

A Green and Solvent Free Protocol for the Synthesis of Bioactive Tetrahydrobenzo[C]Xanthene-8-Ones Using Novel Ionic Liquid L-Pyrrolidine-2-Carboxylic Acid Sulfate (LPCAS)

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Abstract. A simple, solvent free, highly efficient and eco-friendly protocol for the synthesis of tetrahydrobenzo[c] xanthene-8-ones derivatives using novel ionic liquid; L-pyrrolidine-2-carboxylic acid sulfate (LPCAS) as a catalyst has been reported. Important features of this methodology are excellent yield of products, cleaner reaction profile, environmentally friendly and the inexpensive catalyst.

Keywords: Tetrahydrobenzo[c]xanthene-8-ones, ionic liquid, solvent free etc.

1 Introduction

Xanthenes and benzoxanthenes are valuable structures which have been discovered extensively in recent years. Xanthene skeleton is present in number of natural compounds [1]. Most of these derivatives are found to bear diverse biological properties such as bactericidal [2], anti-inflammatory [3], antiviral [4] activities. They act as antagonists for paralyzing the action of zoxazolamine, [5] and are helpful in the photodynamic therapy [6]. Their applications are also reported in laser technology [7]. They are used as dyes [8] and also in pH sensitive fluorescent materials for visualization of bimolecular assemblies [9]. In recent years demand for these biologically and industrially significant molecules has increased.

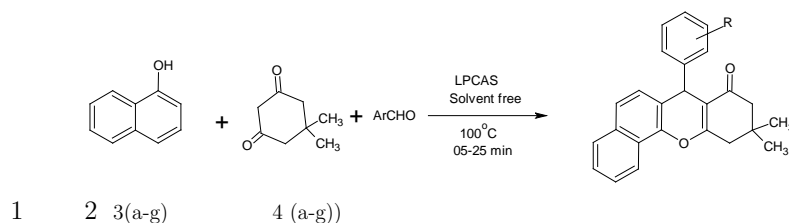
Literature survey shows that, few methods have been only reported for the synthesis of tetrahydrobenzo[a]xanthene-11-ones derivatives using 2-naphthol. Different catalysts such as sulfamic acid [10], p-TSA [11], selectfluor TM [12], iodine [13], silica sulfuric acid [14], Yb(OTf)₃ [15] and ionic liquids [16] were used in the synthesis of benzo[a]xanthenes derivatives. Moreover, the existing methods have not been conceded for the synthesis of tetrahydrobenzo[c]xanthene-8-ones from 1-naphthol because the electron density at 2-position of 1-naphthol is not sufficient for the formation of corresponding ortho-Quinone Methides (o-QMs). As per our knowledge, only three articles which involve the use of proline triflate [17], CAN [18] and Zeolite [19] as a catalyst for the synthesis of tetrahydrobenzo[c]xanthenes-8-ones from 1-naphthol have been reported in the literature. The search for new methods for the synthesis of tetrahydro[c]xanthene-8-ones from 1-naphthol is therefore, exceedingly in demand.

Taking to account the weakness of reported methods and to overcome these problems, we have developed the green protocol for efficient synthesis of tetrahydrobenzo[c]xanthenes-8-ones. Herein we used novel ionic liquid; L-pyrrolidine-2-carboxylic acid sulfate (LPCAS) as a catalyst for the synthesis of tetrahydrobenzo[c]xanthenes-8-one derivatives from 1-naphthol (Scheme 1).

2 Experimental Procedure

All the reagents were purchased from Aldrich/Merck and used without further purification. Melting points were recorded by using digital melting point apparatus EQ730 (Equiptronics) and uncorrected. Progress of reactions and the purity of product formation were monitored on thin layer chromatography using hexane/ethyl acetate 8:2 as eluent. The products were characterized by comparing melting points

and spectral data with authentic samples melting point and spectroscopic data (IR, ^1H NMR). IR spectra were recorded on shimadzu IR Solution 150SUI spectrophotometer using KBr pellet in cm^{-1} . ^1H NMR spectra were recorded on Bruker 400 MHz spectrometer using appropriate solvent and TMS as an internal standard. Chemical shift were expressed in ppm. Mass spectra were predicted on a Jeol JMSD-300 spectrometer. Viscosity was measured on Buckfield CPe40.



Scheme 1. Synthesis of 1 tetrahydrobenzo [c] xanthene-8-ones Derivatives

2.1 General Procedure for the Synthesis of Tetrahydrobenzo[C]Xanthene-8-Ones Derivatives

To a mixture of 1-naphthol (1 mmol), aromatic aldehyde (1 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (1 mmol) L-Pyrrolidine-2-carboxylic acid sulfate (LPCAS) (1 mmol) was added and the mixture was stirred at 100°C for appropriate time. The progress of reaction was monitored on TLC. After completion of reaction, the reaction mixture was cooled to room temperature and water (10 ml) was added. The separated solid was filtered off and the crude product was recrystallized from ethanol to afford the pure product. Similarly the other derivatives were also prepared as indicated in Table 1.

Table 1. Synthesis of tetrahydrobenzo[c]xanthenes-8-ones catalyzed by LPCAS (3a-j)

Sr. No.	Aldehyde	Time (min)	Yield (%)	Melting Point ($^\circ\text{C}$)		References
				Observed	Reported	
4a	Benzaldehyde	15	95	154-156	155-157	[17]
4b	3-Nitro benzaldehyde	05	95	156-158	157-158	[17]
4c	4-hydroxy benzaldehyde	05	87	182-184	185-187	[17]
4d	4-chloro benzaldehyde	05	89	186-188	185-186	[17]
4e	4-Methoxy benzaldehyde	25	95	204-206	207-209	[17]
4f	4-Hydroxy-3-methoxybenzaldehyde	10	90	232-234	235-237	[18]
4g	2-chloro benzaldehyde	05	92	178-180	180-188	[17]

2.2 Spectral Data of Selected Compound

Compound 4a: FTIR (KBr) (cm^{-1}): 3057, 2818, 1627, 1622, 1377, 1224, 1029, 511. ^1H NMR (400 MHz, DMSO): δ ppm 6.8–7.3 (m, 11H, ArH); 5.6(s, 1H); 2.2 (s, 2H); 1.9 (d, J= 17.2 Hz, 2H); 0.95 (s, 3H, CH_3); 0.92(s, 3H, CH_3).

Compound 4b: FTIR (KBr) (cm^{-1}): 3101, 2805, 1620, 1517, 1342, 1082, 510. ^1H NMR (400 MHz, DMSO): δ ppm 7.5 (m, 4H, ArH); 7.3 (m, 3H, ArH); 7.1 (m, 3H, ArH); 5.1 (s, 1H); 2.25–2.23 (m, 2H); 2.20–2.19 (m, 2H); 0.87 (s, 6H, 2 CH_3)

Compound 4d: FTIR (KBr) (cm^{-1}): 3003, 2790, 1651, 1523, 1402, 1012, 550. ^1H NMR (400 MHz, DMSO): δ ppm 7.18-8.66(m, 11H, Ar-H), 5.59(s, 1H), 2.51-2.69(m, 2H), 2.15-2.35(d, 2H), 0.88-1.06(s, 6H, 2 CH_3).

Compound 4e: FTIR (KBr) (cm^{-1}): 3057, 2996, 1647, 1508, 1379, 1029, 540. ^1H NMR (400 MHz, DMSO): δ ppm 6.69-8.6(m, 11H, Ar-H), 5.52(s, 1H), 3.67(s, 3H, OCH_3), 2.63(m, 2H), 2.14-2.29(d, 2H), 0.89-1.05(s, 6H, 2 CH_3).

Compound 4f: FTIR (KBr) (cm^{-1}): 3400, 3084, 2945, 1591, 1396, 1024, 560. ^1H NMR (400 MHz,

DMSO): δ ppm 7.5 (m, 4H, ArH); 7.3 (m, 3H, ArH); 7.1 (m, 3H, ArH); 5.1 (s, 1H); 3.74 (s, 3H, OCH₃); 2.5–2.15 (m, 2H); 2.14–1.9 (m, 2H); 0.84 (s, 6H, 2 CH₃).

3 Result and Discussions

Tetrahydrobenzo[c]xanthene-8-ones derivatives 4(a-j) were synthesized by condensing 1-naphthol (1 mmol) 1, 5,5-dimethyl-1,3-cyclohexanedione (1 mmol) 2 with various aromatic aldehydes (1 mmol) 3(a-g) at 100 °C using Bronsted ionic liquid L-Pyrrolidine-2-carboxylic acid sulfate (1 mmol) as a catalyst (Scheme 1). The results were reported in Table 1.

The efficiency of IL catalyst has been determined and compared with the reported acid catalysts for the synthesis of 10,10-dimethyl-7-phenyl-7,9,10,11-tetrahydro-benzo[c]xanthene-8-one (4a).

In presence of Proline triflate in water, the reaction proceeds within 5 hours offering 79 % yield of the product (entry 1, Table 1). In the presence of CAN in DCM-ethanol/Ultrasonication the reaction mixture on heating for 120 mins. afforded 85 % of product (entry 2, Table 2).

Similarly in presence of HY Zeolite, the same reaction proceeds in 60 mins. offering 87 % of product (entry 3, Table 2). Whereas, when the reaction is carried out using ionic liquid L-pyrrolidine-2-carboxylic acid sulfate it completes just in 15 minutes and offers the product in 95 % (entry 4, Table 2).

All the above results have showed that, the catalyst proved its efficiency in terms of product yield and reaction times (Table 2). All the known synthesized compounds were confirmed by comparing their melting points with standards and new compounds were confirmed from spectroscopic data (IR, ¹H NMR).

An advantage of the novel ionic liquid catalyst (L-Pyrrolidine-2-carboxylic acid sulfate) is; it is cost effective and more efficient as compare to other reported ionic liquids.

Table 2. Comparison of different catalysts

Entry	Aldehyde	Conditions	Time	Yield(%)	Ref.
1	Proline triflate	H ₂ O/reflux	5 hours	79	[17]
2	CAN	DCM-ethanol/Ultrasonication	120 mins	85	[18]
3	HY Zeolite	Solvent free/80 °C	60 mins	87	[19]
4	L-Pyrrolidine-2-carboxylic acid sulfate(LPCAS)	Solvent free/100 °C	15 mins	95	This work

4 Conclusions

We have developed a novel, eco-friendly protocol for the synthesis of tetrahydrobenzo[c]xanthene-8-ones via one pot condensation of 1-naphthol, aromatic aldehydes and dimedone using LPCAS as a ionic liquid catalyst. The distinguishing features of this new protocol include a simple procedure, high catalytic activity, short reaction time, excellent yields.

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