KBr): $\bar{\nu}$ = 3407, 3273, 1695, 1664, 1593 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.12 (3H, s, CH_3), 1.25 (3H, s, CH_3), 2.22 (1H, d, *J* = 16.4 Hz), 2.35 (1H, d, *J* = 16.6 Hz), 2.53 (1H, d, *J* = 16.5 Hz), 3.32 (3H, s, CH_3), 3.56 (3H, s, CH_3), 5.62 (1H,s, CH), 7.42-7.51 (4H, m, CH), 8.12 (1H, s, CH), 12.58 (1H, s, NH) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 18.3, 27.1, 27.4, 28.7, 29.3, 32.6, 42.4, 50.9 89.0, 114.3, 121.5, 124.5, 125.4, 126.2, 127.3, 129.7, 130.0, 130.7, 135.3, 161.4, 203.2 ppm.

5-(3-Bromophenyl)-1,3,8,8-tetramethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-trione ***(4j):***

m.p.= 279-280 °C. IR (KBr): $\bar{\nu}$ = 3412, 1665, 1609 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.25 (3H, s, CH_3), 1.26 (3H, s, CH_3), 2.24 (1H, d, *J* = 16.4 Hz), 2.33 (1H, d, *J*= 16.6 Hz), 2.45 (1H, d, *J* = 16.5 Hz), 2.52 (1H, d, *J*= 16.7 Hz), 3.27 (3H, s, CH_3), 3.57 (3H, s, CH_3), 5.13 (1H,s, CH), 7.44-7.11 (4H, m, CH), 9.12 (1H, s, NH) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 18.5, 27.0, 27.2, 28.6, 29.1, 32.4, 41.4, 50.0, 90.2, 113.1, 122.5, 124.1, 125.6, 126.0, 127.1, 129.6, 129.8, 130.4, 134.8, 161.2, 203.0 ppm.

5-(2-Methoxyphenyl)-1,3,8,8-dimethyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6-trione ***(4k):***

m.p. >300 °C. IR (KBr): $\bar{\nu}$ = 3243, 3156, 2967, 1694, 1665, 1658, 1343, 1243, 1172, 1054 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.13 (3H, s, CH_3), 1.26 (3H, s, CH_3), 2.19 (1H, d, *J* = 16.5 Hz), 2.23 (1H, d, *J* = 16.6 Hz), 2.42 (1H, d, *J* = 16.4 Hz), 2.47 (1H, d, *J* = 16.6 Hz), 3.03 (3H, s, OCH_3), 3.48 (3H, s, CH_3), 3.65 (3H, s, CH_3), 4.93 (1H, s, CH), 6.76-7.24 (m, 4H, ArH), 9.02 (1H, s, NH) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 21.5, 27.4, 28.0, 31.2, 32.6, 38.1, 39.0, 42.1, 56.2, 91.0, 112.2, 120.3, 121.5, 127.9, 134.1, 143.0, 147.5, 147.9, 150.2, 150.5, 161.2, 193.6 ppm.

5-Phenyl-1,5,6,7,8,9-hexahydro-2H-pyrazolo[5,4-b] quinolin-6-one ***(6a):***

m.p.= 218-219 °C. IR (KBr): $\bar{\nu}$ = 3423, 3228, 3161, 2965, 1614, 1525, 1463 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 0.93 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.91 (3H, s, CH_3), 1.97-2.16 (2H, m, CH_2), 2.51 (2H, s, CH_2), 4.96 (1H, s, CH), 7.06-7.51 (11H, m, ArH), 9.37 (1H, s, NH) ppm.

5-(4-Nitrophenyl)-1,5,6,7,8,9-hexahydro-2H-pyrazolo[5,4-b]quinolin-6-one ***(6e):***

m.p.= 227-228 °C. IR (KBr): $\bar{\nu}$ =3457, 3235, 3147, 2957, 1617, 1529 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 0.91 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.86 (3H, s, CH_3), 1.97-2.24 (2H, m, CH_2), 2.58 (2H, s, CH_2), 5.23 (1H, s, CH), 7.46-8.13 (10H, m, ArH), 9.54 (1H, s, NH) ppm.

5-(2,4-Dichloro)-1,5,6,7,8,9-hexahydro-2H-pyrazolo[5,4-b]quinolin-6-one ***(6g):***

m.p.= 286-288 °C. IR (KBr): $\bar{\nu}$ = 3398, 3245, 3178, 2958, 1610 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6): δ= 0.89 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.85 (3H, s, CH_3), 2.11-2.24 (2H, m, CH_2), 2.56-2.71 (2H, m, CH_2), 5.39 (1H, s, CH), 7.21-7.54 (9H, m, ArH), 9.56 (1H, s, NH) ppm.

3. Results and Discussion

In this paper, the three component condensation of aldehyde, 5,5-dimethyl-1,3-cyclohexadione and 6-amino-1,3-dimethyluracil or 5-amino-3-methyl-1-phenypyrazole in the presence of a heterogeneous solid acid catalyst of cellulose sulfuric acid (CSA) for the preparation of tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-triones and hexahydro-2*H*-pyrazolo[5,4-*b*] quinoline-6-ones have been studied (Scheme 1). We initially investigated a reaction between 5,5-dimethyl-1,3-cyclohexadione **1**, 4-chlorobenzaldehyde **2c**, and 6-amino-1,3-dimethyluracil **3** as model compounds for the optimization of the reaction conditions in the presence of cellulose sulfuric acid catalyst. To optimize the reaction conditions, the above experiment was performed in various solvents including water, acetonitrile, dimethylformamide, ethanol, dichloro-methane, and a solvent-free system, the best result was obtained after 30 min under solvent-free conditions. Subsequently, the effect of the amount of catalyst in this reaction was studied. The best results were obtained using 0.06 g of catalyst under solvent-free conditions (96%) (Table 1, Entry 11). Using lower amounts of catalyst resulted in lower yields, and in the absence of catalyst the yield of the product was found to be nil (Table 1, Entry 1, 2).

Under the optimized reaction conditions, the generality of the reaction was fully investigated with different aldehydes, 5,5-dimethyl-1,3-cyclohexadione and 6-amino-1,3-dimethyluracil or 5-amino-3-methyl-1-phenypyrazole to produce tetrahydropyrimido[4,5-*b*] quinoline-2,4,6-trione and hexahydro-2*H*-pyrazolo [5,4-*b*]quinoline-6-one derivatives. The results are summarized in Table 2. These results show the effects of electron-withdrawing and electron-donating groups on the time required and the yield of the reactions.

Table 1. Optimization of the reaction conditions.[a]

Entry	Catalyst	Condition	Reaction time	Yield (%) [b]	Ref.
1	-	Solvent-free/ 25 ˚C	24 h	-	-
2	-	Solvent-free/ 90 ˚C	15 h	Trace[c]	[26]
3	*p*-TSA	H_2O/ 90 ˚C	150 min	89	[26]
4	$InCl_3$	H_2O/ reflux	60 min	91	[27]
5	[BMIm]Br	Solvent-free/ 95 ˚C	210 min	90	[25]
6	Fe_3O_4@SiO_2-SO_3H	H_2O/ 70 ˚C	25 min	92	[28]
7	CSA (0.03)	Solvent-free/ 25 ˚C	10 h	Trace[c]	-
8	CSA (0.05)	Solvent-free/ 25 ˚C	8 h	Trace[c]	-
9	CSA (0.03)	Solvent-free/ 90 ˚C	240 min	56	-
10	CSA (0.05)	Solvent-free/ 90 ˚C	120 min	87	-
11	CSA (0.06)	Solvent-free/ 90 ˚C	30 min	96	-
12	CSA (0.06)	CH_3CN/ reflux	60 min	74	-
13	CSA (0.06)	CH_2Cl_2/ reflux	90 min	67	-
14	CSA (0.06)	DMF/ reflux	90 min	64	-
15	CSA (0.06)	EtOH/ reflux	45 min	91	-
16	CSA (0.06)	H_2O/ reflux	40 min	92	-
17	CSA (0.07)	Solvent-free/ 100 ˚C	30 min	94	-

[a]A mixture of 5,5-dimethyl-1,3-cyclohexadione **(1)**, 4-chlorobenzaldehyde **(2c)**, and 6-amino-1,3-dimethyluracil **(3)**.
[b]Isolated yield.
[c]Knoevenagel condensation product was obtained as a major one.

It is noteworthy that presence of electron-donating and electron-accepting as well as steric desired substituents on the reacting aldehydes do not affect the overall yield and rate of the reactions advisable. The results represented that the reactions were performed within 25-45 min of heating, and the favorable products were provided in good yields (Table 2).

The structures of compounds **4a-k** and **6a-g** were confirmed by IR and ^{1}H NMR spectroscopy. The IR spectrum of compound **4k**, for example, show absorption bands at 3243, 3156, 2967, 1694, 1665, 1658, 1343, 1243, 1172, and 1054 cm^{-1} indicating the presence of N-H, C=O, and C-O groups in this molecule. Aromatic protons of this compound were seen at δ 6.76-7.24 in its ^{1}HNMR spectrum resonating with proper integrals and splittings. Aliphatic region of this spectrum exhibits five singlet peaks at δ 1.13, 1.26, 3.03, 3.48, and 3.56 arising from protons of the methyl and methoxy groups along with the characteristic sharp signal of the methine proton at δ 4.93 and methylene protons at δ 2.19-2.47. In addition, there is one singlet signal appeared at δ 9.02 in the spectrum accounting for the presence of the N-H group in the molecule. The ^{13}CNMR spectrum of **4k** displays 22 distinct lines with appropriate chemical shifts corresponding to the structure of this compound.

We also investigated the reusability of the catalyst. For this purpose after completion of the reaction, the catalyst was separated from the reaction mixture by simple filtration, washing with CH_2Cl_2, and drying in a vacuum oven at 60 ˚C for 5 h prior to reuse in subsequent reactions. The catalyst can be reused at least four additional times in subsequent reactions without significant loss in product yield (Fig. 1).

Table 2. Synthesis of tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-triones **4a-k** and hexahydro-2*H*-pyrazolo[5,4-*b*]quinoline-6-ones **6a-g**.

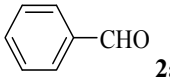
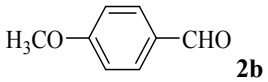
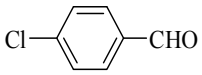
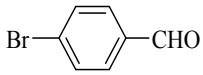
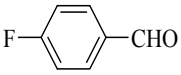
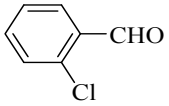
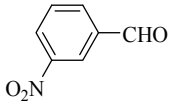
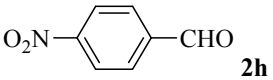
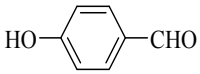
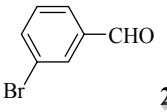
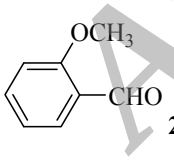
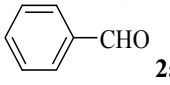
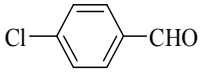
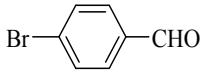
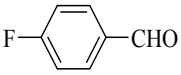
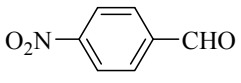
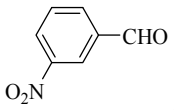
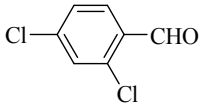
Entry	Aldehyde	Product[a]	Time (min)	Yield (%)[b]	m.p. (°C) Found	m.p. (°C) Reported[c]
1	 **2a**	**4a**	25	94	267-269	268-270
2	 **2b**	**4b**	35	89	>300	>300
3	 **2c**	**4c**	30	96	289-290	290-292
4	 **2d**	**4d**	40	91	278-280	280-282
5	 **2e**	**4e**	30	93	232-234	234-236
6	 **2f**	**4f**	35	89	>300	>300
7	 **2g**	**4g**	30	95	219-221	220-223
8	 **2h**	**4h**	25	94	221-223	222-224
9	 **2i**	**4i**	45	92	>300	>300
10	 **2j**	**4j**	30	95	279-280	280-282
11	 **2k**	**4k**	35	93	>300	-
12	 **2a**	**6a**	25	97	217-219	218-219
13	 **2c**	**6b**	40	96	218-220	219-221
14	 **2d**	**6c**	25	98	238-240	239-241
15	 **2e**	**6d**	45	92	174-176	175-176

Table 2. *(Continued)*

16	 **2h**	**6e**	25	97	226-228	227-228
17	 **2g**	**6f**	25	95	220-222	222-223
18	 **2h**	**6g**	30	94	285-287	-

[a]All products were characterized by ^{1}H NMR and IR spectral data and comparison of their melting points with those of authentic samples.
[b]Isolated yield.
[c]Refs. [26, 28, 29].

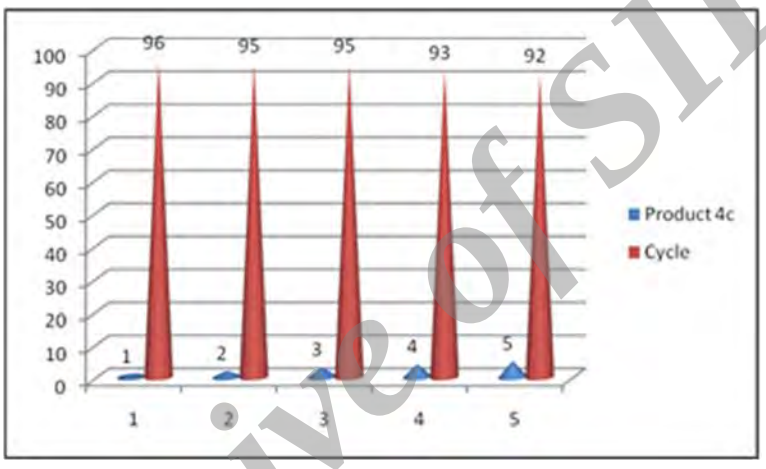


Fig. 1. Reusability of the catalyst in product 4c.

A possible mechanism for the synthesis of tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-trione **4** and hexahydro-2*H*-pyrazolo[5,4-*b*]quinoline-6-one **6** using the domino coupling is outlined in Scheme 2. The first step is believed to be the acid-catalyzed Knoevenagel condensation between the aldehyde and 5,5-dimethyl-1,3-cyclohexadione to generate adduct **7** ,which acts as Michael acceptor. The 6-amino-1,3-dimethyluracil **3** or 5-amino-3-methyl-1-phenypyrazole **5** attacks to adduct **7** in a Michael-type fashion to produce an open chain intermediate **8**. Intermediate **8** undergoes intramolecular cyclization by the reaction of nucleophilic amino function to carbonyl group followed by dehydration to form product **4** or **6**.

4. Conclusions

In conclusion, we have described a facile, environmentally benign one-pot and three-component method for the preparation of tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-triones and hexahydro-2*H*-pyrazolo [5,4-*b*]quinoline-6-ones, using cellulose sulfuric acid as an efficient bio-supported and recyclable solid acid catalyst under solvent-free conditions. Simple experimental procedure, excellent yields of the products, recyclability of the catalyst with no loss in its activity, use of nontoxic, user friendly process and easy work up procedure are the merits of this procedure.

Acknowledgements

We gratefully acknowledge financial support from the Research Council of Islamic Azad University Rasht Branch.

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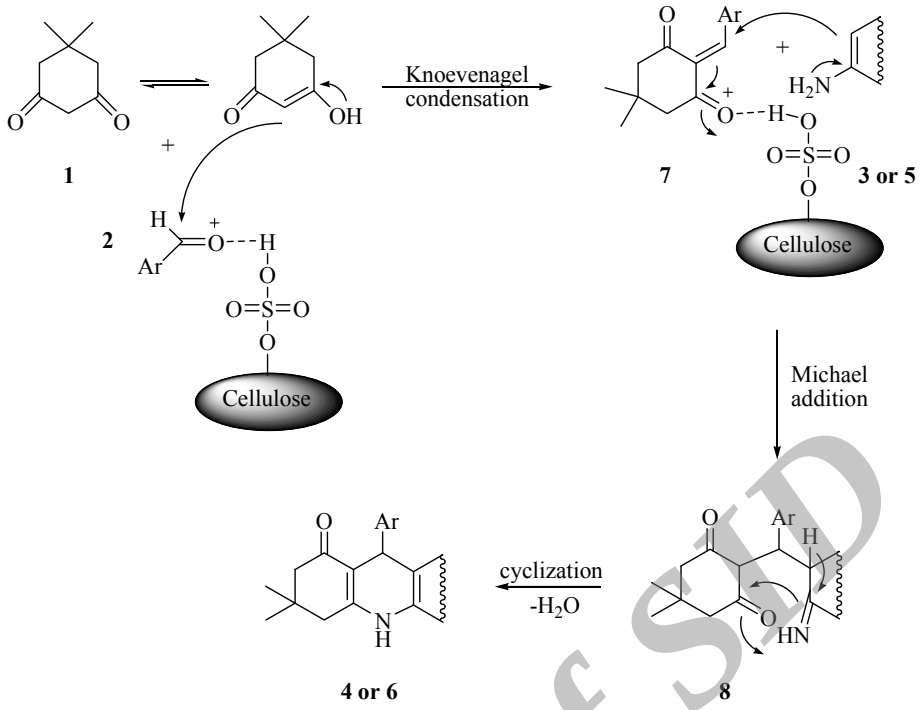

Scheme 2. A plausible mechanism for the synthesis of tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-triones **4a-k** and hexahydro-2*H*-pyrazolo[5,4-*b*]quinoline-6-ones **6a-g** in the presence of cellulose sulfuric acid (CSA).

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