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An efficient synthesis of 1,8-dioxooctahydroxanthenes promoted by Thiamine hydrochloride (VB_1)

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Abstract: Thiamine hydrochloride (Vitamin-B_1) has been utilized as an efficient environmentally benign catalyst for one pot synthesis of 1,8-dioxooctahydroxanthene derivatives. Solvent-free reaction of aromatic aldehyde and dimedone afforded corresponding xanthenes derivatives in good to excellent yields. Catalytic competency of thiamine hydrochloride was extensively studied. The advantages of present protocol were the use of an easily available, biodegradable, less expensive catalyst and simple workup.

Keywords: Thiamin hydrochloride (VB_1), aldehyde, dimedone, 1,8-dioxooctahydroxanthene, biodegradable catalyst.

Introduction

During the last few decades, xanthene derivatives have gained much attention due to their wide spread applications such as antibacterial, anti-inflammatory and antiviral agents [1, 2]. They have been extensively used in synthesis of biodegradable agrochemicals [3, 4] and in photodynamic therapy [5]. Due to outstanding applicability of this class of compounds, their synthesis has been a great challenge for organic chemists. Several methods were reported in literature for the synthesis of 1,8-dioxooctahydroxanthene derivatives by using multi-component reaction of aldehyde and dimedone. The conventional protocols involving acid or base catalyzed condensation of active methylene bearing carbonyl compounds with aldehyde [6]. The catalyst used hitherto includes $InCl_3.4H_2O$ [7], *p*-dodecylbenzene sulphonic acid (DSA) [8], *p*-toluensulphonic acid (PTSA) [9], $NaHSO_4$-SiO_2 or silica chloride [10], amberlyst-15 [11], β-Cyclodextrin [12], polyaniline-*p*-toluene sulphonate salt [13], $HClO_4$-SiO_2 or PPA-SiO_2 [14], 2,4,6-trichloro-1,3,5-triazine [15], $BiCl_3$ [16], diammonium hydrogen phosphate [17], [bmim]HSO_4 [18], tetrabutyl ammonium hydrogen sulfate [19], solid state dehydration [20], ultrasound [21] and microwave [22] assisted synthesis. However,

many of these reported methods are associated with some shortcomings such as prolonged reaction time, lack of environment safety and use of expensive catalyst. Hence, there is scope for further development of new protocols with release of minimum waste and more superficial for isolation of the products. In continuation to the current scenario of Green Chemistry, the development of environmentally benign and economically viable protocols for the synthesis of biologically active compounds is of prime importance.

Thiamine hydrochloride popularly known as vitamin-B_1 is a colorless compound having molecular formula $C_{12}H_{17}N_4OS$ (Mol. Wt. = 265). It can be synthesized by bacteria, fungi, and plants. Sunflower seed is one of the best sources of vitamin-B_1. Molecular structure of VB_1 shows presence of amino-pyrimidine and a thiazole ring linked by a methylene bridge (**Figure 1**). It is soluble in polar solvents such as water, methanol, glycerol etc. but insoluble in less polar organic solvents. It is stable in acidic medium but unstable in alkaline medium [23, 24]. The best-characterized form of thiamine is thiamine pyrophosphate (TPP), a coenzyme in the catabolism of sugars and amino acids (Figure 2). The use of VB_1 as a popular catalyst for organic transformations has been reported in literature previously [25-29].

Herein, we have reported the multi-component condensation reaction of dimedone (2 eq) and aldehydes (1 eq.) using Vit-B_1 as an efficient and biodegradable organocatalyst in water as well as under solvent-free conditions (**Scheme 1**).

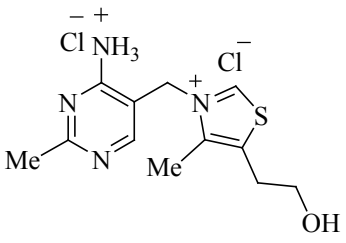


Figure 1 Thiamine hydrochloride (VB1).

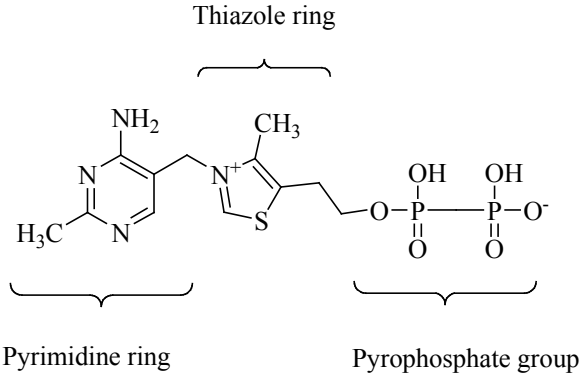


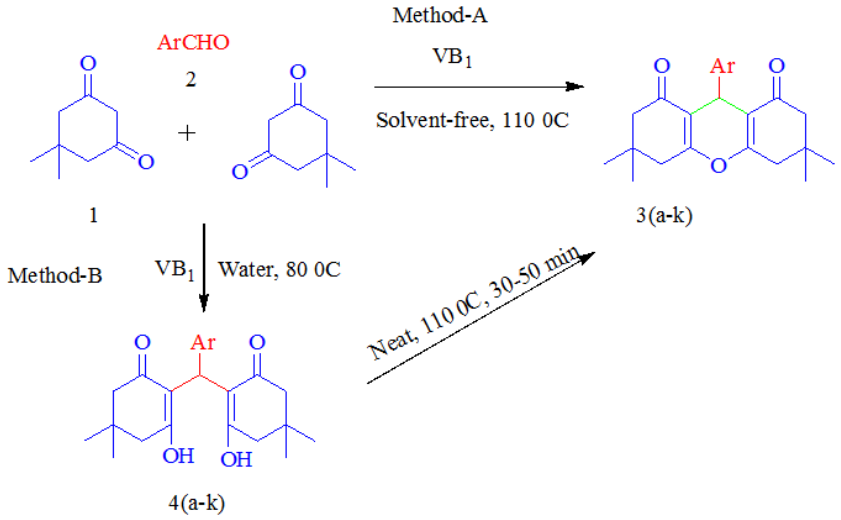
Figure 2 Thiamine pyrophosphate

Result and discussion

In continuation to our ongoing research on the development of novel synthetic methodologies [30], the catalytic efficiency of Vit-B_1 for the multi-component reaction of dimedone and aromatic aldehyde has been studied (**Scheme 1**). The optimization of reaction was conducted by stepwise procedure using varying amount of catalyst as well as a series of polar or nonpolar solvents at various temperatures (**Table 1**). The model reaction of dimedone (4 mmol) and benzaldehyde (2 mmol) was conducted in presence and absence of catalyst under solvent-free condition at room temperature as well as at 80 to 110°C. As indicated by TLC, the initiation of reaction was not observed under solvent-free conditions at room temperature after prolonged stirring (18 hrs) in absence of catalyst. Then same reaction was conducted in presence of varying amount of VB_1 as 5, 10, 15, 20, 25 mol%, till there is no initiation of reaction was observed on TLC and staring material was isolated as such. Hence, effect of temperature was studied for same reaction at 80-110 ^{0}C with 5, 10, 15, 20 mol % of catalyst. It has been observed that when temperature was raised from 80-110 ^{0}C, maximum yield of the desired 1,8-dioxo-octahydroxanthene (**3a**) was obtained at 110 ^{0}C with 20 mol % catalyst after 1.2 hrs (M**ethod-A: Table 2, Entry-3a, Yield = 98%**). Further increase of catalyst amount

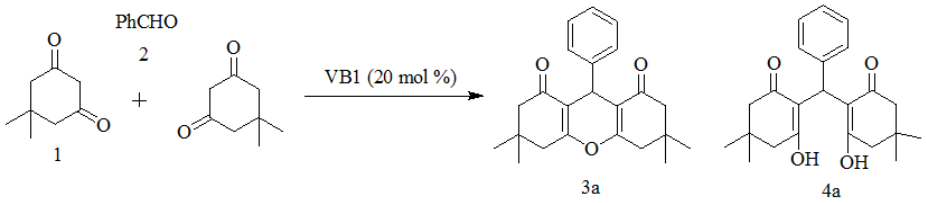
as 25 mol % and temperature (120 ^{0}C) did not showed satisfactory improvement in yield of the final product.

The effect of various solvents was checked by conducting the same reaction in methanol, ethanol, carbon tetrachloride, *N,N*-dimethyl formamide, 1,4-dioxane, dichloromethane and water under reflux. The results were summarized in **Table 1**. It has been found that when reaction was carried out in water, the product **4a** was obtained in excellent yield (**Method-B: Reaction time = 30 min; Yield = 94 %**) rather than formation of **3a**. Similarly, some representative reactions were conducted for the formation of **4(a-k)** (Table 2). In addition, we have planned the 1,8-dioxo-octahydroxanthenes by heating **4(a-k)** at 110 ^{0}C to gave compounds **3** in excellent yields (**Table 2**).



Scheme 1. Thiamine hydrochloride catalyzed reaction of aldehyde and dimedone.

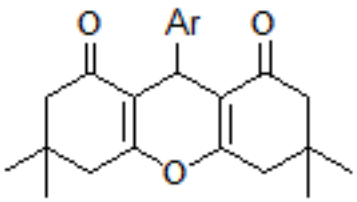
Table 1. Reaction optimization results for **3a** and **4a**.



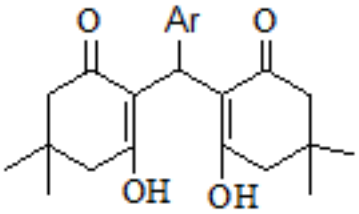
Entry	Solvent	Catalyst amount (mol %)	Time(min.)	Yield (%)[a,b,c]	
				3a	4a
1.	MeOH	20	120	0	70[a]
2.	CH_2Cl_2	20	120	0	Trace[a]
3.	CCl_4	20	120	0	Trace[a]
4.	DMF	20	120	<30	<25[c]
5.	CH_3CN	20	120	Trace	56[a]
6.	1,4-dioxane	20	120	0	Trace[a]
8.	Water	20	120	0	94[b]
7.	Solvent free	20	120	98	0[c]

[a] Reaction was carried out under reflux conditions (entry 1-6).
[b] Reaction is carried at 80^{0}C. [c]Reaction is conducted at room temperature(25^{0}C).

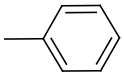
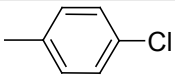
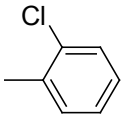
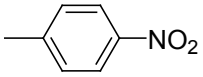
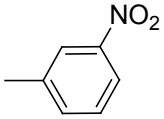
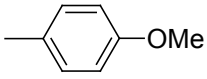
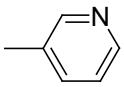
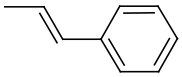
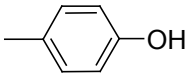
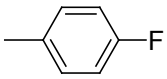
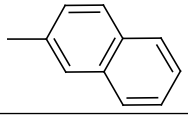
Table 2 VB_1 catalyzed synthesis of multi-component reaction of dimedone and aldehyde in water or solvent free conditions.



3



4

Entry	Ar	Product		Time hr/min.		Yield (%) [a,b]		Ref.
		3	4	3	4	3	4	
1.		**3a***	**4a**	1.2	30	98	94	[3, 9,13]
2.		**3b***	**4b**	1.0	50	82	89	[2, 9,13]
3.		**3c***	**4c**	2.0	30	99	77	[3,9]
4.		**3d***	**4d**	0.5	30	100	98	[3, 9,13]
5.		**3e**	**4e**	0.5	30	93	90	[3,9]
6.		**3f**	**4f**	2.5	40	88	94	[39]
7.		**3g**	**4g**	1.5	60	91	79	[19]
8.		**3h**	**4h**	1.0	120	79	82	[3,9,13]
9.		**3i**	**4i**	1.0	100	75	71	[3,9]
10.		**3j**	**4j**	1.5	30	83	94	[7,13]
11.		**3k**	**4k**	2.0	50	98	88	[19]

[a] Isolated yield of the products.
[b]Products were characterized by IR, ^{1}HNMR and Mass spectral data and comparison of authentic compounds.
*Compounds **3(a-d)** are prepared by **Method-B.**

In all cases, the xanthenes derivatives were obtained in excellent yields and prevent the problem of environmental safety. The important features of the present method are that acid sensitive substrate such as pyridine-3-carboxaldehyde underwent smooth reaction under present reaction conditions and product **3g** was obtained in 91% yield (**Table 2, entry 7**). All compounds synthesized were known compounds and confirmed by comparing the characterization data with previous reports [3,8,18].

Experimental Section

Apparatus and analysis

All chemicals were used AR grade and purchase from commercial sources. Melting points were recorded in open capillary and are uncorrected. Reaction was monitored using Thin Layer Chromatography (TLC) in petroleum ether: ethyl acetate (4.5:0.5) solvent system. The visualization of TLC spots was done by iodine vapors. The products were characterized using IR, ^{1}H-NMR and Mass spectroscopic techniques and confirmed by comparison with compounds reported in the literature.

General procedure for the synthesis of 1, 8-dioxo-octahydroxanthene derivatives 3(a-k): Method-A.

To a mixture of aldehyde (2 mmol) and dimedone (4 mmol), VB_1 (20 mole %) was added. Reaction mixture was heated at 110^{0}C for specified time (Table 2). After completion of reaction (as indicated by TLC) reaction mixture was cooled, solid mass was mixed with water to obtain the crystalline products with excellent yield. Further, products were purified by recrystallization in ethanol.

General procedure for the synthesis of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexane-1-one derivatives 4(a-k) in water: Method-B: To a suspension of aldehyde (2 mmol) and dimedone (4mmol) in water (10 mL), VB_1 (20 mol%) was added. Reaction mixture was heated at 80^{0}C for specific time (Table 2). After completion of reaction (as indicated by TLC), reaction mixture was cooled and filtered. The products were purified by recystalization in ethanol.

Spectral data of representative compounds

3a) M.P = 203-205 ^{0}C[13]; IR (KBr cm^{-1}): 3051, 2968, 1682, 1660, 1520, 1460, 1145, 760, 715. cm^{-1}; ^{1}H-NMR: δ 0.95 (s, 6H), 1.14(s, 6H), 2.13-2.45(m, 6H), 4.81(s, 1H), 7.30-7.90 (m, 5H). Mass (*m/z*): MF= $C_{23}H_{26}O_3$ (MW=350) =350.79(M+1).

3d) M.P. = 194-196°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 6H, 2 × -CH_3), 1.16 (s, 6H, 2 × -CH_3), 2.24-2.44 (m, 8H, 4 × -CH_2), 5.57 (s, 1H, -CH), 7.03-7.51 (m, 4H, Ar), 11.87 (s, 1H, OH).

3g) M.P. = 183-185 ^{0}C; IR (KBr cm^{-1}): 3025, 2945, 1622, 1570, 1429,1370, 1290, 1090, 854 cm^{-1}; ^{1}HNMR: δ 0.87 (s, 3H, CH_3), 1.14(s, 3H, CH_3), 1.20(s, 6H, 2CH_3), 2.26(m, 4H, 2CH_3), 2.71(m, 3H), 3.20 (d, 1H, J= 14H), 4.8(s, 1H), 7.76-8.68 (m, 4H). Mass (*m/z*): (MW=351) =351.3(M+1).

3k) M.P. =193-194 ^{0}C; IR (KBr cm^{-1}): 3070, 2950, 2875, 1682, 1667, 1510, 1459, 1160, 830, 744. cm^{-1}; ^{1}H-NMR: δ 0.97 (s, 3H, CH_3), 1.12(s, 6H), 2.19 (q, 4H), 2.50 (s, 4H), 4.91(s, 1H), 7.36-7.78(m, 5H). Mass (*m/z*): MF= $C_{27}H_{28}O_3$ (MW=400) = 399.8(M+1).

4a) M.P. = 137-138^{0}C[2]; ^{1}H-NMR:1.10 (s, 6H, -CH_3), 1.22 (s, 6H, CH3), 2.30–2.47 (m, 8H, CH2), 5.47 (s, 1H, CH), 7.01 (d, J = 8.4 Hz, 2H, Ph-H), 7.23 (d, J = 8.4 Hz, 2H, Ph-H), 11.56 (brs, 1H, OH), 11.87 (s, 1H, OH).

4c) M.P = 199-200^{0}C [2]; ^{1}H-NMR: 1.12 (s, 6H, CH3), 1.28 (s, 6H, CH3), 2.33–2.52 (m, 8H,

CH2), 5.54 (s, 1H, CH), 7.41–7.46 (m, 2H, Ph-H), 8.01 (s, 1H, Ph-H), 8.05 (d, J = 8.4 Hz, 1H, Ph-H), 11.58 (brs, 1H, OH), 11.86 (s, 1H, OH).

Conclusion

In conclusion, we have developed an efficient, environment friendly and high yielding protocol for the synthesis of 1,8-dioxo-octahydroxanthene. Vitamin-B_1 plays duel role in solvent-free conditions and in water. The corresponding xanthenes derivatives are obtained in good to excellent yields.

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