Iranian Journal of Catalysis 6(4), 2016, 313-318

IRANIAN JOURNAL OF CATALYSIS

Thiamine hydrochloride (vitamin B_1) as an efficient catalyst for the synthesis of 4-(3*H*)-Quinazolinone derivatives using grinding method

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Received 20 April 2015; received in revised form 30 July 2015; accepted 16 August 2015

ABSTRACT

Herein we explore facile synthesis of 4-(3*H*)-Qunazolinone derivatives, achieved by the cyclocondensation of anthranilic acid, aromatic amines and triethyl orthoformate in presence of thiamine hydrochloride (Vitamin B_1) as a catalyst, using grinding method. This protocol offers several advantages such as reusability of catalyst, excellent yield, shorter reaction time and economic availability.

***Keywords**: Anthranilic acid, Multi-component reaction, 4-(3H)-Quinazolinones, Thiamine hydrochloride (Vitamin B_1).*

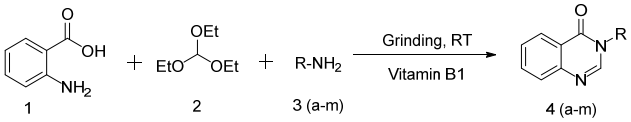
1. Introduction

Quinazolinone derivatives are one of the most important class of biodynamic heterocycles due to their wide range of biological activities such as anticancer [1], antitubercular agent [2], anti-inflammatory and antioxidant [3], anticonvusant agent [4], antimicrobial [5], antitumor [6], ACHE inhibitor [7], antiviral [8] and calcilytic activities [9-10]. Owing to the broad range of pharmacological, biological activities and development of new method for synthesis of quinazolinones derivative is still desirable.

Synthesis of 4-(3*H*)-quinazolinone includes cyclocondensation of anthranilic acid, triethyl orthoformate and aromatic amines. Several methods have been reported for the synthesis of 4 (3*H*)-quinazolinones which includes NH_4Cl [11], P-TSA [12], Iodine, [13], $Ce(CH_3SO_3).2H_2O$ [14], CAN [15], $SrCl_2.6H_2O$ [16], $Zn(ClO_4)$ [17], $NH_4(NO_3).9H_2O$ [18] and heteropolyacids [19]. However these protocols suffer from one or more disadvantages like poor yield, tedious work-up procedure, prolonged reaction time, expensive and toxic catalysts and solvents. Therefore, development of new methods for synthesis of 4-(3*H*)-quinazolinones is important and much in demand.

Thiamine hydrochloride well known as Vitamin B_1 (VB_1) have gaining paramount importance due to their potential catalytical activity in organic transformation [20]. Vitamin B_1 also employed for synthesis of various heterocycles such as benzo-[4,5] imidazo-[1,2*a*] pyrimidine and 1,2,4-triazolo-[1,5-*a*] pyrimidine derivatives [21] and dihydropyridines [22]. Vitamin B_1 act as phase transfer catalyst (PTC) and can catalyzed number of chemical reactions. [23-26]

In recent years, grinding method gaining much more importance because of its performance under solvent free as well as environment-friendly conditions [27-29]. The utility of grinding method has been reported for various organic transformations such as Reformatsky reactions [30], Knoevenagel's reaction [31], Michael's additions [32], aldol condensation [33], coupling reactions [34] and Dieckmann condensations [35]. Most of these organic transformations are carried out at room temperature in absence of solvent using only a mortar and pestle. In owing to importance of catalytical activity of thiamine hydrochloride and grinding method, we developed a new methodology for the synthesis of 4-(3*H*)-quinazolinones *via* cyclocondensation of anthranilic acid, triethyl orthoformate and aromatic amines using thiamine hydrochloride as catalyst under solvent free condition (Scheme 1).



Scheme 1. Synthesis of 4-(3*H*)-quinazolinone derivatives.

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2. Experimental

2.1. General

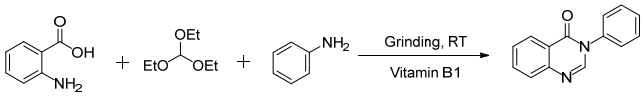
All chemical were purchased from Aldrich chemical company and used without further purification. ^{1}HNMR spectra were recorded on Bruker Advance 400, in DMSO in presence TMS as an internal standard.^{13}CNMR spectra recorded on Bruker DRX-300 in DMSO as solvent. Mass spectra were recorded on water UPLC TQD Mass spectrometer, showing M^{+} peak. Melting points were recorded in open capillary method and are uncorrected.

2.2. General procedure for synthesis of 4 (3H)-quinazolinones derivatives

A mixture of anthranilic acid (1 mmol), triethyl orthoformate (1.2 mmol), aromatic amine (1.2 mmol) and 10 mol % of VB_1 as catalyst was thoroughly ground with a pestle in an open mortar at r.t. for appropriate time. The reaction was monitored by thin layer chromatography (TLC), after completion of reaction the solid product was extracted by dichloro methane and filtered. The residue was catalyst that is VB_1 which was dried and then reused at least five consecutive cycles. The organic layer was separated under reduce pressure and product was crystallized using ethanol as solvent. A series of 4 (3*H*)-quinazolinone derivatives (**4a-m**) was synthesized using above procedure. The products were confirmed by melting point and compared with reported melting point.

3. Results and Discussion

The cyclocondensation of Anthranilic acid **1** (1 mmol), triethyl orthoformate **2** (1.2 mmol) and aniline **3a** (1.2 mmol) was considered as model reaction to determine the optimum reaction conditions (**Scheme 2**).



Scheme 2. Standard model reaction.

Initially, we carried out model reaction in presence of water as solvents at room temperature (r.t.), reflux, neat conditions and grinding method along with different acidic catalysts.Ssame protocol is carried out using ethanol as solvent, we observed that a very small amount of product was obtained (**Table 1,** entries 1-3). Therefore we decided to search for a suitable catalyst for synthesis of 4-(3*H*)-quinazolinone derivatives. When we employed VB_1 as catalyst using grinding method at r.t. for model reaction, we found that this is desired protocol for model reaction which gave product (**4a**) with 95 % yield within 45 min. (**Table 1,** entry 5).

Moreover, we examined the of amount of catalyst for the model reaction such as 5, 10, 15 and 20%, we found that the yields were affected by amount of catalyst loaded but best results was obtained with 10 mol % of VB_1 which gave desire product (4a) with 95 % yield (Table 2, entry 4). There is no significant change in the yield beyond 10 mol % of VB_1.

Under optimum condition (grinding at r.t., 10 mol % Vitamin B_1), a series of 4-(3*H*)-quinazolinone derivatives have been synthesized and the results are summarized in (**Table 3**).

In order to explore the versatility of this protocol, we extended our study for the synthesis of wide variety of 4-(3*H*)-quinazolinone derivatives (**4a-m**) using different substituted aromatic amines under optimized conditions (**Table 3,** entries 1-13).

Electron donating and withdrawing group on aromatic amine did not show any considerable difference in the yield of 4-(3*H*)-quinazolinone derivatives (**4a-m**). We had also investigated the reaction with aliphatic amine such as n-butylamine. We found that there is no product formation takes place when we used aliphatic amine instead of aromatic amine (**Table 3,** entries 14).

Further, we screen out the reusability of said catalyst according to typical experimental conditions. After completion of reaction the desire product (**4a**) was extracted with dichloro methane and filtered. The catalyst insoluble in dichloro methane so, by filtration method the catalyst was recycled and reused for model reaction at least 5 times which yielded product 95, 93, 92 , 91 and 90 % respectively (**Table 4,** entries 1-3).

We predicted plausible mechanism of catalytic activity of VB_1 for the synthesis of 4-(3*H*)-quinazolinones derivatives (**Scheme 3**) Firstly the Vitamin B_1 act as mild acidic in nature which increase the electrophilicity of carbon of triethyl orthoformate which will lead to formation of imidic ester (**5)** by reaction of anthranilic acid and triethyl orthoformate. In next step, the electrophilicity of imidic ester is enhanced by VB_1 then imidic ester and aromatic amine reacted to form amidine intermediate (**6**). Then last step VB_1 will enhancing electrophilicity of carbonyl carbon of carboxylic group of anthranilic acid which will result of cyclocondensation with amidine lead to formation of desire product (**4a**).

4. Conclusions

We have demonstrated new eco-friendly methodology for the synthesis of 4-(3*H*)-quinazolinones derivatives in presence of Vitamin B_1 as catalyst, using grinding method at room temperature. Merit of this methodology over other existing one are excellent yield within short reaction time, low cost of catalyst and simple reaction procedure. This protocol provides wide range of access to compounds that are useful in medicinal and heterocyclic chemistry.

Table 1. Optimization of catalysts and solvents for model reaction.

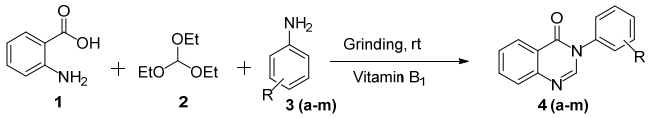
Entry	Catalyst 10 mol %	Solvent	Time (min)	% Yield[b]
1	None	Water (r.t.)	180	50
		Water (reflux)	180	54
		Ethanol (r.t.)	180	51
		Ethanol (reflux)	180	52
		Neat at 90°C	180	55
		Grinding at r.t.	180	43
2	Camphor sulfuric acid	Water (r.t.)	180	56
		Water (reflux)	180	54
		Ethanol (r.t.)	180	49
		Ethanol (reflux.)	180	55
		Neat at 90°C	180	51
		Grinding at r.t.	180	42
3	Boric acid	Water (r.t.)	180	45
		Water (reflux)	180	53
		Ethanol (r.t.)	180	40
		Ethanol (reflux.)	180	45
		Neat at 90°C	180	53
		Grinding at r.t.	180	48
4	Cellulose sulfuric acid	Water (r.t.)	180	44
		Water (reflux)	180	45
		Ethanol (r.t.)	180	51
		Ethanol (reflux.)	180	51
		Neat at 90°C	180	51
		Grinding at r.t.	180	46
5	VB_1	Water (r.t.)	180	60
		Water (reflux)	180	65
		Ethanol (r.t.)	180	64
		Ethanol (reflux)	180	63
		Neat at 90°C	180	67
		Grinding at r.t.	**45**	**95**

Table 2. Effect of mol % of Vitamin B_1 on model reaction.[a]

Entry	Catalyst (Mol %)	Time (Min)	% Yield[b]
1	5	45	89
2	**10**	**45**	**95**
3	15	45	95
4	20	45	95

[a]Reaction conditions: anthranilic acid (1 mmol), triethyl orthoformate (1.2 mmol), aromatic amine (1.2 mmol) and 10 mol % Vitamin B_1 using grinding method at r.t.
[b]Isolated yields.

Table 3. VB_1 catalyzed synthesis of **4a-m**[a].



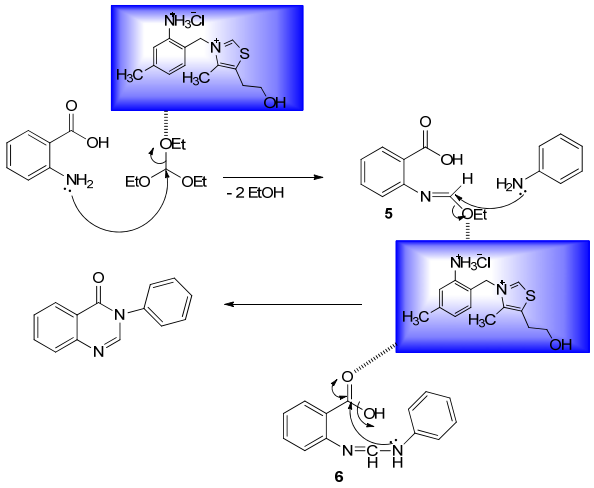
Entry	Product	R	Time (min)	Yield[b]	m.p. (°C)		Ref.
					Found	Reported	
1	**4a**	C_6H_5	45	95	138-140	139-141	[19]
2	**4b**	4-Me-C_6H_4	50	94	144-146	145-148	[36]
3	**4c**	4-MeO-C_6H_4	45	91	132-134	133-135	[36]
4	**4d**	4-Cl-C_6H_4	55	92	121-123	122-124	[36]
5	**4e**	2-MeO-C_6H_4	48	89	150-152	150-153	[36]
6	**4f**	2-Cl-C_6H_4	54	94	117-119	117-118	[36]
7	**4g**	2-Me-C_6H_4	57	90	156-158	157-159	[36]
8	**4h**	2,4-$(Cl)_2$-C_6H_3	54	88	230-232	230-234	[19]
9	**4i**	3-Me-C_6H_4	53	87	136-138	138-140	[36]
10	**4j**	4-NO_2-C_6H_4	55	84	164-166	165-166	[36]
11	**4k**	3-NO_2-C_6H_4	52	93	153-155	154-156	[36]
12	**4l**	3,4-$(Cl)_2$-C_6H_3	50	93	158-160	160-164	[19]
13	**4m**	4-Br-C_6H_4	48	91	145-147	147-149	[36]
14	**4n**	n-C_4H_9	60	-	-	-	-

[a]Reaction conditions: Anthranilic acid (1 mmol), triethyl orthoformate (1.2 mmol), aromatic amine (1.2 mmol) and 10 mol % Vitamin B_1 using grinding method at r.t.
[b]Isolated yields.

Table 4. Reusability of Vitamin B_1 for model reaction[a].

Cycle	Time (min)	Yield[b] (%)
1	45	95
2	45	93
3	45	92
4	45	91
5	45	90

[a]Reaction conditions: anthranilic acid (1 mmol), triethyl orthoformate (1.2 mmol), aromatic amine (1.2 mmol) and 10 mol % VB_1 using grinding method at r.t.
[b]Isolated yields.



Scheme 3. Plausible mechanism for synthesis of 4-(3*H*)-quinazolinone derivatives.

Acknowledgment

One of the Author, MSS is honored by CSIR, New Delhi, bestowing him Emeritus scientist position, Hence we acknowledges the CSIR authorities. The DSK also thankful to Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad for providing laboratory facilities. The scanning help received from SAIF, CDIR, Lucknow is gratefully acknowledged.

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