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A CONVENIENT ONE-POT SYNTHESIS OF TETRAHYDROBENZO-[C]-XANTHENE-1,11-DIONE DERIVATIVES IN AQUEOUS MEDIUM

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ABSTRACT

A simple and efficient one-pot synthesis of xanthene derivatives was achieved in excellent yield *via* the three-component reaction of aromatic aldehydes, 4-hydroxyl coumarin and 5,5-dimethylcyclohexane-1,3-dione using pyrrolidine based organocatalyst in solvent water.

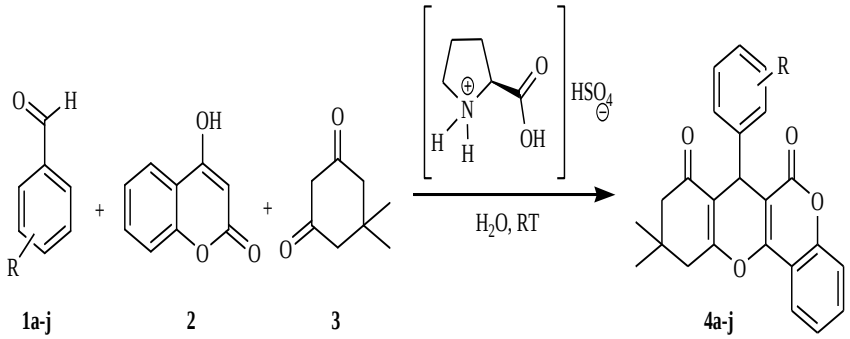
KEYWORDS: One-pot synthesis, Organocatalyst, Tetrahydrobenzo[C]Xanthene-1,11-dione, 4-Hydroxyl coumarin, 5,5-Dimethylcyclohexane-1,3-dione.

INTRODUCTION

Xanthenes and benzoxanthenes have concerned considerable interest because they possess various biological activities such as antibacterial[1], anti-inflammatory[2] and antiviral activities.[3] These structural moieties have also found a function as antagonists for paralyzing the action of zoxazolamine[4] and demonstrate efficacy in photodynamic therapy.[5] In addition, these compounds have been in use as dyes[6] and pH-sensitive fluorescent materials for visualization of biomolecular assemblies[7] and utilized in laser technologies.[8] In this way, a broad utility range has made xanthenes prime synthetic candidates, thereby accentuating the need to develop newer synthetic routes for scaffold manipulation of xanthene derivatives.

Recently, multi-component reactions (MCRs) have received much attention from organic chemists as they offer important advantages over conventional linear-type synthesis such as high atom economy, low cost, reduction in overall reaction time and operational simplicity.[9-12] Therefore due to our interest in organocatalyzed one-pot synthesis[13-15] herein we describe

a convenient protocol for synthesis of tetrahydrobenzo[C]xanthene-1,11-diones in excellent yields using pyrrolidine based organocatalyst (**Scheme 1**).



Scheme 1

Experimental

All solvents were used as commercial anhydrous grade without further purification. The column chromatography was carried out over silica gel (80-120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^{1}H spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ solvent and TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker-300 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on Polaris-Q Thermoscintific GC-MS.

General procedure for synthesis of tetrahydrobenzo[C]xanthene-1,11-diones

Aromatic aldehyde (1 mmol), 4-hydroxyl coumarin (1mmol) and 5,5-dimethylcyclohexane-1,3-dione (1.2 mmol) were added to a 50 mL round bottom flask containing pyrrolidine based organocatalyst (15 mol %) in solvent water. The mixture was then stirred at room temperature for appropriate time (monitored by TLC) as indicated in table 2. After completion of the reaction, the precipitate was collected by suction and purified by crystallization from ethyl alcohol to give desired products.

Compound (4b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 7.2 Hz, 1H), 7.52-7.55 (m, 1H), 7.02-7.24 (m, 6H), 4.84 (s, 1H), 2.60 (d, J = 7.6 Hz, 1H), 2.47 (d, J = 7.6 Hz, 1H), 2.30 (d, J = 7.6 Hz, 1H), 2.20 (d, J = 7.6 Hz, 1H), 1.24 (s, 3H), 1.20 (s, 3H).; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 195.6, 162.3, 160.7, 154.5, 152.8, 140.9, 133.2, 132.9, 130.6, 128.9, 128.4, 127.7, 124.0, 122.1, 116.5, 114.6, 113.2, 106.1, 50.2, 40.3, 33.2, 32.1, 29.3, 27.3; GC-MS (m/z): 406 (M^+).

Compound (4h)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J=7.4 Hz, 1H), 7.58–7.55 (m, 1H), 7.48–7.31 (m, 4H), 6.52 (d, J=8.7 Hz, 2H), 4.83 (s, 1H), 3.67 (s, 3H), 2.52 (d, J=17.4 Hz, 1H), 2.46 (d, J=17.4 Hz, 1H), 2.21 (d, J=16.2 Hz, 1H), 2.27 (d, J=16.2 Hz, 1H), 1.12 (s, 3H), 1.09 (s, 3H).; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 195.5, 161.4, 160.2, 158.4, 153.6, 152.4, 134.5, 132.3, 129.9, 124.7, 124.5, 122.8, 116.9, 115.6, 113.8, 113.5, 107.2, 55.1, 50.5, 40.5, 32.6, 32.1, 29.0, 27.4.; GC-MS (m/z): 402 (M^+).

RESULTS AND DISCUSSION

In order to find out most promising condition for the synthesis tetrahydrobenzo[C]xanthene-1,11-diones, a model reaction was performed using reaction of 4-chloro benzaldehyde, 4-hydroxylcoumarin and 5,5-dimethylcyclohexane-1,3-dione with different ratios of pyrrolidine based organocatalyst in solvent water. In our optimization study, we found that amount of the catalyst plays a major role in determining the desired product yield. At catalyst concentration 5 mol%, reaction offered 54% product yield and the reaction was completed in 4 hours. When catalyst loading was increased to 10 mol%, an improved result was observed. The reaction was completed within 3 hours and offered 68 % product yield. At 15 mol % catalyst loading, reaction afforded 77% yield of desired product. Afterward, the best optimized reaction condition was achieved at the catalyst loading of pyrrolidine based organocatalyst to 20 mol% in solvent water. It gives excellent 91% product yield with 2 hours reaction time. More increase in the catalyst loading to 25 mol% did not reveal an improvement in the product yield or reaction time. The model reaction in absence of catalyst in solvent water showed reduced performance with respect to the yield and reaction time.

Table 1: Effect of of pyrrolidine based organocatalyst loading for synthesis of tetrahydrobenzo[C]xanthene-1,11-diones[a]

Entry	Pyrrolidine based organocatalyst (mol %)	Time (hrs)	Yield[b] (%)
1	5	4.00	54
2	10	3.00	68
3	15	2.30	77
4	**20**	**2.00**	**91**
5	25	2.00	36
6	-	8.00	32

[a]Conditions: 4-Chloro benzaldehyde (1 mmol), 4-hydroxyl coumarin (1 mmol) and 5,5-dimethylcyclohexane-1,3-dione (1.2 mmol), pyrrolidine based organocatalyst (mol %), Water (10 mL) at RT. Reaction was monitored by thin layer-chromatography. [b]Isolated yield

Table 2: Pyrolidine based organocatalyzed one-pot synthesis of tetrahydrobenzo[C] xanthene-1,11-diones[a].

Entry	R	Products	Time (hrs)	Mp. (^oC)	Yield (%)[b]
1	H	4a	3.30	218-219	87
2	4-Cl	4b	2.00	236-237	91
3	4-NO_2	4c	4.00	221-223	80
4	3,4-OCH_3	4d	3.00	182-184	81
5	4-OH	4e	3.00	178-180	85
6	2-Cl	4f	2.30	227-229	89
7	4-CH_3	4g	3.30	210-212	88
8	4-OCH_3	4h	3.00	190-192	82
9	3-OCH_3- 4-OH	4i	4.00	264-266	84
10	2,4-Cl	4j	2.30	257-258	88

[a]Conditions: Aromatic aldehyde (1 mmol), 4-hydroxyl coumarin (1mmol) and 5,5-dimethylcyclohexane-1,3-dione (1.2 mmol), pyrrolidine based organocatalyst (20 mol %), Water (10 mL) at RT. Reaction was monitored by thin layer-chromatography. [b]Isolated yield

Under the optimized reaction conditions, different aromatic aldehyde were allowed to react with 4-hydroxylcoumarin and 5,5-dimethylcyclohexane-1,3-dione. All the reactions proceeded efficiently with wide range of aromatic aldehydes affording good to excellent yield of the corresponding products (Table 2, entry 1-10).

CONCLUSION

In conclusion, we have developed a simple and efficient method for the synthesis of tetrahydrobenzo[C]xanthene-1,11-diones by one-pot reaction of aromatic aldhyde, 4-hydroxylcoumarin and 5,5-dimethylcyclohexane-1,3-dione using pyrrolidine based organocatalyst in solvent water at room temperature condition. The easy experimental operation, mild reaction condition and good to excellent yield with a wide range of aromatic aldehydes are some of the remarkable features of this protocol.

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