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Thiamine hydrochloride (VB1) as an efficient catalyst for the synthesis of 4*H*-pyrimido [2,1-*b*] benzothiazole derivatives.

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Abstract: An efficient and convenient synthesis of 4H-pyrimido [2,1-b] benzothiazole derivatives have been achieved via one pot cyclocondensation of aromatic aldehydes, 2-aminobenzthiazole and ethyl acetoacetate using thiamine hydrochloride in water under reflux condition. The thiamine hydrochloride (VB1) act as an efficient catalyst and has advantages over other catalysts such as high yield of products, reusable catalyst, shorter reaction time, easily available and simple workup procedure.

Keywords: Thiamine hydrochloride (VB1), 4*H*-pyrimido [2,1-*b*] benzothiazole, 2-aminobenzthiazole.

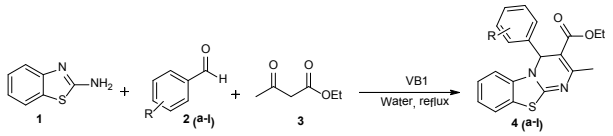
Introduction:

Heterocyclic compounds are highly important due to broad spectrum of their pharmacological properties which includes broad application in medicinal chemistry [1]. In recent years much attentions has been paid to wards synthesis of 4*H*-pyrimido [2,1-*b*] benzothiazole derivatives due to their high affinity central benzodiazepine receptor ligands [2,3]. Pyrimido benzothiazole derivatives have also been known for their antimicrobial properties [4-6], anti-allergy [7], anti-tumor, anti-viral activities [8], anti-fungicidal, anti-herbicidal activities utilized in the chemotherapy of characinoid patients [9]. Owing to biological importance of 4*H*-pyrimido [2,1-*b*] benzothiazole, therefore various methods have been developed for synthesis of 4*H*-pyrimido [2,1-*b*] benzothiazole *via* cyclocondensation of aromatic aldehydes, 2-aminobenzthiazole and ethyl acetoacetate using lewis acids $AlCl_3$ [10], TBAHS [11], hydrotalcite [12], N,N-dichloobis (2,4,6 tri chlorophenyl) urea [13], 1,1,3,3-N,N,N',N'-teramethyl guanidinium trifluroacetate (TMGT) [14] and FeF_3 [15], however most of these methods suffers from one or more disadvantage such as prolonged reaction time,

toxic solvents, expensive catalysts. Thus, the need for development of an alternate protocol is desirable.

Thiamine hydrochloride (VB1) is a naturally occurring water soluble, biodegradable catalyst and applications of VB1 in many organic transformations have been well reported [16]. VB1 is also employed in the synthesis of various heterocyclic compounds such as [1,2,4] triazolo [1,5-a] pyrimidine derivatives [17], dihydropyridines [18], 1,2-dihydro-napth-[1,2-*e*] [1,3] oxazine-3-one [19] and pyrimidinones [20]. Phase transfer catalyst (PTC) and catalyzed varieties of chemical reactions [21-24].

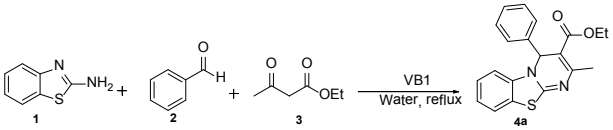
Considering paramount importance of VB1, herein we wish to report VB1 as an efficient catalyst for the synthesis of 4*H*-pyrimido [2,1-*b*] benzothiazole derivatives using water as solvent under reflux condition **(Scheme-1)**.



Scheme 1 Synthesis of 4*H*-pyrimido [2,1-*b*] benzothiazole derivatives (**4a-l**)

Results and discussion:

For the optimization of reaction condition, firstly we consider the cyclocondensation of 2-aminobenzothiazole (1 mmol), benzaldehyde (1 mmol) and ethyl acetoacetate (1 mmol) which gave desire product (**4a**) was considered as model reaction (**Scheme 2**).



Scheme 2. Standard model reaction.

Firstly, we carried model reaction in absence of catalyst and without solvent at 90 °C after 3 hr the model reaction gave desire product (**4a**) with 45 % yield then we screen out different catalyst with and without solvent water for model reaction (summarized in **Table 1**).

Table 1 Optimization of catalysts for model reaction.

Entry	Catalyst 10 mol %	Solvent	Time (min)	% Yield[b]
1	None	Neat at 90°C Water (reflux)	180 180	45 56
2	Cellulose sulfuric acid	Neat at 90°C Water (reflux)	180 180	44 49
3	Silica supported perchloric acid	Neat at 90°C Water (reflux)	180 180	68 58
4	**VB1**	**Neat at 90°C** **Water (reflux)**	**180** **60**	**78** **96**

But when we used VB1 as catalyst and water as solvent under reflux condition for model reaction then we found that it gave 96 % yield within 1 hr. we consider this is desire protocol for model reaction then in next step we carried out model reaction in different solvent such as ethanol, DMF, toluene and water but best result was achieved using water as solvent under reflux condition which gave 96 % yield within 1 hr (**Entry 4, Table 2**).

Table 2 screening of solvents for model reaction[a].

Entry	Solvent	Time (min)	yield[b]
1	ethanol	180	67
2	DMF	180	61
3	toulene	180	69
4	Water	60	96

[a]Reaction conditions: 2-aminobenzothiazole (1 mmol), benzaldehyde (1 mmol)

and ethyl acetoacetate (1 mmol) and 10 mol % VB1 using water as solvent under reflux condition. [b]Isolated yields.

Then we examine the effect of mol % of VB1 of on model reaction such as 5 %, !0 %, 15 % AND 20 %. We observed that 10 mol % was appropriate amount for model reaction which gave best result (**Entry 2, Table 3**).

Table 3 Effect of mol % of VB1 on model reaction[a]

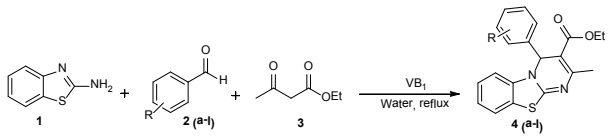
Entry	Catalyst (Mol %)	Time (Min)	% Yield[b]
1	5	60	90
2	**10**	**60**	**96**
3	15	60	96
4	20	60	96

[a]Reaction conditions: 2-aminobenzothiazole (1 mmol), benzaldehyde (1 mmol)

and ethyl acetoacetate (1 mmol) and 10 mol % VB1 using water as solvent under reflux condition. [b]Isolated yields.

To show the general applicability of this method various aryl aldehydes **2 (a-l)** were efficiently reacted with 2-aminobenzothiazole **1** and ethylacetoacetate **3** which gave corresponding products **4 (a-l)** (**All entries, Table 4**). The effect of electron donating or withdrawing group on aromatic aldehydes did not show any considerable effect in term of yield under these reaction conditions.

Table 4 VB1 catalyzed synthesis of **4a-l**[a]**.**



Entry	Product	R-aldehyde	Time (Min)	Yield[b]	Melting point (°C)	
					Found	Reported
1	**4a**	C_6H_5	60	96	172-173	173-175
2	**4b**	4-Me-C_6H_4	70	94	152-154	154-155
3	**4c**	4-MeO-C_6H_4	80	95	138-140	140-141
4	**4d**	4-Cl- C_6H_4	75	92	140-142	142-143
5	**4e**	2-MeO- C_6H_4	70	94	143-145	145-146
6	**4f**	2-Cl- C_6H_4	80	92	123-125	125-127
7	**4g**	4-HO-C_6H_4	70	93	208-209	209-210
8	**4h**	4-F- C_6H_3	85	90	168-162	160-161
9	**4i**	2-F-C_6H_4	80	94	138-140	139-140
10	**4j**	4-NO_2- C_6H_4	75	92	152-153	155-156
11	**4k**	3-Cl- C_6H_4	85	94	135-138	139-140
12	**4l**	4-Br- C_6H_4	75	95	165-166	166-167

[a]Reaction conditions: 2-aminobenzothiazole (1 mmol), benzaldehyde (1 mmol) and ethyl acetoacetate (1 mmol) and 10 mol % VB1 using water as solvent under reflux condition. [b]Isolated yields.

The reusability of the catalyst is an important advantage and makes them useful for commercial application. Keeping in this mind we have screen out the reusability of catalyst for model reaction, we found that the said catalyst reused and recycled for 4 times for the synthesis of desire product (**4a**) without significant loss of activity the result were summarized in (**Table 5**).

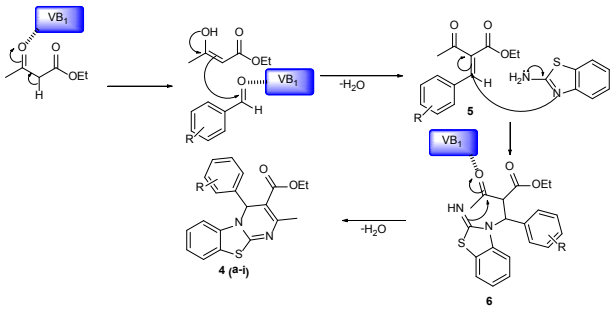
Table 5 Effect of mol % of VB1 on model reaction[a]

Entry	Catalyst (Mol %)	Time (Min)	% Yield[b]
1	5	60	90
2	**10**	**60**	**96**
3	15	60	96
4	20	60	96

[a]Reaction conditions: 2-aminobenzothiazole (1 mmol), benzaldehyde (1 mmol)

and ethyl acetoacetate (1 mmol) and 10 mol % VB1 using water as solvent under reflux condition. [b]Isolated yields.

In scheme 3, we have proposed a plausible mechanism for the synthesis of 4*H*-pyrimido [2,1-*b*] benzothiazole derivatives. In first step, the VB1 activates active methylene group of ethyl acetate which lead to formation of alkene (**5**), then Micheal addition will takes place between 2-aminobenzothiazole and alkene (**5**) which forms iminium ion (**6**). The VB1 which enhances the electrophilicity of carbonyl carbon compound and then cyclocondensation takes place which gave corresponding derivatives **4** (**a-i**).



Scheme 3 Plausible mechanism for synthesis 4*H*-pyrimido [2,1-*b*] benzothiazole derivatives.

Experimental:

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

General procedure for the synthesis derivatives (4a-i) 4H-pyrimido [2,1-b] benzothiazole derivatives.

A mixture of 2-aminobenzothiazole (**1 mmol**), aromatic aldehydes (**1 mmol**) and ethyl acetoacetate (**1 mmol**) and VB1 10 mol % in 10 ml water as solvent reflux for an appropriate time (all entries in **Table 4**). After completion of reaction (TLC), the products are extracted with DCM then solvent was removed under reduced pressure solid products were obtained which were crystallized by using ethanol. The catalyst which was insoluble in water recycled by concentrate water and reused for 4 times.

The spectral data of representative compounds (**4c**) and (**4f)** are furnish here.

Ethyl 4-(4-methoxyphenyl)-2-methyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylate (4c)

mp 141–144 °C.. ^{1} **H-NMR** ($CDCl_3$, δ ppm) 1.25 (t, 3H,CH_3), 2.41 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.15 (q, 2H, OCH2), 6.35 (s, 1H, CH), 7.02–7.10 (m, 1H, Ar-H), 7.16–7.24 (m, 3H, Ar-H), 7.33–7.54 (m, 3H, Ar-H), 8.10 (d, 1H, Ar-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 23.01, 57.49, 59.88, 60.52, 65.53, 102.34, 111.72, 120.70, 122.02, 123.90, 126.94, 128.02, 128.40, 129.59, 132.50, 140.98, 154.71, 163.43, 166.29; **Mass** EI-MS *m*/*z* cal. 380.46, *m*/*z* obs. $[M^{+\cdot}+H]$ = 381.

Ethyl 4-(2-chlorophenyl)-2-methyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylate (4f)

mp 123–125 °C.. ^{1} **H NMR** ($CDCl_3$, δ ppm): 1.21 (t, 3H, CH3), 2.40 (s, 3H, CH_3), 4.12 (q, 2H, OCH2), 6.69 (s, 1H, CH), 7.1–7.14 (m, 2H, Ar-H), 7.19–7.28 (m, 2H, Ar-H), 7.33 (d, 1H, Ar-H), 7.41 (d, 2H, Ar-H), 7.56 (d, 1H, Ar-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 14.31, 23.56, 54.39, 59.84, 102.72, 111.69, 121.85, 123.21, 123.96, 126.60, 128.03, 129.39, 129.58, 130.36, 131.37, 138.11, 139.51, 155.23, 163.13, 166.14;

Mass EI-MS *m*/*z* cal. 384.04, *m*/*z* obs. [$M^{+\cdot}$+H] = 385.

Conclusion:

In summary, this article describes the a green, simple and efficient protocol for the synthesis of 4*H*-pyrimido [2,1-*b*] benzothiazole derivatives by reaction between aminobenzothiazole, aromatic aldehydes and ethyl acetoacetate in presence of VB1 and using water as solvent under reflux condition. The merit of this protocol are cleaner reaction conditions, shorter reaction time, improved yields and simple workup procedure and also catalyst reused for four times with small decrease in the catalytic activity of recovered catalyst.

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