

An efficient green synthesis of some new 4H-pyrimido[2,1,*b*]benzimidazoles and 4H-pyrimido[2,1,*b*]benzothiazoles promoted by guanidinium chloride

Razieh Talaei, Abolfazl Olyaei*

Department of Chemistry, Payame Noor University, PO BOX 19395-3697, Tehran, Iran.

Received 26 January 2016; received in revised form 30 March 2016; accepted 24 April 2016

ABSTRACT

A facile and highly efficient protocol was applied successfully to synthesize 4H-pyrimido[2,1,*b*]benzimidazoles and 4H-pyrimido[2,1,*b*]benzothiazoles through one-pot three-component cyclocondensation reactions of 2-aminobenzimidazole or 2-aminobenzothiazole with dimedone and aromatic aldehydes in the presence of guanidinium chloride under solvent-free conditions. The reactions using guanidinium chloride provided high to excellent yields of the products. The key advantages of this process are operational simplicity, inexpensive catalyst, short reaction time, simple workup and non-chromatographic purification, which make it an attractive route for the synthesis of benzimidazolo/benzothiazolo quinazolinones. Due to these advantages, several benzimidazolo/benzothiazolo quinazolinones as important pharmaceutical molecules can be prepared in high yield and high purity.

Keywords: Aldehydes, Guanidinium chloride, Solvent-free, Benzimidazoloquinazolinone, Benzothiazoloquinazolinone.

1. Introduction

The chemistry benzimidazoquinazolinones is interesting because of the diverse range of their biological properties, including anticancer [1] anti-inflammatory [2] anticonvulsant activities [3]. Moreover; benzothiazoloquinazolinones represent an important structural motif in medicinal chemistry and can be found in drugs and natural products [4-8]. In recent years, several different strategies for the synthesis of 4H-pyrimido [2,1,*b*] benzimidazoles and 4H-pyrimido [2,1,*b*] benzothiazoles have been developed by using catalysts such as 1-butyl-3-methylimidazolium bromide as an ionic liquid [9], I₂ [10], sulfamic acid [11], microwave [12], SBA-Pr-SO₃H [13], tetrabutylammonium hydrogen sulfate (TBAHS) [14] kaolin [15] Hydrotalcite [16] aluminum trichloride [17] Boric acid [18] *N,N'*-dichlorobis (2,4,6-trichlorophenyl) urea [19], anhydrous zinc chloride [20] and FeF₃ [21]. However, some of the synthetic strategies suffer with certain limitations such as expensive catalysts, low yields of products, long reaction times, tedious procedures for the preparation of catalysts and tedious work-up conditions.

Recently, guanidinium salts have been successfully employed as a novel chiral phase-transfer catalyst in the conjugate addition of nitroalkanes with enones [22] and synthesis of β -nitroalcohols [23]. Moreover, these organocatalysts provide an environment to the process of activating the nucleophile, the electrophile or both reagents through weak interactions, such as hydrogen bonding or ion pairing or much stronger interactions such as covalent bonding. Due to our interest in developing multi-component and solvent-free reactions [24], we have described a successful strategy for the efficient and convenient synthesis of substituted 4H-pyrimido [2,1,*b*] benzimidazoles and 4H-pyrimido [2,1,*b*] benzothiazoles by condensation of 2-aminobenzimidazole or 2-aminobenzothiazole with aromatic aldehydes and dimedone in the presence of guanidinium chloride under solvent-free condition.

2. Experimental

2.1. General

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The

*Corresponding author email: olyaei_a@pnu.ac.ir
Tel.: +98 28 3322 4024; Fax: +98 28 3322 6400

^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker DRX-300 AVANCE spectrometers. Chemical shifts (δ) are reported in ppm and are referenced to the NMR solvent. Mass spectra (Electron Impact 70 eV) of the products were obtained with a HP (Agilent technologies) 5973 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

2.2. General procedure for the synthesis of 4H-pyrimido [2, 1, b] benzimidazoles **5** and 4H-pyrimido [2, 1, b] benzothiazoles **6**

To a mixture of 2-aminobenzimidazole or 2-aminobenzothiazole (1 mmol), dimedone (0.14 g, 1 mmol) and aromatic aldehyde (1 mmol), guanidinium chloride (10 mol %) was added. The mixture was heated at 110°C for the appropriate time. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was cooled to room temperature and EtOH (5 mL) was added until solid products precipitated. The precipitate was filtered, washed with ethanol, and dried. The crude product **5** was stirred for 5 min in boiling EtOH and the resulting precipitate was filtered. The product **5** thus obtained was found to be pure upon TLC examination. The crude product **6** was recrystallized from ethanol to get the pure final product.

3. Results and Discussion

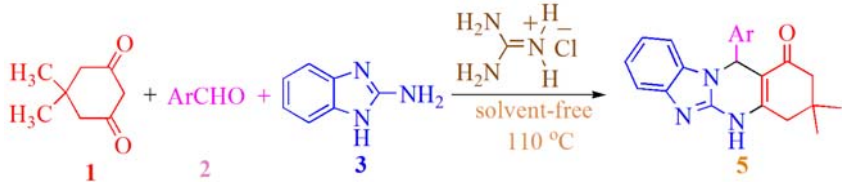
Initially, a model reaction was conducted by taking 2-aminobenzimidazole (1 mmol), benzaldehyde (1 mmol) and 5,5-dimethylcyclohexane-1,3-dione (dimedone) (1 mmol) in the presence of 10 mol% of guanidinium chloride as organocatalyst at a

temperature of $80\text{--}140^\circ\text{C}$ under solvent-free conditions. We were pleased to find that the reaction proceeded smoothly and almost complete conversion of reactants was observed at 110°C to afford the desired product (**5a**) in 91% yield within 30 min. To optimize the amount of the catalyst, the reaction was carried out with different amounts of the catalyst (2, 5, 7, 15 and 20 mol %) under solvent-free condition. It was found that 10 mol% gives the best results. After optimizing the experimental conditions, to explore the synthetic scope and the generality of the present protocol, various reactions were performed with a wide variety of aromatic aldehydes with 2-aminobenzimidazole and dimedone for the syntheses of benzimidazoloquinazolinones. The percentage yields of the products (**5a-g**) are shown in Table 1. It is interesting to note that the pure products of all these reactions can be obtained just by boiling of the crude materials in ethanol by avoiding tedious work-up and column-chromatographic separation.

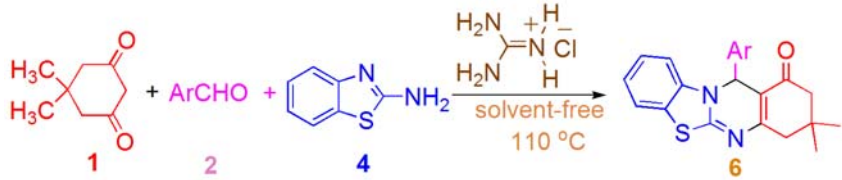
As shown in Table 1, it was clear that a variety of aromatic aldehydes with electron-withdrawing or electron-donating groups were employed as substrates and the reactions afforded the corresponding products in high to excellent yields.

Encouraged by the remarkable results obtained with the above reaction conditions, and in order to show the generality and scope of this new protocol, we used 2-aminobenzothiazole, benzaldehyde and dimedone in the presence of guanidinium chloride catalyst (10 mol %) at 110°C as a model reaction. It was observed that the desired product **6a** was obtained in 89% yield within 120 min. Notably, a wide range of aromatic aldehydes were well tolerated under the reaction conditions (Table 2).

Table 1. Synthesis of 4H-pyrimido[2, 1, b]benzimidazoles **5** after 30 min.



Entry	Aromatic	Product	Yield (%)	m.p. ($^\circ\text{C}$)		Ref.
				Found	Reported	
1	C_6H_5	5a	91	> 300	> 300	[11]
2	4-MeO C_6H_4	5b	89	> 300	> 300	[11]
3	4-Me C_6H_4	5c	90	> 300	> 300	[25]
4	4-F C_6H_4	5d	92	> 300	> 300	[26]
5	3- NO_2 C_6H_4	5e	91	> 300	> 300	[27]
6	2- NO_2 C_6H_4	5f	87	>300	-	-
7	3-OH C_6H_4	5g	88	>300	-	-

Table 2. Synthesis of 4H-pyrimido[2,1,b]benzothiazoles **6** after 120 min.


Entry	Aromatic	Product	Yield (%)	m.p.(°C)		Ref.
				Found	Reported	
1	C ₆ H ₅	6a	89	223-225	205-206	[21]
2	4-Me C ₆ H ₄	6b	88	209-211	202-204	[21]
3	3-NO ₂ C ₆ H ₄	6c	90	240-241	-	-
4	3-OH C ₆ H ₄	6d	89	292-294	-	-
5	4-Cl C ₆ H ₄	6e	92	202-203	-	-
6	4-F C ₆ H ₄	6f	91	178-180	-	-

All of the pure products can be obtained just by recrystallization of the crude materials from ethanol by avoiding tedious work-up and column-chromatographic separation. Also, it was clear that a variety of aromatic aldehydes with electron-withdrawing or electron-donating groups were employed as substrates and the reactions afforded the corresponding products.

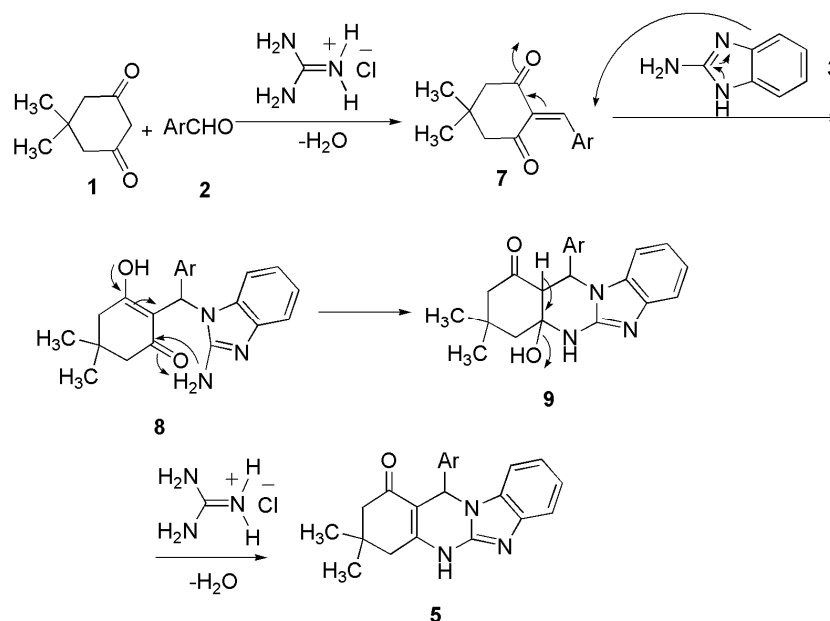
In order to demonstrate the merits of the present method in comparison with other reported methods in the synthesis of 4H- pyrimido [2, 1, b] benzimidazoles and 4H- pyrimido [2, 1, b] benzothiazoles with benzaldehyde, we have tabulated some of results in Table 3. The results show the promising features of this method in terms of inexpensive catalyst and the yield of the product with those reported in the literature. Additionally, the present catalyst seems to be more beneficial from the economical and accessibility point of view (entries 3, 7).

All new products were well characterized by ¹H NMR, ¹³C NMR, FTIR, mass spectra, elemental analyses and the melting point and the known products were characterized by ¹H NMR, FTIR and the melting point.

To the best of our knowledge, synthesis of compounds **5f-g** and **6c-f** has not previously been reported in the literature. A possible mechanism for the 4H- pyrimido [2, 1, b] benzimidazoles formation is outlined in (Scheme 1). Concerning the reaction mechanism, we suggest that initially, guanidinium chloride protonates the carbonyl group of aldehyde, which then condenses with dimedone to produce the adduct **7**. Michael addition reaction of nitrogen number 3 in 2-aminobenzimidazole **3** to adduct product **7** creates intermediate **8**. The reaction of amino group with carbonyl group of **8** and then elimination of water in the presence of guanidinium chloride produces the desired products **5** in excellent yield.

Table 3. Studying efficiency of the presence method over some reported catalysts.

Entry	Catalyst	Conditions	Product	Time (min)	Yield (%)	Ref.
1	I ₂	CH ₃ CN / reflux	5a	10	84.6	[10]
2	SBA-Pr-SO ₃ H	Solvent-free/ heat	5a	10	90	[13]
3	Guanidinium chloride	Solvent-free/ 110°C	5a	30	91	Present work
4	FeF ₃ (10 mol%)	Solvent-free/ 100°C	6a	30	97	[21]
5	Hydrotalcite	Solvent-free/ 70°C	6a	60	65	[16]
7	Guanidinium chloride	Solvent-free/ 110°C	6a	120	89	Present work



Scheme 1. Plausible mechanism for the formation of 4H-pyrimido[2,1-b]benzimidazole **5**.

4. Conclusions

In conclusion, the present method employing guanidinium chloride is an efficient, one-pot procedure for the preparation of 4H-pyrimido [2,1,*b*] benzimidazoles and 4H-pyrimido[2,1,*b*]benzothiazoles in neat conditions. It is suggested that guanidinium chloride as a polyfunctional organocatalyst (Bronsted acid and donating hydrogen bonding) shows a high catalytic activity. The current strategy offers several advantages such as high to excellent yields and non-chromatographic purification, low amount of catalyst, safe, cheap and environmentally benign and an easy experimental workup procedure.

Acknowledgment

The authors thank the Research Council of Payame Noor University for financial support.

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