SYNTHESIS OF TETRAHYDROBENZO[*b*]PYRAN DERIVATIVES USING THIAMINE HYDROCHLORIDE (VB_1) AS A GREEN CATALYST

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Keywords: Thiamine hydrochloride (VB_1), green approach, tetrahydrobenzo[*b*]pyran derivatives.

An environmentally safer synthesis of 2-amino-tetrahydro-4H-chromenes derivatives using vitamin B_1 was achieved by one pot synthesis. In this reaction condensation of various aromatic aldehydes, malononitrile and dimedone at room temperature without addition of any other catalyst has been done. The desired products can be separated directly from the reaction mixture with high purity. This synthetic method is inexpensive, efficient, as well as eco-friendly.

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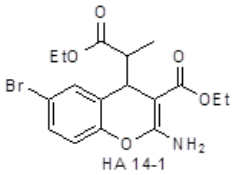
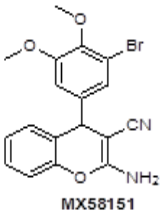
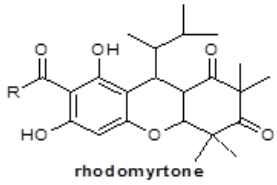
Introduction

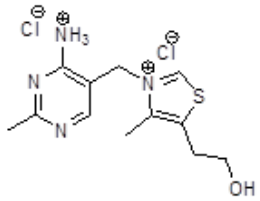
Multi-component reactions (MCRs) is an important tool for efficient synthesis of wide variety of heterocycle's such as tetrahydrobenzo[*b*]pyran as its derivatives belong to a major class of natural products. In recent decades tetrahydrobenzo[*b*]pyran and their derivatives have attain considerable attention of scientist community due to their wide range of biological and pharmacological properties such as HA 14-1, MX58151 and rhodomyrtone.



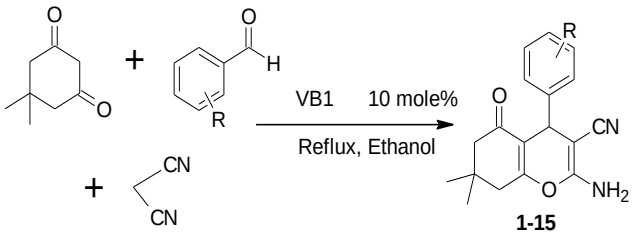




Tetrahydrobenzo[*b*]pyran constitutes the structural unit of a series of natural products. These derivatives can be employed as potent antibacterial such as rhodomyrtone pigments, photoactive materials, etc.[1] The derivatives of tetrahydrobenzo[*b*]pyran showing biological properties as antioxidant[2] spasmolytic and anti-HIV,[3] anticancer,[4] diuretic[5] and anti-anaphylactic activities[6] also widely used in cosmetics, pigments and utilized as potential biodegradable agrochemicals,[7] antibacterial,[8] molluscicidal[9] anti-coagulant and Parkinsons disease,[10] photoactive materials,[11] etc. Several techniques have been reported for the synthesis of 2-aminotetrahydro-4H-chromene derivatives, such as microwave,[12] reflux,[13] ultrasonication,[14] electrochemical synthesis[15] and green synthesis.[16] Realizing the importance of 4H-pyran derivatives, in recent decades various methods has been reported for the synthesis of 4H-benzo[*b*]pyran with the aim of obtaining more biologically potent heterocyclic systems using different catalysts via three-component condensations including the use of amino functionalized silica gel,[17] ionic liquids,[18] Nano-ZnO,[19] hexadecyltrimethyl ammonium bromide,[20] iodine,[21] 2,2,2-trifluoroethanol,[22] $BF_3.OEt_2$,[23] 4-amino-1-(2,3-dihydroxy-propyl)pyridinium salts,[24] SiO_2 NPs,[25] NaBr,[26] triethylene-tetraammonium trifluoroacetate[27] and $PhB(OH)_2$,[28] etc. Herein we synthesized tetrahydrobenzo[*b*]pyran derivatives by condensing various aromatic aldehydes, malononitrile and dimedone at room temperature in presence of vitamin B_1 as catalyst.



Thiamine hydrochloride (VB_1)



Scheme 1. Synthesis of tetrahydrobenzo[*b*]pyran derivatives by using thiamine hydrochloride (VB_1)

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Table 1. Synthesized of 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-chromene-3-carbonitrile derivatives

Entry	Aldehydes	Time , min	Yield, %	Melting point, ^{O}C	Ref. No.
1	4-Chlorobenzaldehyde	15	90	211-213	[22]
2	4-Hydroxybenzaldehyde	20	85	205-207	[25]
3	Furan-2-carboxaldehyde	15	92	228-230	[27,28]
4	4-Nitrobenzaldehyde	10	96	193-195	[22]
5	4-Bromobenzaldehyde	10	94	193-195	[22,27,29]
6	4-Methoxybenzaldehyde	20	88	197-199	[25,29]
7	2-Nitrobenzaldehyde	10	91	225-228	[1]
8	4-Methylbenzaldehyde	15	88	208-210	[22,29]
9	4-Cyanobenzaldehyde	10	95	220-222	[24]
10	Benzaldehyde	15	90	220-222	[24,28]
11	3,4-dimethoxybenzaldehyde	15	85	168-170	[25]
12	3-Nitrobemzaldehyde	10	94	206-209	[25,28,29]
13	4-(trifluoromethyl)benzaldehyde	10	92	235-237	[29]
14	3-Bromobenzaldehyde	20	92	225-227	[25]

Table No. 2: Study of effect of catalyst and solvents on yield of product

	Catalyst	Temperature	Solvent	Time	Yield (%)	Reference
1	2,2,2-Trifluoroethanol	Reflux	--	5 h	90	[Khaksar S., *et al.* (2012)][22]
2	BF_3OEt_2	Reflux	Ethanol	2 h	85-90	[Sethukumar A., *et al.* (2012)][23]
3	4-Amino-1-(2,3-dihydroxy propyl) pyridinium hydroxide [ADPPY] [OH]	60-65 °C	Ethanol	48 h	87	[Salvi P. P., *et al.* (2011)]][24]
4	Triethylenetetraammonium-trifluoro acetate	Reflux	Ethanol	10 min	57-90	[Zheng J., et al. (2011)]][27]
5	$PhB(OH)_2$	Reflux	Ethanol-water	10-60 min	42-95	[Nemouchi S., *et al.* (2012)]][28]
6	Thiamine hydrochloride	Reflux	Ethanol	10-30 min	87-96	Present work

Materials and methods

All the chemicals were of commercial grade reagent; purchased from Spectrochem and Sigma aldrich chemical companies in high purity, used without further purification. Melting points were determined in open capillaries visual melting point apparatus. Infrared (IR) spectra in KBr were recorded using a Perkin-Elmer FT-IR spectrometer 65. ^{1}H NMR spectra were recorded on 400 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. The progress of reactions was monitored on TLC (Thin Layer Chromatography).

General procedure for the synthesis of tetrahydrobenzo[*b*]pyran derivatives

In 25 mL round bottom flask a mixture of appropriated amount of aromatic aldehydes (1 mmol), malononitrile (1.3 mmol), dimedone (1 mmol) and catalyst VB_1 10 mol %, in ethanol (5 mL) was refluxed for appropriated time. The progress of reaction was monitored on TLC. On completion of reaction, the mixture was cooled to room temperature; the crude product was filtered off and washed with water to remove (the catalyst because it is water soluble).

The resulting solid was recrystalized in ethanol to obtain pure tetrahydrobenzo[*b*]pyran derivative. Similarly other derivatives were also prepared as mentioned in Table1.

Spectral analysis of some tetrahydrobenzo[*b*]pyran derivatives:

3e: 2-amino-4-(4-bromophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile

White solid; yield 95%; mp 220-222°C; Recrystallised from ethanol; IR (KBr) 1422, 2193, 2231.2, 2967, 3224, 3382 cm^{-1}: H1 NMR (CDCl3) 1.00-1.20 (s, 6H), 2.5 (s, 2H), 3.50 (s, 2H), 4.3 (s, 1H), 6.2 (d, 2H), 7.3 (d, 2H), 8.02 (s, 2H) ∂ (ppm).

3j: 2-amino-4-(4-cyanophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile

White solid; yield 95%; m.p. 220-222°C; Recrystallised from ethanol; IR (KBr) 1422, 2193, 2231.2, 2967, 3224, 3382 cm^{-1}: H^1 NMR ($CDCl_3$) 1.00-1.20 (s, 6H), 2.5 (s, 2H), 3.50 (s, 2H), 4.3 (s, 1H), 6.2 (d, 2H), 7.3 (d, 2H), 8.02 (s, 2H) ∂ (ppm)

Results and discussion

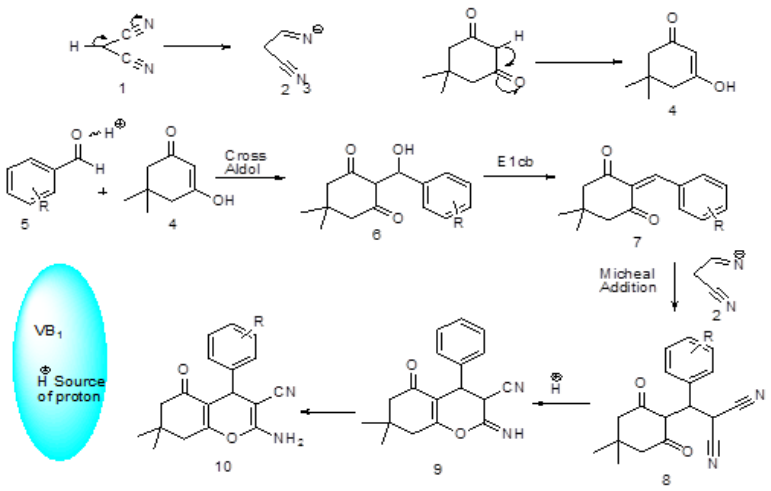
In order to optimize the reaction condition for solvents temperature and yield; the reaction was carried out under various conditions and the results are listed in Table 2. In an optimized reaction conditions, a mixture of dimedone **a** (1 mmol), malononitrile **c** (1.3 mmol), and 4-nitrobenz aldehyde **b** (1 mmol) in ethanol (5 mL) was mixed with 10 mol % thiamine hydrochloride and refluxed for 30 minutes. The reaction proceeds very cleanly at 50-60 ^{0}C temperature and was free of side products. After completion of the reaction as monitored on TLC and simple workup it affords the products in excellent yields (Scheme 1). Among the solvents tested, the reaction in DCM, acetonitrile, chloroform, DMF, DMSO, methanol and ethanol in catalyst free condition gaves poor yield of products. Whereas, in ethanol it affords quite good yield of product **(**Table2 entry 1 to 7); but the reaction required 120 minutes time for completion under reflux condition. In evaluation of catalyst concentration using ethanol as a solvent, 10 mol % of catalyst affords excellent yield of products (Table 2, entry 8 to 13). Further increase in catalyst concentration and temperature does not affect the yield and reaction time of completion. Optimization of temperature of reaction, the reaction was reflux at room temperature, 30, 40, 50, 60 and 70 ^{0}C using 10 mol % of the catalyst gave excellent yield at 50-60 ^{0}C of the desired product (Table 2 entry 14-15).

In order to show generality and scope of this new protocol, we used various substituted aromatic aldehydes and the results obtained are summarized in Table 1. The electron donating aromatic aldehydes gives low yield of products as compared to electron withdrawing substituted aldehydes. The electron withdrawing aldehydes required less time for completion of reactions (Table 1).

Optimization of several conditions like solvent, catalyst concentration and temperature has been also studied as reported in **(**Table 3**)**.

Plausible reaction mechanism

The thiamine hydrochloride (VB_1) was acts as Bronsted-Lowry acid (proton donor)[29]. Malanonitrile and dimedone undergo tautomerism **1** to **2** and **3** to **4**. The dimedone **4** on cross Aldol condensation with aromatic aldehydes **5** gives intermediate **6**, which on E_1cb elimination gives intermediate **7**. The intermediate **7** on Michael addition with **2** gives intermediate **9**. The intermediate **9** on rearrangement and cyclization gives desired product 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-chromene-3-carbonitrile **10**.



Conclusion

In conclusion, thiamine hydrochloride (VB_1) has been used as an efficient and eco-friendly catalyst for the synthesis of 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-chromene-3-carbonitrile derivatives. As the catalyst (VB_1) is water soluble; it can be easily separated and reused after evaporation of water. Simple work-up procedure, shorter reaction time, mild reaction condition and excellent yields makes this methodology to be efficient.

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