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SYNTHESIS OF 1,8-DIOXO-OCTAHYDROXANTHENES WITH THIAMINE CHLORIDE IN ECO-FRINDLY AND SOLVENT FREE CONDITION

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Abstract- A novel, simple and environmentally friendly method is reported for the preparation of 1,8-dioxo-octahydroxanthene derivatives by the reaction of dimedon with various aromatic aldehydes, using thiamine chloride as a recyclable catalyst under solvent-free conditions. This procedure has following benefits; simple workup, moderate reaction times, good yields, and completely compatible with environment.

Keywords: octahydroxanthene - thiamine chloride - solvent-free -dimedon

Introduction

Heterocyclic compounds such as xanthenes used in the basic material of dyes, fluorescent material, sensitizers in photodynamic therapy1 and laser technologies 2,3. Xanthens have been widely used by pharmaceutical and organic chemists for the antiviral4 and antibacterial5 properties.

Different methods have been reported for the synthesis of benzoxanthenes and xanthenes, including the reaction of aldehydes with dimedon in the presence of different catalyst, such as NH4H2PO4 6, sulfamic acid 7, PW acid 8, heteropoly acids (HPAs) 9, and others10-14.However, some of these methods suffer from disadvantages such as low to moderate yields, long reaction times, special apparatus, excess reagents, and the use of toxic catalysts. Thus, development of a new procedure for the synthesis of xanthenes derivative would be highly desirable. Among various heterogeneous acidic catalysts, thiamine chloride has many advantages such as low cost, ease of preparation, eco-friendly and easy work-up. We investigated the synthesis of xanthenes in the presence of thiamine chloride under heating conditions.

Experimental

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland). Melting points were determined with capillary tube in a Büchi B-540 apparatus. Infra-red(IR) spectrum were obtained on a Shimadzu-IR 470 spectrophotometer . ^{1}HNMR spectrums were measured on a Bruker-500 or 300 MHz instrument using tetramethylsilane as an internal standard.

General procedure for the preparation of 1,8-dioxo- 1,2,3,4,5,6,7,8-octahydroxanthenes:A mixture of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (1mmol, 0.14 g), aldehyde (0.5mmol) and thiamine chloride (20 mol%, 0.033 g) was stirred at 100 °C for appropriate time. Progress of reaction was monitored by TLC(n-hexan-ethyl acetate).The mixture was cooled to room temperature and water was added to dissolve catalyst and filtered to recover the catalyst via evaporating of water. The products were recrystallized from 1 to 5 ml hot ethanol and a few drop of water. All of the products are known and were characterized by IR and 1H NMR spectroscopic data and their melting points are compared with authentic samples. The selected spectral data of four representative xanthenes are given below.

Characterization data of xantenes derivatives

(3h):3,3,6,6-Tetramethyl-9-(4-clorophenyl)-1,8-dioxooctahydroxanthene

IR (KBr) 3025, 2985, 1680, 1665, 1620, 1490cm^{-1}.

^{1}HNMR (300MHz; CDCl3;): δH 1.00(s, 6H), 1.12 (s, 6H), 2.22 (dd, 4H,J= 1.6, J = 3.6, 2×CH2, H-4,5), 2.49(s, 4H, 2×CH2,H-2,7), 4.74 (s, 1H, H-9), 7.18–7.27 (m, 4H, ArH);

3,3,6,6-Tetramethyl-9-(3-clorophenyl)-1,8-dioxooctahydroxanthene

IR (KBr) 3028, 2995, 1677, 1659, 1614, 1488,1355, 1198, 1180, 1092, 1020, 845, 842 cm^{-1}

^{1}HNMR (300MHz; CDCl3; Me4Si): δ H 1.02 (s, 6H), 1.12 (s, 6H), 2.23 (dd, 4H,J = 21, J = 15, 2×CH2, H-4, 5), 2.49 (s, 4H, 2×CH2,H-2, 7), 4.75 (s, 1H, H-9), 7.11–7.28 (m, 4H, ArH);

3j) 3,3,6,6-Tetramethyl-9-(4-dimethyle aminophenyl)-1,8-dioxooctahydroxanthene

^{1}HNMR (300 MHz; CDCl3; Me4Si): δ 1.02 (s, 6H); 1.11 (s, 6H); 2.14–2.27 (dd, J = 21,J=16 Hz, 4H, 2× CH2); 2.46 (s, 4H, 2×CH2); 2.89 (s, 6H, NMe2); 4.61 (s, 1H,CH); 7.13–7.25 (m, 4H, Ar).

3e) 3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-1,8-dioxooctahydroxanthene

IR (CHCl3): 3023, 2967, 1669, 1588, 1529,1348, 1200, 1010 cm^{-1}

^{1}HNMR (500 MHz; DMSO-d6; Me4Si): δ 1.02(s, 6H), 1.15 (s, 6H), 2.18–2.30 (m, 4H), 2.53(s, 4H, 2×CH2), 4.76 (s, 1H), 7.50(d, J = 8 Hz, 2H), 8.12 (d, J = 8.1 Hz, 2H);

Result and discussions

The utility and catalytic activity of thiamine chloride was investigated for the synthesis of some organic compounds. In this work, we report the synthesis of octahydroxanthenes in the presence of thiamine chloride under heating conditions. Thiamine chloride is an efficient and reusable catalyst for the synthesis of octahydroxanthene derivatives that which were compared with similar catalysts (Table 1).

Table 1: comparison of the catalyst

Entry	*Catalyst (%mol)*	*condition*	*Time(min)*	*Y (%)*	*Ref*
1	*TC (thiamine chloride)*	*Solvent-free -100 ℃*	*90*	*85*	
2	*PW acid*	*Solvent-free -100 ℃*	*90*	*91*	*9b*
3	*HClO4-SiO2*	*Solvent-free -125 ℃*	*8*	*92*	*14*
4	*I2*	*Solvent-free -90 ℃*	*180*	*88*	*15*
5	*Dowex-50 W*	*Solvent-free -100 ℃*	*120*	*86*	*16*
6	*TiO2 (15%)*	*Solvent-free -90 ℃*	*12*	*57*	*17*

ParaChlorobenzaldehyde (1 mmol) with dimedone (2mmol) was mixed in order to obtain the optimized conditions. Performing the reaction at different temperatures and solvents in the presence of thiamine chloride revealed that the best condition was solvent-free at 100 ºC with molar ratio of aldehyde: dimedone: thiamine chloride to be 1:2:0.2 .Whereas, the yield of the product increased by amount of catalyst, but more than 20% molar does not have any effect on efficiency. When the same reaction was performed in the absence of the catalyst, the corresponding product was obtained in only 20% yield (Table 2).

Table 2: optimization reaction in the presence of thiamine chloride under different conditions.

Entry	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Cat(%mol)	*10*	*20*	*30*	*40*	*20*	*20*	*20*	*20*
Temp (°C)	*100*	*100*	*105*	*105*	*60*	*80*	*100*	*120*
Yield(%)	*62*	*85*	*87*	*86*	*35*	*60*	*85*	*80*

We have also examined the effect of temperature in a solvent-free condition. Rising temperature leads to increase in yields. For example the reaction of parachlorobenzaldehyde with dimedone at 100 °C in a solvent-free condition gave 85% yield of product (Table 2), while decreasing the temperature to 60 °C leads to the product in 35% yield. Therefore, our optimized condition is 20 mol% of thiamine chloride and 100 °C without solvent. The reusability of the thiamine chloride catalyst was also examined. After each run, the product was washed with water and filtered (thiamine chloride dissolves in water), the water was evaporated and the catalyst was washed with CHCl3 and reused. A gradual decline in activity was observed.

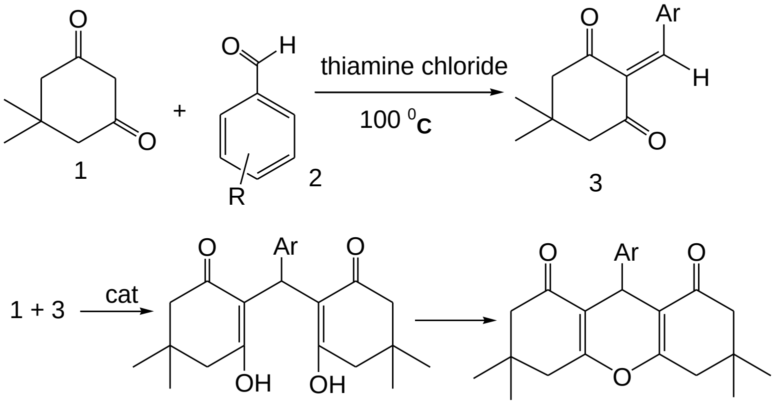
Various aldehydes were used for the synthesis of octahydroxanthenes derivatives under heating conditions. We have demonstrated a simple and eco-friendly method for the synthesis of octahydroxanthenes using thiamine chloride as an efficient catalyst. Short reaction times, moderate to high yields, a clean process, simple methodology, easy workup, and green conditions are some advantages of this protocol.

The type of side chain of aromatic aldehyde affected a strong influence on the reaction yields. aldehydes bearing electron-donating group increases the yield where as Electron-withdrawing groups reduced speed and yield of the reaction(Table 3).

Table 3: Compound with catalyzed by thiamine chloride under solvent-free condition

Entry	*Ar-CHO*	*Time (min)*	*Yield (%)*	*m.p (found)*	*(mp) Reported*
3a	*2-CH3-PhCHO*	*50*	*95*		
3b	*3-CH3-PhCHO*	*80*	*90*		
3c	*4-CH3-PhCHO*	*50*	*88*	*220-222*	*218-219 [19]*
3d	*4-Br-PhCHO*	*20*	*70*	*234-237*	
3e	*4-NO2-PhCHO*	*100*	*62*	*221-223.5*	*224-226 [10]*
3f	*4-F-PhCHO*	*80*	*89*	*184-186*	*184-185*
3g	*2-F-PhCHO*	*130*	*65*	*174-176*	
3h	*4-Cl-PhCHO*	*80*	*85*	*232-233.5*	*231-233[13]*
3i	*4-OH-PhCHO*	*80*	*88*	*245-246.5*	*245-250 [20]*
3j	*4-(Me)2N-PhCHO*	*60*	*90*	*221-223*	*218-220 [13]*

Mechanism of the reaction was reported before.(Scheme 1)[18]. In which, intermediate 3 was formed through Knoevenagel reaction between dimedone and aldehyde, and subsequently, elimination of water occurred from the intermediate 3 to give compound 4.



Scheme 1: Mechanism of the Knoevenagel reaction between dimedone and aldehyde

Work-up procedure is very simple that consist of adding water to the reaction mixture to remove the catalayst. The crude product was crystallized in ethanol to give pure octahyroxanthene. Absence of OH absorptions in the 1HNMR and IR spectra confirms the structure of our products. In all the 1HNMR spectra (CDCl3, 25 °C), the characteristic peak of 10-H xanthene was appeared in 5–6 ppm region as a singlet.

Conclusion

A novel and green method has been presented for the synthesis of 1,8-dioxooctahydroxanthene derivatives in the presence of thiamine chloride as catalyst. short reaction time, easy workup, clean process, solvent-free conditions, and moderated yields are some advantages of this procedure.

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